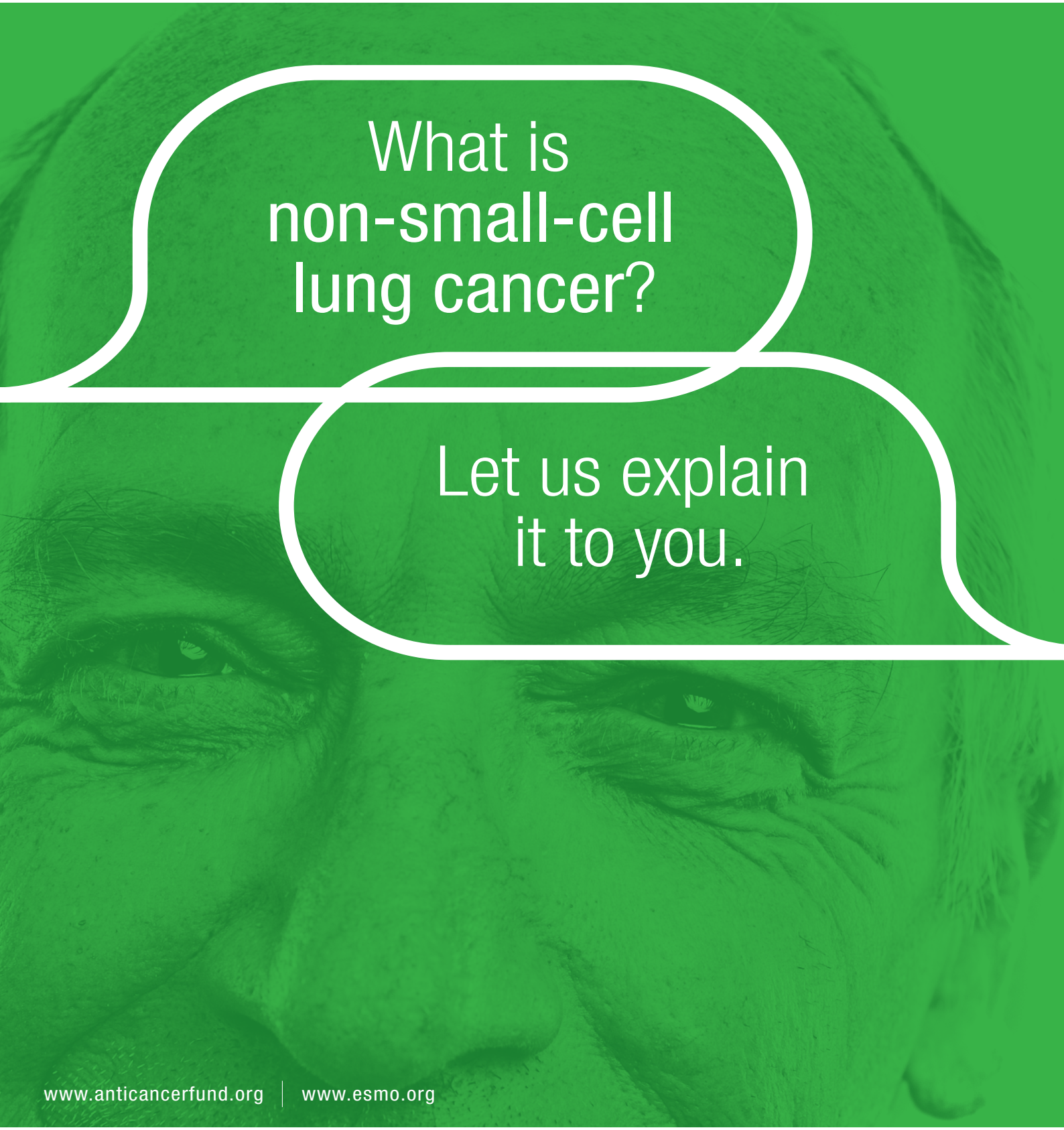
Non-Small-Cell Lung Cancer



Anticancer Fund

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

ESMO/ACF Patient Guide Series
based on the ESMO Clinical Practice Guidelines

NON-SMALL CELL LUNG CANCER (NSCLC)

A GUIDE FOR PATIENTS

PATIENT INFORMATION BASED ON ESMO CLINICAL PRACTICE GUIDELINES

This guide for patients has been prepared by the Anticancer Fund as a service to patients, to help patients and their relatives better understand the nature of non-small cell lung cancer (NSCLC) and appreciate the best treatment choices available according to the subtype of NSCLC. We recommend that patients ask their doctors about what tests or types of treatments are needed for their type and stage of disease. 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. This guide for patients has been produced in collaboration with ESMO and is disseminated with the permission of ESMO. It has been written by a medical oncologist and reviewed by two oncologists from ESMO including the lead author of the clinical practice guidelines for professionals. It has also been reviewed by patient representatives from ESMO's Cancer Patient Working Group.

More information about the Anticancer Fund: www.anticancerfund.org

More information about the European Society for Medical Oncology: www.esmo.org

For words marked with an asterisk, a definition is provided at the end of the document.

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This text was written by Dr. Giulio Metro (for the Anticancer Fund) and reviewed by Dr. Gauthier Bouche (the Anticancer Fund), Dr. Svetlana Jezdic (ESMO), Dr. Giannicola D'Addario (ESMO), Dr. Lucio Crinò (ESMO), Dr. Enriqueta Felip (ESMO), Pr. Gabriela Kornek (ESMO Cancer Patient Working Group), Pr. Lorenz Jost (ESMO Cancer Patient Working Group) and Stefania Vallone (Women Against Lung Cancer in Europe and Global Lung Cancer Coalition).

The first update was done by Dr. Giulio Metro (for the Anticancer Fund) and was reviewed by Dr. Svetlana Jezdic (ESMO), Stefania Vallone (Women Against Lung Cancer in Europe) and Simonetta Rapetti (Women Against Lung Cancer in Europe).

This is the second update of this guide. Updates reflect changes in the successive versions of the ESMO Clinical Practice Guidelines. The second update was done by Dr. Ana Ugarte (ACF) and was reviewed by Dr. Svetlana Jezdic (ESMO), Prof. Martin Reck (ESMO), and Vanessa Marchesi, PhD (ESMO).

FACTSHEET ABOUT NON-SMALL CELL LUNG CANCER (NSCLC)

Definition of non-small cell lung cancer (NSCLC)

- NSCLC is a group of lung cancers in which the tumour cells do not look small under a microscope, as opposed to small cell lung cancer, another type of lung cancer.
- The three main types of NSCLC are squamous cell carcinoma, adenocarcinoma, and large cell carcinoma of the lung. They are diagnosed in the same way but treatment may differ according to the type of disease.

Diagnosis

- Lung cancer can be suspected if a person has symptoms such as cough, increased production of sputum, shortness of breath, hoarseness, chest pain and blood in the sputum, or after a clinical examination.
- Radiological examinations* are mandatory to define the extension and stage of the disease.
- A piece of the tumour (biopsy) must be obtained for analysis in a laboratory to confirm the diagnosis and get more details about the characteristics of the tumour.

Treatment according to the extension of the disease (classified into different stages)

- Stage I and stage II NSCLC are called localized or early-stage cancers.
  - Removal of the tumour by surgery is the treatment of choice.
  - Radiotherapy is an alternative if surgery is not feasible because of medical reasons or if the patient refuses it.
  - Chemotherapy after surgery should be considered in all patients with stage II disease who can tolerate it.
- Stage III NSCLC is called locally advanced cancer.
  - The most important question for this stage of NSCLC is: can the tumour be resected by surgery or not? This question and decision about the best treatment must be discussed by a team of several specialists (surgeons, medical oncologists*, radiation oncologists* radiologists* etc.).
  - If the tumour is considered resectable:
    - Surgery is the best option. The use of chemotherapy before surgery may help to reduce the extent of the disease and make its removal by surgery possible.
    - Radiotherapy* after surgery may be considered when the tumour is removed entirely.
  - If the tumour is considered unresectable, radiotherapy should be given, either during or after chemotherapy.
  - Chemotherapy should be considered in all patients who can tolerate it.
- Stage IV NSCLC is called metastatic* because it has spread beyond the lung which was initially affected.
  - Since the tumour has spread, it is not possible to remove it by surgery. Only systemic therapies (therapies that travel throughout the body in the bloodstream) will be able to reach and affect the tumour.
  - Intravenous* chemotherapy with a two-drug combination is standard of care in patients without pre-defined molecular characteristics (i.e. modification of genes called EGFR* and ALK*), which are identified when the tumour biopsy* is analysed. The choice of drugs used will mainly depend on the fitness of the patient and on the type of tumour.

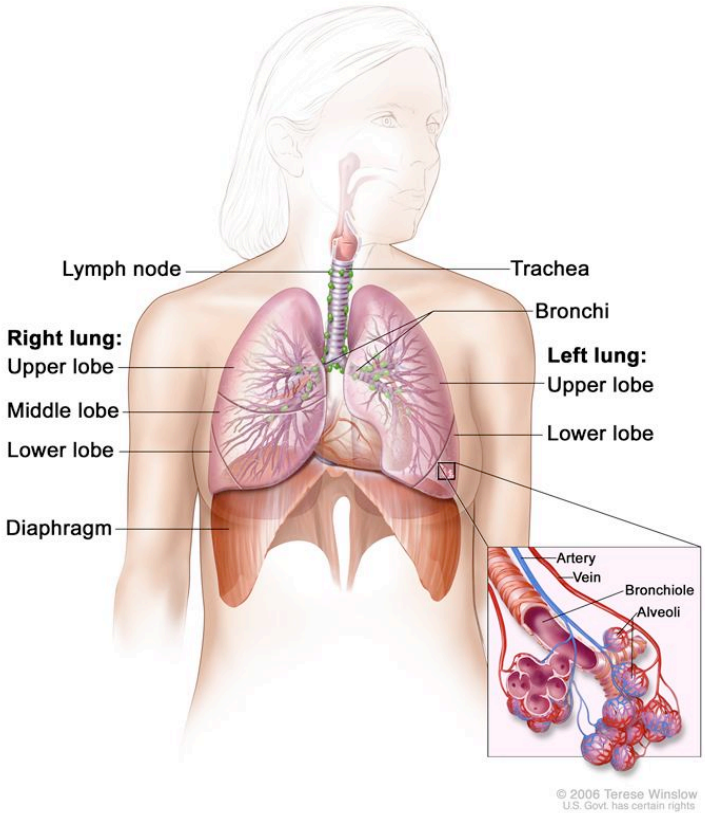
- Patients with EGFR* mutations or ALK* rearrangements, are best treated with orally administered biological drugs.
- Maintenance therapy may be given to patients in good clinical condition. The aim of this type of therapy is to prolong the effect of first-line chemotherapy on tumour control. This can be administered as continuation maintenance (therapy using one or more of the agents used as first-line therapy) or switch maintenance therapy (using an agent different from those used in the first-line setting). The choice of maintenance treatment might be related to response after first-line chemotherapy and recovery from toxicity of the previous treatment.
- Second- and third-line treatments may be proposed, depending on the treatment received in the first-line and on the general status of the patient.

Follow-up

- Patients with completely resected tumours are followed-up with clinical examinations every 3 to 6 months and a yearly CT-scan*.
- Patients with advanced disease who are treated with systemic therapy are seen by doctors every month in order to evaluate tolerance of the treatment. Efficacy is assessed through radiological examinations* performed every to 2 to 3 months.

DEFINITION OF NON-SMALL CELL LUNG CANCER

Non-small cell lung cancer (NSCLC) describes a group of lung cancers. These cancers are named "non-small cell" because the cells found in the tumour do not look small under a microscope, as opposed to another less common type of lung cancer called small-cell lung cancer (SCLC), which is characterised by the small size of the cells that it is composed of.
NSCLC may arise anywhere in the tissue that lines the air passages in the lung. Whenever possible, NSCLC is further divided into squamous (squamous cell cancer) and non-squamous (mainly adenocarcinoma) cancer based on specific histopathological* features, which has important therapeutic implications.
This guide is exclusively focused on NSCLC, which accounts for 85 to 90% of all lung cancer cases.



Anatomy of the respiratory system, showing the trachea and both lungs and their lobes and airways. Lymph nodes* and the diaphragm* are also shown. Oxygen is inhaled into the lungs and passes through the thin membranes of the alveoli* and into the bloodstream (see inset).*

IS NSCLC FREQUENT?

In developed areas, such as North America and Europe, lung cancer is the second and third most commonly diagnosed cancer in men and women, respectively. Lung cancer also represents the most frequent cause of cancer-related deaths in both sexes worldwide.
In Europe, approximately 291,000 men and 100,000 women were diagnosed with lung cancer in 2008. Every year, 93 out of 100,000 individuals are diagnosed with lung cancer.
There are considerable variations in lung cancer rates across different countries in Europe, which is reflected by the lifetime risk of developing this type of cancer. Between birth and 75 years, less than 3 out of 100 Swedish men and about 4 out of 100 Portuguese men will develop lung cancer, which are the lowest rates in Europe. This estimate goes up to more than 9 in every 100 men in Croatia and 10 in every 100 men in some areas of Poland. These variations are not only observed between countries but also within countries. In women, the risk of developing lung cancer is lower and varies between countries and less within countries. Northern countries have the highest rates (up to 4 in every 100 women in Iceland, Denmark and UK) while the lowest rates are observed in Spain (with less than 1 in every 100 women). These variations are mainly explained by smoking habits decades ago. Therefore, in the majority of European countries the incidence continues to rise in women, but is decreasing in men. This trend seems to occur later in Southern and Eastern Europe than in the Northern regions. These variations reflect the different smoking habits between regions.
NSCLC represents 85 to 90% of all lung cancers. Approximately 90% of lung cancers among men and 80% among women are related to smoking.

WHAT CAUSES NSCLC?

NSCLC is a cancer for which active cigarette smoking represents a well-established and characterised risk factor. However, as for other cancers, the cause of NSCLC may be multifactorial, with several other factors potentially contributing to its development in a synergistic manner. In addition, the emerging understanding of NSCLC genetics indicates the relevance of interactions between environmental and genetic factors in causing NSCLC.
Before reviewing the main risk factors for NSCLC, it is important to state that a risk factor increases the risk of cancer occurring, but is neither necessary nor sufficient to cause cancer. In fact, a risk factor is not a cause in itself. **Therefore, it could be that some people with the following risk factors will never develop NSCLC and some people without any of the following risk factors may nonetheless develop NSCLC.**

- **Active cigarette smoking**: NSCLC is one of the few cancers where a single risk factor, namely cigarette smoking, can be recognised by far as the leading cause. Epidemiologic studies* have shown that active cigarette smoking is responsible for up to 90% of all lung cancers. Of note, the duration of smoking seems to be much more relevant as a contributing risk factor compared with the number of cigarettes smoked per day. Therefore, giving up smoking at any age can translate into a much more significant reduction in NSCLC risk than simply reducing the number of cigarettes smoked per day.

- **Passive smoking**: Also referred to as "second-hand smoke" or "environmental tobacco smoke", this increases the risk of NSCLC, albeit far less markedly compared to active cigarette smoking.
- **Radon**: A radioactive gas produced from the decay of naturally occurring uranium*. Radon gas is ubiquitous at very low levels in outdoor air, and can accumulate indoors by entering homes through cracks in floors, walls and foundations. However, domestic radon exposure is very much dependent on how houses are built and ventilated. On the other hand, as an occupational risk factor, it is particularly relevant for underground miners who are usually exposed to high levels of radon.
- **Asbestos**: This mineral is a well-established occupational carcinogen*. It is used in a variety of products for the purpose of thermal insulation, fire proofing, acoustic insulation, roofing, flooring and in several other building materials. In the presence of active cigarette smoking, asbestos exposure has a synergistic effect on the increase of NSCLC risk. At the present time, many countries (including those in the European Union) have banned the use of asbestos, in whole or in part, due to the strong relationship that exists between asbestos exposure and mesothelioma* (another thoracic cancer which arises in the pleura*).

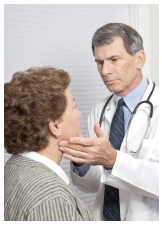
Other factors have been suspected to be associated with an increased risk of NSCLC. These include outdoor air pollutants, acquired lung diseases (including those that develop as a result of occupational exposure to dust e.g. as for miners), indoor air pollution (e.g. coal-fuelled stoves and cooking fumes) suspected to contribute to non-smoking-related lung cancer in women, dietary habits, viral factors and genetic susceptibility. The evidence that these factors increase the risk of developing NSCLC is far less consistent compared with the previously mentioned risk factors. However, along with other non-smoking-related risk factors, they might play an important role in those cases of NSCLC that arise in individuals who have never been exposed to smoking during their lifetime.

HOW IS NSCLC DIAGNOSED?

At the present time, there is no clear evidence that screening[1] with low-dose CT-scan* should be a routine procedure in people who are at higher risk of developing NSCLC (i.e. smokers). Therefore, the diagnosis of NSCLC can only be suspected on the basis of the symptoms reported by the patient. Here, the most common symptoms are described. Non-specific symptoms may include loss of appetite, weight loss and fatigue, whereas more specific symptoms, such as cough, increased production of sputum, shortness of breath (dyspnoea), hoarseness/lowering of the voice (dysphonia), chest pain and presence of blood in the sputum, are related to the presence of the primary tumour. In addition, the intrathoracic* spread of lung cancer by direct extension of the primary tumour may produce a variety of other symptoms. These may be caused by the involvement of nerves, chest wall and pleura*, or visceral* structures (e.g. pericardium* and oesophagus). For instance, chest wall and pleural invasion by the primary tumour usually cause localised chest pain or pleural effusion*. On the other hand, pericardial and oesophageal involvement can cause pericardial effusion* and dysphagia (difficulty in swallowing), respectively.
In some other cases, NSCLC becomes evident when it has already spread to other parts of the body, in which case the first symptoms of the disease may reflect this metastatic* spread (e.g. bone pain in the case of bone metastases*, or headache and/or neurologic symptoms in the case of brain metastases).

Besides the aforementioned symptoms and signs, the diagnosis of NSCLC is based on the following examinations:

1. **Clinical examination:** Even if the diagnosis of lung cancer cannot be made based on the findings of the clinical respiratory examination, this examination should always be part of a patient's work-up if respiratory symptoms are reported and/or abnormal findings are detected on radiological test(s)*.
   The clinical respiratory examination includes chest inspection, palpation, percussion, and auscultation. Lung auscultation findings must be interpreted carefully and put into context with the patient's medical background and other clinical findings. Clinical examination should include physical palpation of superficial lymph node* groups of the neck as well as those located just above the clavicles (supraclavicular*).



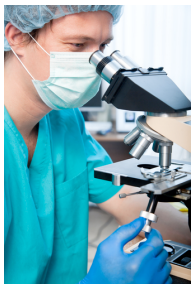
2. **Radiological examination*:** Radiological tests are crucial in order to both confirm a diagnosis of NSCLC and to define its extension.
   - **Chest X-ray***: This is commonly the first test during a patient's work-up.

[1] Screening consists of performing an examination in order to detect cancer at an early stage, before any sign of the cancer appears. A systematic screening is proposed if a safe and acceptable examination can be performed and if this examination is able to detect cancer in the majority of cases. It should also be proven that treating cancers detected by screening is more effective than treating cancers diagnosed because signs of cancer were present.

- **CT-scan* of the chest and upper abdomen**: This is an X-ray*-based medical test which is necessary for correct staging* of NSCLC. It allows a precise evaluation of the extension of the primary tumour in the lung and the presence/absence of enlarged regional lymph node(s)* as well as the presence/absence of other nodules in the lung(s) and/or metastatic* disease in the abdomen (e.g. liver).
- **CT-scan* of the brain**: This is necessary in order to exclude the presence of brain metastases*. It is recommended as a pre-operative tool in nearly all cases of surgically-resectable NSCLC, as well as in those patients with metastatic NSCLC for whom brain involvement is suspected based on clinical symptoms.
- **MRI* of the brain**: This is often preferred to a CT-scan* since it allows a more accurate study of the brain.
- **PET/CT-scan**: This is a nuclear medical imaging test, which allows both the morphology and metabolic activity of the tumour to be examined. It is recommended as a pre-operative test in all cases of surgically-resectable NSCLC.
- **Bone scan**: This is a nuclear medical imaging test which is performed in order to check if NSCLC has metastasised* to the bones. It is indicated by the presence of bone pain, elevated serum calcium* or an elevated alkaline phosphatase test*. If a PET/CT-scan* is done as part of the staging* work-up, a bone scan does not need to be performed.

3. **Histopathological examination*:** This is the laboratory examination of the cells made by taking a sample of the tumour tissue (a biopsy*) and dissecting it. Histopathological examination* is recommended in virtually all cases of NSCLC as it is the only method that can confirm such a diagnosis. Below, we report the most common examinations that can be performed in order to obtain a biopsy*. Generally speaking, biopsies* can be obtained from the primary tumour (bronchoscopy or CT-guided needle lung biopsy), from the regional lymph node(s)* located in the chest (biopsy* taken by endobronchial or oesophageal ultrasound*-guided route, or by mediastinoscopy), or from metastases* if the disease has spread outside the lung.

   - **Bronchoscopy**: This is a technique used to visualise the inside of the airways with an instrument inserted through the nose or mouth. It allows the practitioner to examine the patient's airways for abnormalities such as tumours from which biopsies* can be taken.
   - **CT-guided needle lung biopsy***: This is used when bronchoscopy is unlikely to succeed in obtaining a biopsy (e.g. in case of peripheral NSCLC). A needle is inserted through the chest into the tumour with the guidance of a CT-scan*.
   - **Endobronchial ultrasound*-guided sampling (EBUS)**: This technique allows confirmation of the involvement of regional lymph node(s)* in case radiological tests* suggest that this is the case. During a bronchoscopy, an ultrasound* probe* is used to help identify any suspicious lymph nodes* that may be present in the surroundings of the airways, from which a biopsy is collected via trans-bronchial needle aspiration*.
   - **Oesophageal ultrasound*-guided sampling (EUS)**: Similar to EBUS, this technique is useful in determining the involvement of regional lymph nodes*. Unlike EBUS, the instrument is inserted through the oesophagus.



- **Mediastinoscopy**: This procedure enables visualisation of the contents of the mediastinum* with a scope that is inserted through an incision approximately 1 cm above the junction of the breastbone with the collarbone. It is used to obtain a biopsy* of the mediastinal lymph nodes*. Less invasive techniques, such as the previously mentioned EBUS and EUS, are progressively replacing mediastinoscopy for histopathological* confirmation of involvement of the mediastinal* lymph nodes* when this is clinically suspected based on radiological examination.
- In case the disease has spread to distant sites of the body, a biopsy* can be obtained from a metastatic* lesion (this does not apply to brain metastases*). Different imaging techniques (e.g. ultrasound*, CT-scan*) or just clinical examination (in case of a superficially palpable lesion) can help guide the biopsy* of the metastasis*.

4. **Cytological examination:** In contrast to histopathological examination*, which is carried out on a tissue sample of the tumour, cytological examination is the laboratory examination of cancerous cells spontaneously detached from the tumour. However, although it may be sufficient for the diagnosis of NSCLC, cytology may have some limitations in the distinction between squamous versus non-squamous cancer due to the scarcity of the examined material. Also, biological examination of the tumour (see next paragraph) may be less reliable if performed on cancerous cells compared with that carried out on tumour tissue samples. Here we report the most common methods for obtaining samples for a cytological examination of NSCLC:
   - **Bronchoscopy**: Bronchial washings* and collection of secretions are usually performed during bronchoscopy in order to search for the presence of cancerous cells.
   - **Thoracentesis/pleural drainage**: These techniques allow fluid aspiration from the pleural cavity* in case of pleural effusion*. The removed fluid is then analysed in the laboratory for the detection of cancerous cells. If necessary, chemical pleurodesis* to avoid recurrence* of pleural effusion can be performed after total fluid aspiration.
   - **Paricardiocentesis/pericardial drainage:** These techniques allow fluid aspiration from the pericardial cavity* in case pericardial effusion* is present. Again, the removed fluid is analysed in the laboratory to look for cancerous cells.

WHAT IS IMPORTANT TO KNOW TO GET THE OPTIMAL TREATMENT?

Doctors will need to consider many factors, related both to the patient and the cancer, in order to decide on the best treatment.

Relevant information about the patient

- Age
- Performance status*, which evaluates patients' general well-being and ability to perform activities of daily life.
- Personal medical history, including type and number of other diseases, such as heart disease, pulmonary disease and diabetes*
- Smoking history
- Results from blood tests performed to assess the white blood cells*, red blood cells*, and platelets*, as well as liver and renal function.
- If a surgical intervention seems to be an option to treat the cancer, some tests will be performed prior to surgery to evaluate lung function. The goal of these tests is to estimate whether the expected lung function that will remain after the surgical removal of the lung (or part of it) will be sufficient to avoid serious shortness of breath.

Relevant information about the cancer

- **Staging***

Doctors use staging* to assess the extent of the cancer and the prognosis* of the patient. The TNM staging system is commonly used. The combination of size of the tumour and invasion of nearby tissue (T), involvement of regional lymph nodes* (N) and metastatic* spread of the cancer to distant sites and/or organs of the body (M), will classify the cancer into one of the stages described below.
The stage is fundamental in order to make the right decision about the treatment. As a general rule, the lower the stage, the better the prognosis*. Staging* is usually performed twice: after clinical and radiological examinations* and after surgery, in case of surgically resected tumours. Staging* is more accurate when surgery is performed since it is also based on information obtained during the laboratory examination of the removed tumour.
The table below presents the different stages of NSCLC. The definitions are somewhat technical, so it is recommended to ask your doctor for a more detailed explanation.

Stage I	The tumour is less than or equal to 5 cm in its greatest dimension and there is no involvement of the regional lymph nodes*
Stage IIA	The tumour is larger than 5 cm but does not go beyond 7 cm in its greatest dimension and there is no involvement of the regional lymph nodes* or The tumour is less than or equal to 5 cm in its greatest dimension, but there is involvement of the homolateral* regional lymph nodes* located at the hilum*

Stage IIB	The tumour is larger than 5 cm but does not go beyond 7 cm in its greatest dimension and there is involvement of the homolateral* regional lymph nodes* located at the hilum* or The tumour is larger than 7 cm in its greatest dimension (but still contained within the lung), or there is a second tumour nodule in the same lobe* and there is no involvement of the regional lymph nodes
Stage IIIA	The tumour does not go beyond 7 cm in its greatest dimension and there is involvement of the homolateral* regional lymph nodes* located at the mediastinum* or The tumour is larger than 7 cm in its greatest dimension (but still contained within the lung), or there is a second tumour nodule in the same lobe* and there is involvement of the homolateral* regional lymph nodes* located at the hilum* or mediastinum* or The tumour invades, by direct extension, the tissue between the lungs (e.g. heart, oesophagus), or there is a second tumour nodule in another lobe* of the same lung, with or without involvement of the homolateral* regional lymph nodes* located at the hilum*
Stage IIIB	The tumour invades, by direct extension, the tissue between the lungs (e.g. heart, oesophagus), or there is a second tumour nodule in another lobe* of the same lung, and there is involvement of the homolateral* regional lymph nodes* located at the mediastinum* or Regardless of the tumour dimension there is involvement of the contralateral* regional lymph nodes* located at the hilum* or mediastinum* or those located at supraclavicular sites*
Stage IV	Regardless of the tumour dimension and involvement of the regional lymph nodes*, the tumour has spread to distant sites and/or organs of the body. Involvement of the pleura* (including pleural effusion* with documented cancerous cells) and of the contralateral* lung is considered stage IV

- **Results of the biopsy***

The biopsy* will be examined in the laboratory. This examination is called histopathology*. A second histopathological examination* involves the examination of the tumour and the lymph nodes* if the tumour is surgically resected. Results of the examination of the biopsy* should include:

- **Histological type***

  Histological type* is based on the type of cells that the tumour is composed of. In general, NSCLC is mainly divided into squamous cancer, which comprises approximately one quarter of all NSCLCs and usually originates in the tissue that lines the larger airways, or non-squamous cancer (including the two numerically important groups of adenocarcinoma and large cell carcinoma), which usually begins in more distal airways. This distinction (squamous versus non-squamous cancer) is relevant for therapeutic purposes. In fact, non-squamous cancers may benefit from certain systemic anti-cancer therapies that have been shown to be effective only in patients with this histological subtype (see systemic therapy* under treatment plan for stage IV NSCLC).

- **Grade**

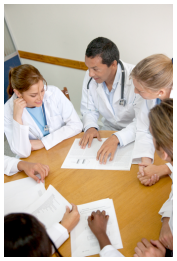
  Grade is based on how different from normal lung cells tumour cells look and on how quickly they grow. The grade will be any value between one and three, although some tumour cells may look so different from normal lung cells that a grade cannot be assigned. These tumours are usually referred to as undifferentiated. The grade reflects the aggressiveness of tumour cells: the higher the grade, the more aggressive the tumour.

- **Biological examination of the tumour**

  Tissue specimens from metastatic* NSCLC belonging to the non-squamous subtype should be evaluated for the presence of specific mutations* in the epidermal growth factor receptor (EGFR*) gene. Even though such mutations* are rare (approximately 10% in Caucasians, with a higher prevalence in never smokers, tumours of adenocarcinoma subtype, women and patients of East-Asian origin), the detection of an EGFR* gene mutation has important prognostic and therapeutic implications in patients with metastatic NSCLC (see systemic therapy* under treatment plan for stage IV NSCLC). EGFR* testing is not recommended in patients with a diagnosis of squamous cell carcinoma, except in never/former light smokers (<15 packs per year).

  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 never smokers, the adenocarcinoma subtype (5%), and in younger patients. Detecting ALK* rearrangements has important therapeutic implications for patients with metastatic NSCLC (see systemic therapy* under treatment plan for stage IV NSCLC), due to the existence of drugs targeting ALK* (e.g. crizotinib*).

WHAT ARE THE TREATMENT OPTIONS?



Planning of the treatment involves an inter-disciplinary team of medical professionals who are involved in the treatment of cancer patients. This is a meeting of different specialists, called multidisciplinary opinion* or tumour board review. In this meeting, the planning of treatment will be discussed according to the relevant information mentioned before.

The treatment will usually combine therapies that:

- Act on the cancer locally, such as surgery or radiotherapy*
- Act on the cancer cells all over the body by systemic therapy* such as chemotherapy* and biological therapy*

The type of treatment will generally depend on the patient's clinical condition and preferences, the stage of the cancer and the characteristics of the tumour.

The treatments listed below have their benefits, their risks and their contraindications*. It is recommended that patients ask their doctors about the expected benefits and risks of every treatment in order to be fully informed about the consequences of the treatment. For some patients, several possibilities are available and the choice should be discussed after weighing up the benefits and risks of each option.

At every step of the treatment, it may also be possible to participate in a clinical trial. A clinical trial is a research study conducted with patients to evaluate whether a new treatment is safe and whether it works. Clinical trials are performed to test the efficacy of drugs and also non-drug treatments, such as radiotherapy* or surgery, and combinations of different treatments.

Sometimes, doctors will propose that you participate in a clinical trial. You have the right to accept or refuse without any consequences for the quality of your treatment. If your doctor does not propose any clinical trial but you really want to participate in one, the best way is to ask your doctor or oncologist* if there is any clinical trial for your type of cancer taking place near your home or in your country.

Treatment plan for stage I-II (early) NSCLC

Stage I-II NSCLC is one that is localised within the lung, and, thus, curable with radical surgery in the majority of cases. At these stages, only factors such as old age and the presence of other severe disease condition(s) may represent a contraindication* to curative surgical resection.*

Surgery:

Surgery is the only treatment offering a chance for a cure at these stages. Therefore, radical surgery consisting of removal of the involved lobe*, namely lobectomy, plus removal of the lymph nodes* located in the chest is the standard form of care in such patients.

Radiotherapy*:

Radiotherapy* is an option for patients who are not candidates for surgery because of medical conditions contraindicating* surgery or if they refuse surgery. Among different techniques, conformal stereotactic radiotherapy*, namely a type of external radiation therapy that precisely delivers a high dose of radiation to the tumour in a short period of time, is usually adopted for stage I patients. By contrast, other standard schedules of radiotherapy are used to treat stage II patients.

Systemic therapy*:

Intravenous* adjuvant* chemotherapy* is an option following surgery for stage II NSCLC, especially in the presence of lymph node* involvement. Chemotherapy* with four cycles of a two-drug combination including a platinum agent (about three months of treatment) has the potential to significantly reduce the risk of disease recurrence* and significantly improve survival. In clinical practice, the best candidates for adjuvant chemotherapy* are patients in good clinical condition, without significant concomitant diseases* and who recovered quickly after surgery.

Treatment plan for stage III (locally advanced) NSCLC

Although still localised within the lung, stage III NSCLC is generally one that cannot be treated with radical surgery, at least not as initial treatment, due to local extension. However, it should be noted that stage III NSCLC represents a very heterogeneous disease condition where it is not possible to recommend a "one size fits all" strategy to follow since the treatment modality may vary from case to case. That is why multidisciplinary involvement of different specialists is key to treatment success of stage III NSCLC, and the best approach for patients with locally advanced NSCLC may be an integration of all treatment modalities (surgery, radiotherapy* and chemotherapy*).*

Surgery:

The long-term outcome of surgery for stage III NSCLC is strictly dependent on the extent of tumour based on the involvement of the lymph nodes* located in the mediastinum* which may separate stage III NSCLC into resectable (most patients with stage IIIA disease) and unresectable (all patients with stage IIIB disease).

Surgery is generally employed as an initial treatment only in patients whose mediastinal* lymph node* involvement becomes evident at histological examination* of the removed tumour. Alternatively, surgery can be employed following the administration of neoadjuvant* chemotherapy* with or without concurrent radiotherapy* in those patients with resectable stage III NSCLC where mediastinal* lymph node* involvement has been detected pre-operatively during tumour staging*.

Tests that determine the amount of lung function that is expected to remain after surgery are very important when making a decision about the possibility of an operation which seems to be technically feasible. The lung function that is expected to remain should be sufficient to avoid serious shortness of breath. Insufficient expected lung function after surgery may prevent the operation from being performed.

Radiotherapy:

Radiotherapy* is employed with the intent to prevent loco-regional spread of the disease. It can be administered either as post-operative treatment following surgery or with curative intent in replacement of surgery for unresectable stage III NSCLC. In the latter case, concurrent chemotherapy is often administered (see next paragraph).

Systemic therapy*:

Intravenous* chemotherapy* with a two-drug combination including a platinum agent should be offered to all stage III patients who can tolerate it. Chemotherapy* may be administered either as neoadjuvant* or adjuvant* therapy in those patients with resectable or resected stage III NSCLC, respectively. On the other hand, patients with unresectable stage III NSCLC are better treated with chemotherapy* given either concomitantly or before radiotherapy*. In this case, concomitant chemo-radiotherapy is generally preferred because of higher efficacy. However, concomitant chemo-radiotherapy is usually more toxic compared with the sequential approach of chemotherapy* followed by radiotherapy*; therefore it should be reserved for selected patients, such as younger patients and those with good performance status*.

Treatment plan for stage IV (metastatic*) NSCLC

Stage IV NSCLC is one that has spread to distant sites and/or organs of the body. The most common sites of metastases are the bones, brain, liver, adrenal glands, pleura* and the other lung. Since metastases spread through the bloodstream, they can be present either at diagnosis (in nearly 40% of patients), or become evident over time during the follow-up of a radically resected NSCLC.*

Surgery:

Since stage IV NSCLC has spread beyond the lung, it is considered to be inoperable as surgery would be unable to remove the entire tumour and offer a chance of cure. Exceptions to this rule are patients with a solitary brain, lung or adrenal metastasis* and no evidence of other metastatic disease sites apart from the primary tumour.
Surgical interventions can also be useful to relieve the symptoms caused by the disease in the thorax or in the bones.

Radiotherapy*:

Radiotherapy* may be indicated as palliative treatment for patients who complain of specific symptoms that derive from metastatic* involvement of certain organs. For instance, radiotherapy can be helpful in controlling bone pain due to NSCLC spreading to the bones or to treat headache and/or weakness associated with the presence of brain metastases.

Systemic therapy*:

Systemic therapy is the mainstay of treatment of stage IV NSCLC. The main goals of systemic therapy are:

- To improve quality of life
- To prolong survival

Decisions regarding systemic therapy should take into account several issues, including clinico-pathological* characteristics (such as histology*, age, performance status*, presence of other diseases and the patient's preferences) and biological features (such as the presence of an EGFR* gene mutation* or ALK* rearrangement). The initial treatment proposed is called first-line treatment. Second- and third-lines of treatment may be proposed afterwards, depending on the response to previous therapies and on the general status of the patient.

First-line treatment

- First-line treatment: chemotherapy*
  - Intravenous* chemotherapy with a two-drug combination including a platinum agent (either cisplatin* or carboplatin*) is standard of care in patients without EGFR* mutations or ALK* rearrangement.
  - In the subgroup of non-squamous tumours and in patients treated with third-generation regimens, including gemcitabine* and taxanes*, cisplatin should be the platinum agent of choice.
  - Pemetrexed-based chemotherapy should be the treatment of choice in patients with non-squamous tumours and it should be restricted to non-squamous NSCLC in any line of treatment.
  - Carboplatin* is preferred to cisplatin in patients with contraindications* to intravenous* hydration (e.g. cardiac or renal impairment).
  - Non-platinum-based combination chemotherapy should only be considered if platinum therapy is contraindicated.
  - Chemotherapy achieves benefits in patients with performance status equal to 2 when compared to best supportive care. Single-agent chemotherapy with gemcitabine, vinorelbine, or taxanes represents an option for these patients. Carboplatin-based combinations have shown good results with acceptable toxicity and should be considered in eligible patients with performance status of 2.
  - Patients who are not in good clinical condition (performance status 3 or 4) should be offered best supportive care.
  - In elderly patients (aged ≥ 70 years), carboplatin-based chemotherapy should be considered in eligible patients in good clinical condition (performance status 0 to 2) and without concomitant diseases*. In other patients, single agent chemotherapy may be considered. This should be discussed with your doctor.

- First-line treatment: biological therapy*
    - Mono-therapy with an orally administered tyrosine kinase inhibitor* of EGFR*, such as gefitinib*, erlotinib* and afatinib*, is the preferred option in patients whose tumour carries an EGFR gene mutation* (approximately 15% of all NSCLCs). All tumours of non-squamous histology* should be tested for the presence of an EGFR gene mutation, particularly those that arise in patients who are either non-smokers or have smoked moderately in the past. Since they are generally well-tolerated and have a convenient oral formulation, an EGFR inhibitor can also be offered to patients with a very poor performance status* of 3 and 4 as long as an EGFR gene mutation is detected in the tumour.
    - Patients with NSCLC tumours harbouring an ALK* rearrangement should be offered treatment with the ALK* inhibitor crizotinib.
    - Bevacizumab* is a monoclonal antibody* that binds to the vascular endothelial growth factor (VEGF*), which is a protein circulating in the blood that is required for the growth of blood vessels. Bevacizumab prevents VEGF from activating the VEGF receptor on the cells and therefore inhibits the growth of blood vessels within the tumour. Intravenous* bevacizumab may be added to a carboplatin*-paclitaxel* regimen only in patients with tumours of non-squamous histology* and good performance status* (0 or 1). For safety reasons, careful patient selection is crucial in order to limit the potential adverse effects of bevacizumab. Squamous histology represents a major contraindication* to bevacizumab therapy. Also, patients who complain of severe haemoptysis* as well as those with centrally-located or excavated tumours are usually excluded from bevacizumab therapy. The combination of bevacizumab and other platinum-based chemotherapies may be considered in eligible patients with non-squamous NSCLC.

- First-line treatment: timing, duration and maintenance therapy
    - First-line treatment should always be initiated while the patient has good performance status*, namely at a time when he/she is able to better tolerate the potential side effects of systemic therapies*.
    - For most patients, four cycles of chemotherapy are recommended, with a maximum of six cycles.
    - In patients with good clinical condition, maintenance therapy may be given in order to prolong the effect of first-line chemotherapy on tumour control. This can be administered as continuation maintenance or switch maintenance therapy. This refers either to the maintained use of an agent included in first-line treatment or the introduction of a new agent after four cycles of platinum-based chemotherapy, respectively.
    - The switch maintenance therapy includes erlotinib* and it is an option for patients with stable disease after induction treatment.
    - Continuing maintenance therapy includes pemetrexed and it is indicated following completion of first-line cisplatin plus pemetrexed chemotherapy in patients with non-squamous histology, stabilisation of disease, or response after first-line chemotherapy and recovery from toxicity of the previous treatment.

Second- and third-line treatments

These treatments may be administered following disease progression after first-line therapy in patients who are still fit enough to receive further therapy (performance status* of 0 to 2).
Monochemotherapy with docetaxel or pemetrexed* (the latter for non-squamous cancer only) or targeted agent erlotinib* (in patients with unknown EGFR* status or without EGFR* mutations) improves tumour-related symptoms and survival. In patients with EGFR* mutated tumours, single-agent erlotinib*, gefitinib* or afatinib* should be given as second-line* therapy, if patients have not received them previously. In subsequent lines of treatment, erlotinib is indicated for patients with unknown EGFR* status or those without EGFR* mutations who have not yet received EGFR tyrosine kinase inhibitors (TKIs)*, and have performance status 0 to 3. In general, any patient with a tumour bearing an EGFR* mutation should receive an EGFR TKI* in any line of therapy, if not received previously.

Patients with a tumour carrying a rearrangement of the ALK gene (about 5% of all patients) can also be treated with crizotinib* in the second and third-line if they have not received it previously.

Treatment of oligometastatic NSCLC

Oligometastases is a term that refers to the presence of a maximum of five metastatic lesions. If they appear one month before or after the primary tumour was identified they are called synchronous metastases. When they appear after the primary tumour was treated they are called metachronous metastases. The biology and prognoses of these two disease states may differ. Radical treatment with surgery, radiotherapy and chemotherapy could be considered but, since there is no standard of care yet to treat oligometastases, it is suggested that in these cases patients are treated preferentially in a clinical trial.

Treatment of brain metastases

Patients with poor performance status are given best supportive care. Patients with good performance status and younger than 65 years old, with no other extracranial metastases and with more than three brain metastases could receive whole brain radiotherapy. A single brain metastasis could be treated either with surgery or stereotactic radiosurgery (a special type of radiotherapy in which the radiation beams are very precise to reduce damage to the surrounding normal tissue). Stereotactic radiosurgery is preferred when two or three brain metastases are present.

Palliative therapies:

Other therapies help at different stages in NSCLC treatment: endoscopy can be used to relieve airway obstruction, surgical procedures can be used in case of pleural effusions, and radiotherapy could also, together with its palliative effects in brain metastases, help to treat bone metastases, especially if they are causing pain. Bone modifying agents (zoledronic acid and denosumab) also help to treat bone metastases. In general, early palliative care is recommended in parallel with the standard of care for the cancer itself. It has been shown that it could improve quality of life and mood, and diminishes the need for aggressive treatment and may even improve survival.

Clinical trials of new drugs are often proposed to patients with stage IV NSCLC. Participation in clinical trials should be encouraged.

Response evaluation:

The response to treatment has to be evaluated to check if there is any benefit of the treatment compared to the adverse events experienced. Response evaluation is recommended after 2-3 months of systemic therapy* for stage IV NSCLC. This evaluation relies on repetition of the initial radiographic test showing the tumour lesions.
In the case of curative radiotherapy* for stage III NSCLC, a minimum of 2 months have to elapse between the end of treatment and response evaluation in order to see the beneficial effects of radiotherapy*.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF THE TREATMENT?

In this paragraph we report the most common side effects of surgery, radiotherapy* and chemotherapy*. However, the following list is not exhaustive. Therefore, patients should carefully discuss the potential side effects related to the proposed treatment(s) with their doctor.

- Surgery
  - Haemothorax: A condition that results from blood accumulating in the pleural cavity.*
  - Pulmonary contusion: A bruise of the lung tissue caused by damage, typically due to trauma during surgery.
  - Post-operative pneumonia
  - Persistent air leak: A condition where the lung is unable to re-inflate properly following surgery due to surgical damage to the lung tissue.
- Radiotherapy*
  - Side effects with an early onset: These side effects usually occur within six months after completion of radiotherapy. They often include esophagitis (inflammation of the oesophagus), pneumonia, cough and prolonged hoarseness.
  - Side effects with a late onset: These side effects typically occur after six months from completion of radiotherapy and most commonly include shortness of breath, caused by a loss in lung elasticity, and pneumonia.
- Systemic therapy*
  - Chemotherapy*: The side effects of chemotherapy vary in frequency and severity based on the type of agent and/or combination regimens employed. Therefore, patients are encouraged to thoroughly discuss with their doctor the main side effects associated with the chemotherapy regimen that has been proposed. However, the side effects of chemotherapy often include: loss of appetite, fatigue, hair loss, nausea and/or vomiting, increased susceptibility to infections and bleeding, anaemia* and diarrhoea.

    Apart from these, each drug can also have different unwanted effects. The most common ones are listed above, although not everyone will have side effects, or experience them to the same extent.
    - Cisplatin* may lead to hearing loss and kidney damage. Kidney function is tested before starting treatment. To prevent damage it is very important to drink a lot of water during treatment with this drug.
    - Paclitaxel* can cause peripheral neuropathy* which is dependent upon the dose administered, the duration of the infusion, and the schedule of administration. Presenting symptoms include numbness, paraesthesia* and burning pain in a glove-and-stocking distribution*. Symptoms are often symmetrical, and usually have their origins distally in the lower extremities. Patients commonly report the simultaneous onset of symptoms in toes and fingers, but asymmetric presentations have been described too. Facial involvement is less common. Although mild symptoms have been reported to improve or resolve completely within several months after discontinuation of therapy, the symptoms and deficits have been reported to persist longer in patients who develop severe neuropathy*.

- Biological therapy*: These side effects are usually termed ‘class-related’ since they are specific to the biological agent administered.
  - Bevacizumab* may give rise to hypertension*, proteins in the urine and increased risk of thromboembolic* or haemorrhagic disorders*.
  - Gefitinib*, erlotinib* and afatinib* can cause cutaneous rash and diarrhoea.
  - Crizotinib* can cause vision disorder, nausea, diarrhoea, vomiting, oedema*, constipation, fatigue, elevation of liver enzymes and neutropenia (a decrease in the number of a type of white blood cell* called neutrophils).

WHAT HAPPENS AFTER THE TREATMENT?

Regular follow-up visits are an important step for patients who have undergone radical surgery for NSCLC.

Follow-up with doctors

After the treatment has been completed, doctors will propose a follow-up programme aiming to:

- Evaluate treatment complications:

Treatment complications related to surgery, adjuvant* chemotherapy* or radiotherapy* (see side effects of the therapies) should be carefully evaluated every 3 to 6 months.

- Detect possible disease recurrence*:

At the present time, no evidence suggests that earlier detection of recurrence* (and therefore initiation of specific treatment) may lead to a better clinical outcome. Notwithstanding, given that most recurrences* occur within the fourth year after surgery, follow-up visits (including physical examination and evaluation of any symptoms) are generally recommended at an interval of 3 to 6 months for the first three years following surgery and annually thereafter.
Annual chest CT scan and, to a lesser extent, chest X-ray* are both considered appropriate tools for radiological follow-up; CT scan is preferred because it has the potential advantage over chest X-ray* of early detection of a new primary lung tumour.

- Detect possible new primary lung tumours:

Patients who have undergone radical surgery for NSCLC are at higher risk for developing a second new primary lung tumour. It is sometimes hard to distinguish between tumour recurrence* and a new primary lung tumour based on the radiographic tests only. Case discussion within a multidisciplinary opinion/team* can help differentiate the two scenarios and, therefore, choose the most appropriate treatment option.

Smoking cessation

Given the strong link between smoking and the development of lung cancer, giving up smoking at any time is always advisable in patients affected with NSCLC. Therefore, smoking cessation should be viewed as an integral part of NSCLC treatment(s), regardless of the stage of the disease. Remarkably, smoking cessation in stage I to III patients has been associated with a decrease in both risk of recurrence* and risk of a second primary lung tumour, eventually resulting in decreased NSCLC-related mortality. Smoking may also interact with systemic therapy. For example, it reduces the proportion of erlotinib that enters into the circulation and, therefore, its active effect.

Returning to normal life

It can be hard to live with the idea that the cancer might return. Patients having difficulties in returning to normal life may be provided with psychological support, whereas other people may find helpful support from ex-patients groups.

What if the cancer comes back?

If the cancer comes back it is called a recurrence.* The treatment depends on the extent of the recurrence.
Some patients in whom the tumour comes back as a recurrence at a single site may benefit from a loco-regional approach, such as surgical removal or radiotherapy*. However, this approach is limited to a very small group of patients. Recurrent tumours should normally be regarded as metastatic* cancers and therefore approached as explained in the paragraph “Treatment plan for Stage IV NSCLC”.
In some cases, biopsy* of the metastasis* may be indicated since it may result in a change in the treatment decision. This may be particularly true for patients with a long disease-free interval* after surgical resection. Re-biopsy in these patients may be useful in order to differentiate between disease recurrence and a new primary lung tumour (in cases where the recurrence is detected in the lung), to ascertain the histologic type* of lung tumour (non-squamous versus squamous versus other), or to repeat the EGFR* mutation* test if a non-squamous cancer is detected.

DEFINITIONS OF MEDICAL TERMS

Adjuvant (treatment)
Adjuvant treatment in cancer is a therapy that helps another therapy to reach its ultimate goal and reinforces its effect. For example, radiotherapy and/or chemotherapy* help a surgery to accomplish its goal of eliminating a cancerous tumour. In a non-oncological context, it can also be an agent added to vaccines to stimulate the immune system's response to an antigen.

Afatinib
Afatinib is a targeted agent for use in EGFR* mutated, metastatic NSCLC. Afatinib acts as an irreversible inhibitor of EGFR* and human epidermal growth factor 2 (HER2).

ALK
The ALK gene makes a protein called ALK (anaplastic lymphoma kinase). ALK gene rearrangement is mainly found in the adenocarcinoma lung cancer subtype, never smokers and younger patients. Testing for the presence of the rearrangement is important because a targeted therapy called crizotinib is available for patients with ALK-positive tumours.

Alkaline phosphatase (test)
An enzyme that is normally present in high concentrations in growing bone and in bile. Abnormally high levels of it in the blood may indicate disease in bone, liver or bile duct.

Alveoli
Tiny air sacs at the end of the bronchioles (tiny branches of air tubes) in the lungs. The alveoli are where the lungs and the bloodstream exchange carbon dioxide and oxygen. Carbon dioxide in the blood passes into the lungs through the alveoli. Oxygen in the lungs passes through the alveoli into the blood.

Anaemia
A condition characterized by the shortage of red blood cells* or hemoglobin. Hemoglobin is the part of the red blood cell that carries oxygen from the lungs to the whole body and in patients with anemia this process is diminished.

Bevacizumab
Bevacizumab is a monoclonal antibody* that has been designed to recognize and attach itself to a specific structure (called an antigen) that is found in certain cells in the body or is circulating in the body. Bevacizumab has been designed to attach to vascular endothelial growth factor (VEGF*), a protein circulating in the blood that is required for the growth of blood vessels. By attaching to VEGF, bevacizumab stops it having an effect and, as a result, cancer cells cannot develop their own blood supply and are starved of oxygen and nutrients, helping to slow down the growth of tumours.

Biological therapy
Treatment to stimulate or restore the ability of the immune system to fight cancer, infections, and other diseases. Also used to lessen certain side effects that may be caused by some cancer treatments. Also called immunotherapy, biotherapy, or biological response modifier (BRM) therapy.

Biopsy
The removal of cells or tissues for examination by a pathologist. The pathologist may study the tissue under a microscope or perform other tests on the cells or tissue. There are many different types of biopsy procedures. The most common types include: (1) incisional biopsy, in which only a sample of tissue is removed; (2) excisional biopsy, in which an entire lump or suspicious area is removed; and (3) needle biopsy, in which a sample of tissue or fluid is removed with a needle. When a wide needle is used, the procedure is called a core biopsy. When a thin needle is used, the procedure is called a fine-needle aspiration biopsy.

Bronchial washings
A procedure in which cells are taken from the inside of the airways that lead to the lungs. A bronchoscope (a thin, tube-like instrument with a light and a lens for viewing) is inserted through the nose or mouth into the lungs. A mild salt solution is washed over the surface of the airways to collect cells, which are then looked at under a microscope. Bronchial washing is used to find infections and it may also help to detect cancer or changes in cells that may lead to cancer.

Carboplatin
A drug that is used to treat advanced ovarian cancer that has never been treated or symptoms of ovarian cancer that have come back after treatment with other anticancer drugs. It is also used with other drugs to treat advanced, metastatic*, or recurrent* NSCLC and is being studied in the treatment of other types of cancer. Carboplatin is a form of the anticancer drug cisplatin* but causes fewer side effects than cisplatin* in patients. It attaches to DNA in cells and may kill cancer cells. It is a type of platinum compound.

Carcinogen
Something that causes cancer.

Chemotherapy
A type of cancer treatment using drugs that kill cancer cells and/or limit their growth. These drugs are usually administered to the patient by slow infusion into a vein but can also be administered orally, by direct infusion to the limb or by infusion to the liver, according to the location of the cancer.

Cisplatin
A drug used to treat many types of cancer. Cisplatin contains the metal platinum. It kills cancer cells by damaging their DNA and stopping them from dividing. Cisplatin is a type of alkylating agent.

Clinico-pathological
Concerning the signs and symptoms of the disease observed directly by the doctor and the damage that the disease produces to the cells observed in laboratory.

Concomitant diseases
Diseases which occur at the same time.

Contraindication
Condition or symptom that prevents the administration of a given treatment or procedure to the patient. Contraindications are either absolute, meaning the treatment should never be given to patients with this condition or symptom, or relative, meaning that the risk can be outweighed by the benefits in some patients with this condition or symptom.

Contralateral
Relating to the opposite side of the body.

Crizotinib
Crizotinib is used to treat adults with NSCLC when the disease is advanced and has already been treated before. It is only used for ALK-positive NSCLC, which means that the cancer cells contain certain defects affecting the gene responsible for a protein called ALK*.

CT-scan
A form of radiography in which body organs are scanned with X-rays and the results are synthesized by a computer to generate images of parts of the body.

Diabetes
Any of several diseases in which the kidneys make a large amount of urine. Diabetes usually refers to diabetes mellitus in which there is also a high level of glucose (a type of sugar) in the blood because the body does not make enough insulin (a hormone needed for cells to absorb and use glucose) or use it the way it should.

Diaphragm
The thin muscle below the lungs and heart that separates the chest from the abdomen.

Disease-free interval
In cancer, the length of time that a patient survives without any signs or symptoms of the original cancer or any other type of cancer after the end of treatment. In a clinical trial, measuring the disease-free survival is one way to see how well a new treatment works. Also called DFS and disease-free survival time.

EGFR (Epidermal growth factor receptor)
This is a type of protein called a tyrosine kinase which is found on the surface of some cells. Epidermal growth factor binds to EGFR, causing cells to divide. It is found at abnormally high levels on the surface of many types of cancer cells, which means that these cells divide excessively in the presence of epidermal growth factor. Also called ErbB1 and HER1.

Epidemiologic study
Research conducted in human populations in which the investigator(s) examines the associations between the presence of a health effect, for instance cancer, and a factor that is speculated to cause it, for instance a chemical.

Erlotinib
Erlotinib is an anticancer medicine that belongs to the group 'EGFR inhibitors'. Erlotinib blocks EGFRs, which can be found on the surface of some tumour cells. As a result of this, the tumour cells can no longer receive the messages needed for growth, progression and spreading (metastasis*). This stops the cancer from growing, multiplying and spreading through the body.

Gefitinib
Gefitinib is a tyrosine kinase inhibitor*. This means that it blocks specific enzymes known as tyrosine kinases. These enzymes can be found on the surface of cancer cells. One example of a tyrosine kinase is EGFR*, which is involved in the growth and spread of cancer cells. By blocking EGFR, Gefitinib helps to slow down the growth and spread of the cancer. Gefitinib only works in non-small cell lung cancer cells that have a mutation* in EGFR.

Gemcitabine
The active ingredient in a drug that is used to treat pancreatic cancer that is advanced or has spread. It is also used with other drugs to treat breast cancer that has spread, advanced ovarian cancer, and non-small cell lung cancer that is advanced or has spread. It is also being studied in the treatment of other types of cancer. Gemcitabine blocks the cell from making DNA and may kill cancer cells. It is a type of antimetabolite.

Glove-and-stocking distribution
Term to describe the pattern of signs and symptoms of a disorder that affects hands and feet symmetrically. The signs and symptoms of such a disease wrap around hands like gloves and feet like socks.

Haemoptysis
Haemoptysis is the coughing of blood originating from the respiratory tract below the level of the larynx. Haemoptysis should be differentiated from haematemesis, which is a term for vomiting of blood from the gastrointestinal tract, and pseudohaemoptysis, a situation where a cough reflex is stimulated by blood not derived from the lungs or bronchial tubes, this may be from the oral cavity or nasopharynx (eg, following an epistaxis – nose bleeding) or following aspiration of haematemesis into the lungs.

Haemorrhagic disorder
Any one of a group of diseases in which bleeding occurs with no apparent reason or when heavy and prolonged bleeding occurs after an injury. It originates from a problem in coagulation or flaws in the structure of blood vessels.

Hilum
A notch or deep depression in a bodily organ or gland through which nerves, ducts and/or blood vessels enter and exit the organ or gland.

Histologic(al) type
The category in which a tumour is grouped, considering the characteristics of its cells and other structures under the microscope.

Histopathology/Histology/Histopathological examination
The study of diseased cells and tissues using a microscope.

Homolateral
Referring to the same side of the body in comparison to a given point in the body.

Hypertension
A blood pressure of 140/90 or higher. Hypertension usually has no symptoms. It can harm the arteries and cause an increase in the risk of stroke, heart attack, kidney failure, and blindness. Also called high blood pressure.

Intrathoracic
Occurring, located or performed inside the thorax or chest cavity.

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

Lobe
A portion of an organ, such as the liver, lung, breast, thyroid or brain.

Lymph node
A rounded mass of lymphatic tissue that is surrounded by a capsule of connective tissue. Lymph nodes filter lymph (lymphatic fluid) and they store lymphocytes (a type of white blood cell). They are located along lymphatic vessels. Also called lymph gland.

Mediastinum/mediastinal
The area between the lungs. The organs in this area include the heart and its large blood vessels, the trachea, the oesophagus, the thymus, and lymph nodes* but not the lungs.

Mesothelioma
A benign (not cancerous) or malignant (cancerous) tumour affecting the lining of the chest or abdomen. Exposure to asbestos particles in the air increases the risk of developing malignant mesothelioma.

Metabolic activity/metabolism
The chemical changes that take place in a cell or an organism. These changes make energy and materials that cells and organisms need to grow, reproduce, and stay healthy. Metabolism also helps get rid of toxic substances.

Metastasis/Mestastatic/Metastize
The spread of cancer from one part of the body to another. A tumour formed by cells that have spread is called a metastatic tumour or a metastasis. The metastatic tumour contains cells that are like those in the original tumour.

Monoclonal antibody
Monoclonal antibodies are antibodies that are made in a laboratory and bind to only one specific type of protein. These antibodies are exactly the same as they are produced by clones of the same parent cell.

Magnetic Resonance Imaging (MRI)
An imaging technique used in medicine that uses magnetic resonance (magnetism and radio waves) to create a picture of organs and tissues inside the body. Sometimes, a fluid is injected that enhances the contrast between different tissues to make structures more clearly visible.

Multidisciplinary opinion/team
A treatment planning approach in which a number of doctors who are experts in different specialties (disciplines) review and discuss the medical condition and treatment options of a patient. In cancer treatment, a multidisciplinary opinion may include that of a medical oncologist* (who provides cancer treatment with drugs), a surgical oncologist (who provides cancer treatment with surgery), and a radiation oncologist (who provides cancer treatment with radiation). Also called tumour board review.

Mutation
A change in the sequence of base pairs in the DNA that makes up a gene. Mutations in a gene do not necessarily change the gene permanently.

Neoadjuvant (chemo)therapy
Treatment given as a first step to shrink a tumour before the main treatment, which is usually surgery, is given. The goal of neoadjuvant therapy is not to cure the disease but to lower the side effects or strengthen the effects of the main therapy and to increase the chances for long-term survival. Examples of neo-adjuvant therapy include chemotherapy, radiation therapy, and hormone therapy.

Oedema
An abnormal collection of fluid beneath the skin or in a body cavity.

Oncologist (medical/radiation)
A doctor who specializes in treating cancer. Some oncologists specialize in a particular type of cancer treatment. For example, a radiation oncologist specializes in treating cancer with radiation.

Paclitaxel
A drug used to treat breast cancer, ovarian cancer, and AIDS-related Kaposi sarcoma. It is also used together with another drug to treat NSCLC. Paclitaxel is also being studied in the treatment of other types of cancer. It blocks cell growth by stopping cell division and may kill cancer cells. It is a type of antimitotic agent.

Paraesthesia
An abnormal touch sensation, such as burning or prickling, that occurs without an outside stimulus.

Performance status
The performance status evaluates the patient's physical abilities by giving a score from 0 (a fully active patient) to 4 (a patient that is completely disabled due to his/her disease).

Pericardial effusion
An abnormal collection of fluid inside the sac that covers the heart.

Pericardial cavity
The space between the layer of tissue that wraps around the heart (the visceral* pericardium*) and the tissue that lines the cavity that contains the heart (the parietal pericardium). This space contains a fluid that lubricates the surface of both pericardia and allows easy movement of the heart.

Pericardium
The pericardium is a double-walled sac that surrounds the heart and the roots of the great blood vessels. It has several functions: it keeps the heart contained in the chest cavity and also prevents the heart from overexpanding when blood volume increases. Within the pericardium lies the pericardial cavity*. This cavity is filled with pericardial fluid which reduces friction between the pericardial membranes.

Peripheral neuropathy
A type of nerve damage that causes pain, numbness, tingling, swelling, or muscle weakness in different parts of the body. It usually begins in the hands or feet and gets worse over time. Peripheral neuropathy may be caused by physical injury, infection, toxic substances, disease (such as cancer, diabetes*, kidney failure or malnutrition), or drugs, including anticancer drugs. Also called neuropathy.

Pemetrexed
A drug used alone or with another drug to treat certain types of NSCLC and malignant pleural* mesothelioma*. It is being studied in the treatment of other types of cancer. Pemetrexed disodium blocks DNA synthesis and may kill cancer cells. It is a type of folate antagonist.

Platelet
Small cell fragments that play a fundamental role in the formation of blood clots. Patients with a low platelet count are at risk of severe bleeding. Patients with a high platelet count are at risk of thrombosis, the formation of blood clots that can block blood vessels and result in stroke or other severe conditions, and can also be at risk of severe bleeding because of platelet dysfunction.

Pleura
A thin layer of tissue that covers the lungs and lines the interior wall of the chest cavity. It protects and cushions the lungs. This tissue secretes a small amount of fluid that acts as a lubricant, allowing the lungs to move smoothly in the chest cavity while breathing.

Pleural effusion
An abnormal collection of fluid between the thin layers of tissue (pleura*) lining the lung and the wall of the chest cavity.

Pleural cavity
The space enclosed by the pleura*, which is a thin layer of tissue that covers the lungs and lines the interior wall of the chest cavity.

Pleurodesis
A medical procedure that uses chemicals or drugs to cause inflammation and adhesion between the layers of the pleura* (a thin layer of tissue that covers the lungs and lines the interior wall of the chest cavity). This prevents the build-up of fluid in the pleural cavity. It is used as a treatment for severe pleural effusion*.

Probe
A long, thin instrument used to explore wounds, cavities or body passages.

Prognosis
The likely outcome or course of a disease; the chance of recovery or recurrence*.

Radiological examination/test
A test that uses imaging technology (such as radiography, ultrasound*, CT-scan* and nuclear medicine) to visualize organs, structures and tissues within the body to both diagnose and treat diseases.

Radiologist
A doctor who specializes in the diagnosis of disease and injury with the use of imaging devices such as those used for X-rays, CT-scans* or MRIs*.

Radiation Oncologist
A specialist treating cancer with radiation. He or she is different from a radiologist* who performs imaging tests to diagnose and follow up on different conditions.

Radiotherapy
A therapy in which radiation, oriented to the specific location of the cancer, is used in the treatment of cancer.

Recurrence
Cancer or disease (usually auto-immune) that has come back, usually after a period of time during which the cancer or disease was not present or could not be detected. This may happen at the same location as the original (primary) tumour or in another part of the body. Also called recurrent cancer or recurrent disease.

Red blood cell
The most common type of blood cell. It is the substance that makes the blood appear red. The main function of these cells is to transport oxygen from the lungs to tissues throughout the body.

Serum calcium
Level of calcium that is found in the blood. This can be measured by performing a special test in a laboratory.

Staging
Performing exams and tests to determine the extent of the cancer within the body, especially whether the disease has spread from the original site to other parts of the body. It is important to know the stage of the disease in order to plan the best treatment.

Supraclavicular sites
Area of the body situated right above the clavicle or collar bone.

Systemic therapy/treatment
Treatment using substances that travel through the bloodstream, reaching and affecting cells all over the body. Chemotherapy* and immunotherapy are examples of systemic therapy.

Taxane
A type of drug that blocks cell growth by stopping mitosis (cell division). Taxanes interfere with microtubules (cellular structures that help move chromosomes during mitosis). They are used to treat cancer. A taxane is a type of mitotic inhibitor and a type of antimicrotubule agent.

Thromboembolic disorder
Condition in which a blood clot (thrombus) forms inside the blood vessels, due to abnormalities in the process of coagulation or flaws in the structure of the blood vessels. These blood clots can break off and start circulating in the bloodstream (often known as emboli) and cause major organ damage or death by blocking normal blood circulation.

TKI/Tyrosine kinase inhibitor
A drug that inhibits tyrosine kinases, which are proteins involved in cell communication and growth and may therefore prevent tumour growth. Some tyrosine kinase inhibitors are used to treat cancer.

Trans-bronchial needle aspiration
Technique to obtain a sample of the pulmonary tissue or tissues surrounding the trachea and bronchia. A needle is inserted through the wall of the airways (trachea or bronchia) to reach the tissue from which a sample is needed.

Ultrasound
A procedure in which high-energy sound waves are bounced off internal tissues or organs and make echoes. The echo patterns are shown on the screen of an ultrasound machine, forming a picture of body tissues

Uranium
A silvery-white metallic radioactive element. It naturally occurs in nature and it is found worldwide in soil. Its normal decay results in the production of radon, a gas associated with the occurrence of lung cancer.

Vascular endothelial growth factor (VEGF)
A substance made by cells that stimulates new blood vessel formation.

Vinorelbine
An anticancer drug that belongs to the family of plant drugs called vinca alkaloids.

Visceral
Having to do with the viscera, which are the soft internal organs of the body, including the lungs, the heart, and the organs of the digestive, excretory, reproductive, and circulatory systems.

White blood cell
Cells of the immune system that are involved in the body's defense against infections.

X-ray
A form of radiation used to take images of the inside of objects. In medicine, X-rays are commonly used to take images of the inside of the body.

The ESMO / Anticancer Fund 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.
These guides are produced by the Anticancer Fund in close collaboration with the ESMO Guidelines Working Group and the ESMO Cancer Patient Working Group.

For more information please visit www.esmo.org and www.anticancerfund.org

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