Immunotherapeutic Considerations Treating the MMR Deficient and Proficient Locally advanced Rectal Cancer

Uqba Khan, MD

Assistant Professor in Clinical Medicine

Department of Hematology/Oncology

Weill Cornell Medicine

New York Presbyterian Brooklyn Methodist Hos

Disclosures

- **Advisory Board:** Astra Zeneca, Amgen, Guardant, Cardinal Health

Outline

- Prognostic and Predictive Significance of MMR/MSI
- Importance of incorporating immunotherapy in locally advanced rectal cancer
- Implications of MMR in advanced CRC
- Neo-adjuvant immunotherapy in advanced colon cancer
- Checkpoint inhibitors in locally advanced rectal cancer
- Ongoing trials

Why we need immunotherapy in LARC?

Traditional Therapy (Chemotherapy + Radiation + Surgery)
Fecal Incontinence
Sexual Dysfunction
Urinary Dysfunction
Peripheral Neuropathy
Colostomy
Quality of Life

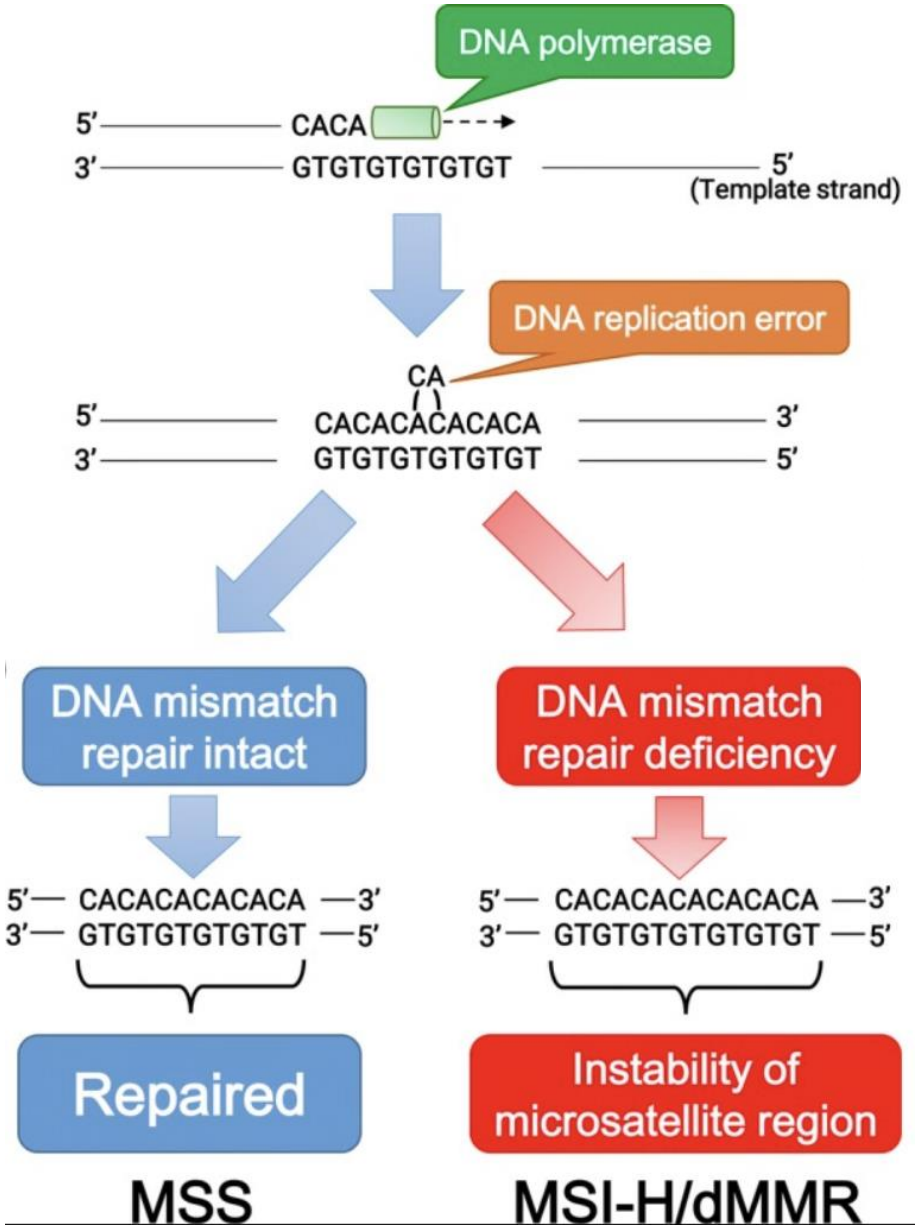
Immunotherapy
Higher cCR
Potentially avoid CRT and Surgery
Better side effect profile
Avoid long term side effects
Better Survival
Improved Quality of life

Mismatch Repair Pat

MMR pathway plays an important role in maintaining DNA fidelity by repairing DNA replication errors

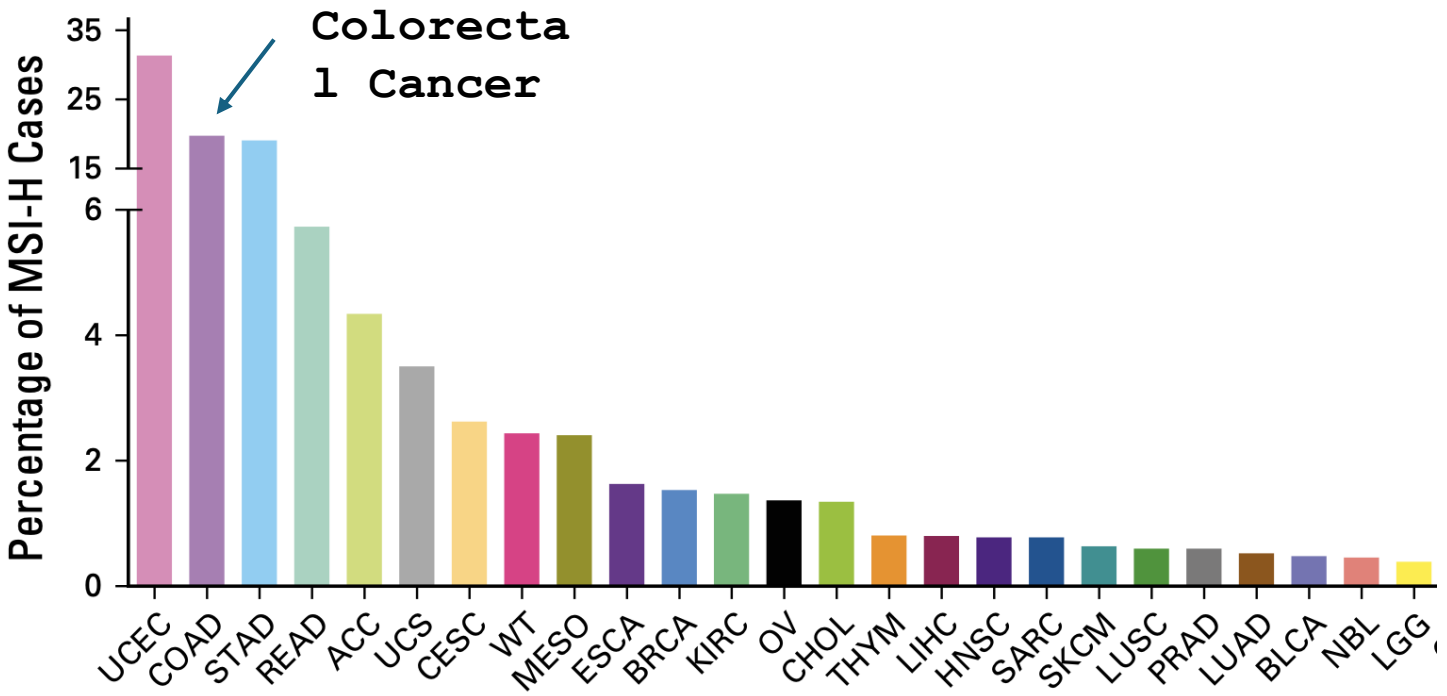
MMR deficiency leads to a molecular feature of microsatellite instability (MSI) and predisposes to cancer

Lynch Syndrome is caused by heterozygous germline mutations in one of the four key MMR genes, MLH1, MSH2, MSH6, and PMS2.



Eso et al. J Gastroenterolo

MSI-Most relevant Biomarker for CRC



- 5-10% of rectal cancers have MMR-deficiency
- Mismatch repair deficiency is known to occur in some tumors either by somatic mutation of MMR genes or via inherited germline MMR pathway mutation, as in Lynch syndrome

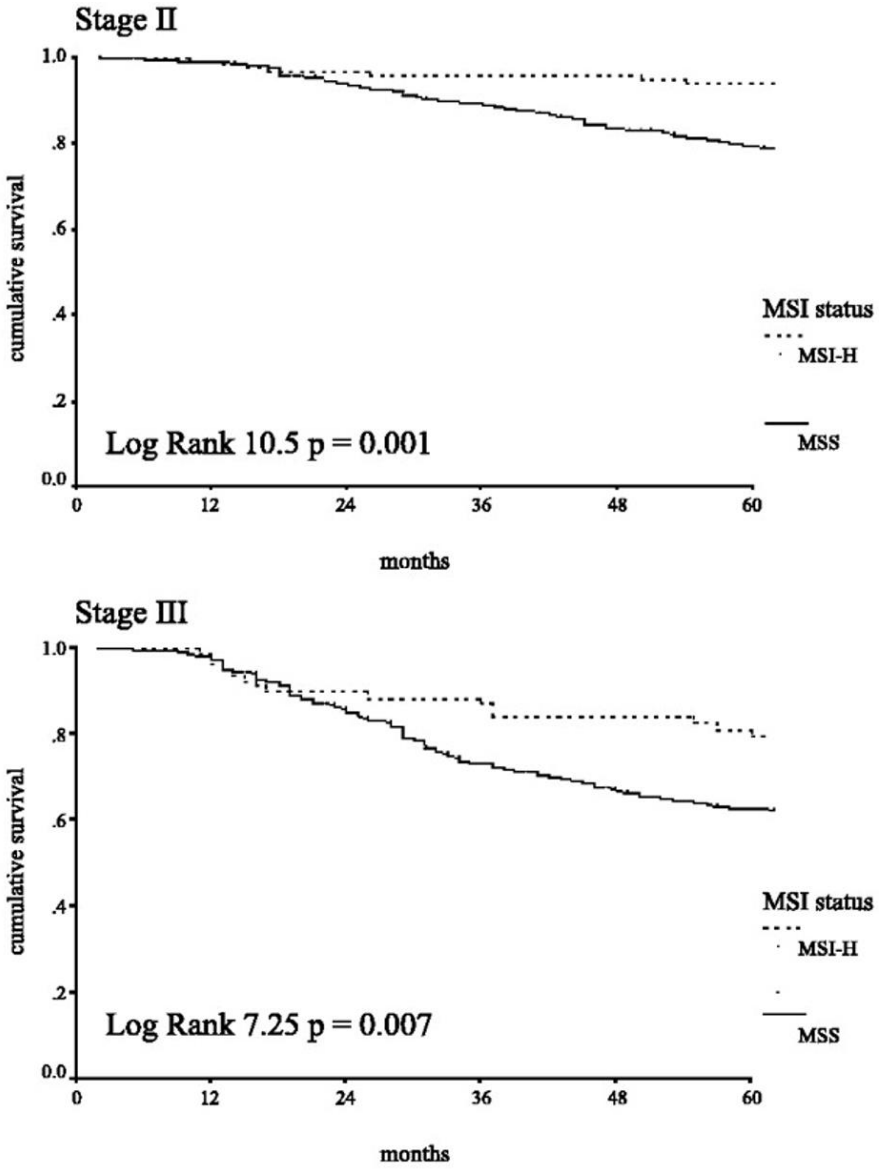
Bonneville et al. JCO Precisio

MSI- is both Prognostic & Predictive Biomarker

- Improved overall survival in stage II and III CRC with MSI-H tumors

- High efficacy of checkpoint inhibitors in MSI-High tumors

- Fluorouracil-based chemotherapy is less effective in MSI-H patients.



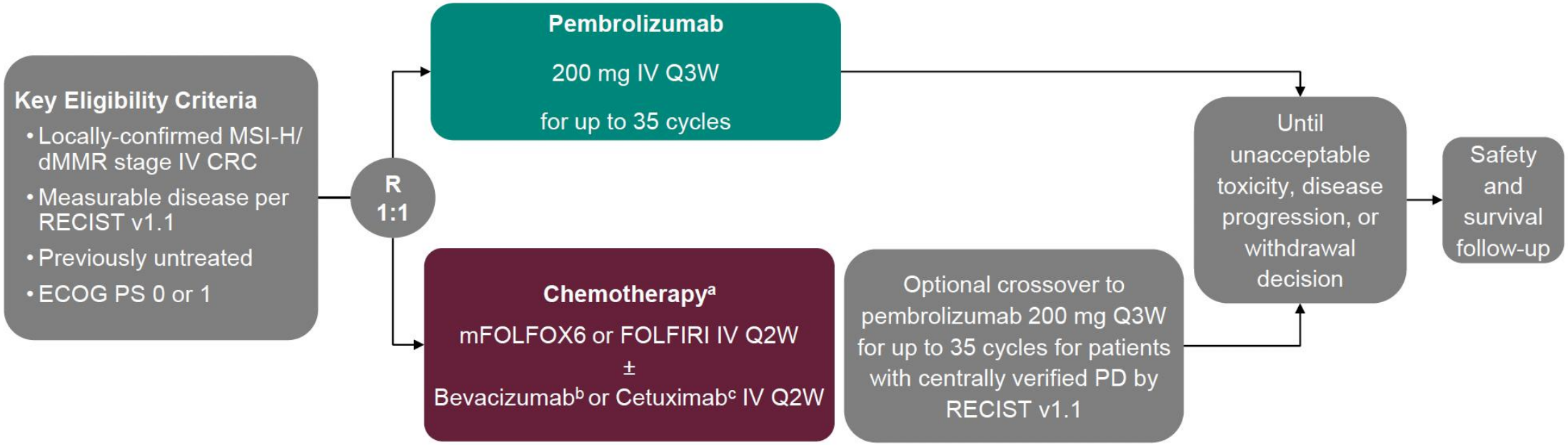
MMR-D and MMR-P CRC: 2 Different Clinical Entities

MMR-Proficient CRC	MMR-Deficient CRC
Approx. 85%	Approx. 15%
Less Favorable Survival	Better Survival
5FU based chemo works better	5FU based chemo is less effec
Immunotherapy less effective	Immunotherapy very effective
Chemo- SOC in mCRC	Immunotherapy SOC mCRC

Early Signals- Immunotherapy works better in both **early stage** Proficient and

Immunotherapy Trials in MMR-Deficient Metastatic CRC and Localized Colon Cancer

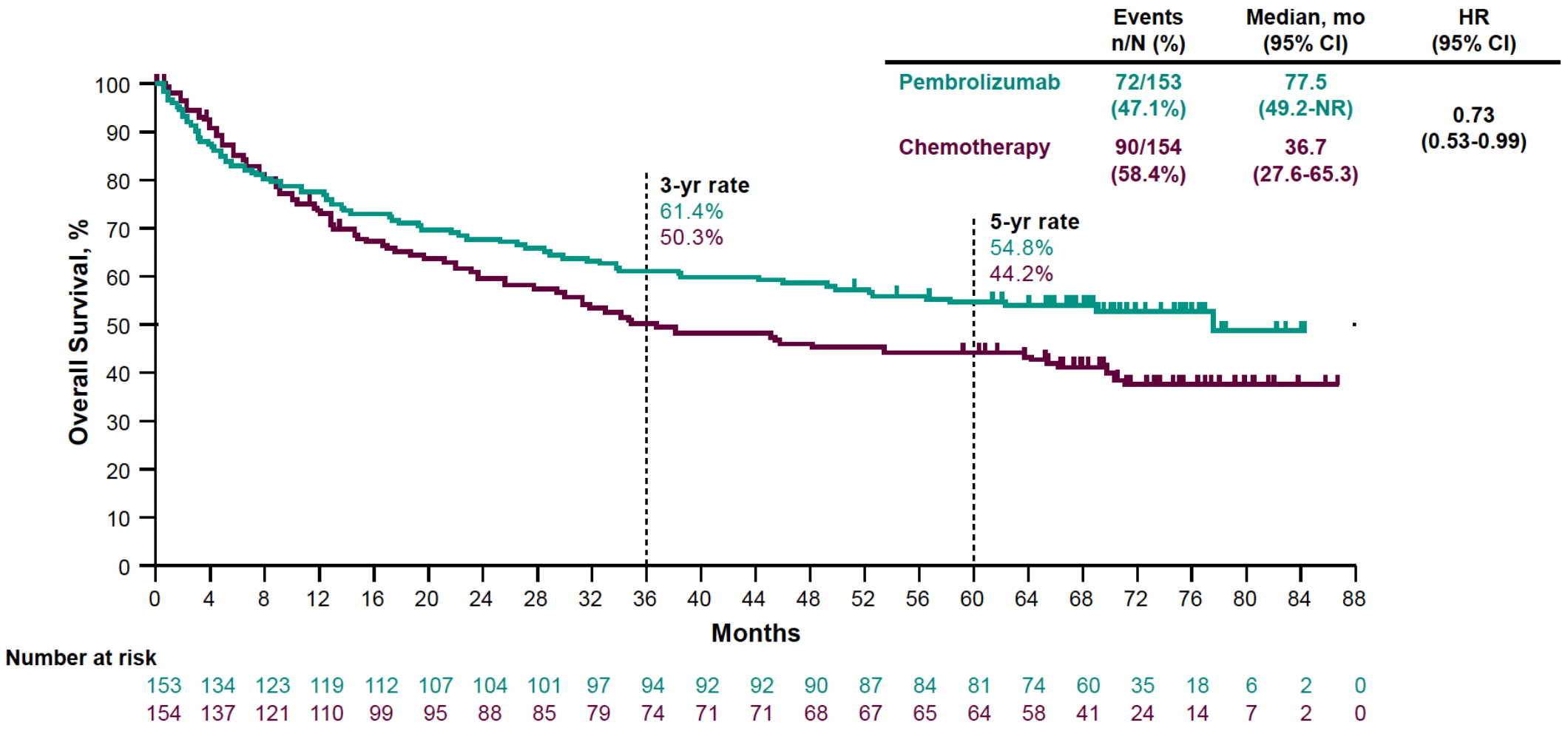
Keynote 177- Is immunotherapy better than standard chemo in stage 4 MSI-H CRC?



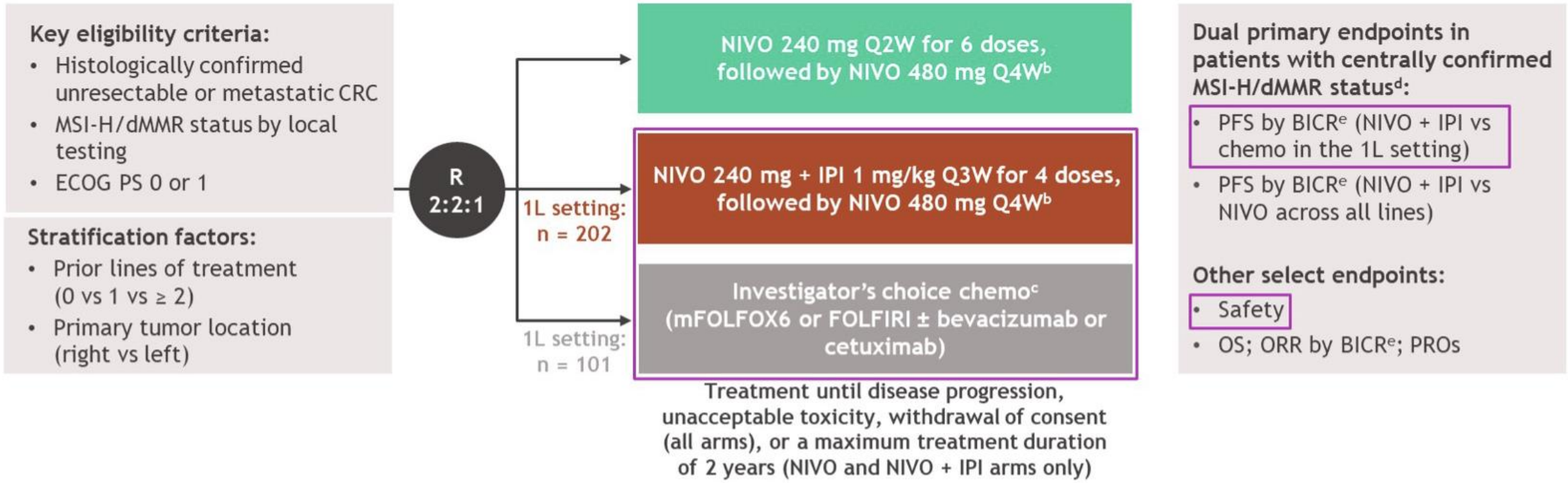
- **Dual primary end points:** PFS per RECIST v1.1 by BICR; OS
- **Secondary end point:** Safety
- **Exploratory end point:** DOR per RECIST v1.1 by BICR

- **Median time from randomization to data cutoff:** 73.3 months (6.1 years; range, 64.9-89.2 months)

Improved Overall Survival with Pembrolizumab



Checkmate 8HW- Can dual immunotherapy improve survival in MSI-H mCRC



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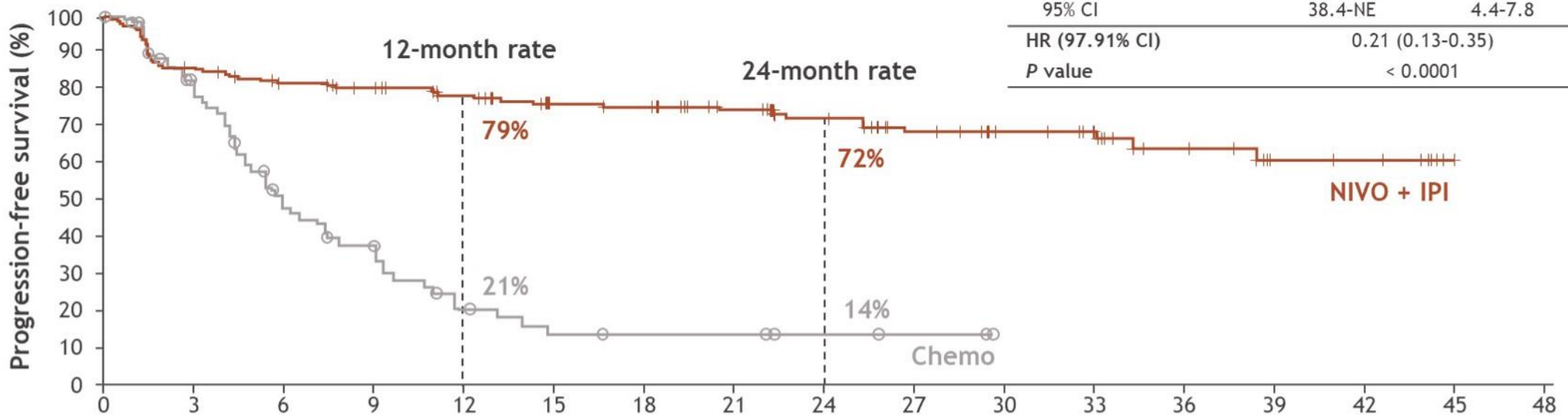
NIVO +IPI clearly improved PFS

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 171)	Chemo (n = 84)
Median PFS,[a,b] mo	NR	5.9
95% CI	38.4-NE	4.4-7.8
HR (97.91% CI)	0.21 (0.13-0.35)	
P value	< 0.0001	



No. at risk																	
NIVO + IPI	171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Chemo	84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

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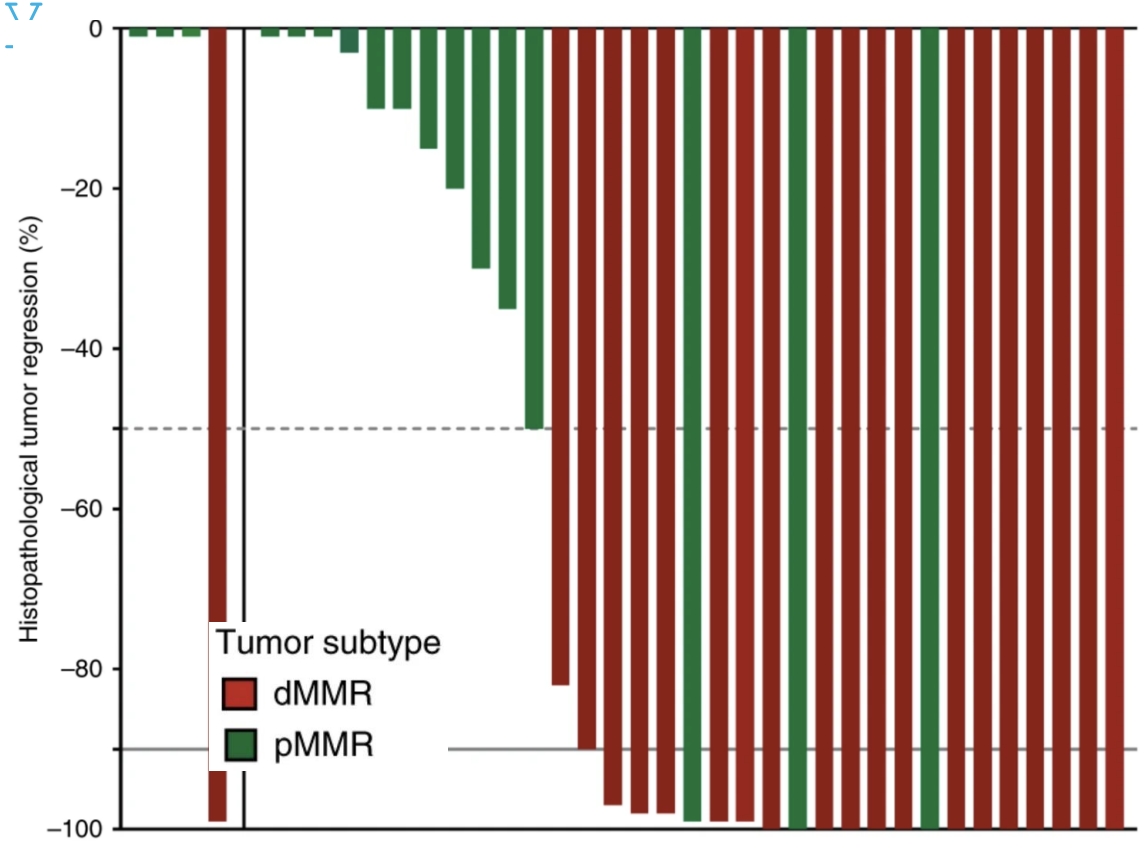
NICHE-1 Study

Patients with dMMR or pMMR non-metastatic tumors received a single dose of ipilimumab and two doses of nivolumab before surgery

	dMMR tumors ($n = 21$)	pMMR tumors ($n = 19$)
Age at enrollment (years)		
Median (range)	58.4 (22-82)	65.9 (44-77)
Sex (n (%))		
Female	12 (57)	10 (53)
Male	9 (43)	9 (47)
Eastern Cooperative Oncology Group performance status		
0	21 (100)	19 (100)
Clinical disease stage (n (%))		
I	2 (9.5)	5 (20)
II	2 (9.5)	7 (35)
IIIA	1 (4.8)	1 (5)
IIIB	10 (47.6)	6 (30)
IIIC	6 (28.6)	1 (5)
Primary tumor location (n (%))		
Right colon	14 (67)	8 (42)
Left colon	5 (24)	11 (58)
Transverse colon	2 (10)	1 (5)
Lynch syndrome	7 (33)	0 (0)



Pathological response was observed in 20/20 (100%) dMMR tumors with 12 pathological complete responses. In pMMR tumors, 4/15 (27%) showed pathological responses.

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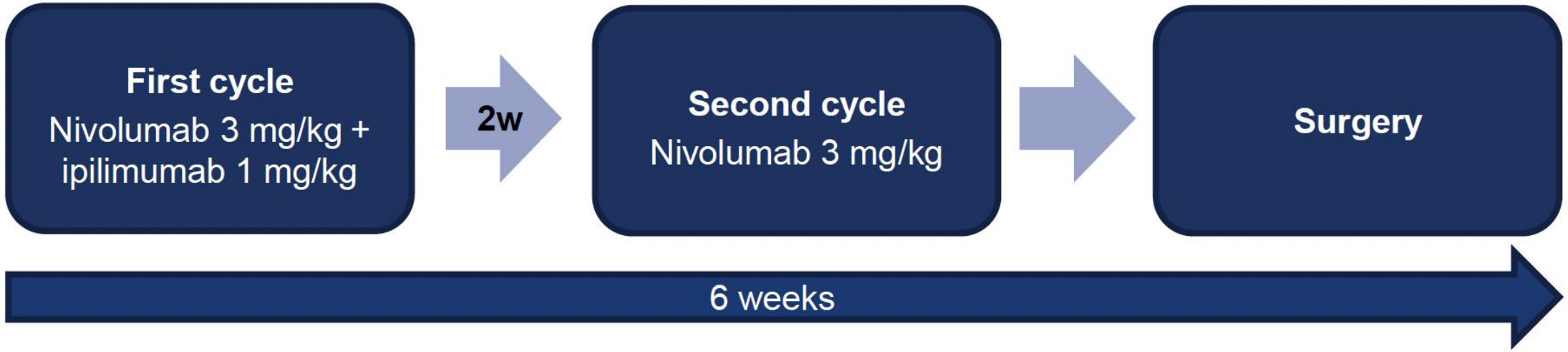
NICHE-2: Neoadjuvant immunotherapy in locally advanced MMR-deficient colon cancer



Key eligibility criteria

- Non-metastatic dMMR colon cancer, previously untreated
- cT3 and/or N+ based on radiographic staging
- No clinical or radiologic signs of obstruction or perforation

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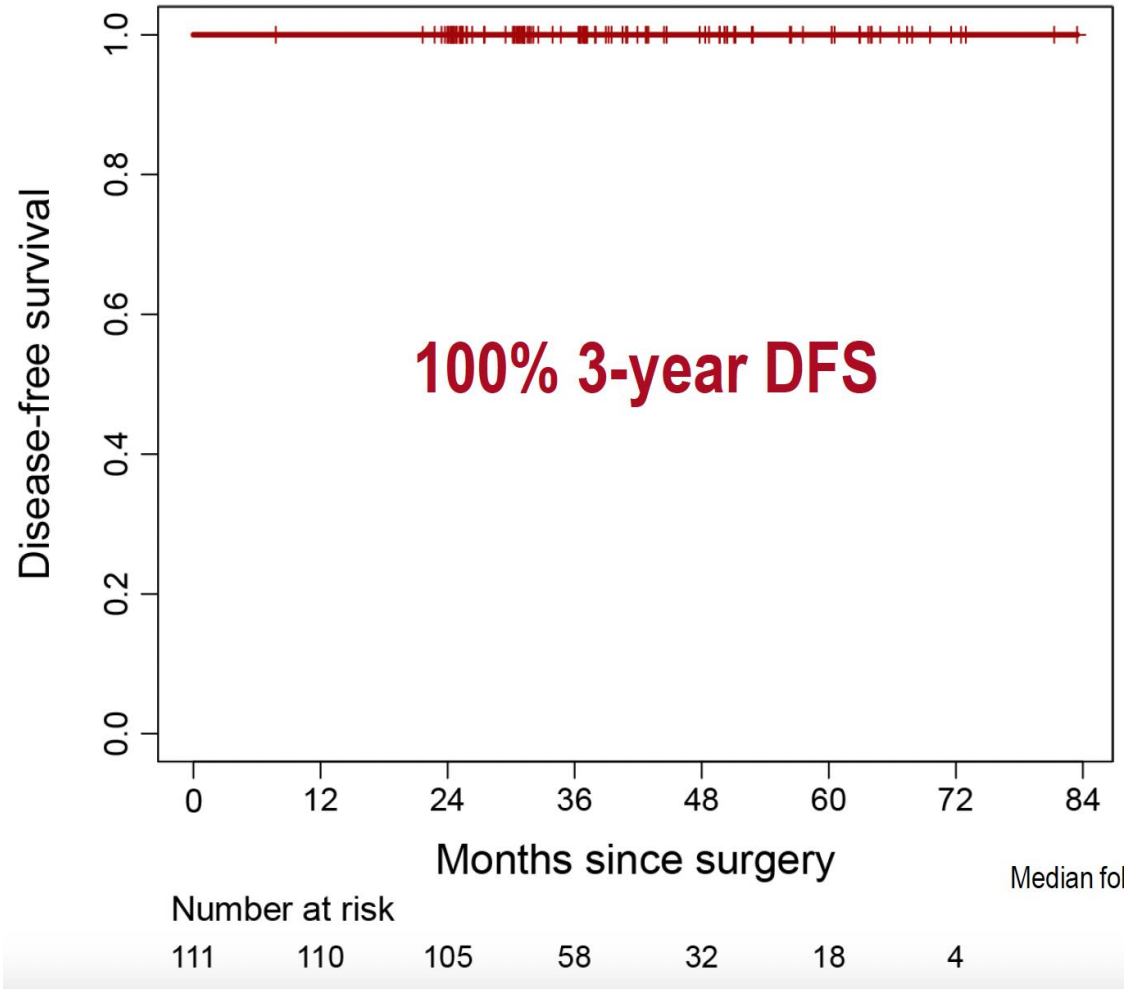
Results From NICHE-2 Study

Characteristic	All patients, *n* = 115
Median age (range) – yr	60 (20-82)
Female sex – no. (%)	67 (58)
Tumor stage – no. (%)	
cT2	17 (15)
cT3 or cT3-4	24 (21)
cT4a	41 (36)
cT4b	33 (29)
Nodal status – no. (%)	
cN0	38 (33)
cN+	77 (67)
Lynch syndrome – no. (%)	37 (33)

Five patients had grade 3 or 4 adverse events



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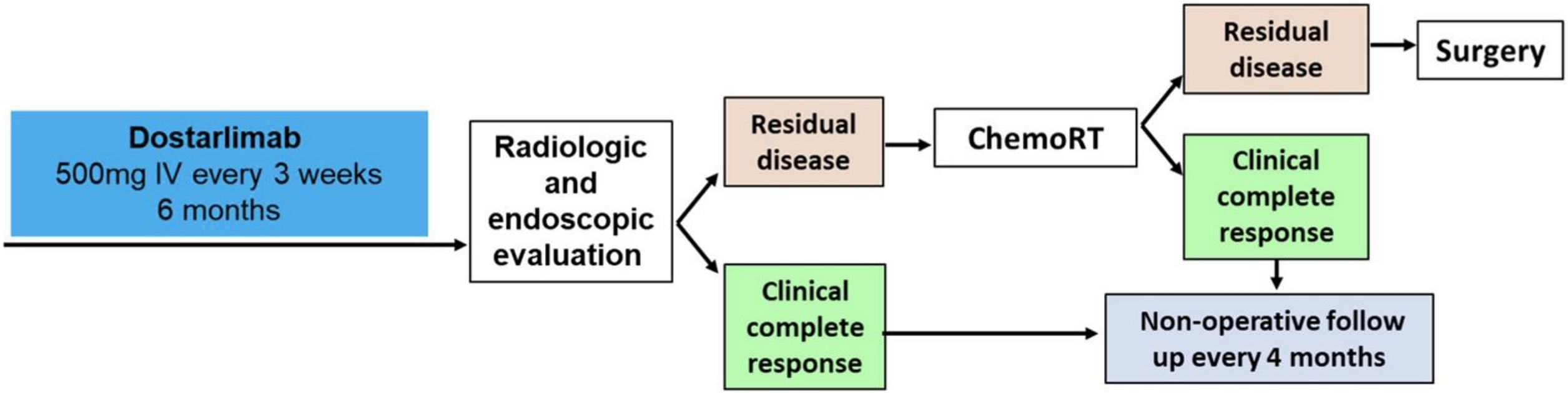
Take Away Points From MMR-Deficient Colon Cancer

- Immunotherapy is standard of care for initial management of stage 4 MMR-Deficient CRC
- Pembrolizumab and IPI/NIVO are superior to traditional chemotherapy
- Immunotherapy is safe and side effects are manageable
- There is promising data for use of immunotherapy in locally advanced colon cancer

Neo-Adjuvant Immunotherapy in MMR-deficient Locally Advanced Rectal Cancer

Dostarlimab- Study Design



Cercek et al. ASCO 20

Patient Characteristics

Mostly locally advanced rectal cancer

85% node positive

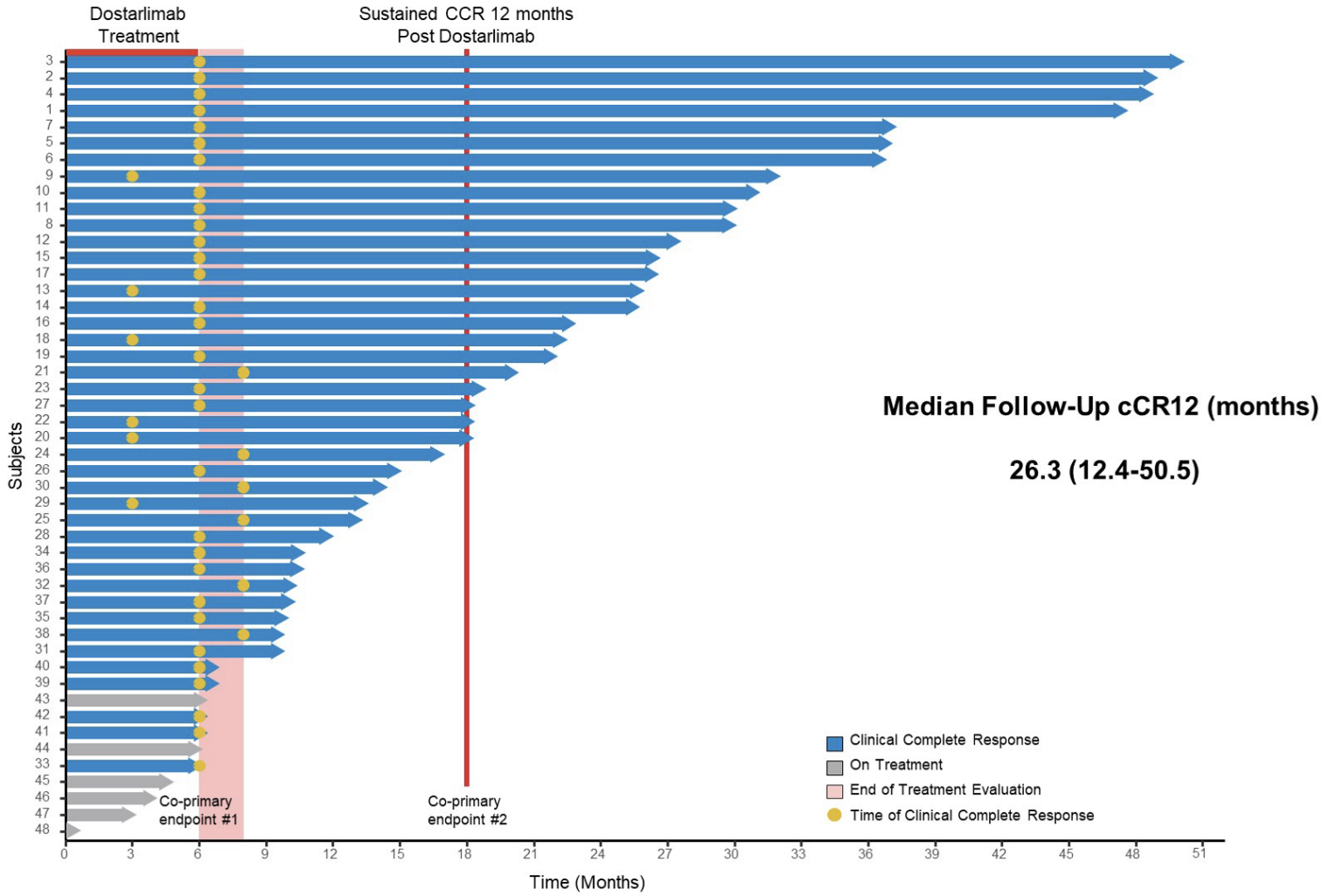
31% T4 primary tumors

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)**

Cercek et al. ASCO 20

Durable Responses

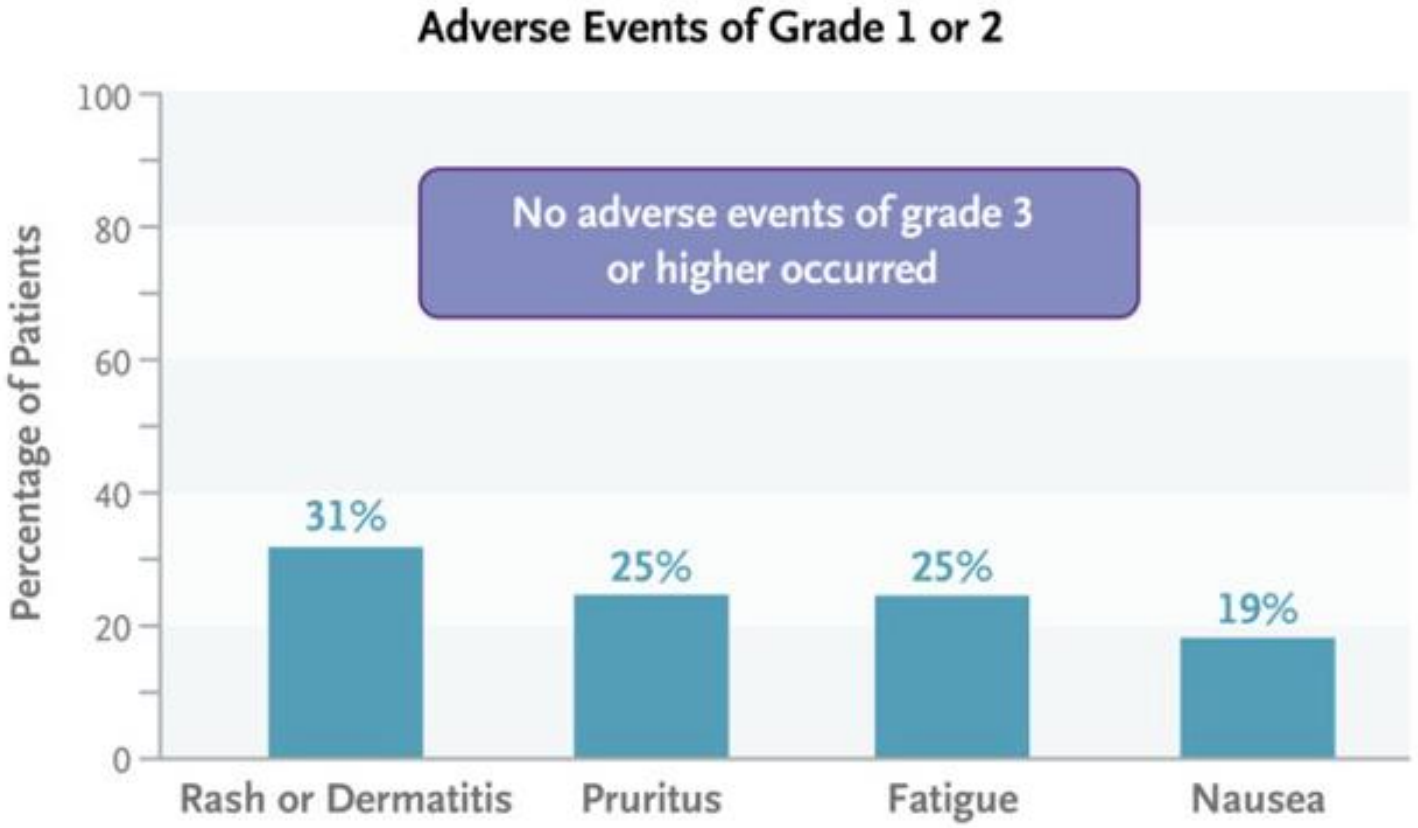
- 100% complete clinical response in 42 patients
- Durable responses
- No recurrence for over 2 years
- No patient required chemotherapy, radiation or surgery



Cercek et al. ASCO 2(

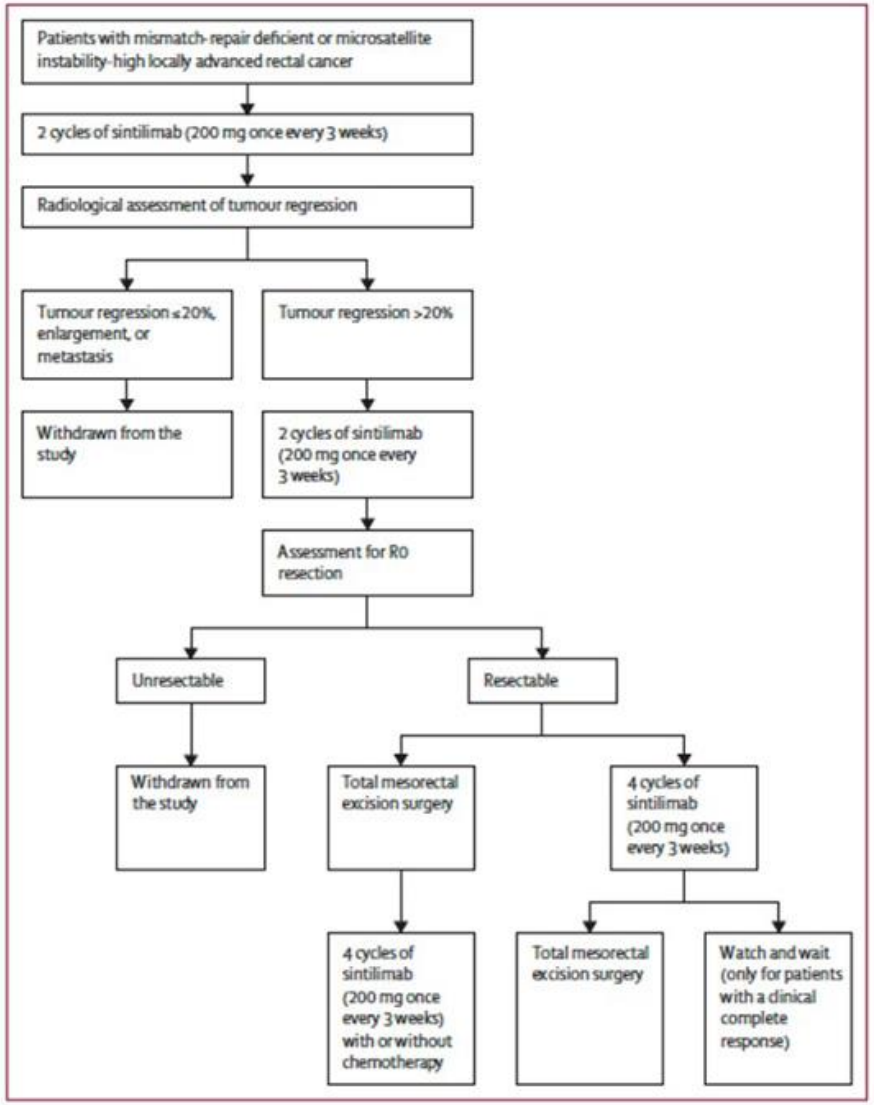
Toxicity

- Very well tolerated
- No grade 3 or higher adverse events



Cercek et al. NEJM 2

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



	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**

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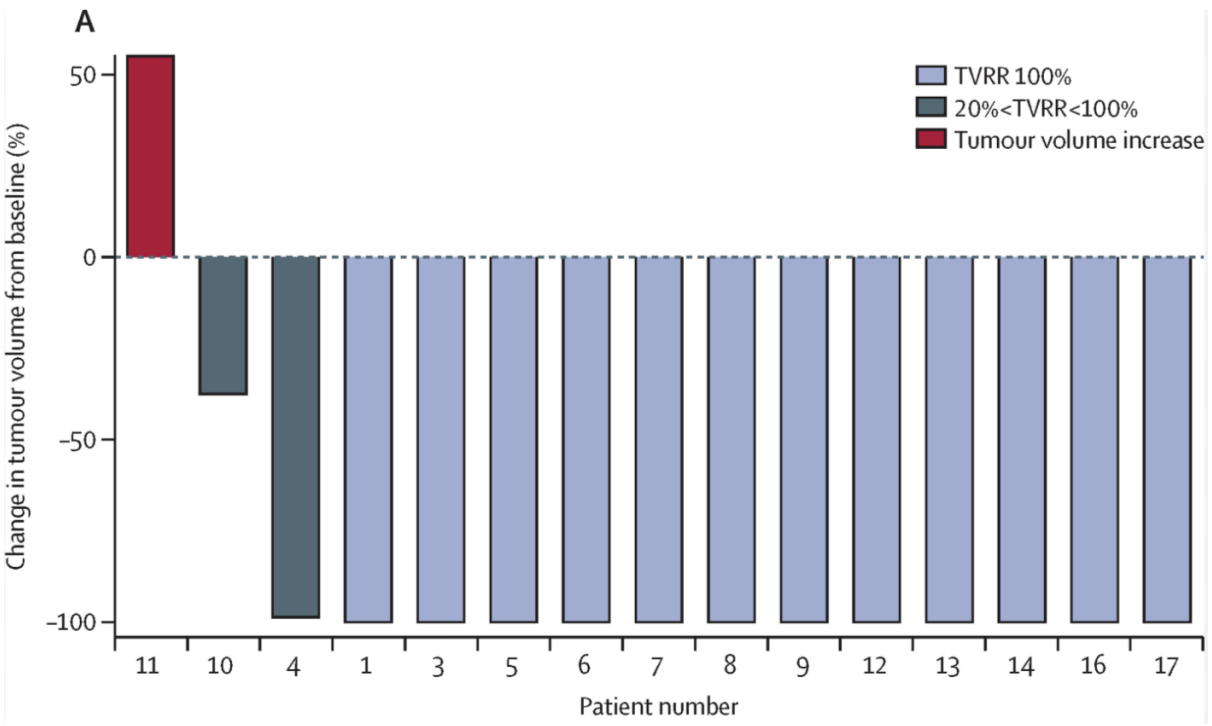
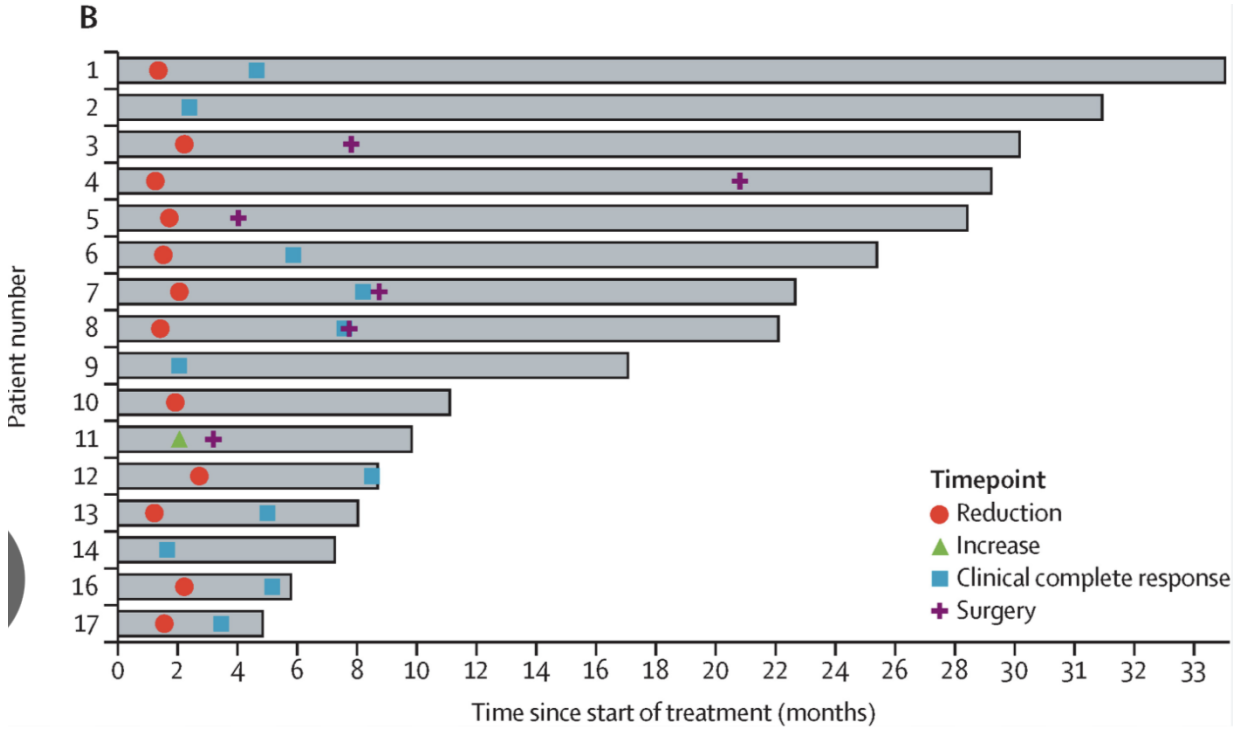
Results- High Responses with Sintilimab

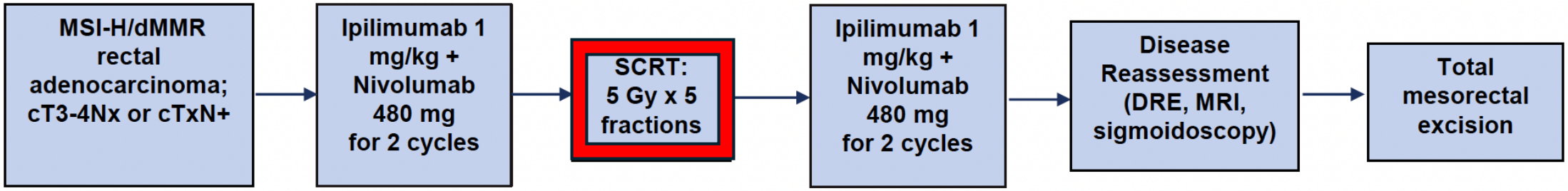




Complete response was noted for 12 (75%; 95% CI 47–92) of 16 patients

Chen et al. Lancet GH

Neoadjuvant nivolumab plus ipilimumab in microsatellite instability-high/deficient mismatch repair rectal tumors: ECOG-ACRIN EA2201



Eligibility:

- cT3/4Nx or cTxN+ rectal adenocarcinoma (within 15 cm of anal verge)
- MSI-H and/or dMMR by local testing
- No active autoimmune disease
- No chronic prolonged systemic steroids

NCT04751370

Statistical Design:

- Two-stage, single-arm, phase II multicenter study (N = 31)

Primary endpoint:

- pCR rate (or pCR + cCR if low TME rate)

1 cycle = 28 days
Short course radiation therapy (SCRT): 25 Gy

Results- 57% complete response

	n = 14
pCR plus cCR rate (95% CI)	8/14 57.1% (31.2%-83.1%)
pCR rate of those who underwent TME	3/3 (100%)

Protocol treatment received (n = 14):

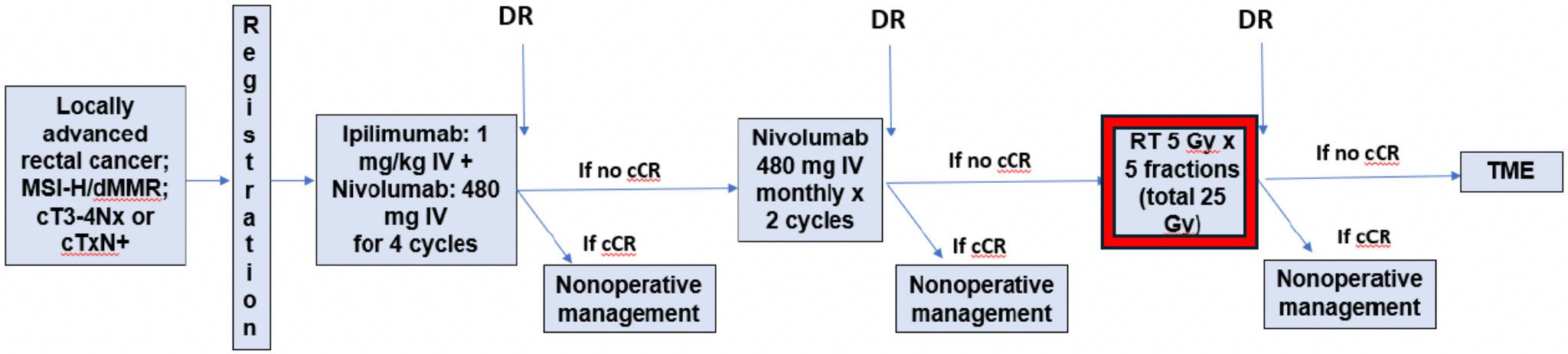
- Nivo/ipi: 14/14 patients (range, 1-4 cycles; median 4; mean 3.29)
- SCRT: 12/14 patients
- TME: 3/14 patients

Reasons for not completing all protocol-specified treatment (n=11):

- TME deferred due to achievement of cCR (n=5)
- Subject consent withdrawal (n=2)
- Adverse events (n=4)

Change in the study design due to results of other trials showing improved outcomes with immunotherapy alone

EA2201 Schema



Primary endpoint: Clinical complete response rate (cCR)

All 4 cycles of nivolumab/ipilimumab upfront (prior to consideration of SCRT an
with 2 additional cycles of nivolumab monotherapy to be given prior to SCRT and

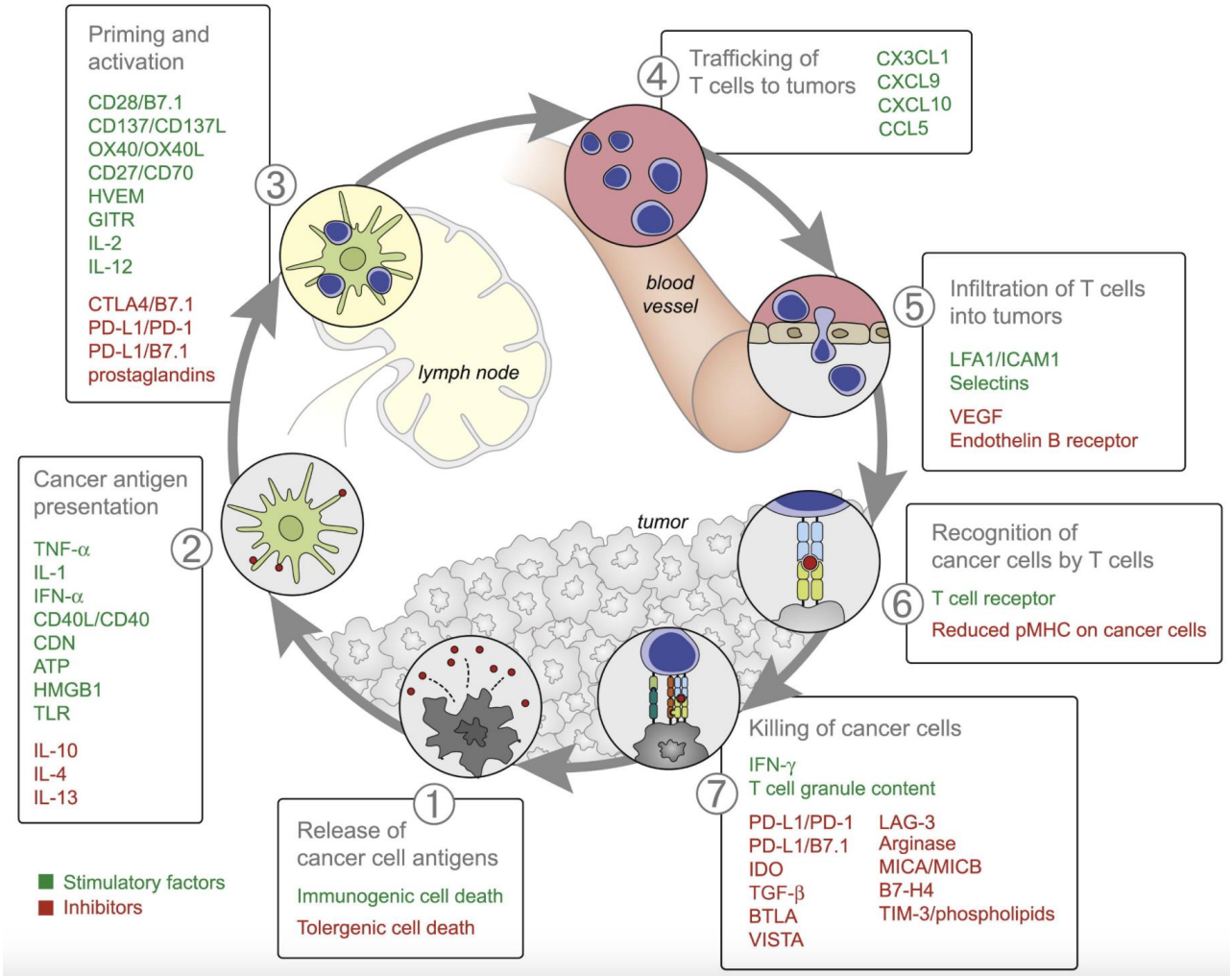
Kristen K. Ciombor, ESMO

Immunotherapy in MMR-Proficient Colon and Rectal Cancer

MMR-Proficient CRC and Immunotherapy

- MMR-Proficient tumors are biologically different
- MMR proficient tumors are typically characterized by an immune-excluded microenvironment
- Reduced or inactive CD8 T-cell lymphocytes and diminished expression of immune checkpoint proteins on the tumor cells.
- Clinical trials have evaluated the combination of checkpoint inhibitors with other immunomodulatory cancer therapies to increase cellular immunogenicity.
- To Date: No major success

90-95% of all IARC



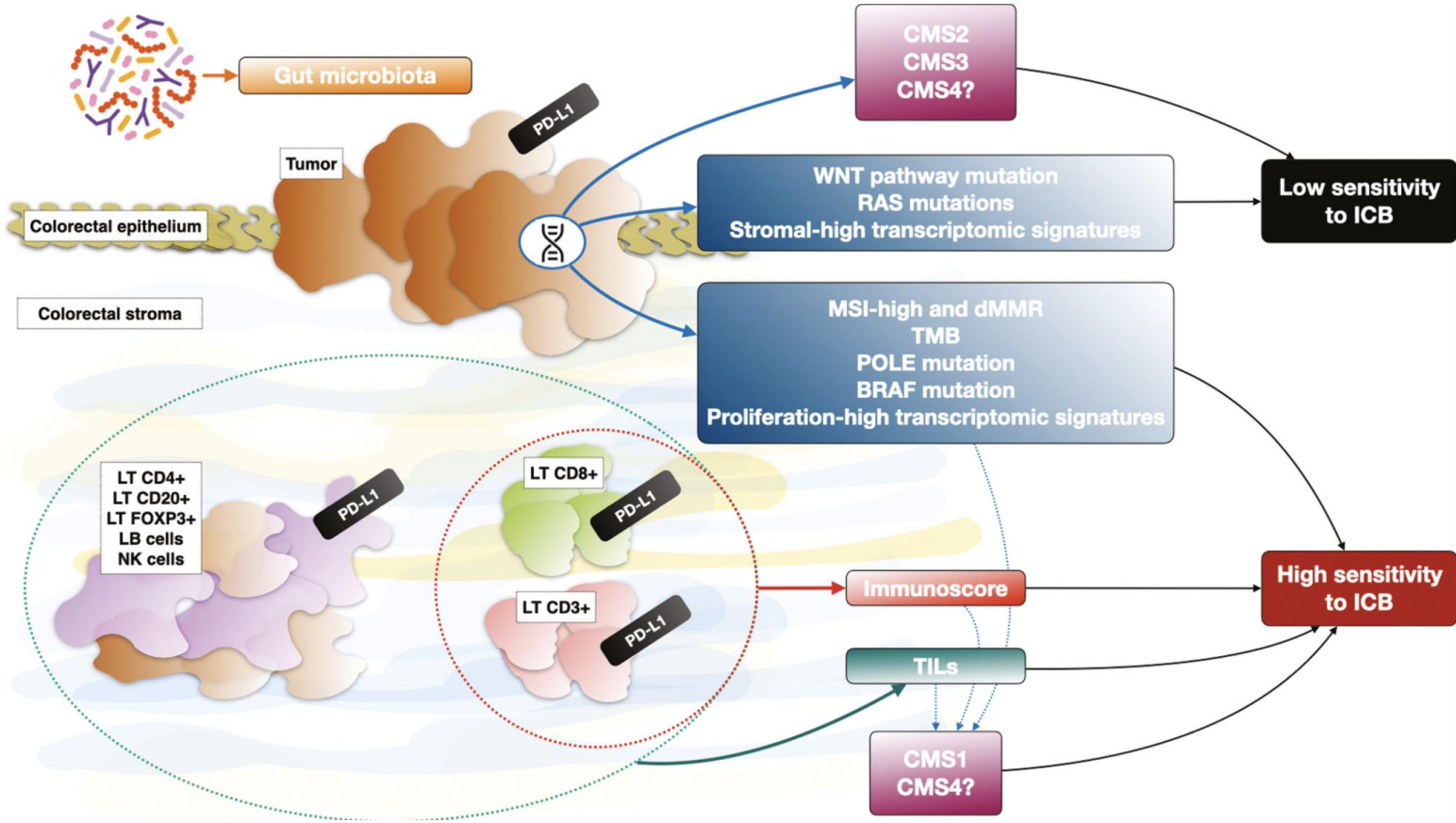
Chen et al. Immunity

Predictive Biomarkers for Immunotherapy in MSS CRC

No single biomarker can independently predict responses to ICB in patients with CRC except MMR status

Potential Biomarkers

- Immunoscore, TILs, TMB
- Intestinal Microbiota Signature
- POLE mutations

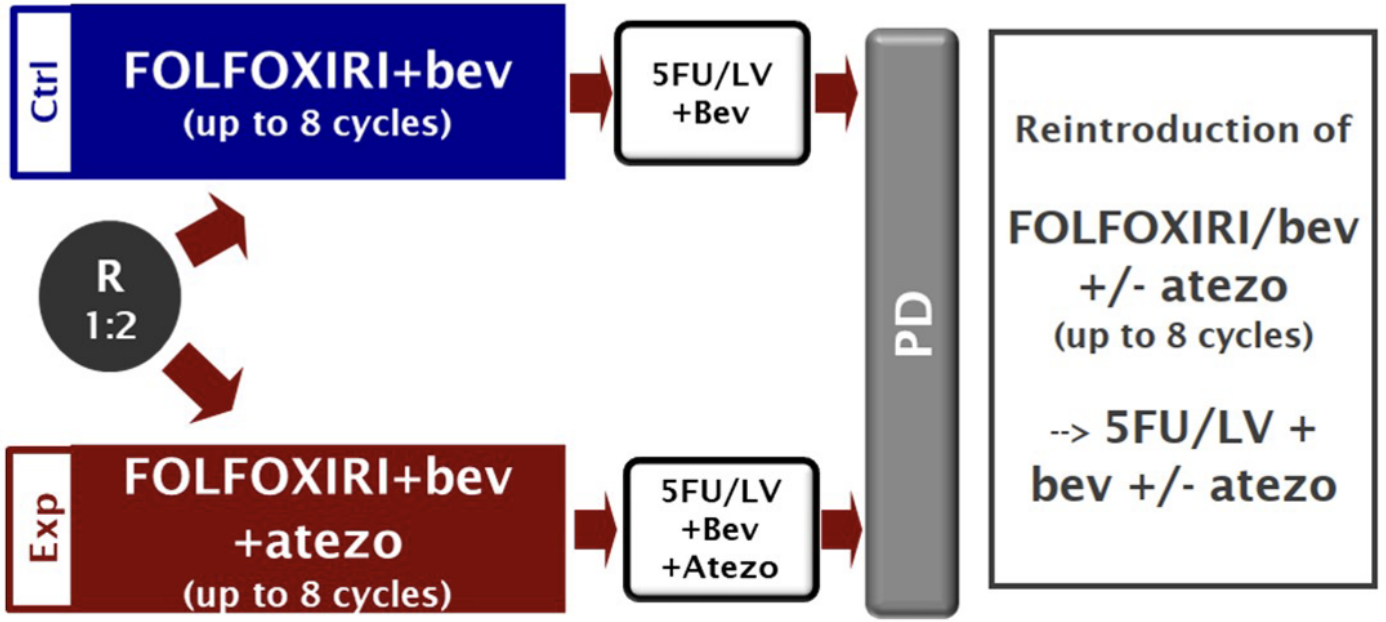


González-Montero et al. The Oncolog

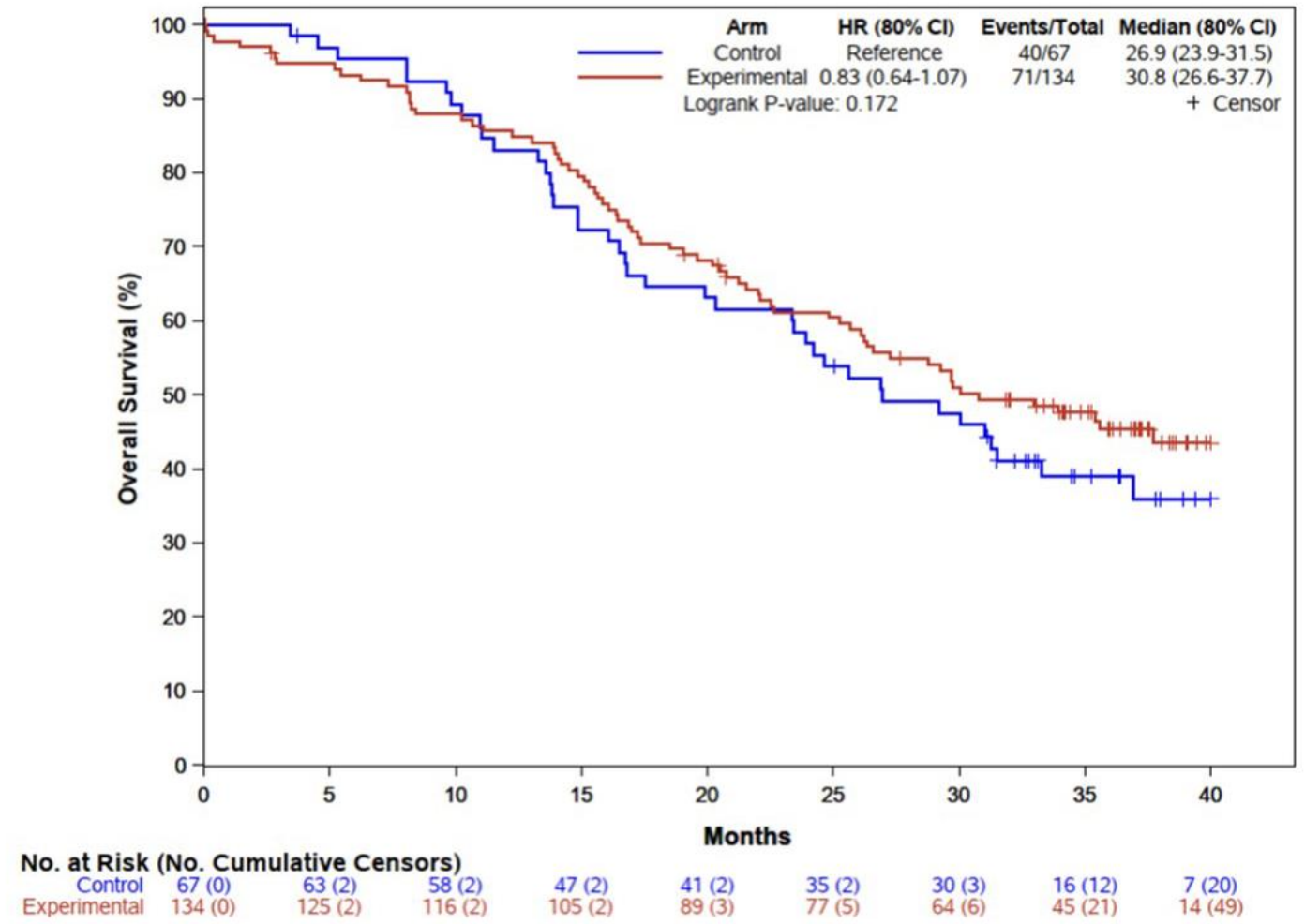
Immunotherapy in CRC-MSS in first line setting
ATEZOTRIBE Study

Key eligibility criteria

- Previously untreated, unresectable and RECIST v1.1-measurable mCRC
- Age 18-75 years
- ECOG PS ≤ 2 (ECOG PS= 0 if age= 71-75 years)
- Adjuvant oxaliplatin-containing chemotherapy not allowed
- Adjuvant fluoropyrimidine monotherapy allowed if more than 6 months elapsed between the end of adjuvant and first relapse
- Adequate bone marrow, liver and renal functions
- No contraindications to ICI



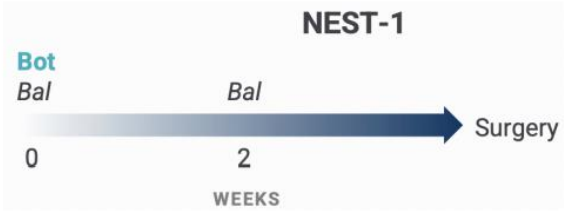
No Overall Survival Benefit of addition of Atezolizumab in pMMR CRC



Neoadjuvant botensilimab plus balstilimab in resectable MMR proficient and deficient CRC NEST Study

NEST Protocol (NCT05571293):

- **NEST-1** 1 dose of 75mg Botensilimab (BOT)
  - 2 doses of 240mg Balstilimab (BAL) 2 weeks apart



- **NEST-2**
  - 1 dose of 75mg Botensilimab (BOT)
  - Up to 4 doses of 240mg Balstilimab (BAL) 2 weeks apart

Resectable non-metastatic colon cancer

No contraindication for IO administration

Surgical resection occurs within 1-6 weeks after completion of therapy

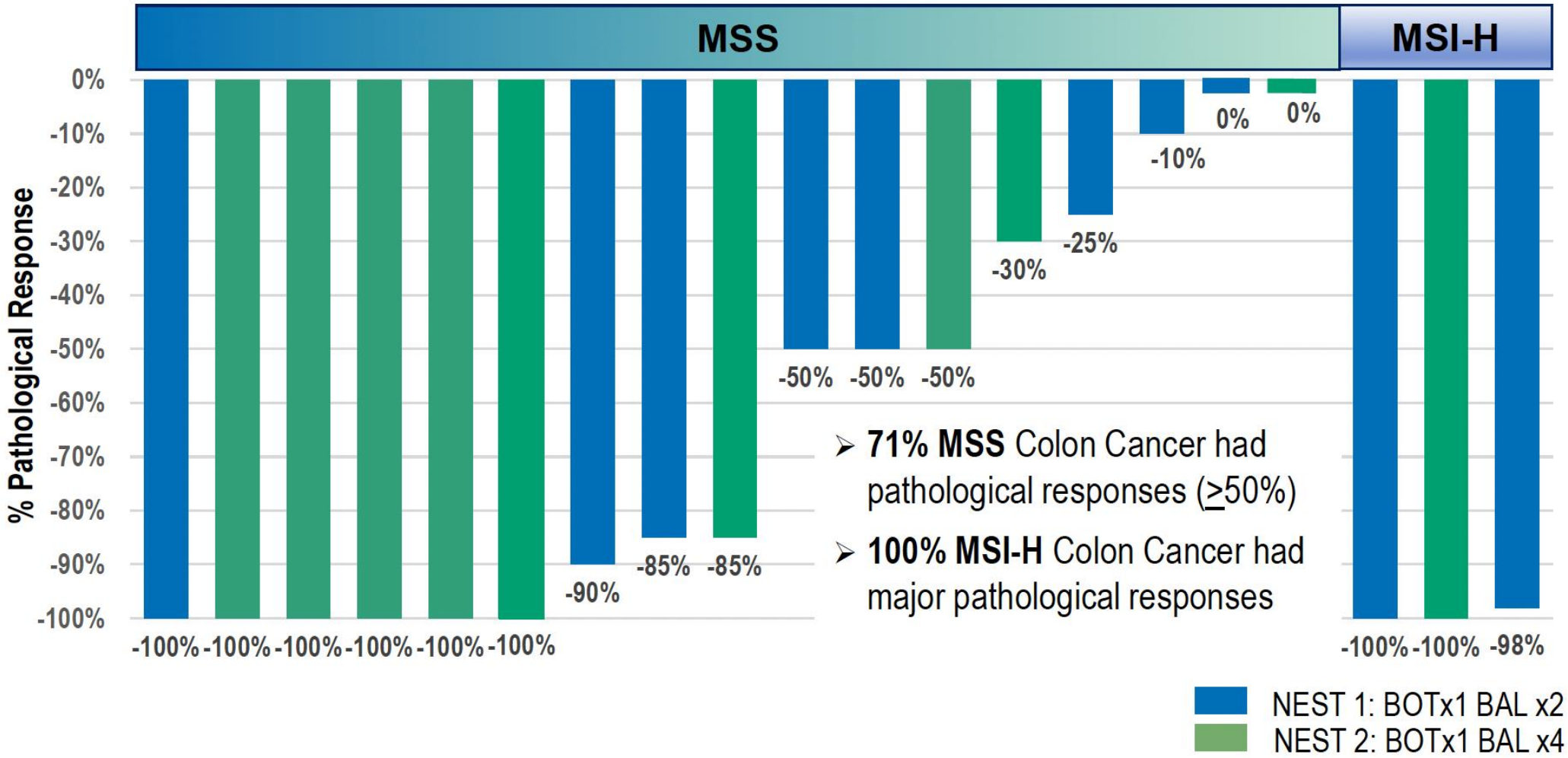
Patient Characteristics and AEs

	NEST 1 (N=10)	NEST 2 (N=10)
Median Age (range)-yr	67(35-79)	67 (23-76)
Sex (F)	70%	40%
Median Time to OR from C1D1 (range), days	29.5 (21-38)	57 (45-81)
Adjuvant Chemotherapy	70%	Too early to report
Unresolved irAE*	0%	0%

*2 patients with Grade 3 diarrhea/colitis managed with infliximab and short course steroids

Neoadjuvant BOT/BAL was **safe** and did **not delay** planned surgery

Exceptional Responses in pMMR



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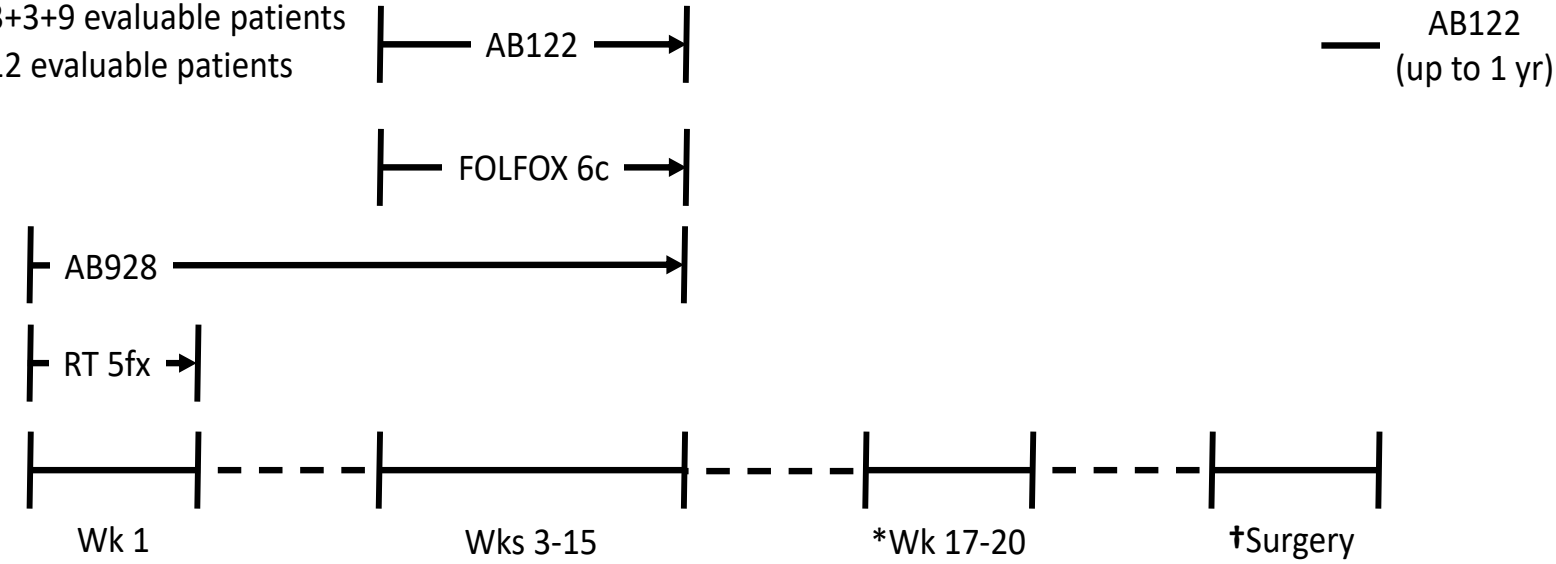
Ongoing Studies

A Phase I-II Study to Test the Safety and Efficacy of PD1 Inhibitor (AB122) and Dual Adenosine Receptor Antagonist (AB928) with Chemotherapy after Short-Course Radiation [**PANTHER** Trial] for MSS Rectal Cancer - **NCT05024097**

Hypothesis: Short-course radiotherapy combined with the potent dual antagonist of adenosine receptors, Etrumadenant (AB928) and the PD1 checkpoint inhibitor, Zimberelimab (AB122) synergize to harness T-cell mediated rejection of rectal tumors resulting in better pathologic downstaging (≥ 45% CRs) as compared to historical controls (≤ 25% CRs).

Enrollment Criteria
Treatment Naïve (cT3N0 or cT1-3N1)
ECOG PS 0-1
No prior IO/pelvic RT
Stage 1: N = 3+3+9 evaluable patients
Stage 2: N = 12 evaluable patients

Part 2: Simon's two-stage design



AB928 150mg PO daily
AB122 240mg IV every 2wks

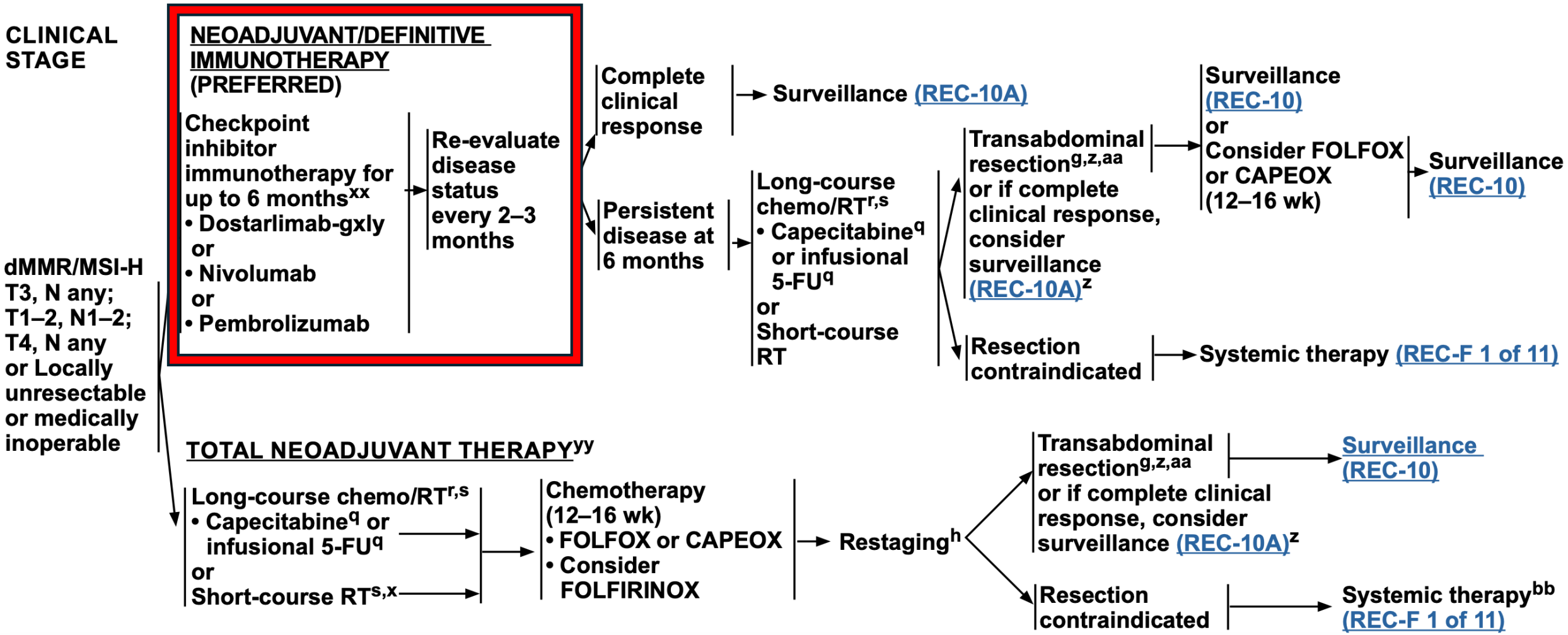
***Clinical Response Assessment**
MRI
DRE
Endoscopy

†Pathologic Response Assessment

Weill Cornell Medicine

Slide Courtesy of Dr. Encouse Golden

NCCN Guidelines for MSI-H Rectal Cancer



Take Away Points!

- It is essential to check MMR status before starting therapy in LARC
- Immunotherapy should be preferred initial treatment for MMR-deficient LARC (unless there is a contraindication)
  - Manageable side effects
  - Higher and durable response
- Duration of therapy?
- Single vs Dual check point inhibitors?
- Long-term data is needed
- Immunotherapy in MMR-proficient LARC is not recommended outside of a clinical trial