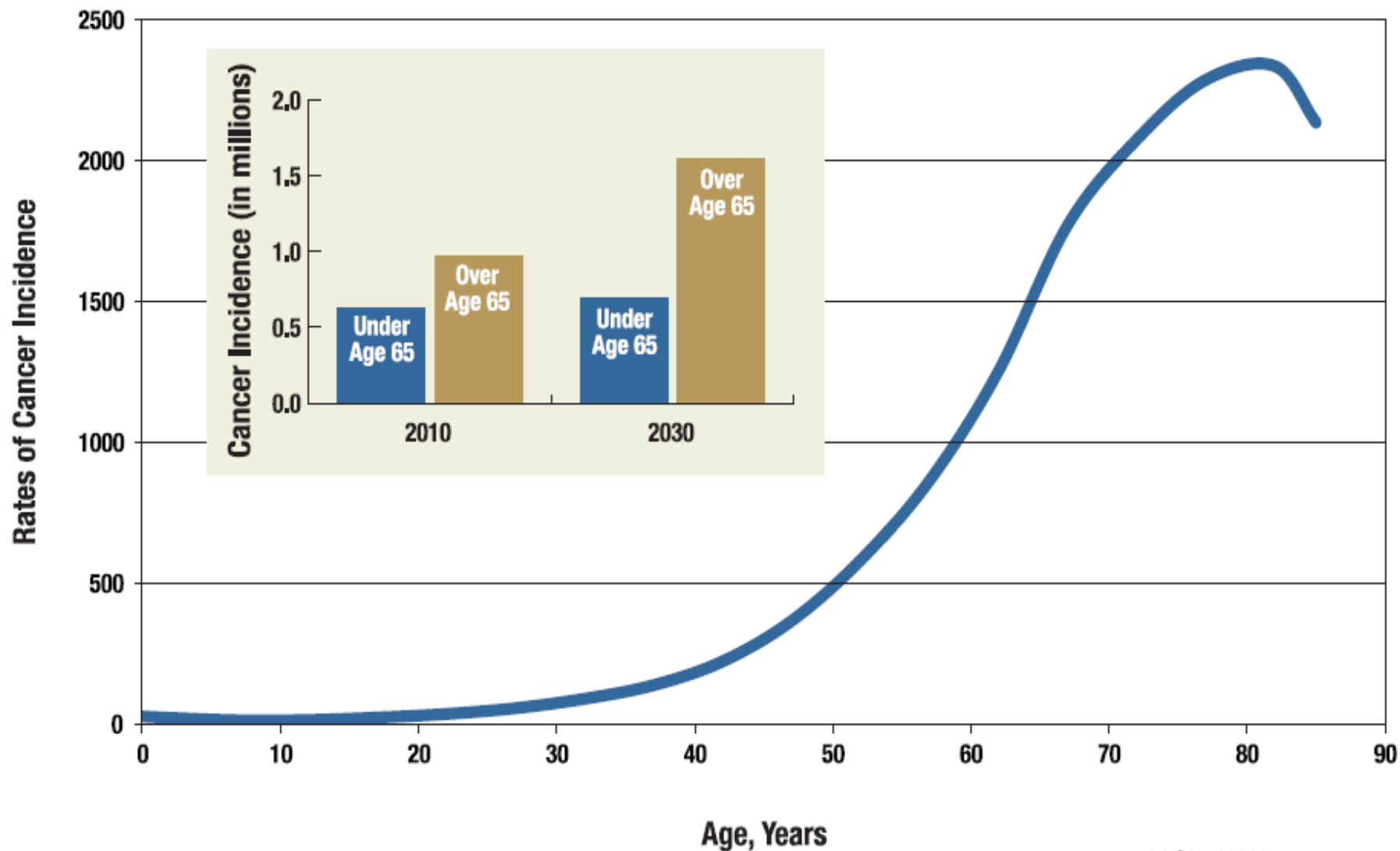




Clinical Pharmacology of the targeted therapy in oncology

Regina Demlova, MD, PhD, Ass.prof.

AACR Cancer Progress Report 2012

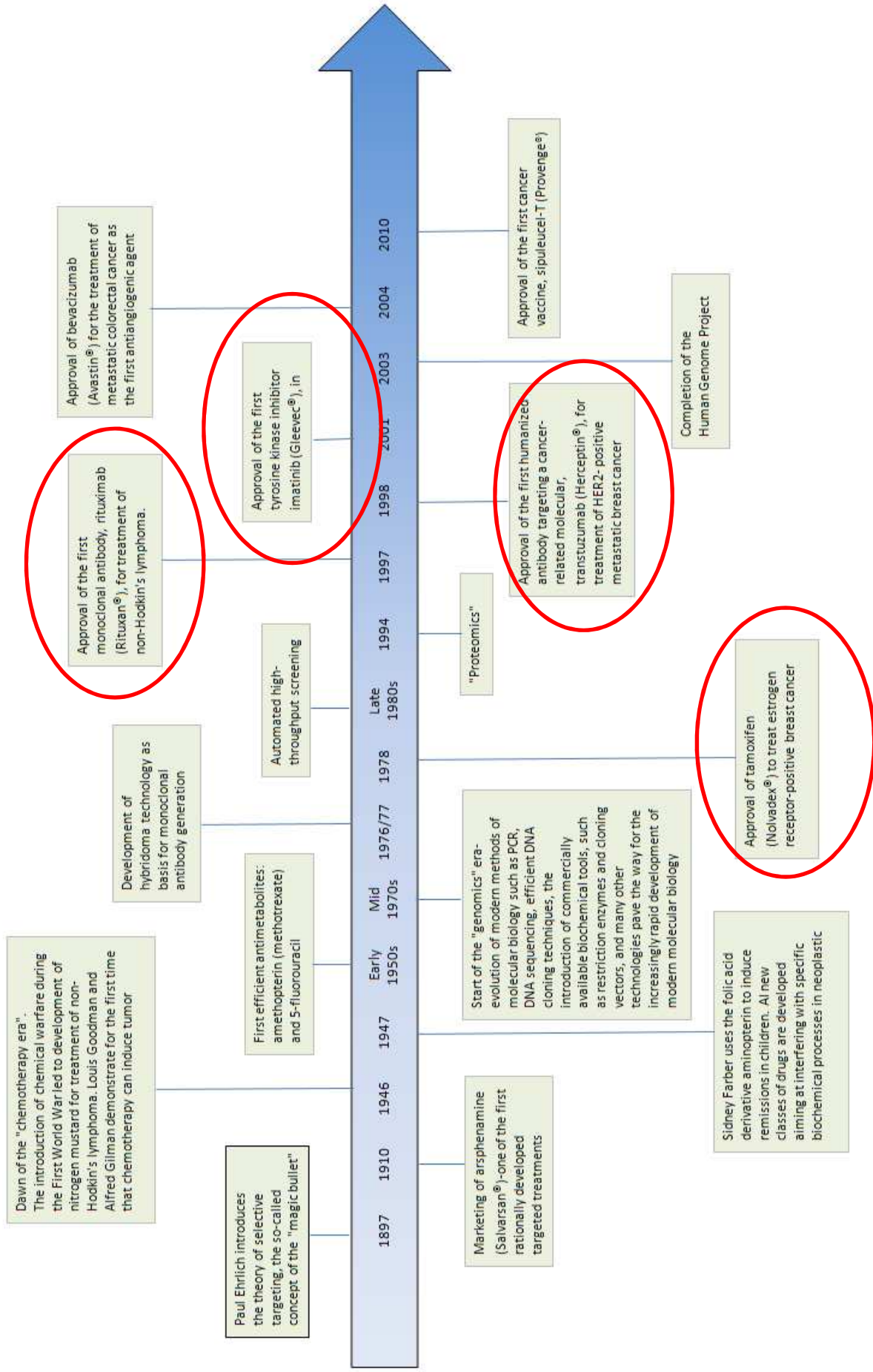


Complex Cancer Therapy

- Surgery
- Radiotherapy - Cytostatics
- Pharmacotherapy
 - Targeted Therapy

Classification of cytostatics

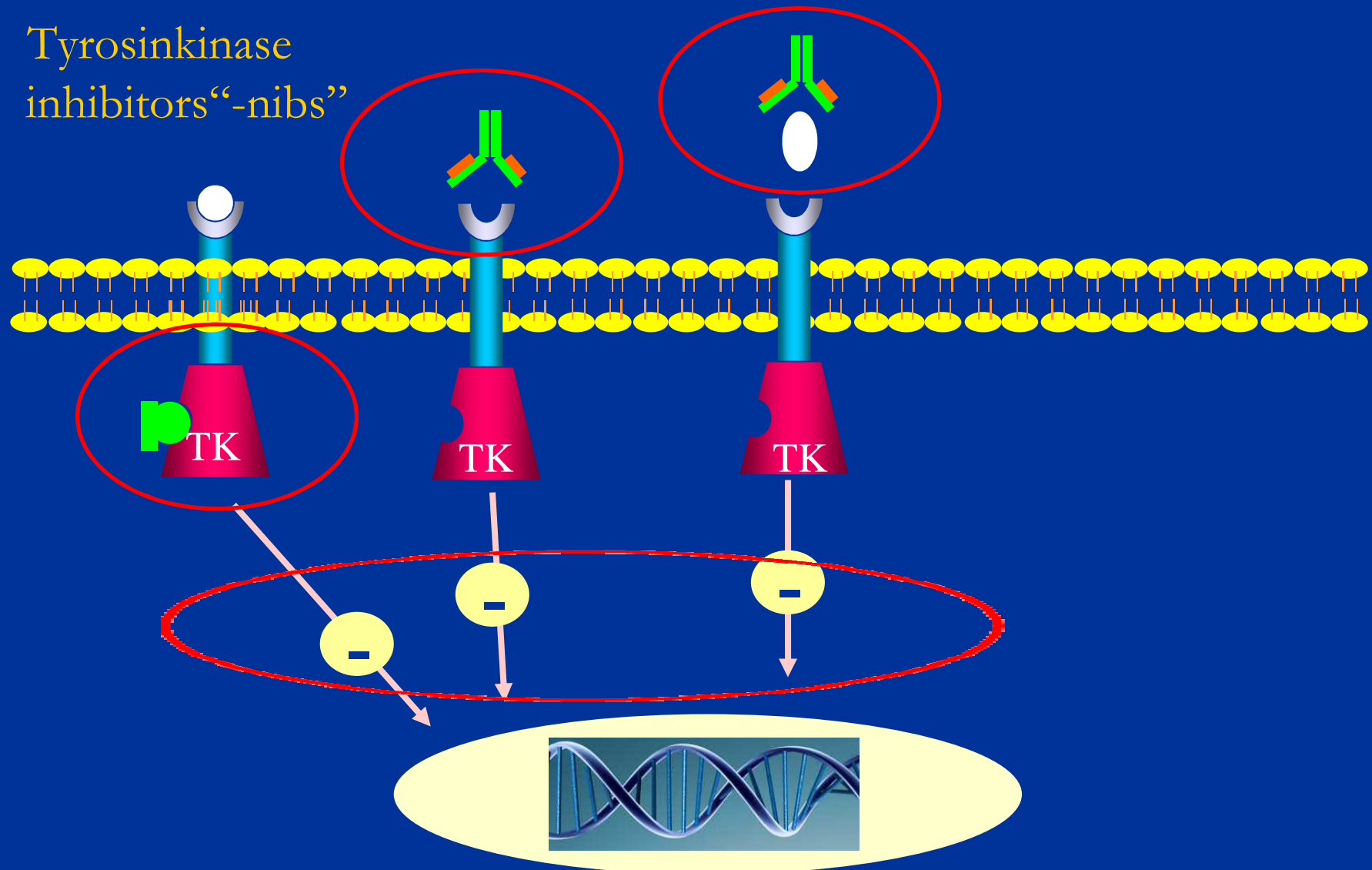
Alkylating agents	antimetabolites	Mitotic agents	Anticancer antibiotics	others
BUSULFAN	CYTOSIN	ETOPOSID	BLEOMYCIN	L-ASPARAGINASA
CARMUSTIN	ARABINOSID	TENIPOSID	DACTINOMYCIN	HYDROXYUREA
CHLORAMBUCIL	FLOXURIDIN	VINBLASTIN	DAUNORUBICIN	PROCARBAZIN
CISPLATIN	FLUOROURACIL	VINCRISTIN	DOXORUBICIN	
CYKLOFOSFAMID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

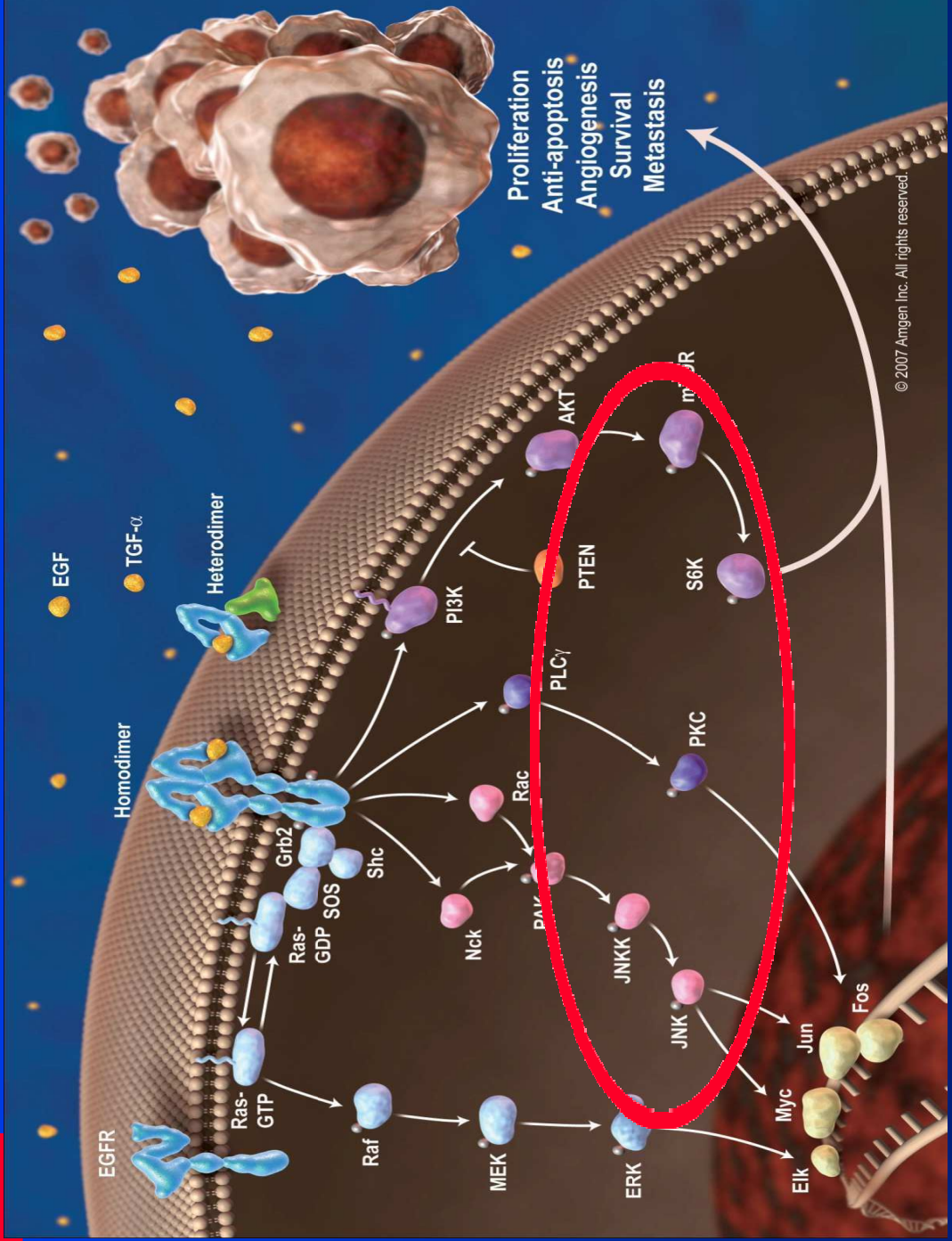


Pharmacological inhibition of the signal transduction

Monoclonal antibodies“-mabs”

Tyrosinkinase inhibitors“-nibs”





Current „targets“

Receptors

- EGFR
 - VEGF
 - PDGF
 - FGF
- Multikinase inhibitors

Signaling pathways

- Bcr-Abl
- mTOR
- B-Raf
- K-Ras, N-Ras
- PI3K
- c-Kit
- ALK, c-met

- - mAbs nebo - nibs

Current „targets“

Receptors

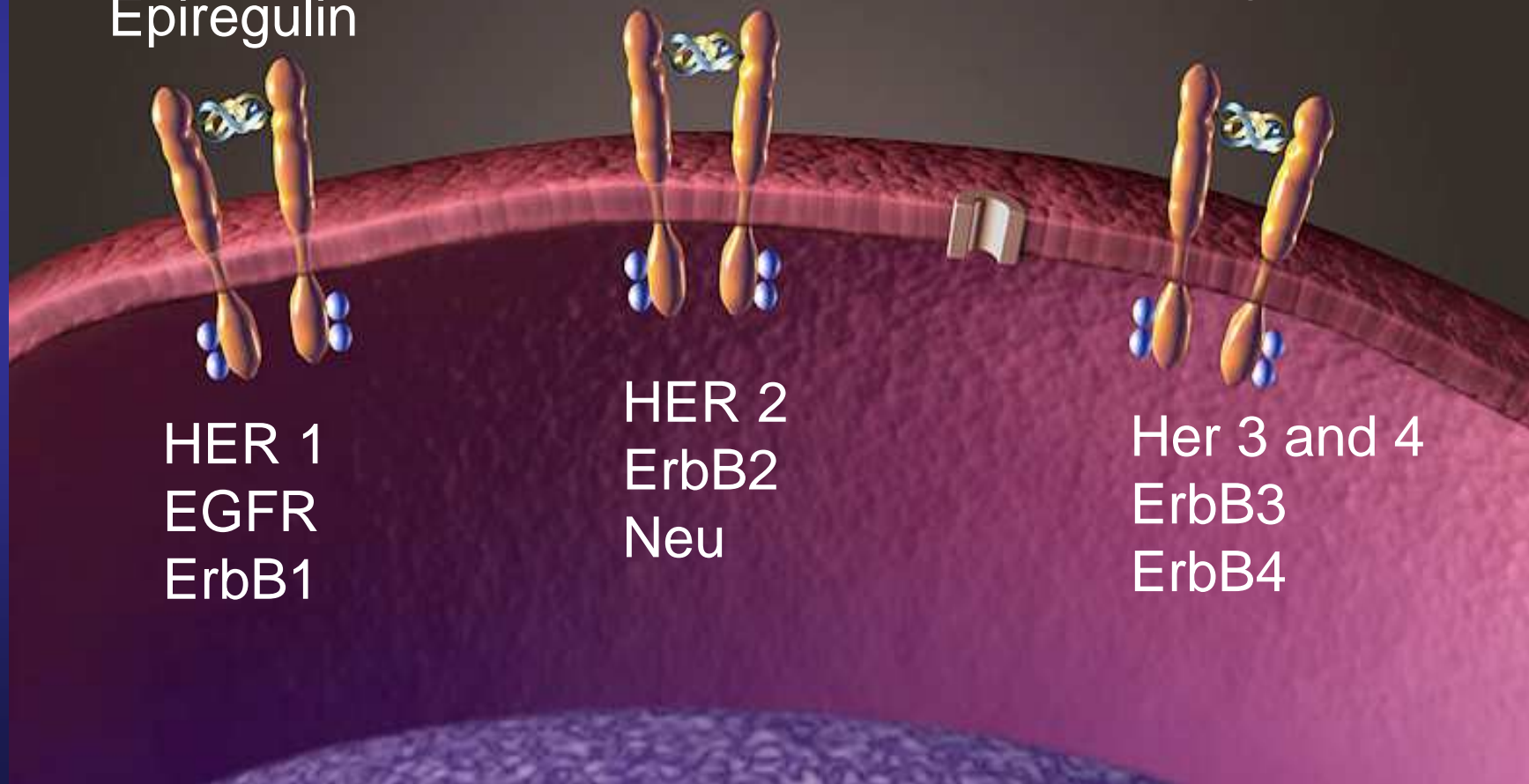
- EGFR

- Example: breast cancer

EGF
TGFalpha
Amphiregulin
Betacellulin
Epiregulin

No known ligand

Epiregulin
Neuregulins



HER 1
EGFR
ErbB1

HER 2
ErbB2
Neu

Her 3 and 4
ErbB3
ErbB4

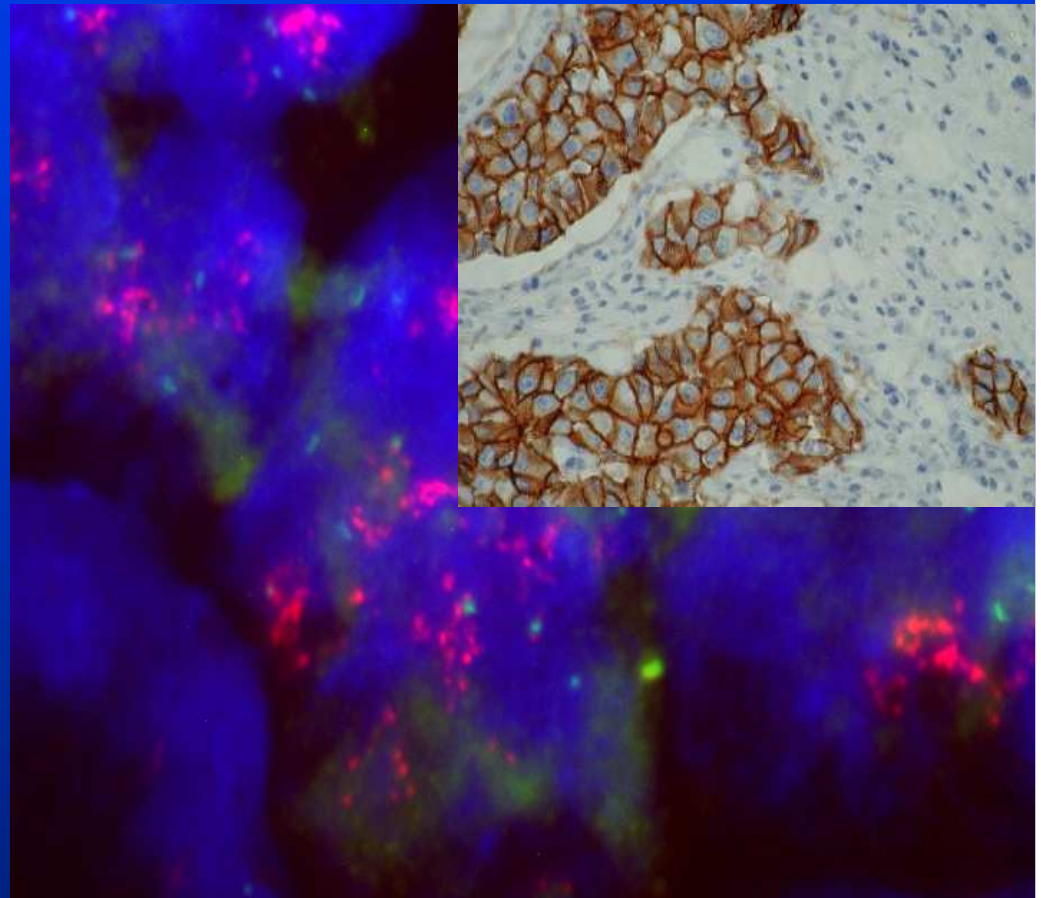
HER-2 positive breast cancer

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

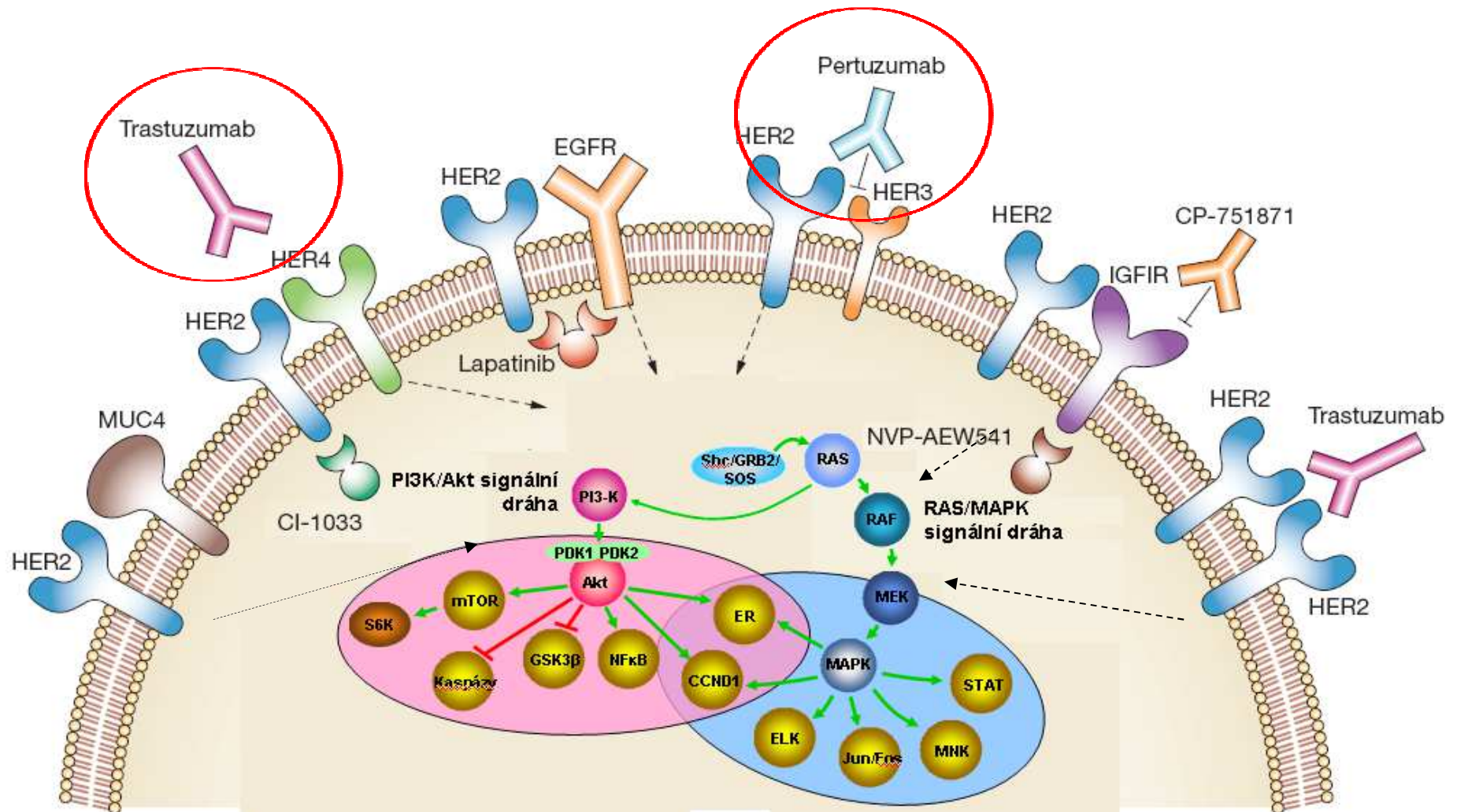
Methods : IHC, FISH

Incidence:

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

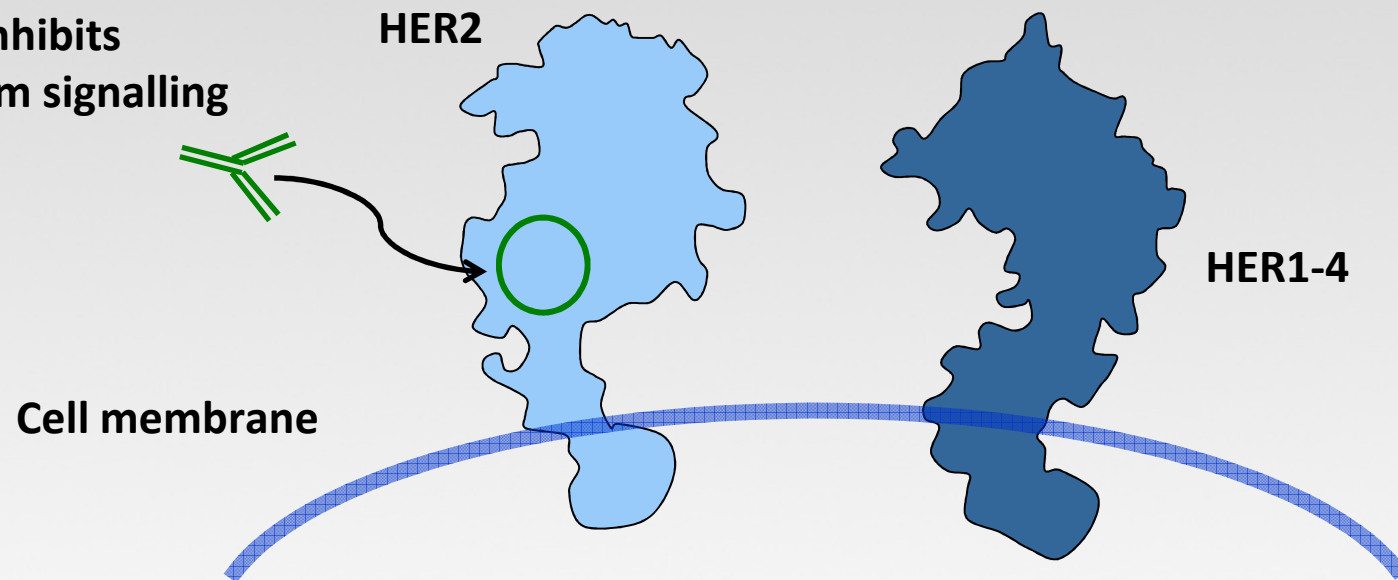


Her-2 receptor and mAbs

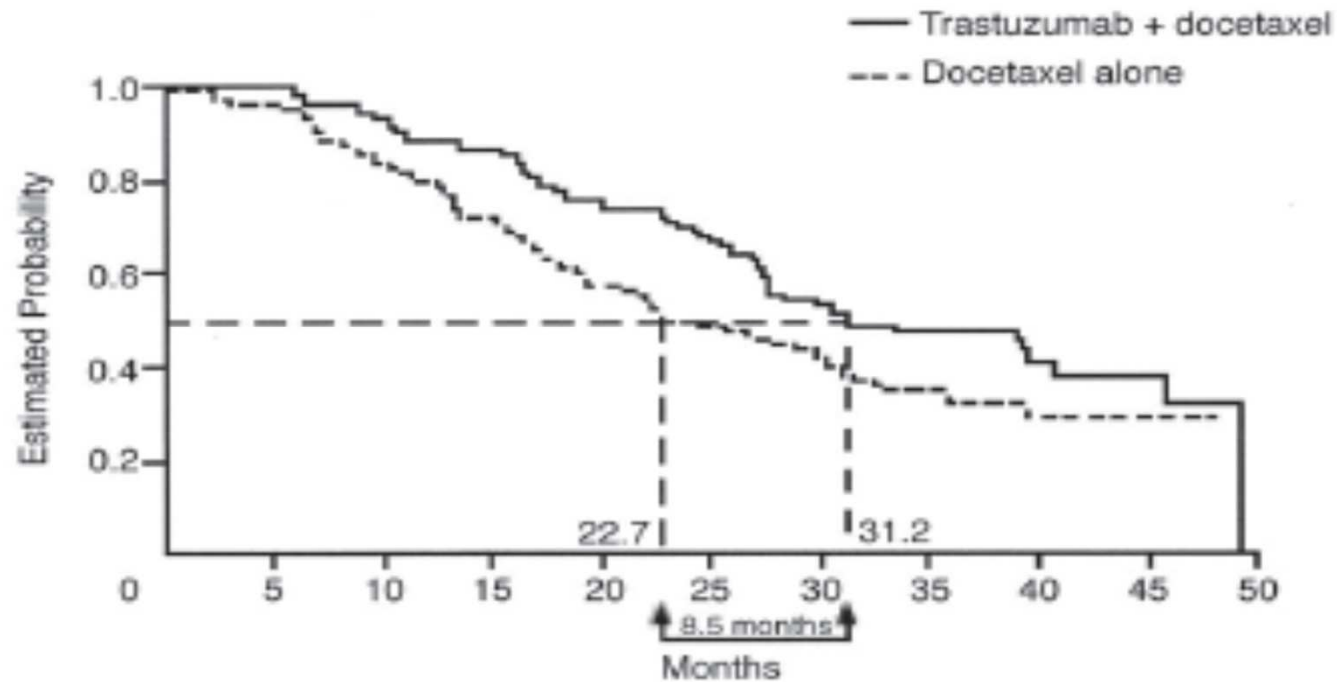


Trastuzumab (HERCEPTIN): Mechanisms of Action

Trastuzumab
binds to subdomain IV
and inhibits
downstream signalling



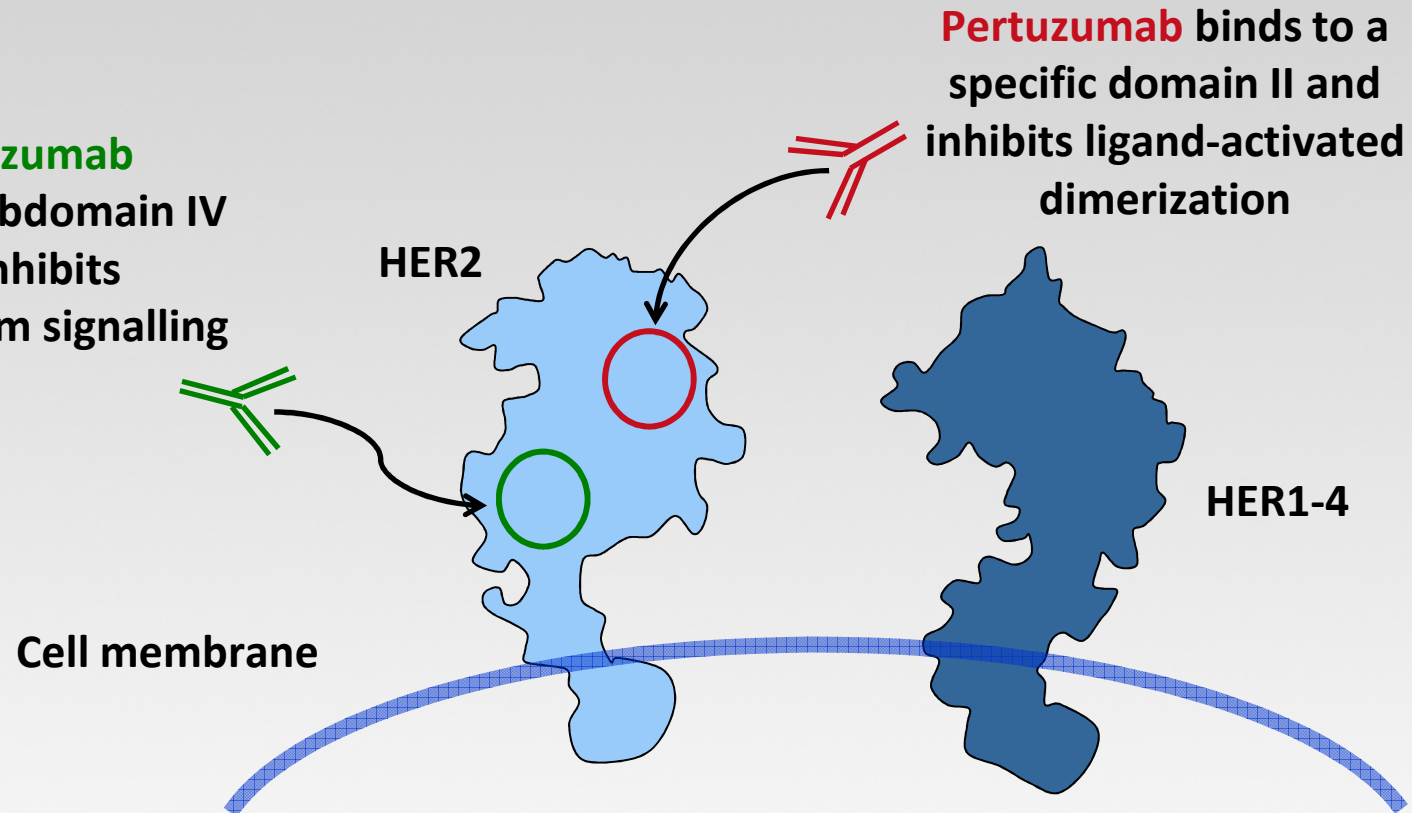
trastuzumab – 1st line of metastatic breast cancer



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

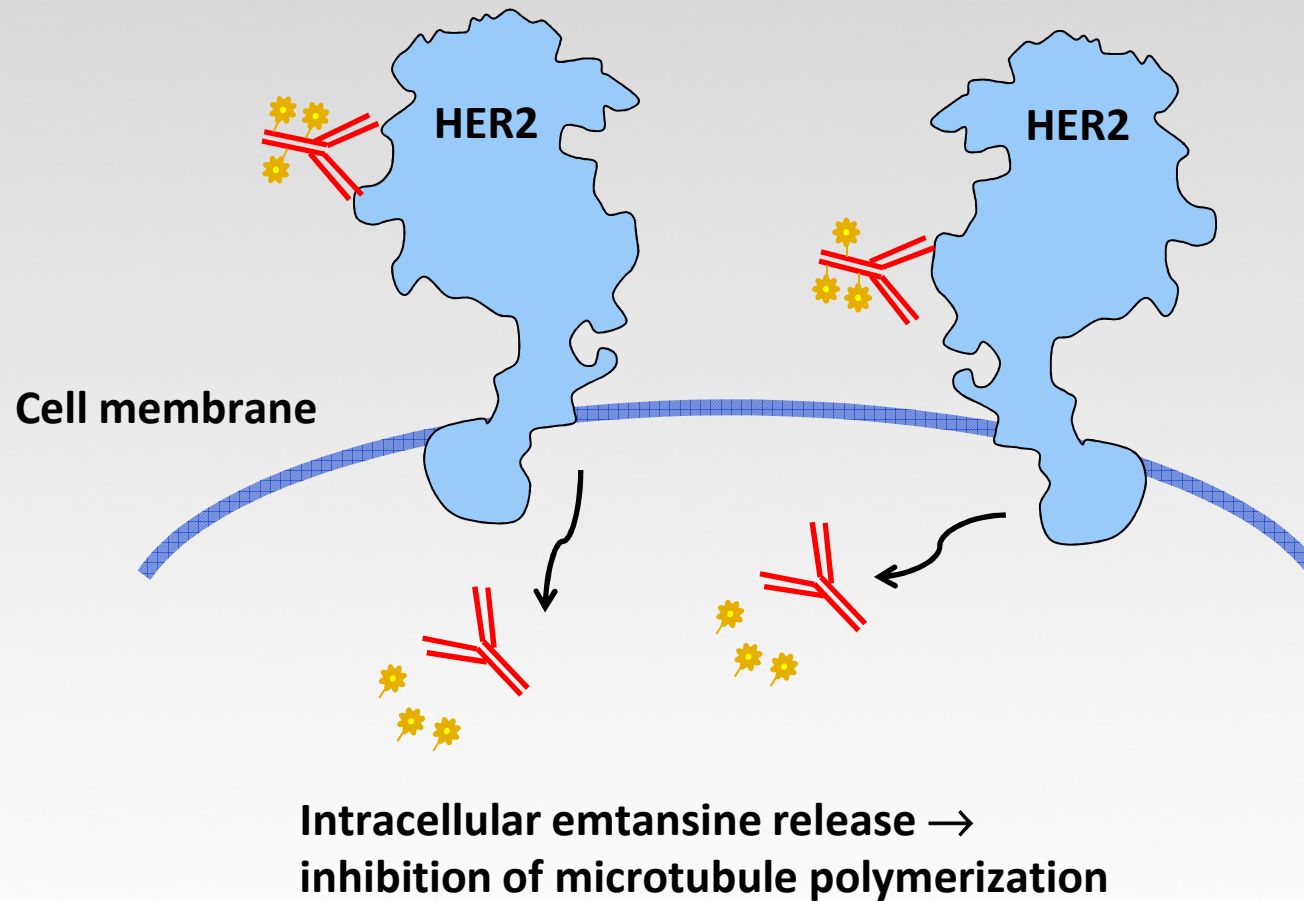
Pertuzumab (PERJETA): Mechanisms of Action

Trastuzumab
binds to subdomain IV
and inhibits
downstream signalling



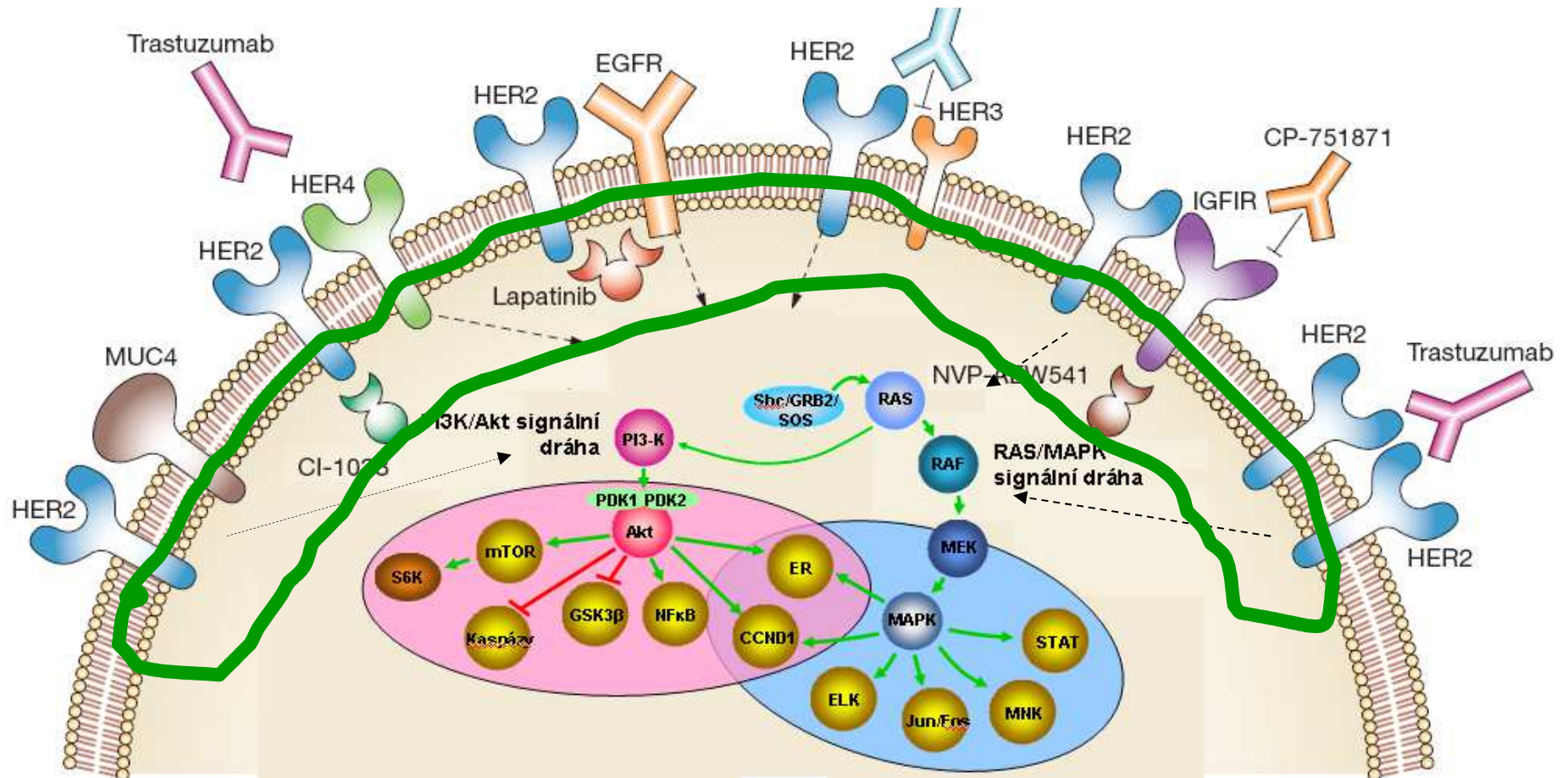
The combined regimen of pertuzumab and trastuzumab offers the potential for a more comprehensive HER blockade

T-DM1: Antibody Drug Conjugate trastuzumab + emtansin conjugate



HER-2 TARGETING – nibs

Tyrosinkinases inhibitors

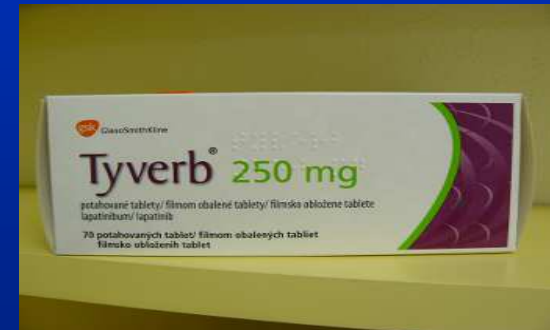
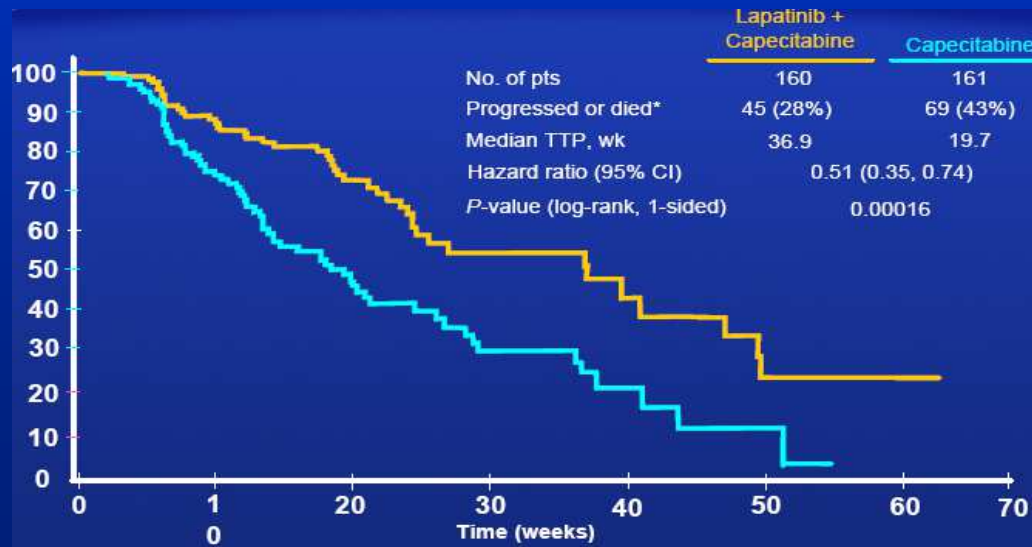


LAPATINIB (Tyverb®) – tyrosinkinase inhibitor

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

INDICATION:

Metastatic breast carcinoma after trastuzumab failure



Konecny et al, 2006, Allen et al, 2002

Authorised –mAbs

Generický název	Firemní název	„target“	indikace
bevacizumab	Avastin	VEGF	Colorectal Ca, breast Ca, NSCLC, renal ledviny
cetuximab	Erbitux	EGFR1	Colorectal Ca, H&N
panitumumab	Vectibix	EGFR1	Colorectal Ca
rituximab	Mabthera	CD20	CLL, NHL
pertuzumab	Perjeta	HER-2	Breast Ca
trastuzumab	Herceptin	HER-2	Breast Ca

Authorised - nibs

Generický název	Firemní název	Indikace
imatinib	Glivec	CML, GIST
dasatinib	Sprycel	CML, ALL
nilotinib	Tasigna	CML
gefitinib	Iressa	NSCLC
erlotinib	Tarceva	NSCLC, pankreatic Ca
lapatinib	Tyverb	Breast Ca
sorafenib	Nexavar	Renal Ca, HCC
sunitinib	Sutent	Renal Ca

Authorised - nibs

Generický název	Firemní název	Indikace
pazopanib	Votrient	Renal Ca
afatinib	Giotrif	NSCLC
bosutinib	Bosulif	CML
vemurafenib	Zelboraf	melanoma
crizotinib	Xalkori	NSCLC
regorafenib	Stivarga	Colorectal Ca
dabrafenib	Tafinlar	melanoma
everolimus	Afinitor	Renal Ca

Renal Carcinoma

- 1st line treatment – nibs (multi target)
- 2nd line treatment – mTOR inhibition

Kasuistic study – oncological patient

Mr. P.P., 68 years old patient – metastatic renal carcinoma

Primary tumor in right ren, bone metastases

Diagnostic methods we can use - „staging“ ?

Kasuistic study – oncological patient

Medical History:

- Past medical history: hypertenzion, atrial fibrilation
- Family diseases - father myocardial infarction 39 years
- Social history (medicine) - married, 2 children
- Allergies - none
- Sexual history, obstetric/gynecological history - insignificant

- What is missing?

Kasuistic study – oncological patient

Pharmacological medication:

Concor (bisoprolol 2,5 mg tbl ½ -0-0)

Pradaxa (dabigatran 150 mg tbl 1-0-1)

Mechanism of action?

Treatment options?

1. Surgery + radiotherapy
2. Chemotherapy
3. Hormonotherapy
4. Targeted therapy

1st line treatment?

1. sunitinib nebo sorafenib
2. bevacizumab
3. interferon
4. everolimus

Kasuistic study – oncological patient

- sunitinib 50 mg – route of administration ?
- half-life 25 hours – dosing ?
- main adverse effects ?

After the 3 months of the treatment:

LABS:

Sodium 142 mmol/l, Potassium 3,6 mmol/l, Chlorides 103 mmol/l,
Urea 3,8 mmol/l, Kreatinin 80 μ mol/l, Leucocytes 3,1 10^9 /l, Hb 130
g/l,

Performance status (PS) :0 BP 165/105

ECHOKARDIOGRAPHY: EF LV 85%, without changes

Abnormal results?

1. natrium
2. potassium
3. chlorides
4. urea
5. kreatinin
6. leukocytes
7. hemoglobin
8. PS
9. BP
10. ECHO

Kasuistic study – oncological patient

- Next control labs – timing ?
- BP
- Leukocytes
- Next oncological follow-up ?

Kasuistic study – oncological patient

- According to CT – progression of the disease, progression of the primary tumor and bone metastases
- Next treatment strategy ?

2nd line teratment ?

1. chemotherapy
2. interferon
3. targeted therapy

Kasuistic study – oncological patient

mTOR inhibitor ?

Generic name ? Trade name ?

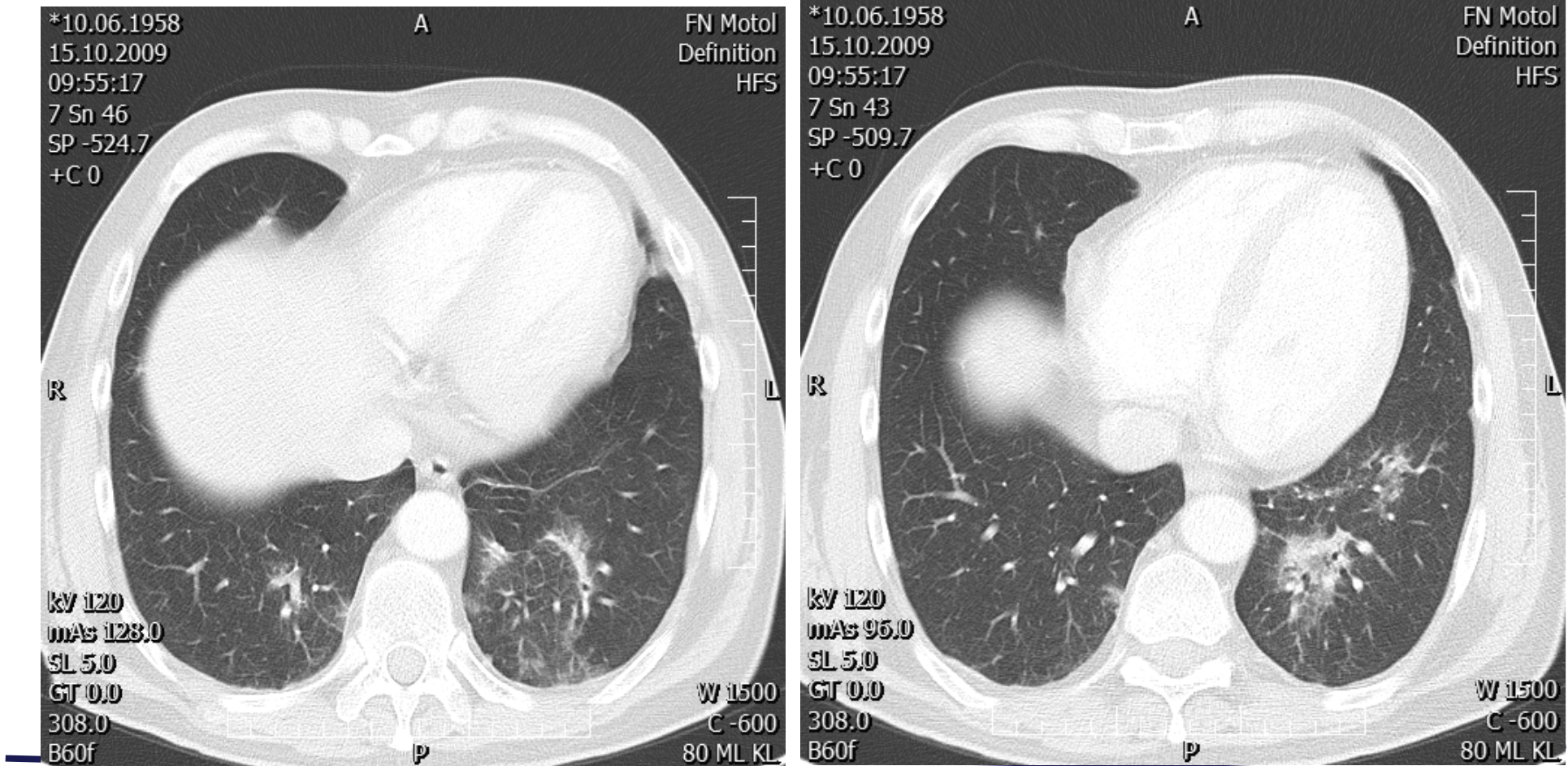
Mechanism of action ?

Kasuistic study – oncological patient

- everolimus 10 mg p.o.

- Cough and deterioration of breath
- Diferential diagnoses ?
- Evaluations ?

Interstitial pneumonitis (non-infectious etiology)



Next steps ?

1. Stop Afinitor treatment
2. Decreasing of the dose Afinitor
3. Interruption of the Afinitor +
corticotherapy

Kasuistic study – oncological patient

1. Interruption of the Afinitor + corticotherapy

- glucocorticoids ?

Relative potencies of adrenal steroids

1. hydrocortisone
2. triamcinolon
3. dexamethazon

Relative potencies of adrenal steroids – anti-inflammatory effect

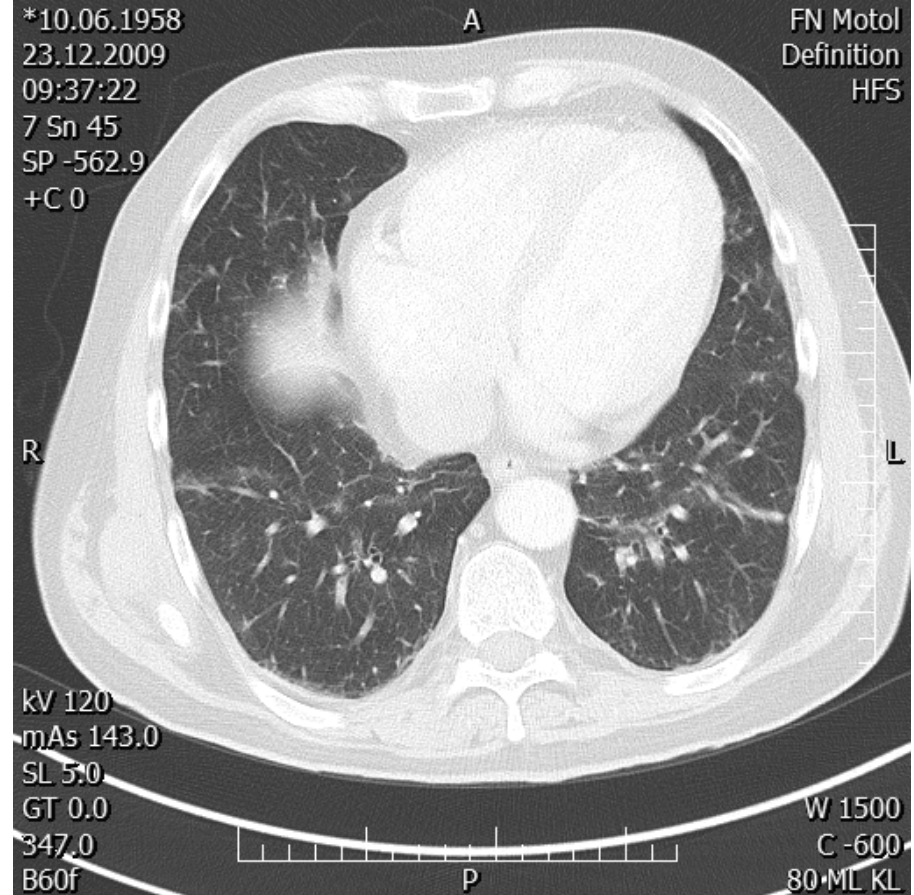
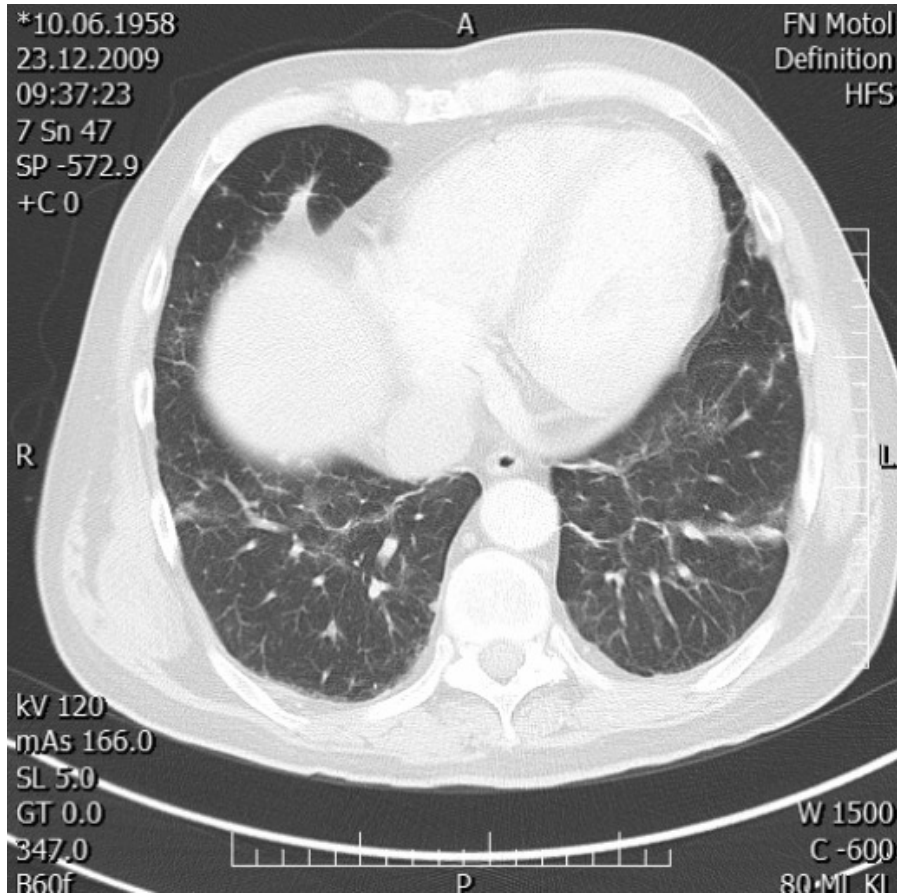
1. Hydrocortisone – 1 (20 mg)
2. Triamcinolon – 5 (4 mg)
3. Dexamethazon – 30 (0,75 mg)

Kasuistic study – oncological patient

Prednison 60 mg orally

- After the month ad integrum / how we can stop the corticosteroids ?
- Reinitiation Afinitor 5 mg p.o.

Interstitial pneumonitis – after the treatment



Next 3 months of the Afinitor treatment...

- Everolimus 5 mg denně

Labs before mTOR

TG 2,41 mmol/l (0,7-1,7) LDL- chol 4.35 mmol/l glu 5.4 mmol/l

Labs after 3 months treatment

- **TG 45,9 mmol/l glu 15,7 – asymptomatic**

Therapy interruption

Kasuistic study – oncological patient

- After one week TG:15,7 mmol/l
- Hypolipidemics
- Oral antidiabetics ? Primary monotherapy for overweight patients?
- After two weeks: TG 4.11mmol/l , gly 5,6 mmol/l

Kasuistic study – oncological patient

- After 3 months the porgression according to RECIST criteria
- Treatment with Afinitor was stopped
- Only symptomatic treatment - ?

Progression of pain....

During the period without treatment there was progression of spinal pain to the left leg. Scale of pain: grade 9 (maximum of 10). Bone metastases in the segment L5.

Pain treatment ?

Next steps....?

1. Non-opioid analgetics + co-analgetics
2. Opioids
3. Radiotherapy

Opioid analgetics

Mechanism of action ?

Pharmacodynamic differences ?

Main drugs ?

Main adverse effects?

Next lecture.....

22.3.2016

Pharmacotherapy of patients with ischemic coronary heart disease and acute coronary syndrome