

LUNG
CANCER:
NEW
TREATMENT
DIRECTIONS



LUNG CANCER ALLIANCE

1-800-298-2436

LungCancerAlliance.org

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WHAT'S NEW IN LUNG CANCER?

There have been many exciting advances in the field of lung cancer. Until the mid-2000's, treatment options were mostly limited to surgery, chemotherapy and radiation. Now, people diagnosed with lung cancer often have newer, more targeted treatment options. The way lung cancer is detected and monitored during therapy is also changing. The purpose of this brochure is to help you understand advances in the treatment of lung cancer and what they mean for you.



ADVANCEMENTS

DIAGNOSIS AND MONITORING

A tissue biopsy, which involves removing tissue from the cancer to examine it under the microscope is necessary to confirm a person has lung cancer and to tell what kind of lung cancer it is.

As lung cancer spreads, it can change. Understanding those changes may provide different treatment options. In the past, tissue biopsies were not often repeated. Today, biopsies may be done again later to help guide treatment decisions. Other new approaches are being researched, including “liquid biopsy,” which uses blood or other fluids, like urine, to try to study gene changes without the need for another tissue biopsy. These tests are still being studied and are not as common as tissue biopsies.

CHANGES TO GENES

Lung cancer is not one disease—there are several subtypes of lung cancer and many ways that normal cells in the lungs change into cancer. Research into how cancer develops has led to therapies that target cancer in some very specific ways.

To understand targeted therapies, it helps to review how cells work and how they can change into cancer.

A cell is the basic unit in our body that makes up all our organs and structures. Cells have different functions that are performed by parts inside the cell. Their nucleus or “brain” contains chromosomes, 23 from each parent. The chromosomes carry genes which are made up of material including DNA (deoxyribonucleic acid). These genes control the functions of the cell.

Over time, genes can undergo changes. The changes may happen over generations or over a lifetime in response to things we eat, drink or to which we are exposed or by random chance. Some changes are helpful. Some do not make a difference one way or the other. But other changes can lead to the development of diseases, including abnormal growth of cells, such as cancer.

CHANGES IN GENES THAT TRIGGER CANCER

You will read and hear terms like mutations, fusions, alterations, translocations, deletions and rearrangements to describe various types of changes that happen inside cells that can trigger abnormal behavior of the cells.

It is helpful to know the gene (which has a short name, usually three or four letters, sometimes with numbers) where the change occurred to help match your tumor to a treatment.

GENES THAT ARE CHANGED

- Epidermal Growth Factor Receptor (EGFR) mutation
- Anaplastic Lymphoma Kinase gene fusion (ALK)
- Kirsten RAt Sarcoma (KRAS) mutation
- C-Ros Oncogene 1, Receptor tyrosine kinase (ROS1) fusion
- V-Raf Murine Sarcoma Viral Oncogene Homolog B (BRAF) mutations
- Human Epidermal growth factor Receptor 2 (HER2) mutation
- Mesenchymal-Epidermal Transition (MET) amplification
- Mitrogen-activated protein 2K1 (MAP2K1 or MEK) mutations
- Vascular Endothelial Growth Factor (VEGF)/ Vascular Endothelial Growth Factor R (VEGFR)

Molecular Profiling ... Molecular Testing ...
Biomarker Testing ... Mutation Testing ...
Tumor Testing

IS THERE A DIFFERENCE?

In order to know what kind of gene changes happened in the cancer, it must be tested. These tests may be done with samples collected at the time of the first biopsy to diagnose the cancer or on a new sample when another biopsy is done when the cancer grows or comes back. This testing may be called molecular profiling, molecular testing, biomarker testing, mutation testing or tumor testing. What all these tests have in common is to find changes in the cancer that make it grow and spread. There are a lot of known changes that are common in each of the different types of lung cancer. If a specific change is found in the cancer, it is said to have tested "positive."

Many of the identified gene changes only occur in small percentages of lung cancer. Currently many more gene changes have been identified than there are approved treatments, but much research is ongoing to find treatments to target all of the known changes.

Two of the most promising directions in lung cancer treatment are targeted therapies, which target particular ways that cancer grows and immunotherapies, approaches that use the body's immune system to fight the cancer.

TARGETED THERAPIES

Targeted therapies are aimed at a particular “target” in the tumor cell, with the goal of stopping the cancer from continuing to grow.

Targeting is meant to spare the rest of the body from side effects, unlike chemotherapy, which kills any fast growing cells in the body, including cancer. Most targeted therapies are in pill form. Targeted therapies can also be monoclonal antibodies (see page 12) that are specifically targeted for a certain gene change and given through a vein. An easy way to identify the difference between the two types of therapies is to look at the names. The generic names for oral targeted drugs end in –ib (Tarceva’s generic name is erlotinib) and those of monoclonal antibodies, which are always given through an injection end in –mab (Opdivo’s generic name is nivolumab).

The two gene changes in lung cancer that have targeted therapies approved by the Food and Drug Administration (FDA) are epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK). Doctors also have the choice of using drugs approved in other cancers if your tumor has the proper gene change.

Researchers are learning more about how these gene changes cause cancer. The changes happen in different ways, which means that certain drugs may be better choices for certain changes. Talk with your doctor to make sure you understand the specific results of your tests.

DRUGS FOR EGFR (EPIDERMAL GROWTH FACTOR RECEPTOR) MUTATIONS

There are three approved drugs against this activating gene change:

- **Tarceva (erlotinib)**
- **Gilotrif (afatinib)**
- **Iressa (gefitinib)**

Currently only available through a special access program in the US, it is approved in over 90 countries and expected to be approved in the US later this year.



These drugs were approved based on specific studies presented to the FDA, but biologically are generally similar. Afatinib is the newest member to be approved and was approved based on data on patients with a particular type of change in EGFR compared to chemotherapy.

EGFR inhibitors quit working because the cancer figures out a way around the treatment, which is called “resistance” to the drug. New drugs for use after resistance to EGFR targeted therapies are expected to be approved in 2015. These include rociletinib and AZD9291 that target the T790M mutation in EGFR, which is the most common form of resistance.

DRUGS FOR ALK (ANAPLASTIC LYMPHOMA KINASE) GENE CHANGES

- **Xalkori (crizotinib):** approved for treatment of lung cancer that has spread to other parts of the body and is ALK positive
- **Zykadia (ceritinib):** approved for treatment of ALK positive lung cancer patients only after treatment with Xalkori

ALK inhibitors also quit working because the cancer figures out a way around the treatment. New drugs are showing promise against the ALK fusion and are being tested in patients whose tumors have become resistant. Examples include brigatinib and alectinib.

There is also an approved drug called Avastin (bevacizumab) that targets VEGF to prevent blood vessel growth. This “starves” the tumor to keep it from growing. There is currently no molecular test to determine if a tumor will respond well to Avastin.

MORE ABOUT TARGETED THERAPIES

- While targeted therapies may have fewer overall side effects compared to chemotherapy, the most common side effects (rash and diarrhea) may be severe. Talk with your treatment team about how you might manage them. Other side effects may include vision disturbances and liver function abnormalities, fatigue, nausea, heart and lung problems.
- Patients have a 60-80% chance of responding to an oral targeted therapy compared to a 20-30% chance with chemotherapy. The duration of response is also 2-3 times longer with these treatments. Talk to your doctor about what you might expect from your therapy and monitor how it is working. If your therapy stops working (develops “resistance”) there are new drugs being approved for these “resistant” tumors, so these may be another option for you.
- Targeted therapies cost more than most chemotherapy. The companies that make targeted drugs have programs to help you access their medications so if you need help paying for them, do not hesitate to reach out. We can direct you to these assistance programs (HelpLine at 1-800-298-2436).

IMMUNOTHERAPY

Immunotherapy treatment helps the body's own immune system fight cancer.

The body's immune system fights off infection and other foreign invaders that can make us sick. Without help, the immune system does not work well against cancer for several reasons. Cancer develops when normal cells go awry so the immune system may not see the cancer as a foreign invader. Cancer cells can fool the immune system so it can not work against the cancer properly. Also, the immune system may not be strong enough to fight the cancer.

Immunotherapy, also called immuno-oncology, is a way of increasing the body's natural defenses to target and attack the cancer and to make the immune system work better against the cancer. Many types of immunotherapies are being tested to treat lung cancer, including monoclonal antibodies, adoptive T-cell transfer, checkpoint inhibitors and vaccines.

MONOCLONAL ANTIBODIES

Antibodies are proteins produced in blood to fight toxins or foreign substances in the body. Monoclonal antibodies (mAbs) are manmade in a laboratory and are designed to attack a specific target on or around the cancer cells. mAbs can be used alone or with other drugs to target defects in the cancer cells or to make the cancer cells more receptive to the body's immune system. They can also carry other drugs or substances directly to the cancer (called antibody-drug conjugates).

ADAPTIVE T-CELL TRANSFER

T-cells are a type of white blood cell that moves through the body looking for abnormal cells and infections and attacking them. For this type of therapy, T-cells in the blood are removed and changed to make them more effective against the tumors. They are then replicated and put back into the patient to improve the immune system's anti-cancer response. Clinical trials of adaptive T-cell transfer are ongoing, but this method is not yet FDA-approved.

CHECKPOINT INHIBITORS

“Checkpoints” prevent the immune system from attacking normal cells in the body. Cancer cells can fool the checkpoints so the cancer can continue to grow without being slowed down or stopped. Treatments called checkpoint inhibitors work to fix the problem at the checkpoint so that the immune system works against the cancer.

Programmed death 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) are receptors on immune cells that are checkpoints. Cancer cells can make proteins, such as programmed death-ligand 1 (PD-L1), that attach to these receptors on the immune system’s fighter T-cells to keep them “off”. New therapies work to block either the receptor or the protein to keep the immune cells “on” so they fight the cancer.

Some newly approved drugs and drugs in late-stage clinical trials (all currently approved for use in patients with a form of skin cancer called melanoma) are checkpoint inhibitors, including:

- Opdivo (nivolumab), works on the PD-1 pathway, and has FDA approval for squamous cell lung cancer after failure of platinum-based chemotherapy; also being studied in other types of lung cancer.
- Keytruda (pembrolizumab) works on the PD-1 pathway and is expected to gain approval for lung cancer soon.
- Yervoy (ipilimumab) targets the CTLA-4 checkpoint.

Additional drugs such as MPDL3280A (targeting PD-L1) and tremelimumab (targeting CTLA-4) are also being tested. Combining drugs that target the PD-1/PD-L1 and CTLA-4 checkpoints may be especially effective and research is ongoing to test this approach.

VACCINES

There are two types of cancer vaccines: therapeutic vaccines, which can treat cancer and prophylactic vaccines, which can prevent cancer.

Therapeutic vaccines being studied to treat lung cancer are based on the same concept as the flu shot. A small amount of a foreign protein (antigen) is injected into the body. For cancer, this can be a cancer-associated protein or an actual sample of the cancer. The goal of the vaccine is to teach the immune system what to attack to efficiently fight the cancer. Cimavax is an example of a therapeutic vaccine that is being studied in lung cancer.

Prophylactic vaccines have yet to show they are effective in lung cancer.



MORE ABOUT IMMUNOTHERAPY

- Immunotherapy is given through a vein like chemotherapy but other methods like injections or bone marrow transplants may be used as well.
- Response to an immunotherapy may be different from that of chemotherapy or targeted therapies. With immunotherapy the cancer may seem to grow initially, even if the treatment is working.
- Some immunotherapies have been or are about to be approved to treat lung cancer, but many approaches are only available through clinical trials.
- Side effects from immunotherapy may include flu-like symptoms, rashes, diarrhea and problems with the lungs, liver, kidneys or hormone-producing glands such as thyroid or the pituitary. These side effects are caused by the increased activity of the immune system. Close monitoring is necessary for early detection and successful management of these side effects.

KNOW YOUR OPTIONS

Innovative approaches to better understand and treat lung cancer are being tested and put into practice more quickly than ever before. Knowing your treatment options is important so you can be an informed and empowered member of your team. Talk with your doctor to see if one of these new treatments is right for you. To see if you qualify for a research study, call our Clinical Trial Matching Service at 1-800-698-0931.

WHERE CAN I GO FOR MORE INFORMATION?

For more information about lung cancer and current treatments, to discuss support options or for referral to other resources, please contact us:

HELPLINE | 1-800-298-2436

**CLINICAL TRIAL
MATCHING SERVICE** | 1-800-698-0931

WEBSITE | lungcanceralliance.org

E-MAIL | support@lungcanceralliance.org

MAIL | 1700 K Street, Suite 660, Washington, DC 20006

WHAT WE DO

- Offer personalized support, information and referral services at no cost through a team of trained, dedicated staff members to help patients, their loved ones and those at risk.
- Advocate for increased lung cancer research funding and equitable access, coverage and reimbursement for screening, treatment, diagnostics and testing.
- Conduct nationwide education campaigns about the disease, risk and early detection.



LUNG CANCER ALLIANCE

SAVING LIVES AND ADVANCING RESEARCH BY
EMPOWERING THOSE LIVING WITH AND AT RISK
FOR LUNG CANCER



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