

Lung Cancer and ROS1 Fusions

This material will help you understand:

- the basics of lung cancer
- the role of the ROS1 gene in lung cancer
- if there are any drugs that might work better if you have certain changes in the ROS1 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?

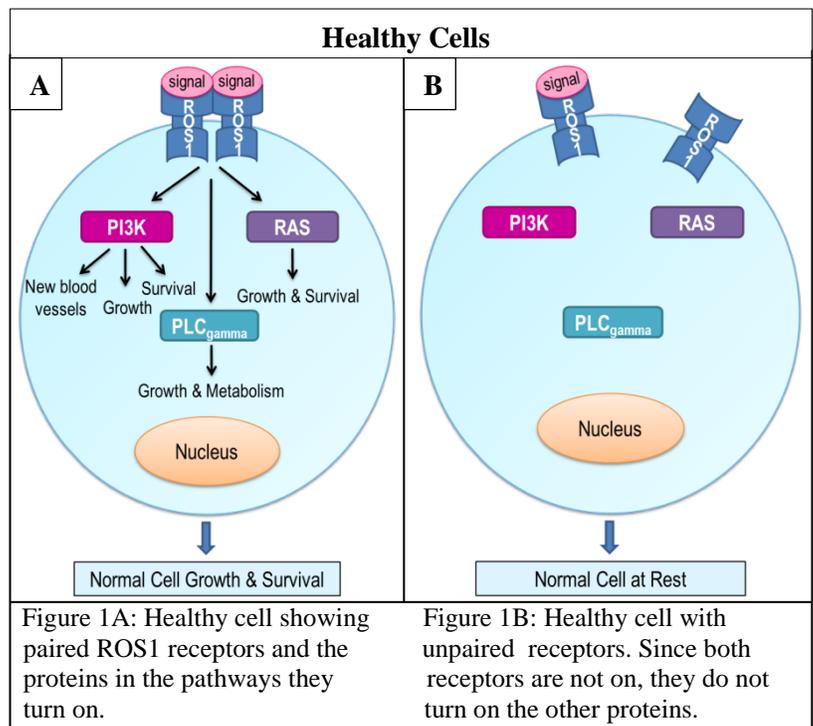
After a while, your cancer cells may stop responding to the drug(s). This means your cancer may start to grow again. Your doctor will do regular checkups to watch for this. If the cancer starts to come back, your doctor can try another drug or treatment.

What is ROS1?

ROS1 (pronounced “Rōs 1”) is the name of both a gene and a protein. The ROS1 gene contains the instructions for making the ROS1 protein. ROS1 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 ROS1. When the outside part of ROS1 receives the signal, it activates, or turns on, the ROS1 protein. It then pairs with another activated ROS1. This pairing turns on the part of ROS1 inside the cell.

When the inside part of ROS1 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 ROS1 (Figure 1A). Paired ROS1 can turn on at least two different cell growth and survival pathways. When the signal stops, the receptor 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 ROS1 mutations in lung cancer?

About 1 in 50 non-small cell lung cancers (NSCLCs) have a change in the ROS1 gene that alters the ROS1 protein. The most common change is a gene fusion. ROS1 fusions are often in adenocarcinomas, a type of NSCLC. They are more common in light smokers and never smokers. ROS1 fusions are also linked to an earlier age of diagnosis.

What is a ROS1 fusion?

A ROS1 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 ROS1 gene is fused to part of another gene. The protein made by the fusion contains parts from each gene. In ROS1 fusion proteins, the part of the protein inside the cell is from ROS1. The outside part is from another protein.

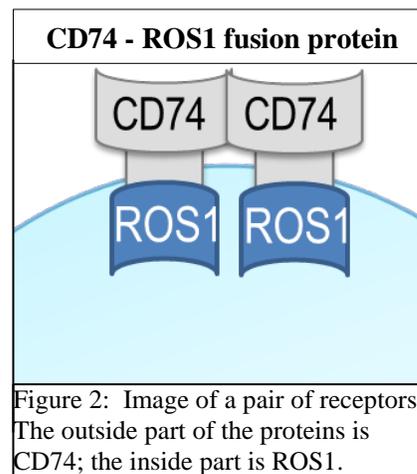
What genes can be fused to ROS1?

SLC34A2, CD74 and TPM3 are a few examples of genes that fuse to ROS1.



What is the effect of a ROS1 fusion?

Sometimes, a ROS1 fusion gene can make a working protein. The part of the protein inside the cell is from ROS1. The outside part is from another protein. Figure 2 is an image of a CD74-ROS1 fusion protein. Many of the proteins made from genes fused with ROS1 can pair up, even without a signal. This results in the ROS1 part always being on. This can cause cells to grow out of control and lead to cancer.



Are there targeted therapies for ROS1 fusions?

ROS1 fusions are a target for inhibitor drugs. Crizotinib is a drug that targets the inside part of ROS1 (Figure 3). This drug inhibits, or stops, the inside part of ROS1 from turning on other proteins. Other similar targeted therapy drugs might also work.

Crizotinib may work well for your cancer. But, after a while, your cancer cells may stop responding to this drug. So, your doctor may prescribe another drug. You should talk to your doctor about your treatment options.

What if I have a different mutation in ROS1 or “no mutation”?

Your cancer cells might have other 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.

