Journal of Neuro-Oncology
https://doi.org/10.1007/s11060-020-03592-8

CLINICAL STUDY

Trametinib for the treatment of recurrent/progressive pediatric low-grade glioma

Neevika Manoharan[1,2] · Jungwhan Choi[3] · Christine Chordas[1] · Mary Ann Zimmerman[1] · Jacqueline Scully[1] · Jessica Clymer[1] · Mariella Filbin[1] · Nicole J. Ullrich[1,4] · Pratiti Bandopadhayay[1] · Susan N. Chi[1] · Kee Kiat Yeo[1]

Received: 15 June 2020 / Accepted: 7 August 2020

Abstract

Purpose Pediatric low-grade gliomas (pLGGs) are the most common CNS tumor of childhood and comprise a heterogenous group of tumors. Children with progressive pLGG often require numerous treatment modalities including surgery, chemotherapy, rarely radiation therapy and, more recently, molecularly targeted therapy. We describe our institutional experience using the MEK inhibitor, trametinib, for recurrent/progressive pLGGs.

Methods We performed a retrospective, IRB-approved, chart review of all pediatric patients treated with trametinib for recurrent/progressive pLGGs at Dana-Farber/Boston Children's Cancer and Blood Disorder Center between 2016 and 2018.

Results Eleven patients were identified, of which 10 were evaluable for response. Median age at commencement of trametinib treatment was 14.7 years (range 7.3–25.9 years). Tumor molecular status included KIAA1549-BRAF fusion (n = 4), NF1 mutation (n = 4), FGFR mutation (n = 1) and CDKN2A loss (n = 1). Median number of prior treatment regimens was 5 (range 1–12). Median duration of treatment with trametinib was 19.2 months (range 3.8–29.8 months). Based on modified RANO criteria, best responses included partial (n = 2), minor response (n = 2) and stable disease (n = 6). Two patients remain on therapy (29.8 and 25.9 months, respectively). The most common toxicities attributable to trametinib were rash, fatigue and gastrointestinal disturbance. Five patients required dose reduction for toxicities. Two patients experienced significant intracranial hemorrhage (ICH) while on trametinib. While it is unclear whether ICH was directly attributable to trametinib, therapy was discontinued.

Conclusion Trametinib appears to be an effective treatment for patients with recurrent/progressive pLGG. The toxicities of this therapy warrant further investigation, with particular attention to the potential risk for intracranial hemorrhage. Early phase multi-institutional clinical trials are underway.

Keywords Trametinib · MEK inhibitor · Low-grade glioma · Pediatric · MAPK · Central nervous system neoplasms

Introduction

Pediatric low-grade gliomas (pLGGs) constitute a heterogenous group of WHO grade I and II tumors, and are the most common central nervous system (CNS) tumor in children [1, 2]. These tumors are histologically classified based on the most important constitutive cell type, which includes astrocytic, oligodendroglial, mixed oligoastrocytic or mixed glioneuronal morphology. Of these, pilocytic astrocytomas (WHO grade I) are the most prevalent CNS tumor in children, accounting for almost one-quarter of all pediatric CNS tumors [3, 4]. For some patients, complete surgical resection of pLGGs in anatomically accessible locations of the brain and spine can be curative [5–7]. However, patients with tumors in eloquent anatomical regions typically cannot be

✉ Kee Kiat Yeo
keek_yeo@dfci.harvard.edu

1 Dana-Farber Cancer Institute, Boston Children's Cancer and Blood Disorder Center, 450 Brookline Ave, Boston, MA 02215-5450, USA

2 Kids Cancer Centre, Sydney Children's Hospital, Sydney, Australia

3 Department of Radiology, Boston Children's Hospital, Boston, USA

4 Department of Neurology, Boston Children's Hospital, Boston, USA

Published online: 11 August 2020

treated with complete resection and often require adjuvant therapy [1, 8]. These patients experience a higher rate of recurrence/progression and significantly greater tumor- and treatment-related morbidity [9, 10].

Multiple conventional chemotherapeutic regimens are used for the treatment of pLGG including combinations of carboplatin and vincristine (carbo/VCR); monotherapy with vinblastine (VBL), carboplatin, bevacizumab, or temozolomide; and combination therapy with thioguanine, procarbazine, lomustine and vincristine (TPCV) [10–15]. While these regimens are relatively efficacious in stabilizing disease, a significant proportion of patients still experience disease progression or recurrence during or subsequent to the completion of therapy. For example, the Children's Oncology Group (COG) pLGG study, CCG A9952, showed an excellent 5-year overall survival (OS) of 86% for children with pLGG without neurofibromatosis type 1 (NF1) but a significantly poorer 5-year progression-free survival (PFS) of 45% [10]. This discordance between OS and PFS in pLGG can be explained by the chronic indolent nature of pLGG, characterized by a slow, persistent and at-times erratic growth pattern throughout childhood and early adolescence, followed by a permanent cessation of tumor growth and senescence in early adulthood [16]. Malignant transformation is rare. For a subgroup of patients, pLGG represents a chronic disease for which multiple therapeutic approaches are required to achieve disease control [17]. These chemotherapeutic approaches are associated with variable side effect profiles including myelosuppression, immunosuppression, need for central line access and its inherent infectious risk, peripheral neuropathy, ototoxicity, infertility and secondary malignancy [10]. While radiotherapy has been shown to be an effective treatment modality for LGG, it is often deferred or avoided in young children due to the risk of neurocognitive sequelae, endocrinopathies, secondary malignancy and cerebrovascular disease [18–21]. Additionally, radiotherapy has also been shown to be an independent predictor of poorer overall survival in pLGG [17].

The mitogen activated protein kinase/extracellular-signal-regulated kinase (MAPK/ERK) pathway has been identified as a critical pathway involved in the oncogenesis of pLGG [22–26]. Most commonly, alterations involving the MAPK/ERK pathway in pLGG are due to the activation of the *BRAF* oncogene. In the vast majority of pilocytic astrocytomas, this occurs through a tandem duplication resulting in a *KIAA1549-BRAF* fusion. On the other hand, approximately 10–20% of all pLGG harbor an activating $BRAF^{V600}$ point mutation [27]. In addition to *BRAF* alterations, other somatic abnormalities involving the MAPK/ERK pathway have also been found in pLGG, further validating the key role of this oncogenic pathway in pLGGs [24]. Among others, these include abnormalities that affect NF1, FGFR1, KRAS and NTRK [28–30].

Targeting the MAPK/ERK pathway offers a novel therapeutic approach for incompletely resected or surgically inaccessible pLGG. MEK inhibitors, such as trametinib and selumetinib, are potent oral small molecule inhibitors of MEK1/2 (downstream target of MAPK pathway) that have been shown to cause regression of pLGG in vitro and in vivo [31, 32]. Recently, the Pediatric Brain Tumor Consortium (PBTC) completed early-phase clinical trials of selumetinib in pediatric patients with recurrent, refractory or progressive LGGs. These trials established a tolerable toxicity profile and demonstrated efficacy of selumetinib in pLGGs harboring common BRAF aberrations and NF1-associated pLGG [33, 34]. Given that selumetinib was only recently approved by the FDA for NF1-associated plexiform neurofibroma (approved 4/10/2020), trametinib (approved 5/29/2013) has in recent years been commonly used off-label in the treatment of patients with pLGG, with relatively limited data on the safety and efficacy in the pediatric population. Herein, we describe our institutional experience treating patients with recurrent/progressive pLGG with trametinib.

Methods

Patient selection

Patients treated for recurrent or progressive pediatric low-grade glioma between 2016 and 2018 were identified using an institutional database. Eligible patients were treated with trametinib for recurrent or progressive pLGG at Dana-Farber Cancer Institute/Boston Children's Cancer and Blood Disorder Center. Patients were excluded if they were treated with trametinib on a clinical trial. The Dana-Farber Cancer Institute institutional review board approved this retrospective review with waiver of individual consent.

Assessment

De-identified patient demographic information, clinicopathological features, molecular features, treatment regimens, clinical course, duration of follow-up and survival outcome were extracted from the medical records. *KIAA1549-BRAF* fusion was elucidated by FISH and/or array comparative genomic hybridization (CGH) in a CLIA-certified laboratory. Additional somatic mutations and pertinent rearrangements were identified using a combination of $BRAF^{V600}$ targeted PCR, CGH and OncoPanel, a validated targeted next-generation sequencing assay for the detection of somatic variants of cancer [35]. NF1 was diagnosed clinically.

Analysis

Tumor response evaluations were performed by pediatric neuro-radiologist (JC) based on modified Response Assessment in Neuro-Oncology (RANO) criteria [36]. In addition to the conventional RANO criteria, the modified RANO criteria includes minor response (MR), which is defined as 25–50% reduction in tumor size. Grading for toxicities were based on the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Results

Patient characteristics

We identified 11 patients (N = 6 males and 5 females) with radiological and/or histopathological features consistent with the diagnosis of pediatric low-grade glioma (pLGG) who were treated with trametinib for recurrent/progressive disease. Median age at start of trametinib was 14.7 years (range 7.3–25.9 years). The majority of patients (n = 6) had tumors located in the optic pathway and/or hypothalamic region. All patients started treatment at the recommended adult dose of trametinib (0.025 mg/kg daily). The median number of prior treatment regimens was 5 (range 1–12), and the median treatment duration with trametinib was 19.2 months (range 3.8–29.8 months). One patient (patient 6) was not eligible for toxicity/outcome evaluation due to early discontinuation of trametinib only one week after initiation of therapy, due to intratumoral hemorrhage diagnosed radiologically. Nine of eleven patients had histological confirmation of diagnosis of pLGG. Two patients with a clinical diagnosis of NF1 and optic pathway tumor did not undergo tumor biopsy. Molecular testing was attempted on all patients who underwent tumor biopsy or resection, with one patient having insufficient tissue for testing. Molecular analysis identified four patients with *KIAA1549-BRAF* fusion, one patient with a *FGFR* mutation and one patient with heterozygous *CDKN2A* loss. Four patients had a clinical diagnosis of neurofibromatosis type 1 and of these patients, two had confirmation of *NF1* inactivating mutations on tumor testing with OncoPanel [35]. Patient characteristics are described in Table 1.

Response and outcome

Ten patients were evaluable for toxicity and/or response. Six patients achieved stable disease (SD), two patients achieved minor responses (MR) and two patients achieved a partial response (PR) as best response (Figs. 1, 2). The median time-to-best radiological response was 9.8 months (range 3.8–22 months) with no significant objective visual improvement observed in patients with optic pathway gliomas. Two patients remain on therapy with trametinib (29.8 and 25.9 months on therapy, respectively) and three patients discontinued treatment after experiencing disease progression during treatment with trametinib. Two patients discontinued trametinib due to significant toxicity. Three patients (patients 4, 7 and 10) completed their respective planned courses of treatment, with two patients continuing to show stable disease 3.3 and 2.9 years after completion of trametinib. The one other patient (patient 7) showed evidence of disease progression after being off therapy for 6.5 months. Of note, patient 8 underwent a surgical procedure for tumor cyst progression after 4.9 months of treatment with trametinib and was subsequently restarted on the drug. This patient was not considered to be evaluable for radiographic response after surgical resection due to new radiological baseline. Patient responses are described in Table 1.

The most common toxicities observed were skin rash, fatigue and gastrointestinal disturbance. All of the ten evaluable patients experienced skin toxicity (Grade 1–3), seven (7/10, 70%) experienced gastrointestinal toxicities (Grade 1–3) and six (6/10, 60%) experienced fatigue (Grade 1–3). Grade 1 eosinophilia was noted in four patients. One patient (patient 4) required treatment interruption and dose reduction for retinal pigment epithelial detachment, with resolution of side effect after holding treatment for 4 weeks. For this patient, trametinib was restarted at 75% dosing without recurrence of retinal pigment epithelial detachment. Two patients (20%) experienced alopecia/hair thinning. Five patients (50%) required dose reduction for toxicities. Of note, due to its unclear significance, creatine kinase levels were not uniformly followed in all patients. Both patients who had CK levels monitored demonstrated grade 1 elevation and were asymptomatic. Toxicities are as listed in Table 2.

Two patients experienced symptomatic ICH while on trametinib (at 5 and 498 days), with another patient developing asymptomatic intratumoral petechial hemorrhage. Patient 1 experienced an atraumatic and acute neurological deterioration with alteration of mental status 16.4 months after commencing trametinib and was found to have a significant intracranial hemorrhage including intratumoral and peritumoral components (Fig. 3). This patient suffered devastating neurological sequelae including short-term memory loss, speech and swallow dysfunction and did not make a significant neurological recovery despite intensive rehabilitation. Patient 6 developed acute-onset right hemiplegia 5 days after initiation of trametinib in the setting of previous surgical laser ablation for a left thalamo-capsular pilocytic astrocytoma and was found to have a significant intratumoral hemorrhage. She regained some degree of functional strength with intensive rehabilitation. Patient 5 developed asymptomatic intratumoral petechial hemorrhage 22 months

Table 1 Patient characteristics and response

ID	Age at start of trametinib	Sex	Tumor location	Histology	Molecular status	No. of prior treatment regimens	Best response (% reduction)	Best response*	Time to best response (months)	Duration of treatment on trametinib (months)	Reason for discontinuation of trametinib
1	16.3	M	Optic pathway/ hypothalamus	Low grade glioma	FGFR mutation	5	10.9	SD	4.8	16.4	Intracranial hemorrhage
2	8.1	M	Optic pathway/ hypothalamus	N/A	Clinical NF1	3	66.7	PR	12.9	14.1	Clinical progression
3	19.6	F	Cervicomedullary junction	Pilocytic astrocytoma	Heterozygous CDKN2A loss	12	32.4	MR	4.5	29.8	N/A[#]
4	14.1	F	Optic pathway/ hypothalamus	Pilocytic astrocytoma	KIAA 1549-BRAF fusion	5	48	MR	20.9	27.2	Completion of therapy
5	15.9	M	Brain stem	Pilocytic astrocytoma	Unknown	5	24.6	SD	22.0	22.0	Intratumoral petechial hemorrhage
6	25.9	F	Midbrain/thalamic	Pilocytic astrocytoma	KIAA 1549-BRAF fusion	1	Not evaluable[^]				Intracranial hemorrhage
7	14.7	F	Hypothalamus	Pilomyxoid astrocytoma	KIAA 1549-BRAF fusion	4	21	SD	9.7	12.7	Completion of therapy
8	12.1	M	Septum pellucidum	Low grade glioma	NF1	6	0.6	SD	4.8	25.9	N/A[#]
9	7.3	F	Optic pathway/ hypothalamus	Pilocytic astrocytoma	KIAA 1549-BRAF fusion	4	6.5	SD	3.8	3.8	Clinical progression
10	17.2	M	Brain stem	Low grade glioma	NF1	1	8	SD	15.7	24.2	Completion of therapy
11	12.4	M	Optic pathway/ hypothalamus	N/A	Clinical NF1	5	70	PR	9.9	14.2	Progression

*Based on modified RANO for LGG

[^]Non evaluable due to ICH after 5 days of therapy

[#]Continues on therapy

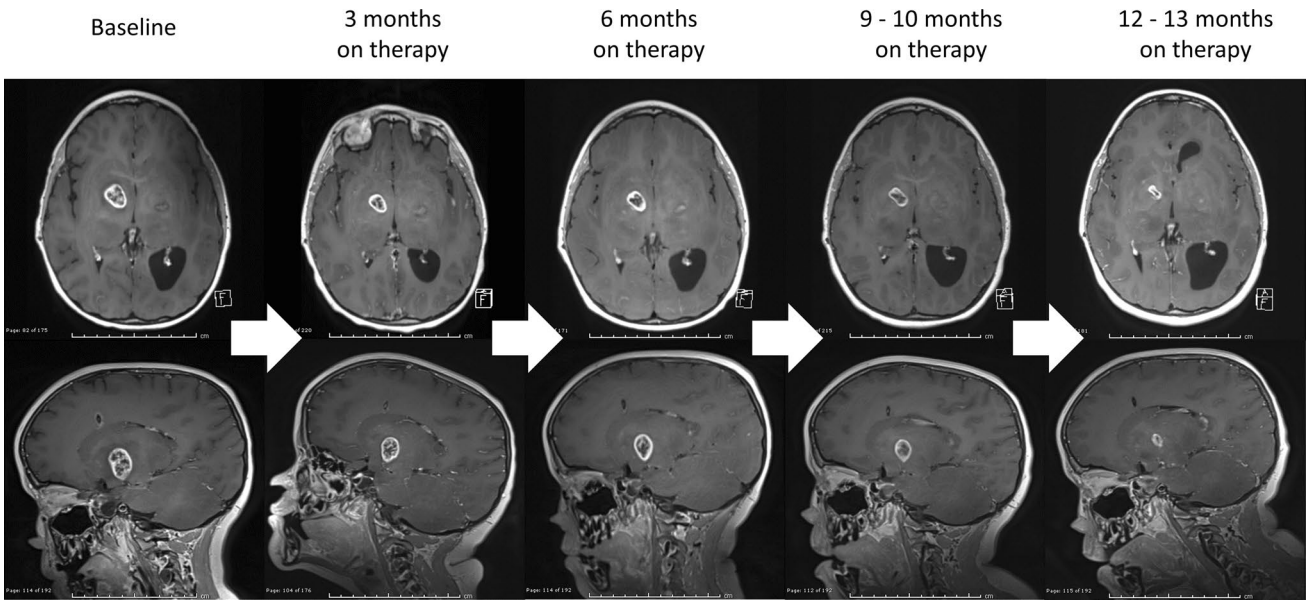

Fig. 1 Axial and sagittal T1 weighted contrast enhanced images demonstrate decreasing size of an enhancing tumor in the right globus pallidus (partial response per modified RANO)

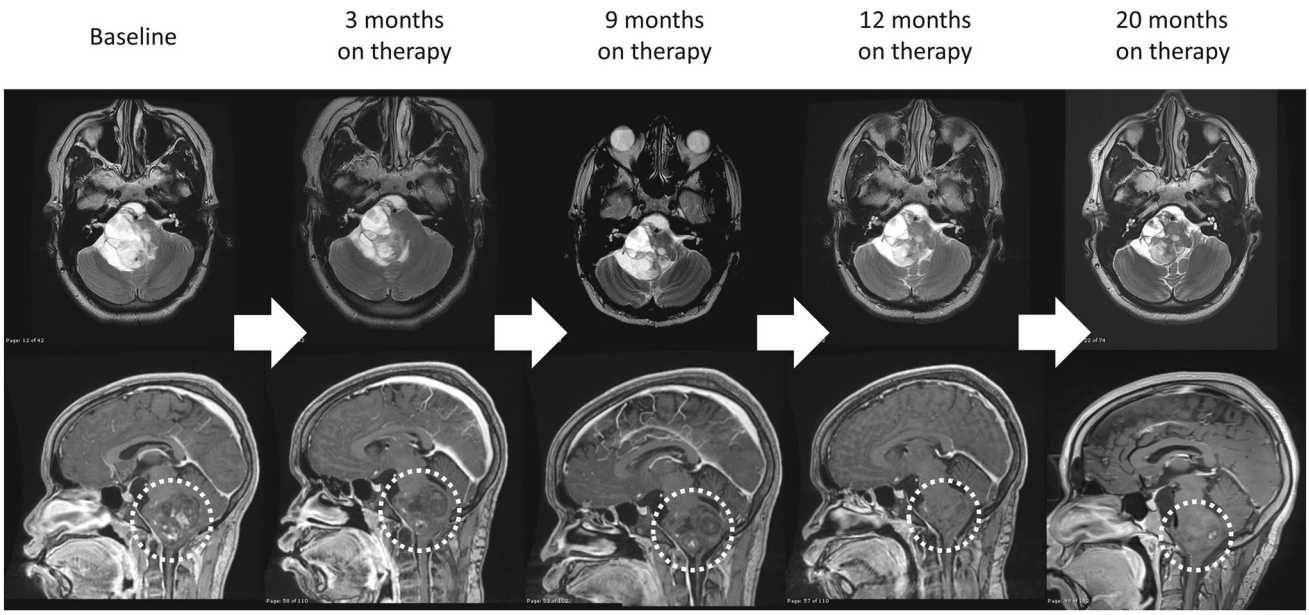

Fig. 2 Axial T2 weighted and sagittal T1 weighted contrast enhanced images demonstrate gradually decreasing size and enhancement (dotted circle) of a mixed cystic and solid tumor centered in the right cervicomedullary junction (minor response per modified RANO)

after trametinib. While it is unclear whether these incidences of ICH were attributable to trametinib, therapy was discontinued immediately for all three patients.

Discussion

Despite excellent long-term overall survival, incompletely resected pLGGs are often associated with substantial disease-related morbidity and frequent disease recurrences necessitating multiple modalities of treatment including

Table 2 Toxicities

Toxicity	Grade				No. of patients requiring dose reduction	No. of pts requiring permanent cessation of drug
	1	2	3	4		
N						
Skin Acneiform rash Maculopapular rash Palmar-plantar erythrodysesthesia Inflammatory eruptions Dry skin	4	4	2			
Fatigue	1	4	1		1	
Gastrointestinal Diarrhea Nausea Abdominal discomfort Anorexia Stomatitis	4	2	1		2	
Paronychia	1	2				
Abnormal LFTs			1		1	
ICH		1		1		2
Intratumoral petechial hemorrhage	1					1
Ophthalmological						
Retinal pigment epithelial detachment			1		1	
Alopecia/hair thinning	1	1				
Hyperlipidemia	2					
Eosinophilia	4					
Elevated CK	2					

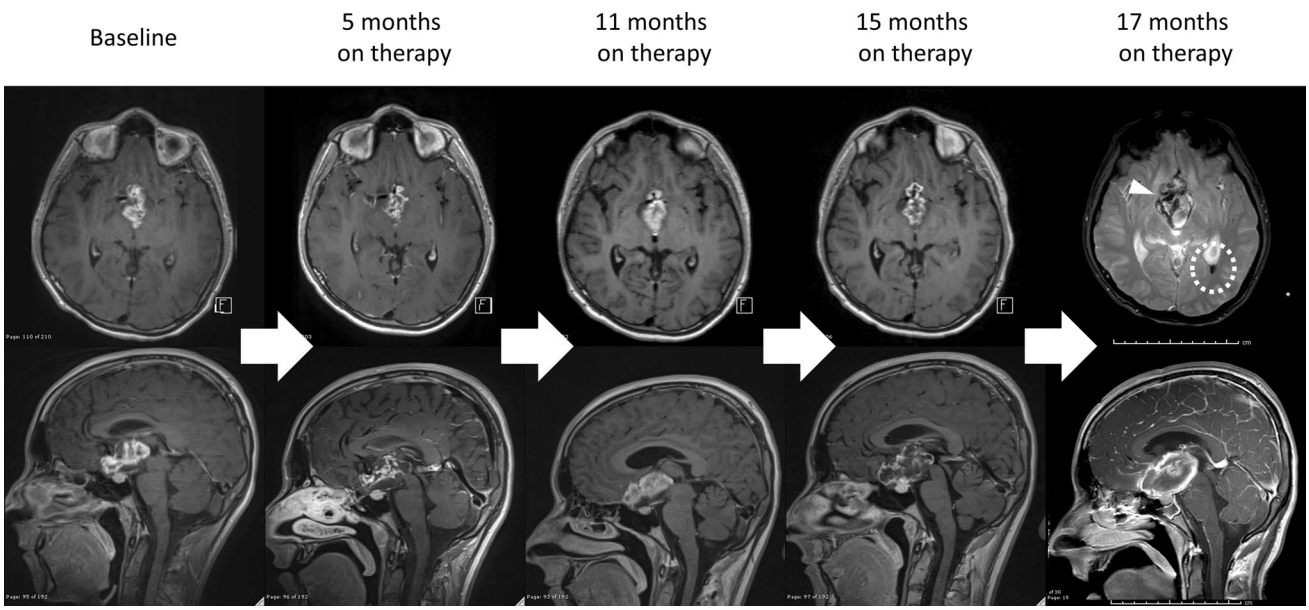

Fig. 3 Axial and sagittal T1 contrast enhanced images demonstrate an optic pathway tumor with response at 5 months of therapy followed by gradually increasing size of the mass at 11 and 15 months. Axial T2* and sagittal T1 contrast enhanced images at 17 months on therapy demonstrate development of tumoral hemorrhage (white arrowhead) as well as intraventricular hemorrhage with layering of the blood product in the occipital horn of the left lateral ventricle (dotted circle)

repeated aggressive surgical resection and numerous chemotherapy regimens. Even with these approaches, many patients suffer from significant neurological and endocrinological sequelae, including vision loss, growth failure, hypothalamic obesity and motor dysfunction [5, 17, 37]. In recent years, development of targeted therapies has dramatically changed the landscape of pLGG treatment by targeting the MAPK/ERK pathway, the characteristic genetic aberration in pLGG [22–24]. Several drugs that target the MAPK pathway have been developed, including inhibitors of MEK1/2 (selumetinib, trametinib, binimetinib, cobimetinib) and BRAF (dabrafenib, vemurafenib) [32, 34, 38]. These therapies offer both novel opportunities to patients with relapsed/refractory disease but also present unique challenges including distinct adverse effects [34, 38].

This cohort represents a relatively large case series of recurrent/progressive pLGG treated with trametinib and adds to the emerging literature on the use of these targeted agents in children and young adults with CNS tumors [39, 40]. In this study, we report tumor responses in a heterogenous and heavily pre-treated patient cohort that includes a subset of patients with NF1. Of note, two patients with NF1 optic pathway tumor did not undergo biopsy for histopathological confirmation and was diagnosed based on clinical and radiographic features. This practice is consistent with the recommendation from the NF1 consensus conference [41]. The heterogeneity in patient population, tumor location and molecular diagnosis are in line with the published literature on pLGG [17, 27, 42]. Our findings show that the best radiological tumor response of PR occurred in two patients with NF1 (patient 2 & 11), while minor responses (MR) were observed in two patients with variable molecular findings including *KIAA1549-BRAF* fusion and heterozygous CDKN2A loss. As best response, all evaluable patients had stable disease or better. Majority of patients had at least sustained stable disease, with three patients eventually discontinuing therapy secondary to clinical or radiographic progression. For patients with initial radiographic response (stable disease or better) prior to radiographic disease progression, median duration of disease stabilization was one year. Given the favorable response in this heavily pre-treated cohort, these findings support the use of trametinib as an effective treatment for recurrent/progressive pLGG and are consistent with several other smaller case series, as well as the recently published PBTC phase 2 trial of selumetinib in pediatric patients with recurrent, refractory or progressive pLGG [34, 39, 40, 43, 44].

Trametinib was generally well tolerated in our patient cohort. All evaluable patients experienced skin toxicity, with severity ranging from a mild maculopapular or acneiform rash to more significant inflammatory eruptions, requiring both topical and systemic antibiotic as well as anti-inflammatory management strategies. Skin toxicity has been well established as the most frequent toxicity with MEK inhibitors [39, 45, 46]. Paronychia is also a common side effect associated with MEK inhibitors, and these were seen in our patient group, with some requiring antimicrobial management. Despite its common occurrence, no patients in our cohort required dose reduction or therapy cessation for skin or nail toxicity. Other toxicities that were observed commonly included gastrointestinal disturbances and fatigue, with two patients undergoing dose reduction for these toxicities (see Table 2). One patient required temporary cessation and subsequent dose reduction of trametinib due to reversible grade 3 bilateral retinal pigment epithelial detachment. Of note, two patients in our cohort experienced significant intracranial hemorrhages (ICH) and one patient developed asymptomatic intratumoral petechial hemorrhage, all resulting in permanent cessation of trametinib. It is important to note that both patients with symptomatic ICH had tumor- and/or treatment-related factors that may have been causative or contributory to a risk of ICH. Patient 1 was noted to have a tumor with surrounding vascular enhancement and had previously received bevacizumab, which has a known risk of hemorrhagic complications [47]. Patient 6, on the other hand, underwent laser ablation as a component of her surgical resection and it is unclear whether this contributed to her subsequent ICH. Of note, none of these patients exhibited any clinical (no bruising/bleeding/petechial rash) or laboratory findings (normal platelet counts) indicative of an increased risk of bleeding prior to developing ICH. Intra-tumoral hemorrhage and ICH have been reported in the literature with targeted biologic therapies. As such, until toxicity/safety data are available from larger cohorts, careful consideration is necessary when contemplating initiation of these therapies, especially in patients with other risk factors associated with the development of intratumoral/intracranial hemorrhage [48, 49].

Notably, our patient population represented an older cohort of patients with pLGG with a median age of 14.7 years at start of trametinib. In addition, the tablet formulation often precludes administration in very young patients who may not be able to swallow tablets. In our cohort, there was a lack of significant improvement in visual acuity. This lack of visual improvement is not unexpected, as longstanding visual impairment due to disease and optic nerve atrophy are generally thought to be irreversible [50]. Of note, one patient (patient 2) developed worsening of visual acuity despite excellent response to trametinib, necessitating cessation of therapy for clinical progression. Another interesting finding in our analysis was the time-to-best radiological response in our cohort. The median time-to-best radiological response in our cohort was 9.8 months, which is substantially longer than the time-to-best response previously described with

BRAF inhibitors [51]. In fact, one patient in our cohort had their best radiological response (24.6% tumor reduction) 22 months after initiation of treatment. Our finding suggests the need for a protracted treatment course to achieve best tumor response and is consistent with the findings in patients with NF1-associated plexiform treated with selumetinib, where the median time-to-best response was reported after 20 cycles [52]. It is important to note however, that the long-term morbidity of targeted agents such as trametinib is not yet known, and the optimal treatment duration for pLGG with these agents is unclear.

For several patients in our cohort, their histological diagnosis was finalized as low-grade glioma, without specific WHO grading. This reflects the difficulty in grading some pLGGs, given the well-established overlapping morphological features of certain entities within this group. Precise histological diagnosis is particularly challenging for midline tumors, for which a small biopsy is typically all that is available [53]. It is noteworthy that all three patients in our cohort with histological diagnosis of low-grade glioma (without specific WHO grading) had midline tumors. One patient in our cohort demonstrated heterozygous loss of CDKN2A. This patient underwent comprehensive genetic testing that were otherwise negative except for this finding. While loss of CDKN2A has been associated with increased risk for malignant progression, the level of risk is unclear [54].

This study is limited by the small sample size and single institution retrospective design. In addition, this cohort is molecularly heterogeneous. Although this is consistent with the known landscape of pLGG, this also limits the ability to make more specific inferences or analysis. Despite these limitations, with the increasingly common use of trametinib for pediatric brain tumors, our experience adds meaningful clinical data to use of trametinib in pLGG.

Conclusion

In summary, our single institution experience shows that trametinib appears to be an effective treatment for patients with recurrent/progressive pLGG in a heterogeneous and pre-treated patient cohort. The toxicities of this therapy warrant further investigation, particularly the potential increase in risk for intracranial hemorrhage. Early-phase clinical trials using trametinib in the treatment of children with pLGG are currently underway to better evaluate tumor response and toxicity profile in a larger cohort.

Acknowledgements The authors have no further acknowledgments.

Funding No conflicts of interests or external funding to report.

Compliance with ethical standards

Conflict of interest No conflicts of interests or competing interests to report.

References

1. Chalil A, Ramaswamy V (2016) Low grade gliomas in children. J Child Neurol 31:517–522. https://doi.org/10.1177/0883073815599259
2. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS (2018) CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2011–2015. Neuro Oncol 20:iv1–iv86. https://doi.org/10.1093/neuonc/noy131
3. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW (2016) The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 131:803–820. https://doi.org/10.1007/s00401-016-1545-1
4. Rickert CH, Paulus W (2001) Epidemiology of central nervous system tumors in childhood and adolescence based on the new WHO classification. Childs Nerv Syst 17:503–511. https://doi.org/10.1007/s003810100496
5. Gajjar A, Sanford RA, Heideman R, Jenkins JJ, Walter A, Li Y, Langston JW, Muhlbauer M, Boyett JM, Kun LE (1997) Low-grade astrocytoma: a decade of experience at St. Jude Children's Research Hospital. J Clin Oncol 15:2792–2799. https://doi.org/10.1200/JCO.1997.15.8.2792
6. Stokland T, Liu JF, Ironside JW, Ellison DW, Taylor R, Robinson KJ, Picton SV, Walker DA (2010) A multivariate analysis of factors determining tumor progression in childhood low-grade glioma: a population-based cohort study (CCLG CNS9702). Neuro Oncol 12:1257–1268. https://doi.org/10.1093/neuonc/noq092
7. Wisoff JH, Sanford RA, Heier LA, Sposto R, Burger PC, Yates AJ, Holmes EJ, Kun LE (2011) Primary neurosurgery for pediatric low-grade gliomas: a prospective multi-institutional study from the Children's Oncology Group. Neurosurgery 68:1548–1554. https://doi.org/10.1227/NEU.0b013e318214a66e (**discussion 1554–1545**)
8. Sievert AJ, Fisher MJ (2009) Pediatric low-grade gliomas. J Child Neurol 24:1397–1408. https://doi.org/10.1177/0883073809342005
9. Bouffet E, Jakacki R, Goldman S, Hargrave D, Hawkins C, Shroff M, Hukin J, Bartels U, Foreman N, Kellie S, Hilden J, Etzl M, Wilson B, Stephens D, Tabori U, Baruchel S (2012) Phase II study of weekly vinblastine in recurrent or refractory pediatric low-grade glioma. J Clin Oncol 30:1358–1363. https://doi.org/10.1200/JCO.2011.34.5843
10. Ater JL, Zhou T, Holmes E, Mazewski CM, Booth TN, Freyer DR, Lazarus KH, Packer RJ, Prados M, Sposto R, Vezina G, Wisoff JH, Pollack IF (2012) Randomized study of two chemotherapy regimens for treatment of low-grade glioma in young children: a report from the Children's Oncology Group. J Clin Oncol 30:2641–2647. https://doi.org/10.1200/JCO.2011.36.6054
11. Lassaletta A, Scheinemann K, Zelcer SM, Hukin J, Wilson BA, Jabado N, Carret AS, Lafay-Cousin L, Larouche V, Hawkins CE, Pond GR, Poskitt K, Keene D, Johnston DL, Eisenstat DD, Krishnatry R, Mistry M, Arnoldo A, Ramaswamy V, Huang A, Bartels U, Tabori U, Bouffet E (2016) Phase II weekly vinblastine for chemotherapy-naive children with progressive

low-grade glioma: a Canadian Pediatric Brain Tumor Consortium Study. J Clin Oncol 34:3537–3543. https://doi.org/10.1200/JCO.2016.68.1585
12. de Blank P, Bandopadhayay P, Haas-Kogan D, Fouladi M, Fangusaro J (2019) Management of pediatric low-grade glioma. Curr Opin Pediatr 31:21–27. https://doi.org/10.1097/MOP.0000000000000717
13. Dodgshun AJ, Maixner WJ, Heath JA, Sullivan MJ, Hansford JR (2016) Single agent carboplatin for pediatric low-grade glioma: a retrospective analysis shows equivalent efficacy to multiagent chemotherapy. Int J Cancer 138:481–488. https://doi.org/10.1002/ijc.29711
14. Hwang EI, Jakacki RI, Fisher MJ, Kilburn LB, Horn M, Vezina G, Rood BR, Packer RJ (2013) Long-term efficacy and toxicity of bevacizumab-based therapy in children with recurrent low-grade gliomas. Pediatr Blood Cancer 60:776–782. https://doi.org/10.1002/pbc.24297
15. Chintagumpala M, Eckel SP, Krailo M, Morris M, Adesina A, Packer R, Lau C, Gajjar A (2015) A pilot study using carboplatin, vincristine, and temozolomide in children with progressive/symptomatic low-grade glioma: a Children's Oncology Group studydagger. Neuro Oncol 17:1132–1138. https://doi.org/10.1093/neuonc/nov057
16. Tabori U, Vukovic B, Zielenska M, Hawkins C, Braude I, Rutka J, Bouffet E, Squire J, Malkin D (2006) The role of telomere maintenance in the spontaneous growth arrest of pediatric low-grade gliomas. Neoplasia 8:136–142. https://doi.org/10.1593/neo.05715
17. Bandopadhayay P, Bergthold G, London WB, Goumnerova LC, Morales La Madrid A, Marcus KJ, Guo D, Ullrich NJ, Robison NJ, Chi SN, Beroukhim R, Kieran MW, Manley PE (2014) Long-term outcome of 4,040 children diagnosed with pediatric low-grade gliomas: an analysis of the Surveillance Epidemiology and End Results (SEER) database. Pediatr Blood Cancer 61:1173–1179. https://doi.org/10.1002/pbc.24958
18. Chadderton RD, West CG, Schuller S, Quirke DC, Gattamaneni R, Taylor R (1995) Radiotherapy in the treatment of low-grade astrocytomas. II. The physical and cognitive sequelae. Childs Nerv Syst 11:443–448
19. West CG, Gattamaneni R, Blair V (1995) Radiotherapy in the treatment of low-grade astrocytomas. I. A survival analysis. Childs Nerv Syst 11:438–442
20. Ullrich NJ, Robertson R, Kinnamon DD, Scott RM, Kieran MW, Turner CD, Chi SN, Goumnerova L, Proctor M, Tarbell NJ, Marcus KJ, Pomeroy SL (2007) Moyamoya following cranial irradiation for primary brain tumors in children. Neurology 68:932–938. https://doi.org/10.1212/01.wnl.0000257095.33125.48
21. Merchant TE, Kun LE, Wu S, Xiong X, Sanford RA, Boop FA (2009) Phase II trial of conformal radiation therapy for pediatric low-grade glioma. J Clin Oncol 27:3598–3604. https://doi.org/10.1200/JCO.2008.20.9494
22. Jones DT, Kocialkowski S, Liu L, Pearson DM, Backlund LM, Ichimura K, Collins VP (2008) Tandem duplication producing a novel oncogenic BRAF fusion gene defines the majority of pilocytic astrocytomas. Cancer Res 68:8673–8677. https://doi.org/10.1158/0008-5472.CAN-08-2097
23. Forshew T, Tatevossian RG, Lawson AR, Ma J, Neale G, Ogunkolade BW, Jones TA, Aarum J, Dalton J, Bailey S, Chaplin T, Carter RL, Gajjar A, Broniscer A, Young BD, Ellison DW, Sheer D (2009) Activation of the ERK/MAPK pathway: a signature genetic defect in posterior fossa pilocytic astrocytomas. J Pathol 218:172–181. https://doi.org/10.1002/path.2558
24. Jones DT, Kocialkowski S, Liu L, Pearson DM, Ichimura K, Collins VP (2009) Oncogenic RAF1 rearrangement and a novel BRAF mutation as alternatives to KIAA1549:BRAF fusion in activating the MAPK pathway in pilocytic astrocytoma. Oncogene 28:2119–2123. https://doi.org/10.1038/onc.2009.73
25. Pfister S, Janzarik WG, Remke M, Ernst A, Werft W, Becker N, Toedt G, Wittmann A, Kratz C, Olbrich H, Ahmadi R, Thieme B, Joos S, Radlwimmer B, Kulozik A, Pietsch T, Herold-Mende C, Gnekow A, Reifenberger G, Korshunov A, Scheurlen W, Omran H, Lichter P (2008) BRAF gene duplication constitutes a mechanism of MAPK pathway activation in low-grade astrocytomas. J Clin Investig 118:1739–1749. https://doi.org/10.1172/JCI33656
26. Zhang J, Wu G, Miller CP, Tatevossian RG, Dalton JD, Tang B, Orisme W, Punchihewa C, Parker M, Qaddoumi I, Boop FA, Lu C, Kandoth C, Ding L, Lee R, Huether R, Chen X, Hedlund E, Nagahawatte P, Rusch M, Boggs K, Cheng J, Becksfort J, Ma J, Song G, Li Y, Wei L, Wang J, Shurtleff S, Easton J, Zhao D, Fulton RS, Fulton LL, Dooling DJ, Vadodaria B, Mulder HL, Tang C, Ochoa K, Mullighan CG, Gajjar A, Kriwacki R, Sheer D, Gilbertson RJ, Mardis ER, Wilson RK, Downing JR, Baker SJ, Ellison DW, St. Jude Children's Research Hospital-Washington University Pediatric Cancer Genome P (2013) Whole-genome sequencing identifies genetic alterations in pediatric low-grade gliomas. Nat Genet 45:602–612. https://doi.org/10.1038/ng.2611
27. Packer RJ, Pfister S, Bouffet E, Avery R, Bandopadhayay P, Bornhorst M, Bowers DC, Ellison D, Fangusaro J, Foreman N, Fouladi M, Gajjar A, Haas-Kogan D, Hawkins C, Ho CY, Hwang E, Jabado N, Kilburn LB, Lassaletta A, Ligon KL, Massimino M, Meeteren SV, Mueller S, Nicolaides T, Perilongo G, Tabori U, Vezina G, Warren K, Witt O, Zhu Y, Jones DT, Kieran M (2017) Pediatric low-grade gliomas: implications of the biologic era. Neuro Oncol 19:750–761. https://doi.org/10.1093/neuonc/now209
28. Varan A, Sen H, Aydin B, Yalcin B, Kutluk T, Akyuz C (2016) Neurofibromatosis type 1 and malignancy in childhood. Clin Genet 89:341–345. https://doi.org/10.1111/cge.12625
29. Collins VP, Jones DT, Giannini C (2015) Pilocytic astrocytoma: pathology, molecular mechanisms and markers. Acta Neuropathol 129:775–788. https://doi.org/10.1007/s00401-015-1410-7
30. Jones DT, Hutter B, Jager N, Korshunov A, Kool M, Warnatz HJ, Zichner T, Lambert SR, Ryzhova M, Quang DA, Fontebasso AM, Stutz AM, Hutter S, Zuckermann M, Sturm D, Gronych J, Lasitschka B, Schmidt S, Seker-Cin H, Witt H, Sultan M, Ralser M, Northcott PA, Hovestadt V, Bender S, Pfaff E, Stark S, Faury D, Schwartzentruber J, Majewski J, Weber UD, Zapatka M, Raeder B, Schlesner M, Worth CL, Bartholomae CC, von Kalle C, Imbusch CD, Radomski S, Lawerenz C, van Sluis P, Koster J, Volckmann R, Versteeg R, Lehrach H, Monoranu C, Winkler B, Unterberg A, Herold-Mende C, Milde T, Kulozik AE, Ebinger M, Schuhmann MU, Cho YJ, Pomeroy SL, von Deimling A, Witt O, Taylor MD, Wolf S, Karajannis MA, Eberhart CG, Scheurlen W, Hasselblatt M, Ligon KL, Kieran MW, Korbel JO, Yaspo ML, Brors B, Felsberg J, Reifenberger G, Collins VP, Jabado N, Eils R, Lichter P, Pfister SM, International Cancer Genome Consortium PedBrain Tumor P (2013) Recurrent somatic alterations of FGFR1 and NTRK2 in pilocytic astrocytoma. Nat Genet 45:927–932. https://doi.org/10.1038/ng.2682
31. Kolb EA, Gorlick R, Houghton PJ, Morton CL, Neale G, Keir ST, Carol H, Lock R, Phelps D, Kang MH, Reynolds CP, Maris JM, Billups C, Smith MA (2010) Initial testing (stage 1) of AZD6244 (ARRY-142886) by the Pediatric Preclinical Testing Program. Pediatr Blood Cancer 55:668–677. https://doi.org/10.1002/pbc.22576
32. Kieran MW (2014) Targeting BRAF in pediatric brain tumors. Am Soc Clin Oncol Educ Book. https://doi.org/10.14694/EdBook_AM.2014.34.e436
33. Banerjee A, Jakacki RI, Onar-Thomas A, Wu S, Nicolaides T, Young Poussaint T, Fangusaro J, Phillips J, Perry A, Turner D, Prados M, Packer RJ, Qaddoumi I, Gururangan S, Pollack IF, Goldman S, Doyle LA, Stewart CF, Boyett JM, Kun LE, Fouladi M (2017) A phase I trial of the MEK inhibitor selumetinib (AZD6244) in pediatric patients with recurrent or refractory low-grade glioma:

a Pediatric Brain Tumor Consortium (PBTC) study. Neuro Oncol 19:1135–1144. https://doi.org/10.1093/neuonc/now282
34. Fangusaro J, Onar-Thomas A, Young Poussaint T, Wu S, Ligon AH, Lindeman N, Banerjee A, Packer RJ, Kilburn LB, Goldman S, Pollack IF, Qaddoumi I, Jakacki RI, Fisher PG, Dhall G, Baxter P, Kreissman SG, Stewart CF, Jones DTW, Pfister SM, Vezina G, Stern JS, Panigrahy A, Patay Z, Tamrazi B, Jones JY, Haque SS, Enterline DS, Cha S, Fisher MJ, Doyle LA, Smith M, Dunkel IJ, Fouladi M (2019) Selumetinib in paediatric patients with BRAF-aberrant or neurofibromatosis type 1-associated recurrent, refractory, or progressive low-grade glioma: a multicentre, phase 2 trial. Lancet Oncol. https://doi.org/10.1016/S1470-2045(19)30277-3
35. Garcia EP, Minkovsky A, Jia Y, Ducar MD, Shivdasani P, Gong X, Ligon AH, Sholl LM, Kuo FC, MacConaill LE, Lindeman NI, Dong F (2017) Validation of OncoPanel: a targeted next-generation sequencing assay for the detection of somatic variants in cancer. Arch Pathol Lab Med 141:751–758. https://doi.org/10.5858/arpa.2016-0527-OA
36. Wen PY, Chang SM, Van den Bent MJ, Vogelbaum MA, Macdonald DR, Lee EQ (2017) Response assessment in neuro-oncology clinical trials. J Clin Oncol 35:2439–2449. https://doi.org/10.1200/JCO.2017.72.7511
37. Liu APY, Hastings C, Wu S, Bass JK, Heitzer AM, Ashford J, Vestal R, Hoehn ME, Ghazwani Y, Acharya S, Conklin HM, Boop F, Merchant TE, Gajjar A, Qaddoumi I (2019) Treatment burden and long-term health deficits of patients with low-grade gliomas or glioneuronal tumors diagnosed during the first year of life. Cancer 125:1163–1175. https://doi.org/10.1002/cncr.31918
38. Kieran MW, Geoerger B, Dunkel IJ, Broniscer A, Hargrave D, Hingorani P, Aerts I, Bertozzi AI, Cohen KJ, Hummel TR, Shen V, Bouffet E, Pratilas CA, Pearson ADJ, Tseng L, Nebot N, Green S, Russo MW, Whitlock JA (2019) A Phase I and pharmacokinetic study of oral dabrafenib in children and adolescent patients with recurrent or refractory BRAF V600 mutation-positive solid tumors. Clin Cancer Res 25:7294–7302. https://doi.org/10.1158/1078-0432.CCR-17-3572
39. Kondyli M, Larouche V, Saint-Martin C, Ellezam B, Pouliot L, Sinnett D, Legault G, Crevier L, Weil A, Farmer JP, Jabado N, Perreault S (2018) Trametinib for progressive pediatric low-grade gliomas. J Neurooncol 140:435–444. https://doi.org/10.1007/s11060-018-2971-9
40. Perreault S, Larouche V, Tabori U, Hawkin C, Lippe S, Ellezam B, Decarie JC, Theoret Y, Metras ME, Sultan S, Cantin E, Routhier ME, Caru M, Legault G, Bouffet E, Lafay-Cousin L, Hukin J, Erker C, Jabado N (2019) A phase 2 study of trametinib for patients with pediatric glioma or plexiform neurofibroma with refractory tumor and activation of the MAPK/ERK pathway: TRAM-01. BMC Cancer 19:1250. https://doi.org/10.1186/s12885-019-6442-2
41. Packer RJ, Iavarone A, Jones DTW, Blakeley JO, Bouffet E, Fisher MJ, Hwang E, Hawkins C, Kilburn L, MacDonald T, Pfister SM, Rood B, Rodriguez FJ, Tabori U, Ramaswamy V, Zhu Y, Fangusaro J, Johnston SA, Gutmann DH (2020) Implications of new understandings of gliomas in children and adults with NF1: report of a consensus conference. Neuro Oncol 22:773–784. https://doi.org/10.1093/neuonc/noaa036
42. Jones DTW, Kieran MW, Bouffet E, Alexandrescu S, Bandopadhayay P, Bornhorst M, Ellison D, Fangusaro J, Fisher MJ, Foreman N, Fouladi M, Hargrave D, Hawkins C, Jabado N, Massimino M, Mueller S, Perilongo G, Schouten van Meeteren AYN, Tabori U, Warren K, Waanders AJ, Walker D, Weiss W, Witt O, Wright K, Zhu Y, Bowers DC, Pfister SM, Packer RJ (2018) Pediatric low-grade gliomas: next biologically driven steps. Neuro Oncol 20:160–173. https://doi.org/10.1093/neuonc/nox141
43. Miller C, Guillaume D, Dusenbery K, Clark HB, Moertel C (2017) Report of effective trametinib therapy in 2 children with progressive hypothalamic optic pathway pilocytic astrocytoma: documentation of volumetric response. J Neurosurg Pediatr 19:319–324. https://doi.org/10.3171/2016.9.PEDS16328
44. Drobysheva A, Klesse LJ, Bowers DC, Rajaram V, Rakheja D, Timmons CF, Wang J, Koral K, Gargan L, Ramos E, Park JY (2017) Targeted MAPK pathway inhibitors in patients with disseminated pilocytic astrocytomas. J Natl Compr Cancer Netw 15:978–982. https://doi.org/10.6004/jnccn.2017.0139
45. Blumenschein GR Jr, Smit EF, Planchard D, Kim DW, Cadranel J, De Pas T, Dunphy F, Udud K, Ahn MJ, Hanna NH, Kim JH, Mazieres J, Kim SW, Baas P, Rappold E, Redhu S, Puski A, Wu FS, Janne PA (2015) A randomized phase II study of the MEK1/MEK2 inhibitor trametinib (GSK1120212) compared with docetaxel in KRAS-mutant advanced non-small-cell lung cancer (NSCLC) dagger. Ann Oncol 26:894–901. https://doi.org/10.1093/annonc/mdv072
46. Anforth R, Liu M, Nguyen B, Uribe P, Kefford R, Clements A, Long GV, Fernandez-Penas P (2014) Acneiform eruptions: a common cutaneous toxicity of the MEK inhibitor trametinib. Australas J Dermatol 55:250–254. https://doi.org/10.1111/ajd.12124
47. Hapani S, Sher A, Chu D, Wu S (2010) Increased risk of serious hemorrhage with bevacizumab in cancer patients: a meta-analysis. Oncology 79:27–38. https://doi.org/10.1159/000314980
48. le Lee M, Feun L, Tan Y (2014) A case of intracranial hemorrhage caused by combined dabrafenib and trametinib therapy for metastatic melanoma. Am J Case Rep 15:441–443. https://doi.org/10.12659/AJCR.890875
49. Loyson T, Werbrouck E, Punie K, Bonne L, Vandecaveye V, Bechter O (2018) Hemorrhage of liver and bone metastases as a result of rapid response to dual BRAF/MEK inhibition in metastatic melanoma: a case report. Melanoma Res 28:147–150. https://doi.org/10.1097/CMR.0000000000000419
50. Campen CJ, Gutmann DH (2018) Optic pathway gliomas in neurofibromatosis type 1. J Child Neurol 33:73–81. https://doi.org/10.1177/0883073817739509
51. Hargrave DR, Bouffet E, Tabori U, Broniscer A, Cohen KJ, Hansford JR, Geoerger B, Hingorani P, Dunkel IJ, Russo MW, Tseng L, Dasgupta K, Gasal E, Whitlock JA, Kieran MW (2019) Efficacy and safety of dabrafenib in pediatric patients with BRAF V600 mutation-positive relapsed or refractory low-grade glioma: results from a phase I/IIa study. Clin Cancer Res 25:7303–7311. https://doi.org/10.1158/1078-0432.CCR-19-2177
52. Dombi E, Baldwin A, Marcus LJ, Fisher MJ, Weiss B, Kim A, Whitcomb P, Martin S, Aschbacher-Smith LE, Rizvi TA, Wu J, Ershler R, Wolters P, Therrien J, Glod J, Belasco JB, Schorry E, Brofferio A, Starosta AJ, Gillespie A, Doyle AL, Ratner N, Widemann BC (2016) Activity of selumetinib in neurofibromatosis type 1-related plexiform neurofibromas. N Engl J Med 375:2550–2560. https://doi.org/10.1056/NEJMoa1605943
53. Ryall S, Tabori U, Hawkins C (2020) Pediatric low-grade glioma in the era of molecular diagnostics. Acta Neuropathol Commun 8:30. https://doi.org/10.1186/s40478-020-00902-z
54. Mistry M, Zhukova N, Merico D, Rakopoulos P, Krishnatry R, Shago M, Stavropoulos J, Alon N, Pole JD, Ray PN, Navickiene V, Mangerel J, Remke M, Buczkowicz P, Ramaswamy V, Guerreiro Stucklin A, Li M, Young EJ, Zhang C, Castelo-Branco P, Bakry D, Laughlin S, Shlien A, Chan J, Ligon KL, Rutka JT, Dirks PB, Taylor MD, Greenberg M, Malkin D, Huang A, Bouffet E, Hawkins CE, Tabori U (2015) BRAF mutation and CDKN2A deletion define a clinically distinct subgroup of childhood secondary high-grade glioma. J Clin Oncol 33:1015–1022. https://doi.org/10.1200/JCO.2014.58.3922