Advances and Innovations in Endoscopic Oncology and Multidisciplinary Gastrointestinal Cancer Care

Immunotherapy for Non-Operative Management of GI Cancers: The Role of Endoscopy and Circulating Tumor DNA (ctDNA)

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Disclosures

- Consultant/Advisor for Bristol Myers Squibb, Gritsone Bio, GSK, Merck, Nouscom & Roche
- Grant/Research Support from AstraZeneca, Bristol Myers Squibb, Eli Lilly, Merck, Nouscom & Roche

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of Pembrolizumab, Nivolumab, Ipilimumab, Cemiplimab, AND Dostarlimab will be addressed.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

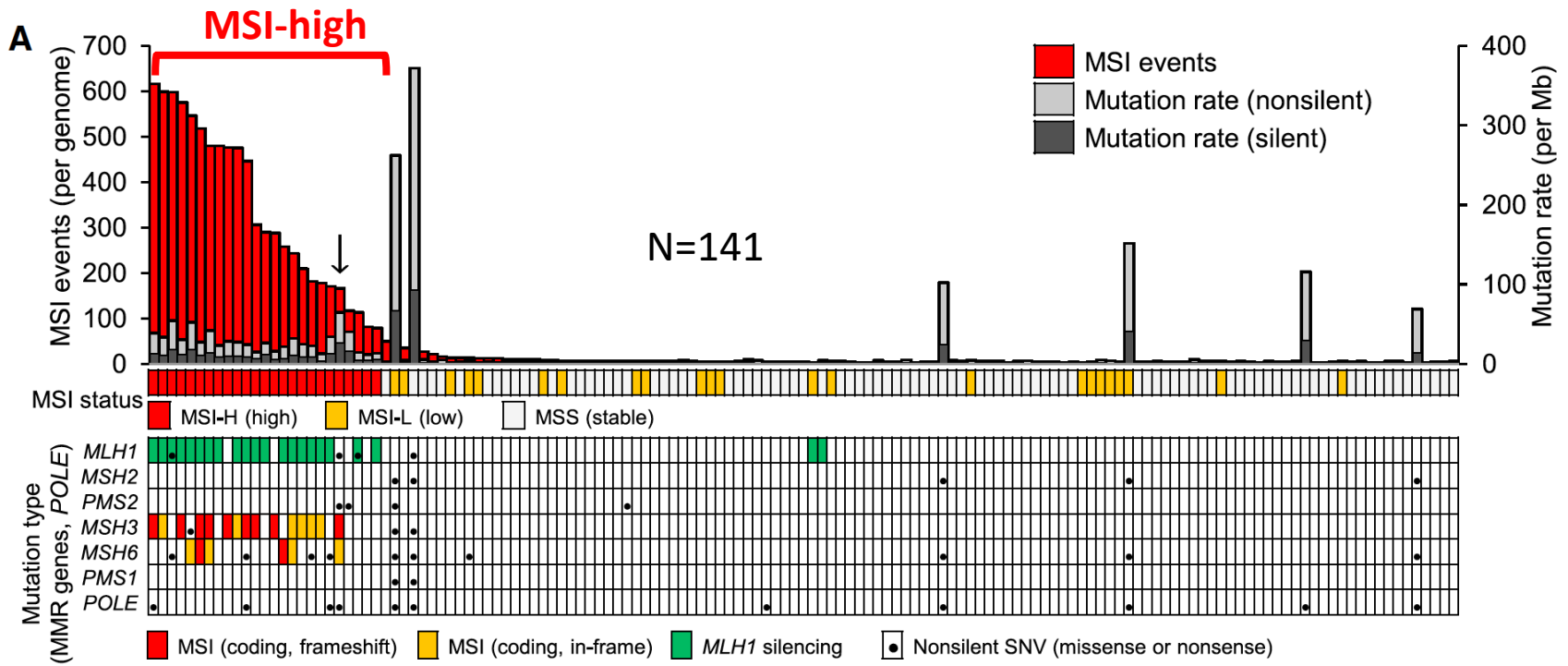
The following CLC & IB components will be addressed in this presentation:

- *Will discuss population-based challenges to surveillance post nonoperative management.*
- *Discuss patient selection for nonoperative management.*

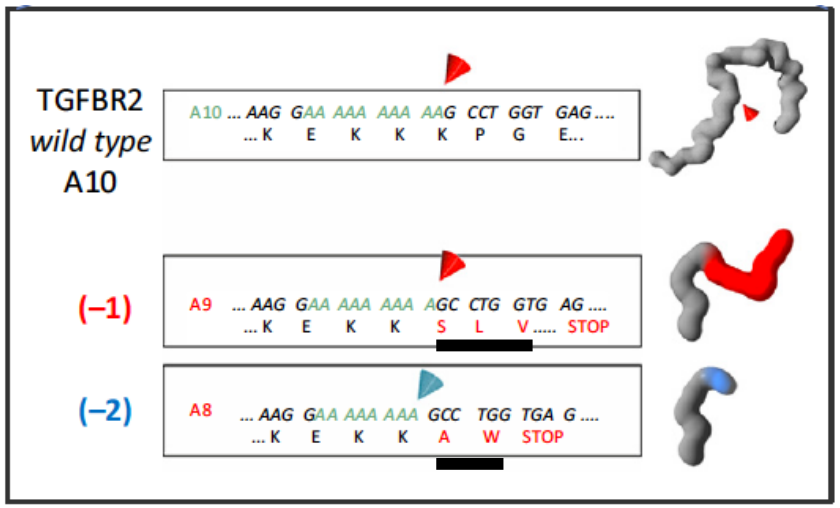
Agenda

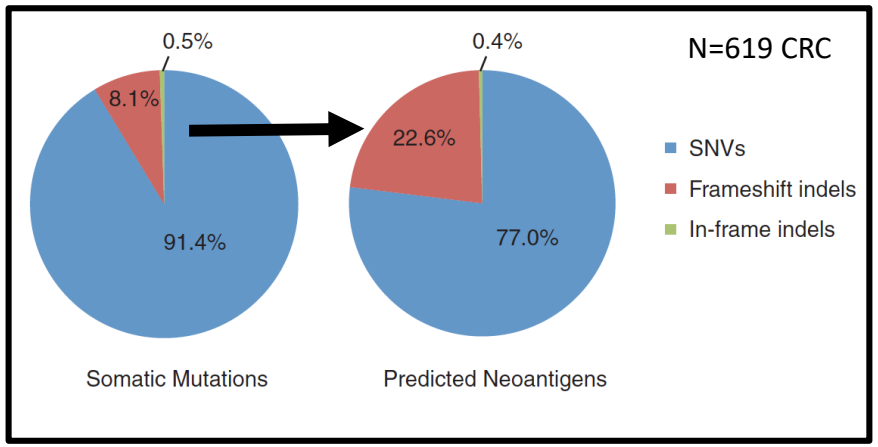
- dMMR/MSI-H Cancer
- IO in Metastatic dMMR/MSI-H Cancers
- Neoadjuvant Therapy for Localized dMMR/MSIH Cancers
  - Non-operative management our goal?
  - How best to stage and monitor response?

dMMR or MSI-H CRC: Frameshift Neoantigens



Stage	MSI-H
II	22%
III	12%
IV	3.5%

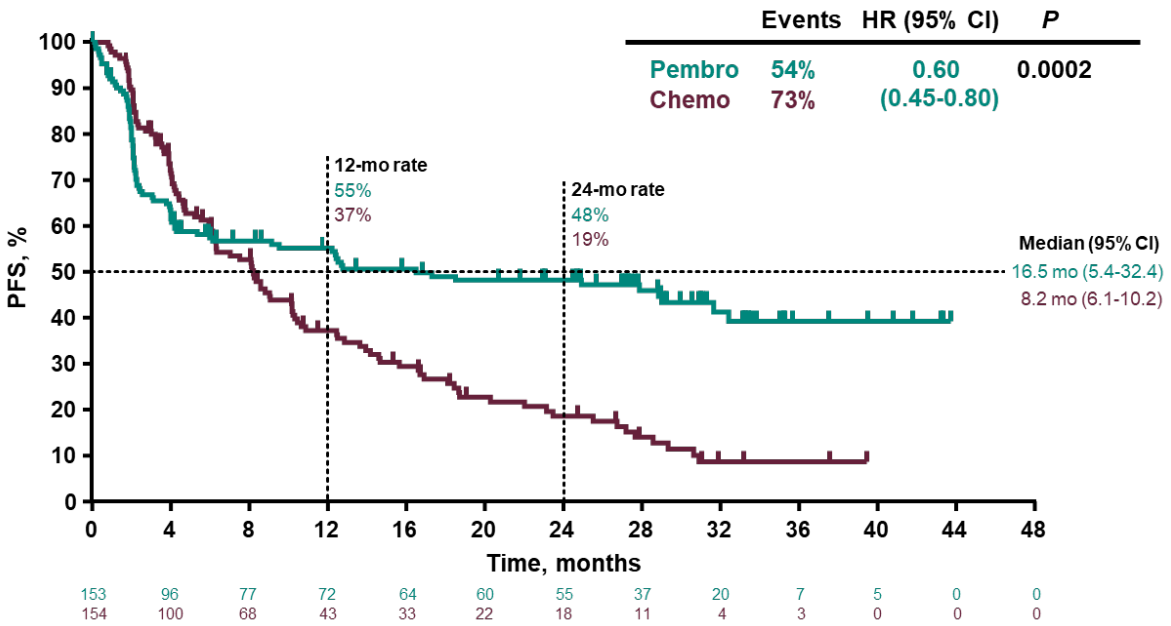




Giannakis et al. Cell Report 2016; Kloor et al. Trends in Cancer 2016; Chalmers et al. Genomic Medicine 2017; 2013 Kim et al. Cell

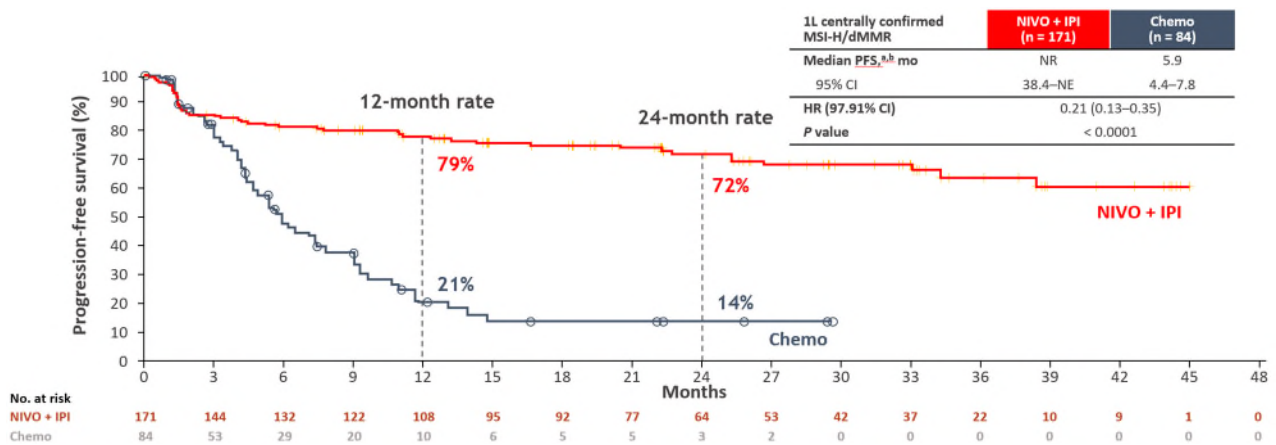
Keynote 177

Pembrolizumab



Checkmate 8HW

Nivolumab + Ipilimumab



Phase III trials of PD-1-Based Therapy vs. Chemotherapy in 1st line dMMR/MSI-H mCRC

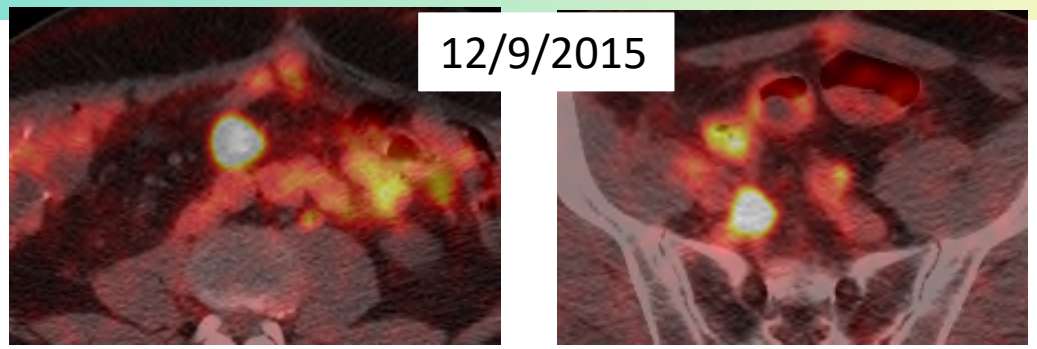
Andre T et al. *NJEM 2020, Andre T et al. GI ASCO 2024*

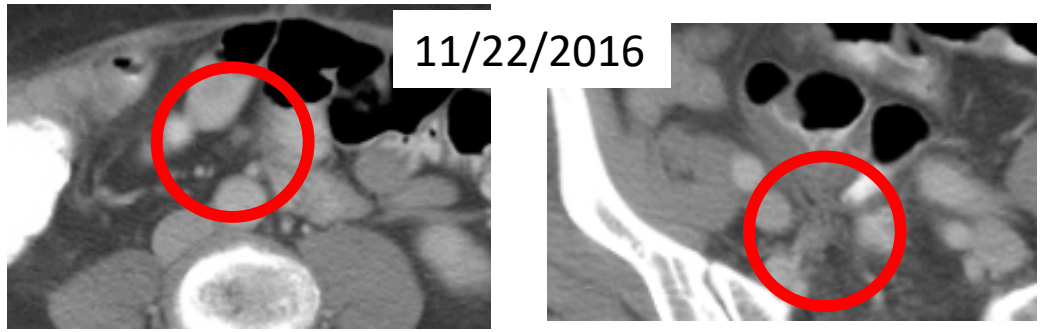
=

Immunotherapy for MSI-H/dMMR Cancers

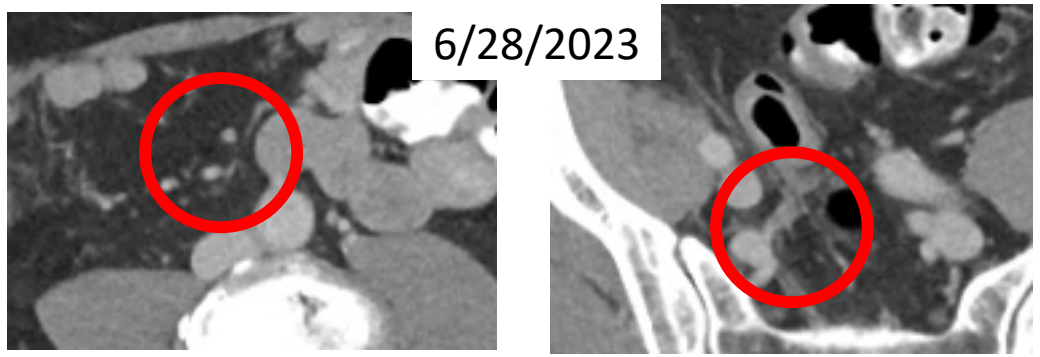
Patient Case

- 3/2014-5/2014 adjuvant FOLFOX
- **5/14/2014 recurrence right retroperitoneum**
- 6/2014 xeloda/xrt
- 9/5/2014 re-resection
- **2/11/2015 recurrence right retroperitoneum**
- 2/2015-4/2015 Folfiri/bev
- 5/29/2014 re-resection
- **12/9/2015 recurrence abdominal adenopathy**
- **1/7/2016 Nivolumab on trial**
- 11/22/2016 therapy stopped due to Grade 3 immune arthritis

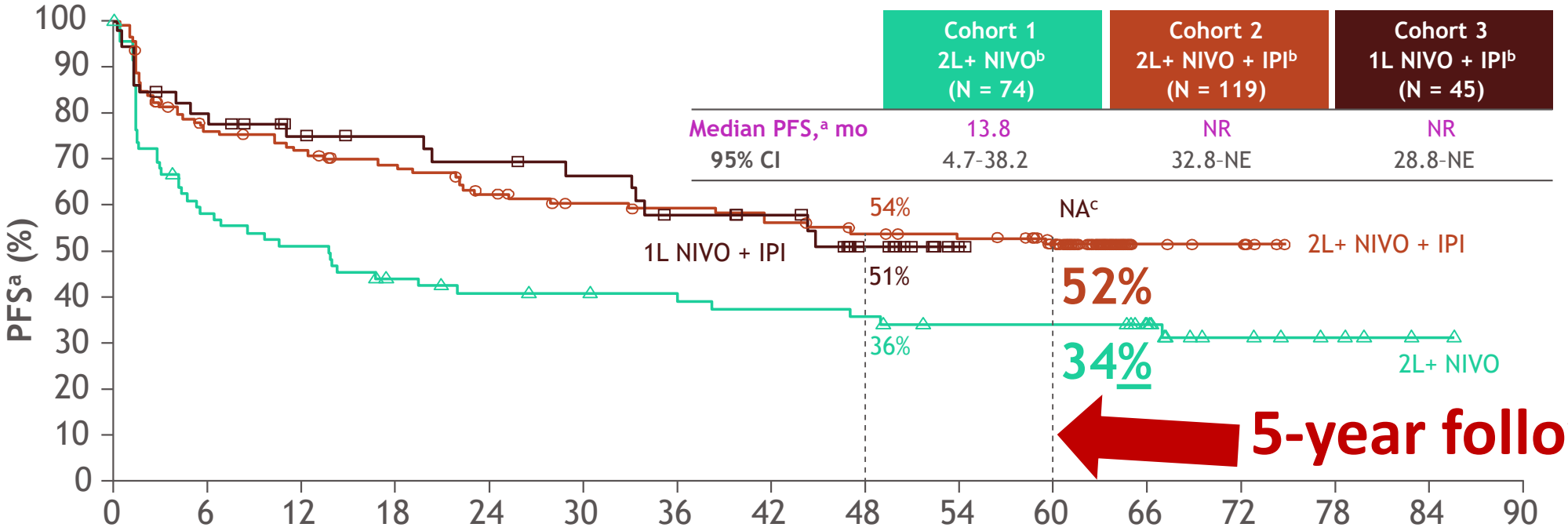


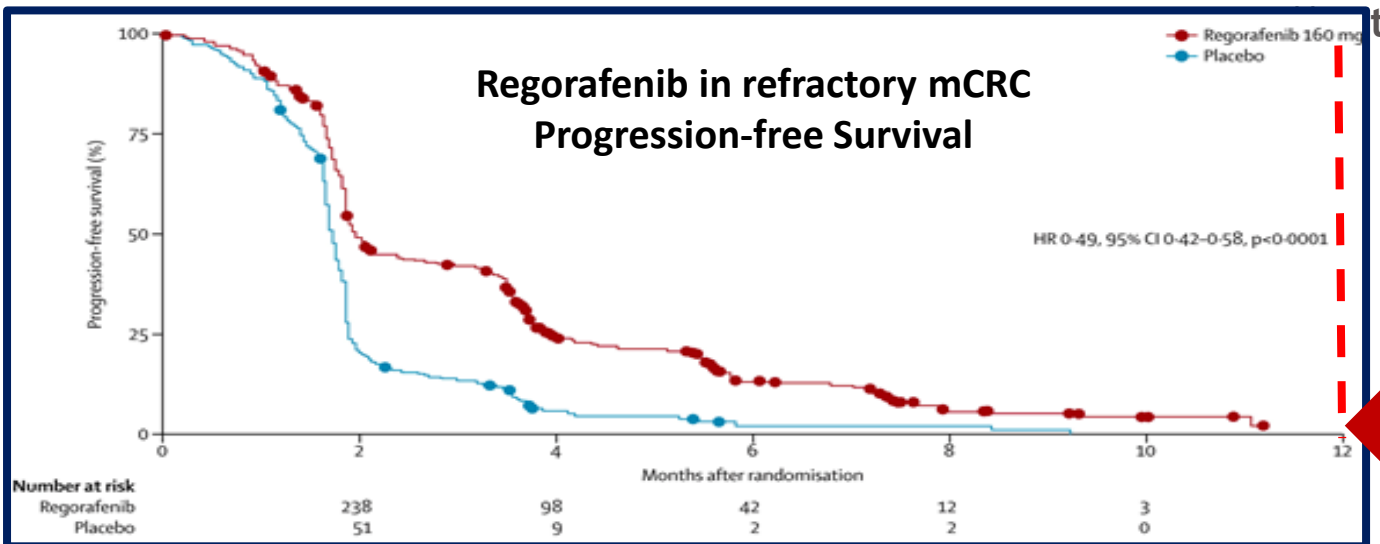


6+ years



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



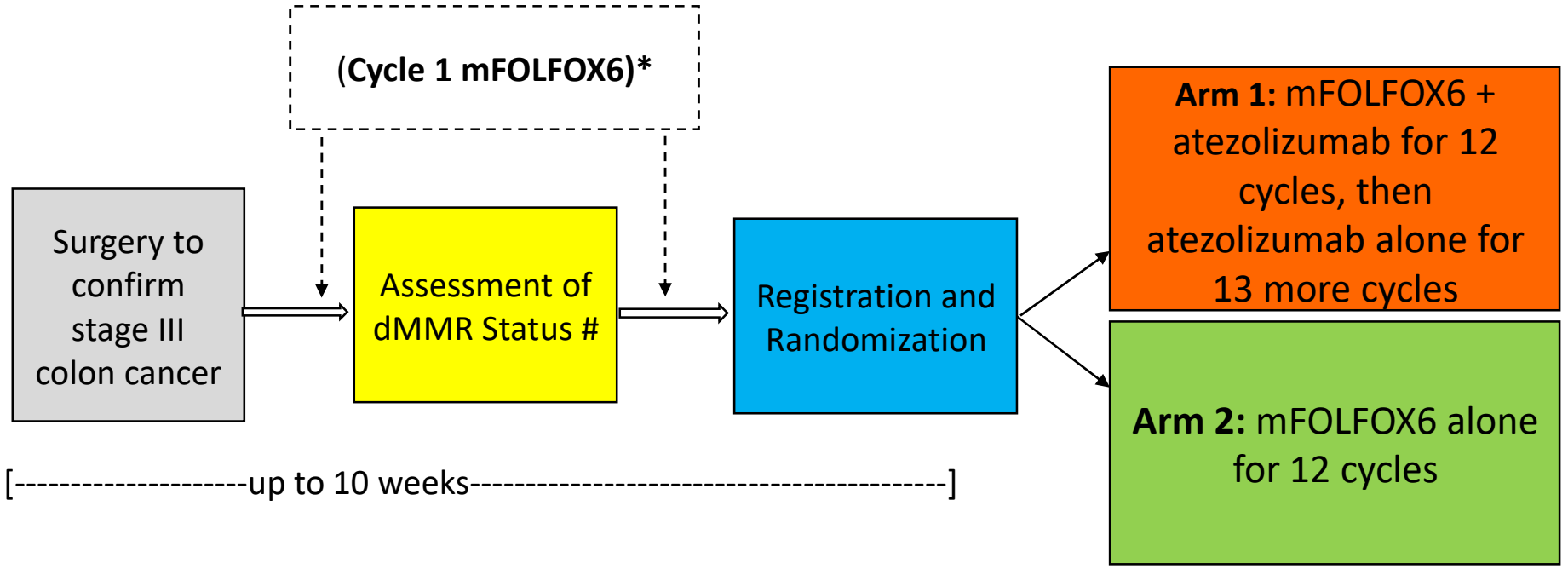


1 year PFS = 0%

Overman et al. ASCO 2022

Localized dMMR CRC

Adjuvant PD-L1 for Stage III colon cancer: ATOMIC Study (A021502)

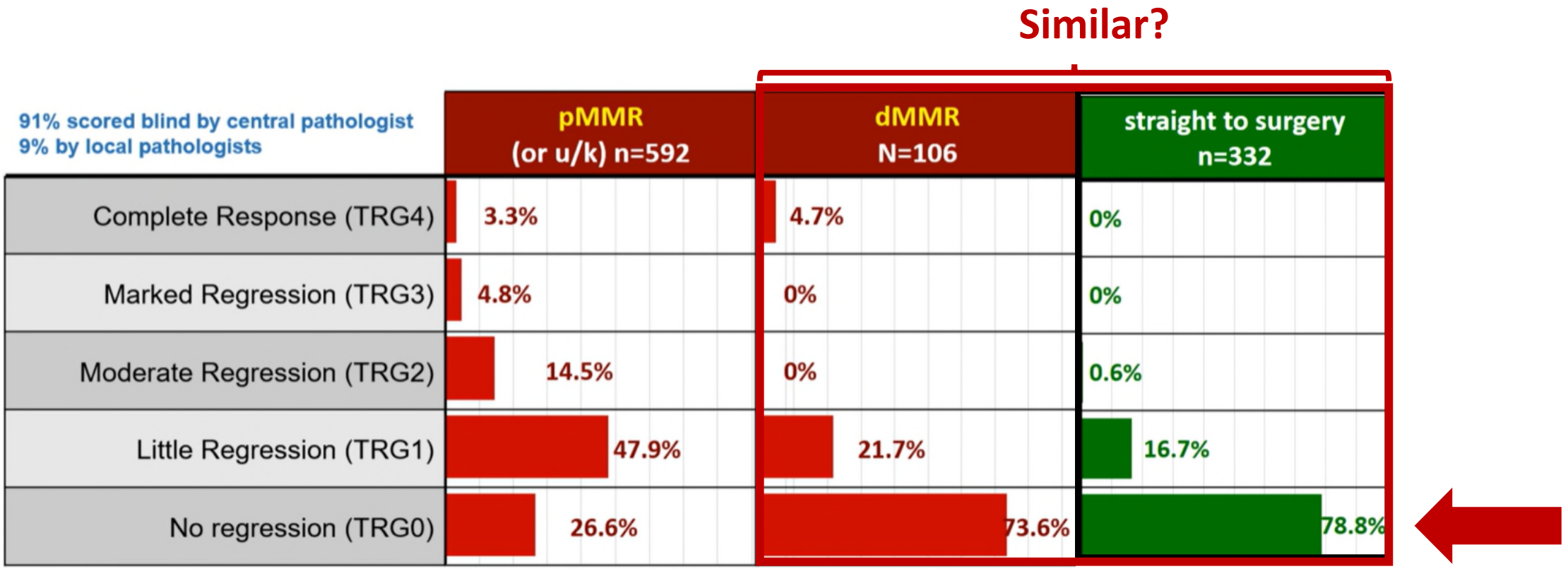


Enrollment completed

NCT02912559

PI: Frank Sinicrope

Neoadjuvant Therapy for dMMR Cancers: FOXTROT Trial



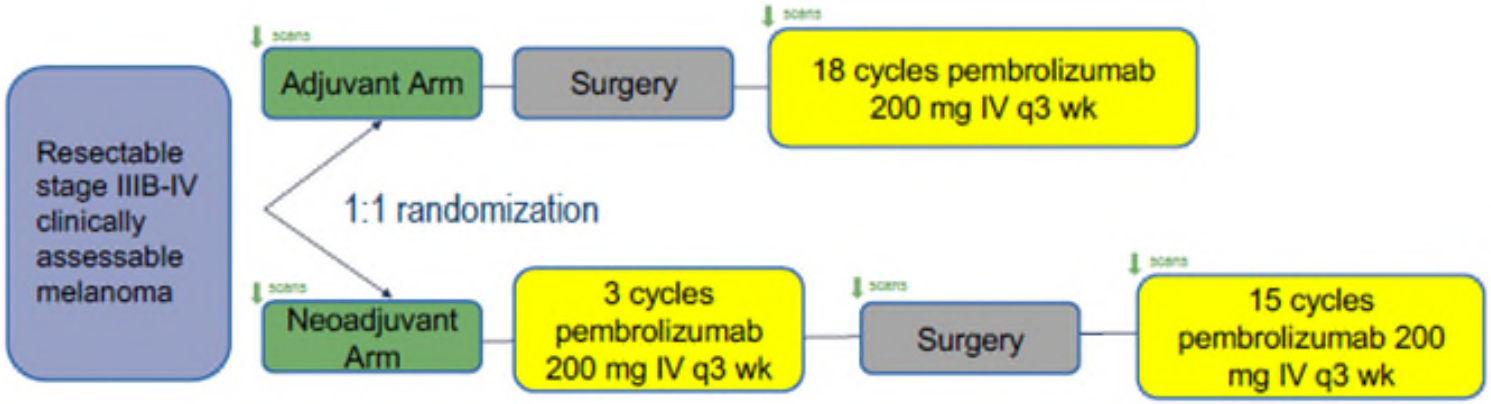
Foxtrot Control Arm

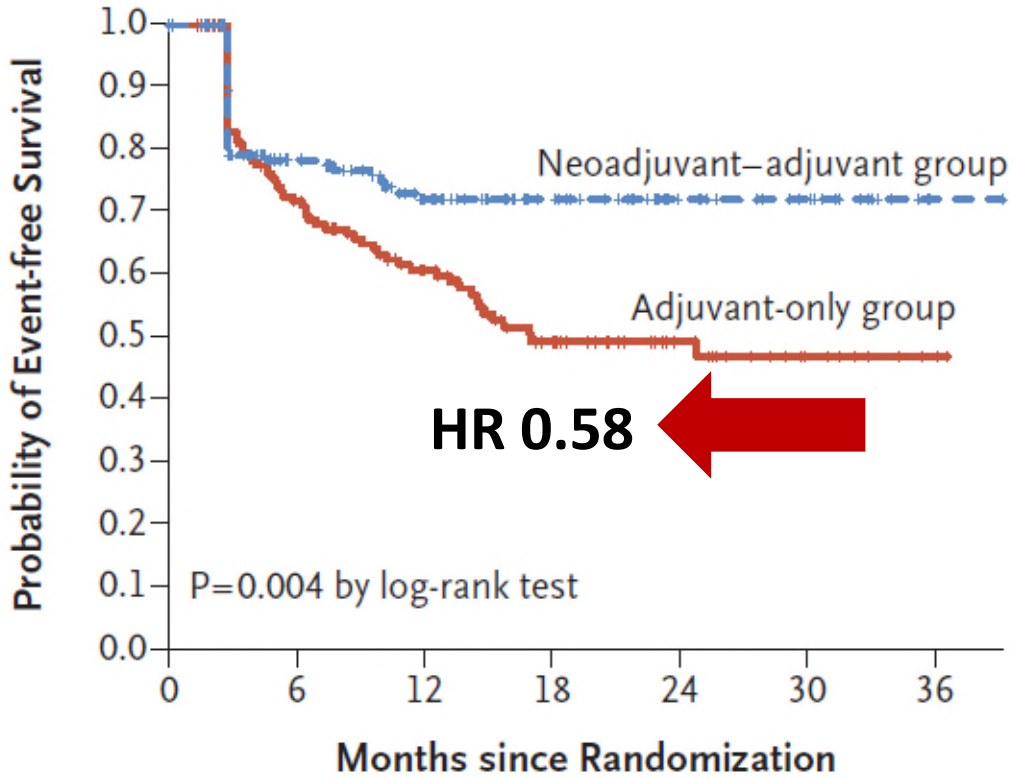
Inclusion: CT-predicted T4 or T3 with extramural depth ≥1mm *(depth beyond muscularis propria)*

- 351 control patients
  - 9 stage I (3%)
  - 74 low-risk stage II (21%)
    - EMVI negative, not poorly diff, no budding

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

SWOG 1801: Melanoma





2 year EFS
72% vs 49%

Neoadjuvant arm:
pCR was 21%

Patel et al. NJEM 2023

The NEW ENGLAND JOURNAL of MEDICINE

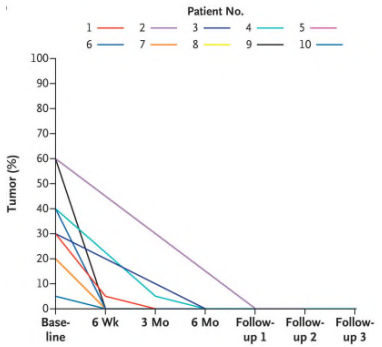
PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

Dostarlimab

NICHE-2 Clinical Trial

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

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



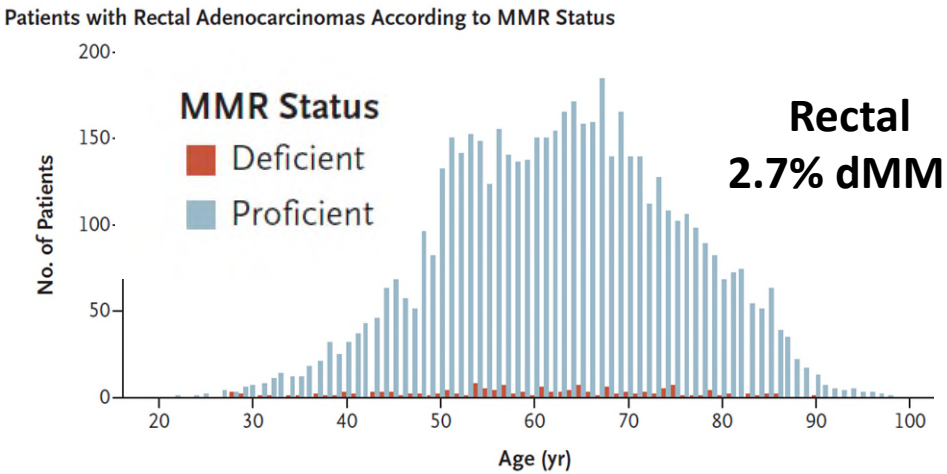
The New York Times

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

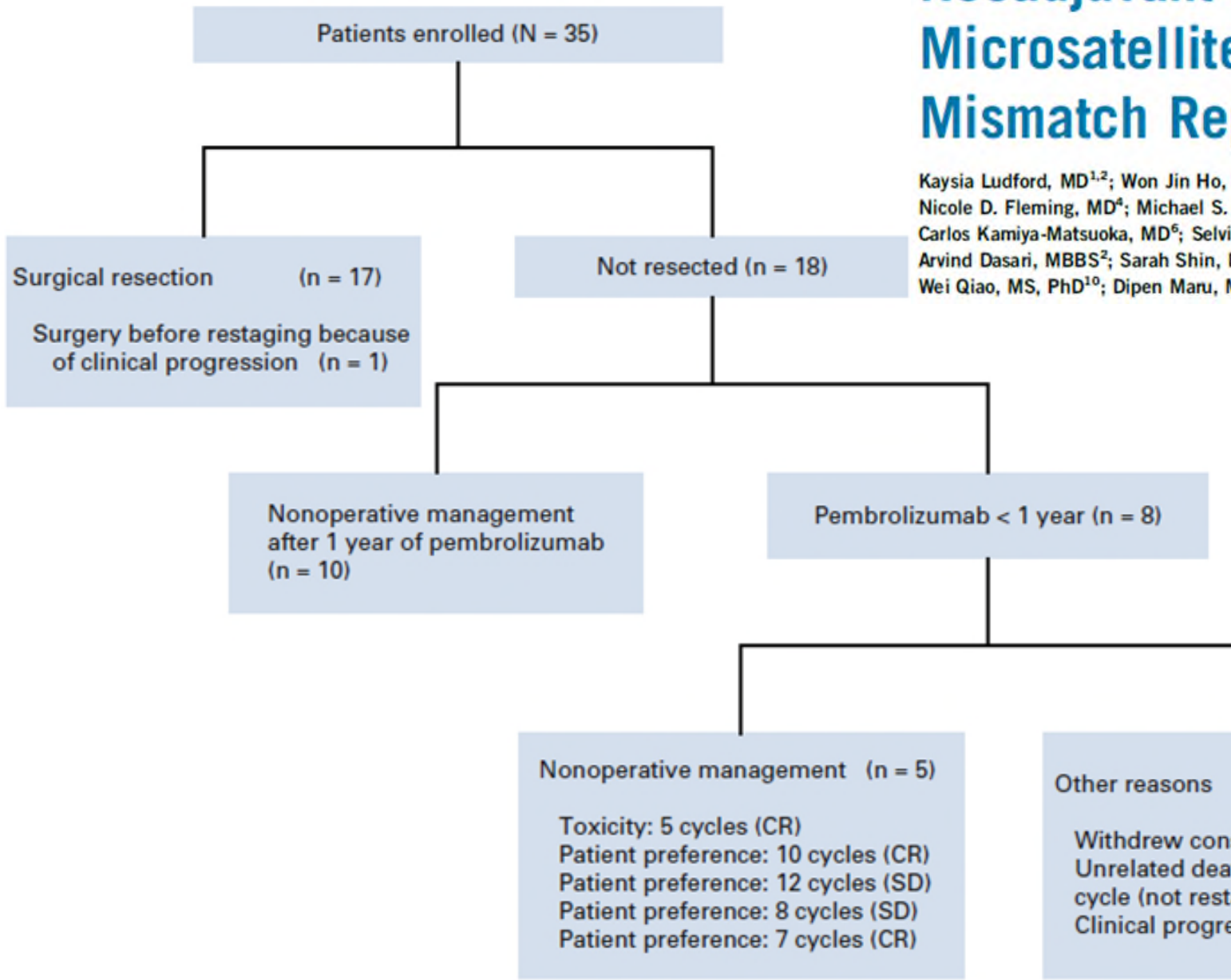
5 fold greater rate!

Chalabi et al Nat Med 2020 and ESMO 2022

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]

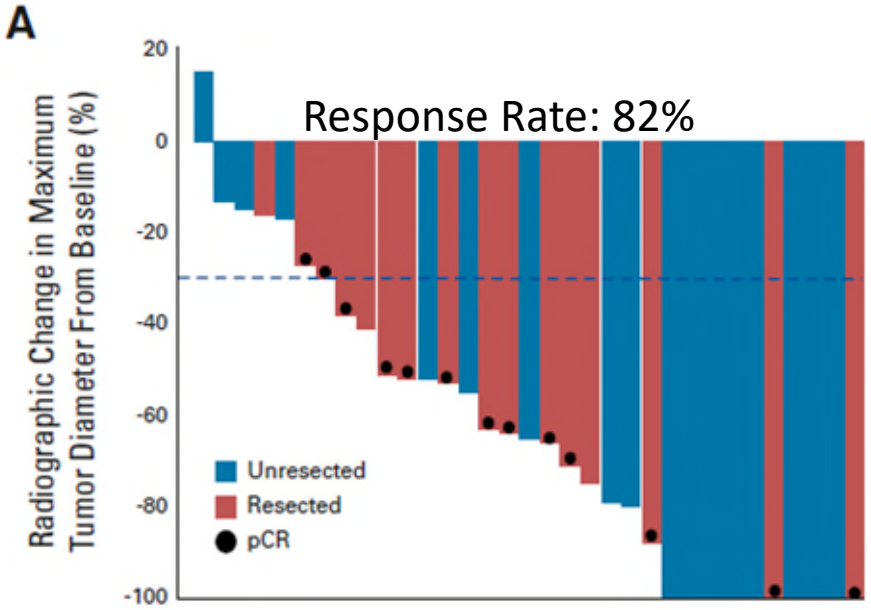


Tumor types	
Colon adenocarcinoma	19 (54)
Rectal adenocarcinoma	8 (23)
Pancreatic adenocarcinoma	2 (6)
Duodenal adenocarcinoma	2 (6)
Other[a]	4 (11)

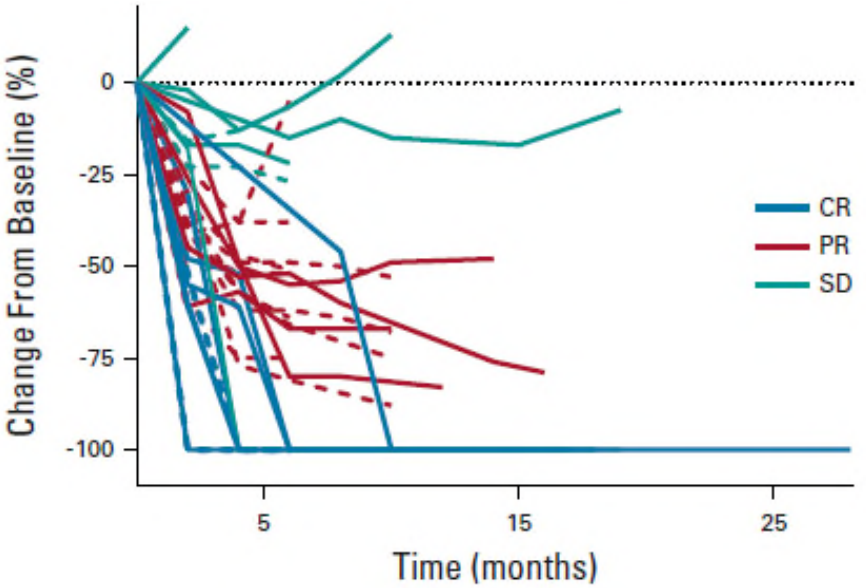
[a]Other: gasrtic (n = 1), ampullary (n = 1), meningioma (n = 1), and endometrial (n = 1).

Ludford and Overman et al. JCO 2023

Neoadjuvant Pembrolizumab Efficacy

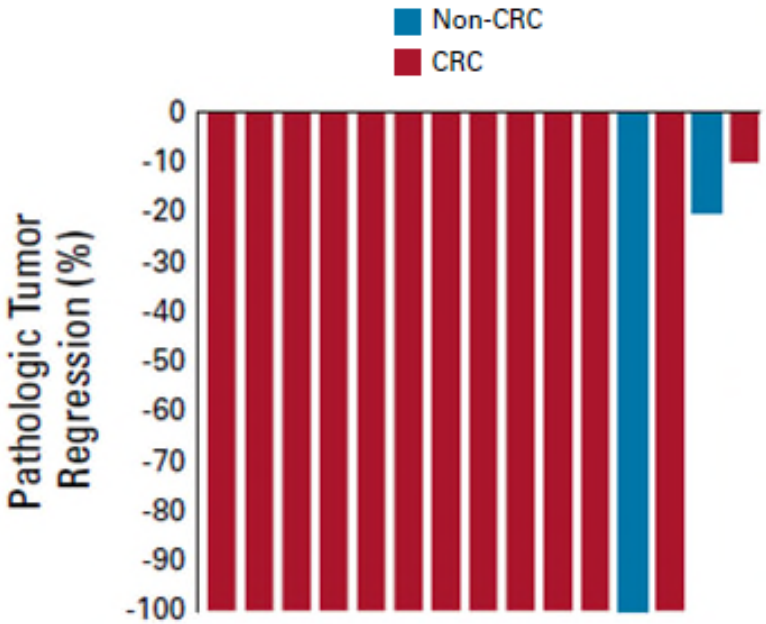


N=35
(CRC N=27)



6 Progression events

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

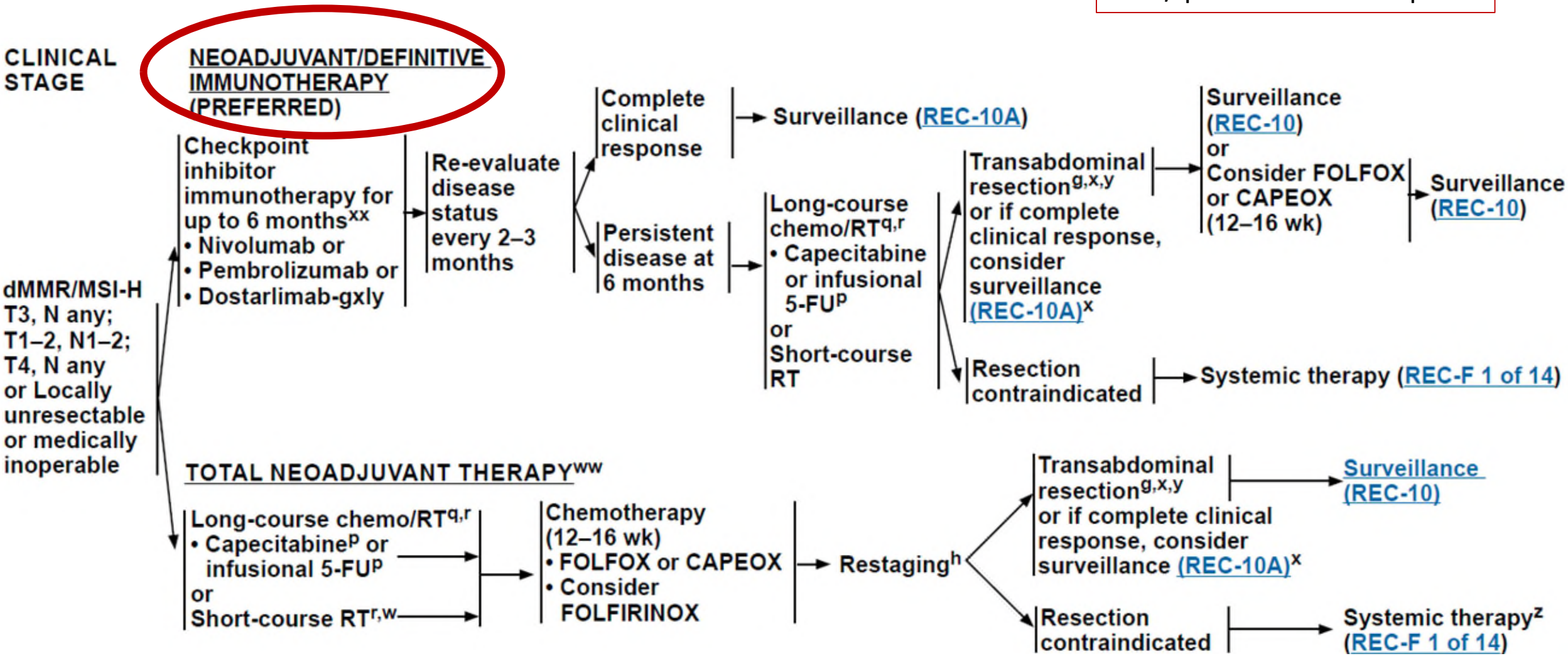


- 17 patients when to surgery
  - pCR 67%
  - in CRC pts pCR 79%

Ludford and Overman et al. JCO 2023

NCCN Rectal update 4.25.2023

Dostarlimab:	100% CCR
Pembrolizumab:	79% pCR
Nivo/Ipi:	67% pCR

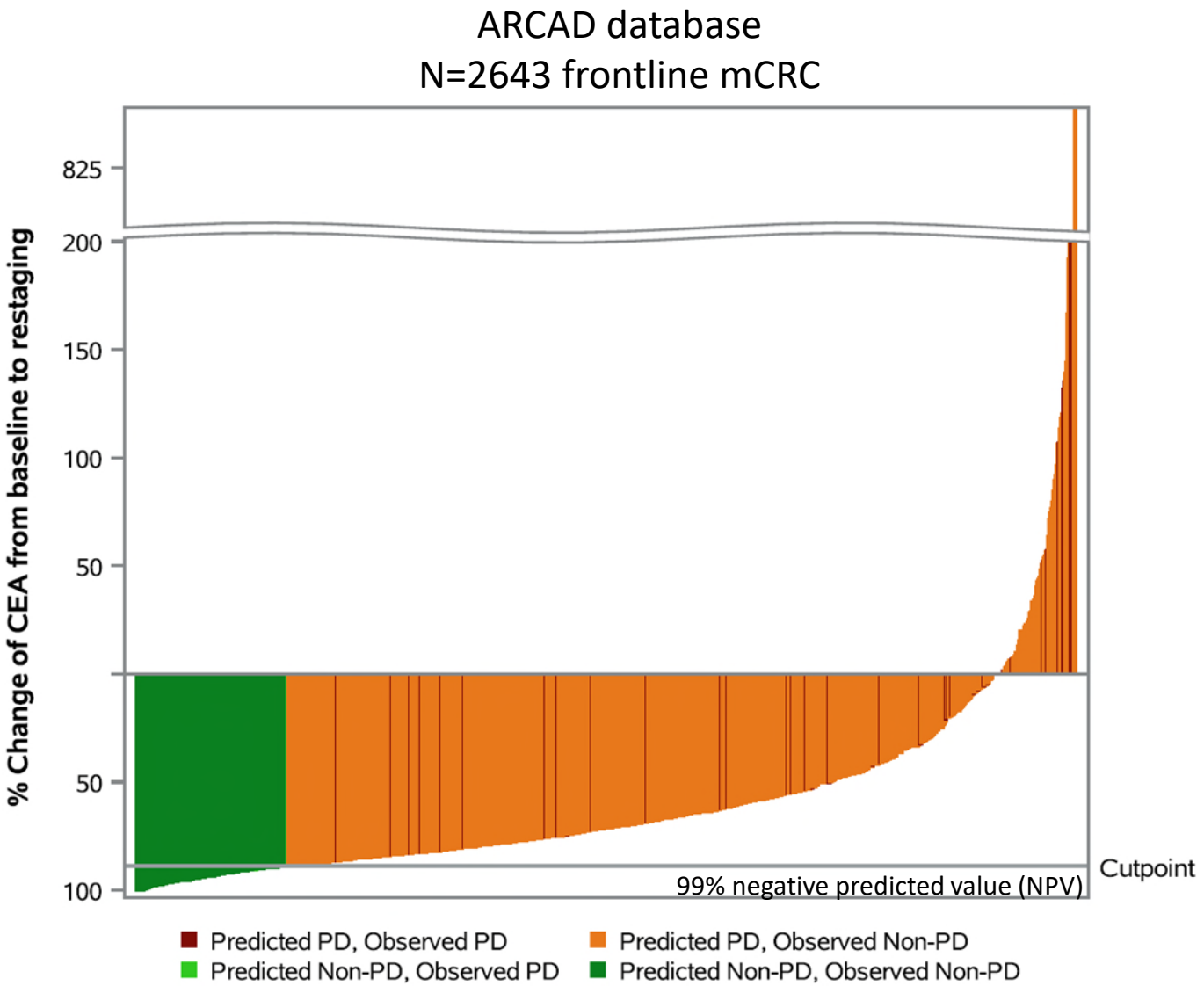


Limitations of Radiographic Disease Assessment

Foxtrot Control Arm

- Inclusion: CT-predicted T4 or T3 with extramural depth ≥1mm *(depth beyond muscularis propria)*

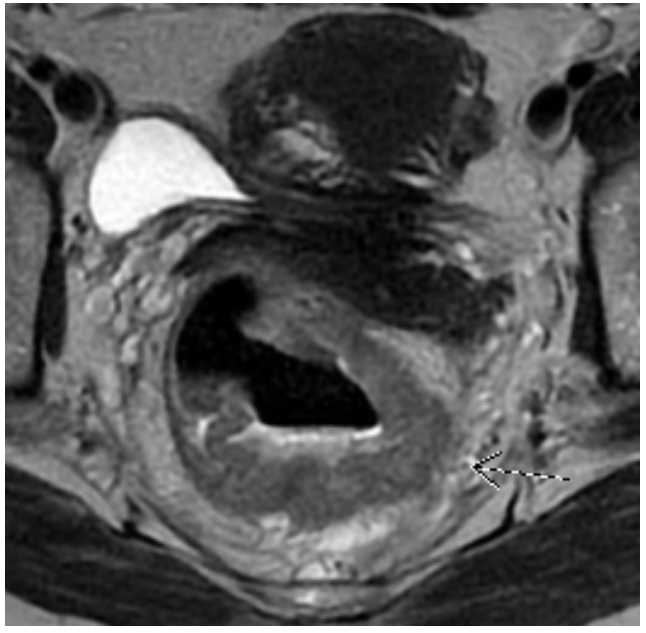
- 351 control patients
  - 9 stage I (3%)
  - 74 low-risk stage II (21%)
    - EMVI negative, not poorly diff, no budding



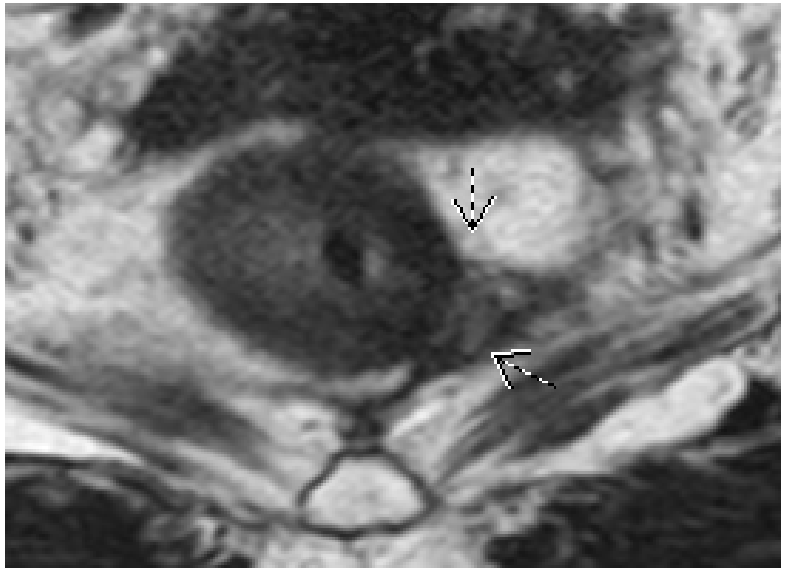
Morton et al. JCO 2023, Gulhati + Overman et al. JNCI 2000

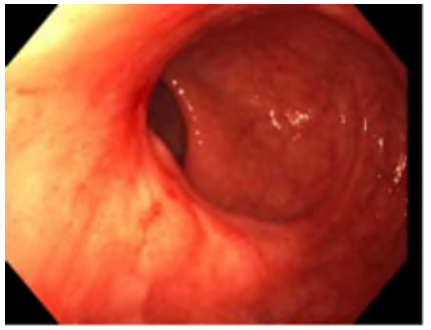
Rectal Case Presentation

- 51y/o Caucasian female with Lynch and mT3N1 mucinous adenoca



Pembro x 6m





Endoscopy: “rectal scar”

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).

Rectal Case Presentation

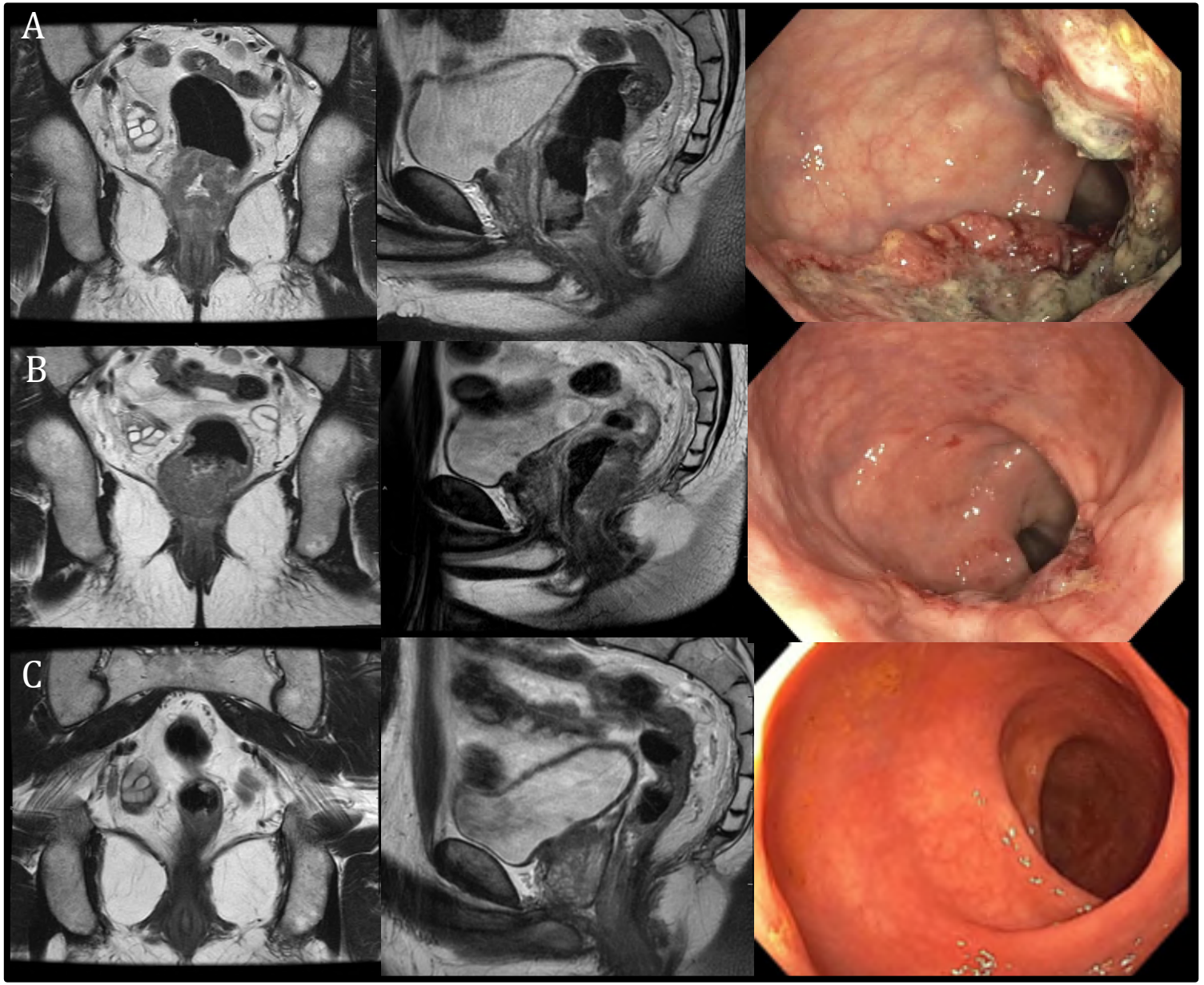
- 52y/o dMMR mT3bN+ at 2.7cm from AV
- Treated with vudalimab (PD1/CTLA4 bispecific)

Baseline

8 weeks

IMPRESSION:
Impression:
Assessment of Response: Ulcerated non circumferential lower rectal cancer now appears increased. There is now involvement of the levator at the left posterior lateral side, consistent with T4b disease
.Residual tumor with little or no fibrosis, (TRG3)

16 weeks



Challenges with Neoadjuvant PD1 Benefit Prediction

- 38 localized dMMR CRC pts
  - Clinical benefit (CB) defined as:
    - pCR after undergoing surgical resection or
    - no evidence of PD on imaging or endoscopy ≥6 months following the last dose of IO

Patient #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38
Primary Site	R	C	R	C	M	R	C	C	R	R	R	R	R	C	C	R	R	C	C	C	C	C	C	C	C	M	R	R	C	C	R	R	C	C	R	C	R	R
Best Radiographic Response	n/a	PR	PR	PR	PR	CR	CR	CR	SD	CR	PR	PR	SD	PR	PR	PR	PR	CR	CR	SD	PR	PR	n/a	PR	CR	PR	SD	CR	n/a	PR	SD	SD	PR	PR	PR	PR	n/a	PR
Best Endoscopic Response	CR	PR	CR	NCR	CR	CR	CR	NCR	n/a	CR	CR	CR	n/a	SD	PR	CR	CR	CR	n/a	CR	NCR	SD	CR	NCR	NCR	CR	NCR	PR	PD	SD	n/a	SD	PR	n/a	NCR	n/a	n/a	PR
Pathologic Outcome	n/a	CR	n/a	CR	CR	n/a	CR	CR	CR	n/a	CR	n/a	n/a	CR	n/a	n/a	n/a	n/a	n/a	n/a	CR	CR	n/a	CR	n/a	n/a	n/a	n/a	n/a	NR	n/a	n/a	NCR	PR	PR	NR	NR	NR
Clinical Benefit	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	n/a	N	N	N	N	N	N	N	N	N	N

Mucinous CB (N=15):

Radiographic

- CR in 5
  - Surgery in 1: pCR
- PR 8
  - Surgery in 6: pCR
- SD 2

Endoscopic

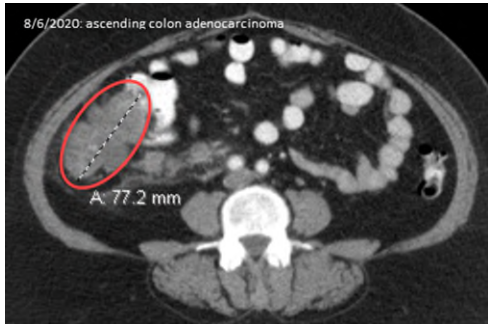
- Endo CR in 11
- Non endo CR in 4
  - stricture (2)
  - residual polyp at scar
  - ulceration w/ scarring (at 3.5m of PD1)

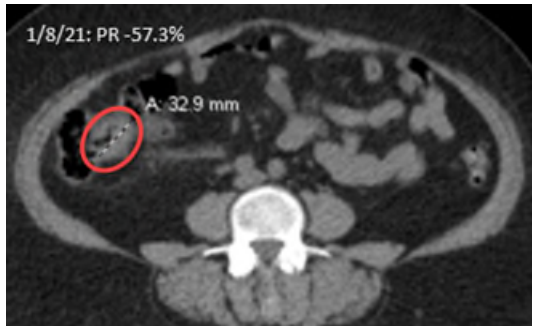
Fox + Overman et al. EJC 2023

Colon Case Presentation

- 74y/o dMMR cT4N1 ascending colon mucinous adenoca
- Pembrolizumab 9/2020 to 3/2021

Pembro x 12 (6m)



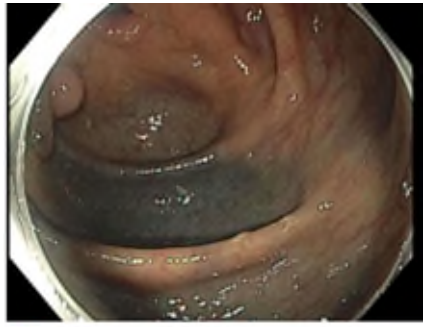


8/2020

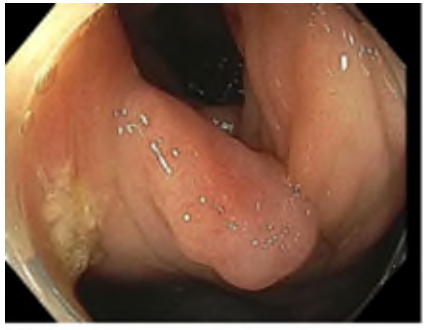
2/2021

4/2021

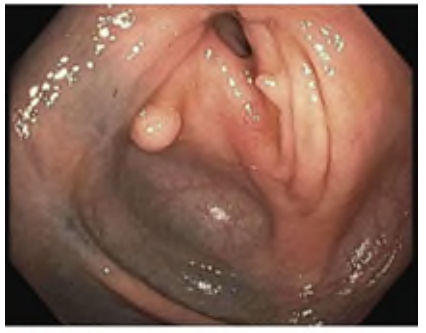
5/2021



7 tattoo asc



8 luminal narrowing prox asc



5 Ascending Colon, stenosis

pCR

Large obstructing mass seen in the proximal ascending colon. Biopsies. Also localized using India ink

Rectal Case Presentation

- 70y/o dMMR mT3bN+ at 8cm
- Treated with Pembrolizumab + short course XRT

Pembro x 12 (6m)

25Gy

7/2021

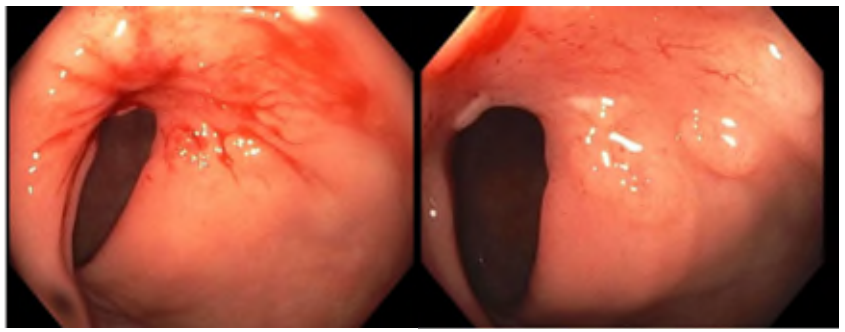
1/2022 (3m of Pembro)

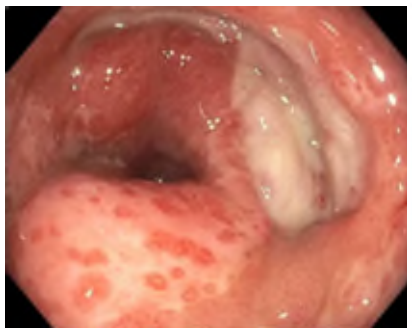
5/2022

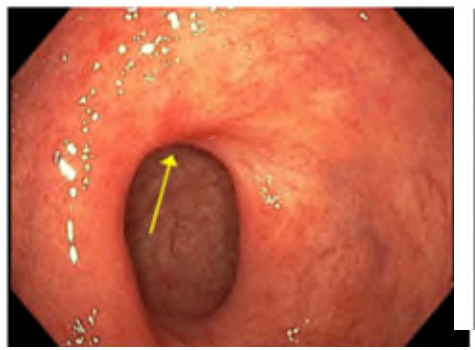
8/2022

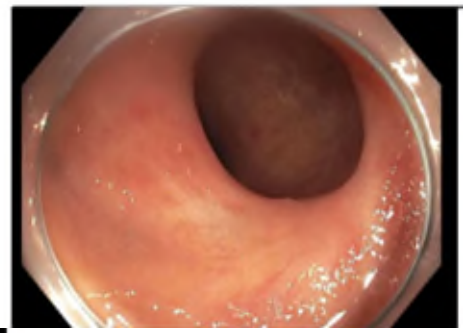
3/2023

8/2023









An ulcerated, fungating and infiltrative bleeding 5 cm mass of malignant appearance was found in the mid rectum at a distance between 8 cm and 13 cm from the anus. The mass caused a partial obstruction. The scope traversed the lesion.

Challenges in Endoscopic Assessment

- Frequency of scopes
- Timing of assessments
- Assessing response
  - “scarring” w/o descriptor
  - “stricture”
  - “residual polyp”
  - “malignant appearing stenosis”
  - “erythematous mucosa”
  - “subtle mucosal changes”

PROSPECT, ALLIANCE N1048

11.2.4 Clinical Tumor Response Based on Proctoscopy Can be Classified as the Following:

- *Complete response (100%)*
- *Major response (51% to 100% smaller)*
- *Moderate response (21% to 50% smaller)*
- *Minimal response (0% to 20% smaller)*
- *Progression (tumor has enlarged)*
- *Unable to determine*

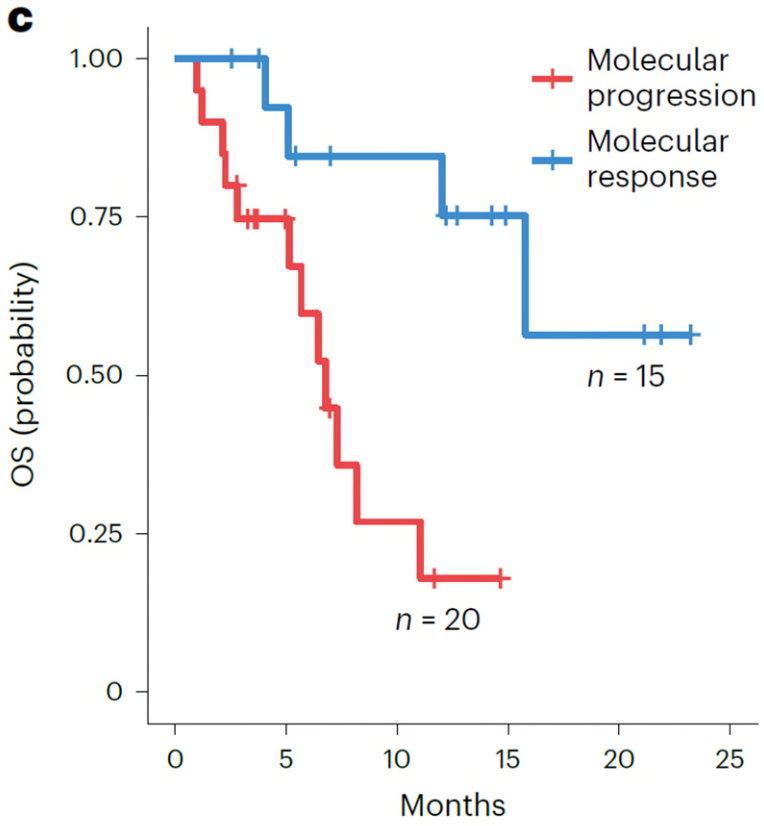
Table 2 Memorial Sloan Kettering Regression Schema

	Complete Response	Near Complete Response
Endoscopy	Flat, white scar Telangiectasia No ulcer No nodularity	Irregular mucosa Small mucosal nodules or minor mucosal abnormality Superficial ulceration Mild persisting erythema of the scar

Smith et al. BMC Cancer 2015

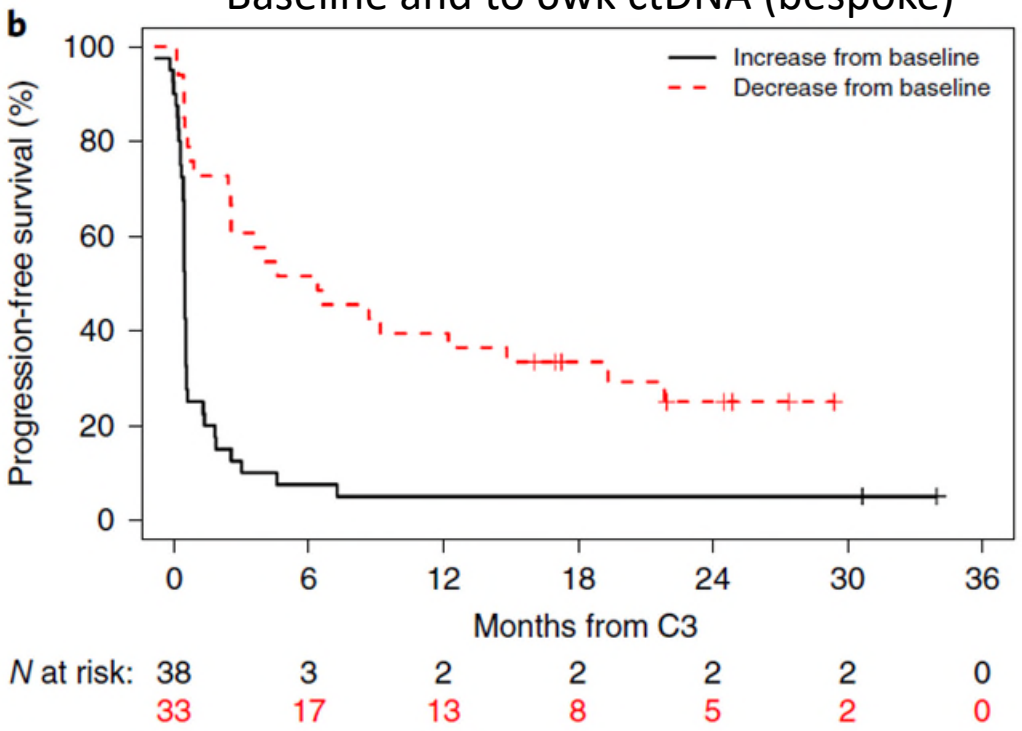
Predictors of Treatment Benefit: ctDNA kinetics

Metastatic NSCLC



Metastatic Solid Tumors

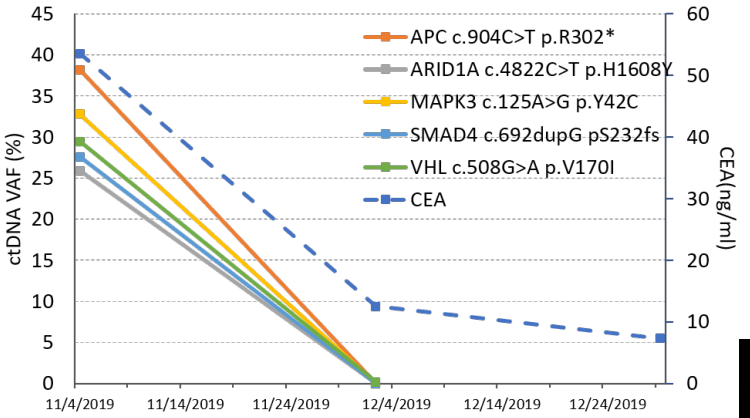
Baseline and to 6wk ctDNA (bespoke)



Bratman et al. Nature Cancer 2020; Anagnostou et al. Nature Med 2023

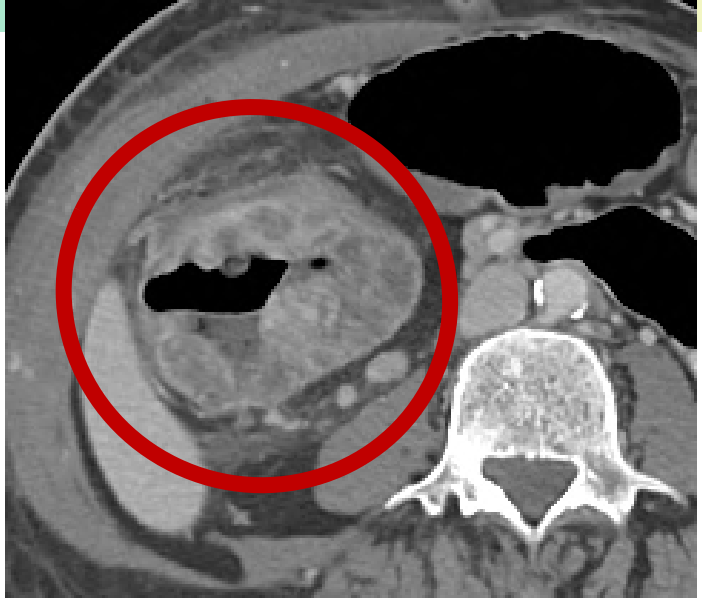
Colon Case Presentation

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

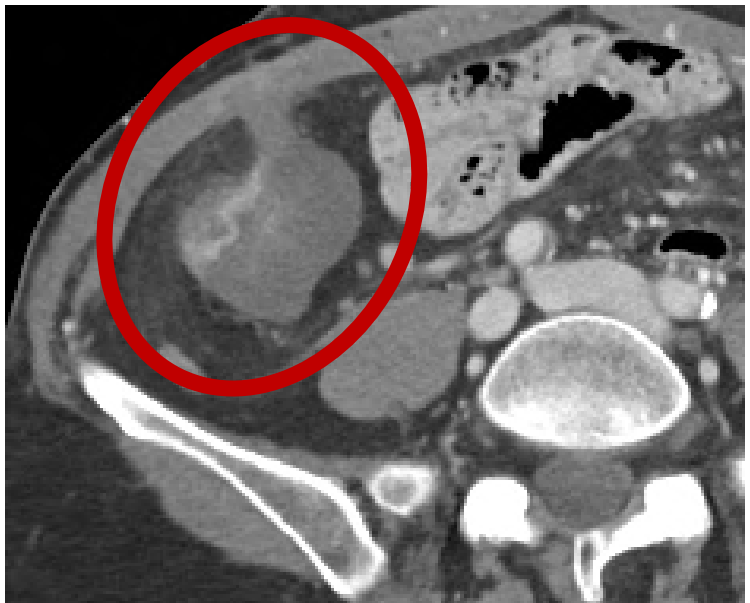


DIAGNOSIS

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.

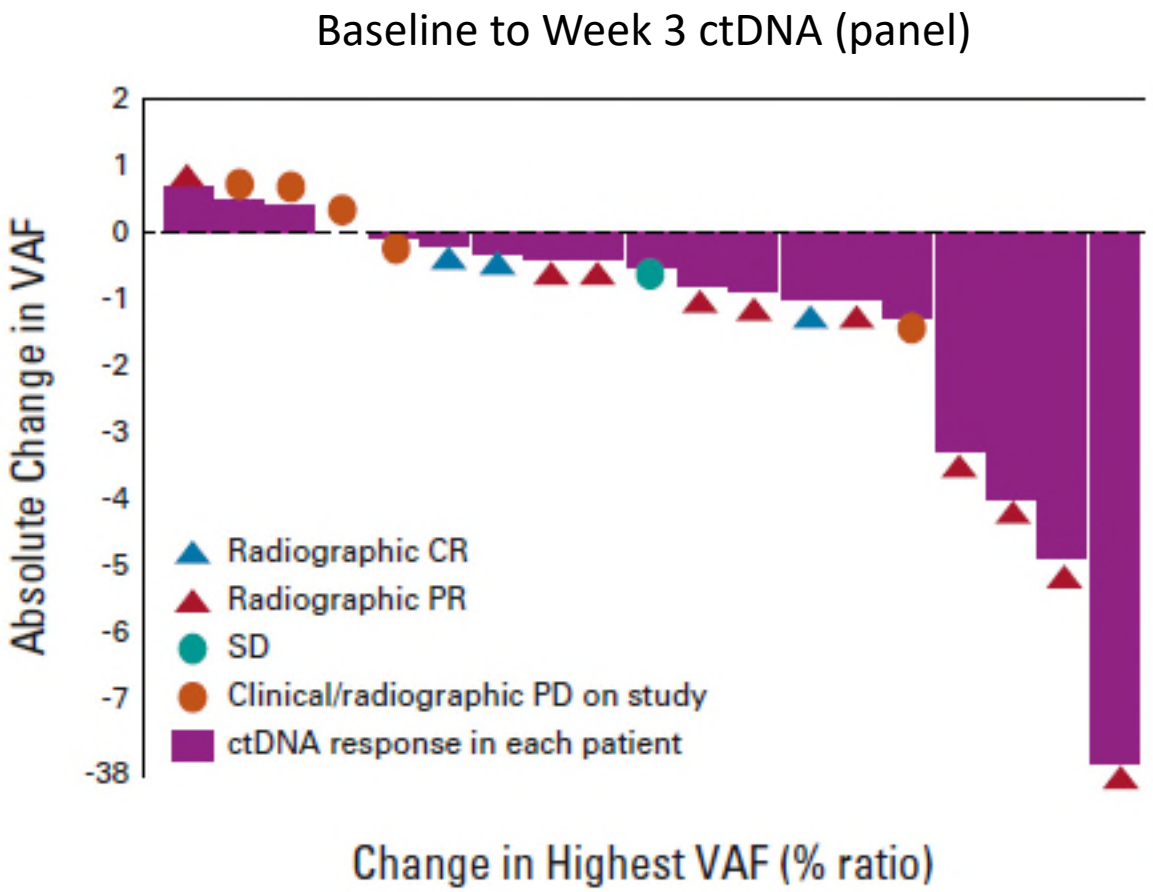


Pembro x 6m



Predictors of Treatment Benefit: ctDNA kinetics

- Pembrolizuamb for Localized dMMR Cancers (N=35)
- 70 gene panel-based testing (LBP-70)
- 19 detectable baseline



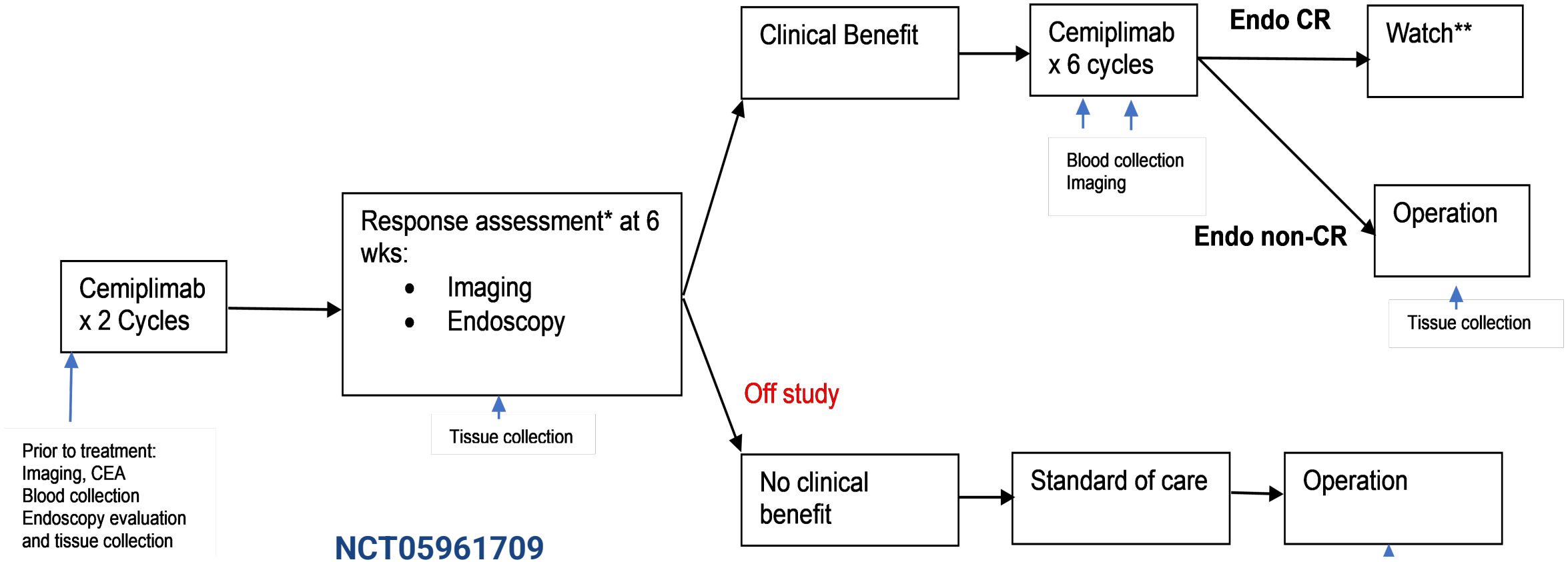
13 resected CRC pts

- 7 baseline ctDNA (mean VAF 8.5%)
  - 5 cleared ctDNA
    - 4 pCR
    - 1 near-pCR (carcinoma in 1/91lns)
  - 2 did not clear ctDNA: no pCR

- pCR status by baseline ctDNA
  - 6/6 with no baseline ctDNA had pCR
  - 4/7 had pCR

Ludford and Overman et al. JCO 2023

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

Conclusions

- Test all metastatic GI patients for MMR/MSI
- PD1 based nonoperative management for dMMR localized rectal is the standard
- The role of PD1 therapy for nonoperative management of localized dMMR cancers should be considered and prospectively studied
- Refinement of neoadjuvant PD1 based therapy response criteria is needed
  - Endoscopic assessment should be heavily weighted in tx response assessment
- There is an emerging role for ctDNA kinetics to determine neoadjuvant treatment benefit