

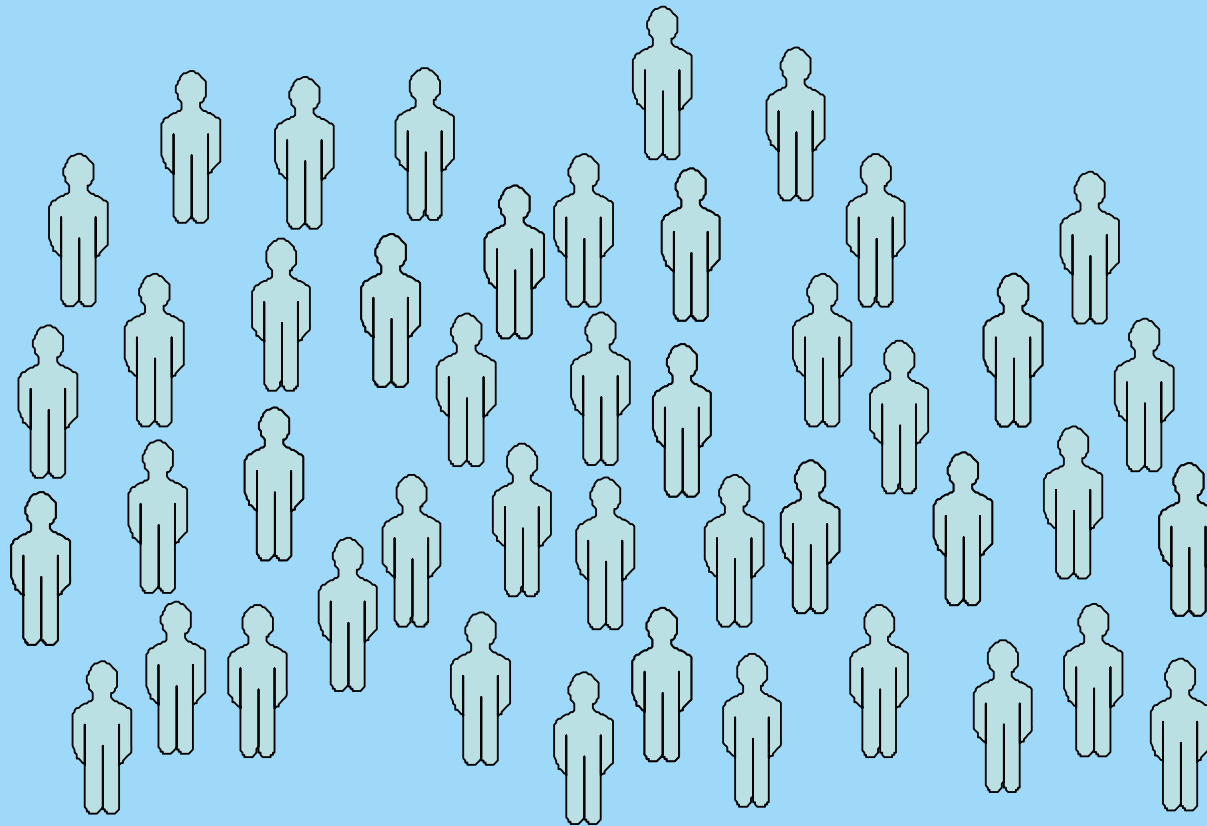
Individualisierte Tumorthherapie

Beispiel gastrointestinale Karzinome

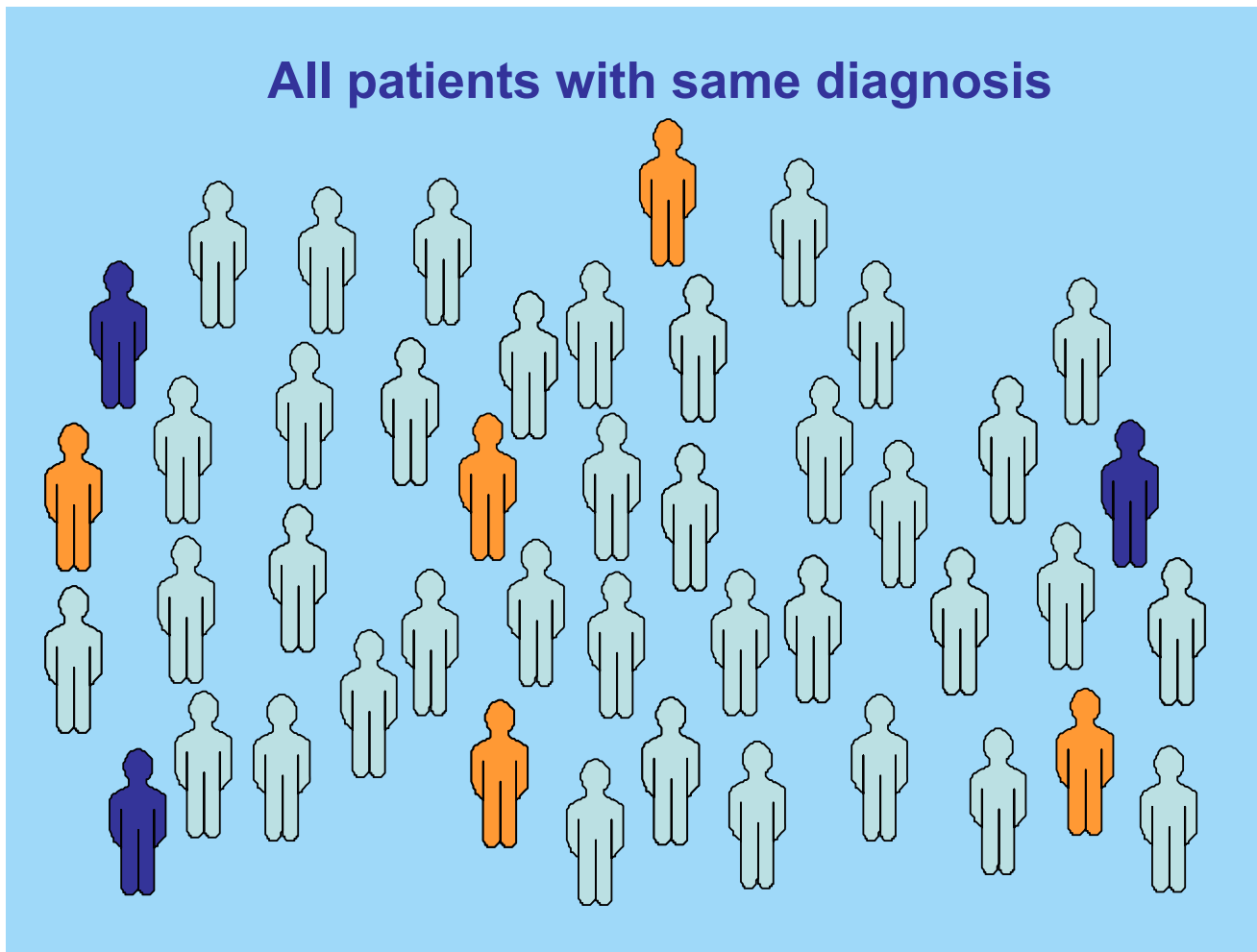


Jan Stöhlmacher,
Universitätsklinikum Carl Gustav Carus
Dresden

All patients with same diagnosis



All patients with same diagnosis



Klinische Beobachtung (CPT-11/Cetuximab Chemotherapie-Kombination)

Patient 1

++++

Mukositis

+++

Diarrhoe

++

KM-Toxizität

-

Haut-Toxizität

+

Tumor Ansprechen

Patient 2

++

+

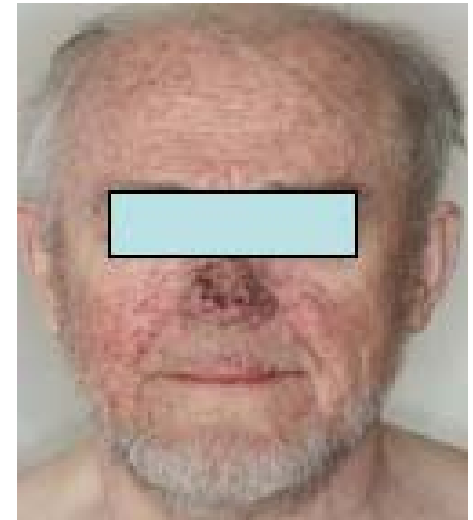
-

+++

++++

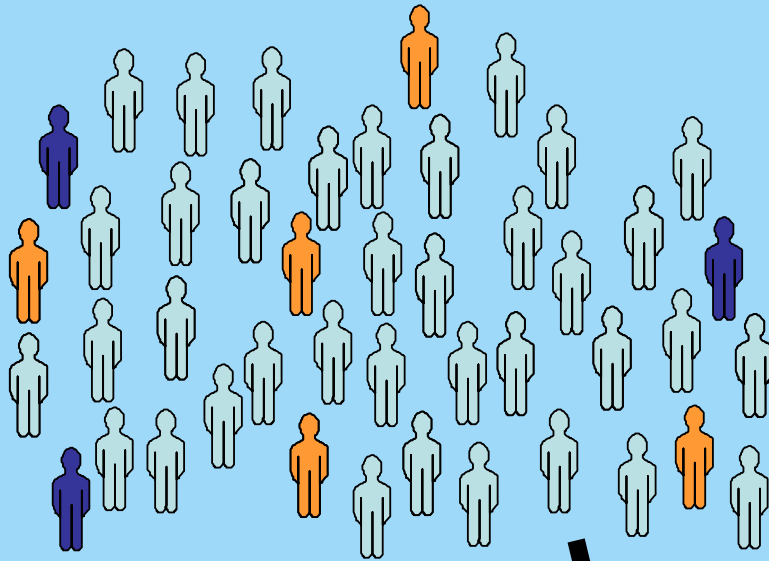
Inter-individuelle Unterscheide in
Haupt- und Nebenwirkung

Typische Toxizitäten einer EGFR-Therapie



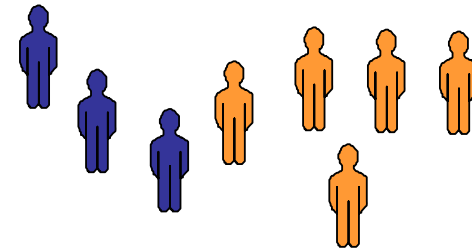
Akne und periunguale Granulationen

All patients with same diagnosis



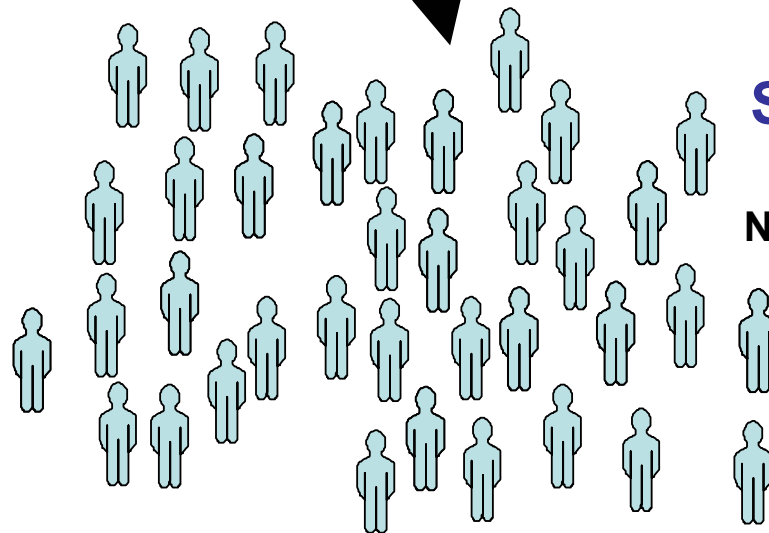
Alternate therapy

**non-responders
and toxic responders**



Standard therapy

**Responders and Patients
Not Predisposed to Toxicity**



Gründe für pharmakogenetisches Screening in der Onkologie

Inter - individuelle Variationen in Ansprechen und Toxizität

Erkennung letaler Gefährdungen

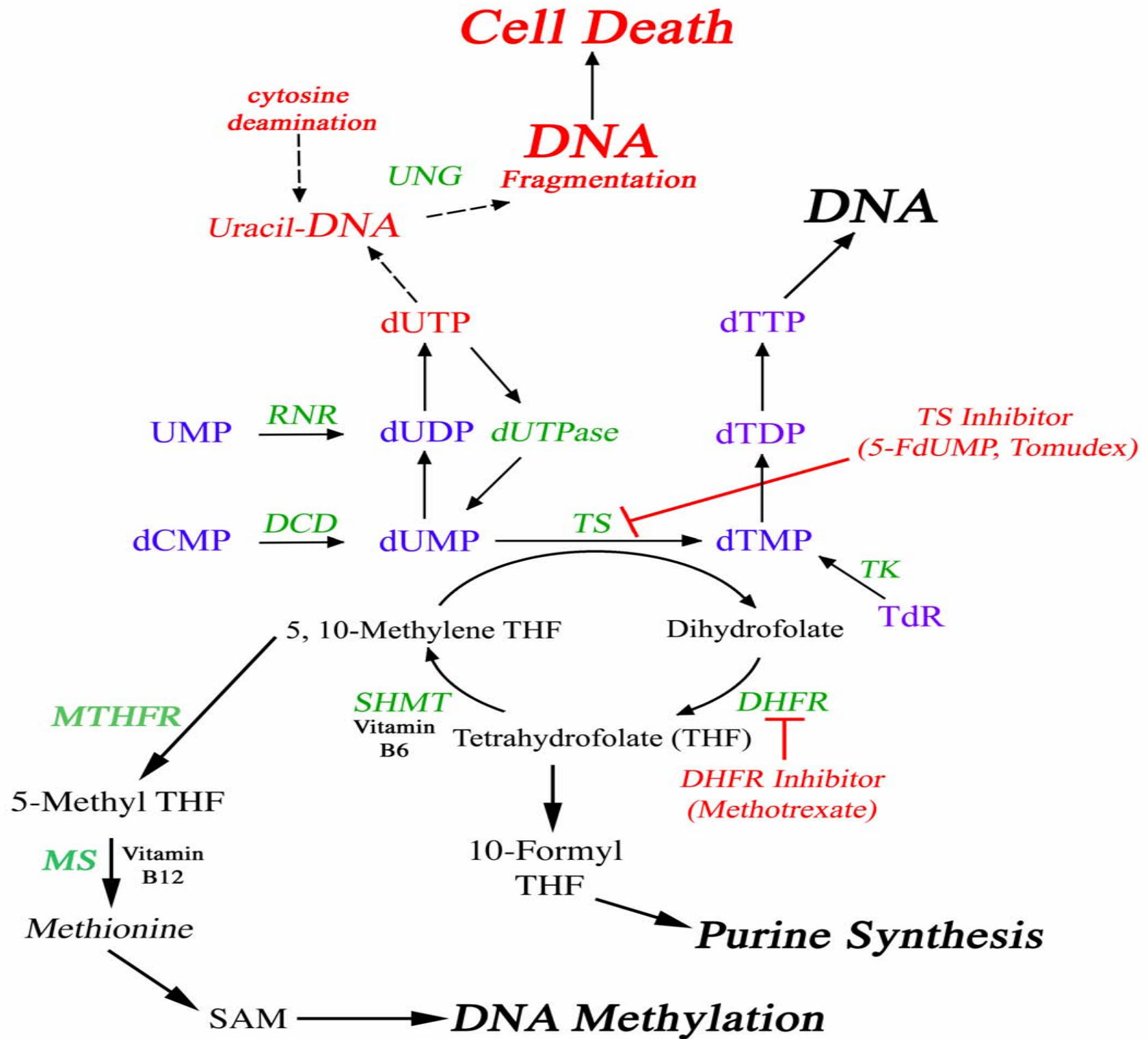
Steigende Auswahl aktiver Therapien

Explodierende Kosten

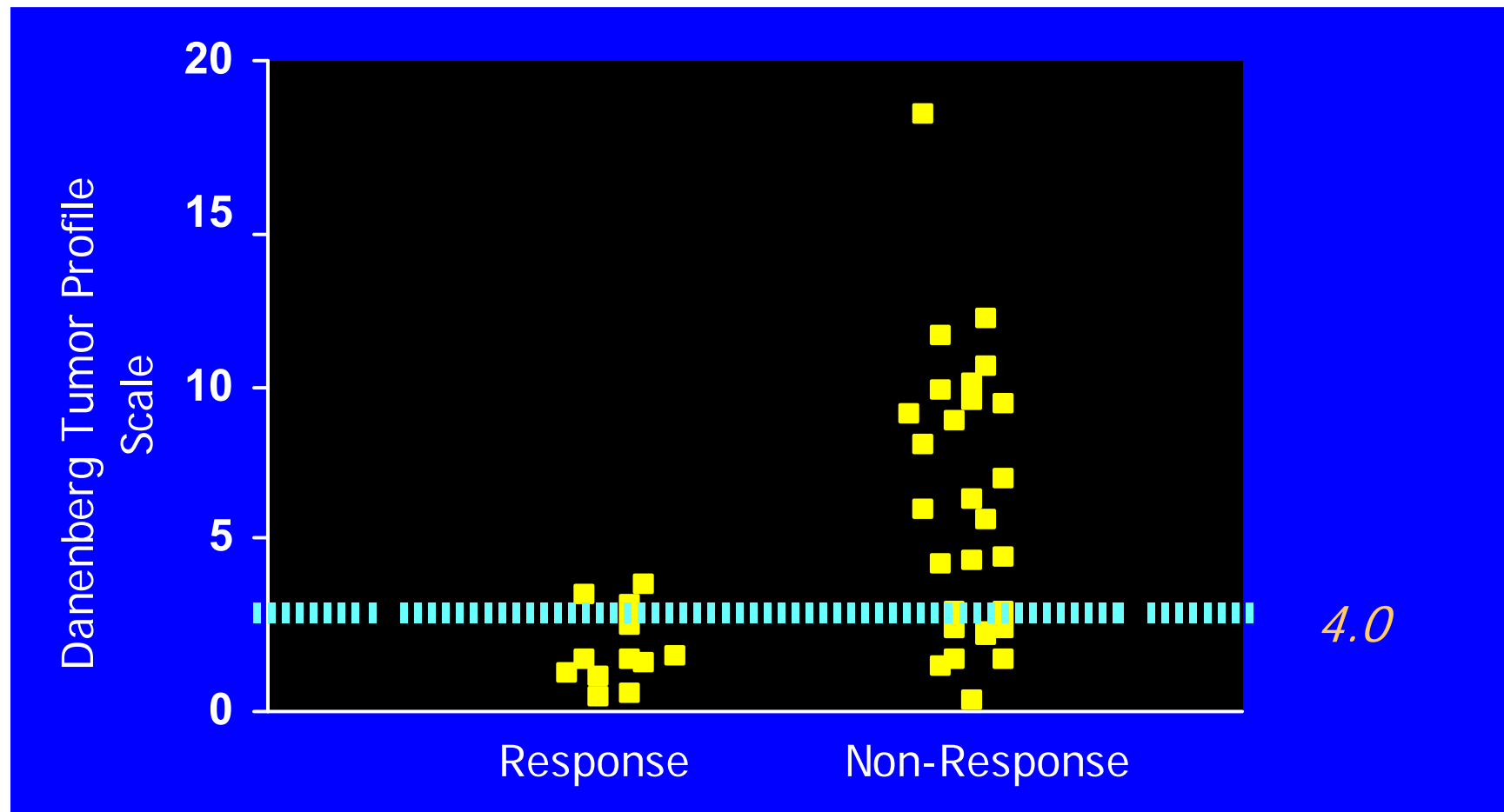
Beispiele pharmakogenetischer Untersuchungen

- 1 Fluoropyrimidine (5-FU, Capecitabine) und Platin**
- 2 Topoisomerase-Inhibitoren (Irinotecan)**
- 3 EGFR-Inhibitoren (Cetuximab, Panitumumab)**

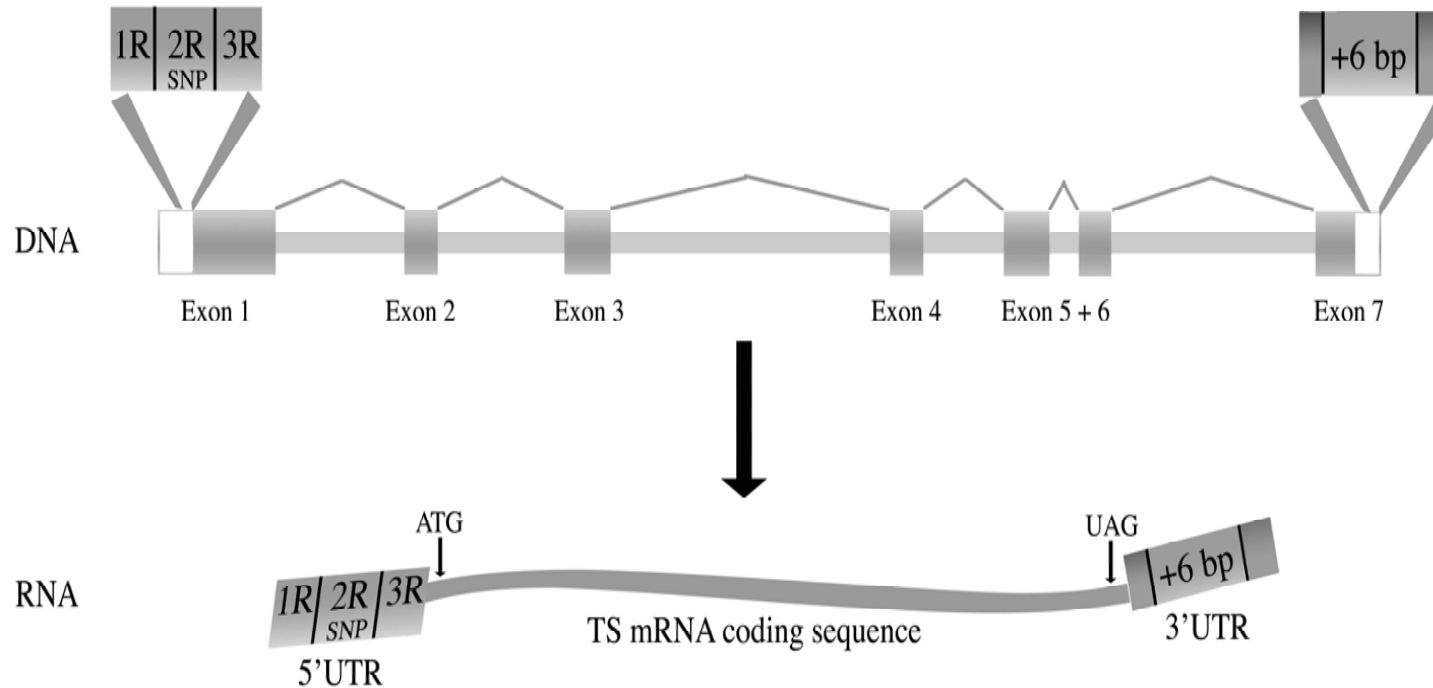
Fluoropyrimidine und Platinderivate



TS Gen Expression und Ansprechen auf 5-FU in kolorektalen Karzinomen (UICC IV)



Polymorphismen - TS Gen



Courtesy Prof. Ladner, USC

TS mRNA Expression
2R << 3R
(*in-vitro*)

Horie et al. *Cell Struct Funct* 1995

TS Genotyp und TS Genexpression CRC (UICC IV)

Genotyp	Metastase (Leber)			Vergleich TS means	
				Genotyp	P-value
	n	TS mean	95% CI	Overall	0.011
3/3	15	9.42	5.51, 16.12	3/3 vs 2/2	0.003
2/3	26	5.53	3.68, 8.31	3/3 vs 2/3	0.12
2/2	11	2.60	1.39, 4.87	2/3 vs 2/2	0.048

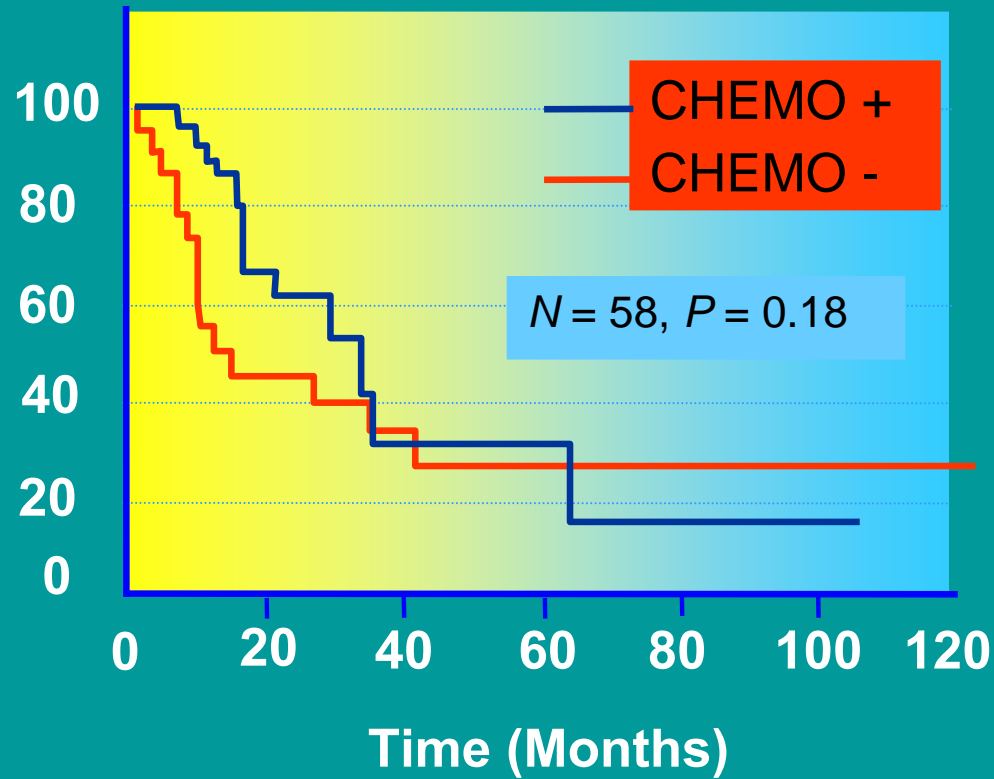
TS Polymorphismus - Ansprechen / Toxizität auf 5-FU

	3/3	3/2	2/2	P-value
				0.041
Response	2 (!)	3	4	
No response	20	17	4	
				0.008
Toxicity I	9	1	0	
Toxicity II	7	12	3	
Toxicity III	6	6	5	

TS Polymorphismus und 5-FU in CRC (UICC III)

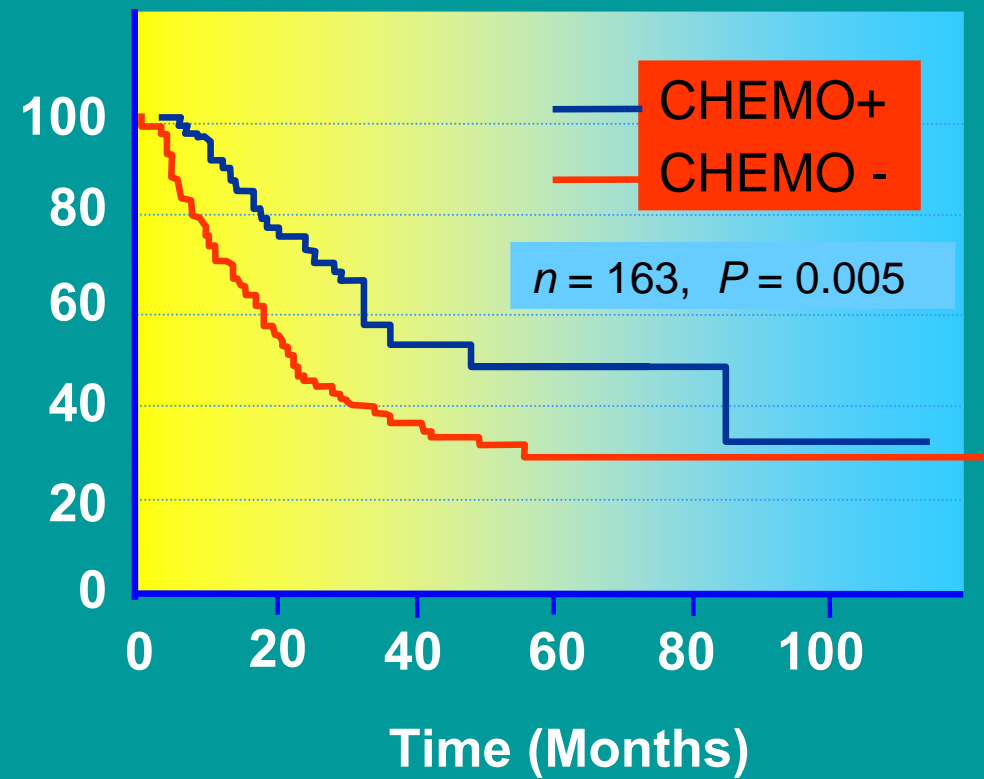
A 3R/3R

Survival

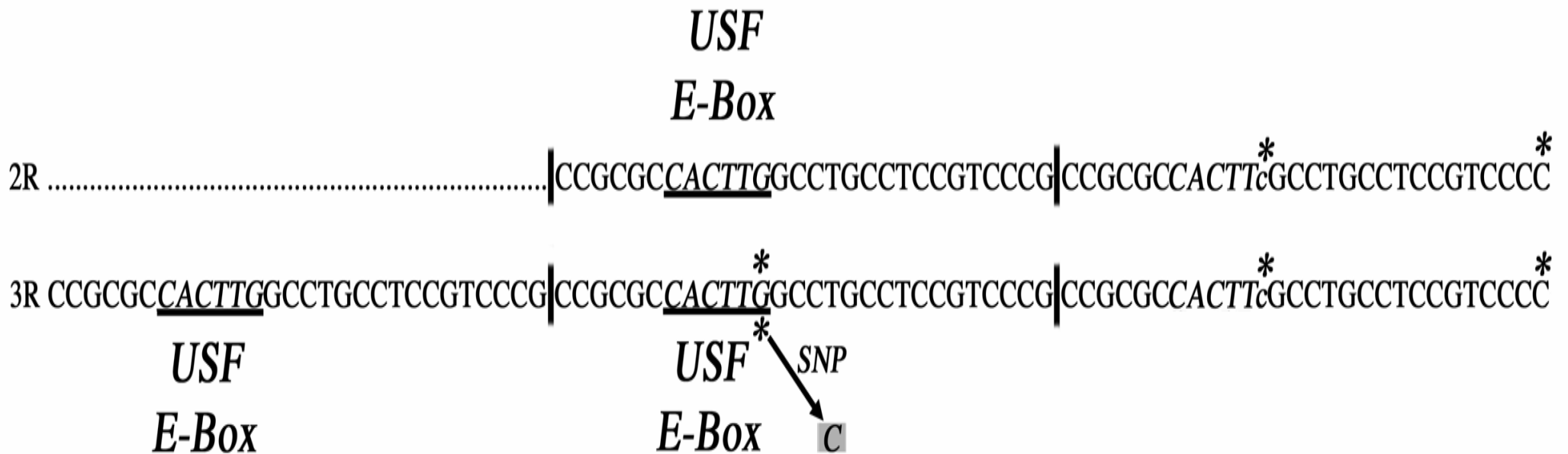


B 2R/2R & 2R/3R

Survival



Sequenz TS – Repeat Polymorphism



G → C funktionelle Umwandlung 3R → 2R

Klinischer Einfluß des TS G/C SNPs

Studie in CRC n=89, 5-FU-basierte Chemotherapie

TS Genotype	Responder	Non-Responder
2/2	12 (71%)	5 (29%)
2/3	21 (57%)	16 (43%)
3/3	16 (46%)	19 (54%)
		P=0.23
2/2+2/3C+3C/3C	32 (65%)	17 (35%)
2/3G+3C/3G+3G/3G	17 (43%)	23 (57%)
		P=0.035

Glutathione S-transferase P1 - Polymorphism Ile105Val

- ▲ GSTP1 verstärkt exprimiert in CRC**
- ▲ SNP (A/G) in Position +313 (exon 5) resultiert in einer Substitution von Isoleucin (ILE) durch Valin (VAL) (SNP in Substratbindungsdomäne lokalisiert)**
- ▲ GSTP1-105Val zeigt verminderte Enzymaktivität**

GSTP1-105 Polymorphismus bei 2nd line 5-FU/Oxaliplatin in Dukes D CRC

Genotyp	Patienten	Überleben* und 95% CI
Alle	107	9.6 (7.9, 12.3)
GSTP1		
ILE/ILE	52	7.9 (5.4, 9.6)
ILE/VAL	45	13.3 (8.4, 23.7)
VAL/VAL	10	24.9+ (9.4, 24.9+)

* In Monaten, P<0.001

GSTP1-105 Polymorphismus und Oxaliplatin-Toxizität

FOLFOX-4 Arm der Intergroup N9741 Studie (n=299)

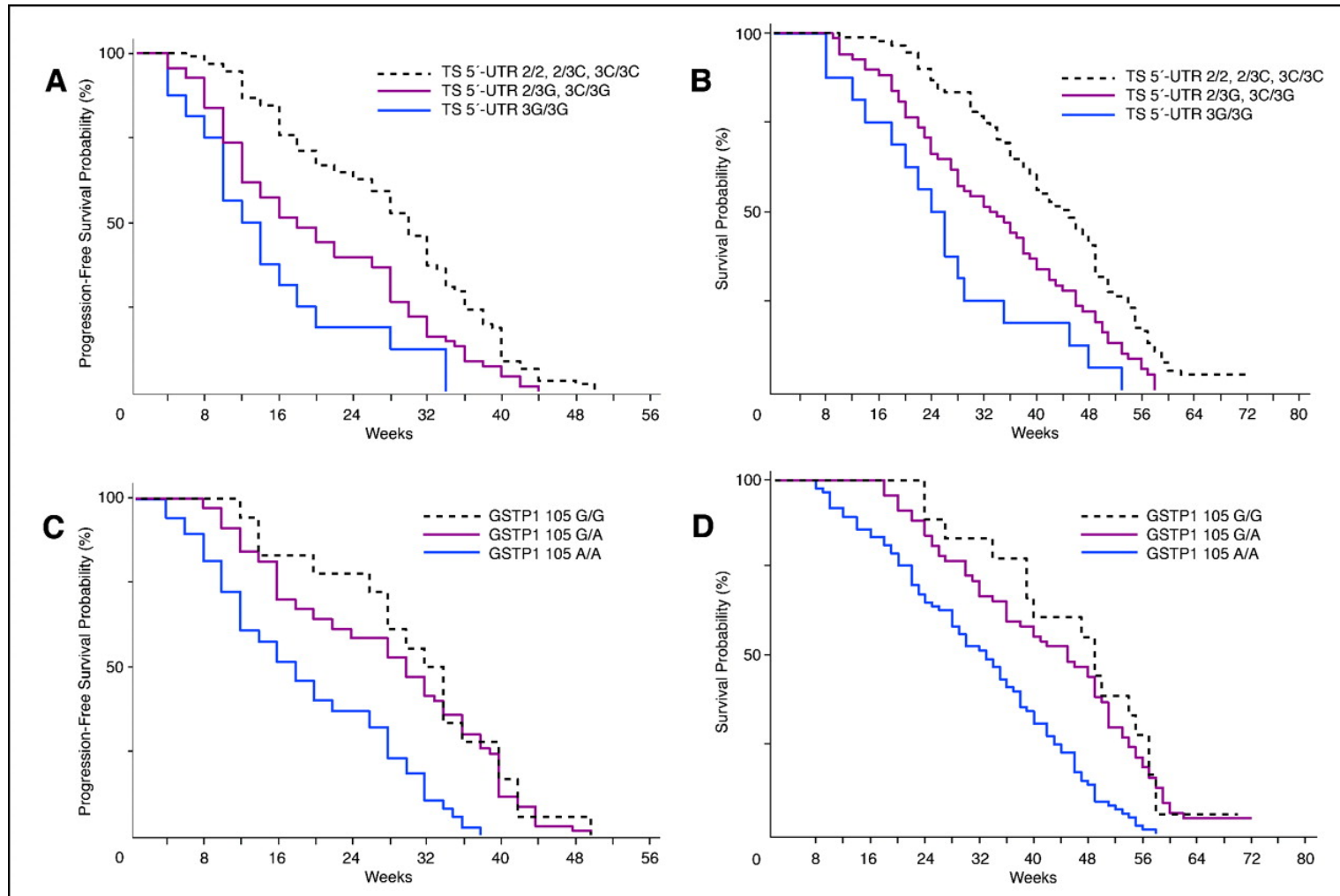
	ILE/ILE	ILE/VAL	VAL/VAL	P-value
Therapieabbruch (Neurotox)	9.2%	10%	23.7%	0.039

Patienten mit GSTP1-105 VAL/VAL oder GSTP1-105 ILE/VAL entwickeln früher eine periphere Neurotoxizität

Grad 2 (p=0.027) + Grad 3 (p=0.030)

Gastric cancer (n=175), Cisplatin + 5FU chemotherapy

Progression-free (PFS) and overall survival (OS) by thymidylate synthase gene (TS) 5'-untranslated region (5'-UTR) and GSTP1 105 genotypes



Ruzzo, A. et al. J Clin Oncol; 24:1883-1891 2006

Ein Polymorphismus oder Score ?

Genomische Polymorphismen bei Zweitlinien- Chemotherapie mit 5-FU/Oxaliplatin

Factors	Patients	Survival	
		Adj. Relative Risk ¹	Adj. p-value ¹
XPD 751			0.048
Favorable: LYS/LYS	40	1	
Unfavorable	66	1.82	
ERCC1-19007			0.045
Favorable: C/C	30	1	
Unfavorable	76	1.98	
TS3'			0.058
Favorable: +6BP/+6BP	37	1	
Unfavorable	65	1.75	
Unknown	4		
GST-P1			0.051
Favorable: VAL/VAL	10	1	
Unfavorable	96	2.53	

1. based on Cox proportional hazards model; stratified by ECOG and tumor localization with all four genes included

Genomische Polymorphismen bei Zweitlinien-Chemotherapie mit 5-FU/Oxaliplatin

Günstige Genotypen

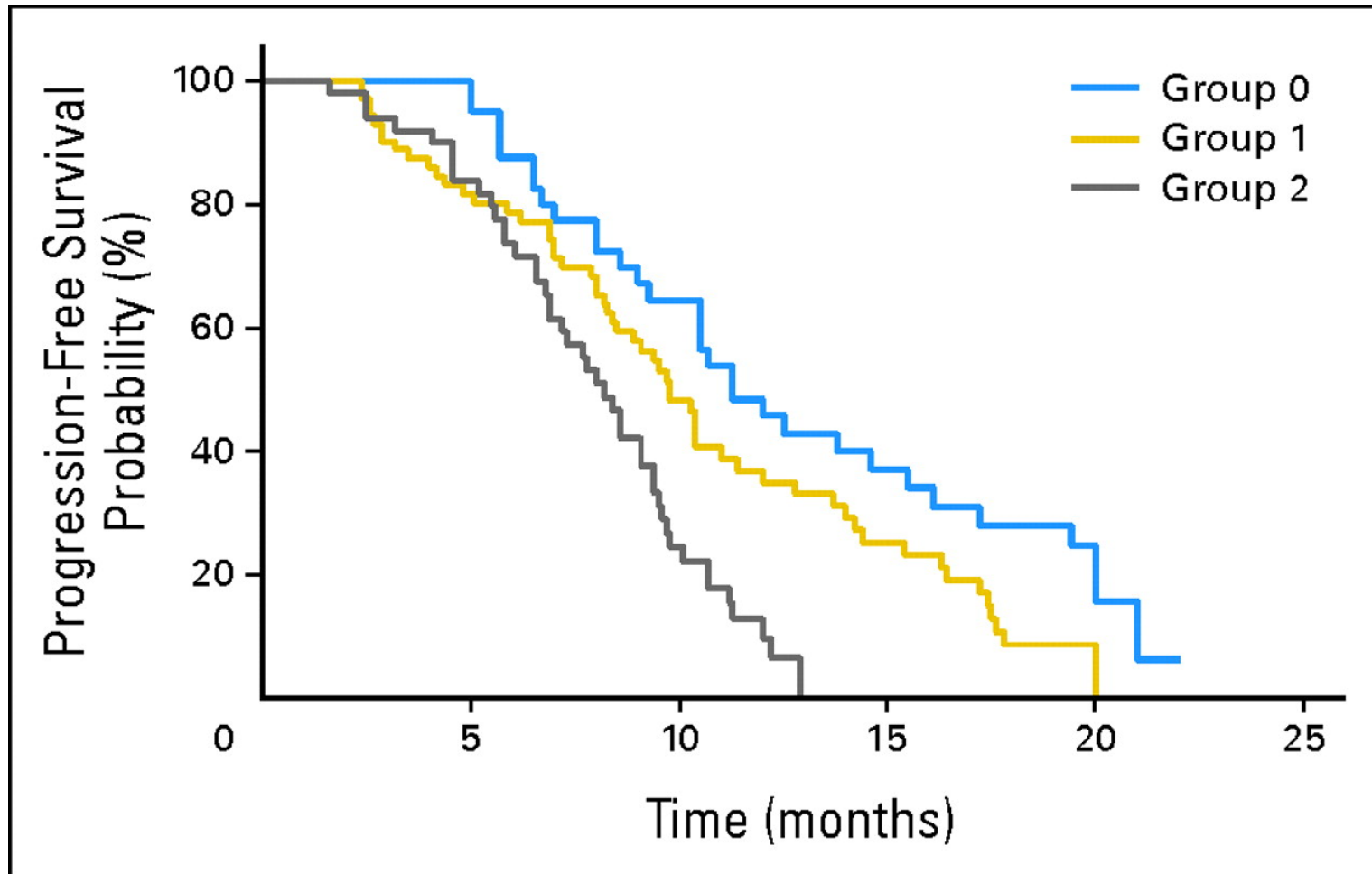
Überleben (95% CI)

2 (Lys/Lys, Val/Val, C/C, +6bp/+6bp)	17.4 Monate (9.4; 26.5)
1 (Lys/Lys, Val/Val, C/C, +6bp/+6bp)	10.2 Monate (6.8;15.3)
0 (Lys/Lys, Val/Val, C/C, +6bp/+6bp)	5.4 Monate (4.3; 6.0)

P<0.001

Pharmacogenetic profiling for colorectal cancer (n=166), FOLFOX-4 First-Line

Progression-free survival curves of patients without risk genotypes* (group 0), patients with one risk genotype* (group 1), and patients with two risk genotypes* (group 2)

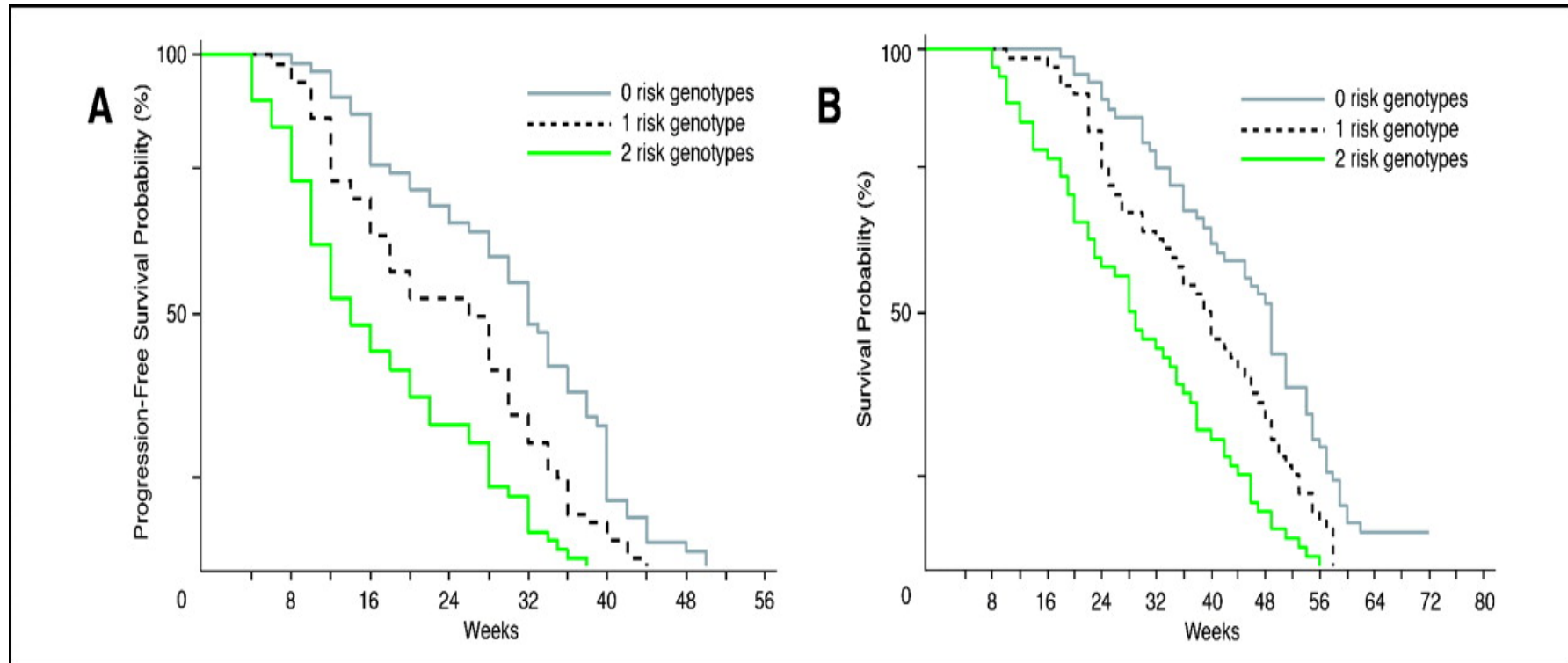


Ruzzo, A. et al. J Clin Oncol; 25:1247-1254 2007

*Risk genotypes: ERCC1-118T/T, XPD-751 A/C und XPD-751 C/C

Pharmacogenetic profiling for Gastric cancer patients (n=175)

Progression-free (PFS) and overall survival (OS) curves in carriers of 0 risk genotypes* (61 patients), one risk genotype* (57 patients) and two risk genotypes* (57 patients)



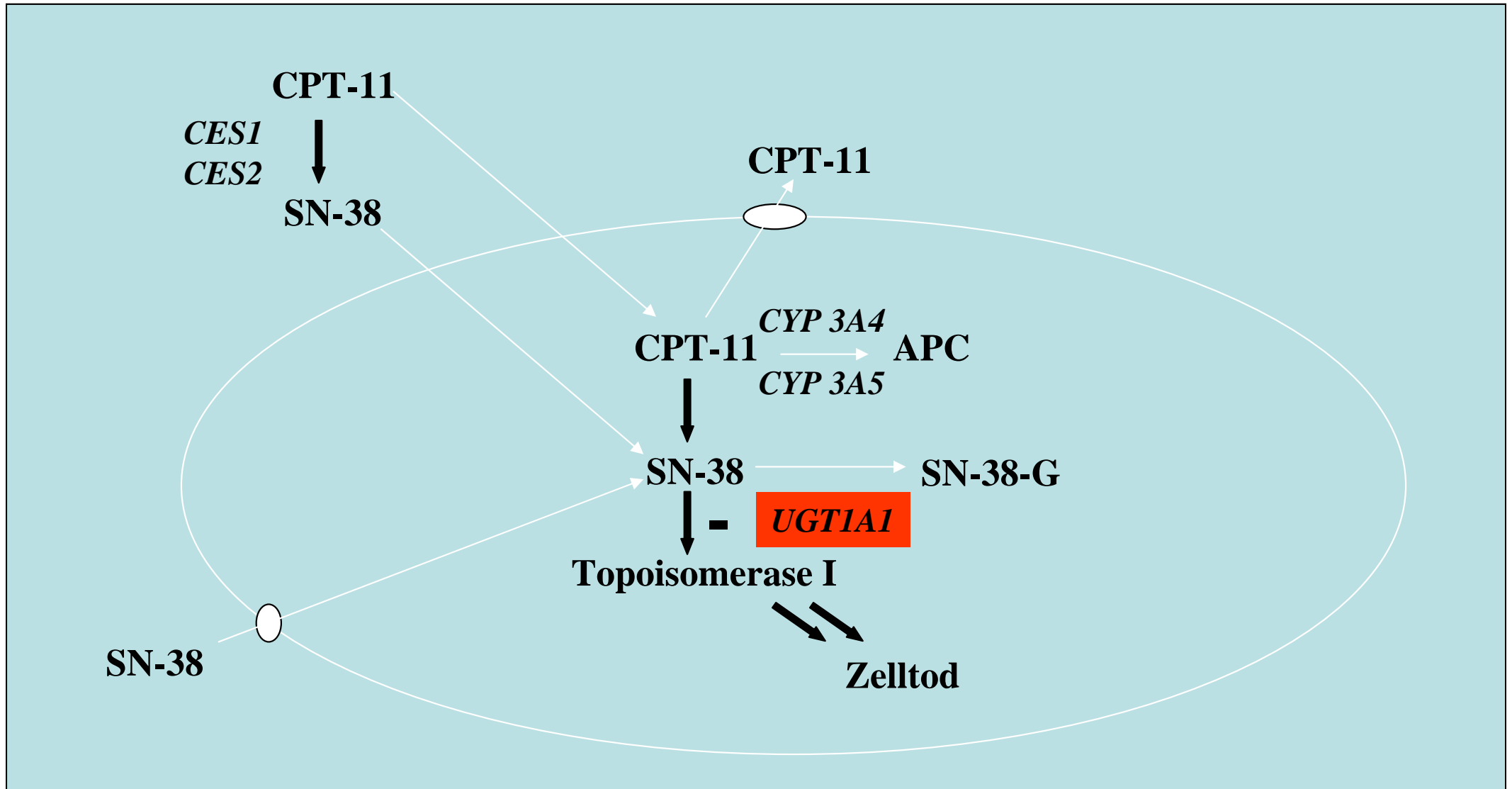
Ruzzo, A. et al. J Clin Oncol; 24:1883-1891 2006

*Risiko- TS 5' 3G und GSTP1 ¹⁰⁵ Ile/Ile Genotypen:

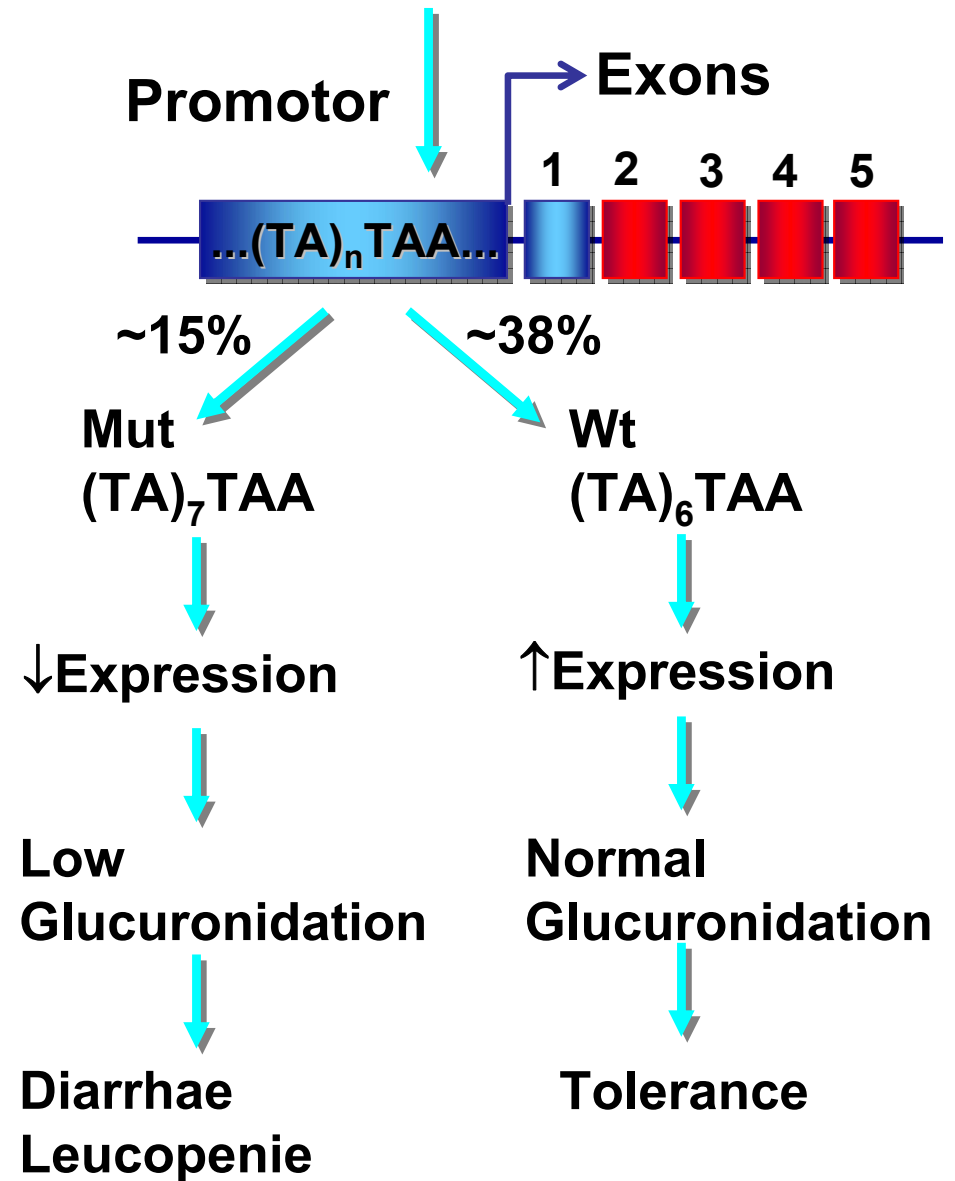
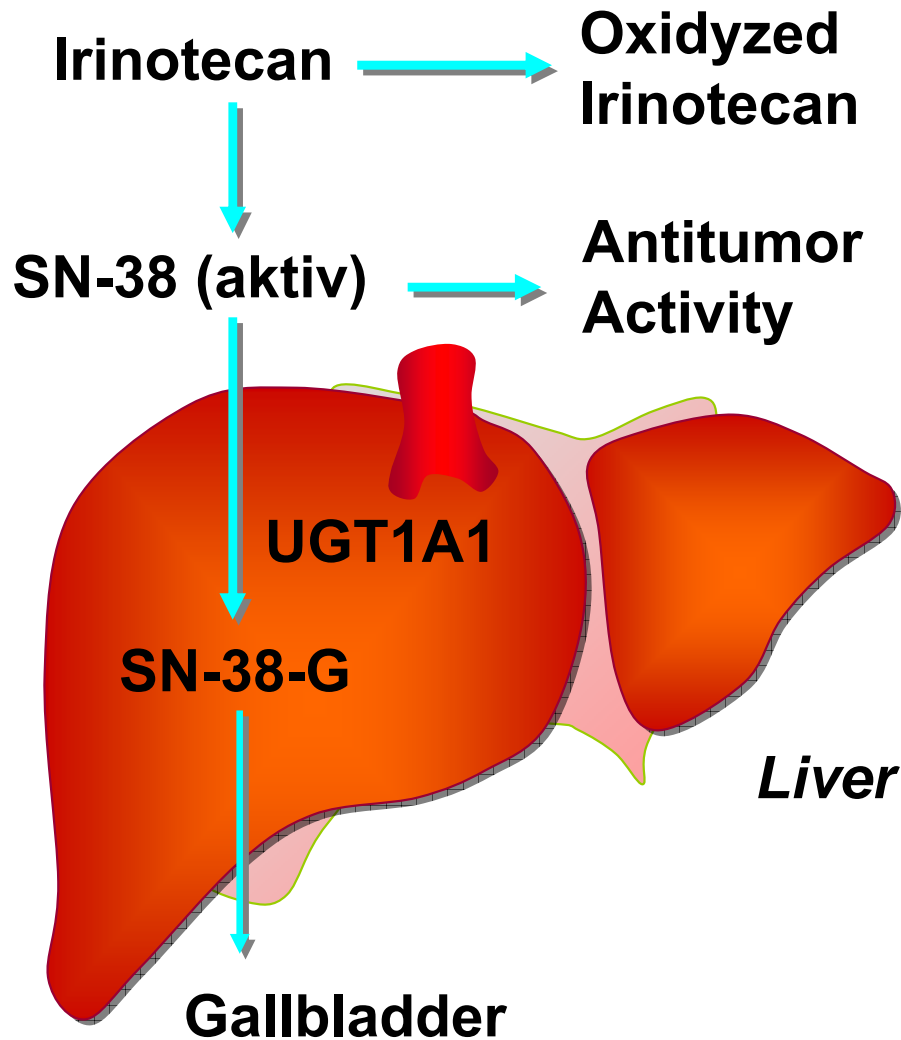
Topoisomerase Inhibitoren

Irinotecan

Mechanismus und Metabolismus von CPT-11



UGT1A1 – Polymorphismus



Risiko für Grad 3+4 Neutropenie unter CPT-11
7/7 vs 6/6 + 6/7 Genotypes
- unadjusted Odds Ratio

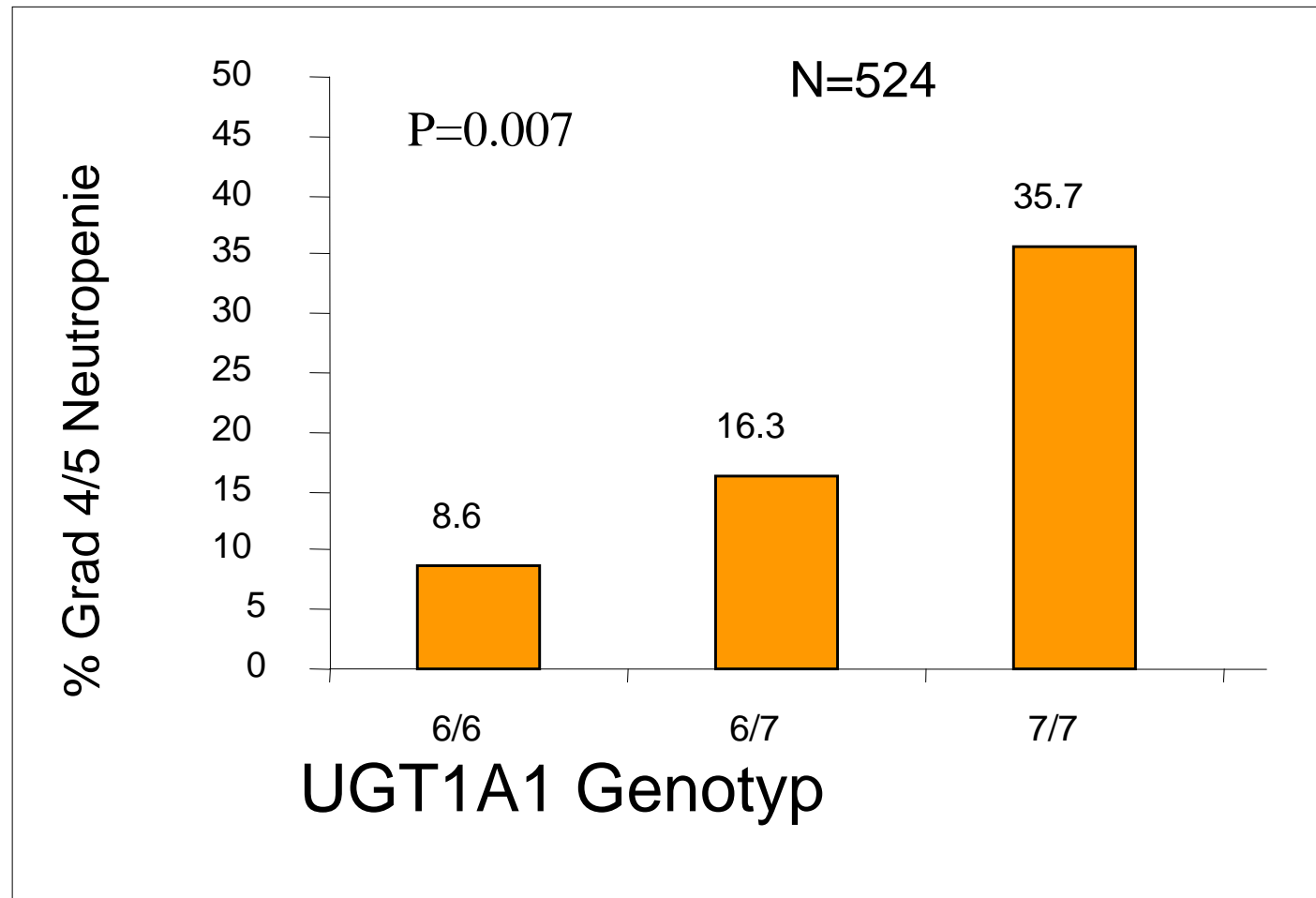
Author	n/N (%)		Est. Odds Ratio	95% CI
	7/7	6/6 + 6/7		
Innocenti	3/6 (50%)	3/53 (6%)	16.7	2.3 - 120.6
Rouits	4/7 (57%)	10/66 (15%)	7.5	1.4 - 38.5
Marcuello ^a	4/10 (40%)	18/85 (21%)	2.5	0.6 - 9.7
Ando ^b	4/7 (57%)	22/111 (20%)	5.4	1.1 - 25.9

^aGr 3+ neutropenia.

^bGr 4 leukopenia and/or Gr 3+ diarrhea.

From Parodi et al, FDA Subcommittee presentation, November, 2004

UGT1A1 Polymorphismus und Neutropenie unter CPT-11



Revised Camptosar[®] label

population is homozygous for the UGT1A1*28 allele. In a prospective study, in which irinotecan was administered as a single-agent on a once-every-3-week schedule, patients

Patients with Reduced UGT1A1 Activity

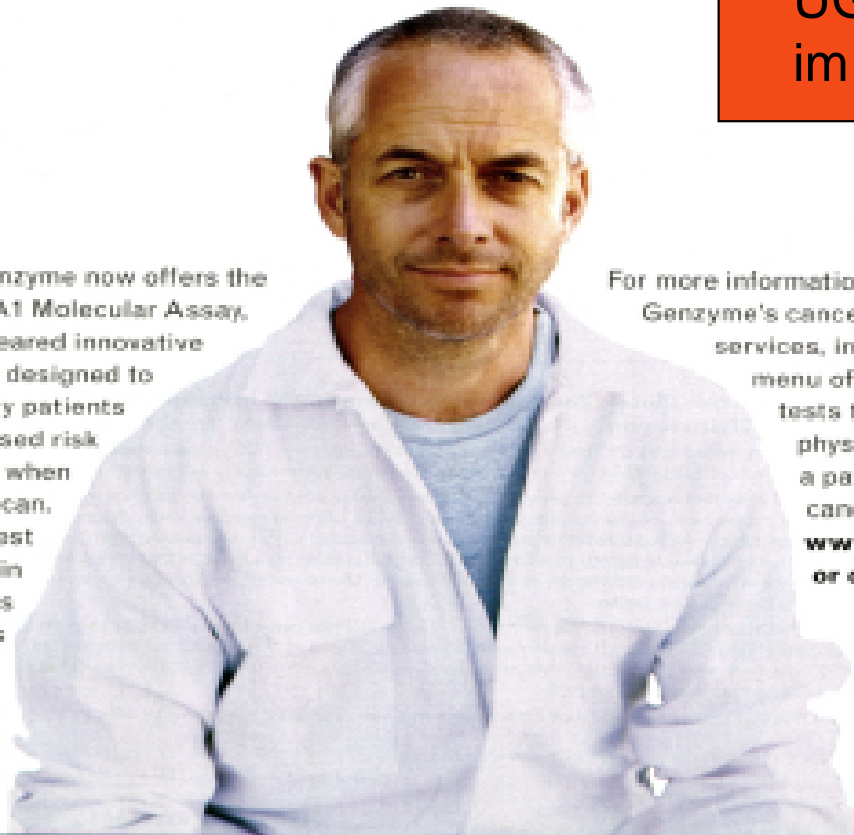
Individuals who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia following initiation of CAMPTOSAR treatment. A reduced initial dose should be considered for patients known to be homozygous for the UGT1A1*28 allele (see DOSAGE AND ADMINISTRATION). Heterozygous patients (carriers of one variant allele and one wild-type allele which results in intermediate UGT1A1 activity) may be at increased risk for neutropenia; however, clinical results have been variable and such patients have been shown to tolerate normal starting doses.

A reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele (See CLINICAL PHARMACOLOGY and WARNINGS). The appropriate dose reduction in this patient population is not known.

Carl has metastatic colorectal cancer.
Now Genzyme can help you determine his
risk of serious adverse effects

before
he starts therapy.

Revidierter CPT-11 Beipackzettel &
UGT1A1 Test von FDA zugelassen
im Sommer 2005



Genzyme now offers the
Invader® UGT1A1 Molecular Assay,
an FDA-cleared innovative
screening test designed to
help you identify patients
who are at increased risk
for severe toxicity when
treated with Irinotecan.
This simple blood test
will assist you in
making adjustments
in your patient's
therapy before
adverse effects
occur.

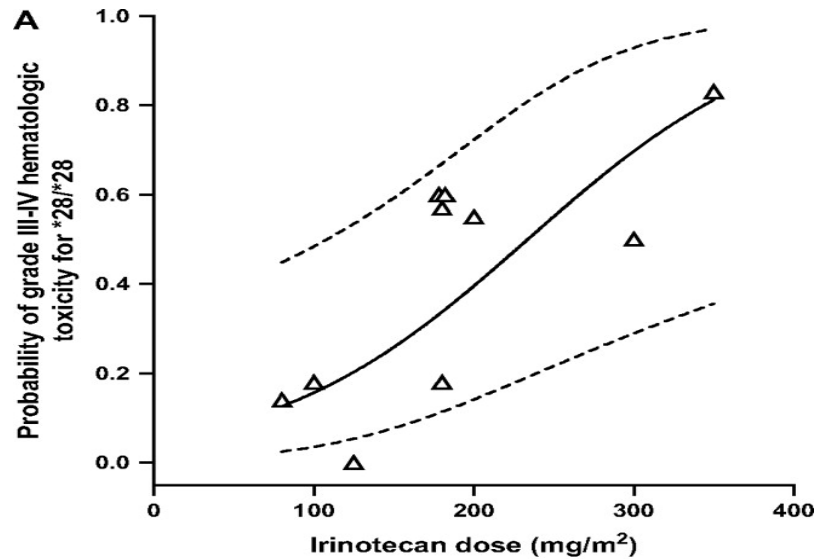
For more information about
Genzyme's cancer testing
services, including our
menu of innovative
tests that can help
physicians understand
a patient's response to
cancer therapy, visit
www.genzymegenetics.com
or call (800) 447-5816.

Invader® is a registered trademark of
Third Wave Technologies, Inc.
The Invader® UGT1A1 Molecular Assay™
is manufactured and distributed by Third
Wave Technologies, Inc.

Experience Tomorrow's Cancer Testing Laboratory Today.

genzyme

Metaanalyse zum UGT1A1 Genotyp und CPT-11 Toxizität n=821 (9 Studien)

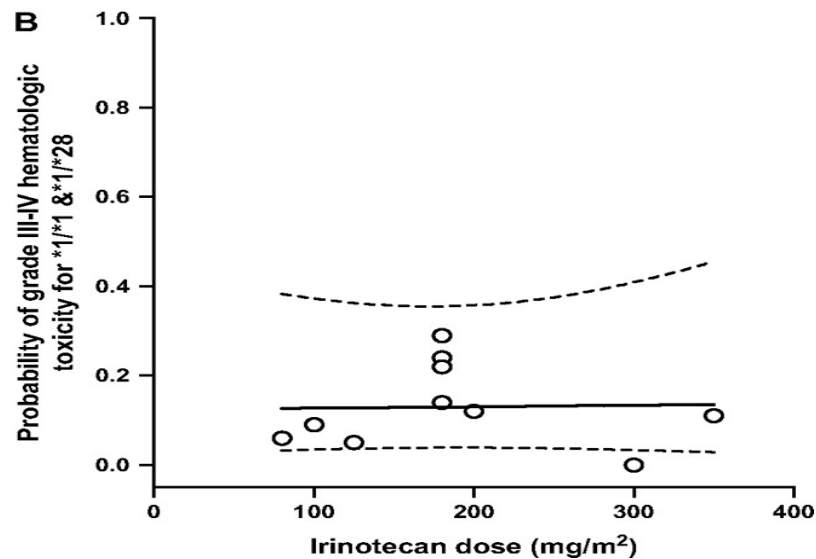


Relationships between irinotecan dose and incidence of hematologic toxicity in patients with a

UGT1A1*28/*28 genotype (A)

and in those with a

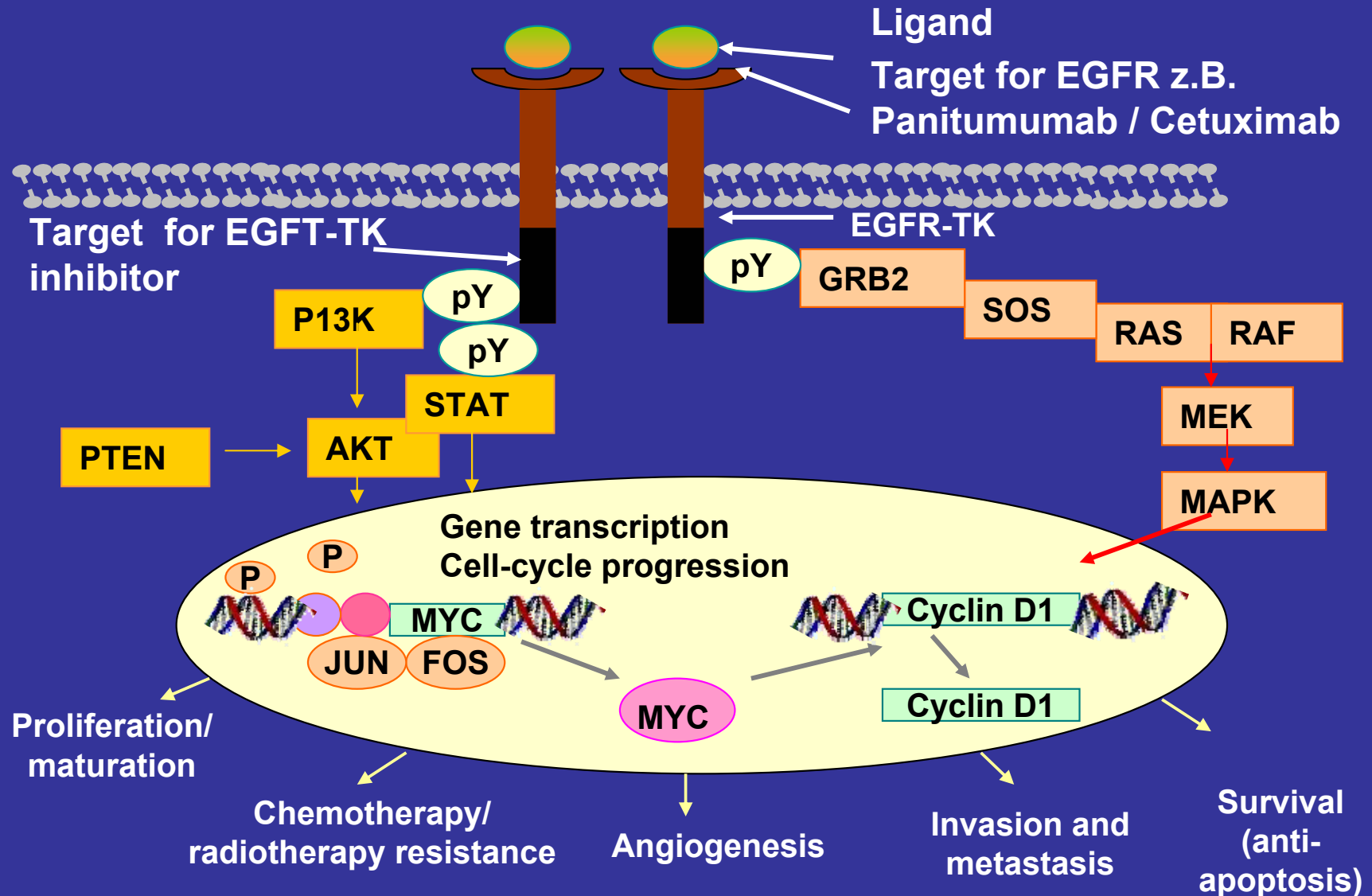
UGT1A1*1/*1 or UGT1A1*1/*28 genotype (B)



**EGFR – Inhibitoren
(Panitumumab, Cetuximab)**

KRAS - Mutationen

EGF Rezeptor und KRAS - Funktion



Rationale für Untersuchung von KRAS

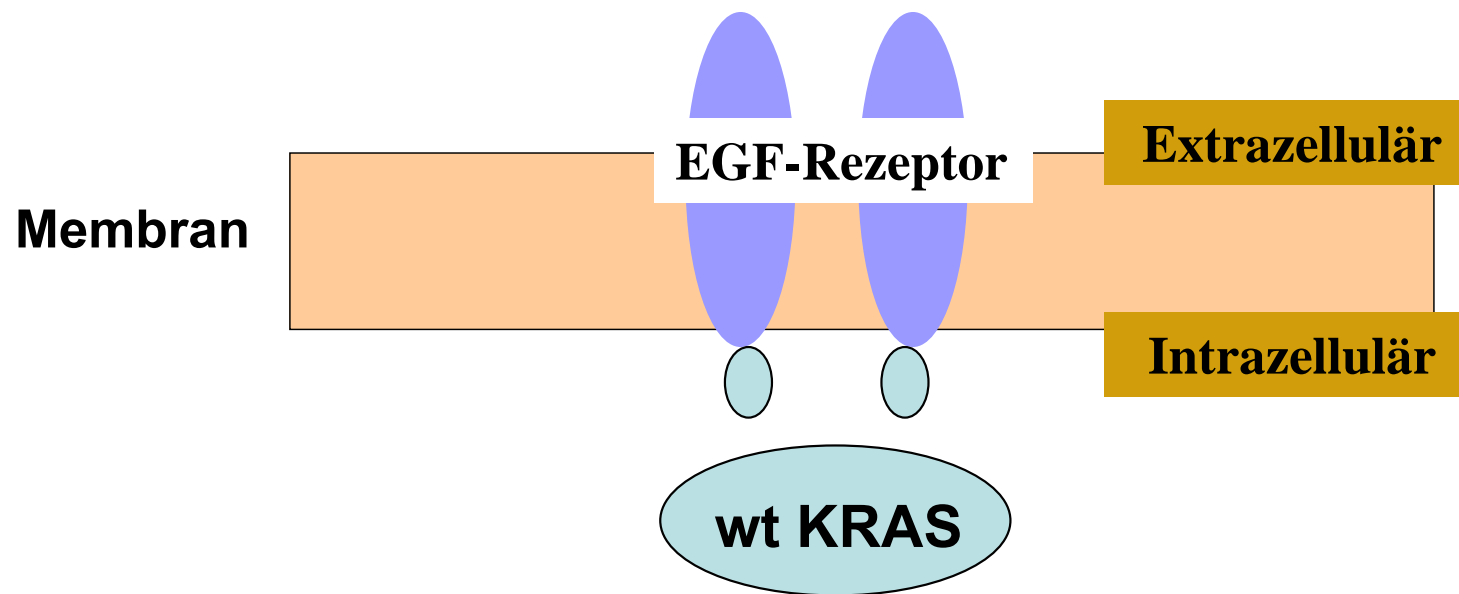
Erreichbarer Aktivierungszustand von KRAS

ist mit entscheidend bei EGFR-Inhibition -

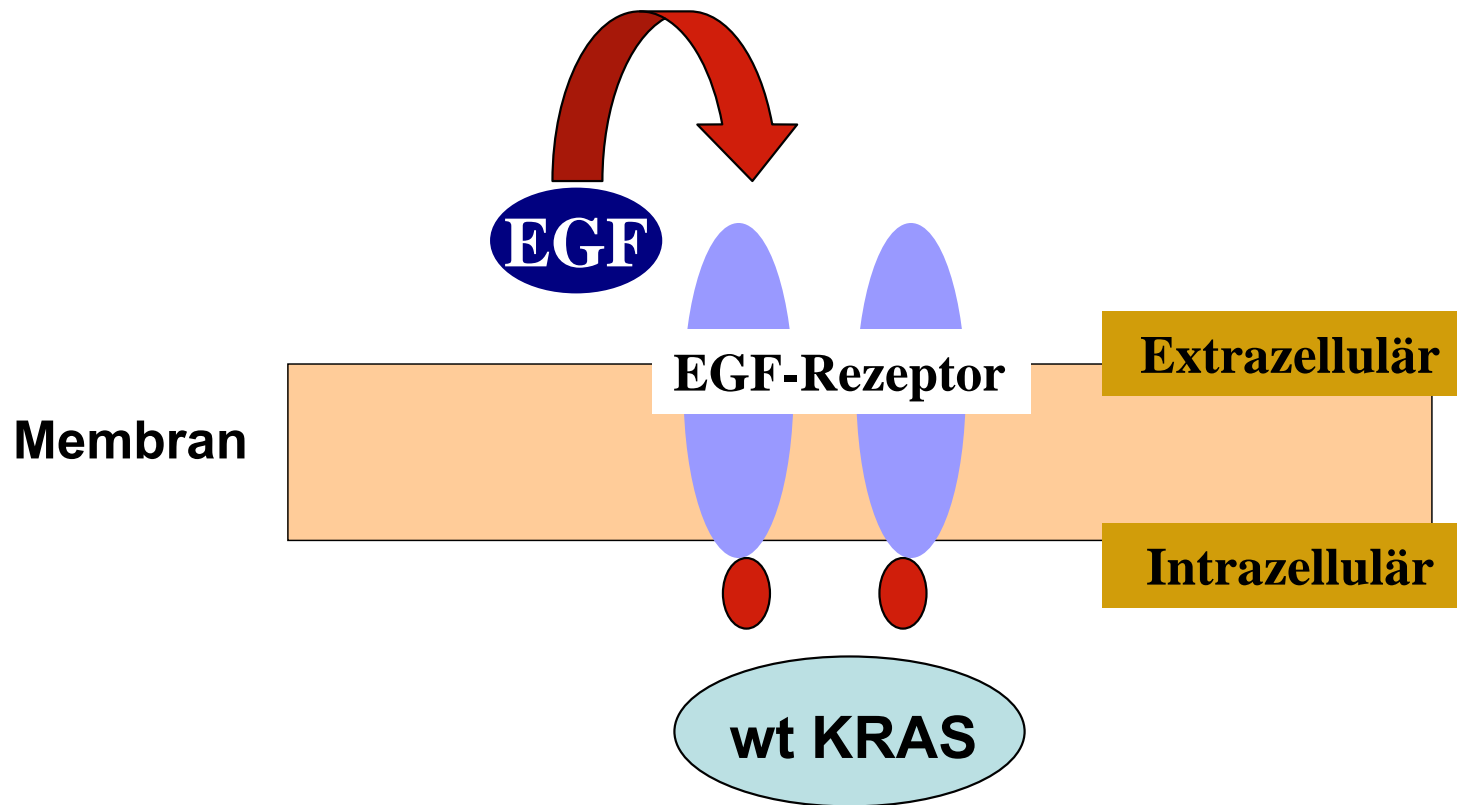
nicht allein der Aktivitätszustand von EGFR

Aktivierende KRAS Mutationen in 35-45% der CRC

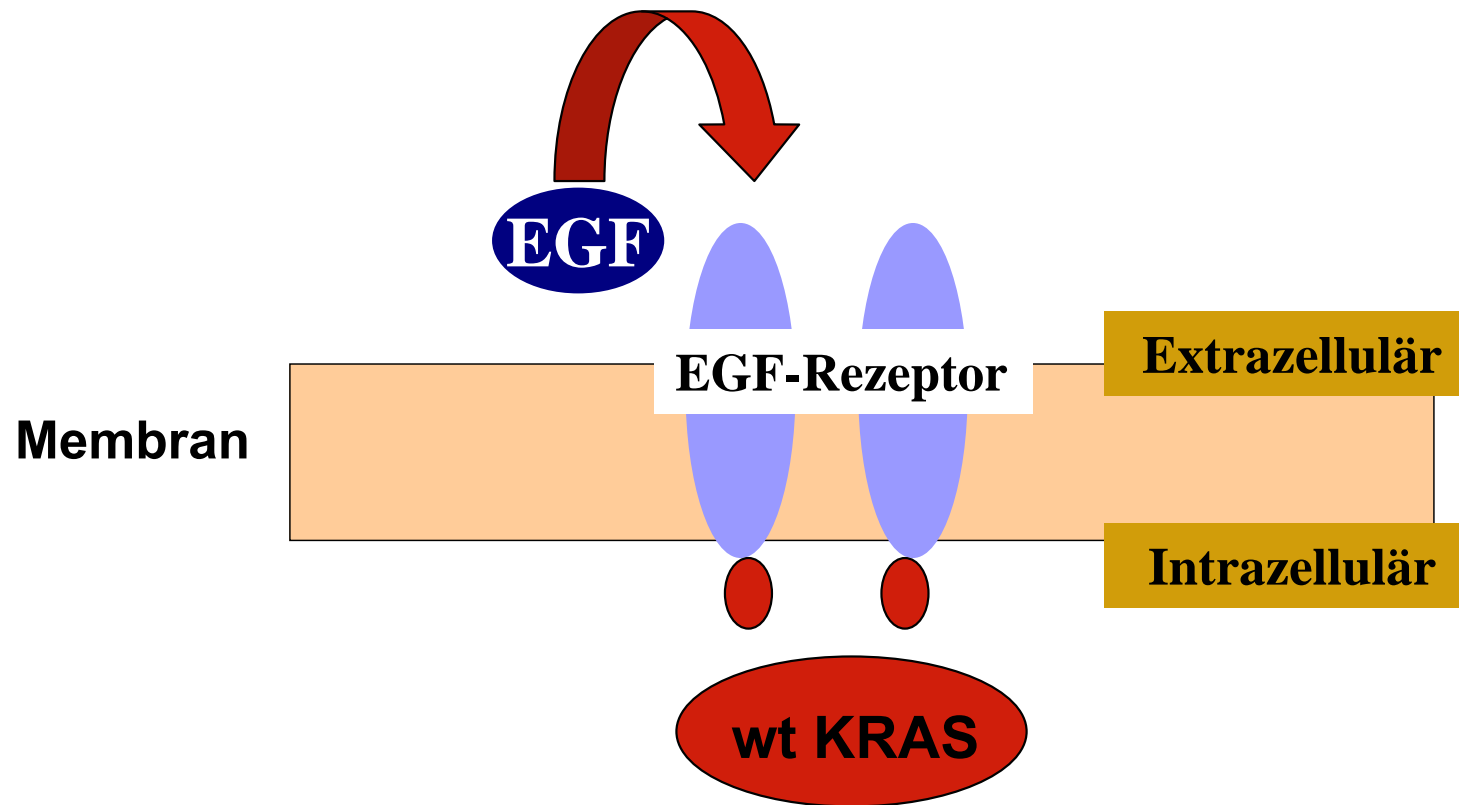
Pathway ohne KRAS - Mutationen



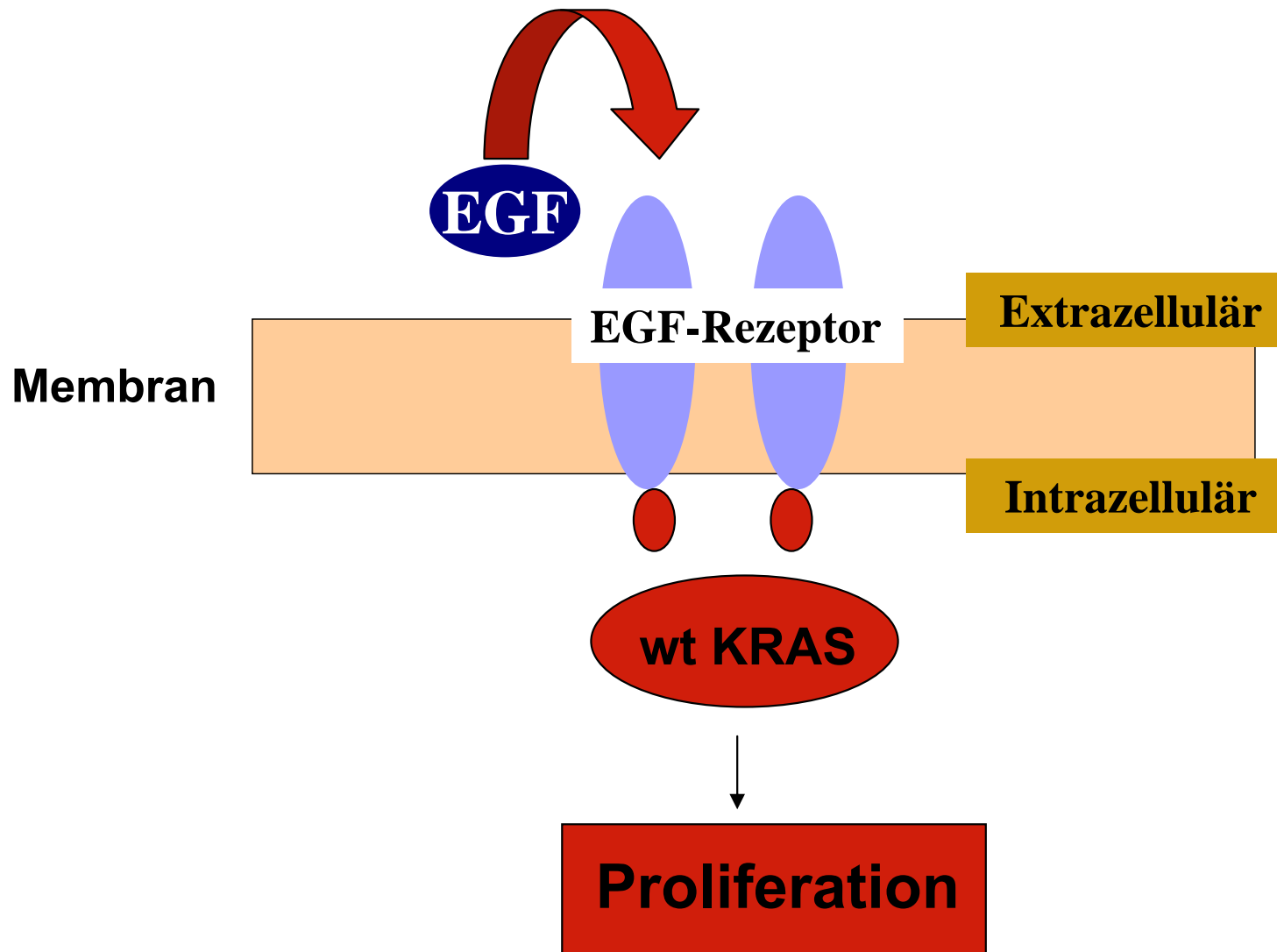
Pathway ohne KRAS - Mutationen



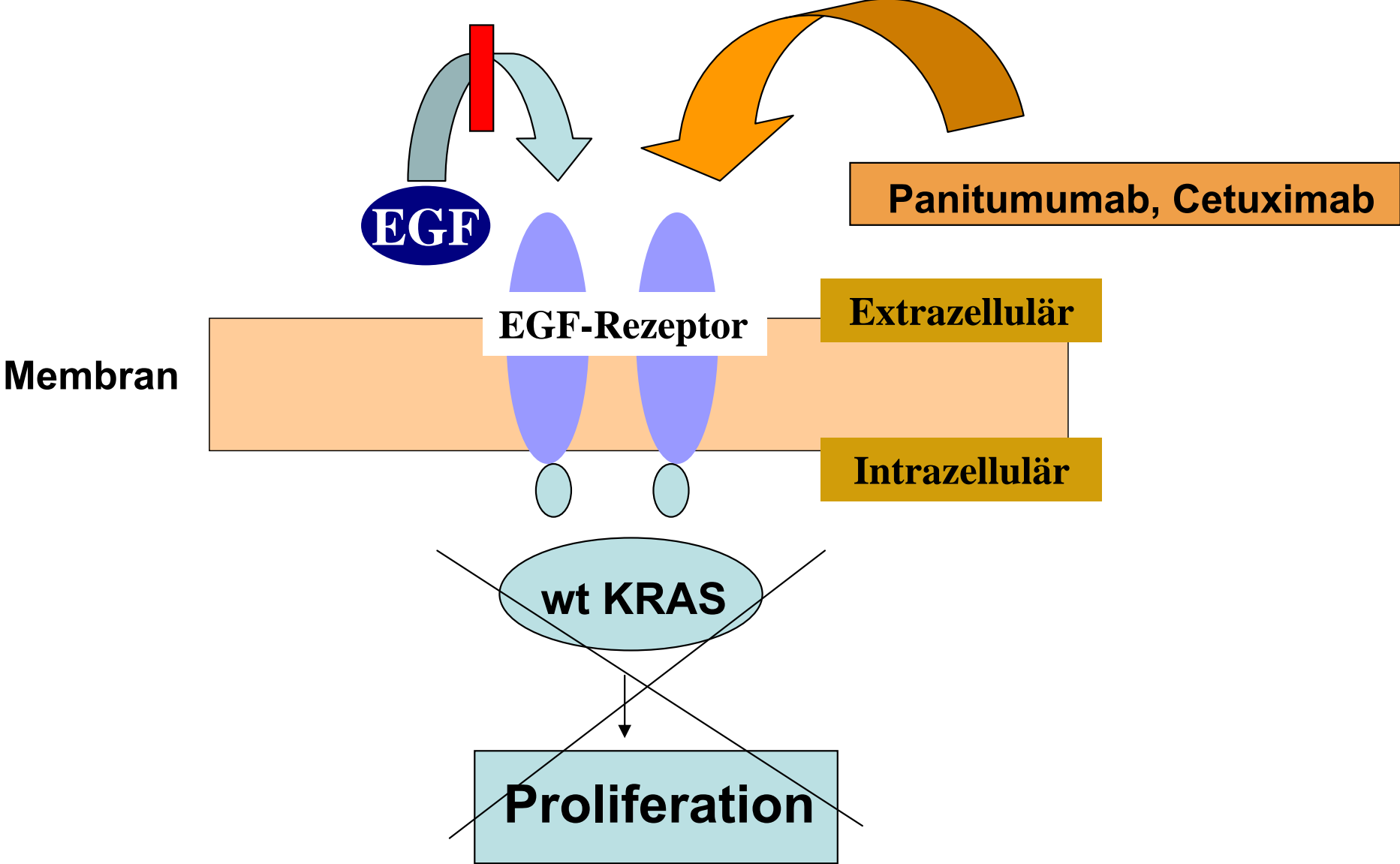
Pathway ohne KRAS - Mutationen



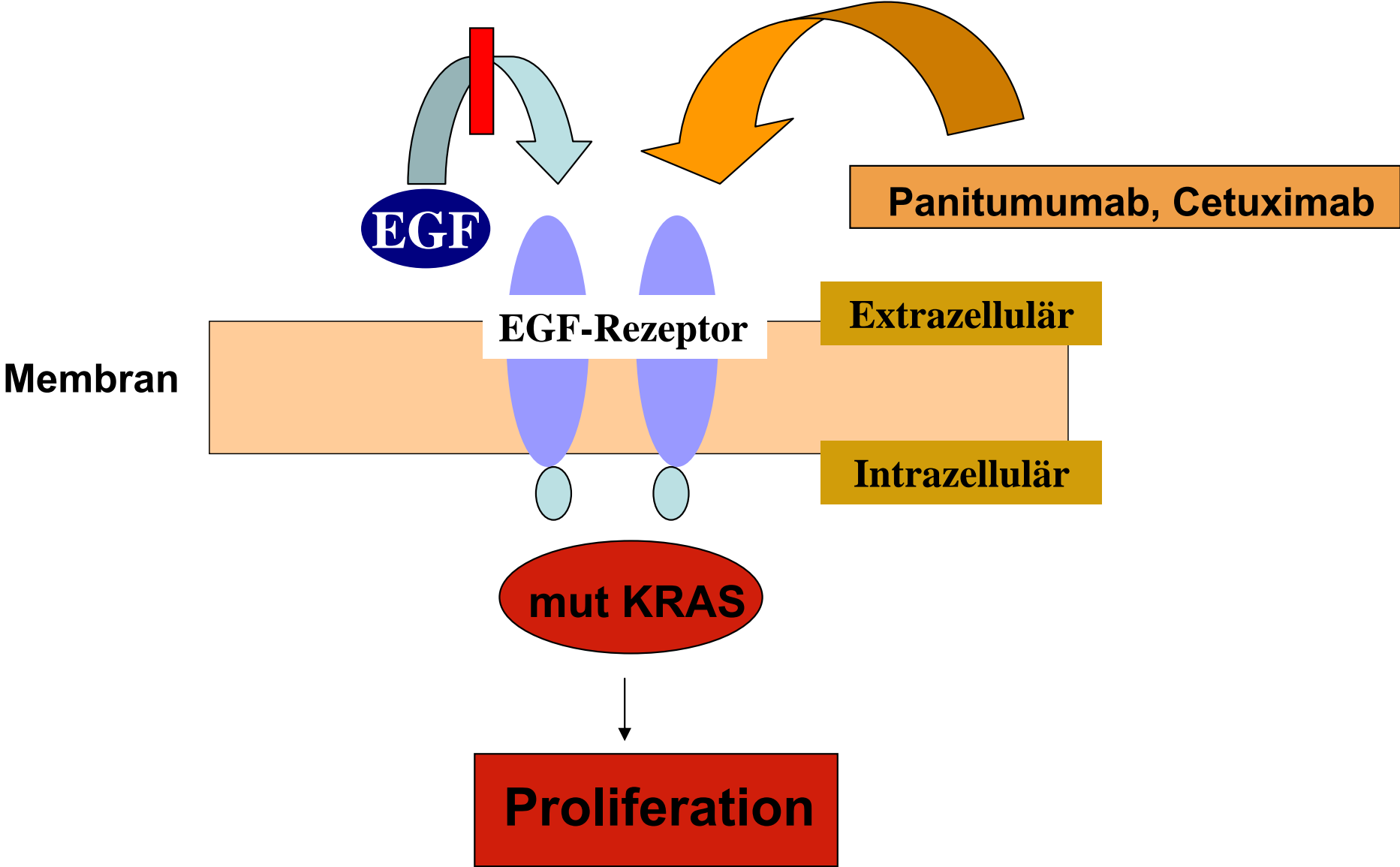
Pathway ohne KRAS - Mutationen



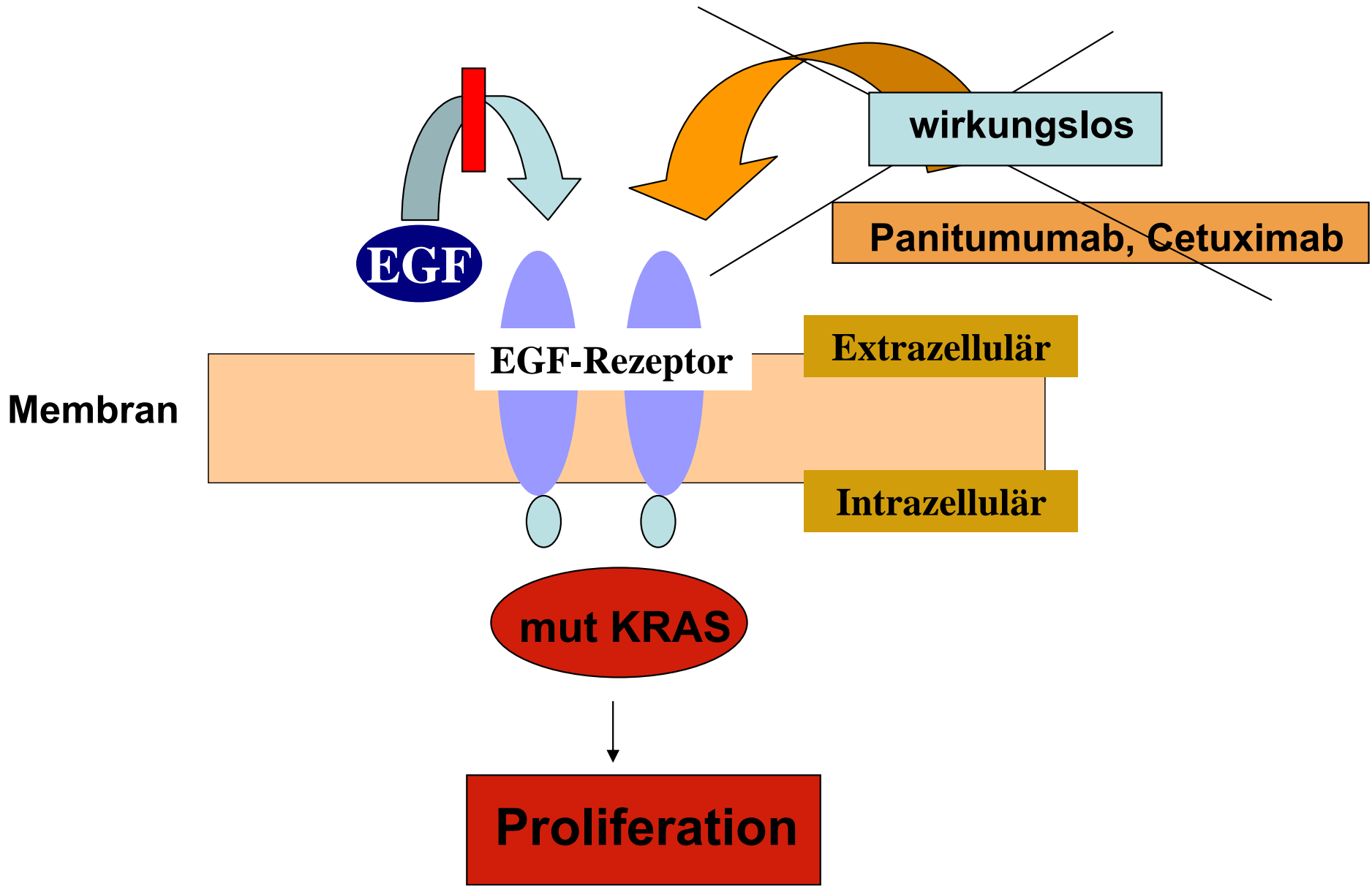
Pathway ohne KRAS - Mutationen

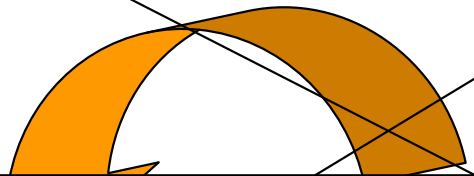
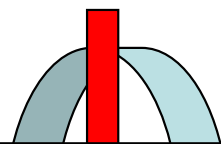


Pathway mit KRAS - Mutationen



Pathway mit KRAS - Mutationen





unab

Mem

**KRAS Mutationen sind
aktivierende Mutationen**

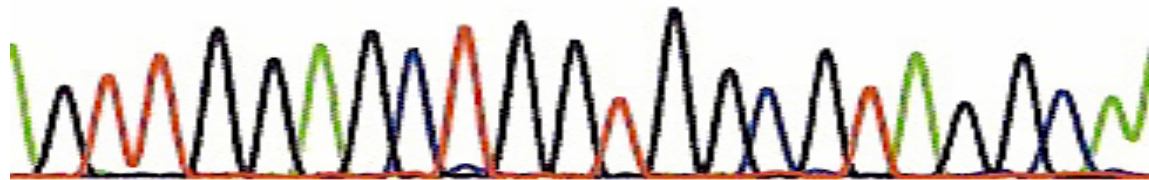
**Proliferationsreiz wird unabhängig von
EGF-Rezeptor Inhibition vermittelt**



Formen von KRAS - Mutationen

AGTTGGAGCTGCTGCCGTAGGCA
92 105

Wildtype



12
GGT (Glycine)

13
GGC (Glycine)

Basensequenz	Aminosäure	Basensequenz	Aminosäure
GTT	Valine	GAC	Aspartat
GAT	Aspartat	GCC	Alanin
AGT	Serin	GTC	Valin
TGT	Cystein		

**Translationale Daten zu KRAS
beim Kolorektalen Karzinom
(Cetuximab)**

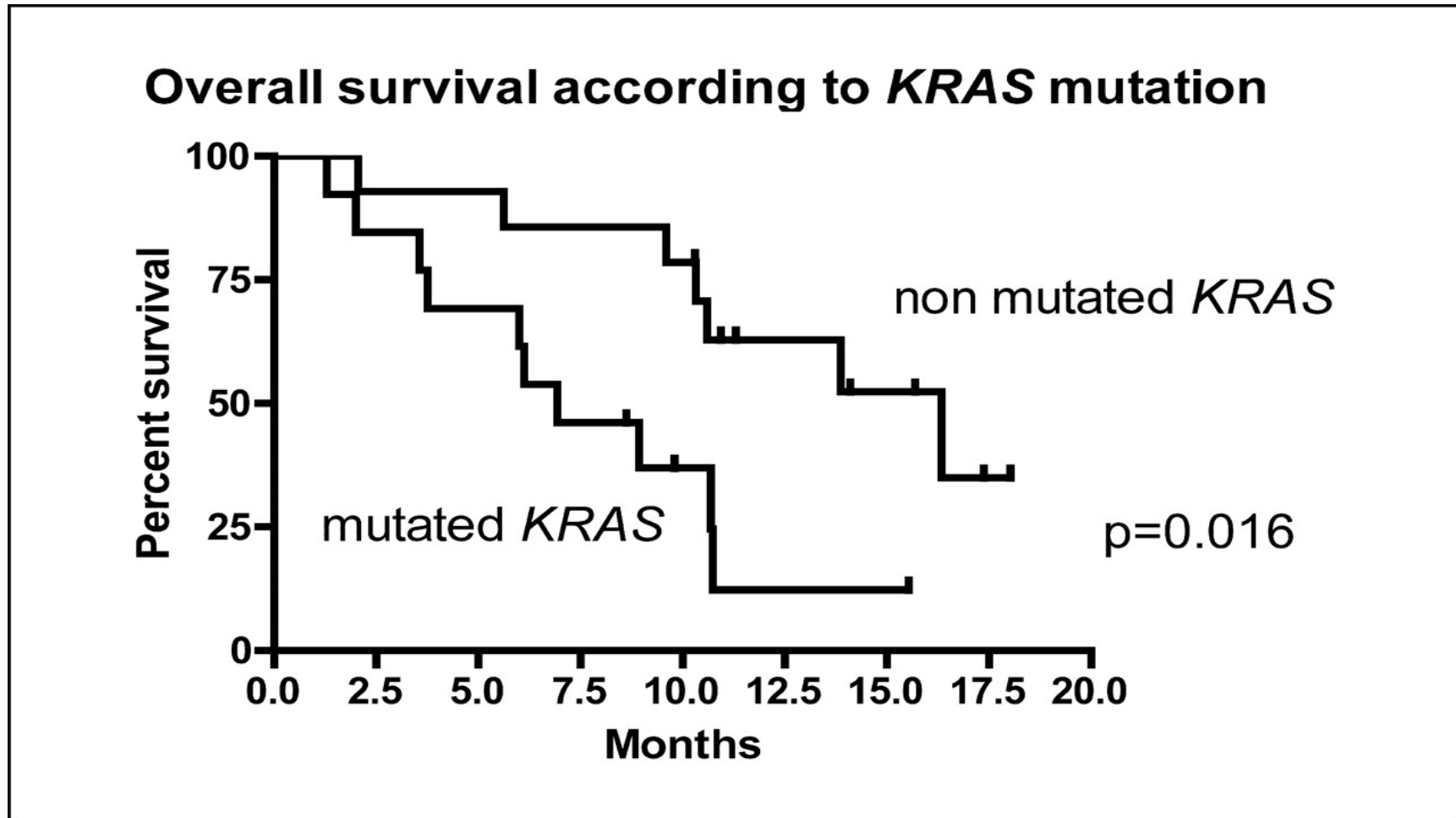
KRAS - Mutationen in CRC unter EGFR-Inhibition

2nd & 3rd Line CRC Patienten (Cetuximab ± Irinotecan) n=76

K – ras Mutation Nachweis p<0.001

	Positiv	Negativ
	27 (100%)	49 (100%)
Non-responder	27 (100%)	24 (49%)
Responder	0 (!)	25 (51%)

KRAS - Mutationen in CRC unter EGFR-Inhibition



KRAS - Mutationen in CRC unter EGFR-Inhibition

2nd & 3rd Line CRC Patienten (Cetuximab \pm Irinotecan) n=76

K – ras Mutation Nachweis $p < 0.001$

Positiv

Negativ

	27 (100%)	49 (100%)
Non-responder	27 (100%)	24 (49%)
Responder	0 (!)	25 (51%)

Assoziation auch in multivariater Analyse einschl. Hauttoxizität* signifikant

HR 3.50 (95% CI 1.88-6.51; $p < 0.0001$)

*Progression bei KRAS-Mutation in Patienten mit Hauttoxizität > G1°

KRAS - Mutationen in CRC unter EGFR-Inhibition

Author	n (total)	Responder bzw. Disease control* n(%)	
		KRAS wt	KRAS mutant
Lievre et al. AACR 2007	25 (76)	25 (100%)	0 (0%)
Finocchiaro et al. ASCO 2007	15 (81)	13 (87%)	2 (13%)
Ford et al.* JCO 25:3230-7	27 (80)	24 (89%)	3 (11%)
De Roock et al. ASCO 2007	8 (37)	8 (100)	0 (0%)
		75 (100%)	5 (7%)

Cappuzzo et al. ECCO 2007 #3002: 85 pts. KRAS mut sign. weniger Ansprechen

KRAS - Mutationen in CRC unter EGFR-Inhibition

Author	n (total)	Responder bzw. Disease control* n(%)	
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		75 (100%)	5 (7%)

Cappuzzo et al. ECCO 2007 #3002: 85 pts. KRAS mut sign. weniger Ansprechen

KRAS - Mutationen in CRC unter EGFR-Inhibition

Tumor shrinkage

De Roock et al. ASCO 2007 #4132

N = 37 Patienten

Messung der Tumorgröße im Vergleich zu Baseline nach 12 + 24 Wo

	KRAS wt	KRAS mut	
12 Wochen	23% ↓	2.6% ↑	p=0.0081
24 Wochen	46% ↓	1.3% ↓	p=0.0015

SD-Patienten : nur Patienten mit KRAS wt zeigten Abnahme der Tumorgröße

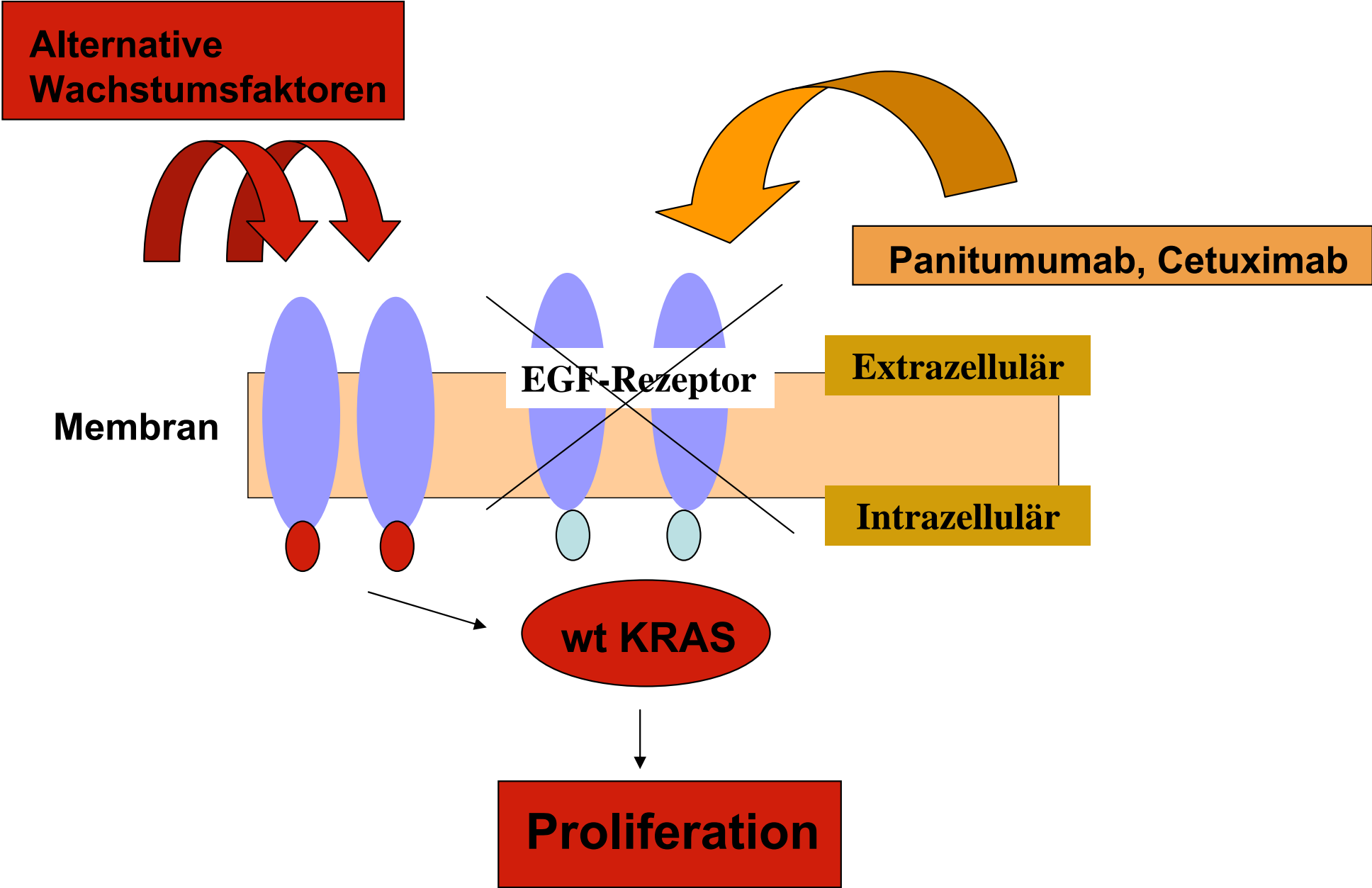
Assoziation mit Tumor shrinkage → neoadjuvante Konzepte !

KRAS - Mutationen in CRC unter EGFR-Inhibition

2nd & 3rd Line CRC Patienten (Cetuximab ± Irinotecan) n=76

	K – ras Mutation Nachweis $p<0.001$	
	Positiv	Negativ
	27 (100%)	49 (100%)
Non-responder	27 (100%)	24 (49%)
Responder	0 (!)	25 (51%)

Pathway ohne KRAS - Mutationen



Zusammenfassung

Erste pharmakogenetische Daten mit klinischem Potential

5-FU

TS-Polymorphismen

Platinderivate

GSTP1 Polymorphismen

Score erscheint sinnvoll

Irinotecan

UGT1A1 Polymorphismus

EGFR-Inhibitoren

KRAS Mutationen