Targeted therapy in oncology

(basic principles, main categories and adverse events)

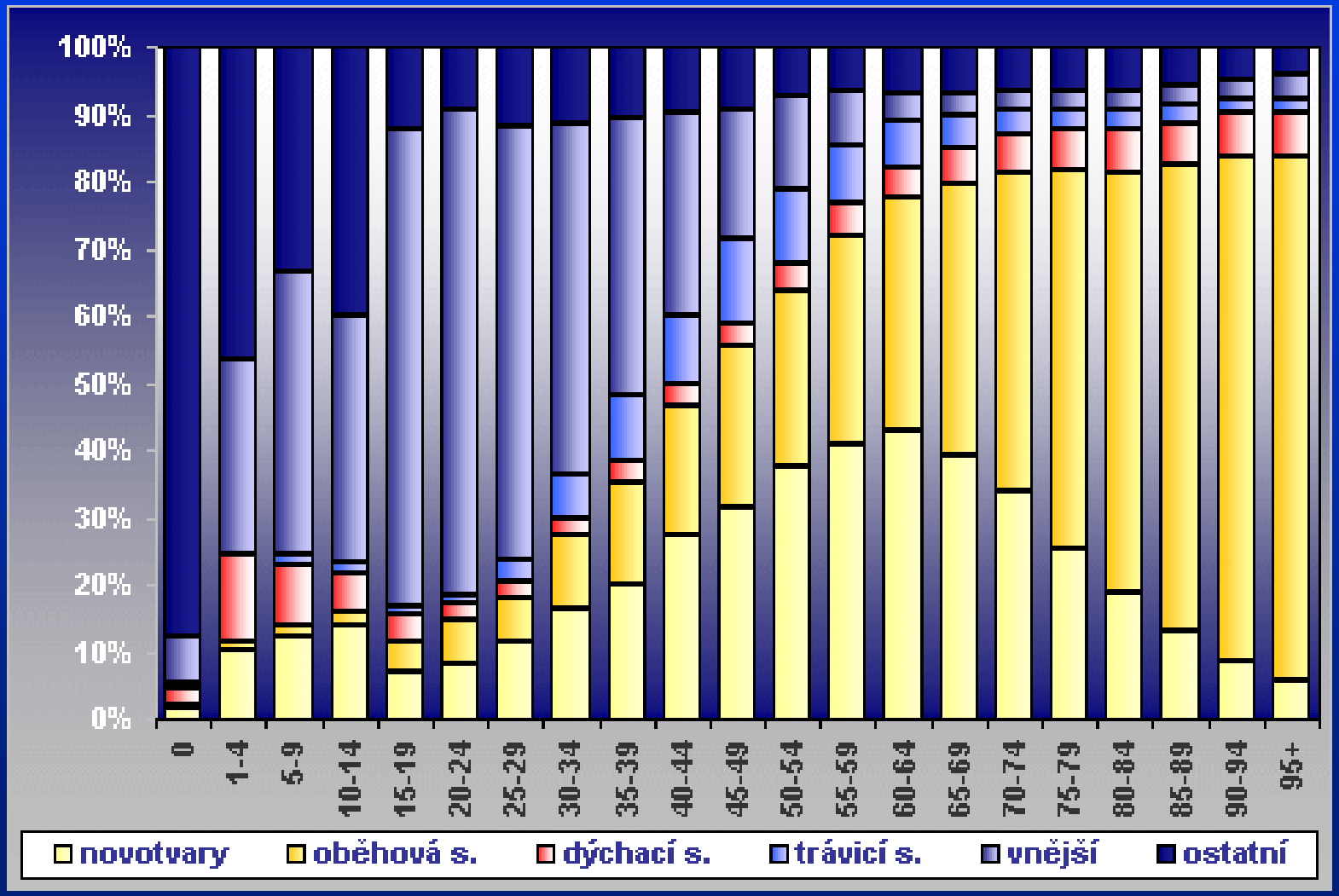
Regina Demlova, MD, Ph.D.

Cancer epidemiology

- **Czech republic**
  - population: 10 266 646 (2006)
  - life expectancy: men: 73,45 / women: 79,67 years
  - mortality: 107 938 (2005)

  - **Incidence -** 521,3 / 100 000 (2004)
  - **Mortality -** 28 255 (26,2%)

Cancer epidemiology



Deaths by selected dg. causes of death and age, CR, 2005

Cancer epidemiology

The most common solid tumors in czech men (2005):

- **1. prostatic cancer (4 846)**
- **2. colorectal cancer (4 746)**
- **3. lung cancer (4 632)**

Cancer epidemiology

The most common solid tumors in czech women (2005):

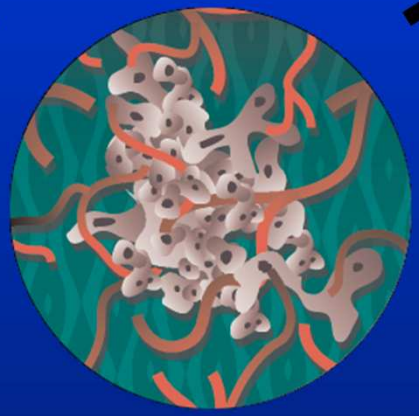
- **1. breast cancer (5 533 / 5 790 + TIS)**
- **2. colorectal cancer (3 236)**
- **3. endometrial Ca – corpus uteri (1 782)**

Cancer cell

Genetic instability

-
own production of growth factors, loss of sensitivity to inhibiting signals

Demage of the death cells (apoptosis)



Invasion and metastatic process

Getting unlimited replication potential

Induction of angiogenesis

Anticancer treatment

Fighting against cancer cell is aimed especially to:

1) Reduce its continued proliferation
   x cell cycle
   x growth factors and their receptors

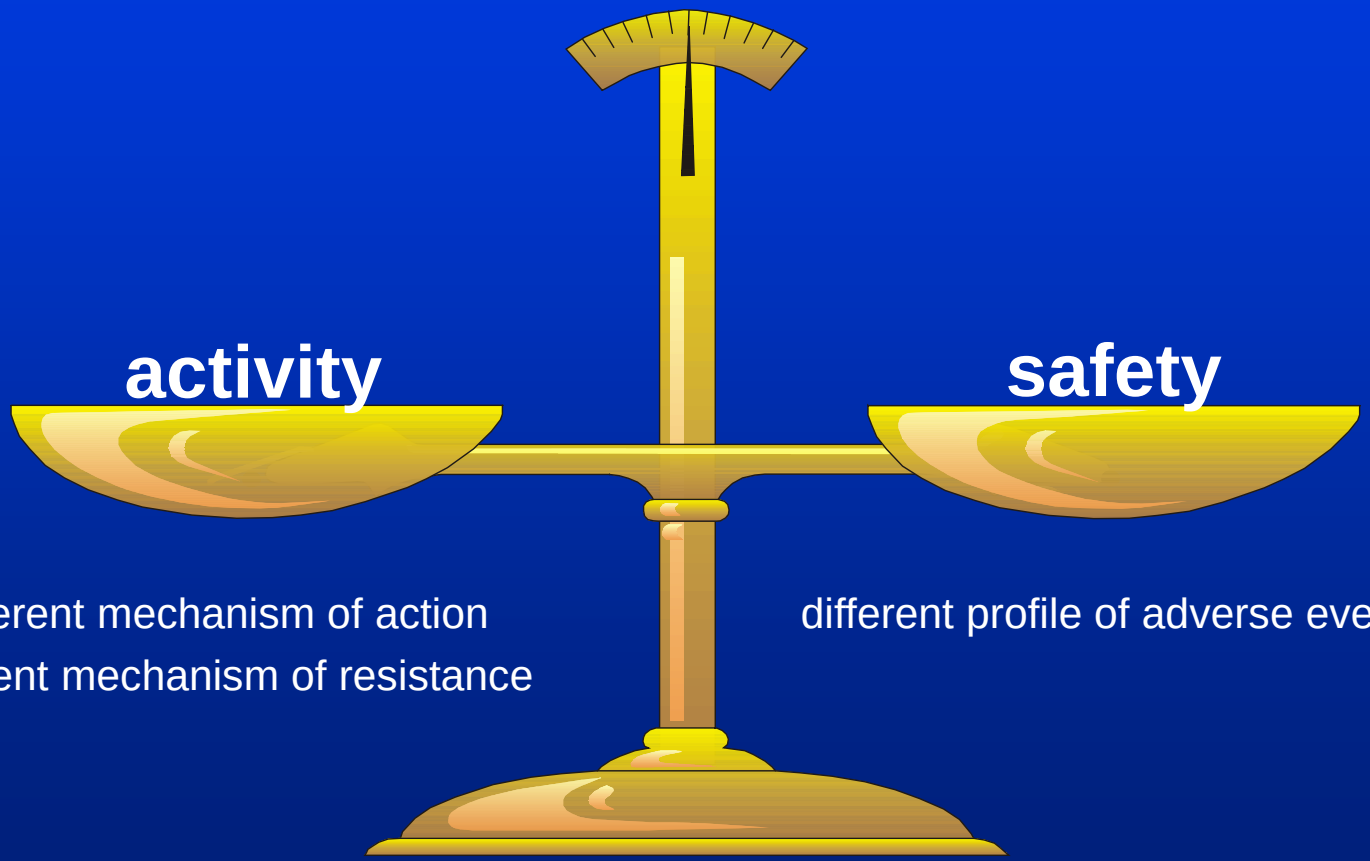
2) avoidance of necessary nutrients
   x angiogenesis
   x of nucleic acids in the cell and the formation of DNA

Classification of cytostatics

Alkylating agents	antimetabolites	Mitotic agents	Anticancer antibiotics	others
BUSULFAN	CYTOSIN	ETOPOSID	BLEOMYCIN	L-ASPARAGINASA
CARMUSTIN	ARABINOSID	TENIPOSID	DACTINOMYCIN	HYDROXYUREA
CHLORAMBUCIL	FLOXURIDIN	VINBLASTIN	DAUNORUBICIN	PROCARBAZIN
CISPLATIN	FLUOROURACIL	VINCRISTIN	DOXORUBICIN	
CYKLOFOSFAMID	MERCAPTOPURIN	VINDESINE	MITOMYCIN-C	
IFOSFAMID	METHOTREXAT	TAXANY	MITOXANTRON	
MELFALAN			PLICAMYCIN	

Targeted therapy - is designed to target cells with specific receptors for treatment

Increasing of efficacy



different mechanism of action
different mechanism of resistance

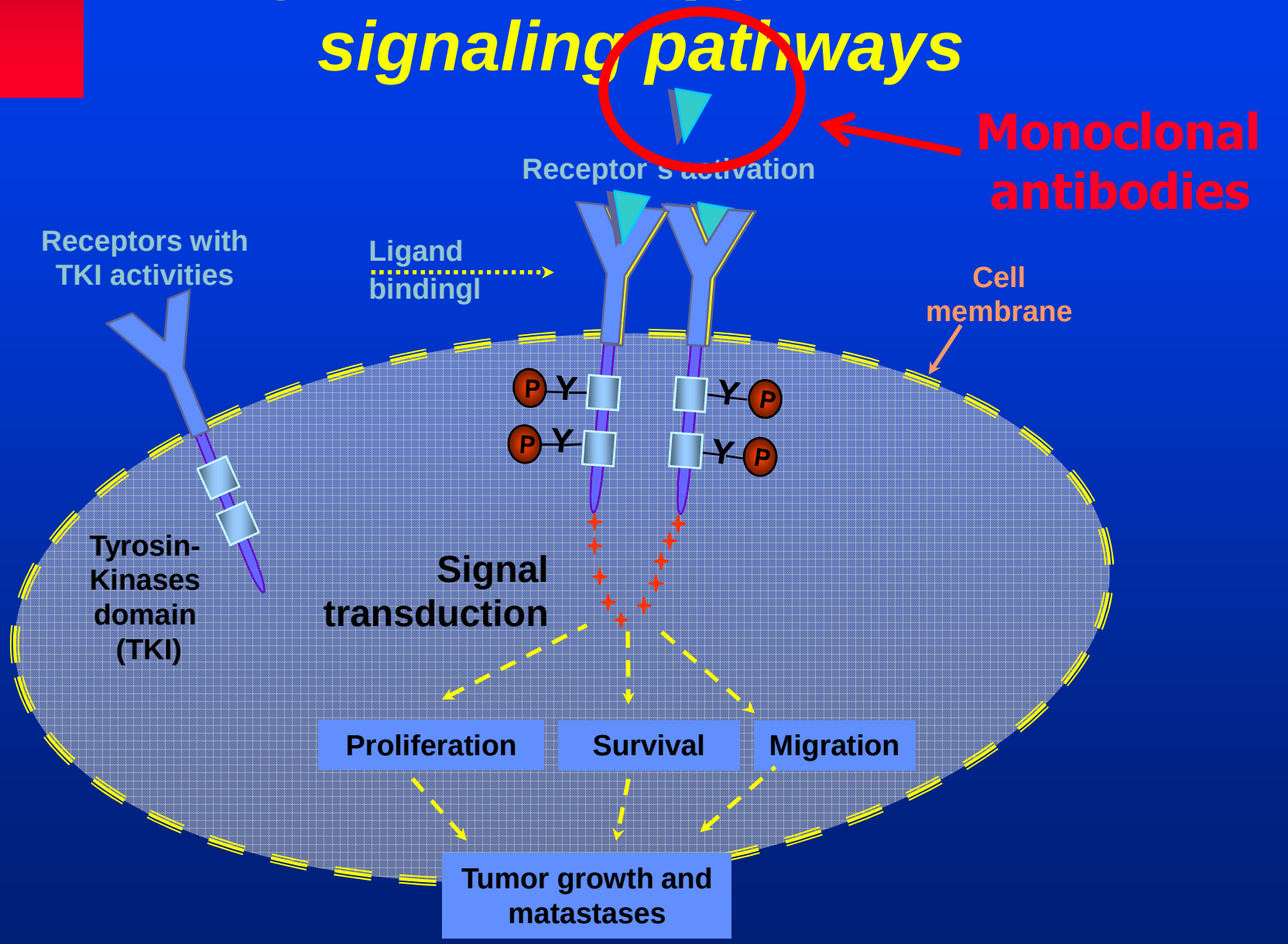
different profile of adverse events

Principles of targeted therapy

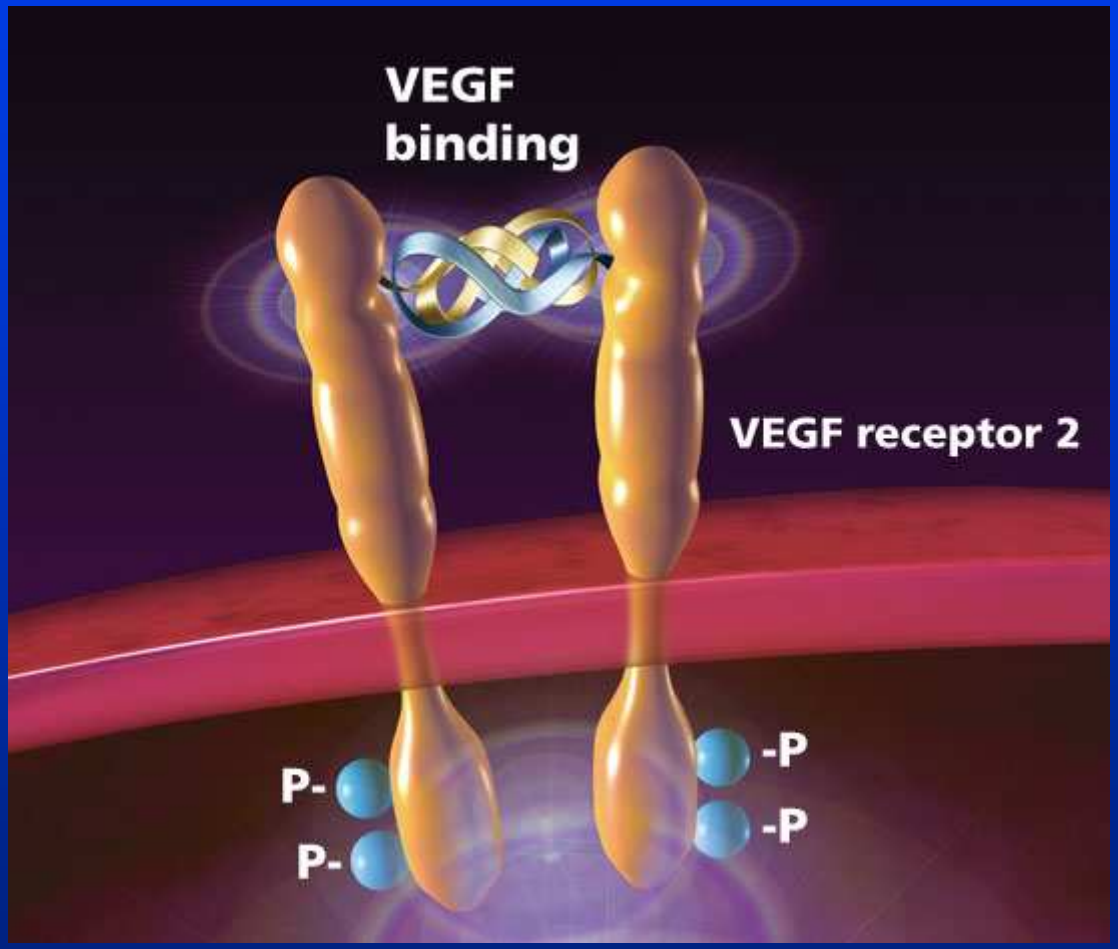
1. **Influence/disruption the binding of natural ligand to the receptor –**
   monoclonal antibodies

Example: e.g. Bevacizumab - binds to VEGF and prevents it from binding to VEGF-R receptors.

Targeted therapy – receptor signaling pathways



Principles of targeted therapy



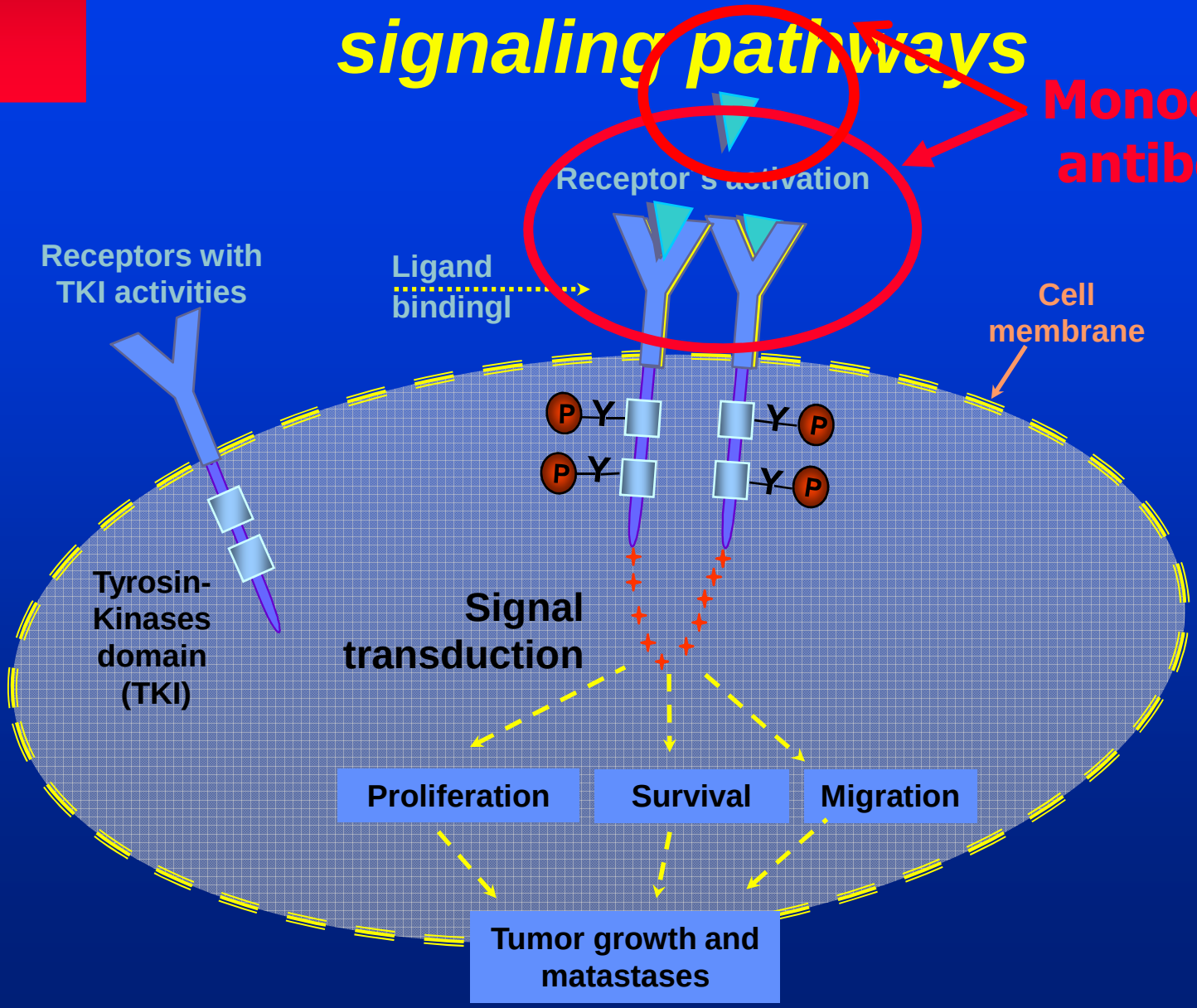
Principles of targeted therapy

1. Influence/disruption the binding of natural ligand to the receptor

2. **Direct binding of antibodies to the receptor – monoclonal antibodies**

   (e.g. cetuximab)

Targeted therapy – receptor signaling pathways



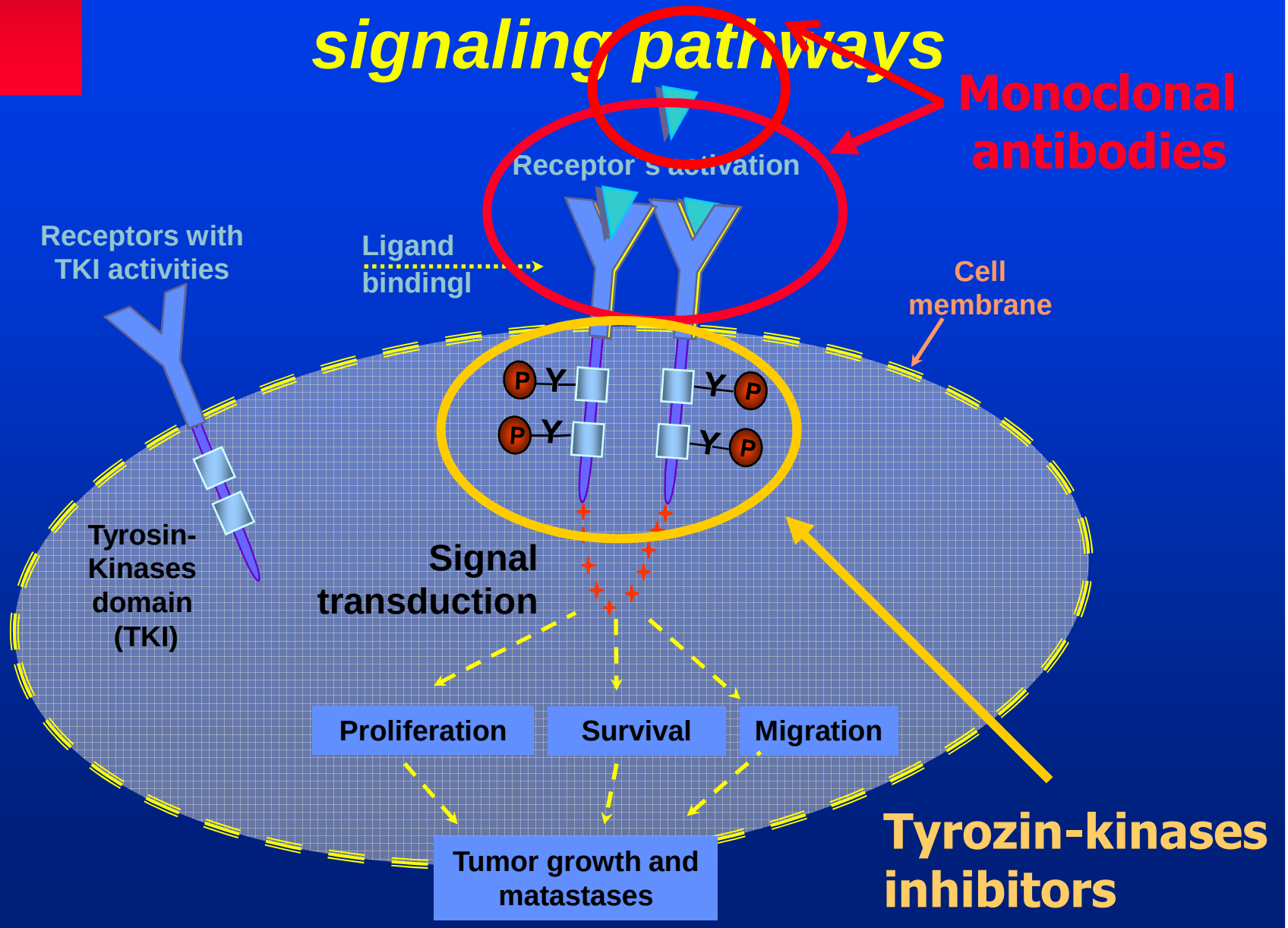
Principles of targeted therapy

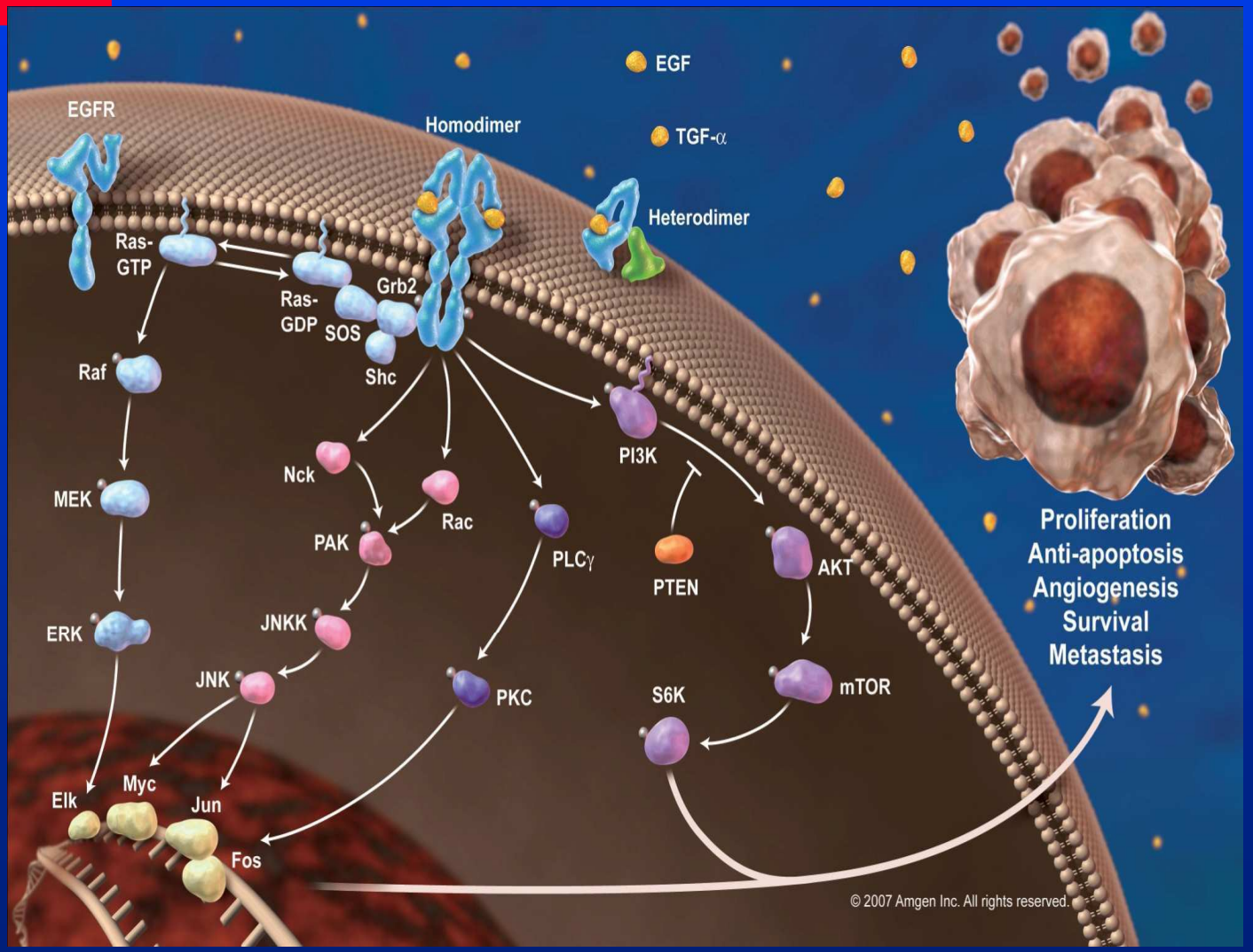
1. Disposal of the signal from binding to receptor (e.g. bevacizumab)

2. Direct binding of antibodies to the receptor (e.g. cetuximab)

3. **Disposal of the intracellular signaling pathway (e.g. lapatinib, sunitinib, sorafenib)**

Targeted therapy – receptor signaling pathways




EGF
EGFR
Homodimer
TGF-α
Heterodimer
Ras-GTP
Ras-GDP
Grb2
SOS
Shc
Raf
MEK
ERK
Nck
Rac
PAK
JNKK
JNK
PLCγ
PKC
PI3K
PTEN
AKT
S6K
mTOR
Elk
Myc
Jun
Fos
Proliferation
Anti-apoptosis
Angiogenesis
Survival
Metastasis
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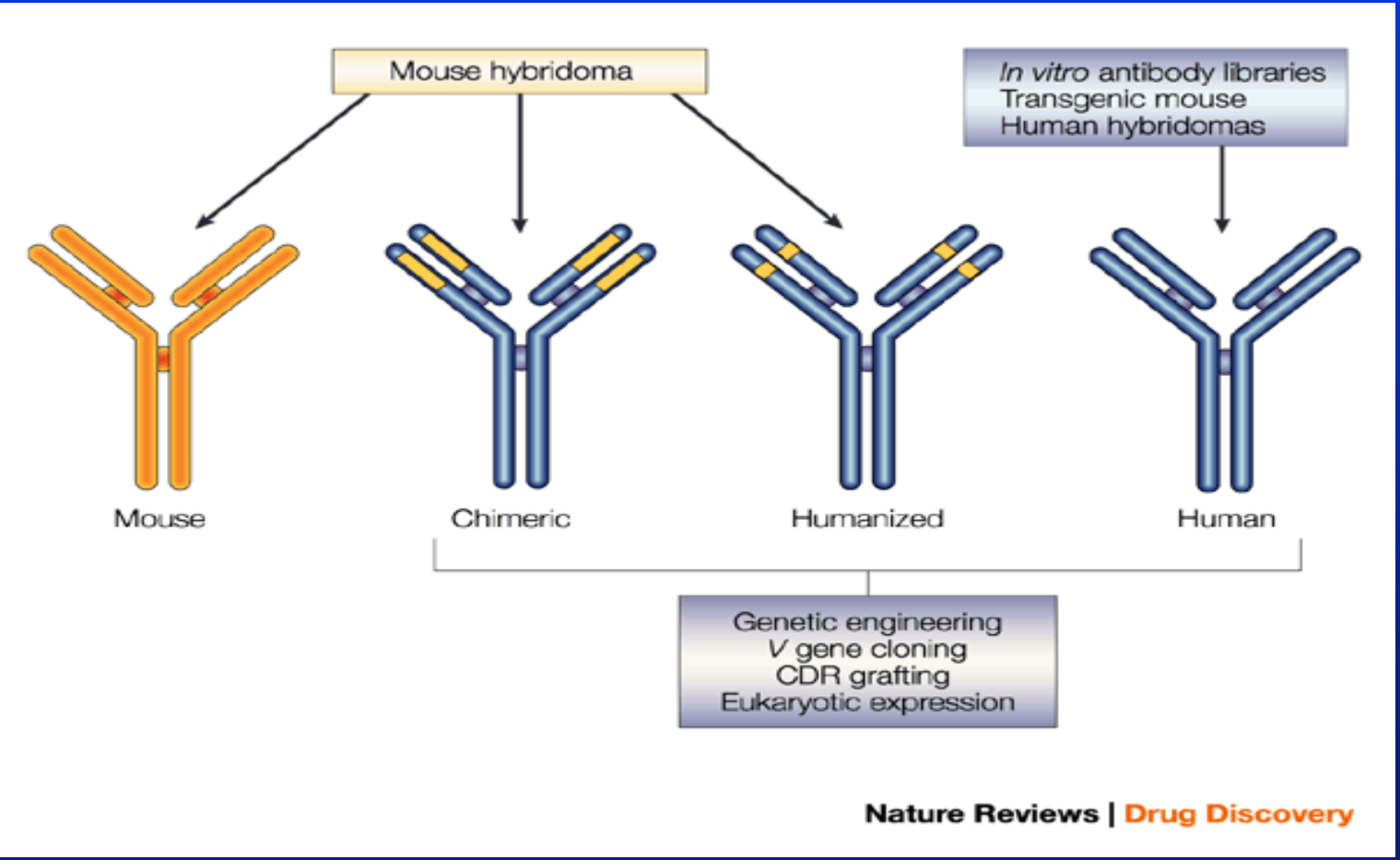
Basic terminology

- ✓ Monoclonal antibodies have the suffix **„mab“**
  (e.g. cetuximab, trastuzumab)

- ✓ Inhibitors of enzymatic reactions (Tki) have the suffix **„nib“**
  (e.g. imatinib, erlotinib)

Nomenclature of monoclonal antibodies



Nomenclature of monoclonal antibodies

Marking and identification of monoclonal antibody according to the origin is secured by inserting the letter:

- ✓ o - mouse (-o-mab) — abagovomab
  a - rat (-a-mab)
  e - hamster (-e-mab)
  i - primates (-i-mab) — cetuximab

- ✓ mu - human (-mu-mab) — panitumumab
  zu - humanized (-zu-mab) — trastuzumab
  xi - chimeric (-xi-mab) — rituximab

Nomenclature of Tki - what does „nib“ mean?

- ✓ „nib“ refers to the pharmacologic action of the drug
- ✓ „nibs“ are inhibitors
- ✓ the letters before “nib” tell you what is being inhibited

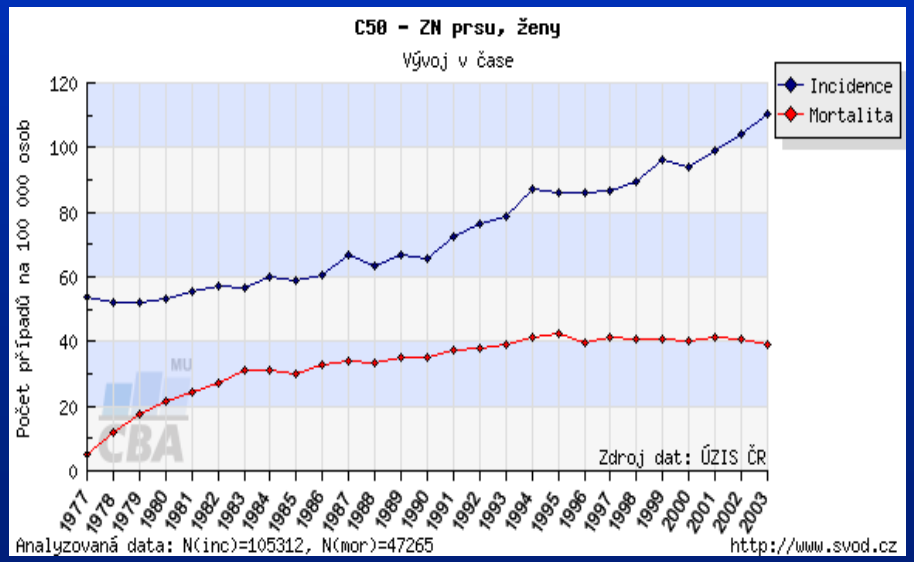
• a-nib – angiogenesis inhibitor	pazopanib
• ti-nib – tyrosine kinase inhibitor	lapatinib
• rafe-nib – raf kinase inhibitor	sorafenib

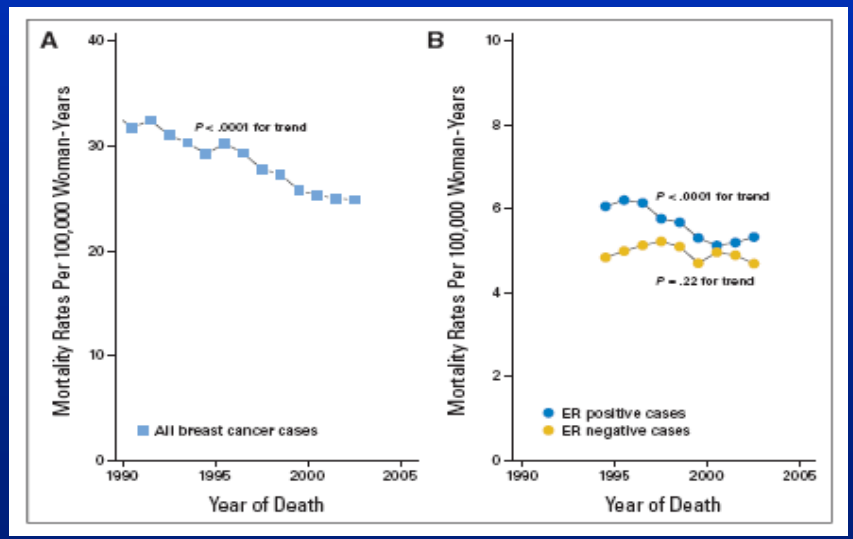
Example : breast carcinoma

- The most common cancer in czech women
- High mortaliy

Decreasing of mortality

- CZ: 1994-2003 o 19,5%
- USA :1989-2003 25%
-



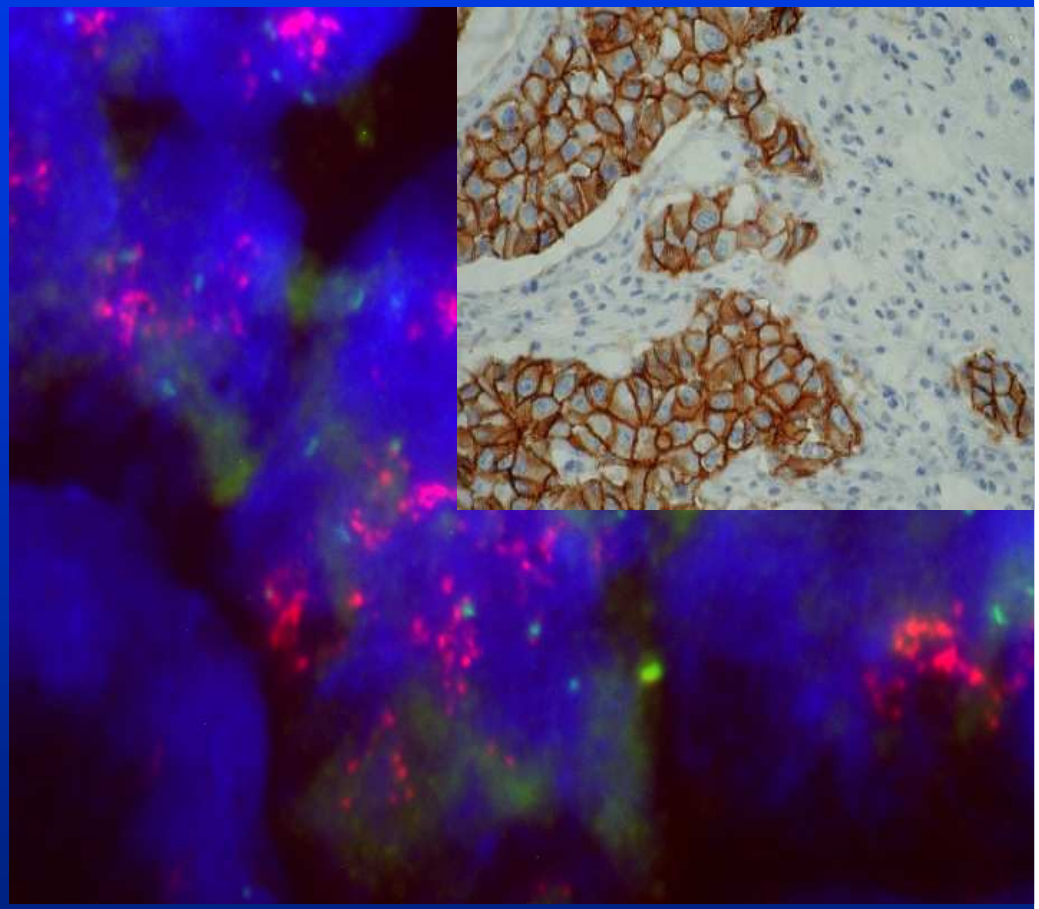


Reference: 1www.SVOD.cz, 2 Jatoi I., et al. JCO 2007;25(12)

HER-2 positive breast cancer

1985 – identification of the human Her-2/neu gene as a negative prognostic marker

Methods : IHC, FISH

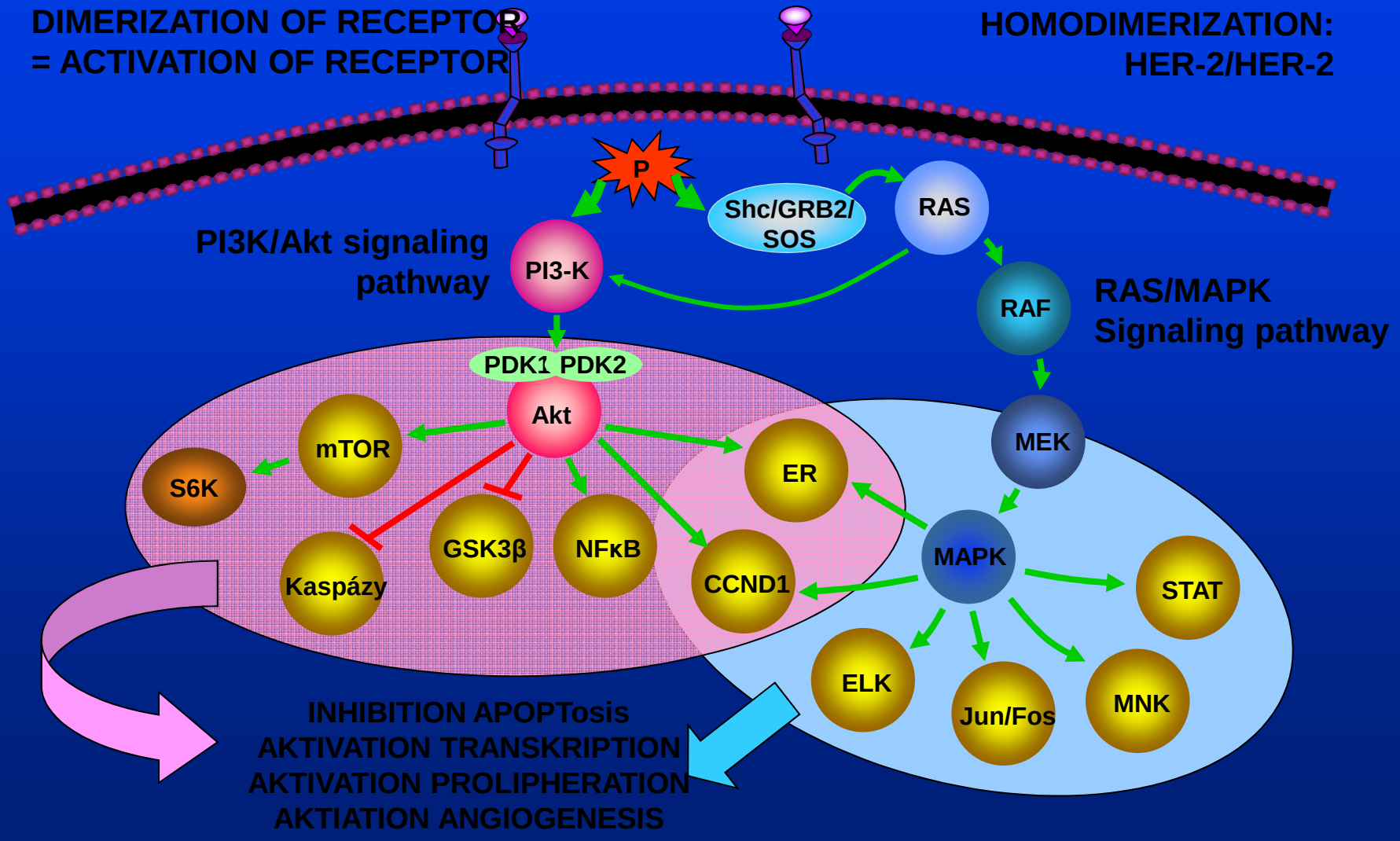


Incidence:

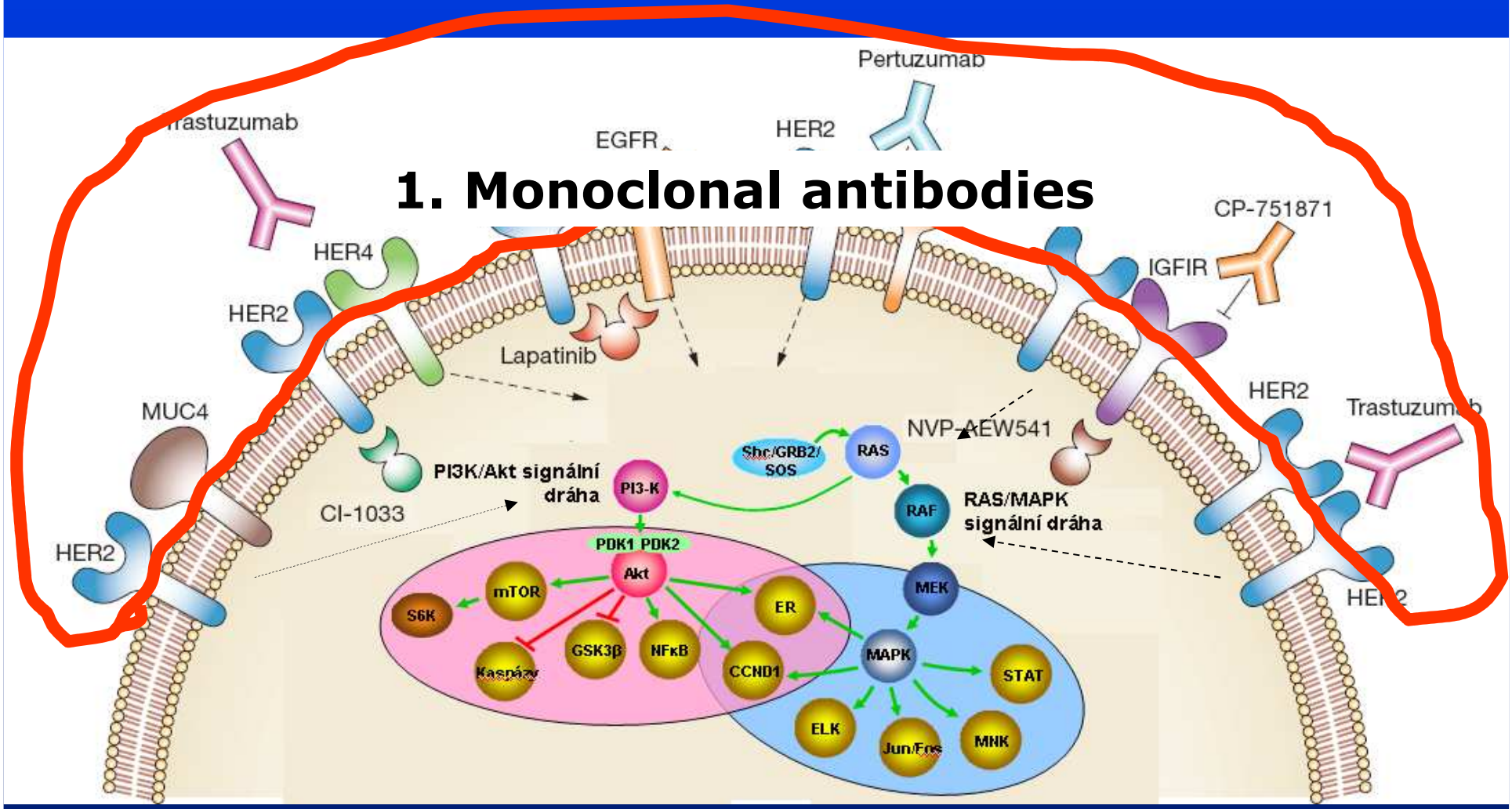
- **worldwide: 10-25%**
- **european: 17%**
- **czech: 14,2%**

Yang-Feng et al. Cytogenet. Cell Genet. 1985; Slamon et al, Science 1987; Pegram et al, JCO 1998; Owens et al. Clin Breast Can 2004; Al-Kuraya K et al. Mod Pathol 2000; Fabian et al, Sborník BOD 2006,

HER-2 SIGNALING PATHWAY

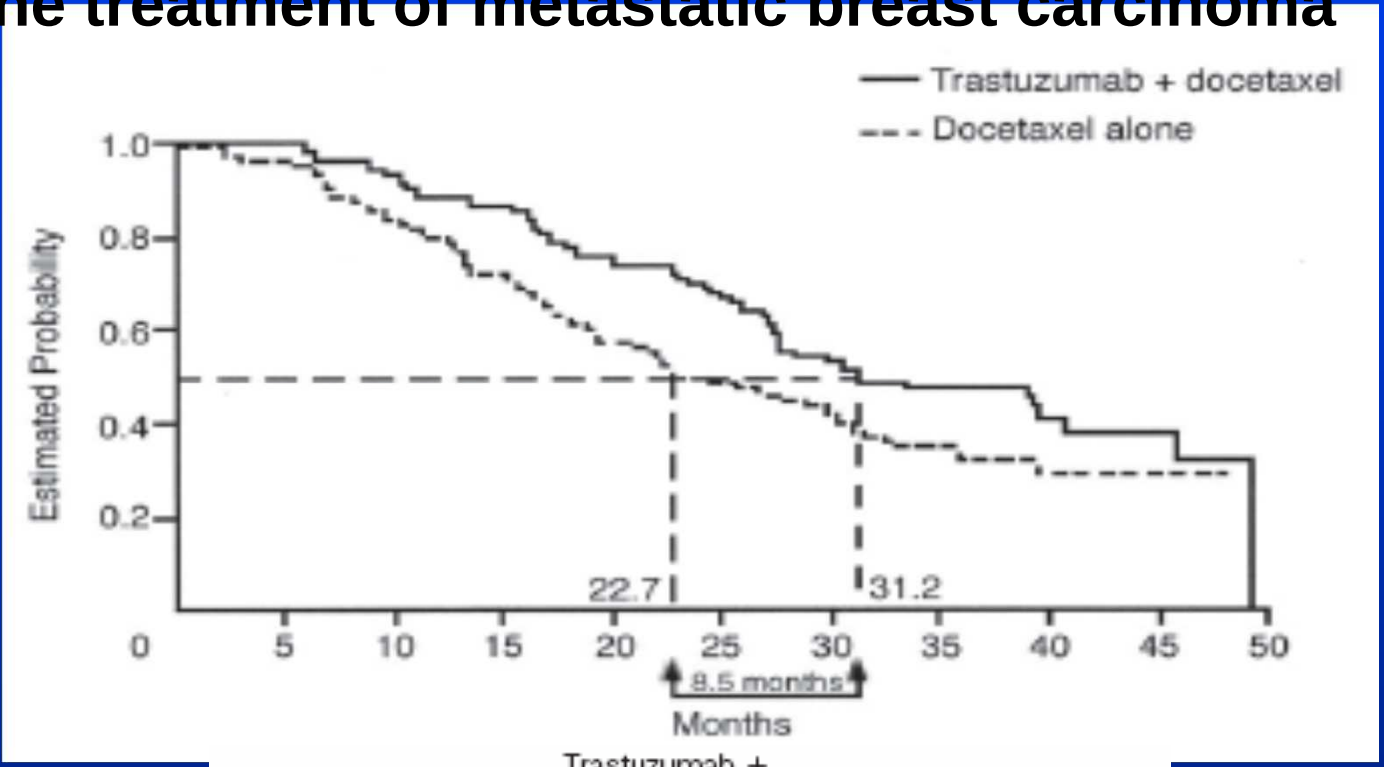


HER-2 TARGETING



TRASTUZUMAB – monoklonal antibody

1st line treatment of metastatic breast carcinoma



Outcome	Trastuzumab + Docetaxel (n = 92)	Docetaxel Alone (n = 94)	*P*
ORR, %	61	34	.0002
CR, %	7	2	
PR, %	54	32	
TTP, median, months	11.7	6.1	.0001
OS, median, months*	31.2	22.7	.0325

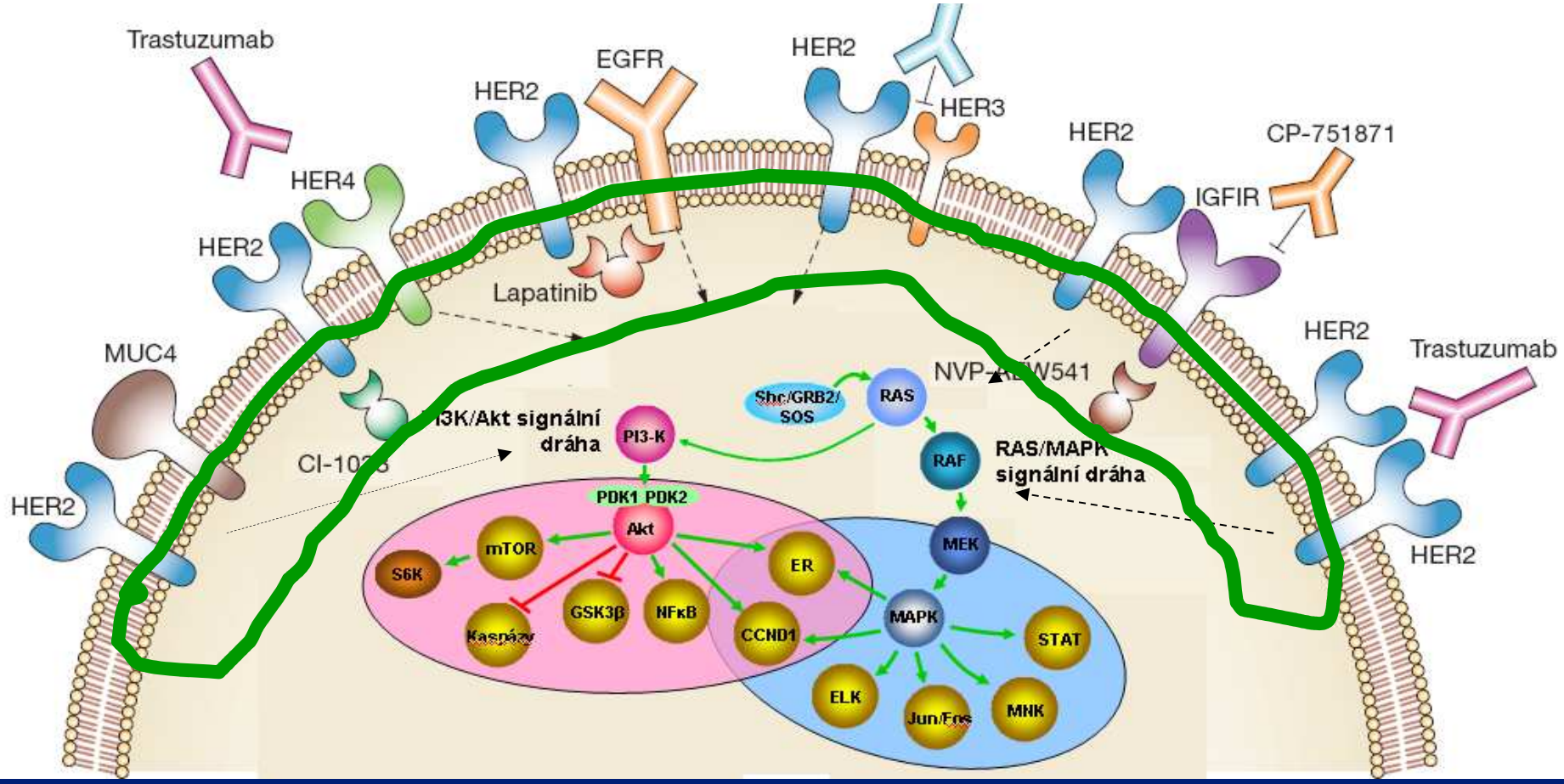
Marty, JCO 2005

TRASTUZUMAB (Herceptin®)

- INDICATIONS:
  treatment of locally advanced and metastatic HER-2 positive breast cancer
- ADVERSE EVENTS:
  allergic reaction, fever, chills, hypotension
  cardiotoxicity
  diarrhea, nausea, vomiting, rash
  muscle and joint pain
  pulmonary infiltrates, penumonitis

HER-2 TARGETING

2. Tyrozikinases inhibitors

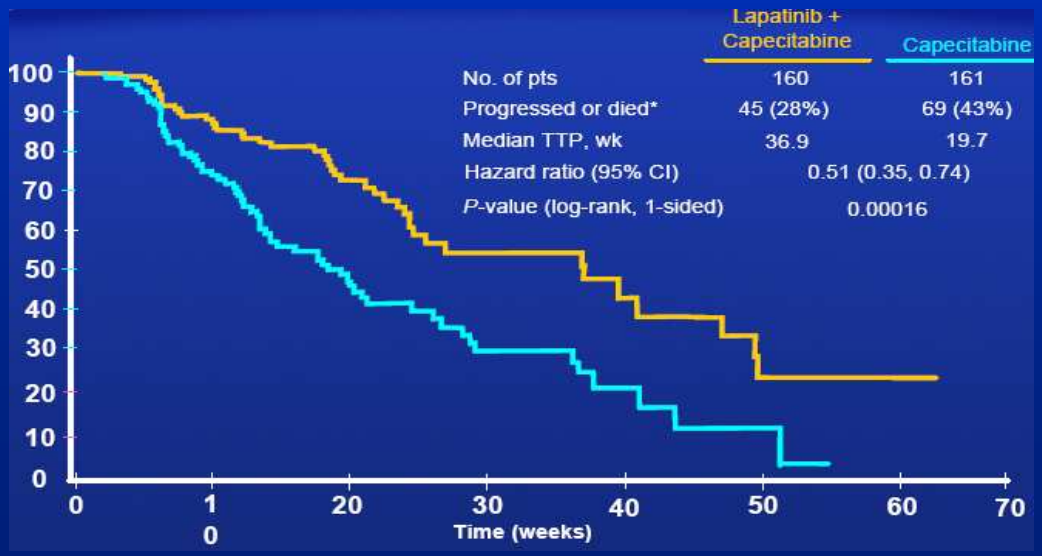


LAPATINIB (Tyverb®) – tyrosinkinase inhibitor

- Reversible inhibitor EGFR (HER-1), HER-2
- Activity in trastuzumab-rezistent tumors
- Oral administration, well tolerated

INDICATION:

Metastatic breast carcinoma after trastuzumab failure



Konecny et al, 2006, Allen et al, 2002

LAPATINIB (Tyverb®)

MAIN ADVERSE EVENTS:

- Gastrointestinal toxicity (diarrhea, dehydration, abdominal pain, nausea, vomiting)
- dermal toxicity - rash, pruritus, dry skin

Targeted therapy - other drugs targeting EGFR

- **Monoclonal antibodies** (e.g. cetuximab, panitumumab
- **Tyrosin-kinases inhibitors** (e.g gefitinib /EGFR

Cetuximab (ERBITUX®)

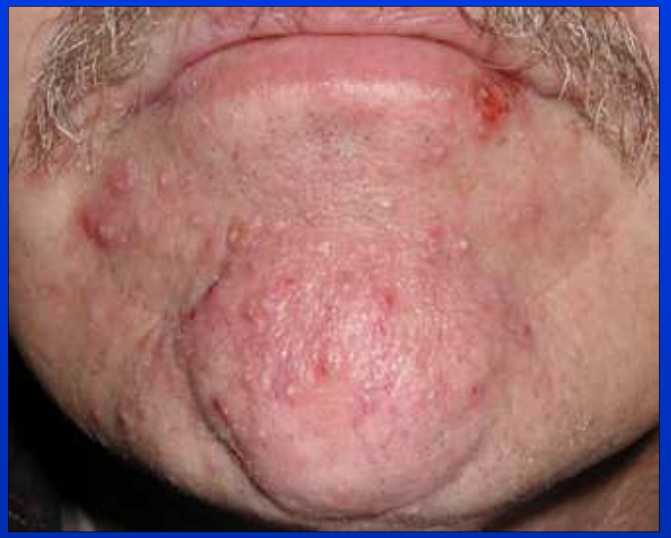
INDICATION:

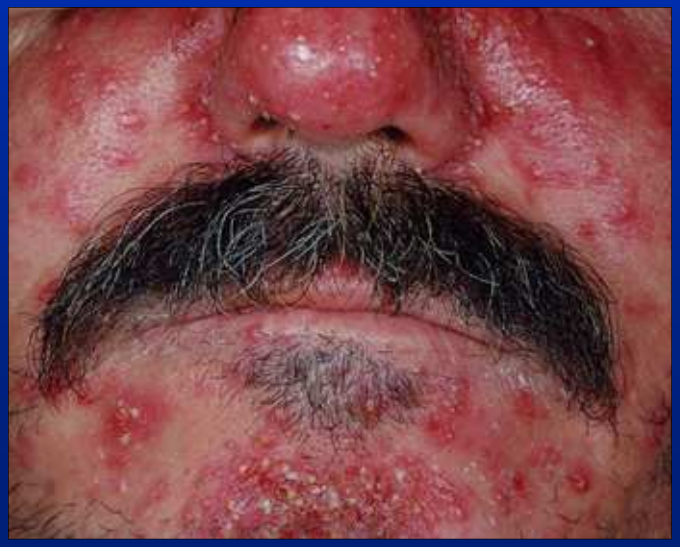
- Anti - EGFR Mab
- **metastatic colorectal cancer**

AE:

- Akneiform rash 76 – 90%

  Prognostic marker ??? !!!
- Alergic reaction
- Diarrhoea
- Fatigue





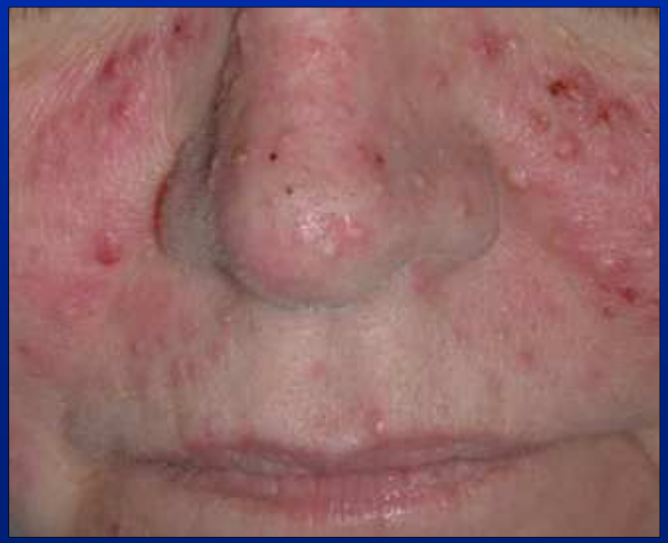
Panitumumab (VECTIBIX®)

INDICATION:

- Anti - EGFR Mab
- **metastatic colorectal cancer**

AE:

- Akneiform rash
- Diarrhoea
- Fatigue



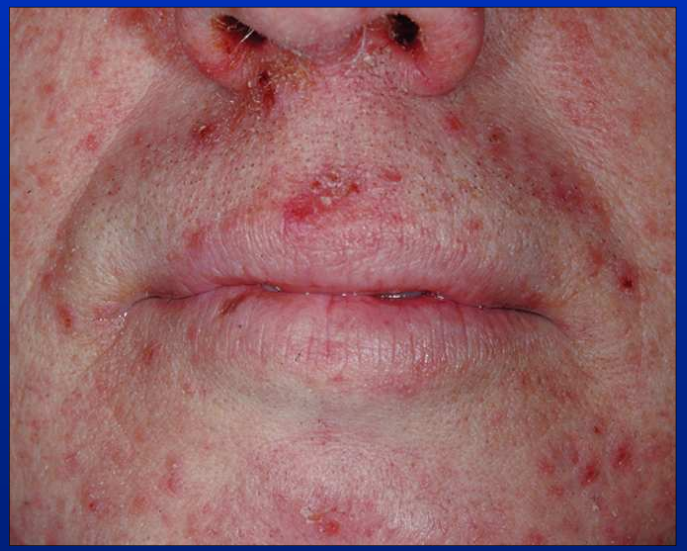
Erlotinib (TARCEVA®)

INDICATION:

- Inhibitor of EGFR-kinases inhibitor
- NSCLC after chemotherapúy failure
- Metastatic pancreatic cancer

AE:

- akneiform rash
- anorexie, diarrhoea
- conjunctivitis
- pneumonitis



Example : colorectal carcinoma and VEGF targeting

- The growth of malignant tumor needs the continuous supply of oxygen and nutrients
- Simple diffusion and not enough nutrition to the cells under the influence of hypoxia
- Tumor produced a series mediators, particularly VEGF (vascular endothelial factor).

VEGF - bevacizumab

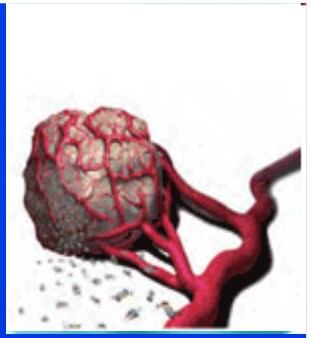
- VEGF binds to receptors (VEGF-R) on the surface of normal endothelial cells.
- The result is the formation of blood vessels in the tumor and its vascularization, tumor growth and metastasis.

VEGF - bevacizumab

- Antibody against VEGF, Avastin (bevacizumab), binds to VEGF and prevents it from binding to receptors.

- This induced inhibition of angiogenesis and its long-term use leads to regression of tumor vasculature, the normalization of surviving tumor vessels and inhibition of recovery and growth of new blood vessels

Bevacizumab (AVASTIN®)



INDICATION:

- Metastatic colorectal carcinoma
- Metastatic breast Ca, renal Ca, NSCLC

ADVERSE EVENTS:

- Akceleration of hypertenzion
- proteinurie
- Trombembolic complication

Targeted therapy - other drugs targeted to VEGFR, PDGFR, c-kit

- **Tyrosin-kinases inhibitors** (e.g sunitinib and sorafenib *(VEGFR, PDGFR, c-kit)*, imatinib *(c-kit)*

Sunitinib maleát (SUTENT®)

- Multikinases inhibitor (PDGFR, VEGFR, c-KIT…)

INDICATION:

- Renal CA after failure of INF
- GIST after failure of imatinib

AE:

- **hand-foot syndrom (cca 13% pts.)**
- Diarrhoea, nausea
- bronchospasm
- neutropenia, trombocytopenia
- hypertension

Sorafenib (NEXAVAR®)

- Multikinases inhibitor (PDGFR, VEGFR, c-KIT…)

INDICATION :

- Metastatic renal cancer
- Inoperable hepatic cancer

AE:

- **hand-foot syndrom**
- alopecia,
- diarrhoea, vomiting
- headache

Current possibilities and using of targeted therapy

- **Breast carcinoma**
  - **trastuzumab, bevacizumab, lapatinib**
- **Colorectal cancer**
  - **bevacizumab, cetuximab, panitumumab**
- **Non-small cell lung cancer**

  - erlotinib , bevacizumab, cetuximab
- **Renal carcinoma**
  - **sunitinib, sorafenib, bevacizumab, temsirolimus, everolimus**
- **GIST**
  - **imatinib, sunitinib**
- **Pancreatic cancer**
- **erlotinib**
- **Head and neck cancer**
  - **cetuximab**
- **Hepatocellular carcinoma**
  - **sorafenib**

Summary

- Targeted therapy = a modern form of an active anticancer therapy
- Well tolerated
- A different toxicity profile
- Expensive
- The future of anticancer treatment