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What you need to know about...

targeted therapy






LUNGEVITY
Transforming Lung Cancer

foreword

About LUNGevity

LUNGevity is the nation's premier lung cancer-focused nonprofit, changing outcomes for people with lung cancer through research, education, and support.

About the LUNGevity PATIENT EDUCATION SERIES

LUNGevity has developed a comprehensive series of materials for lung cancer patients and their caregivers, focused on understanding how lung cancer develops, how it can be diagnosed, and treatment options. Whether you or someone you care about has been diagnosed with lung cancer, or is concerned about lung cancer risk, we have resources to help you.

The medical experts and lung cancer survivors who provided their valuable expertise and experience in developing these materials all share the belief that well-informed patients make their own best advocates.

In addition to this and other booklets in the LUNGevity patient education series, information and resources can be found on LUNGevity's website at www.LUNGevity.org.

This patient education booklet was produced through a charitable donation from:

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introduction

Targeted therapy is a type of treatment that uses drugs to attack cancer cells directly, including the cells of some kinds of lung cancers. As scientists have learned about driver mutations and cell surface proteins that cause cancer, they have been able to develop drugs that act to prevent the cancer cells from growing and dividing uncontrollably.

This booklet will help you:

- Learn about the mutations and cell surface proteins that can cause lung cancer
- Find out how lung cancer is tested for these mutations and proteins
- Learn what targeted therapy options are currently available
- Understand whether targeted therapy might be a good treatment option for you

YOU'LL FIND A GLOSSARY TOWARD THE END OF THIS BOOKLET.
Words included in the glossary appear **blue** the first time that they are used.

01 driver mutations and overexpressed cell surface proteins

What are driver mutations and overexpressed cell surface proteins?

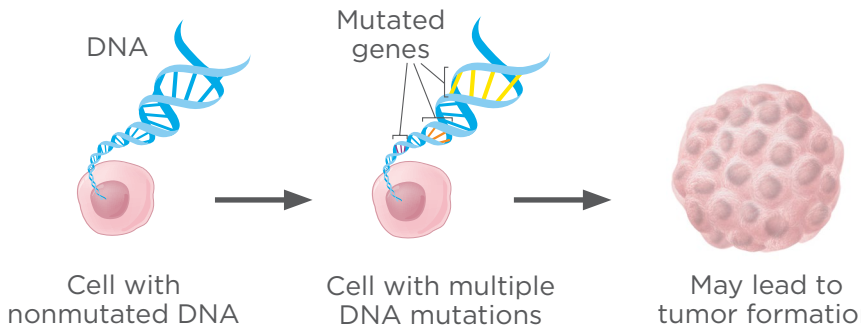
Driver mutations and **overexpressed** cell surface proteins are lung cancer **biomarkers**, molecular indicators that a particular type of lung cancer is present. This presence determines whether any of a number of **targeted therapies** may be right for patients as part of their treatment plan.

Driver mutations

All organs and tissues in our body are made up of cells, and each of these cells contains thousands of **genes**. Genes are made up of **DNA**, material that carries a specific code that is used ultimately to make **proteins** that have specific functions in cells. It is essential for each gene to have the correct DNA code, or instructions, for making its

protein. When the DNA is correct, the protein is able to perform the correct function.[1]

MUTATION



When a gene has an error in its DNA code, it is said to be mutated. **Mutations** occur often, and normally the body can correct them. However, depending on where the mutation occurs in a gene, the mutation may become part of the cell's blueprint. Over time, an accumulation of many mutations in different genes can result in the formation of a **tumor**.[2] Mutations that cause cancer are called driver mutations.

Mutations can be:

- **Acquired (also called somatic):** Present only in the tumor and not passed on to children
- **Inherited (also called germline):** Present in all cells of the body and passed on to children

Virtually all of the mutations that occur and inform treatment decisions in **lung cancer** are acquired. Inherited mutations are still being researched in lung cancer.[3]

In this booklet, we are only discussing acquired mutations.

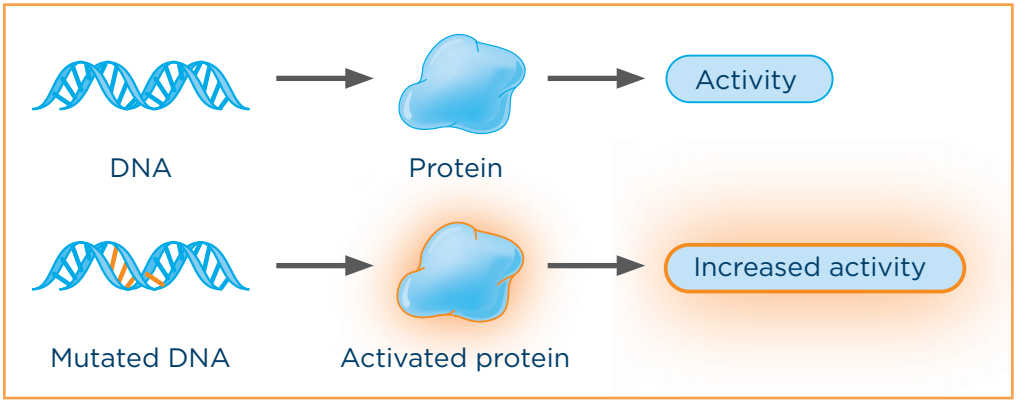
What are the different types of driver mutations?

Several types of driver mutations cause cancer. Some of these include the following:

Activating mutation

An **activating mutation** is a change in the DNA sequence that can cause changes in the protein made by the gene so that it is always active. This may lead to uncontrolled cell growth.[4]

ACTIVATING MUTATION

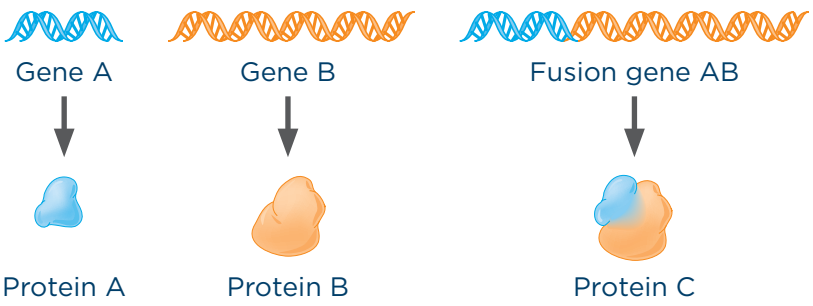


An example of an activating mutation in **lung adenocarcinoma**, a type of **non-small cell lung cancer (NSCLC)**, is the V600E mutation in the BRAF gene.[5]

Fusion

Fusion, or rearrangement, occurs when a part of one gene fuses with, or attaches to, a part of another gene. The fused gene then produces a unique protein that promotes abnormal, unchecked cell growth.[4] The gene rearrangement may also be referred to as a translocation.

FUSION PROTEIN

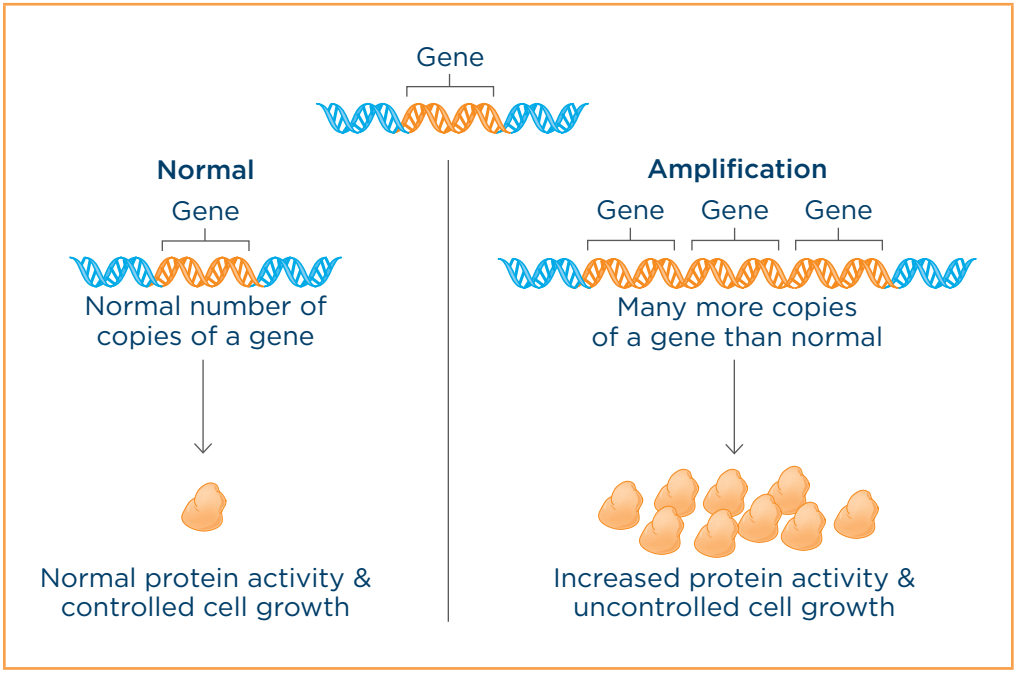


Examples of fusion genes in lung adenocarcinoma include EML4-ALK and CD74-ROS1.[6]

Amplification

Amplification means that there are many more copies of a gene than normal. This causes protein overexpression and leads to increased protein activity and uncontrolled cell growth.[7]

AMPLIFICATION

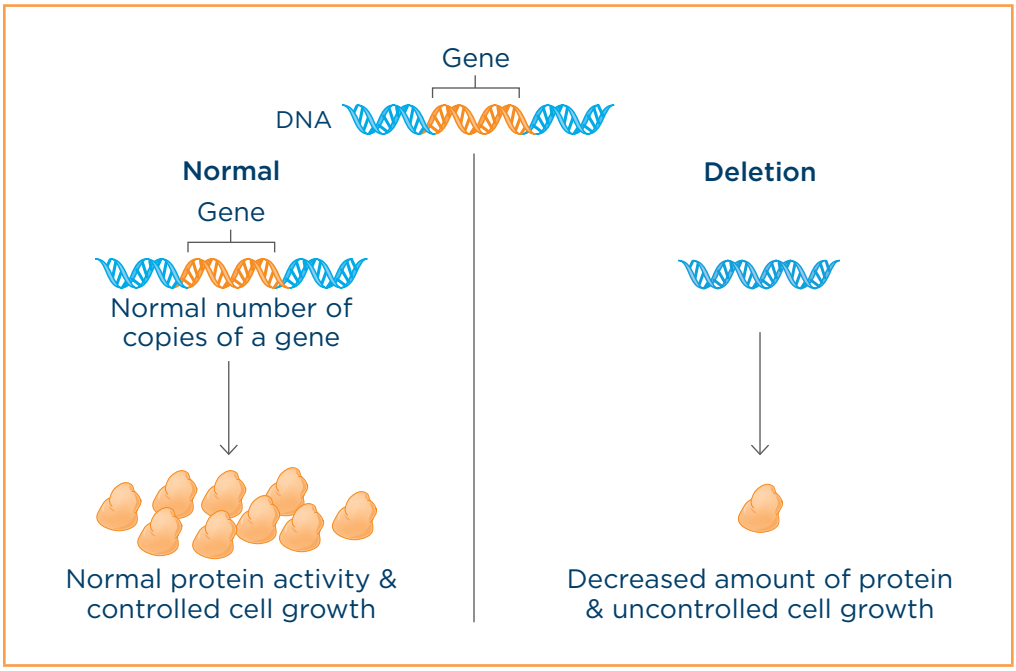


Examples of genes that can be amplified in lung adenocarcinoma include HER2 (ERBB2) and MET.[8]

Deletion

Deletion means that part of or the entire gene is missing in the cancer cells. The deletion then leads to reduced levels of normal protein being produced by the cancer cells and uncontrolled cell growth.[5]

DELETION



Examples of deleted genes in **small cell lung cancer (SCLC)** include TP53 and RB1.[7]

Driver mutations in lung cancers

Lung cancer describes many different types of cancer that start in the lung or related structures. There are two different ways of describing what kind of lung cancer a person has:

- **Biomarker profile** (also called molecular profile, **genomic** profile, or signature profile): The genomic characteristics, as well as any other unique biomarkers, found in a person's cancer
- **Histology**: What the cells look like under a microscope; histological types include NSCLC and SCLC. Subtypes of NSCLC include lung adenocarcinoma, **squamous cell lung cancer**, **large cell lung cancer**, and some rarer types

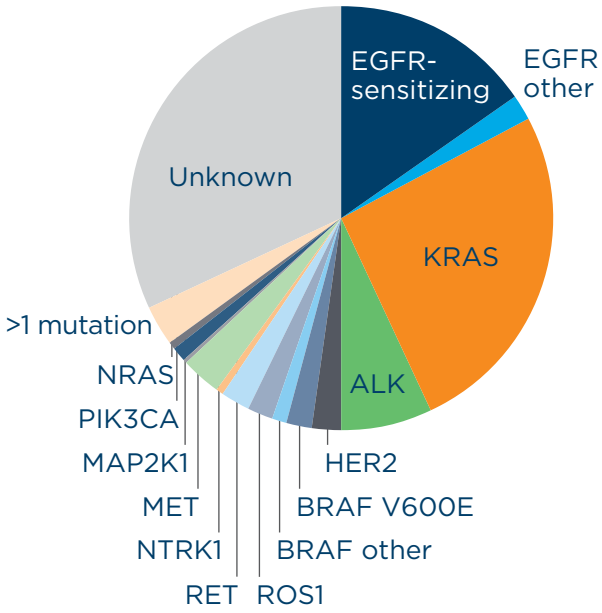
A person's lung cancer may or may not have one of the many known driver mutations. So far, scientists have identified more than 20 different driver mutations that can be found in NSCLC and SCLC, and they are continuing to look for more.[8]

These driver mutations can be identified through **biomarker testing**. This testing is typically performed on a piece of tumor tissue taken during a **biopsy** but, in some cases, on a blood sample. The presence of a driver mutation may determine whether a patient can be prescribed one of the targeted therapies approved by the **U.S. Food and Drug Administration (FDA)** and/or is potentially eligible for a **clinical trial**. Biomarker testing is discussed in more detail in a later chapter of this booklet.

Right now, scientists have the most information about the driver mutations in lung adenocarcinoma.[8]

In patients with lung adenocarcinoma, the driver mutations that currently have targeted therapies approved by the FDA include ALK, BRAF V600E, EGFR, HER2 (ERBB2), KRAS G12C, MET exon 14 skipping, NRG1, NTRK, RET, and ROS1.[9,10]

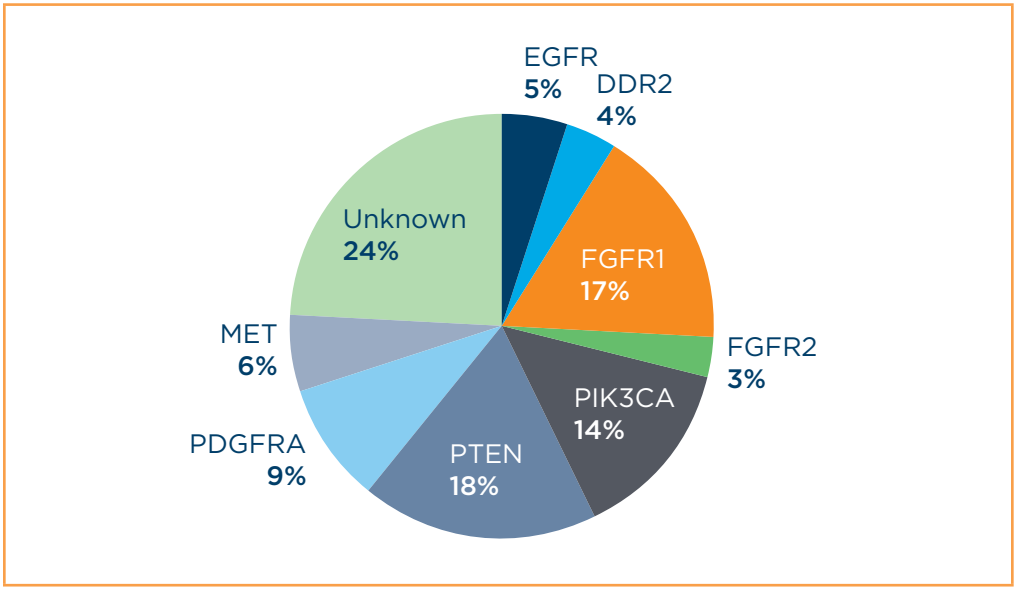
DRIVER MUTATIONS IN LUNG ADENOCARCINOMA



Driver mutations in lung adenocarcinoma	
ALK fusion	7%
BRAF other	1%
BRAF V600E	2%
EGFR other	2%
EGFR-sensitizing	15%
HER2 (ERBB2)	2%
KRAS	25%
MAP2K1	0–5%
MET splice	3%
NRAS	0–5%
NRG1	<1%
NTRK	0–5%
PIK3CA	1%
RET fusion	2%
ROS1 fusion	2%
>1 mutation	3%
Unknown	31%

Scientists are also making progress in understanding and targeting mutations in squamous cell lung cancer. Driver mutations unique to squamous cell lung cancer have not yet been identified; those that more commonly occur in lung adenocarcinoma, such as EGFR mutations or MET exon 14 skipping mutations, may also occur in squamous cell lung cancer.[7]

DRIVER MUTATIONS IN SQUAMOUS CELL LUNG CANCER



Driver mutations in SCLC and other types of lung cancer are also being studied. However, there are as of yet no targeted therapy drugs that are FDA approved for them. This may change, so patients should check with their healthcare team.[8]

Overexpressed cell surface proteins

Normal cell surface proteins are found on the outside of cells, where they have an important role in determining how the cell works, including helping to control its growth.[13] Cancer cells, however, produce abnormally large amounts of these proteins. Too much protein makes cancer cells grow quickly and spread to other parts of the body.

There are two overexpressed cell surface proteins currently seen in lung cancer that can be treated by targeted therapies. These are as follows:

- HER2: May sometimes be referred to as ERBB2. Note that changes in the HER (ERBB2) gene can also occur; these are driver mutations
- c-MET: Also known as MET protein and hepatocyte growth factor receptor. Note that this is different from the MET exon 14 skipping driver mutation, which has a different treatment

02 targeted therapy

What is targeted therapy?

Targeted therapy is a type of cancer treatment that identifies and attacks specific parts of cancer cells and the signals that proteins send to cancer cells that cause them to grow and divide uncontrollably.[14] Targeted therapies are precise; they prevent the growth and spread of cancer cells only. They do not harm the body's normal, healthy cells.

Because each targeted therapy works to control a specific driver mutation or overexpressed cell surface protein, a patient may be treated with that targeted therapy only if they have the mutation or protein for which the targeted therapy is intended.

Targeted therapies are approved primarily for patients whose lung cancer is **locally advanced** or **metastatic**, that is, when the cancer has spread from its original site to other places in the body.

Targeted therapies are sometimes also called:

- Biomarker-driven therapies
- Precision medicines
- Molecularly targeted drugs
- Molecularly targeted therapies

Targeted therapies work differently from the other three types of lung cancer drug treatments. To summarize the differences[14]:

- **Targeted therapy:** Blocks the cancer cells' growth and division; leaves healthy cells alone
- **Standard chemotherapy:** Attacks the cancer cells directly but also attacks healthy cells
- **Immunotherapy:** Stimulates the body's immune system to attack the cancer cells
- **Angiogenesis inhibitor:** Stops the formation of new blood vessels to cut off the tumor's blood supply

In addition, targeted therapies are administered orally (typically by pill once or twice daily), while other drug treatments are most likely to be administered **intravenously**.

A targeted therapy is given to a patient until **disease progression**—where the lung cancer continues to grow and spread—or the side effects of the drug become intolerable.

Kinase inhibitors

Kinases are specific proteins that act as **enzymes** to control cell functions, including **cell signaling**, cell growth, and cell division.[14] There are different types of kinases. The proteins encoded by the ALK, EGFR, HER2 (ERBB2), MET, NTRK, RET, and ROS1 genes are all examples of a type of kinase called a **tyrosine kinase**, while the BRAF gene encodes a different type. If a gene has a driver mutation, the kinases can signal the cancer cell to grow and divide.[14]

Most targeted therapy drugs that have been approved so far by the FDA for the treatment of driver mutations in NSCLC are kinase inhibitors, which block cell functions and keep the cancer from

growing and dividing. Except for the BRAF V600E combination treatment, all of the inhibitors are **tyrosine kinase inhibitors (TKIs)**.

Antibody-drug conjugates

The targeted therapy drug that has been approved so far by the FDA for the treatment of cell surface proteins in NSCLC is an **antibody-drug conjugate (ADC)**, which binds to proteins on the cancer cell and blocks their function. In the case of the overexpressed cell surface protein HER2 (ERBB2), however, both an ADC and a kinase inhibitor may be prescribed.

Other targeted therapies

There are also FDA-approved targeted therapies other than kinase inhibitors and ADCs for the treatment of lung cancer, including those for KRAS- and NRG1-positive lung cancers.

Where do targeted therapies fit into a treatment plan?

Sometimes, treatment with a targeted therapy will be the only treatment a patient receives. However, a targeted therapy may also be used before, together with, or after other treatments; treatment will depend on when the driver mutation or overexpressed cell surface protein was discovered, the patient's response to treatment, and other individual factors that the healthcare team considers. The other treatments are most likely to include another targeted therapy, chemotherapy, chemotherapy-immunotherapy, an angiogenesis inhibitor, and/or **radiation therapy**. In addition, in those cases

where a targeted therapy is appropriate and there is more than one approved therapy for a particular driver mutation, the healthcare team again considers factors specific to the patient before prescribing a particular treatment.

FDA-approved targeted therapies

Genes with driver mutations or overexpressed cell surface proteins in NSCLC for which there are currently FDA-approved targeted therapies are as follows:

- ALK
- BRAF V600E
- c-MET
- EGFR
- HER2 (ERBB2) [driver mutation]
- HER2 (ERBB2) [overexpressed cell protein]
- KRAS G12C
- MET exon 14 skipping
- NRG1
- NTRK
- RET
- ROS1

In addition, clinical trials are currently studying promising drugs to target these and other driver mutations and cell surface proteins. Visit www.LUNGevity.org for a complete list of approved therapies.

ALK driver mutation

An ALK (anaplastic lymphoma kinase) rearrangement is a fusion between two genes: ALK and, most commonly, echinoderm microtubule-associated protein-like 4 (EML4). The fusion of these two genes produces an abnormal ALK protein that causes cancer cells to grow and spread.

About 5% of patients with NSCLC in Western populations have tumors with an ALK mutation. A similar frequency has been reported in Asian populations. An ALK fusion is more common among younger patients (median age at diagnosis is 52 years), nonsmokers or light smokers, and those with lung adenocarcinomas. It has rarely been found in patients with squamous cell lung cancer.[4]

What are the approved ALK TKIs?

There are currently six FDA-approved ALK TKIs:[16-21]

- Alectinib (Alecensa®): Approved for adult patients with metastatic ALK-positive NSCLC, as detected by an FDA-approved test. Also approved for the **adjuvant** treatment in adult patients following tumor resection of ALK-positive NSCLC (tumors ≥4 cm or node positive), as detected by an FDA-approved test
- Brigatinib (Alunbrig®): Approved for patients with metastatic ALK-positive NSCLC, as detected by an FDA-approved test
- Ceritinib (Zykadia®): Approved for patients with metastatic ALK-positive NSCLC, as detected by an FDA-approved test
- Crizotinib (Xalkori®): Approved for patients with metastatic ALK-positive NSCLC, as detected by an FDA-approved test
- Ensartinib (Ensacove™): Approved for adult patients with locally advanced or metastatic ALK-positive NSCLC who have not previously received an ALK inhibitor
- Lorlatinib (Lorbrena®): Approved for adult patients with metastatic ALK-positive NSCLC, as detected by an FDA-approved test

BRAF V600E driver mutation

Mutations in the BRAF V600E gene occur in 1%–3% of lung adenocarcinoma patients. Most of these patients are current or former smokers.[23]

What are the approved BRAF V600E combination inhibitors?

There are currently two FDA-approved combination BRAF V600E targeted treatments:[24,25]

- Combination treatment of dabrafenib (Tafinlar®) with a MEK kinase inhibitor, trametinib (Mekinist®): Approved for first- and subsequent-line treatment for patients with metastatic BRAF V600E-positive NSCLC, as detected by an FDA-approved test
- Combination treatment of encorafenib (Braftovi®) with binimetinib (Mektovi®): Approved for the first- and subsequent-line treatment for adult patients with metastatic BRAF V600E-positive NSCLC, as detected by an FDA-approved test

c-MET overexpressed cell surface protein

Approximately 25% of patients with NSCLC show overexpression of the c-MET cell surface protein.

What is the approved c-MET ADC?

There is currently one FDA-approved c-MET ADC:[26]

- Telisotuzumab vedotin-tllv (Emrelis™): Approved for the treatment of adult patients with locally advanced or metastatic nonsquamous NSCLC with high c-MET protein overexpression (≥50% of tumor cells with strong [3+] staining), as determined by an FDA-approved test. Patients should have received a prior systemic therapy

EGFR driver mutation

Approximately 15% of patients with NSCLC in the U.S. and 35% of patients from East Asia have tumors with an EGFR (epidermal growth factor receptor) driver mutation. Regardless of the patient's ethnicity, EGFR driver mutations are more often found in tumors of females and nonsmokers. Most commonly, these patients have lung adenocarcinomas.[9,27]

What are the approved EGFR targeted therapies?

There are currently a number of FDA-approved EGFR targeted therapies:[28-31,33-37]

- Afatinib (Gilotrif®): Approved for **first-line treatment** of patients with metastatic NSCLC whose tumors have EGFR nonresistant mutations, as detected by an FDA-approved test (the most common of these are the exon 19 deletions and the exon 21 [L858R] substitution mutations)
- Amivantamab (Rybrevant®):
  - Approved for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy
  - Approved in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test
  - Approved in combination with lazertinib for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, as detected by an FDA-approved test
  - Approved in combination with carboplatin and pemetrexed for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, whose disease has progressed on or after treatment with an EGFR TKI
- Dacomitinib (Vizimpro®): Approved for first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, as detected by an FDA-approved test
- Datopotamab deruxtecan-dlnk (Datroway®): Approved for the treatment of adults with locally advanced or metastatic EGFR-

positive NSCLC who have received prior EGFR-directed therapy and platinum-based chemotherapy

- Erlotinib: Approved for the treatment of patients with EGFR-positive metastatic NSCLC. This includes patients whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, as detected by an FDA-approved test, who are receiving first-line or **maintenance treatment**, or second- or greater-line treatment after progression following at least one prior chemotherapy regimen. Erlotinib is also approved in combination with ramucirumab (Cyramza®), an angiogenesis inhibitor, for the first-line treatment of metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations

  Note: Only generic versions of erlotinib are now prescribed in the U.S. Patients should speak with their healthcare team if they have any questions about what this means for their treatment.
- Gefitinib (Iressa®): Approved for the first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, as detected by an FDA-approved test
- Mobocertinib (Exkivity™): Originally approved for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, and who have received prior platinum-based chemotherapy

  Note: Following discussions with the FDA, Exkivity™ has been officially withdrawn from the U.S. market Patients may be able to maintain access through an established compassionate-use program. For more information, please visit exkivity-update.com
- Osimertinib (Tagrisso®):
  - Approved for first-line treatment of adult patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, as detected by an FDA-approved test

  - Approved for treatment of adult patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy
  - Approved for adjuvant treatment of adult patients with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, as detected by an FDA-approved test, after tumor resection
  - Approved in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with locally advanced or metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, as detected by an FDA-approved test
- Sunvozertinib (Zegfrovy™): Approved for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy

HER2 (ERBB2) driver mutation

Approximately 3% of patients with NSCLC have the HER2 (ERBB2) driver mutation. This mutation is seen more often in patients who have lung adenocarcinoma, are female, and are nonsmokers.[38,40,74]

What are the approved HER2 (ERBB2) treatments?

There are currently three FDA-approved HER2 (ERBB2) treatments:[39, 41, 74]

- Sevabertinib (Hyrnuo®): Approved for the treatment of adult patients with locally advanced or metastatic nonsquamous NSCLC whose tumors have HER2 (ERBB2) tyrosine kinase domain (TKD) activating mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy

- Trastuzumab deruxtecan (Enhertu®): Approved for the treatment of adult patients with unresectable or metastatic HER2-positive NSCLC who have received one prior systemic therapy
- Zongertinib (Hernexeos®): Approved for the treatment of adult patients with unresectable or metastatic nonsquamous NSCLC whose tumors have HER2 (ERBB2) tyrosine kinase domain (TKD) activating mutations, as detected by an FDA-approved test, and who have received prior systemic therapy

HER2 (ERBB2) overexpressed cell surface protein

Approximately 2%–30% of patients with NSCLC have overexpressed HER2 (ERBB2) cell surface protein, depending on which technique is used to determine whether there is overexpression.[38]

What is the approved HER2 (ERBB2) ADC?

There is currently one FDA-approved HER2 (ERBB2) ADC:[39]

- Trastuzumab deruxtecan (Enhertu®): Approved for the treatment of adult patients with unresectable or metastatic HER2-positive NSCLC who have received at least one prior systemic therapy

KRAS driver mutation

KRAS driver mutations are very common in NSCLC. The KRAS G12C driver mutation is found among about 11% of NSCLC patients and is most likely to be detected among current and former smokers.[71]

What are the approved KRAS-targeted therapies?

There are currently two FDA-approved KRAS-targeted therapies, both for the KRAS G12C driver mutation:[72,73]

- Adagrasib (Krazati™): Approved for the treatment of adult patients with KRAS G12C-positive locally advanced or metastatic NSCLC who have received at least one prior systemic therapy

- Sotorasib (Lumakras™): Approved for the treatment of adult patients with KRAS G12C-positive locally advanced or metastatic NSCLC who have received at least one prior systemic therapy

MET exon 14 skipping driver mutation

Approximately 3%–4% of NSCLC patients have a mutation that leads to MET (mesenchymal-epithelial transition) exon 14 skipping. There are several types of MET exon 14 skipping mutations, all of which have the same effect—the production of a MET protein that can cause cancer cells to grow and divide. Patients with MET mutation-positive lung cancers are most likely to have a history of smoking; a minority are never-smokers.[42,43]

What are the approved MET TKIs?

There are currently two FDA-approved MET TKIs:[44,45]

- Capmatinib (Tabrecta™): Approved for the treatment of adult patients with metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping, as detected by an FDA-approved test
- Tepotinib (Tepmetko®): Approved for the treatment of adult patients with metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping

NRG1 driver mutation

The NRG1 driver mutation is rare, found in only about 0.2% of lung cancer patients, most of whom have lung adenocarcinoma.[46]

What is the approved NRG1-targeted therapy?

There is currently one FDA-approved NRG1 targeted therapy:[47]

- Zenocutuzumab-zbco (Bizengri®): Approved for adults with advanced, unresectable, or metastatic NRG1-positive NSCLC with disease progression on or after prior systemic therapy

NTRK driver mutation

About 1%–4% of NSCLC patients have an NTRK (neurotrophic receptor kinase) gene fusion. NTRK fusions are more likely to be seen in patients who are light smokers or never-smokers.[48,49]

What are the approved NTRK TKIs?

There are currently three FDA-approved NTRK TKIs:[50-52]

- Entrectinib (Rozlytrek®): Approved for the treatment of adult and pediatric patients 12 years of age and older with **solid tumors** that:
  - Have an NTRK gene fusion without a known **acquired resistance** mutation,
  - Are metastatic or where surgical resection (removal) is likely to result in severe **morbidity**, *and*
  - Have progressed following treatment or have no satisfactory alternative therapy
- Larotrectinib (Vitrakvi®): Approved for the treatment of patients with NTRK solid tumors that:
  - Have an NTRK gene fusion without a known acquired resistance mutation,
  - Are metastatic or where surgical resection is likely to result in severe morbidity, *and*
  - Have progressed following treatment or have no satisfactory alternative therapy

- Repotrectinib (Augtyro®): Approved for adults and pediatric patients 12 years and older with solid tumors that:
  - Are NTRK positive,
  - Are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and
  - Have progressed following treatment or have no satisfactory alternative therapy

RET driver mutation

Approximately 1% of NSCLC patients have a RET (rearranged during transfection) fusion. RET patients have been seen to be more likely to have lung adenocarcinoma and be nonsmokers.[53,54]

What are the approved RET TKIs?

There are currently two FDA-approved RET TKIs:[55,56]

- Pralsetinib (Gavreto™): Approved for the treatment of adult patients with metastatic RET fusion-positive NSCLC, as detected by an FDA-approved test
- Selpercatinib (Retevmo®): Approved for the treatment of adult patients with metastatic RET fusion-positive NSCLC

ROS1 driver mutation

A ROS1 (receptor tyrosine kinase 1) rearrangement is a fusion between two genes, ROS1 and another gene. As with ALK, the fusion of the two genes produces an overexpressed protein that causes cancer cells to grow and spread.

About 1%–2% of patients with NSCLC in the U.S. and about 2%–3% in East Asia have tumors with a ROS1 mutation. ROS1-positive tumors are more commonly found among younger patients (median age at diagnosis is 50 years), females, never-smokers, and patients with lung adenocarcinomas.[9,57]

What are the approved ROS1 TKIs?

There are currently four FDA-approved ROS1 TKIs:[19,50,52,58]

- Crizotinib (Xalkori®): Approved for patients with metastatic NSCLC whose tumors are ROS1 positive, as detected by an FDA-approved test
- Entrectinib (Rozlytrek®): Approved for adult patients with metastatic NSCLC whose tumors are ROS1-positive
- Repotrectinib (Augtyro®): Approved for adult patients with locally advanced or metastatic ROS1-positive NSCLC
- Taletrectinib (Ibtrozi™): Approved for the treatment of locally advanced and metastatic ROS1-positive NSCLC patients

Management of targeted therapy side effects

Targeted therapies can cause side effects. However, just because a side effect is possible does not mean that a patient will experience it. Before beginning treatment with a targeted therapy, the patient should discuss with the healthcare team what side effects, both common and rare, might occur and how to prevent or ease them.

The patient should speak with the healthcare team if and when new side effects begin, as treating them early on is often more effective than trying to treat them once they have already become severe.

In addition, it needs to be determined whether the symptoms are related to the treatment or not. What side effects are being experienced may impact future treatment plans. Although most side effects go away when treatment is over, some can last a long time.

Resistance to targeted therapies

The biggest challenge of targeted therapies is that a majority of patients with lung cancer who initially benefit from them eventually develop resistance. Acquired resistance can be defined as disease progression in a patient after initial benefit from a targeted therapy.[59]

With TKIs, cancer cells are adept enough to bypass roadblocks to their survival and often further mutate to overcome the effects of TKIs. Another way a tumor can become resistant to TKIs is by activating a different signaling pathway in the cell to bypass the pathway that the TKI uses to kill the cells. In a small number of cases among EGFR patients, the lung adenocarcinoma may even transform into other histologies, such as SCLC.[59-61]

Research is underway to develop strategies to overcome resistance in tumors and to keep the TKIs effective against cancer for longer periods of time. Approaches include the following:[62,63]

- Simultaneously prescribing multiple TKIs, in case a different mutation in the cell has been activated
- Developing the next generation of inhibitors that will inhibit not only the activity of the mutated gene but also the mutant form it could change into
- Prescribing other combination treatments (e.g., a TKI in combination with chemotherapy, immunotherapy, or radiation therapy)

In the meantime, if a patient's cancer has progressed after treatment with a TKI, a decision needs to be made about the next treatment option. A patient's healthcare team may recommend that a biopsy be done on one of the tumors that is growing to determine whether there is a new mutation but will consider all of the treatment options mentioned above and make a determination based on the patient's particular situation.

Likewise, patents can develop resistance to ADCs. There are multiple reasons for this. Ongoing research on ways to overcome resistance includes developing new ADCs and combining ADCs with other drugs.[64]

Finding a clinical trial that might be right for you

If you are considering participating in a clinical trial, start by asking your healthcare team whether there is one that might be a good match in your geographic area. In addition, there are several resources to help you find one that may be a good match.

People are often surprised that a clinical trial is not the last option one turns to when standard treatments have failed. Today, clinical trials may present the FIRST line of treatment.

RESOURCES TO HELP YOU NAVIGATE YOUR CLINICAL TRIALS SEARCH:

- **LUNGevity Clinical Trial Matching Service** (https://connect.careboxhealth.com/en-US/partner/lcctal)
  - Find available clinical trials by type of lung cancer and geographic location
  - Also find information and links to the medical centers at which these clinical trials are taking place

Continued on page 28

RESOURCES TO HELP YOU NAVIGATE YOUR CLINICAL TRIALS SEARCH:

Continued from page 27

- **National Cancer Institute (NCI):** www.clinicaltrials.gov
- **My Cancer Genome:** www.mycancergenome.org
  - My Cancer Genome gives up-to-date information on what mutations make cancers grow and related treatment options, including available clinical trials
- **Lung-MAP:** www.lung-map.org
  - For patients with NSCLC, Lung-MAP is a collaboration of many research sites across the country. Lung-MAP uses a unique approach to match patients to one of several drugs being developed

QUESTIONS TO ASK YOUR HEALTHCARE TEAM ABOUT TARGETED THERAPY:

- Why do you recommend a targeted therapy for me?
- What driver mutation do I have?
- Do I have an overexpressed cell surface protein?
- What kind of targeted therapy will I get?
- Will targeted therapy be my only treatment, or will it be combined with another treatment?
- How often will I take this therapy, and for how long?
- How and when will I know if the treatment is working?
- How often do I need to be seen between treatments for a physical exam and/or lab work?
- Are there any tests or procedures I will need during the treatment?
- What side effects can I expect?
- What can I do to manage these side effects?
- How will this treatment affect my daily life? Will I be able to work, exercise, and perform my usual activities?
- What tests will I need after treatment is completed?
- Are there any long-term health issues I should expect from treatment with targeted therapy?
- How much will my treatment cost?

03 biomarker testing

To find out whether targeted therapy is appropriate for a person who has been diagnosed with lung cancer, that person's tumor tissue or blood will be tested for the presence of driver mutations and overexpressed cell surface proteins. Patients who have a mutation or protein that a specific FDA-approved therapy targets are candidates for that treatment. The process of testing for a mutation in a tumor is called biomarker testing (also known as mutation, genomic, or molecular testing).

Biomarker testing should be an ongoing part of the discussions with a patient's healthcare team. Any decision to test for biomarkers should be made together and will depend on a number of factors, including the type and **stage** of lung cancer, the current treatment plan, overall health, and patient preferences.

While biomarker testing may also be used to determine whether an immunotherapy drug is an appropriate treatment, in this booklet, biomarker testing is discussed only in the context of whether a targeted therapy is an appropriate treatment.

For a more comprehensive look at biomarker testing, download LUNGevity's Biomarker Testing booklet at www.LUNGevity.org.

How is biomarker testing performed?

Currently, tissue biopsies are the only way to confirm a diagnosis of lung cancer; they are also the standard way to detect driver mutations and overexpressed cell surface proteins. However, under certain circumstances, a **liquid biopsy**, a test done on a sample of blood, may be used to detect driver mutations.

Tissue biopsies

There are a number of tissue collection techniques, including **bronchoscopy**, **endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)**, **transthoracic needle biopsy (TTNB)**, **thoracoscopy**, and **thoracentesis**. Regardless of how the tissue is collected, a patient should confirm with their healthcare team before the tissue is removed that, if possible, enough tissue will be collected so that all necessary biomarker tests can be performed.

After the tumor tissue is collected, it is sent to a laboratory for testing. Ideally, what is sometimes called comprehensive biomarker testing will be done. In comprehensive biomarker testing, driver mutations in multiple genes are tested for at the same time, rather than sequentially. These may include not only the ones with approved treatments but also other known driver mutations. For patients with a driver mutation with a targeted therapy, this means that treatment may start sooner. In addition, some of the driver mutations currently without approved treatments may have treatments being tested now or in the near future in clinical trials to which a patient could be matched. An advantage of comprehensive biomarker testing is that when a new mutation target is discovered, it can easily be added to the set of mutations being tested for. Comprehensive biomarker testing can be done via a process known as next-generation sequencing, or NGS.

Overexpressed cell surface proteins are detected by immunohistochemistry (also known as IHC). Typically, a pathologist uses special dyes or stains that color cell surface proteins so that they can be seen under a microscope.

Liquid biopsies

Liquid biopsies have the advantage of requiring only a simple blood sample (which contains DNA from the tumor) drawn from a vein rather than sampling of tissue, which comes with some discomfort and risk. Test results come back sooner as well, and the same type of testing for multiple driver mutations done on tissue samples can be done on the blood samples. In several studies, it has been shown that liquid biopsies can be very effective in detecting the driver mutations that have targeted therapies to treat them.[65-69]

At this time, liquid biopsies may help a patient's healthcare team[66]:

- Determine if a targetable mutation is present at the time of diagnosis and decide if targeted therapies are appropriate
- Check if the patient's cancer has become resistant to a targeted therapy and decide the next treatment option
- Monitor the patient's response to a particular targeted therapy

If a liquid biopsy test is negative, results from the tissue biopsy are used to make treatment decisions at diagnosis. If a liquid biopsy is negative as the cancer spreads or comes back, a tissue biopsy may be recommended. It is important to note that not all cancer cells shed DNA, so not all patients can be successfully tested via liquid biopsy.

Who should have their tumor tested, and when?

The decision to have a tumor tested and when to test it depend on a number of factors. Below are common recommendations for biomarker testing.

LUNG ADENOCARCINOMA COMMON RECOMMENDATIONS FOR BIOMARKER TESTING

Stage of lung cancer	Recommendations for biomarker testing
Stages IB, II, and III	• Testing for mutations in the EGFR and ALK genes should be conducted • Testing for the BRAF V600E, HER2 (ERBB2), KRAS, MET exon 14 skipping, NRG1, NTRK, RET, and ROS1 mutations at the time of diagnosis and surgical resection is not always recommended but may be considered. The decision should be made on an individual basis • PD-L1 immunohistochemistry should also be conducted to determine whether immunotherapy might be beneficial • HER2 (ERBB2) and c-MET immunohistochemistry may be conducted to determine whether targeted therapies may be considered
Stage IV	• Tumors should be tested for ALK, BRAF V600E, EGFR, HER2 (ERBB2), KRAS, MET exon 14 skipping, NRG1, NTRK, RET, and ROS1 at the time of diagnosis. Testing for other biomarkers may be helpful in deciding eligibility for clinical trials • PD-L1 (for immunotherapy) and HER2 (ERBB2) and c-MET (for targeted therapies) immunohistochemistry should also be conducted to determine whether immunotherapy or targeted therapy might be beneficial in the **first-line** setting

SQUAMOUS CELL LUNG CANCER COMMON RECOMMENDATIONS FOR BIOMARKER TESTING

Stage of lung cancer	Recommendations for biomarker testing
Stages I, II, and III	• Testing for mutations in the EGFR and ALK genes should be conducted • Testing for the BRAF V600E, HER2 (ERBB2), KRAS, MET exon 14 skipping, NRG1, NTRK, RET, and ROS1 mutations at the time of diagnosis and surgical resection are not always recommended but may be considered. The decision should be made on an individual basis • PD-L1 immunohistochemistry should also be conducted to determine whether immunotherapy might be beneficial
Stage IV	• Tumors should be tested for ALK, BRAF V600E, EGFR, HER2 (ERBB2), KRAS, MET exon 14 skipping, NRG1, NTRK, RET, and ROS1 at the time of diagnosis. Testing for other biomarkers may be helpful in deciding eligibility for clinical trials • PD-L1 (for immunotherapy) and HER2 (ERBB2) and c-MET (for targeted therapies) immunohistochemistry should also be conducted to determine whether immunotherapy or targeted therapy might be beneficial in the first-line setting

SMALL CELL LUNG CANCER (SCLC) COMMON RECOMMENDATIONS FOR BIOMARKER TESTING

Stage of lung cancer	Recommendations for biomarker testing
All stages	Biomarker testing can be considered for patients with extensive-stage SCLC, at the time of diagnosis or at the time of relapse—if not previously done, because this may change management. Biomarker testing may be needed for limited-stage SCLC to enroll in clinical trials

Testing to identify other possible driver mutations in the tumor may help a patient find clinical trials. These trials are testing new treatments for mutations in other types of lung cancer. Therefore, patients should consider biomarker testing for other mutations and cell surface proteins if those driver mutations and overexpressed cell proteins that already have treatment options are not found.

QUESTIONS TO ASK YOUR HEALTHCARE TEAM ABOUT BIOMARKER TESTING:

Before getting biomarker testing:

- What are you trying to find with biomarker tests?
- Have I already had any biomarker tests? Which ones?
- Who performs these tests?
- How are the tests performed?
- Are there any complications from these tests?
- How long will it take to get the test results?
- Where can I get more information about biomarker testing?
- Are there any limitations of biomarker testing?
- Will insurance pay for these tests?

After getting biomarker testing:

- What tests were done?
- What are the results of these tests?
- How will the results affect my treatment?
- The test results are negative: should I be retested?
- The test results are not clear: should I be retested?
- Are there any medications that target my type of lung cancer?
- Will I need these tests again? If so, why? When?
- Are there any clinical trials open to me based on these results?
- How can I get a copy of my report?

04 glossary[70]

Acquired resistance—A disease progression after a complete or partial response to treatment, or disease progression after six months or more of stable disease, after treatment with a targeted therapy

Activating mutation—A mutation that causes increased protein activity. This overly active protein may lead to uncontrolled cell growth

Adjuvant therapy—The additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy

Amplification—A usually massive replication of genetic material and especially of a gene or DNA sequence

Angiogenesis inhibitor—A drug or substance that keeps new blood vessels from forming. In cancer treatment, angiogenesis inhibitors may prevent the growth of new blood vessels that tumors need to grow

Antibody-drug conjugate (ADC)—A substance made up of a monoclonal antibody chemically linked to a drug. The monoclonal antibody binds to specific proteins or receptors found on certain types of cells, including cancer cells. The linked drug enters these

cells and kills them without harming other cells. Some antibody-drug conjugates are used to treat cancer. Also called ADC

Biomarker—A biological molecule found in blood, other bodily fluids, or tissue that is a sign of a normal or abnormal process, or of a condition or disease

Biomarker profile—The genomic characteristics, as well as any other unique biomarkers, found in a person's cancer. The information is used to identify and create targeted therapies that are designed to work for a specific cancer tumor profile. Also called molecular profile, genomic profile, or signature profile

Biomarker testing—A way to look for genes, proteins, and other substances that can provide information to help determine a treatment plan

Biopsy—The removal of cells or tissues for examination by a pathologist. The pathologist may study the tissue under a microscope or perform other tests on the cells or tissue

Bronchoscopy—A procedure that uses a bronchoscope to examine the inside of the trachea, bronchi, and lungs. A bronchoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue; this tissue can then be checked under a microscope for signs of disease. The bronchoscope is inserted through the nose or mouth

Cell signaling—The process by which a cell responds to substances outside the cell through signaling molecules found on the surface of and inside the cell. Most molecules that lead to cell signaling are chemical substances, such as hormones, neurotransmitters, and growth factors, that bind to a specific protein receptor (signaling molecule) on or in a cell. The signals are then passed from one molecule to another inside the cell, which results in a specific cell response, such as cell division or cell death. Cell signaling is important for cells to grow and work normally. Cells that have overexpressed signaling molecules may become cancer cells

Chemotherapy—A treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing

Clinical trial—A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called clinical research trial or study

Deletion—The absence of a section or all of a gene. Deletion results in reduced protein levels being produced by the cell

Disease progression—The continuation in the growth or spread of cancer

DNA—The molecules inside cells that carry genetic information and pass it from one generation to the next. Also called deoxyribonucleic acid

Driver mutation—Mutation that can cause cancer; see Mutation

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)—A type of bronchoscopy that uses a flexible bronchoscope fitted with an ultrasound device. The ultrasound uses high-frequency sound waves to make pictures of the insides of the body. The flexible tube is moved around to get a clear picture of the lung tissue. The picture is viewed on a computer screen to decide the optimal position for a biopsy

Enzyme—A special protein that the body produces to control its cells and carry out chemical reactions quickly. Sometimes enzymes signal cancer cells to grow

First-line treatment or therapy—The first therapy given for a disease. It is often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation. When used by itself, first-line therapy is the one accepted as the best treatment. If it doesn't cure the disease or if it causes severe side effects, other treatments

may be added or used instead. Also called induction therapy, primary therapy, or primary treatment

Fusion—A gene made by joining parts of two different genes. Once fused together, they produce an abnormal protein that promotes unchecked cell growth

Gene—The coded instructions within a cell that control how the cell grows in a systematic and precise way

Genomic—Relating to a body's genes

Histology—The study of tissues and cells under a microscope; also used to indicate what the cells look like

Immunotherapy—A type of cancer therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases. Some types of immunotherapies only target certain cells of the immune system. Others affect the immune system in a general way

Intravenous—Into or within a vein. Intravenous usually refers to a way of giving a drug or other substance through a needle or tube inserted into a vein. Also called IV

Large cell lung cancer—A type of non-small cell lung cancer (NSCLC) in which the cells are large and look overexpressed when viewed under a microscope

Liquid biopsy—A test done on a sample of blood to look for cancer cells from a tumor that are circulating in the blood or for pieces of DNA from tumor cells that are in the blood. A liquid biopsy may be used to help find cancer at an early stage. It may also be used to help plan treatment, find out how well a treatment is working, or find out if the cancer has come back. Being able to take multiple samples of blood over time may also help the healthcare team understand what kind of molecular changes are taking place in a tumor

Locally advanced—Cancer that has spread from where it started to nearby tissue or lymph nodes

Lung adenocarcinoma—One type of non-small cell lung cancer (NSCLC) that usually develops in the cells lining the lungs. It is the most common type of lung cancer seen in nonsmokers

Lung cancer—A cancer that begins in tissues of the lung, usually in the cells lining air passages

Maintenance treatment—A therapy that is given to help keep cancer from coming back after it has disappeared following the initial therapy. It may include treatment with drugs, vaccines, or antibodies that kill cancer cells, and it may be given for a long time

Metastatic—Having to do with metastasis, which is the spread of cancer from the primary site, or place where it started, to other places in the body

Morbidity—The medical problems caused by a treatment

Mutation—Any change in the gene sequence of a cell. Mutations may be caused by mistakes during cell division, or they may be caused by exposure to gene-damaging agents in the environment. Certain mutations may lead to cancer or other diseases

Non-small cell lung cancer (NSCLC)—A group of lung cancers that are named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main subtypes of NSCLC are lung adenocarcinoma, squamous cell lung cancer, and large cell lung cancer. NSCLC is the most common kind of lung cancer

Overexpression—The expression of too many copies of a protein or other substance. Overexpression of certain proteins or other substances may play a role in cancer development

Protein—A molecule made up of amino acids that is needed for the body to function properly. Proteins are the basis of body structures, such as skin and hair, and of other substances, such as enzymes, cytokines, and antibodies

Radiation therapy—The use of high-energy radiation from X-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed inside the body near cancer cells (internal radiation therapy). Also called irradiation and radiotherapy

Small cell lung cancer (SCLC)—A fast-growing cancer that forms in tissues of the lung and can spread to other parts of the body. Named small for how the cancer cells look under a microscope

Solid tumor—An abnormal mass of tissue that usually does not contain cysts or liquid areas. Solid tumors may be benign (noncancerous) or malignant (cancerous). Solid tumors include lung cancer tumors

Squamous cell lung cancer—A type of non-small cell lung cancer (NSCLC) that usually starts near a central bronchus. It begins in squamous cells, which are thin, flat cells that look like fish scales. Also called squamous cell carcinoma

Stage—The extent of a cancer in the body

Targeted therapy—A type of treatment that uses drugs to identify and attack specific types of cancer cells with less harm to normal cells. Some targeted therapies block the action of certain enzymes, proteins, or other molecules involved in the growth and spread of cancer cells

Thoracentesis—A procedure that removes fluid that may build up around a lung. A needle is inserted through the skin into the lung, and fluid is removed. The fluid is checked for cancer cells

Thoracoscopy—The examination of the inside of the chest using a thoracoscope. A thoracoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue to be checked under a microscope for signs of disease

Transthoracic needle biopsy (TTNB)—A technique to biopsy certain lung nodules and also some lymph nodes. Sometimes referred to as transthoracic needle aspiration (TTNA) or percutaneous needle biopsy. A very thin needle is inserted through the chest wall to get a tissue sample

Tumor—An abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Tumors may be benign (noncancerous) or malignant (cancerous). Also called neoplasm

Tyrosine kinase—A specific enzyme produced by the body to control cell functions, including cell signaling, growth, and division. These enzymes may be too active or found at high levels in some types of cancer cells

Tyrosine kinase inhibitor (TKI)—A type of targeted therapy that blocks the action of enzymes called tyrosine kinases in order to keep cancer cells from growing

U.S. Food and Drug Administration (FDA)—The agency in the U.S. federal government whose mission is to protect public health by making sure that food, cosmetics, and nutritional supplements are safe to use and truthfully labeled. The FDA also makes sure that drugs, medical devices, and equipment are safe and effective and that blood for transfusions and transplant tissue are safe

05 references

1. NIH National Human Genome Research Institute. Deoxyribonucleic acid (DNA) fact sheet. https://www.genome.gov/about-genomics/fact-sheets/Deoxyribonucleic-Acid-Fact-Sheet. Posted August 24, 2020. Accessed May 5, 2025.
2. American Cancer Society. How targeted therapies are used to treat cancer. https://www.cancer.org/cancer/managing-cancer/treatment-types/targeted-therapy/what-is.html. Reviewed June 29, 2021. Accessed May 10, 2025.
3. NCCN. NCCN guidelines for patients: early and locally advanced non-small cell lung cancer. Version 7.2024. National Comprehensive Center Network website. https://www.nccn.org/patients/guidelines/content/PDF/lung-early-stage-patient.pdf. Posted June 26, 2024. Accessed May 5, 2025.
4. Pao W, Ladanyi M. Detecting gene alterations in cancer. My Cancer Genome website. https://www.mycancergenome.org/content/page/detecting-gene-alterations-in-cancers. Updated May 27, 2019. Accessed May 5, 2025.
5. Loo E, Khalili P, Beuhler K, et al. BRAF V600E mutation across multiple tumor types: correlation between DNA-based sequencing and mutation-specific immunohistochemistry. *Appl Immunohistochemistry Mol Morphol*. 2018;26(10):709-713. Doi: 10.1097/PAI.0000000000000516. Accessed May 10, 2025.

6. Solomon B, Lovly C. Anaplastic lymphoma kinase (ALK) fusion oncogene positive non-small cell lung cancers. In: Lilenbaum RC, ed. *UpToDate*: UpToDate, Inc; 2021. https://www.uptodate.com/contents/anaplastic-lymphoma-kinase-alk-fusion-oncogene-positive-non-small-cell-lung-cancer/print. Updated February 10, 2021. Accessed May 10, 2025.
7. Byers LA, Rudin CM. Small cell lung cancer: where do we go from here? *Cancer.* 2015;121(5):664-672.
8. Oh D-Y, Jung K, Song J-Y, et al. Precision medicine approaches to lung adenocarcinoma with concomitant MET and HER2 amplification. *BMC Cancer*. 2017;17(1):535.
9. Hirsch FR, Suda K, Wiens J, Bunn PA, Jr. New and emerging targeted treatments in advanced non-small cell lung cancer. *Lancet*. 2016;388(10048):1012-1024.
10. Skoulidis F, Heymach J. Co-occurring genomic alterations in non-small cell lung cancer biology and therapy. *Nat Rev Cancer.* 2019;19(9):495-509.
11. —
12. —
13. Stutsman. Definition of cell surface proteins. Sciencing. https://www.sciencing.com/definition-cell-surface-proteins-6340015/. Updated August 30, 2022.
14. NCI. NCI dictionary of cancer terms. National Cancer Institute website. https://www.cancer.gov/publications/dictionaries/cancer-terms. Accessed September 20, 2025.
15. —
16. Alecensa (alectinib) capsules [package insert]. Genentech, Inc. South San Francisco, CA. https://www.gene.com/download/pdf/alecensa_prescribing.pdf. Revised April 2024. Accessed May 10, 2025.
17. Alunbrig (brigatinib) tablets [package insert]. ARIAD Pharmaceuticals, Inc. Cambridge, MA. https://www.accessdata.

fda.gov/drugsatfda_docs/label/2020/208772s008lbl.pdf. Revised May 2020. Accessed May 10, 2025.

18. Zykadia (ceritinib) capsules [package insert]. Novartis Pharmaceuticals Corporation. East Hanover, NJ. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205755 s011lbl.pdf. Revised November 2017. Accessed May 10, 2025.
19. Xalkori (crizotinib) capsules [package insert]. Pfizer, Inc. New York, NY. http://labeling.pfizer.com/showlabeling.aspx?id=676. Revised September 2023. Accessed May 10, 2025.
20. Ensacove (ensartinib) capsules [package insert]. Xcovery Holdings, Inc. Miami, FL. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218171s000lbl.pdf. Approved December 2021. Accessed May 10, 2025.
21. Lorbrena (lorlatinib) tablets [package insert]. Pfizer, Inc. New York, NY. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210868s000lbl.pdf. Revised March 2021. Accessed May 10, 2025.
22. —
23. Alvarez JG, Otterson GA. Agents to treat BRAF-mutant lung cancer. *Drugs Context*. 2019;8:212566.
24. Tafinlar (dabrafenib) + Mekinist (trametinib). Novartis website. https://www.novartis.com/us-en/sites/novartis_us/files/tafinlar.pdf. Revised April 2025. Accessed October 21, 2025.
25. Braftovi (encorafenib) capsules [package insert]. Array BioPharma, Inc. Boulder, CO. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/210496s018lbl.pdf. Updated October 2023. Accessed May 10, 2025.
26. FDA grants accelerated approval to telisotuzumab vedotin-tllv for NSCLC with high c-MET protein expression. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-telisotuzumab-vedotin-tllv-nsclc-high-c-met-protein-overexpression. Accessed July 8, 2025.

27. Zhang Y-L, Yuan J-Q, Wang K-F, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. *Oncotarget*. 2016;7(48):78985-78993.
28. Gilotrif (afatinib) tablets [package insert]. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/201292s014lbl.pdf. Revised January 2018. Accessed May 10, 2025.
29. Rybrevant (amivantamab-vmjw) injection [package insert]. Janssen Biotech, Inc. Horsham, PA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761210s004lbl.pdf. Revised September 2024. Accessed September 23, 2024.
30. Vizimpro (dacomitinib) tablets [package insert]. Pfizer, Inc. New York, NY. https://www.accessdata.fda.gov/drugsatfda_docs/label/21.10.3390/life14010064.018/211288s000lbl.pdf. Approved September 2018. Accessed May 10, 2025.
31. FDA grants accelerated approval to datopotamab deruxtecan-dlnk for EGFR-mutated non-small cell lung cancer. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-datopotamab-deruxtecan-dlnk-egfr-mutated-non-small-cell-lung-cancer. Posted June 23, 2025. Accessed June 27, 2025.
32. —
33. Iressa (gefitinib) tablets [package insert]. AstraZeneca Pharmaceuticals LP. Wilmington, DE. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206995s003lbl.pdf. Revised August 2018. Accessed May 10, 2025.
34. Lazcluse (lazertinib) tablets [package insert]. Janssen Biotech, Inc. Horsham, PA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/219008s000lbl.pdf. Approved 2024. Accessed May 10, 2025.
35. FDA approves mobocertinib for EGFR exon 20-positive mNSCLC. Targeted Oncology website. https://www.targetedonc.com/view/

fda-approves-mobocertinib-for-egfr-exon-20-positive-mnsclc. Posted September 15, 2021. Accessed May 10, 2025.

36. Tagrisso (osimertinib) tablets [package insert]. AstraZeneca Pharmaceuticals LP. Wilmington, DE. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/2021208065s030lbl.pdf. Revised February 2024. Accessed May 10, 2025.
37. FDA grants accelerated approval to sunvozertinib for metastatic non-small cell lung cancer with EGFR exon 20 insertion mutations. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-sunvozertinib-metastatic-non-small-cell-lung-cancer-egfr-exon-20. Posted July 2, 2025. Accessed July 29, 2025.
38. Loeffler E, et al. HER2 alterations in non-small cell lung cancer: biologico clinical consequences and interest in therapeutic strategies. *Life*. 2024;14(1):64. Doi: 10.3390/life14010064.
39. Enhertu (fam-trastuzumab deruxtecan-nxti) injection [package insert]. Daiichi Sankyo, Inc. Basking Ridge, NJ. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761139s021lbl.pdf. Revised August 2022. Accessed May 10, 2025.
40. NCI. NCI Cancer Currents Blog. Enhertu marks first targeted therapy for HER2-mutant lung cancer. https://www.cancer.gov/news-events/cancer-currents-blog/2022/fda-lung-cancer-enhertu-her2#:~:text=Results%20of%20the%20DESTINY%2DLung02,a%20median%20of%209%20months. Posted September 13, 2022.
41. FDA grants accelerated approval for zongertinib for non-squamous NSCLC with HER2 TKD activating mutations. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-zongertinib-non-squamous-nsclc-her2-tkd-activating-mutations. Posted August 8, 2025. Accessed August 10, 2025.
42. MET. My Cancer Genome website. https://mycancergenome.org/content/gene/met. 2017. Accessed November 17, 2020.

43. Email exchange with Mark Awad, MD, PhD. Dana-Farber Cancer Institute. June 5, 2020.
44. Tabrecta (capmatinib) tablets [package insert]. Novartis Pharmaceuticals Corporation. East Hanover, NJ. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213591s000lbl.pdf. Revised May 2020. Accessed May 10, 2025.
45. Tepmetko (tepotinib) tablets [package insert]. EMD Serono, Inc. Rockland, MA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214096s000lbl.pdf. Posted February 3, 2021. Accessed May 10, 2025.
46. Liu S. NRG1 fusions: biology to therapy. *Lung Cancer.* 2021;158:2-28. Doi: 10.1016/lungcon.2021.05.011.
47. Bizengri (zenocutuzumab-zbco) injection [package insert]. Merus NV. Cambridge, MA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761352s001lbl.pdf. Approved 2024. Accessed May 10, 2025.
48. NTRK1. My Cancer Genome website. https://mycancergenome.org/content/gene/ntrk1. Published 2017. Accessed October 21, 2025.
49. Farago AF, Taylor MS, Doebele RC, et al. Clinicopathologic features of non-small cell lung cancer harboring an NTRK1 gene fusion. *JCO Precis Oncol.* 2018;2:PO.19.00037.
50. Rozlytrek (entrectinib) capsules [package insert]. Genentech USA, Inc. South San Francisco, CA. https://www.gene.com/download/pdf/rozlytrek_prescribing.pdf. Revised October 2023. Accessed May 10, 2025.
51. Vitrakvi (larotrectinib) capsules [package insert]. Loxo Oncology, Inc. Stamford, CT. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211710s000lbl.pdf. Revised November 2018. Accessed May 10, 2025.
52. Augtyro (repotrectinib) capsules [package insert]. Bristol-Myers Squibb. Princeton, NJ. https://www.accessdata.fda.gov/

drugsatfda_docs/label/2024/218213s001lbl.pdf. Revised June 2024. Accessed July 29, 2025.

53. RET. My Cancer Genome website. https://mycancergenome.org/content/gene/ret. Published 2017. Accessed November 17, 2020.
54. Lin C, Wang S, Xie W, et al. The RET fusion gene and its correlation with demographic and clinicopathological features of non-small cell lung cancer: a meta-analysis. *Cancer Biol Ther*. 2015;16(7):1019-1028.
55. Gavreto (pralsetinib) capsules [package insert]. Blueprint Medicines Corporation. Cambridge, MA. https://accessdata.fda.gov/drugsatfda_docs/label/2020/204701s000lbl.pdf. Revised September 2020. Accessed May 10, 2025.
56. Retevmo (selpercatinib) capsules [package insert]. Lilly USA, LLC. Indianapolis, IN. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213246s000lbl.pdf. Revised May 2020. Accessed May 10, 2025.
57. Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med*. 2014;371(21):1963-1971.
58. FDA approves taletrectinib for ROS1-positive non-small cell lung cancer. News release. U.S. FDA. https://tinyurl.com/4v5bkvfh. Posted June 11, 2025. Accessed June 13, 2025.
59. Camidge DR, Pao W, Sequist LV. Acquired resistance to TKIs in solid tumors: learning from lung cancer. *Nat Rev Clin Oncol*. 2014;11:473-481.
60. Schmid S, Früh M, Peters S. Targeting MET in EGFR resistance in non-small cell lung cancer—ready for daily practice? *Lancet Oncol*. 2020;21(3):320-322.
61. Marcoux N, Gettinger SN, O'Kane G, et al. EGFR-mutant adenocarcinomas that transform to small-cell lung cancer and other neuroendocrine carcinomas: clinical outcomes. *J Clin Oncol*. 2019;37(4):278-285.

62. Gao J, Li H-R, Jin C, et al. Strategies to overcome acquired resistance to EGFR TKI in the treatment of non-small cell lung cancer. *Clin Transl Oncol*. 2019;21(10):1287-1301.
63. Lovly CM. Combating acquired resistance to tyrosine kinase inhibitors in lung cancer. *Am Soc Clin Oncol Educ Book*. 2015;2015:e165-e173.
64. Li S, Zhao X, Fu K, et al. Resistance to antibody-drug conjugates: a review. *Acta Pharm Sin B*. 2025;15(2):737-756. Doi: 10.1016/apsb.2024.12.036.
65. Lovly CM, Berger MF, Vnencak-Jones CL. Circulating DNA. My Cancer Genome website. https://www.mycancergenome.org/content/page/circulating-dna. Updated April 3, 2019. Accessed November 19, 2020.
66. Revelo AE, Martin A, Velasquez R, et al. Liquid biopsy for lung cancers: an update on recent developments. *Ann Transl Med*. 2019;7(15):349.
67. United States Food and Drug Administration. FDA approves first liquid biopsy next-generation sequencing companion diagnostic test. FDA website. https://www.fda.gov/news-events/press-announcements/fda-approves-first-liquid-biopsy-next-generation-sequencing-companion-diagnostic-test. Posted August 7, 2020. Accessed November 19, 2020.
68. Ingram I. Second liquid biopsy ok'd for tumor profiling in all solid cancers. MedPage Today website. https://www.medpagetoday.com/hematologyoncology/prostatecancer/88298. Posted August 27, 2020. Accessed November 19, 2020.
69. United States Food and Drug Administration. FDA approves liquid biopsy NGS companion diagnostic test for multiple cancers and biomarkers. FDA website. https://www.fda.gov/drugs/fda-approves-liquid-biopsy-ngs-companion-diagnostic-test-multiple-cancers-and-biomarkers#:~:text=On%20October%2026%20and%20November,DNA%20isolated%20

from%20plasma%20specimens. Posted November 6, 2020. Accessed November 19, 2020.

70. NCI. NCI dictionary of cancer terms. https://www.cancer.gov/publications/dictionaries/cancer-terms/
71. Reita D, Pabst L, Pencreach E, et al. Direct targeting KRAS mutation in non-small cell lung cancer: focus on resistance. *Cancers (Basel)*. 2022;14(5):1321. Doi: 10.3390/cancers14051321.
72. Krazati (adagrasib) tablets [package insert]. Mirati Pharmaceuticals, Inc. San Diego, CA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216340s005lbl.pdf. Revised June 2024. Accessed May 10, 2025.
73. Lumakras (sotorasib) tablets [package insert]. Amgen, Inc. Thousand Oaks, CA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214665s000lbl.pdf. Revised January 2023. Accessed May 10, 2025.
74. Hyrnuo (sevabertinib) tablets [package insert]. Bayer HealthCare. Whippany, NJ. https://labeling.bayerhealthcare.com/html/products/pi/HYRNUO_PI.pdf. Approved 2025. Accessed December 16, 2025.

06 notes

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