Immunotherapy for Colorectal Cancer

University of Tennessee Health Science Center
Surgical Oncology Symposium: *State of the Art Management of Colorectal Cancer*

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Disclosures

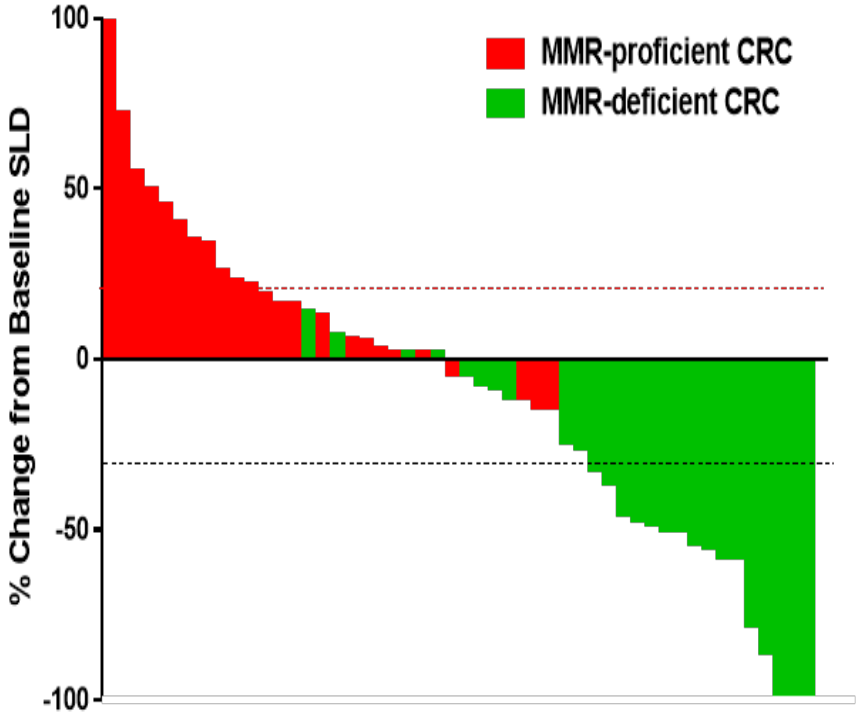
- Research funding: GSK, Seagen
- Advisory Role: Merck, Pfizer, Roche, GSK, Janssen, Bayer, Seagen

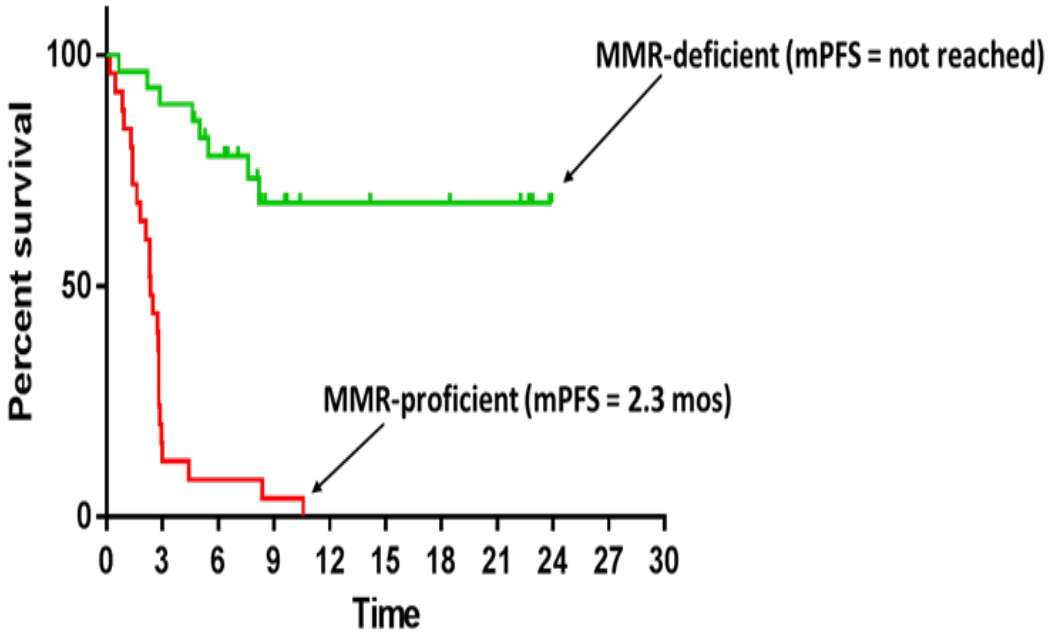
Metastatic MMRd/MSI Colorectal Cancer

MSI: Colorectal

Keynote 16: Pembrolizumab

Refractory mCRC





Le DT et al. *N Engl J Med.* 2015;372(26):2509-2520.

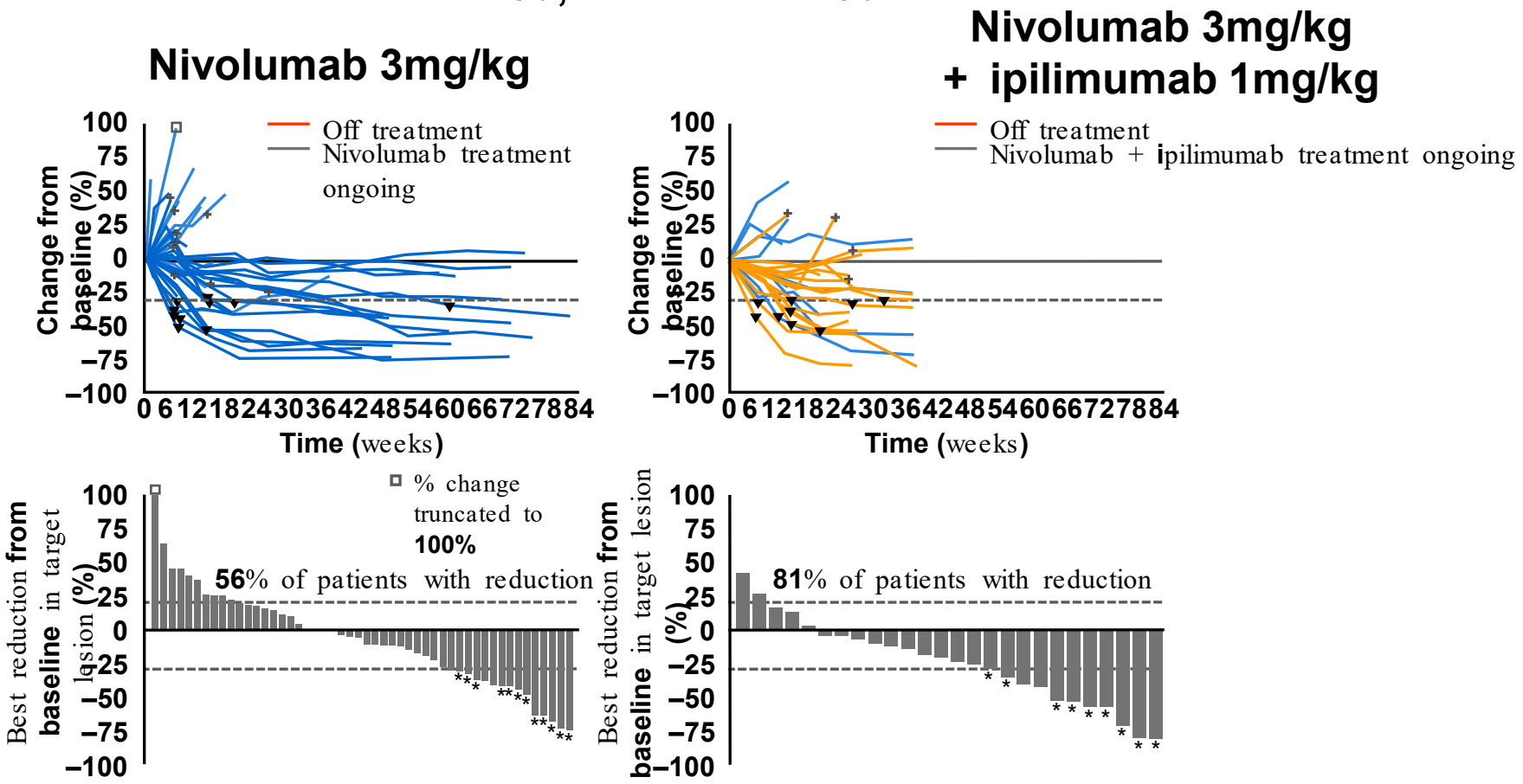
MSI: Colorectal

CheckMate142

Refractory mCRC

Nivolumab ± ipilimumab (CheckMate142, phase II)

RR = 31%; DCR = 69%



Overman MJ et al. *J Clin Oncol.* 2018;36(8):773-779.

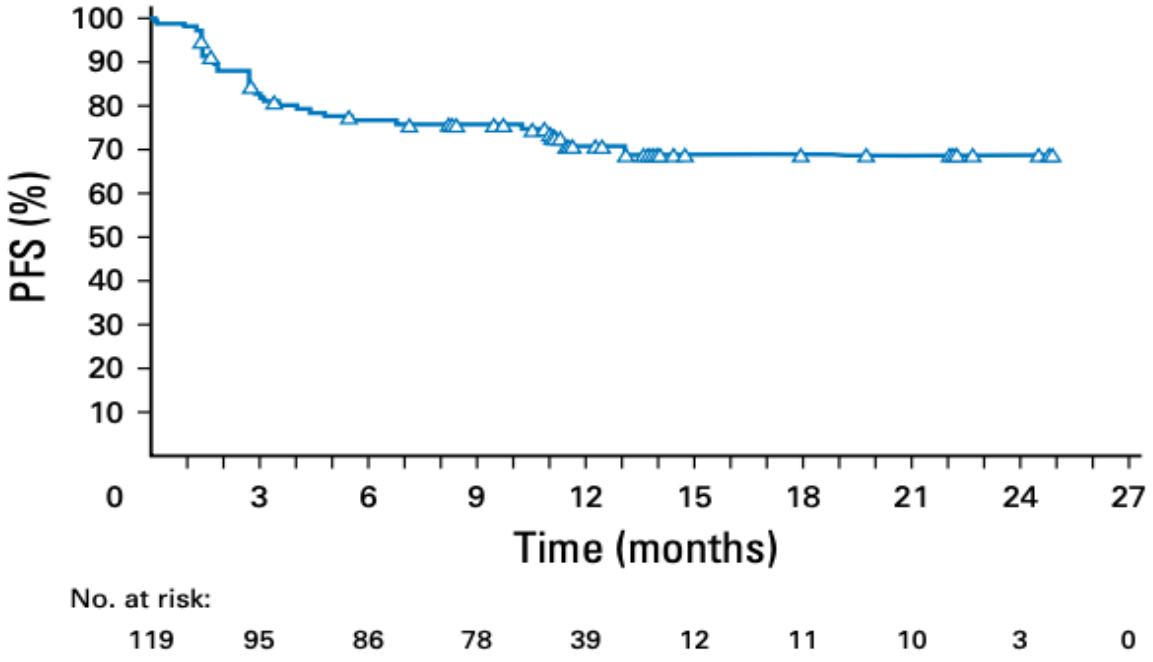
MSI: Colorectal

CheckMate142

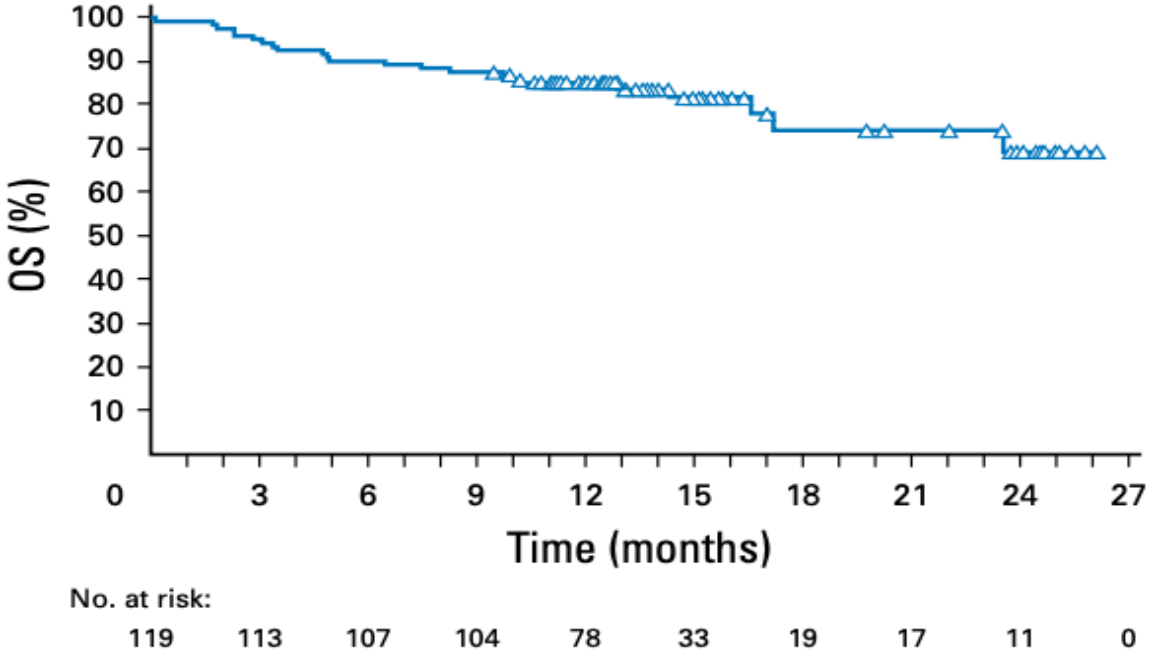
Refractory mCRC

Nivolumab ± ipilimumab (CheckMate142, phase II)

Progression-Free Survival



Overall Survival



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Overman MJ et al. *J Clin Oncol.* 2018;36(8):773-779.

MSI: Colorectal

KEYNOTE-177: First-Line Pembrolizumab vs Chemo

Antitumor Response

	Pembrolizumab N = 153		Chemotherapy N = 154
ORR, n (%)	**67 (43.8)**		**51 (33.1)**
Difference, estimate (95% CI) *P*-value		10.7 (-0.2-21.3) 0.0275	
Best Overall Response, n (%)			
Complete response	17 (11.1)		6 (3.9)
Partial response	50 (32.7)		45 (29.2)
Stable disease	32 (20.9)		65 (42.2)
Disease control rate (CR+PR+SD)	99 (64.7)		116 (75.3)
Progressive disease	45 (29.4)		19 (12.3)
Not evaluable	3 (2.0)		2 (1.3)
No assessment	6 (3.9)		17 (11.0)
Median time to response (range), mo	2.2 (1.8-18.8)		2.1 (1.7-24.9)

Data cut-off: 19Feb2020; Response assessed per RECIST v1.1 by BICR.

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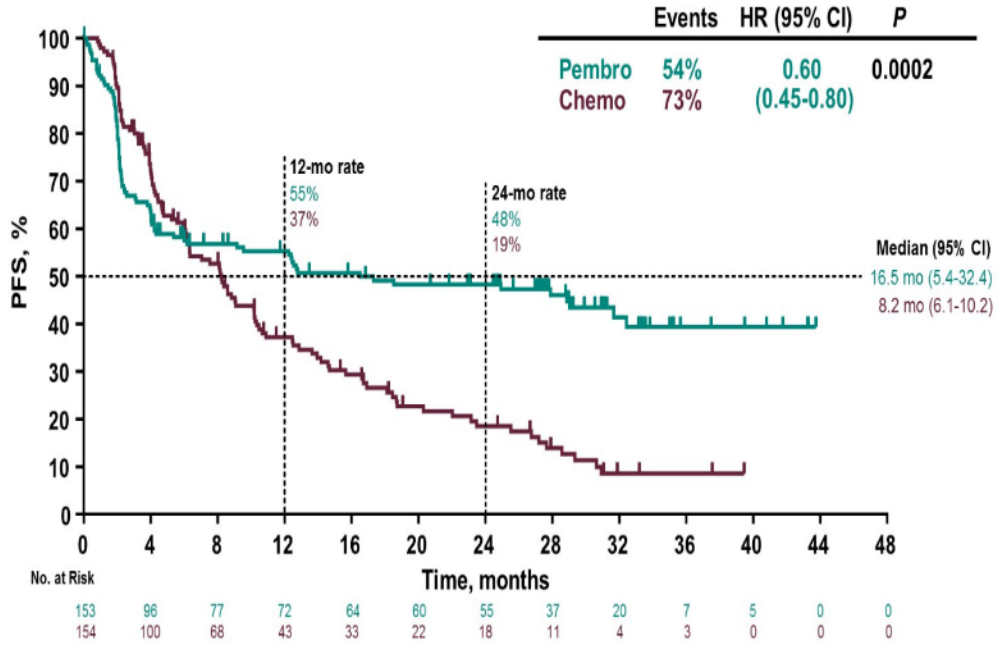
Progression-Free Survival



Median 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. Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.0117; Data cut-off: 19Feb2020.

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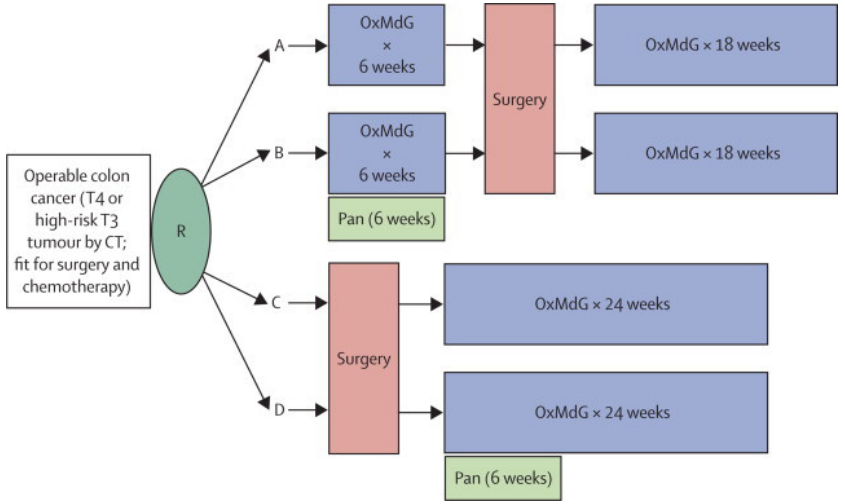
Andre T et al. *J Clin Oncol.* 2020;38(suppl): Abstract LBA4.

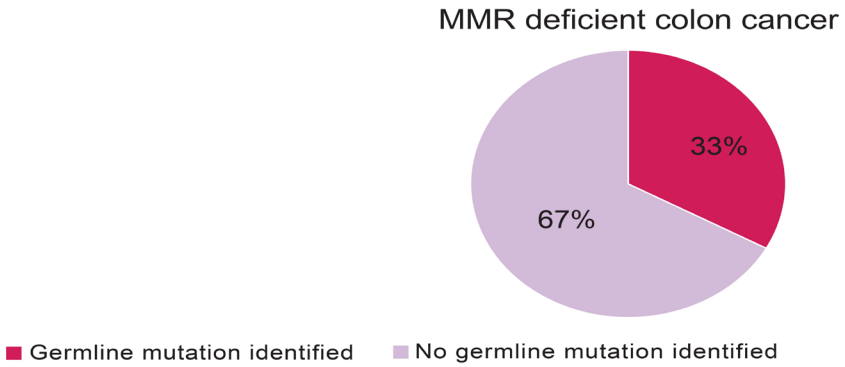
Neoadjuvant therapy for early stage MMRd/MSI colorectal cancer

Locally Advanced MSI (dMMR) Colorectal Cancer

- About 15% of all colon cancers
- Less sensitive to chemotherapy
  - Adjuvant therapy
  - Neoadjuvant colon – FoXTROT
  - Neoadjuvant rectal - TNT
- Associated with Lynch Syndrome (rectal > colon)



MSI status was associated with a significantly higher rate of poor/no response (96% vs. 66%, $p < 0.0001$)



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)

MSI = microsatellite instability; dMMR = deficient mismatch repair; TNT = total neoadjuvant therapy.

Foxtrot Collaborative Group. *Lancet Oncol*. 2012;13(11):1152-60. Cercek A, et al. *Clin Can Res*. 2020;26(13):3271-3279.

Neoadjuvant therapy for early stage MMRd/MSI *rectal cancer*

Rectal Cancer

- Therapy for locally advanced rectal cancer includes a combination of chemotherapy, radiation and surgery
- While cure is frequently achieved, radiation and surgery have life-altering consequences
- Following chemotherapy and radiation, a portion become candidates for non-operative management.

Formijne Jonkers Int J Colorectal Dis 2012
Smith JJ, JAMA Oncol 2019
Cercek A, J Natl Compr Canc Netw 2014
Garcia-Aguilar J Clin Oncol 2022

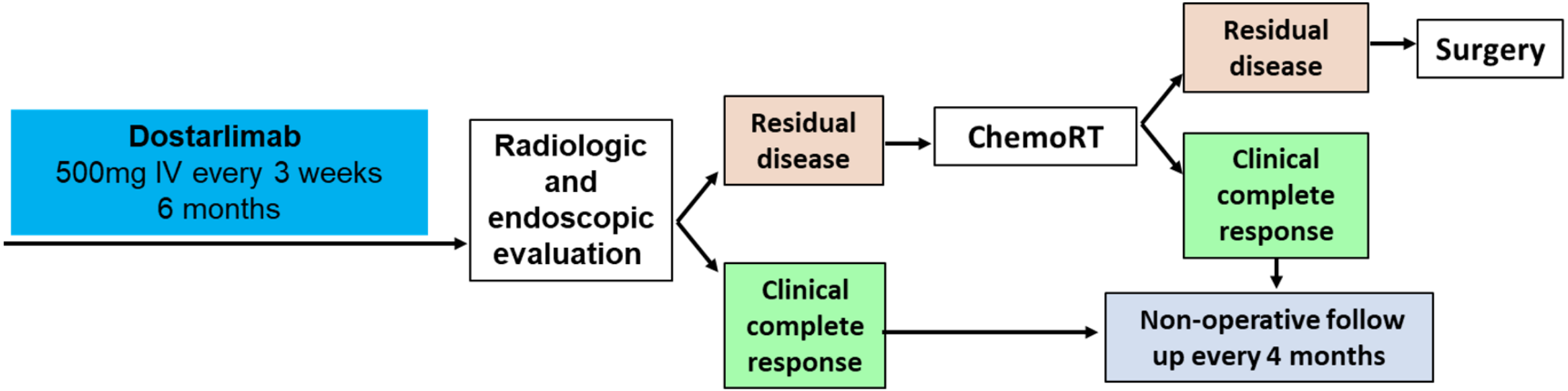
Hypothesis:

In mismatch repair deficient rectal cancer, PD-1 blockade may be able to either:

a) replace chemotherapy

b) replace chemo *and* radiation therapy

c) replace chemo *and* radiation, *and* surgery



Patient population: Stage II and III mismatch repair deficient rectal cancer

Target Enrollment: 30 subjects (expanded, enrollment ongoing)

Study Design: Simon's two stage minimax design

Cercek et al, NEJM 2022; JSMO 2023

NCT04165772

Study Objectives

Primary Objectives

- Overall response rate of PD-1 blockade with or without chemoradiation
- Pathologic complete response (pCR) or clinical complete response (cCR) rate at 12 months after PD-1 blockade with or without chemoradiation

Secondary Objective

- Safety and tolerability

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Response Criteria

Overall response

Rectal MRI and endoscopic exam graded as stable disease (SD), partial response (PR), near complete response (nCR) and complete response (CR)

Clinical complete response (cCR)

Endoscopic exam:

- Visual disappearance of the rectal primary
- Normal digital rectal exam

Rectal MRI

- Lack of signal at DWI with scar on T2WI (DWI volume = 0)
- Each target lymph node must have decreased short axis to <0.5cm

Maas M, et al., Ann Surg Oncol 2015;22:3873-80

Demographic and disease characteristics at baseline N=36

		Value (%)
Sex		
	Male	17 (47)
	Female	19 (53)
Age, median (range)		50 (range 26-78)
Race/Ethnicity		
	White non-Hispanic	24 (67)
	Hispanic	3 (8)
	Black or African American	4 (11)
	Asian-Far East/Indian Subcontinent	5 (14)
Tumor Staging		
	T 0/1/2	10 (28)
	T3	17 (47)
	T4	9 (25)
Nodal Staging		
	Node-positive	34 (94)
	Node-negative	2 (6)
Germline Mutation Status n= 26		
	MSH2, MLH1, MSH6, or PMS2	18 (69)
	Negative	8 (31)

Cercek NEJM 2022; JSMO 2023

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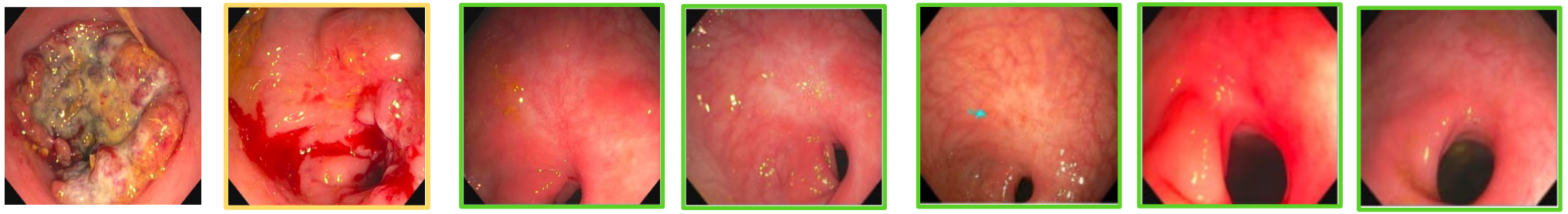
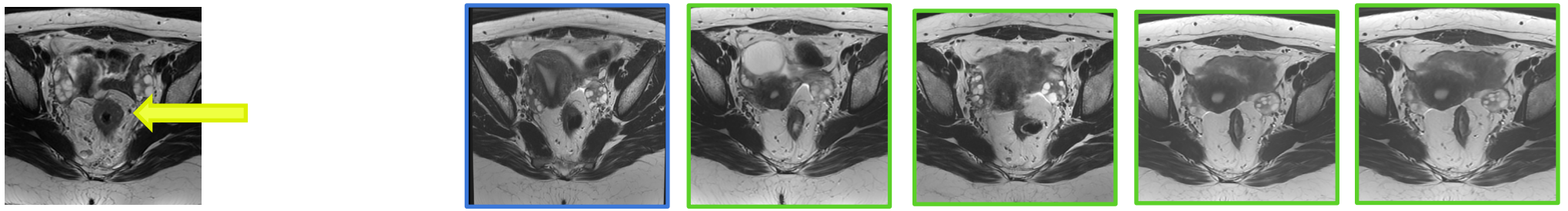
Cercek NEJM 2022; JSMO 2023

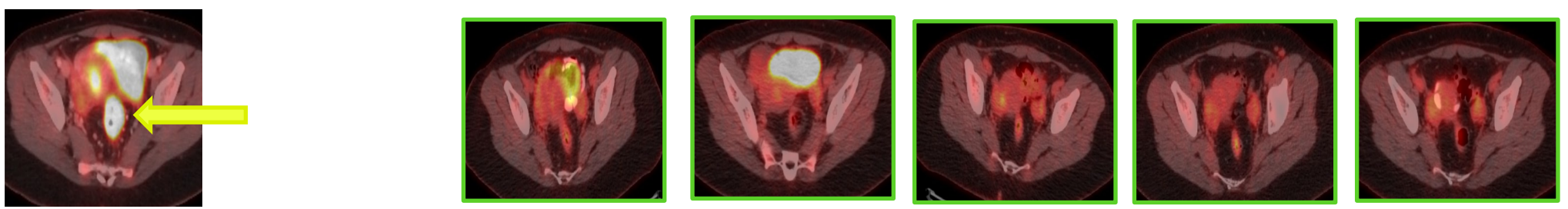
SD / STABLE DISEASE
PR / PARTIAL RESPONSE
NCR / NEAR COMPLETE RESPONSE
CR / COMPLETE RESPONSE

DOSTARLIMAB

BASELINE | 6 WEEKS | 3 MONTHS | 6 MONTHS | FU2 / 14 MONTHS | FU3 / 18 MONTHS | FU4 / 22 MONTHS



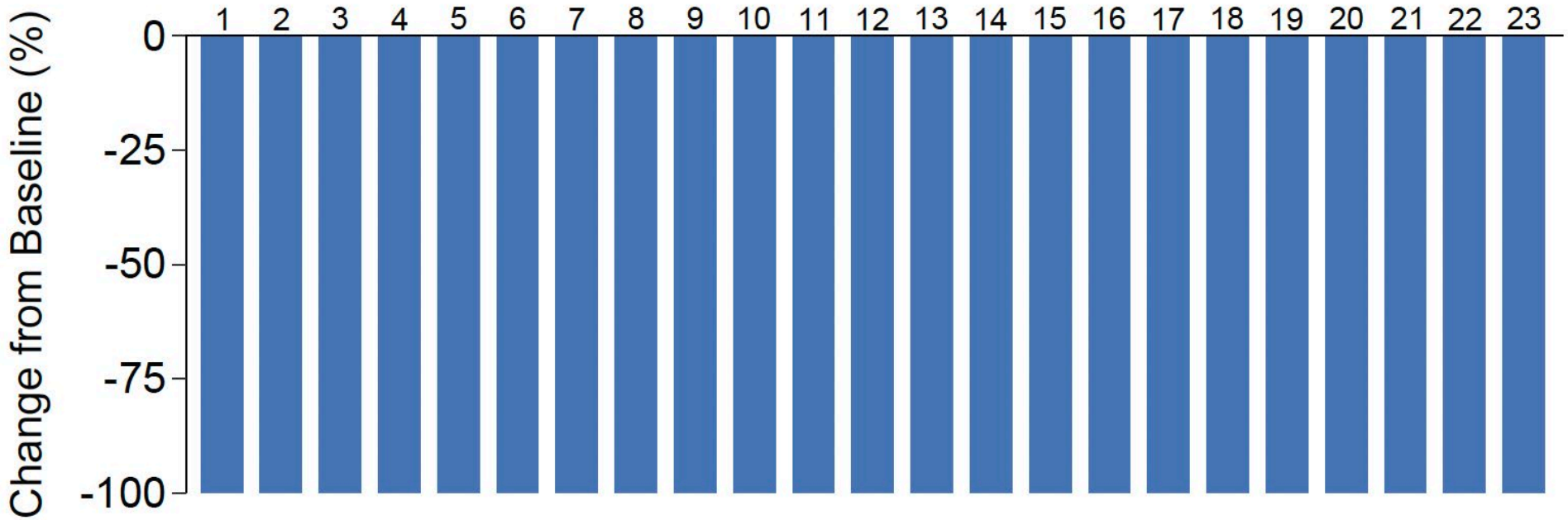




Cercek NEJM 2022; JSMO 2023

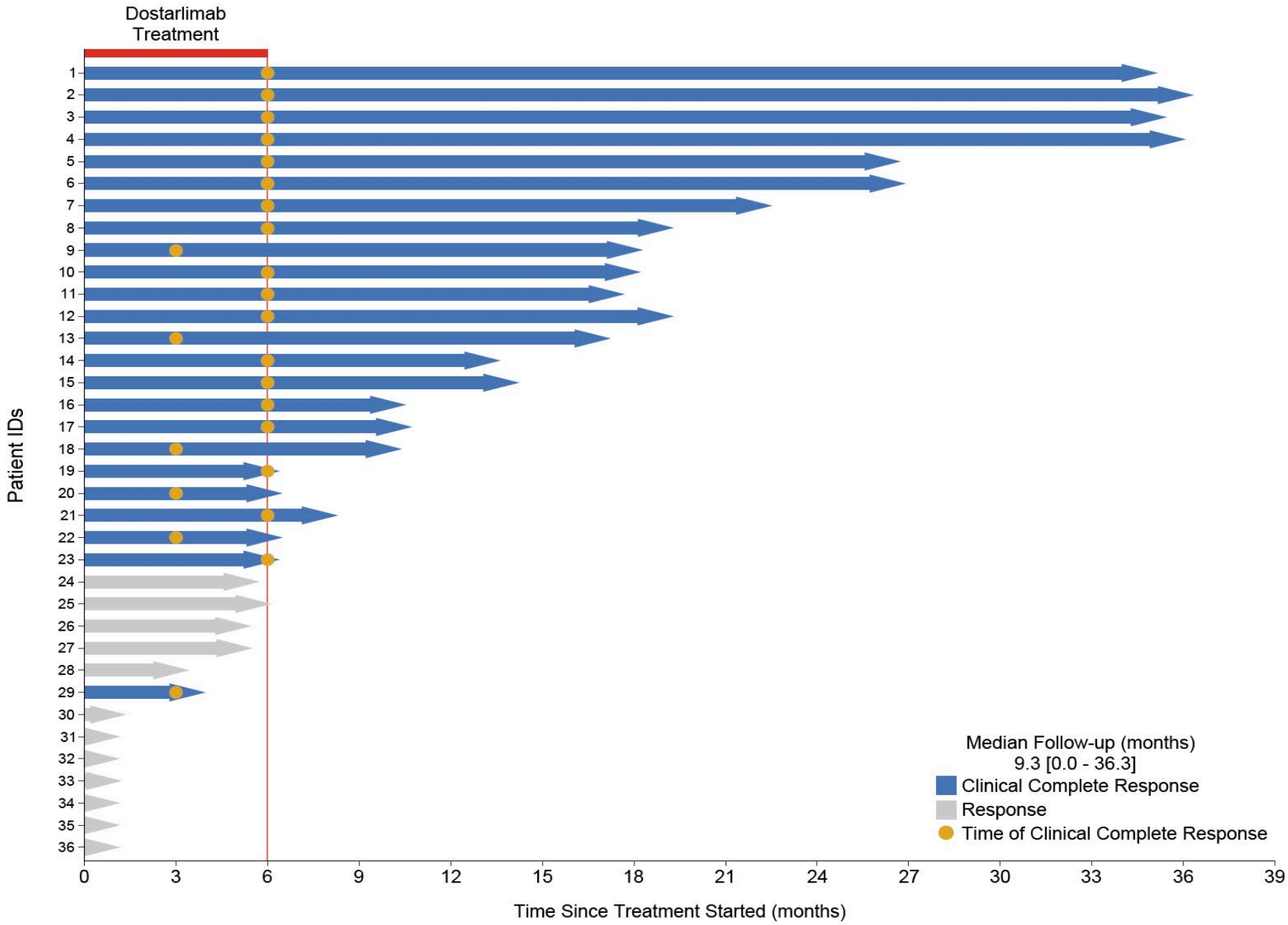
Responses

patients who completed dostarlimab N=23



Cercek NEJM 2022; JSMO 2023

Duration of response



Cercek NEJM 2022; JSMO 2023

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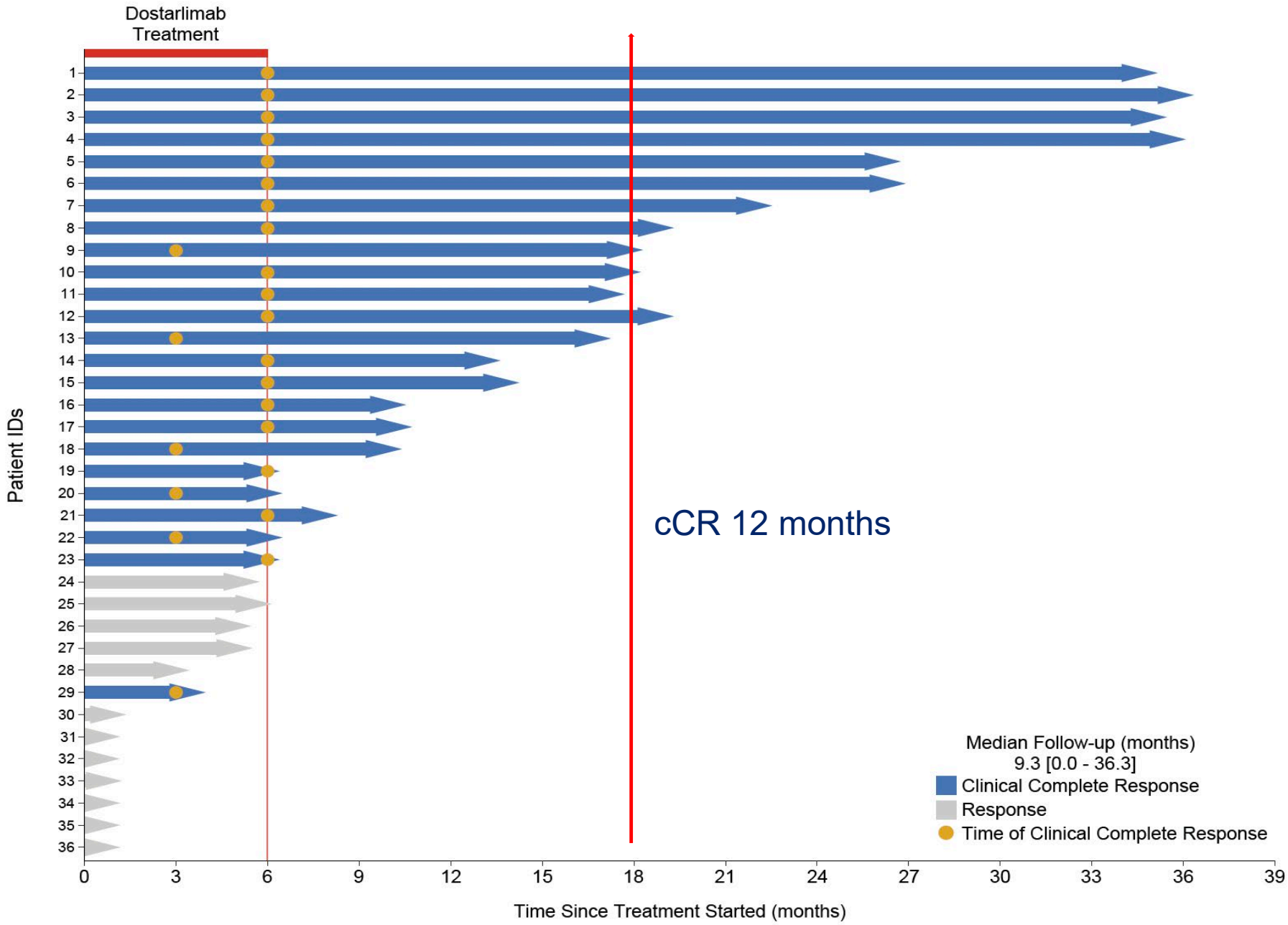


Cercek NEJM 2022; JSMO 2023

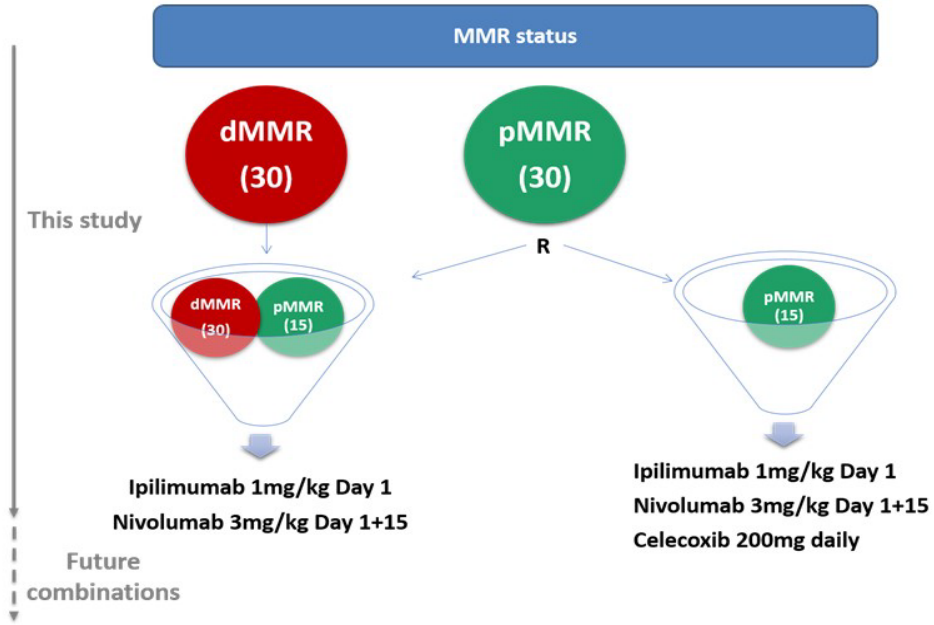
Conclusions

- Highlights the importance of biomarker directed therapy in early stage disease
- Neoadjuvant PD-1 therapy incorporated into NCCN guidelines for MMRd locally advanced rectal cancer
- Clinical trial is ongoing
- Longer follow up is needed

Neoadjuvant therapy for early stage MMRd/MSI colon cancer

NICHE study design

- Open-label, exploratory study with an adaptive design
- **Study population:** non-metastatic, resectable and previously untreated adenocarcinoma of the colon
- **Original cohorts:** 30 patients with dMMR and 30 with pMMR tumors
- **Treatment** in all patients: nivolumab 3 mg/kg on D1+15 *plus* ipilimumab 1 mg/kg on D1
  - **pMMR cohort:** randomized to additionally receive celecoxib
  - **Surgery within 6 weeks** of registration
- Tumor and normal tissue at baseline and resection, plasma + PBMCs baseline during treatment and follow-up



Chalabi M, et al. Presented at: ASCO;2022. Chalabi M, et al *Nat Med*. 2020;26(4):566-576.

Baseline characteristics

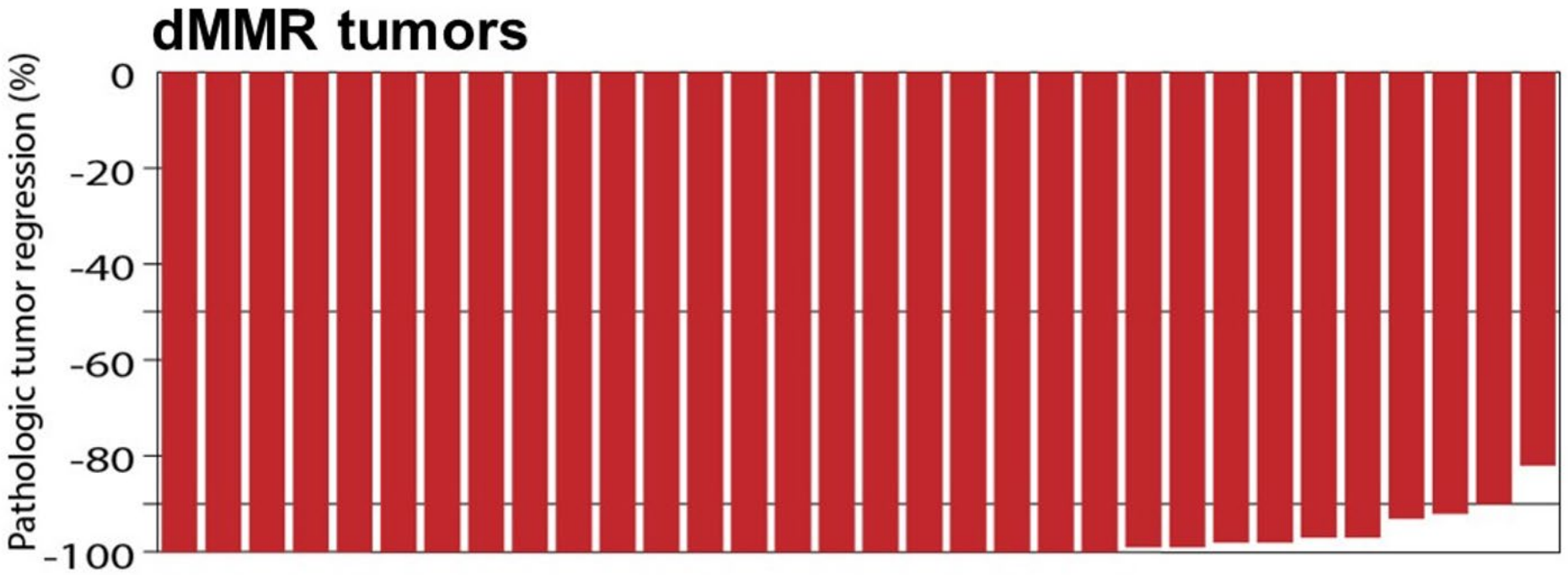
	dMMR (*n*= 32)	pMMR (*n*= 33) *
Age, median (range)	54 (22-82)	62 (44-77)
Sex		
Male	14 (44%)	18 (55%)
Female	18 (56%)	15 (45%)
Clinical T stage		
T2	6 (19%)	11 (33%)
T3	10 (31%)	19 (58%)
T4	15 (47%)	1 (3%)
Tx	1 (3%)	2 (6%)
Clinical N stage		
N-	7 (22%)	20 (61%)
N+	25 (78%)	13 (39%)
Primary tumor location		
Right colon	20 (62%)	8 (24%)
Left colon	8 (25%)	23 (70%)
Transverse colon	4 (13%)	2 (6%)
Lynch syndrome	13 (41%)	0 (0%)

* Two pMMR patients excluded from efficacy analysis due to not matching inclusion criteria

Chalabi M, et al. Presented at: ASCO;2022. Chalabi M, et al *Nat Med*. 2020;26(4):566-576.

NICHE Updated Results

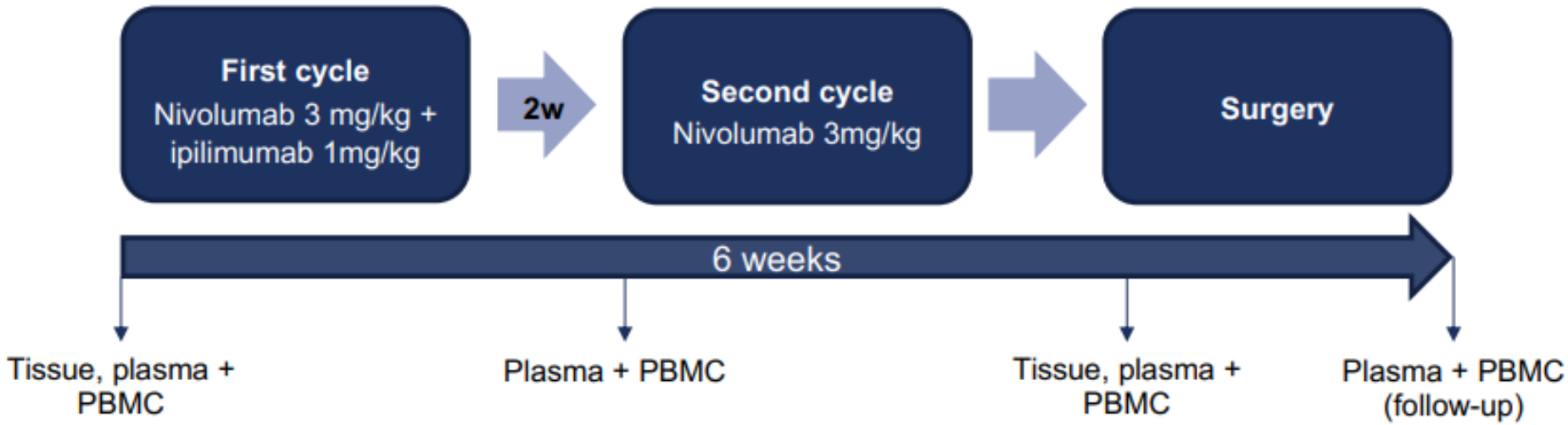
Pathologic Response	dMMR n=32
Major (<10% viable tumor)	31 (97%)
Complete	**22 (69%)**
Partial (< 50% viable tumor)	1 (3%)
Nonresponders (> 50% viable tumor)	0 (0%)



Chalabi M, et al. Presented at: ASCO;2022. Chalabi M, et al *Nat Med*. 2020;26(4):566-576.

NICHE-2 study design

- Investigator-initiated, non-randomized multicenter* study



*6 participating hospitals in the Netherlands
PBMC = peripheral blood mononuclear cells

Chalabi M, et al. ESMO 2022

NICHE-2:Patient characteristics

Characteristic	Number at risk (%) of intention to treat population *n* = 112
Age, median (range)	60 (20-82)
ECOG performance status	
0	97 (87)
1	15 (13)
Female Sex	65 (58%)
Radiologic stage	
I/II	14 (13%)
Low risk III	15 (13%)
High risk III	83 (74%)
Primary tumor location	
Right colon	76 (68%)
Left colon	19 (17%)
Transverse colon	17 (15%)
Lynch syndrome	35 (31%)
Unknown	10 (9%)

Chalabi M, et al. ESMO 2022

NICHE-2: Adverse Events

4% grade 3-4 immune-related AE

Immune-related Adverse Events (*n*=112)	*n* (%)
Patients with any AE	68 (61)
Grade ≥ 3	4 (4)
AEs leading to delay in surgery ≥ 2 weeks	2 (2)

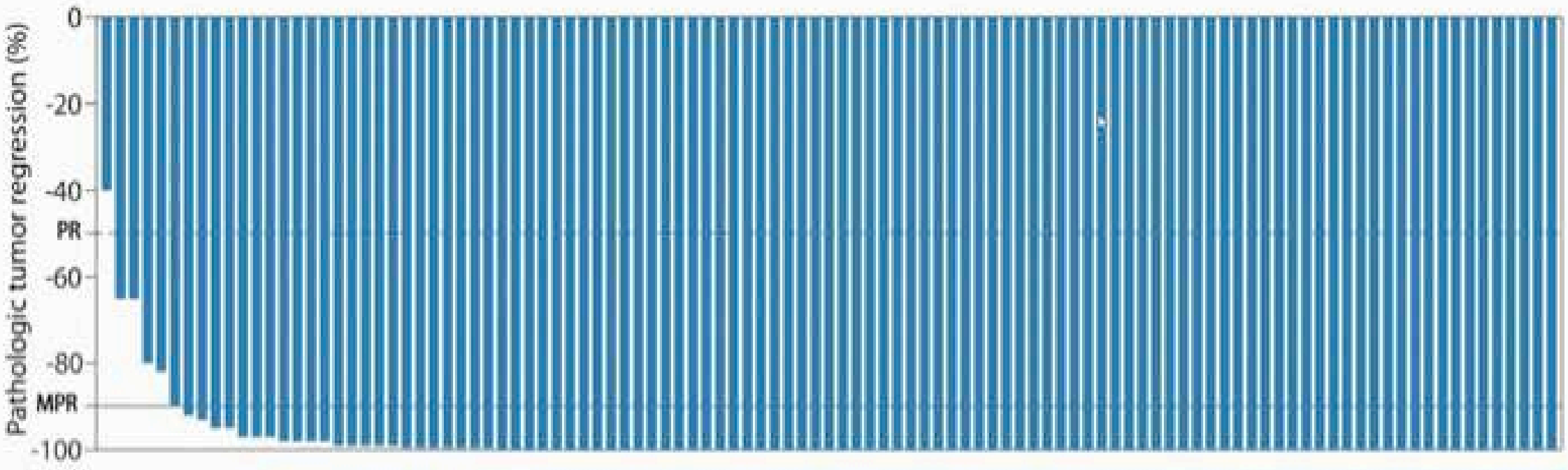
Most common grade 1-2 AEs were infusion reactions, dry mouth, hyper- or hypothyroidism, fatigue and flu-like symptoms

Immune-related Adverse Events (*n*=112)	Grade 3	Grade 4
Amylase increase	1	-
Lipase increase	-	1
Hepatitis	1	-
Myositis	1	-
Rash	1	-

Five events observed in 4 (4%) patients. Amylase and lipase increases were asymptomatic and resolved without intervention. Rash and hepatitis were treated with prednisone and resolved completely. Myositis was treated with prednisone and mycophenolate and has resolved completely.

NICHE-2:Results

Complete pathologic response 67%



112 patients

- 4 weeks of therapy: 3 mg/kg of nivolumab plus 1 mg/kg of ipilimumab, then only nivolumab
- Surgery within 6 weeks of enrolling on the trial.

Chalabi M, et al. ESMO 2022

NICHE-2:Results

Pathologic response (RVT)		Patients *n*= 107
Yes	**(≤ 50%)**	**106 (99%)**
Major	(≤10%)	**102 (95%)**
Complete	(0%)	**72 (67%)**
Partial	(10% - 50%)	4 (4%)
No	**(≥50%)**	**1 (1%)**

RVT = residual viable tumor

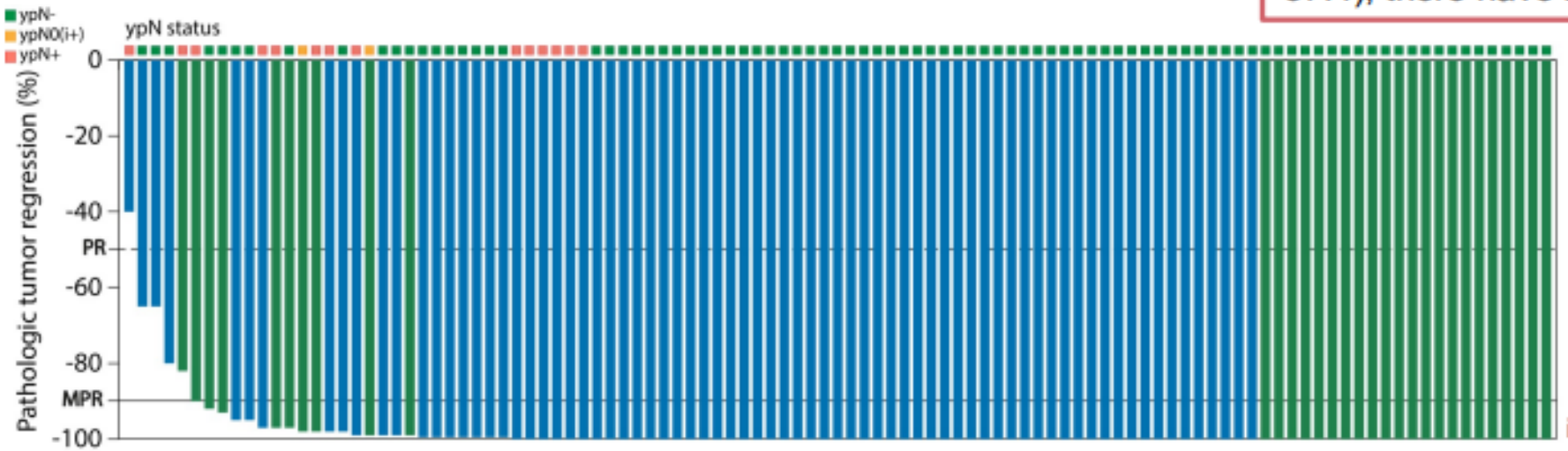
Adjuvant chemotherapy (CTx)

14 patients with ypN+ disease
- 3 patients received adjuvant CTx*
- 5 patients >70 years
- 6 patients refused

* 1 non-responder, 1 partial responder and 1 MPR

Disease recurrence

With a median follow-up of 13.1 months (1.4 - 57.4), there have been no disease recurrences



Green bars = NICHE-1 cohort
Blue bars = NICHE-2 cohort

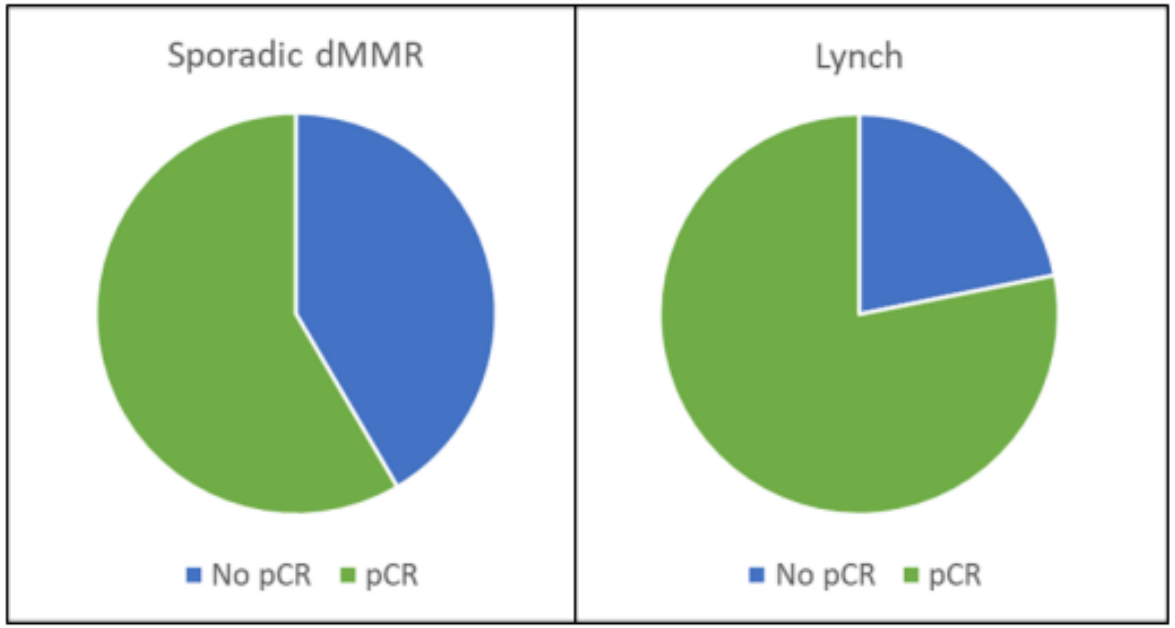
ypN- = tumor-free lymph nodes; ypN+ = lymph nodes with tumor, including micrometastases; ypN(i+) = lymph nodes with isolated tumor cells

NICHE-2: Responses

pCR rate in Lynch *vs* sporadic tumors

	No pCR	pCR	
Sporadic tumor *n* = 65	27 (42%)	38 (58%)	**p = 0.056**
Lynch Syndrome *n* = 32	7 (22%)	25 (78%)	

N totals 97 patients in the per protocol population for whom Lynch status was available at data cut-off

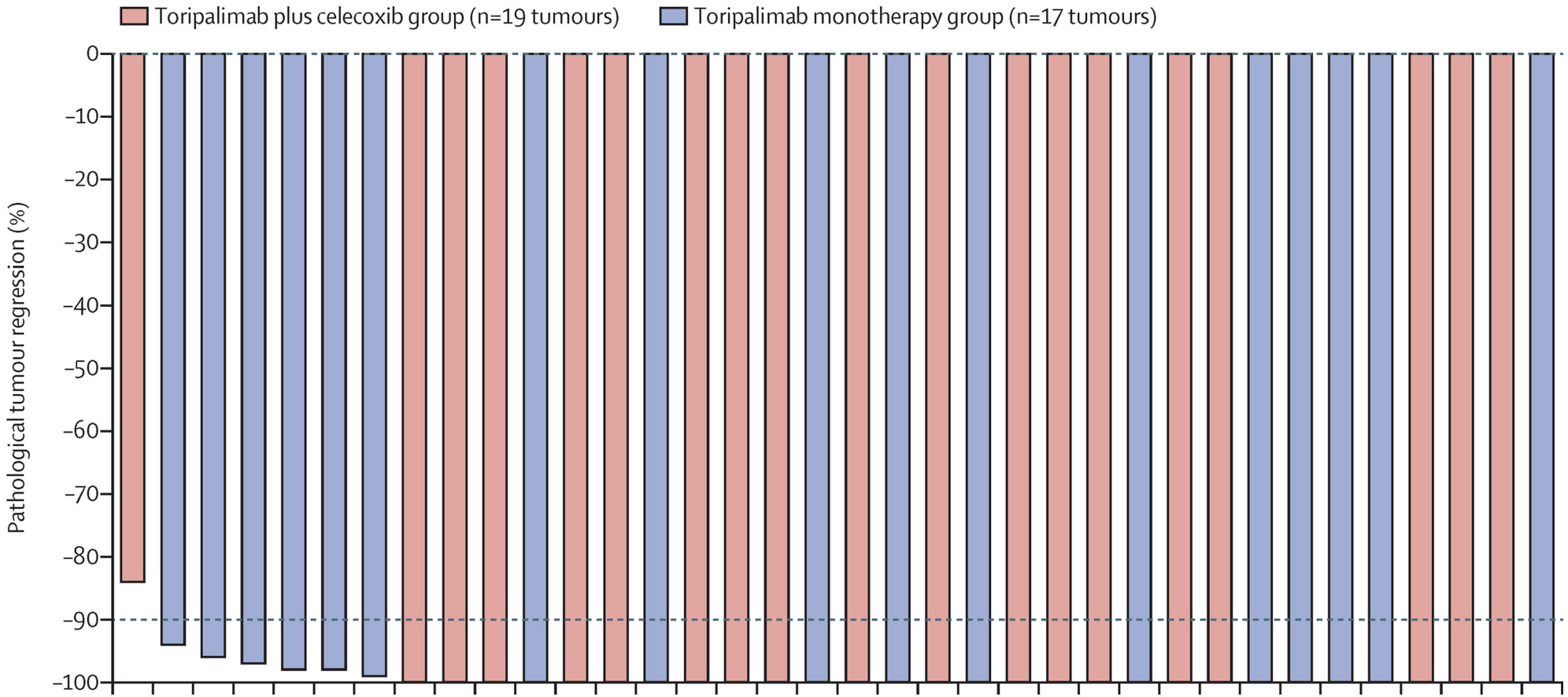


NICHE-2: Results

- Long term outcomes

  --Awaiting data co-primary endpoint 3 year DFS

Neoadjuvant PD-1 blockade with toripalimab, with or without celecoxib, in mismatch repair-deficient or microsatellite instability-high, locally advanced, colorectal cancer (PICC): a single-centre, parallel-group, non-comparative, randomised, phase 2 trial



Treatment: Toripalimab (anti PD1) for 3 months with or without celecoxib

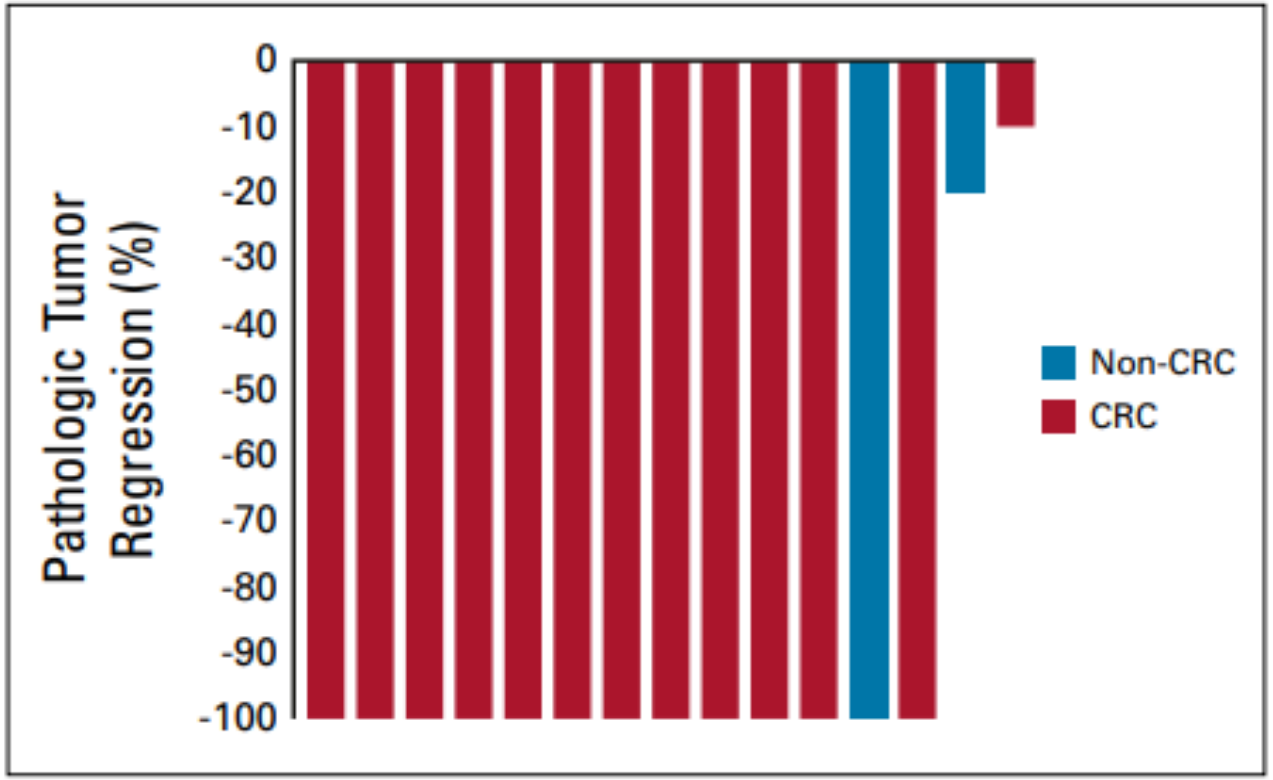
Hu et al, The Lancet Gastroenterology and Hepatology 2021

Phase II study of neoadjuvant pembrolizumab in localized unresectable MSI solid tumors

Included 19 MSI colon cancer patients

17 underwent surgery

pCR 65%



Ludford et al JCO 2023

Neoadjuvant Immunotherapy in MMRd/MSI Colon Cancer

- Significant tumor regression, 67-75% complete pathologic response
- Duration of immunotherapy was varaible 1-6 mo

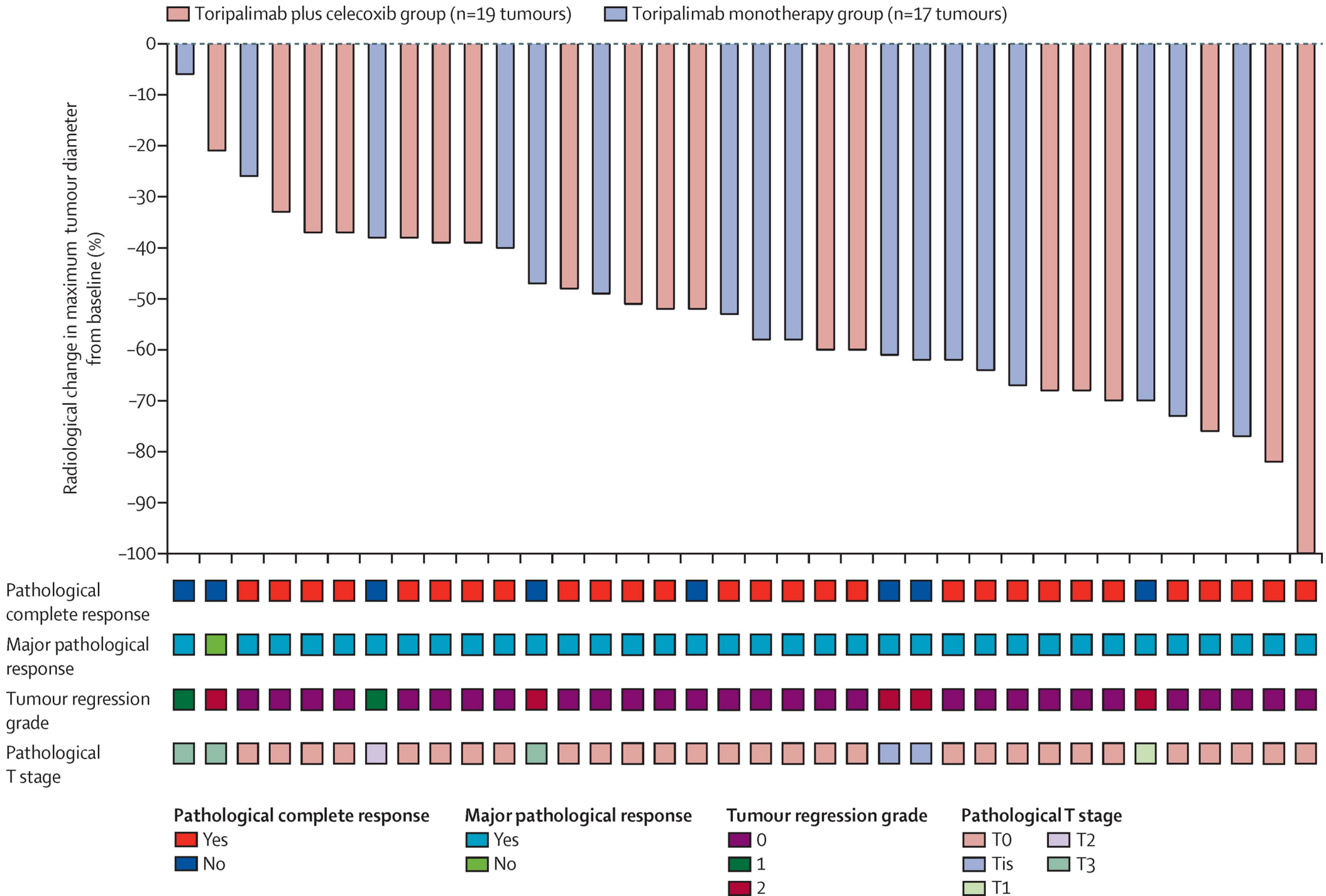
Neoadjuvant Immunotherapy in MMRd/MSI Colon Cancer

Organ preservation?

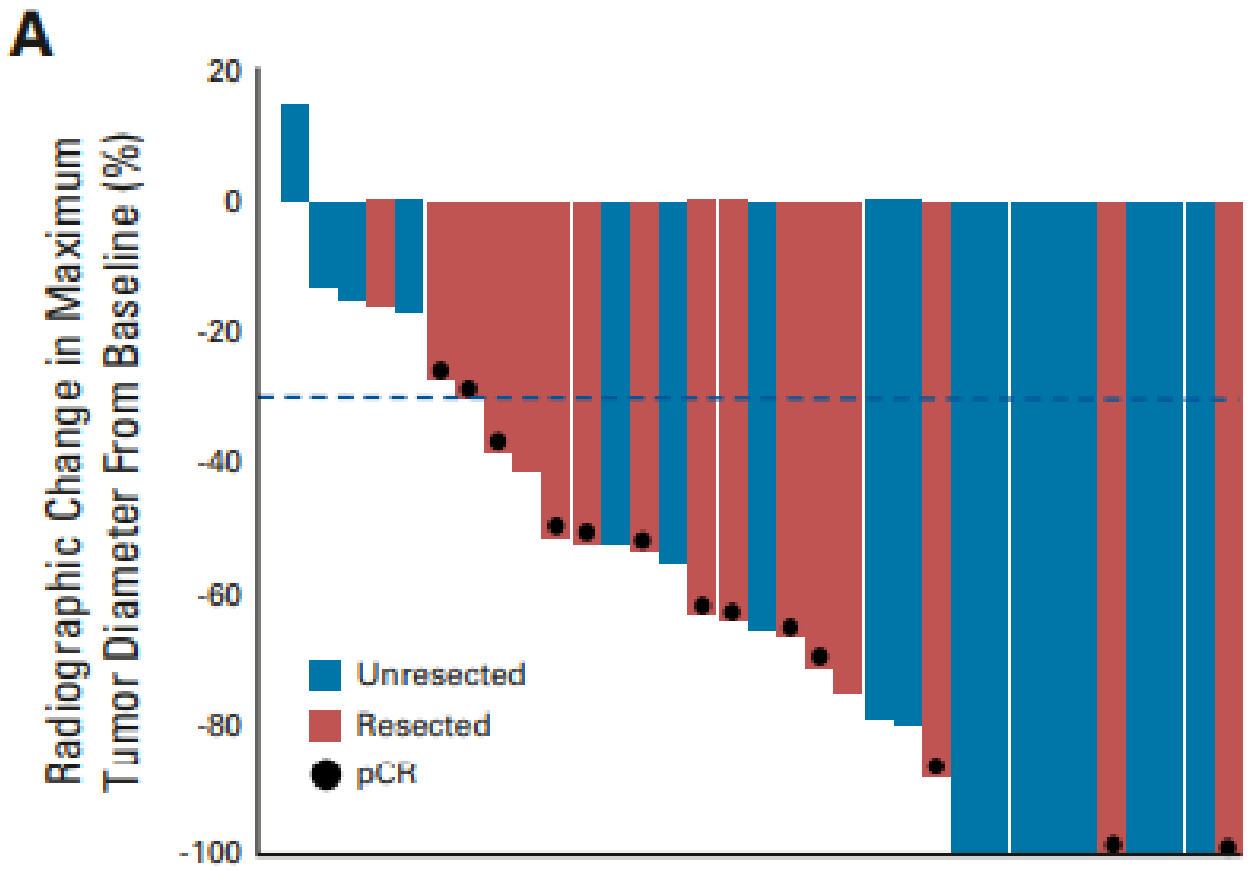
In rectal cancer MRI and endoscopic evaluation correlate with cCR assessment

In colon cancer assessment cCR is challenging

In metastatic setting resected lesions reported pCR up to 60%


Toripalimab plus celecoxib group (n=19 tumours)
Toripalimab monotherapy group (n=17 tumours)
Radiological change in maximum tumour diameter from baseline (%)
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
Pathological complete response
Major pathological response
Tumour regression grade
Pathological T stage
Pathological complete response
Yes
No
Major pathological response
Yes
No
Tumour regression grade
0
1
2
Pathological T stage
T0
Tis
T1
T2
T3

Phase II study of neoadjuvant pembrolizumab in localized unresectable MSI solid tumors



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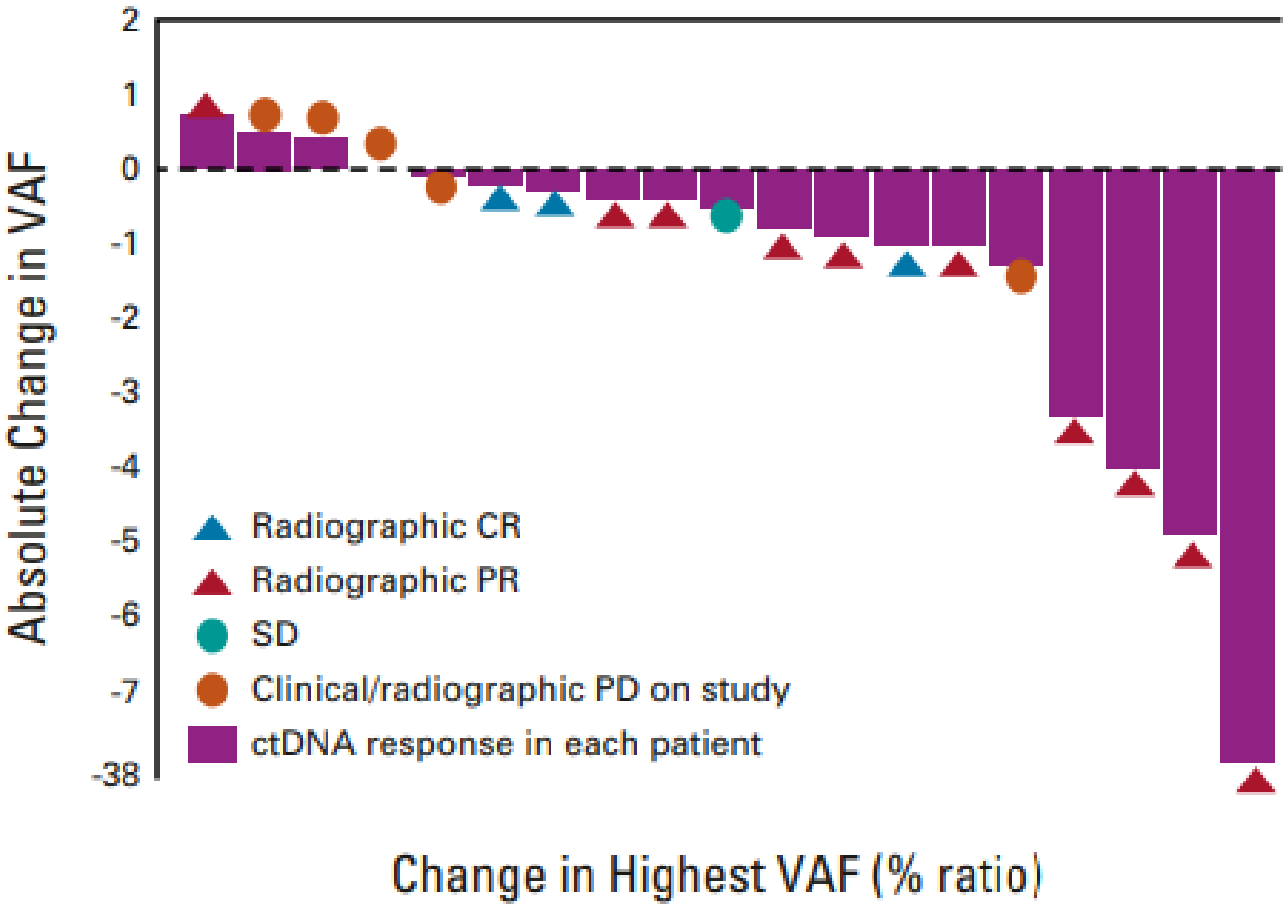
ctDNA as a measure of complete response?

Only 54% had +ctDNA at start of treatment

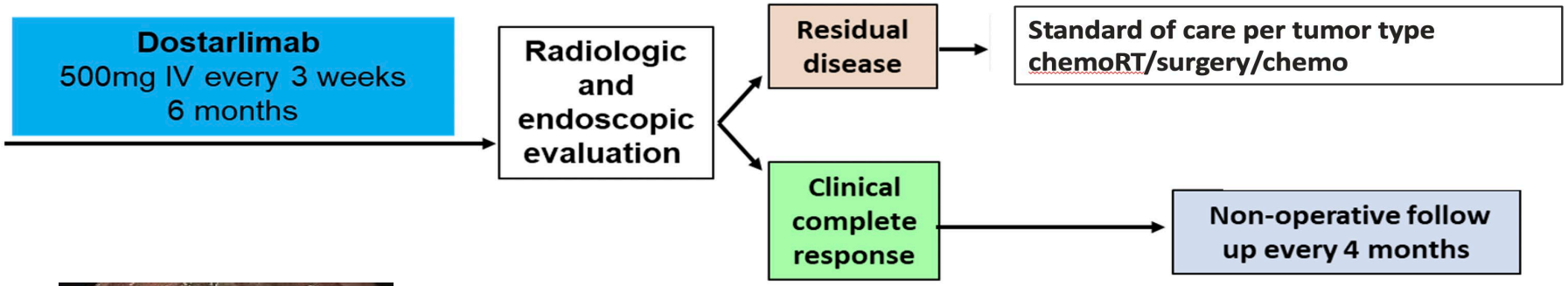


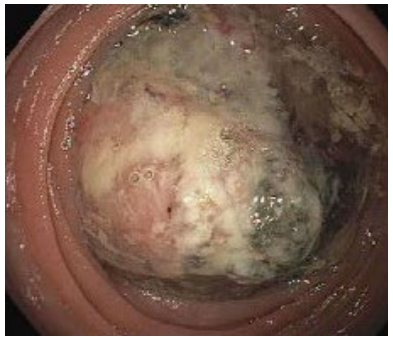
Ludford et al JCO 2023

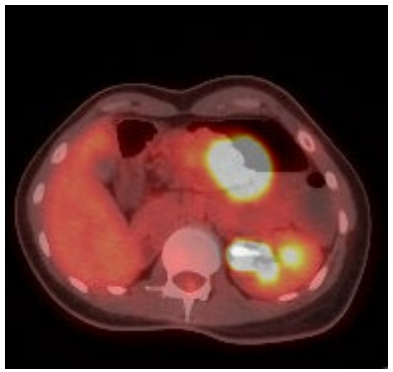
Additional Clinical Challenges in organ preservation colon cancer

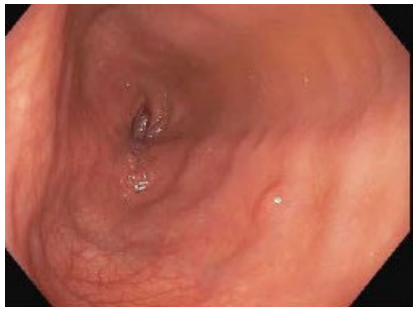
- Response can be associated with significant scarring which leads to strictures

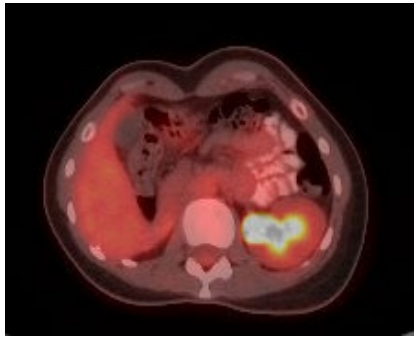
NCT 04165772











Complete response:
negative bx
No residual disease on endoscopy
Negative PET and CT

Clinically:
Symptomatic stricture

Unpublished data

Ongoing Neoadjuvant Trials for MMRd/MSI Colon and Rectal Cancer

NCT Number	Class of ICB agent(s)	ICB agent	Setting	Additional Agents	Response Endpoint	Microsatellite status of Included Tumors	Phase
NCT03926338	PD-1	Toripalimab	Neoadjuvant	COX2(Celecoxib)	pCR	MSI	I/II
NCT05371197	PD-1	Envafolimab	Neoadjuvant	-	pCR	MSI	II
NCT05197322 NEOPRISM-CRC	PD-1	Pembrolizumab	Neoadjuvant	-	pCR	MSI	II
NCT04165772	PD-1	Dostarlimab	Neoadjuvant	-	cCR Salvage surgery if required	MSI	II
NCT03026140	PD-1, CTLA-4, IL-8, Anti-LAG3	Ipilimumab +Nivolumab +/- celecoxib, Nivolumab + BMS-986253, Nivolumab+ Relatlimab	Neoadjuvant	COX2 (Celecoxib)	pCR	MSS/MSI	II

Conclusion

- Studies highlight the clinical impact of biomarker driven therapy in early-stage disease
- In colon cancer organ preservation should be pursued
- Duration of therapy is unclear and inconsistent
- Longer duration would likely yield higher responses in colon cancer
- Radiographic determination of clinical complete response is challenging in colon cancer
- Improved assessment of complete response; ctDNA, novel imaging?

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Thank you!