EARLY-STAGE MSI-H RECTAL CANCER: IMMUNOTHERAPY FIRST

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DISCLOSURE

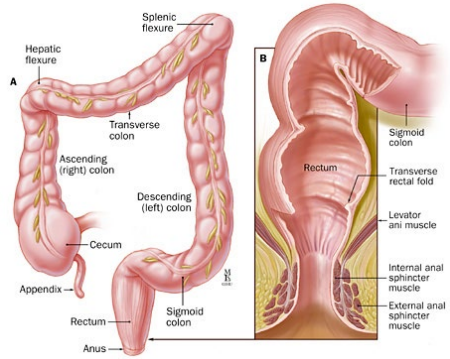
Research funding: Taiho Oncology, Ipsen Pharmaceuticals, GSK, Bristol Myers Squibb, PCI Biotech AS, ASCO, Calithera Biosciences, Inc., SynCore Biotechnology Co. Ltd., Suzhou Transcenta Therapeutics Co., Ltd, Corcept Therapeutics Inc., Hutchison MediPharma, Boehringer Ingelheim, Xencor Inc., Cue Biopharma, Inc., Merck, Syros Pharmaceuticals Inc., Inhibitex Inc, Arcus Biosciences Inc., ImmunoGen

Consulting/Advisory Role: Ipsen Pharmaceuticals, Aadi Bioscience, Taiho, Pfizer, Seagen Inc., Bristol Myers Squibb, AstraZeneca, Exelixis, Takeda

"It's not personal,
Sonny.
It's strictly business."

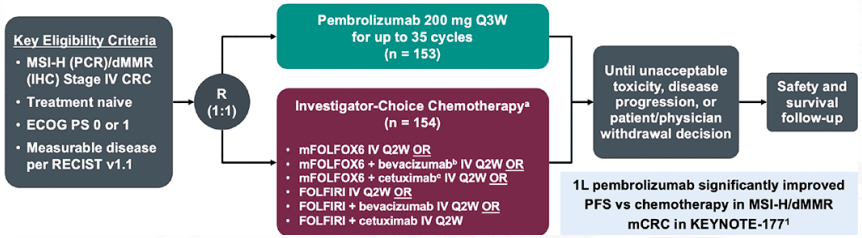
FACTS…

- No head-to-head prospective comparison of surgery first vs. IO first
- We are debating the best options currently available but there is room for improvement
- We may not always agree on points, but we all want the best for our patients
- Quality of life is crucial for any cancer treatment, especially for curative intent modalities for early stage cancers



Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study

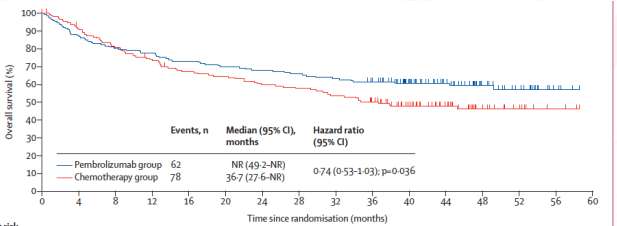
*Luis A Diaz Jr, Kai-Keen Shiu, Tae-Won Kim, Benny Vittrup Jensen, Lars Henrik Jensen, Cornelis Punt, Denis Smith, Rocio Garcia-Carbonero, Manuel Benavides, Peter Gibbs, Christelle de la Fourchardiere, Fernando Rivera, Elena Elez, Dung T Le, Takayuki Yoshino, Wen Yan Zhong, David Fogelman, Patricia Marinello, Thierry Andre, on behalf of the KEYNOTE-177 Investigators**



	Pembrolizumab (n=153)	Chemotherapy (n=154)
Age, years	63 (52-73)	63 (48-72)
Sex		
Female	82 (54%)	72 (47%)
Male	71 (46%)	82 (53%)
ECOG performance status		
0	75 (49%)	84 (54%)
1	78 (51%)	70 (46%)
Stage		
Recurrent disease	80 (52%)	74 (48%)
Newly diagnosed	73 (48%)	80 (52%)
Liver metastasis	71 (46%)	54 (35%)
Geographical region		
Asia	22 (14%)	26 (17%)
Western Europe or North America	109 (71%)	113 (73%)
Rest of the world	22 (14%)	15 (10%)
Race or ethnicity		
White	113 (74%)	116 (75%)
Asian	24 (16%)	26 (17%)
Black	9 (6%)	5 (3%)
Race not reported or missing	7 (5%)	7 (5%)
Not Hispanic or Latino	128 (84%)	131 (85%)
Hispanic or Latino	11 (7%)	10 (6%)
Ethnicity not reported, missing, or unknown	14 (9%)	13 (8%)
Tumour location		
Right-sided tumour	102 (67%)	107 (69%)
Left-sided tumour	46 (30%)	42 (27%)
Other or unknown tumour location	5 (3%)	5 (3%)
Previous lines of therapy		
Previous adjuvant therapy only	33 (22%)	37 (24%)
Previous neoadjuvant therapy (perioperative)	5 (3%)	8 (5%)
No previous therapy	115 (75%)	109 (71%)
BRAF, *KRAS*, and *NRAS* status		
BRAF, *KRAS*, and *NRAS* all wildtype	43 (28%)	38 (25%)
KRAS or *NRAS* mutant	33 (22%)	39 (25%)
BRAF^{V600E} mutant and *KRAS* or *NRAS* not mutant	35 (23%)	44 (29%)
BRAF^{V600E} mutant and *KRAS* or *NRAS* mutant	0	2 (1%)
Unknown*	42 (27%)	31 (20%)

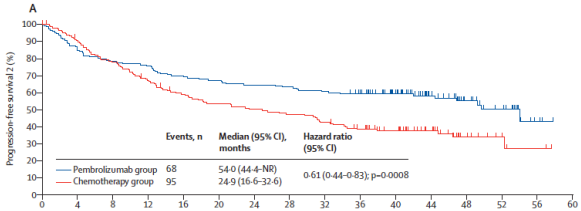
Diaz LA Jr, et al. Lancet Oncol. 2022 May;23(5):659-670.

KEYNOTE-177



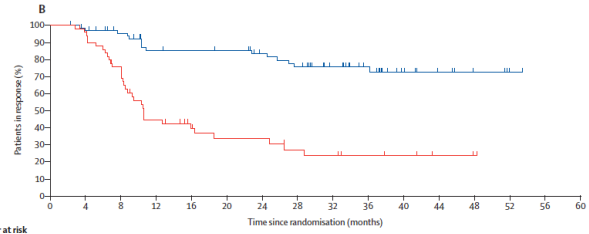
Number at risk (number censored)

Pembrolizumab group	153 (0)	134 (0)	123 (0)	119 (0)	112 (0)	107 (0)	104 (0)	101 (0)	97 (2)	92 (23)	70 (45)	48 (64)	28 (75)	16 (78)	4 (91)	0 (91)
Chemotherapy group	154 (4)	137 (4)	121 (5)	110 (6)	99 (6)	95 (6)	88 (6)	85 (6)	79 (9)	71 (24)	53 (41)	36 (58)	18 (65)	11 (73)	3 (76)	0 (76)



Number at risk (number censored)

Pembrolizumab group	153 (0)	131 (0)	120 (0)	116 (0)	107 (0)	103 (0)	99 (0)	97 (0)	93 (4)	87 (24)	67 (47)	43 (62)	26 (71)	15 (82)	3 (85)	0 (85)
Chemotherapy group	154 (4)	136 (4)	117 (5)	100 (7)	86 (7)	78 (7)	73 (7)	69 (7)	62 (10)	53 (19)	43 (33)	29 (49)	11 (54)	6 (57)	2 (59)	0 (59)



Number at risk (number censored)

Pembrolizumab group	69 (2)	66 (7)	59 (10)	50 (11)	49 (12)	48 (16)	43 (16)	39 (24)	31 (32)	23 (43)	11 (47)	7 (50)	4 (52)	2 (54)	0 (54)	0 (54)
Chemotherapy group	51 (1)	48 (3)	36 (5)	20 (9)	14 (10)	11 (10)	11 (11)	8 (11)	7 (13)	5 (14)	4 (16)	2 (17)	1 (18)	0 (18)	0 (18)	0 (18)

Diaz LA Jr, et al. Lancet Oncol. 2022 May;23(5):659-670.

NEOADJUVANT DOSTARLIMAB

The NEW ENGLAND JOURNAL of MEDICINE

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PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

A. Cercek, M. Lumish, J. Sinopoli, J. Weiss, J. Shia, M. Lamendola-Essel, I.H. El Dika, N. Segal, M. Shcherba, R. Sugarman, Z. Stadler, R. Yaeger, J.J. Smith, B. Rousseau, G. Argiles, M. Patel, A. Desai, L.B. Saltz, M. Widmar, K. Iyer, J. Zhang, N. Gianino, C. Crane, P.B. Romesser, E.P. Pappou, P. Paty, J. Garcia-Aguilar, M. Gonen, M. Gollub, M.R. Weiser, K.A. Schalper, and L.A. Diaz, Jr.

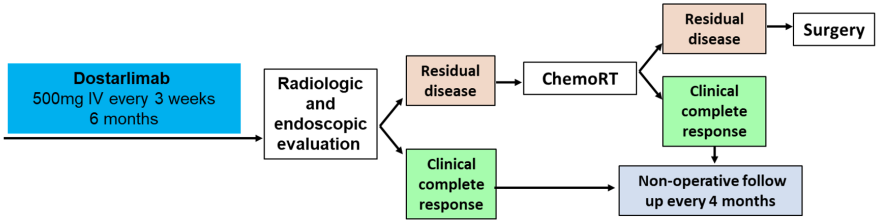

Table 1. Demographic and Disease Characteristics of the Patients at Baseline.

Characteristic	Value
Patients enrolled — no. (%)	16 (100)
Female sex — no. (%)	10 (62)
Median age (range) — yr	54 (26–78)
Race — no. (%)*	
White	11 (69)
Asian	3 (19)
Black	2 (12)
Hispanic or Latinx ethnic group — no. (%)*	1 (6)
ECOG performance-status score — no. (%)†	
0	12 (75)
1	4 (25)
Tumor stage — no. (%)	
T1 or T2	4 (25)
T3	9 (56)
T4	3 (19)
Nodal status — no. (%)	
Positive	15 (94)
Negative	1 (6)
Median distance of tumor from anal verge (range) — cm	5 (0.9–8.9)

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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

Individual responses to PD-1 blockade with dostarlimab

Patients who completed 6-months of dostarlimab

ID	Age	Stage T	Stage N	FU (months)	Digital rectal exam response	Endoscopic best response	Rectal MRI best response	Overall response
1	38	T4	N+	23.8	CR	CR	CR	**cCR**

Courtesy – Andrea Cercek, MD

Patient #2

Courtesy – Andrea Cercek, MD

Individual responses to PD-1 blockade with dostarlimab

Patients who completed 6-months of dostarlimab

ID	Age	Stage T	Stage N	FU (months)	Digital rectal exam response	Endoscopic best response	Rectal MRI best response	Overall response
1	38	T4	N+	23.8	CR	CR	CR	**cCR**
2	30	T3	N+	20.5	CR	CR	CR	**cCR**

Courtesy – Andrea Cercek, MD

Individual responses to PD-1 blockade with dostarlimab

Patients who completed 6-months of dostarlimab

ID	Age	Stage T	Stage N	FU (months)	Digital rectal exam response	Endoscopic best response	Rectal MRI best response	Overall response
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**

Courtesy – Andrea Cercek, MD

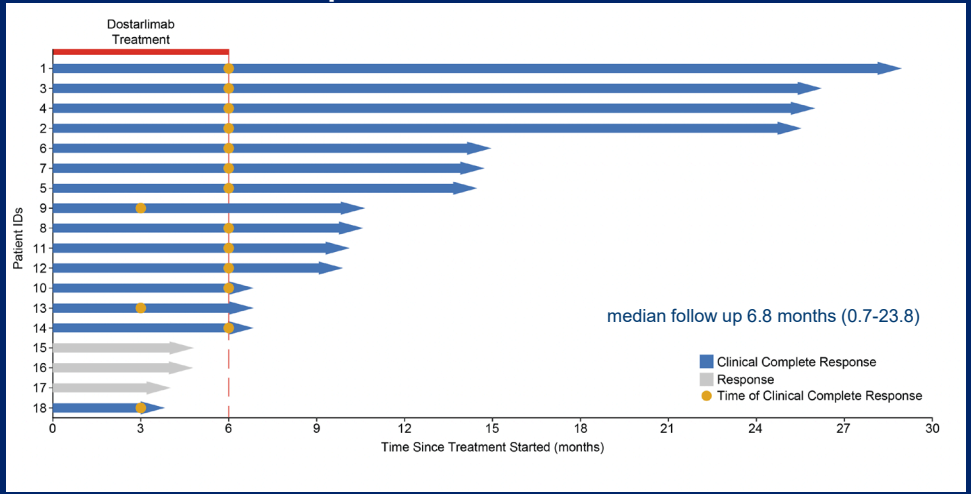
Individual responses to PD-1 blockade with dostarlimab

Patients who completed 6-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**

Courtesy – Andrea Cercek, MD

Duration of response



Courtesy – Andrea Cercek, MD

NEOADJUVANT IMMUNOTHERAPY – RECTAL CANCER

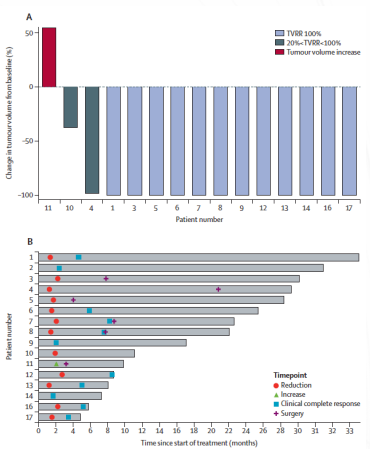
Study	Sample size	Neoadjuvant IO	cCR	pCR
Gong Chen[1]	17 (100%)	Sintilimab	75%; W/W	50% (Sx)
Kaysia Ludford[2]	8 (23%)	Pembrolizumab	-	79%
Huabin Hu[3]	6 (18%)	Toripalimab +/- Celecoxib	-	(88% vs. 65%)

1. Chen G, et al. Lancet Gastroenterol Hepatol. 2023 May;8(5):422-431.
2. Kaysia Ludford, et al. Journal of Clinical Oncology 2023 41:12, 2181-2190
3. Hu H, et al. Lancet Gastroenterol Hepatol. 2022 Jan;7(1):38-48

NEOADJUVANT IMMUNOTHERAPY – RECTAL CANCER

Neoadjuvant PD-1 blockade with sintilimab in mismatch-repair deficient, locally advanced rectal cancer: an open-label, single-centre phase 2 study

Gong Chen*, Ying Jin*, Wen-Long Guan*, Rong-Xin Zhang*, Wei-Wei Xiao*, Pei-Qiang Cai, Min Liu, Jun-Zhong Lin, Fu-Long Wang, Cong Li, Ting-Ting Quan, Shao-Yan Xi, Hui-Zhong Zhang, Zhi-Zhong Pan, Feng Wang†, Rui-Hua Xu†



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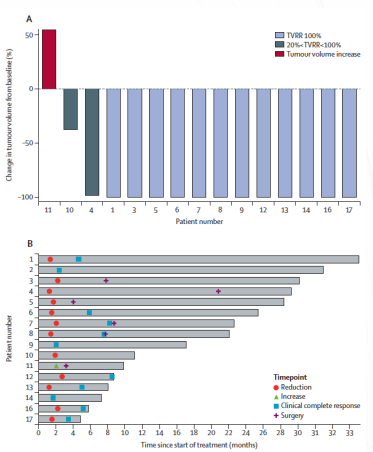
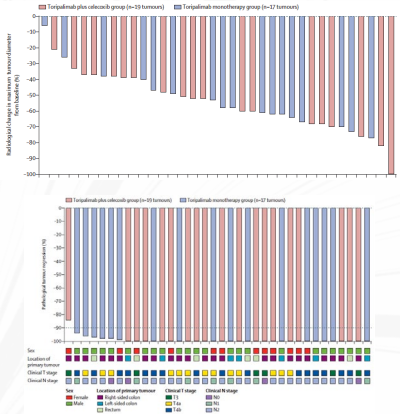


Neoadjuvant PD-1 blockade with toripalimab, with or without celecoxib, in mismatch repair-deficient or microsatellite instability-high, locally advanced, colorectal cancer (PICC): a single-centre, parallel-group, non-comparative, randomised, phase 2 trial

Huabin Hu*, Liang Kang*, Jianwei Zhang*, Zezhou Wu*, Hui Wang, Meijin Huang, Ping Lan, Xiaojian Wu, Chao Wang, Wuteng Cao, Jiancong Hu, Yan Huang, Liang Kuang, Huaimiao Wang, Lizhen Shi, Yue Cai, Cailu Shen, Jieyu Ling, Xiaoyu Xie, Yonghua Cai, Xiaowen He, Ruwu Dou, Jiaming Zhou, Tenghui Ma, Xingwei Zhang, Shuangling Luo, Weihao Deng, Li Ling, Hao Liu, Yanhong Deng



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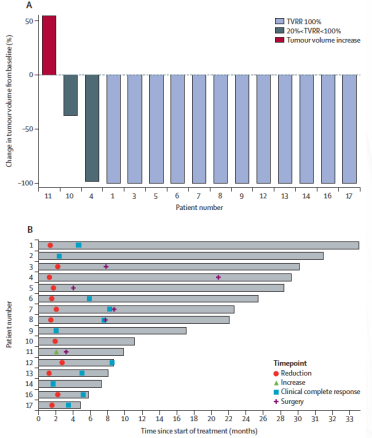

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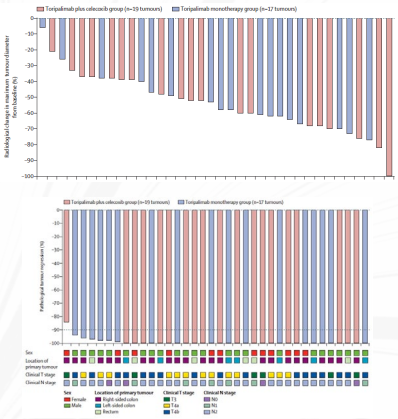
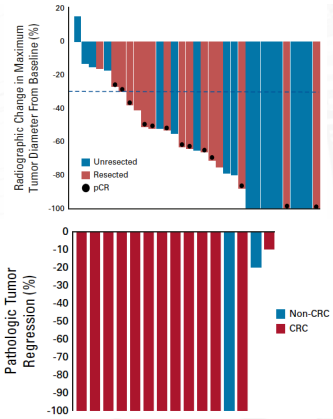


original reports

Neoadjuvant Pembrolizumab in Localized Microsatellite Instability High/Deficient Mismatch Repair Solid Tumors

Kaysia Ludford, MD[1,2]; Won Jin Ho, MD[3]; Jane V. Thomas, MD[2]; Kanwal P.S. Raghav, MBBS[2]; Mariela Blum Murphy, MD[2]; Nicole D. Fleming, MD[4]; Michael S. Lee, MD[2]; Brandon G. Smaglo, MD[2]; Y. Nancy You, MD[4]; Matthew M. Tillman, MD[5]; Carlos Kamiya-Matsuoka, MD[6]; Selvi Thirumurthi, MD[7]; Craig Messick, MD[8]; Benny Johnson, DO[2]; Eduardo Vilar, MD, PhD[9]; Arvind Dasari, MBBS[2]; Sarah Shin, BS[1]; Alexei Hernandez, BS[1]; Xuan Yuan, MD[1]; Hongqui Yang[1]; Wai Chin Foo, MD[9]; Wei Qiao, MS, PhD[10]; Dipen Maru, MD[9]; Scott Kopetz, MD, PhD[2]; and Michael J. Overman, MD[2]



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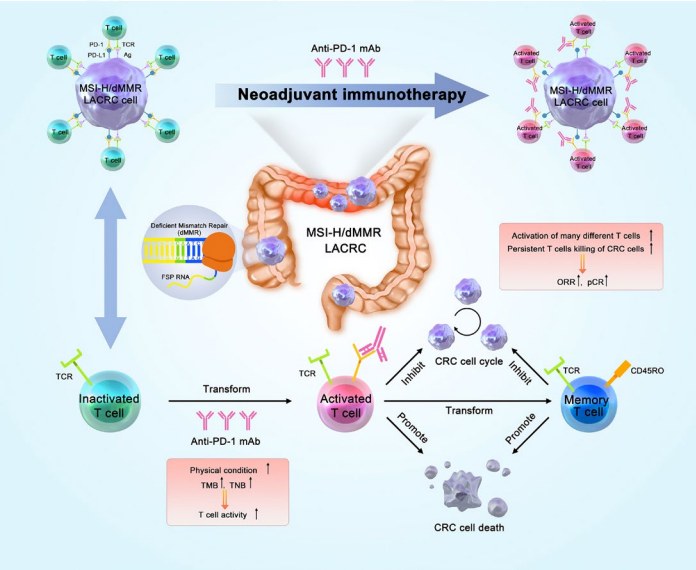
NEOADJUVANT IMMUNOTHERAPY



Zhang X, et al. Front Immunol. 2022 Mar 17;13:795972.

CLINICAL TOXICITY

Surgery

- significant morbidity - bowel, urinary, and sexual dysfunction; secondary malignancy; infertility; and substantially impaired QoL
- Pelvic radiation, TME associated with urinary dysfunction in 35-51%
- Less likely to be sexually active (M:50% and F:32%; vs. 91% and 61% before treatment; $p<0.004$)
- Virtually all patients undergoing TME require temporary colostomy; 20-30% requiring APR

IO

- No adverse events of grade 3 or higher were reported.
- Most common grade 1 or 2 AEs
  - rash or dermatitis (31%)
  - pruritus (25%)
  - Fatigue (25%),
  - Nausea (19%).
  - Thyroid-function abnormalities in 1 patient (6%)

Chill HH, et al. BMC Womens Health. 2021;21(1):237. Contin P, et al. Int J Colorectal Dis. 2014;29(2):165-75. Hendren SK, et al. Ann Surg. 2005:242(2):212–23. Hassan I, Cima RR. J Surg Oncol. 2007;96:684-92.

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dMMR/MSI-H Rectal Cancer

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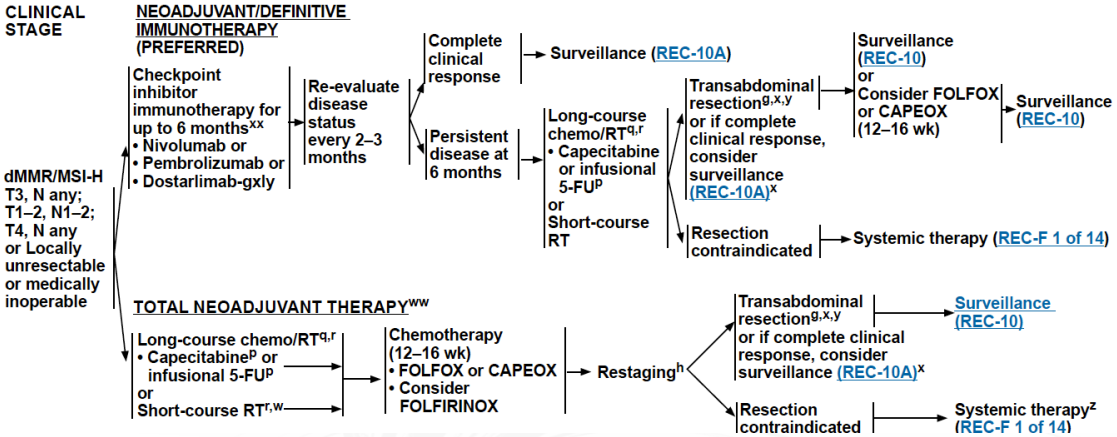

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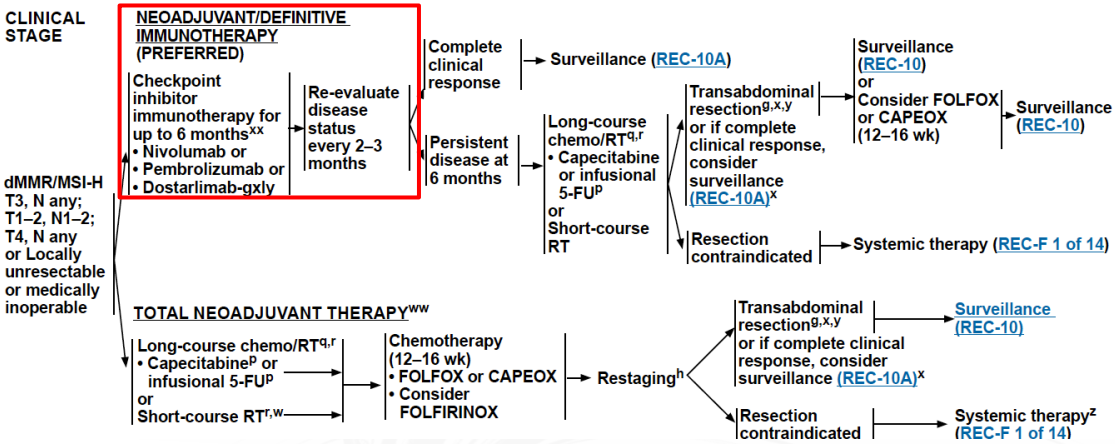

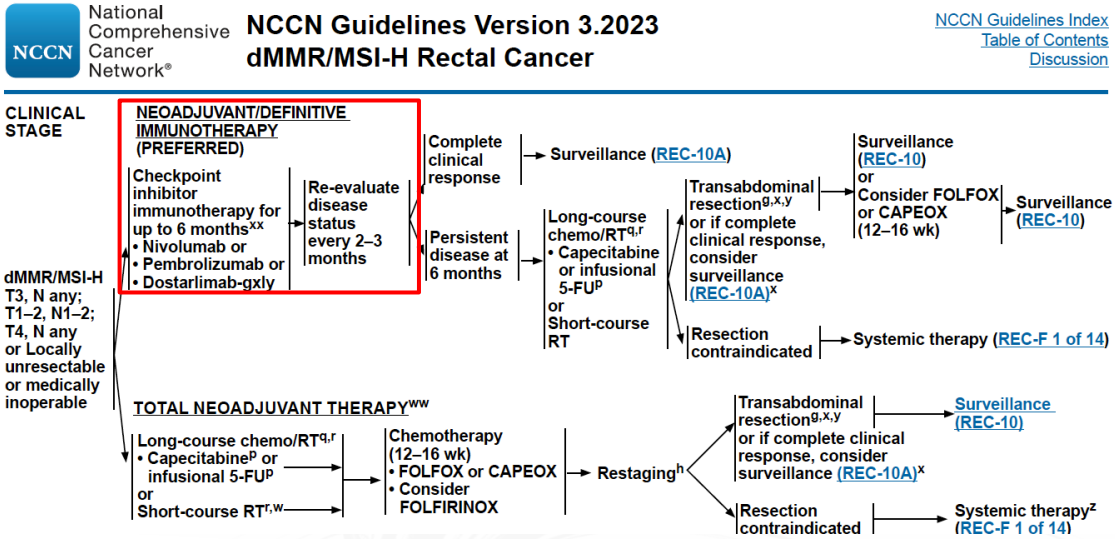
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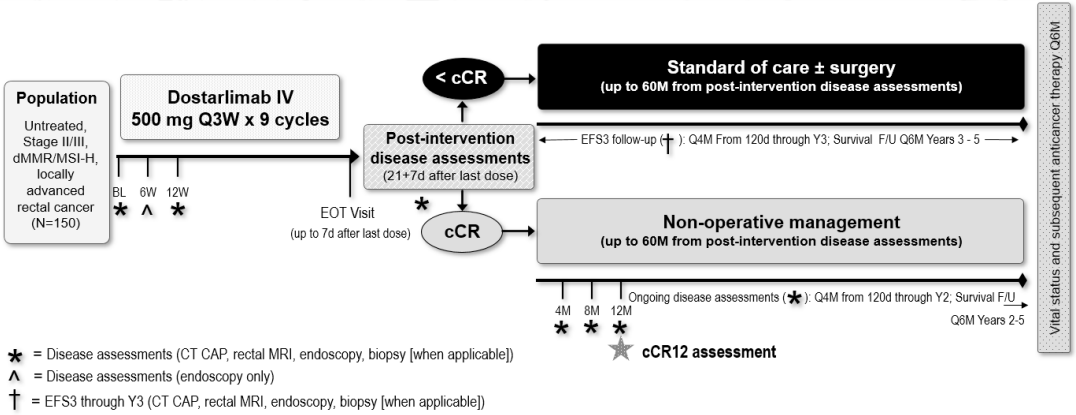
CLINICAL STAGE
dMMR/MSI-H T3, N any; T1–2, N1–2; T4, N any or Locally unresectable or medically inoperable
NEOADJUVANT/DEFINITIVE IMMUNOTHERAPY (PREFERRED)
Checkpoint inhibitor immunotherapy for up to 6 months[xx]
• Nivolumab or
• Pembrolizumab or
• Dostarlimab-gxly
Re-evaluate disease status every 2–3 months
Complete clinical response
Surveillance (REC-10A)
Persistent disease at 6 months
Long-course chemo/RT[q,r]
• Capecitabine or infusional 5-FU[p]
or
Short-course RT
Transabdominal resection[g,x,y] or if complete clinical response, consider surveillance (REC-10A)[x]
Surveillance (REC-10)
or
Consider FOLFOX or CAPEOX (12–16 wk)
Surveillance (REC-10)
Resection contraindicated
Systemic therapy (REC-F 1 of 14)
TOTAL NEOADJUVANT THERAPY[ww]
Long-course chemo/RT[q,r]
• Capecitabine[p] or infusional 5-FU[p]
or
Short-course RT[r,w]
Chemotherapy (12–16 wk)
• FOLFOX or CAPEOX
• Consider FOLFIRINOX
Restaging[h]
Transabdominal resection[g,x,y] or if complete clinical response, consider surveillance (REC-10A)[x]
Surveillance (REC-10)
Resection contraindicated
Systemic therapy[z] (REC-F 1 of 14)

??T1–2N0; T3N0

ON-GOING TRIALS…

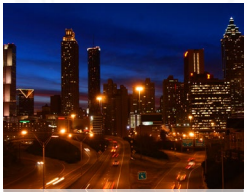
AZUR-1: Phase 2, Single-Arm, Open-Label Study with Dostarlimab Monotherapy in Participants with Untreated Stage II/III dMMR/MSI-H Locally Advanced Rectal Cancer

- Primary objective: To estimate the efficacy of Dostarlimab in Stage II/III (locally advanced) dMMR/MSI-H rectal cancer
- Endpoint: cCR12 - maintenance of cCR for 12 months.



CONCLUSION

- Checkpoint Inhibitors have demonstrated superior efficacy/toxicity outcomes in MSI-H rectal tumors, compared to historical rates for TNT or surgical resection
- Additional efforts (large confirmatory clinical trials) are ongoing, with appropriate translational science for biomarker development and understanding of resistance mechanisms
- Immunotherapy should be the frontline treatment in the management of appropriate cases



THANK YOU