Molekular gesteuerte Therapie beim kolorektalen Karzinom

Dominik Modest
13.10.2024
DGHO 2024
Basel

Medizinische Klinik mit Schwerpunkt Hämatologie, Onkologie und Tumorimmunologie | CVK.

Offenlegung Interessenskonflikte

Stintzing Sebastian

1. **Anstellungsverhältnis oder Führungsposition**
   Charité – Universitaetsmedizin Berlin

2. **Beratungs- bzw. Gutachtertätigkeit**
   AMGEN, AstraZeneca, Bayer, BMS, CV6, Daiichi-Sanyko, ESAI, Lilly, Merck KGaA, MSD, Pierre-Fabre, Roche, Sanofi, Servier, Taiho, Takeda

3. **Besitz von Geschäftsanteilen, Aktien oder Fonds**
   keine

4. **Patent, Urheberrecht, Verkaufslizenz**
   keine

5. **Honorare**
   AMGEN, AstraZeneca, Bayer, BMS, Daiichi-Sanyko, ESAI, Leo-Pharma, Lilly, Merck KGaA, MSD, Pierre-Fabre, Roche, Sanofi, Servier, Taiho, Takeda

6. **Finanzierung wissenschaftlicher Untersuchungen**
   Merck KGaA, Pierre-Fabre, Servier, Roche

7. **Andere finanzielle Beziehungen**
   keine

8. **Immaterielle Interessenkonflikte**
   keine

Molekulare Subgruppen im mCRC

BRAF	BRAF	BRAF	BRAF	BRAF	BRAF	MSI	MSI	MSI	MSI
Her2	Her2	Her2	KRAS G12C	KRAS G12C	KRAS G12C	Gene fusion			
					RAS/BRA F WT	RAS/BRA F WT	RAS/BRA F WT	RAS/BRA F WT	RAS/BRA F WT
RAS/BRA F WT	RAS/BRA F WT	RAS/BRA F WT	RAS/BRA F WT	RAS/BRA F WT	RAS/BRA F WT	RAS/BRA F WT	RAS/BRA F WT	RAS/BRA F WT	RAS/BRA F WT
RAS/BRA F WT	RAS/BRA F WT	RAS/BRA F WT	RAS/BRA F WT	RAS/BRA F WT	RAS/BRA F WT	RAS/BRA F WT	RAS/BRA F WT	RAS/BRA F WT	RAS/BRA F WT

The Cancer Genome Atlas Network, NATURE 2012

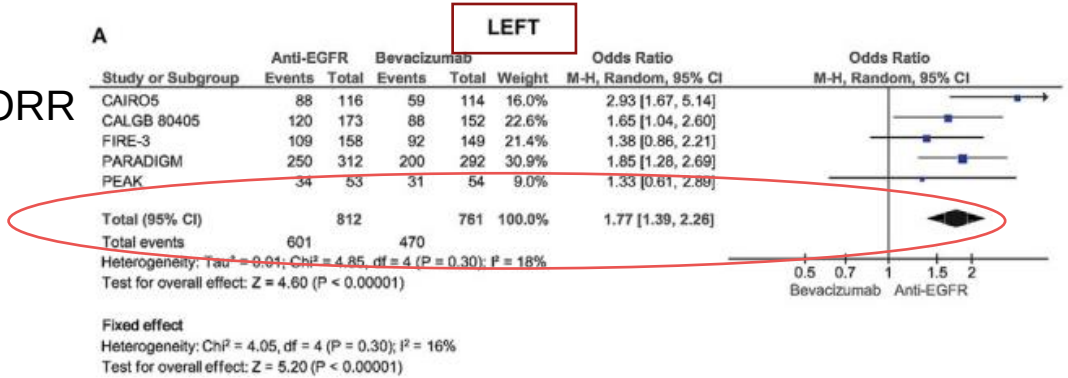
Aspekte

1. EGFR-targetable
2. BRAF V600E MT
3. Her2 pos.
4. KRAS G12C MT
5. Rare alterations

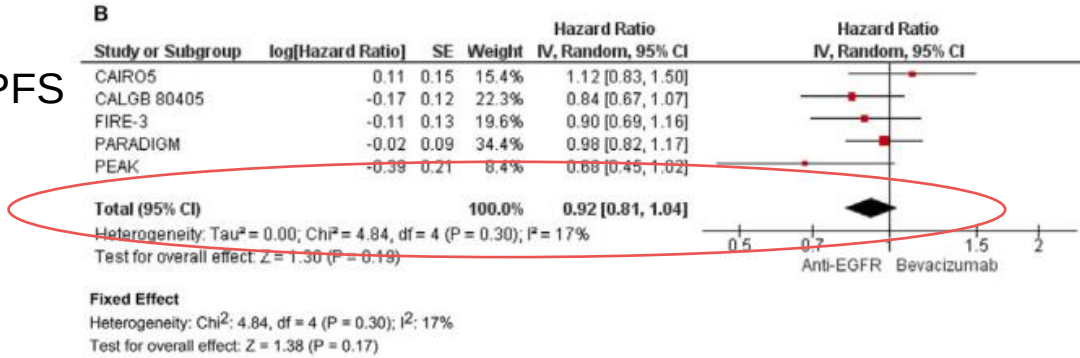
   →Gene fusions

EGFR-mAB vs. VEGF-mAB

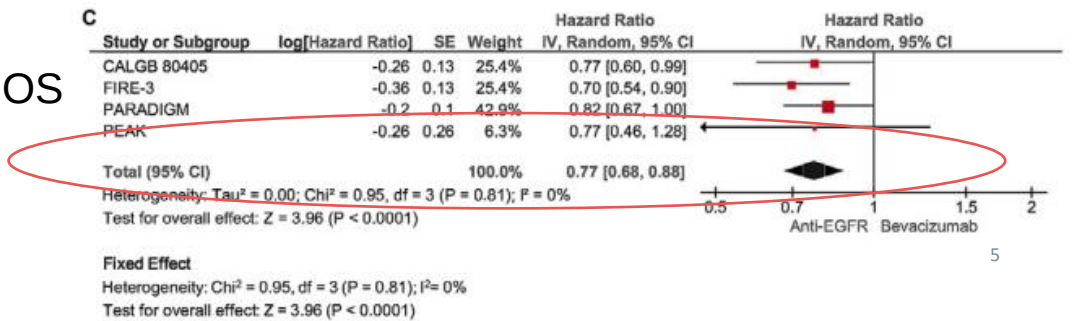
ORR



PFS



OS



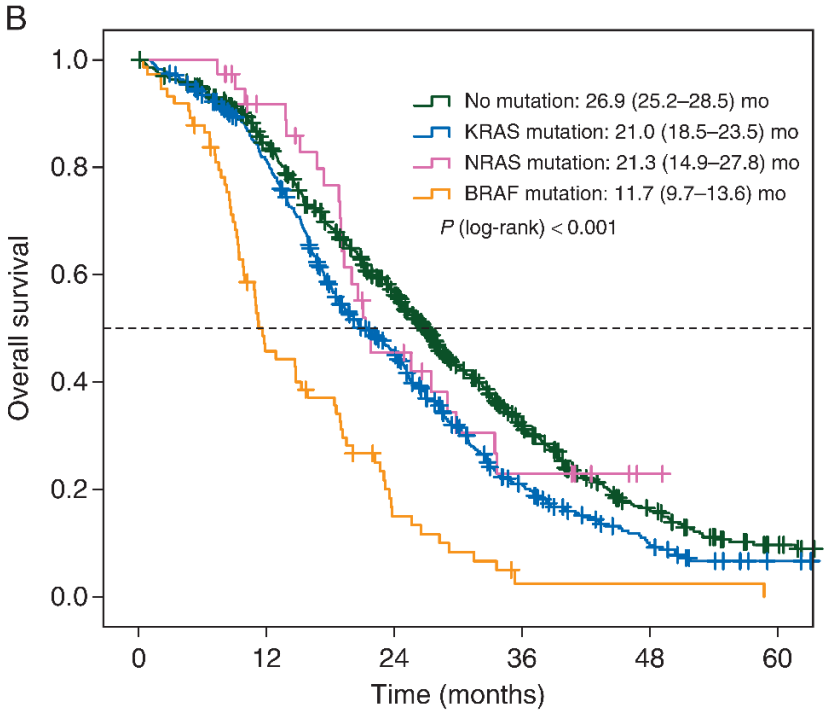
Rossini D et al. Eur J Cancer 2023

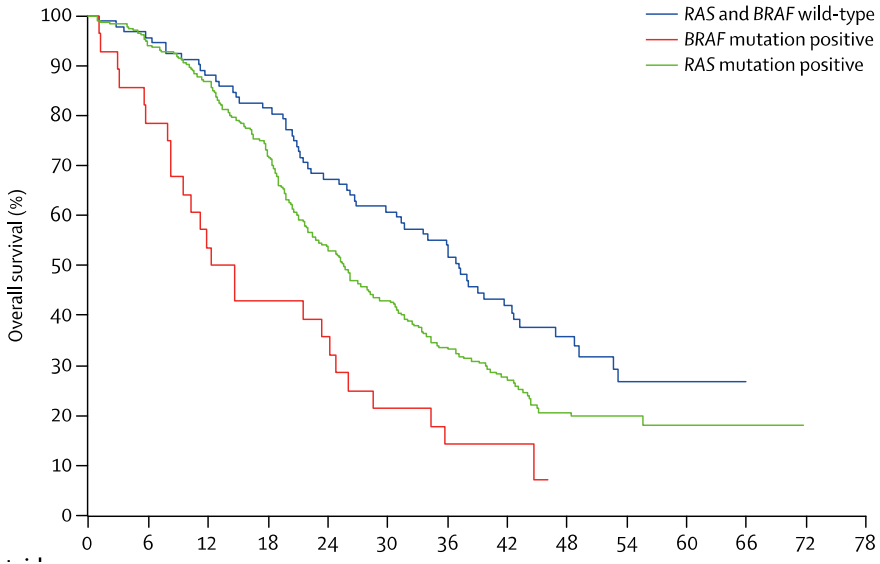
Aspects to discuss

1. EGFR-targetable
2. BRAF V600E MT
3. Her2 pos.
4. KRAS G12C MT
5. Rare alterations

   →Gene fusions

Prognose des BRAF V600E MT mCRC





Cremolini et al, Lancet Oncol 2015; Modest DP et al, Ann Oncol 2016

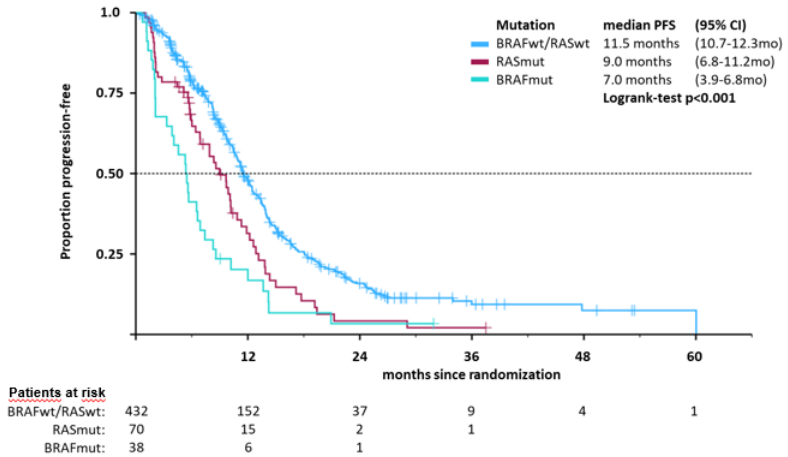
FIRE-4 Studie

Prognose bei unterschiedlicher molekularer Pathologie

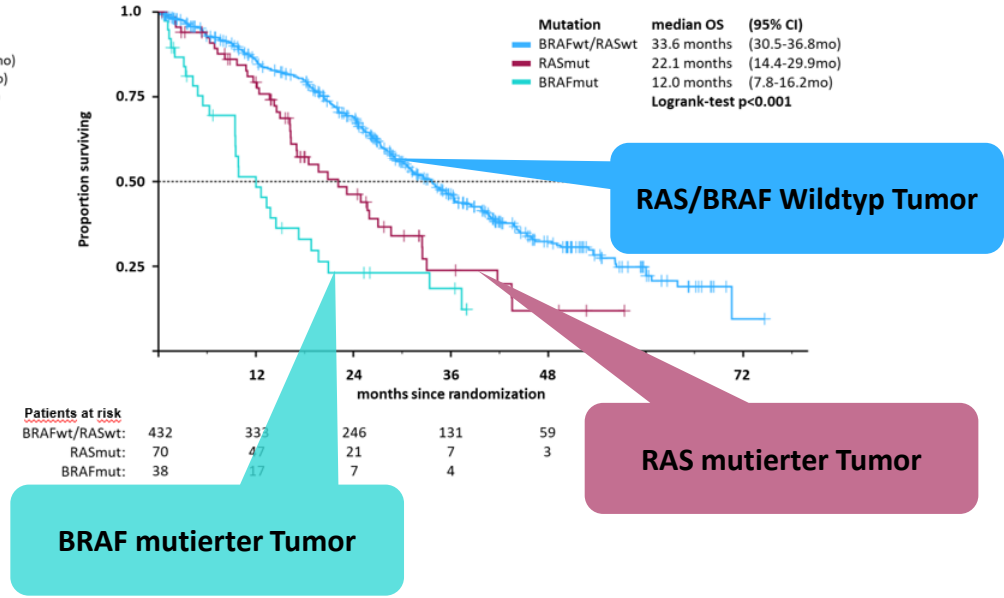
R → **FOLFIRI + Cetuximab**

R → **FOLFIRI + Cetuximab → 5FU + Bev**

Progressionsfreies Überleben (PFS)

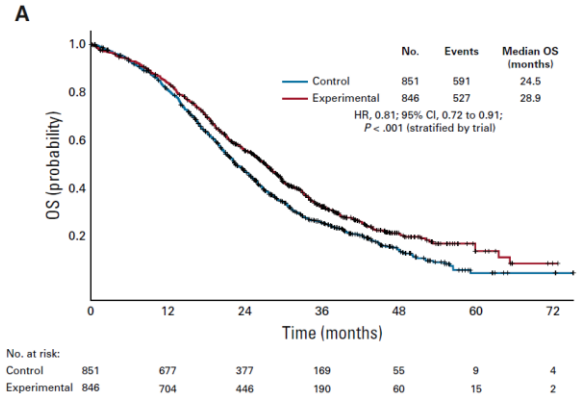


Gesamtüberleben (OS)

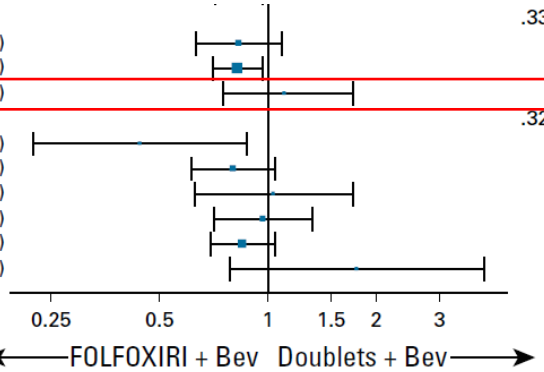


Stintzing S. et al ASCO 2023

Chemotherapie bei BRAF V600E MT- 2x oder 3x?

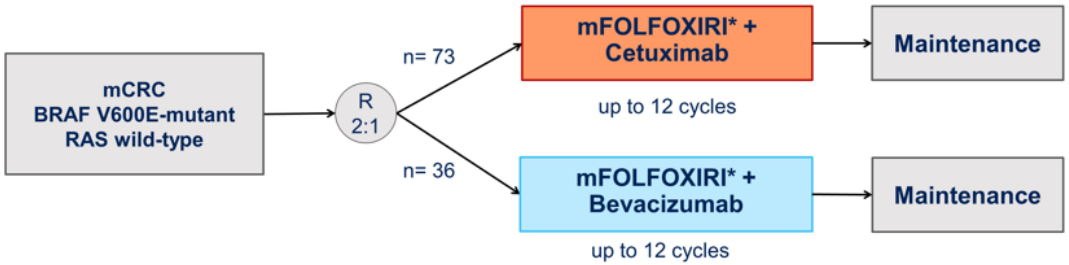


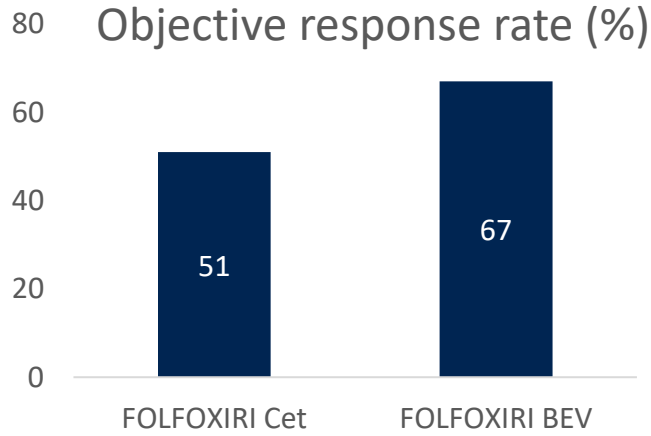
RAS and *BRAF* status				.337
RAS-BRAF wt	107 of 172 (62.2)	99 of 177 (55.9)	0.83 (0.63 to 1.10)	
RAS mut	316 of 430 (73.5)	289 of 422 (68.5)	0.82 (0.70 to 0.97)	
BRAF mut	43 of 54 (79.6)	53 of 61 (86.9)	1.11 (0.75 to 1.73)	
Site-*RAS*/*BRAF*				.320
Right-*RAS*/*BRAF* wt	21 of 31 (67.7)	21 of 44 (47.7)	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)	



Cremolini et al, J Clin Oncol 2020

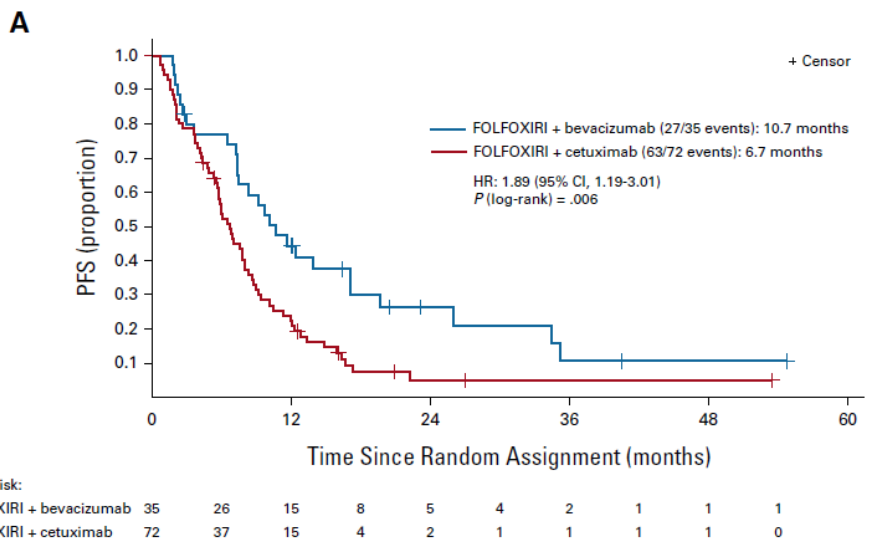
EGFR-mAb vs Bevacizumab beim BRAF V600E MT mCRC

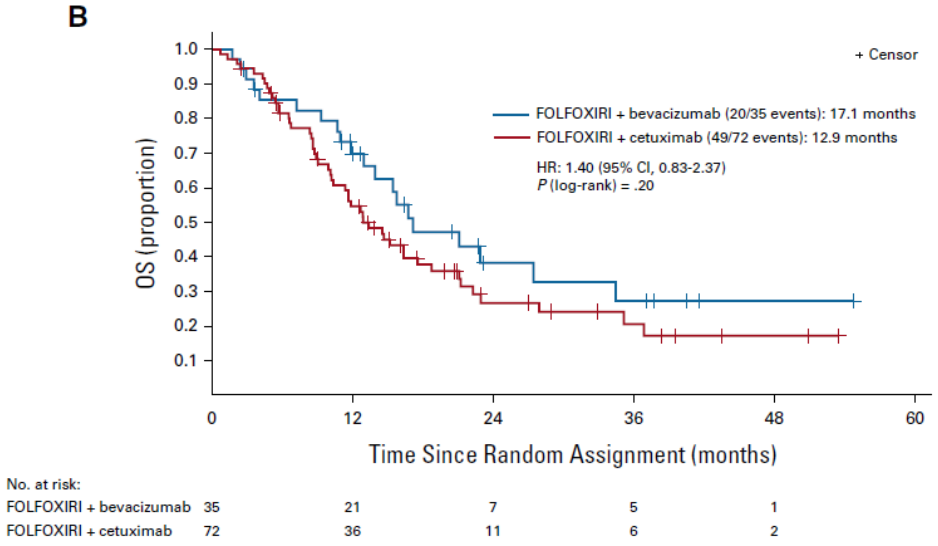




Stintzing S et al., ASCO 2021 and J Clin Oncol 2023

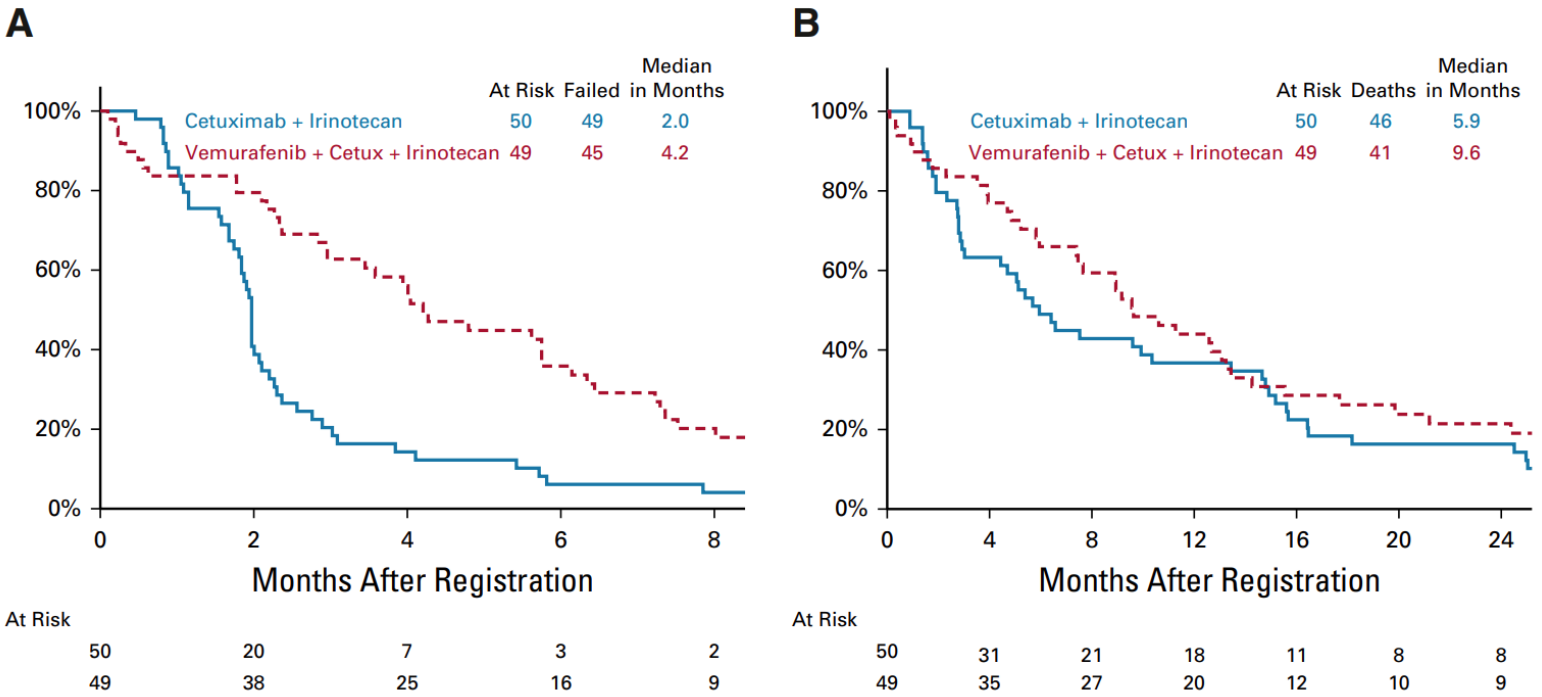
EGFR-mAb vs Bevacizumab beim BRAF V600E MT mCRC





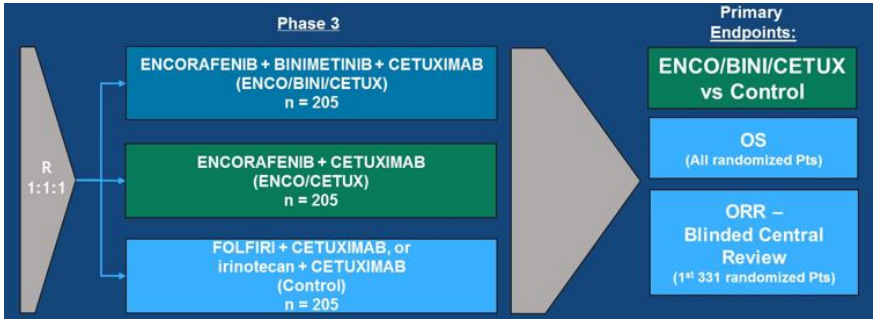
Stintzing S et al., J Clin Oncol 2023

EGFRmAB + Irinotecan vs BRAFi + Irinotecan + EGFR-mAb – erste rand. Daten

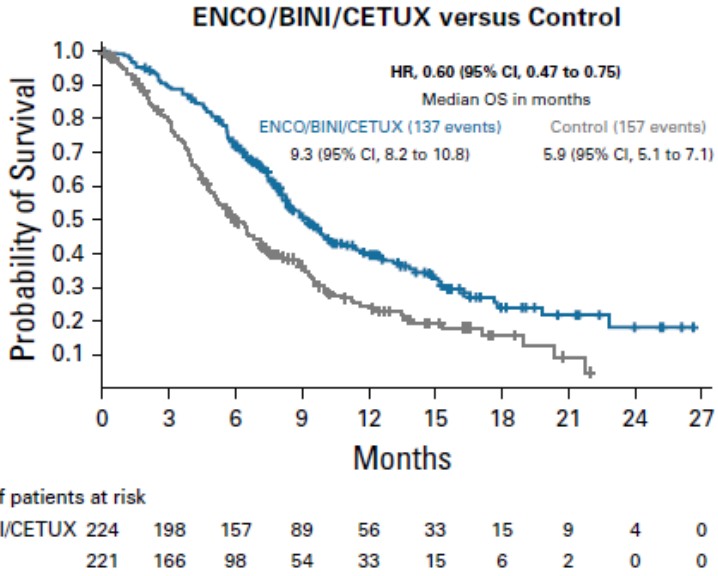


Kopetz S., J Clin Oncol 2020

BEACON trial: E+B+C vs E+C vs SOC



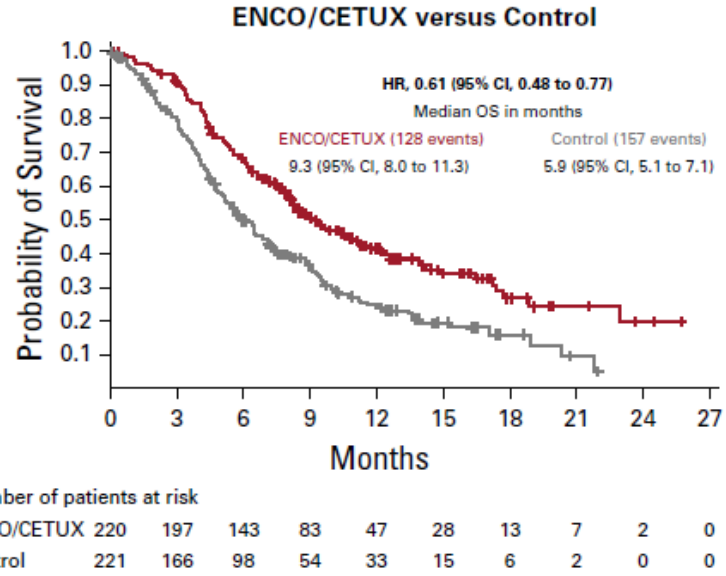
A



Number of patients at risk

ENCO/BINI/CETUX	224	198	157	89	56	33	15	9	4	0
Control	221	166	98	54	33	15	6	2	0	0

B



Number of patients at risk

ENCO/CETUX	220	197	143	83	47	28	13	7	2	0
Control	221	166	98	54	33	15	6	2	0	0

Kopetz S et al ASCO 2020, Tabernero J Clin Oncol 2021

1L trial in MSS/BRAF V600E: BREAKWATER

Safety Lead-In

Participants who have received ≤ 1 prior treatment for mCRC

Cohort 1 (n=30)
Encorafenib 300 mg QD
+ Cetuximab 500 mg/m² Q2W
+ FOLFIRI Q2W in 28-day cycles

Cohort 2 (n=27)
Encorafenib 300 mg QD
+ Cetuximab 500 mg/m² Q2W
+ mFOLFOX6 Q2W in 28-day cycles

Primary Endpoint
- Safety (frequency of DLTs)

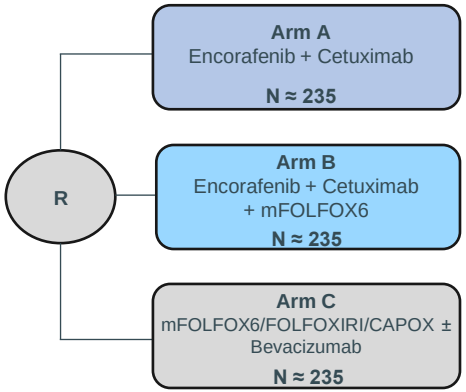
Secondary Endpoints
- Safety (AEs, dose interruptions/ modifications/discontinuations)
- PKs
- Antitumor activity by investigator (ORR, DOR, TTR, PFS, OS)

Inclusion Criteria
- BRAF V600E mCRC (blood or tumor tissue)
- ≤ 1 prior systemic treatment for mCRC
- Evaluable disease (RECIST 1.1)
- ECOG PS 0 or 1
- Adequate BM, hepatic, and renal function

Exclusion Criteria
- Prior treatment with BRAFi/EGFRi or both oxaliplatin and irinotecan
- Symptomatic brain metasases
- MSI-H or dMMR tumors[a]

Phase 3

Participants who have not received prior systemic treatment for mCRC



Primary Endpoint
- PFS by BICR

Secondary Endpoints
- OS
- ORR, DOR, and TTR by BICR and by investigator
- PFS by investigator
- Safety
- PROs
- Biomarkers

[a]Unless patient ineligible to receive immune checkpoint inhibitors due to pre-existing medical condition.
BM, bone marrow; DLT, dose-limiting toxicity; dMMR, deficient mismatch repair; EC, encorafenib + cetuximab; MSI-H, microsatellite instability-high; PK, pharmacokinetic; SLI, safety lead-in.
1. Cohen R, et al. *J Natl Cancer Inst*. 2021; **2.** Tabernero J, et al. *J Clin Oncol*. 2021; **3.** Van Cutsem E, et al. Presented online at: ESMO World Congress on Gastrointestinal Cancer; 2021. Abstract O-10.

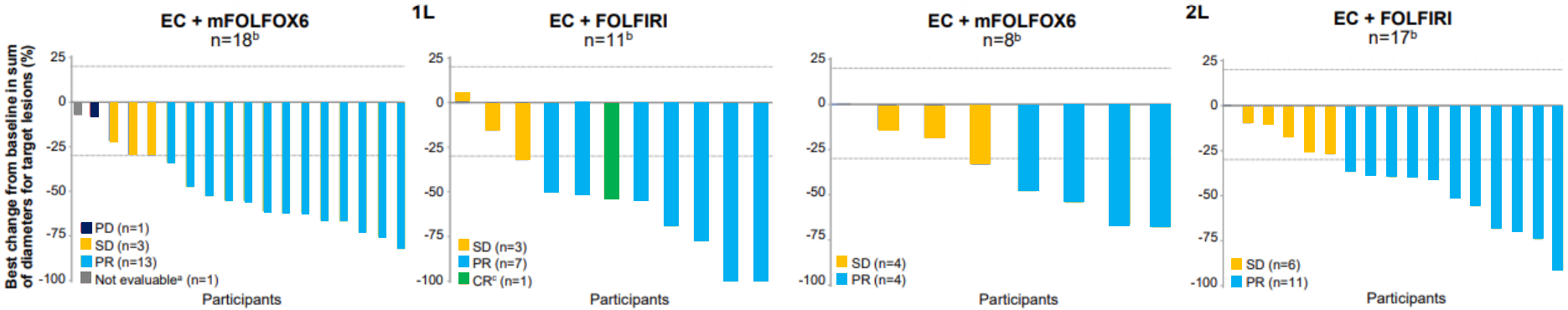
Actual Study Start Date: December 21, 2020
Estimated Primary Completion Date: September 16, 2024
Estimated Study Completion Date: November 15, 2026

ClinicalTrials.gov Identifier: NCT04607421

Modified from:
Tabernero J et al. ESMO 2022, LBA26 & Präsentation

Overview of Response

	1L		2L	
	EC + mFOLFOX6	EC + FOLFIRI	EC + mFOLFOX6	EC + FOLFIRI
Confirmed best overall response by investigator, n (%)	**n=19**	**n=12**	**n=8**	**n=18**
ORR, % (95% CI)	68.4 (46.0–84.6)	66.7 (39.1–86.2)	50.0 (21.5–78.5)	61.1 (38.6–79.7)
CR	0	1 (8.3)	0	0
PR	13 (68.4)	7 (58.3)	4 (50.0)	11 (61.1)
SD	3 (15.8)	3 (25.0)	4 (50.0)	6 (33.3)
PD	1 (5.3)	0	0	0
Non-CR/non-PD	1 (5.3)	1 (8.3)	0	0
Not evaluable[a]	1 (5.3)	0	0	1 (5.6)
Responders	**n=13**	**n=8**	**n=4**	**n=11**
mTTR, weeks (range)	6.9 (5.9–25.9)	6.6 (6.1–7.0)	9.4 (6.4–18.9)	12.9 (6.1–37.0)
mDOR, months (95% CI)	7.6 (4.1–not estimable)	Not estimable (10.6–not estimable)	Not estimable (2.7–not estimable)	Not estimable (3.4–not estimable)
≥6 months, n (%)	6 (46.2)	7 (87.5)	2 (50.0)	6 (54.5)



Data cutoff: 16 May 2022

[a]Reasons included SD <6 weeks after treatment start date (1 patient in the EC + mFOLFOX6 arm in the 1L setting) and early death (1 patient in the EC + FOLFIRI arm in the 2L setting). [b]Only includes participants with target lesions at baseline and ≥1 non-missing post-baseline % change from baseline assessment up to time of PD or new anti-cancer therapy. [c]This participant had a nodal target lesion that did not completely disappear but became non-pathological by size (<10 mm).

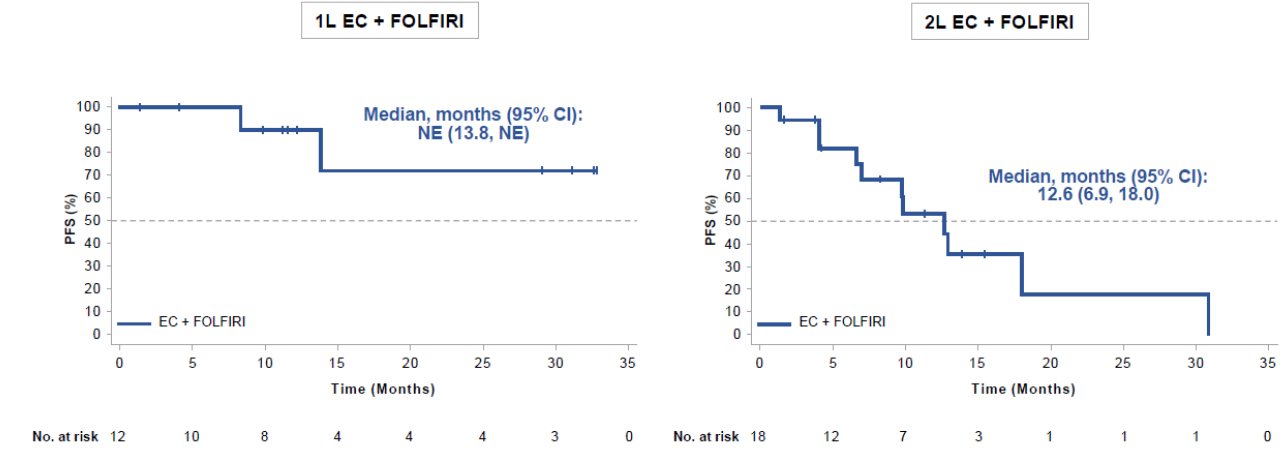
CR, complete response; EC, encorafenib + cetuximab; PD, progressive disease; PR, partial response; SD, stable disease.

Modified from:
Tabernero J et al. ESMO 2022, LBA26 & Präsentation

Summary of Antitumor Activity by BICR by Line of Therapy

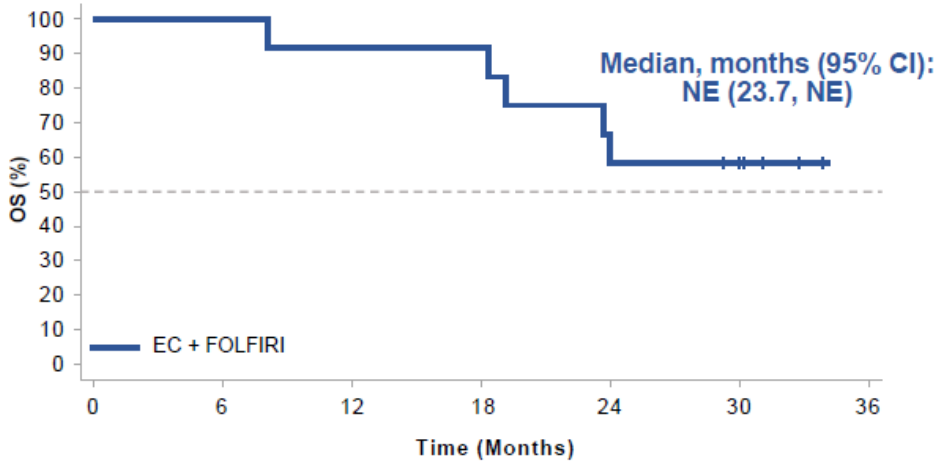
	EC + FOLFIRI	
	1L (n=12)	2L (n=18)
Best overall response, n (%)[a,b]		
CR	2 (16.7)	1 (5.6)
PR	8 (66.7)	7 (38.9)
SD	1 (8.3)	7 (38.9)
Non-CR/non-PD	1 (8.3)	2 (11.1)
PD	0	0
Not evaluable	0	1 (5.6)[c]
ORR (CR + PR), n (%)[b]	10 (83.3)	8 (44.4)
95% CI[d]	55.2, 95.3	24.6, 66.3
Median DOR, months[b,e]	NE	12.5
95% CI[f]	12.4, NE	5.5, NE
Median PFS, months[b]	NE	12.6
95% CI[f]	13.8, NE	6.9, 18.0
Median OS, months	NE	19.7
95% CI[f]	23.7, NE	13.9, 25.1

Progression-Free Survival by BICR by Line of Therapy



Overall Survival by Line of Therapy

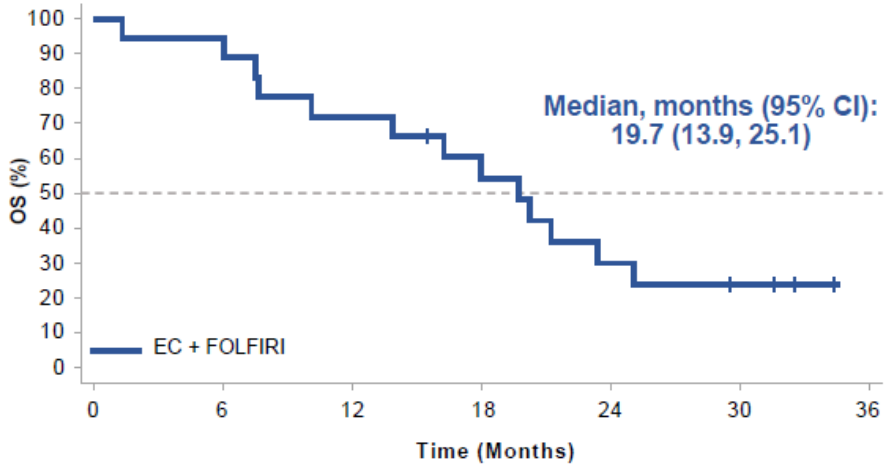
1L EC + FOLFIRI



No. at risk	12	12	11	11	7	5	0

Median time to follow-up:
31.1 months (95% CI, 30.0, 33.9)

2L EC + FOLFIRI



No. at risk	18	16	13	9	5	3	0

Median time to follow-up:
31.6 months (95% CI, 29.5, NE)

Take home messages BRAF MT mCRC

1. BRAF MT sind ca. 10% der mCRC Population

   →Mehrheitlich MSS aber MSI-H häufig

   →Prognose ist schlecht (insb. bei MSS)

2. 1L Therapie sollte mit Doublette (FOLFOX) plus Bev erfolgen

   →Die Triplette (FOLFOXIRI) kann in klinischen Szenarien (Ansprechen) hilfreich sein

3. Encorafenib/Cetuximab ist der SOC ab der 2L

Aspekte

1. EGFR-targetable
2. BRAF V600E MT
3. Her2 pos.
4. KRAS G12C MT
5. Rare alterations

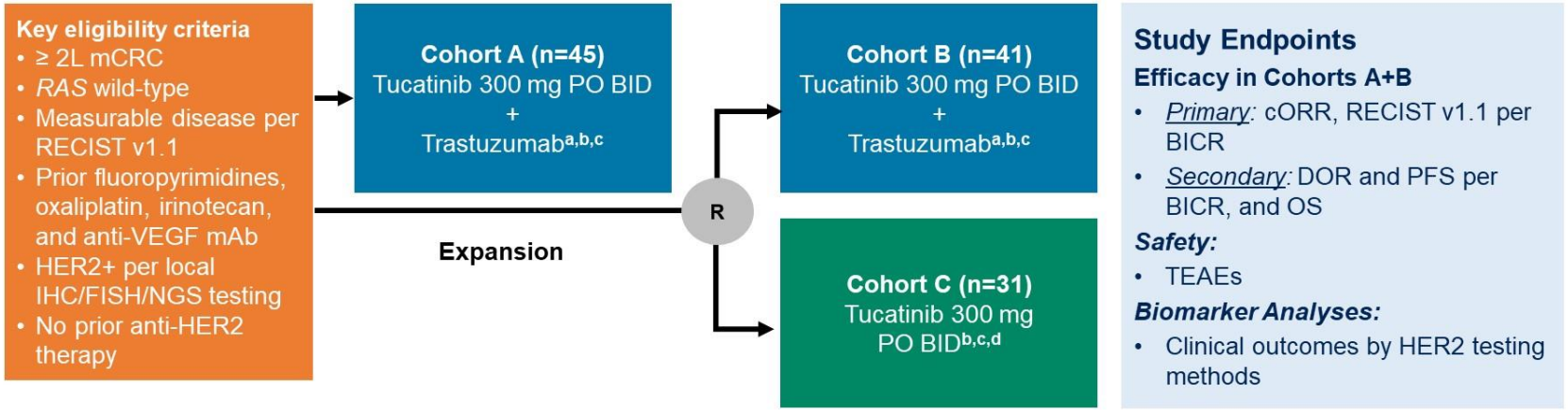
   →Gene fusions

HER2 als Target beim mKRK

Studienergebnisse

	HERACLES-A	MOUNTAINEER	My PAthway	TRIUMPH	TAPUR	HERACLES-B	DESTINY-CRC01 IHC 3+	DESTINY-CRC02 5.4mg/kg Q3W
Verwendete Substanz	Trastuzumab Lapatinib	Trastuzumab Tucatinib	Trastuzumab Pertuzumab	Trastuzumab Pertuzumab	Trastuzumab Pertuzumab	Pertuzumab T-DM1	Trastuzumab Deruxtecan	Trastuzumab Deruxtecan
Anzahl von Patienten	27	23	57	18	28	31	53	83
ORR	30%	52%	32%	35%	25%	9.7%	45.3%	37.8%
PFS	4.8mo	8.1mo	2.9mo 5.3m RASwt	4.0mo	4.0mo	4.1mo	6.9mo	5.9mo
OS	10.6mo	18.7mo	11.5mo 14m RASwt		25mo ? short fu		15.5mo	13.4mo

MOUNTAINEER: Multi-Center, Open-Label, Phase 2 Trial (NCT03043313)



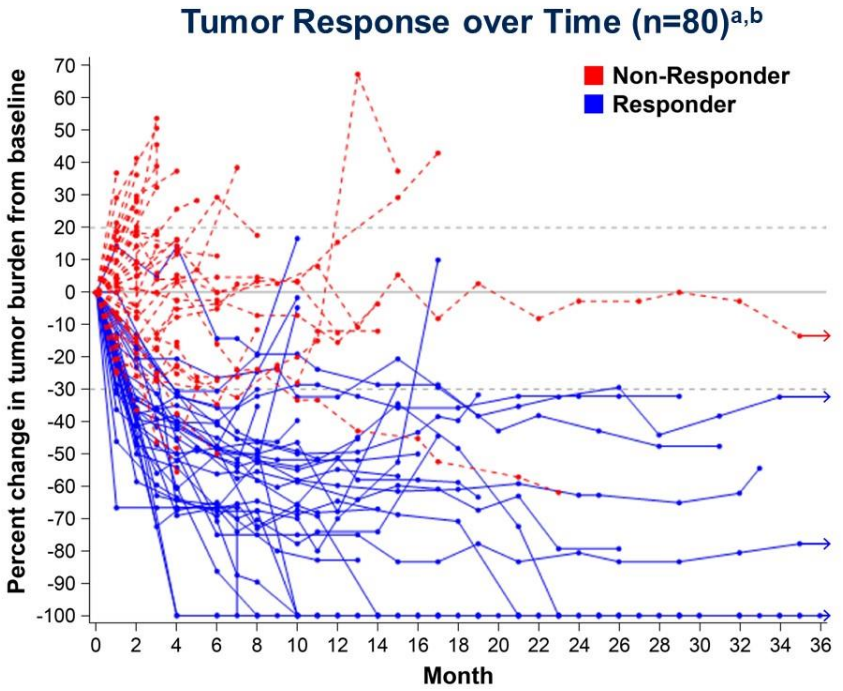
For the final analysis (cutoff date of November 2, 2023), the efficacy and safety endpoints evaluated remained the same. Biomarker analyses, including a long-term responder analysis, were exploratory

[a] 6 mg/kg Q3W (loading dose 8 mg/kg); [b] each treatment cycle is 21 days; [c] Patients remained on therapy until evidence of radiographic or clinical progression or death, unacceptable toxicity, withdrawal of consent, or study closure; [d] Patients were allowed to cross over and receive tucatinib and trastuzumab if they experienced radiographic progression at any time point or if they had not achieved a partial or complete response by week 12.
≥ 2L, second line and later; BICR, blinded independent central review; BID, twice a day; cORR, confirmed objective response rate; DOR, duration of response; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; mAb, monoclonal antibody; mCRC, metastatic colorectal cancer; NGS, next-generation sequencing; OS, overall survival; PFS, progression-free survival; PO, orally; Q3W, every 3 weeks; R, randomization; *RAS*: rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumors; TEAE; treatment-emergent adverse event; VEGF, vascular endothelial growth factor.

Final Analysis: Efficacy Outcomes

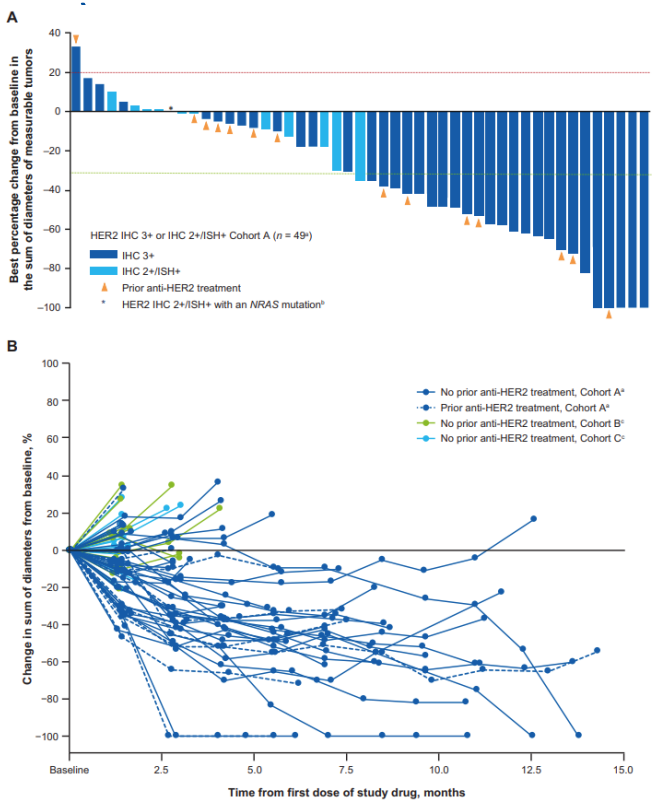
	Cohorts A+B Final analysis (n=84)
cORR, % (95% CI)	**39.3** (28.8–50.5)
Median DOR, mo (95% CI)	**15.2** (8.9–20.5)
Median PFS, mo (95% CI)	**8.1** (4.2–10.2)
Median OS, mo (95% CI)	**23.9** (18.7–28.3)

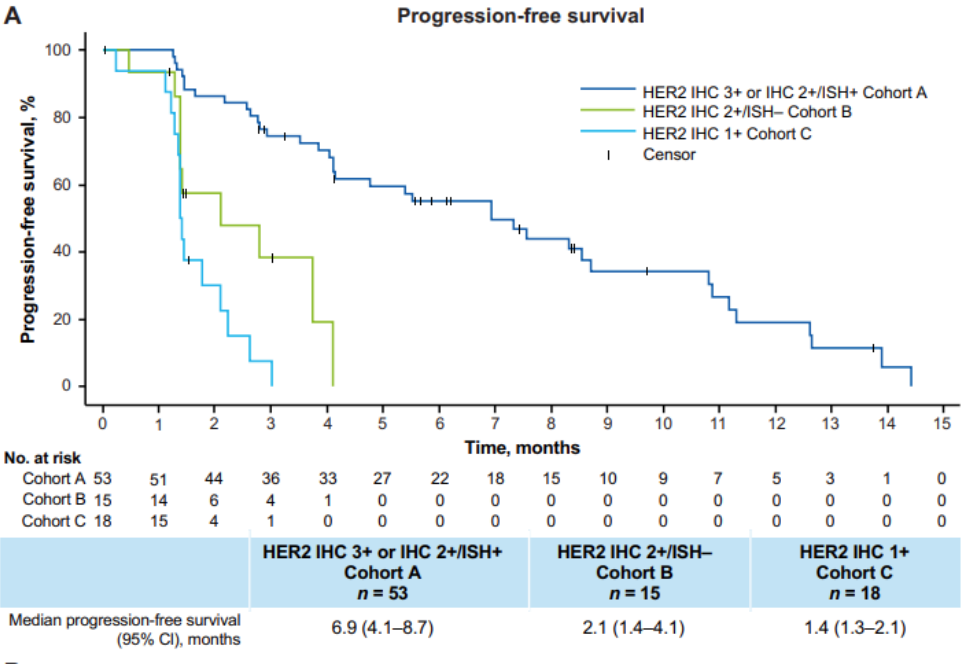
- Median follow-up: 32.4 months



[a] Data up to 36 months are included; [b] Arrows denote treatment duration beyond 36 months.
CI, confidence interval; cORR, confirmed objective response rate; DOR, duration of response; mo, months; OS, overall survival; PFS, progression-free survival.

Trastuzumab-Deruxtecan in her2-expressing mCRC (DESTINY-CR





	HER2 IHC 3+ or IHC 2+/ISH+ Cohort A *n* = 53	HER2 IHC 2+/ISH– Cohort B *n* = 15	HER2 IHC 1+ Cohort C *n* = 18
Median progression-free survival (95% CI), months	6.9 (4.1–8.7)	2.1 (1.4–4.1)	1.4 (1.3–2.1)

Yoshino T et al Nature Comm 2023

Take home messages her2- positive mCRC

1. Die Kohorten umfassen fast ausschließlich RAS WT mCRC

2. Keine Therapieoption hat aktuell eine Zulassung, aber die Daten sind sehr konsistent
   →HER2/neu sollte getestet werden

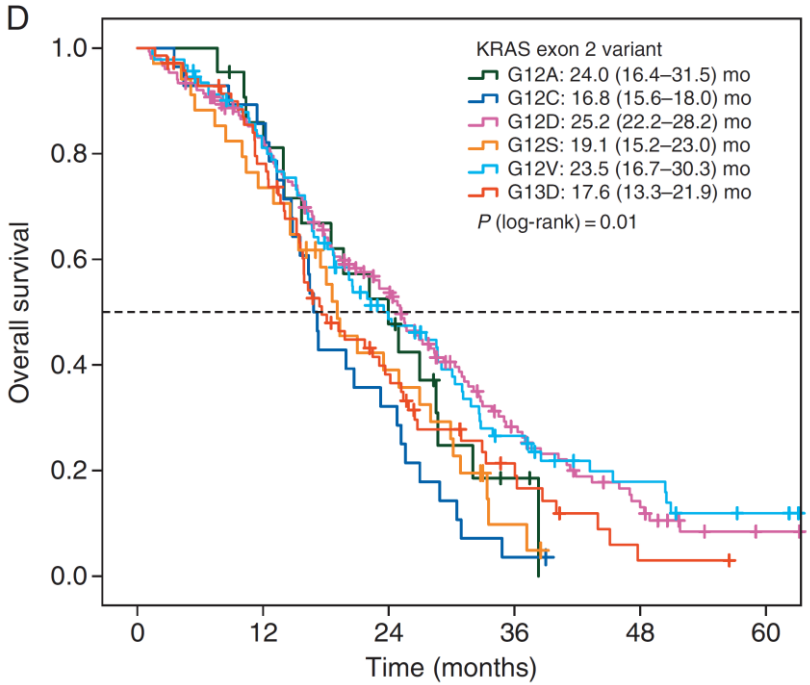
3. Laufende rand. Studien entwickeln neue Regime (Mountaineer-03)

Aspects to discuss

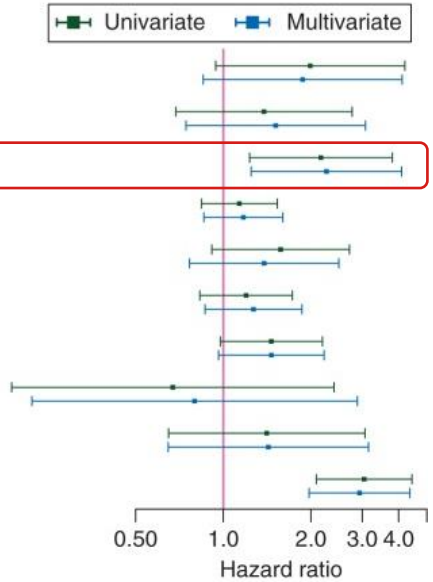
1. EGFR-targetable
2. BRAF V600E MT
3. Her2 pos.
4. KRAS G12C MT
5. Rare alterations

   →Gene fusions

KRAS G12C mCRC



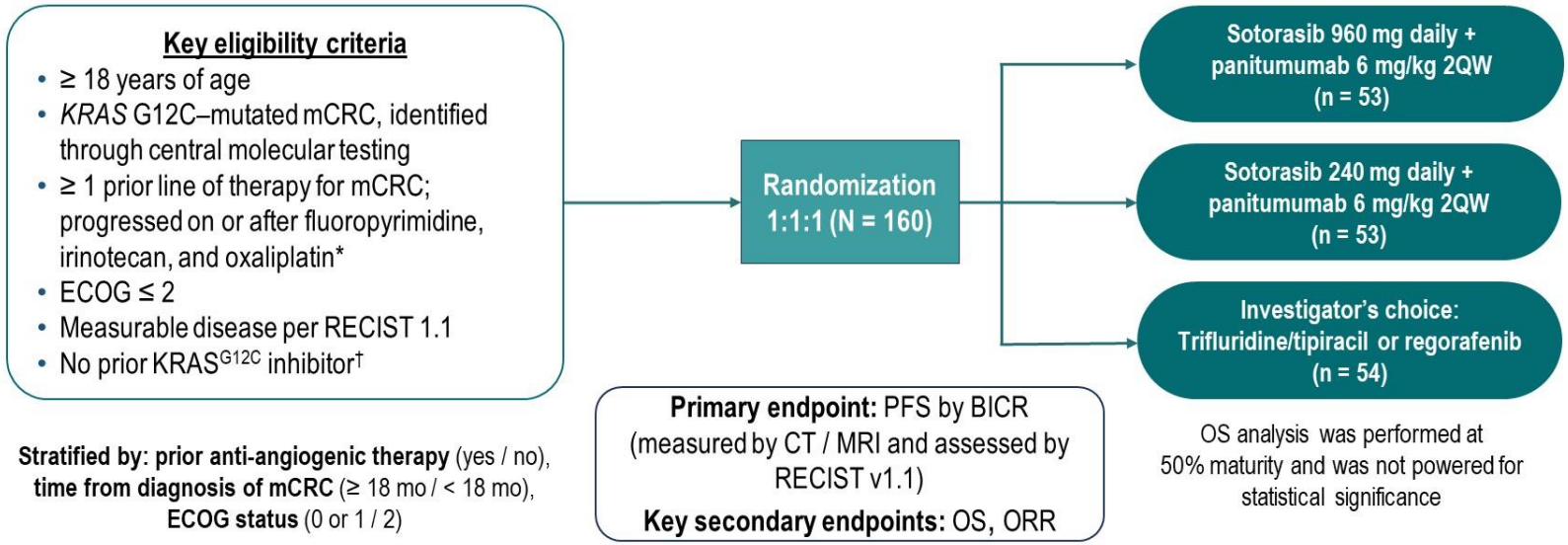
	HR	95% CI	*P*–value
A146T vs. WT	1.87	(0.85, 4.11)	0.227
G12A vs. WT	1.51	(0.74, 3.08)	0.654
G12C vs. WT	2.26	(1.25, 4.1)	0.001
G12D vs. WT	1.17	(0.86, 1.6)	0.807
G12S vs. WT	1.38	(0.77, 2.49)	0.733
G12V vs. WT	1.27	(0.87, 1.86)	0.565
G13D vs. WT	1.46	(0.96, 2.22)	0.102
NG12D vs. WT	0.8	(0.22, 2.89)	1.000
Q61H vs. WT	1.43	(0.65, 3.15)	0.900
V600E vs. WT	2.94	(1.97, 4.37)	4e–13



Modest DP et al., Ann Oncol. 2016; 27: 1746–175

CodeBreaK 300 Phase 3 Study Design

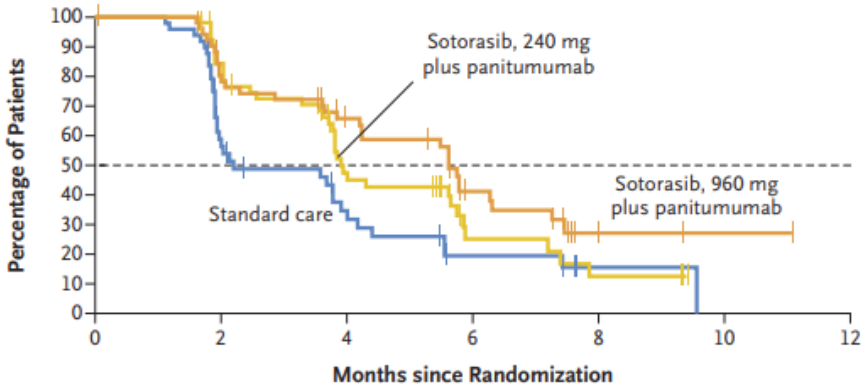
Global, randomized, open-label, active-controlled study of sotorasib + panitumumab in mCRC (NCT05198934)



*Patients deemed by the investigator not to be candidates for fluoropyrimidine, irinotecan, or oxaliplatin may still be eligible if ≥ 1 prior line of therapy was received for metastatic disease and trifluridine and tipiracil and/or regorafenib were deemed appropriate next line of therapy. †Patients with prior treatment with trifluridine and tipiracil and with regorafenib were excluded, where the investigator's choice would be these agents.
2QW, every 2 weeks; BICR, blinded independent central review; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; KRAS, Kirsten rat sarcoma; mCRC, metastatic colorectal cancer; MRI, magnetic resonance imaging; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

CB300 primary endpoint

A **Progression-free Survival (Intention-to-Treat Population)**

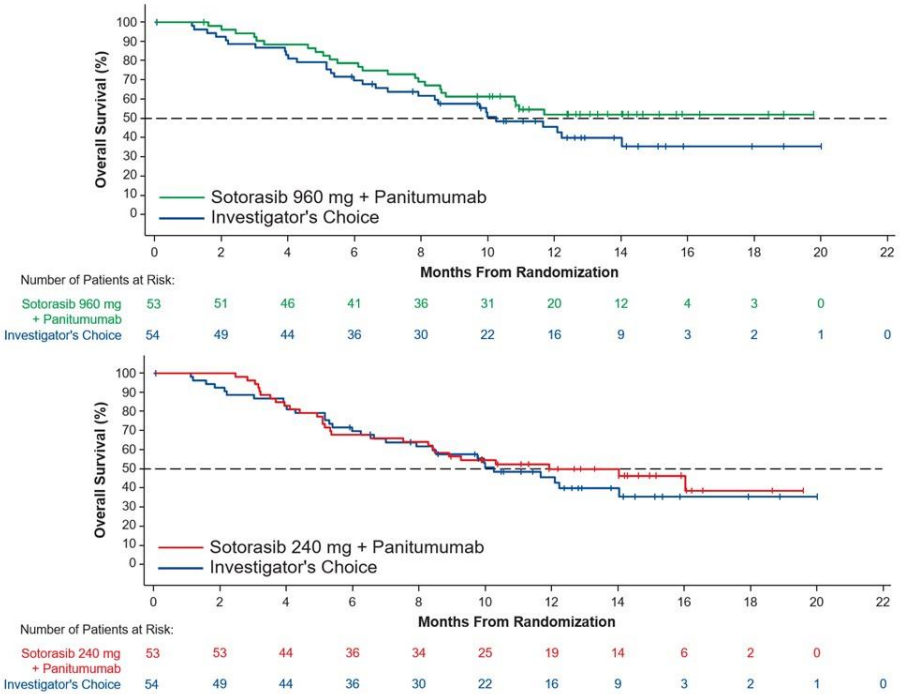


No. at Risk							
Sotorasib, 960 mg plus panitumumab	53	40	28	13	2	1	0
Sotorasib, 240 mg plus panitumumab	53	43	20	6	3	0	
Standard care	54	24	12	5	1	0	

	Median Progression-free Survival	Hazard Ratio for Disease Progression or Death (95% CI)	Two-Sided P Value
	mo		
Sotorasib, 960 mg plus Panitumumab	5.62	0.49 (0.30–0.80)	0.006
Sotorasib, 240 mg plus Panitumumab	3.91	0.58 (0.36–0.93)	0.03
Standard Care	2.20		

Pietrantonio F et al NEJM 2023

Secondary Endpoint: Protocol-Specified Final OS in Intent-to-Treat Population



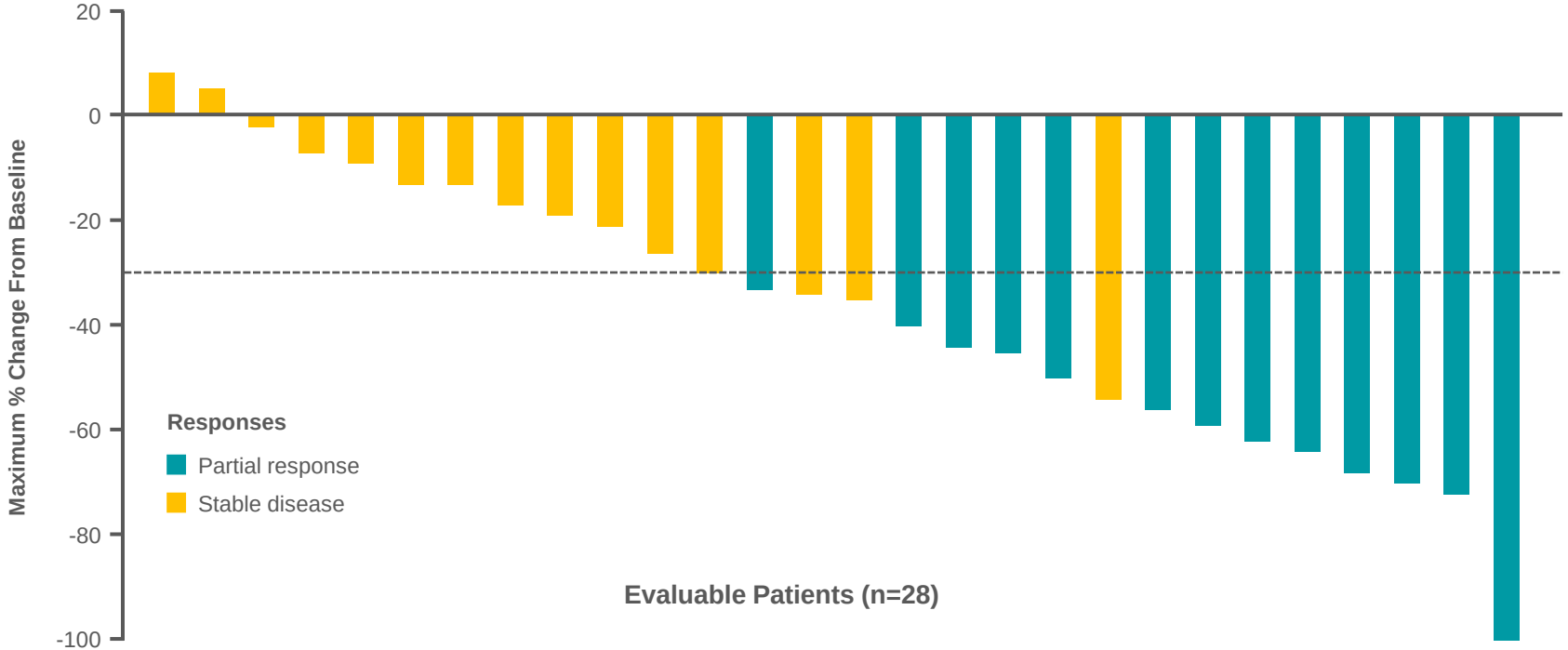
	Sotorasib 960 mg + Panitumumab (n = 53)	Sotorasib 240 mg + Panitumumab (n = 53)	Investigator's Choice (n = 54)
Median (95% CI) OS, months*	NE (8.6–NE)	11.9 (7.5–NE)	10.3 (7.0–NE)
HR (95% CI)†	0.70 (0.41–1.18)	0.83 (0.49–1.39)	–
P-value (2-sided)‡	0.20	0.50	–
Number of deaths (%)	24 (45)	28 (53)	30 (56)

- **After a median follow-up of 13.6 months, sotorasib (240 mg and 960 mg) + panitumumab showed a trend of improved OS versus investigator's choice, with 30% reduction in risk of death for sotorasib 960 mg + panitumumab**

*Estimated using the Kaplan-Meier method, 95% CIs from log-log transformation. †HRs and 95% CIs from stratified Cox proportional hazards model. HR < 1.0 indicates a lower risk and a longer OS for [sotorasib + panitumumab] versus [trifluridine and tipiracil or regorafenib]. ‡*P*-value from stratified log-rank test. Data cutoff, 18 December 2023. CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival.

PRESENTED BY: Marwan G. Fakih, MD

Adagrasib + Cetuximab in Previously Treated Patients with KRAS^{G12C}-Mutated CRC: Best Tumor Change From Baseline



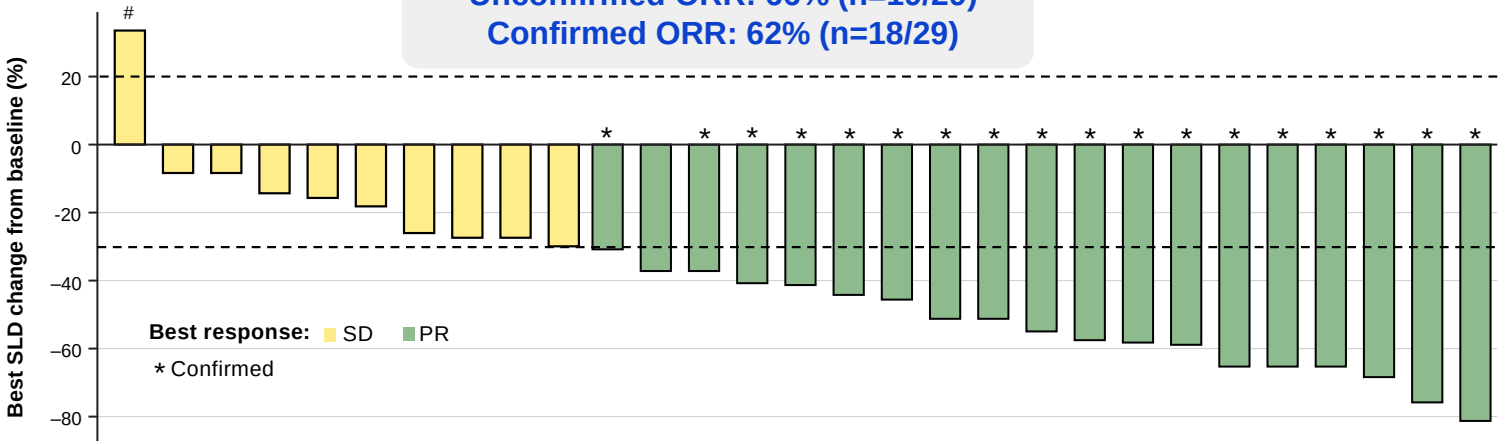
- Confirmed objective responses[a] were observed in 46% (13/28[b]); DCR was 100% (28/28)
- Tumor shrinkage of any magnitude occurred in 93% of patients

[a]ORR defined as the proportion of patients documented to have a confirmed CR or PR according to RECIST 1.1 as the best response. Patients who could not be assessed for response were counted as not evaluable. [b]Response per investigator assessment (n=28; four patients are not included due to no post-baseline assessment of target lesions)

Data as of June 16, 2022 (median follow-up, 17.5 months)

Divarasib in combination with cetuximab showed encouraging anti-tumour activity in patients with CRC and *KRAS G12C* mutation

Unconfirmed ORR: 66% (n=19/29)
Confirmed ORR: 62% (n=18/29)



Divarasib dose level (mg)	400	400	400	400	200	400	400	400	400	200	200	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400
Baseline SLD (mm)	15	74	87	144	90	121	84	84	109	38	43	65	59	59	87	86	33	43	35	189	90	24	83	59	57	83	35	62	53
Days on treatment	181	167	181	49	84	80	169	210	167	232	138	140	197	173	167	92	168	138	183	124	174	294	161	213	342	160	188	71	265
Active on treatment	Y	N	Y	Y	N	N	N	N	Y	N	N	Y	Y	Y	N	Y	N	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y
Prior KRAS G12Ci	N	N	N	N	Y	N	N	N	Y	N	Y	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N

Indicates ≥4 months on treatment

Assessment of SD based on investigator interpretation of RECIST in light of response of non-target lesions.

Data presented as of clinical cut-off: 21 Nov 2022

Assessment of SD based on investigator interpretation of RECIST in light of response of non-target lesions

Take home messages KRAS G12C mCRC

1. KRAS G12C ist eher aggressiver als andere, häufigere Varianten (G12D, G12V,…)

2. Die Kombinationen aus G12i und EGFR liefern konstant hohe Effektivität

3. Codebreak 300 ist eine positive Phase 3 Studie mit einigen Diskussionspunkten

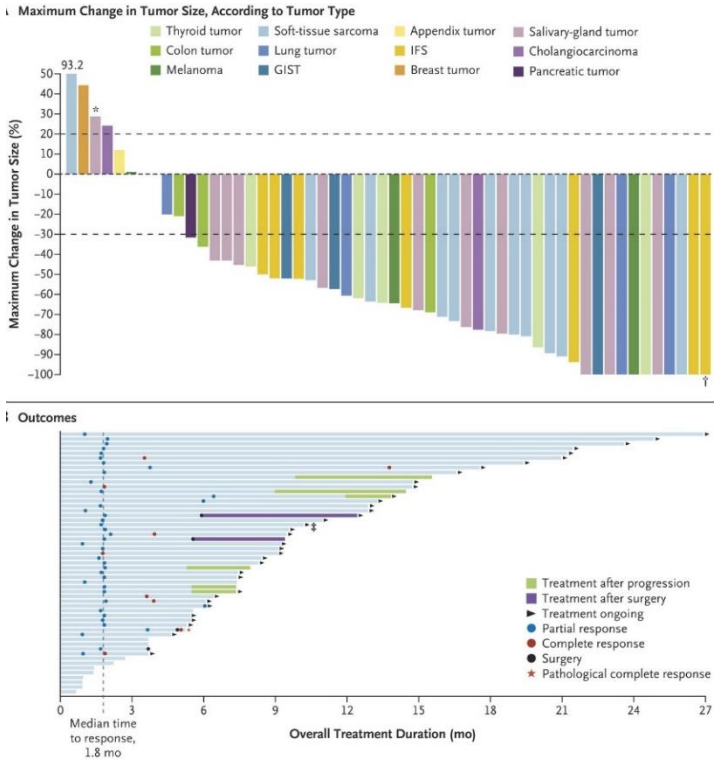
4. Biolgische Regime (KRYTSAL-10) und Kombinationen aus biol. Therapie mit Chemotherapy (CB301) sind in Phase-3 Studien in Entwicklung

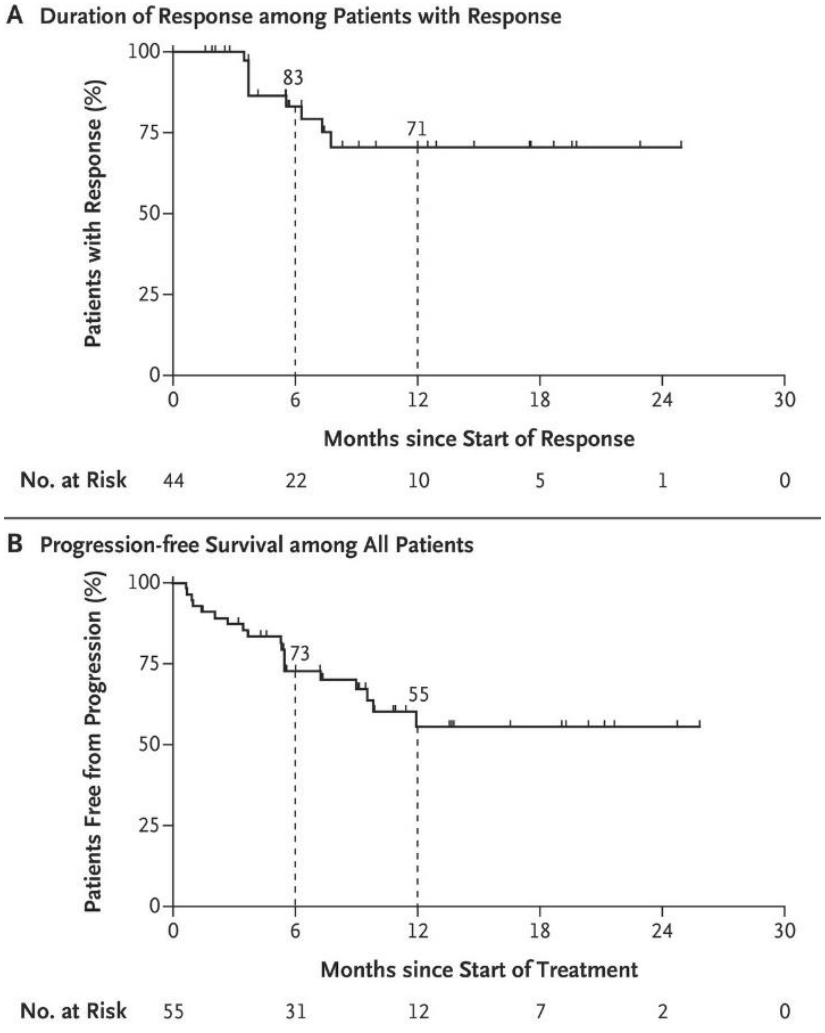
Aspekte

1. EGFR-targetable
2. BRAF V600E MT
3. Her2 pos.
4. KRAS G12C MT
5. Rare alterations

   →Gene fusions

Larotrectinib: TRK Fusions!





A Drilon et al. N Engl J Med 2018;378:731-739

Take home message gene fusions

1. Genfusionen sind sehr selten und noch am häufigsten in MSI-H mCRC*

   →Eher schlechte Prognose*

2. NTRK Fusionen kann man behandeln

3. Gucken Sie auch nach seltenen Alterationen

*Pietrantonio F et al. JNCI 2017

Thank you for your kind attention