Neoadjuvant Immunotherapy in MSI-H Rectal Cancer

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Rectal Cancer

- Therapy for locally advanced rectal cancer has included 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.

What is important for patients?

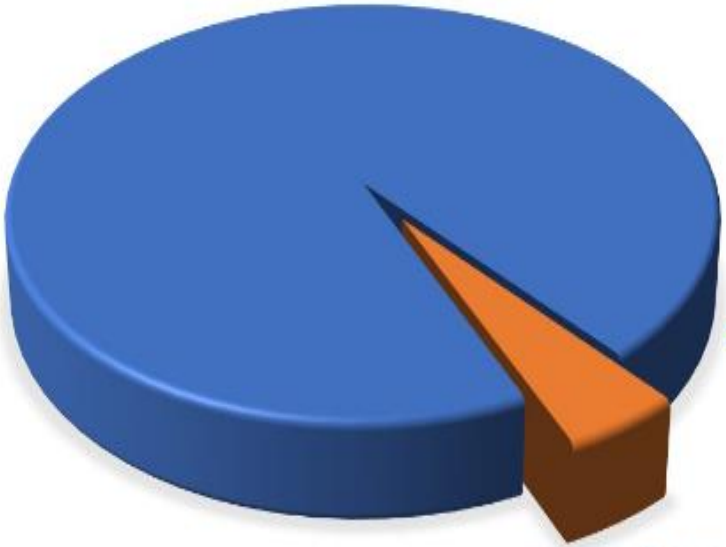
- Patients highly value QoL and avoiding a stoma
- Apparently more than their doctors

	Patients (n=94)		Clinicians (n=128)	
1	colostomy	24	worries about cancer recurrence	31
2	faecal incontinence	20	fecal incontinence	21
3	urinary dysfunction	20	sexual dysfunction	15
4	worries about cancer recurrence	18	urinary dysfunction	12
5	sexual dysfunction	11	colostomy	11
6	to live longer	6	to live longer	10

Rectal Cancer: Mismatch repair deficient (dMMR/MSI)

About 5-10% of all rectal cancers

Less sensitive to chemotherapy



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)

dMMR/MSI mCRC sensitive to ICB in metastatic disease

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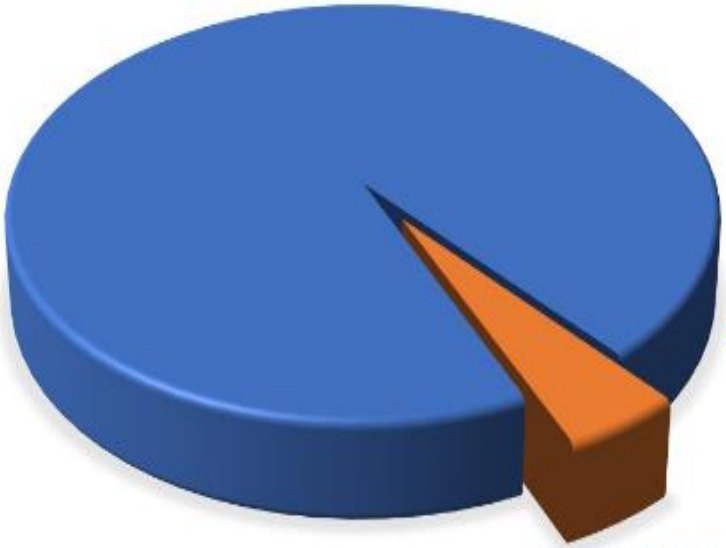

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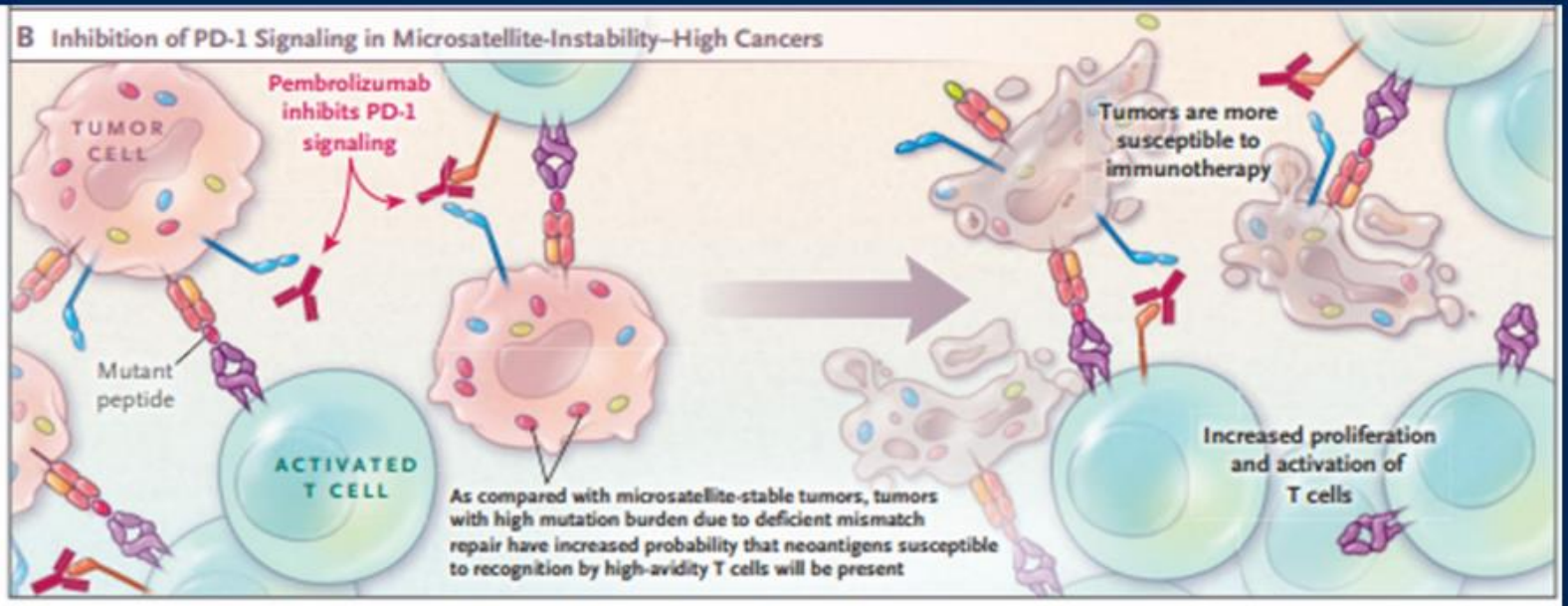
Microsatellite Instability/Mismatch Repair Deficiency in Cancer



Signaling Mechanism of PD-1 and PD-L1 and Inhibition of PD-1 Signaling in Microsatellite-Instability–High Cancers.

MHC1 denotes major histocompatibility complex 1.

Table 1. Immune checkpoint inhibitors in MSI/dMMR metastatic colorectal cancer.

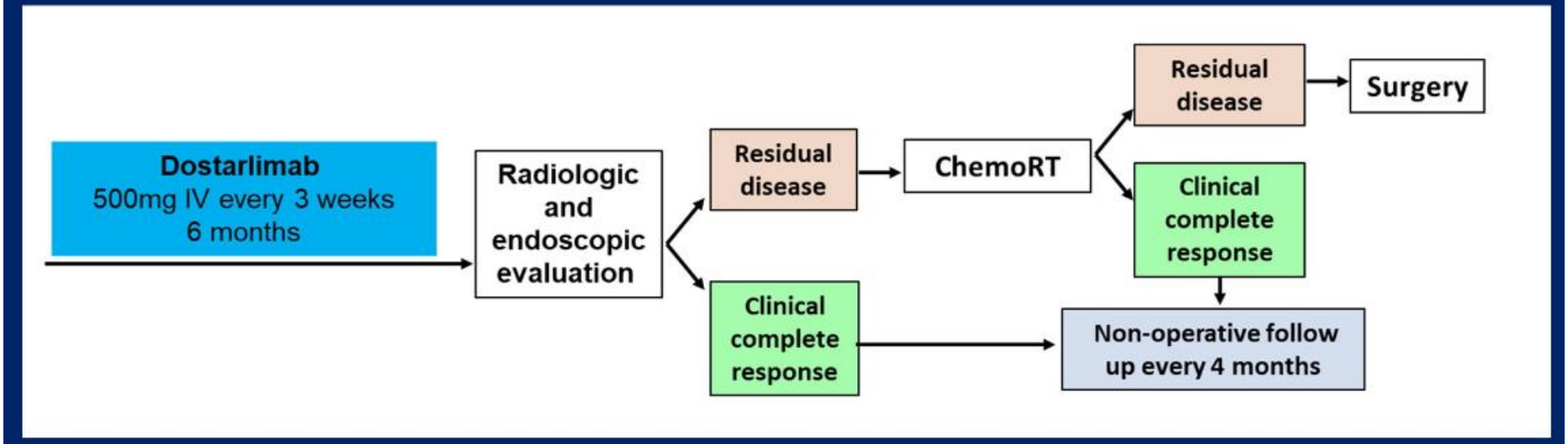
Clinical Trials	Prior Systemic Treatment	*n*	CR (%)	PR (%)	SD (%)	PD (%)	NE (%)	1-Year PFS Rate (%)	1-Year OS Rate (%)	2-Year PFS Rate (%)	2-Year OS Rate (%)	Median Follow-Up (Months)
Keynote-016 [11]												
Pembrolizumab	≥1	28	11	46	32	4	7	-	-	-	-	8.7
Keynote-164 [12–14]												
Pembrolizumab, cohort A	≥2	61	3	30	18	46	3	34	72	31	55	31
Pembrolizumab, cohort B	≥1	63	8	25	24	40	3	41	76	37	63	24
CheckMate-142 [15–18]												
Nivolumab	≥1	74	9	24	31	31	5	44	-	-	-	21
Nivolumab + Ipilimumab	≥1	119	6	52	28	12	3	71	85	60	74	25.4
Nivolumab + Ipilimumab	0	45	13	56	16	13	2	77	83	74	79	29.0
NIPICOL [19]												
Nivolumab + Ipilimumab	≥2	57	19	40	30	5	3	73	84	-	-	18.1
CD-ON-MEDI4736-1108 [20]												
Durvalumab	≥1	36	22		-	-	-	38			54	29
NCT02227667 [20]												
Durvalumab	≥1	11	27		-	-	-	36				30
GARNET [21]												
Dostarlimab	≥1	69	36		-	-	-	-	-	-	-	-

Neoadjuvant immunotherapy – pros

- Response rates to immunotherapy higher in early vs advanced disease
  - Better outcome with neoadjuvant vs adjuvant (melanoma)
- Improved surgical outcomes - less extensive surgery / complete omission of surgery
- Inform on prognosis – guide (neo-)adjuvant therapy

- Recent data in MSI-H/dMMR locally advanced rectal cancer
  - Dostarlimab in MSI-H locally advanced rectal cancer (Cercek)
  - Sintilimab in MSI-H locally advanced rectal cancer (Chen)
  - Toripalimab +/- celecoxib in MSI-H localized CRC (Hu)
  - NICHE, NICHE-2 in MSI-H localized colon cancer (Chalabi)
  - Pembrolizumab in MSI-H localized solid tumors (Ludford)

AZUR – 1



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

Target Enrollment: 30 subjects

Study Design: Simon's two stage minimax design

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

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

Patient Demographics N= 48	N (%)
Female Sex	**28 (58)**
Median Age (range)	**51 (26,78)**
Race	
White	**37 (77)**
Asian	**5(10)**
Black	**6 (13)**
Non Hispanic/Latino	**42 (85)**
Hispanic/Latino	**6 (13)**
Tumor Stage	
T 0/1/2	**10 (21)**
T 3	**23 (48)**
T 4	**15 (31)**
N +	**41 (85)**
Median Distance from anal verge (cm)	**5.1 (0, 14.8)**

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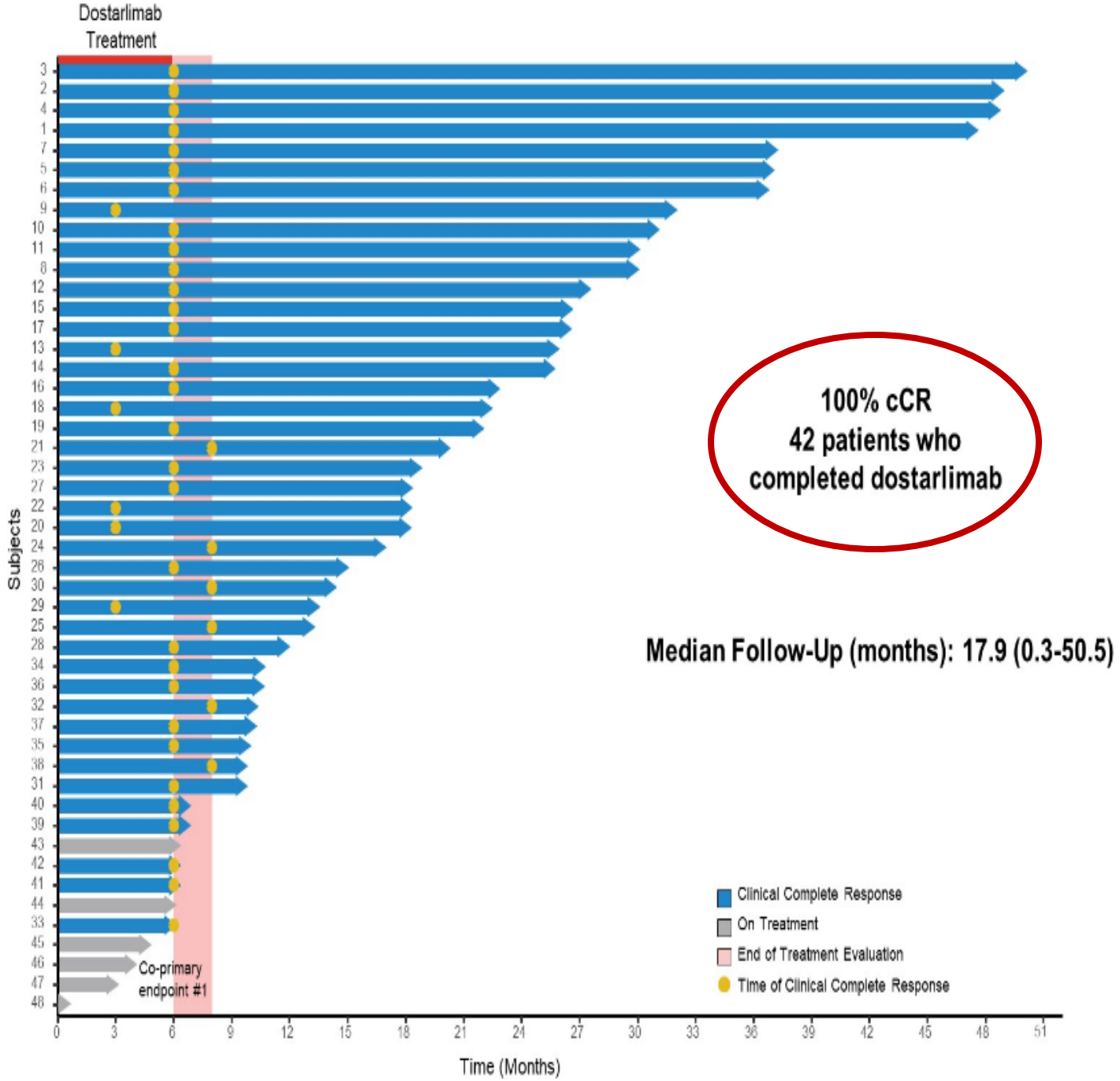
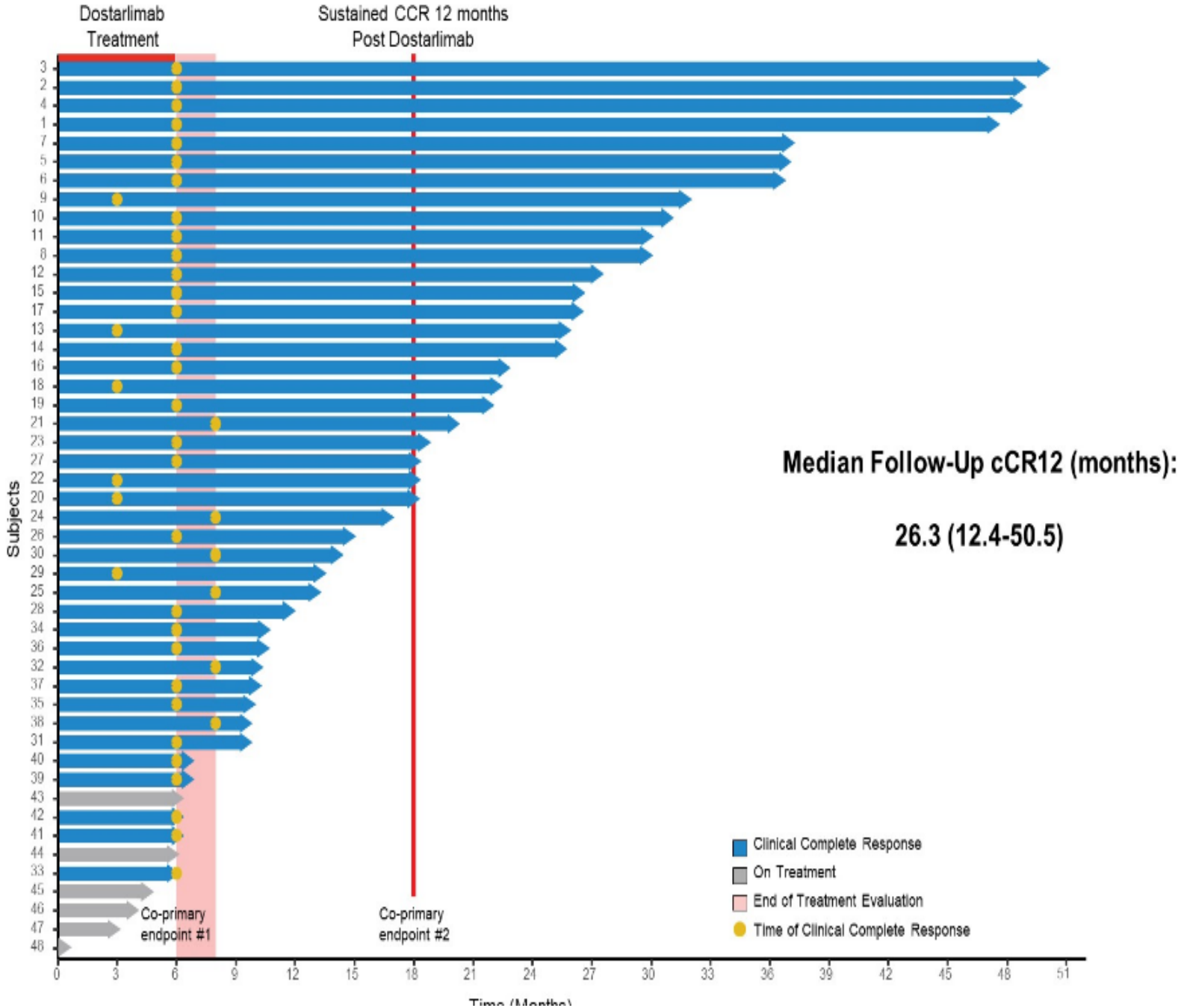

Dostarlimab
Treatment
Subjects
3
2
4
1
7
5
6
9
10
11
8
12
15
17
13
14
16
18
19
21
23
27
22
20
24
26
30
29
25
28
34
36
32
37
35
38
31
40
39
43
42
41
44
33
45
46
47
48
Co-primary
endpoint #1
0
3
6
9
12
15
18
21
24
27
30
33
36
39
42
45
48
51
Time (Months)
100% cCR
42 patients who
completed dostarlimab
Median Follow-Up (months): 17.9 (0.3-50.5)
Clinical Complete Response
On Treatment
End of Treatment Evaluation
Time of Clinical Complete Response


Dostarlimab Treatment
Sustained CCR 12 months Post Dostarlimab
Subjects
Co-primary endpoint #1
Co-primary endpoint #2
Median Follow-Up cCR12 (months):
26.3 (12.4-50.5)
Clinical Complete Response
On Treatment
End of Treatment Evaluation
Time of Clinical Complete Response
Time (Months)

Most Common AEs

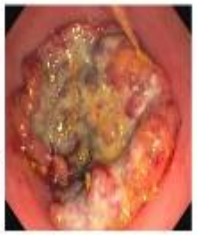
	All Grades	Grade 3 or 4
Dermatologic -no.(%)		
Pruritus	6 (13)	0 (0)
Rash / dermatitis	10 (21)	0 (0)
Gastrointestinal-no.(%)		
Diarrhea	4 (9)	0 (0)
Nausea	4 (9)	0 (0)
Constitutional-no.(%)		
Fatigue	5 (11)	0 (0)
Fever	3 (6)	0 (0)
Endocrine-no.(%)		
Hypothyroidism	5 (11)	0 (0)

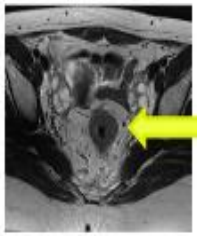
Patient #2

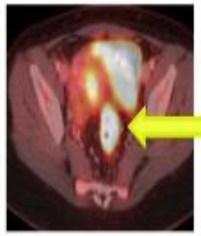
- SD / STABLE DISEASE
- PR / PARTIAL RESPONSE
- NCR / NEAR COMPLETE RESPONSE
- CR / COMPLETE RESPONSE

DOSTARLIMAB

BASELINE	6 WEEKS	3 MONTHS	6 MONTHS	FU2 / 14 MONTHS	FU3 / 18 MONTHS	FU4 / 22 MONTHS
ENDOSCOPY						
MRI RECTUM						
PET/CT						







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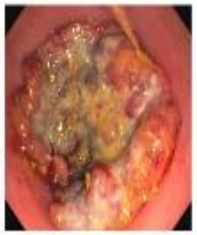
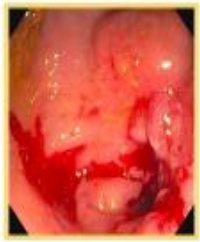
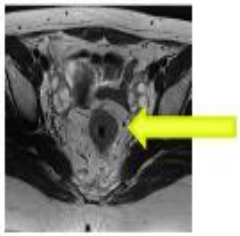
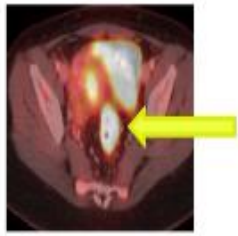
ENDOSCOPY						
MRI RECTUM						
PET/CT						

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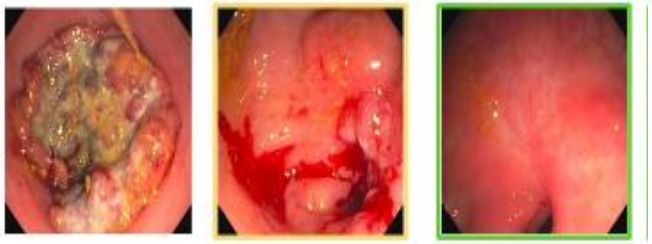

MRI RECTUM

PET/CT

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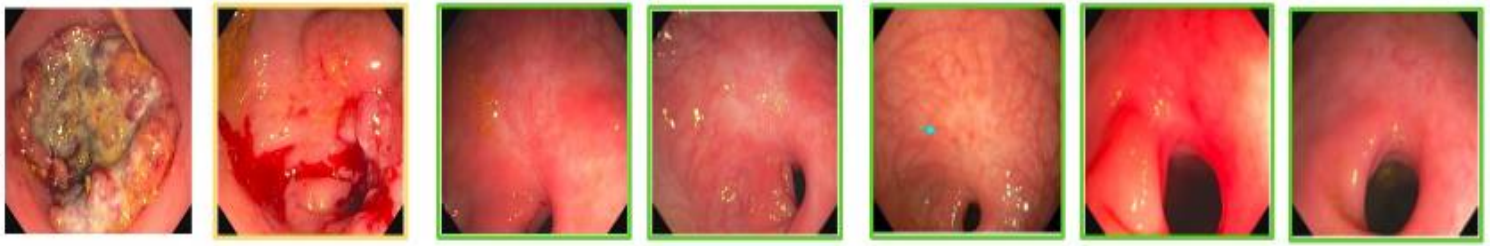

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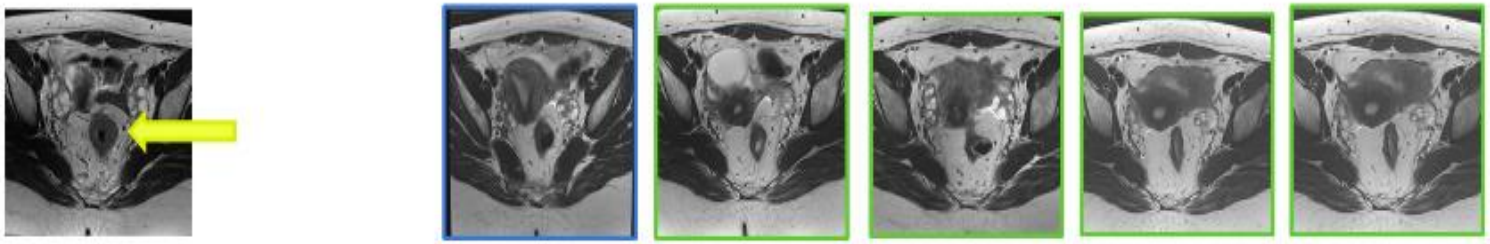
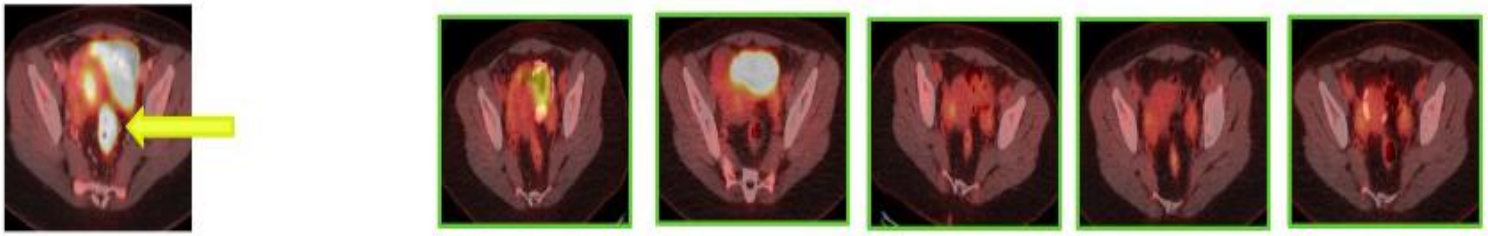


PET/CT



Conclusions

- 100% clinical complete response in all 42 patients who completed dostarlimab
- Clinical complete responses are durable over 2 years
- No patients have required chemotherapy, radiation or surgery
- AZUR1 Global confirmatory study of dostarlimab in dMMR rectal cancer is ongoing

Sintilimab in MSI-H LARC

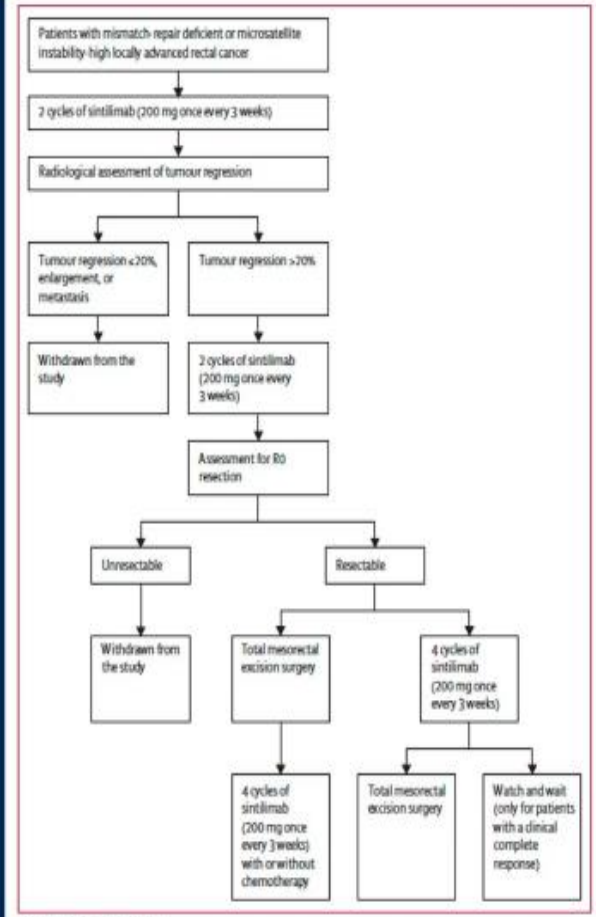


Figure 1: Treatment schema

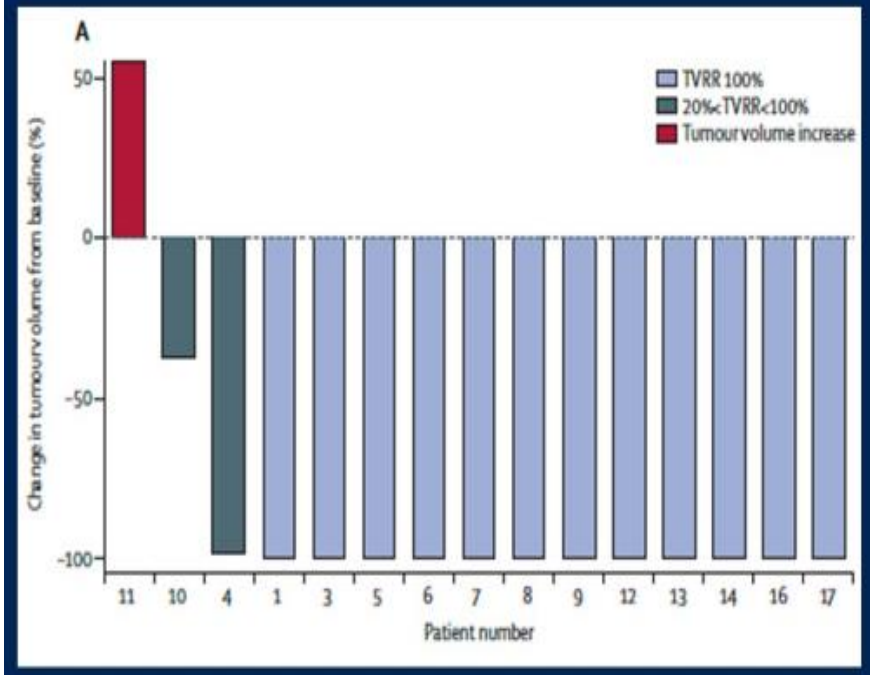
	Patients (n=17)
Sex	
Female	6 (35%)
Male	11 (65%)
Median age, years	50 (35-59)
Lynch syndrome	6 (35%)
ECOG performance status score	
0	10 (59%)
1	7 (41%)
Clinical T stage	
T1–2	2 (12%)
T3	10 (59%)
T4	5 (29%)
Clinical N stage	
N0	3 (18%)
N+	14 (82%)
Mesorectal fascia positive	4 (24%)
Extramural vascular invasion	5 (29%)
Mismatch repair status	
MLH1 or PMS2 deficient, or both	7 (41%)
MSH2 or MSH6 deficient, or both	9 (53%)
Not available*	1 (6%)

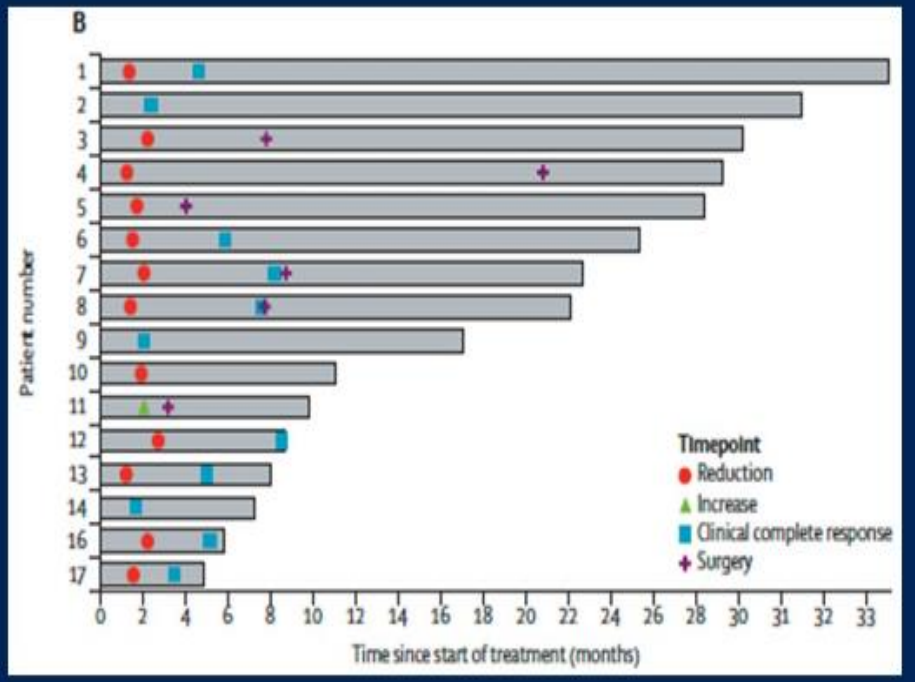
Data are n (%) or median (IQR). Eastern Cooperative Oncology Group. *Confirmed as microsatellite instability-high status by PCR.

Table 1: Clinical characteristics of patients at baseline

Chen, *Lancet GH* 2023

Sintilimab in MSI-H LARC





CR (pCR or cCR) = 75%; 9 pts with cCR (no sx); 3/6 pts s/p sx with pCR

Chen, *Lancet GH* 2023

Toripalimab +/- Celecoxib in MSI-H Localized CRC

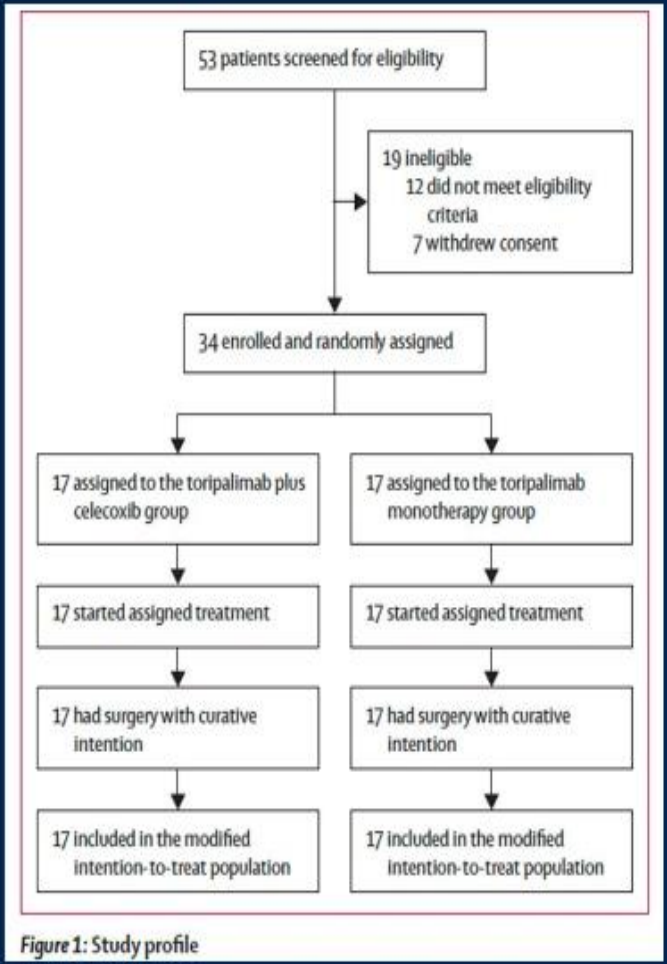


Figure 1: Study profile

	Toripalimab plus celecoxib group (n=17)*	Toripalimab monotherapy group (n=17)
Age at randomisation, years		
Median (IQR)	45 (35-58)	53 (45-60)
Range	23-69	31-69
Sex		
Female	8 (47%)	3 (18%)
Male	9 (53%)	14 (82%)
ECOG performance status		
0	7 (41%)	8 (47%)
1	10 (59%)	9 (53%)
Suspected Lynch syndrome†	4 (24%)	1 (6%)
Previously received neoadjuvant chemotherapy	4 (24%)	5 (29%)
Primary tumour location		
Ascending colon	5/19 (26%)	6 (35%)
Hepatic flexure	3/19 (16%)	3 (18%)
Transverse colon	4/19 (21%)	2 (12%)
Descending colon	0	1 (6%)
Sigmoid colon	3/19 (16%)	3 (18%)
Rectum	4/19 (21%)	2 (12%)
Clinical T stage		
T3	5/19 (26%)	1 (6%)
T4	14/19 (74%)	16 (94%)
Clinical N stage		
N0	3/19 (16%)	1 (6%)
N1	3/19 (16%)	4 (24%)
N2	13/19 (68%)	12 (71%)

Hu, *Lancet Gastro Hep* 2022

Toripalimab +/- Celecoxib in MSI-H Localized CRC

	Toripalimab plus celecoxib group (n=17)*	Toripalimab monotherapy group (n=17)
Pathological complete response†	15 (88%; 95% CI 64–99)	11 (65%; 95% CI 38–86)
Major pathological response‡	16 (94%; 95% CI 71–100)§	17 (100%; 95% CI 81–100)
Pathological tumour regression		
0% viable tumour	18/19 (95%)	11 (65%)
1–10% viable tumour	0	6 (35%)
11–50% viable tumour	1/19 (5%)	0
51–100% viable tumour	0	0
Tumour regression grade		
0	18/19 (95%)	11 (65%)
1	0	2 (12%)
2	1/19 (5%)	4 (24%)
3	0	0
Pathological T stage		
ypT0	18/19 (95%)	11 (65%)
ypTis	0	2 (12%)
ypT1	0	1 (6%)
ypT2	0	1 (6%)
ypT3	1/19 (5%)	2 (12%)
Pathological N stage		
ypN0	18/19 (95%)	17 (100%)
ypN1	1/19 (5%)	0
Pathological disease stage		
ypT0N0M0	17/19 (89%)	11 (65%)
ypTisN0M0–0	0	2 (12%)
ypT1N0M0–I	0	1 (6%)
ypT2N0M0-I	0	1 (6%)
ypT3N0-IIA	1/19 (5%)	2 (12%)
ypT0N1aM0-IIA	1/19 (5%)	0

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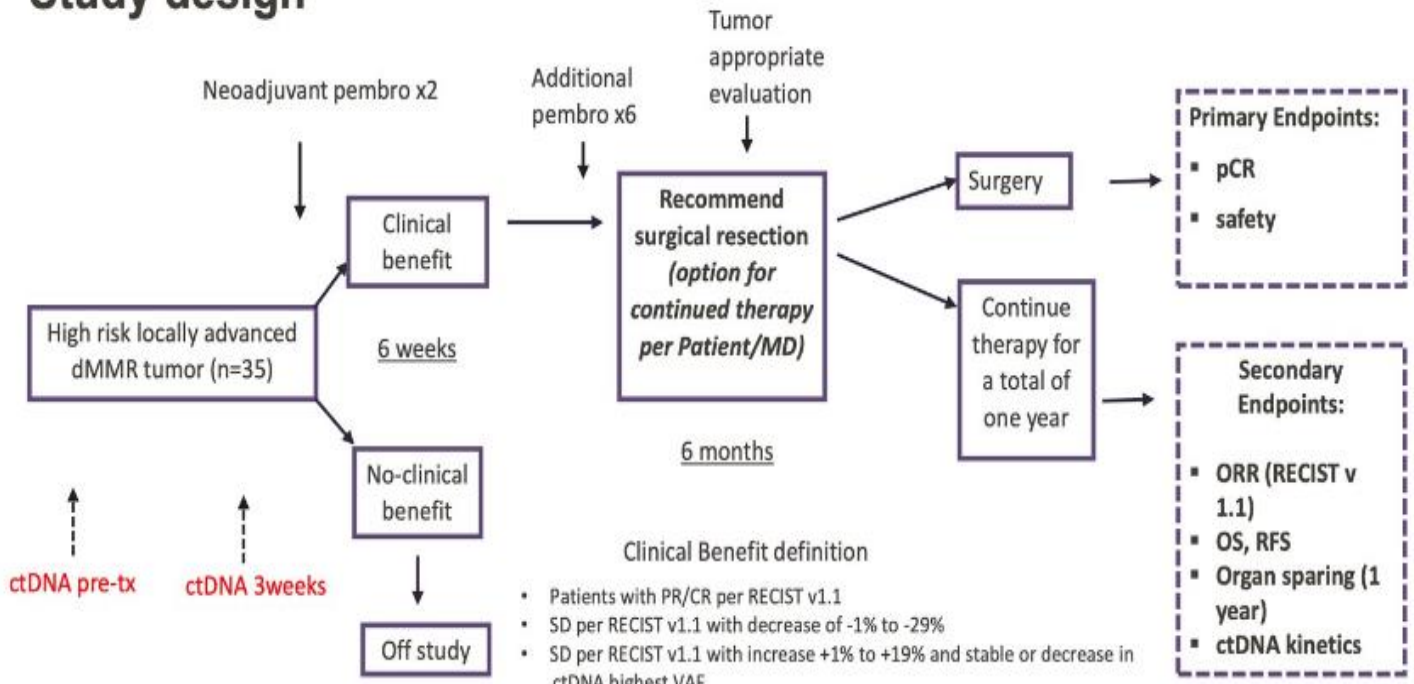
Study design



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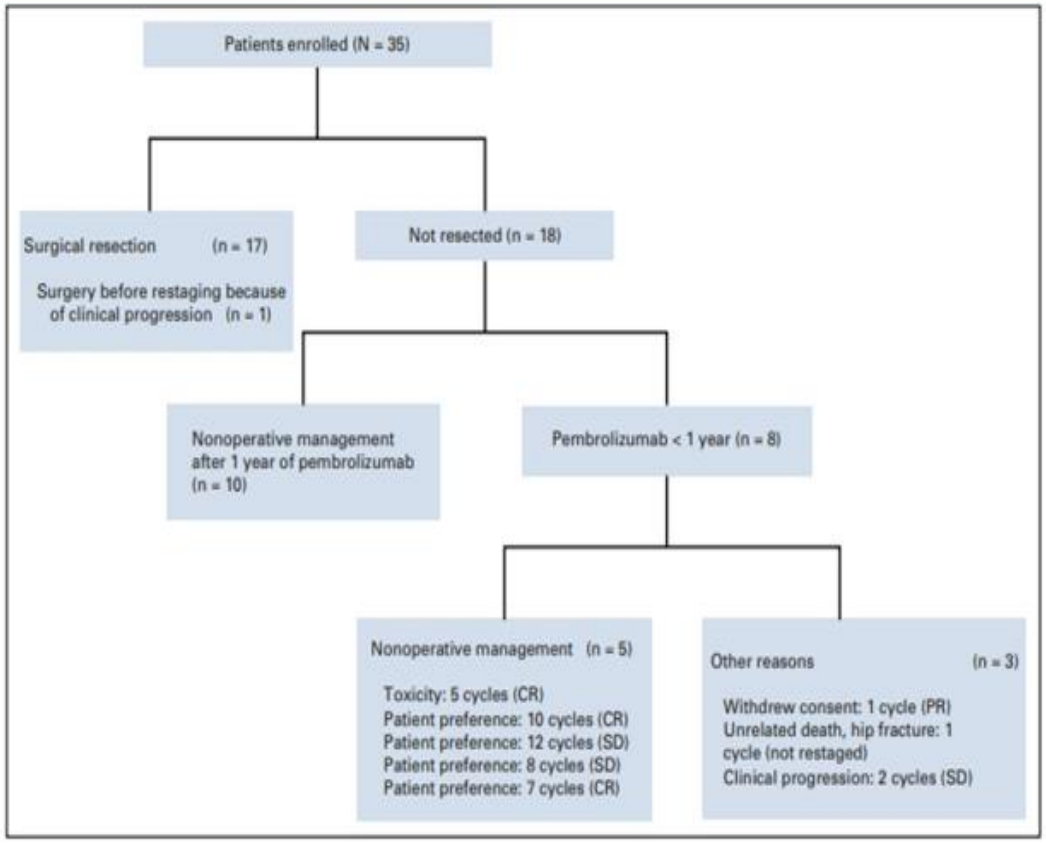


FIG 1. CONSORT diagram. CR, complete response; PR, partial response; SD, stable disease.

Ludford K et al., *JCO* 2023, online ahead of print

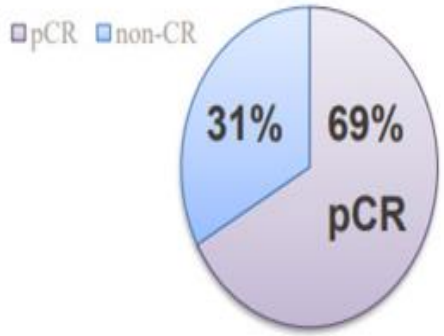
TABLE 1. Baseline Patient Characteristics

Characteristic	No. (%)
Age at diagnosis, year	
Mean	57
Median (range)	62 (25-90)
Sex	
Female	15 (43)
Male	20 (57)
Race	
White	33 (94)
Other	2 (6)
ECOG PS	
0-1	33 (94)
2	2 (6)
Tumor types	
Colon adenocarcinoma	19 (54)
Rectal adenocarcinoma	8 (23)
Pancreatic adenocarcinoma	2 (6)
Duodenal adenocarcinoma	2 (6)
Other[a]	4 (11)
Clinical stage[b]	
II	8 (23)
III	26 (74)
Etiology of dMMR	
Sporadic	19 (54)
Lynch syndrome	16 (46)
Resectability	
Resectable	26 (74)
Unresectable	9 (26)
Prior therapy	
None	26 (74)
Radiation	4 (11)
Surgery	3 (9)
Chemotherapy	2 (6)

Neoadjuvant pembrolizumab yields high rates of pCR

- Median follow up: 9.5 months (range 0.8-17.5m)

Pathologic response rate in patients who received at least 3 cycles of pembro (13 of 15 surgical patients evaluable)

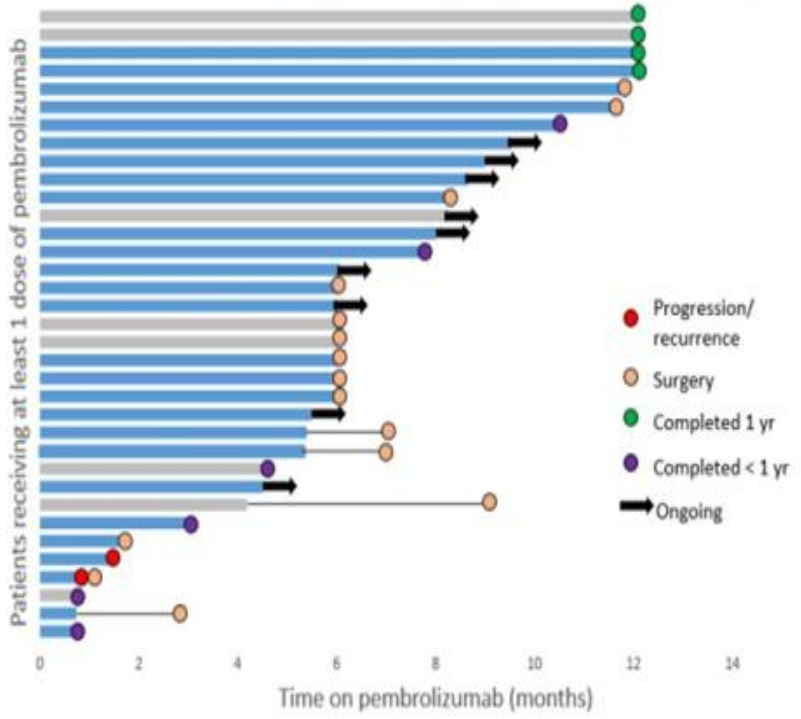


Pathologic response in all surgical patients (n=15)

Tumor	Stage	# cycles	Path stage
Colon	T4N0M0	8	T0N0(0/34LN)
Colon	T4N1M0	8	T0N0(0/122LN)
Colon	T4N1M0	14	T0N0(0/32LN)
Colon	T4N0M0	16	T0N0(0/13LN)
Colon	T4N1M0	8	T0N0(0/35LN)
Rectal	T3N1M0	11	T0N0(0/31LN)
Colon	T4N1M0	8	T0N0(0/27LN)
Colon	T4N1M0	8	T0N0(0/46LN)
Colon	T3NxM0	8	T0N0(0/24LN)
Colon	TxN1M0	1	T0N0(0/35LN)
Colon	T4N1M0	3	T0N1a(1/91LN)
Panc	T2N1M0	8	T1N1(3/37LN)
Panc	T3N0M0	5	T2N0(0/30LN)
Endometrial	IIIC	8	T1aN0(0/5LN)
Rectal	T3N1bM0	2	T4bN0(0/43LN)

Low rates of progression on neoadjuvant pembrolizumab

Swimmer plot of CRC (blue) and non-CRC patients (gray) showing duration of pembrolizumab (n =35)



- 4 patients completed 1 yr of pembro without surgery:
  - median f/u of 3 months (0,2,4,5 months)
  - no recurrences
- Reasons for surgery <6 months:
  - 1 month: clinical progression
  - 2 months: PR, colonic obstruction (pCR)
  - 3 months: PR, transaminitis (pCR)
- Endoscopic evaluation done in 22 of 28 luminal patients:
  - Complete endoscopic response in 12/22 (55%)
  - near complete response in 4/22 (18%)

Smith et al. BMC Cancer 2015

Neoadjuvant treatment of dMMR colon cancers

Previous data from NICHE-1 (*n*=32) show that immune checkpoint blockade is highly effective in non-metastatic dMMR colon cancers

- 100% pathologic responses and 60% pathologic complete responses

ARTICLES
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nature medicine

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

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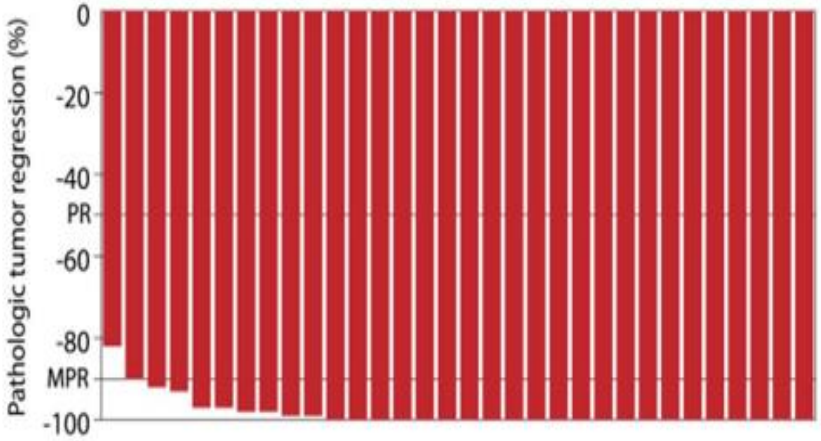
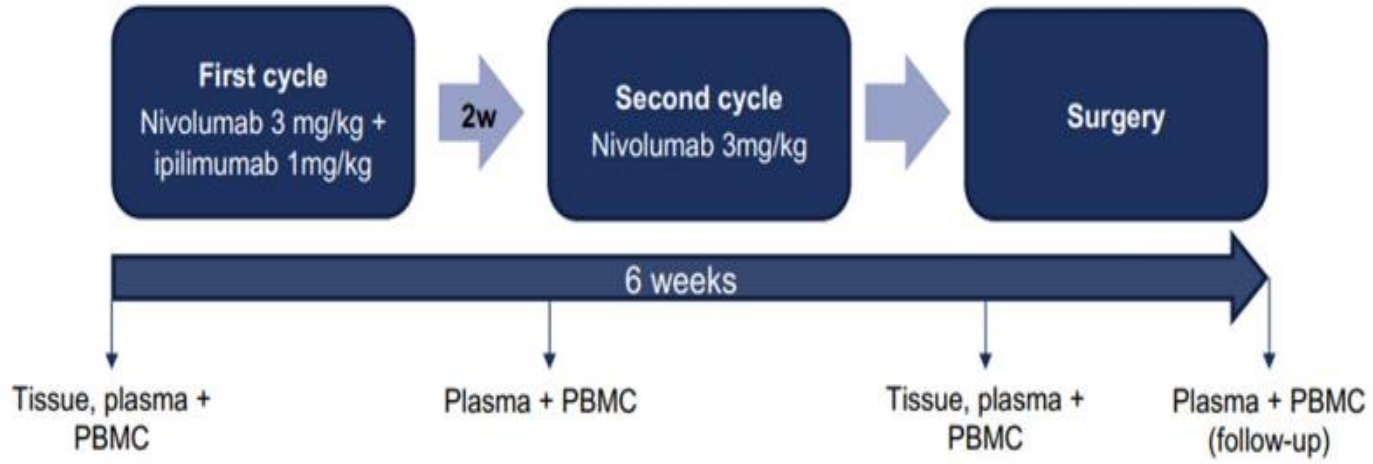


PARIS 2022 ESMO congress

Chalabi et. al, Nat Med 2020; Verschoor et. al, ASCO 2022

NICHE-2 study design

- Investigator-initiated, non-randomized multicenter* study



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

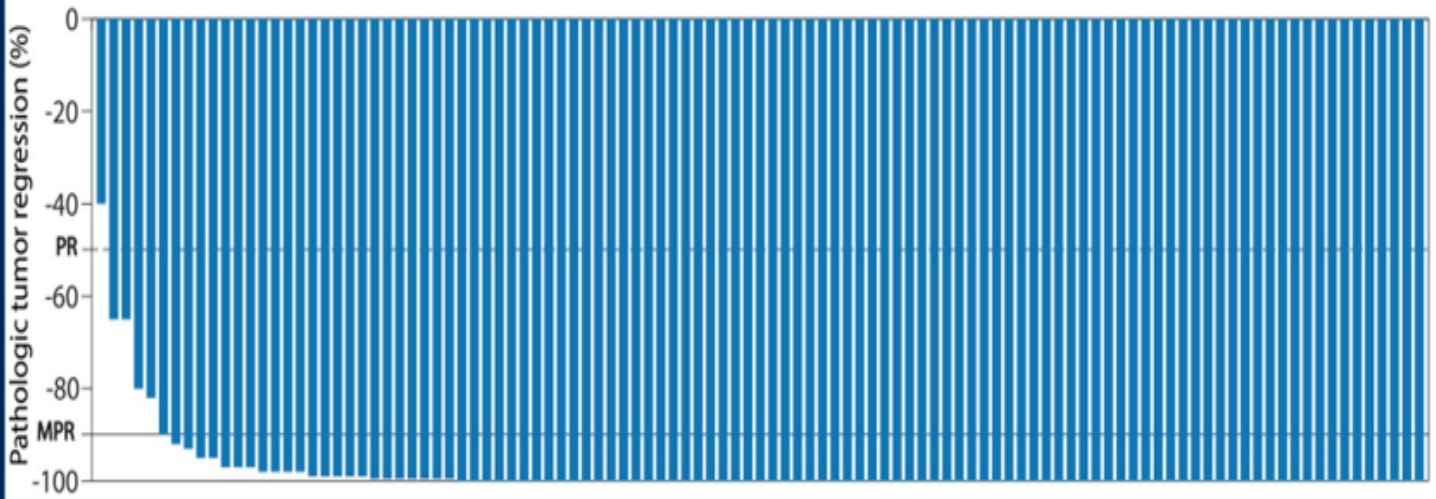
Baseline patient characteristics

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%)

Radiologic T stage	
T2	17 (15%)
T3 + T3/4a	25 (22%)
T4a	**39 (35%)**
T4b	**31 (28%)**
Radiologic N stage	
N0	14 (13%)
N1	**29 (26%)**
N2	**69 (62%)**

Radiologic high-risk with both T4 and N2	**54 (48%)**

Major pathologic response in 95% of patients; 67% pCR



Major pathologic response in 95% of patients; 67% pCR

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

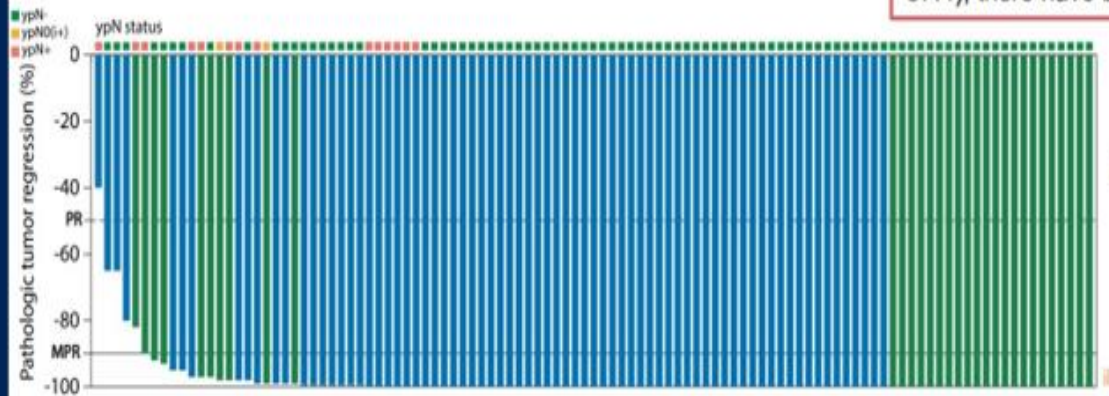
Adjuvant chemotherapy (CTx)

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



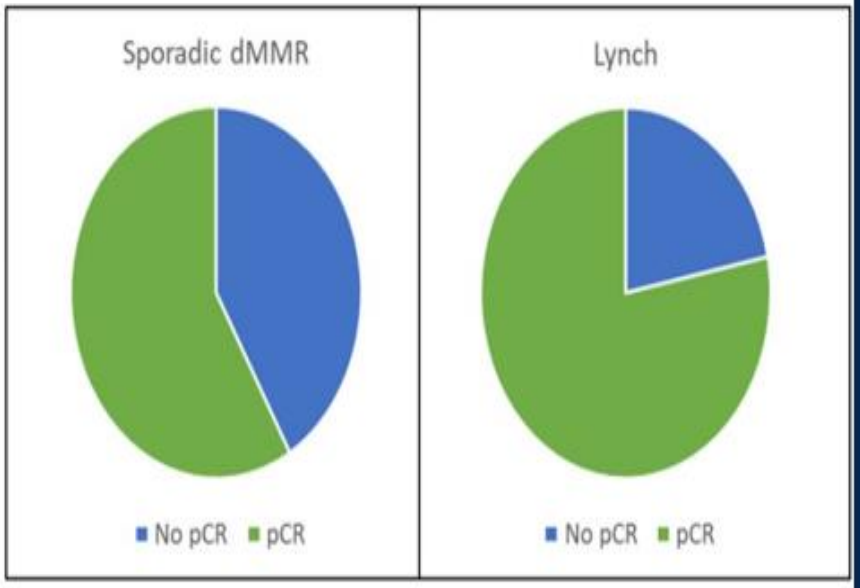
Green bars = NICHE-1 cohort
Blue bars = NICHE-2 cohort

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

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%)	

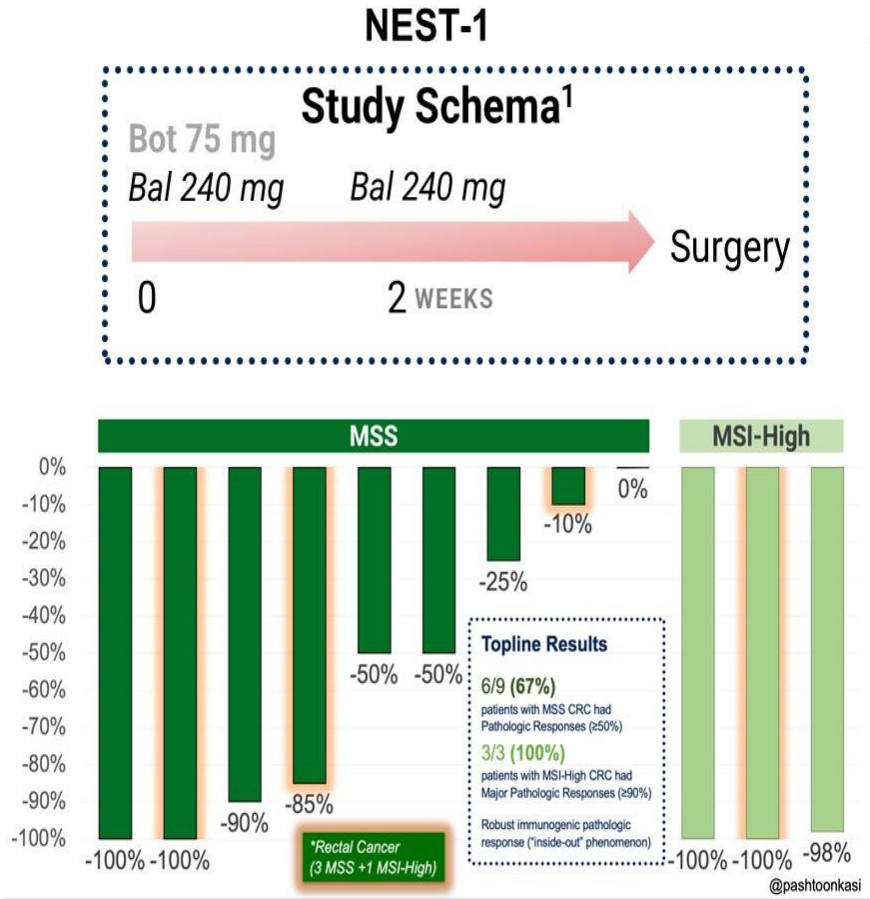
N totals 97 patients in the per protocol population for whom Lynch status was available at data cut-off



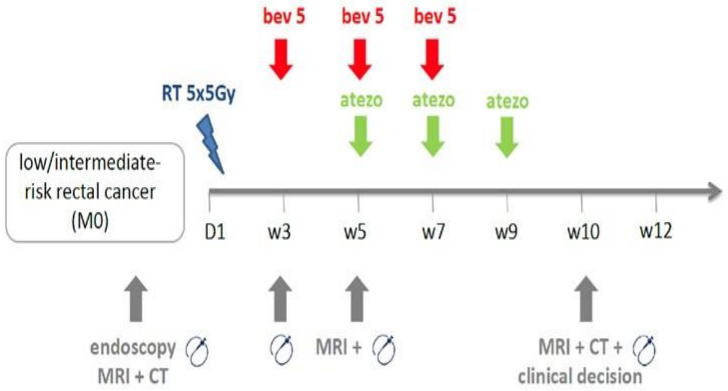
Conclusions from NICHE2

- Only 4% grade 3-4 immune-related adverse events (amylase/lipase, hepatitis, myositis, rash)
  - Any AEs: 61%
- 100% R0 resections; 98% of patients underwent timely surgery (safety primary endpoint)
- 100% (32/32) of dMMR patients had response to nivo/ipi (69% pCR, 95% major pathologic responses)
  - Only 2 doses of nivo, 1 dose of ipi prior to surgery
- Potential for nonoperative management?
  - Colonoscopic surveillance, radiographic discordance, etc
- Biomarker studies, ctDNA dynamics eagerly awaited

Neoadjuvant immunotherapy in pMMR tumors



Kasi et al, ASCO GI 2024



- Data from first 18 patients in TARZAN study
  - 10/18 (56%) patients with a clinical (near-) complete response at 10 weeks
  - After at least 1 year follow-up (range 14-33 months): 9/18 (50%) patients remain without surgery

Without chemotherapy

Verschoor…Chalabi et al, ASCO GI 2023

Conclusions

- Imperative to test for MSI-H/dMMR in patients with localised rectal cancer at diagnosis
- Immunotherapy results in CCR in most of the patients
- Immunotherapy has the potential to spare patients from surgery , radiotherapy and chemotherapy
- Immunotherapy is tolerable

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
dMMR/MSI-H Rectal Cancer

NCCN Guidelines Index
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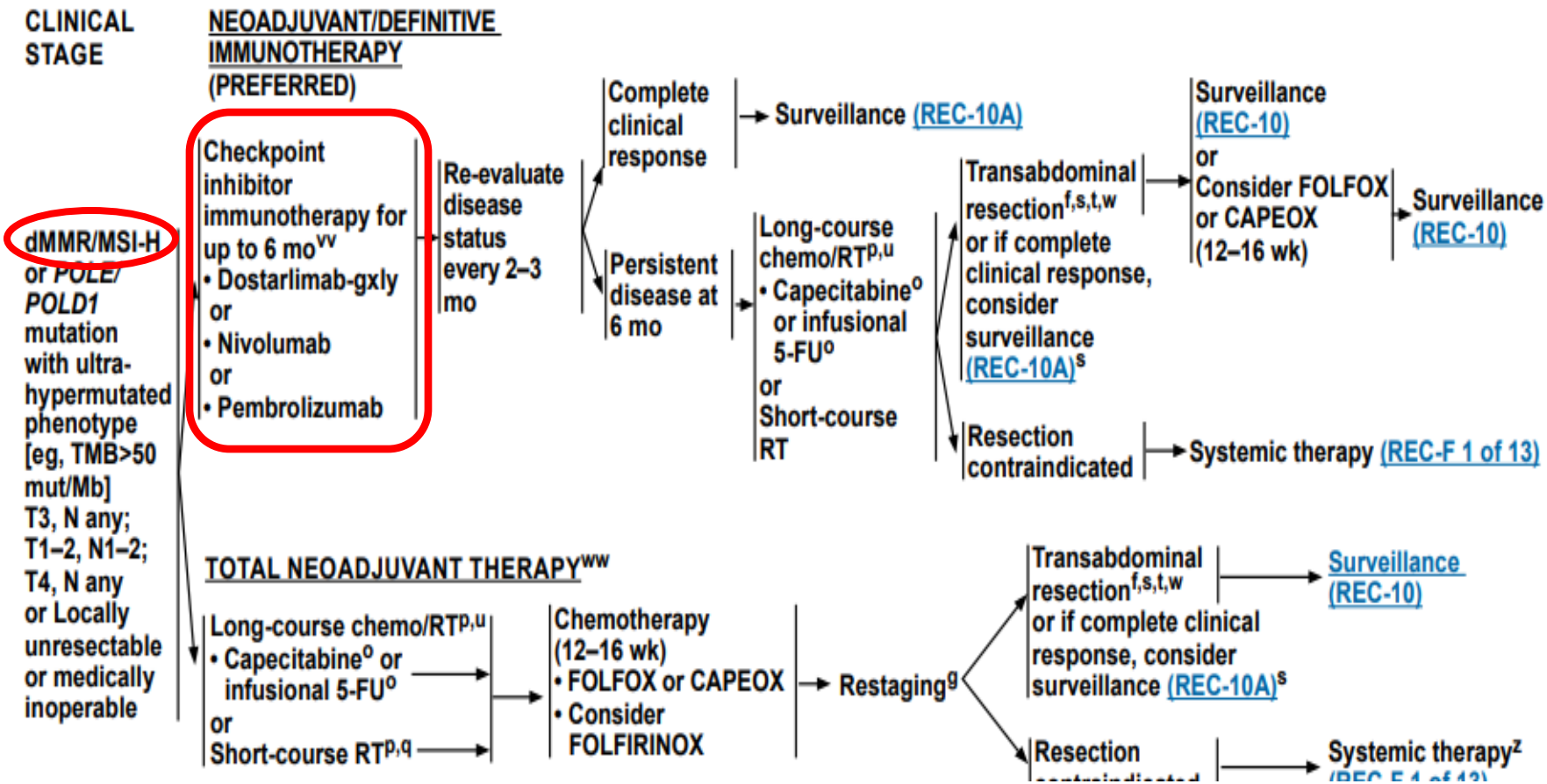


THANK YOU!