Immunotherapy and Mismatch Repair Deficiency

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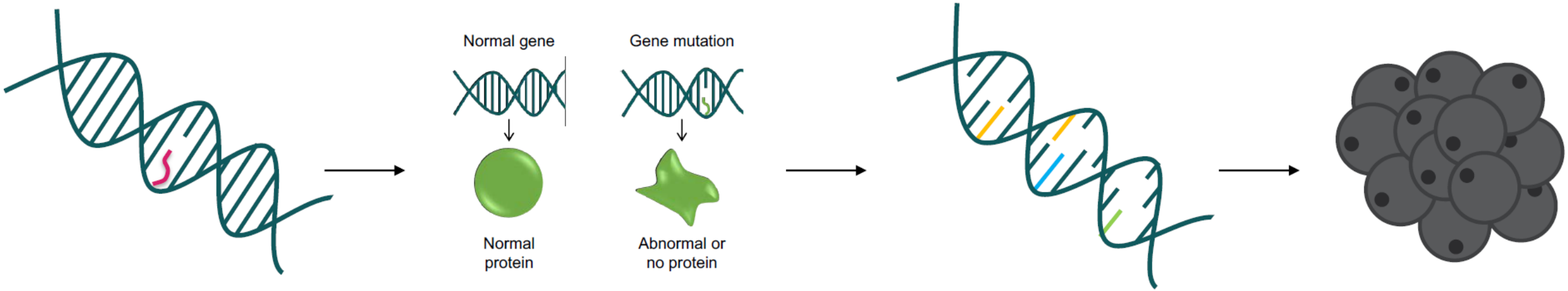
State of art for dMMR locally advanced rectal cancer until October 2023

- dMMR tumors: ~10% of early-stage disease

- Rectal cancer usually treated by total mesorectal excision (TME) +/- neoadjuvant treatment that can lead to organ preservation:
    - <30% in intermediate (N+) – locally advanced disease(T4, MRF+)
    - 60% in early-stage disease (max 4cm and no lymph node involvement)

- Relative resistance to chemotherapy

dMMR/MSI-High cancers



Sporadic or Lynch syndrome-related mutations can occur in MMR genes *MLH1*, *MSH2*, *MSH6* or *PMS2*[1,2]

Mutations in MMR genes lead to the loss of MMR protein activity, resulting in DNA mismatches[1,2]

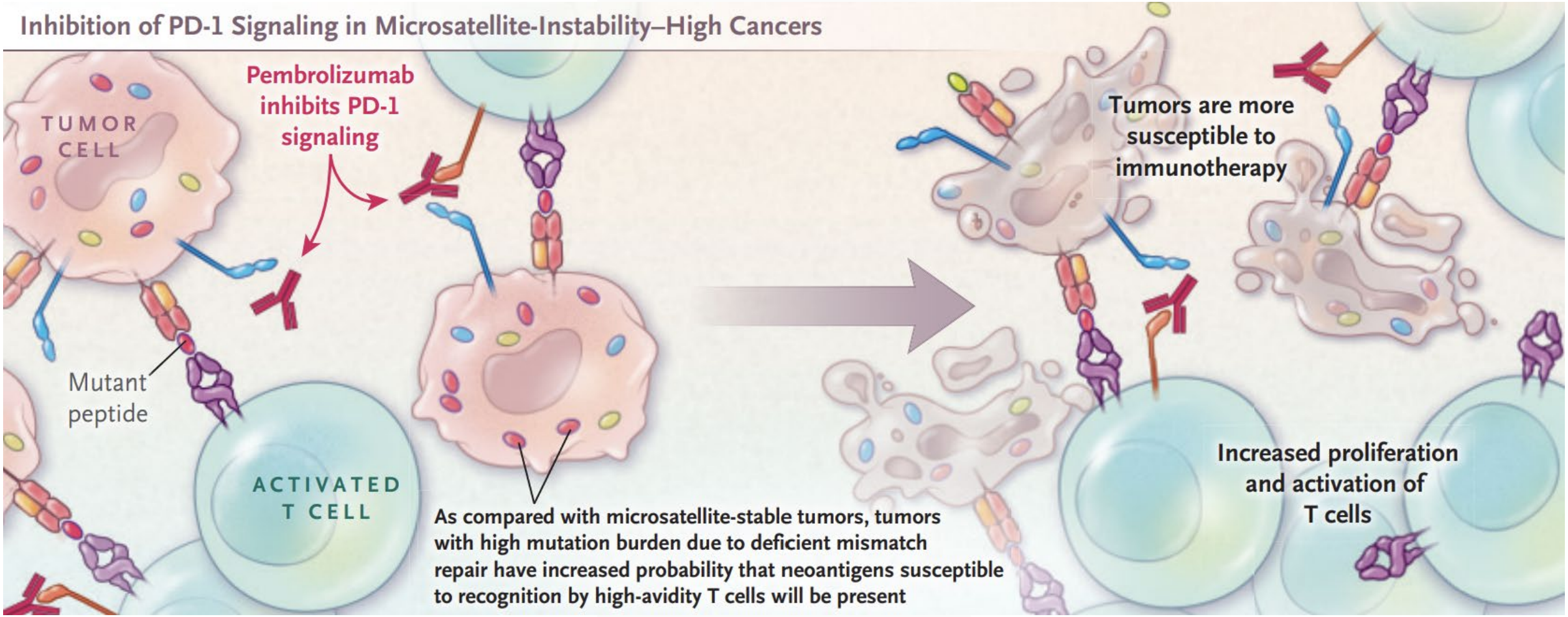
The persistence of DNA mismatches results in MSI, and mutations are incorporated into the genetic code[1]

The accumulation of genetic mutations promotes tumourigenesis[1]

Figure adapted from Boland CR et al. 2010 and Kawakami H et al. 2015.

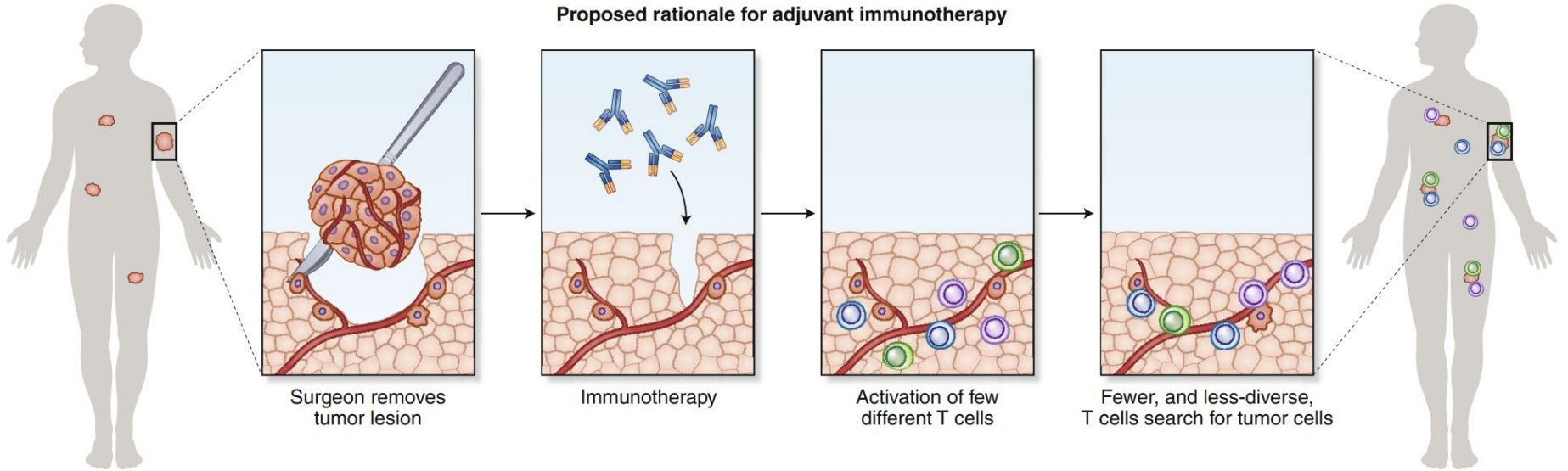
1. Boland CR et al. *Gastroenterology* 2010;138:2073–2087; 2. Kawakami H et al. *Curr Treat Options Oncol* 2015;16:30.

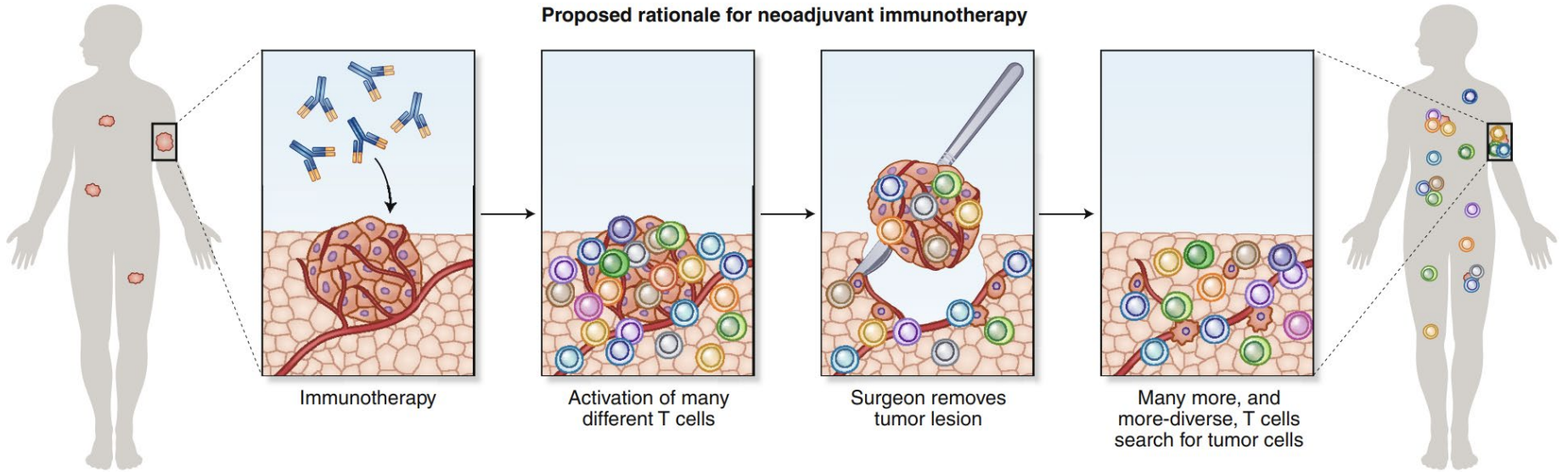
dMMR/MSI-High cancers and PD-1 inhibitors



First FDA Approval Agnostic of Cancer Site — When a Biomarker Defines the Indication, Lemery et al., NEJM 2017

Scientific rationale for neoadjuvant immunotherapy





- Larger amount of antigens
- Tumor draining lymph nodes in situ
- Larger pool of tumor-reactive T cells + expansion of more tumor-resident T cell clones

Hypothesis

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

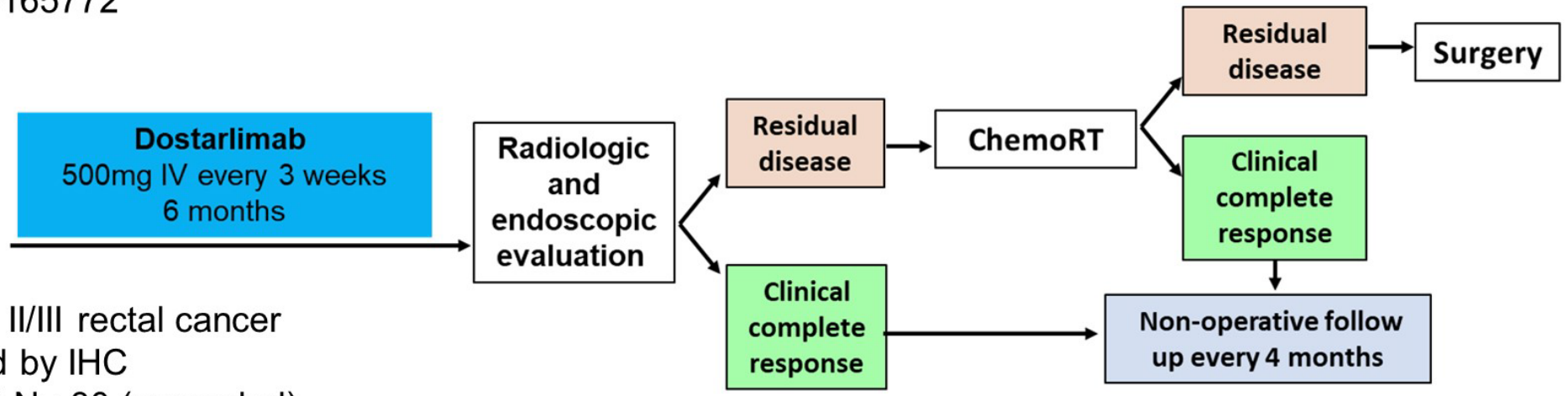
a) replace chemotherapy

b) replace chemo *and* radiation therapy

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

Neoadjuvant PD-1 blockade in dMMR locally advanced rectal cancer

NCT04165772



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

Primary Endpoints:

- ORR after completion of PD-1 alone or in combination with chemoRT
- pCR or sustained cCR for 12 mo after completion of PD1 alone or in combination with chemoRT

Sample Collection: ctDNA, biopsy, imaging

Baseline, 6 weeks, 3 mo, 6 mo and q4 mo during NOM

Cercek, et al. NEJM 2022

Demographic and disease characteristics of the patients at baseline

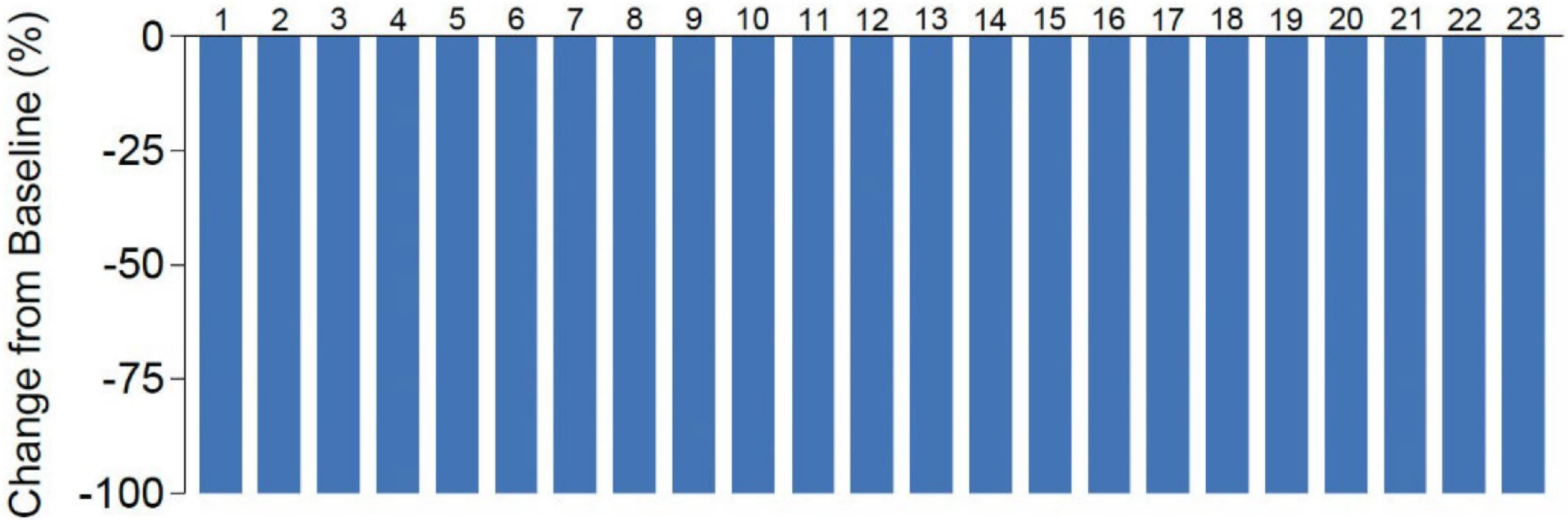
	Value (%)
Sex	
Male	6 (33)
Female	12 (67)
Age, median (range)	54 (26-78)
Race/Ethnicity	
White non-Hispanic	11 (61)
Hispanic	1 (6)
Black or African American	3 (17)
Asian-Far East/Indian Subcontinent	3 (17)
Tumor Staging	
T1/2	4 (22)
T3, T4	14 (78)
Nodal Staging	
Node-positive	17 (94)
Node-negative	1 (6)
Germline Mutation Status n=17	
MSH2, MLH1, MSH6, or PMS2	10 (59)
Negative	7 (41)
BRAF V600E wild type	18 (100)
Tumor Mutational Burden (mut/Mb), mean (range)	67 (36 -106)

Cercek, ASCO 2022

Overall response rate after six months of dostarlimab

- 100% cCR with 6 months of dostarlimab monotherapy

- 0% underwent RT, CRTx and/or surgery



Cercek, ASCO 2022

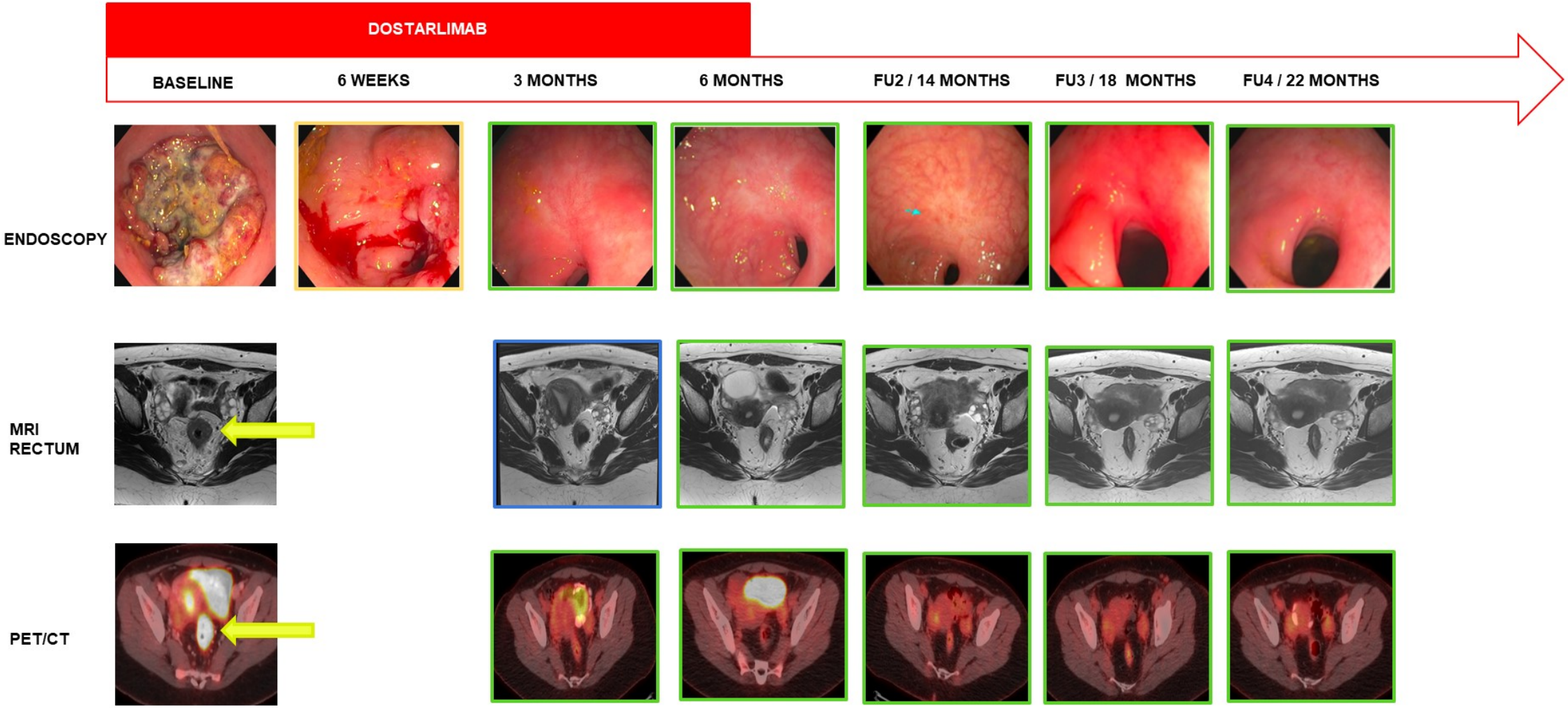
Overall response rate after six months of dostarlimab

ID	Age	Stage T	Stage N	FU (months)	Digital rectal exam response	Endoscopic best response	Rectal MRI best response	Overall response 100%
1	38	T4	N+	23.8	CR	CR	CR	**cCR**
2	30	T3	N+	20.5	CR	CR	CR	**cCR**
3	61	T1/2	N+	20.6	CR	CR	CR	**cCR**
4	28	T4	N+	20.5	CR	CR	CR	**cCR**
5	53	T1/2	N+	9.1	CR	CR	CR	**cCR**
6	77	T1/2	N+	11.0	CR	CR	CR	**cCR**
7	77	T1/2	N+	8.7	CR	CR	CR	**cCR**
8	55	T3	N+	5.0	CR	CR	CR	**cCR**
9	68	T3	N+	4.9	CR	CR	CR	**cCR**
10	78	T3	N-	1.7	CR	CR	CR	**cCR**
11	55	T3	N+	4.7	CR	CR	CR	**cCR**
12	27	T3	N+	4.4	CR	CR	CR	**cCR**
13	26	T3	N+	0.8	CR	CR	CR	**cCR**
14	43	T3	N+	0.7	CR	CR	CR	**cCR**

Cercek, ASCO 2022

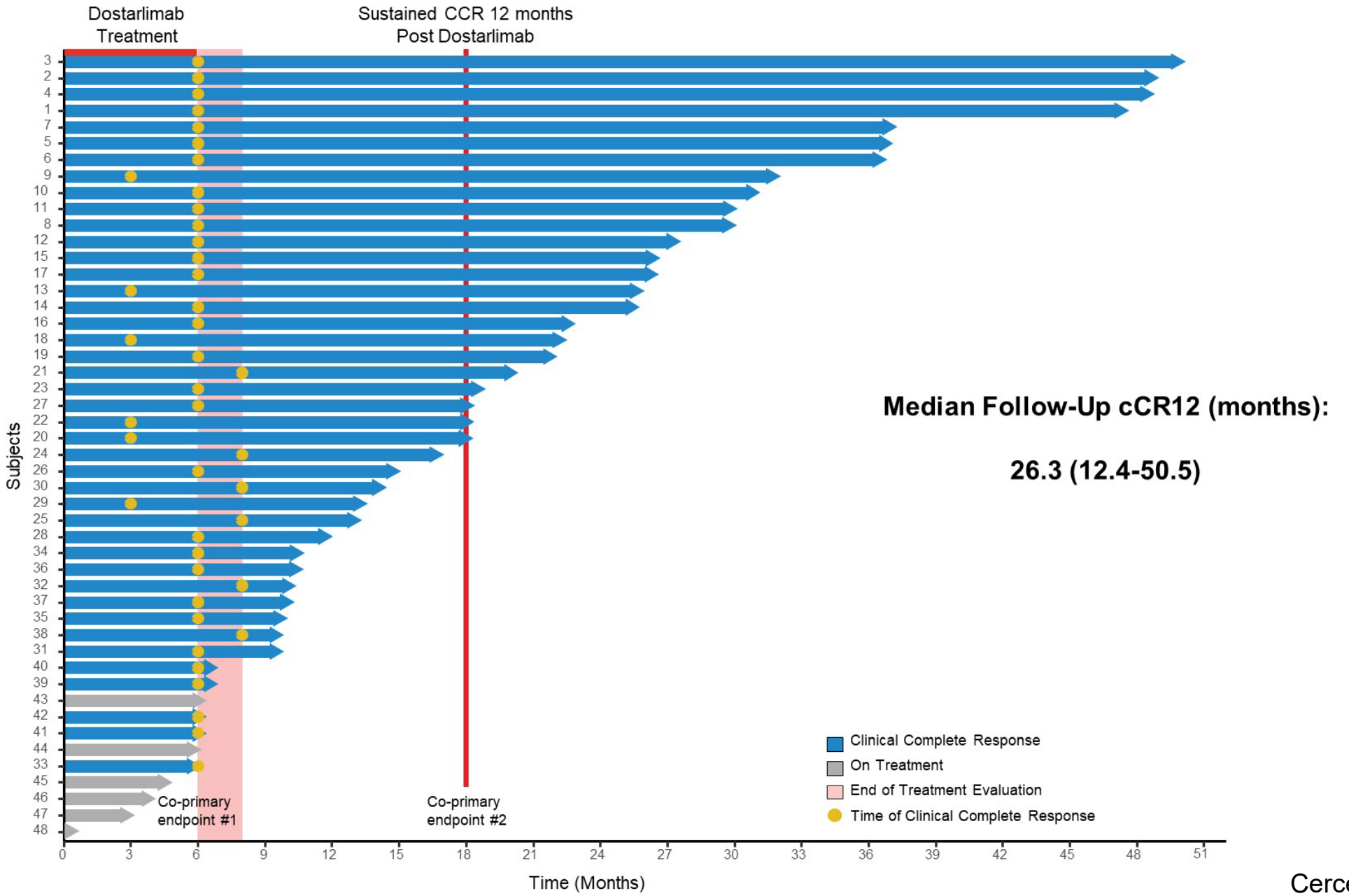
Patient #2

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



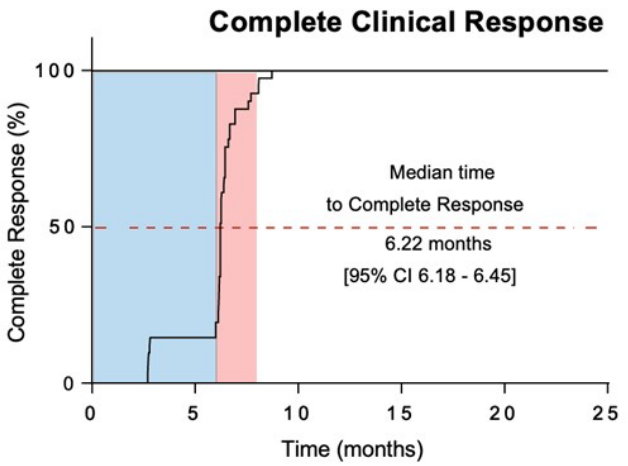
Cercek, ASCO 2022

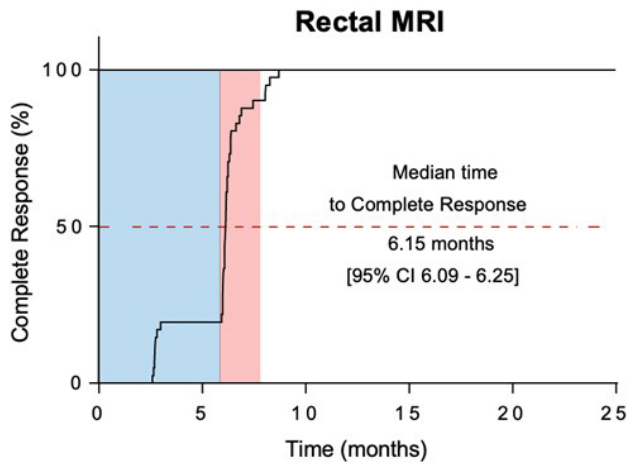
Update 2024 (42 patients)

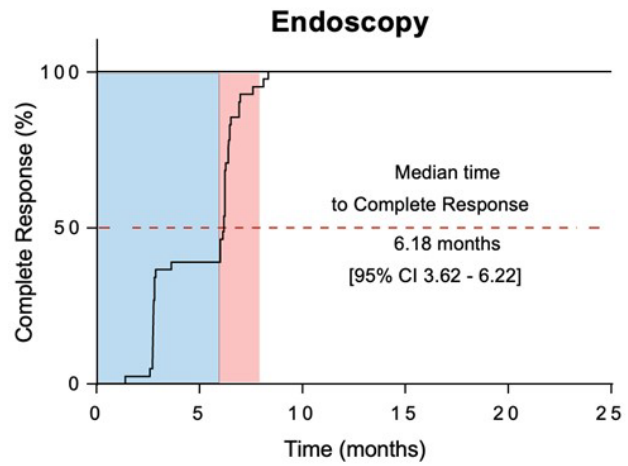


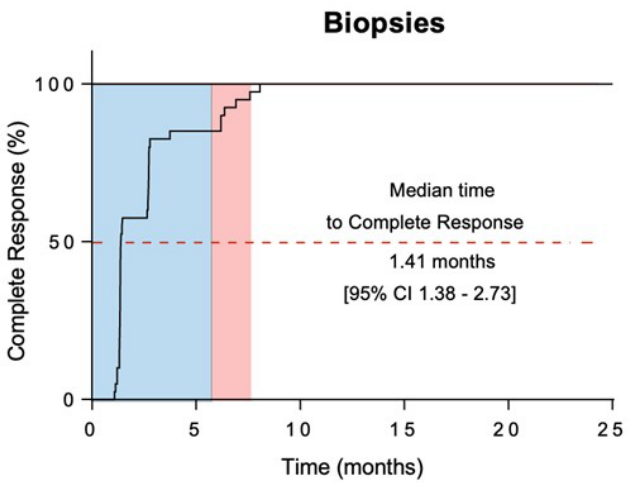
Cercek, ASCO 2024

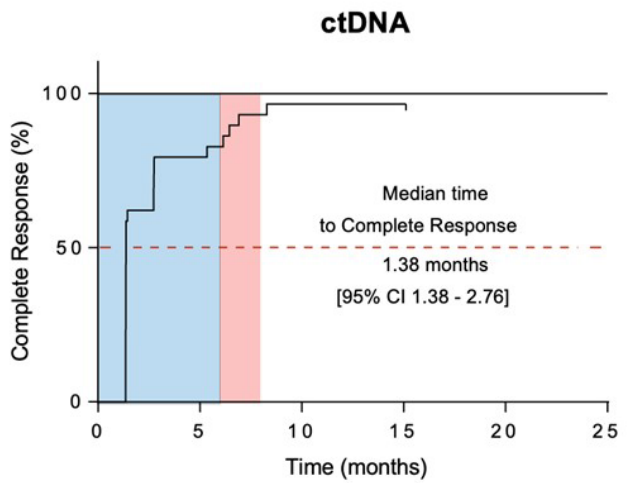
Time to clinical Complete Response

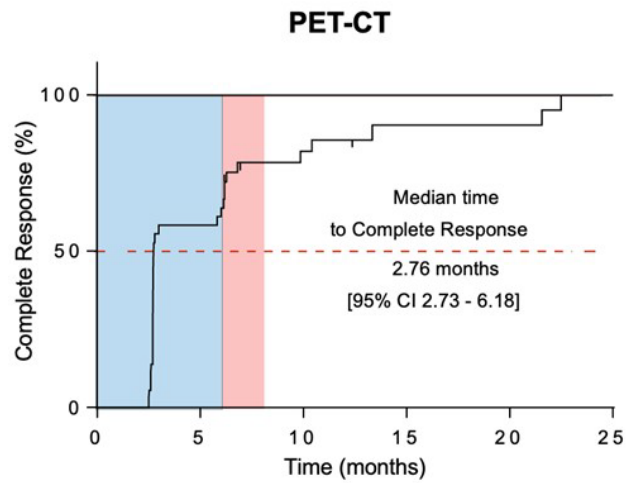


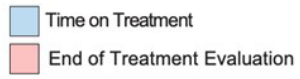












Cercek, ASCO 2024

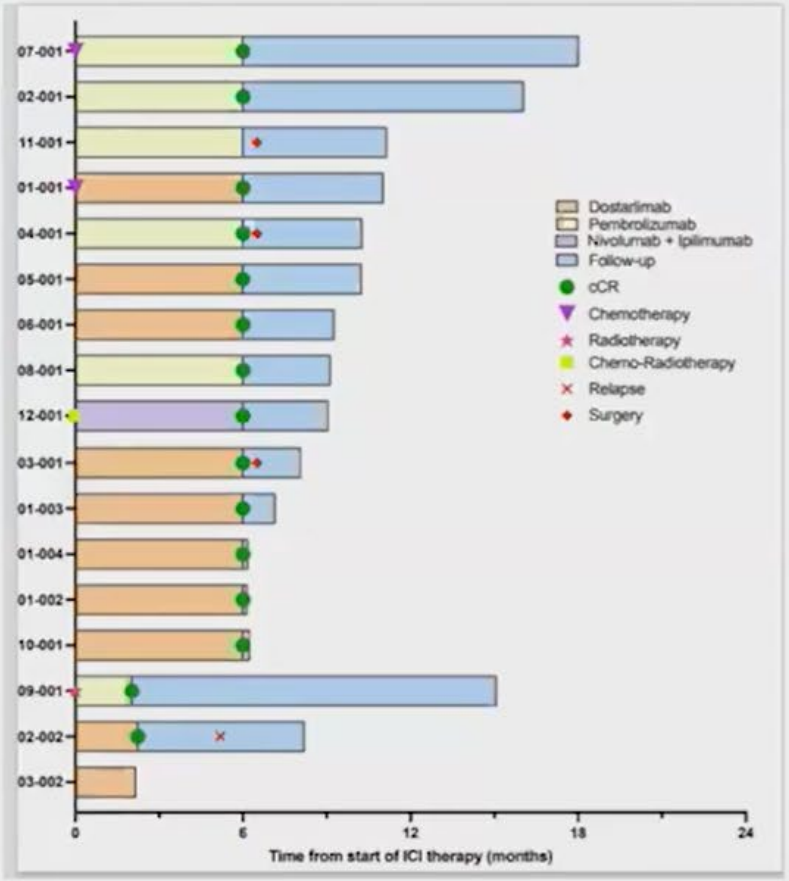
Adverse events

	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)

Cercek, ASCO 2022

Curative immune checkpoint inhibitors therapy in patients with mismatch repair-deficient locally advanced rectal cancer: a real-world observational study

F. Tosi[1], L. Salvatore[2,3], E. Tamburini[4], S. Artale[5], S. Lonardi[6], S. Marchetti[7], A. Pastorino[8], F. Pietrantonio[9], A. Puccini[10], F. L. Rojas-Llimpe[11], B. Vincenzi[12], S. Mariano[1], F. Negri[13], K. Bencardino[1], C. Pinto[14], C. Aschele[7†] & S. Siena[1,15*†]



July 22 – Dec 23

17 pts / 12 institutions

Dostarlimab (12) / Pembrolizumab (7) / Ipi / Nivo (1)

14 completed 6-m ICI tx

13/14 cCR

1/14 operated ypTis

3 did not complete 6-m ICI tx

1 social constraints
(**cCR** maintained at 8 m)
1 non-onc intestinal occlusion
(**cCR** maintained at 15 m)
1 **pneumonitis**
(**cCR** but progression at 6-m)

Tosi et al ESMO Open 2024

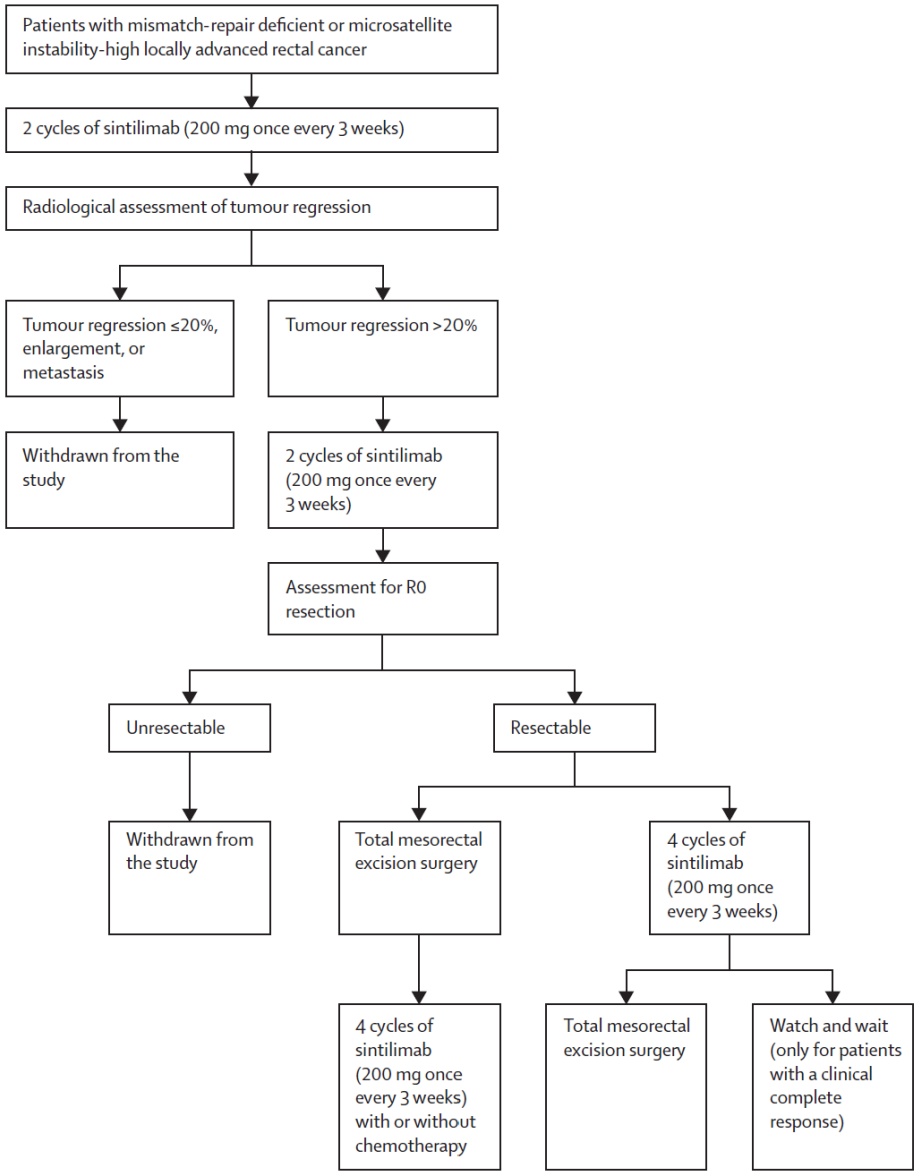
GAZZETTA UFFICIALE
DELLA REPUBBLICA ITALIANA

AGENZIA ITALIANA DEL FARMACO

DETERMINA 23 ottobre 2023

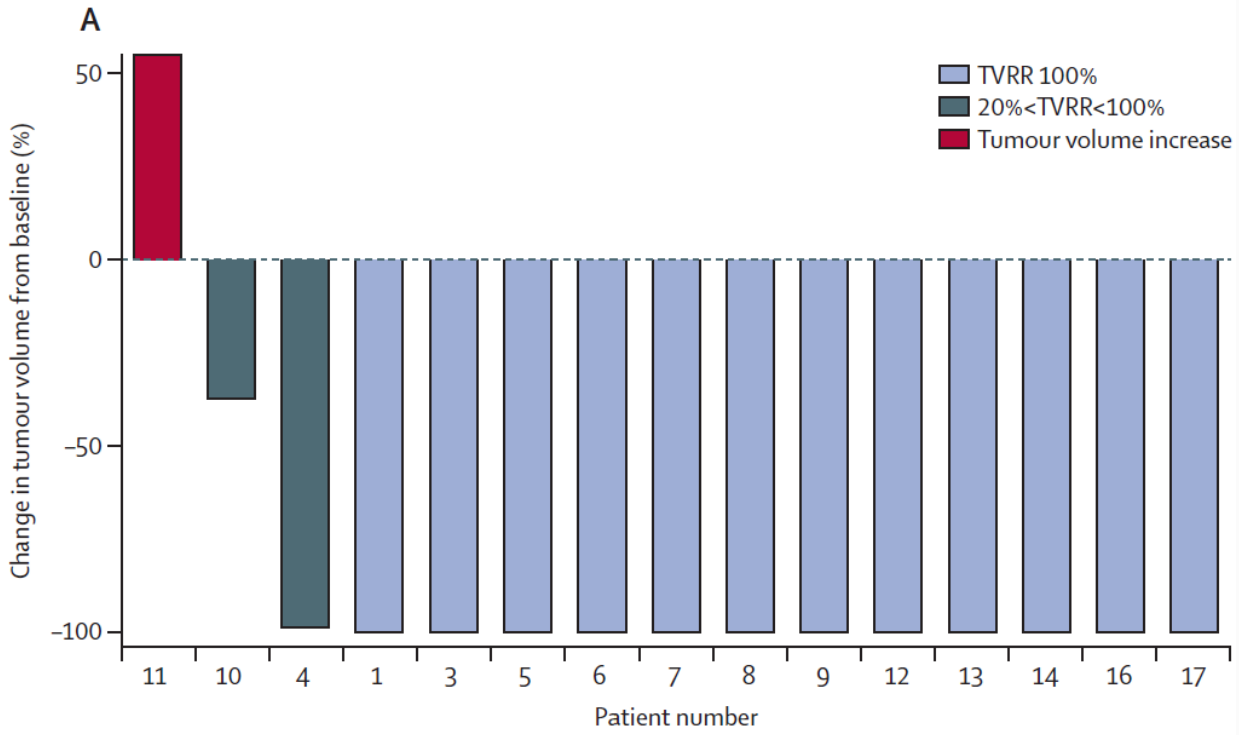
Inserimento del medicinale Dostarlimab nell'elenco istituito ai sensi della legge n. 648/1996 per il trattamento dell'adenocarcinoma localmente avanzato del retto (LARC) (stadio II-III) con MSI-H. (Determina n. 130342/2023). (23A05957) (GU Serie Generale n.252 del 27-10-2023)

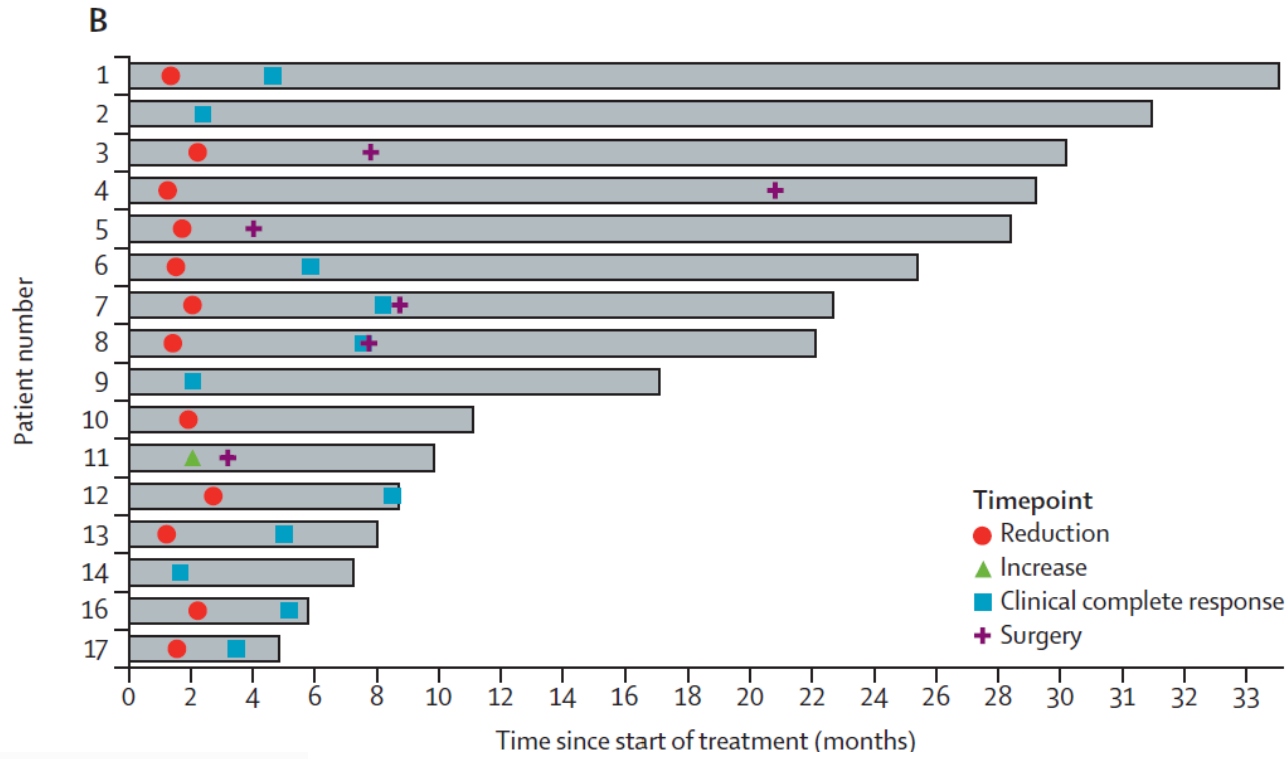
Sintilimab in MSI-H LARC



Chen, Lancet GH 2023

Sintilimab in MSI-H LARC





CR (pCR or cCR)= 75%; 9 pts with Ccr; 3/6 with pCR

Chen, Lancet GH 2023

Sintilimab in MSI-H LARC

	Grade 1–2	Grade 3–4
Constitutional		
Fatigue	3 (18%)	0
Fever	3 (18%)	0
Respiratory		
Cough	1 (6%)	0
Flu-like symptoms	2 (12%)	0
Gastrointestinal		
Diarrhoea	2 (12%)	0
Vomiting	1 (6%)	0
Constipation	2 (12%)	0
Intestinal obstruction	1 (6%)	0
Renal		
Increased creatinine	1 (6%)	0
Skin		
Rash	1 (6%)	0
Endocrine		
Hypothyroidism	1 (6%)	0
Hyperthyroidism	1 (6%)	0
Adrenocortical insufficiency	1 (6%)	0
Neurological		
Encephalitis	0	1 (6%)
Peripheral neuropathy	1 (6%)	0

Data are n (%).

Table 3: Treatment-related adverse events in patients

Chen, Lancet GH 2023

Toripalimab +/- Celecoxib in MSI-H localized CRC

	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%)
Clinical disease stage		
II	3/19 (16%)	1 (6%)
III	16/19 (84%)	16 (94%)
Histological appearance		
Well differentiated	4/19 (21%)	2 (12%)
Moderately differentiated	8/19 (42%)	13 (76%)
Poorly differentiated	7/19 (37%)	2 (12%)
Loss of expression of mismatch repair proteins		
MLH1 or PMS2, or both	10/19 (53%)	6 (35%)
MSH2 or MSH6, or both	9/19 (47%)	11 (65%)
Microsatellite instability testing by PCR		
High microsatellite instability	10/19 (53%)	9 (53%)
Not tested	9/19 (47%)	8 (47%)

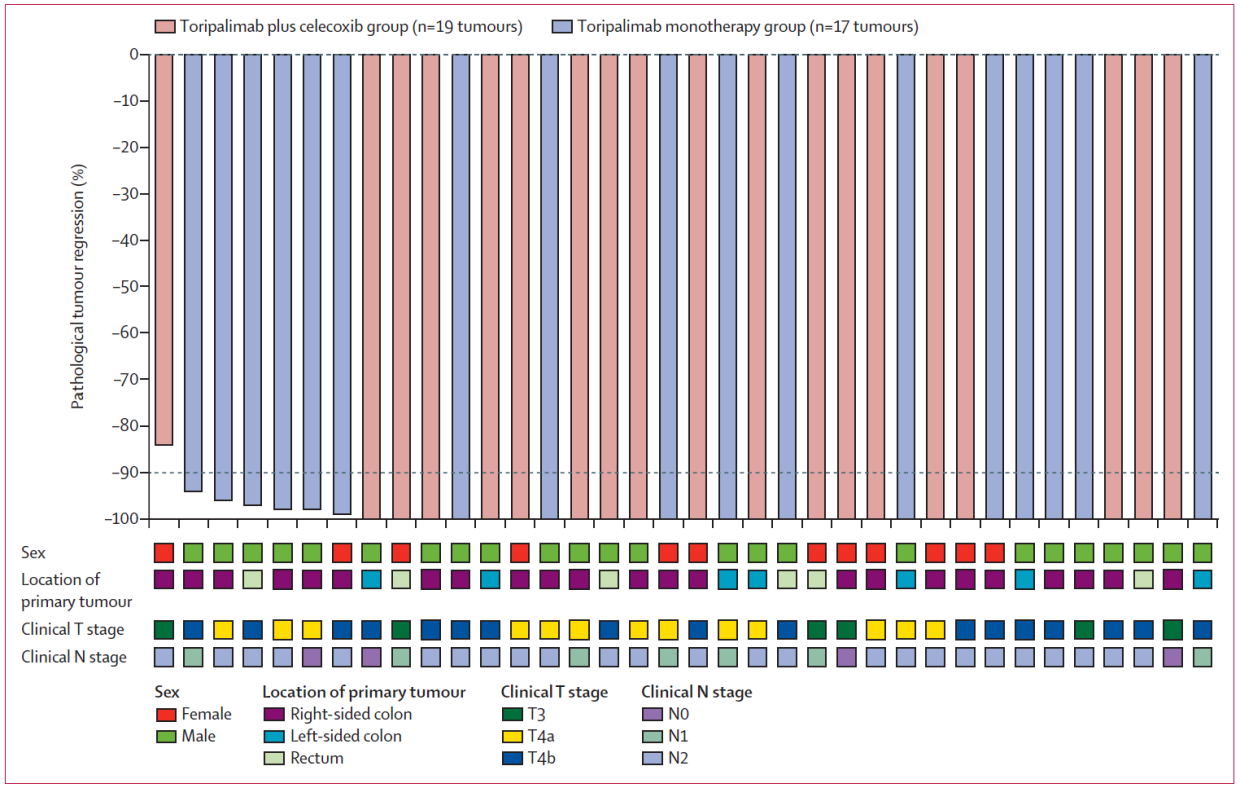
Hu, Lancet GH 2022

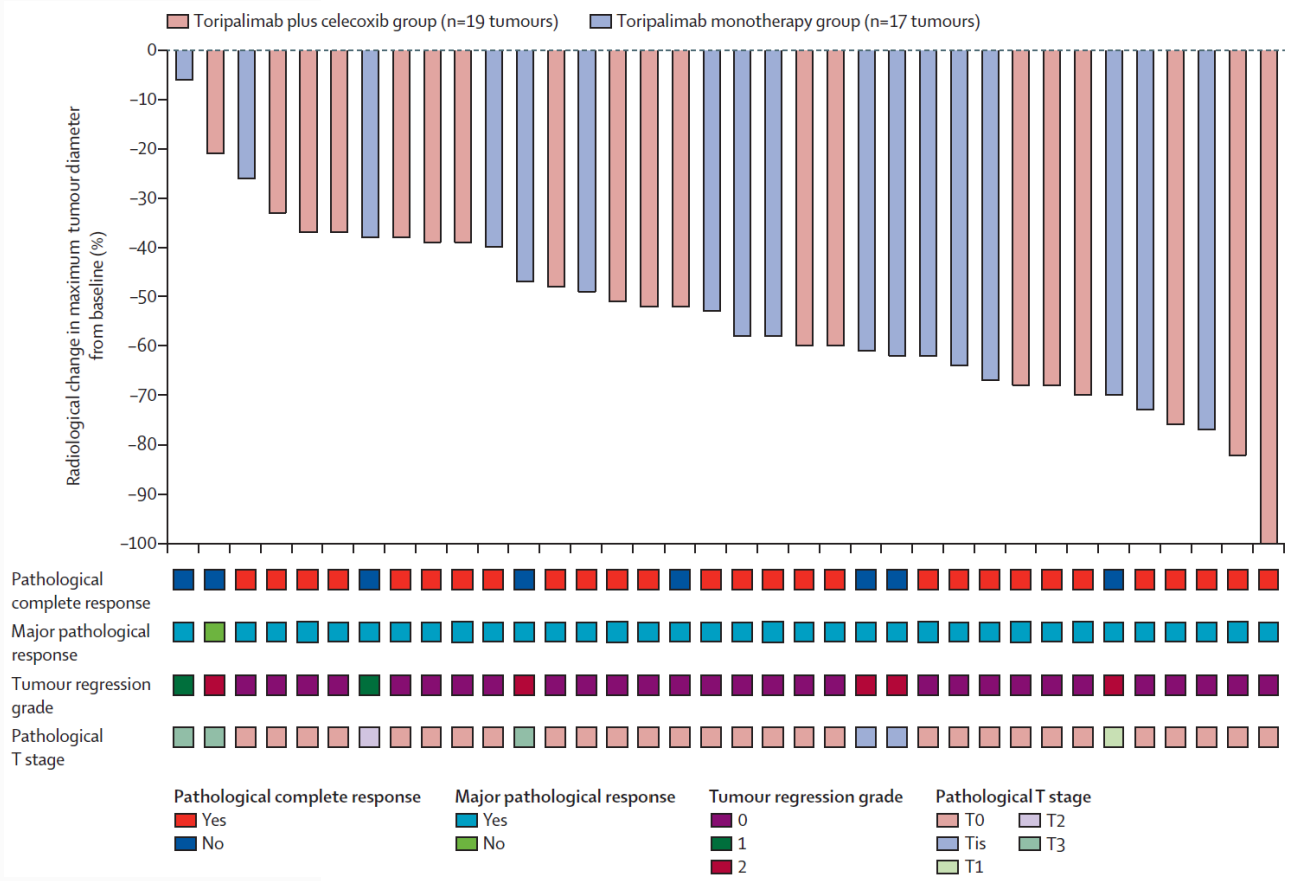
Toripalimab +/- Celecoxib in MSI-H localized CRC

	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

Hu, Lancet GH 2022

Toripalimab +/- Celecoxib in MSI-H localized CRC





Hu, Lancet GH 2022

Ongoing trials for MSI-H localized CRC

Source (ClinicalTrials.gov identifier)	Study phase	Patient population	Target accrual, No. of patients	Treatment	Primary end point	Secondary end point
Cercek et al,[31] 2022; Helwick,[33] 2022 (NCT04165772)	2	dMMR LARC	30	Dostarlimab, with or without CRT and with or without TME	Sustained cCR at 12 mo, pCR	NA
Chen et al,[34] 2021 (NCT04304209)	2	dMMR LARC	61	Sintilimab with or without TME	pCR	NA
Ciombor et al,[35] 2022 (NCT04751370)	2	dMMR LARC	31	Ipilimumab plus nivolumab and short-course RT with or without TME	pCR	5-y DFS, OS, safety
Shiu et al,[36] 2022 (NCT05197322)	2	High-risk stage II and III dMMR CRC	32	Pembrolizumab plus surgery	pCR	3-y RFS, OS, safety
Coutzac et al,[37] 2022)	2	Localized dMMR colon, endometrial, gastric, and other carcinomas	120	Pembrolizumab plus surgery	pCR	3-y RFS, OS, safety
ClinicalTrials.gov[38] (NCT05662527)	2	Stage I to III dMMR CC	85	Pembrolizumab plus surgery	pCR	Safety
ClinicalTrials.gov[39] (NCT05645094)	2	dMMR LARC	38	Envafolimab with or without CRT and with or without TME	cCR, pCR	3-y RFS, OS, ORR, TRG, safety, QOL
ClinicalTrials.gov[40] (NCT05116085)	2	dMMR stage II and III CRC	38	Tislelizumab	mPR	pCR, EFS, safety
ClinicalTrials.gov[41] (NCT05131919)	2	Unresectable dMMR CRC	25	Pembrolizumab with or without surgery	ORR	mPR, ctDNA, RFS, Safety
Li et al,[42] 2022 (NCT04636008)	1b	dMMR LARC	20	Sintilimab and short-course RT with or without TME	Safety	pRR, complete resection rate, QOL
ClinicalTrials.gov[43] (NCT05239546)	2	dMMR stage II and III CC	29	Dostarlimab plus surgery	mPR	3-y DFS, OS, ORR, metastatic disease rate

Neoadjuvant Immune Checkpoint Inhibitor Therapy for Localized Deficient Mismatch Repair Colorectal Cancer A Review, Oluwadunni, JAMA Oncology 2023

Conclusions

- Imperative to test for dMMR/MSI-H in patients with LARC
- PD-1 blockade induces cCR in many MSI-H/dMMR patients
- Generalizability? Differences in Lynch vs. non-Lynch?
- Optimal duration of immunotherapy needed is unknown
- Must complete enrollment of ongoing trials to determine long-term outcomes, generalizability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Grazie