Molekular gesteuerte Therapiemöglichkeiten in der Erstliniensituation und in den Folgelinien

Charité- Universitätsmedizin Berlin

Med. Klinik m. S. Hämatologie, Onkologie und Tumorimmunologie

Campus Virchow Klinikum

Dr. med. A. Kurreck | 16. Oktober 2023 | Hamburg

Agenda

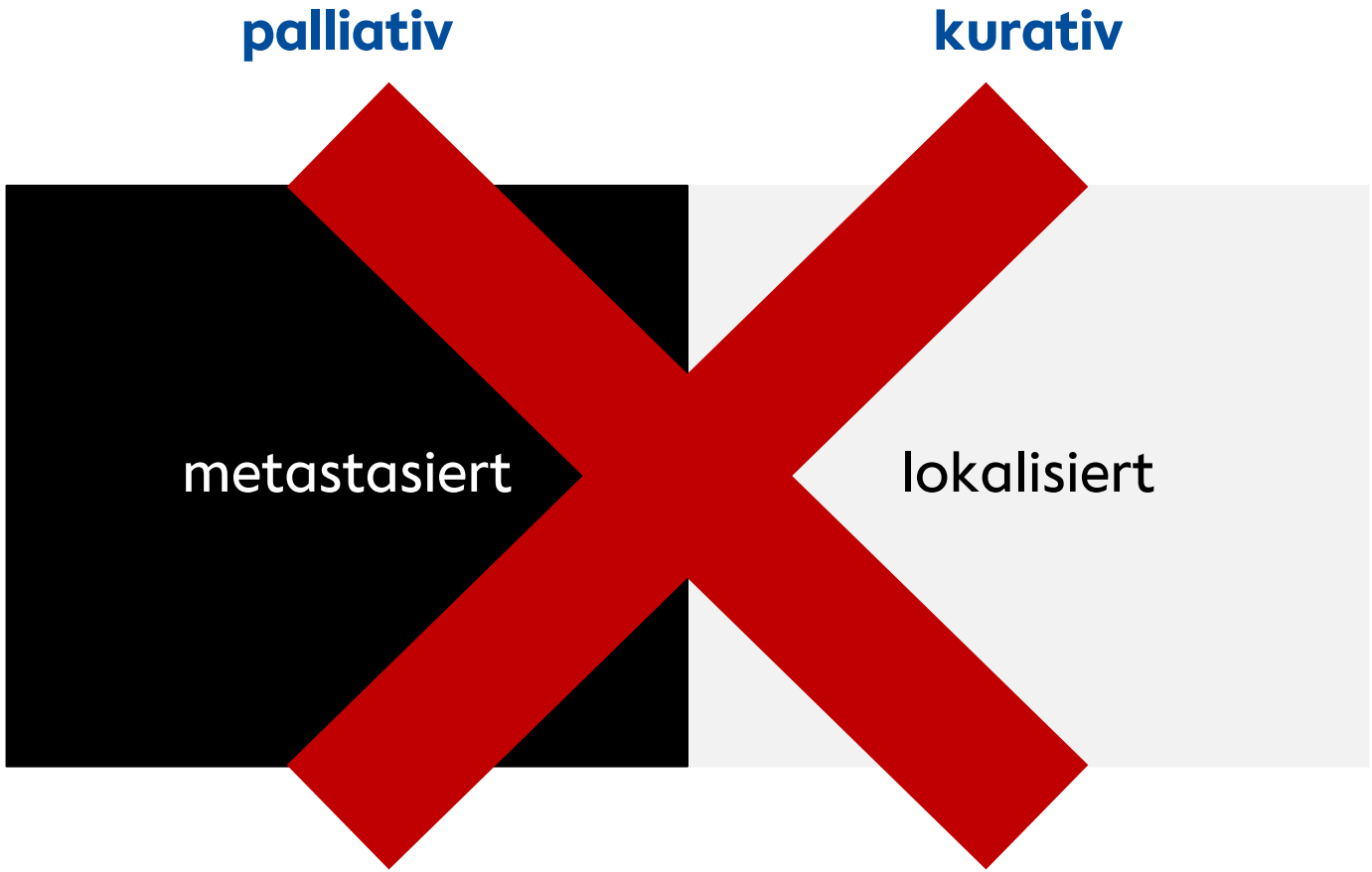
1. **Therapieziele und Behandlungsstrategien**
2. **Molekular gesteuerte Standardtherapien**
    - 2.1 RAS
    - 2.2 BRAF V600E
3. **Neue molekular zielgerichtete Therapien**
    - 3.1 KRAS G12C
    - 3.2 HER2
    - 3.3 Seltene targets

Therapieziele und Behandlungsstrategien

Therapiezielsetzung

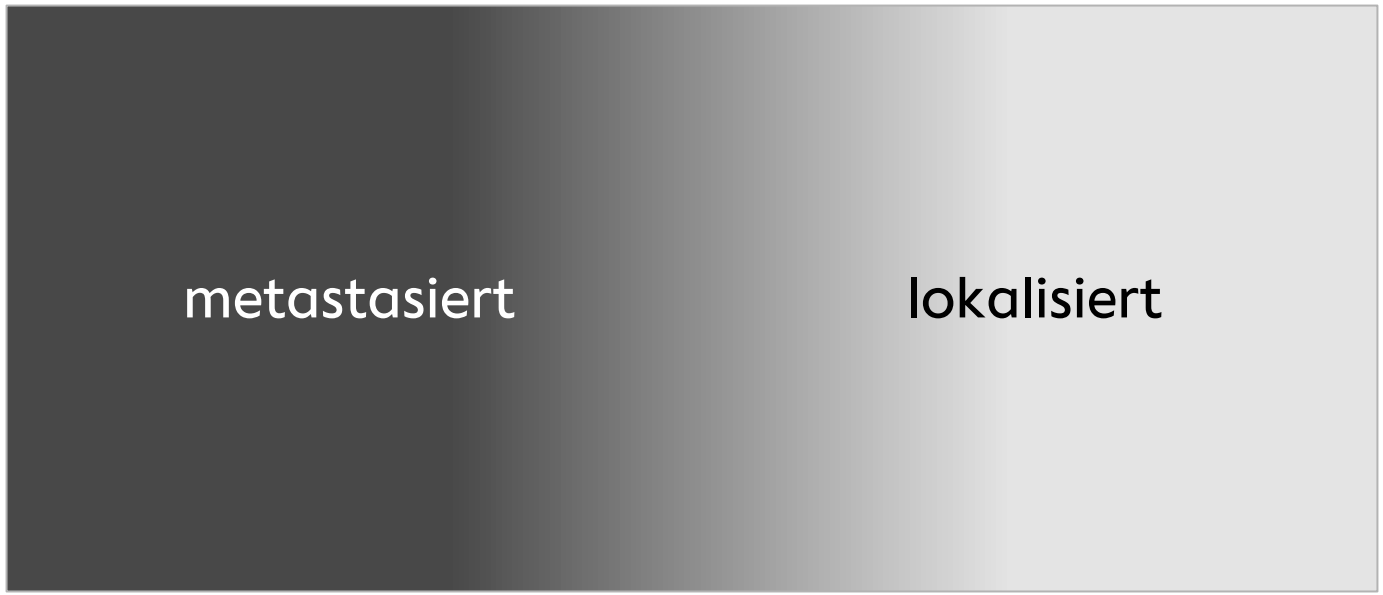
palliativ	kurativ
metastasiert	lokalisiert

Therapiezielsetzung

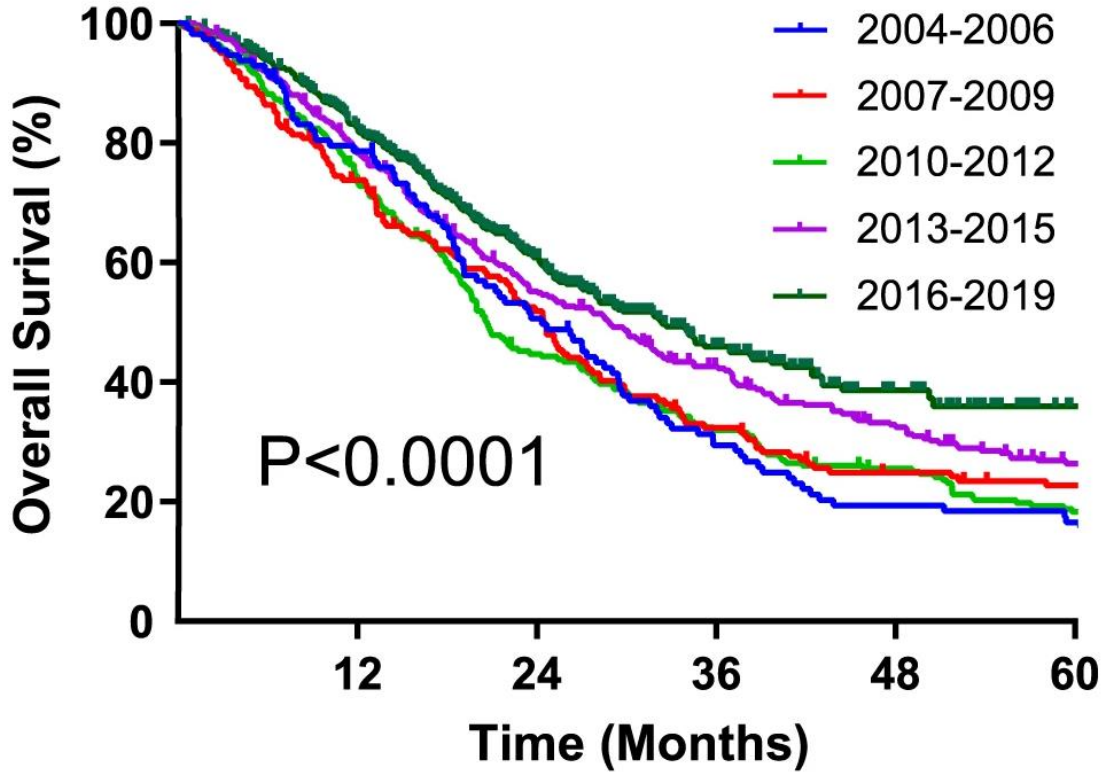


Therapiezielsetzung

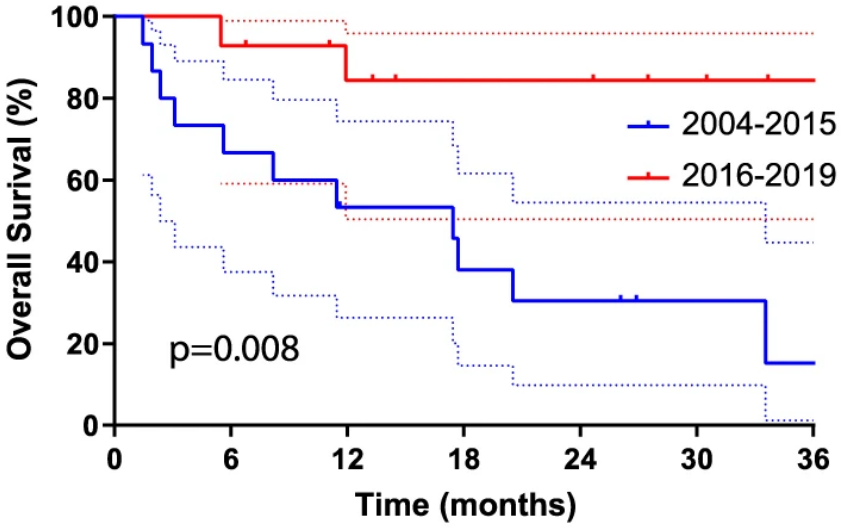
palliativ **potenziell kurativ** **kurativ**

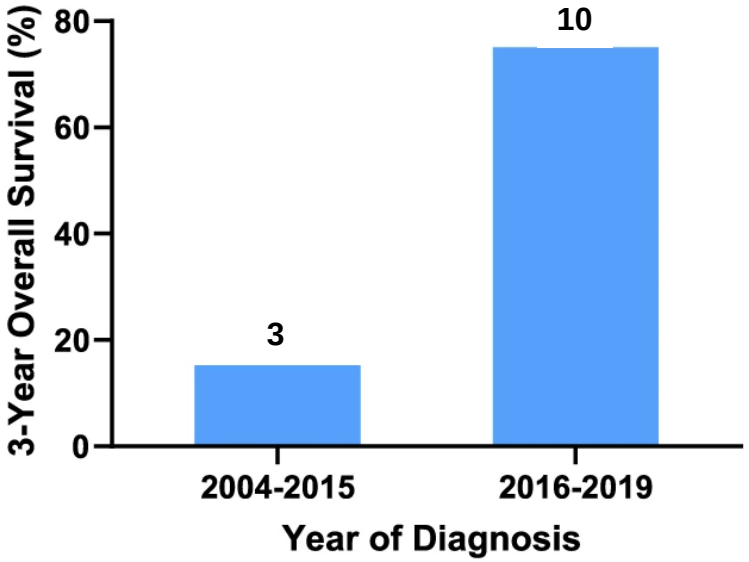


Survival improvement in mCRC over the years



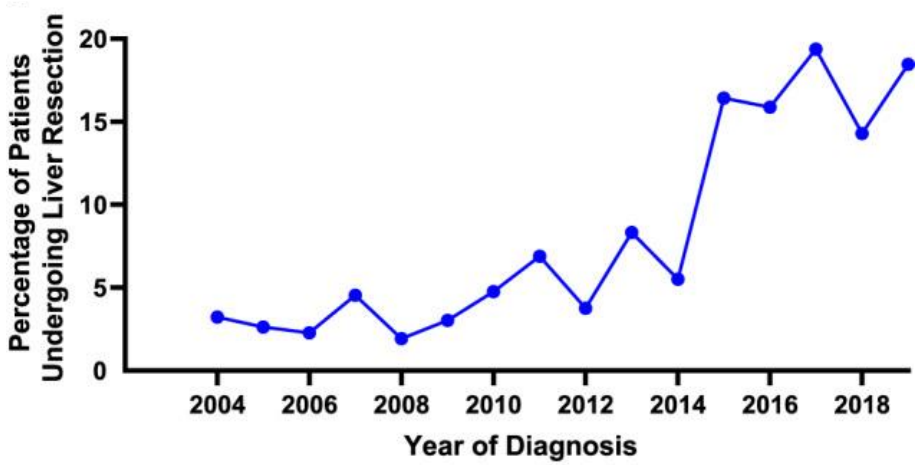
MSI-H

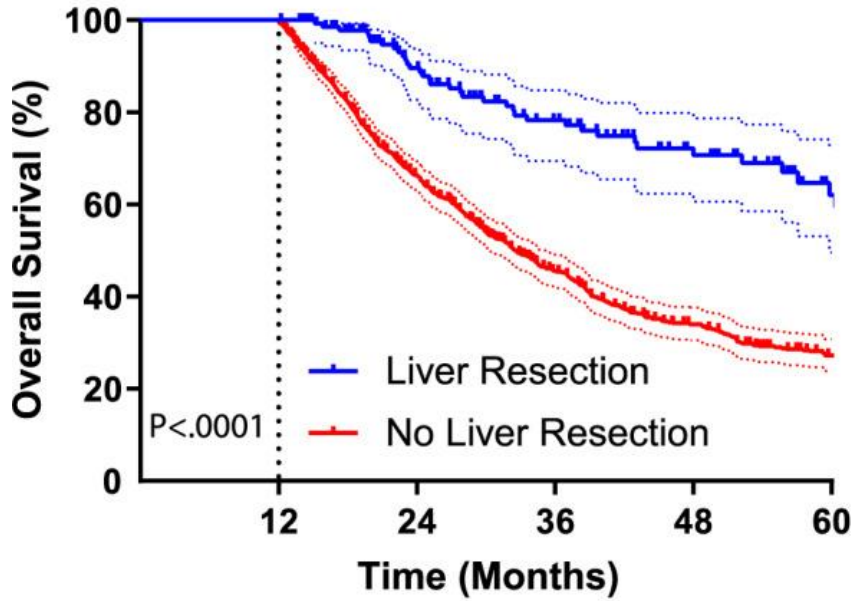


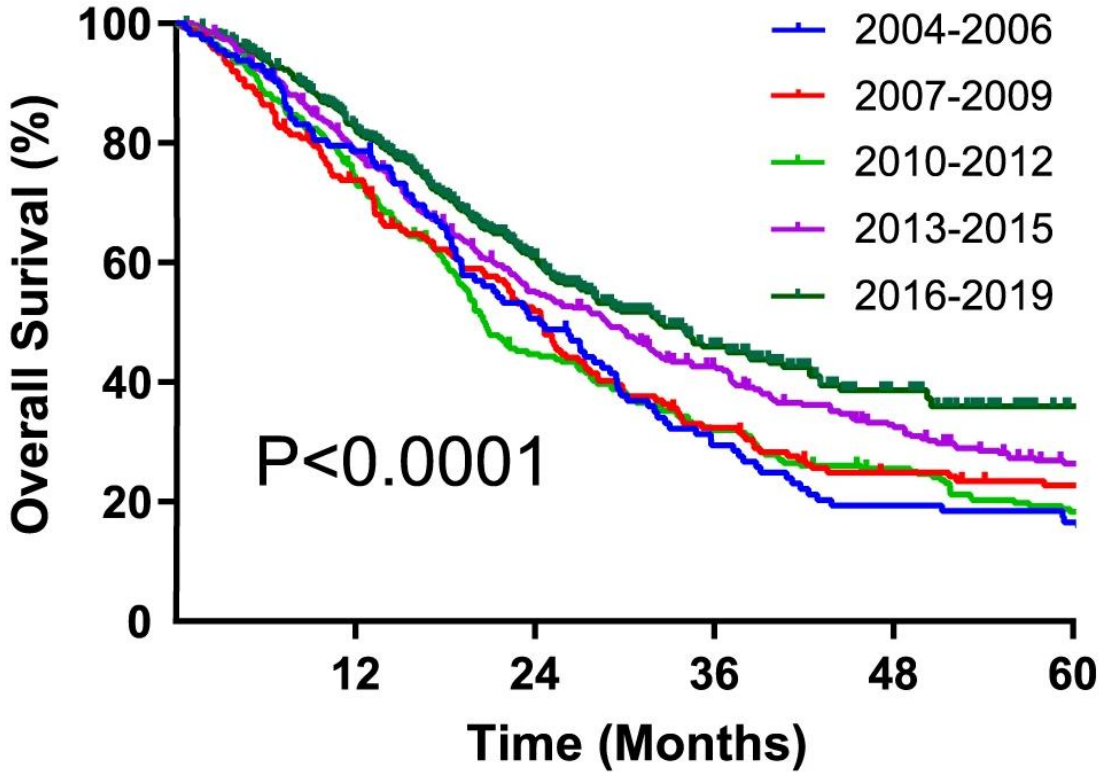


FA Zeineddine et al. *Precis. Onc.* 2023.

Survival improvement in mCRC over the years







Wichtigkeit der Multidisziplinarität in der onkologischen Behandlung

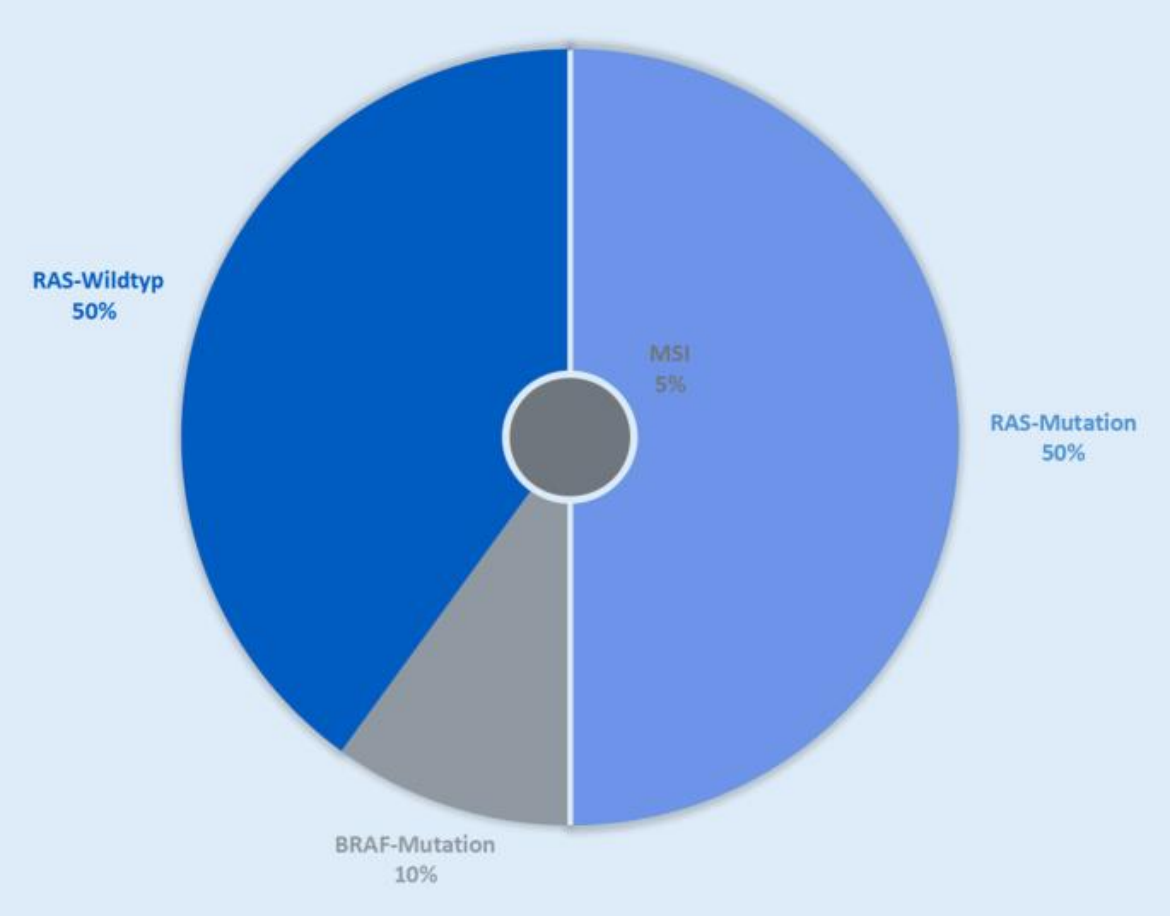
FA Zeineddine et al. *Precis. Onc.* 2023.

Molekular gesteuerte Standardtherapien

Bestimmung der molekularen Subgruppe im mKRK

Empfehlung der ESMO guideline 2022:

'*Testing for **MMR** status and **KRAS, NRAS** exon 2, 3 and 4 and **BRAF** mutations is recommended in **all patients** at the time of **mCRC** diagnosis [I, A].*'

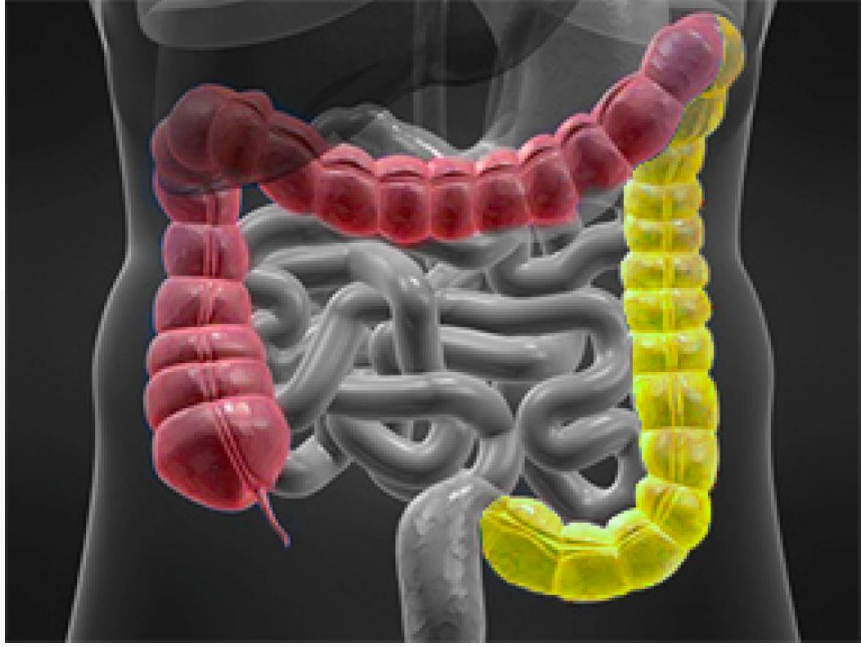


Kurreck et al. *Onkologe* 2021.

Molekular gesteuerte Standardtherapien

RAS WT und RAS MT

Evolution der Systemtherapie



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2000

2017

Saltz[1]	5-FU/LV bolus		12.6
Douillard[2]	5-FU/LV infusion		14.1
Saltz[1]	IFL		14.8
Douillard[2]	FOLFIRI		17.4
Goldberg[3]	FOLFOX		19.5
Hurwitz[4]	IFL + bevacizumab	AVF2107g	20.3
Falcone[6]	FOLFOXIRI	Italian GONO Trial	22.6
Saltz[5]	XELOX/FOLFOX + bevacizumab	NO16966	21.3
Bokemeyer[7]	FOLFOX + cetuximab	OPUS	22.8*
Van Cutsem[8]	FOLFIRI + cetuximab	CRYSTAL	23.5*
Douillard[9]	FOLFOX + panitumumab	PRIME	23.9*
Passardi[10]	FOLFOX or FOLFIRI	ITACA	20.6
	FOLFOX or FOLFIRI + bevacizumab	ITACA	20.6
Heinemann[11]	FOLFIRI + bevacizumab	FIRE-3	25.0*
	FOLFIRI + cetuximab	FIRE-3	28.7*
Cremolini[12]	FOLFIRI + bevacizumab	TRIBE	25.8
	FOLFOXIRI + bevacizumab	TRIBE	31.0
Venook[13]	Chemo + bevacizumab	CALGB	29.0*
	Chemo + cetuximab	CALGB	29.9*

0 5 10 15 20 25 30 35 40 45

OS (months)

⇦ Anti-EGFR Therapie

*KRAS WT tumours.

PARADIGM: Studiendesign

1st line

Phase 3, randomized, open-label, multicenter study (NCT02394795)

Patients with *RAS* WT mCRC

- Unresectable disease
- No previous chemotherapy[a]
- Age: 20–79 years
- ECOG performance status 0–1
- At least 1 evaluable lesion
- Adequate organ function
- Life expectancy ≥ 3 months

N=823

R 1:1

Panitumumab+ mFOLFOX6[b]

Bevacizumab+ mFOLFOX6[b]

Primary endpoint

- OS: left-sided[c] population; if significant, analyzed in overall population

Secondary endpoints

- PFS, RR, DOR, R0 resection: left-sided[c] and overall populations
- Safety: all treated patients

Exploratory endpoints

- ETS, depth of response, DCR: left-sided[c] and overall populations

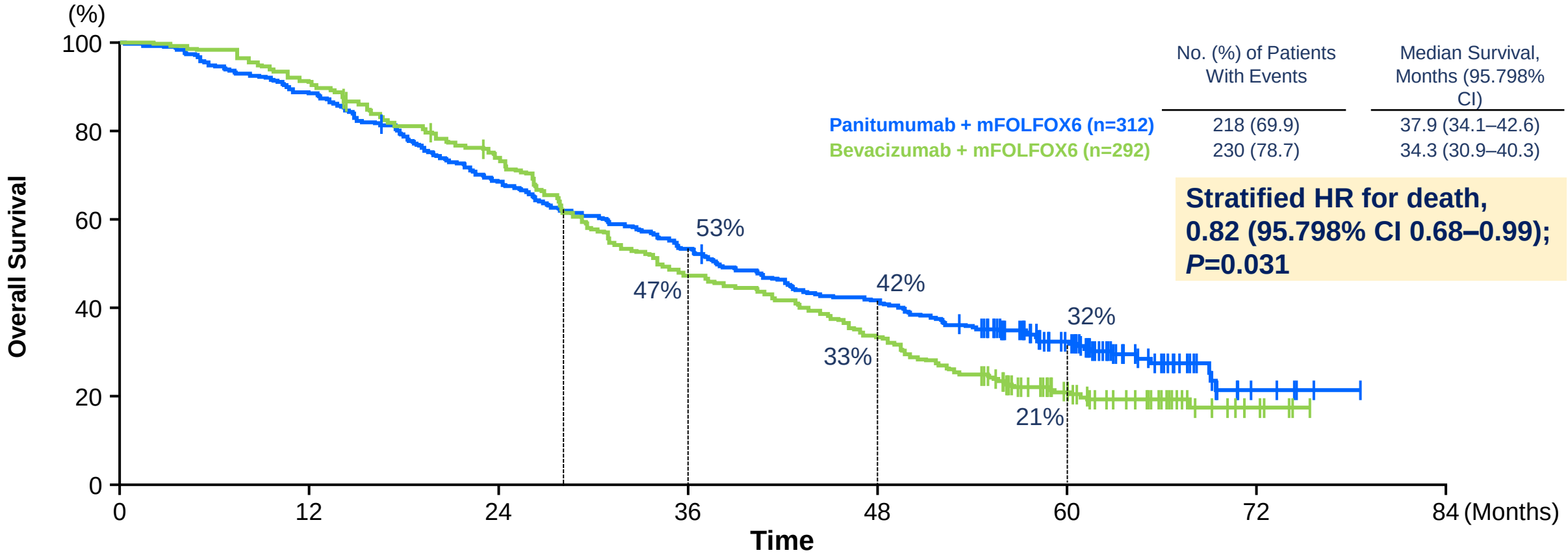
Stratification factors

- Institution
- Age: 20–64 vs 65–79 years
- Liver metastases: present vs absent

DCR, disease control rate; DOR; duration of response; ECOG, Eastern Cooperative Oncology Group; ETS, early tumor shrinkage; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression free survival; RR, response rate; R0, curative resection; WT, wild type.

[a]Adjuvant fluoropyrimidine monotherapy allowed if completed > 6 months before enrollment. [b]Until disease progression, unacceptable toxicity, withdrawal of consent or investigator's judgement or curative intent resection. [c]Primary tumor in descending colon, sigmoid colon, rectosigmoid, and rectum.

PARADIGM: OS in Left-sided Population

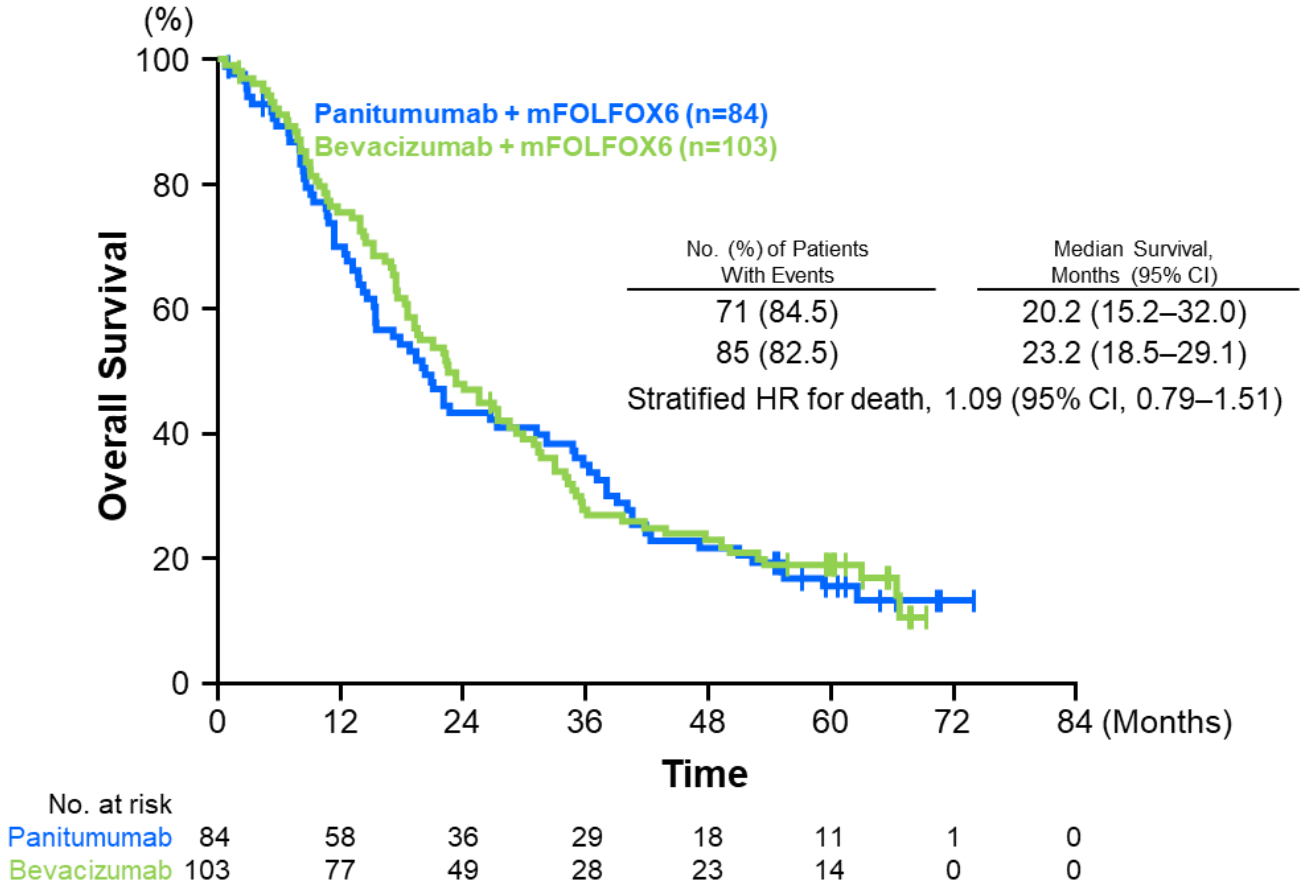


	No. (%) of Patients With Events	Median Survival, Months (95.798% CI)
Panitumumab + mFOLFOX6 (n=312)	218 (69.9)	37.9 (34.1–42.6)
Bevacizumab + mFOLFOX6 (n=292)	230 (78.7)	34.3 (30.9–40.3)

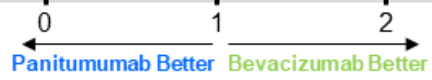
Stratified HR for death, 0.82 (95.798% CI 0.68–0.99); *P*=0.031

No. at risk								
Panitumumab	312	276	213	166	129	68	5	0
Bevacizumab	292	266	212	136	96	40	5	0

PARADIGM: OS in Right-sided Population

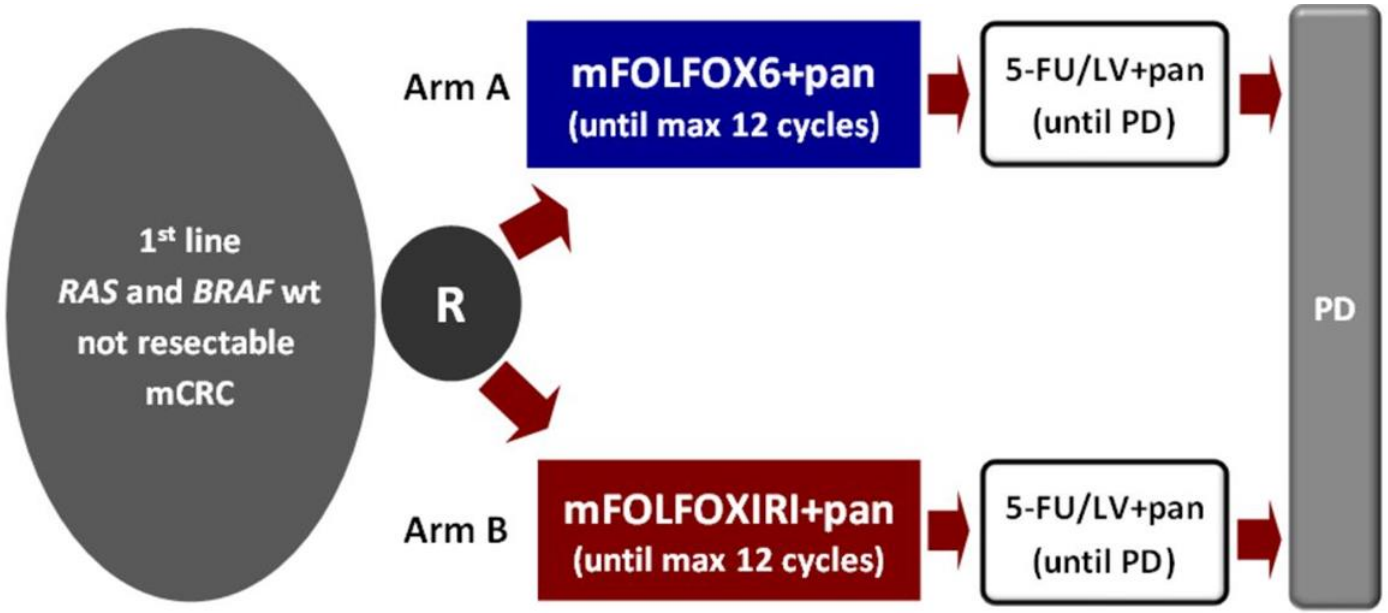


Subgroup		Events/Patients: Panitumumab + mFOLFOX6	Events/Patients: Bevacizumab + mFOLFOX6	Hazard Ratio (95% CI)
	Overall*	71/84	85/103	1.09 (0.79-1.51)
Age	20-64 yr	22/26	32/39	1.26 (0.73-2.17)
	65-79 yr	49/58	53/64	0.97 (0.66-1.44)
Sex	Male	37/41	51/61	1.04 (0.68-1.60)
	Female	34/43	34/42	1.08 (0.67-1.74)
ECOG PS	0	54/65	68/82	0.96 (0.67-1.37)
	1	16/18	17/21	1.33 (0.66-2.67)
No. of organs with metastasis	0-1	31/40	30/44	1.27 (0.77-2.10)
	≥2	40/44	55/59	0.94 (0.63-1.42)
Liver metastasis	No	26/35	29/37	0.87 (0.51-1.49)
	Yes	45/49	56/66	1.23 (0.83-1.83)
Organs with metastasis	Liver only	13/14	15/21	1.66 (0.79-3.50)
	Other	58/70	70/82	0.93 (0.66-1.32)
Primary tumor resection	No	30/33	28/30	0.87 (0.51-1.45)
	Yes	41/51	57/73	1.09 (0.73-1.63)



*Stratified Hazard Ratio is shown with 95% CI.

TRIPLETE trial



1st line

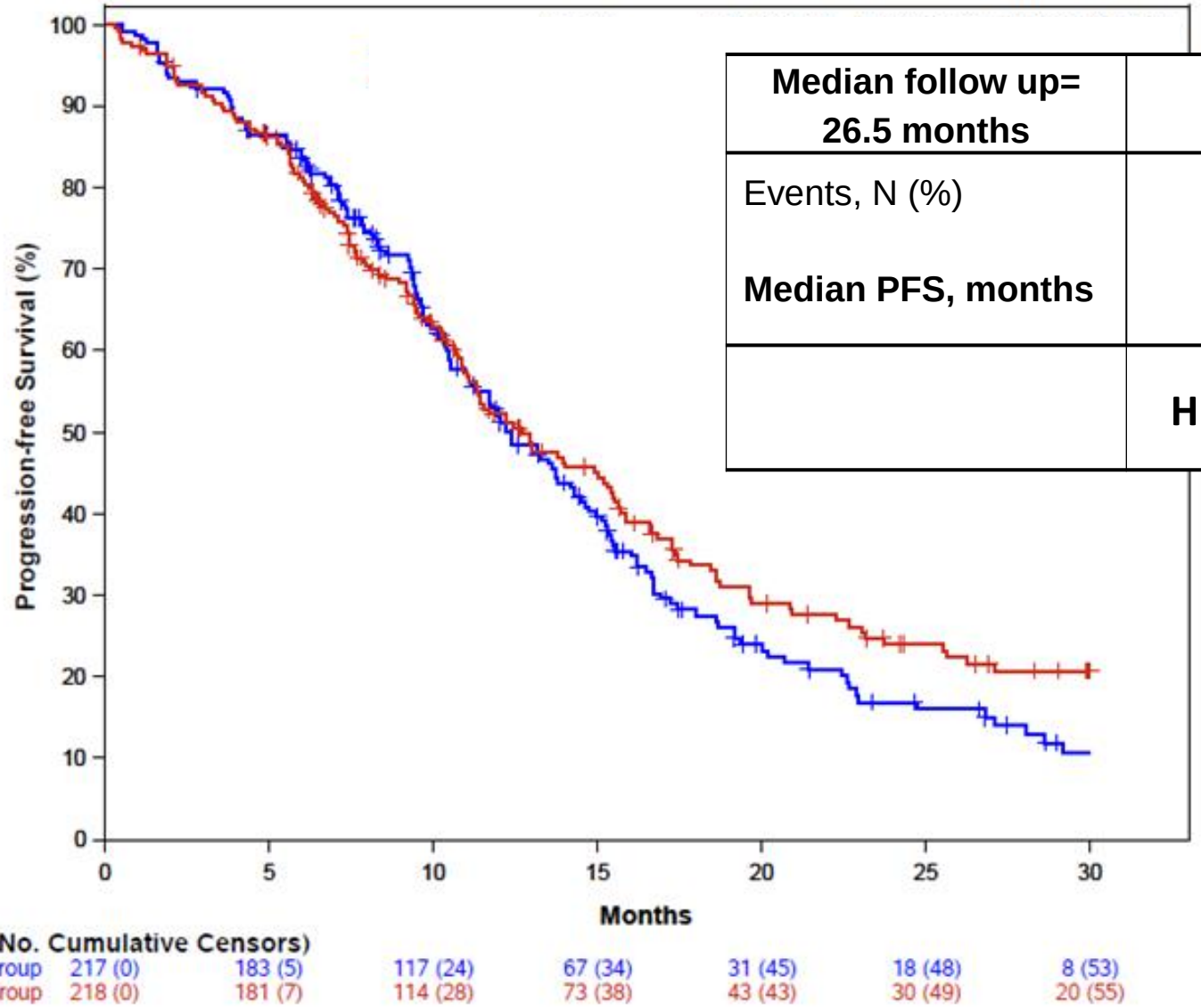
Stratification factors:

- ECOG Performance Status (0-1 vs 2)
- Primary tumor location (right vs left)
- Metastatic spread (liver-only vs not liver-only)

57 participating centers
From September 2017 to September 2021

	FOLFOX/Pan N = 213	mFOLFOXIRI/Pan N = 218	OR [95%CI], p
Response Rate	76%	73%	0.87 [0.56-1.34], p=0.526
R0 Resection Rate	29%	25%	0.81 [0.53-1.23], p=0.317

Progression-free survival



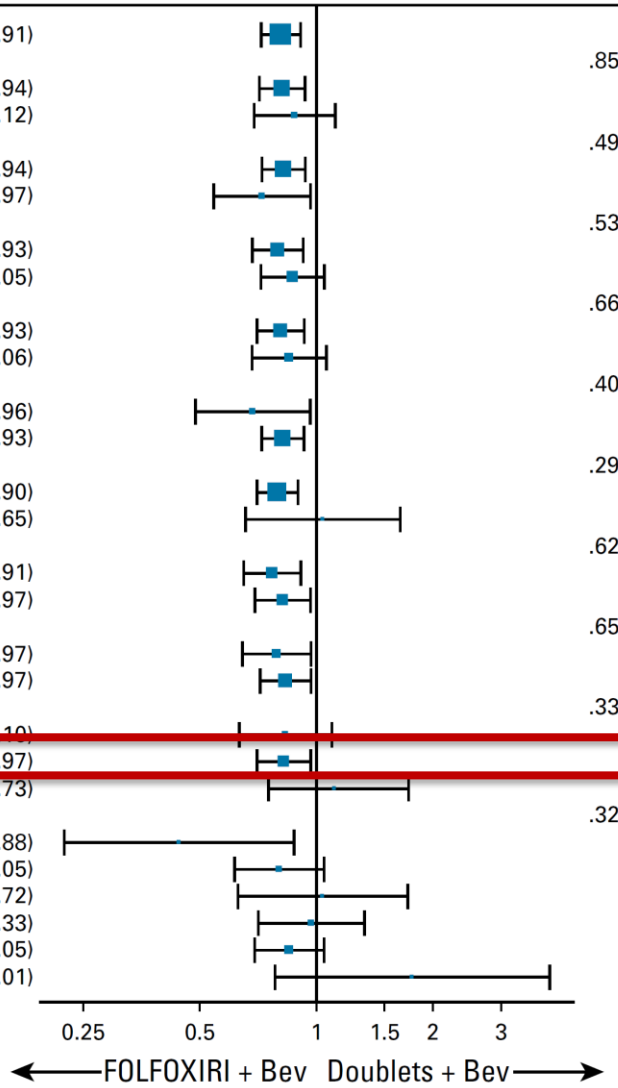
Median follow up= 26.5 months	FOLFOX/Pan N = 217	mFOLFOXIRI/Pan N = 218
Events, N (%)	157 (72%)	148 (68%)
Median PFS, months	**12.3**	**12.7**
	HR = 0.88 [95% CI: 0.70-1.11] p=0.277	

Kein Vorteil mit Chemo-Triplette

Chemo-Dublette vs. -Triplette plus Bevacizumab in RAS MT

1st line

Subgroup	Doublets + Bev No. Events of Total (%)	FOLFOXIRI + Bev No. Events of Total (%)	HR (95% CI)	P
Intention to treat population	591 of 851 (69.4)	527 of 846 (62.3)	0.81 (0.72 to 0.91)	
ECOG PS				.855
0	441 of 656 (67.2)	398 of 667 (59.7)	0.82 (0.71 to 0.94)	
1-2	149 of 192 (77.6)	126 of 175 (72.0)	0.88 (0.69 to 1.12)	
Age, years				.492
< 70	493 of 722 (68.3)	436 of 707 (61.7)	0.82 (0.72 to 0.94)	
> 70	98 of 129 (76.0)	91 of 139 (65.5)	0.72 (0.54 to 0.97)	
Sex				.533
Male	376 of 518 (72.6)	307 of 489 (62.8)	0.80 (0.68 to 0.93)	
Female	215 of 333 (64.6)	220 of 357 (61.6)	0.87 (0.72 to 1.05)	
Liver only				.665
No	441 of 596 (74.0)	358 of 543 (65.9)	0.81 (0.70 to 0.93)	
Yes	150 of 254 (59.1)	168 of 300 (56.0)	0.85 (0.68 to 1.06)	
Time to metastases				.408
Metachronous	83 of 130 (63.8)	57 of 130 (43.8)	0.69 (0.49 to 0.96)	
Synchronous	508 of 720 (70.6)	470 of 716 (65.6)	0.82 (0.72 to 0.93)	
Previous adjuvant				.296
No	552 of 790 (69.9)	492 of 782 (62.9)	0.79 (0.70 to 0.90)	
Yes	39 of 61 (63.9)	35 of 63 (55.6)	1.04 (0.66 to 1.65)	
Primary resection				.623
No	284 of 386 (73.6)	267 of 400 (66.8)	0.77 (0.65 to 0.91)	
Yes	307 of 465 (66.0)	260 of 445 (58.4)	0.82 (0.69 to 0.97)	
Tumor site				.656
Right	185 of 255 (72.5)	193 of 295 (65.4)	0.79 (0.64 to 0.97)	
Left/rectum	367 of 535 (68.6)	317 of 496 (63.9)	0.83 (0.72 to 0.97)	
RAS and *BRAF* status				.337
RAS-*BRAF* wt	107 of 172 (62.2)	99 of 177 (55.9)	0.83 (0.63 to 1.10)	
RAS mut	316 of 430 (73.5)	289 of 422 (68.5)	0.82 (0.70 to 0.97)	
BRAF mut	43 of 54 (79.6)	53 of 61 (86.9)	1.11 (0.75 to 1.73)	
Site-*RAS*/*BRAF*				.320
Right-*RAS*/*BRAF* wt	21 of 31 (67.7)	21 of 44 (47.7)	0.44 (0.22 to 0.88)	
Right-*RAS* mut	110 of 149 (73.8)	113 of 168 (67.3)	0.80 (0.62 to 1.05)	
Right-*BRAF* mut	33 of 40 (82.5)	34 of 39 (87.2)	1.04 (0.63 to 1.72)	
Left-*RAS*/*BRAF* wt	79 of 134 (59.0)	78 of 132 (59.1)	0.97 (0.71 to 1.33)	
Left-*RAS* mut	199 of 273 (72.9)	173 of 250 (69.2)	0.85 (0.69 to 1.05)	
Left-*BRAF* mut	9 of 13 (69.2)	19 of 22 (86.4)	1.77 (0.78 to 4.01)	



FOLFOXIRI besser,
aber erhöhte Toxizität

Cremolini *JCO* Aug 2020.

CAIRO5 - study design

1st line

Initially unresectable CRLM

PANEL EVALUATION: confirm unresectability

Unresectability at baseline: not resectable by surgery-only in one stage

RAS / BRAF^{V600E} mutated *and/or* right-sided primary

FOLFOX/FOLFIRI + bevacizumab

FOLFOXIRI + bevacizumab

FOLFOX or FOLFIRI by patient preference

PANEL EVALUATION every 2 months for resectability assessment

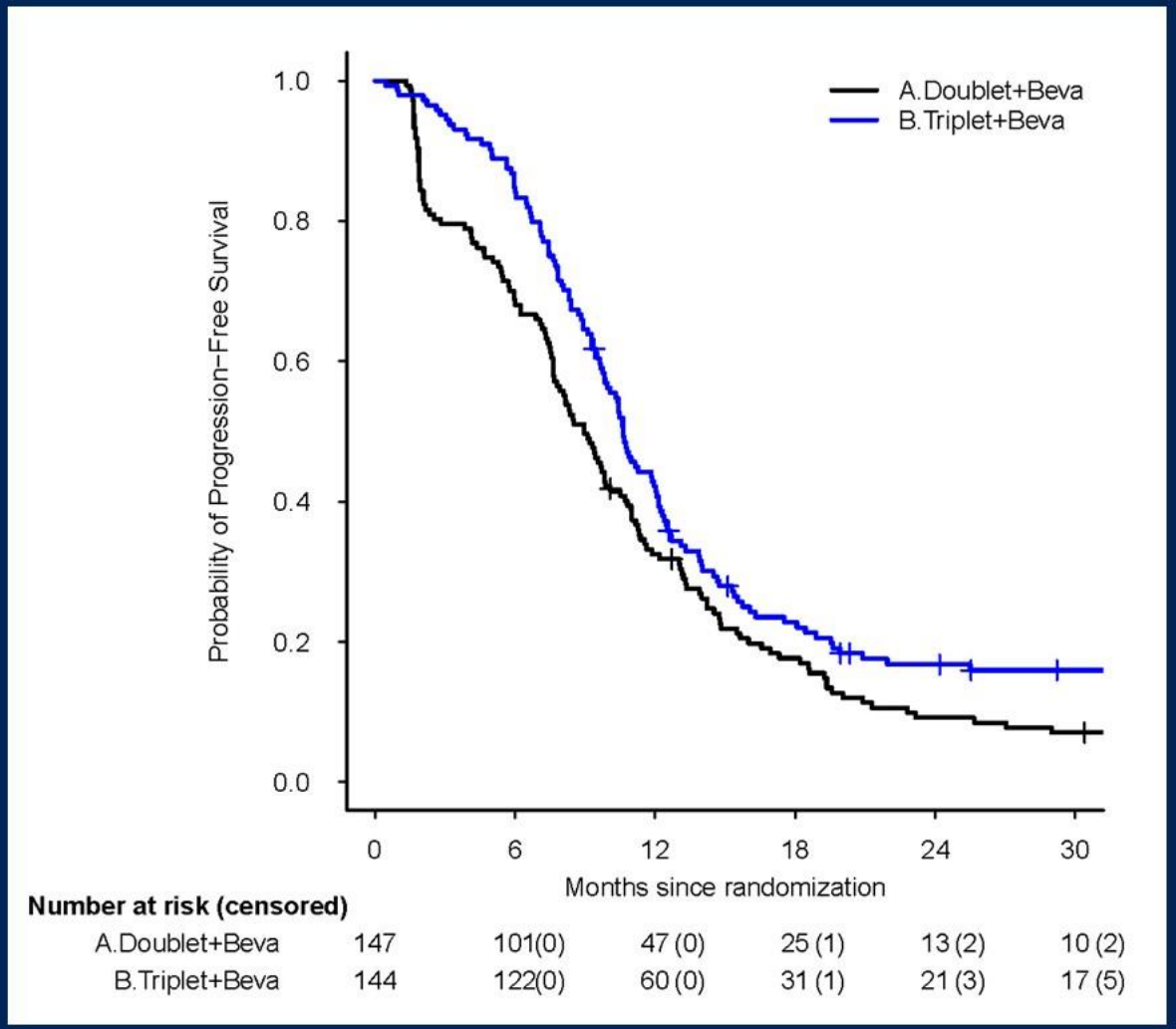
All established local treatments allowed (i.e. ablation, 2-stage surgery, portal vein embolization)

Stratification parameters:
- potentially resectable vs permanently unresectable (panel)
- serum LDH (normal vs abnormal)
- *BRAF*^{V600E} mutation (yes vs no)
- choice oxaliplatin vs irinotecan

Statistics:
257 events, HR 0.70 for PFS
80% power 2-sided log-rank test at 5%, assuming median PFS of 8.7 months for doublet chemo+bevacizumab

PRESENTED BY:
Prof. Cornelis J.A. Punt, MD, PhD

CAIRO5 – progression-free survival

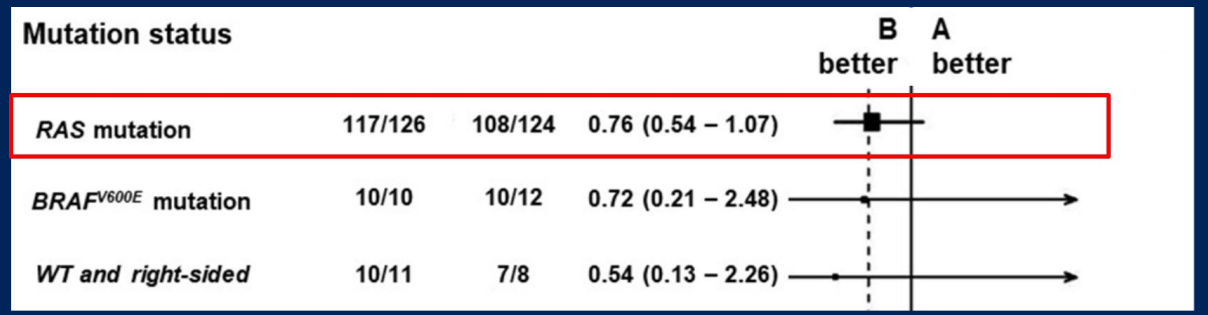


Median follow up 41 months

FOLFOX/FOLFIRI + bevacizumab 9.0 months
FOLFOXIRI + bevacizumab 10.6 months

HR 0.77, 95% CI 0.60-0.99, p=0.038

Data on overall survival not yet mature

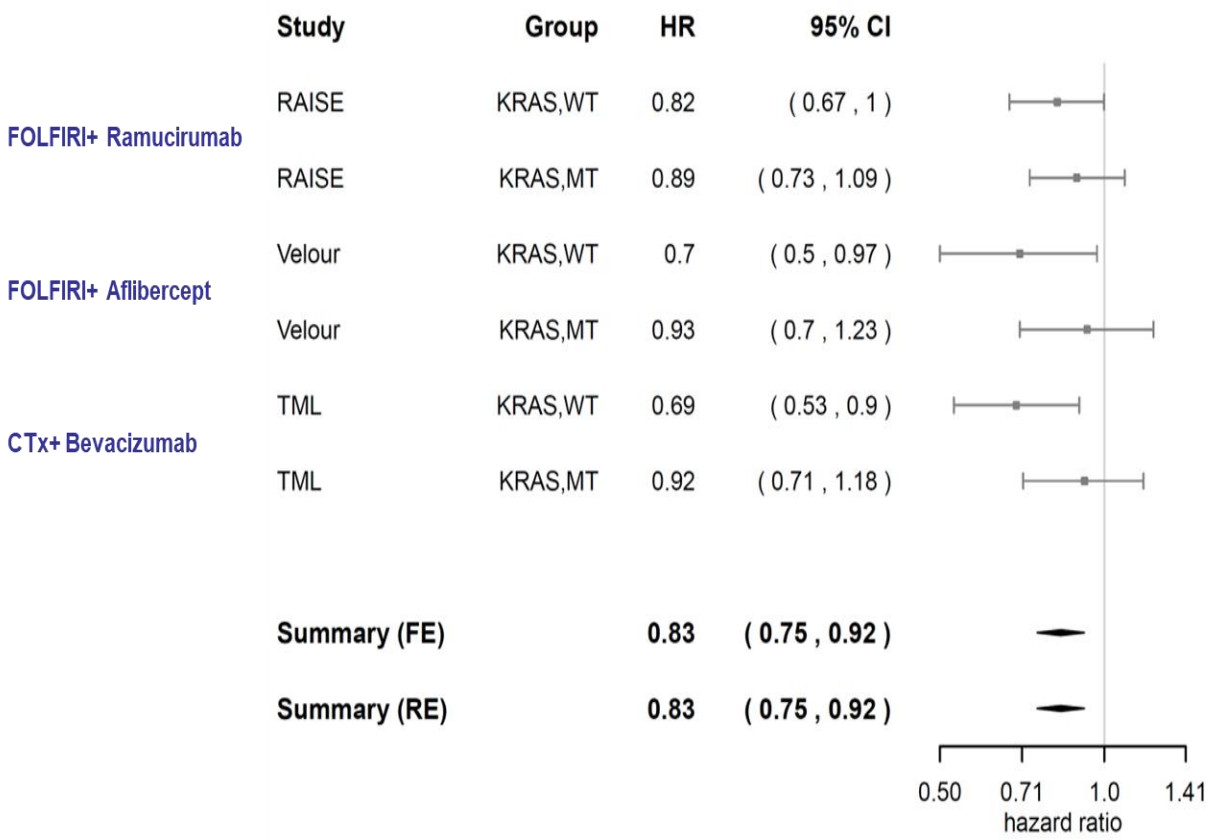


Adapted from:

Prof. Cornelis J.A. Punt, MD, PhD

Anti-VEGF vs. anti-EGFR in der 2nd line

Anti-VEGF in 2nd line entsprechend RAS-Status



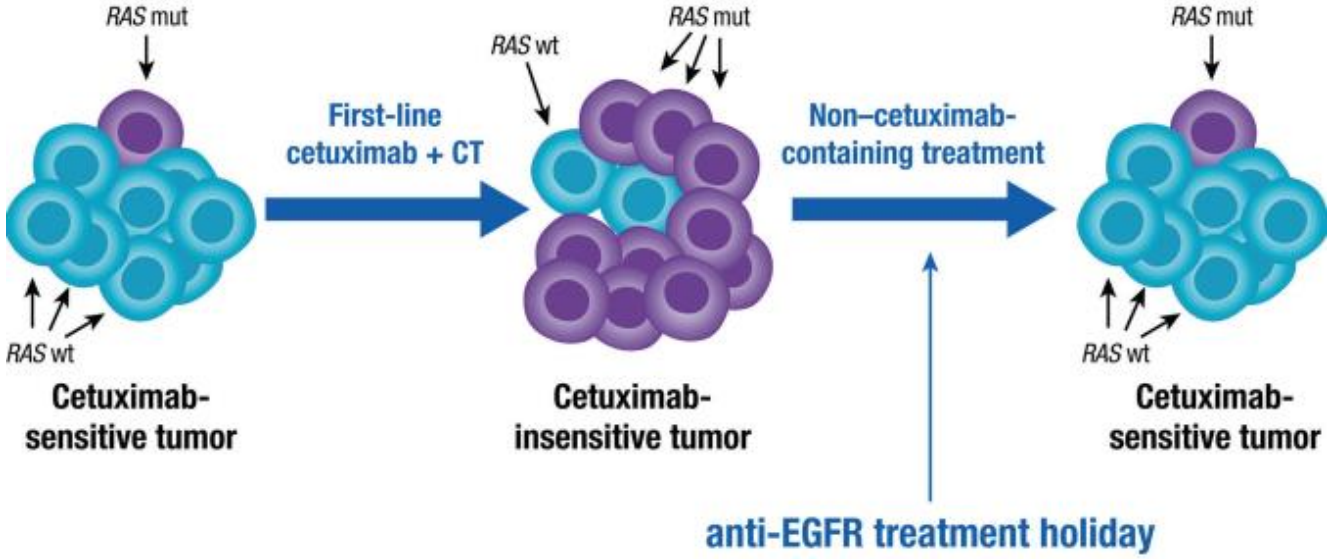
Anti-EGFR in 2nd line bei RAS WT

Studie	Regime	n	PFS (Monate)	p HR	OS (Monate)	p HR
EPIC	Irinotecan	1298	2.6	0.001 ✔	10.0	0.71 ✖
	Irinotecan+ Cetuximab		4.0	0.69	10.7	0.98
20050181	FOLFIRI	597	4.9	0.023 ✔	12.5	0.37 ✖
	FOLFIRI+ Panitumumab		6.7	0.82	14.5	0.92
PiCCOLO	FOLFIRI	460	3.9	0.009 ✔	12.5	0.12 ✖
	FOLFIRI+ Panitumumab		5.9	0.73	14.5	0.85

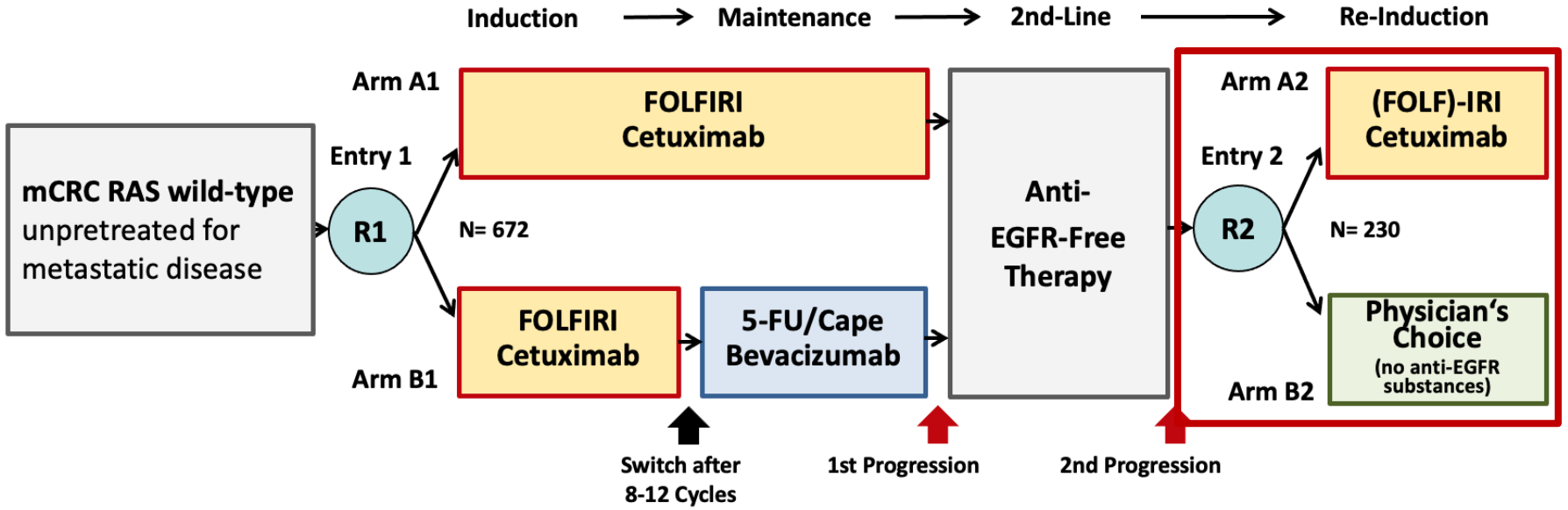
Kubicka *Ann Oncol* 2014; Tabernero *Lancet Oncol* 2015; van Cutsem *JCO* 2014, Wirapati *ASCO* 2017, Stahler *J Cancer Res Clin Oncol* 2020. Sobrero et al. *JCO* 2008; Peeters M et al. *Ann Oncol* 2014; Seymour MT et al. *Lancet Oncol* 2013.

EGFR-rechallenge

last line



FIRE-4: Studiendesign



Primärer Endpunkt:
OS nach Randomisation 2

Sekundäre Endpunkte:
PFS der 1st line Therapie, ORR, Toxizität

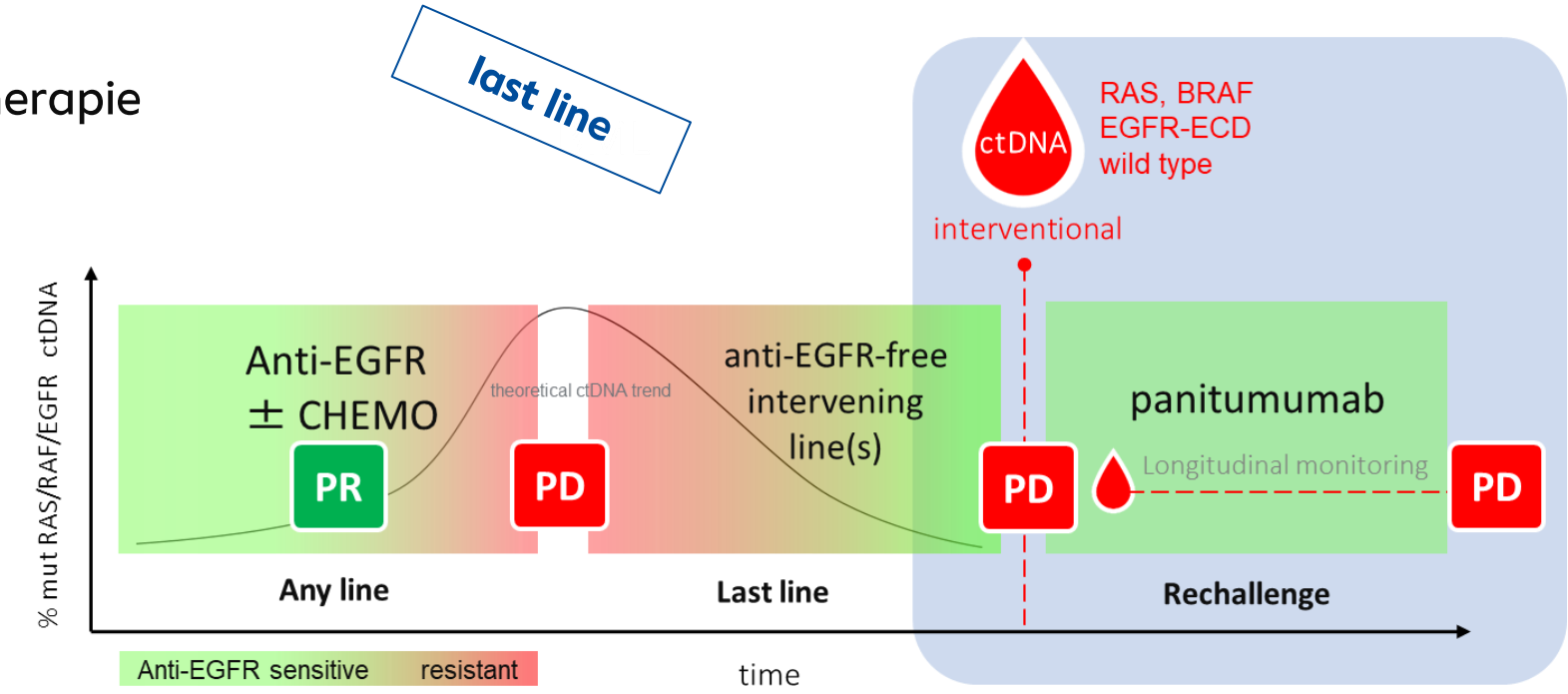
Goldberg et al. *ESMO open* 2018.

CHRONOS: EGFR-rechallenge ctDNA-gestützt

- RAS/BRAF WT mKRK
- CR oder PR unter initialer anti-EGFR Therapie
- PD unter anti-EGFR-freier Vortherapie

Best Response RECIST 1.1 by centralized revision	N	%
Responses (PR+CR)	**8**	**30**
Partial Response	8*	30
Stable Disease ≥4 months	9	33
Stable Disease <4 months	2	7
Control of disease (PR+SD ≥ 4 months)	**17**	**63**
Progressive Disease	8	30
Total	27	100

* Two PR were unconfirmed

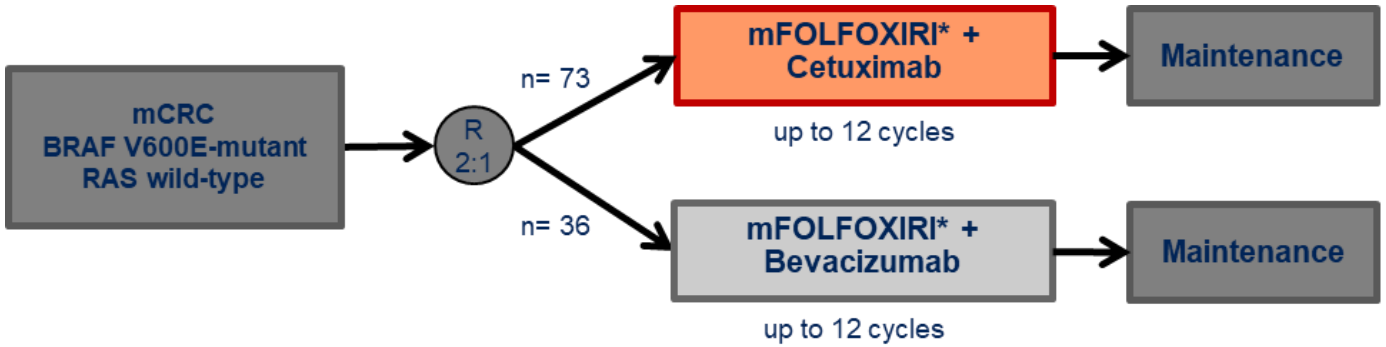


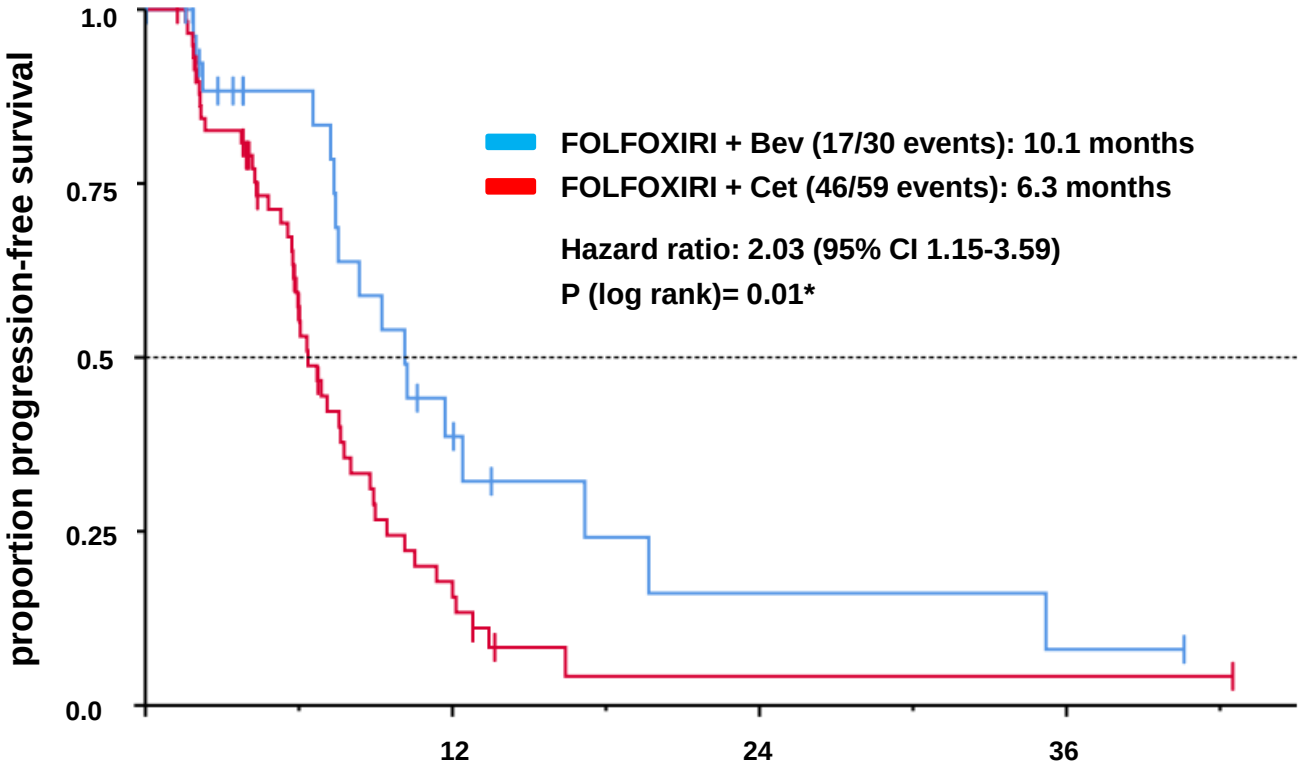
Sartore-Bianchi et al. *Nat Med.* 2022.

Molekular gesteuerte Standardtherapien

BRAF V600E MT und MSS

FIRE-4.5: anti-EGFR vs. anti-VEGF in BRAF MT mKRK





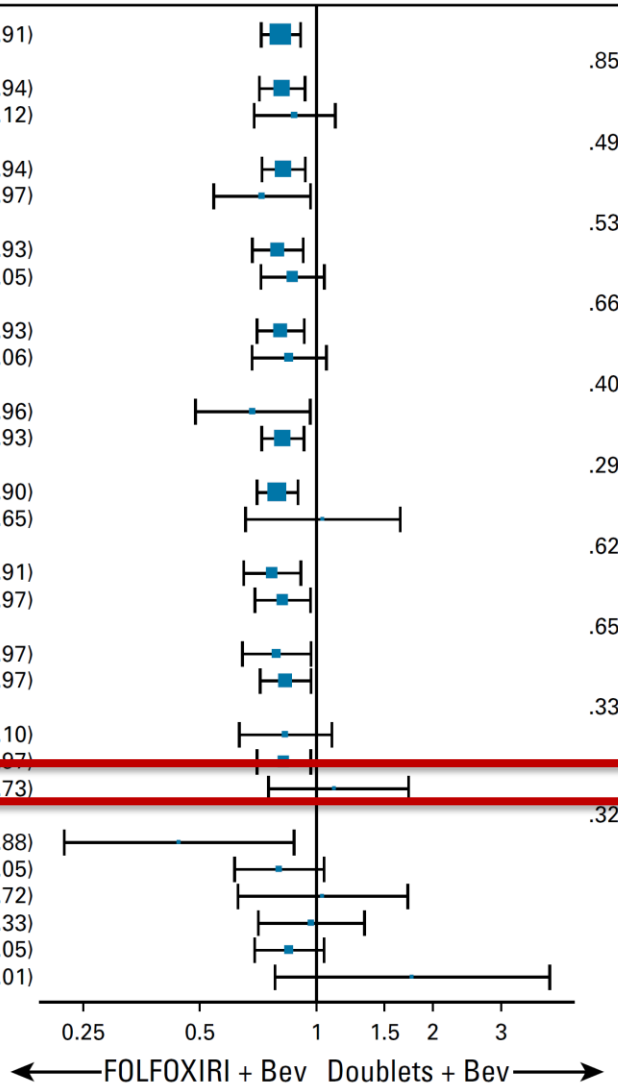
RECIST, % (n)	FOLFOXIRI Cetuximab (n=59)	FOLFOXIRI Bevacizumab (n=30)
Complete Response	3.4% (2)	6.7% (2)
Partial Response	45.8% (27)	53.3% (16)
Stable Disease	32.2% (19)	30.0% (9)
Progressive Disease	18.6% (11)	10.0% (3)
Objective Response	**49.2% (29)**	**60.0% (18)**
	p= 0.33	
	OR= 1.55 (80%CI: 0.87-2.78)	
Disease Control Rate	81.4% (48)	90.0% (27)
	p=0.29	
	OR = 2.06 (95% CI: 0.53-8.04)	

Modifiziert nach ASCO 2021.

Chemo-Dublette vs. -Triplette plus Bevacizumab in BRAF MT

1st line

Subgroup	Doublets + Bev No. Events of Total (%)	FOLFOXIRI + Bev No. Events of Total (%)	HR (95% CI)	P
Intention to treat population	591 of 851 (69.4)	527 of 846 (62.3)	0.81 (0.72 to 0.91)	
ECOG PS				.855
0	441 of 656 (67.2)	398 of 667 (59.7)	0.82 (0.71 to 0.94)	
1-2	149 of 192 (77.6)	126 of 175 (72.0)	0.88 (0.69 to 1.12)	
Age, years				.492
< 70	493 of 722 (68.3)	436 of 707 (61.7)	0.82 (0.72 to 0.94)	
> 70	98 of 129 (76.0)	91 of 139 (65.5)	0.72 (0.54 to 0.97)	
Sex				.533
Male	376 of 518 (72.6)	307 of 489 (62.8)	0.80 (0.68 to 0.93)	
Female	215 of 333 (64.6)	220 of 357 (61.6)	0.87 (0.72 to 1.05)	
Liver only				.665
No	441 of 596 (74.0)	358 of 543 (65.9)	0.81 (0.70 to 0.93)	
Yes	150 of 254 (59.1)	168 of 300 (56.0)	0.85 (0.68 to 1.06)	
Time to metastases				.408
Metachronous	83 of 130 (63.8)	57 of 130 (43.8)	0.69 (0.49 to 0.96)	
Synchronous	508 of 720 (70.6)	470 of 716 (65.6)	0.82 (0.72 to 0.93)	
Previous adjuvant				.296
No	552 of 790 (69.9)	492 of 782 (62.9)	0.79 (0.70 to 0.90)	
Yes	39 of 61 (63.9)	35 of 63 (55.6)	1.04 (0.66 to 1.65)	
Primary resection				.623
No	284 of 386 (73.6)	267 of 400 (66.8)	0.77 (0.65 to 0.91)	
Yes	307 of 465 (66.0)	260 of 445 (58.4)	0.82 (0.69 to 0.97)	
Tumor site				.656
Right	185 of 255 (72.5)	193 of 295 (65.4)	0.79 (0.64 to 0.97)	
Left/rectum	367 of 535 (68.6)	317 of 496 (63.9)	0.83 (0.72 to 0.97)	
RAS and *BRAF* status				.337
RAS-BRAF wt	107 of 172 (62.2)	99 of 177 (55.9)	0.83 (0.63 to 1.10)	
RAS mut	316 of 430 (73.5)	289 of 423 (68.5)	0.83 (0.70 to 0.97)	
BRAF mut	43 of 54 (79.6)	53 of 61 (86.9)	1.11 (0.75 to 1.73)	
Site-*RAS*/*BRAF*				.320
Right-*RAS*/*BRAF* wt	21 of 31 (67.7)	21 of 44 (47.7)	0.44 (0.22 to 0.88)	
Right-*RAS* mut	110 of 149 (73.8)	113 of 168 (67.3)	0.80 (0.62 to 1.05)	
Right-*BRAF* mut	33 of 40 (82.5)	34 of 39 (87.2)	1.04 (0.63 to 1.72)	
Left-*RAS*/*BRAF* wt	79 of 134 (59.0)	78 of 132 (59.1)	0.97 (0.71 to 1.33)	
Left-*RAS* mut	199 of 273 (72.9)	173 of 250 (69.2)	0.85 (0.69 to 1.05)	
Left-*BRAF* mut	9 of 13 (69.2)	19 of 22 (86.4)	1.77 (0.78 to 4.01)	

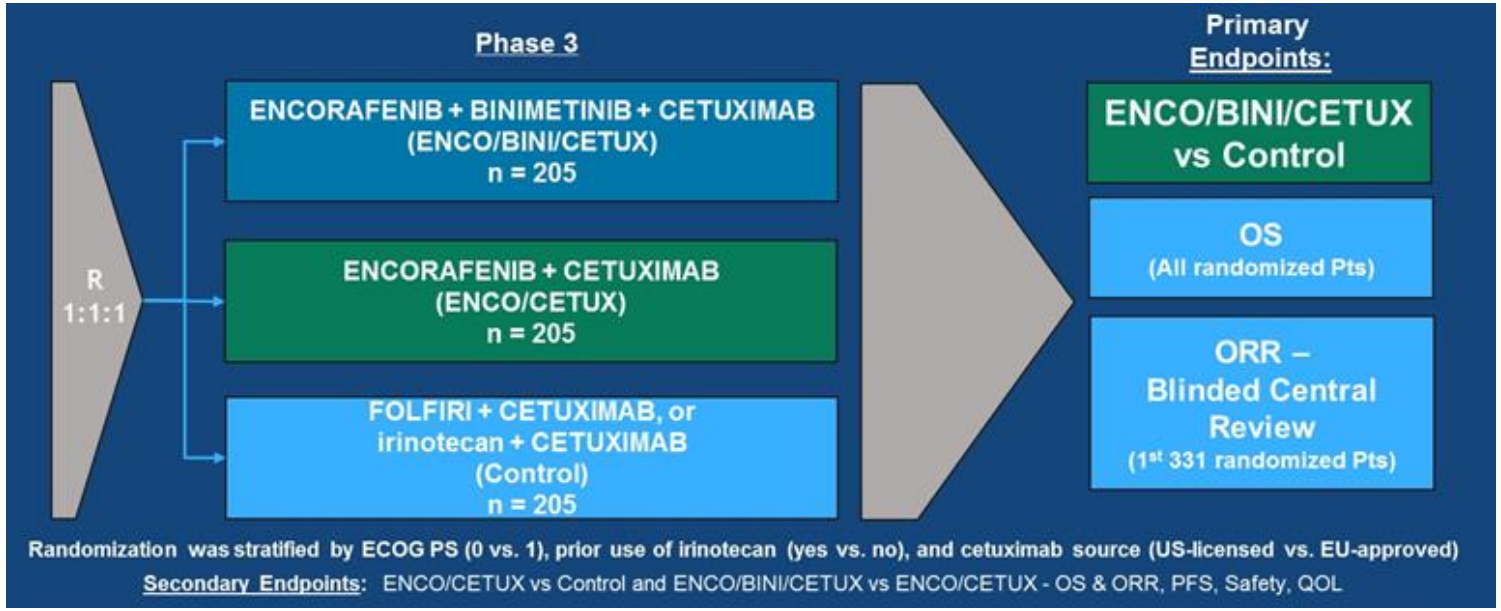


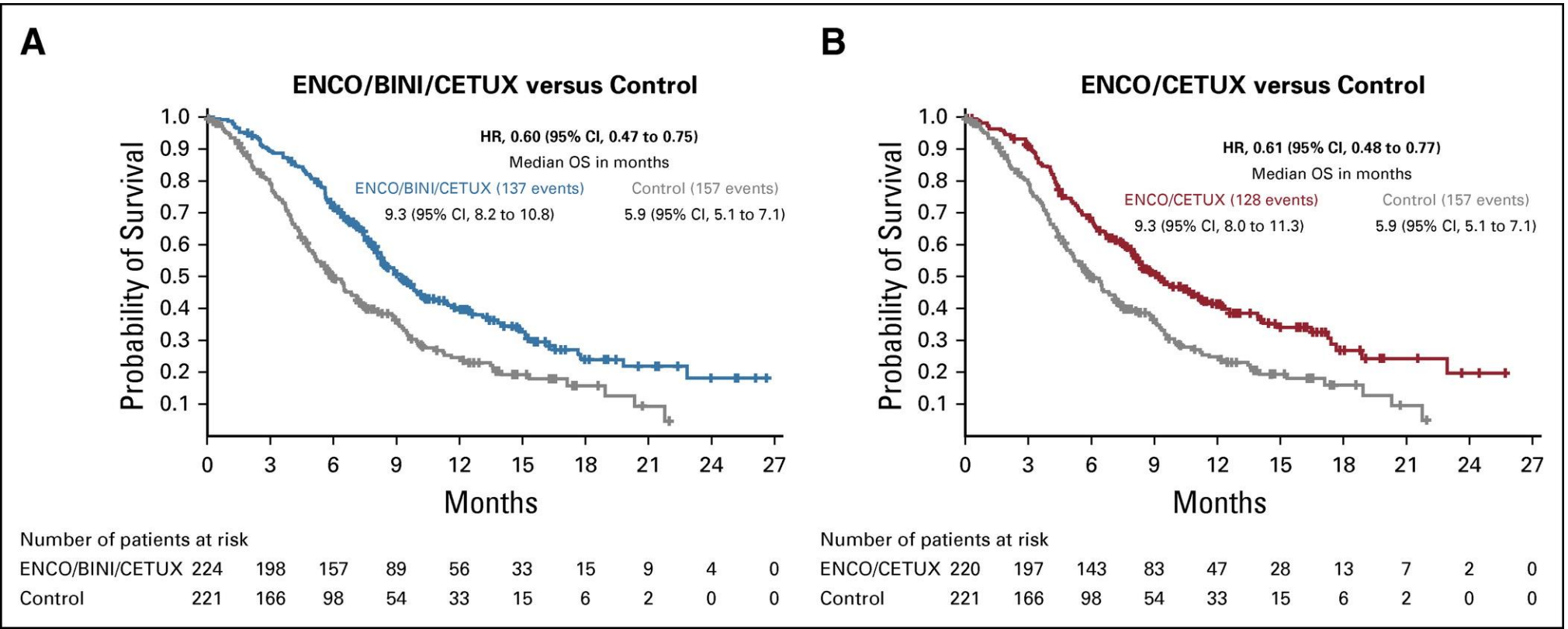
Vergleichbare Wirksamkeit
bei deutlich erhöhter Toxizität
mit FOLFOXIRI

Cremolini *JCO* Aug 2020.

BEACON trial

BRAF MT mKRK



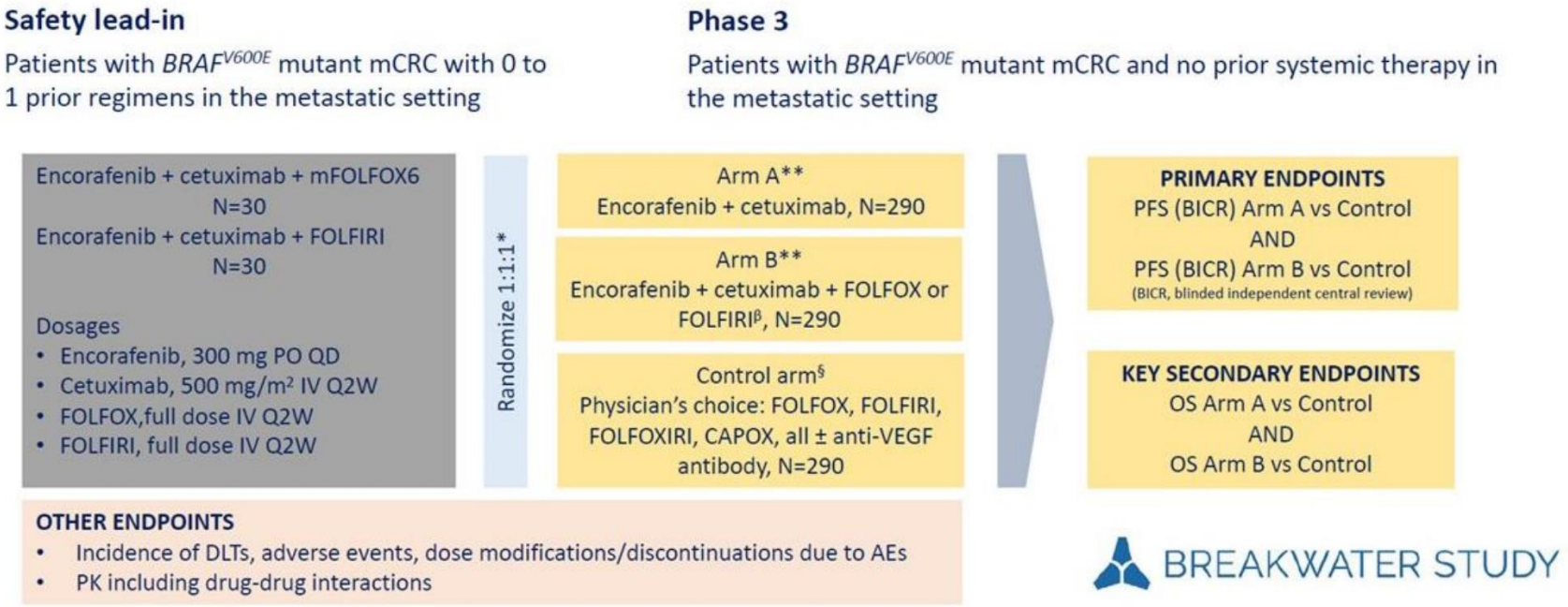


2nd line

Kopetz et al., *ASCO* 2020.

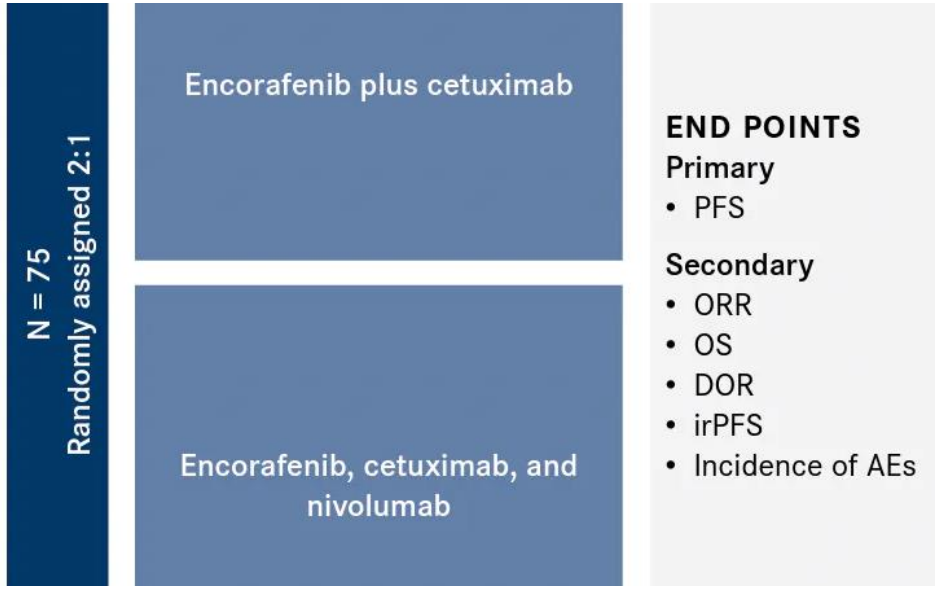
1st line: Kombination mit Chemotherapie

Kopetz et al., *ASCO* 2021.



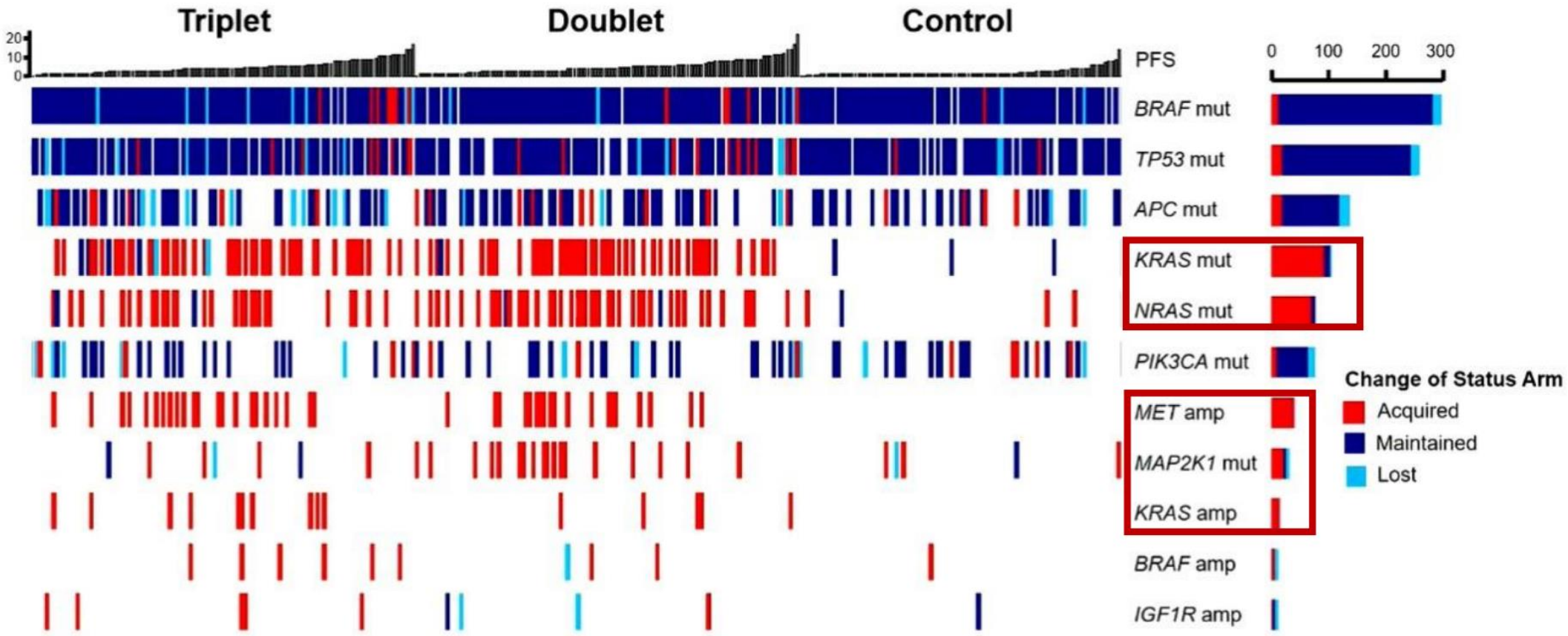
Last line: Kombination mit Immuncheckpointinhibition

Morris et al., *ASCO Gastrointestinal Cancers Symposium* 2022.



SWOG 2107 study

Sekundäre Resistenzentwicklung



Kopetz et al., *ESMO* 2022.

Zusammenfassung: Molekular gesteuerte Standardtherapien

- **Molekulare Testung** zum Zeitpunkt der Erstdiagnose des mKRK (MMR/MSI, KRAS/NRAS, BRAF)

1st line

- **RAS/ BRAF WT**

  linksseitiger Primarius: Vorteil für EGFR-basierte Therapie, Kombination mit Chemo-Dublette

  rechtsseitiger Primarius: kein Vorteil für EGFR-basierte Therapie, Chemo-Dublette+ Bevacizumab

- **RAS MT**: Chemo-Triplette+ Bevacizumab (wenn tolerabel)
- **BRAF MT**: Chemo-Dublette+ Bevacizumab

2nd line

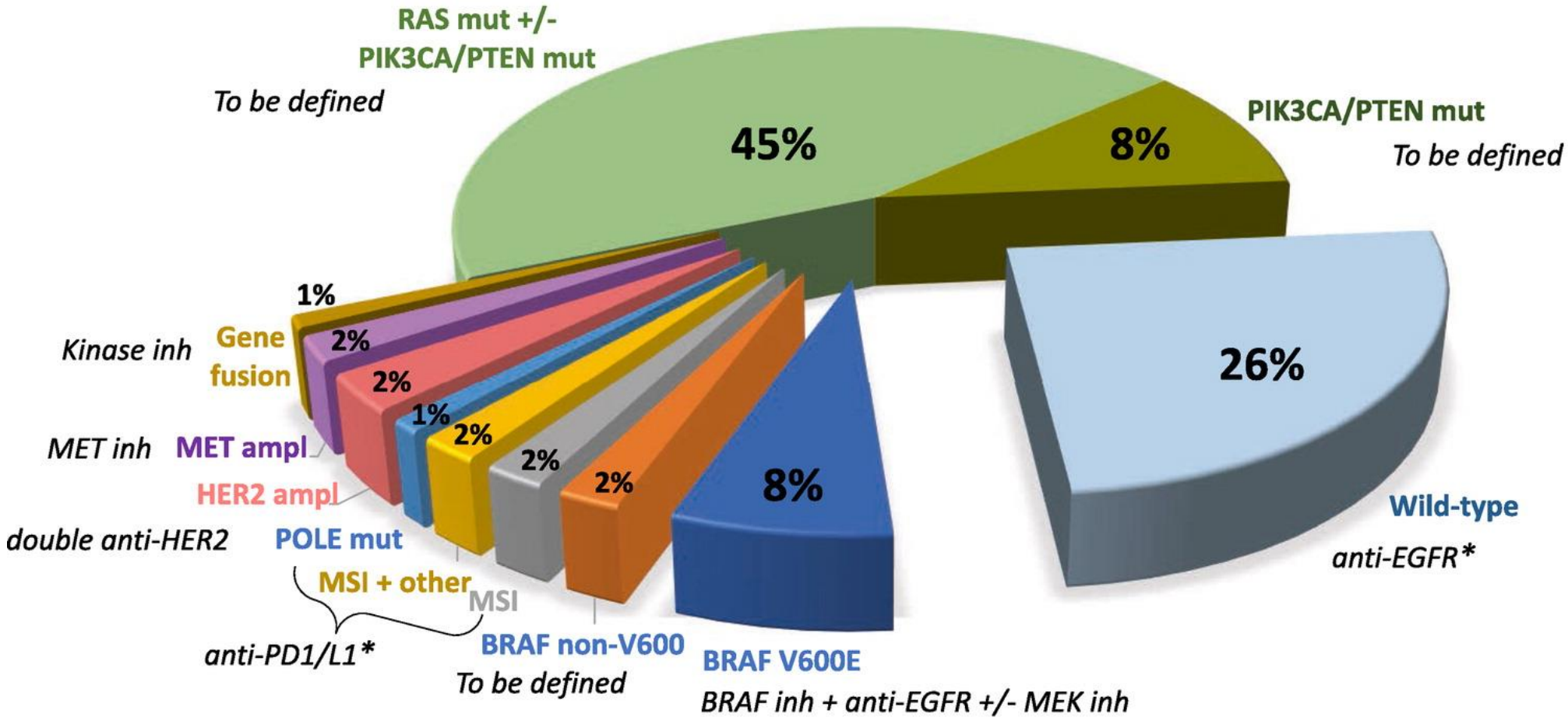
- **RAS/ BRAF WT und RAS MT**: FOLFOX ↔ FOLFIRI, Kombination mit VEGF-Antikörper
- **BRAF MT**: Encorafenib+ Cetuximab ist Standard → 1st line Kombination mit Chemotherapie erwartbar

last line

- **RAS/ BRAF WT:** EGFR-Rechallenge häufig praktiziert, liquid biopsies zukünftig hilfreich

Neue molekular zielgerichtete Therapien

Therapeutisch (potenziell) relevante targets im mKRK

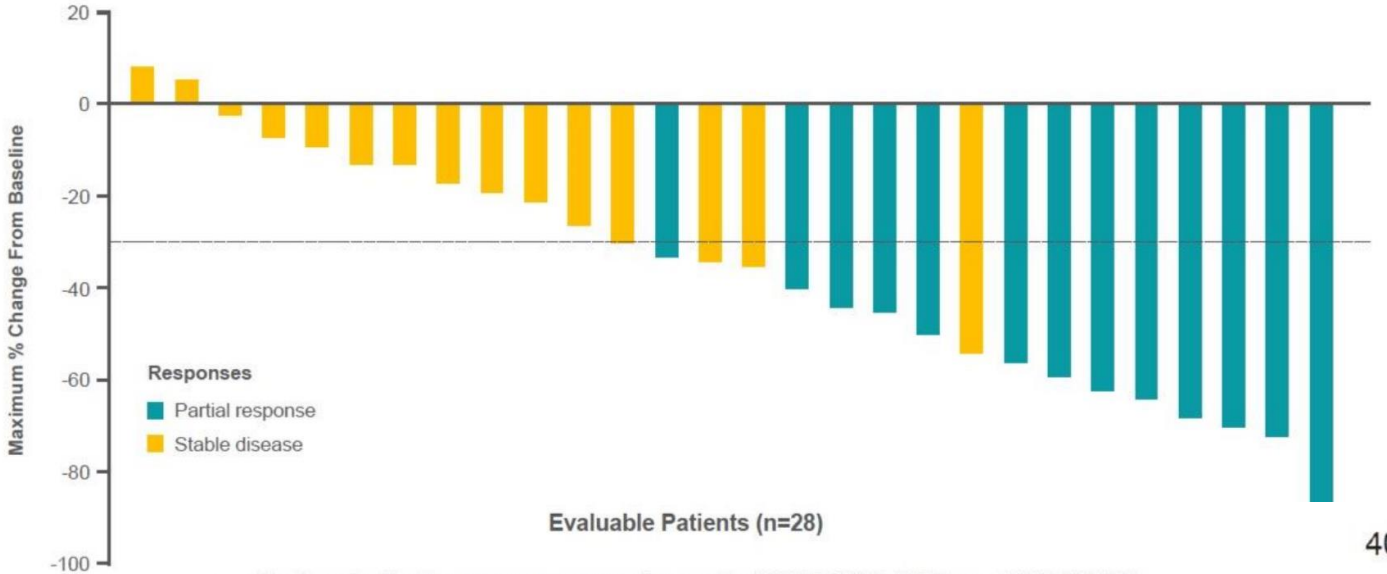


Dienstmann, Salazar, Tabernero, *ASCO* 2018.

Neue molekular zielgerichtete Therapien

KRAS G12C MT

KRAS G12C Inhibition plus anti-EGFR Antikörper



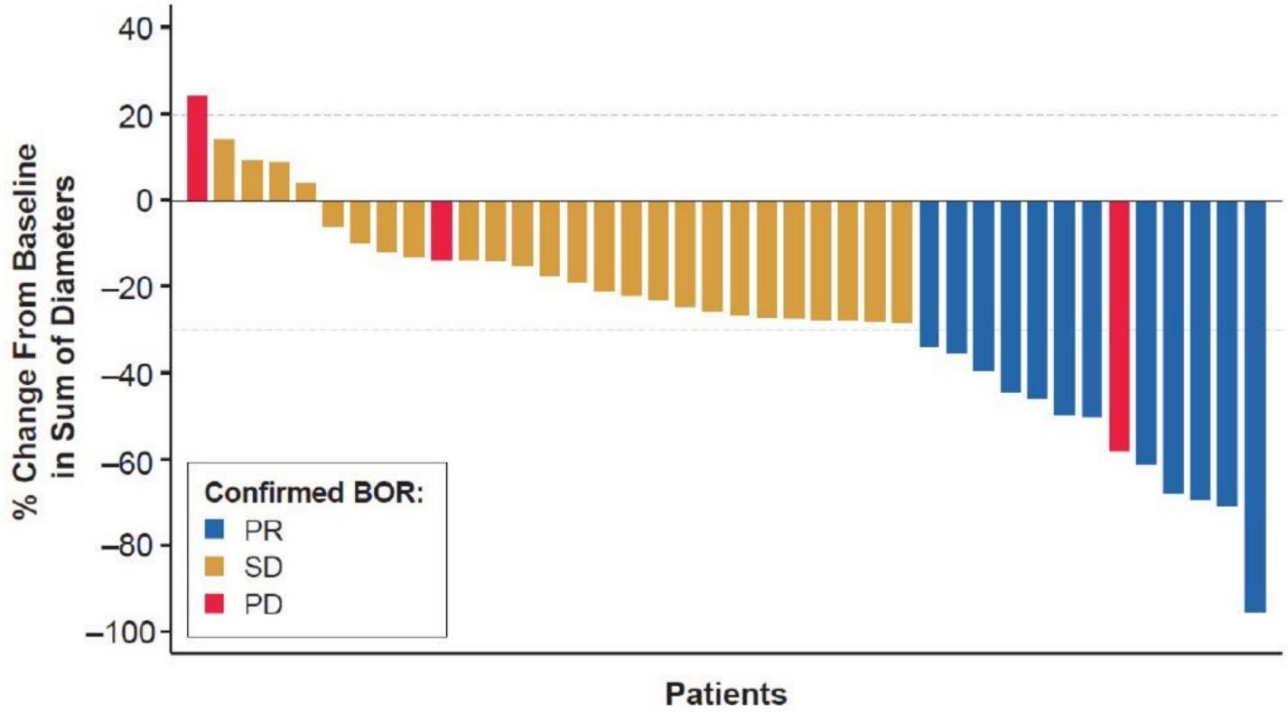
- Confirmed objective responses were observed in 46% (13/28[a]); DCR was 100% (28/28)
- Tumor shrinkage of any magnitude occurred in 93% of patients

Adagrasib+ Cetuximab

- ORR 46%
- DCR 100%

Sotorasib+ Panitumumab

- ORR 30%
- DCR 93%



ESMO 2022.

KRAS G12C Inhibition: aktuelle Entwicklungen

Target	Drug	Clinical Trial	Phase	Description (regarding mCRC)	NCT
KRAS G12C	Sotorasib (AMG510)	CodeBreak 101	1b	Masterprotocol sotorasib monotherapy /combination with anti-PD1. MEKi, SHP2i, pan-ErbBin, antiPDL1, antiEGFR, Cht, mTORi, or CDK4/6i	4185883
		CodeBreak 100	1-2	Sotorasib in monotherapy in pre-treated mCRC	3600883
		CodeBreak 300	3	Sotorasib+panitumumab vs investigator choice pre-treated mCRC	5198934
	Adagrasib (MRTX849)	KRYSTAL-1	1-2	Adabrasib in monotherapy or combination with cetuximab in pre-treated mCRC	3785249
		KRYSTAL-10	3	Adagrasib in combination with Cetuximab vs Chemotherapy in 2°L mCRC	4793958
		KRYSTAL-2	1-2	Adabrasib in combination with TNO155 (SHP2 inh)	4330664
		KYSTAL-14	1	BI 1701963 (SOS1 inh) alone and in combination with MRTX849	4975256
	JDQ443	KontRASt-01	1b-2	JDQ443 single agent and JDQ443 in combination with TNO155 and tislelizumab	4699188
	GDC-6036	4449874	1	GDC-6036 in Patients With Advanced or Metastatic Solid Tumors With a KRAS G12C Mutation	4449874
	LY3537982	4956640	1-2	LY3537982 in monotherapy or in combination with other drugs (erlotinib, abemaciclib, TN0155, and other)	4956640
	BI1823911	4973163	1	BI 1823911 alone/combination with BI 1701963 (SOS1 inh)	4973163
	JAB21822	5002270	1-2	JAB-21822 monotherapy and combination with cetuximab	5002270

- **Einsatz in früheren Therapielinien**
- **Neue KRAS G12C Inhibitoren**
- **Inhibitoren für KRAS G12D, G12V und G12R**
- **Pan-KRAS Inhibitoren**
- **Innovative Therapiekombinationen**

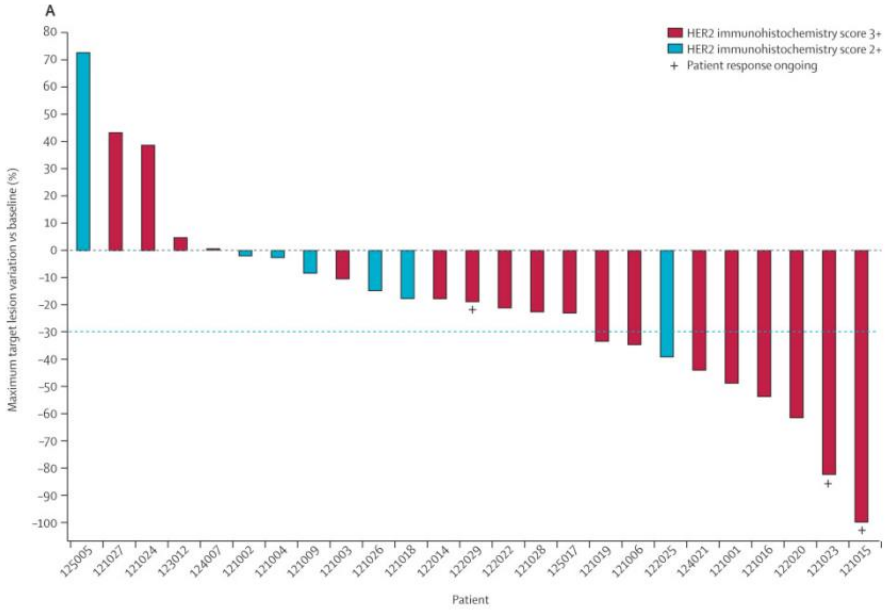
E Elez, *ESMO* 2022.

Neue molekular zielgerichtete Therapien

HER2 Expression/ Amplifikation

Chemotherapie-freie last-line beim HER2+ mKRK

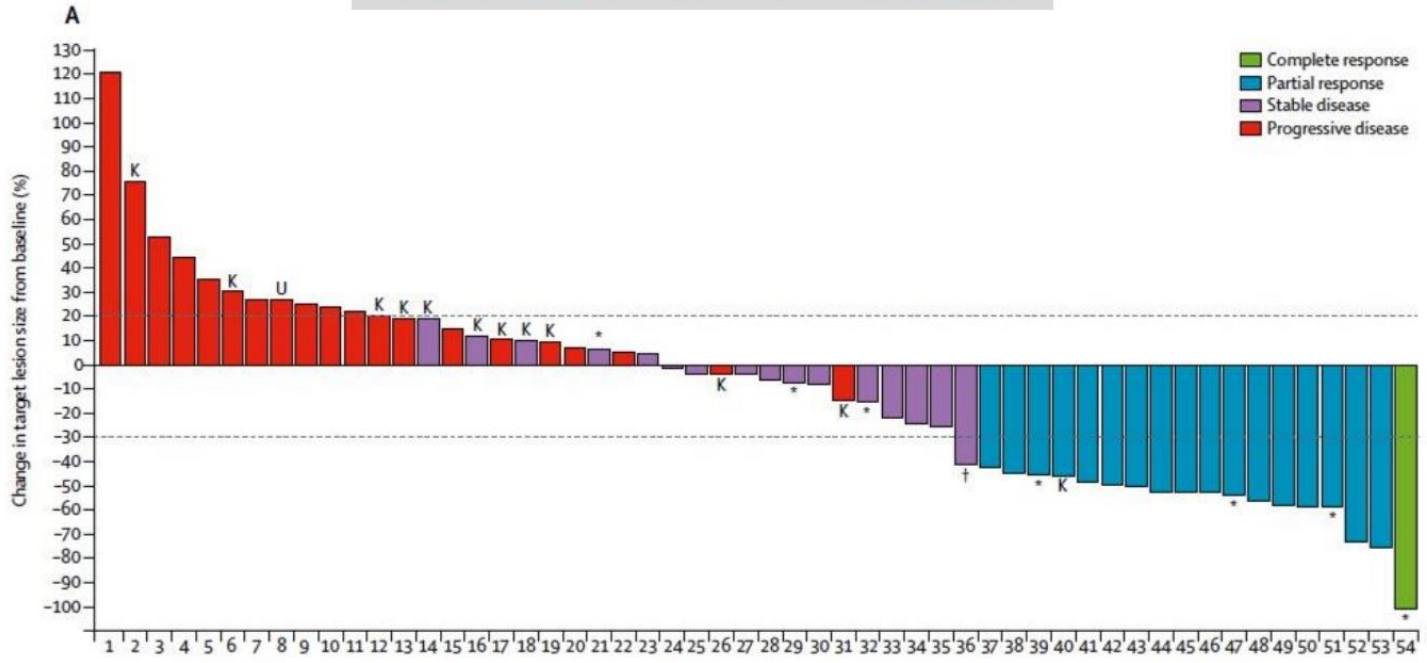
HERACLES
Trastuzumab plus lapatinib



Lancet Oncology 2016 , 17: 738–746

ORR 30%

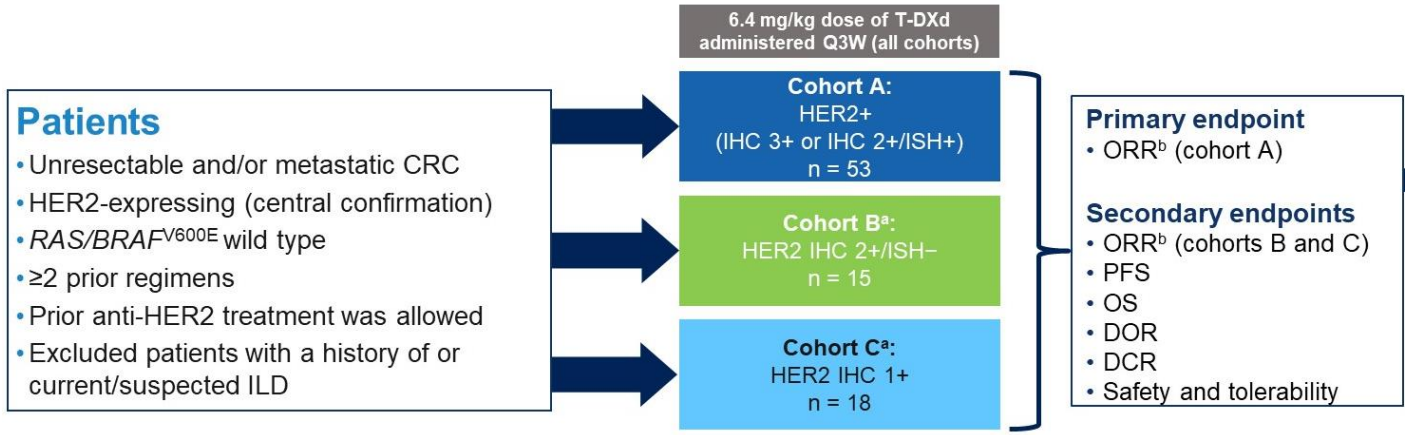
MyPathway
Trastuzumab plus pertuzumab

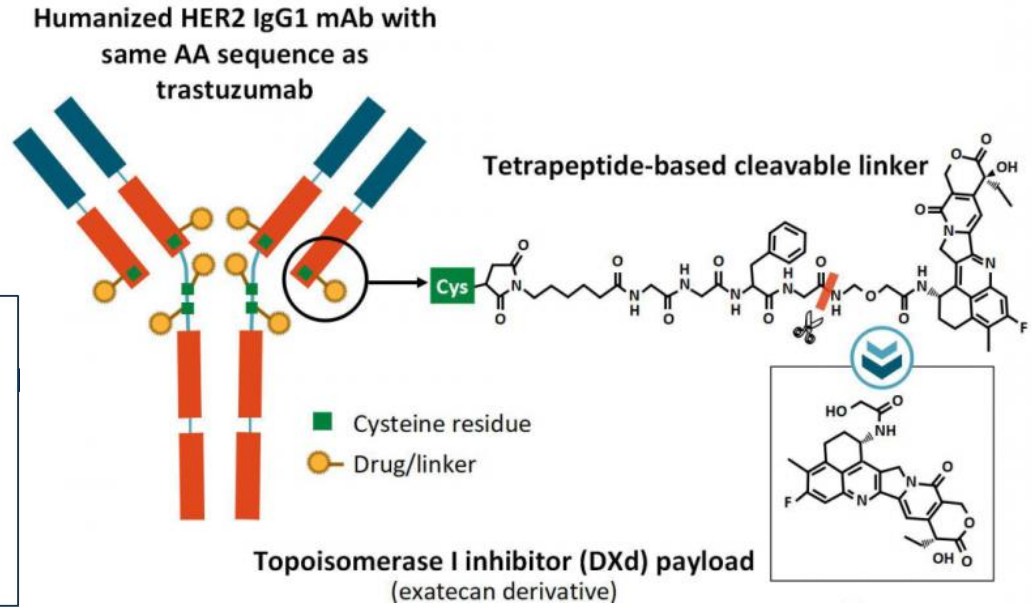


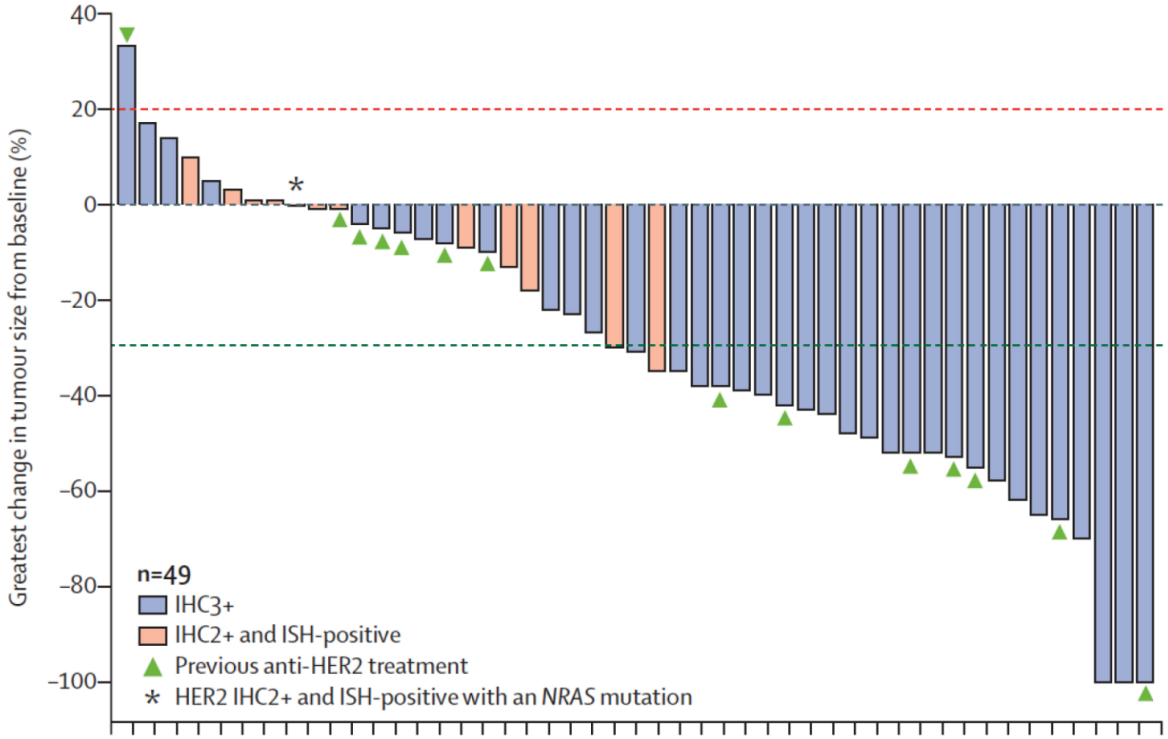
Lancet Oncol 2019; 20: 518–30

ORR 40%
KRAS-WT

DESTINY-CRC01







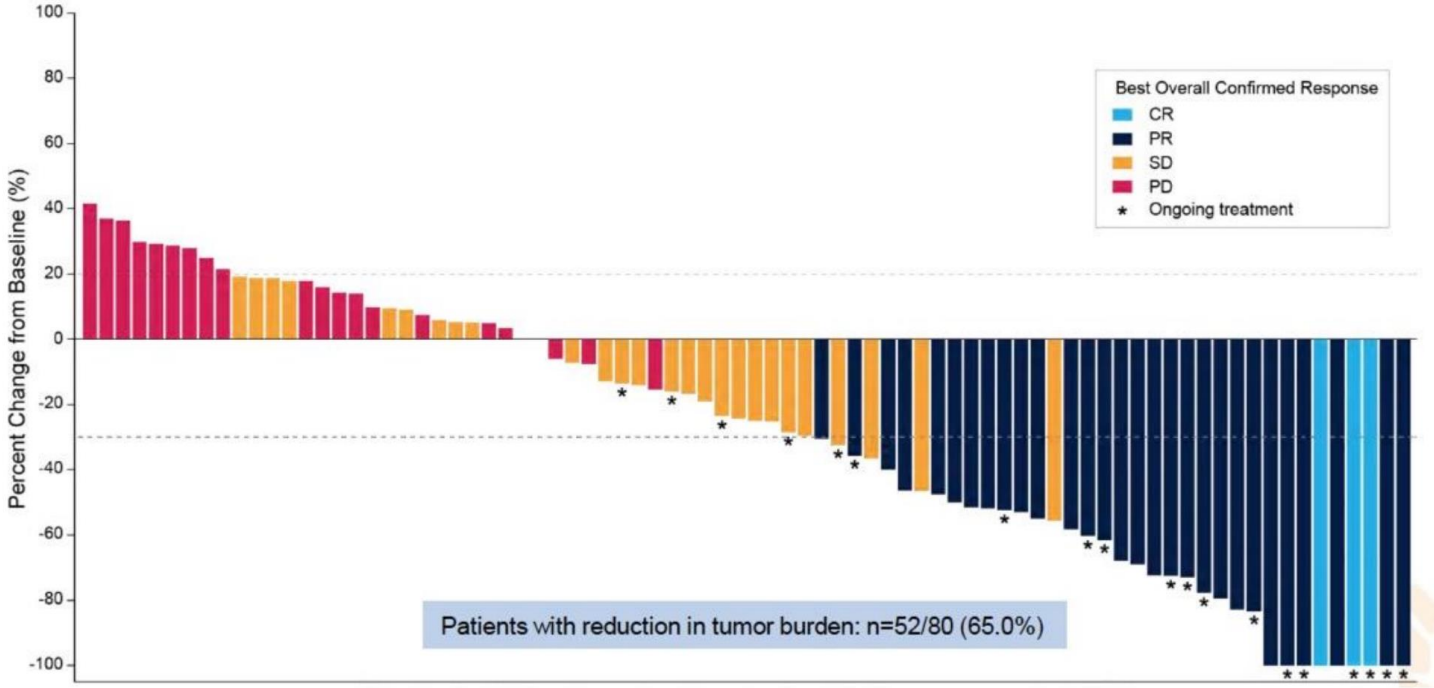
	HER2+ Cohort A (N = 53)
Confirmed ORR by ICR	**45.3% (n = 24)** (95% CI, 31.6%-59.6%)
CR	1.9% (n = 1)
PR	43.4% (n = 23)
SD	37.7% (n = 20)
PD	9.4% (n = 5)
Not evaluable	7.5% (n = 4)[a]
Disease control rate	83.0% (95% CI, 70.2%-91.9%)
Duration of response, median	Not reached (95% CI, 4.2 months-NE)

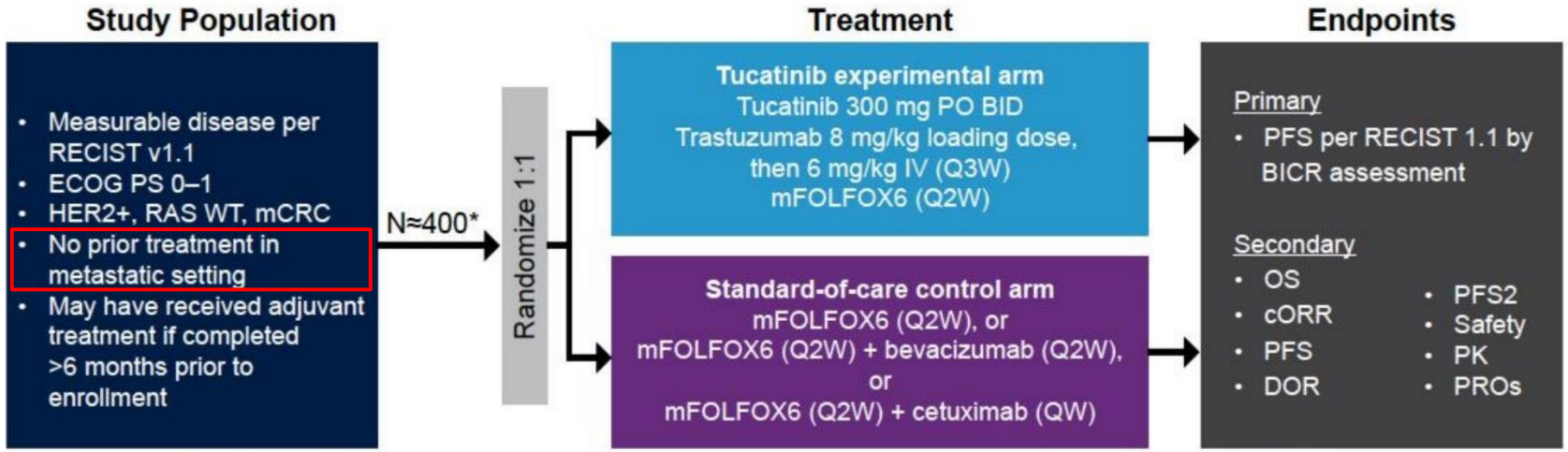
Siena et al., *Lancet Oncol.* 2021.

Trastuzumab und Tucatinib plus Chemotherapie

MOUNTAINEER

- Vorbehandelte mKRK
- HER2 amplifiziert/ überexprimiert
- ORR 38,1%
- DCR 71,4%
- Mediane DOR 12,4 Monate





MOUNTAINEER-03

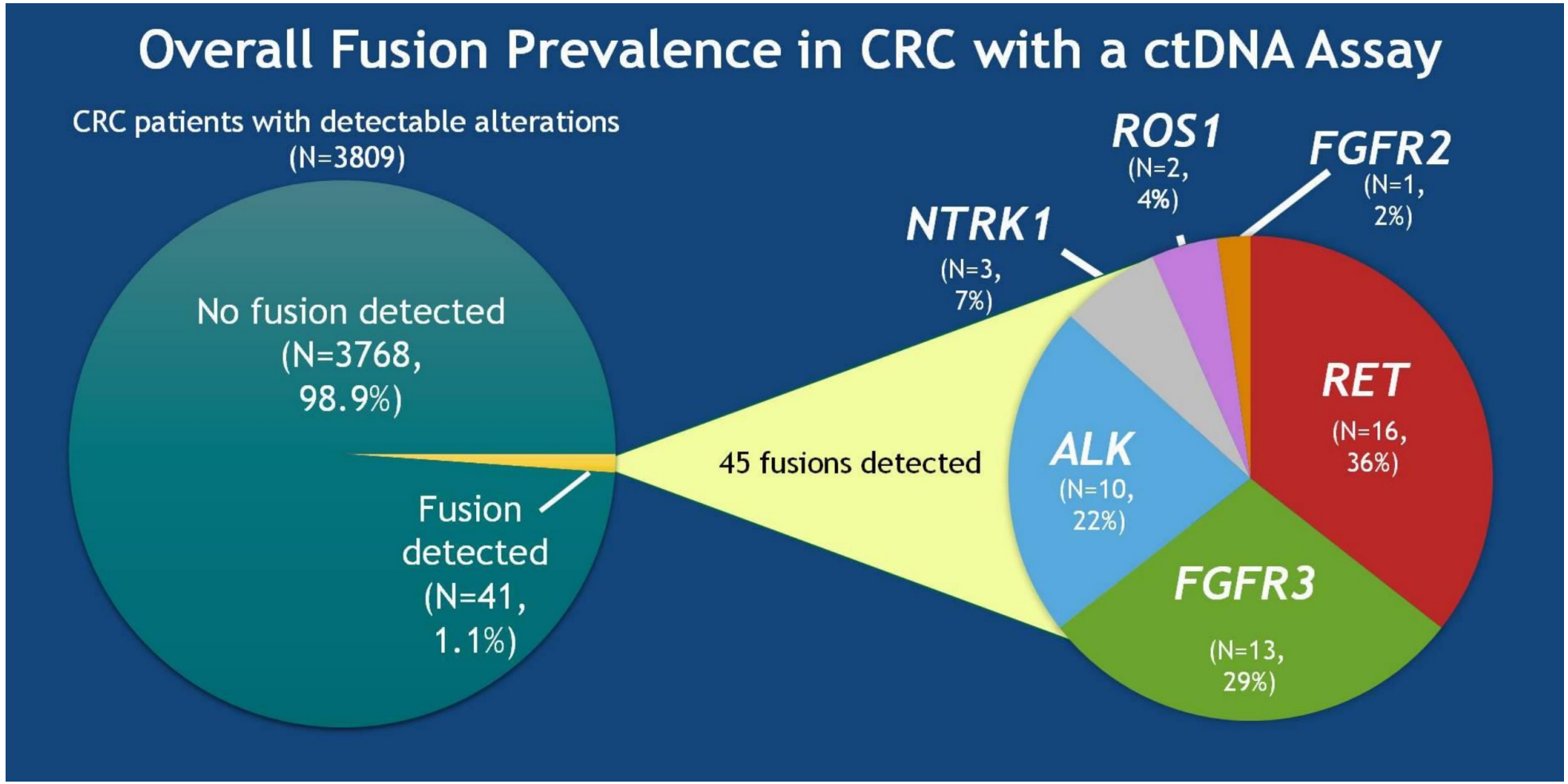
Trial in progress...

Strickler et al., *ESMO GI* 2022. Bekali-Saab et al. *ASCO Gastrointestinal Cancers Symposium* 2023.

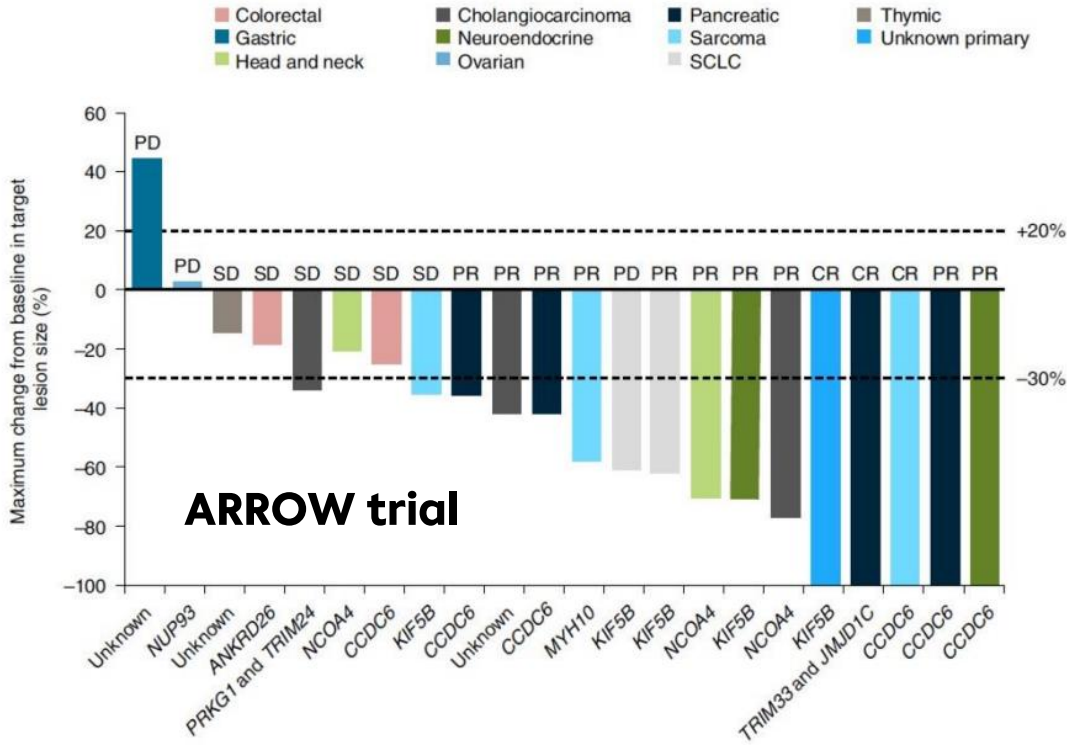
Neue molekular zielgerichtete Therapien

Seltene targets

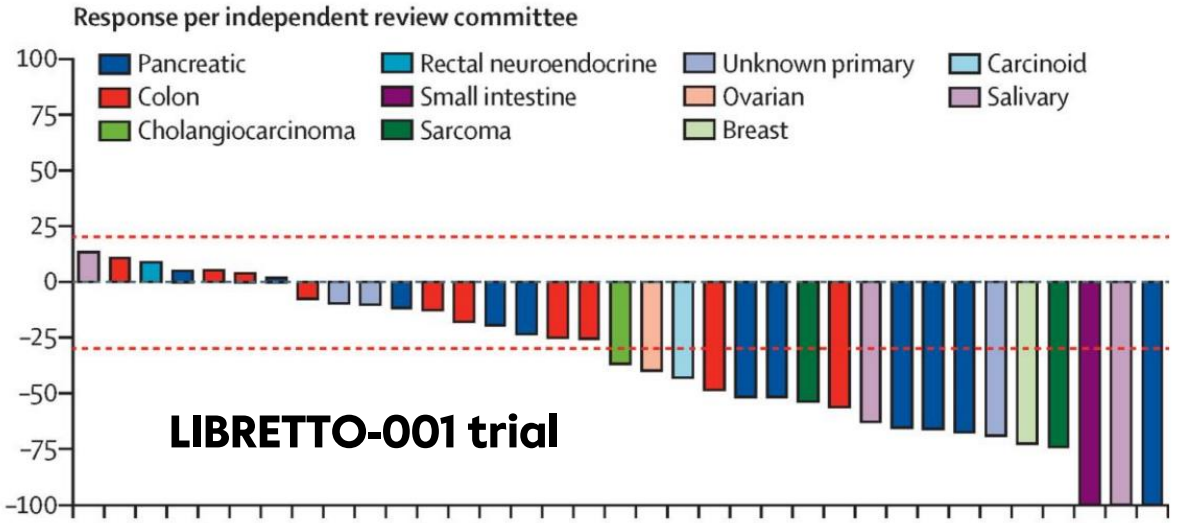
Genfusionen als seltene targets im mKRK



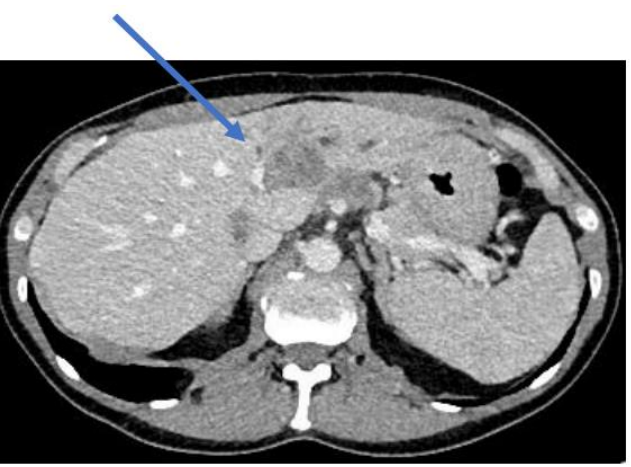
Clifton et al., *ASCO* 2018.

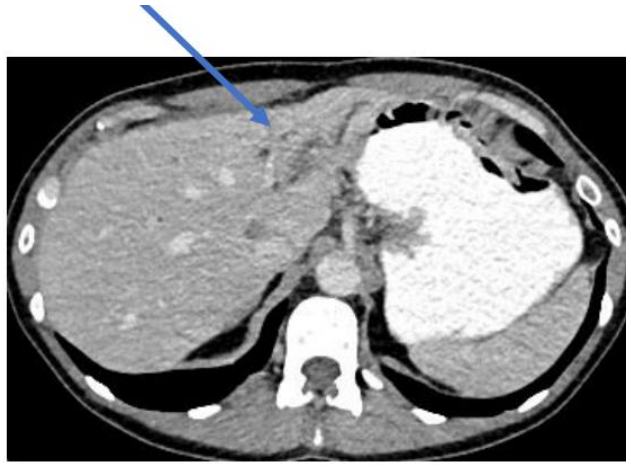


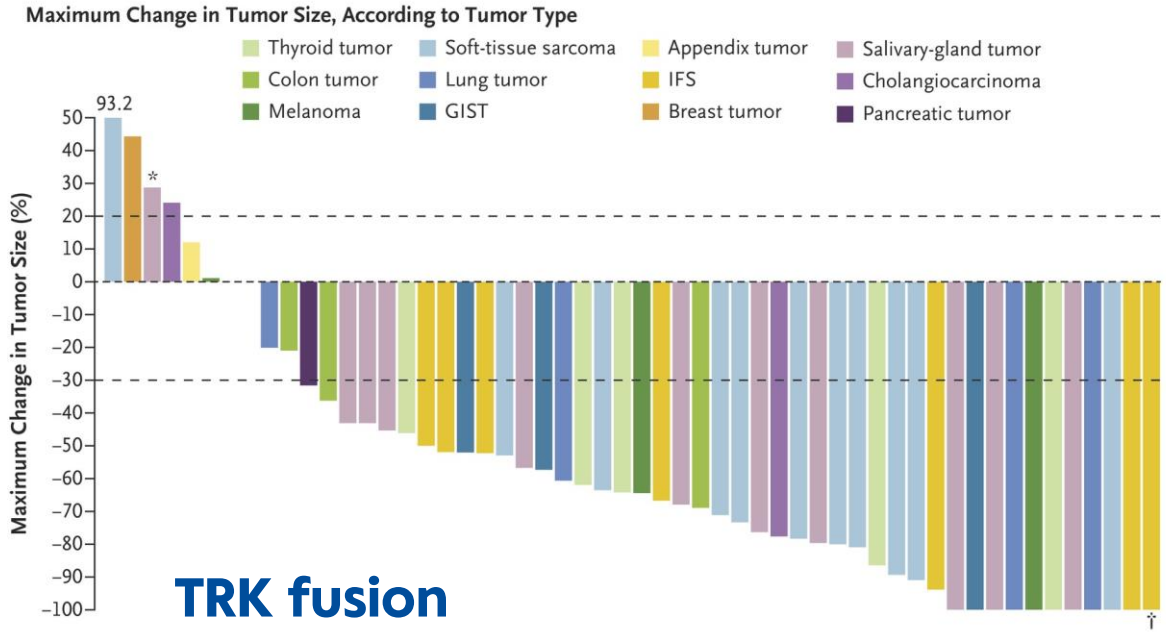
RET fusion



Crizotinib targeting **ROS1 fusion** in mCRC







Zusammenfassung: Neue molekular zielgerichtete Therapien

- **KRAS G12C MT:**

  Einsatz KRAS G12C Inhibitoren in früheren Therapielinien, innovative Wirkstoffkombinationen,

  Entwicklung von Pan-KRAS Inhibitoren

- **HER2 Amplifikation/ Expression:**

  Studien in allen Therapielinien, Chemotherapie-freie Kombinationen, Kombinationen mit Chemotherapie

  → zeitnahe Aufnahme **HER2** in **molekulare Standardtestung**

- **Erweitertes molekulares Profiling** bei nicht-RAS MT mKRK Patienten sinnvoll

- Behandlung möglichst vieler mKRK Patienten mit seltenen targets im Rahmen **klinischer Studien**!

Vielen Dank für Ihre Aufmerksamkeit!