Update in metastatic Colorectal Cancer

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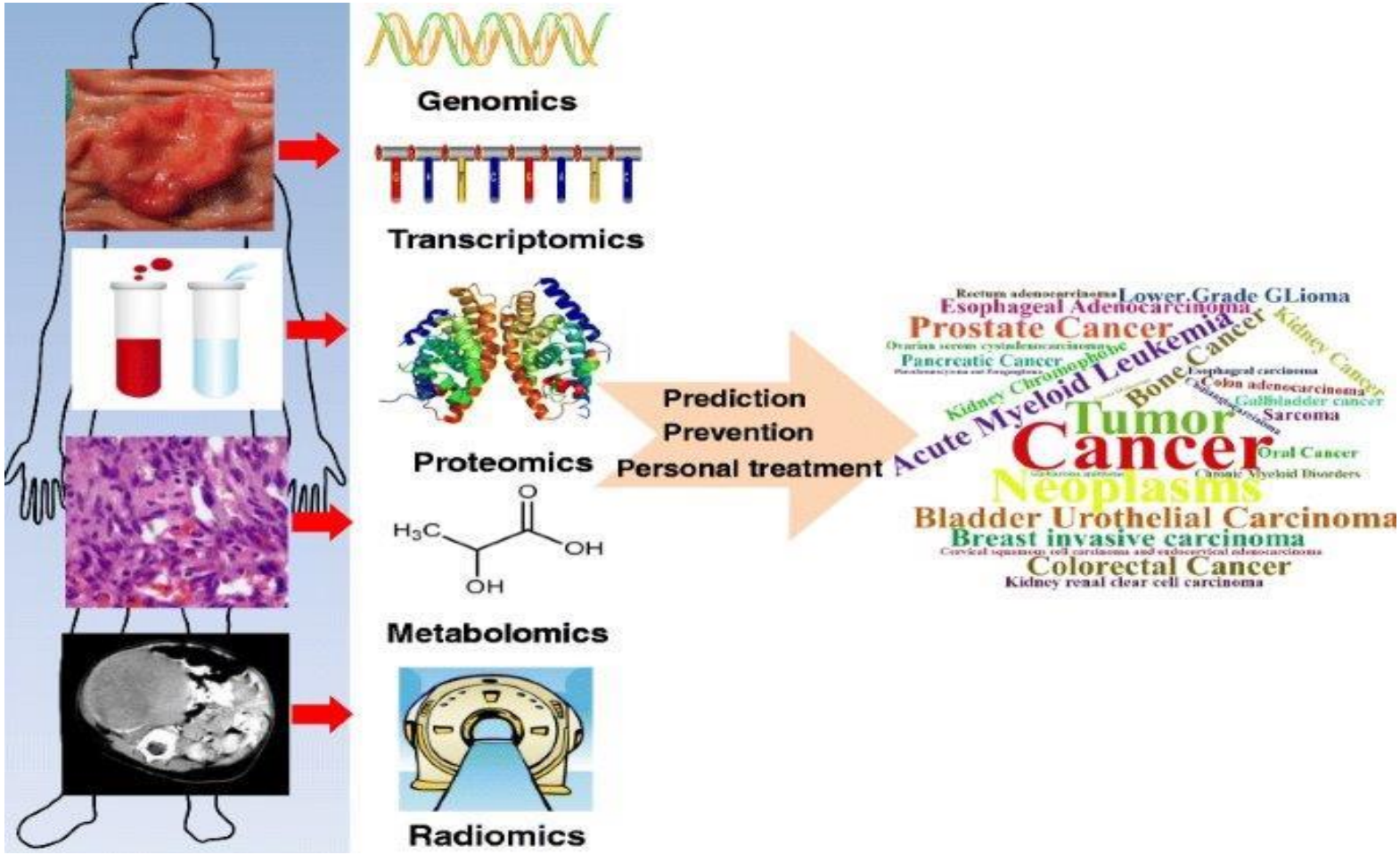
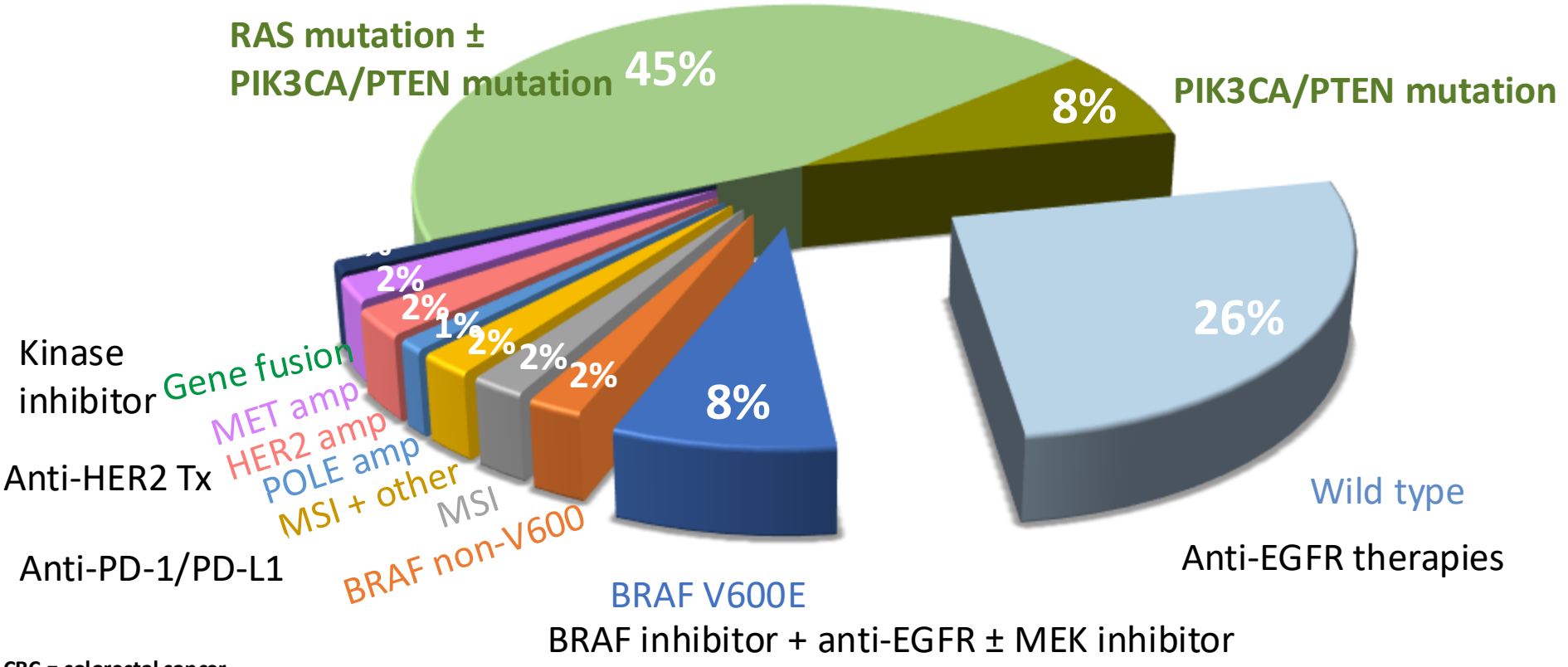

Genomics
Transcriptomics
Proteomics
Metabolomics
Radiomics
Prediction
Prevention
Personal treatment
Lower Grade GLioma
Esophageal Adenocarcinoma
Prostate Cancer
Pancreatic Cancer
Kidney Cancer
Bone Cancer
Acute Myeloid Leukemia
Kidney Chromophobe
Colon adenocarcinoma
Gallbladder cancer
Sarcoma
Tumor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

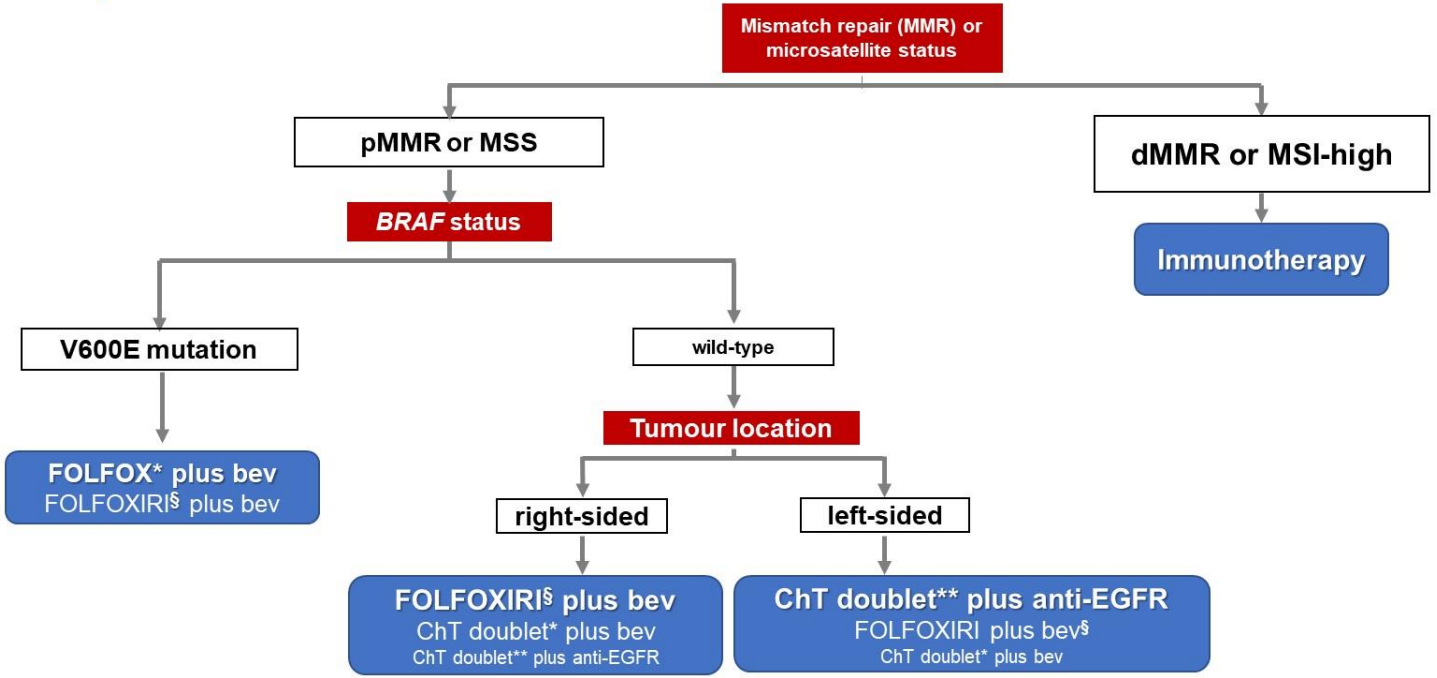
Genomic Markers in CRC



CRC = colorectal cancer.

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

Treatment algorithm for the choice of the upfront therapy for *RAS* wt mCRC patients



Bev: bevacizumab; ChT: chemotherapy.

* Fluoropyrimidine monotherapy if not fit for doublet chemotherapy
** 5-fluorouracil/leucovorin if not fit for doublet chemotherapy;
§ only if <75 years old (71-75 years old with ECOG Performance Status 0)

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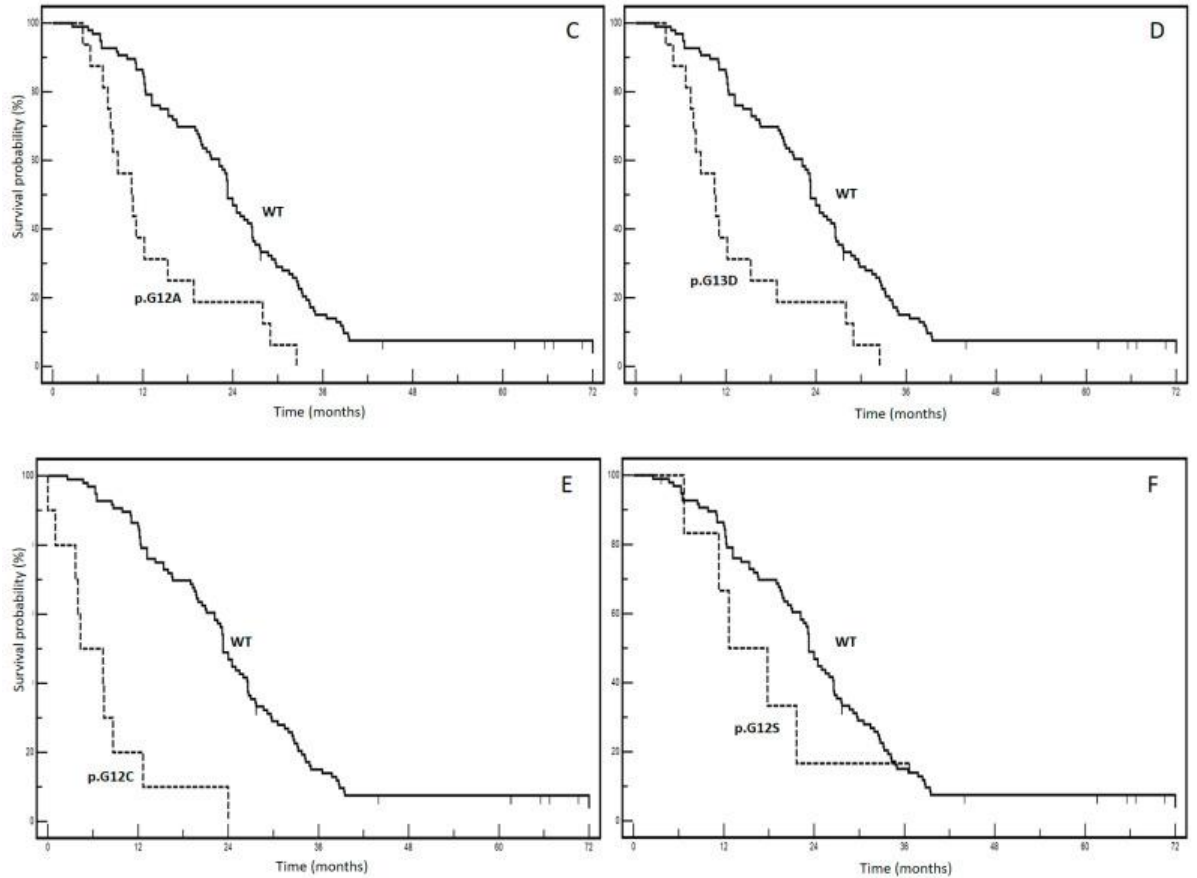
Novel Approaches

1. RAS (G12C)

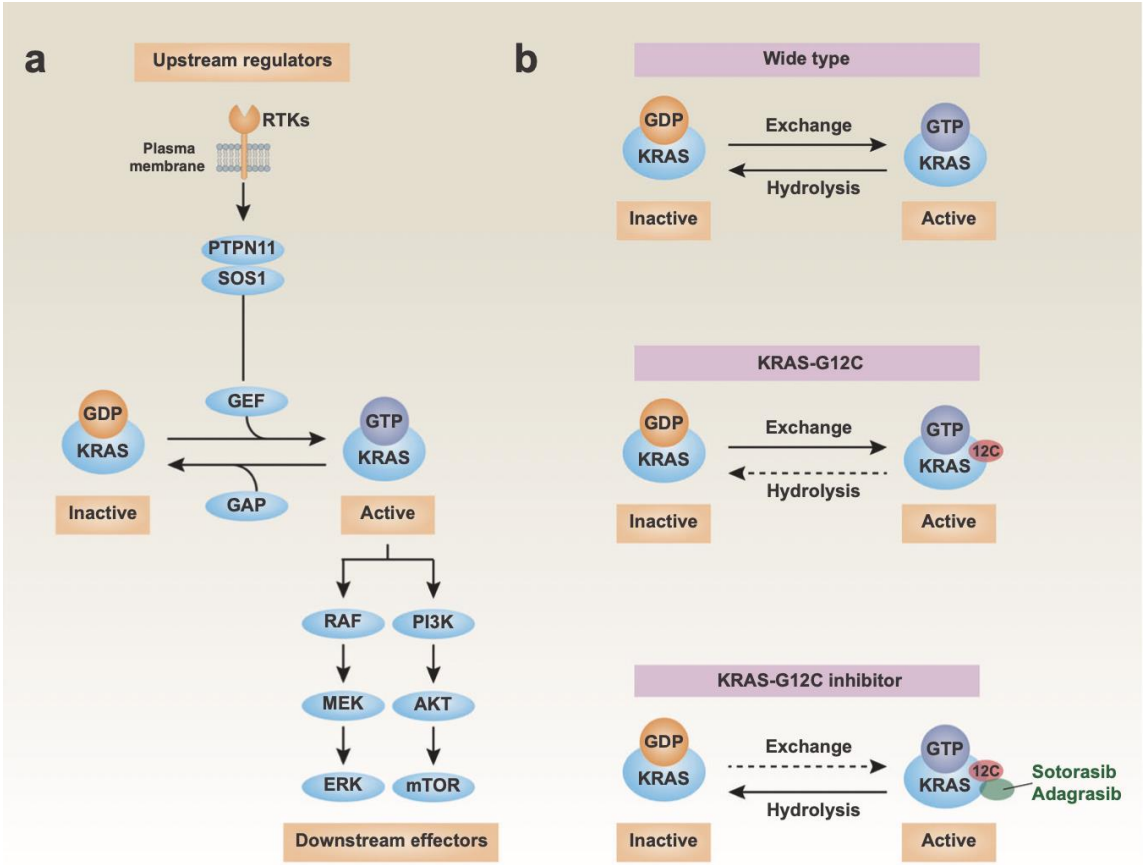
KRAS G12C Mutations Appear to Confer a Worse Prognosis

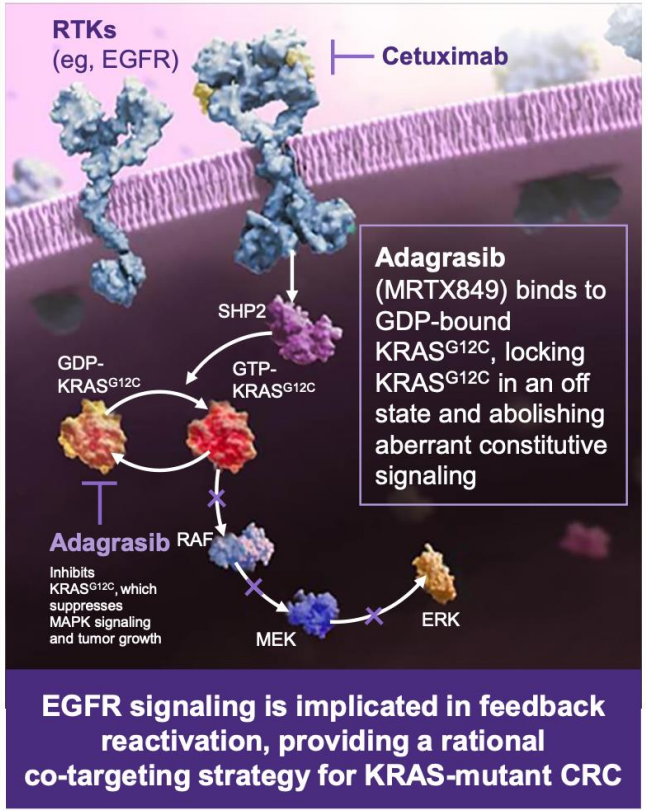
KRAS G12C



Ottaiano et al. *Cancers* 2023;15(14):3579.

KRAS G12C Inhibitors (3-4% of mCRC)

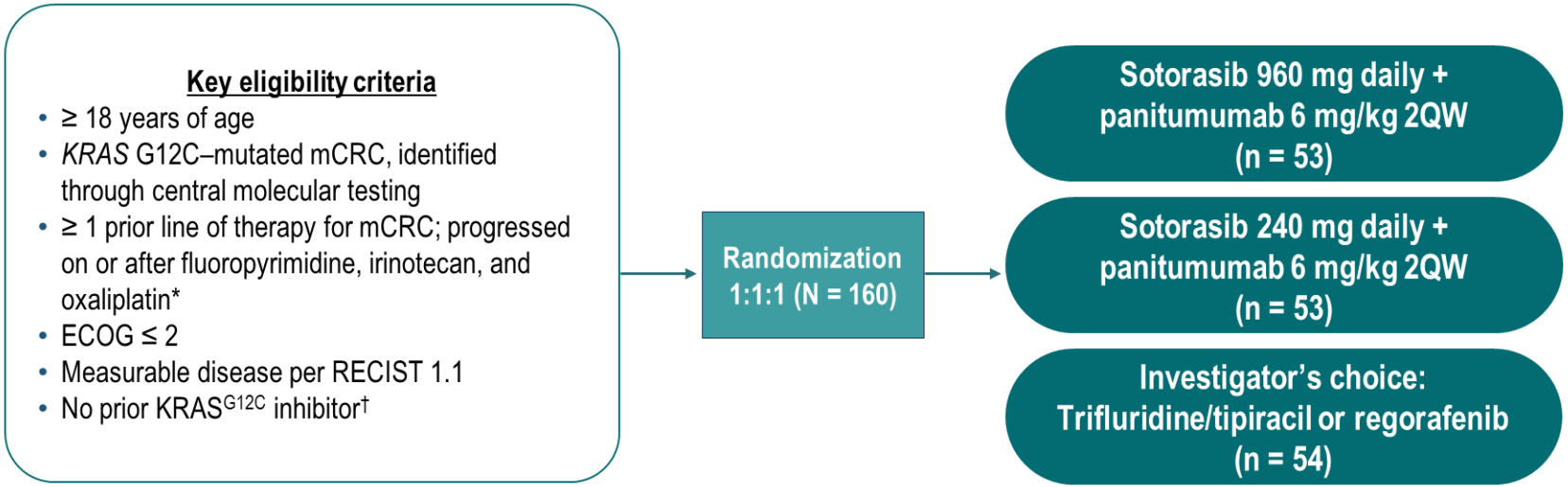




Liu et al, Cancer Gene Therapy 2021

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

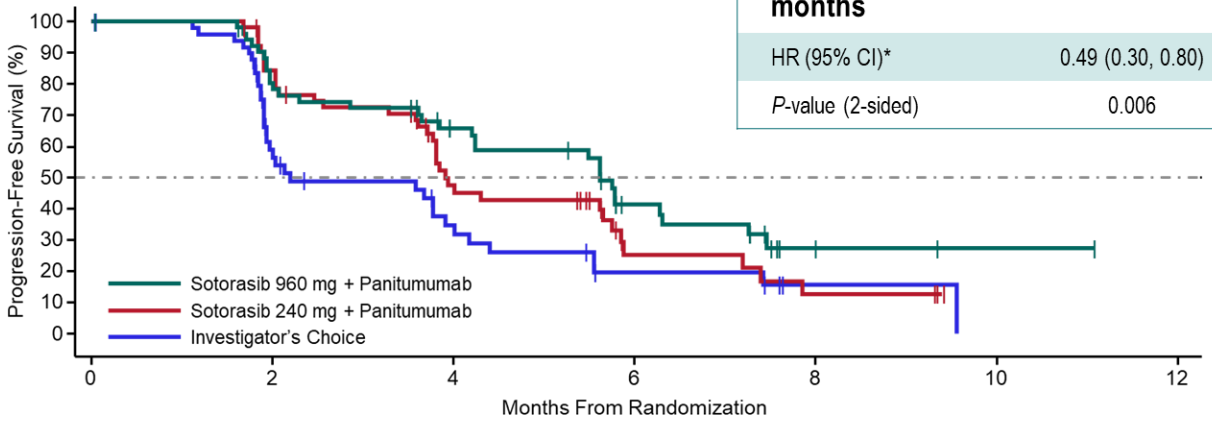
Primary endpoint: PFS by BICR (measured by CT / MRI and assessed by RECIST v1.1)
Key secondary endpoints: OS, ORR

*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

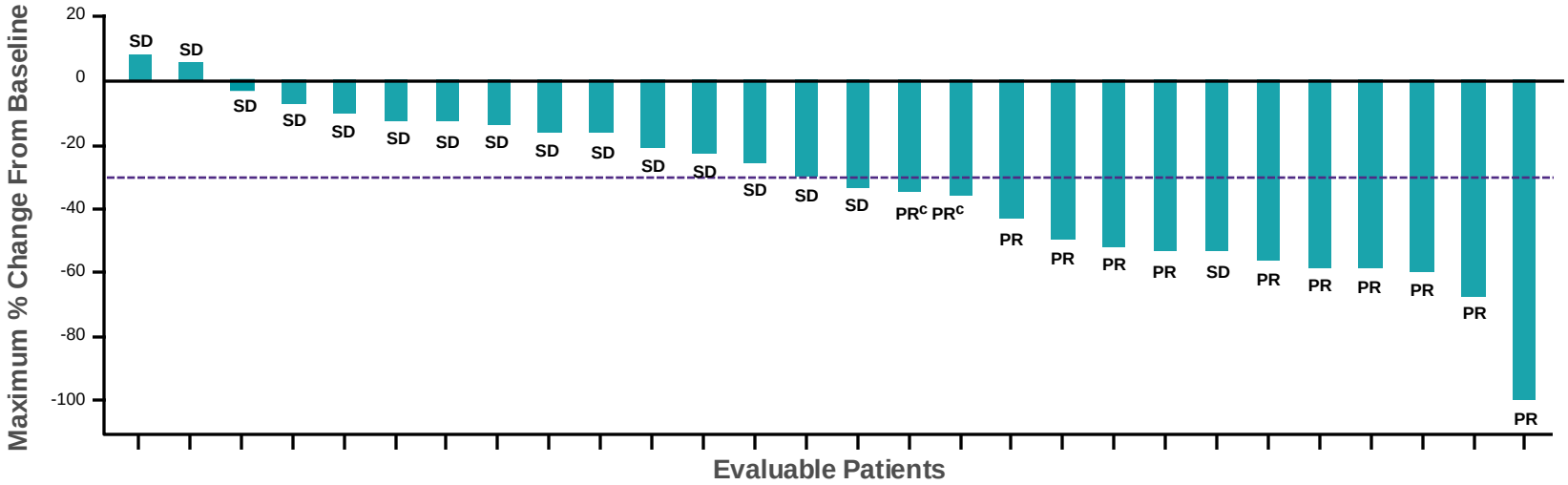
Response by BICR	Sotorasib 960 mg + Panitumumab (n = 53)	Sotorasib 240 mg + Panitumumab (n = 53)	Investigator's Choice (n = 54)
ORR, % (95% CI)*†	26 (15.3–40.3)	6 (1.2–15.7)	0 (0–6.6)
Complete response, n (%)	1 (2)	0	0
Partial response, n (%)	13 (25)	3 (6)	0
Stable disease, n (%)	24 (45)	33 (62)	25 (46)
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

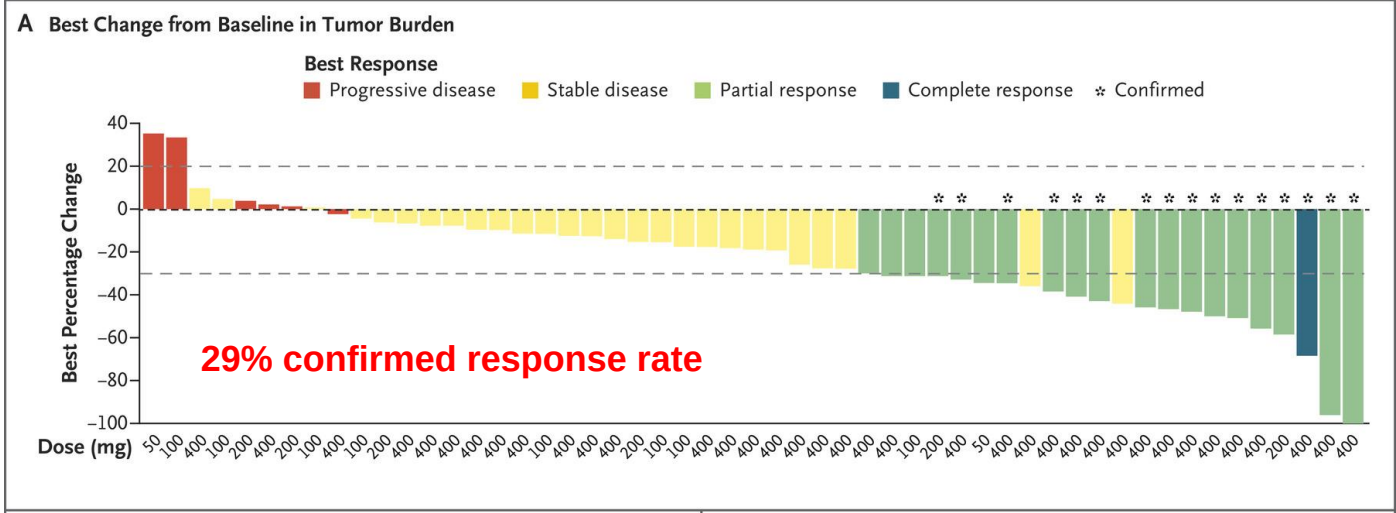
Best Tumor Change From Baseline (n=28)[a,b]

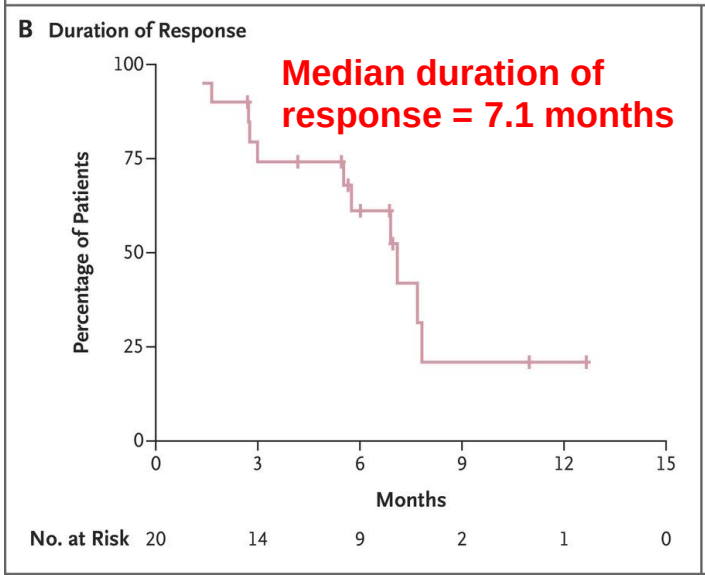


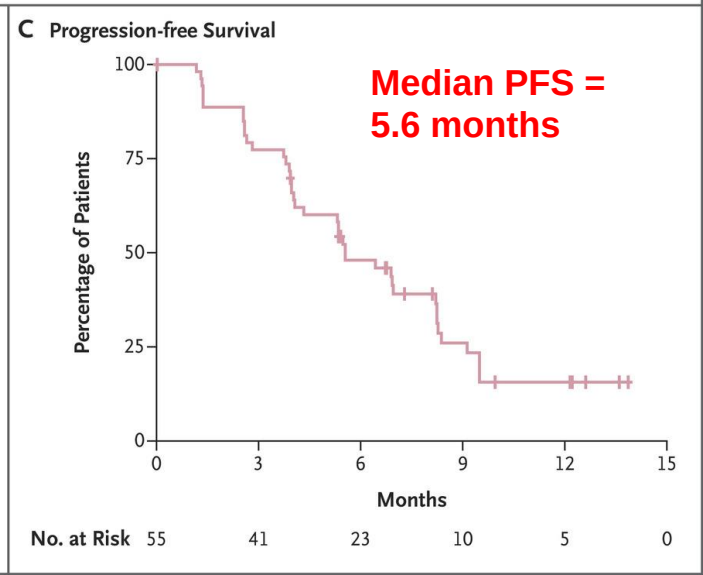
- Response rate was 43% (12/28), including 2 unconfirmed PRs
- SD was observed in 57% (16/28) of patients
- Clinical benefit (DCR) was observed in 100% (28/28) of patients
- No apparent association between response rate and molecular status was shown in an exploratory analysis[e]

[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)*

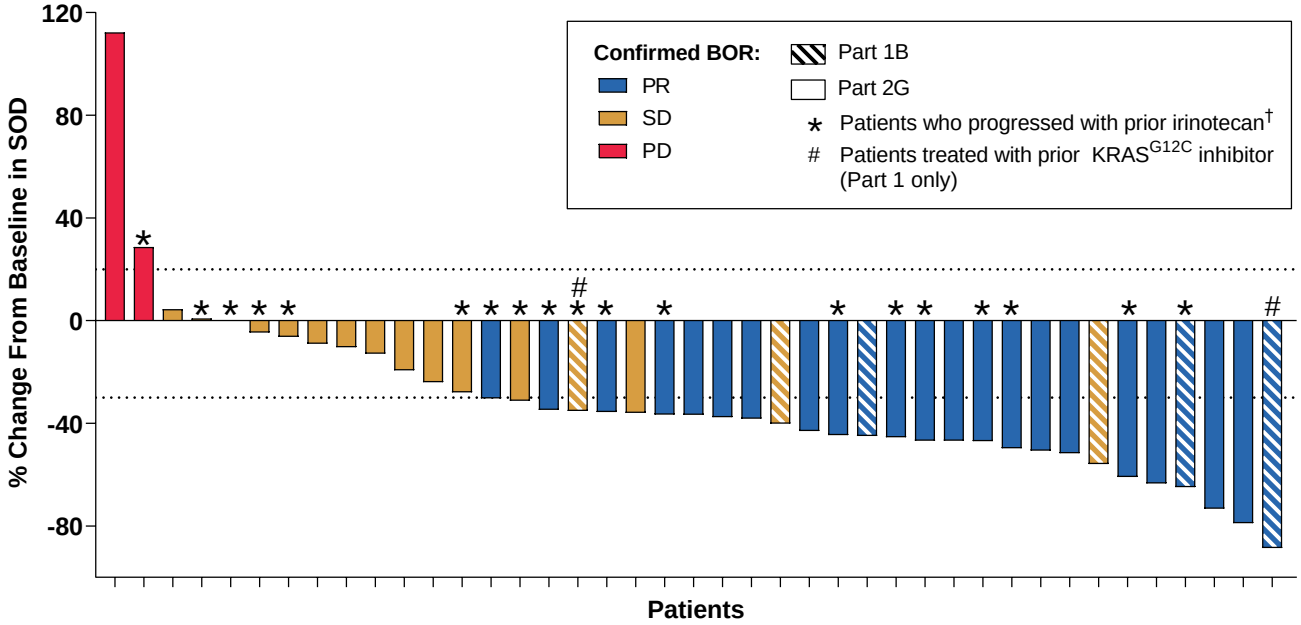






Sacher et al. *N Engl J Med* 2023.

Tumor Response with Sotorasib and FOLFIRI



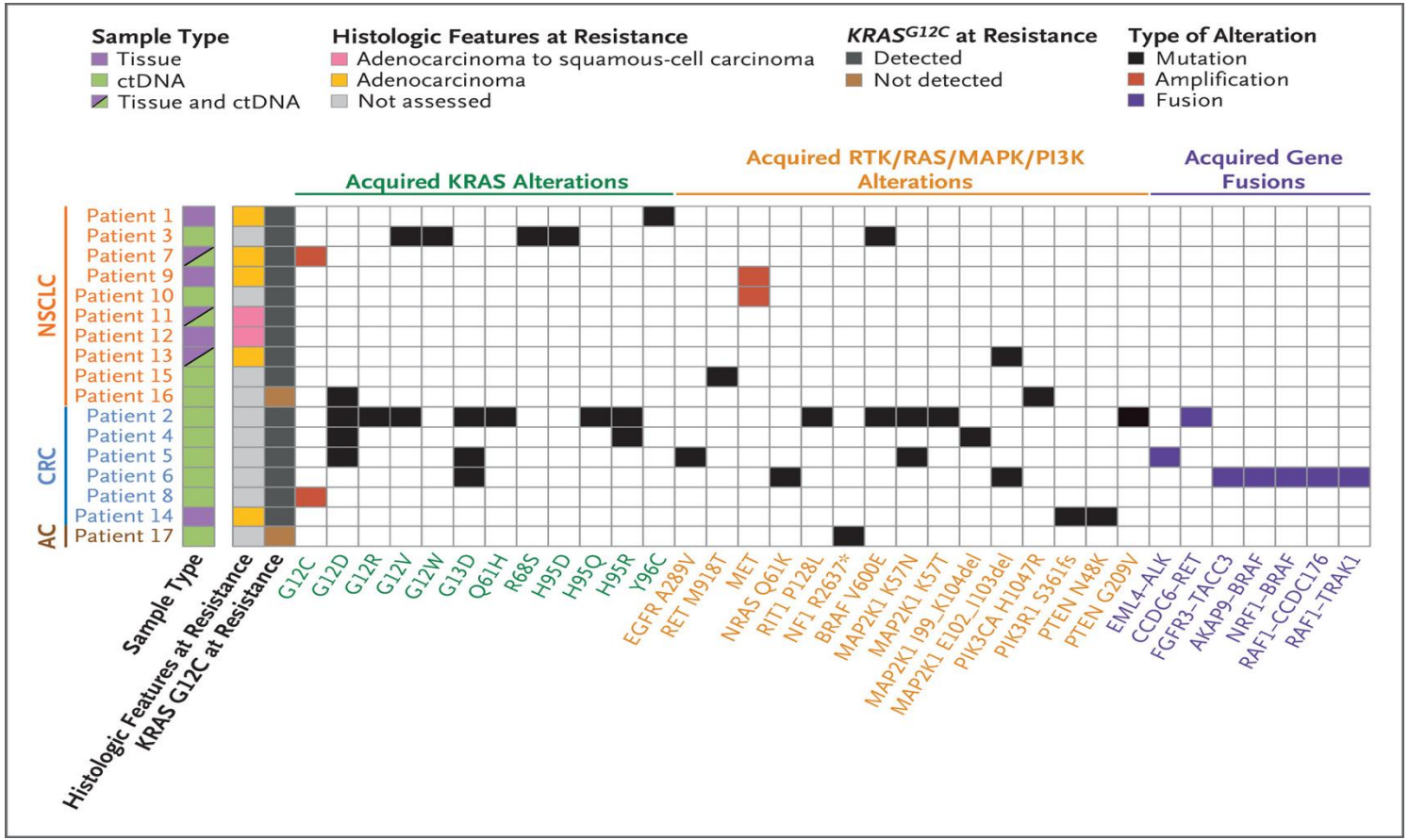
Data cutoff, April 13, 2023.

†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

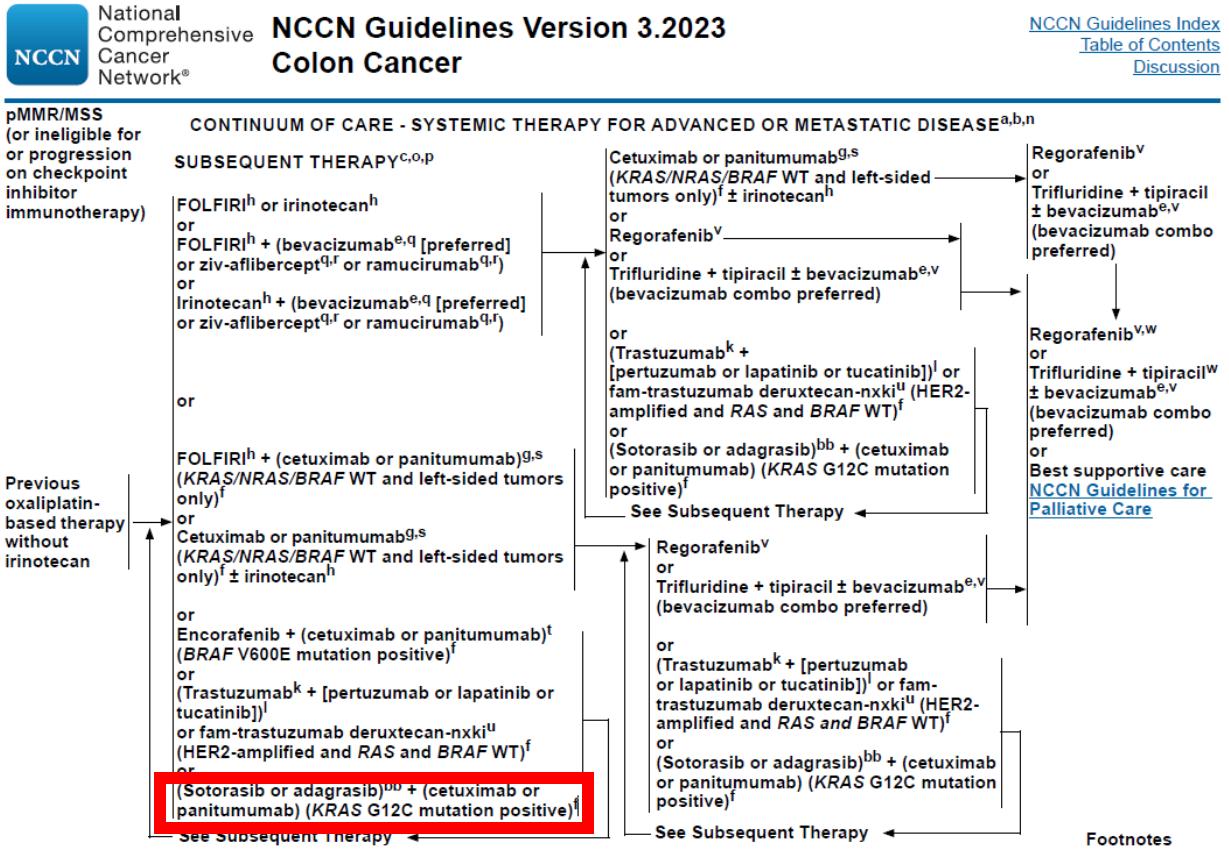


Awas et al NEJM 2021

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 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

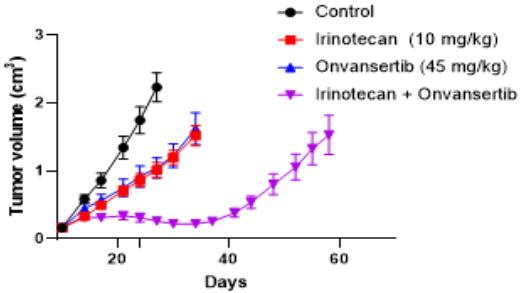
NCCN Colon Cancer Update 2023



NCCN Guidelines Colon Cancer v3.2023

Rationale: Synergy in combination with irinotecan

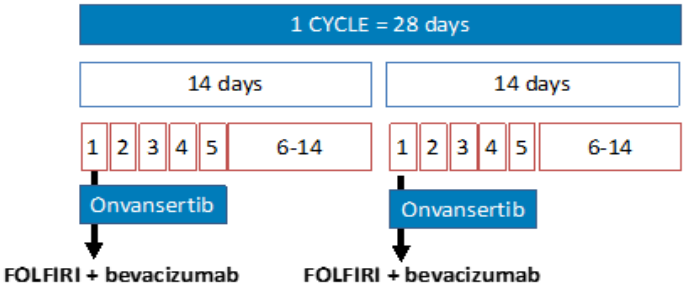
- In a KRAS mutant CRC mouse model, the combination of onvansertib and irinotecan significantly reduced tumor growth compared with either drug alone[5]



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

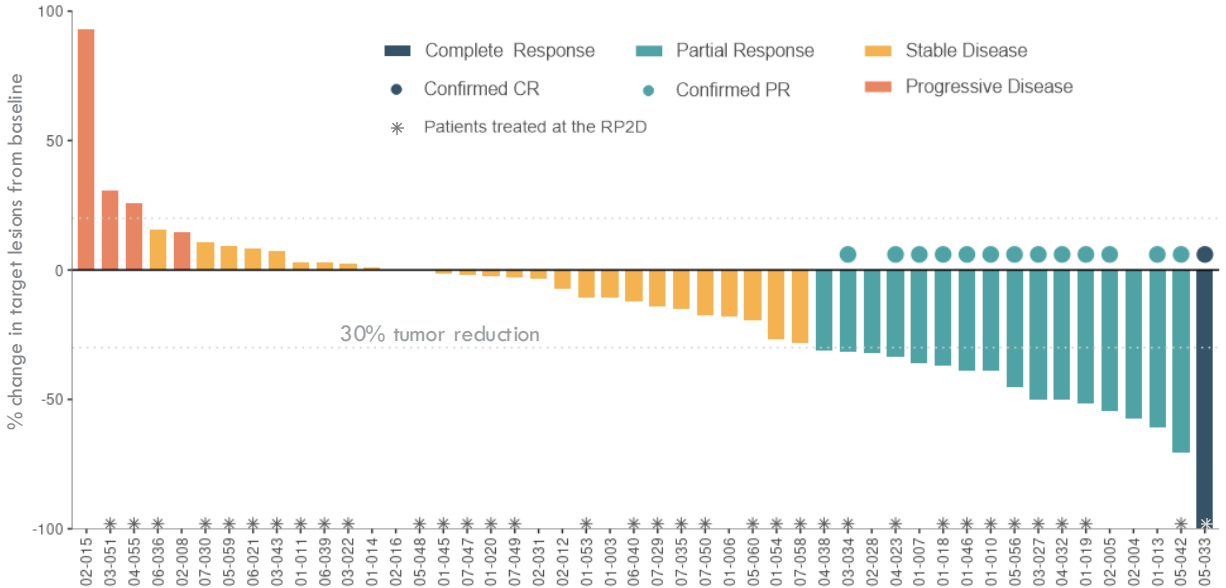
Efficacy Endpoints:

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 CCR2024

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

Lenz et al CCR 2024

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

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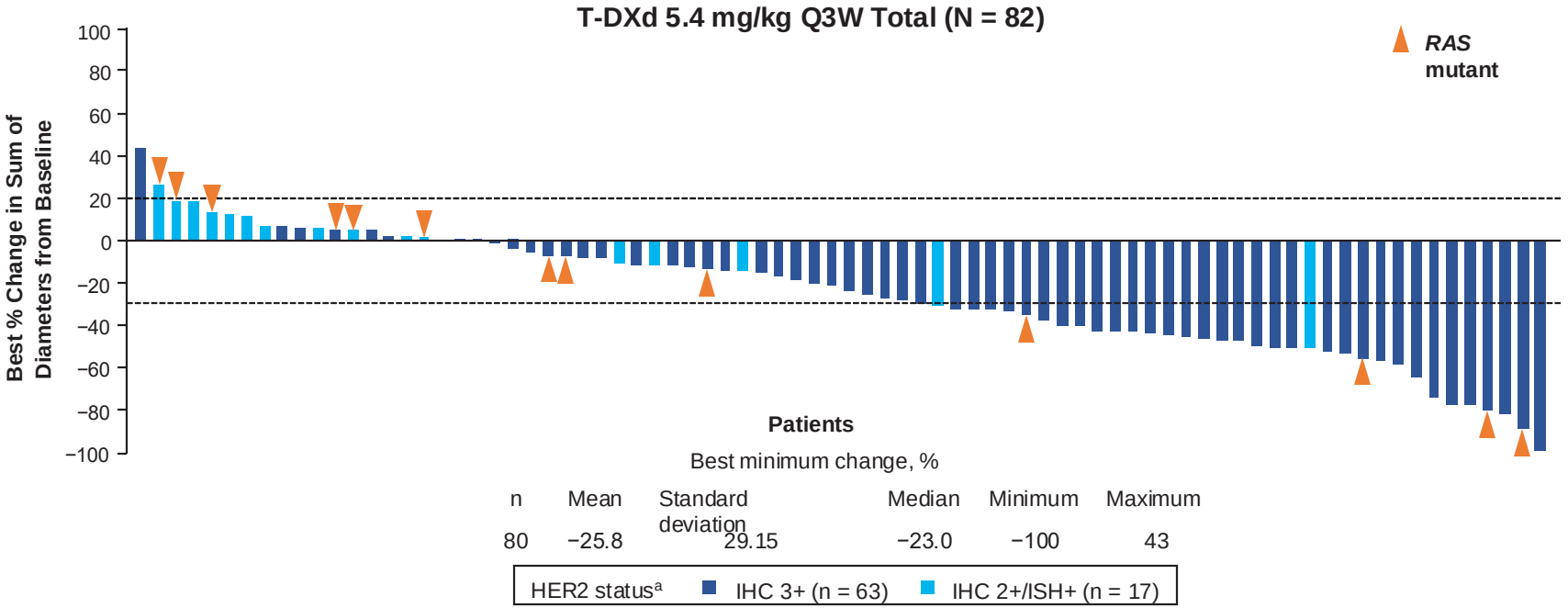
The University of Texas MD Anderson Cancer Center, Houston, TX, USA

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.

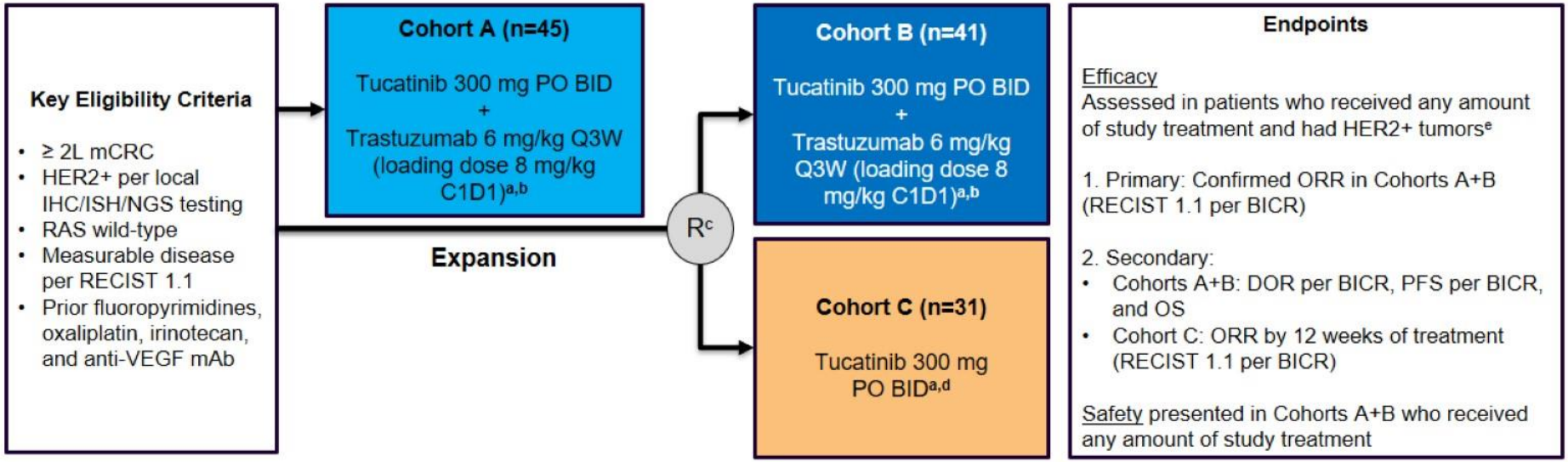
Best Percentage Change in Sum of Diameters by BICR for T-DXd 5.4 mg/kg



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

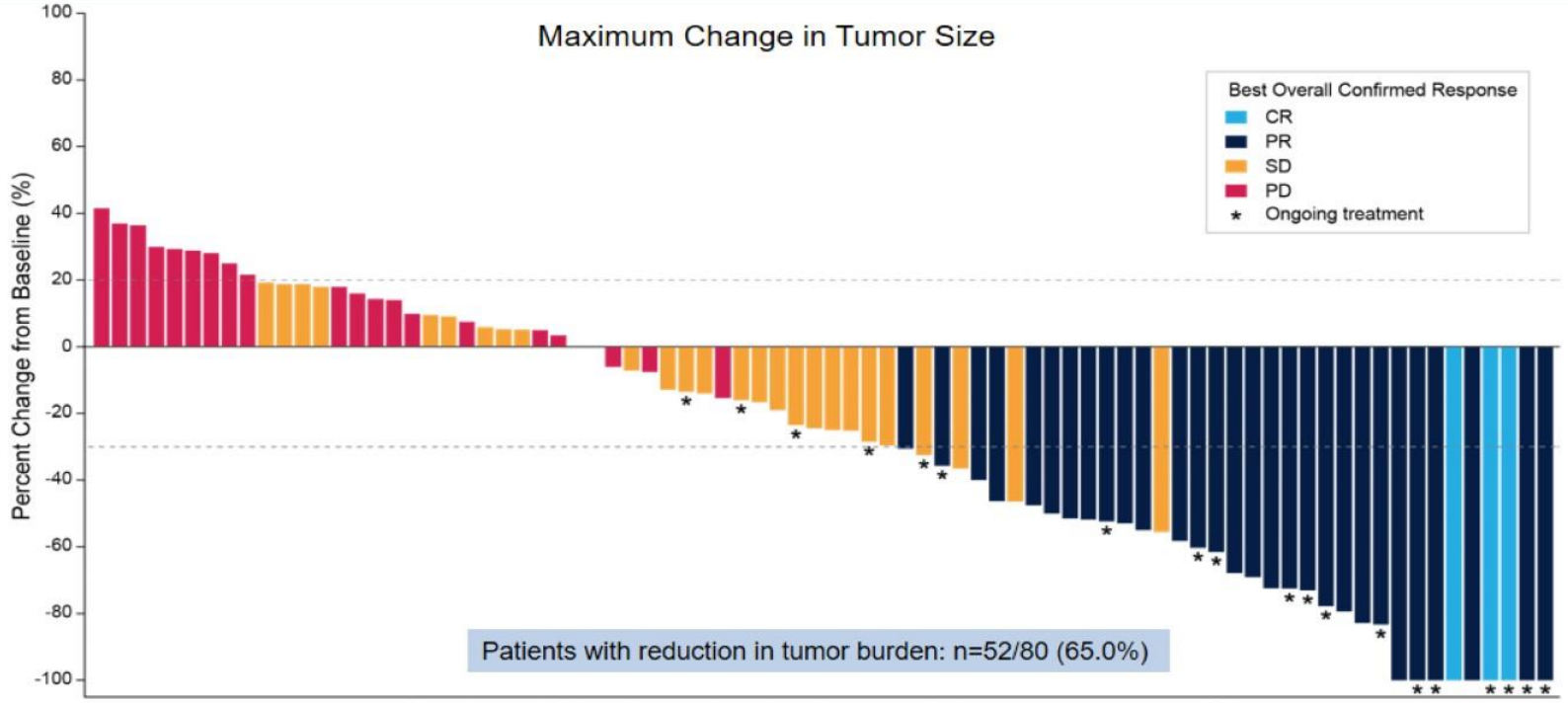
a Each treatment cycle is 21 days; b Patients remained on therapy until evidence of radiographic or clinical progression, unacceptable toxicity, withdrawal of consent, or study closure; c Stratification: Left sided tumor primary vs other; d Patients were allowed to cross over and receive tucatinib and 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

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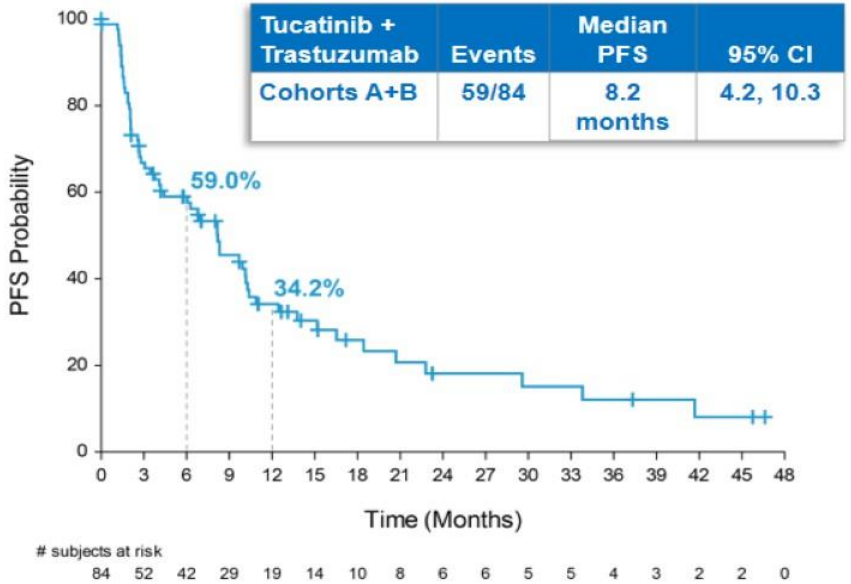
Tucatinib + Trastuzumab: PFS and OS

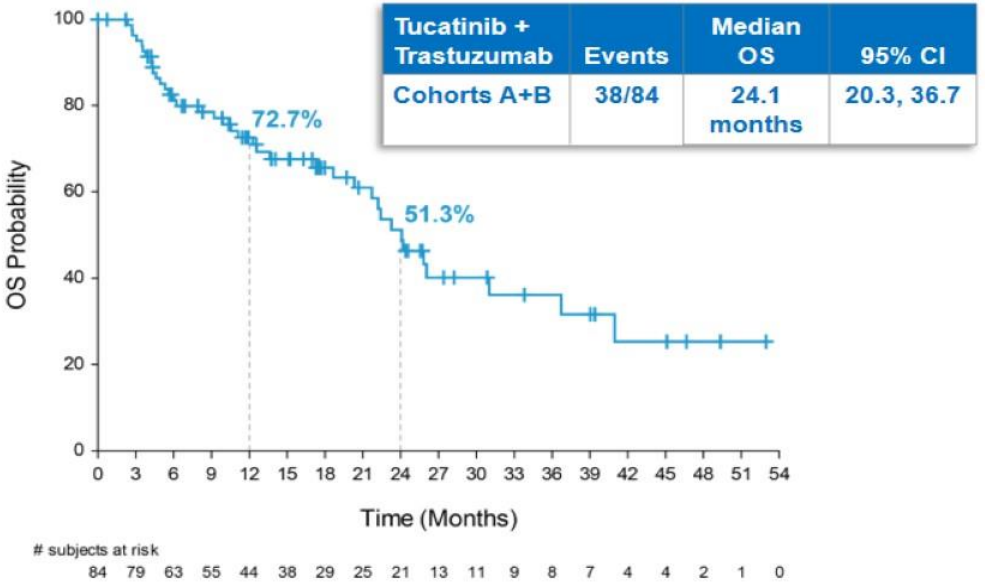
Progression-free Survival per BICR

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.

Take Home Messages : HER2+ mCRC

- Confirmed ORR in IHC2+/ISH+ is lower than IHC3+ but remained clinically relevant for TT (= Her2 Dependency), but not as much with TDxd (= Her2 expression).
- May exclude EGFRi
- Trastuzumab and Tucatanib (TT ; FDA approved) initial line following chemotherapy line(s)
  - RAS WT and IHC2+/ISH+ or IHC 3+
- T-DXd @ 5.4 mg/Kg as subsequent line of therapy to TT
  - RAS MT/WT and IHC 3+
  - Data supports activity post prior anti-Her2 Rx
  - Toxicities remain concerning
  - ? Retesting for Her2 ?

cORR: confirmed objective response rate; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; ISH: in situ hybridization

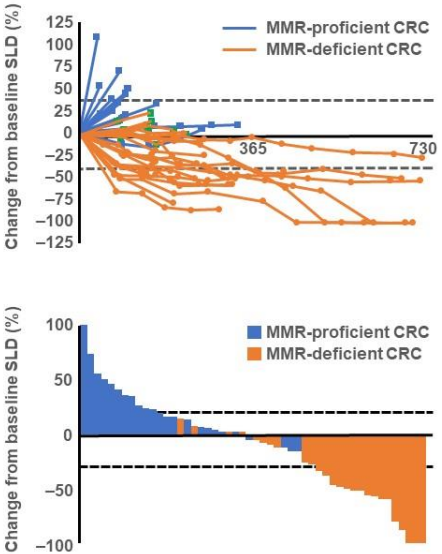
Raghav K, et al. Presented at: ASCO;2023.

IO in MSI H

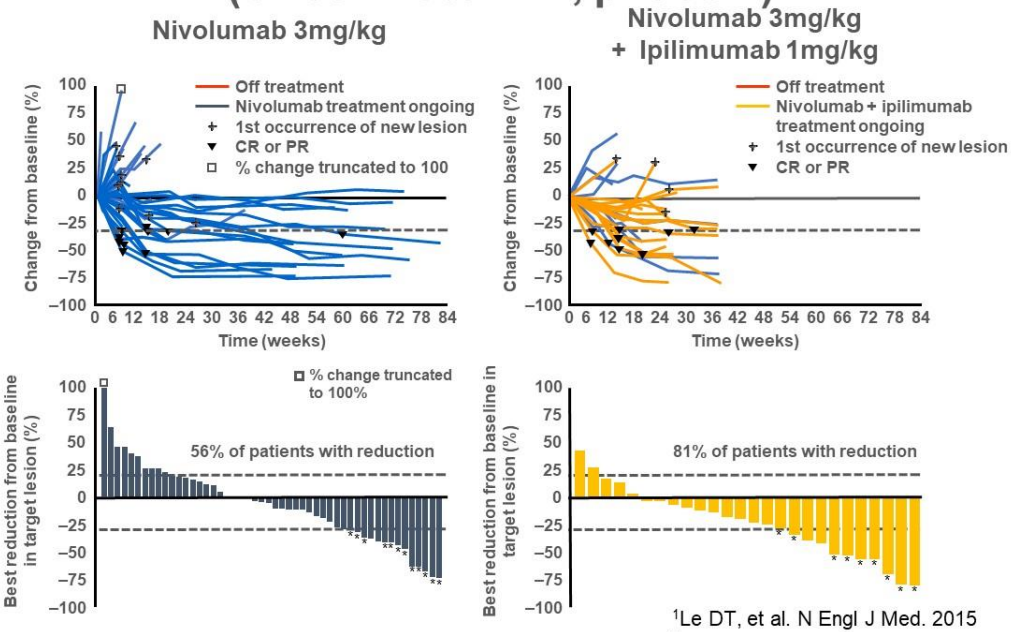
Nivo/Ipi in first line

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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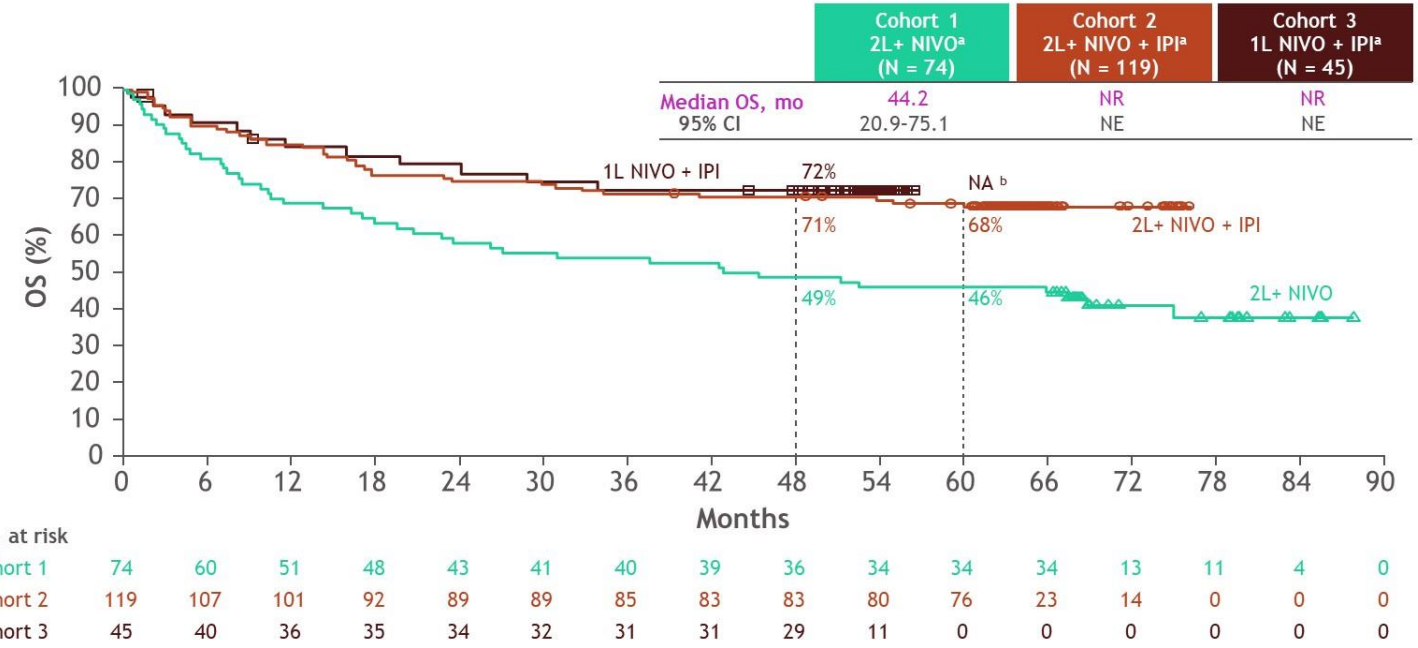
Overall survival



- 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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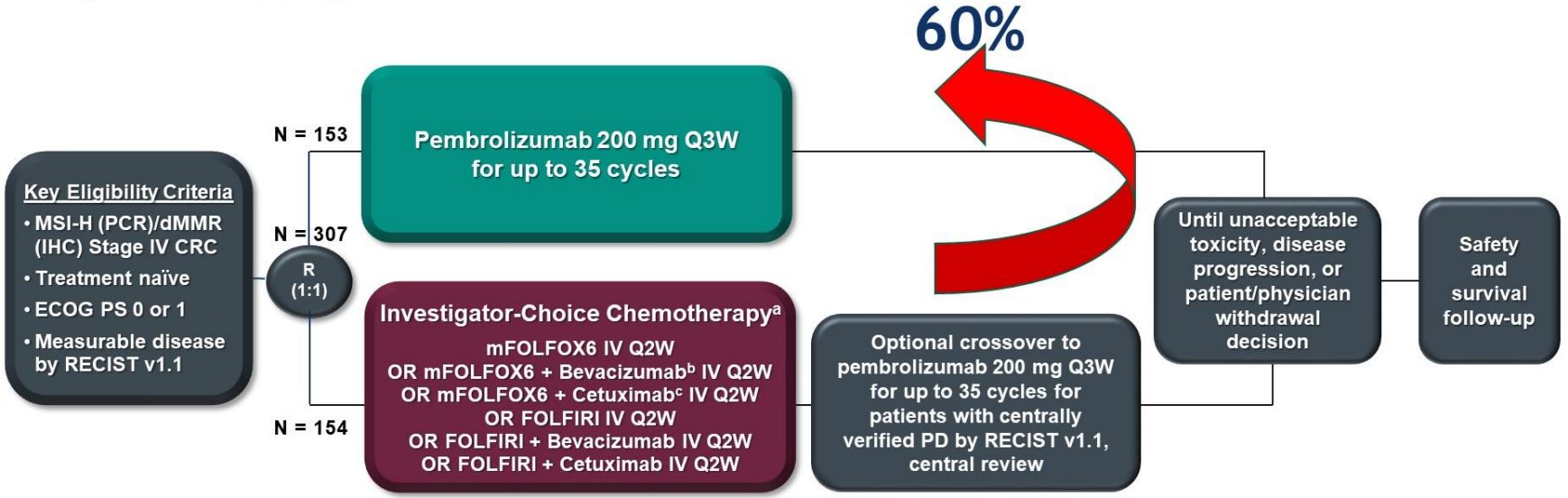
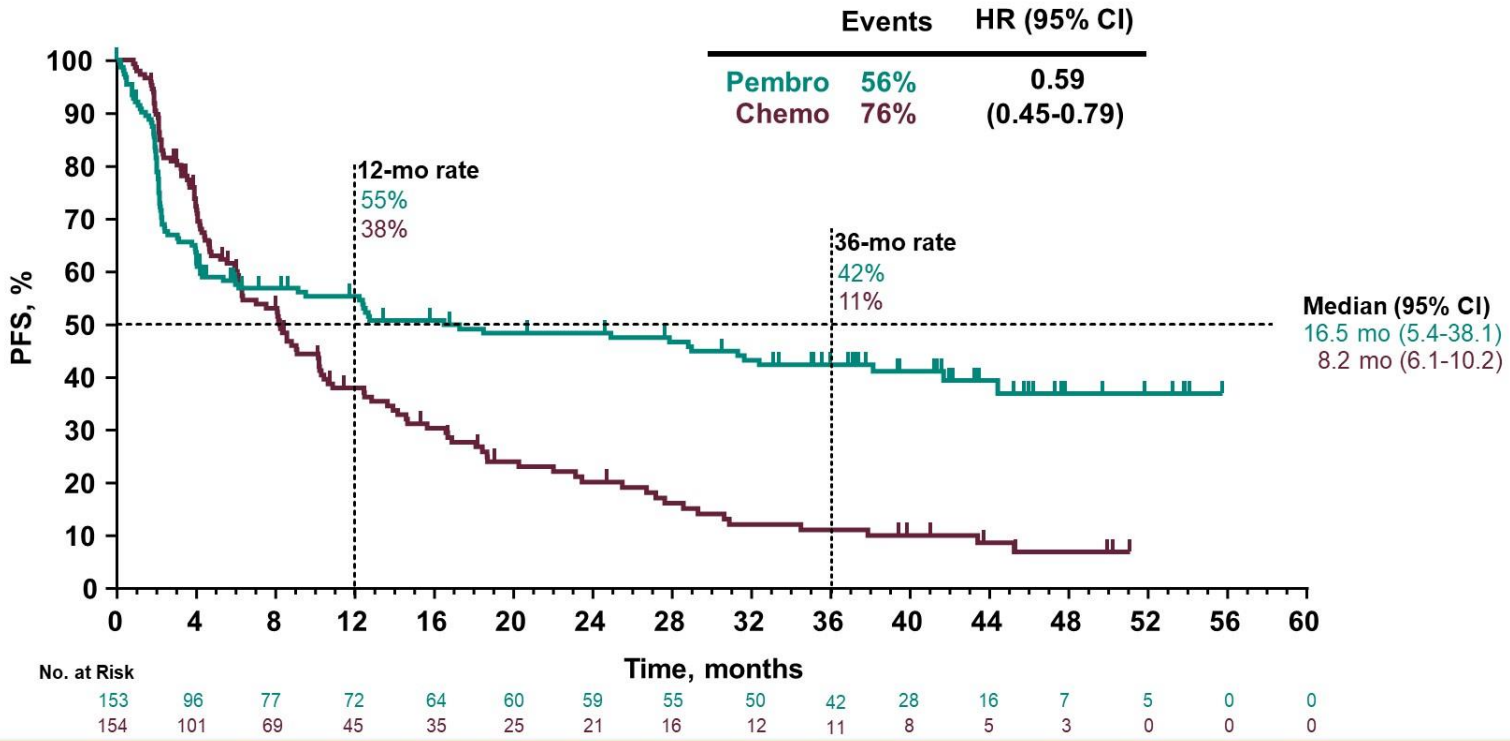
KEYNOTE-177 Study Design
(NCT02563002)



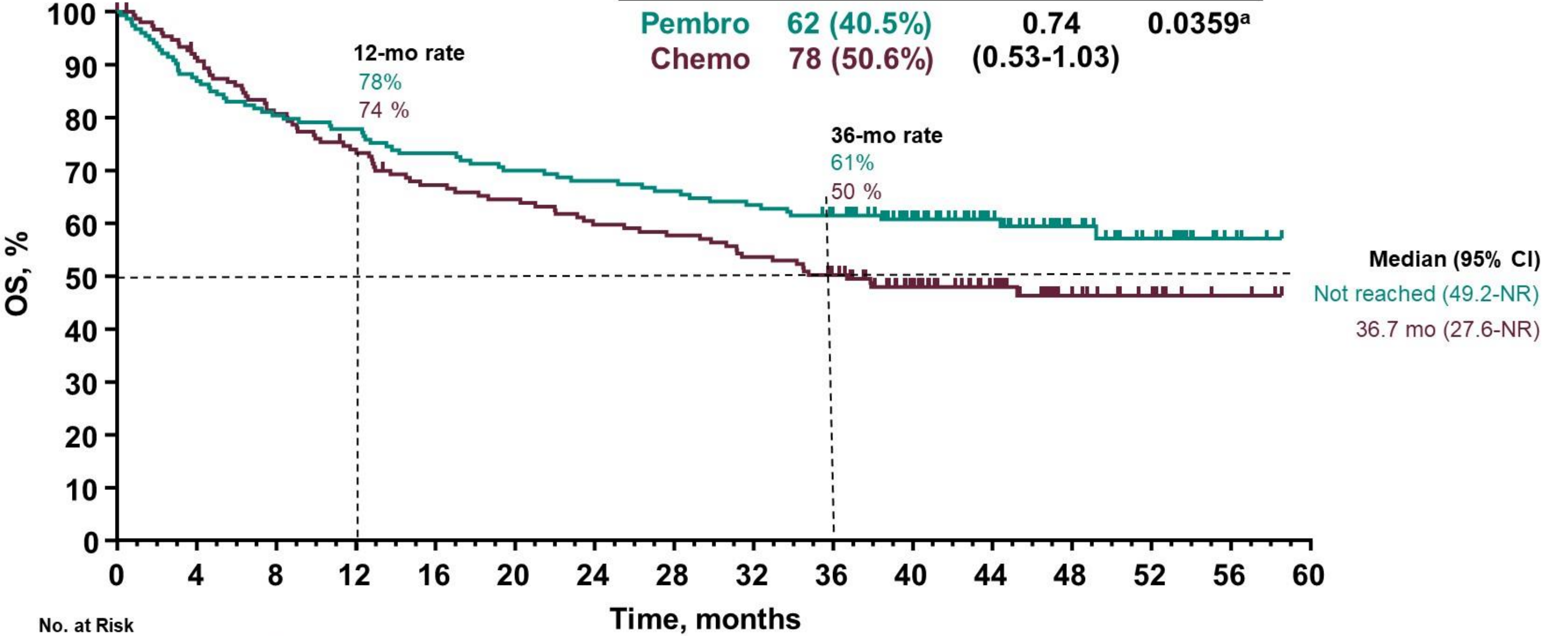
- Dual-primary endpoints: PFS per RECIST v1.1, BICR; OS
- Secondary endpoints: ORR per RECIST v1.1 by BICR, PFS2, HRQoL, safety
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

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%)		



No. at Risk

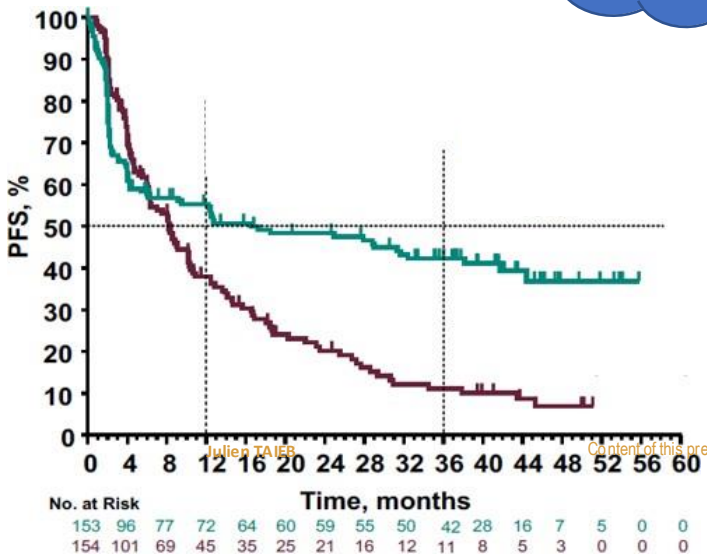
153	134	123	119	112	107	104	101	97	92	70	48	28	16	4	0
153	137	121	110	99	95	88	85	79	71	53	36	18	11	3	0

[a]Pembrolizum[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 cens[illegible] (95% CI 0.42-1.04) and 0.77 (95% CI 0.44-1.38). Data cut-off: 19Feb2021.

Discussion

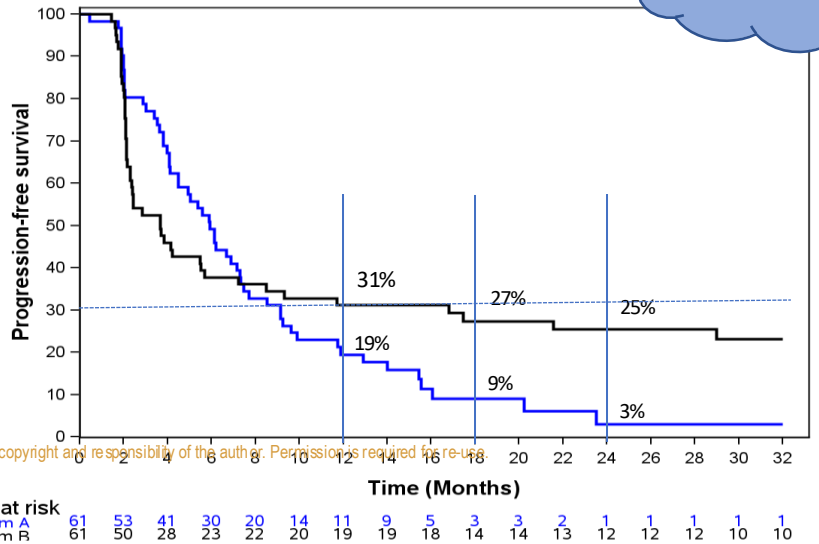
KEYNOTE 177

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

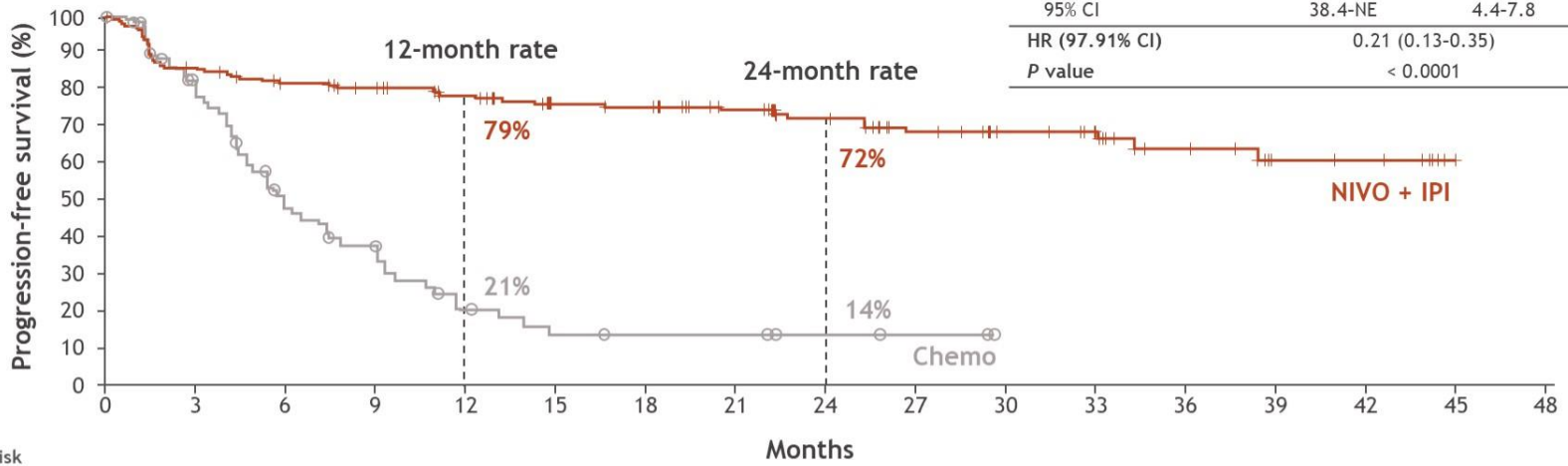
Heinz-Josef Lenz,[1] Sara Lonardi,[2] Elena Elez Fernandez,[3] Eric Van Cutsem,[4] Lars Henrik Jensen,[5] Jaafar Bennouna,[6] Guillermo Ariel Mendez,[7] Michael Schenker,[8] Christelle de la Fouchardiere,[9] Maria Luisa Limon Miron,[10] Takayuki Yoshino,[11] Jin Li,[12] José Luis Manzano Mozo,[13] Giampaolo 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	



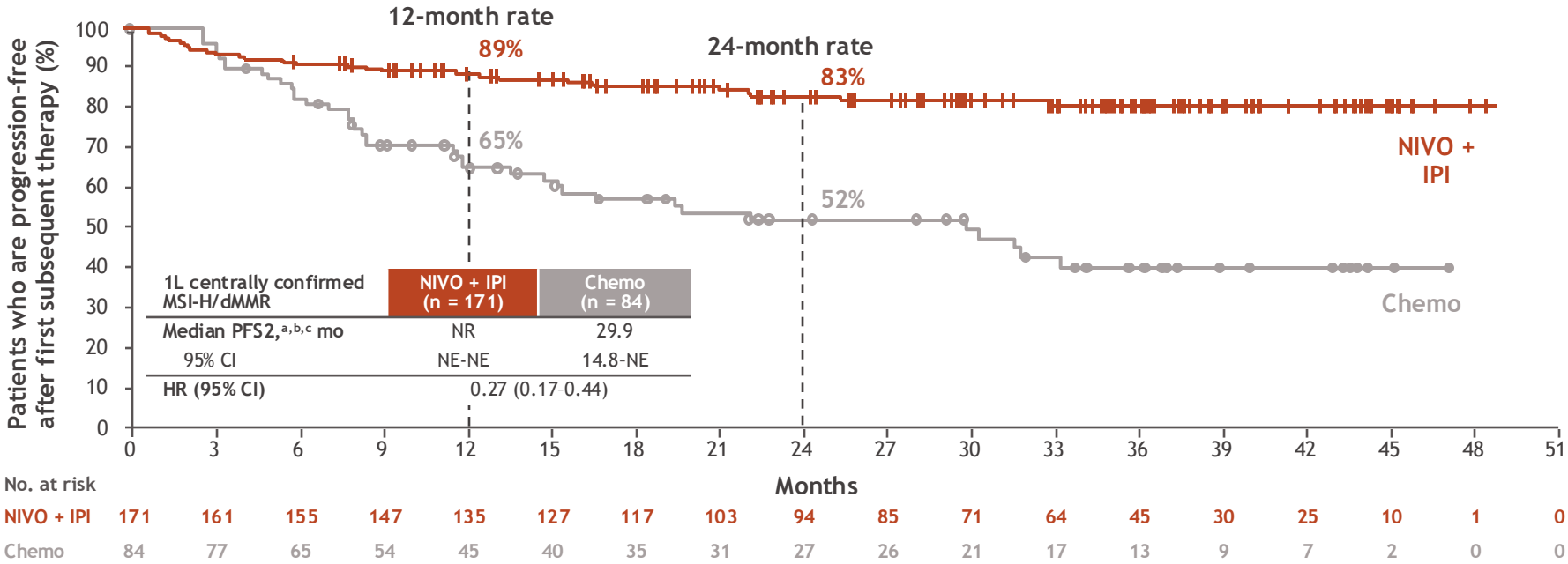
No. at risk																	
NIVO + IPI	171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Chemo	84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

- 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.

Take Home Messages

- MSI H tumor should be treated in first line with immunotherapy
- CTLA4/PD(L)1 combination should be considered for first line therapy
- PFS2 increased with immunotherapy given in first line
- Ipi 1mg/kg q 6 weeks not increased toxicity compared to nivo alone

This is where all footnotes and references go.

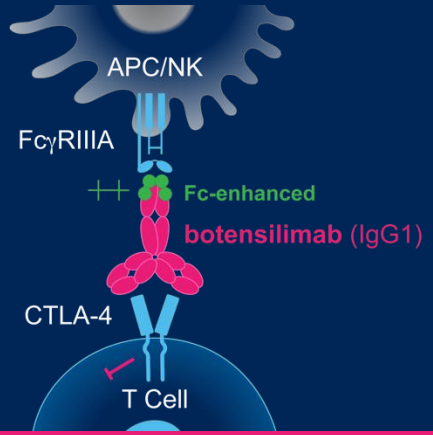
IO in MSS

1. Role of CTLA
2. Novel Immune therapies for MSS CRC
3. Role of liver metastases

Novel Immunotherapy Agents

botensilimab

Fc-enhanced CTLA-4 Inhibitor

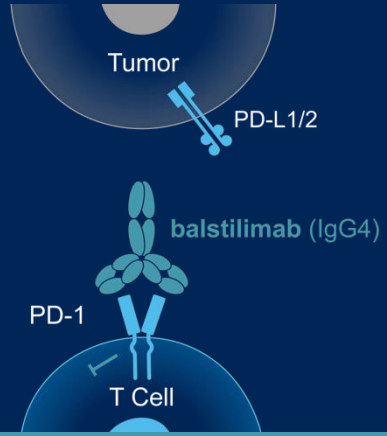


Active in cold and IO refractory tumors[1,2]:

- ↑ T cell priming, expansion, memory[3,4]
- ↑ Frequency of activated DCs
- ↑ Treg depletion
- ↓ Complement mediated toxicity

balstilimab

PD-1 Inhibitor

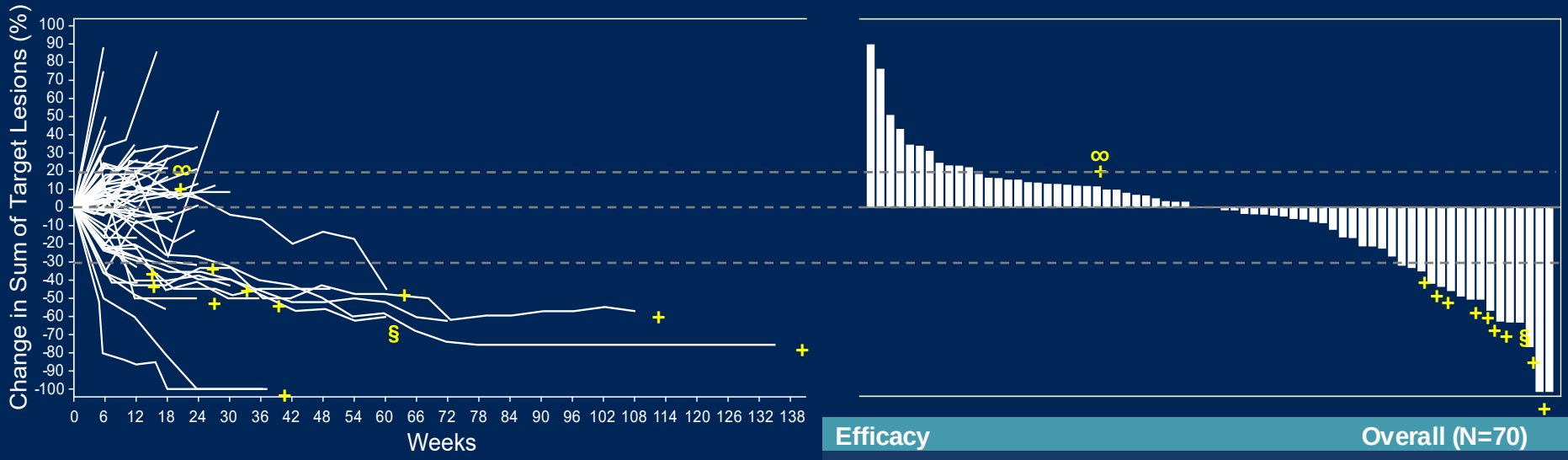


Safety and efficacy analogous to approved anti-PD-1 mAbs[5,6]

- > 750 patients treated; 10 ongoing trials / 2 completed
- Complete blocker of PD-1-PD-L1/2 interactions
- Enhanced T cell activation and effector function

El-Khoueiry AB, et al. Presented at: ASCO;2023. El-Khoueiry AB, et al. Presented at: SITC;2021. Poster 479. Wilky B, et al. SITC;2022. Abstract 778. Waight JD, et al. *Cancer Cell*. 2018;33(6):1033-1047. NCT03860272. Accessed July 1, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT03860272. O'Malley DM, et al. *Gynecol Oncol*. 2021;163(2):274-280. O'Malley DM, et al. *J Clin Oncol*. 2022; 40(7):762-771.

Efficacy: Durable Objective Responses



Efficacy	Overall (N=70)
ORR*, % (95% CI)	**23** (xx-xx)
BOR, n (%)	
CR	1 (1)
PR	15 (21)
SD	37 (53)

Efficacy	Overall (N=70)
DCR (CR + PR + SD), % (95% CI)	76 (64-85)
Median DOR, months (95% CI)	10 (3-NR)
Median PFS, months (95% CI)	**4.1 (2.8-5.5)**
Median F/U, months (Min, Max)	6 (2, 31)

Responder Characteristics (n=16)

- 3 with prior I-O (all refractory)
- 1/13 TMB >10 mut/Mb
- 1/8 PD-L1 positive (≥1%)
- 11 RAS mutant

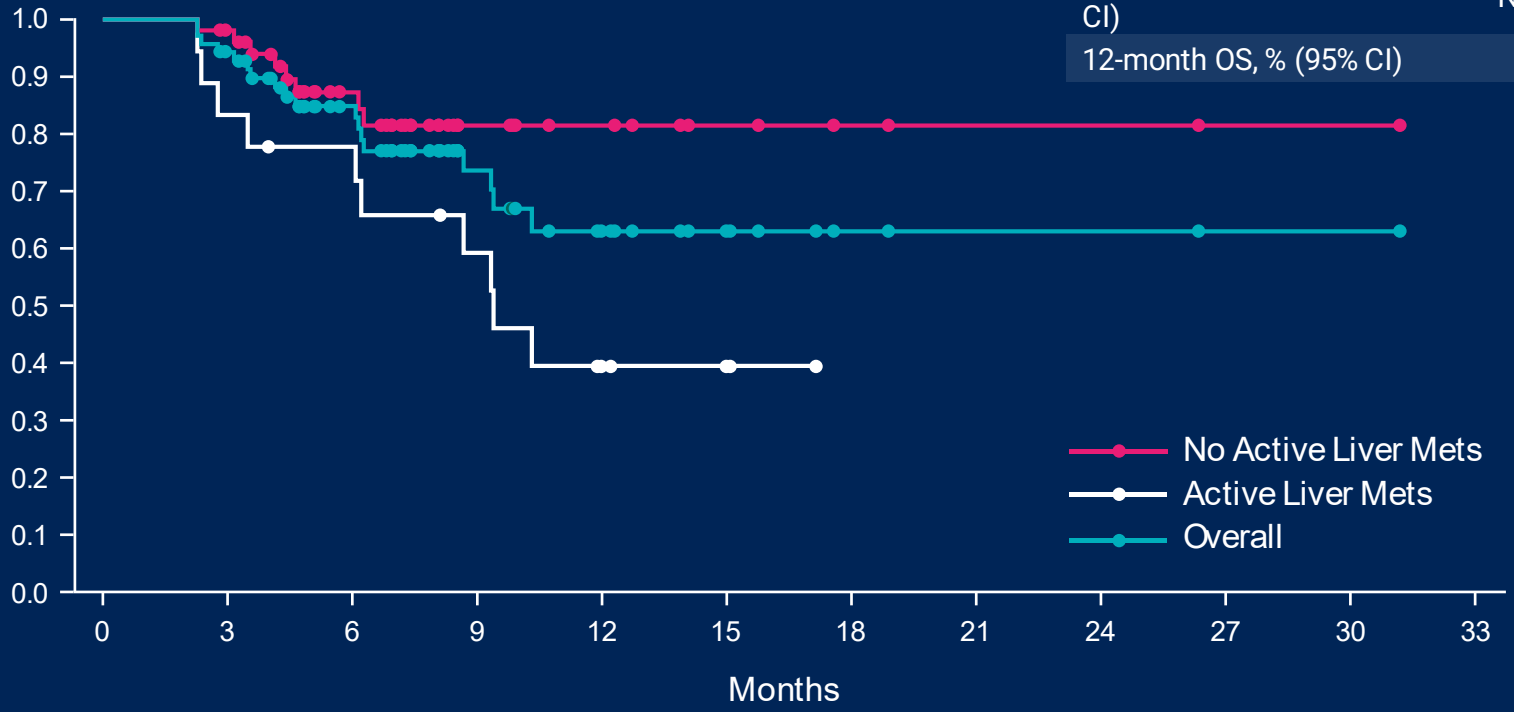
*Includes unconfirmed responses. + Ongoing responses (n=11/16). ∞ Resected target lesions showed complete pathologic response § Response by iRECIST.

El-Khoueiry AB, et al. Presented at: ASCO;2023.

Overall Survival by Liver Involvement

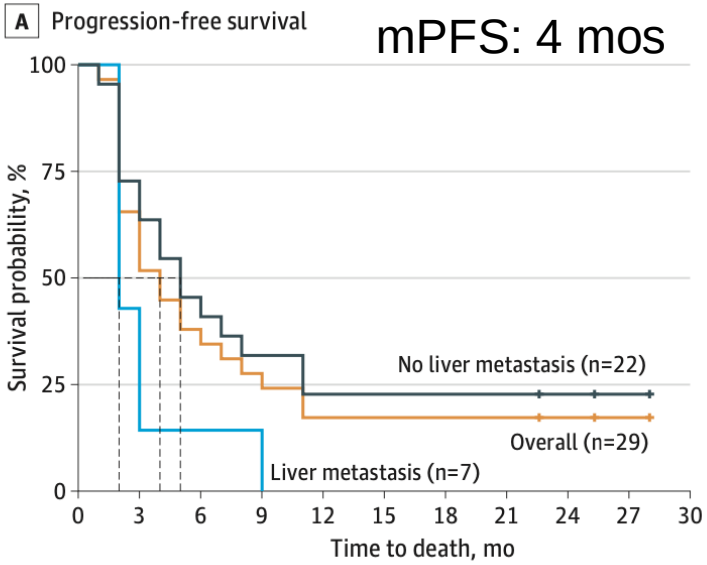
Efficacy evaluable population, N=70

Efficacy	Overall
Median OS, months (95% CI)	NR (10.3-NR)
12-month OS, % (95% CI)	63 (46-76)

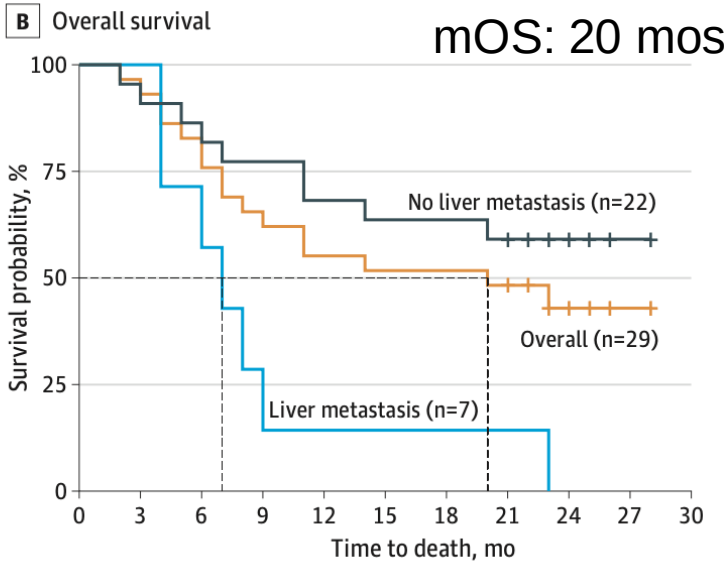


El-Khoueiry AB, et al. Presented at: ASCO;2023.

Phase 1 Study Rego/Nivo/Ipi in MSS mCRC



No. at risk											
Overall	29	19	11	8	5	5	5	5	2	1	0
Liver metastasis	7	3	1	1	0	0	0	0	0	0	0
No liver metastasis	22	16	10	7	5	5	5	5	2	1	0



No. at risk											
Overall	29	28	24	19	16	15	15	14	7	1	0
Liver metastasis	7	7	5	2	1	1	1	1	0	0	0
No liver metastasis	22	21	19	17	15	14	14	13	7	1	0

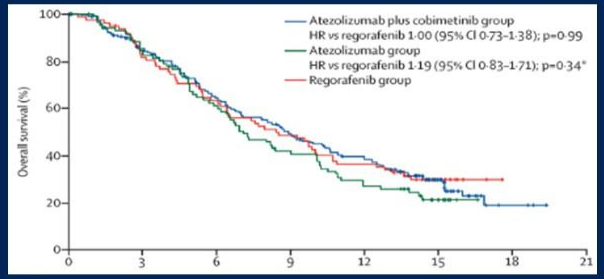
RR: No liver mets (22): 36%, Liver mets (7): 0%

Fakih M, et al. *JAMA Oncol*. 2023;9(5):627-634.

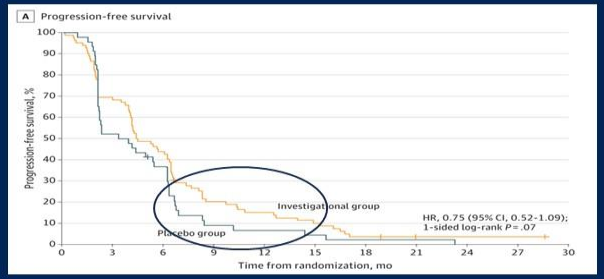
Knowledge Prior to ASCO 2023

Randomized PII/III studies with IO+ for MSS mCRC: From Negative to Borderline Positive

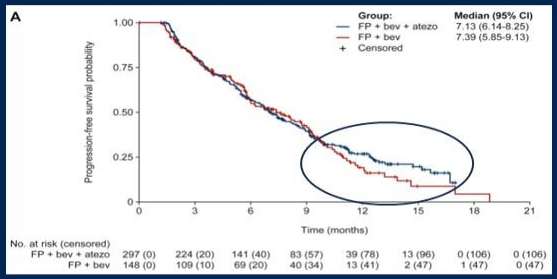
Imblaze 370 : Ref L Atezo +/- cobi vs. Rego



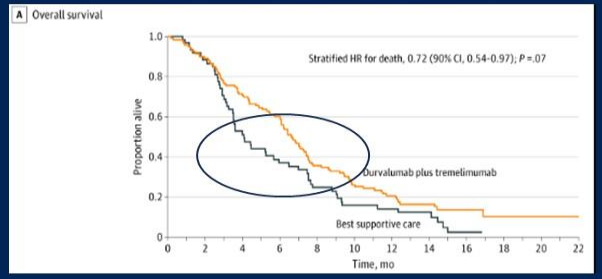
BACCI : Ref L Cape/Bev +/- Atezo/PBO



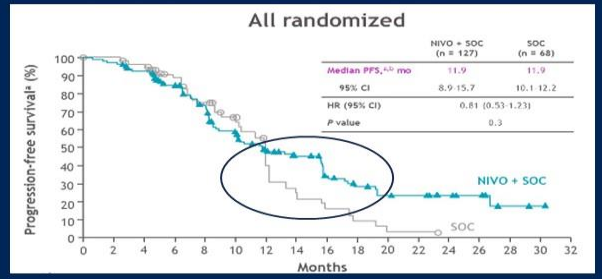
MODUL : Maint FP/Bev +/- Atezo



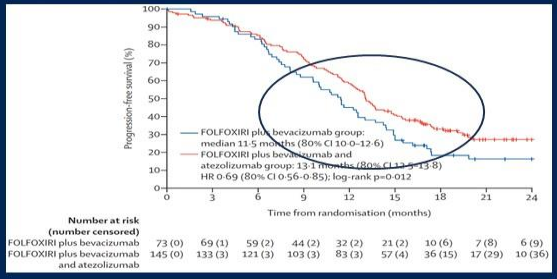
CO.26 : Ref L Tremi/Durva vs. BSC



CM 9X8: 1L mFOLFOX6 + Bev +/- Nivo



AtezoTRIBE: 1L FOLFOXIRI/Bev +/- Atezo

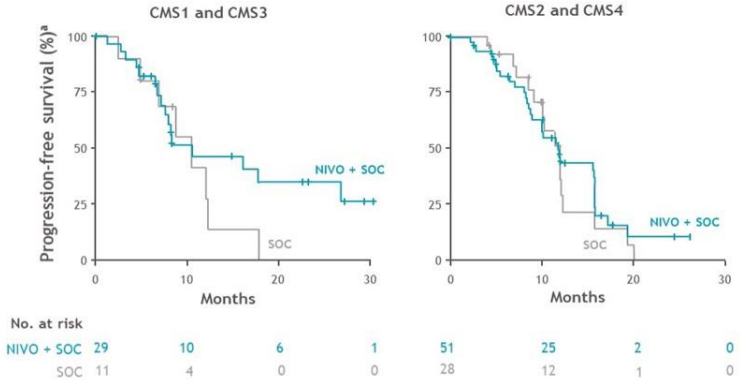


Eng C et al . *Lancet Oncol* 2019; Mettu N et al . *JAMA NO*, 2022; Tabernero J et al . *ESMO Open* 2022; Chen E et al , *JAMA Oncol*, 2020; Lenz HJ. ASCO GI 2022; Antoniotti C et al . *Lancet Oncol* 2022

Bekaii-Saab T, et al. Presented at: ASCO;2023.

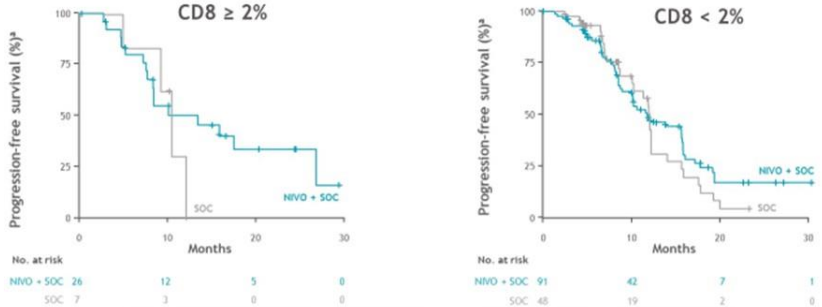
mFOLFOX6 +/- nivolumab for first line CRC (CheckMate 9X8)

CMS Subsets



Median PFS (95% CI), mo	Baseline CMS status[a,b,c]	
	CMS1 and CMS3[d]	CMS2 and CMS4
NIVO + SOC (n = 80)	10.6 (7.6-NE)	11.8 (10.1-15.7)
SOC (n = 39)	10.4 (6.9-NE)	11.9 (10.1-19.3)

CD8+ Subsets



Median PFS (95% CI), mo	Baseline tumor CD8 levels[a,b,c]	
	CD8 ≥ 2%	CD8 < 2%
NIVO + SOC (n = 117)	13.2 (8.25-NE)	11.8 (10.0-15.7)
SOC (n = 55)	10.4 (9.1-NE)	11.9 (10.25-14.1)

- PFS did not meet statistical significance
  - Numerically higher PFS rates were observed after 12 months
  - Higher ORR and more durable responses with NIVO + SOC

Lenz ASCO GI 2022 abstract 8

FOLFOXIRI Plus Bevacizumab and Atezolizumab as upfront Treatment of Unresectable mCRC Patients: Updated and Overall Survival Results of the Phase II Randomized AtezoTRIBE Study

Carlotta Antoniotti, Daniele Rossini, Filippo Pietrantonio, Lisa Salvatore, Federica Marmorino, Margherita Ambrosini, Sara Lonardi, Maria Bensi, Roberto Moretto, Stefano Tamberi, Ilaria Toma, Alessandro Passardi, Maria Caterina De Grandis, Veronica Conca, Federica Palermo, Alessandro Cappetta, Aurelie Catteau, Luca Boni, Jérôme Galon, Chiara Cremolini

On behalf of GONO Foundation investigators

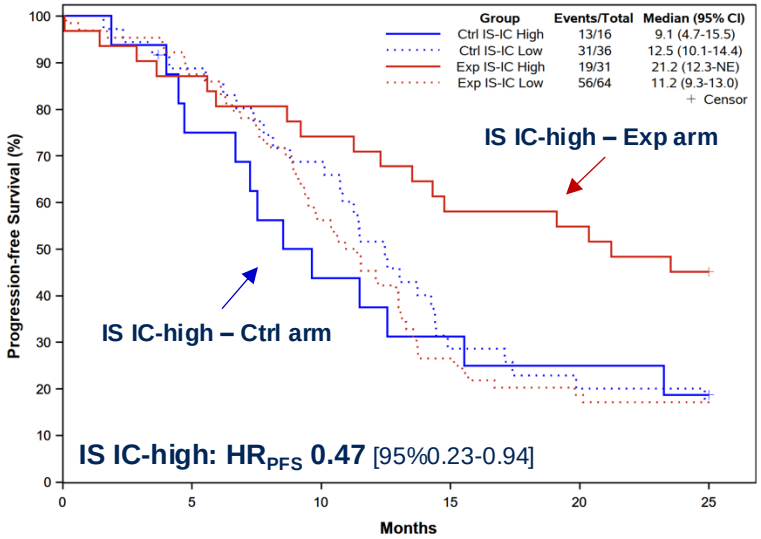
Carlotta Antoniotti, MD PhD

University Hospital of Pisa, Italy

Carlotta Antoniotti C, et al. Presented at: ASCO;2023.

Outcomes According to Immunoscore IC and Arm – pMMR Cohort

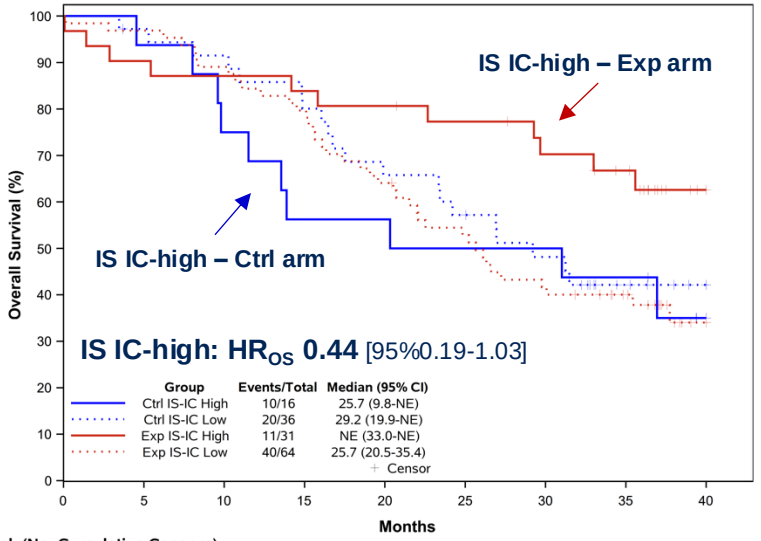
Progression-Free Survival



No. at Risk (No. Cumulative Censors)

Ctrl IS-IC High	16 (0)	12 (0)	7 (0)	5 (0)	4 (0)	3 (0)
Ctrl IS-IC Low	36 (0)	31 (1)	24 (1)	10 (1)	7 (1)	6 (1)
Exp IS-IC High	31 (0)	27 (0)	23 (0)	18 (0)	17 (0)	14 (0)
Exp IS-IC Low	64 (0)	56 (0)	36 (0)	17 (0)	12 (0)	11 (0)

Overall Survival



No. at Risk (No. Cumulative Censors)

Ctrl IS-IC High	16 (0)	15 (0)	12 (0)	9 (0)	9 (0)	8 (0)	8 (0)	6 (1)	2 (4)
Ctrl IS-IC Low	36 (0)	34 (1)	32 (1)	28 (1)	23 (1)	20 (1)	16 (2)	8 (8)	4 (12)
Exp IS-IC High	31 (0)	28 (0)	27 (0)	26 (0)	25 (0)	23 (1)	20 (2)	17 (4)	5 (15)
Exp IS-IC Low	64 (0)	62 (0)	57 (0)	51 (0)	41 (0)	33 (1)	26 (1)	19 (7)	4 (20)

Carlotta Antoniotti C, et al. Presented at: ASCO;2023.

Our Goal: Right Treatment, Right Time

- Genetic testing of tumor at time of diagnosis and if repeat at time of progression
- Germline testing of patients if evidence of predisposition
- Active monitoring with liquid biopsies
- Accelerating access to clinical trials
- Identification of druggable novel targets
- Multi-omics approach in the future (ai)

Immanuel Kant (Photo from a steel engraving)

The one who knows more, may decide better