2025 DEBATES AND DIDACTICS in Hematology and Oncology

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center
Where Science Becomes Hope

JULY 24 - 27, 2025 • SEA ISLAND, GEORGIA

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Targeted Therapies in Advanced Colorectal Cancer: Beyond RAS and BRAF

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Disclosure

Research funding: Taiho Oncology, Ipsen Pharmaceuticals, GSK, Bristol Myers Squibb, Boehringer Ingelheim, Xencor Inc., ASCO, Cue Biopharma, Inc., Merck, Inhibitex Inc, Arcus Biosciences Inc., AstraZeneca, Loxo/Lilly Oncology

Consulting/Advisory Role: Ipsen Pharmaceuticals, GSK, Cue Biopharma, Inc., Abbvie, Taiho, Bristol Myers Squibb, AstraZeneca, Exelixis, Takeda, Boehringer Ingelheim, Loxo Oncology

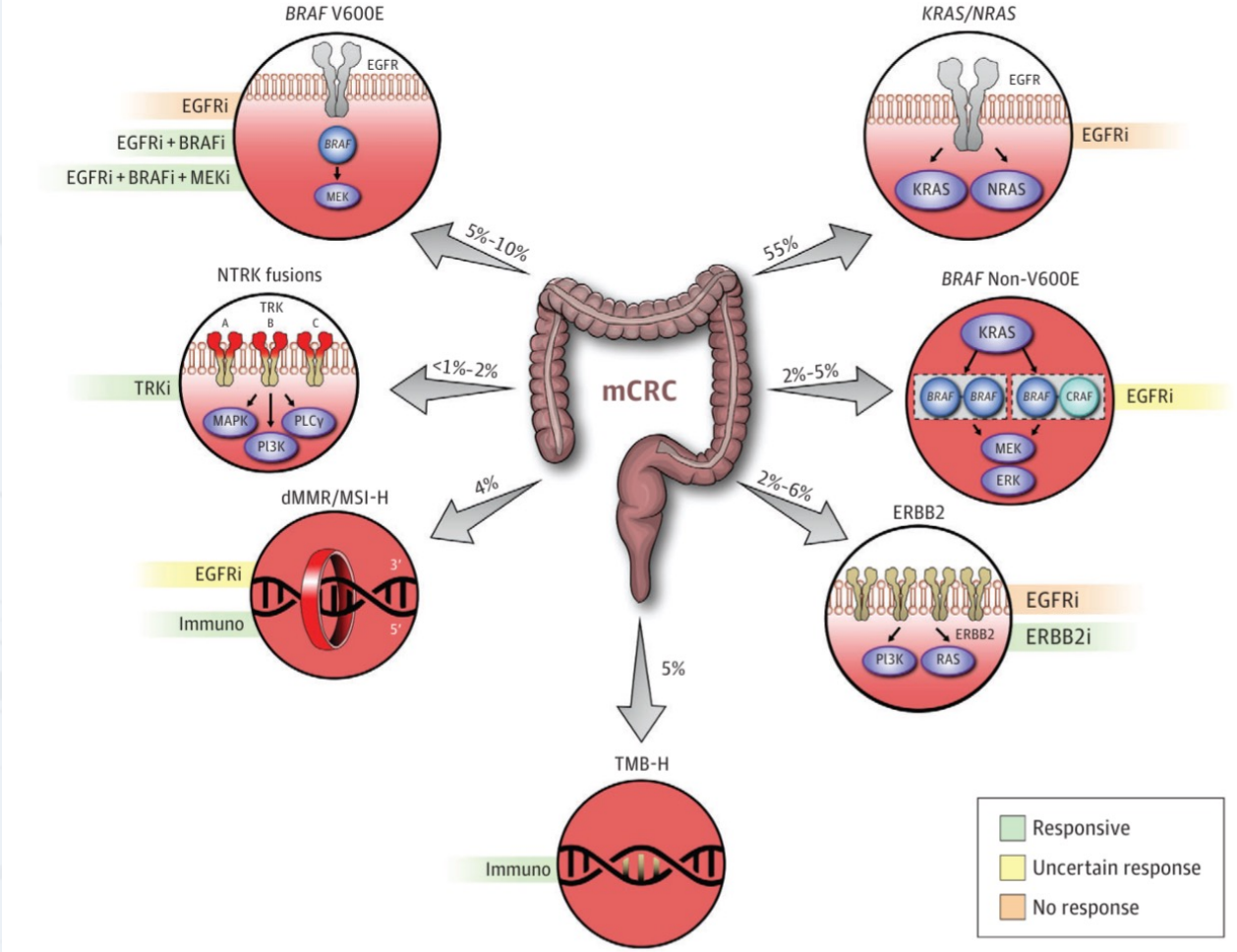
Independent Data Monitoring Committee: Compass Therapeutics, Inc.

Learning Objectives

- Review current and emerging molecular targets in advanced CRC
- Discuss relevant novel targeted therapies
- Identify future treatment strategies

Molecular targets in CRC

Figure 1. Established or Investigational Biomarkers for Treating Metastatic Colorectal Cancer (mCRC)

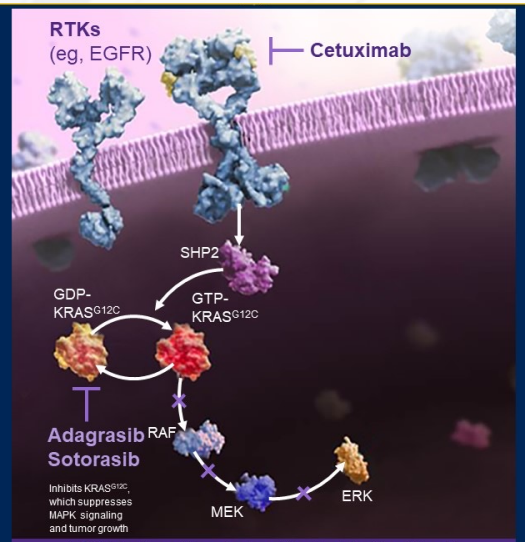


Targets	Drug
EGFR (RAS/RAF wild-type)	• Cetuximab • Panitumumab
VEGF	• Bevacizumab • Ziv-aflibercept • Ramucirumab • Regorafenib
PDL-1 (dMMR or MSI-H)	• Pembrolizumab • Nivolumab +/- ipilumumab • Dostarlimab
BRAF V600E mutation	• Encorafenib + anti-EGFR
ERBB2 (HER2) overexpression (+RAS/RAF wild-type)	• Trastuzumab + Tucatinib Pertuzumab Lapatinib • Trastuzumab deruxtecan
TRK fusion	• Larotrectinib • Entrectanib
RET fusion	• Selpercatinib

Strickler JH, et al. JAMA Oncol. 2022 May 1;8(5):760-769

KRAS G12C

- $KRAS^{G12C}$ mutations occur in 3–4% of CRC, act as oncogenic drivers, and are a negative predictor of cetuximab efficacy[1–4]
- The KRAS protein cycles between guanosine triphosphate (GTP)-on and guanosine diphosphate (GDP)-off states and has a protein resynthesis half-life of ~24 hours[5,6]
- **Adagrasib**, a covalent inhibitor of $KRAS^{G12C}$, irreversibly and selectively binds $KRAS^{G12C}$ in its inactive, GDP-bound state and was optimized for desired properties[7]
- **Sotorasib** is another first-in-class, irreversible inhibitor of the KRASG12C protein[8]
- Combining KRAS G12C inhibitors with an epidermal growth factor receptor (EGFR) inhibitor, may enhance inhibition of KRAS-dependent signaling or overcome adaptive feedback to improve outcomes[9]



EGFR signaling is implicated in feedback reactivation, providing a rational co-targeting strategy for KRAS-mutant colorectal cancer (CRC)

1. Zehir A, et al. *Nat Med*. 2017;23(6):703-713; 2. Schirripa M, et al. *Clin Colorectal Cancer*. 2020;S1533-0028(20)30067-0; 3. NIH TCGA: *The Cancer Genome Atlas*. February 11, 2021; https://www.cbioportal.org; 4. Modest DP, et al. *Oncology*. 2012;83:241-247; 5. Bos JL, et al. *Cell*. 2007;129:865-877; 6. Shukla S, et al. *Neoplasia*. 2014;16(2):115-128; . Hallin J, et al. *Cancer Discov*. 2020;10(1):54-71;8. Lanman BA, et al. J Med Chem. 2020;63:52-65. 9. Tabernero J, et al. Presented at ESMO 23rd World Congress on Gastrointestinal Cancer; June 30-July 3, 2021; virtual.

KRYSTAL-1 Phase 1b/2 CRC cohort Study

CODEBREAK 101 SUBPROTOCOL H STUDY

Yaeger R, et al. N Engl J Med. 2023 Jan 5;388(1):44-54; Kuboki, Y, et al. Nat Med 30, 265–270 (2024)

KRYSTAL-1

Phase 2
CRC Monotherapy

Phase 1b
CRC Combination

Adagrasib 600 mg BID

Adagrasib 600 mg BID + cetuximab

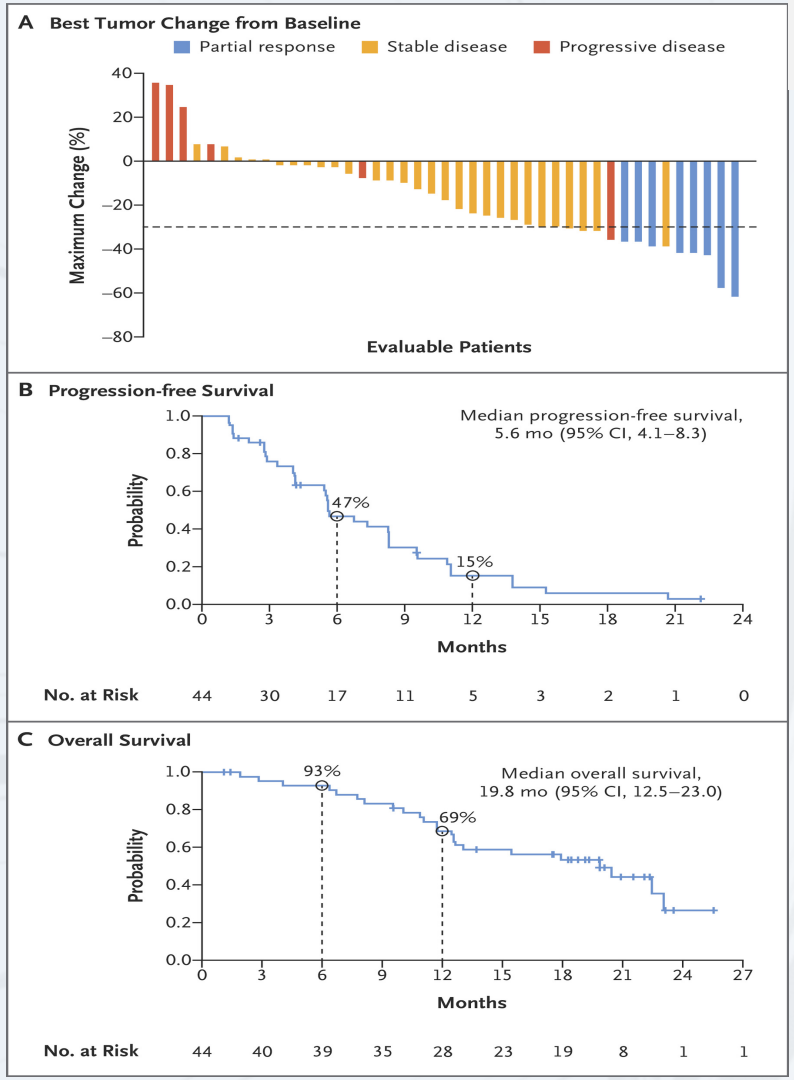
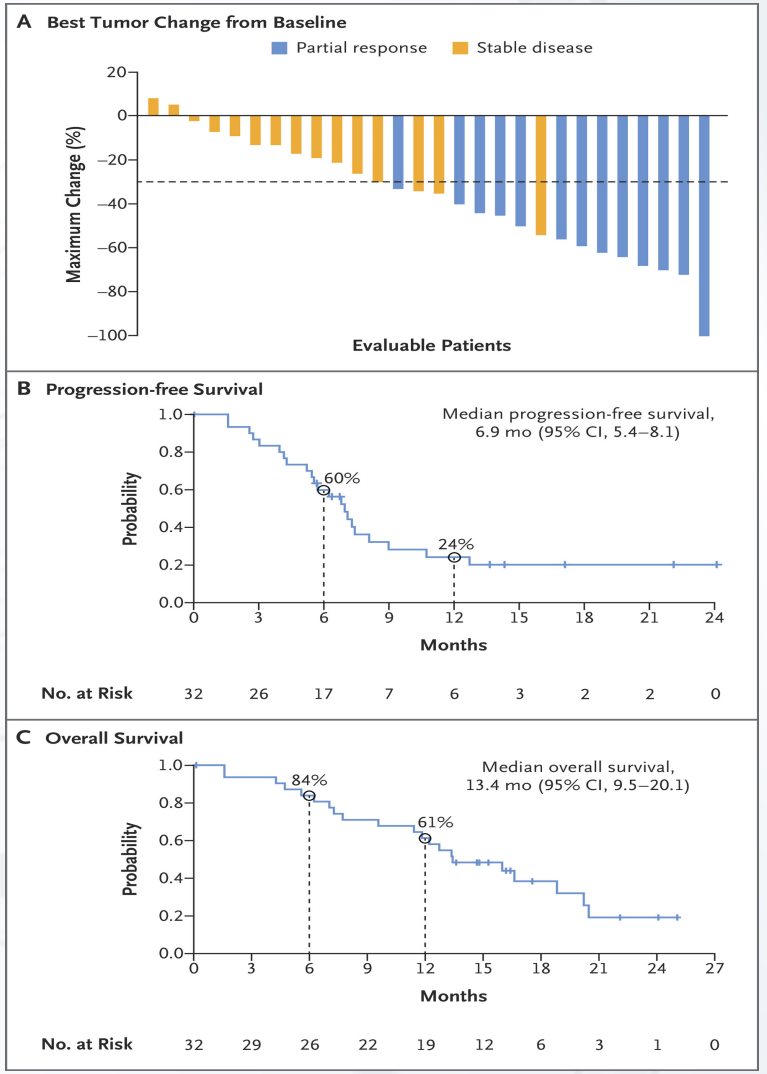


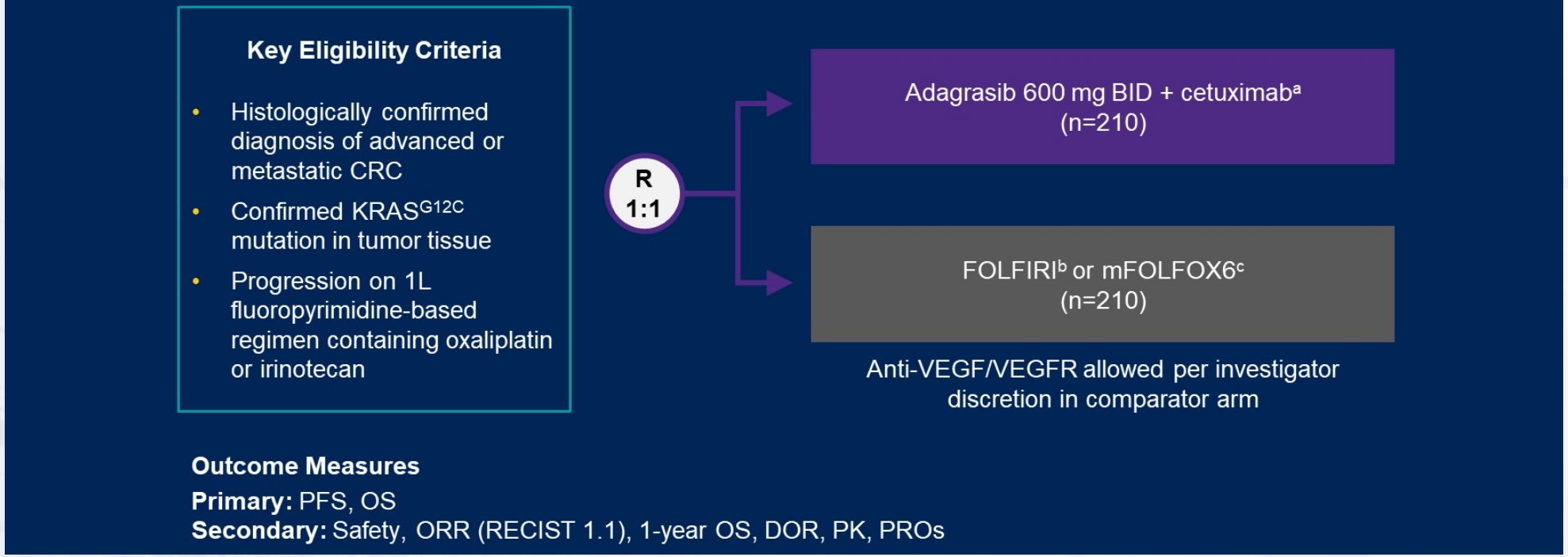
Table 2. Overall Summary of Clinical Activity.*

Variable	Adagrasib Monotherapy (N=43)†	Adagrasib plus Cetuximab (N=28)‡
Objective response§		
Per blinded independent central review — no. of patients	10	13
% (95% CI)	23 (12–39)	46 (28–66)
As confirmed by investigator — no. of patients	8	13
% (95% CI)	19 (8–33)	46 (28–66)
Best overall response — no. (%)		
Complete response	0	0
Partial response	8 (19)	13 (46)
Stable disease	29 (67)	15 (54)
Progressive disease	6 (14)	0
Not evaluable	0	0
Median duration of response — mo	4.3	7.6
95% CI	2.3–8.3	5.7–NE
Median progression-free survival — mo¶	5.6	6.9
95% CI	4.1–8.3	5.4–8.1
Median overall survival — mo¶	19.8	13.4
95% CI	12.5–23.0	9.5–20.1



Yaeger R, et al. N Engl J Med. 2023 Jan 5;388(1):44-54

KRYSTAL-10 (849-010): Phase 3 Randomized, Open-Label Trial of 2L Adagrasib + Cetuximab vs Chemotherapy in metastatic CRC With $KRAS^{G12C}$ Mutation

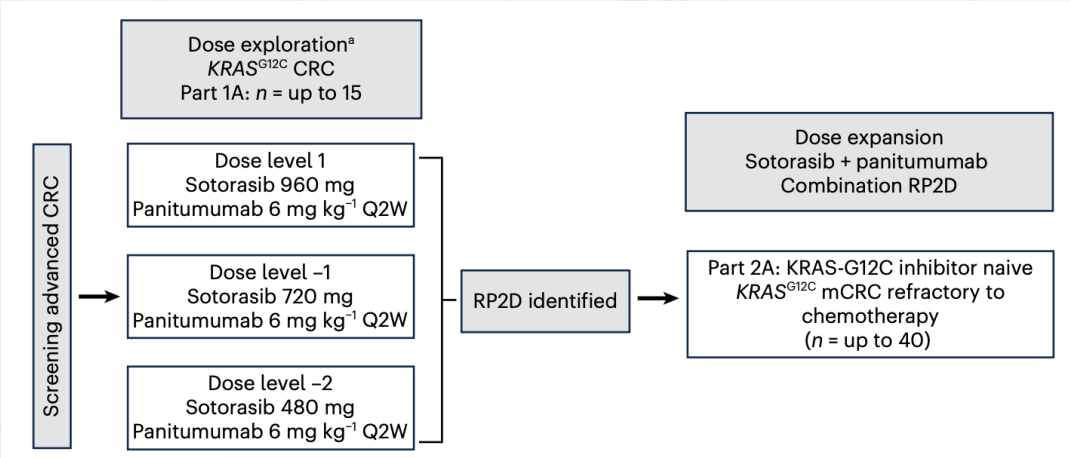


Outcome Measures

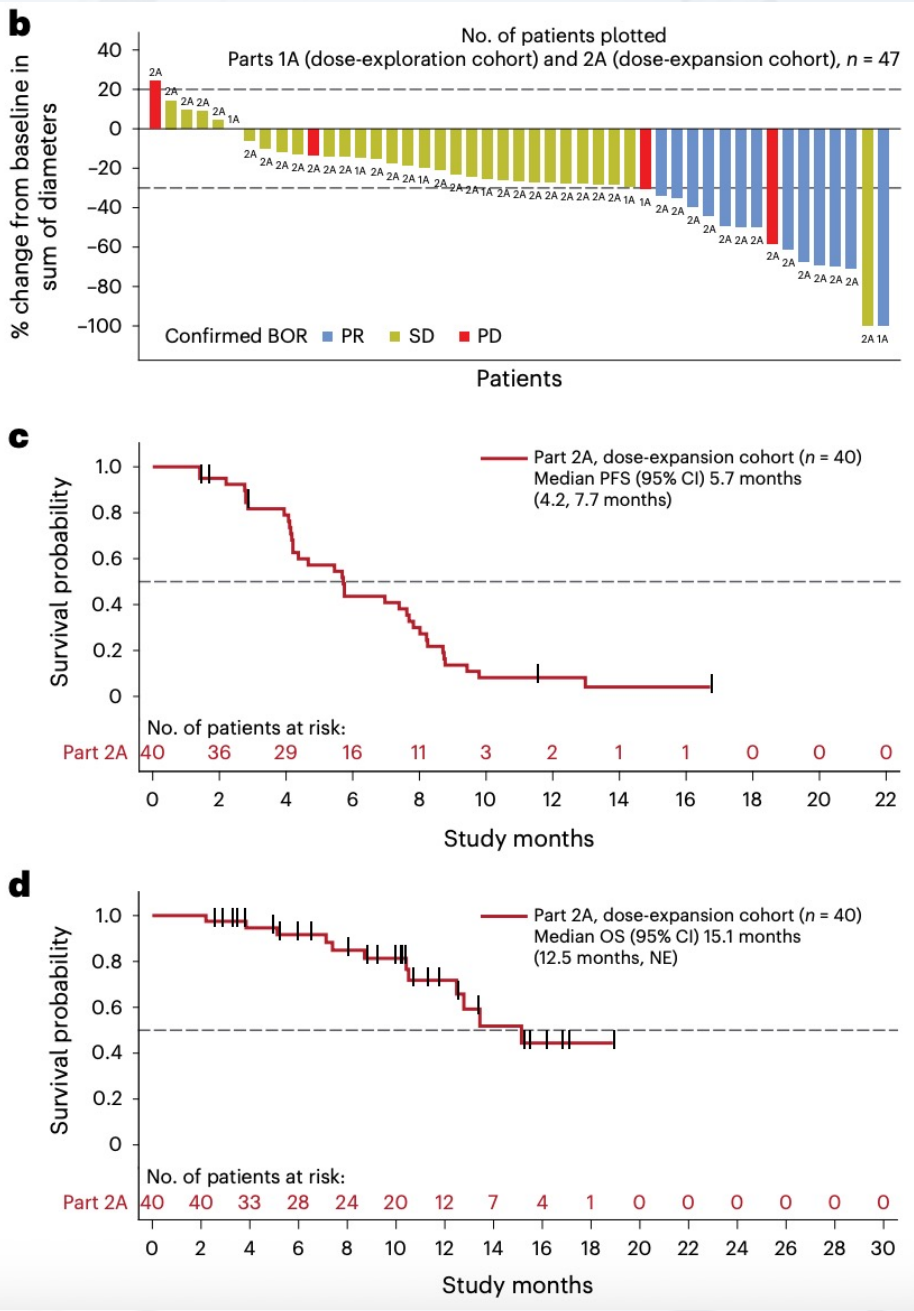
Primary: PFS, OS

Secondary: Safety, ORR (RECIST 1.1), 1-year OS, DOR, PK, PROs

CodeBreaK 101



Outcomes	Dose-exploration cohort (*n*=8)	Dose-expansion cohort (*n*=40)
Objective response, *n* (%) (95% CI)[a]	1 (12.5) (0.3, 52.7)	12 (30.0) (16.6, 46.5)
Disease control rate, *n* (%) (95% CI)[b]	6 (75.0) (34.9, 96.8)	37 (92.5) (79.6, 98.4)
Best response, *n* (%)		
Confirmed complete response	0 (0)	0 (0)
Confirmed partial response	1 (12.5)	12 (30.0)
Stable disease	5 (62.5)	25 (62.5)
Progressive disease	1 (12.5)	3 (7.5)
Not evaluable	0	0
No assessment[c]	1 (12.5)	0
Median time to response, months (range)[d]	1.4 (1.4–1.4)	1.5 (1.3–4.1)
Median duration of response (KM), months (95% CI)[d]	–	5.3 (2.8, 7.4)
Median progression-free survival (KM), months (95% CI)	–	5.7 (4.2, 7.7)
Median overall survival (KM), months (95% CI)	–	15.2 (12.5, NE)



CodeBreaK 101

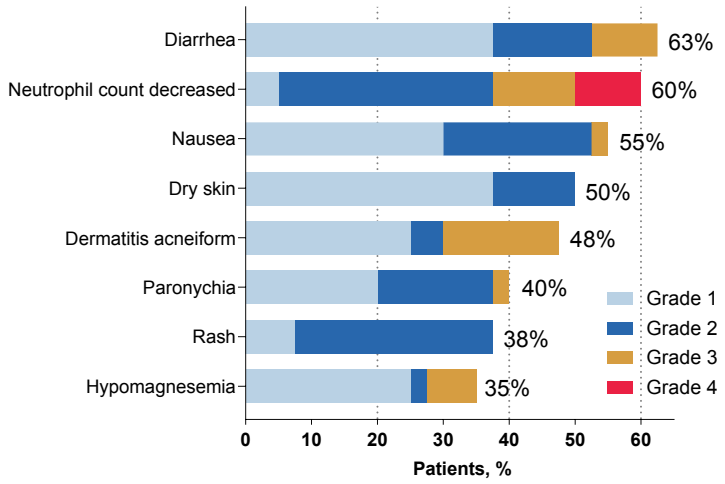
BARCELONA 2024 ESMO congress

Sotorasib, panitumumab, and FOLFIRI in the first-line setting for *KRAS* G12C–mutated metastatic colorectal cancer: safety and efficacy analysis from the phase 1b CodeBreaK 101 study

Salvatore Siena,[1] Kensei Yamaguchi,[2] Jose Ruffinelli,[3] Elena Corral,[4] Yasutoshi Kuboki,[5] Chiara Cremolini,[6] Ivan Victoria,[7] Elena Elez,[8] John Strickler,[9] Muhammad Furqan,[10] Babar Bashir,[11] Chidozie Nduka,[12] Jane Hippenmeyer,[13] Emily Chan,[14] Caihong Xia,[14] Toshiki Masuishi[15]

ORR by Investigator Assessment*	Sotorasib + Panitumumab + FOLFIRI (N = 40)
ORR, n (%)	31 (**78**)
Complete response†	0
Partial response	31 (78)
Stable disease	7 (18)
Progressive disease	1 (3)
Not evaluable‡	1 (3)
Patients with liver metastasis only, n / N (%)	7 / 7 (**100**)
Left-sided tumor, n / N (%)	22 / 27 (82)
Right-sided tumor, n / N (%)	6 / 10 (60)

TRAEs Occurring in ≥ 30% of All patients



CodeBreaK 101 subprotocol H phase 1b, multicenter, open-label study*: sotorasib + panitumumab + FOLFIRI in first-line *KRAS* G12C–mutated mCRC

Key eligibility criteria

- *KRAS* G12C–mutated mCRC, identified through local molecular testing
- $KRAS^{G12C}$ inhibitor–naivety
- No prior systemic treatment for metastatic disease

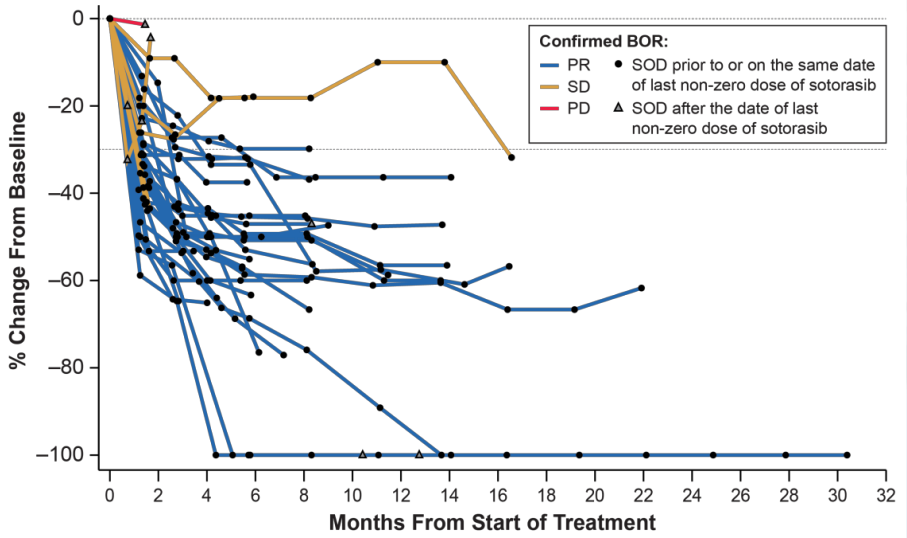
Sotorasib 960 mg was determined as the R2PD in part 1 cohort B‡

Part 2: Cohort F Dose expansion† (N = 40)

Sotorasib: 960 mg PO daily
+
Panitumumab: 6 mg/kg IV Q2W
+
FOLFIRI IV Q2W

Primary endpoint: Safety and tolerability
Secondary endpoints: Anti-tumor efficacy (ORR, DCR, DOR, TTR, PFS per RECIST v1.1, and OS) and PK

Change From Baseline in Sum of Target Lesions



RAS inhibition

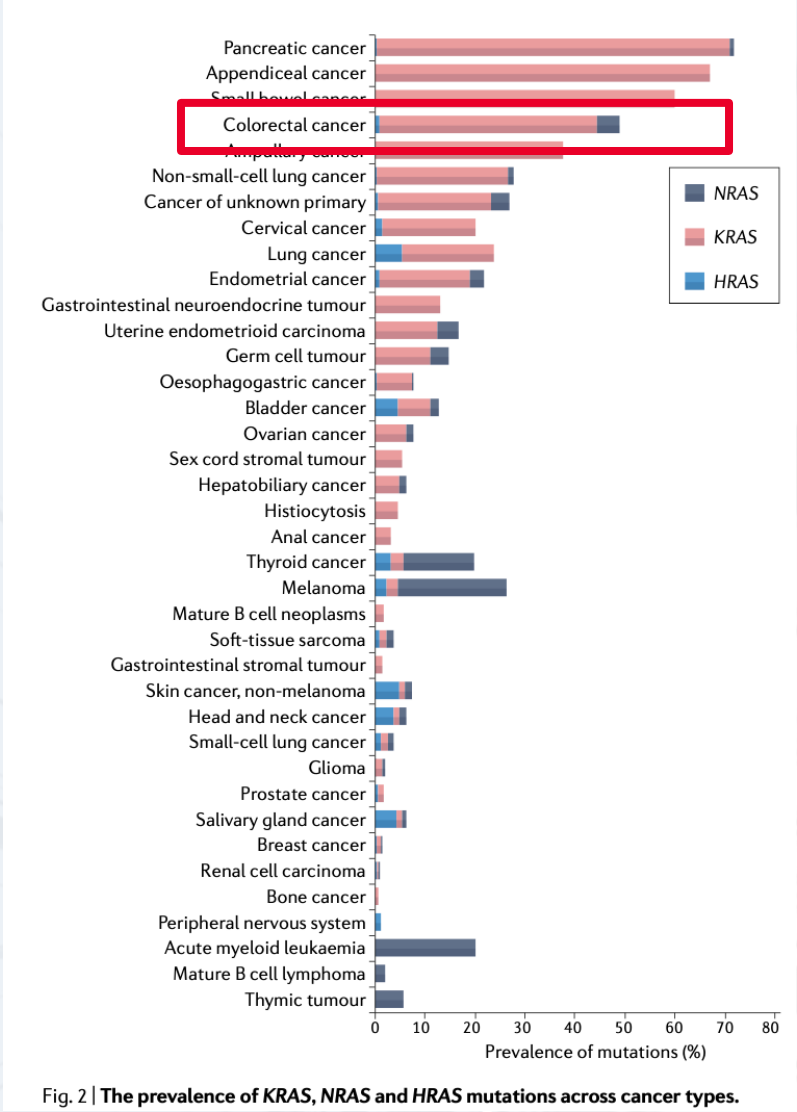
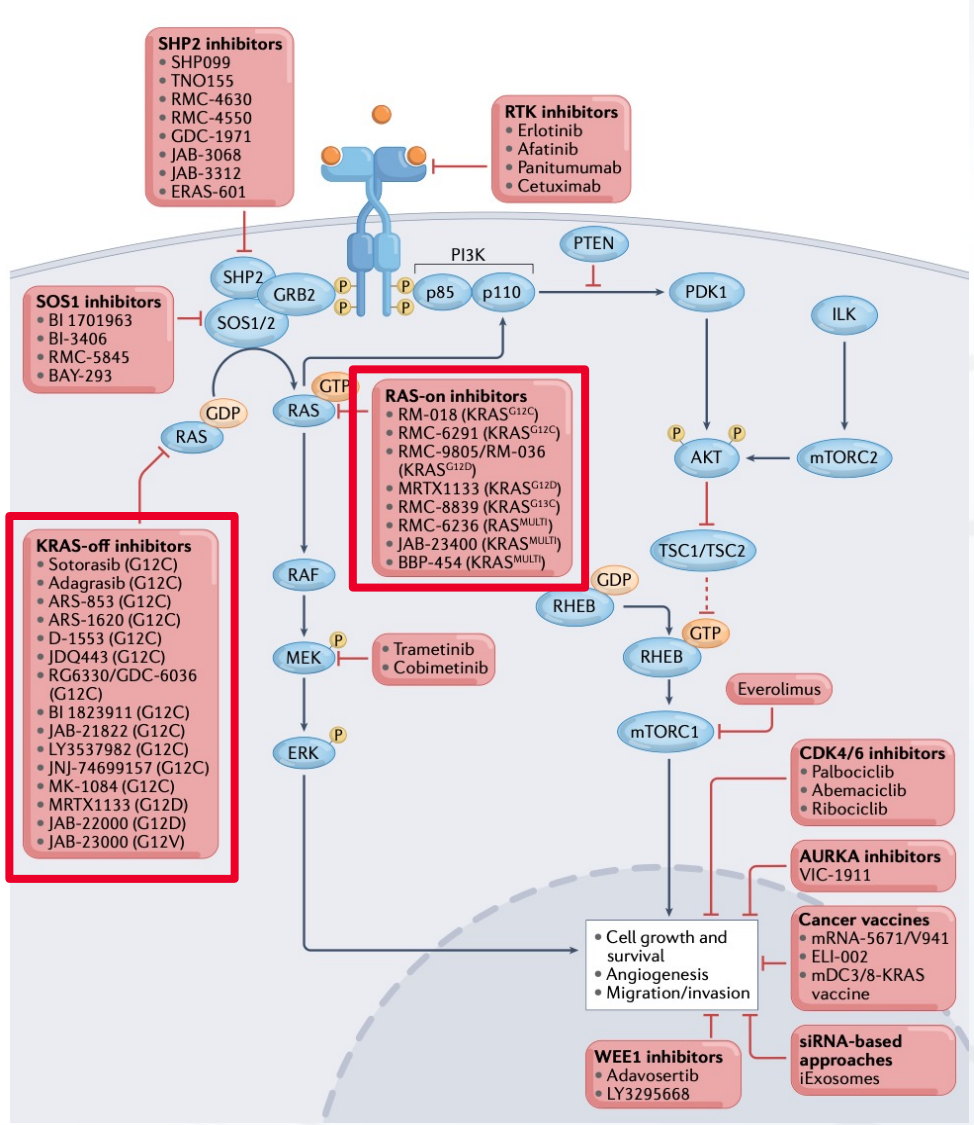
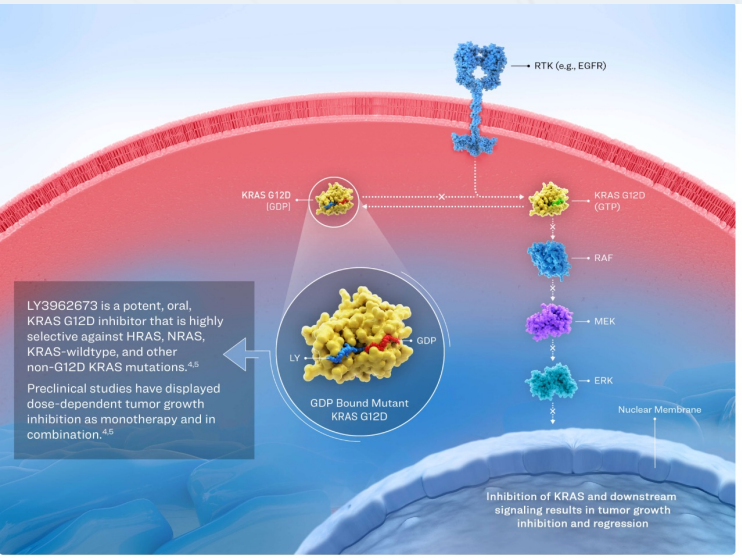


Fig. 2 | **The prevalence of *KRAS*, *NRAS* and *HRAS* mutations across cancer types.**

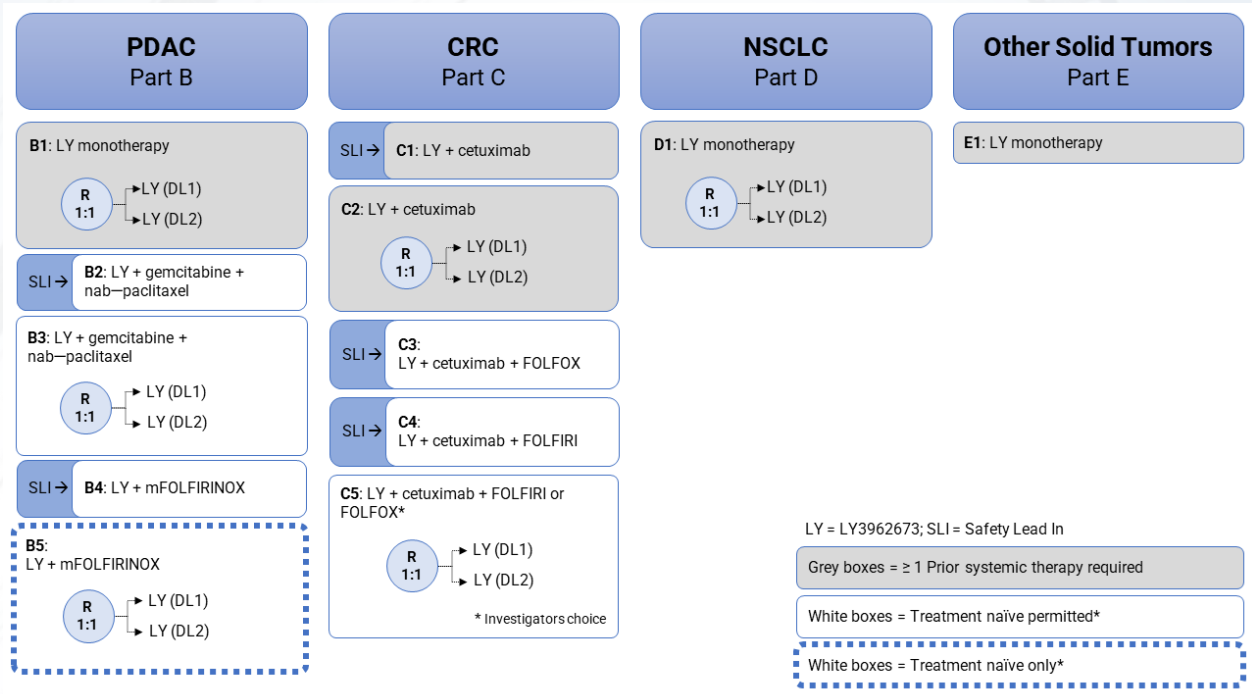


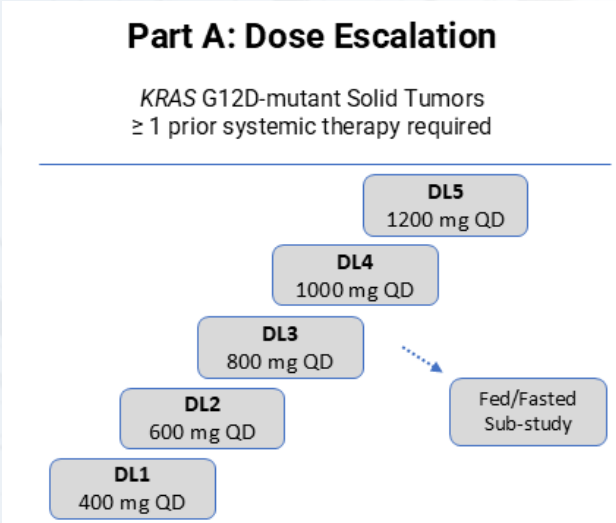
MOONRAY-01: Phase 1a/b of LY3962673 in KRAS G12D-Mutant Solid Tumors



Kano Y[1]; Hofmann MH[2]; Ostrem JML and Shokat KM[3]; Gong X[4]; Iyer C[5]

Figure 2: Phase 1b Trial Schema





b) Part C – CRC

i) Histologically or cytologically confirmed *KRAS* G12D mutant CRC.

ii) **Cohorts C1 and C2:** Must have received ≥ 1 prior fluoropyrimidine-based therapy for CRC.

iii) **Cohorts C3, C4, and Cohort C5:** Individuals may be treatment naïve for advanced or metastatic CRC.

iv) **Cohorts C3, C4, and C5:** Individuals may not have previously received the 5-FU-based regimen planned to be administered on study more than 28 days prior to the start of study treatment.

BRAF V600E

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Encorafenib, Cetuximab, and mFOLFOX6 in *BRAF*-Mutated Colorectal Cancer

BREAKWATER (NCT04607421) is an open-label, multicenter, phase 3 study in first line BRAF V600E-mutant mCRC

Inclusion criteria

- Age ≥16 years (or ≥18 years based on country)
- No prior systemic treatment for metastatic disease
- Measurable disease (RECIST 1.1)
- BRAF V600E-mutant mCRC by local or central laboratory testing
- ECOG PS 0 or 1
- Adequate bone marrow, hepatic, and renal function

Exclusion criteria

- Prior BRAF or EGFR inhibitors
- Symptomatic brain metastases
- MSI-H/dMMR tumors (unless patients were ineligible to receive immune checkpoint inhibitors due to a pre-existing medical condition)
- Presence of a *RAS* mutation

R 1:1:1[a,b] N=637

- EC (n=158)
- EC + mFOLFOX6 (n=236)
- SOC (n=243)[c]

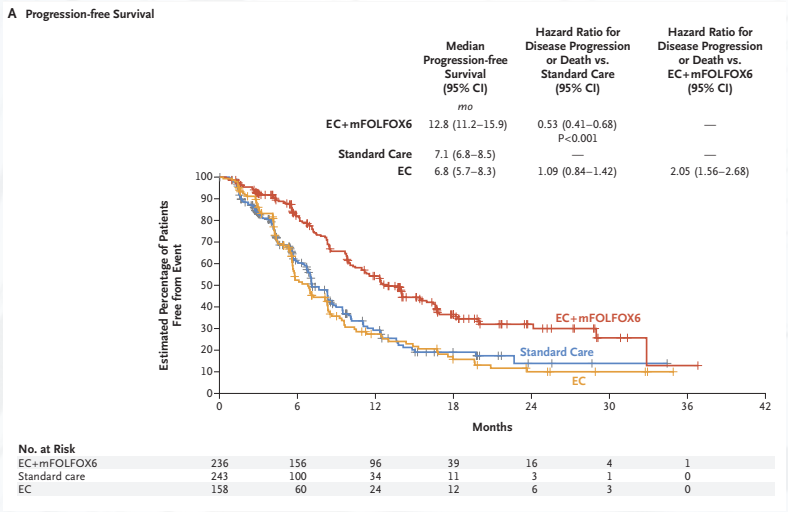
Stratified by regions (US/Canada vs Europe vs Rest of World) and ECOG PS (0 vs 1)

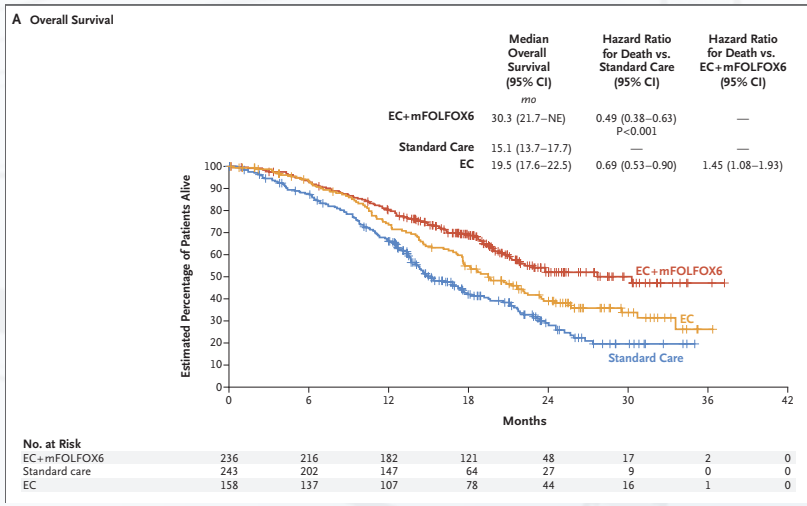
Dual primary endpoints:
PFS and ORR[d] by BICR (EC + mFOLFOX6 vs SOC)

Key secondary endpoint:
OS (EC + mFOLFOX6 vs SOC)

Table 2. Most Frequent Adverse Events during Treatment (Safety Analysis Set).*

Event	EC (N=153)		EC+mFOLFOX6 (N=232)		Standard Care (N=229)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)					
Nausea	31 (20.3)	2 (1.3)	125 (53.9)	7 (3.0)	114 (49.8)	9 (3.9)
Anemia	32 (20.9)	10 (6.5)	107 (46.1)	35 (15.1)	58 (25.3)	9 (3.9)
Diarrhea	28 (18.3)	2 (1.3)	97 (41.8)	3 (1.3)	115 (50.2)	11 (4.8)
Decreased appetite	25 (16.3)	1 (0.7)	87 (37.5)	5 (2.2)	62 (27.1)	3 (1.3)
Vomiting	22 (14.4)	2 (1.3)	84 (36.2)	9 (3.9)	51 (22.3)	5 (2.2)
Neutrophil count decreased	2 (1.3)	1 (0.7)	79 (34.1)	44 (19.0)	67 (29.3)	39 (17.0)
Arthralgia	53 (34.6)	1 (0.7)	73 (31.5)	6 (2.6)	12 (5.2)	1 (0.4)
Rash	27 (17.6)	1 (0.7)	70 (30.2)	3 (1.3)	9 (3.9)	0
Asthenia	28 (18.3)	1 (0.7)	68 (29.3)	12 (5.2)	34 (14.8)	3 (1.3)
Pyrexia	26 (17.0)	2 (1.3)	67 (28.9)	5 (2.2)	36 (15.7)	1 (0.4)
Peripheral neuropathy	2 (1.3)	0	64 (27.6)	18 (7.8)	54 (23.6)	8 (3.5)
Constipation	22 (14.4)	1 (0.7)	63 (27.2)	1 (0.4)	52 (22.7)	1 (0.4)
Peripheral sensory neuropathy	3 (2.0)	0	62 (26.7)	16 (6.9)	54 (23.6)	8 (3.5)
Fatigue	33 (21.6)	2 (1.3)	61 (26.3)	6 (2.6)	64 (27.9)	8 (3.5)
Neutropenia	3 (2.0)	2 (1.3)	56 (24.1)	35 (15.1)	57 (24.9)	23 (10.0)
Alopecia	13 (8.5)	0	53 (22.8)	0	26 (11.4)	0
Platelet count decreased	3 (2.0)	0	53 (22.8)	3 (1.3)	32 (14.0)	4 (1.7)
Lipase increased	10 (6.5)	5 (3.3)	52 (22.4)	40 (17.2)	27 (11.8)	14 (6.1)
Abdominal pain	25 (16.3)	5 (3.3)	47 (20.3)	11 (4.7)	53 (23.1)	3 (1.3)





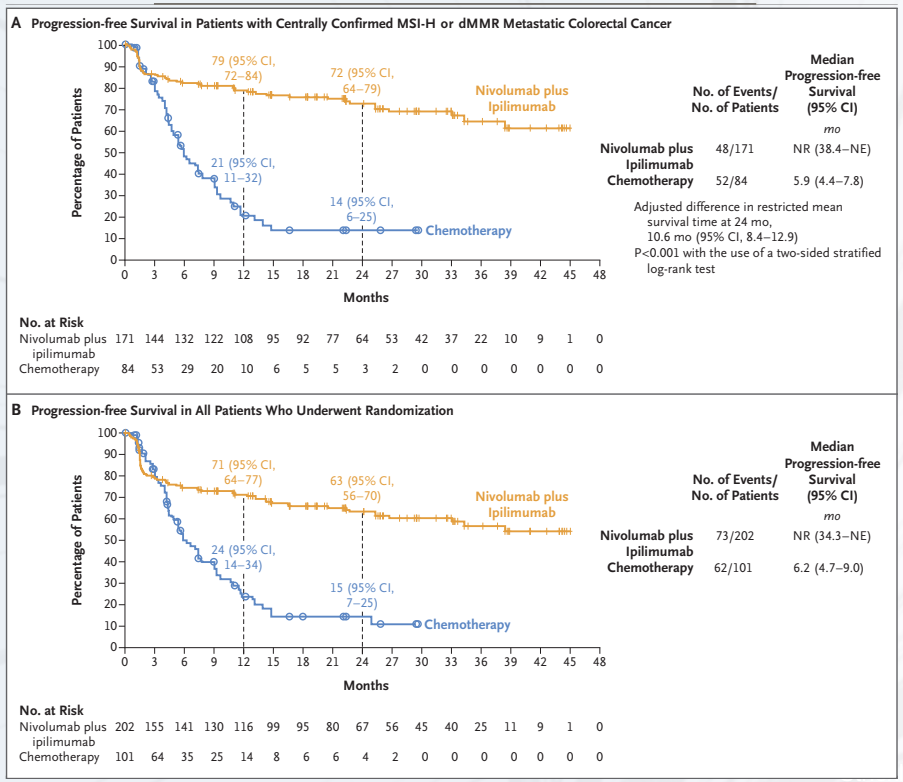
MMRd (CHECKMATE 8HW)

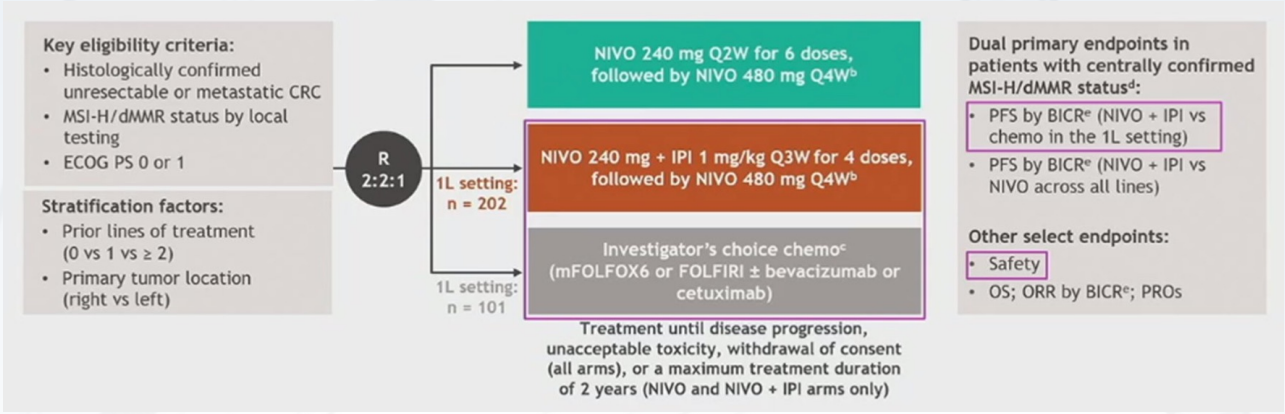
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Microsatellite-Instability–High Metastatic Colorectal Cancer

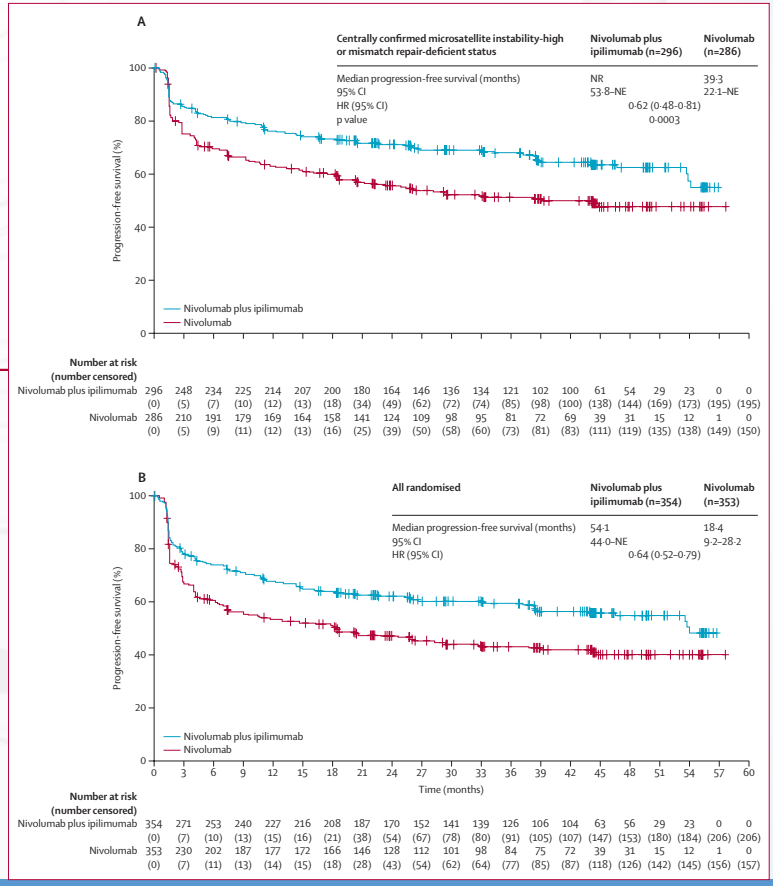
T. André, E. Elez, E. Van Cutsem, L.H. Jensen, J. Bennouna, G. Mendez, M. Schenker, C. de la Fouchardiere, M.L. Limon, T. Yoshino, J. Li, H.-J. Lenz, J.L. Manzano Mozo, G. Tortora, R. Garcia-Carbonero, L. Dahan, M. Chalabi, R. Joshi, E. Goekkurt, M.I. Braghiroli, T. Cil, E. Cela, T. Chen, M. Lei, M. Dixon, S. Abdullaev, and S. Lonardi, for the CheckMate 8HW Investigators*





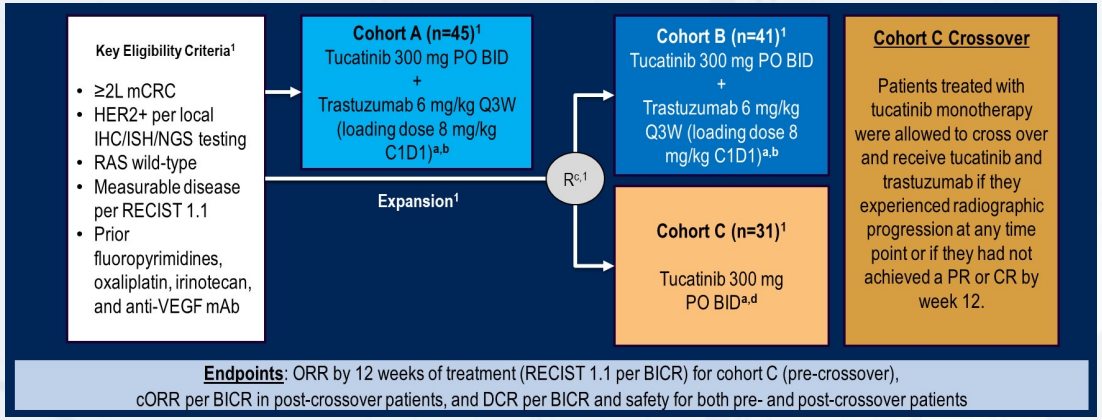
Nivolumab plus ipilimumab versus nivolumab in microsatellite instability-high metastatic colorectal cancer (CheckMate 8HW): a randomised, open-label, phase 3 trial

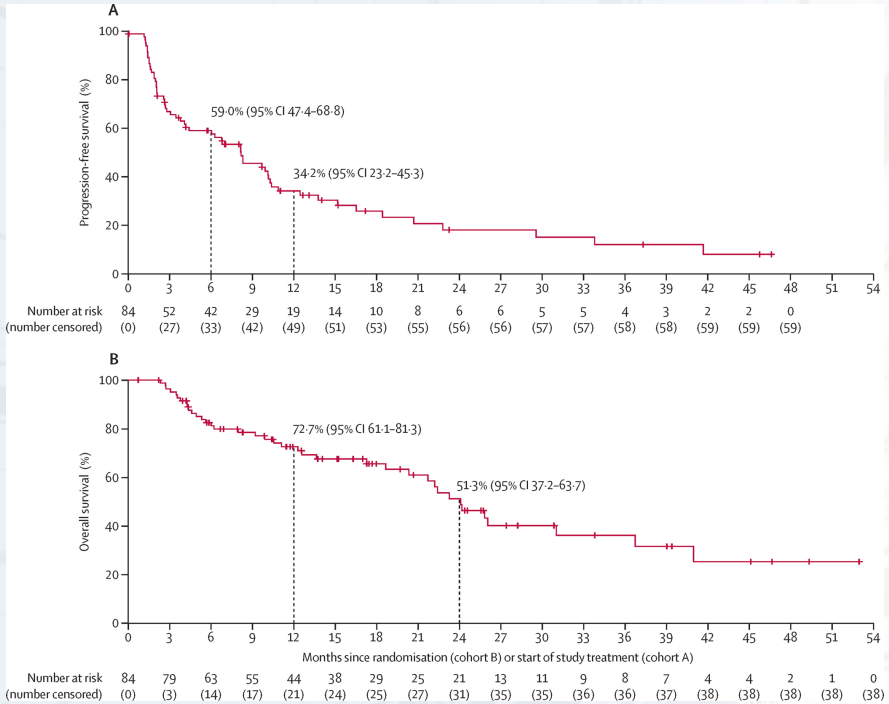
Thierry André, Elena Elez, Heinz-Josef Lenz, Lars Henrik Jensen, Yann Touchefeu, Eric Van Cutsem, Rocio Garcia-Carbonero, David Tougeron, Guillermo Ariel Mendez, Michael Schenker, Christelle de la Fouchardiere, Maria Luisa Limon, Takayuki Yoshino, Jin Li, Jose Luis Manzano Mozo, Laetitia Dahan, Giampaolo Tortora, Myriam Chalabi, Eray Goekkurt, Maria Ignez Braghiroli, Rohit Joshi, Timucin Cil, Francine Aubin, Elvis Cela, Tian Chen, Ming Lei, Lixian Jin, Steven I Blum, Sara Lonardi



Andre T, et al. N Engl J Med. 2024 Nov 28;391(21):2014-2026
André T, et al. Lancet. 2025 Feb 1;405(10476):383-395.

HER2 (MOUNTAINEER)





Tucatinib plus trastuzumab for chemotherapy-refractory, HER2-positive, *RAS* wild-type unresectable or metastatic colorectal cancer (MOUNTAINEER): a multicentre, open-label, phase 2 study

*John H Strickler, Andrea Cercek, Salvatore Siena, Thierry André, Kimmie Ng, Eric Van Cutsem, Christina Wu, Andrew S Paulson, Joleen M Hubbard, Andrew L Coveler, Christos Fountzilas, Adel Kardosh, Pashtoon M Kasi, Heinz-Josef Lenz, Kristen K Ciombor, Elena Elez, David L Bajor, Chiara Cremolini, Federico Sanchez, Michael Stecher, Wentao Feng, Tanios S Bekaii-Saab, on behalf of the MOUNTAINEER investigators**

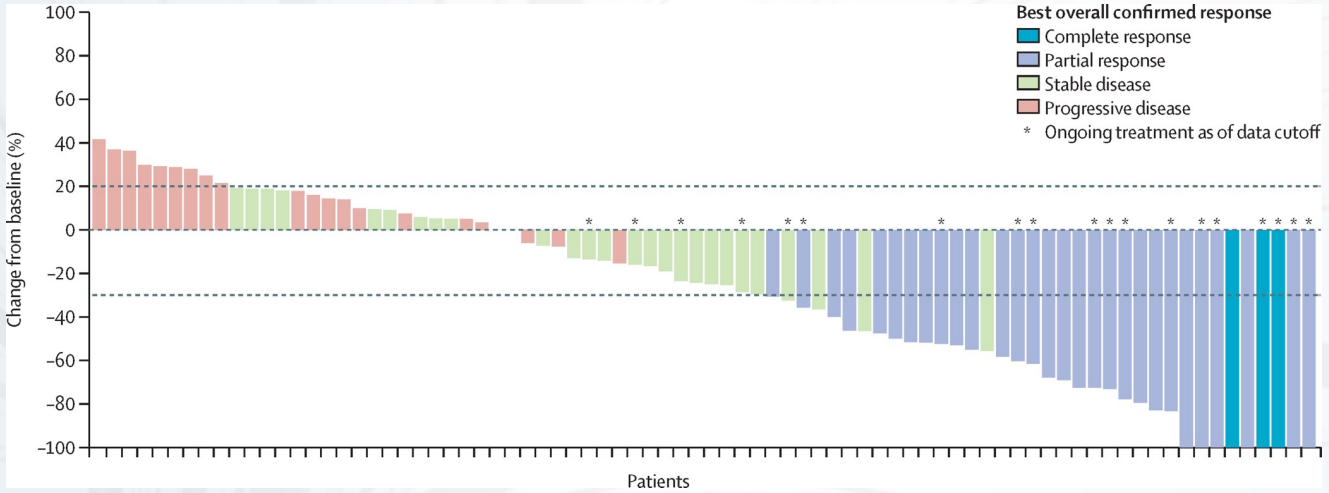
	Tucatinib plus trastuzumab (n=84)	Tucatinib monotherapy (n=30)
Age, years		
Median (IQR)	55·0 (44·5–62·0)	59·5 (52·0–66·0)
<65 years	72 (86%)	19 (63%)
≥65 years	12 (14%)	11 (37%)
Sex		
Male	51 (61%)	15 (50%)
Female	33 (39%)	15 (50%)
Ethnicity		
Hispanic, Latino/a, or of Spanish origin	3 (4%)	1 (3%)
Not Hispanic, Latino/a, or of Spanish origin	64 (76%)	25 (83%)
Not available*	17 (20%)	4 (13%)
Race		
American Indian or Alaska Native	1 (1%)	0
Asian	3 (4%)	0
Black or African American	3 (4%)	3 (10%)
White	65 (77%)	23 (77%)
Multiple	1 (1%)	0
Not available*	11 (13%)	4 (13%)
Geographical region		
North America	69 (82%)	16 (53%)
Europe	15 (18%)	14 (47%)
ECOG performance status score†		
0	50 (60%)	17 (57%)
1	31 (37%)	13 (43%)
2	3 (4%)	0
Site of primary tumour		
Left colon and rectum‡	71 (85%)	27 (90%)
Transverse colon	7 (8%)	0
Right colon§	5 (6%)	3 (10%)
Multiple or overlapping sites	1 (1%)	0
RAS wild-type status¶	84 (100%)	30 (100%)

Strickler JH, et al. Lancet Oncol. 2023 May;24(5):496-508

HER2 (MOUNTAINEER)

- Dual HER2 blockade Tucatinib/trastuzumab had clinically meaningful anti-tumor activity and favorable tolerability
- First FDA-approved anti-HER2 regimen for metastatic colorectal cancer

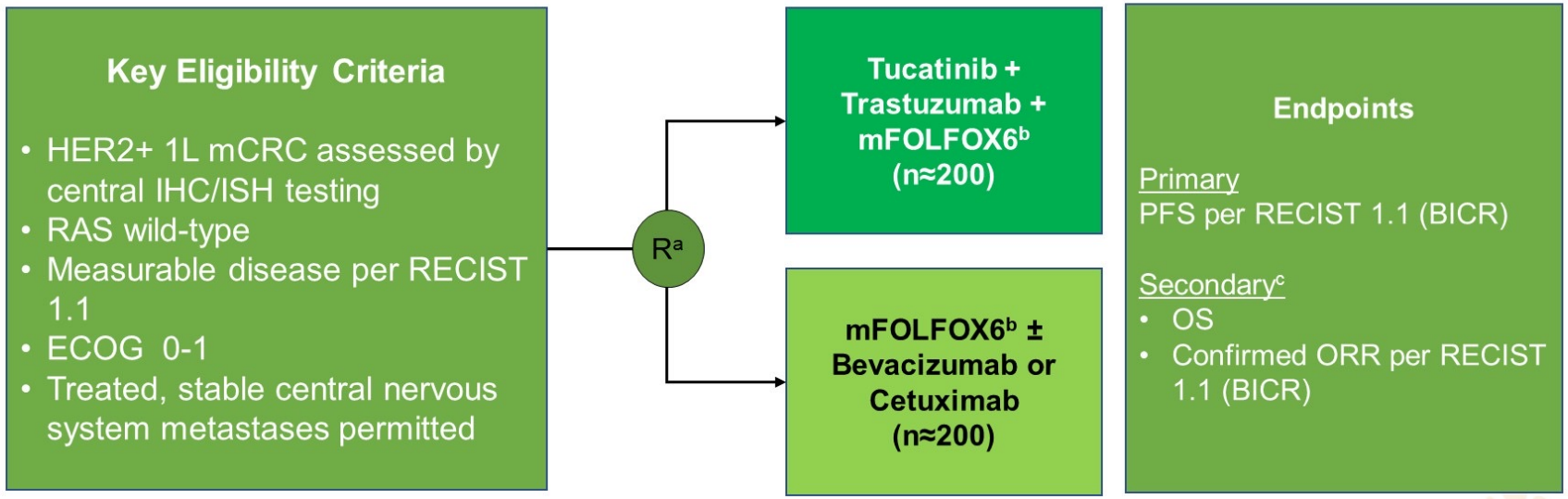
Responses		Tucatinib + Trastuzumab Cohorts A+B n=84[1]	Tucatinib Monotherapy Cohort C n=30	Tucatinib + Trastuzumab Post-Crossover n=28
Best overall response per BICR[a], n (%)	CR	3 (4%)	0	0
	PR	29 (35%)	1 (3.3)	5 (17.9)
	SD[b]	28 (33%)	23 (76.7)	18 (64.3)
	PD	22 (26%)	4 (13.3)	5 (17.9)
	Not available[c]	2 (2%)	2 (6.7)	0
ORR per BICR, % (95% CI)[d]		38 (27.7-49.3)[f]	3 (0.1-17.2)[g]	18 (6.1-36.9)[f]
DCR[e] per BICR, n (%)		60 (71.4)	24 (80.0)	23 (82.1)



	Grade 1–2	Grade 3	Grade 4
Any adverse event	49 (57%)	27 (31%)	6 (7%)
Diarrhoea	52 (60%)	3 (3%)	0
Fatigue	36 (42%)	2 (2%)	0
Nausea	30 (35%)	0	0
Infusion-related reaction	18 (21%)	0	0
Pyrexia	17 (20%)	0	0
Decreased appetite	16 (19%)	0	0
Dermatitis acneiform	16 (19%)	0	0
Chills	15 (17%)	1 (1%)	0
Cough	14 (16%)	0	0
Vomiting	14 (16%)	0	0
Back pain	13 (15%)	2 (2%)	0
Arthralgia	13 (15%)	1 (1%)	0
Dyspnoea	12 (14%)	0	0
Abdominal pain	11 (13%)	2 (2%)	0
Constipation	11 (13%)	1 (1%)	0
Myalgia	11 (13%)	0	0
Anaemia	9 (10%)	0	0
Anxiety	9 (10%)	0	0
Hypertension	9 (10%)	6 (7%)	0
Pain in extremity	7 (8%)	1 (1%)	0
Nephrolithiasis	3 (3%)	1 (1%)	0
Flank pain	3 (3%)	2 (2%)	0
Aspartate aminotransferase increase	3 (3%)	0	2 (2%)
Alanine aminotransferase increase	2 (2%)	1 (1%)	2 (2%)

Strickler JH, et al. Lancet Oncol. 2023 May;24(5):496-508

MOUNTAINEER-03:
Global, Randomised, Open-Label, Phase 3 Trial



- participants may have received a maximum of 2 doses of mFOLFOX6 in the locally advanced unresectable or metastatic setting prior to randomization.
- participants may have received prior chemotherapy for CRC in the adjuvant setting provided that it was completed >6 months prior to enrollment.

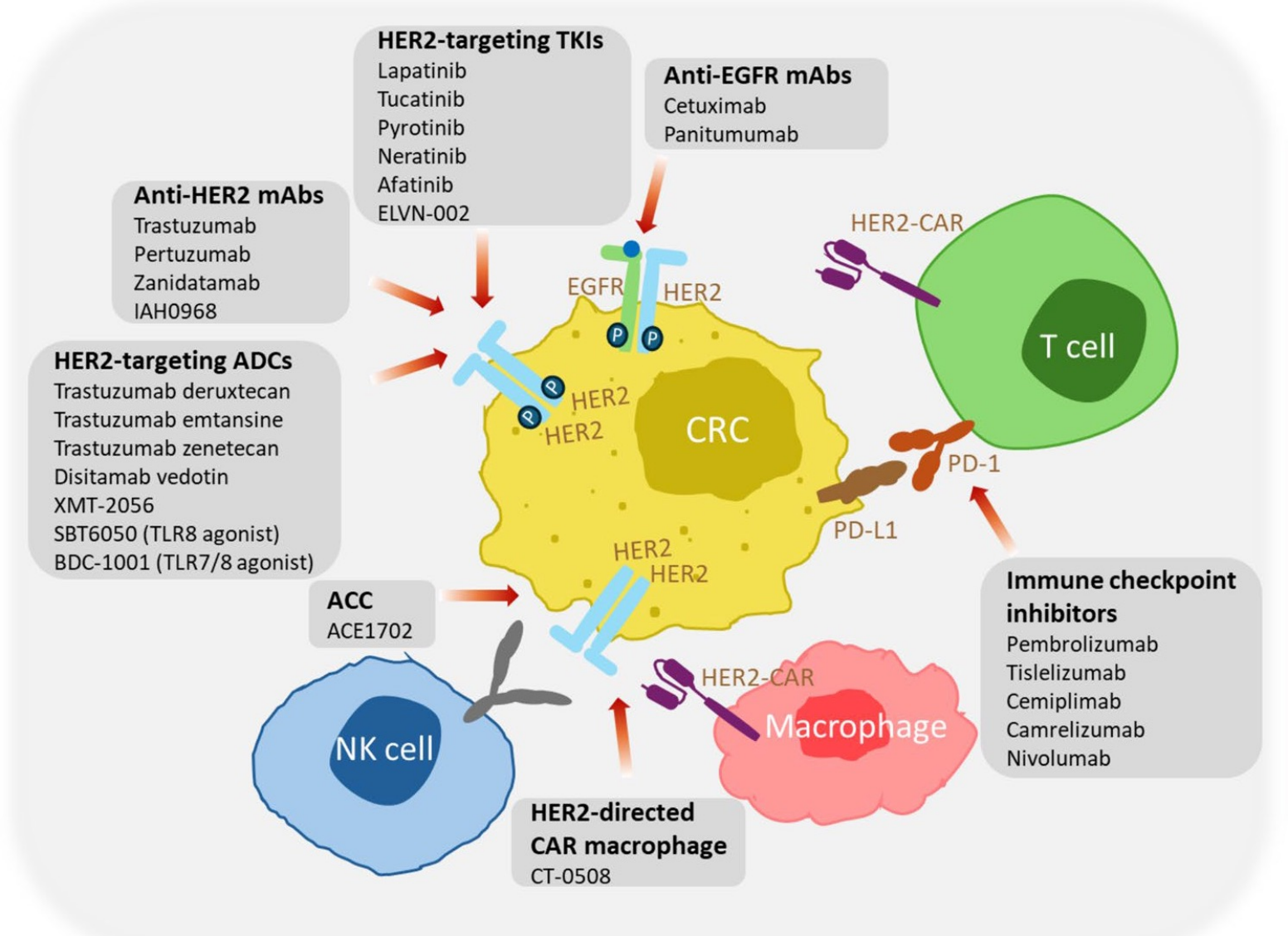
HER2 Inhibition In Advanced CRC

Table 1. HER2-targeted therapies in HER2+ mCRC.

Clinical trial	Therapies	Patients, N	ORR, % (95% CI)	PFS, months
HERACLES-A [17]	Lapatinib + trastuzumab	32 (response evaluable)	28	4.7
MyPathway [18]	Pertuzumab + trastuzumab	57[†] (all patients)	32[†] (20–45)	2.9
		43 (HER2+, *KRAS* WT)	40 (25–56)	5.3
		13 (HER2+, *KRAS* mutated)	8 (0.2–36)	1.4
HERACLES-B [19]	Pertuzumab + T-DM1	31	9.7	4.1
TAPUR [20]	Trastuzumab + pertuzumab	38	25	17.2 weeks
TRIUMPH [21]	Pertuzumab + trastuzumab	30	30 (14–50) in tissue-positive patients	4.0 in tissue-positive patients
			28 (12–49) in ctDNA-positive patients	3.1 in ctDNA-positive patients
DESTINY-CRC01 [22]	Trastuzumab deruxtecan	53	45.3[‡]	6.9
MOUNTAINEER [23]	Tucatinib + trastuzumab	84 (HER2+, *RAS* WT)	38.1[‡] (27.7–49.3)[§]	8.2
HER2-FUSCC-G [24]	Trastuzumab + pyrotinib	11 (ongoing)	45.5	7.8

Strickler JH, et al. Future Oncol. 2025 Feb;21(3):303-311

HER2 Inhibition In Advanced CRC



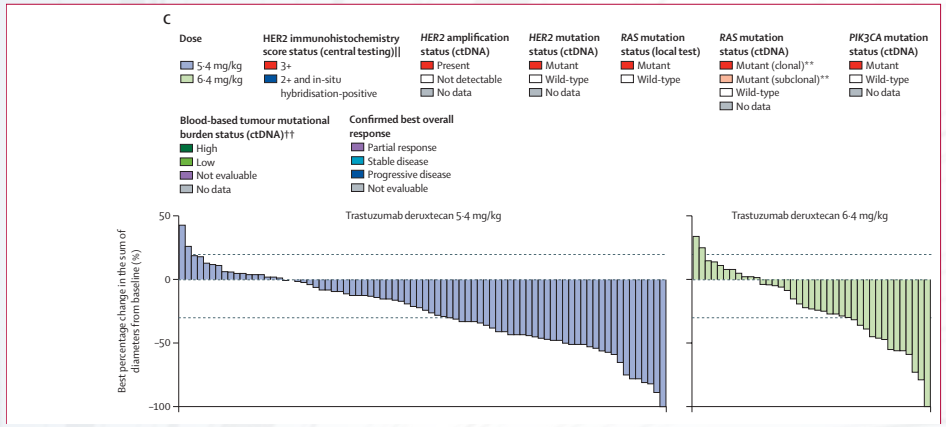
Benli Y, et al. Clin Transl Oncol (2025)

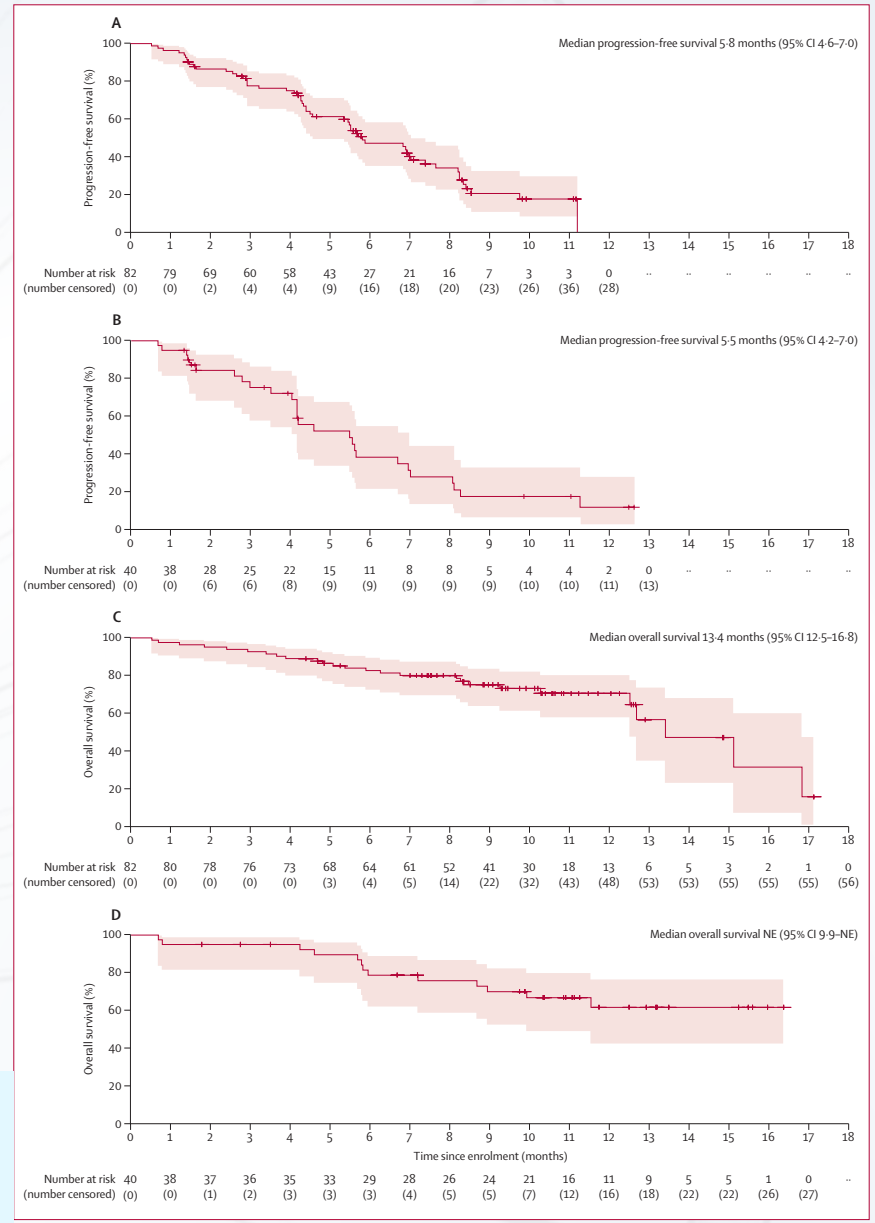
DESTINY CRC-02

Trastuzumab deruxtecan in patients with HER2-positive advanced colorectal cancer (DESTINY-CRC02): primary results from a multicentre, randomised, phase 2 trial

Kanwal Raghav, Salvatore Siena*, Atsuo Takashima, Takeshi Kato, Marc Van den Eynde, Filippo Pietrantonio, Yoshito Komatsu, Hisato Kawakami, Marc Peeters, Thierry Andre, Sara Lonardi, Kensei Yamaguchi, Jeanne Tie, Cristina Gravalos Castro, Hung-Chih Hsu, John H Strickler, Tae-You Kim, Yongjun Cha, Daniel Barrios, Qi Yan, Takahiro Kamio, Kojiro Kobayashi, Aislyn Boran, Makito Koga, John D Allard, Takayuki Yoshino*

	Trastuzumab deruxtecan 5·4 mg/kg group (n=82)	Trastuzumab deruxtecan 6·4 mg/kg group (n=40)
Confirmed objective response rate* (% [95% CI)	31 (37·8% [27·3–49·2])	11 (27·5% [14·6–43·9])
Complete response	0	0
Partial response	31 (38%)	11 (28%)
Stable disease	40 (49%)	23 (58%)
Progressive disease	8 (10%)	4 (10%)
Not evaluable	3 (4%)	2 (5%)
Confirmed disease control rate* (% [95% CI])	71 (86·6% [77·3–93·1])	34 (85·0% [70·2–94·3])
Confirmed clinical benefit rate* (% [95% CI])	37 (45·1% [34·1–56·5])	13 (32·5% [18·6–49·1])
Median duration of response*, months (95% CI)	5·5 (4·2–8·1)	5·5 (3·7–NE)
Median progression-free survival*, months (95% CI)	5·8 (4·6–7·0)	5·5 (4·2–7·0)
Patients with events	54 (66%)	27 (68%)
Median overall survival, months (95% CI)	13·4 (12·5–16·8)	NE (9·9–NE)
Patients with events	26 (32%)	13 (33%)
Median follow-up, months (IQR)	8·9 (6·7–10·5)	10·3 (5·9–12·7)
Median treatment duration†, months (IQR)	5·5 (3·6–8·4)	4·9 (2·8–8·5)
Median total dose†, mg/kg (IQR)	37·8 (26·9–59·4)	40·8 (25·4–66·1)
Median cycles initiated† (IQR)	7·0 (5·0–11·0)	7·0 (4·0–11·0)

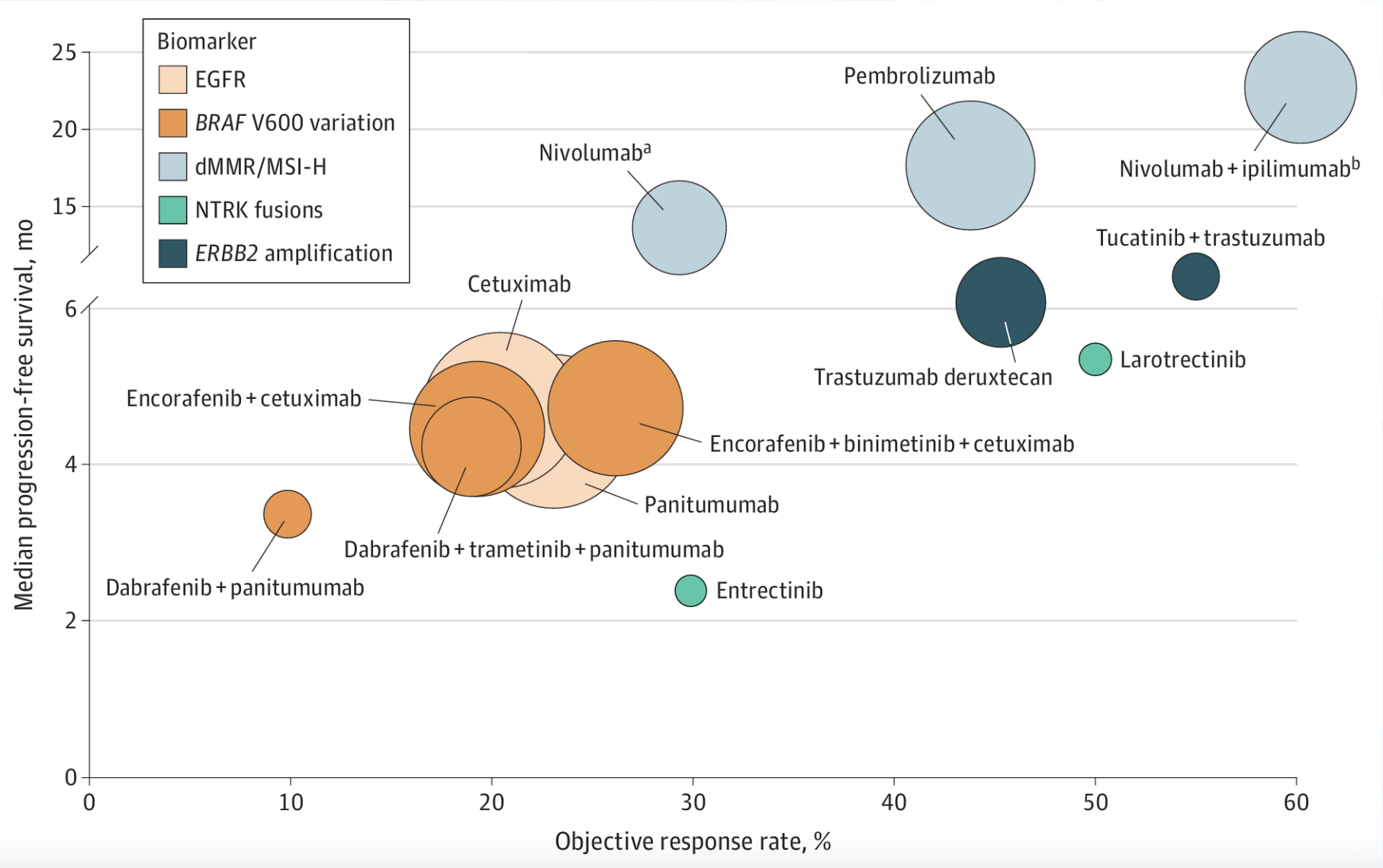




- most common G3 or worse TRAE – 5.4 mg/kg (neutropenia 16%, anemia 7%, nausea 7%, and leucopenia 6% vs. 6.4 mg/kg (neutropenia 26%, anemia 21%, thrombocytopenia 10% leucopenia 10%).
- TR-SAE 13% vs. 15% resp. Death in one patient (1%) in the 5.4 mg/kg group (due to hepatic failure)
- interstitial lung disease or pneumonitis 8% (G1 or 2) vs. 13% (G1 or 2 X 4; one grade 5).

Raghav K, et al. Lancet Oncol. 2024 Sep;25(9):1147-1162.

ORR, PFS



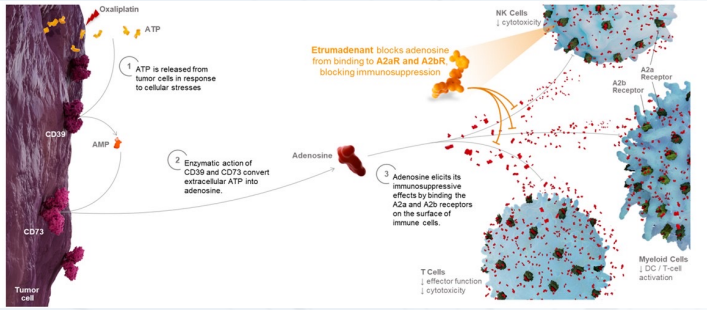
Strickler JH, et al. JAMA Oncol. 2022 May 1;8(5):760-769

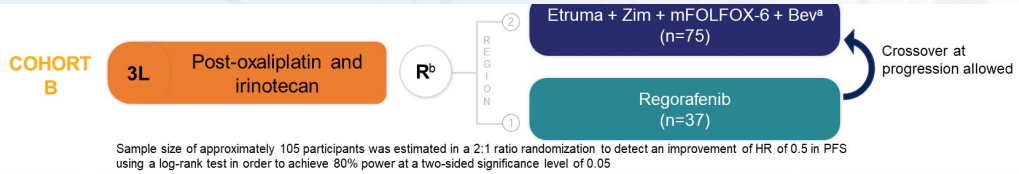
Adenosine inhibition (ARC – 9)

2024 ASCO ANNUAL MEETING

ARC-9: A Randomized Study to Evaluate Etrumadenant Based Treatment Combinations in Previously Treated Metastatic Colorectal Cancer

Zev A. Wainberg,[1] Sae-Won Han,[2] Soohyeon Lee,[3] Keun-Wook Lee,[4] Scott Kopetz,[5] Jonathan Mizrahi,[6] Yong Sang Hong,[7] Francois Ghiringhelli,[8] Antoine Italiano,[9] David Tougeron,[10] Brandon Beagle,[11] Mathew Boakye,[11] Tingting Zhao,[11] Joon Rhee,[12] Dimitry S.A. Nuyten,[11] Michael Cecchini[13]





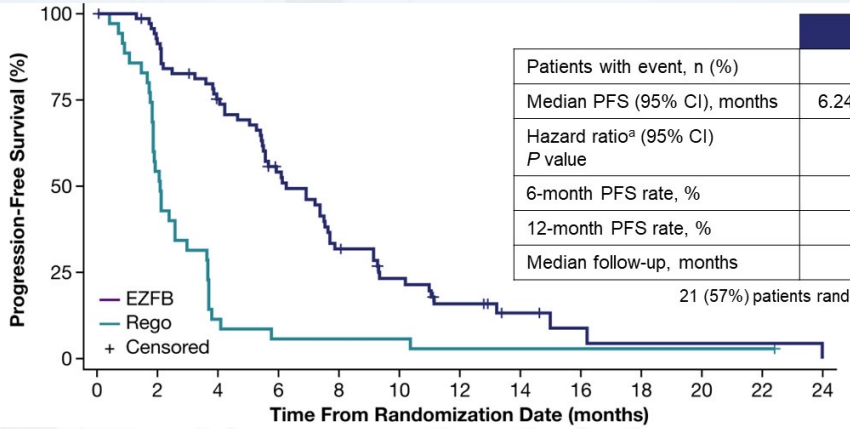
Sample size of approximately 105 participants was estimated in a 2:1 ratio randomization to detect an improvement of HR of 0.5 in PFS using a log-rank test in order to achieve 80% power at a two-sided significance level of 0.05

Key inclusion criteria	• Histologically confirmed unresectable mCRC
	• Measurable disease per RECIST v1.1
	• ECOG PS of 0 or 1
	• Disease progression **on or after** treatment with oxaliplatin and irinotecan containing chemotherapy in combination with anti-VEGF(R) or anti-EGFR
	  • **≤ 2 prior lines** of treatment in the metastatic setting
	  • Re-introduction of an initially successful induction regimen, per investigator judgement, not counted as one additional line of treatment
	  • **Metastatic setting:** could not have progressed ≤2 months of last dose of oxaliplatin
	  • **Adjuvant setting:** will count as line of treatment if progressed ≤6 months of last dose
	  • Patients treated with FOLFIRINOX meet this eligibility criteria if they did not progress ≤2 months of last dose of oxaliplatin

Key exclusion criteria	• Prior treatment with immune checkpoint blockade therapies • Mutation in the *BRAF* oncogene; patients with unknown *BRAF* status will be required to undergo testing at a local laboratory and provide results at screening

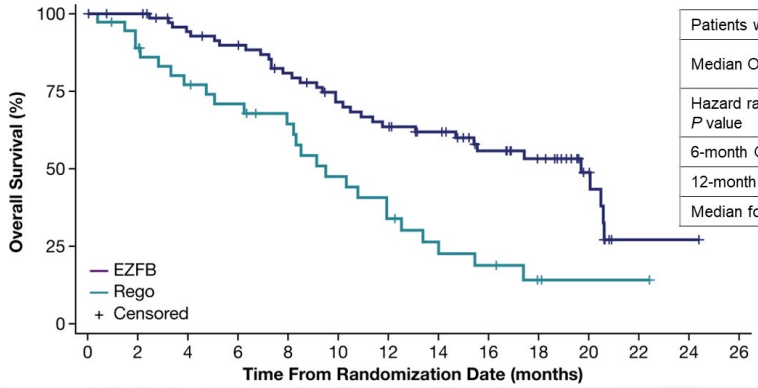
Primary Endpoints
PFS (Investigator assessed)

Key Secondary Endpoints
OS
ORR (Investigator assessed)
Safety



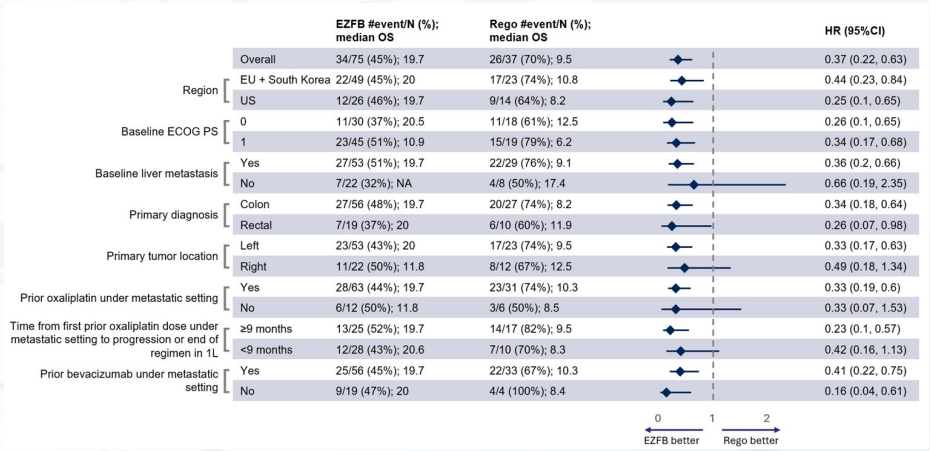
	EZFB	Rego
Patients with event, n (%)	58 (77)	34 (92)
Median PFS (95% CI), months	6.24 (5.49, 7.52)	2.07 (1.84, 2.96)
Hazard ratio[a] (95% CI) *P* value	0.27 (0.17, 0.43) <0.001	
6-month PFS rate, %	54	6
12-month PFS rate, %	16	3
Median follow-up, months	20.4	

21 (57%) patients randomized to rego crossed over to EZFB



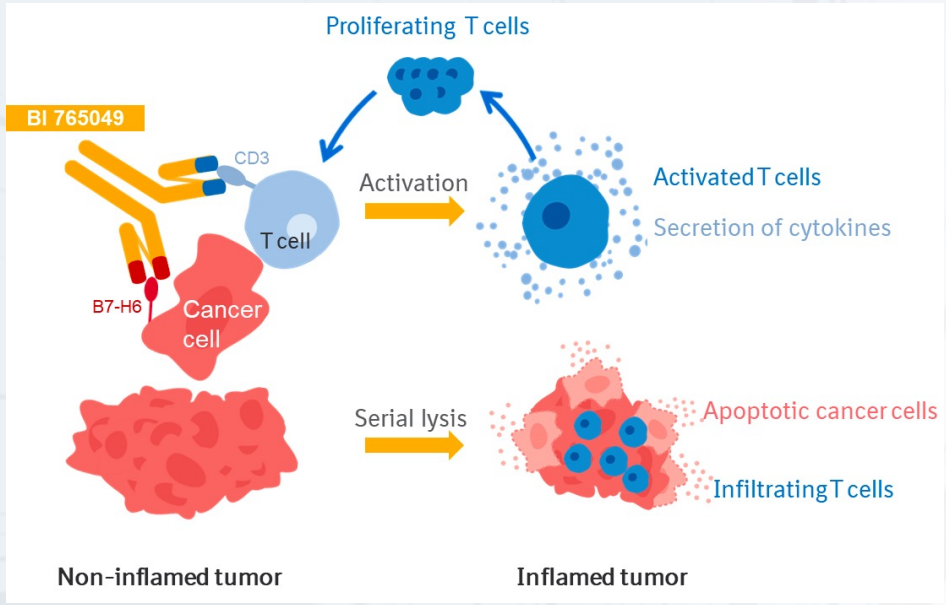
	EZFB	Rego
Patients with event, n (%)	34 (45)	26 (70)
Median OS (95% CI), months	19.68 (14.69, 20.60)	9.49 (7.95, 12.52)
Hazard ratio[a] (95% CI) *P* value	0.37 (0.22, 0.63) <0.001	
6-month OS rate, %	90	71
12-month OS rate, %	64	34
Median follow-up, months	20.4	

21 (57%) patients randomized to rego crossed over to EZFB



B7H6 TCE (1454-0015)

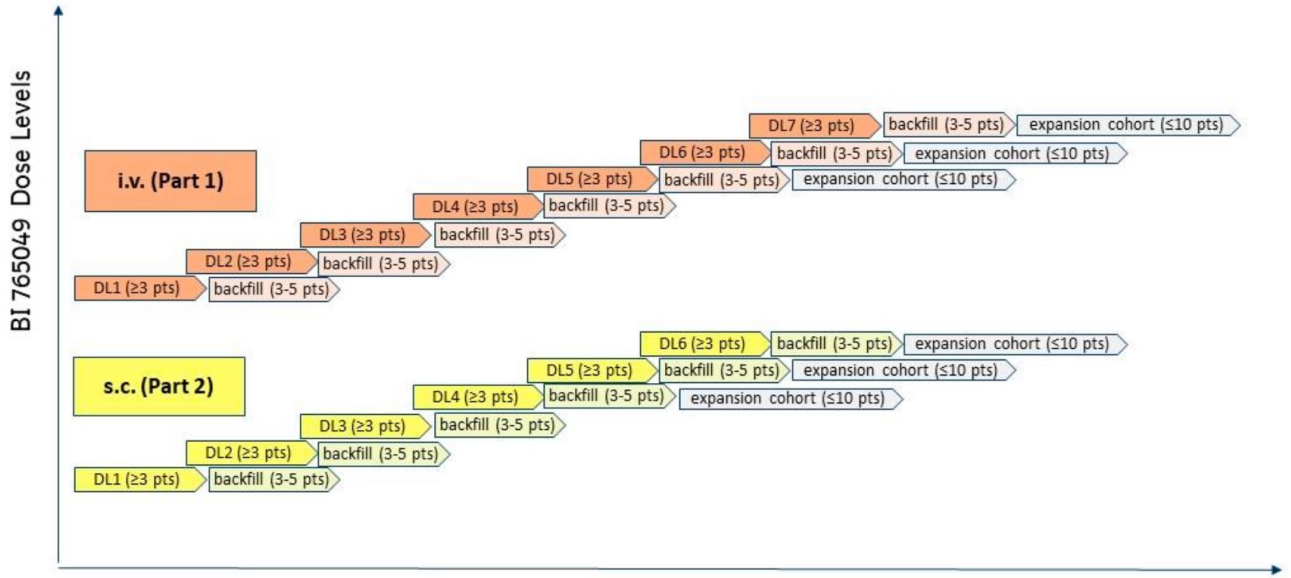
Phase I study of BI 765049 in advanced, unresectable, and/or metastatic colorectal carcinoma (CRC), gastric carcinoma (GC), or pancreatic ductal adenocarcinoma (PDAC)



Engages any T cell (independent of T-cell receptor specificity)

- ***Apoptosis of tumor cells***
- ***Activation, cytokine secretion, and local proliferation of CTLs***
- ***Conversion of a non-inflamed into an inflamed tumor microenvironment***

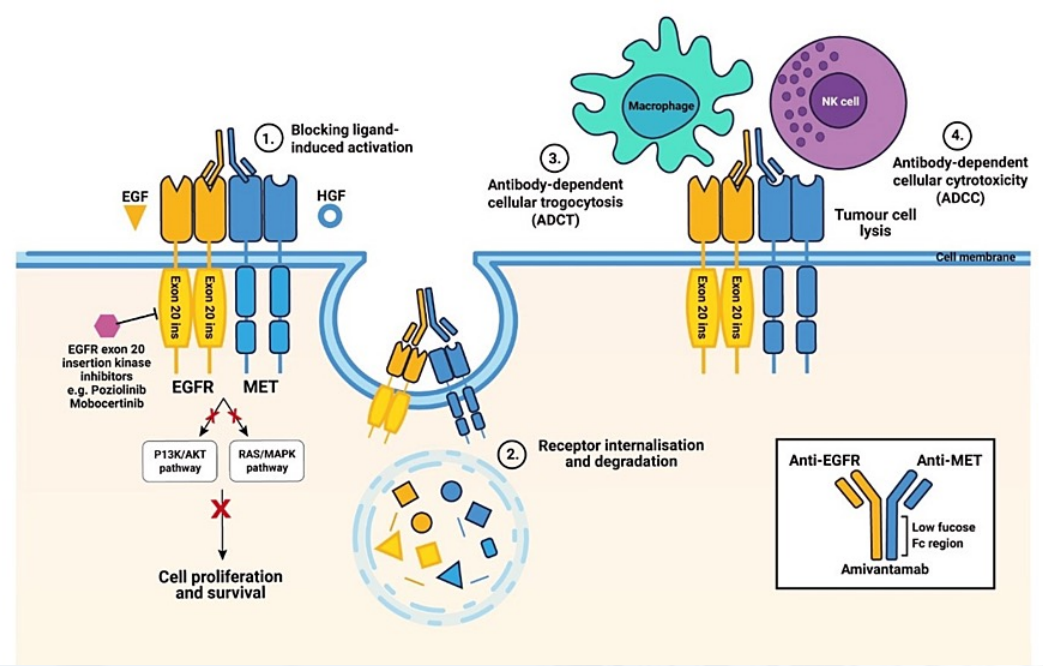
BI 765049 creates a bridge between B7-H6-expressing tumor cells and Cytolytic T cells (CTLs) and directs their cytolytic activity selectively to these tumor cells



c-MET inihibition (OrigAMI)

Randomized phase 3 study of amivantamab versus cetuximab and mFOLFOX6 or FOLFIRI as first-line treatment in left-sided RAS/BRAF WT mCRC

AMIVANTAMAB



Key Eligibility Criteria

- Unresectable or metastatic left-sided CRC
- Treatment naïve for unresectable or metastatic CRC
- KRAS/NRAS/BRAF wild type

28-day Treatment Cycles

Randomization (1:1; N=1000)

Arm A
Amivantamab* + mFOLFOX6 or FOLFIRI (N=500)

Arm B
Cetuximab† + mFOLFOX6 or FOLFIRI (N=500)

Stratification factors
Chemotherapy (mFOLFOX6/FOLFIRI)
Limited disease‡ (yes/no)
Prior adjuvant therapy (yes/no)

‡ Defined as up to two metastatic sites and up to 5 metastatic lesions in each site

* 1600 mg (BW <80kg) or 2240 mg (BW ≥ 80kg).
Cycle 1: Weekly administration (ie. Days 1, 8, 15, and 22)
Cycle 2+: bi-weekly administration (ie. Days 1 and 15)
† Biweekly regimen: 500 mg/m^2 on Days 1 and 15; or
Weekly regimen: 400 mg/m^2 on C1D1 then 250 mg/m^2 weekly

Primary Endpoint:
- Progression-free survival (PFS) by blinded independent central review

Secondary Endpoints:
- Efficacy (OS, ORR, DOR, PFS2)
- Safety (AE, laboratory abnormalities)
- PROs (e.g. EORTC QLQ-C30, EORTC QLQ-CR29)

FDA approved (carboplatin and pemetrexed) for NSCLC with EGFR exon 19 deletions or L858R mutations

Conclusion

- Targeted therapies continue to improve the treatment landscape for advanced CRC
- Precision oncology is no longer reserved for treatment refractory disease; expanding frontline targeted treatment options