

Lung Cancer and the BRAF V600E Mutation

This material will help you understand:

- the basics of lung cancer
- the role of the BRAF gene in lung cancer
- if there are any drugs that might work better if you have certain changes in the BRAF gene

What is lung cancer?

Lung cancer is a type of cancer that starts in the lungs. It is the number one cause of cancer deaths in the world. Doctors name lung cancers based on how lung cells look under a microscope. There are two main groups of lung cancer: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Most people with lung cancer have NSCLC. Adenocarcinoma, squamous cell carcinoma, and large cell carcinoma are types of NSCLC.

What causes lung cancer?

Cancer is a result of changes in our genes. Genes contain the instructions for making proteins. Changes in genes, called mutations, may result in changes in proteins. These changes may cause cells to grow out of control which could lead to cancer.

The biggest risk factor for lung cancer is exposure to cigarette smoke. But, not all lung cancers are due to smoking. Other risk factors include exposure to radon gas, asbestos and pollution.

What are the most common current treatments for lung cancer?

Doctors may treat lung cancer using one or more of these options:

- **Surgery** – operation that removes as much of a cancer tumor as possible.
- **Radiation** – treatment that uses high-energy beams to kill cells in the area where the cancer is growing.
- **Traditional chemotherapy** – drugs that kill growing cells. All cells grow. Cancer cells usually grow faster than most healthy cells. So, these drugs kill more cancer cells. But because these drugs kill healthy cells too, this can cause unwanted side effects.
- **Precision medicine therapy** – treatments that target proteins involved in cancer. These therapies mainly kill cancer cells and not healthy cells. This also means you may have fewer side effects. Two types of precision medicine therapies are:
 - **Small molecule therapy** – mainly acts on cells with specific protein changes. Small molecule therapy uses drugs to target those proteins. Genetic testing can tell if your cancer cells have protein changes that can be targeted. Small molecule therapy is a type of targeted therapy.
 - **Immune-based therapy** – works with your body's defense system to fight cancer. These can mark cancer cells so they are easier for your immune system to find.

Can I pass on mutations found in my cancer cells to my children?

You cannot pass on mutations found only in your cancer cells to your children.

How well does cancer drug treatment work?

After a while, your cancer cells may stop responding to the drug(s). This means your cancer may start to grow again. Your doctor will do regular checkups to watch for this. If the cancer starts to come back, your doctor can try another drug or treatment.

What is BRAF?

BRAF (pronounced “B-răf”) is the name of both a gene[📄] and a protein[📄]. The BRAF gene contains the instructions for making the BRAF protein. BRAF is a member of the RAF family of proteins. Their main job is to help control cell growth. RAF proteins are part of a pathway. Proteins in pathways work together to do specific jobs within the cell. Some of the other proteins in this pathway include RAS, MEK and ERK. This is shown in the healthy cell image below (Figure 1). This pathway is a signaling pathway[📄]. It passes signals from outside the cell to the cell’s nucleus. The nucleus is the control center of the cell. These signals may tell the cell to grow, divide, or die. These are all normal cell functions. The body turns the signals on and off as needed.

What is BRAF’s role in the growth pathway?

In healthy cells, the growth signal turns proteins[📄] “on.” As the signal reaches each protein in the pathway, it turns on the protein. BRAF receives the signal via RAS. BRAF passes it on to MEK, and MEK passes it on to ERK. ERK is the last protein in the pathway. When ERK is on, it turns on genes[📄] in the nucleus that help cells grow. When the signal stops, the proteins turn off.

How do mutations in proteins affect pathways?

If a mutation[📄] affects one or more proteins[📄] in a pathway, the proteins may not be able to be turned on or off as expected. This can cause cells to grow out of control and lead to cancer.

How common are BRAF mutations in lung cancer?

About 1 in 50 lung cancers have a mutation[📄] in the BRAF gene[📄] that changes the BRAF protein[📄]. BRAF mutations are more common in current or former smokers.

What is the BRAF V600E mutation?

BRAF V600E is a specific variation in the BRAF protein[📄]. Proteins are long chains of amino acids[📄]. The BRAF protein has 766 amino acids. BRAF with no mutation[📄] at amino acid position 600 has a valine, or V for short. The amino acid at position 600 in BRAF with the V600E mutation is a glutamic acid, or E for short. V600E is the most common BRAF mutation in melanoma.

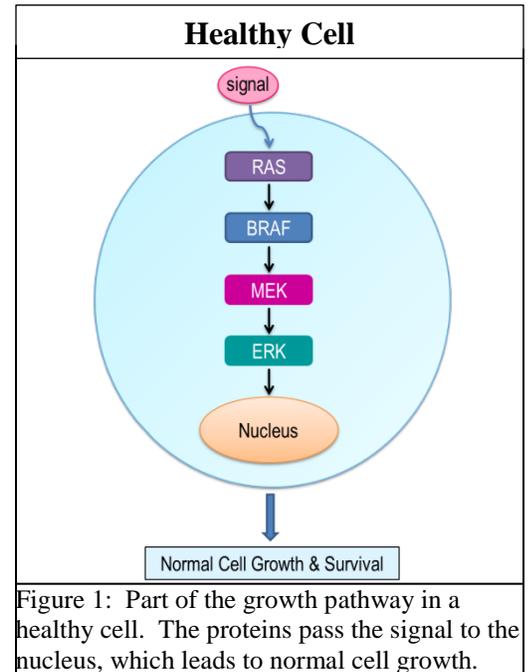
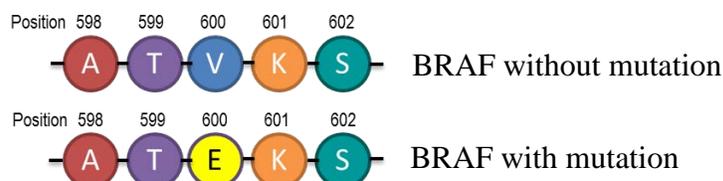


Figure 1: Part of the growth pathway in a healthy cell. The proteins pass the signal to the nucleus, which leads to normal cell growth.



What is the effect of this mutation?

The V600E mutation is in the part of BRAF that passes along the cell growth signal. In cells with this mutation, BRAF can always turn on MEK. This keeps the growth pathway on. Cells with this mutation can grow out of control, which can lead to cancer (Figure 2).

Are there targeted therapies for BRAF V600E?

The BRAF V600E mutation is a target for BRAF inhibitor drugs. The drugs dabrafenib and vemurafenib are BRAF inhibitors. These drugs stop the BRAF protein with the mutation from turning on MEK (Figure 3). MEK is another protein in this cell growth pathway.

BRAF inhibitors work well. But, after a while, your cancer cells may stop responding to these drugs. So, your doctor may also prescribe a MEK inhibitor drug. MEK inhibitors keep MEK from turning on ERK. Trametinib, selumetinib, and cobimetinib are common MEK inhibitors that may work well in cancer cells with BRAF mutations. Taking both a BRAF and a MEK inhibitor helps make sure this growth pathway is off. The drugs inhibit the growth of cells with this mutation and may lead to cell death.

What if I have a different mutation in BRAF or “no mutation”?

Your cancer cells might have mutations in this gene or in other genes that were not tested. Your genetic test results will still help your doctor determine the best treatment for you.

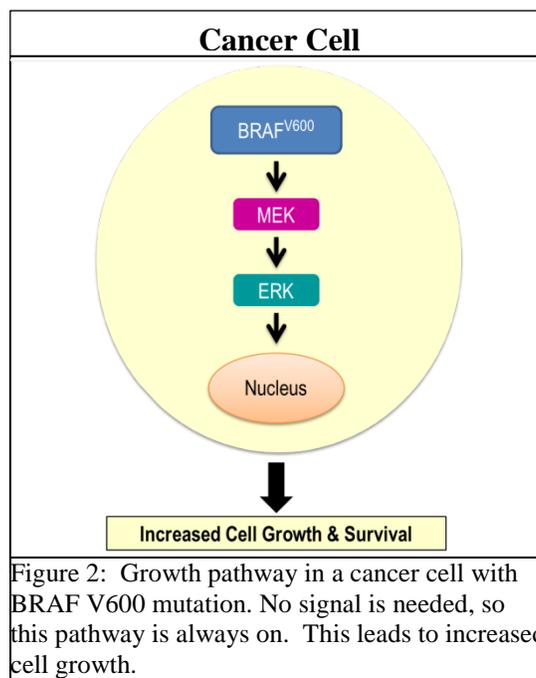


Figure 2: Growth pathway in a cancer cell with BRAF V600 mutation. No signal is needed, so this pathway is always on. This leads to increased cell growth.

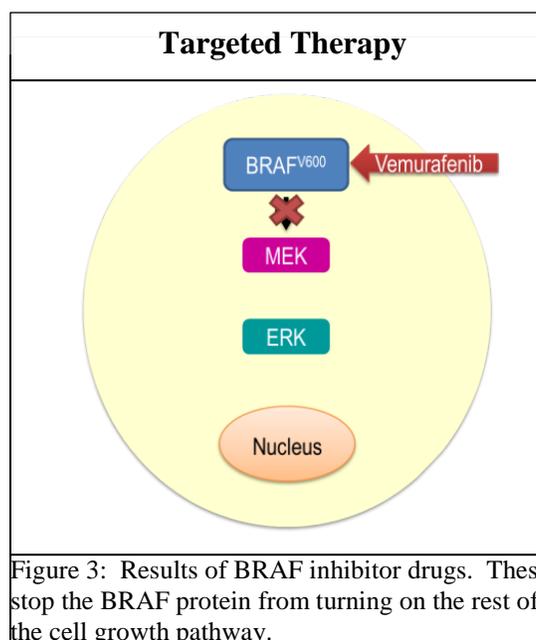


Figure 3: Results of BRAF inhibitor drugs. These stop the BRAF protein from turning on the rest of the cell growth pathway.