HHS Public Access

Author manuscript

Clin Cancer Res. Author manuscript; available in PMC 2024 July 17.

Published in final edited form as:

Clin Cancer Res. 2024 January 17; 30(2): 263–268. doi:10.1158/1078-0432.CCR-23-1503.

FDA Approval Summary: Dabrafenib in combination with trametinib for BRAF V600E mutation-positive low-grade glioma

Michael I. Barbato[1], **Jeannette Nashed**[1], **Diana Bradford**[1], **Yi Ren**[1], **Sachia Khasar**[1], **Claudia P. Miller**[1], **Banu S. Zolnik**[1], **Hong Zhao**[1], **Yangbing Li**[1], **Youwei Bi**[1], **Stacy S. Shord**[1], **Anup K. Amatya**[1], **Pallavi S. Mishra-Kalyani**[1], **Barbara Scepura**[1], **Raniya A. Al-Matari**[1], **Richard Pazdur**[1,2], **Paul G. Kluetz**[1,2], **Martha Donoghue**[1,2], **Harpreet Singh**[1,2], **Nicole Drezner**[1]

[1]Center for Drug Evaluation and Research, U.S. Food and Drug Administration

[2]Oncology Center of Excellence, U.S. Food and Drug Administration

Abstract

On March 16, 2023, the U.S. Food and Drug Administration (FDA) approved dabrafenib in combination with trametinib (Tafinlar®, Mekinist®, Novartis Pharmaceuticals Corporation) for the treatment of pediatric patients with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy. FDA also approved oral formulations of both drugs suitable for patients who cannot swallow pills. This approval was based on the LGG cohort from Study CDRB436G2201 (NCT02684058), a multicenter, open-label trial in which pediatric patients with LGG with a BRAF V600E mutation were randomized 2:1 to dabrafenib plus trametinib (D+T) or carboplatin plus vincristine (C+V). The overall response rate (ORR) by independent review based on RANO LGG (2017) criteria was assessed in 110 patients randomized to D+T (n=73) or C+V (n=37). ORR was 47% (95% CI: 35, 59) in the D+T arm and 11% (95% CI: 3.0, 25) in the C+V arm. Duration of response (DOR) was 23.7 months (95% CI: 14.5, NE) in the D+T arm and not estimable (95% CI: 6.6, NE) in the C+V arm. Progression-free-survival (PFS) was 20.1 months (95% CI: 12.8, NE) and 7.4 months (95% CI: 3.6, 11.8) (HR=0.31 [95% CI: 0.17, 0.55]; p= <0.001) in the D+T and C+V arms, respectively. The most common (> 20%) adverse reactions were pyrexia, rash, headache, vomiting, musculoskeletal pain, fatigue, diarrhea, dry skin, nausea, hemorrhage, abdominal pain and dermatitis acneiform. This represents the first FDA approval of a systemic therapy for the first-line treatment of pediatric patients with LGG with a BRAF V600E mutation.

Introduction

Alteration of the classical mitogen-activated protein kinase (MAPK) pathway has been identified as one of the most frequently dysregulated mechanisms in pediatric cancer pathogenesis;[1,2] BRAF V600E mutations are one mechanism of activation of the

Corresponding Author: Michael I. Barbato, Office of Oncologic Diseases, CDER, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993. Phone 301-467-6607 Fax: 301-796-9909. Michael.Barbato@FDA.HHS.GOV.

Disclosure of Potential Conflicts of Interest: The authors report no financial interests or relationships with the commercial sponsors of any products discussed in this report.

MAPK pathway.[3,4,5] Pediatric LGG represents 30% of all childhood brain tumors, with approximately 1300 new cases per year in the US and only about 17% of these harboring a BRAF V600E mutation.[6,7] Overall survival (OS) for newly diagnosed LGG is > 90% at 20 years; however, BRAF V600E mutation is associated with poorer survival.[8] Many patients with LGG experience sequelae of their disease or treatment, which can include cognitive impairment or delay, endocrine deficiencies, secondary malignancies, cardiovascular toxicity, and growth abnormalities. Due to the location of some tumors in the optic pathway, visual impairment is a significant concern, and threatened vision is an indication for systemic treatment.[9]

Prior to the approval of dabrafenib in combination with trametinib, there were no approved therapies specifically for pediatric patients with LGG with BRAF V600E mutation who had not received prior systemic therapy. Systemic treatment options for patients with LGG include several standard chemotherapeutic regimens (carboplatin with vincristine; vinblastine; temozolomide; and thioguanine, procarbazine, lomustine, and vincristine). In pediatric patients with LGG receiving conventional chemotherapy irrespective of BRAF V600E mutation status, overall response rates (ORRs) reported in the literature range from 26 to 35%.[10,11] In pediatric patients receiving conventional chemotherapy for LGG with BRAF V600E mutation, reported ORRs range from 10 to <23%.[7,12]

Dabrafenib and trametinib are oral inhibitors of BRAF and MEK, respectively. In this summary, we discuss FDA's review of the marketing application that led to the landmark approval of dabrafenib in combination with trametinib for the first-line treatment of pediatric patients 1 year of age and older with BRAF V600E mutation-positive LGG who require systemic therapy.

Regulatory History

On May 29, 2013, dabrafenib and trametinib were first approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. On March 1, 2016, FDA issued a Written Request to study dabrafenib and trametinib in pediatric patients with BRAF V600 mutation-positive tumors, including high and low grade gliomas.[13] A tissue agnostic approval was granted on June 22, 2022 for dabrafenib in combination with trametinib for the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.[14,15] FDA granted orphan drug status to dabrafenib in combination with trametinib and breakthrough therapy designation for the treatment of pediatric patients 1 year of age and older with LGG (WHO grades 1 and 2) with a BRAF V600E mutation who require systemic therapy on March 27, 2022. The new drug applications (NDAs) for new oral formulations of dabrafenib and trametinib were submitted on August 17, 2022. The NDA review included use of the Assessment Aid to facilitate FDA review, received Priority Review designation, and was conducted in conjunction with international regulatory agencies as part of Project Orbis.[16,17,18,19,20,21]

Mechanism of Action

Dabrafenib is a kinase inhibitor. Its targets include wild-type and some mutated forms of BRAF kinases (V600E, V600K, and V600D). Some mutations in the BRAF gene, including BRAF V600E, result in constitutively active BRAF kinases that may stimulate tumor cell growth.[14] Trametinib is a reversible inhibitor of mitogen-activated extracellular signal-regulated kinase 1 (MEK1) and MEK2 activation and downstream activity. BRAF V600E mutations result in constitutive activation of the BRAF pathway, including MEK1 and MEK2. Dabrafenib and trametinib, as single agents, inhibit cell growth of various BRAF V600 mutation-positive tumors in vitro and in vivo.[15] Use of dabrafenib with trametinib results in greater growth inhibition of BRAF V600 mutation-positive tumor cells in vitro and prolongs tumor growth inhibition in BRAF V600 mutation-positive tumor xenografts compared with either drug alone.

Clinical Pharmacology

The approved recommended weight-based dosages of dabrafenib and trametinib for pediatric patients[14,15] were supported by three pediatric studies including pivotal Study G2201 (CDRB436G2201), supportive Study A2102 (CDRB436A2102) and Study X2101 (CDRB212X2101). The population pharmacokinetics (PopPK) analyses supported weight-based dosing for both trametinib and dabrafenib in patients 1 to <18 years of age. Although the dosages of both dabrafenib and trametinib administered in the pediatric clinical trials varied based on patient's age and weight, age was not a significant covariate of the exposures after accounting for weight (6 to 156 kg). Simulations based on the pediatric PopPK model predicted that steady-state exposures of dabrafenib and trametinib in combination in pediatric patients with weight-based dosing are generally comparable to those in the adult population at the approved recommended dosages. The exposure-response (E-R) analyses also supported the proposed pediatric dosages as no clear E-R relationships for ORR or PFS were observed in pediatric patients with LGG and high-grade glioma (HGG). In addition, the E-R relationships for safety in pediatric patients were broadly consistent with previous E-R analyses in adults with melanoma.

Clinical Trials

The approval of dabrafenib and trametinib was based on results of the LGG cohort of Study G2201 (NCT02684058), an international, randomized open-label clinical trial which included pediatric patients with BRAF V600E mutation-positive LGG (WHO grades 1 and 2) requiring first systemic therapy. Patients were randomized 2:1 to dabrafenib plus trametinib (D+T) or carboplatin plus vincristine (C+V). The primary efficacy outcome was overall response rate (ORR) per Response Assessment in Neuro-oncology (RANO) LGG criteria, as evaluated by blinded independent central review (BICR).[22,23] Additional efficacy outcome measures included duration of response (DOR), progression-free survival (PFS) and overall survival (OS). The investigators' analysis of Study G2201 has been published.[24] FDA's independent analyses of data submitted by the Applicant in the applications are presented below.

Demographics, Disease Characteristics and Prior Treatment—The primary efficacy analysis population included 110 pediatric patients with BRAF V600E mutation-positive LGG requiring first systemic therapy (Table 1). The efficacy population included patients with 12 histologic subtypes of LGG (WHO grades 1 and 2); the most common subtypes were pilocytic astrocytoma and ganglioglioma (Table 2). Most patients across the treatment arms had prior surgery (85% in the D+T arm and 78% in the C+V arm); none of the patients received chemotherapy or radiotherapy prior to study enrollment. The study was conducted in 58 centers across 20 countries. There is limited knowledge regarding the specific incidence of BRAF V600E mutation by race and ethnicity in pediatric patients with LGG, but the demographic and baseline disease characteristics of the primary efficacy population are generally representative of U.S. patients.

Efficacy results—The confirmed ORR by BICR demonstrated a statistically significant improvement among the 73 patients treated with D+T (47% [95% CI: 35, 59]) compared to those (n=37) treated with C+V (11% [95% CI: 3.0, 25], p <0.001). PFS per BICR was tested hierarchically following ORR. The median PFS was 20.1 months (95% CI: 12.8, not estimable [NE]) in the D+T arm compared to 7.4 months (95% CI: 3.6, 11.8) in the C+V arm with a hazard ratio (HR) of 0.31 ([95% CI: 0.17, 0.55], p <0.001). The median DOR per BICR based on an additional 7.4 months of follow-up from the time of the primary analysis was 23.7 months (95% CI: 14.5, NE) for the 34 responders in the D+T arm, whereas the median was not estimable (95% CI: 6.6, NE) for the 4 responders in the C+V arm (Table 3).[14,15] Efficacy was generally consistent across subgroups by age without meaningful differences in outcome. At the time of the interim analysis of OS, conducted when all patients had completed at least 32 weeks of treatment or had discontinued earlier, there was one death on the C+V arm. The OS results at interim analysis did not reach statistical significance.

Change in visual acuity (VA) for patients with deterioration of VA (as determined by the investigator) as an indication for treatment was not included as an efficacy measure in the LGG cohort of the G2201 study; however, VA through routine ophthalmologic assessments for safety was assessed throughout the study. Review of VA data among responding patients in the D+T (n=19) arm and C+V (n=9) arm indicated that most patients' symptoms in both groups were stable or improved while receiving therapy. Given the small number of patients with VA assessments and response data, conclusions on the effect of D+T on visual outcomes are limited.

Safety Results—The safety review evaluated primary safety data from patients enrolled in the LGG cohort of Study G2201 and data from a pooled pediatric safety population of 166 patients who received D+T at the recommended phase 2 doses (RP2Ds) in Study G2201 and Study X2101. In the LGG cohort of Study G2201, patients in the D+T arm experienced fewer grade 3–4 adverse events (AEs) than those in the C+V arm (47% vs 94%); serious AEs (SAEs) occurred at similar frequencies between arms (40% in the D +T arm vs 39% in the C+V arm).[25,26] There was one death due to disease progression in the C+V arm. Treatment discontinuation due to AEs was lower in the D+T arm (4% vs 18% in the C+V arm). AEs that led to treatment discontinuation in the D+T arm were chills, fatigue,

headache, pyrexia, and weight increase. The most frequent adverse reactions observed in the LGG cohort of Study G2201 are provided in Table 4.[14,15]

A new safety signal of weight increase was observed in Study G2201, with 15% of patients in the D+T arm experiencing an event of which 7% were Grade 3; no patients experienced weight increase on the C+V arm. Weight gain did not appear wholly attributable to tumor location (e.g., hypothalamic tumors) or expected weight increases in growing children based on FDA's review.

There were no significant safety concerns identified during application review requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS). Two post-marketing requirements (PMRs) to address safety in the pediatric population were issued to assess the potential for growth plate abnormalities and other effects on growth and development and the incidence of known serious risks including new primary malignancies, cardiomyopathy, and ocular toxicities.[25,26]

Dabrafenib in combination with trametinib for the treatment of pediatric patients with relapsed or refractory HGG with a BRAF V600E mutation

In addition to a randomized evaluation of LGG, Study G2201 enrolled patients with relapsed or progressive BRAF V600E mutant HGG in a single arm (n=41) in accordance with the Written Request (WR) issued by the FDA. The primary outcome measure for the HGG cohort was ORR as assessed by BICR per RANO 2010 criteria. For patients in the HGG cohort, the median age was 13 years (range: 2–17); 56% were female. The majority of patients were White (61%), with 27% Asian and 2.4% Black patients. Prior anti-cancer treatments included surgery (98%), radiotherapy (90%), and chemotherapy (81%). The ORR was 56% (95% CI: 40, 72) and median DOR was not reached (95% CI: 9.2, NE). For the 23 responders, DoR was ≥ 6 months for 78% of patients, ≥ 12 months for 48% of patients, and ≥ 24 months for 22% of patients. Secondary time-to-event endpoints measured in this cohort, such as PFS and OS, are not interpretable in absence of a comparator arm and were considered descriptive only.[14,15] Pediatric patients 6 years and older with relapsed or progressive BRAF V600E mutant HGG are included in the tissue agnostic indication, therefore the applicant did not seek an independent indication for these patients; the results from the HGG cohort of Study G2201 are included in product labeling.[14,15]

Regulatory Insights

FDA's approval of dabrafenib and trametinib for pediatric patients with LGG with a BRAF V600E mutation represents both the first systemic and first targeted therapy approved in the first-line setting in this population. The approval was based on demonstration of a clinically meaningful and statistically significant improvement in ORR and PFS in pediatric patients with LGG with a BRAF V600E mutation treated with D+T vs C+V, representing evidence of clinical benefit of D+T in this population. Key considerations in the review of the application included assessment of the contribution of each individual agent of the combination regimen to the observed treatment effect and a critical evaluation of the risks of treatment in the setting of a disease with a long natural history, in order to adequately inform the benefit-risk assessment.

FDA determined that the effect on ORR, DOR, and PFS in patients treated with D+T compared to those treated with C+V observed in Study G2201 was clinically meaningful (Table 5) and, when considered in the context of the supportive clinical data in patients with glioma and other tumor types, demonstrates substantial evidence of effectiveness. The improvement observed in PFS was critical in assessing benefit in the first line setting in a disease with a long natural history; although OS results did not reach statistical significance, there was no observed detriment in OS in patients treated with D+T. A post-marketing commitment was included in the approval letter to provide the results of the final analyses of PFS and OS from the LGG cohort of Study G2201 when all patients have been followed for two years.

For drugs approved in combination, the contribution of each drug component to the treatment effect needs to be adequately demonstrated. FDA considered evidence from prior clinical trials of dabrafenib and trametinib as single agents in pediatric patients with glioma, which demonstrated improvement in ORR (compared to trametinib alone) and DOR (compared to treatment with dabrafenib alone) with the combination of D+T.[25,26] FDA also considered that the body of published scientific evidence across other tumor types, such as BRAF V600E mutation-positive melanoma, supported the use of the combination over either product as a single agent in patients with BRAF V600E-driven tumors.[27]

Given the generally excellent overall survival in pediatric LGG and the expected prolonged duration of treatment with D+T in these patients, additional information was requested to ensure that the risks of treatment are adequately characterized. Post-marketing requirements (PMRs) were issued to assess any effects on growth and development, and to further characterize the known serious risks of new primary malignancies, cardiomyopathy, and ocular toxicities in pediatric patients with LGG.[28,29]

Functional impairments as a result of disease or treatment may have a great impact on pediatric patients with LGG and may drive the decision to initiate treatment. Although the reason for initiating treatment (i.e., clinical or radiologic progression, threatened vision, etc.) was documented, change in neurologic or visual impairment over time was not a prospectively defined objective of the trial. Visual acuity, however, was collected as part of clinical care and remained stable or improved in most patients with threatened vision. Additional assessment of visual acuity in patients with LGG treated on Study G2201 is included as part of a post-marketing commitment (PMC). Prospective collection of functional outcomes including vision and cognitive performance is crucial to further inform benefit: risk assessments in future studies in this population.

Randomized controlled designs are the gold standard to demonstrate evidence of safety and effectiveness, allowing for assessment of comparative safety and time to event endpoints. Feasibility concerns are often cited as a reason not to pursue a randomized trial in rare cancers; however, the conduct of a randomized controlled trial in this molecularly defined population with an estimated U.S. incidence of a few hundred patients per year is a notable example of a successfully conducted randomized controlled trial achieved through multiregional, global enrollment. Compelling results from single arm trials evaluating ORR and DOR have led to FDA approvals, generally in rare, molecularly defined populations

including pediatric indications.[30] The tissue agnostic approval of dabrafenib in combination with trametinib in patients with unresectable or metastatic solid tumors with BRAF V600E mutations in a refractory treatment setting relied upon single-arm ORR and DOR data, including data from pediatric patients with gliomas. BRAF V600E mutation-positive pLGG is relatively rare and evidence of antitumor activity of D+T in pediatric patients with gliomas was observed in prior single arm studies. Although data from single arm trials may be used to support traditional approval in specific contexts, and despite these early efficacy signals, the LGG cohort of Study G2201 was conducted with an appropriate control arm and enabled an evaluation of a time-to-event endpoint (PFS) as well as a comparison of toxicities between arms, both critical to clinical decision-making particularly in the front-line setting in a disease with a long natural history. Randomized trials can be critical to the understanding of a drug's activity and safety and should be considered early in development, even in rare populations.

Conclusion

Dabrafenib and trametinib are the first targeted therapies approved for the first-line treatment of pediatric patients with LGG with a BRAF V600E mutation. In addition, the new oral dosage forms provide dosing options for patients who are unable to swallow pills. Hundreds of pediatric patients with LGG in the United States will potentially benefit from these landmark approvals, which address a significant unmet medical need in this patient population.

References:

1). Davies H, Bignell GR, Cox C, et al. : Mutations of the BRAF gene in human cancer. Nature 417:949–954, 2002 [PubMed: 12068308]

2). Braicu C, Buse M, Busuioc C, et al. : A comprehensive review on MAPK: A promising therapeutic target in cancer. Cancers (Basel) 11:1618, 2019 [PubMed: 31652660]

3). Zhao Y, Adjei AA: The clinical development of MEK inhibitors. Nat Rev Clin Oncol 11:385–400, 2014 [PubMed: 24840079]

4). Knight T, Irving JA: Ras/Raf/MEK/ERK pathway activation in childhood acute lymphoblastic leukemia and its therapeutic targeting. Front Oncol 4:160, 2014 [PubMed: 25009801]

5). Murugan AK, Dong J, Xie J, et al. : MEK1 mutations, but not ERK2 mutations, occur in melanomas and colon carcinomas, but none in thyroid carcinomas. Cell Cycle 8:2122–2124, 2009 [PubMed: 19411838]

6). Diwanji TP, Engelman A, Snider JW, Mohindra P. Epidemiology, diagnosis, and optimal management of glioma in adolescents and young adults. Adolesc Health Med Ther. 2017 Sep 22;8:99–113. doi: 10.2147/AHMT.S53391.. [PubMed: 28989289]

7). Lassaletta A, Zapotocky M, Mistry M, Ramaswamy V, Honnorat M, Krishnatry R, Guerreiro Stucklin A, Zhukova N, Arnoldo A, Ryall S, Ling C, McKeown T, Loukides J, Cruz O, de Torres C, Ho CY, Packer RJ, Tatevossian R, Qaddoumi I, Harreld JH, Dalton JD, Mulcahy-Levy J, Foreman N, Karajannis MA, Wang S, Snuderl M, Nageswara Rao A, Giannini C, Kieran M, Ligon KL, Garre ML, Nozza P, Mascelli S, Raso A, Mueller S, Nicolaides T, Silva K, Perbet R, Vasiljevic A, Faure Conter C, Frappaz D, Leary S, Crane C, Chan A, Ng HK, Shi ZF, Mao Y, Finch E, Eisenstat D, Wilson B, Carret AS, Hauser P, Sumerauer D, Krskova L, Larouche V, Fleming A, Zelcer S, Jabado N, Rutka JT, Dirks P, Taylor MD, Chen S, Bartels U, Huang A, Ellison DW, Bouffet E, Hawkins C, Tabori U. Therapeutic and Prognostic Implications of BRAF V600E in Pediatric Low-Grade Gliomas. J Clin Oncol. 2017 Sep 1;35(25):2934–2941. doi: 10.1200/JCO.2016.71.8726. Epub 2017 Jul 20.. [PubMed: 28727518]

8). de Blank P, Bandopadhayay P, Haas-Kogan D, Fouladi M, Fangusaro J. Management of pediatric low-grade glioma. Curr Opin Pediatr. 2019 Feb;31(1):21–27. doi: 10.1097/MOP.0000000000000717. [PubMed: 30531227]

9). Armstrong GT, Liu Q, Yasui Y, Huang S, Ness KK, Leisenring W, Hudson MM, Donaldson SS, King AA, Stovall M, Krull KR, Robison LL, Packer RJ. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2009 Jul 1;101(13):946–58. doi: 10.1093/jnci/djp148. Epub 2009 Jun 17. [PubMed: 19535780]

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. Randomized study of two chemotherapy regimens for treatment of low-grade glioma in young children: a report from the Children's Oncology Group. J Clin Oncol. 2012 Jul 20;30(21):2641–7. doi: 10.1200/JCO.2011.36.6054. Epub 2012 Jun 4. [PubMed: 22665535]

11). Gnekow AK, Walker DA, Kandels D, Picton S, Giorgio Perilongo, Grill J, Stokland T, Sandstrom PE, Warmuth-Metz M, Pietsch T, Giangaspero F, Schmidt R, Faldum A, Kilmartin D, De Paoli A, De Salvo GL; of the Low Grade Glioma Consortium and the participating centers. A European randomised controlled trial of the addition of etoposide to standard vincristine and carboplatin induction as part of an 18-month treatment programme for childhood (≤16 years) low grade glioma - A final report. Eur J Cancer. 2017 Aug;81:206–225. doi: 10.1016/j.ejca.2017.04.019. Epub 2017 Jun 22. Erratum in: Eur J Cancer. 2017 Dec 13; [PubMed: 28649001]

12). Nobre L, Zapotocky M, Ramaswamy V, Ryall S, Bennett J, Alderete D, Balaguer Guill J, Baroni L, Bartels U, Bavle A, Bornhorst M, Boue DR, Canete A, Chintagumpala M, Coven SL, Cruz O, Dahiya S, Dirks P, Dunkel IJ, Eisenstat D, Faure Conter C, Finch E, Finlay JL, Frappaz D, Garre ML, Gauvain K, Bechensteen AG, Hansford JR, Harting I, Hauser P, Hazrati LN, Huang A, Injac SG, Iurilli V, Karajannis M, Kaur G, Kyncl M, Krskova L, Laperriere N, Larouche V, Lassaletta A, Leary S, Lin F, Mascelli S, McKeown T, Milde T, Morales La Madrid A, Morana G, Morse H, Mushtaq N, Osorio DS, Packer R, Pavelka Z, Quiroga-Cantero E, Rutka J, Sabel M, Salgado D, Solano P, Sterba J, Su J, Sumerauer D, Taylor MD, Toledano H, Tsang DS, Valente Fernandes M, van Landeghem F, van Tilburg CM, Wilson B, Witt O, Zamecnik J, Bouffet E, Hawkins C, Tabori U. Outcomes of BRAF V600E Pediatric Gliomas Treated With Targeted BRAF Inhibition. JCO Precis Oncol. 2020 May 20;4:PO.19.00298. doi: 10.1200/PO.19.00298. [PubMed: 32923898]

13). U.S. Food and Drug Administration. Written Request. https://www.fda.gov/drugs/development-resources/qualifying-pediatric-exclusivity-under-section-505a-federal-food-drug-and-cosmetic-act-frequently.

14). U.S. Food and Drug Administration. Drugs@FDA [database on the internet]. Dabrafenib USPI. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/202806s025lbl.pdf

15). U.S. Food and Drug Administration. Drugs@FDA [database on the internet]. Trametinib USPI. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/204114s025lbl.pdf

16). U.S. Food and Drug Administration. Breakthrough Therapy https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy.

17). U.S. Food and Drug Administration. Orphan Drug Designation https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/designating-orphan-product-drugs-and-biological-products.

18). U.S. Food and Drug Administration. New Drug Application https://www.fda.gov/drugs/types-applications/new-drug-application-nda.

19). U.S. Food and Drug Administration. Assessment aid. Available from: https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid

20). U.S. Food and Drug Administration. Priority Review https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review.

21). U.S. Food and Drug Administration. Project Orbis https://www.fda.gov/about-fda/oncology-center-excellence/project-orbis.

22). van den Bent MJ, Wefel JS, Schiff D, Taphoorn MJ, Jaeckle K, Junck L, Armstrong T, Choucair A, Waldman AD, Gorlia T, Chamberlain M, Baumert BG, Vogelbaum MA, Macdonald DR, Reardon DA, Wen PY, Chang SM, Jacobs AH. Response assessment in neuro-oncology (a

report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas. Lancet Oncol. 2011 Jun;12(6):583–93. doi: 10.1016/S1470-2045(11)70057-2. Epub 2011 Apr 5. [PubMed: 21474379]

23). Wen PY, Chang SM, Van den Bent MJ, Vogelbaum MA, Macdonald DR, Lee EQ. Response Assessment in Neuro-Oncology Clinical Trials. J Clin Oncol. 2017 Jul 20;35(21):2439–2449. doi: 10.1200/JCO.2017.72.7511. Epub 2017 Jun 22. 2. [PubMed: 28640707]

24). Bouffet Eric, Hansford Jordan, Maria Luisa Garré Junichi Hara, Ashley Plant-Fox Isabelle Aerts, Locatelli Franco, Van der Lugt Jasper, Papusha Ludmila, Sahm Felix, Tabori Uri, Cohen Kenneth J, Packer Roger J, Witt Olaf, Sandalic Lali, da Silva Ana Bento Pereira, Russo Mark W, Hargrave Darren R. Primary analysis of a phase II trial of dabrafenib plus trametinib (dab + tram) in BRAF V600–mutant pediatric low-grade glioma (pLGG). 10.1200/JCO.2022.40.17_suppl.LBA2002 Journal of Clinical Oncology 40, no. 17_suppl (June 10, 2022) LBA2002–LBA2002. Published online June 08, 2022.

25). U.S. Food and Drug Administration. NDA Multi-disciplinary Review and Evaluation (NDA 217514) and Approval Package: TAFINLAR (dabrafenib). Available here: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/217514Orig1s000TOC.cfm

26). U.S. Food and Drug Administration. NDA Multi-disciplinary Review and Evaluation (NDA 217513) and Approval Package: MEKINIST (trametinib). Available here: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/217513Orig1s000TOC.cfm

27). Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, Garbe C, Jouary T, Hauschild A, Grob JJ, Chiarion Sileni V, Lebbe C, Mandalà M, Millward M, Arance A, Bondarenko I, Haanen JB, Hansson J, Utikal J, Ferraresi V, Kovalenko N, Mohr P, Probachai V, Schadendorf D, Nathan P, Robert C, Ribas A, DeMarini DJ, Irani JG, Casey M, Ouellet D, Martin AM, Le N, Patel K, Flaherty K. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med. 2014 Nov 13;371(20):1877–88. doi: 10.1056/NEJMoa1406037. Epub 2014 Sep 29. [PubMed: 25265492]

28). U.S. Food and Drug Administration. Approval letter. Dabrafenib. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/217514Orig1s000ltr.pdf

29). U.S. Food and Drug Administration. Approval letter. Trametinib. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/217513Orig1s000ltr.pdf

30). Bradford D, Singh H, Donoghue M. FDA regulatory considerations for the review of drugs intended to treat pediatric cancers and rare tumors. Curr Opin Pediatr. 2023 Feb 1;35(1):48–54. doi: 10.1097/MOP.0000000000001201. Epub 2022 Nov 11.

Table 1:

Demographics and Baseline Characteristics

Demographic variable	Dabrafenib plus Trametinib (N=73)	Carboplatin plus Vincristine (N=37)	All patients (N=110)
Age, median (range)	10 years (1 – 17)	8 years (1 – 17)	9.5 years (1 – 17)
< 6 years	20 (27%)	14 (38%)	34 (31 %)
6 <12 years	25 (34%)	11 (30%)	36 (33%)
12 – <18 years	28 (38%)	12 (32%)	40 (36%)
Sex (Male, Female)	29 (40%), 44 (60%)	15 (40%), 22 (60%)	44 (40.0%), 66 (60.0%)
Prior therapy			
Surgery	62 (85%)	29 (78%)	91 (83%)
Systemic therapy	1 (1.4%)	0%	0%
Race			
White	55 (75%)	25 (68%)	80 (73%)
Asian	5 (7%)	3 (8%)	8 (7%)
Black or AA	2 (2.7%)	3 (8%)	5 (4.5%)
Not reported	2 (2.7%)	1 (2.7%)	3 (2.7%)
Unknown	6 (8%)	4 (11%)	10 (9%)
Other	3 (4.1%)	1 (2.7%)	4 (3.6%)
Ethnicity			
Not Hispanic or Latino	48 (66%)	17 (46%)	65 (59%)
Hispanic or Latino	8 (11.0%)	4 (11%)	12 (11%)
Unknown	5 (7%)	5 (14%)	10 (9%)
Not reported	12 (16%)	11 (30%)	23 (21%)

AA: African American

Source: U.S. Food and Drug Administration. NDA Multi-disciplinary Review and Evaluation and Approval Packages, TAFINLAR and MEKINIST[25,26]

Table 2:

Pathology at Diagnosis

Histology	Dabrafenib plus Trametinib (N=73)	Carboplatin plus Vincristine (N=37)	All patients N=110
Astrocytoma	1 (1.4)	1 (2.7)	2 (1.8)
Desmoplastic astrocytoma NOS	0	1 (2.7)	1 (0.9)
Desmoplastic Infantile Astrocytoma	2 (2.7)	1 (2.7)	3 (2.7)
Diffuse Astrocytoma	1 (1.4)	1 (2.7)	2 (1.8)
Diffuse Glioma NOS	2 (2.7)	0	2 (1.8)
Ganglioglioma	21 (29)	9 (24)	30 (27)
Glioneuronal NOS	2 (2.7)	1 (2.7)	3 (2.7)
Infantile Desmoplastic GG	1 (1.4)	0	1 (0.9)
LGG NOS	14 (19)	6 (16)	20 (18)
Pilocytic astrocytoma	22 (30)	12 (32)	34 (31)
Pleomorphic xanthoastrocytoma	6 (8)	4 (11)	10 (9)
Primitive neuroectodermal tumor	0	1 (2.7)	1 (0.9)
Missing	1 (1.4)	0	1 (0.9)

NOS: not otherwise specified, LGG: low grade glioma, GG: ganglioglioma

Source: U.S. Food and Drug Administration NDA Multi-disciplinary Review and Evaluation and Approval Packages, TAFINLAR and MEKINIST[25,26]

Table 3:

Efficacy Results Based on Independent Review in Study G2201 (LGG cohort)

	Dabrafenib plus Trametinib N=73	**Carboplatin plus Vincristine N=37**
Overall Response Rate		
ORR% (95% CI)	46.6 (34.8, 58.6)	10.8 (3.0, 25.4)
P value	< 0.001	
Complete response (CR), n (%)	2 (2.7)	1 (2.7)
Partial response (PR), n (%)	32 (44)	3 (8)
Duration of Response		
Median (95% CI), months	23.7 (14.5, NE)	NE (6.6, NE)
% with observed DOR ≥ 12 months	56	50
% with observed DOR ≥ 24 months	15	25
Progression-Free Survival		
Median (95% CI), months	20.1 (12.8, NE)	7.4 (3.6, 11.8)
Hazard ratio (95% CI)	0.31 (0.17, 0.55)	
P value	< 0.001	

Source: U.S. Food and Drug Administration (2023) dabrafenib (Tafinlar®) and trametinib (Mekinist®) USPI. [14,15]

Table 4:

Adverse Reactions (≥ 15%) in Pediatric LGG Patients Who received Dabrafenib in Combination with Trametinib in Study G2201[a]

Adverse Reactions	Dabrafenib plus Trametinib N=73		Carboplatin plus Vincristine N=33	
	All grades (%)	Grade ≥ 3 (%)	All grades (%)	Grade ≥ 3 (%)
Gastrointestinal				
Vomiting	34	1	48	3
Diarrhea[b]	29	0	18	6
Nausea	25	0	45	0
Abdominal Pain[c]	25	0	24	0
Constipation	12	0	36	0
Stomatitis[d]	10	0	18	0
General				
Pyrexia[e]	68	8	18	3
Fatigue[f]	33	0	39	0
Nervous system				
Headache[g]	47	1	33	3
Dizziness[h]	15	0	9	3
Peripheral Neuropathy[i]	7	0	45	6
Vascular Disorders				
Hemorrhage[j]	25	0	12	0
Skin				
Rash[k]	51	2.7	18	3
Dry skin	26	0	3	0
Dermatitis acneiform[l]	22	0	0	0
Alopecia	3	0	24	0
Musculoskeletal And Connective Tissue Disorders				
Musculoskeletal Pain[m]	34	0	30	0
Pain in jaw	1.4	0	18	0
Metabolism And Nutrition Disorders				
Decreased Appetite	5	0	24	0
Respiratory, Thoracic And Mediastinal Disorders				
Oropharyngeal Pain	11	0	18	0
Psychiatric Disorders				
Anxiety	1.4	0	15	3
Immune System Disorders				
Hypersensitivity	0	0	15	3

Adverse Reactions	Dabrafenib plus Trametinib N=73		Carboplatin plus Vincristine N=33	
	All grades (%)	Grade ≥ 3 (%)	All grades (%)	Grade ≥ 3 (%)
Infections and infestations				
Upper Respiratory Tract Infection	15	0	6	0
Injury, Poisoning And Procedural Complications				
Infusion Related Reaction	0	0	15	3
Investigations				
Weight Increased	15	7	0	0

[a] NCI CTCAE version 4.03

[b] Includes diarrhea, colitis, enterocolitis, and enteritis.

[c] Includes abdominal pain and upper abdominal pain.

[d] Includes stomatitis, cheilitis, mouth ulceration, aphthous ulcer, and glossitis.

[e] Includes pyrexia and body temperature increased.

[f] Includes fatigue and asthenia.

[g] Includes headache and migraine with aura.

[h] Includes dizziness, and vertigo.

[i] Includes peripheral neuropathy, peripheral motor neuropathy, peripheral sensorimotor neuropathy, paresthesia, neuralgia, hypoaesthesia and peripheral sensory neuropathy.

[j] Includes epistaxis, post procedural hemorrhage, hematuria, upper gastrointestinal hemorrhage, and hemorrhage intracranial.

[k] Includes rash, rash macular, rash maculo-papular, rash pustular, rash papular, rash erythematous, eczema, erythema multiforme, dermatitis, dermatitis exfoliative, skin exfoliation, palmar-plantar erythrodysaesthesia syndrome and dermatitis bullous.

[l] Includes dermatitis acneiform, acne and acne pustular.

[m] Includes back pain, myalgia, pain in extremity, arthralgia, bone pain, non-cardiac chest pain, neck pain and musculoskeletal stiffness.

Source: U.S. Food and Drug Administration (2023) dabrafenib (Tafinlar®) and trametinib (Mekinist®) USPI. [14,15]

Table 5:

FDA Benefit-Risk Analysis

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Approximately 1600 pediatric patients are diagnosed with LGG each year in the US.[6] • 17% of pediatric patients with LGG have BRAF V600E mutations.[7] • For pediatric patients with LGG, overall survival is generally > 90%; there is some variation based on molecular subtype, especially BRAFV 600E mutation which is associated with a poorer outcome.[8,12] Disease and treatment sequelae are common and may include functional, neurologic or endocrine complications.	• BRAF V600E mutant LGG is a rare tumor that may be life-threatening; patients may also experience significant morbidities, including vision loss and neurologic complications.
Current Treatment Options	• For patients who require therapy beyond surgical resection, the standard of care consists of chemotherapeutic regimens: carboplatin and vincristine; thioguanine, procarbazine, lomustine, and vincristine (TCPV); and single agent vinblastine. • ORRs for these therapies in pediatric patients with LGG range from 26 – 35%; however, for patients with BRAF V600E mutation, the reported ORR with traditional chemotherapy regimens is lower (10 – < 23%).[7,12]	• There is an unmet medical need to treat pediatric patients with BRAF V600E mutant LGG. • Prior to this approval, there were no FDA approved treatment options for pediatric patients with LGG with BRAF V600E mutations who require first-line systemic therapy after surgical resection.
Benefit	• The primary efficacy data supporting the application is derived from a Study G2201, a global, multi-center, randomized, open-label study conducted in pediatric patients ages 1 to < 18 years with BRAF V600E mutation-positive, progressing LGG who required systemic treatment. • The D+T arm demonstrated an ORR of 47% (95% CI: 35, 59) compared to the C+V arm which demonstrated an ORR of 11% (95% CI: 3.0, 25), with a p-value <0.001. The median DOR for the D+T arm was 23.7 months (95% CI: 14.5, NE). • The median PFS was 20.1 months (95% CI: 12.8, NE) in the D+T arm and 7.4 months (95% CI: 3.6, 11.8) in the C+V arm, with a HR of 0.31 (95% CI, 0.18, 0.55; p<0.001). • Review of VA data among responding patients with impaired or threatened vision in the D+T (n=19) arm and C+V (n=8) arm indicated that the majority of patients' symptoms in both groups were stable or improved while receiving therapy. Given the small number of patients with VA assessments and response data, conclusions on the effect of D+T on visual outcomes are limited.	• Based on the substantial improvement in ORR and PFS with demonstration of durable responses, the statutory evidentiary standard for regular approval has been adequately met. • A post-marketing commitment was issued to obtain the final analysis for OS and PFS once all patients with LGG have been followed for at least 2 years. • The Applicant will provide an analysis of change in visual acuity over the course of treatment will be conducted.
Risk and Risk Management	• The pooled safety database for these NDAs includes 166 pediatric patients with advanced solid tumors harboring BRAFV600E mutations who received at least one dose of dabrafenib and trametinib at the respective RP2Ds. • The most common (> 20%) adverse reactions in the pooled pediatric population were pyrexia (66%), rash (54%), headache (40%), vomiting (38%), musculoskeletal pain (36%), fatigue (31%), dry skin (31%), diarrhea (30%), nausea (26%), epistaxis and other bleeding events (25%), abdominal pain (24%) and dermatitis acneiform (23%).	• The observed safety profile is acceptable in the context of the treatment of progressive disease and is overall consistent with the known adverse effects of D+T. • There were no significant safety concerns identified during NDA review requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS).

Source: Adapted from U.S. Food and Drug Administration, NDA Multi-disciplinary Review and Evaluation and Approval Package: dabrafenib (Tafinlar®) and trametinib (Mekinist®).[25,26]