

BRAF and MEK Inhibitors in Pediatric CNS Tumors

Subjects: Cell Biology

Contributor: Dario Talloa, Silvia Triarico, Pierpaolo Agresti, Stefano Mastrangelo, Giorgio Attinà, Alberto Romano, Palma Maurizi, Antonio Ruggiero

BRAF is a component of the MAPK and PI3K/AKT/mTOR pathways that play a crucial role in cellular proliferation, differentiation, migration, and angiogenesis. Pediatric central nervous system tumors very often show mutations of the MAPK pathway, as demonstrated by next-generation sequencing (NGS), which now has an increasing role in cancer diagnostics.

Keywords: central nervous system (CNS) tumors ; BRAF ; MEK

1. Pediatric Low-Grade Glioma (pLLG)

Pilocytic astrocytoma (PA) is the most common pediatric low-grade glioma (pLGG), accounting for approximately 15.6% of brain tumors that arise up to 19 years old ^[1]. Its development is more common in the first two decades of life, with peak of incidence from age 0 to 9. PAs are most commonly found in infratentorial structures such as the cerebellum but they also frequently arise in midline brain structures like the optic nerves, the hypothalamus, and the brain stem. The updated WHO 2021 classification describes this entity as a grade 1 lesion, due to its slow potential for growth, which correlates to its good prognosis with a 10-year overall survival estimated between 85% and 96% ^[2]. Nevertheless, PA may impact heavily on the child's quality of life with frequent neurological and endocrine complications due to the lesion itself or to the prolonged treatment needed. The mainstay of therapy for symptomatic or progressive PA is complete surgical resection whenever surgically feasible. If the tumor is completely resected, no further therapy is needed; incomplete resection, most frequently due to the anatomical location, can be followed by a prolonged period of stability of the lesion, nonetheless, some cases may require additional therapy. In the absence of radical surgery, chemotherapy or radiotherapy may be adopted to treat the residual lesions, so the main focus is still on optimizing long-term treatment to reduce early and late side effects. The most commonly used chemotherapy regimen is carboplatin and vincristine for intensified induction chemotherapy, or vinblastine alone ^[3].

PA may not completely respond to first-line therapy, requiring extensive radiological and clinical monitoring to accurately determine the need for additional therapy. Radiotherapy is to be employed in progressive and refractory disease only and it should be avoided in younger children because of long-term adverse effects. Moreover, at the molecular level, PA often shows alterations in MAPK pathways, mostly point mutations in genes and fusions which include genes such as *BRAF*, *KRAS*, *FGFR1*, *NF1*, and many more. MAP/ERK pathway mutations are found in more than 90% of PA; the most commonly found genetic aberration is the *KIAA1549-BRAF* fusion in 60–70% of cases, while *BRAF* V600E mutation is found in 10% of PA ^[4].

Numerous agents targeting the MAPK pathway, such as MAP/ERK kinase or *BRAF* inhibitor, are currently being tested. One of the most extensively studied drugs is selumetinib (AZD6244); a phase 2 trial (NCT01089101) enrolled 25 eligible patients for treatment with selumetinib at the recommended dosage of 25 mg/sqm/dose bis in die (BID) for a maximum of 26 courses. Out of these 25 patients, six (6/25, 24%) showed partial response, fourteen (14/25, 56%) had stable disease while five patients had a progression of disease. Two-year progression-free survival (PFS) was 78% ± 8.5%. Nineteen patients out of the 25 who were enrolled underwent visual acuity evaluation: five of them showed improvement of the visual fields while the other fourteen patients showed stability of the visual fields. Among the most common toxicities were grade 1 and 2 creatine phosphokinase elevation (CPK), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) elevation, hypoalbuminemia, skin rash, vomiting, diarrhea, headache, and anemia. These results show that selumetinib may be well tolerated and can be effective to prolong disease stability in children with recurrent or progressive optic pathways and hypothalamic glioma. All of the 25 patients had received chemotherapy previously and 19 of the 25 received surgery before treatment with selumetinib ^[5]. A phase 3 clinical trial (NCT04166409) compares carboplatin and vincristine with selumetinib alone in previously untreated pLGG, that do not have a *BRAF* V600E mutation and are not associated with systemic neurofibromatosis type 1 ^[6].

Trametinib is another MEK-1/2 inhibitor, studied in the pediatric trial NCT02124772 both alone and combined with dabrafenib, a *BRAF* inhibitor. Route of administration is a crucial factor in pediatric patients. Younger children might not be able to swallow bigger pills, capsules or tablets and the dosage offered by solid forms of the drugs might be inadequate for them. In the trial, both trametinib and dabrafenib were available in tablets as well as oral suspension. This trial also accounted for the palatability of the oral suspension together with how easy they were to reconstitute and administer to the patients. Adherence to therapy is always a factor to be considered in pediatric patients and oral suspensions are useful both for patients who cannot properly swallow tablets and for measuring in an easier way the correct dosage. Preliminary available data show that the oral solutions of trametinib and dabrafenib were not difficult to swallow for the patients, but no clear conclusion can be drawn on palatability because of missing data collected from patients over 12 years old. In Part D of this trial a separate section was designed for participants affected by pLGG to be treated with trametinib in combination with dabrafenib. Maximum observed plasma concentration (C_{max}) of dabrafenib in this group was 1360 ng/mL, it should be noted that this geometric mean was obtained on an analysis on only nineteen of the twenty patients enrolled in this group. Of the twenty patients, eight suffered from serious adverse effect (8/20, 40%) ranging from decreased white blood cell count to seizures (only one event reported) and decrease in cardiac ejection fraction (only one event reported); there was also one episode of tonsillitis and one episode of respiratory distress [7].

There are many MEK inhibitors (like cobimetinib and binimetinib) and many *BRAF* inhibitors (like vemurafenib and dabrafenib) which are currently being studied and tested as possible targeted therapies. A completed phase I/II clinical trial (NCT01677741) enrolled 32 patients with recurrent, progressive or refractory solid tumors with *BRAF* V600E mutation with the aim to study the safety, tolerability, and pharmacokinetics of dabrafenib. Dabrafenib was available both as capsules and as oral suspension; the latter was to be used for any patient unable to safely swallow capsules. The data regarding pLGG enrolled in the trial showed a response rate of 44% and a 1-year estimated PFS of 85% [8].

A pediatric phase 2 trial that aimed to test sorafenib in children with recurrent LGG was halted when unexpected progression happened in 9 of 11 patients, 3 of which had the KIAA1549-*BRAF* fusion and *NF1*. This effect has been confirmed to be due to paradoxical extracellular signal-regulated kinase (ERK) activation, which was demonstrated in vitro both in *BRAF* wild type, *BRAF* fusion, and *NF1*-deficient tumor cells in vitro [9]. It was also proven that KIAA1549-*BRAF* fusion kinase functions as a homodimer that is resistant to the first generation of *BRAF* inhibitors, like vemurafenib, which targets the monomeric form of *BRAF*. For this reason, first generation *BRAF* inhibitors should not be used in glioma which shows this fusion. Second generation *BRAF* inhibitors, like DAY101 (formerly TAK-580, MLN2480), are able to target both monomeric and dimeric forms of *BRAF* bypassing the paradoxical activation of the pathway. In the trial NCT03429803 pediatric patients with radiological evidence of recurrence or progression of disease of non-hematologic malignancies that had evidence of activation of the MAPK pathway were treated with DAY101, aiming for the maximum tolerated dose (MTD) [10].

Pleomorphic xanthoastrocytoma (PXA) is a rare primary CNS tumor most commonly diagnosed in the second decade of life, without any gender predilection, with cases as young as 2 years reported [11]. Like other primary CNS tumors, molecular characterization is important for the prognosis at the moment of the diagnosis, but the WHO classification system has not yet officially described PXA *BRAF* mutated and *BRAF* wild-type as distinct clinical entities. The 2021 WHO classification of CNS tumors defines PXA a grade 3 lesion only if it shows by ≥ 5 mitoses per 10 HPF (high power field); if it has less it is considered a grade 2 lesion. The most common primary location is the temporal lobe [12]. The most frequently mutated gene in PXAs is *BRAF*, which can be found in 2/3 of typical PXA, less commonly in its anaplastic variant, which might imply different molecular pathogenesis. *BRAF* V600E mutation is the one more commonly observed, but fusions of *BRAF* and other different mutations have been described [12][13]. OS and PFS are worse in the anaplastic PXA, but the presence of *BRAF* V600 mutations is associated with longer OS rates both in typical and anaplastic PXA. Due to the rarity of PXA, optimal management of these lesions must take into consideration case reports and case series. Gross total resection was associated with longer PFS, but not with better OS, if compared with subtotal resection and biopsy (5-years PFS 92.3% vs. 41.7%, $p = 0.0002$) [14]. Similarly, radiotherapy may play a role in residual or recurrent disease. The role of systemic therapy is still being defined but it should be noted that as highlighted in a recent brief review of literature from 2019 regarding PXAs by Shaikh et al., traditional chemotherapy is considered minimally effective in the treatment of PXAs. Given the high incidence in PXA of targetable mutations there have been clinical trials ongoing regarding the use of *BRAF* inhibitors both in monotherapy and associated with MEK inhibitors.

A phase 2 clinical trial (NCT05180825), called PLGG-MEKTRIC, is ongoing for comparing trametinib (Mekinist™) with standard chemotherapy with vinblastine during 18 courses of 4 weeks each in pediatric low-grade glioma and mixed glioneuronal tumors, including PXA, without *BRAF* V600E mutation or correlation to NF-1. Its primary endpoint is 3-year PFS, but data regarding the difference in PFS and OS according to molecular biomarkers are also analyzed [15].

Another phase 2 clinical trial (NCT02684058) will investigate the activity of dabrafenib in combination with trametinib in two different cohorts, LGG and high-grade glioma (HGG) with *BRAF* V600E mutation, actively comparing the LGG experimental cohort with traditional chemotherapy with carboplatin and vincristine. The primary endpoint is the overall response rate (ORR) in the first 32 weeks of treatment. ORR will be assessed through MRI and/or CT scans using Response Assessment in Neuro-Oncology Criteria (RANO) criteria [16]. The results from the VE-BASKET study which is an open-label, non-randomized, multicohort study for *BRAF* V600E-mutant non melanoma tumors, showed that in seven PXA treated with vemurafenib only one showed complete response, two showed partial responses, and three patients had stable disease. Arthralgia, melanocytic nevus, palmar-plantar erythrodysesthesia, and photosensitivity reaction were the most common adverse effect, whereas maculopapular rash was the most common grade 3 and 4 event and no grade 5 treatment-related events were observed. These results confirmed that vemurafenib shows safe antitumor activity in some patients with *BRAF* V600E mutant glioma, with the highest response rate observed in low-grade tumors, such as PXA [17].

Oligodendroglioma and diffuse astrocytoma were originally part of a broad group, which generically described them as diffuse gliomas. The tumors that showed histological characteristics common to both types of lesions were also included in this group. The 2016 WHO classification of Tumors of the Central Nervous System changed this by introducing a differentiation on a molecular basis. As an example, the diagnosis of anaplastic oligodendroglioma requires the presence of two mutations: both isocitrate dehydrogenase 1 or 2 mutations (IDH-mt) and 1p/19q co-deletion have to be present. Anaplastic astrocytoma on the other hand was divided into IDH wild type and IDH mutated tumors. IDH-mt tumors usually present themselves with low-grade histology at the diagnosis that tends to evolve slowly in time, nonetheless they have a more favorable prognosis than IDH-wt tumors. Diffuse astrocytoma and oligodendrogliomas account for 13% of primary brain and other CNS gliomas [18]. Oligodendrogliomas in pediatric and young adult patients are rare and their molecular pathogenesis has been shown to be different from that of oligodendroglioma in adults [2]. A study reported two cases of grade II and grade III oligodendroglioma respectively in a 14-year-old girl and an 11-year-old boy. In both cases, no evidence of 1p/19q co-deletions or mutations of IDH1, TP53, CIC, and H3F3A genes were found. Instead, both cases showed MAPK/ERK pathways activation as proven through immunohistochemical analysis and RT-PCR analysis and Sanger sequencing that showed the presence of KIAA1549_Ex15-*BRAF*_Ex9 fusion protein. This was the first study that demonstrates the occurrence of KIAA1549-*BRAF* fusion in pediatric oligodendroglioma, highlighting the importance of molecular characterization at the diagnosis. Further longitudinal studies are required to better describe the incidence of these mutations as a possible target for therapy [19]. It should be noted that pediatric diffuse gliomas rarely have the above-mentioned genetic mutations. The rate of *BRAF* mutation in the pediatric diffuse glioma is around 3% for fusion and 8%–43% for V600E, implying that pediatric diffuse glioma has a different molecular underpinning from the diffuse glioma that manifests in the adult [3][20]. As it has become the norm for other low and intermediate lesions, it has become common practice to operate early on low-grade glioma-like lesions when radical surgery is considered feasible and safe. As for PAs and PXAs, focal radiation therapy is a possible approach for unresectable or recurrent diseases but should be reserved for more aggressive lesions because of the long-term side effects, especially on cognitive development, that are more severe if radiation therapy is used in the first years of life [21]. Currently, new radiation techniques may be adopted, like proton therapy that can minimize the damage to adjacent structures. The trial NCT04065776 is currently ongoing to determine the feasibility of hippocampal avoidance (HA) for pLGG located in the midline or suprasellar region, and the clinical outcome is being assessed comparing various neurocognitive scores, which mainly focus on memory as a direct measure of hippocampal damage. Depending on tumor location, the dosage used will be 52.2 CGE or 54 CGE in 29 or 30 fractions. There is no trial that has compared chemotherapy alone with chemotherapy and radiotherapy combined; because of this combination therapy might be considered in relapsed or recurrent disease after first line treatment with the age of the patients being one of the most important factors in deciding whether or not radiation therapy should be implemented [20]. The trial NCT04923126 is an open-label, multi-center, phase ½ study of the MEK inhibitor mirdametininb (PD-0325901), which preclinical studies have reported to have potentially superior blood-brain-barrier penetration compared to other MEK inhibitors [22], in patients with pLGG. Both patients with relapsed or progressed disease and previously untreated subjects are eligible for the study, in the presence of MAPK pathway activation or *NF1*, *NF2*, and other germline mutations. The treatment with mirdametininb in this trial is going to be administered twice daily on days 1–28 for up to 26 cycles (24 months) in the absence of disease progression or unacceptable toxicity. Interim results as recently reported by Vinitsky et al. are promising; of eleven patients recruited six had at least one follow-up disease evaluation: four of them showed minor response (>25–50% decrease); no disease progression has been observed; there were no grade 3 or 4 adverse events; and no MEK-related cardiomyopathy or retinopathy [23].

2. Pediatric High-Grade Glioma (pHGG)

Pediatric High-Grade Glioma (pHGG) comprises almost 15% of all primary brain tumors in children. pHGGs encompass many clinical entities that are very different from each other, for their histological and molecular features. Molecular

profiling of pediatric HGGs is different from HGGs of the adult [24]. Different histological subtypes of pHGGs can harbor distinct genetic drivers that can offer potential therapeutic targets and offer a better prognosis, like *BRAF* mutations in epithelioid glioblastoma and anaplastic pleomorphic xanthoastrocytoma (aPXA) [25].

The 2021 WHO classification of Tumors of the Central Nervous System distinguishes four types of diffuse pediatric high-grade gliomas: diffuse midline glioma H3 K27-altered; diffuse hemispheric glioma H3 G34-mutant; diffuse pediatric-type high-grade glioma H3-wildtype; and IDH-wildtype, infant-type hemispheric glioma [26]. However, most articles cited are dated before the 2021 WHO classification, researchers are going to discuss hemispheric pHGGs, like anaplastic astrocytoma, glioblastoma (GBM), and high-grade midline tumors, formerly diffuse midline glioma (DMG), in order to avoid confusion.

Anaplastic astrocytoma (incidence 0.1/100.000 patients from age 0 to 19 years) is a Grade 3 lesion and GBM (incidence 0.18/100.000 patients from age 0 to 19 years) is a Grade 4 lesion, these are the clinical entities that constitute hemispheric HGG [1]. Gliomatosis cerebri (GC) is not considered a distinct clinical entity since the 2016 WHO classification; instead, it can be described as a highly infiltrative growth pattern that can be considered a phenotypic manifestation of HGG, both in pediatric patients and adults [27][28]. Although there is no widely accepted recommended standard of care, and treatment must be tailored for each patient, most surgically approachable lesions undergo gross tumor resection (GTR) followed by focal irradiation and additional chemotherapy, most commonly temozolomide, an oral alkylating agent, usually both during and after radiation therapy. A better understanding of the tumor's molecular background is a possible step toward increasing survival. A 20-year systematic review and meta-analysis of 129 patients in 2018 showed a cumulative OS of 4.0 months (95% CI 1.9–6.1) [29]. The incidence of *BRAF* mutations in adult GBM is estimated to be 1–3% while in teenage patients and young adults GBM these mutations are much more frequent with incidence up to 50% in the epithelioid variant [30]. The revised 2016 WHO classification of tumors of the CNS was the first one to introduce a new clinical entity: the diffuse midline glioma (DMG) H3 K27M mutated, designating it as a distinct entity from other midline lesions. The presence of H3 K27M alterations in any infiltrating midline gliomas determines the assignment to WHO grade IV. H3 K27M alterations may rarely occur in low-grade midline gliomas and posterior fossa ependymomas, but the clinical relevance of this occurrence is not yet fully understood [31]. Pagès et al. in 2018 reported a co-occurrence of H3 K27M and *BRAF* V600E mutation in five pediatric midline gangliogliomas; all five cases were Grade 1 without anaplastic features and one of them underwent spontaneous malignant in situ transformation 7 years after the diagnosis. The results of the data from this report suggested that the presence of H3 K27M mutation in tumor with no malignant feature should not automatically define the lesion as Grade 4 and that *BRAF* status should always be assessed. There are only a few cases reported in literature of these two mutations occurring simultaneously and their meaning is not fully understood and should be investigated further. High-grade midline gliomas, similarly to hemispheric pHGG, have an unfavorable prognosis, with a median survival time of less than 1 year. Commonly only a stereotactic biopsy is performed since most of these lesions show diffuse growth patterns making them ineligible for radical surgery [32].

There are numerous ongoing clinical trials regarding targeted therapies toward *BRAF* and MAPK pathways among pediatric HGGs. The trial NCT03919071 is actively recruiting pediatric patients with newly diagnosed HGG with *BRAF* V600E mutations and without H3 K27M mutation in order to treat these patients firstly with radiation therapy and then with a combined therapy comprised of dabrafenib and trametinib in order to estimate the event-free survival (EFS) to compare this EFS to contemporary historical controls. Therapy with dabrafenib and trametinib is going to be administered four weeks after completion of RT. The patients will receive dabrafenib mesylate orally twice daily and trametinib once daily on days 1–28. In this trial, treatment repeats every 28 days for up to 24 cycles in the absence of disease progression or unacceptable toxicity [33]. The trial NCT03220035 is a phase II of the pediatric MATCH trial, which aims to study how effective vemurafenib is in treating patients with tumors with V600E mutations that have advanced locally, have relapsed, recurred, or do not respond to treatment, with the primary objective of determining the response rate. In this trial patients will receive vemurafenib orally on days 1–28. Like other trials, cycles of therapy repeat every 28 days in this case for up to 2 years in the absence of disease progression or unacceptable toxicity [34]. Other trials like NCT02639546, currently completed, have tried to evaluate the safety, tolerability and pharmacokinetics of newer molecules, such as cobimetinib, with a dose-escalation stage and an expansion stage after finding the recommended dose. Cobimetinib is available and has been used in this trial, both in tablet and suspension form. Only five cases of HGG were recruited and none of them showed complete or partial response after 2 months of therapy. Further studies are still needed to understand which molecular pathway may offer the best results in terms of OS and PFS, but currently, the biggest obstacle is the insufficient number of patients studied due to the low incidence of these tumors [35].

3. Other Tumors

Ganglioglioma is a rare, slow-growing, and defined tumor, with both cystic and solid neuronal and glial elements, that usually occurs at the pediatric and young adult age. They are considered indolent tumors and surgical resections are potentially curative, however complete resection is not always possible. *BRAF* V600E and *BRAF* fusions have been reported among patients with ganglioglioma [36]. Dayiha et al. studied a large cohort of 53 pediatric patients with ganglioglioma and found that *BRAF* V600E mutation correlates with shorter recurrence-free survival, alerting to the need for the identification of this high-risk group and determining future *BRAF*-targeted therapies and disease surveillance strategies [35].

Diffuse Leptomeningeal Glioneuronal Tumor (DLGNT) is a rare tumor that usually occurs in children and adolescents, characterized by the leptomeningeal spread of oligodendroglial-like cells. Most DLGNT are indolent, but sometimes they can progressively enlarge in size and increase in number, going into an advanced stage [37]. The hallmark molecular feature of this tumor seems to be co-deletion of 1p/19q and the pathologic activation of the MAPK, which may occur in 80% of DLGNT, mostly KIAA1549:*BRAF* fusions, that were found in 66% of them. Thus, MEK inhibitors may be promising therapeutic targets for improving the clinical outcome of patients with DLGNT [38].

Polymorphous Low-Grade Neuroepithelial Tumor of the Young (PLNTY) was described in 2017 by Huse et al. as a new entity of low-grade, oligodendroglioma-like neuroepithelial tumor, with astrocytic and ependymal appearance. The most common location of PLNTY is subcortical in the temporal lobe and because of this, they are frequently epileptogenic tumors. Over-activation of the MAPK pathway is frequently observed in these tumors, making it a potential target for therapy. In Huse's original series, three of seven cases were *BRAF* V600E mutant and the remaining cases exhibited fusion events involving FGFR2/FGFR3 [39].

References

1. Ostrom, Q.T.; Patil, N.; Cioffi, G.; Waite, K.; Kruchko, C.; Barnholtz-Sloan, J.S. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2013–2017. *Neuro-Oncology* 2020, 22 (Suppl. S1), iv1–iv96.
2. Krishnatry, R.; Zhukova, N.; Guerreiro Stucklin, A.S.; Pole, J.D.; Mistry, M.; Fried, I.; Ramaswamy, V.; Bartels, U.; Huang, A.; Laperriere, N.; et al. Clinical and treatment factors determining long-term outcomes for adult survivors of childhood low-grade glioma: A population-based study. *Cancer* 2016, 122, 1261–1269.
3. De Blank, P.; Bandopadhyay, P.; Haas-Kogan, D.; Fouladi, M.; Fangusaro, J. Management of pediatric low-grade glioma. *Curr. Opin. Pediatr.* 2019, 31, 21–27.
4. The St. Jude Children's Research Hospital–Washington University Pediatric Cancer Genome Project. Whole-genome sequencing identifies genetic alterations in pediatric low-grade gliomas. *Nat. Genet.* 2013, 45, 602–612.
5. Fangusaro, J.; Onar-Thomas, A.; Poussaint, T.Y.; Wu, S.; Ligon, A.H.; Lindeman, N.I.; Banerjee, A.; Packer, R.; Kilburn, L.B.; Pollack, I.F.; et al. LTBK-01. Updates on the phase II and re-treatment study of AZD6244 (Selumetinib) for children with recurrent or refractory pediatric low-grade glioma: A pediatric brain tumor consortium (PBTC) study. *Neuro-Oncology* 2018, 20 (Suppl. S2), i214.
6. Schreck, K.C.; Grossman, S.A.; Pratilas, C.A. *BRAF* Mutations and the Utility of RAF and MEK Inhibitors in Primary Brain Tumors. *Cancers* 2019, 11, 1262.
7. Geoerger, B.; Moertel, C.L.; Whitlock, J.; McCowage, G.B.; Kieran, M.W.; Broniscer, A.; Hargrave, D.R.; Hingorani, P.; Kilburn, L.B.; Mueller, S.; et al. Phase 1 trial of trametinib alone and in combination with dabrafenib in children and adolescents with relapsed solid tumors or neurofibromatosis type 1 (NF1) progressive plexiform neurofibromas (PN). *J. Clin. Oncol.* 2018, 36, 10537.
8. Rankin, A.; Johnson, A.; Roos, A.; Kannan, G.; Knipstein, J.; Britt, N.; Rosenzweig, M.; Haberberger, J.; Pavlick, D.; Severson, E.; et al. Targetable *BRAF* and *RAF1* Alterations in Advanced Pediatric Cancers. *Oncologist* 2021, 26, e153–e163.
9. Karajannis, M.A.; Legault, G.; Fisher, M.J.; Milla, S.S.; Cohen, K.J.; Wisoff, J.H.; Harter, D.H.; Goldberg, J.D.; Hochman, T.; Merkelson, A.; et al. Phase II study of sorafenib in children with recurrent or progressive low-grade astrocytomas. *Neuro-Oncology* 2014, 16, 1408–1416.
10. Sievert, A.J.; Lang, S.S.; Boucher, K.L.; Madsen, P.J.; Slaunwhite, E.; Choudhari, N.; Kellet, M.; Storm, P.B.; Resnick, A.C. Paradoxical activation and RAF inhibitor resistance of *BRAF* protein kinase fusions characterizing pediatric astrocytomas. *Proc. Natl. Acad. Sci. USA* 2013, 110, 5957–5962.

11. Davies, K.G.; Maxwell, R.E.; Seljeskog, E.; Sung, J.H. Pleomorphic xanthoastrocytoma—Report of four cases, with MRI scan appearances and literature review. *Br. J. Neurosurg.* 1994, 8, 681–689.
12. Srinivasa, K.; Cross, K.A.; Dahiya, S. BRAF Alteration in Central and Peripheral Nervous System Tumors. *Front. Oncol.* 2020, 10, 574974.
13. Schindler, G.; Capper, D.; Meyer, J.; Janzarik, W.; Omran, H.; Herold-Mende, C.; Schmieder, K.; Wesseling, P.; Mawrin, C.; Hasselblatt, M.; et al. Analysis of BRAF V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma. *Acta Neuropathol.* 2011, 121, 397–405.
14. Ida, C.M.; Rodriguez, F.J.; Burger, P.C.; Caron, A.A.; Jenkins, S.M.; Spears, G.M.; Aranguren, D.L.; Lachance, D.H.; Giannini, C. Pleomorphic Xanthoastrocytoma: Natural History and Long-Term Follow-Up. *Brain Pathol.* 2015, 25, 575–586.
15. Pediatric Low-Grade Glioma—MEKinhibitor TRial Vs. Chemotherapy (PLGG—MEKTRIC). Available online: <https://clinicaltrials.gov/ct2/show/NCT05180825> (accessed on 6 June 2022).
16. Phase II Pediatric Study with Dabrafenib in Combination with Trametinib in Patients with HGG and LGG. Available online: <https://clinicaltrials.gov/ct2/show/NCT02684058> (accessed on 6 June 2022).
17. Kaley, T.; Touat, M.; Subbiah, V.; Hollebecque, A.; Rodon, J.; Lockhart, A.C.; Keedy, V.; Bielle, F.; Hofheinz, R.D.; Joly, F.; et al. BRAF Inhibition in BRAFV600-Mutant Gliomas: Results From the VE-BASKET Study. *J. Clin. Oncol.* 2018, 36, 3477–3484.
18. Ellison, D.W.; Hawkins, C.; Jones, D.T.W.; Onar-Thomas, A.; Pfister, S.M.; Reifenberger, G.; Louis, D.N. cIMPACT-NOW update 4: Diffuse gliomas characterized by MYB, MYBL1, or FGFR1 alterations or BRAF. *Acta Neuropathol.* 2019, 137, 683–687.
19. Suri, V.; Jha, P.; Agarwal, S.; Pathak, P.; Sharma, M.C.; Sharma, V.; Shukla, S.; Somasundaram, K.; Mahapatra, A.K.; Kale, S.S.; et al. Molecular profile of oligodendrogliomas in young patients. *Neuro-Oncology* 2011, 13, 1099–1106.
20. Evaluation of Hippocampal-Avoidance Using Proton Therapy in Low-Grade Glioma. Available online: <https://clinicaltrials.gov/ct2/show/NCT04065776> (accessed on 6 June 2022).
21. SJ901: Evaluation of Mirdametinib in Children, Adolescents, and Young Adults with Low-Grade Glioma. Available online: <https://clinicaltrials.gov/ct2/show/NCT04923126> (accessed on 6 June 2022).
22. Haumann, R.; Videira, J.C.; Kaspers, G.J.L.; van Vuurden, D.G.; Hulleman, E. Overview of Current Drug Delivery Methods Across the Blood–Brain Barrier for the Treatment of Primary Brain Tumors. *CNS Drugs* 2020, 34, 1121–1131.
23. Jones, C.; Perryman, L.; Hargrave, D. Paediatric and adult malignant glioma: Close relatives or distant cousins? *Nat. Rev. Clin. Oncol.* 2012, 9, 400–413.
24. Mackay, A.; Burford, A.; Molinari, V.; Jones, D.T.W.; Izquierdo, E.; Brouwer-Visser, J.; Giangaspero, F.; Haberler, C.; Pietsch, T.; Jacques, T.S.; et al. Molecular, Pathological, Radiological, and Immune Profiling of Non-brainstem Pediatric High-Grade Glioma from the HERBY Phase II Randomized Trial. *Cancer Cell* 2018, 33, 829–842.e5.
25. Komori, T. The 2021 WHO classification of tumors, 5th edition, central nervous system tumors: The 10 basic principles. *Brain Tumor Pathol.* 2022, 39, 47–50.
26. George, E.; Settler, A.; Connors, S.; Greenfield, J.P. Pediatric Gliomatosis Cerebri: A Review of 15 Years. *J. Child. Neurol.* 2016, 31, 378–387.
27. Herrlinger, U.; Jones, D.T.W.; Glas, M.; Hattungen, E.; Gramatzki, D.; Stuplich, M.; Felsberg, J.; Bähr, O.; Gielen, G.H.; Simon, M.; et al. Gliomatosis cerebri: No evidence for a separate brain tumor entity. *Acta Neuropathol.* 2016, 131, 309–319.
28. Kline, C.; Felton, E.; Allen, I.E.; Tahir, P.; Mueller, S. Survival outcomes in pediatric recurrent high-grade glioma: Results of a 20-year systematic review and meta-analysis. *J. Neurooncol.* 2018, 137, 103–110.
29. Behling, F.; Barrantes-Freer, A.; Skardelly, M.; Nieser, M.; Christians, A.; Stockhammer, F.; Rohde, V.; Tatagiba, M.; Hartmann, C.; Stadelmann, C.; et al. Frequency of BRAF V600E mutations in 969 central nervous system neoplasms. *Diagn. Pathol.* 2016, 11, 55.
30. Sturm, D.; Pfister, S.M.; Jones, D.T.W. Pediatric Gliomas: Current Concepts on Diagnosis, Biology, and Clinical Management. *J. Clin. Oncol.* 2017, 35, 2370–2377.
31. Khalid, S.I.; Kelly, R.; Adogwa, O.; Carlton, A.; Tam, E.; Naqvi, S.; Kushkuley, J.; Ahmad, S.; Woodward, J.; Khanna, R.; et al. Pediatric Brainstem Gliomas: A Retrospective Study of 180 Patients from the SEER Database. *Pediatr. Neurosurg.* 2019, 54, 151–164.

32. Dabrafenib Combined with Trametinib after Radiation Therapy in Treating Patients with Newly-Diagnosed High-Grade Glioma. Available online: <https://clinicaltrials.gov/ct2/show/NCT03919071> (accessed on 6 June 2022).
33. Vemurafenib in Treating Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With BRAF V600 Mutations (A Pediatric MATCH Treatment Trial). Available online: <https://clinicaltrials.gov/ct2/show/NCT03220035> (accessed on 6 June 2022).
34. Safety and Pharmacokinetics of Cobimetinib in Pediatric and Young Adult Participants with Previously Treated Solid Tumors (iMATRIXcobi). Available online: <https://clinicaltrials.gov/ct2/show/NCT02639546> (accessed on 6 June 2022).
35. Dahiya, S.; Haydon, D.H.; Alvarado, D.; Gurnett, C.A.; Gutmann, D.H.; Leonard, J.R. BRAF(V600E) mutation is a negative prognosticator in pediatric ganglioglioma. *Acta Neuropathol.* 2013, 125, 901–910.
36. Rodriguez-Viciana, P.; Warne, P.H.; Dhand, R.; Vanhaesebroeck, B.; Gout, I.; Fry, M.J.; Waterfield, M.D.; Downward, J. Phosphatidylinositol-3-OH kinase as a direct target of Ras. *Nature* 1994, 370, 527–532.
37. Tiwari, S.; Yadav, T.; Pamnani, J.; Mathew, J.M.; Elhence, P.; Praneeth, K.; Vedant, D.; Khera, P.S.; Garg, P.; Vyas, V. Diffuse Leptomeningeal Glioneuronal Tumor: A Unique Leptomeningeal Tumor Entity. *World Neurosurg.* 2020, 135, 297–300.
38. Huse, J.T.; Snuderl, M.; Jones, D.T.; Brathwaite, C.D.; Altman, N.; Lavi, E.; Saffery, R.; Sexton-Oates, A.; Blumcke, I.; Capper, D.; et al. Polymorphous low-grade neuroepithelial tumor of the young (PLNTY): An epileptogenic neoplasm with oligodendroglioma-like components, aberrant CD34 expression, and genetic alterations involving the MAP kinase pathway. *Acta Neuropathol.* 2017, 133, 417–429.
39. Deng, M.Y.; Sill, M.; Chiang, J.; Schittenhelm, J.; Ebinger, M.; Schuhmann, M.U.; Monoranu, C.M.; Milde, T.; Wittmann, A.; Hartmann, C.; et al. Molecularly defined diffuse leptomeningeal glioneuronal tumor (DLGNT) comprises two subgroups with distinct clinical and genetic features. *Acta Neuropathol.* 2018, 136, 239–253.

Retrieved from <https://encyclopedia.pub/entry/history/show/65774>