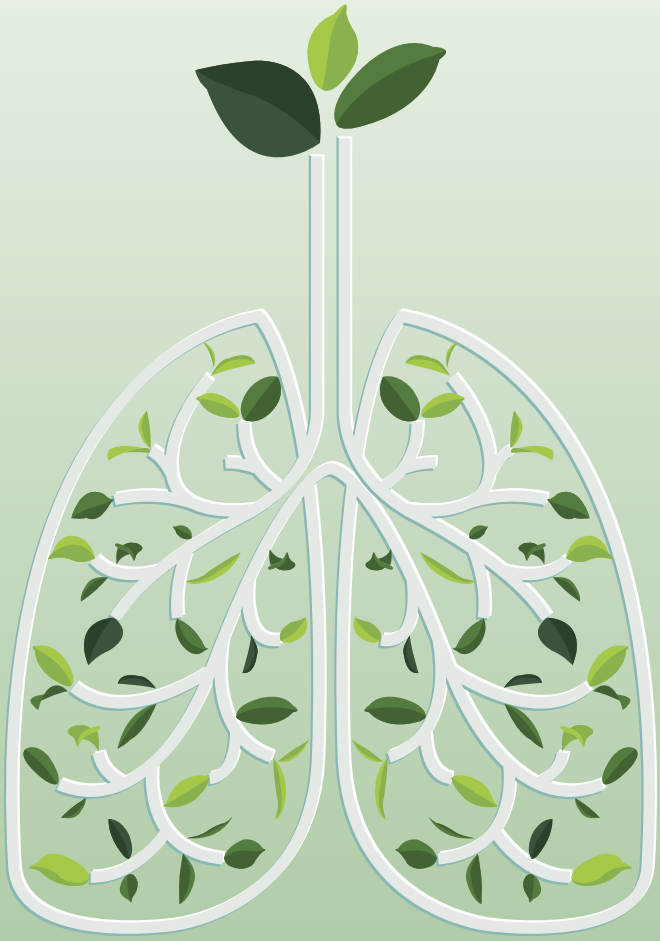
Pulmonary Dictionary



Preface

Many patients affected by cancer feel that they would like to get as much information as possible when it comes to course and outcome of their treatment. The physician's words are not always enough, instead they want to find out more about their disease and about the results from the clinical studies that have been performed.

If you are not used to reading and interpreting things such as study results or biomarkers, it may feel like entering a jungle of abbreviations and expressions. What do all these abbreviations mean? And what do the numbers actually tell us? We have put together a small dictionary that we hope will be a good help along the way, and that hopefully can provide answers to the most frequently asked questions.

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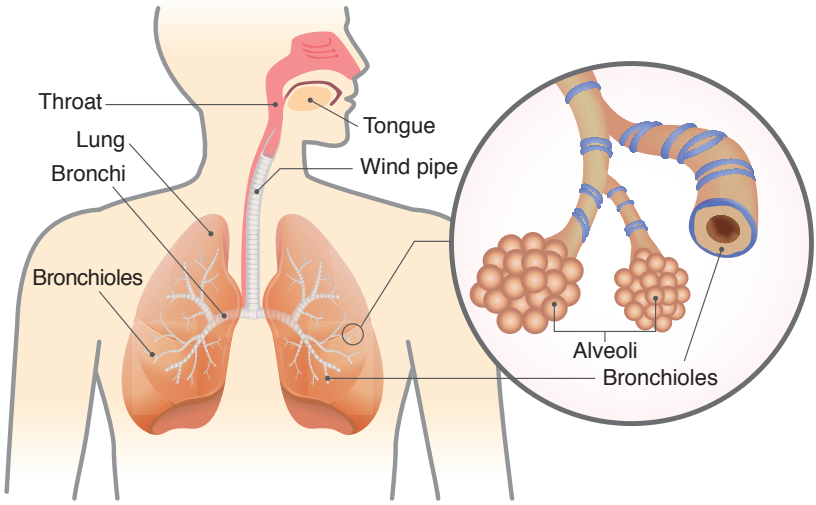
Table of Contents

Lung Cancer

Lung cancer is traditionally divided into two main groups; non-small cell lung cancer (or “NSCLC”) and small cell lung cancer (or ”SCLC”). Approximately 80% of all lung cancer cases are non-small cell lung cancers, which can further be classified into several subgroups according to histology, i.e. depending on the appearance of the cancer cells. The most common histological subtypes of non-small cell lung cancer are adenocarcinoma and squamous cell carcinoma. Adenocarcinoma arises in glandular cells in the lungs, while squamous cell carcinoma arises in the bronchi.

“Primary lung tumor” refers to the initial tumor which has started in a lung (in lung cells). When the same tumor spreads to the other lung or further in the body by the lung cancer cells entering the blood vessels or lymph vessels, they can build **“secondary lung tumors”** or **“metastases”**.

NSCLC often spreads within the lungs and sometimes to the bone and to the brain.



Anatomy

Anatomy means the science of how the human body is built.

Alveoli

The alveolus, also known as the air sac, is the structure in your lungs where gas exchange occurs, i.e. where oxygen is transported into the lungs and carbon dioxide is transported out to be exhaled via your breath.

Bronchi

The bronchus, also known as air pipe, branches from the lower end of the trachea (windpipe) and consists of small cilia to capture foreign particles.

Bronchioles

Bronchioles are smaller air pipes that lead from the bronchi to the alveoli where the gas exchange occurs.

The windpipe

The windpipe, also known as trachea, transports air.

Lung lobe

The lungs are divided into lung lobes. The right lung consists of three lobes and the left of two lung lobes.

Pleura

The pleura is a form of membrane that consists of two layers and has the function of suspending the lung.

The function of the lung is to transport oxygen from the air to the blood and in return transport carbon dioxide from the blood out to the air.

Biomarkers

The development of molecular medicine has during the last decade provided new knowledge which enables the lung cancer to be further divided into different subgroups depending on which gene alterations, called mutations, are present in the tumor.

In all healthy cells there are key genes that control how much and how quickly cells should grow and divide in an optimal way. If any of these genes and pathways are damaged, the optimal functionality may change and then cause cancer. Such gene mutations are called **"driver mutations"** as they are driving the development of the tumor.

Some mutation-driven tumors are today treatable with **targeted therapies** - called this way because they target incorrect signaling pathways in the tumor cells. Targeted therapies are designed to kill only cancer cells and, as far as possible, leave the body's healthy cells unharmed

The gene mutations that can currently be treated, and that completely or in part cause lung cancer, include: **ALK, ROS1, EGFR, BRAF,** and **NTRK**. As all these genes produce receptors that belong to a class of *tyrosine kinases*, each of their targeted therapies are called *Tyrosine Kinase Inhibitors* or **TKIs**.

Gene Mutations

ALK (anaplastic lymphoma kinase):

Is a gene that gives instructions for making a protein called ALK-receptor tyrosine kinase. The ALK-receptor is normally located on the cell surface and is activated when the cell environment sends a signal which wakes up the-ALK receptor. The activated ALK-receptor forwards the signal from the cell surface down to the cell nucleus which tells the cell that it is time to grow and divide.

When the ALK-gene is mutated, it provides the incorrect instructions for the production of the ALK-receptor. This abnormal form of ALK-receptor can activate itself without any control from the cell's environment, which can cause an uncontrolled growth of cancer cells. A lung cancer driven by ALK is called **ALK-positive lung cancer** or **ALK+ NSCLC**. Targeted therapies for this type of lung cancer are called **ALK TKI**s.

ROS1 (c-ros oncogene 1):

Is a gene that gives instructions for the production of ROS1 protein. As ROS1 and ALK are closely related from an evolutionary perspective, the mechanism behind tumor development is similar: in the lung cells, the ROS1 gene becomes damaged and leads to production of a deformed ROS1 receptor. The new receptor is no longer controllable and thereby sends a constant growth signal to cells, which causes a tumor to form.

A lung cancer driven by ROS1 is called **ROS1-positive lung cancer** or **ROS1+ NSCLC**. Targeted therapies for this type of lung cancer are called **ROS1 TKI**s.

EGFR (Epidermal Growth Factor Receptor):

The EGF-Receptor can become damaged and cause various diseases, including lung cancer. In the lung cells, a healthy EGFR plays the role of sending signals from the cell surface to the cell nucleus, which results in the normal division and survival of the cell. This signal

should however only be sent when the EGFR is activated by the cell environment. When the gene for EGFR is damaged, a new version of the EGF receptor is created. This mutated receptor is constantly active and is able to work faster and independently, without any need for activation from the cell environment. Similar to the ALK and ROS1 cases, this results in an uncontrollable cell division and formation of a tumor

A lung cancer driven by EGFR is called **EGFR-mutated lung cancer** or **EGFRm NSCLC**. Targeted therapies for this type of lung cancer are called **EGFR TKI**s.

BRAF (proto-oncogene B-Raf):

Is a gene that gives instructions for making the protein BRAF. BRAF plays an important role in transferring chemical signals from the outside of the cell surface to the cell nucleus in order to control the maturation, division and growth of the cells. When a BRAF-gene becomes mutated it can lead to many different diseases, including lung cancer. The mutation in the BRAF gene leads to its product, the BRAF receptor, becoming overactive and driving tumor development.

A lung cancer driven by BRAF is called **BRAF-mutated lung cancer** or **BRAFm NSCLC**. Targeted therapies for this type of lung cancer are called **BRAF TKI**s.

NTRK (Neurotrophic Tyrosine Receptor Kinase):

Includes a group of genes that form proteins called TRK. Similar to ALK and ROS1, an NRTK gene can break and be mixed with parts of another gene. This change creates a mutated NTRK gene, which in turn produces an incorrectly shaped TRK protein. As TRK proteins play an important role in i.e. the regulation of cell division, such mutations can result in an uncontrolled stimulation that leads to cancer. NRTK+ lung cancer is very uncommon and can be treated with targeted drugs against NRTK.

Immunological Biomarkers

Some lung tumors, which many times do not have treatable gene mutations, can avoid the immune system in a highly effective way. It is very important for a tumor's survival to be invisible to the body's immune system since our immune cells are able to attack and kill tumor cells if they successfully recognize them as dangerous. Tumor cells on the other hand can produce large quantities of proteins (for example PD-L1) that inhibit the immune system and simply trick the immune cells into thinking that nothing is wrong. This mechanism is the basis for modern immunotherapies - drugs that prevent the inhibition of the immune system and therefore help the patient's own immune cells to attack the cancer.

PD-1/PD-L1 checkpoint:

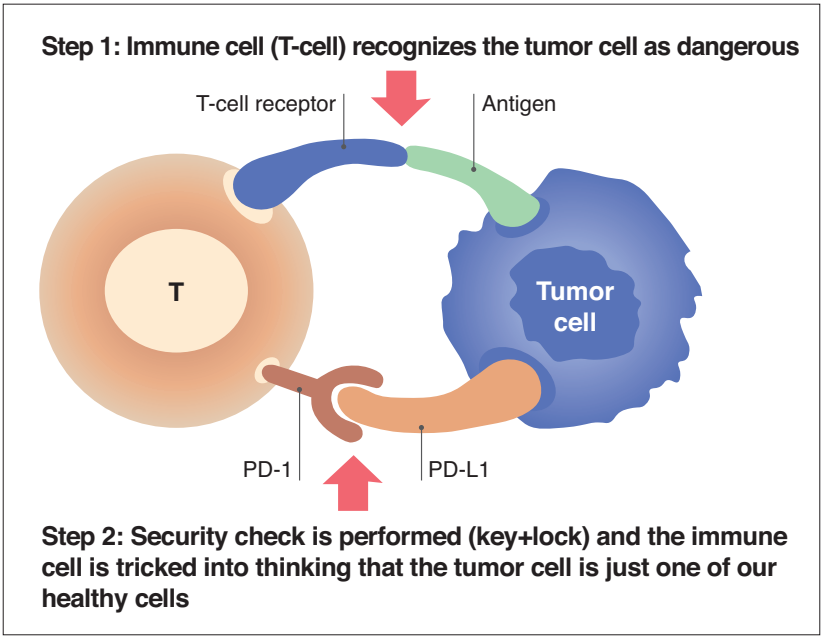
This is an essential mechanism in our bodies, which involves two components:

- PD-1 (Programmed cell death – protein 1), and
- PD-L1 (Programmed death – ligand 1)

The so-called "checkpoint inhibitors" refer to these. Up until now it is mainly drugs that inhibit "the checkpoint" PD-1 or PD-L1 that have reached clinical use within lung cancer. These two molecules normally work as a lock and key with the purpose of ensuring that our immune system does not attack our own body by mistake. PD-1 (the lock) is located on the surface of our immune cells while PD-L1 (the key) is located, amongst other places, on the surface of healthy cells.

The immune cells constantly scan our body to discover hazardous intruders and when they recognize a dangerous cell (for example tumor cells, but also bacteria, viruses or even our own diseased cells), the immune cells attack and kill these. See the schematic illustration on the next page.

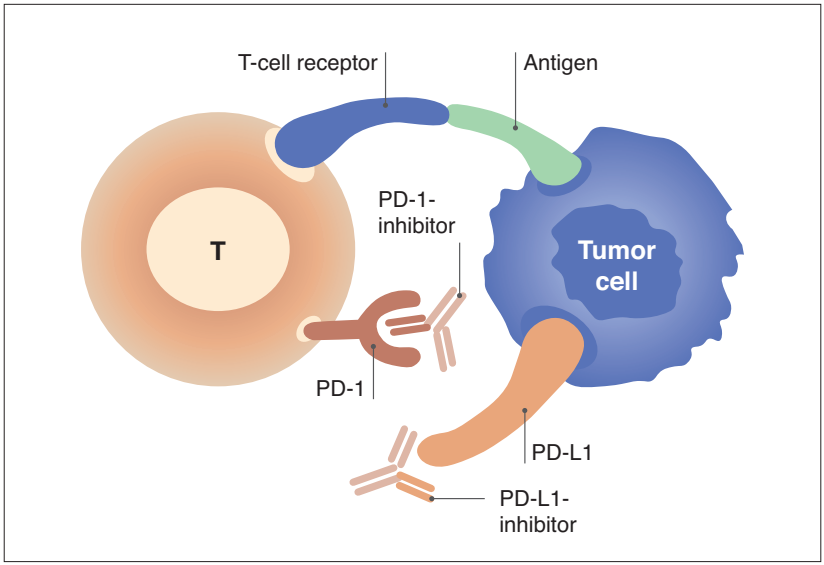
Cancer cells can learn how to produce large quantities of PD-L1 and display them on their surface. Thereby, the immune cells are left to believe that the cancer cell is not dangerous, and the attack is stopped. By waving around lots of these ”I am not dangerous” - PD-L1 flags, the cancer tricks our immune system, hides, and continues to grow in the body. In addition to the PD-L1-security check, there are also other security checkpoints, for example CTLA-4, which just like PD-L1 can help the cancer to avoid the body's own immune system.



Adapted from: The new era of immune checkpoint inhibitors; Guha M, *The Pharmacology Journal*, 2014

Current **immunotherapies** work by stopping the interaction between the tumor cells' PD-L1 (the key) and the immune cells' PD-1 (the lock), so that the tumor can no longer trick the immune system. Because these drugs remove the security check, they are referred to as **checkpoint inhibitors** and they work by either:

- binding and blocking PD-L1 (**"PD-L1 inhibitor"**) or
- binding and blocking PD-1 (**"PD-1 inhibitor"**):



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Lung cancer patients who have tumors with very high PD-L1 levels are more likely to respond to immunotherapy. Therefore, a PD-L1 test is performed on lung cancer patients.

Similar to the PD-(L)1 inhibitors, there are currently immunotherapies that can inhibit CTLA-4 and that can sometimes be given together with PD-1 inhibitors to patients with non-small cell lung cancer.

Clinical Diagnostics

To find out if a lung cancer is driven by a gene mutation or if the patient's immune system has the potential to fight the cancer, it is necessary to do a diagnostic test, which is performed on samples taken from tumor cells (biopsy) or sometimes immune cells.

The following is an explanation of some expressions that are common within clinical diagnostics.

Biopsy:

Means that a tissue sample is taken to analyze if there are tumor cells in your body.

Bronchoscopy:

Is a procedure in which the physician inserts a flexible tube into the bronchi to be able to see what they look like and to be able to take samples used for diagnostic tests.

Diagnostic tests:

Different scientific methods are currently used to for example test if the patient has a tumor that is driven by a gene mutation or if the patient shows signs of a suppressed immune system. These tests help determine the correct diagnosis and the best treatment choice.

Within lung cancer diagnostics, the following types of tests are often used:

- **Immunohistochemistry (IHC)** - uses specific fluorescent antibodies to find cancer-driving receptors (such as EGFR, ALK, ROS1, etc.) in the patient's tumor samples. When the antibody finds and binds to the receptor, a measurable light signal is created and the test is considered positive. With this assessment one can also predict how the person will respond to specific targeted drugs.

- **Fluorescent in situ hybridization (FISH)** – is used to see if the patient's tumor contains gene mutations and if it is driven by them. The damaged gene is found by using different glowing "markers" used to identify where the gene is damaged and in how many cells. FISH can find complex damage in many genes such as ALK, ROS1, or NTR.
- **Next-Generation Sequencing (NGS)** - reads (sequences) our genes and can analyze large parts of genetic material in one assay. NGS can be used to analyze the presence of a number of predetermined cancer biomarkers and can contribute in choosing the best treatment option.

Pathologist:

Is a physician who is specifically trained to perform diagnostic tests on patient samples. A pathologist assesses if a change is benign or malignant, determines the cancer type and if the tumor is expressing the different molecular changes described above.

Grade:

The grade of the tumor depends on how the tumor cells look under the microscopes. A lower grade generally means a slower tumor growth while a higher grade means a more aggressively (rapidly) growing tumor. A tumor can be of grade 1 to grade 3.

Stage:

Provides information on how much a tumor has spread in the body:
Stage 1: the tumor is located in the lung where it started
Stage 2: tumor cells are located in the lung and nearby lymph nodes
Stage 3: tumor cells are located in the lung and in lymph nodes in the middle of the chest cavity
Stage 3A: when the affected lymph nodes are on the same side of the chest cavity as the original tumor

Stage 3B: when the tumor cells are also located in the lymph nodes on the other side of the chest, or in the lymph nodes above the clavicle
Stage 4: the cancer has spread to both lungs, to the pleura or to other organs

Tumor:

Is a lump that can be benign (not harmful) or malignant (harmful). Benign tumors can become large but they do not spread in the body (do not metastasize). A malignant tumor is called cancer and has the ability to grow rapidly and spread (metastasize) to other organs.

Chest X-ray or computed tomography scan (CT, PET-CT), ultrasound, bone scan:

Provide images of the tumor and are assessment methods that can show if cancer is present and if it has spread.

Clinical Study Terms

A **clinical trial** or a **clinical study** is an assessment of e.g. a new treatment or a new drug in humans. Within *oncology* (the science of tumor diseases), clinical studies are always performed in patients with cancer (and not on healthy individuals) for the purpose of, e.g. finding out or confirming how safe or effective a treatment is.

All clinical trials have **inclusion criteria** and **exclusion criteria,** i.e. rules about which patients are suitable or not suitable for a study.

Advanced:

Advanced cancer can be locally advanced or metastatic.

- Locally advanced means that the cancer has developed into a cancer that has spread outside of the lung to nearby areas.
- Once the cancer has reached other organs - caused metastases (mets/secondary cancer) - it is more difficult to treat.
- Sometimes the number of metastases found at the discovery of cancer can be low, which is called oligometastatic disease.

WHO and ECOG (Eastern Cooperative Oncology Group) Score/Performance Status (PS):

Is a measurement which describes the patient's well-being and level of functioning. The ECOG scale goes from 0 (fully functional) to 5 (death) and is evaluated by a physician in order to monitor the progression of the disease and its impact on the patient's life. It also helps to choose the optimal treatment.

Objective Response Rate (ORR) or tumor response:

The proportion of patients (%) in the study which are considered to have responded to the investigational treatment. A patient is often considered as a "responder" if their tumor has either:
- shrunk (reached partial response - PR),
- completely disappeared (reached complete response - CR).

Stable disease:

When the tumor that is being treated within a clinical trial stops growing but does not decrease in volume it is referred to as stable disease (SD).

Progressive disease:

If the tumor continues to grow despite the study treatment, it is called progressive disease (PD).
Stable disease and progressive disease are not considered a response (i.e. these tumors are not considered to respond to treatment).

Progression-free survival (PFS):

Time from the first dose of the study drug (or time from randomization) until disease progression or death regardless of cause.

Duration of Response (DOR):

Time from first documented tumor response until disease progression or death regardless of cause.

Randomization:

The process where patients are randomly divided in different treatment groups (via computer programs), e.g. to a group that is treated with a new drug or to a group that is treated with standard drugs. The randomization ensures impartial allocation of patients into study groups and reduces bias.

Time to tumor response (TTR):

Time from first dose (or time from randomization) to first documented tumor response.

Overall Survival (OS):

Time from first dose (or time from randomization) to death regardless of cause.

Treatment Terms

Neoadjuvant treatment:

A treatment that is given before a surgical procedure with the primary purpose of shrinking the tumor so that it is easier to remove surgically or to treat with radiation.

Adjuvant Treatment:

A treatment that is given after surgery to reduce the risk of a relapse.

Cytostatics/Cytotoxics/Chemotherapy:

Is a form of treatment that affects the dividing cells in the body. Since the cancer cells grow significantly faster than our healthy cells, the chemotherapy hits them the hardest. The normal cells still get affected, which is why the patients have various side effects such as hair loss. Chemotherapy can be given as tablets or intravenously to the blood.

Curative treatment:

Curative treatment refers to a treatment that is intended to cure.

Multidisciplinary teams:

A multidisciplinary team that consists of e.g. oncologists, pulmonologists, surgeons, radiologists, pathologists, and nurses. They have different expertise areas and together they review each patient case to discuss what the next step will be for the specific patient.

Radiation therapy/radiotherapy:

A treatment using strong radiation energy to damage tumor cells with the purpose of removing a tumor, slowing the disease or relieving the symptoms. Radiation therapy can sometimes replace surgery and in a better way preserve the function of the organ.

Second opinion:

Included in the Swedish Patient Act (2014:821). In case of life threatening or serious illness, you have the right to a renewed medical assessment, a so-called second opinion. Primarily the patient should turn to their supervising physician that writes a referral for the renewed medical assessment. You may choose by yourself which clinic or specialist you want to be referred to. *Source Cancerfonden [The Swedish Cancer Society].*

Specialist nurse:

Is a nurse with in-depth knowledge within a particular field.

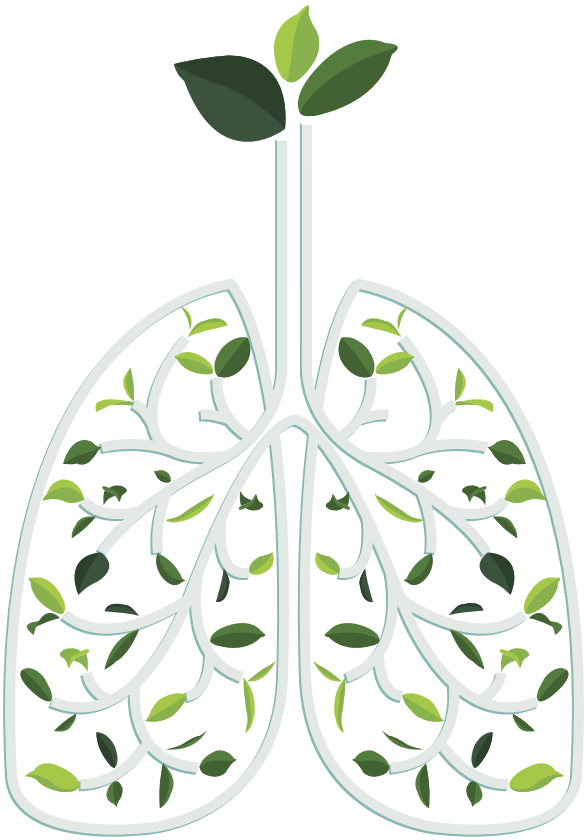
Symptom:

Sign of disease.

Tumor burden:

The number of cancer cells, the size of a tumor, or the amount of cancer that exists in the body.

Lungcancerföreningen [The Swedish Lung Cancer Association] is run by a group of volunteering patients, relatives and dedicated healthcare professionals. Under this name we, amongst other things, organize the annual lung cancer day, local lectures, patient meetings, maintain a support telephone service, participate in different impactful meetings, write debate articles and show our presence, so that our group does not end up on the back of the agenda or become more stigmatized. By becoming a member, you provide funds and mandate for the association to advocate and to keep the operations going.



Lungcancer föreningen