

Lung Cancer and the ALK G1269A Mutation

This material will help you understand:

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

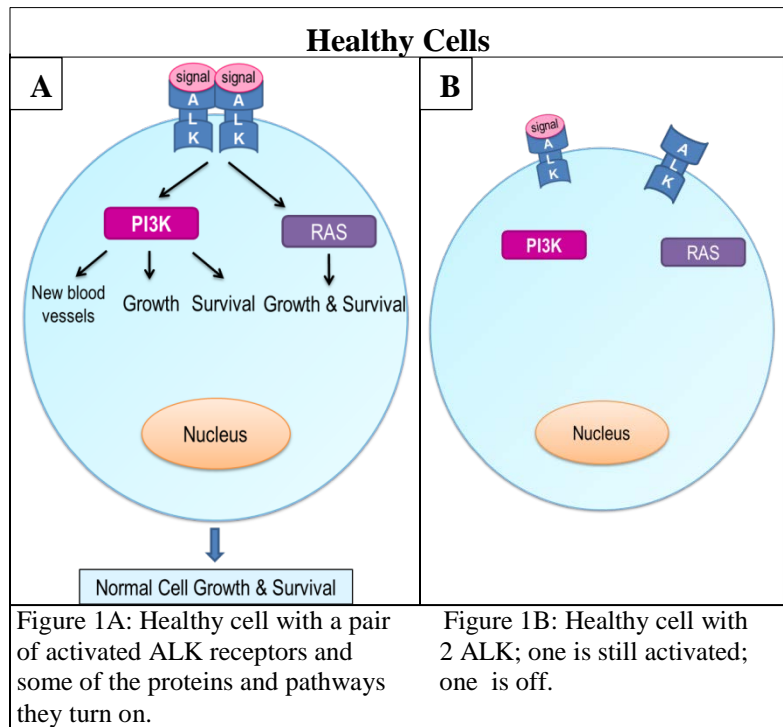
After a while, your cancer cells may stop responding to the drug(s). This means your cancer may start to grow again. Your doctor will do regular checkups to watch for this. If the cancer starts to come back, your doctor can try another drug or treatment.

What is ALK?

ALK (pronounced “ālk”) is the name of both a gene[📄] and a protein[📄]. The ALK gene contains the instructions for making the ALK protein. ALK is short for anaplastic lymphoma kinase[📄]. ALK is a receptor[📄]. Receptors are proteins that are often in cell membranes. The cell membrane is the outside surface of a cell. Receptors have three basic parts. One part is outside the cell, one part crosses the cell membrane, and one part is inside the cell. Receptors receive signals from outside the cell. These signals may tell the cell to grow, divide, or die. Each receptor usually receives one specific signal.

In healthy cells, the signal binds to ALK. When the outside part of ALK receives the signal, it activates, or turns on, the ALK protein. It then pairs with another activated ALK. This pairing turns on the part of ALK inside the cell.

When the inside part of ALK is on, it can then turn on other proteins. These other proteins are usually in pathways. Proteins in pathways work together to do specific jobs within the cell. The healthy cell image shows some of the proteins and pathways turned on by ALK (Figure 1A). ALK can turn on at least two different cell growth and survival pathways. When the signal stops, the ALK proteins turn off and separate (Figure 1B).



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 ALK mutations in lung cancer?

About 1 in 15 non-small cell lung cancers (NSCLCs) have a change in the ALK gene[📄] that changes the ALK protein[📄]. The most common change is a gene fusion[📄]. ALK fusions are more common in light smokers and never smokers. ALK fusions are also linked to an earlier age of diagnosis.

What is an ALK fusion?

An ALK fusion is a protein[📄] made from a gene fusion[📄]. A fusion is when two different things are stuck together. In this case, part of the ALK gene[📄] is fused to part of another gene. The protein made by the fusion contains parts from each gene. In ALK fusion proteins, the part of the protein inside the cell is from ALK. The outside part is from another protein.

What genes can be fused to ALK?

The most common gene fused to ALK is EML4. TFG and KIF5B are examples of other genes fused to ALK.



What is the effect of an ALK fusion?

Sometimes, an ALK fusion gene can make a working protein. The part of the protein inside the cell is from ALK. The outside part is from another protein. Figure 2 is an image of a TFG-ALK fusion protein. Many of the proteins made from genes fused with ALK can pair up, even without a signal. This results in the ALK part always being on. This can cause cells to grow out of control and lead to cancer.

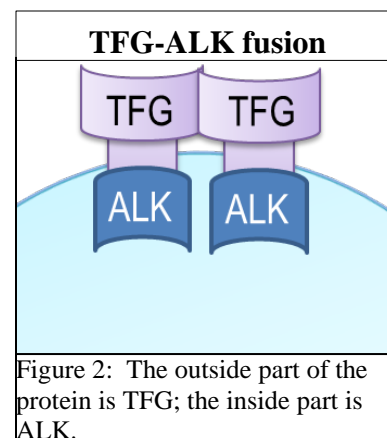


Figure 2: The outside part of the protein is TFG; the inside part is ALK.

Are there targeted therapies for ALK fusions?

There are targeted therapies for ALK fusions. They target the ALK part of the fusion protein. The drug crizotinib is an ALK inhibitor. This drug stops the part of ALK inside from turning on other proteins. Ceritinib is also an ALK inhibitor. Your treatment may start with one of these. Or, you might also get a traditional chemotherapy drug at the same time.

Targeted therapies often work well at first. But, after a while, your cancer cells may stop responding to these drugs. So, your doctor may also prescribe another drug. You should talk to your doctor about your treatment options.

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

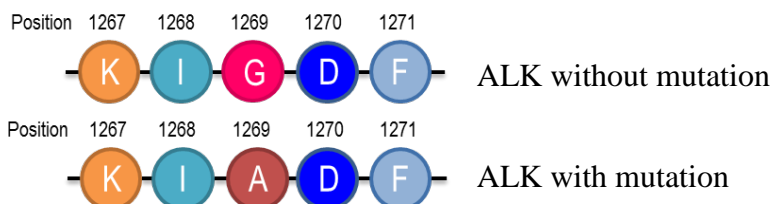
Your cancer cells might have mutations in this gene or in other genes that were not tested. Your genetic test results will still help your doctor determine the best treatment for you.

Why do I have another ALK mutation?

Your cancer cells may stop responding to ALK inhibitors. This can occur for many reasons. One reason is that your cells may develop a second mutation that affects the ALK part of the protein. These new mutations allow cancer cells to start growing again.

What is the ALK G1269A mutation?

G1269A is a specific variation in the part of the ALK protein¹ that is inside the cell. Proteins are long chains of amino acids². The ALK protein has 1,620 amino acids. The inside part of the protein starts at amino acid 1116 and goes to the end of the protein chain. ALK with no mutation³ at amino acid position 1269 has a glycine, or G for short. The amino acid at position 1269 in ALK with the G1269A mutation is an alanine, or A for short.



What is the effect of this mutation?

This mutation⁴ is in the part of ALK that is inside the cell. Thus, it is also found in ALK fusion⁵ proteins⁶. This mutation allows cells to grow in the presence of ALK inhibitor drugs.

Are there targeted therapies⁷ for ALK G1269A?

At this time, it is unclear if any drugs target ALK with this specific mutation⁸. But, there are inhibitor drugs for another protein⁹. This protein is HSP90, which can help cancer cells survive. You should talk to your doctor about your treatment options.