Diagnosis and treatment of cancer in the 21st century

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European Commission

Content of the lesson

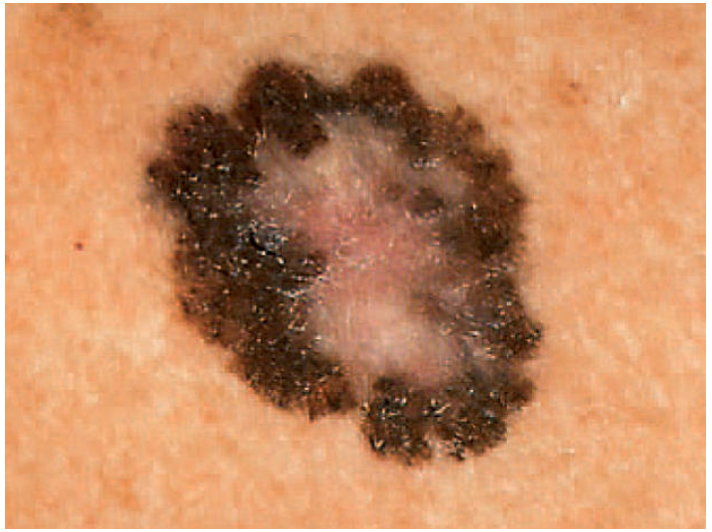
- Introduction
- Diagnosis of cancer
- Treatment of cancer

Introduction

- The methods to diagnose cancer have evolved over time
- From a diagnosis with clinical methods only (clinical observation, autopsy), followed by a pathological diagnosis, we are now in the era of DNA-analysis of the tumour: molecular diagnosis

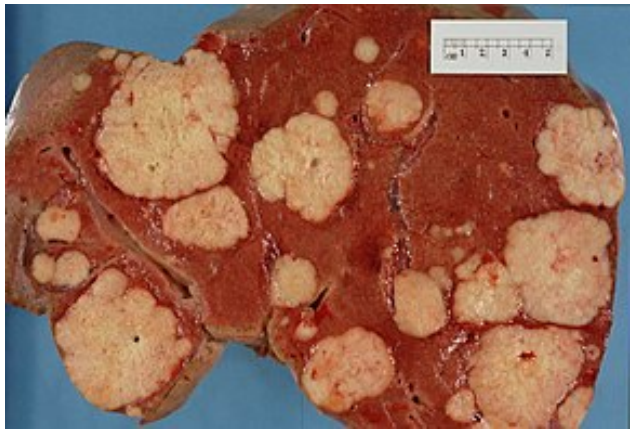
Rembrandt van Rijn, 1632:
the anatomic lesson of Dr. Nicolaes Tulp

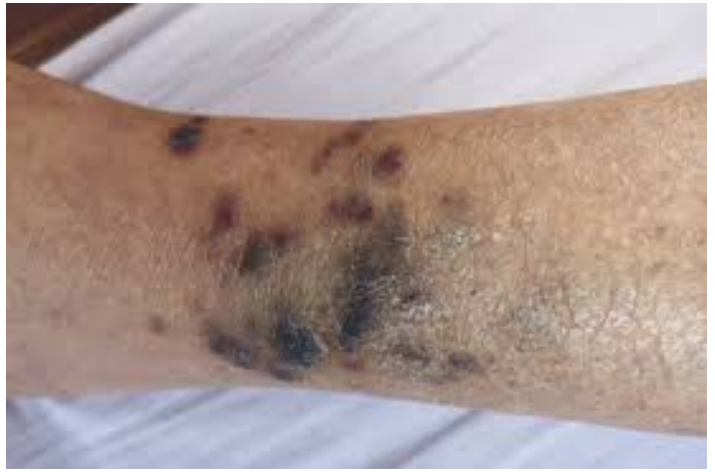
Clinical diagnosis (basis of diagnosis = 1/2)



melanoma

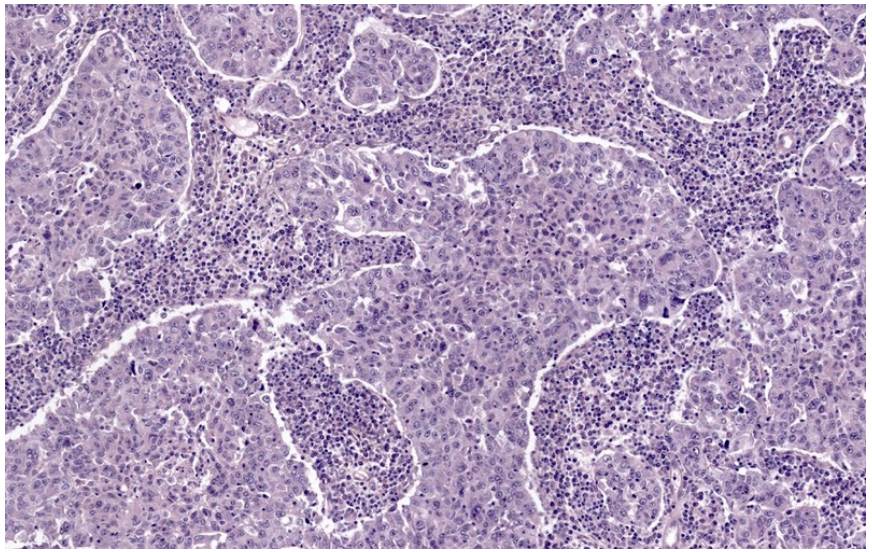
metastatic cancer



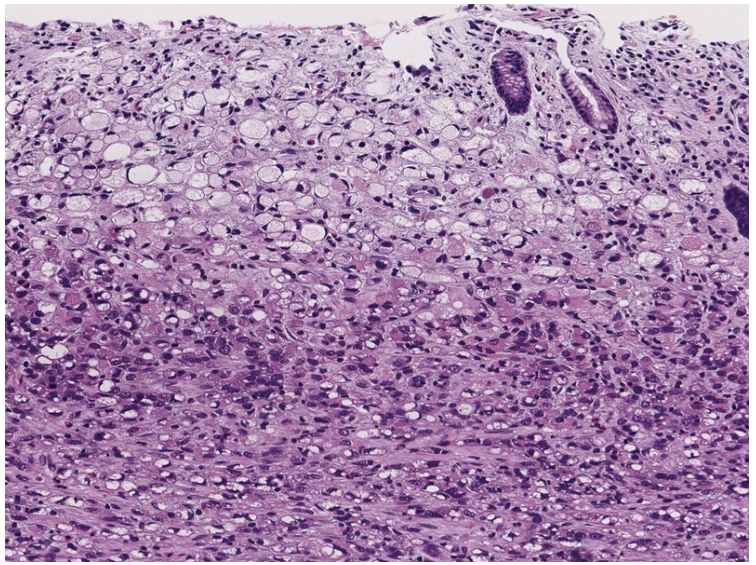


Kaposi sarcoma

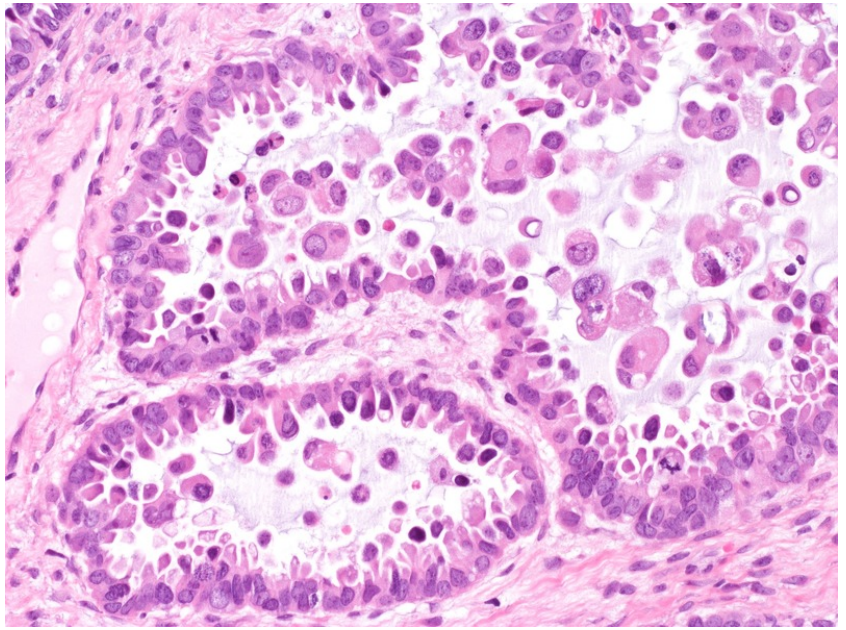
Pathological diagnosis (basis of diagnosis=5/6/7)



Breast carcinoma NST



Gastric cancer



Clear cell carcinoma
of the ovary

Molecular diagnosis (basis of diagnosis=??)

- In all cancers changes in the DNA of the cancer cells have occurred
- The type of these changes may be different for tumours originating from the same organ, while tumours in different organs may have the same changes
- As these changes may be relevant for targeted therapies it is essential to detect all relevant changes in the DNA of cancer cells
- For detection these changes there are different techniques available
- A molecular diagnosis is especially relevant for patients with cancer that cannot be cured by surgery

New rules for the basis of diagnosis

- As the methods for the diagnosis of cancer have changed, the basis of diagnosis as we have registered in the past in cancer registries is now (partly) outdated
- New rules have been defined by a working group of the ENCR
- As soon as the rules have been officially approved a webinar will be organised to explain the new rules

Diagnosis of cancer detection of molecular changes

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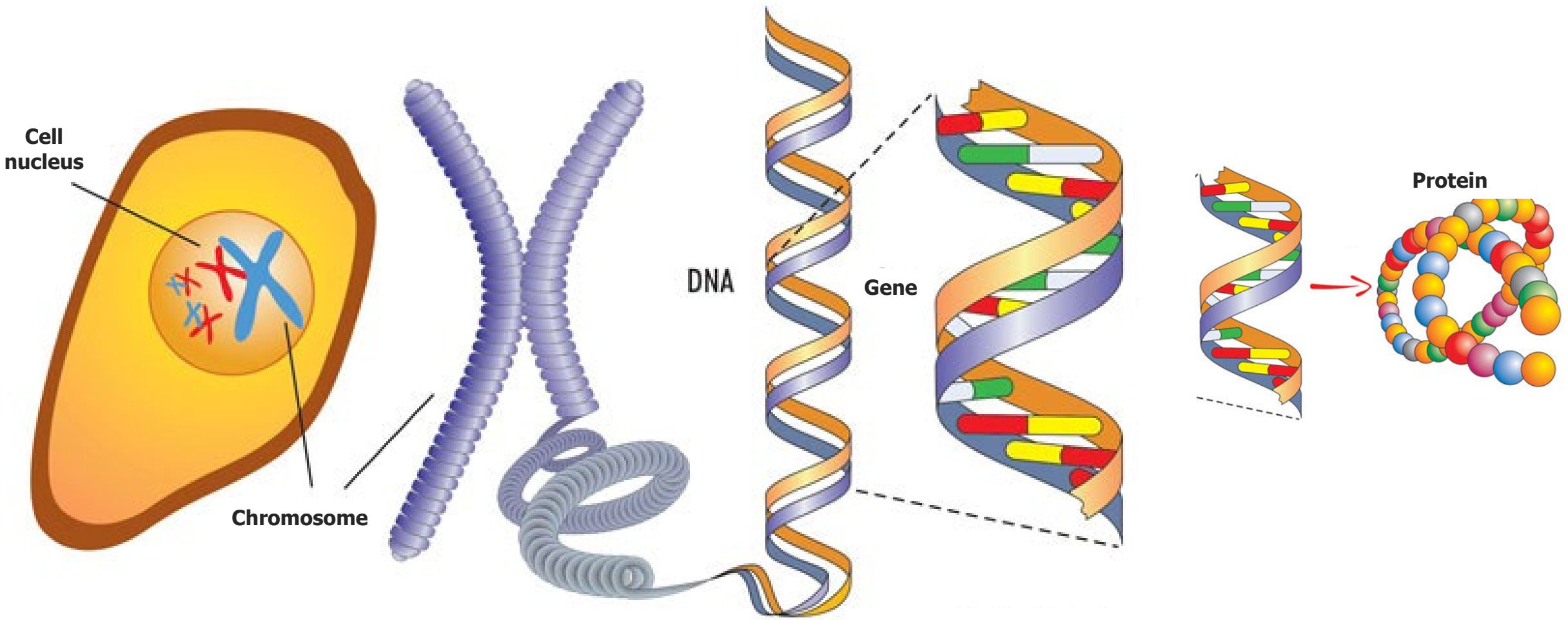
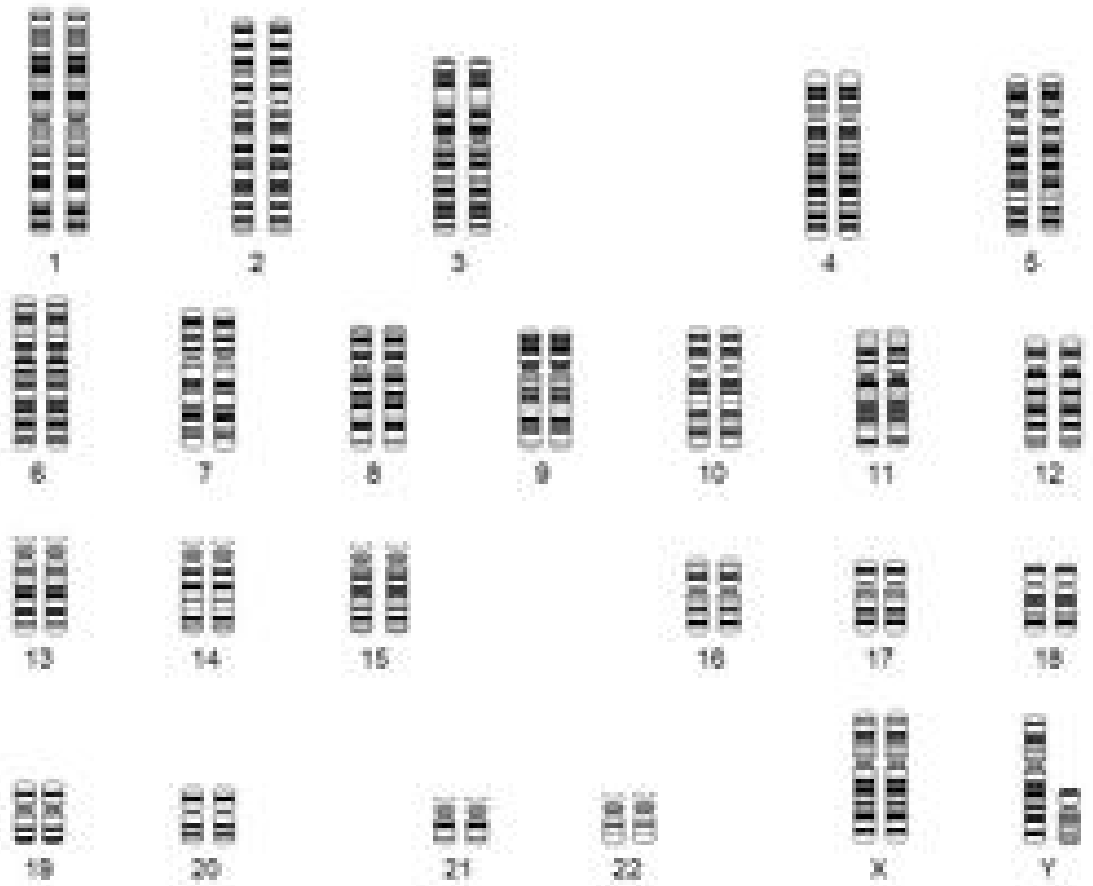
DNA



Molecular diagnosis

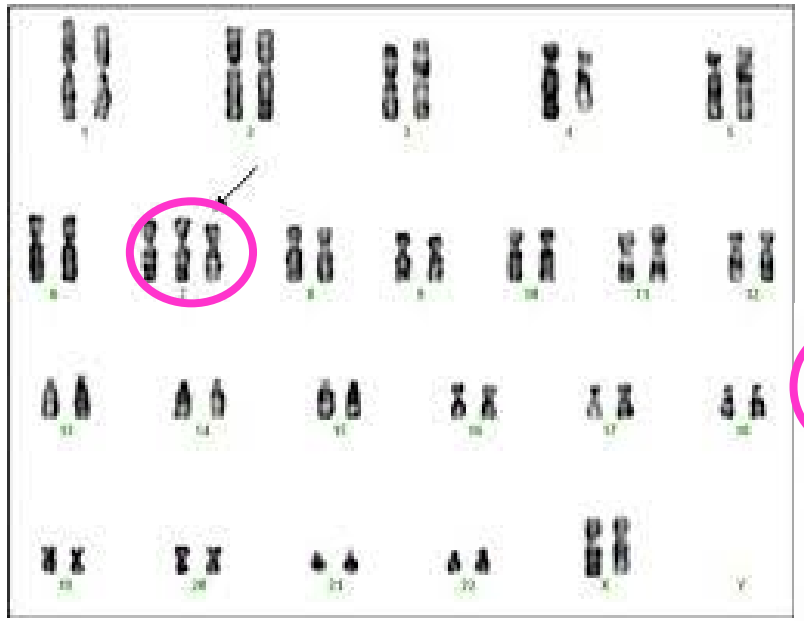
- Make a 'photo' of the chromosomes → karyotyping
- Search for the presence of certain proteins → immunophenotyping, immunohistochemistry
- Search for changes in the DNA-strings → FISH, sequencing

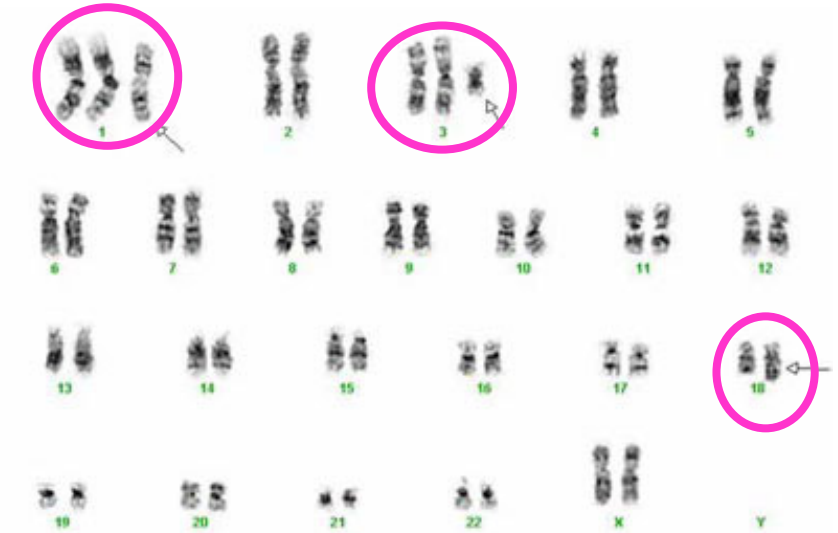
Karyotyping



- Photo of the chromosomes
- Each (normal) cell has 46 chromosomes
- In cancer cells a (part of a) chromosome can be missing, duplicated or displaced

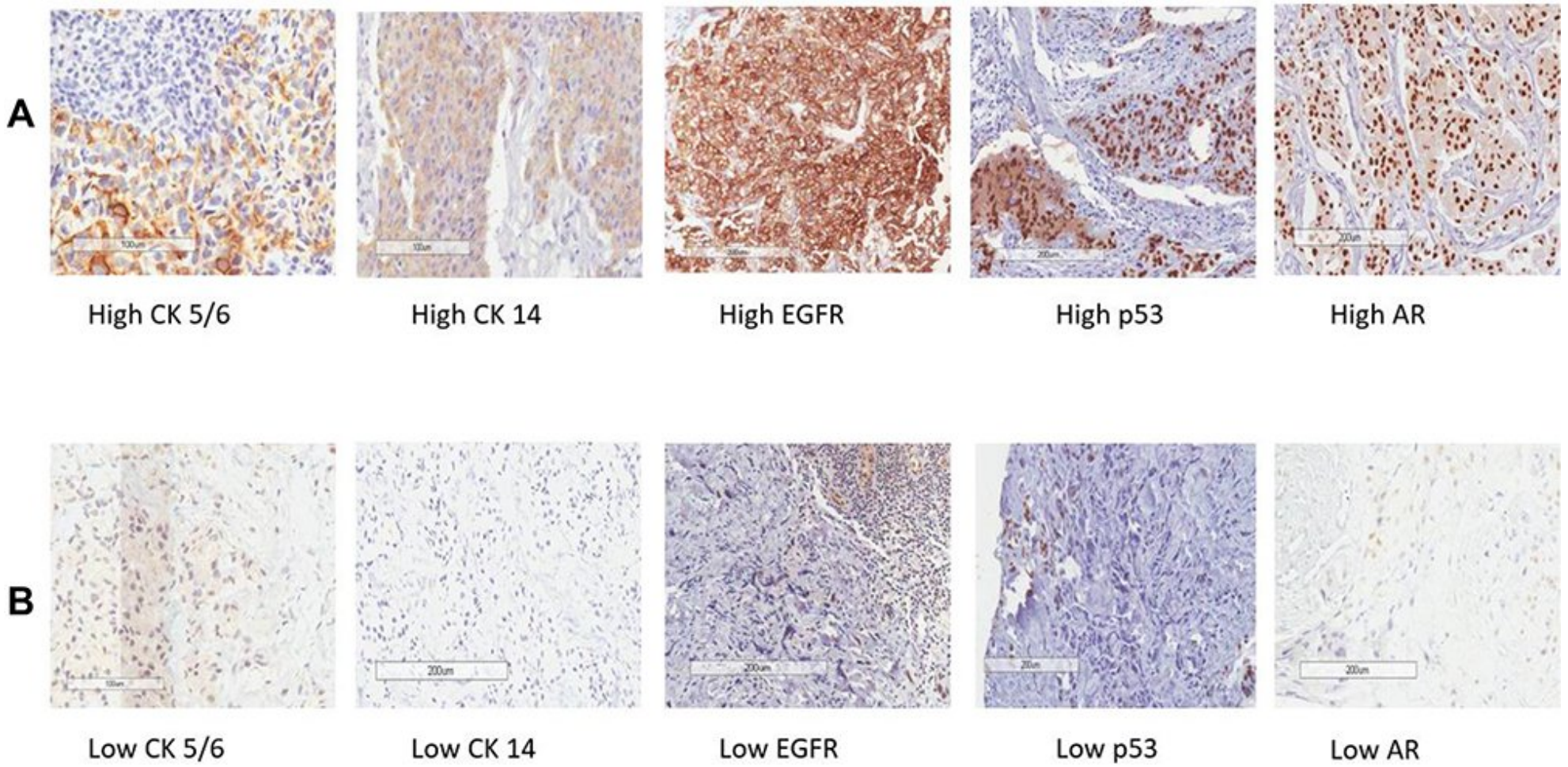
Karyotyping: some examples





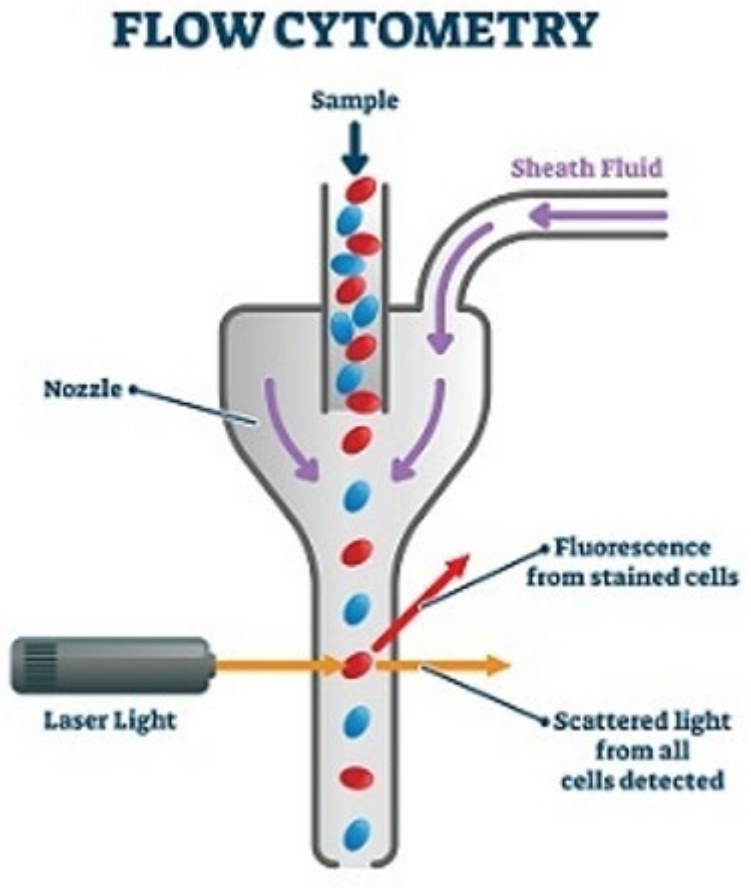
ISCN: 48,XX,+der(1)t(1;1)(q10;q21),+ider(3)(q10)del(3)(q21q29),der(18)t(9;18)(p22;q23)

Immunohistochemistry (for tissues)



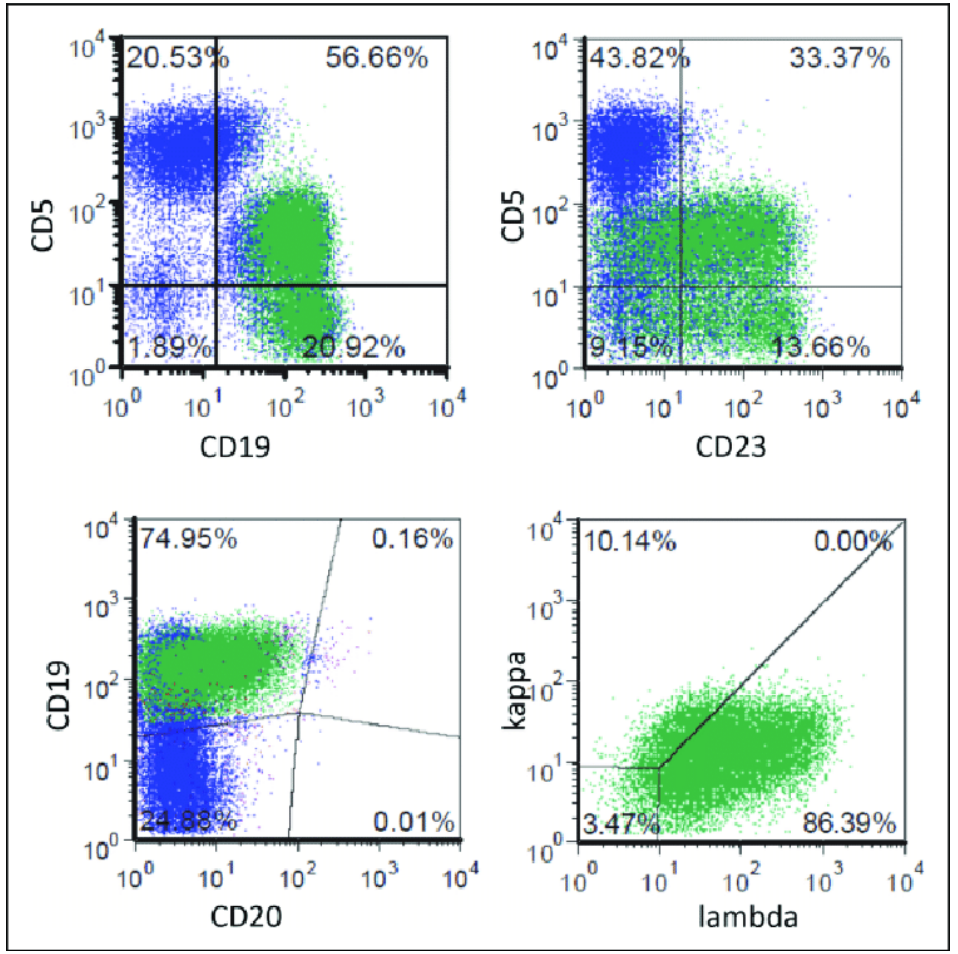
Flow cytometry (for cells)

- Flow cytometry is an instrument measuring multiple physical characteristics of a single cell such as size and granularity as the cell flows in suspension through a measuring device
- Its working depends on the light scattering features of the cells under investigation, which may be derived from dyes or monoclonal antibodies targeting either extracellular molecules located on the surface or intracellular molecules inside the cell
- This approach makes flow cytometry a powerful tool for detailed analysis of complex populations in a short period of time.



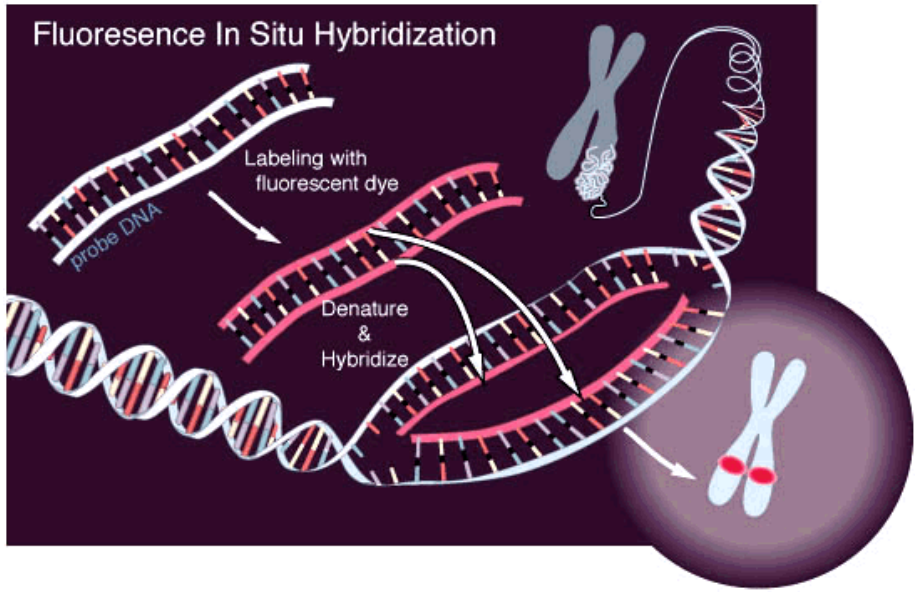
Flow cytometry

- By combining positivity or negativity for different proteins in the cell membrane different cell populations can be discriminated, including malignant cell clones



FISH: Fluorescence *in situ* hybridisation (FISH)

- A fragment of RNA ('probe') is labelled with a fluorescent dye
- The probe binds to specific parts of the DNA (a gene or a larger part of the DNA)
- If the probe binds to a gene or part of DNA you see a fluorescent dot



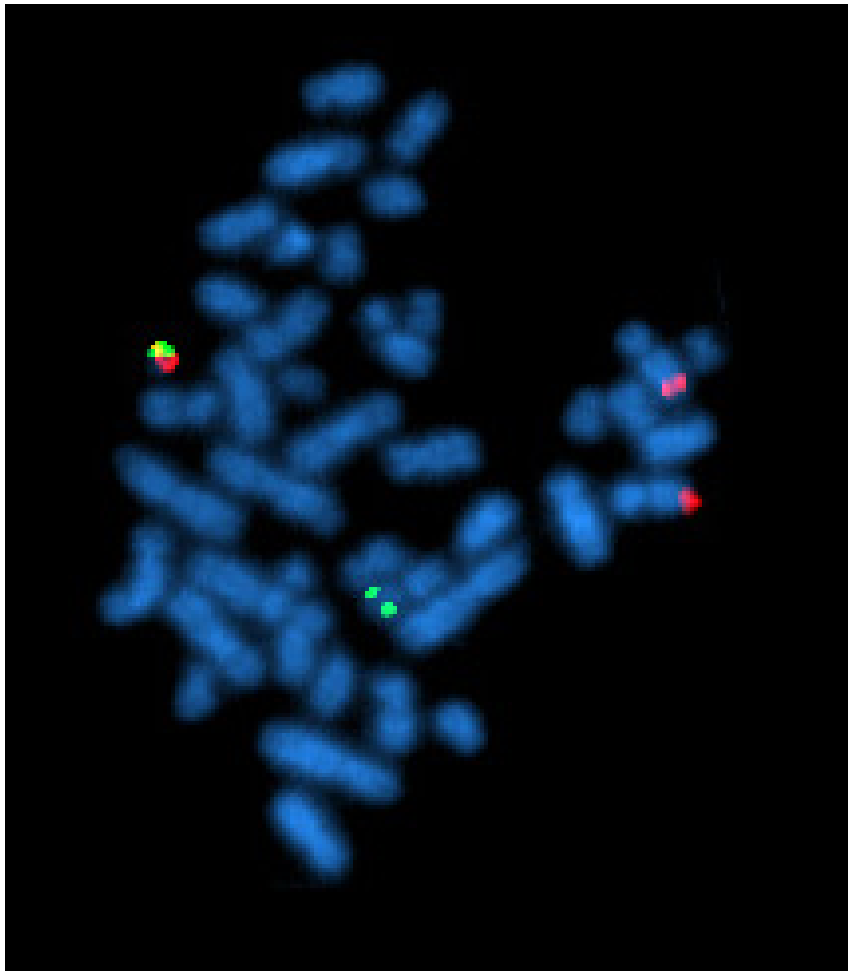
FISH: example

In CML there is a translocation of chromosomes 9 and 22 = t(9;22)

Chromosome 9 is labelled red and chromosome 22 green.

The normal situation is that you see 2 pairs of dots of the same colour (4 dots in total of each colour).

If there is a combination red/green, the translocation is present.



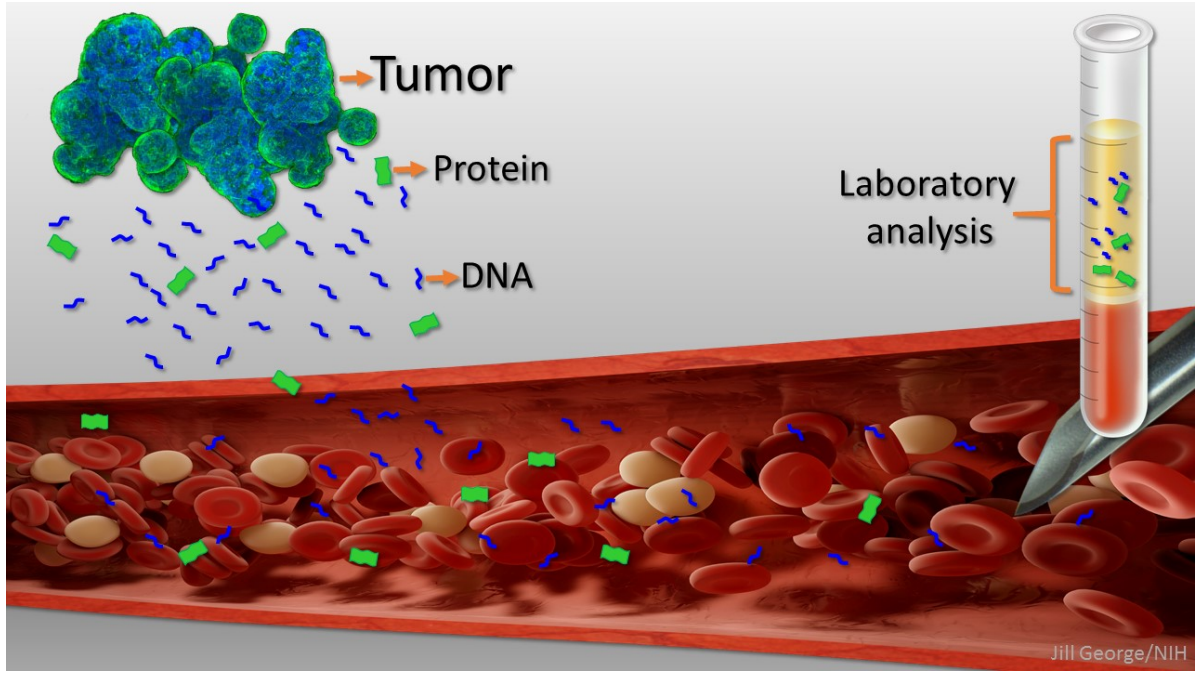
Sequencing

Sequencing is the process of determining the nucleic acid sequence – the order of the four bases (adenine, guanine, cytosine and thymine) in the DNA (of cancer cells). There are different methods in use to do this:

- Targeted sequencing / genpanel PCR (several genes)
- Next generation sequencing (NGS; dozens of genes)
- Whole genome sequencing (WGS; hundreds of genes)

Liquid biopsy

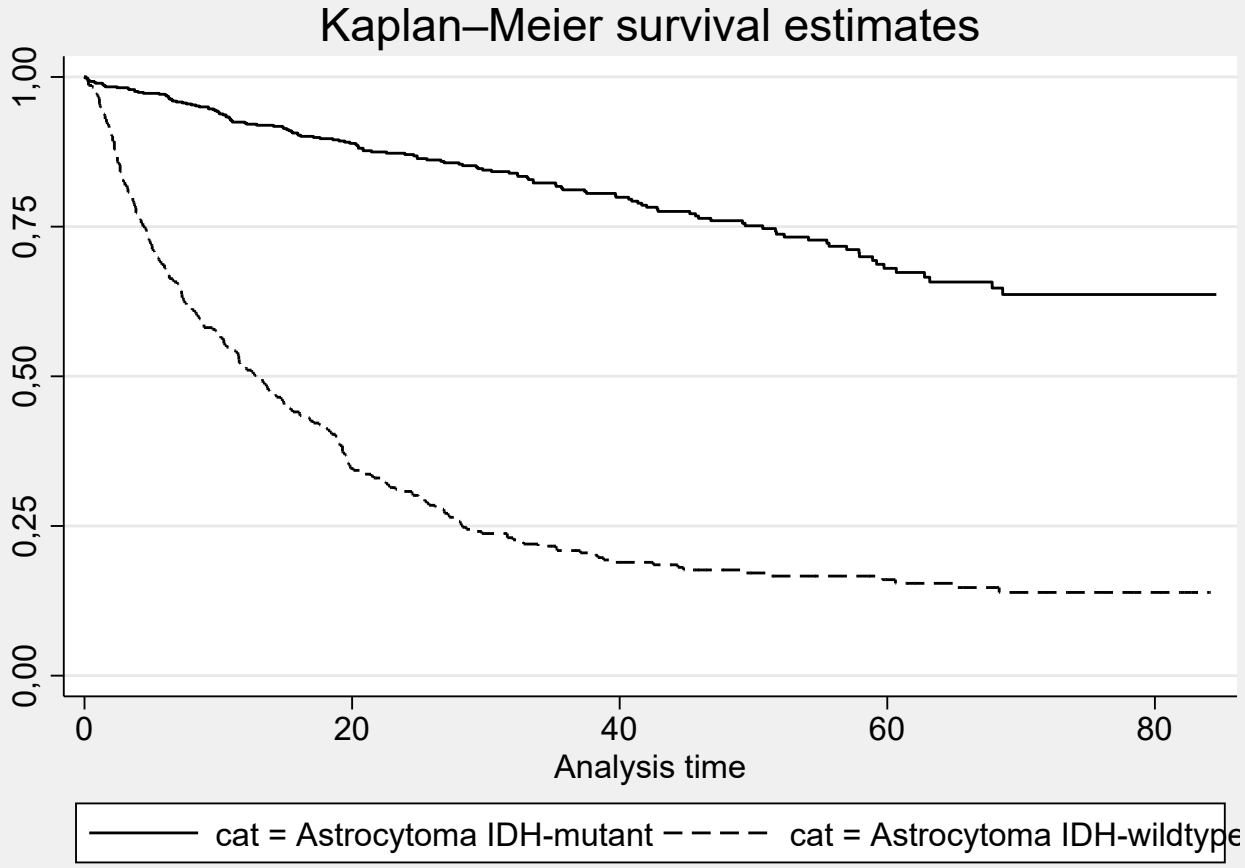
- In case of metastatic disease circulating tumour cells can be detected in blood or other fluids
- Circulating tumour DNA (not in cells) can also be detected with sequencing techniques
- Liquid biopsies are mostly performed on peripheral blood, but other fluids are possible (liquor)
- Already used for the diagnosis of NSCLC (with NGS)
- Might be used for screening purposes in future

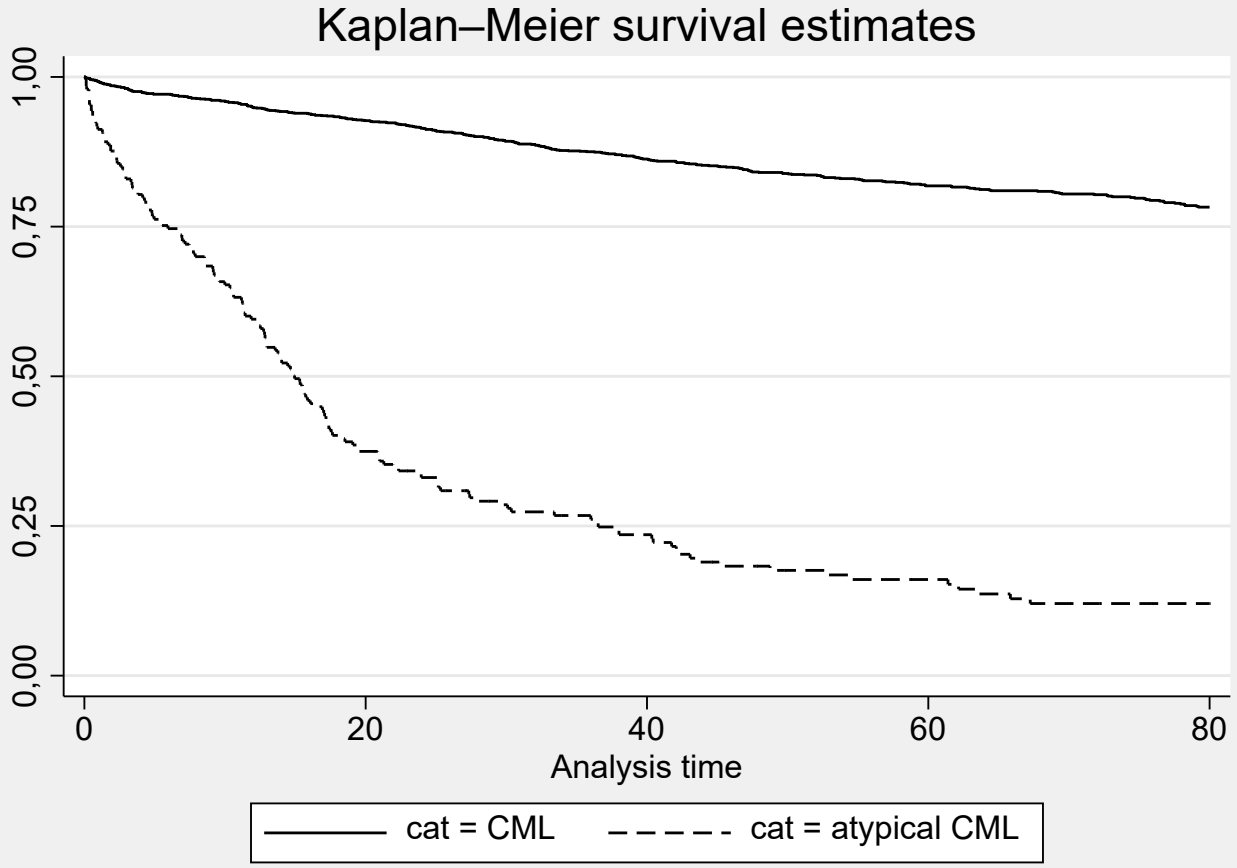


Cancer entities with a molecular diagnosis

Glioblastoma	IDH-wildtype M9440/3	IDH-mutant M9445/3
Medulloblastoma	SHH-activated and TP53-wildtype M9471/3 WNT-activated M9475/3	SHH-activated and TP53-mutant M9476/3 non-WNT/non-SHH M9477/3
Diffuse midline glioma	H3 K27M-mutant M9385/3	NOS M9380/3
Ependymoma	RELA fusion-positive M9396/3	NOS M9391/3
Chronic myelogenous leukaemia	BCR/ABL positive M9875/3	BCR/ABL negative M9876/3
Acute myeloid leukemia	DEK-NUP214+ M9865/3 PML/RAR-alpha+ M9866/3 RPN1-EVI1+ M9869/3 CBF-beta/MYH11+ M9871/3	with mutated NPM1 M9877/3 with biallelic mutation of CEBPA M9878/3 with mutated RUNX1 M9879/3 RBM15-MKL1+ M9911/3
B lymphoblastic leukemia/lymphoma	BCR-ABL1+ M9812/3 MLL rearranged M9813/3 TEL-AML1+ M9814/3 with hyperdiploidy M9815/3	with hypodiploidy M9816/3 IL3-IGH+ M9817/3 E2A-PBX1+ M9818/3 BCR-ABL1-like M9819/3

Some examples: survival by molecular category





Treatments

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Treatments

Chemotherapy

Radiotherapy

Chemotherapy

European Commission

Chemotherapy

- Chemotherapy is aimed at inhibition of growth of the tumour
- Traditional chemotherapy inhibits the division of cells
- Not only cancer cells are effected by traditional chemotherapy, but also normal dividing tissues, such as the skin, the epithelium of the gastro-intestinal tract and the bone marrow
- Targeted therapy aims to attack only cancers cells, but not normal cells by targeting at specific processes in cancer cells (more or less comparable to antibiotics that kill bacteria but not human cells)

Targeted therapies; different categories

- Protein kinase inhibitors (L01E), e.g. imatinib
- Monoclonal antibodies (L01F), e.g. rituximab
- Other antineoplastic agents (L01X)
  - Proteasome inhibitors (L01XG), e.g. bortezomib
  - Histone deacetylase inhibitors (L01XH), e.g. vorinostat
  - Hedgehog pathway inhibitors (L01XJ), e.g. vismodegib
  - PARP inhibitors (L01XK), e.g. olaparib
  - Other antineoplastic agents, e.g. venetoclax

Protein kinase inhibitors

- Protein kinases are enzymes that add a phosphate group to a protein
- The phosphate groups are added to amino acids, such as tyrosine (tyrosine kinase)
- Protein kinases regulate many cellular pathways, including acting as growth factor receptor on the surface of cells
- In cancer, protein kinases may be hyperactive due to a mutation or overexpression
- By inhibition of the protein kinases growth of the cancer can be slowed down

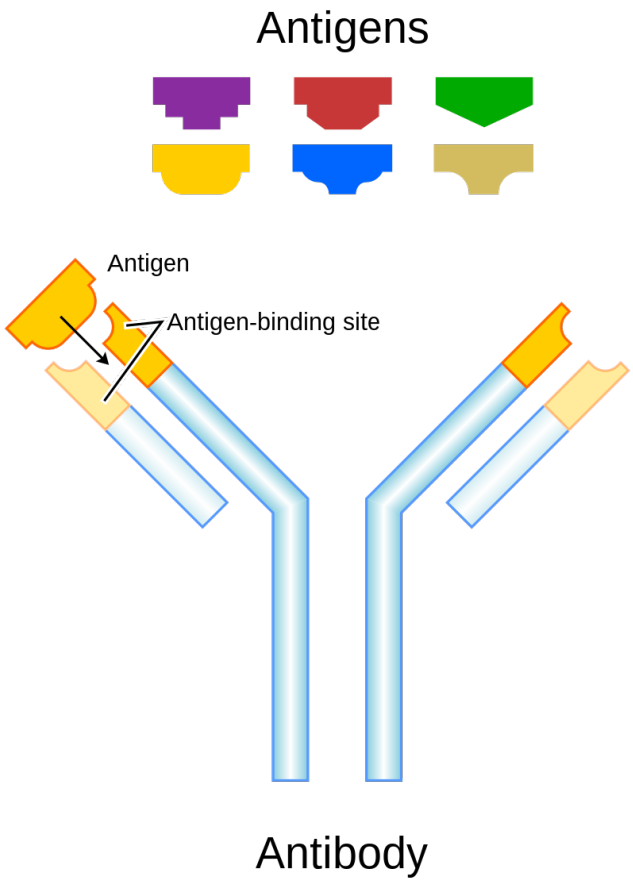
Protein kinase inhibitors

Examples of protein kinase inhibitors of are:

- Imatinib (CML, GIST)
- Sunitinib (renal cell carcinoma)
- Vemurafenib (melanoma)

Monoclonal antibody therapy

- A monoclonal antibody is an antibody made by cloning of a unique white blood cell, which means that all the antibodies are exactly the same
- In monoclonal antibody therapy, monoclonal antibodies are used that bind to certain (cancer) cells or proteins in order to stimulate the patient's immune system to attack those (cancer) cells
- Monoclonal antibody therapy is considered a form of immunotherapy because it is aimed at stimulating the immune system



Monoclonal antibody therapy

Examples are:

- Trastuzumab (Herceptin): HER2+ breast cancer
- Rituximab: CD20+ non-Hodgkin lymphoma (B-cell)
- Cetuximab: colorectal cancer
- Ipilimumab: melanoma
- Nivolumab: non-small cell lung cancer

As also other cancers may have the same molecular aberration, monoclonal antibodies may also used for treating other cancers, such as trastuzumab in HER2+ gastric cancer

Monoclonal antibody therapy

Monoclonal antibody therapy can be used as a monotherapy, but also in combinations, such as

- R(=rituximab)-CHOP for diffuse large B-cell lymphoma
- Trastuzumab+pembrolizumab for breast cancer

Other neoplastic agents

- Proteasome inhibitors are used for the treatment of multiple myeloma
- PARP inhibitors are used for the treatment of hereditary cancers, such as BRCA1/BRCA2+ ovarian cancer
- Hedgehog pathway inhibitors are used for inhibition of aberrant Hedgehog signalling in tumour progression and cancer stem cell maintenance
- Histone deacetylase inhibitors induce cell cycle arrest, differentiation and apoptosis

What is the effect of targeted therapies in clinical practice?

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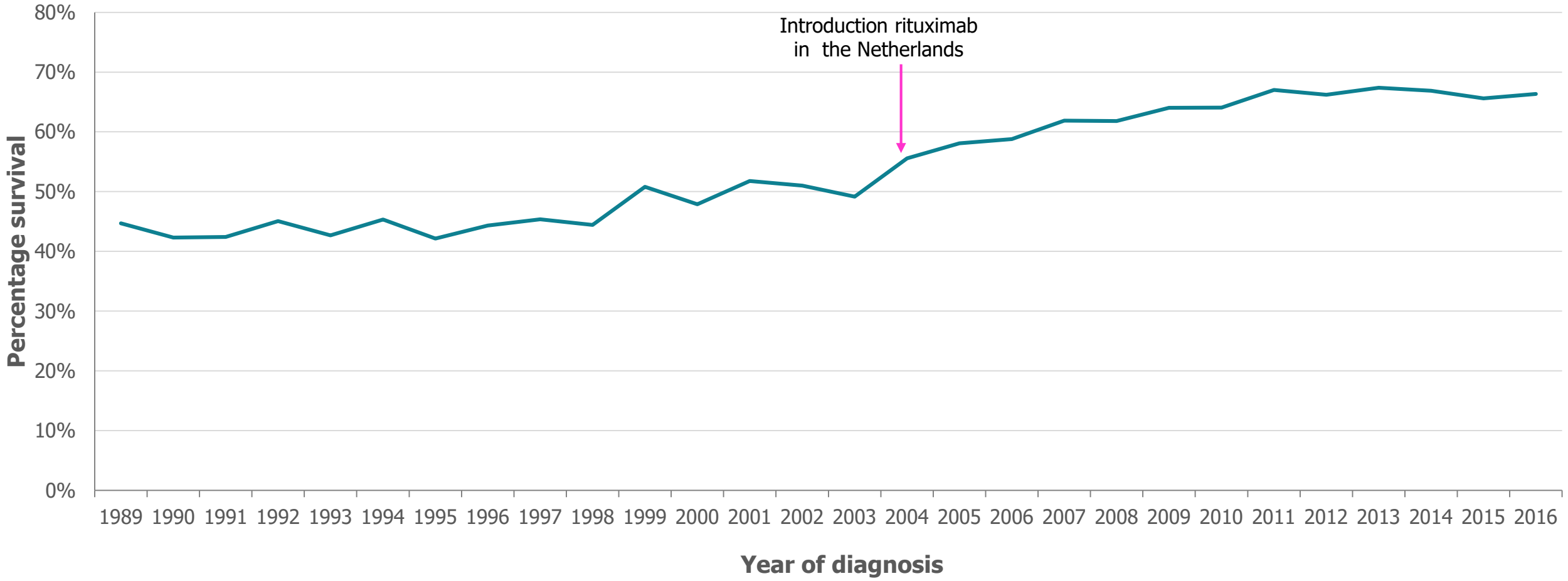
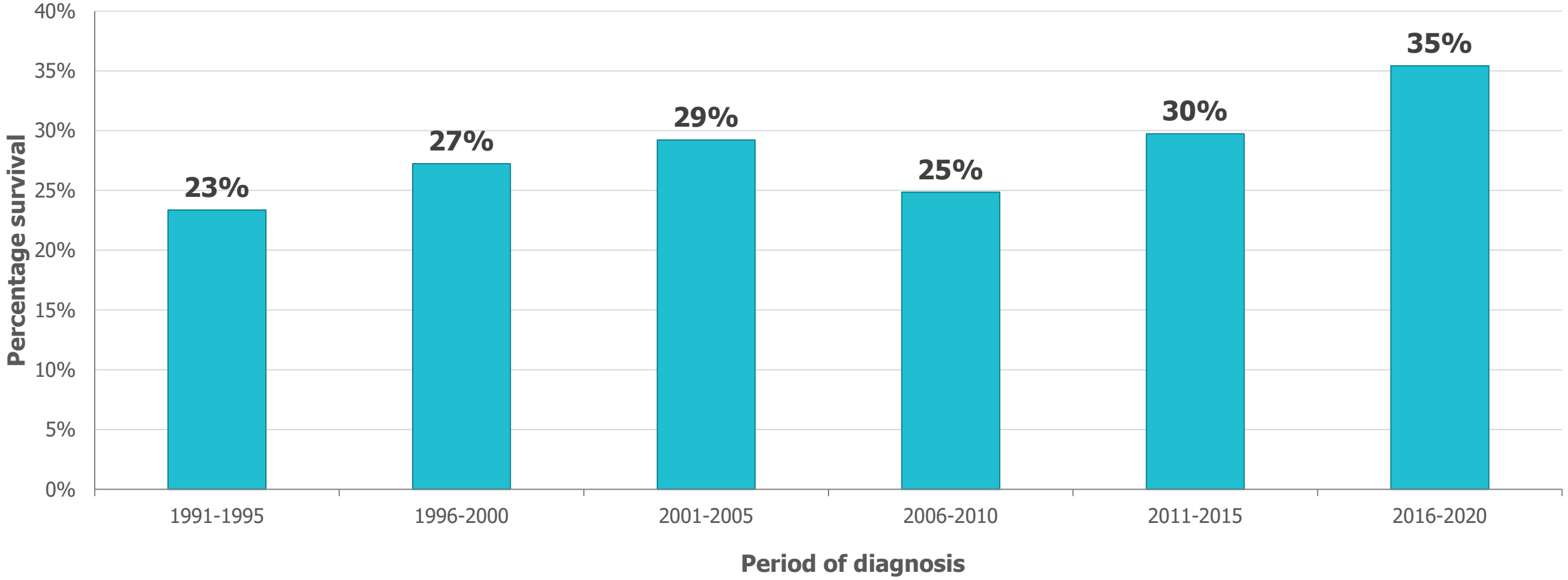
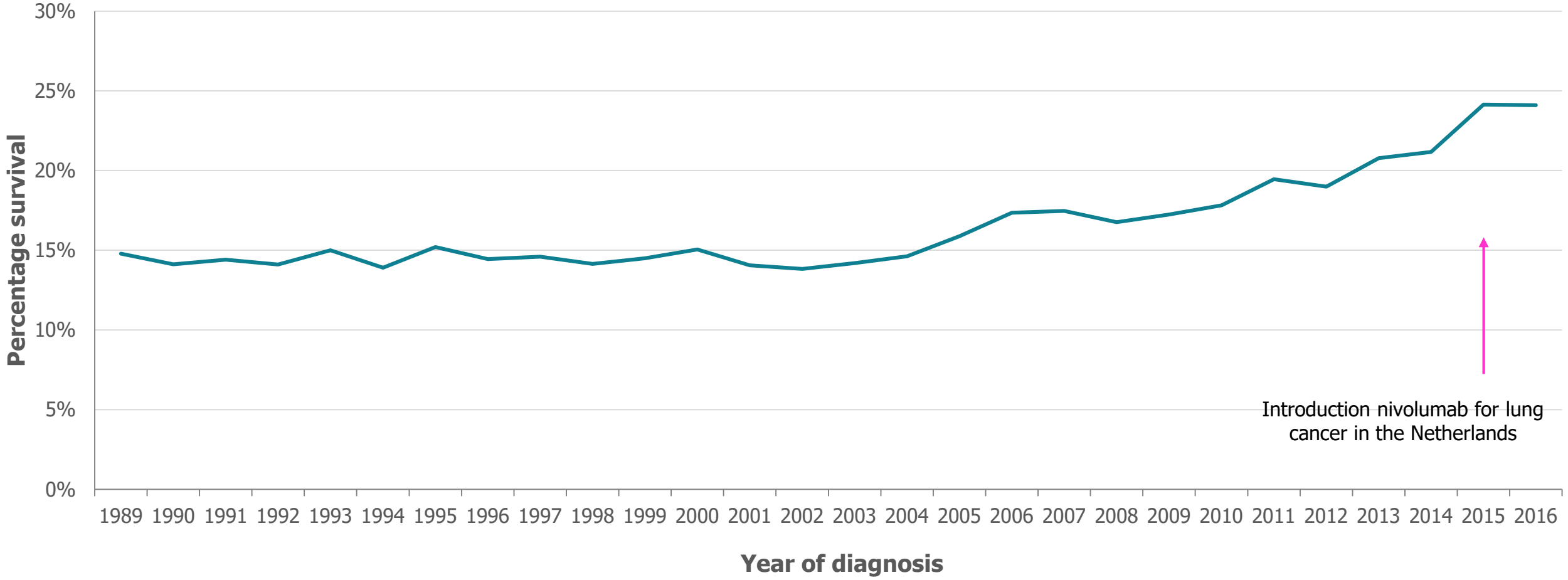
5-year relative survival of DLBCL in the Netherlands



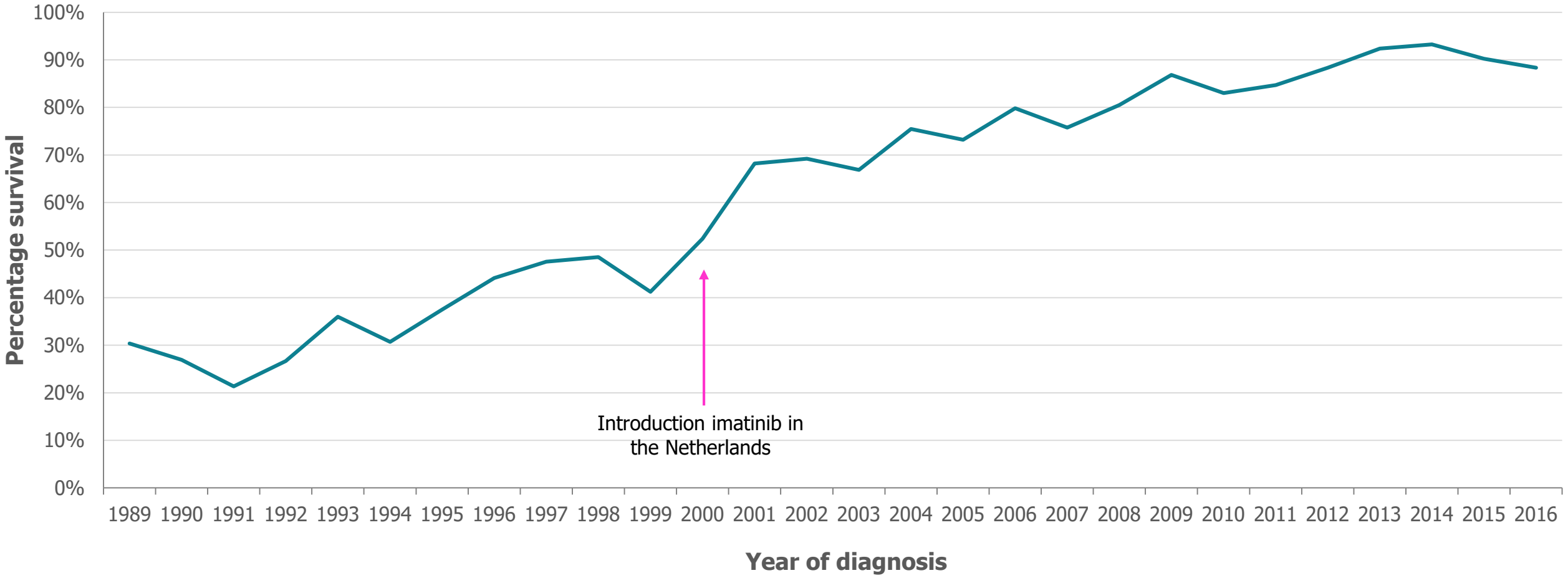
5-year relative survival of metastatic melanoma in the Netherlands



5-year relative survival of NSCLC in the Netherlands



5-year relative survival of CML in the Netherlands



Effect of targeted therapies on survival

- Targeted therapies increase survival in selected patients
- Its effect is dependent on the presence/absence of specific genetic abnormalities
- After some time many cancers develop resistance against the targeted therapy (such as bacteria may develop resistance against antibiotics)
- For many abnormalities there is not yet a targeted therapy
- In many cancers no specific genetic abnormality has been found

Recent developments in radiotherapy

European Commission

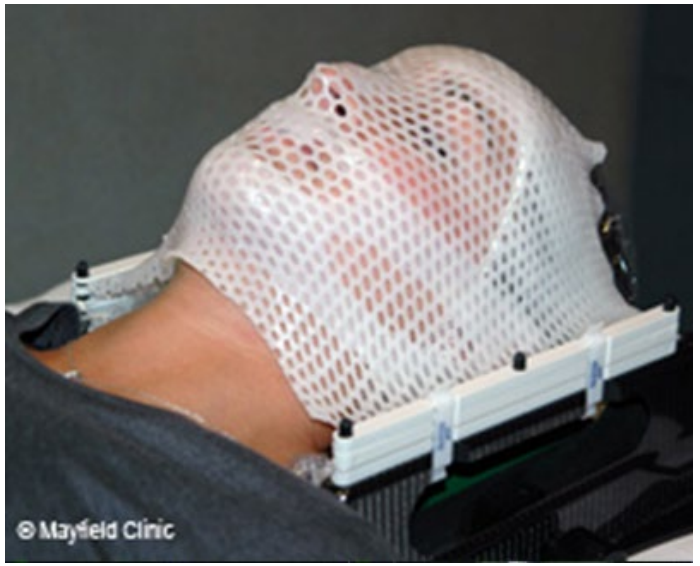
Developments in radiotherapy

As with external beam radiotherapy also normal tissues may be damaged new techniques were developed to minimize the damage to normal tissues

- Stereotactic radiotherapy
- Proton therapy

Stereotactic radiotherapy

- Stereotactic external Beam RadioTherapy (SBRT) is a technique to focus the radiotherapy as much as possible on the tumour
- By using CT- and MRI-scans a three- or four-dimensional picture is made of the tumour area
- Higher dose to the tumour
- Is used for brain tumours and lung cancer (including metastases to the brain and lung)
- Immobilization of the patient is necessary



Proton therapy

- In comparison to external beam radiotherapy the dose of the protons is deposited over a narrow range with a minimal dose to the healthy surrounding tissues
- Higher costs
- The oldest facility in Europe (since 1984) is in Switzerland
- Most countries now have their own facilities
- Mainly for children and brain tumours (if SBRT is not possible)

Questions?

Please be aware that any question on coding can be submit at the website of the ENCR:
https://www.encr.eu/ask-an-expert

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