City of Hope

Annual

Advances and Innovations in Endoscopic Oncology and Multidisciplinary Gastrointestinal Cancer Care

Paradigm Shift in MSI Colorectal Cancers

Andreas M. Kaiser, MD FACS FASCRS

Professor of Surgery
Chief, Division of Colorectal Surgery
City of Hope



Disclosures

- Consultant for Virtual Incision *(relationship has ended)*.

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.

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:

- Impact of socioeconomic and social/cultural background to access to care.
- Failure to recognize malignancy in younger than screening population.

Background - MSI-H/dMMR

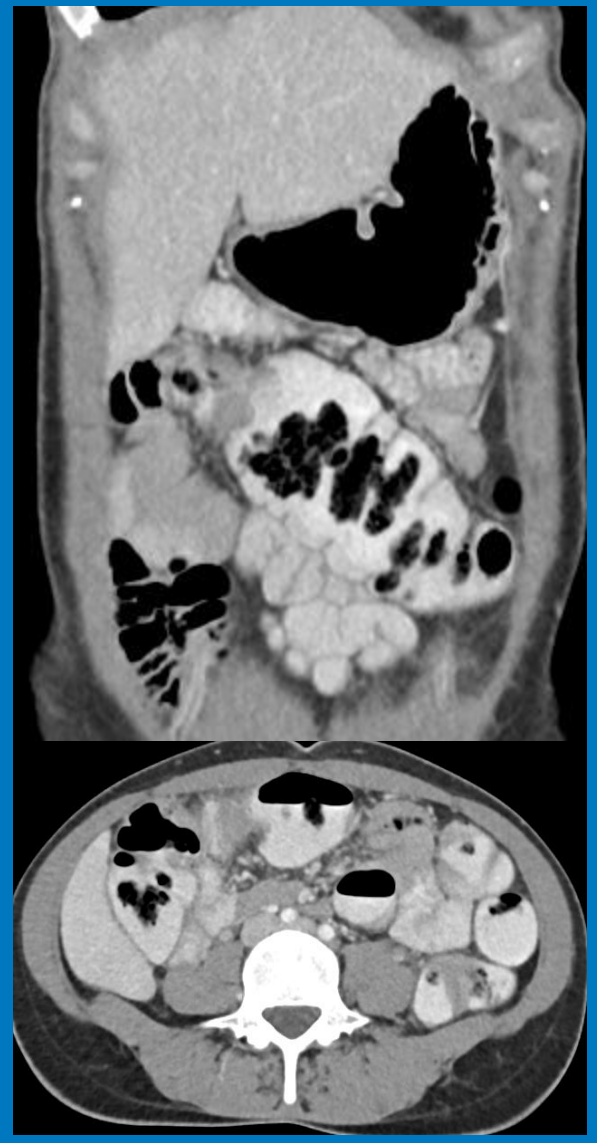
- Approximately 15% of all colorectal cancers are MSI-H/dMMR:
  - 15–20% germline (Lynch syndrome)
  - ~80–85% sporadic
    - ✓somatic MLH1 promoter hypermethylation in setting of the CpG island methylator phenotype (CIMP)
  - biallelic ("double") somatic MMR inactivation:
    - ✓increasingly recognized category which accounts for a substantial share of MSI-H tumors that are neither MLH1-hypermethylated nor germline (45–68% of unexplained dMMR cases).
- MSI-H more common in right-sided colon cancer than in rectal cancer. Rectal adenocarcinoma with notably lower rate (~3–5%) than colon cancer (~10–20%).

Johannet P - Nat Rev Clin Oncol 2025

Case study 1

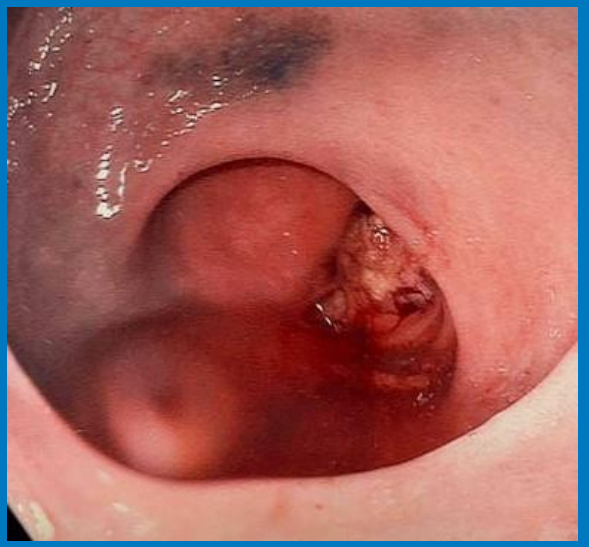
- 41 y/o female with strong family history of CRC → screening.
- Colonoscopy: large partially obstructing mass in proximal transverse colon.
- Pathology: dMMR poorly differentiated adenocarcinoma, MLH1/PMS2 deficient.

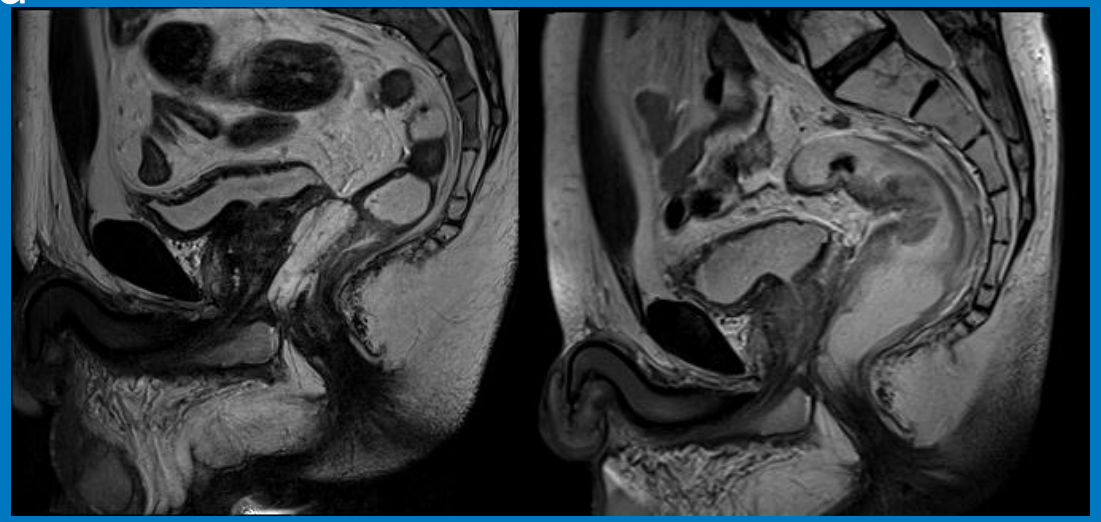
Surgery or no surgery?



Case study 2

- 87 y/o male with history of RT for prostate CA, rectal bleeding
- Colonoscopy: Non-obstructing mass at 12 cm.
- Pathology: dMMR moderately differentiated adenocarcinoma, MLH1/PMS2 deficient → hypermethylated.





Sadly: hindsight: visible lesion 4 yrs earlier

Surgery or no surgery?

Stage gradient biologically meaningful

Stage	MSI-H/dMMR prevalence
Stage I	16.6%
Stage II	19.9%
Stage III	12.4%
Stage IV (metastatic)	7.3%
Overall (all stages)	14.2%

- Lower prevalence in stage IV reflects that MSI-H tumors are less likely to metastasize (higher neoantigen burden and immune surveillance), not that they convert to MSS

Johannet P - Nat Rev Clin Oncol 2025

MSI-H/dMMR – Lynch syndrome

➢Lynch syndrome (formerly HNPCC):

- most common hereditary colorectal cancer (CRC) syndrome
- affecting 1 in 280-400 individuals.
- autosomal dominant germline pathogenic variants in DNA mismatch repair (MMR) genes:
  - ✓*MLH1* (~40%)
  - ✓*MSH2* (~35%)
  - ✓*MSH6* (~20%)
  - ✓*PMS2* (~5%),
  - ✓3’ deletions in *EPCAM* (1-3%) causing epigenetic silencing of *MSH2*

Johannet P - Nat Rev Clin Oncol 2025

HNPCC (now Lynch syndrome) – management in 2011

- Amsterdam
- Bethesda
- Guessing
- Surgery

Guidelines for the management of these marker-and/or family history positive patients are increasingly well defined. However, many young patients do not have a positive family history (Amsterdam negative), and/or they either had no genetic testing done or were found to be genetic marker-negative. There is no consensus in the literature about defining the best management for these patients. Approaches vary from a segmental resection to a (sub-) total colectomy with ileosigmoid or -rectal anastomosis or a proctocolectomy. The future risk of metachronous cancers after a limited resection and the role of a piece of mind need to be weighed against the potential negative impact on quality of life after more extensive resections. Although the literature is limited, we suggest that marker- and Amsterdam-negative young patients (<50 years old) with a colon cancer should consider an extended resection with an ileosigmoid anastomosis.

Cannom RR – Semin Colon Rectal Surg 2011;22:1270-130

The shift in one sentence 2011 → 2026

- MSI/dMMR status is no longer a prognostic footnote. It is a treatment-defining variable that can move immunotherapy before surgery, shrink the operation, and in selected rectal cancers avoid surgery altogether.

TEST EARLY

Universal MMR/MSI identification

TREAT FIRST

ICI before knife in selected localized disease

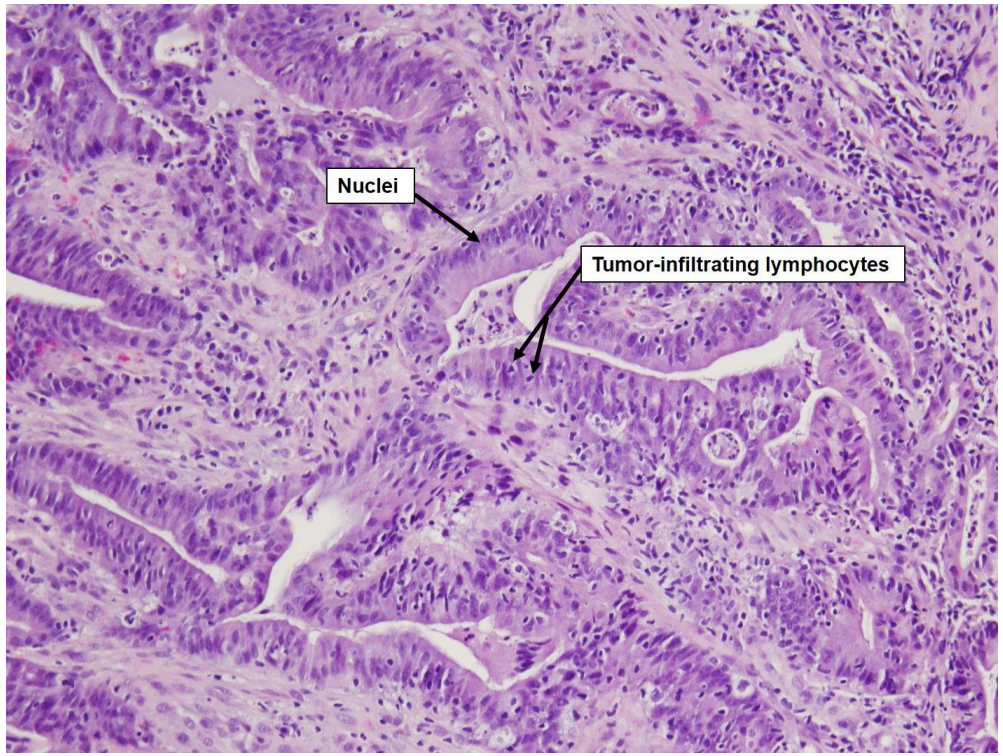
OPERATE SMARTER

De-escalate only with rigorous response assessment

Universal MMR/MSI testing on all CRC, with reflex *BRAF* V600E and/or *MLH1* promoter methylation testing (for *MLH1*-loss tumors) → remainder to germline testing
Molecular diagnosis must precede irreversible treatment decisions

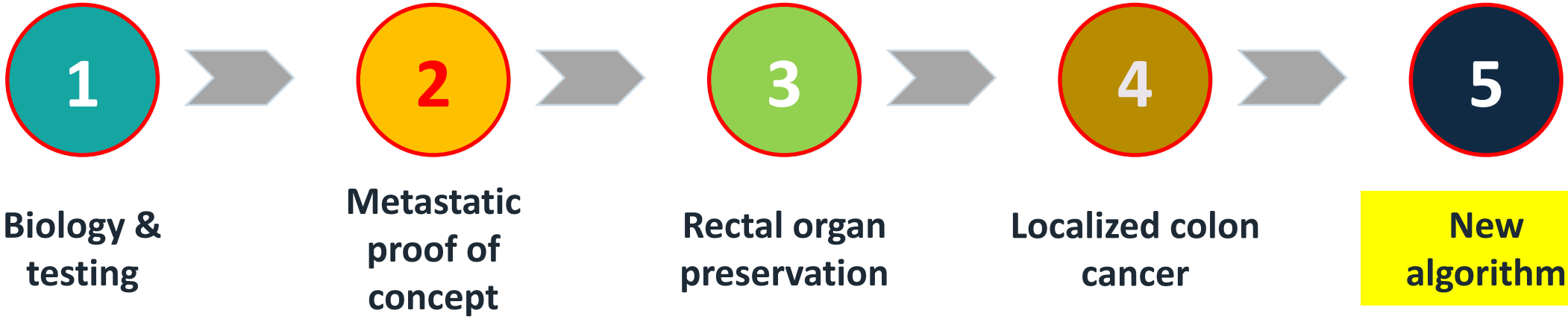
dMMR creates an immunologic target

- Loss of MLH1, MSH2, MSH6, or PMS2 function
- Replication errors accumulate at microsatellites
- Frameshift neoantigens increase immune visibility
- Pathology: often poorly differentiated adenocarcinoma with cribriform and medullary growth pattern, signet ring cells, and mucinous differentiation; prominent host immune response (Crohn-like lymphoid reaction, tumor-infiltrating lymphocytes
- PD-1 blockade releases an already primed immune response



Le DT – Science 2017;357:409-413.

Evolution of treatment



Note: small/necrotic biopsy → subclonal/weak staining → discordant IHC/MSI → false “resistance” → wrong treatment?

MSI-H/dMMR metastatic disease

PROOF OF CONCEPT

City of Hope®

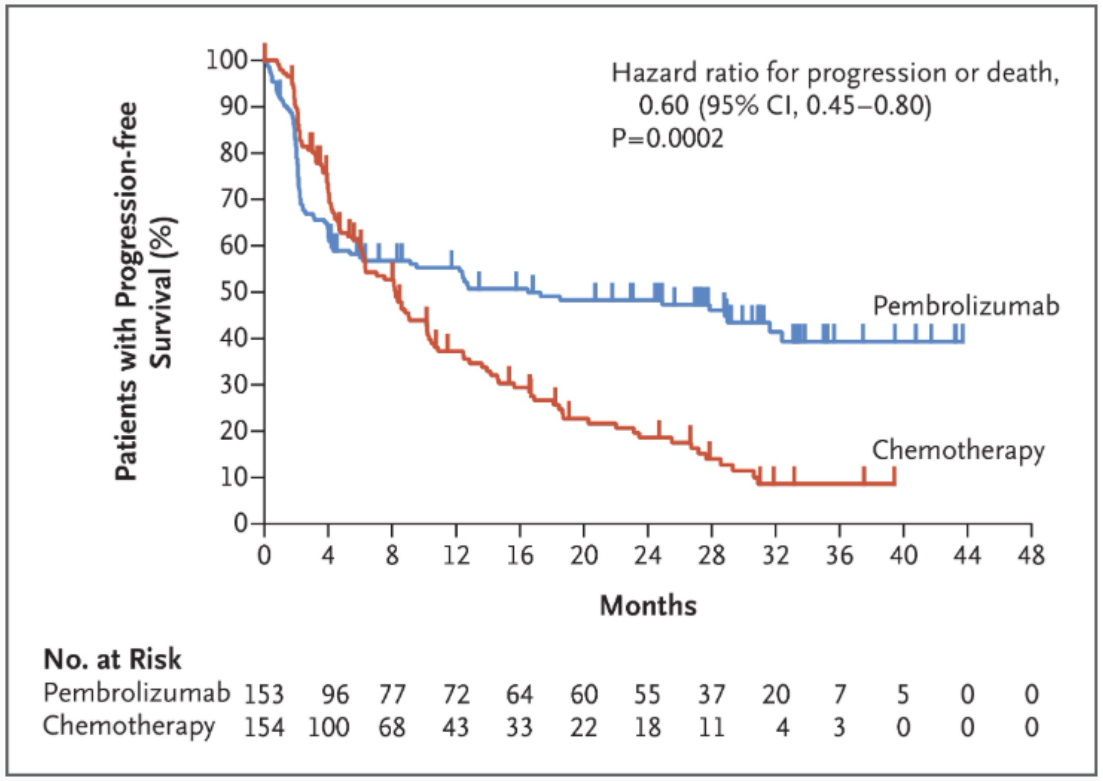
MSI-H/dMMR metastatic disease

➢ **KEYNOTE-177 (2016-2018):**

- Randomized open-label phase III in untreated MSI-H/dMMR mCRC, ECOG 0-1
- N=307 (1:1, crossover allowed):
  - ✓153 pembro: Pembrolizumab 200 mg q3wk
  - ✓154 chemo: mFOLFOX6/FOLFIRI ± bevacizumab/cetuximab

➢ Outcome:

- Objective response rate with pembro: 45.1%
- Median PFS 16.5 vs 8.2 mo (HR 0.60)
- 5-yr median OS 77.5 vs 36.7 mo (HR 0.73)
- OS confounded by 62% effective crossover
- grade 3–5 AE 22% vs 66%



Andre T – NEJM 2020
Diaz LA - Lancet. Oncol - 2022.

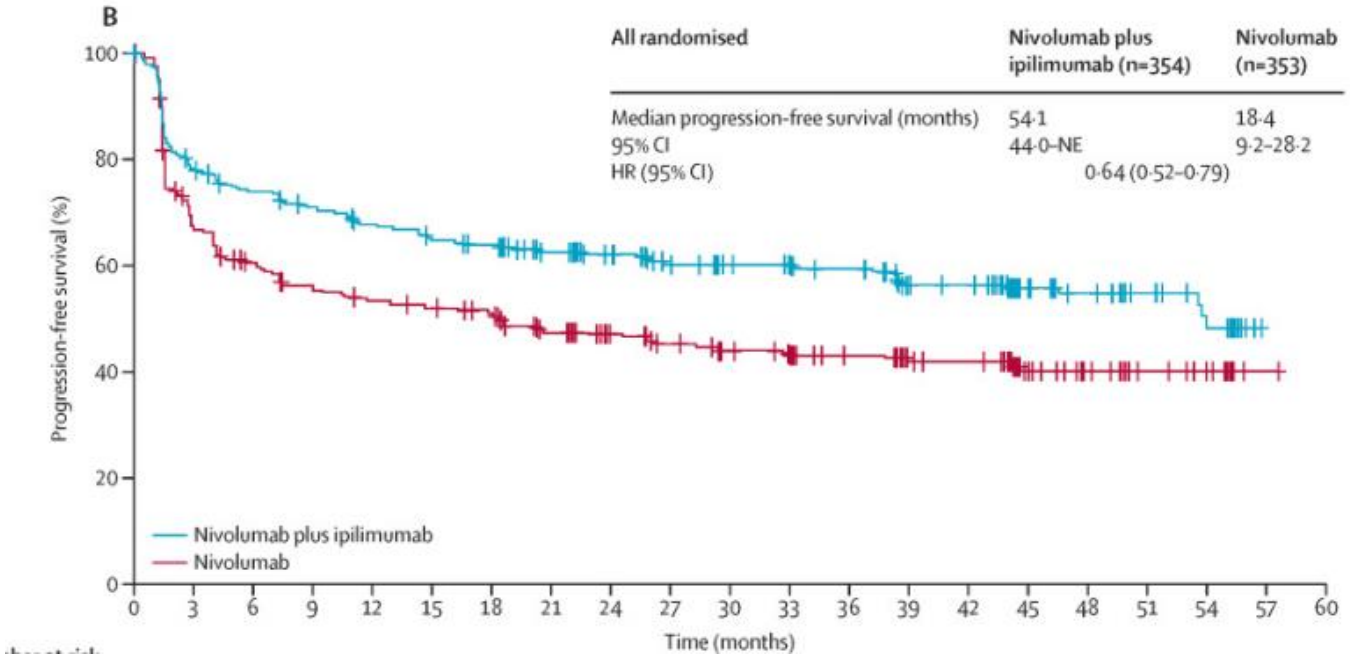
MSI-H/dMMR metastatic disease

➢ CheckMate 8HW (2019-2023)

- Randomized open-label phase III in unresectable/metastatic MSI-H/dMMR CRC
- N=839 randomized, 2:2:1)
  - ✓354 Nivolumab + ipilimumab
  - ✓353 Nivolumab
  - ✓132 chemotherapy

➢ Outcome:

- PFS after min f/u 16.7 months:
  - ✓ Nivo+ipi: 54.1 months, 74% @24 months, 29% mort
  - ✓ Chemo: 5.9 months, 11% @ 24 months, 42% mort
- nivo+ipi vs nivo HR 0.62
- grade 3–4 TRAE 22% (nivo+ipi) vs 14% (nivo)



Andre T – NEJM 2024
Andre T – Lancet 2025

MSI-H/dMMR metastatic disease

➢ CheckMate 8HW (2019-2023)

- Randomized open-label phase III in unresectable/metastatic MSI-H/dMMR CRC
- N=839 randomized, 2:2:1)
  - ✓354 Nivolumab + ipilimumab
  - ✓353 Nivolumab
  - ✓132 chemotherapy

➢ Outcome:

- PFS after min f/u 16.7 months:
  - ✓ Nivo+ipi: 54.1 months, 74% @24 months, 29% mort
  - ✓ Chemo: 5.9 months, 11% @ 24 months, 42% mort
- nivo+ipi vs nivo HR 0.62
- grade 3–4 TRAE 22% (nivo+ipi) vs 14% (nivo)

	Nivolumab plus ipilimumab group (n=296)	Nivolumab group (n=286)	p value
Objective response rate (95% CI)	209 (71%) [65–76]	165 (58%) [52–64]	0·0011
Best overall response			..
Complete response	90 (30%)	80 (28%)	..
Partial response	119 (40%)	85 (30%)	..
Stable disease	40 (14%)	53 (19%)	..
Progressive disease	30 (10%)	54 (19%)	..
Unevaluable	17 (6%)	14 (5%)	..
Median time to response, months (IQR)	2·8 (1·4–4·2)	2·8 (1·5–4·2)	..
Median duration of response, months (95% CI)	NR (NE)	NR (NE)	..

Data are n (%), unless otherwise indicated. NE=not estimable. NR=not reached.

Table 2: **Best overall response by blinded review in patients with centrally confirmed microsatellite instability-high or mismatch repair-deficient status**

	Any grade/ grade 3 or 4 n(%)/n(%)
Non-endocrine events	
Rash	23 (7%)/ 5 (1%)
Diarrhoea/colitis	21 (6%)/ 12 (3%)
Hepatitis	13 (4%)/ 6 (2%)
Pneumonitis	7 (2%)/ 4 (1%)
Nephritis and renal dysfunction	6 (2%)/ 2 (1%)
Hypersensitivity	0
Endocrine events	
Hypothyroidism/thyroiditis	62 (18%)/ 3 (1%)
Hyperthyroidism	42 (12%)/ 0
Adrenal insufficiency	35 (10%)/ 10 (3%)
Hypophysitis	23 (7%)/ 11 (3%)
Diabetes mellitus	4 (1%)/ 2 (1%)

Andre T – NEJM 2024
Andre T – Lancet 2025

MSI-H/dMMR metastatic disease

- Residual mass ≠ viable cancer
- Radiographic CR ≠ pathologic sterilization
- “Resectable before ICI” does not mandate immediate surgery

- Map original disease sites
- Use serial imaging and tumor markers
- ctDNA
- Local or organ targeted therapy for oligoprogression
- Primary tumor site?

ICI does not abolish surgical emergencies

Obstruction / perforation / bleeding	Diversion, resection, stent
Asymptomatic primary	Systemic ICI
Near-obstructing bulky tumor	Preemptive surgical plan and close monitoring
Response with limited metastases	Reassess curative local strategies (met and primary)

MSI-H/dMMR localized/resectable disease

EXTRAPOLATION OF CONCEPT TO RECTAL CANCER

City of Hope®

MSI-H/dMMR rectal cancer

- **MSK Single-arm phase II:**
  - Non-randomized: previously untreated dMMR stage II–III rectal adenocarcinoma
  - N=12 (of 16)
  - Dostarlimab 500 mg q3wk ×6 mo; then CRT+surgery only if no cCR
- Outcome:
  - 100% cCR (12/12); none required CRT or surgery; no progression/recurrence (range 6–25 mo)
  - Sustained response @12 months
  - No surgeries, no RT

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JUNE 23, 2022 VOL. 386 NO. 25

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

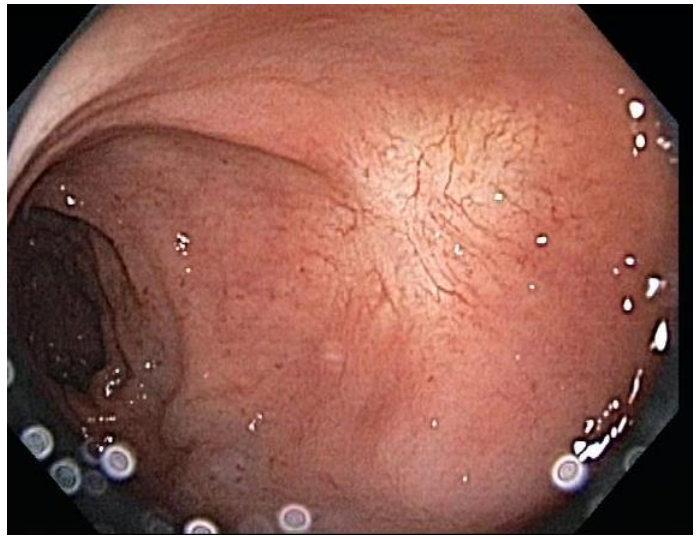
A. Cercek, M. Lumish, J. Sinopoli, J. Weiss, J. Shia, M. Lamendola-Essel, I.H. El Dika, N. Segal, M. Shcherba, R. Sugarman, Z. Stadler, R. Yaeger, J.J. Smith, B. Rousseau, G. Argiles, M. Patel, A. Desai, L.B. Saltz, M. Widmar, K. Iyer, J. Zhang, N. Gianino, C. Crane, P.B. Romesser, E.P. Pappou, P. Paty, J. Garcia-Aguilar, M. Gonen, M. Gollub, M.R. Weiser, K.A. Schalper, and L.A. Diaz, Jr.



Cercek A – NEJM 2022

cCR in rectal cancer

- **pMMR RC post TNT**



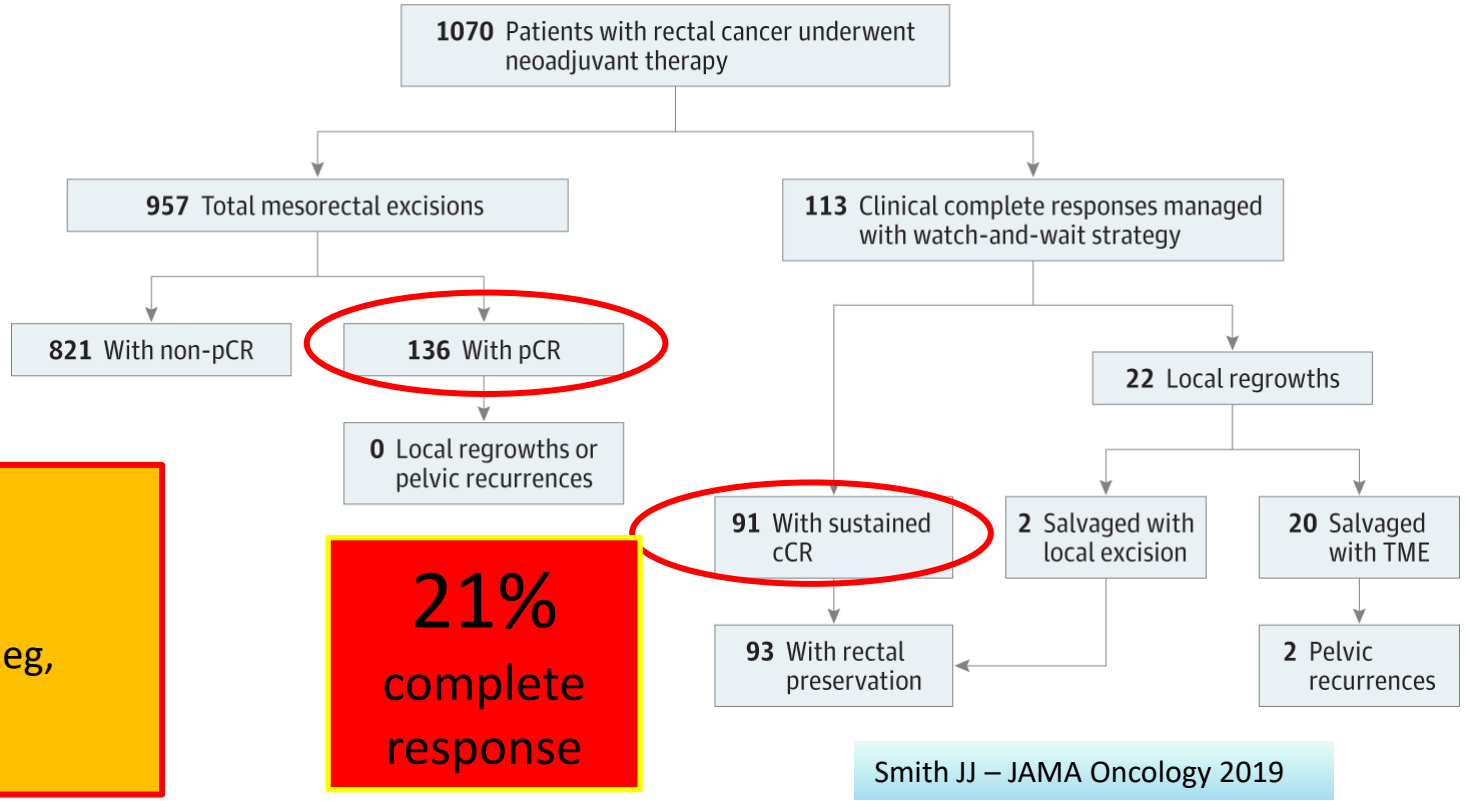
cCR Criteria for W&W:

- ✓ Inert flat non-ulcerated mucosa, maybe some telangiectasias
- ✓ No palpatory, endoscopic, radiological residua (eg, diffusion-weighted MRI)
- ✓ Compliant patient → frequent surveillance

JAMA Oncology | Original Investigation

Assessment of a Watch-and-Wait Strategy for Rectal Cancer in Patients With a Complete Response After Neoadjuvant Therapy

J. Joshua Smith, MD, PhD; Paul Strombom, MD; Oliver S. Chow, MD; Campbell S. Roxburgh, MD, PhD; Patricio Lynn, MD; Anne Eaton, MS; Maria Widmar, MD; Karuna Ganesh, MD, PhD; Rona Yaeger, MD; Andrea Cercek, MD; Martin R. Weiser, MD; Garrett M. Nash, MD, MPH; Jose G. Guillem, MD, MPH; Larissa K. F. Temple, MD, MSc; Sree B. Chalasani, MD; James L. Fuqua, MD; Iva Petkovska, MD; Abraham J. Wu, MD; Marsha Reyngold, MD, PhD; Efsevia Vakiani, MD, PhD; Jinru Shia, MD; Neil H. Segal, MD, PhD; James D. Smith, MD, PhD; Christopher Crane, MD; Marc J. Gollub, MD; Mithat Gonen, PhD; Leonard B. Saltz, MD; Julio Garcia-Aguilar, MD, PhD; Philip B. Paty, MD

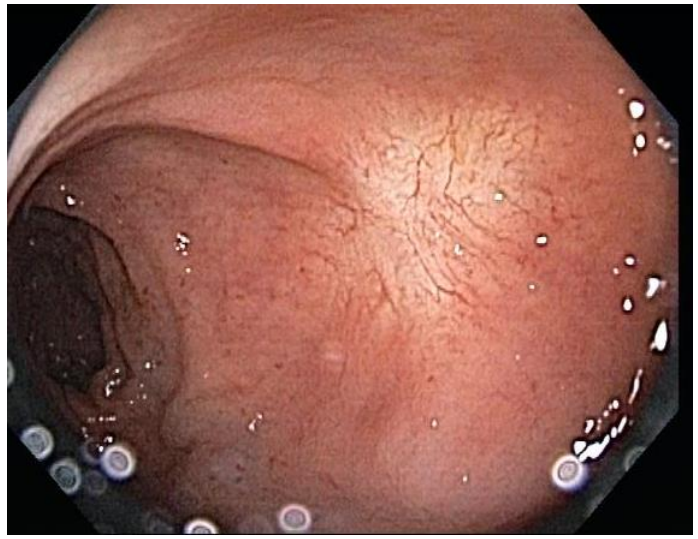


21% complete response

Smith JJ – JAMA Oncology 2019

cCR in rectal cancer

➢ pMMR RC post TNT



cCR Criteria for W&W:
- ✓ Inert flat non-ulcerated mucosa, maybe some telangiectasias
- ✓ No palpatory, endoscopic, radiological residua (eg, diffusion-weighted MRI)
- ✓ Compliant patient → frequent surveillance

➢ dMMR/MSI-H RC post ICI

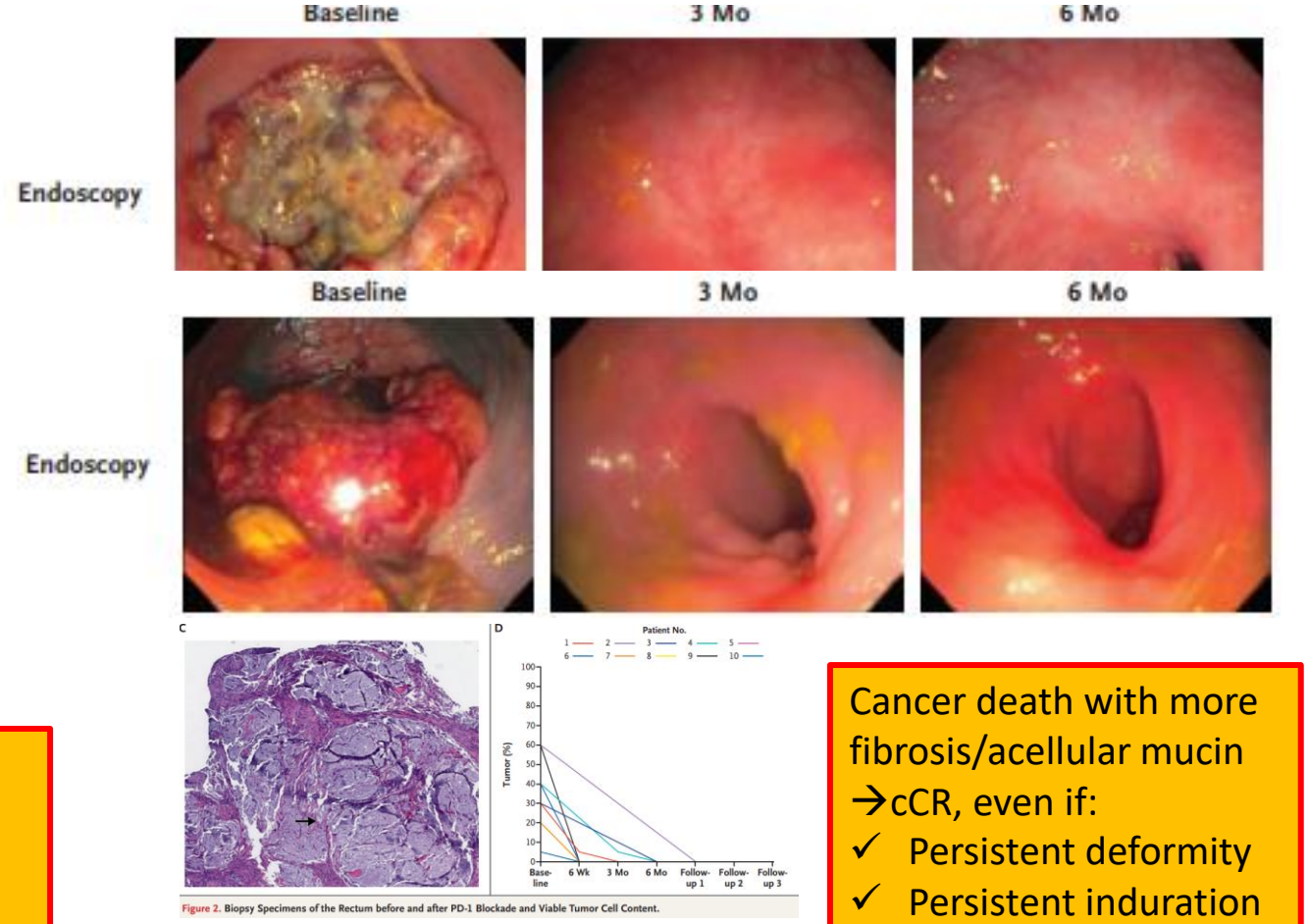
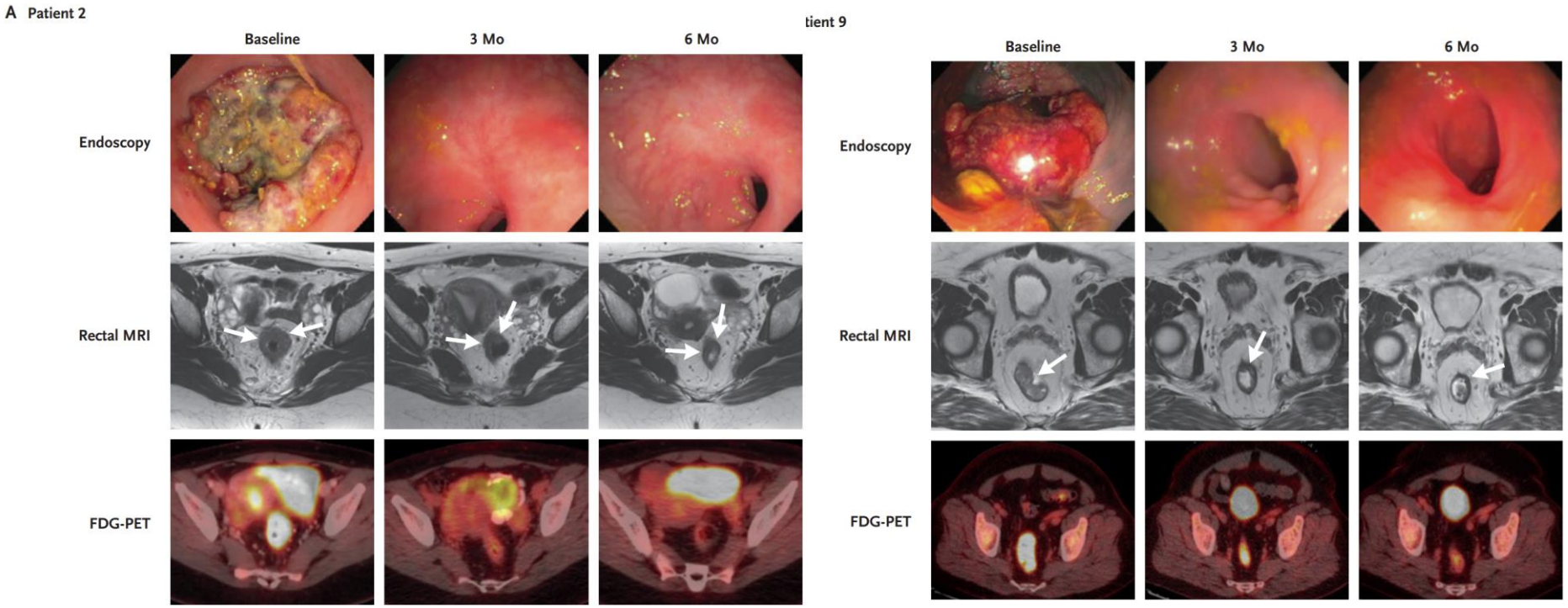


Figure 2. Biopsy Specimens of the Rectum before and after PD-1 Blockade and Viable Tumor Cell Content.

Cercek A – NEJM 2022

Cancer death with more fibrosis/acellular mucin →cCR, even if:
- ✓ Persistent deformity
- ✓ Persistent induration
- ✓ MRI thickening
- ✓ PET activity

cCR in MSI-H/dMMR rectal cancer



Cercek A – NEJM 2022

Cancer death with more fibrosis/acellular mucin →cCR, even if:

- ✓ Persistent deformity
- ✓ Persistent induration
- ✓ MRI thickening
- ✓ PET activity

We have to get used to the fact that cCR in dMMR tumors:

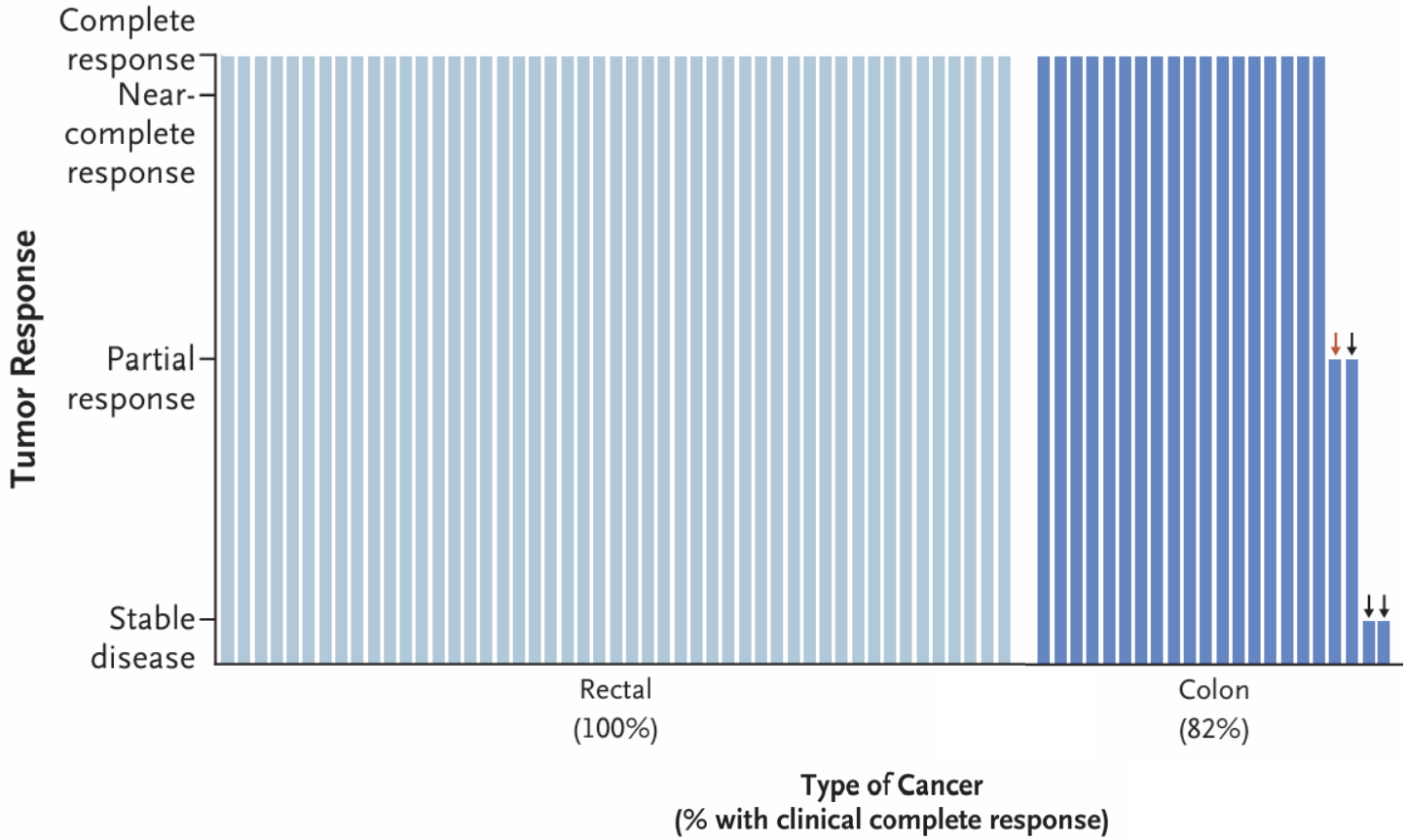
- Looks very different than in pMMR
- May be complete even if it does not pass prior standard criteria

MSI-H/dMMR tumors incl rectal cancer



- **MSK Expanded phase II with 2 cohorts:**
  - Cohort 1: n=49 dMMR stage II–III rectal adenocarcinoma
  - Cohort 2: N=67 dMMR solid tumors
  - Dostarlimab 9 cycles, nonoperative management if cCR

- Outcome:
  - Cohort 1:
    - ✓ All 49 patients who completed treatment had cCR → nonoperative management.
    - ✓ 37 patients had sustained cCR at 12 months
    - ✓ 2-yr RFS 96% (1 regrowth, 1 node);
  - Cohort 2:
    - ✓ cCR 65%(35/54 who completed treatment)
    - ✓ cCR in 82% of colon



Cercek A – NEJM 2025

MSI-H/dMMR rectal cancer

Effect of one or two cycles of dual immunotherapy with nivolumab and ipilimumab in patients with mismatch repair-deficient rectal cancer (RESET-R): interim results from a multicentre, single-arm, phase 2 trial

Line Schmidt Tarpgaard, Laurids Østergaard Poulsen, Ismail Gögenur, Tobias Freyberg Justesen, Søren Rafael Rafaelsen, Nadia Øgaard, Christina Demuth, Claus Lindbjerg Andersen, Lise Ventzel, Pernille Øhlenschläger Larsen, Anne Ramlov, Ken Ljungmann, Michael Bødker Lauritzen, Laura Vittrup Diness, Jakob Lykke, Vinicius Araújo Barbosa de Lima, Søren Kjær, Søren Salomon, Per Vadgaard Andersen, Per Pfeiffer

➢ **RESET-R:**

- Single-arm phase II (non-randomized), two-stage, multicenter (Denmark)
- N=16 (interim) Stage I–III dMMR rectal adenocarcinoma, ECOG 0–1, no prior therapy; 63% N+; 31% Lynch
- Nivolumab 3 mg/kg (d1,15) + ipilimumab 1 mg/kg (d1); 2nd cycle if not cCR at d43

➢ Outcome:

- 100% cCR (11 after 1 cycle, 5 after 2)
- no surgery/CRT
- no recurrence at median 16 mo
- grade 3 irAE 19%

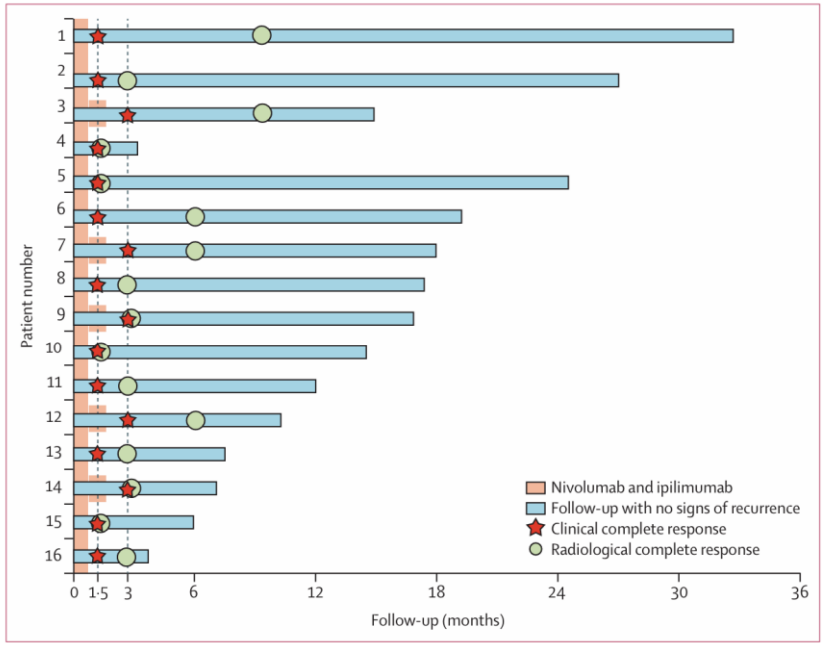


Figure 2: **Time to clinical and radiological complete response and follow-up duration for individual patients**
Dashed lines indicate day 43 and 93 evaluations.

RESET-R interim results suggest that short-course dual-agent regimens might have similar efficacy to longer single-agent therapy while further reducing treatment duration and cost.

Schmidt Tarpgaard L – Lancet Gastro Hep 2026

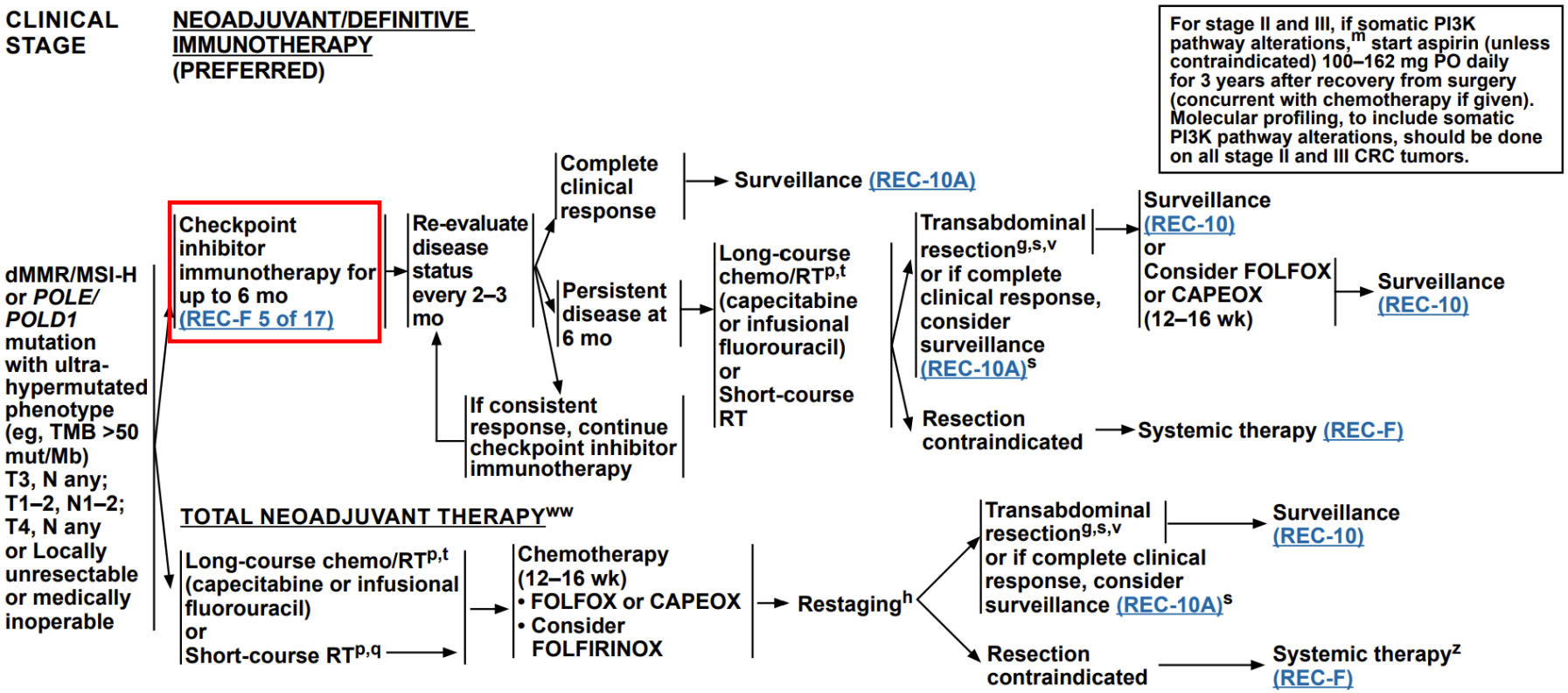
MSI-H/dMMR rectal cancer

PLEASE NOTE that use of this NCCN Content is governed by the End-User License Agreement and you MAY NOT distribute this Content or use it with any artificial intelligence system, machine learning model, or large language model or other artifical intelligence tool.
Printed by Andreas Kaiser on 10/2/2026 8:18:16 PM. Copyright © 2026 National Comprehensive Cancer Network, Inc. All Rights Reserved.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2026
dMMR/MSI-H Rectal Cancer

NCCN Guidelines Index
Table of Contents
Discussion



Immunotherapy

= preferred

initial strategy

= true paradigm shift

driven by ability to reliably reassess local response with DRE, endoscopy, and MRI

(unlike in colon cancer)

MSI-H/dMMR localized/resectable disease

EXTRAPOLATION OF CONCEPT TO COLON CANCER

City of Hope®

Colon cancer - treatment sequence

Historical sequence

- Biopsy → staging → operation
- Extent of surgery: ?
- Pathology reveals dMMR afterwards
- Adjuvant choices discussed postop

Modern sequence

- Biopsy → MMR/MSI → final plan
- Tumor board → ICI, surgery, or surveillance
- Operation redesigned around response
- Extent of surgery: ?

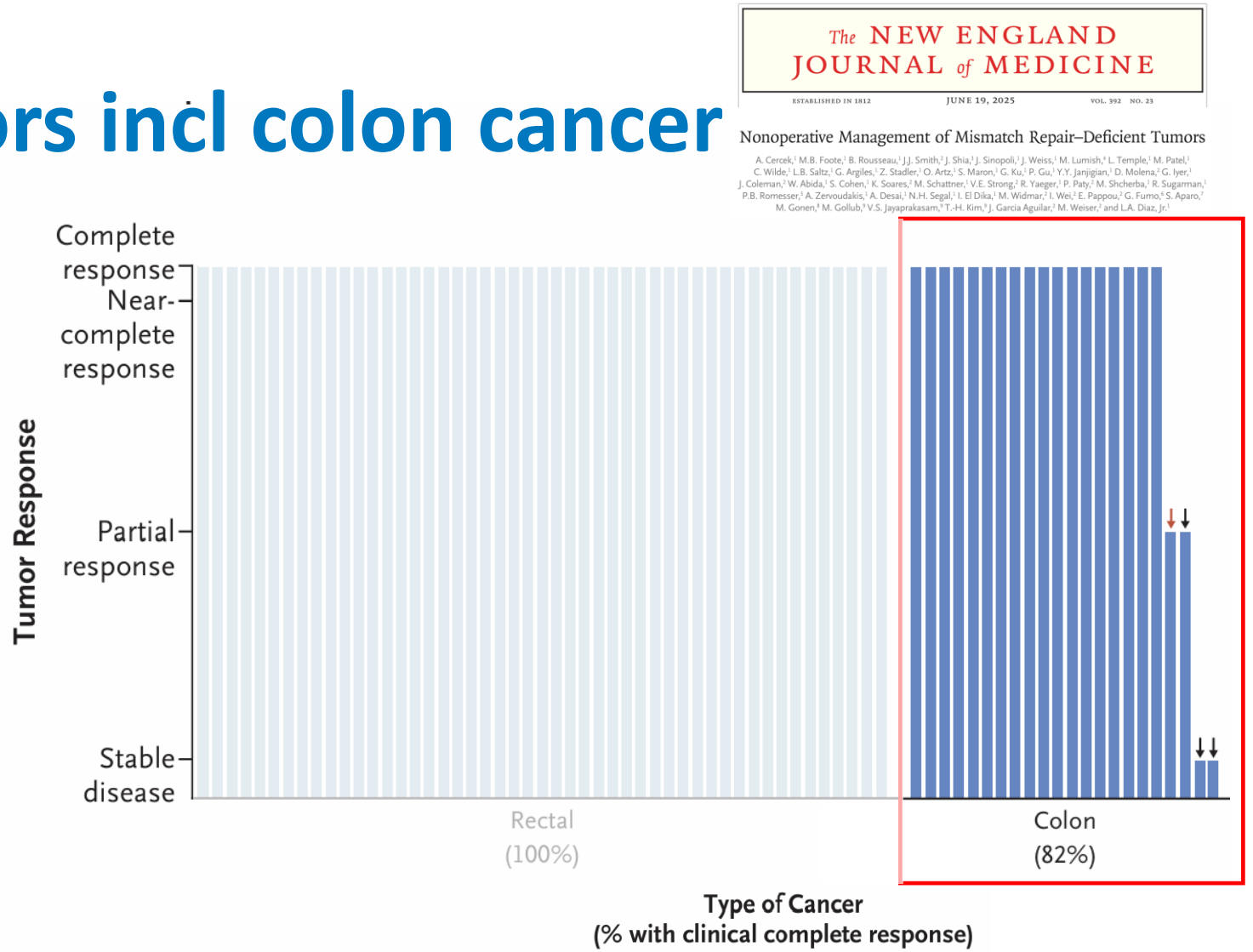
Adjuvant treatment for MSI-H tumors:

- Stage II: known NOT to benefit from single-agent fluoropyrimidine
- Stage III: adjuvant FOLFOX
- Stage IV: treated identically to pMMR with cytotoxic doublets ± biologics — poor responses

MSI-H/dMMR tumors incl colon cancer

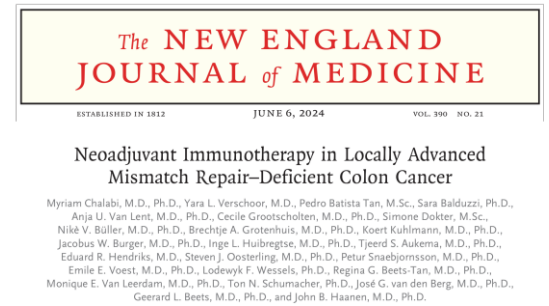
- **MSK Expanded phase II with 2 cohorts:**
  - Cohort 1: N=49 dMMR stage II–III rectal adenocarcinoma
  - Cohort 2: N=67 dMMR solid tumors
  - Dostarlimab 9 cycles, nonoperative management if cCR

- Outcome:
  - Cohort 1:
    - ✓ All 49 patients who completed treatment had cCR → nonoperative management.
    - ✓ 37 patients had sustained cCR at 12 months
    - ✓ 2-yr RFS 96% (1 regrowth, 1 node);
  - Cohort 2:
    - ✓ cCR 65%(35/54 who completed treatment)
    - ✓ cCR in 82% of colon

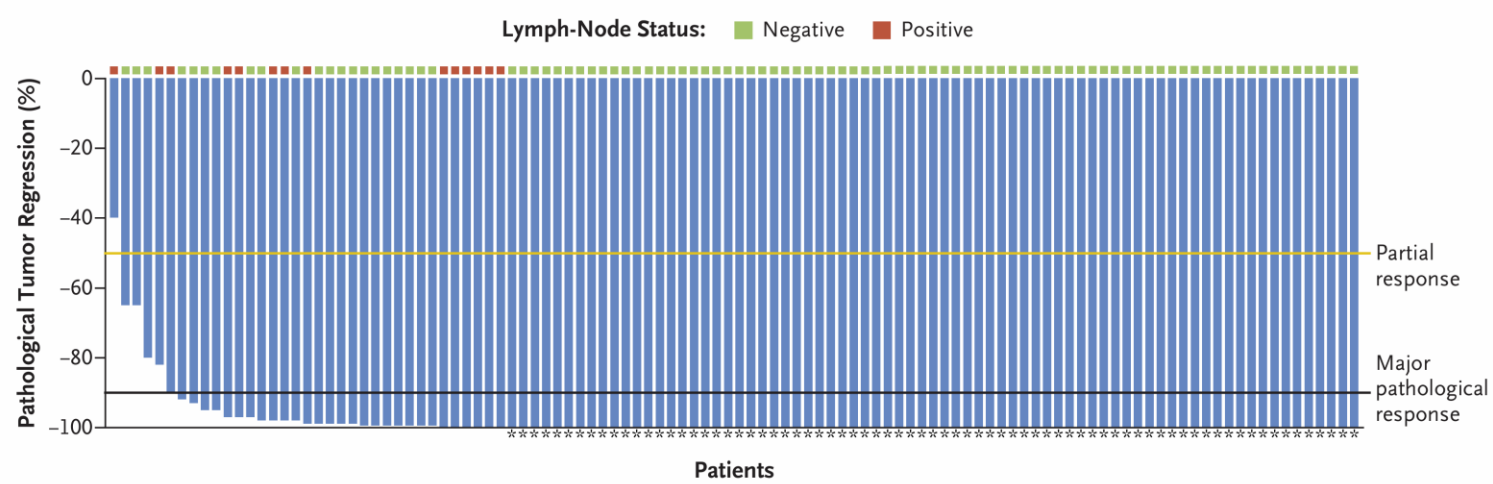


Cercek A – NEJM 2025

MSI-H/dMMR tumors incl colon cancer



- **NICHE-2 / NICHE:** Single-arm phase II (non-randomized)
  - Previously untreated, dMMR, clinical stage II–III resectable colon adenocarcinoma, no metastases; enriched for high-risk cT3–T4/N+.
  - Exclusions: clinical obstruction, prior immunotherapy, active autoimmune disease
  - N=111/115 dMMR colon cancer
  - Nivolumab 3 mg/kg days
- Outcome:
  - pCR 68%
  - Major pathological response 95%
  - Any pathologic response 98%
  - 100% R0
  - no recurrences at median 26 mo



Chalabi M – NEJM 2024

MSI-H/dMMR colon cancer

Trial (PMID)	Design / randomization	Key inclusion criteria	N	Regimen	Primary outcome(s)	Key results
NICHE-2 / NICHE	Single-arm phase II (non-randomized)	Previously untreated, dMMR, clinical stage II/III resectable colon CA, no metastases; enriched for high-risk cT3-T4/N+. Exclusions: clinical obstruction, prior immunotherapy, active autoimmune disease	115 enrolled (111 evaluable for pathology)	Nivolumab 3 mg/kg days 1+15, ipilimumab 1 mg/kg day 1; surgery ≤6 wk	Safety + 3-yr DFS (dual)	pCR 68%, MPR 95%, pathologic response 98%; 100% R0; no recurrences at median 26 mo
NICHE-3	Single-arm phase II (non-randomized)	Locally advanced resectable dMMR colon cancer	59	Nivolumab 480 mg + relatlimab 480 mg, 2 cycles (day 1, 29); surgery ≤8 wk	Pathologic response (≤50% RVT)	Response 97%, MPR 92%, pCR 68%; 1 recurrence at median 8 mo; grade 3-4 irAE 10%
RESET-C	Single-arm phase II (non-randomized), multicenter (Denmark)	Localized stage I-III dMMR colon cancer; median age 74	85 (84 surgical)	Pembrolizumab single cycle 4 mg/kg (max 400 mg); surgery 3-5 wk later	pCR	pCR 44%, MPR 57%; stage-dependent pCR (61% stage I-II vs 33% stage III); 1 recurrence at median 18.4 mo; grade 3 AE 11%
IMHOTEP	Single-arm phase II (non-randomized), multicenter	Localized resectable dMMR/MSI CRC; 71% clinical stage III	81 (72 efficacy)	Pembrolizumab 400 mg q6wk x1-2 preop, then 1 yr total	pCR (ypT0N0)	pCR 52.7%; 46% after 1 cycle vs 68% after 2 cycles; 3 recurrences at median 24.5 mo; grade ≥3 irAE 15.7% (1 grade 5)
NEOPRISM-CRC	Single-arm phase II, TMB-stratified	High-risk stage II-III dMMR/MSI-H CRC	32	Pembrolizumab x3 (TMB-high/med) or x1 (TMB-low)	pCR	pCR 59% (ITT 53%), MPR 78%; no recurrences at median 6 mo
IBI310 + sintilimab (randomized)	Randomized phase Ib - the only randomized neoadjuvant comparison	Localized dMMR/MSI-H CRC	101	IBI310 (anti-CTLA-4) x1 + sintilimab x2 vs sintilimab x2	pCR	pCR 77% (combination) vs 43% (monotherapy), p=0.0007

Assessment of ICI response

CT / MRI / PET

Wall thickening
Nodes remain enlarged
Fibrosis and immune infiltrate
Residual mass may persist

Surgical pathology

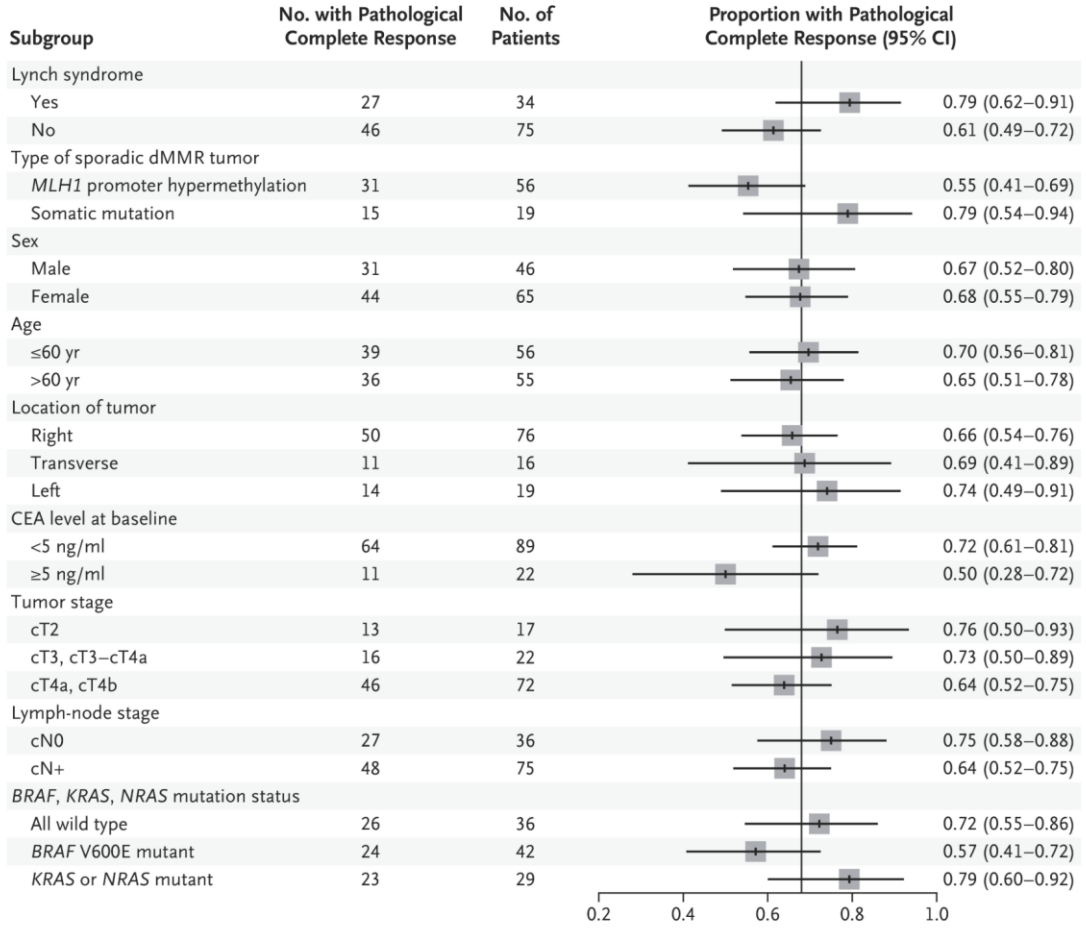
Tumor bed mapping
Viable tumor percentage
Regression pattern
Nodes and margins

- Imaging underestimates pathologic response
- SURGEON TAKEAWAY Do not escalate or abandon an effective strategy based on size criteria alone.

ICI for MSI-H/dMMR CRC

- cCR and pCR:
  - Are NOT 100%, in fact pCR in 2/3 of pts only
  - Complete response can result in persistent problem pathology, e.g. stricture

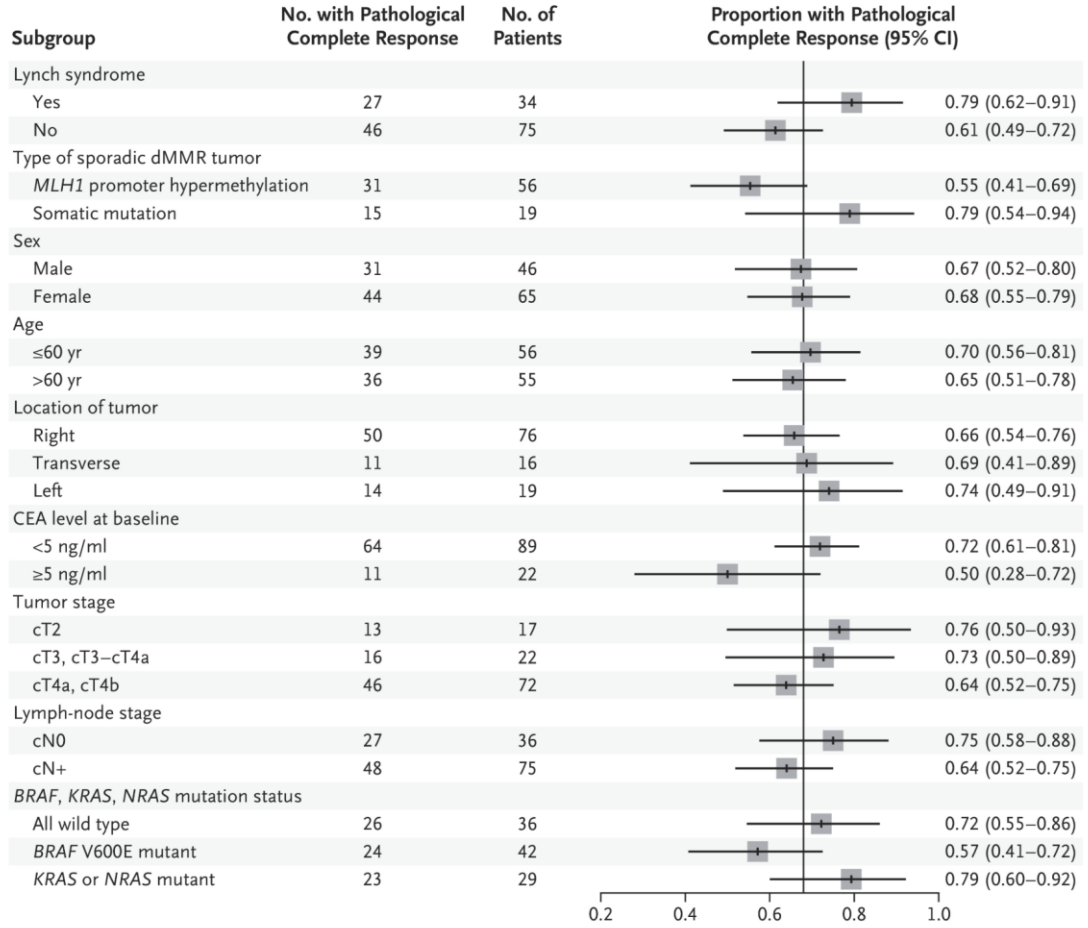
Setting / regimen	Response rate	Still needs / underwent surgery
Colon, neoadjuvant nivo+ipi (NICHE-2)	68% pCR, 95% MPR, 0 recurrences at 3 yr	Essentially all resected
Colon, neoadjuvant nivo+relatlimab (NICHE-3)	68% pCR, 92% MPR	All resected
Colon, single-cycle pembrolizumab (RESET-C)	44% pCR, 57% MPR	Nearly all resected
Colon, pooled systematic review	pCR 44-78%, MPR 57-95%	Most proceed to colectomy
Rectal, dostarlimab monotherapy (Cercek)	~100% cCR, sustained	Majority avoid surgery



deGooyer PGM – Nature Med 2024

ICI for MSI-H/dMMR CRC

- cCR and pCR:
  - Are NOT 100%, in fact pCR in 2/3 of pts only
  - Complete response can result in persistent problem pathology, e.g. stricture
- Surgery alone is already curative in most stage II cases → impressive pathologic responses do not by themselves justify replacing surgery
- No survival benefit has yet been proven, and no validated nonoperative pathway exists
- Toxicity is not trivial. In NICHE-2, permanent (largely endocrine) dysfunction developed in ~11% of patients, all of whom still underwent surgery



Subgroup	No. with Pathological Complete Response	No. of Patients	Proportion with Pathological Complete Response (95% CI)
Lynch syndrome			
Yes	27	34	0.79 (0.62–0.91)
No	46	75	0.61 (0.49–0.72)
Type of sporadic dMMR tumor			
MLH1 promoter hypermethylation	31	56	0.55 (0.41–0.69)
Somatic mutation	15	19	0.79 (0.54–0.94)
Sex			
Male	31	46	0.67 (0.52–0.80)
Female	44	65	0.68 (0.55–0.79)
Age			
≤60 yr	39	56	0.70 (0.56–0.81)
>60 yr	36	55	0.65 (0.51–0.78)
Location of tumor			
Right	50	76	0.66 (0.54–0.76)
Transverse	11	16	0.69 (0.41–0.89)
Left	14	19	0.74 (0.49–0.91)
CEA level at baseline			
<5 ng/ml	64	89	0.72 (0.61–0.81)
≥5 ng/ml	11	22	0.50 (0.28–0.72)
Tumor stage			
cT2	13	17	0.76 (0.50–0.93)
cT3, cT3–cT4a	16	22	0.73 (0.50–0.89)
cT4a, cT4b	46	72	0.64 (0.52–0.75)
Lymph-node stage			
cN0	27	36	0.75 (0.58–0.88)
cN+	48	75	0.64 (0.52–0.75)
BRAF, *KRAS*, *NRAS* mutation status			
All wild type	26	36	0.72 (0.55–0.86)
BRAF V600E mutant	24	42	0.57 (0.41–0.72)
KRAS or *NRAS* mutant	23	29	0.79 (0.60–0.92)

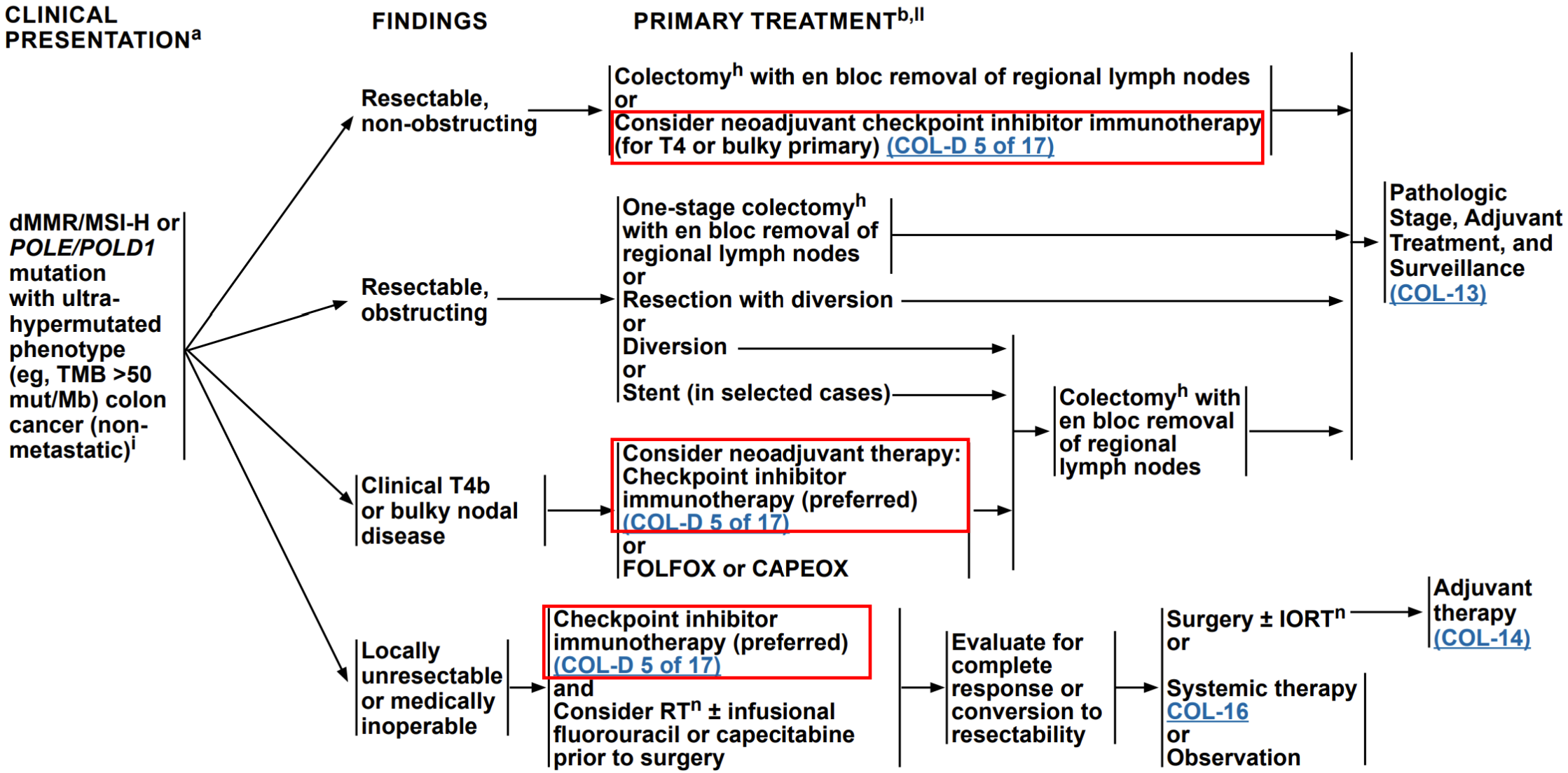
deGooyer PGM – Nature Med 2024

PLEASE NOTE that use of this NCCN Content is governed by the End-User License Agreement, and you MAY NOT distribute this Content or use it with any artificial intelligence model or tool.
Printed by Andreas Kaiser on 9/27/2026 10:25:25 PM. Copyright © 2026 National Comprehensive Cancer Network, Inc. All Rights Reserved.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2026
dMMR/MSI-H Colon Cancer

NCCN Guidelines Index
Table of Contents
Discussion



Risk–benefit analysis

➢Colon:

- Benefit of replacing surgery with ICI unproven
- Surgery low-risk relative to cure rates already achieved
- Response cannot be confirmed nonoperatively
- ICI adds a ~10% risk of permanent endocrine toxicity.
- Upfront surgery stays first choice
- Neoadjuvant ICI is an acceptable/preferred option mainly to enable R0 resection in T4/bulky/unresectable disease.

➢Rectal:

- Morbidity of proctectomy (stoma, low anterior resection syndrome, genitourinary/sexual dysfunction)
- Balance decisively shifted toward immunotherapy-first
- Organ preservation in cCR patients now NCCN-preferred approach
- Surgery as salvage

Gosavi R – Ann Surg Oncol 2026

Words of caution

- Level of evidence differs sharply by setting.
  - Practice-changing neoadjuvant data (NICHE-2/3, dostarlimab, RESET) are all single-arm phase II with no surgical comparator and immature survival data (follow-up 8–30 months)
  - NICHE investigators argue that randomized neoadjuvant-ICI-versus-surgery trial would be unethical given the response gap, but this leaves DFS/OS benefit over surgery alone formally unproven
- Only the metastatic trials are randomized phase III:
  - KEYNOTE-177's OS was not statistically significant at several analyses because of ~62% crossover, though the 5-year update showed median OS more than doubled
- The single randomized neoadjuvant signal (IBI310 + sintilimab) favors dual over single-agent checkpoint blockade (pCR 77% vs 43%)
- Denominator and definition heterogeneity
  - explain much of pCR variability (44–78%) across colon trials — regimen, number of cycles, time-to-surgery, and whether pCR is reported ITT or per-protocol all differ

Residual role of surgery remains high

- Rectal cancer: Organ preservation important.
- Colon cancer: Nearly all patients in neoadjuvant trials proceeded to colectomy with high R0 rates
- No validated criteria exist to skip resection

Gosavi R – Ann Surg Oncol 2026

- French expert consensus
  - reinforces that in surgically fit patients with resectable, non-cT4 colon cancer, upfront surgery remains standard of care

Karoui M – ESMO Open 2026

- NCCN guidelines 2.2026:
  - for dMMR/MSI-H non-metastatic colon cancer that is resectable and non-obstructing, primary treatment is colectomy with en-bloc removal of regional lymph nodes; neoadjuvant checkpoint inhibitor immunotherapy is offered only as a "consider" option for T4 or bulky primaries

NCCN Colon 2.2026

Many unresolved matters

- Optimal agent, combination, and duration?
- Can pathologic response be predicted without resection?
- Which colon cancers can safely avoid colectomy?
- How should ctDNA influence response and surveillance?
- What is the best salvage strategy after ICI failure?
- Extent of surgery: segmental vs extended?

Emergency / unstable → resect or divert

Stable localized colon → neoadjuvant ICI pathway + planned colectomy

Stable rectal → ICI + cCR assessment; consider NOM

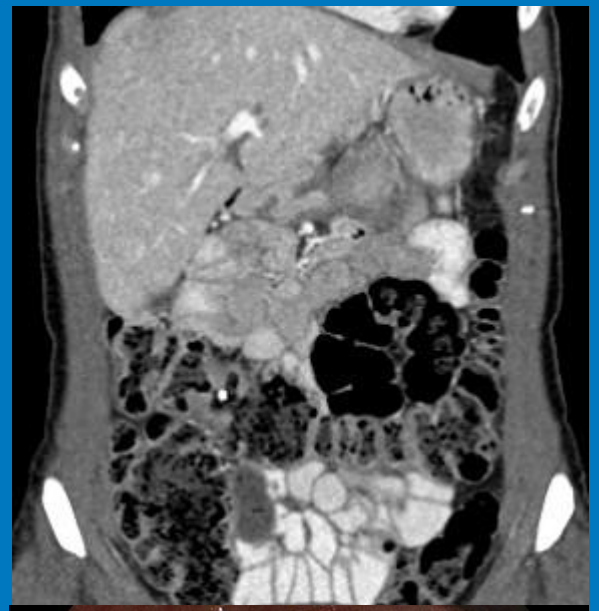
Metastatic → systemic ICI; local therapy only for defined indications

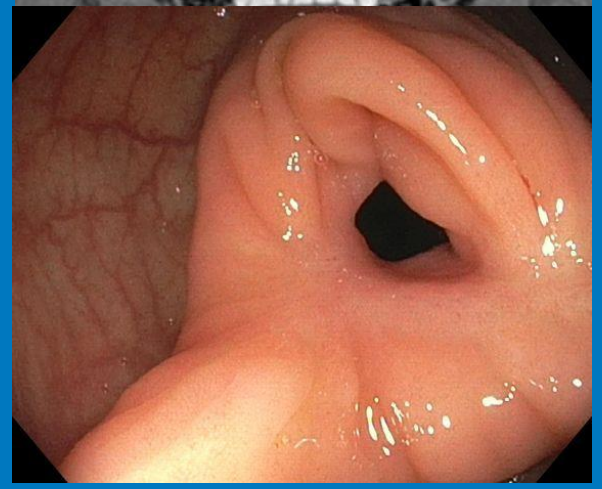
TAKEAWAY The evidence is practice-changing, but not yet permission for uncontrolled de-escalation.

Case study 1

- 41 y/o female with strong family history of CRC → screening → MLH1/PMS2-deficient tumor → MLH1 gene mutation
- Immune checkpoint inhibitor treatment → resolution of tumor
- But: Resulting stricture → right colon nor surveillable →

Surgery yes:
Robotic right hemi + TAH
with transvaginal specimen extraction



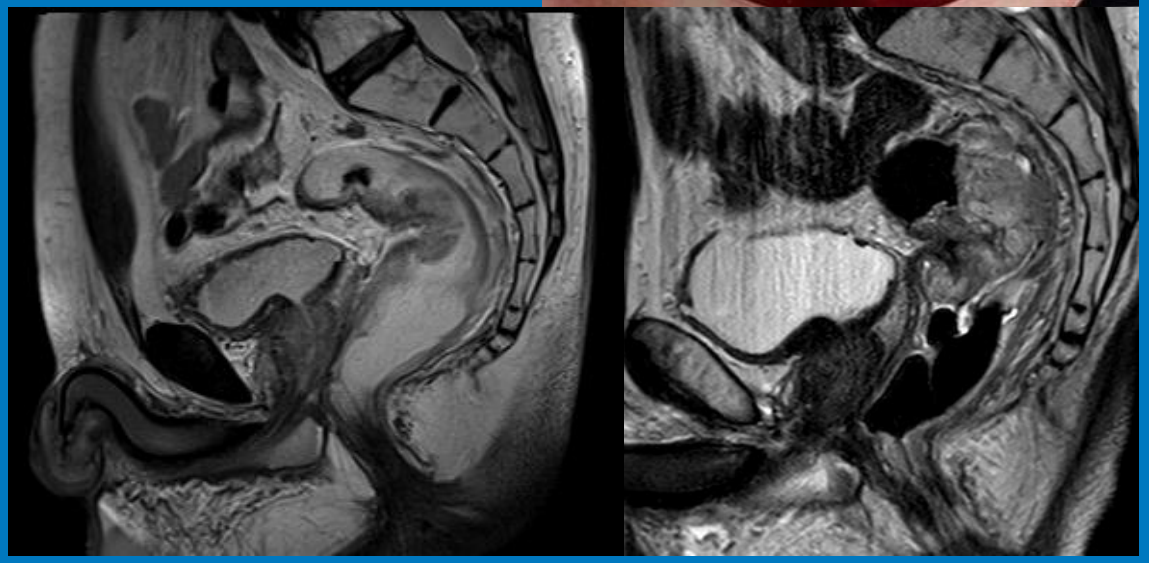


Case study 2

- 87 y/o male with history of RT for prostate CA, rectal bleeding
- 6 months of ICI → tumor progression → pending obstruction



Surgery yes:
Robotic APR



- Subsequent course:
- Liver metastases → FOLFOX/BEV
- Y90
- IPI/NIVO → ctDNA turning negative

Thank you!



Andreas M Kaiser, MD FACS FASCRS

Professor of Surgery
Chief, Division of Colorectal Surgery
City of Hope National Medical Center (NCI-CCC)
1500 E. Duarte Road, Belardi Pavilion Suite 2230
Duarte, CA 91010

Phone: (626) 218-7100
Fax: (626) 765-3900 | Mobile Fax: (626) 243-2607
Mobile: (323) 472-1620

Email: akaiser@coh.org
Web site: https://www.cityofhope.org/faculty/andreas-kaiser

City of Hope