11. Jahrestagung der Berlin-Brandenburgischen Gesellschaft für Gastroenterologie und Hepatologie

Endlich Relevanz für molekulare Marker beim KRK?!

Thomas Seufferlein

Klinik für Innere Medizin I

Universität Ulm

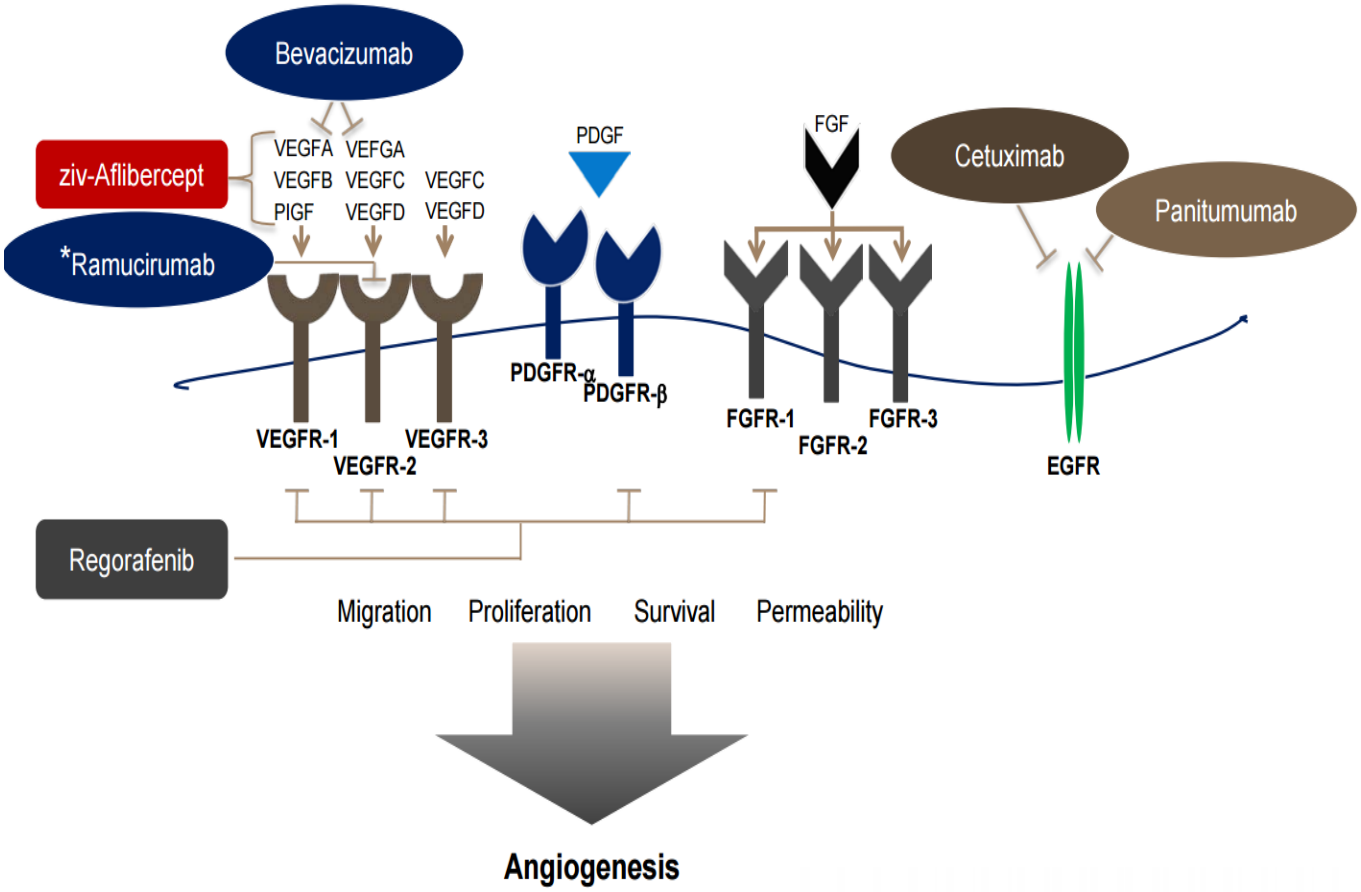
ulm university universität ulm

Therapiespektrum beim metastasierten KRK

Combination Chemo

- FOLFOX
- FOLFIRI
- XELOX
- FLOX
- XELIRI
- FOLFOXIRI
- TAS102

Targeted Therapy



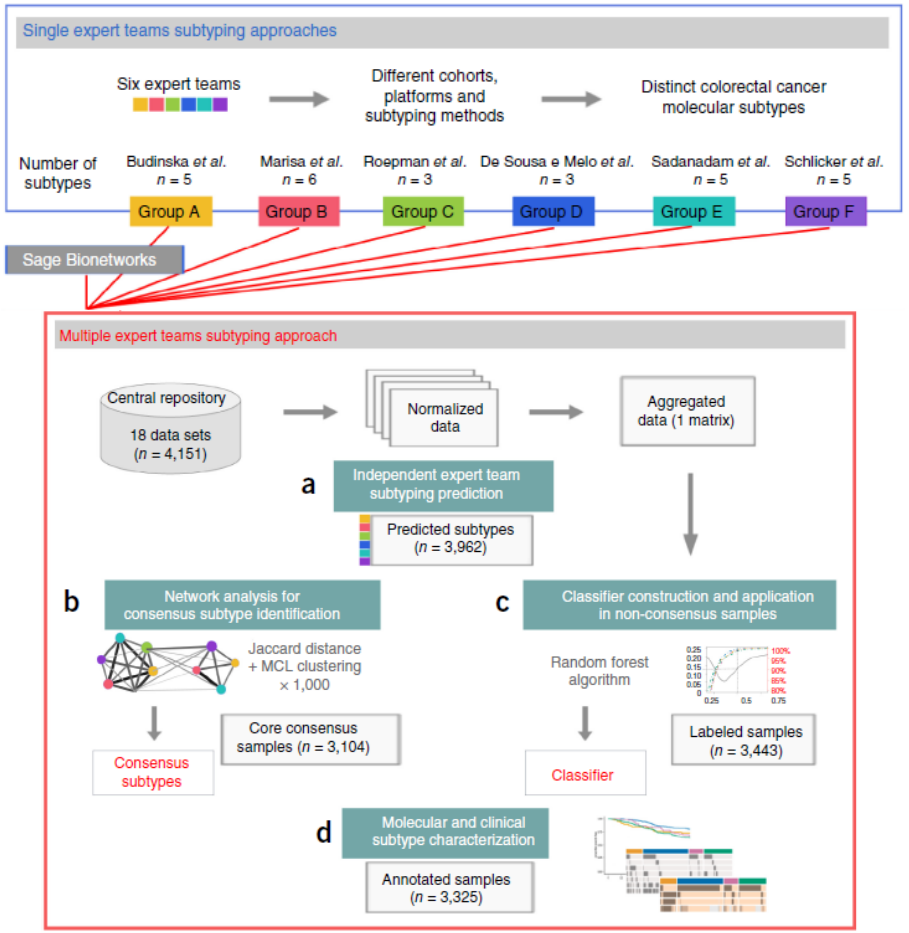
Fakih. J Clin Oncol. 2015;33:1809-1824.; Clarke & Hurwitz. J Gastrointest Oncol. 2013;4:253

Molekulare Klassifizierung kolorektaler Karzinome

The consensus molecular subtypes of colorectal cancer

- 6 unabhängige Klassifikations-systeme

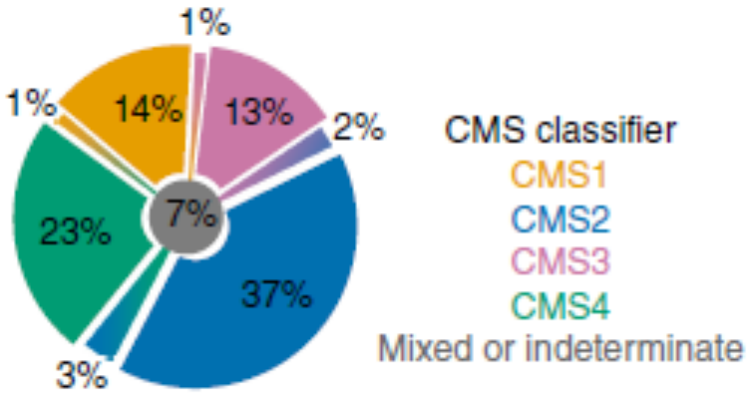
- 4 Consensus molecular subtypes (CMSs)
- Primärtumor

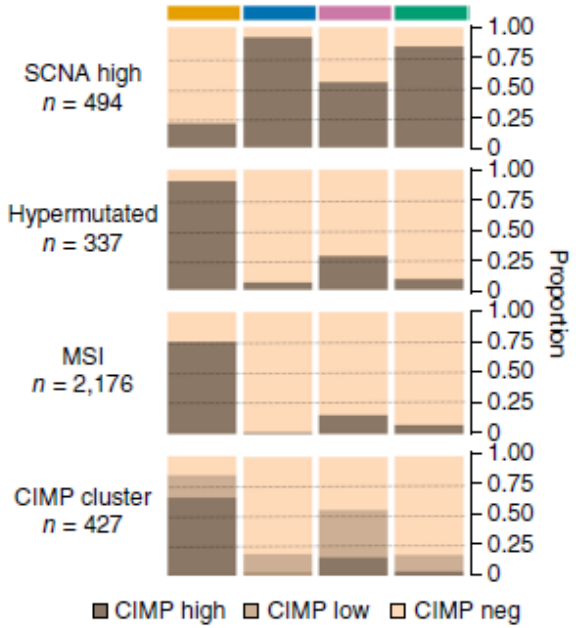


Guinney , Nat. Med. 2015

The consensus molecular subtypes of colorectal cancer

- **CMS1: Mikrosatellite instability, immune, 14%**
  - **Hypermutiert, hypermethyliert, MSI**
  - **Starke Immunaktivierung**
  - **Überexpression von Proteinen der DNA Damage Repair**
- **CMS2: Canonical, 37%**
  - **Epithelial: WNT und MYC Signalaktivierung**
- **CMS3: Metabolic, 13%**
  - **Epithelial, metabolische Dysregulatoin**
- **CMS4: Mesenchymal, 23%**
  - **TGFb-Aktivierung: Stromale Invasion**
  - **Angiogenese**
- **Mixed: 13%**
  - **Mischtyp oder intratumorale Heterogenität**



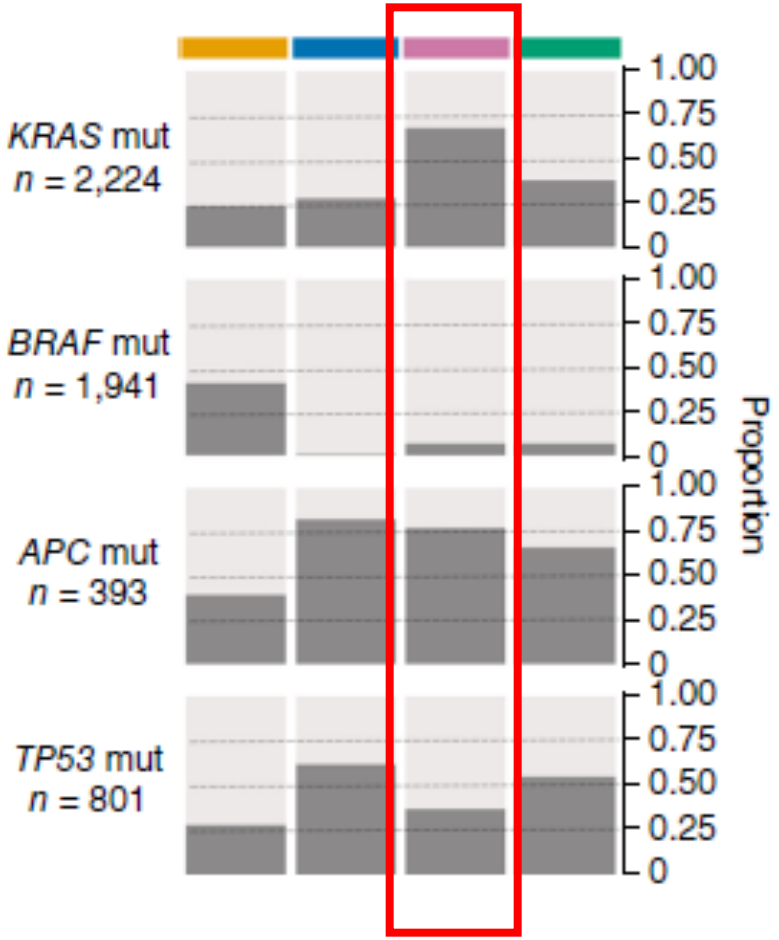


Prognostische Relevanz der Subgruppen

CMS1 MSI immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration, TGF-β activation, angiogenesis
Worse survival after relapse			Worse relapse-free and overall survival

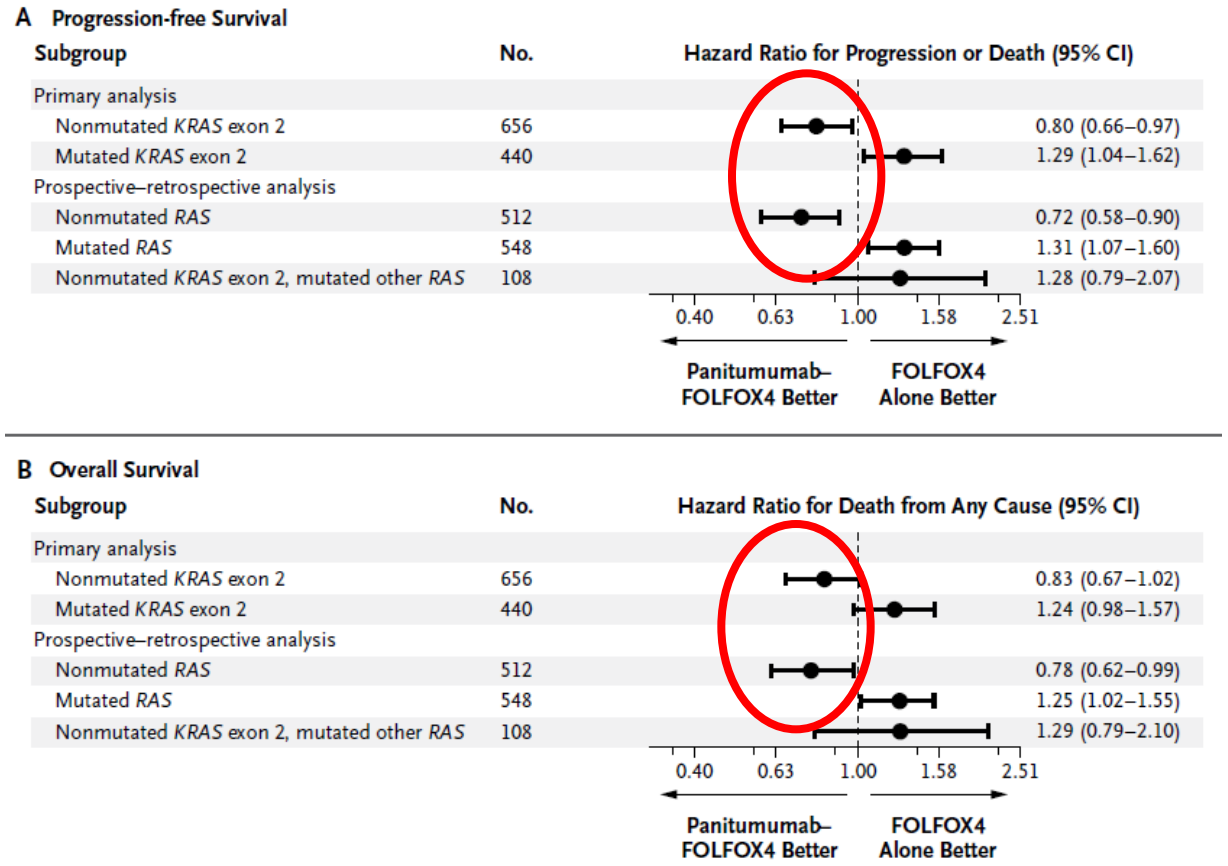
Guinney , Nat. Med. 2015

Ras Mutationen in den Subgruppen



Guinney , Nat. Med. 2015

Nur Patienten mit Ras Wildtyp Status profitieren von einer anti-EGFR Therapie



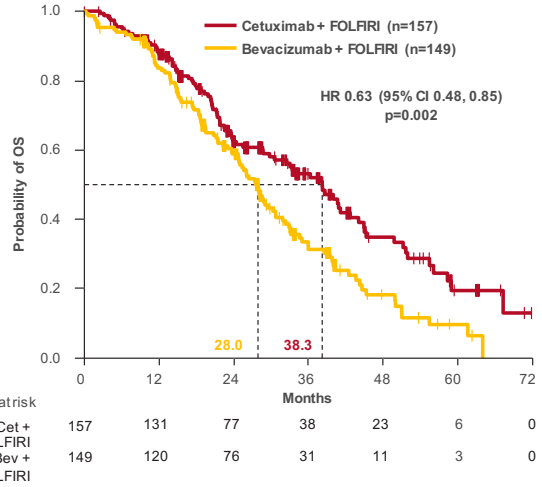
Douillard et al., NEJM 2013

„Molekulare Anatomie“ des KRK

Links

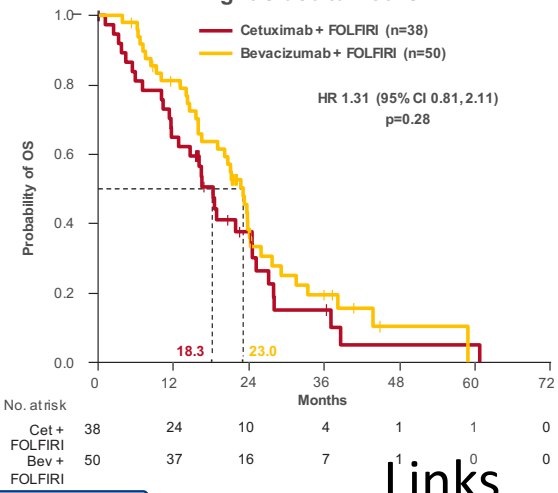
FIRE-3: OS

Left-sided tumours



Rechts

Right-sided tumours



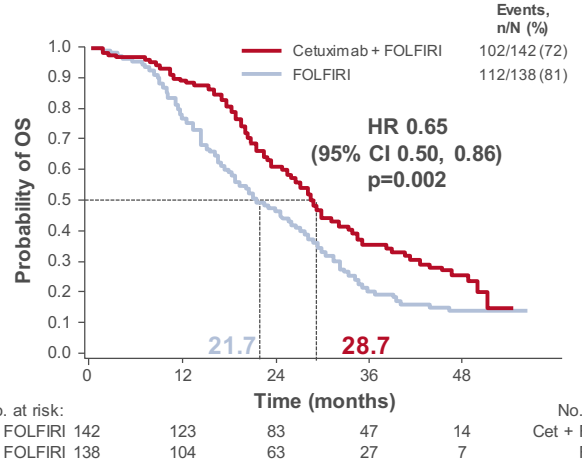
Interaction p-value: 0.009

Alle Tumoren Ras Wildtyp!

CRYSTAL: OS

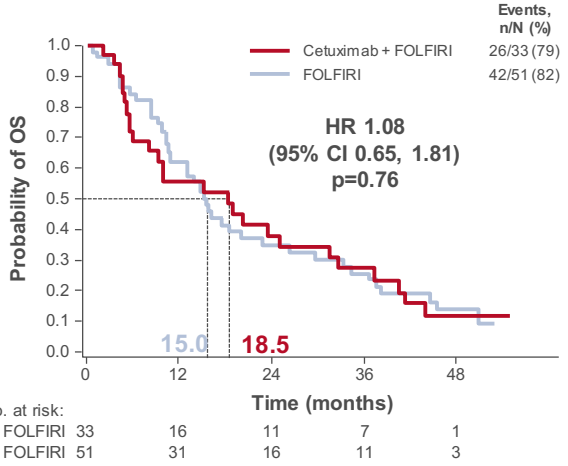
Links

Left-sided tumours



Rechts

Right-sided tumours



Interaction p-value: 0.17

Special session chaired by J Tabernero and F Ciardiello
Presentations by V Heinemann (FIRE-3) and E Van Cutsem (CRYSTAL)

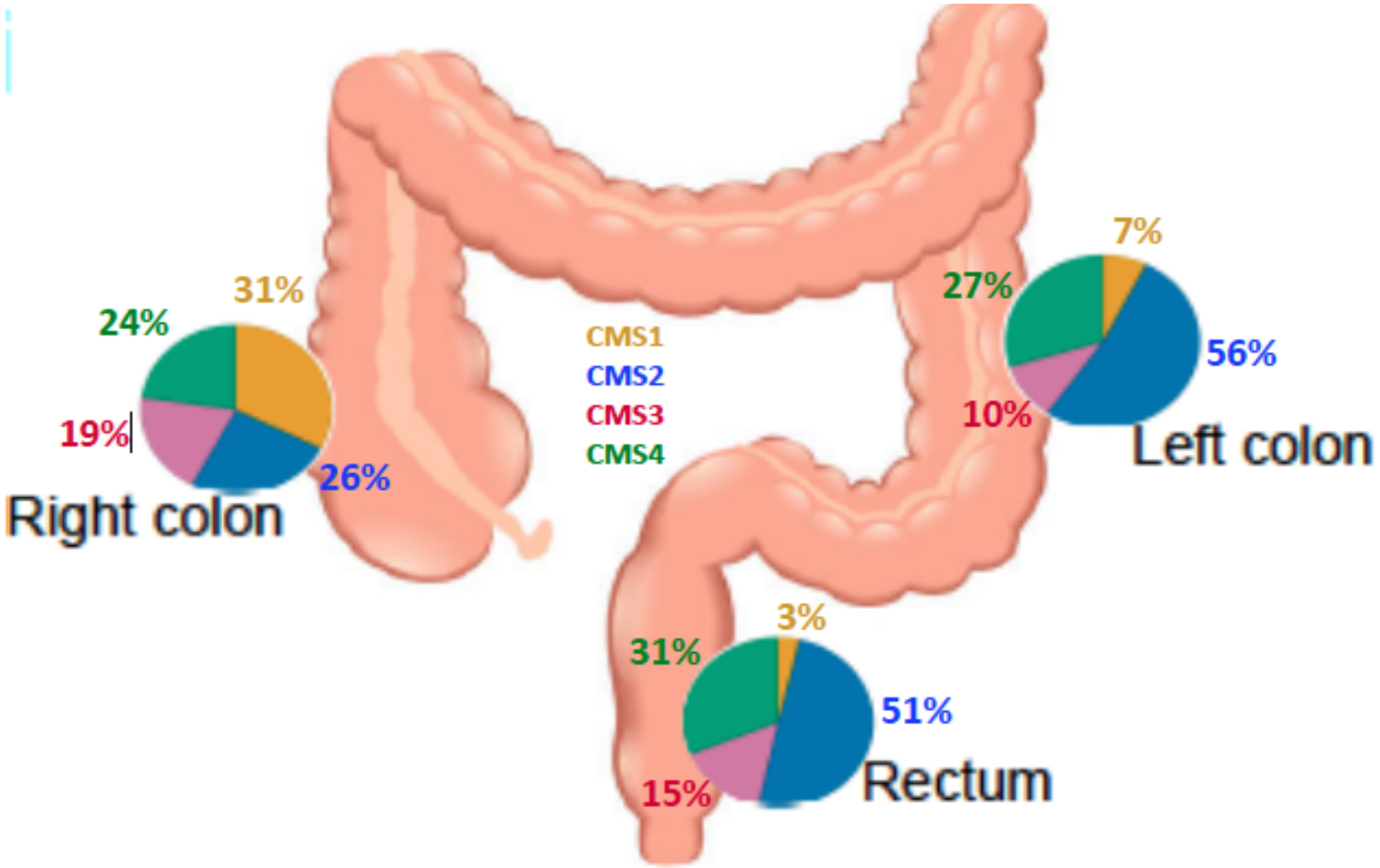
„Sideness“

- Patienten mit linksseitigem Primärtumor und Ras Wildtyp Kombinationschemotherapie und anti-EGFR Antikörper
- Patienten mit rechtsseitigem Primärtumor und Ras Wildtyp profitieren nicht von einer anti-EGFR Therapie wie die obige Gruppe und sollten eine Kombinationschemothera-pie mit anti-VEGF erhalten.

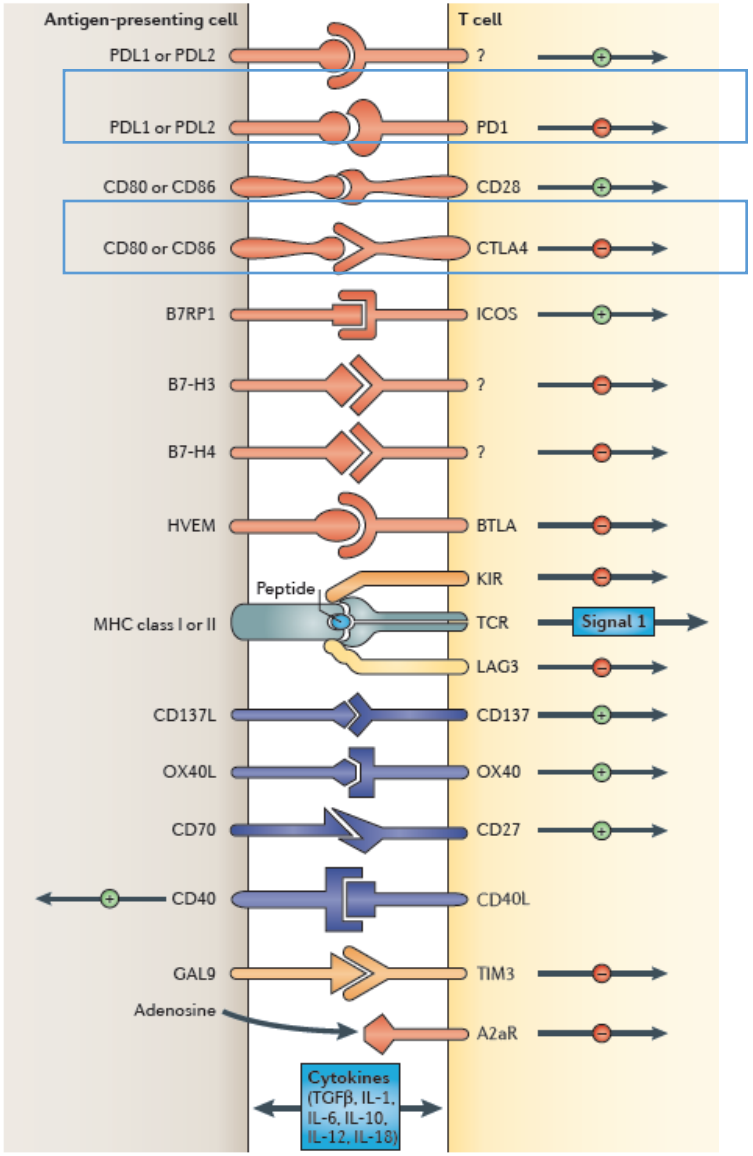
Favours left

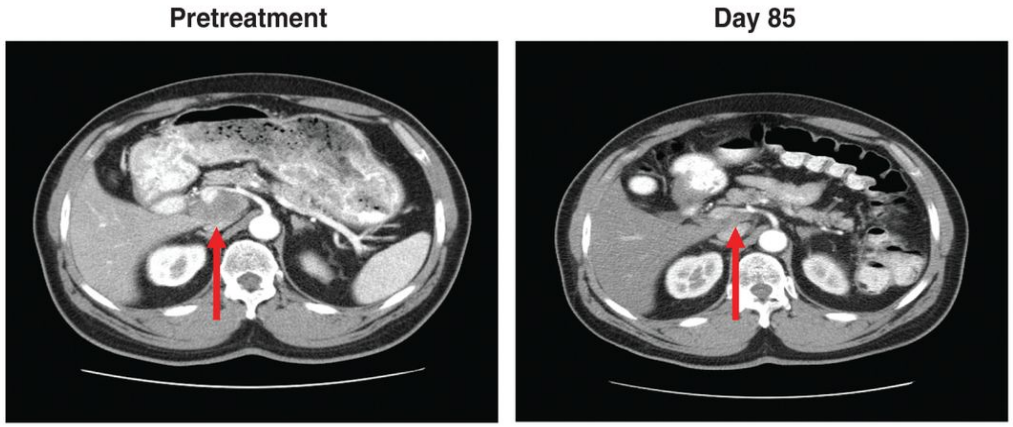
Statement AIO KRK Leitgruppe 2016

Tumorlokalisation und CMS

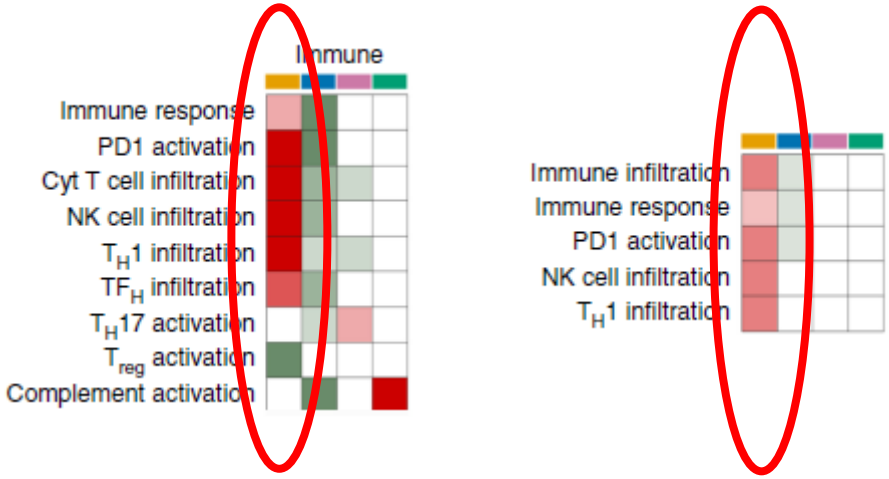


CMS I und Immunphänotyp





MSI CRC Patient mit anti-PD1 mAb behandelt



Lipson, Clin Cancer Res 2013

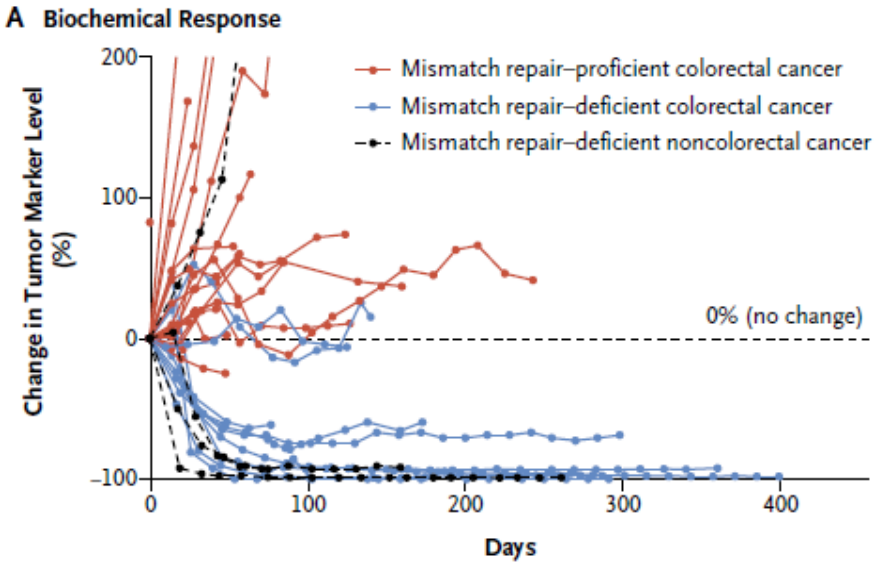
CMS1: Hypermutiert, MSI

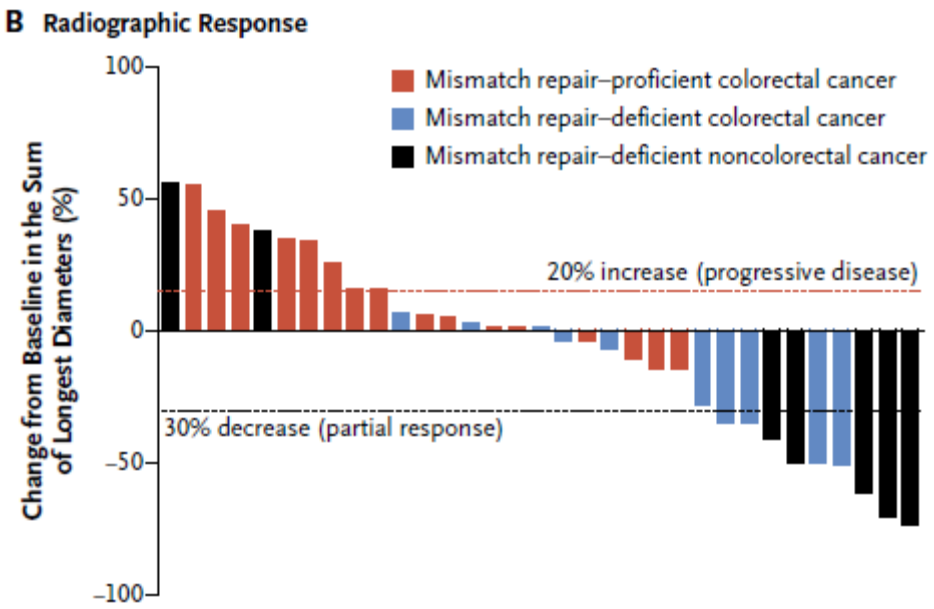
Hypothese:

- Je „fremder“ ein Tumor für das körpereigene Immunsystem, desto höher die Effektivität einer Interferenz mit dem PD-1 Signalweg
- Konzept für hypermutierte/MSI Tumoren

TCGA

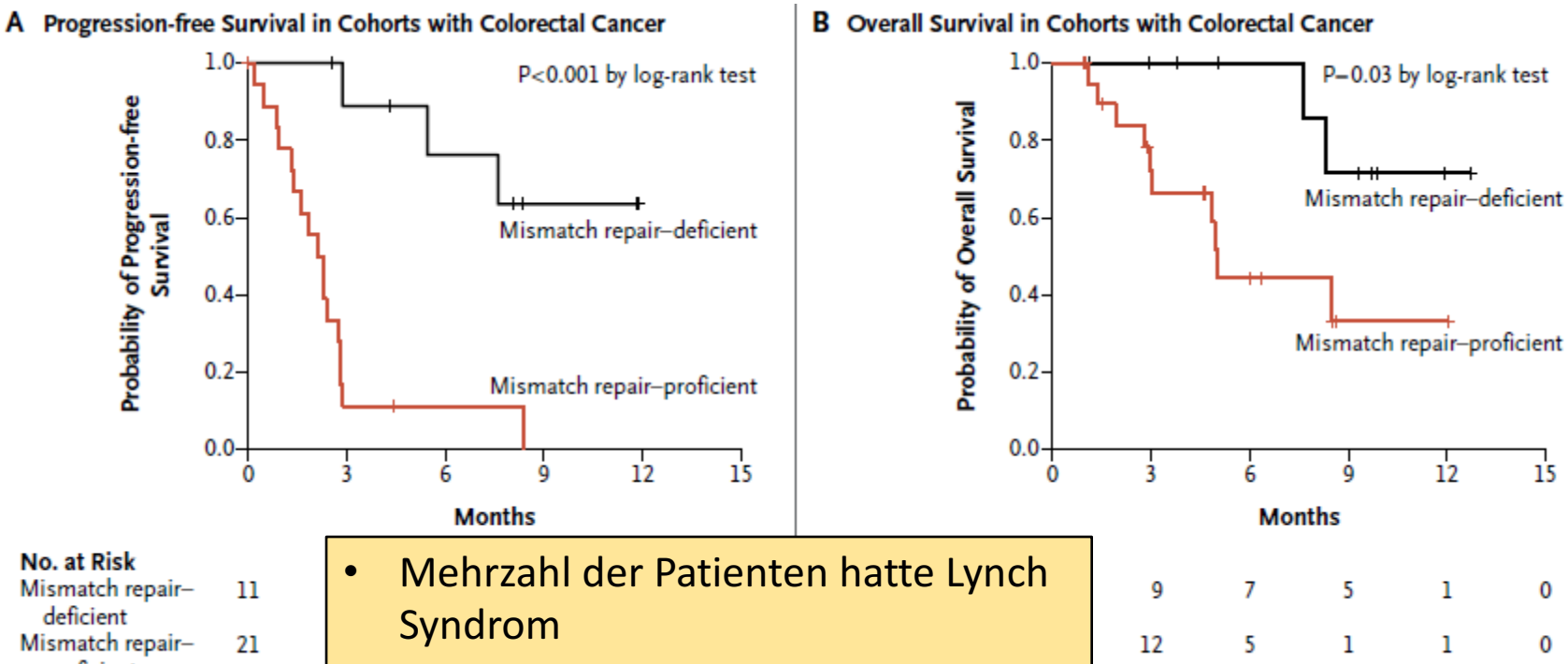
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency





Le et al., NEJM 2015

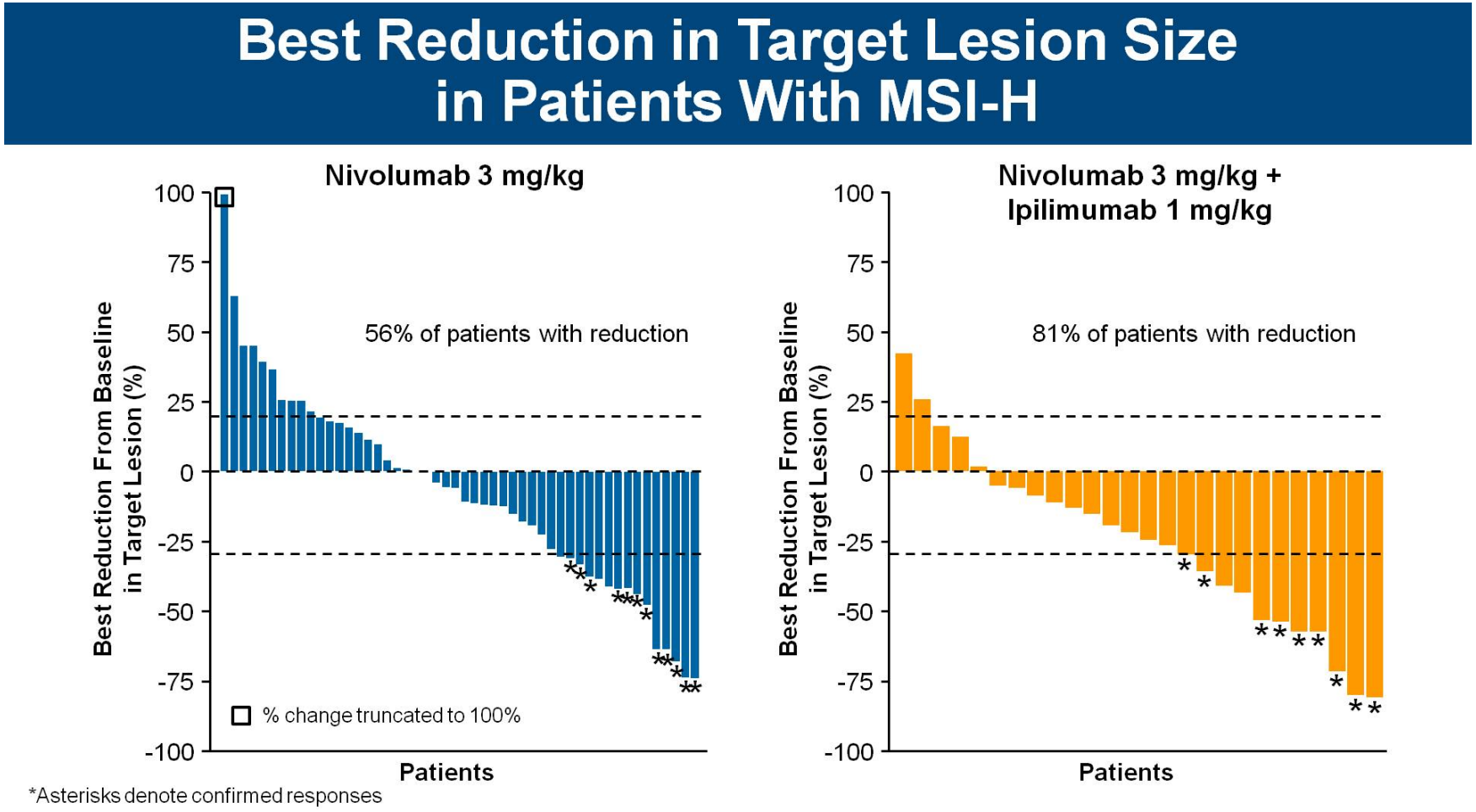
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency



- Mehrzahl der Patienten hatte Lynch Syndrom
- Gesamtgruppe SIV: Nur geringerer Prozentsatz mit MSI-H
- Aber: Interessante Daten für die MSI-H /CMS I Subgruppe

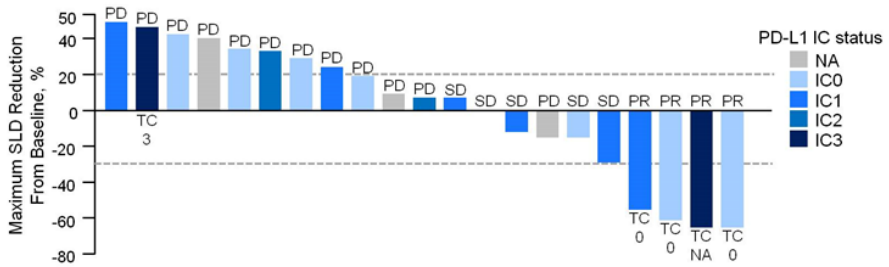
Le et al., NEJM 2015

Checkpointinhibitoren bei MSI-H Tumoren



Checkpointinhibitoren bei MSI-H Tumoren: LBA-01: Safety and efficacy of cobimetinib (cobi) and atezolizumab (atezo) in a Phase 1b study of metastatic colorectal cancer (mCRC) – Bendell J, et al

Efficacy: Change in Tumor Burden



- 4 patients had partial responses (confirmed per RECIST v1.1)
- MSI status of CRC patients was examined by NGS-based scoring: 3 of 4 responders were mismatch-repair proficient (not MSI-H); 1 responder had unknown MSI status and was not evaluable
- Tumor volume reduction was not associated with PD-L1 status: TC3 (n =

PD-L1 IHC status on tumor cells (TC) and tumor-infiltrating immune cells (IC) defined as: TC3 = TC ≥ 50% PD-L1+ cells; IC3 cells; IC2 = IC ≥ 5% and < 10% PD-L1+ cells; TC1 = TC ≥ 1% and < 5% PD-L1+ cells; IC1 = IC ≥ 1% and < 5% PD-L1+ cells NA, not available; NGS, next generation sequencing. Efficacy-evaluable patients. 2 patients missing or unevaluable are not i

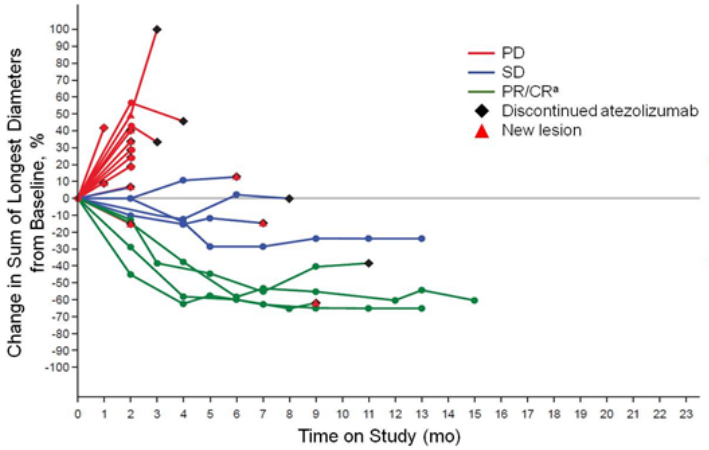
PRESENTED AT: ASCO ANNUAL MEETING '16

Bendell J, et a

MEK-Inhibitor (soll TiL Zahl im Tumor erhöhen) plus PD1/PDL1 Blockade

Eventuell Konzept für „kalte“, MSS-KRKs

Efficacy: Change in Tumor Burden Over Time



- Median duration of response was not reached (range: 5.4 to 11.1+ mo)
- Responses are ongoing in 2 of 4 responding patients

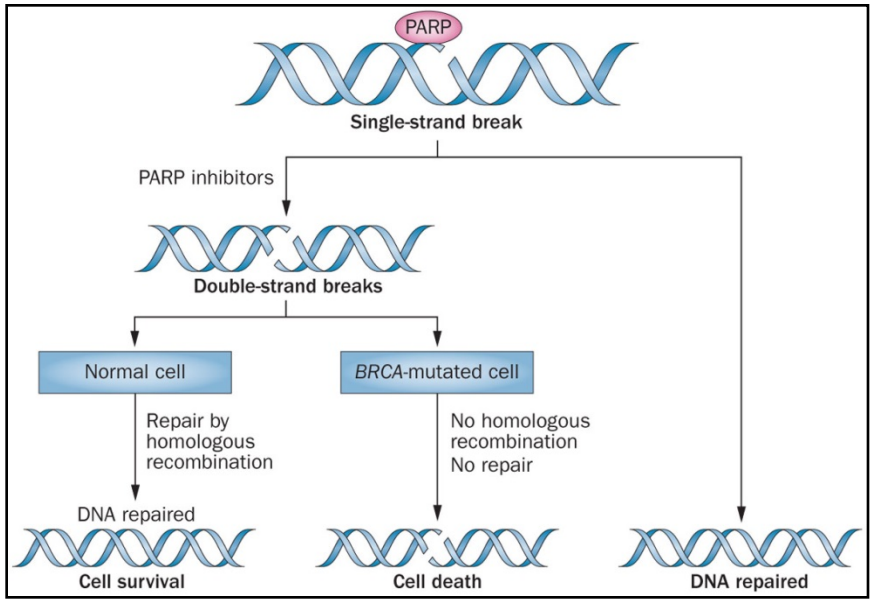
[a]Confirmed per RECIST v1.1. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease. Efficacy-evaluable patients. 2 patients missing or unevaluable are not included. Data cut-off February 12, 2016.

PRESENTED AT: ASCO ANNUAL MEETING '16

Bendell J, et al. Cobimetinib and atezolizumab in CRC. ASCO 2016

CMS1: DNA Damage Response

- BRCA, ATM, ATR
- BRCA mutierte Tumoren sensitiv gegen DNA-Repair-Inhibitoren und DNA-schädigende Agentien
  - Platin-basierte Therapien, PARP-Inhibitoren
- 5-fach gesteigertes Risiko für KRK bei BRCA1 Mutationsträgern jünger als 50 Jahren
- ATM inaktiviert in 37% der hypermutierten KRKs

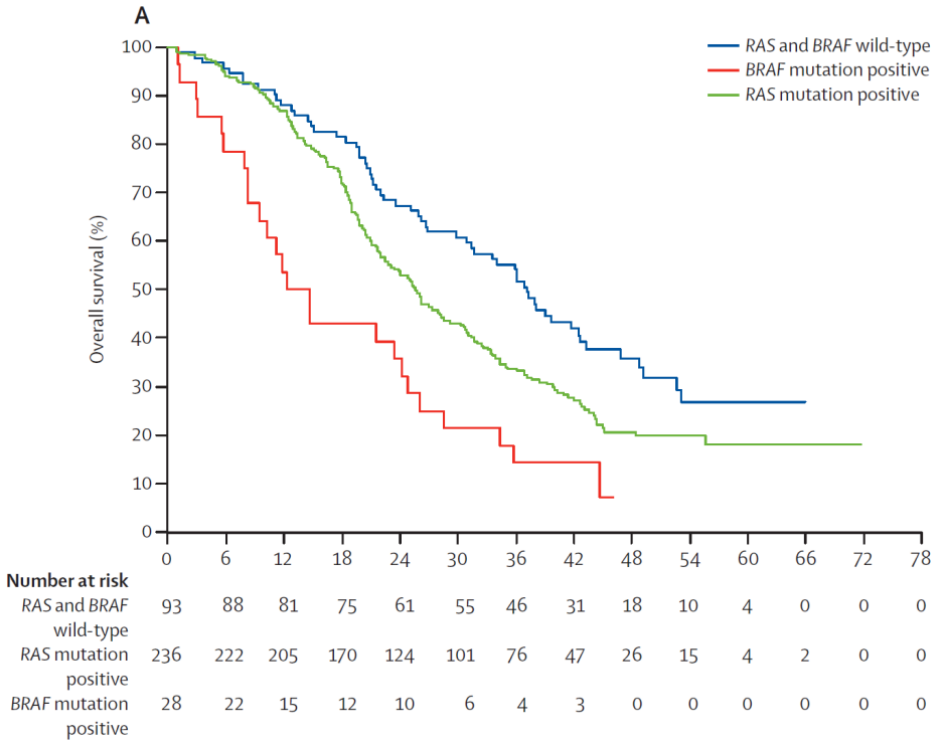


BRCA/ATM Inhibitoren: Olaparib, Talazoparib, E7449, VX970 (ATR Kinase)

Sonnenblick, Nat. Rev. Clin. Oncol. 2014; Holter, JCO 2015; Waddell Nature 2015; Sopik, Clin Genetics

BRAF V600E Mutationen

- Nur in etwa 6% der KRKs
- Im SIV (negativ) prognostisch



	Overall survival		
	Median (months)	Hazard ratio	p value
Intention-to-treat population			
FOLFIRI plus bevacizumab (n=256)	25·8 (22·5–29·1)	0·80 (0·65–0·98)	0·03
FOLFOXIRI plus bevacizumab (n=252)	29·8 (26·0–34·3)	..	..
Extended *RAS* and *BRAF* subgroup population			
FOLFIRI plus bevacizumab (n=176)	24·9 (21·1–29·1)	0·84 (0·66–1·07)	0·16
FOLFOXIRI plus bevacizumab (n=181)	28·6 (25·4–33·6)	..	..
***RAS* and *BRAF* wild-type subgroup**			
FOLFIRI plus bevacizumab (n=45)	33·5 (22·3–39·7)	0·77 (0·46–1·27)	0·52*
FOLFOXIRI plus bevacizumab (n=48)	41·7 (30·1–53·1)	..	..
***BRAF*-mutation-positive subgroup**			
FOLFIRI plus bevacizumab (n=12)	10·7 (3·1–24·8)	0·54 (0·24–1·20)	..
FOLFOXIRI plus bevacizumab (n=16)	19·0 (8·2–28·6)	..	..
***RAS*-mutation-positive subgroup**			
FOLFIRI plus bevacizumab (n=119)	23·9 (20·5–27·9)	0·88 (0·65–1·18)	..
FOLFOXIRI plus bevacizumab (n=117)	27·3 (22·0–31·3)	..	..
***RAS* wild-type subgroup**			
FOLFIRI plus bevacizumab (n=57)	26·8 (20·5–35·9)	0·78 (0·51–1·20)	0·66†
FOLFOXIRI plus bevacizumab (n=64)	37·1 (24·1–42·7)	..	..

Cremolini et al. Lancet Oncol 2015

Therapie bei BRAF Mutation

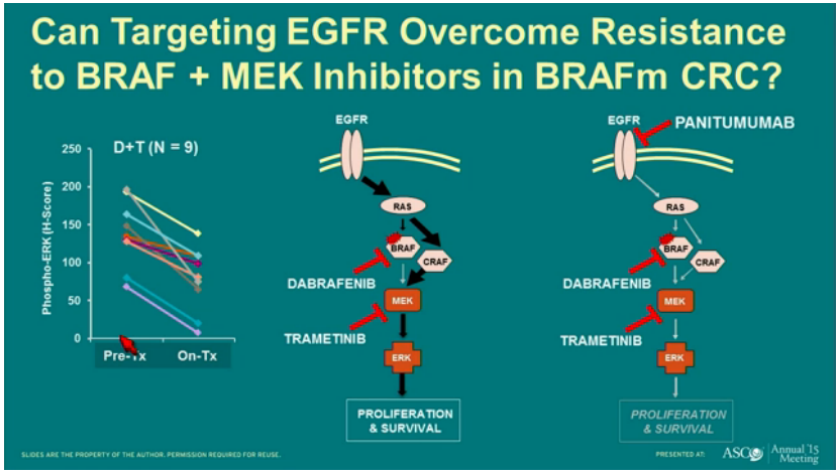
Braf-Inhibition alleine wegen redundanter Signaltransduktion nicht effektiv -> Doppel-/Triple Targeting

Einschlußkriterien
- *BRAF*^{V600E} Mutation mCRC
- ECOG PS 0–1
- Meßbare Erkrankung (RECIST)

(n=69)

R

- Arm 1: Panitumumab + Dabrafenib (n=20)
- Arm 2: Panitumumab + Dabrafenib + Trametinib (n=35)
- Arm 3: Panitumumab + Trametinib *(Ongoing;* n=14)

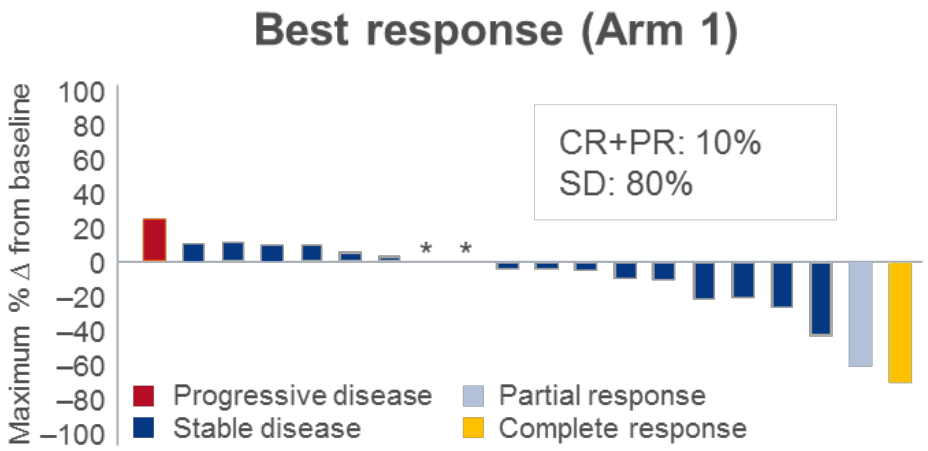


Primäre Endpunkte: Safety, Ansprechrate, PFS

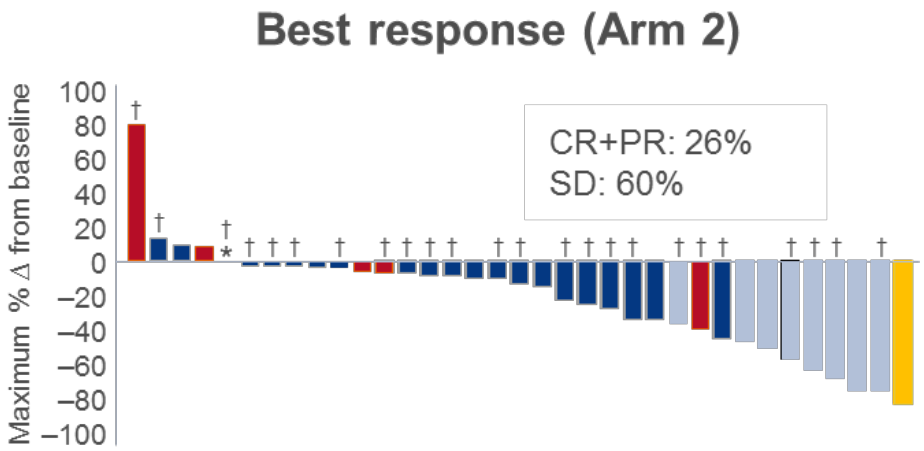
Corcoran et al. J Clin Oncol 2015 (abstr.)

Therapie bei BRAF Mutation:

Zweifachtherapie



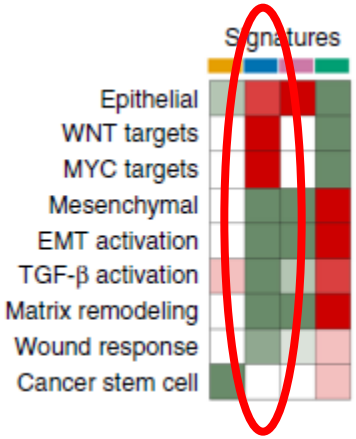
Dreifachtherapie

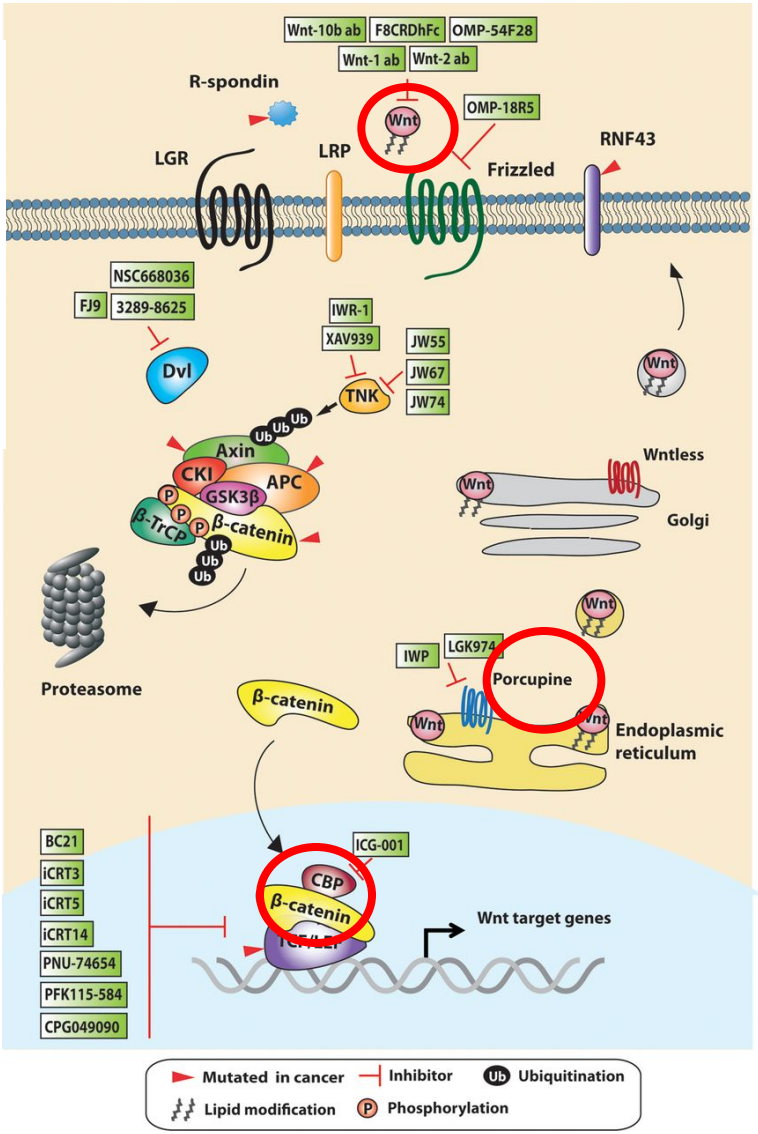


Corcoran et al. J Clin Oncol 2015 (abstr.)

CMS2

- CMS2
  - WNT und MYC Signalaktivierung
  - MYC schwer zu targeten, da essentiell
  - WNT Inhibitoren in Phase I Studien
    - CGX1321
      - Small molecule
    - PRI-724
      - CBP/b-catenin Antagonist
    - ETC-1922159
      - Porcupine inhibitor

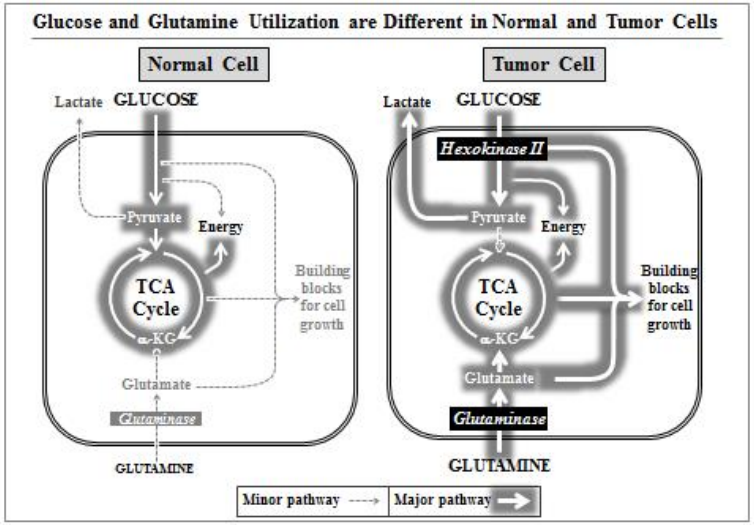


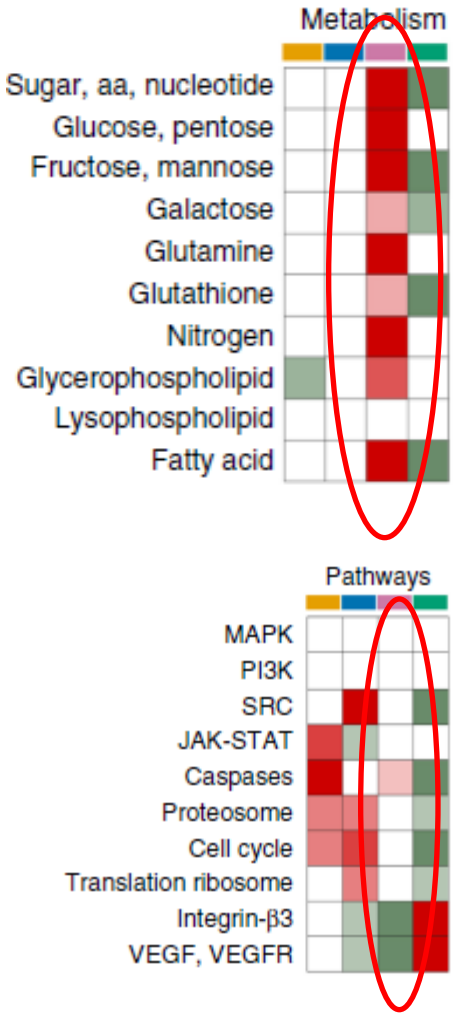


Novellasdemunt, AJP 2015

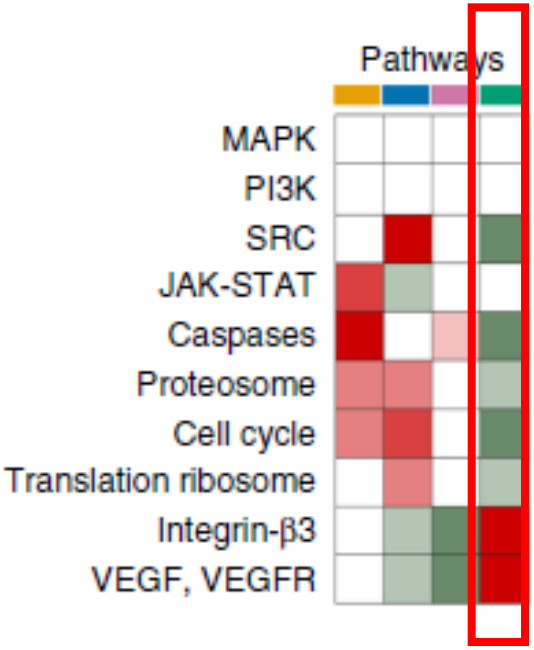
CMS 3 - metabolic

- Targeting des Tumormetabolismus
  - Pyruvatdehydrogenasekinase-inhibitoren
  - Glutaminaseinhibitoren
    - **CB-839**

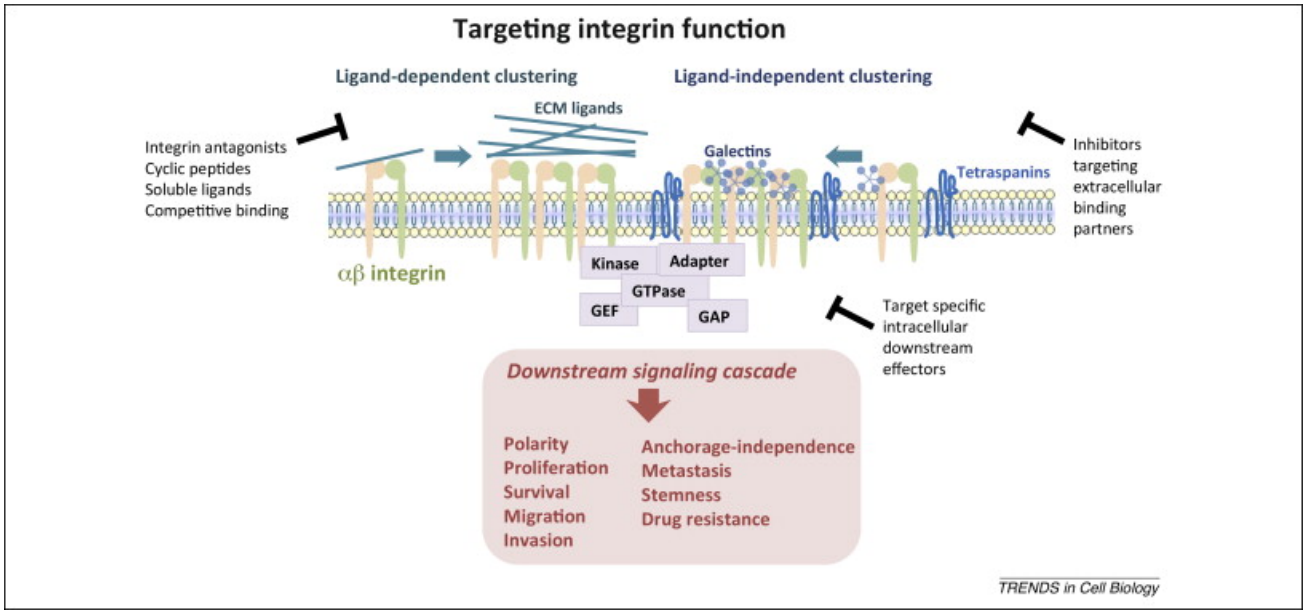




CMS4

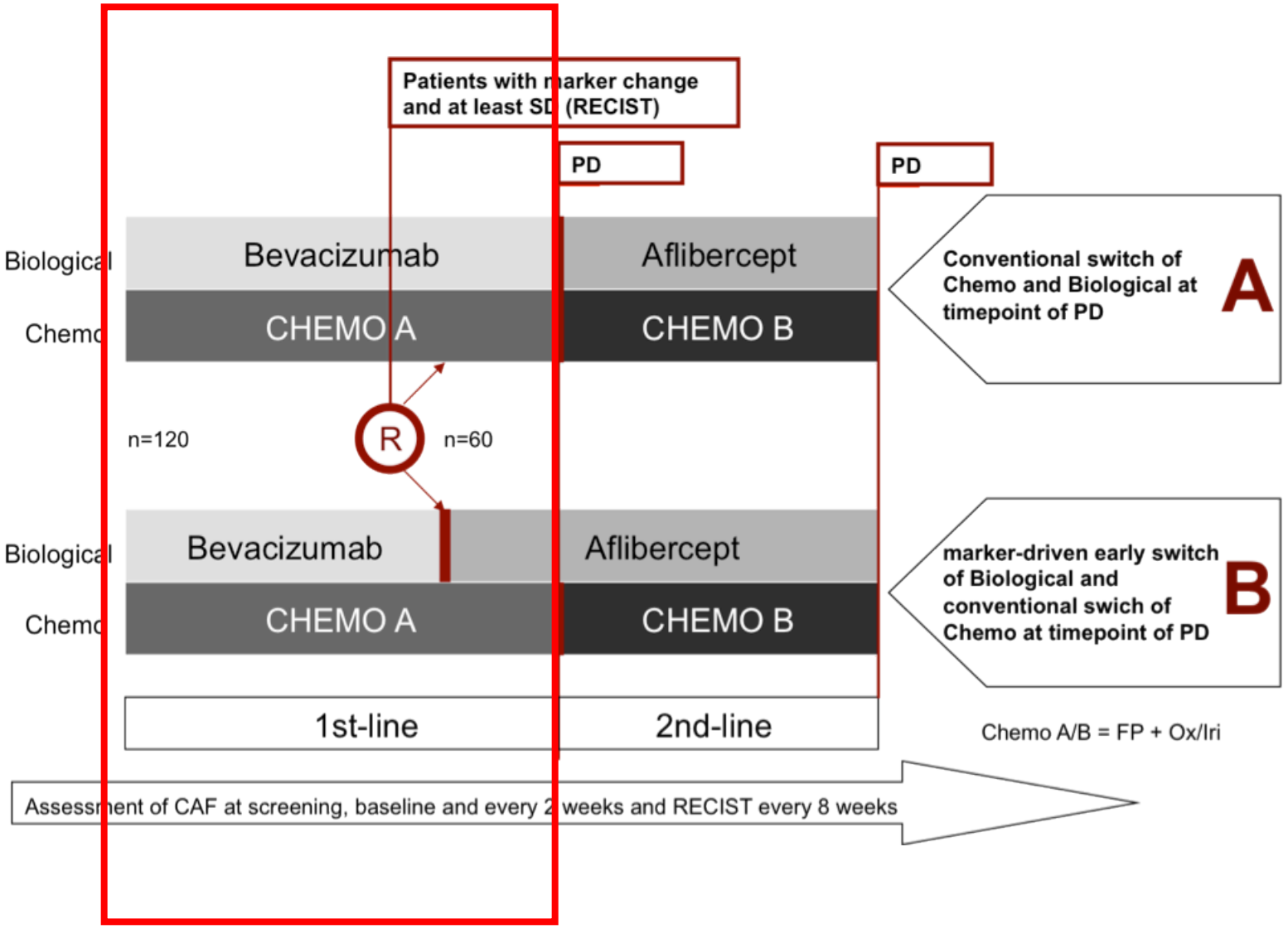


- TGFb-Aktivierung
- Stromale Invasion
  - MEDI 522/Etaracizumab
    - mAb gegen avb3 Integrin
- Angiogenese
  - Bevacizumab
  - Aflibercept
  - Ramucirumab



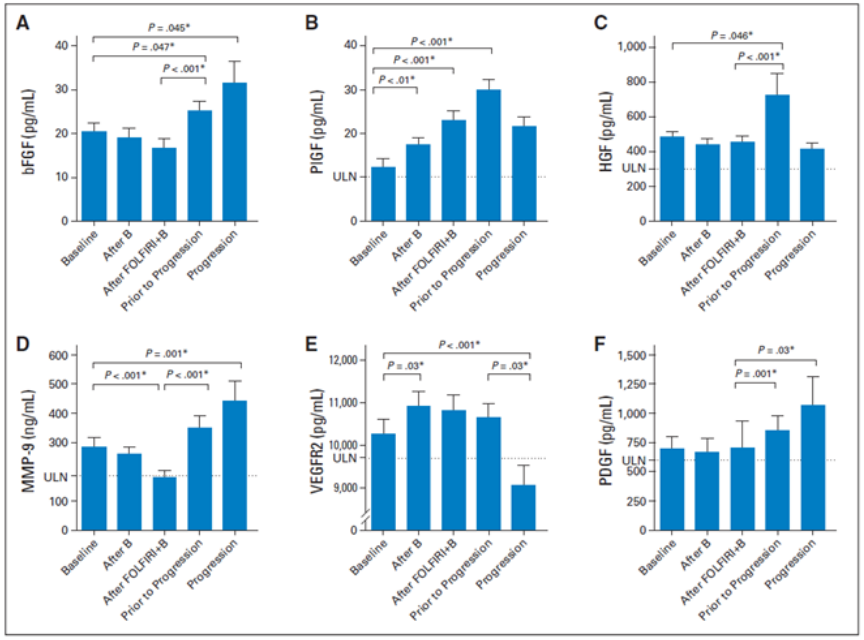
Seguin, TCB 2015

PERMAD Trial



PERMAD data evaluation

- no use of absolute values/ cut offs
- definition of a ***composite marker***, that integrates the course and kinetics of various cytokines by bioinformatics
- predictive value of such a marker for resistance to bevacizumab and switch to aflibercept?

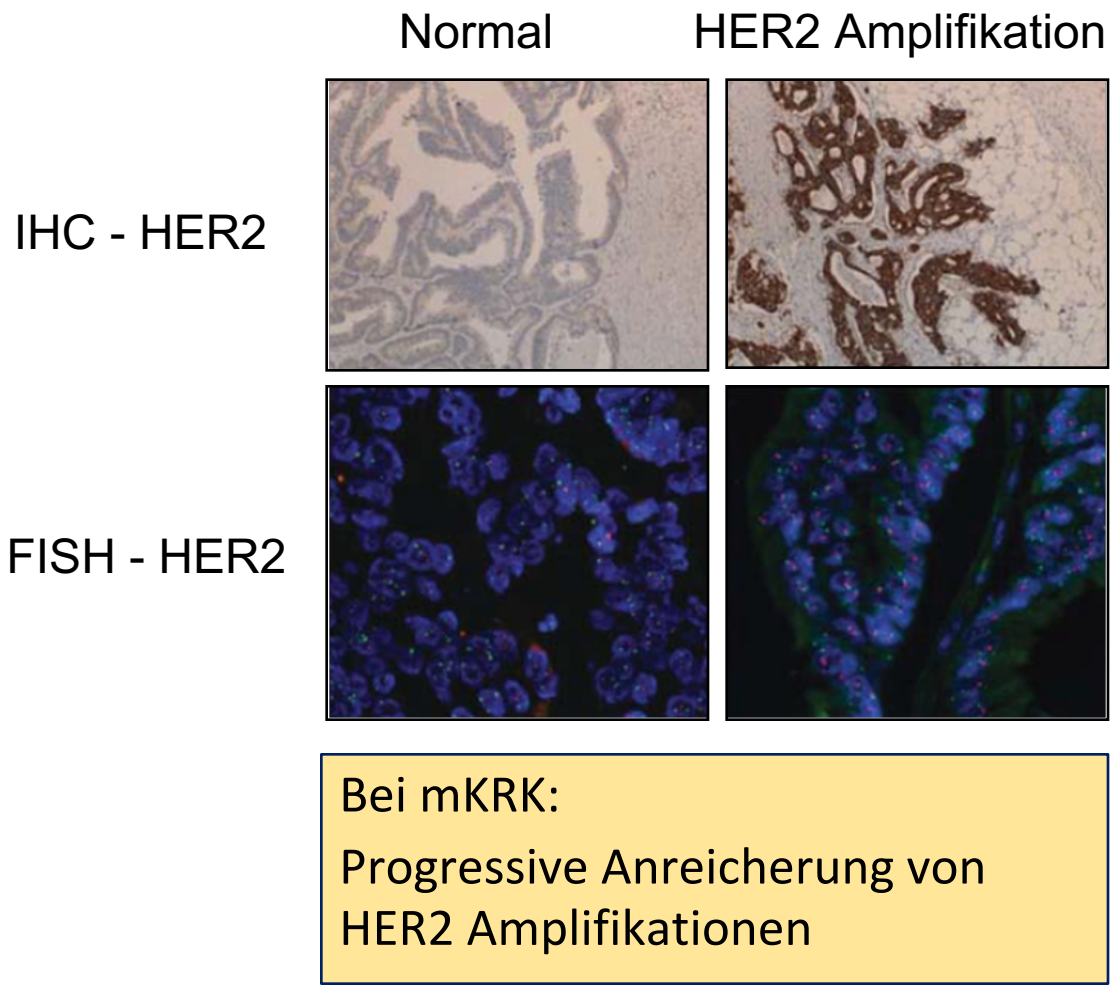


PERMAD: What is done?

- PlGF
- Ang 2
- VEGF
- G-CSF
- sVEGFR2
- HGF
- bFGF
- MMP-9

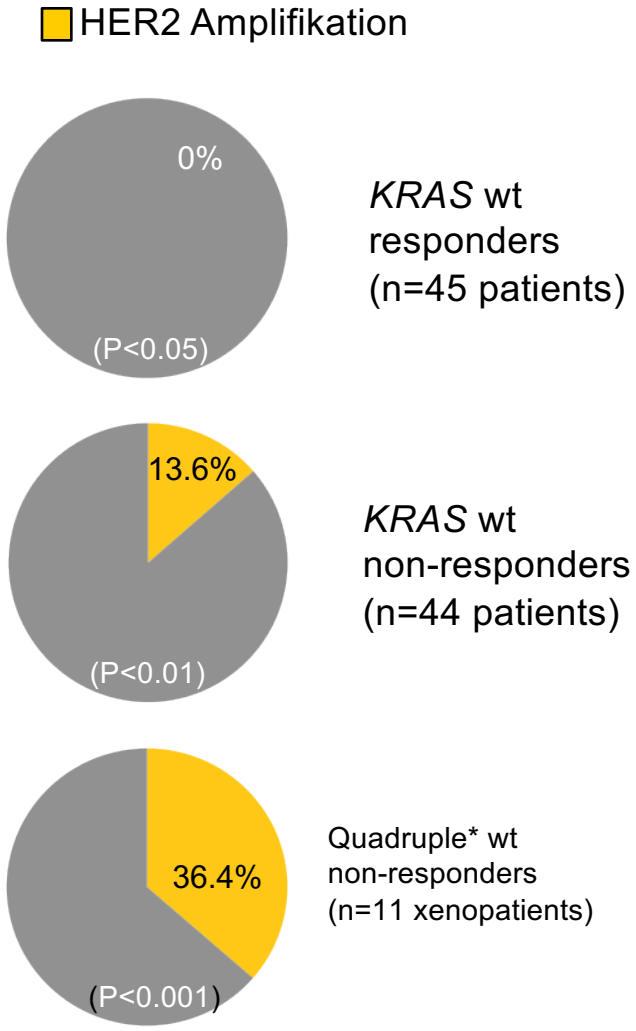
- screening (d -28 until -7),
- baseline (d1 prior to Tx)
- every 2 weeks (first phase)
- every 4 weeks in the randomized part

Tumorevolution: HER2 Amplifikation beim KRK unter Therapie



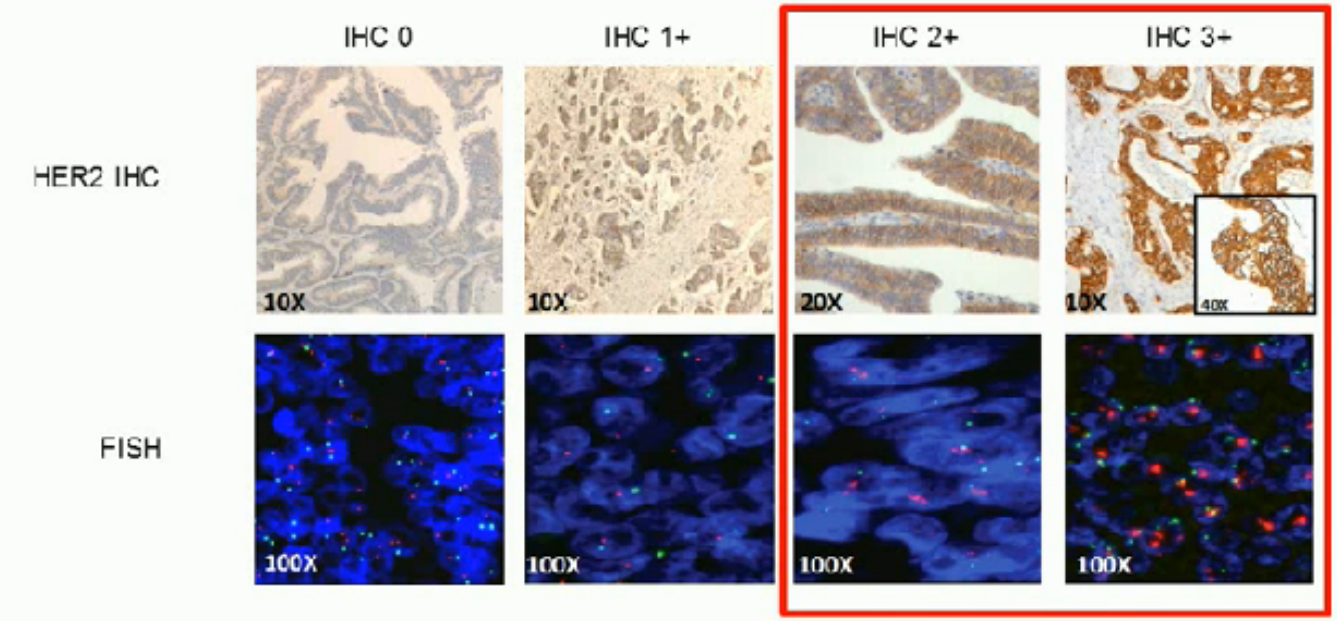
Bei mKRK:

Progressive Anreicherung von HER2 Amplifikationen



Bertotti A et al. Cancer Discov 2011;1:508-23

Heracles Studie



Positive tumor cells ≥ 50%

Eligible for HERACLES Trial

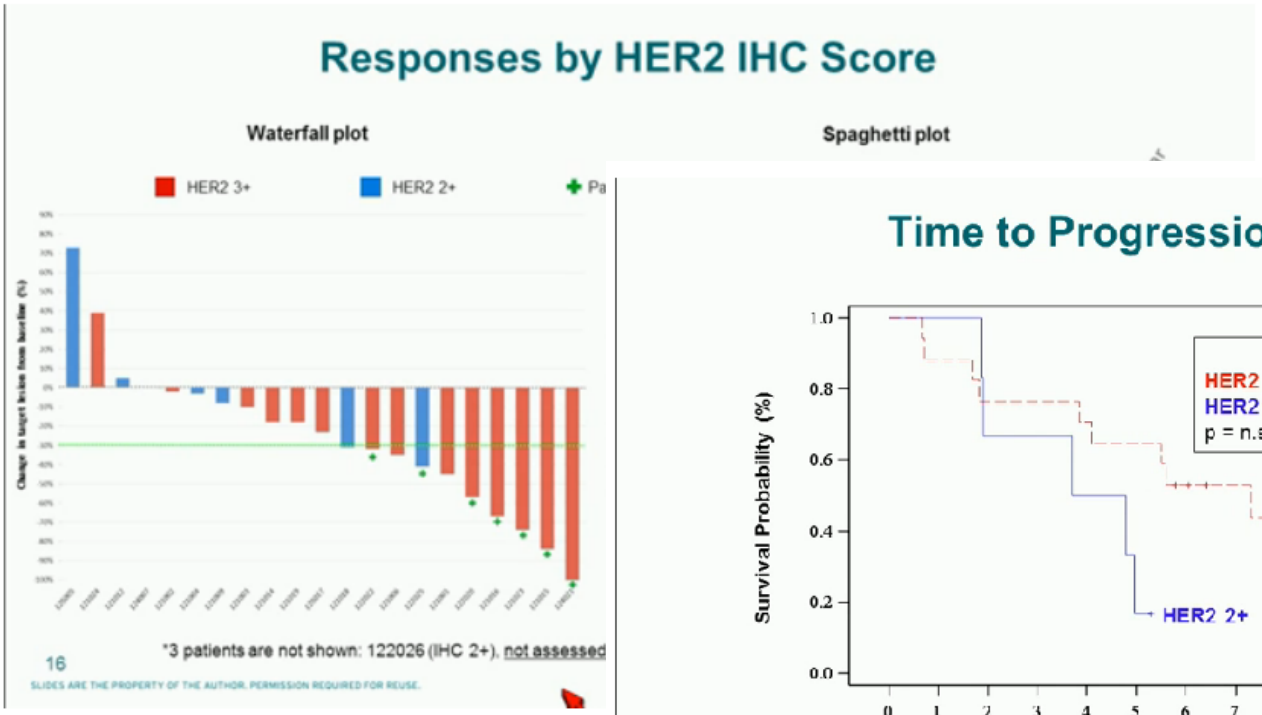
Valtorta E. et al, Modern Pathol 2015, in press

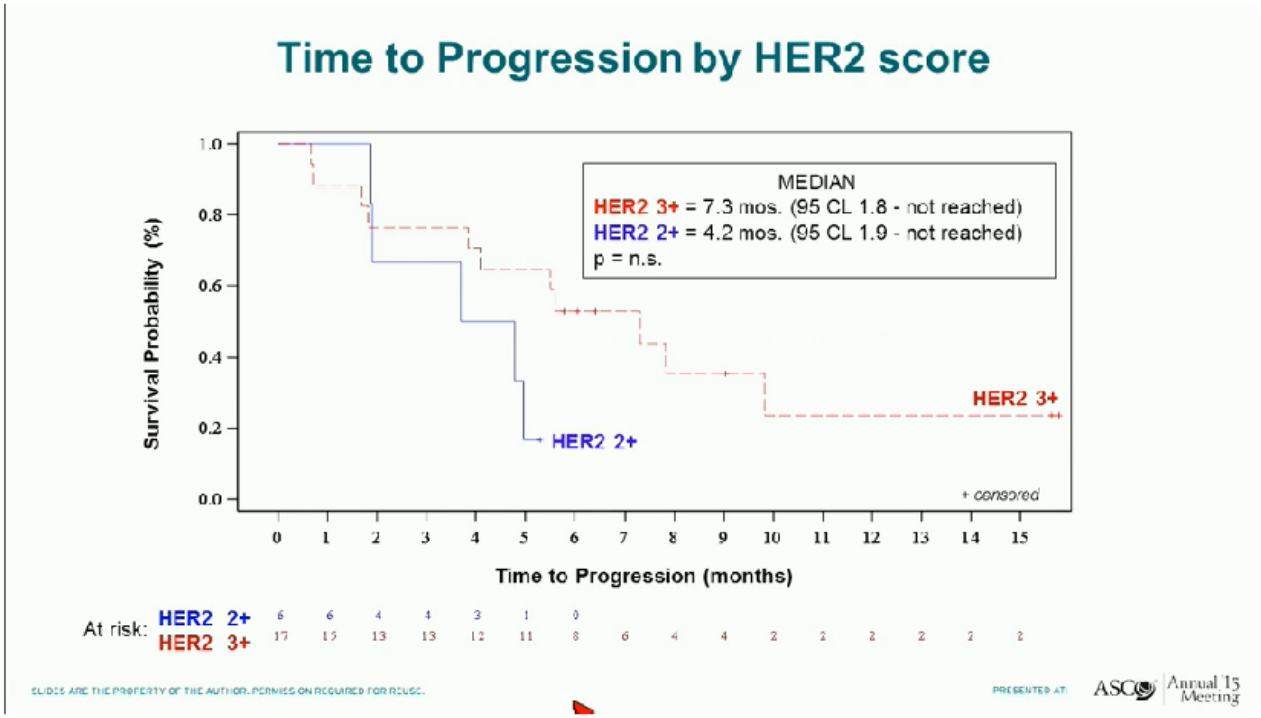
PRESENTED AT: ASCO Annual 15 Meeting

- Kras WT
- Vorbehandlung mit 5-FU, Iri, Ox, Cetuximab oder Panitumumab obligatorisch
- ECOG 0-1
- Primärer Endpunkt: ORR
- Therapie mit Trastuzumab plus Lapatinib

In der Studie:
5.4% der Ausgangspopulation

HERACLES-Studie

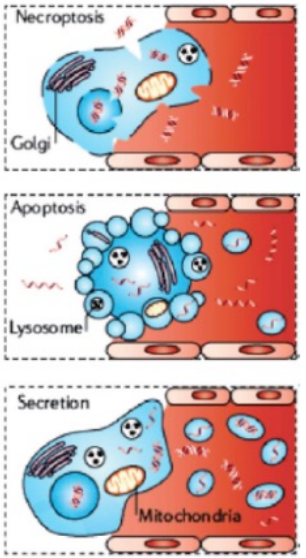


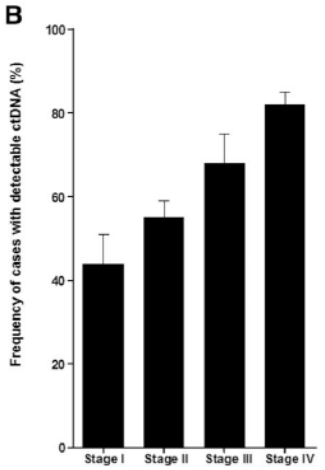


Therapie gut toleriert (Haut-/GI-Toxizität)

Wie monitoren wir eine Tumorerkrankung? Wie finden wir neu aufgetretene Mutationen?

- Zirkulierende DNA
  - cfDNA, ctDNA
  - Freigesetzt durch Zellturnover oder via Exosomen
  - Kleine Fragmente (180-200 bp) im Plasma
  - Fortgeschrittene Tumore: ctDNA in >75% detektierbar
    - 73% CRC



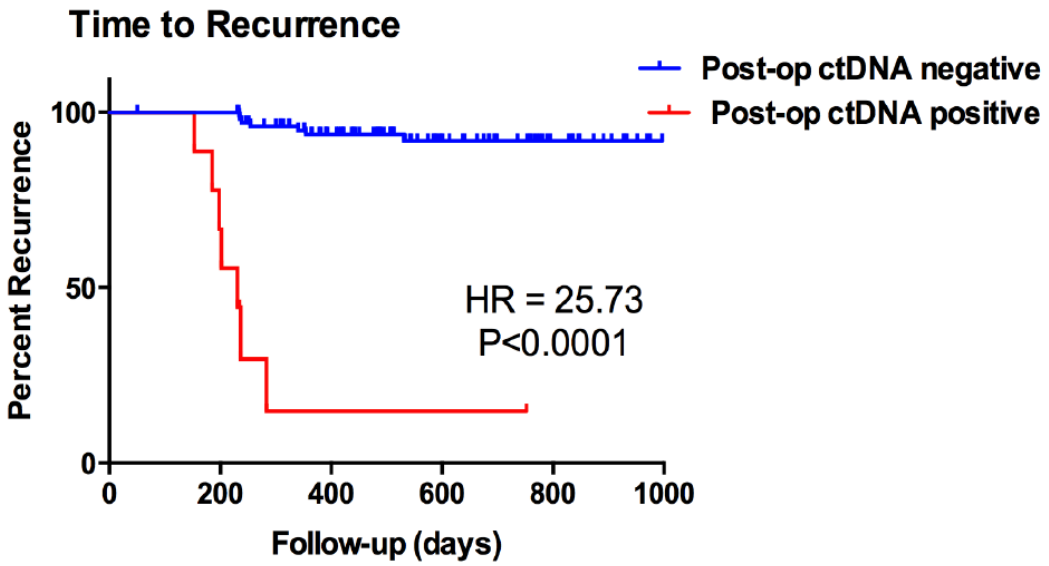


Bettegowda, Sci Transl Med 2014

Detektion von MRD – KRK Stadium II/III

	Recurrence	No recurrence	Total
Post-op ctDNA - positive	7	2	9
Post-op ctDNA - negative	7	96	103
Total	14	98	112

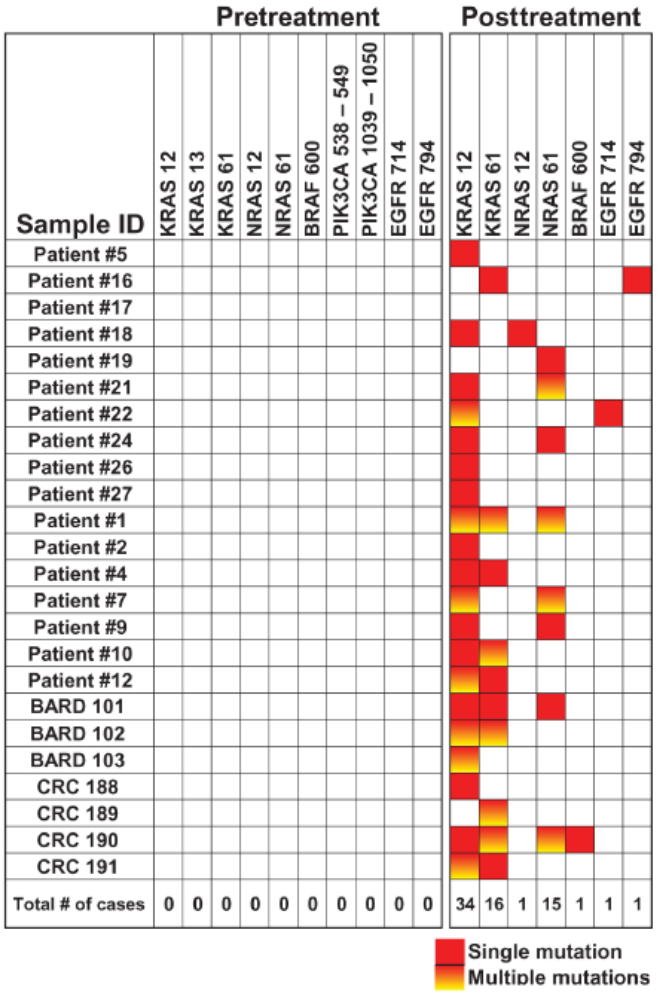
Fisher's Exact P < 0.0001
RR = 11.44
(95% CI 5.16 – 25.37)



Tie, J Clin Oncol 32:5s, 2014 (suppl; abstr 11015)

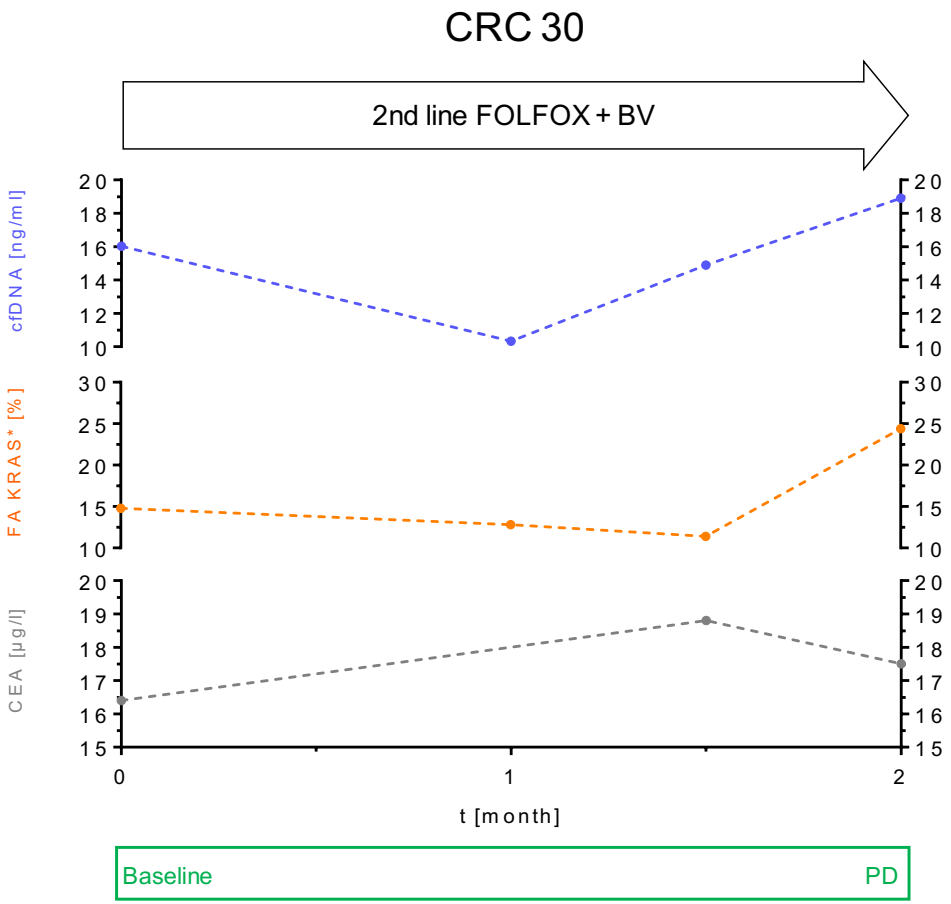
Monitoring von Tumorevolution unter einer anti-EGFR Therapie

- Tumortherapie triggert die Evolution multipler Subklone im Tumor
- Beispiel: CRC: Kras Codon 12 Mutationen analysiert mittels ctDNA
  - Sensitivität: 87.2%
  - Spezifität: 99.2%
  - Therapie-assoziierte Resistenz:
    - 96% eine oder mehrere Mutationen mim MEK-ERK Signalweg
    - 50% in Kras
    - Häufige Mutationen in Codon 61 von Kras



Bettegowda, Sci Transl Med 2014; Diaz et al., Nature 2012

Monitoring von Therapieansprechen



RAS-Status Gewebe			
	Exon 2	Exon 3	Exon 4
KRAS	G12D	WT	WT
NRAS	n.a.	n.a.	n.a.

* KRAS: **G12A, G12C, G12D, G12R, G12S, G12V, G13D**

Berger, … Seufferlein, under revision

Endlich Relevanz für molekulare Marker beim KRK?!

Ja, definitiv

	Ras-Status*	B-RAF V600E	HER2	MSI	(BRCA/ATM)
Erstdiagnose SIV	X	X		X	
SIV fortgeschrittene Erkrankung			X		X

*K-RAS exons 2, 3 und 4 (Codons 12, 13, 59, 61, 117 und 146) und n-RAS Exone 2, 3 und 4 (Codons 12, 13, 59, 61 und 117).

Endlich Relevanz für molekulare Marker beim KRK?!

- Molekulare Klassifizierung: Chance zur Anreicherung von Subgruppen zur Stratifizierung für klinische Studien, aber:
  - Nur für Primärtumor etabliert
  - Signaturen für Metastasen verwendbar?
- Therapeutische Konsequenzen wirklich klar?
  - CMS1: Immuntherapie
  - CMS2: WNT Inhibitoren
  - CMS3: Targeting metabolischer Pathways
  - CMS4: TGFb Inhibitoren
- Tumorevolution innovativ monitoren (ctDNA)
- Mögliche Konsequenzen:
  - Bessere Definition von Subgruppen
  - Effektivere Therapie über das „continuum of care“
  - schnellere Wirkstoffforschung


Vielen Dank für ihre Aufmerksamkeit!