Clinical and Genetic Epidemiology Winter School

15.02.2017

Pharmacogenomics

Part 2 – PGx of Cancer

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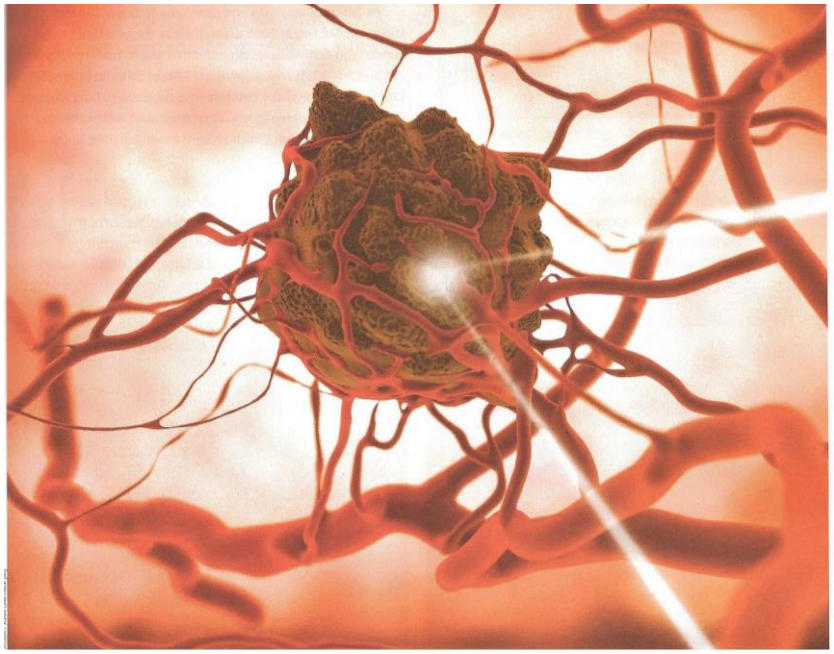
University Hospital Schleswig-Holstein, Campus Kiel
Institute of Experimental and Clinical Pharmacology

The term

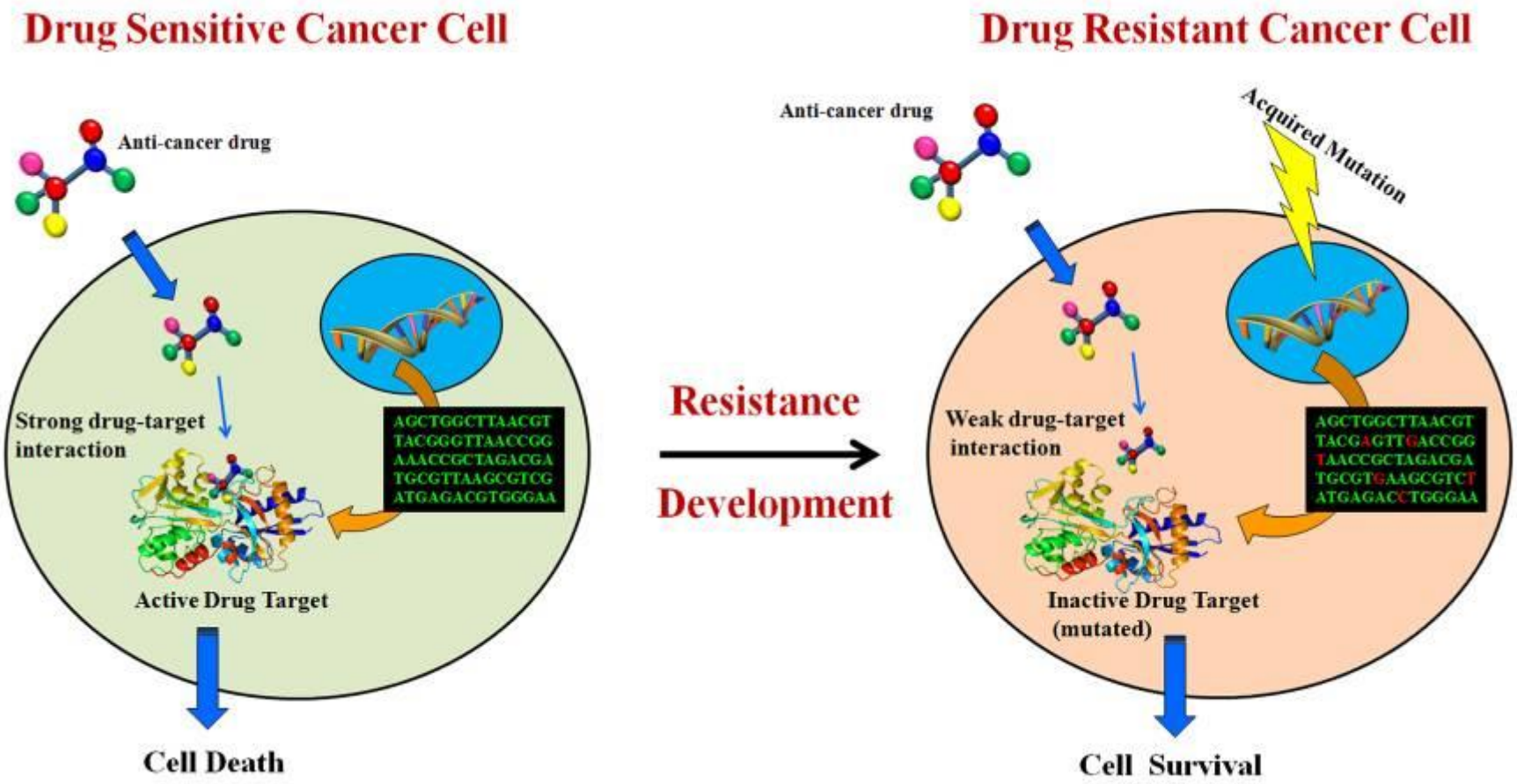
“resistance”

is often known from the treatment of bacteria

What is chemoresistance in cancer?



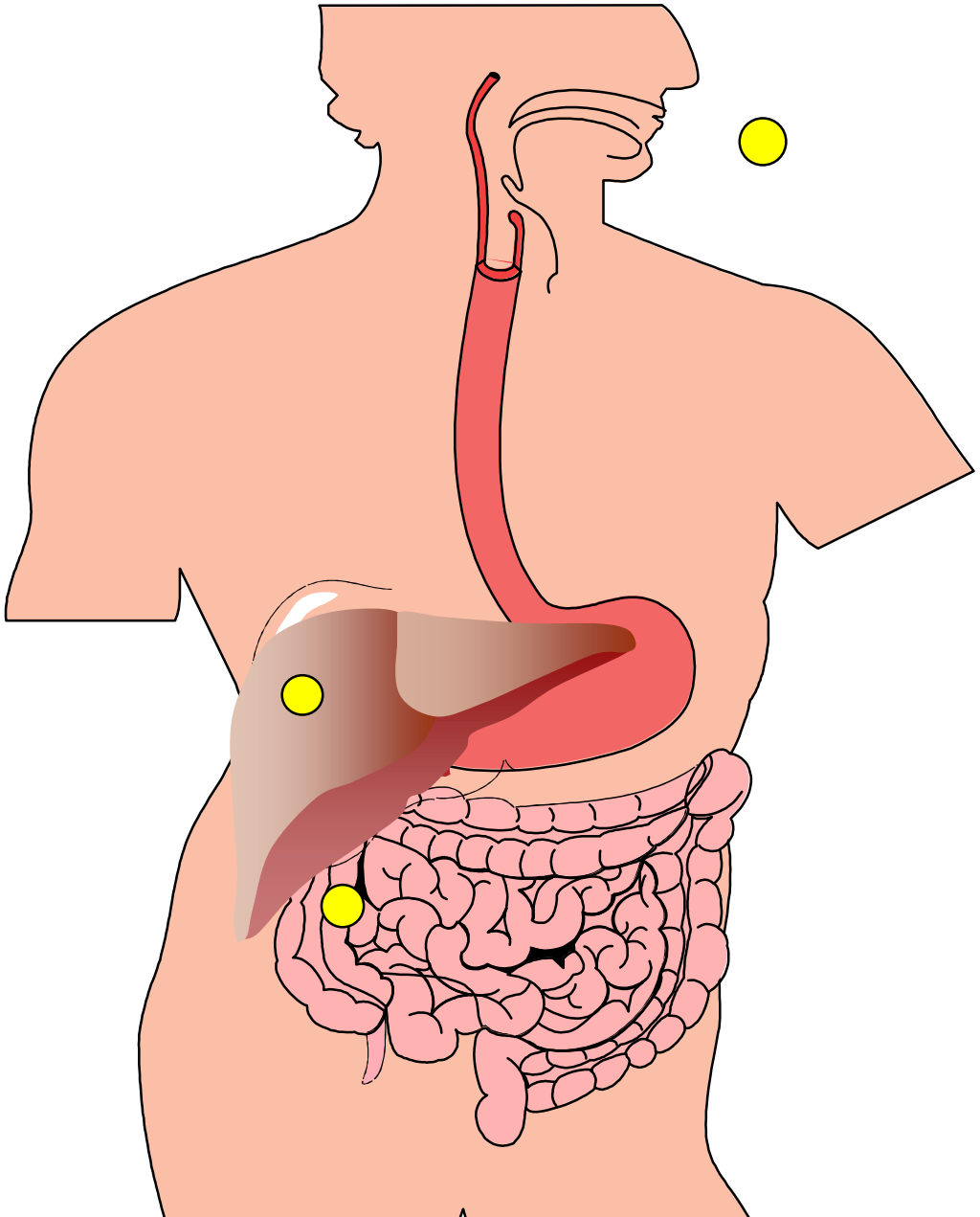
Causes of chemotherapy resistance in cancer

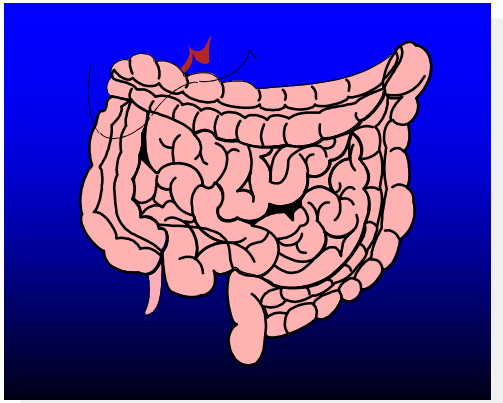


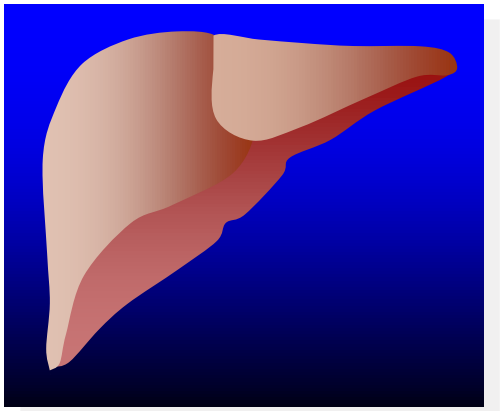
Causes of chemotherapy resistance in cancer

- Primary resistance: Tumor type is insensitive to anti-tumor agent
- The anti-cancer drug is non-specific (damage of healthy tissue, severe adverse effects)
- Secondary resistance: Tumor cells develop resistance (e.g. new mutation in kinase-pathways, over-epression of efflux-transporters)
- Failure of activation of pro-drugs

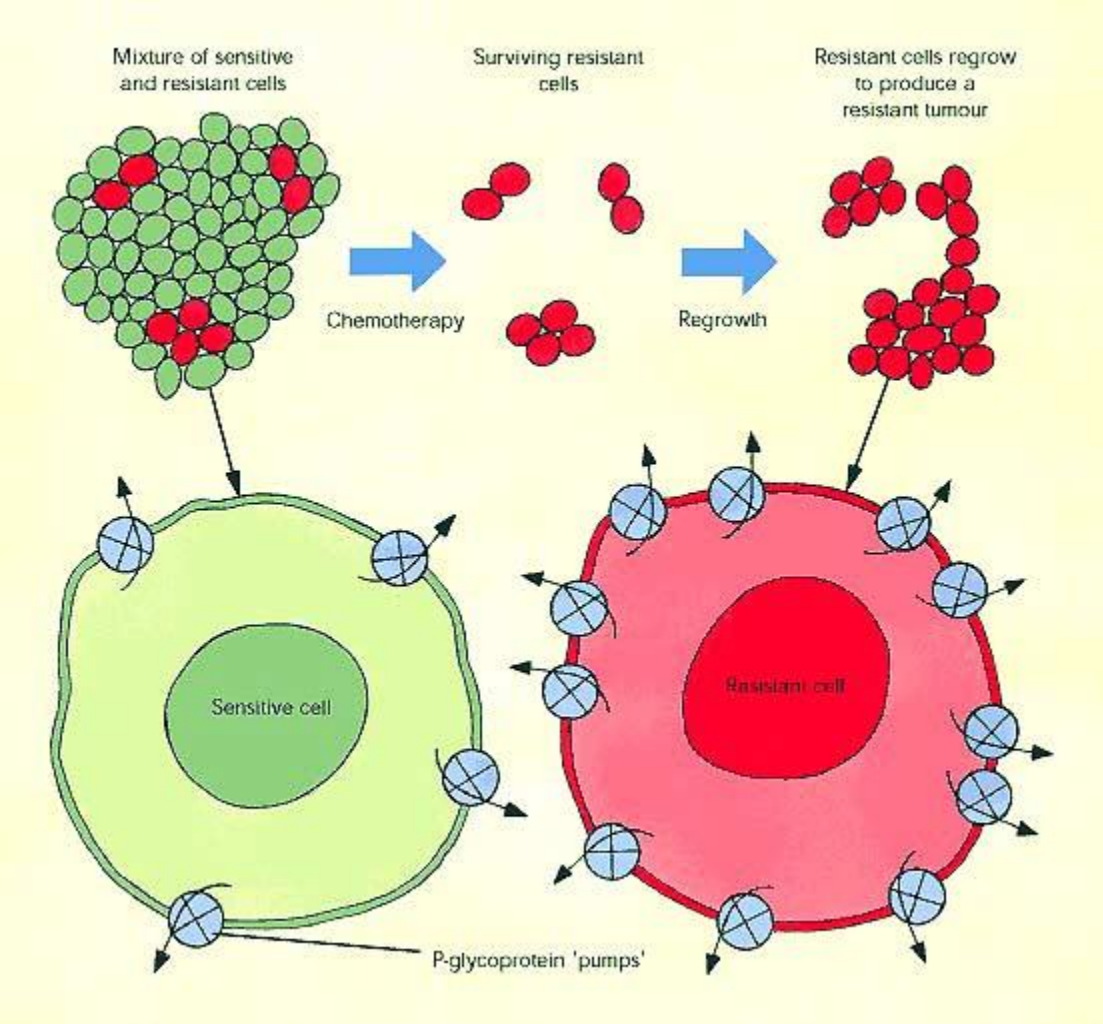
Drug Transport



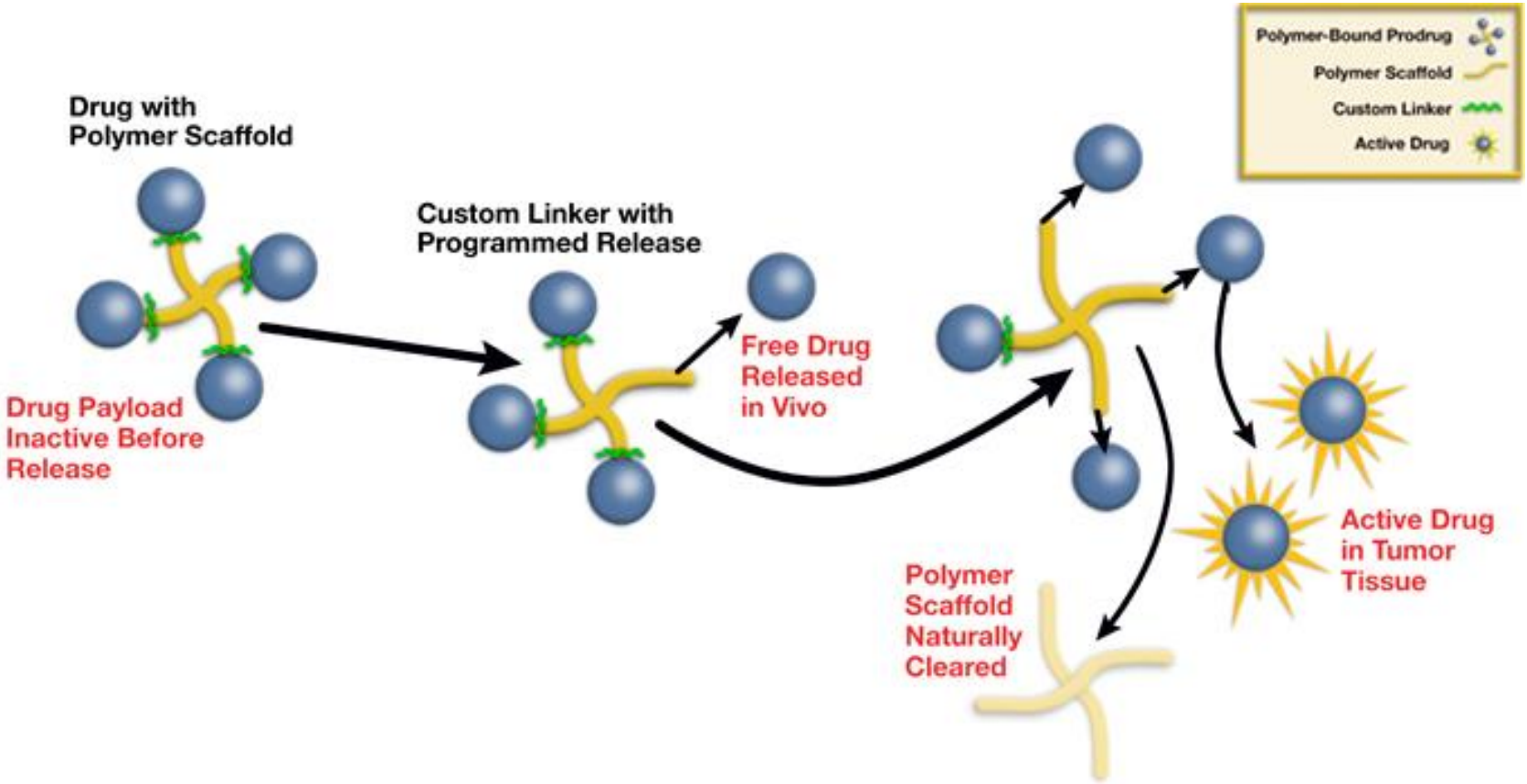




Tumor cells often overexpress efflux pumps

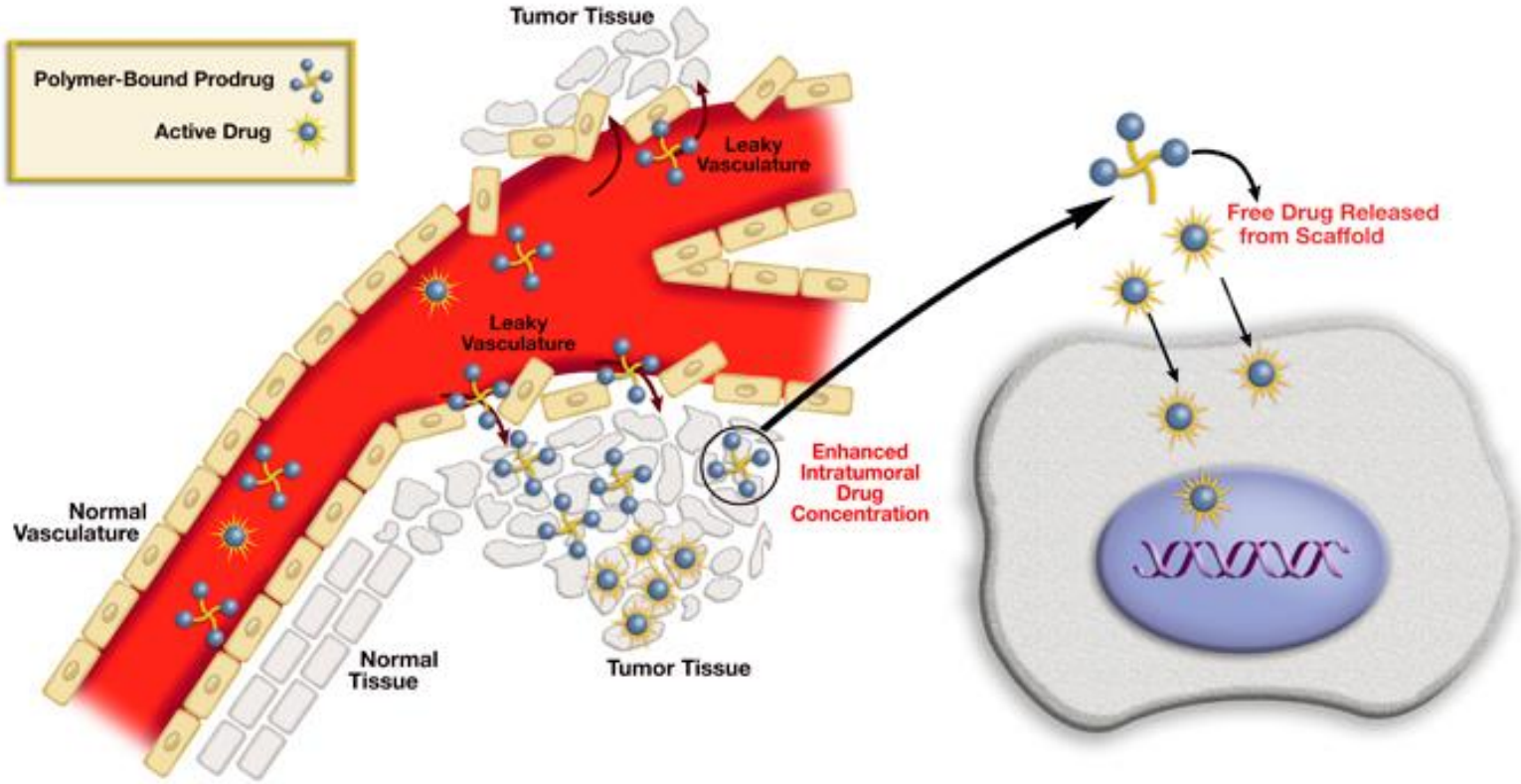


How to enhance the drug-concentration in tumor cells?

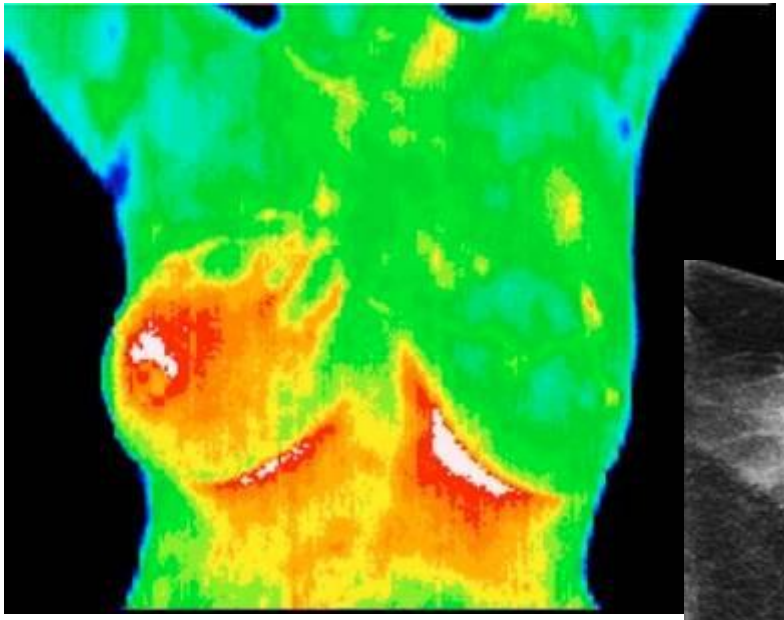


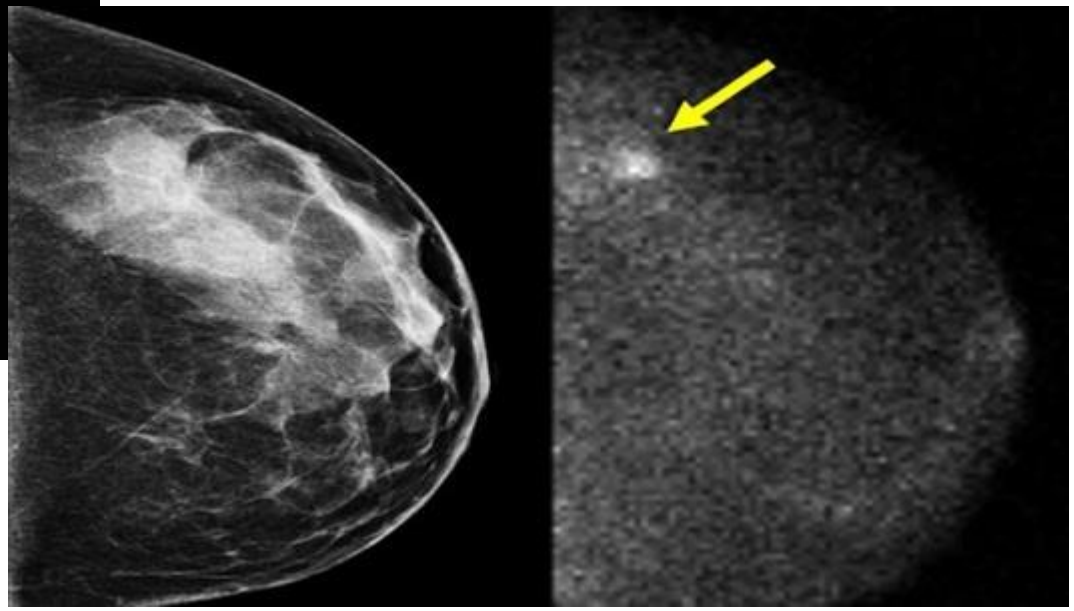
Eldon et. al. AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, October 2007.

Accumulation of active drug in tumor tissue



Eldon et. al. AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, October 2007.





Breast cancer

- Breast cancer is the most common invasive cancer in women
- Breast cancer comprises 22.9% of invasive cancers in women and 16% of all female cancers

Source: Wikipedia

Chemotherapeutics in breast cancer

Neoadjuvant chemotherapy (in estrogen/gestagen receptor positive tumors)

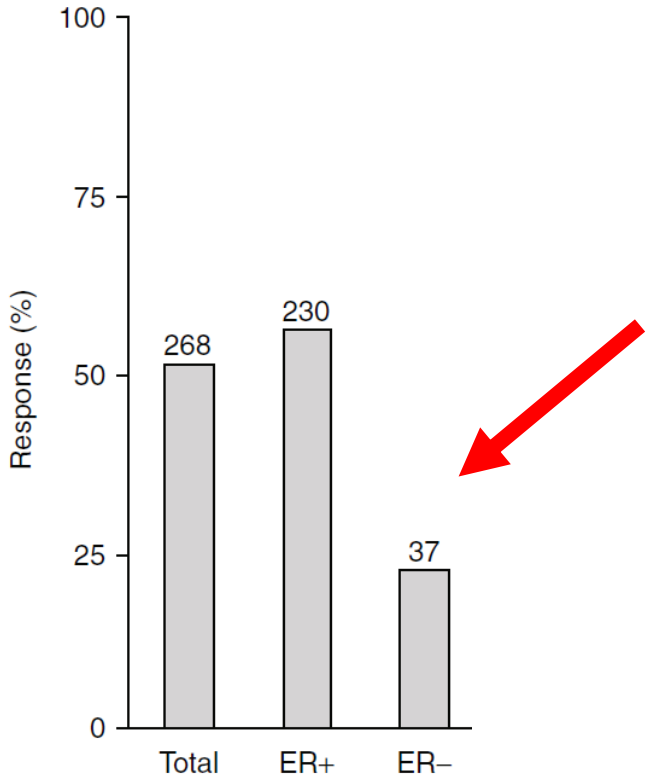
Antiestrogens	Tamoxifen
	Aromatase inhibitors

Adjuvant chemtherapy (in estrogen/gestagen receptor negative tumors)

Toposisomerase inhibitors	Anthracyclin
Mitotic inhibitors	Taxan (Docetaxel, Paclitaxel)
HER2 inhibitor	Trastuzumab

Tamoxifen inhibits the estrogen receptor

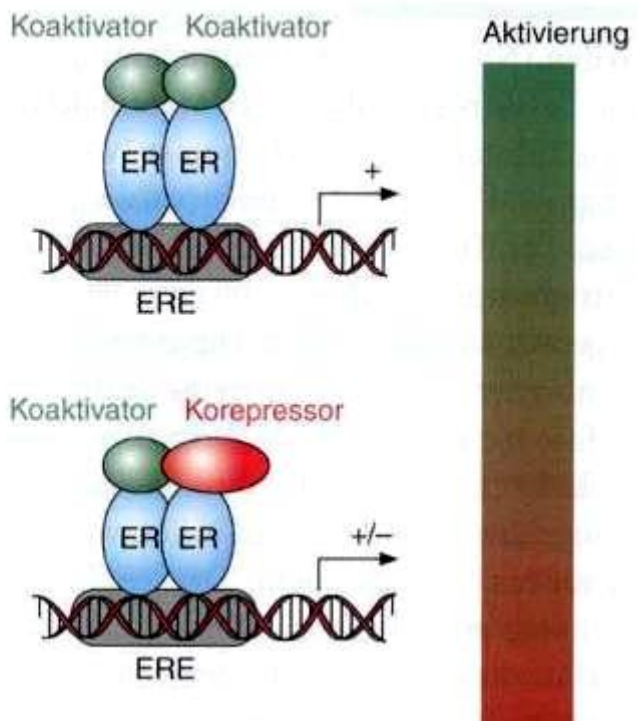
Therapy response to tamoxifen



Activation / Tumor cell progression

Estrogen

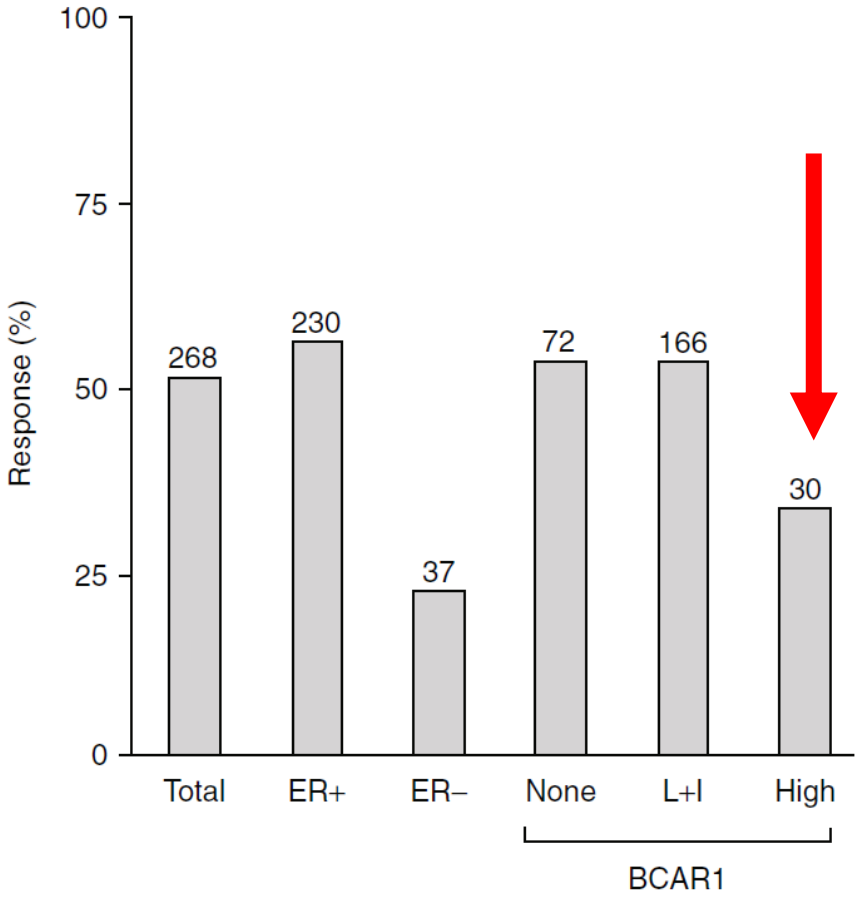
Tamoxifen



Partly inhibition / Tumor cell suppression

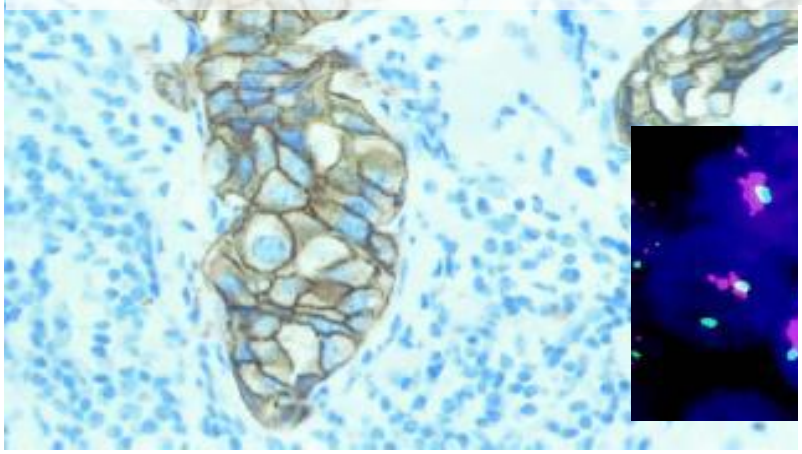
Tamoxifen effects a diminished by BCAR (breast cancer antiestrogen receptor) gene over-expression

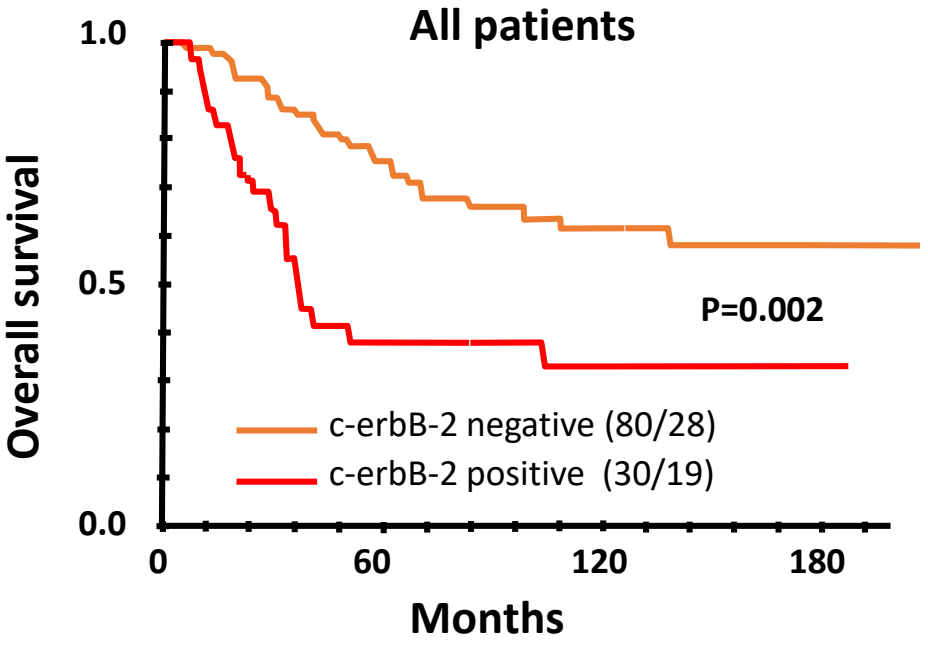
Therapy response to tamoxifen



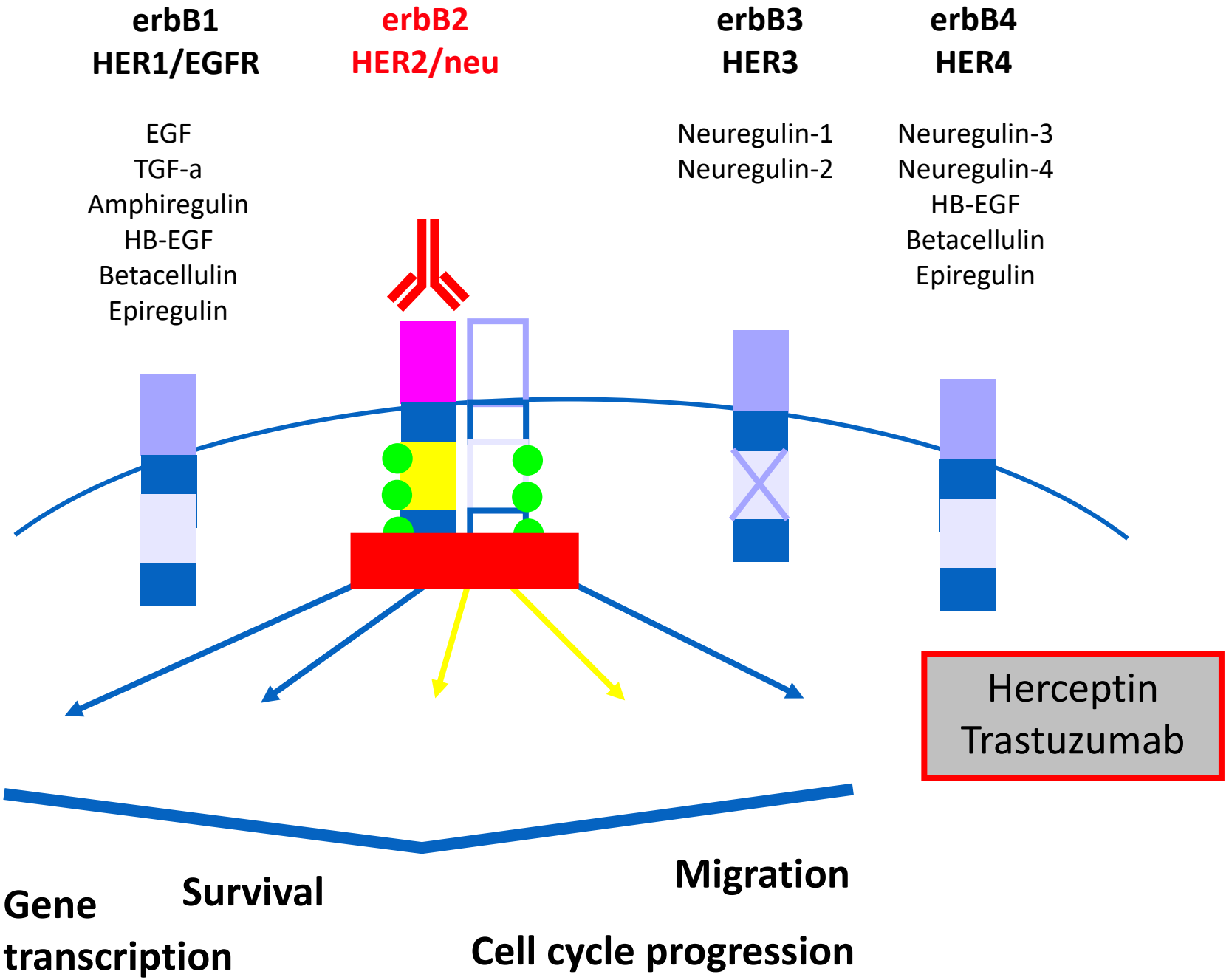
HER2 overexpression diminishes tamoxifen response

25-30% of breast tumor specimens show amplification/overexpression of erbB2/HER2/neu

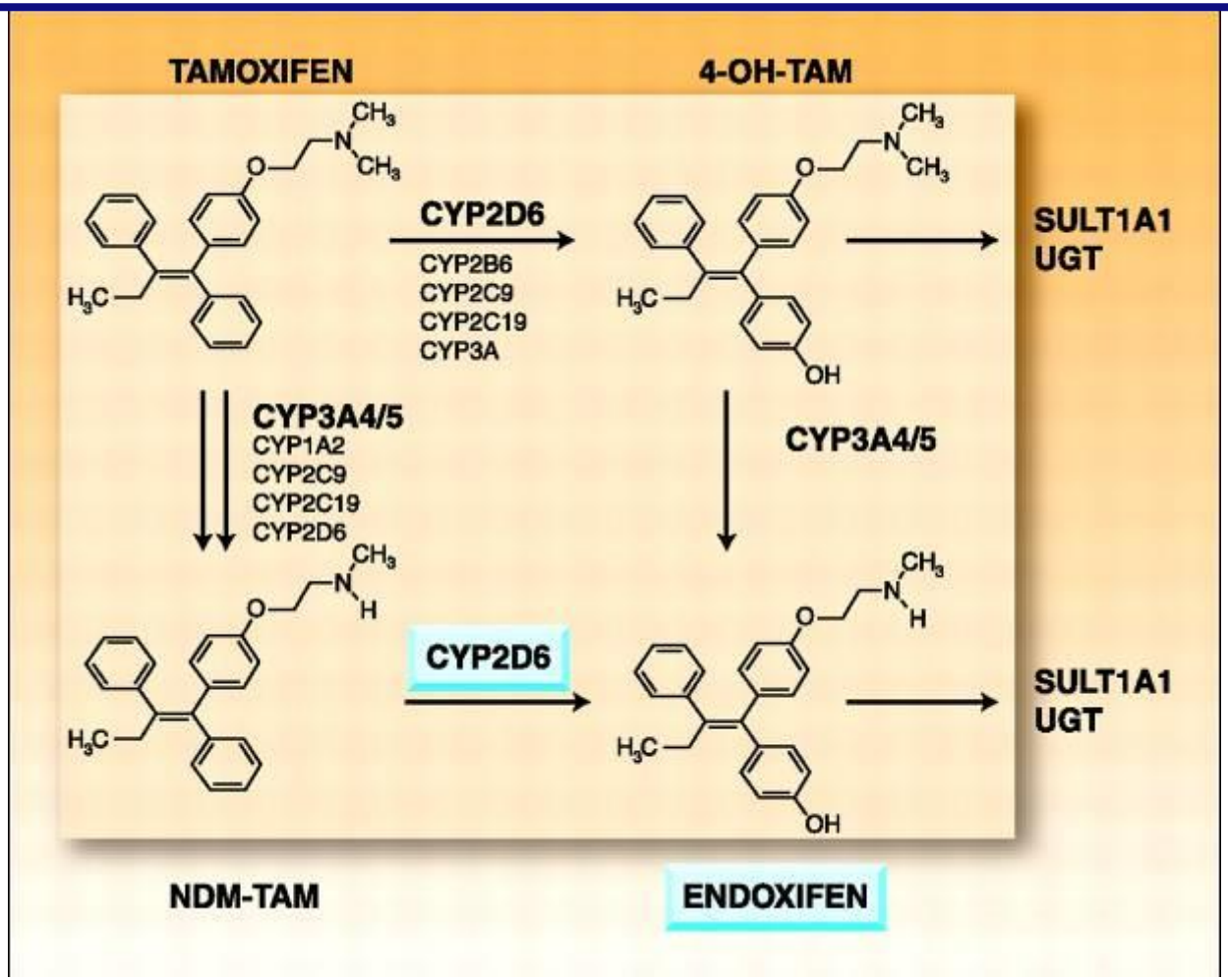




Agrup et al. Breast Cancer Res Treat 2000

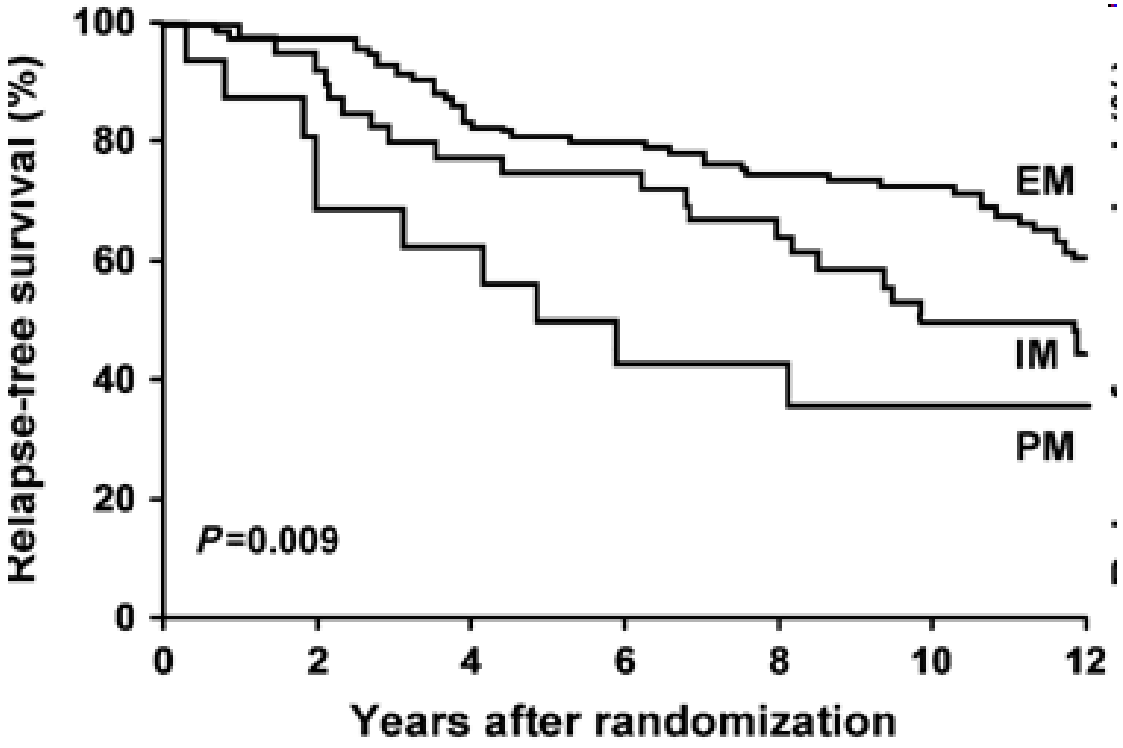

erbB1
HER1/EGFR
erbB2
HER2/neu
erbB3
HER3
erbB4
HER4
EGF
TGF-a
Amphiregulin
HB-EGF
Betacellulin
Epiregulin
Neuregulin-1
Neuregulin-2
Neuregulin-3
Neuregulin-4
HB-EGF
Betacellulin
Epiregulin
Herceptin
Trastuzumab
Gene transcription
Survival
Migration
Cell cycle progression

Metabolic activation of tamoxifen



Dezentje, V. O. et al. Clin Cancer Res 2009;15:15-21

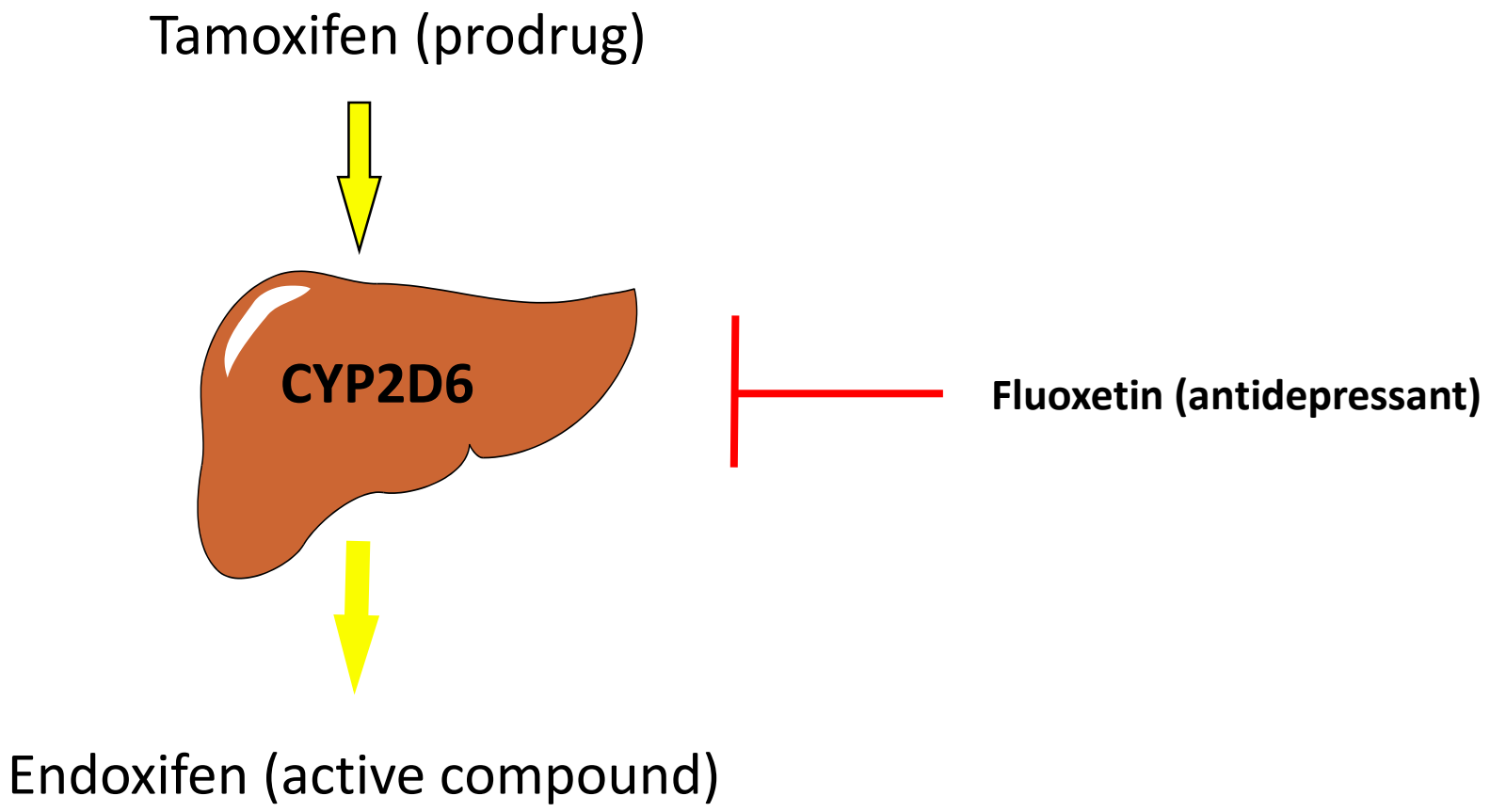
Impact of *CYP2D6* on clinical outcome of tamoxifen treatment in breast cancer



Kaplan–Meier estimates of RFS based on metabolizer status (extensive, intermediate, or poor).

Goetz et al. Breast Cancer Res. Treat. 2007; 101:113–121

Antidepressants can compromise the response to tamoxifen



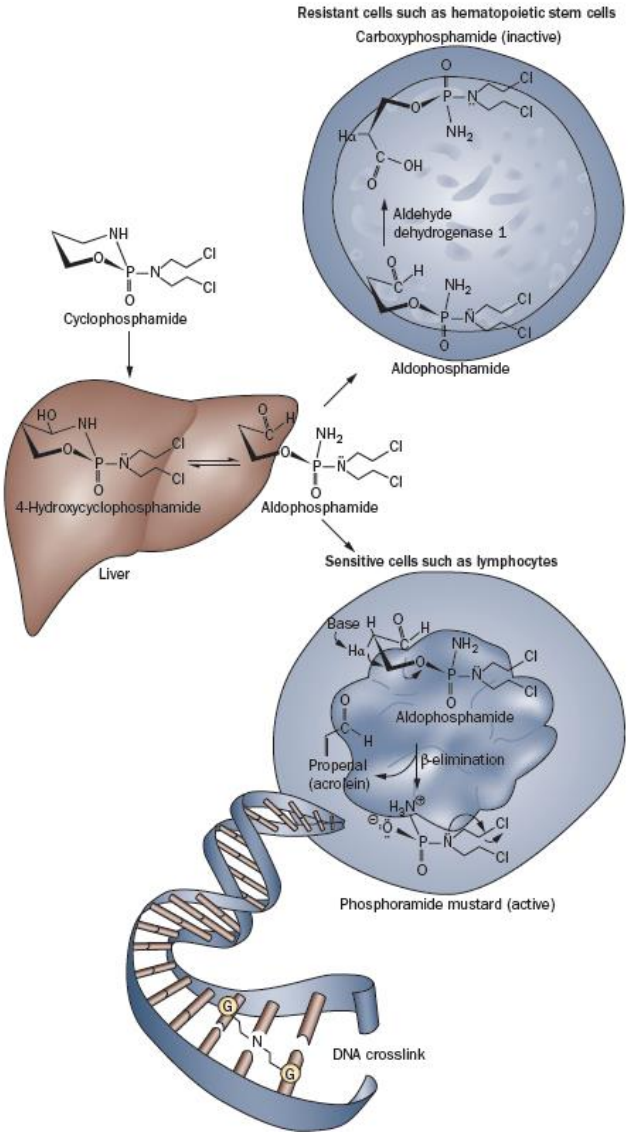
Impact of polymorphic drug-metabolizing enzymes in cancer treatment

Enzyme	Drug	Poor metabolizers	Relevance
CYP2D6	Tamoxifen	7-10%	high
CYP2C19	**Cyclophosphamide**	**3-5%**	
DPD	5-Fluorouracil	<1%	
TPMT	Azathioprine, 6-MP	0.6%	
UGT1A1	Irinotecan	10-15%	

Cyclophosphamide

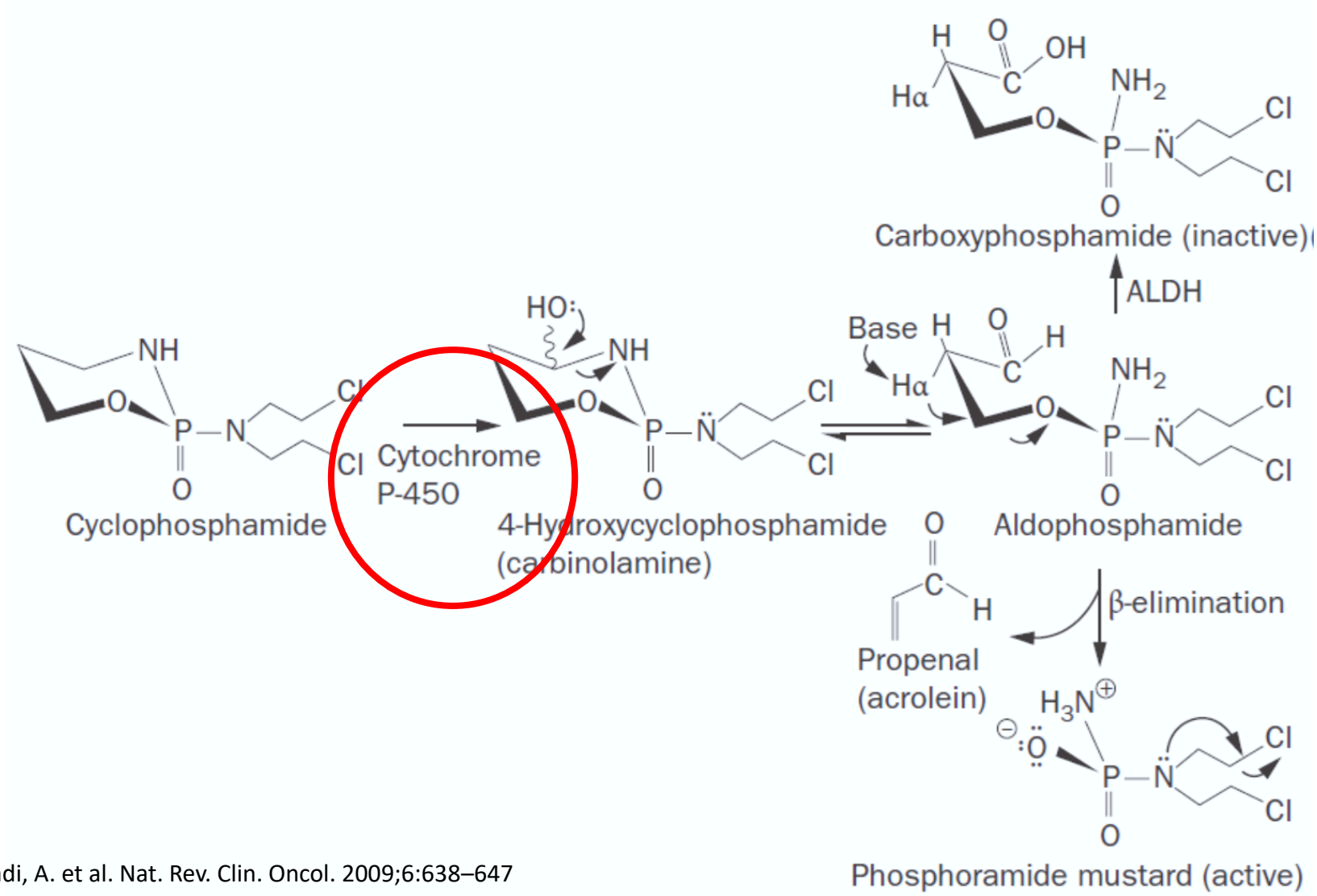
Cytotoxic agent

The activated compound reacts with DNA and forms „adducts“



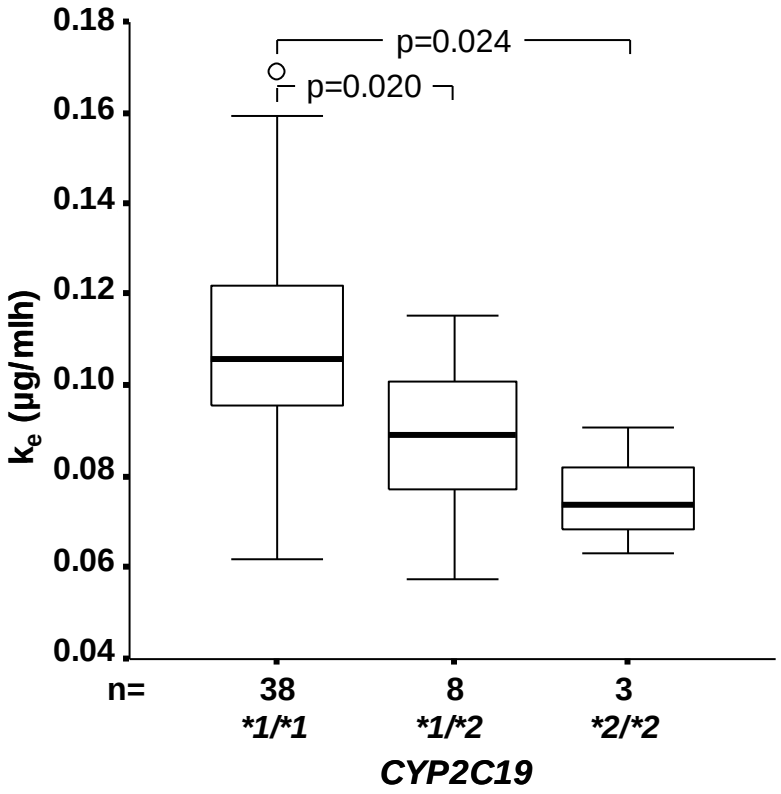
Emadi, A. et al. Nat. Rev. Clin. Oncol. 2009;6:638–647

Bioactivation and metabolism of cyclophosphamide



Emadi, A. et al. Nat. Rev. Clin. Oncol. 2009;6:638–647

Cyclophosphamide elimination in NHL-patients, excluding high-dose therapy (< 1000 mg/ m²).

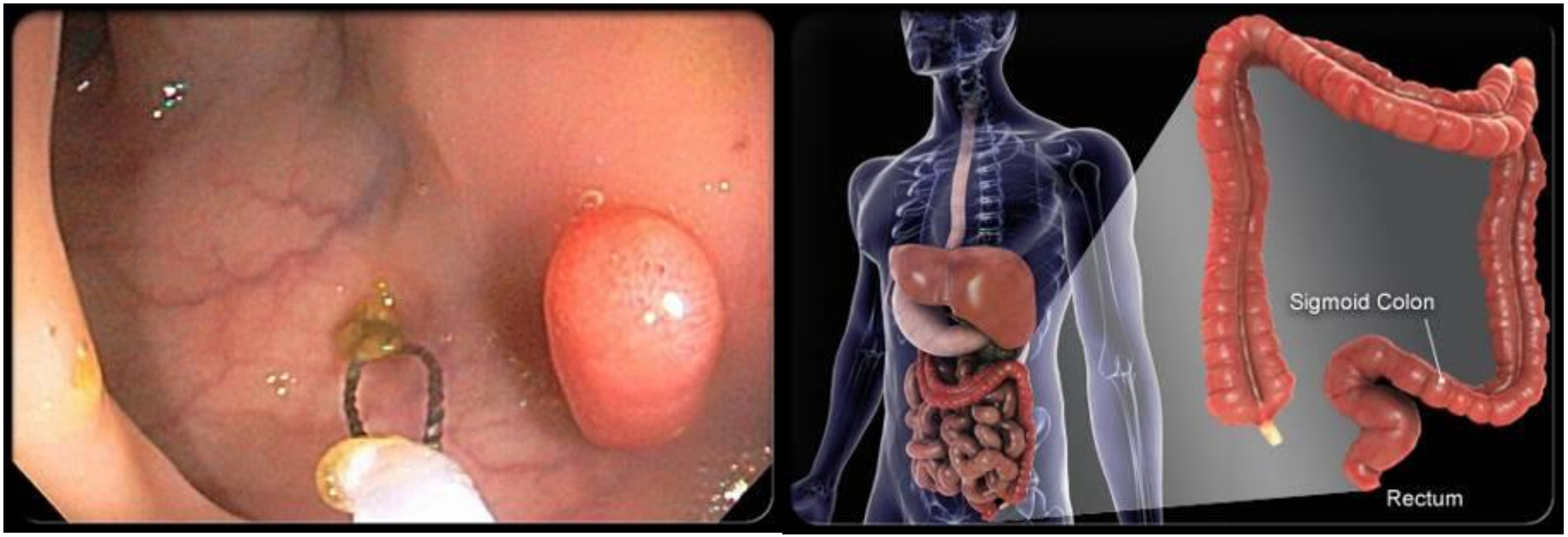


Timm et al. Pharmacogenomics J. 2005;5:365-73.

Association of total leukocyte count at 10th post chemotherapy day to DME genotypes

Gene	Genotype	Number (%)		p^a
		≤2,500 mm^{-3}	>2,500 mm^{-3}	
CYP2B6	**1/*1 *1/variant*	19 (73.1)	30 (83.3)	0.33
	variant/variant	7 (26.9)	6 (16.7)	
CYP2C9	**1/*1*	20 (71.4)	25 (64.1)	0.53
	**1/*2, *1/*3, **2/*3, *3/*3*	8 (28.6)	14 (35.9)	
CYP2C19	**1/*1*	13 (46.4)	26 (66.7)	0.10
	**1/*2 + *2/*2*	15 (53.6)	13 (33.3)	
CYP3A5	**1/*1 + *1/*3*	14 (50)	14 (38.9)	0.37
	**3/*3*	14 (50)	23 (61.1)	
ALDH3A1	**1/*1*	3 (10.7)	7 (17.9)	0.42
	**1/*2 + *2/*2*	25 (89.3)	32 (82.1)	
	**1/*1 + *1/*2*	15 (53.6)	25 (64.1)	0.39
	**2/*2*	13 (46.4)	14 (35.9)	
GSTA1 -69/-52	**A/*A*	17 (60.7)	10 (25.6)	0.004
	**A/*B + *B/*B*	11 (39.3)	29 (74.4)	

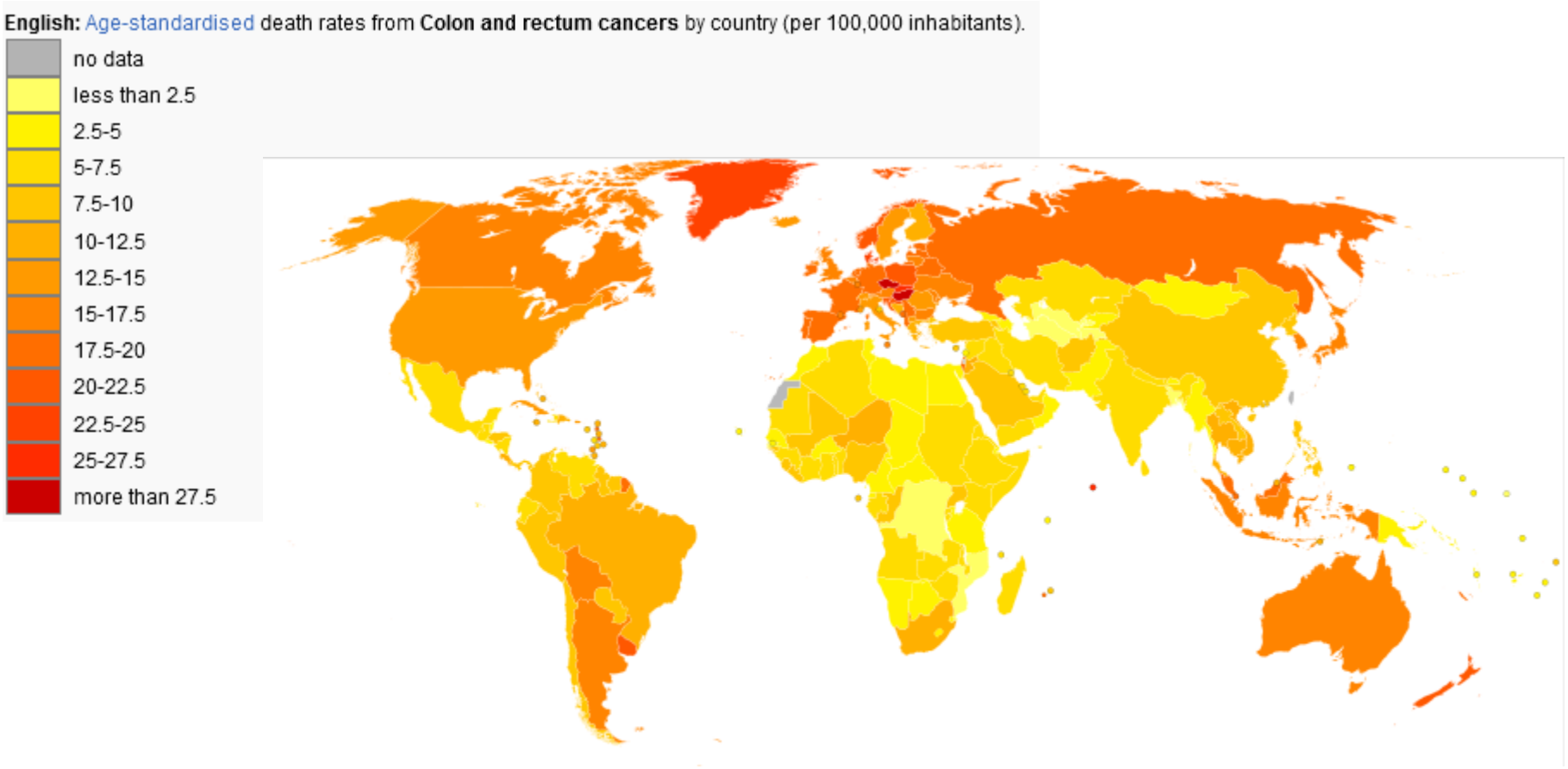
Afsar *et al.* Eur J Clin Pharmacol 2012;68:389–395



Colorectal cancer

- Second most common cause of cancer in women
- third most common in men

Source: MedicineNet.com



Colorectal cancer

Globally incidences vary 10-fold with highest rates in the Australia, New Zealand, Europe and the US and lowest rates in Africa and South-Central Asia.

Source: Wikipedia

nature medicine

A colorectal cancer classification system that associates cellular phenotype and responses to therapy

Anguraj Sadanandam[1,2], Costas A Lyssiotis[3,4,14,15], Krisztian Homicsko[2,5,15], Eric A Collisson[6], William J Gibb[7], Stephan Wullschleger[2], Liliane C Gonzalez Ostos[2], William A Lannon[3,14], Carsten Grotzinger[8], Maguy Del Rio[9], Benoit Lhermitte[10], Adam B Olshen[11,12], Bertram Wiedenmann[8], Lewis C Cantley[3,4,14], Joe W Gray[13] & Douglas Hanahan[2]

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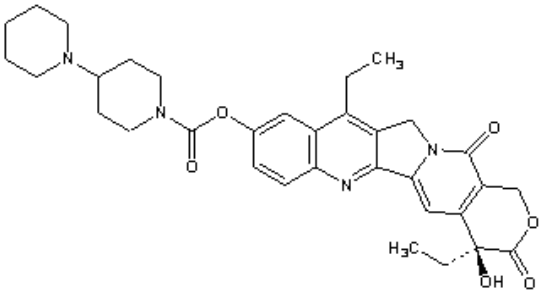
Chemotherapeutics in colorectal cancer

Thymidilate synthase inhibitor	5-Fluorouracil / Capecinabine
Topoisomerase inhibitor	**Irinotecan / SN-38**
DNA crosslinks	Oxaliplatine
VEGF inhibitor	Bevacizumab
EGFR inhibitors	Cetuximab, gefitinib

Irinotecan pathway



Blood

Neutropenia

Irinotecan

CES2

CES1

BCHE

SN-38

Cell Membrane

Liver

Cell Death

CDC45L

TDP1

NFKB1

XRCC1

ADPRT

TOP1

Cancer Cell

Irinotecan

BCHE

CES1

CES2

SN-38

UGT1A1

UGT1A3

UGT1A8

UGT1A4

UGT1A9

UGT1A6

UGT1A10

SN-38G

ABCC2

ABCB1

ABCC2

ABCB1

ABCC2

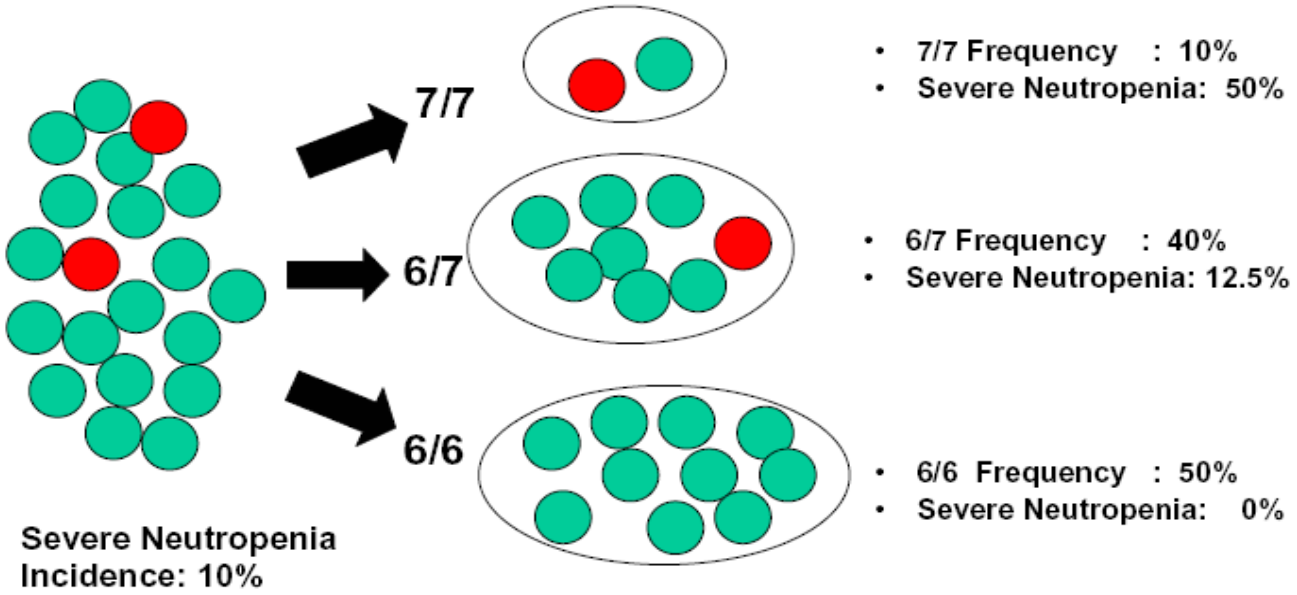
ABCG2

Bile

www.pharmgkb.org

Frequency of neuropenia dependent on UGT1A1 genotype

Innocenti (2004) study population (N=66),
Campto single agent (350mg/m²)



adapted from Parodi 2005

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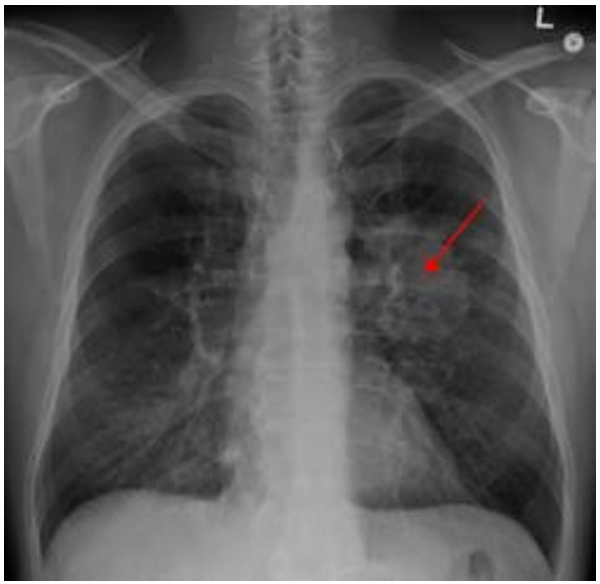
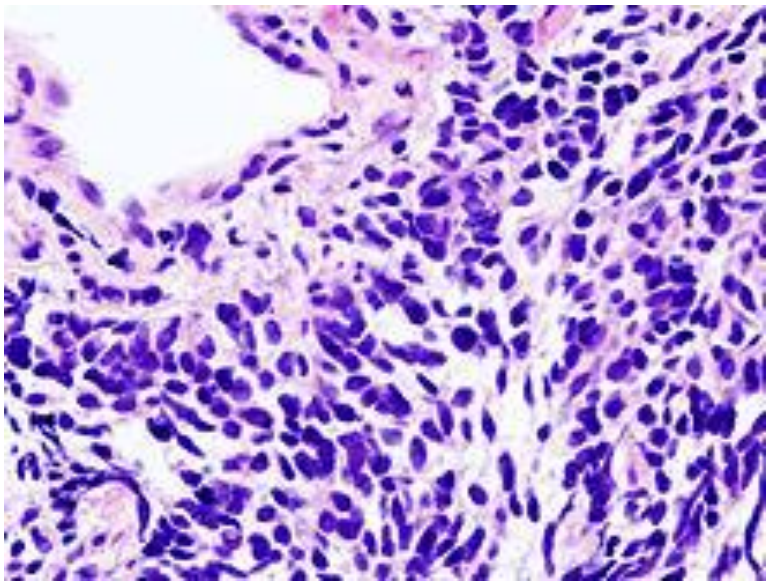


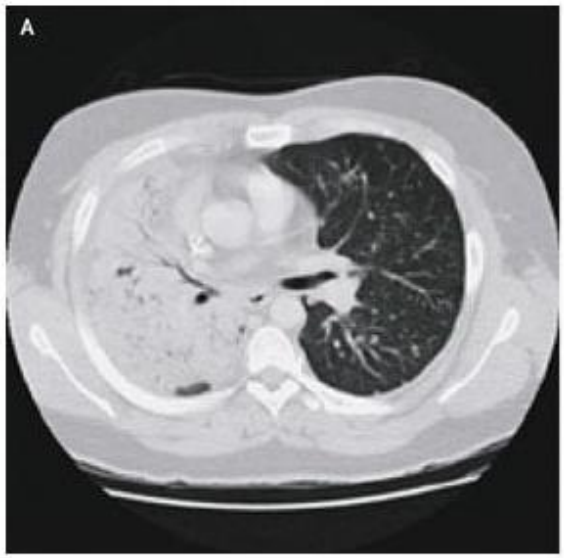


Lung cancer

- Worldwide, lung cancer is the most common cancer among men in terms of both incidence and mortality
- Third highest incidence of cancer in women

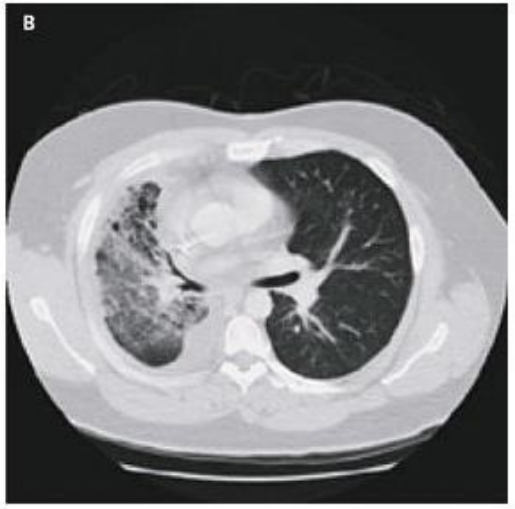
Source: Wikipedia

Impact of pharmacogenetics to the treatment of lung cancer



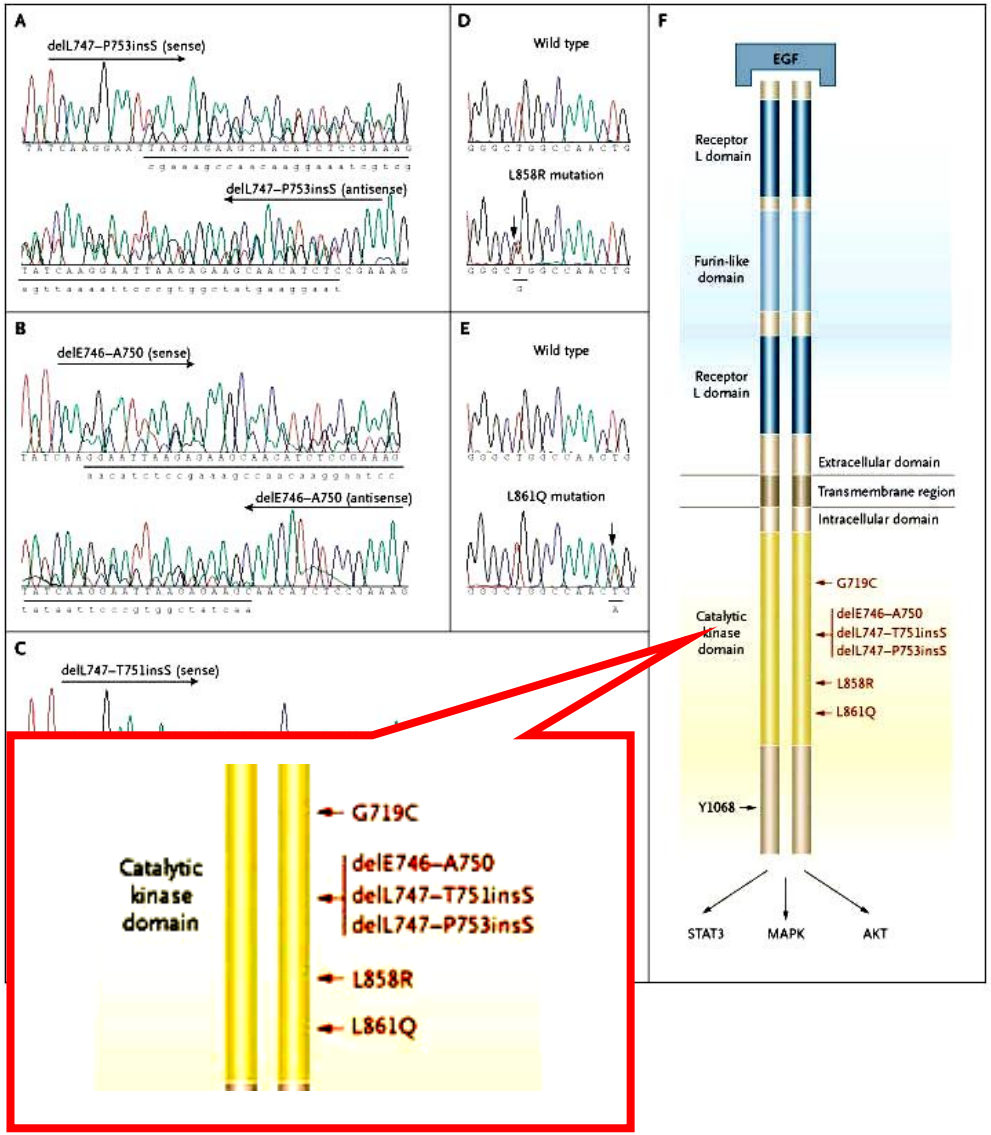
More than 90% of non-small cell lung carcinoma patients do not profit from the tyrosine-kinase inhibitor gefitinib, an EGF1-receptor antagonist.

10% demonstrate a rapid, sometimes drastic clinical improvement



Lynch, T. J. et al. N Engl J Med 2004;350:2129-2139

Mutations of the EGFR gene in gefitinib-responsive tumors

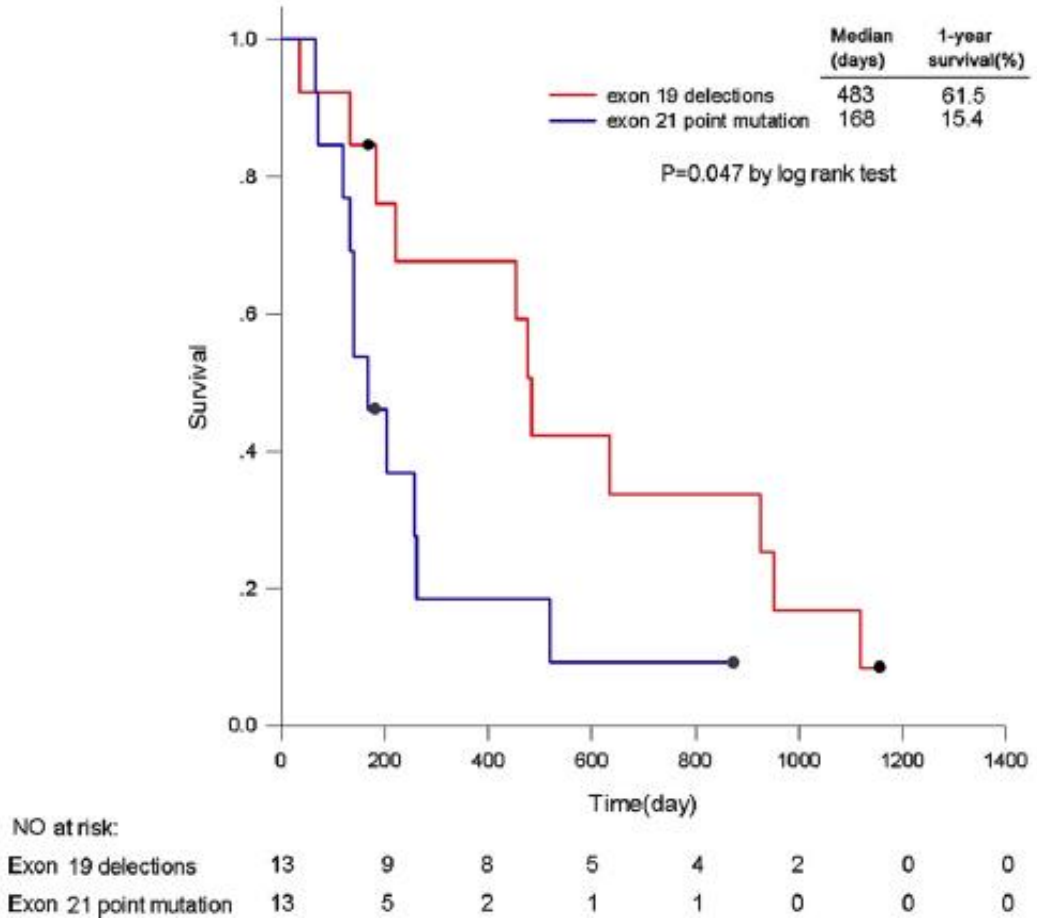


8 out of 9 gefitinib-sensitive patients had EGF-receptor gene mutations.

None of refractory patients had any mutations

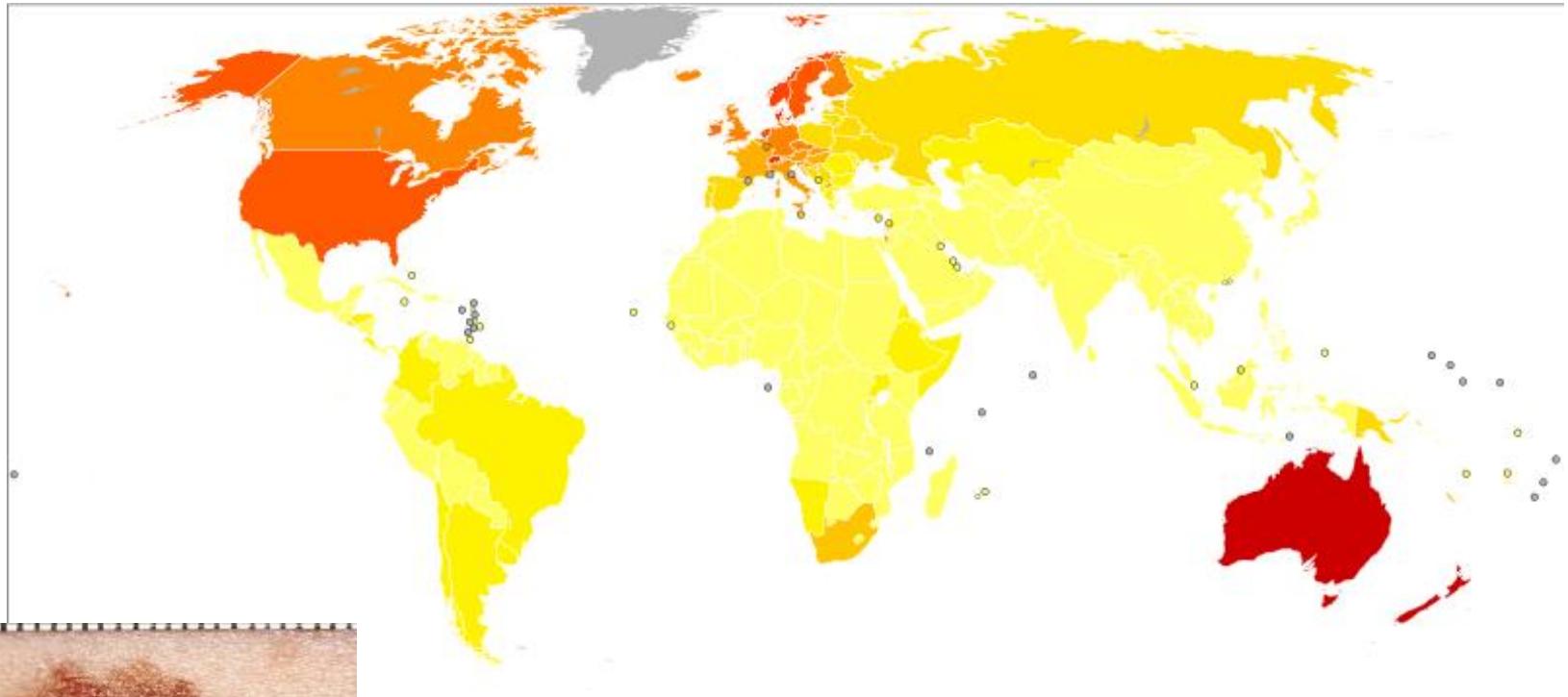
Lynch, T. J. et al. N Engl J Med 2004;350:2129-2139

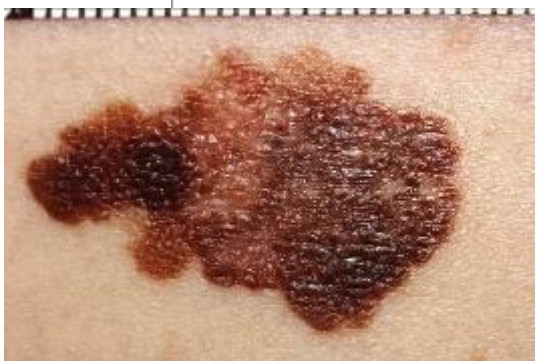
NSCLC progression and gefitinib response



Zhou et al., Cancer Lett 2008; 265:307-317

Malignant melanoma

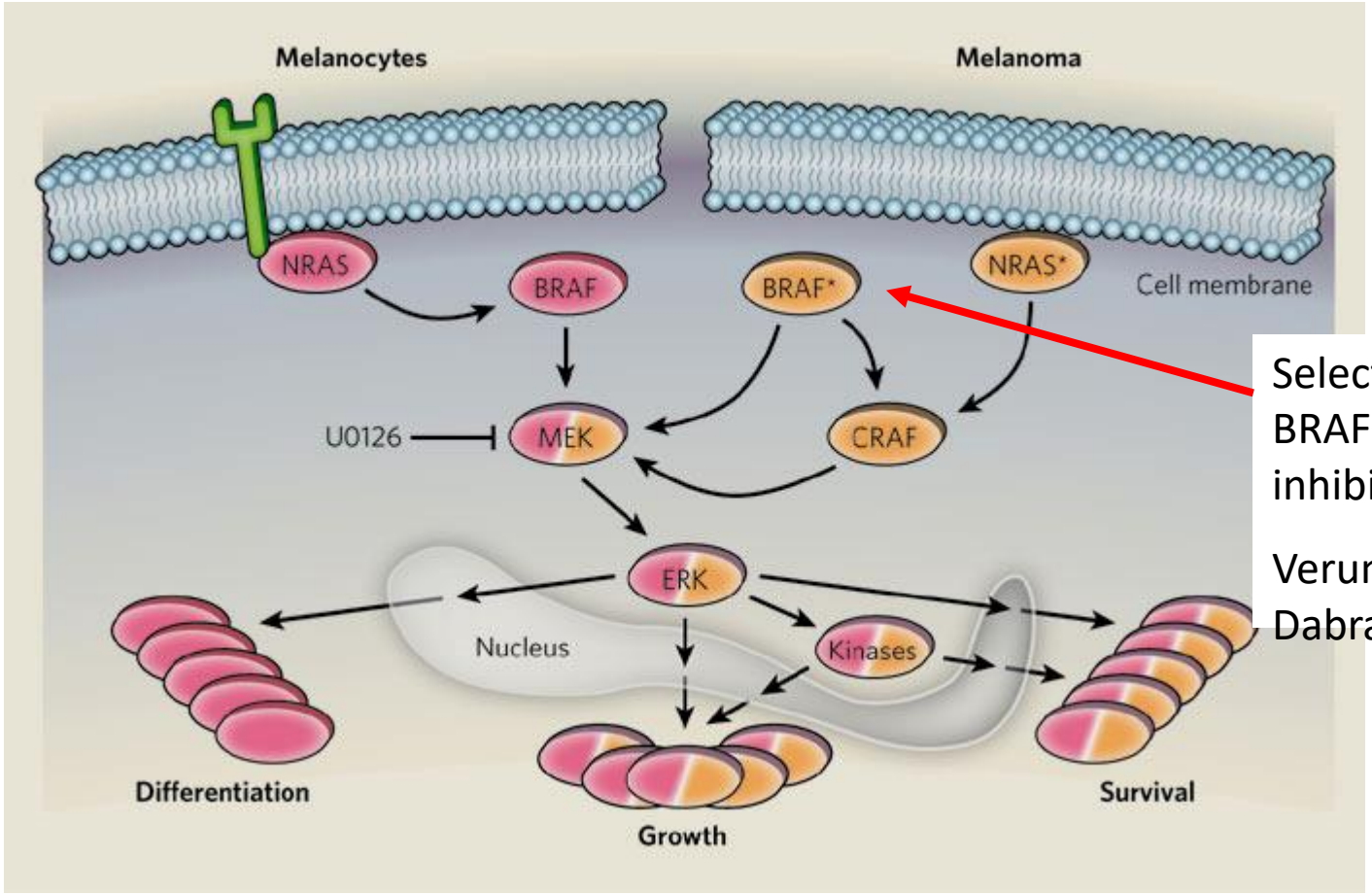




Globally, in 2012, melanoma occurred in 232,000 people and resulted in 55,000 deaths.[1] Australia and New Zealand have the highest rates of melanoma in the world.

Source: Wikipedia

The BRAF-mediated pathway in health and cancer

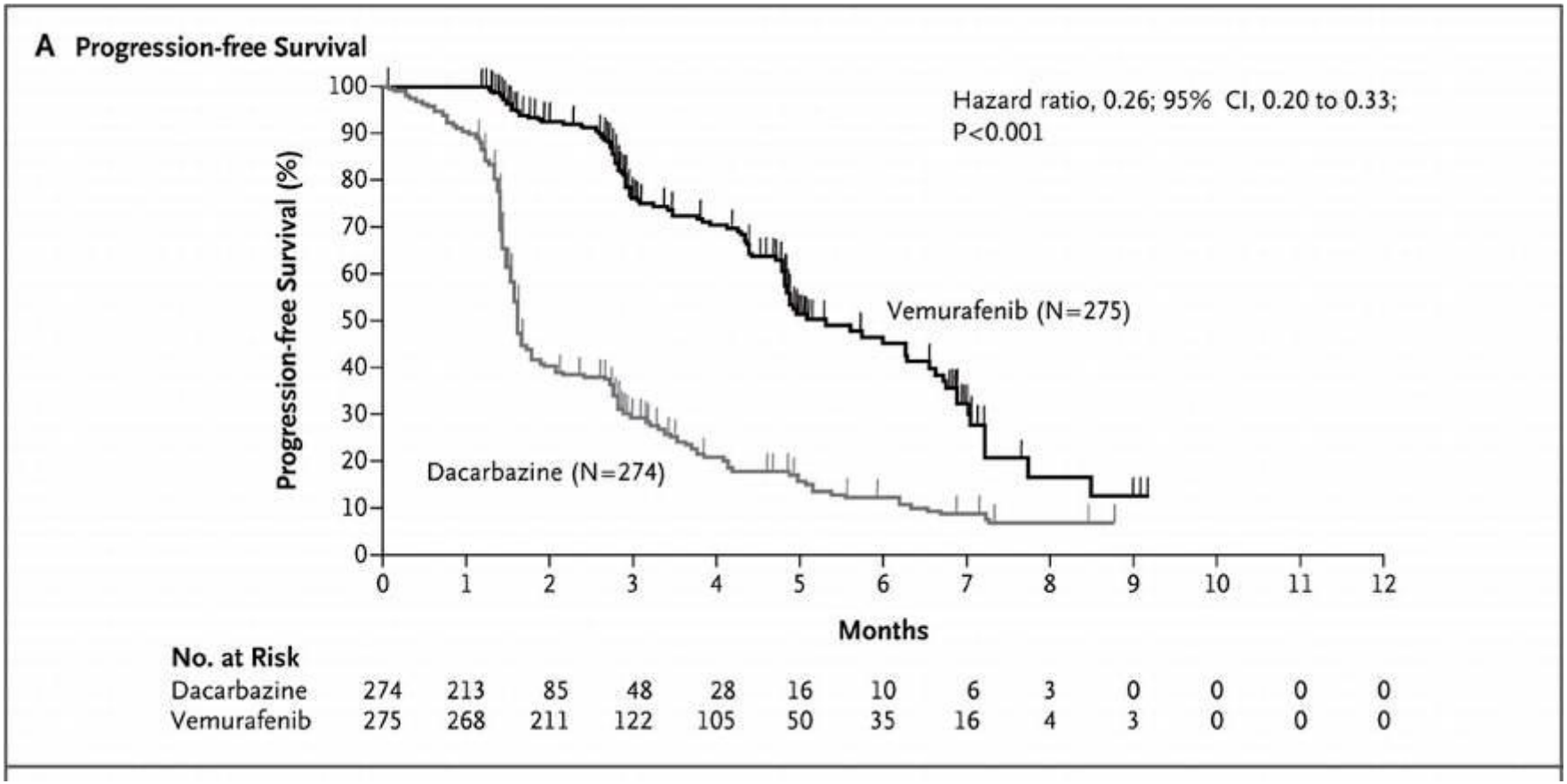


Selective BRAF inhibitors:

Verumafenib
Dabrafenib

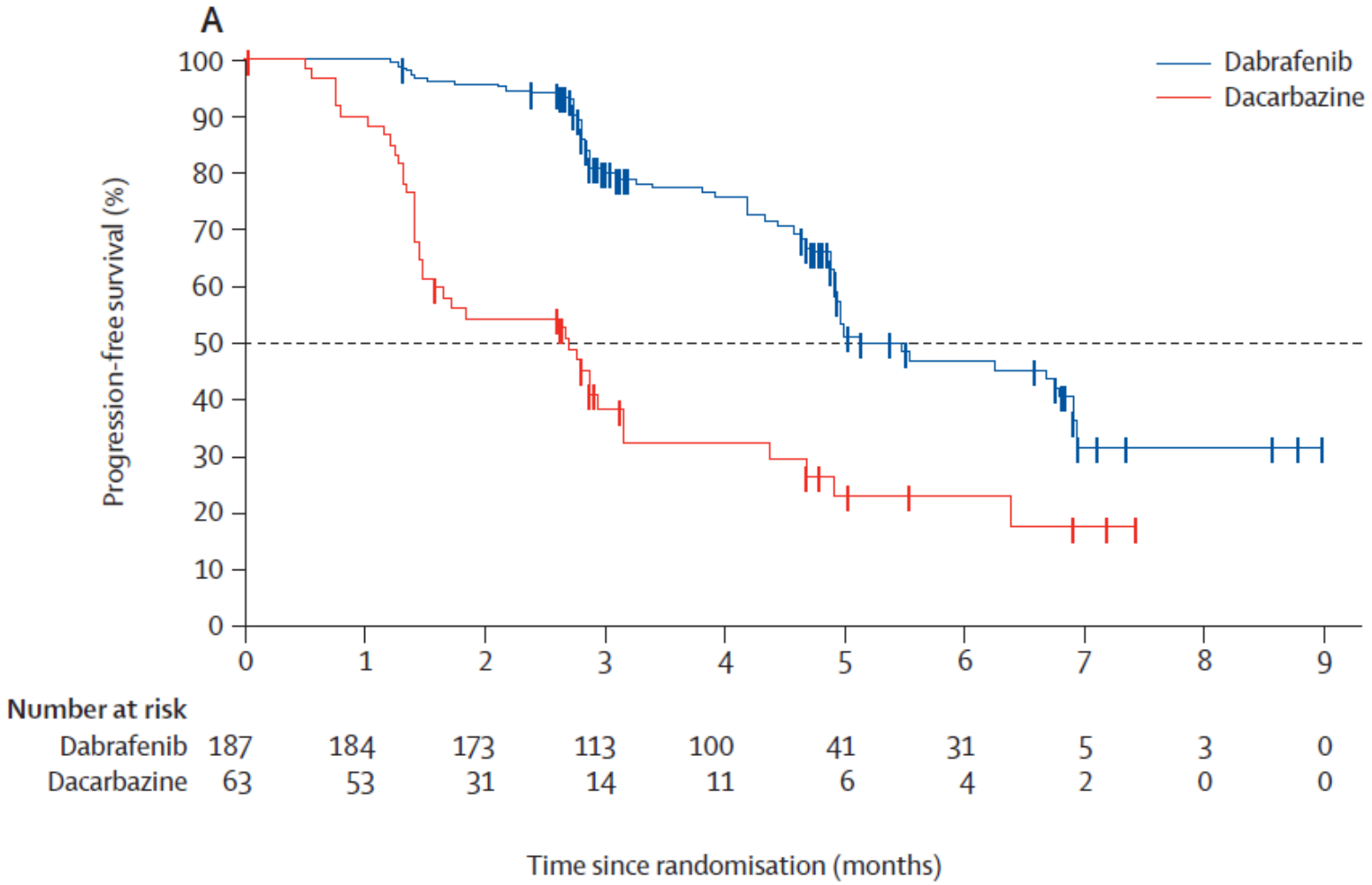
Huang and Marais, Nature 2009;459:336-337

Verumafenib in BRAF-mutated malignant melanoma:
Progression-free survival compared to dacarbazine treatment



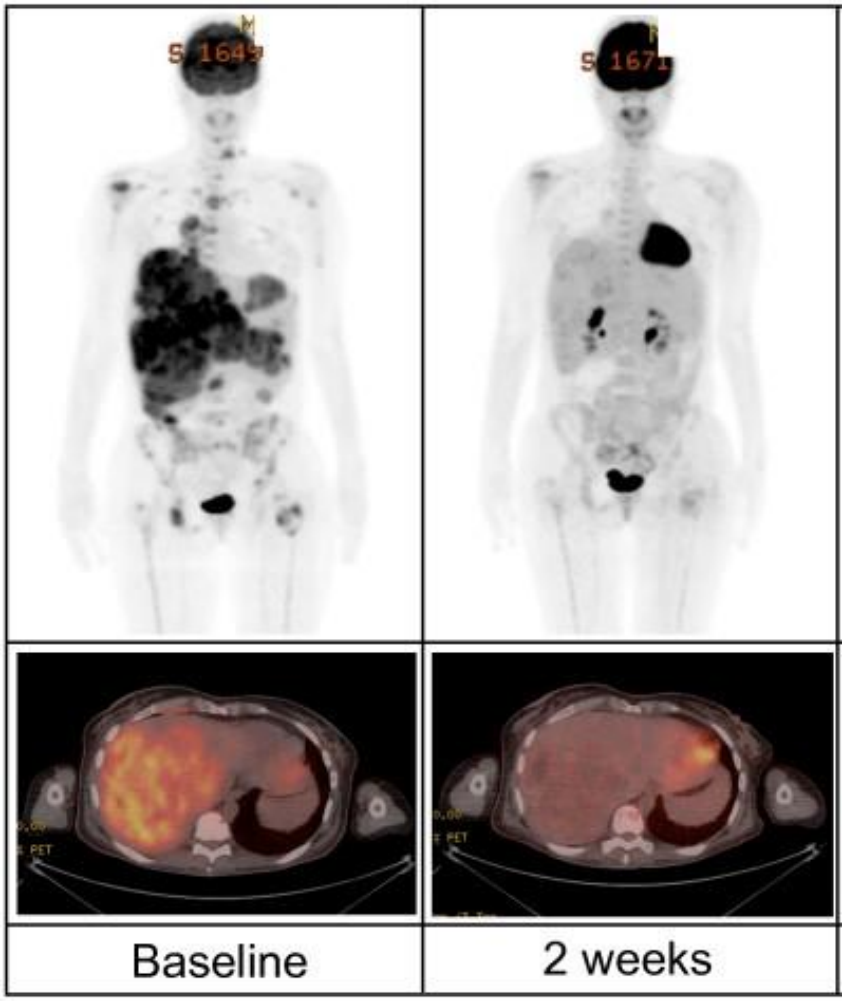
Chapman et al. N Engl J Med 2011;364:2507-2516.

Dabrafenib in BRAF-mutated malignant melanoma:
Progression-free survival compared to dacarbazine treatment



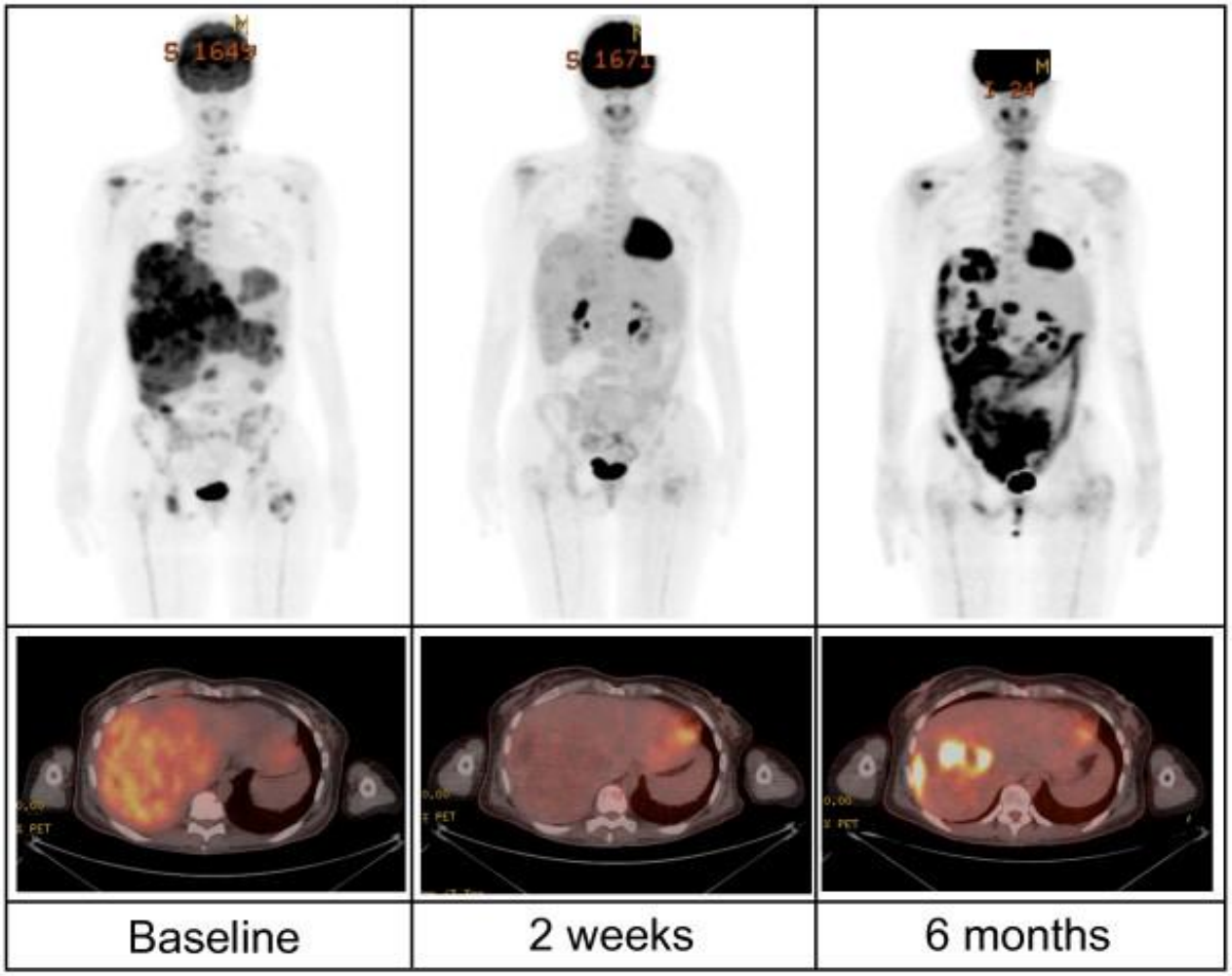
Hauschild et al. Lancet 2012; 380: 358–65

Typical response for patients on BRAF inhibitor verumafenib



Finn et al. BMC Medicine 2012, 10:23

Typical response for patients on BRAF inhibitor verumafenib



Finn et al. BMC Medicine 2012, 10:23

Companian diagnostics in oncology
(Examples)

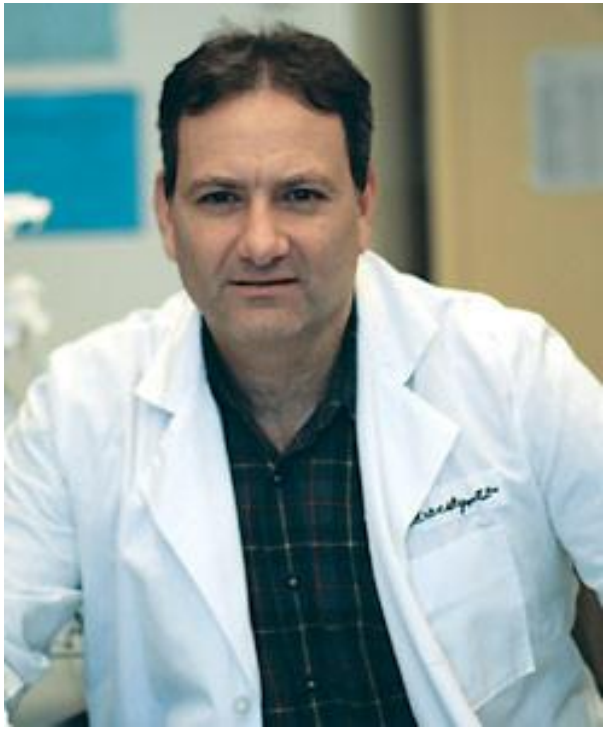
Drug	Target	Indication	Prerequisit
Trastuzumab	HER2/neu	Breast cancer	**HER2/neu$^{(+)}$, mut. KRAS$^{(-)}$**
Cetuximab	EGFR	Colon cancer,	**EGFR$^{(+)}$, mut. KRAS$^{(-)}$**
Panitumumab	EGFR	Colon cancer	**EGFR$^{(+)}$, mut. KRAS$^{(-)}$**
Erlotinib	EGFR	Lung cancer (NSCLC)	**mut. EGFR$^{(+)}$**
Gefitinib	EGFR	Lung cancer (NSCLC)	**mut. EGFR$^{(+)}$, T790M$^{(-)}$**
Vemurafenib	BRAF	Malignant melanoma	**mut. BRAF$^{(+)}$**
Dabrafenib	BRAF	Malignant melanoma	**mut. BRAF$^{(+)}$**
Imatinib	BCR/ABL	CML	**Ph$^{(+)}$, BRC/ABL$^{(+)}$, T315I$^{(-)}$**

Personalized Medicine

"The application of **genomic** and **molecular data** to better target the delivery of health care, facilitate the discovery and clinical testing of new products, and help determine a person's predisposition to a particular disease or condition."

Personalized Med. 6(5) 479-480 (2009).

Novel approaches



David Sidransky

Published OnlineFirst June 14, 2011; DOI: 10.1158/1535-7163.MCT-11-0233

Molecular Cancer Therapeutics

Spotlight on Clinical Response

A Pilot Clinical Study of Treatment Guided by Personalized Tumorgrafts in Patients with Advanced Cancer

Manuel Hidalgo[1,4,5,6], Elizabeth Bruckheimer[3], N.V. Rajeshkumar[1], Ignacio Garrido-Laguna[1], Elizabeth De Oliveira[1], Belen Rubio-Viqueira[4,5], Steven Strawn[3], Michael J. Wick[7], James Martell[3], and David Sidransky[1,2]

ScienceNews
MAGAZINE OF THE SOCIETY FOR SCIENCE & THE PUBLIC

FEATURE HUMANS & SOCIETY, BODY & BRAIN

Of Mice and Man

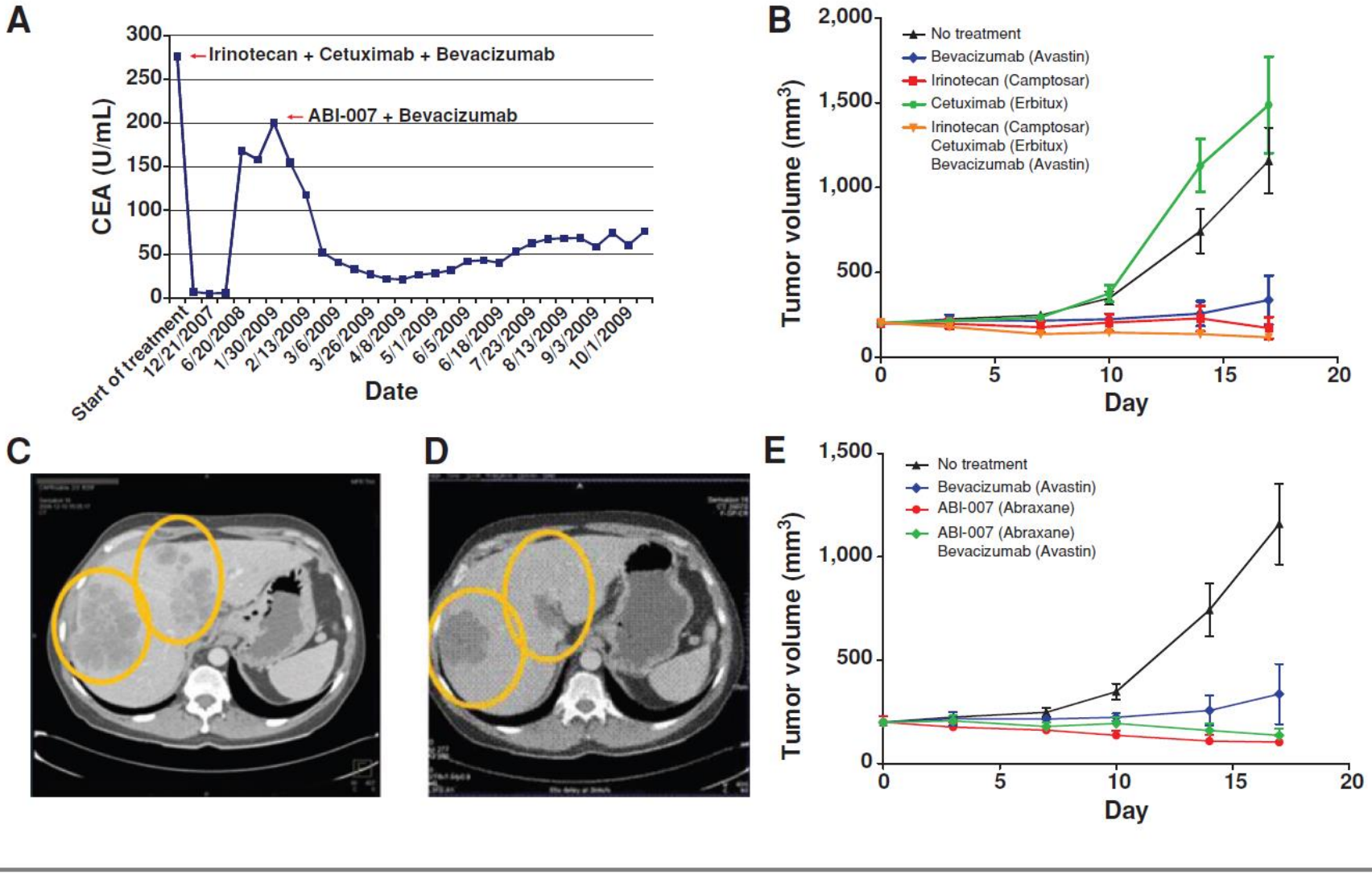
The lab mouse is being remodeled to better mimic how humans respond to disease

BY SUSAN GAIDOS 10:37AM, MARCH 7, 2013

Magazine issue: March 23, 2013

A humanized mouse implanted with a human tumor is one of the many being used to help doctors identify the best treatments for a patient's cancer.

MARY CALVERT/THE NEW YORK TIMES/REDUX PICTURES


A
300
250
200
150
100
50
0
CEA (U/mL)
←Irinotecan + Cetuximab + Bevacizumab
← ABI-007 + Bevacizumab
Start of treatment
12/21/2007
6/20/2008
1/30/2009
2/13/2009
3/6/2009
3/26/2009
4/8/2009
5/1/2009
6/5/2009
6/18/2009
7/23/2009
8/13/2009
9/3/2009
10/1/2009
Date
B
2,000
1,500
1,000
500
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Tumor volume (mm3)
No treatment
Bevacizumab (Avastin)
Irinotecan (Camptosar)
Cetuximab (Erbitux)
Irinotecan (Camptosar)
Cetuximab (Erbitux)
Bevacizumab (Avastin)
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Tumor volume (mm3)
No treatment
Bevacizumab (Avastin)
ABI-007 (Abraxane)
ABI-007 (Abraxane)
Bevacizumab (Avastin)
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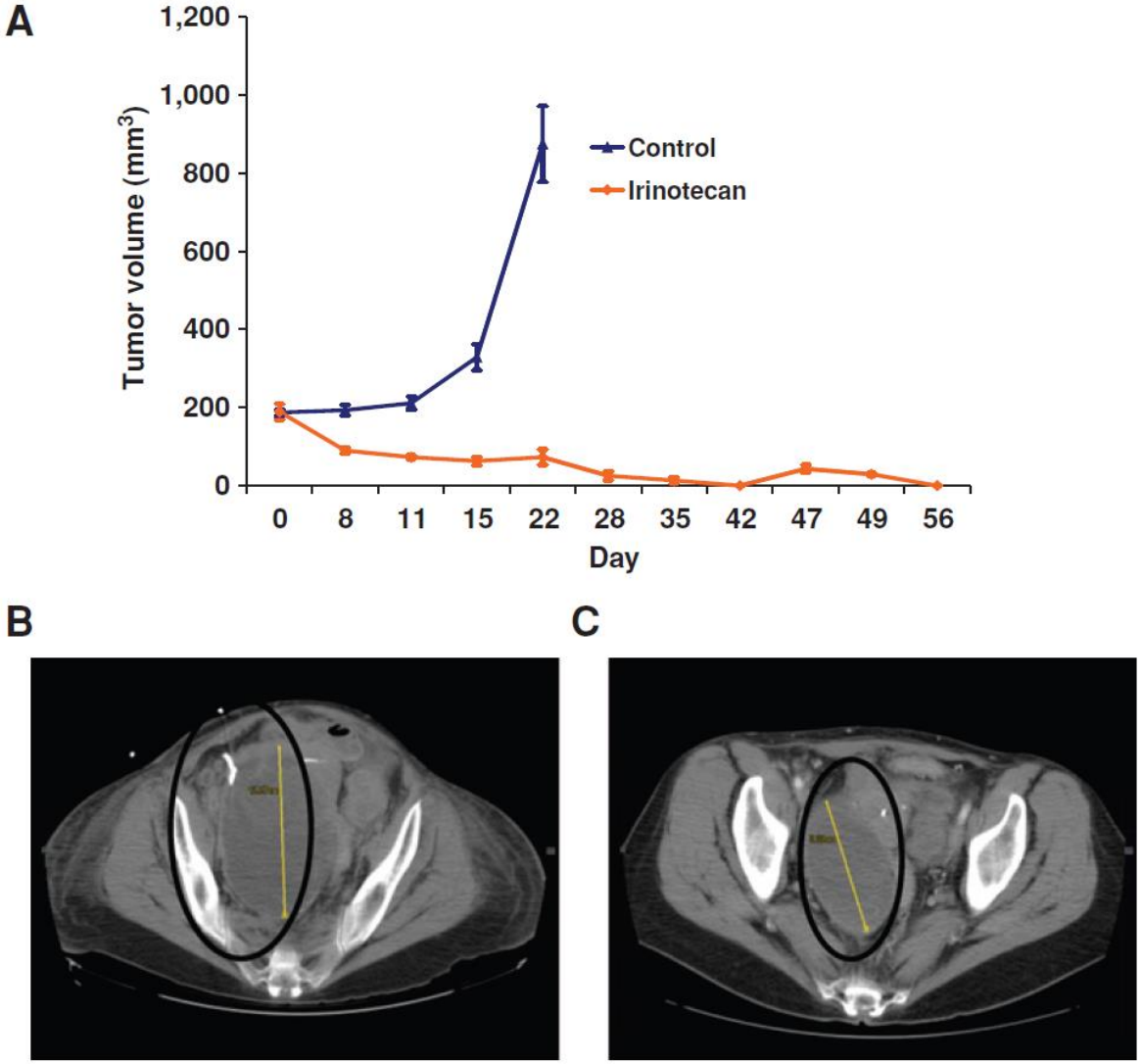
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1,000
800
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400
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0
Tumor volume (mm3)
Control
Irinotecan
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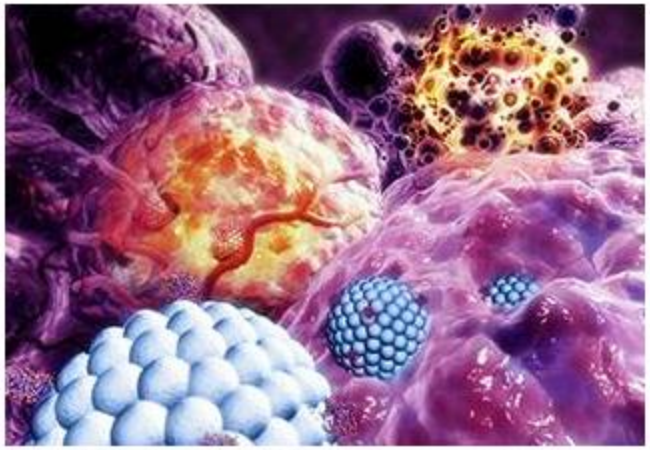
8
11
15
22
28
35
42
47
49
56
Day
B
C

James Netterwald, PhD

August 20, 2013

Nanotechnology: The Evolution of Cancer Drug Delivery

Nanotechnology is the use of nanosized particles for medical applications that originated in the 1960s with the discovery of liposomes—lipids that self-assemble into nanoparticulate spheres when exposed to water.[1]



Nanoparticles (blue) destroying tumor (purple), causing their destruction (orange) / Science Source

These spheres can encapsulate small molecule pharmaceuticals, including the chemotherapeutic agents doxorubicin (Doxil®) and paclitaxel (Abraxane®), which have been formulated into several marketed liposome-based nanopharmaceuticals. The technology is constantly evolving, with other nanopharmaceuticals in development; two drug candidates are also in the pipeline.

Overcoming chemoresistance in cancer

- Overcoming resistance by targeted delivery
- Inhibition of efflux pumps
- Combination of targeted drugs
- Consideration of individual profile
- Ex-vivo testing in xenografs

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Thank you
for your attention

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KIEL NANO SURFACE & INTERFACE SCIENCE

KON KielOncologyNetwork

REGISTRIERTE BIOBANK
Deutsches Biobanken-Register

Bundesministeriu für Bildung und Forschung

Inflammation at Interfaces