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Trametinib-based Treatment of Pediatric CNS Tumors: A Single Institutional Experience

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Summary: MEK inhibitors are an emerging therapy with increasing use in mitogen-activated protein kinase-driven central nervous system (CNS) tumors. There is limited data regarding efficacy and toxicity in pediatric patients. We report our clinical experience with trametinib-based therapy for the treatment of 14 consecutive pediatric patients with recurrent low-grade glioma (N = 11) or high-grade CNS tumors (N = 3) with MAP kinase pathway mutations. Patients received trametinib as monotherapy (N = 9) or in combination (N = 5) with another antineoplastic agent. Nine patients (64%) were progression free during treatment. Five patients showed a partial response, while 4 had stable disease. Two patients (14%) progressed on therapy. All partial responses were in patients with low-grade tumors. The remaining 3 patients were not evaluable due to toxicity limiting duration of therapy. Two of 3 patients with low-grade glioma with leptomeningeal dissemination showed radiographic treatment response. Five patients reported improved clinical symptoms while on trametinib. Adverse events on trametinib-based therapy included dermatologic, mouth sores, fever, gastrointestinal, infection, neutropenia, headache, and fatigue, and were more common in patients using combination therapy. Trametinib-based therapy demonstrated signals of efficacy in our single institutional cohort of pediatric patients with mitogen-activated protein kinase-driven CNS tumors. Our observations need to be confirmed in a clinical trial setting.

Key Words: brain tumors, trametinib, targeted agents, MEK

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Over the last decade, next generation sequencing of pediatric brain tumors has led to the identification of driver mutations which suggest potential pharmacologic targets. As genetic sequencing moved from the research realm into the clinical standard of care, many questions have arisen regarding how to best utilize this data to be clinically beneficial to patients, especially those who relapse or progress through the current standard therapy regimens. The Ras-mitogen-activated protein kinase (MAPK) is one of the most frequently altered pathways identified through genetic sequencing in some pediatric brain tumors. Mutations in this pathway are found in close to 100% of pilocytic astrocytomas, the most prevalent type of low-grade glioma (LGG),[1] and are also common in other LGG subtypes. Mutations in *NF1*, and *KIAA1549-BRAF* fusions are found most commonly, with *BRAF* V600E point mutations occurring frequently as well.[2,3] There are reports of less common mutations within the MAPK pathway as well, such as other *BRAF* fusions and *FGFR1* mutations.[1] The high frequency of these findings have led to the recommendation to obtain molecular analysis on all LGG and glial-neuronal tumors, at minimum testing for *BRAF* fusion or *BRAF* V600E mutations by sequencing or immunohistochemistry.[1]

Alterations in this MAP kinase pathway are also identified on sequencing for higher grade tumors, albeit at a lower frequency. In high-grade glioma (HGG), MAP kinase pathway mutations are seen in a smaller subset of patients. *BRAF* V600E was positive in 6% of a large study of pediatric HGG.[4] With the increased identification of mutations in the MAPK pathway, there has been a growing interest in the use of small molecule inhibitors which target the MAPK pathway. To date, there have been a small number of completed clinical trials with published data using these agents. Thus far, the pediatric trials investigating these targeted agents have focused on patients with LGG, the most common type of central nervous system (CNS) tumor in children, accounting for at least 30% of all CNS tumors.[1] These tumors generally have excellent overall survival with approximately a 90% 20-year overall survival.[5] However, event free survival is much lower, with many patients requiring several courses of treatment.[6] Before the understanding of the MAPK-driven nature of pediatric LGG, the available treatment options were maximal safe resection, radiation in selected cases, and traditional cytotoxic chemotherapy. Several different chemotherapy regimens have been studied for LGG. The Children's Oncology Group (COG) protocol A9952 compared vincristine and carboplatin with TPCV (thioguanine, procarbazine, lomustine, and vincristine) and found no statistically significant difference in outcome between the 2 regimens.[7] This was followed by ACNS0223 which found similar event free survival when temozolamide was added to carboplatin and vincristine.[8] Patients with recurrent LGG were treated with weekly vinblastine alone, and 33% were reported to have some response.[6] Pediatric Brain Tumor Consortium (PBTC) trials have reported progression free responses with lenalidomide and combination bevacizumab with irinotecan.[9,10] Bevacizumab alone has also shown some efficacy in treatment of LGG.[11]

Published trials of kinase inhibitors in pediatric LGG to date include investigations of sorafenib (a multikinase inhibitor), everolimus (an mTOR inhibitor), and selumetinib (a MEK inhibitor).[12–14] The phase II study of multikinase inhibitor sorafenib in patients with recurrent or progressive

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LGG was terminated early due to an unacceptable number of patients with progressive disease (PD), likely due to paradoxical ERK activation based upon in vitro studies.[12] A phase II study of the mTOR inhibitor everolimus, which also inhibits the MAPK pathway, included 23 children with recurrent LGG without neurofibromatosis type 1 (NF1). Results included 4 partial responses, 13 with stable disease, and 6 with PD.[13] The agent was well tolerated and a subsequent study with focus on biomarkers is underway by the Pacific Pediatric Neuro-Oncology Consortium (NCT01734512).[1] Selumetinib (AZD6244) is a (MEK)1/2 inhibitor which has been tested in phase I and a recently published phase II trial.[14] The phase 1 study included 38 children with progressive or recurrent LGG, and demonstrated a 25% sustained partial response with a 2-year progression free survival of 69 ± 9.8%.[15] Four of the 5 children with sustained partial response had tissue available and all of these had *KIAA1549-BRAF* fusion. The phase II trial for selumetinib in patients with recurrent, refractory, or progressive pediatric LGG demonstrated a sustained partial response in 36% of patients with WHO grade I pilocytic astrocytoma (9 of 25) with either *BRAF-KIAA1549* or *BRAF* V600E mutations and 40% sustained partial response in those with NF1 associated LGG WHO grades I and II (10 of 25) with a median follow-up time of 48 to 60 months at the time of publication.[14]

There is less existing literature for the use of targeted therapy in pediatric HGGs, which represent another 6.5% of childhood CNS tumors with a dismal prognosis and <20% 5-year overall survival.[16] MEK inhibitors are occasionally used in "personalized medicine" trials. There are single published cases which describe the use of MAPK targeting agents[17,18]; however, there is no data from completed studies specifically aiming to describe the response of pediatric HGG to MAPK pathway inhibition.

Trametinib is an orally available MEK1/2 inhibitor, in the same class as selumetinib. Trametinib was initially approved for melanoma with *BRAF* V600E or *BRAF* V600K mutations, and has subsequently been studied alone and in combination with dabrafenib in other *BRAF* V600E mutated malignancies.[19,20] It is currently FDA approved for some patients with *BRAF* mutant melanoma and non–small cell lung cancer, and is also used off-label for some other *BRAF* mutant cancers, including those discussed herein. Minimal data are available regarding the clinical efficacy of this agent in pediatric LGG as aside from small case series[2] as there are no studies which have been completed using trametinib for pediatric brain tumors. A phase I/II trial of trametinib in pediatric glioma and plexiform neurofibroma is currently recruiting in Canada (NCT03363217). A phase II trial of the BRAF inhibitor dabrafenib in combination with trametinib for pediatric patients with LGG or HGG tumors harboring the *BRAF* V600E mutation is underway in several countries (NCT02684058), but results from these trials are not yet available. We present our single institution experience with trametinib based therapy in a cohort of pediatric patients treated with LGG, HGG, and other CNS tumors.

MATERIALS AND METHODS

We performed a retrospective chart review of 14 consecutive pediatric patients with HGG, LGG, embryonal tumor, or atypical neurocytoma, treated with trametinib, either as monotherapy or in combination with another agent at Rady Children's Hospital, San Diego, from January 2015 to September 2019. Patients were selected for MEK inhibition treatment either due to a known mutation within the MAP kinase pathway, or due to a histopathologic diagnosis known to very commonly be driven by elements of the MAP kinase pathway, such as pilomyxoid astrocytoma. All patients had next generation sequencing performed on tumor tissue in a CLIA certified laboratory.

Trametinib was given orally, with a starting dose of 0.025 mg/kg/dose once daily. As trametinib was prescribed off-label, patients and families were counseled on known risks, side effects, and available data regarding trametinib before the initiation of single agent or combination therapy. The duration of treatment was individualized for each patient, based upon the clinical response, radiologic response, and tolerance to therapy of each patient. Laboratory monitoring included complete blood count and comprehensive metabolic panel, which was assessed before initiation of therapy, and monthly during treatment. Because of the potential cardiac toxicity of MEK inhibitors, baseline echocardiogram and electrocardiogram were obtained and followed every three months while on therapy. Routine magnetic resonance imaging (MRI) was performed every 8 to 12 weeks from the initiation of treatment and during therapy, or more frequently if clinically indicated. magnetic resonance imaging responses were characterized by diameter-based measurement on a single-axial section containing the largest diameter of the tumor on T1 postgadolinium sequences by a pediatric neuroradiologist, and in some cases correlated with T2 fluid attenuation inversion recovery (FLAIR) sequences. Clinical response and adverse events were evaluated by the treating pediatric neuro-oncologist at the time of clinic visit. For patients with toxicity warranting dose reduction, trametinib was typically given at 50% of prior dose. The study was approved by the University of California San Diego Institutional Review Board.

RESULTS

The demographic and treatment characteristics of 14 patients (9 males and 5 females) with a diagnosis of LGG (N = 10), atypical neurocytoma (N = 1), HGG (N = 2), or primary leptomeningeal CNS embryonal tumor, NOS, WHO grade IV (N = 1), treated with trametinib-based therapy (median age, 10.8 y; range, 5.2 to 17.1 y) are shown in Table 1. The patients included in this study were relapsed or refractory to standard treatment and many were heavily pretreated. Seven of the 14 patients (50%) had previously received prior radiation therapy. Eight (57%) had received ≥3 prior pharmacologic regimens (Table 1). The 3 patients who had not received prior pharmacologic therapy included a K27M HGG patient who had completed radiation, a patient with NF1 and juvenile pilocytic astrocytoma with leptomeningeal spread whose parents declined conventional chemotherapy. All patients had molecular sequencing information available, with the most common genetic aberration being *BRAF-KIAA1549* fusion in 5 patients (Table 2).

Nine of the 14 patients were progression-free (64%) during trametinib therapy. Objective response was seen in 5 (36%) of the patients, all with partial responses, while 4 (28%) had stable disease after starting therapy. No patients with a high-grade tumor were observed to have a reduction in tumor size on therapy; 1 patient with diffuse intrinsic pontine glioma had stable disease at last evaluation, 8 weeks on therapy. Best radiographic response was seen at a median of 18 weeks (range, 13 to 34 wk). Examples of radiographic response are shown in Figures 1 and 2. Figure 2 highlights the responses seen in 2 of 3 patients with LGGs with leptomeningeal dissemination. In addition to the radiologic response, significant clinical responses were seen in 5 patients, including reduction of drooling,

TABLE 1. Demographic and Treatment Characteristics of Patients Treated With Trametinib-based Therapy for Pediatric Glioma

Demographic	All Patients (N = 14), n (%)
Age at initial diagnosis, median (range) (y)	3.5 (0.6-12.1)
Age at time of trametinib based therapy, median (range) (y)	10.8 (5.2-17.1)
Sex	
Male	9 (64)
Female	5 (36)
Diagnosis	
WHO grade I-II	11 (79)
Juvenile pilocytic astrocytoma	5 (36)
Pilomyxoid astrocytoma	2 (14)
Optic pathway glioma*	2 (14)
Ganglioglioma	1 (7)
Atypical neurocytoma	1 (7)
Plexiform neurofibroma*	1 (7)
WHO grade IV	3 (21)
Primary leptomeningeal embryonal tumor, NOS	1 (7)
Glioblastoma multiforme	1 (7)
Diffuse intrinsic pontine glioma	1 (7)
Primary tumor location	
Posterior fossa	1 (7)
Temporal lobe†	2 (14)
Suprasellar/optic chiasm/optic pathway†	5 (36)
Thalamo-peduncular	1 (7)
Tectum	1 (7)
Brainstem	2 (14)
Cervical spinal cord, intramedullary	2 (14)
Primary leptomeningeal	1 (7)
Prior chemotherapy regimens	
None	3 (21)
1	2 (14)
2	1 (7)
≥3	8 (57)
Prior radiation	
Yes	7 (50)
No	7 (50)
Weeks of trametinib-based therapy, median (range)	28 (3-57)
Best response based on imaging	
Total	
Complete response	0 (0)
Partial response	5 (36)
Stable disease	4 (28)
Progressive disease	2 (14)
No interval evaluation while on therapy	3 (21)
Improved clinical symptoms	5 (36)
Single agent trametinib	
Partial response	3 (33)
Stable disease	1 (11)
Progressive disease	2 (22)
Unable to evaluate	3 (33)
Combination therapy	
Partial response	3 (60)
Stable disease	2 (40)
Progressive disease	0 (0)
Unable to evaluate	0 (0)
Time to best response for those with partial response, median (range) (wk)	18 (13-34)
Time to progression in those with progressive disease (range) (mo)	7-8
Ongoing treatment	5 (36)
Reason for discontinuation	
Progressive disease	2 (14)
Toxicity	4 (28)
Completion of planned therapy	1 (7)
Provider recommendation	1 (7)
Noncompliance	1 (7)
Clinically significant mutation status	
BRAF-KIAA1549 fusion	5 (36)
BRAF V600E	1 (7)
Other	7 (50)
None	1 (7)

*Patient had both optic pathway glioma and plexiform neurofibroma.
†Patient had temporal/chiasmatic tumor.

vomiting, headache, improved gait and reduction of seizure frequency Of the 5 patients with *BRAF* fusion, 2 had a partial response, 1 had PD, 1 had stable disease while on therapy (in the context of poor compliance), and 1 was unevaluable due to short duration of therapy limited by toxicity. These results are similar to the response we saw in the cohort as a whole.

Combination therapy was used in 5 patients including 4 with recurrent LGGs and 1 with diffuse intrinsic pontine glioma. The agents used with trametinib were panobinostat, everolimus, bevacizumab, and temozolomide (Table 2). A higher proportion of patients on combination therapy versus single agent therapy experienced partial response (60% vs. 33%), and stable disease (40% vs. 11%). No patients on combination therapy experienced PD.

Treatment was discontinued in 9 (64%) patients, while 5 (36%) patients remain on treatment at the time of data collection. Treatment was discontinued in 4 patients due to toxicity. One patient self-discontinued therapy, 1 due to provider choice, and 1 due to completion of planned therapy course. Two patients had a progression of disease during treatment after initial tumor stability on trametinib based therapy, with a time to progression of 7 to 8 months. These include 1 patient with pilomyxoid astrocytoma with non-enhancing leptomeningeal disease who had received 3 prior treatment regimens, and 1 patient with atypical neurocytoma who was refractory to radiation therapy. No patients died while on therapy, but 2 of the patients in this cohort have died since discontinuation. Both died from complications of PD, 1 with HGG who only received 3 weeks of trametinib, and 1 with primary leptomeningeal embryonal tumor NOS who was poorly compliant with treatment. After discontinuation of trametinib-based therapy, PD was observed as early as 10 weeks (patient 4; Table 2). Two patients are stable at time of publication had partial response followed by stable disease after 24 weeks (patient 1) and 150 weeks (patient 6, a child with NF1 who received trametinib and everolimus therapy for posterior fossa juvenile pilocytic astrocytoma and leptomeningeal spread).

Dose reduction and toxicity of trametinib occurred in patients on combination therapy and in patients on single agent therapy. The most common adverse event was dermatologic, occurring in 64% of all patients (Table 3). The next most commonly observed adverse events were mouth sores in 36%, and fever in 28%. In general, rates of adverse events were slightly higher in patients receiving combination therapy than with trametinib as a single agent; however, this group included only 5 total patients. Nine of 14 patients (64%) had adverse events requiring dose reduction or

TABLE 2. Clinical Characteristics of Patients Receiving Trametinib

Pt #	Clinical Diagnostic Information	Prior Therapy	Prior XRT	Clinically Significant Mutations	Trametinib Alone or in Combination	Trametinib Dose Reduced?	Duration of Use (wk) (Reason d/c'd)	Best Imaging Response/Status After Discontinuation	Clinical Response to Trametinib
1	17 yo w/suprasellar JPA (dx at age 1)	1. Carbo/VCR 2. 6TG, CCNU, procarbazine, vcr 3. Oral temodar 4. Avastin 5. Everolimus	Photon	*KIAA1549*/*BRAF* fusion	Alone	No	26 Provider choice due to comorbid conditions	PR/SD at 24 wk	None
2	11 yo w/brainstem ganglioglioma (dx at age 4)	1. Carbo/VCR 2. Avastin 3. Everolimus	Photon	No clinically significant mutations identified	Alone	Yes	57 Continuing Tx	PR	Decreased drooling
3	10 yo w/bilateral optic pathway gliomas (dx at age 7 mo)	1. Carbo/VCR 2. Temozolomide 3. 6TG, CCNU, procarbazine, VCR 4. Avastin 5. Everolimus 6. Vinblastine 7. Sorafenib 8. Hyperbaric Oxygen 9. Poly ICLC	NA	*BRAF* V600E	Alone	No	5 Toxicity	NA	None
4	8 yo w/intramedullary cervical cord pilomyxoid astrocytoma w/ leptomeningeal spread (dx at age 1)	1. Carbo/VCR 2. Avastin/Irinotecan	Proton	Gain of chromosome 8	1. + Everolimus 2. + Avastin/ oral temodar	Yes	38 Toxicity	SD/PD after 10 wk	None
5	13 yo w/primary leptomeningeal CNS Embryonal tumor, NOS (dx at age 12)	1. Carbo/VCR	Photon	Amplification of *AKT3, IKBKE, IRS2, MCL1 FGF4, MDM4, P13K3C2B KIAA1549/ BRAF* fusion *AMR457 NOTCH2*	Yes, Everolimus	Yes	13 Pt Compliance	SD/PD after 11 wk	None
6	10 yo w/NF1 and posterior fossa JPA with leptomeningeal spread (dx at age 7)	None	NA	*NF1* splice site 2251 +1G > A, splice side 3708+1G > A, *PDGFRA* A491T	Yes, Everolimus	No	51 Completed Planned Therapy	PR/SD at 150 wk	Decreased vomiting
7	6 yo suprasellar chiasmatic JPA (dx at age 10 mo)	1. Carbo/VCR 2. Vinblastine 3. Avastin 4. Everolimus	NA	*KIAA1549*/*BRAF* fusion	Alone	No	6 Toxicity	NA	None

8	16 yo w/hx of NF1 and optic glioma and plexiform neurofibroma (dx at age 7)	None	NA	*NF1*	Alone	Yes	23 Continuing Tx	SD	Decreased HA and decreased pain of plexiform neurofibroma
9	8 yo w/intramedullary cervical cord JPA w/leptomeningeal spread (dx at age 3)	1. Avastin 2. Carbo/VCR 3. Vinblastine 4. Nivolumab 5. Everolimus	NA	*KIAA1549*/*BRAF* fusion	Alone	No	60 Continuing Tx	PR	Decreased HA and seizures
10	5 yo w/thalamo-peducular pylomyxoid astrocytoma (dx at age 1)	1. Carbo/VCR 2. Avastin 3. Everolimus	NA	*KIAA1549*/*BRAF* fusion	Alone	Yes	28 PD	PD	None
11	16 yo w/temporal atypical neurocytoma (dx at age 13)	1. Avastin	Proton and photon	*EWSR1 ATF-EWSR1* fusion; *MUTYH* G382D; monosomy 14	Alone	No	36 PD	PD	None
12	5 yo w/temporal and chiasmatic GBM (dx. at age 3)	1. Temozolamide 2. Avastin 3. Pablociclib 4. Nivolumab	Photon	*CCND2* amplification, *CDK4* amplification, *MDM2* amplification	Alone	No	3 Toxicity	NA	None
13	11 yo w/DIPG (dx at age 11)	None	Photon	*H3F3A* K28M, *FGFR1* N546K, *PTPN11* N308D, *ATRX* R480Kfs*9	+ Panobinostat	Yes	8 Continuing Tx	SD	None
14	7 yo tectal JPA w/leptomeningeal spread- brain and spine (dx at age 3)	1. Carbo/VCR 2. Avastin 3. Everolimus/ Avastin		*EGFR* R222C	+ Avastin	No	37 Continuing Tx	PR	Improved gait

Diagnostic characteristics, treatment information, molecular genetics, and response to therapy for each patient included in the cohort.

CCNU indicates lomustine; DIPG, diffuse intrinsic pontine glioma; GBM, glioblastoma multiforme; HA, headache; JPA, juvenile pilocytic astrocytoma; NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease; TG, thioguanine; VCR, vincristine; XRT, radiation therapy.

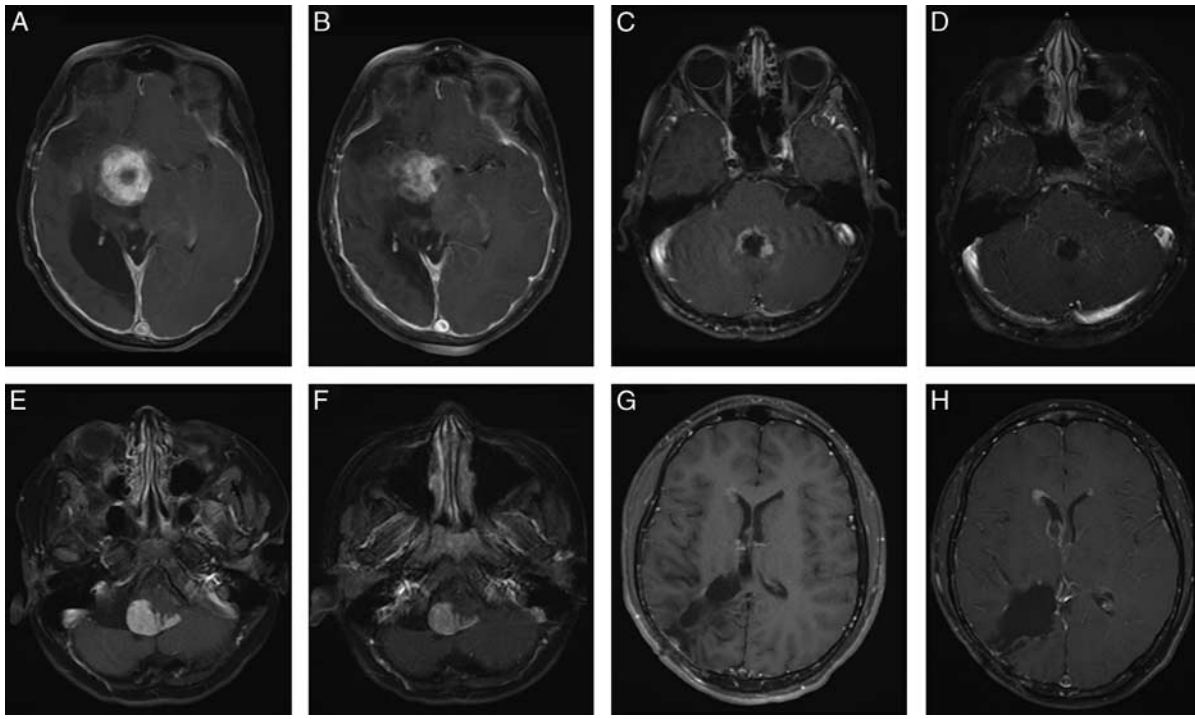

FIGURE 1. Imaging response of select patients on trametinib therapy. Neuroimaging for patient #1 with a suprasellar JPA is shown in (A) (baseline) and (B) (follow-up) demonstrating a partial response. Imaging for patient #6 with a posterior fossa JPA and NF1 is shown in (C) (baseline) and (D) (follow-up). A partial response was also seen in patient #2 with a brainstem ganglioglioma shown in (E) (baseline) and F (follow-up). An example of progression on therapy is shown in (G) (baseline) and H (follow-up) in patient #11 with an atypical neurocytoma. JPA indicates juvenile pilocytic astrocytoma; NF1, neurofibromatosis type 1.

cessation of therapy. Three patients (21%) stopped therapy due to adverse events without first dose reducing, while 6 (43%) continued on therapy at a reduced dose. Three of those 6 continue on a reduced dose at time of publication, while 1 subsequently discontinued therapy due to further toxicity, one self-discontinued, and another stopped due to PD.

DISCUSSION

Our single institution experience with trametinib in a cohort of 14 consecutive pediatric patients with recurrent/refractory low grade or high-risk high-grade CNS tumors adds to the existing data available regarding small molecule inhibitors of the MAPK pathway, with a comparable progression free survival to existing literature. While larger cohorts of patients treated with the similar MEK inhibitor selumetinib[14] have been published, this represents the largest published cohort of patients treated with trametinib to date. All patients had next generation sequencing data available before initiation of therapy. Our cohort represents some of the first data available for patients using trametinib for pediatric LGG in combination with other biological agents, and in patients with high-grade CNS tumors. Our findings also highlight the clinical responses in addition to neuroimaging findings for patients on trametinib, suggesting that future clinical trials should involve symptoms and quality of life evaluations as part of response assessment. Leptomeningeal spread is notoriously difficult to treat, but we observed some improvement in leptomeningeal enhancement in some patients in this cohort on trametinib who demonstrated progression after standard carboplatin-based therapy.

Trametinib-based therapy was tolerated with toxicity similar to previous reports of adverse effects from MEK inhibitor therapy.[14,21] The side effects of MEK inhibitors including trametinib are distinct when compared with traditional cytotoxic chemotherapy. Cutaneous toxicity is the most commonly observed toxicity, with over 50% of patients observing rashes and photosensitivity.[21] These reactions can occur several months after initiation of therapy. Our cohort had a similar overall incidence of dermatologic manifestations, ranging from very mild exanthems to more severe reactions, in some cases necessitating dose reduction or discontinuation of therapy. There have also been cases of cardiac dysfunction with decreased left ventricular ejection fraction, and hypertension and pericarditis.[22,23] Our patients were followed every 3 months with electrocardiogram and echocardiogram, but no dose limiting cardiac toxicities were observed. Ocular toxicity has been described, particularly central serous retinopathy, retinal vein occlusion, and pigment epithelial detachments. All of our patients on trametinib are also followed with ophthalmology examinations at regular intervals determined based on disease location, aggressiveness, and current visual status. No ocular toxicity was seen in our cohort. Pyrexia and gastrointestinal distress have also been described with MEK inhibitors, which we encountered occasionally in our cohort as well. Patients on combination therapy experienced higher rates of treatment response in this cohort, but also experienced higher rates of adverse events. With the minimal pharmacodynamic and efficacy data available at this time, the choice to place a

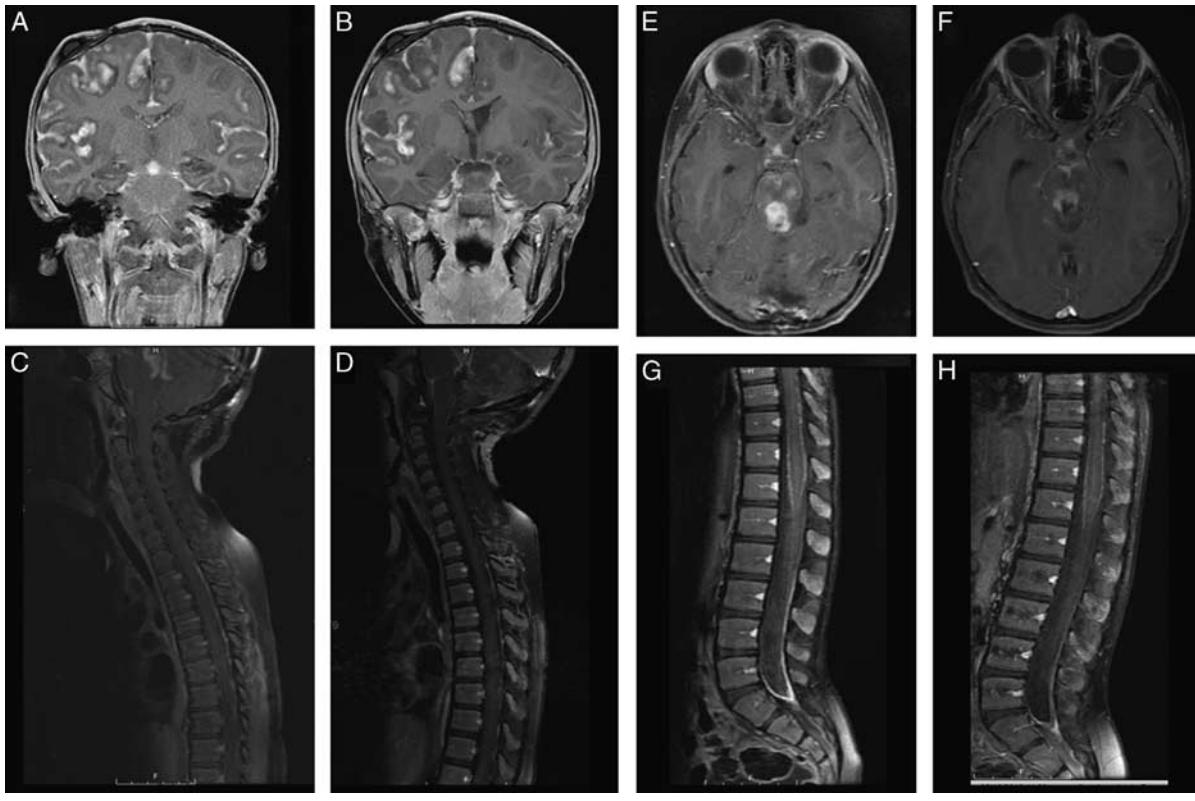

FIGURE 2. Imaging response in select patients on trametinib based therapy with leptomeningeal disease. A–D, Correspond to baseline (A, C) and follow-up (B, D) brain and spine imaging on patient #9 with a diagnosis of cervical cord JPA with leptomeningeal spread. E–H, Baseline (E, G) and follow-up (F, H) imaging for patient #14 with tectal JPA with leptomeningeal spread. JPA indicates juvenile pilocytic astrocytoma.

patient on a monotherapy or combination therapy is highly individualized and based upon the potential benefits and risks of treating with more than one agent at a time. The relatively high prevalence of toxicity and requirement for dose reduction for both monotherapy and combination therapy highlights the need for dedicated study of the optimal dosing of MEK inhibitors, both alone and as part of a combination regimen.

There are several shortcomings in our reported series in addition to the retrospective review and off-label use of the therapy in the absence of a formalized clinical trial. First, although it is the largest reported cohort to date of patients treated with trametinib, it is still a relatively small data set, further limited by only 11 of the 14 patients having evaluable imaging while on treatment, whereas the other patients stopped therapy due to tolerability before any interval imaging. Second, the cohort contains a variety of tumor diagnoses with both low-grade and high-grade histology represented. Furthermore, trametinib was used in combination with other agents in 5 of the 14 patients. Thus, neither response nor

TABLE 3. Adverse Events During Trametinib Therapy

	n (%)			
Adverse Event	**Total Patients, N = 14**	**Sx Requiring Dose Reduction or Cessation of Therapy, N = 14**	**Trametinib Alone, N = 9**	**Trametinib Used in Combination, N = 5**
Dermatologic (rash)	9 (64)	6 (43)	5 (55)	4 (80)
Mouth sores	5 (36)	3 (21)	3 (33)	2 (40)
GI (nausea, decreased appetite)	1 (7)	1 (7)	1 (11)	0
Fevers	2 (14)	2 (14)	1 (11)	1 (20)
Infections	1 (7)	0	1 (11)	0
Hematologic (neutropenia)	1 (7)	0	0	1 (20)
Other (headache, fatigue)	1 (7)	1 (7)	1 (11)	0

Adverse events experienced by patients on trametinib and broken down based on single agent or combination therapy. Some patients experienced multiple toxicities and dose reductions and cessation of therapy occurred due to a combination of toxicities in some cases. For this reason, percentages of each column add up to more than 100% and represent that % of total patients in the cohort who experienced that toxicity.

toxicity in these patients is fully attributable to the trametinib. Although the toxicities observed are similar to prior reports with MEK inhibitors, it is difficult to generalize the incidence of dose reduction or cessation. Dose adjustments were made based upon a combination of clinician and parental discretion, and not strictly by Common Terminology Criteria for Adverse Events severity as would be done in a clinical trial. Therefore, rates of dose adjustment may be higher in our cohort than is observed elsewhere.

Although the experience of this cohort contributes to our current understanding of the clinical efficacy and tolerability of MEK inhibitors in a variety of clinical scenarios, many questions remain, which would optimally be addressed in future clinical trials. These include the relative efficacy of the different MEK inhibitor formulations, clinical utility as a single agent versus in combination with other therapies, the relative toxicity profiles (both short and long term) of single and combination therapy, and ideal duration of therapy. Durability of clinical response is important to evaluate, as is response to rechallenge. In addition, stratifying response based upon molecular profile and histopathologic diagnosis would provide critical information. To evaluate these research questions would require a large cohort of patients and long-term follow-up, likely in the context of a multicenter consortium based trial. The COG recently opened a Phase 2 study with combination trametinib and dabrafenib after radiation in newly diagnosed *BRAF*V600E-Mutant HGG patients (NCT03919071). PBTC also has an upcoming trial looking at trametinib in combination with hydroxychloroquine in pediatric patients with *BRAF* fusion positive or NF1-associated recurrent or progressive gliomas and trametinib with dabrafenib and hydroxychloroquine in *BRAF* V600E mutant recurrent or progressive gliomas. The COG also has an upfront trial to compare single agent MEK inhibition (selumetinib) to carboplatin and vincristine in patients with NF-1 associated LGG (NCT03871257). Data from this study will help determine whether MEK inhibition should be considered as a first line therapy in this population. While these efforts are underway, reports from smaller cohorts such as this one provides useful information for both clinicians and families.

Trametinib is an oral targeted therapy that demonstrated signals of efficacy in our single institutional cohort of pediatric patients with MAP kinase-driven CNS tumors treated with trametinib-based therapy. Although it was well tolerated in some patients, toxicity was dose limiting in others with rates that were similar to reported findings with other formulations of MEK inhibitors. Further ongoing research will improve our understanding of trametinib-based therapy and delineate its role in pediatric neuro-oncology.

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