WEST CANCER CENTER & RESEARCH INSTITUTE
partner of OneOncology

Novel Advances in Colon and Rectal Carcinomas

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Overview of Precision Medicine Approaches in GI Cancers

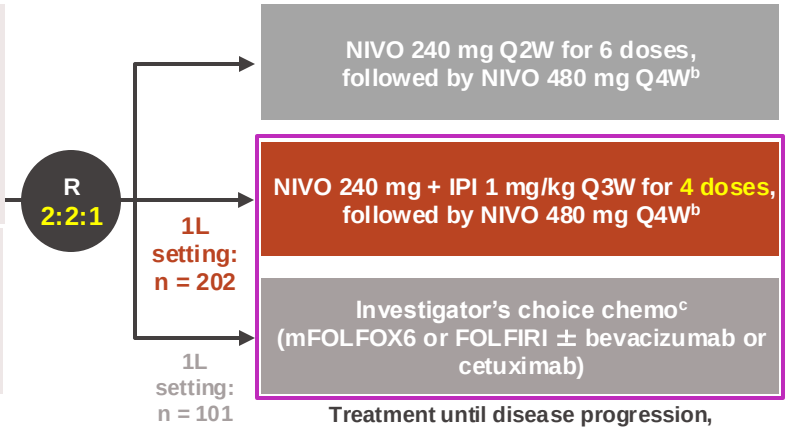
GI Cancer	Negative predictive markers	Positive predictive markers	Cancer-agnostic markers
Gastroesophageal		HER-2 PD-L1 CLDN18.2 FGFR2b	MSI-H/ MMR-D POLe/d TMB? NTRK fusions RET fusions KRAS G12C BRAF V600E NRG1 fusions ARGHAP-CLDN fusions?
CRC	RAS mutations BRAF V600E Sidedness HER-2?	HER-2 BRAF V600E MSI-H/ MMR-D KRAS G12C	
Biliary cancers (IHCC!)		IDH-1 FGFR fusions HER-2 BRAF V600E mut	
Pancreas cancer		BRCA (-like) NRG-1 fusions	
HCC		(AFP high)	

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)

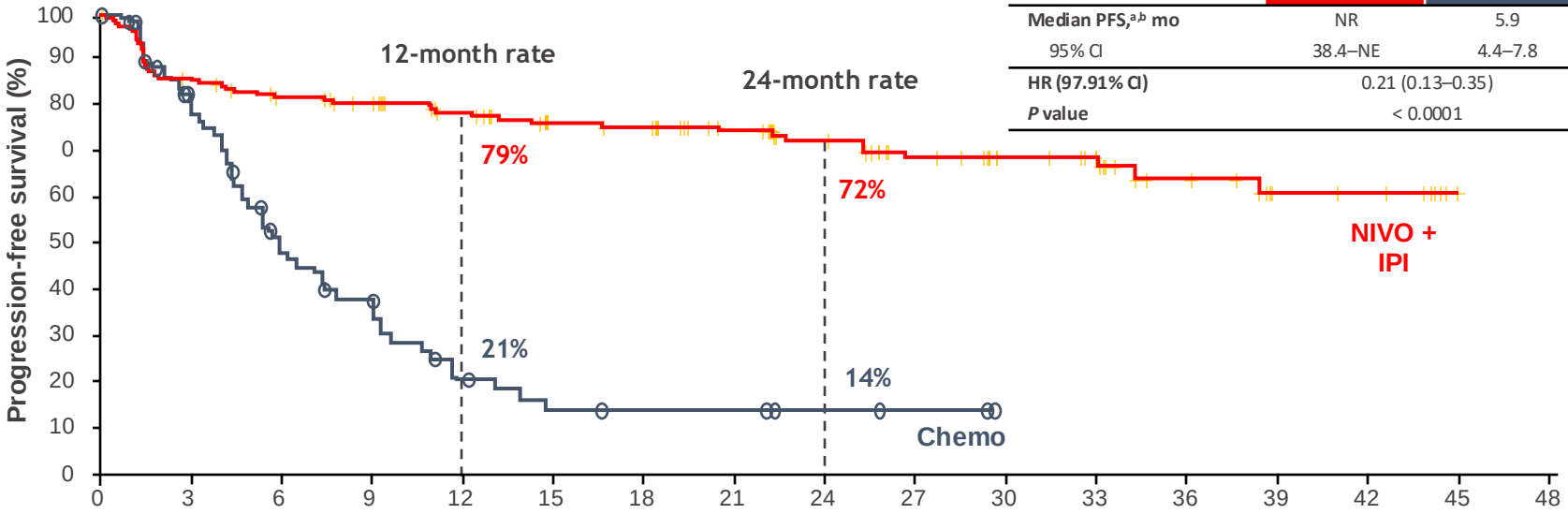
Other select endpoints:
- Safety
- OS; ORR by BICR[e]; PROs

- 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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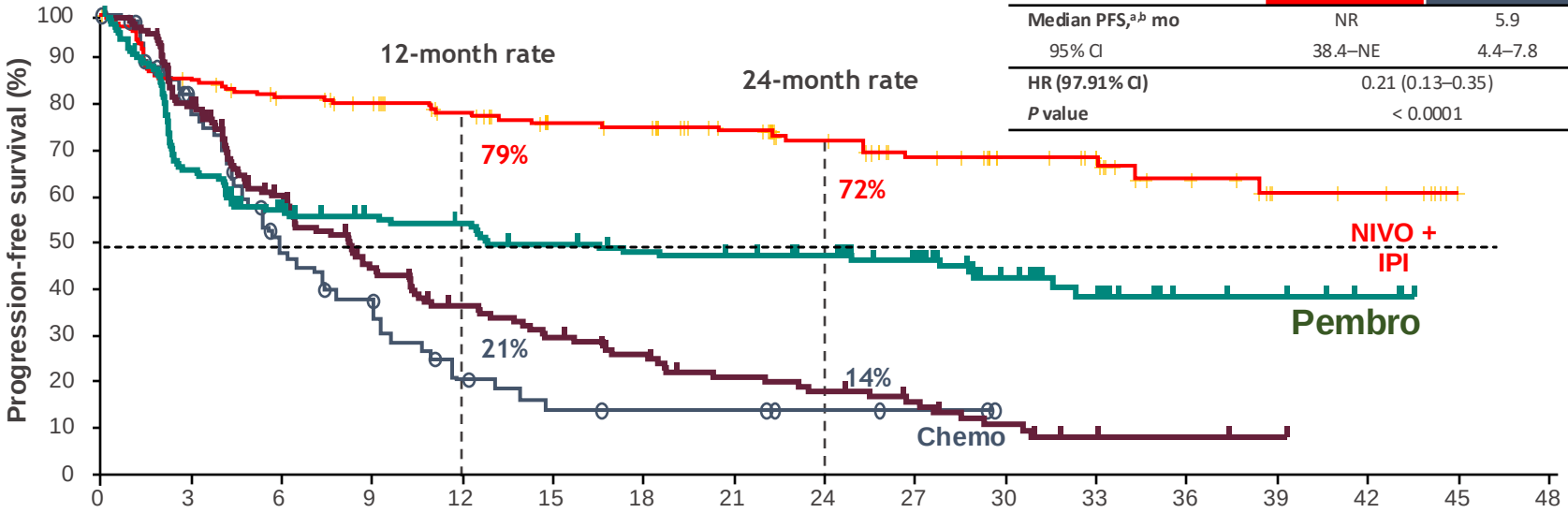

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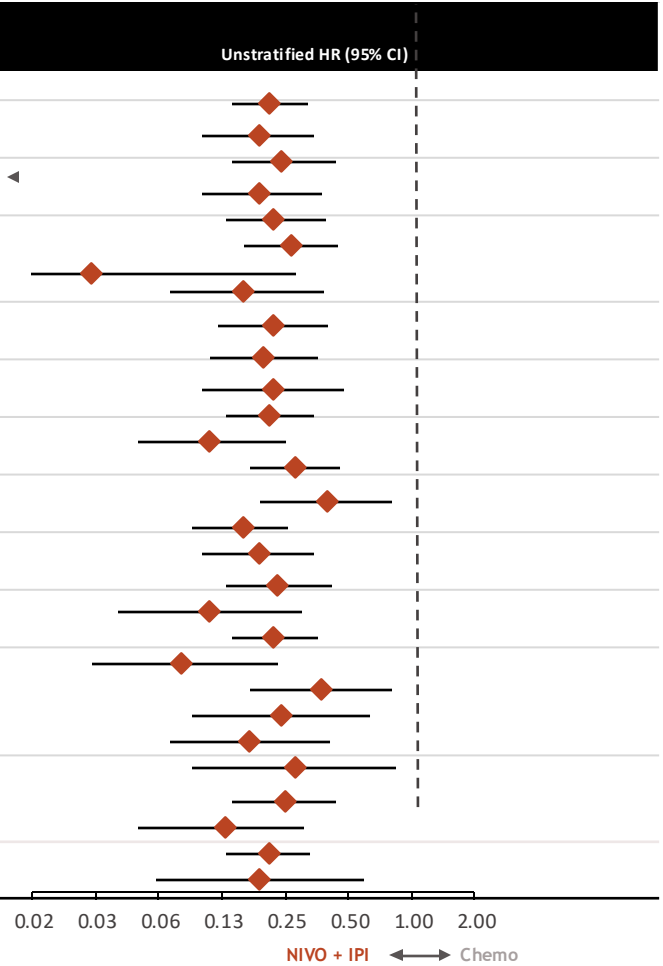
[a]Per BICR. [b]Median follow-up, 24.3 months.

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



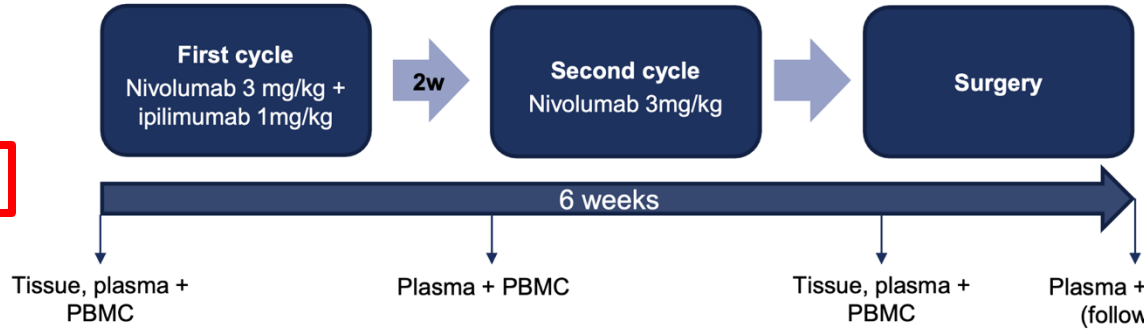
[a]Per BICR.

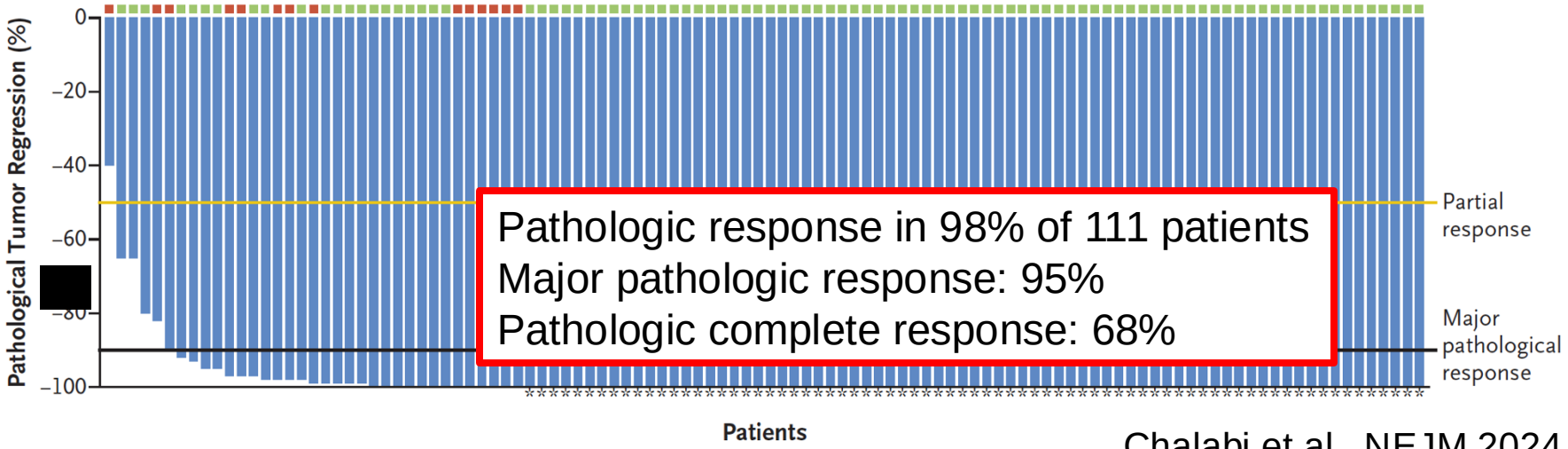
My Conclusions on first-line IO in MSI-H CRC

- **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
- **In cross-trial comparison Nivo/Ipi seems to be more active and avoid 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 Immunotherapy in dMMR/ MSI-H Colon Cancer

Only 2 doses of immunotherapy

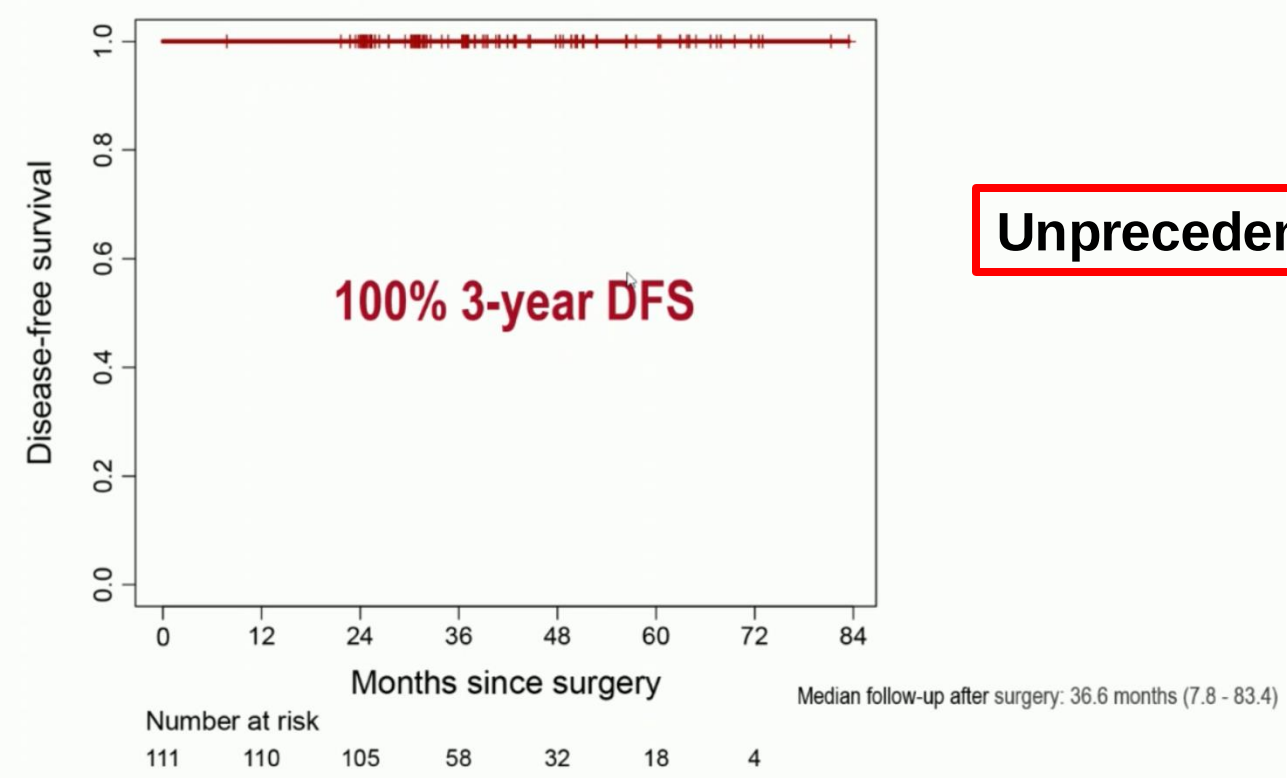




Pathologic response in 98% of 111 patients
Major pathologic response: 95%
Pathologic complete response: 68%

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

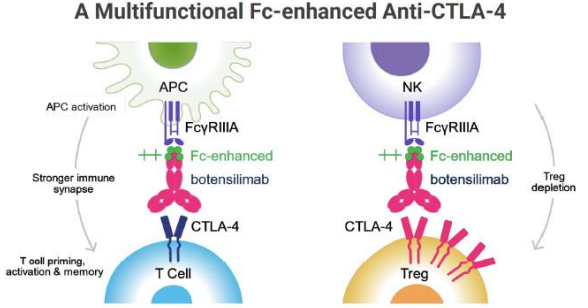
Chalabi et al., ESMO 2024

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**

Botensilimab + Balstilimab, N=87

Botensilimab (FC-enhanced Anti-CTLA-4)

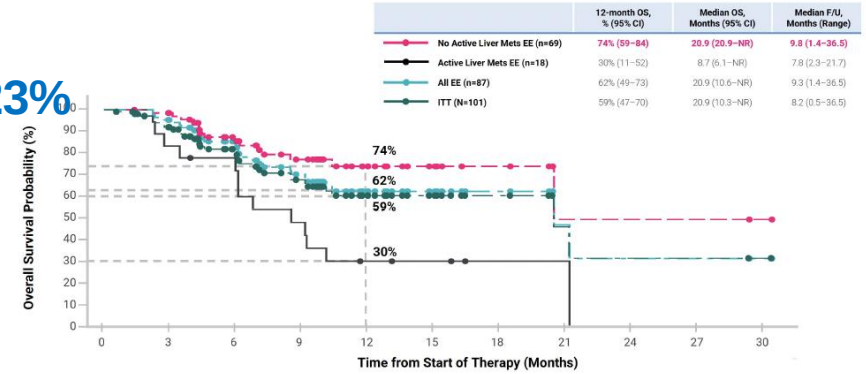


- **Enhanced** T cell priming, expansion, memory[5,6]
- **Enhanced** frequency of APCs
- **Enhanced** Treg depletion
- **Reduced** complement mediated toxicity

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

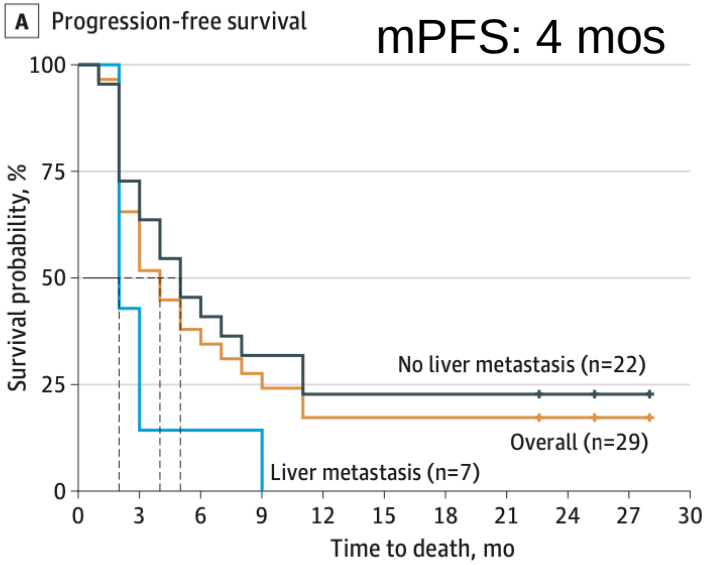
	All EE n=87*	No Active Liver Mets EE n=69†	Active Liver Mets EE n=18‡
Confirmed ORR, n % (95% CI)	18% (11–28)	23% (14–35)	0% (0–19)
BOR, n (%)			
CR	1 (1)	1 (1)	0
PR	15 (17)	15 (22)	0
SD	45 (52)	39 (57)	6 (33)
PD	26 (30)	14 (20)	12 (67)
DCR (CR + PR + SD), % (95% CI)	70% (59–80)	80% (68–88)	33% (13–59)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

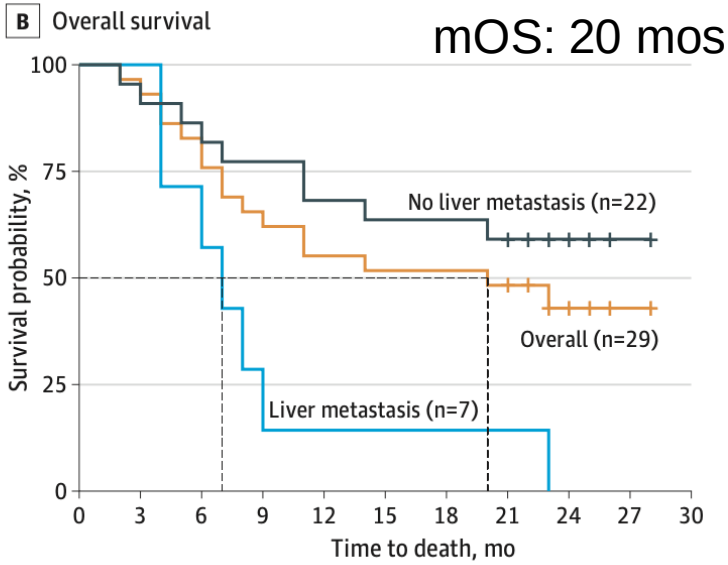


Bullock, ESMO GI 2023

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

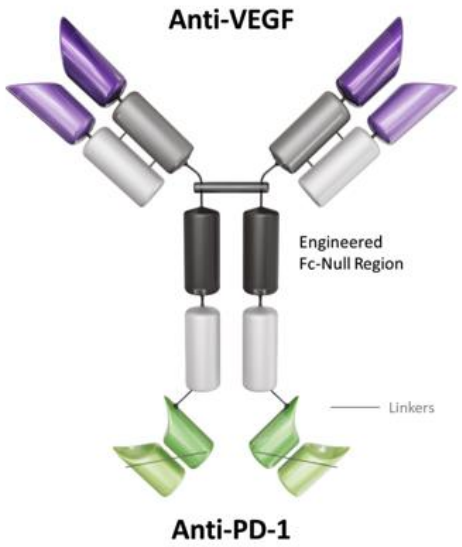
RR: No liver mets (22): 36%, Liver mets (7): 0%

Fakih et al., JAMA Oncol 2023

My Thoughts on B&B study

- **BAL-BOT shows interesting activity in metastatic MSS/pMMR CRC without liver metastases**
  - Reminiscent of data generated with Rego/Nivo (+/- Ipi) and Pembro/Lenvatinib (Note: Phase 3 LEAP-17 negative!
  - Observed activity attenuated in updated analysis, now <20% RR, however durability of response >9 months
- **More data and randomized comparison needed to see if time-related endpoints can be met**
- **We need to find a way to make CRC liver metastases respond to IO therapy -> high unmet need!**

Ivonescimab: Bispecific Antibody

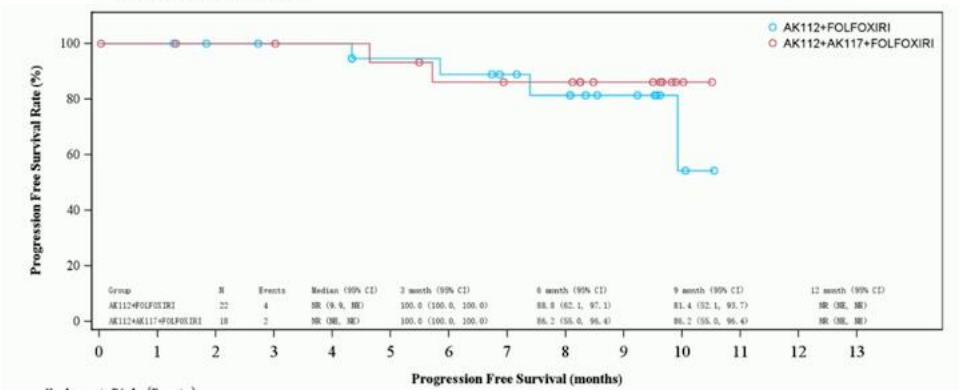


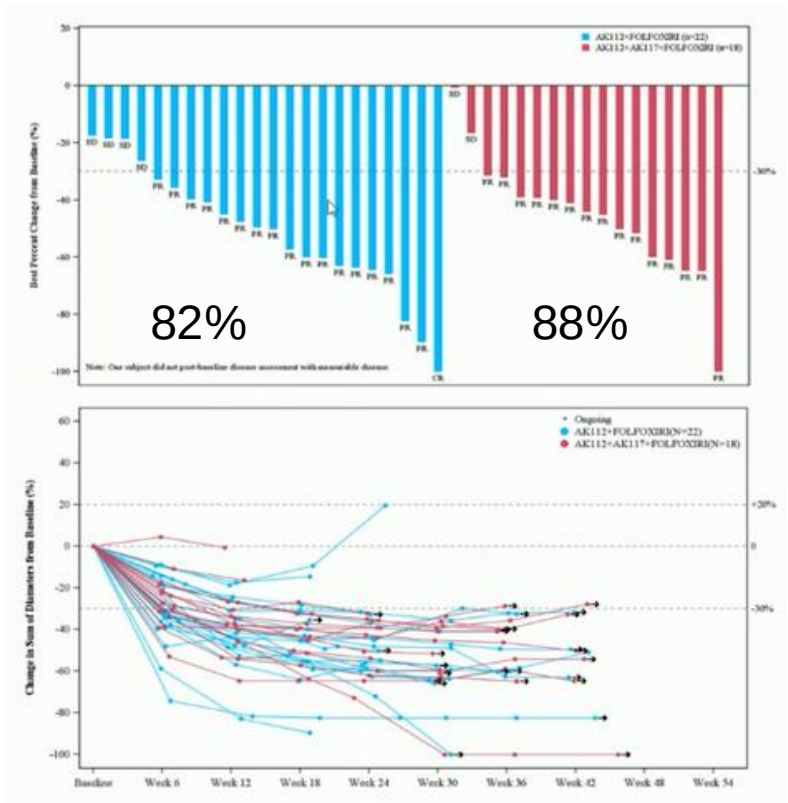
- **Simultaneous interaction of PD-1 & VEGF blockades can drive synergistic anti-tumor activity**
  Inhibiting VEGF can help improve the effect of immunotherapy by modulating the tumor microenvironment
  Enhancing the PD-1 blockade helps activate T cells
- **Cooperative Binding**
  Increased Binding 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

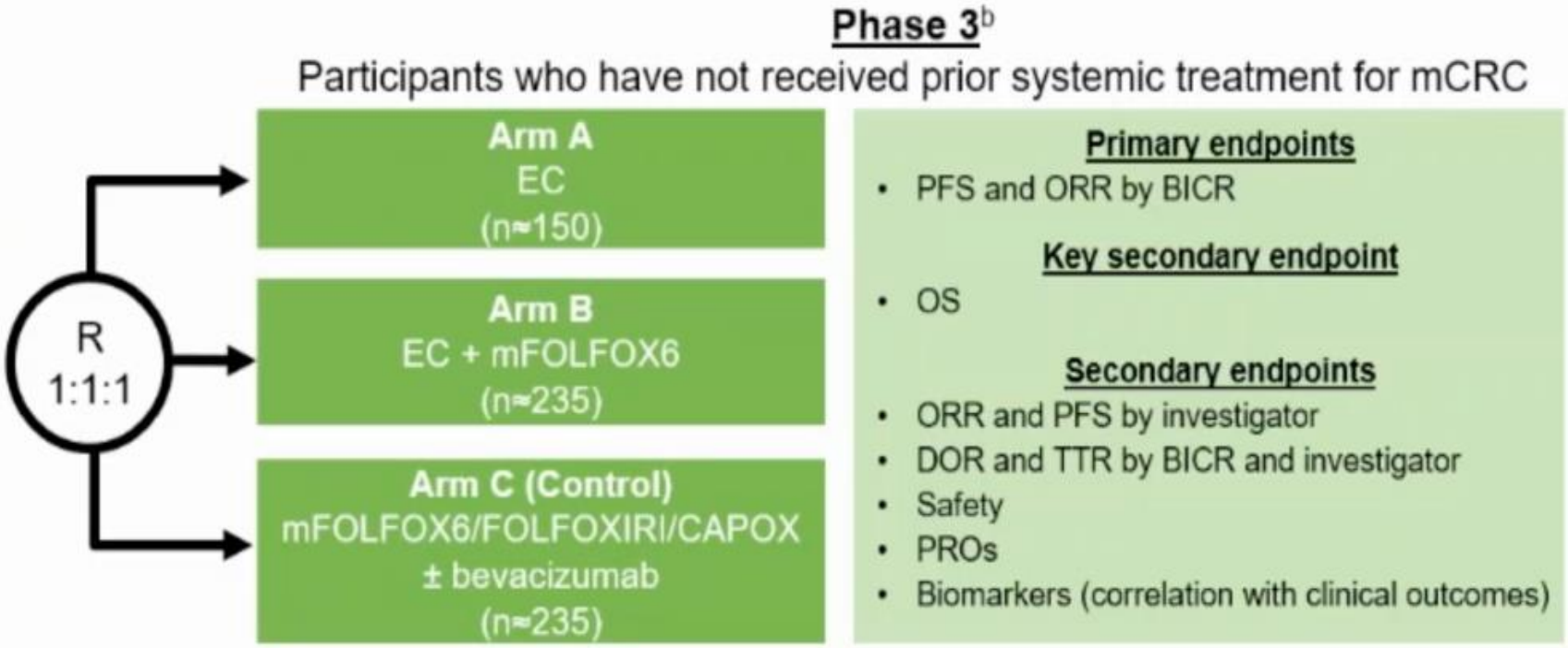




Ligufalimab: IgG4 anti-CD47 antibody

Deng et al., ESMO 2024

BREAKWATER: First-line Encorafenib+ Cetuximab+ Chemo in BRAF V600E mut CRC



BREAKWATER: First-line Encorafenib + Cetuximab + FOLFOX in BRAF V600E mut CRC

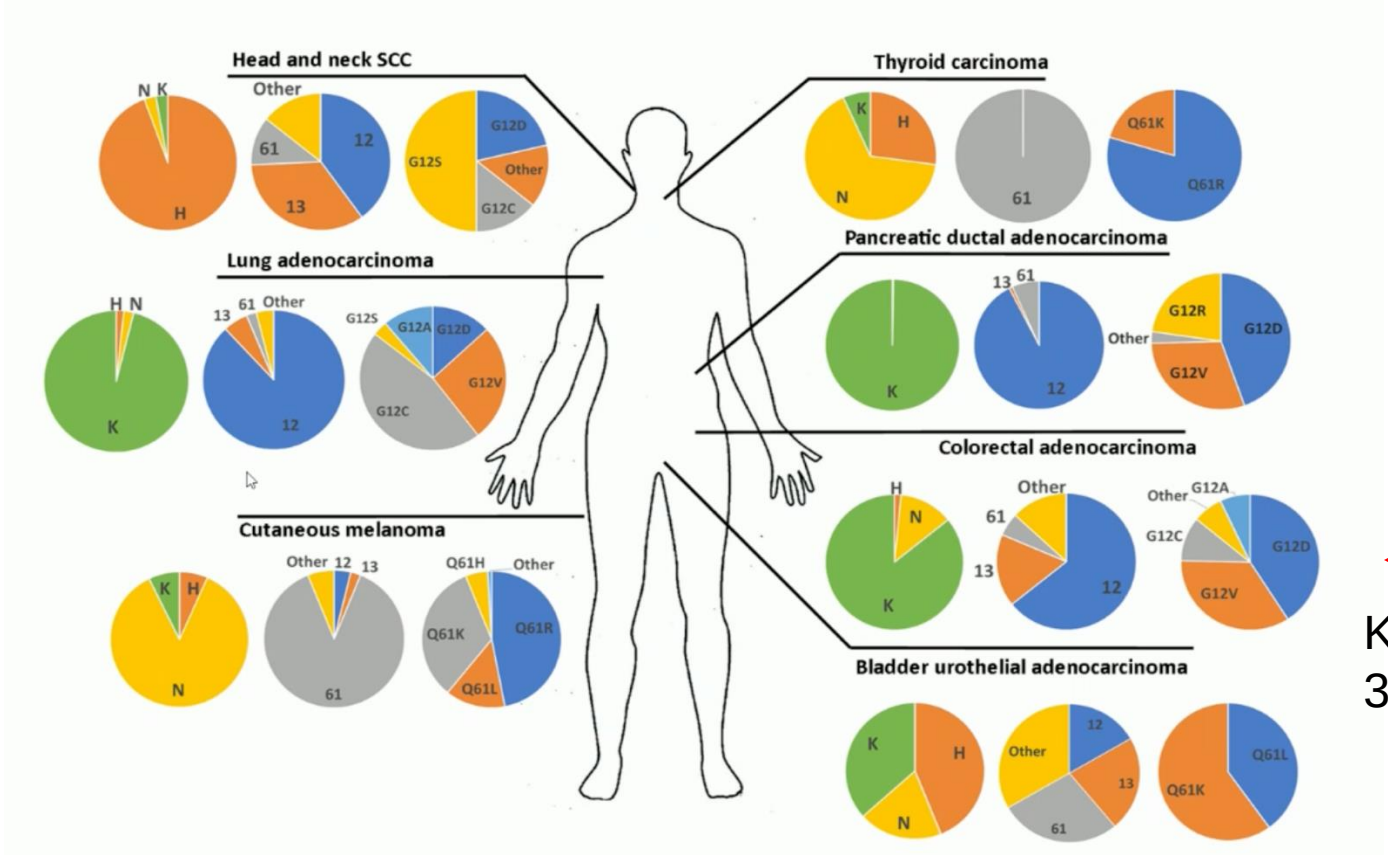
- Accelerated FDA approval on December 20, 2024 for mFOLFOX6 + encorafenib + cetuximab
- Only 47% of patients per arm reported (110/235)
- No data on time-related endpoints (PFS/OS) yet!

	N	RR (%)		mDOR (mos)
FOLFOX +/- BEV	110	61 (52-70)	P=0.0008	13.9
Chemo* + encorafenib + cetuximab	110	40 (31-49)		11.1

*FOLFOX, FOLFOXIRI or CAPOX

FDA. December 20, 2024. Accessed December 20, 2024.
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-encorafenib-cetuximab-and-mfolfox6-metastatic-colorectal-cancer-braf

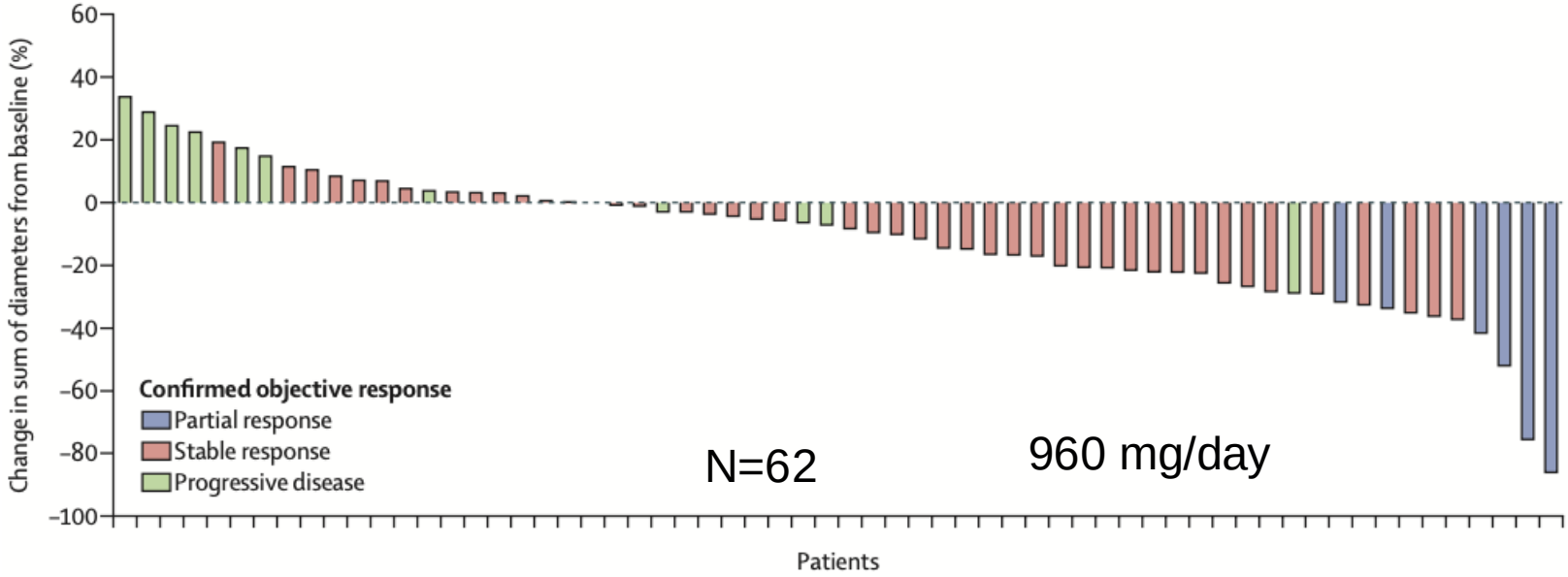
RAS mutation in various cancers



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)

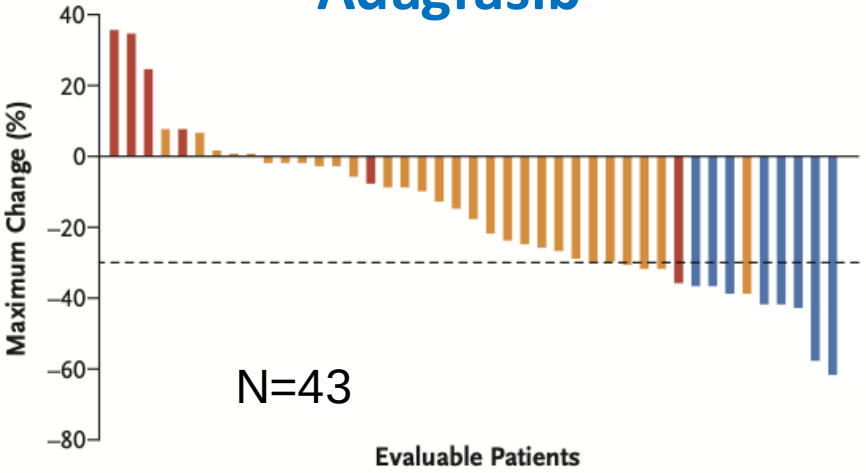
PFS: 4.0 mos

OS: 10.6 mos

Fakih et al. Lancet Oncol 2021

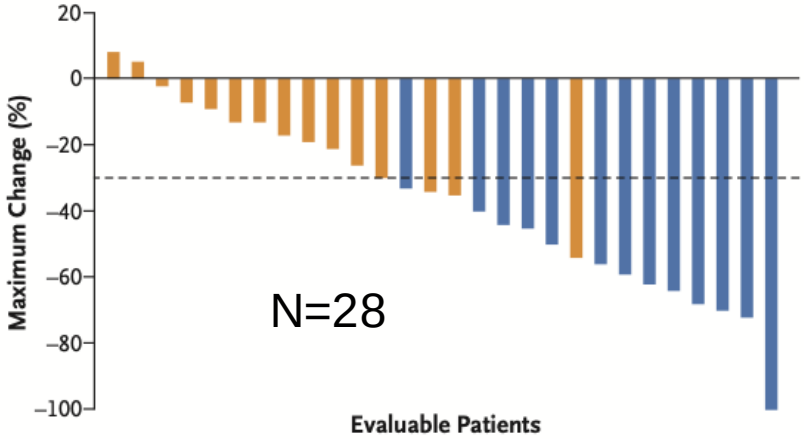
KRYSTAL-1:

Adagrasib



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

Adagrasib + Cetuximab

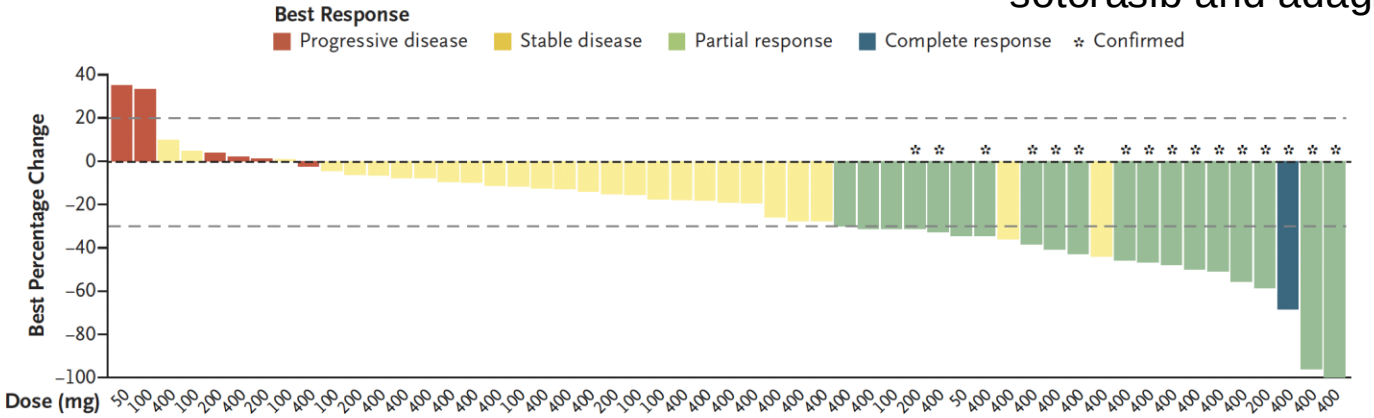


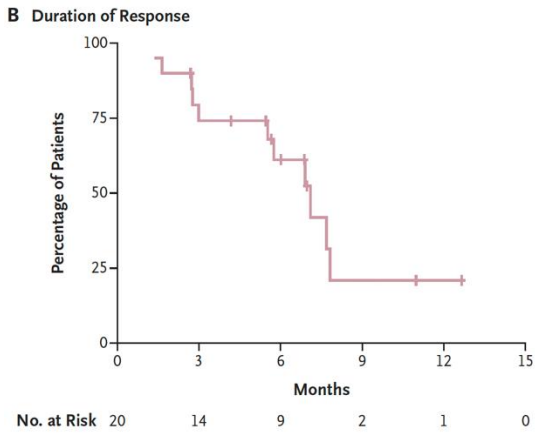
RR: 46%
DOR: 7.6 mos
PFS: 6.9 mos
OS: 13.4 mos

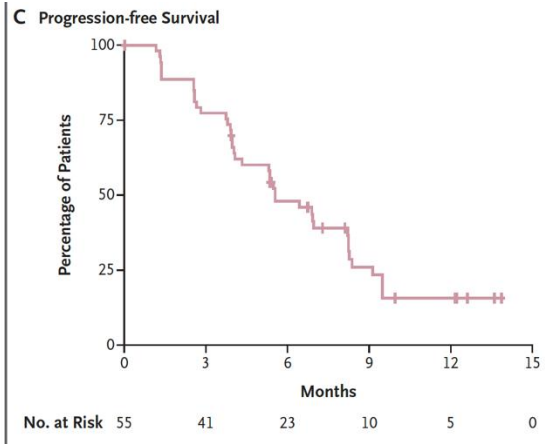
Yaeger et al. NEJM 2022

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



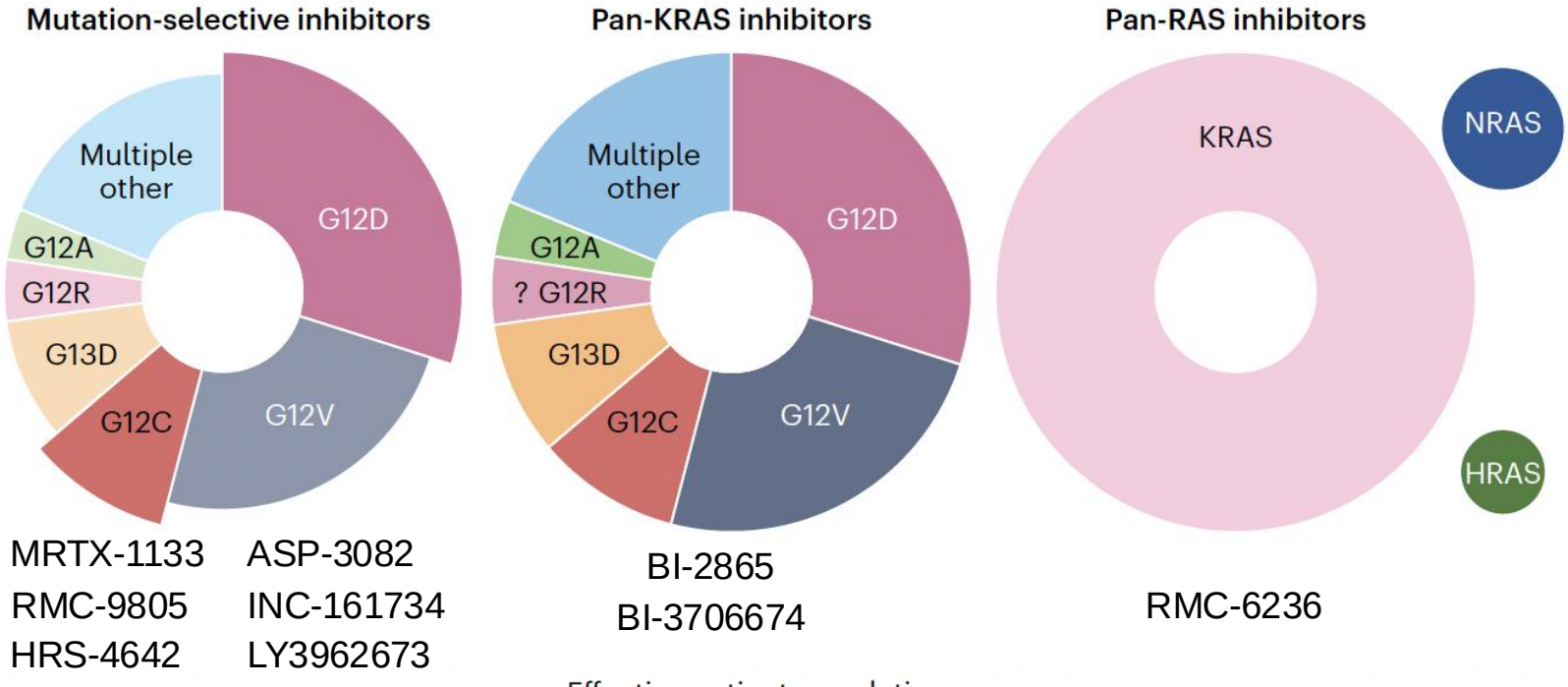




RR 37%
DCR 89%
mDOR 7.1 mos
mPFS 5.6 mos

Sacher et al, NEJM 2023

RAS Inhibitors



Corcoran, Nat Med 2023

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)	—

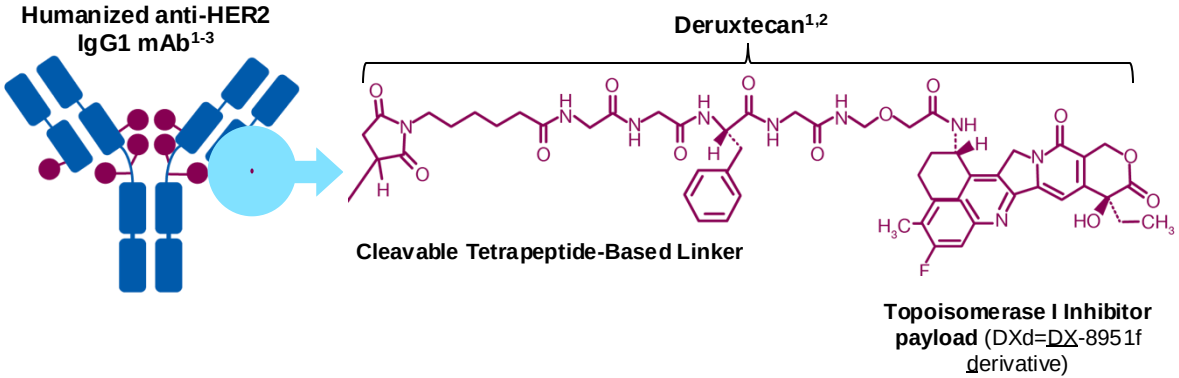
[a] In NCCN guidelines. [b] ORR in subgroup with prior HER2 rx 43.8% (19.8-70.1); without prior HER2 rx 45.9% (29.5-63.1). [c] Did not meet primary endpoint. T-DM1 had 0% response rate in MATCH Arm Q[8] and MSKCC Basket Trial.[9]

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:

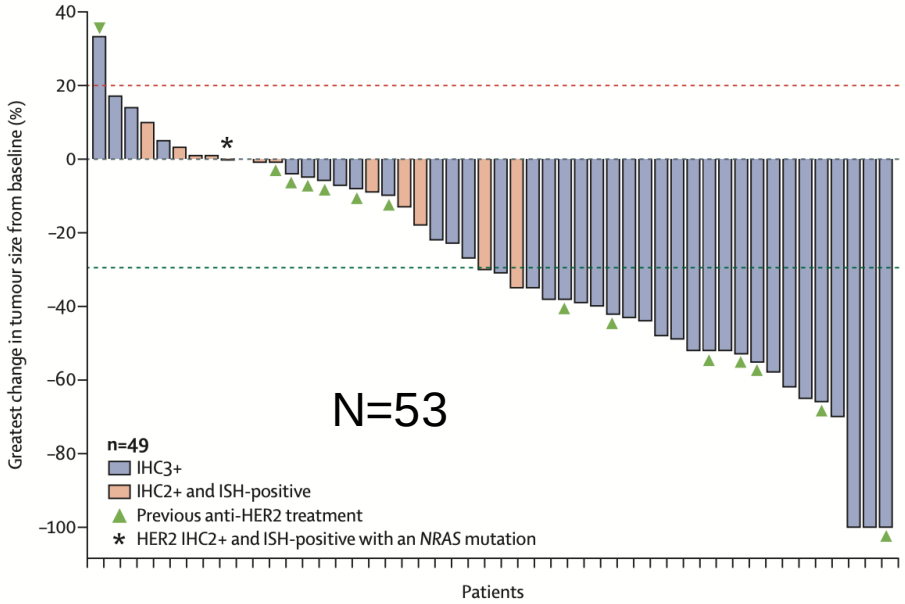
- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker

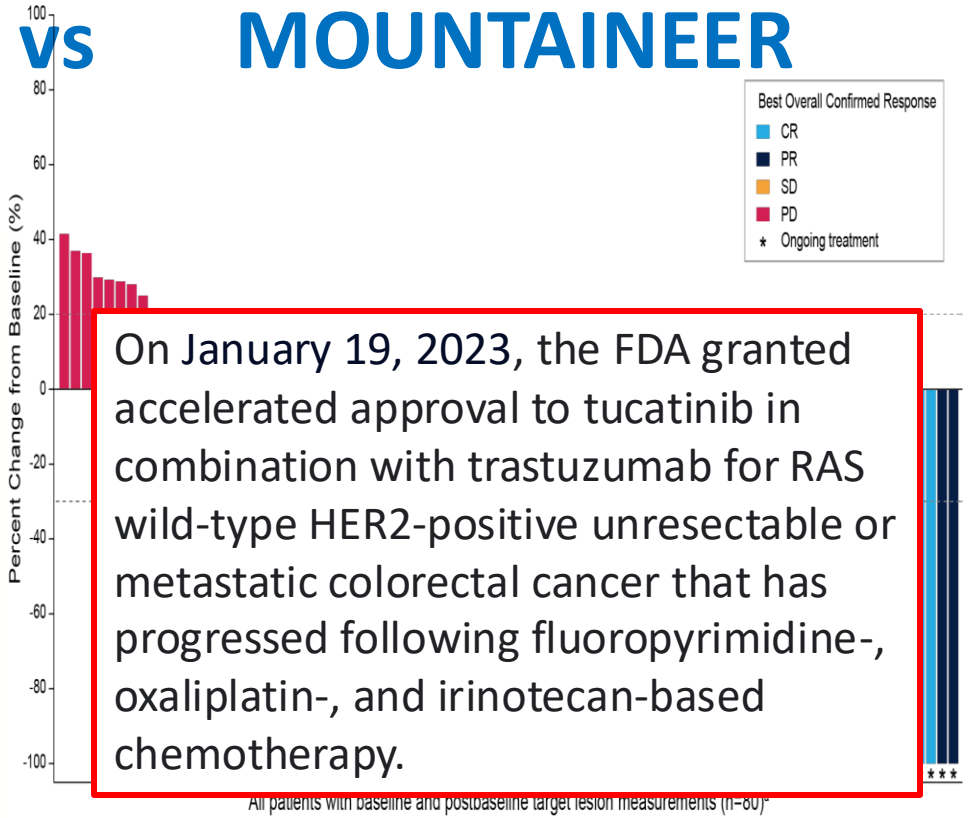


Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug to antibody ratio ≈ 8
Payload with short systemic half-life
Stable linker-payload
Tumor-selective cleavable linker
Membrane-permeable payload

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.

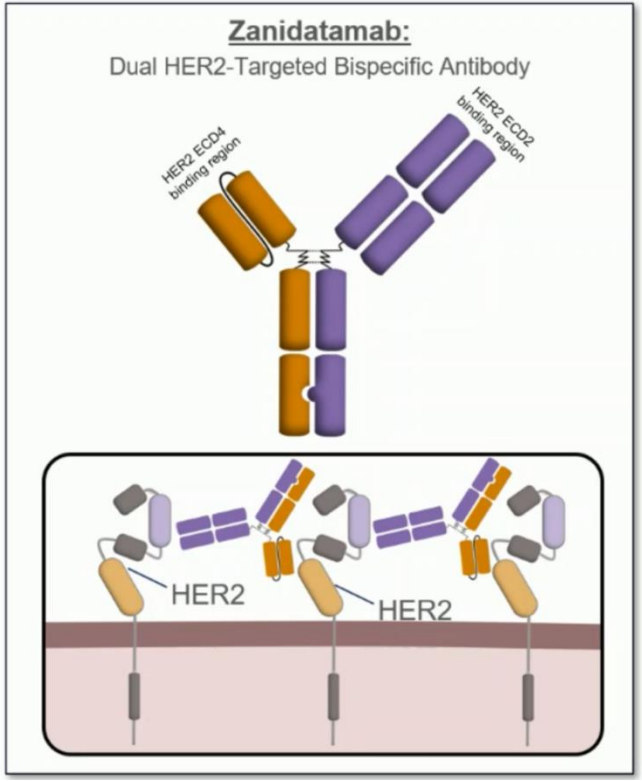
Median # of prior lines: Destiny: 4, MOUNTAINEER: 2

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

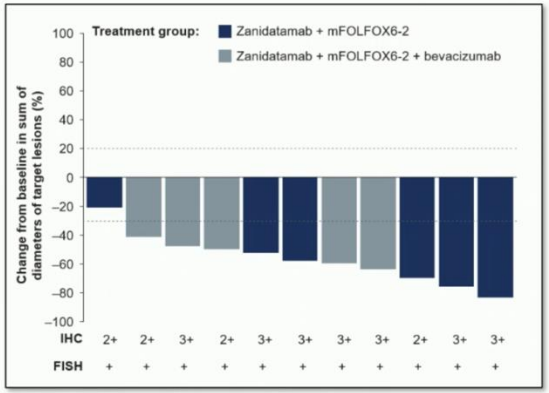
CRC patients treated (Part 1) N=13
DLT evaluable[e] n=12
Response evaluable n=11

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

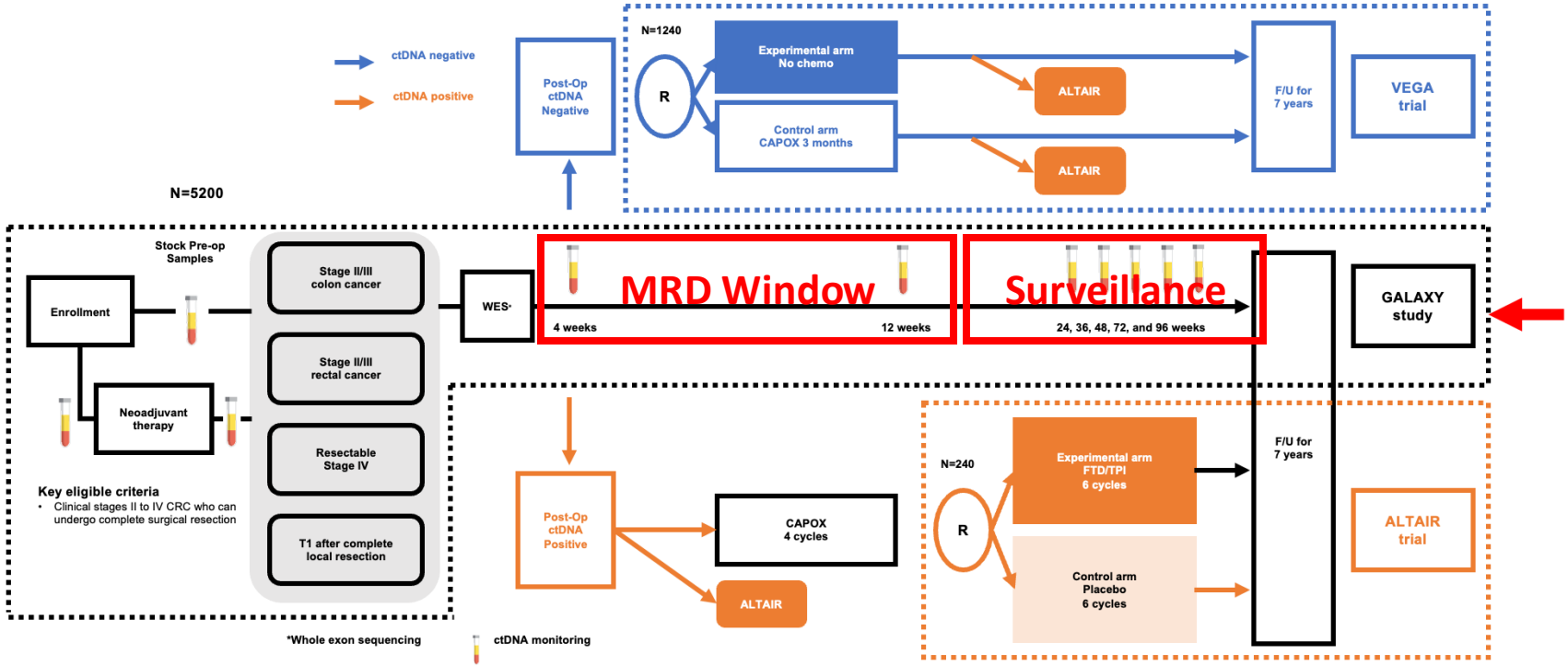
Median (range) duration of response:
Not reached (2.9+-16.7+) months



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

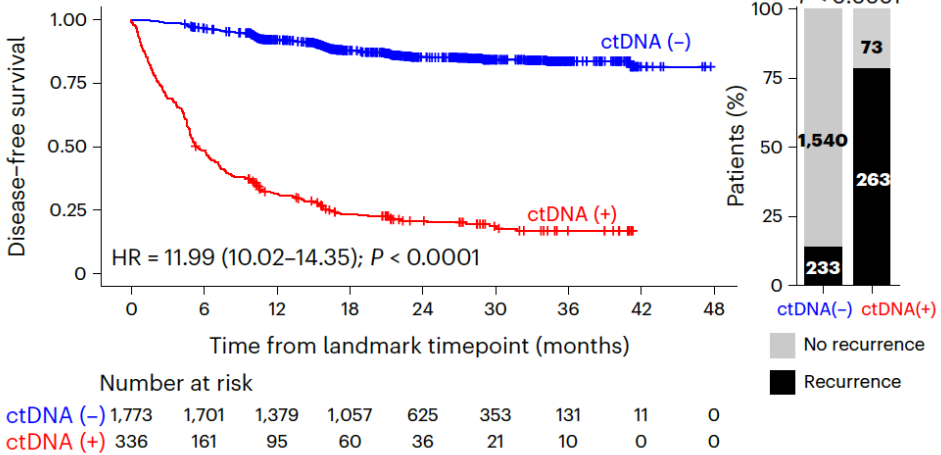
Rha et al., ESMO 2024

CIRCULATE Japan: Comprehensive Analysis of Role of ctDNA in Management of CRC



Kotaka et al., ASCO GI 2022

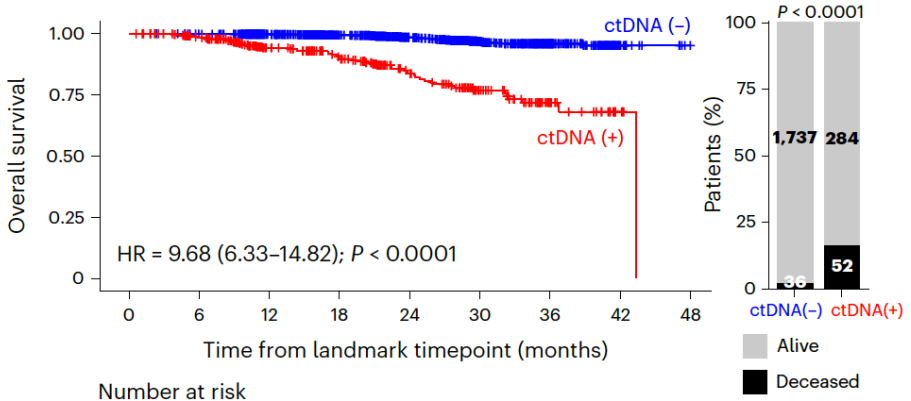
DFS and OS by ctDNA in MRD window



Number at risk

ctDNA (–)	1,773	1,701	1,379	1,057	625	353	131	11	0
ctDNA (+)	336	161	95	60	36	21	10	0	0

ctDNA status	Negative	Positive
Events %	13.14 (233/1773)	78.27 (263/336)
24M-DFS % (95% CI)	85.10 (83.20–86.9)	20.57 (16.14–25.37)
30M-DFS % (95% CI)	84.10 (82.0–86.0)	18.50 (14.0–23.40)
36M-DFS % (95% CI)	83.50 (81.20–85.60)	16.70 (12.10–21.90)
mDFS (mo)	NR	5.34 (4.83–6.70)



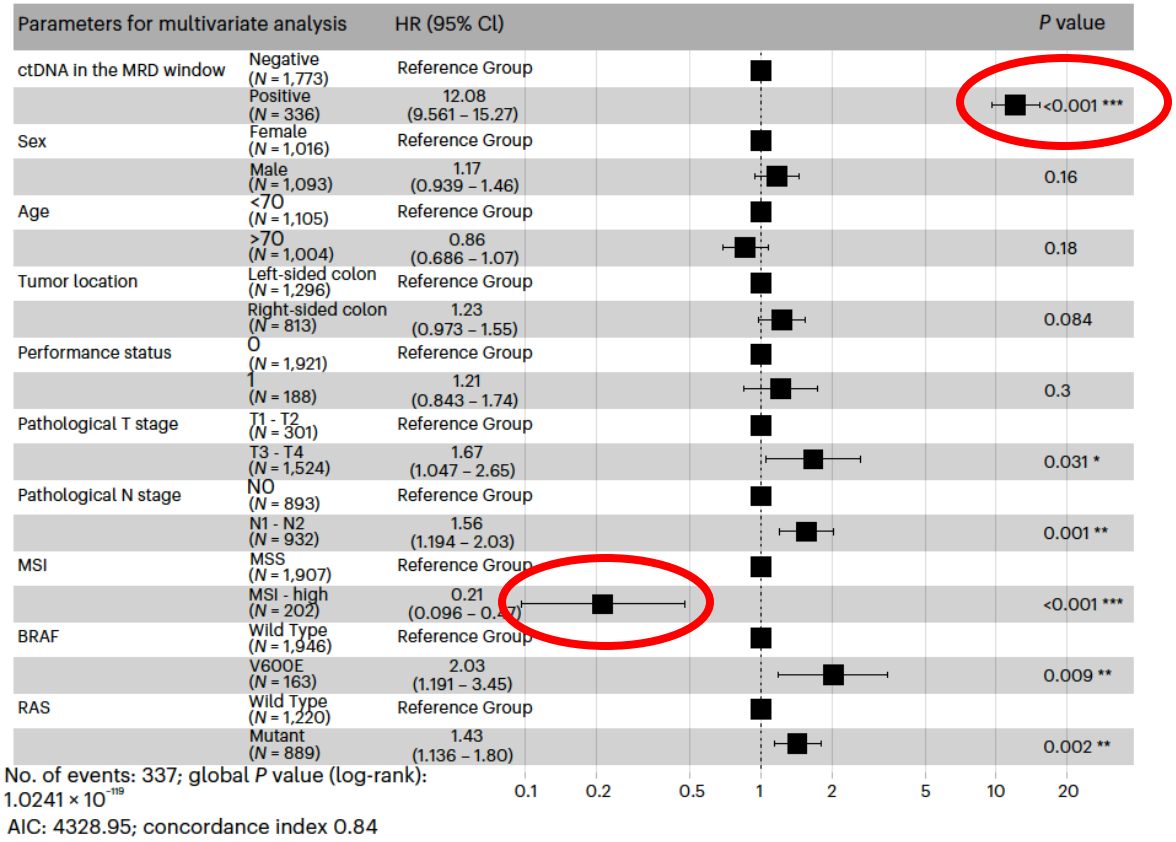
Number at risk

ctDNA (–)	1,773	1,765	1,511	1,252	825	497	185	19	1
ctDNA (+)	336	309	228	189	119	73	24	4	0

ctDNA status	Negative	Positive
Events %	2.03 (36/1773)	15.48 (52/336)
24M-OS % (95% CI)	98.50 (97.70–99.10)	83.65 (77.84–88.06)
30M-OS % (95% CI)	96.80 (95.40–97.80)	76.90 (69.80–82.50)
36M-OS % (95% CI)	96.0 (94.30–97.20)	71.80 (63.40–78.60)
mOS (mo)	NR	43.40 (NR–NR)

Nakamura et al., Nat Med 2024

Multifactorial Regression Model for DFS



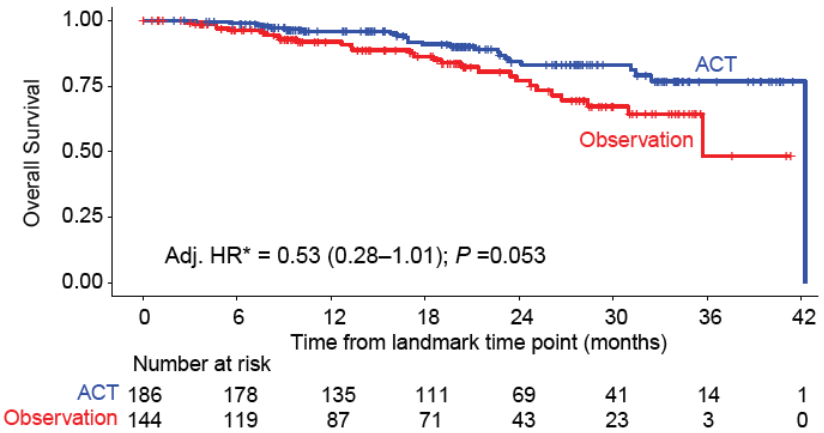
No. of events: 337; global *P* value (log-rank): 1.0241×10^{-119}

AIC: 4328.95; concordance index 0.84

Nakamura et al., Nat Med 2024

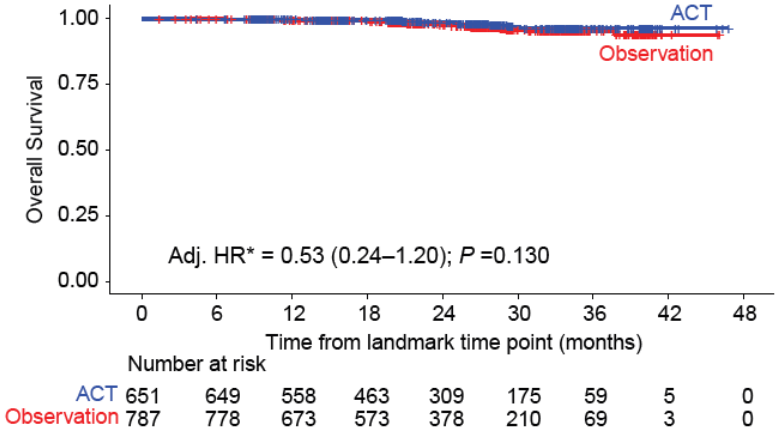
Benefit of Adjuvant Therapy?

MRD-positive



ctDNA status	ACT	Observation
Events %	12.90 (24/186)	19.44 (28/144)
24M-OS % (95% CI)	84.31 (76.04-89.91)	76.93 (66.0–88.74); *P* =0.239**
mOS (mo)	NR	35.70 (35.70–NR)

MRD-negative



ctDNA status	ACT	Observation
Events %	1.69 (11/651)	2.67 (21/787)
24M-OS % (95% CI)	98.60 (96.80-99.40)	97.60 (95.90–98.60); *P* =0.254**
mOS (mo)	NR	NR

Nagata et al., ESMO 2024

My Conclusions on ctDNA in early stage CRC

- **The detection of ctDNA-MRD after surgery is the strongest prognostic indicator to date, more important than TNM tumor stage!**
- **Conversion from positive to negative ctDNA post-op can be achieved with systemic chemotherapy and has DFS benefit**
  - Sustained clearance is associated with better outcome than transient clearance
  - ctDNA positivity can help make decision FOR adjuvant therapy in settings where conventional staging would suggest no therapy
  - Withholding adjuvant therapy based on negative ctDNA tests is being tested in prospective trials (see CIRCULATE trials)
- **Lung metastases are the “blind spot” of current ctDNA tests**
  - There is still room for improvements, new tests to come to the market

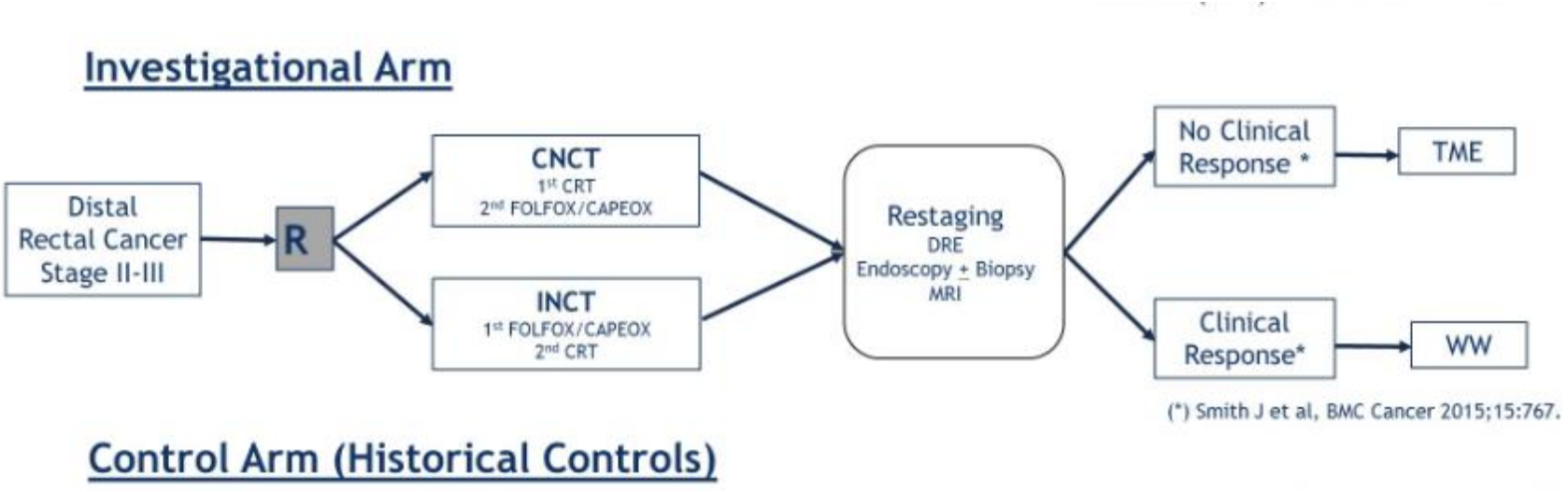
Recent Trial Data in Rectal Cancer

Study	Intervention	Eligibility	Median age [range]	PS	Results
PRODIGE3 (N=461)	Folfirinox→ chemoXRT→ Sx→ chemo Vs. chemoXRT→ Sx→chemo	cT3/T4, any N,	62 [26-75]	0-1	7Y DFS: 67.6% TNT arm vs. 62.5% SOC arm (p=0.048) 7y mets free survival:TNT arm 73.6% vs. 65.4% SOC arm (p=0.011)
RAPIDO (N=920)	LC-CRT → Sx→ adj chemo vs. SC-RT→ Chemo→ Sx→ Adj Chemo	High risk: cT4a/b, N+	62 [55-68]	0-1	5y OS: 81.7% for TNT vs. 80.3% for SOC (P=0.5) 5y DrTF: 27.8% for TNT vs. 34% for SOC (p=0.048)
OPRA (N=324)	Induction chemo→ CRT vs. CRT→ Consolidation chemotherapy	Stage II or III T3-4, any N	59 [51-68]	0-1	5y DFS: 72% for induction vs. 71% for Consolidation. 5y TME-free was 39% in induction vs. 54% for consolidation
PROSPECT (N=1100)	CRT vs. FOLFOX with selective CRT followed by Sx	T2N+, T3N-/+	57 [19-91]	0-2	DFS: FOLFOX+selective CRT was non inferior to CRT prior to surgery

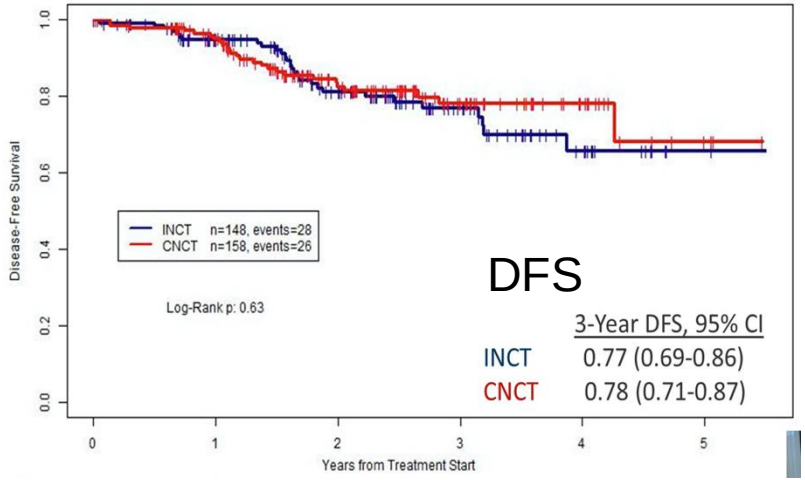
TNT

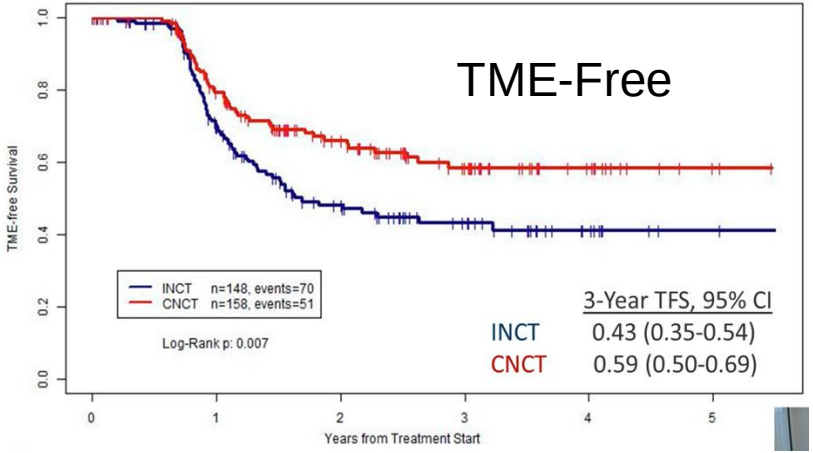
Garcia-Aguilar et al. JCO 2022; Schrag et al. ASCO 2023; Conroy et al. ASCO 2023; Bahadoer et al. Lancet 2021

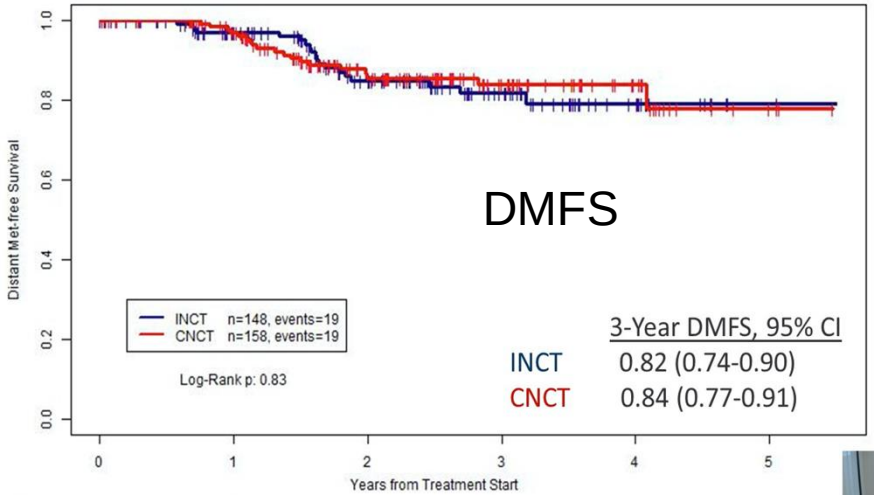
Non-operative Management: OPRA



Garcia-Aguilar et al, JCO 2022



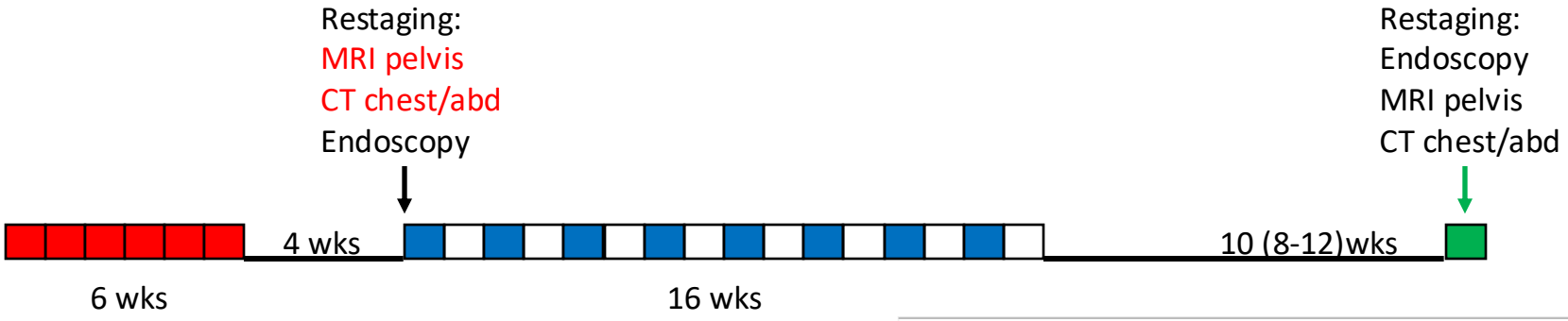




ypTNM (surgery)	INCT (n=70)	CNCT (n=50)
pCR	7 (10%)	4 (8%)
In situ	3 (4.3%)	3 (6%)
I	27 (39%)	14 (28%)
II	22 (31%)	16 (32%)
III	10 (14%)	12 (24%)
IV	1 (1.4%)	1 (2%)

Garcia-Aguilar et al, JCO 2022.

JANUS – TNT/TDT for Rectal Cancer



Radio-chemo:
Cape 825 mg/m2 BID
on days of radiation
54 Gy in 6 weeks
(30 radiation days)

mFOLFOXIRI or
mFOLFOX6

Total time until decision on surgery:
9 months!

Evaluations during treatment – Arm 1 (LCRT THEN FOLFOX OR LCRT THEN CAPOX)

Study Week (+/- 14 days)	Pre	10	12	14	16	18	20	22	24	28/30[1, 2]
Colorectal surgeon eval	X	X								X
Med Onc[3]	X	X	X	X	X	X	X	X	X	X
Rad Onc	X	X								
DRE	X	X								X
Sigmoidoscopy	X	X								X
Biopsy[4]	X									
MRI Rectum	X									X
CT CAP[5]	X									X
CBC & diff[6]	X									
CMP & CEA	X	X								X
Pregnancy Test	X									

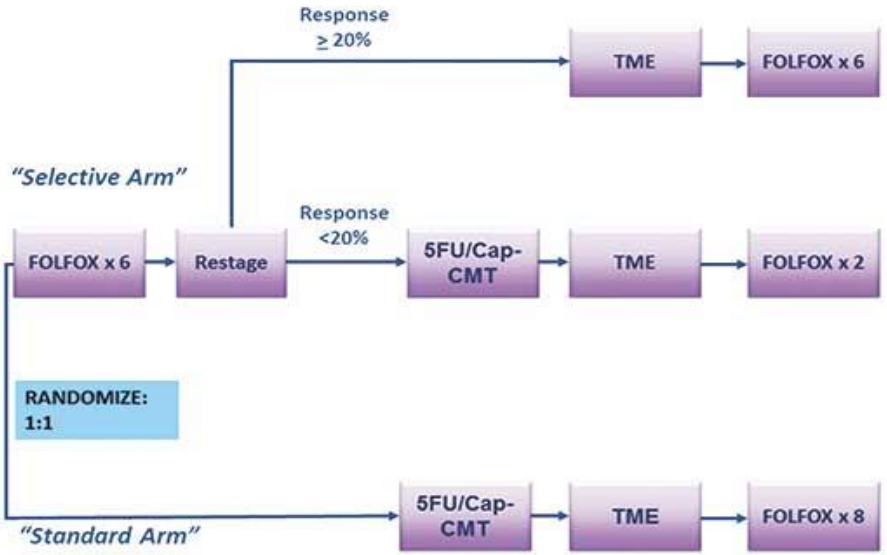
[1] Time of evaluation dependent on duration of neoadjuvant chemotherapy FOLFOX (16 weeks) or CAPOX (15 weeks)

[2] 8-12 weeks (+/- 4 weeks) after completion of all neoadjuvant therapy

PROSPECT – Chemo vs Chemo-Rads

- **Eligibility:**
- **T2 N1, T3N0, T3N1**
- **Candidates for LARs**
  - 80% had tumors > 5 cm from verge

N=1128 started Tx

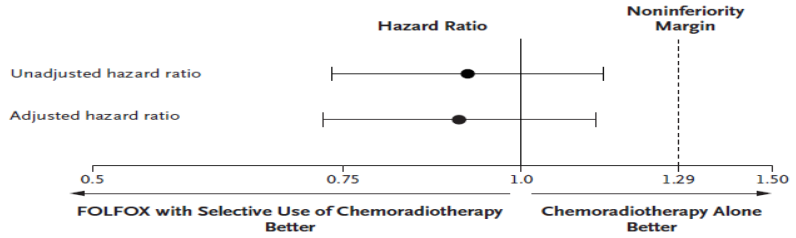


Only 6.5%!

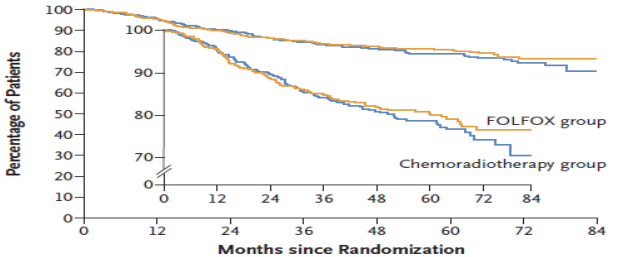
Schrag et al. NEJM 2023

PROSPECT – outcomes data

A Analysis of Noninferiority for Disease-free Survival



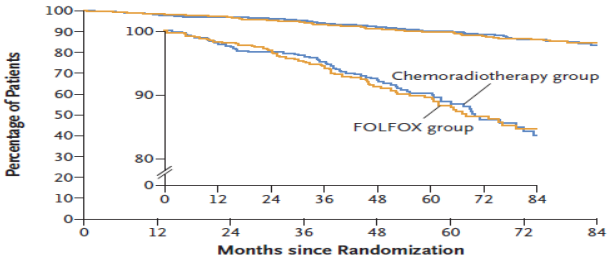
B Disease-free Survival



No. at Risk								
FOLFOX group	585	543	489	443	342	200	97	42
Chemoradiotherapy group	543	500	456	395	295	181	80	37

Group	No. of Events/ Total No.	Hazard Ratio (90.2% CI)	5-Year Estimate (percent)	Stratified P Value for NI
FOLFOX group	114/585	0.92 (0.74–1.14)	80.8 (77.9–83.7)	0.005
Chemoradiotherapy group	113/543	Reference	78.6 (75.4–81.8)	—

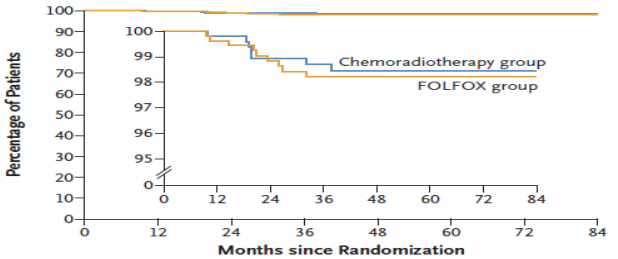
C Overall Survival



No. at Risk								
FOLFOX group	585	565	551	531	429	287	212	120
Chemoradiotherapy group	543	527	513	486	380	273	182	107

Group	No. of Events/ Total No.	Hazard Ratio (95% CI)	5-Year Estimate (percent)
FOLFOX group	74/585	1.04 (0.74–1.44)	89.5 (87.0–92.2)
Chemoradiotherapy group	67/543	Reference	90.2 (87.6–92.9)

D Freedom from Local Recurrence



No. at Risk								
FOLFOX group	585	542	483	438	339	195	95	39
Chemoradiotherapy group	543	499	455	389	289	175	78	36

Group	No. of Events/ Total No.	Hazard Ratio (95% CI)	5-Year Estimate (percent)
FOLFOX group	9/585	1.18 (0.44–3.16)	98.2 (97.1–99.4)
Chemoradiotherapy group	7/543	Reference	98.4 (97.3–99.6)

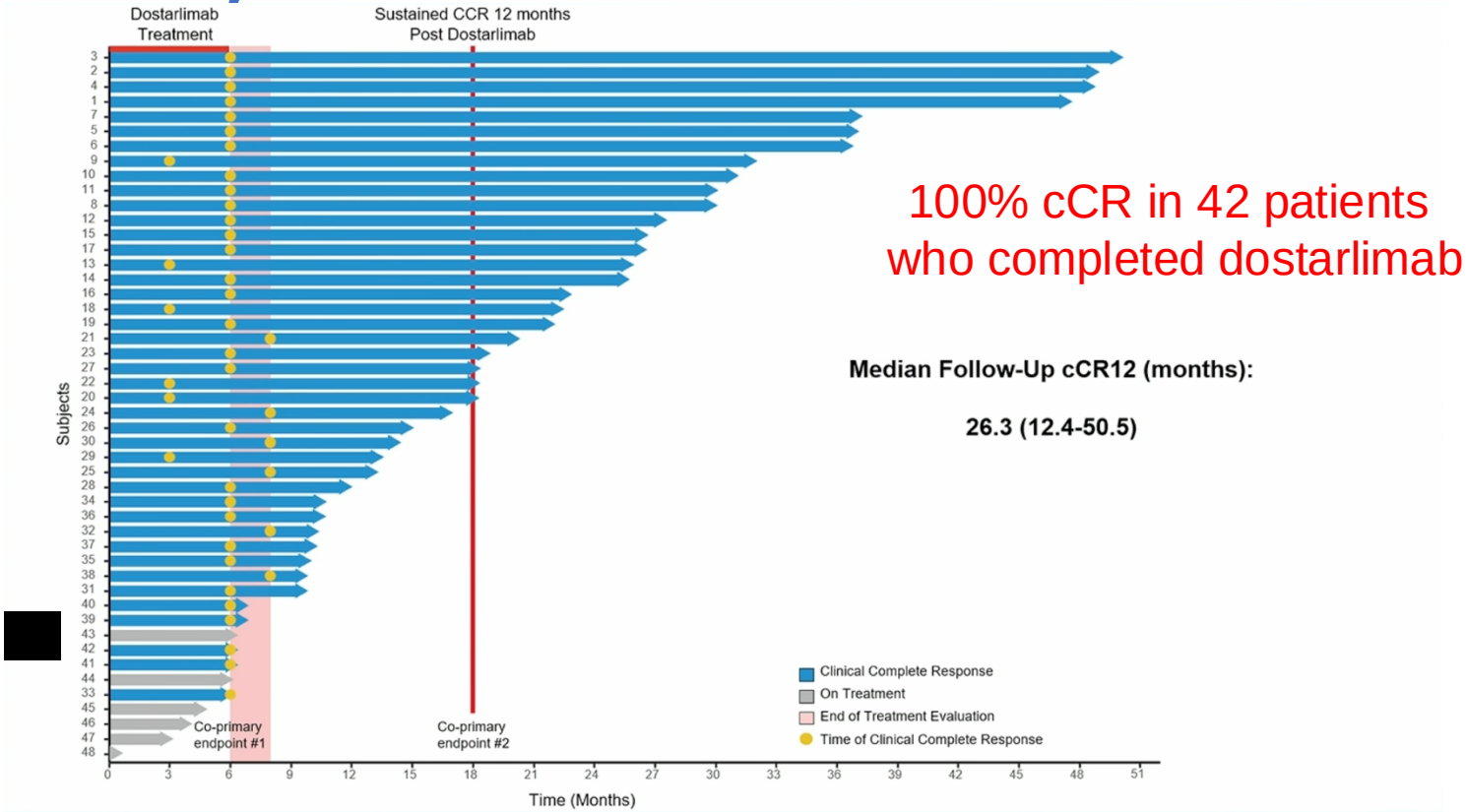
Schrag et al. NEJM 2023

Neoadjuvant/ Definitive Immunotherapy in dMMR/ MSI-H Rectal Cancer (N=48)

Patient Demographics N= 48	N (%)
Female Sex	**28 (58)**
Median Age (range)	**51 (26,78)**
Race	
White	**37 (77)**
Asian	**5(10)**
Black	**6 (13)**
Non Hispanic/Latino	**42 (85)**
Hispanic/Latino	**6 (13)**
Tumor Stage	
T 0/1/2	**10 (21)**
T 3	**23 (48)**
T 4	**15 (31)**
N +	**41 (85)**
Median Distance from anal verge (cm)	**5.1 (0, 14.8)**

Cercek et al., ASCO 2024 (update from NEJM 2022)

Neoadjuvant/ Definitive Immunotherapy in dMMR/ MSI-H Rectal Cancer



Cercek et al., ASCO 2024 (update from NEJM 2022)

My Conclusions on current management of rectal cancer

- **Management of rectal cancer requires input from a multidisciplinary tumor conference**
- **Highly individualized treatment decisions take patient- and tumor-related factors into account**
  - For MSI-H/dMMR cancers neoadjuvant or definitive IO therapy is SOC!
  - For low-lying rectal cancers avoiding a permanent ostomy using TNT/TDT strategies is pertinent
  - If a TNT/TDT approach is used, patients need to be compliant in surveillance
- **Primary goal: Provide highest chance for cure**
- **Secondary goal: Avoid unnecessary toxicity and/ or long-term changes in QOL (e.g. LARS, permanent ostomy)**

Thank you!

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