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Pediatric Brain Tumors: Current Knowledge and Therapeutic Opportunities

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Introduction

Great progress has been made in many areas of pediatric oncology. However, tumors of the central nervous system (CNS) remain a significant challenge. A recent explosion of data has led to an opportunity to understand better the molecular basis of these diseases and is already providing a foundation for the pursuit of rationally chosen therapeutics targeting relevant molecular pathways. The molecular biology of pediatric brain tumors is shifting from a singular focus on basic scientific discovery to a platform upon which insights are being translated into therapies.

High Grade Glioma

Histopathology and Genetics

Pediatric high grade gliomas (pHGGs) are histologically indistinguishable from HGGs occurring in adults (aHGGs) and are graded according to the WHO classification of CNS tumors. High grade gliomas include WHO grade III and IV tumors[1]. Histologically, grade III glioma (anaplastic astrocytoma) is characterized by atypical nuclei, increased cellularity, and increased mitotic activity[1]. Grade IV glioma, also known as glioblastoma multiforme (GBM), is the most pathologically advanced and clinically aggressive[2]. These tumors are characterized by vascular proliferation and necrosis in addition to the characteristics of grade III glioma[1]. The distribution of sites within the CNS in which these high grade tumors occur

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varies amongst age groups: aHGGs typically occur in the cerebral cortex, while pHGGs are more widely distributed[3]. The highest grade of oligodendroglioma, referred to as anaplastic oligodendroglioma (WHO grade III), and mixed oligo-astrocytomas are observed, albeit rarely, in pHGG patients[4].

Molecularly, pHGGs are distinct from aHGG and are characterized by gene amplifications, deletions, and other types of mutations[5–18]. These are summarized in Figure 1. The most commonly amplified genes in pHGGs are receptor tyrosine kinases including *PDGFRA*, *EGFR*, *KIT*, *IGF1R*, and *MET*[12,14,16,17] (Figure 1A). The most commonly deleted genes include *CDKN2A*, *TP53*, and *ADAM3A*[6,8,9,12] (Figure 1A). Other mutations, both activating and inactivating, have been reported (Figure 1B), and amongst the inactivating mutations, homozygous inactivation of p53 and histone 3.3 (*H3F3A*) are the most common. While the genetic differences amongst gliomas occurring at different locations in the CNS have not been completely characterized, data available to date suggest that a K27M mutation in histone3.3 occurs at a much lower rate in non-brainstem HGG (NBS-HGG) than in DIPG[3,18]. Also, a G34R mutation in histone 3.3 is thought to be present exclusively in NBS-HGG[18]. The histone 3.3 K27M mutation acts as a dominant negative inhibitor of histone methylation,[11] and patients whose HGG bear that mutation have distinctive DNA methylation patterns that alone are sufficient to define a subgroup of pHGG[13]. Gene rearrangements are also observed in glioma leading to fusion products that may serve as tumor specific drug targets. In pHGG, both the neurotrophic tyrosine kinase receptors (NTRKs)[15] and *PDGFRA*[19] have fusion variants that drive the transformation of normal CNS cells[19]. Differences in the genomic alterations between pediatric and adult high-grade gliomas have been identified. *PDGFRA* is amplified much more frequently in pHGG than in aHGG[17] and *EGFR* is more commonly amplified than *PDGFRA*[17] in aHGG. Additionally, histone 3.3 mutations are observed almost exclusively in pHGGs[7].

Current Therapy and Therapeutic Opportunities

Current treatment for pHGG occurring in the cerebrum typically includes initial surgery followed by radiation and chemotherapy[20]. There is widespread agreement that total resection of tumor tissue improves patient outcome. For patients treated on the Children's Cancer Group study CCG945, patients with >90% resection had improved 5-year progression-free survival (35+/− 7% compared to 17+/− 4%)[21]. Focal radiation therapy has also become standard in the treatment of patients greater than 3 years of age with pHGG. However, the toxicities of radiation therapy in children can be particularly significant because of the increased sensitivity of the developing brain to irradiation[22,23]. Long-term side effects in survivors include cognitive deficits, cerebrovascular disease, and secondary tumors and can oftentimes reduce patients' quality of life[24]. The role of chemotherapy in managing patients with pHGG is uncertain, and although evidence of efficacy is modest[25,26], chemotherapeutic agents are often employed in the treatment of these patients[27]. While the results of a Children's Oncology Group trial evaluating temozolomide for the treatment of pediatric patients with high grade glioma were disappointing[28], the drug continues to be utilized in the treatment of these patients. Tolerability and ease of administration may be important factors in the choice of chemotherapy for pediatric patients. Regimens containing nitrosoureas are also employed[20,27]. Given the lack of effective

therapies for pHGG, patients should be treated on a clinical trial if possible. When gliomas recur, the treatment approach depends on the therapy patients have received previously as the potential for repeated surgery or additional radiation is often limited by previous treatment.

Currently, novel agents targeting key pathologic pathways or the products of mutated genes are under investigation for the treatment of pHGG. Imatinib, an inhibitor of PDGFR activation and a prototypic targeted therapy, has been examined in a phase 1 clinical trial conducted in pHGG patients and a tolerable dose was determined[29]. However, no phase II results are available and a suspected link between Imatinib and increased hemorrhage in these patients has raised concerns of unacceptable toxicity[29]. Other inhibitors of PDGFR are also being evaluated in clinical trials (see Table 1).

Invasion of normal tissue is a hallmark of HGG that typically makes complete tumor resection impossible and fuels recurrence after surgery[30]. Inhibiting pathways that regulate invasion may be advantageous to patients with HGG[31]. Cilengitide, an inhibitor of αvβ3 and αvβ5 integrins, has activity decreasing *in vitro* surrogates of tissue invasion and has been actively studied in multiple cancers[32]. In an early phase trial of cilengitide as a single agent in patients with relapsed pHGG, no effect on patient outcomes was noted[33,34]. Further studies of cilengitide combined with other agents in adults with GBM provided no evidence of anti-invasive activity and did not affect survival[35,36].

A potential reason why targeted therapies have, to date, had limited success in the treatment of patients with pHGG is intra-tumoral variation in target gene expression.The widespread genetic heterogeneity of HGG suggests that cytotoxic agents with increased activity or combination therapy with agents targeting different genetic alterations within the same tumor could be especially advantageous[37]. Targeting mechanisms of tumor invasion to inhibit tumor spreading, while simultaneously targeting genetic drivers (such as *PDGFRA* or *NRTK*), might further enhance patient survival. Additional therapeutic strategies being explored in patients with pHGG include dendritic cell-based vaccination and angiogenesis inhibition; however, to date, their use has not provided a survival advantage[38–41].

The presence of H3.3 mutations and aberrant methylation patterns in pHGG suggests that epigenetic modifiers may be effective therapies for these tumors. Panobinistat, a histone deacetylase inhibitor, has shown preclinical activity against pHGG and clinical trials with this agent are planned[42]. The combination of a histone demethylase inhibitor with panobinostat was synergistic *in vitro* and in xenograft models of DIPG[43] and suggests that this drug combination could have activity in pHGG with H3.3 mutations.

Medulloblastoma

Histopathology and Genetics

Medulloblastoma accounts for 15–20% of pediatric brain tumors [44]. While it can occur at any age from infancy through adulthood, it is most typically seen in children with bimodal incidence peaks between three and four and eight and nine years of age [45]. It arises in the

cerebellum and commonly invades the fourth ventricle with about one third of cases developing metastases throughout the neuraxis.

Medulloblastoma is a primitive embryonal tumor composed of densely packed, small, round, blue cells with irregular nuclei and appears undifferentiated or less commonly, with neuronal features[2]. Neuronal markers such as synaptophysin are often focally expressed [46]. The 2007 WHO classification of tumors of the CNS describes five histologic variants of medulloblastoma including classic histology, anaplastic, large cell variant, desmoplastic/nodular, and medulloblastoma with extensivenodularity[2]. While these histologic variants have prognostic relevance, molecular analysis has allowed for the more precise classification of these tumors. There are four well-recognized molecular subgroups of medulloblastoma: WNT (wingless), SHH (Sonic Hedgehog), Group 3, and Group 4[47]. Subtype specific genetic alterations in medulloblastoma that include mutations and amplifications are summarized in Figure 2 [48,49]. As suggested by the nomenclature, the molecular drivers of oncogenesis in the first two groups are better understood. WNT is a family of receptors involved in embryogenesis and cell cycle control[50]. This subgroup comprises approximately 10% of tumors and has the best prognosis with overall survival near 90%. It occurs predominantly in older children[47,51]. The most common mutations in the WNT subgroup occur in *CTNNB1* encoding β-catenin, and this subtype of medulloblastoma can be identified by nuclear accumulation of β-catenin[52]. WNT medulloblastoma is also associated with losses of chromosome 6[53].

The SHH group accounts for approximately 30% of medulloblastoma[48]. SHH signaling is physiologically initiated by the SHH ligand binding to the receptor Patched1 (PTCH1) which leads to the de-repression of smoothened (SMO) activity and activation of GLI transcription factors[49]. Mutations in this pathway most commonly occur in *PTCH1*, but alterations in SMO and suppressor of fused (SUFU) have also been described in SHH medulloblastoma[54]. Deletions of 9q are most commonly found in this group.

The molecular pathogenesis of Group 3 (25% of cases) and Group 4 (35% of cases) is not as well understood[47,48]. Group 3 tumors have a poor prognosis with approximately 50% overall survival at five years. Group 3 disease is characterized by an increased frequency of copy number alterations, including loss of chromosome 17p and gain of 17q to generate an isochromosome 17q. High levels of MYC expression are also seen in Group 3 tumors and a subset of these has amplification of *MYCN*. Group 3 tumors have the worst prognosis of the four molecular subgroups and patients frequently have metastatic disease at diagnosis. While targeted therapies for Group 3 medulloblastoma have not been identified, high throughput screening has identified the combination of gemcitabine and pemetrexed as a possible therapy for this subtype[55]. Group 4 also has a high degree of chromosomal copy number aberrations as well as isochrome17q. It is characterized by a neuronal molecular signature and amplification of *MYCN*, *MLL2*, and *MLL3* and *KDM6A*, a histone demethylase.

The parsing of medulloblastoma into four distinct molecular groups has greatly advanced the field and additional subdivisions within each group are being uncovered. Recent work by Northcott and colleagues evaluated somatic copy number aberrations in 1087 unique medulloblastomas[56]. They identified the presence of tandem duplication of the Parkinson's

gene *SNCAIP* in a subgroup of Group 4 medulloblastomas. They also identified recurrent translocations of *PVT1* restricted to Group 3 tumors [56]. In a recent multicenter study prognostically relevant cytogenetic features were identified that may continue to further stratify medulloblastoma within the current four molecular groups [57].

Current Therapy and Therapeutic Opportunities

The current management of medulloblastoma in children greater than three to five years of age includes maximal safe resection of the tumor followed by a combination of radiation and chemotherapy [58–60]. Disease is classified as "average risk" in patients with a total or near-total resection and no evidence of tumor dissemination at the time of diagnosis. These patients are treated with adjuvant craniospinal radiation and a boost to the tumor bed followed bychemotherapy. This therapeutic strategy leads to five-year event free survival in more than 80% of these patients [61]. However, the toxicity of surgical resection of a posterior fossa lesion, neuraxis radiation and chemotherapy are considerable. Long-term sequelae include cerebellar mutism, hearing loss, endocrine abnormalities, and neurocognitive deficits [62].Recent clinical trials have begun to explore decreasing the dose of craniospinal radiation in an effort to decrease the late effects. Patients with disseminated disease at diagnosis or sub-totally resected tumors are considered to have "high-risk" disease[63,64]. Infants and young children with medulloblastoma present a particular therapeutic challenge. Because of the high risk of neurologic sequelae, radiation therapy has been either avoided or delayed in these patients and they have received upfront chemotherapy alone[58,65].

The molecular characterization of medulloblastoma provides opportunities to improve patient care both through improving the stratification of disease and the identification of therapeutic targets. WNT tumors have an excellent prognosis using current therapies with ten-year event free survival rates above 95% [66–68]. This information suggests a strategy of de-intensifying therapy for patients with this group of medulloblastoma in an attempt to decrease late effects[69,70]. While *MYCN* amplification or the fusion gene *PVT1-MYC* is known to occur in Group 3 tumors, these abnormalities have been difficult to target therapeutically. Early clinical trials targeting the SHH pathway have shown some efficacy in the treatment of medulloblastoma with alterations in the SHH pathway. In a phase 1 study of vismodegib, which represses the SHH pathway by inhibition of SMO, in children with recurrent medulloblastoma activity was seen in one out of 3 evaluable patients with SHH medulloblastoma and 0 of 10 patients with other medulloblastoma subtypes [71]. Preclinical data using both xenograft and transgenic murine models have shown that tumors with abnormalities downstream of SMO such as SUFU or GLI2 are resistant to SMO inhibition [72,73], suggesting that further stratification of patients will be necessary in order to optimize the use of pharmacological inhibition at various points in the SHH pathway.

Ependymoma

Histopathology and Genetics

Ependymomas occur in both children and adults and can arise throughout the entire neuraxis. While spinal cord tumors are more common in adults, in pediatric patients approximately 70% of ependymomas arise in the posterior fossa[2,74]. The WHO divides

ependymomas into three subtypes. WHO Grade I ependymomas include myxopapillary ependymomas, which typically occur in the spine, and subependymomas that can occur in any location of the neuraxis. WHO grade II lesions are characterized by perivascular pseudorosettes on light microscopy with grade III ependymoma showing features of anaplasia including cellular pleomorphism and frequent mitoses[75]. Grade II ependymoma have been divided into four subtypes that include cellular, clear cell, papillary, and tanycytic. These neoplasms are characterized by considerable histopathological variation between tumors as well as within tumors, and this feature has led to difficulty discriminating between WHO grade II and WHO grade III tumors[74,76]. Based on the inherent difficulties in histopathological classification of ependymoma, molecular classification of these diseases has been proposed[77].

Molecular analysis has been used by multiple groups to subclassify ependymomas. Complex chromosomal rearrangements and copy number abnormalities due to chromothripsis are seen in supratentorial ependymomas. These alterations as well as mRNA and microRNA profiles were used to separate ependymomas into nine subgroups that correlate with tumor location[78]. The functional consequences of genomic abnormalities identified in this work have been investigated. Activation of ephrin-type B receptor 2 (*EPHB2*) in a subpopulation of neuronal stem cells with Cyclin-dependent kinase inhibitor 2A loss led to the development of supratentorial ependymoma in a murine model[78]. A majority of supratentorial ependymomas also contain fusion of the v-rel avian reticuloendothelialiosis viral oncogene homologue A (*RELA*) with the uncharacterized gene *C11orf95*[79]. The C11orf95-RELA fusion protein drives aberrant NF-kB transcription, and expression of this fusion protein leads to the formation of tumors with characteristics of ependymoma in preclinical models[79]. An additional 84 candidate oncogenes and 39 candidate tumor suppressor genes identified in these studies have recently been explored. Their ability to transform mouse embryonic *Cdkn2a–Cdkn2b*$^{-/-}$ cerebral neural stem cells was tested in an *in vivo* system[80]. This approach identified ten oncogenes and eight tumor suppressor genes that could induce ependymoma formation. These genes are involved in a number of cellular processes including vesicle trafficking and DNA modification and repair[80].

There are significant genomic differences between posterior fossa ependymoma and supratentorial ependymoma. Posterior fossa tumors have been divided into posterior fossa A and posterior fossa B subtypes[81]. Posterior fossa A tumors do not exhibit the dramatic DNA rearrangements seen in supratentorial tumors, but are instead characterized by lack of DNA copy number abnormalities and absence of recurrent DNA mutations[82]. These tumors have increased DNA methylation of CpG islands that leads to transcriptional silencing of targets of polycomb repressive complex 2 (PRC2)[82]. Treatment of posterior fossa A ependymoma cells in primary culture with drugs targeting PRC2 or with DNA demethylating agents impairs cell proliferation[82]. Unlike posterior fossa A tumors, the posterior fossa group B tumors have numerous large scale chromosomal abnormalities[81].

Current Therapy and Therapeutic Opportunities

For subependymoma complete surgical resection of the tumor can be curative and in patients with subtotal resection observation can be considered[83]. Upfront therapy for myxopapillary

ependymoma includes an attempt at complete *en bloc* resection[84,85]. While historically, radiation therapy was not done for completely resected myxopapillary ependymoma, some evidence suggests that post-operative radiation therapy may improve disease free survival for these patients[84,86–88]. For WHO grade II and WHO grade III ependymoma an initial attempt at maximal safe surgical resection should be made. The extent of resection is correlated with survival in these patients[89,90] and survival rates are improved in cases where a gross total resection can be achieved[91]. Local post-operative radiation therapy is also employed in these cases. A review of children under 3 years of age treated for ependymoma showed that there was significantly better three year overall survival in patients who received post-operative radiation therapy (81%) compared to those that did not (58%)[92]. The preliminary results of a phase II trial of conformal radiation therapy reported an estimated 3-year progression free survival of approximately 75%[93]. If resection is incomplete a second look surgery can be considered[94]. The role of chemotherapy in the treatment of patients with ependymoma remains to be defined. Two completed studies did not find a survival advantage to the addition of chemotherapy to the treatment of ependymoma[95]. However, in the Children's Cancer Group study CCG9942 patients with a sub-total resection of the primary tumor who received pre-irradiation chemotherapy had similar 5-year EFS to children who underwent gross total resection of the tumor[96]. Studies are currently underway to better define the role of chemotherapy in these patients. Children's Oncology Group (COG) trial ACNS0121 evaluated the role of chemotherapy and second look surgery in pediatric patients with ependymoma. The trial is closed to enrollment, but results are not yet published. A trial examining the impact of chemotherapy in pediatric patients with ependymoma is also ongoing (ACNS0831).

Recurrent ependymoma continues to have a dismal prognosis[97]. Palliative local therapy including both surgery and radiation therapy modalities can be considered and may provide some benefit to these patients[98–100]. This strategy is being explored in a current trial (NCT02125786). Expression of *ERBB2* and *ERBB4* is seen in approximately 75% of pediatric ependymoma [101]. Based on these data, lapatinib, a small molecule inhibitor of *ERBB1*, *ERBB2*, and *ERBB4* was used in combination with bevacizumab for the treatment of pediatric patients with recurrent ependymoma, but proved ineffective in this patient population[102]. Other therapeutic options including everolimus and vaccine-based strategies are being evaluated for patients with recurrent disease (Table 1).

Diffuse Intrinsic Pontine Glioma

Histopathology and Genetics

Diffuse intrinsic pontine glioma (DIPG) is a leading cause of mortality in children with brain tumors. Even with administration of focal radiation therapy, median overall survival remains only 10–12 months[103 73 104,105]. The diagnosis of DIPG is currently based on characteristic radiographic findings[106]. This has led to a paucity of untreated tumor tissue, limiting efforts to determine the genomic and molecular alterations that are characteristic of DIPG. Despite this challenge, our understanding of DIPG has improved in part as a result of autopsy material becoming available [107 13] and in part because of new biopsy protocols [108,109]. Diffuse intrinsic pontine glioma (DIPG) usually present with a histopathology similar to

GBM[3] but may have characteristics of lower grade tumors. Myriad clinical trials have failed to improve survival beyond that seen in patients receiving focal radiation. These trials have evaluated the intensification of chemotherapy, variations in radiotherapy, and multiple adjuvant chemotherapeutic combinations. [110 111 112]

As the landscape of DIPG biology evolves, identification of molecular phenotypes may impact prognostication as well as provide the potential for therapeutic targeting[113]. Approximately three-quarters of pediatric DIPG samples contain histone mutations, primarily histone 3.1 or 3.3 [18] (Figure 1) with some groups showing a worse prognosis for patients with these mutations[113]. Multiple investigators have emphasized the role of these frequent H3 gene mutations in the tumorigenesis of DIPG, highlighting the importance of epigenetic alterations[15,114]. Other frequently reported abnormalities in DIPG include mutations in *TP53*, *MET*, *KRAS* [106,115], *CDK4* and *ATRX* (Figure 1), as well as increased expression of *PDGFRA*, *MYC*, *EGFRv3*, *PARP*, *SHH*, *ERBB1*, and *ACVR* [110–112]. Genomic and expression profiles led one analysis to segregate DIPGs into two subgroups: a more aggressive PDGFRA-driven subtype and a mesenchymal subtype with increased *STAT3* expression[116]. Based on these data, xenograft and transgenic mouse models have been generated [107,113], the latter caused by overexpression of PDGF-B with Ink4a-ARF loss, which should facilitate preclinical testing of therapeutic agents for DIPG[117].

The absence of a single driver pathway in DIPG emphasizes the need to identify specific tumor subsets susceptible to a particular targeted approach. Further, the utility of upfront biopsies to define these tumors is under debate, as is the adequacy of small biopsies in the context of considerable intratumoral heterogeneity[18,118].

Current Therapy and Therapeutic Opportunities

The current standard of care for patients with DIPG is fractionated external beam radiation therapy to a dose of 60Gy[119,120]. Although radiation intensification has been attempted without success in DIPG, some groups continue to attempt optimization of this sole effective treatment modality in DIPG. The checkpoint kinase WEE1 is expressed in DIPG and its inhibition enhances radiation sensitivity in preclinical models[121]. Studies include using hypofractionated irradiation and radiosensitization with a Wee1 inhibitor are ongoing (Table 1).

Additional efforts are underway to improve drug delivery to these tumors by overcoming the blood-brain barrier and increased intratumoral pressure. Strategies include intra-arterial infusion of chemotherapy, including melphalan, and convection-enhanced delivery (CED). CED is a process requiring neurosurgical placement of catheters through which therapeutic agents are continuously delivered under positive pressure directly into the tumor. CED-based delivery of drugs has been investigated for the treatment of DIPG. The delivery of ^{124}I-8H9 (an antibody attached to a radioisotope) to the brain using CED has been studied in preclinical models[122] and a clinical trial using this approach is currently underway (NCT01502917). IL13-PE38QQR (a fusion molecule of Pseudomonas exotoxin with human IL-13) has also been used in a phase 1 trial targeting DIPG (NCT00880061). Modification of the chemotherapeutic backbone of existing drug classes such as taxanes to improve CNS penetration is also being used as a strategy to increase drug delivery to DIPG[123,124]. This is

exemplified by a study using a novel taxane, cabazitaxel, which has improved CNS penetrance for the treatment of DIPG and HGG (NCT01751308).

Several trials use molecular markers identified using pre-treatment biopsies to determine therapy. In one current study all patients receive an initial diagnostic biopsy followed by standard focal irradiation, which is combined with an EGFR inhibitor (erlotinib, if EGFR activation is noted), and/or temozolomide (if O6-methylguanine-DNA methyltransferase (MGMT) displays a methylated promoter). All patients also receive bevacizumab, an anti-VEGF agent (NCT01182350). Another biopsy-dependent treatment protocol will use varying combinations of erlotinib, dasatinib, and everolimus depending on the overexpression of *EGFR* and loss of *PTEN* in newly diagnosed DIPG (NCT02233049).

Other studies seek to leverage the recognition and tumor-control capacity of the immune system against DIPG. One such study utilizes Pidilizumab, an anti-PD-1 monoclonal antibody to block tumor-driven immunosuppression, while another uses lenalidomide, a derivative of thalidomide with antiangiogenic and immunomodulatory properties in combination with radiotherapy (NCT01952769).

Pediatric Low-Grade Glioma

Pediatric low-grade glioma (PLGG) is the most common type of pediatric astrocytoma and pediatric brain tumor in general [125,126]. According to the World Health Organization (WHO), PLGG are Grade I or II and include pilocytic astrocytoma (PA), subependymal giant cell astrocytoma (SEGA), pilomyxoid astrocytoma (PMA), pleomorphic xanthoastrocytoma (PXA) and low-grade fibrillary astrocytoma or diffuse astrocytoma [125–128]. Of these, the PA is the most common type of glioma in children [125,128].

Histopathology and Genetics

PA is composed of a biphasic pattern of tightly packed bipolar cells intermingled with hypocellular, microcystic areas of loosely packed astrocytes[126]. The tumor cells may also contain long, thin, hair-like cytoplasmic extensions [126]. Rosenthal fibers, eosinophilic granular bodies (EGBs) with occasionally appearing oligodendroglial-resembling cells [129] and rare mitotic bodies are present in PA [126]. In contrast to PA, the PMA lack Rosenthal fibers and EGBs[130], but contain a characteristic myxoid/extracellular mucoid matrix with highly compacted monomorphic cells usually located around blood vessels [126,127,130]. The PXA contains characteristic lipid laden xanthomatous astrocytes [127] and shows pleomorphic cells [126] and spindle shaped cells with EGBs [126]. Copious amounts of extracellular reticulin with occasional lymphocytes are also seen in PXA [126]. The diffuse astrocytomas are characterized by a lack of abundant mitotic figures or vascular proliferation but are diffusely infiltrative into the normal brain parenchyma [126,127].

PLGG is characterized by numerous gene mutation and copy number alterations summarized in Figure 3[131–135]. The most common alterations in PLGG result in constitutive activation of the RAS/MAP signaling pathway [131–133]. In patients with neurofibromatosis, inactivation of the RAS-GTPase activating protein neurofibromin leads to constitutive activation of RAS [134,135] most commonly resulting in tumors of the optic pathway [136]. In

non-NF1 associated PLGG, the most common somatic alteration is the fusion of a truncated BRAF protein with an uncharacterized protein KIAA1549 [131–133,136,137]. This fusion is caused when the kinase domain of BRAF fuses with the truncated KIAA1549, resulting in loss of BRAF regulation and activation of the MAP kinase pathway [131–133,136,137]. A small number of PLGG harbor other fusion proteins involving BRAF [138]. Approximately 11 percent of PLGG have an activating mutation, BRAFV600E [139], which is also found in melanoma, colon, and thyroid cancer [140–142]. This substitution of valine for glutamic acid leads to constitutive activation of the BRAF[143]. In addition to neurofibromin and BRAF alterations, the MAP kinase and PI3K/mTOR pathways are activated in a subset of PLGG through intragenic duplication of the tyrosine kinase domain (TKD) of the fibroblast growth factor receptor 1 (FGFR1), resulting in auto-phosphorylation of FGFR1 [138]. Genomic alterations outside of the RAS/MAP pathway have been identified in a subclass of PLGG, diffusely infiltrating PLGG. These tumors have activating rearrangements of the *MYB or MYBL1* genes, resulting in high levels of the MYB transcription factor [138,144].

Current Therapies and Therapeutic Opportunities

Current therapies for low grade gliomas include carboplatin or TPCV (thioguanine, procarbazine, CCNU, vincristine) [145,146]. Carboplatin can either be given alone on a monthly schedule [145] or weekly along with vincristine [147,148] as per the Children's Oncology Group A9952 study [149]. This large, multicenter trial found that patients treated with TPCV had no statistically significant difference in disease free survival compared to patients treated with carboplatin/vincristine [149]. There was no increase in incidence of treatment related second malignancies in patients treated with TPCV. Other chemotherapeutic agents including single agent vinblastine or temozolomide as well as combinations of vinblastine plus carboplatin or actinomycin-D plus vincristine have activity against low-grade gliomas and are reasonable options for these patients[150]. Differences in the route of administration and logistics may lead to one regimen or another being chosen due to issues of patient adherence and convenience [149].

The common mutations in *BRAF* and the near-universal activation of the mitogen-activated protein (MAP) kinase pathway in PLGG have prompted clinical trials for recurrent/refractory PLGG evaluating the BRAF inhibitor dabrafenib as well as MAP kinase inhibitors selumetinib (AZD6244) and trametinib. Activation of mammalian target of rapamycin (mTOR) is also widely found in PLGG [126,151,152], and a trial of the mTOR inhibitor everolimus has completed enrollment and due to promising early responses, a follow-up clinical trial is ongoing.

Subependymal Giant Cell Astrocytoma

Subependymal giant cell astrocytoma (SEGA) is a WHO Grade I PLGG [127] and one of the spectrum of tumors associated almost exclusively with the genetic disorder tuberous sclerosis [126,153,154].

Histopathology and Genetics

SEGA grow under the ependymal surface and show gemistocytic-, spindled- and ganglion-like cells with rare mitotic figures or necrosis [126]. They are usually not infiltrative but can have tumor cells with pleomorphic nuclei [126]. Occasionally, the tumor cells can exhibit neuronal and glial differentiation, hence sometimes giving these tumors a designation of mixed glial-neuronal neoplasms [155–157].

The majority of patients who develop SEGA harbor inactivating mutations in either *TSC1* (encoding the Hamartin protein) or *TSC2* gene (encoding Tuberin protein) [158]. These two proteins heterodimerize and are key negative regulators of mTOR and cell growth [158]. Inactivation of either of the two genes in SEGA leads to increased mTOR activity, enabling cell growth and proliferation [159].

Current Treatments and Translational Opportunities

The standard therapy for SEGA has been complete surgical excision, which is recommended for tumors exhibiting growth or causing symptoms such as signs of intracranial hypertension[160]. Alterations in upstream regulators of mTOR lead to universal activation of this pathway in SEGA [126,159]. Treatment with the mTOR inhibitor everolimus (a rapamycin analogue) is effective at reducing the growth of these tumors and decreasing the frequency of seizures [161]. The use of mTOR inhibitors has been advocated in patients with tumors that are not amenable to surgical resection, where complete resection of the tumor is unlikely, or in tumors with more rapid regrowth following surgery[160,162]. The advent of newer, more potent mTOR inhibitors may lead to further improvements in care for patients with SEGA.

Conclusion

An evolving understanding of the molecular underpinnings of tumorigenesis in the pediatric CNS is changing the practice of pediatric neuro-oncology. Novel strategies targeting specific genetic and epigenetic abnormalities found in subgroups of tumors are being added to more established treatment regimens using cytotoxic drugs. Continued cooperation in the pediatric oncology community will be required to develop these new treatment strategies and identify groups of patients that will benefit from them.

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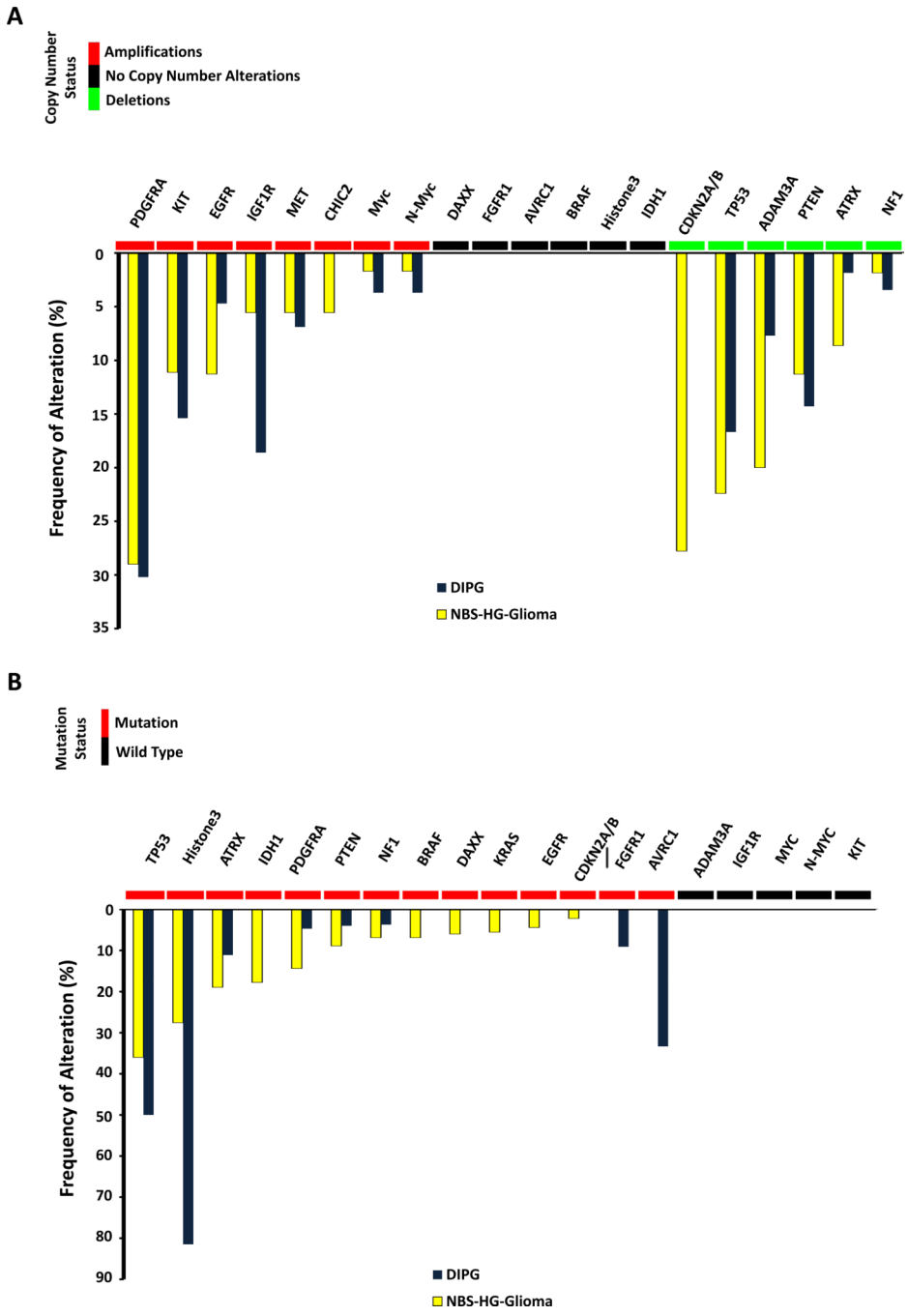

Figure 1.

Genetic alterations observed in pHGG. (A) Copy number alterations and (B) mutations of the major genes with genetic alterations observed in non-brainstem high grade glioma (NBS-HGG) and DIPG[5–18].

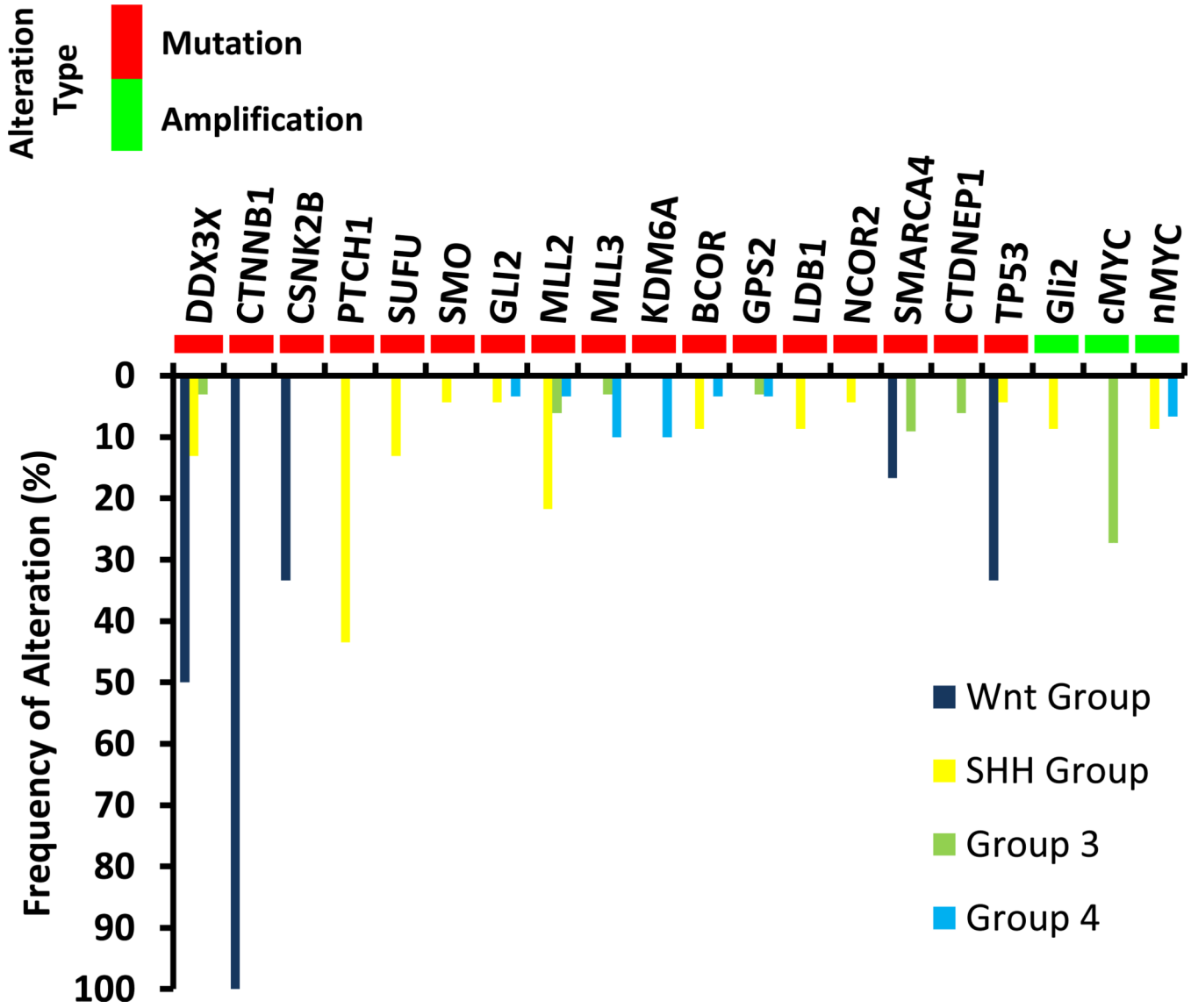

Figure 2.
Genetic alterations across medulloblastoma subtypes[56,163].

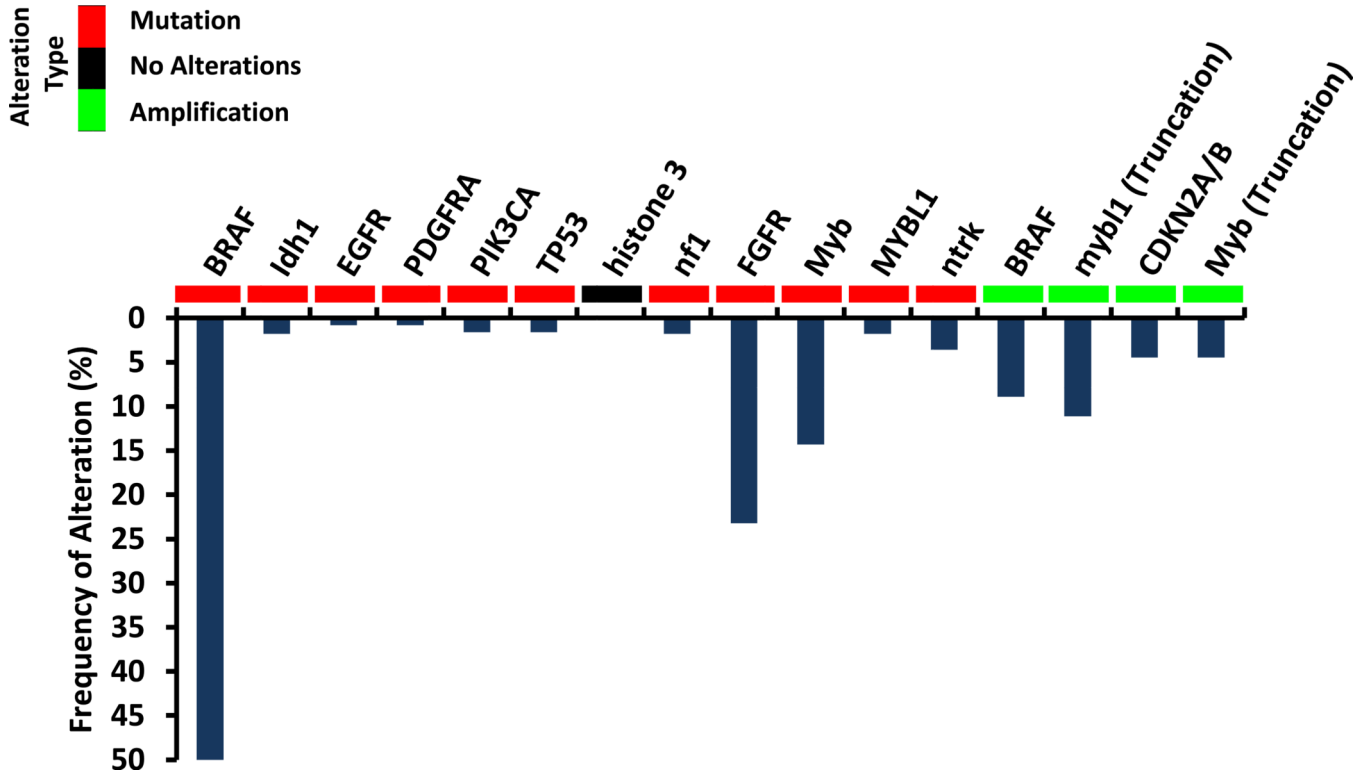

Figure 3.
Genetic alterations observed in pLGG[138,139,144]

TABLE 1

Treatment trials targeting molecular abnormalities in pediatric brain tumors

Clinical Trial Number	Tumor Type	Title	Agent	Target	Sponsor
NCT01902771	HGG	Dendritic Cell Vaccine Therapy With In Situ Maturation in Pediatric Brain Tumors	dendritic cell vaccine	vaccine	University of Miami
NCT00074334 (terminated)	HGG	TP-38 Toxin in Treating Young Patients With Recurrent or Progressive Supratentorial High-Grade Glioma	TP-38 (TGFa-PE38 immunotoxin) via local delivery		PBTC
NCT02031965	HGG	Oncolytic HSV-1716 in Treating Younger Patients With Refractory or Recurrent High Grade Glioma That Can Be Removed By Surgery	HSV-1716 (intratumoral)		PBTC
NCT01393912	DIPG / HGG	PDGFR Inhibitor Crenolanib in Children/Young Adults with DIPG or recurrent HGG	crenolanib	PDGFR	St. Jude Children's Research Hospital
NCT01644773	DIPG / HGG	Study of the Combination of Crizotinib and Dasatinib in Pediatric Research Participants With Diffuse Pontine Glioma and High-Grade Glioma	crizotinib dasatinib	c-Met / Alk PDGFR/src/c-kit	St. Jude Children's Research Hospital
NCT00890786	DIPG / HGG	A study of bevacizumab therapy in patients with newly diagnosed HGG or DIPG	bevacizumab	VEGF	Children's Hospital Medical Center, Cincinnati
NCT00879437	DIPG / HGG	Valproic Acid and Radiation Followed by Maintenance Valproic Acid and Bevacizumab in Children With High Grade Gliomas or Diffuse Intrinsic Pontine Glioma	valproic acid bevacizumab	HDAC VEGF	Baylor College of Medicine
NCT02359565	DIPG / HGG	Pembrolizumab in Treating Younger Patients With Recurrent, Progressive, or Refractory High-Grade Gliomas or Diffuse Intrinsic Pontine Gliomas	pembrolizumab	PD-1	PBTC
NCT01952769	DIPG / HGG	Anti PD1 Antibody in Diffuse Intrinsic Pontine Glioma	CT-011 (pidilizumab)	PD-1	Hadassah Medical Oganization, Jerusalem, Israel
NCT01400672	DIPG	Imiquimod/Brain Tumor Initiating Cell (BTIC) Vaccine in Brain Stem Glioma	imiquimod / vaccine from cell line GBM-6	Vaccine	Masonic Cancer Center, University of Minnesota
NCT01502917	DIPG	Convection-Enhanced Delivery of ^{124}I-8H9 for Patients With Non-Progressive Diffuse Pontine Gliomas Previously Treated With External Beam Radiation Therapy	^{124}I-8H9	B7-H3	MSKCC

Clinical Trial Number	Tumor Type	Title	Agent	Target	Sponsor
NCT01182350	DIPG	Molecularly Determined Treatment of Diffuse Intrinsic Pontine Gliomas (DIPG)	bevacizumab erlotinib temozolomide	VEGF EGFR	Dana-Farber Cancer Institute
NCT02233049	DIPG	Biological Medicine for Diffuse Intrinsic Pontine Glioma (DIPG) Eradication (BIOMEDE)	erlotinib everolimus dasatinib	EGFR mTOR PDGFR/src/c-kit	Gustave Roussy, Cancer Campus, Grand Paris
NCT01165333	DIPG	Cilengitide in Combination With Irradiation in Children With Diffuse Intrinsic Pontine Glioma	cilengitide	αvβ3 and αvβ5 integrins	Centre Oscar Lambret, Lille, France
NCT01922076	DIPG	WEE1 Inhibitor MK-1775 and Local Radiation Therapy in Treating Younger Patients With Newly Diagnosed Diffuse Intrinsic Pontine Gliomas	MK-1775	Wee1	COG phase 1 consortium
NCT01189266	DIPG	Vorinostat and Radiation Therapy Followed by Maintenance Therapy With Vorinostat in Treating Younger Patients With Newly Diagnosed Diffuse Intrinsic Pontine Glioma	vorinostat	HDAC	COG
NCT01514201	DIPG	Veliparib, Radiation Therapy, and Temozolomide in Treating Younger Patients With Newly Diagnosed Diffuse Pontine Gliomas	Velaparib (ABT-888)	PARP	PBTC
NCT01884740	glioma	Phase I/II Trial Of Super-Selective Intraarterial Infusion Of Erbitux and Bevacizumab For Treatment Of Relapsed/Refractory Intracranial Glioma In Patients Under 22 Years Of Age	cetuxumab bevacizumab	HER2 VEGF	Weill Medical College of Cornell University
NCT01130077	glioma	A Pilot Study of Glioma Associated Antigen Vaccines in Conjunction With Poly-ICLC in Pediatric Gliomas	glioma antigen peptides vaccine	vaccine	University of Pittsburgh
NCT01795313	ependymoma	Immunotherapy for recurrent ependymomas in children Treatment for Recurrent Ependymomas Using HAL-A2 Restricted Tumor Antigen Peptides in Combination with Imiquimod	imiquimod vaccine	vaccine	University of Pittsburgh
NCT02125786	ependymoma	A Trial of Surgery and Fractionated Re-Irradiation for Recurrent Ependymoma	re-irradiation		St. Jude Children's Research Hospital
NCT01188096	LGG	A Trial of Poly-ICLC in the Management of Recurrent Pediatric Low Grade Gliomas	poly-ICLC	Immune modulatory	UCSD
NCT01887522	LGG	Study of Vinblastine in Combination With Nilotinib in Children, Adolescents, and Young Adults (VINILO)	nilotinib vinblastine	PDGFR	Gustave Roussy, Cancer Campus, Grand Paris
NCT01734512	LGG	PNOC 001: Phase II study of Everolimus for	everolimus	mTORR	PNOC

Clinical Trial Number	Tumor Type	Title	Agent	Target	Sponsor
		Recurrent or Progressive low-grade gliomas in Children			
NCT01089101	LGG	Selumetinib in treating young patients with recurrent or refractory low grade glioma	selumetinib	MEK1	PBTC
NCT02332889	HGG Medullo-blastoma CNS PNET	Phase I/II: Decitabine/Vaccine Therapy in Relapsed/Refractory Pediatric High Grade Gliomas/Medulloblastomas/CNS PNETs	dendritic cell vaccine targeting NY-ESO-1; MAGE-A1, and MAGE-A3	vaccine	University of Louisville
NCT02255461	CNS tumors	Palbociclib Isethionate in Treating Younger Patients With Recurrent, Progressive, or Refractory Central Nervous System Tumors	palbociclib	CDK4,6	PBTC
NCT01677741	Phase 1	A Study to determine safety, tolerability and pharmacokinetics of oral Dabrafenib in children and adolescent subjects	dabrafenib	BRAF	GlaxoSmithKline
NCT02124772	Tumors with V600 mutation	Study to investigate safety, Pharmakokinetic (PK), pharmacodynamics (PD) and clinical activity of Trametinib in subjects with cancer or plexiform neurofibromas and Trametinib in combination with Dabrafenib in subjects with cancers harboring V600 mutations	dabrafenib trametinib	BRAF MEK	GlaxoSmithKline