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THE DIMINISHING ROLE OF SURGERY IN MSI-HIGH RECTAL CANCER

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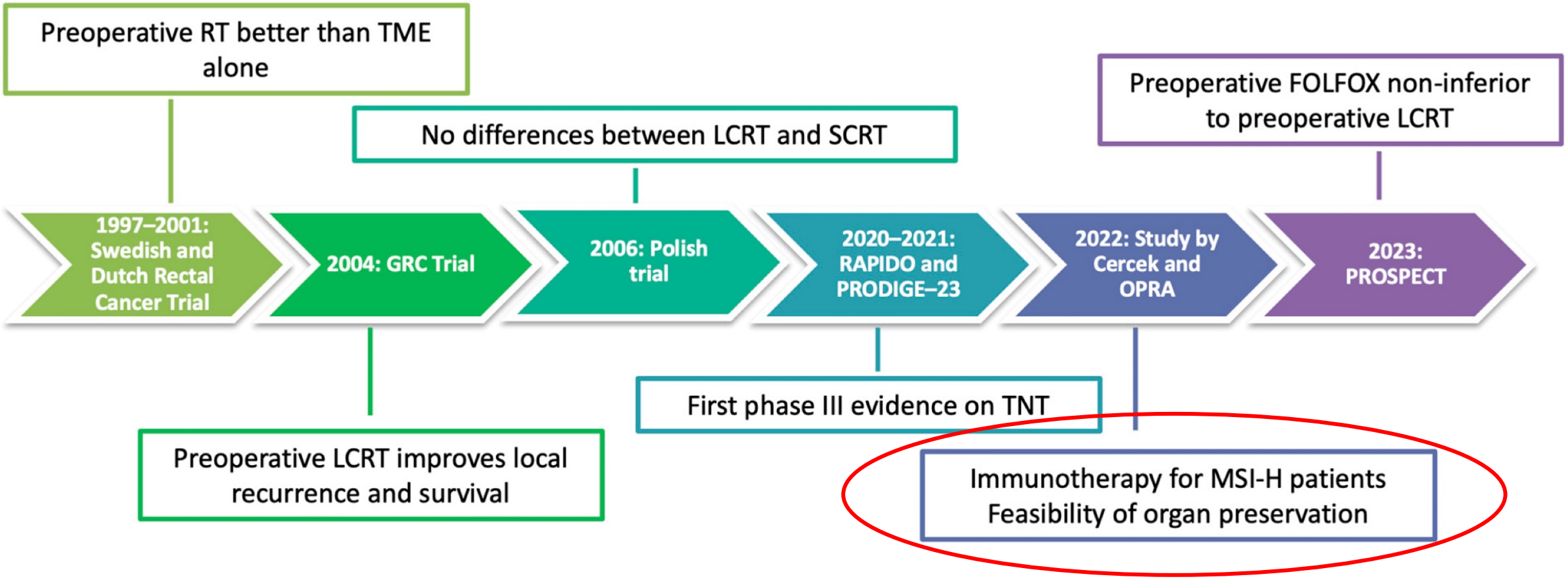
NCI Designated Comprehensive Cancer Center

DISCLOSURES

- Coherus Oncology (Research support, institution)

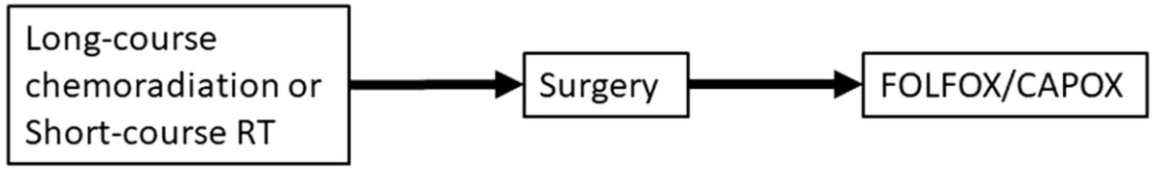
RECTAL CANCER TREATMENT TIMELINE



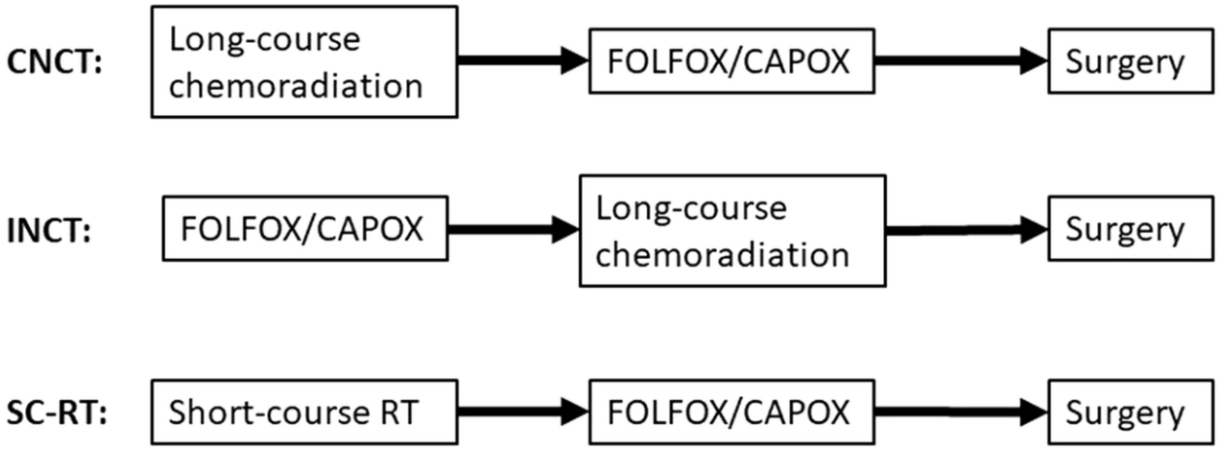
Daspra et al Int. J. Mol. Sci. 2023, 24, 12159

TOTAL NEOADJUVANT TREATMENT OF LARC

a) Standard treatment sequencing



b) Total neoadjuvant treatment sequencing

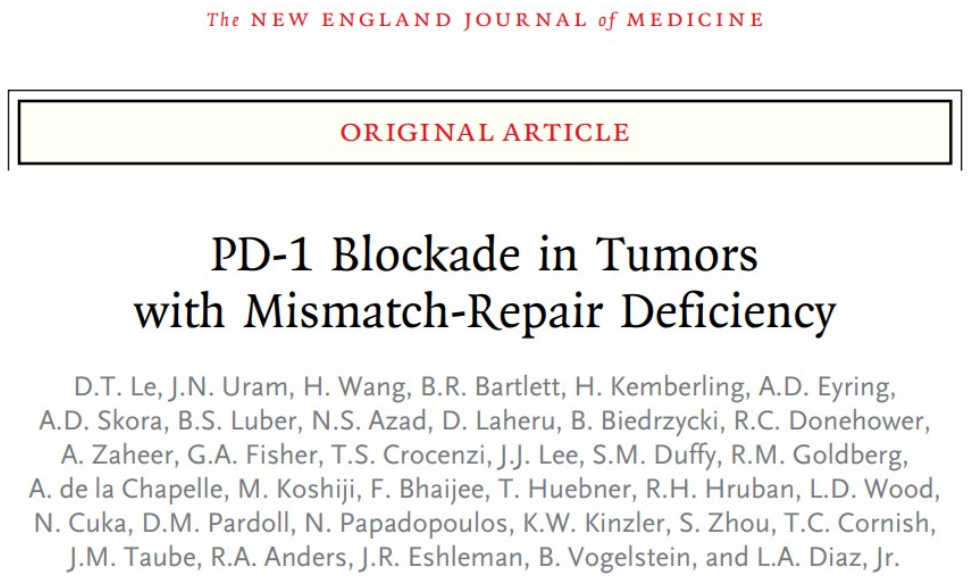


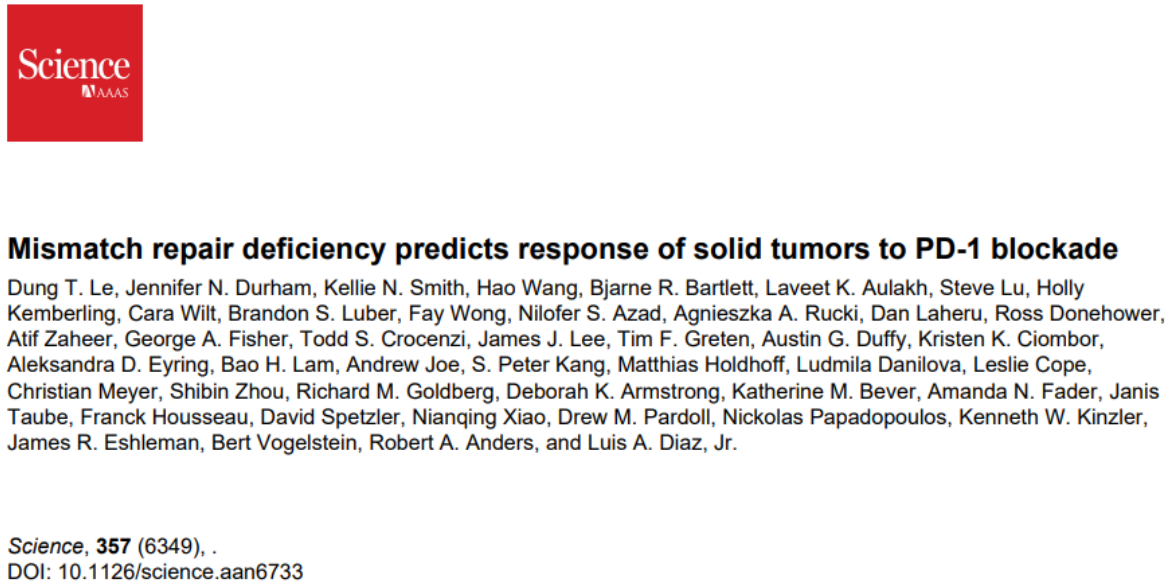
Non-operative management if clinical complete response after TNT

Shiao JC, Fakhoury KR, Olsen J. Total Neoadjuvant Therapy for Rectal Cancer: Current Colorectal Cancer Reports 2020. Garcia-Aguilar J, Patil S, Gollub MJ et al. J Clin Oncol 2022

MSI-H CRC

- MSI-H is predictive of immune checkpoint inhibitor (ICI) efficacy in advanced CRC
- 2.7% – 5% of rectal cancer is MSI-H

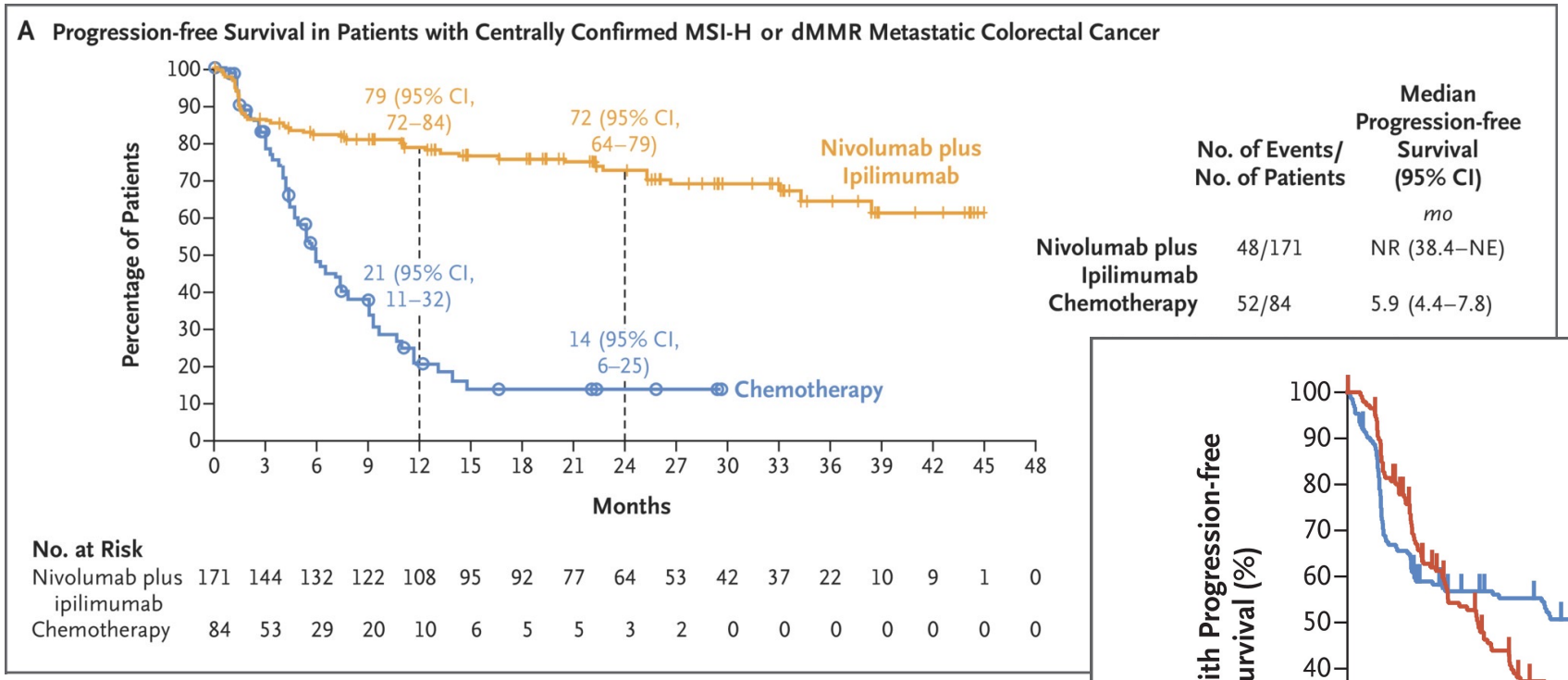




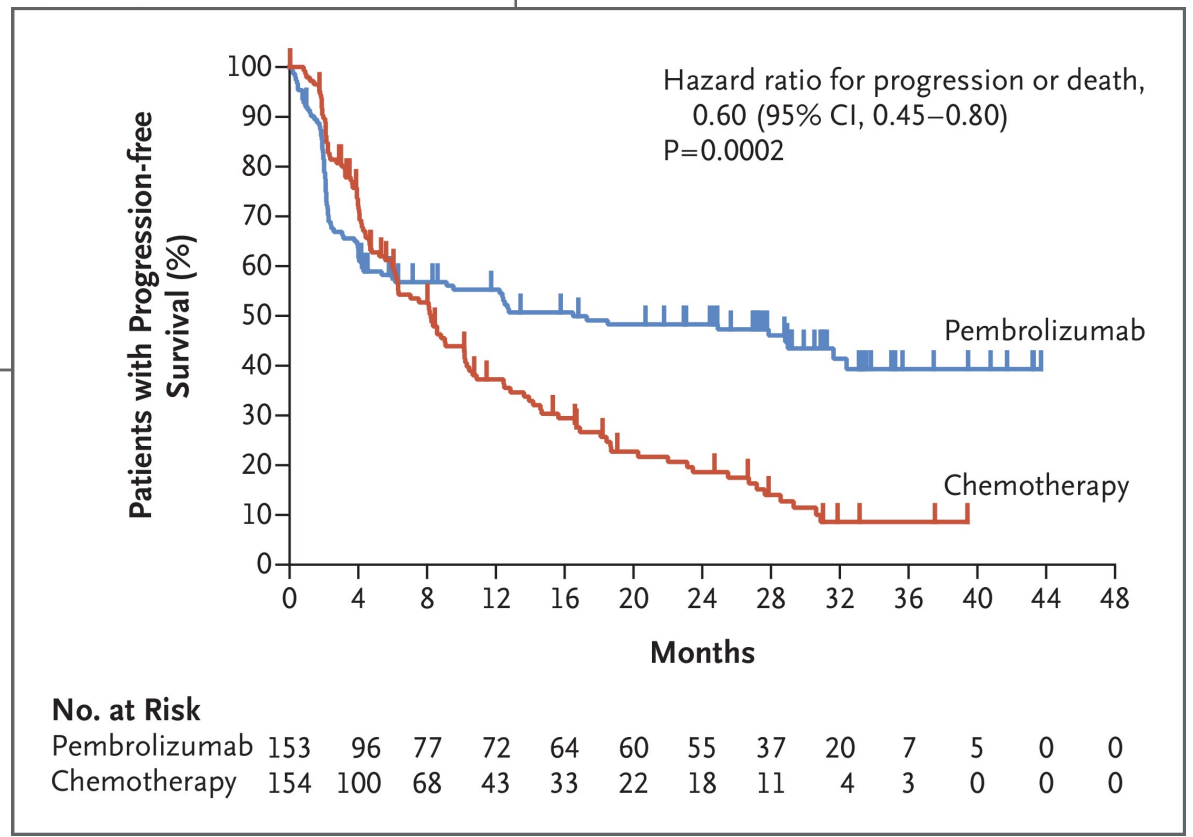
Le DT, Uram JN, Wang H et al. N Engl J Med 2015. Le DT, Durham JN, Smith KN, et al. Science. 2017;357(6349):409-413. Papke DJ, Jr., Yurgelun MB, Noffsinger AE et al. N Engl J Med 2022. Cercek A, Lumish M, Sinopoli J, et al. N Engl J Med. 2022

MSI-H METASTATIC CRC

Checkmate 8HW



Keynote 177



Andre, et al. N Engl J Med 2024; Andre, et al. N Engl J Med 2020

MSI-H CRC IS CHEMORESISTANT

- FOxTROT trial: Neoadjuvant FOLFOX for stage II-III colon cancer
  - Regression 7% (8 of 115) in MSI-H vs 23% (128 of 553) in MSI-L

- MSKCC Rectal cancer cohort: 29% MSI-H vs 0% MSI-L rectal tumors progressed on FOLFOX (P = 0.0001).

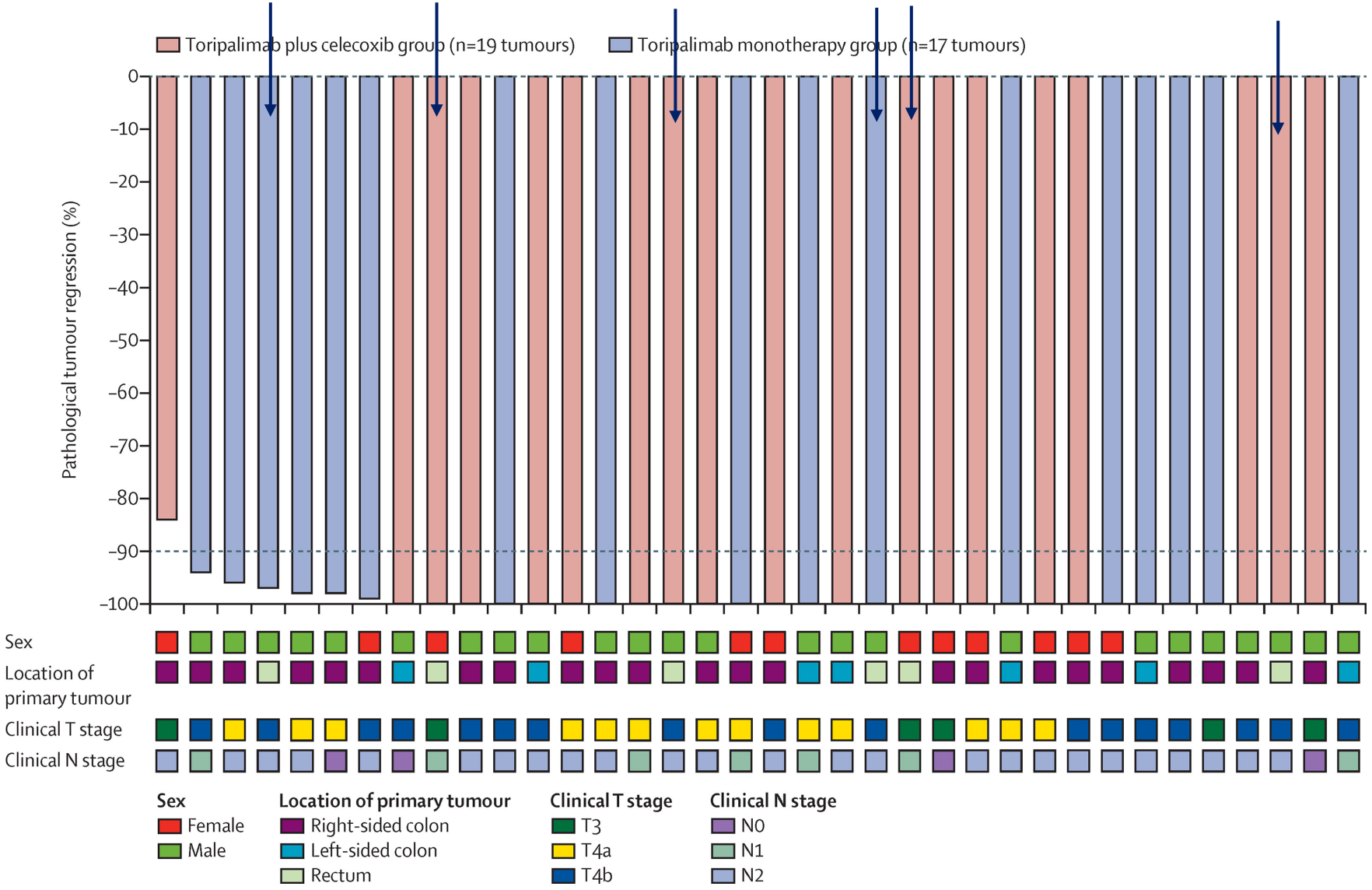
Rectal cancer treated with total neoadjuvant therapy chemotherapy and chemoRT followed by TME

Outcome	No. of patients (%) dMMR	pMMR
FOLFOX as initial treatment	*n = 21*	*n = 63*
Progression of disease	6 (29)	0
Response or stable disease	15 (71)	63 (100)
Chemoradiation as initial treatment	*n = 16*	*n = 48*
Progression of disease	0	0
Complete pathologic response	2 (13)	8 (17)

Morton D, et al. J Clin Oncol. 2023, Cercek A, et al. Clin Cancer Res. 2020

TORIPALIMAB IN MSI-H RECTAL CANCER N=6/34

- 6/6 underwent surgery
- The pathCR rate was 67% (4/6)
- 3-year DFS 85% - 100%
- 3-year OS rate 91% - 100%.



Hu H, Kang L, Zhang J, et al. Lancet Gastroenterol Hepatol. 2022 Hu H, Zhang J, Xie X et al. 542P Long-term outcomes phase II PICC trial. Annals of Oncology 2024

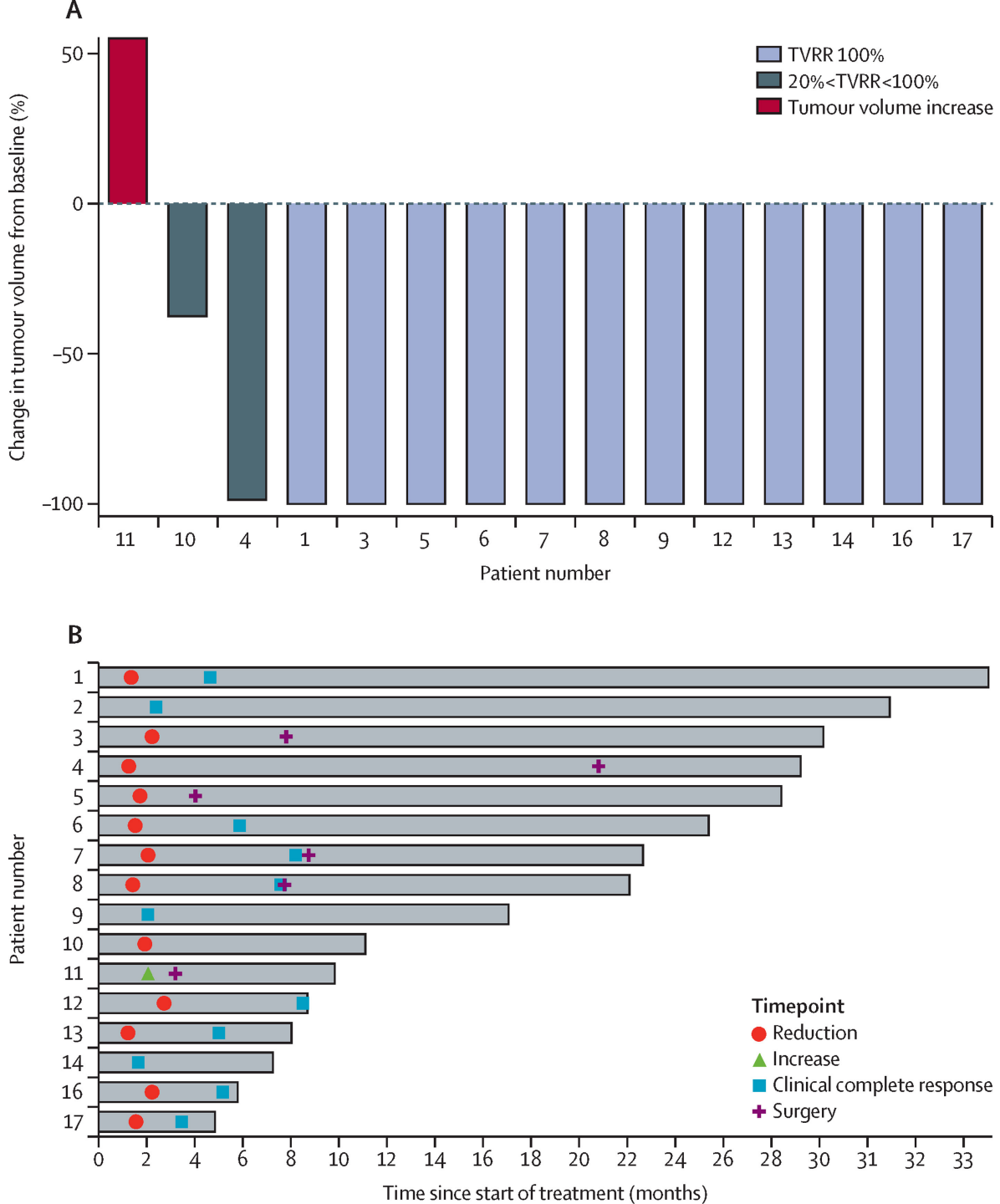
PEMBROLIZUMAB IN MSI-H RECTAL CANCER N=8/35

- Pembrolizumab for 6 – 12 months
- 6/8 LARC patients - non-operative management NOM
  - 2 had cCR, 3 cPR, 1 cSD
- 2/8 underwent surgery
  - 1 had clinical PD and ypT4N0 at pathology
  - the second patient had pCR.
- Discordant endoscopic, radiologic and pathologic response

Ludford K, Ho WJ, Thomas JV, et al. J Clin Oncol. 2023. Emiloju OE, Sinicrope FA. A Review. JAMA Oncol 2023

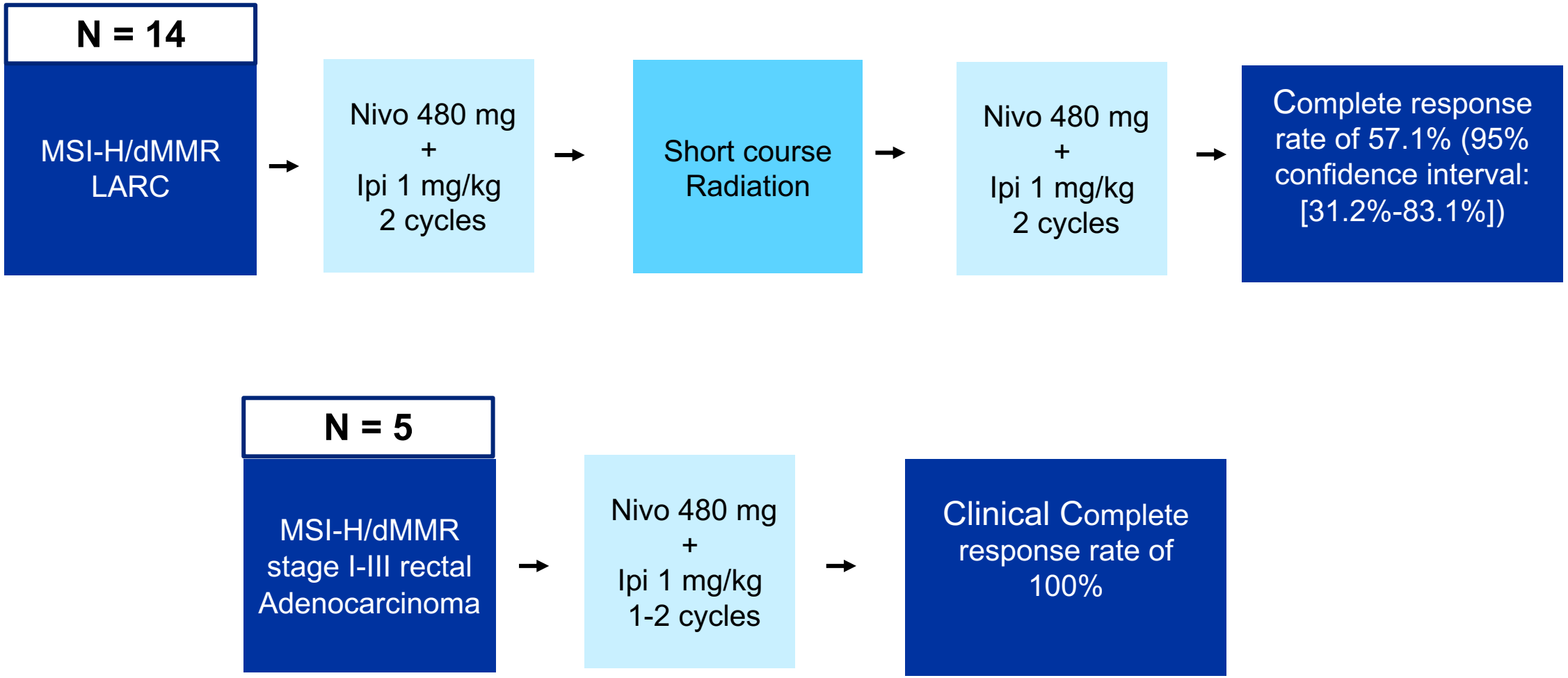
SINTILIMAB IN MSI-H RECTAL CANCER N=16

- Sintilimab for 3-6 months
- 9/16 had cCR - NOM
- 6/16 had surgery
  - 3/6 pathCR
  - 1/6 no path response
  - 2/6 incomplete path response



Chen G, Jin Y, Guan WL et al. Lancet Gastroenterol Hepatol 2023

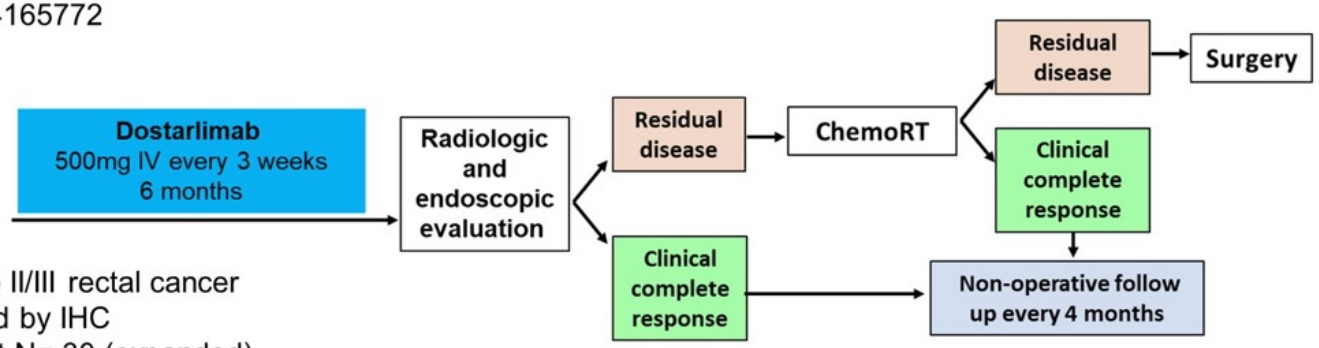
IPI+NIVO IN MSI-H RECTAL CANCER



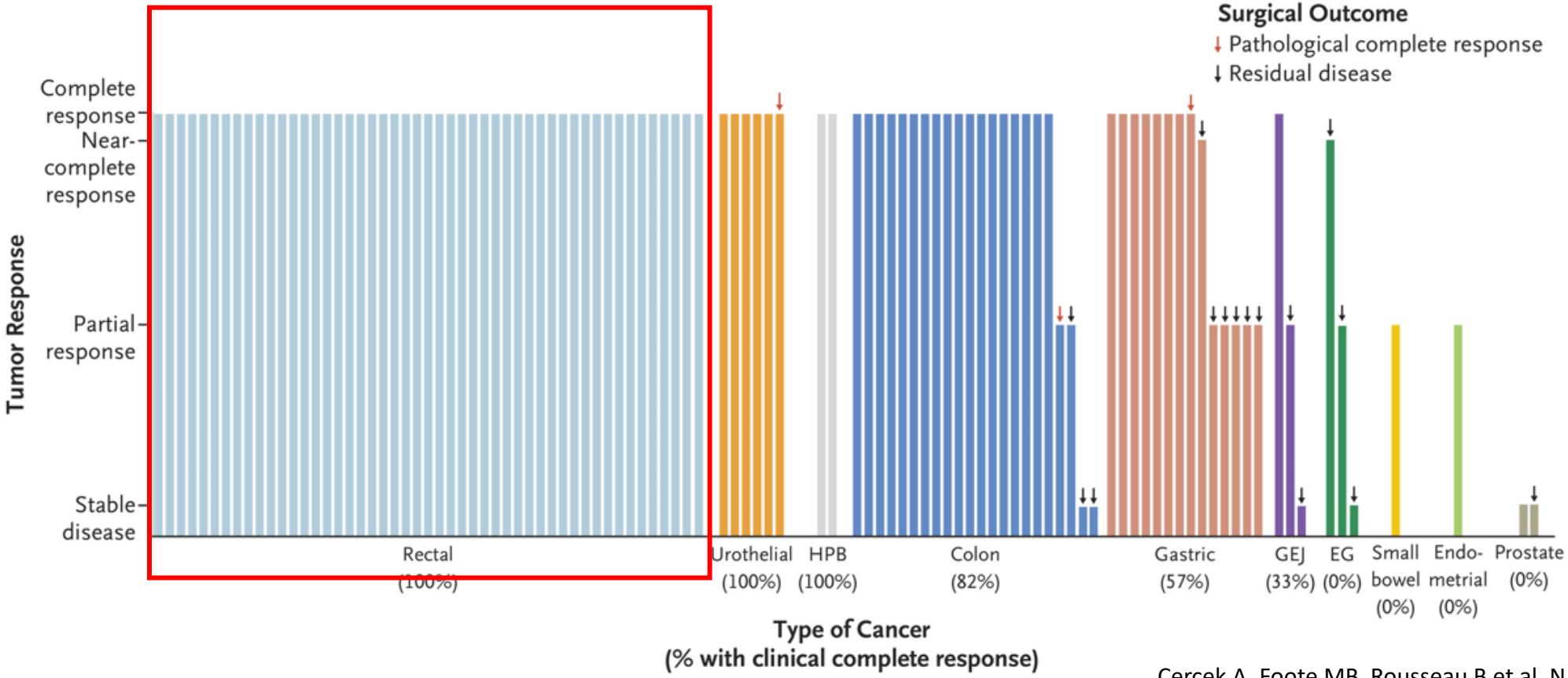
Ciombor KK, Hong S, Eng C et al. 242MO ECOG-ACRIN EA2201. Annals of Oncology 2024
Pfeiffer P, Andersen PV, Salomon S et al. Journal of Clinical Oncology 2024

DOSTARLIMAB IN MSI-H RECTAL CANCER N=50

NCT04165772

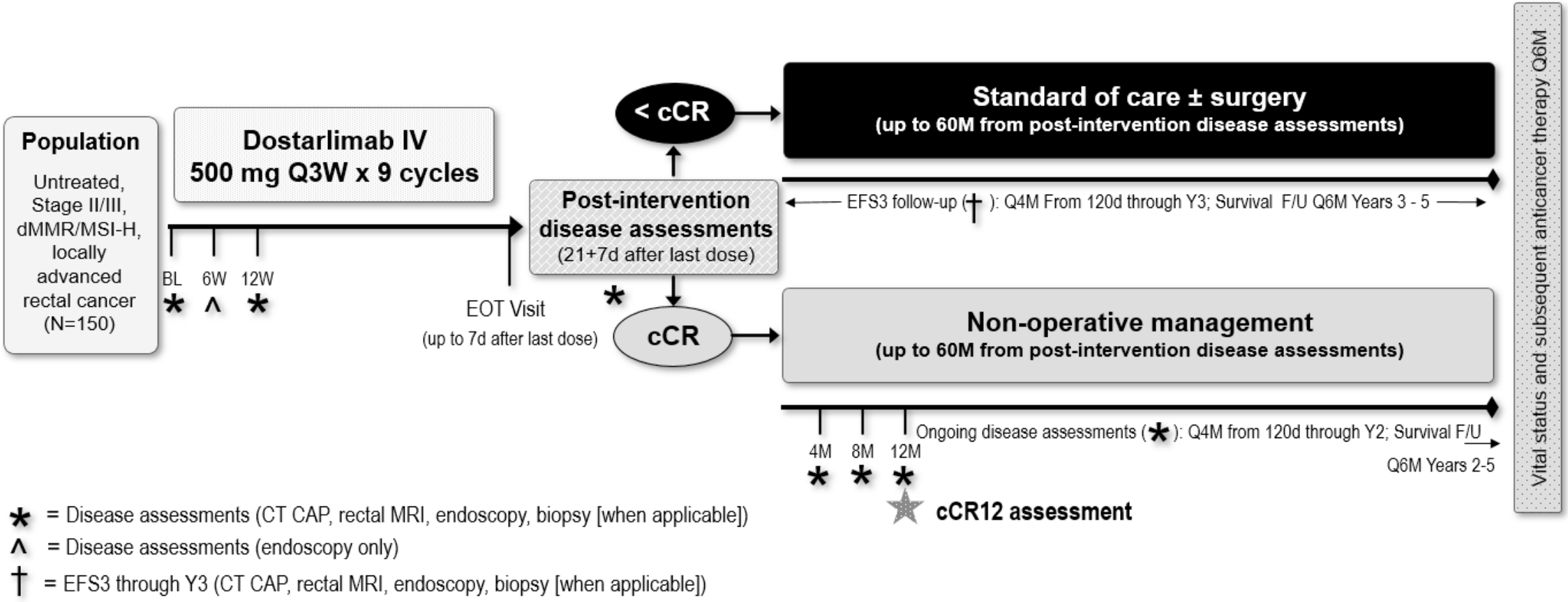


Stage II/III rectal cancer
MMRd by IHC
Target N= 30 (expanded)



Cercek A, Foote MB, Rousseau B et al. N Engl J Med 2025

AZUR-1: SINGLE-ARM STUDY WITH DOSTARLIMAB IN STAGE II/III MSI-H LARC



* = Disease assessments (CT CAP, rectal MRI, endoscopy, biopsy [when applicable])

^ = Disease assessments (endoscopy only)

† = EFS3 through Y3 (CT CAP, rectal MRI, endoscopy, biopsy [when applicable])

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
dMMR/MSI-H Rectal Cancer

NCCN Guidelines Index
Table of Contents
Discussion

CLINICAL STAGE

NEOADJUVANT/DEFINITIVE IMMUNOTHERAPY (PREFERRED)

dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb] T3, N any; T1–2, N1–2; T4, N any or Locally unresectable or medically inoperable

- Checkpoint inhibitor immunotherapy for up to 6 mo[vv]
  - Dostarlimab-gxly
  - or
  - Nivolumab
  - or
  - Pembrolizumab
- → Re-evaluate disease status every 2–3 mo
  - Complete clinical response → Surveillance (REC-10A)
  - Persistent disease at 6 mo → Long-course chemo/RT[p,u]
    - Capecitabine[o] or infusional 5-FU[o]
    - or
    - Short-course RT
    - → Transabdominal resection[f,s,t,w] or if complete clinical response, consider surveillance (REC-10A)[s] → Surveillance (REC-10)
    - → Resection contraindicated → Systemic therapy (REC-F 1 of 13)

TOTAL NEOADJUVANT THERAPY[ww]

- Long-course chemo/RT[p,u]
  - Capecitabine[o] or infusional 5-FU[o]
  - or
  - Short-course RT[p,q]
- → Chemotherapy (12–16 wk)
  - FOLFOX or CAPEOX
  - Consider FOLFIRINOX
- → Restaging[g]
  - Transabdominal resection[f,s,t,w] or if complete clinical response, consider surveillance (REC-10A)[s] → Surveillance (REC-10)
  - Resection contraindicated → Systemic therapy[z] (REC-F 1 of 13)

NONOPERATIVE MANAGEMENT OF MSI-H LARC

- Lower GI Endoscopy
  - Sigmoidoscopy Q 3–4 months x 2yrs, then Q 6 months until 5 yrs
  - Colonoscopy at 1 yr, repeat in 3 years, then Q 5 yrs
  - Annual colonoscopy in Lynch syndrome
- Radiology
  - MRI rectum Q 6 months for up to 3 yrs
  - CT chest/abdomen Q 6–12 months x 5 yrs
    - Include CT pelvis when no longer doing MRI pelvis
- H and P, CEA Q 3–6 months for 2 yrs and then Q 6 months until 5 yrs
- Emerging role of ctDNA, not yet routinely performed

National Comprehensive Cancer Network. Rectal Cancer (Version 2.2025).

NONOPERATIVE MANAGEMENT- NOT YET ROUTINE FOR MSI-H COLON
ATOMIC TRIAL

N = 712

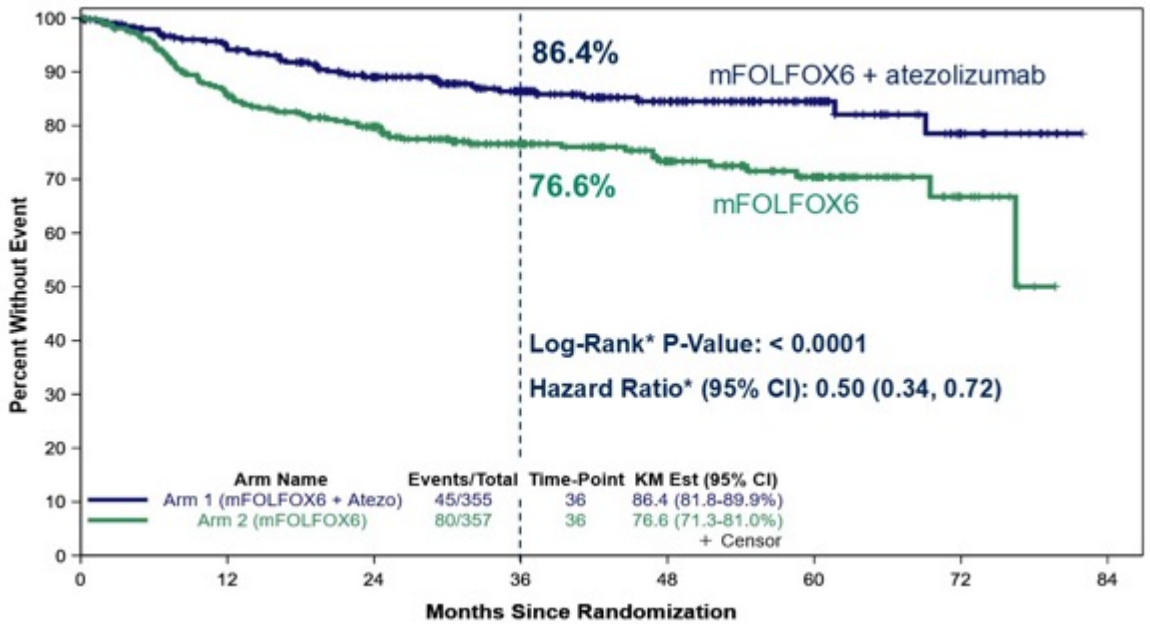
R0 resected stage III MSI-H colon cancer

n=355

mFOLFOX6 + Atezolizumab x 6 months, then Atezolizumab x 6 months

mFOLFOX6
6 months

n=357



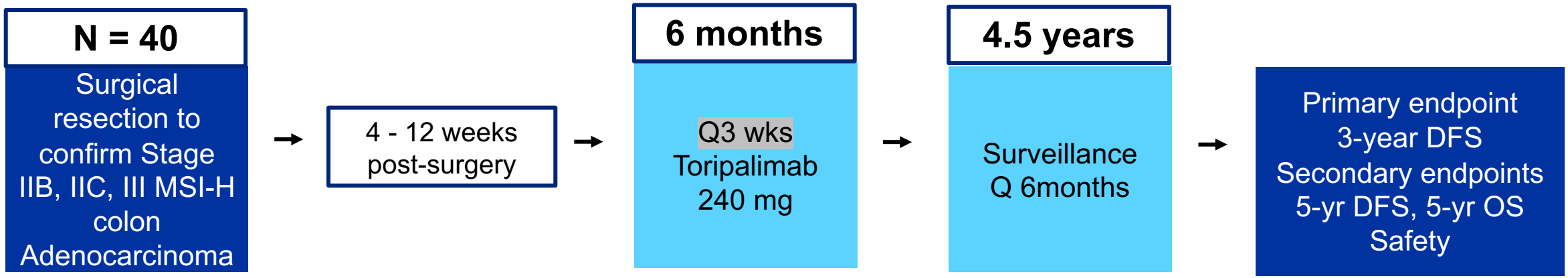
Unmet Need to assess the role of immunotherapy alone after surgery for MSI-H stage IIB-III colon cancer

WINSHIP 6483
Study of immunotherapy alone after surgery for MSI-H stage IIB-III colon cancer

Sinicrope FA, Ou F-S, Arnold D et al. (Alliance A021502; ATOMIC). Journal of Clinical Oncology 2025; 43 (17_suppl): LBA1-LBA1

WINSHIP 6483

Figure 1: Single Arm Phase II Trial of Adjuvant Toripalimab in Patients with Stage IIB, IIC, or III MSI-H/dMMR Colon Cancer



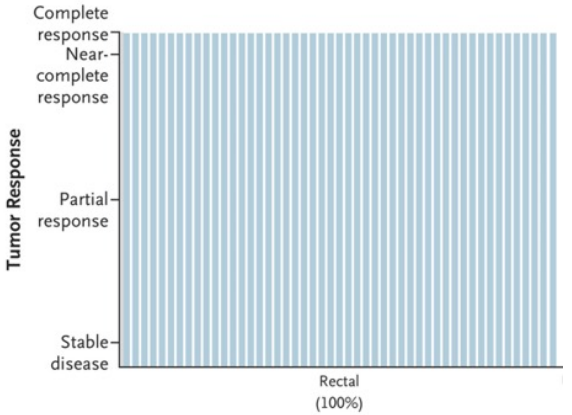
ADVERSE EFFECTS OF TRIMODALITY THERAPY FOR RECTAL CANCER

- Short- and long-term morbidity from surgery
  - Temporary or permanent colostomy
  - Low anterior resection syndrome
  - Bladder, bowel, and sexual dysfunction
  - Impairment of future fertility
  - Perioperative risks including infections, VTE, anastomotic leaks
- Short- and long-term morbidity from radiation therapy for rectal cancer
  - Bladder, bowel, and sexual dysfunction
  - Impairment of future fertility

Bloemen JG, Visschers RG, Truin W et al. Dis Colon Rectum 2009. Krogsgaard M, Kristensen HO, Furnee EJB et al. Support Care Cancer 2022. Collard MK, Tuech JJ, Sabbagh C et al. (GRECCAR). Colorectal Dis 2025. Hendren SK, O'Connor BI, Liu M et al. Prevalence of male and female sexual dysfunction is high following surgery for rectal cancer. Ann Surg 2005. Lange MM, Maas CP, Marijnen CA et al. Br J Surg 2008

CONCLUSION: DIMINISHING ROLE OF SURGERY IN MSI-HIGH RECTAL CANCER

- Up to 100% clinical CR rate without RT or surgery in MSI-H rectal cancer
- Indications for Surgery
  - Patients who do not achieve a cCR with ICI, or with ICI followed by RT
    - Primary resistance to ICI
  - Absolute contraindication to ICI
  - Complications of ICI- stricture fistula obstruction



- Multidisciplinary team approach for MSI-H LARC
  - GI, Med Onc, Pathology, Radiology, Rad Onc, Surgery

National Comprehensive Cancer Network. Rectal Cancer (Version 2.2025). Cercek A, Foote MB, Rousseau B et al. N Engl J Med 2025

THANK YOU