Canada's Drug Agency
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Drugs Health Technologies Health Systems

Reimbursement Review

Dabrafenib Plus Trametinib

Requester: Public drug programs
Therapeutic area: Low-grade gliomas with *BRAF* V600 mutations

Key Messages

What Are Low-Grade Gliomas?

- Low-grade gliomas (LGGs) 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 years, from 2001 to 2015.

What Are the Treatment Goals and Current Treatment Options for LGGs?

- The goals of treatment are to achieve tumour control, improve progression-free survival (PFS), minimize toxicities from treatment, and maintain functional outcomes such as vision.
- Currently in Canada, the preferred first-line treatment for LGGs is complete surgical removal (resection) of the tumour. When complete resection is not possible, chemotherapy with vinblastine monotherapy or carboplatin plus vincristine is recommended as standard first-line treatment.
- When cancer has progressed or relapsed, second-line therapy currently includes targeted therapies with dabrafenib monotherapy, and dabrafenib-trametinib combination therapy 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 and trametinib are drugs that block specific molecules involved in cancer cell growth and survival.
- Health Canada has approved dabrafenib plus trametinib for pediatric patients aged 1 year or 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 patients (aged < 18 years) and young adult patients (aged 18 to 39 years) for first-line or later therapy in LGGs with residual disease and with known *BRAF* V600 mutations.

Key Messages

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 therapy, and dabrafenib monotherapy.
- The clinical evidence was identified through systematic searches of the available literature. The review was informed by 1 patient group submission and 1 clinician 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 (RCT), by 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 (the 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 the study by Bouffet et al.:

- there was improved PFS, 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 (OS) could not be determined because 1 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 (HRQoL) measure, precluding any conclusions being drawn
- fewer discontinuations due to adverse events (AEs) and grade 3 or higher AEs occurred with dabrafenib plus trametinib versus chemotherapy. Frequencies of serious AEs and any AEs were similar between the groups.

Key Messages

The single-arm ROAR trial suggested that more than half of adult patients with relapsed or refractory *BRAF* V600E–mutated LGG achieved overall response. However, HRQoL 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 plus trametinib, and to assess the clinical significance of the findings.

Economic Evidence

Reimbursing dabrafenib plus trametinib as a first-line or later therapy for LGGs, for the treatment of adult and pediatric patients 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
CBR	clinical benefit rate
CDA-AMC	Canada’s Drug Agency
CI	confidence interval
CNS	central nervous system
CR	complete response
ECOG	Eastern Cooperative Oncology Group
HR	hazard ratio
HRQoL	health-related quality of life
ITT	intention to treat
LGG	low-grade glioma
OR	odds ratio
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
pLGG	pediatric low-grade glioma
POGO	Pediatric Oncology Group of Ontario
PR	partial response
RCT	randomized controlled trial
RR	risk ratio
SAE	serious adverse event
SD	standard deviation

Background and Review Methods

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 for first-line or later therapy for LGGs in pediatric and young adult patients 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	For pediatric patients (aged 1 year to < 18 years), Health Canada–recommended dosages for dabrafenib and trametinib are based on weight ranges.[a] For adult patients (aged ≥ 18 years): • 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 or 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	For first-line or later therapy for LGGs in pediatric and young adult patients with residual disease and with known *BRAF* V600 mutations

CDA-AMC = Canada's Drug Agency; LGG = low-grade glioma.

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

Review Methods

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) and 1 clinical group submission from the Pediatric Oncology Group of Ontario (POGO). The full submissions received are available in the consolidated input document on the project landing page.

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 input is summarized in the Disease Background, Current Management, and Unmet Needs and Existing Challenges sections of this report.

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

Disease Background

LGGs are the most common CNS tumour found in children and young adults, accounting for about one-third of reported cases.[1] According to WHO, LGGs are classified as grade 1 and 2 tumours, which are slow-growing tumours.[2] From 2001 to 2015, the incidence of pLGGs in Canada was reported as 1.41 cases per 100,000 person-years in children aged 0 to 14 years.[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 LGGs 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 LGGs 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 nonspecific, including headache, vomiting, dizziness, functional deficits, and others mentioned previously. Parents actively seek answers and advocate for further evaluation by health care providers to reach 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 estimate for pLGGs is 95% in some LGG tumour types,[6] with 20-year survival estimates up to 87%.[7] However, pLGGs are associated with significant risk of progression, and PFS after treatment with conventional chemotherapy ranges from around 40% to 50%.[8,9] Morbidities associated with pLGGs can include neurologic impairments like seizures, behavioural and/or cognition disorders, and visual dysfunction (including blindness).

Research suggests that the majority (90%) of pLGG tumours have alterations to the MAPK pathway, which is involved in cell growth, proliferation, and survival.[10] About 17% of pLGGs have the *BRAF* V600E mutation, disrupting the MAPK pathway, which has implications for treatment and prognosis. People who have *BRAF* V600E–mutated tumours have a 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 LGGs are to improve tumour response, prevent worsening of symptoms, and improve seizure control while limiting harms. They shared that patients with LGGs harbouring *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 more than 90% and 5-year and 8-year OS rates more than 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 the use of 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 the 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 a 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 LGGs but is no longer used in clinical practice because of the availability of dabrafenib.

Key characteristics of dabrafenib and trametinib are summarized with other treatments available for LGGs in the Working Papers document.

Unmet Needs and Existing Challenges

The following is based on input provided by 1 patient group, 1 clinician group, and clinical experts consulted for this review.

The patient group (through the previous Pediatric Low-Grade Glioma Multi-Stakeholder Meeting) highlighted that pLGGs have profound long-term physical, emotional, and financial impacts on patients and their families. They expressed that different aspects of care — including access to specialist physicians, high costs, and access to novel and potentially more effective treatment approaches — can vary based on geographical location, health care 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 the transition from care in pediatric centres to adolescent or adult centres, as well as fragmented care versus an 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.

POGO highlighted that while current conventional treatment options for LGG (i.e., surgery, cytotoxic chemotherapies, and radiation) may be reasonably effective, they carry significant challenges for patients and families, which make these treatments undesirable in early lines of therapy. Total surgical resection is not always possible considering the size and location of the tumour. Radiation therapy can cause serious late and long-term effects, including neurocognitive damage and a second malignancy. Chemotherapy requires weekly infusion visits and unplanned assessments due to infectious complications produced by cytotoxic therapy, and does not always result in adequate or durable tumour response rates. POGO advocated the use of dabrafenib plus trametinib for patients with tumours harbouring *BRAF* V600 mutations and emphasized it has changed the treatment paradigm for LGG.

The clinical experts also noted that some patients, especially those with a *BRAF* V600 mutation, do not experience an adequate response 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. Tumour recurrence is a serious concern for patients with unresectable or incompletely

resected tumours. There are no treatments available to reverse vision impairment or endocrinopathies caused by the tumour.

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 patients with pLGGs and their families. Oral medications can be administered at home, which potentially increases treatment adherence; reduces the need for hospital visits; and allows for fewer missed days at school, time with friends, and work.

Potential Place in Therapy

Contents within this section have been informed by input from the clinician group and 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 and clinician group, dabrafenib in combination with trametinib is expected to become favoured over other systemic therapies for first-line treatment for patients with *BRAF* V600–mutated LGGs, particularly those who have residual tumours after surgery or unresectable tumours.

Patient Population

The clinical experts and clinician group identified newly diagnosed patients with *BRAF* V600–mutated pLGGs 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 for diagnosis and treatment initiation. Molecular confirmation of *BRAF* V600 status with DNA testing is still important; however, it should not be a barrier to initiating treatment. The experts 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 HRQoL, preservation or improvement in functional outcomes, and a PFS of at least 40% at 5 years. While complete tumour response and improved neurologic status are the goals of therapy, partial response (PR), stable disease, and the absence of neurologic deterioration are also clinically important and may be considered a successful therapy response.

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, which 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, adult neuro-oncologists, pediatric oncologists, and adult oncologists. The clinician group also indicated that the treating teams should have the resources to monitor the patient regularly for evidence of treatment response or disease progression. Resources and expertise to monitor for possible AEs and provide supportive care should be available. Specific AEs that should be monitored include skin toxicity, gastrointestinal symptoms, epistaxis, weight gain, paronychia, fevers, pancreatitis, cardiotoxicity, and ophthalmologic toxicity. A multidisciplinary case conference review including neurosurgeons, pathologists, and medical and radiation neuro-oncology should be encouraged.

Clinical Review

Methods

We conducted a systematic review to identify RCT evidence for dabrafenib and trametinib as first-line or later therapy for LGGs for the treatment of pediatric and young adult patients 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 input. Selected outcomes are those considered relevant to expert committee deliberations. Detailed methods for literature searches, study selection, and data extraction are in the Working Papers document.

Table 2: Systematic Review Eligibility Criteria

Criteria	Description
Population	Pediatric and young adult patients[a] with residual disease and with known *BRAF* V600 mutations, for first-line or later therapy in low-grade gliomas
Intervention	For pediatric patients (aged 1 year to < 18 years), recommended dosages for dabrafenib and trametinib are based on weight ranges.[b] For adult patients (≥ 18 years of age): • Dabrafenib: 150 mg oral, twice daily • Trametinib: 2 mg oral, once daily

Criteria	Description
Comparators[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 AEs, deaths
	• AEs of special interest:
	  ◦ Left ventricular dysfunction
	  ◦ Retinal pigment epithelial detachment, retinal vein occlusion
	  ◦ Interstitial lung disease
	  ◦ Skin toxicity
	  ◦ Venous thromboembolism
	  ◦ Major hemorrhagic events
	  ◦ Noninfectious febrile events
	  ◦ Teratogenicity

Study design	Published phase II, III, and IV clinical trials

AE = adverse event; CDA-AMC = Canada's Drug Agency; SAE = serious adverse event.

[a]A young adult was defined as an individual aged 18 to 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. Refer to the Working Papers document for dosing tables.

[c]Vemurafenib, a first-generation BRAF inhibitor, was initially considered for evaluation and listed in the proposed scope document by 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 it was considered 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 document 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.

Systematic Review

Description of Studies

Study Characteristics

Characteristics of the included studies are summarized in Table 3.

The Bouffet et al. trial[14] and the ROAR trial[15,16] were both phase II, open-label, multicentre trials evaluating dabrafenib plus trametinib in *BRAF* V600 mutation–positive LGGs that were sponsored by Novartis, but with key differences in the study design, patient population, stage of treatment, and geographic scope. The Bouffet et al. trial was a multicentre, randomized, open-label trial comparing the efficacy and safety of dabrafenib in combination with trametinib to carboplatin and vincristine as first-line therapy for pLGGs with *BRAF* V600 mutations. The ROAR study was single-arm, multicentre basket trial in 9 cohorts of patients with recurrent or refractory BRAF V600E–mutated cancers, including LGGs. The population was restricted to children in the Bouffet et al. study (N = 110), enrolled at 58 sites across 20 countries, compared to only adult patients in the ROAR trial (N = 13), enrolled at 10 sites in 8 countries. Both trials included study sites in Canada.

Results

Patient Disposition

Details of patient disposition can be found in the Bouffet et al.[14] and the Subbiah et al. articles.[16]

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.

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 II, open-label, multicentre randomized trial[a] N = 110	• Patients aged 1 to 17 years, diagnosed with LGGs with *BRAF* V600 mutations and confirmed by RANO-LGG criteria • Nonsurgical patients scheduled to begin first-line systemic therapy or patients with progressive disease after surgery	• Malignancy other than *BRAF* V600-mutant LGG • Previous treatment with another RAF inhibitor, MEK inhibitor, or ERK inhibitor • Any systemic anticancer therapy • Radiation therapy to CNS glioma	**Intervention:** • Dabrafenib: oral, 2 equal doses per day for patients: ◦ aged < 12 years: 5.25 mg/kg/day ◦ aged ≥ 12 years: 4.5 mg/kg/day • Trametinib: oral, once daily for patients: ◦ aged < 6 years: 0.032 mg/kg/day ◦ aged ≥ 6 years: 0.025 mg/kg/day **Comparator:** • Carboplatin plus vincristine[b]	**Primary end point:** • Independently assessed ORR **Secondary end points:** • Investigator-assessed ORR • CBR • 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 II, multicentre, open-label, single-arm basket trial N = 13 with LGG	• Patients aged ≥ 18 years with measurable nonenhancing disease (except pilocytic astrocytoma) using the RANO criteria for LGGs • Patients with *BRAF* V600E mutations with confirmed recurrent or progressive LGG • Grade 1 LGG required to be symptomatic and evaluated by central panel of neuro--	• 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 before enrolment • Radiotherapy within 3 months before enrolment • Enzyme-inducing	**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

Study name, design, and sample size	Key inclusion criteria	Key exclusion criteria	Intervention and comparator	Relevant end points
	oncologists • Grade 2 LGG ineligible for chemotherapy	anticonvulsants within 2 weeks before enrolment		

CBR = clinical benefit rate; CNS = central nervous system; DOR = duration of response; HRQoL = health-related quality of life; LGG = low-grade glioma; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcome; PROMIS = Patient-Reported Outcomes Measurement Information System; RANO = Response Assessment in Neuro-Oncology.

[a]The study was part of a larger glioma trial that was designed and conducted in 2 cohorts with pediatric glioma: 1 with low-grade glioma and 1 with high-grade glioma.

[b]Carboplatin and vincristine were 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 was 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]The ROAR study was a basket trial conducted in 9 cohorts of patients with *BRAF* V600E 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]

The ROAR trial was a single-arm, nonrandomized basket trial that enrolled 13 adult patients with *BRAF* V600E–mutated LGGs. At the data cut-off of September 14, 2020, 5 patients (38%) were still receiving treatment, 1 patient (8%) was in follow-up, 3 patients (23%) had withdrawn consent to participate, and 4 patients (31%) had died due to disease progression. As of the data cut-off date of December 10, 2021, the 6 remaining patients (46%) had completed the study (sponsor terminated the study).

Baseline Characteristics

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

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 (%)	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 (%)			
Asian	5 (7)	3 (8)	3 (23)
Black or African American	2 (3)	3 (8)	0
White	55 (75)	25 (68)	10 (77)
Unknown	6 (8)	4 (11)	0
Other	3 (4)	1 (3)	0
Missing	2 (3)	1 (3)	0
Karnofsky-Lansky or ECOG performance status scores, 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)	—
Previous anticancer treatment, n (%)			
Any therapy	62 (85)	29 (78)	13 (100)
Surgery	62 (85)	29 (78)	13 (100)[b]

Characteristic	Bouffet et al. (2023)		ROAR trial
	Dabrafenib plus trametinib (N = 73)	Chemotherapy (N = 37)	Dabrafenib plus trametinib (N = 13)
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 to 199.9)	2.4 months (0.7 to 62.2)	6.9 years (0.1 to 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)

ECOG = Eastern Cooperative Oncology Group; NR = not reported.

[a]Karnofsky performance status and Lansky performance status apply to patients aged at least 16 years and younger than 16 years, respectively, in the Bouffet et al. study. The ECOG performance status scale 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 more than 4 weeks before 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 the Bouffet et al. study, local *BRAF* status is presented when available; 4 patients were enrolled based on centrally determined *BRAF* status. For the 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 before treatment with no local result entered and before 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 months) and to carboplatin was 7.8 months (range, 2.8 to 16.1 months) 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 study, as of the data cut-off date of September 12, 2020, the mean duration of exposure to dabrafenib was 27.3 months (standard deviation [SD] = 20.6) and to trametinib was 26.7 months (SD = 20.9). The mean duration

of exposure as of the data cut-off 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 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.

Efficacy

Results for efficacy outcomes important to this review are presented in Table 5 and Table 6. The 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 trial are 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 cut-off 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 1 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. OS 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% confidence interval [CI], 12.8 to not evaluable [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 (HR) 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 response [CR] or PR, 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.
- The 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 scenario, the proportion of patient eyes that improved after baseline was higher in the dabrafenib plus trametinib group than in the chemotherapy group, and the proportion of eyes that worsened or remained stable after baseline was lower in the dabrafenib plus trametinib group. However, no statistical testing was performed and no CIs were calculated to aid comparison between the treatment groups.
- Improvements in HRQoL — based on parental observation, using the Patient-Reported Outcomes Measurement Information System (PROMIS) Parent Proxy Global Health 7 + 2 questionnaire — were observed for the dabrafenib and trametinib group up to week 104, whereas worsening HRQoL was observed in the chemotherapy group up 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 trial (Table 6 and Figure 2) include the following:

- The median patient follow-up duration was 32.2 months (interquartile range [IQR], 25.1 to 47.8 months) as of the data cut-off 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 cut-off date.
- Four patients died in the LGG cohort. OS could not be estimated because of the small number of events.
- Median PFS was 9.2 months (95% CI, 4.7 to 33.0 months) by independent assessment, as of the December 10, 2021, data cut-off. Eight patients had disease progression and 1 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 cut-off date of December 10, 2021.
- Median duration of response (DOR) 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 plus PR plus stable disease), and HRQoL outcomes were not reported.

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

Outcomes	Bouffet et al. (2023)			
	Dabrafenib plus trametinib (N = 73)	Chemotherapy (N = 37)	Dabrafenib plus 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 One death in chemotherapy group (from low-grade glioma)			
Progression-free survival				
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 plus 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 plus PR plus 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)

Outcomes	Bouffet et al. (2023)			
	Dabrafenib plus trametinib (N = 73)	Chemotherapy (N = 37)	Dabrafenib plus trametinib (N = 73)	Chemotherapy (N = 37)
	Independent assessment		Investigator assessment	
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]				
At 6 months	86 (66 to 94)	100 (100 to 100)	NR	NR
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]

Outcomes	Dabrafenib plus 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 cut-off date of August 23, 2021

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

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

[d]The P value was computed using the log-rank test at the 1-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 the 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 CR or PR that occurred before the week 16 visit.

[i]Four patients did not have a valid postbaseline assessment. Two patients had stable disease or unconfirmed CR or PR that occurred before the week 16 visit.

[j]The Odds ratio (dabrafenib plus trametinib versus chemotherapy) and 2-sided 95% CI are from a logistic regression with treatment as the only covariate. Odds ratios and risk ratios greater than 1 favours dabrafenib plus trametinib.

[k]The P values were computed using a chi-squared test (Mantel-Haenszel) at a 1-sided 2.5% level of significance.

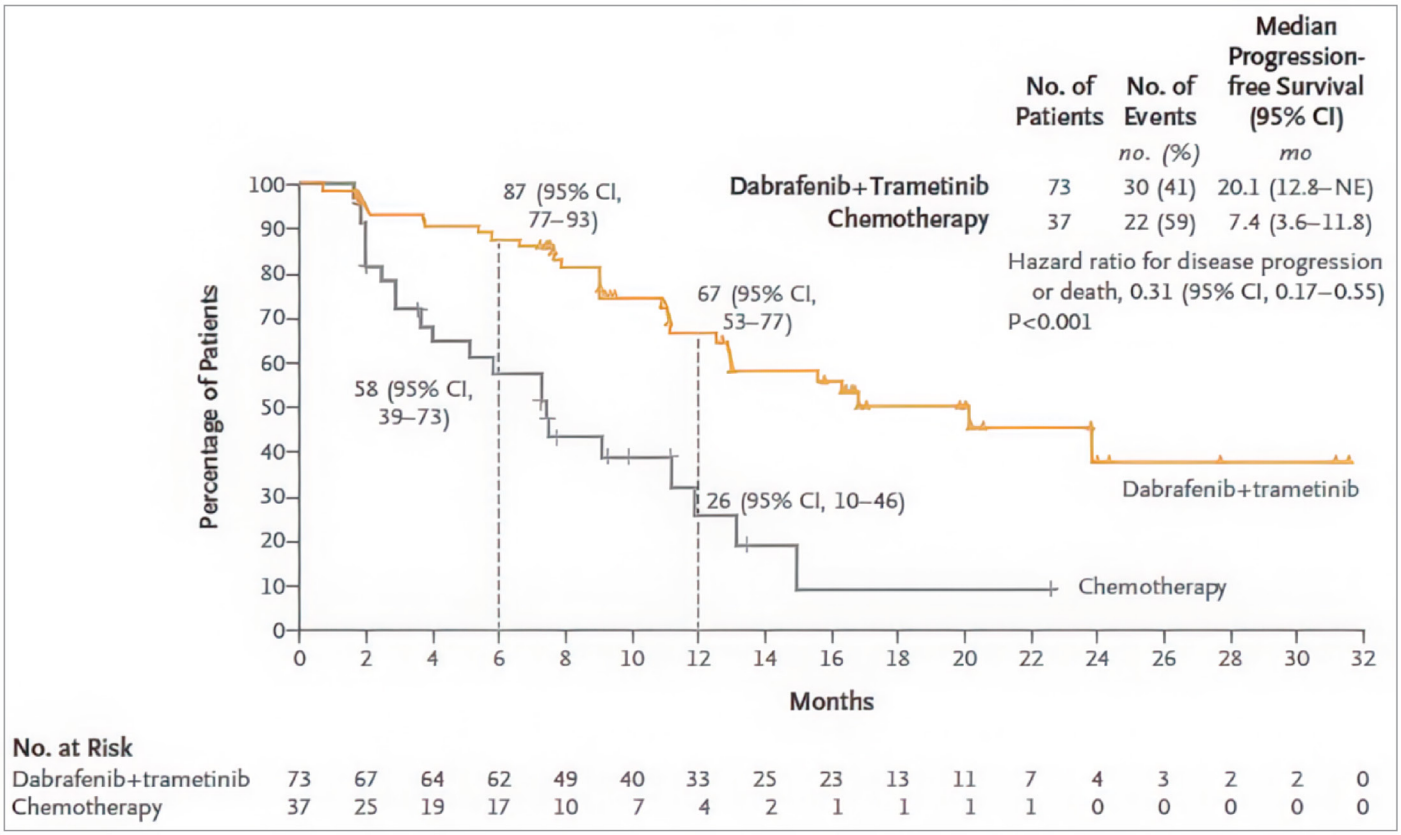
[l]Stable disease for 24 weeks or longer was recorded at 23 weeks or later (i.e., ≥ 161 days) from treatment start date.

[m]"Improved" means 0.2 logMAR improvement; "stable" means neither 0.2 logMAR improvement nor worsening; "worsening" means 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.

Figure 1: Progression-Free Survival in the Dabrafenib Plus Trametinib and Chemotherapy Groups in the Bouffet et al. (2023) Study



CI = confidence interval; mo = months; NE = not evaluable; No. = number; RANO = Response Assessment in Neuro-Oncology.

Notes: Progressive-free survival was measured in the 2 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 to 1120. Copyright (2025) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Table 6: Summary of Key Efficacy Results for the ROAR Trial

Outcome[a]	ROAR trial	
	Dabrafenib plus 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

Outcome[a]	ROAR trial	
	Dabrafenib plus trametinib (N = 13)	
	Independent assessment	Investigator assessment
Overall response rate (CR plus 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 DOR, 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 the data cut-off date of December 10, 2021.

[b]By independent radiology review, 9 patients (69%) had disease progression, and 1 patient (8%) died without disease progression. Three patients (23%) were censored due to end of follow-up.

[c]By investigator assessment in 13 patients, 6 patients (46%) had disease progression. Seven patients (54%) 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 postbaseline assessments.

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

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

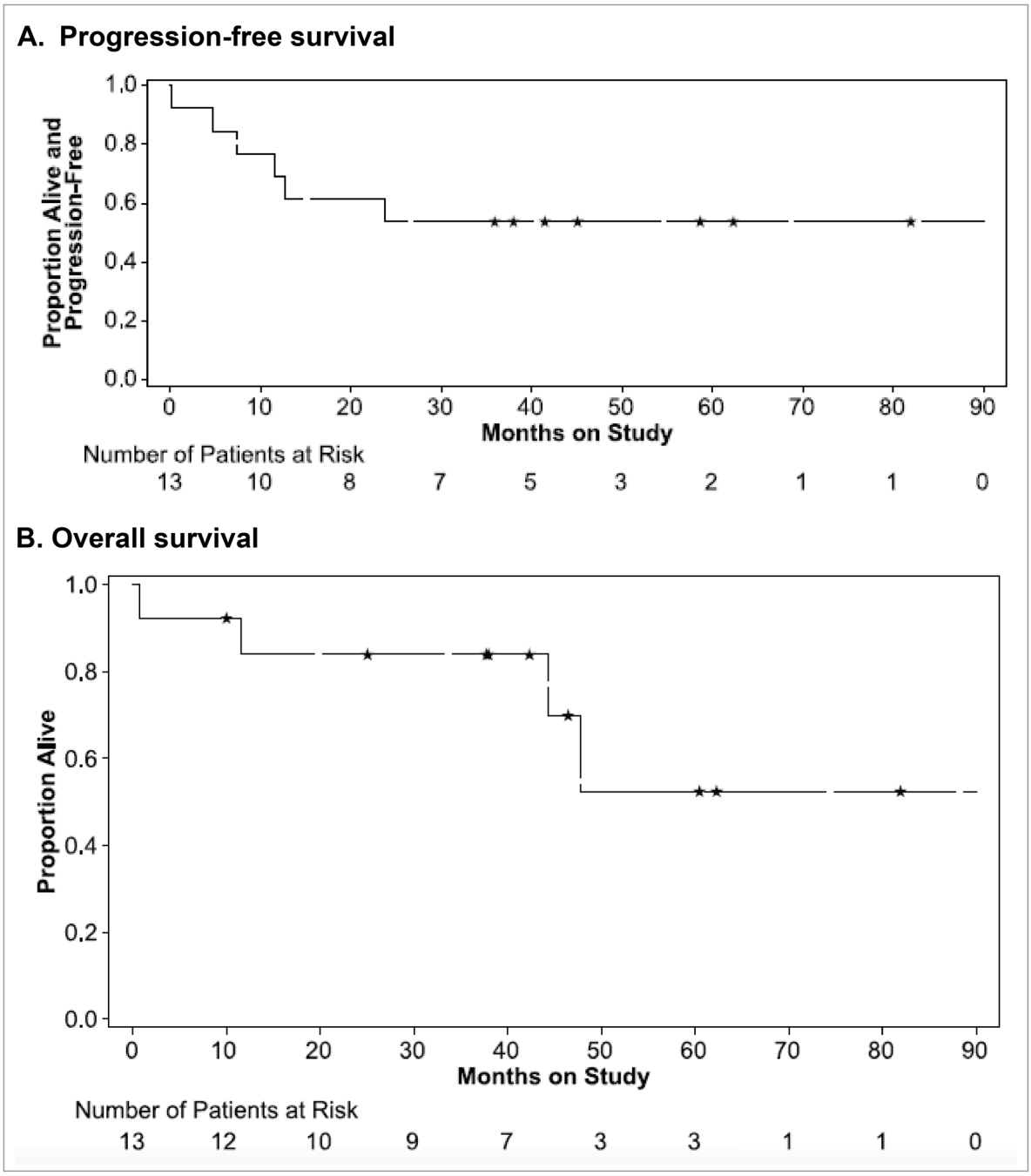
Harms

Detailed results for harms for each included study are in the following publications: Bouffet et al. (2023), Subbiah et al. (2023).

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

- All patients (100%) in the Bouffet et al. study were reported to have at least 1 AE.
- Fewer patients in the dabrafenib plus trametinib group than in the chemotherapy group had AEs of grade 3 or higher (47% versus 94%, respectively).
- Serious adverse events (SAEs) were reported at a similar rate in the dabrafenib plus trametinib group and the chemotherapy group (40% versus 39%, respectively).

Figure 2: Progression-Free Survival and Overall Survival for Dabrafenib Plus Trametinib in the ROAR Study



- Treatment discontinuation due to AEs occurred at a lower rate in the dabrafenib plus trametinib group than in the chemotherapy group (4% versus 18%, respectively) in Bouffet et al. trial.
- No deaths coded as AEs were reported in the trial.
- The most common AEs in the Bouffet et al. study in the dabrafenib plus trametinib group and the chemotherapy group were pyrexia (68% versus 18%), headache (47% versus 27%), vomiting (34% versus 48%), and fatigue (32% versus 30%).
- Some adverse events of special interest (AESIs) 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% versus 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 patients (21%) in the dabrafenib plus trametinib group and 1 patient (3%) in the chemotherapy group of the Bouffet et al. study had epistaxis reported as an AE.

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

- Almost all patients (92%) in the ROAR study were reported to have at least 1 AE.
- Grade 3 or higher AEs occurred but no aggregate data for the LGG cohort were reported at the latest data cut-off (December 10, 2021) in the Subbiah et al. article.
- Three patients (23%) in the ROAR trial experienced SAEs.
- Treatment with dabrafenib plus trametinib was discontinued for 2 patients due to AEs.
- No deaths coded as AEs were reported in the LGG cohort.
- Out of the AESIs, no patient was reported to have experienced interstitial lung disease or 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 1 patient (8%). Cardiac-related events were reported in 1 patient (8%) in the Subbiah et al. study.

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

Variable	Bouffet et al. (2023)	
	Dabrafenib plus trametinib (N = 73)	Chemotherapy (N = 33)
Any AEs, n (%)	73 (100)	33 (100)
SAEs, n (%)	29 (40)	13 (39)
Grade ≥ 3 AEs, n (%)	34 (47)	31 (94)
Discontinuation due to AEs, n (%)	3 (4)	6 (18)
AESIs, n (%)		
Left ventricular dysfunction	NR	NR

Variable	Bouffet et al. (2023)	
	Dabrafenib plus trametinib (N = 73)	Chemotherapy (N = 33)
Retinal pigment epithelial detachment	NR	NR
Retinal vein occlusion	NR	NR
Interstitial lung disease	NR	NR
Venous thromboembolism	NR	NR
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; SAE = serious adverse event.
Source: Bouffet et al. (2023).[14]

Table 8: Summary of Key Harms for the ROAR Trial

Variable	ROAR trial
	Dabrafenib plus trametinib (N = 13)
Any AEs, n (%)	12 (92.3)
SAEs, n (%)	3 (23.1)
Grade ≥ 3 AEs, n (%)	NR[a]
Discontinuation due to AEs, n (%)	2 (15)
AESIs, 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 event; AESI = adverse event of special interest; NR = not reported; SAE = serious adverse event.
[a]Grade 3 or higher AEs occurred but no aggregate data for the LGG cohort were reported at the latest data cut-off (December 10, 2021) in the Subbiah et al. article.
[b]An unspecified cardiac-related event was reported in 1 patient.
Source: Subbiah et al. (2023).[16]

Critical Appraisal

Internal Validity

In the RCT by Bouffet et al., 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 Canada's Drug Agency (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 underestimate or overestimate 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% of patients in various characteristics, including performance status, previous anticancer therapy, histologic grade at initial diagnosis, and *BRAF* mutation status in the Bouffet et al. trial. Whether the missing data led to bias, and the influence on the study result, is unclear.

Dose modifications and dose delays were appropriately specified in the Bouffet et al. study protocol and reflected recommended actions based on AEs per the respective product monographs and labels for each of the drug treatments administered. The percentages of patients who required dose reductions or dose interruptions were similar between the treatment arms, and were primarily the result of AEs. 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 OS is not clear; however, given the small numbers, few deaths, and the fact that 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 DOR 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 the Bouffet et al. study potentially introduce a high risk of bias by systematically excluding patients who discontinue treatment early, switch therapy, or have missing assessments. For example, 1 of the censoring rules states that patients with 2 or more missing tumour assessments before disease progression or death were censored, meaning their data were 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 1 treatment arm, this could artificially inflate the estimated DOR 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 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 in Bouffet et al.'s supplemental material). The number of patients with data at week 56 (the last assessment for the chemotherapy group) was 30 dabrafenib plus trametinib group and 4 in the chemotherapy group, 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 patients with poorer responses who required alternative treatment. If treatment switching occurred at different rates between groups, informative censoring could have led to inflated DOR 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 1 patient in the trial started a new anticancer treatment before an outcome event occurred.

The ROAR trial was a single-arm, phase II basket trial that included patients with LGG as 1 of the cohorts. The trial lacked a comparator group, which 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 the 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. The level of concordance in the ROAR trial for the LGG cohort was 46.2%, although 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 reduced risk of bias with this approach to assessing tumour response.

This open-label design also makes the patient-reported outcomes and AEs susceptible to reporting bias. Given the limitations associated with the available data related to changes in HRQoL from the Bouffet et al. trial, it is difficult 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, and DOR) are standard in oncology trials and, as mentioned previously, tumour responses were objectively evaluated using RANO criteria. No major concerns regarding the validity or measurement properties of outcomes were identified, although the absence of a comparator arm in the ROAR trial and small number of events for OS and PFS in both trials makes interpretation of these efficacy results difficult. In addition, the link between ORR and OS 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 ORR as a surrogate for OS.

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

External Validity

The Bouffet et al. and ROAR studies enrolled predominantly white patients (70% and more), which aligns with the racial diversity of pediatric and young adults commonly encountered in practice in Canada, as noted by the clinical experts. The clinical experts indicated that the study inclusion criteria, which specified patients had to have a confirmed LGG diagnosis and *BRAF* V600 mutation, are critical in making treatment decisions and consistent with what would be expected in clinical practice. Clinical experts raised concern over the inclusion of 1 patient with a diagnosis of choroid plexus papilloma in the ROAR 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, while the ROAR 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 years). Because the median represents the midpoint of the age distribution, at least half of the trial participants were aged 33 years or younger. The age distribution was reported in wide ranges across the cohorts; for the LGG cohort, all patients were included in the age category of 18 to 64 years. 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 trial used the Eastern Cooperative Oncology Group (ECOG) performance status scale for adults. 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 scales are standard measures to enrol 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 plus trametinib combination therapy also has been increasingly used as the first-line treatment for *BRAF* V600–mutated pLGG in clinical practice, and it is 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 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 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 2 patients with treatment discontinuation due to AEs. 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 carboplatin and vincristine chemotherapy, which is the current SOC in Canada for LGGs as confirmed by clinical experts. However, vinblastine monotherapy and dabrafenib monotherapy were identified as relevant comparators for this review. No studies were identified comparing dabrafenib plus trametinib to vinblastine or dabrafenib monotherapy in the target population. As noted previously, the ROAR trial did not include a control group and provided 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 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: OS, PFS, and ORR. Given the long OS of patients with LGGs, 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 LGGs, requiring extended follow-up times to observe meaningful differences in OS, which may not be feasible within typical clinical trial time frames.

The consulted clinical experts considered the follow-up durations of the trials to be reasonable for evaluating treatment effects on ORR and PFS for LGGs. The experts expressed that functional outcomes such as vision, as well as HRQoL, were important outcomes because patients with LGGs 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 LGGs. 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 PFS when patients received dabrafenib plus trametinib compared to chemotherapy with carboplatin and vincristine. Although the between-group differences (with 95% CIs) were not reported, the 6-month and 12-month probabilities 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. OS could not be estimated in the trial because there were no deaths reported for the dabrafenib plus trametinib treatment group, and 1 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 LGGs 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 time of 19 months in the Bouffet et al. trial was sufficient to observe the key outcomes of interest (PFS and ORR). Although a 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 study was a single-arm trial of dabrafenib plus trametinib and did not provide comparative efficacy data. The study reported that dabrafenib plus trametinib led to a 54% ORR in adult patients with recurrent or relapsed *BRAF* V600E–mutated LGG. The clinical experts noted that this result is likely clinically meaningful because they would not expect SOC chemotherapy to achieve this magnitude of ORR. Moreover, the experts highlighted that observed improvements in the patients with PR and stable disease were acceptable goals in a setting with limited treatment options. In addition, the clinical experts noted that 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 CIs for median PFS and ORR — preclude drawing firm conclusions on the results.

Harms

Across both the Bouffet et al. and ROAR trials, nearly all patients experienced at least 1 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 or higher AEs occurred twice as frequently in the chemotherapy group compared to the dabrafenib plus trametinib group, suggesting a potential advantage with the targeted therapy. Additionally, discontinuations due to AEs were lower in patients treated with dabrafenib plus trametinib (4%) than in 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 remain 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 populations with LGG.

Conclusion

The Bouffet et al. trial showed that dabrafenib plus trametinib as first-line systemic therapy for pLGGs in patients 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 the Bouffet et al. trial suggest lower frequencies of discontinuations due to AEs and grade 3 or higher 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, as first-line or later therapy in LGGs, for the treatment of adult and pediatric patients 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 costs 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 aged at least 1 year 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 aged 8 years), 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 as first-line or later therapy for the treatment of LGGs in adult and pediatric patients with residual disease and with known *BRAF* V600 mutations is expected to increase overall drug acquisition costs. Additional items for consideration are as follows:

- Evidence from the Bouffet et al. trial[14] demonstrated that, compared to carboplatin plus vincristine, dabrafenib plus trametinib given as first-line systemic therapy to patients with LGGs with residual disease and known *BRAF* V600 mutations may offer clinical benefits in overall response rate and PFS, as well as in withdrawals due to AEs and grade 3 or higher AEs.
- 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 in mid-2025.[18] As such, it is possible that 1 or more generic versions of trametinib may become available. If so, the daily and 28-day cost of the dabrafenib plus trametinib regimen would be lower than what is 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 gliomas 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 that 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 30, 2024.

Conclusion

The reimbursement of dabrafenib plus trametinib for the treatment of LGGs 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 higher 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 2 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 weighing less than 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 comparators. As this was not available, the cost-effectiveness of dabrafenib plus trametinib relative to carboplatin plus vincristine, vinblastine monotherapy, or dabrafenib monotherapy for the treatment of LGGs could not be determined.

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