Treatment Landscape of metastatic Colorectal Cancer

Heinz-Josef Lenz

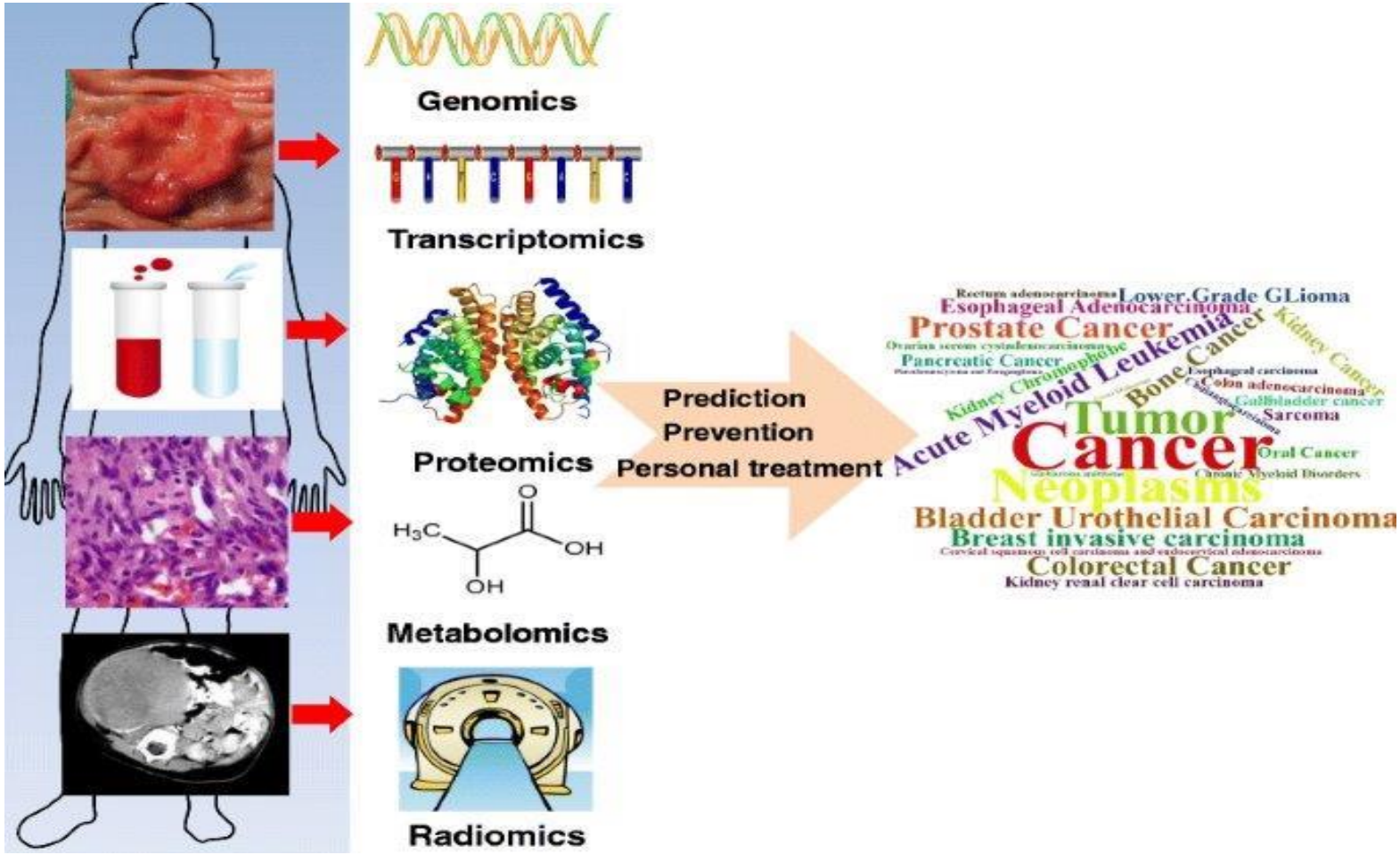
Professor of Medicine and Preventive Medicine
Deputy Cancer Center Director

J Terrence Lanni Chair in Cancer Research

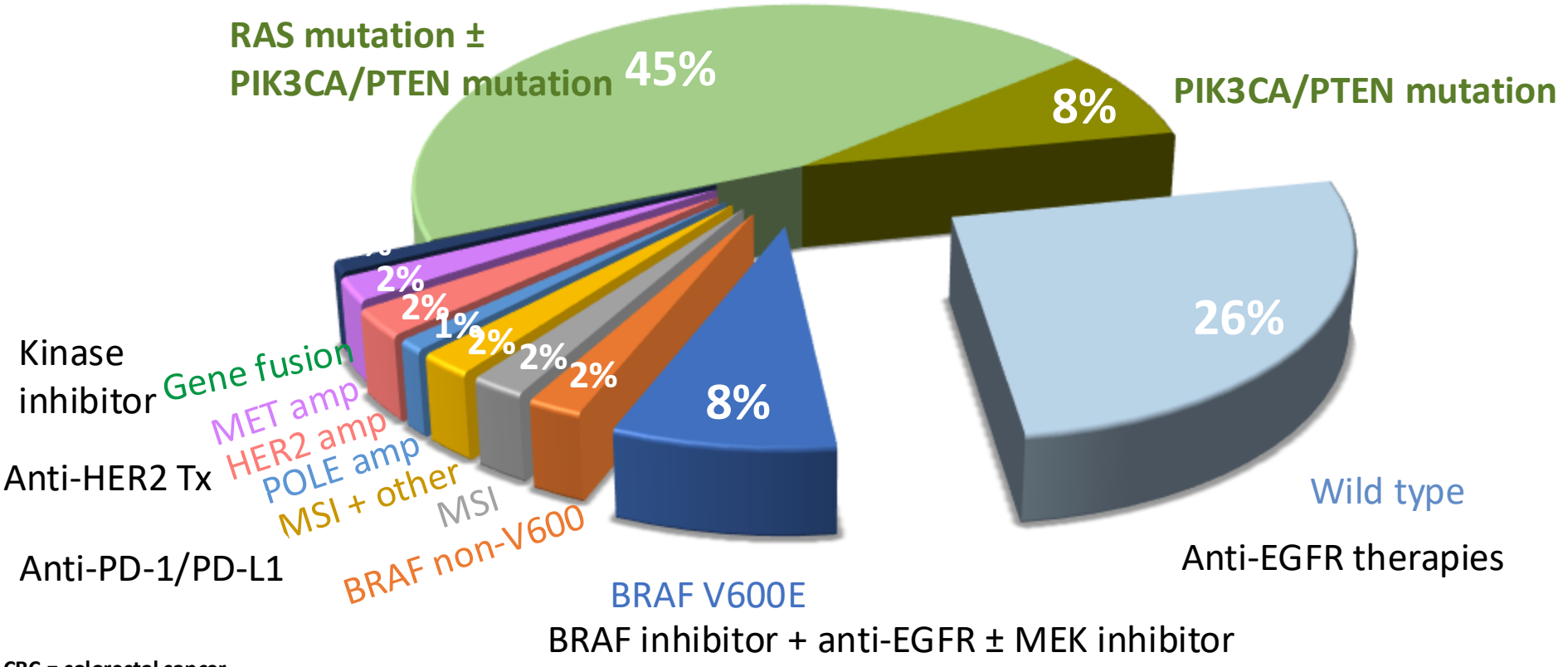
Director, USC Center for Cancer Drug Development

USC/Norris Comprehensive Cancer Center

Los Angeles, California


Genomics
Transcriptomics
Proteomics
Metabolomics
Radiomics
Prediction
Prevention
Personal treatment
Lower Grade GLioma
Esophageal Adenocarcinoma
Prostate Cancer
Pancreatic Cancer
Kidney Cancer
Bone Cancer
Acute Myeloid Leukemia
Kidney Chromophobe
Colon adenocarcinoma
Gallbladder cancer
Sarcoma
Tumor
Cancer
Oral Cancer
Neoplasms
Bladder Urothelial Carcinoma
Breast invasive carcinoma
Colorectal Cancer
Kidney renal clear cell carcinoma

Genomic Markers in CRC



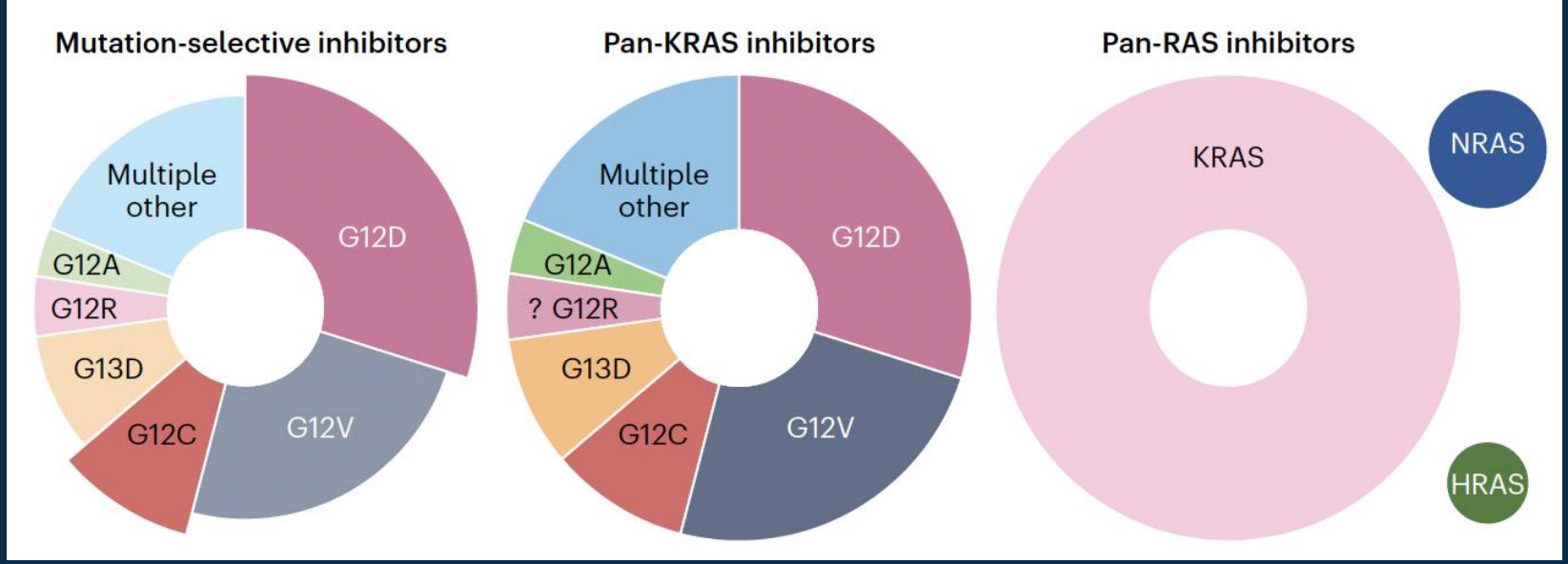
CRC = colorectal cancer.

Dienstmann R, et al. *Am Soc Clin Oncol Educ Book*. 2018;38:231-238.

Novel Approaches

1.RAS (G12C)

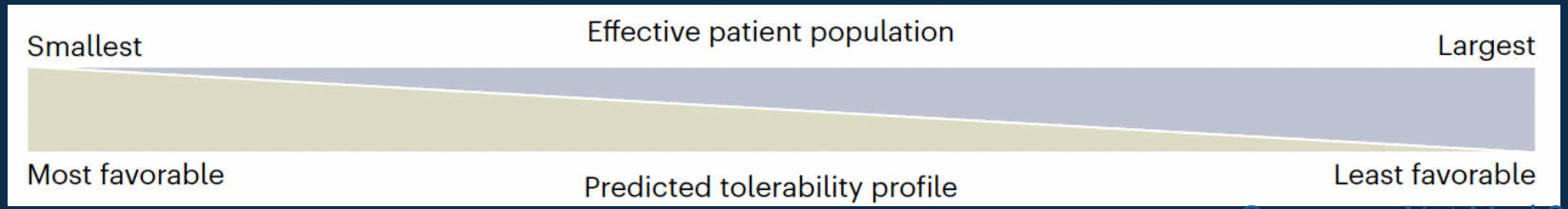
2. Pan Ras Inhibitors



MRTX-1133 ASP-3082
RMC-9805 INC-161734
HRS-4642 LY3962673

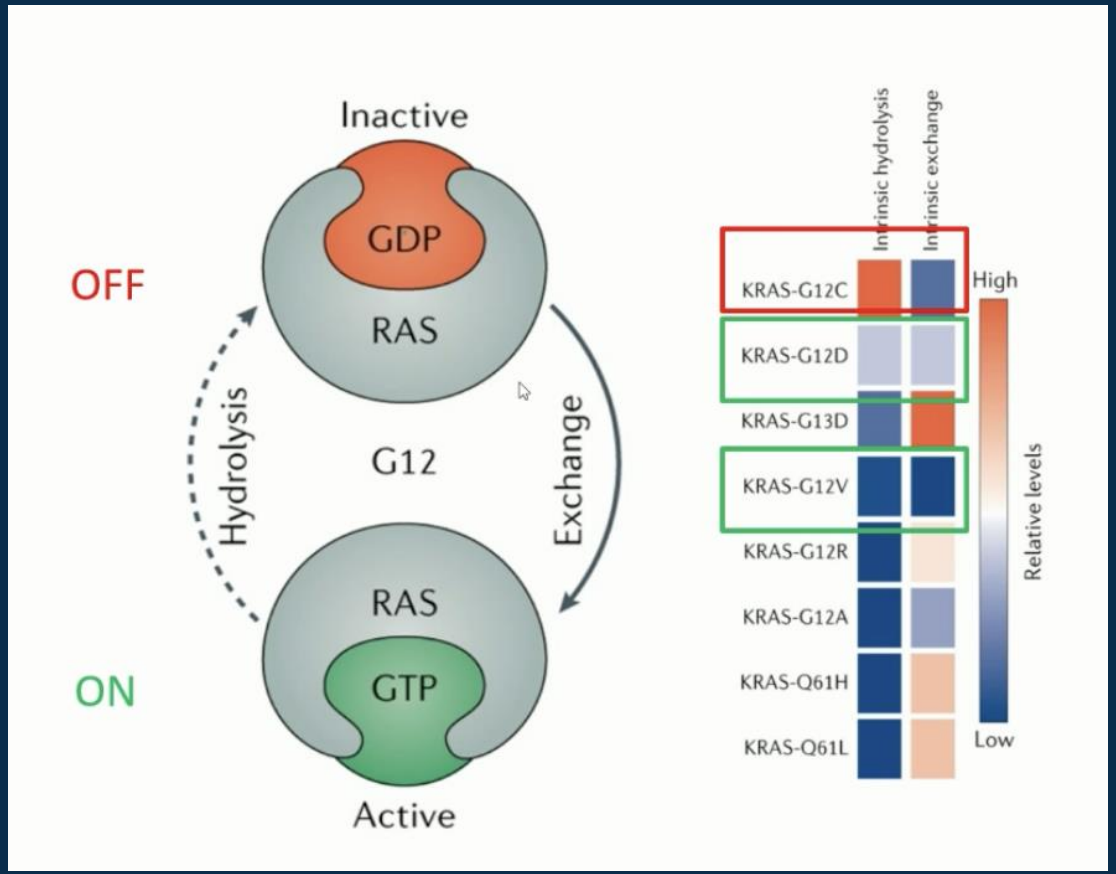
BI-2865
BI-3706674

RMC-6236



Corcoran, Nat Med 2023

RAS mutation in various cancers



KRAS G12V and G12D have a much lower rate of intrinsic hydrolysis
-> Off state inhibitors not as active

Hunter et al., Mol Cancer Res 2015
Moore et al., Nat Rev Drug Disc 2020

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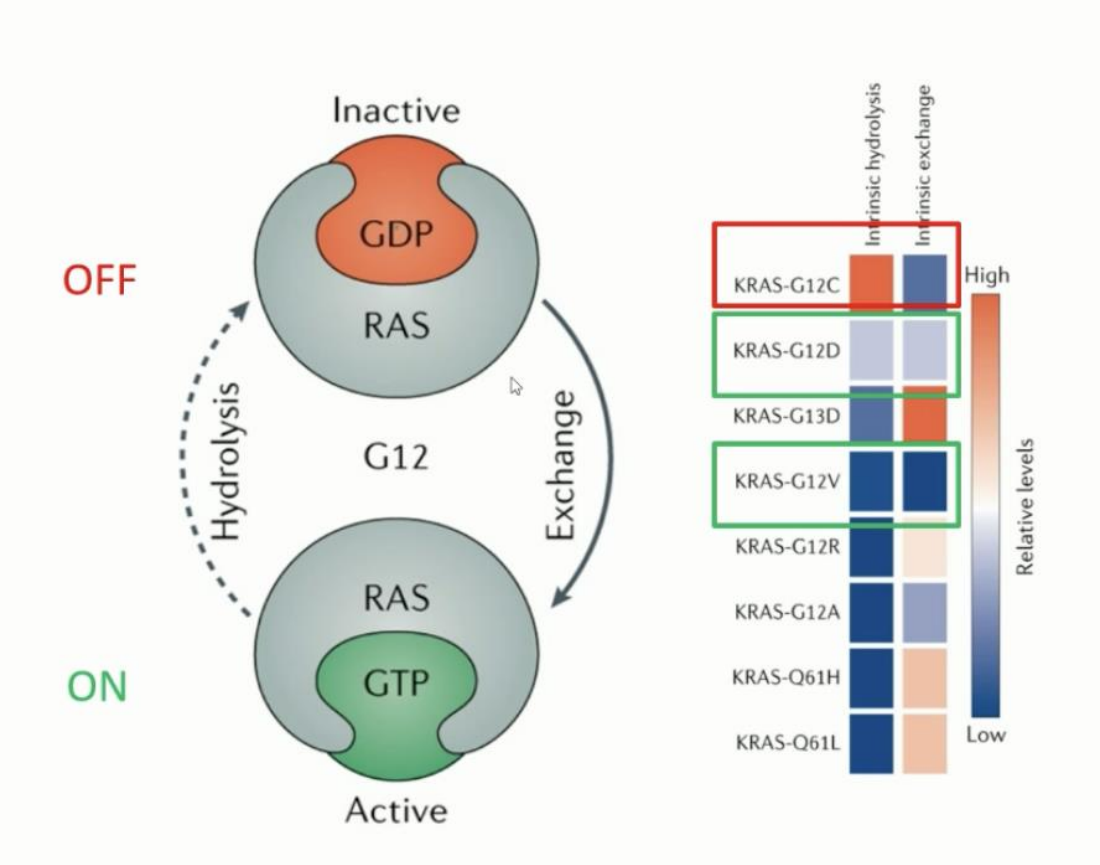

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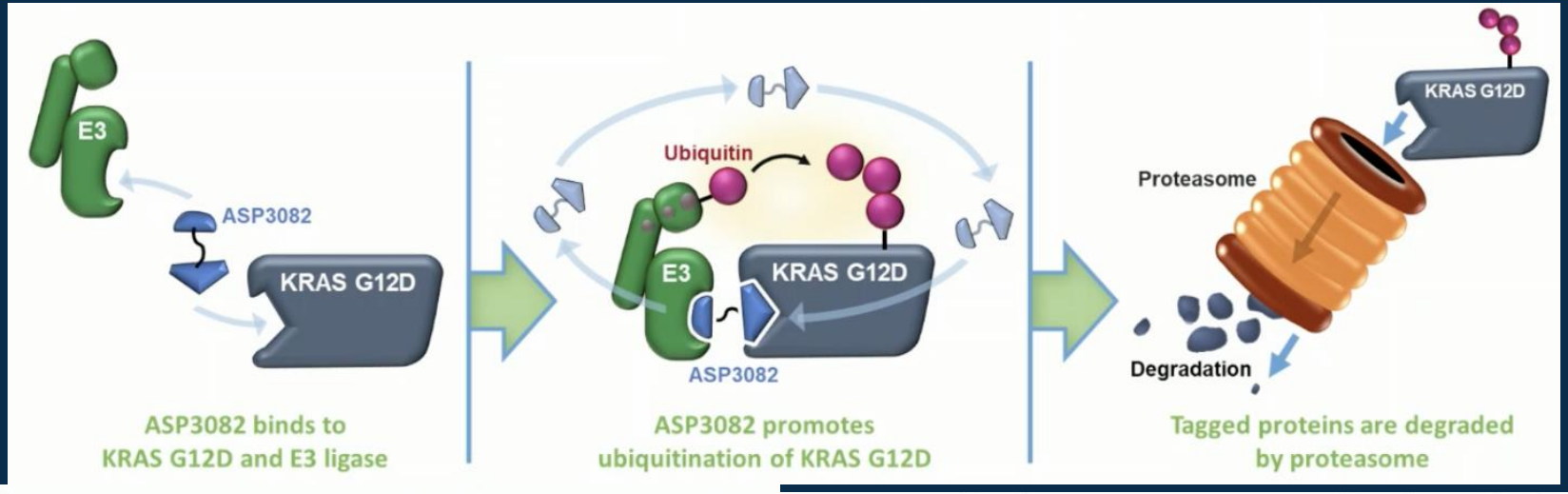
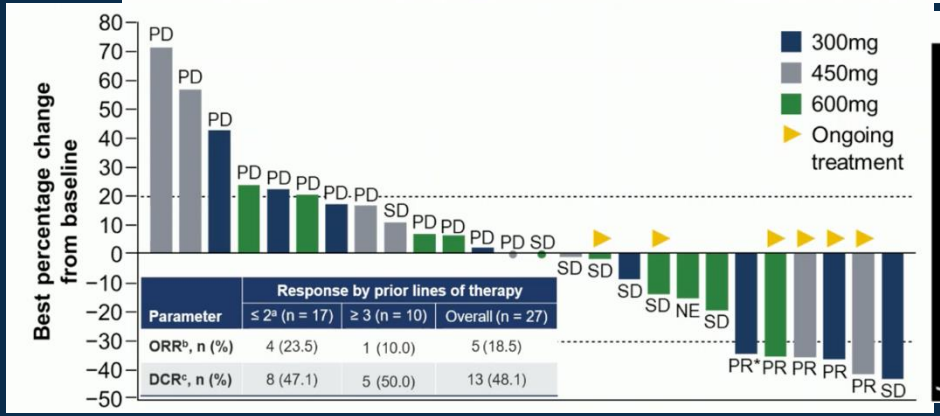
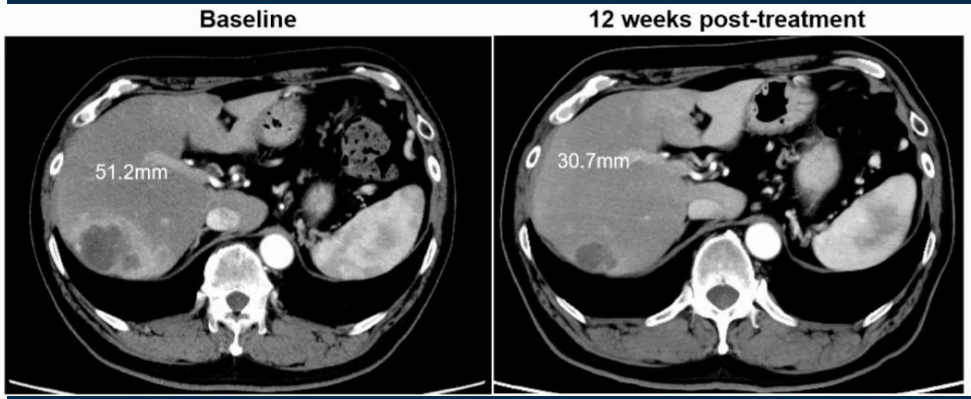
Moore et al., Nat Rev Drug Disc 2020

ASP3082 – KRAS G12D targeted protein degrader (Park, ESMO 2024)

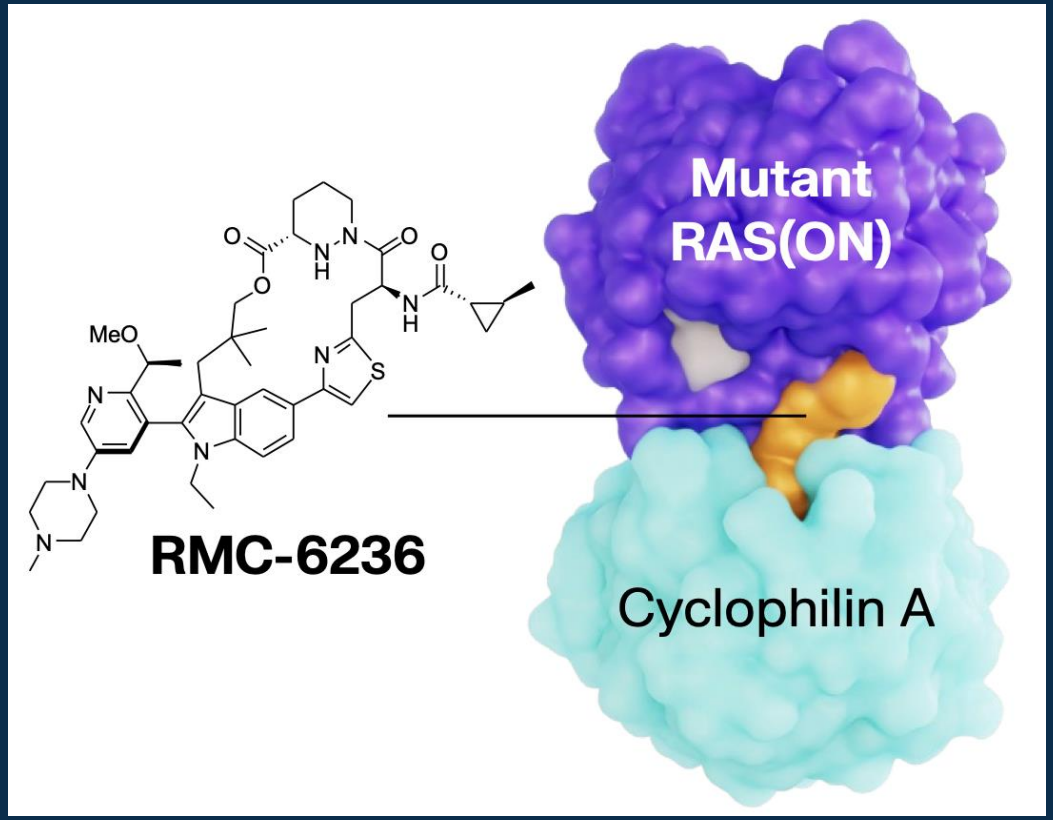




Parameter	Response by prior lines of therapy		
	≤ 2[a] (n = 17)	≥ 3 (n = 10)	Overall (n = 27)
ORR[b], n (%)	4 (23.5)	1 (10.0)	5 (18.5)
DCR[c], n (%)	8 (47.1)	5 (50.0)	13 (48.1)



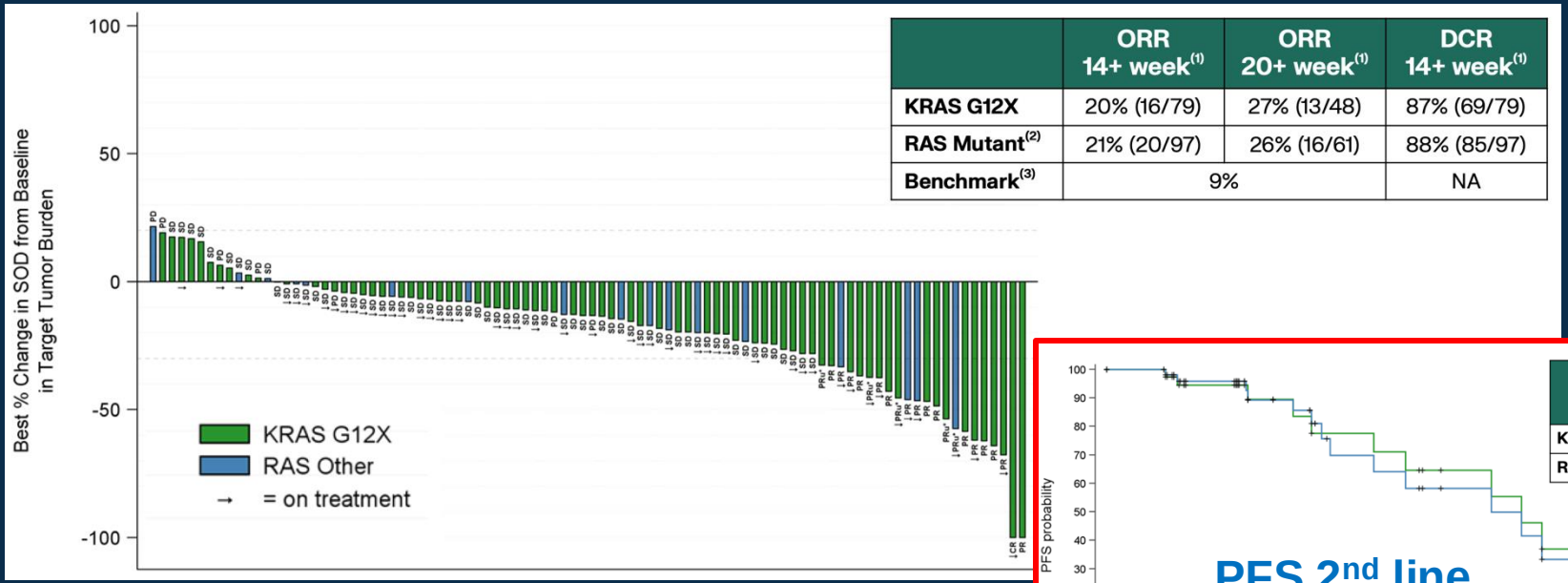
RMC-6236



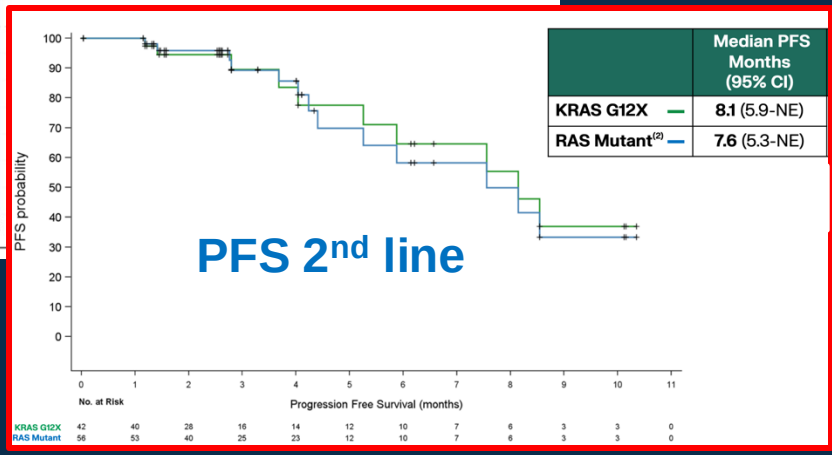
- Inhibitor recruits and binds to chaperone protein Cyclophilin A
- Tri-complex tailored to bind different RAS(ON) proteins
- Conformation change and steric inhibition of oncogenic activity

Schulze et al., Science 2023

Activity of RMC-6236 in 2nd+ Line mPDAC



	ORR 14+ week[1]	ORR 20+ week[1]	DCR 14+ week[1]
KRAS G12X	20% (16/79)	27% (13/48)	87% (69/79)
RAS Mutant[2]	21% (20/97)	26% (16/61)	88% (85/97)
Benchmark[3]	9%		NA



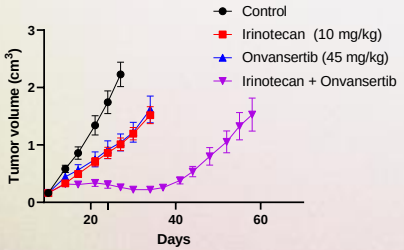
N=127

Revolution Medicines, Update from AACR 2024, 5/11/24 data cut-off

Phase 1b/2 Trial Rationale and Study Design: Adding Onvansertib to Standard-of-Care

Rationale: Synergy in combination with irinotecan

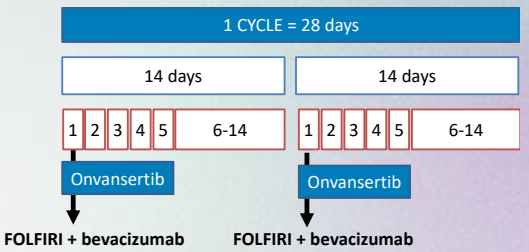
- In a KRAS mutant CRC mouse model, the combination of onvansertib and irinotecan significantly reduced tumor growth compared with either drug alone[5]



Study Design: Phase 1b/2 open-label

- Second-line treatment of KRAS mutant metastatic CRC patients
- Phase 1b dose escalation with Phase 2 expansion at RP2D

Dosing Schedule



Enrollment Status as of April 1, 2020

Number of patients (N)	Cohort 1 Onvansertib 12 mg/m²	Cohort 2 Onvansertib 15 mg/m²	Cohort 3 Onvansertib 18 mg/m²
Treated	6	3	3
Completing 1st cycle	6	3	0
Currently on Treatment	5	2	3

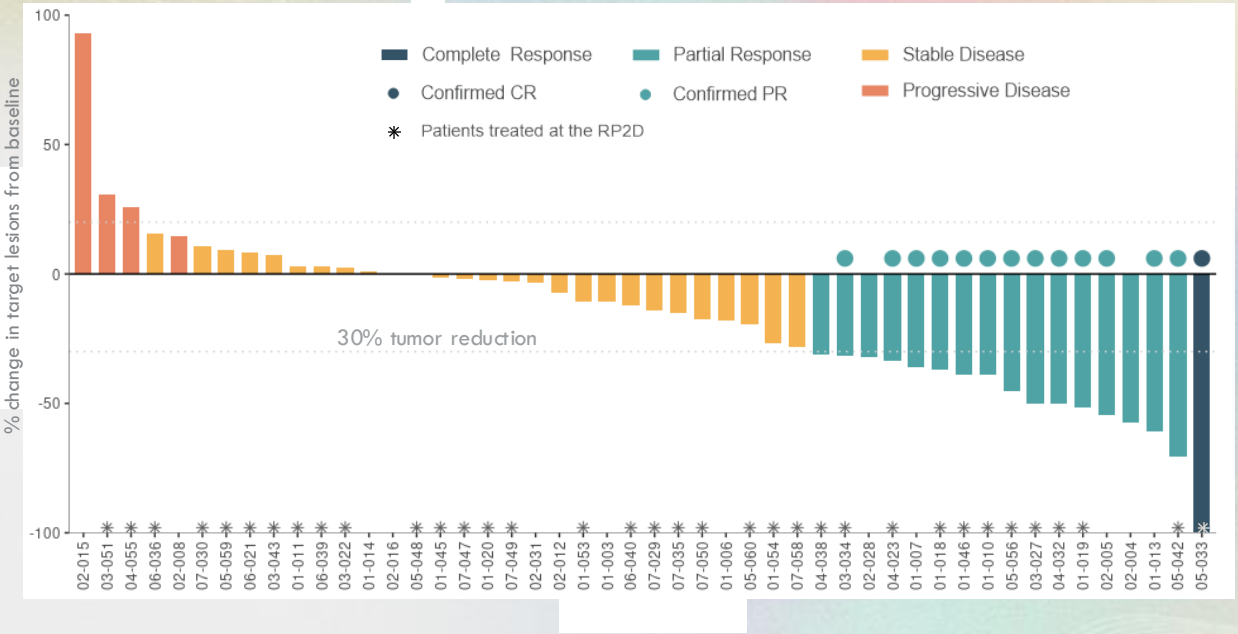
Efficacy Endpoints:

- **Primary:** Objective response rate (ORR) in patients who receive at least 1 cycle of treatment
- **Secondary:** Progression-free survival (PFS) and reduction in KRAS allelic burden

Lenz et al CCR 2022, Lenz et al JCO 2024 in press

Patients achieved a strong, durable response with onvansertib + SoC

Best Radiographic Response* – all doses (as of July 25, 2022)



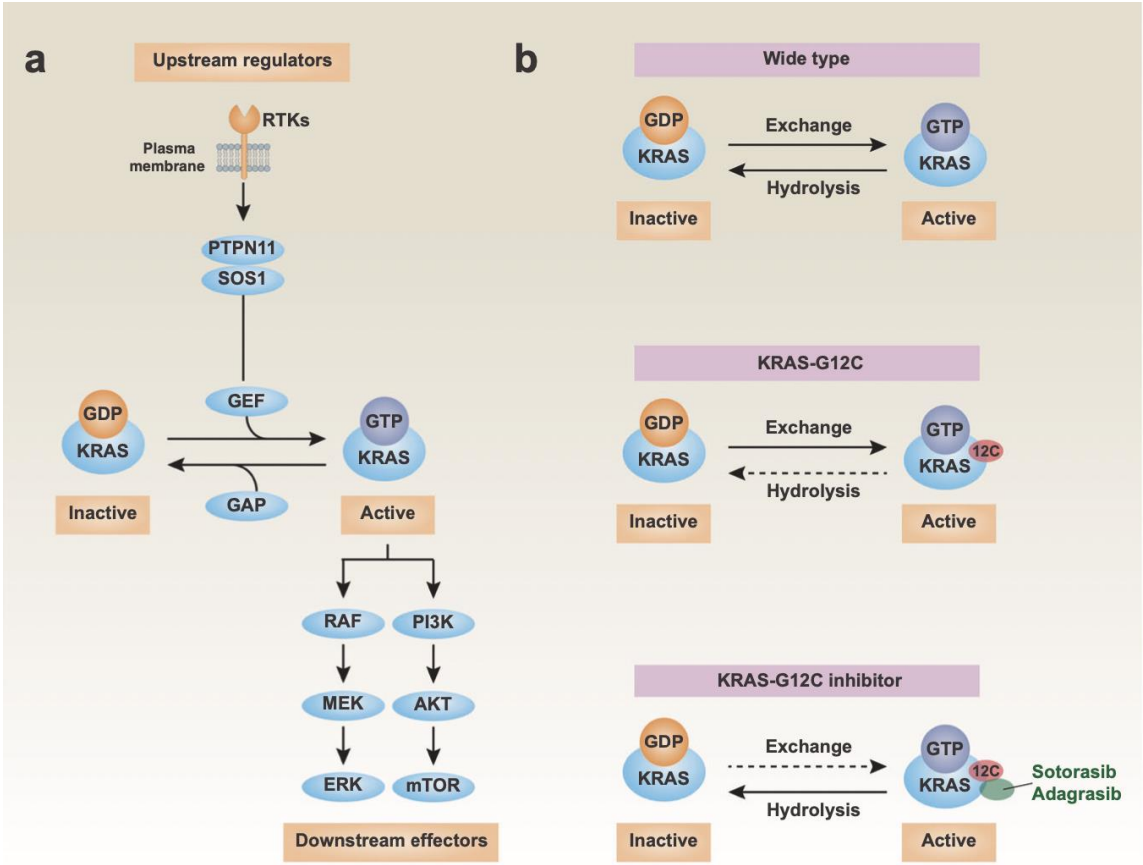
	All Doses	RP2D
Objective Response Rate* (CR + PR)	35% (17/48)	34% (12/35
Disease Control Rate (CR + PR + SD)	92% (44/48)	94% (33/35)

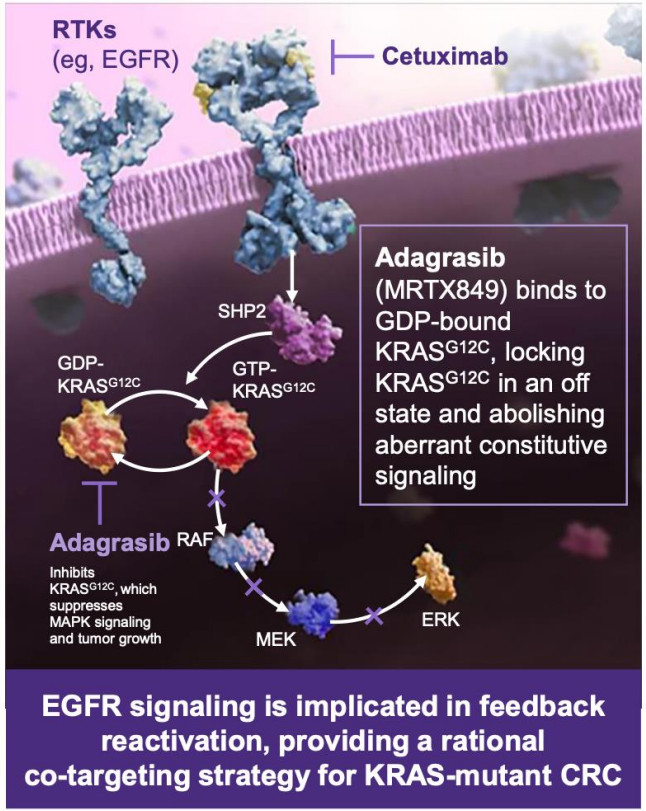
Durability

Median Duration of Response	11.7 months	12.5 months

- Radiographic response determined per RECIST 1.1. Waterfall plot and table reflect interim data as of July 25, 2022 from an ongoing trial and unlocked database
- Lenz et al JCO 2024 in press

KRAS G12C Inhibitors (3-4% of mCRC)

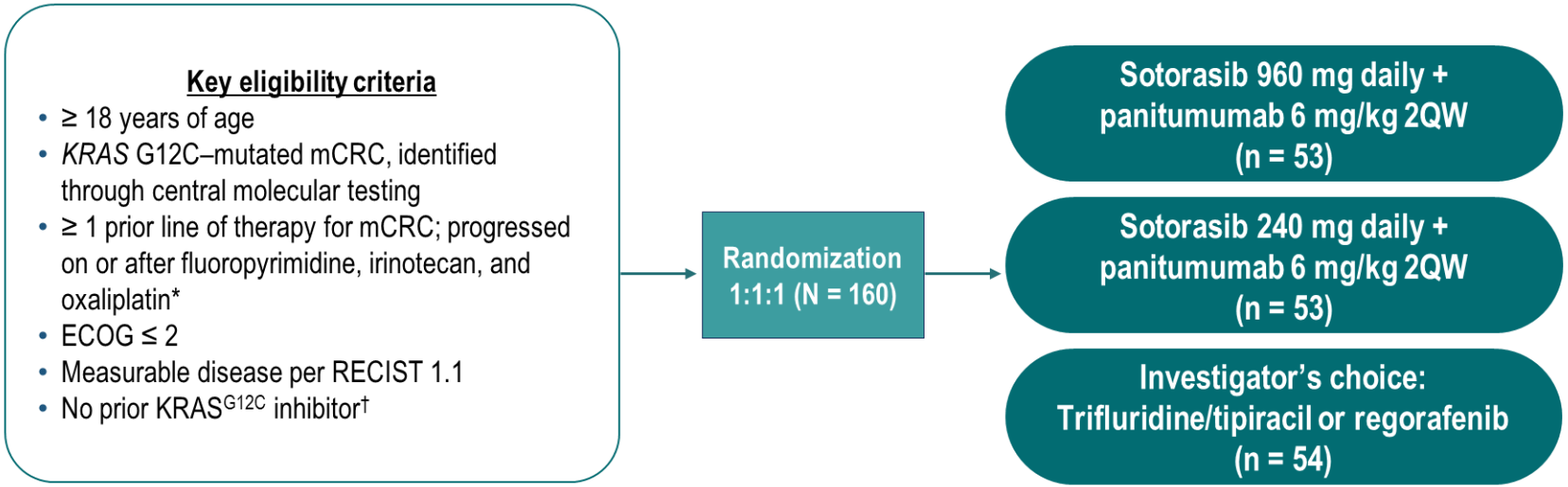




Liu et al, Cancer Gene Therapy 2021

CodeBreaK 300 Phase 3 Study Design

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



Stratified by: prior anti-angiogenic therapy (yes / no), **time from diagnosis of mCRC** (≥18 mo / <18 mo), **ECOG status** (0 or 1 / 2)

Treat until disease progression, start of another anti-cancer treatment, withdrawal of consent , or intolerance of treatment

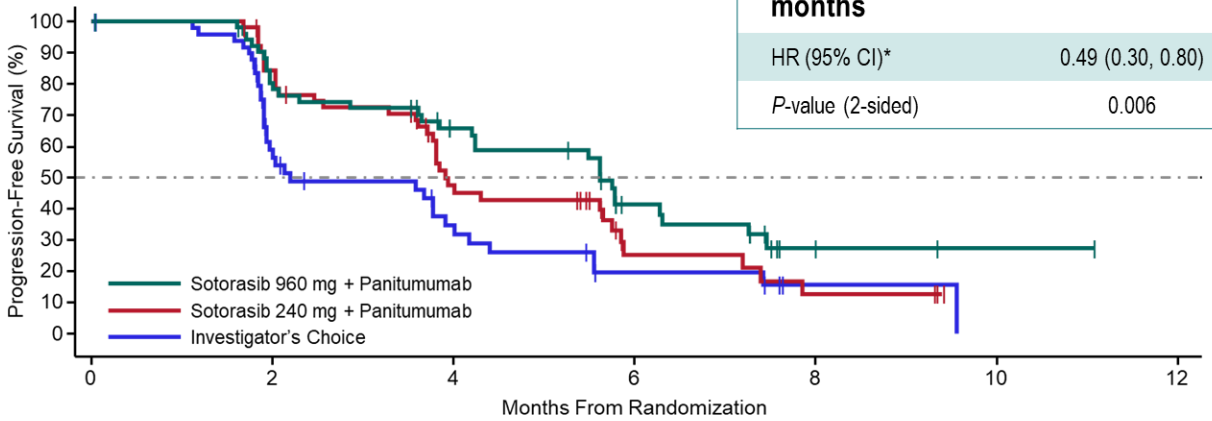
Primary endpoint: PFS by BICR (measured by CT / MRI and assessed by RECIST v1.1)
Key secondary endpoints: OS, ORR

*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.

Primary Endpoint: PFS in Intent-to-Treat Population

	Sotorasib 960 mg + Panitumumab (n = 53)	Sotorasib 240 mg + Panitumumab (n = 53)	Investigator's Choice (n = 54)
Median PFS, months	**5.6**	**3.9**	**2.2**
HR (95% CI)*	0.49 (0.30, 0.80)	0.58 (0.36, 0.93)	–
P-value (2-sided)	0.006	0.030	–



Number of Patients at Risk:

Sotorasib 960 mg + Panitumumab	53	40	28	13	2	1	0
Sotorasib 240 mg + Panitumumab	53	43	20	6	3	0	
Investigator's Choice	54	24	12	5	1	0	

After a median follow-up of 7.8 months, sotorasib (240 mg and 960 mg) in combination with panitumumab significantly improved PFS by BICR versus investigator's choice

PFS was tested using stratified log-rank test. *HR is sotorasib 960 mg + panitumumab / investigator's choice therapy, or sotorasib 240 mg + panitumumab / investigator's choice therapy.
BICR, blinded independent central review; HR, hazard ratio; PFS, progression-free survival.

Activity Outcomes

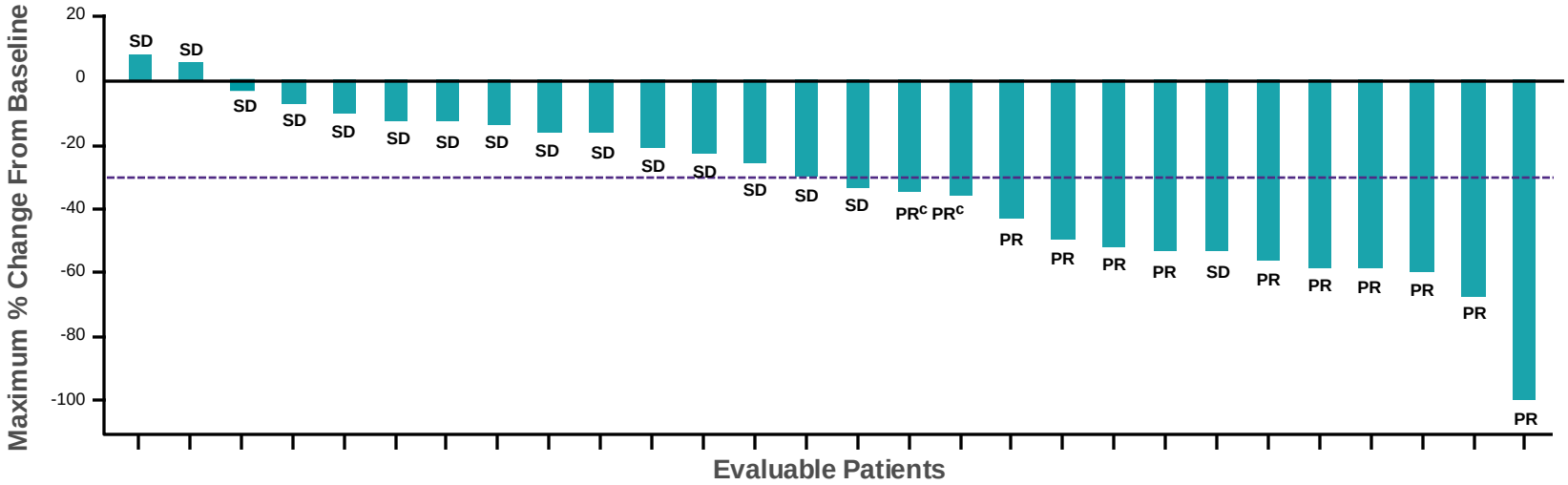
Response by BICR	Sotorasib 960 mg + Panitumumab (n = 53)	Sotorasib 240 mg + Panitumumab (n = 53)	Investigator's Choice (n = 54)
ORR, % (95% CI)*†	26 (15.3–40.3)	6 (1.2–15.7)	0 (0–6.6)
Complete response, n (%)	1 (2)	0	0
Partial response, n (%)	13 (25)	3 (6)	0
Stable disease, n (%)	24 (45)	33 (62)	25 (46)
Progressive disease, n (%)	12 (23)	13 (25)	17 (31)
Not evaluable / not done, n (%)	3 (6)	2 (4)	11 (20)
DCR, % (95% CI)*	72 (57.7–83.2)	68 (53.7–80.1)	46 (32.6–60.4)

ORR and DCR by BICR were higher with sotorasib (960 mg and 240 mg) + panitumumab versus investigator's choice

The intention-to-treat analysis set included all patients who underwent randomization.
*95% CIs were estimated using the Clopper-Pearson method. BICR, blinded independent central review; DCR, disease control rate; ORR, objective response rate
†Two patients (4%) in the 240 mg arm and 1 patient (2%) in the investigator's choice arm had non-complete response/non-progressive disease; these patients had BICR assessed non-target disease only

Adagrasib + Cetuximab in Patients With Advanced CRC: Best Overall Response

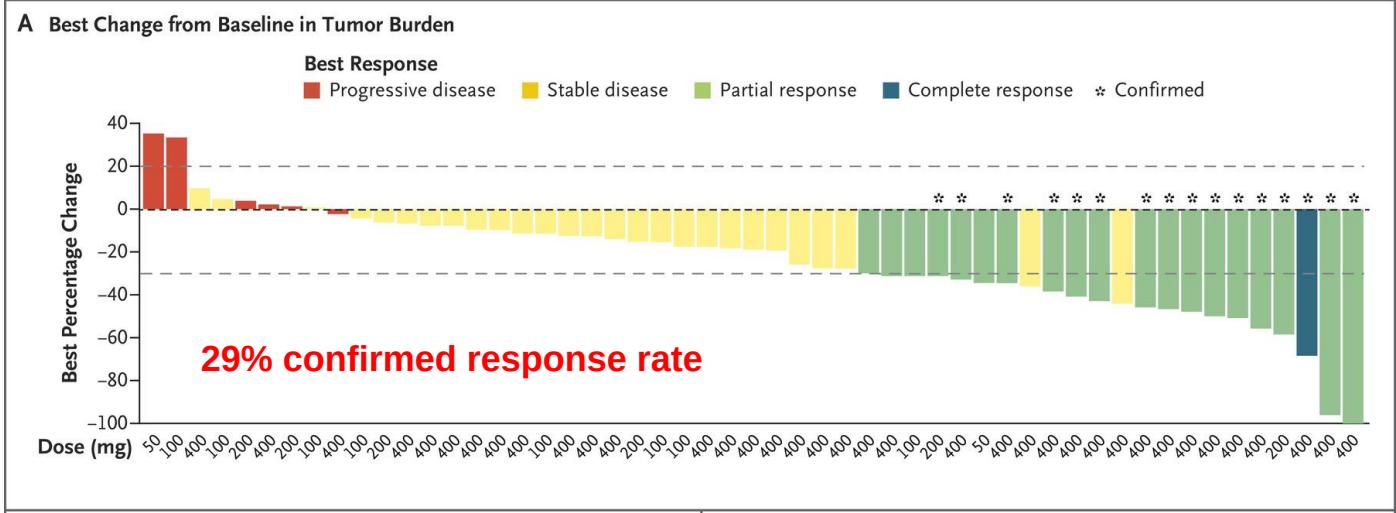
Best Tumor Change From Baseline (n=28)[a,b]

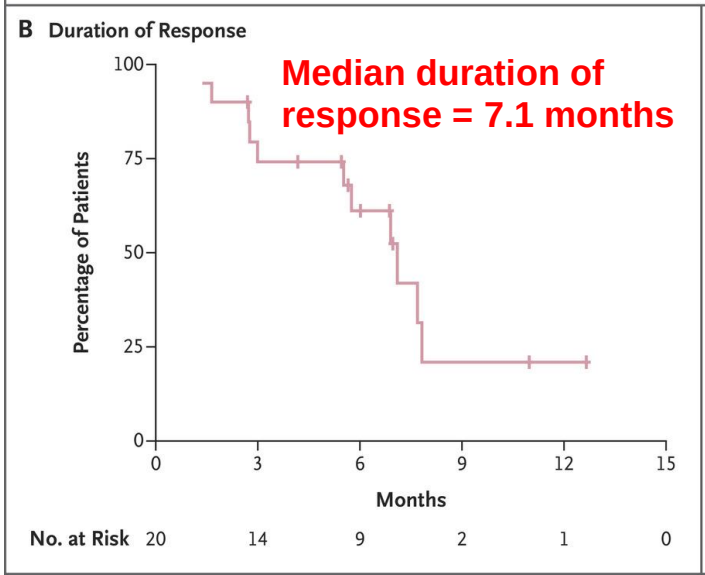


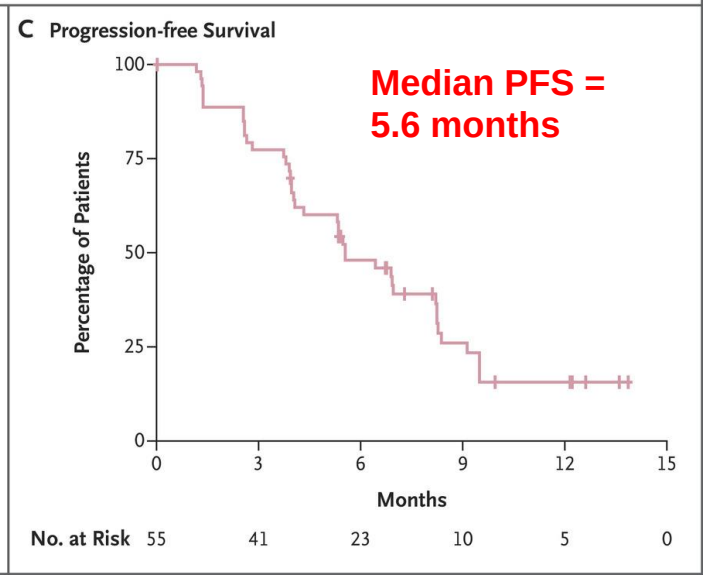
- Response rate was 43% (12/28), including 2 unconfirmed PRs
- SD was observed in 57% (16/28) of patients
- Clinical benefit (DCR) was observed in 100% (28/28) of patients
- No apparent association between response rate and molecular status was shown in an exploratory analysis[e]

[a]All results are based on investigator assessments. [b]Evaluable population (n=28) excludes 4 patients who withdrew consent prior to the first scan. [c]At the time of the 9 July 2021 data cutoff, 2 patients had uPRs.
[e]Molecular status (BRAF V600E mutation, MSI-H or dMMR, EGFR amplification, TP53 mutation, PIK3CA mutation) includes patients with conclusively evaluable test results.
Data as of 9 July 2021 (median follow-up: 7 months).

Divarasib in metastatic KRAS G12C mCRC *(n = 55)*

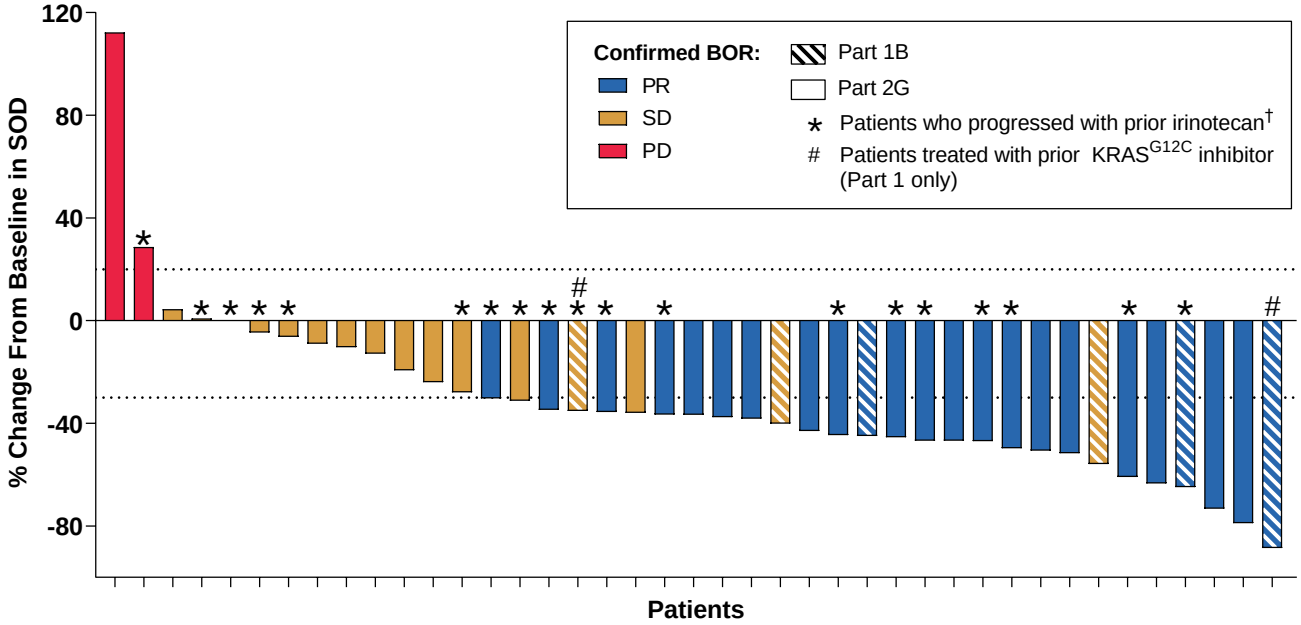






Sacher et al. *N Engl J Med* 2023.

Tumor Response with Sotorasib and FOLFIRI



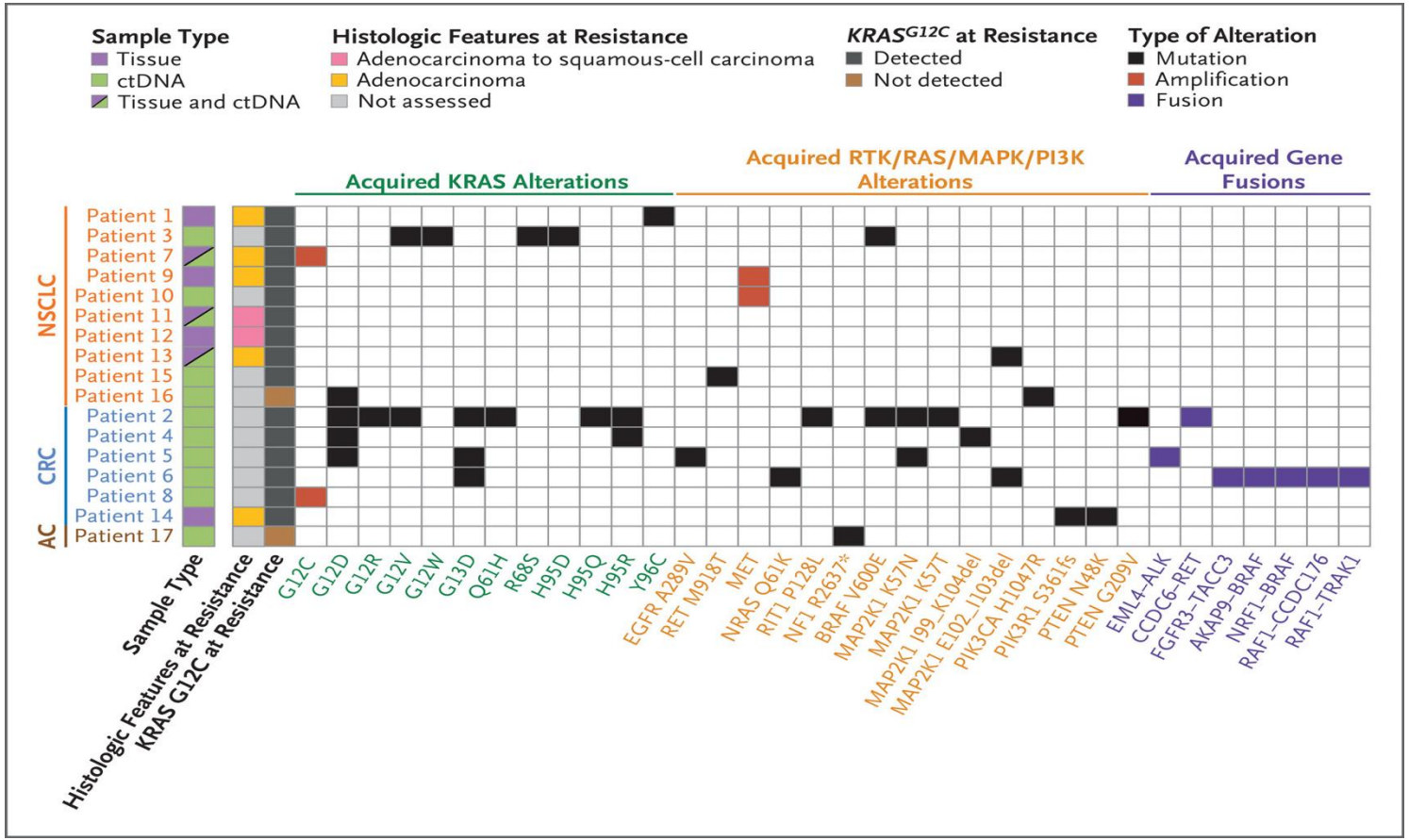
Data cutoff, April 13, 2023.

†Patients whose disease progressed on prior irinotecan include those with clinical or radiographic progression.

‡42 patients enrolled at least 7 weeks before analysis cutoff were included for response summary; 1 patient with no post-baseline scan is not shown in figure but is included in the denominator.

- **Reduction in RECIST target lesions was observed in 86% of patients‡**

Hong DS, et al. Poster presented at: American Society of Clinical Oncology; June 2-6, 2023; Chicago, IL. Abstract #3513

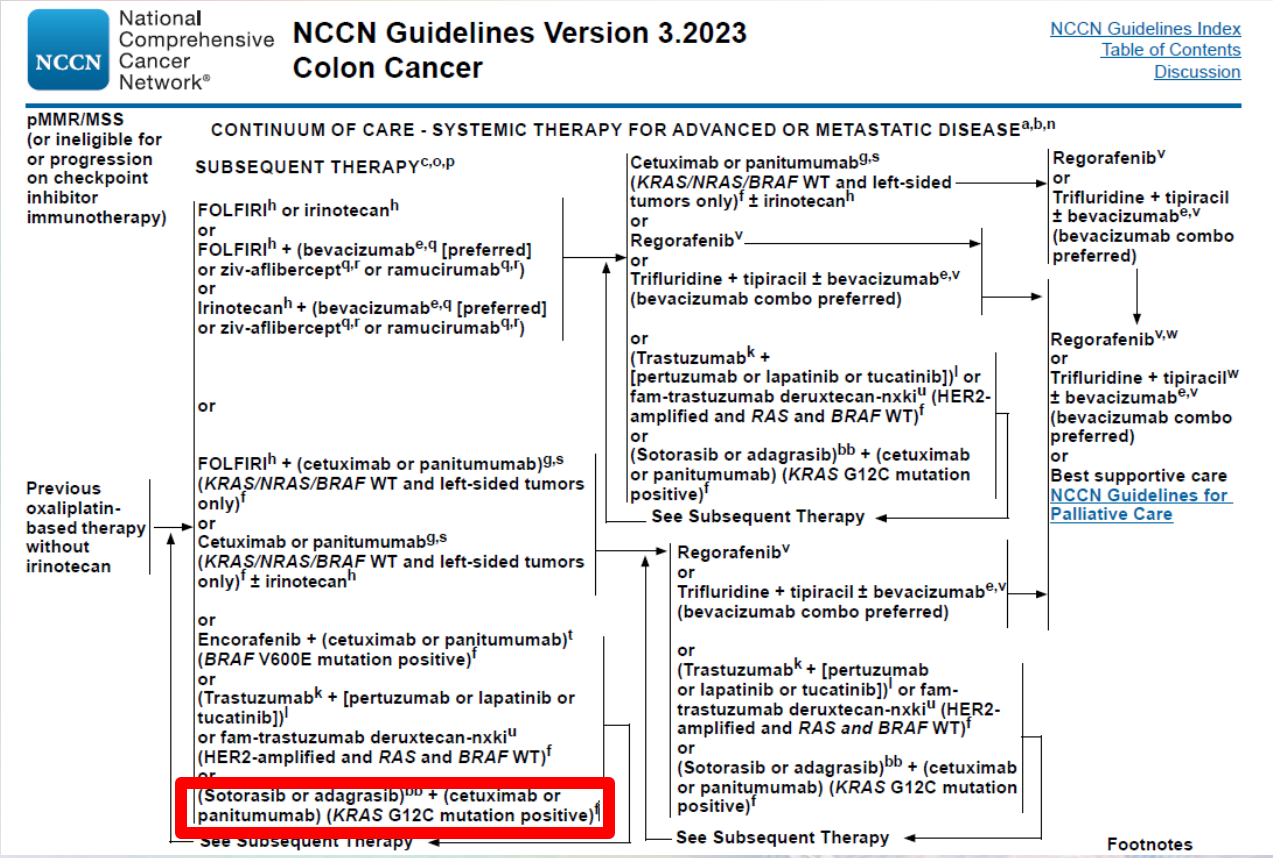


Awas et al NEJM 2021

Take Home Points:

- KRAS G12C is present in approximately 3% of all patients with mCRC
- Emerging data with G12C inhibitors + anti EGFR antibodies show significant response rates and promising progression-free survival
- Promising results seen with pan ras and pankras inhibitors, and the field is becoming increasingly crowded
- Combinations are well-tolerated, but dermatologic toxicity is seen in over half the patients treated
- Early data with chemotherapy (FOLFIRI) show impressive response rates

NCCN Colon Cancer Update 2023



Onvansertib with FOLFIRI shows promising efficacy

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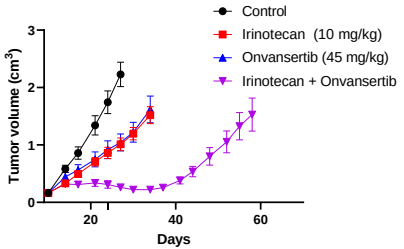

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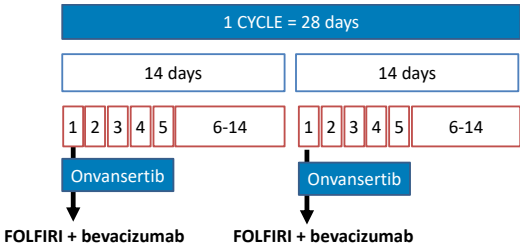

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Lenz et al CCR 2022, Lenz et al JCO 2024

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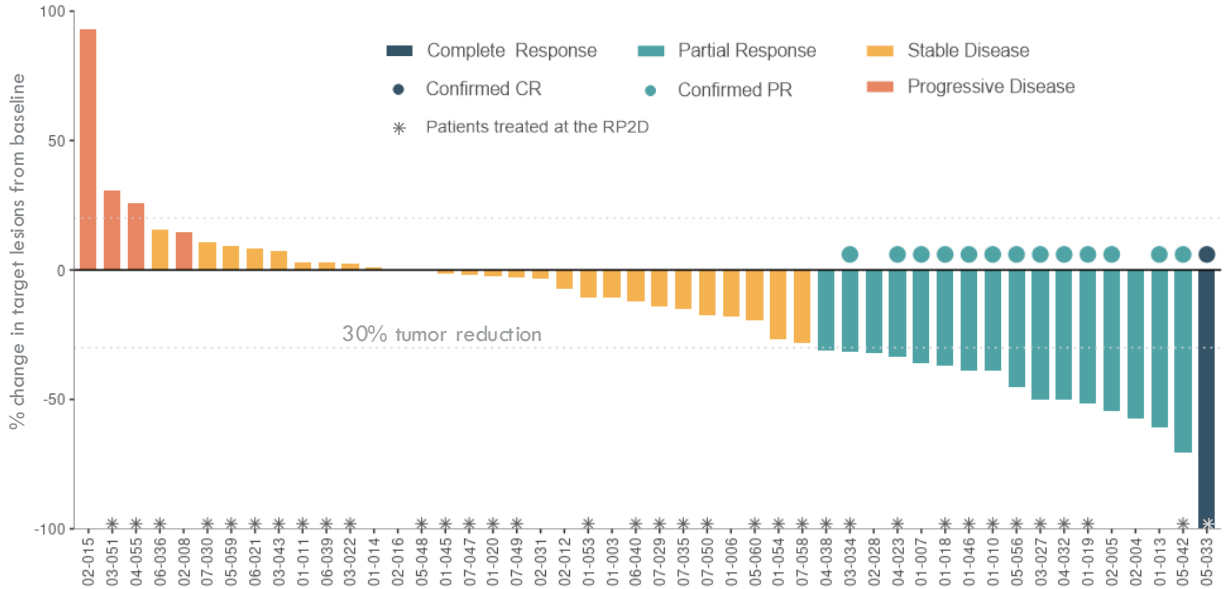

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Durability

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* Radiographic response determined per RECIST 1.1. Waterfall plot and table reflect interim data as of July 25, 2022 from an ongoing trial and unlocked database

New Updates on Targeting Her2

1. Tucanitib (new kid on the block)

Key Clinical Trials in *HER2*+ mCRC

Trial	Regimen	N	ORR, %	Median PFS, mo	Median OS, mo
HERACLES-A[1]	Trastuzumab + lapatinib[a]	27	30 (14-50)	4.8 (3.7-7.4)	10.6 (7.6-15.6)
MyPathway (*KRAS*wt subgroup)[2]	Trastuzumab + pertuzumab[a]	43	40 (25-56)	5.3 (2.7-6.1)	14 (8-NE)
TRIUMPH[3]	Trastuzumab + pertuzumab[a]	17 (tissue)	35 (14-62)	4 (1.4-5.6)	—
TAPUR[4] **(no *RAS* data)**	Trastuzumab + pertuzumab[a]	28	25 (11-45)	4 (2.6-6.3)	25 (6-NE)
MOUNTAINEER[5] **(Cohorts A + B)**	**Trastuzumab + tucatinib**	**86**	**38 (28-39)**	**8.2 (4.2-10.3)**	**24.1 (20.3-36.7)**
DESTINY-CRC01[6,b] **(Cohort A)**	**T-DXd**	**54**	**45 (32-60)**	**6.9 (4.1-8.7)**	**15.5 (8.8-20.8)**
HERACLES-B[7,c]	T-DM1 + pertuzumab	30	10 (0-28)	4.8 (3.6-5.8)	—

[a] In NCCN guidelines. [b] ORR in subgroup with prior HER2 rx 43.8% (19.8-70.1); without prior HER2 rx 45.9% (29.5-63.1). [c] Did not meet primary endpoint. T-DM1 had 0% response rate in MATCH Arm Q[8] and MSKCC Basket Trial.[9]

1. Sartore-Bianchi A et al. *Lancet Oncol.* 2016;17:738-746. 2. Meric-Bernstam F, et al. *Lancet Oncol.* 2019;20:518-530. 3. Nakamura Y, et al. ESMO 2019. Abstract 1057. 4. Gupta R, et al. ASCO GI 2020. Abstract 132. 5. Strickler J, et al. ESMO GI 2022. Abstract LBA 2. 6. Yoshino T, et al. Nat Com 2023 in press. 7. Sartore-Bianchi A. ESMO 2019. Abstract 3857. 8. Jhaveri KL, et al. *Ann Oncol.* 2019;30:1821-1830. 9. Li BT, et al. *J Clin Oncol.* 2018;36:2532-2537.

T-DXd in Patients with HER2-Overexpressing/Amplified (HER2+) Metastatic Colorectal Cancer (mCRC): Primary Results from the Multicenter, Randomized, Phase 2 DESTINY-CRC02 Study

Kanwal Raghav

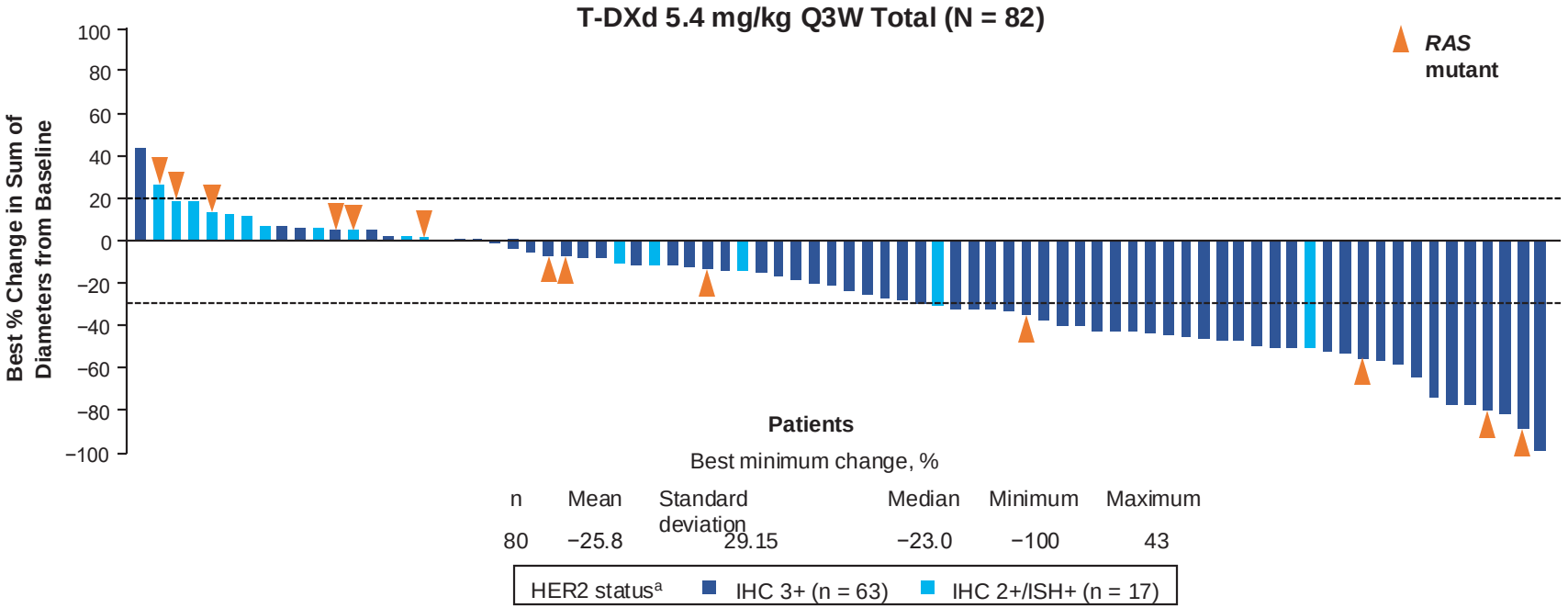
The University of Texas MD Anderson Cancer Center, Houston, TX, USA

June 4, 2023

Additional authors: Salvatore Siena, Atsuo Takashima, Takeshi Kato, Marc Van Den Eynde, Maria Di Bartolomeo, Yoshito Komatsu, Hisato Kawakami, Marc Peeters, Thierry Andre, Sara Lonardi, Kensei Yamaguchi, Jeanne Tie, Christina Gravalos Castro, John Strickler, Daniel Barrios, Qi Yan, Takahiro Kamio, Kojiro Kobayashi, Takayuki Yoshino

Raghav K, et al. Presented at: ASCO;2023.

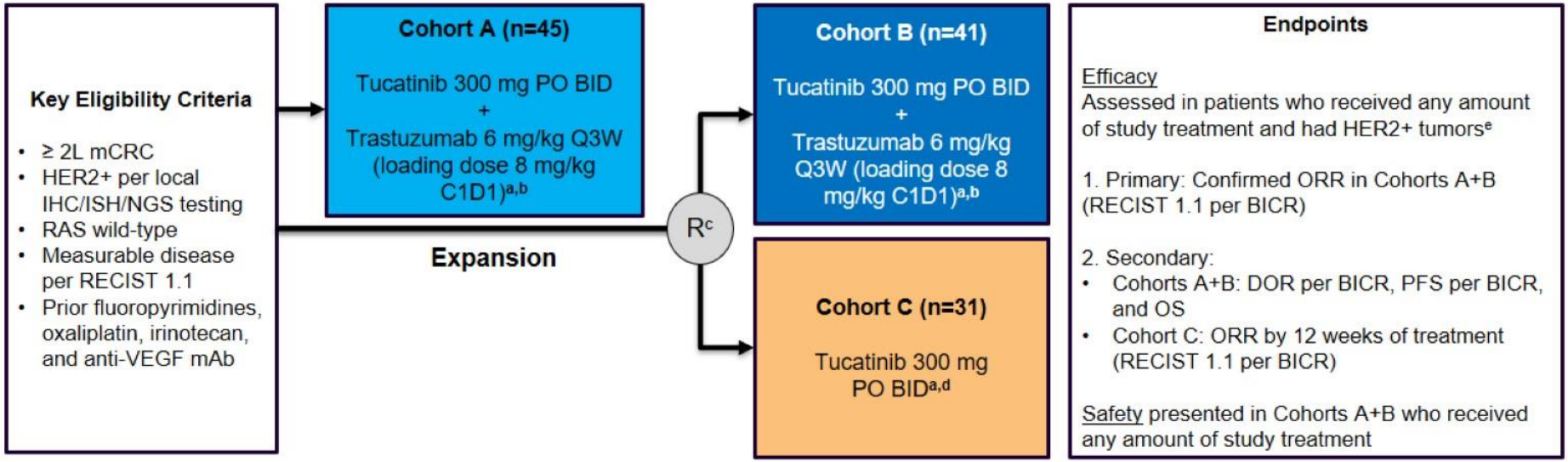
Best Percentage Change in Sum of Diameters by BICR for T-DXd 5.4 mg/kg



BICR, blinded independent central review; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; Q3W, every 3 weeks; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.
Only patients with measurable disease at baseline and at least one postbaseline tumor assessment were included in the waterfall graphs.
[a]HER2 status was assessed by central laboratory.

Raghav K, et al. Presented at: ASCO;2023.

MOUNTAINEER: Global, Open-Label, Phase 2 Trial



MOUNTAINEER began as a US Investigator-Sponsored Trial and initially consisted of a single cohort (Cohort A) and was expanded globally to include patients randomised to receive tucatinib + trastuzumab (Cohort B) or tucatinib monotherapy (Cohort C)

Data cut-off for current analysis, March 28, 2022

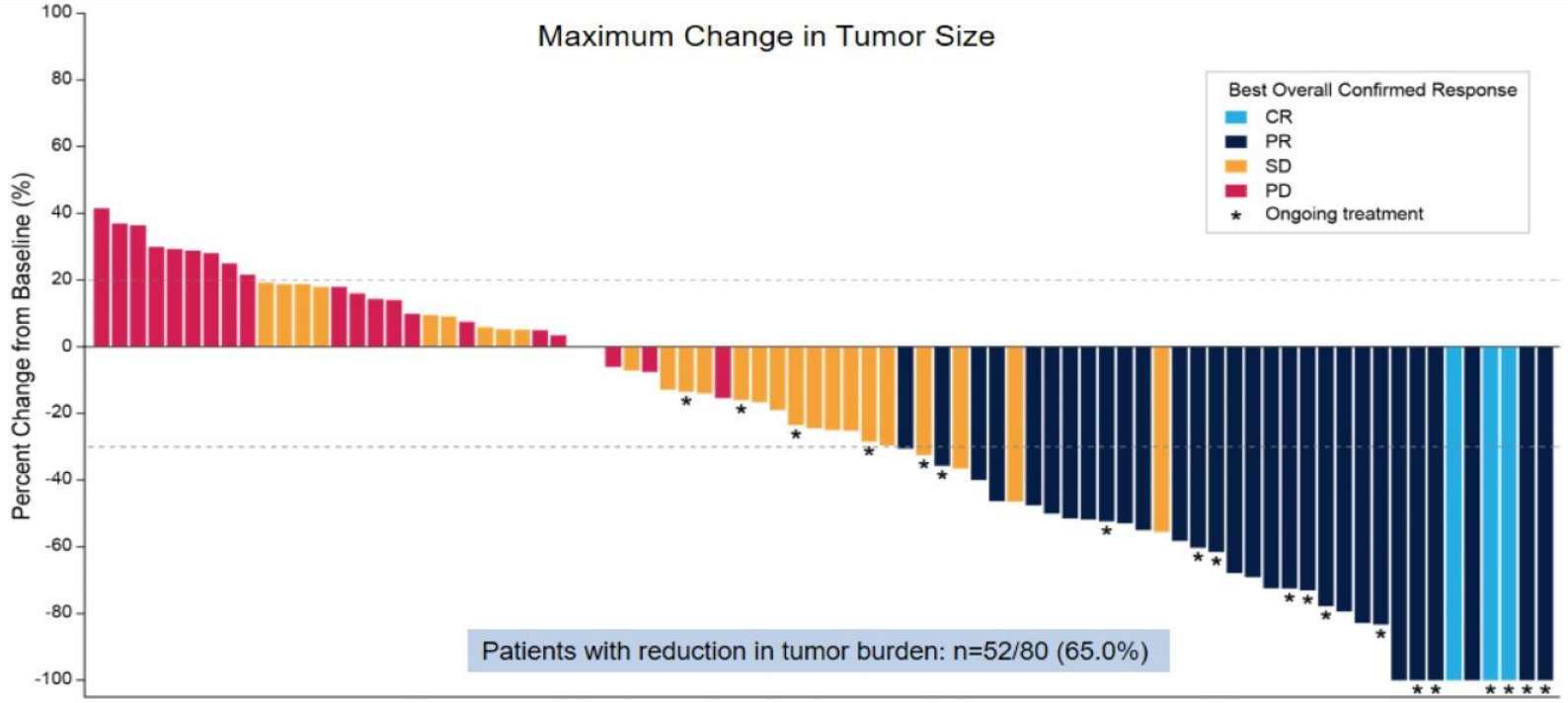
a Each treatment cycle is 21 days; b Patients remained on therapy until evidence of radiographic or clinical progression, unacceptable toxicity, withdrawal of consent, or study closure; c Stratification: Left sided tumor primary vs other; d Patients were allowed to cross over and receive tucatinib and trastuzumab if they experienced radiographic progression at any time point or if they had not achieved a PR or CR by week 12; e Patients had HER2+ tumors as defined by one or more protocol required local tests: IHC 3+ (n=46), amplification by ISH (n=36), or amplification by NGS (n=69)

2L+, second line and later; BICR, blinded independent central review; BID, twice a day; C1D1, cycle 1 day 1; CR, complete response; DOR, duration of response; HER2, human epidermal growth receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mAb, monoclonal antibody; mCRC, metastatic colorectal cancer; NGS, next-generation sequencing; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; Q3W, every 3 weeks; PR, partial response; R, randomisation; RAS, rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumors; US, United States; VEGF, vascular endothelial growth factor.

https://clinicaltrials.gov/ct2/show/NCT03043313

Stricker J, et al. Presented at: ESMO-WCGI;202.

Tucatinib + Trastuzumab: Change in Tumor Size



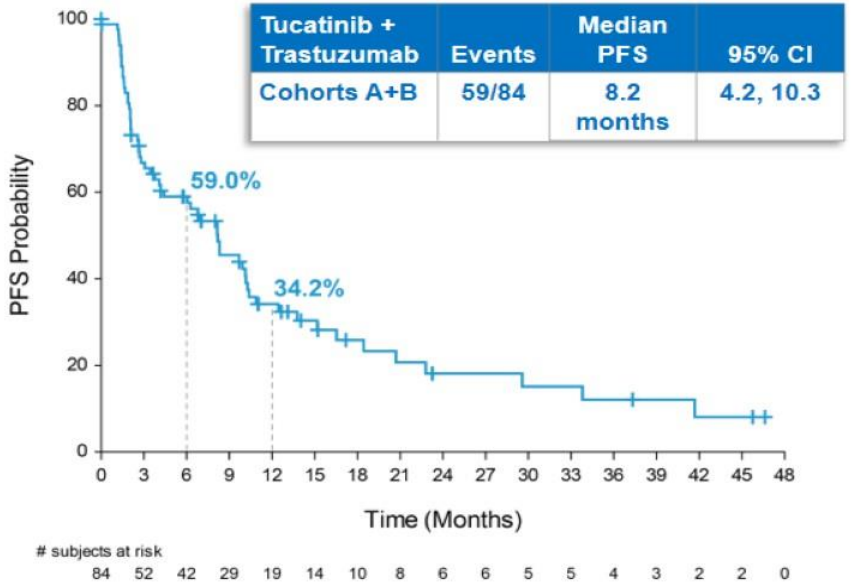
a Four patients who did not have baseline and/or post-baseline target lesion measurements are excluded
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
Data cutoff: 28 Mar 2022

Raghav K, et al. Presented at: ASCO;2023.

Tucatinib + Trastuzumab: PFS and OS

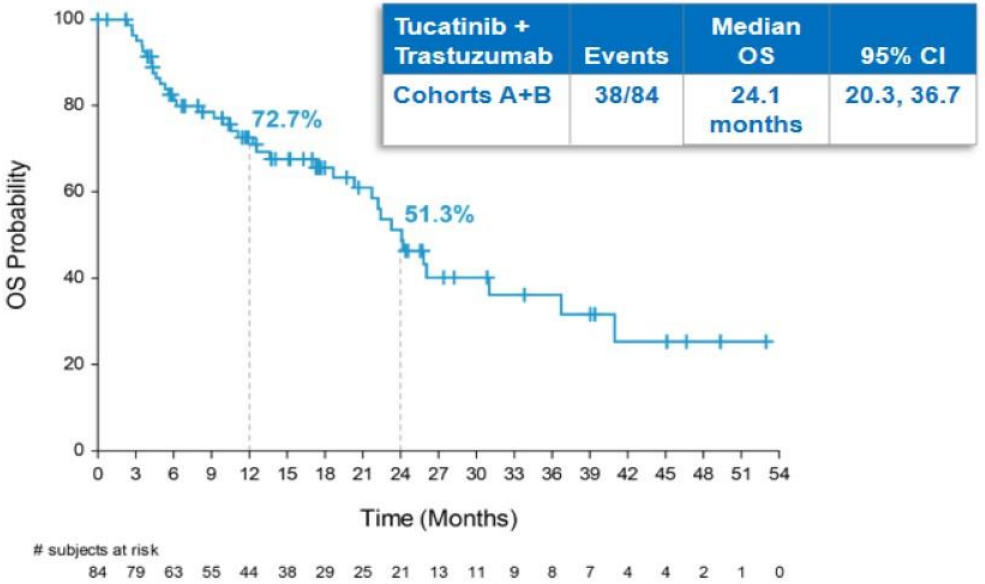
Progression-free Survival per BICR

Tucatinib + Trastuzumab	Events	Median PFS	95% CI
Cohorts A+B	59/84	8.2 months	4.2, 10.3



Overall Survival

Tucatinib + Trastuzumab	Events	Median OS	95% CI
Cohorts A+B	38/84	24.1 months	20.3, 36.7



Median follow-up for Cohorts A+B was 20.7 months (IQR, 11.7, 39.0)

BICR, blinded independent central review; IQR, interquartile range; OS, overall survival; PFS, progressive-free survival.
Data cutoff: 28 Mar 2022

Raghav K, et al. Presented at: ASCO;2023.

Anti-HER2 Therapies: FDA approved for HER2+ mCRC

FDA grants accelerated approval to tucatinib with trastuzumab for colorectal cancer

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On January 19, 2023, the Food and Drug Administration (FDA) granted accelerated approval to tucatinib [redacted].) in combination with trastuzu type HER2-positive unresectable or metastatic colorectal cancer that ha following fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemother

FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for unresectable or metastatic HER2-positive solid tumors

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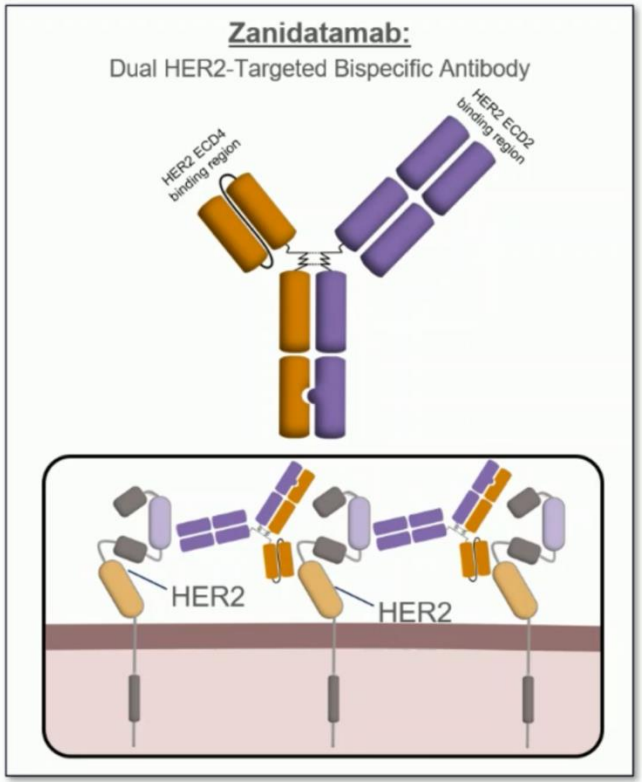
On April 5, 2024, the Food and Drug Administration granted accelerated approval to fam-trastuzumab deruxtecan-nxki ([redacted], Inc.) for adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

Zanidatamab – bispecific antibody



Key eligibility criteria:

- Unresectable, locally advanced, recurrent or metastatic CRC
- HER2-expressing/amplified tumours (IHC 3+; or *HER2* gene amplified) based upon central assessment
- Extended *RAS*- and *BRAF*-wildtype based on local or central assessment
- ECOG PS ≤1
- No prior HER2-targeted agents
- No prior systemic therapy for metastatic disease
  - ✓ One prior cycle of 5-FU based chemotherapy for was permitted

Physician's choice of chemotherapy regimen (≥6 cycles):[a]

28-day cycle: **Zanidatamab + mFOLFOX6-2**
(Zanidatamab 1200/1600 mg[b] + mFOLFOX6-2: Leucovorin 400 mg/m² and oxaliplatin 85 mg/m² on days 1 and 15; 5-FU 1200 mg/m²/day on days 1-2 and 15-16)

OR

28-day cycle: **Zanidatamab + mFOLFOX6-2 + bevacizumab**
(Zanidatamab 1200/1600 mg[b] + mFOLFOX6-2 + bevacizumab: 5 mg/kg on days 1 and 15)

Tumour assessment Q6W per RECIST v1.1[1]
DLTs evaluated during the first 28-week cycle
Mandatory premedication for IRR[c] and antidiarrhoeal[d] prophylaxis

Primary endpoints (Part 1):
- DLTs
- AEs and SAEs
- Laboratory abnormalities
- Dose reductions

Secondary endpoints (Part 1):
- Objective response rate
- Disease control rate
- Duration of response
- Progression-free survival

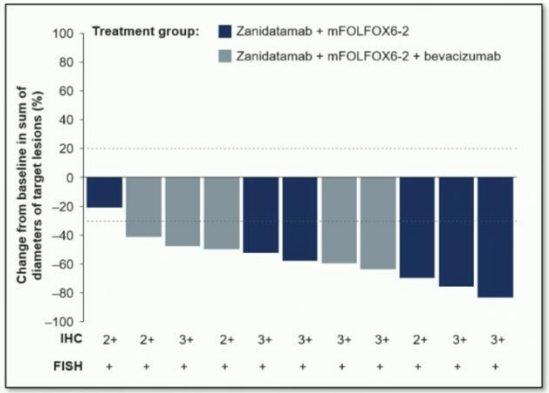
CRC patients treated (Part 1) N=13
DLT evaluable[e] n=12
Response evaluable n=11

ClinicalTrials.gov: NCT03929666

Data cut-off: 31 October 2023

	Zanidatamab + mFOLFOX6-2 (n=6)	Zanidatamab + mFOLFOX6-2 + bevacizumab (n=5)	Total (N=11)
cORR			
n (%)	5 (83.3)	5 (100)	10 (90.9)
95% CI	35.9, 99.6	47.8, 100	58.7, 99.8
cBOR, n (%)			
CR	0 (0)	0 (0)	0 (0)
PR	5 (83.3)	5 (100)	10 (90.9)
SD	1 (16.7)	0 (0)	1 (9.1)
PD	0 (0)	0 (0)	0 (0)
DCR[b]			
n (%)	6 (100)	5 (100)	11 (100)
95% CI	54.1, 100	47.8, 100	71.5, 100

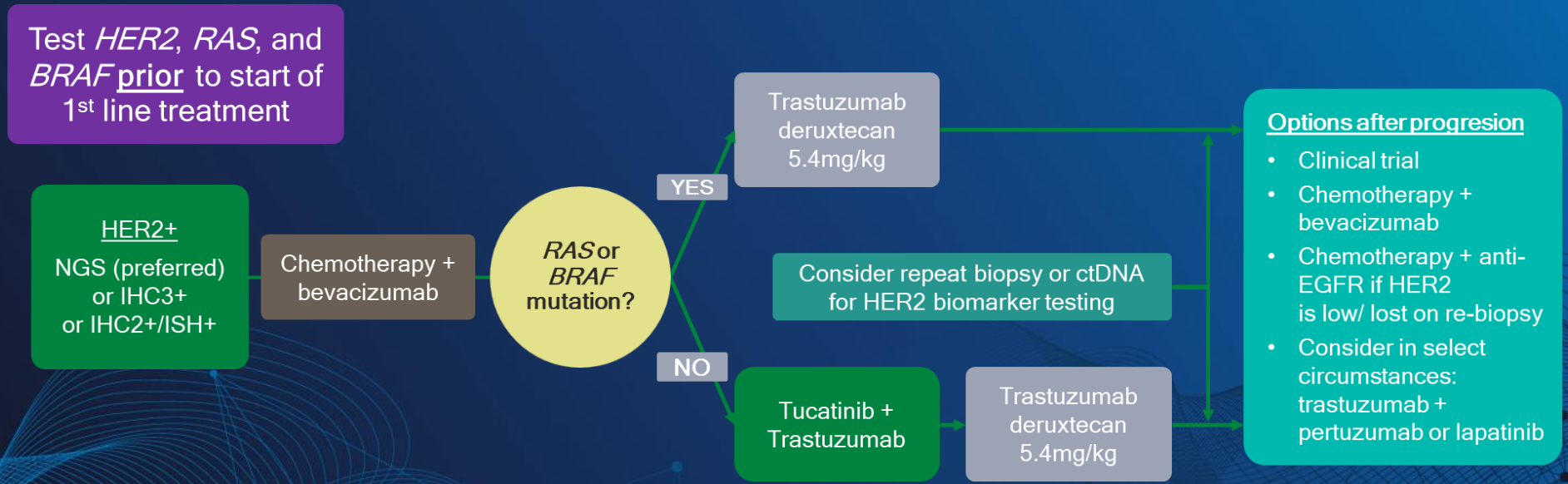
Median (range) duration of response:
Not reached (2.9+-16.7+) months



Dotted lines indicate 20% increase or 30% decrease in sum of diameters of target tumours.

Rha et al., ESMO 2024

How I treat HER2+ MSS Metastatic CRC



TARGETING BRAF V600E

BREAKWATER: Study Design

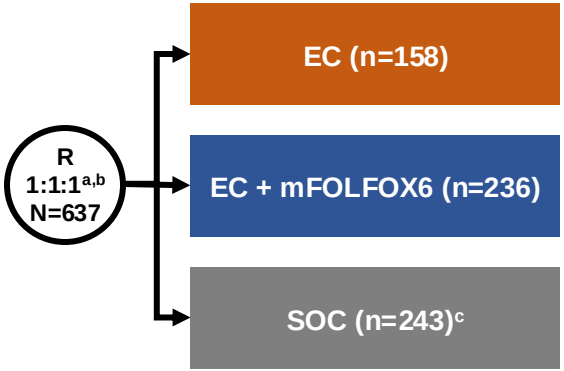
- BREAKWATER (NCT04607421) is an open-label, multicenter, phase 3 study in first line BRAF V600E-mutant mCRC

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

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



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)

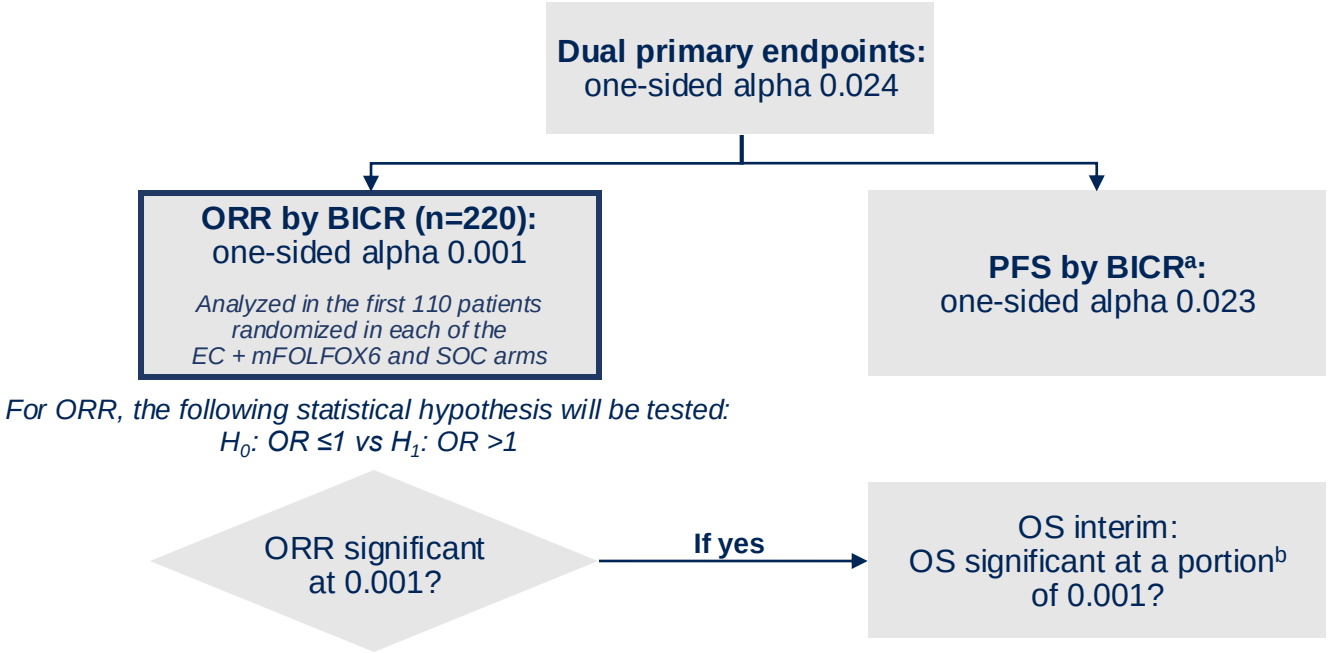
Key secondary endpoint:
OS (EC + mFOLFOX6 vs SOC)

Here we present the primary analysis of ORR by BICR (one of the dual primary endpoints), an interim analysis of OS, and safety in the EC + mFOLFOX6 and SOC arms

[a]Following a protocol amendment, enrollment to the EC arm was stopped and patients were randomized 1:1 to the EC+mFOLFOX6 or SOC arms; data in the EC arm will be reported at a later date. [b]Patients were enrolled between November 16, 2021, and December 22, 2023. [c]mFOLFOX6/FOLFOXIRI/CAPOX ± bevacizumab. [d]In the first 110 patients in each of the EC+mFOLFOX6 and SOC arms.

CAPOX, capecitabine/oxaliplatin; BICR, blinded independent central review; dMMR, deficient mismatch repair; EC, encorafenib plus cetuximab; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; FOLFOXIRI, fluorouracil/leucovorin/oxaliplatin/irinotecan; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high cancer; RECIST, Response Evaluation Criteria in Solid Tumors.

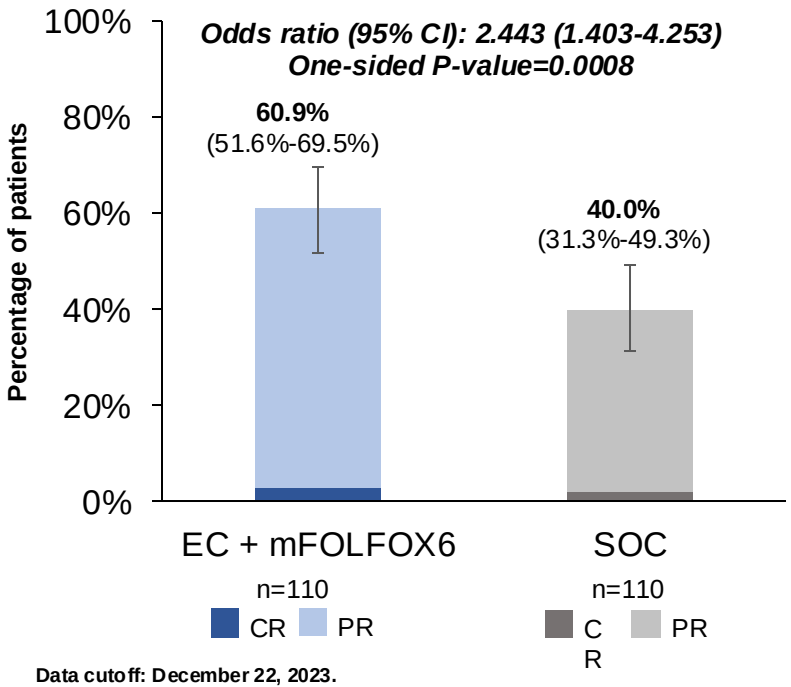
BREAKWATER: Statistical Analysis



[a]PFS by BICR in all randomized patients will be analyzed once the required number of events has been observed.
[b]Following a prespecified hierarchical testing procedure to control the family-wise type I error rate, based on the proportion of information fraction observed at the time of the OS interim analysis.
BICR, blinded independent central review; EC, encorafenib plus cetuximab; H_0, null hypothesis; H_1, alternative hypothesis; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; OR, odds ratio for objective response of EC+mFOLFOX6 vs SOC; SOC, standard of care.

Overview of Response by BICR

Confirmed ORR by BICR



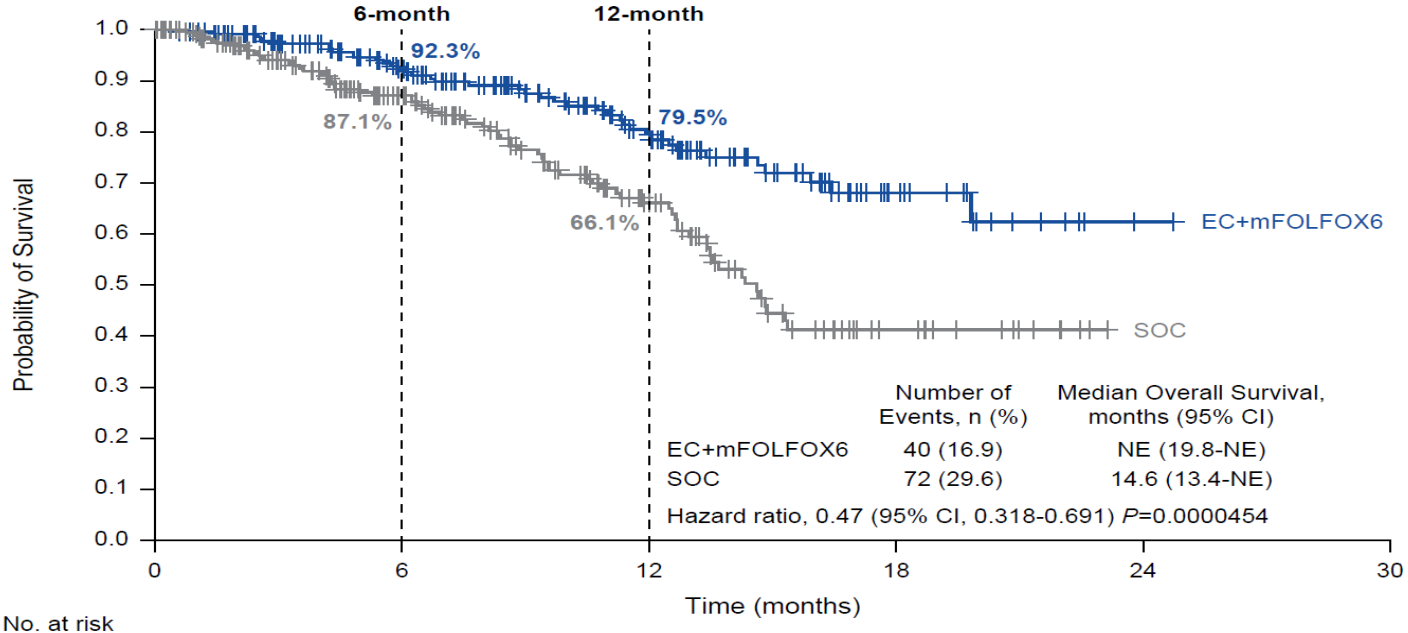
Confirmed Best Overall Response, TTR, and DOR by BICR

	EC + mFOLFOX6 n=110	SOC n=110
Confirmed best overall response, n (%)		
CR	3 (2.7)	2 (1.8)
PR	64 (58.2)	42 (38.2)
SD	31 (28.2)	34 (30.9)
Non-CR/non-PD	3 (2.7)	4 (3.6)
PD	3 (2.7)	9 (8.2)
NE	6 (5.5)	19 (17.3)
	n=67	**n=44**
TTR, median (range), weeks	7.1 (5.7-53.7)	7.3 (5.4-48.0)
Estimated DOR, median (range), months	13.9 (8.5-NE)	11.1 (6.7-12.7)
Patients with a DOR of ≥6 months, n (%)	46 (68.7)	15 (34.1)
Patients with a DOR of ≥12 months, n (%)	15 (22.4)	5 (11.4)

Data cutoff: December 22, 2023.

BICR, blinded independent central review; CR, complete response; DOR, duration of response; EC, encorafenib plus cetuximab; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease; SOC, standard of care; TTR, time to response.

Interim Overall Survival[a]



Data cutoff: December 22, 2023.

[a]OS was tested following the prespecified plan with one-sided alpha of 0.000000083, calculated as a portion of the nominal one-sided alpha of 0.001. Statistical significance was not achieved at this time.

EC, encorafenib plus cetuximab; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; NE, not estimable; SOC, standard of care.

Conclusions

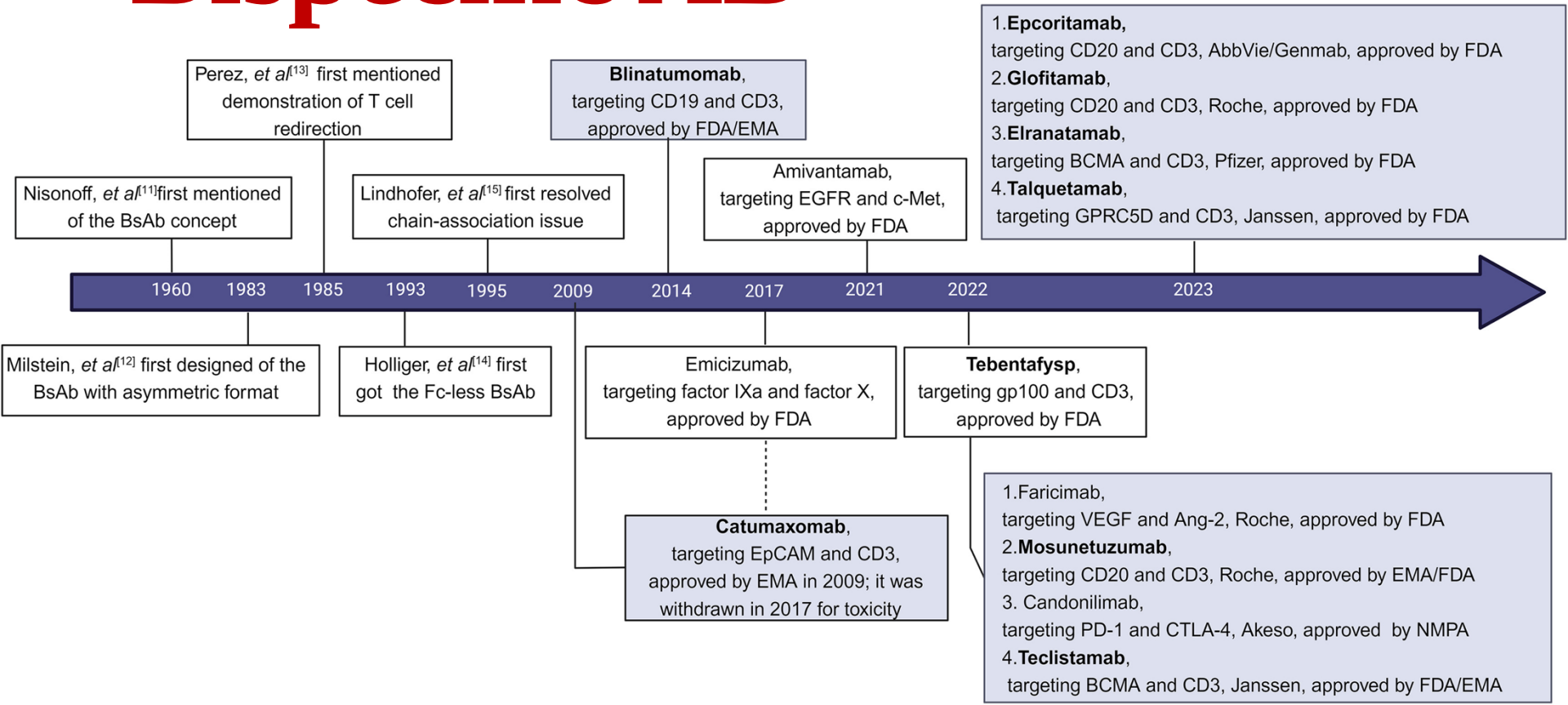
- BREAKWATER showed a statistically significant and clinically meaningful benefit in ORR by BICR, one of the dual primary endpoints, with EC + mFOLFOX6 vs SOC that was rapid and durable
  - Data showed a trend for OS improvement with EC + mFOLFOX6 vs SOC; follow-up is ongoing, with planned additional interim and final analyses
- EC + mFOLFOX6 was generally tolerable
  - There was no substantial increase in chemotherapy dose reduction or discontinuation due to AEs compared with the SOC arm
  - The most frequently reported TEAEs were consistent with those expected for each of the study drugs
- Prespecified analyses of mature PFS and OS data are planned
- The BREAKWATER study supports EC + mFOLFOX6 as a new first-line SOC for patients with BRAF V600E-mutant mCRC

These results also formed the basis for the accelerated approval by the FDA (as part of Project FrontRunner) of EC + mFOLFOX6 for the treatment of patients with BRAF V600E-mutant mCRC—including in the first line setting

EC, encorafenib plus cetuximab; FDA, US Food and Drug Administration; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; SOC, standard of care; TEAE, treatment-emergent adverse event.

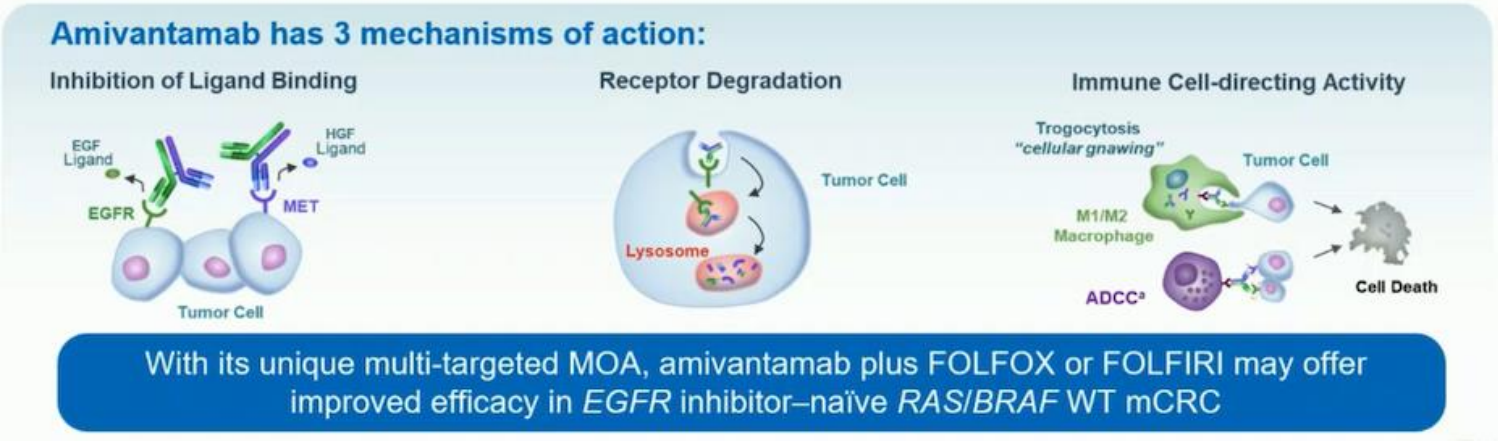
TARGETING C-MET

Bispecific AB



EGFR-MET Bispecific Antibody: Amivantamab

- MET alterations are associated with poor prognosis in CRC and are common mechanisms of resistance to EGFR inhibitors
- Amivantamab is a bispecific EGF receptor-directed and mesenchymal epithelial transition (MET) receptor-directed antibody
- FDA Approved in NSCLC with EGFR exon 20 insertion mutations



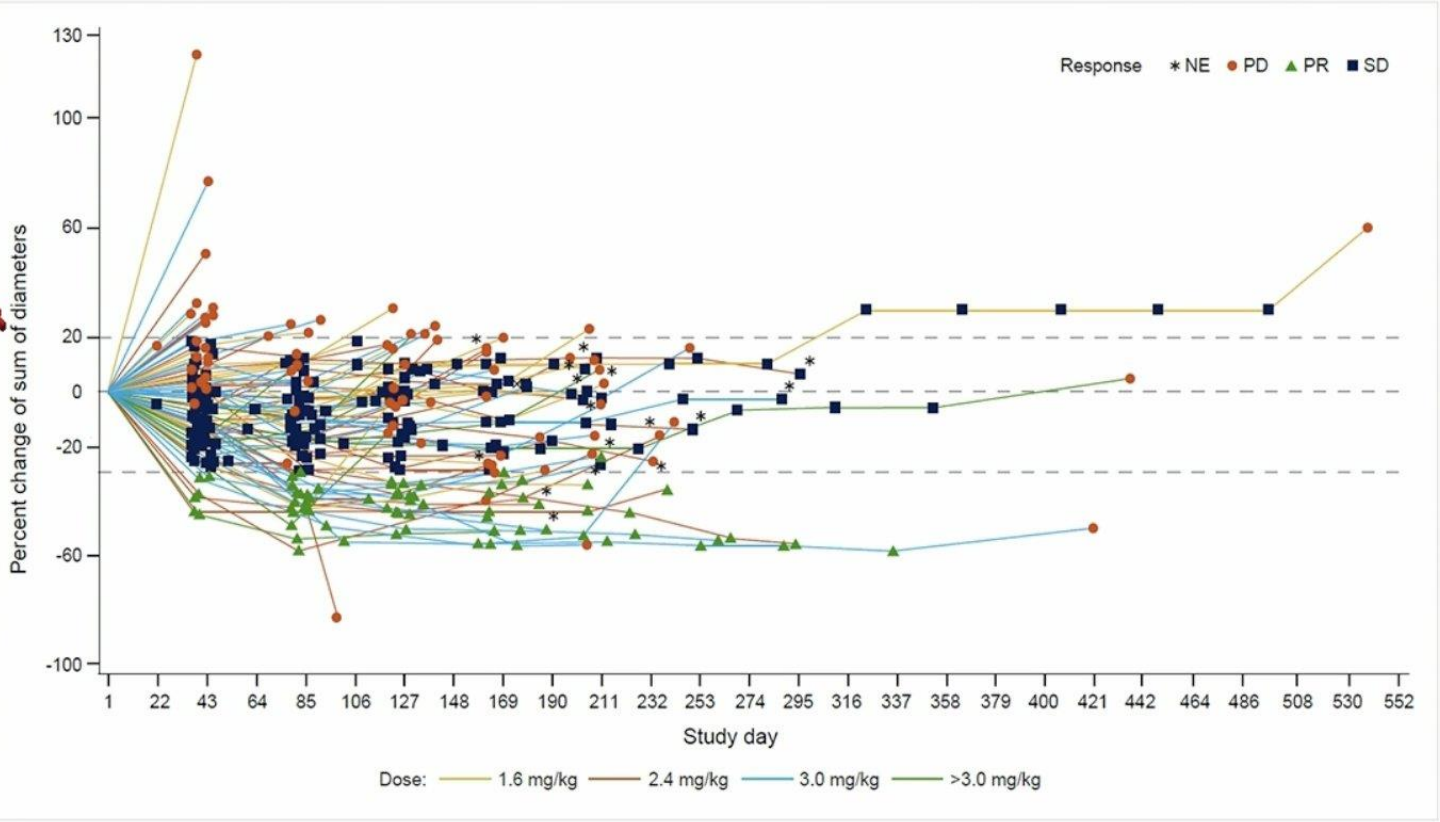
Pietrantonio et al., ESMO 2024

Amivantamab: Single Agent Activity in CRC

- OrigAMI-1: Open-label phase 1b/2 study
- 93 patients with refractory mCRC
- RAS/ BRAF wild-type, HER-2 negative

Cohort	N	RR (%)	mDOR (mo)	mPFS (mo)
Left-sided, no prior EGFR mAb	17	41	7.5	5.7
Left-sided, prior EGFR mAB	54	24	7.4	3.75
Right-sided	18	6	NE	3.5

ABBV-400: Observed responses across all doses in 3L+ CRC



	Total* (N=122)
ORR, n (%)	20 (16)
CBR12, n (%)	61 (50)
CBR24, n (%)	35 (29)
DOR, months (95% CI)	5.5 (4.1–NE)

*Includes 9 patients who received dose >3 mg/kg in dose escalation; The maximum tolerated dose was established as 3.0 mg/kg.
CBR12/24, clinical benefit rate at 12/24 weeks (complete response plus partial response plus stable disease); DOR, duration of response; NE, not evaluable; PD, progressive disease; PR, partial response; ORR, overall response rate; SD, stable disease.

Amivantamab: Combination with Chemo

Dose escalation identified amivantamab 1050 mg IV (1400 mg if ≥80 kg) weekly for the first 4 weeks, then every 2 weeks in combination with standard mFOLFOX6 or FOLFIRI dosing as the RP2D

Key Eligibility Criteria

- ECOG PS score of 0–1
- Eligible for 1L or 2L therapy
- No prior EGFRi

Cohort D: Amivantamab + mFOLFOX6 (n=20)

Cohort E: Amivantamab + FOLFIRI (n=23)

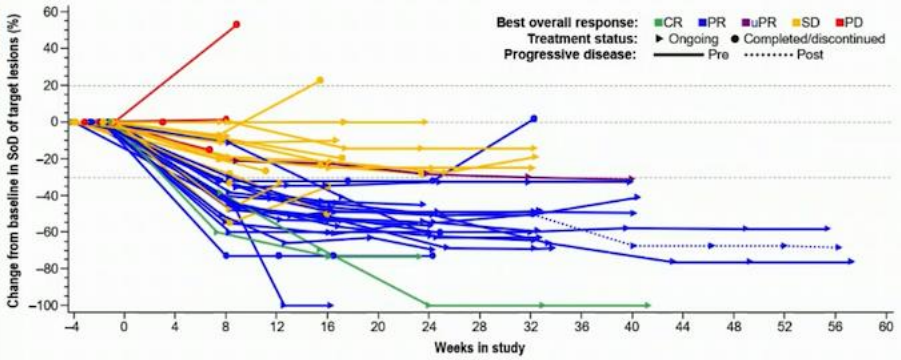
Primary Endpoint: Safety

Secondary Endpoints

- ORR
- DoR
- DCR
- PFS

Investigator-assessed	Total (N=43)
ORR[a,b]	49% (95% CI, 33–65)
Median DoR[c]	7.4 months (95% CI, 5.6–NE)
Median time to response[c]	8.3 weeks
DCR	88% (95% CI, 75–96)
Median PFS	7.5 months (95% CI, 7.4–NE)
Received curative intent surgery, n	6 completed (3 more scheduled)

Patients could undergo curative intent surgery and were censored upon procedure completion



- Median (range) follow-up was 7.3 months (1.1–14.4)
- 67% (29/43) of patients remain on treatment[d]
- ORR was 64% among patients on 1L therapy and 44% among patients on 2L therapy

40% of pts in 1st Line

Do these data warrant phase 3 trials in CRC?

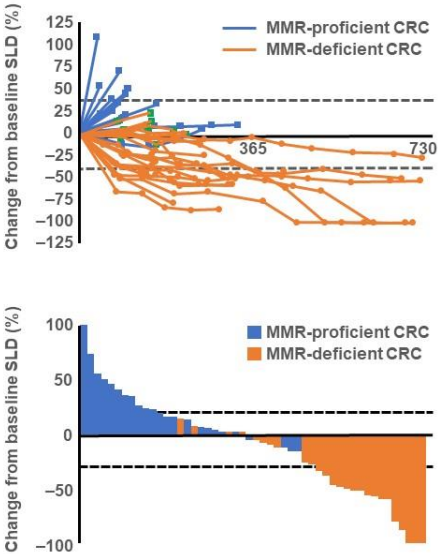
Pietrantonio et al., ESMO 2024

IO in MSI H

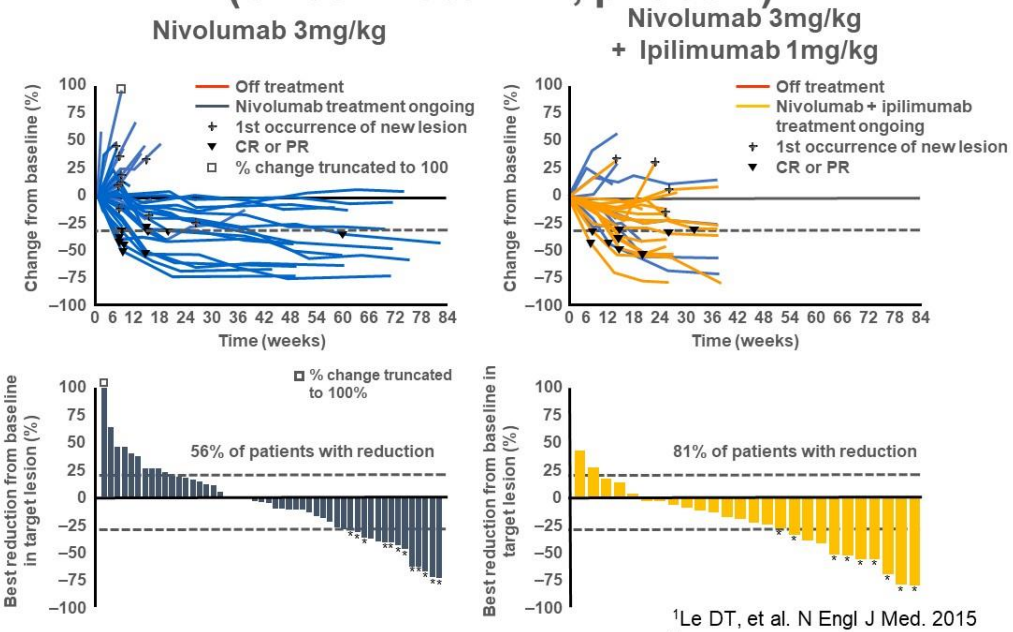
Nivo/Ipi in first line

MSI-high CRCs are responsive to PD-1 inhibitors

Pembrolizumab (KEYNOTE 016, phase II)[1,*]



Nivolumab ± Ipilimumab (CheckMate-142, phase II)[2]



[1]Le DT, et al. N Engl J Med. 2015
[2]Overman MJ, et al. Lancet Oncol. 2017

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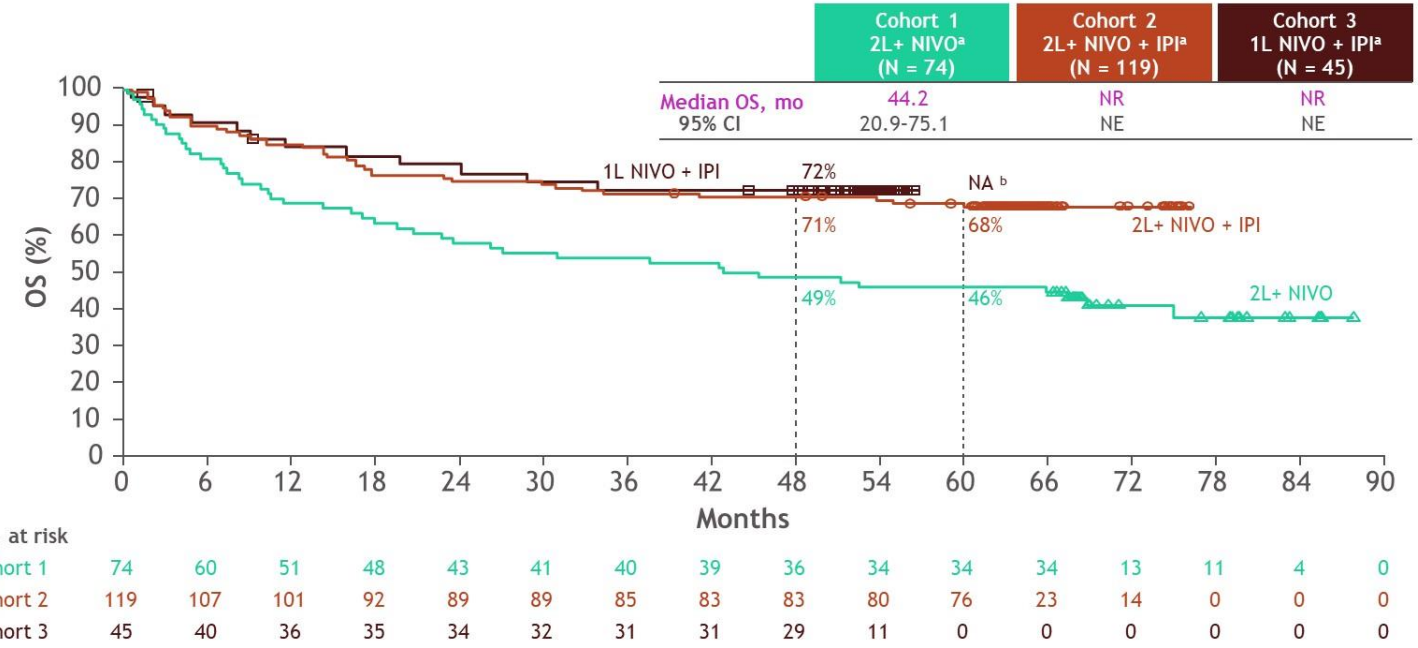
Overall survival



- Median OS was 44.2 months in cohort 1 and not reached in cohorts 2 and 3
  - 48-month OS rates were 49% (cohort 1), 71% (cohort 2), and 72% (cohort 3)
  - 60-month OS rates were 46% (cohort 1), 68% (cohort 2), and not available for cohort 3

[a]Study cohorts were neither randomized nor designed for a formal comparison; [b]Minimum follow-up for cohort 3 was 47.6 months.

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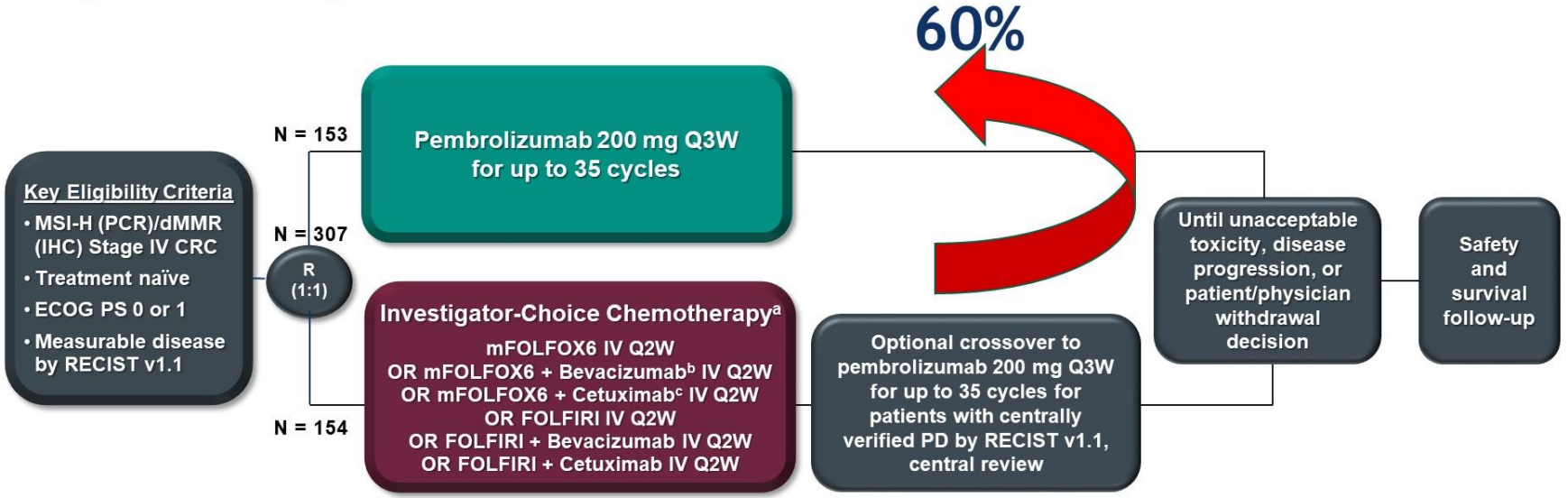
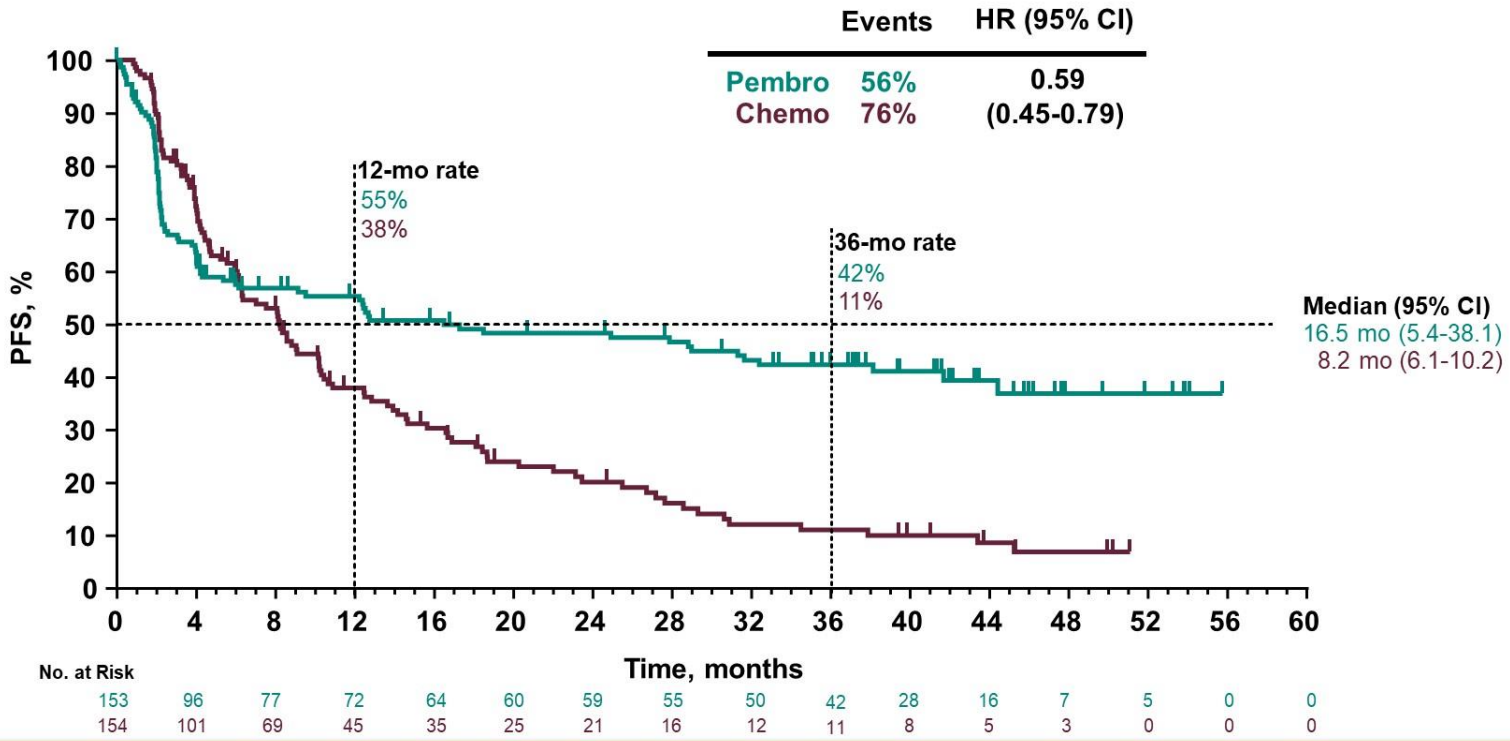
KEYNOTE-177 Study Design
(NCT02563002)



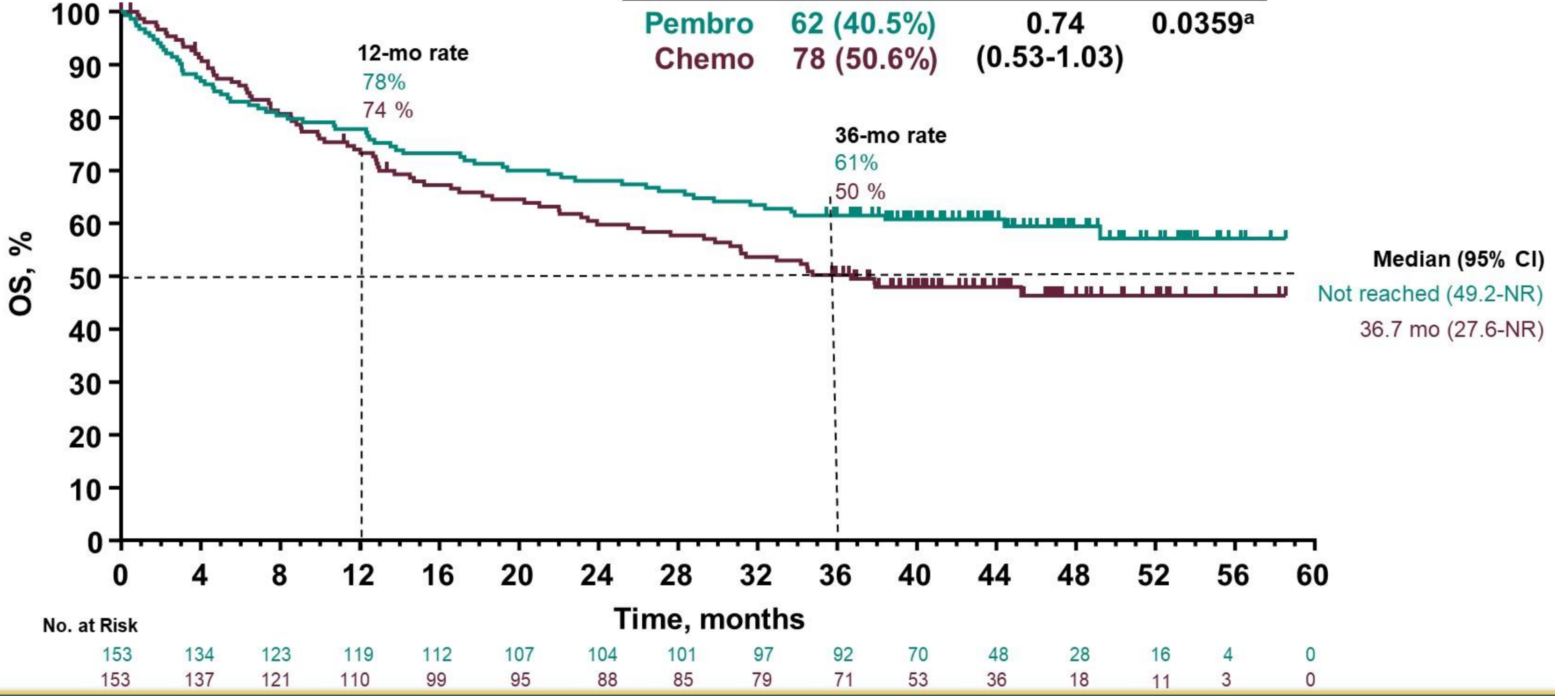
- Dual-primary endpoints: PFS per RECIST v1.1, BICR; OS
- Secondary endpoints: ORR per RECIST v1.1 by BICR, PFS2, HRQoL, safety
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

Progression-Free Survival



Overall Survival

	Events, n (%)	HR (95% CI)	*P*
Pembro	62 (40.5%)	0.74 (0.53-1.03)	0.0359[a]
Chemo	78 (50.6%)		



[a]Pembrolizum[illegible] su[illegible] one-sided α > 0.0246 [illegible] sensitivity analyses to adjust for crossover effect by rank-preserving structure failure time model and inverse probability of censo[illegible] (95% CI 0.42-1.04) and 0.77 (95% CI 0.44-1.38). Data cut-off: 19Feb2021.

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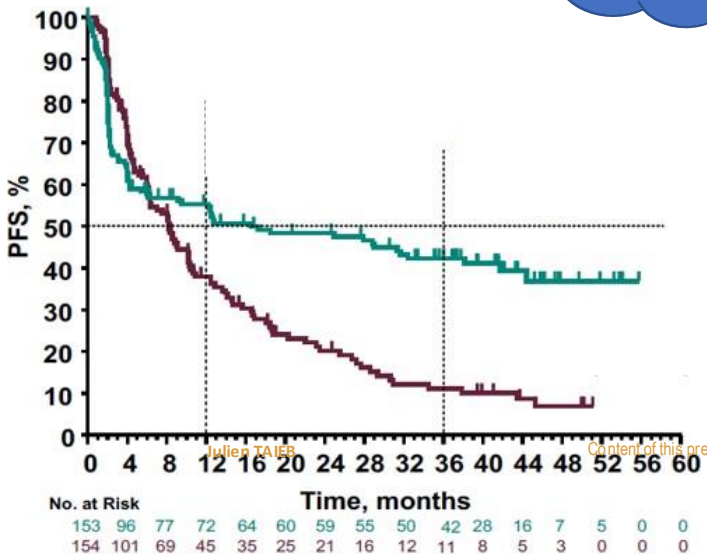
Discussion

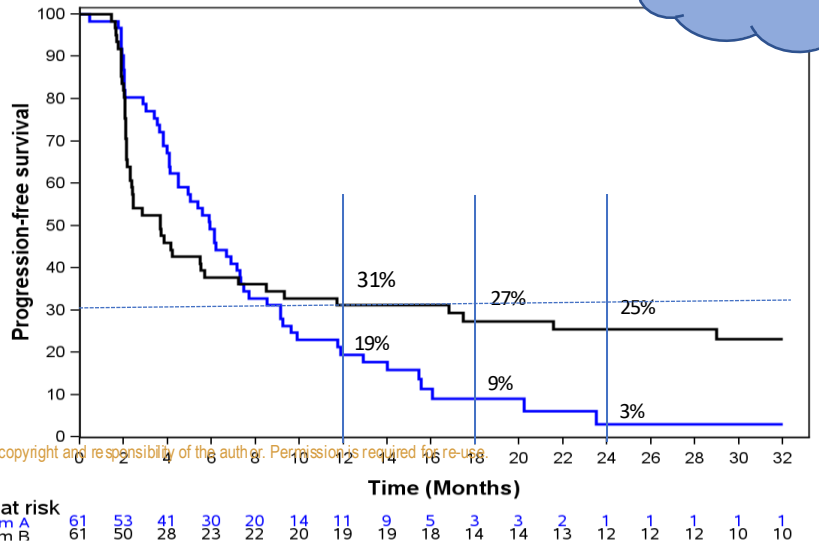
KEYNOTE 177

Anti-PD-1



PRODIGE 54-SAMCO

Anti-PD-L-1



2024 ASCO ANNUAL MEETING

Nivolumab plus ipilimumab vs chemotherapy as first-line treatment for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: expanded efficacy analysis from CheckMate 8HW

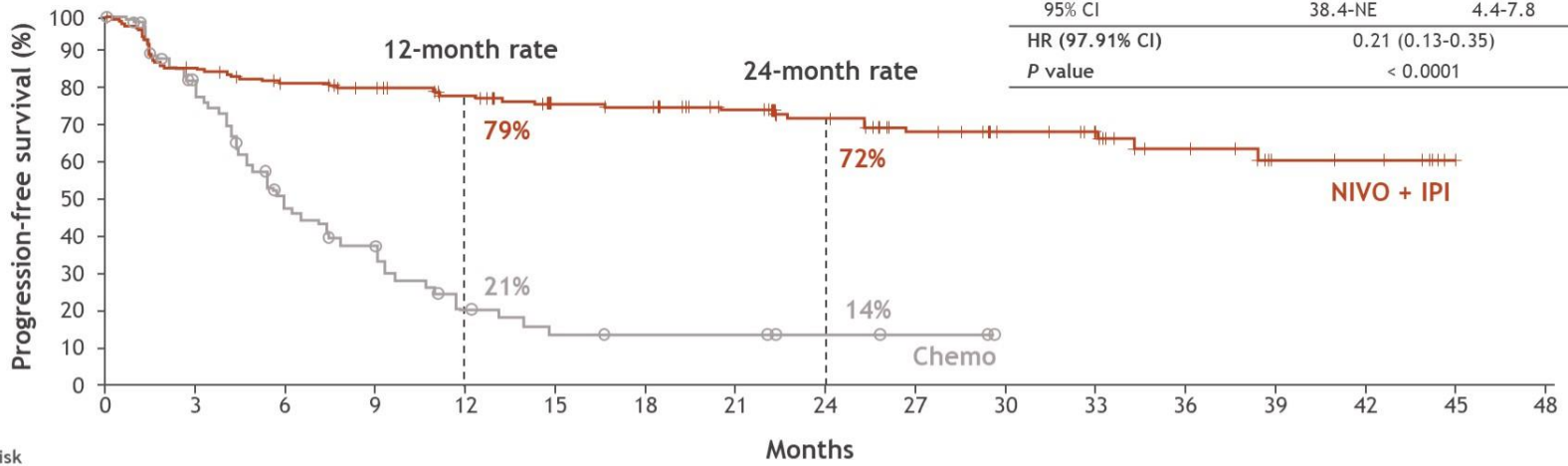
Heinz-Josef Lenz,[1] Sara Lonardi,[2] Elena Elez Fernandez,[3] Eric Van Cutsem,[4] Lars Henrik Jensen,[5] Jaafar Bennouna,[6] Guillermo Ariel Mendez,[7] Michael Schenker,[8] Christelle de la Fouchardiere,[9] Maria Luisa Limon Miron,[10] Takayuki Yoshino,[11] Jin Li,[12] José Luis Manzano Mozo,[13] Giampaolo Tortora,[14] Rocio Garcia-Carbonero,[15] Rohit Joshi,[16] Elvis Cela,[17] Tian Chen,[17] Lixian Jin,[17] Thierry Andre[18]

[1]University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; [2]Istituto Oncologico Veneto IOV-IRCCS, Padua, Italy; [3]Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain; [4]University Hospitals Gasthuisberg and University of Leuven (KU Leuven), Leuven, Belgium; [5]University Hospital of Southern Denmark, Vejle Hospital, Vejle, Denmark; [6]Centre Hospitalier Universitaire de Nantes, Nantes, France; [7]Hospital Universitario Fundacion Favaloro, Buenos Aires, Argentina; [8]Centrul de Oncologie Sf Nectarie, Craiova, Romania; [9]Centre Léon Bérard, Lyon Cedex, France; [10]Hospital Universitario Virgen del Rocío, Sevilla, Spain; [11]National Cancer Center Hospital East, Chiba, Japan; [12]Shanghai East Hospital, Shanghai, China; [13]Institut Català d'Oncologia, Badalona, Spain; [14]Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [15]Hospital Universitario 12 de Octubre Imas12, Complutense University of Madrid, Madrid, Spain; [16]Cancer Research SA, Adelaide, Australia; [17]Bristol Myers Squibb, Princeton, NJ; [18]Sorbonne Université and Hôpital Saint Antoine, Assistance Publique Hôpitaux de Paris, Paris, France

Abstract number 3503

Progression-free survival

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 171)	Chemo (n = 84)
Median PFS,[a,b] mo	NR	5.9
95% CI	38.4-NE	4.4-7.8
HR (97.91% CI)	0.21 (0.13-0.35)	
P value	< 0.0001	



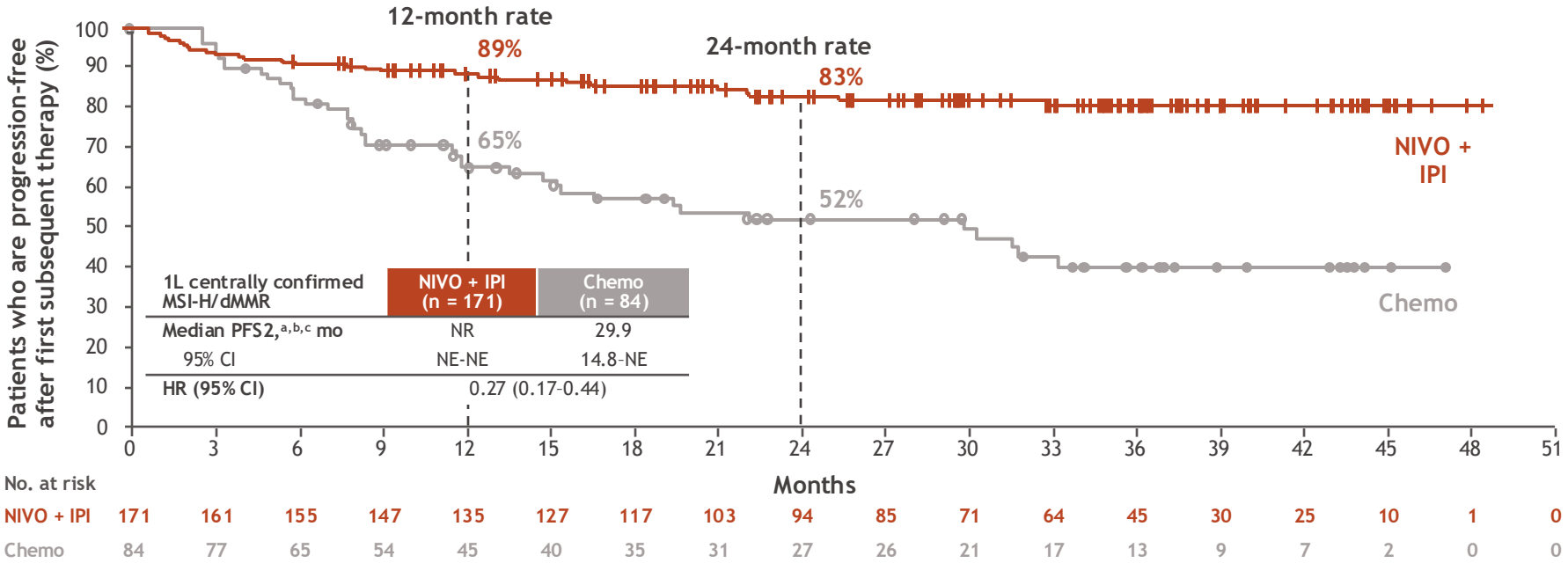
No. at risk																	
NIVO + IPI	171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Chemo	84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

- PFS benefit with NIVO + IPI vs chemo was robust and consistent across the sensitivity analyses, including PFS by BICR in 1L all randomized patients (HR, 0.32; 95% CI, 0.23-0.46)

Lenz et al ASCO 2024

[a]Per BICR. [b]Median follow-up, 24.3 months.

PFS2: progression-free survival after subsequent therapy



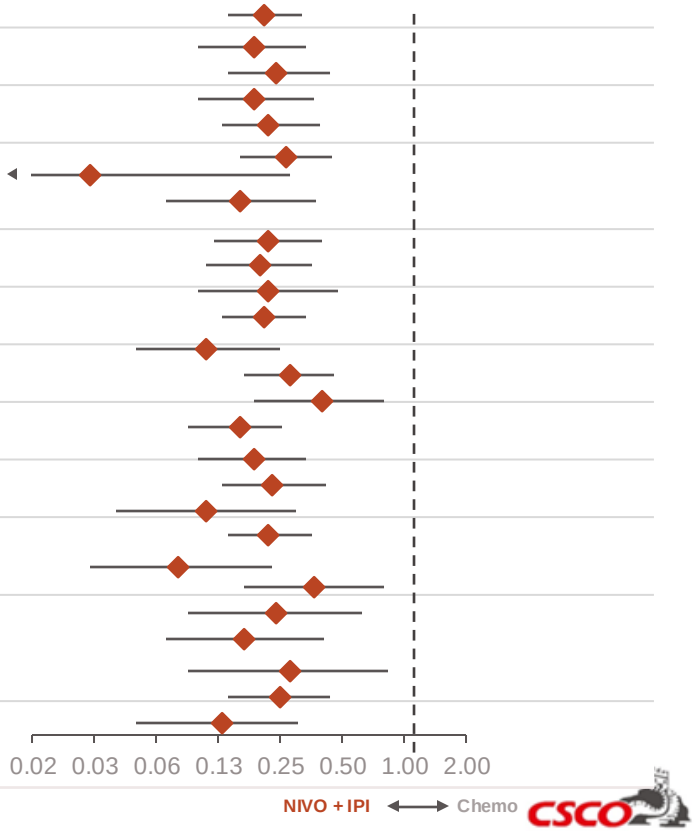
- PFS2[a] favored NIVO + IPI vs chemo with a 73% reduction in the risk of death or disease progression after first subsequent therapy

Lenz et al ASCO 2024

[a]Defined as time from randomization to progression after subsequent systemic therapy, initiation of second subsequent systemic therapy, or death. [b]Per investigator. [c]Median follow-up in patients with centrally confirmed MSI-H/dMMR, 31.6 months.

PFS benefits across all subgroup

Category (1L centrally confirmed MSI-H/dMMR)	Subgroup	Median PFS,[a] mo		Unstratified HR
		NIVO + IPI	Chemo	
Overall (N = 255)		NR	5.9	0.21
Age, years	< 65 (n = 138)	NR	5.7	0.19
	≥ 65 (n = 117)	NR	5.9	0.24
Sex	Male (n = 117)	NR	5.9	0.19
	Female (n = 138)	NR	6.2	0.22
Region	US/Canada/Europe (n = 167)	NR	5.7	0.27
	Asia (n = 28)	NR	7.4	0.03
	Rest of world (n = 60)	NR	6.2	0.16
ECOG PS	0 (n = 142)	NR	9.0	0.22
	1 (n = 113)	NR	4.2	0.20
Tumor sidedness	Left (n = 70)	NR	4.4	0.22
	Right (n = 185)	NR	7.1	0.21
Liver metastases[a]	Yes (n = 87)	NR	5.9	0.11
	No (n = 166)	NR	5.4	0.28
Lung metastases[a]	Yes (n = 53)	13.2	4.9	0.40
	No (n = 200)	NR	6.2	0.16
Peritoneal metastases[a]	Yes (n = 115)	NR	4.4	0.19
	No (n = 138)	NR	7.4	0.23
Tumor cell PD-L1 expression	≥ 1% (n = 55)	NR	3.4	0.11
	< 1% (n = 191)	NR	6.5	0.22
***BRAF*/*KRAS*/*NRAS* mutation status**	*BRAF*/*KRAS*/*NRAS* wild type (n = 58)	34.3	5.4	0.08
	BRAF mutant (n = 72)	NR	9.2	0.37
	KRAS or *NRAS* mutant (n = 45)	NR	5.7	0.24
	Unknown (n = 74)	NR	4.9	0.17
Lynch syndrome	Yes (n = 31)	NR	7.4	0.28
	No (n = 152)	NR	6.2	0.25
	Unknown (n = 66)	NR	5.5	0.13

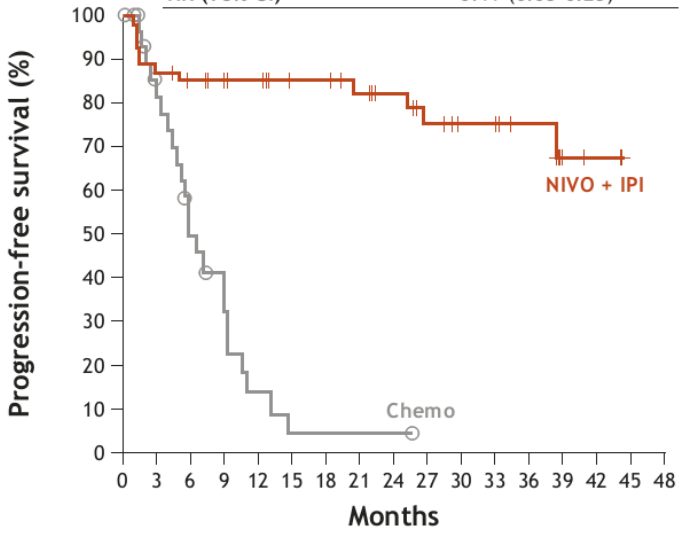


[a]Per BICR.

PFS by Liver mets

Liver metastases: Yes

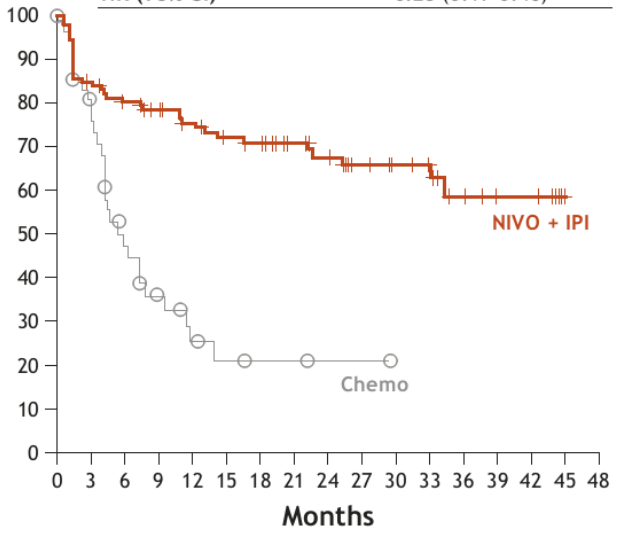
1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 55)	Chemo (n = 32)
Median PFS,[a,b] mo	NR	5.9
95% CI	38.4-NE	4.3-9.2
HR (95% CI)	0.11 (0.05-0.25)	



No. at risk																	
NIVO + IPI	55	49	44	41	38	33	33	28	24	20	17	15	10	3	2	0	0
Chemo	32	22	12	9	3	1	1	1	1	0	0	0	0	0	0	0	0

Liver metastases: No

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 114)	Chemo (n = 52)
Median PFS,[a,b] mo	NR	5.4
95% CI	34.3-NE	4.2-9.6
HR (95% CI)	0.28 (0.17-0.46)	

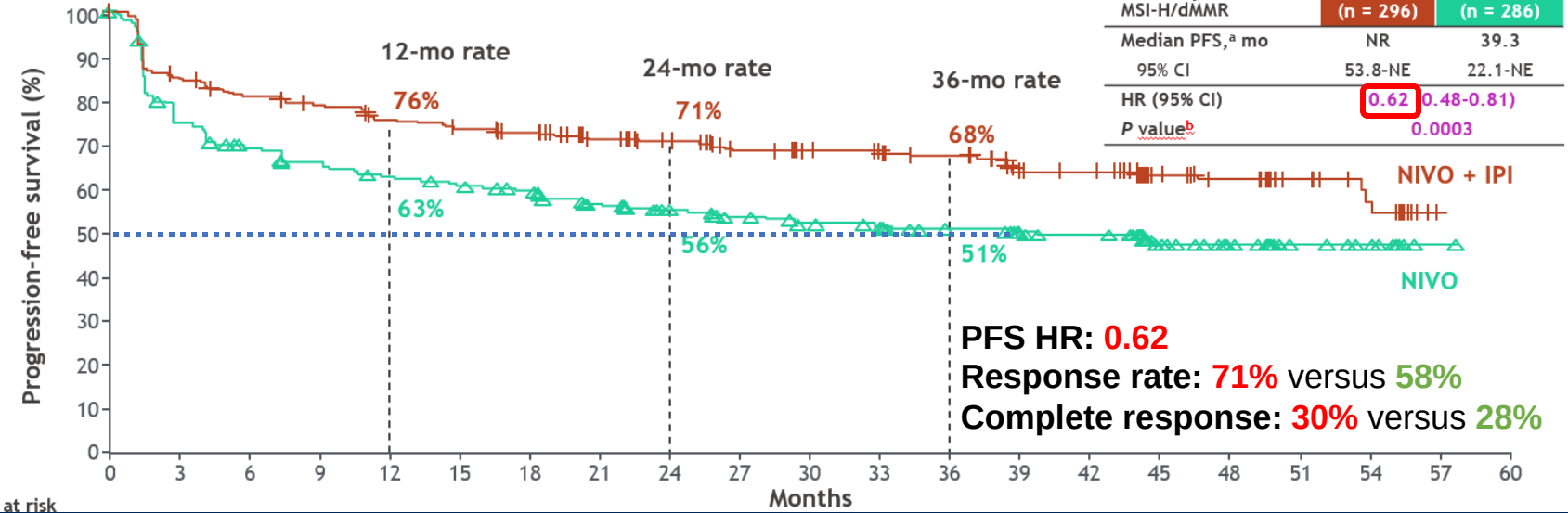


114	95	88	81	70	62	59	49	40	33	25	22	12	7	7	1	0
52	31	17	11	7	5	4	4	2	2	0	0	0	0	0	0	0

[a]Median follow-up in patients with centrally confirmed MSI-H/dMMR, 31.6 months. [b]Per BICR.

ABSTRACT LBA143: nivolumab/ipilimumab vs nivolumab for MSI-H/dMMR mCRC (Andre)

Progression-free survival



Centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 296)	NIVO (n = 286)
Median PFS,[a] mo	NR	39.3
95% CI	53.8-NE	22.1-NE
HR (95% CI)	0.62	(0.48-0.81)
P value[b]	0.0003	

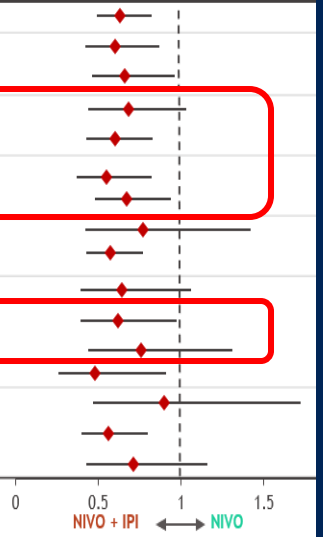
Note: PFS curves separate early and flatten nicely

Andre et al, *GI Symposium* 2025

ABSTRACT LBA143: nivolumab/ipilimumab vs nivolumab for MSI-H/dMMR mCRC (Andre)

Progression-free survival subgroup analysis

Category (centrally confirmed MSI-H/dMMR)	Subgroup	Median PFS,[a] mo		Unstratified HR
		NIVO + IPI	NIVO	
Overall (N = 582)		NR	39.3	0.63
Age, years	< 65 (n = 321)	NR	NR	0.60
	≥ 65 (n = 261)	NR	29.4	0.66
Liver metastases[a,b]	Yes (n = 210)	NR	NR	0.68
	No (n = 368)	NR	33.2	0.60
Peritoneal metastases[a,b]	Yes (n = 226)	54.1	24.8	0.55
	No (n = 352)	NR	NR	0.67
Tumor cell PD-L1 expression	≥ 1% (n = 133)	NR	NR	0.77
	< 1% (n = 427)	NR	24.8	0.57
BRAF/KRAS/NRAS mutation status	*BRAF/KRAS/NRAS* all wild type (n = 156)	NR	44.3	0.64
	BRAF mutant (n = 179)	NR	25.9	0.62
	KRAS or *NRAS* mutant (n = 125)	NR	NR	0.76
	Unknown (n = 114)	54.1	38.1	0.48
Clinical history of Lynch syndrome	Yes (n = 83)	53.8	38.1	0.90
	No (n = 334)	NR	44.3	0.56
	Unknown (n = 156)	NR	33.2	0.71



- PFS consistently favored NIVO + IPI vs NIVO in prespecified subgroups across all lines of therapy

Benefit seen across subgroups:

+/- Liver metastases*
+/- Peritoneal metastases
+/- BRAF mutation
+/- PD-L1

* Lack of responses with botensilimab (CTLA-4) plus balstilimab (PD-1) in patients with liver metastases in MSS mCRC (Bullock, *Nat Med* 2024)

Andre et al, *GI Symposium* 2025

What we know in MSS mCRC about IO

- Checkpoint inhibitors targeting PD-1/PD-L1 as single agents have no activity in microsatellite stable (MSS) colorectal cancer

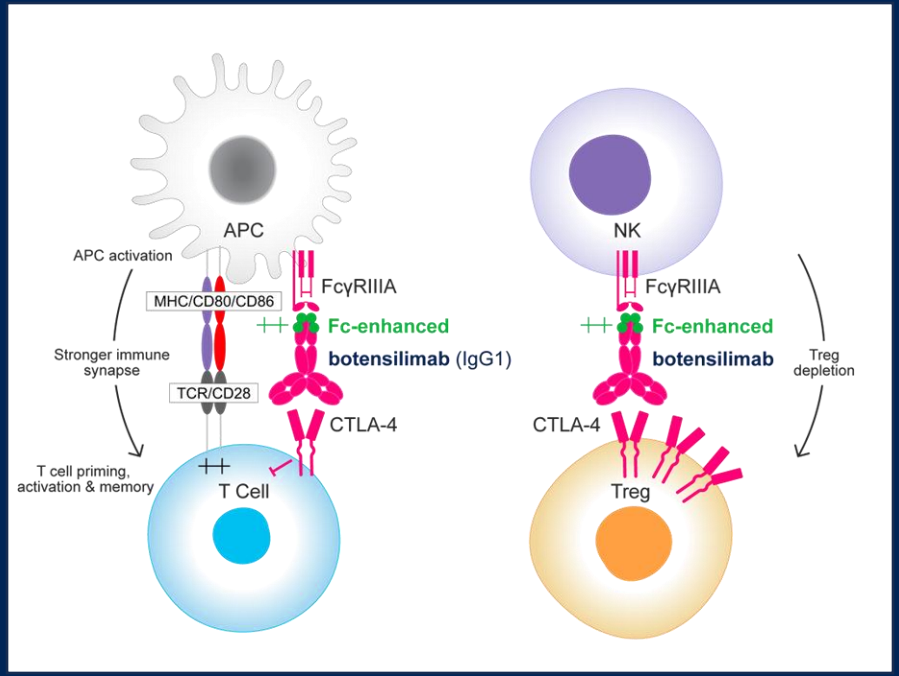
- Limited activity noted with anti PD-1/PD-L1 and “first generation” CTLA4 antibodies
  - Durvalumab+tremelimumab:
    - ORR 1%; DCR 22.7%; median PFS 1.8 mo; median OS 6.6 mo
  - Nivolumab+ipilimumab
    - mPFS 1.4 mo

Chen EX et al, JAMA Oncol 2020
Overman MJ et al, J Clin Oncol 2016

Botensilimab: multifunctional Fc enhanced anti-CTLA-4 antibody

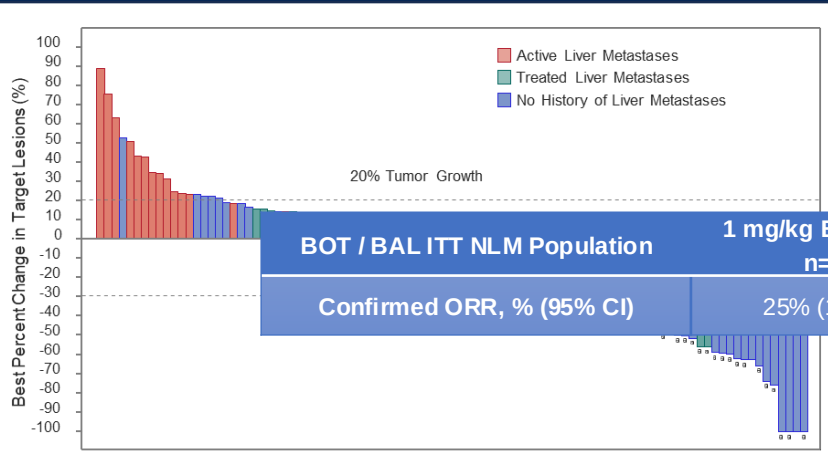
Botensilimab
Multifunctional Fc-enhanced Anti-CTLA-4 Antibody

- **Enhances** T cell priming, expansion, memory
- **Activates** APCs/myeloid cells
- **Enhances** Treg depletion
- **Improves** safety by reducing complement-mediated toxicities (eg, hypophysitis)



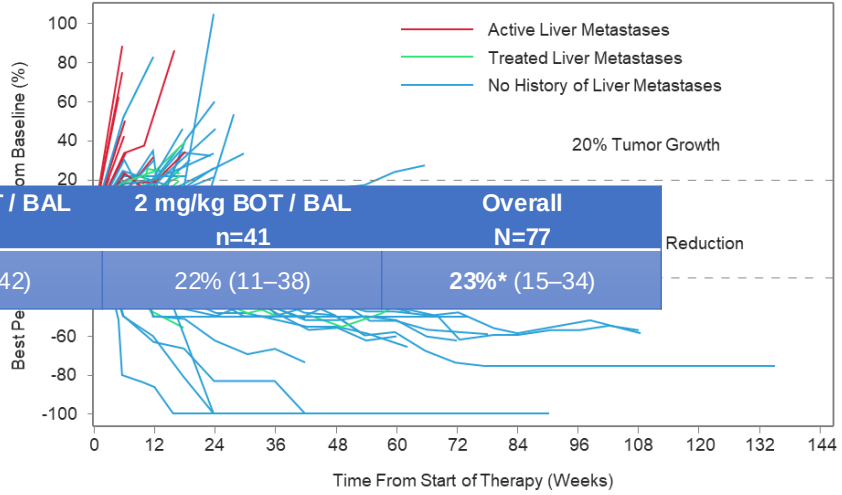
Bullock A, et al. Nature Medicine. 2024; Chand C, et al. Cancer Discov. 2024

Botensilimab+Balstilimab: Phase I expansion in MSS CRC



BOT / BAL ITT NLM Population	1 mg/kg BOT / BAL n=36	2 mg/kg BOT / BAL n=41	Overall N=77
Confirmed ORR, % (95% CI)	25% (12–42)	22% (11–38)	**23%*** (15–34)

ORR 17% in 101 evaluable patients



Median OS 20.9 months (95% CI, 10.6 months–NR)
12-month OS rate 60% (95% CI, 49–69%)

Bullock A, et al. Nature Medicine. 2024; Chand C, et al. Cancer Discov. 2024

Botensilimab+Balstilimab Global Phase 2

Randomized

75 mg BOT Q6W
- ITT: n=38
- Safety: n=37

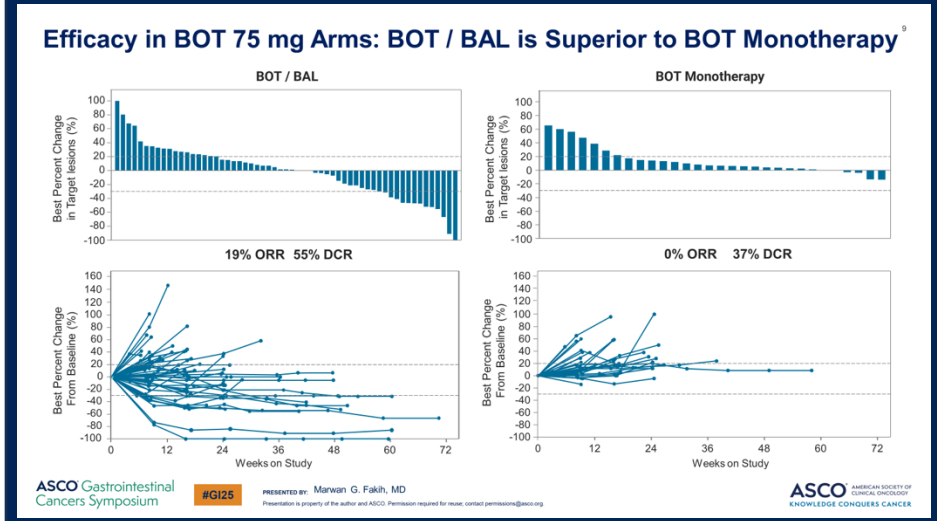
75 mg BOT Q6W + 240 mg BAL Q2W
- ITT: n=62
- Safety: 62

150 mg BOT Q6W
- ITT: n=40
- Safety: n=39

150 mg BOT Q6W + 240 mg BAL Q2W
- ITT: n=61
- Safety: 60

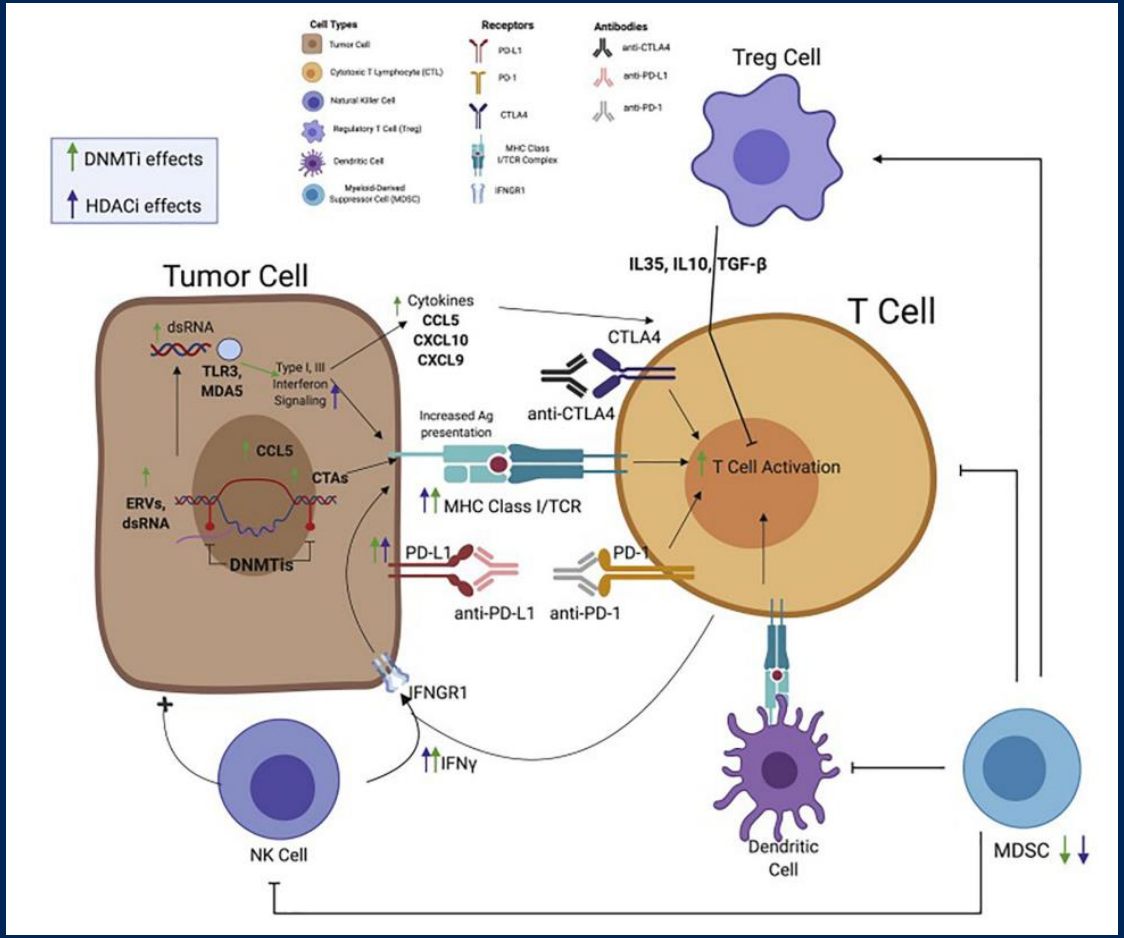
SOC (trifluridine/tipiracil or regorafenib)
- ITT: n=33
- Safety: n=21

- Total ITT: N=234
- Total Safety: n=219



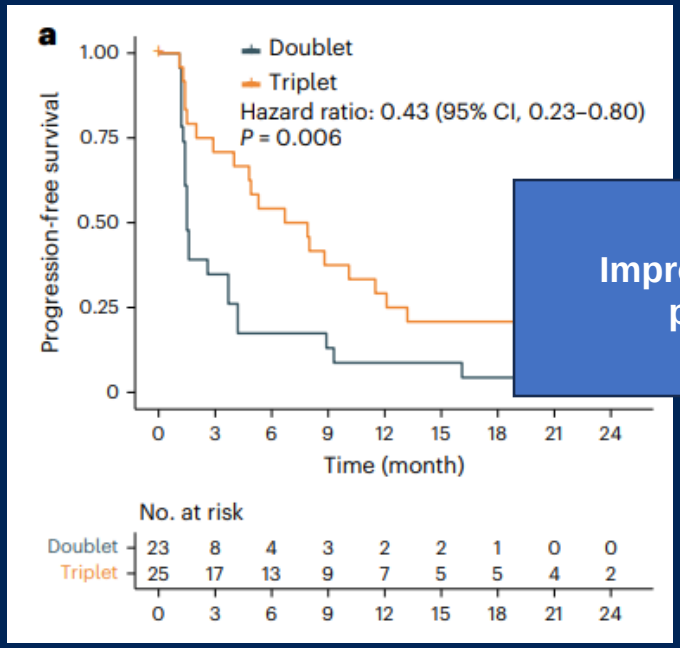
Fakih M et al, ASCO GI 2025

Immunomodulatory effects of epigenetic therapy

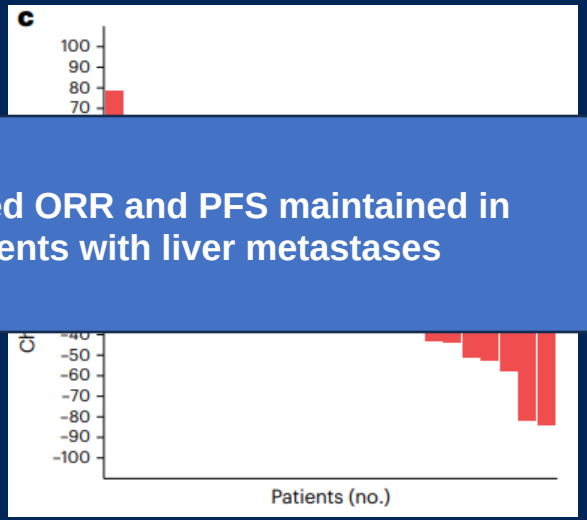


Gomez S et al, Semin Cancer Biol 2020

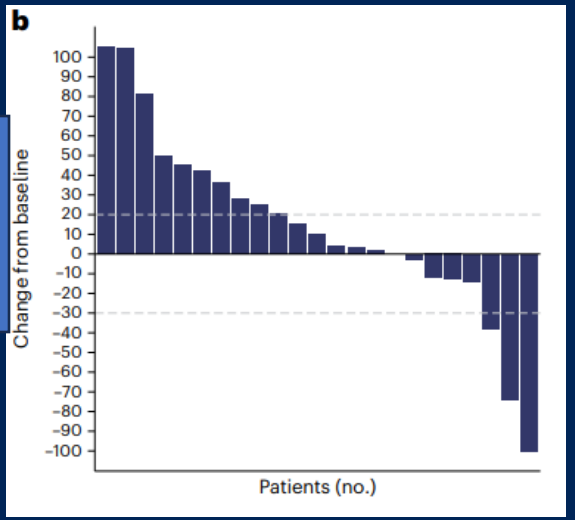
Combined anti-PD-1, HDAC inhibitor and anti-VEGF for MSS/pMMR colorectal cancer: a randomized phase 2 trial



Chidamide/Sintilimab/Bev



Chidamide/Sintilimab



Improved ORR and PFS maintained in patients with liver metastases

ORR 44%
(44.0%; 95% CI, 24.4%–65.1%)

ORR 13%
(13.0%; 95% CI, 2.8%–33.6%

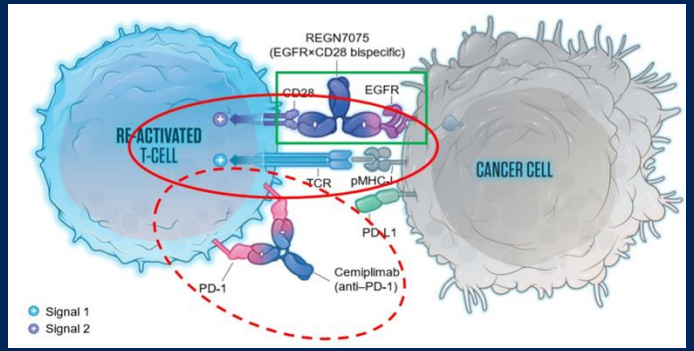
Wang F et al, Nat Med. 2024

Increasing engagement of various cellular compartments in TME
Bispecifics
Cell engagers

Bispecific antibodies: tumor cell binding mediated immune co-stimulation

REGN7075: binds EGFR on tumors and CD28 on cytotoxic T cells

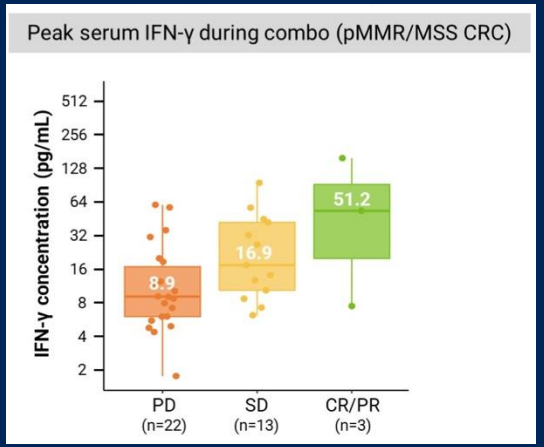
Facilitate T cell activation through endogenous tumor antigens



All MSS CRC patients (N=51) ORR: 5.9%

MSS CRC patients without liver metastases (N=15) ORR 20%

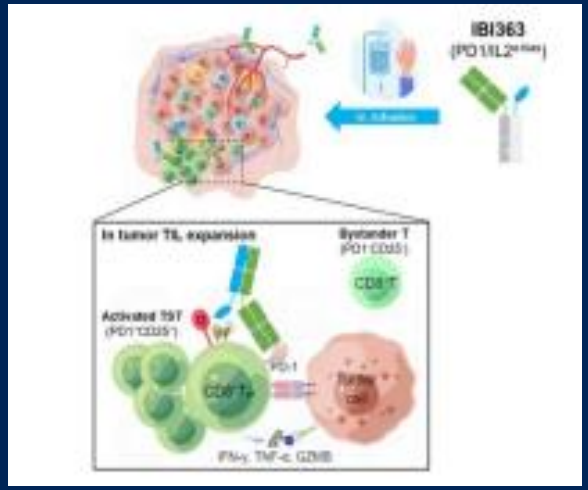
Tumor response*, n (%)	Patients (n=15)
ORR (CR+PR), 95% CI	3 (20.0), 4.3–48.1
CR	1 (6.7)
PR	2 (13.3)
SD	9 (60.0)
NE	3 (20.0)
DCR (CR+PR+SD), 95% CI	12 (80.0), 51.9–95.7



Segal N et al, ASCO 2024

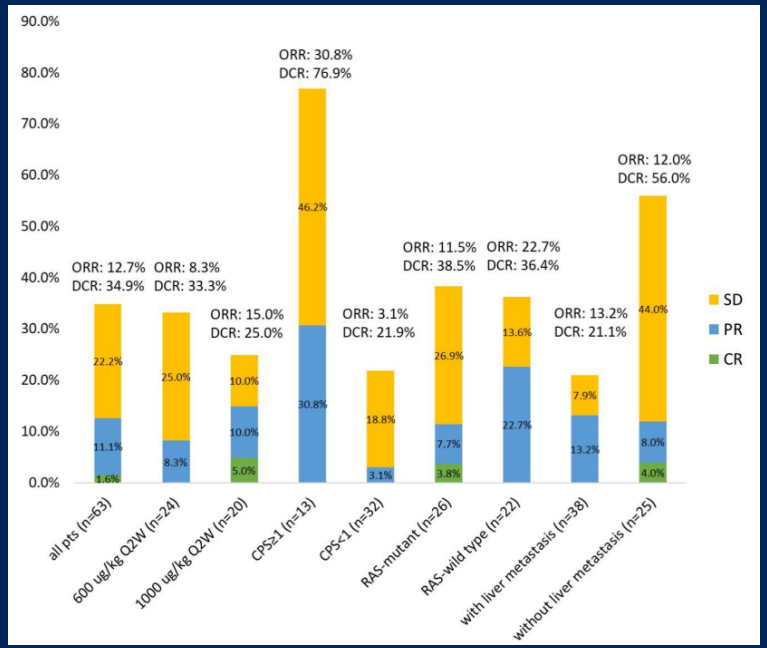
Bispecific antibodies: co-targeting a checkpoint and a cytokine

IBI 363: PD-1/IL2$^{\alpha bias}$ bispecific antibody



Specifically activated PD1^{+}CD25^{+} tumor specific T cells
Activates peripheral regulatory T cells

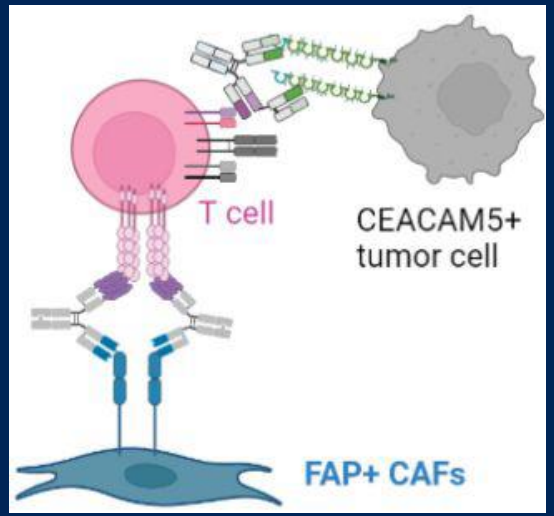
Phase I N=68; MSS 84%; 16% unknown



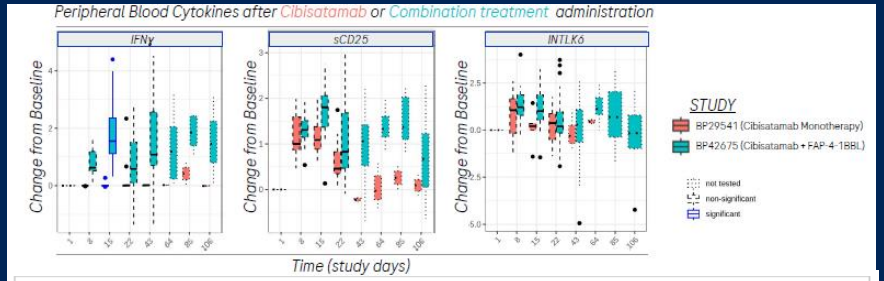
Shi W et al, Acta Pharmaceutica Sinica B 2024; Chen Y et al, poster presentation ASCO 2024

Combinatorial Approaches: cell engager with a bispecific: two signals to enhance anti cancer immunity

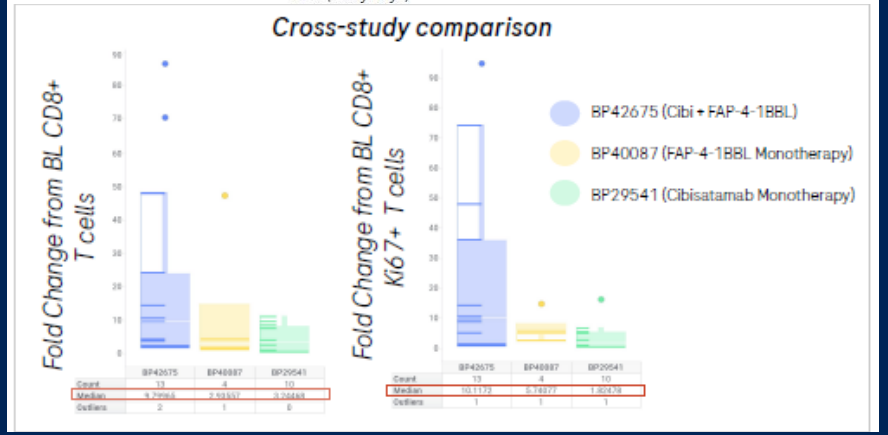
Cibisatamab, T cell engager targeting CEA on tumor cells and CD3 on T cells
+
FAP-4-1BBL, bispecific fusion protein carrying 4-1BB ligand and αFAP binding site



Combination leads to superior T cell activation in peripheral blood with increase in IFNγ, soluble CD25, and interleukin 6



Combination results in Superior Intratumoral CD8+ T cell infiltration

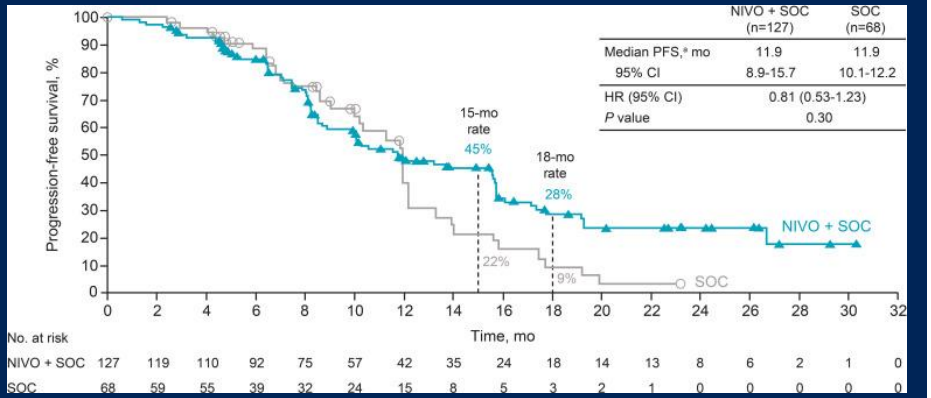


Melero I et al, ESMO 2024

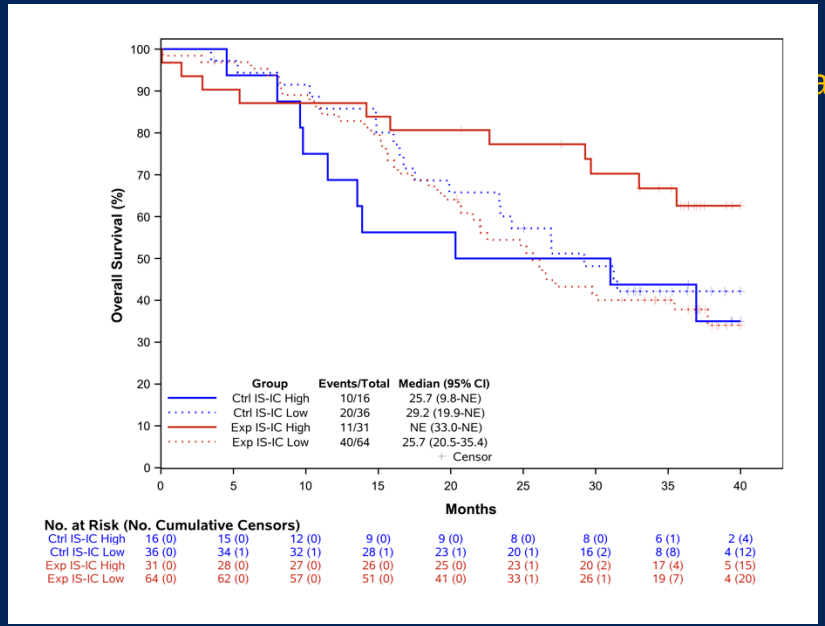
Combination with chemotherapy

Can cytotoxic chemotherapy potentiate the effect of checkpoint inhibitors in MSS CRC

Checkmate 9X8
mFOLFOX6+Bev with and without nivolumab



Did not meet primary endpoint of mPFS improvement
Higher PFS rates at 15 and 18 months and higher ORR



Lenz HJ et al, J Immunother Cancer 2024
Antoniotti C et al, J Clin Oncol 24

Conclusions

Various emerging, innovative approaches will soon lead to major advances in IO treatment options for colorectal cancer

- Targeted Therapies moving into 1l: G12C inhibitor, pan ras inhibitor, her2 and Braf V600E inhibitors
- MSI
  - PD1/CTL4 shows high efficacy in 1L and should be considered SOC
  - Novel inhibitors develop to overcome innate resistance
- MSS
  - IO moving in combination into 1L with chemo/beva
  - Bot/Bal promising efficacy in extrahepatic disease (toxicity)
- Augmented Immunotherapy
  - Combination of IO agents, bispecific mAbs (e.g. T-cell engagers)
- Cellular Therapies
  - Developing

Missing

1. Josh Millstein
2. Evanthia Torres
3. Yan Yang
4. Priya Jayachandran
5. Unnati Shah
6. Francesca Battaglin

Immanuel Kant (Photo from a steel engraving)

The one who knows more, may decide better