Bringing Personalized Medicine to Colorectal Cancers

18th Annual New Orleans Summer Cancer Meeting

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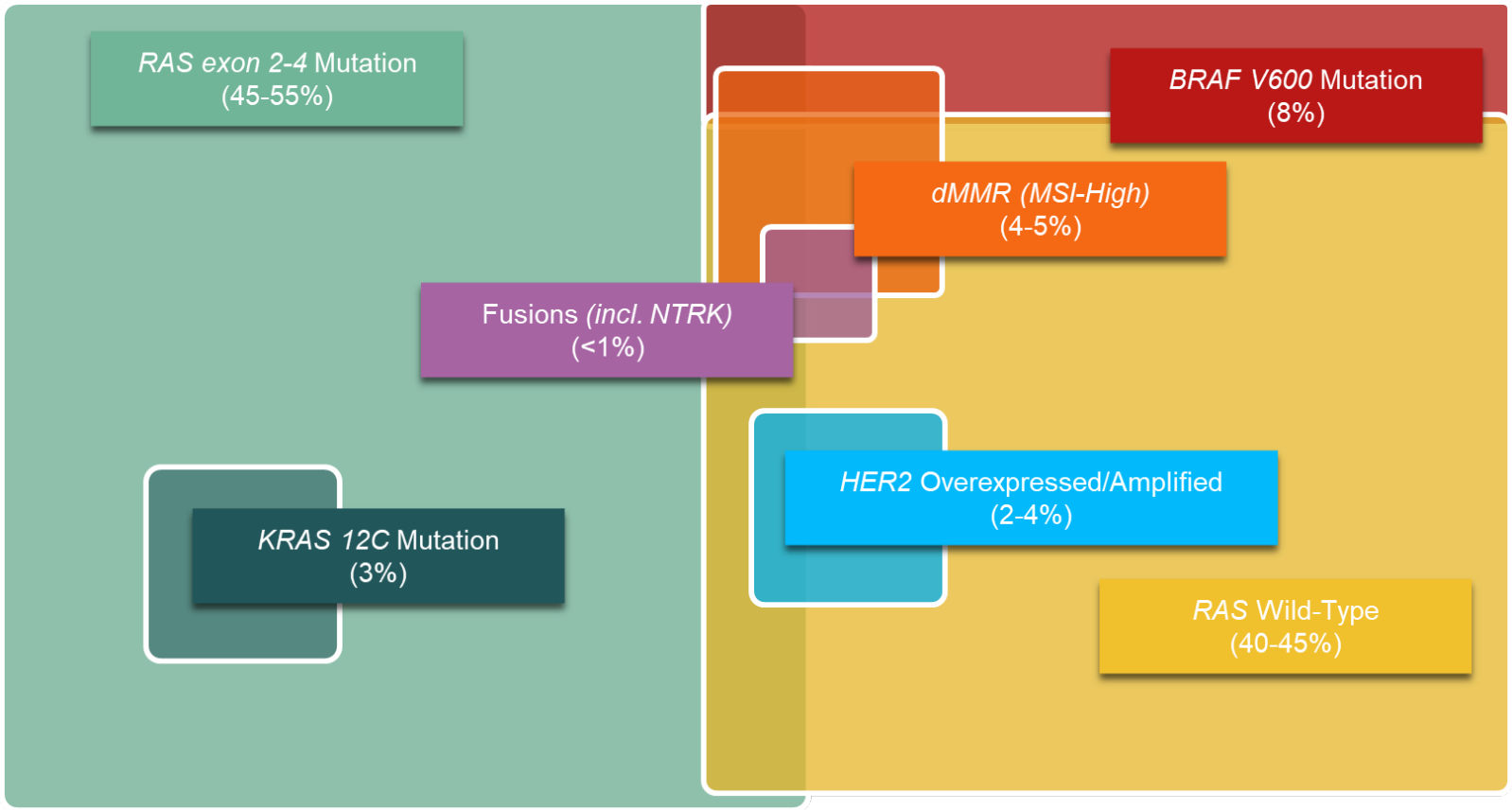
Agenda

- Genomic Landscape of CRC
- dMMR/MSI-H
- HER2
- BRAF V600E
- KRAS G12C

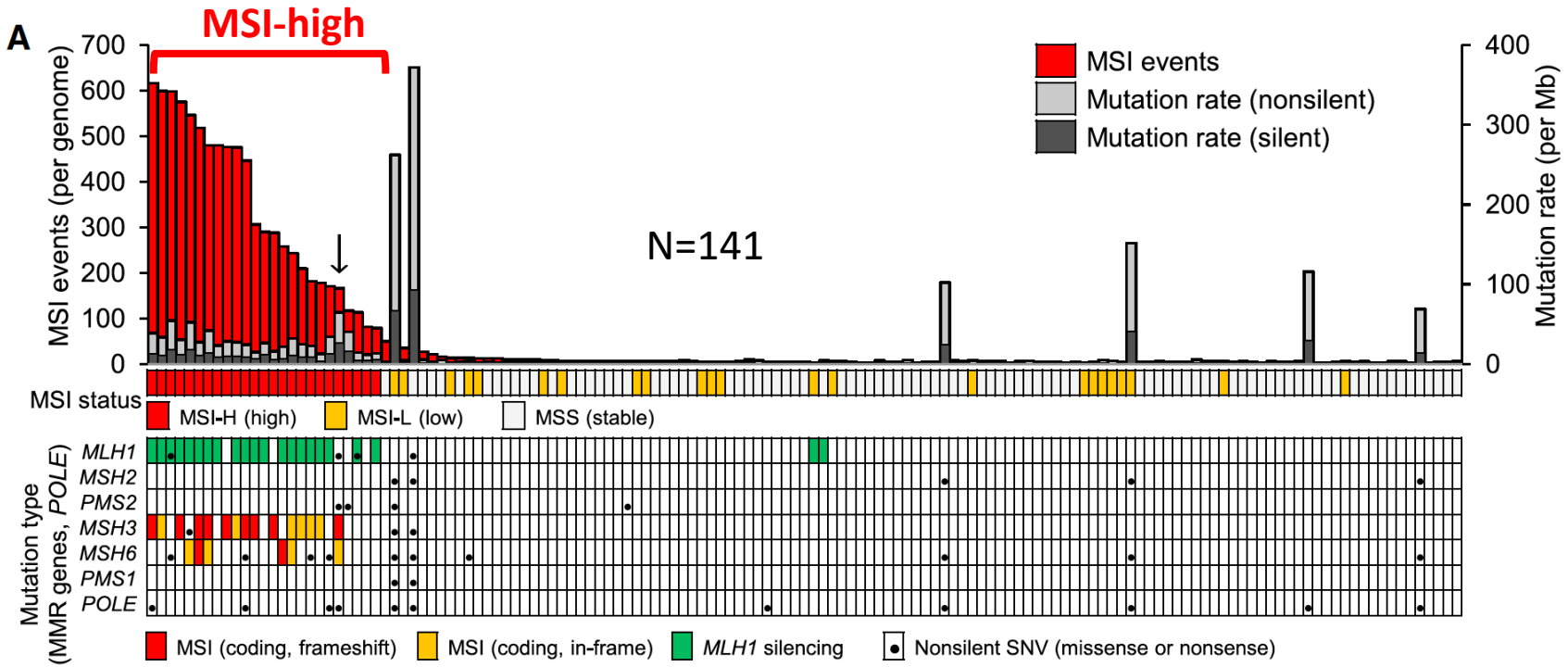
CRC: Molecular Landscape

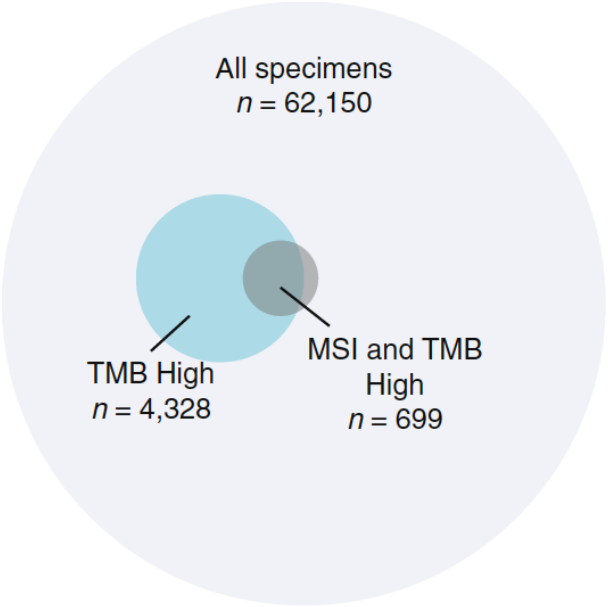


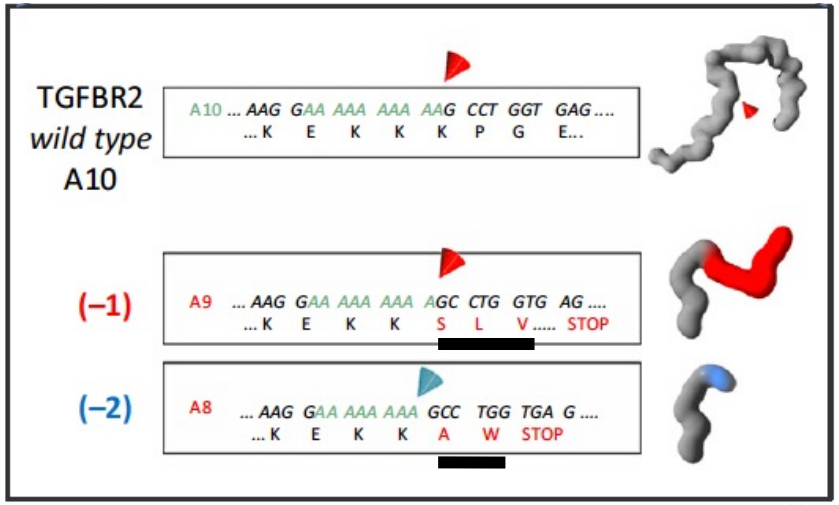
Targets	Drug
EGFR (RAS/RAF wild-type)	• Cetuximab • Panitumumab
VEGF	• Bevacizumab • Ziv-aflibercept • Ramucirumab • Regorafenib
PDL-1 (dMMR or MSI-H)	• Pembrolizumab • Nivolumab +/- ipilumumab • Dostarlimab
BRAF V600E mutation	• Encorafenib + anti-EGFR
ERBB2 (HER2) overexpression (+RAS/RAF wild-type)	• Trastuzumab + Tucatinib Pertuzumab Lapatinib • Trastuzumab deruxtecan
TRK fusion	• Larotrectinib • Entrectanib
RET fusion	• Selpercatinib

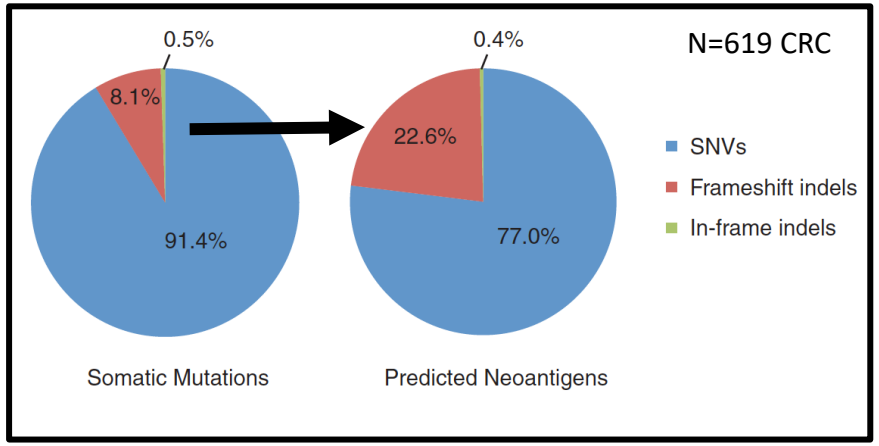
With permission from Kanwal Raghav

dMMR or MSI-H CRC: Frameshift Neoantigens







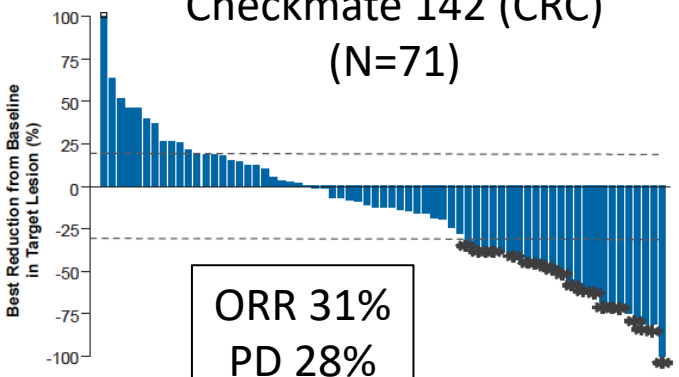


Giannakis et al. Cell Report 2016; Kloor et al. Trends in Cancer 2016; Chalmers et al. Genomic Medicine 2017; 2013 Kim et al. Cell

PD1 Monotherapy in dMMR/MSI-H Cancers

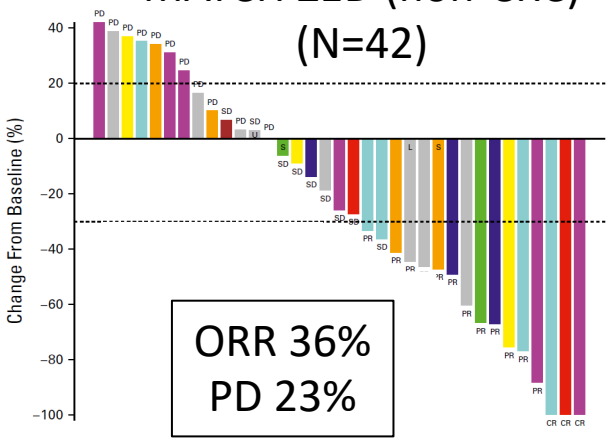
Nivolumab

Checkmate 142 (CRC)
(N=71)



ORR 31%
PD 28%

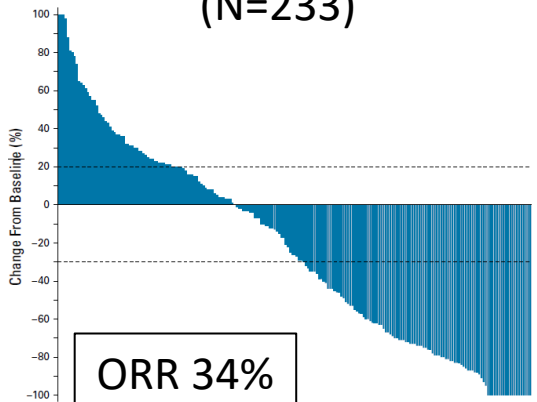
MATCH Z1D (non-CRC)
(N=42)



ORR 36%
PD 23%

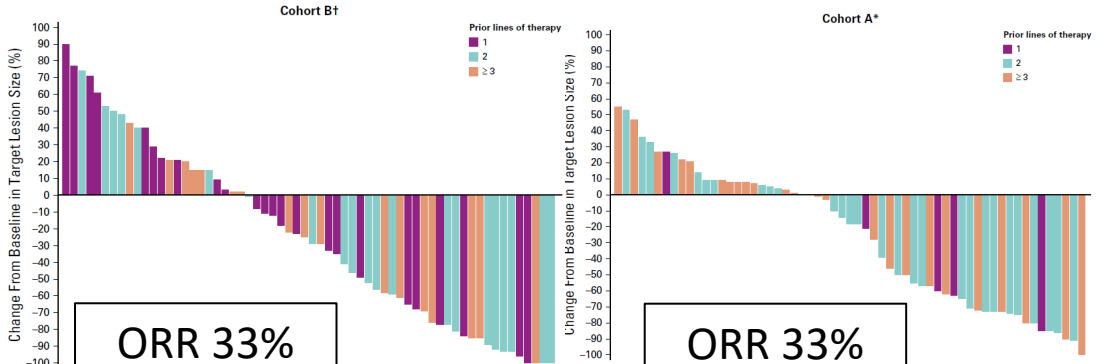
Pembrolizumab

Keynote 158 (non-CRC)
(N=233)



ORR 34%
PD 39%

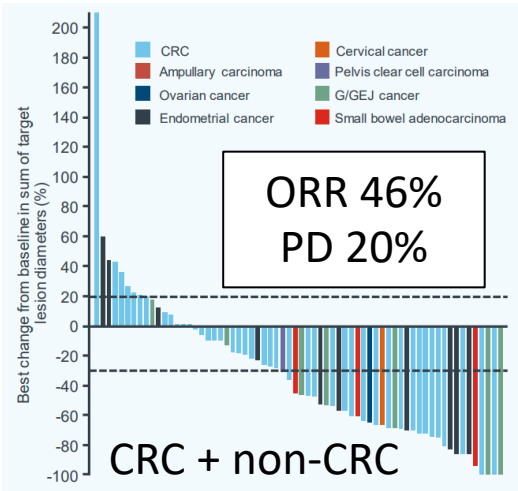
Keynote 164 (CRC)
(N=124)



ORR 33%
PD 46%

ORR 33%
PD 40%

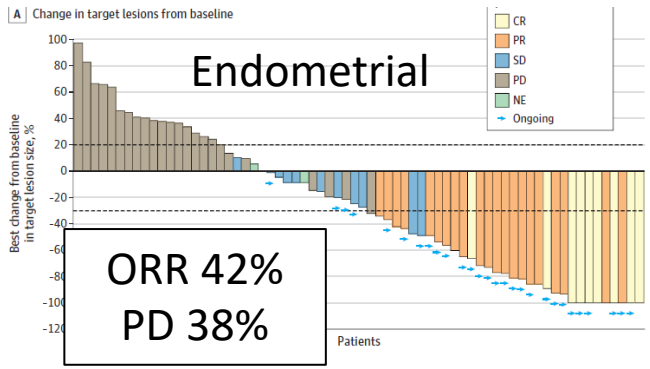
Tislelizumab



ORR 46%
PD 20%

CRC + non-CRC

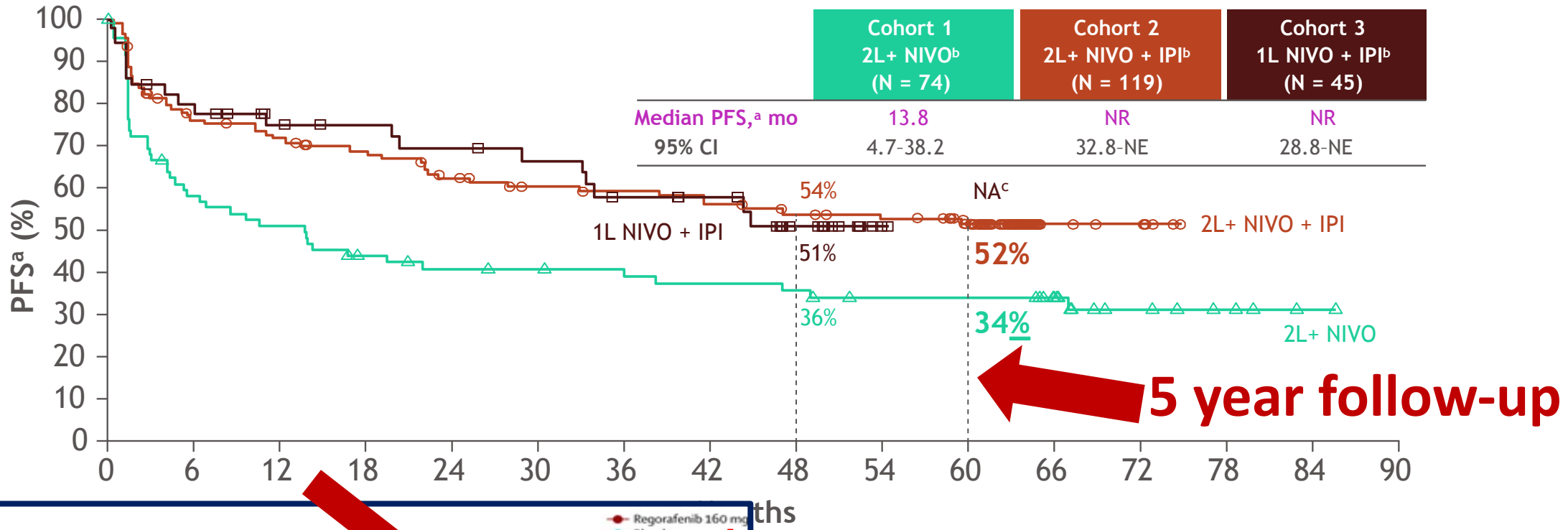
Dostarlimab



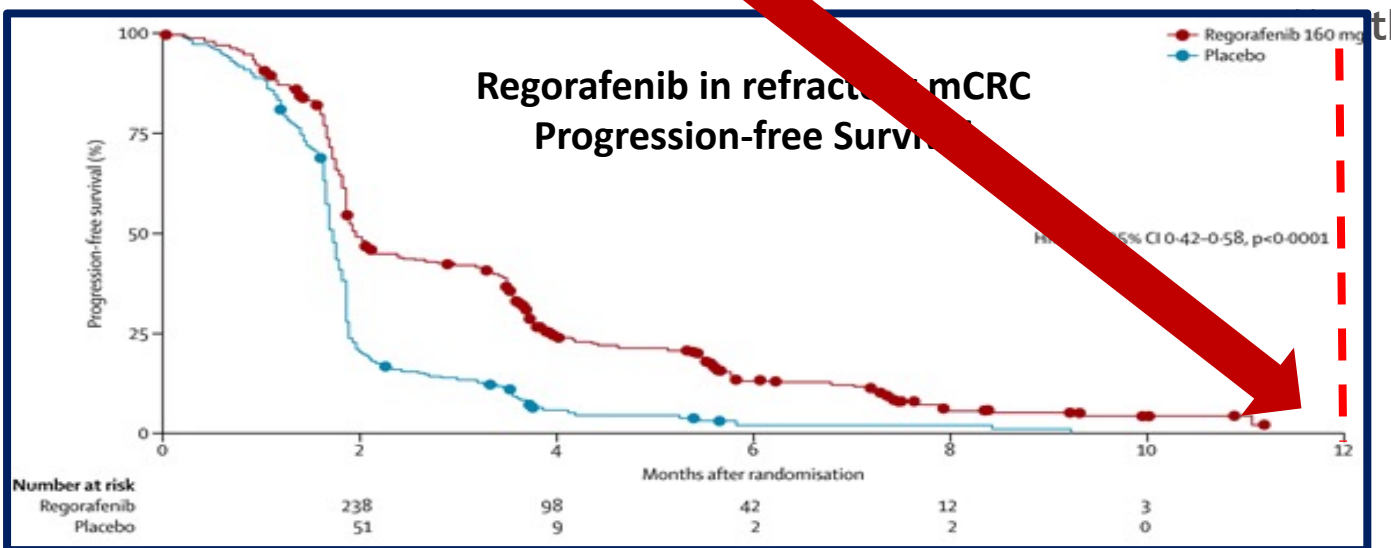
ORR 42%
PD 38%

Overman M, et al. *Lancet Onc*. 2017; Lee JW, et al. *JCO*. 2020; Marabelle A, et al. *JCO*. 2019; Azad S, et al. *JCO*. 2019; Oaknin et al. JAMA Onc 2020; Li et al ASCO 2021

CHECKMATE-142 Five Year Follow-up: Progression-free survival

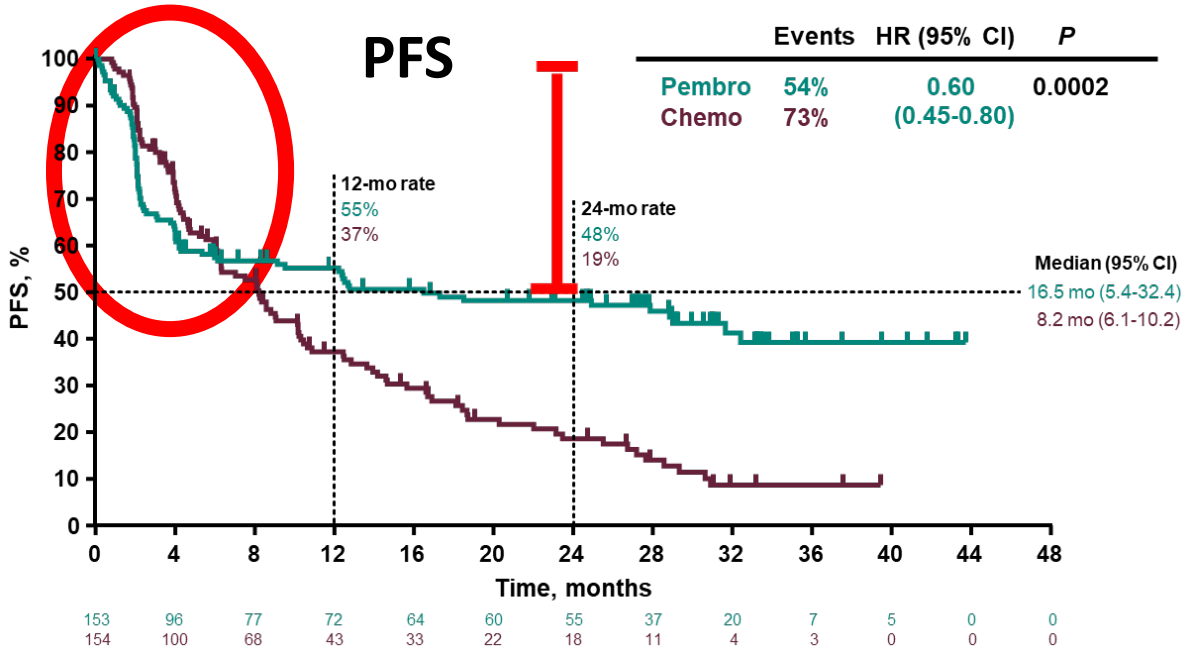


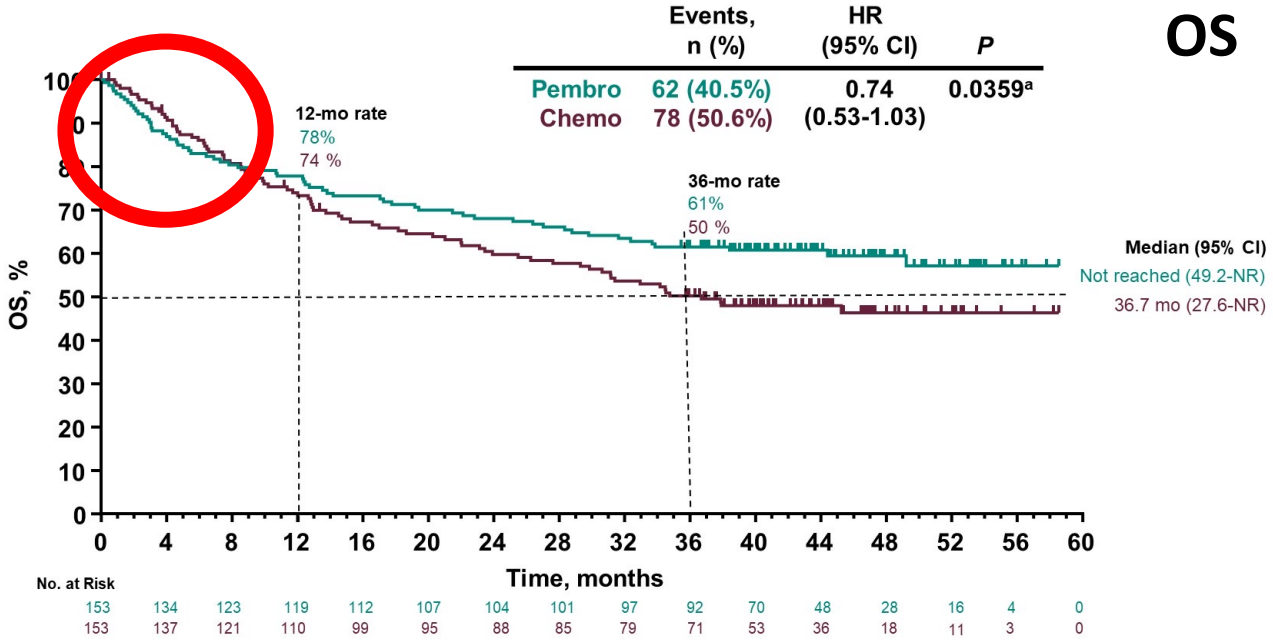
5 year follow-up



Overman et al. ASCO 2022

Keynote 177: 1st line pembrolizumab vs chemotherpay





	Pembrolizumab N = 153	Chemotherapy N = 154
Progressive disease	**45 (29.4)**	**19 (12.3)**

(chemotherapy arm PD: 12.3%)

Andre T et al. *NJEM 2020*

Ongoing Phase III Trials First Line dMMR mCRC

NRG GI004/SWOG 1610

dMMR/MSI-H mCRC without prior systemic treatment for metastatic disease (N = 211)

R

- **Atezolizumab (Arm 2: Single Agent)**
- **mFOLFOX6/Bevacizumab (Arm 1: Control)** — ARM closed 6/4/2020
- **mFOLFOX6/Bevacizumab + Atezolizumab (Arm 3: Combination)**

PI: (SWOG): Michael Overman, MD
PI: (NRG Oncology):Caio Max Sao Pedro Rocha LIma MD

Checkmate 8HW

- Recurrent or mCRC
- Known MSI-H/dMMR status by local testing
- ECOG performance status 0 or 1

R

N ≈ 494

- NIVO monotherapy
- NIVO+IPI
- Investigator's choice chemotherapy[b,c]

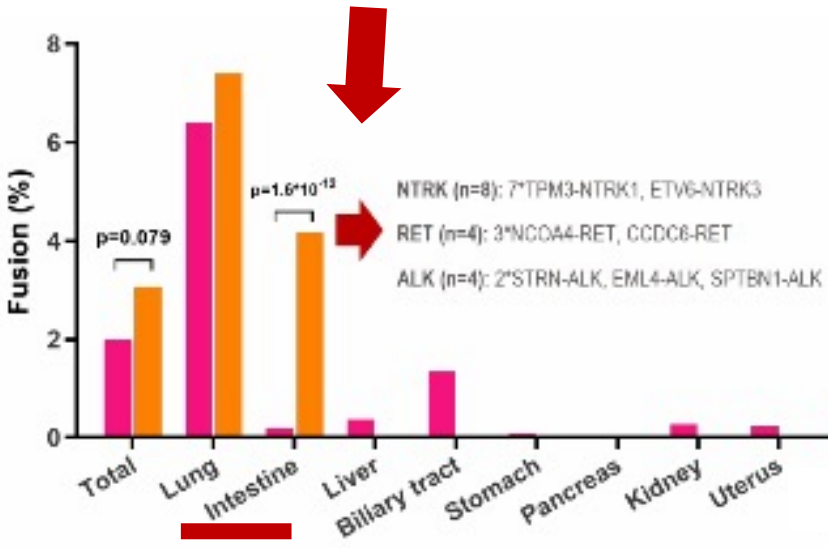
[a]ClinicalTrials.gov, NCT04008030.
[b]Only patients with 0 or 1 prior systemic treatments for mCRC can be randomized to the chemotherapy arm.

Rocha Lima et al. GI ASCO 2022; Abdullaev et al. GI ASCO 2021

Fusions in mCRC and RAS/RAF wt and MLH1 methylation

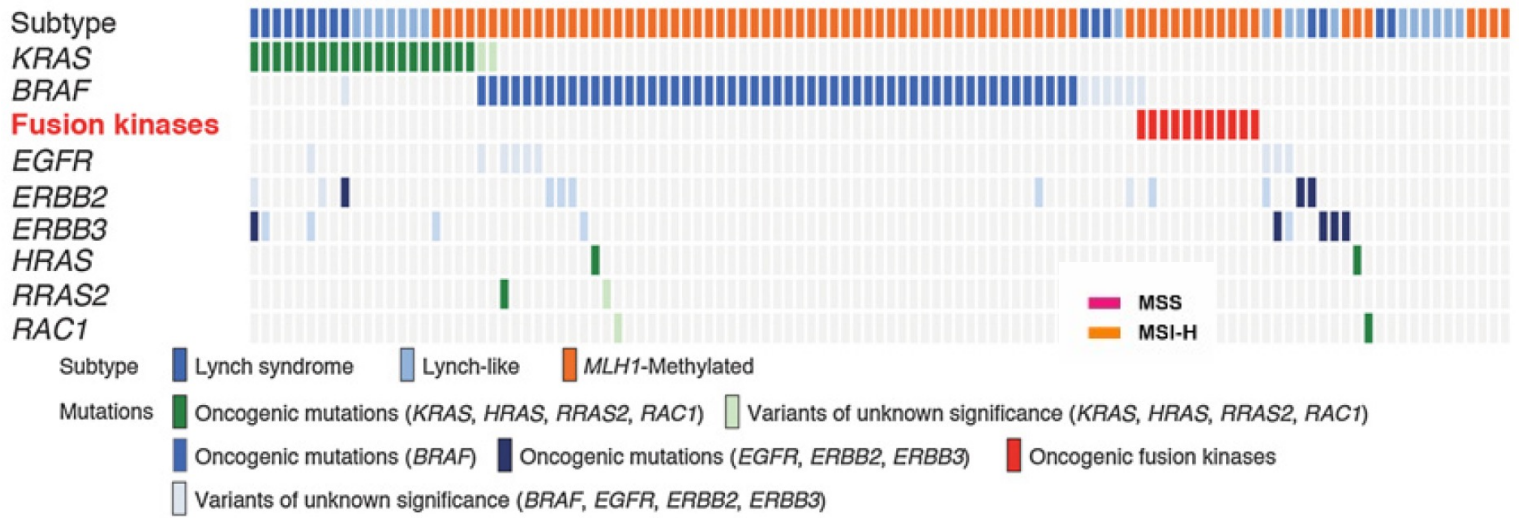
3DMed NGS tumor/nml
20,296 solid tumor specimens
4891 CRC specimens

- CRC fusion rate:
  - **MSS: 0.2%**
  - **MSI-H: 7.85%**



- 2,314 CRC from MSK-IMPACT NGS:
  - Fusion rate 5% of dMMR/MSI-H (0.4% of pMMR/MSS)
  - **42% of dMMR/MSI-H, RAS/RAF wt and MLH1 hypermethylation**

- 162 MSI-H CRC:
  - Fusion rate: 10%
  - **55% of dMMR/MSI-H, RAS/RAF wt and MLH1 hypermethylation**

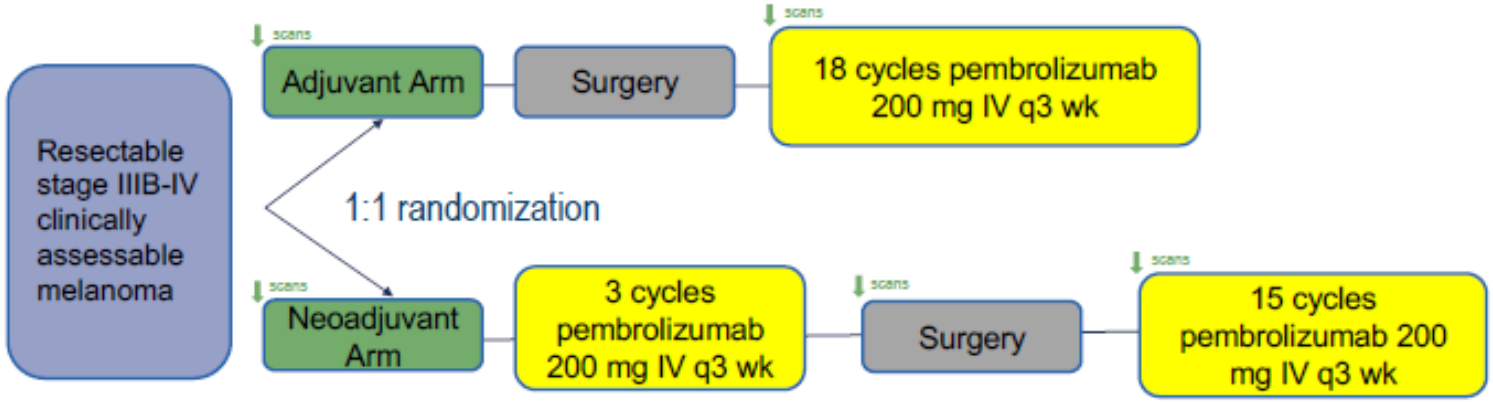


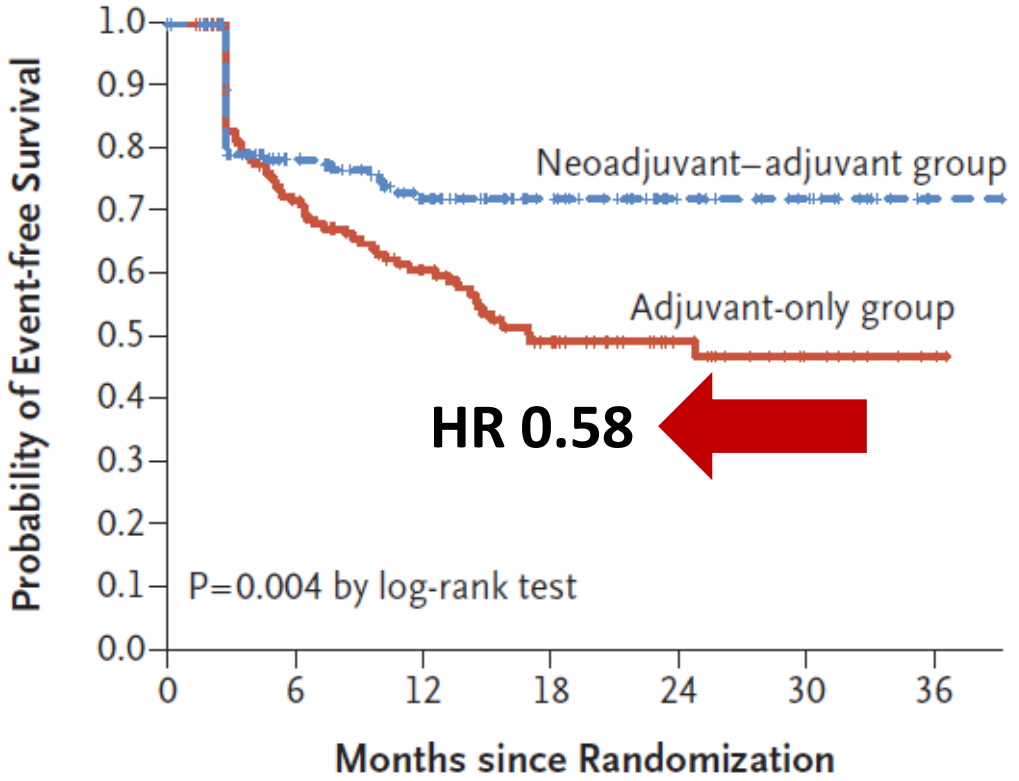
Cocco et al. Can Res 2019; Sato et al. CCR 2018, Fu et al. ESMO 2020 a83MO

Questions for dMMR localized Colorectal Cancer

- Is adjuvant or neoadjuvant the correct approach?
- Should organ preservation be our goal?
- Is chemotherapy needed?
- Is PD1 monotherapy enough?
- How do we do neoadjuvant PD1 therapy for dMMR colon cancer?
  - How best to clinically stage colon cancer?
  - How best to assess disease response?
  - How long to treat?

SWOG 1801: Melanoma



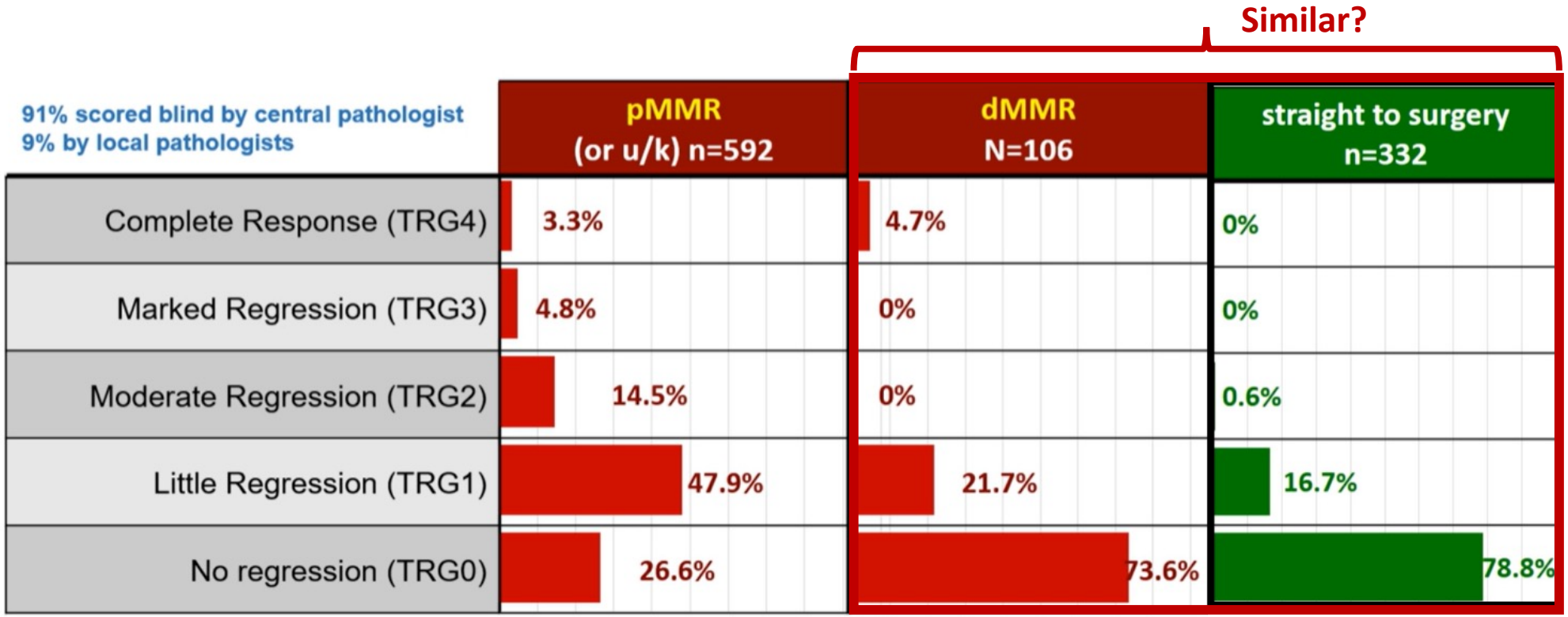


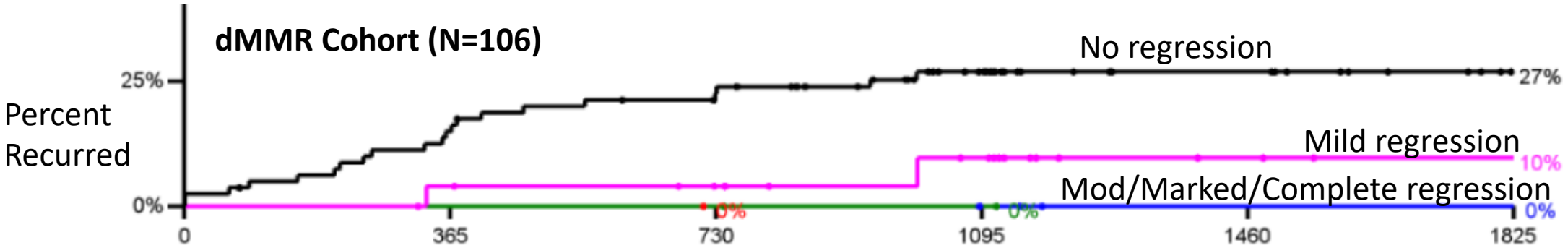
2 year EFS
72% vs 49%

Neoadjuvant arm:
pCR was 21%

Patel et al. ESMO 2022 and NJEM 2023

Neoadjuvant Therapy for dMMR Cancers: FOXTROT Trial





Seymour et al. ESMO 2019 and Morton et al. JCO 2023

The NEW ENGLAND JOURNAL of MEDICINE

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

Dostarlimab, anti-PD1

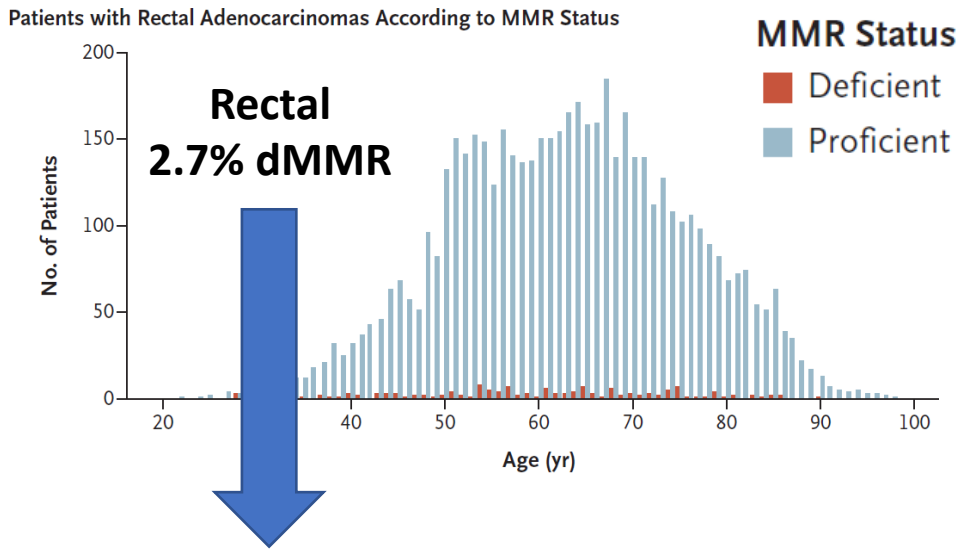
The New York Times

A Cancer Trial's Unexpected Result: Remission in Every Patient

The study was small, and experts say it needs to be replicated. But for 18 people with rectal cancer, the outcome led to "happy tears."

Dana-Farber/Brigham Women's
16,083 CRC endoscopic biopsies

- **5553 rectal**
- **10,530 colon**



Rectal
2.7% dMMR

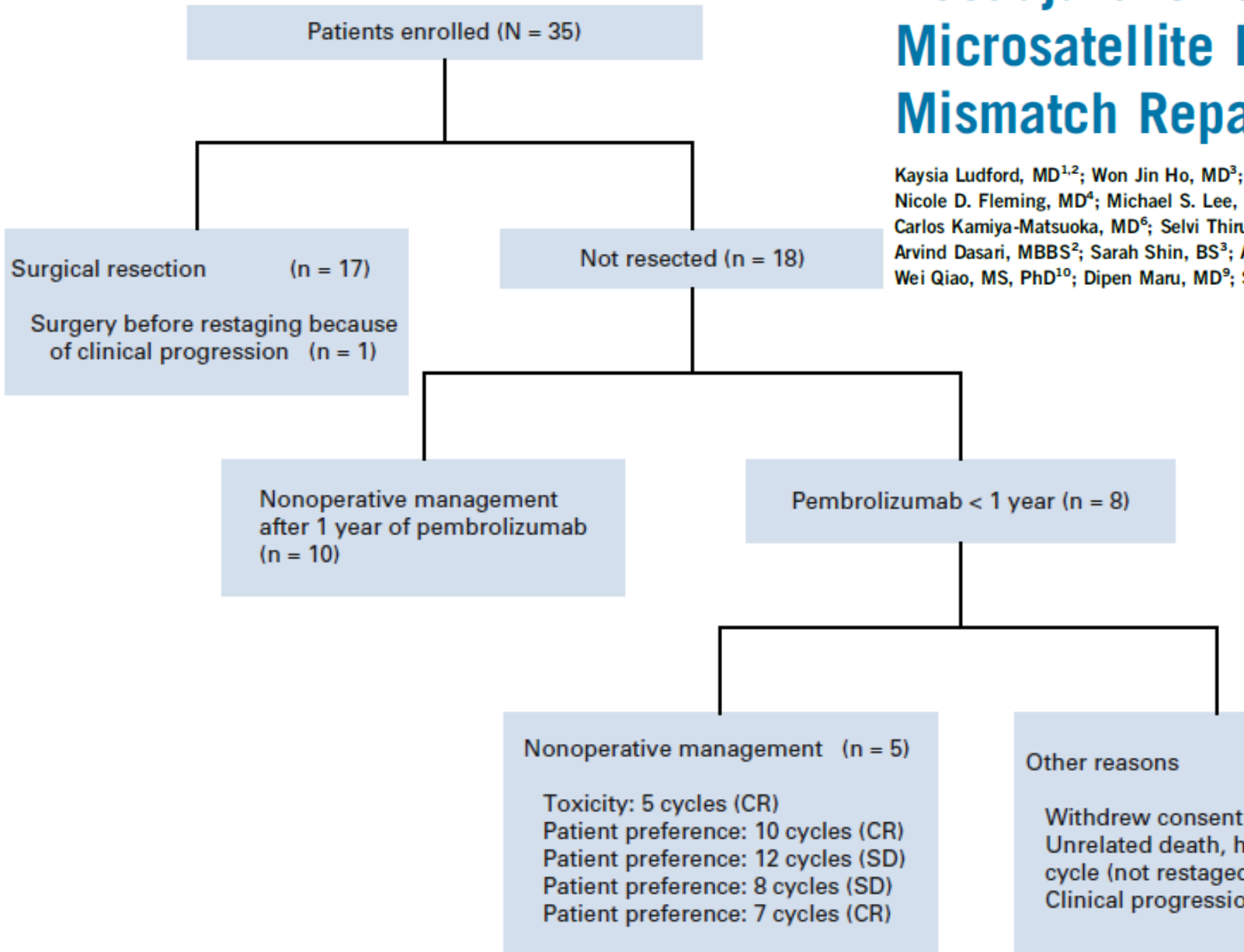
Colon
13.4% dMMR

5 fold greater rate!

Cercek et al. NEJM 2022, Papke NEJM 2022

Neoadjuvant Pembrolizumab in Localized Microsatellite Instability High/Deficient Mismatch Repair Solid Tumors

Kaysia Ludford, MD[1,2]; Won Jin Ho, MD[3]; Jane V. Thomas, MD[2]; Kanwal P.S. Raghav, MBBS[2]; Mariela Blum Murphy, MD[2]; Nicole D. Fleming, MD[4]; Michael S. Lee, MD[2]; Brandon G. Smaglo, MD[2]; Y. Nancy You, MD[5]; Matthew M. Tillman, MD[5]; Carlos Kamiya-Matsuoka, MD[6]; Selvi Thirumurthi, MD[7]; Craig Messick, MD[5]; Benny Johnson, DO[2]; Eduardo Vilar, MD, PhD[8]; Arvind Dasari, MBBS[2]; Sarah Shin, BS[3]; Alexei Hernandez, BS[3]; Xuan Yuan, MD[3]; Hongqui Yang[3]; Wai Chin Foo, MD[9]; Wei Qiao, MS, PhD[10]; Dipen Maru, MD[9]; Scott Kopetz, MD, PhD[2]; and Michael J. Overman, MD[2]

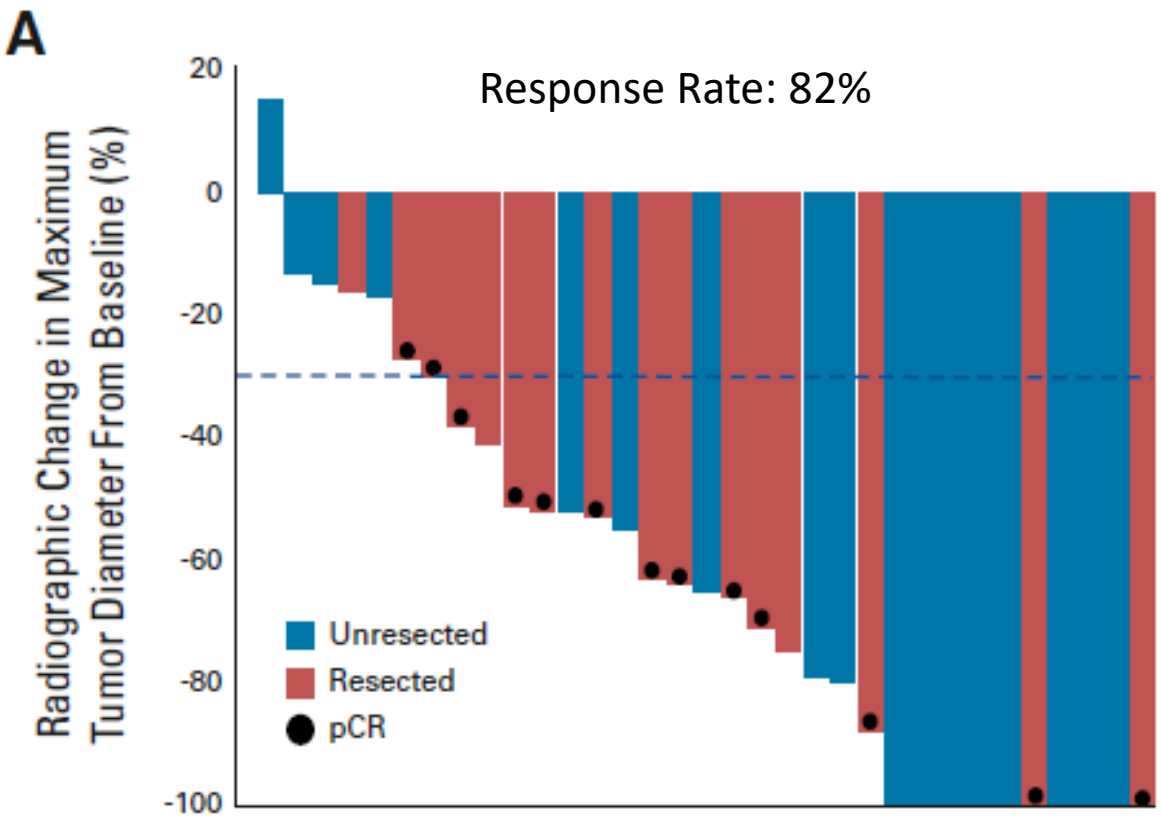


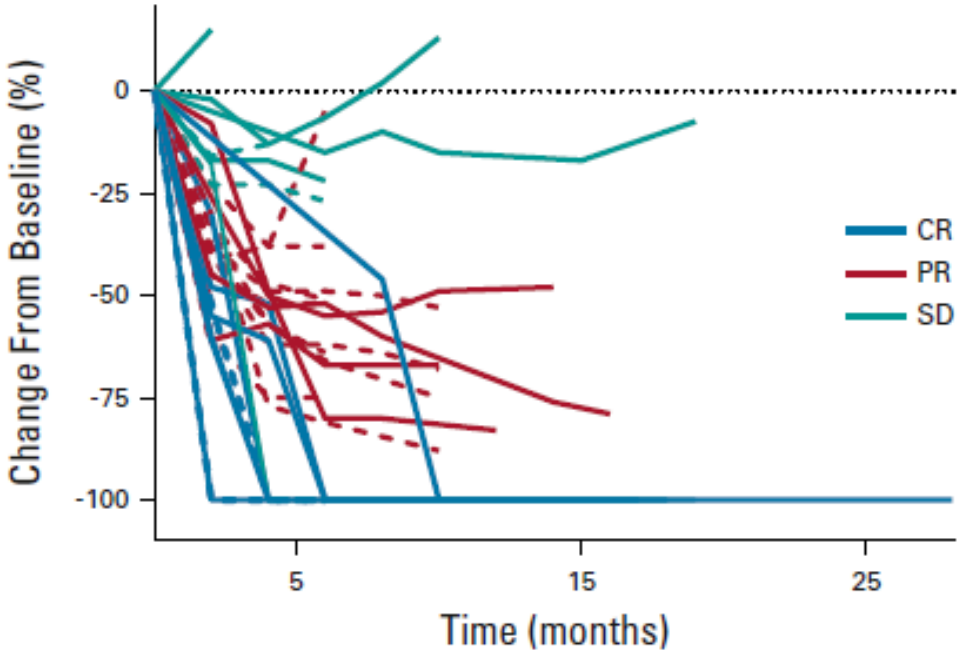
Tumor types	
Colon adenocarcinoma	19 (54)
Rectal adenocarcinoma	8 (23)
Pancreatic adenocarcinoma	2 (6)
Duodenal adenocarcinoma	2 (6)
Other[a]	4 (11)

[a]Other: gasrtic (n = 1), ampullary (n = 1), meningioma (n = 1), and endometrial (n = 1).

Ludford and Overman et al. JCO 2023

Neoadjuvant Pembrolizumab Efficacy

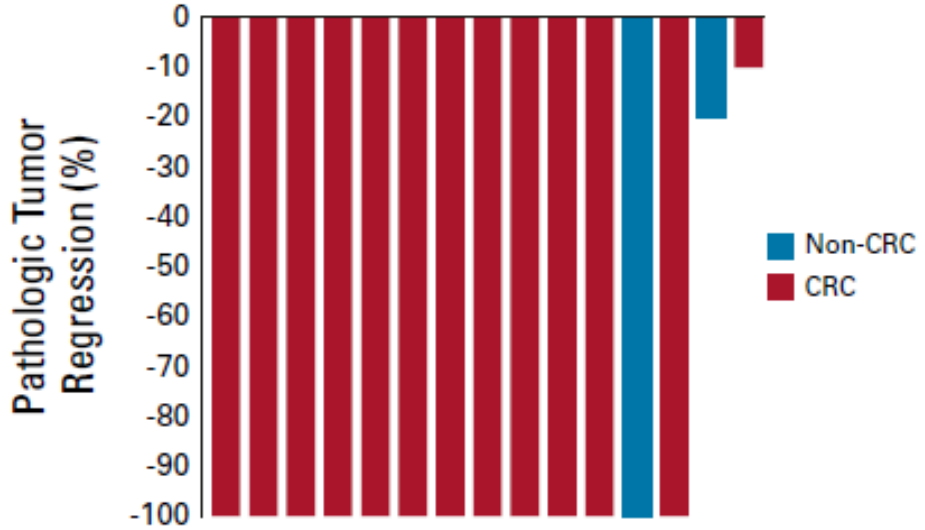




6 Progression events (N=35):

CRC N =27

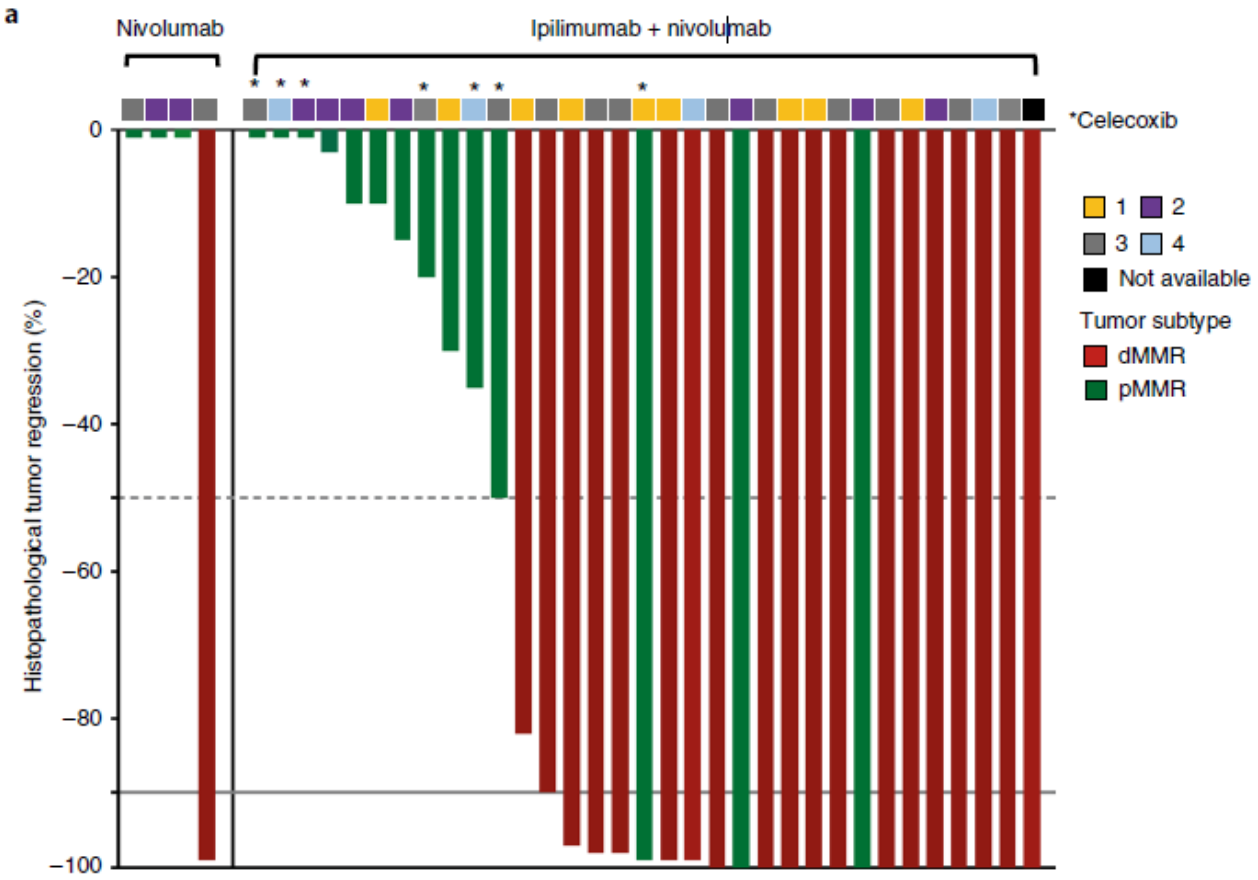
- 2 pancreas
- 2 CRC intrinsic:
  - Non luminal recurrence with peri anastomosis node progression
  - clinical PD (ypt4bN0)
- 2 CRC adaptive:
  - 6months PR (nodal response but luminal tumor progression)
  - 9m SD (NGS not consistent with dMMR)



Ludford and Overman et al. JCO 2023

NICHE Clinical Trial

- Median duration from first tx to surgery 32 days (IQR: 28-35)



NICHE-2 Clinical Trial

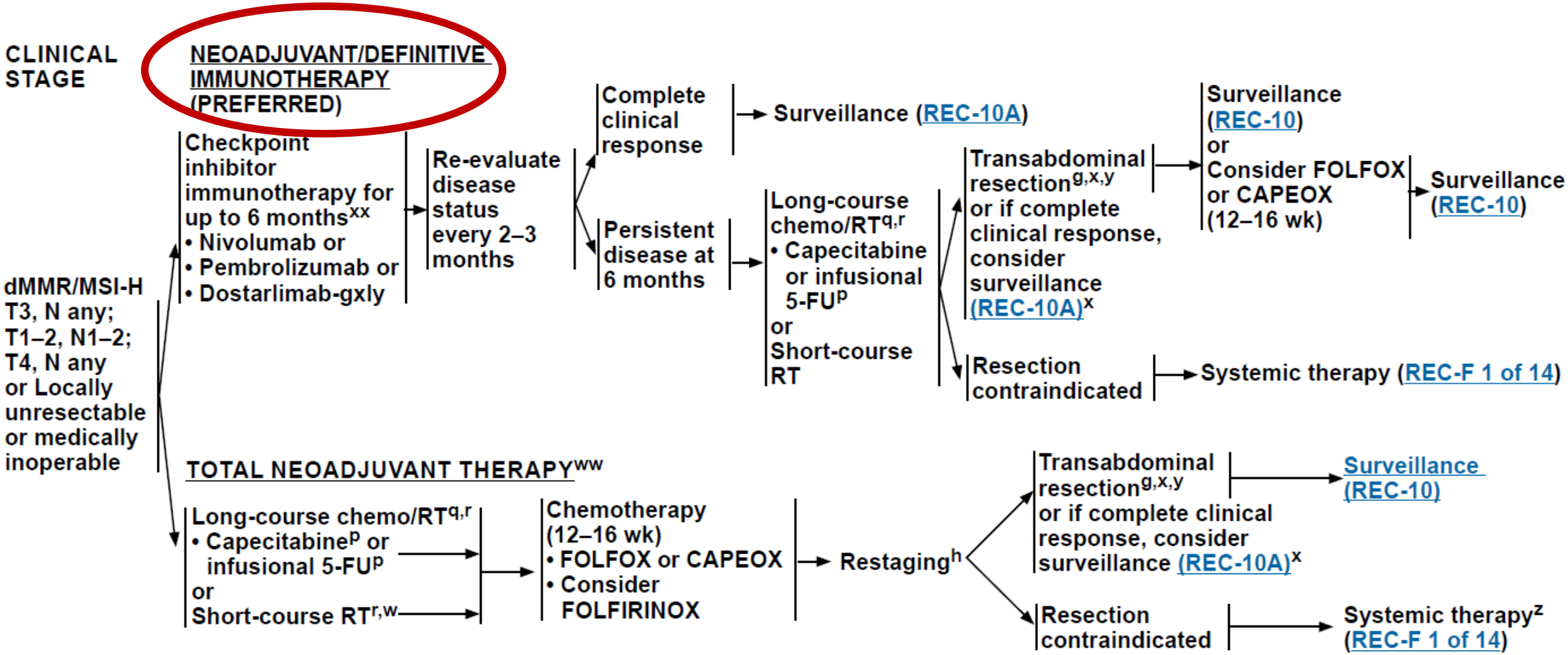
- **Ipilimumab 1mg/kg Day1**
- **Nivolumab 3mg/kg Day 1 + 15**

- Median duration from first tx to surgery 35 days

Path Response	Patients (N=107)
YES	**106 (99%)**
• Major (<10%)	102 (95%)
• **Complete (0%)**	**72 (67%)**
• Partial (10-50%)	4 (4%)
NO	**1 (1%)**

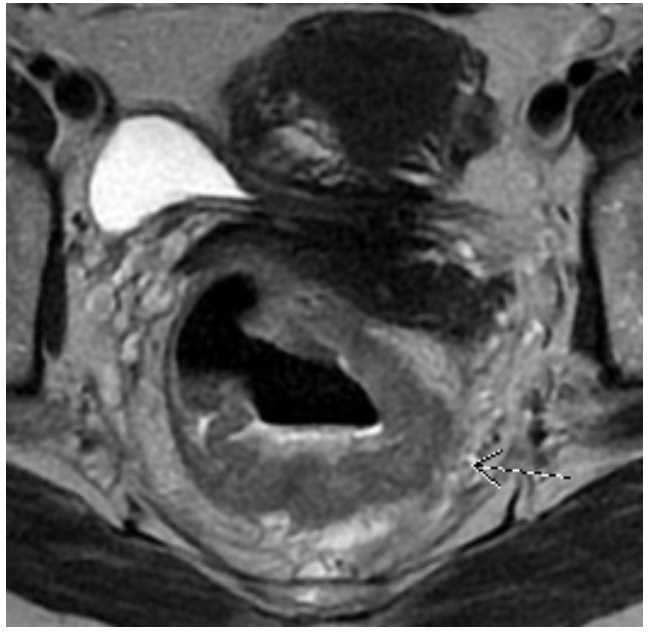
Chalabi et al Nat Med 2020 and ESMO 2022

NCCN Rectal update 4.25.2023

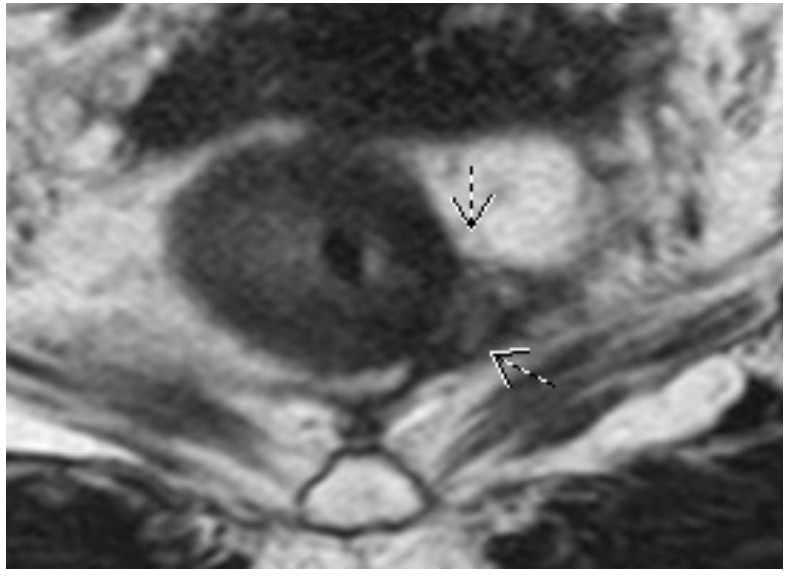


Rectal Case Presentation

- 51y/o Caucasian female with Lynch and mT3N1



Pembro x 6m



MRI Impression:

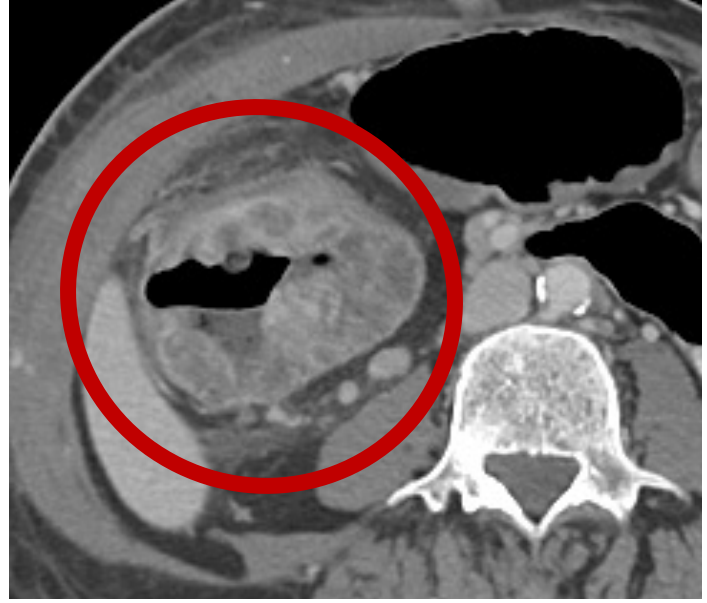
"Recurrent tumoral inseparable from the left levator. Residual tumor with significant fibrosis, (TRG2)"

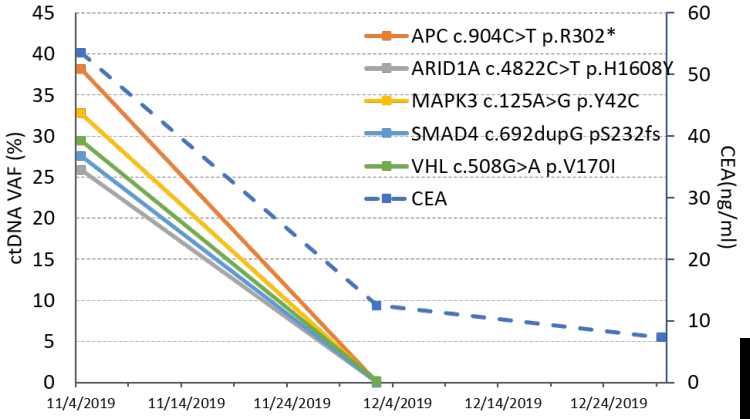
APR

C: Sigmoid colon, rectum and anus, abdominoperineal resection:
Chronic histiocytic inflammation, fibrosis and acellular mucin, negative for residual dysplasia and malignancy.
Treatment effect (fibrosis and acellular mucin) extends into perirectal soft tissue and focally at radial margin, without residual neoplastic cells.
No lymphovascular or perineural invasion identified.
Thirty-one lymph nodes, negative for malignancy; five with treatment effect without residual neoplastic cells (0/31).

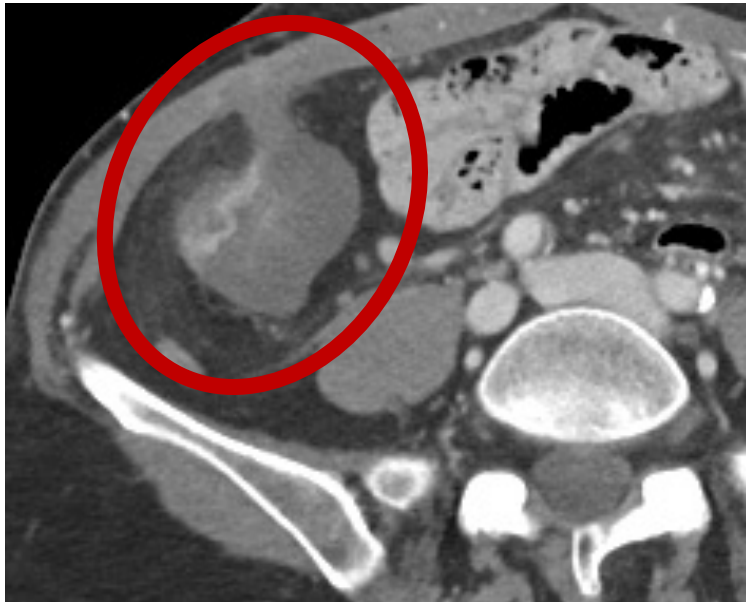
Colon Case Presentation

- 63y/o Caucasian female with locally advanced ascending sporadic dMMR colon cancer





Pembro x 6m



DIAGNOSIS

A. LYMPH NODE, HIGHEST MIDDLE COLIC, BIOPSY:
Fibroconnective tissue, negative for malignancy.
No lymph node tissue identified.

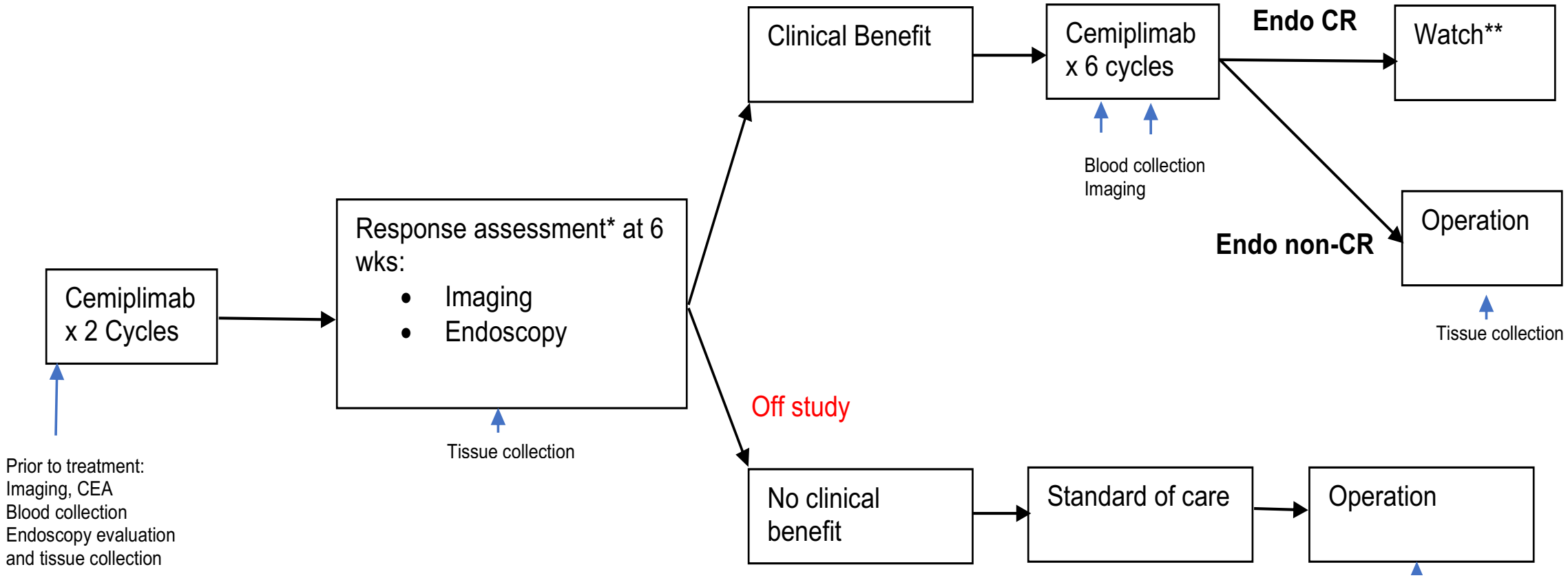
B. SOFT TISSUE, INFERIOR ABDOMINAL WALL, BIOPSY:
Fibroconnective tissue, negative for malignancy.

C. SOFT TISSUE, SUPERIOR ABDOMINAL WALL, BIOPSY:
Fibroconnective tissue, negative for malignancy.

D. SOFT TISSUE, DRAIN TRACT, BIOPSY:
Fibroconnective tissue, negative for malignancy.

E. TERMINAL ILEUM, ILEOSTOMY, APPENDIX, RIGHT COLON WITH ABDOMINAL WALL, RIGHT HEMICOLECTOMY WITH EN BLOC ILEOSTOMY AND ABDOMINAL WALL RESECTION:
Acellular mucin pools, without viable tumor cells.
No residual dysplasia or invasive carcinoma identified.
Abdominal wall with necrotic nodules without viable tumor. (Please see addendum report)
Thirty-four lymph nodes, negative for malignancy (0/34).
See CAP protocol below.

Phoenix Trial: Phase II trial of cemiplimab for the non-operative management of localized dMMR colon cancer



The week 6 tumor evaluation is designed to verify no luminal progression of tumor by endoscopy and all patients must have endoscopic response (complete or incomplete) on endoscopic assessment

MDACC trial
Overman PI

NCCN guidelines for mCRC

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2022
Colon Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS

Panitumumab[31]
(*KRAS/NRAS/BRAF* WT and left-sided tumors only)
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

Regorafenib
Regorafenib 160 mg PO daily on days 1–21[32]
or
First cycle: Regorafenib 80 mg PO daily on days 1–7, followed by 120 mg PO daily on days 8–14, followed by 160 mg PO daily on days 15–21[33]
Subsequent cycles: Regorafenib 160 mg PO daily on days 1–21
Repeat every 28 days

Trifluridine + tipiracil ± bevacizumab[e,34,35]
Trifluridine + tipiracil 35 mg/m² up to a maximum dose of 80 mg per dose (based on the trifluridine component)
PO twice daily days 1–5 and 8–12
Bevacizumab 5 mg/kg on days 1 and 15
Repeat every 28 days

Pembrolizumab[36] (dMMR/MSI-H only)
Pembrolizumab 2 mg/kg IV every 3 weeks
or Pembrolizumab 200 mg IV every 3 weeks
or Pembrolizumab 400 mg IV every 6 weeks

Nivolumab[37] (dMMR/MSI-H only)
Nivolumab 3 mg/kg every 2 weeks
or Nivolumab 240 mg IV every 2 weeks
or Nivolumab 480 mg IV every 4 weeks

Nivolumab + ipilimumab[38] (dMMR/MSI-H only)
Nivolumab 3 mg/kg (30-minute IV infusion) and ipilimumab 1 mg/kg (30-minute IV infusion) once every 3 weeks for four doses, followed by Nivolumab 3 mg/kg IV or nivolumab 240 mg IV every 2 weeks or Nivolumab 480 mg IV every 4 weeks

Dostarlimab-gxly[39] (dMMR/MSI-H only)
Dostarlimab-gxly 500 mg IV every 3 weeks for 4 doses followed by 1000 mg IV every 6 weeks

Trastuzumab[ff] + pertuzumab[40]
(HER2-amplified and *RAS* and *BRAF* WT)
Trastuzumab 8 mg/kg IV loading dose on day 1 of cycle 1, followed by 6 mg/kg IV every 21 days
Pertuzumab 840 mg IV loading dose on day 1 of cycle 1, followed by 420 mg IV every 21 days

Trastuzumab[ff] + lapatinib[41]
(HER2-amplified and *RAS* and *BRAF* WT)
Trastuzumab 4 mg/kg IV loading dose on day 1 of cycle 1, followed by 2 mg/kg IV weekly
Lapatinib 1000 mg PO daily

Trastuzumab[ff] + tucatinib[42]
(HER2-amplified and *RAS* and *BRAF* WT),
Trastuzumab 8 mg/kg IV loading dose on day 1 of cycle 1, followed by 6 mg/kg IV every 21 days
Tucatinib 300mg PO twice daily

Dual HER2 Inhibition

Fam-trastuzumab deruxtecan-nxki[43]
Fam-trastuzumab deruxtecan-nxki 6.4 mg/kg IV on day 1
Repeat every 21 days

HER2 Antibody-drug Conjugate

Encorafenib + cetuximab[44-46]
(*BRAF* V600E mutation positive)
Encorafenib 300 mg PO daily
Cetuximab 400 mg/m² followed by 250 mg/m² weekly

Encorafenib + panitumumab[44-46]
(*BRAF* V600E mutation positive)
Encorafenib 300 mg PO daily
Panitumumab 6 mg/kg IV every 14 days

Larotrectinib[47] (*NTRK* gene fusion-positive)
100 mg PO twice daily

Entrectinib[48] (*NTRK* gene fusion-positive)
600 mg PO once daily

Selpercatinib[49] (*RET* gene fusion-positive)
Patients ≥50 kg: 160 mg PO twice daily
Patients <50 kg: 120 mg PO twice daily

[e] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[ff] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

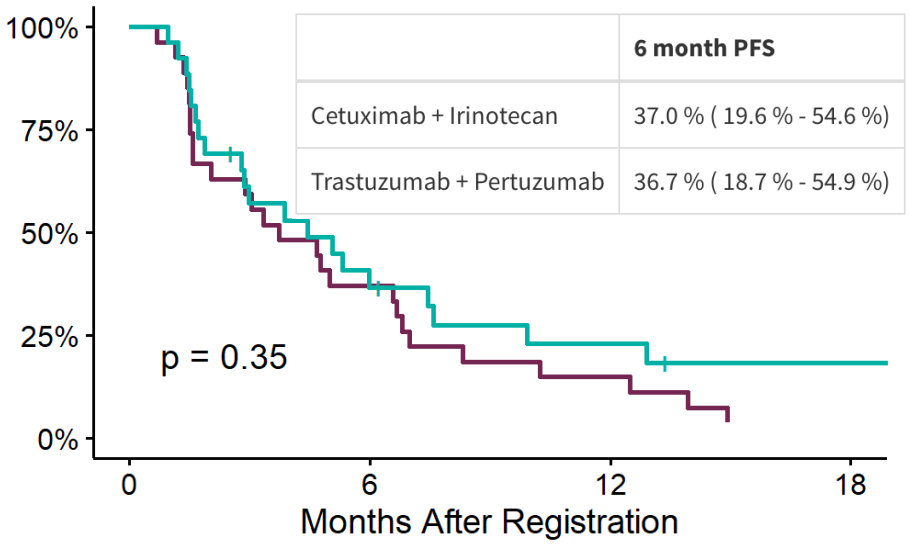
References

Her2 Targeting in mCRC

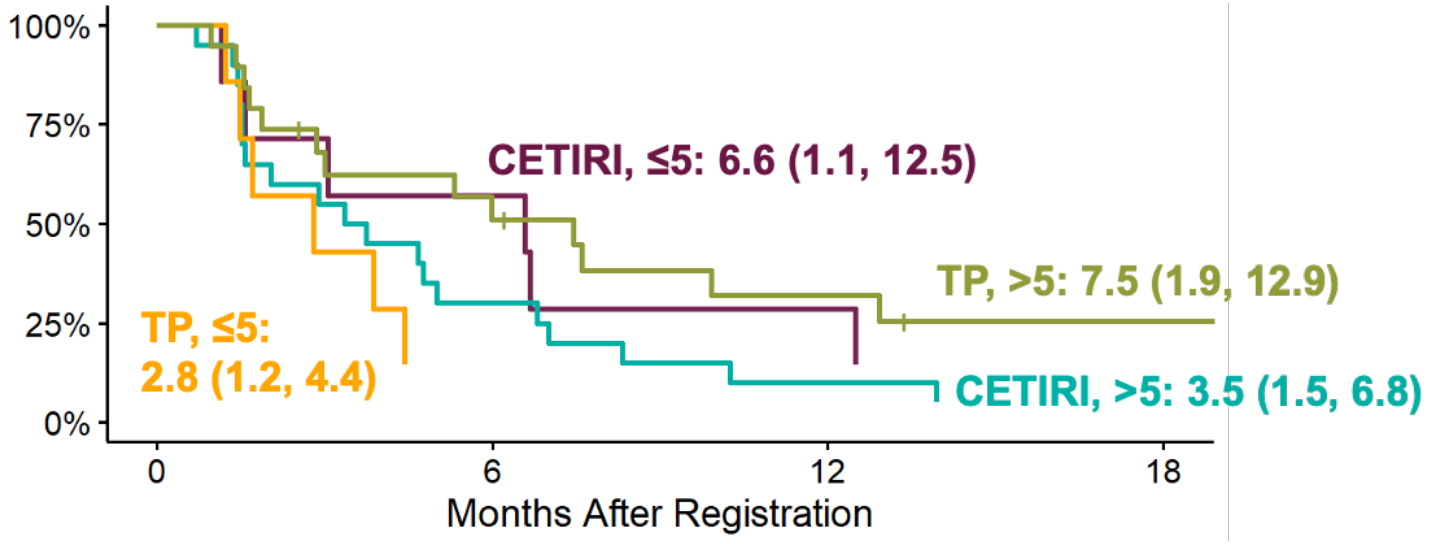
Regimen	Trial (n) – year	ORR	PFS	OS	Most common Grade 3+ AEs
Trastuzumab + lapatinib	HERACLES-A (n=32) – 2016	28%	4.7m	10m	Fatigue 16% Decreased LVEF 6%
Trastuzumab + pertuzumab	MyPathway (n=84; 57 evaluable) – 2019	32%	2.9m	11.5m	Hypokalemia 5% Abdominal pain 5%
Pertuzumab and T-DM1	HERACLES-B (n=31) – 2020	9.7%	4.1m	Not reported	Thrombocytopenia 7%
Trastuzumab deruxtecan	DESTINY-CRC01 (N=78; 53 HER2+) – 2021	45.3%	6.9m	15.5m	Neutropenia 15% Anemia 13%
Trastuzumab + tucatinib	MOUNTAINEER (n=117) - 2022	38.1%	8.2m	24.1m	Hypertension 7% Diarrhea 3.5%

Wu et al. ASCO 2023

S1613 (Efficacy)



	6 month PFS
Cetuximab + Irinotecan	37.0 % (19.6 % - 54.6 %)
Trastuzumab + Pertuzumab	36.7 % (18.7 % - 54.9 %)

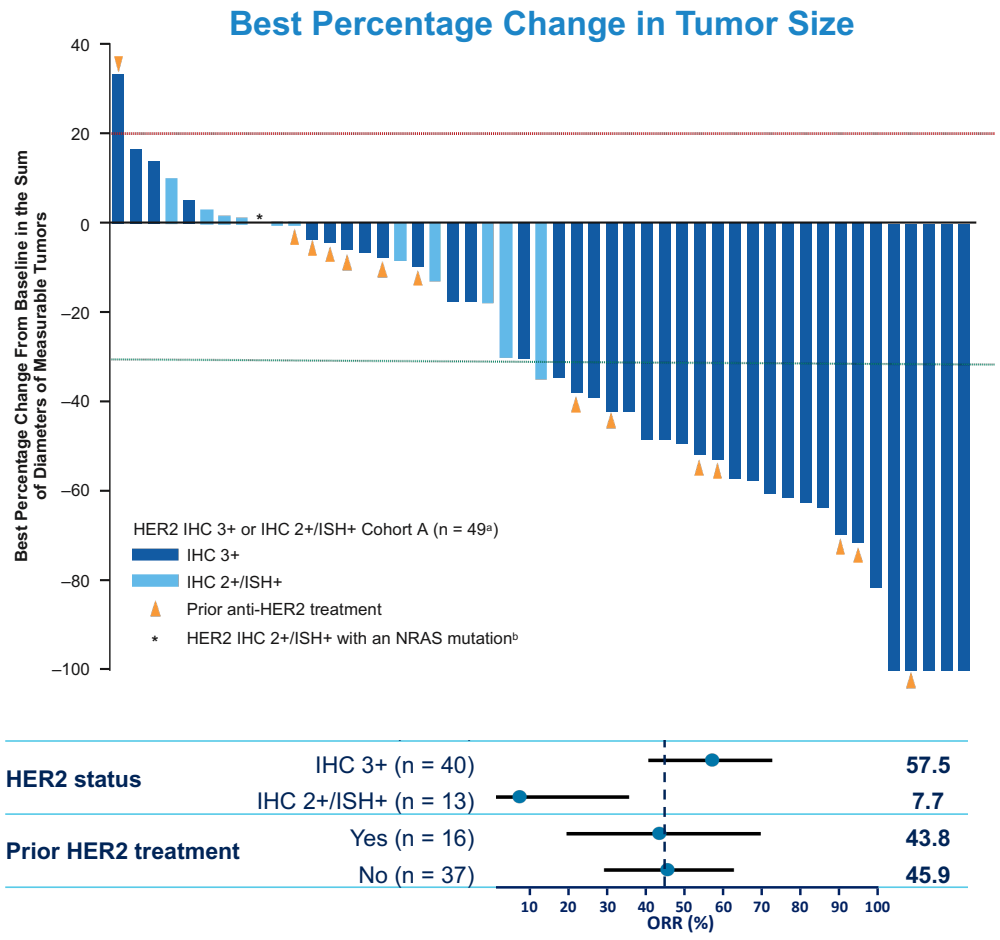


Endpoint	TP					CETIRI					Crossover TP
	All	HCR		Piri		All	HCR		Piri		
		> 5	≤ 5	Yes	No		> 5	≤ 5	Yes	No	
N	26	19	7	11	15	27	20	7	13	14	20
mPFS[1]	4.4	7.5	2.8	3.0	7.5	3.7	3.5	6.6	3.1	4.7	5.7
6mo-PFS[2]	37	51	0	18	51	37	30	57	31	43	48
ORR[2]	31	42	0	27	33	24	21	33	15	33	29
mOS[1]	NR	NR	32.3	20.0	NR	24.7	24.8	23.2	17.5	33.8	NA
2yr-OS[2]	64%	62	71	49	77	52%	61	36	30	64	NA

Raghav GI ASCO (2023)

DESTINY-CRC01: Trastuzumab Deruxtecan (T-DXd)

	HER2 IHC 3+ or IHC 2+/ISH+ Cohort A n = 53
Confirmed ORR by ICR, n (%)	24 (45.3) [95% CI, 31.6-59.6]
CR	0
PR	24 (45.3)
SD	20 (37.7)
PD	5 (9.4)
NE[a]	4 (7.5)
DCR, % (95% CI)	83.0 (70.2-91.9)
Median DOR (95% CI), months	7.0 (5.8-9.5)
Median treatment duration (95% CI), months	5.1 (3.9-7.6)
Median PFS (95% CI), months	6.9 (4.1-8.7)
Median OS (95% CI), months	15.5 (8.8-20.8)

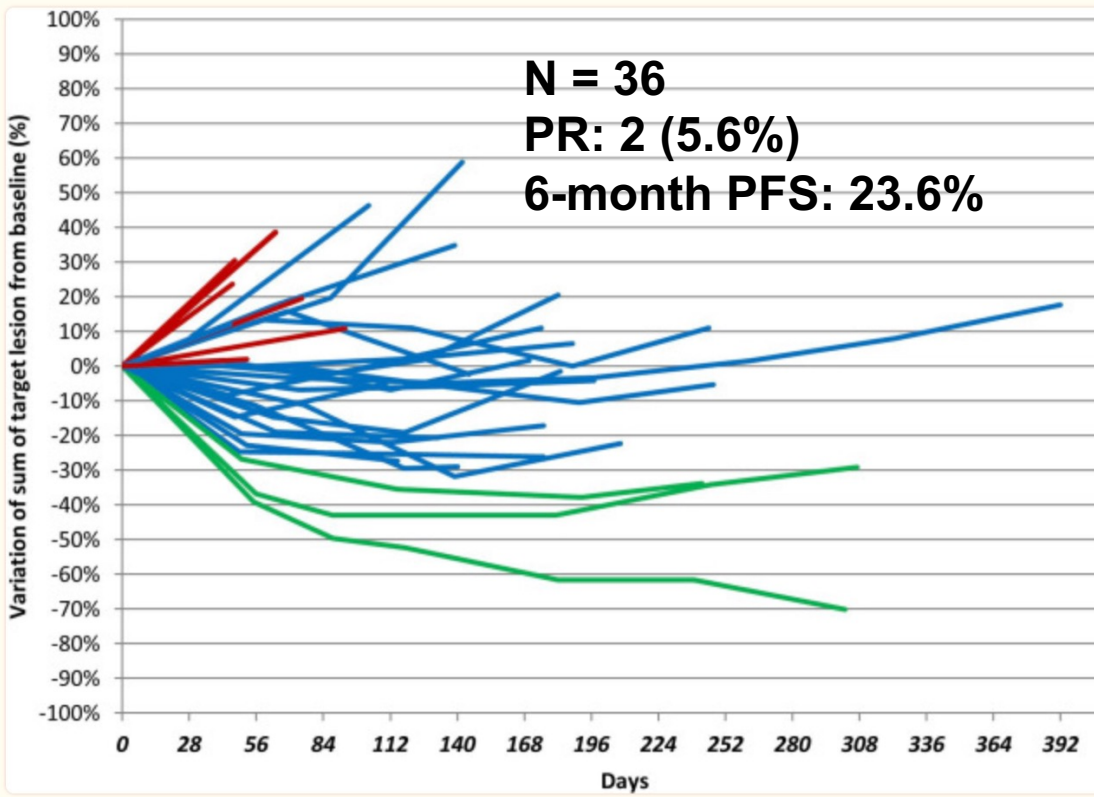


Yoshino et al. Nature Com 2023

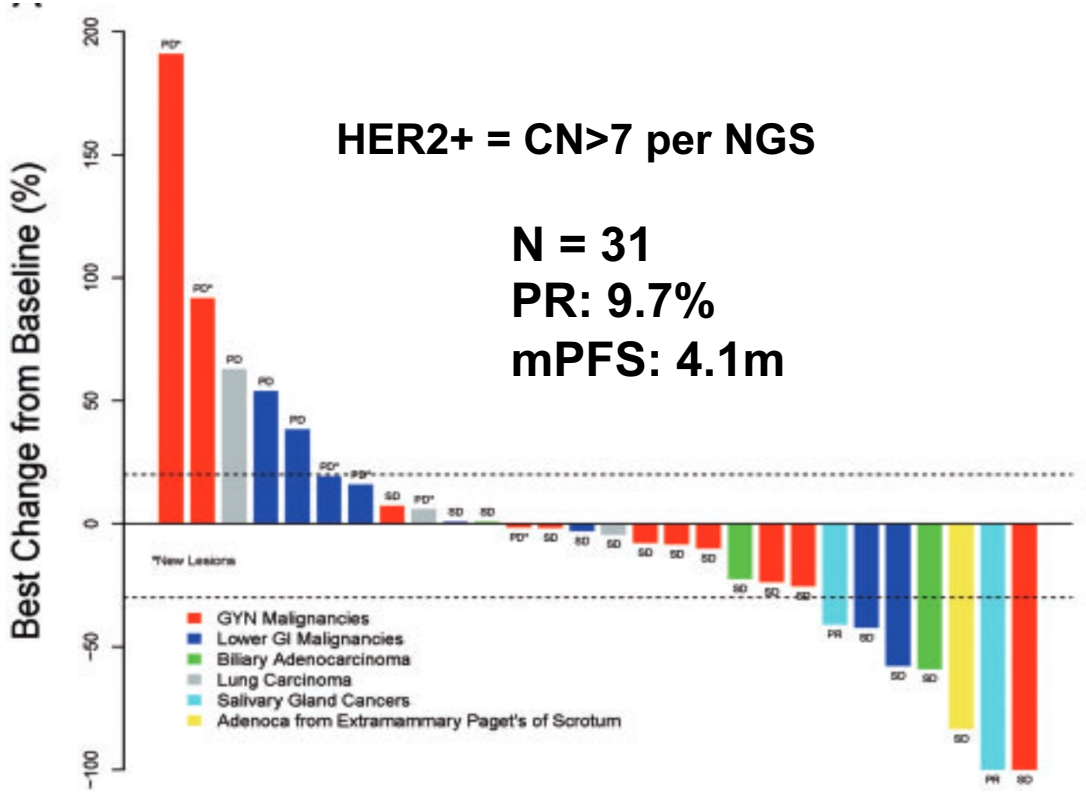
T-DM1: ado-trastuzumab emtansine

Limited Activity in Refractory HER-2 Positive mCRC

HERACLES-B Trial



NCI-MATCH trial (EAY131) Subprotocol Q



Sartore-Bianchi ESMO Open (2020), Jhaveri AOO (2019)

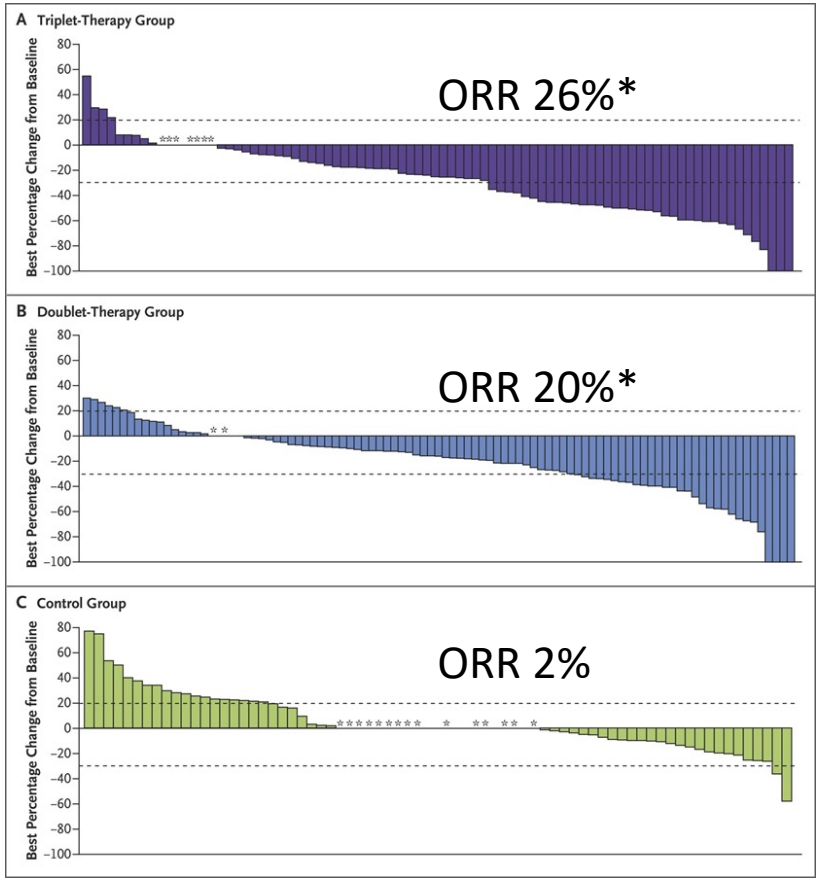
BEACON phase III: BRAF + anti-EGFR therapy

Treatment refractory, *BRAF*^{V600E}, *RAS*^{WT} metastatic CRC

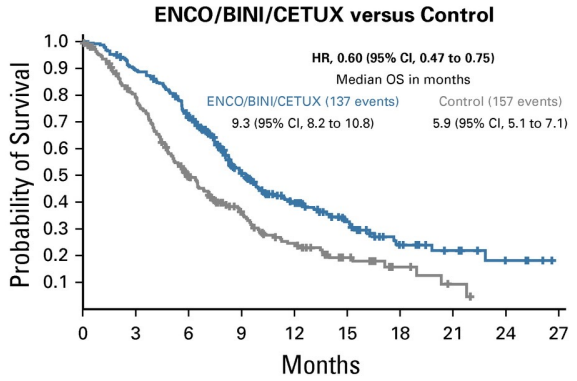
- **Encorafenib + cetuximab + binimetinib**
- **Encorafenib + cetuximab**
- **Irinotecan + cetuximab**

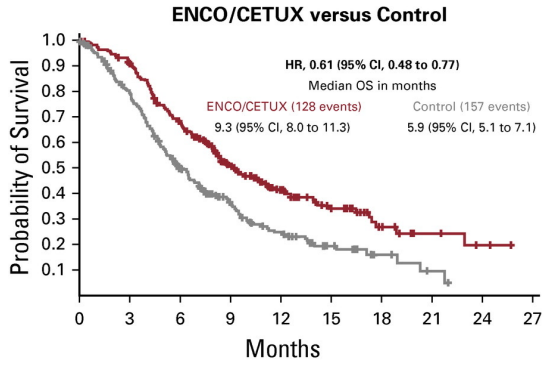
N=665 (1:1:1 randomization)

Encorafenib 300 mg daily
Binimetinib 45 mg twice daily
Cetuximab 2500 mg/m^2 every eek



*denotes statistical significance relative to control arm





Kopetz S et al, NEJM 2019

BREAKWATER Frontline Trial and Rationale

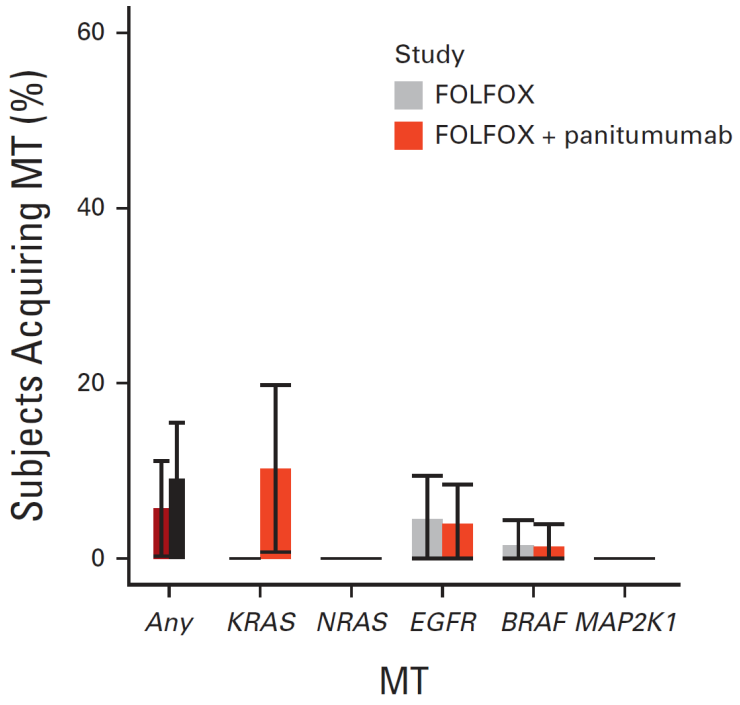
NCT04607421

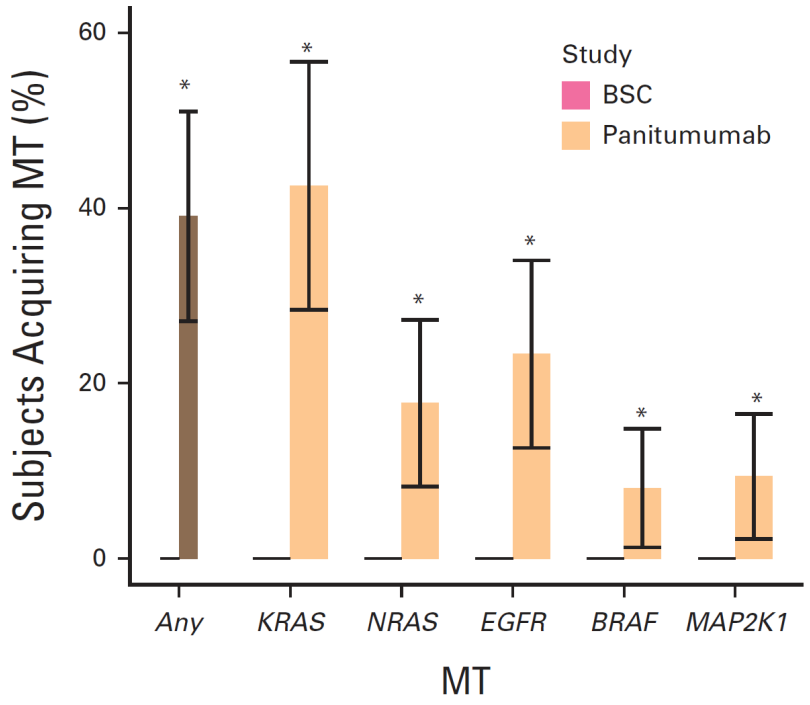
- *BRAF*^{V600E} metastatic CRC
- No prior systemic therapy for metastatic disease

N = 290 per arm

Randomize 1:1:1

- Standard chemotherapy
- Encorafenib + cetuximab
- FOLFOX + encorafenib + cetuximab

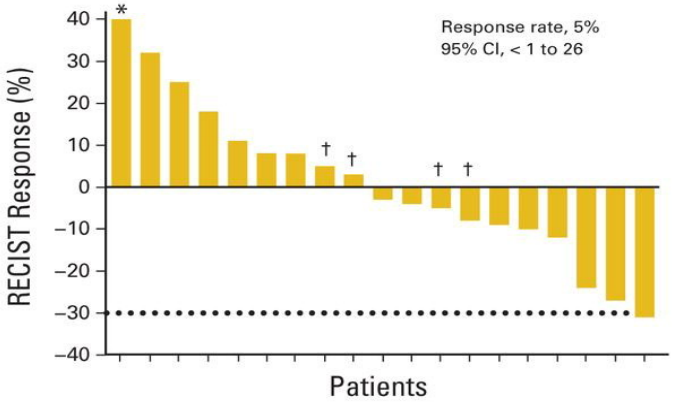




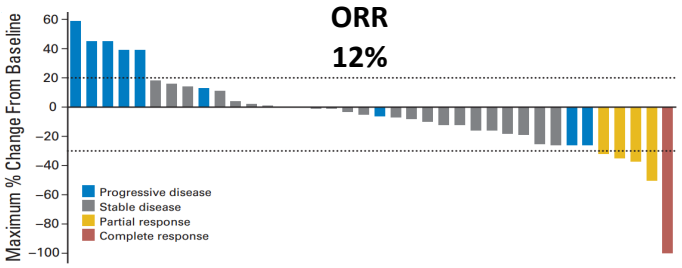
Parseghian et al. JCO 2023

Tumor Agnostic BRAF^{V600E} for CRC?

Vemurafenib



Dabrafenib + trametinib



FDA grants accelerated approval to dabrafenib in combination with trametinib for unresectable or metastatic solid tumors with BRAF V600E mutation

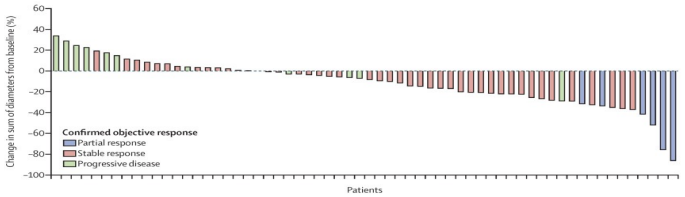
On June 22, 2022, the Food and Drug Administration granted accelerated approval to dabrafenib in combination with trametinib for the treatment of adult and pediatric patients ≥ 6 years of age with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. Dabrafenib in combination with trametinib is not indicated for patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition. Dabrafenib is not indicated for patients with wild-type BRAF solid tumors.

	N	ORR (%)	mPFS (months)	mOS (months)
Vemurafenib	21	5	2.1	7.7
Dabrafenib	11	11	NA	NA
Encorafenib	18	0	4	NA
Dabrafenib + trametinib	43	12	3.5	NA

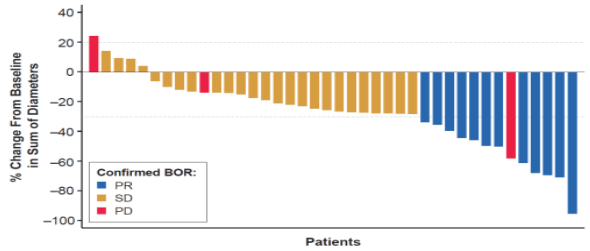
Kopetz S et al JCO 2015; Corcoran RB et al JCO 2015; Falchook GS et al 2012; Gomez-Roca CA et al Annals Oncol 2014

Targeting KRAS^{G12C} +/- EGFR in pts w/ *KRAS^{G12C}* CRC

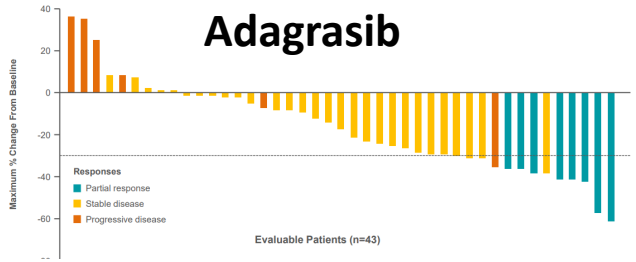
Sotorasib



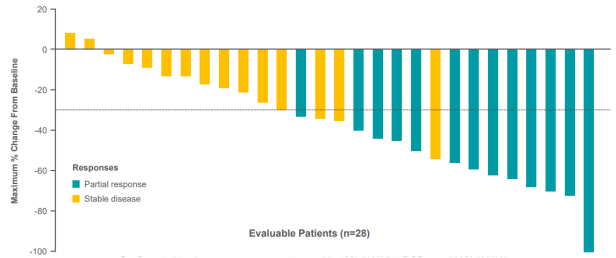
Sotorasib + panitumumab



Adagrasib



Adagrasib + cetuximab



	Sotorasib	Sotorasib + panitumumab
N	62	40
ORR (%)	10	30
DCR (%)	82	93
PFS (m)	4.0	5.7
OS (m)	10.6	NE
DoR (m)	4.2	4.4

	Adagrasib	Adagrasib + cetuximab
N	43	28
ORR (%)	19	46
DCR (%)	86	100
PFS (m)	5.6	6.9
OS (m)	19.8	13.4
DoR (m)	4.3	7.6

Fakih MG et al Lancet Oncol 2022; Kuboki Y et al ESMO 2022; Klempner S et al ESMO 2022

CodeBreak 101: Targeting KRAS G12C Plus Chemotherapy

Key eligibility criteria

- *KRAS* G12C–mutated mCRC, identified through local molecular testing
- No dose reduction or intolerance to prior $KRAS^{G12C}$ inhibitor treatment (Part 1 only)
- $KRAS^{G12C}$ inhibitor-naive (Part 2 only)
- ≥ 1 prior treatment for advanced disease
- No dose reduction or delay due to 5-FU or irinotecan toxicity if previously received

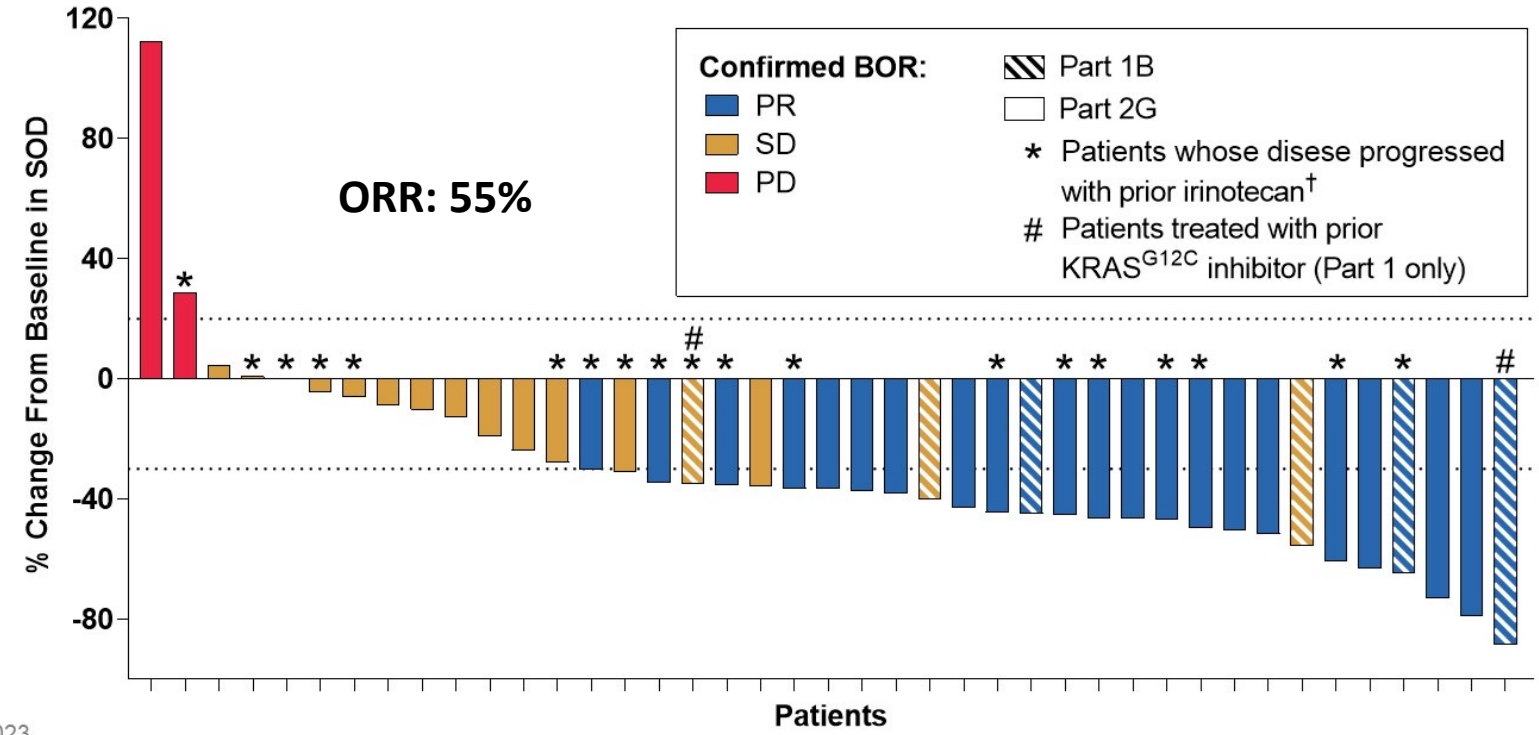
→ **Part 1: Cohort B dose exploration† (N = 6)**

Dose Level 1:
Sotorasib: 960 mg PO daily
+
Panitumumab: 6 mg/kg IV Q2W
+
FOLFIRI IV Q2W

→ **No DLTs were observed, and Dose Level 1 was declared the RP2D‡**

→ **Part 2: Cohort G dose expansion† (N = 40)**

Sotorasib: 960 mg PO daily
+
Panitumumab: 6 mg/kg IV Q2W
+
FOLFIRI IV Q2W



Data cutoff, April 13, 2023.

Hong et al. ASCO 2023

Outlook for targeting $KRAS^{mut}$ mCRC

Mutant-specific KRAS inhibitors			
Programs (company)	**IND**	**Target**	**Phase**
Sotorasib/AMG 510 (Amgen)		$KRAS^{G12C}$	Approved
Adagrasib/MRTX849 (Mirati)			Clinical
D-1553 (InventisBio)			
JDQ443 (Novartis)			
RG6330/GDC-6036 (Roche)			
LY3537982 (Eli Lilly)			
BI 1823911 (Boehringer Ingelheim)			
JAB-21822 (Jacobio)			
GFH925 (GenFleet)			
GH35 (Genhouse Bio)			
MRTX1133 (Mirati)		$KRAS^{G12D}$	Preclinical
KRASG12D1-3 (Boehringer Ingelheim)			
RAS(ON) G12D (Revolution Medicines)			
RAS(ON) G13C (Revolution Medicines)		$KRAS^{G13C}$	

Pan-(K)RAS inhibitors			
Programs (company)	**IND**	**Target**	**Phase**
RSC-1255 (RasCal Therapeutics)		Pan-RAS	Clinical
BI-pan-KRAS1-4 inhibitors (Boehringer Ingelheim)		Pan-KRAS: $KRAS^{G12D/V}$, KRAS wild-type	Preclinical
BI-pan-KRASdegrader1 (Boehringer Ingelheim)		Pan-KRAS: $KRAS^{G12C/D/V/A}$, $KRAS^{G13C}$, $KRAS^{A146T/P}$, $KRAS^{Q61E/P}$, KRAS wild-type	
RMC-6236 (Revolution Medicines)		Pan-RAS: $KRAS^{G12D/V}$, $KRAS^{G13D}$, $KRAS^{Q61K}$, RAS wild-type	

Hofmann M et el, Cancer Discovery 2022

Conclusions

- Test mCRC for genomic markers: NGS panel
- Treat dMMR/MSI-H mCRC with PD1 based therapy
  - Manage dMMR/MSI-H rectal cancers non-operatively
- For Her2 amplified mCRC dual HER2 inhibition is active
- For BRAF V600E, BRAF + EGFR targeted agents improves survival
- For *KRAS*^{G12C} mCRC combination therapy is coming