



## Dabrafenib Therapy and *BRAF* and *G6PD* Genotype

Laura Dean, MD<sup>1</sup>

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### Introduction

Dabrafenib is a kinase inhibitor used in the treatment of patients with unresectable or metastatic melanoma with specific *BRAF* variants. Dabrafenib can be used as a single agent to treat melanoma with the *BRAF* V600E variant, or in combination with the MEK inhibitor trametinib to treat melanoma with *BRAF* V600E or V600K variants.

*BRAF* is an intracellular kinase in the mitogen-activated protein kinases (MAPK) pathway. *BRAF* is involved in regulating important cell functions such as cell growth, division, differentiation, and apoptosis. *BRAF* is also a proto-oncogene—when mutated it has the ability to transform normal cells into cancerous cells.

Variation in the kinase domain of *BRAF* have been 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 normally be required. The V600E variant is detected in approximately 50% of melanomas (1, 2).

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 treatment of patients with wild-type *BRAF* melanoma.

The label also states that patients who have glucose-6-phosphate dehydrogenase (G6PD) deficiency should be monitored for signs of hemolytic anemia while taking dabrafenib (3).

### Drug: Dabrafenib

Dabrafenib is a *BRAF* kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma. It acts by decreasing signaling through the MAPK pathway, leading to the reduced transcription of genes involved in various cellular responses.

Dabrafenib can be used as a single agent to treat melanoma with *BRAF* V600E variant, or in combination with trametinib to treat melanoma with *BRAF* V600E or V600K variants (3). Dabrafenib and other *BRAF* inhibitors have also demonstrated responses in patients with rare *BRAF* V600 variants (V600R, V600D) (4). These agents appear to be less active in pre-clinical studies of melanomas with atypical (non-V600) variants (e.g. L597, K601) (5).

Skin cancer is the most common of all cancers. Although melanoma is the least common type of skin cancer, accounting for approximately 1% of cases, it is responsible for the majority of deaths from skin cancer. In the US, the lifetime risk of melanoma is approximately 2.5% for whites, 0.5% for Hispanics, and 0.1% for blacks (6).

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 98% for localized disease, to only 16% for patients with metastatic disease.

For patients with advanced metastatic or unresectable malignant melanoma, treatment options typically include immunotherapy and targeted therapy. Although chemotherapy was once widely used, it does not increase survival and therefore its use is now limited to patients who are not candidates for further treatment with either immunotherapy or targeted therapy, and for whom there is no appropriate clinical trial.

High-dose interleukin 2 (IL2) therapy may be successful in a minority of cases, but can only be used in select patients with good organ function because of the risk of severe toxicity. Immunotherapy drugs include antibodies that target programmed cell death protein 1 (PD-1), e.g., nivolumab and pembrolizumab (7); and ipilimumab, a monoclonal antibody that targets cytotoxic T-lymphocyte-associated protein 4 (CTLA4). Oncolytic virus therapy with T-VEC (talimogene laherparepvec) is one of the newer immunotherapy drugs approved for melanoma.

Targeted therapies are designed to inhibit components of the MAPK signaling pathway, primarily when it is constitutively activated in melanomas with the activating *BRAF* variant, V600E. Drugs in this category include [vemurafenib](#) and dabrafenib, which inhibit BRAF, and trametinib and cobimetinib, which target downstream kinases MEK1 and MEK2, respectively.

Dabrafenib is a potent inhibitor of the kinase domain of the variant *BRAF* V600E. It acts by decreasing signaling through the MAPK pathway, leading to the reduced transcription of genes involved in various cellular responses. Combining dabrafenib with MEK inhibitors has been shown to extend survival (8, 9), and dabrafenib is often used in combination with a MEK inhibitor, e.g., trametinib.

Dabrafenib increased progression-free survival, compared to cytotoxic chemotherapy (e.g., dacarbazine), in patients with advanced melanoma with the *BRAF* V600E variant (10, 11). However, at this time there are no randomized trials that compare targeted therapies such as dabrafenib, with immunotherapy, and there are no data regarding the appropriate combinations and sequencing of these therapies for patients with a V600E variant.

A recent phase 3 trial for patients with melanoma with a V600E variant was stopped early because of positive results. The study found that the combination of dabrafenib plus trametinib led to a higher 3-year overall survival rate, compared to vemurafenib monotherapy (25% versus 11%). In addition, the incidence of cutaneous squamous cell carcinoma was decreased in patients taking the combination of dabrafenib plus trametinib (12).

The drug label advises that a dermatological evaluation should be carried out prior to initiating dabrafenib therapy, and every 2 months during therapy. The most common adverse events associated with dabrafenib are skin lesions (benign and malignant). Other side effects include fever, arthralgia, fatigue, alopecia, and palmar-plantar erythrodysesthesia syndrome (“hand-foot syndrome”).

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, dabrafenib should only be used after the presence of *BRAF* V600E variant in tumor specimens has been confirmed using an FDA-approved test (3). The FDA also recommends to permanently discontinue dabrafenib use in patients who develop RAS mutation-positive non-cutaneous malignancies.

## Gene: *BRAF*

RAF is a family of intracellular kinases within the MAPK signaling pathway. The RAF family has three members, ARAF, BRAF, and CRAF (13). RAF, along with RAS (see below), 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 (14).

Germline mutations in *BRAF*, as well as other components of the MAPK signaling pathway, are associated with birth defects, such as cardiofaciocutaneous syndrome, characterized by heart defects, mental retardation, and a distinctive facial dysmorphism. Somatic *BRAF* mutations are also associated with several malignancies, including lung adenocarcinoma, mucinous adenoma, ductal carcinoma of the pancreas, colorectal carcinoma, and malignant melanoma.

Variations in *BRAF* are detectable in approximately 50% of malignant melanomas, and drive progression of the disease (1, 2). The *BRAF* variant V600E accounts for approximately 90% of variants. This variant is a substitution of adenine for thymine at position 1799 and results in the substitution of valine for glutamate at codon 600. The variant BRAF protein kinase is constitutively active and a highly potent oncogene, with an increase in kinase activity by as much as 500-fold compared to the wild-type (15). The second most common *BRAF* variant is V600K. Substitutions at other sites are rarer (16, 17).

Several drugs are being developed to target *BRAF* variants, and so far, two drugs have been FDA- approved: vemurafenib and dabrafenib. Unfortunately, less progress has been made in developing targeted therapies for melanoma with wild-type *BRAF*. There are fewer treatment options available, but these include immunotherapy and MEK inhibitors (7, 18).

## Gene: *G6PD*

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an inherited X-linked recessive disorder that results from genetic variation in the *G6PD* gene. The *G6PD* gene is located on the X chromosome and G6PD deficiency occurs almost exclusively in males, who have only one X chromosome. G6PD deficiency mainly affects red blood cells, which carry oxygen from the lungs to tissues throughout the body.

G6PD deficiency affects 400 million people worldwide (19), and is common among African Americans, affecting approximately 12% (20). G6PD deficiency appears to be protective against malaria infection (21).

G6PD catalyzes the initial step in the hexose monophosphate (HMP) pathway. In mature red blood cells, the HMP pathway is the only source of NADPH, a coenzyme essential for protection against oxidative stress and repair of oxidative damage.

Red blood cells that are G6PD deficient are more susceptible to oxidative stress caused by exposure to drugs (e.g. sulfamethoxazole, primaquine, and dabrafenib), infections, diabetic ketoacidosis, or following ingestion of fresh fava beans (favism). Because of the oxidative stress, the red blood cells become rigid, become trapped, and are subsequently destroyed by macrophages in the spleen, bone marrow, and liver. Premature and/or fast destruction of red blood cells is called hemolysis and can result in hemolytic anemia.

Most affected individuals are asymptomatic; however, those with symptoms may suffer from episodes of acute hemolytic anemia or chronic hemolytic anemia. The management of hemolytic episodes depends on the severity of hemolysis. More severe cases may require a transfusion of packed red blood cells. Folic acid may be given to prevent the worsening of anemia in individuals with folate deficiency.

The normal (wild-type) copy of the *G6PD* gene is known as G6PD A+ (p.Asn126Asp), and is found in up to 30% of blacks from Africa (22). More than 400 genetic variants of the *G6PD* gene have been identified so far, and most are missense point mutations (23). Common variants include:

- G6PD A- (p.Asn126Asp and p.Val68Met) which is associated with mild to moderate hemolysis, and is found in up to 15% of African-Americans (24)
- G6PD Mediterranean (p.Ser218Phe) which can cause severe hemolysis, and is the most common variant in Caucasians (25)
- G6PD Canton (p.Arg489Leu) which can cause severe hemolysis, and is found in Asians (26)

All individuals with G6PD deficiency should avoid oxidizing agents when possible, including specific drugs and chemicals. Dabrafenib can cause hemolytic anemia. The FDA-approved drug label for dabrafenib warns that “dabrafenib, which contains a sulfonamide moiety, confers a potential risk of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Monitor patients with G6PD deficiency for signs of hemolytic anemia while taking dabrafenib” (3).

No cases of hemolytic anemia associated with dabrafenib have been published, although it is unclear whether individuals with G6PD deficiency have received dabrafenib.

## Genetic Testing

The NIH Genetic Testing Registry, GTR, displays genetic tests that are currently available for the genes [BRAF](#) and [G6PD](#).

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 states that dabrafenib is not indicated for treatment of patients with wild-type *BRAF* melanoma.

G6PD deficiency is typically diagnosed by screening tests that measure the activity of G6PD in red blood cells. A false positive may result immediately after an episode of hemolysis, so the test should be repeated at a later date. Molecular genetic testing can be used to confirm the diagnosis of G6PD, and may also be used to screen females with a family history of G6PD to see if they are carriers (27).

Screening for G6PD deficiency is recommended so that affected individuals can avoid agents that can cause oxidative stress and trigger hemolysis. G6PD deficiency is inherited in an X-linked recessive pattern. A heterozygous mother has a 50% chance of passing G6PD deficiency to a son and a 50% chance of passing the carrier trait to a daughter. Affected fathers pass the variant *G6PD* to their daughters, but not to their sons.

## Therapeutic Recommendations based on Genotype

**This section contains excerpted<sup>1</sup> information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.**

### **2016 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.

Limitation of Use: Dabrafenib is not indicated for treatment of patients with wild-type BRAF melanoma.

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>.

[...]

Dabrafenib, which contains a sulfonamide moiety, confers a potential risk of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Monitor patients with G6PD deficiency for signs of hemolytic anemia while taking dabrafenib.

Please review the complete therapeutic recommendations that are located here: (3).

## Nomenclature

### Selected BRAF variants

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
V600E	p.Val600Glu	NM_004333.4:c.1799T>A	NP_004324.2:p.Val600Glu	rs113488022
V600K	p.Val600Lys	NM_004333.4:c.1798_1799delGTinsAA	NP_004324.2:p.Val600Lys	rs121913227
V600R	p.Val600Arg	NM_004333.4:c.1798_1799delGTinsAG	NP_004324.2:p.Val600Arg	rs121913227
V600D	p.Val600Asp	NM_004333.4:c.1799_1800delTGinsAT	NP_004324.2:p.Val600Asp	rs121913377

### Selected G6PD variants

Common allele name / condition	Alternative names / condition	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
G6PD A-	p.Asn126Asp and p.Val68Met	NM_000402.4:c.466A>G NM_000402.4:c.292G>A	NP_001035810.1:p.Asn126Asp NP_001035810.1:p.Val68Met	rs1050828
G6PD Mediterranean	p.Ser218Phe	NM_000402.4(G6PD):c.653C>T	NP_000393.4:p.Ser218Phe	rs5030868
GP6D Canton	p.Arg489Leu	NM_000402.4(G6PD):c.1466G>T	NP_000393.4:p.Arg489Leu	rs72554665

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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