What is Non-Small-Cell Lung Cancer?

Let us answer some of your questions.
Non-small-cell lung cancer (NSCLC)
An ESMO guide for patients

Patient information based on ESMO Clinical Practice Guidelines

This guide has been prepared to help you, as well as your friends, family and caregivers, better understand the nature of non-small-cell lung cancer (NSCLC) and the treatments that are available. It includes information on the different subtypes of NSCLC, the causes of the disease and how it is diagnosed, and up-to-date guidance on the types of treatments that may be available and any possible side effects.

The medical information described in this document is based on the ESMO Clinical Practice Guidelines (CPG) for NSCLC, which are designed to help medical oncologists with the diagnosis and management of early stage, locally advanced and metastatic NSCLC. All ESMO CPGs are prepared and reviewed by leading experts using evidence gained from the latest clinical trials, research and expert opinion.

The information included in this guide is not intended as a replacement for your doctor’s advice. Your doctor knows your full medical history and will help guide you regarding the best treatment for you.

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Non-small-cell lung cancer

Lung cancer: A summary of key information

Introduction to lung cancer

- Lung cancer arises from cells in the lung that have grown abnormally and multiplied to form a lump or tumour.
- Non-small-cell lung cancer (NSCLC) is a type of lung cancer, which is differentiated from small-cell lung cancer (SCLC) because of the way the tumour cells look under a microscope. The three main types of NSCLC are squamous cell carcinoma, adenocarcinoma and large cell (undifferentiated) carcinoma of the lung. They are diagnosed in the same way but may be treated differently.
- Lung cancer is the fourth most common cancer in Europe; NSCLC represents 85-90% of all lung cancers. Smoking is the biggest risk factor for the development of lung cancer.
- In Europe, there has been a decrease in lung cancer mortality among men, while it is increasing in women — this reflects a difference in smoking trends between the sexes.

Diagnosis of NSCLC

- Lung cancer may be suspected if a person has symptoms such as persistent cough or chest infection, breathlessness, hoarseness, chest pain or coughing up blood. Other symptoms may be fever, appetite loss, unexplained weight loss and fatigue.
- Following a clinical examination, your doctor will arrange for an x-ray and/or computed tomography (CT) scan (or might use other technologies, such as positron emission tomography [PET] CT scan or magnetic resonance imaging [MRI]) to evaluate the position and extent of the cancer. Examination of a biopsy (cells or tissue taken from the tumour) will confirm a diagnosis of NSCLC.

Treatment options for NSCLC

- Types of treatment include:
  - Surgery
  - Radiotherapy — the use of measured doses of radiation to damage cancer cells and stop them growing.
  - Chemotherapy — the use of anti-cancer drugs to destroy cancer cells. Chemotherapy can be given alone or with other treatments.
  - Targeted therapy — newer drugs that work by blocking the signals that tell cancer cells to grow.
  - Immunotherapy — a type of treatment designed to boost the body’s natural defenses in order to fight cancer.
- Combinations of different treatment types are frequently offered based on the stage and type of NSCLC and on the patient’s condition and comorbidities (additional diseases or disorders experienced at the same time). Adjuvant treatment — the use of anticancer drugs after or in combination with another form of cancer treatment — may be used in some patients.
• Cancer is ‘staged’ according to tumour size, involvement of regional lymph nodes and whether it has spread outside the lung to other parts of the body. This information is used to help decide the best treatment.

• Early-stage (stage I-II) NSCLC:
  - Surgery is the main treatment for early-stage NSCLC.
  - Chemotherapy may be given after surgery (adjuvant chemotherapy) in patients with stage II NSCLC.
  - Radiotherapy (either stereotactic ablative radiotherapy [SABR] or conventional radiotherapy) is an alternative to surgery in patients who are unable or unwilling to have surgery.
  - Adjuvant radiotherapy may be given when it has not been possible to completely remove the tumour during surgery.

• Locally advanced (stage III) NSCLC:
  - Treatment is likely to involve different types of therapy (multimodal therapy).
  - If it is possible to remove the tumour (i.e. the tumour is resectable), treatment options include:
    - Induction therapy (initial treatment[s] given to shrink the tumour before a second planned treatment) consisting of chemotherapy with or without radiotherapy, followed by surgery.
    - Surgery followed by adjuvant chemotherapy and/or radiotherapy.
    - Chemoradiotherapy (i.e. chemotherapy and radiotherapy given at the same time).
  - The type of treatment – and sometimes the sequence of treatments – offered to patients with resectable stage III NSCLC will depend on the extent and complexity of the surgery required to remove the tumour.
  - In unresectable stage III NSCLC, chemoradiotherapy is the preferred treatment. Alternatively, chemotherapy and radiotherapy can be given sequentially (i.e. one after the other) in patients unable to tolerate concurrent treatment.

• Metastatic (stage IV) NSCLC:
  - NSCLC is referred to as metastatic or stage IV disease when it has spread beyond the lung which was initially affected.
  - It is rarely possible to remove metastatic NSCLC with surgery or to treat it radically with radiotherapy.
  - Intravenous chemotherapy with a two-drug combination (with or without the addition of the targeted therapy called bevacizumab) is the main treatment for patients with metastatic NSCLC. New options using first-line immunotherapy are under evaluation and pembrolizumab has recently been approved for use in this setting. Thus, immunotherapy is likely to replace or complement first-line chemotherapy in selected patients in the next few years.
  - The choice of drugs used will largely depend on the general health of the patient and the histological subtype of the tumour.
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- Patients whose tumours contain specific mutations (alterations) to the epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genes (determined by molecular testing using a tumour biopsy) are best treated with oral targeted therapies given continuously.

- After 4-6 cycles of doublet chemotherapy (i.e. two chemotherapy drugs given together), maintenance treatment (treatment to help keep the cancer from coming back) with a chemotherapy drug called pemetrexed, with or without a targeted therapy called bevacizumab, may be given to patients in good general health. The targeted therapy erlotinib may be offered as maintenance treatment in patients whose tumours have EGFR mutations.

- Should the cancer come back (relapse or recurrence), second- and third-line treatments may be offered. Suitable second- and third-line treatments depend on which first-line treatment has been received and on the general health of the patient. Treatment options include: Chemotherapy (pemetrexed or docetaxel), immunotherapy (nivolumab or pembrolizumab), antiangiogenic therapy (nintedanib or ramucirumab) in combination with docetaxel, and targeted therapies (afatinib, gefitinib, erlotinib, crizotinib, ceritinib, alectinib or osimertinib).

  - The activity of immunotherapy is influenced by the amount of programmed death-ligand 1 (PD-L1) protein in the tumour (determined by molecular testing using a tumour biopsy). Pembrolizumab – but not nivolumab – can only be prescribed in tumours that are PD-L1 positive. Other immunotherapy drugs are under evaluation in clinical trials.

  - Patients whose tumours have EGFR mutations who have received first-line treatment with erlotinib, gefitinib or afatinib, and who have a confirmed EGFR T790M mutation, may be subsequently treated with osimertinib.

  - Patients whose tumours have ALK rearrangements and who have received first-line treatment with crizotinib may be treated with second-line ceritinib or alectinib. Other ALK inhibitors are under evaluation in clinical trials.

Follow-up after treatment

- Patients who have completed treatment for stage I-III NSCLC are followed-up with clinical and radiological examinations every 3-6 months for the first 2-3 years and annually after that.

- Patients who have completed treatment for metastatic disease are followed up with radiological examinations every 6-12 weeks (depending on their suitability for further treatment) so that second-line therapy can be started if needed.
Anatomy of the lungs

The lungs form part of our respiratory (breathing) system, which includes:

- Nose and mouth.
- **Trachea** (windpipe).
- **Bronchi** (tubes that go to each lung).
- Lungs.

Anatomy of the respiratory system, showing the **trachea**, **bronchi**, and lungs. As we breathe in, air passes from our nose or mouth, through the **trachea**, **bronchi** and **bronchioles**, before it reaches tiny air sacs called **alveoli** – this is where oxygen from the air passes into the bloodstream (see inset image).
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What is lung cancer?

Lung cancers typically start in the cells that line the bronchi and parts of the lung such as the bronchioles or alveoli. There are two main types of primary lung cancer:

- Small-cell lung cancer (SCLC): This type gets its name from the small size of the cells that it is composed of when viewed under a microscope.
- Non-small-cell lung cancer (NSCLC): This is the more common type of lung cancer, and accounts for 85-90% of all lung cancers (Novello et al., 2016).
  - This guide will focus exclusively on NSCLC.

What subtypes of NSCLC are there?

The three main histological subtypes of NSCLC are:

- **Adenocarcinoma**: About 40% of all lung cancers are adenocarcinomas. These tumours start in mucus-producing cells that line the airways.
- **Squamous cell carcinoma (SCC)**: About 25-30% of all lung cancers are SCC. This type of cancer develops in cells that line the airways and is usually caused by smoking.
- **Large cell (undifferentiated) carcinoma**: This type makes up around 10-15% of all lung cancers. It gets its name from the way that the cancer cells look when they are examined under a microscope.

What are the symptoms?

The most common symptoms of lung cancer, including NSCLC, are:

- Persistent cough.
- Coughing blood.
- Chest infection that won’t go away or keeps coming back.
- Chest or shoulder pain that won’t go away.
- Difficulty breathing/breathlessness.
- Hoarseness or lowering of the voice.
- Wheezing.
- Unexplained weight loss.
- Feeling extremely tired.

Other, non-specific symptoms, may include:

- Fever
- Loss of appetite.
- Unexplained weight loss.

You should see your doctor if you experience any of these symptoms. However, it is important to remember that these symptoms are common in people who do not have lung cancer; they may also be caused by other conditions.
How common is NSCLC?

Lung cancer represents the fourth most common cancer in Europe

In 2012, there were more than 410,000 new cases of lung cancer diagnosed in Europe (12% of the total number of new cancer cases) (Ferlay et al., 2013):

- 291,000 new cases in men.
- 119,000 new cases in women.

Lung cancer is the second most common cancer in men (after prostate cancer) and the third most common in women (after breast and colorectal cancer) (Ferlay et al., 2013). Incidence rates of lung cancer are higher in more developed countries than in less developed countries; these variations largely reflect the differences in the stage and degree of the tobacco epidemic (Torre et al., 2015).

In Europe, there has been a decrease in lung cancer mortality among men, while it is increasing in women — this reflects the difference in smoking prevalence trends between the sexes (Malvezzi et al., 2016, Novello et al., 2016).

The majority of cases of lung cancer are diagnosed in patients aged 65 years and over, and the median age at diagnosis is 70 years.

NSCLC is the most common type of lung cancer, representing 85-90% of all lung cancers
Non-small-cell lung cancer

Estimated lung cancer incidence rates by sex and world area in 2012 (Torre et al., 2015).
What causes NSCLC?

Smoking is the biggest risk factor for developing lung cancer. However, there are other risk factors that can also increase the chances of developing lung cancer. It is important to remember that having a risk factor increases the risk of cancer developing but it does not mean that you will definitely get cancer. Likewise, not having a risk factor does not mean that you definitely won’t get cancer.

Smoking

Tobacco smoking is the leading cause of lung cancer. In Europe, it is responsible for 90% of cases in men and 80% of cases in women (Novello et al., 2016). The number of years that a person has been a smoker is more important than the number of cigarettes smoked per day; therefore, giving up smoking at any age can reduce the risk of developing lung cancer more than cutting down on the number of cigarettes smoked per day.

Passive smoking

Passive smoking, also referred to as ‘second-hand smoke’ or ‘environmental tobacco smoke’, increases the risk of developing NSCLC but to a lesser extent than if you are a smoker.

Radon

Radon is a radioactive gas that is produced during the breakdown of naturally-occurring uranium in soil and rocks, particularly granite. It can pass through from the ground into homes and buildings. Exposure to excessive levels of radon is thought to be a significant causative factor in patients with lung cancer who have never smoked. This may be particularly relevant for underground miners who are usually exposed to high levels of radon if the mines in which they work are in a particular geographical region.
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Genetic susceptibility
It is thought that some people may be more likely to develop lung cancer based on their genetic makeup (Bailey-Wilson et al., 2004). Having a family history of lung cancer, or other types of cancer, increases the risk of developing lung cancer to some degree. In people who are genetically predisposed to lung cancer, smoking further increases the risk.

Household and environmental pollutants
Other factors described as risk factors for the development of NSCLC include exposure to asbestos and arsenic. There is evidence that lung cancer rates are higher in cities than in rural areas, although factors other than outdoor air pollution may be responsible for this pattern. It has also been suggested that indoor air pollution from use of coal-fuelled stoves may be a factor in some countries (Novello et al., 2016). For example, in China there is an increased rate of lung cancer in women, despite the fact that a lower proportion of women are smokers in China compared with some European countries.

At the present time, there is no clear evidence that screening for NSCLC should be a routine procedure in people who are at a higher risk of developing the disease based on the above risk factors.
How is NSCLC diagnosed?

Most patients with NSCLC are diagnosed after seeing their doctor to report symptoms such as a persistent cough, a chest infection that won't go away, dyspnoea, wheezing, coughing blood, chest or shoulder pain that won't go away, hoarseness or lowering of the voice, unexplained weight loss, loss of appetite or extreme fatigue.

A diagnosis of lung cancer is based on the results of the following examinations and tests:

**Clinical examination**

Your doctor will carry out a clinical examination. He/she will examine your chest and check for the lymph nodes in your neck. If there is a suspicion of lung cancer, he/she may arrange for a chest x-ray, or possibly a CT scan, and refer you to a specialist for further testing.

**Imaging**

Imaging is used to confirm a suspected diagnosis of lung cancer, and to investigate how far the cancer has progressed.

Different imaging techniques include:

- **Chest x-ray**: A chest x-ray will enable the specialist to check your lungs for anything that looks abnormal. This is usually the first test that is carried out, based on your symptoms and the clinical examination.

- **CT scan of chest and upper abdomen**: A series of images are taken, which build up a three-dimensional picture of the inside of your body. This allows the specialist to gather more information about the cancer such as the exact location of the tumour in your lungs, whether nearby lymph nodes are affected, and whether the cancer has spread to other areas of the lungs and/or parts of your body. It is a painless procedure and usually takes about 10-30 minutes.

- **CT scan or magnetic resonance imaging (MRI) scan of the brain**: This test allows doctors to rule out or confirm whether the cancer has spread to your brain. An MRI scan uses powerful magnetism to build up detailed images. You may be given an injection of dye into a vein in your arm to help the images show up more clearly. The scan won’t hurt but may be slightly uncomfortable as you will need to lie still inside the scanning tube for about 30 minutes. You will be able to hear and speak to the person doing the scan.
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- **Positron emission tomography (PET)/CT scan**: A combination of a CT scan and a PET scan. PET uses low-dose radiation to measure the activity of cells in different parts of the body, so a PET/CT scan gives more detailed information about the part of the body being scanned. A mildly radioactive drug will be injected into a vein in the back of your hand or arm and then you will need to rest for about an hour while it spreads throughout your body. The scan itself will take 30-60 minutes and, although you will need to lie still, you will be able to speak to the person operating the scanner. A PET/CT scan is often carried out to detect whether the cancer has spread to the bones.

**Histopathology**

**Examination of a biopsy is recommended for all patients with NSCLC as it helps to determine the best treatment approach**

Histopathology is the study of diseased cells and tissues using a microscope; a biopsy of the tumour allows a sample of cells to be closely examined. Examination of a biopsy is recommended for all patients as it is used to confirm a diagnosis of NSCLC, to identify the histological subtype of NSCLC, and to identify any abnormal proteins within the tumour cells that could help to determine the best treatment for you (Novello et al., 2016).

Techniques for obtaining a biopsy include:

- **Bronchoscopy**: A doctor or specially-trained nurse examines the insides of the airways and lungs using a tube called a bronchoscope. It is carried out under local anaesthetic. During a bronchoscopy, the doctor or nurse will take samples of cells (biopsies) from the airways or lungs.

- **CT-guided needle lung biopsy**: If a biopsy is difficult to obtain with a bronchoscopy, your doctor may choose to obtain a biopsy during a CT scan. In this procedure, you will have a local anaesthetic to numb the area. A thin needle is then inserted through your skin into your lung so that the doctor can remove a sample of cells from the tumour. This should only take a few minutes.

- **Endobronchial ultrasound-guided sampling (EBUS)**: This technique is used to confirm whether the cancer has spread to nearby lymph nodes, after radiological examinations have suggested that this might be the case. A bronchoscope, containing a small ultrasound
probe, is passed through the trachea to see whether any nearby lymph nodes are larger than normal. The doctor can pass a needle along the bronchoscope to take biopsies from the tumour or the lymph nodes. This test can be uncomfortable but shouldn’t be painful. It takes less than an hour and you should be able to go home the same day after it is finished.

- **Oesophageal ultrasound-guided sampling (EUS):** Similar to EBUS, this technique is used to confirm whether the cancer has spread to nearby lymph nodes, after radiological examinations have suggested that this might be the case. However, unlike EBUS, the ultrasound probe is inserted through the oesophagus.

- **Mediastinoscopy:** This procedure is more invasive than EBUS/EUS but is recommended as an extra test if EBUS/EUS does not confirm that the cancer has spread to nearby lymph nodes or if the lymph nodes requiring investigation cannot be reached by EBUS. A mediastinoscopy is carried out under general anaesthetic and requires a short stay in hospital. A small cut is made in the skin at the front of the base of your neck and a tube passed through the cut into your chest. A light and a camera attached to the tube allow the doctor to closely look at the middle of your chest – the mediastinum – for any abnormal lymph nodes, as these are the first areas that the cancer may spread to. Samples of tissue and lymph nodes can be taken for further examination.

*Ask your doctor for details if you have any questions about these procedures*

**Cytopathology**

Whereas histopathology is the laboratory examination of tissue or cells, cytology (or cytopathology) is the examination of cancerous cells spontaneously detached from the tumour. Common methods for obtaining samples for cytological examination include:

- **Bronchoscopy:** Bronchial washings (in which a mild salt solution is washed over the surface of the airways) and the collection of secretions can be carried out during a bronchoscopy to look for the presence of cancerous cells.

- **Thoracentesis/pleural drainage:** Pleural effusion is an abnormal collection of fluid between the thin layers of tissue (pleura) that line the lung and the wall of the chest cavity. This fluid can be taken from the pleural cavity by thoracentesis or pleural drainage and examined in the laboratory for the presence of cancerous cells.

- **Pericardiocentesis/pericardial drainage:** Pericardial effusion is an abnormal collection of fluid between the heart and the sac that surrounds the heart (pericardium). This fluid can be taken from the pericardial cavity by pericardiocentesis or pericardial drainage and examined in the laboratory for the presence of cancerous cells. These techniques are carried out in the hospital, usually with the aid of ultrasound to help position the needle. You will be given a local anaesthetic and monitored closely for any complications afterwards.

Because of the location of your lungs in your body, obtaining samples of cells/tissue can be difficult and it may be necessary to repeat some of these tests if results are found to be inconclusive.
How will my treatment be determined?

After a diagnosis is confirmed, your cancer specialist will look at a number of factors to help plan your treatment. This includes information about yourself and about the cancer.

**Patient-related factors**
- Your age.
- Your general health.
- Your medical history.
- Your smoking history.
- Results of blood tests and scans.

**Cancer-related factors**
Treatment also depends on the type of lung cancer that you have (histopathology or cytopathology results), where it is in the lung (its location) and whether it has spread to other parts of the body (imaging results).

**Staging**

It is important for your doctor to know the stage of the cancer so that he/she can determine the best treatment approach.

Staging of the cancer is used to describe its size and position and whether it has spread from where it started. Cancer is staged using a number/letter system – described as stages IA-IV. Generally, the lower the stage the better the prognosis. Staging considers:

- How big the cancer is (tumour size).
- Whether it has spread into the lymph nodes.
- Whether it has metastasised (spread) to other areas within the lungs or to other parts of the body.

Staging is usually carried out twice: After clinical and radiological examinations; and after surgery, in the case of surgically resected tumours.
The different stages of NSCLC are described in the table below.

<table>
<thead>
<tr>
<th>STAGE IA</th>
<th>Early-stage NSCLC</th>
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<tbody>
<tr>
<td>• The tumour is no larger than 3 cm, is still inside the lung and has not spread to any of the nearby lymph nodes</td>
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<tr>
<th>STAGE IB</th>
<th>Early-stage NSCLC</th>
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<tr>
<td>• The tumour is 3-5 cm in size, is still inside the lung and has not spread to any of the nearby lymph nodes</td>
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<thead>
<tr>
<th>STAGE IIA</th>
<th>Early-stage NSCLC</th>
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<tr>
<td>• The tumour is 5-7 cm in size, is still inside the lung and has not spread to any of the nearby lymph nodes; or</td>
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<tr>
<td>• The tumour is no larger than 5 cm, has spread to nearby lymph nodes but is not in any other part of the body</td>
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<tr>
<th>STAGE IIB</th>
<th>Locally advanced NSCLC</th>
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<td>• The tumour is 5-7 cm in size, has spread to nearby lymph nodes but is not in any other part of the body; or</td>
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<tr>
<td>• The tumour is larger than 7 cm or there is more than one tumour in the same lobe; it has not spread to nearby lymph nodes but may invade other parts of the lung, the airway or the surrounding areas just outside the lung, e.g. the diaphragm</td>
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<tr>
<th>STAGE IIIA</th>
<th>Locally advanced NSCLC</th>
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<tr>
<td>• The tumour is no larger than 7 cm, has spread to nearby lymph nodes but is not in any other part of the body; or</td>
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<tr>
<td>• The tumour is larger than 7 cm or there is more than one tumour in the same lobe; it has spread to nearby lymph nodes and may invade other parts of the lung, the airway or the surrounding areas just outside the lung, e.g. the diaphragm; or</td>
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<tr>
<td>• The tumour is of any size and invades tissues and structures further away from the lung, such as the heart, windpipe or oesophagus, but it has not spread to other parts of the body; or there is more than one tumour in different lobes of the same lung. The cancer may or may not have spread to nearby lymph nodes</td>
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<tr>
<th>STAGE IIIB</th>
<th>Metastatic NSCLC</th>
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<tr>
<td>• The tumour is of any size and invades tissues and structures further away from the lung, such as the heart, windpipe or oesophagus, but it has not spread to other parts of the body; or there is more than one tumour in different lobes of the same lung; the cancer has also spread to nearby lymph nodes; or</td>
<td></td>
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<tr>
<td>• The tumour is of any size and may or may not invade tissues and structures further away from the lung, such as the heart, windpipe or oesophagus; or there is more than one tumour in different lobes of the same lung; the cancer has spread to more lymph nodes, but not to other parts of the body</td>
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<tr>
<th>STAGE IV</th>
<th>Metastatic NSCLC</th>
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<td>• The tumour is of any size and may or may not have spread to the lymph nodes. The cancer is in both lungs, has spread to another part of the body (e.g. the liver, adrenal glands, brain or bones) or it has caused a collection of fluid around the lung or heart that contains cancer cells. Metastases are present either at diagnosis (in nearly 40% of patients) or they are discovered during follow-up tests of previously treated NSCLC</td>
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AJCC/UICC system 7th edition – abridged version (Novello et al., 2016)

An 8th edition of the AJCC/UICC staging system has been published, which contains detailed descriptions of tumour size and classification of metastatic disease according to whether it is oligometastatic, thoracic (in the chest) or widespread (AJCC, 2016).

AJCC, American Joint Committee on Cancer; NSCLC, non-small-cell lung cancer; UICC, Union for International Cancer Control
Type of NSCLC

Biopsy results
Your biopsy will be examined in the laboratory to determine:

- The histological subtype (SCC, adenocarcinoma or large cell carcinoma).
- Grade.
- Tumour biology.

Histological subtype
The histological subtype of the tumour can influence the type of treatment you will receive. For example, non-squamous cancers may benefit from certain anti-cancer therapies that have been shown to be effective only in patients with this histological subtype.

Grade
Grade is based on how different tumour cells look from normal lung cells, and on how quickly they grow. The grade will be a value between one and three and reflects the aggressiveness of tumour cells; the higher the grade, the more aggressive the tumour.

Biological testing of the tumour
Tissue specimens from metastatic NSCLC belonging to the non-squamous subtype should be tested for the presence of specific mutations in the EGFR gene. Even though such mutations are rare (approximately 10-12% in Caucasians with adenocarcinoma), the detection of an EGFR gene mutation has important prognostic and therapeutic implications in patients with metastatic NSCLC. EGFR testing is not recommended in patients with a diagnosis of SCC, except in never/former light smokers (<15 pack years) (Novello et al., 2016).

Routine testing for rearrangement in the ALK gene is now standard of care and should be carried out, if possible, in parallel with EGFR mutation analysis. ALK rearrangement is more frequent in people who have never smoked, those with the adenocarcinoma subtype (5%) and in younger patients (aged <50 years old). Detecting ALK rearrangements has important therapeutic implications for patients with metastatic NSCLC due to the existence of drugs targeting ALK (e.g. crizotinib, ceritinib and alectinib) (Novello et al., 2016).

Programmed death-ligand 1 (PD-L1): This is a cellular protein thought to be involved in helping the tumour to evade detection by the body’s immune system. The amount of PD-L1 present in a tumour may influence the decision to treat the cancer with anti-PD-L1 immunotherapy.
Who is involved in planning my treatment?

In most hospitals, a team of specialists will plan the treatment they feel is best for your individual situation. This multidisciplinary team of medical professionals may include:

- A surgeon.
- A medical oncologist (a doctor who specialises in the medical management of cancer).
- A radiation oncologist.
- A chest physician.
- A nurse specialist.
- A radiologist (or radiographer) who has been involved in the assessment of any x-rays and scans.
- A pathologist who has been involved in the analysis of your tumour biopsy.

Other services that may be offered include: a dietician, a social worker, a community care nurse, a physiotherapist, a clinical psychologist and a palliative care service (who can assist with pain management). After consultation with the multidisciplinary team, your doctor, possibly with other members of the care team, will talk to you about the best treatment plan for your situation (Novello et al., 2016). They will explain the benefits and potential drawbacks of different treatments.
What are the treatment options for NSCLC?

Aims of treatment

In early-stage NSCLC, when the cancer is confined to the lung and therefore considered to be curable, the main treatment is surgical resection (Vansteenkiste et al., 2013; Vansteenkiste et al., 2014). For locally advanced NSCLC, multimodal therapy is usually adopted to help shrink or in some cases completely remove the cancer (Eberhardt et al., 2015). For metastatic NSCLC, when the cancer has spread to other parts of the body, and cure is not an option, various systemic treatments may be used in an attempt to slow down tumour growth and improve symptoms and quality of life – this is called supportive or palliative care (Novello et al., 2016).

Overview of treatment types

The treatment you receive will depend on the stage and type of cancer, as well as your general health and treatment preferences, which will be discussed together with your doctor. You may have a combination of treatments. The main types of treatment are listed below:

- **Surgery** may be possible to remove NSCLC if it is diagnosed at an early stage. The type of operation that is offered will depend on the size and location of the cancer (Vansteenkiste et al., 2013; Vansteenkiste et al., 2014):
  - A **wedge** or **segment resection** is the removal of a very small amount of the lung; this is sometimes offered if the cancer is at a very early stage
  - A **lobectomy** is the removal of one of the lobes of the lung; it is the standard surgical treatment for NSCLC
  - A **pneumonectomy** is the total removal of one of the lungs; it is a more complex surgical resection than lobectomy or wedge (segment) resection.

- **Chemotherapy** works by disrupting the way that cancer cells grow and divide. However, these drugs can also affect normal cells. Chemotherapy can be given before or after surgery for NSCLC. Some people have chemotherapy at the same time as radiotherapy — this is called chemoradiotherapy. Chemotherapy may be given to try to cure the cancer or to prolong life and control symptoms (palliative care) (Vansteenkiste et al., 2013; Vansteenkiste et al., 2014; Novello et al., 2016).

- **Targeted therapies** and **antiangiogenic therapies** are drugs that block specific signalling pathways in cancer cells that encourage them to grow (Novello et al., 2016).
Radiotherapy is a type of treatment that uses ionising radiation, which damages the DNA of cancerous cells, causing the cells to die. It may be used instead of surgery to try to cure early-stage NSCLC. Radiotherapy can be given after chemotherapy or concurrently (chemoradiotherapy). Radiotherapy is also used to control symptoms when the cancer is more advanced or has spread to other parts of the body. There are various different techniques for delivering radiotherapy, including SABR (when available), a type of external beam radiation therapy that delivers a high dose of radiation specifically to the tumour (Vansteenkiste et al., 2013; Novello et al., 2016).

Your doctor and specialist nurse can discuss all of the possible treatment options available to you to help you to make an informed decision about the best way forward for you.

The response to any treatment you receive will be assessed regularly to see how effective the treatment is and to check whether the benefits outweigh any side effects that you might experience. Evaluation of response is recommended after 2-3 months of systemic anti-cancer treatment for stage IV NSCLC. This relies on repetition of the initial imaging tests that showed the cancer (Novello et al., 2016).
Early-stage NSCLC that is confined to the lung may be curable with surgery

Surgery is the main treatment approach for early-stage NSCLC (Vansteenkiste et al., 2013; Vansteenkiste et al., 2014). This involves removing the cancer and some of the nearby lymph nodes in the chest. The number of lymph nodes removed is dependent on the type of surgery performed. Surgical resection of NSCLC is a major operation and you need to be in good general health to be able to cope with it. The type of operation will either be a lobectomy (preferred) or a wedge (segment) resection and may be carried out via open surgery or video-assisted thoracic surgery (VATS), depending on the preference of your surgeon (Vansteenkiste et al., 2013; Vansteenkiste et al., 2014).

The lymph nodes removed during surgery will be examined under a microscope to check for cancer cells. Knowing if the cancer has spread to the lymph nodes also helps your doctors decide if you need further treatment with adjuvant chemotherapy or radiotherapy (Vansteenkiste et al., 2013; Vansteenkiste et al., 2014).

Adjuvant chemotherapy may be given in patients with stage II NSCLC. Your general health and your postoperative recovery will be taken into account when deciding whether you should be offered adjuvant chemotherapy. A combination of two different drugs is preferred (one of them being cisplatin), and it is likely that you will be offered 3 or 4 cycles of treatment (Vansteenkiste et al., 2013; Vansteenkiste et al., 2014).

Adjuvant radiotherapy is another option when it has not been possible to completely remove the tumour during surgery (Vansteenkiste et al., 2013; Vansteenkiste et al., 2014).

In patients with stage I NSCLC who are unwilling or unable to undergo surgery, SABR may be offered. This treatment will be given to you as an outpatient over 3–8 visits. If your tumour is larger than 5 cm (stage II NSCLC) and/or is located at the centre of the lung, radical radiotherapy using more conventional daily or accelerated schedules is preferred (Vansteenkiste et al., 2013; Vansteenkiste et al., 2014).
## Treatment of early (stage I-II) NSCLC – summary

(Vansteenkiste et al., 2013; Vansteenkiste et al., 2014)

<table>
<thead>
<tr>
<th>TREATMENT TYPE</th>
<th>PATIENTS</th>
<th>TREATMENT DETAILS</th>
<th>CONSIDERATIONS</th>
</tr>
</thead>
</table>
| Surgery        | Stage I or II NSCLC | • Operation is either:  
- **Lobectomy**: The removal of one of the lobes of the lung (preferred option), or  
- **Wedge or segment resection**: Only a small amount of the lung is removed (sometimes used for very early NSCLC)  
• Carried out either by open surgery or by **VATS** | • Risks associated with major surgery  
• Recovery time (shorter with **VATS**)  
• Usually able to go home 3-7 days after surgery  
• Requires post-operative pain control |

| Adjuvant chemotherapy | Stage II NSCLC, following surgery  
Stage IB NSCLC following surgery, if primary tumour is >4 cm in size  
(Not recommended in stage IA NSCLC) | • A combination of two different drugs usually given **intravenously** (one of which is **cisplatin**)  
• Typically, 3-4 cycles of treatment | • Need to recover from surgery before starting **chemotherapy**  
• Pre-existing medical conditions may affect whether you will be suitable for **chemotherapy** |

| SABR | Preferred for stage I, if surgery not carried out | • More precise than **conventional radiotherapy**; very small areas can be targeted with a high dose  
• Shorter treatment time vs **conventional radiotherapy** (2-week course) | • **SABR** is associated with low toxicity in patients with **COPD** and in elderly patients  
• Surgery may be offered afterwards if **SABR** is not successful or if there are complications |

| Radical radiotherapy | Tumours >5 cm and/or centrally located  
Following incomplete surgery | • Conventional (4-7-week course of treatment of short, daily sessions Monday to Friday) or **accelerated schedule** (an increased number of treatments delivered over a shorter timeframe) | |

*COPD, chronic obstructive pulmonary disease; NSCLC, non-small-cell lung cancer; SABR, stereotactic ablative radiotherapy; VATS, video-assisted thoracic surgery*
Non-small-cell lung cancer

Treatment options for locally advanced (stage III) NSCLC

Treatment for locally advanced disease is likely to involve different types of therapy

Locally advanced NSCLC represents a very diverse disease (see stages IIIA and IIIB in the AJCC/UICC staging system table) and so it is not possible to recommend a ‘one size fits all’ approach to treatment. Some patients with stage III NSCLC have a tumour that is considered resectable, i.e. your doctor/surgeon thinks that it can be completely removed by surgery either straight away or after a course of chemotherapy (with or without radiotherapy). On the other hand, some patients with stage III NSCLC have a tumour that is considered unresectable, i.e. surgery is not possible due to the size/location of the tumour and involvement of lymph nodes in the middle of the chest. The best approach to treatment of stage III NSCLC is therefore likely to be a combination of various treatment types (surgery, chemotherapy and/or radiotherapy), called multimodal therapy (Vansteenkiste et al., 2013; Eberhardt et al., 2015).

In patients staged with potentially resectable stage III NSCLC, treatment options are generally either induction therapy with chemotherapy or chemoradiotherapy, followed by surgery (preferred for those whose tumour is likely to be completely removed by lobectomy) or chemoradiotherapy. In patients with unresectable stage III NSCLC, the preferred treatment is chemoradiotherapy. Alternatively, sequential chemotherapy and then radiotherapy may be given to patients who are unable to tolerate concurrent treatment (Vansteenkiste et al., 2013; Eberhardt et al., 2015).

Chemotherapy is an integral part of the treatment of stage III NSCLC. Generally, a cisplatin-based combination regimen (two different drugs) is offered. You will usually be offered 2–4 cycles, whether chemotherapy is given alone or as part of course of chemoradiotherapy. In some patients who undergo surgery upfront for NSCLC that is thought to be stage I or II, but found to be stage III during surgery, then adjuvant chemotherapy will likely be administered after the surgery (Vansteenkiste et al., 2013; Eberhardt et al., 2015).

When radiotherapy is given concurrently with chemotherapy for stage III NSCLC, it is given as conventional daily doses and treatment should not exceed 7 weeks. It may be given as an accelerated schedule as part of a pre-operative chemoradiotherapy course, but any potential advantages to the likely outcome of surgery will need to be weighed up against potential greater toxicity. When given sequentially, an accelerated schedule of radiotherapy may be given, i.e. higher doses over a shorter timeframe (Vansteenkiste et al., 2013; Eberhardt et al., 2015).
## Treatment of locally advanced (stage III) NSCLC – summary

*Vansteenkiste et al., 2013; Eberhardt et al., 2015*

<table>
<thead>
<tr>
<th>TREATMENT TYPE</th>
<th>PATIENTS</th>
<th>TREATMENT DETAILS</th>
<th>CONSIDERATIONS</th>
</tr>
</thead>
</table>
| **Surgery**    | **Resectable stage III NSCLC** | • Preferred when a complete resection by lobectomy is expected, to spare as much lung tissue as possible  
• May require a pneumonectomy (removal of one lung) in some patients  
• May be offered after an initial course of chemotherapy (+/- radiotherapy) – called induction therapy | • Outcome depends on the extent of involvement of the lymph nodes at the centre of the chest – may not be known until after surgery  
• Lung function tests are important before deciding on surgery |
| **Chemotherapy** | **Resectable stage III NSCLC** | • Intravenous cisplatin-based regimen is preferred (cisplatin-etoposide or cisplatin-vinorelbine)  
• Typically, 2-4 cycles of treatment are given | • A carboplatin-based combination may be chosen if you have other medical conditions that could affect how you tolerate chemotherapy  
• It is likely that you will experience more side effects if chemotherapy is given concurrently with radiotherapy |
|                | **Unresectable stage III NSCLC** | • If your tumour is considered resectable, chemotherapy may be given before surgery as induction therapy (chemotherapy +/- radiotherapy)  
• If you have surgery upfront and it is found that the cancer had spread to lymph nodes in the chest, you may be offered adjuvant chemotherapy | |
| **Radiotherapy** | **Resectable stage III NSCLC** | • May be given post-operatively in patients who have had incomplete resection  
• When given pre-operatively concurrently with chemotherapy, may be conventional doses or as an accelerated schedule | |
|                | **Unresectable stage III NSCLC** | • May be given as conventional daily doses as part of a chemoradiotherapy schedule (up to 7 weeks), or sequentially (after chemotherapy) as an accelerated schedule | |

NSCLC, non-small-cell lung cancer
Non-small-cell lung cancer

Treatment options for metastatic (stage IV) NSCLC

Chemotherapy is the main treatment for metastatic NSCLC

Metastatic NSCLC is usually considered inoperable. Complete removal of the tumour(s) is very unlikely and therefore a chance of cure cannot be offered. However, surgical interventions can relieve symptoms caused by the disease spreading to other parts of the body. Similarly, radiotherapy may help control symptoms that arise due to the disease spreading to certain organs, including the brain and bones (Novello et al., 2016).

Systemic anticancer treatment is the main treatment for stage IV NSCLC, the aims of which are to improve quality of life and to prolong survival. There are many different types of drugs available and the choice of which drugs are offered will largely depend on your general health and the type of tumour that you have (Novello et al., 2016).

Intravenous chemotherapy with a two-drug combination (doublet chemotherapy) is the main treatment for patients with metastatic NSCLC whose cancer does not contain specific modifications to the EGFR or ALK genes or high levels of the PD-L1 protein (determined by molecular testing using a tumour biopsy). Doublet chemotherapy is likely to include a platinum-based compound plus either gemcitabine, vinorelbine or a taxane. Addition of pemetrexed or the targeted agent bevacizumab may also be considered for non-squamous NSCLC. In patients whose general health is poor, single-agent chemotherapy with gemcitabine, vinorelbine or docetaxel is another treatment option (Novello et al., 2016).

Patients whose tumours have EGFR mutations or ALK rearrangements are best treated with oral targeted therapies. Gefitinib, erlotinib or afatinib are options for EGFR-mutated tumours and crizotinib is offered to patients who have an ALK rearrangement (Novello et al., 2016).

Patients whose tumours express relatively high levels of PD-L1 protein (determined by molecular testing using a tumour biopsy) may receive first-line immunotherapy with pembrolizumab.

After 4–6 cycles of doublet chemotherapy, maintenance treatment with pemetrexed, with or without bevacizumab, may be given to patients in good general health with non-squamous tumours to prolong the effect of first-line chemotherapy on tumour control. Erlotinib may be offered as maintenance treatment in patients whose tumours have EGFR mutations (Novello et al., 2016).
Further lines of treatment may be offered, depending on the first-line treatment received and on the general health of the patient. Treatment options include: **Chemotherapy** (pemetrexed or docetaxel), **immunotherapy** (nivolumab or pembrolizumab), antiangiogenic agents (nintedanib or ramucirumab) plus docetaxel, and **targeted therapies** (afatanib or erlotinib). Patients whose tumours have **EGFR mutations** who have received first-line treatment with erlotinib, gefitinib or afatinib, and who have a confirmed abnormality called a **T790M mutation**, may be treated with second-line osimertinib. Patients whose tumours have **ALK rearrangements** who have received first-line treatment with crizotinib may be treated with second-line ceritinib or alectinib (Novello et al., 2016).
Non-small-cell lung cancer

Treatment of metastatic (stage IV) NSCLC – summary *(Novello et al., 2016)*

<table>
<thead>
<tr>
<th>TREATMENT TYPE</th>
<th>PATIENTS</th>
<th>TREATMENT DETAILS</th>
<th>CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>EGFR- and ALK-negative tumours • Good general condition, no other major medical conditions</td>
<td>First line: • Intravenous platinum-based regimen preferred (2 drug combination including cisplatin or carboplatin + gemcitabine, vinorelbine or a taxane) • Pemetrexed may be incorporated into the treatment regimen in non-squamous histology • 4-6 cycles (may be offered maintenance treatment with single agent pemetrexed after 4 cycles) Second line: • Pemetrexed (non-squamous type) or docetaxel</td>
<td>• Response to platinum-based therapy, toxicity and patient’s general health after initial treatment needs to be considered when deciding upon maintenance treatment • Patients with a very poor general condition are not suitable for chemotherapy; best supportive care is the only treatment</td>
</tr>
<tr>
<td></td>
<td>Less fit patients/elderly</td>
<td>First line: • Carboplatin-based regimen preferred; may be offered single-agent treatment with gemcitabine, vinorelbine or docetaxel</td>
<td></td>
</tr>
<tr>
<td>Targeted therapy</td>
<td>EFGR mutation</td>
<td>First line: • Gefitinib, erlotinib or afatinib Second line: • Osimertinib</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ALK rearrangement</td>
<td>First line: • Crizotinib Second line: • Ceritinib • Alectinib</td>
<td></td>
</tr>
<tr>
<td>Targeted therapy in tumours without specific mutations</td>
<td></td>
<td>First line: • Intravenous bevacizumab may be added to a platinum-based regimen (non-squamous type) in patients in good general condition • Necitumumab + gemcitabine/cisplatin is an option for SCC expressing EGFR Second line: • Erlotinib, nintedanib + docetaxel (adenocarcinoma), ramucirumab + docetaxel, afatinib</td>
<td>• As most targeted agents are generally well tolerated, they may also be offered to patients with a moderate/poor general condition</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>TREATMENT TYPE</th>
<th>PATIENTS</th>
<th>TREATMENT DETAILS</th>
<th>CONSIDERATIONS</th>
</tr>
</thead>
</table>
| Immunotherapy  | EGFR- and ALK-negative tumours  
• Good general condition, no other major medical conditions | **First line:**  
• Pembrolizumab (in patients with tumours strongly positive for PD-L1)  
**Second line:**  
• Nivolumab or pembrolizumab (in patients with tumours positive for PD-L1) |  |
| Surgery        | Can be used for relief of symptoms caused by cancer spreading | Minimally-invasive procedures can be helpful, e.g. placement of a stent to alleviate obstruction of the airways |  |
| Radiotherapy   | Can be used for relief of symptoms caused by cancer spreading | **Radiotherapy** can achieve symptom control for bone and brain metastases  
• It can also relieve symptoms caused by airway obstruction |  |

*ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor; NSCLC, non-small-cell lung cancer; PD-L1, programmed death-ligand 1; SCC, squamous cell carcinoma*
Non-small-cell lung cancer

Oligometastatic disease
When the cancer has spread beyond the site at which it started but is not yet widely metastatic, it is called oligometastatic disease. If you have synchronous oligometastases diagnosed within 1 month of your primary tumour, it may be possible to achieve long-term disease-free survival following chemotherapy and radical local treatment, such as high-dose radiotherapy or surgery; inclusion in a suitable clinical trial may be advised by your doctor (Novello et al., 2016). Similarly, if you have a limited number of metachronous oligometastases that appear following treatment for your primary tumour, you may be offered treatment with high-dose radiotherapy or surgery (Novello et al., 2016).

Clinical trials
Your doctor may ask you whether you would like to take part in a clinical trial. This is a research study conducted with patients in order to (ClinicalTrials.gov, 2017):

- Test new treatments
- Look at new combinations of existing treatments, or change the way they are given to make them more effective or reduce side effects
- Compare the effectiveness of drugs used to control symptoms
- Find out how cancer treatments work.

Clinical trials help to improve knowledge about cancer and develop new treatments, and there can be many benefits to taking part. You would be carefully monitored during and after the study, and the new treatment may offer benefits over existing therapies. It’s important to bear in mind, however, that some new treatments are found not to be as good as existing treatments or to have side effects that outweigh the benefits (ClinicalTrials.gov, 2017).

Clinical trials help to improve knowledge about diseases and develop new treatments – there can be many benefits to taking part

You have the right to accept or refuse participation in a clinical trial without any consequences for the quality of your treatment. If your doctor does not ask you about taking part in a clinical trial and you want to find out more about this option, you can ask your doctor if there is a trial for your type of cancer taking place nearby (ClinicalTrials.gov, 2017).
Supportive care

There is a range of other therapies available that can also help with the management of NSCLC. These include bone modifying agents (e.g. zoledronic acid and denosumab, used to reduce the occurrence of fractures commonly associated with the presence of bone metastases), stents (for relieving major airway obstructions that can cause dyspnoea), pain management and nutritional support (Novello et al., 2016). Generally, early supportive care is recommended in parallel with treatments for the cancer itself: it may improve your quality of life and mood and lessen the need for aggressive treatment (Novello et al., 2016).
What are the possible side effects of treatment?

As with any medical treatment, you may experience side effects from your anti-cancer treatment. The most common side effects for each type of treatment are highlighted below, along with some information on how they can be managed. You may experience side effects other than those discussed here. It is important to talk to your doctor or nurse specialist about any potential side effects that you are concerned about.

Fatigue is very common in patients undergoing cancer treatment, and can result from either the cancer itself or the treatments. Your doctor or nurse can provide you with strategies to limit the impact of fatigue, including getting enough sleep, eating healthily and staying active (Cancer.Net, 2016c).

It is important to talk to your doctor about any treatment-related side effects that you are concerned about.

Surgery

Side effects following cancer surgery vary depending on the location and type of the surgery and your general health (Cancer.Net, 2016a). Common side effects following lung resection are summarised in the table.

<table>
<thead>
<tr>
<th>POSSIBLE SIDE EFFECT</th>
<th>HOW THE SIDE EFFECT MAY BE MANAGED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Pain or discomfort following surgery is common and can usually be controlled using pain-relief medication. Always let your doctor or nurse know if you are in pain, so they can treat it as soon as possible (Macmillan, 2015a)</td>
</tr>
<tr>
<td>Infection</td>
<td>You will be taught how to lower the risk of infection occurring. Signs of infection include redness, warmth, increased pain and weeping from around the wound. If you notice any of these signs, contact your nurse or doctor (Cancer.Net, 2016a)</td>
</tr>
<tr>
<td>Prolonged air leak</td>
<td>Air leak is a natural occurrence after lung resection but its prolongation to over 7 days increases the risks of other complications. Your surgeon will take precautions to minimise the risk of prolonged air leak (Ziarnik et al., 2015)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>The risk of pneumonia can be decreased by following advice provided by your doctor, e.g. you should perform any recommended physiotherapy exercises (e.g. coughing), start walking/moving about as soon as possible after surgery and refrain from smoking. If pneumonia occurs, then it can usually be treated with an antibiotic (Ziarnik et al., 2015)</td>
</tr>
</tbody>
</table>

Common side effects of lung cancer surgery and how they can be managed.
Radiotherapy

For some patients, radiotherapy causes few or no side effects; for others, the side effects can be severe. Side effects occur because radiation therapy can damage healthy tissues near the treatment area. The side effects will depend upon the location of the treatment area, the radiation dose and your general health. Usually, side effects start to appear after 2 or 3 weeks of treatment, and resolve a few weeks following the final treatment (Cancer.Net, 2016b).

<table>
<thead>
<tr>
<th>POSSIBLE SIDE EFFECT</th>
<th>HOW THE SIDE EFFECT MAY BE MANAGED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin damage (e.g. dryness, itching, blistering, or peeling)</td>
<td>These side effects usually go away a few weeks after treatment has finished. If skin damage becomes a serious problem, then your doctor may change your treatment plan (Cancer.Net, 2016b)</td>
</tr>
<tr>
<td>Oesophagitis</td>
<td>After 2–3 weeks of radiotherapy to the chest, you may have difficulty swallowing, heartburn or indigestion. This is because radiotherapy can cause inflammation in the oesophagus. Your doctor or nurse will be able to advise you on how to cope with these symptoms and may prescribe medicines to help (Macmillan, 2015b)</td>
</tr>
<tr>
<td>Radiation pneumonitis (cough, fever and fullness of chest)</td>
<td>Patients receiving radiotherapy to the chest may develop a condition called radiation pneumonitis. This generally appears between 2 weeks and 6 months following radiotherapy but is usually temporary. Tell your doctor or nurse if you experience any of the signs of radiation pneumonitis (Cancer.Net, 2016b)</td>
</tr>
</tbody>
</table>

Common side effects of radiotherapy used to treat lung cancer and how they can be managed
Chemotherapy

Side effects from chemotherapy vary depending upon the drugs and the doses used – you may get some of those listed below but you are very unlikely to get all of them. Patients who receive a combination of different chemotherapy drugs are likely to experience more side effects than those who receive a single chemotherapy drug. The main areas of the body affected by chemotherapy are those where new cells are being quickly made and replaced (bone marrow, hair follicles, the digestive system, the lining of your mouth). Reductions in your levels of neutrophils (a type of white blood cell) can lead to neutropenia, which will make you more susceptible to infections. Some chemotherapy drugs can affect fertility – if you are worried about this, speak to your doctor before treatment starts. Most side effects of chemotherapy are temporary and can be controlled with drugs or lifestyle changes – your doctor or nurse will help you to manage them (Macmillan, 2016a).

<table>
<thead>
<tr>
<th>CHEMOTHERAPY DRUG</th>
<th>POSSIBLE SIDE EFFECT</th>
<th>HOW THE SIDE EFFECTS MAY BE MANAGED</th>
</tr>
</thead>
</table>
| **Cisplatin** (Macmillan, 2016b) | • Increased risk of infection  
  • Neutropenia  
  • Thrombocytopenia  
  • Anaemia  
  • Nausea/vomiting  
  • Anorexia  
  • Changes in kidney function  
  • Tinnitus/changes in hearing  
  • Peripheral neuropathy  
  • Fatigue  
  • Taste changes  
  • Diarrhoea  
  • Decreased fertility  
  • Increased risk of thrombosis | • Your blood cell counts will be monitored frequently throughout your treatment in order to detect any neutropenia, anaemia or thrombocytopenia – your doctor may adjust your treatment according to test results, and will advise you on how to prevent infections.  
• Effects on the gastrointestinal system (nausea, vomiting, diarrhoea, taste changes) may result in loss of appetite (anorexia). Your doctor will be able to help you to prevent or manage these side effects.  
• Report any signs of peripheral neuropathy (tingling or numbness in your hands or feet) to your doctor, who will help you to manage this side effect.  
• You will have tests before and during treatment to check how well your kidneys are functioning. You will be asked to drink plenty of fluids to prevent your kidneys from becoming damaged.  
• Tell your doctor if you notice any changes in your hearing or experience tinnitus. Changes in hearing are usually temporary but can occasionally be permanent. |
| **Carboplatin** (Macmillan, 2015c) | • Neutropenia  
  • Thrombocytopenia  
  • Anaemia  
  • Increased risk of infection  
  • Nausea  
  • Vomiting  
  • Constipation  
  • Fatigue  
  • Renal (kidney) toxicity  
  • Hepatic (liver) toxicity | • Your blood cell counts will be monitored frequently throughout your treatment in order to detect any neutropenia, anaemia or thrombocytopenia – your doctor may adjust your treatment according to test results, and will advise you on how to prevent infections.  
• Your doctor will be able to help you prevent or manage any nausea, vomiting or constipation.  
• You will have tests before and during treatment to check how well your kidneys and liver are functioning, and you will be asked to drink plenty of fluids to prevent your kidneys from becoming damaged. |

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## Chemotherapy Drug: Docetaxel (Taxotere SPC, 2005)

<table>
<thead>
<tr>
<th>Possible Side Effect</th>
<th>How the Side Effects May Be Managed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>Your blood cell counts will be monitored frequently throughout your treatment in order to detect any neutropenia, anaemia or thrombocytopenia — your doctor may adjust your treatment according to test results, and will advise you on how to prevent infections.</td>
</tr>
<tr>
<td>Increased risk of infections</td>
<td></td>
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<tr>
<td>Anaemia</td>
<td></td>
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<tr>
<td>Thrombocytopenia</td>
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<tr>
<td>Peripheral neuropathy</td>
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<tr>
<td>Nausea</td>
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<td>Vomiting</td>
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<tr>
<td>Diarrhoea</td>
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<td>Stomatitis</td>
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<tr>
<td>Anorexia</td>
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<tr>
<td>Asthenia</td>
<td></td>
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<tr>
<td>Skin reaction</td>
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<td>Oedema</td>
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<tr>
<td>Alopecia</td>
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## Chemotherapy Drug: Etoposide (Vepesid SPC, 2016)

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</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>Your blood cell counts will be monitored frequently throughout your treatment in order to detect any neutropenia, anaemia, thrombocytopenia or leukopenia — your doctor may adjust your treatment according to test results, and will advise you on how to prevent infections.</td>
</tr>
<tr>
<td>Anaemia</td>
<td></td>
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<tr>
<td>Leukopenia</td>
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<tr>
<td>Thrombocytopenia</td>
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<tr>
<td>Constipation</td>
<td></td>
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<td>Nausea</td>
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<tr>
<td>Vomiting</td>
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<tr>
<td>Anorexia</td>
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<tr>
<td>Asthenia</td>
<td></td>
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<tr>
<td>Changes in liver function</td>
<td></td>
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<tr>
<td>Alopecia</td>
<td></td>
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</table>

## Additional Information

- **Report any signs of peripheral neuropathy** (tingling or numbness in your hands or feet) to your doctor, who will help you to manage this side effect.
- Effects on the gastrointestinal system (nausea, vomiting, diarrhoea) and stomatitis may result in loss of appetite (anorexia) or feelings of weakness (asthenia). Your doctor will be able to help you to prevent or manage these side effects.
- Let your doctor know if you experience any skin reactions or fluid retention/swelling (oedema) — they will help you to manage these side effects.
- **Alopecia** can be upsetting for many patients; your doctor will provide you with information on how to cope with this side effect.

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**ESMO Patients Guide**

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## Non-small-cell lung cancer

<table>
<thead>
<tr>
<th>CHEMOTHERAPY DRUG</th>
<th>POSSIBLE SIDE EFFECT</th>
<th>HOW THE SIDE EFFECTS MAY BE MANAGED</th>
</tr>
</thead>
</table>
| **Paclitaxel** (Abraxane SPC, 2013) | • Neutropenia  
• Anaemia  
• Leukopenia  
• Thrombocytopenia  
• Lymphopenia  
• Fever  
• Nausea  
• Diarrhoea  
• Vomiting  
• Constipation  
• Stomatitis  
• Anorexia  
• Fatigue  
• Asthenia  
• Rash  
• Arthralgia  
• Myalgia  
• Peripheral neuropathy  
• Alopecia | • Your blood cell counts will be monitored frequently throughout your treatment in order to detect any neutropenia, anaemia, leukopenia, thrombocytopenia or lymphopenia – your doctor may adjust your treatment according to test results, and will advise you on how to prevent infections. Report any fever to your doctor, as this may be a sign of infection.  
• Effects on the gastrointestinal system (nausea, vomiting, diarrhoea, constipation, stomatitis) may result in loss of appetite (anorexia) or feelings of fatigue/asthenia. Your doctor will be able to help you to prevent or manage these side effects.  
• Let your doctor know if you experience arthralgia, myalgia or rash and they will help you to manage these side effects.  
• Report any signs of peripheral neuropathy (tingling or numbness in your hands or feet) to your doctor, who will help you to manage this side effect.  
• Alopecia can be upsetting for many patients; your doctor will provide you with information on how to cope with this side effect. |
| **Pemetrexed** (Alimta SPC, 2017) | • Neutropenia  
• Anaemia  
• Leukopenia  
• Stomatitis  
• Pharyngitis  
• Nausea  
• Anorexia  
• Fatigue  
• Rash | • Your blood cell counts will be monitored frequently throughout your treatment in order to detect any neutropenia, anaemia, or leukopenia – your doctor may adjust your treatment according to test results, and will advise you on how to prevent infections.  
• Effects on the gastrointestinal system (stomatitis, pharyngitis, nausea) may result in loss of appetite (anorexia). Your doctor will be able to help you to prevent or manage these side effects.  
• Let your doctor know if you develop a rash – they will help you to manage this side effect. |
## Vinorelbine (Vinorelbine SPC, 2014)

<table>
<thead>
<tr>
<th>Possible Side Effect</th>
<th>How the Side Effects May Be Managed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>Your blood cell counts will be monitored frequently throughout your treatment in order to detect any neutropenia or anaemia — your doctor may adjust your treatment according to test results, and will advise you on how to prevent infections.</td>
</tr>
<tr>
<td>Anaemia</td>
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<tr>
<td>Neurological disorders</td>
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<td>Stomatitis</td>
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<tr>
<td>Nausea</td>
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<td>Vomiting</td>
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<tr>
<td>Constipation</td>
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<tr>
<td>Oesophagitis</td>
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<tr>
<td>Skin reactions</td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td></td>
</tr>
</tbody>
</table>

- Report any signs of neurological disorders (e.g. loss of reflexes, weakness of the legs and feet) to your doctor, who will decide how to manage these side effects.
- Your doctor will be able to help you to prevent or manage any effects on the gastrointestinal system (stomatitis, nausea, vomiting, constipation, oesophagitis).
- Let your doctor know if you experience any burning or skin changes at the injection site, so that they can decide how to manage these.
- Alopecia can be upsetting for many patients; your doctor will provide you with information on how to cope with this side effect.

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**Very common side effects with chemotherapy (used as single drugs) in the treatment of NSCLC.** The most recent Summary of Product Characteristics (SPCs) for individual drugs can be located at: http://www.ema.europa.eu/ema/.
### Targeted therapies, antiangiogenic therapies and immunotherapies

Common side effects in patients treated with targeted therapies, antiangiogenic therapies or immunotherapy include effects on the gastrointestinal system (e.g. diarrhoea, vomiting, nausea), skin problems (e.g. rash, dry skin, nail changes, discolouration) and hypertension (high blood pressure). Many of the side effects from targeted therapies can be effectively prevented or managed effectively. Always tell your doctor or nurse as soon as possible if you notice any side effects from taking a targeted therapy, antiangiogenic therapy or immunotherapy.

<table>
<thead>
<tr>
<th>THERAPY</th>
<th>POSSIBLE SIDE EFFECTS</th>
<th>HOW THE SIDE EFFECTS MAY BE MANAGED</th>
</tr>
</thead>
</table>
| Alectinib       | • Nausea • Constipation • Oedema • Myalgia                                            | • Report any nausea or constipation to your doctor, who will be able to help you to prevent or manage these side effects.  
• Let your doctor know if you develop any oedema (fluid retention) or myalgia (muscle pain) – they will help you to manage these side effects. |
| (Alecensa SPC, 2017) |                                                                                      |                                                                                                     |
| Bevacizumab     | • Neutropenia • Leukopenia • Thrombocytopenia • Peripheral neuropathy • Wound healing complications • Bleeding disorders • Hypertension • Stomatitis • Constipation • Diarrhoea • Nausea • Vomiting • Anorexia • Skin reactions • Dysguesia • Fatigue • Dysarthria • Headache • Watery eyes • Dyspnoea • Rhinitis • Arthralgia | • Your blood cell counts will be monitored frequently throughout your treatment in order to detect any neutropenia, leukopenia or thrombocytopenia – your doctor may adjust your treatment according to test results, and will advise you on how to prevent infections.  
• Report any signs of peripheral neuropathy (tingling or numbness in your hands or feet) to your doctor, who will help you to manage this side effect.  
• Any treatment will be delayed until wounds have healed satisfactorily.  
• Your blood pressure will be monitored throughout treatment and any hypertension will be managed appropriately.  
• Effects on the gastrointestinal system (stomatitis, constipation, diarrhoea, nausea, vomiting) and dysguesia (taste changes) may result in loss of appetite (anorexia). Your doctor will be able to help you to prevent or manage these side effects.  
• Let your doctor know if you develop any skin reactions (e.g. rash, dry skin, discolouration) – they will help you to manage these side effects.  
• Report any other side effects, including changes in vision, dyspnoea (breathlessness), dysarthria (difficulty with speech), arthralgia (painful joints) or headache to your doctor, who will help you to manage these side effects. |
<p>| (Avastin SPC, 2016) |                                                                                      |                                                                                                     |</p>
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<th>THERAPY</th>
<th>POSSIBLE SIDE EFFECT</th>
<th>HOW THE SIDE EFFECTS MAY BE MANAGED</th>
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<tr>
<td><strong>Gefitinib</strong></td>
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<tr>
<td>(Iressa SPC, 2016)</td>
<td>Diarrhoea, Anorexia, Asthenia, Changes in liver function, Skin reactions</td>
<td>Diarrhoea may result in loss of appetite (anorexia) and asthenia (weakness). Your doctor will be able to help you to prevent or manage these side effects. You will have tests before and during treatment to check how well your liver is functioning. Let your doctor know if you develop any skin reactions (e.g. rash, acne, dry skin, itchiness) – they will help you to manage these side effects.</td>
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<td><strong>Erlotinib</strong></td>
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<tr>
<td>(Tarceva SPC, 2017)</td>
<td>Increased risk of infection, Diarrhoea, Nausea, Vomiting, Stomatitis, Anorexia, Fatigue, Dry eyes, Conjunctivitis, Dyspnoea, Cough, Rash</td>
<td>Your doctor will advise you on how to prevent infections. Effects on the gastrointestinal system (diarrhoea, nausea, vomiting, stomatitis) may result in loss of appetite (anorexia). Your doctor will be able to help you to prevent or manage these side effects. Let your doctor know if you develop any problems with your eyes (e.g. dry eyes, conjunctivitis), experience increased dyspnoea (breathlessness) or cough, or develop a rash – they will help you to manage these side effects.</td>
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<tr>
<td><strong>Afatinib</strong></td>
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<tr>
<td>(Giotrif SPC, 2016)</td>
<td>Diarrhoea, Nausea, Vomiting, Stomatitis, Decreased appetite, Epistaxis, Skin reactions (rash, acne, dry skin, itchiness), Nail disorders</td>
<td>Effects on the gastrointestinal system (diarrhoea, nausea, vomiting, stomatitis) may result in loss of appetite (anorexia). Your doctor will be able to help you to prevent or manage these side effects. Let your doctor know if you experience epistaxis (nose bleeds) – they will help you to manage this side effect. Report any skin reactions or nail changes to your doctor – they will help you to manage these side effects.</td>
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<tr>
<td><strong>Crizotinib</strong></td>
<td></td>
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<tr>
<td>(Xalkori SPC, 2017)</td>
<td>Neutropenia, Anaemia, Leukopenia, Peripheral neuropathy, Changes in liver function, Vomiting, Diarrhoea, Nausea, Constipation, Dysgeusia, Fatigue, Impaired vision, Bradycardia, Dizziness, Oedema, Rash</td>
<td>Your blood cell counts will be monitored frequently throughout your treatment in order to detect any neutropenia, anaemia or leukopenia – your doctor may adjust your treatment according to test results, and will advise you on how to prevent infections. Report any signs of peripheral neuropathy (tingling or numbness in your hands or feet) to your doctor, who will help you to manage this side effect. You will have tests before and during treatment to check how well your liver is functioning. If you experience diarrhoea, nausea, vomiting, constipation, or changes in your sense of taste (dysgeusia), your doctor will be able to help you to prevent or manage these side effects. Let your doctor know if you develop any problems with your eyes, experience dizziness, oedema (fluid retention) or develop a rash – they will help you to manage these side effects.</td>
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<td>THERAPY</td>
<td>POSSIBLE SIDE EFFECT</td>
<td>HOW THE SIDE EFFECTS MAY BE MANAGED</td>
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<tr>
<td>Ramucirumab* (Cyramza SPC, 2016)</td>
<td>• Neutropenia</td>
<td>• Your blood cell counts will be monitored frequently throughout your treatment in order to detect any neutropenia or thrombocytopenia – your doctor may adjust your treatment according to test results, and will advise you on how to prevent infections.</td>
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<tr>
<td></td>
<td>• Thrombocytopenia</td>
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<td></td>
<td>• Hypertension</td>
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<td></td>
<td>• Epistaxis</td>
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<td>• Stomatitis</td>
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<td></td>
<td>• Fatigue/asthenia</td>
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<td>• Oedema</td>
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<td>• Your doctor may adjust your treatment according to test results, and will advise you on how to prevent infections.</td>
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<tr>
<td>Nintedanib* (Vartegaf SPC, 2016)</td>
<td>• Neutropenia</td>
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<td></td>
<td>• Peripheral neuropathy</td>
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<td></td>
<td>• Diarrhoea</td>
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<td></td>
<td>• Vomiting</td>
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<td></td>
<td>• Nausea</td>
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<td></td>
<td>• Mucositis</td>
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<td>• Stomatitis</td>
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<td></td>
<td>• Changes in liver function</td>
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<td></td>
<td>• Rash</td>
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<td></td>
<td>• Your doctor may adjust your treatment according to test results, and will advise you on how to prevent infections.</td>
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<td></td>
<td>• Report any signs of peripheral neuropathy (tingling or numbness in your hands or feet) to your doctor, who will help you to manage this side effect.</td>
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<td>• If you experience diarrhoea, nausea, vomiting, a sore mouth or lips, your doctor will be able to help you to prevent or manage these side effects.</td>
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<td>• You will have tests before and during treatment to check how well your liver is functioning.</td>
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<td>• Let your doctor know if you develop any rash – they will help you to manage this side effect.</td>
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<tr>
<td>Necitumumab* (Portrazza SPC, 2016)</td>
<td>• Vomiting</td>
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<td>• Stomatitis</td>
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<tr>
<td></td>
<td>• Weight loss</td>
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<td></td>
<td>• Altered levels of minerals and salts (hypocalcaemia, hypophosphataemia, hypokalaemia, hypomagnesaemia)</td>
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<td>• Skin reactions</td>
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<td></td>
<td>• Fever</td>
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<td></td>
<td></td>
<td>• If you experience vomiting or a sore mouth or lips, your doctor will be able to help you to prevent or manage these side effects, and limit any weight loss.</td>
</tr>
<tr>
<td></td>
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<td>• Your body’s levels of minerals and salts will be monitored during your treatment – your treatment may be adapted according to any changes.</td>
</tr>
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<td></td>
<td>• Let your doctor know if you experience any skin reactions (e.g. rash, dry skin, discolouration), your doctor will be able to help you to prevent or manage these side effects.</td>
</tr>
<tr>
<td>Osimertinib* (Tagrisso SPC, 2017)</td>
<td>• Neutropenia</td>
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<td></td>
<td>• Leukopenia</td>
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<td></td>
<td>• Thrombocytopenia</td>
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<tr>
<td></td>
<td>• Diarrhoea</td>
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<td></td>
<td>• Stomatitis</td>
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<td></td>
<td>• Skin reactions (rash, dry skin, itchiness)</td>
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<td></td>
<td>• Nail disorders</td>
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<td></td>
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<td>• Your blood cell counts will be monitored frequently throughout your treatment in order to detect any neutropenia, leukopenia or thrombocytopenia – your doctor may adjust your treatment according to test results, and will advise you on how to prevent infections.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If you experience diarrhoea or a sore mouth or lips, your doctor will be able to help you to prevent or manage these side effects.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Report any skin reactions or nail changes to your doctor – they will help you to manage these side effects.</td>
</tr>
<tr>
<td>THERAPY</td>
<td>POSSIBLE SIDE EFFECT</td>
<td>HOW THE SIDE EFFECTS MAY BE MANAGED</td>
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</tr>
<tr>
<td><strong>Ceritinib</strong></td>
<td>• Anaemia</td>
<td>• Your blood cell counts will be monitored frequently throughout your treatment in order to detect any <em>anaemia</em> — your doctor may adjust your treatment according to test results.</td>
</tr>
<tr>
<td>(Zykadia SPC, 2016)</td>
<td>• Changes in liver function</td>
<td>• You will have tests before and during treatment to check how well your liver is functioning.</td>
</tr>
<tr>
<td></td>
<td>• Diarrhoea</td>
<td>• If you experience diarrhoea, nausea, vomiting, constipation, indigestion, heartburn or problems swallowing, your doctor will be able to help you to prevent or manage these side effects.</td>
</tr>
<tr>
<td></td>
<td>• Nausea</td>
<td>• Report any rashes to your doctor — they will help you to manage this side effect.</td>
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<tr>
<td></td>
<td>• Vomiting</td>
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<td></td>
<td>• Constipation</td>
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<tr>
<td></td>
<td>• Dyspepsia, acid reflux, dysphagia</td>
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<tr>
<td></td>
<td>• Decreased appetite</td>
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<td></td>
<td>• Fatigue</td>
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<td></td>
<td>• Rash</td>
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<tr>
<td><strong>Nivolumab</strong></td>
<td>• Neutropenia</td>
<td>• Your blood cell counts will be monitored frequently throughout your treatment in order to detect any <em>neutropenia, lymphopenia, leukopenia, anaemia or thrombocytopenia</em> — your doctor may adjust your treatment according to test results, and will advise you on how to prevent infections.</td>
</tr>
<tr>
<td>(Opdivo SPC, 2015)</td>
<td>• Lymphopenia</td>
<td>• You will have tests before and during treatment to check how well your liver is functioning.</td>
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<tr>
<td></td>
<td>• Leukopenia</td>
<td>• Your doctor will be able to help you to prevent or manage any diarrhoea or nausea.</td>
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<tr>
<td></td>
<td>• Thrombocytopenia</td>
<td>• Your body’s levels of minerals and salts will be measured during your treatment — your treatment may be adapted according to any changes.</td>
</tr>
<tr>
<td></td>
<td>• Anaemia</td>
<td>• Let your doctor know if you experience any skin rash or itchiness — they will be able to help you to prevent or manage these side effects.</td>
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<td></td>
<td>• Changes in liver function</td>
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<tr>
<td></td>
<td>• Diarrhoea</td>
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<td>• Nausea</td>
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<td>• Fatigue</td>
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<td>• Altered levels of minerals and salts</td>
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<td>(hypercalcaemia, hyperkalaemia, hypokalaemia,</td>
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<td>hypomagnesaemia, hyponatraemia)</td>
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<td></td>
<td>• Rash</td>
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<td></td>
<td>• Pruritus</td>
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<tr>
<td><strong>Pembrolizumab</strong></td>
<td>• Diarrhoea</td>
<td>• Your doctor will be able to help you to prevent or manage any diarrhoea or nausea.</td>
</tr>
<tr>
<td>(Keytruda SPC, 2015)</td>
<td>• Nausea</td>
<td>• Let your doctor know if you experience any skin rash or itchiness or joint pain — they will be able to help you to prevent or manage these side effects.</td>
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<td></td>
<td>• Rash</td>
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<td></td>
<td>• Pruritus</td>
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<td></td>
<td>• Arthralgia</td>
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<td>• Fatigue</td>
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</table>

*Very common side effects with targeted therapy and antiangiogenic therapy in the treatment of NSCLC. The most recent Summary of Product Characteristics (SPCs) for individual drugs can be located at: [http://www.ema.europa.eu/ema/](http://www.ema.europa.eu/ema/).

*In combination with docetaxel chemotherapy; *Very common side effects reported when administered in combination with gemcitabine and cisplatin.*
What happens after my treatment has finished?

Follow-up appointments

You will be able to discuss any concerns you have at your follow-up appointments

After your treatment has finished, your doctor will arrange follow-up appointments. You will have regular chest x-rays and/or CT scans to check that there are no further tumours. Your doctor will also evaluate any treatment complications or side effects related to surgery, radiotherapy and/or chemotherapy. The frequency of these appointments will be tailored to your situation, and will depend on the stage of the cancer when you were initially diagnosed and the treatment that you have had (Vansteenkiste et al., 2013; Novello et al., 2016).

Recommendations

- After surgery for stage I-III NSCLC, you should be seen every 3-6 months for the first 2-3 years and then yearly after that (Vansteenkiste et al., 2013).
- After SABR, you may have a CT scan every 6 months, particularly if you are suitable for salvage treatment should there be any complications (Vansteenkiste et al., 2014).
- After treatment for metastatic disease, depending on your suitability for further treatment, your doctor will see you every 6-12 weeks so that second-line therapy can be started promptly, if needed (Novello et al., 2016).
- If you have had multi-modality treatment for stage III disease you are likely to have brain scans to monitor for the development of brain metastases, for which you may be offered treatment (Eberhardt et al., 2015).

What if I need more treatment?

Cancer that comes back is called a recurrence. The treatment that you will be offered depends on the extent of the recurrence. When the tumour comes back as a recurrence at a single site, you may be offered treatment such as surgical removal or radiotherapy. However, this approach is limited to a very small group of patients. Recurrent tumours are normally regarded as metastatic cancers and you can usually have further chemotherapy with different drugs. Sometimes, targeted therapy drugs are given with chemotherapy (see section ‘Treatment options for metastatic (stage IV) NSCLC’ for more information).

In some cases, a repeated biopsy of the tumour may be carried out as it may result in a change to the treatment decision. This may be particularly true if you have been cancer-free for some time after surgical resection. Where available, patients who were previously treated for NSCLC with an EGFR-activating mutation may undergo a liquid biopsy to detect any T790M mutation (also called plasma EGFR mutational analysis). This will involve providing a small blood sample for analysis. Re-biopsy may be useful to differentiate between disease...
recurrence and a new primary lung tumour (if the recurrence is detected in the lung) to ascertain the type of tumour or to repeat the EGFR mutation test if a non-squamous cancer is detected (Vansteenkiste et al., 2013; Vansteenkiste et al., 2014; Eberhardt et al., 2015; Novello et al., 2016).

Looking after your health

After you have had treatment for NSCLC, you may feel very tired and emotional. It is important to take good care of yourself and get the support that you need.

- **Stop smoking:** If you are a smoker, it is important to stop smoking as soon as you can as it may reduce the risk of disease recurrence (Vansteenkiste et al., 2013; Vansteenkiste et al., 2014; Eberhardt et al., 2015; Novello et al., 2016). Your doctor and nurse can offer help with stopping smoking.

- **Take plenty of rest when you need it:** Give your body time to recover and make sure you rest as much as you can. Complementary therapies, such as aromatherapy, may help you relax and cope better with side effects. Your hospital may offer complementary therapy; ask your doctor for details.

- **Eat well and keep active:** Eating a healthy diet and keeping active can help improve your fitness. It is important to start slowly, with gentle walking, and build up as you start to feel better.

Emotional support

It is common to be overwhelmed by your feelings when you have been diagnosed with cancer and when you have been through treatment. If you feel anxious or depressed, talk to your doctor or nurse – they can refer you to a specialist counsellor or psychologist who has experience of dealing with emotional problems of people dealing with cancer. It may also help to join a support group so that you can talk to other people who understand exactly what you are going through.
Support groups

In Europe, there are some lung cancer patient advocacy groups, which help patients and their families to navigate the lung cancer landscape. They can be local, national or international, and they work to ensure patients receive appropriate and timely care and education. These groups can provide you with the tools you may need to help you better understand your disease, and to learn how to cope with it, living the best quality of life that you can.

You can access information from the following organisations:

- **Global Lung Cancer Coalition (GLCC):** [www.lungcancercoalition.org](http://www.lungcancercoalition.org)
- **Lung Cancer Europe (LuCE):** [www.lungcancereurope.eu](http://www.lungcancereurope.eu)
- **Women Against Lung Cancer in Europe (WALCE) educational booklets:**
  [www.womenagainstlungcancer.eu/?lang=en](http://www.womenagainstlungcancer.eu/?lang=en)
References


Non-small-cell lung cancer


GLOSSARY

ACCELERATED SCHEDULE
A higher dose of radiation is given at each treatment and there are fewer total treatments than in a conventional radiotherapy schedule. The total amount of radiation given is about the same in each schedule.

ADENOCARCINOMA
The most common type of lung cancer; it develops from mucus-producing cells that line the airways.

ADRENAL GLANDS
Glands in the body that produce hormones, such as adrenaline and steroids. They are located above the kidneys.

ADJUVANT (CHEMOTHERAPY OR RADIOTHERAPY)
Additional treatment given after the primary treatment to reduce the chance of the cancer coming back; usually refers to radiotherapy and/or chemotherapy after surgery.

AFATINIB
A type of targeted therapy called a tyrosine kinase inhibitor, which works by blocking signals within cancer cells and stopping the action of epidermal growth factor receptor, causing cancer cells to die. It is administered as a once daily tablet.

AIR LEAK
When air escapes from the airways (bronchioles, alveoli) into the parts of the lung where air is not usually present.

ALECTINIB
A type of targeted therapy called a tyrosine kinase inhibitor, which works by blocking a protein called anaplastic lymphoma kinase. It only works in cancer cells with an abnormal version of this protein. It is administered twice-daily as oral capsules.

ANAPLASTIC LYMPHOMA KINASE REARRANGEMENTS (ALK)
Anaplastic lymphoma kinase is a cell surface protein. Rearrangement of the ALK gene is an abnormality found in some cancer cells, including NSCLC.

ALOPECIA
Hair loss.

ALVEOLI
Tiny air sacs within the lungs that allow oxygen and carbon dioxide to move between the lungs and bloodstream.

ANAEMIA
A condition characterised by the shortage of red blood cells or haemoglobin (a protein in red blood cells that carries oxygen throughout the body).

ANOREXIA
A lack or loss of appetite.

ANTIANGIOGENIC THERAPY
A type of therapy that interferes in the growth and survival of new blood vessels (angiogenesis), which plays a critical role in the growth and spread of cancer.

ANTIBIOTIC
A type of drug used to treat and prevent bacterial infections.

ARSENIC
A naturally occurring substance that has been widely used in some industries (copper or lead smelting; agriculture/pesticides), but has been linked to cancer, including lung cancer.

ARTHRALGIA
Pain in a joint(s).

ASBESTOS
A natural, fibrous material that was previously widely used as a building material. Its use is now banned throughout Europe as it is linked to lung diseases, including cancer.

ASTHENIA
Abnormal feeling of weakness or lack of energy.

BEVACIZUMAB
A type of targeted therapy used to treat some cancers, including advanced NSCLC. It is a monoclonal antibody that targets vascular endothelial growth factor and prevents the cancer cells from developing their own blood supply, thus helping to slow down tumour growth.

BIOPSY
A medical procedure in which a small sample of cells or tissue is taken for examination under a microscope.

BLOOD VESSELS
The structures (tubes) carrying blood through the tissues and organs of the body – they include veins, arteries and capillaries.

BONE MARROW
A spongy tissue found inside some bones (e.g. hip and thigh bones). It contains stem cells, which are cells that can develop into the red blood cells, white blood cells or platelets.

BRADYCARDIA
Abnormally slow heart rate.

BRONCHI
The right bronchus and the left bronchus (the bronchi) are the two main airways that take air into the lungs.
GLOSSARY

BRONCHOLES
The bronchi divide into smaller bronchioles, which then lead to the alveoli

BRONCHOSCOPE
A thin, fibre-optic cable that is inserted into the airways (usually through the nose or mouth)

BRONCHOSCOPY
A clinical investigation where your doctor examines your airways using a bronchoscope

CARBOPLATIN
A type of chemotherapy that is administered through a drip into a vein in your arm or chest

CELESTINI
A type of targeted therapy that works by inhibiting a protein called anaplastic lymphoma kinase. It is administered as a once-daily capsule to patients who have previously received crizotinib

CHEMORADIOThERAPY
Chemotherapy and radiotherapy given together

CHEMOTHERAPY
A type of cancer treatment using medicine that kills the cancer cells by damaging them, so that they cannot reproduce and spread

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)
A type of lung disease characterised by long-term poor airflow. The main symptoms include shortness of breath and cough

CISPLATIN
A type of chemotherapy that is administered through a drip into a vein in your arm or chest

CLINICAL TRIAL
A study that compares the effects of one treatment with another

COMORBIDITIES
Additional diseases or disorders experienced by the patient at the same time

COMPUTED TOMOGRAPHY (CT)
A scan using x-rays and a computer to create detailed images of the inside of your body

CONCURRENT
Different types of treatment (e.g. chemotherapy and radiotherapy) given at the same time

CONJUNCTIVITIS
Inflammation of the membrane that covers the eyeball and lines the eyelid

CONVENTIONAL RADIOTHERAPY
Refers to radiotherapy that is given to the tumour as a fraction of the complete dose over several sessions – treatment usually consists of a small daily dose over several weeks

CRIZOTINIB
A type of targeted therapy called a tyrosine kinase inhibitor, which works by blocking a protein called anaplastic lymphoma kinase. It only works in cancer cells with an abnormal version of this protein. It is administered as a twice-daily capsule

DIAPHRAGM
The muscle that separates the chest cavity from the abdomen; the diaphragm contracts and relaxes as we breathe in and out

DOCETAXEL
A type of chemotherapy that is administered through a drip into a vein in your arm or chest

DOUBLET CHEMOTHERAPY
A combination of two different types of chemotherapy administered at the same time

DYSPNEA
Shortness of breath

DYSPHAGIA
The medical term for difficulties with swallowing

DYSPNOEA
Shortness of breath

EARLY-STAGE (CANCER)
Cancer that has not spread to the lymph nodes or other parts of the body

EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR)
A protein involved in cell growth and division. It is found in abnormally high amounts on the surface of many types of cancer cells

EPISTAXIS
The medical term for a nose bleed
**GLOSSARY**

**ERLOTINIB**
A type of targeted therapy called a tyrosine kinase inhibitor, which works by blocking signals within cancer cells and stopping the action of epidermal growth factor receptor, causing cancer cells to die. It is administered as a once-daily tablet.

**ETOPOSIDE**
A type of chemotherapy that is administered through a drip into a vein in your arm or chest, or as an oral tablet or capsule.

**FATIGUE**
Overwhelming tiredness.

**FIRST-LINE**
The initial treatment given to a patient.

**GASTROINTESTINAL SYSTEM**
The system of organs responsible for getting food into and out of the body and for making use of food to keep the body healthy – includes the oesophagus, stomach and intestines.

**GEFITINIB**
A type of targeted therapy called a tyrosine kinase inhibitor, which works by blocking signals within cancer cells that tell the cells to grow. It is administered as a once-daily tablet.

**GEMCITABINE**
A type of chemotherapy that is administered through a drip into a vein in your arm or chest.

**GENERAL ANAESTHETIC**
A medication that causes a reversible loss of consciousness.

**GRADE**
Cancer grade is based on how different tumour cells look from normal cells under a microscope, and on how quickly they grow. The grade will be a value between one and three and reflects the aggressiveness of tumour cells; the higher the grade, the more aggressive the tumour.

**HAIR FOLLICLE**
A small sac in the skin from which hair grows from.

**HEPATIC**
Relating to the liver.

**HISTOLOGICAL SUBTYPE**
Cancer type based on the type of tissue in which the cancer started.

**HYPERCALCAEMIA**
An abnormally high level of calcium in the blood.

**HYPERKALAEMIA**
An abnormally high level of potassium in the blood.

**HYPERTENSION**
Abnormally high blood pressure.

**HYPOCALCAEMIA**
An abnormally low level of calcium in the blood.

**HYPOKALAEMIA**
An abnormally low level of potassium in the blood.

**HYPOMAGNESAEAMIA**
An abnormally low level of magnesium in the blood.

**HYPONATRAEMIA**
An abnormally low level of sodium in the blood.

**IMMUNOTHERAPY**
A type of cancer treatment that stimulates the body’s immune system to fight the cancer.

**INDUCTION THERAPY**
Initial treatment with chemotherapy and/or radiotherapy to shrink the tumour before a second planned treatment (for example, surgery).

**INTRAVENOUS**
Administered into a vein.

**IONISING RADIATION**
Any type of particle or electromagnetic wave that carries enough energy to ionize or remove electrons from an atom (e.g. x-rays).

**LARGE CELL (UNDIFFERENTIATED) CARCINOMA**
A type of NSCLC that does not look like adenocarcinoma or squamous cell carcinoma under the microscope.

**LEUKOPENIA**
A decrease in the number of leukocytes (a type of white blood cell) in the blood, which places individuals at increased risk of infection.

**LIQUID BIOPSY**
Tests performed in blood samples or other body fluids to detect the presence of substances that have originated in a tumour, and therefore, indicate the presence of a cancer.
### GLOSSARY

**LOBECTOMY**
A type of lung cancer surgery in which one lobe of a lung is removed. (The right lung has three lobes, and the left lung has two lobes)

**LOBE**
A (usually rounded) part of an organ that appears to be separate in some way from the rest of that organ

**LOCAL ANAESTHETIC**
A medication that causes reversible absence of pain sensation around the site of administration

**LOCALLY ADVANCED**
Cancer that has spread from where it started to nearby tissue or lymph nodes

**LYMPH**
The fluid that circulates throughout the lymphatic system; it contains infection-fighting white blood cells

**LYMPH NODES**
Small structures throughout the lymphatic system that work as filters for harmful substances, such as cancer cells or bacteria

**LYMPHATIC SYSTEM**
A network of tissues and organs that help rid the body of toxins, waste and other unwanted materials. The primary function of the lymphatic system is to transport lymph, a fluid containing infection-fighting white blood cells, throughout the body

**LYMPHOPENIA**
An abnormally low level of lymphocytes (a type of white blood cell) in the blood, which places individuals at increased risk of infection

**MAGNETIC RESONANCE IMAGING (MRI)**
A type of scan that uses strong magnetic fields and radio waves to produce detailed images of the inside of the body

**MAINTENANCE TREATMENT**
Treatment given after the initial cycles of chemotherapy with the aim of keeping the cancer under control

**METACHRONOUS OLIGOMETASTASES**
Oligometastases that appear following treatment for a primary tumour

**METASTATIC**
A cancer that has spread from its (primary) site of origin to different parts of the body

**METASTASIS (METASTASES)**
A cancerous tumour or growth that has originated from a primary tumour/growth in another part of the body (plural = metastases)

**MONOCLONAL ANTIBODY**
A type of targeted therapy. Monoclonal antibodies recognise and attach to specific proteins produced by cells. Each monoclonal antibody recognises one particular protein. They work in different ways depending on the protein they are targeting

**MUCOSIS**
Inflammation and ulceration of the membranes lining the gastrointestinal system

**MULTIDISCIPLINARY TEAM**
A group of health care workers who are members of different disciplines (e.g. oncologist, nurse specialist, physiotherapist, radiologist) and provide specific services to the patient. The activities of the team are brought together using a care plan

**MULTIMODAL THERAPY**
A treatment approach that includes two or more treatment types – usually some combination of surgery, chemotherapy and radiotherapy

**MUTATION**
A permanent alteration in the DNA sequence that makes up a gene, such that the sequence differs from what is found in most people

**MYALGIA**
Pain in a muscle(s)

**NECITUMUMAB**
A targeted therapy (monoclonal antibody) that blocks activity of epidermal growth factor receptor. It is administered through a drip into a vein in your arm or chest and in combination with two types of chemotherapy (gemcitabine and cisplatin)

**NEUROLOGICAL**
Relating to the nerves and the nervous system

**NEUTROPENIA**
An abnormally low level of neutrophils in the blood, which increases risk of infection

**NEUTROPHIL**
A type of white blood cell that play an important role in fighting off infection
GLOSSARY

**NINTEDANIB**
A type of targeted therapy that blocks proteins called protein kinases, which are present in cancer cells and involved in cancer cell growth. It is administered as a twice-daily capsule.

**NIVOLUMAB**
A type of immunotherapy that blocks a protein called PD-1 on the surface of certain immune cells called T-cells; this activates the T-cells to find and kill cancer cells. It is administered through a drip into a vein in your arm or chest.

**NURSE SPECIALIST**
A nurse specialised in the care of patients with a certain condition (e.g. cancer).

**OEDEMA**
A build-up of fluid in the body which causes the affected tissue to become swollen.

**OESOPHAGITIS**
Inflammation of the oesophagus.

**OESOPHAGUS**
The food pipe; the tube that connects your throat with your stomach.

**OLIGOMETASTATIC DISEASE (OLIGOMETASTASES)**
Cancer that has spread from its original site to a limited number of other sites/organisms; disease progression may occur at these sites but without spread to additional organs (oligometastases can be described as either synchronous or metachronous).

**ONCOLOGIST**
A doctor who specialises in the medical management of cancer.

**OSIMERTINIB**
A type of targeted therapy called a tyrosine kinase inhibitor, which works by blocking signals within cancer cells and stopping the action of epidermal growth factor receptor, causing cancer cells to die. It is administered as a once-daily tablet to patients who have previously been treated with another tyrosine kinase inhibitor.

**PACLITAXEL**
A type of chemotherapy that is administered through a drip into a vein in your arm or chest.

**PALLIATIVE CARE**
The care of patients with advanced, progressive illness. It focuses on providing relief from pain, symptoms and physical and emotional stress, without dealing with the cause of the condition.

**PASSIVE SMOKING**
The inhalation of smoke by a person who is not actively smoking themselves.

**PATHOLOGIST**
Doctor who diagnoses disease by examining cell and tissue samples.

**PEMBROLIZUMAB**
A type of immunotherapy that blocks a protein called PD-1 on the surface of certain immune cells called T-cells; this activates the T-cells to find and kill cancer cells. It is administered through a drip into a vein in your arm or chest.

**PEMETREXED**
A type of chemotherapy drug used to treat NSCLC, which is given intravenously (directly into your bloodstream through a vein in your arm or chest).

**PERICARDIUM**
The membrane that encloses the heart.

**PERIPHERAL NEUROPATHY**
Damage to the nerves in the extremities of the body. Symptoms may include pain, sensitivity, numbness or weakness in the hands, feet or lower legs.

**PHARYNGITIS**
Inflammation of the pharynx, which is in the back of the throat.

**PLATELETS**
Tiny blood cells that help your body form clots to stop bleeding.

**PLATINUM-BASED**
A class of chemotherapy that includes cisplatin and carboplatin.

**PLEURA**
One of the two membranes around the lungs. These two membranes are called the visceral and parietal pleurae.

**PNEUMONECTOMY**
The surgical removal of a lung or part of a lung.

**PNEUMONIA**
Inflammation of the lung, usually caused by an infection.

**POSITRON EMISSION TOMOGRAPHY (PET)**
An imaging test that uses a dye with radioactive tracers, which is injected into a vein in your arm.

**PRIMARY LUNG CANCER**
A cancer that first started in the lungs.
Non-small-cell lung cancer

GLOSSARY

PRIMARY TUMOUR
The tumour where the cancer first started to grow

PROGNOSIS
The likely outcome of a medical condition

PROGRAMMED DEATH LIGAND-1 (PD-L1)
A cellular protein thought to be involved in helping the tumour to evade detection by the body’s immune system

PRURITUS
Severe itching of the skin

RADIATION PNEUMONITIS
Symptoms of cough, fever and fullness of the chest that usually appear between 2 weeks and 6 months following radiotherapy but are usually temporary

RADIOACTIVE
A material that is unstable and spontaneously emits energy (radiation)

RADIOLOGICAL EXAMINATION
A test that uses x-rays or other medical imaging techniques to visualise the body and organs for the detection of signs of cancer or other abnormalities

RAY OF LIGHT
A doctor specialised in diagnosing and treating disease and injury through the use of medical imaging techniques such as x-rays, computed tomography, magnetic resonance imaging, positron emission tomography and ultrasound

RADIOOTHERAPY
Treatment involving the use of high-energy radiation, which is commonly used to treat cancer

RAMUCIRUMAB
A type of targeted therapy that blocks the action of vascular endothelial growth factor, and prevents the cancer cells from developing their own blood supply, thus helping to slow down tumour growth. It is administered through a drip into a vein in your arm or chest in combination with another type of chemotherapy

RESECTABLE
Able to be removed (resected) by surgery

RHINITIS
Inflammation of the lining inside the nose

SECOND LINE
The second treatment given to a patient once the initial (first-line) therapy has not worked or has been stopped because of the occurrence of side effects or other concerns

SEGMENT (OR WEDGE) RESECTION
Surgical removal of the segment of the lung where the tumour is located

SEQUENTIALLY
Treatment given one after the other

SQUAMOUS CELL CARCINOMA (SCC)
A type of NSCLC; usually occurs in the central part of the lung or in one of the bronchi

STENT
A small tube that is used to keep an airway or artery open

STEREOTACTIC ABLATIVE RADIOThERAPY (SABR)
A specialised type of radiotherapy that is given to the tumour from many different directions using detailed scans to ensure precise targeting so that higher doses can be given over a shorter time

STOMATITIS
Inflammation of the inside of the mouth

SUPPORTIVE CARE
Care that provides relief from pain, symptoms and physical and emotional stress, without treating the cancer itself

SYNCHRONOUS OLIGOMETASTASES
Oligometastases diagnosed within a few months of a primary tumour

SYSTEMIC ANTICANCER TREATMENT
Drugs that spread throughout the body to treat cancer cells wherever they may be. They include chemotherapy, hormonal therapy, targeted therapy, and immunotherapy

T790M MUTATION
A mutation of the epidermal growth factor receptor (also known as Threonine 790 Methionine [Thr790Met] mutation)
# Glossary

## Targeted Therapy
A newer type of cancer treatment that uses drugs or other substances to precisely identify and attack cancer cells, usually while doing little damage to normal cells.

## Taxane
A class of chemotherapy that includes paclitaxel and docetaxel.

## Third-line
A third line of treatment given to a patient once the previous two lines (first-line and second-line) of therapy have not worked or have been stopped because of the occurrence of side effects or other concerns.

## Thrombocytopenia
A deficiency of platelets in the blood. This causes bleeding into the tissues, bruising, and slow blood clotting after injury.

## Thrombosis
The formation of a blood clot inside a blood vessel, obstructing the flow of blood through the blood system.

## Tinnitus
The hearing of a sound (such as ringing, whining or buzzing) when no external sound is present.

## Trachea
The windpipe – the wide, hollow tube that connects the larynx (or voice box) to the bronchi of the lungs.

## Tumour
A lump or growth of abnormal cells. Tumours may be benign (not cancerous) or malignant (cancerous). In this guide, the term ‘tumour’ refers to a cancerous growth, unless otherwise stated.

## Tyrosine Kinase Inhibitor (TKI)
A type of targeted therapy that inhibits tyrosine kinases, which are substances that send growth signals to cells.

## Ultrasound
A type of medical scan where sound waves are converted into images by a computer.

## Unresectable
Unable to be removed (resected) by surgery.

## Uranium
A naturally radioactive element.

## Vascular Endothelial Growth Factor (VEGF)
A protein produced by cells that stimulates the growth of new blood vessels.

## Video-assisted Thoracic Surgery (VATS)
A surgical procedure that allows doctors to see inside the chest and lungs. It is a form of ‘keyhole’ surgery.

## Vinorelbine
A type of chemotherapy that is administered through a drip into a vein in your arm or chest.

## Wedge (or segment) resection
Surgical removal of the segment of the lung where the tumour is located.

## X-ray
An imaging test, using a type of radiation that can pass through the body, that allows your doctor to see inside your body.
Non-small-cell lung cancer

This guide has been prepared to help you, your friends and your family better understand the nature of non-small-cell lung cancer (NSCLC) and the treatments that are available. The medical information described in this document is based on the clinical practice guidelines of the European Society for Medical Oncology (ESMO) for the management of early-stage, locally advanced or metastatic NSCLC. We recommend that you ask your doctor about the tests and types of treatments available in your country for your type and stage of NSCLC.
We can help you understand non-small-cell lung cancer and the available treatment options.

The ESMO Guides for Patients are designed to assist patients, their relatives and caregivers to understand the nature of different types of cancer and evaluate the best available treatment choices. The medical information described in the Guides for Patients is based on the ESMO Clinical Practice Guidelines, which are designed to guide medical oncologists in the diagnosis, follow-up and treatment in different cancer types.

For more information, please visit www.esmo.org