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

Reimbursement Review

Review Report

Dabrafenib plus Trametinib

(Non-Sponsored Review)

Therapeutic area: Low-grade gliomas with BRAF V600 mutations

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Key Messages

What is Low-Grade Gliomas (LGG)?

- Low-grade gliomas are the most common type of central nervous system (CNS) tumours found in children, adolescents and young adults, accounting for about one-third of all CNS tumours. LGGs are a diverse group of tumours that differ in terms of location in the CNS, histology type, and molecular profile.
- The incidence of LGGs in Canada was reported as 1.41 cases per 100,000 person years in children aged 0 to 14 from 2001 to 2015.

What are the Treatment Goals and Current Treatment Options for Low-Grade Gliomas?

- The goals of treatment are to achieve tumour control, improve progression-free survival, minimize toxicities from treatment and maintain functional outcomes such as vision
- Currently in Canada, the preferred first-line treatment for LGG is complete surgical removal (resection) of the tumour. Where complete resection is not possible, chemotherapy with vinblastine monotherapy or carboplatin plus vincristine is recommended as standard first line treatment.
- Where cancer has progressed or relapsed, second-line therapy currently includes targeted therapies with dabrafenib monotherapy, dabrafenib-trametinib combination for patients identified to have BRAF V600 mutations. Radiation therapy is generally avoided in children and younger people due to the risk of significant long-term neurologic and cognitive damage.

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

- Dabrafenib plus trametinib are medicines that block specific molecules involved in cancer cell growth and survival.
- Health Canada has approved dabrafenib plus trametinib for pediatric patients 1 year of age and older with LGG with a BRAF V600E mutation who require systemic therapy
- At the request of the participating public drug programs, we reviewed dabrafenib plus trametinib to inform a recommendation on whether the treatment should be publicly reimbursed for pediatric and young adult patients for 1st line or greater therapy in low grade gliomas with residual disease and with known BRAF V600 mutations.

How Did We Evaluate Dabrafenib plus Trametinib?

- We reviewed the clinical evidence on the beneficial and harmful effects and compared costs of dabrafenib plus trametinib versus other treatments used in Canada for pediatric and young adult patients with LGG. Relevant comparators were vinblastine, carboplatin plus vincristine combination, and dabrafenib monotherapy.
- The clinical evidence was identified through systematic searches of the available literature. The review was informed by a patient group submission in response to our call for input and by input from the participating public drug programs on potential implementation issues. Additionally, we consulted 2 clinical experts in pediatric neuro-oncology to provide insight during the review process.

What Did We Find?

Clinical Evidence

- We reviewed the following evidence:
    - 1 randomized controlled trial (Bouffet et al.) comparing dabrafenib plus trametinib to carboplatin plus vincristine as first-line therapy in pediatric patients with BRAF V600 mutated LGG.
    - 1 single arm cohort within a basket trial (ROAR trial) of dabrafenib plus trametinib in adult patients with relapsed BRAF V600E mutated LGG
- For the comparison of dabrafenib plus trametinib versus carboplatin plus vincristine from Bouffet et al.:

- There was improved progression-free survival, overall response rate and clinical benefit rate with dabrafenib plus trametinib compared with chemotherapy.
- The effects of dabrafenib plus trametinib versus chemotherapy on overall survival could not be determined because one death (in the chemotherapy group) occurred in the trial.
- Comparative results between the treatment arms were not reported for the health-related quality of life measure, precluding any conclusions being drawn.
- Fewer discontinuations due to adverse events (AEs) and Grade 3 or greater AEs occurred with dabrafenib plus trametinib versus chemotherapy. Frequencies of serious AEs and any AEs were similar between the groups.

- The single-arm ROAR trial suggested that greater than half of adult patients with relapsed or refractory BRAF V600E-mutated LGG achieved overall response. However, health-related quality of life outcomes were not evaluated. The small sample size (N = 13) and lack of a comparator make it difficult to determine whether the observed results are attributable to dabrafenib and trametinib or to assess the clinical significance of the findings.

Economic Evidence

- Reimbursing dabrafenib plus trametinib for the treatment of adult and pediatric patients as first-line or greater therapy in low-grade gliomas with residual disease and with known BRAF V600 mutations is expected to increase costs to the public drug programs.

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Abbreviations

AE	adverse event
AESI	adverse event of special interest
BRAF	serine/threonine-protein kinase B-Raf
CBR	clinical benefit rate
CI	confidence interval
CNS	central nervous system
CR	complete response
D+T	dabrafenib plus trametinib
ECOG	Eastern Cooperative Oncology Group
ERK	extracellular regulated kinase
HR	hazard ratio
HRQoL	health-related quality of life
ITT	intention to treat
LGG	low-grade glioma
MAPK	mitogen activated protein kinase
MEK	mitogen-activated extracellular signal-regulated kinase
OR	odds ratio
ORR	overall response rate or objective response rate
OS	overall survival
PFS	progression-free survival
PLGG	pediatric low-grade glioma
PR	partial response
RAF	rapidly accelerated fibrosarcoma
RCT	randomized controlled trial
RR	risk ratio
SAE	serious adverse event
SD	standard deviation

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 pediatric and young adult patients for first-line or greater therapy in low-grade gliomas (LGGs) with residual disease and with known BRAF V600 mutations. The focus will be placed on comparing dabrafenib plus trametinib to relevant comparators and identifying gaps in the current evidence. The economic review consists of a cost comparison for dabrafenib plus trametinib compared with relevant comparators for the same population. The relevant comparators for the review were vinblastine, carboplatin plus vincristine, and dabrafenib.

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 (Tafinlar), 50 mg and 75 mg oral capsules and 10 mg dispersible tablets for oral suspension. Trametinib (Mekinist) 0.5 mg and 2 mg tablets, 4.7 mg/bottle powder for oral solution, (0.05 mg/mL after reconstitution)
Relevant Health Canada indication	Dabrafenib in combination with trametinib is indicated for patients 1 year of age and older with LGG with a BRAF V600E mutation who require systemic therapy A validated test is required to identify the BRAF V600 mutation status to select patients appropriate for treatment with dabrafenib or trametinib as monotherapies or in combination.
Mechanism of action	Dabrafenib is a small molecule that selectively inhibits RAF kinases, including BRAF, which results in blocking the MAPK pathway that regulates the proliferation and survival of tumour cells in different cancers. Trametinib is a small molecule selective inhibitor of MEK1 and MEK2 proteins, which are components of the MAPK pathway, causing tumour cell growth inhibition and cell death. Dabrafenib and trametinib combination therapy simultaneously blocks the MAPK pathway (including RAS/RAF/MEK/ERK) by dual inhibition of the RAF and MEK kinases in BRAF V600 mutations. This dual inhibition of the MAPK pathway reduces tumour cell growth and proliferation.
Recommended dosage	Pediatric patients, 1 year to <18 years of age, Health Canada recommended dosages for dabrafenib and trametinib are based on weight ranges[a] Adult patients, ≥18 years of age: Dabrafenib: 150 mg oral, twice daily; Trametinib: 2 mg oral, once daily
Data protection status	Dabrafenib – data protection ended in July 2021 Trametinib – data protection ended in July 2021
Status of generic drugs / biosimilars	Dabrafenib – no generic on the market or under review Trametinib – no generic on the market or under review
Information on the CDA-AMC review	
Requestor	Provincial Advisory Group

Item	Description
Indication under consideration for reimbursement	Pediatric and young adult patients for first-line or greater therapy in LGGs with residual disease and with known BRAF V600 mutations

BRAF = protein kinase B-raf; ERK = extracellular regulated kinase; LGG = low-grade glioma; MAPK = mitogen-activated protein kinase; MEK = Mitogen-activated extracellular signal-regulated kinase; RAF = rapidly accelerated fibrosarcoma; RAS = rat sarcoma.

[a] Recommended dosages for dabrafenib and trametinib for pediatric patients are as per product manographs. See Working Papers document for dosing tables.

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. We received 1 patient group submission from Advocacy for Canadian Childhood Oncology Research Network (Ac2orn). The full submissions received are available in the consolidated input document <insert hyperlink or citation>.

Input from patient and clinician groups is considered throughout the review, including in the selection of outcomes to include in the Clinical Review and in the interpretation of the clinical evidence. Relevant patient and clinician group input and industry input is summarized in the Disease Background, Current Management, and Unmet Needs and Existing Challenges sections.

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 pediatric neurooncologists with expertise in the diagnosis and management of pediatric low-grade glioma participated as part of the review team, with representation from Alberta and Nova Scotia.

Disease Background

Low-grade gliomas (LGGs) are the most common CNS tumour found in children and young adults, accounting for about one-third of reported cases.[1] According to the World Health Organization (WHO), LGGs are classified as Grade 1 and 2 tumours, which are slow growing tumours.[2] The incidence of pLGGs in Canada was reported as 1.41 cases per 100,000 person years in children aged 0 to 14 from 2001 to 2015.[3] LGGs constitute a diverse group of tumours that differ greatly in terms of location in the CNS, histological grades and subtypes, and molecular alterations. The key signs and symptoms of LGG vary depending on the location of the tumour.[4] Common symptoms include headaches, nausea and vomiting, confusion, memory loss, personality changes, vision problems (for tumours with optic pathway involvement), and seizures.

The diagnosis of LGG in children often follows a complex and indirect path, as highlighted in the 2022 Pediatric Low-Grade Glioma Multi-Stakeholder Meeting.[5] Symptoms are usually consistent but non-specific, including headache, vomiting, dizziness, functional deficits and others mentioned previously. Parents actively seek answers and advocate for further evaluation by health care providers to achieve a diagnosis. After the discovery of the tumour, everything accelerates and becomes urgent, especially if there is long delay from onset of symptoms. Patients are quickly referred to a specialized tertiary children's hospital for advanced imaging and further investigations.

The 10-year survival estimates for pLGGs is 95% in some LGG tumour types[6] and a 20-year survival of up to 87%.[7] However, pLGG are associated with significant risk of progression and progression-free survival after treatment with conventional chemotherapy range around 40 to 50%.[8,9] Morbidities associated with pLGGs can include neurological impairments like seizures, behavioral and/or cognition disorders, and visual dysfunction including blindness.

Research suggests that the majority (90%) of pLGG tumours have alterations to the mitogen activated protein kinase (MAPK) pathway, which is involved in cell growth, proliferation, and survival.[10] About 17% of pediatric low-grade gliomas have the BRAF

V600E mutation, disrupting the MAPK pathway, which has implications for treatment and prognosis. People who have BRAF V600E mutated tumours have poorer response to chemotherapy and radiation, increased risk of recurrence after standard therapy, and shorter survival rates.[11]

Current Management

Treatment Goals

The clinical experts consulted for this review emphasized that the primary goals of treating LGG are to improve tumour response, prevent worsening of symptoms, and improve seizure control while limiting harms. They shared that patients with LGG harboring the BRAF V600 mutations do not typically respond well to conventional chemotherapy while radiotherapy remains undesirable.

Current Treatment Options

The preferred treatment for LGG is maximal surgical resection when the tumour's location allows. The extent of tumour resection is a key determinant of survival outcomes. Cure rates of over 90% and 5-year and 8-year overall survival rates over 95% have been achieved in cases where the tumour is completely or nearly completely removed.[12]

In patients with unresectable tumours or incomplete resection, standard of care (SOC) is chemotherapy using carboplatin and vincristine or vinblastine given weekly.[8,9] The goal of chemotherapy is to prevent disease progression. Despite chemotherapy, 50% of patients have recurrent and progressive disease and need additional therapy.[8,9] Second-line therapies in Canada for progressive or relapsed pLGG cancers include targeted therapies — BRAF inhibitors (e.g., dabrafenib) with or without MEK inhibitors (e.g., trametinib, selumetinib) — depending on the type of MAPK alteration identified in the tumour. Radiation therapy is generally delayed or avoided in young children due to the risk of significant long-term neurologic and cognitive damage as well as increased risk of subsequent malignancy.

Clinical experts acknowledged that due to poor response of BRAF V600 mutated LGG to chemotherapy or radiation, dabrafenib monotherapy or in combination with trametinib is increasingly used as first-line treatment for this subgroup of patients. However, due to lack of provincial funding, access has been requested through compassionate access programs. Input from clinical experts indicated that vemurafenib, a first generation BRAF inhibitor, was previously used in relapsed or progressive LGG but is no longer used in clinical practice since the availability of dabrafenib.

Key characteristics of dabrafenib and trametinib are summarized with other treatments available for low-grade glioma in the Working Papers document in Table 1.

Unmet Needs and Existing Challenges

The following is based on input provided by patient group and clinical experts consulted for this review.

The patient group (through the previous multi-stakeholder meeting for pLGG) highlighted that pLGG has profound long-term physical, emotional, and financial impacts on the child and their families. They expressed that different aspects of care - access to specialist physicians, high costs and access to novel and potentially more effective treatment approaches - can vary based on geographical location, healthcare institution and clinicians, making access burdensome. Caregivers and families experience financial burden for medical tests, loss of income and missed time from work; travel and accommodation for accessing treatment options; the cost of accessing high-cost therapies, home care and other supports; and the need for resources for emotional and psychosocial support. Additional challenges include lack of coordination in transition from care in pediatric centres to adolescent/adult centres, fragmented care vs integrated care pathway to access medical and psychosocial resources. An increased focus on mental health services and social support for patients and their families was advocated by the patient group.

The clinical experts noted that some patients, especially those with BRAF V600 mutation, do not adequately respond to first-line conventional chemotherapy. Symptom improvement is often slow with chemotherapies, taking up to 6 months. Chemotherapy has been associated with multiple relapses and toxicities. There are no treatments available to reverse vision impairment or endocrinopathies caused by the tumour. Tumour recurrence is a serious concern for patients with unresectable or incompletely resected tumours. Considering current available treatments are associated with high relapse rates, toxicities and tolerability issues to varying extents, there are significant unmet needs for more effective, less toxic and better tolerated treatments. Oral medications such as dabrafenib and trametinib were specifically highlighted as being potentially beneficial to both pLGG patients and their families can be administered at home, outside of treatment centres in terms of increasing treatment adherence, reducing the need for hospital visits, allowing fewer missed days at school, with friends and work.

Potential Place in Therapy

Contents within this section have been informed by input from the clinical experts consulted for the purpose of this review. The following has been summarized by the review team.

Potential Place in Therapy

According to the clinician experts, dabrafenib in combination with trametinib is expected to become favoured over other systemic therapies for first-line treatment for patients with BRAF V600 mutated LGG, particularly those who have residual tumour after surgery.

Patient Population

The clinical experts identified newly diagnosed patients with BRAF V600 mutated pLGG as best suited for first line systemic therapy with dabrafenib plus trametinib. Potentially eligible patients should be selected based on confirmed BRAF V600 status, which requires molecular diagnostic testing that is standard practice at most Canadian institutions providing integrated pathology services. Due to the need to treat brain tumours quickly, immunohistochemistry can be the quicker method to diagnosis and treatment initiation. However, molecular confirmation of BRAF V600 status with DNA testing is still important but should not be a barrier to initiating treatment. They expressed that the stage of disease would not impact the use of this combination as first-line treatment compared with conventional chemotherapy.

Assessing the Response to Treatment

Patients undergoing treatment with dabrafenib plus trametinib should be monitored for treatment response, disease progression and possible side effects. Clinical assessments and serial brain MRIs should be performed every 3 to 6 months during treatment and at follow-up after the patient is off therapy. The experts indicated that a clinically meaningful response to treatment includes a reduction in the frequency and severity of symptoms, maintenance or improvement in health-related quality of life, preservation or improvement in functional outcomes, and a progression-free survival of equal or greater than 40% at 5 years. While complete tumour response is the goal of therapy, partial response and stable disease are also clinically important.

Discontinuing Treatment

The clinical experts indicated that dabrafenib plus trametinib therapy should be discontinued in cases of tumour progression or significant toxicity. Discontinuation should be done with caution due to potential tumour rebound that has been observed with discontinuing dabrafenib monotherapy. Additionally, the clinical experts explained that these therapies may still slow tumour growth despite disease progression or resistance, emphasizing the need for careful evaluation before discontinuation. A minimum treatment duration of 36 months is recommended by the Canadian Pediatric Brain Tumour Group.[13] The clinical experts highlighted that many patients may require lifelong therapy, and medication can be adjusted to the lowest dose needed to maintain tumour response.

Prescribing Considerations

Dabrafenib and trametinib treatment should be prescribed and managed by specialists such as pediatric neuro-oncologists, neuro-oncologists, pediatric oncologists, adult oncologists. Specific adverse events that should be monitored include skin toxicity, gastrointestinal symptoms, epistaxis, weight gain, paronychia, fevers, pancreatitis, cardiotoxicity, ophthalmologic toxicity.

CLINICAL REVIEW

Methods

We conducted a systematic review to identify RCT evidence for dabrafenib and trametinib for the treatment of pediatric and young adult patients for first-line or greater therapy in LGGs with residual disease and with known *BRAF* V600 mutations. Studies were selected according to the eligibility criteria in Table 2.

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 group inputs. Selected outcomes are those considered relevant to expert committee deliberations. Detailed methods for literature searches, study selection and data extraction are in Working Papers in Appendix 2.

Table 2: Systematic Review Eligibility Criteria

Criteria	Description
Population	Pediatric and young adult patients[a] for first-line or greater therapy in low-grade gliomas with residual disease and with known *BRAF* V600 mutations
Intervention	Pediatric patients, 1 year to <18 years of age, recommended dosages for dabrafenib and trametinib based on weight ranges[b] Adult patients, ≥18 years of age: Dabrafenib: 150 mg oral, twice daily Trametinib: 2 mg oral, once daily
Comparator[c]	• Carboplatin plus vincristine • Vinblastine • Dabrafenib

Outcomes	**Efficacy outcomes:**
	• Overall survival
	• Progression-free survival
	• Overall response rate
	• Clinical Benefit rate
	• Duration of response
	• Time to response
	• Health-related quality of life (with preference for disease-specific measures)
	• Functional outcomes (e.g., vision)
	
	Safety outcomes:
	• AEs, SAEs, AEs of grade ≥3, discontinuation due to AE, deaths
	• Adverse events of special interest:
	  ○ Left ventricular dysfunction
	  ○ Retinal pigment epithelial detachment, Retinal vein occlusion
	  ○ Interstitial lung disease
	  ○ Skin toxicity
	  ○ Venous thromboembolism
	  ○ Major hemorrhagic events

	○ Non-infectious febrile events ○ Teratogenicity
Study design	Published phase II, III, and IV clinical trials

AE = adverse event; BRAF = protein kinase B-raf; SAE = serious adverse event

[a] Young adult was defined as an individual aged 18-39 years as suggested by drug plan and clinical expert input.

[b] Recommended dosages for dabrafenib and trametinib for pediatric patients are as per product manographs. See Working papers for dosing tables.

[c] Vemurafenib, a first generation BRAF inhibitor was initially considered for evaluation and listed in the proposed scope document CDA-AMC. However, clinical experts advised that it is no longer used in practice and would not be a relevant comparator. It was removed from the protocol as out of scope for the review.

Clinical Evidence

An information specialist conducted a peer reviewed literature search of key bibliographic databases, trial registries, and grey literature sources. The initial search was completed on October 30, 2024, with alerts maintained until the Formulary Management Expert Committee meeting on March 20, 2025. Refer to the Working Papers for detailed search strategies.

From the search of databases and registers for primary studies, we identified 106 unique records. After screening titles and abstracts, 94 records were excluded. The full text of 12 records were reviewed and 3 reports corresponding to 2 studies were included. No additional relevant records were identified via other sources.

A list of excluded studies, including reasons for exclusion, is in the Working Papers document in Table 7.

Systematic Review

Description of Studies

Study Characteristics

Characteristics of the included studies are summarized in Table 3.

Bouffet et al. trial[14] and the Rare Oncology Agnostic Research (ROAR) LGG trial[15,16] were both Phase 2 open-label multicentre trials evaluating dabrafenib plus trametinib in BRAF V600 mutation-positive LGG sponsored by Novartis, but with key differences in the study design, patient population, stage of treatment and geographic scope. Bouffet et al. was a multicentre randomized open-label trial comparing efficacy and safety of dabrafenib in combination with trametinib to carboplatin and vincristine as first line therapy in the pLGG with BRAFV600 mutations. The ROAR study was single arm, multicentre basket trial in nine cohorts of patients with recurrent or refractory BRAF V600E mutated cancers, including LGG. The population was restricted to only children in the Bouffet et al. study (N=110) enrolled at 58 sites across 20 countries compared to only adult patients in the ROAR LGG trial (N=13) enrolled at 10 sites in 8 countries. Both trials included study sites in Canada.

Table 3: Characteristics of Studies Included in the Systematic Review

Study name, design, and sample size	Key inclusion criteria	Key exclusion criteria	Intervention and comparator	Relevant end points
Bouffet et al. 2023 Phase 2 open-label, multicentre randomized trial[a] N = 110	• Patients aged 1-17 years, diagnosed with LGG with BRAF V600 mutations and confirmed by RANO-LGG criteria • Nonsurgical patients scheduled to begin	• Malignancy other than BRAF V600 mutant LGG. • Previous treatment with another RAF inhibitor, MEK inhibitor, or ERK inhibitor.	**Intervention:** Dabrafenib: oral, 2 equal doses per day for patients: • < 12 years of age: 5.25 mg/kg/day • ≥ 12 years of age: 4.5 mg/kg/day	**Primary end point:** Independently assessed ORR **Secondary end points:** • Investigator-assessed ORR • CBR

Study name, design, and sample size	Key inclusion criteria	Key exclusion criteria	Intervention and comparator	Relevant end points
	first-line systemic therapy or patients with progressive disease after surgery	• Any systemic anticancer therapy • Radiation therapy to CNS glioma	Trametinib: oral, once daily for patients: • < 6 years of age: 0.032 mg/kg/day • ≥ 6 years of age: 0.025 mg/kg/day **Comparator:** Carboplatin plus vincristine[b]	• DOR • Time to response • PFS • OS • PROs and HRQoL using PROMIS Parent proxy Global Health 7+2 scale • Visual acuity[c] • Harms • Exploratory outcome - baseline biomarker assessment
ROAR trial[d] – LGG Wen et al. 2022 Subbiah et al. 2023 Phase 2, multicentre, open-label, single-arm, basket trial N = 13 with LGG	• Patients aged ≥18 with measurable non-enhancing disease (except pilocytic astrocytoma) using the RANO LGG criteria • Patients with BRAF V600E mutation with confirmed recurrent or progressive LGG • Grade 1 LGG required to be symptomatic and evaluated by central panel of neuro-oncologists • Grade 2 LGG ineligible for chemotherapy	• Previous treatment with BRAF and/or MEK inhibitor • Chemotherapy, immunotherapy, biologic or chemoradiation within prior 21 days • Chemotherapy or biologic without evidence of delayed toxicity within 14 days prior to enrollment • Radiotherapy within 3 months before enrolment • Enzyme-inducing anticonvulsants within 2 weeks before enrolment.	**Intervention:** Dabrafenib 150 mg orally twice daily and trametinib 2 mg orally once daily **Comparator:** No comparator – single arm trial	**Primary end point:** Investigator assessed ORR **Secondary end points:** • PFS • DOR • OS • Harms

BRAF = protein kinase B-raf; CBR= clinical benefit rate; CNS = central nervous system; DOR = duration of response; ERK = extracellular regulated kinase; HRQoL = health-related quality of life; LGG = low-grade glioma; MEK = mitogen-activated protein kinase-ERK kinase; ORR = overall response rate or objective response rate; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcome; RAF = rapidly accelerated fibrosarcoma; RANO = Response Assessment in Neuro-Oncology; ROAR = Rare Oncology Agnostic Research.

[a] The study was part of a larger glioma trial that was designed and conducted in two cohorts of pediatric glioma, one low-grade glioma and one high-grade glioma.

[b] Carboplatin and vincristine was dosed according to the doses and schedule used in the Children's Oncology Group A9952 trial.[8]

[c] Change from baseline in visual acuity data were protocol-specified for collection but analyzed post hoc in a subgroup of patients with suprasellar, chiasmatic, or hypothalamic tumours (N = 25 on dabrafenib plus trametinib and N = 11 on chemotherapy).

[d] ROAR study was a basket trial conducted in nine cohorts of patients with BRAFV600E mutation-positive rare cancers, including anaplastic thyroid carcinoma, biliary tract cancer, gastrointestinal stromal tumour, adenocarcinoma of the small intestine, low-grade glioma, high-grade glioma, hairy cell leukemia, and multiple myeloma. The ROAR study enrolled participants from 27 sites in 13 countries.

Sources: Bouffet et al. (2023),[14] Wen et al. (2022),[15] Subbiah et al (2023).[16]

Patient Disposition

Patient disposition for the Bouffet et al. trial[14] is presented in Figure S1 supplementary appendix of the article. Patient disposition for the ROAR LGG study is presented in Subbiah et al. (2023)[16] Extended data Figure 1.

In the Bouffet et al. trial, pediatric patients were screened for eligibility and 110 patients were randomized in a 2:1 ratio to dabrafenib plus trametinib (N = 73) or to chemotherapy with carboplatin plus vincristine (N = 37). Four patients randomized to the chemotherapy arm withdrew from the study before receiving treatment due to a decision by the parent or guardian (3 patients) or by the physician investigator (1 patient). At the data cut off on August 23, 2021, 61 of 73 patients (83.6%) remained on dabrafenib plus trametinib and 8 of 37 patients (21.6%) remained on chemotherapy. Of the patients assigned to receive treatment, 12 of 73 patients (16.4%) in the dabrafenib plus trametinib group and 16 of 37 patients (43.2%) in the chemotherapy group discontinued treatment. The most common reason for treatment discontinuation was progressive disease in both groups (6.8%in the dabrafenib plus trametinib group and 24.3% for chemotherapy). Nine of 37 patients in the chemotherapy arm (24.3%) had progressive disease and crossed over to the dabrafenib plus trametinib group.

ROAR was a single arm, non-randomized basket trial that enrolled 13 adult patients with BRAF V600E-mutated LGG. At the data cutoff of September 14, 2020, five patients (38%) were still receiving treatment, one patient (8%) was in follow-up, three patients (23%) had withdrawn consent to participate, and four patients (31%) had died due to disease progression. As of the data cutoff date of December 10, 2021, the 6 remaining patients (46%) had completed the study (sponsor terminated the study).

Baseline Characteristics

The key patients' baseline characteristics from each included study are outlined in Table 4. Detailed baseline characteristics can be found in Bouffet et al. (2023) Table 1, Wen et al. (2022) Table 1, and Subbiah et al. (2023) Table 1.

Table 4: Summary of Baseline Characteristics of Studies Included in the Systematic Review

Characteristic	Bouffet et al. (2023)		ROAR trial
	Dabrafenib plus Trametinib (N = 73)	Chemotherapy (N = 37)	Dabrafenib plus Trametinib (N = 13)
Age, median (range), years	10.0 (1 to 17)	8.0 (1 to 17)	33 (18 to 58)
1 to <6, n (%)	20 (27)	14 (38)	0
6 to <12, n (%), n (%)	25 (34)	11 (30)	0
12 to <18, n (%)	28 (38)	12 (32)	0
Sex, Male, n (%)	29 (40)	15 (41)	4 (31)
Race, n (%)			
White	55 (75)	25 (68)	10 (77)
Asian	5 (7)	3 (8)	3 (23)
Black or African American	2 (3)	3 (8)	0
Unknown	6 (8)	4 (11)	0
Other	3 (4)	1 (3)	0
Missing	2 (3)	1 (3)	0
Karnofsky-Lansky or ECOG performance status, n (%)[a]			
100	40 (55)	18 (49)	ECOG 0 = 5 (38)
90	20 (27)	9 (24)	ECOG 1 = 7 (54)
80	5 (7)	2 (5)	ECOG 2 = 1 (8)
70	3 (4)	3 (8)	—
<70	2 (3)	0	—
Missing	3 (4)	5 (14)	—

Characteristic	Bouffet et al. (2023)		ROAR trial
	Dabrafenib plus Trametinib (N = 73)	Chemotherapy (N = 37)	Dabrafenib plus Trametinib (N = 13)
Previous anticancer treatment, n (%)			
Any therapy	62 (85)	29 (78)	13 (100)
Surgery	62 (85)	29 (78)	13 (100)[b]
Radiotherapy	0	0	8 (62)
Systemic treatment (biologic or chemotherapy)	1 (1)[c]	0	7 (53)
Missing	0	3 (8)	0
Histological grade at initial diagnosis, n (%)[d]			
Grade 1	60 (82)	28 (76)	6 (46)
Grade 2	12 (16)	8 (22)	7 (54)
Missing	1 (1)[e]	1 (3)[e]	0
Time since diagnosis, median (range), months or years	4.9 months (0.9−199.9)	2.4 months (0.7−62.2)	6.9 years (0.1−25.6)
BRAF mutation status, n (%)[f]			
V600E	70 (96)	35 (95)	8 (62)
Nonmutant	0	1 (3)[g]	2 (15)
Other	3 (4)[h]	0	NR
Missing	0	1 (3)[i]	NR
Insufficient samples or invalid results	NR	NR	3 (23)

BRAF = protein kinase B-raf; ECOG =Eastern Cooperative Oncology Group; NR = not reported.

[a] Karnofsky performance status and Lansky performance status apply to patients aged ≥16 years and <16 years, respectively in the Bouffet et al. study. ECOG was used to assess performance status in the ROAR study.

[b] One patient was reported to have biopsy only, while 12 patients had undergone resection.

[c] Patient received steroids for symptom control >4 weeks prior to study entry; patient met eligibility criteria.

[d] Histological data were investigator determined at initial diagnosis and may not necessarily reflect histology at study entry.

[e] Data were not reported by the institution.

[f] For Bouffet et al. study, local BRAF status is presented when available; 4 patients were enrolled based on centrally determined BRAF status. For ROAR study, BRAF mutation status was locally assessed or confirmed at central reference laboratory.

[g] One patient discontinued participation in the trial after confirmation of non-BRAF V600 mutation.

[h] Three patients had local BRAF status of "other" after it had been centrally determined as V600E.

[i] One patient withdrew consent prior to treatment with no local result entered and prior to central result analysis

Sources: Bouffet et al. (2023),[14] Wen et al. (2022),[15] Subbiah et al. (2023).[16]

Treatment Exposure and Concomitant Medications

The median duration of treatment exposure to dabrafenib was 17.4 months (range, 0.6 to 34.4) and to carboplatin was 7.8 months (range, 2.8 to 16.1) in the Bouffet et al. study. Exposure data to trametinib and vincristine were not reported; however, the article stated that exposures to trametinib and vincristine were similar to those with dabrafenib and carboplatin, respectively. In the ROAR LGG study, as of the data cutoff date of September 12, 2020 the mean duration of exposure to dabrafenib was 27.3 months (SD 20.6) and to trametinib was 26.7 months (SD 20.9). The mean duration of exposure as of the data cutoff date of December 10, 2021 was only reported for all cohorts and not specifically for the LGG cohort.

Data on adherence or concomitant medications were not reported for either study.

The ROAR LGG study reported that 4 patients received subsequent anticancer therapy: all 4 received radiation, 3 had surgery, 2 received chemotherapy (temozolomide and vinblastine), and 1 was treated with bevacizumab. Data on subsequent therapies were not reported in the Bouffet et al. study.

Results

Efficacy

Results for efficacy outcomes important to this review are presented in Tables 5 and 6. Kaplan-Meier curve for PFS as reported for the Bouffet et al. trial is displayed in Figure 1. Kaplan-Meier curves for PFS and OS for the ROAR LGG trial is displayed in Figure 2.

Key efficacy results from the Bouffet et al. study (Table 5 and Figure 1) include the following:

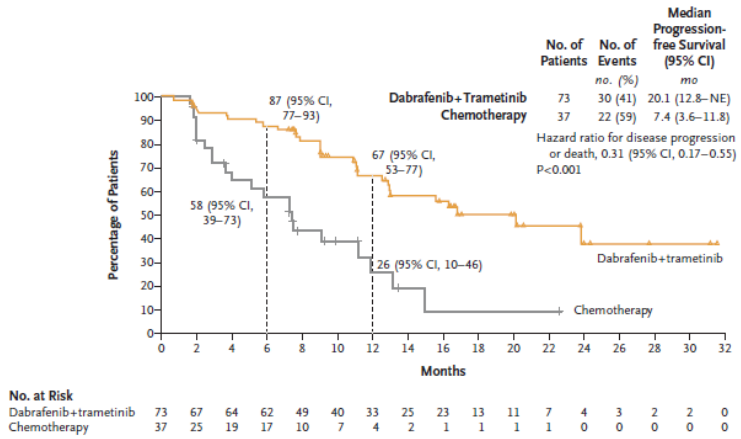
- As of the data-cutoff date of August 23, 2021, the median follow-up was 18.9 months (range, 7.9 to 35.4 months).
- No deaths occurred in patients treated with dabrafenib and trametinib and one patient died from LGG in the chemotherapy group. This patient had crossed over to receive dabrafenib plus trametinib for 22 weeks and died 23 days after the last crossover dose. Overall survival was not estimated because of the lack of events.
- The Kaplan-Meier estimated probabilities of PFS as determined by the independent review at 6 months and 12 months, respectively, were higher in the dabrafenib and trametinib group (87% and 67%) than in the chemotherapy group (58% and 26%). The median PFS was 20.1 months (95% CI 12.8 to NE) and 7.4 months (95% CI 3.6 to 11.8) in the dabrafenib and trametinib group as compared with the chemotherapy group, respectively. The hazard ratio for PFS favoured dabrafenib and trametinib over chemotherapy (HR 0.31, 95% CI 0.17 to 0.55)..
- Dabrafenib plus trametinib improved the ORR (47%, 95% CI 35% to 59%]) compared to chemotherapy (11%, 95% CI 3% to 25%) according to independent assessment.
- More patients treated with dabrafenib and trametinib (86%, 95% CI 76% to 93%) achieved clinical benefit (defined as complete or partial response or stable disease for ≥ 24 weeks) as per independent assessment compared to those treated with chemotherapy (46%, 95% CI 30% to 63%).
- The timing of first response was presented per patient in each treatment group; no summative data were reported. The article narratively reported that most tumour responses (according to both independent and investigator assessment) occurred within 4 months after randomization in patients who received dabrafenib plus trametinib. Visual inspection of the figure provided in the article suggests the same timing of response happened for patients who responded to chemotherapy.
- Kaplan-Meier estimated median duration of tumour response was 20.3 months with dabrafenib and trametinib but was not evaluable for the chemotherapy group.
- In the best case, the proportion of patient eyes that improved post-baseline was higher in the dabrafenib plus trametinib group than in the chemotherapy group, and the proportion of eyes that worsened or remained stable postbaseline were lower in the dabrafenib plus trametinib group. However, no statistical testing or confidence intervals were calculated to aid comparison between the treatment groups.
- Improvements in health-related quality of life (HRQoL) — based on parental observation using the PROMIS Parent Proxy Global Health 7+2 questionnaire —were observed for the dabrafenib and trametinib group out to week 104, whereas worsening HRQoL was observed in the chemotherapy group out to week 56. Data were presented graphically only; no summary statistics or between group differences in scores were reported.

Key efficacy results from the ROAR LGG trial (Table 6 and Figure 2) include the following:

- The median patient follow-up duration was 32.2 months (IQR 25.1 to 47.8) as of the data cutoff date of September 12, 2020, The median patient follow-up duration was reported across all cohorts and was not specified for the LGG cohort at the December 10, 2021 data cutoff date.
- Four patients died in the LGG cohort. Overall survival could not be estimated because of the small number of events.

- Median PFS was 9.2 months (95% CI 4.7 to 33.0) by independent assessment as of the December 10, 2021 data cutoff. Eight patients had disease progression and one died without disease progression.
- Of 13 patients with recurrent or relapsed LGG treated with dabrafenib plus trametinib, 7 patients (54%; 95% CI 25% to 81%) had an ORR by independent review as of the data cutoff date of December 10, 2021.
- Median duration of response by independent assessment was 19.4 months (95% CI 3.8 to not reached) as of December 10, 2021.
- Time to response, clinical benefit (CR + PR + stable disease), and HRQoL outcomes were not reported.

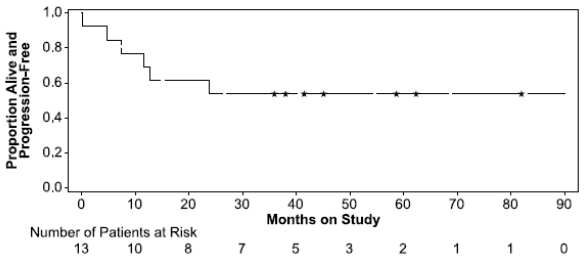
Figure 1: Progression-free Survival in Dabrafenib Plus Trametinib and Chemotherapy groups in Bouffet et al. (2023) study



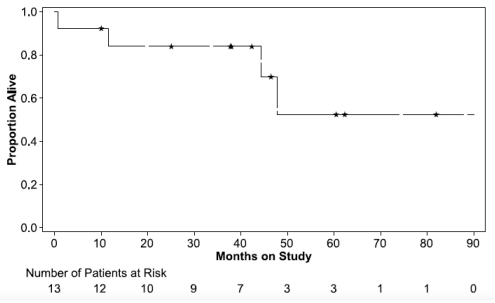
CI = confidence interval. NE = not evaluable. Progressive-free survival was measured in the two trial groups by independent review according to RANO criteria. The vertical dashed lines indicate the values at 6 months and 12 months.
Source: Bouffet et al. (2023) From *N Engl J Med*, Bouffet E et al., Dabrafenib plus Trametinib in Pediatric Glioma with *BRAF* V600 Mutations, 389(12), 1180-1120. Copyright © (2025) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Figure 2: Progression-free Survival and Overall survival Dabrafenib plus Trametinib in ROAR LGG study

A. Progression-free survival



B. Overall survival



Source: Subbiah V, et al., Copyright 2023. This work is licensed under the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

Table 5: Summary of Key Efficacy Results for Bouffet et al. (2023)

Outcome[a]	Bouffet et al. (2023)			
	Dabrafenib + Trametinib (N = 73)	Chemotherapy (N = 37)	Dabrafenib + Trametinib (N = 73)	Chemotherapy (N = 37)
	Independent Assessment		Investigator Assessment	
Overall survival				
Number of patients who died, n	No deaths in dabrafenib plus trametinib group 1 death in chemotherapy group (from low-grade glioma)			
Progression-free survival (PFS)				
Number of patients with PFS Events, n (%)	30 (41)	22 (59)	9 (12)	9 (24)
PFS, median (95% CI) months[b]	20.1 (12.8 to NE)	7.4 (3.6 to 11.8)	NE (NE to NE)	NE (12.6 to NE)
HR (95% CI)[c]	0.31 (0.17 to 0.55)		0.37 (0.14 to 0.93)	
P value[d]	< 0.001		NR	
PFS, % (95% CI) at 6 months[b]	87 (77 to 93)	58 (39 to 73)	93 (84 to 97)	77 (58 to 88)
PFS, % (95% CI) at 12 months[b]	67 (53 to 77)	26 (10 to 46)	91 (81 to 96)	74 (54 to 86)
Overall response rate (CR+PR)[e]				
Follow-up time, median (range), months	18.9 months (7.9 to 35.4)			
Complete response, n (%)	2 (3)	1 (3)	3 (4.1)	0
Partial response, n (%)	32 (44)	3 (8)	37 (50.7)	5 (13.5)
Stable disease, n (%) [f,g]	30 (41)	15 (41)	28 (38.4)	18 (48.6)
Progressive disease, n (%)	8 (11)	12 (32)	4 (5.5)	7 (18.9)
Unknown response, n (%)	1 (1)[h]	6 (16)[i]	1 (1.4)	7 (18.9)
Number of patients with ORR (%; 95% CI)	34 (47; 35 to 59)	4 (11;3 to 25)	40 (55; 43 to 67)	5 (14; 5 to 29)
Odds Ratio (95% CI)[j]	7.19 (2.30 to 22.40)		7.76 (2.7 to 22.2)	
Risk Ratio (95% CI)[j]	4.31 (1.70 to 11.20)		4.05 (1.8 to 9.4)	
P value[k]	< 0.001		< 0.001	
Clinical benefit rate (CR + PR + Stable disease)[l]				
Number of patients, n (%; 95% CI)	63 (86; 76 to 93)	17 (46; 30 to 63)	67(92; 83 to 97)	22 (60; 42 to 75)
Odds Ratio (95% CI)[j]	7.41 (2.90 to 18.80)		7.61 (2.6 to 22.0)	
Risk Ratio (95% CI)[j]	1.88 (1.30 to 2.70)		1.54 (1.2 to 2.0)	
P value[k]	< 0.001		< 0.001	
Duration of response				
Disease progression or death in patients with response, n (%)	10 (29)	2 (50)	1 (2.5)	1 (20.0)
Duration of response, median (95% CI) months[b]	20.3 (12.0 to NE)	NE (6.6 to NE)	NE (25.5 to NE)	NE (5.3 to NE)
Patients with continuing response, % (95% CI)[b]	86 (66 to 94)	100 (100 to 100)	NR	NR

Outcome[a]	Bouffet et al. (2023)			
	Dabrafenib + Trametinib (N = 73)	Chemotherapy (N = 37)	Dabrafenib + Trametinib (N = 73)	Chemotherapy (N = 37)
At 6 months				
At 12 months	70 (46 to 85)	50 (6 to 85)	100	80 (20.4 to 96.9)
At 24 months	NR	NR	100	NE (NE to NE)
Change in Visual Acuity in patients with suprasellar, chiasmatic, or hypothalamic tumours in the Safety Analysis Set[m,n]				
	Dabrafenib + Trametinib (N=25)		**Chemotherapy (N=11)**	
Best case post baseline, n	41		18	
Improved	14 (34.1)		2 (11.1)	
Stable	26 (63.4)		14 (77.8)	
Worsened	1 (2.4)		2 (11.1)	
Worst case post baseline, n	41		18	
Improved	6 (14.6)		1 (5.6)	
Stable	25 (61.0)		9 (50.0)	
Worsened	10 (24.4)		8 (44.4)	

CBR, clinical benefit rate; CI = confidence interval; CR = complete response; DOR = duration of response; HR = hazard ratio; NE = not evaluable; NR = not reported; OR = odds ratio; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RR = risk ratio.

[a] Based on data cutoff date of August 23, 2021

[b] PFS and DOR outcomes were estimated using Kaplan-Meier method.

[c] Hazard ratios for PFS was estimated using unstratified and unadjusted Cox proportional hazards model.

[d] P value was computed using the log-rank test at the one-sided 2.5% level of significance.

[e] The primary end point was independently-assessed tumour ORR assessed centrally.

[f] Stable disease for 16 weeks or longer was recorded at 15 weeks or later (i.e., ≥ 105 days) from treatment start date.

[g] Scans meeting the criteria for minor response were categorized as stable disease for this trial.

[h] One patient had stable disease or unconfirmed complete or partial response that occurred before the week 16 visit.

[i] Four patients did not have a valid post baseline assessment. Two patients had stable disease or unconfirmed complete or partial response that occurred before the week 16 visit.

[j] Odds ratio (dabrafenib + trametinib vs chemotherapy) and two-sided 95% CI are from a logistic regression with treatment as the only covariate. For both odds and risk ratios >1 favors dabrafenib + trametinib.

[k] The P values were computed using χ 2 test (Mantel-Haenszel) at a one-sided 2.5% level of significance.

[l] Stable disease for 24 weeks or longer was recorded at 23 weeks or later (i.e., ≥ 161 days) from treatment start date.

[m] Improved = 0.2 logMAR improvement; stable = neither 0.2 logMAR improvement nor worsening; worsening = 0.2 logMAR worsening

[n] Percentages are taken from the n at each time point, which corresponds to the number of eyes (left and right), not the number of patients

Sources: Bouffet et al. (2023),[14] Bouffet et al. (2023)[14] supplementary materials.

Table 6: Summary of Key Efficacy Results for ROAR LGG trial

Outcome[a]	ROAR LGG trial	
	Dabrafenib + Trametinib (N = 13)	
	Independent Assessment	Investigator Assessment
Overall survival		
Number of patients who died, n	4 (due to disease progression)	
Median OS, months (95% CI)	NE	
Progression-free survival		
Number of patients with PFS Events, n (%)	9 (69)[b]	6 (46)[c]
PFS, median (95% CI) months	9.2 (4.7 to 33.0)	NE
Objective response rate (CR + PR)[d]		
Follow-up time, median (range), months	NR	
Complete response, n (%)	1 (8)	1 (8)
Partial response, n (%)	6 (46)	6 (46)
Minor response, n (%)	1 (8)	2 (15)
Stable disease, n (%)	2 (15)	3 (23)
Progressive disease, n (%)	0	1 (8)
Not evaluable	3 (23)[e]	0
Number of patients with ORR (%; 95% CI)	7 (54; 25 to 81)	7 (54; 25 to 81)
Duration of response[f]		
Disease progression or death in patients with response, n (%)	7 (88)	2 (22)
Median duration of response, months (95% CI)	19.4 (3.8 to not reached)	Not reached (5.5 to not reached)

CI = confidence interval; CR = complete response; DOR =, duration of response; HR = hazard ratio; NE = not evaluable; NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response.

[a] This analysis was conducted in the intention to treat evaluable population (N=13) based on data cutoff date of December 10, 2021.

[b] By independent radiology review, nine (69%) patients had disease progression, and one (8%) patient died without disease progression. Three (23%) patients were censored due to end of follow-up.

[c] By investigator assessment in 13 patients, six (46%) patients had disease progression. Seven (54%) patients were censored due to end of follow-up.

[d] The primary end point was investigator-assessed ORR. Both independent and investigator assessments of tumour response were performed in the trial

[e] Three patients were not evaluable by independent review. One patient had no measurable disease at baseline, and another had no post-baseline assessments.

[f] Confirmed responders by independent assessment (N=8) and investigator assessment (N=9)

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

Harms

Detailed results for harms for each included study are in the following publications: Bouffet et al. (2023) Table 3, Subbiah et al. (2023) Table 4, Extended Data Table 1, Extended Data Table 4.

Key harms results from the Bouffet et al. study (Table 7) include the following:

- All patients (100%) in the Bouffet study were reported to have at least one AE.
- Fewer patients in dabrafenib plus trametinib group than in the chemotherapy group had adverse events of grade 3 or higher (47% vs. 94%).

- Serious adverse events (SAEs) were reported at a similar rate in dabrafenib plus trametinib group than the chemotherapy (40% vs. 39%).
- Treatment discontinuation due to adverse events occurred at a lower rate with dabrafenib plus trametinib group than with chemotherapy (4% vs.18%) in Bouffet et al. trial
- No deaths coded as AEs were reported in the trial.
- Most common AEs in the Bouffet study in the dabrafenib plus trametinib vs chemotherapy groups were: pyrexia (68% vs 18%), headache (47% vs. 27%), vomiting (34% vs. 48%), fatigue (32% vs. 30%).
- Some adverse events of special interest (AESI) were reported in the Bouffet et al. study. Skin toxicity, including dry skin and rash occurred more frequently with dabrafenib plus trametinib than chemotherapy (e.g., dry skin: 26% vs. 3%). Likewise, pyrexia occurred at a higher rate with dabrafenib plus trametinib than with chemotherapy.
- No AEs related to major hemorrhagic events were reported in the studies. Fifteen (21%) patients in the dabrafenib plus trametinib group and 1 (3%) patient in chemotherapy group of the Bouffet et al. study had epistaxis reported as an AE.

Key harms results from the ROAR LGG study (Table 8) include the following:

- Almost all patients (92%) in the ROAR LGG study were reported to have at least one AE.
- Grade 3 or higher AEs occurred but no aggregate data for the LGG cohort was reported at the latest data cut off December 10, 2021 in the Subbiah et al. article.
- Three patients (23%) in the ROAR LGG trial experienced SAEs.
- Treatment with dabrafenib plus trametinib was discontinued for two patients due to AEs.
- No death coded as AEs was reported in the LGG cohort.
- Out of the adverse events of special interest, no patient was reported to experience interstitial lung disease and venous thromboembolism.
- Skin toxicity occurred in almost all patients in the ROAR trial (84.6%). Unspecified ocular events and unspecified bleeding events were reported as AEs. Uveitis was reported in one patient (8%). Cardiac-related events were reported in one patient (8%) in the Subbiah et al study.

Table 7: Summary of Key Harms for Bouffet et al. trial

Variable	Bouffet et al. (2023)	
	Dabrafenib plus Trametinib (N = 73)	Chemotherapy (N = 33)
Any AEs, n (%)	73 (100)	33 (100)
Serious adverse events, n (%)	29 (40)	13 (39)
Grade ≥3 adverse event, n (%)	34 (47)	31 (94)
Discontinuation due to adverse event, n (%)	3 (4)	6 (18)
AESI, n (%)		
Left ventricular dysfunction	NR	NR
Retinal pigment epithelial detachment	NR	NR
Retinal vein occlusion	NR	NR
Interstitial lung disease	NR	NR
Venous thromboembolism	NR	NR

Variable	Bouffet et al. (2023)	
	Dabrafenib plus Trametinib (N = 73)	Chemotherapy (N = 33)
Major hemorrhagic events (bleeding events)	NR	NR
Pyrexia	50 (68)	6(18)
Skin toxicity		
Dry skin	19 (26)	1 (3)
Rash	14 (19)	3 (9)

AE = adverse event; AESI = adverse event of special interest; NR = not reported

Source: Bouffet et al. (2023)[14]

Table 8: Summary of Key Harms for ROAR LGG trial

Variable	ROAR LGG trial
	Dabrafenib plus Trametinib (N = 13)
Any AEs, n (%)	12 (92.3)
Serious adverse events, n (%)	3 (23.1)
Grade ≥3 adverse event, n (%)	NR[a]
Discontinuation due to adverse event, n (%)	2 (15)
AESI, n (%)	
Left ventricular dysfunction	NR[b]
Retinal pigment epithelial detachment	NR
Retinal vein occlusion	NR
Interstitial lung disease	0
Bleeding events	3 (23.1)
Teratogenicity	NR
Venous thromboembolism	0
Pyrexia	10 (76.9)
Skin toxicity	11 (84.6)
Ocular events	7 (53.8)

AE = adverse events; AESI = adverse event of special interest; NR = not reported

[a] Grade 3 or higher AEs occurred but no aggregate data for the LGG cohort was reported at the latest data cut off December 10, 2021 in the Subbiah et al. Article.

[b] Unspecified cardiac-related event was reported in one patient.

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

Critical Appraisal

Internal Validity

In the Bouffet RCT, randomization was achieved using Interactive Response Technology and procedures that helped conceal allocation. Due to the relatively small sample sizes and 2:1 randomization ratio some differences between treatment groups for baseline characteristics are possible although not clinically meaningful (age, race, performance status, previous anticancer treatment, histological grade at diagnosis, and time since diagnosis). The clinical experts consulted by CDA-AMC did not expect the observed imbalances to significantly affect the results of the trial. It is possible that the reported treatment effects in the trial under- or over-estimate the real effect of dabrafenib plus trametinib versus chemotherapy.

There is a potential risk of bias related to missing data at baseline assessments. Missing data accounted for 1% to 14% patients on various characteristics including performance status, previous anticancer therapy, histologic grade at initial diagnosis, BRAF mutation status in the Bouffet trial. Whether the missing data led to bias and the influence on the study result is unclear.

Dose modifications and dose delay were appropriately specified in the Bouffet et al. study protocol and reflected recommended actions based on adverse events per the respective product monographs and labels for each of the drug treatments administered. The percentages of patients who required dose reduction or dose interruption were similar between the treatment arms and primarily the result of adverse events. Only 1 patient permanently discontinued treatment for a protocol deviation in the chemotherapy group. Thus, the observed dose modifications, delays, and discontinuations were consistent with expected harms profiles and did not introduce significant imbalances between treatment arms that could have confounded the study outcomes. One patient (in the dabrafenib plus trametinib arm) discontinued therapy for a new anticancer treatment. Nine patients with centrally confirmed disease progression crossed over to receive dabrafenib plus trametinib. The degree to which crossover may have influenced overall survival is not clear; however, given the small numbers, few deaths, and crossover from chemotherapy to dabrafenib plus trametinib would potentially bias toward the null, it is unlikely that crossover had a significant impact on the results. Overall, there is no clear evidence of deviations to the interventions that would influence results in a clinically meaningful manner.

Handling of missing data in the Bouffet et al. trial was described in the supplemental statistical analysis plan for the secondary outcomes of duration of response and PFS, and in the supplemental material for the article related to scoring the PROMIS Parent Proxy Global Health 7+2 questionnaire. The censoring rules in Bouffet et al. potentially introduce a high risk of bias by systematically excluding patients who discontinue treatment early, switch therapy, or have missing assessments. For example, one of the censoring rules states that patients with two or more missing tumour assessments before disease progression or death were censored, meaning their data was excluded from the analysis. This is problematic because disease progression can often correlate with missed assessments (e.g., due to worsening condition, treatment discontinuation, or clinical deterioration). If missing assessments are more frequent in one treatment arm, this could artificially inflate the estimated duration of response or PFS for that group by selectively removing high-risk patients. No sensitivity analyses testing alternative approaches for handling missing data were specified or reported. The number of patients per group for whom this approach applied to was not reported. Therefore, it is unknown what potential impact this may have had on the results. Regarding the analysis of the PROMIS Parent Proxy Global Health 7+2 questionnaire, it was reported that handling of missing data was according to the user guide for the instrument and that no imputation was applied for missing data and results. The article and related supplemental material did not report how many patients in each group contributed to the baseline assessment. By week 5, data were gathered from 48 of 73 patients in the dabrafenib plus trametinib group and from 16 of 37 patients in the chemotherapy group (as per Figure S7, Bouffet et al. supplemental material). The number of patients with data at week 56 (the last assessment for the chemotherapy group) was 30 and 4, respectively. Combined with the lack of summary statistics and between group statistical testing, the number of missing evaluations makes interpreting the HRQoL data very difficult and no conclusions regarding the effects of either treatment on this outcome are appropriate.

Other censoring rules had the potential to influence the results of the Bouffet et al. trial. For example, if a patient started a new anticancer therapy before documented progression, they would be censored at the last adequate tumour assessment. This approach assumes that patients who switch therapy before documented progression are no longer at risk of progression under the original treatment, which may systematically exclude poorer responders who required alternative treatment. If treatment switching occurred at different rates between groups, informative censoring could have led to inflated duration of response and PFS, potentially overestimating the apparent treatment benefit. A sensitivity analysis that ignored new anticancer therapy was planned to assess the impact of this censoring rule. However, the results of this analysis were not found in the supplemental materials for the

Bouffet et al. article. While this raises some uncertainty, it is unlikely to be a critical flaw, as only one patient in the trial started a new anticancer treatment before an outcome event occurred.

The ROAR trial was a single-arm, phase 2 basket trial that included LGG as one of the cohorts. The trial lacked a comparator group and makes it challenging to evaluate whether the treatment effect is due to dabrafenib plus trametinib therapy and whether the magnitude of the treatment effect is clinically important. The sample size was very small in the ROAR trial LGG cohort (N = 13), which increases the potential for variability and decreased reliability in the efficacy and harms data. The effect estimates are at high risk of bias and may overestimate efficacy and underestimate the safety outcomes.

Both the Bouffet et al. and ROAR trials were open-label trials that lacked blinding meaning patients and investigators were aware of assigned treatments. Because investigators were aware of treatment in both studies, there was potential for observer bias in outcome assessment (for ORR, clinical benefit, PFS, and DOR) and in investigator decisions regarding treatment due to disease progression. Both trials assessed tumours according to the Response Assessment in Neuro-Oncology (RANO) criteria, which would help consistency and accuracy in tumour assessments. Both Bouffet et al. and ROAR studies reported response-based end points from independent assessments and investigator assessments. Tumour response assessments were primarily done by central independent radiology review with investigator assessed tumours as secondary in the Bouffet et al. trial; the opposite approach was used in the ROAR trial. Estimates of tumour response per independent review tend to be more conservative than those by investigator assessment and are recommended by regulators, especially in open-label trials.[17] The results for ORR by independent review were more conservative in the Bouffet et al. trial; the results for ORR were the same in the ROAR trial, but the estimates of PFS were more conservative with independent review than by investigator assessment. Measuring the degree of concordance between independent and investigator assessment was specified in the statistical analysis plan but was not reported in the Bouffet et al. trial article. The level of concordance in the ROAR trial for the LGG cohort was 46.2%, even though the aggregate results reported for ORR were similar with 7 patients (54%) achieving response as determined by investigator and independent assessment. Use of centralized independent review is an appropriate way to mitigate the potential bias related to the open label design. Results from both trials based on independent review were given greater emphasis by CDA-AMC reviewers because of the reduce risk of bias with this approach to assessing tumour response.

This open label design also makes the patient-reported outcomes and adverse events susceptible to bias reporting bias. Given the limitations associated with the available data related to changes in HRQoL from the Bouffet et al. trial it is hard to determine what impact the open-label design had on this outcome. Because the ROAR trial did not evaluate HRQoL this limitation is not relevant for that study. AEs appeared to be consistent with the well-documented events expected for the treatments used in both trials; however, the relatively small sample sizes make it more difficult to determine whether knowledge of treatment assignment influenced AE reporting.

The efficacy outcomes used in both studies (OS, PFS, ORR, DOR) are standard in oncology trials and as mentioned tumour responses were objectively evaluated using RANO criteria. No major concerns regarding the validity or measurement properties of outcomes were identified, although in the absence of a comparator arm in the ROAR trial and small number of events for overall survival and PFS in both trials makes interpretation of these efficacy results difficult. As well, the link between ORR and overall survival is not well-established. This is in part due to the indolent nature of LGG especially in younger patients, making it difficult to empirically establish the ORR as a surrogate for overall survival.

No adjustments for multiple statistical comparisons were applied in either study.

External Validity

The Bouffet et al. and ROAR LGG studies enrolled predominantly white patients (70% and over) which aligns with the racial diversity of pediatric and young adults commonly encountered in practice. The clinical experts indicated that the study inclusion criteria, which specified patients had to have confirmed LGG diagnosis and BRAF V600 mutation is critical in making treatment decisions and consistent with what would be expected in clinical practice. Clinical experts raised concern over the inclusion of one patient with a diagnosis of choroid plexus papilloma in the ROAR LGG study, which is clinically different from gliomas. No rationale for including a patient with choroid plexus papilloma was reported in the article.

The Bouffet et al. trial enrolled children younger than 18 years of age while the ROAR LGG enrolled adults aged 18 years and older. Therefore, the evidence from the Bouffet et al. trial may be generalizable in terms of age to the target population for reimbursement of dabrafenib plus trametinib. However, it is unclear how well the population enrolled in the ROAR trial represents young adults, which was defined as the age range from 18 to 39 years. The median age in the LGG cohort of that trial was 33 years (range:18 to 58). Because the median represents the midpoint of the age distribution, at least half of the trial participants were 33 or younger. The age distribution was reported in wide ranges across the cohorts; for the LGG cohort all patients were included in the 18-to-64-year category. Thus, without more information about the age distribution above the median it is unclear exactly what fraction of the population was older than 39 years. Nonetheless, the median age of the LGG cohort falls within the defined range for young adults, suggesting that at least half of the participants were in this category.

The Bouffet et al. study used the Karnofsky and Lansky performance status scales to select pediatric patients for the trial while the ROAR LGG trial used the Eastern Cooperative Oncology Group (ECOG) for adults which were applied to the appropriate age group. These scales are validated tools that are widely used to assess the patients' functional capacity and ability to perform activities of daily living. The clinical experts agreed that performance status are standard measures to enroll patients in trials. Outside of trials, they are not the key criteria in deciding to treat patients in clinical practice.

The clinical experts indicated that the dabrafenib and trametinib combination therapy also has been increasingly used as the first-line treatment for BRAF V600 mutated pLGG patients in clinical practice and usually accessed through compassionate access programs. The dosage prescribed is justified using the doses referenced in the Bouffet et al. study. The dosages and administration of dabrafenib plus trametinib used in the ROAR LGG trial for adult patients was aligned to dosing approved by Health Canada. Dose modifications including interruptions, reductions and discontinuation were reported in the Bouffet et al. study. In the ROAR LGG trial, dose adjustments and interruptions were permitted for patients unable to tolerate the protocol-specified dose until tolerability improved. The only data reported from the ROAR trial concerned two patients with treatment discontinuation due to adverse events. In general, the specified procedures for dose adjustments were consistent with what is recommended in the product monographs for dabrafenib and trametinib.

The comparator in the Bouffet et al. trial was chemotherapy, carboplatin and vincristine, which is current standard of care in Canada for LGG as confirmed by clinical experts. However, vinblastine and dabrafenib monotherapy were identified as relevant comparators for this review. No studies were identified comparing dabrafenib plus trametinib to vinblastine and dabrafenib monotherapy in the target population. As mentioned, the ROAR trial was did not include a control group and provides no comparative evidence to inform the review.

Adherence to study treatments and use of concomitant treatments were not reported in the Bouffet et al. trial, so whether these were aligned with clinical practice in Canada is unknown. The ROAR LGG study similarly did not report on adherence and concomitant medications. New anticancer (subsequent) therapies were reported for 4 patients and the treatments were consistent with available options.

Clinically important outcomes were evaluated in the included studies: overall survival, PFS, and ORR. Given the long overall survival of patients with LGG, the clinical experts expressed that ORR and PFS were more applicable primary end points than OS to the patient population. Another limitation of OS as an end point is the slow progression of LGG, requiring extended follow-up times to observe meaningful differences in OS, which may not be feasible within typical clinical trial timeframes.

The consulted clinical experts considered the follow-up durations of the trials to be reasonable evaluating treatment effects on ORR and PFS for LGGs. The experts expressed that functional outcomes, such as vision, and HRQoL were important outcomes because patients with LGG often experience worsening symptoms and declining HRQoL over time, despite surviving. However, only the Bouffet et al. study reported data on visual acuity and global health scores.

The clinical experts noted that the independent review based on the RANO criteria is standard practice, as clinicians rely on radiological and clinical assessments to evaluate treatment response in patients with LGG. However, they also highlighted that applying these criteria in a clinical trial may be more restrictive than in clinical practice setting, which could affect the generalizability of the results of the trials to real-world settings. Additionally, the investigator assessed tumour response outcomes may reflect practice better than the independent review assessed results.

Discussion

Efficacy

The Bouffet et al. trial demonstrated an improvement in progression-free survival when patients received dabrafenib and trametinib compared to chemotherapy with carboplatin and vincristine. Although the between group differences (with 95% CIs) were not reported, the 6- and 12-month probability of PFS were approximately 30% and 40% higher, respectively, in favour of dabrafenib plus trametinib. The clinical experts indicated that the results for PFS are clinically meaningful. The results for PFS were supported by apparently large differences in ORR (36%) and clinical benefit (40%) that the clinical experts also considered important results. Overall survival could not be estimated in the trial because there were no deaths reported for the dabrafenib and trametinib treatment group and one patient died from LGG in the chemotherapy group. Nonetheless, the clinical experts emphasized the importance of PFS as an outcome and achieving a difference in the trial is aligned with treatment goals, especially considering the indolent nature of LGG and the impact tumours have on patients' lives. Likewise, preventing progression and improving tumour response were patient-important outcomes highlighted from the Pediatric Low-Grade Glioma Multi-stakeholder Meeting. Therefore, the results of the Bouffet et al. trial reflect this input for these treatment goals.

Clinical experts indicated that the median follow up times of 19 months in the Bouffet et al. trial was sufficient to observe the key outcomes of interest (PFS and ORR). Although longer duration of follow-up may provide data to capture information on OS, the available evidence suggests that a higher proportion of patients treated with dabrafenib plus trametinib had confirmed response demonstrating efficacy over treatment with chemotherapy.

The ROAR LGG study was a single arm trial of dabrafenib and trametinib and does not provide comparative efficacy data. The study reported that dabrafenib plus trametinib led to 54% ORR in adult patients with recurrent or relapsed BRAF V600E-mutated LGG. The clinical experts noted this result is likely clinically meaningful because they would not expect standard of care chemotherapy to achieve this magnitude of ORR. Moreover, the experts highlighted that observed improvements in the patients with partial response and stable disease were acceptable goals in a setting with limited treatment options. As well, the clinical experts considered the median PFS (by independent review) of greater than 9 months was also likely clinically important. However, the limitations of the trial, especially the lack of a comparator, small sample size, and wide variance in treatment effects as evidenced by wide confidence intervals for median PFS and ORR preclude drawing firm conclusions on the results.

Harms

Across both the Bouffet et al. and ROAR LGG trials, nearly all the patients experienced at least one AE. SAEs occurred at similar frequencies in the dabrafenib plus trametinib and chemotherapy treatment arms in the Bouffet et al. trial, while SAEs were reported in less than 25% of the patients in the ROAR trial. Notably, grade ≥ 3 AEs occurred twice more frequently in the chemotherapy group compared to the dabrafenib plus trametinib group, suggesting a potential advantage with the targeted therapy. Additionally, discontinuations due to adverse events were lower in patients treated with dabrafenib plus trametinib (4%) than patients treated with chemotherapy (18%). This is an important factor for decision-making, especially for a patient population that may require prolonged treatment.

The AE profile of dabrafenib plus trametinib suggests it may be favoured compared to chemotherapy, particularly given the lower frequency of grade 3 or higher AEs and treatment discontinuations. However, the long-term harms of targeted therapy remains an important consideration because LGG patients often have extended survival and may be at risk for cumulative toxicities. Importantly, no deaths coded as AEs were reported in both trials, which is encouraging. However, as emphasized, the available evidence likely does not provide sufficient follow-up to fully understand the longer-term harms associated with dabrafenib plus trametinib in the pediatric and young adult population with LGG.

Conclusion

The Bouffet et al. trial showed that dabrafenib plus trametinib as first-line systemic therapy for pLGG with residual disease and known BRAF V600 mutations may offer benefits in terms of ORR and PFS compared with standard chemotherapy of carboplatin and vincristine. The single-arm ROAR trial with 13 patients suggests dabrafenib plus trametinib has clinical benefit (for ORR) in adult patients with relapsed or recurrent LGG; however, the lack of a randomized comparator and small sample size limits its interpretability. HRQoL data were collected in the Bouffet et al. trial using the PROMIS Parent Proxy Global Health 7+2 scale, but results were only presented graphically without comparative statistics and in a reduced sample of patients, precluding definitive conclusions.

Harms results from Bouffet et al. suggest lower frequencies of discontinuations due to AEs and Grade 3 or greater AEs with dabrafenib plus trametinib compared with chemotherapy. SAEs and any AEs were similar in the treatment groups in the Bouffet et al. trial.

No comparative evidence was identified to assess the relative treatment effects of dabrafenib plus trametinib versus vinblastine or dabrafenib alone for this review.

Economic Review

The economic review consisted of a cost comparison for dabrafenib plus trametinib compared with carboplatin plus vincristine and vinblastine monotherapy for the treatment of adult and pediatric patients as first-line or greater therapy in low-grade gliomas with residual disease and with known BRAF V600 mutations.

For adult patients, based on public list prices, dabrafenib plus trametinib is expected to have a cost of $18,018 per patient per standardized 28-day cycle. (Table 1), while vinblastine monotherapy and carboplatin plus vincristine are expected to have a cost of $764 and up to $1,410 per patient per standardized 28-day cycle, respectively. Therefore, the incremental cost of dabrafenib plus trametinib compared with vinblastine is $17,255 per adult patient per 28 days, and at least $16,608 per adult patient per 28 days compared to carboplatin plus vincristine.

For pediatric patients, no public prices were identified for dabrafenib 10 mg tablets for suspension or for trametinib 4.7 mg per bottle oral solution, both indicated for patients of at least 1 year of age and weighing at least 8 kg. As such, the cost of treatment for patients weighing less than 26 kg or who cannot take regular capsules or tablets is unknown. For pediatric patients weighing at least 26 kg who can take regular capsules or tablets, dabrafenib plus trametinib is expected to have a cost of $9,063 to $18,018 per standardized 28-day cycle, depending on body weight. Vinblastine monotherapy is expected to cost $212 to $764 per 28-day cycle for patients aged 1 to 17 years (with body surface areas between 0.5 and 1.8 m^2) while carboplatin plus vincristine is expected to cost up to $1,410 per 28-day cycle. When considering pediatric patients weighing at least 26 kg and having a body surface area of at least 0.9 m^2 (approximately equivalent to median measures for patients of 8 years of age), the incremental cost of dabrafenib plus trametinib as regular capsules or tablets is expected to range from $7,777 to $16,608 per patient per 28 days compared to carboplatin plus vincristine, and from $8,681 to $17,255 per patient per 28 days compared with vinblastine, depending on patient size and weight.

As such, the reimbursement of dabrafenib plus trametinib for the treatment of adult and pediatric patients as first-line or greater therapy in low-grade gliomas with residual disease and with known BRAF V600 mutations is expected to increase overall drug acquisition costs. Additional items for consideration are provided in the following bullets:

- Evidence from the Bouffet trial[14] demonstrated that, compared to carboplatin plus vincristine, dabrafenib plus trametinib given as first-line systemic therapy to patients with LGG with residual disease and known BRAF V600 mutations may offer clinical benefits in overall response rate and progression-free survival, as well as in withdrawals due to adverse events and Grade ≥3 adverse events.
- The comparative effectiveness of dabrafenib plus trametinib against vinblastine monotherapy is unknown. This limits the ability to evaluate the regimen's relative efficacy and safety across all relevant treatment options available in Canada.

- The patent for trametinib is expected to expire mid-2025.[18] As such, it is possible that one 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-expiring patent for dabrafenib expires in 2029.
- Dabrafenib monotherapy was noted as being a comparator of potential interest according to clinical expert input obtained by CDA-AMC, however it does not currently appear to be funded for the treatment of glioma by public payers. The incremental cost of dabrafenib plus trametinib compared to dabrafenib alone would be $9,580 per adult patient per 28 days, or $4,844 to $9,580 per patient per 28 days, depending on weight, for pediatric patients weighing at least 26 kg.
- 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 October 30th, 2024.

Conclusion

The reimbursement of dabrafenib plus trametinib for the treatment of low-grade glioma is expected to increase overall drug acquisition costs. Based on the clinical review conclusions, dabrafenib plus trametinib may offer clinical benefits in ORR and PFS compared with carboplatin plus vincristine, while withdrawals due to AEs and Grade 3 or greater AEs may also be more favourable with dabrafenib plus trametinib. No evidence was identified comparing dabrafenib plus trametinib to vinblastine, thus the comparative efficacy between the two regimens is unknown.

For adult patients, the incremental cost of dabrafenib plus trametinib is expected to be approximately $16,608 per patient per 28-day cycle compared to carboplatin plus vincristine, and $17,255 per patient per 28 days compared to vinblastine. For pediatric patients using regular capsules and tablets, the incremental cost of dabrafenib plus trametinib is expected to range from $7,777 to $16,608 per patient per 28 days compared to carboplatin plus vincristine, and from $8,681 to $17,255 per patient per 28 days compared with vinblastine. As no prices for dabrafenib suspension tablets or trametinib oral solution were found, the incremental cost of dabrafenib plus trametinib in patients under 26 kg or who cannot take regular capsules or tablets is unknown.

Given that dabrafenib plus trametinib is associated with increased drug acquisition costs and incremental benefit in terms of ORR and PFS compared to carboplatin and vincristine, a cost-effectiveness analysis would be required to determine the cost-effectiveness of dabrafenib plus trametinib relative to its comparators. As this was not available, the cost-effectiveness of dabrafenib plus trametinib relative to carboplatin plus vincristine, vinblastine, or dabrafenib monotherapy for the treatment of low-grade glioma could not be determined.

References

1. Ostrom QT, de Blank PM, Kruchko C, et al. Alex's Lemonade Stand Foundation infant and childhood primary brain and central nervous system tumors diagnosed in the United States in 2007–2011. *Neuro Oncol*. 2015;16(Suppl 10):x1–x36.
2. Louis DN, Perry A, Reifenberger G,et al. The 2016 World Health Organization classification of tumors of the centralnervous system: a summary. *Acta Neuropathol* 2016; 131: 803-820.
3. Larouche V, Toupin A-K, Lalonde B, Simonyan D, Jabado N, Perreault S. Incidence trends in pediatric central nervous system tumors in Canada: a 15 years report from Cancer and Young People in Canada (CYP-C) registry. *Neurooncol Adv* 2020;2(1):vdaa012.
4. Goebel AM, Gnekow AJ, Kandels D, Witt O, Schmidt R, Driever PH. Natural History of Pediatric Low-Grade Glioma Disease - First Multi-State Model Analysis. *J Cancer* 2019;10:6314-6326.
5. Health Technology Report: Pediatric low-grade glioma Multi-stakeholder Dialogue Lessons Learned Report. Ottawa: Ottawa (ON): CADTH; 2022: https://www.cda-amc.ca/sites/default/files/RWE/pdf/multi-stakeholder_dialogue_optimizing-the_use-of_real-world_evidence_for_decision-making_for_pediatric_low-grade_glioma_in%20_canada.pdf. Accessed 2025 Jan 8.
6. Ostrom QT, Price M, Ryan K, et al. CBTRUS statistical report: pediatric brain tumor foundation childhood and adolescent primary brain and other central nervous system tumors diagnosed in the United States in 2014–2018. *Neuro Oncol*. 2022;24(Suppl 3):iii1–iii38.
7. Bandopadhayay P, Bergthold G, London WB, et al. Long-term outcome of 4,040 children diagnosed with pediatric low-grade gliomas: an analysis of the Surveillance Epidemiology and End Results (SEER) database. *Pediatr Blood Cancer*. 2014;61(7):1173-1179.
8. Ater JL, Zhou T, Holmes E, et al. Randomized study of two chemotherapy regimens for treatment of low-grade glioma in young children: A report from the Children's Oncology Group. *J. Clin. Oncol*. 2012;30:2641‑2647.
9. Lassaletta A, Scheinemann K, Zelcer SM, et al. Phase II Weekly Vinblastine for Chemotherapy-Naive Children with Progressive Low-Grade Glioma: A Canadian Pediatric Brain Tumor Consortium Study. *J Clin Oncol*. 2016;34:3537‑3543.
10. Ryall S, Tabori U, Hawkins C. Pediatric low-grade glioma in the era of molecular diagnostics. *Acta Neuropathol Commun* 2020;8(1):30
11. Lassaletta A, Zapotocky M, Mistry M, et al. Therapeutic and Prognostic Implications of BRAF V600E in Pediatric Low-Grade Gliomas. *J Clin Oncol*. 2017;35(25):2934–2941.
12. Wisoff JH, Sanford RA, Heier LA, et al. Primary neurosurgery for pediatric low-grade gliomas: A prospective multi-institutional study from the Children's Oncology Group. *Neurosurg.* 2011;68 (6): 1548–1555.
13. Erker C, Vanan MI, Larouche V, et al. Canadian Consensus for Treatment of BRAF *V600E* Mutated Pediatric and AYA Gliomas. *Curr Oncol*. 2024;31(7):4022-4029.
14. Bouffet E, Hansford JR, Garrè ML, et al. Dabrafenib plus Trametinib in Pediatric Glioma with *BRAF* V600 Mutations. *N Engl J Med*. 2023;389(12):1108-1120.
15. Wen PY, Stein A, van den Bent M, et al. Dabrafenib plus trametinib in patients with $BRAF^{V600E}$-mutant low-grade and high-grade glioma (ROAR): a multicentre, open-label, single-arm, phase 2, basket trial. *Lancet Oncol*. 2022;23(1):53-64
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.
17. Dello Russo C, Navarra P. Local Investigators Significantly Overestimate Overall Response Rates Compared to Blinded Independent Central Reviews in Uncontrolled Oncology Trials: A Comprehensive Review of the Literature. *Front Pharmacol*. 2022;13:858354.
18. Health Canada. Patent Register. 2025; https://pr-rdb.hc-sc.gc.ca/pr-rdb/index-eng.jsp. Accessed 2025 Jan 20.