Systemic therapy

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European Commission

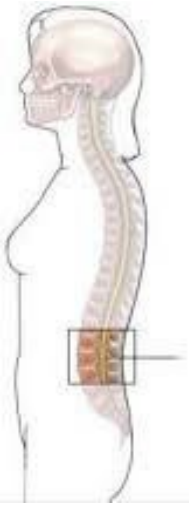
Systemic therapy

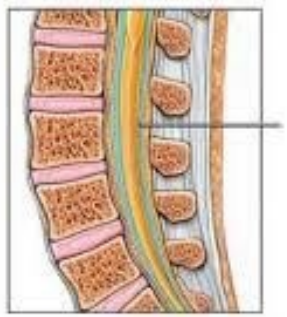
- Systemic therapy is aimed at treating cancer that is disseminated throughout the body (metastatic disease and most haematological malignancies)
- However, systemic therapy can also be used for localized tumours
  - Reduction of tumour load before an operation (neo-adjuvant systemic therapy)
  - To 'treat' potential metastatic disease even when this is not visible at imaging (adjuvant systemic therapy → reduction of the risk of recurrent disease)
  - In cases that local treatment is not possible or is contraindicated

Systemic therapy

- Systemic therapy reaches all tissues via the blood, either by direct infusion of the drug(s) into a blood vessel or indirectly via the gastrointestinal tract for drugs that are administered orally

- Because of the blood-brain barrier systemic therapy for the CNS has to be administered intrathecally



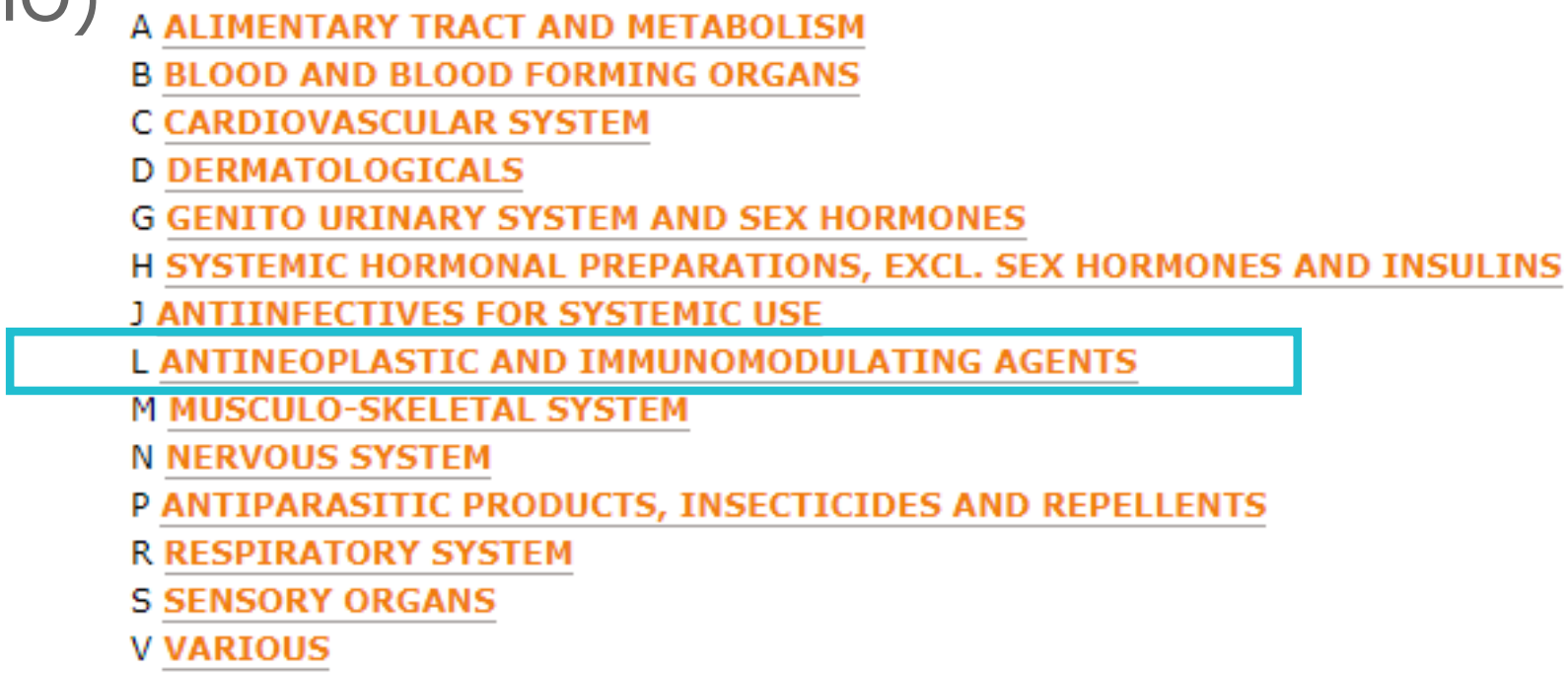


Types of systemic therapy

- Chemotherapy
  - 'traditional' chemotherapy
  - 'targeted' therapy
- Endocrine (hormonal) therapy
- Immunotherapy

ATC codes

- Each drug has an 'Anatomical Therapeutic Chemical' (ATC) code; The classification system is maintained by the World Health Organization (WHO)



See https://www.whocc.no/atc_ddd_index/

ATC codes: 4 subcategories in category L

L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS

L01 ANTINEOPLASTIC AGENTS

L02 ENDOCRINE THERAPY

L03 IMMUNOSTIMULANTS

L04 IMMUNOSUPPRESSANTS

L01 Antineoplastic agents

L01A ALKYLATING AGENTS
L01B ANTIMETABOLITES
L01C PLANT ALKALOIDS AND OTHER NATURAL PRODUCTS
L01D CYTOTOXIC ANTIBIOTICS AND RELATED SUBSTANCES
L01E PROTEIN KINASE INHIBITORS
L01F MONOCLONAL ANTIBODIES AND ANTIBODY DRUG CONJUGATES
L01X OTHER ANTINEOPLASTIC AGENTS

Chemotherapy

- Chemotherapy is aimed at inhibition of growth of the tumour
- Traditional chemotherapy (L01A-L01D) inhibits the division of cells, for example by inhibiting DNA replication
- 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 → adverse effects
- Targeted therapy (L01E-L01X) 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) → less adverse effects

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

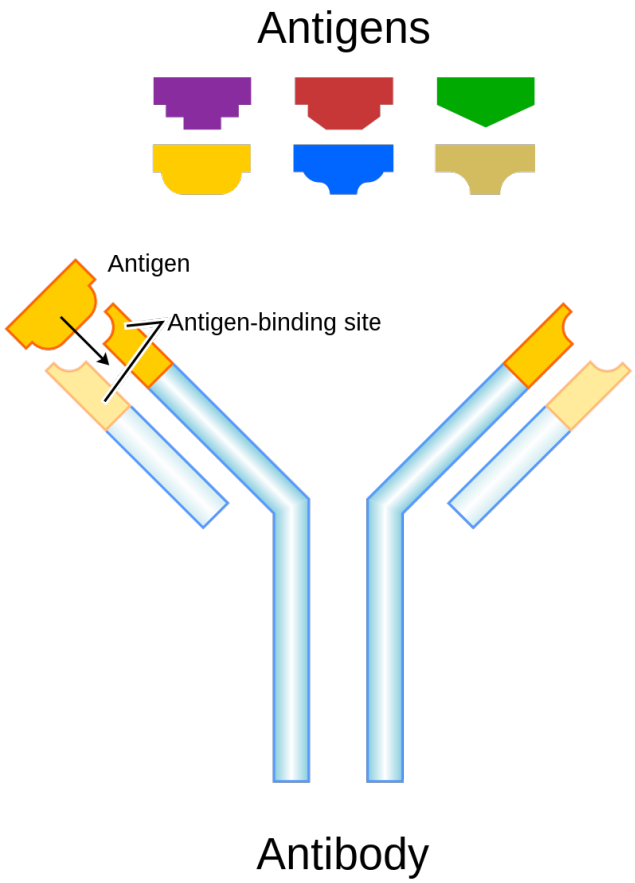
Protein kinase inhibitors

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)
- Durvalumab: PD-L1+ NSCLC
- 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 (e.g. bortezomib) 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

L02 Endocrine therapy

L02A HORMONES AND RELATED AGENTS

L02B HORMONE ANTAGONISTS AND RELATED AGENTS

- Includes hormones for the treatment of prostate cancer (buserelin, goserelin), as well as hormone antagonists for the treatment of breast cancer (tamoxifen, aromatase inhibitors) or prostate cancer (abiraterone, nilutamide, etc.)

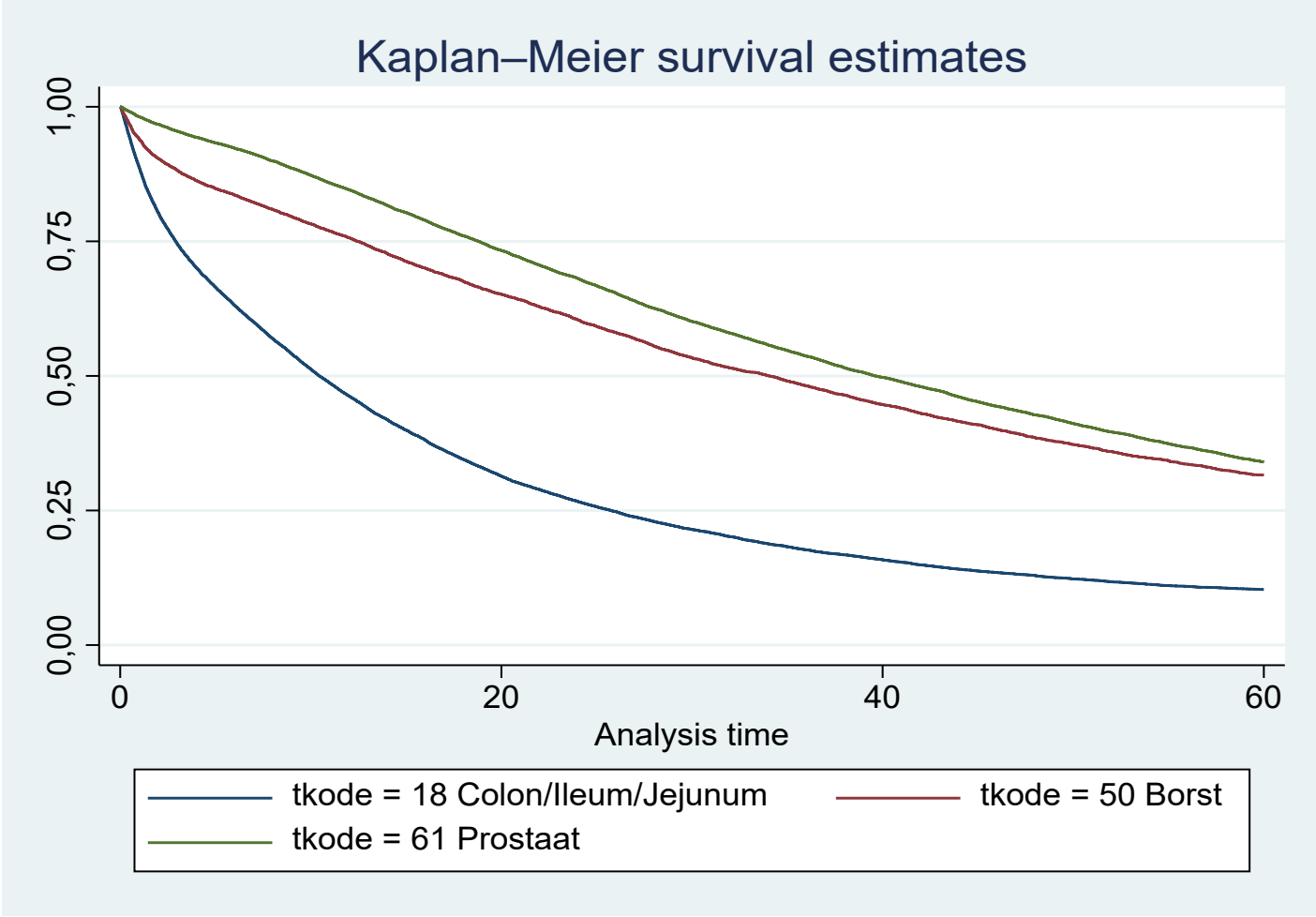
Hormone therapy in breast cancer

- Hormone receptor positive breast cancers (ER+/PR+)
- Hormones bind to the receptors and stimulate tumour growth
- By blocking this process, tumour growth is inhibited
  - Tamoxifen (L02BA01): blocks to the receptor
  - Aromatase inhibitors (L02BG): decrease the production of oestrogens
  - Ovariectomy: most oestrogens are produced in the ovaries thus ovariectomy also decreases the oestrogen production
- Mostly adjuvant (tamoxifen), but also neo-adjuvant, in elderly patients that cannot be operated and in metastatic disease (aromatase inhibitors)

Hormone therapy in prostate cancer

- Androgens ([dihydro]testosterone) stimulate tumour growth
- By blocking the action of androgens, tumour growth is inhibited
  - Orchiectomy: a major part of the androgens is produced in the testicles thus orchiectomy decreases the androgen production
  - LHRH agonists (L02AE): lower the amount of testosterone produced in the testicles ('chemical castration')
  - LHRH antagonists (L02B): work more quickly, also lower testosterone
- Mostly in metastatic disease, but also in localized disease if local treatment (surgery, radiotherapy) is not possible or does not have the preference

Survival of metastatic cancer



Hormone therapy in other cancers

- Ductal carcinoma of the salivary glands: goserelin, bicalutamide

- Endometrial carcinoma (endometrioid, serous): megestrol, medroxyprogesterone, tamoxifen

- (Serous) ovarian carcinoma: tamoxifen, aromatase inhibitors

L03 Immunostimulants

- L03AA: *colony stimulating factors* for MDS
- L03AB: *interferon* for myeloproliferative neoplasms (EV, ET, myelofibrosis)
- L03AX03: *BCG vaccine* for bladder cancer

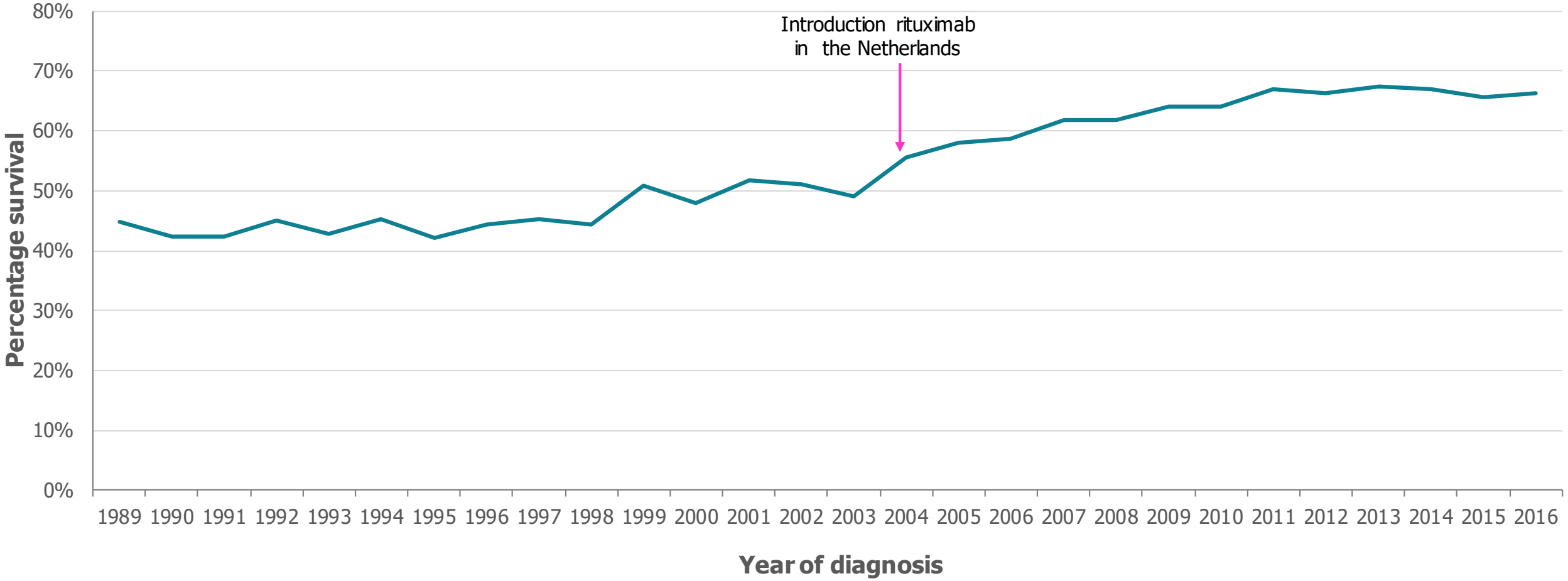
L04 Immunosuppressants

- L04AX02 thalidomide for multiple myeloma
- L04AX04 lenalidomide for multiple myeloma, MDS/AML and other haematological malignancies
- L04AX06 pomalidomide for multiple myeloma

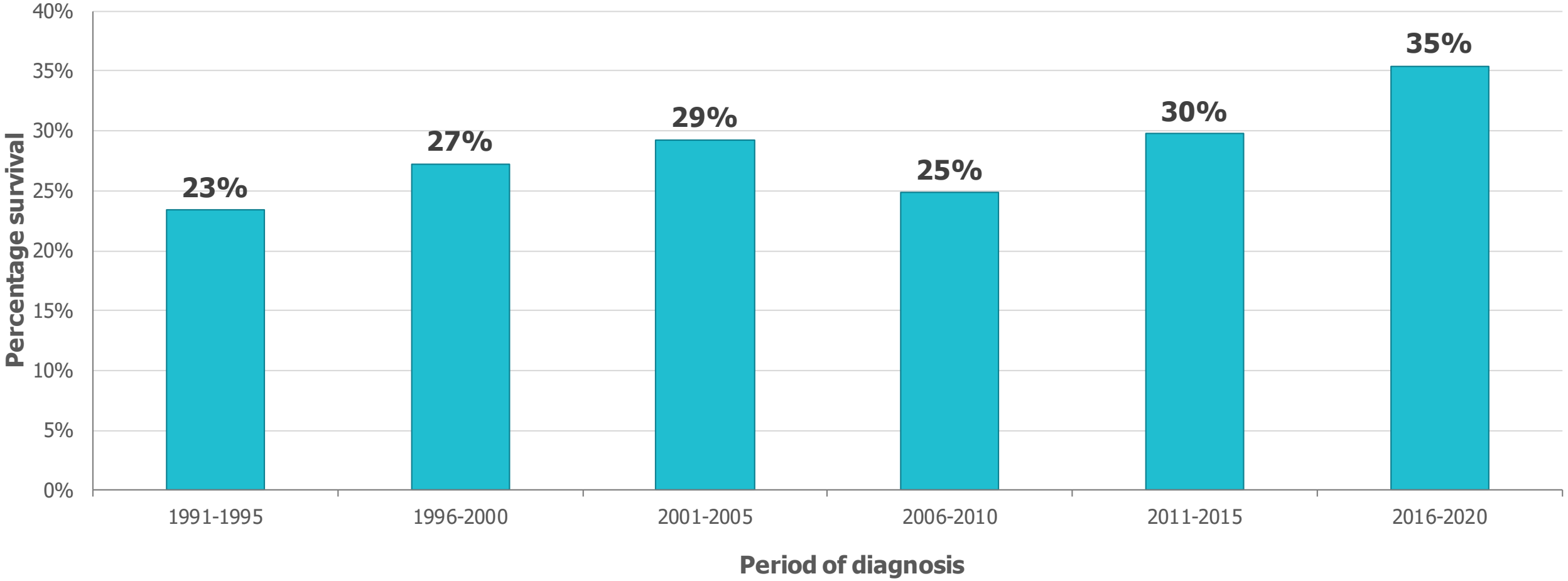
What is the effect of targeted therapies in clinical practice?

European Commission

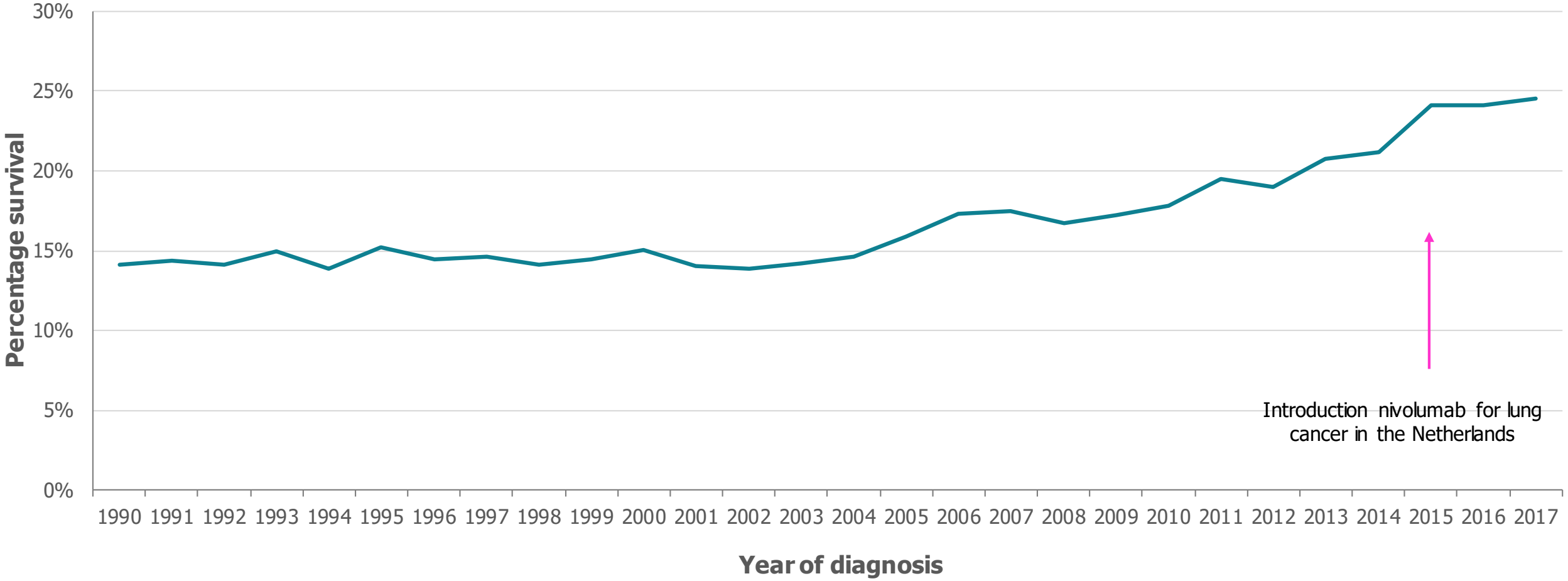
5-year relative survival of DLBCL in the Netherlands



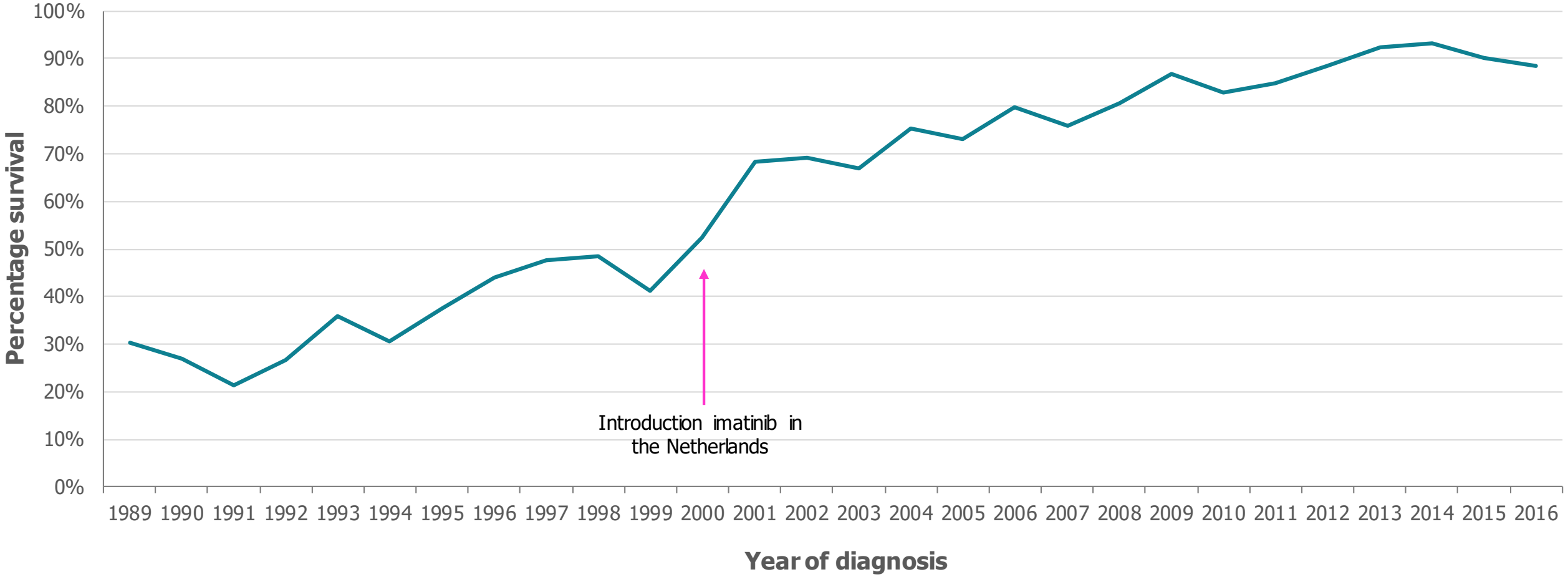
5-year relative survival of metastatic melanoma in the Netherlands



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

Targeted therapy

- The number of available drugs is increasing fast
- Might possibly lead to the cure of more and more patients with metastatic disease
- Still unclear if targeted therapy should be used during the rest of a life
- Targeted therapy is often very expensive and therefore not affordable in low-income countries

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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