Update zur Therapie des metastasierten kolorektalen Karzinoms

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CCC MÜNCHEN
COMPREHENSIVE
CANCER CENTER

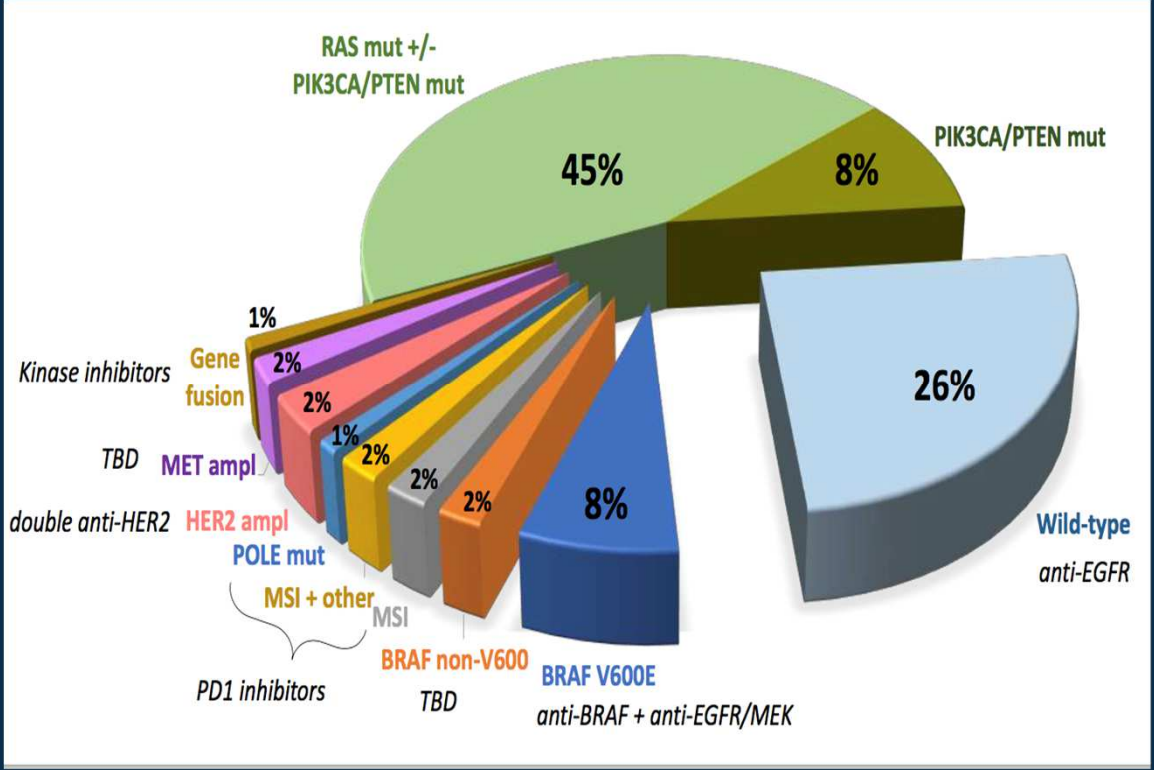
Molecular Subgroups of Colorectal Cancer

Genomic classification	• RAS mutation • BRAF V600 and non V600 mutation • HER2 amplification • Gene fusions • MSI and POLE mutations
Transcriptomic classification	• Consensus Molecular Subtypes (CMS)
Integrative classification (Sidedness of primary tumor)	• Right colon versus left colon

Extended molecular diagnostics: NGS-based panel sequencing ➔ molecular tumor board

Dienstamnn R, ESMO 2017

Genomic Classification of mCRC: New Avenues



Specific treatments for rare subtypes

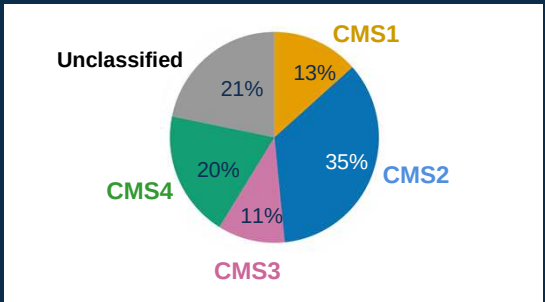
- MSI
- BRAF
- HER2 +
- TRK fusions

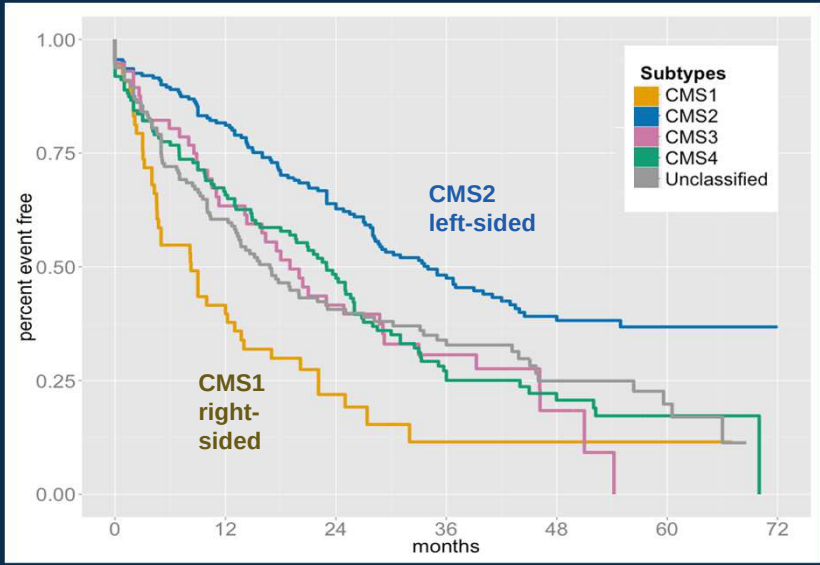
Rodrigo Dienstman, ESMO

Consensus Molecular Subtypes (CMS)

Transcriptomic Classification

CMS1 MSI immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI, SCNA low, CIMP low	SCNA high
BRAF mutations		**KRAS mutations**	
Immune infiltration and activation	**WINT and MYC activation**	Metabolic deregulation	Stroma infiltration, TNFß activation, angiogenesis
Worse survival			Worse RFS and OS





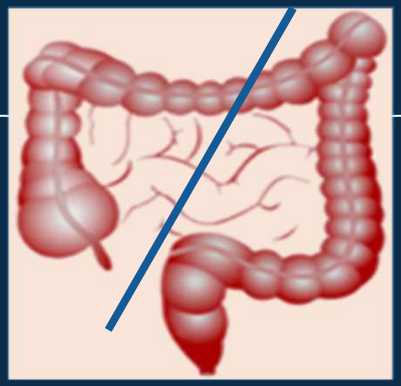
CMS has a strong prognostic relevance

Guinney J et al. Nat Med 2015

Integrative Classification: Right- vs. Left-Sided Tumors

Right Colon
20–40%

- Lower incidence
- More female
- Higher TNM stage
  - larger tumors
  - more mucinous
- Stronger immunogenicity
- Predominantly CIMP, MSI, BRAF
- Poor survival

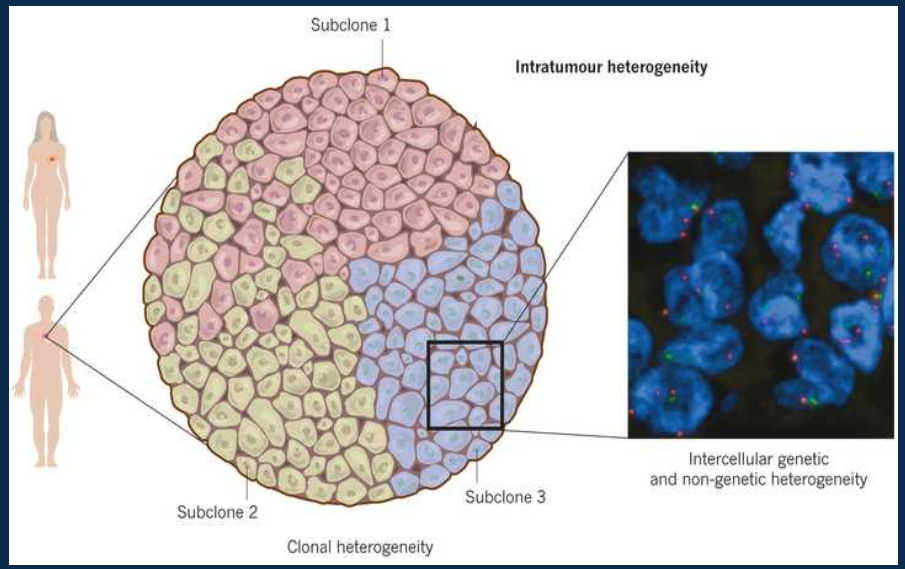


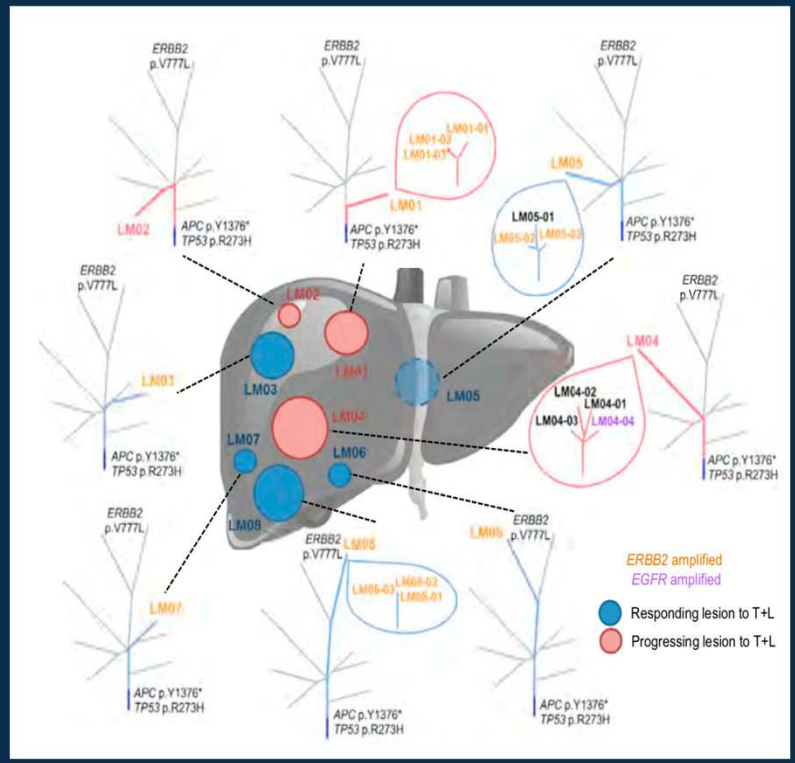
Left Colon + Rectum
60–80%

- More frequent
- More male
- Lower TNM smaller tumors
- Less immunogenic
- Predominantly chromosomal instability
- Better survival

Heterogeneous clonal evolution

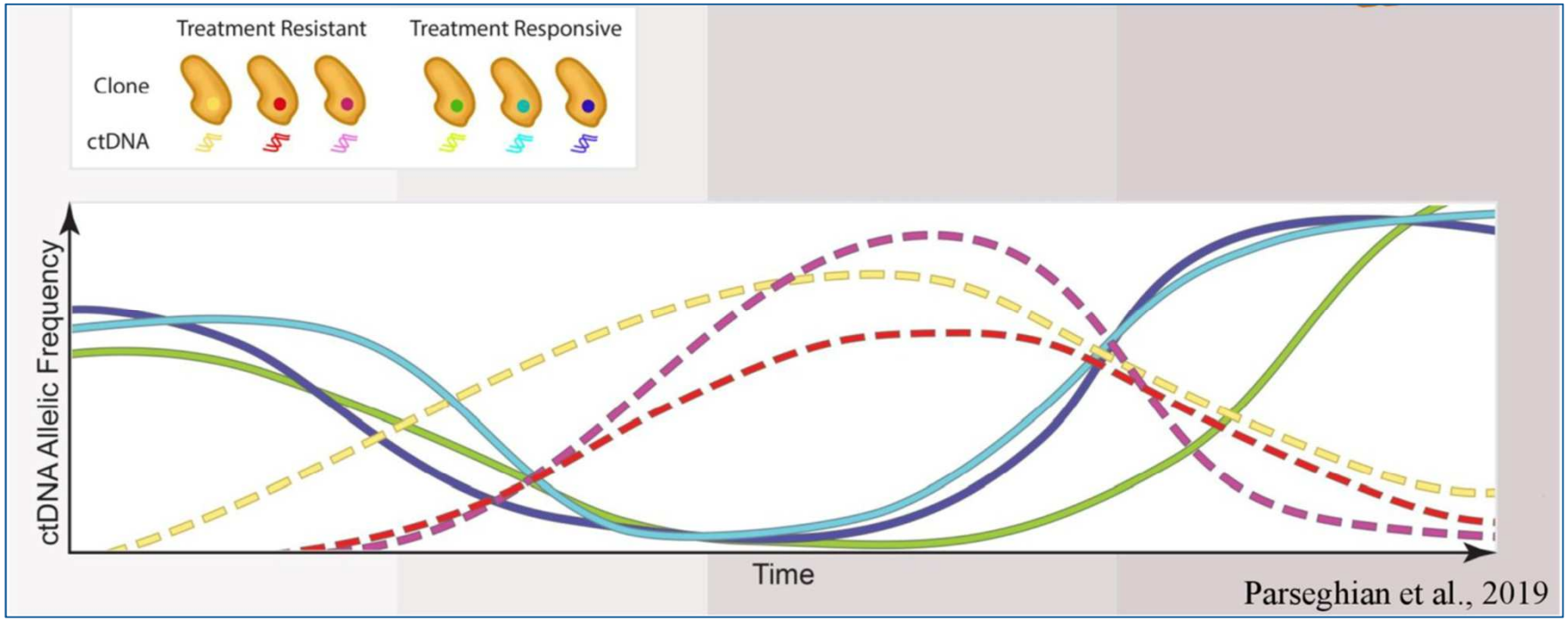
dependent on localisation of metastasis



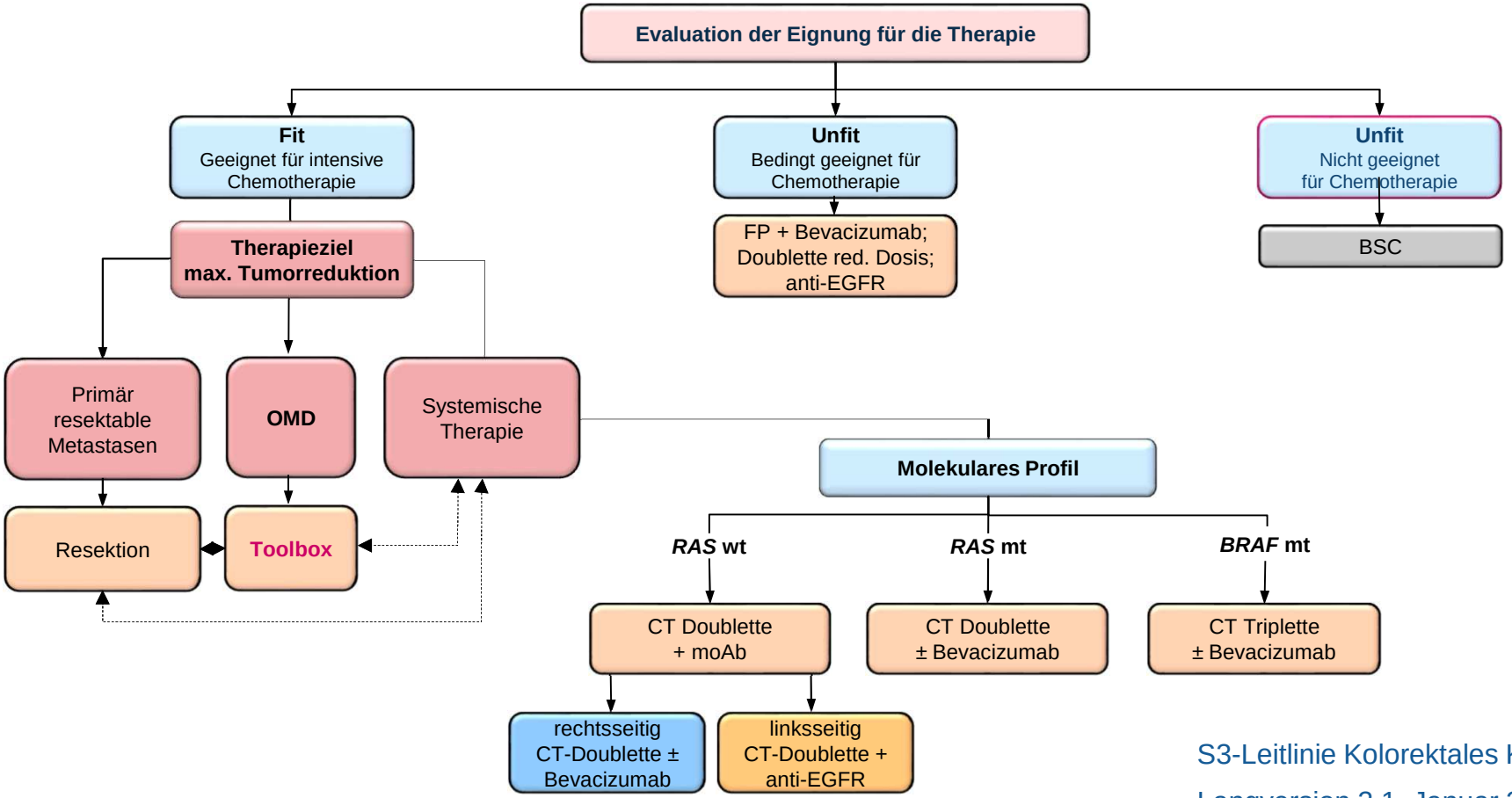


Siravegna G, et al. *Cancer Cell.* 2018;34(1):148-162.

Dynamische Evolution und Verschwinden von Mutationen in Abhängigkeit vom Selektionsdruck der Therapie



S3-LL: Therapiealgorithmus Erstlinientherapie des mKRK



S3-Leitlinie Kolorektales Karzino

Langversion 2.1. Januar 2019

1st-Line Behandlung bei RAS Wildtyp mCRC

rechtsseitig

schlechtere Prognose

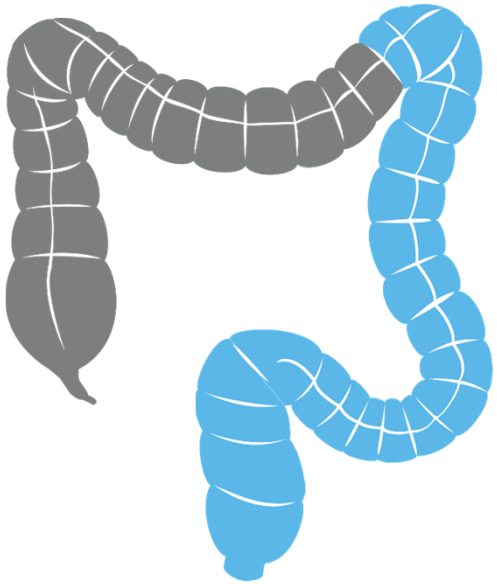
Ziel = OS

Chemo ± Bevacizumab

FOLFOXIRI + Bev

Ziel = ORR / Conversion

Chemo + anti-EGFR



linksseitig

bessere Prognose

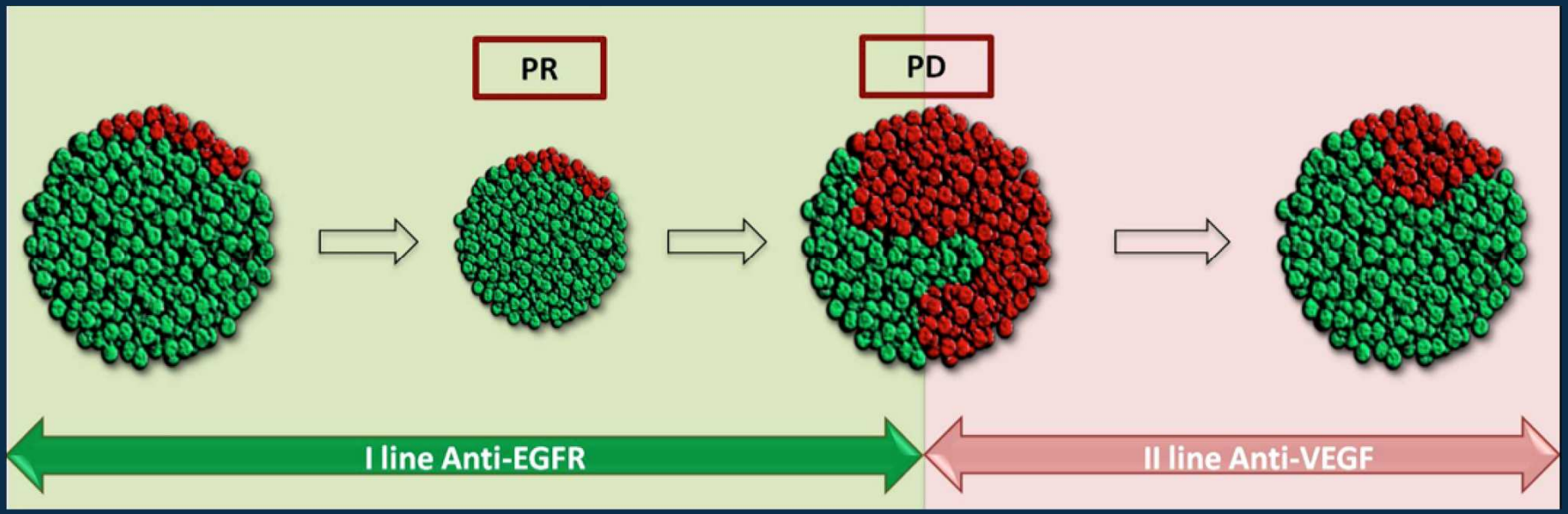
Ziel = OS / ORR

Chemo + anti-EGFR

Arnold D, et al. *Ann Oncol*. 2017;28(8):1713-1729.

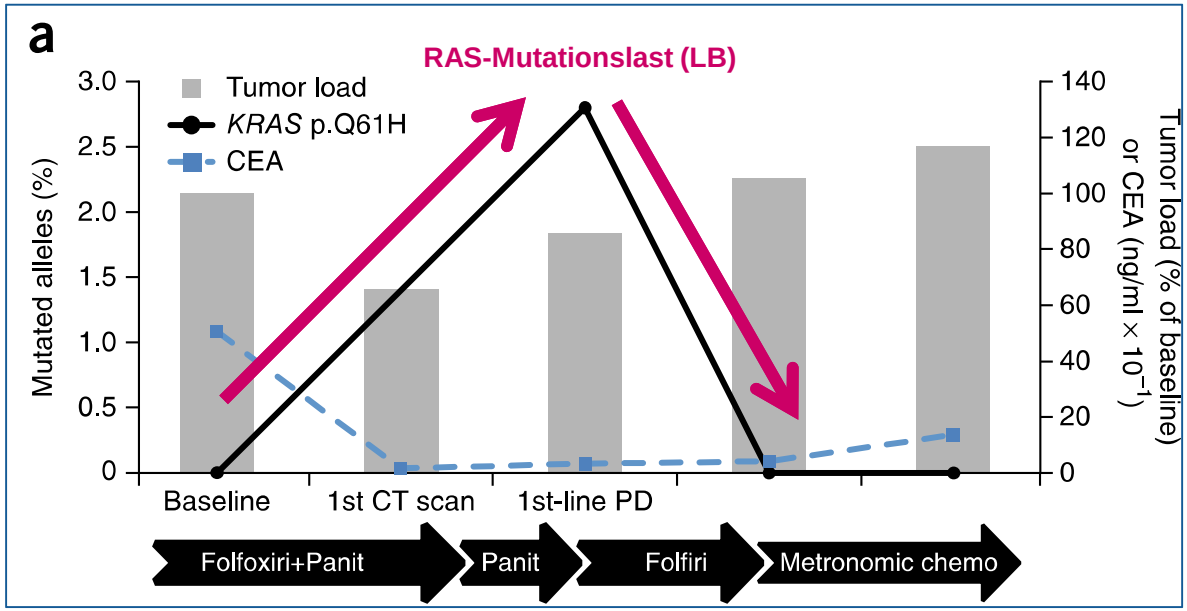
Temporary clonal evolution

due to selective pressure of therapy



Reversion of resistance after stop of anti-EGFR-therapy

Entwicklung von RAS Mutationen unter einer anti-EGFR Therapie



Abfall der RAS-Mutationslast nach Absetzten der anti-EGFR Therapie

Mögliche Relevanz der Liquid Biopsie in der Therapieführung

Parseghia et al, Ann Oncol;30(2): 243-249, 2019
Siravegna *et al*, Nature Medicine 21, 795–801, 2015

Re-challenge

strategy after anti-EGFR pre-treatment

Anti-EGFR induction

Doublet + anti-EGFR agent

Window therapy

Doublet + bevacizumab

Re-challenge

Chemo + anti-EGFR agent

- if CR or PR in 1st line
- or SD ≥ 6 months in 1st line

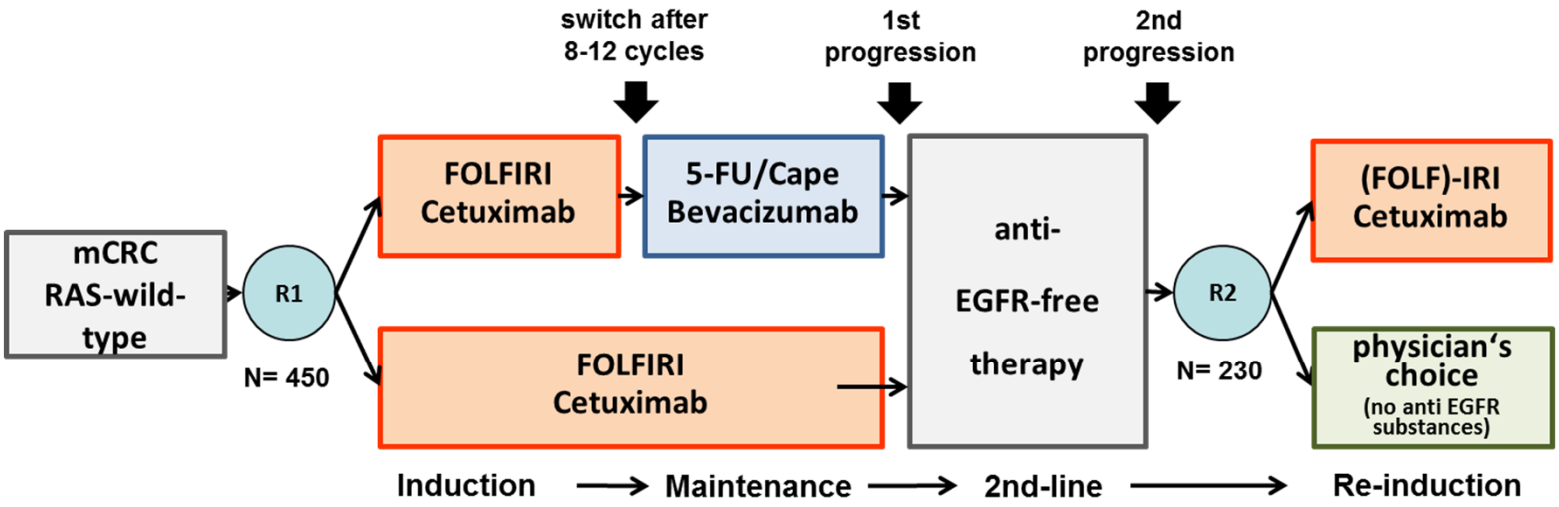
- exclusion of RAS mutation by liquid or tumor biopsy

Questions:

- Optimal **duration** of window therapy
- Optimal **interval** from end of anti-EGFR

FIRE-4 Studie: anti-EGFR Re-challenge

1st-line Therapie bei RAS wt mCRC



Primary Endpoint: OS3 after randomisation R2

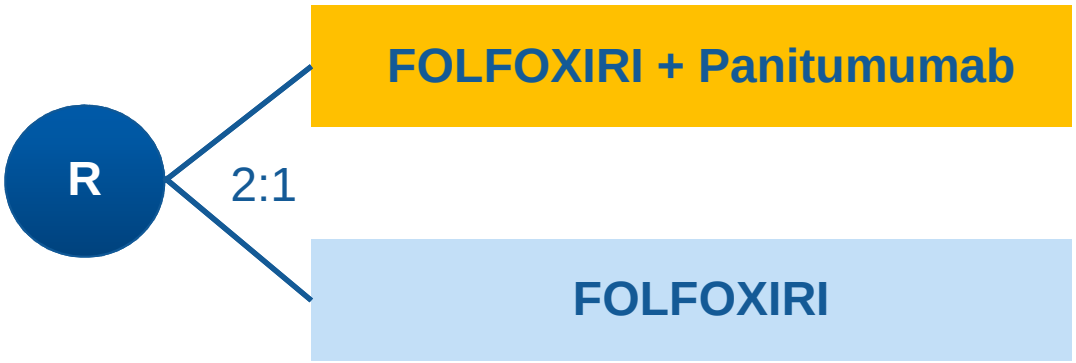
Secondary Endpoint: PFS in 1st-line

Intensivierte Therapie

Triplette + anti-EGFR AK

VOLFI-Studie

1st-line Therapie
beim RASwt mCRC



Phase II Studie; n = 99

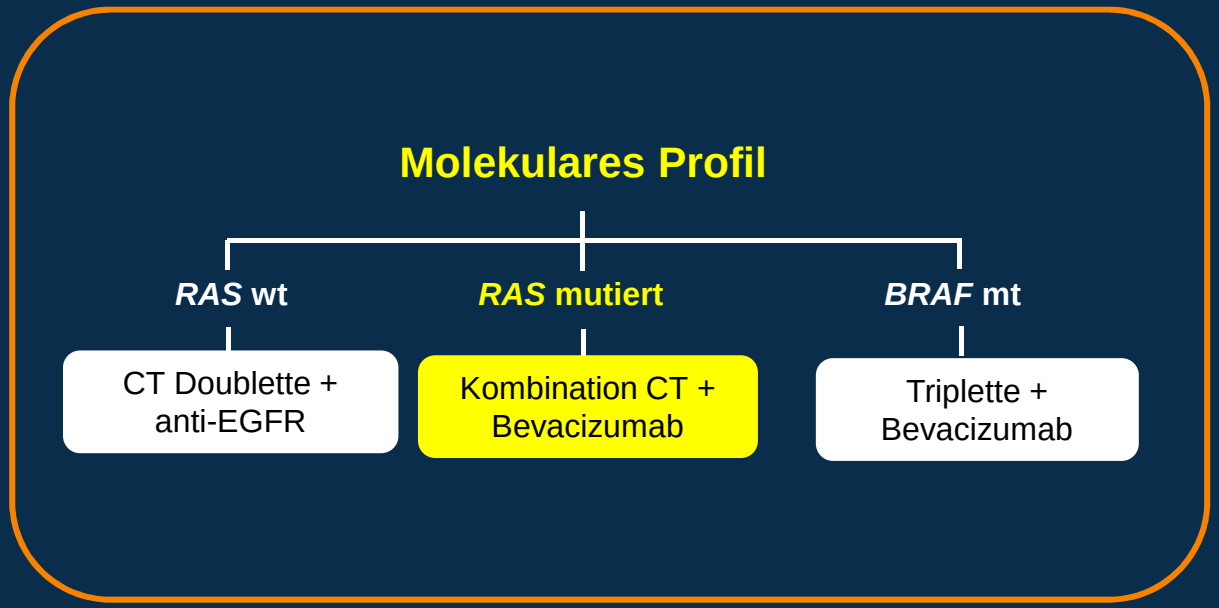
VOLFI: ORR in Abhängigkeit von Lokalisation / Biologie

	N	mFOLFOXIRI + panitumumab (%)	FOLFOXIRI (%)	Odds ratio	P
Full analysis set	96	**87.3**	**60.6**	4.47	0.004
Left	78	**90.6**	**68.0**	4.52	0.02
Right	18	**70.0**	**37.5**	3.89	0.34
RAS/BRAF wt	60	**86.0**	**64.7**	3.36	0.08
BRAF mut	16	**85.7**	**22.2**	21.00	0.04

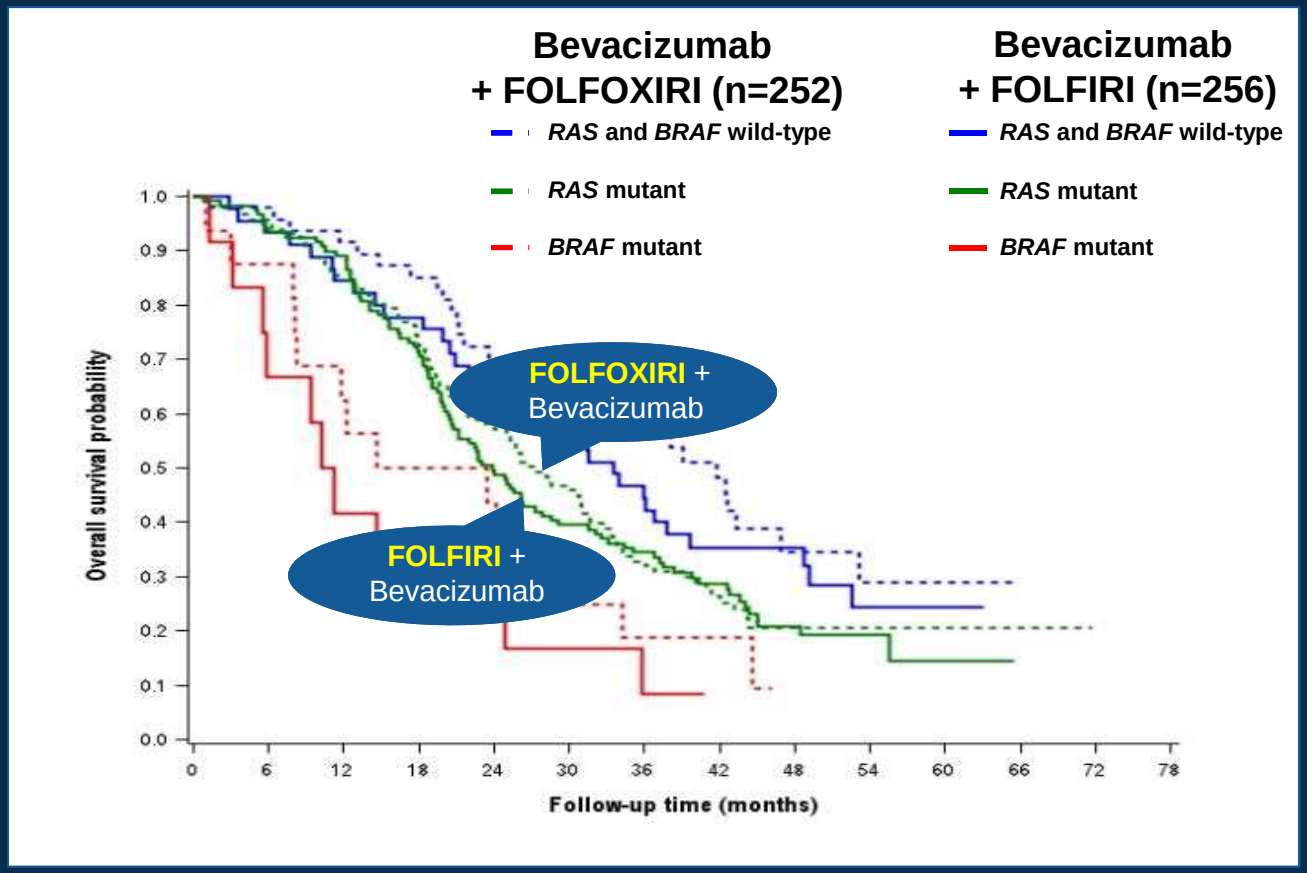
VOLFI: OS in Abhängigkeit von Lokalisation / Biologie

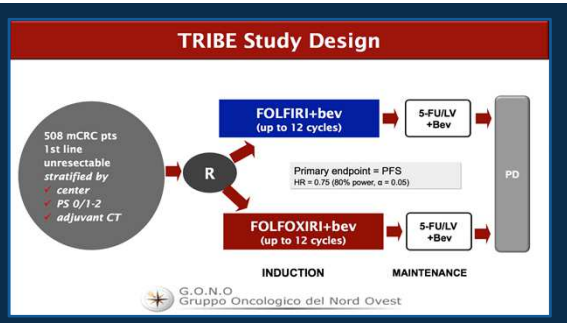
	N	mFOLFOXIRI + panitumumab (mo)	FOLFOXIRI (mo)
ITT	96	**35.7**	**29.8**
Left	78	**39.9**	**35.3**
Right	18	**11.5**	**22.0**
RAS/BRAF wt	60	**43.5**	**35.3**
BRAF mut	16	**8.0**	**9.0**

RAS mutiertes mCRC



TRIBE Study: RAS mutant mCRC

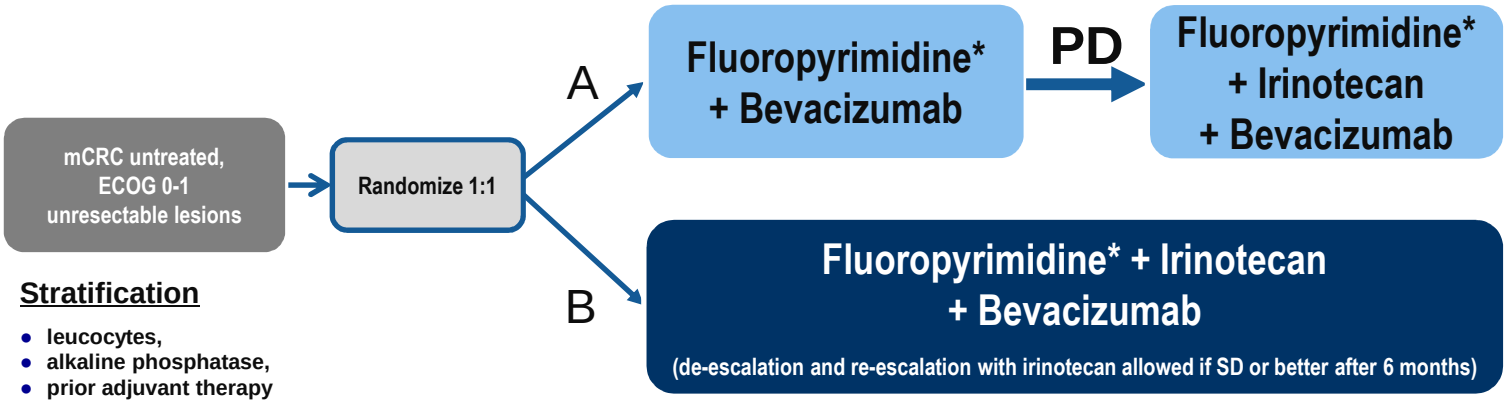




No significant OS benefit from treatment intensification in RAS-mut mCRC

Cremolini C, et al. Lancet Oncol 2015;16:1306–1315

AIO: XELAVIRI



Arm A

Capecitabine plus bevacizumab q3w

capecitabin 2 x 1250 mg/m^2 day 1-14

bevacizumab 7.5 mg/kg day 1

5-FUFA plus bevacizumab q2w

folinic acid 400 mg/m^2 day 1

5-FU 400 mg/m^2 bolus day 1

5-FU 2400 mg/m^2 46 h day 1-2

bevacizumab 5.0 mg/kg day 1

Arm B

CAPIRI plus bevacizumab q3w

capecitabin 2 x 800 mg/m^2 day 1-14

Irinotecan 200mg/m^2 day 1

bevacizumab 7.5 mg/kg day 1

FOLFIRI plus bevacizumab q2w

folinic acid 400 mg/m^2 day 1

5-FU 400 mg/m^2 bolus day 1

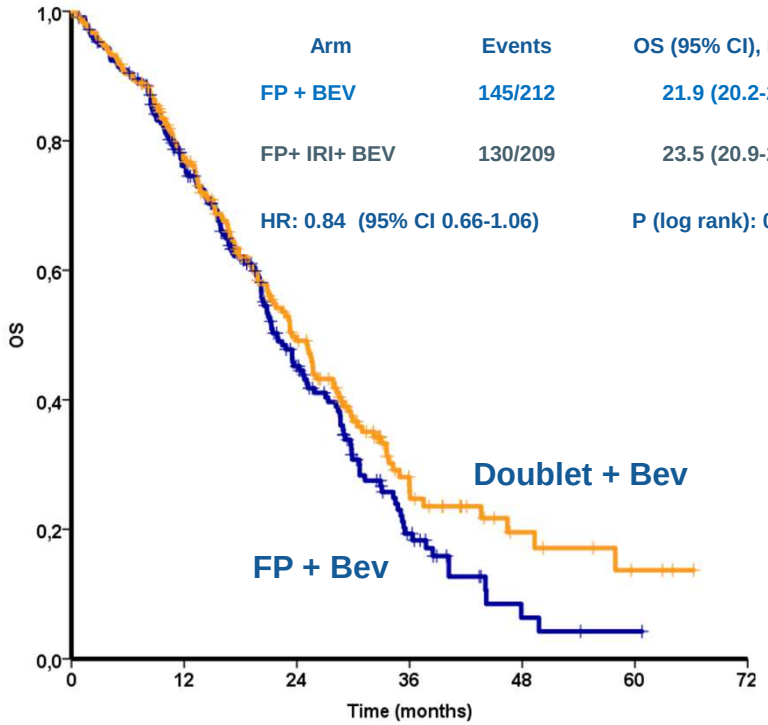
5-FU 2400 mg/m^2 46 h day 1-2

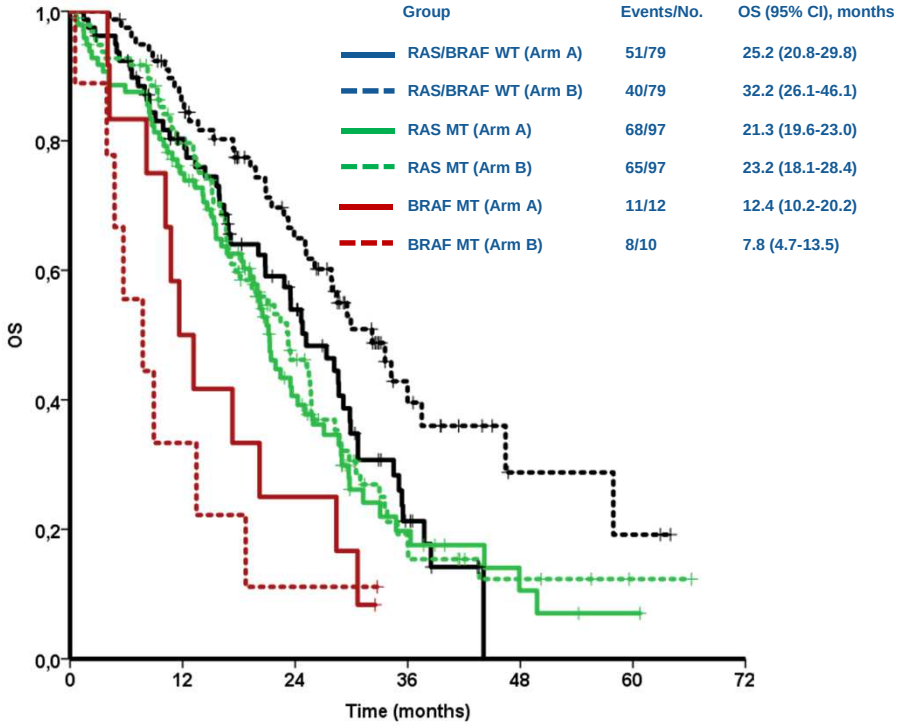
irinotecan 180 mg/m^2 day1

bevacizumab: 5.0 mg/kg day 1

Modest D, ...Heinemann V, JCO accepted

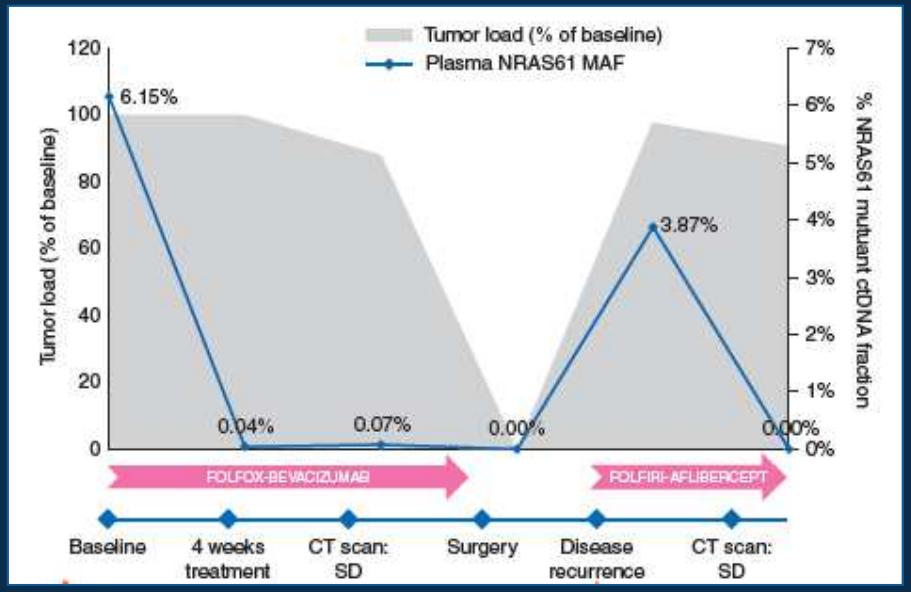
XELAVIRI: Overall Survival

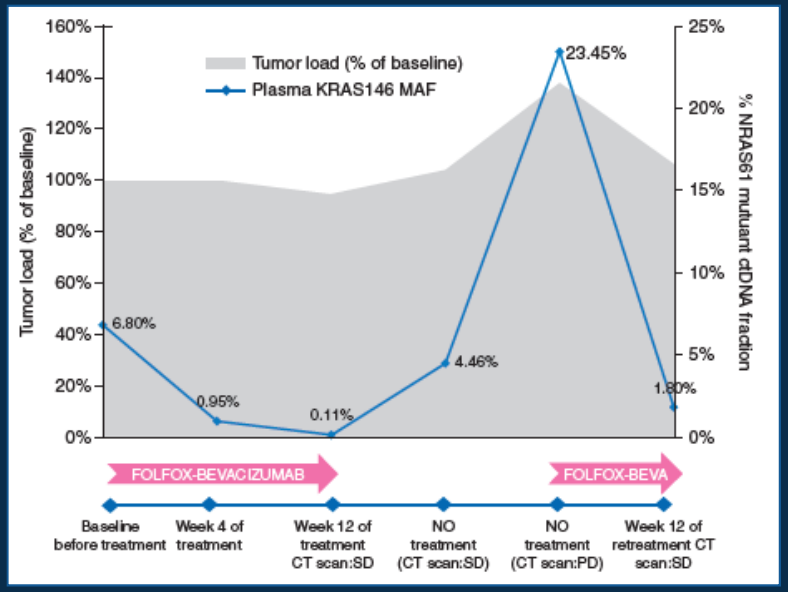




Doublet plus Bev not better than FP plus Bev in patients with RAS mutant tumors

Elimination des RAS-mutierten Klons durch intensive 1st-line Chemotherapie

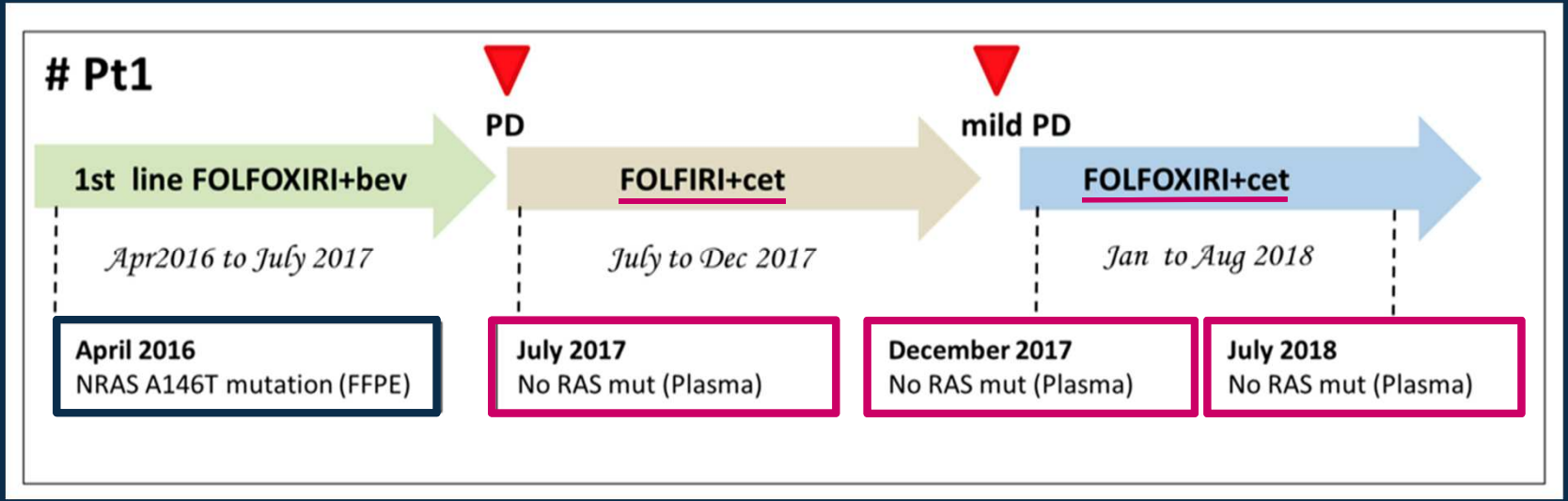




Longitudinale Analyse von Plasma RAS ctDNA

Vidal et al. Annals of Oncology

Elimination of RAS mutant clone by intensive therapy

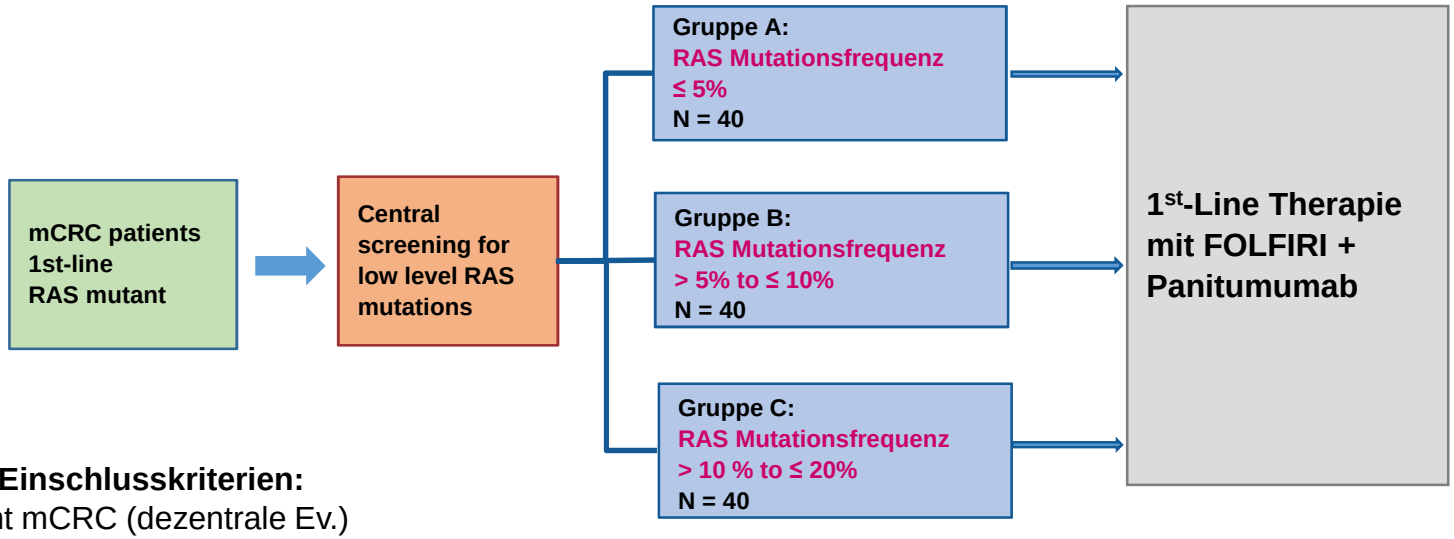


- Elimination of RAS-mutant clones by intensive chemotherapy in **5/11** patients (ctDNA)
- Benefit from anti-EGFR-based therapy

Raimondi C, et al. Cancers 2018

FIRE-5: Low-RAS Studie (AIO-TF-0118)

Erstlinientherapie des RAS-mutierten mKRK



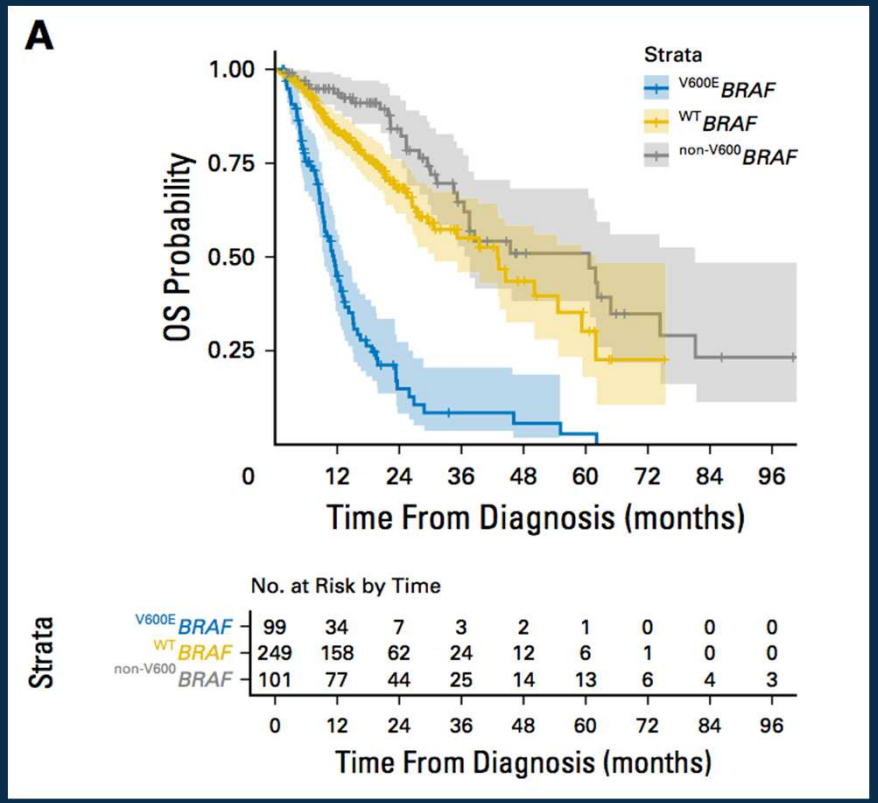
Wesentliche Einschlusskriterien:

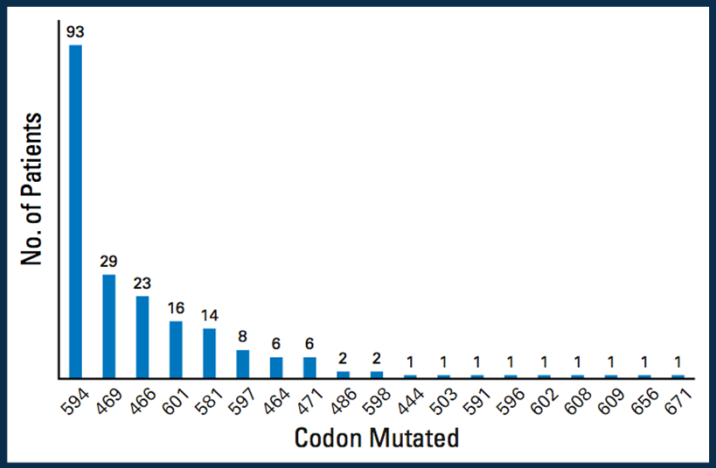
- RAS mutant mCRC (dezentrale Ev.)
- ECOG 0-2
- Fit für Doublet CT

Primärer Endpunkt: ORR

Sekundäre Endpunkte: PFS, OS

BRAF non-V600 in Metastatic Colorectal Cancer

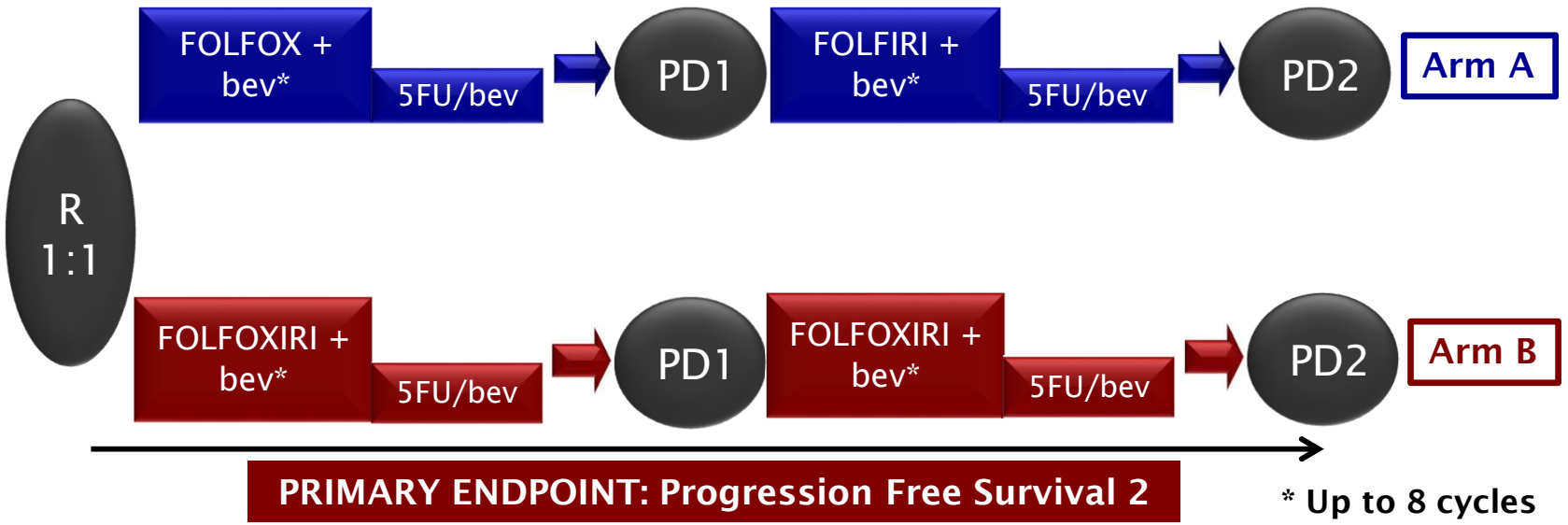




> male
> younger patients
> left-sided tumours
< high grade tumours
< peritoneal metastasis

Jones JC, et al. JCO 2017

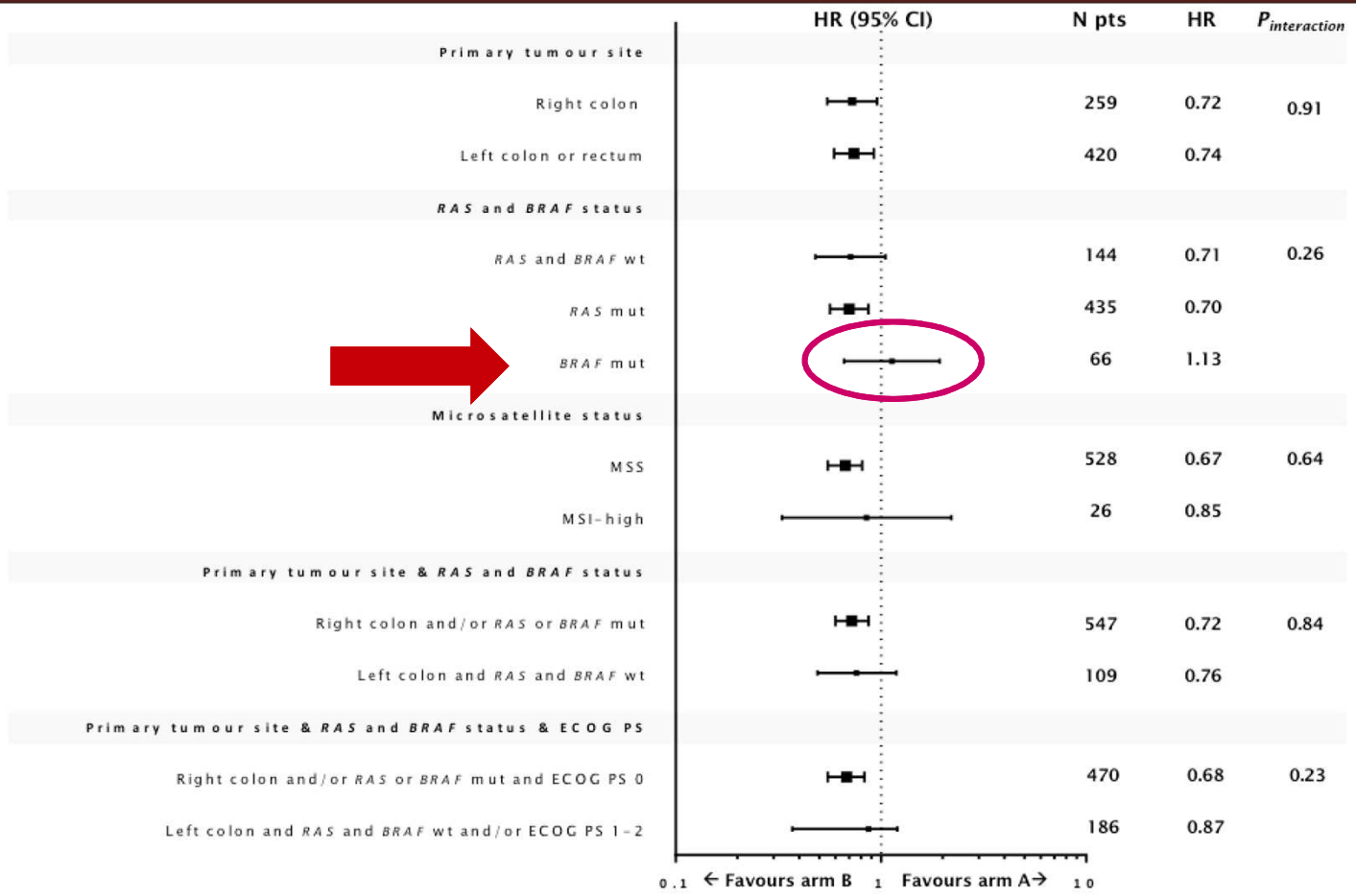
TRIBE2: Study design and endpoints



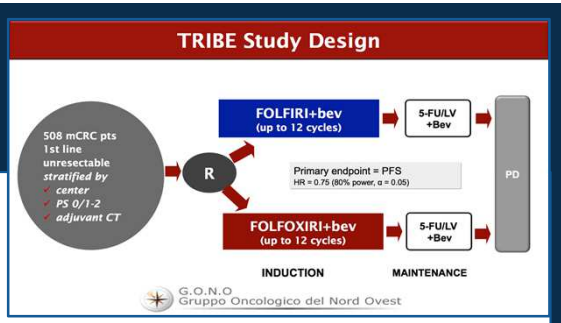
SECONDARY ENDPOINTS

- 1st and 2nd Progression-Free Survival
- RECIST Response Rate in 1st and 2nd line
- Resection Rate
- Safety profile in 1st and 2nd line
- Overall Survival

Subgroup analyses – sidedness and molecular characteristics- PFS2



Behandlung bei BRAF-Mutation

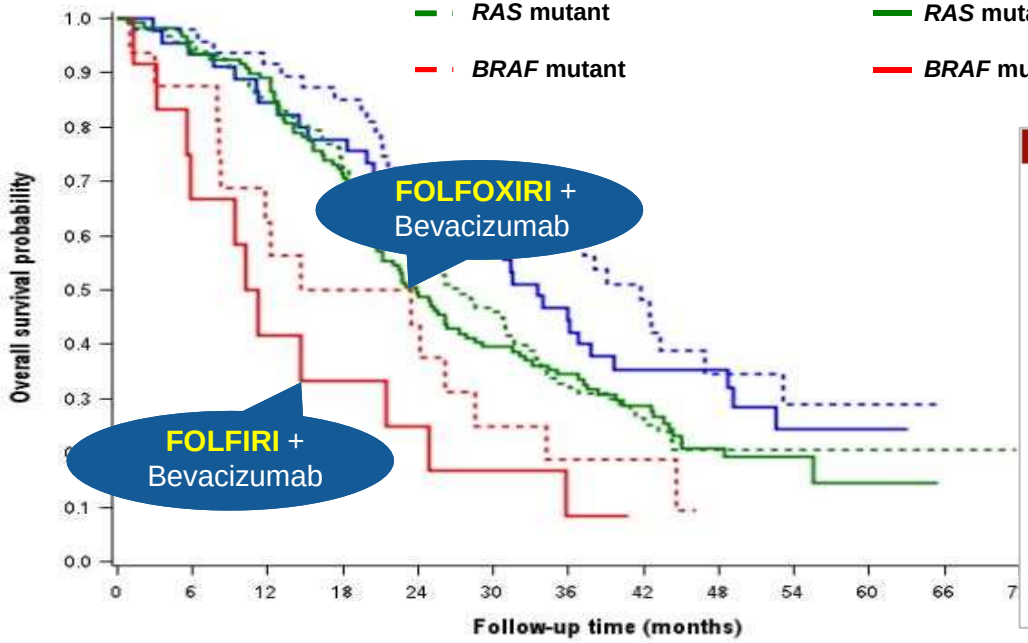


Bevacizumab + FOLFOXIRI (n=252)

- ***RAS*** **and** ***BRAF*** **wild-type**
- ***RAS*** **mutant**
- ***BRAF*** **mutant**

Bevacizumab + FOLFIRI (n=256)

- ***RAS*** **and** ***BRAF*** **wild-type**
- ***RAS*** **mutant**
- ***BRAF*** **mutant**



Treatment effect in molecular subgroups

	N	FOLFIRI + bev Median OS	FOLFOXIRI + bev Median OS	HR [95% CI]	p
ITT population	508	25.8	29.8	0.80 [0.65-0.98]	0.030
RAS and *BRAF* evaluable	357	24.9	28.6	0.84 [0.66-1.07]	0.159
RAS and *BRAF* wt	93	33.5	41.7	0.77 [0.46-1.27]	
RAS mutated	236	23.9	27.3	0.88 [0.65-1.18]	0.522*
BRAF mutated	28	10.7	19.0	0.54 [0.24-1.20]	N=12 + 16
RAS wild-type	121	26.8	37.1	0.78 [0.51-1.20]	0.658*
RAS mutated	236	23.9	27.3	0.88 [0.65-1.18]	

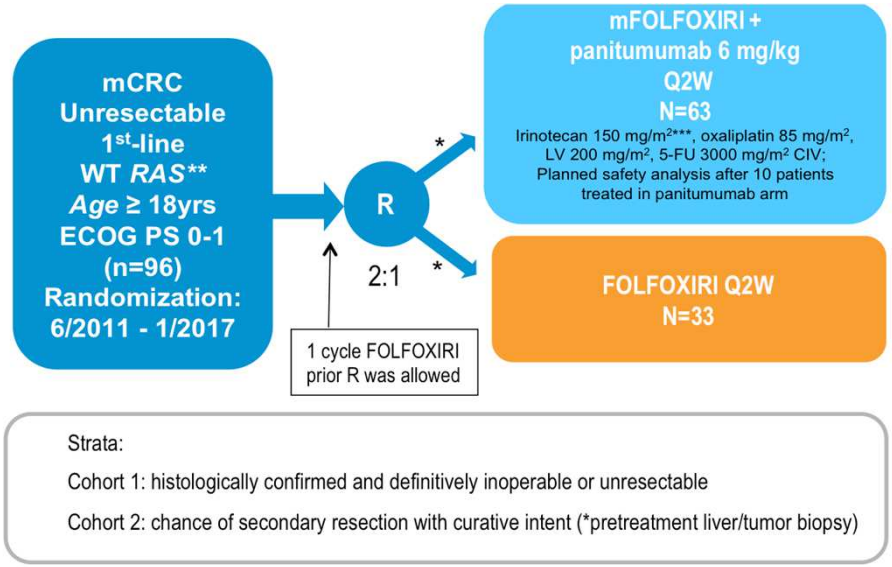
* p for interaction

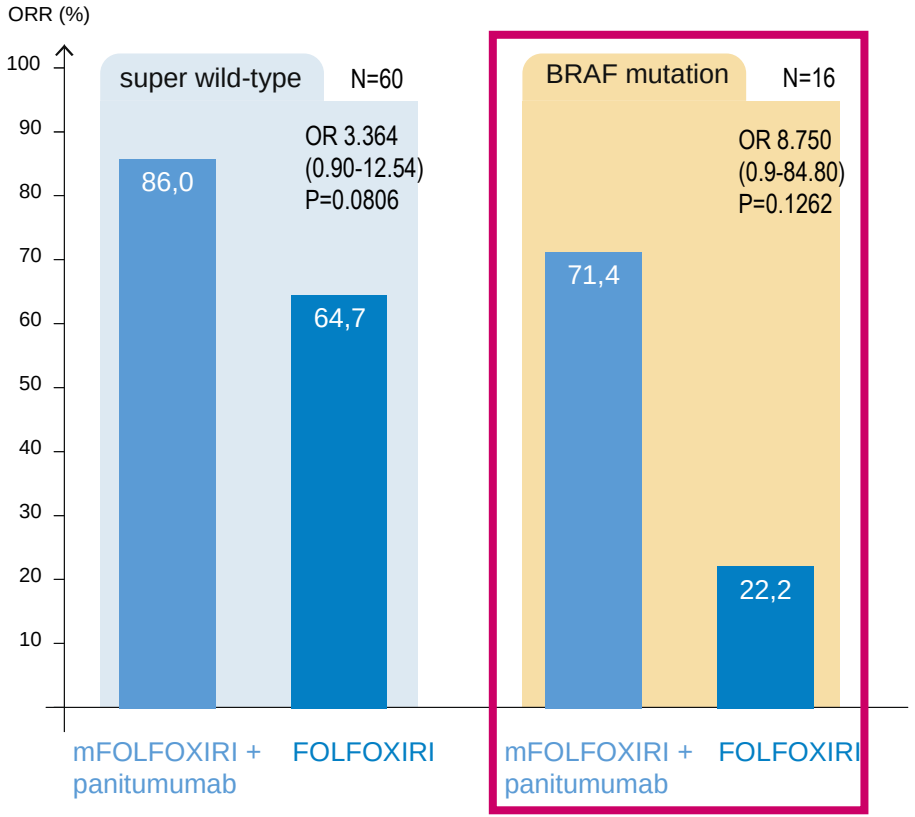
Cremolini C, et al. Lancet Oncol 2015;16:1306–1315

EVALUATION OF RESPONSE SIDEDNESS + GENOTYPE

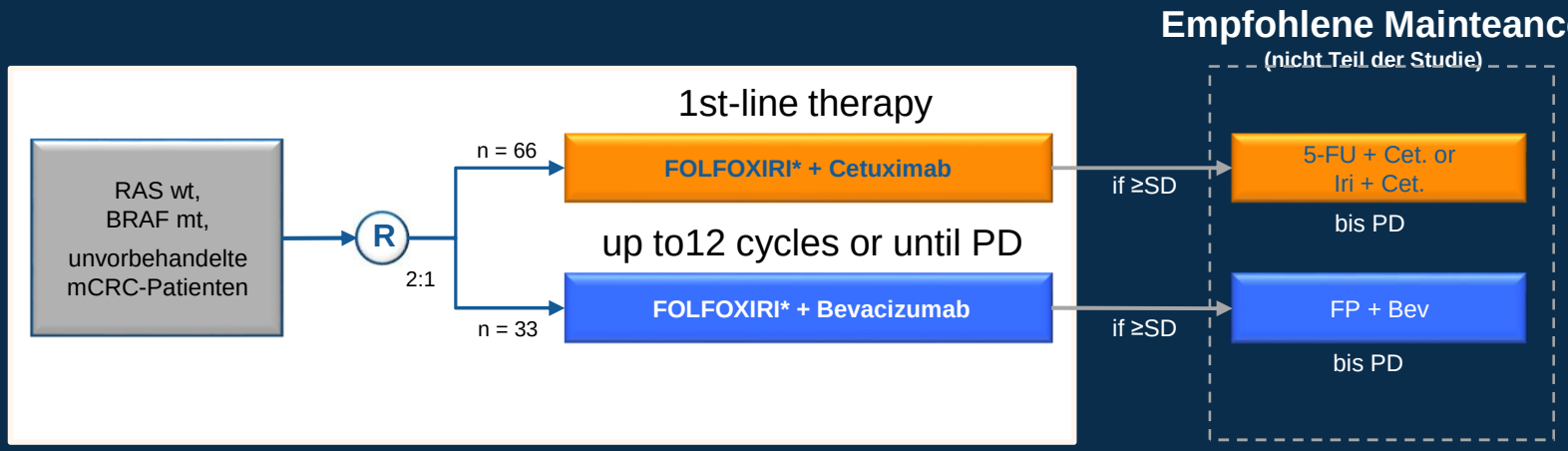
AIO

VOLFI Studie





FIRE 4.5:
Rekrutierende Studie beim BRAF mutierten mCRC



Phase II Studie

Primärer Endpunkt: ORR

Sekundäre Endpunkte: PFS, OS, ETS, DpR

Aktuell: 80/99 Patienten rekrutiert

FOLFOXIRI Dosierung:

Irinotecan:	150mg/m²
FA (racemic):	400mg/m²
Oxaliplatin:	85 mg/m²
5-FU:	3000mg/m² iv für 48h

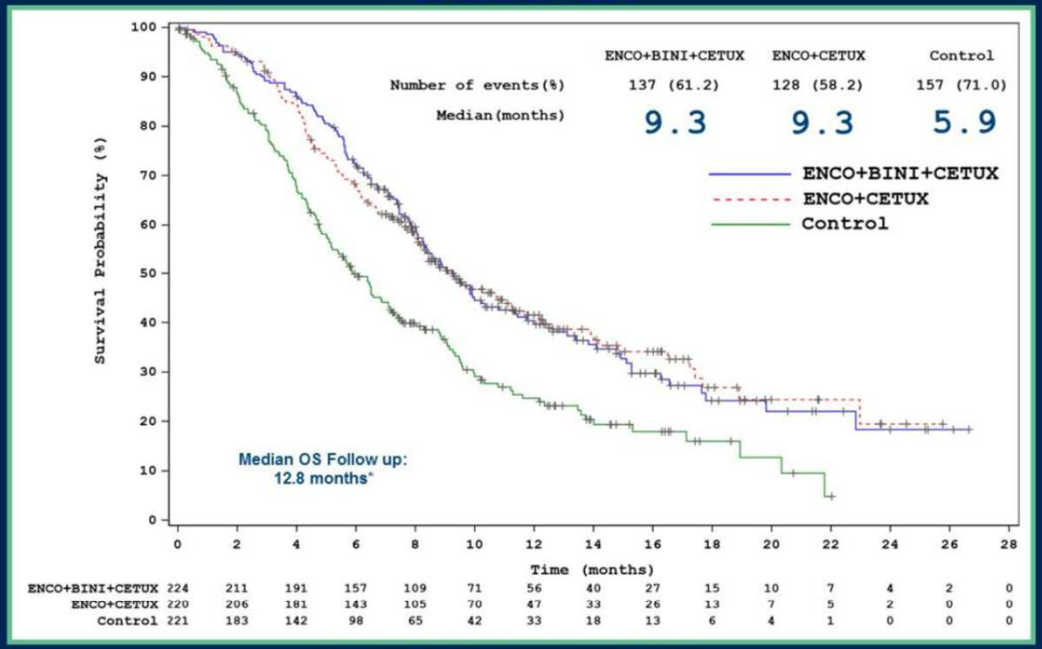
* de-escalation to FOLFIRI if toxicity is observed

BEACON CRC: Updated Analysis

- In this updated analysis of BEACON CRC (which includes ORR for all randomized patients (additional 364 patients) and 6 months additional follow-up):
  - The triplet and doublet demonstrated improved OS and ORR in patients with BRAF V600E-mutant mCRC when compared with current standard of care chemotherapy

The full updated BEACON results with subgroup analysis will be submitted to a future congress

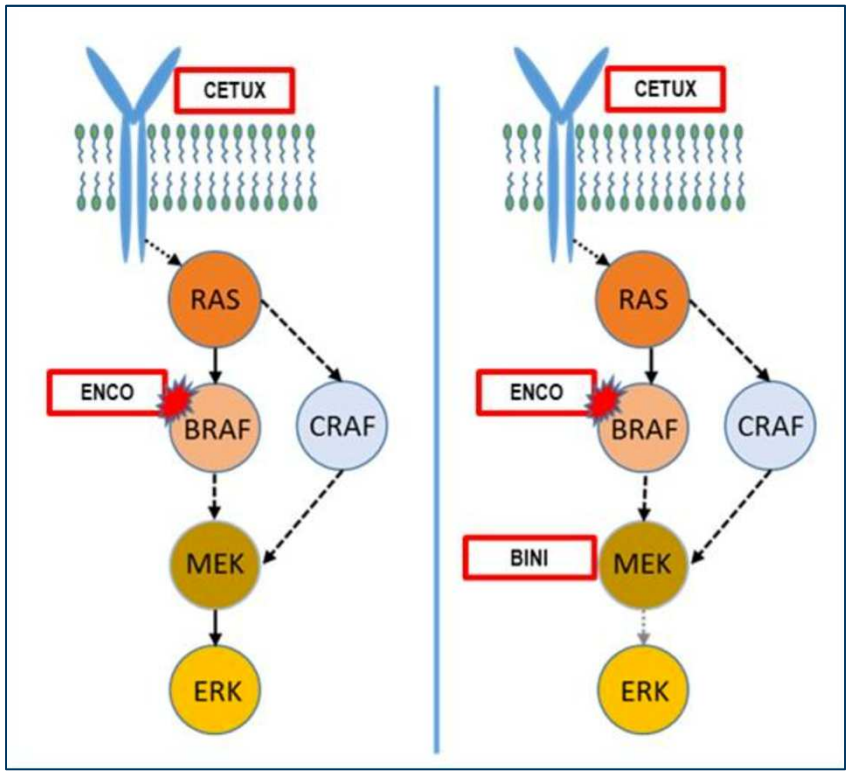
Overall Survival



Objective Response Rate

Confirmed Response by blinded central review	Triplet N=224	Doublet N=220	Control N=221
Objective Response Rate	**27%**	**20%**	**2%**
95% (CI)	(21%, 33%)	(15%, 25%)	(<1%, 5%)
p-value vs. Control	<0.0001	<0.0001	

Therapie beim BRAFV600E - mutierten mCRC



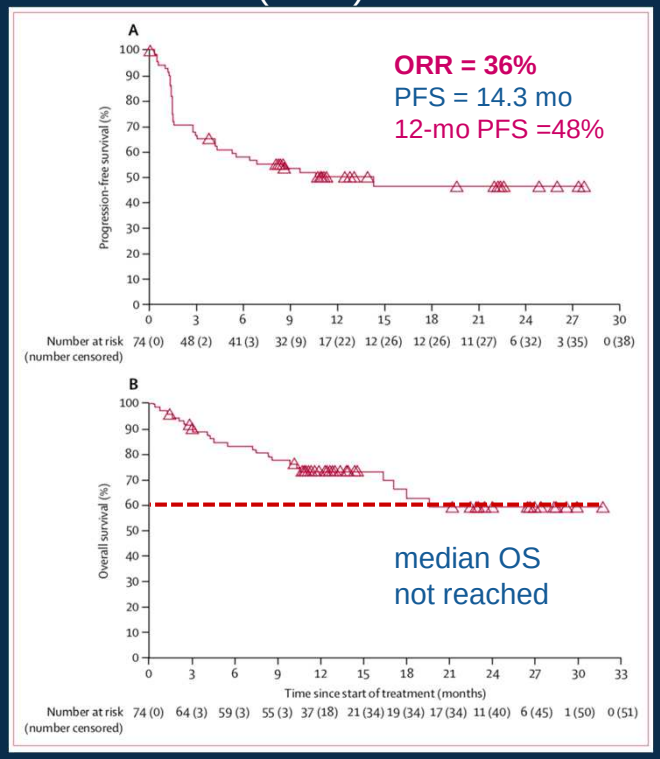
Schlussfolgerung

Encorafenib plus Cetuximab
mit oder ohne Binimetinib
induzierte einen längeren Erhalt der QoL als die Standardtherapie im Vergleichsarm

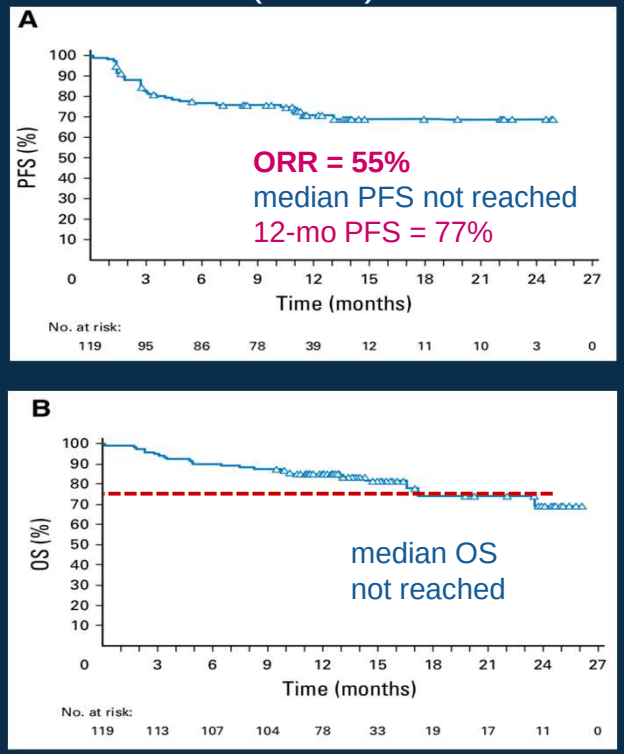
Scott Kopetz at 2020 Gastrointestinal Cancer Symposium

CheckMate 142: Nivolumab in MMRd mCRC

Nivolumab 3mg/kg
(n=74)



Nivolumab 3mg/kg + **Ipilimumab** 1mg/kg
(n=119)

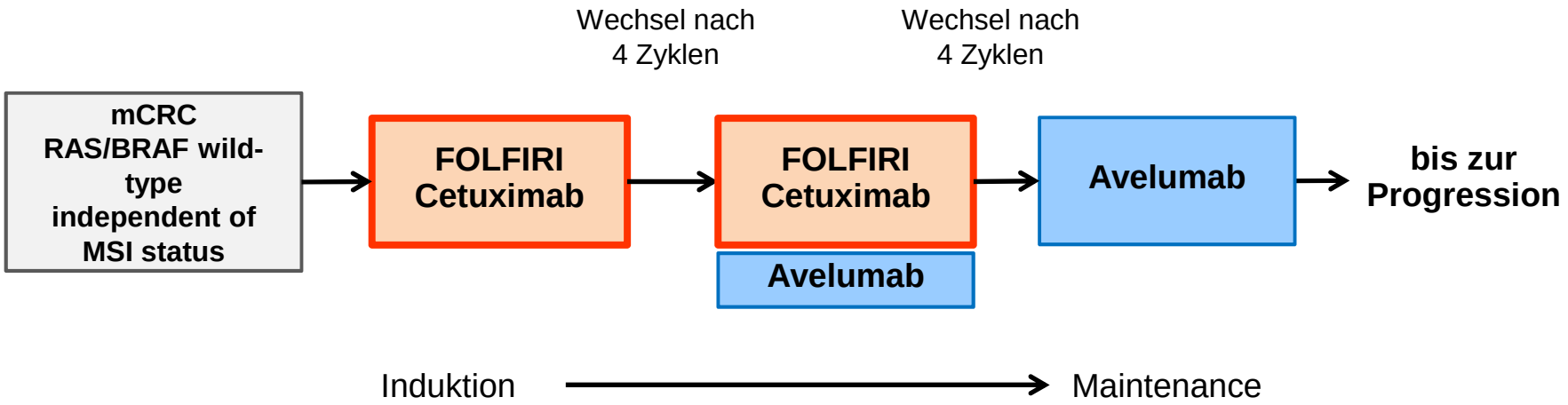


* Nivo 3mg/kg q2w until PD
** Nivo 3mg/kg plus Ipi 1 mg/kg q 3w for 4 doses, then Nivo 3mg/kg q2w

Overman MJ, Lancet Oncol 2017
Overman MJ, JCO 2017

FIRE-6 Avelumab in MMRp mCRC

Phase-IIa Design (n = 55)



Primärer Endpunkt: **PFS**

Sekundäre Endpunkte: Sicherheit, ORR, OS,
PFS Rate nach 12 Monaten
Translationale Forschung,

Herzlichen Dank für Ihre Aufmerksamkeit