40th ANNIVERSARY

WEST CANCER CENTER & RESEARCH INSTITUTE

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Beyond Just Chemotherapy in Colorectal Cancer

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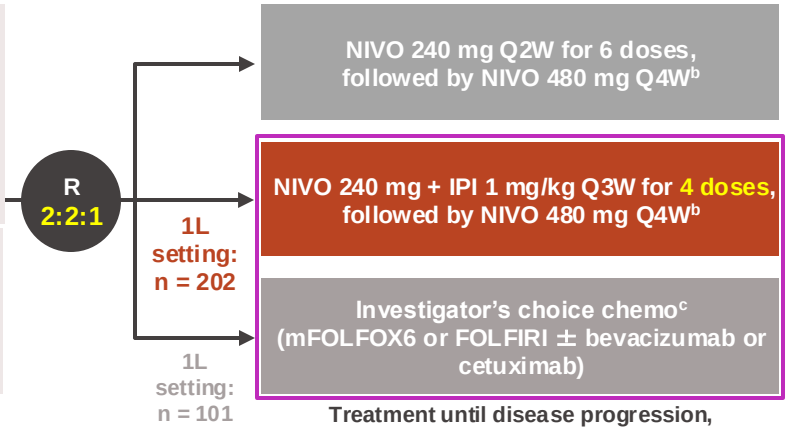
Immunotherapy for dMMR/MSI-H mCRC

CheckMate 8HW study design

- **CheckMate 8HW is a randomized, multicenter, open-label phase 3 study[a]**

Key eligibility criteria:
- Histologically confirmed unresectable or metastatic CRC
- **MSI-H/dMMR status by local testing**
- ECOG PS 0 or 1

Stratification factors:
- Prior lines of treatment (0 vs 1 vs ≥ 2)
- Primary tumor location (right vs left)



Treatment until disease progression, unacceptable toxicity, withdrawal of consent (all arms), or a maximum treatment duration of 2 years (NIVO and NIVO + IPI arms only)

Dual primary endpoints in patients with centrally confirmed MSI-H/dMMR status[d]:
- PFS by BICR[e] (NIVO + IPI vs chemo in the 1L setting)
- PFS by BICR[e] (NIVO + IPI vs NIVO across all lines)

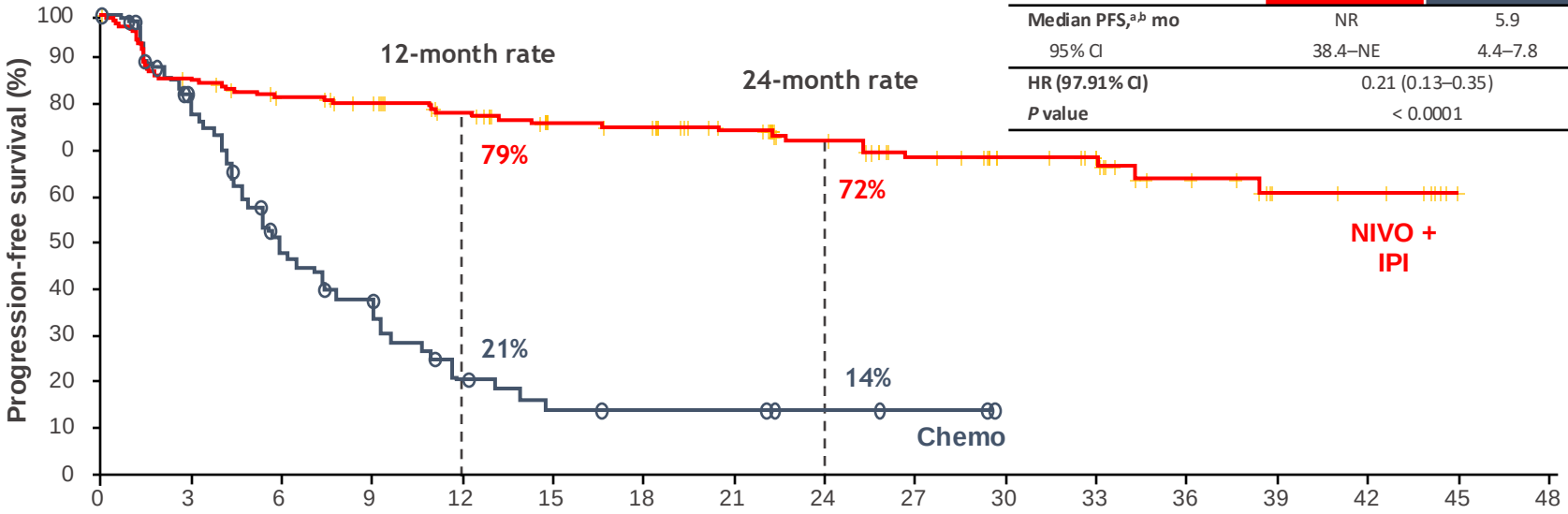
Other select endpoints:
- Safety
- OS; ORR by BICR[e]; PROs

- At data cutoff (October 12, 2023), the median follow-up[f] was 24.3 months

[a]ClinicalTrials.gov. NCT04008030. [b]Patients with ≥ 2 prior lines are randomized only to the NIVO or NIVO + IPI arms. [c]Patients receiving investigator's choice of chemotherapy are eligible to receive NIVO + IPI upon progression (crossover treatment). [d]Confirmed using either immunohistochemistry and/or polymerase chain reaction-based tests. [e]Evaluated using RECIST v1.1. [f]Time between randomization and last known date alive or death.

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)

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

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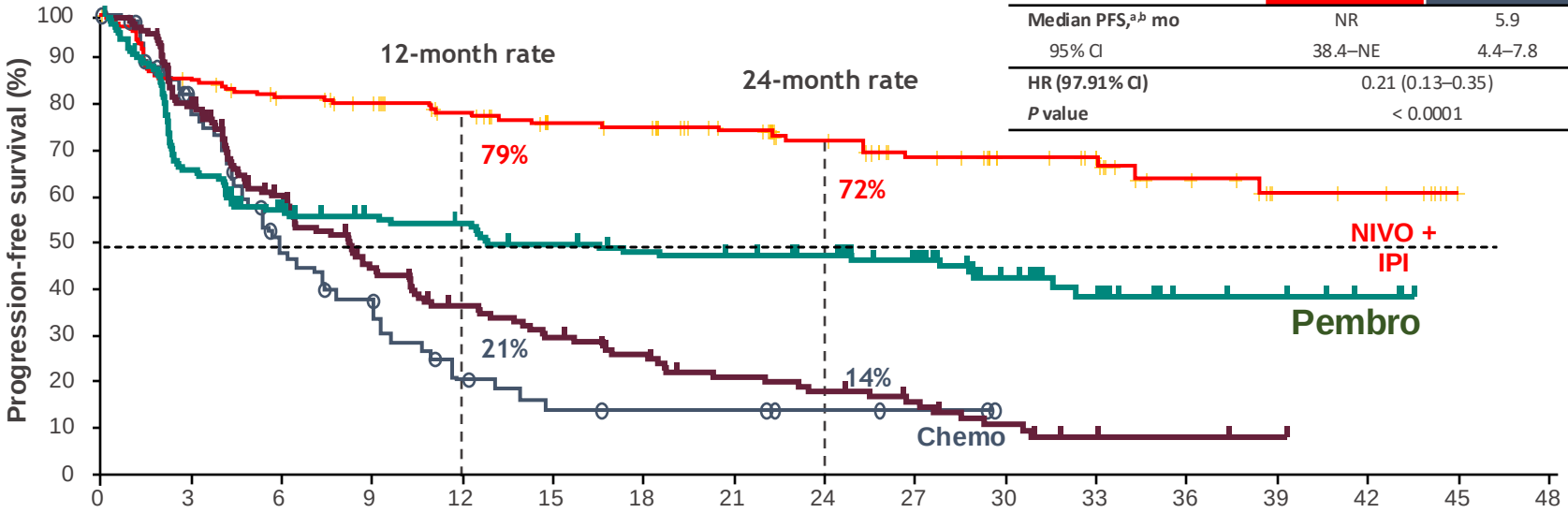

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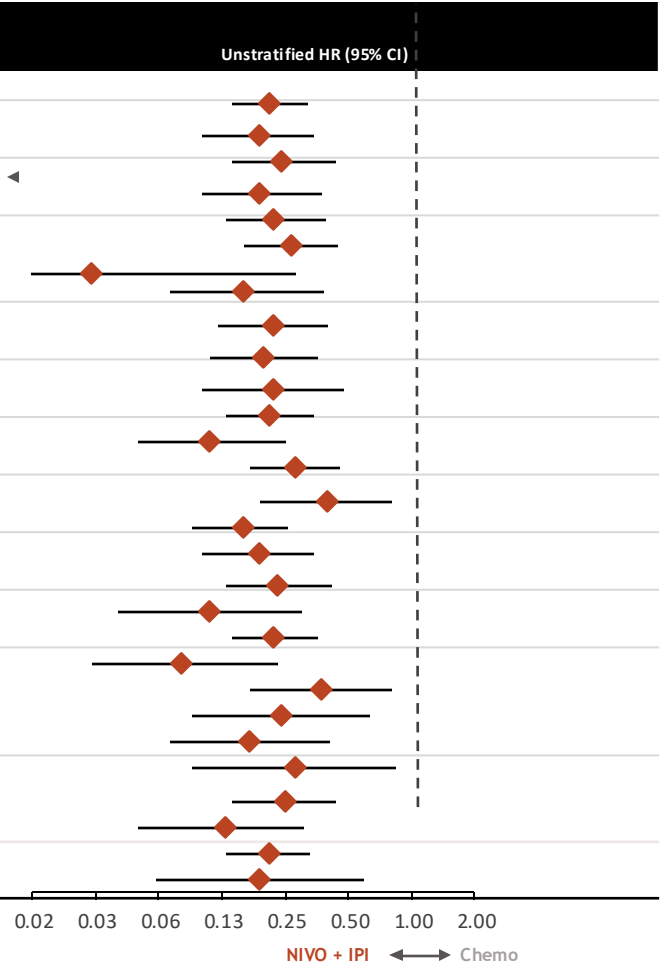
[a]Per BICR. [b]Median follow-up, 24.3 months.

Progression-free survival subgroup analysis

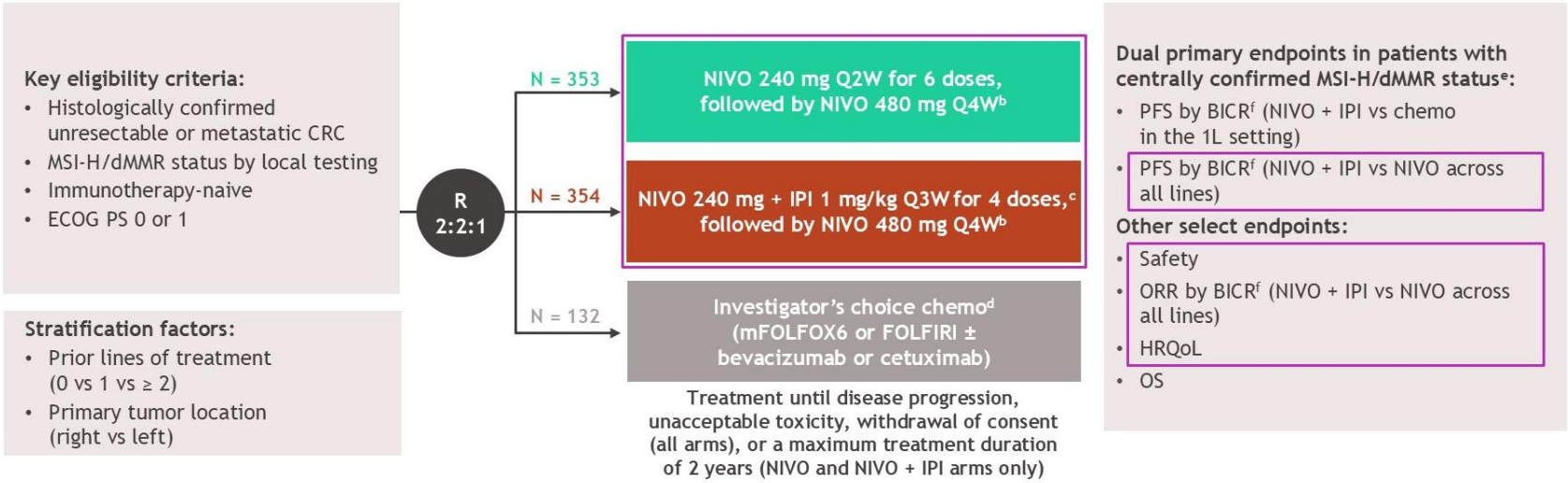
Category (1L centrally confirmed MSI-H/dMMR)	Subgroup	Median PFS,[a] mo		Unstratified HR
		NIVO + IPI	Chemo	
Overall (N = 255)		NR	5.9	0.21
Age, years	< 65 (n = 138)	NR	5.7	0.19
	≥ 65 (n = 117)	NR	5.9	0.24
Sex	Male (n = 117)	NR	5.9	0.19
	Female (n = 138)	NR	6.2	0.22
Region	US/Canada/Europe (n = 167)	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* all 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
Prior surgery related to current cancer	Yes (n = 222)	NR	7.1	0.21
	No (n = 33)	NR	3.0	0.19



[a]Per BICR.

CheckMate 8HW: Nivolumab +/- Ipilimumab

- CheckMate 8HW is a randomized, multicenter, open-label phase 3 study[a]

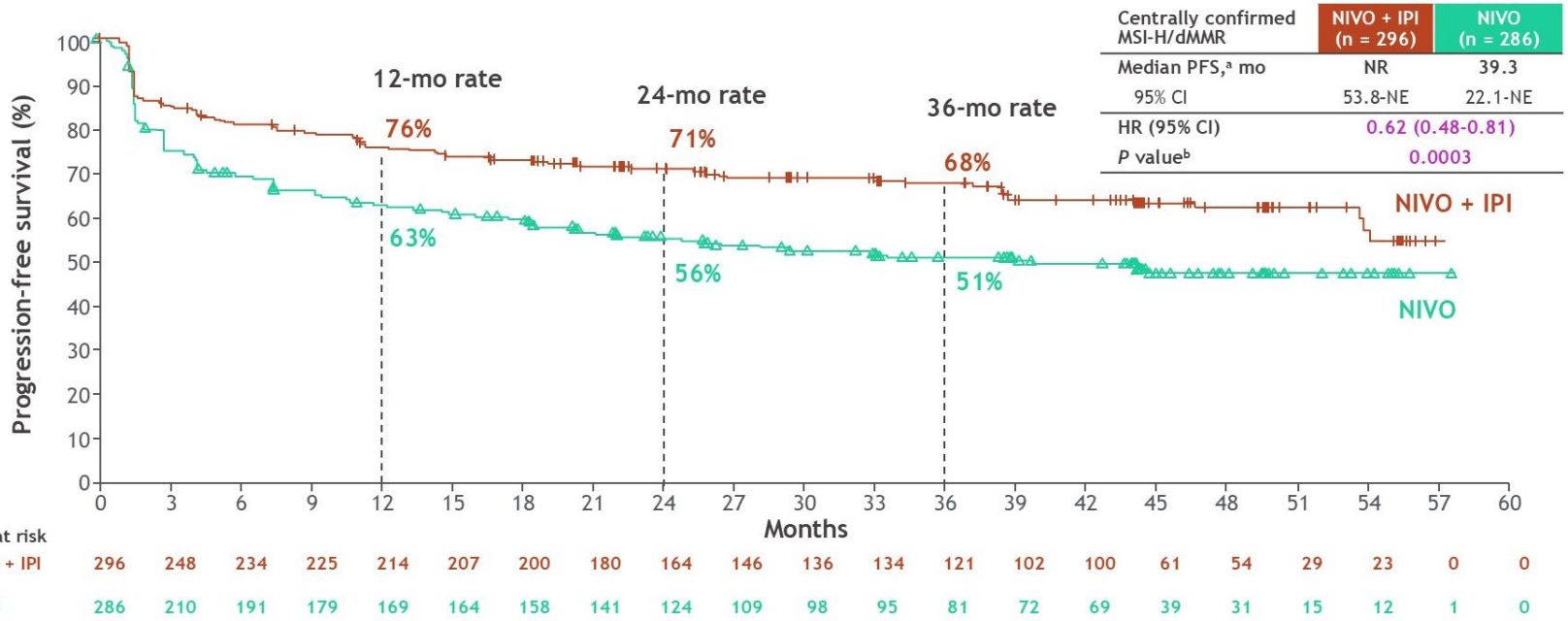


- At data cutoff (August 28, 2024), the median follow-up[g] was 47.0 months (range, 16.7–60.5)

[a]ClinicalTrials.gov. NCT04008030. [b]Patients with ≥ 2 prior lines are randomized only to the NIVO or NIVO + IPI arms. [c]Patients can continue NIVO treatment upon early IPI discontinuation. [d]Patients receiving investigator's choice of chemo are eligible to receive NIVO + IPI upon progression (crossover treatment). [e]Confirmed using either IHC and/or polymerase chain reaction-based tests. [f]Evaluated using RECIST v1.1. [g]Time between randomization and data cutoff among all randomized patients across all 3 treatment arms.

Andre et al., ASCO GI 2025

CheckMate 8HW: PFS



- NIVO + IPI demonstrated statistically significant and clinically meaningful PFS benefit vs NIVO in patients with centrally confirmed MSI-H/dMMR mCRC across all lines of therapy
  - PFS benefit with NIVO + IPI vs NIVO was consistent in all randomized patients (median PFS: 54.1 vs 18.4 months; HR, 0.64 [95% CI, 0.52-0.79])

[a]Per BICR. [b]Boundary for statistical significance, p < 0.0095.

Andre et al., ASCO GI 2025

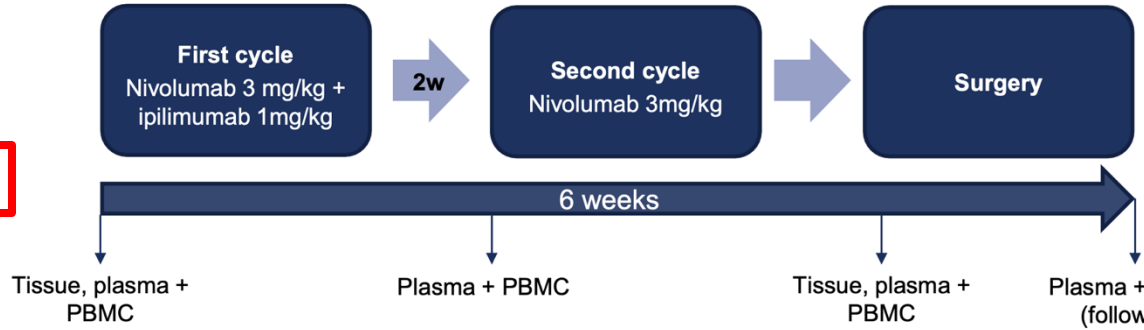
My Conclusions on first-line IO in MSI-H CRC

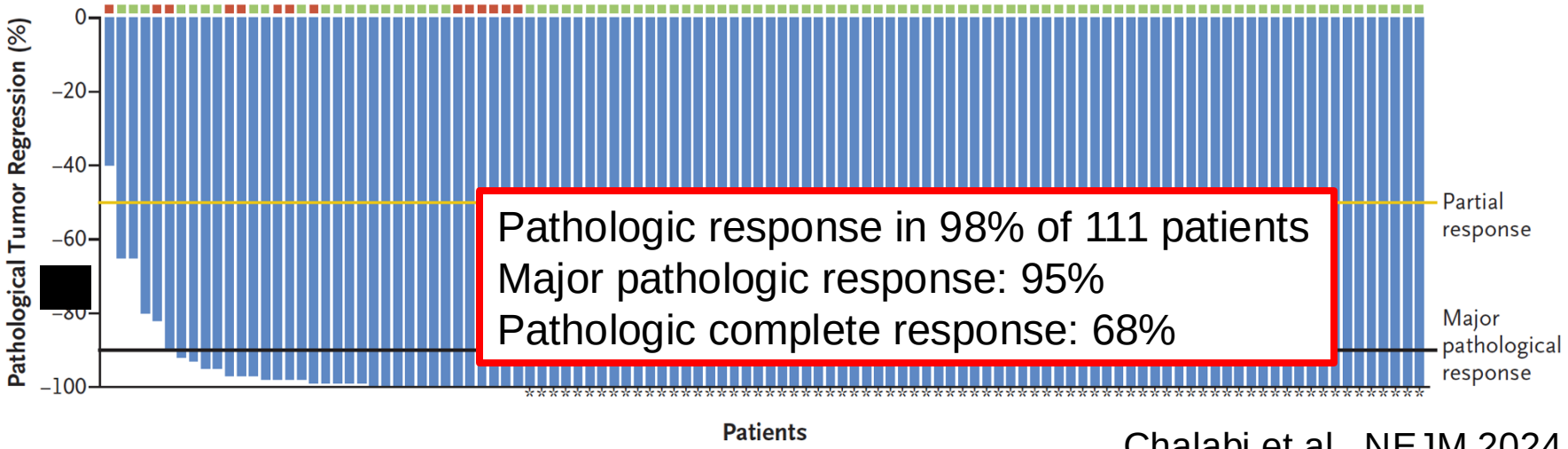
- **Testing for MMR/ MSI status in mCRC is mandatory!**
- **We now have two options for IO therapy n this patient population:**
  - Pembrolizumab single agent – see KN 177
  - Nivolumab/ Ipilimumab – see CM 8HW
- **Nivo/Ipi more active than Nivo and avoids the early crossing of PFS curves**
  - No data available yet on OS, cross-over to IO from chemo
  - All subgroups appear to benefit
- **Data allow for individualized selection of first-line IO**

Neoadjuvant or definitive immunotherapy in early stage colorectal cancer?

Neoadjuvant Immunotherapy in dMMR/ MSI-H Colon Cancer

Only 2 doses of immunotherapy

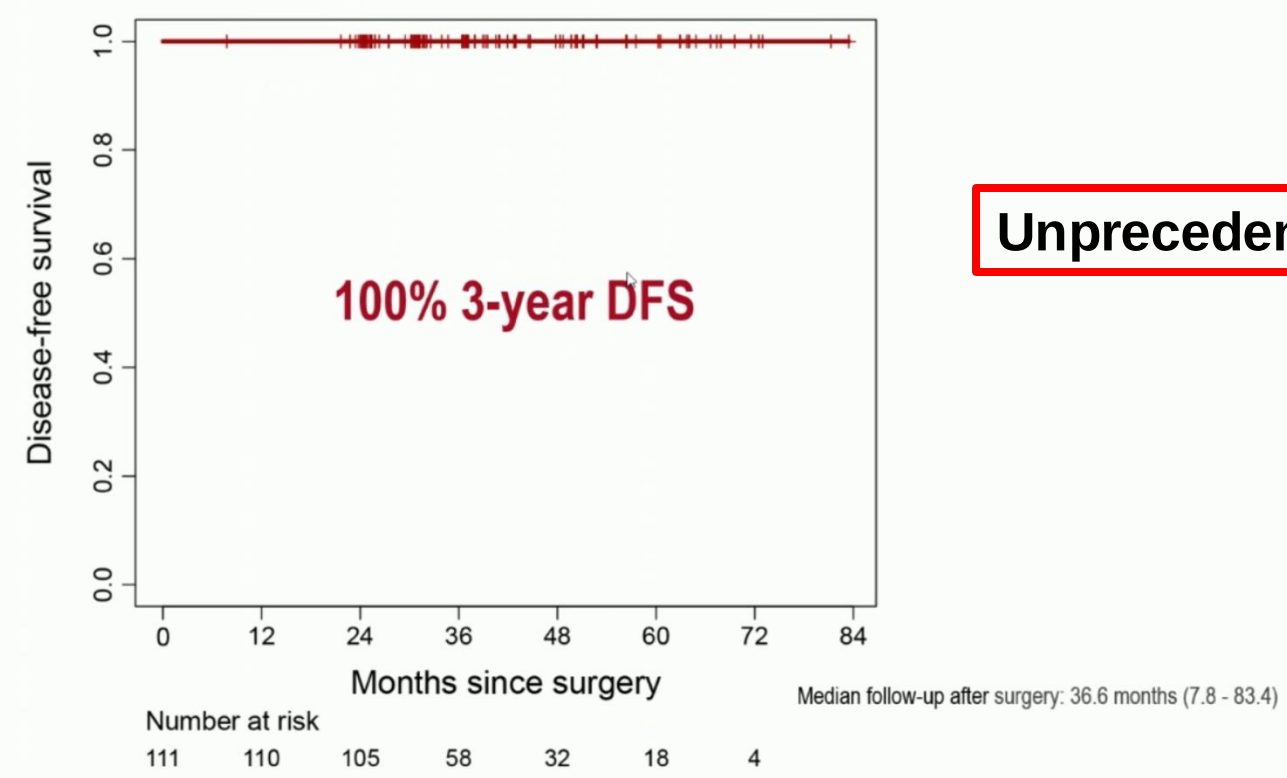




Pathologic response in 98% of 111 patients
Major pathologic response: 95%
Pathologic complete response: 68%

Chalabi et al., NEJM 2024

Neoadjuvant Nivo/Ipi in dMMR early stage colon cancer
3-Year DFR results



Unprecedented data!!

1 dose of Nivo/Ipi -> 1 dose of Nivo -> surgery

Chalabi et al., ESMO 2024

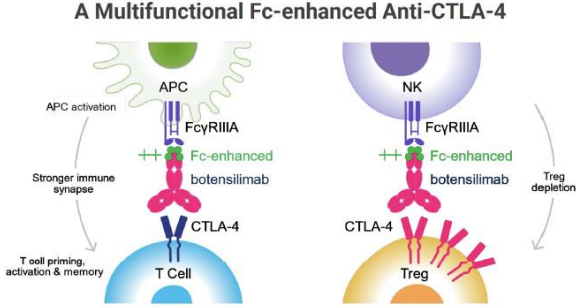
My Thoughts on Neoadjuvant IO Therapy in MSI-H/ dMMR colorectal cancer

- **Upfront, definitive IO therapy has emerged as SOC in MSI-H/ dMMR rectal cancer (see Cercek et al. NEJM 2022)**
  - Hard to beat 100% cCR in rectal cancer, hard to beat NICHE-2
  - Conventional chemo does not work well in these patients
  - Results better than in advanced disease! Why?
- **In colon cancer NICHE-2 provides us with unprecedented data**
  - Emphasizes the need to test every CRC for MMR status
  - Will surgeons listen and send patients to Med Onc before surgery?
    - Which patients need to be treated pre-op?
- **In locally advanced MSI-H/ dMMR colon cancer, I favor IO therapy as neoadjuvant or definitive treatment**

Novel IO Therapy

Botensilimab + Balstilimab, N=87

Botensilimab (FC-enhanced Anti-CTLA-4)

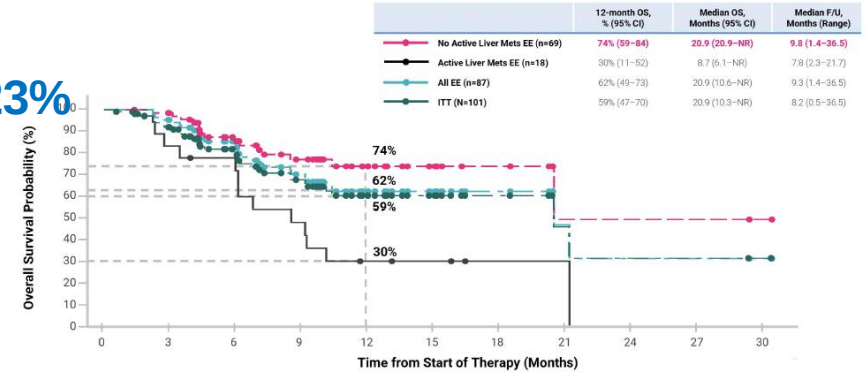


- **Enhanced** T cell priming, expansion, memory[5,6]
- **Enhanced** frequency of APCs
- **Enhanced** Treg depletion
- **Reduced** complement mediated toxicity

Botensilimab + Anti-PD-1 (Balstilimab) Chemorefractory MSS mCRC

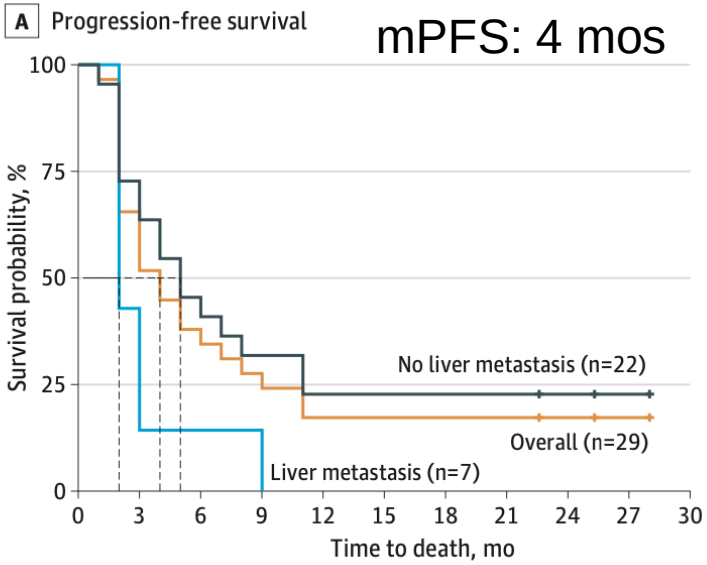
	All EE n=87*	No Active Liver Mets EE n=69†	Active Liver Mets EE n=18‡
Confirmed ORR, n % (95% CI)	18% (11–28)	23% (14–35)	0% (0–19)
BOR, n (%)			
CR	1 (1)	1 (1)	0
PR	15 (17)	15 (22)	0
SD	45 (52)	39 (57)	6 (33)
PD	26 (30)	14 (20)	12 (67)
DCR (CR + PR + SD), % (95% CI)	70% (59–80)	80% (68–88)	33% (13–59)
12-month OS, % (95% CI)	62% (49–73)	74% (59–84)	30% (11–52)
Ongoing responses§	11/16 (69%)		0

RR no liver mets: 23%
RR liver mets: 0%

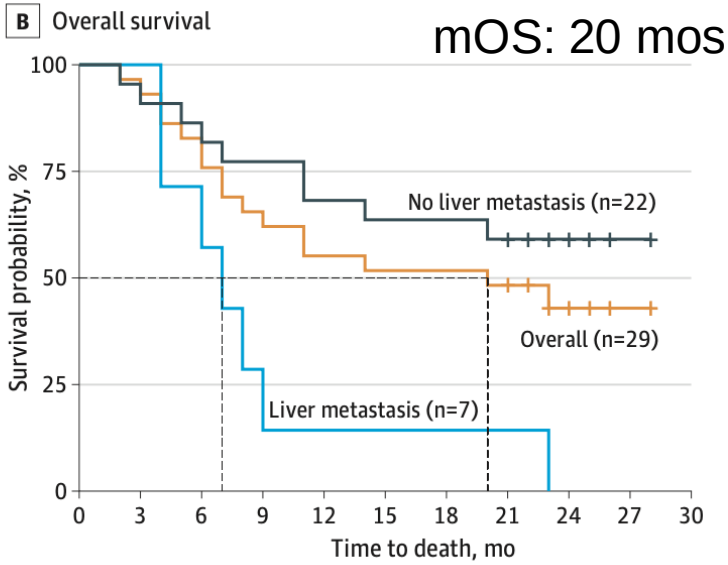


Bullock, ESMO GI 2023

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

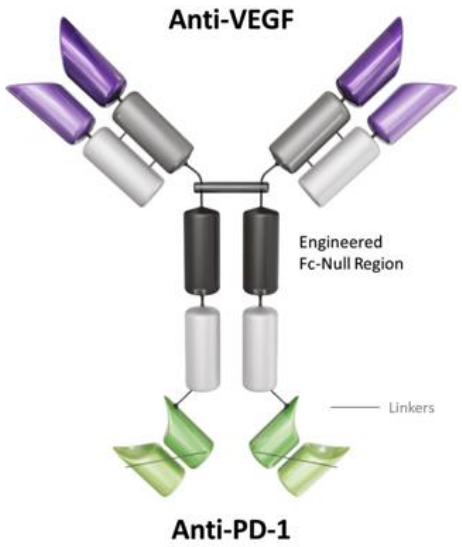


No. at risk											
Overall	29	28	24	19	16	15	15	14	7	1	0
Liver metastasis	7	7	5	2	1	1	1	1	0	0	0
No liver metastasis	22	21	19	17	15	14	14	13	7	1	0

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

Fakih et al., JAMA Oncol 2023

Ivonescimab: Bispecific Antibody

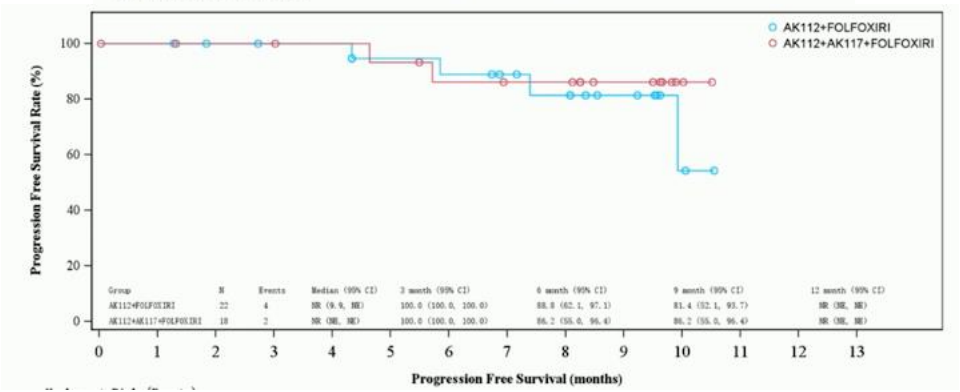


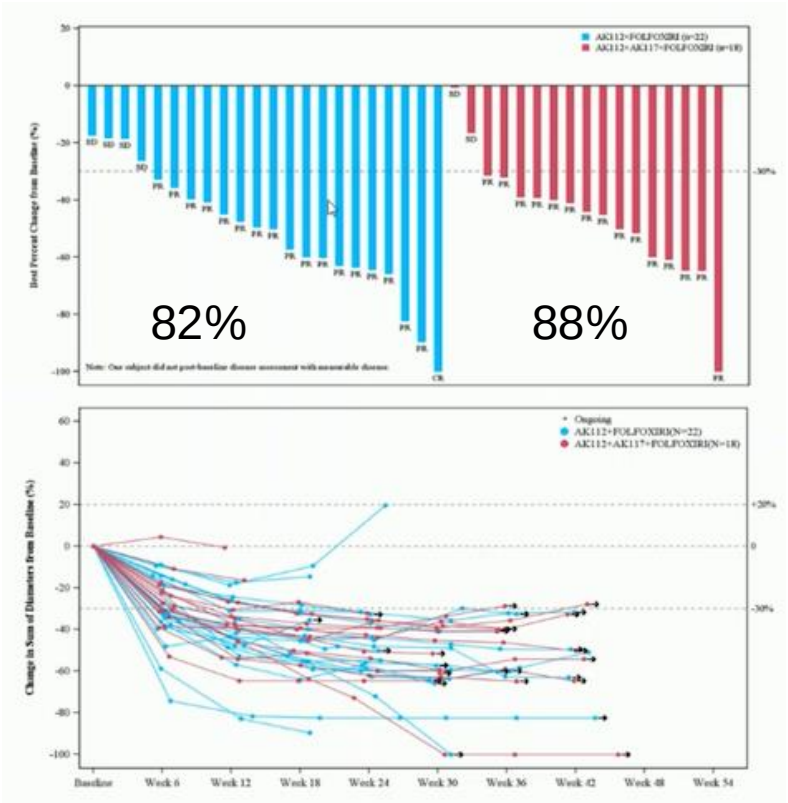
- **Simultaneous interaction of PD-1 & VEGF blockades can drive synergistic anti-tumor activity**
  Inhibiting VEGF can help improve the effect of immunotherapy by modulating the tumor microenvironment
  Enhancing the PD-1 blockade helps activate T cells
- **Cooperative Binding**
  Increased Binding Strength (Affinity)
  Presence of VEGF increases PD-1 binding strength by >18X
  Presence of PD-1 increases VEGF binding strength by >4X
- **Increased Binding of T Cells**
  VEGF dimer leads to potential interconnection or daisy chaining of multiple ivonescimab molecules, which may lead to increased binding of T cells

Ivonescimab: First-Line Combination Trial

	Ivonescimab + FOLFOXIRI n = 22	Ivonescimab + Ligufalimab + FOLFOXIRI n = 17[a]
Investigator-assessed objective response rate		
n	18	15
ORR (95% CI), %	81.8 (59.7-94.8)	88.2 (63.6-98.5)
Investigator-assessed disease control rate		
n	22	17
DCR (95% CI), %	100 (84.6-100)	100 (80.5-100)

[a] One patient had no post-baseline tumor assessment.
Abbreviation: CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, objective response rate; PR, partial response; SD, stable response.
Data cutoff date: Feb 29, 2024





Ligufalimab: IgG4 anti-CD47 antibody

Deng et al., ESMO 2024

Targeting BRAF V600E in First Line

BREAKWATER: Study Design

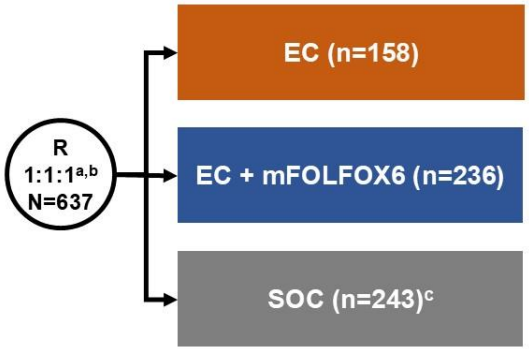
- BREAKWATER (NCT04607421) is an open-label, multicenter, phase 3 study in first line BRAF V600E-mutant mCRC

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
- ECOG PS 0 or 1
- Adequate bone marrow, hepatic, and renal function

Exclusion criteria

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



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.

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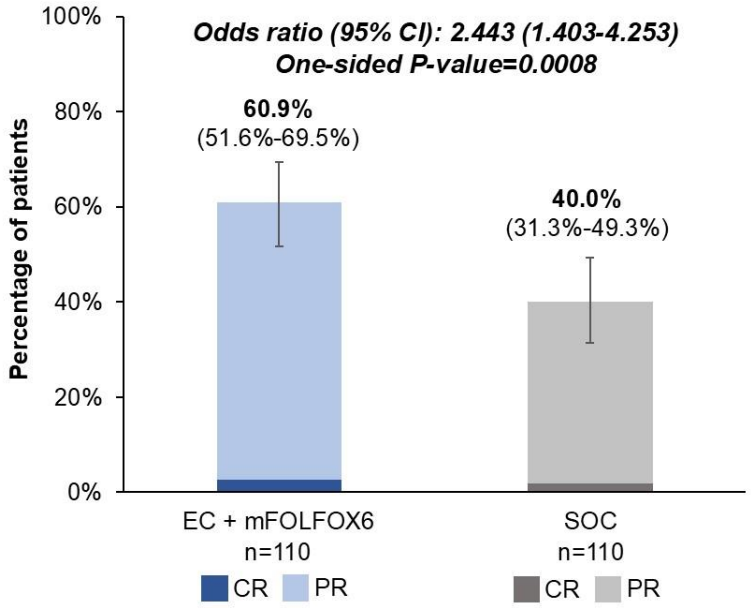
Overview of Response by BICR

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.

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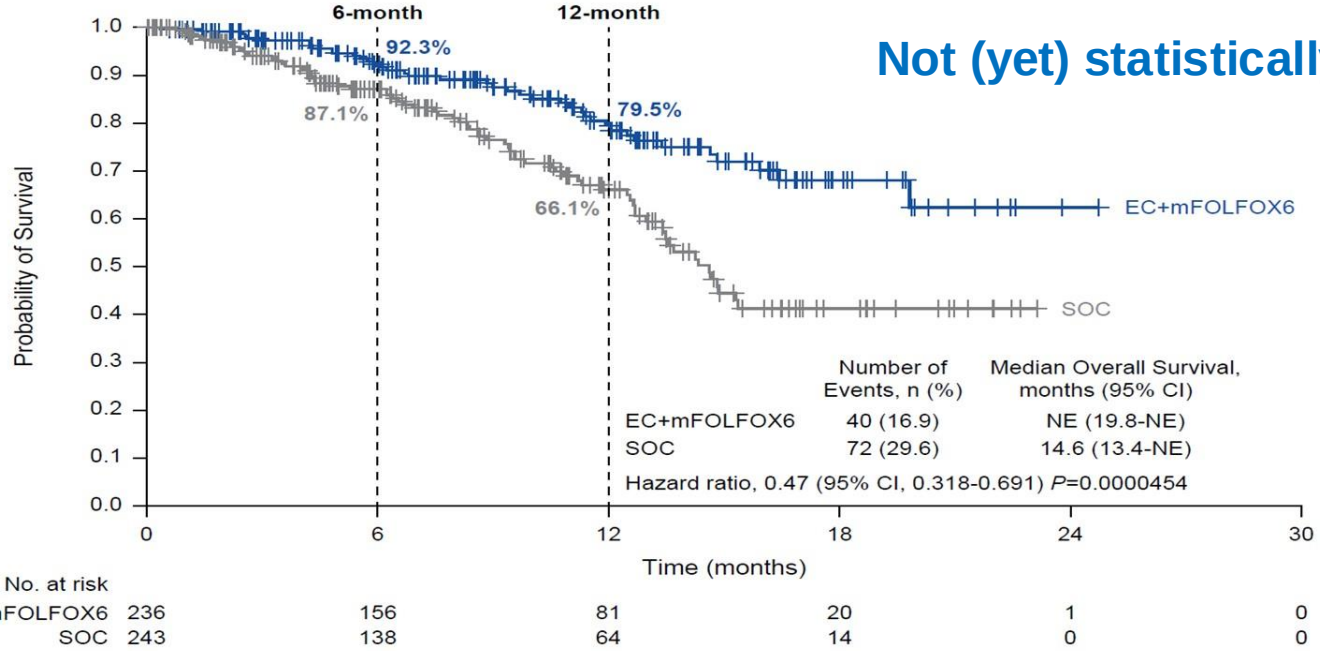
Interim Overall Survival[a]



Not (yet) statistically significant!

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.

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Safety Summary

Patients, n (%)	EC + mFOLFOX6 n=231	SOC n=228
All causality		
TEAE	230 (99.6)	223 (97.8)
Grade 3 or 4 TEAE	171 (74.0)	139 (61.0)
Grade 5 TEAE	10 (4.3)	10 (4.4)
Serious TEAE	87 (37.7)	79 (34.6)
TEAE leading to permanent discontinuation of any study treatment	48 (20.8)	34 (14.9)
TEAE leading to dose reduction of any study treatment	141 (61.0)	109 (47.8)
TEAE leading to dose interruption of any study treatment	196 (84.8)	146 (64.0)
Treatment-related		
AE related to any drug	228 (98.7)	212 (93.0)
Grade 3 or 4 TRAE	161 (69.7)	123 (53.9)
Grade 5 TRAE	0	1 (0.4)[a]
Serious AE related to any drug	42 (18.2)	44 (19.3)

Data cutoff: December 22, 2023.
[a]Sepsis (preferred term).
AE, adverse event; EC, encorafenib plus cetuximab; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; SOC, standard of care; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

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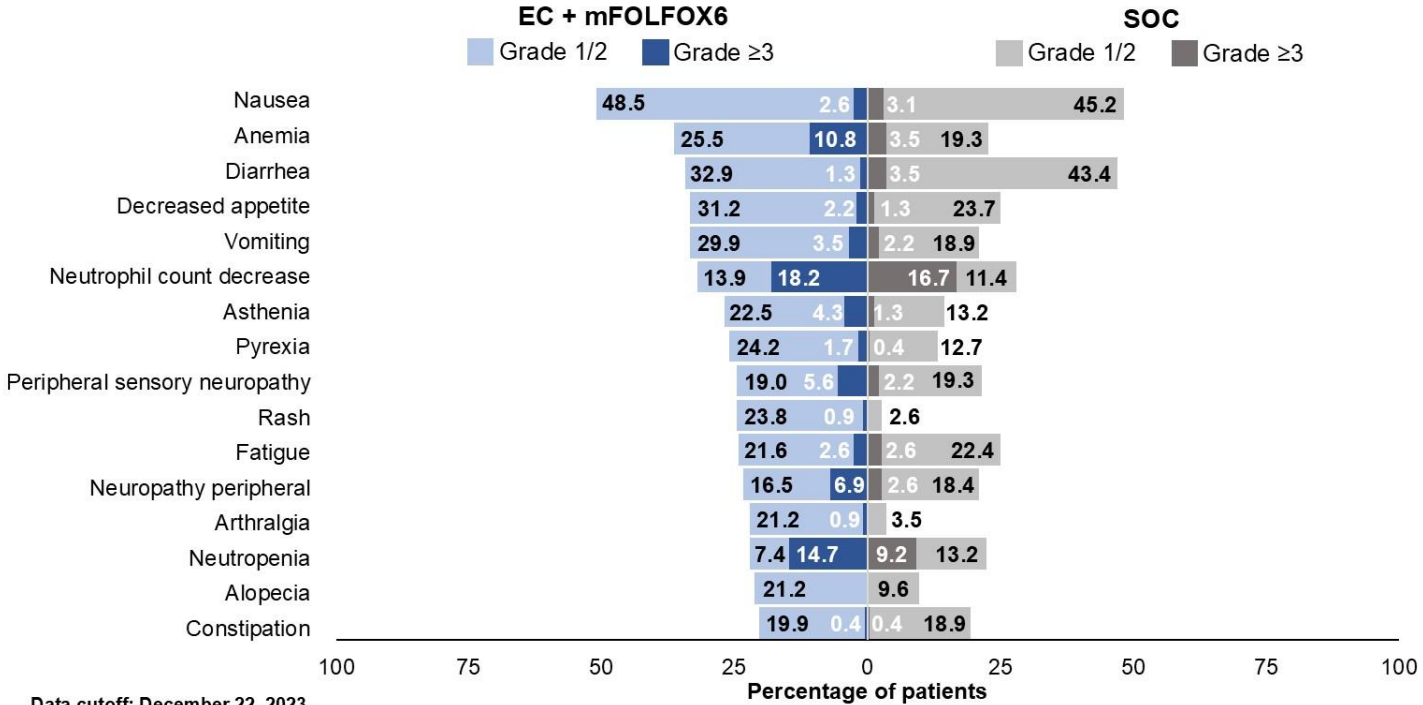
Most Frequent (≥20%)[a] All-Causality TEAEs



Data cutoff: December 22, 2023.

[a]Frequency is based on the EC + mFOLFOX6 arm.

EC, encorafenib plus cetuximab; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; SOC, standard of care; TEAE, treatment-emergent adverse event.

PRESENTED BY: Scott Kopetz, MD, PhD

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Targeting HER2

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[a]**	**86**	**38 (28-39)**	**8.2 (4.2-10.3)**	**24.1 (20.3-36.7)**
DESTINY-CRC01[6,b] **(Cohort A)**	**T-DXd[a]**	**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)	—

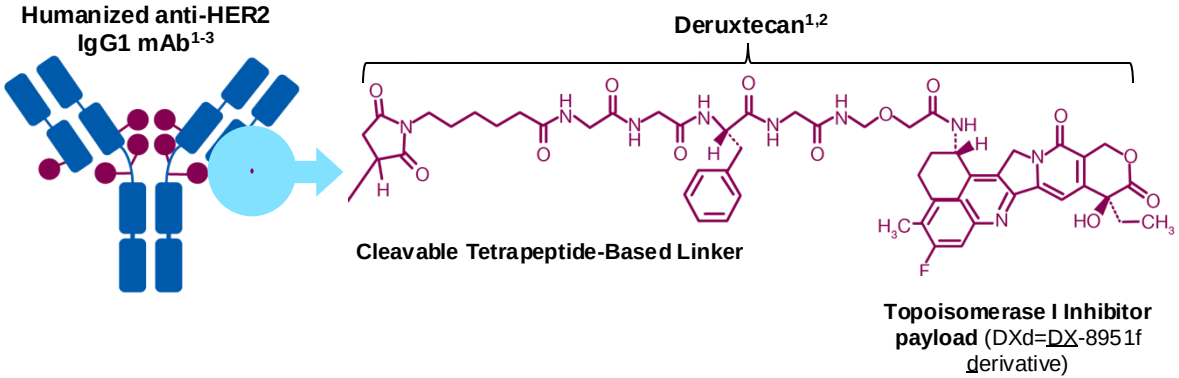
[a] In NCCN guidelines. [b] ORR in subgroup with prior HER2 rx 43.8% (19.8-70.1); without prior HER2 rx 45.9% (29.5-63.1). [c] Did not meet primary endpoint. T-DM1 had 0% response rate in MATCH Arm Q[8] and MSKCC Basket Trial.[9]

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.

Structure and Mechanism of Action of T-DXd

T-DXd is an ADC with 3 components:

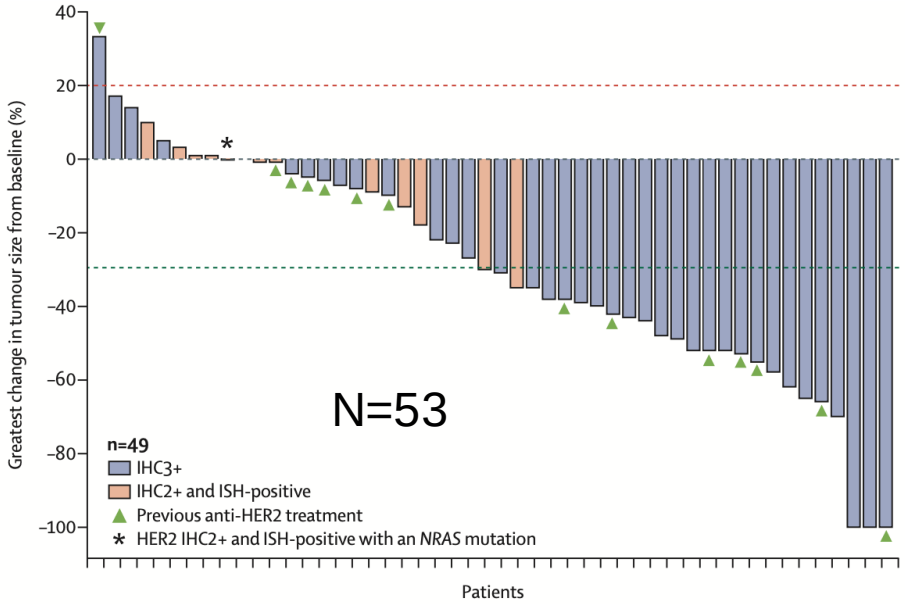
- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker

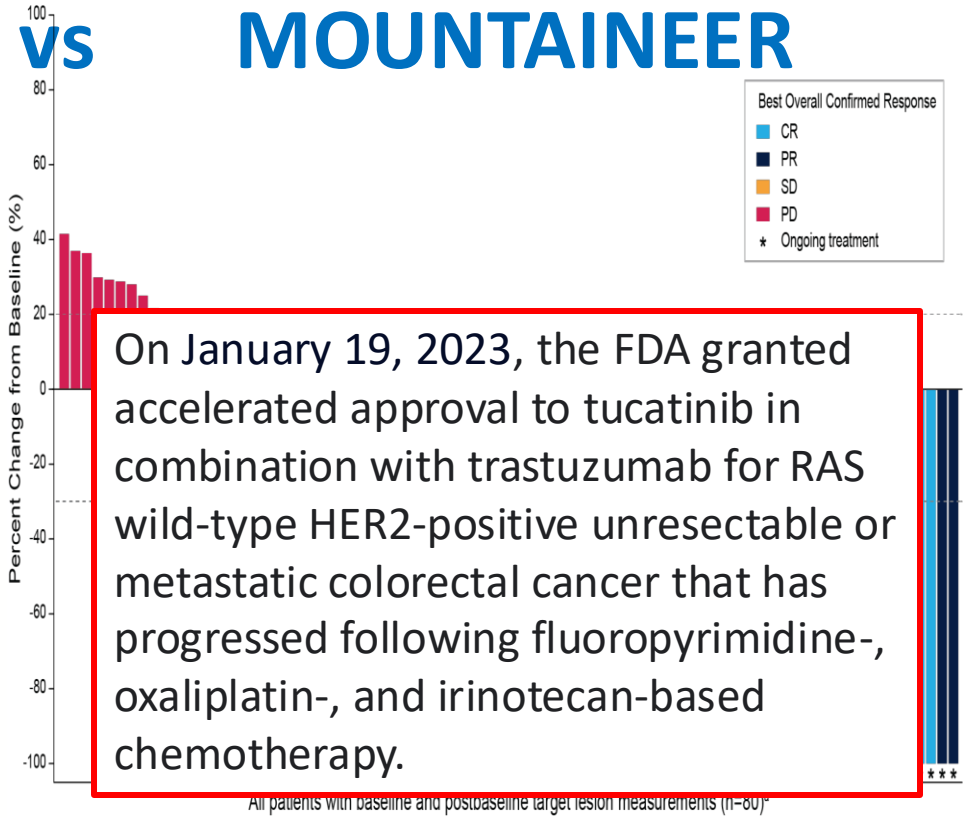


Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug to antibody ratio ≈ 8
Payload with short systemic half-life
Stable linker-payload
Tumor-selective cleavable linker
Membrane-permeable payload

The clinical relevance of these features is under investigation.
ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody.
1. Nakada T, et al. *Chem Pharm Bull* (Tokyo). 2019;67(3):173-185. 2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. 3. Trail PA, et al. *Pharmacol Ther*. 2018;181:126-142.

Destiny-CRC01 vs MOUNTAINEER





On January 19, 2023, the FDA granted accelerated approval to tucatinib in combination with trastuzumab for RAS wild-type HER2-positive unresectable or metastatic colorectal cancer that has progressed following fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

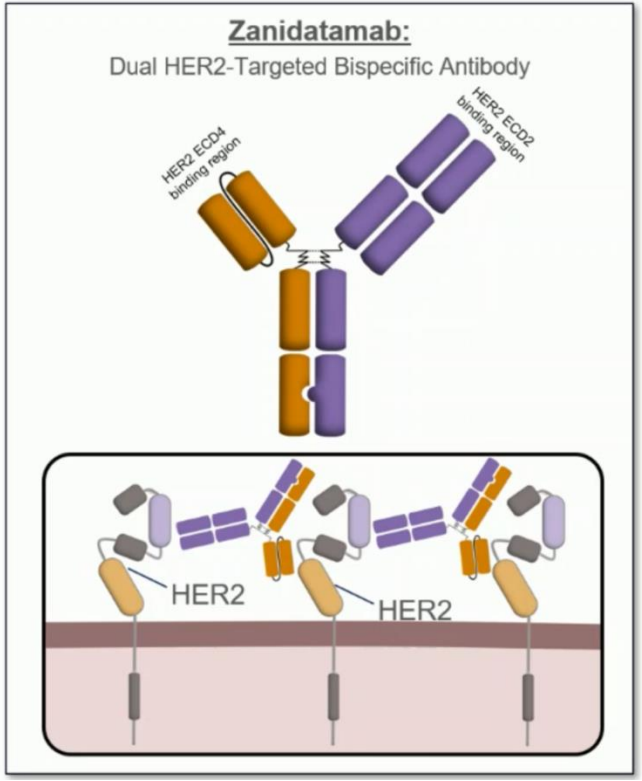
Median # of prior lines: Destiny: 4, MOUNTAINEER: 2

Prior anti-HER-2 therapy: Destiny: 30%, MOUNTAINEER: 0%

Siena et al., Lancet Oncol 2021

Strickler et al., ESMO GI 2022

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

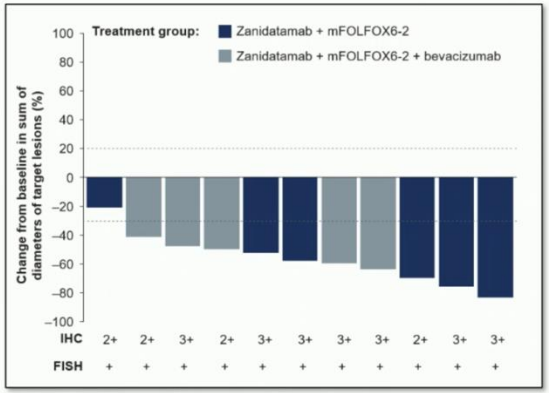
CRC patients treated (Part 1) N=13
DLT evaluable[e] n=12
Response evaluable n=11

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

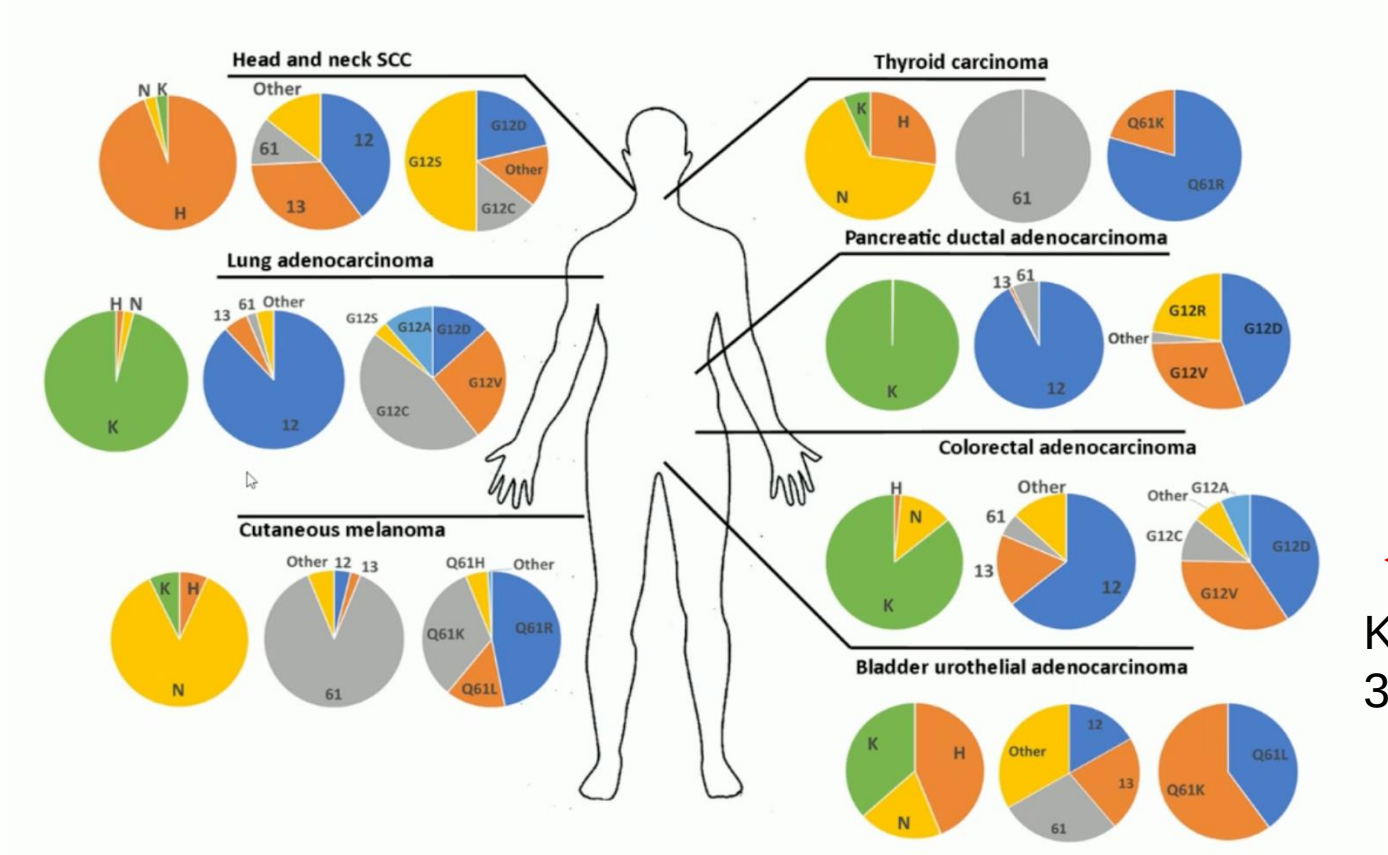


Dotted lines indicate 20% increase or 30% decrease in sum of diameters of target tumours.

Rha et al., ESMO 2024

Targeting RAS

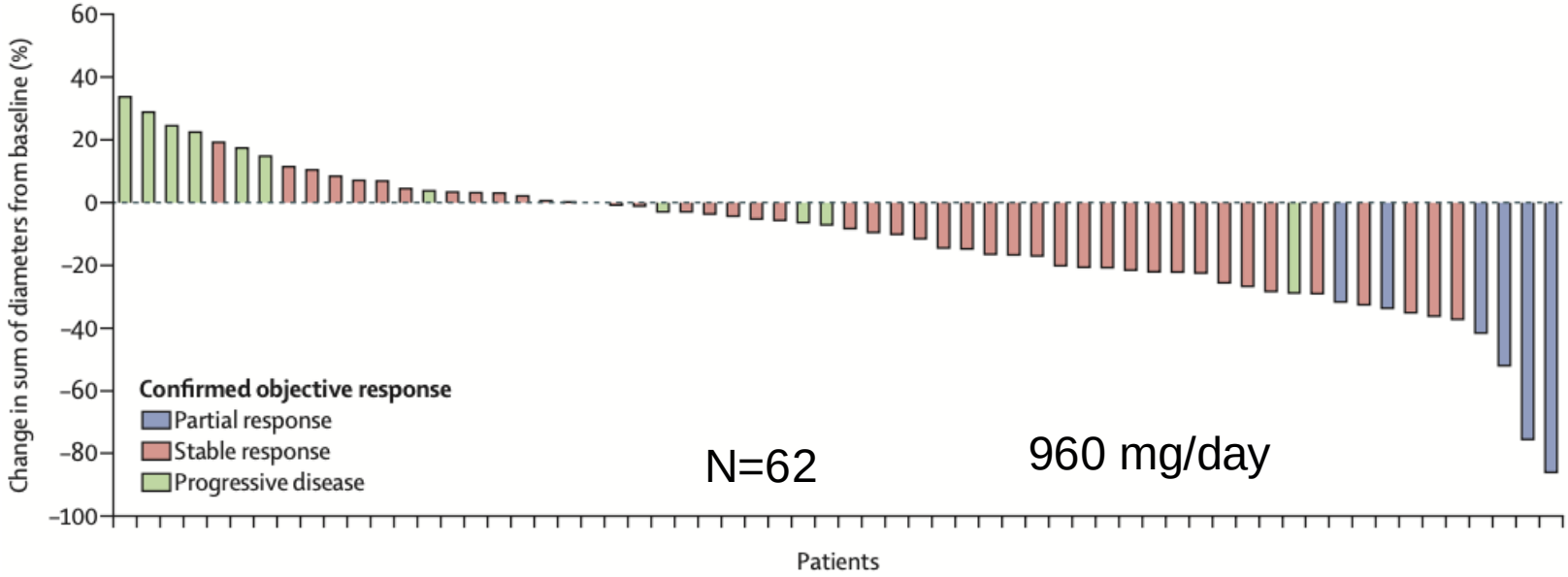
RAS mutation in various cancers



KRAS G12C
3-4% of CRC

Dunnett-Kane et al., Ann Oncol 2020

Sotorasib single agent in mCRC – CodeBreak 100



RR: 9.7% (6 pts)

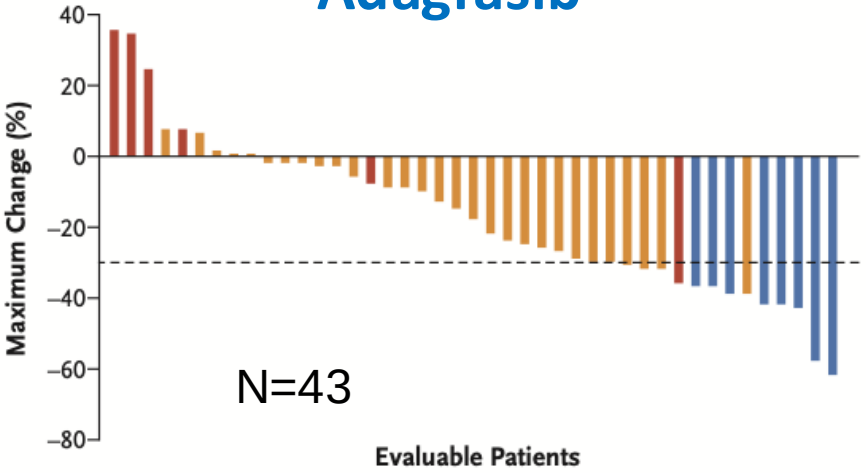
PFS: 4.0 mos

OS: 10.6 mos

Fakih et al. Lancet Oncol 2021

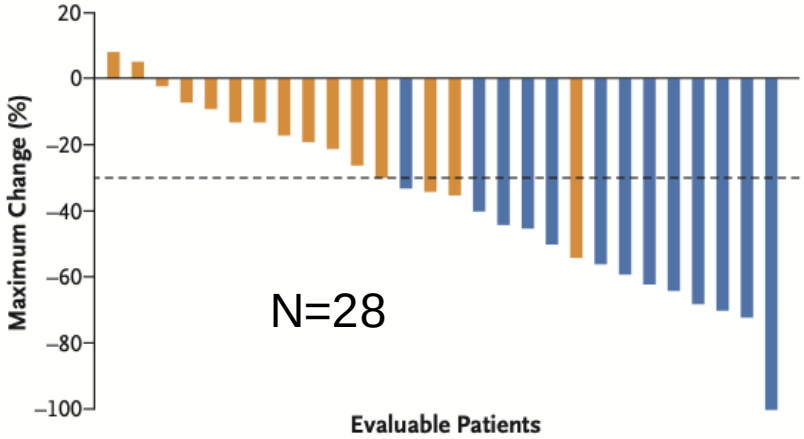
KRYSTAL-1:

Adagrasib



RR: 23%
DOR: 4.3 mos
PFS: 5.6 mos
OS: 19.8 mos

Adagrasib + Cetuximab

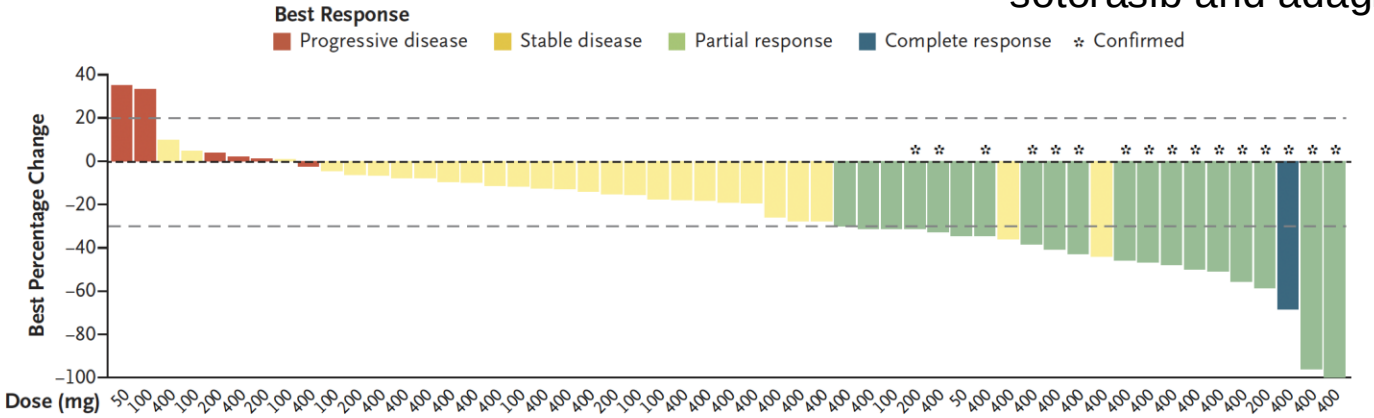


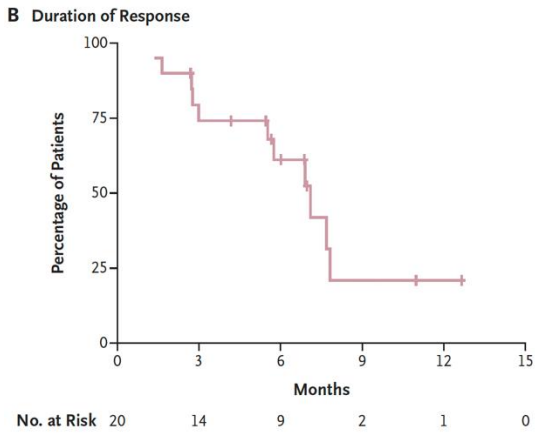
RR: 46%
DOR: 7.6 mos
PFS: 6.9 mos
OS: 13.4 mos

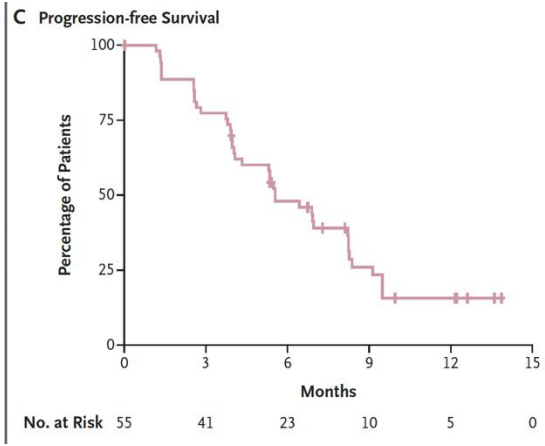
Yaeger et al. NEJM 2022

Divarasib in CRC, N=50

In vitro: 5 to 20 times as potent and up to 50 times as selective in vitro as sotorasib and adagrasib



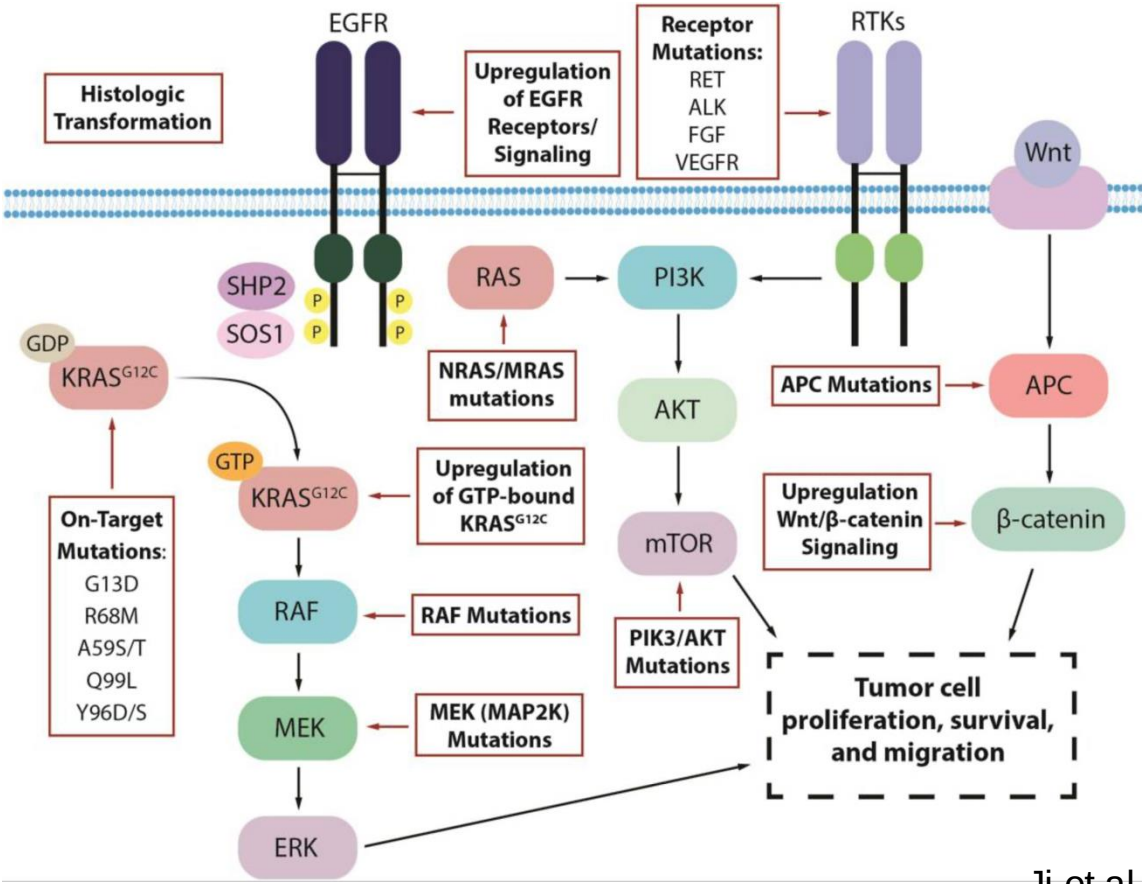




RR 37%
DCR 89%
mDOR 7.1 mos
mPFS 5.6 mos

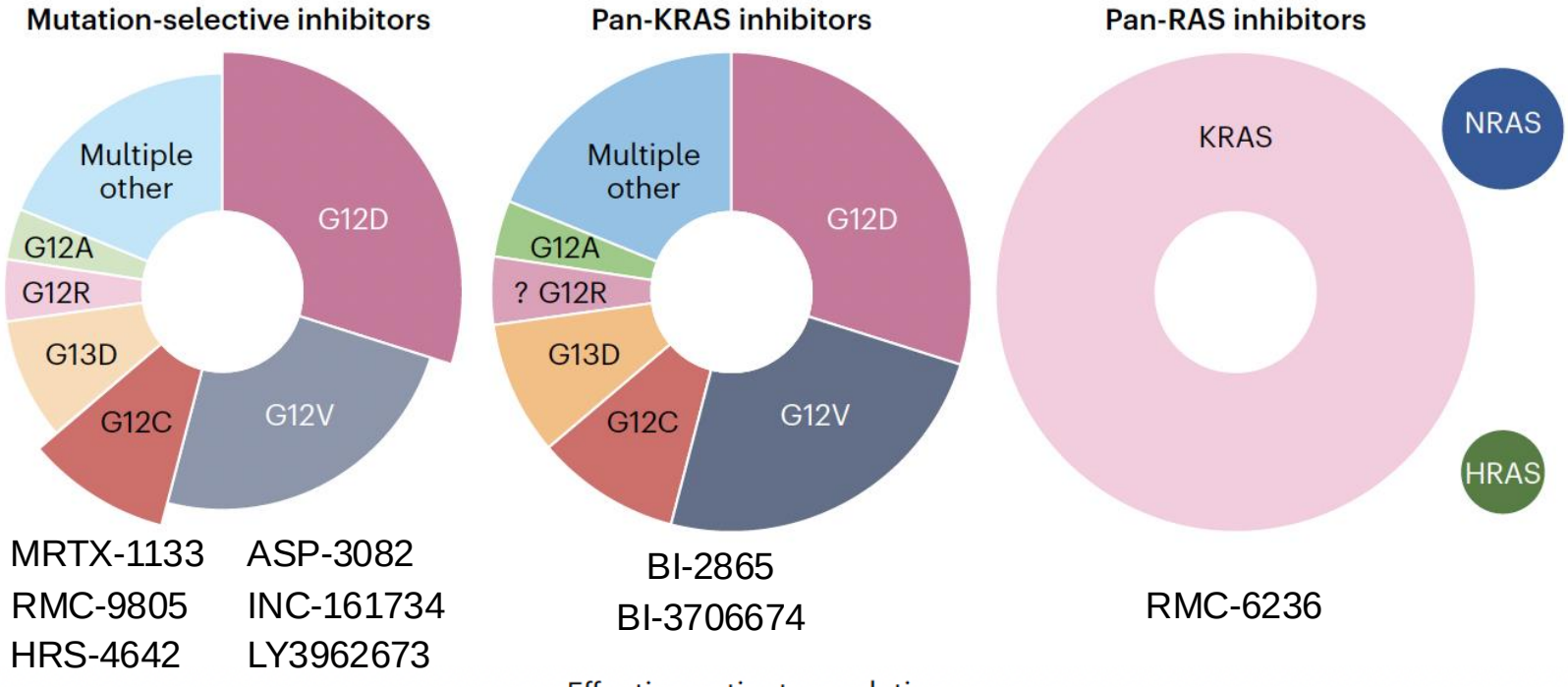
Sacher et al, NEJM 2023

Resistance mechanisms to KRAS G12C inhibitors in CRC



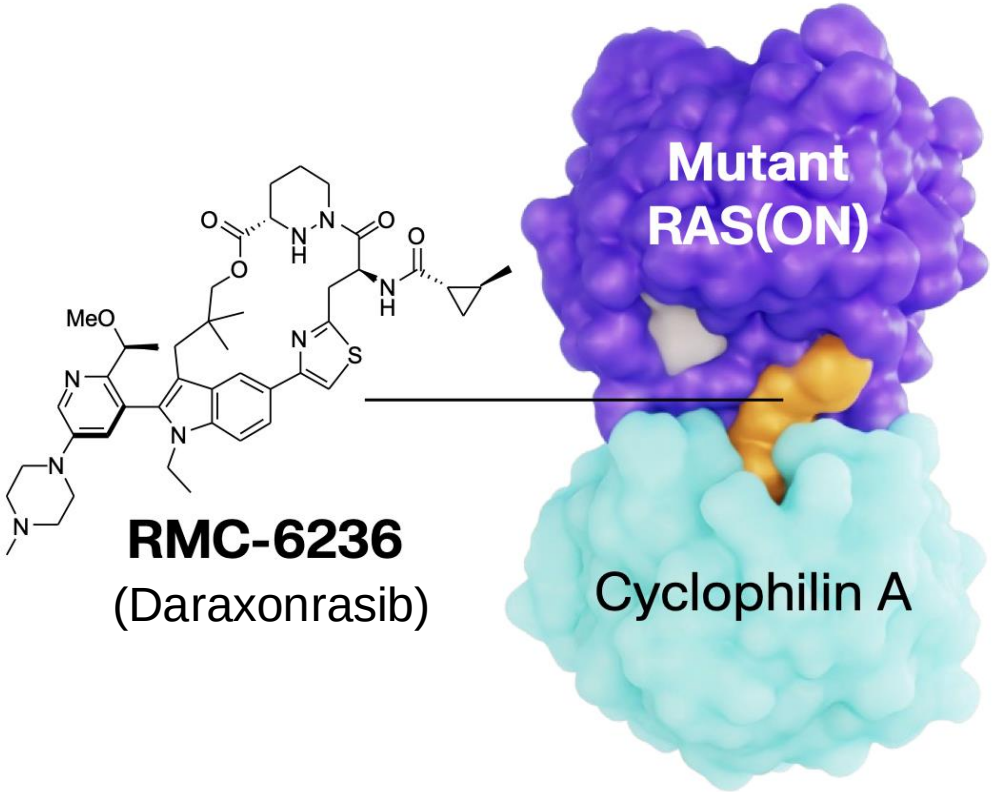
Ji et al, Onco Targets Ther 2022

RAS Inhibitors



Corcoran, Nat Med 2023

Tri-Complex Inhibitors of RAS(ON)

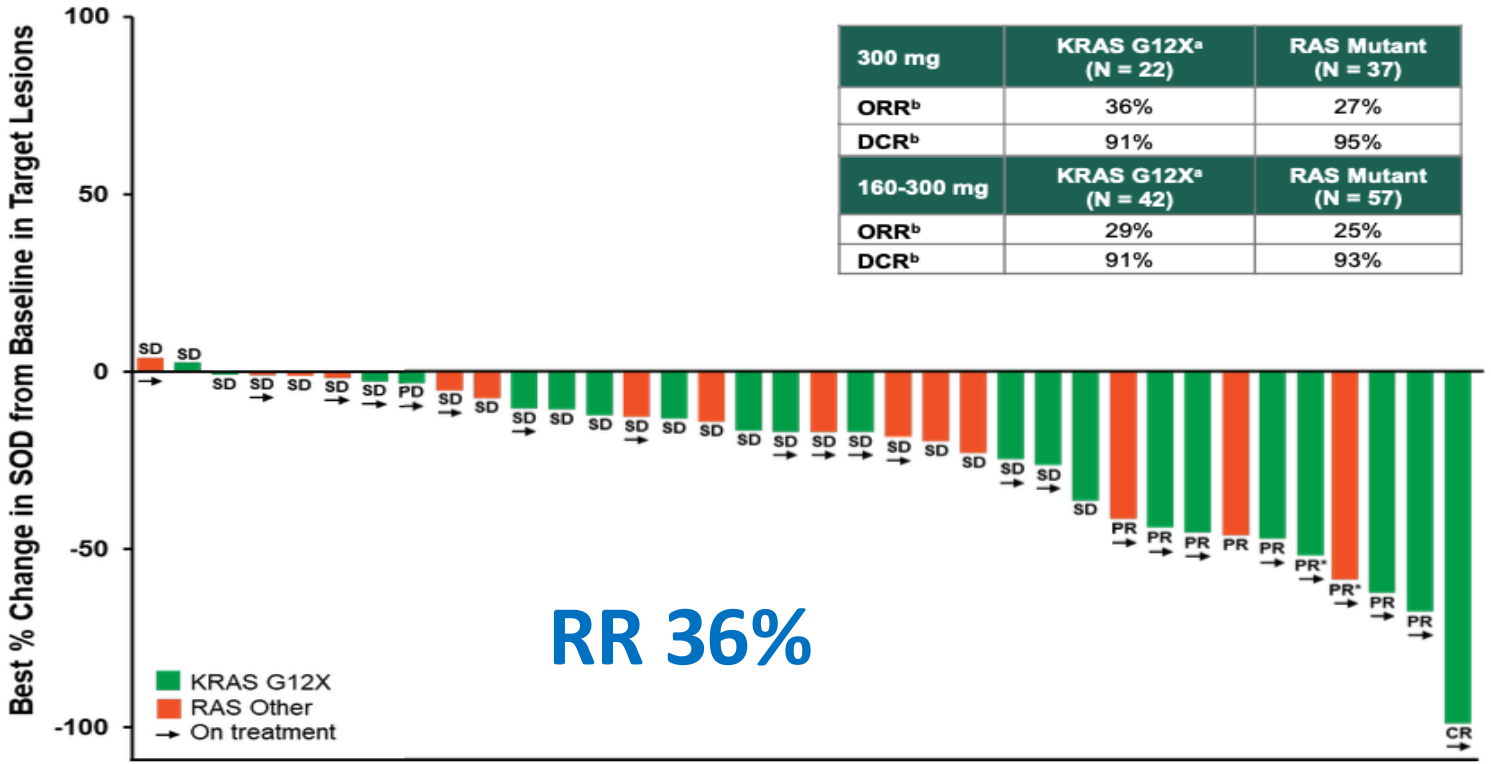


- **Inhibitor recruits and binds to chaperone protein Cyclophilin A**
- **Tri-complex tailored to bind different RAS(ON) proteins**
- **Conformation change and steric inhibition of oncogenic activity**

Schulze et al., Science 2023

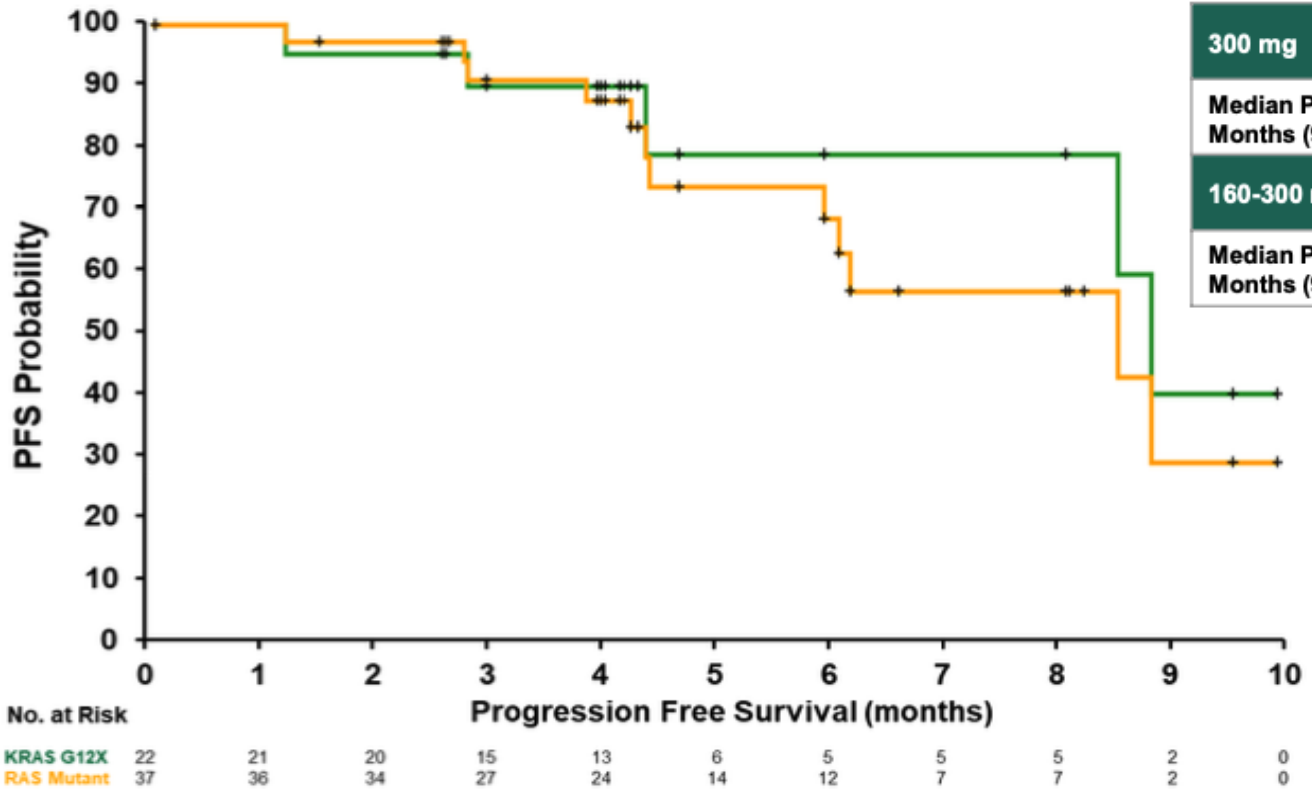
Best Response in 2nd Line PDAC – RMC-6236 300 mg dose

300 mg	KRAS G12X[a] (N = 22)	RAS Mutant (N = 37)
ORR[b]	36%	27%
DCR[b]	91%	95%
160-300 mg	**KRAS G12X[a] (N = 42)**	**RAS Mutant (N = 57)**
ORR[b]	29%	25%
DCR[b]	91%	93%



Garrido-Laguna et al., ASCO GI 2025

PFS in 2nd Line PDAC – 300 mg dose



300 mg	KRAS G12X[a] (N = 22)	RAS Mutant[b] (N = 37)
Median PFS, Months (95% CI)	**8.8** (8.5, NE)	**8.5** (5.9, NE)
160-300 mg	**KRAS G12X[a] (N = 42)**	**RAS Mutant[b] (N = 57)**
Median PFS, Months (95% CI)	**8.5** (5.3, 11.7)	**7.6** (5.9, 11.1)

Garrido-Laguna et al., ASCO GI 2025

Thank you!

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