Recent Advances in the Management of Metastatic Colorectal Cancer

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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

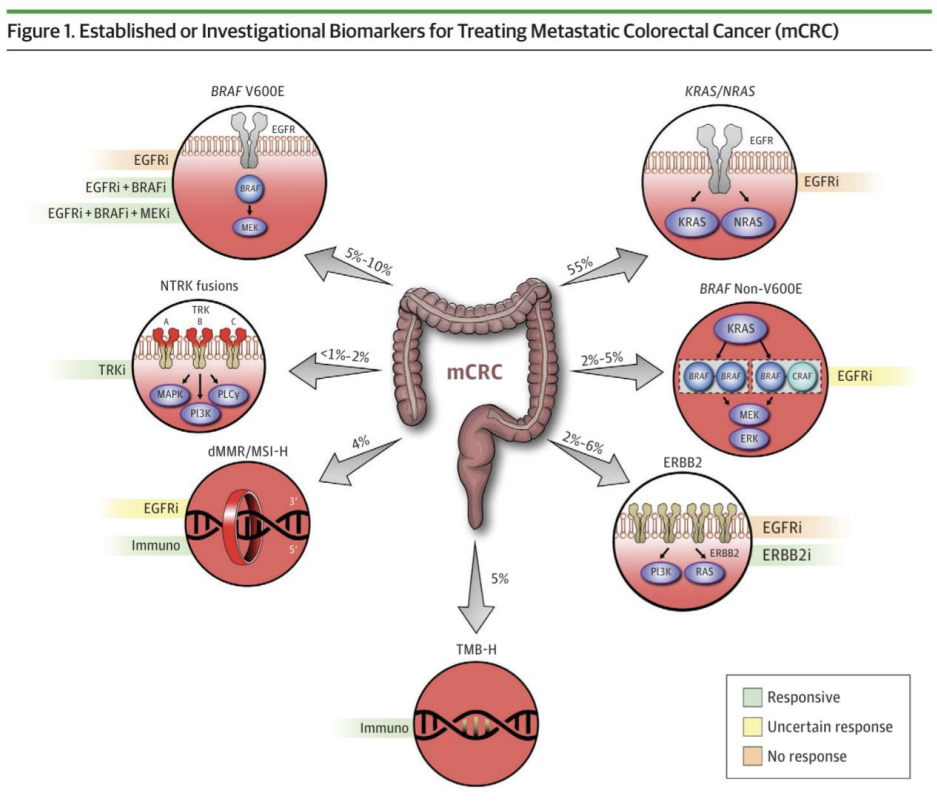
Consulting/Advisory Role: Ipsen Pharmaceuticals, GSK, Cue Biopharma, Inc., Abbvie, Taiho, Bristol Myers Squibb, AstraZeneca, Exelixis, Takeda, Boehringer Ingelheim, Loxo Oncology

Independent Data Monitoring Committee: Compass Therapeutics, Inc.

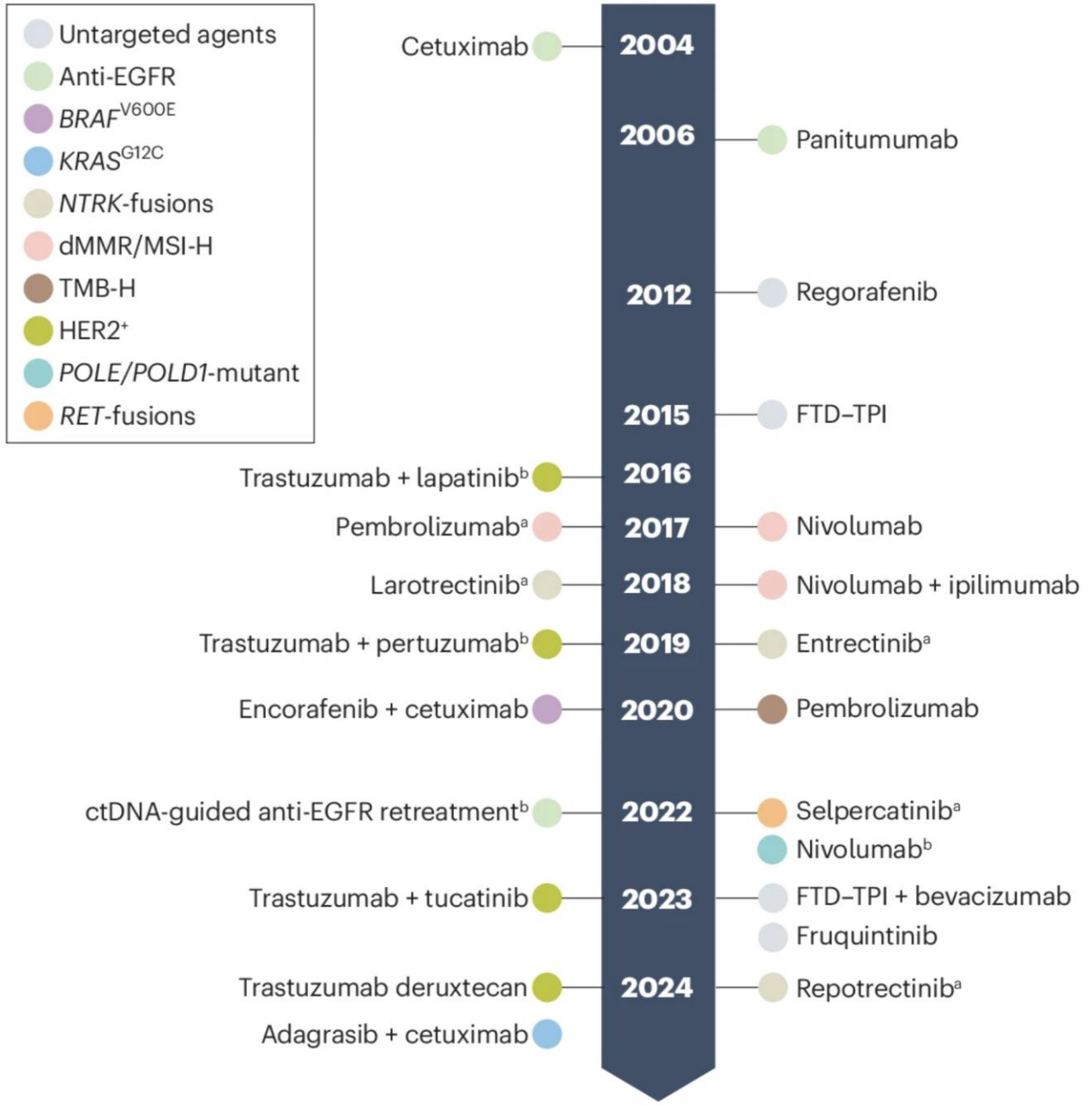
Learning Objectives

- Discuss established molecular targets in mCRC
- Review relevant novel/emerging targets
- Highlight future treatment strategies

Molecular targets in CRC

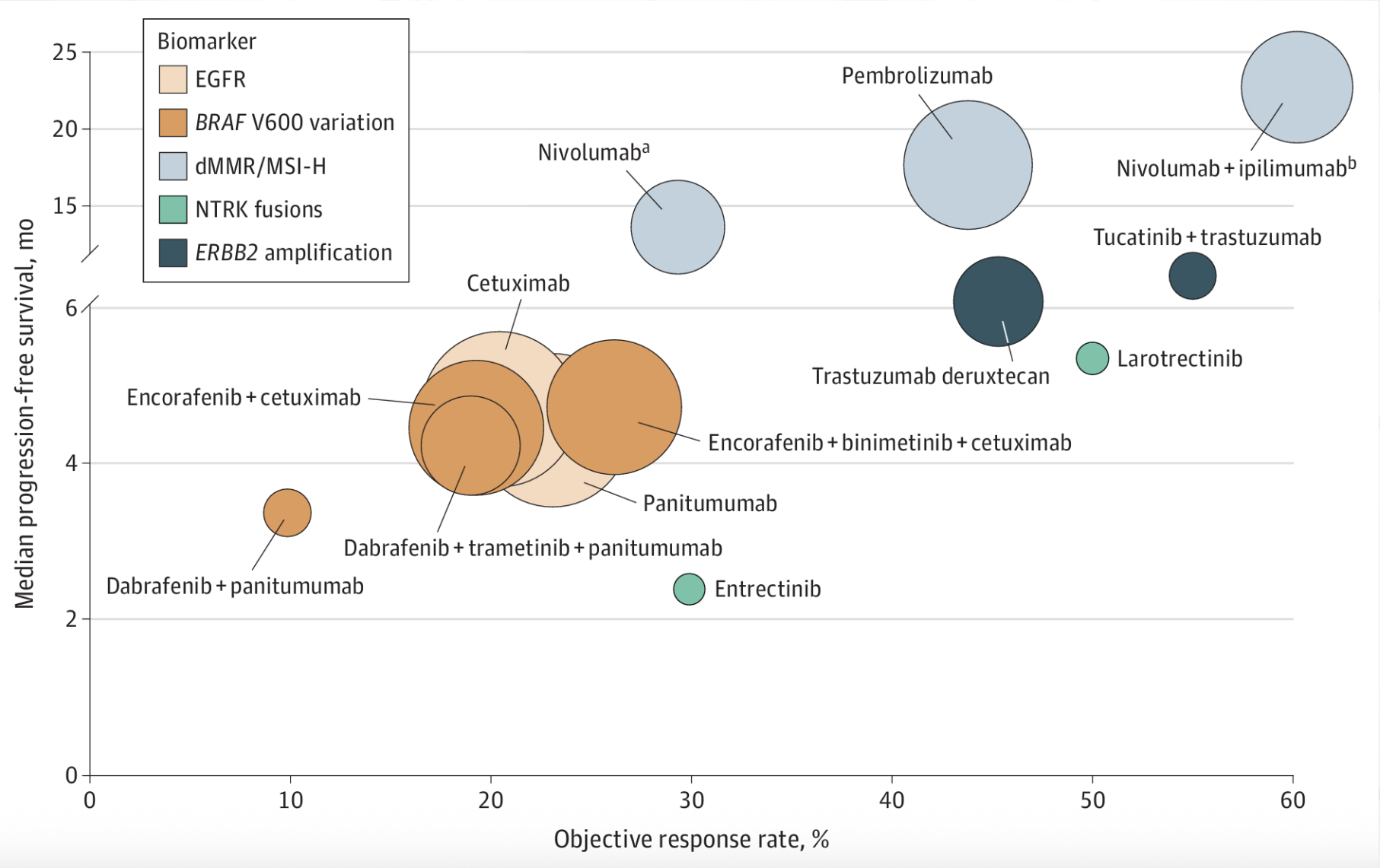


- cMET
- PIK3CA mutations — Adjuvant ASA. Other aberrations in the PI3K–AKT–mTOR pathway?
- Wnt/β-catenin
- DNA Damage Repair
- CEACAM5 (CEA)



Strickler JH, et al. JAMA Oncol. 2022 May 1;8(5):760-769
Ciracì, P. et al. Nat Rev Clin Oncol 22, 28–45 (2025)

ORR, PFS



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

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]

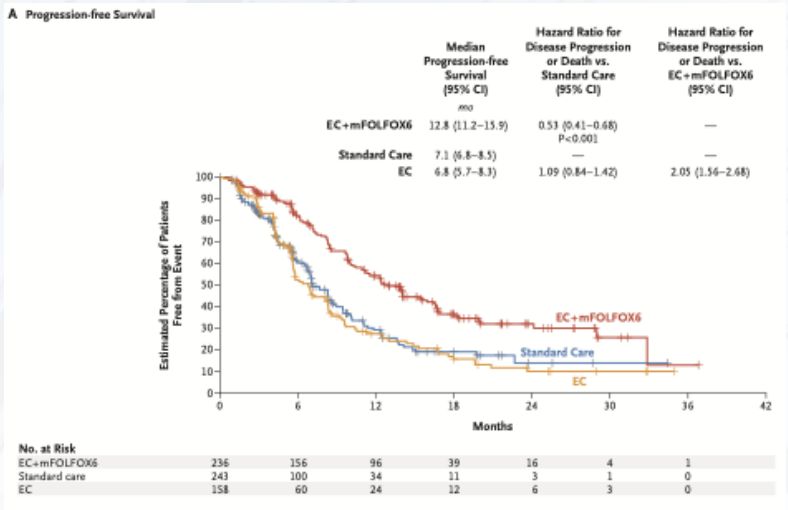
Stratified by regions (US/Canada vs Europe vs Rest of World) and ECOG PS (0 vs 1)

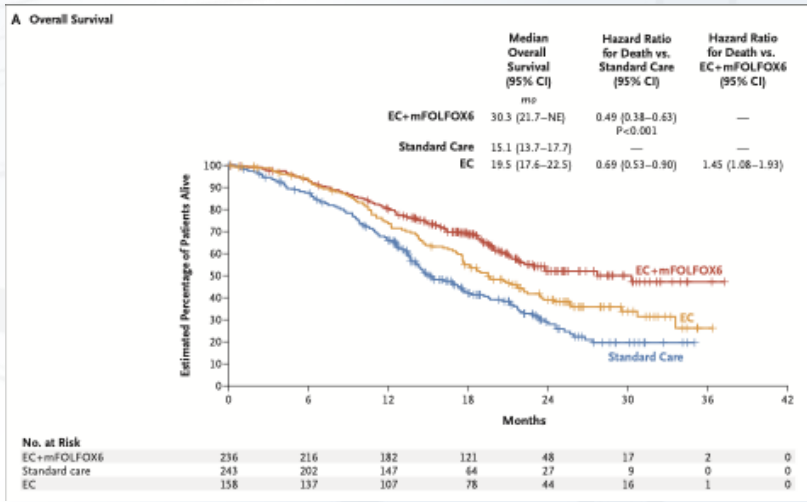
Dual primary endpoints:
PFS and ORR[d] by BICR
(EC + mFOLFOX6 vs SOC)

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)





BRAF V600E

2026 ASCO ANNUAL MEETING

BREAKWATER: Progression-free and overall survival analyses of first-line (1L) encorafenib + cetuximab (EC) + FOLFIRI in BRAF V600E-mutant metastatic colorectal cancer (mCRC)

Scott Kopetz,[1] Josep Tabernero,[2,3] Sara Lonardi,[4] Lin Shen,[5] Harpreet Wasan,[6] Takayuki Yoshino,[7] Eric Van Cutsem,[8] Tae Won Kim,[9] Cathy Eng,[10] Fortunato Ciardiello,[11] Jayesh Desai,[12] Tim Maughan,[13] Rona Yaeger,[14] Tiziana Usari,[15] Xiaoxi Zhang,[16] Elena Beyzarov,[16] Ave Mori,[15] Elizabeth Whalley,[17] Xiaosong Zhang,[18] Elena Élez[2]

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
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Exclusion criteria
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- Presence of a *RAS* mutation

R 1:1[a] N=147

- EC[b] + FOLFIRI[c] (n=73)
- Control (FOLFIRI[c] ± bevacizumab[d]; n=74)

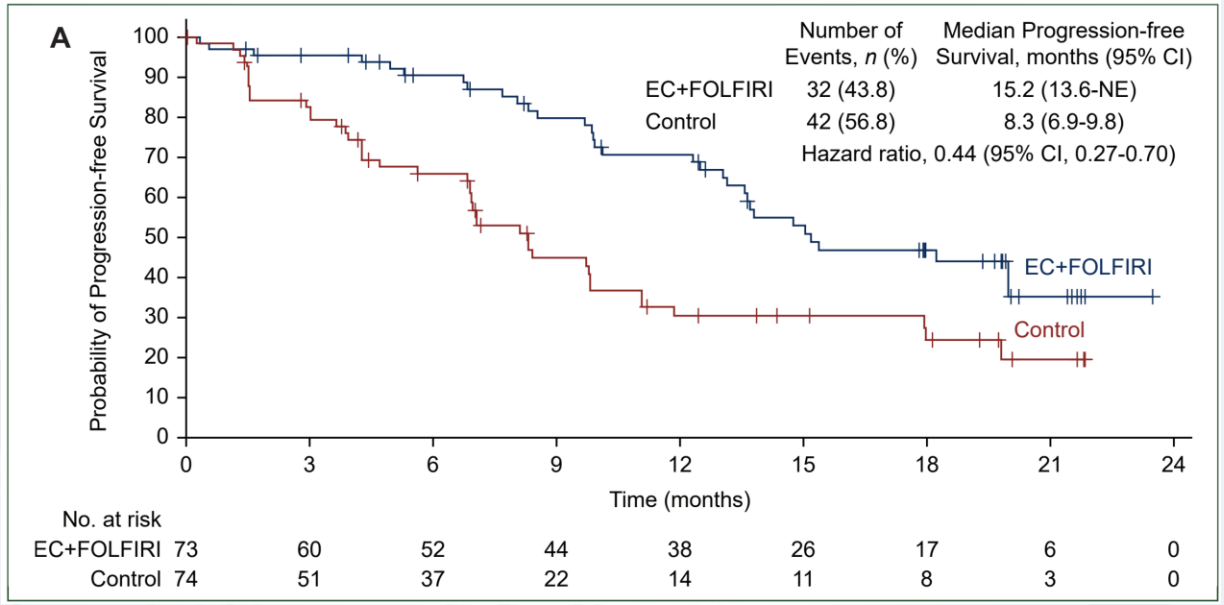
Stratified by ECOG PS

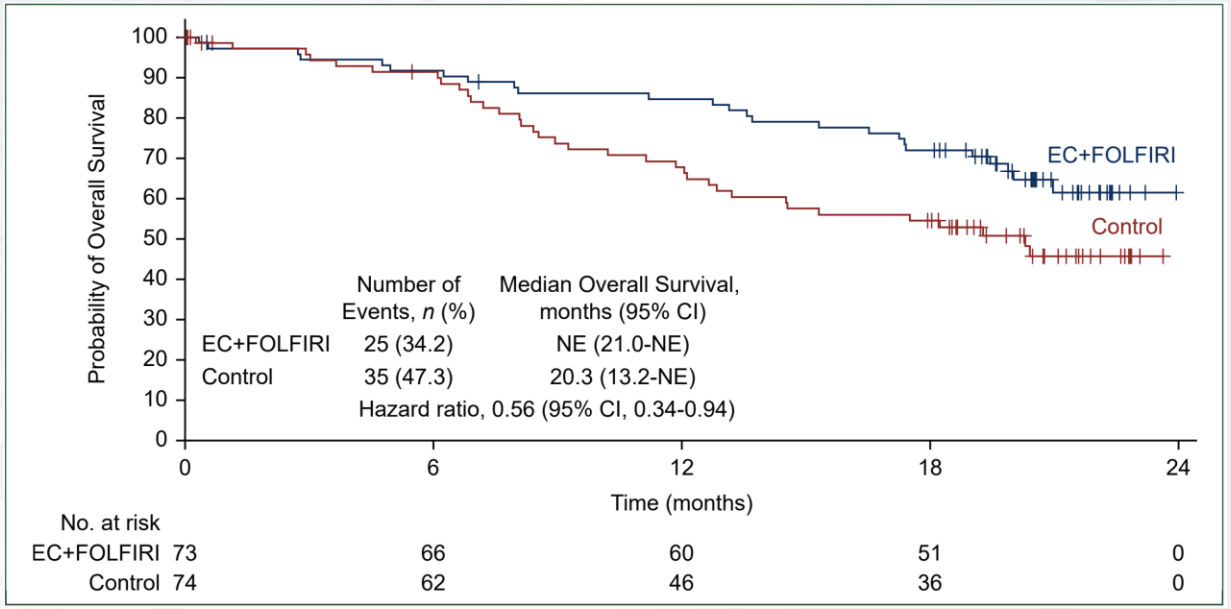
Primary endpoint
- ✓ ORR by BICR:[1] 64.4% vs 39.2%; odds ratio: 2.756 (95% CI 1.420, 5.348); *P*-value[e]=0.0011

Key secondary endpoint
- ❑ PFS by BICR[f]

Secondary endpoint
- ❑ OS

Presented here is the final analysis of PFS by BICR, analysis of OS, and safety



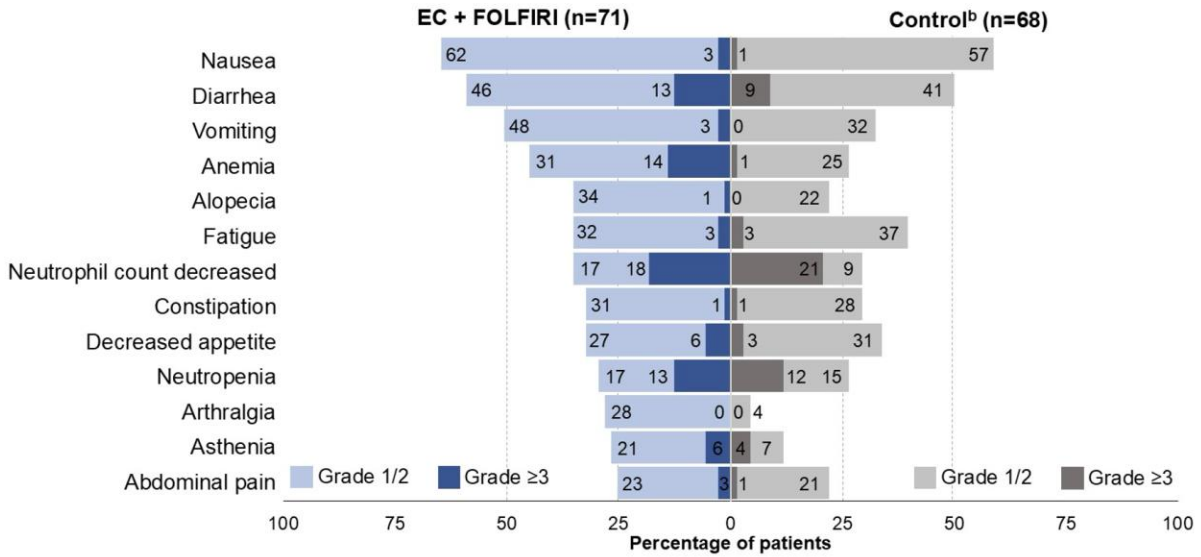


Ann Oncol . 2026 May 31:S0923-7534(26)00179-1.

BRAF V600E

Most Frequent (≥25%)[a] TEAEs (All Causality)

No new safety signals were observed



Dose Modifications Due to TEAEs (All Causality)

The addition of EC to FOLFIRI was generally tolerable, without substantial increase in FOLFIRI discontinuations

Patients, n (%)	EC + FOLFIRI n=71	Control[a] n=68
Discontinuation		
Encorafenib	7 (9.9)	-
Cetuximab	7 (9.9)	-
Other study medication[b]	10 (14.1)	7 (10.3)
Dose reduction		
Encorafenib	17 (23.9)	-
Cetuximab	10 (14.1)	-
Other study medication[b]	48 (67.6)	31 (45.6)
Dose interruption		
Encorafenib	46 (64.8)	-
Cetuximab	47 (66.2)	-
Other study medication[b]	51 (71.8)	52 (76.5)

Ann Oncol . 2026 May 31:S0923-7534(26)00179-1.

KRAS G12C

KRYSTAL-1 Phase 1b/2 CRC cohort Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

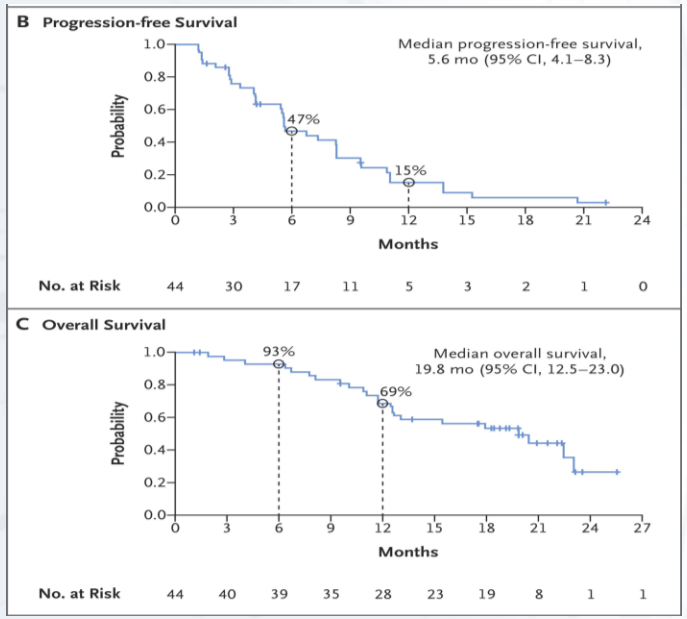
Adagrasib with or without Cetuximab in Colorectal Cancer with Mutated *KRAS* G12C

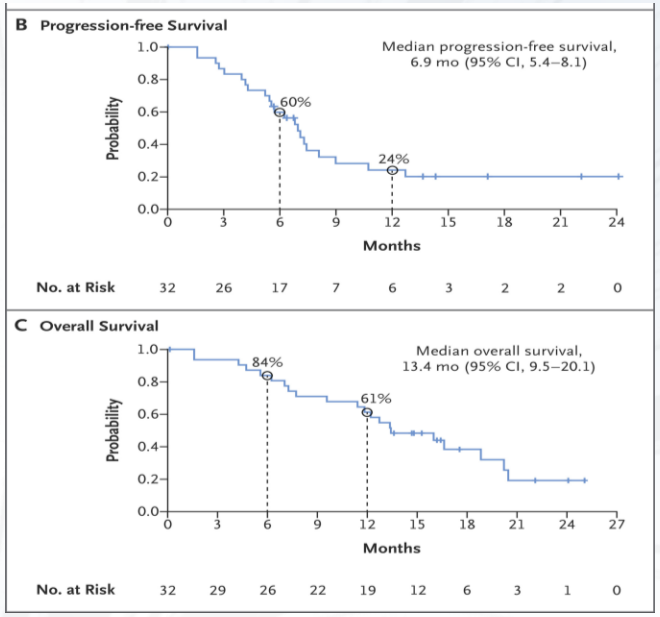
Phase 2
CRC Monotherapy

Adagrasib 600 mg BID

Phase 1b
CRC Combination

Adagrasib 600 mg BID + cetuximab



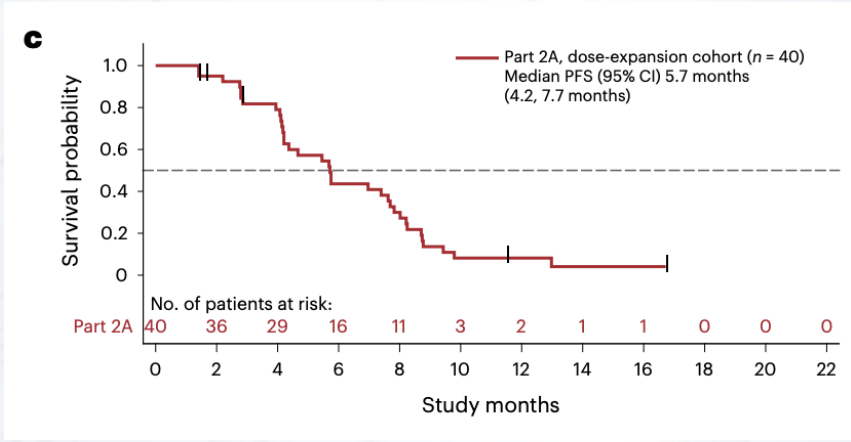


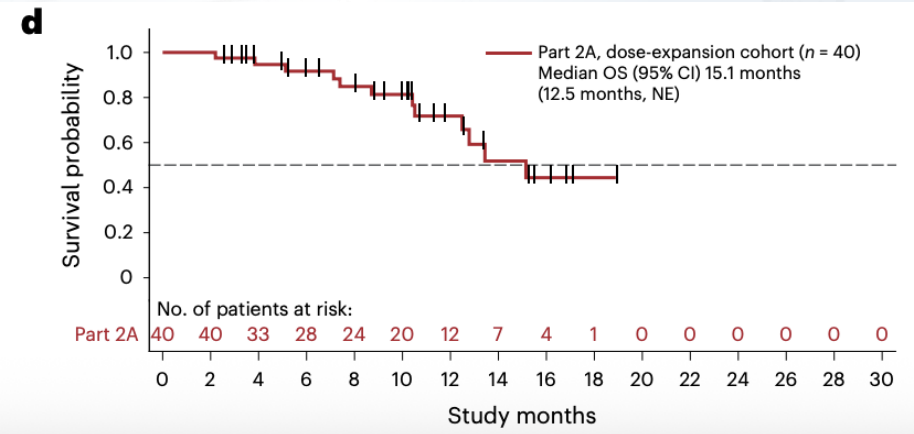
CODEBREAK 101 SUBPROTOCOL H STUDY

nature medicine

Article https://doi.org/10.1038/s41591-023-02717-6

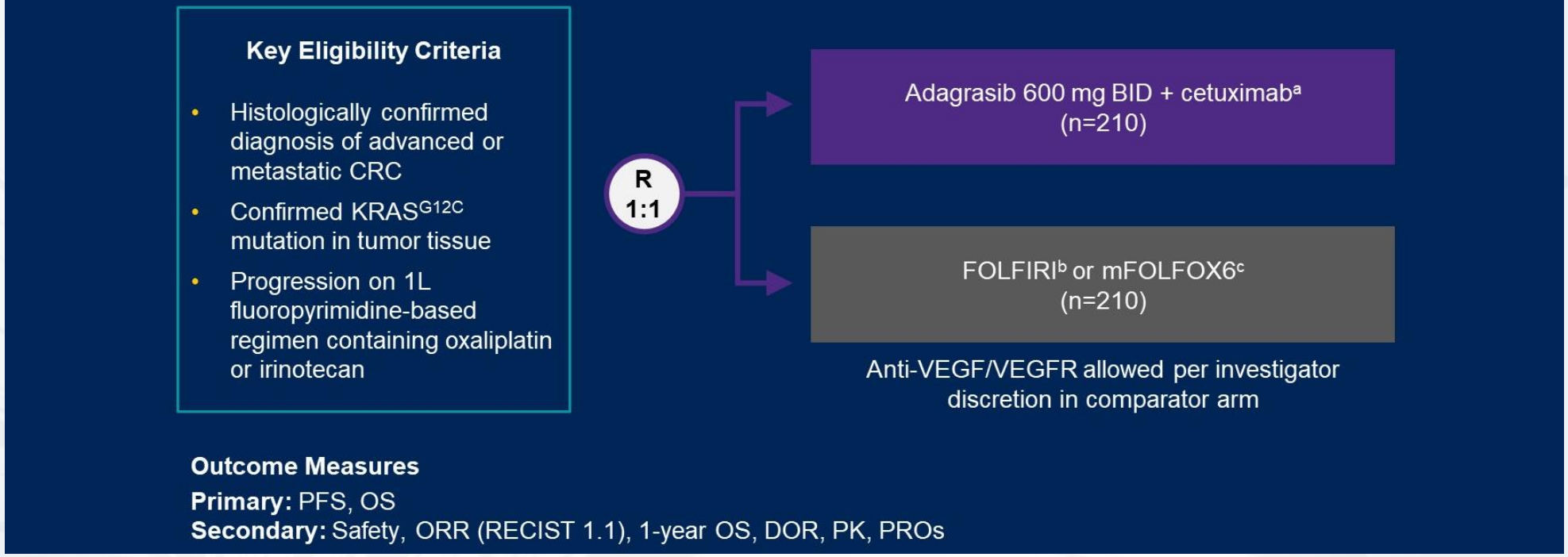
Sotorasib with panitumumab in chemotherapy-refractory *KRAS*^{G12C}-mutated colorectal cancer: a phase 1b trial





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-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

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]

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

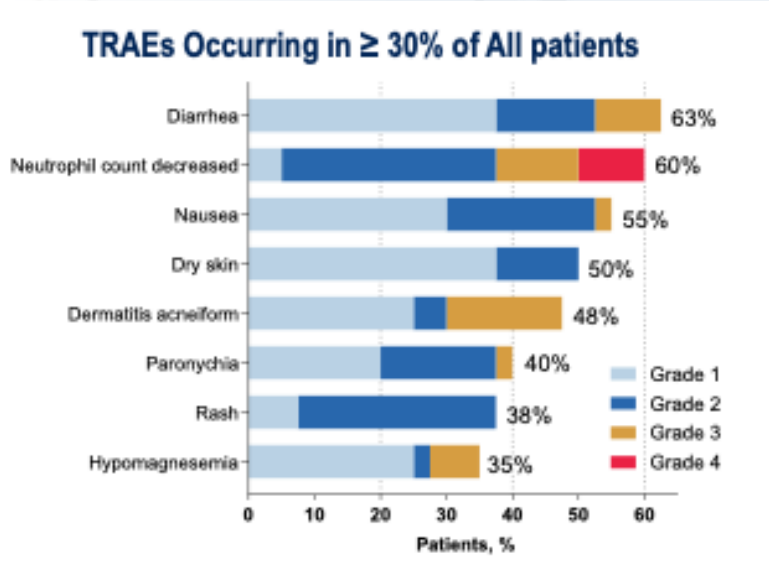
→ **Sotorasib 960 mg was determined as the R2PD in part 1 cohort B‡** →

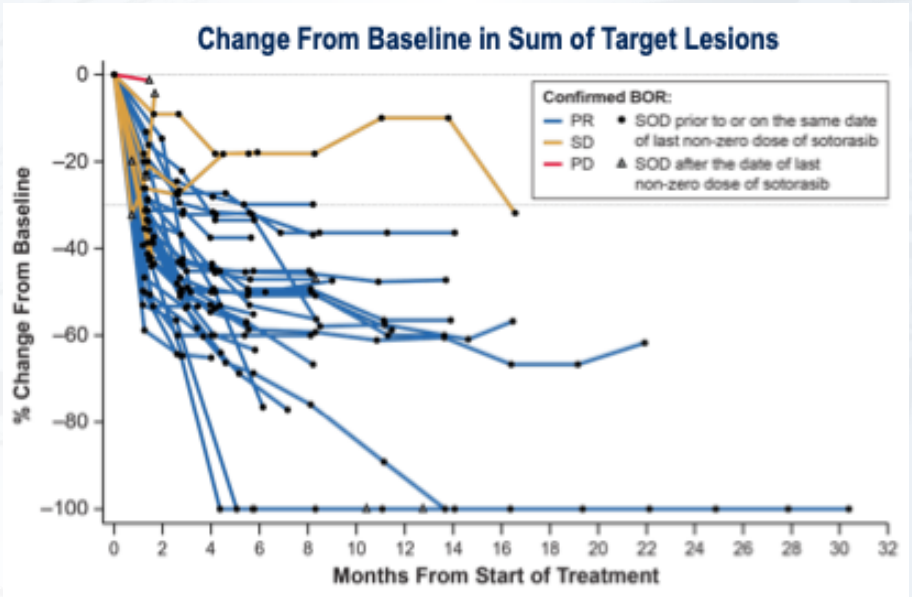
Part 2: Cohort F Dose expansion† (N = 40)

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

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)

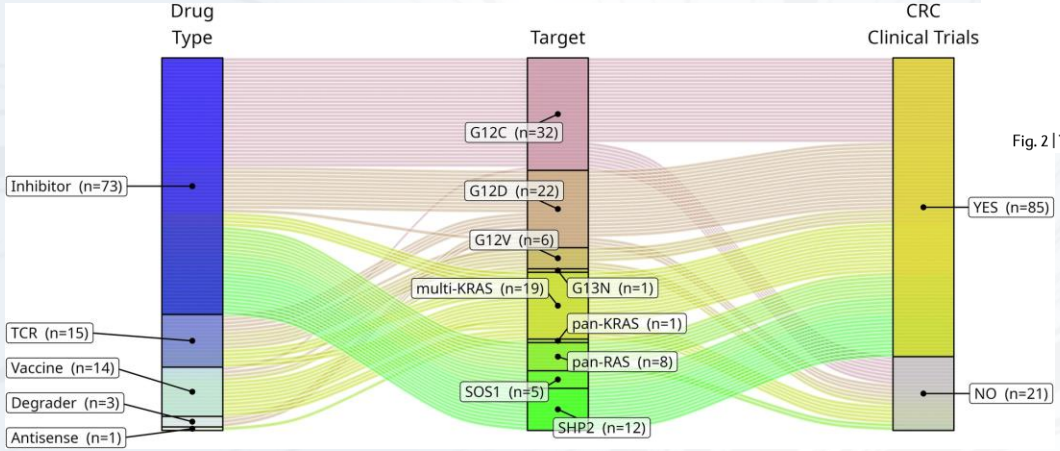




Siena S, et al. Annals of Oncology, 35, S429-S430

BEYOND G12C

- KRAS mutations are common in CRC and predict resistance to EGFR therapy.
- Direct targeting is currently limited to KRAS G12C, where combination with EGFR inhibition is required
- Next-generation KRAS G12D/V inhibitors and immune-based approaches are rapidly evolving.



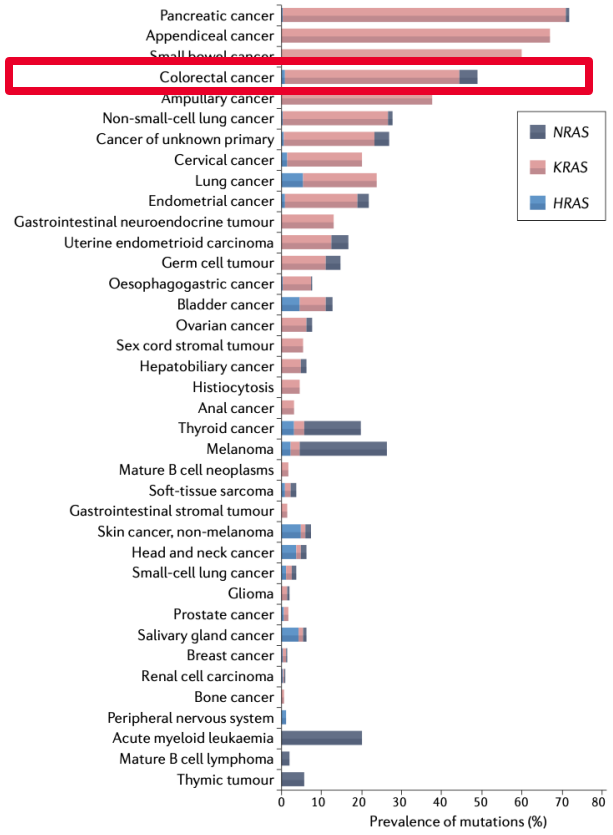
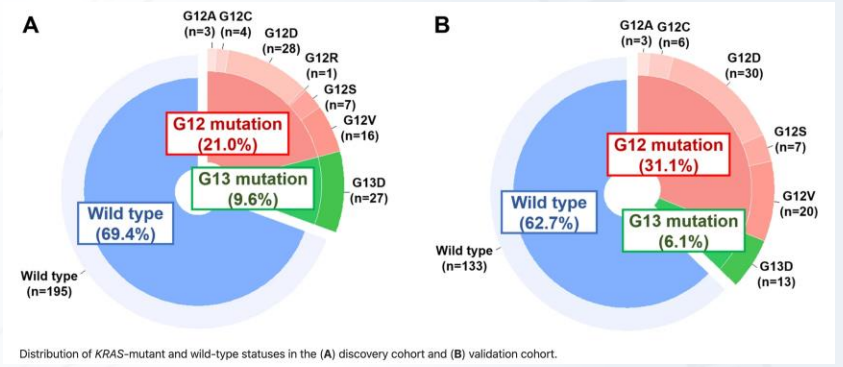
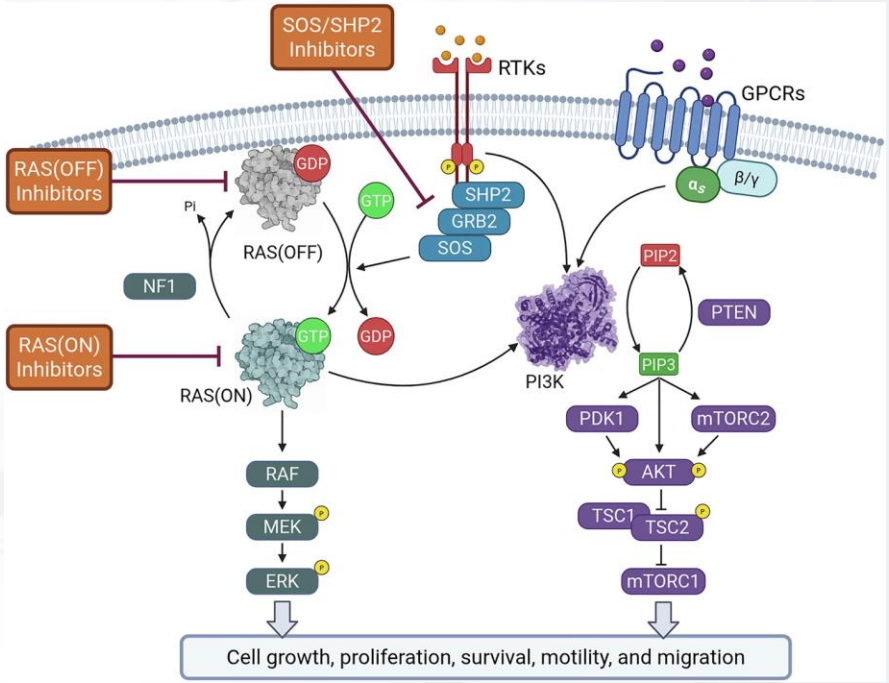


Fig. 2 | **The prevalence of *KRAS*, *NRAS* and *HRAS* mutations across cancer types.**



Distribution of *KRAS*-mutant and wild-type statuses in the (**A**) discovery cohort and (**B**) validation cohort.



npj Precis. Onc. 9, 380 (2025).

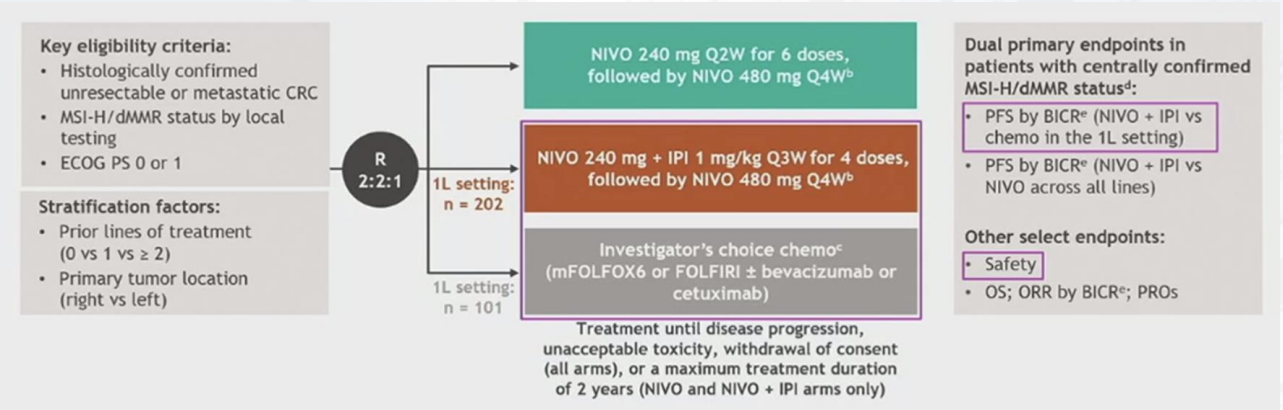
CHECKMATE 8HW – MMRd

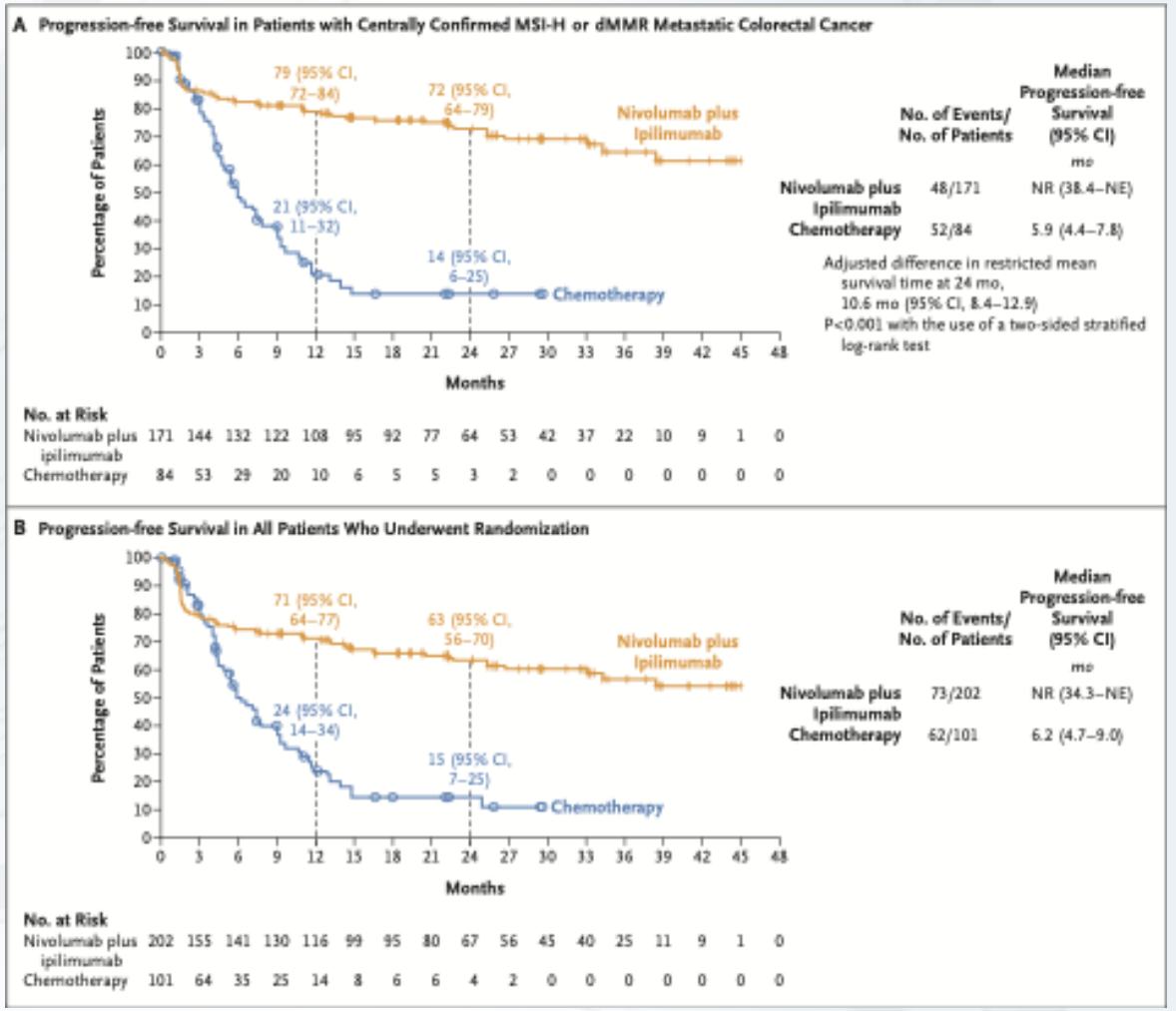
The NEW ENGLAND JOURNAL of MEDICINE

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*





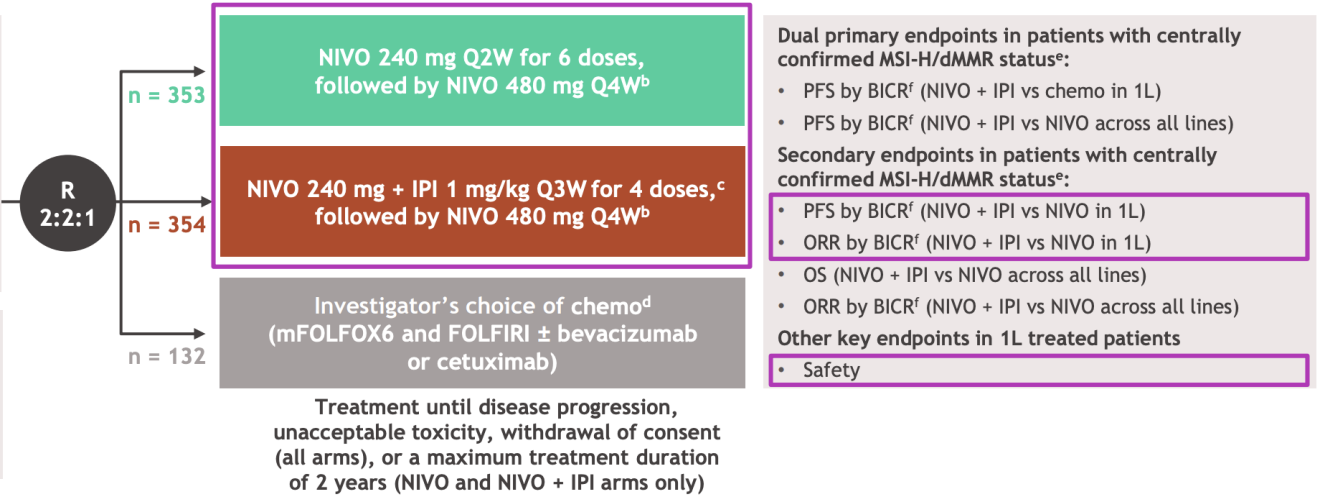
CHECKMATE 8HW – MMRd

BERLIN 2025 ESMO congress

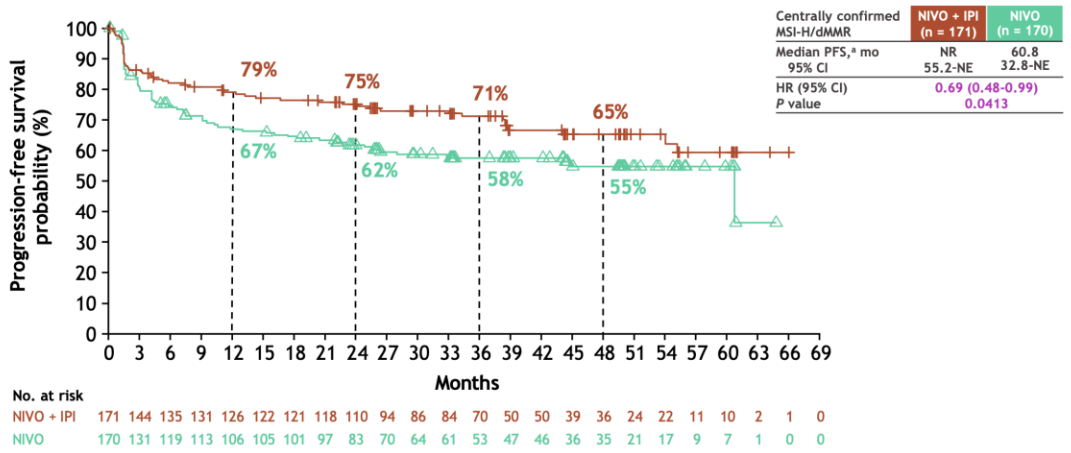
BERLIN GERMANY
17-21 OCTOBER 2025

Nivolumab plus ipilimumab vs nivolumab monotherapy for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: new results from CheckMate 8HW

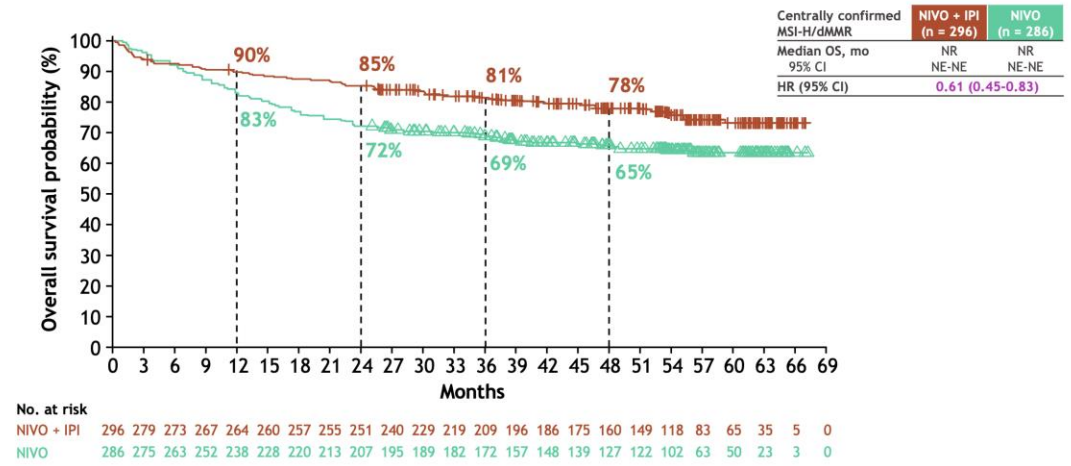
Sara Lonardi,[1] Heinz-Josef Lenz,[2] Elena Elez,[3] Lars Henrik Jensen,[4] Eric Van Cutsem,[5] Yann Touchefeu,[6] Rocio Garcia-Carbonero,[7] David Tougeron,[8] Guillermo Ariel Mendez,[9] Michael Schenker,[10] Christelle de la Fouchardière,[11] Maria Luisa Limon Miron,[12] Takayuki Yoshino,[13] Jin Li,[14] Francine Aubin,[15] Elvis Cela,[16] Li Li,[16] Rachel Tam,[16] Lixian Jin,[16] Thierry Andre[17]



PFS: 1L NIVO + IPI vs NIVO in centrally confirmed patients



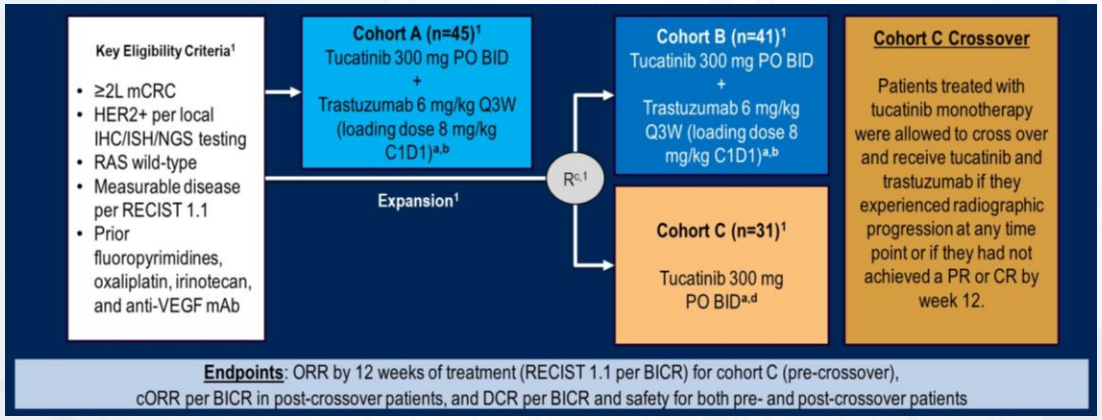
OS: NIVO + IPI vs NIVO across all lines in centrally confirmed patients

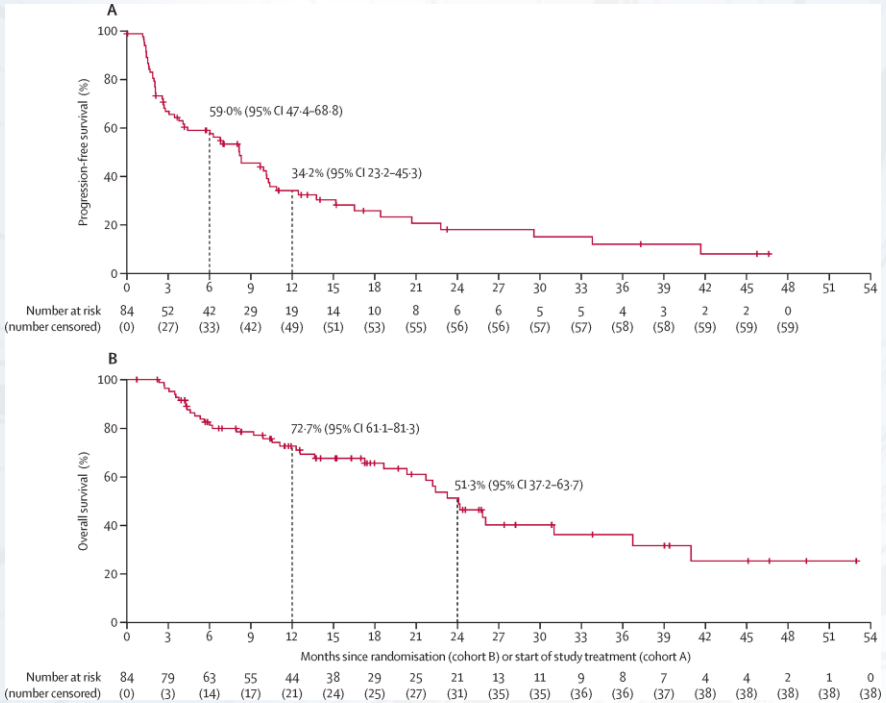


With ~69% of expected events observed (168 of ~243 expected deaths), OS data remain immature

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.

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**

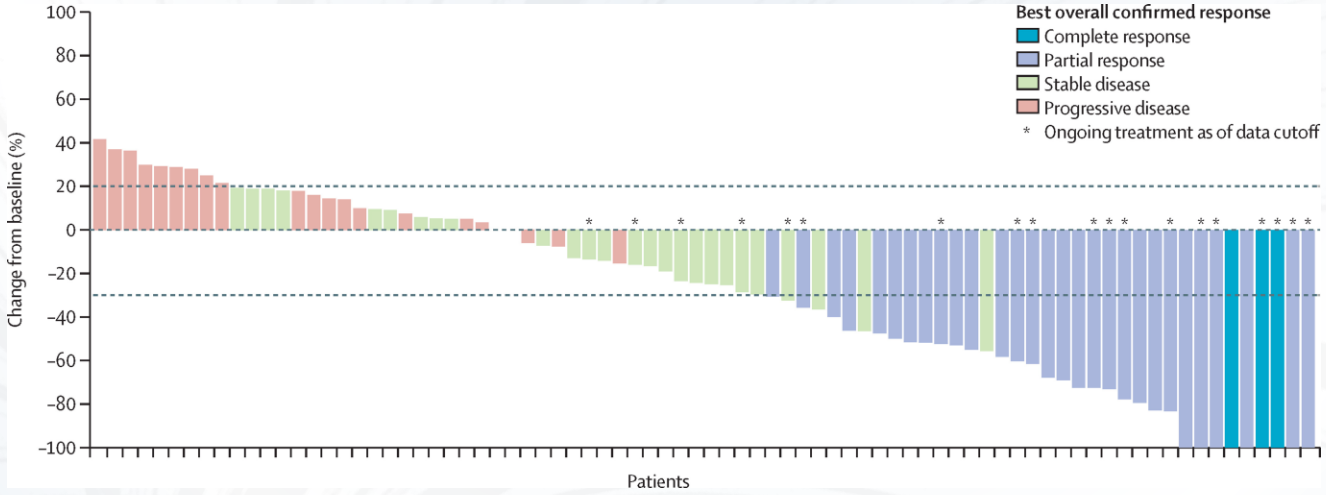
	Tucatinib plus trastuzumab (n=84)	Tucatinib monotherapy (n=30)
Age, years		
Median (IQR)	55·0 (44·5–62·0)	59·5 (52·0–66·0)
<65 years	72 (86%)	19 (63%)
≥65 years	12 (14%)	11 (37%)
Sex		
Male	51 (61%)	15 (50%)
Female	33 (39%)	15 (50%)
Ethnicity		
Hispanic, Latino/a, or of Spanish origin	3 (4%)	1 (3%)
Not 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

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

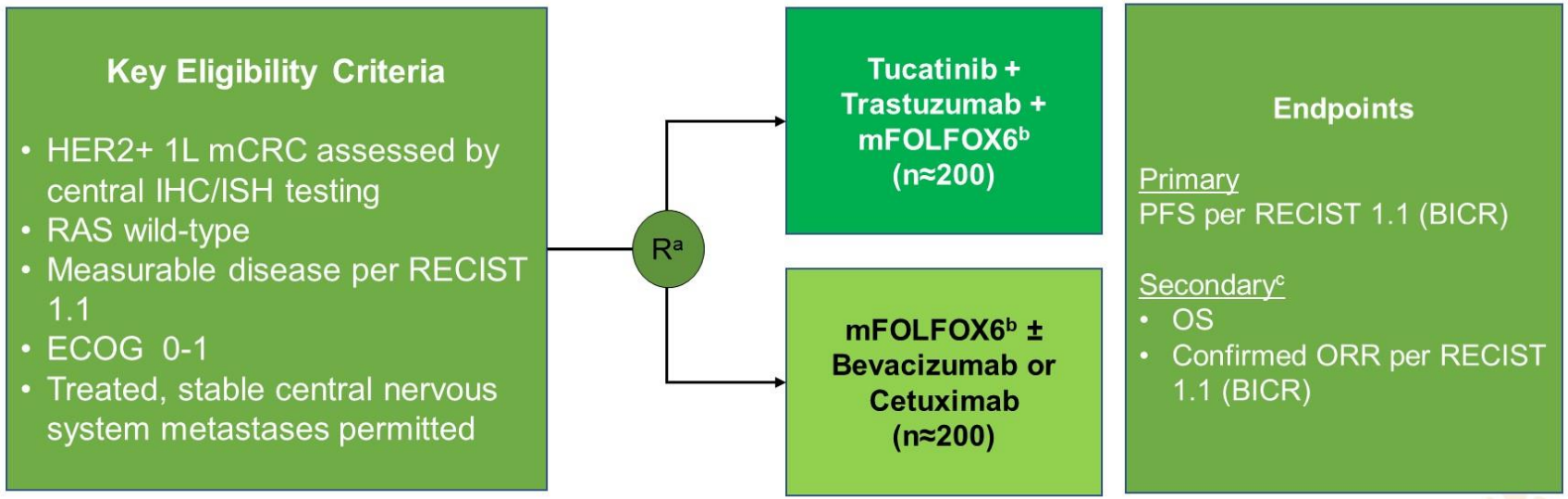
Responses		Tucatinib + Trastuzumab Cohorts A+B n=84[1]	Tucatinib Monotherapy Cohort C n=30	Tucatinib + Trastuzumab Post-Crossover n=28
Best overall response per BICR[a], n (%)	CR	3 (4%)	0	0
	PR	29 (35%)	1 (3.3)	5 (17.9)
	SD[b]	28 (33%)	23 (76.7)	18 (64.3)
	PD	22 (26%)	4 (13.3)	5 (17.9)
	Not available[c]	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.

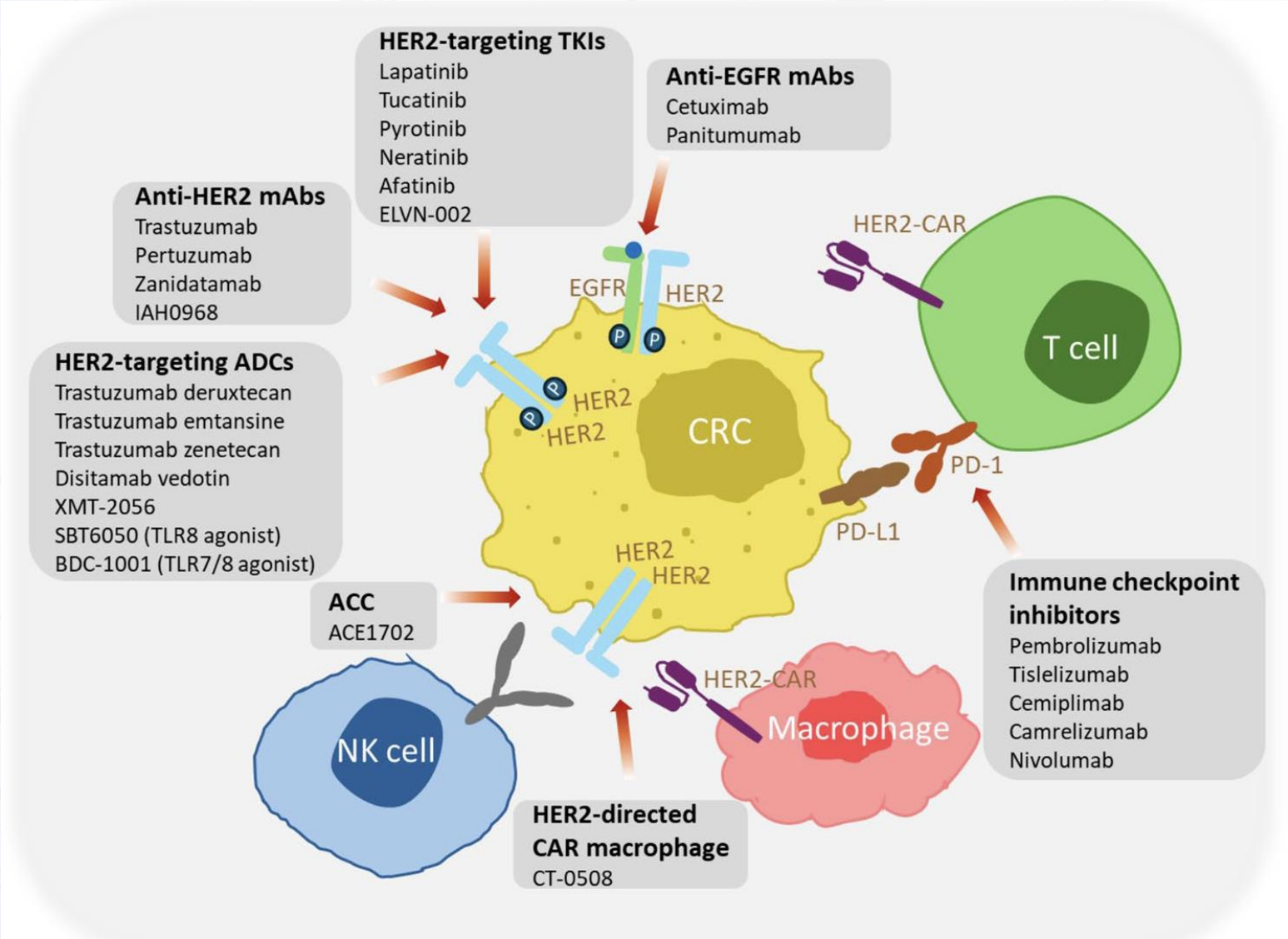
HER2 Inhibition In Advanced CRC

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)

STELLAR-303

Zanzalintinib plus atezolizumab versus regorafenib in refractory colorectal cancer (STELLAR-303): a randomised, open-label, phase 3 trial

J Randolph Hecht, Young Suk Park, Josep Tabernero, Myung-Ah Lee, Soohyeon Lee, Anna C Virgili, Marc Van den Eynde, Elisa Fontana, Marwan Fakih, Gholamreza Asghari, Jane So, Alexander Stein, Olivier Dubreuil, Lubomir Bodnar, Cixin Steven He, Guan Wang, Robina Smith, Cathy Eng, Anwaar Saeed, on behalf of the STELLAR-303 study investigators

Patient Population

- Aged ≥18 years
- Documented to not have MSI-H or dMMR status
- mCRC that radiographically progressed on or was refractory or intolerant to prior standard-of-care therapy, which had to include all the following (if approved and available in the country where the patient is randomized):
  - Fluoropyrimidine, irinotecan and oxaliplatin ± anti-VEGF antibody
  - Anti-EGFR antibody (if *RAS* wild type)
  - BRAF inhibitor (if known *BRAF* V600E mutation)

Stratification Factors

- Geographic region (Asia/rest of the world)
- *RAS* status (wild type/mutant)
- Presence of liver metastases (yes/no)

R 1:1
N=901

Zanzalintinib 100 mg PO QD + Atezolizumab 1200 mg IV Q3W (n=451)*

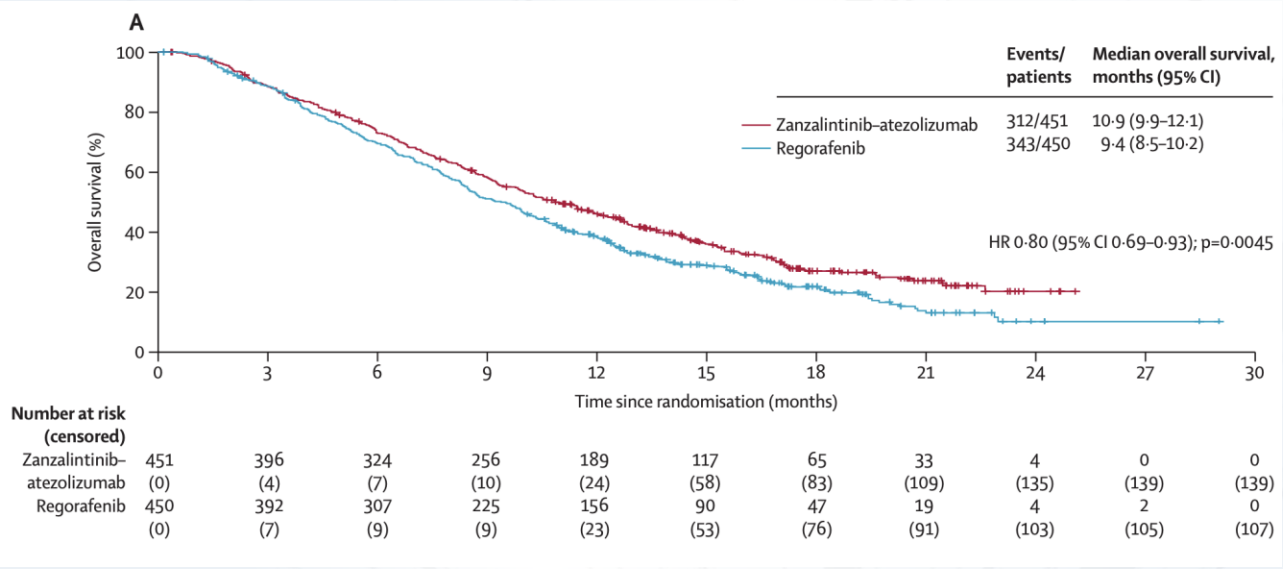
Regorafenib 160 mg PO QD (days 1–21 of each 28-day cycle) (n=450)*

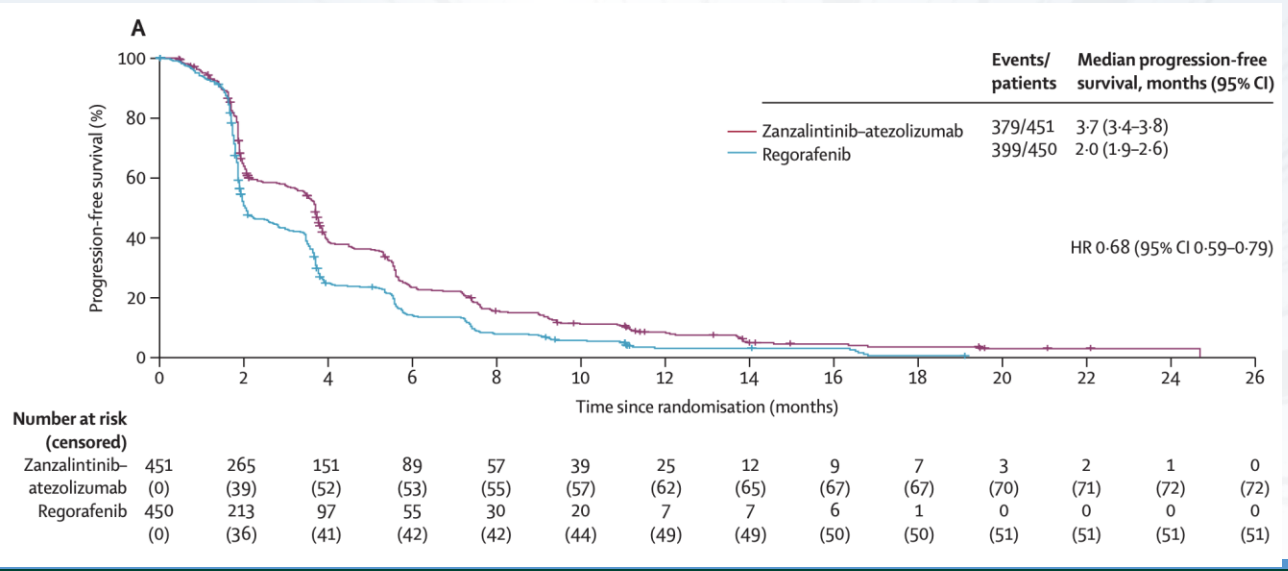
Endpoints

Dual primary	OS in the ITT population OS in patients without liver metastases (nlmITT)
Key secondary	PFS,† ORR,† Safety‡

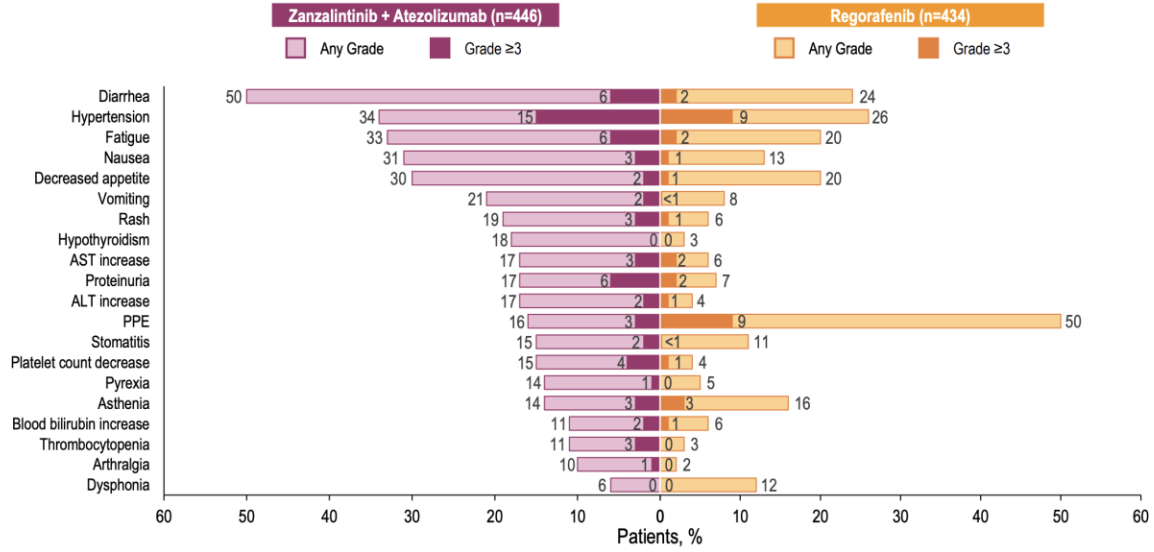
Hecht J, et al. Lancet, 2025; 406, 2360-2370

STELLAR-303





Summary of TRAEs* (Safety Population)



Hecht J, et al. Lancet, 2025; 406, 2360-2370

Conclusion

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