MLS Cleveland 2024

Neoadjuvant Immunotherapy in Gastrointestinal Cancers

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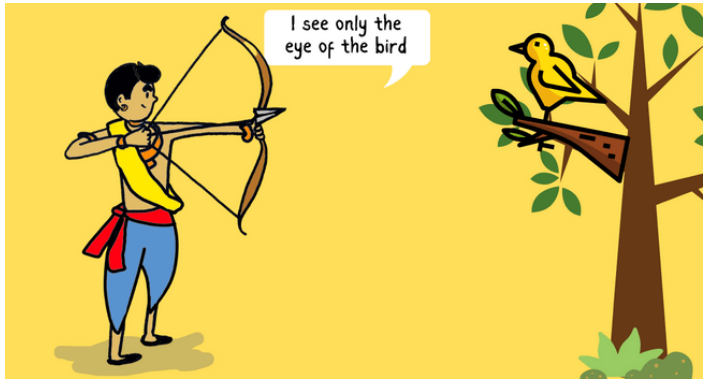
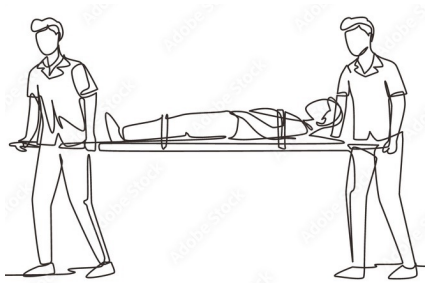
April 13, 2024



My Mission…

Neoadjuvant Immunotherapy (NIT) is a logical option for many patients with localized dMMR/MSI-High GI Cancers

This makes me mad  !!!



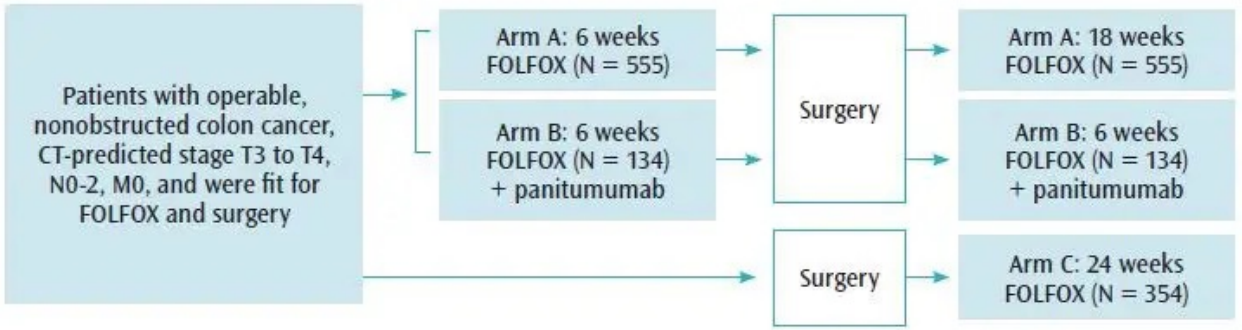
- dMMR/MSI-H Tumor
- Locally Advanced
- Unresectable

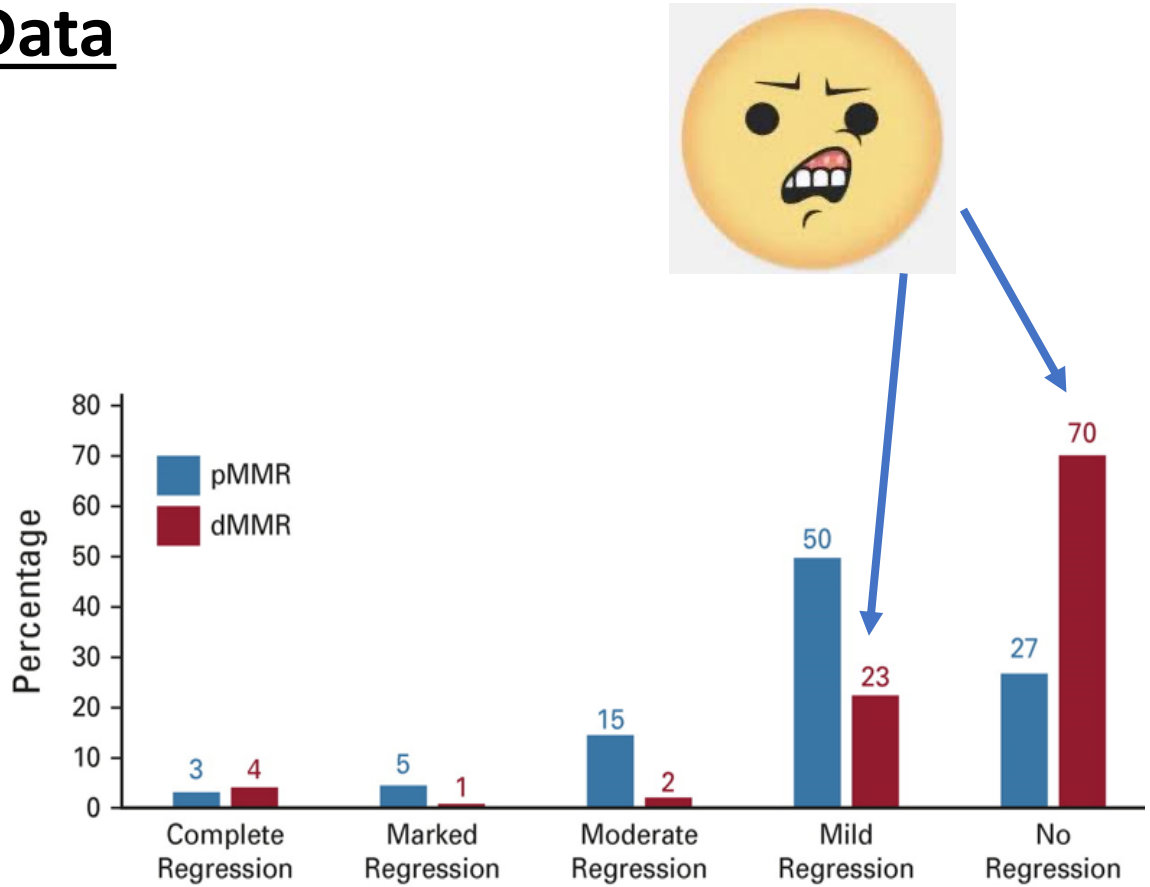
FOLFOX

Chemotherapy has suboptimal anti-tumor activity against dMMR tumors

FOxTROT Data

Trial Design

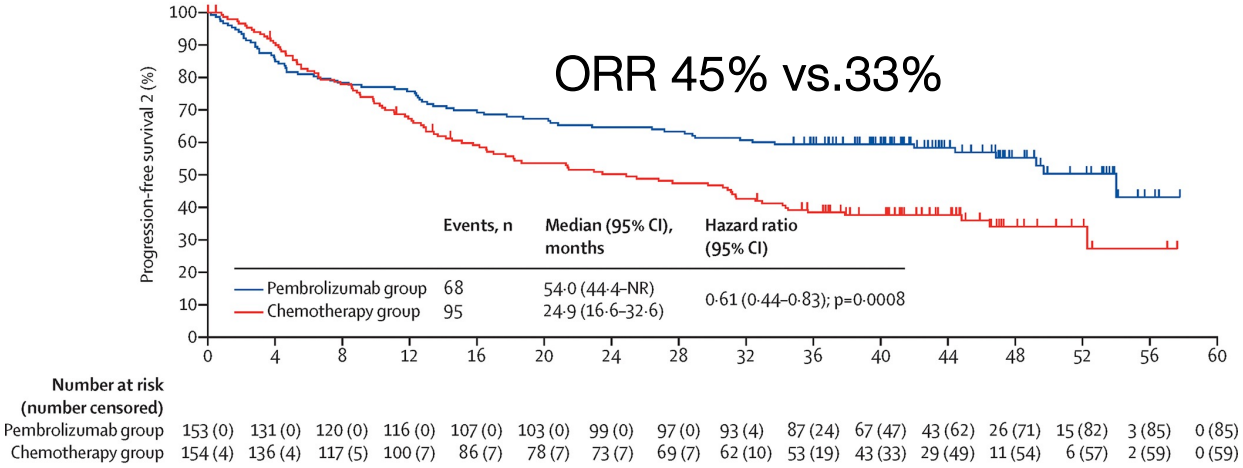




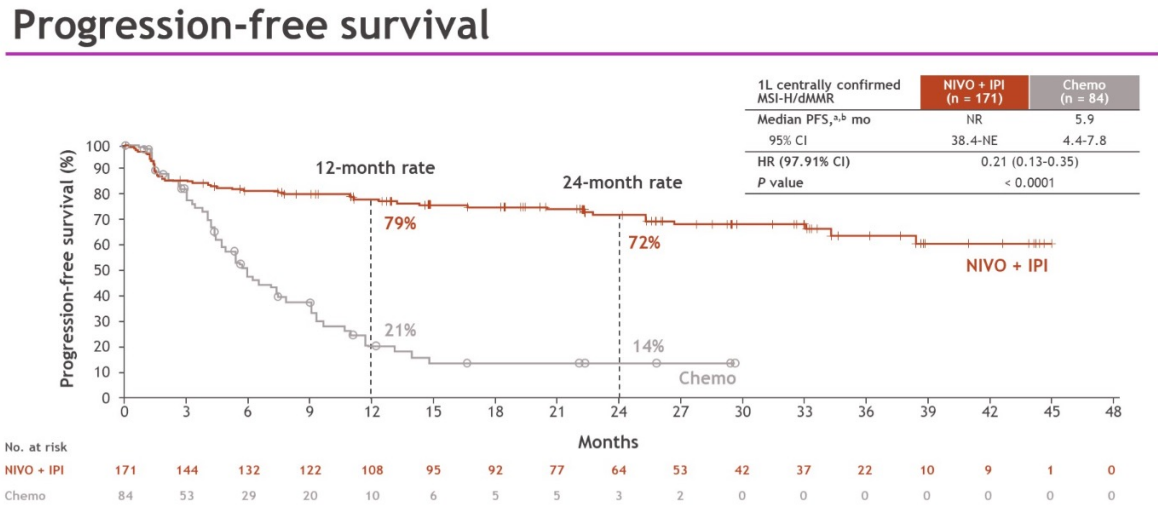
Morton. J Clin Oncol 2023

Randomized Studies in Advanced dMMR/MSI-H CRC

KEYNOTE- 177[1]



CheckMate 8HW[2]



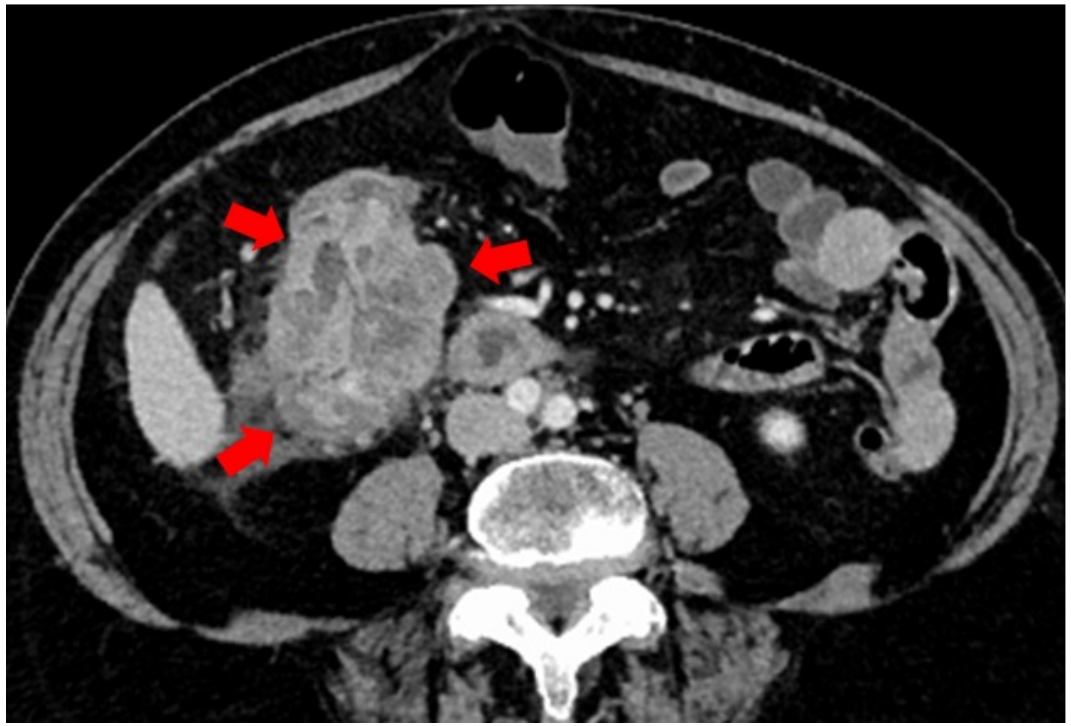
1. Diaz. Lancet Oncol. 2022
2. Andre. ASCO GI 2024

How well does the neoadjuvant immunotherapy (NIT) work?

<u>Real-world patients</u>

1 A Patient with dMMR Hepatic Flexure Adenocarcinoma

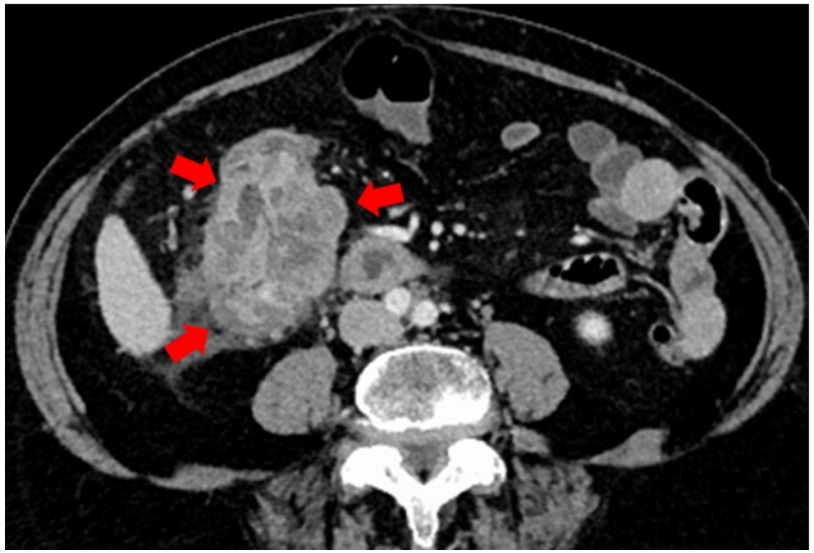
- 78 yr. old female patient
- Abdominal pain, lost 30 pounds
- Multiple co-morbidities (COPD, A.Fib)
- Tumor → MSI-H/dMMR



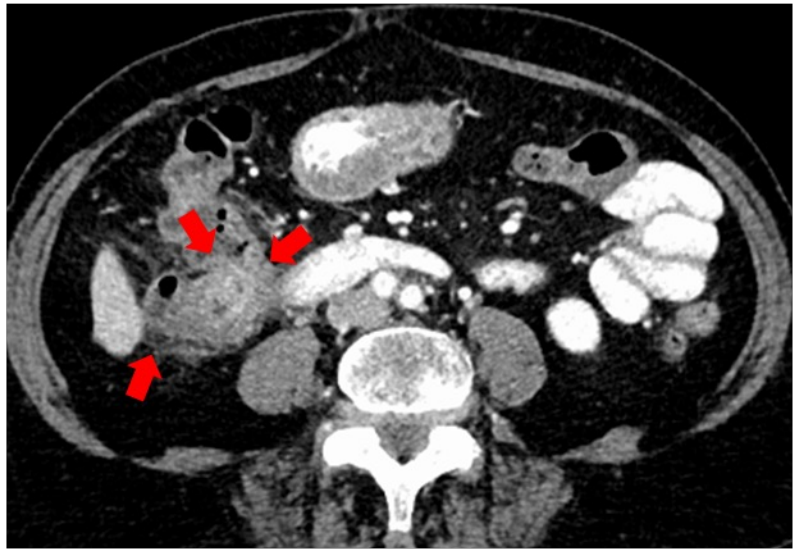
Colorectal surgery evaluation-> <u>NOT a surgical candidate</u>

A Patient with dMMR Hepatic Flexure Adenocarcinoma

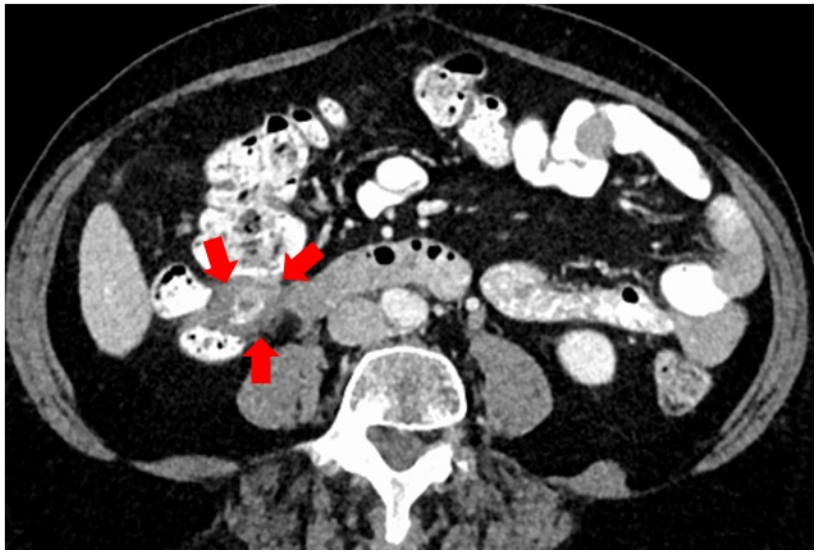
Baseline

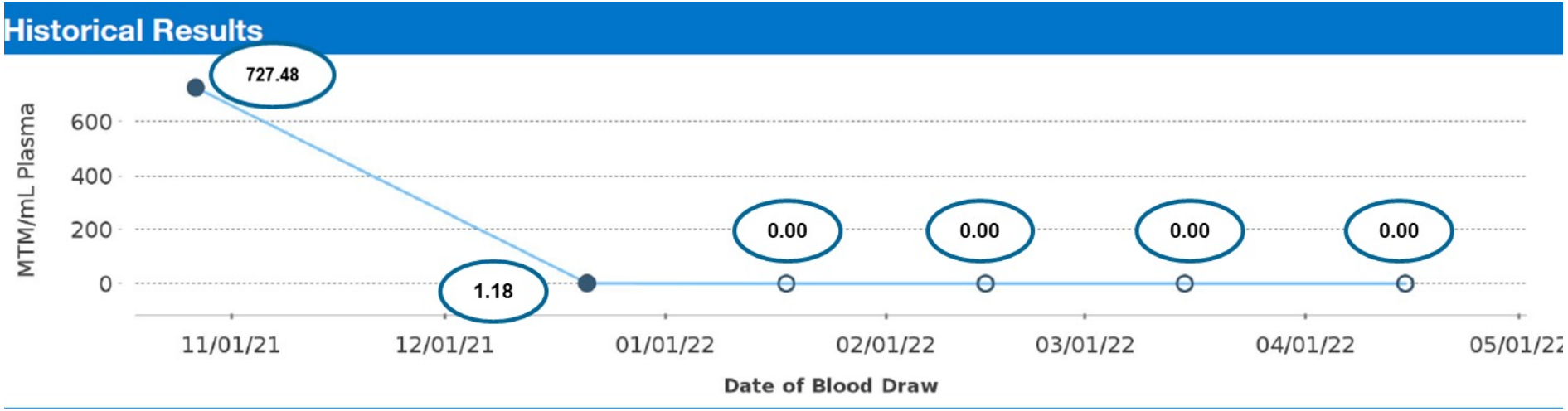


2 months



5 months





In CR 30 months out :

- CT scan
- PET-CT
- Endoscopy
- ctDNA

University Hospitals
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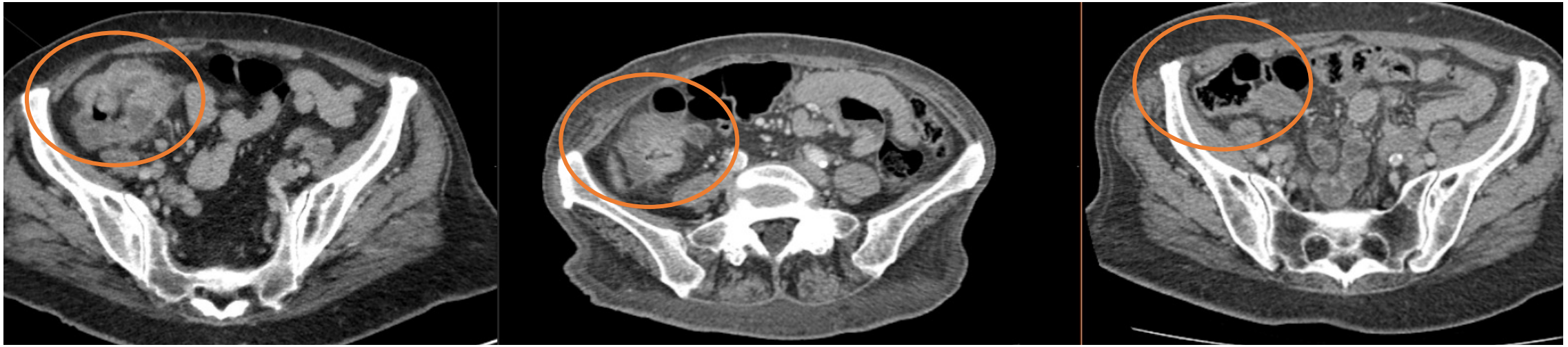
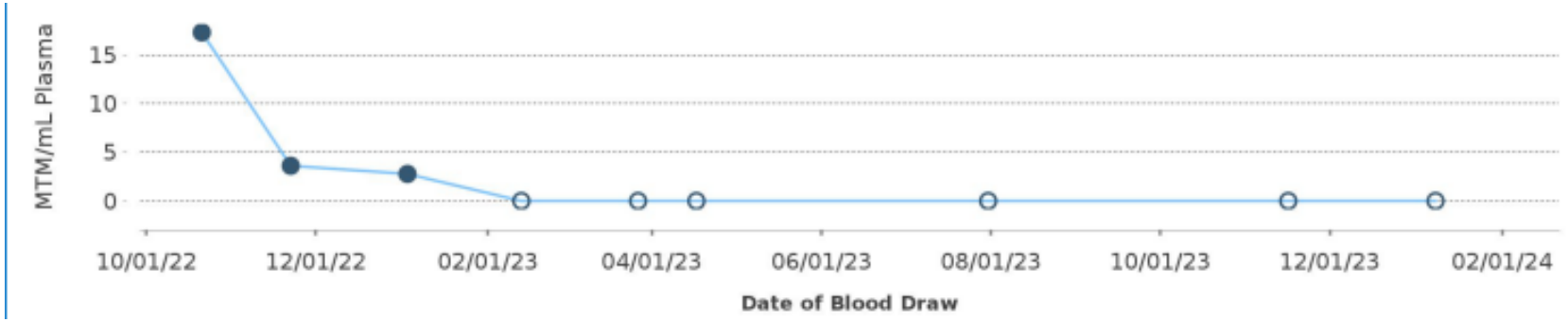
Patient # 2 : A Patient with dMMR sigmoid Colon Cancer

Baseline

3 months

6 months



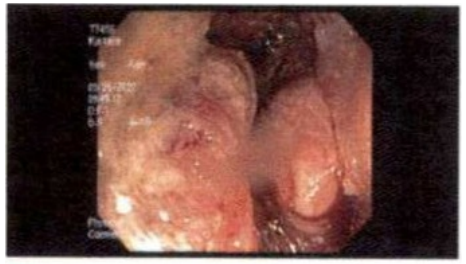


In CR 16 months out :

- CT scan
- PET-CT
- Endoscopy
- ctDNA

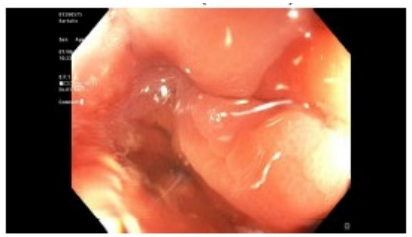
Patient # 3 : A 90-year old Patient with dMMR sigmoid Colon Cancer

Before Immunotherapy

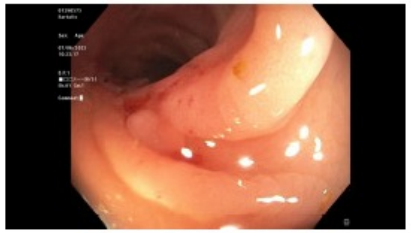


2 Sigmoid Colon

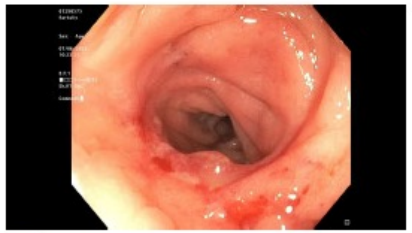
After Immunotherapy



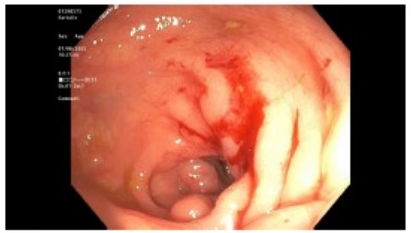
5 Sigmoid Colon



6 Sigmoid Colon



9 Sigmoid Colon

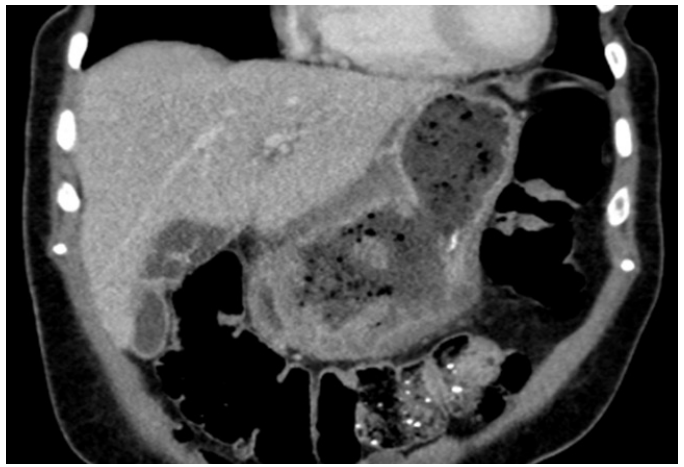


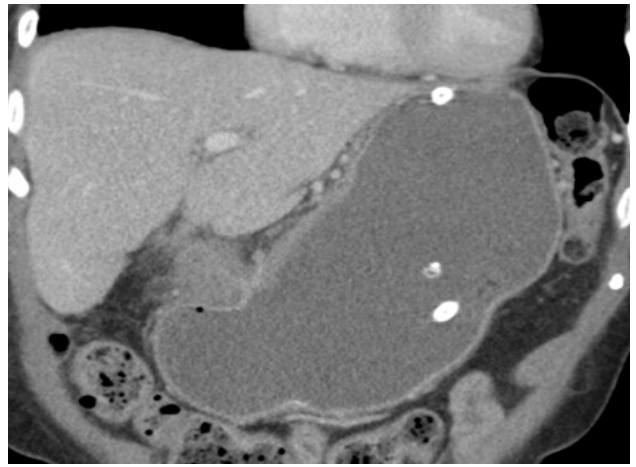
10 Sigmoid Colon

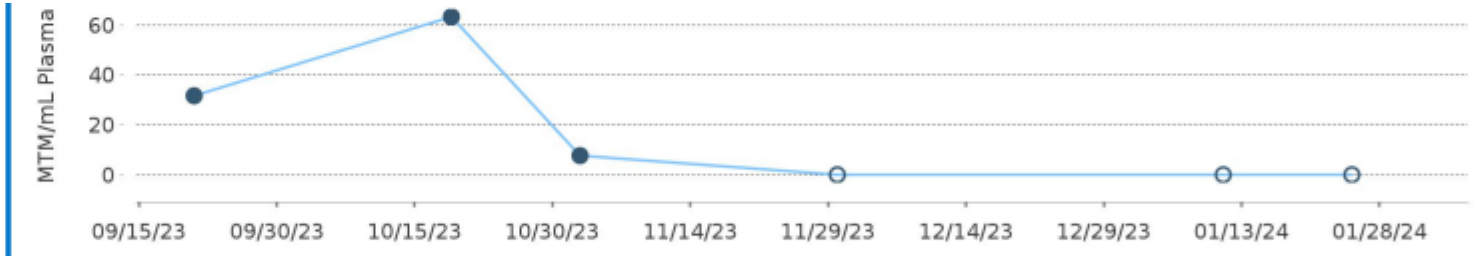
In CR 16 months out :

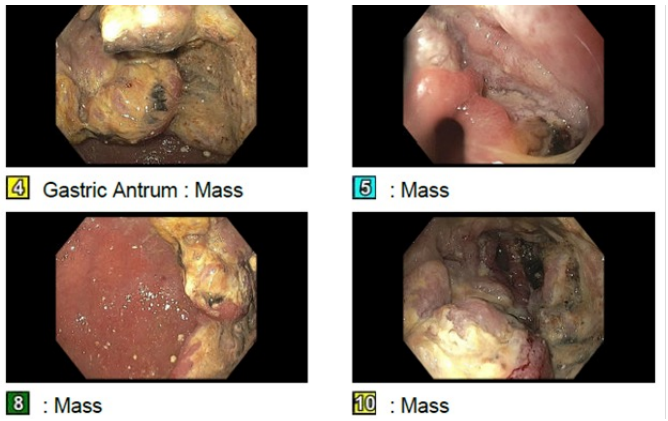
- **CT scan**
- **PET-CT**
- **Endoscopy**

Patient # 4 : A Patient with dMMR Gastric Cancer

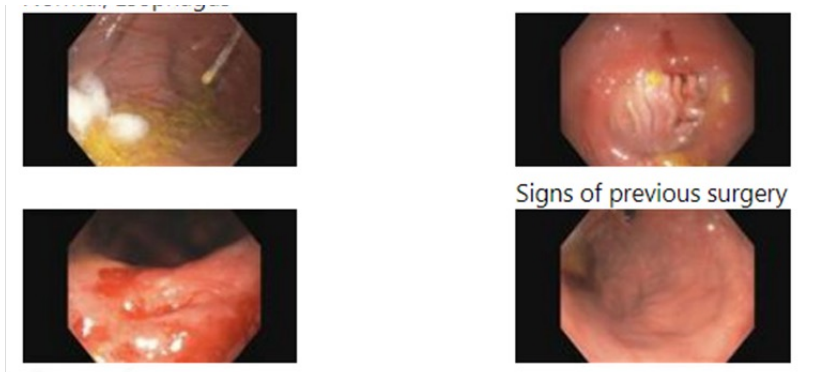








Baseline



6 months

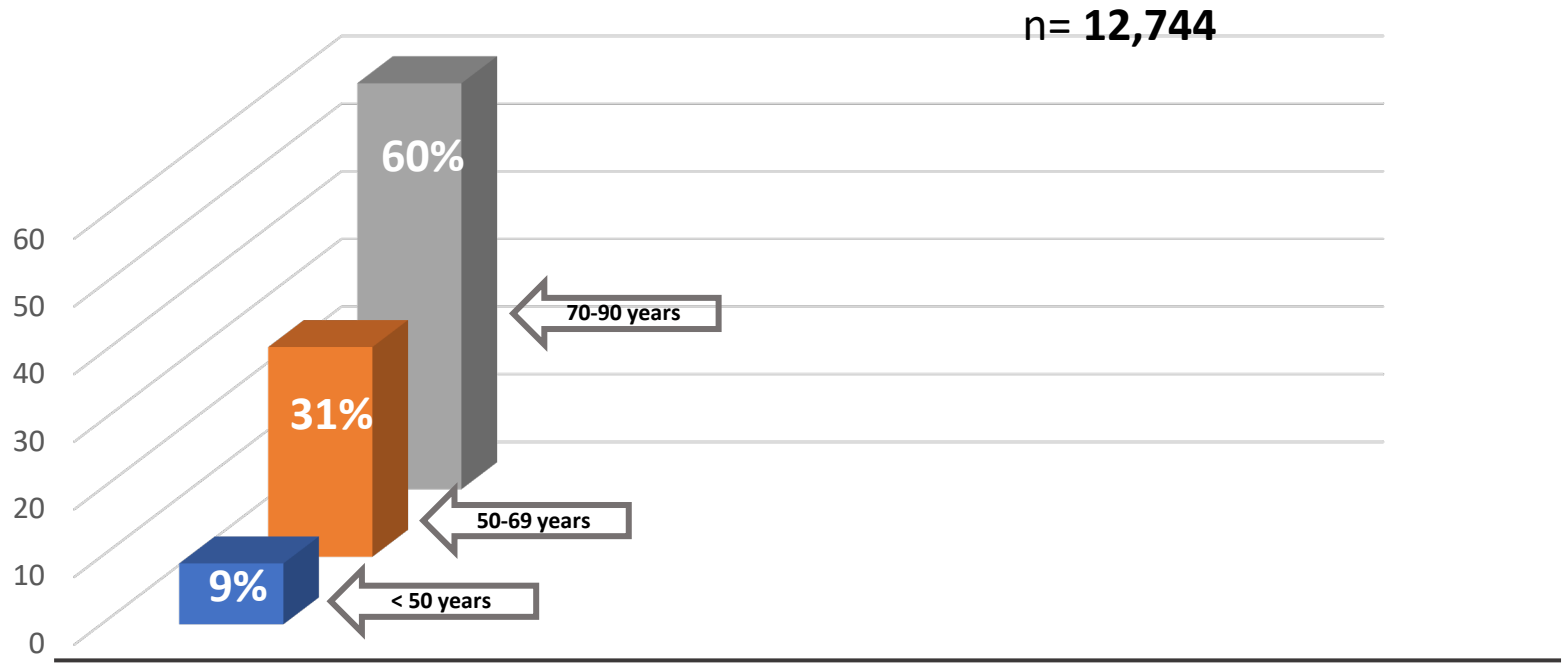
In CR 7 months out :

- **CT scan**
- **PET-CT**
- **Endoscopy**
- **ctDNA**

Rationale for neoadjuvant immunotherapy (NIT) in patients with MSI-H/dMMR localized GI Cancers?

Argument #1 : MSI-H localized GI cancer patients are older

Early-stage (Stage I-III) dMMR CRC: Age Distribution



Gutierrez et al. JCO Precision Oncology 2023

Argument #2: Outcome with the current standard of care is not great!

EJC
EUROPEAN JOURNAL OF CANCER

ORIGINAL RESEARCH | VOLUME 144, P101-112, FEBRUARY 2021

Prognostic variables in low and high risk stage III colon cancers treated in two adjuvant chemotherapy trials

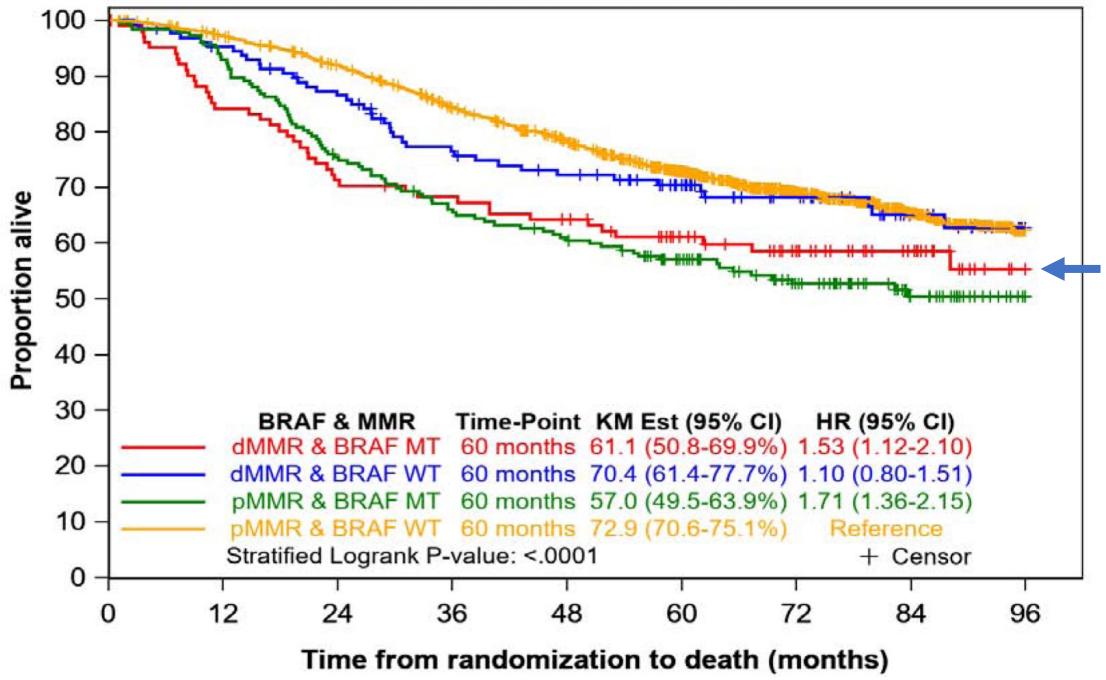
Frank A. Sinicrope • Sakti Chakrabarti • Pierre Laurent-Puig • ... Qian Shi • Steven R. Alberts • Julien Taieb • Show all authors

Published: December 17, 2020 • DOI: https://doi.org/10.1016/j.ejca.2020.11.016 • Check for updates

NCCTG N0147 (Alliance) and PETACC-8 :

- Stage III colon cancer
- Adjuvant FOLFOX +/- cetuximab

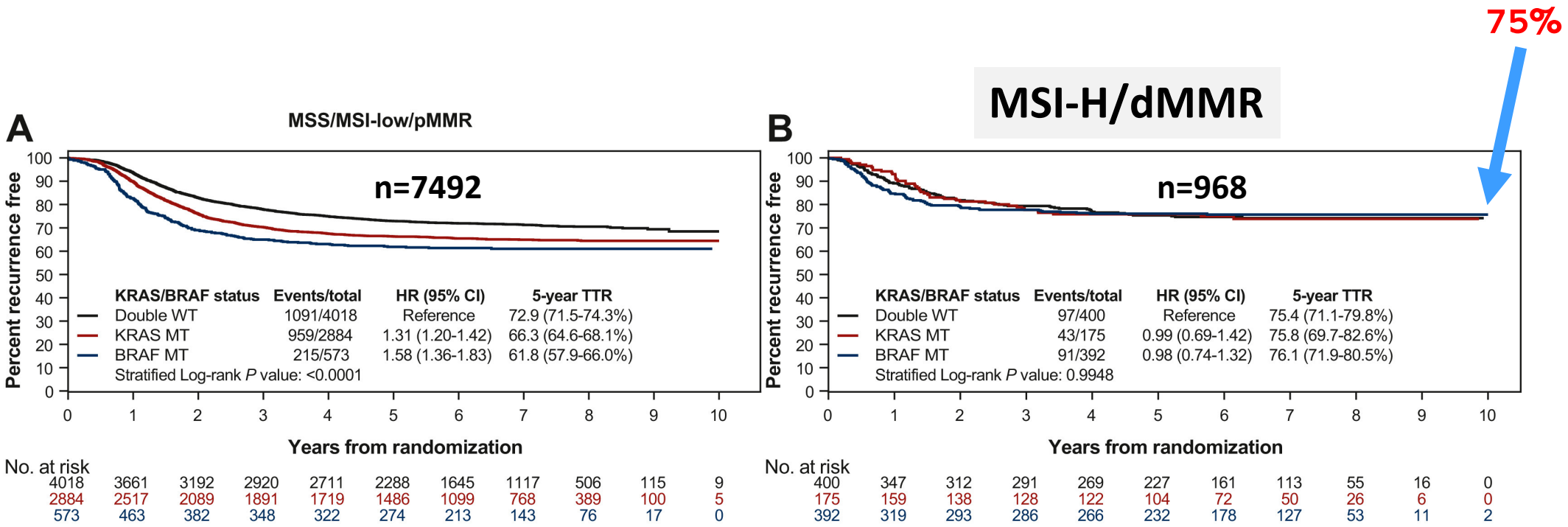
MSI-H high-risk stage III Subgroup



61 %

Stage III Colon Cancer: MSI-H is the driver

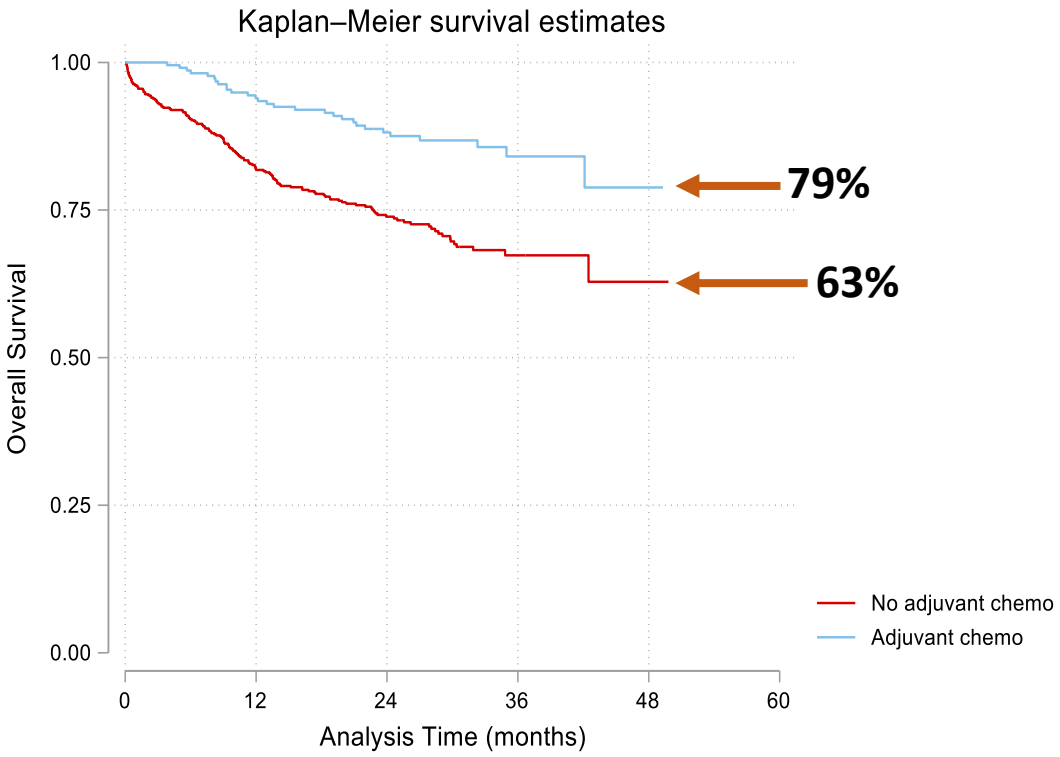
An ACCENT/IDEA database analysis



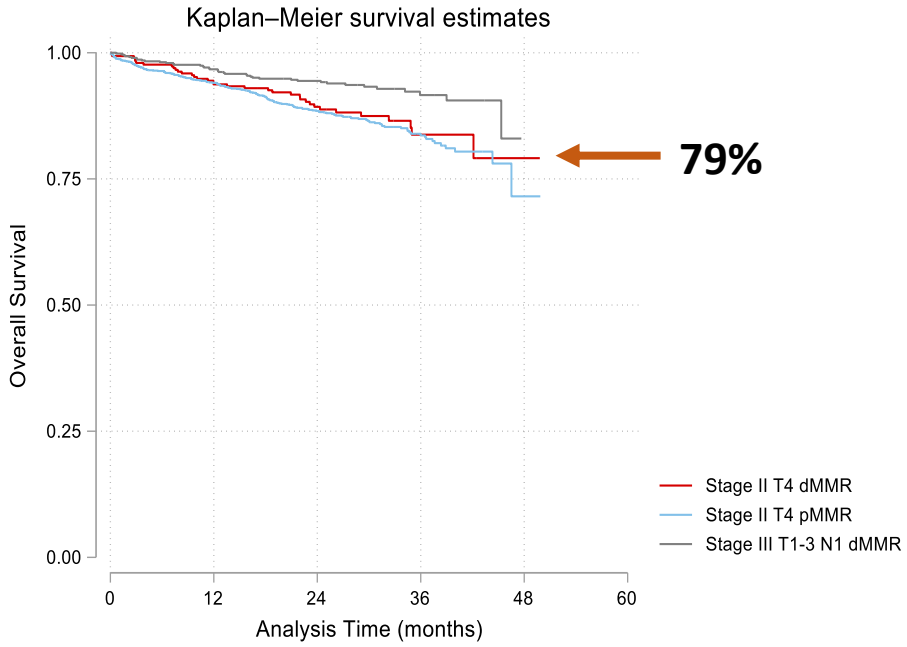
Taieb. Ann Oncol 2023

Overall Survival of Patients with Stage II T4 dMMR Colon Cancer : NCDB Analysis

Overall



< 70 years old

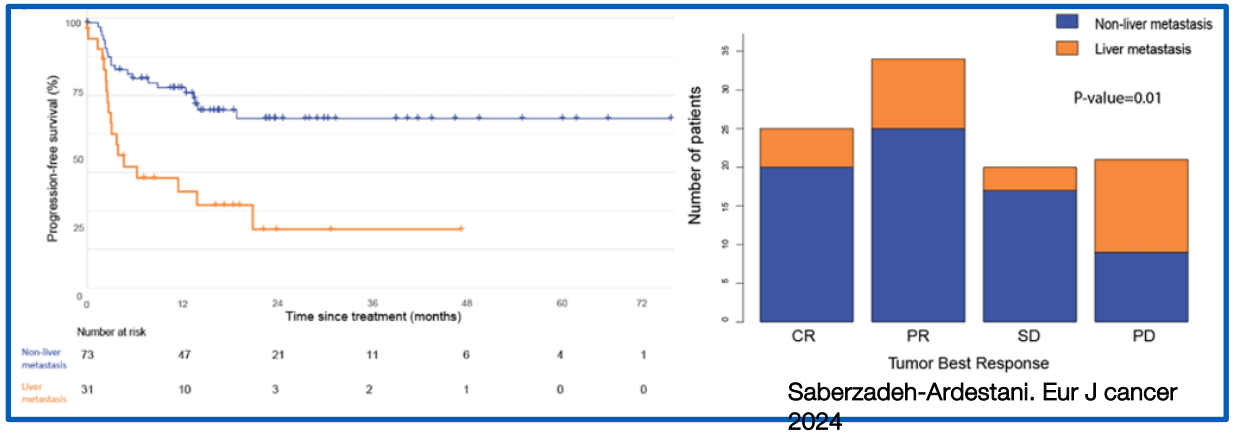


Ahmed,.. Chakrabarti. WGIC 2023

Argument #3:
The checkpoint inhibitors work better in <u>early-stage</u> than advanced dMMR/MSI-H GI Cancers

Biology

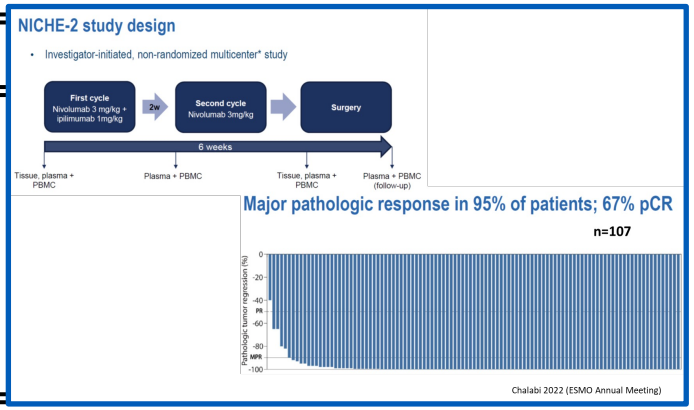
- **Difference in T cell infiltration**
- **A lower degree of systemic immune suppression**
- **The absence of visceral metastases**
- **A lower tumor burden**



Saberzadeh-Ardestani. Eur J cancer 2024

Data

Study	n	Primary Site	NIT	pCR (%)
NICHE-2	107	Colon	IPI +Nivo	67
NICHE-1	20	Colon	IPI +Nivo	60
Ludford et al	17	CRC	Pembrolizumab	65
GERCOR NEONIPIGA	29	Gastric/GEJ	IPI+Nivo	59

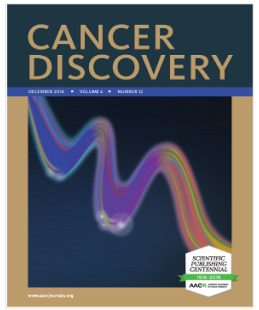


Argument #4:
The checkpoint inhibitors have improved efficacy in the neoadjuvant setting than in the adjuvant setting

CANCER DISCOVERY

ABOUT ARTICLES FOR AUTHORS ALERTS NEWS COVID-19 WEBINARS 10TH ANNI

Volume 6, Issue 12
1 December 2016



RESEARCH ARTICLES | DECEMBER 04 2016

Improved Efficacy of Neoadjuvant Compared to Adjuvant Immunotherapy to Eradicate Metastatic Disease FREE

Jing Liu; Stephen J. Blake; Michelle C.R. Yong; Heidi Harjunpää; Shin Foong Ngiow; Kazuyoshi Takeda; Arabella Young; Jake S. O'Donnell; Stacey Allen; Mark J. Smyth; Michele W.L. Teng

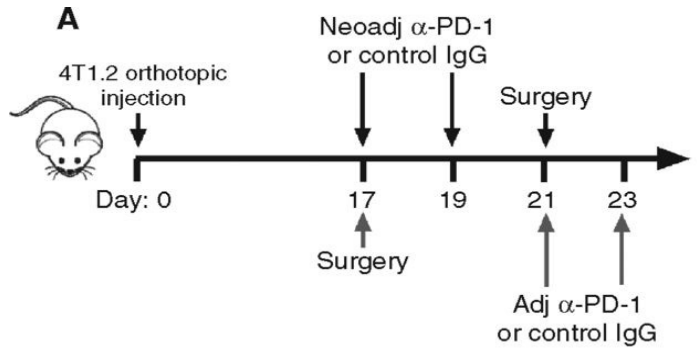
Check for updates

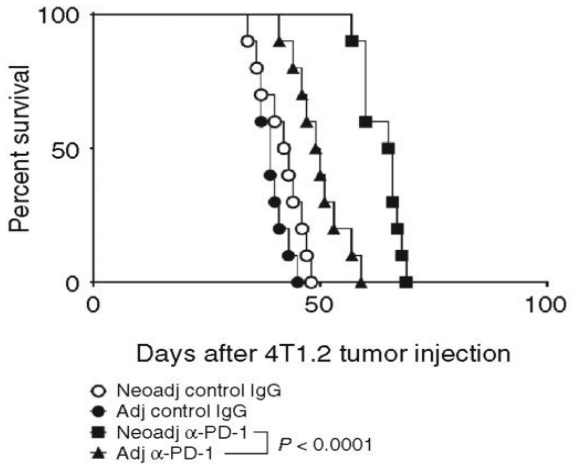
+ Author & Article Information

Cancer Discov (2016) 6 (12): 1382–1399.
https://doi.org/10.1158/2159-8290.CD-16-0577 **Article history**

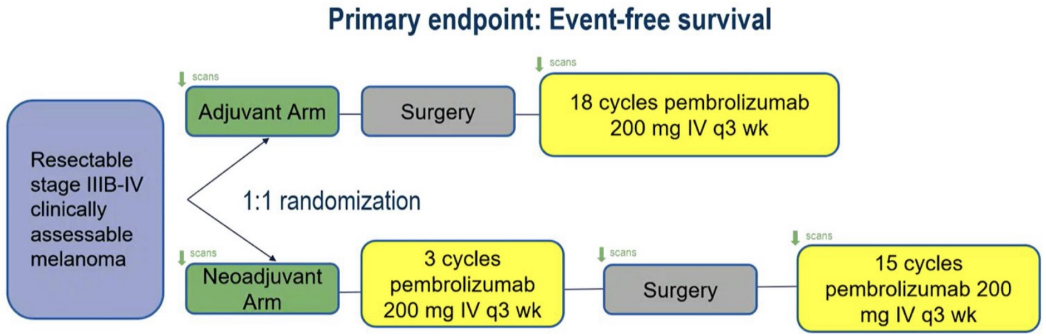
Related Content

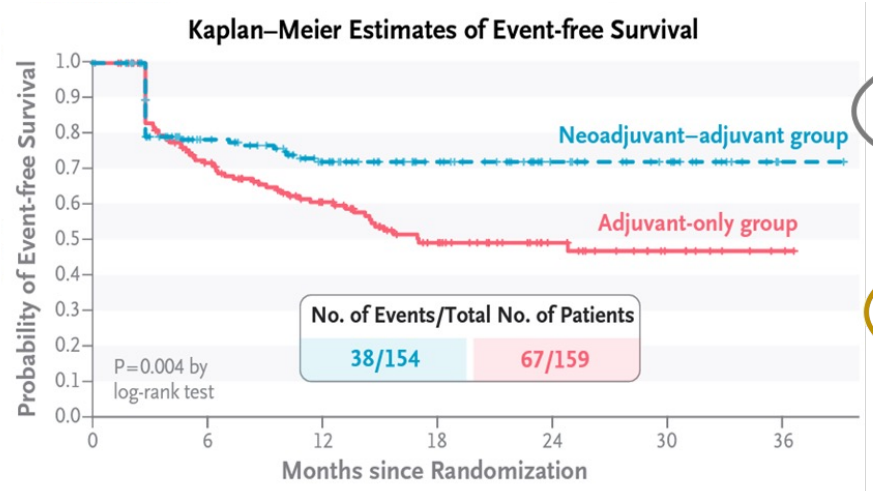
A commentary has been published: Making the Most of Cancer Surgery with Neoadjuvant Immunotherapy
A related article has been published: In This Issue

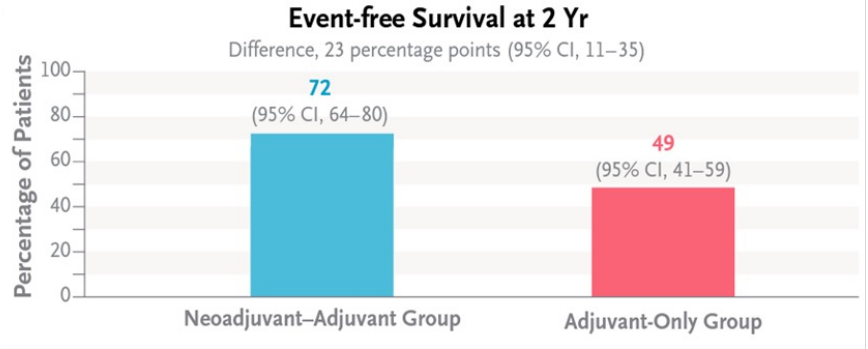




S1801 Study Schema







Median follow-up - 14.7 months

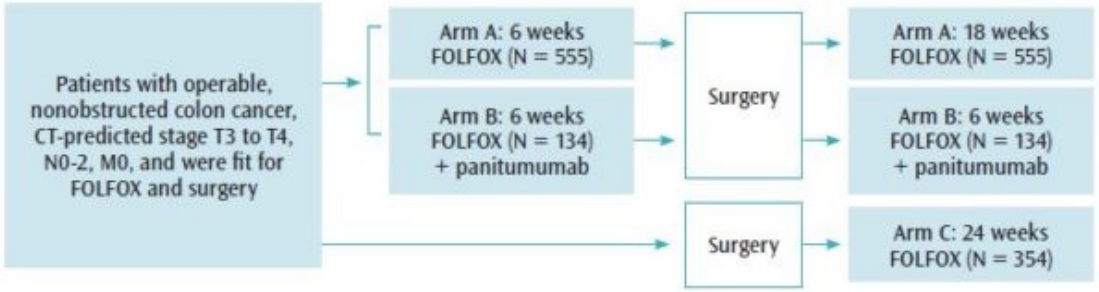
- **pCR 21 % (28/132)**

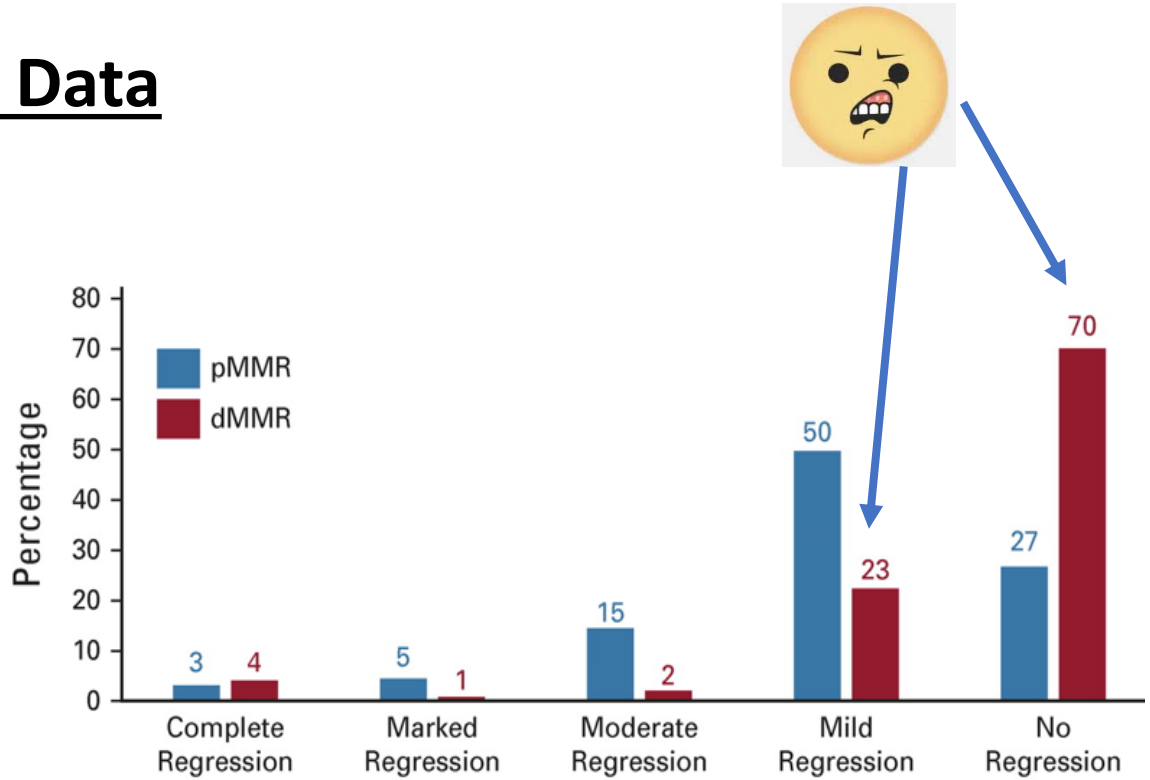
Patel et al. NEJM 2023

Argument #5:
Chemotherapy has suboptimal anti-tumor activity against dMMR tumors

FOxTROT Data

Trial Design



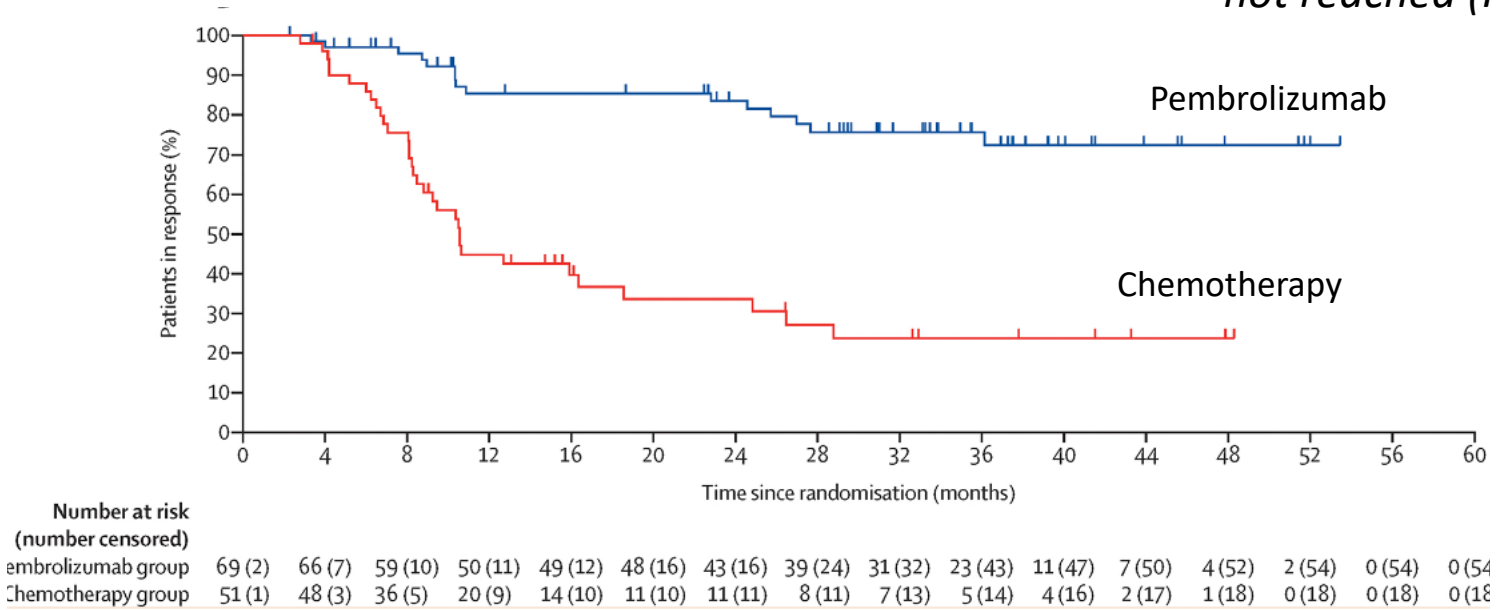


Morton. J Clin Oncol 2023

Argument #6: Durability of Response

KEYNOTE-177 (Pembrolizumab): Long-term result (after a median follow-up of 44.5 months)

The median duration of response with pembrolizumab was not reached (IQR, 36.1 to not reached)



Number at risk (number censored)																
embrolizumab group	69 (2)	66 (7)	59 (10)	50 (11)	49 (12)	48 (16)	43 (16)	39 (24)	31 (32)	23 (43)	11 (47)	7 (50)	4 (52)	2 (54)	0 (54)	0 (54
Chemotherapy group	51 (1)	48 (3)	36 (5)	20 (9)	14 (10)	11 (10)	11 (11)	8 (11)	7 (13)	5 (14)	4 (16)	2 (17)	1 (18)	0 (18)	0 (18)	0 (18

Diaz. Lancet Oncol. 2022

NIT in patients with dMMR/MSI-H Localized GI Cancers : Questions abound……??????

- **Which Immunotherapy ?**
- **Duration of Immunotherapy ?**
- **Response assessment and disease monitoring ?**
- *Progression on immunotherapy ? ➡ Rare*
- *Durability of response ? ➡ Durable*
- *Toxicity ? ➡ Modest*

A Systematic Review Result

JCO® Precision Oncology
An American Society of Clinical Oncology Journal

Outcome of Patients With Early-Stage Mismatch Repair Deficient Colorectal Cancer Receiving Neoadjuvant Immunotherapy: A Systematic Review

Authors: Sakti Chakrabarti, MD, Udhayvir Singh Grewal, MD, Kruti Bhagirath Vora, MD, Aparna Raj Parikh, MD, Diana Almader-Douglas, MA, MLS, AHIP, Amit Mahipal, MPH, MBBS, and Mohamad (Bassam) B. Sonbol, MD | AUTHORS INFO & AFFILIATIONS

Publication: JCO Precision Oncology • Volume 7, Number 7 • https://doi.org/10.1200/PO.23.00182

- n= 423: Colon=326 (77%),Rectal =97 (23%)
- Among the resected patients, 233/334 **(70%) achieved pCR**
- Complete clinical response **(cCR) was reported in 72/89 (81%) patients**
- Cancer progression on initial NIT : 4/423 (0.9%)
- Cancer progression after initial response to NIT (median follow-up 4-27 months : 3/419 (0.7%)
- Grade 3 or higher toxicity reported only in 6.3 % of patients.

DREAM-GI

A National Registry for patients with dMMR/MSI-H GI cancers receiving Neoadjuvant Immunotherapy (NIT)

University Hospitals Seidman Cancer Center

Case Western Reserve University | Case Comprehensive Cancer Center

Initial Findings from the DREAM-GI National Database: Assessing the Efficacy and Safety of Neoadjuvant Immunotherapy (NIT) in Patients with deficient mismatch repair/microsatelliteinstability-high (dMMR/MSI-H) Gastrointestinal (GI) Cancer

Sakti Chakrabarti[1], J. Eva Selfridge[1], Marie Parish[5], David L Bajor[1], Antony Ruggeri[3], Sameer Tolay[4],Madison Conces[1], Melissa Amy Lumish[1], Amr Mohamed[1], Amit Mahipal[1], Aditya V. Shreenivas[2].1. University Hospitals Seidman Cancer Center, Case Western Reserve University (OH). 2. Medical College of Wisconsin (WI), 3. Aurora Cancer Care (WI), 4. SSM Health(WI), 5. Mayo Clinic (MN)

Introduction

Patients with dMMR/MSI-H gastrointestinal (GI) cancer occasionally receive neoadjuvantimmunotherapy (NIT) due to various clinical considerations. To systematically evaluate theoutcome of these patients, we initiated the DREAM-GI national database, intending to harness real-world data to provide crucial insights into the outcomes, safety profile, and response patterns of dMMR/MSI-H GI cancer patients undergoing NIT. Herein, we present the initial findings.

Methods

We developed a centralized database to collect de-identified clinical data from patients with dMMR/MSI-H GI cancers receiving NIT.
We collected data retrospectively and prospectively through September 15, 2023.

Conclusions

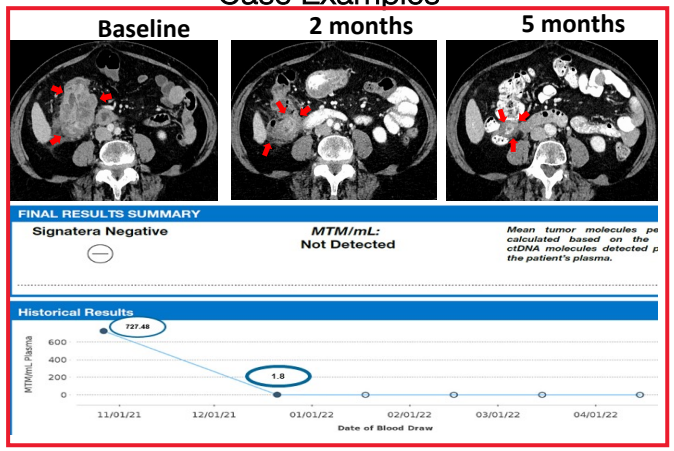
- NIT is associated with remarkable response rate and durability in patients with dMMR/MSI-H GI cancers.
- Progression on NIT is infrequent.
- These real-world data support further investigation of non-operative approaches for patients with dMMR/MSI-H GI cancers.

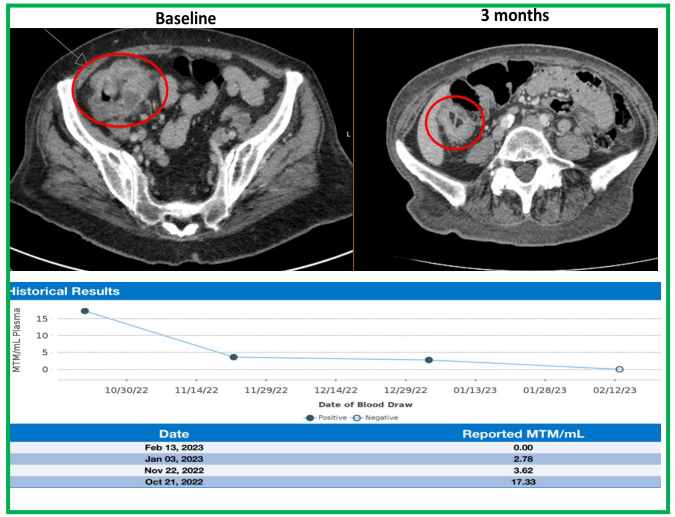
Results

Baseline Characteristics & Treatment of dMMR/MSI-H GI Cancer Patients receiving Neoadjuvant Immunotherapy (n=50)	
Age- median, range (years)	67(32-90)
Sex Male- no (%) Female - no (%)	 29 (58) 21 (42)
Race White - no (%) Black- no (%)	 41 (82) 9 (18)
Clinical stage I-III- no (%) IV- no (%)	 34 (68) 16 (32)
GI Cancer Types CRC- no (%) GE Cancers– no (%) Pancreaticobiliary – no (%)	 31 (62) 07 (14) 12 (24)
NIT Regimens Pembrolizumab- n (%) IPI/Nivo- n (%) IO+Chemo- n (%)	 40 (80) 8 (16) 2 (4)
Treatment-naïve- n (%) Previously treated – n (%)	33 (66) 17 (34)
Median duration of NIT, months (range)	6 (1.5-55)
Surgery – n (%)	5 (10)

Outcomes with NIT (n=47)	
Follow-up (m), Median (range)	14 (2-80)
Time to best response (m), Median (range)	3 (1.5-12)
ORR- % (n)	75 (35)
Radiologic CR – % (n)	43 (20)
Pathologic CR – % (n)	9 (4)
PR- % (n)	24 (11)
Stable Disease – % (n)	15 (7)
Progressive Disease (PD) – % (n)	10 (5)
Median PFS (months)	Not reached
Median OS (months)	Not reached
Median f/u of patients achiving CR (m)	25.5
PD among patients achiving CR - % (n)	0 (0/24)

Case Examples





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Conclusion

- ✓ All GI Cancer patients should have MMR status checked
- ✓ Immunotherapy with ICIs alone is a reasonable option for surgically unfit patients with localized MSI-H/dMMR GI cancers
- ✓ A proportion of patients can possibly achieve longterm remission without surgery
- ✓ Role of NIT in localized dMMR/MSI-H GI cancers should be further investigated

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