

*Mutation driven lung cancer
and its treatment*



Introduction

If you or someone you care for has been diagnosed with a mutation driven lung cancer, and have been offered a targeted therapy treatment, then it's almost certain that you will have a lot of questions.

We have produced this booklet in partnership with lung cancer experts and people affected by lung cancer to help you make positive, informed choices about your treatment and care. Use this booklet along with the information provided by your healthcare team.

Remember that healthcare professionals are usually only too happy to answer your questions and help you with things that may be unclear or causing you concern.

We hope that this booklet answers your questions about lung surgery. If you would still like to talk to someone about this, call our free and confidential **Ask the nurse** service on: **0800 358 7200** or email: lungcancerhelp@roycastle.org

You can also contact one of the many support organisations available in our *Living with lung cancer* booklet. Order a copy by calling us on **0333 323 7200 (option 2)**, or look on our website: www.roycastle.org/usefulcontacts

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Understanding mutation driven lung cancer

What is mutation driven lung cancer?

Cells in our bodies grow, divide and die off in a cycle. They also “communicate” with each other. Sometimes these processes break down because of small but important changes (*mutations*) in the genes within the cells and to proteins on their surface. These mutations are permanent and cause cells to stop working and communicating properly and develop into cancer.

Scientists studying cancer cells at a molecular level (genes and cell structures) have identified some of the mutations in cell genes that are the cause of those cells becoming cancerous and multiplying uncontrollably.

There are many types of gene mutations linked to different cancers, including lung cancer. Lung cancer with one of these mutations is known as *mutation driven* lung cancer.

Some gene mutations are passed down through families (*inherited* or *hereditary* mutations) and some of these may cause cancer.

In lung cancer, mutations are not usually inherited. Instead, they are changes that happen during your lifetime and are called *acquired* mutations. These don't run in the family.

Things outside your body (environmental factors) are responsible for many gene mutations. While lung cancer is most often linked to smoking, an increasing number of people who get it have never smoked.

Other environmental factors that may play a part in someone developing lung cancer include air pollution and exhaust fumes, certain chemicals and radon gas.

In a proportion of lung cancer, the acquired gene mutations appear to be random things that happen. The genes change inside your cells without any obvious outside trigger.

Over the past few years, research has found increasingly detailed information relating to genetic mutations and about how some cancer cells grow and spread. This has led to great advances in understanding, treating and managing some types of lung cancer.

The vast majority of mutations are found in a sub-type of non-small cell lung cancer called adenocarcinoma. About 30 to 40% of people with this type of lung cancer have a driver mutation in the cancer cells.



How is mutation driven lung cancer treated?

As with other types of lung cancer, the best treatment options will depend on whether your lung cancer has been found early (*early stage*) or if it is more advanced.

Mutation driven lung cancer tends to be in non-smokers or light smokers, often affecting people who are younger and fitter than those we would typically expect to be affected. This may mean that people who receive treatment can respond better, opening up longer-term treatment options that would otherwise not be available.

For early-stage lung cancer, whether or not it is gene mutation positive lung cancer, surgery is often the best option.

For mutation driven non-small cell lung cancer that is more advanced or has spread, your doctors may offer you a *targeted* therapy as your main treatment. These treatments have been developed to interrupt the growth of lung cancers linked to some mutation types.

A targeted therapy is a drug that has been designed to block the processes that causes cancer to grow. The drug focuses on, or targets, the mutation, hence targeted therapy. These drugs are also sometimes called *biological* therapies.

For some people, a target therapy may be the first treatment they receive while for others, it may be offered after other treatments such as surgery, radiotherapy, immunotherapy or chemotherapy.

When this type of lung cancer has spread to the bones or brain, it can respond well to targeted therapies. This treatment may be supplemented by radiotherapy.

What are the benefits of targeted therapies?

Some, but not all, people with mutation driven lung cancer respond very well to a targeted therapy. Though not a cure for lung cancer, treatment can often stop people's cancer from growing, and even shrink it.

For people receiving a targeted therapy, there can be benefits. Targeted therapies:

- usually cause cancer shrinkage more often than chemotherapy
- usually cause fewer side effect than chemotherapy and therefore support a better quality of life while on treatment
- may increase life expectancy over chemotherapy

Within a few weeks of starting the treatment, people can often feel better as their symptoms from the cancer reduce. People may notice reduced coughing, easier breathing and reduced pain.

You will usually stay on the treatment as long as you are getting benefit from it. For some people, this may only be for a few months, but for others, they may be on these treatments for several years.

If it looks like your cancer is starting to grow again, your cancer team may suggest a change in your treatment.

“The targeted therapy I have been on has ‘removed’ the majority of my cancer... and I had a lot!”
Cameron

How do doctors decide if targeted therapy is right for me?

To find out if a targeted therapy may be suitable for you, cancer doctors will have to test some of your cancer cells (a *biopsy*). Testing the cancer cells for mutations is known as *molecular analysis* or *biomarker testing*.

For most people, the biopsy and molecular analysis or biomarker testing will happen before any treatment begins. For some people who have surgery, the tests may be carried out on the cancer removed during the operation.

Biopsy tissue is first used to identify the type of cancer, in this case lung cancer, and then lung cancer sub-types. Biomarker testing is then carried out on remaining tissue. Occasionally, a further biopsy may be needed to provide the necessary tissue sample.

Testing for all the mutation types is widely available across the UK, though testing for mutation types known as MET exon 14 skipping and RET (see pages 27 and 29) is not currently routinely available in Scotland.



At some centres, people may have a *liquid biopsy** where a sample of blood is analysed for tiny amounts of genetic material from cancer cells.

If you have already had treatment for lung cancer and it has come back, a further biopsy may need to be done. This is because, when lung cancer comes back, it may have acquired a new mutation, or changed to a different type or sub-type.

This detailed testing of the biopsy is to make sure the treatment you receive is the one that is most effective for you. People whose tumours test positive for these mutations, and who have been given matched targeted treatments, generally gain more benefit than from standard chemotherapy or immunotherapy, though they may also receive these treatments later.

If the molecular analysis doesn't identify a genetic mutation, it may identify specific cancer cell proteins, referred to as *PD-L1*. These proteins cloak the cells in a way that prevents the immune system from identifying them as cells that need to be destroyed. Immunotherapy may be a suitable treatment for this.

Though not a targeted therapy as described earlier, immunotherapy removes the cloak provided by the PD-L1 proteins enabling the body's own immune system to find, attack and kill the cancer cells.

While the biopsy procedure itself may be completed in just a few minutes, the process of examining the biopsy and getting the results can take a few days, or even two or three weeks.

This can be a worrying time, particularly if your results take even longer, so it can help to ask your doctor at the outset about how long it is likely to be until the results of the molecular analysis of your biopsy might be known.



For more information about testing a biopsy for gene mutation positive lung cancer, have a look at our booklet Biomarker testing in lung cancer online at: www.roycastle.org/biomarker-testing-leaflet or order a copy by calling us on 0333 323 7200 (option 2) or emailing: info@roycastle.org

Treating mutation driven lung cancer

Why am I getting a targeted therapy?

Lung cancer, when found early, is usually treated with surgery. When the lung cancer has spread beyond the lungs or when an operation is not possible, other treatment options are considered.

A targeted therapy may be offered to you if:

- your lung cancer is inoperable or not otherwise radically treatable (treated with an intent to cure), also called advanced lung cancer
- you have previously had surgery and your lung cancer has come back
- you have just had surgery for early-stage non-small cell lung cancer that has tested positive for an EGFR mutation (adjuvant treatment)
- tests on a biopsy have shown that you have a type of lung cancer that may respond well to it
- your cancer team thinks it is right for you

As with other lung cancer treatments, your doctor will also look at your general wellbeing and how you are managing everyday life. This will help them work out what is known as your *performance status (PS)*. This is a very important factor when deciding on the best treatment options for you.

The activities they will consider will include how you manage to independently do things like getting dressed, eating, and bathing as well as more complex tasks such as cleaning the house and holding down a job. The most commonly used PS scale ranges from 0 to 4, with 0 being fully able to do things and with no symptoms, and 4 being bedridden.

People with poorer PS, that is if a doctor assesses them as PS 2, 3 or 4, can find it harder to tolerate some cancer treatments. They may have more side effects and see less overall benefit.

Performance status can change over time. Your PS may improve if your cancer-related symptoms reduce as your cancer responds to treatment. Your PS may also worsen as your cancer progresses. It can also get worse because of a build-up of adverse side effects of treatments. You might be able to get a physiotherapist or occupational therapist to help you improve your PS.

You can also positively affect your PS yourself if you exercise more, eat well and generally look after your physical and emotional wellbeing. Having an improved PS could mean you can:

- cope better with your cancer and any symptoms
- increase the effectiveness of your treatment
- improve your tolerance to treatment and recovery from it
- improve your overall wellbeing and quality of life

By taking these positive steps, you may also feel a bit more in control of what's happening to you. They would also make a positive difference to your health and wellbeing. This would improve your treatment options because you would be fitter.

Mutation driven lung cancer has seen rapid developments in treatments over recent years. While most current treatments are for advanced lung cancer, trials are looking at the possibility of using targeted therapy drugs for lung cancers before they have spread (*early stage*), when a cure may be possible, including after surgery.

So, depending on your situation and the type of non-small cell lung cancer that tests show you have, a targeted therapy may be the first treatment you receive. This is known as your first-line treatment.

A targeted therapy is the first-line treatment for some mutation types but not for others. You may receive a targeted therapy as your second- or third-line treatment if a previous line of treatment stops working for you.

Different groups of targeted therapy drugs are used for each mutation type. They affect different processes within the cancer cells.

Although there may be several drugs available to treat the type of mutation the tests show you have, you may not receive all of them over time. The drugs available are listed in the gene mutation types information starting on page 20.

There are several types of targeted therapy licensed to treat lung cancer. Each drug has both a drug name and a brand or trade name.

Doctors will decide which targeted therapy to offer you according to your diagnosis and based on what current evidence suggests is best for you.

If they decide to change your treatment to another targeted therapy drug, for example if a drug stops working for you or troublesome side effects emerge, they may offer you a similar one from the same group.

The drugs may also be given in a particular order if they have been found to be more effective when used that way, maximising the benefit to you.

Some people's lung cancer is found to have spread to the brain, for example, at the time of diagnosis. This may influence the choice of first-line treatment. Some targeted therapy drugs, particularly the more recently developed ones, have been found to be more effective at killing cancer cells in the brain.

Targeted therapy treatments for lung cancer are continually developing. There are many clinical trials underway around the UK, and internationally, looking at the best way to treat lung cancer using targeted therapy (see page 35).

Before any treatment starts, your cancer team will tell you about any risks, benefits and side effects of targeted therapies. You will be asked to sign a treatment consent form to confirm that you have had this discussion and understood it. Only sign it once you feel your questions have been answered to your satisfaction and are happy to proceed with the proposed treatment.



Targeted therapy gives me hope though it doesn't take away the uncertainty but a positive scan every three months does help with this.

Jules

Will all targeted therapy drugs be available to me?

Not all targeted therapy drugs licensed to treat non-small cell lung cancer are currently available as a standard treatment on the NHS.

NHS doctors are only allowed to use drugs as standard treatment that have been approved by either the National Institute for Health and Care Excellence (NICE) for use in England, Wales and Northern Ireland, or the Scottish Medicines Consortium (SMC) for use in Scotland, or are pending a decision by NICE about routine commissioning (England).

NICE and the SMC look at a combination of how well a drug works and the cost of using the drug. They then compare it to other available drugs used for the same health problem.

This can lead to variations in the availability of these drugs on the NHS, depending on which country in the UK you live in and whether or not they have been approved for use on the NHS.

A drug may also be available through the Early Access to Medicines Scheme (EAMS), the Cancer Drugs Fund (CDF) or as part of a clinical trial.

Some drugs may also be made available through Project Orbis. This is an international programme that aims to enable faster patient access to innovative cancer treatments that have potential benefits over existing therapies. It includes the UK's Medicines and Healthcare products Regulation Authority (MHRA).

Some drugs may also be available through compassionate use. This is a way for doctors to offer treatments under development (as yet without NICE or SMC approval) to some people with no other treatment options or not able to take part in a clinical trial.

If you think this may apply to you, ask your doctor about the possibility of receiving a compassionate-use treatment.

The up-to-date approvals for treatments and those that are in the process of getting approval are online at:

- www.scottishmedicines.org.uk/medicines-advice
- www.nice.org.uk/guidance

Do targeted therapies have side effects?

All forms of cancer treatment have side effects of one sort or another and most people experience some side effects with a targeted therapy.

Side effects tend to be more difficult at the start of treatment. Over time, your body may adapt to the treatment and the side effects can reduce.

Your doctors will also tell you about any potentially serious side effects to be aware of as they may need urgent attention. If you do experience symptoms, make sure you tell your cancer team. The more they know about what is happening with you, the better able they are to adjust your treatment so it is the best it can be.

Most side effects can be reduced if your doctor lowers the dose of your treatment and some can be reduced with medication. If side effects do become serious, however, your doctors may stop your treatment temporarily till you are well enough to continue. Sometimes the side effects may be serious enough that you need to permanently stop your targeted therapy treatment.

It is also important to talk to them about new or changing symptoms as, while they may be part of your response to treatment, they may also be a sign that your doctors need to check your lung cancer.

Side effects can make living with your illness more difficult, however most people find ways to help them cope and manage their particular side effects.

The specific side effects for each drug will be listed in the patient information leaflet that will be given to you when you receive your treatment. You can read other information about your treatment's side effects online at the electronic Medicines Compendium (eMC): www.medicines.org.uk



Many people share what works for them and seek ideas from others on the online communities set up for the various types of gene mutation positive lung cancer. Information about this support is in the Gene mutation types and targeted therapies section from page 22.

Common side effects and practical tips for managing them

Some common and severe side effects are listed below, along with practical advice about how you can manage them. While some may sound alarming, the main thing is for you to be aware of how you are feeling and to speak to your medical team if you are worried.

This information may help you manage side effects, but it is still important that you talk to your cancer team if you experience any of them when you start your treatment.

Side effects	Practical advice
Diarrhoea	<ul style="list-style-type: none"> • There are anti-diarrhoea medications, which can help to reduce diarrhoea in most people. • Take small sips of liquids (such as sports drinks without sugar) often throughout the day. • Eat mild food, such as toast and crackers. • Limit spicy foods.
Nail infections (paronychia)	<ul style="list-style-type: none"> • Keep your hands as warm and dry as possible. • Avoid manicures and nail treatments (including varnish and artificial nails), exposing the hands to irritating substances, or wetting and washing them frequently. • Wear gloves for any tasks that involve water, irritants, and chemicals, such as food preparation, washing up, cleaning, using hair dyes, for example. • Avoid biting your nails, trimming or pushing back the nail cuticles. • Keep your nails trimmed and short, using nail clippers. • Your doctor may prescribe treatments such as corticosteroid or antibacterial/antifungal cream, tacrolimus ointment or antibiotic or antifungal tablets.

Continued overleaf...

Side effects	Practical advice
Feeling or being sick	<ul style="list-style-type: none"> • There are anti-sickness drugs that can help reduce sickness in most people. • The type of food that you eat or smell may make you feel worse. • Drink plenty of fluids. • If the sickness continues, speak to your cancer team.
Rash and other skin problems	<ul style="list-style-type: none"> • Moisturise your skin regularly. Your lung cancer nurse or cancer team will advise which creams are best. • Avoid being out in hot sun. • Use a sunscreen of SPF 30 or higher, preferably containing zinc oxide or titanium dioxide. • Wear a hat in the sun. • Avoid over-the-counter spot-related treatments, including products with benzoyl peroxide. • Remove any dermatologist-approved makeup with a gentle liquid cleanser. • Ask your GP for creams or steroids that may help.



Please see our *Managing your lung cancer diagnosis* and *Managing lung cancer symptoms* booklets for more information on managing side effects. Order a copy by calling us on: **0333 323 7200** (option 2).

Side effects have been the worst part of the journey for me and at certain points, they became difficult to manage. Depending on how bad they were, I would be given medication.

When I notice possible side effects, I try not to panic and consult my medical team straight away.

Jules

Severe side effects

You need to contact your lung cancer team for urgent advice if you notice any of these side effects:

- breathing difficulties, shortness of breath or worsening breathing problems
- a cough
- a high temperature (37.5C or higher)
- chest pain
- slow pulse (50 beats per minute or less), feeling tired, dizzy or faint, or losing consciousness
- abdominal (belly) pain, back pain
- itching
- yellowing of the skin and eyes
- changes in mental processes such as confusion, memory loss, and reduced ability to concentrate
- changes in mood including irritability and mood swings
- changes in speech including difficulty speaking, such as slurred or slow speech

You will be given the phone number of your cancer team or chemotherapy helpline to call if you experience difficulties with side effects and need urgent advice.

Name:

Phone number:

Other contact phone number:

Gene mutation types and targeted therapies

Cancer mutation targets are referred to according to the genes involved and are often called by their “gene symbol” (letters that stand for the longer name). Some genetic changes can be treated with a targeted therapy.

The list of targets with treatment options is increasing all the time, as does the list of targeted therapy drugs available.

The gene mutation types of non-small cell lung cancers that currently* have treatment options are:

- ALK (anaplastic lymphoma kinase)
- BRAF (B-Raf proto-oncogene, serine/threonine kinase)
- EGFR (epidermal growth factor receptor)
- KRAS (Kirsten RAt Sarcoma virus)
- MET (mesenchymal-epithelial transition factor)
- NTRK (neurotrophic tropomyosin-related kinase)
- RET (rearranged during transfection)
- ROS1 (relating to the gene c-ros oncogene 1)

Using these letters, someone may be described as having, for example, ALK positive (ALK+) lung cancer.

There are other known targets, including HER2 for example, but there are currently no licensed treatments for those targets.

Lung cancer gene mutation types have been found to have similarities and differences in terms of who develops the mutations and how they affect people, and these are described below.

For each mutation type, there are different targeted therapy drugs that work best and these are listed in each section. Your cancer doctor will speak to you about your treatment options and which drugs may be most suitable for you that are available to you through one of the routes outlined on page 14.

There is also a section below about a targeted therapy drug that is used with chemotherapy to treat some lung cancer adenocarcinoma.

When I was first diagnosed with a rare EGFR mutation (Exon 20), there were no matched targeted therapy treatments available for me.

My only options at the time were chemotherapy and radiotherapy. Within a year, though, mobocertinib was approved and I started treatment.

New treatments like this are being developed all the time... giving us more treatment options and greater hope.

Gini



If you would like to see treatment pathways for gene mutation types and their targeted therapies, you can look on the National Institute for Health and Care Excellence website here: www.nice.org.uk/guidance/ng122

ALK mutation

ALK is a gene that tells the cells in your body how to make some proteins that sit on the surface of the cells. Cells use proteins like these to send messages to each other. ALK related proteins are common on the surface of the cells of the lungs.

When this gene is broken, or mutated, the messages get changed. In the ALK gene, the mutation, sometimes called a rearrangement, causes the cells to multiply and survive without control – causing cancer. Lung cancer with this mutation is known as ALK-positive (or ALK+) lung cancer.

An ALK gene mutation is present in only around 2 to 5% of people with lung cancer so it is quite rare. ALK positive mutations are:

- more common in women than men
- common in women under 50 years old
- associated with never smokers or light smokers
- not known to be linked to environmental causes of cancer such as second-hand smoke, asbestos or air pollution

Treatment

There are currently five drugs approved for treating ALK positive lung cancer:

- alectinib (brand name Alecensa®)
- brigatinib (brand name Alunbrig®)
- ceritinib (brand name Zykadia®)
- crizotinib (brand name Xalkori®)
- lorlatinib (brand name Lorviqua®)

If you are starting treatment, you may receive any of these drugs for your first-line treatment, though less so crizotinib nowadays as other newer drugs may be considered more useful. Subsequent lines of treatment may vary. Brigatinib and ceritinib may be second line after crizotinib, followed by third line lorlatinib. Lorlatinib may be second-line after alectinib, brigatinib or ceritinib. After these lines of treatment, you may be offered chemotherapy, immunotherapy or a combination of both.



ALK Positive UK is a registered charity set up to provide support and advocacy:

Website: www.alkpositive.org.uk

Facebook: www.facebook.com/groups/ALKPositiveUK

Twitter: @UKALKI

BRAF mutation

BRAF is the name of both a gene and a protein. The BRAF protein on the surface of cells helps control cell growth. When there is a mutation in the BRAF gene in the cells, it creates an abnormal protein on the surface of the cells that sends signals that lead to uncontrolled cell growth and cancer.

BRAF mutations have been reported in about 4% of non-small cell lung cancers (NSCLC). BRAF mutations are:

- more common in women
- associated with never smokers

Treatment

There is currently one drug combination that may be available under the Cancer Drugs Fund for treating BRAF positive lung cancer:

- dabrafenib (brand name Tafinlar®) with trametinib (brand name Mekinist®)

You may receive dabrafenib as your first-line treatment or after other treatments.

EGFR mutation

Epidermal growth factor receptor (EGFR) is a protein that is present on the surface of both normal cells and cancer cells. Where a biopsy and molecular tests have found a mutation in the EGFR gene, it is called EGFR-positive (or EGFR+) lung cancer.

An EGFR mutation is present in between 5 and 10% of people with lung cancer, though this can be much higher in people of Eastern Asian descent. EGFR mutations are:

- more common in women than men
- most common in people with lung adenocarcinoma, but can be found in people with other subtypes of non-small cell lung cancer
- often found in never-smokers or people who smoked only lightly
- more common in young adults with lung cancer
- more common in people from Asia, especially East Asia

Treatment

There are currently six drugs approved for treating EGFR positive lung cancer:

- afatinib (brand name Giotrif[®])
- dacomitinib (brand name Vizimpro[®])
- erlotinib (brand name Tarceva[®])
- gefitinib (brand name Iressa[®])
- mobocertinib (brand name Exkivity[®])
- osimertinib (brand name Tagrisso[®])

The EGFR mutation type has variations that will determine which targeted therapy you may be offered. Most common are exon 19 deletion or exon 21 L858 mutation, and rarely exon 20 insertion.

The first five drugs may be available as first-line treatments, and osimertinib may be offered as a second line treatment following afatinib, dacomitinib, erlotinib or gefitinib if the treatment has stopped working and your lung cancer tests positive for the T790M mutation.

For some people with certain rare EGFR mutations, afatinib or erlotinib may be offered as second-line treatment after chemotherapy.

Mobocertinib may be offered to you, following chemotherapy, if your locally advanced or metastatic NSCLC has tested positive for the EGFR mutation with the exon 20 insertion.

Osimertinib may be offered to some people after surgery, whose lung cancer tests positive for an EGFR mutation, usually for a maximum of three years.

Subsequent treatments may include chemotherapy or immunotherapy, or a combination of both.



People with EGFR mutation positive lung cancer have formed online communities where you can go for information and support:
Websites: www.egfrpositive.org.uk
Facebook: www.facebook.com/groups/280511092641290
Twitter: @EgfrUK
Exon20 group: www.exon20group.org

KRAS mutation

The KRAS mutation is an error in a protein in normal cells. Normally KRAS serves as an information hub for signals in the cell that lead to cell growth. When there is a mutation in KRAS, it signals too much and cells grow without being told to and this causes cancer.

KRAS tends to occur more in patients of Western European descent and current or former smokers, but KRAS mutations have been found in people of all different backgrounds. About 30% of lung cancer patients have some kind of KRAS mutation*. Of those, around 40% have the currently treatable mutation KRAS G12C.

Treatment

There are currently two drugs that may be used to treat KRAS G12C positive lung cancer:

- adagrasib (brand name Krazati®)
- sotorasib (brand name Lumykras®)

At the moment, testing positive for KRAS G12C mutation positive lung cancer doesn't mean you will get adagrasib or sotorasib (under the European Access to Medicines Scheme) as your first line treatment.

They are currently given for previously treated KRAS G12C lung cancer, following one or more lines of chemotherapy or a combination of chemotherapy and immunotherapy.

MET exon 14 skipping mutation

If some proteins in cells are not broken down and discarded, they can cause problems. A specific error in the MET gene, called exon 14 skipping, stops the MET protein being broken down. When this protein hangs around longer, it continues to send growth signals that can promote cancer.

MET alterations tend to appear most in adenocarcinoma non-small cell lung cancer (NSCLC), but they can also be seen in squamous NSCLC. About 5% of lung cancer patients have MET exon 14 skipping.

Treatment

There are currently two drugs that may be available to treat MET positive lung cancer:

- capmatenib (brand name Tabrecta®)
- tepotinib (brand name Tepmetko®)

You may receive capmatenib or tepotinib as a first-line treatment. However, even if you test positive for MET exon 14 skipping, you may be offered other treatments before it, such as surgery, radiotherapy, chemotherapy, immunotherapy or a combination of treatments.

If your lung cancer then stops responding to other treatments, you may be able to start on capmatenib or tepotinib.



People with MET mutation positive lung cancer have formed an online community where you can go for information and support:
Websites: www.metcrusaders.org
Facebook: www.facebook.com/groups/255429762943996
Twitter: @metcrusaders

NTRK mutation

As with other genetic mutation lung cancers, NTRK is a gene that tells the cells in your body how to make a type of protein. Cells use proteins like this to send messages to each other.

The NTRK gene has been found to fuse or join with other nearby genes, swapping bits of DNA. When this happens, the protein the NTRK gene promotes becomes abnormal. This abnormal protein can cause the cancer cells to develop and grow at sites throughout the body.

This mutation has been linked to tumour growth in a range of different cancers, including lung cancer. When cells in the lung are affected in this way, the cancer is called NTRK positive lung cancer. This is a very rare lung cancer, found in less than 1% of people with NSCLC. It is unlikely that you would be tested for this until other types of lung cancer and treatment have been explored.

Treatment

There are currently two drugs that can be used to treat NTRK positive lung cancer:

- entrectinib (brand name Rozlytrek®)
- larotrectinib (brand name Vitrekvi®)

At the moment, testing positive for NTRK mutation positive lung cancer doesn't mean you will get these drugs as your first line treatment.

They are currently given for previously treated NTRK+ lung cancer, following one or more lines of chemotherapy or a combination of chemotherapy and immunotherapy.

RET mutation

RET mutations in lung cancer are where a piece of genetic information joins, or fuses, with another leading to uncontrolled cell growth and cancer. This is the most common RET gene error in lung cancer.

These mutations appear in about 1-2% of lung cancer patients and generally appear in adenocarcinoma non-small cell lung cancer.

Patients who have RET rearrangements tend to be younger than the average lung cancer patient and have little to no smoking history.

Treatment

There are currently two drugs that may be used to treat RET positive lung cancer:

- selpercatinib (brand name Retsevmo®)
- pralsetinib (brand name Gavreto®)

At the moment, testing positive for RET mutation positive lung cancer doesn't mean you will get pralsetinib or selpercatinib as your first line treatment. They are currently given for previously treated RET+ lung cancer, following one or more lines of chemotherapy or a combination of chemotherapy and immunotherapy.

ROSI mutation

As with EGFR and ALK, ROSI is a gene that tells the cells in your body how to make a type of protein. Cells use proteins like this to send messages to each other.

The ROSI gene has been found to fuse or join with other nearby genes, swapping bits of DNA. When this happens, the protein the ROSI gene promotes becomes abnormal. This abnormal protein drives the cell to behave like cancer. Lung cancer with this mutation is called ROSI positive (or ROSI+) lung cancer. It tends to be faster growing and can spread to the bones and brain.

ROSI positive cancer is rare and occurs in only between 1 and 2% of non-small cell lung cancers (NSCLC), as well as some other cancers. ROSI positive mutations are:

- crizotinib (brand name Xalkori®)
- entrectinib (brand name Rozlytrek®)

Both of these drugs may be offered to you as your first line treatment if your lung cancer tests positive for the ROSI mutation. Second and subsequent line treatments would likely be chemotherapy, immunotherapy or a combination of both.



People with ROSI mutation positive lung cancer have formed an online community:
Website: www.rosi-cancer.com
Twitter: [@rosi-cancer](https://twitter.com/rosi-cancer)

Nintedanib – targeted therapy with chemotherapy

Although not falling within any previous targeted therapy category, nintedanib is a targeted therapy drug that blocks certain adenocarcinoma cell activity. It is given in combination with a chemotherapy drug, docetaxel (brand name Taxotere®), after first line chemotherapy.

Receiving a targeted therapy treatment

How do you take a targeted therapy?

Targeted therapy drugs for non-small cell lung cancer come as a tablet, which you take by mouth, every day, at home. You should take them at the same time/s each day.

It is very important that you take the tablets according to the instructions your cancer doctor or pharmacist has given you.

Taking extra doses of some medicines can be harmful. In some cases, even one extra dose can cause you problems. If you take extra doses of your medicine by mistake, you must tell your cancer doctor straight away.

If you are sick after taking your tablets, do not take an extra dose, just take your next dose at the usual time.

You can usually keep taking a targeted therapy indefinitely for as long as it keeps working. If you are receiving osimertinib after surgery (adjuvant treatment), your treatment would last up to three years.

I remember when the oncologist told me I had been matched up to the new drug and I would need to only take one tablet a day and would not need chemo, I jumped up and gave the man a hug.

Eric

Can I take the targeted therapy with other medicines or herbal remedies?

Some other medicines or remedies can be harmful to take alongside a targeted therapy.

Tell your cancer doctor or lung cancer nurse specialist about any other medicines you take. This includes prescription medicines, over-the-counter medicines, vitamins, and herbal supplements.

Your cancer doctor may change the dose or choose different medicines while you are taking a targeted therapy.

How do the doctors know if the targeted therapy is working?

It can take some time to assess how well a targeted treatment is working for you. Once you start your treatment, your cancer team will monitor how you are doing through regular follow up appointments with CT or MRI scans or X-rays to help assess what is happening.



If your symptoms have improved this may also suggest that the treatment is working, for example, less cough or breathlessness. If there is evidence that your cancer is responding to the targeted therapy then treatment will continue, as long as you can manage the side effects.

If there is evidence that your cancer is not responding then it is important to know this, so that a decision on an alternative treatment can be made. Sometimes there will be no change in the state of your tumour when an X-ray or scan has been done.

This may seem disappointing but a stable scan or X-ray is a good result, especially if you feel better.

Even if the targeted therapy has not changed the size of the tumour, it may well have delayed the growth. Lung cancer is likely to spread (metastasise) to other parts of the body over time so your doctors may want to carry out periodic CT, MRI or PET scans to check this, especially when the cancer may spread to your brain (see page 39).

Over time, targeted therapies can lose their effectiveness. The cancer cells can develop a resistance to the drugs and start to grow again, and this represents one of the main challenges to effective treatment. Your targeted therapy treatment may stop at this point.

For some people who have an isolated recurrence of their lung cancer, it may be treated with surgery or radiotherapy allowing their targeted therapy treatment to restart or continue.

If your cancer develops resistance and your treatment does stop, your cancer doctor will be able to tell you about other treatments that may be available to you.

Taking a tablet made day-to-day living much more manageable. I take my treatment in the comfort of my own home instead of a medical environment.

It means I have flexibility in my life for things like days out and holidays. I don't need to plan around a hospital treatment regime.

Gini

Future developments in targeted therapy

As more is known about the genetic mutations and how these affect the cells that go on to become cancerous, more targeted therapy drugs are being developed.

Research is also taking place to investigate how cancer cells become resistant to treatment. Researchers are developing and testing new drugs to combat this resistance.

As things move forward, a great deal of research is looking at these mechanisms in detail. It may be that, if your treatment becomes less effective, doctors may take another look at your cancer to see what is happening. New treatment options may be available based on the latest research.

Over time, it is hoped that treatments develop far enough that lung cancer becomes a “manageable condition”.



Clinical trials

There are many clinical trials underway in the UK and internationally, looking at the best way to treat lung cancer using targeted therapies.

Clinical trials are an essential part of medical research. They are a way of finding out if new treatments are better than current best practice.

Progress in medicine depends on people wanting to take part in trials where their own situation may help generate new knowledge about the potential benefits and/or risks of newly developed drugs or treatment approaches.

People take part in clinical trials for different reasons. You may:

- hope that a new experimental treatment will be better than a treatment you would otherwise be offered
- want to be part of “cutting edge” medicine
- hope that others may benefit from the knowledge gained from how the treatment works for you

On some clinical trials, your condition may be monitored more regularly than with standard care. This may include more blood tests, CT scans or other cancer tests. You may also spend more time with your doctor or nurse.

This could mean that any changes in your health, related to the treatment you are having or not, are picked up and acted upon earlier than if you were not in a trial.

Trials recruit a group of people, some of whom receive the new treatment while others receive the current best available treatment. People are randomly allocated to one group or the other, so you may not have any control over whether you receive the new treatment or not.

It is important to keep in mind that the drug trial or research study on a new treatment is only carried out to find out if the new treatment is better than what is currently offered. However, it may be the same, or it may be worse.

Drugs tested in trials may also not be made available to everyone on the NHS after the trial ends, though people already getting the drug may continue to receive it for as long as it is effective.

Targeted therapy drugs and their applications are being developed all the time. Which ones will be used for which type of lung cancer, independently or in combination, and for how long it will be used, will constantly change. In the meantime, your doctors will be offering you the best available treatment and care within clinical guidelines.

Ask your cancer doctor about any clinical trials. Getting into a trial is often based on being able to meet some very specific criteria.

Your cancer doctor will be able to tell you if you are eligible for a trial and where it is taking place.

If you would like to check what clinical trials are available, visit:

- UK Clinical Trials Gateway – www.bepartofresearch.nihr.ac.uk
- Cancer Research UK – www.cancerresearchuk.org/about-cancer/find-a-clinical-trial

Living with mutation driven lung cancer

Many people continue to receive targeted therapies for many months or even years. This is a bit different from other treatments such as chemotherapy, immunotherapy and radiotherapy which generally stop after a period of time or the amount of treatment required.

As long as your cancer continues to respond to the treatment, and any side effects are manageable, you are likely to continue with the targeted drug you are on. It is not uncommon for people on a targeted therapy treatment to experience longer periods of feeling quite well. Taking a daily tablet can cause little or no effect on everyday activities but adjusting to life on treatment may still take some time.

There may even be times when the lung cancer aspects of your life can feel like they are sitting quietly in the background and you can get on with your life as “normal”. You can put your attention on holidays, family, your career and otherwise making the most of your health, maintaining and even improving your fitness.

This is a really positive part of receiving a targeted therapy treatment. However, it is still very important to be vigilant for any changes in your health or signs that your cancer may no longer be under control.

Mutation driven lung cancer continues to be a dynamic area of medicine. Ongoing and increasing research and development means new treatments are regularly becoming available. This may mean there are further lines of treatment available to you in the future if your current treatment stops working.

If you are enjoying better health, you may choose not to engage with the lung cancer community and its associated services, but if it is something you think would be good for you, there is more information about ongoing support on pages 42 to 45.



Our booklet, *Living with lung cancer*, has a lot of helpful information about looking after yourself, money matters, exercise and eating well. You can view the booklet online at: www.roycastle.org or order a copy by calling us on: **0333 323 7200** (option 2).

Will I be able to work when receiving targeted therapy?

The average age of someone diagnosed with gene mutation positive lung cancer is often much younger than that of most people diagnosed with lung cancer. Though diagnosis can happen at any age, many people with this type of lung cancer are in their 40s, 30s or even 20s. This means that more people affected by this type of lung cancer are likely to be in work when they are diagnosed.

Continuing to work while receiving targeted therapy is an option as your treatment is in tablet form that you take at home. Whether you are able to continue to work, or return to work, will depend on your personal situation and how your physical and mental wellbeing are affected by your treatment.

Some people decide to keep their cancer diagnosis private because that's their nature, others because they want to avoid any potential negative reactions from their employer or colleagues.

By law, you don't need to tell your employer about having lung cancer though it may be more practical for you to do so. Your employer may be able to support you and take your condition into consideration.



Brain metastases

As with other cancers, lung cancer can spread from its original tumour site in the lungs. For some people with lung cancer, the cancer can spread to the brain. Cancer that has spread is known as metastatic cancer.

Lung cancer is also often diagnosed once it has already spread beyond the lungs. For some, they will find out that they have brain metastases at the same time as they hear about having lung cancer.

Brain metastases can cause symptoms such as dizziness, headaches or seizures, and these may be what initially prompt doctors to do further tests. Other people have no symptoms and the cancer in the brain is found during routine checks for something else, or ongoing investigations for suspected lung cancer.

Newer treatments for lung cancer, including targeted therapies, are becoming more effective and people are living much longer. The chances of developing brain metastases increase over time, so as people live longer, more people are being found to have brain metastases.

Once established, it is only a matter of time before brain metastases grow to a critical size. Your cancer doctor may decide to offer you more regular CT or MRI scans to check for brain metastases. That way, brain metastases can be found when they are small and there are better treatment options for you.



For more information about brain metastases, please see our *Understanding brain metastases and lung cancer* booklet. Order a copy by calling us on: **0333 323 7200** (option 2).

Driving

Driving is a complex activity, where steady mental and physical capacity is essential. The DVLA gives clear information about how lung cancer affects your driving licence.

If you hold a car or motorcycle licence, and you have lung cancer, you may continue to drive unless:

- you develop problems with your brain or nervous system (including brain metastases)
- your doctor says you might not be fit to drive
- you're restricted to certain types of vehicles or vehicles that have been adapted for you
- your medication causes side effects which could affect your driving

You must notify the DVLA if you have or develop any of these conditions.

Talk to your doctor if you're not sure if your lung cancer causes other symptoms that will affect your driving, or if you must tell DVLA about them.

If you hold a bus, coach or lorry licence and you have lung cancer, you must stop driving and tell DVLA. Only drivers with early stage with no spread (T1 N0 M0) non-small cell lung cancer may be considered on a case-by-case basis for ongoing licensing to drive these vehicles.

Having to stop driving can be difficult for many, particularly if you feel well and are responding to treatment. It impacts your quality of life and the ability to do things you previously took for granted.

DVLA rules for people with lung cancer are quite strict and it is a subject often raised with us and on online forums.

The regulations now mention targeted therapy treatment and if your brain metastases have been successfully treated, you may be able to get your licence back.

There is more information and forms to use to notify the DVLA at:

- www.gov.uk/lung-cancer-and-driving



Ongoing support

As your treatment continues, you will remain in close contact with your medical team. Your oncologist and lung cancer nurse specialist will always try their best to answer any questions you have and make sure you receive all the support and services you need to keep you as well as possible. Your GP and community nurses can also help you with any other health concerns.

Other services that may help you include:

- occupational therapy
- physiotherapy
- SALT (speech and language therapy)
- palliative care team
- complementary therapies

Support from Roy Castle Lung Cancer Foundation

If you or someone you know needs support, we have a range of one-to-one, group, face-to-face and online services that can help.

One-to-one support

Our Ask the nurse service is a nurse-led helpline offering advice on:

- where to get help on side effects
- ways of managing how you, your family and friends are affected by lung cancer
- understanding treatment decisions/options
- any other issues around diagnosis and treatment

Please call our experienced team of nurses free on: **0800 358 7200** or email: lungcancerhelp@roycastle.org



Our *Keep in touch support service* is a free and confidential telephone service for people with lung cancer and their carers, primarily if you are socially isolated and would like some extra contact.

A member of our support team will call at an agreed time, fortnightly or monthly (your choice). The calls will be mainly general conversation and to check on your wellbeing. If you need clinical or practical support you would be put in touch with other services, with your permission. Please call our Information and Support Team on: **0800 358 7200**, or email: info@roycastle.org

Group and online support

Our lung cancer support groups take place around the UK. These groups meet regularly when restrictions relating to COVID-19 permit, and are organised by local lung cancer nurse specialists.

The groups aim to provide you with the opportunity to meet other people affected by lung cancer, get support through sharing experiences and learn more about lung cancer and looking after yourself.

You can find details of your local lung cancer support group at:
www.roycastle.org/supportgroups

We also run online support sessions and, when restrictions relating to COVID-19 permit, lung cancer information days across the UK for people affected by lung cancer. You will have the opportunity to meet other people affected by lung cancer with whom you can share your experiences.



The information days and some online sessions are also attended by lung cancer healthcare professionals including oncologists, thoracic surgeons and lung cancer nurse specialists whom you can ask questions. Find out more by calling: **0333 323 7200** (option 2).

Our online lung cancer forum lets you share your experience through blog posts and questions with other people affected by lung cancer. You can join free and anonymously at:
www.healthunlocked.com/lungcancer

Other online support

There are many other cancer-related website-based discussion forums. They provide an online community for people to ask questions, share knowledge and experiences, exchange ideas and support each other.

Social networks, such as Facebook, have groups where people in similar situations can connect and share information and experiences. These are often closed groups, meaning that membership is controlled, and usually restricted to people affected by the condition or situation covered by the group description.

They can also be international and you can connect to people all over the world with a vast range of experiences, many similar to yours.

Be aware though, that many may not be moderated (where posts and information is checked and screened) by healthcare professionals or experts.

If you would like to be able to record and track your symptoms and how your treatment is going (and share this with others in similar situations), you can use the **Your health companion** app. Download it from Google Play or Apple App Store.

Questions to ask your doctor or nurse

Before choosing a targeted therapy as a treatment option, you should understand the expected benefits, side effects, and risks. Ask your cancer doctor or lung cancer nurse specialist these questions on your next visit. Learn as much as you can about your treatment and get an idea of the expected outcome.

1. What type of targeted therapy will I be getting?
2. What is the aim of the targeted therapy and how may it benefit me?
3. Are there other types of treatment that could be suitable for me instead of a targeted therapy?
4. What are the risks and side effects of the targeted therapy I will be taking? How do these side effects compare with side effects of other treatments? What should I do if I experience any side effects?
5. How long will I have to wait before starting treatment?
6. How will I know if the targeted therapy is working?
7. What can I do to prepare for treatment and reduce the chance of side effects?
8. Will I need to change my lifestyle in any way?
9. If this targeted therapy doesn't work, are there other treatments I can get?
10. Are there any clinical trials I would benefit from?

About our lung cancer information

We follow established quality standards and production principles to make our information trustworthy and easy to read. It is evidence based, following national clinical guidelines and best practice for managing lung cancer.

We believe information that is clear, accurate, evidence based, up to date and easy to use allows people to become better informed and more involved in their health and care.

Our information is written either by our information team or by lung cancer experts. We have a panel of lung cancer experts made up of doctors, nurse specialists and other health professionals involved in the treatment and care of people affected by lung cancer. These people help us on a voluntary basis. You can find out about our Expert Panel at www.roycastle.org/expertpanel

This booklet has been published in partnership with Lung Cancer Nursing UK.



Our information is also reviewed by members of our Reader Panel (made up of people who have experience of lung cancer). This makes sure our lung cancer information meets their needs. You can find out about our Reader Panel at www.roycastle.org/readerpanel

You can find references to sources of information within this booklet at www.roycastle.org/evidence

If you have suggestions for new publications or additions or improvements to our existing range of booklets and factsheets, please let us know at info@roycastle.org

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ROY CASTLE
LUNG CANCER
FOUNDATION

Roy Castle Lung Cancer Foundation is the charity that gives help and hope to people affected by lung cancer. The charity has two aims – supporting people living with lung cancer and saving lives.

Supporting people living with lung cancer

Working closely with lung cancer nurses, we provide information, run lung cancer support groups and offer telephone and online support.

Saving lives

We fund lung cancer research, campaign for better treatment and care for people who have lung cancer, and raise awareness of the importance of early diagnosis.

Our lung cancer prevention work helps people to quit smoking and encourages young people not to start smoking.

Contact us

For more information, call our Lung Cancer Information and Support Services:
0333 323 7200 (**option 2**)
or visit our website: www.roycastle.org

Head Office

Cotton Exchange Building,
Old Hall Street,
Liverpool, L3 9LQ

Email: foundation@roycastle.org

Information and Support Services

Suites 524-528 Baltic Chambers
50 Wellington Street
Glasgow, G2 6HJ

Email: info@roycastle.org

Expect Better

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