

Lung cancer

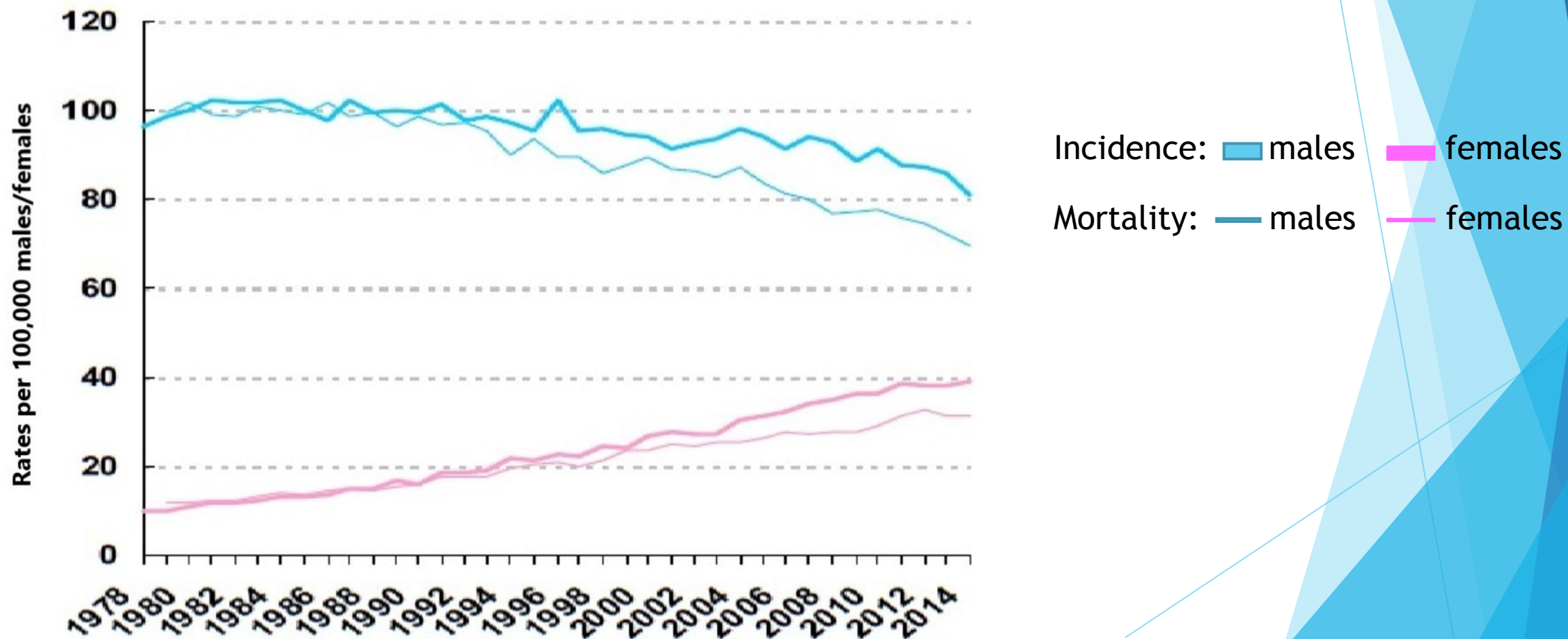
O. Bílek, S. Bořilová, P. Grell



Lung cancer/Lung carcinoma

- ▶ Malignant tumor of lung tissue and bronchi of diverse molecular character
- ▶ Incidence in Czech republic: 42,9/100,000 females, 86,2/100,000 males
- ▶ The most common age at diagnosis is between 50 - 80 years
- ▶ In Czechia
 - 6,700 new cases of lung cancer per year
 - 5,300 deaths per year
- ▶ The deadliest cancer worldwide in both genders
 - accounting for 24% in males and 15% in females
 - **!AND THERE IS STILL NO SCREENING PROGRAMME!**

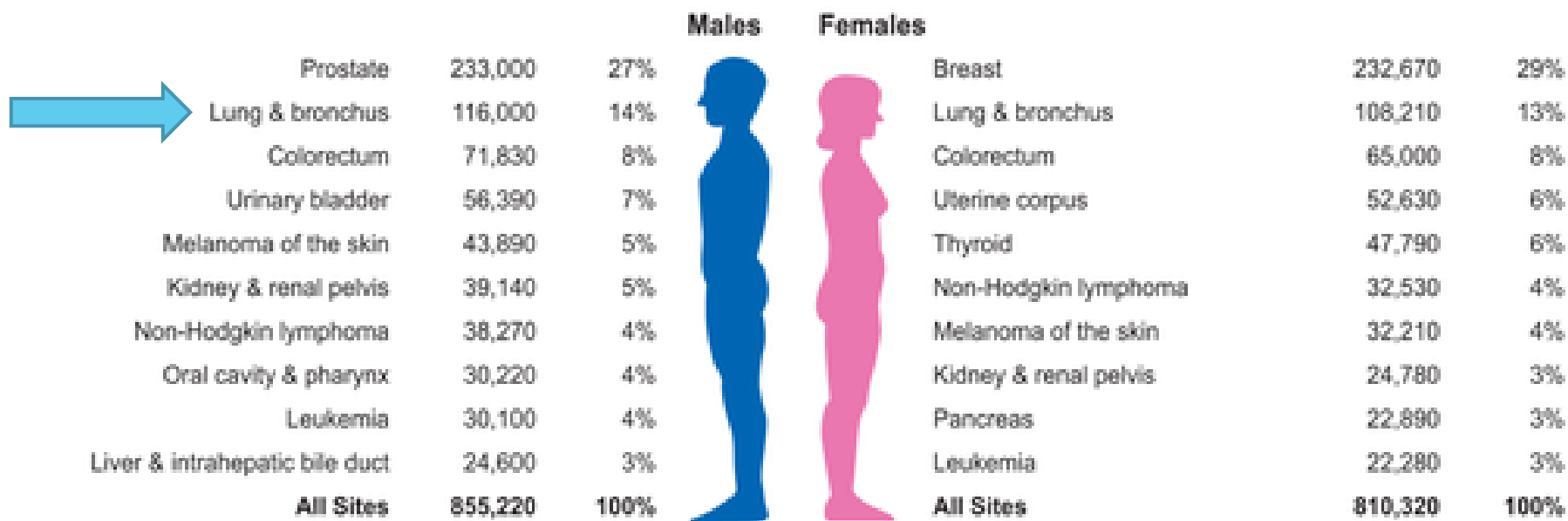
Incidence and mortality of lung cancer in Czech republic



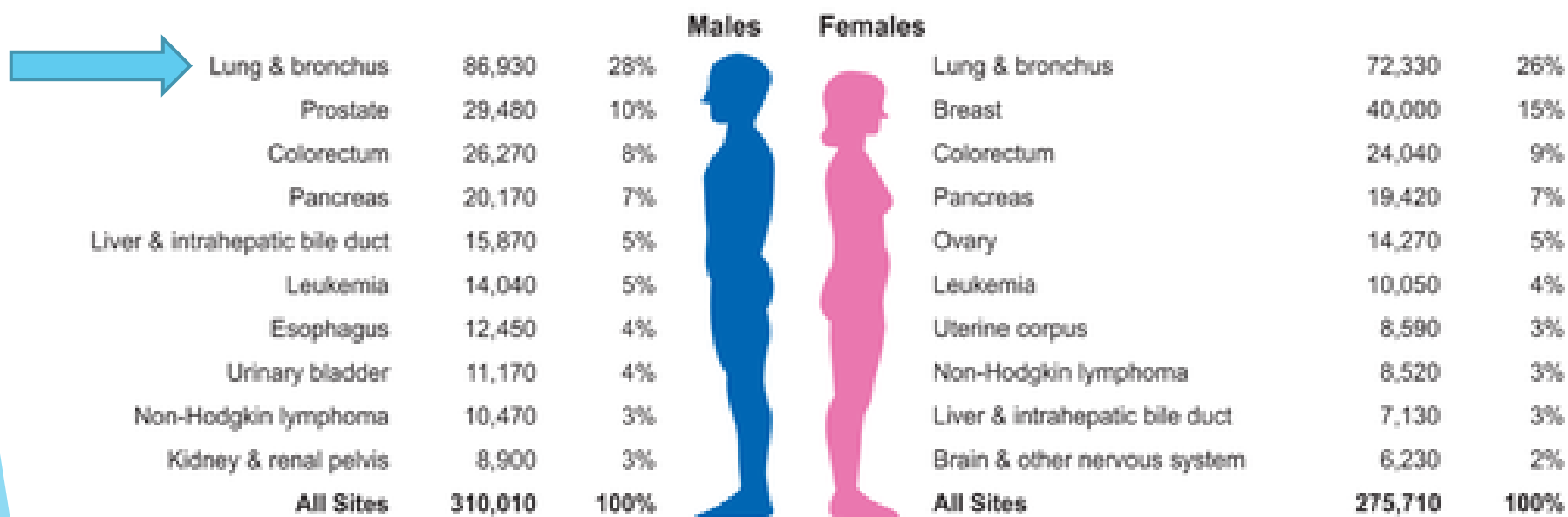
Source: National oncological register

Estimated New Cases*

Ten leading cancer types, USA, 2014

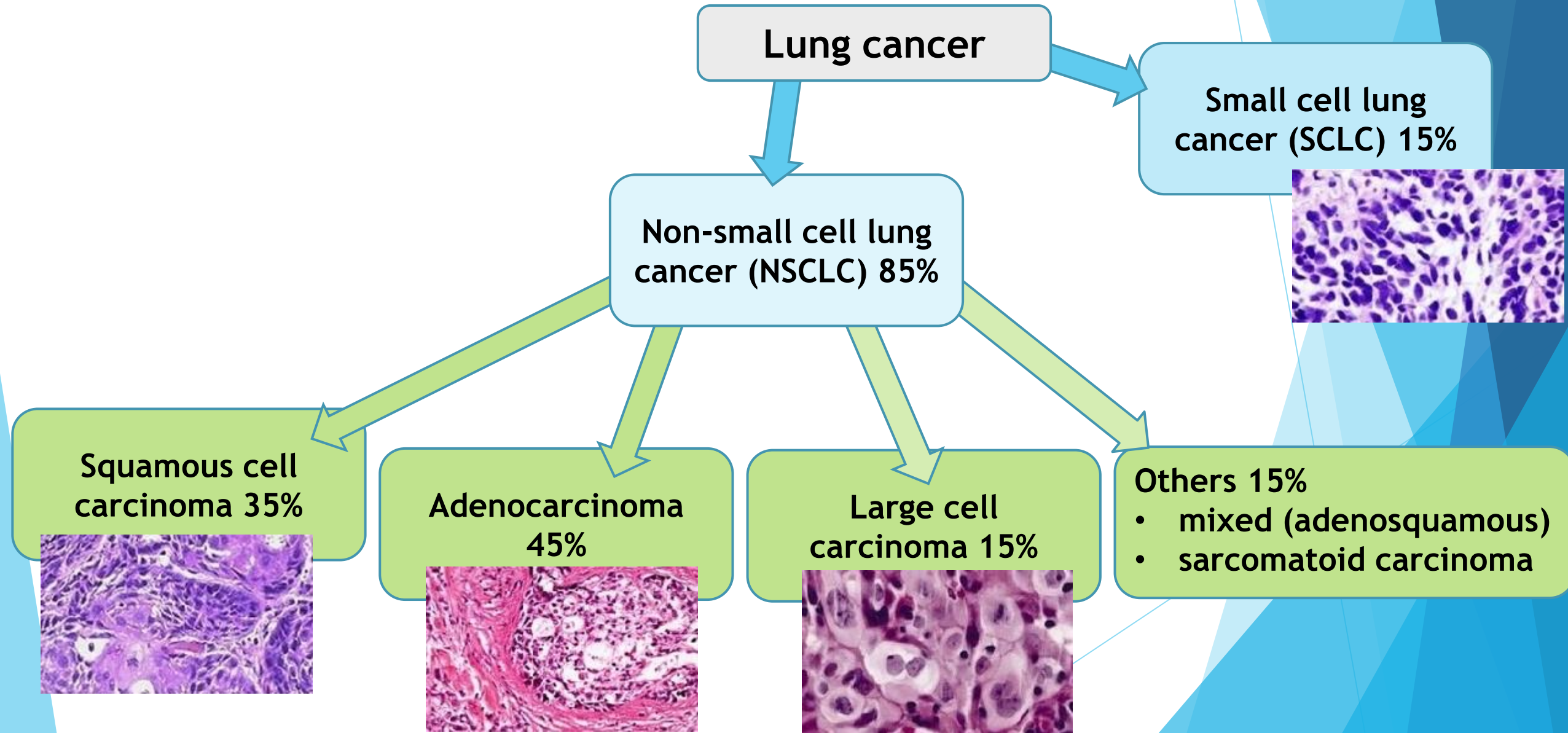


Estimated Deaths

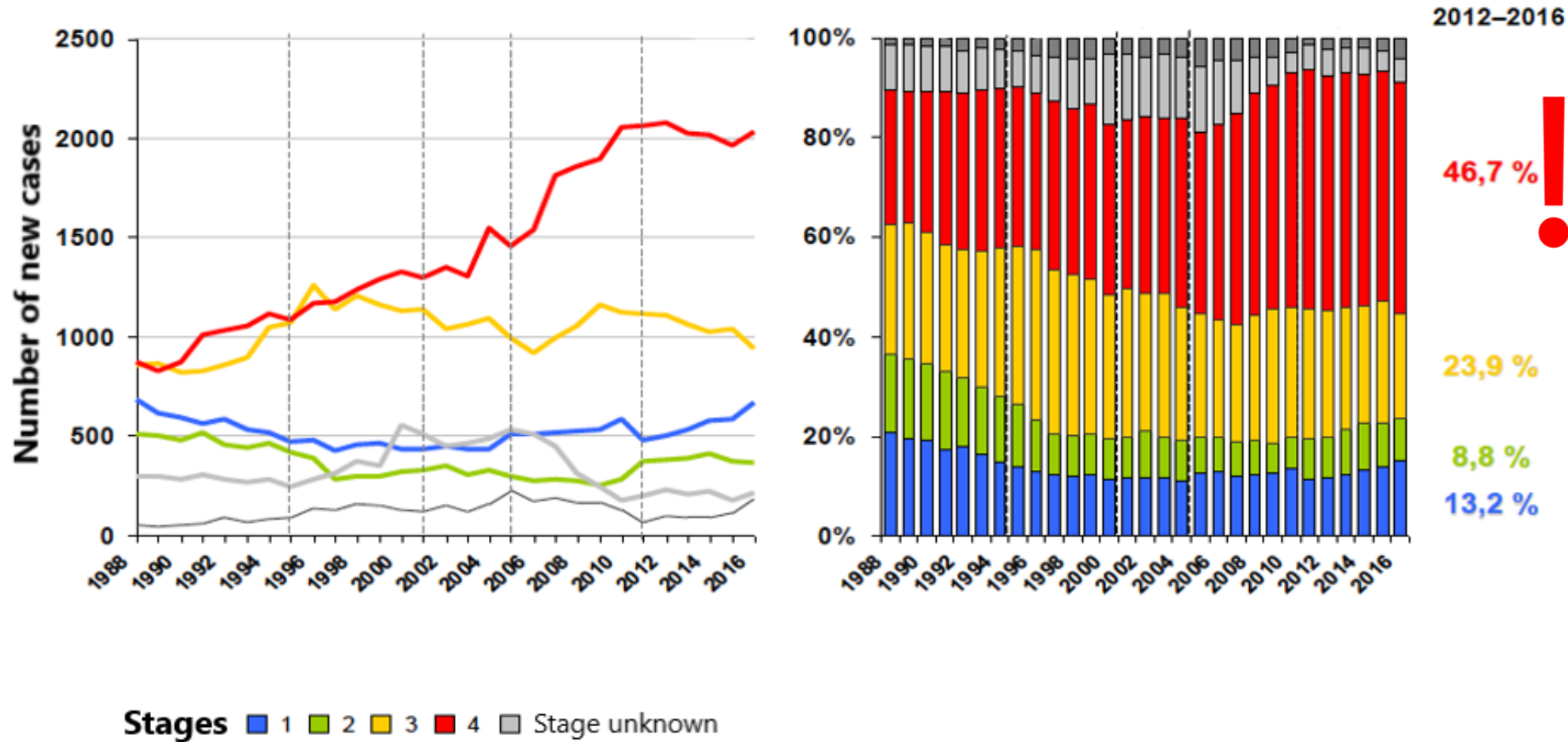


Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014 Jan;64(1):9-29

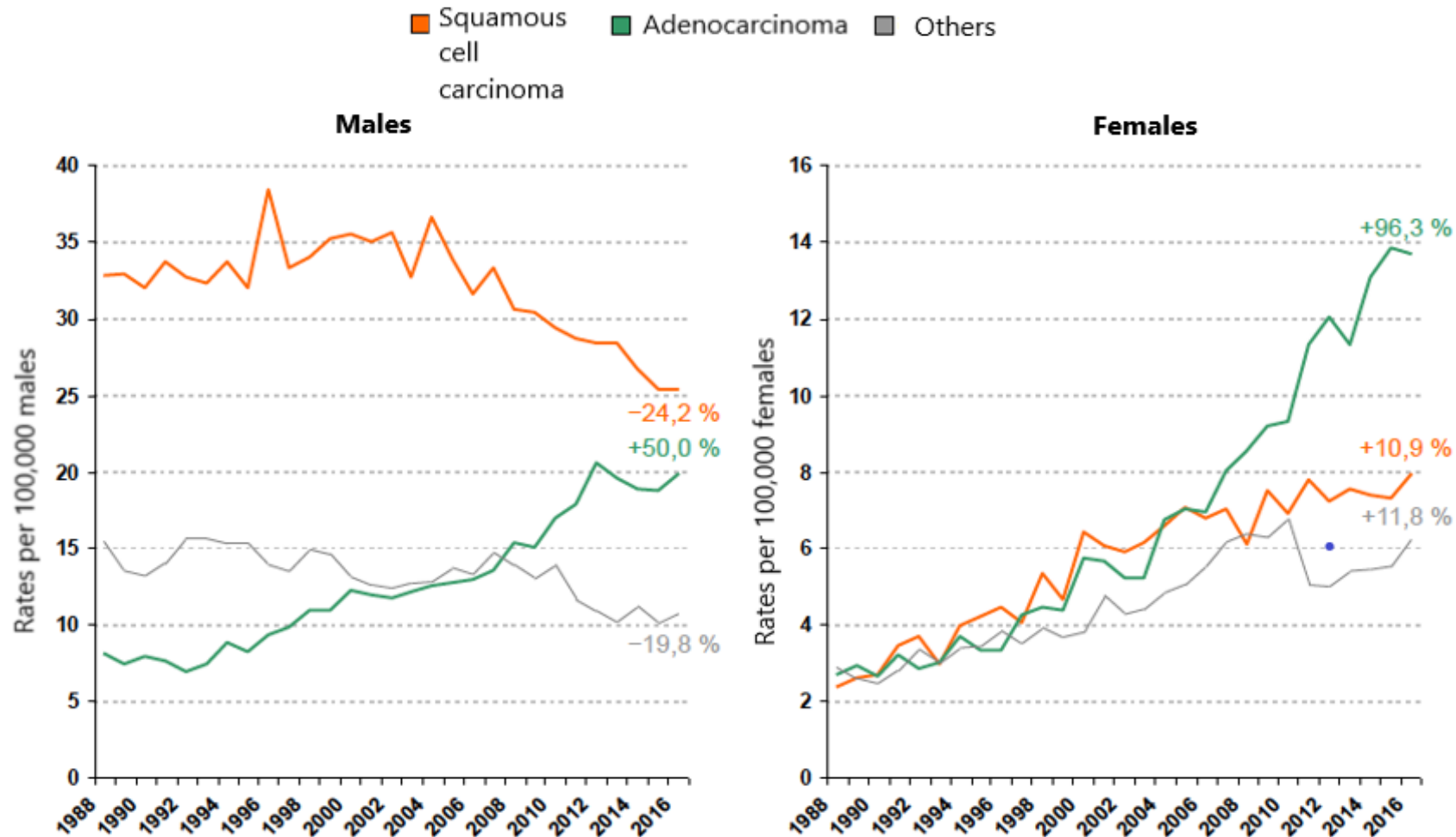
Histopathological types of lung cancer



NSCLC is still mostly diagnosed in advanced stage



Incidence of histological types according to sex



Source: National oncological register

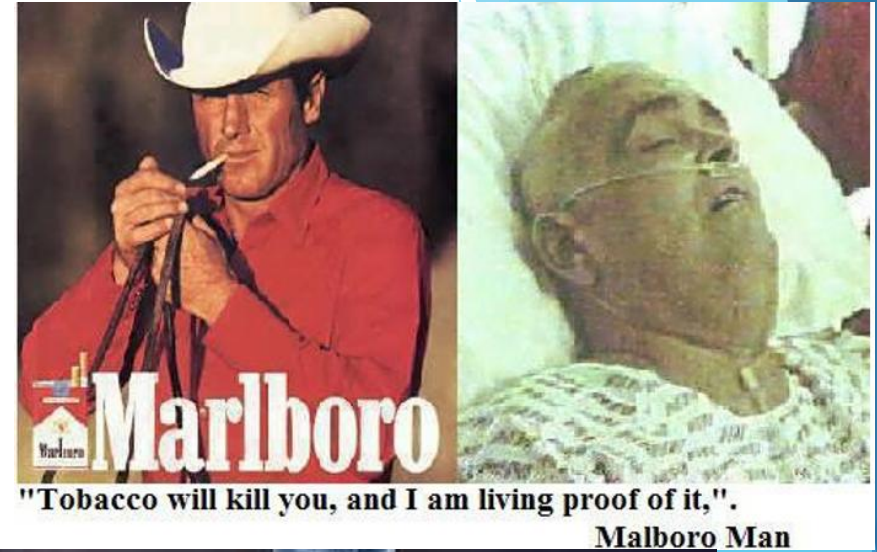
Risk factors

▶ Endogenous

- ▶ Genetic (p53), ↑P450, ↓ glutathione S transferase

▶ Exogenous

- ▶ Tobacco smoking
 - by far the leading risk factor for lung cancer
- ▶ Others
 - Asbestos
 - Arsenic
 - Ionizing radiation
 - Nickel



Signs and symptoms

- ▶ **Patients are often diagnosed in advanced stage of disease**
 - Symptoms not present in early stage
- ▶ **Symptoms due to primary tumor**
 - Cough in 80 % patients (patient with 3 weeks lasting cough should be checked for lung cancer)
 - Dyspnea
 - Hemoptysis
 - Chest pain
 - Pneumonia
 - ❑ **! ALWAYS PERFORM A CONTROL CHEST X-RAY AFTER PNEUMONIA !**

Signs and symptoms

▶ Symptoms due to thoracic extension of tumor

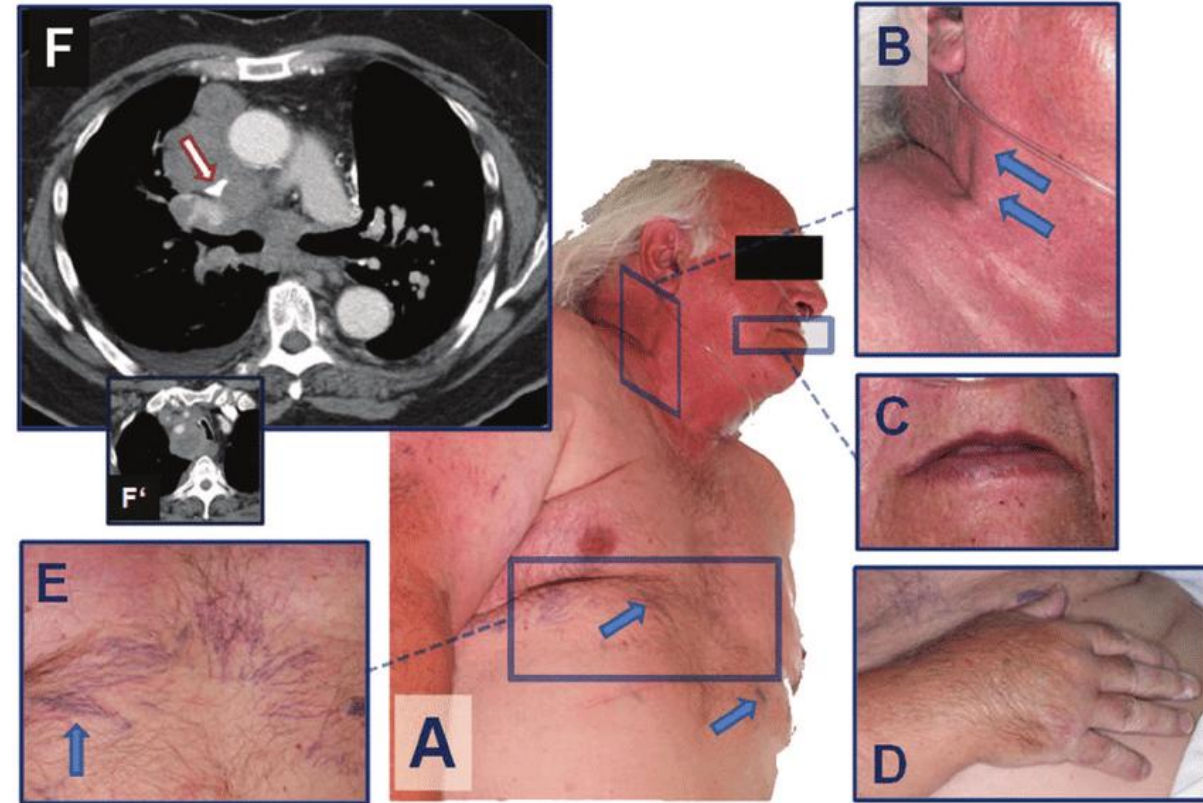
- ▶ Hoarseness (recurrent laryngeal nerve paralysis)
- ▶ Dysphagia
- ▶ Chest pain
- ▶ Vena cava superior syndrome
 - cyanosis
 - fixed raised internal jugular veins
 - swollen face, arms
 - prominent superficial veins throughout the chest wall

▶ Symptoms due to metastases

- ▶ lymph nodes enlargement, bone pain, neurologic deficit (often brain metastases)

▶ Systemic symptoms

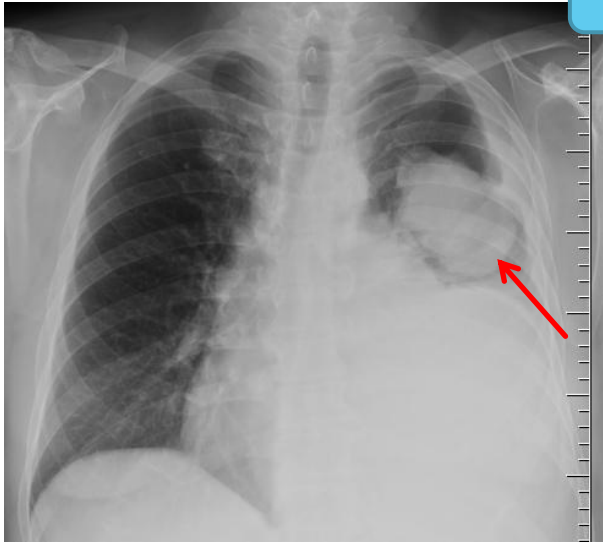
- ▶ anorexia, weakness, weight loss
- ▶ paraneoplastic symptoms: fever, SIADH, hypercalcemia, gynecomastia, hypoglycemia



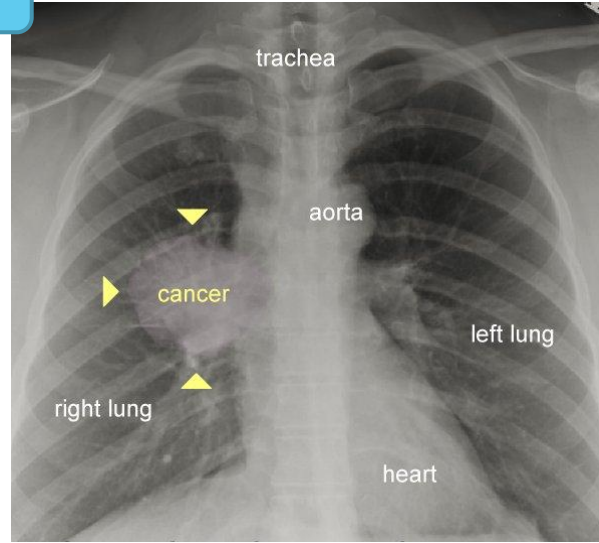
How is lung cancer diagnosed?

Imaging tests

Chest X-ray

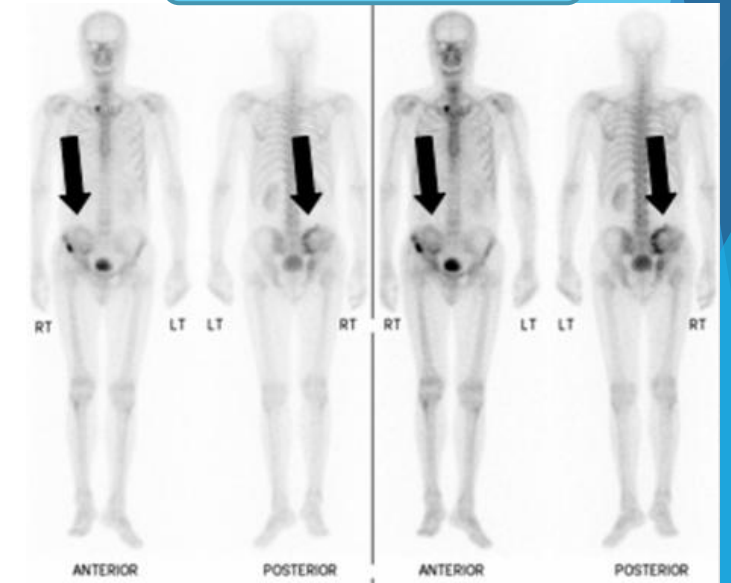


Adenocarcinoma of upper right lobe, pleural infiltration, massive pleural effusion



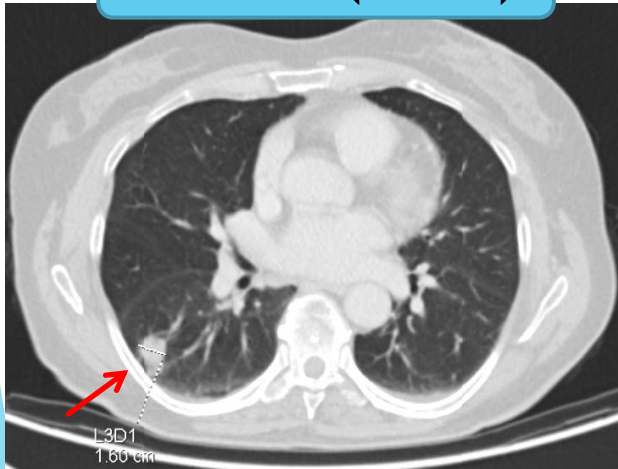
Small cell lung cancer of right lung

Bone scan



Lung adenocarcinoma
Bone metastases of ilium bone

CT scan (HRCT)



Lung cancer of the right lung.
Patient underwent surgery.

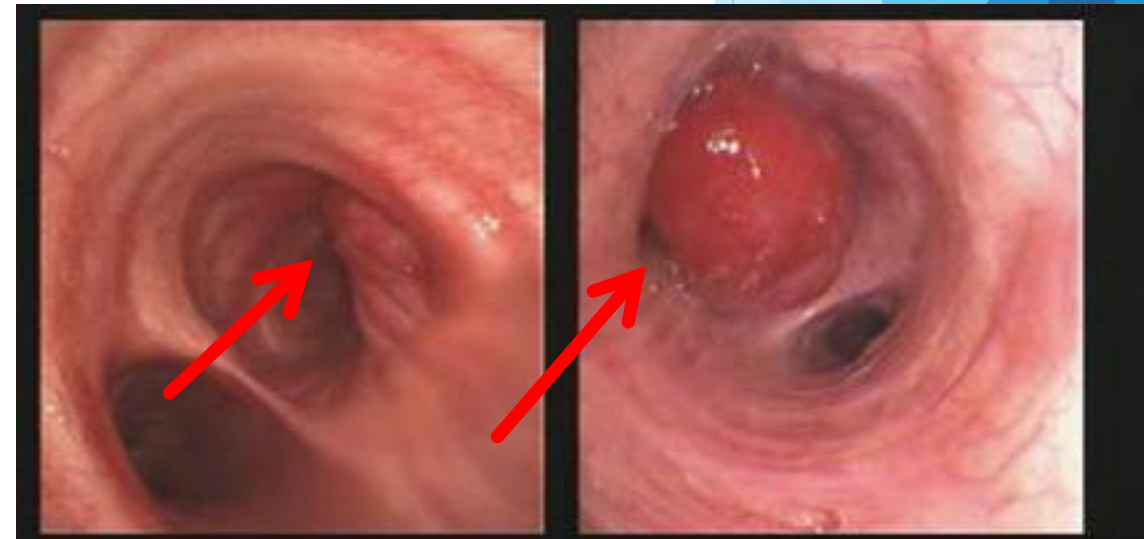
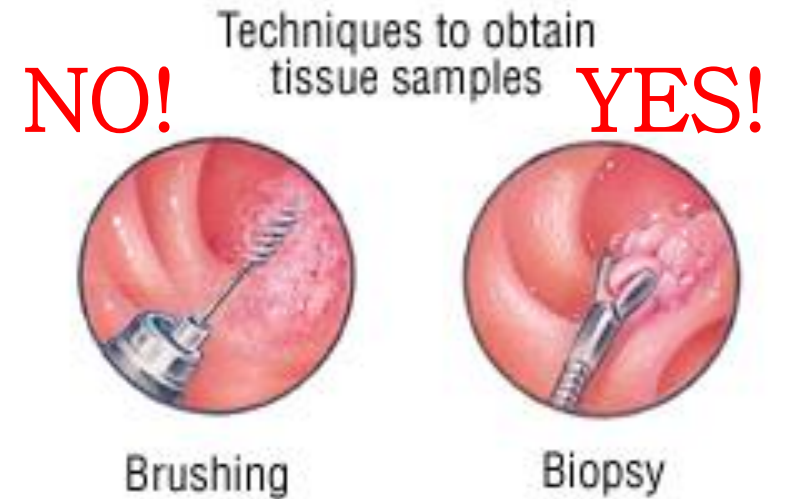
PET/CT



Adenocarcinoma of left hilum.
Pathological mediastinal lymph nodes

Bronchoscopy

- ▶ Rigid/Flexible
- ▶ Diagnostic
 - Description of tumor macroscopic morphology
 - Biopsy
 - Enough biological material for mutational analysis
 - ❖ Cytology (brushing) is not enough!
- ▶ Therapeutic
 - clearing the obstruction of bronchi
 - laser resection
 - stent insertion
 - acute treatment: bleeding, foreign object



Tissue collection for histology analysis and molecular testing

▶ Bronchoscopy

- ▶ collect enough material
- ▶ cytology is not enough!

▶ Endobronchial ultrasound (EBUS)

- ▶ biopsy through bronchial wall under ultrasound control

▶ Percutaneous biopsy under CT control

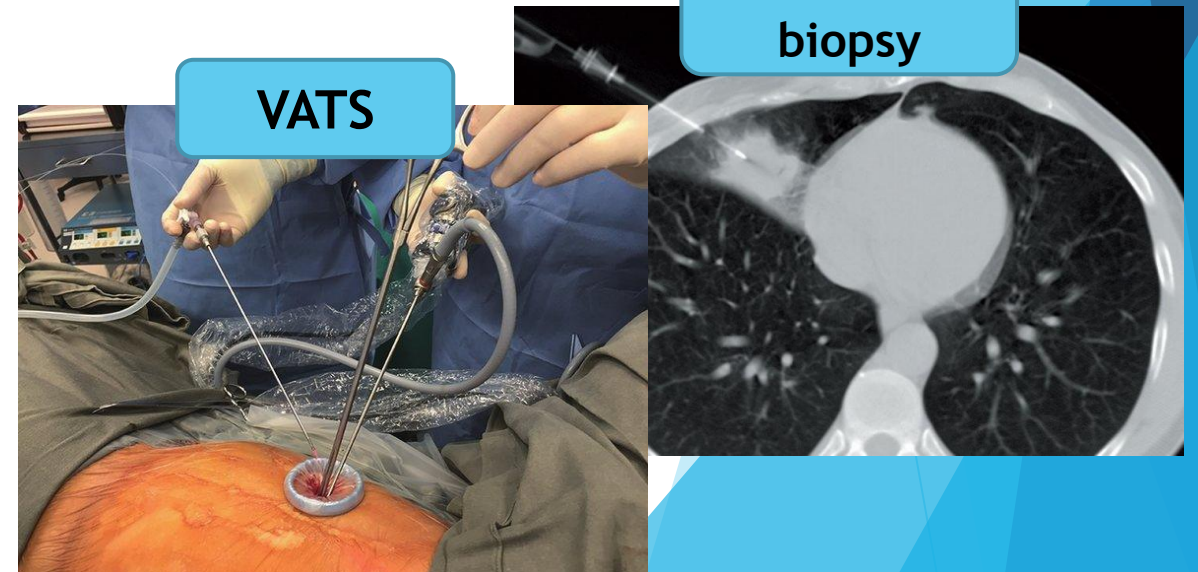
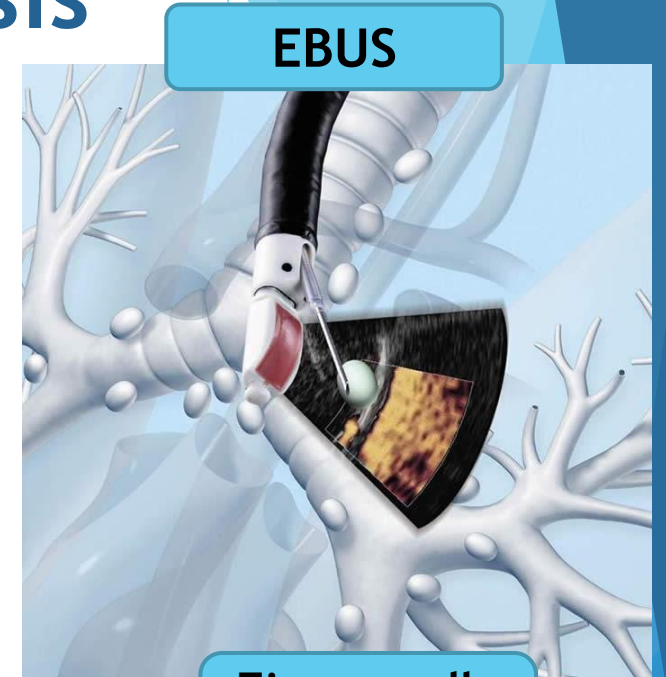
- ▶ fine needle biopsy

▶ Surgery

▶ Endoscopic surgery

- mediastinoscopy
- video-assisted thoracoscopic surgery (VATS)

▶ Open thoracotomy



Laboratory examination

▶ Tumor tissue

- Morphology - cytology, histology
- Immunohistochemistry (IHC) - specific antibodies
- Molecular testing

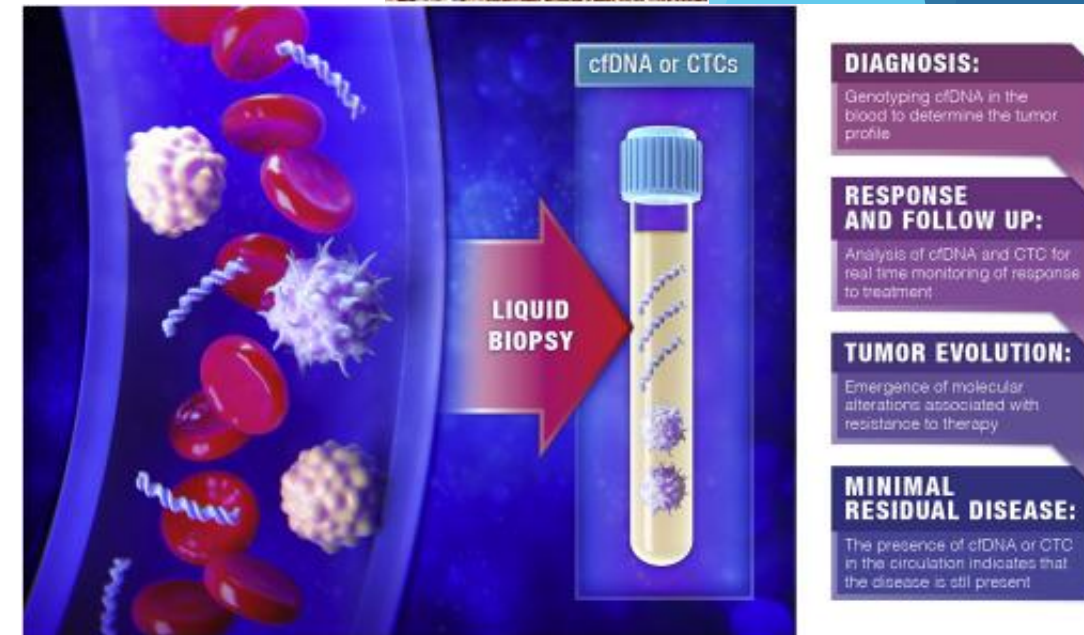
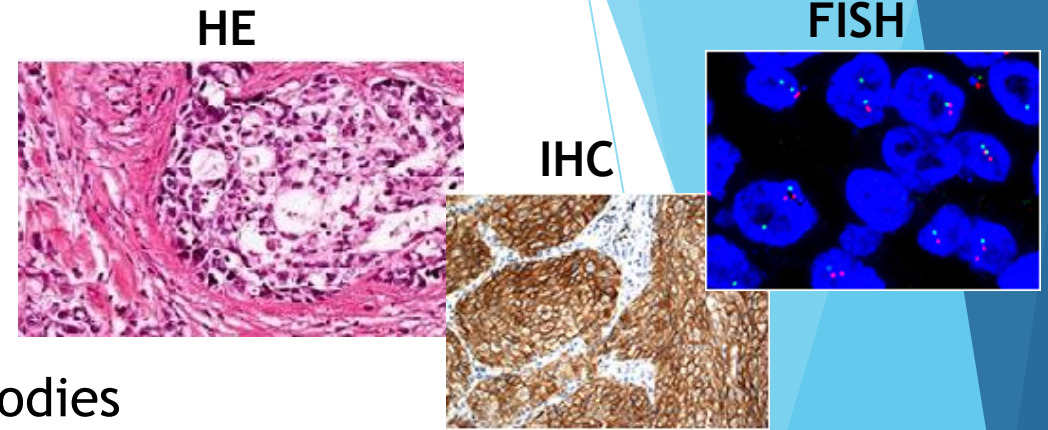
▶ Blood samples

➤ Tumor markers

- ❑ CEA: adenocarcinoma
- ❑ NSE: small cell carcinoma
- ❑ SCC, CYFRA 21-1: squamous cell carcinoma

▶ Liquid biopsy

- blood samples, mutation analysis of extracellular DNA (cfDNA)



How to manage an excellent staging?

▶ Chest X-ray

- mostly negative! insufficient for staging!

▶ CT scan

- Spiral chest CT or HRCT better for interstitial lung disease or small lung lesions
- Abdominal CT - to complete staging and to rule out metastases

▶ PET/CT

- To rule out metastases and to determinate malignant lymph nodes before surgery!

▶ Bone scan

- To determinate bone lesions, mainly useful in adenocarcinomas

▶ Brain scans

- consider CT, MRI or PET/CT if curative treatment is planned or patient is symptomatic

▶ Bronchoscopy

- in centrally situated tumors

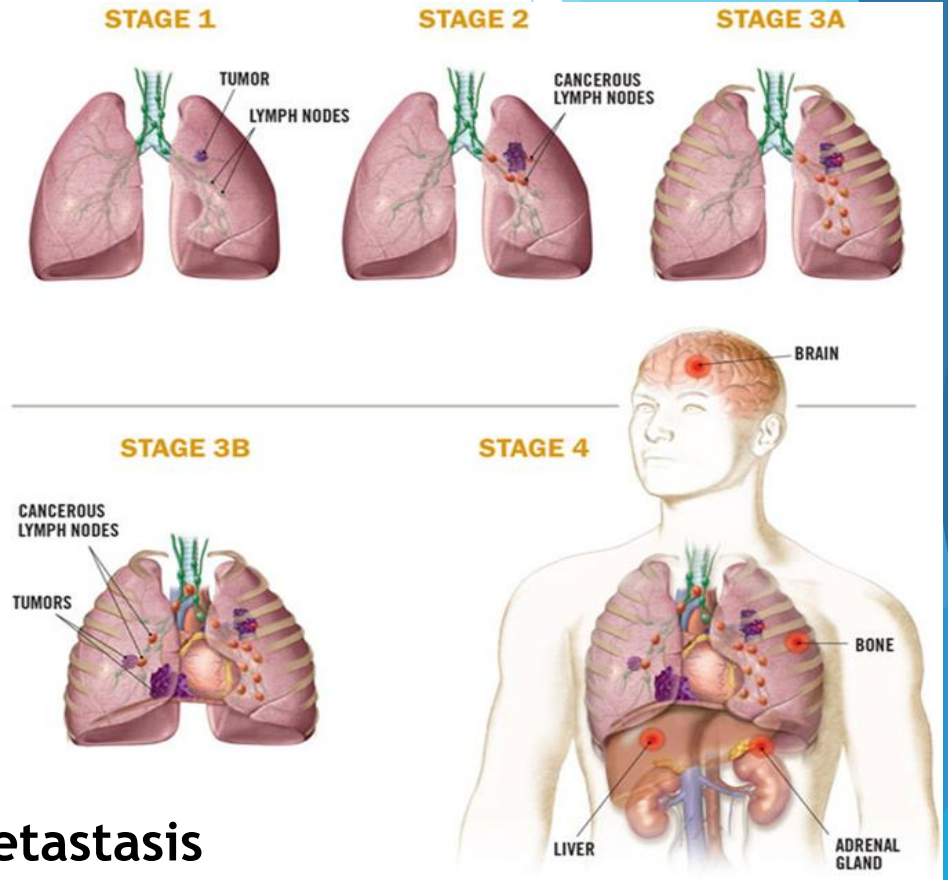
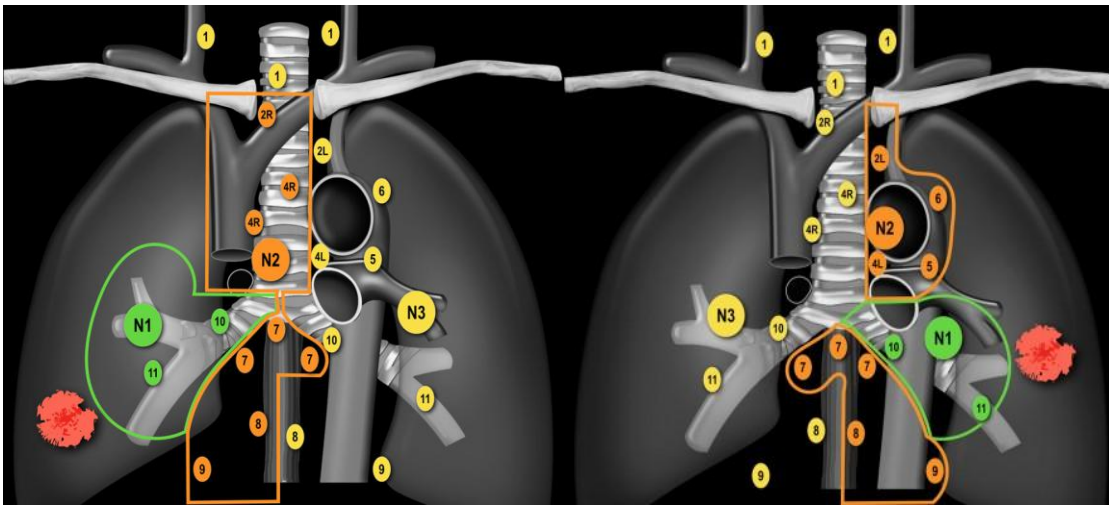
Non - small cell lung cancer (NSCLC)

Staging of NSCLC - TNM classification

▶ Tumor

- ▶ Tumor size
- ▶ Endobronchial location
- ▶ Atelectasis/pneumonitis
- ▶ Visceral pleura invasion
- ▶ Invasion of peripheral/central structures

▶ Nodus lymphaticus



▶ Metastasis

- ▶ M1a thoracic metastases, pericardial/pleural effusion
- ▶ M1b solitary extrathoracic metastasis
- ▶ M1c multiple extrathoracic metastases

Treatment according to clinical stage

▶ Stage I-III A: local + systemic treatment

➤ Surgery

- ❑ Video-assisted thoracoscopic surgery (VATS)
- ❑ Open thoracotomy

➤ Adjuvant chemotherapy (from stage IB)

➤ Radiotherapy +/- chemotherapy

- ❑ when surgery is not indicated
- ❑ studies with immunotherapy in adjuvant setting

▶ Stage IIIB-IV - systemic treatment

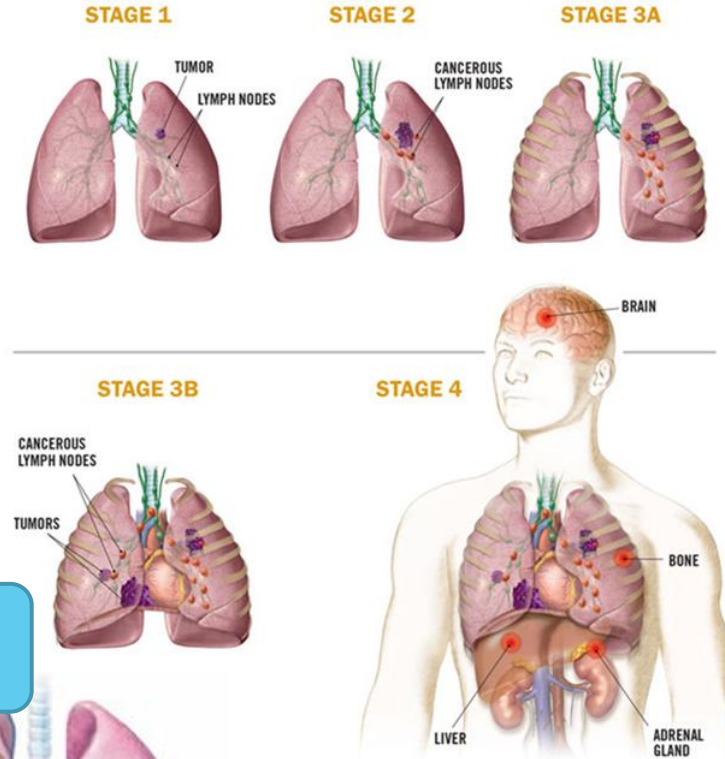
➤ Chemotherapy

➤ Tyrosine kinase inhibitors

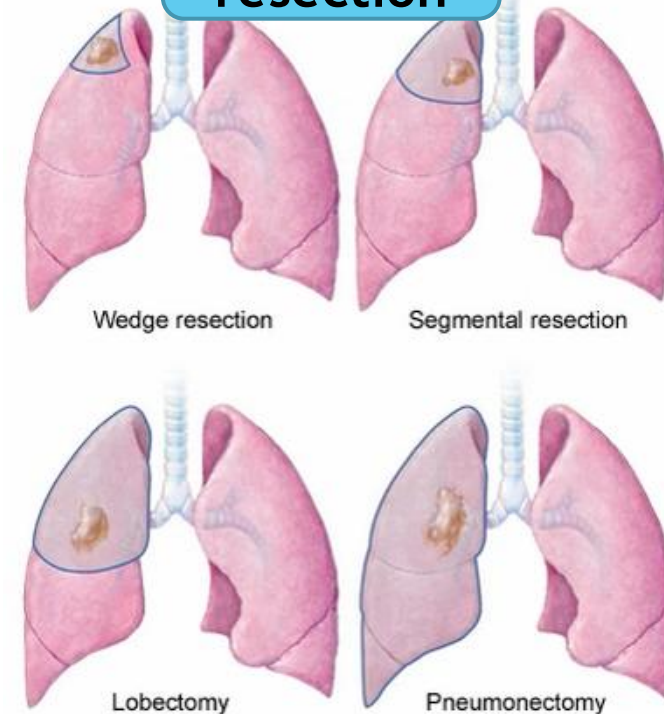
➤ Immunotherapy

➤ Radiotherapy

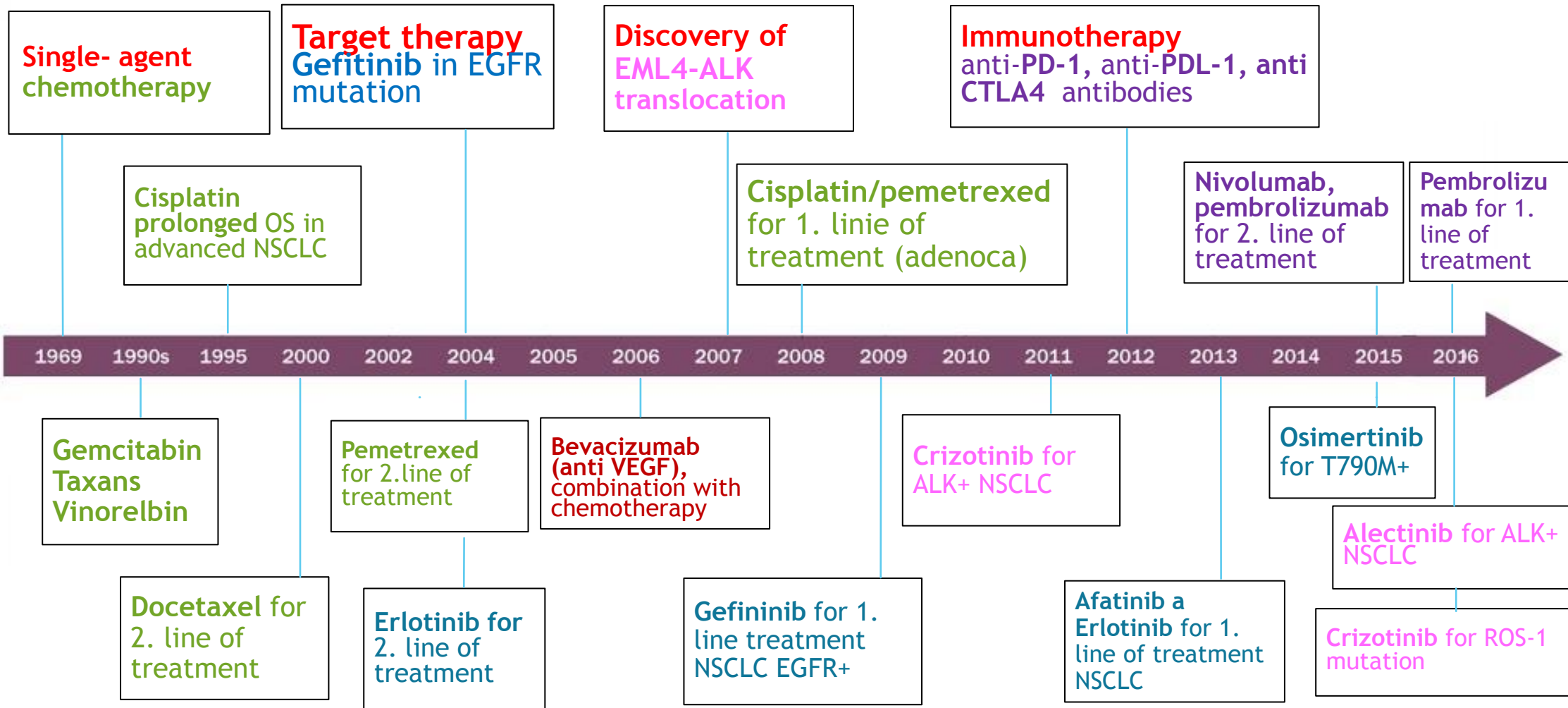
- ❑ definitive radiotherapy in IIIB stage
- ❑ palliative radiotherapy on metastatic lesion



Types of resection



Evolution of systemic treatment of NSCLC



Systemic treatment of NSCLC

The background of the slide features abstract, overlapping geometric shapes in various shades of blue, ranging from light sky blue to deep navy blue. These shapes are primarily located on the right side of the slide, creating a modern, professional aesthetic.

Chemotherapy for NSCLC

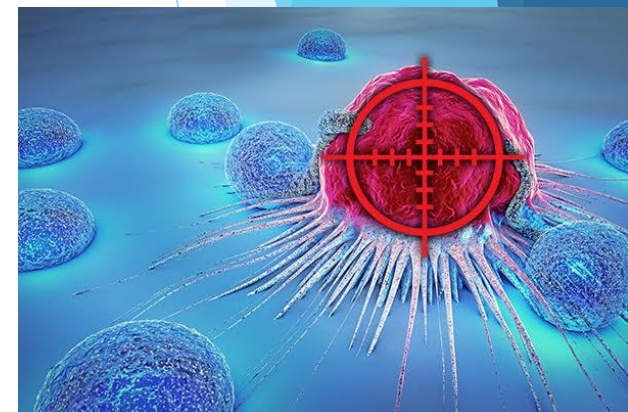
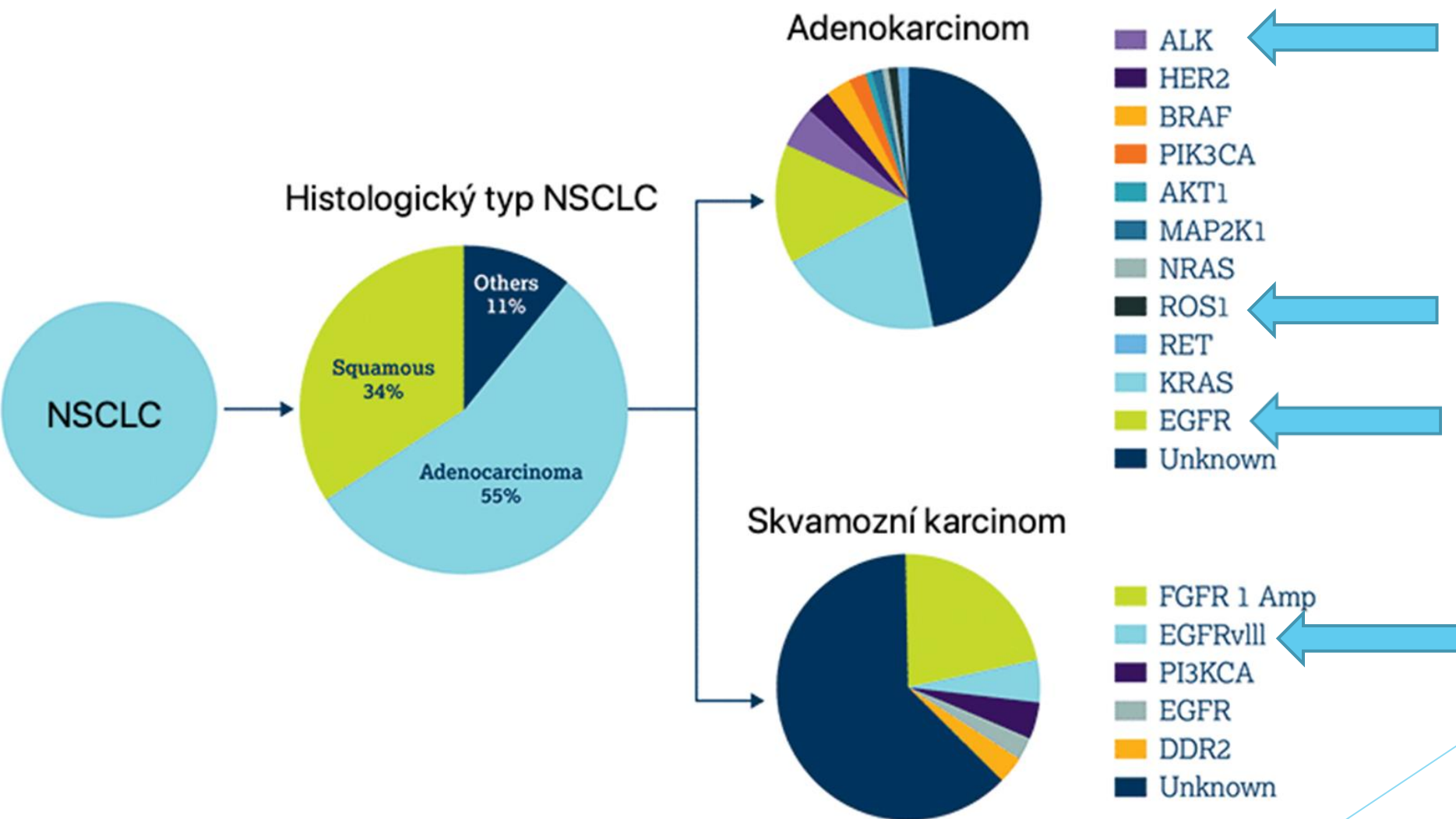
▶ Platinum - based chemotherapy

- ▶ The foundation of systemic treatment for lung cancer
- ▶ Cisplatin, carboplatin

▶ Other chemotherapies

- ▶ Used in monotherapy or in combination with platinum - based chemotherapy
 - Taxanes - paclitaxel, docetaxel
 - Antimetabolites - gemcitabin, pemetrexed
 - Vinca alkaloids - vinorelbine

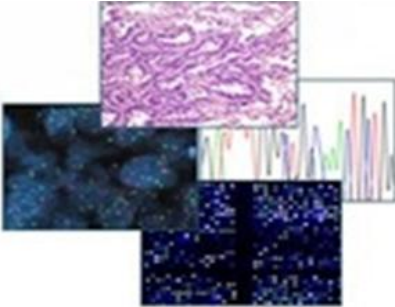
Target therapy for NSCLC



Personalised medicine



Molecular profiling



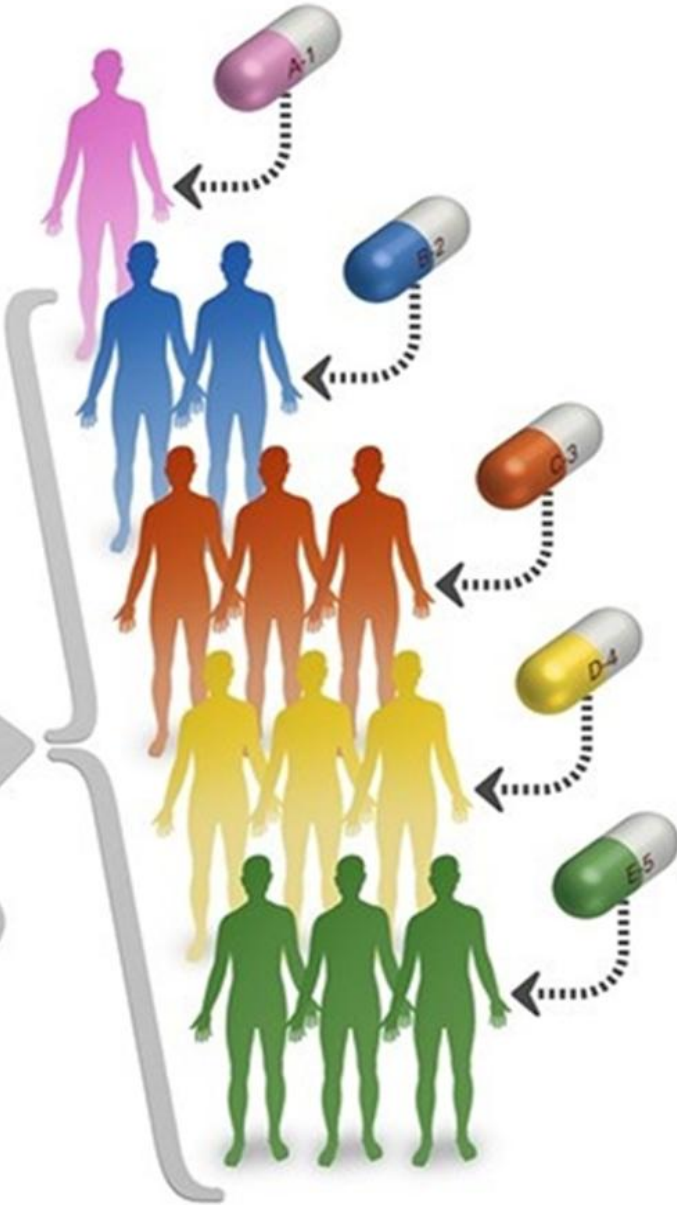
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Prognostic markers

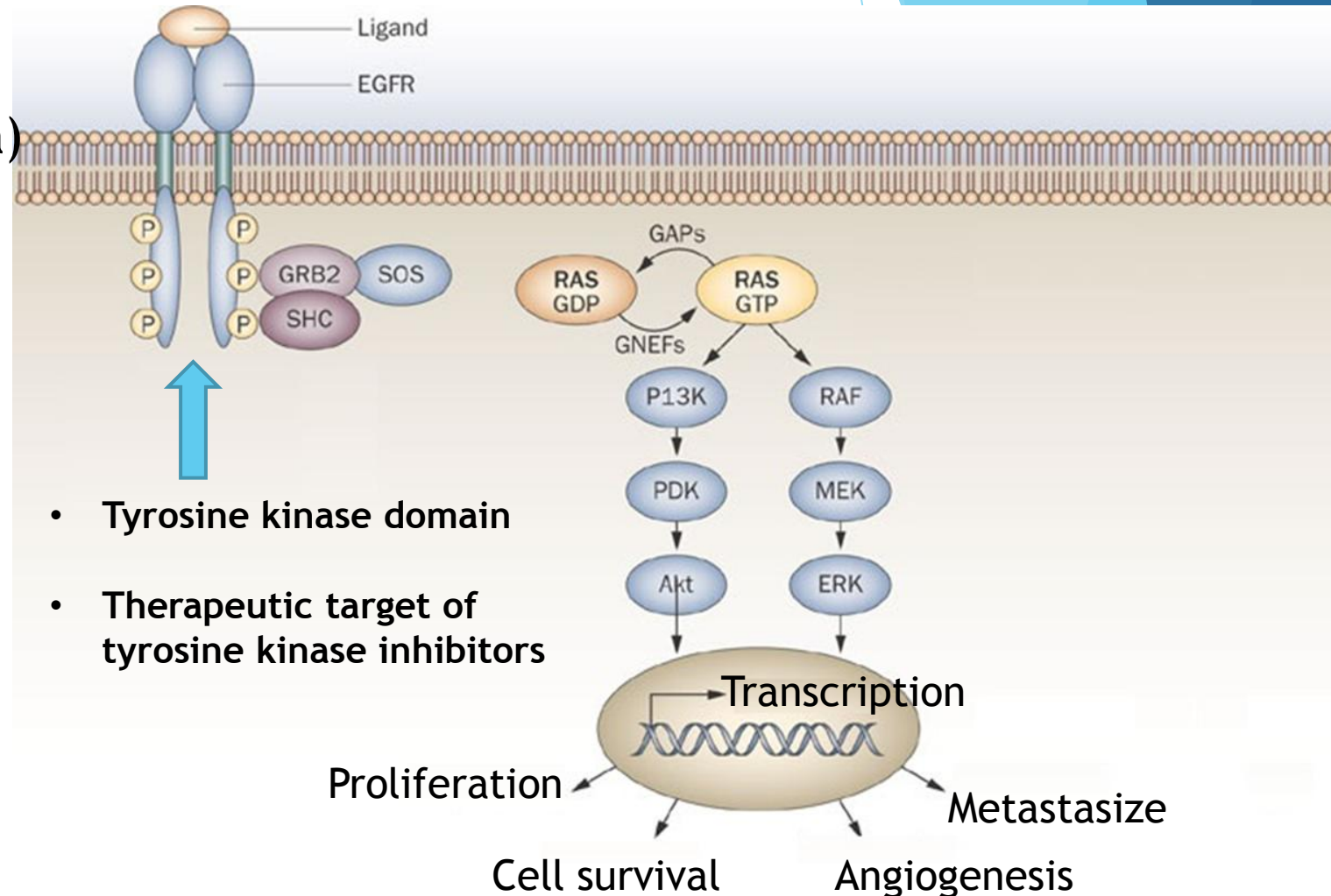


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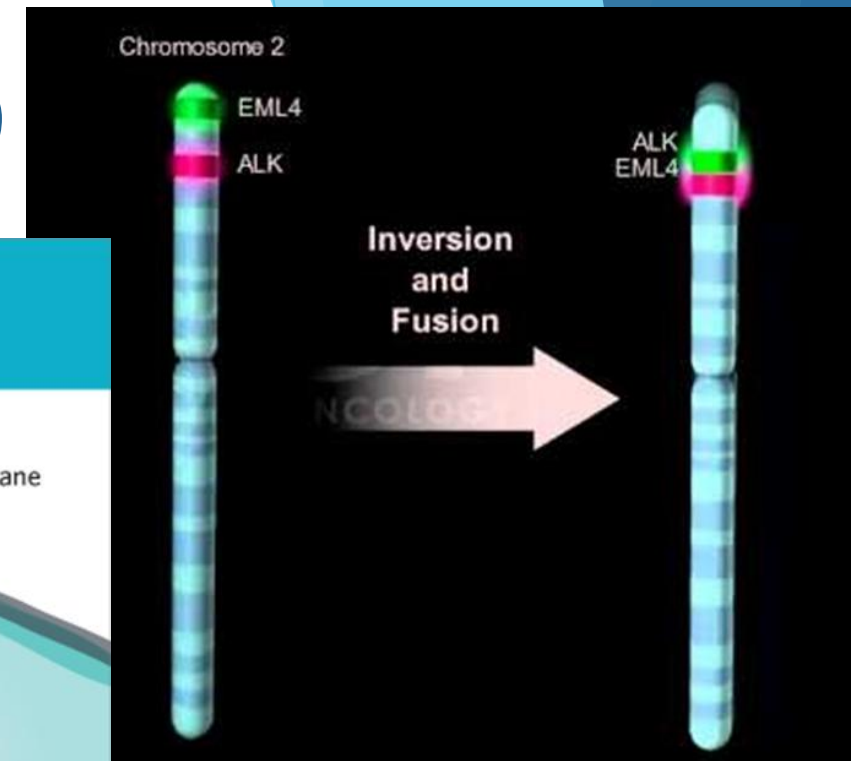
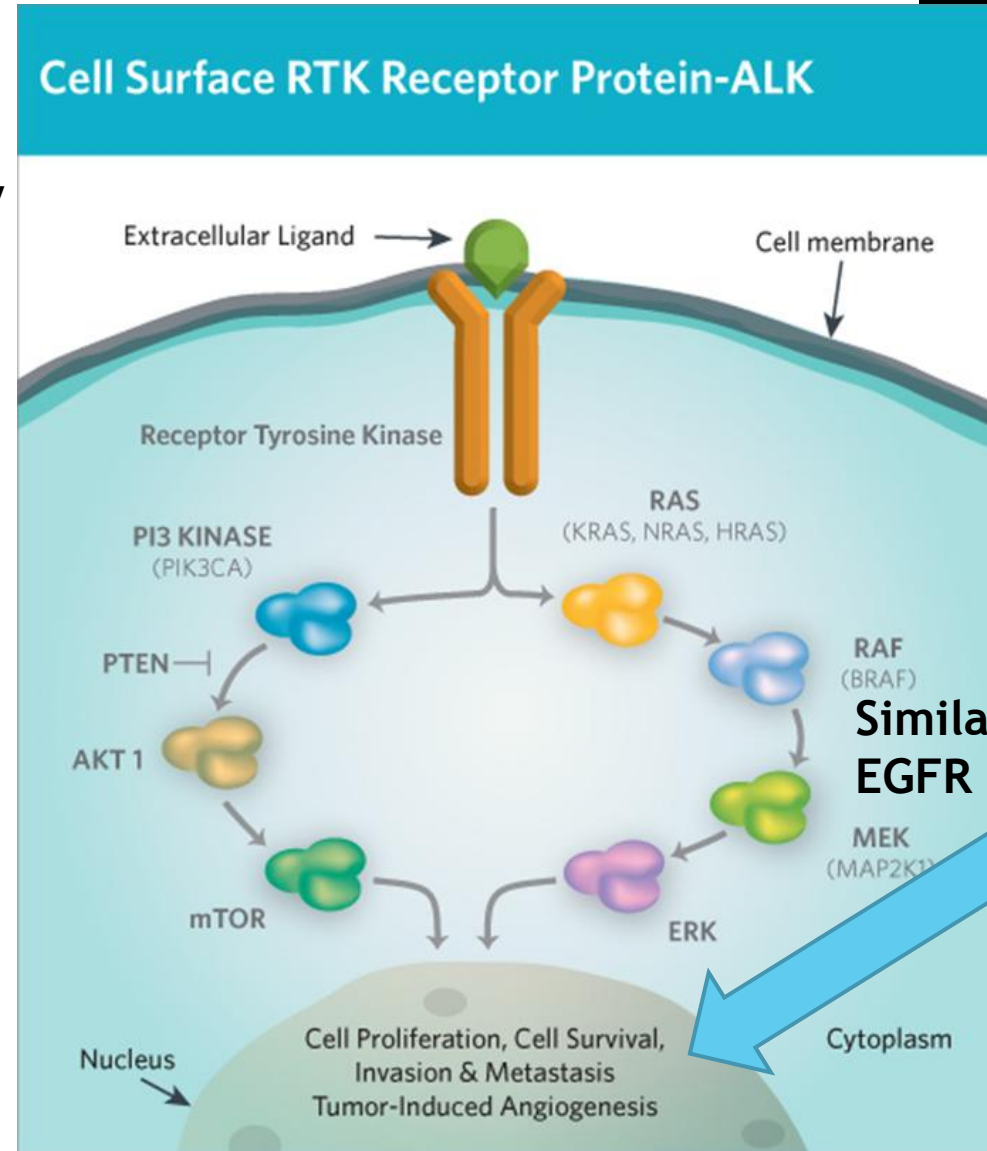
EGFR mutation and its inhibition

- ▶ Responsible for approximately **15 %** of NSCLC (adenocarcinoma)
- ▶ Investigated also from liquid biopsy
- ▶ **Treatment - Tyrosine kinase inhibitors (TKI)**
 - 1st generation of TKI
 - ❑ Gefinitib
 - ❑ Erlotinib
 - 2nd generation of TKI
 - ❑ Afatinib
 - 3rd generation of TKI
 - ❑ Osimertinib



ALK (anaplastic lymphoma kinase) mutation

- ▶ EML-4/ALK fusion gene
- ▶ Responsible for approximately 3-5 % of NSCLC
- ▶ Therapy of ALK+ NSCLC (Tyrosine kinase inhibitors)
 - 1st generation
 - Crizotinib
 - 2nd generation
 - Ceritinib
 - Alectinib
 - 3rd generation
 - Lorlatinib



Similar consequences like EGFR mutation

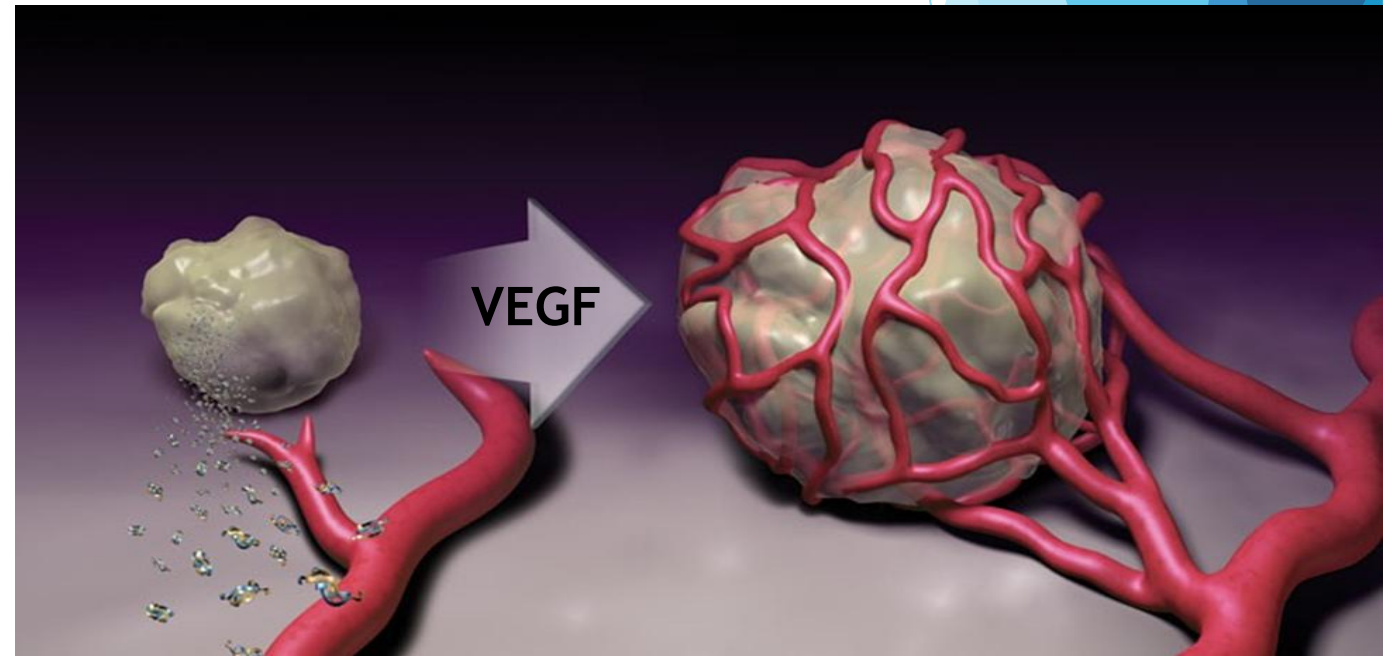
Other target therapy

▶ 1. ROS-1 mutation

- Occurs in 1-2 % of lung adenocarcinoma
- Treatment - Tyrosine kinase inhibitors (TKI)
 - ❑ similar to treatment of ALK+ tumors
 - ❖ crizotinib, lorlatinib

▶ 2. Anti-VEGF therapy (Bevacizumab)

- monoclonal antibody
- inhibition of vascular endothelial factor (VEGF)
- combination with first-line palliative chemotherapy



Immunotherapy - checkpoint inhibitors

▶ Immune checkpoints

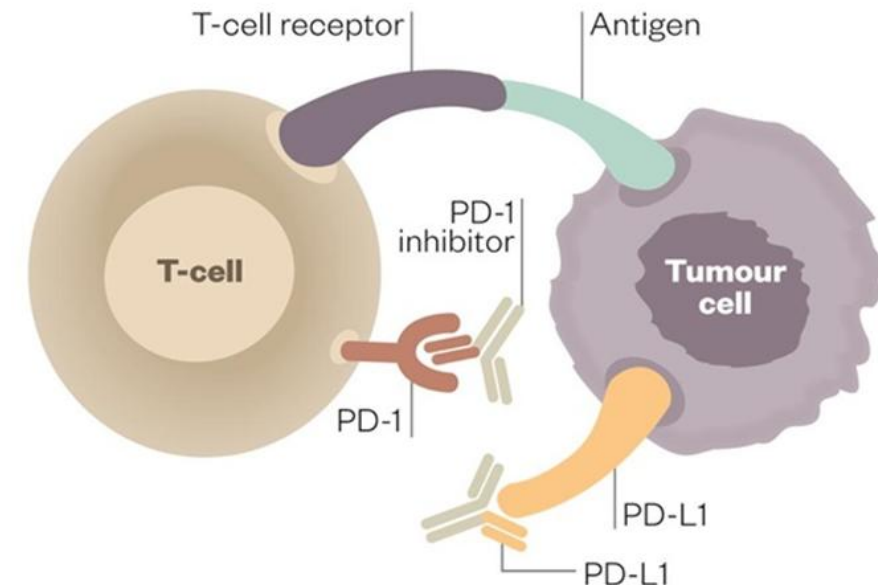
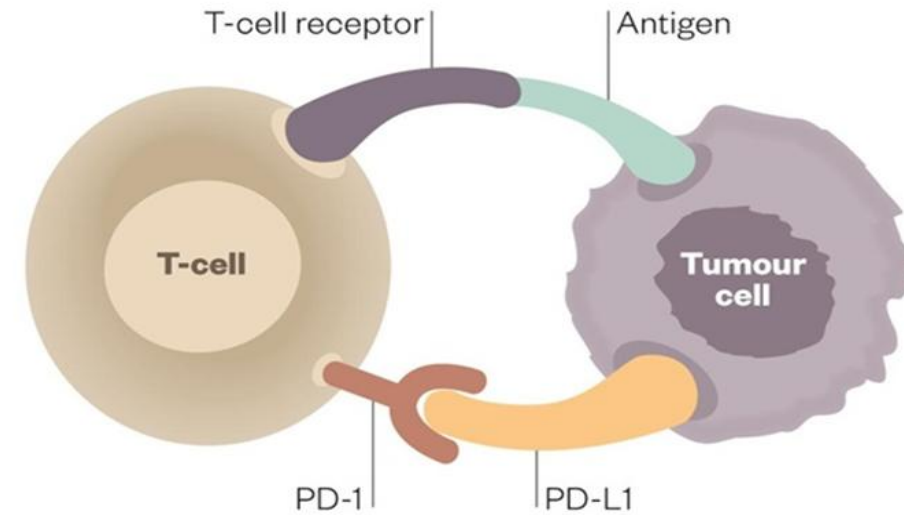
- ▶ key regulators of the immune system
- ▶ stimulation of checkpoints can diminish the immune response to an immunologic stimulus

▶ Inhibition of PD-1/PDL-1

- ▶ restores T- lymphocytes antitumor immunity

▶ Anti PD-1/PDL-1 antibodies

- ▶ anti PD-1 monoclonal antibody
 - pembrolizumab, nivolumab
 - ❖ - standard treatment in Czech republic
 - durvalumab
- ▶ anti PDL-1 monoclonal antibody
 - atezolizumab/avelumab



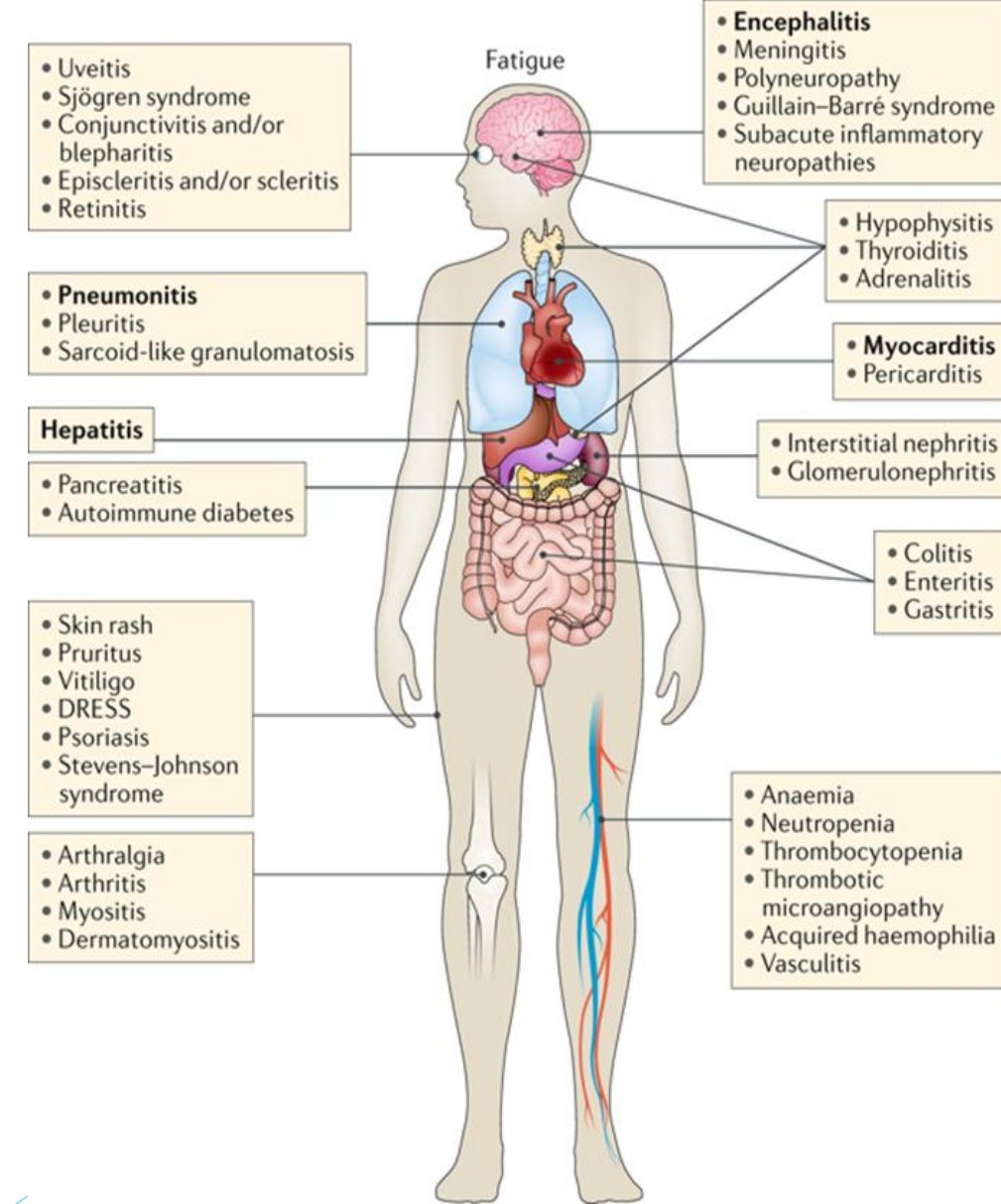
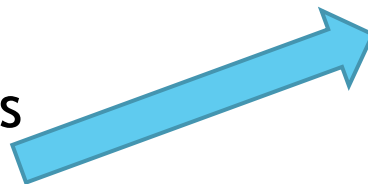
Immunotherapy - checkpoint inhibitors

▶ Benefits

- ▶ New unique mechanism of action
- ▶ Great therapeutic potential

▶ Pitfalls

- ▶ Does not work in every cancer and every patient
 - predictive biomarkers are needed
- ▶ Immune-related adverse effects
 - similar to autoimmune diseases
 - can affect any organ



Small cell lung cancer

- ▶ Highly aggressive cancer type
- ▶ Median overall survival without treatment is 3 months
 - for extensive disease 7 weeks
- ▶ The etiology is strongly linked with smoking
- ▶ TNM classification is identical with TNM for NSCLC in early stages
 - ! **BUT** early stages are rare!
 - Therefore we used a different classification
 - **Limited disease:** tumor limited to lungs and mediastinum with radiotherapy treatment possibility
 - **Extensive disease (70 %):** does not fulfill the conditions for limited disease

Small cell lung cancer - treatment

▶ Surgery

- only exceptions, really rare

▶ Chemotherapy

- platinum - based chemotherapy + etoposide

▶ Radiotherapy

- for limited disease
- palliative radiotherapy for symptomatic metastases (bones, brain)
- more than 50 % patients have brain metastases
 - prophylactic cranial radiotherapy

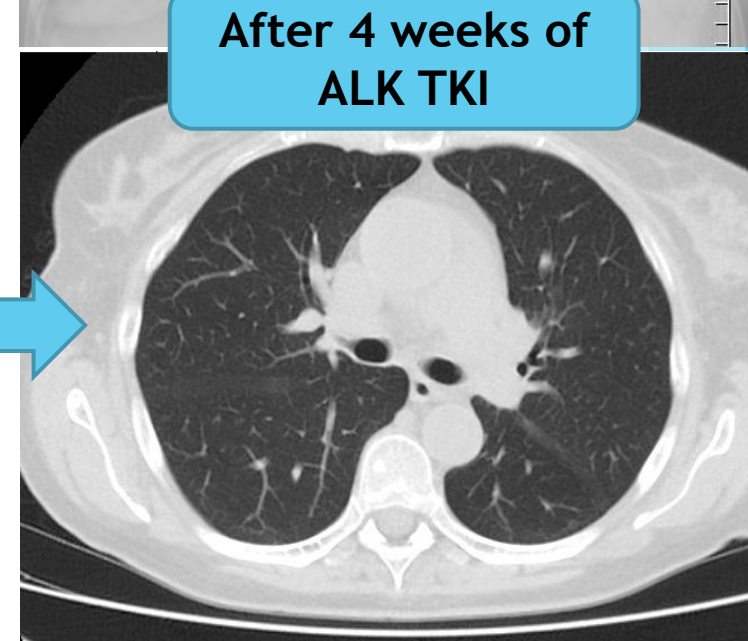
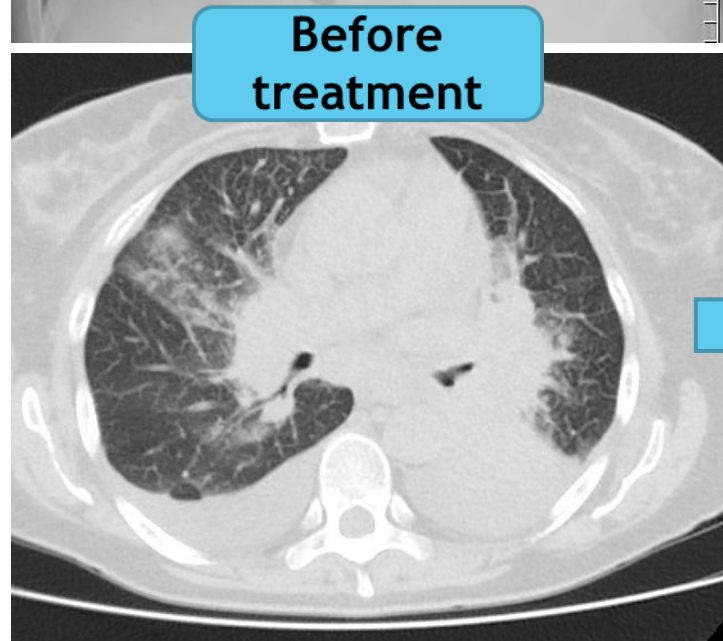
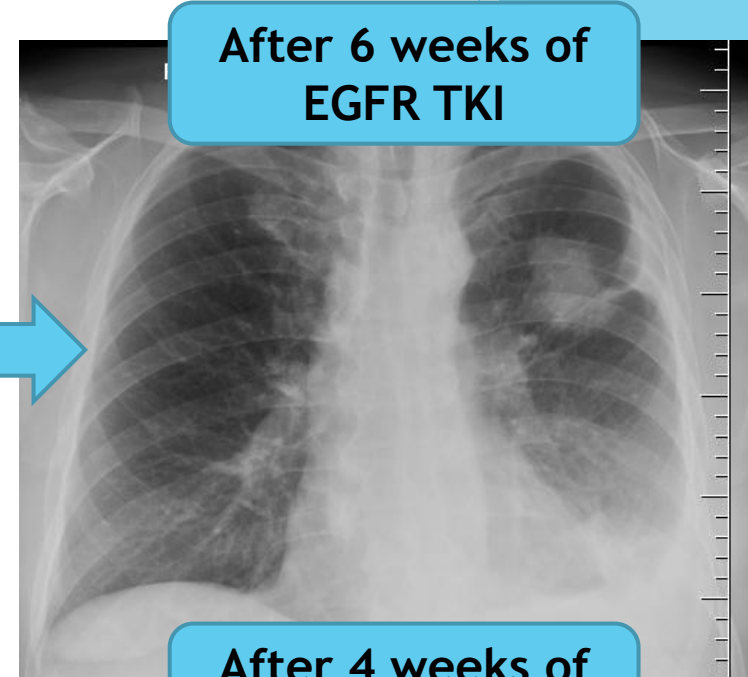
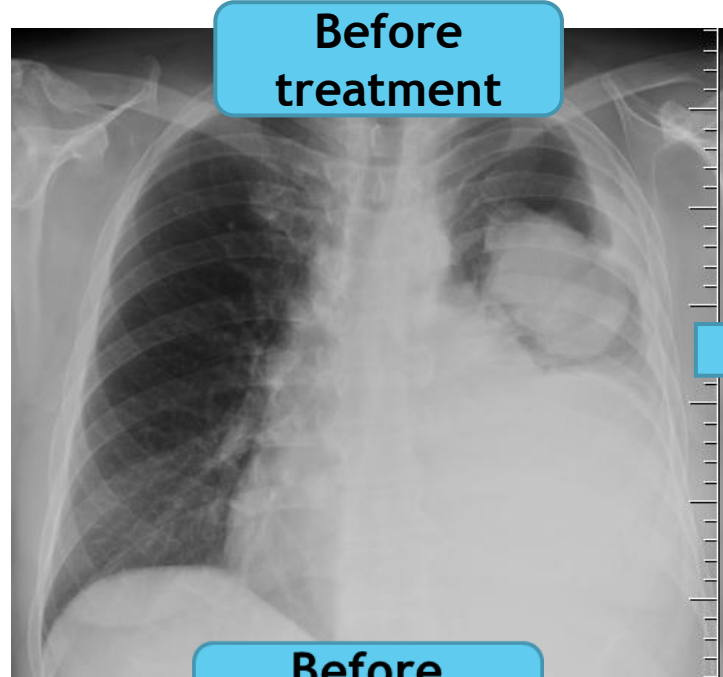
▶ Immunotherapy

- only within studies

Miraculous improvement with target therapy

BUT!!!

- not always is our treatment this effective
- majority of patients are not fit enough to start treatment
- only 50 % of patients will start oncological treatment



Take home message

- ▶ Highly heterogenous disease with various biological characteristics
- ▶ Efforts for early diagnosis
 - KEEP THAT IN MIND in differential diagnosis!
- ▶ Reduction of risk factors - mainly smoking!
- ▶ Introduction of screening programme for smokers?

- ▶ **There are new therapeutic aims (EGFR, ALK, ROS-1, PD-1)**
 - fundamentally changed therapeutic results and patient's quality of life
 - in every NSCLC (mainly adenocarcinoma) we should automatically investigate EGFR, ROS1, ALK, PDL-1

- ▶ **Challenges**
 - To overcome resistance to target therapy
 - New therapeutic targets (RET, MET and others)
 - Search for predictive markers for immunotherapy

**Thank you for your
attention!**

