Targeted Therapy for *BRAF* Mutant Brain Tumors

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Opinion Statement

Molecular heterogeneity has confounded attempts to target individual pathways in brain tumors. However, gliomas with *BRAF* mutations have been identified as being uniquely vulnerable to targeted therapies. Such mutations are predominantly seen in brain tumors of the adolescent and young adult population. Given that accurate and timely identification of such mutations is essential for offering appropriate treatment, treatment centers should offer both immunohistochemical and sequencing methods for detection of these mutations to guide treatment. Additional studies of these tumors at recurrence would also allow identification of breakthrough resistance mechanisms that may also be targetable for treatment. Due to the relative rarity of these tumors, multicenter collaborative studies will be essential in achieving long term control of these tumors.
Introduction and Background

The identification of actionable mutations in cancer has heralded the development of highly effective targeted therapies that have made a dramatic impact on several cancers. One such target is BRAF, also known as v-raf murine sarcoma viral oncogene homolog B (B-raf), a proto-oncogene involved in the transduction of vital cellular signals via the mitogen-activated protein kinase (MAPK) pathway [1, 2]. BRAF aberrations cause abnormal cellular proliferation and survival, and are encountered in about 15% of all cancers [3]. These aberrations are relatively frequent in melanoma (66%), non-small-cell lung cancer (40%), colorectal cancer (12%), and hairy cell leukemia (100%) [1, 4]. Extensive genomic sequencing of brain tumors has revealed that although infrequent, BRAF aberrations do occur in these malignancies and provide an opportunity to target tumors in otherwise challenging locations that are not amenable to conventional treatments like surgery and radiation. In addition, recent insights into the mechanisms of resistance BRAF targeted treatments have allowed new approaches to be developed to enhance the activities of these agents with several clinical trials currently in progress evaluating such strategies in BRAF mutant tumors.

Structure and Biological Role of BRAF

The BRAF gene, located on chromosome 7q34 and consisting of 18 exons, encodes B-Raf, a 766 amino acid 94 kD cytoplasmic serine/threonine kinase—a member of the rapidly accelerated fibrosarcoma (Raf) kinase family. There are three isoforms in this family including B-Raf, C-Raf/Raf-1, and A-Raf which share common structural features, including three conserved regions (CR), CR1, CR2, and CR3, which are important for interaction of these proteins with their partners or encode their enzymatic function: CR1 is comprised a Ras-binding domain (RBD) and cysteine-rich domain (CRD) relevant to the Raf autoinhibition and has high homology across the isoforms, CR2 encompasses a conserved Akt phosphorylation site and is involved in negative regulation of Ras/raf activity, and CR3 consists of a catalytic domain which can be regulated by phosphorylation for kinase activation. Other than these three conserved regions, the Raf isoforms show little identity to each other and have different levels of ability to phosphorylate/activate MEK1/2 with the most active being B-Raf followed by C-Raf/Raf-1 and lastly A-Raf [5, 6]. The Raf kinases are components of the RAS/RAF/MEK/ERK/mitogen-activated protein kinase (MAPK) pathway [2], which is a critical signal transduction pathway that regulates several cellular functions such as proliferation, survival, differentiation, and senescence in response to activation of transmembrane tyrosine kinase (Fig. 1, left panel) [1, 2, 7, 8].

Categories of BRAF Aberrations

In human cancers, approximately 200 different BRAF mutant alleles have been identified. BRAF gene aberrations include activating mutations or duplications/fusions that lead to constitutive kinase activity causing the downstream cellular effects such as proliferation and tumor growth [9]. Based on
the evidence from \textit{BRAF}-mutated cancers, in particular melanoma, thyroid, and colon cancers, recent studies have proposed three classes of \textit{BRAF} mutations \cite{10, 11}. These classes are based upon the ability of mutant \textit{BRAF} to transduce signal as monomers or dimers and their dependency on RAS and kinase activity. Understanding the mechanism of these mutant classes has implications for predicting therapeutic response from targeted therapies.

\textbf{Class I Mutations}

These mutations are independent and do not require an upstream RAS activation or dimerization \cite{11}. Point mutations leading to exchange of valine to a
different amino acid comprise this class. Most commonly described mutation is c.1799T>A leading to substitution of valine by glutamic acid at position 600 (p.V600E) (Fig. 1, right panel). This leads to conformational change that permits BRAF monomers to an active configuration by releasing the auto inhibitory domain, and ultimately allowing activation of downstream effectors (MEK1/2) without the need for dimerization [11, 12].

**Class II Mutations**

This category comprises mutation of codons other than V600E with high or intermediate BRAF kinase activity undergoing constitutive, RAS-independent dimerization [10•]. BRAF fusion mutants, other point mutations, and deletions comprise this class (Fig. 1, right panel). A common fusion encountered is KIAA1549-BRAF. In this mutation, the N-terminal dimerization domain of KIAA fuses with C-terminal kinase domain of BRAF leading to loss of the regulatory domain of BRAF that promotes increase affinity for dimerization and independent BRAF kinase activity [13].

**Class III Mutations**

These mutations require an upstream input and are dependent on RAS for their activity (Fig. 1, right panel). These either have impaired or at times absent kinase activity. The mutant protein causes increased activity by binding tightly to activate RAS compared to the wild-type BRAF and upon dimerization leads to increased activation of the wild-type binding partner [14, 15].

**BRAF Aberrations in Brain Tumors**

Analysis of data from a large cohort (n = 1320) of adult and pediatric brain tumor patients demonstrated that BRAF aberrations are seen, in order of frequency, in pleomorphic xanthoastrocytoma (PXA) (66%), PXA with anaplasia (65%), ganglioglioma (18%), and pilocytic astrocytoma (PA) (9%) and less frequently in other glial tumors (<3%) [16]. Another report analyzing a cohort of 969 patients with various types of brain tumors identified 36 cases (4%) with immunohistochemically positive BRAF V600E mutation [17]. Approximately 10% of PA harbor a BRAF V600E mutation (class I) and over 60–70% have KIAA 1549-BRAF fusions (class II) [18–20]; mutations and fusion aberrations are noted to be mutually exclusive in PA. PAs with a BRAFV600E mutations typically arise in a non-cerebellar location with a recent systematic review reporting presence of BRAF mutations within exon 18 in 158 cases: the frequency of BRAF mutations in different types of tumors included PA (24/187; 13%), ganglioglioma (54/115; 47%), PXA (49/81; 60%), PXA with anaplasia (9/24; 37%), and epithelioid GBM (22/38; 58%).
On the other hand, the KIAA 1549-BRAF fusion was reported in 139 cases, with the following frequency: in PA (120/191; 63%), pilomyxoid astrocytoma (10/13; 77%) and ganglioglioma (9/49; 18%) [21]. Brastianos et al. identified BRAFV600E mutation in 95% all the papillary craniopharyngiomas (CP) in a cohort of 39 patients [22••]. Another report of 73 CP patients identified BRAFV600E mutations in 24.6% and all being papillary CPs [23]. BRAF mutations have been reported in 8.13% of glioma patients, with 6.5% of patients having the canonical BRAFV600E mutation [16, 19•]. Of the 1579 patients queried from various datasets, a BRAF aberration was seen in 116 (7%) with a somatic mutation reported in 6% [24, 25] (data from lower grade glioma: TCGA, PanCancer Atlas; low-grade gliomas: UCSF, 2014; glioma: MSKCC, 2018; glioblastoma: TCGA, PanCancer Atlas; anaplastic oligodendroglioma and anaplastic oligoastrocytoma: MSKCC, 2017; medulloblastoma: Broad Institute, 2012; medulloblastoma: ICGC, 2012; medulloblastoma: PCGP, 2012; medulloblastoma: Sick Kids, 2016; pilocytic astrocytoma: ICGC, 2013) on cBioPortal (Fig. 2).

### BRAF Targeted Therapies in the Brain

Targeted approaches include selective inhibition of the BRAFV600E mutant, which has become the standard treatment of BRAF mutant melanoma, NSCLC, Erdheim–Chester disease, among others [26–28]. There are three FDA-approved drugs in this class: vemurafenib, dabrafenib, and encorafenib. Since reactivation of ERK signaling is a common mechanism of resistance to RAF inhibitors, RAF inhibitors have been combined with MEK inhibitors in patients with BRAF V600E-mutated tumors. FDA-approved MEK inhibitors include cobimetinib, trametinib, and binimetinib. MEK inhibition alone, on the other hand, is used for tumors with BRAF duplication/fusion [29].

### Outcomes/Response Associated with the Targeted Therapies in Brain Tumors

#### Adult Glioma

VE-BASKET is a phase 2, non-randomized histology-agnostic study that included patients with BRAFV600 mutation-positive tumor types [30•]. The study included seven cohorts of patients with NSCLC, ovarian, colorectal, breast cancers, cholangiocarcinoma, multiple myeloma, and “other tumors.” Patients with brain tumors were required to have histologically confirmed glioma (any grade) and confirmation of BRAF V600E mutation. Patients received vemurafenib 960 mg twice per day continuously in 4-week cycles. Twenty-four patients with gliomas were enrolled: 11 with malignant diffuse glioma (6 with GBM and 5 with anaplastic astrocytoma), 7 with
PXA, 2 with pilocytic astrocytoma, 3 with anaplastic ganglioglioma, and 1 with a high-grade glioma, not otherwise specified. One complete response (CR) was observed in a patient with PXA, and five patients achieved partial response (PR): two with PXA, one with anaplastic astrocytoma, one with anaplastic ganglioglioma, and one with pilocytic astrocytoma. The overall response rate in the group was 25% (95% CI 10% to 47%). CR lasted 25.9 months or more (censored at last assessment), and PRs lasted 13.1, 9.9, 7.5, 3.4, and 2.4 months. One patient achieved a PR in the diffuse malignant glioma subgroup and five patients had stable disease.

Wen et al. presented preliminary CNS results of a phase 2, open-label trial of dabrafenib and trametinib in patients with rare tumor types harboring the BRAF V600E mutation [31]. For the high-grade glioma cohort, eligible patients had histologically confirmed recurrent or progressive WHO grade 3 or 4 glioma (including PXA) and had prior treatment with

![BRAF aberrations in human gliomas (cBioPortal)](image)

**Fig. 2 BRAF aberrations in human gliomas (cBioPortal)**
radiotherapy and chemotherapy. The primary endpoint was investigator-assessed overall response rate (ORR) by RANO criteria. An abstract was presented with data on 31 of 37 patients. ORR was 26% (8/31; 95% CI 12–45%), including 1 complete response (CR). Five of 8 responding patients had a duration-of-response ≥12 months.

### Gangliogliomas

In addition to the VE-BASKET trial summarized above that included three patients with anaplastic gangliogliomas, one of whom achieved a partial response, the evidence of activity of BRAF inhibitors in gangliogliomas is limited to case reports. One review of the literature estimated a complete response in 15% (3/20) and partial response in 50% (10/20) of reported pediatric and adult cases with ganglioglioma/anaplastic ganglioglioma at a median of 3.2 months after starting treatment and an estimated progression-free survival of 14 months. Some of those cases were treated with BRAF monotherapy, while others were treated with BRAF/MEK dual inhibition or a BRAF inhibitor and chemotherapy [32].

### Pediatric Low-Grade Astrocytoma

In an abstract presented in 2016, Kieran et al. reported outcomes of treatment with dabrafenib in 32 pediatric patients with relapsed or refractory low-grade glioma [33]. Investigator confirmed overall response was 1 CR and 22 PRs (ORR 72% [95% CI 53–86%]). There were 13 patients with stable disease of ≥6 months. The Pediatric Brain Tumor Consortium then reported the results of a multi-center phase 2 study using the MEK1/2 inhibitor selumetinib in 25 patients with recurrent or progressive BRAF-aberrant or NF-1-associated low-grade glioma [34•]. Selumetinib was provided orally at 25 mg/m² twice daily in 4-week cycles. Nine of 25 patients (36%, [95% CI 18–57]) with pilocytic astrocytomas with BRAF fusion or V600E mutation achieved a partial response with a median follow-up of 36.4 months. Ten of 25 patients (40%, 95% CI [21–61]) with NF-1-associated low-grade glioma achieved a partial response with a median follow-up of 48.6 months. Drobyshcheva et al. reported two cases of disseminated pilocytic astrocytoma with BRAF V600E and BRAF V600D mutations, treated with dabrafenib or dabrafenib and trametinib, respectively [35]. The former patient had resolution of her leptomeningeal disease after 3 months of therapy. The latter patient had stable disease after 11 months of the combination therapy.

### Brain Metastases

The BREAK-MB phase 2 study first examined dabrafenib in 74 and 65 patients with BRAF-V600E mutant melanoma and brain metastases that were
Mechanisms of Resistance to BRAF Targeted Therapy

Mechanistically three different BRAF targeted therapy resistance patterns have been described in cancers harboring a BRAF aberration. These include intrinsic, adaptive, and acquired resistance mechanisms [41]. Presence of additional aberrations like copy number amplifications results in intrinsic resistance which results in lack of any response to initial treatment. Adaptive resistance or a partial response to the therapy can be seen due to de novo cellular epigenetic and transcription pathway alterations which may manifest as a partial and transient response with subsequent progression. Acquired resistance could result from selective pressures imposed by targeted therapy and resultant emergence of alternative clones within the tumor cell population with heterogeneous genetic alteration that can result in recurrence. It remains to be clarified whether all these resistance mechanisms are applicable to BRAF mutated brain tumor targeted treatments. In cases of PXA and PXA with anaplasia, resistance to targeted therapy with small molecule inhibitors like vemurafenib has been described. The typical BRAF mutation (class I) is often associated with sensitivity to targeted therapies; however, structural variations in the kinase domain such as β3-αC deletions and non-canonical BRAF mutations have been associated with resistant to such therapies [42, 43••].
For example, Wang et al. described that the emergence of secondary mutations in *BRAF* in addition to the canonical *BRAF*V600E mutation can confer resistance to dabrafenib in certain brain tumors (ganglioglioma) [44]. In this instance, the tumor showed initial response to dabrafenib but at progression, whole exome sequencing led to the identification of a new *BRAF* L514V mutation in addition to the initial V600E mutation that was not evident in the pretreatment tumor. The L514 residue is situated in the αC-β4-loop of the BRAF kinase domain. The BRAF kinase domain has an αC-β4-loop within the dimer interface that is crucial for the movements between αC-helix-in and αC-helix-out conformations [45]. This change represents an acquired resistance to targeted RAF inhibitor by inducing ERK signaling, promoting RAF dimer formation and thus promoting tumor growth. Resistance to RAF inhibitors has also been described in a cohort of PA cases due a novel recurrent *BRAF* insertion (p.V504_R506dup) [46].

**Clinical Trials Currently Investigating BRAF Targeted Therapies for Brain Tumors**

Presently, there are six clinical trials registered on ClinicalTrials.gov that are either active or in the recruiting stage evaluating BRAF targeted therapies in various primary and secondary brain tumors (ref: www.clinicaltrials.gov) summarized below (Table 1).

**Summary and Future Directions**

Certain subtypes of brain tumors, such as gangliogliomas and craniopharyngiomas, can be genetically simple and driven only by a *BRAF* V600E alteration. Higher grade gliomas, on the other hand, constitute a genetically complex disease with the hallmark of heterogeneity. Targeted therapy has had better success in simpler single-mutation-driven tumors, and more thoughtful data-driven combination approaches are needed for the more complex mutation-bearing tumors. Regardless, in light of the aggressiveness and lack of therapeutic options for high-grade gliomas, the presence of BRAF alterations does provide a unique potential for targeted therapy that has otherwise not been generally successful in gliomas. Due to the relative rarity of these events, multicenter collaborative studies will be essential in accruing sufficient numbers of patients and in assessing the potential for combination therapies in the setting of BRAF alterations in these tumors. Similarly, basket trials that are tumor agnostic have created an opportunity to study cancer patients with such rare mutations. Future basket trials and longitudinal natural history studies will be essential for better understanding of the prognosis and therapeutic implications of BRAF-altered gliomas in the pediatric and adult populations.
Table 1: Clinical trials against brain metastases active as of April 2021 in Clinicaltrials.gov

| NCT number | Title | Status | Conditions | Interventions | Outcome measures | Phases | Age |
|------------|-------|--------|------------|---------------|-----------------|--------|-----|
| NCT02974803 | Concurrent dabrafenib + trametinib with stereotactic radiation in BRAF mutation-positive malignant melanoma and brain metastases | Active, not recruiting | Melanoma, Brain metastases | Drug: dabrafenib, Drug: trametinib | Intracranial objective response rate to concurrent dabrafenib and trametinib with stereotactic radiation in patients with BRAF mutation-positive malignant melanoma and brain metastases; extracranial objective response rate; duration of response; intracranial progression-free survival; overall progression-free survival; number and severity of adverse events | Phase 2 | 18 years and older |
| NCT03973918 | Study of binimetinib with encorafenib in adults with recurrent BRAF V600E-mutated HGG | Recruiting | High-grade glioma with BRAF V600E or BRAF V600K mutations including anaplastic astrocytoma, Anaplastic pleomorphic xanthoastrocytoma, gliosarcoma, Glioblastoma | Drug: encorafenib, Drug: binimetinib, Biological: research bloods, Biological: tumor tissue | Tumor radiographic response per RANO for three treatment cohorts; progression-free survival for three treatment cohorts; overall survival; duration of response; number of participants with adverse events as defined by Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) | Phase 2 | 18 years and older |
| NCT01748149 | Vemurafenib in children with recurrent/refractory BRAF V600E (BRAFV600E)-mutant gliomas | Active, not recruiting | Pediatric recurrent/refractory BRAFV600E-mutant gliomas | Drug: vemurafenib | Overall response rate (ORR), duration of response (DOR), time to response (TTR), overall survival (OS), progression-free survival (PFS), pharmacokinetics (DRB + TMT) including area under the curve (AUC), elimination half-life (t1/2), predose plasma concentration (C0), adverse events, changes in electrocardiogram (ECG), ECHO, palatability of pediatric formulations, PROMIS Parent Proxy scale, clinical benefit rate (CBR) and for the LGG cohort: 2 year overall survival (OS) | Early phase 1 | Up to 25 years |
| NCT03430947 | Vemurafenib plus cobimetinib after radiosurgery in patients with BRAF-mutant melanoma brain metastases | Active, not recruiting | Malignant melanoma stage IV BRAF V600 mutation Brain metastases | Drug: vemurafenib, Drug: cobimetinib | >Best overall response rate in the brain; extracranial best overall response rate; best overall response rate calculated for the whole-body tumor sites; intracranial duration of response, extracranial duration of response, progression-free survival, overall survival, incidence of adverse events, radiomics for long-term control of brain metastases; radiomics for intracranial treatment-related toxicity | Phase 2 | 18 years and older |
| NCT02684058 | Phase II pediatric study with dabrafenib in combination with trametinib in patients with HGG and LGG | Active, not recruiting | Diffuse astrocytoma, anaplastic astrocytoma, oligodendroglioma, childhood anaplastic oligodendroglioma, glioblastoma, pilocytic astrocytoma, giant cell astrocytoma, pleomorphic xanthoastrocytoma, anaplastic pleomorphic xanthoastrocytoma angiocentric glioma, chordoid glioma of third ventricle, gangliocytoma, ganglioglioma, anaplastic ganglioglioma, dyplastic gangliocytoma of cerebellum, desmoplastic infantile astrocytoma and ganglioglioma, papillary glioneuronal tumor, Rosette-forming glioneuronal tumor, Central neurocytoma, extraventricular neurocytoma, cerebellar pilocytic astrocytoma | Drug: dabrafenib, Drug: trametinib, Drug: carboplatin with vincristine | Overall response rate (ORR), duration of response (DOR), time to response (TTR), overall survival (OS), progression-free survival (PFS), pharmacokinetics (DRB + TMT) including area under the curve (AUC), elimination half-life (t1/2), predose plasma concentration (C0), adverse events, changes in electrocardiogram (ECG), ECHO, palatability of pediatric formulations, PROMIS Parent Proxy scale, clinical benefit rate (CBR) and for the LGG cohort: 2 year overall survival (OS) | Phase 2 | 12 months to 17 years |
| NCT number | Title | Status | Conditions | Interventions | Outcome measures | Phases | Age |
|------------|-------|--------|------------|--------------|-----------------|--------|-----|
| NCT04543388 | A FIH study of PF-07284890 in participants with BRAF V600 mutant solid tumors with and without brain involvement | Recruiting | Malignant melanoma, non-small-cell lung brain neoplasms, primary brain neoplasms | Drug: PF-07284890, Drug: binimetinib, Drug: midazolam | Phase 1a and phase 1b—number of participants with dose-limiting toxicities (DLTs), treatment-emergent adverse events (AEs), clinically significant change from baseline in laboratory abnormalities, number of dose interruptions, dose modifications, and discontinuations due to AEs; Phase 1a and phase 1b—overall response; Phase 1a and phase 1b—maximum plasma concentration of PF-07284890 and binimetinib; time to reach maximum plasma concentration of PF-07284890 and binimetinib; area under the plasma concentration-time curve from time 0 to the last time point of quantifiable concentration (AUC_{0-last}) of PF-07284890 and binimetinib; terminal half-life (t_{1/2}) of PF-07284890 and binimetinib; area under the plasma concentration-time curve from time 0 extrapolated to infinity (AUC_{inf}) of PF-07284890 and binimetinib; volume of distribution of PF-07284890 and binimetinib; area under the plasma concentration-time curve over the dosing interval at steady state (AUC_{ss}) of PF-07284890 and binimetinib; trough plasma concentration at steady state (C_{ss,min}) of PF-07284890 and binimetinib; accumulation ratio (R_{a}) of PF-07284890 and binimetinib; Phase 1b: disease control rate (DCR)| Phase 1 | 18 years and older |
Declarations

Conflict of Interest
Appaji Rayi, Iyad Alnahhas, Shirley Ong and Vinay K. Puduvalli declare that they have no conflict of interest. Pierre Giglio owns stock in Vanguard S&P 500 ETF.

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