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Original research

Real-life efficacy and tolerance of trametinib in *BRAF*-rearranged low-grade gliomas: A multicenter study

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Highlights

- Trametinib achieved 78% disease control in BRAF-rearranged pLGGs.
- Activity is observed even in heavily pretreated and refractory tumors.
- Toxicities are frequent but manageable.

Abstract

Background

MEK inhibition has demonstrated activity in pediatric low-grade gliomas (pLGGs) driven by *BRAF* rearrangements, but data on trametinib remain limited, regarding efficacy, short and long-term toxicities.

Methods

We conducted a retrospective multicenter study of patients with *BRAF*-rearranged non NF1 pLGGs receiving trametinib across three French pediatric oncology centers. Plasma concentrations were monitored.

Results

Between 2015 and 2023, 46 patients had a median age of 8.7 years (range 1.2–18.6). Trametinib achieved a radiological disease control rate of 78% (36/46), including 65% partial or minor responses and 13% stable disease, with activity even in heavily pretreated (up to 6 lines) and chemotherapy-refractory tumors. Clinical improvement occurred in 72% of patients. Median treatment duration was 14.2 months (range, 1.0–55.1). Among 35 patients who discontinued treatment, 37% remained treatment-free after a median follow-up of 16.1 months (4.3–44.2). Grade 3 treatment-related adverse events occurred in one-third of patients. Common toxicities included cutaneous events (69%), paronychia (64%), gastrointestinal symptoms (51%), elevated creatine kinase (54%) and transaminases (31%). Ophthalmologic (16%) toxicities and epistaxis (17%) of which 35% were grade 2 and required intervention, were observed. Body mass index Z-score increased during treatment but was clinically significant (≥1 SD) and related to trametinib in only 17% of patients. Pharmacokinetics showed high interpatient variability, with no correlation between plasma concentrations and efficacy or toxicity.

Conclusion

Trametinib demonstrates sustained activity in *BRAF*-rearranged pLGGs, including in heavily pretreated patients. This study represents the largest reported cohort of BRAF-rearranged pLGGs, expanding prior evidence and supporting a class effect of MEK inhibitors.

Keywords

Pediatric low-grade glioma; BRAF rearrangement; KIAA1549::BRAF; MEK inhibition; Trametinib; MAPK pathway; Pharmacokinetics; Toxicity management; Real-word data

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Introduction

Pediatric low-grade gliomas (pLGGs) are the most common brain tumors in children [1]. When feasible, complete surgical resection is the preferred first-line of treatment [2]. In the German SIOP-LGG 2004 cohort almost 30% of patients received chemotherapy and/or radiotherapy following surgery, with a 10-year cumulative incidence of second surgery of 26% [3]. The standard treatment involves chemotherapy, which typically consists of a carboplatin-vincristine combination or weekly vinblastine regimens [4,5]. Unfortunately, at least 45% of patients undergoing chemotherapy experience disease progression when treatment is stopped, requiring additional treatments [[5], [6], [7]]. This exposes patients to adverse events (AE) of both disease progression and multiple chemotherapies [7]. Radiotherapy is another option for progressive pLGGs, but their typical location, optic pathway/brainstem, and young age exposes patients to significant long-term toxicities. [8,9].

The integration of clinical, histological, and molecular features allows stratification of pLGGs [10]. Advancements in molecular research have provided evidence of the predominant activation of the RAS-mitogen-activated protein kinase (RAS/MAPK) pathway in pLGGs [11,12]. Pilocytic astrocytoma, the most common subtype of pLGGs, is highly associated with MAPK pathway activation [[13], [14], [15]]. Within the MAPK pathway, the *KIAA1549::BRAF* fusion stands out as the most common aberration [13,16], which results in a continuous activation of *BRAF* kinase activity due to the loss of the *BRAF* N-terminal autoregulatory domain [17].

MEK inhibitors (MEKi), including trametinib or selumetinib, have shown antitumor activity across tumor types [18]. Recent phase I and II studies reported activities and acceptable toxicities of MEKi as single agent in pLGGs [[19], [20], [21]]. Several trials are evaluating MEKi in untreated or progressive pLGGs such as the randomized PLGG-MEKTRIC trial in France (NCT05180825) and the North American phase II multicentric TRAM 01 trial (NCT03363217).

Novel pan-RAF inhibitors are emerging and are explored in early clinical trials in patients with pLGG [22]. However, this class of agents like tovorafenib raise questions about long-term toxicity in growing children [22]. Trametinib is one of the most used MEKi in patients with pLGGs, along with selumetinib, with toxicity data still being generated through prospective trials and real-world experience [23]. Future pan-RAF approval will require comparison of safety and tolerability profiles. A detailed description of trametinib-associated toxicities, dose modifications, and treatment discontinuation patterns constitutes a necessary benchmark to inform clinical decision-making and guide the implementation of alternative MAPK-targeted therapies in routine pediatric neuro-oncology practice. Moreover, in adults with melanoma, a therapeutic target has been proposed, namely a trough concentration above 10.6 ng/mL, which is consistent with the preclinical target of 10.4 ng/mL (FDA/EMA) [24]. To date, no therapeutic target concentration has been established in the pediatric population.

Although no MEKi is currently approved for pLGGs, these drugs are frequently used off-label in countries where they are accessible. This underscores the need to determine MEKi activity, optimal treatment duration, and clarify disease control after discontinuation, as well as the role of pharmacokinetics in guiding toxicity and response. In this retrospective multicenter study, we reviewed real-life data to explore the use of trametinib in sporadic pLGGs with *BRAF* rearrangements.

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Population

We retrospectively reviewed clinical, histological, molecular biology and radiological files of patients diagnosed with pLGGs treated with trametinib between 2015 and 2023, at three tertiary care pediatric oncology centers in France: Gustave Roussy (GR), Villejuif, Institut Curie (IC), Paris and Institut d'Hématologie et d'Oncologie Pédiatrique (IHOPe), Lyon. Relevant data were extracted from medical records, including patient information, clinical characteristics, radiological findings, …

Patients' characteristics

Forty-six patients were included, with a median age at treatment start of 8.7 years (1.2–18.6) and a median age at diagnosis of 1.9 years (0.2–11). Tumor location was consistent with previously reported pLGGs eligible for medical treatment with a majority in the diencephalon (Table 1). All patients were symptomatic at diagnosis with oculomotor dysfunction (61%), visual impairment (41%) and/or Russell syndrome (35%). Twenty-five patients remained symptomatic at the time of trametinib initiation. …

Discussion

This retrospective study evaluates the efficacy of trametinib in pLGGs with a *BRAF* rearrangement. Our experience shows that the disease is radiologically and clinically controlled in three quarters of patients treated with trametinib. Moreover, more than one-third of the patients who discontinued therapy, maintained disease control for a median duration of 16.1 months after treatment cessation. We also report toxicities that may emerge with short but also prolonged exposure. Although mostly …

CRediT authorship contribution statement

Celine Khouri: Writing – original draft, Methodology, Formal analysis, Data curation. **Amandine Bibollet:** Investigation, Formal analysis. **Yassine Bouchoucha:** Writing – review & editing. **David Combarel:** Methodology, Formal analysis. **Julia Delahousse:** Writing – review & editing. **Isabelle Aerts:** Writing – review & editing. **Franck Bourdeaut:** Writing – review & editing. **Arnault Tauziede-Espariat:** Writing – review & editing. **Alice Metais:** Writing – review & editing. **Pascale Varlet:** Writing – review & …

Ethics approval

The study was approved by the Gustave Roussy Scientific Committee institutional review board (IRB: N°2023–240). …

Declaration

The author Birgit Geoerger is an Editor of the EJC and was not involved in the editorial review or the decision to publish this article. …

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Declaration of Competing Interest

The author Birgit Geoerger is an Associate Editor for this journal and was not involved in the editorial review or the decision to publish this article. The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Samuel Abbou** reports a patent for an oral suspension of temozolomide and has received research funding support as a consultant from FORE Pharmaceuticals, Lilly, Novartis, and Ipsen. **Pierre Leblond** reports …

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