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Dabrafenib Therapy and *BRAF* Genotype

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Introduction

Dabrafenib (brand name Tafinlar) is a kinase inhibitor used in the treatment of individuals with unresectable or metastatic melanoma, metastatic non-small cell lung cancer (NSCLC), locally advanced or metastatic anaplastic thyroid cancer (ATC), pediatric low-grade glioma (LGG), and other unresectable or metastatic solid tumors with specific *BRAF* variants. Dabrafenib can be used as a single agent to treat melanoma with the *BRAF* valine 600 to glutamic acid (V600E) variant or in combination with the MEK inhibitor trametinib to treat multiple tumor types with *BRAF* V600E or V600K variants. (1)

The BRAF protein is an intracellular kinase in the mitogen-activated protein kinases (MAPK) pathway. Functionally, BRAF regulates essential cell processes such as cell growth, division, differentiation, and apoptosis. The gene *BRAF* is also a proto-oncogene—when mutated, it transforms normal cells into cancerous cells.

Variation in the kinase domain of BRAF is associated with various cancers. The most common *BRAF* variant, V600E, constitutively activates the kinase and causes cell proliferation in the absence of growth factors that would usually be needed. The V600E variant is detected in approximately 50% of melanomas, 25% of ATC, 2% of NSCLC, and 20% of pediatric LGGs (2, 3, 4, 5, 6, 7, 8).

The FDA-approved label for dabrafenib states that the presence of *BRAF* mutation in tumor specimens (V600E for dabrafenib monotherapy; V600E or V600K for dabrafenib plus trametinib) should be confirmed using an FDA-approved test before starting treatment with dabrafenib. Dabrafenib is not indicated for the treatment of individuals with wild-type *BRAF* tumors, or the treatment of colorectal cancer due to intrinsic resistance to *BRAF* inhibitor monotherapy. (1)

The label also states that individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency should be monitored for signs of hemolytic anemia while taking dabrafenib (1). However, it is important to note that an independent literature review by the Clinical Pharmacogenetics Implementation Consortium found no publications to support or refute this risk and thus issued no guidance for G6PD deficiency and dabrafenib therapy (9).

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Drug: Dabrafenib

Dabrafenib is a BRAF kinase inhibitor indicated for the treatment of individuals with unresectable or metastatic solid tumors bearing *BRAF* V600 mutations, including melanoma, ATC, NSCLC, and LGGs. The *BRAF* V600 mutated proteins can signal as catalytically active monomers, unlike wild-type RAFs that signal as obligatory dimers. The binding of dabrafenib to *BRAF* V600 monomers leads to decreased signaling through the MAPK pathway and reduced transcription of genes involved in various cellular responses. Resistance to dabrafenib can arise due to somatic alterations that lead to the formation of drug-resistant BRAF dimers, such as somatic variation in the *RAS* genes. Combining dabrafenib with a MEK inhibitor, such as trametinib, has been shown to extend survival (10, 11). Other medications that target MAPK signaling include vemurafenib, another BRAF kinase inhibitor, and cobimetinib, an allosteric inhibitor of the downstream kinases MEK1 and MEK2.

Dabrafenib can be used as a single agent to treat melanoma with the *BRAF* V600E variant or in combination with trametinib to treat tumors with *BRAF* V600E or V600K variants (1). Dabrafenib, with or without trametinib, has also been investigated for treating *BRAF* V600 mutation-positive pediatric Langerhans cell histiocytosis, with phase I and II trials suggesting clinical efficacy in this population (12). Additional tumor types studied for dabrafenib plus trametinib response in the Rare Oncology Agnostic Research (ROAR) study included *BRAF* V600E positive biliary tract cancer, adenocarcinoma of the small intestine, hairy cell leukemia, and multiple myeloma (13). The ROAR results suggest that many cancer types are responsive to this comedication strategy. Notably, colorectal cancer is not an indication for dabrafenib monotherapy based on intrinsic resistance to BRAF inhibition, nor should dabrafenib be used in tumors that do not have *BRAF* mutation (1).

Members of the cytochrome P450 (CYP) family, CYP3A4 and CYP2C8, metabolize dabrafenib. Dabrafenib also induces an increase in CYP3A4 expression in a dose-dependent manner (1, 14). As a result, steady-state plasma concentration for dabrafenib is reached after 14 days of therapy (14). Metabolism by CYP3A4 and 2C8 generates 3 major metabolites, among which hydroxy-dabrafenib is thought to be an active compound, contributing to the inhibition of MAPK signaling (14). Dabrafenib is typically administered twice-daily, 150 mg per adult dose, while the pediatric dosage depends on body weight and formulation (capsule or tablet for oral suspension) (1). Taking the medication without food (either one hour before or 2 hours after a meal) significantly increases bioavailability compared to taking the medicine with a high-fat meal (1, 14).

Skin cancer is the most common of all cancers, and while melanoma only accounts for approximately 1% of cases, it is responsible for most deaths from skin cancer. In the US, the lifetime risk of melanoma is approximately 2.6% for Caucasian individuals, 0.6% for Hispanic individuals, and 0.1% for Black individuals (15). Most cases of malignant melanoma are diagnosed at an early stage when the tumor is localized, and surgical excision can be curative. However, the 5-year survival rate drops from more than 99% for localized disease to only 32% for individuals with metastatic (distant) disease (16). The frequency of *BRAF* V600 driver mutation in melanoma is 40–50% (17).

Anaplastic thyroid cancer has a 39% 5-year survival rate for localized tumors, but this drops to 4% for distant tumors (18). Pathogenic variation in *BRAF* occurs in 20–50% of all individuals with ATC (19). Although ATC diagnosis accounts for only 1–2% of all thyroid malignancies, it represents 15–20% of mortality (20).

Driver mutations in *BRAF* are uncommon in NSCLC, occurring in 3.4% of individuals in a cohort from the United Kingdom (5) and 1–2% of lung adenocarcinomas (21). Among lung cancer diagnoses, NSCLC accounts for 80–85% of all cases and has a 5-year relative survival rate of only 9% for distant (metastatic) disease (22, 23).

Gliomas are the most common primary brain tumor, diagnosed at a frequency of approximately 6 per 100,000 people in the US each year. However, only 5–15% of LGGs have *BRAF* V600 driver mutations (24, 25). Low-

grade gliomas represent 30% of all childhood brain tumors, but *BRAF* V600E is associated with poor survival and an overall response rate (ORR) of less than 23% to conventional chemotherapy (26).

The most common adverse events associated with dabrafenib are skin lesions (benign and malignant). Cutaneous and non-cutaneous malignancies can occur during dabrafenib therapy, though the frequency is reduced when combined with trametinib. The drug label advises carrying out a dermatological evaluation before initiating dabrafenib therapy, every 2 months during therapy, and for up to 6 months following discontinuation. (1)

Skin reactions to BRAF inhibitors, such as dabrafenib, can include rashes, sarcoid-like, and granulomatous reactions (27, 28, 29). Occasionally, sarcoid-like reactions can affect other organ systems, and lesions in the pulmonary or lymphatic tissue should be assessed to determine if they are a progression of the primary cancer or a reaction to the medication (29). Dose reduction of dabrafenib/trametinib therapy or the addition of corticosteroids is often sufficient to resolve the sarcoid or granulomatous reactions when treating melanoma (28, 29). However, discontinuation of therapy for a few weeks may be necessary if intolerable grade 2 or grade 3–4 reactions occur during NSCLC treatment (30). One reported case of severe cutaneous adverse reaction to dabrafenib/trametinib dual therapy ultimately required cessation of therapy and administration of tumor-necrosis-factor-alpha blocking therapy. However, it is unclear if prior chemotherapy may have heightened the severity of the reaction. (31).

Less common but serious side effects to watch for during dabrafenib therapy include hemorrhage, cardiac toxicity, ocular effects, hyperglycemia, and hemophagocytic lymphohistiocytosis. Any grade 4 or persistent grade 3 hemorrhage event is an indication to discontinue dabrafenib therapy. (1) Cardiomyopathy characterized as a decrease in left ventricular ejection fraction of 10% or more from baseline has been observed in 6% of adult individuals during dabrafenib therapy (1). Within the context of NSCLC therapies, dabrafenib and trametinib were associated with increased odds of heart failure as compared to other targeted therapies (reporting odds ratio (ROR)) of 2–2.4) (32). Among ocular side effects, 1–2% of study participants had uveitis presenting with changes in vision, photophobia, or eye pain (1), and pharmacovigilance data from Japan reports a ROR of 6.03 for retinal disorders with dabrafenib therapy (33). Management of ocular inflammation may require the administration of topical steroids or, in severe cases, discontinuation of medication (34).

Other common side effects from dabrafenib therapy include headache, pyrexia, arthralgia, papilloma, and palmar-plantar erythrodysesthesia syndrome (1). Pyrexia is a common reaction to dabrafenib and trametinib therapy used for multiple types of *BRAF* V600 mutated cancers, with a reported frequency of approximately 50% in multiple studies (1, 35, 36), and a temporary dose interruption has been shown to be an effective management strategy (37).

Dabrafenib interacts in vitro with many proteins involved in drug metabolism, creating a possibility of drug-drug interactions. Due to its role as a CYP3A4 substrate and inducer, dabrafenib can influence the metabolism of other CYP3A4 substrates and be the victim of an interaction that significantly alters CYP3A4 activity. Increased CYP3A4 expression by a strong inducer (such as rifampin) can decrease an individual's exposure to dabrafenib, while inhibition (by ketoconazole, for example) of CYP3A4 will increase that individual's exposure to dabrafenib. Conversely, induction of CYP3A4 by dabrafenib resulted in a 65% decrease in exposure to a single dose of midazolam (a CYP3A4 substrate) (1). Dabrafenib can also inhibit CYP2C8, CYP2C9, and CYP3A5 (38). The UDP-glucuronosyltransferase (UGT) family of enzymes that contribute to drug metabolism via glucuronidation may also be inhibited by dabrafenib and lead to drug-drug interactions, particularly UGT1A1, 1A7, 1A8, and 1A9 (39). Drug-transporting enzymes also interact with dabrafenib; P-glycoprotein (encoded by the *ABCB1* gene) and breast cancer resistance protein (encoded by the *ABCG2* gene) both transport dabrafenib and can be inhibited by this interaction (1, 38).

Pregnant women should not take dabrafenib due to likely fetal harm caused by the medication. This warning is based on animal studies, as there is insufficient data on pregnant women to assess the risk of human harm (1). Similarly, there is no clinical data on the use of dabrafenib while breastfeeding. It is predicted that the amount of medication passed to breast milk would be low, given the high proportion bound to plasma proteins (1, 40). The manufacturer recommends discontinuing breastfeeding while taking the medication and for 2 weeks following the last dose (1). Both males and females of reproductive potential require counseling to use contraceptives while taking the medication and for 2 weeks after the last dose. Females should use a non-hormonal contraceptive due to the impaired efficacy of hormonal contraceptives by dabrafenib (1).

Dabrafenib has not been approved for use as a single agent in pediatric individuals but can be used for metastatic solid tumors in individuals 6 years or older or for LGG in individuals one year and older (1). Pediatric use requires weight-guided dosing that also accounts for the specific formulation of the medication; see drug labeling for more information (1). No dose adjustments are recommended for geriatric individuals, regardless of the tumor type treated with dabrafenib. However, this population may be at higher risk of specific side effects such as peripheral edema or anorexia (1). Similarly, there are no specific recommendations for dose adjustment in the context of hepatic impairment, though moderate to severe impairment may result in increased exposure to the medication and its metabolites (1).

Gene: *BRAF*

The RAF protein family are intracellular kinases within the MAPK signaling pathway. The RAF family has 3 members: ARAF, BRAF, and CRAF (41). The *RAF* and *RAS* genes are proto-oncogenes. Proto-oncogenes are genes that, when mutated or expressed at abnormally high levels, can transform normal cells into cancerous cells. Proto-oncogenes typically encode proteins that stimulate cell division, inhibit cell differentiation, and halt cell death. The increased production of oncogenic proteins can lead to the proliferation of poorly differentiated cancer cells (42).

Germline variations in *BRAF*, as well as other components of the MAPK signaling pathway, are associated with congenital anomalies, such as cardiofaciocutaneous syndrome, characterized by heart defects, intellectual disabilities, and distinctive facial dysmorphology. Somatic *BRAF* mutations are also associated with several malignancies, including colorectal carcinoma, lung adenocarcinoma, mucinous adenoma, and malignant melanoma.

Variations in *BRAF* are detectable in approximately 50% of malignant melanomas and drive the progression of the disease (2, 3). The *BRAF* variant V600E accounts for approximately 90% of variants. This variant is a substitution of adenine for thymine at position 1799 of the coding portion of the gene and results in the substitution of valine for glutamate at codon 600 in the expressed protein; the protein-level variation (V600E) is the commonly used description for this change. The variant BRAF protein kinase is constitutively active and a highly potent oncogene, increasing kinase activity by as much as 500-fold compared with the wild-type (43). The second most common *BRAF* variant is V600K. Substitutions at other sites are rarer (44, 45). Several drugs are under development to target *BRAF* variants, and so far, 3 drugs are FDA-approved: vemurafenib, dabrafenib, and encorafenib (46).

The signaling cascade mediated by BRAF is a MAPK pathway that transmits an extracellular signal to the nucleus to influence gene expression promoting cell proliferation and survival. Mitogen ligands activate cell surface receptors that then function as a docking site for a protein complex that includes RAS and a guanine nucleotide exchange factor, leading to the activation of RAS. Activated RAS proteins can then interact with BRAF, leading to dimerization and phosphorylation of the BRAF proteins. Activated BRAF then phosphorylates MEK proteins, activating extracellular signal-regulated kinase (ERK) proteins via phosphorylation. Active ERK has several substrates, including transcription factors that promote gene expression in proliferation and survival. The V600 mutation in BRAF enables the protein to function in a constitutively active manner and as a single

protein rather than as a dimer. The mutated BRAF, therefore, does not require RAS activation for its activation. Mutation of RAS that promotes dimerization in the absence of upstream activation can also lead to signaling cascade activation but rarely cooccur with *BRAF* V600 mutations in BRAF inhibitor treatment-naïve tumors. (47)

Linking *BRAF* Genetic Variation with Treatment Response

Dabrafenib increased progression-free survival (PFS), compared to cytotoxic chemotherapy (for example, dacarbazine), in individuals with advanced melanoma with the *BRAF* V600E variant (48, 49). The phase 3 COMBI-v trial for individuals with melanoma with a V600E variant found that the combination of dabrafenib plus trametinib led to a higher 3-year overall survival (OS) rate and PFS, compared to vemurafenib monotherapy (OS: 45% versus 32%, PFS: 25% versus 11%). Individuals taking the combination of dabrafenib plus trametinib experienced a decreased incidence of cutaneous squamous cell carcinoma (50). The COMBI-d trial also reported similar improved outcomes when comparing dabrafenib and trametinib to dabrafenib monotherapy (51, 52).

However, dabrafenib may not be the best first-line treatment choice for all individuals. The DREAMseq trial (EA6134, ClinicalTrials.gov identifier NCT02224781) saw a higher rate of OS in individuals with *BRAF* V600 mutated metastatic melanoma in response to treatment with nivolumab/ipilimumab as compared to dabrafenib/trametinib. As the rates of grade 3 or higher adverse reactions were similar between both treatment arms, the study authors recommend nivolumab/ipilimumab in treatment naïve metastatic melanoma with *BRAF*V600 mutation, followed by dabrafenib/trametinib if there is disease progression. (53) Dabrafenib/trametinib may be used first in symptomatic melanoma individuals who need a rapid response to therapy (54).

A clinical trial for ATC with *BRAF* V600E mutation reported an ORR of 56% when treated with dabrafenib and trametinib (55). A similar response was observed for NSCLC in clinical trials with both treatment naïve or previously treated NSCLC; subjects showed an ORR of over 60% to dabrafenib and trametinib combination therapy, leading to FDA approval in 2017 (56). The FDA-approved dabrafenib and trametinib combination therapy for pediatric LGG with *BRAF* V600E mutation in March of 2023, following a trial that showed a significant increase in ORR compared to carboplatin and vincristine dual therapy (26).

Dabrafenib and other BRAF inhibitors have also demonstrated responses in individuals with rare *BRAF* V600 variants (V600R, V600D) (57, 58, 59). As dabrafenib and other BRAF kinase inhibitors block signaling from BRAF monomers, they are selectively effective against *BRAF* V600 mutations and not effective against atypical (non-V600) variants at clinically attainable doses (for example, L597, K601) (60). In vitro experiments with BRAF inhibitors, such as dabrafenib, have been found to cause a paradoxical activation of signaling pathways and proliferation in *BRAF* wild-type cells. Therefore, clinicians should only use dabrafenib after confirming the presence of BRAF V600 variants in tumor specimens with an FDA-approved test (1). The FDA also recommends permanently discontinuing dabrafenib use in individuals who develop RAS mutation-positive non-cutaneous malignancies.

Genetic Testing

The NIH Genetic Testing Registry, GTR, displays genetic tests that are available for *BRAF*.

The FDA-approved label for dabrafenib states that the presence of *BRAF* mutation in tumor specimens (V600E for dabrafenib monotherapy; V600E or V600K for dabrafenib plus trametinib) should be confirmed using an FDA-approved test before starting treatment with dabrafenib. The label also says that dabrafenib is not indicated for the treatment of individuals with wild-type *BRAF* melanoma or the treatment of colorectal cancer.

Cancer-specific guidelines on testing, treatment selection, and other best practices for clinical care are available from various clinical experts globally. Medical societies such as the European Society for Medical Oncology, the American Society of Clinical Oncology, the National Comprehensive Cancer Network, and other specialized groups have guidelines available through PubMed or the society's webpage.

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2023 Statement from the US Food and Drug Administration (FDA):

BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma: Dabrafenib is indicated as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.

BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma: Dabrafenib is indicated, in combination with trametinib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test.

Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma

Dabrafenib is indicated, in combination with trametinib, for the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection.

BRAF V600E Mutation-Positive Metastatic NSCLC

Dabrafenib is indicated, in combination with trametinib, for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test

BRAF V600E Mutation-Positive Locally Advanced or Metastatic Anaplastic Thyroid Cancer

Dabrafenib is indicated, in combination with trametinib, for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options

BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors

Dabrafenib is indicated, in combination with trametinib, for the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options ... This indication is approved under accelerated approval based on overall response rate (ORR) and duration of response (DoR) … Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

BRAF V600E Mutation-Positive Low-Grade Glioma

Dabrafenib is indicated, in combination with trametinib, for the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy.

Limitation of Use: Dabrafenib is not indicated for treatment of patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition … Dabrafenib is not indicated for treatment of patients with wild-type BRAF solid tumors.

Patient Selection: Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with dabrafenib as a single agent. Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of treatment with dabrafenib and trametinib. Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics.

[…]

Glucose-6-phosphate Dehydrogenase (G6PD) Deficiency

Advise patients that dabrafenib may cause hemolytic anemia in patients with G6PD deficiency. Advise patients with known G6PD deficiency to contact their healthcare provider to report signs or symptoms of anemia or hemolysis.

Please review the complete therapeutic recommendations that are located here: (1).

Nomenclature

Selected *BRAF* Variants

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
V600E	p.Val600Glu	NM_004333.6:c.1799T>A	NP_004324.2:p.Val600Glu	rs113488022
V600K	p.Val600Lys	NM_004333.6:c.1798_1799delinsAA	NP_004324.2:p.Val600Lys	rs121913227
V600R	p.Val600Arg	NM_004333.6:c.1798_1799delinsAG	NP_004324.2:p.Val600Arg	rs121913227
V600D	p.Val600Asp	NM_004333.6:c.1799_1800delinsAT	NP_004324.2:p.Val600Asp	rs121913377

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS): http://www.hgvs.org/content/guidelines

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