Vemurafenib Therapy and BRAF and NRAS Genotype

Laura Dean, MD

Created: August 15, 2017.

Introduction

Vemurafenib is a kinase inhibitor used in the treatment of patients with unresectable or metastatic melanoma with the BRAF V600E variant.

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 drug label for vemurafenib states that the presence of BRAF V600E mutation in tumor specimens should be confirmed, using an FDA-approved test, before starting treatment with vemurafenib. The label also states that vemurafenib is not indicated for treatment of patients with wild-type BRAF melanoma (3).

Variations in NRAS, also an oncogene, are found in up to 30% of all malignancies and in approximately 15-20% of melanomas. NRAS variants activate MAPK and have been implicated in in acquired resistance to BRAF inhibitors. Vemurafenib’s label warns that one adverse effect associated with therapy may be the progression of pre-existing chronic myelomonocytic leukemia with NRAS mutation (3). Other adverse effects include arthralgia, rash, alopecia, photosensitivity reaction, pruritus, and skin papilloma.
Drug: Vemurafenib

Vemurafenib is a BRAF kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with the \textit{BRAF V600E} variant, as detected by an FDA-approved test. It was one of the first molecularly targeted agents to receive FDA approval for advanced melanoma (3). Off-label uses of vemurafenib include the treatment of other \textit{BRAF V600E} positive tumors that are not responding to traditional treatments, e.g., refractory hairy cell leukemia (4).

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 (5).

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 interleukin2 (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 (PD1), e.g., nivolumab and pembrolizumab (6); 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 \textit{BRAF} mutation, \textit{V600E}. Drugs in this category include vemurafenib and dabrafenib, which inhibit \textit{BRAF}, and trametinib and cobimetinib, which target downstream kinases MEK1 and MEK2, respectively.

Vemurafenib is a potent inhibitor of the kinase domain of the variant \textit{BRAF V600E}. It acts by decreasing signaling through the MAPK pathway, leading to the reduced transcription of genes involved in various cellular responses. Combining vemurafenib with MEK inhibitors may potentiate these effects and has been shown to extend survival (7, 8).

Both targeted therapy with vemurafenib and immunotherapy regimens (e.g., nivolumab plus ipilimumab) have been shown to improve overall survival in patients with metastatic melanoma compared with chemotherapy (9, 10). However, at this time there are no randomized trials that compare targeted therapy with immunotherapy, and there are little
data regarding the appropriate combinations and sequencing of these therapies for patients with a *BRAF* V600E variant.

In the BRIM3 trial, vemurafenib improved overall survival (13.6 versus 9.7 months) and progression-free survival (6.9 versus 1.6 months) when compared to cytotoxic chemotherapy (dacarbazine)\(^{(11)}\). However, virtually every patient treated with a *BRAF* inhibitor eventually demonstrated disease progression \(^{(12)}\). Most patients developed mechanisms of acquired resistance, which is sometimes associated with NRAS variants, and approximately 15% of patients did not achieve tumor regression at all \(^{(11, 13-17)}\).

The most common adverse events associated with vemurafenib are skin lesions (benign and malignant), fever, arthralgia, and fatigue. Skin lesions, such as cutaneous squamous cell carcinoma, tend to occur during the first 8 weeks of treatment. Regular evaluation of the skin is recommended, with excision of suspicious lesions \(^{(18)}\). Liver enzymes (transaminases, alkaline phosphatase, and bilirubin) should also be monitored because of the risk of liver injury. Combining *BRAF* with MEK inhibitors helps reduce the odds of these side effects.

Approximately 50% of cases of metastatic melanoma are found to have the *BRAF* V600E activating variant \(^{(1, 2)}\). Because vemurafenib targets the kinase with this variant, patients without *BRAF* variants or with a different type of *BRAF* variant (e.g., *V600K*) should not be treated with vemurafenib; they will not benefit from vemurafenib therapy and will be needlessly exposed to adverse events. In addition, the FDA drug label warns that *BRAF* inhibitors have been shown to increase cell proliferation in *BRAF* wild-type cells *in vitro*.

**Gene: *BRAF***

*RAF* is a family of intracellular kinases within the MAPK signaling pathway. The *RAF* family has three members, ARAF, BRAF, and CRAF \(^{(19)}\). *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 \(^{(20)}\).

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 dysmorphology. 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 (21). The second most common BRAF variant is V600K. Substitutions at other sites are rarer (22, 23).

Several drugs are being developed to target BRAF mutations, 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 (6, 24).

**Gene: NRAS**

The RAS family contains three genes, HRAS, NRAS, and KRAS, which are essential components of a number of signaling pathways. They act as signal transducers, coupling cell surface receptors to intracellular signaling pathways.

RAS proteins have intrinsic GTPase activity, they are activated by a guanine nucleotide-exchange factor, and inactivated by a GTPase activating protein. RAS proteins regulate cell signal transduction by acting as a switch; they cycle between "on" (GTP-bound) or "off" (GDP-bound) conformations. In the "on" position, RAS proteins transmit extracellular growth signals to the nucleus, primarily via the MAPK pathway. Cells are subsequently stimulated to grow, divide, mature, and differentiate.

Variations in RAS genes lead to RAS proteins that are resistant to GTPase, so that GTP remains permanently bound and the receptor remains "on" providing a continual growth stimulus to cells. Such activating RAS variants are common, having been detected in colorectal cancer, lung cancer, pancreatic cancer, and melanoma.

Variations in NRAS are detectable in 15–30% of melanomas, clustering at codons 12, 13, and 61 (25, 26). These NRAS variants are the second most common oncogenic “driver” mutation in malignant melanomas, behind alternations in BRAF (26).

NRAS variants are associated with more aggressive melanomas, and generally a poorer prognosis (26). Currently, no therapies that specifically target NRAS have been approved. However, in the near future newer targeted therapies will likely provide effective treatment options for NRAS-variant melanoma (26, 27). Off-label, MEK inhibitors, especially in combination with other agents, have exhibited some efficacy in NRAS-variant melanoma.

NRAS variants are also associated with a number of other conditions, including Noonan syndrome (type 6), somatic rectal cancer, follicular thyroid cancer, autoimmune lymphoproliferative syndrome, and juvenile myelomonocytic leukemia.
Genetic Testing

The NIH Genetic Testing Registry, GTR, displays genetic tests that are currently available for the genes *BRAF* and *NRAS*.

The FDA-approved label for vemurafenib states that the presence of the *BRAF* V600E mutation should be confirmed in tumor specimens using an FDA-approved test before starting treatment with vemurafenib. The label also states that vemurafenib is not indicated for treatment of patients with wild-type *BRAF* melanoma.

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.

2016 Statement from the US Food and Drug Administration (FDA):

Vemurafenib is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.

Limitation of Use: Vemurafenib 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 Vemurafenib. Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at [http://www.fda.gov/CompanionDiagnostics](http://www.fda.gov/CompanionDiagnostics).

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

Nomenclature

Selected *BRAF* variants

<table>
<thead>
<tr>
<th>Common allele name</th>
<th>Alternative names</th>
<th>HGVS reference sequence</th>
<th>dbSNP reference identifier for allele location</th>
</tr>
</thead>
<tbody>
<tr>
<td>V600E</td>
<td>p.Val600Glu</td>
<td>NM_004333.4:c.1799T&gt;A</td>
<td>NP_004324.2:p.Val600Glu rs113488022</td>
</tr>
<tr>
<td>V600K</td>
<td>p.Val600Lys</td>
<td>NM_004333.4:c.1798_1799delGTinsAA</td>
<td>NP_004324.2:p.Val600Lys rs121913227</td>
</tr>
<tr>
<td>V600R</td>
<td>p.Val600Arg</td>
<td>NM_004333.4:c.1798_1799delGTinsAG</td>
<td>NP_004324.2:p.Val600Arg rs121913227</td>
</tr>
<tr>
<td>V600D</td>
<td>p.Val600Asp</td>
<td>NM_004333.4:c.1799_1800delTGinsAT</td>
<td>NP_004324.2:p.Val600Asp rs121913377</td>
</tr>
</tbody>
</table>
Selected NRAS variants

<table>
<thead>
<tr>
<th>Common allele name</th>
<th>Alternative names</th>
<th>HGVS reference sequence Coding</th>
<th>Protein</th>
<th>dbSNP reference identifier for allele location</th>
</tr>
</thead>
</table>

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

Acknowledgments

The author would like thank Paul B. Chapman, MD, Medical Oncologist and Head of the Melanoma Section Clinical Immunology Service, Memorial Sloan Kettering Cancer Center, New York; Avadhut Joshi, PhD, Clinical Pharmacogenomics Lead, Translational Software, Bellevue, Washington; Matthew Hardison, PhD, FACMG, Director of BioPharma Laboratory, Aegis Sciences Corporation, Nashville, TN; and Pamala A. Pawloski, PharmD, Research Investigator, HealthPartners Institute, Bloomington, MN; for reviewing this summary.

References


Related Summaries by Gene

Dabrafenib Therapy and BRAF and G6PD Genotype

Related Summaries by Drug Class

Dabrafenib Therapy and BRAF and G6PD Genotype

Tests in GTR by Gene

NRAS gene
BRAF gene