New approaches in treating GI cancers

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What are the determinants of immunotherapy response?

- Presence of metastatic disease → the earlier the better
- Immune cells in the tumor → easier to activate
- Number of mutations in the tumor DNA
  - The stranger the better response to immunotherapy

Types of colorectal cancer

MMR proficient *versus* MMR deficient

MMR proficient / microsatellite stable
85% of patients with early disease
Usually few immune cells in the tumor **(“cold”)**
Limited efficacy of immunotherapy in advanced disease (excl. new emerging data)
Few mutations in the tumor DNA ≅ 80

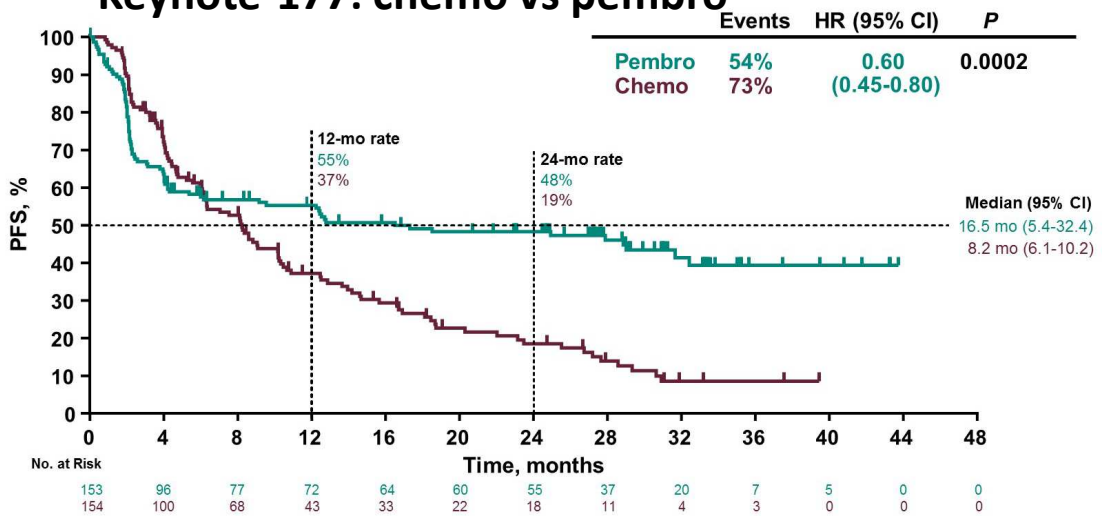
MMR deficient / microsatellite instable
15% of patients with early disease
Many immune cells in the tumor **(“hot”)**
Efficacious in 30-45% in advanced disease
Many mutations in the tumor DNA ≅ 800
Hereditary (Lynch Syndrome) in approximately 1/3 of patients

MMR proficient = pMMR = microsatellite stable = MSS
MMR deficient = dMMR = microsatellite instable = MSI

2024 - Immunotherapy for metastatic MSI CRC

- **Keynote-177**: first RCT in 1st line disease → EMA approval of pembrolizumab

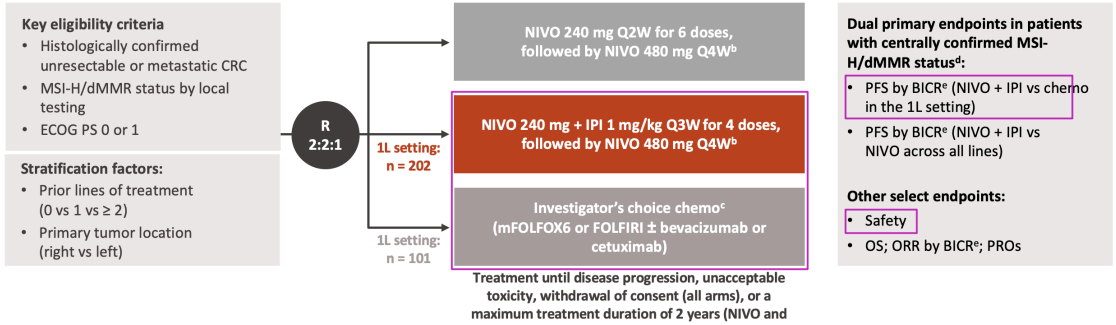
Keynote-177: chemo vs pembro



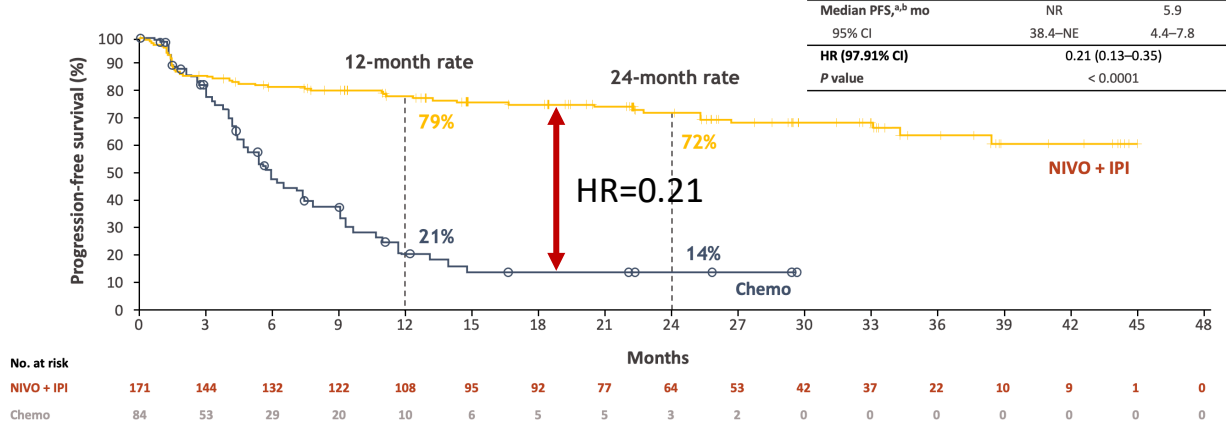
edian study follow-up: 32.4 months (range, 24.0 – 48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR.
uperiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.0117; Data cut-off: 19Feb2020.

Checkmate-8HW: nivo/ipi vs chemo

- CheckMate 8HW is a randomized, multicenter, open-label phase 3 study[a]



Progression-free survival



- PFS benefit with NIVO + IPI vs chemo was robust and consistent across the sensitivity analyses, including PFS by BICR in 1L all randomized patients (HR 0.32; 95% CI, 0.23–0.46)

Andre et al, NEJM, Andre et al, ASCO GI 2024

Neoadjuvant immunotherapy – advantages

- Early eradication of micrometastases
- Less extensive surgery– improved surgical outcomes
- Inform on prognosis – guide (neo-)adjuvant therapy

MORE CURE?

- Window of opportunity studies in cold tumors

Non-metastatic CRC: current standard of care

surgery

pathologist

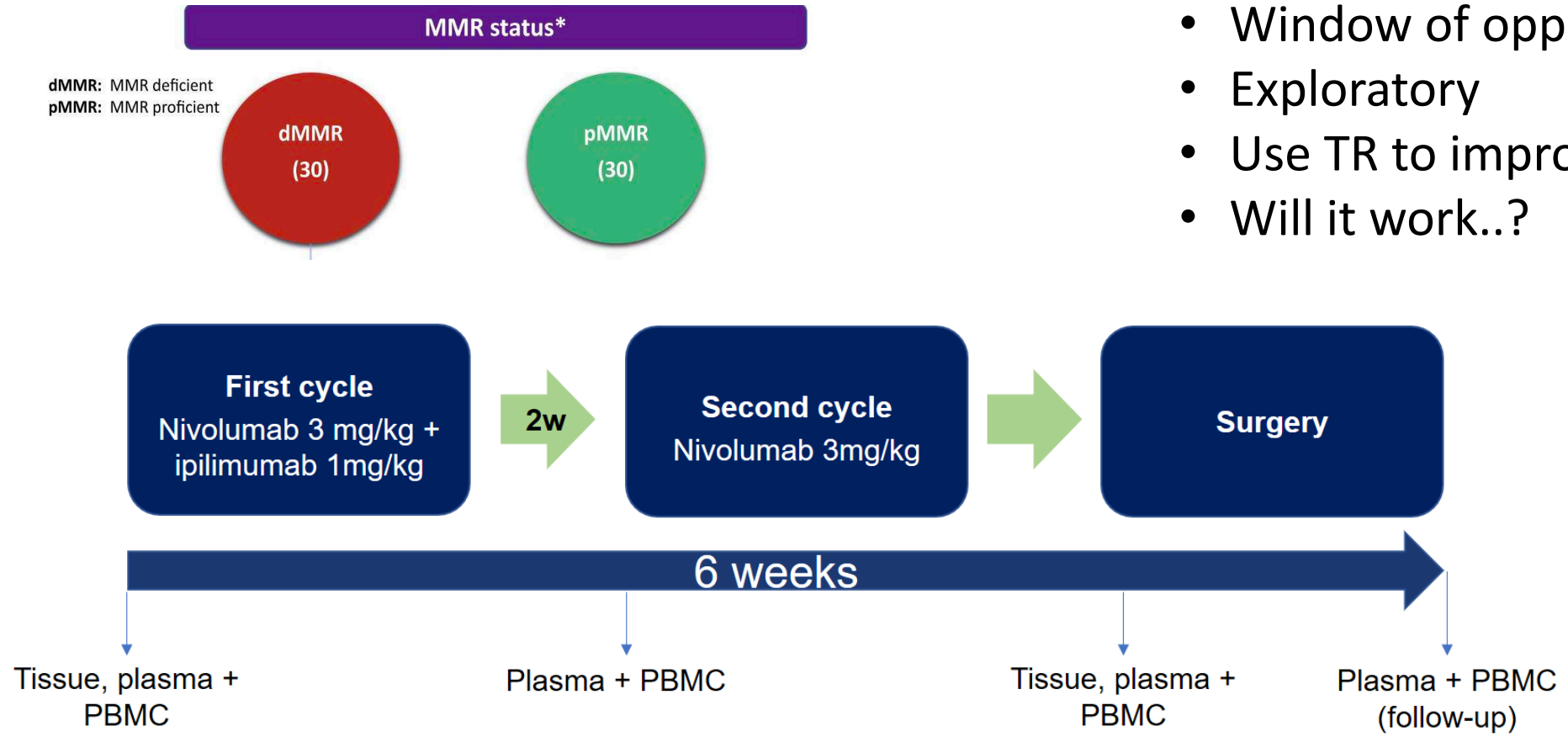
High risk and/or lymph node metastases?

chemotherapy

With neoadjuvant chemotherapy, pathologic responses in:

- **20% of pMMR/MSS tumors**
- **7% of dMMR/MSI tumors**

How the NICHE study started

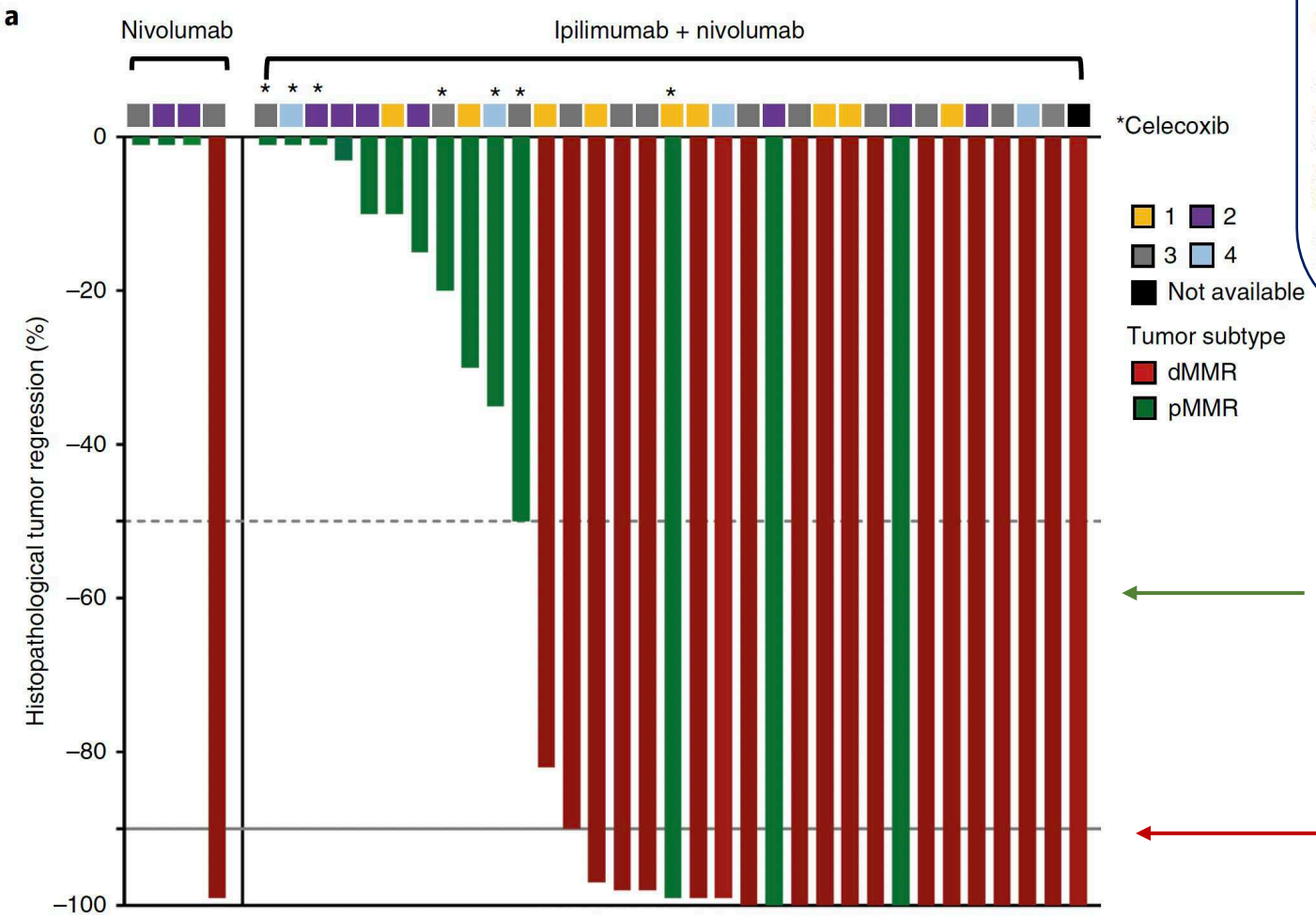


- Window of opportunity study
- Exploratory
- Use TR to improve IO for CRC
- Will it work..?

Chalabi et al, Nat Med 2020, ESMO 2022

Nivolumab = anti-PD1
Ipilimumab = anti-CTLA4

NICHE: first results



ARTICLES
https://doi.org/10.1038/s41591-020-0805-8
nature medicine
Check for updates

Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers

Myriam Chalabi[1,2,3], Lorenzo F. Fanchi[2,4,17], Krijn K. Dijkstra[2,4,17], José G. Van den Berg[5,17], Arend G. Aalbers[6], Karolina Sikorska[7], Marta Lopez-Yurda[7,8], Cecile Grootscholten[1], Geerard L. Beets[6,9], Petur Snaebjornsson[5], Monique Maas[10], Marjolijn Mertz[11], Vivien Veninga[2,4], Gergana Bounova[4,12], Annegien Broeks[13], Regina G. Beets-Tan[9,10], Thomas R. de Wijkerslooth[1], Anja U. van Lent[14], Hendrik A. Marsman[15], Elvira Nuijten[7], Niels F. Kok[6], Maria Kuiper[1], Wieke H. Verbeek[1], Marleen Kok[3,16], Monique E. Van Leerdam[1], Ton N. Schumacher[2,4], Emile E. Voest[1,2,4,17] and John B. Haanen[2,3,17]

pMMR/MSS cohort (*n*=15): 27% pathologic responses

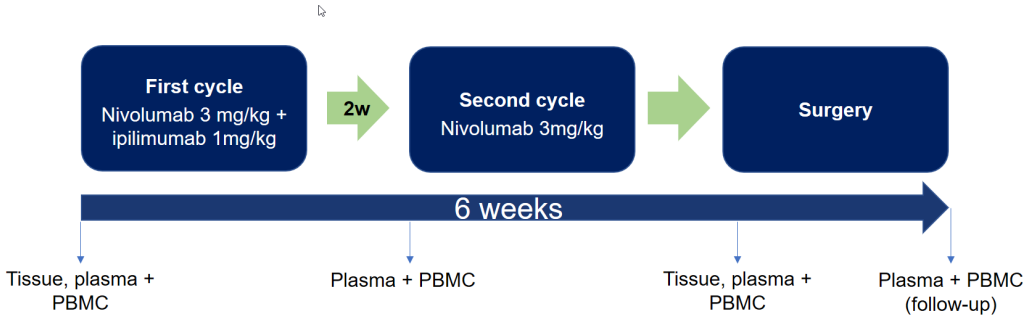
dMMR/MSI cohort (*n*=21): 100% pathologic responses, 60% complete

Neoadjuvant IO in dMMR colon cancer

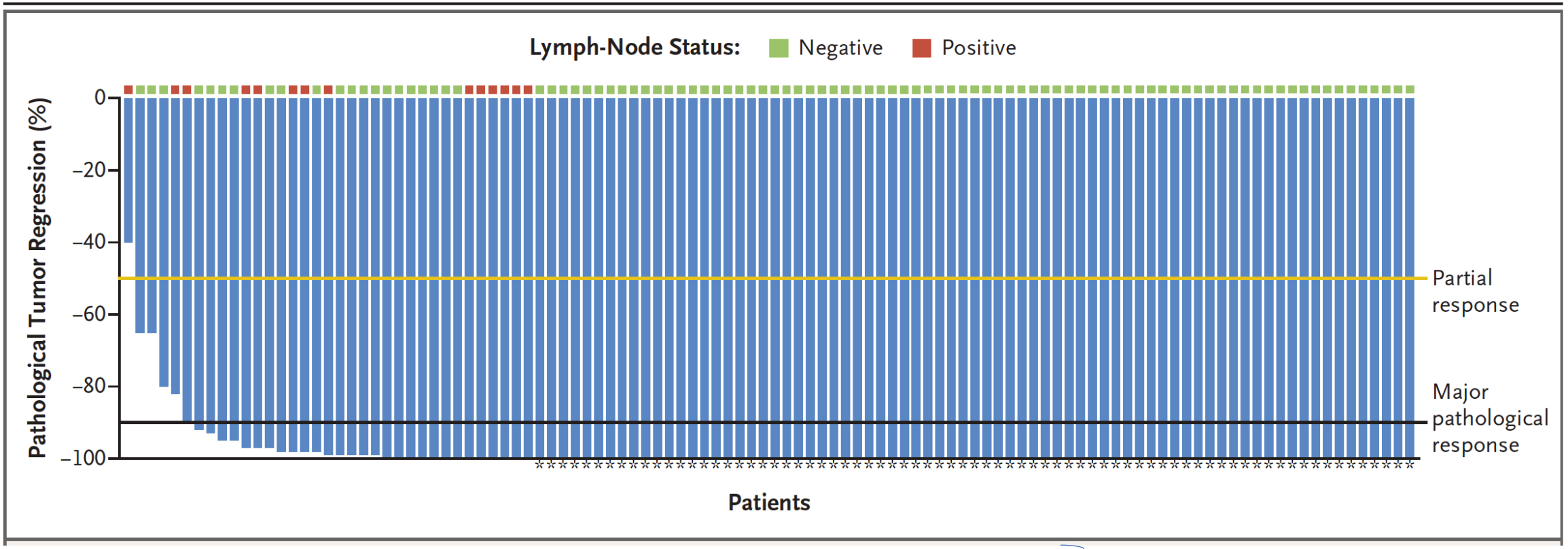
- Can we validate these findings in more patients?
- Is immunotherapy curing more patients with early stage disease?

NICHE-2 Primary Objectives & endpoints

- Safety and feasibility: **Timely surgery** in at least 95% of patients
- 3-year disease-free survival (DFS): **3-year DFS** of **at least 93%**



Neoadjuvant immunotherapy highly effective in locally advanced MSI colon cancer

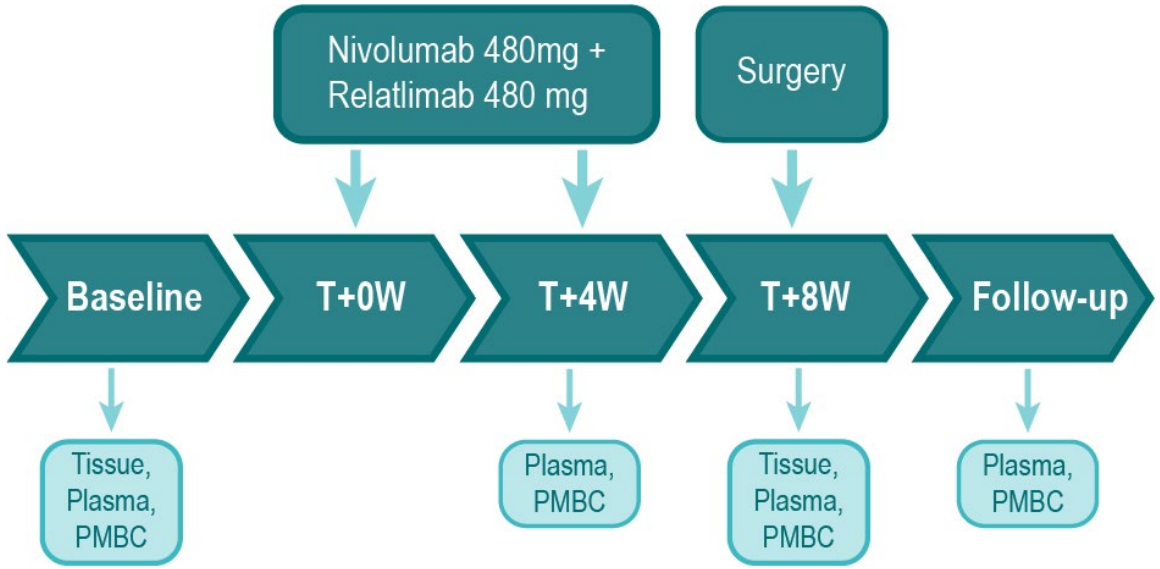


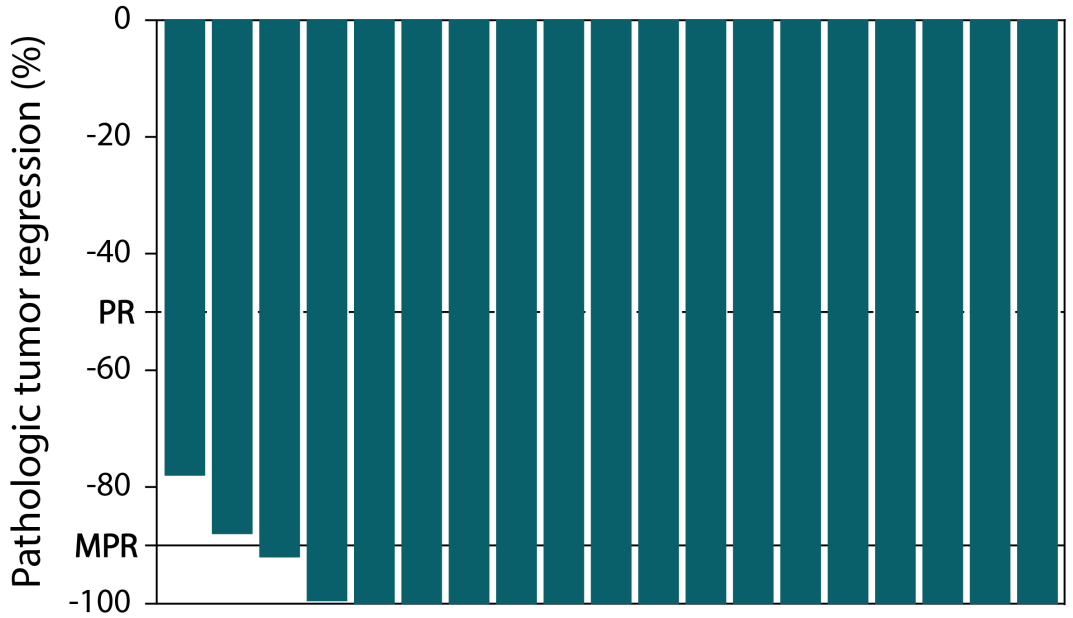
- **95% pathologic complete or near-complete response**
- **68% pathologic complete responses**

After only 5.4 weeks

Chalabi et al, NEJM 2024

NICHE-3: neoadjuvant nivo + rela in dMMR colon cancers





- Compared to NICHE-2 with nivo/ipi: difference in treatment doses, scheduling and timing of surgery
- Only 5% grade 3 irAE, yet 21% endocrinopathies requiring long-term supplementation

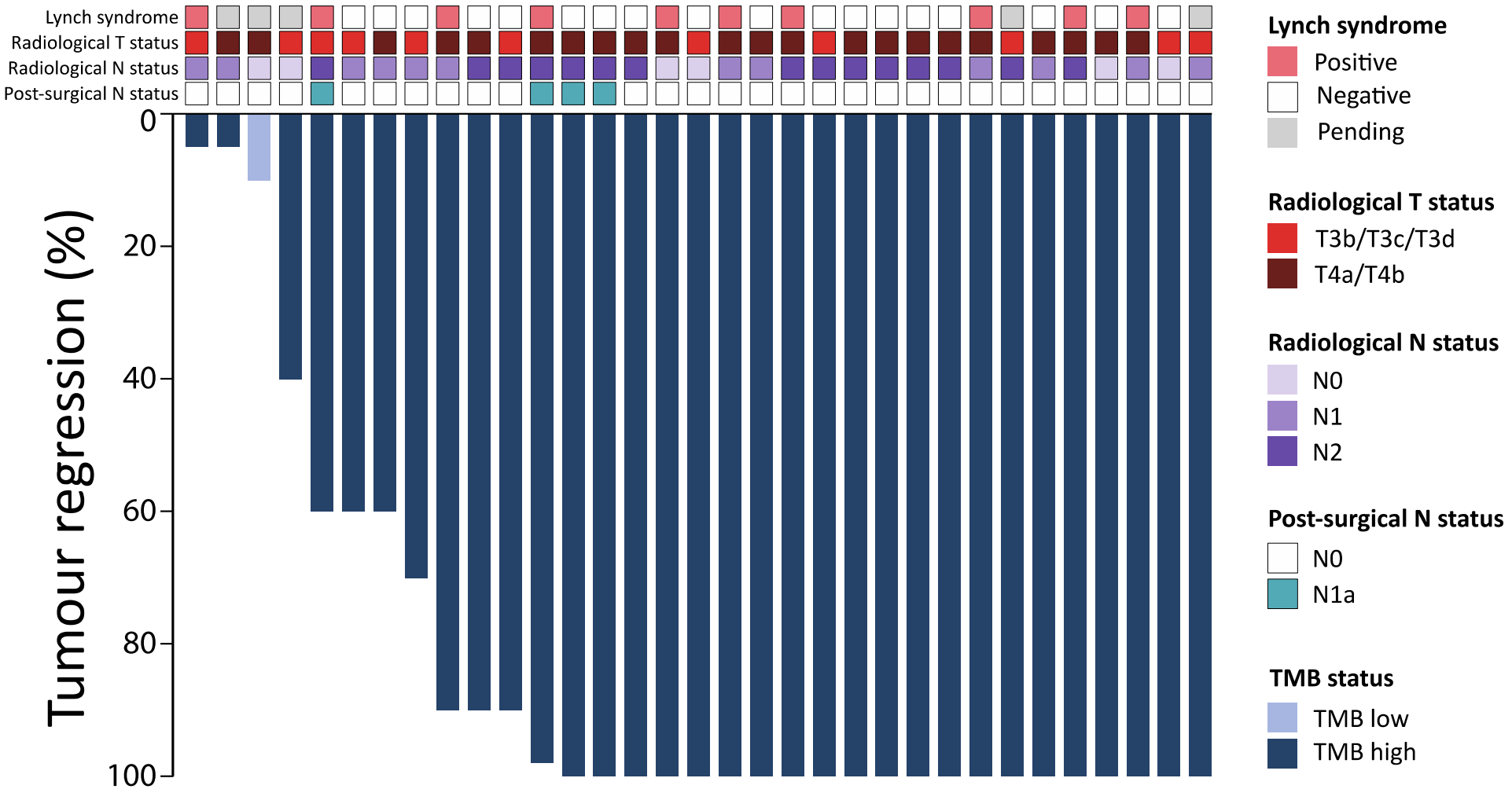
Accrual in stage II (*n*=40) ongoing; first data full cohort expected in 2024

Pathologic response (RVT)	Patients *n* = 19
Yes (≤50%)	**19 (100%)**
Major (≤50%)	17 (89%)
Complete (0%)	15 (79%)
Partial (10-50%)	2 (11%)
No (>50%)	**0**

MADRID 2023 ESMO congress

Verschoor et al, ESMO 2023

NEOPRISM: pCR in 59% of pts aftr 3 cycles of pembrolizumab

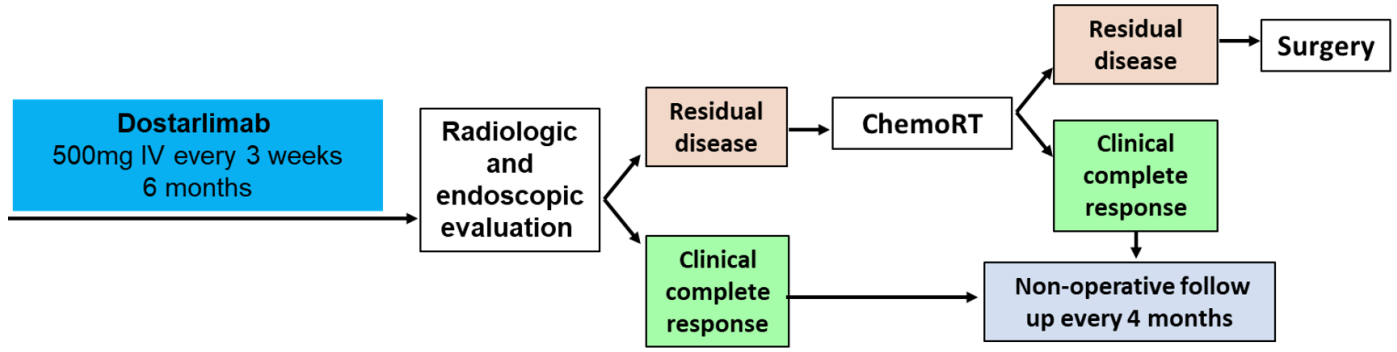


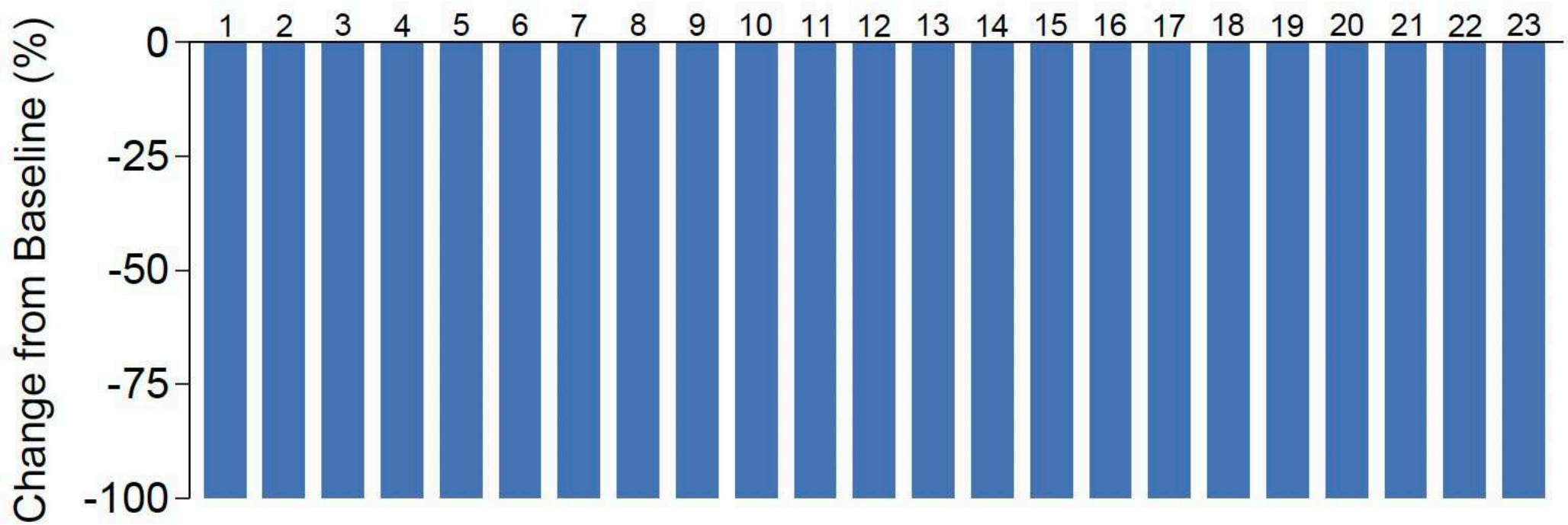
No disease relapse with median follow up of 9.7 months (range 5.3-19.0) and only 2 patients had adjuvant CAPOX

Shiu et al, ASCO 2024

Neoadjuvant anti-PD1 in dMMR rectal cancer

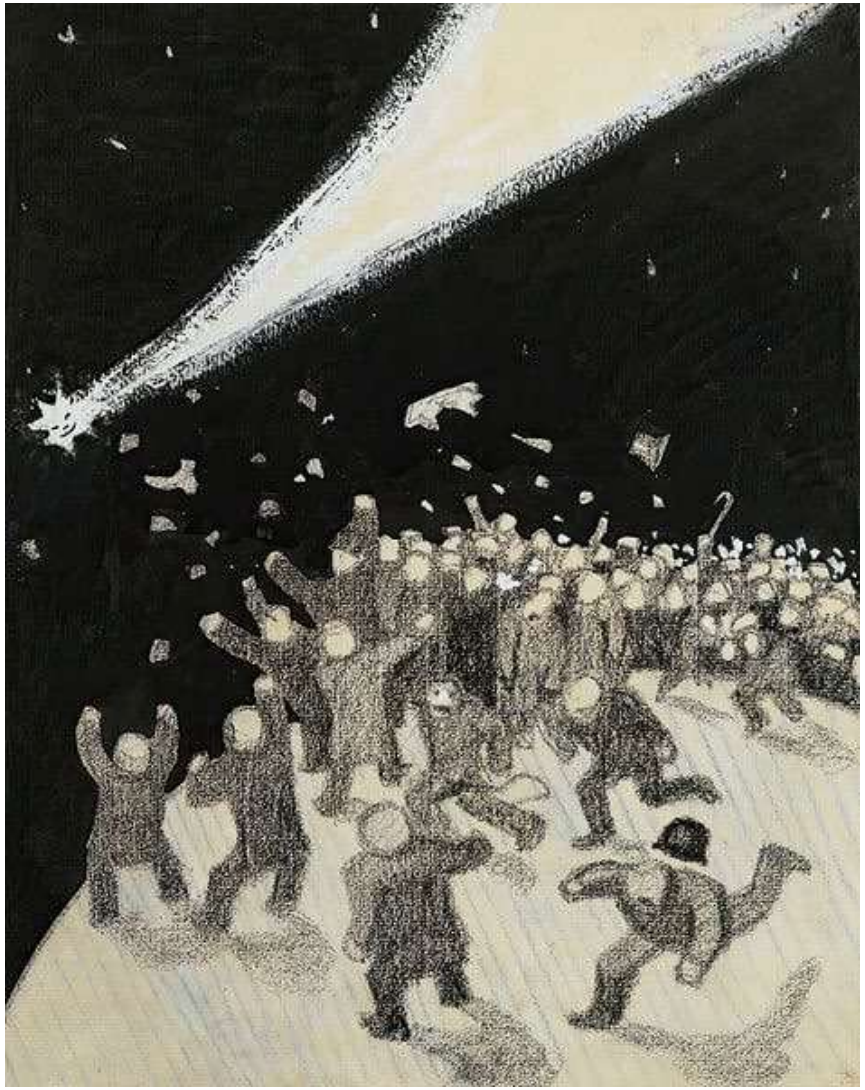
- 100% cCR with 6 months of dostarlimab monotherapy
- 0% underwent RT, CRTx and/or surgery





Cercek et al, *NEJM* 2023, JSMO 2023

MSS CRC: the one that got away?



The disappointment of Juan Gris
Peter Balan

Can we turn pMMR tumors from “cold” to “hot” with neoadjuvant IO?

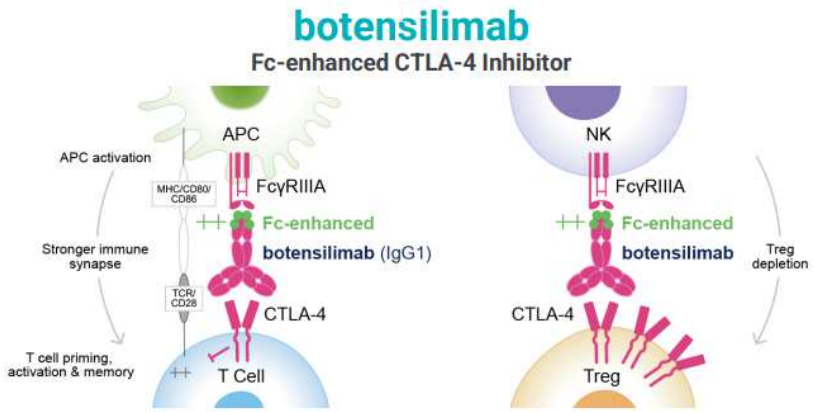
Amsterdam

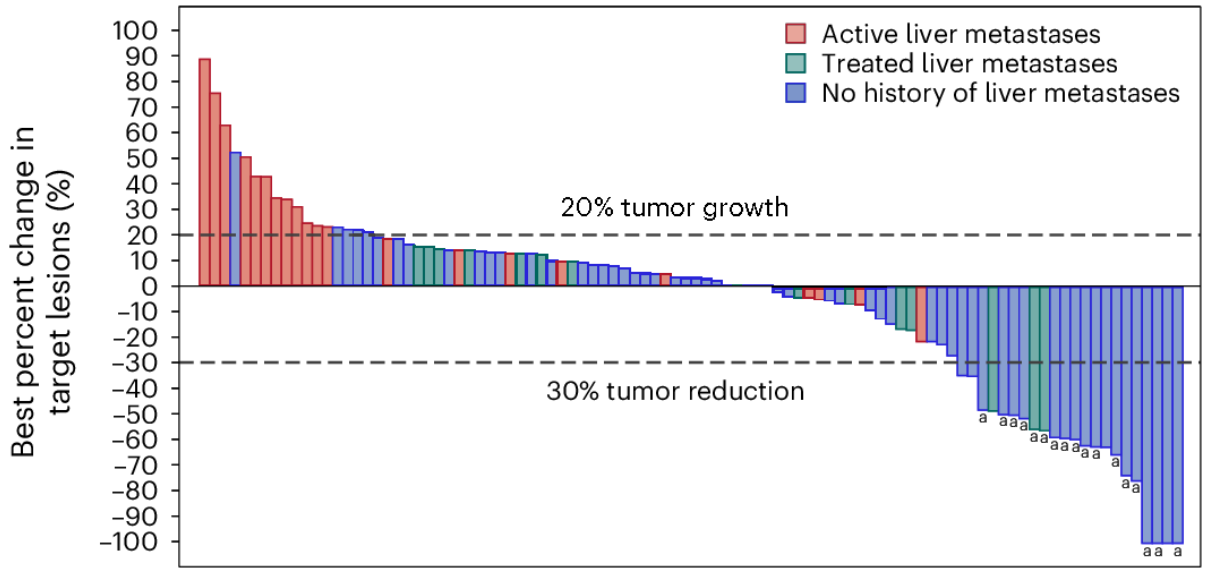
+32℃ =

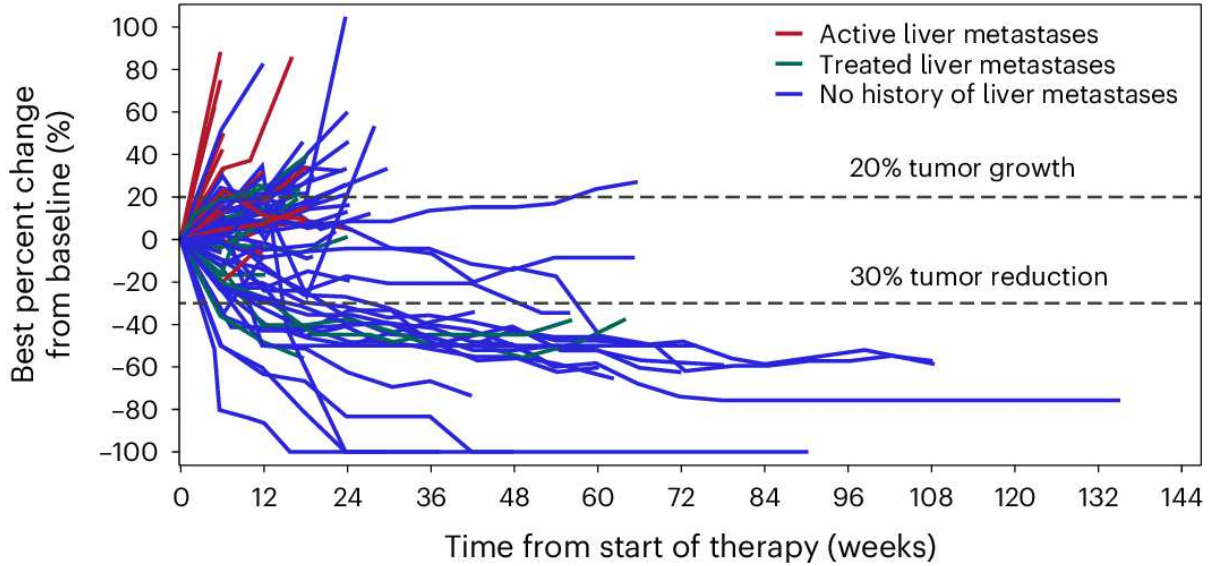
Curacao

BOT+BAL leads to responses in patients with MSS mCRC

- Botensilimab (anti-CTLA4) + balstilimab (anti-PD1)
  - ORR all-comers: 17% (*n*=101); DCR 61%
  - No liver mets (*n*=77): ORR 22%; DCR 73%
  - Active liver mets (*n*=24): ORR 0%; DCR 25%







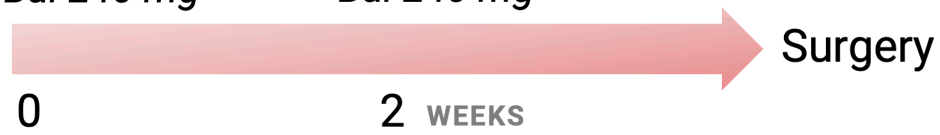
Bullock et al, Nat Med 2024

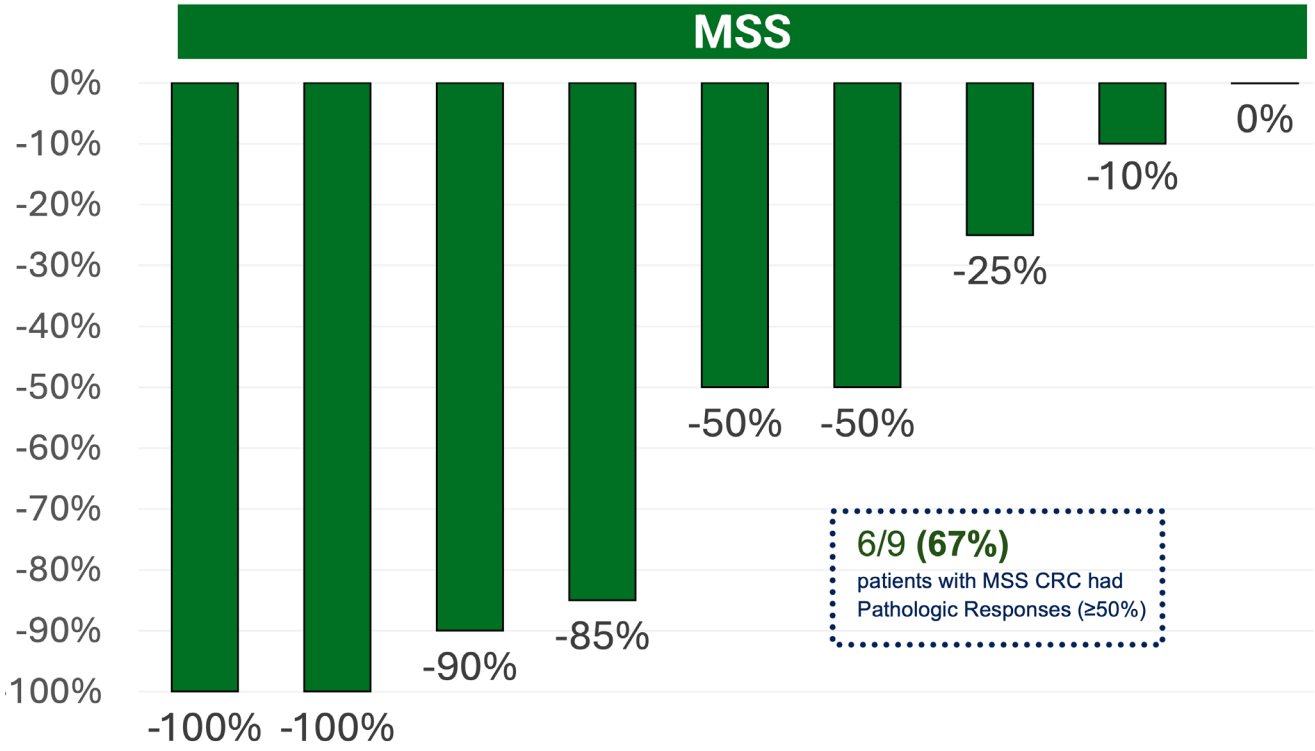
Neoadjuvant bot+bal in early-stage CRC

NEST-1

Study Schema[1]

Bot 75 mg
Bal 240 mg *Bal 240 mg*





Bot = botensilimab (anti-CTLA4)
Bal = balstilimab (anti-PD1)

Adapted from Kasi et al, ASCO GI 2024

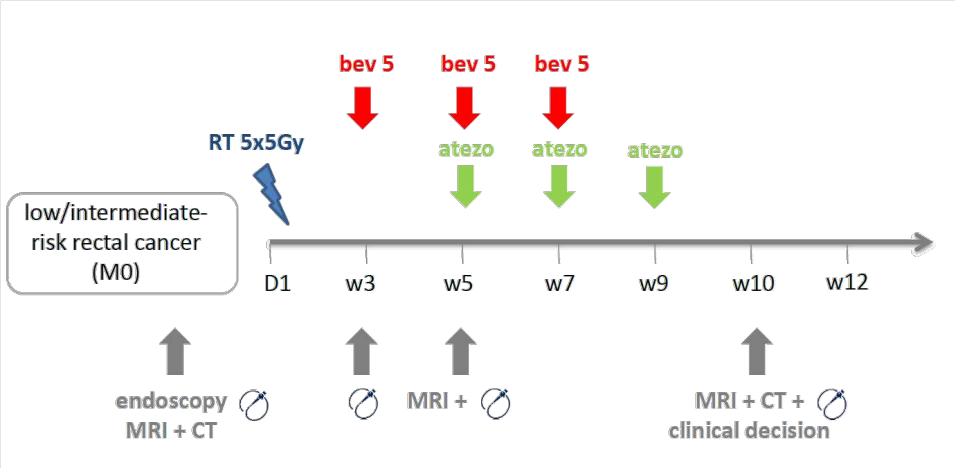
IO for organ preservation in pMMR rectal cancers

TARZAN

Phase 2, single-arm study

Early + intermediate risk rectal cancer

Fully accrued (n=38 pts with pMMR tumors)



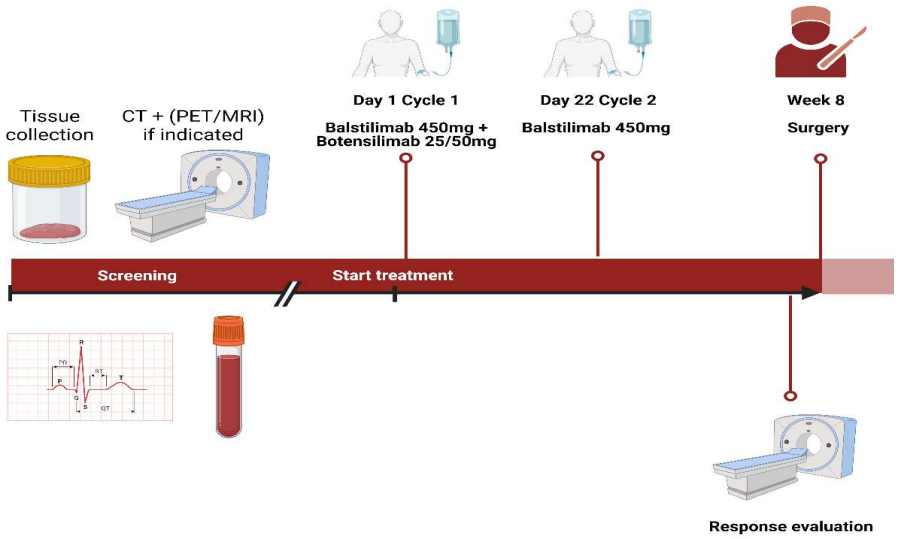
		pMMR cohort n = 38	dMMR cohort n = 6
Follow up, months	**median(range)**	24,3 (5,4 – 51,8)	14,7 (6,9 – 22,2)
Clinical response at 10-12wks	*Complete response*	**7 (18%)**	3 (50%)
	Near-complete response	**10 (23%)***	1 (17%)
	Residual tumor	21 (55%)**	2 (33%)
Organ preservation rate	**n (%)**	**16 (42%)**	**6 (100%)**
Clinical response 10-12 weeks subgroups			
	Clinical response in tumors <40mm	**13/23 (57%)**	3/3 (100%)
	Clinical response in cN0 tumors	**13/22 (59%)**	1/1 (100%)

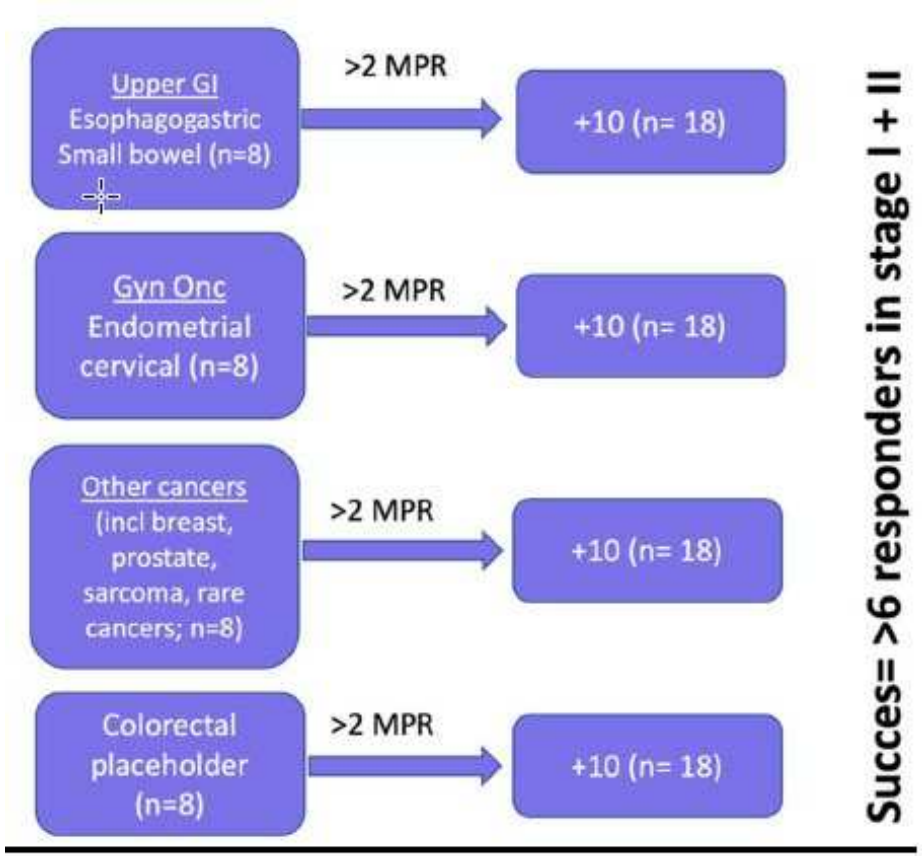
De Gooyer et al, ESMO GI 2024 #247P

De Gooyer et al, ESMO GI 2024 #247P

Future perspectives: NEOASIS
neoadjuvant immunotherapy across tumor types

- All patients with:
  - dMMR/MSI tumors regardless of primary site
  - pMMR/MSS tumors who do not need standard of care neoadjuvant treatment





Treatment:
- 2 cycles of balstimilab = anti-PD1
- 1 cycle of botensilimab = anti-CTLA4

KEY TAKE AWAYS

- Immunotherapy highly effective in patients with dMMR/MSI colorectal cancers
- Intriguing responses to neoadjuvant IO in MSS colorectal cancer
- In MSS mCRC, patients with liver metastases do not benefit from IO: mechanisms of immune evasion still poorly understood
- Selection is one of the main keys to success
  - Not all pMMR colon cancers are created equal
  - Not all metastases are created equal
  - Refinement of mode of action of immunotherapies

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