

Inmunoterapia en cáncer colorectal localizado



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Immune subgroups of CRC.

MSI-H/MMRD: (POL-E/POL-D)

- High number of neoantigens
- IO is part of the Soc
- IO is more active in Localized settings than in metastatic



MSS/MMRP:

- Low number of neoantigens
- IO is not part of the Soc
- IO is more active in localized setting than in metastatic

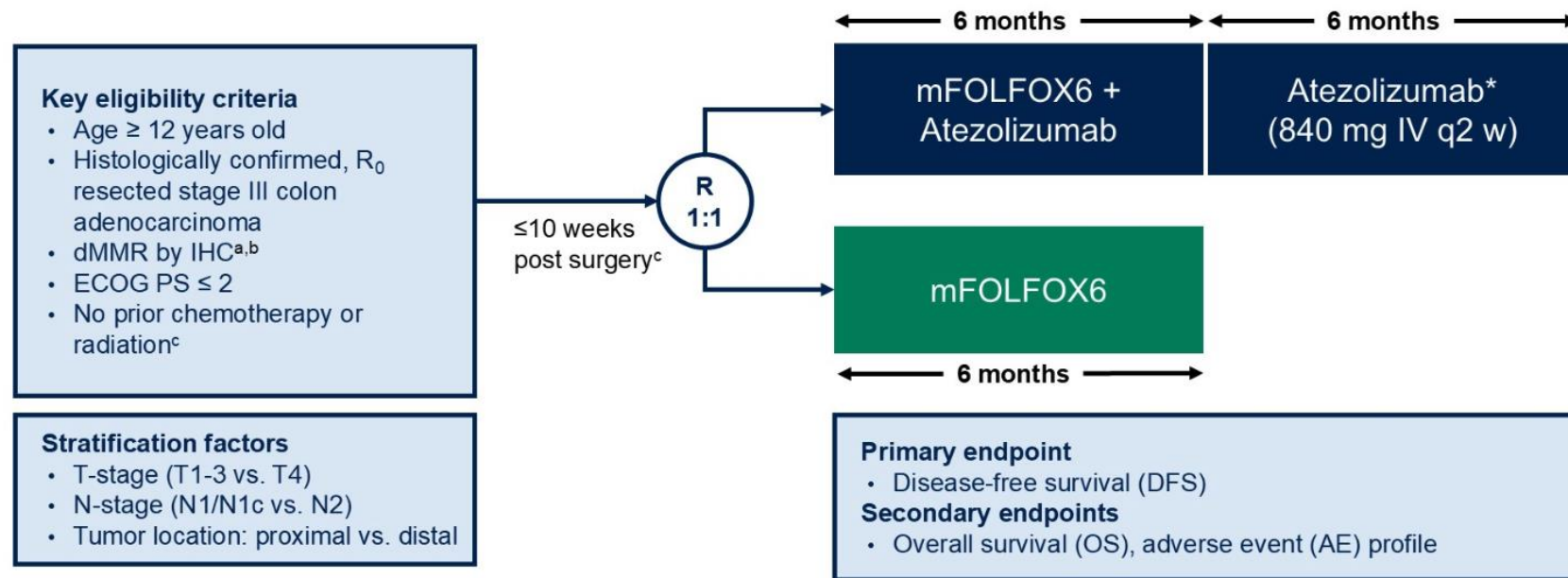
MSI-H/MMRD:

Atomic Trial:

Study Design

4

ATOMIC is a randomized, multicenter, open label phase 3 study



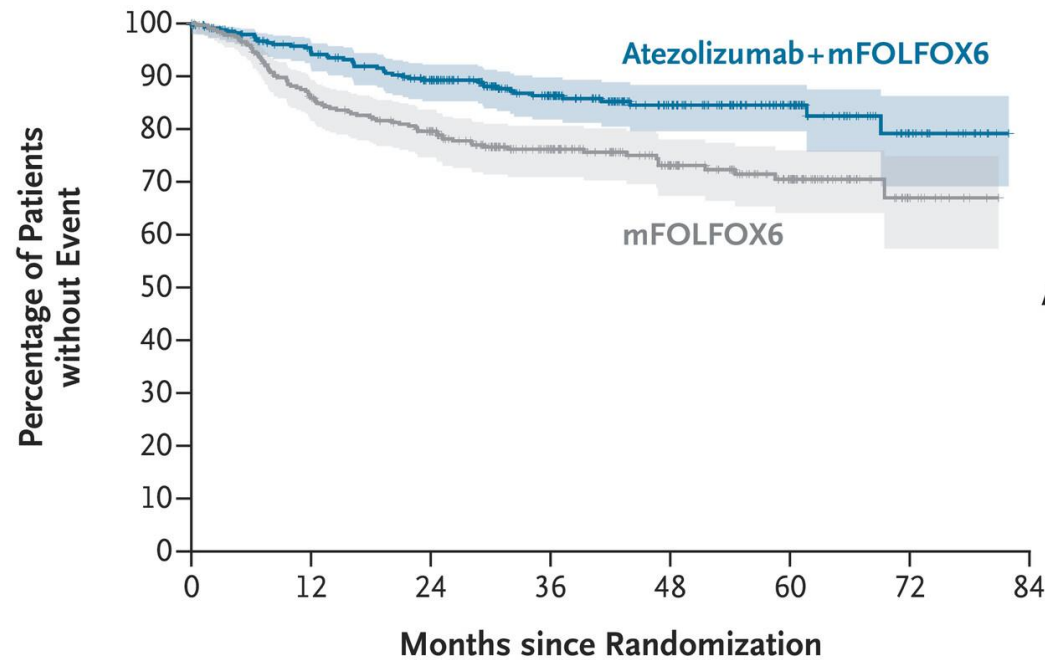
^a dMMR by immunohistochemistry (IHC) locally or at site-selected reference laboratory. Retrospective central confirmation of dMMR also performed.

^b Lynch syndrome included.

^c One cycle of mFOLFOX6 prior to randomization permitted.

*Atezolizumab (anti-PD-L1)

Atomic Trial:

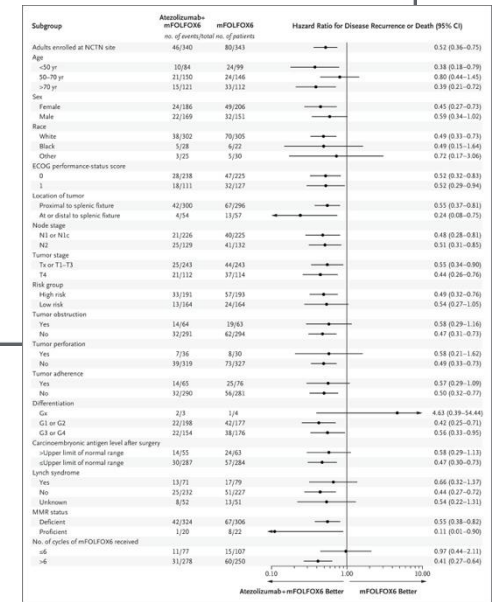


	No. of Events/ Total No. of Patients	3-Yr Disease-free Survival (95% CI) percent
Atezolizumab+ mFOLFOX6	46/355	86.3 (81.8–89.8)
mFOLFOX6	81/357	76.2 (70.9–80.6)

Hazard ratio for disease recurrence or death,
0.50 (95% CI, 0.35–0.73)
Stratified P<0.001 by log-rank test

No. at Risk

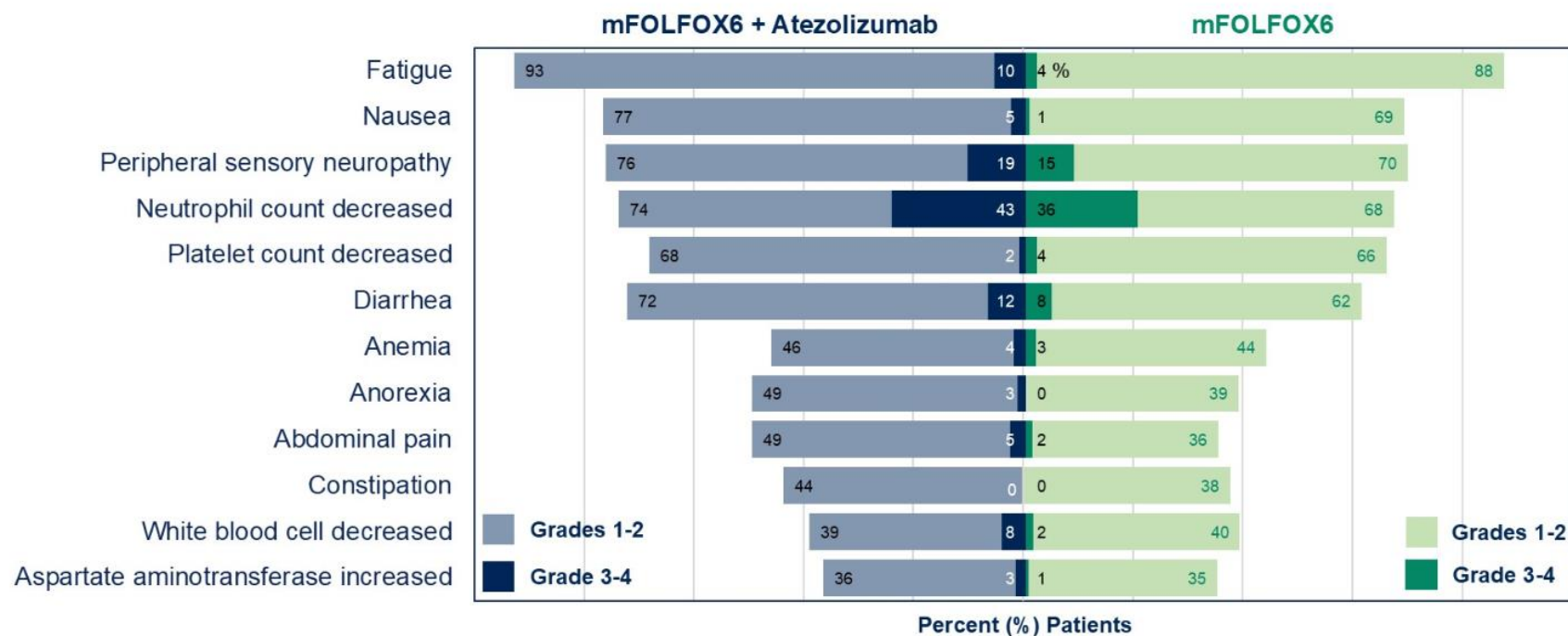
	0	12	24	36	48	60	72	84
Atezolizumab+ mFOLFOX6	355	296	259	181	112	59	17	0
mFOLFOX6	357	264	229	160	109	63	11	0



Atomic Trial:

Patient Safety

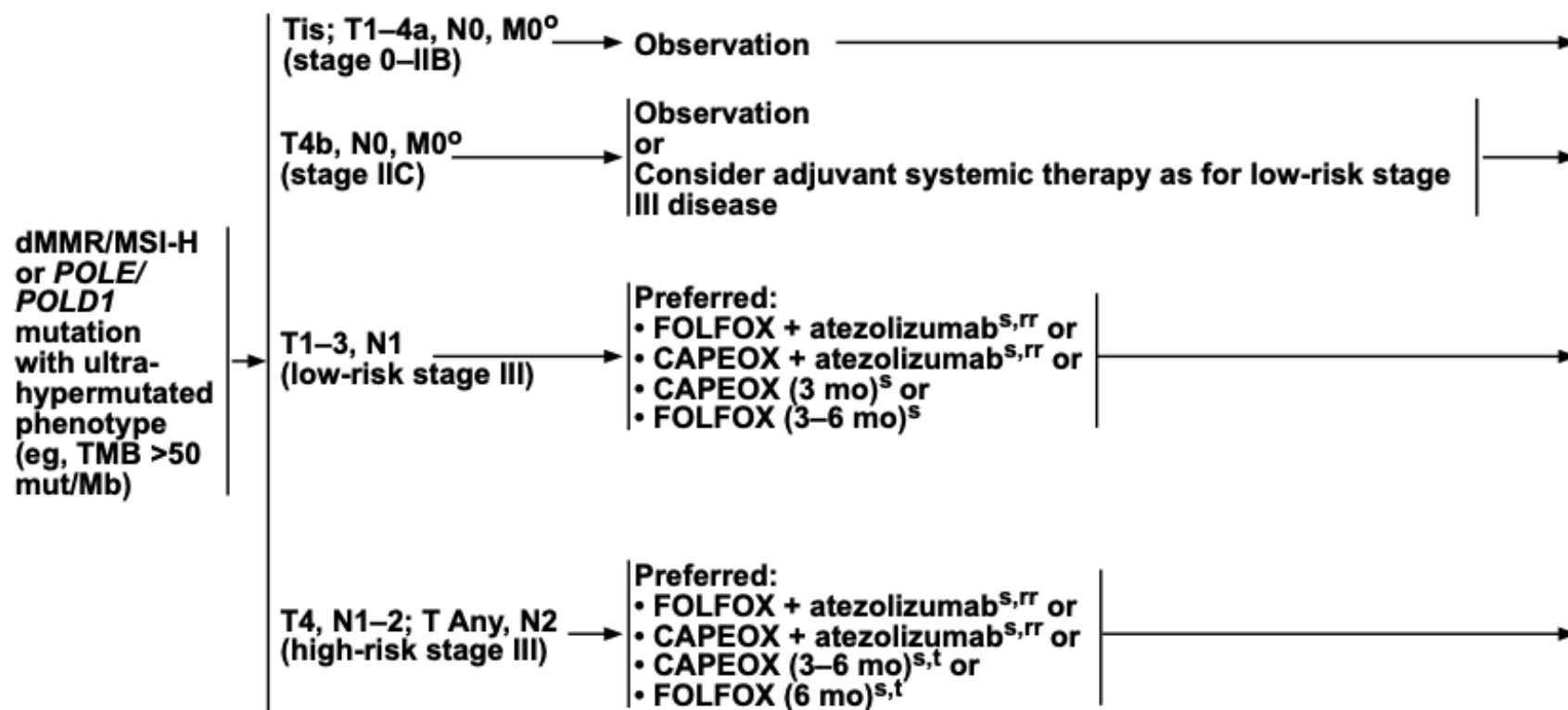
AEs Occurring in > 35% of Evaluable* Patients



	Grades 1-2	Grade 3-4
Neutrophil count decrease	Grade 3, n (%)	100 (28.9%)
	Grade 4, n (%)	49 (14.2%)

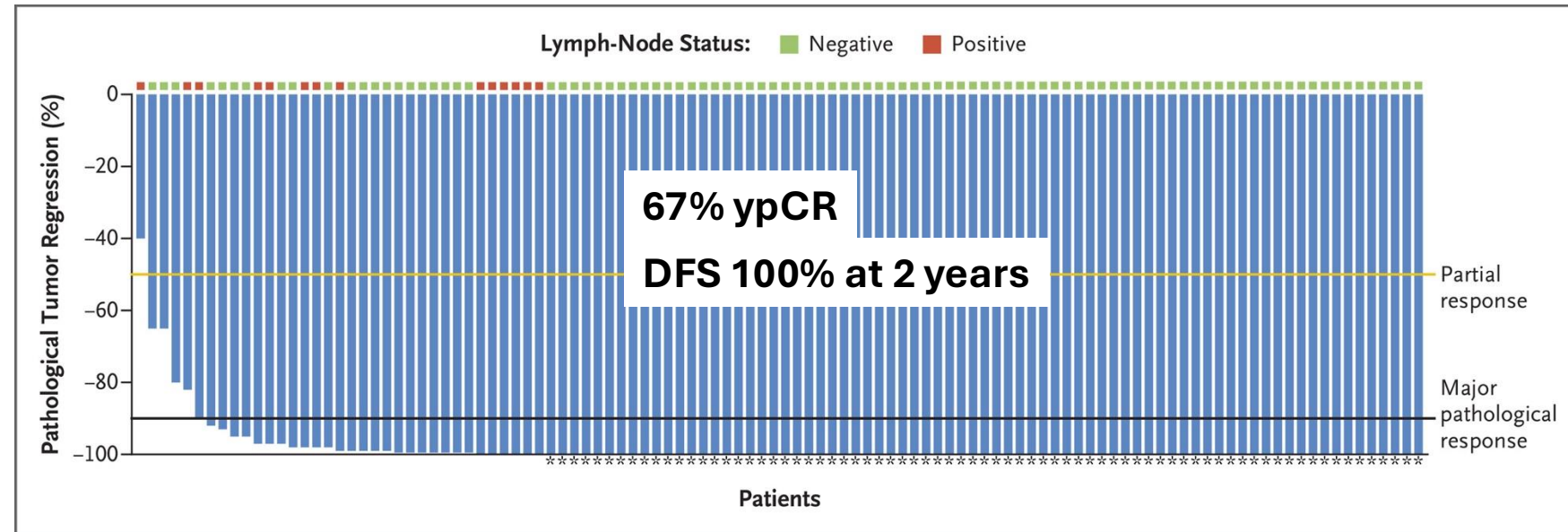
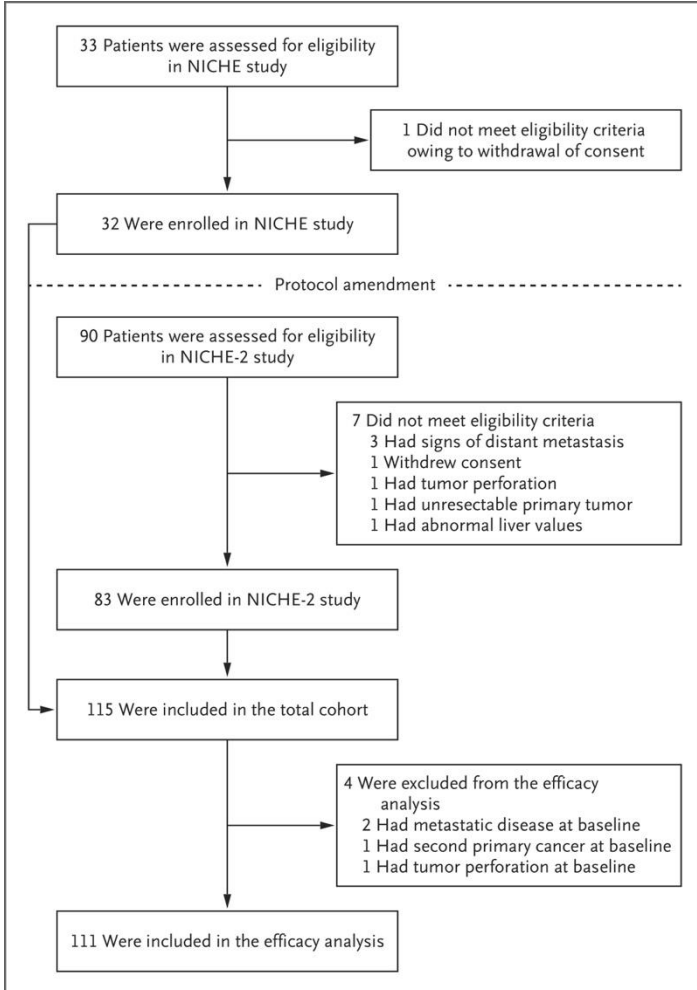
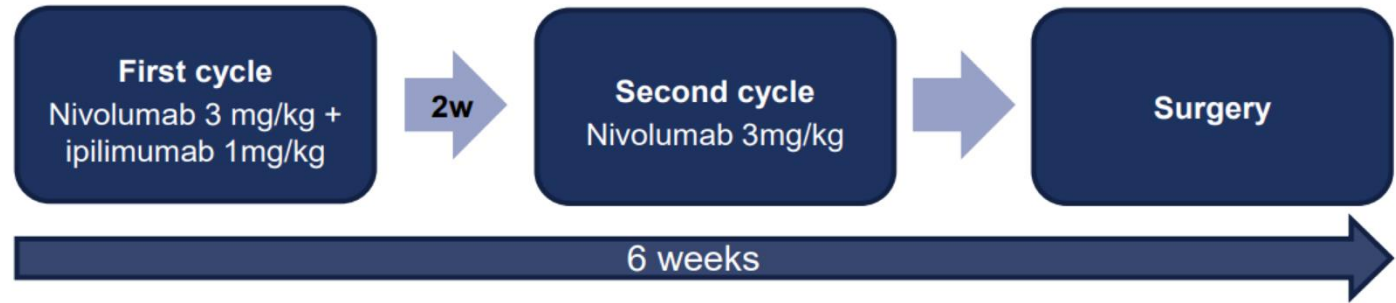
* Evaluable patients: received at least 1 treatment dose

NCCN Guidelines:



Neoadjuvant: Niche 1 & 2 trials:

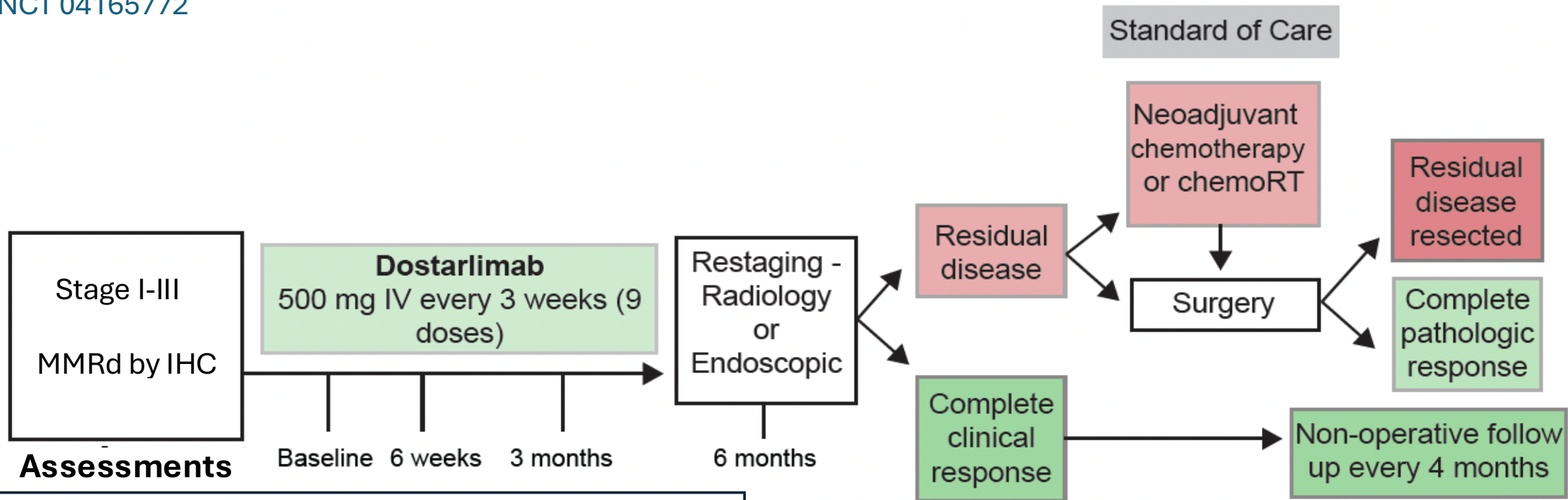
- Investigator-initiated, non-randomized multicenter study



Non-Operative Management:

Neoadjuvant PD-1 blockade in locally advanced MMRd solid tumors

NCT 04165772

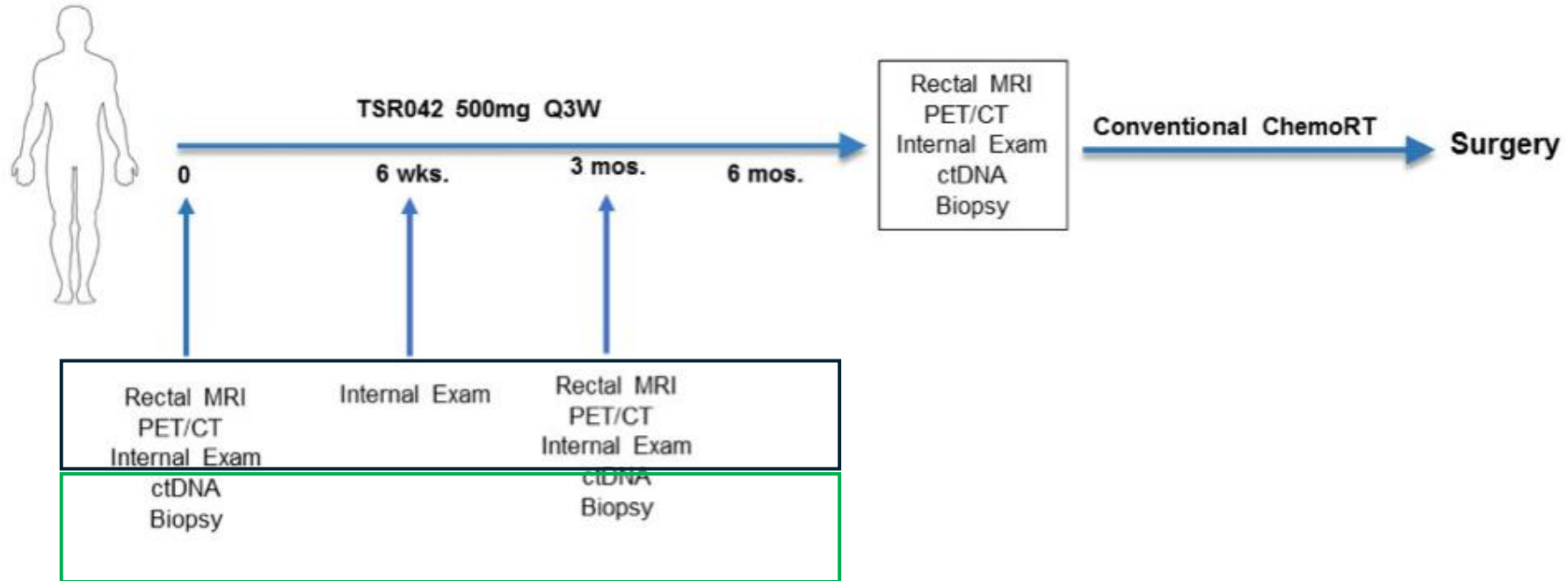


Garcia-Aguilar et al, JCO 2022

Cercek et al, NEJM 2025

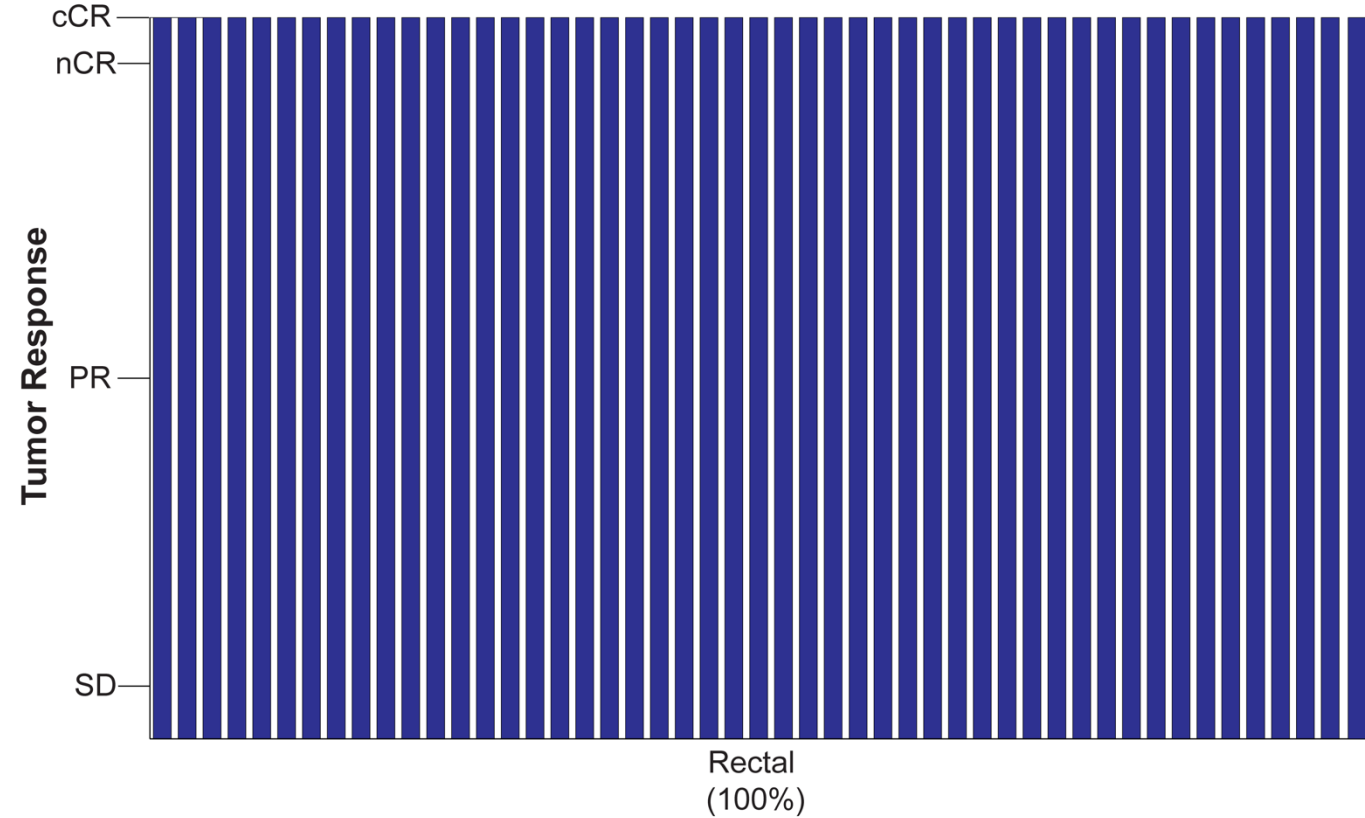
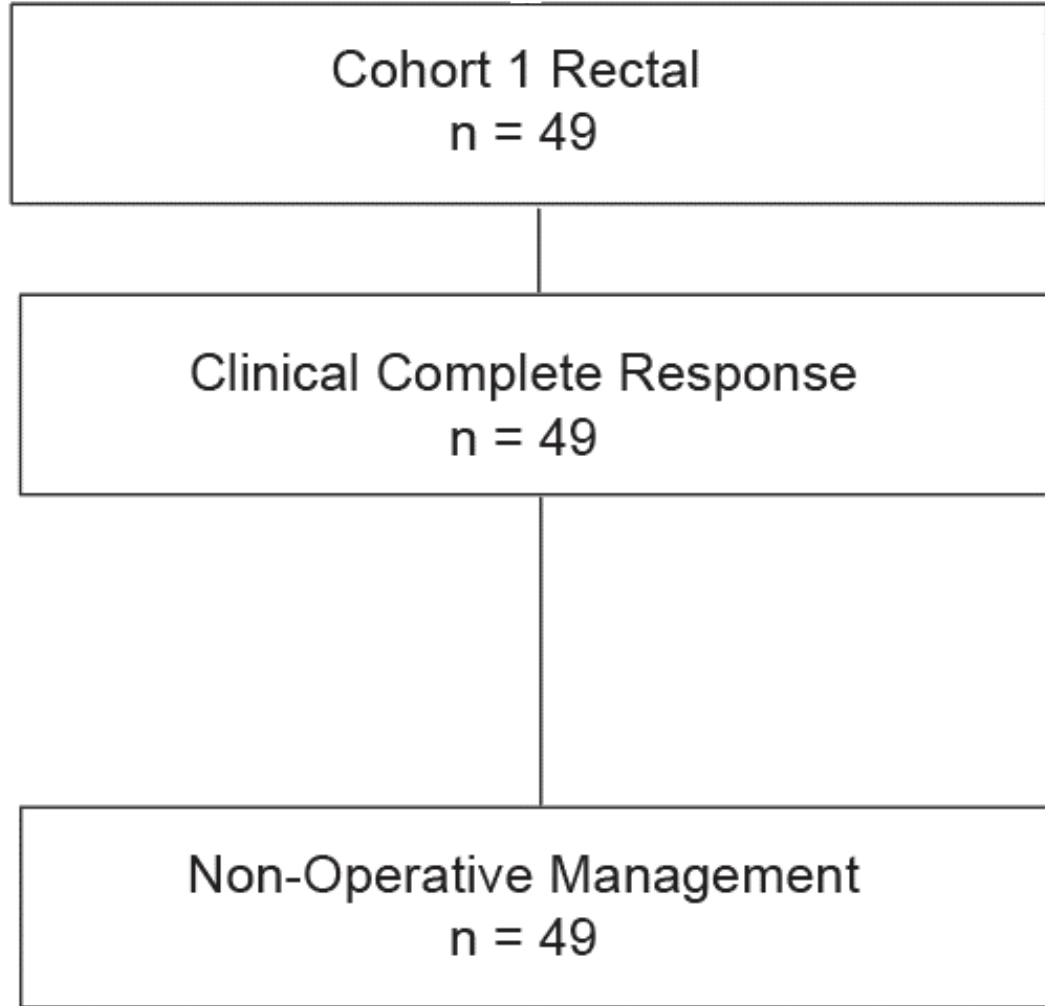
Neoadjuvant PD1 blockade in MMRD locally advanced rectal tumors

Study design:



- Multidisciplinary follow up is crucial for neoadjuvant CRC studies often involves:
 - Surgeons
 - Pathologists
 - Radiologists
 - Oncologists

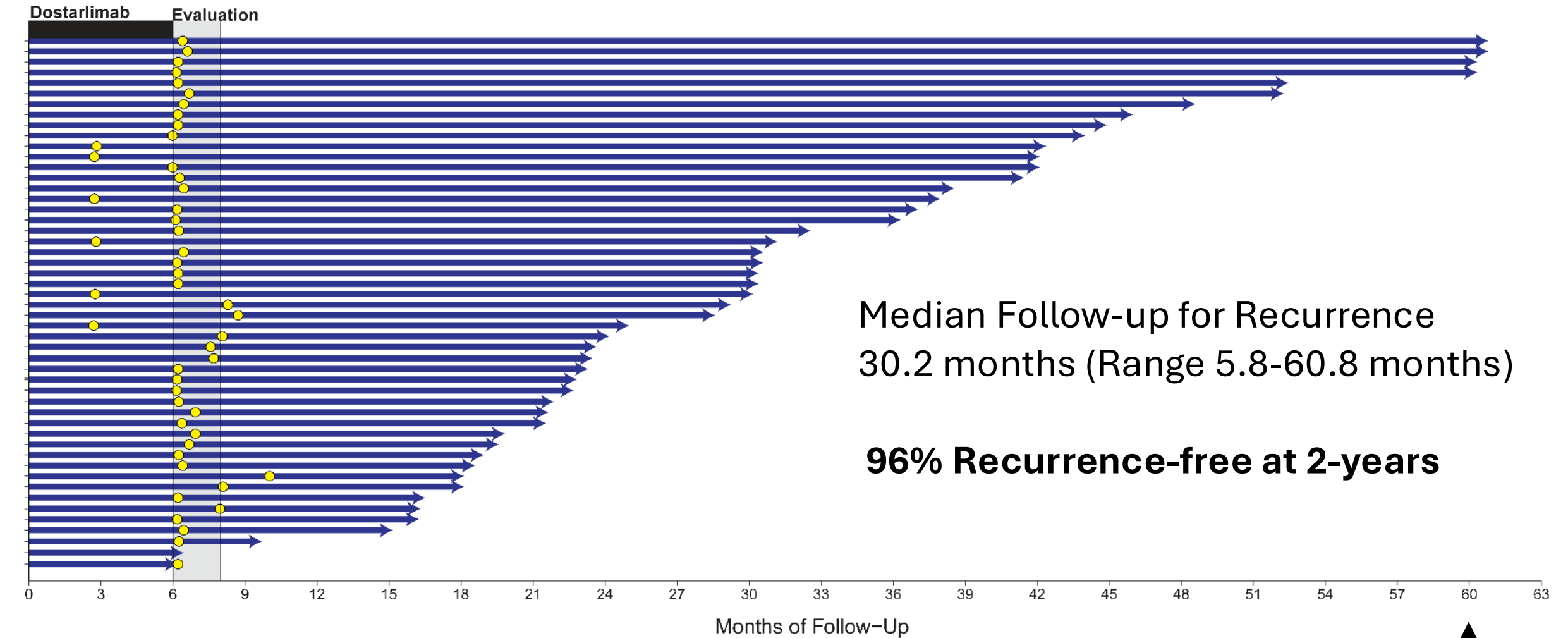
Cohort 1 – Rectal Cancers – Response and Surgical Management



**Rectal cancers achieved 100%
clinical complete responses**

Cohort 1 – Rectal Cancers – Durability of Response

n=50



5-years

Immune related adverse events

Combined Cohort 1 and 2

N=124

	All Grades no. patients (%)	Grade 3 or 4 no. patients (%)
Dermatologic		
Rash/dermatitis *	26 (21)	0 (0)
Pruritus	24 (19)	0 (0)
Gastrointestinal		
Colitis	2 (1.6)	0 (0)
Diarrhea	11(9)	0 (0)
Nausea	8 (6)	0 (0)
Dry mouth	8 (6.5)	0 (0)
Constitutional		
Fatigue	28 (23)	0 (0)
Arthralgia	9 (7)	0(0)
Neurologic		
Headache	4 (3)	0 (0)
Encephalitis	0(0)	1(1)
Endocrine		
Diabetes	0 (0)	1(1)
Hypothyroidism	16 (13)	1 (1)
Respiratory		
Lung Infection	0 (0)	1 (1)
Infections, Other		
Neutrophil count decreased	0(0)	1 (1)
Febrile Neutropenia	0 (0)	1 (1)

35% of patients had no adverse events

60% had grade 1-2 adverse events

5% had grade 3/4 adverse events

No grade 5 adverse events

Neoadjuvant PD1 blockade in MMRD locally advanced rectal tumors

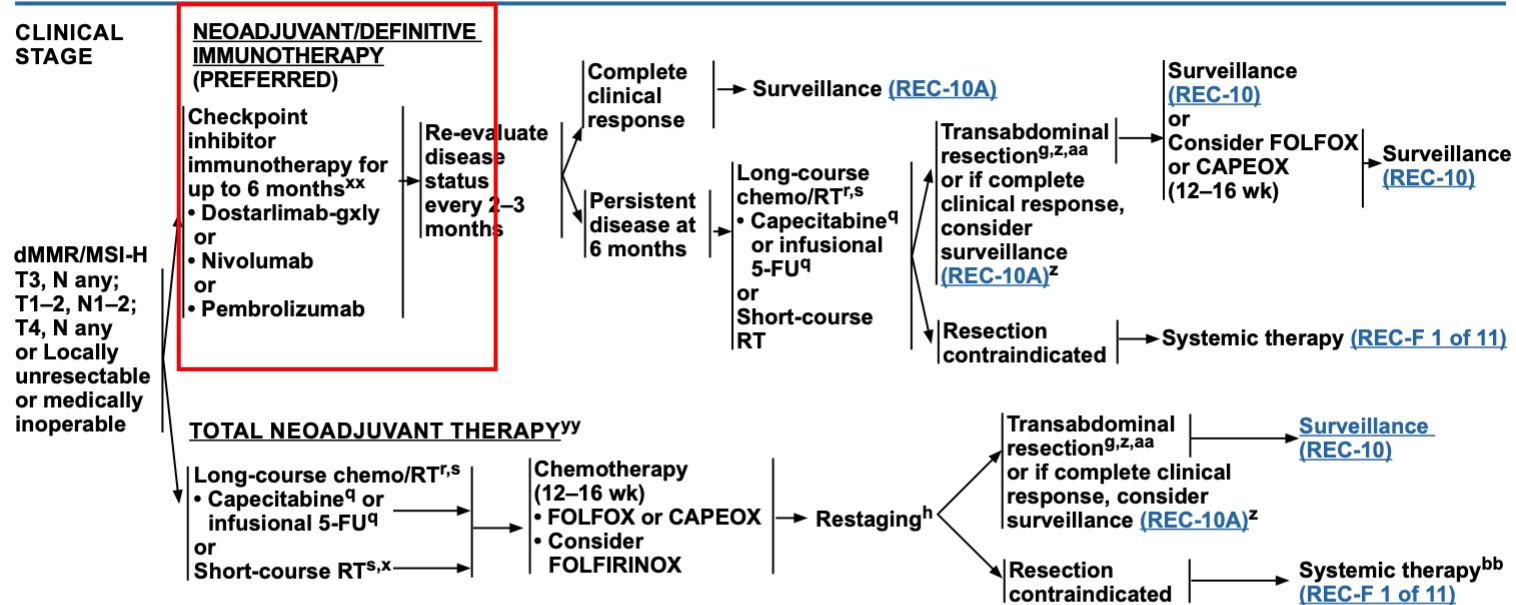
NCCN Guideline recommendation



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2024 dMMR/MSI-H Rectal Cancer

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^g Principles of Surgery (REC-C).

^h Principles of Imaging (REC-A).

^q Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.

^r Principles of Perioperative Therapy (REC-D).

^s Principles of Radiation Therapy (REC-E).

^x Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for downstaging and the possibility of long-term toxicity.

^z In those patients who achieve a complete clinical response with no evidence of residual disease on DRE, rectal MRI, and direct endoscopic evaluation, a “watch and wait,” nonoperative (chemotherapy and/or RT) management approach may be considered in centers with experienced multidisciplinary teams. The degree to which risk of local and/or distant failure may be increased relative to standard surgical resection has not yet been adequately characterized. Decisions for NOM should involve a careful discussion with the patient of their risk tolerance. See Principles of Nonoperative Management (REC-H).

^{aa} For select patients who may be candidates for IORT, see Principles of Radiation Therapy (REC-E).

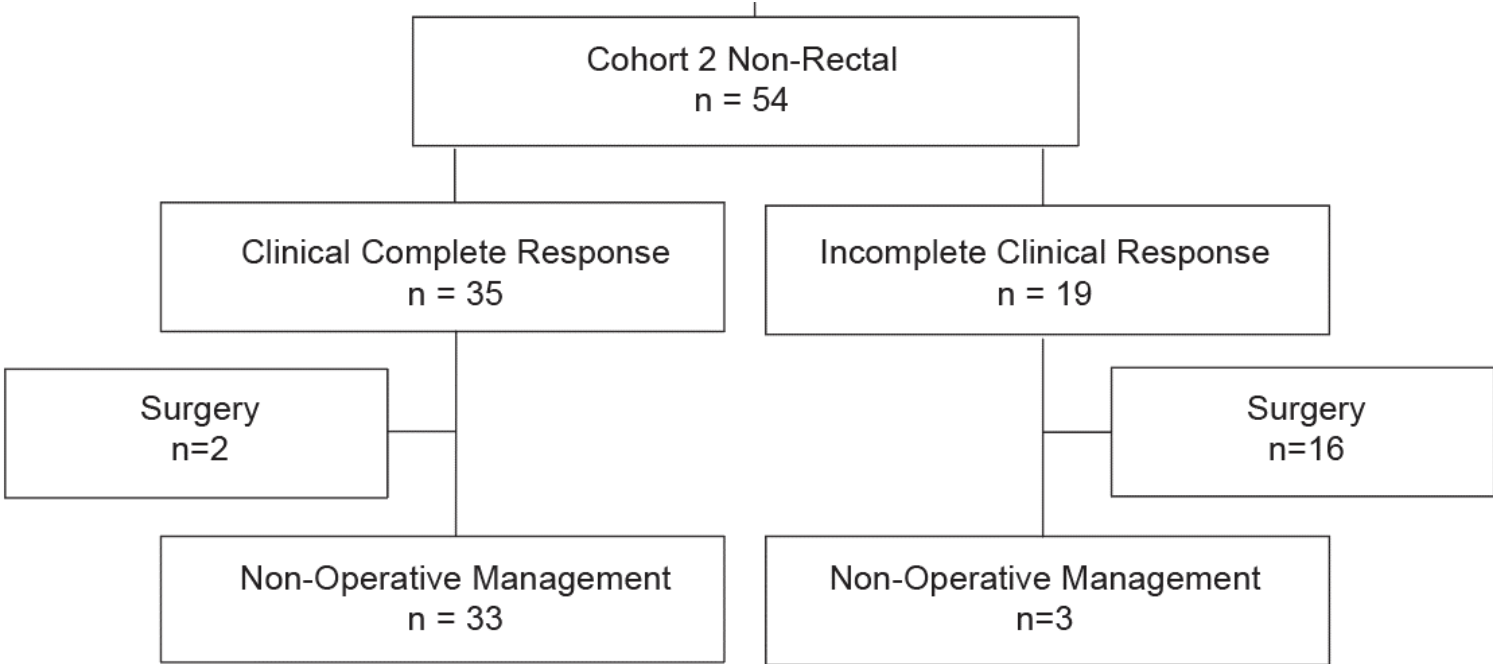
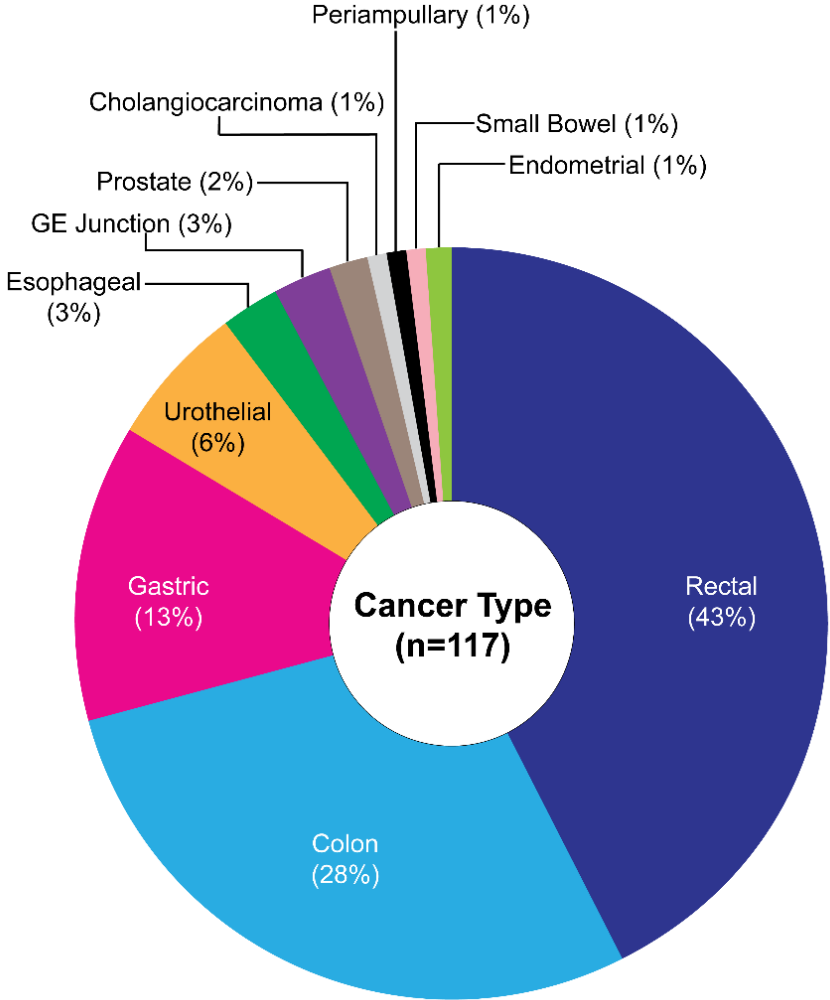
^{bb} FOLFIRINOX is not recommended in this setting.

^{xx} If no previous treatment with a checkpoint inhibitor.

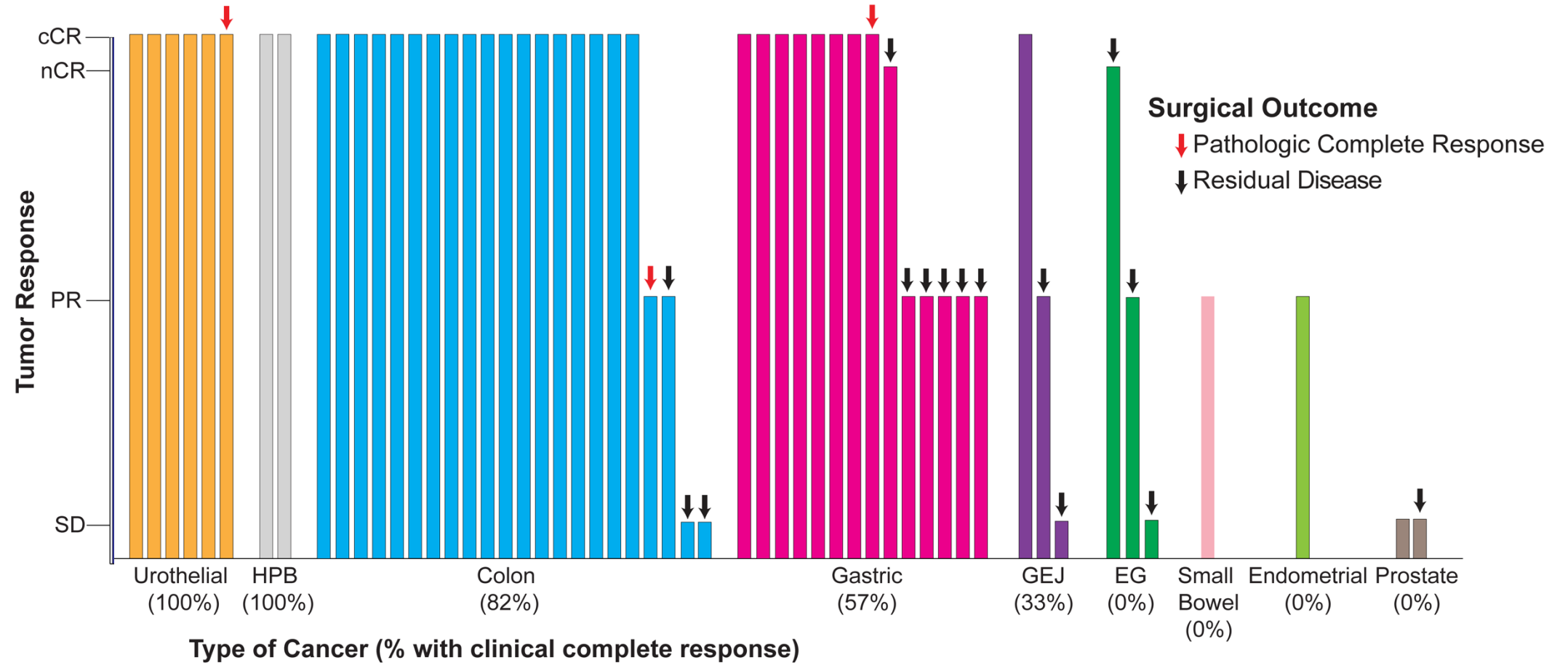
^{yy} In select cases (eg, a patient who is not a candidate for intensive therapy) neoadjuvant therapy with chemo/RT or RT alone may be considered prior to surgery.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Colon Cancer:



Cohort 2 – Non-rectal cancer – Responses and Surgical Management

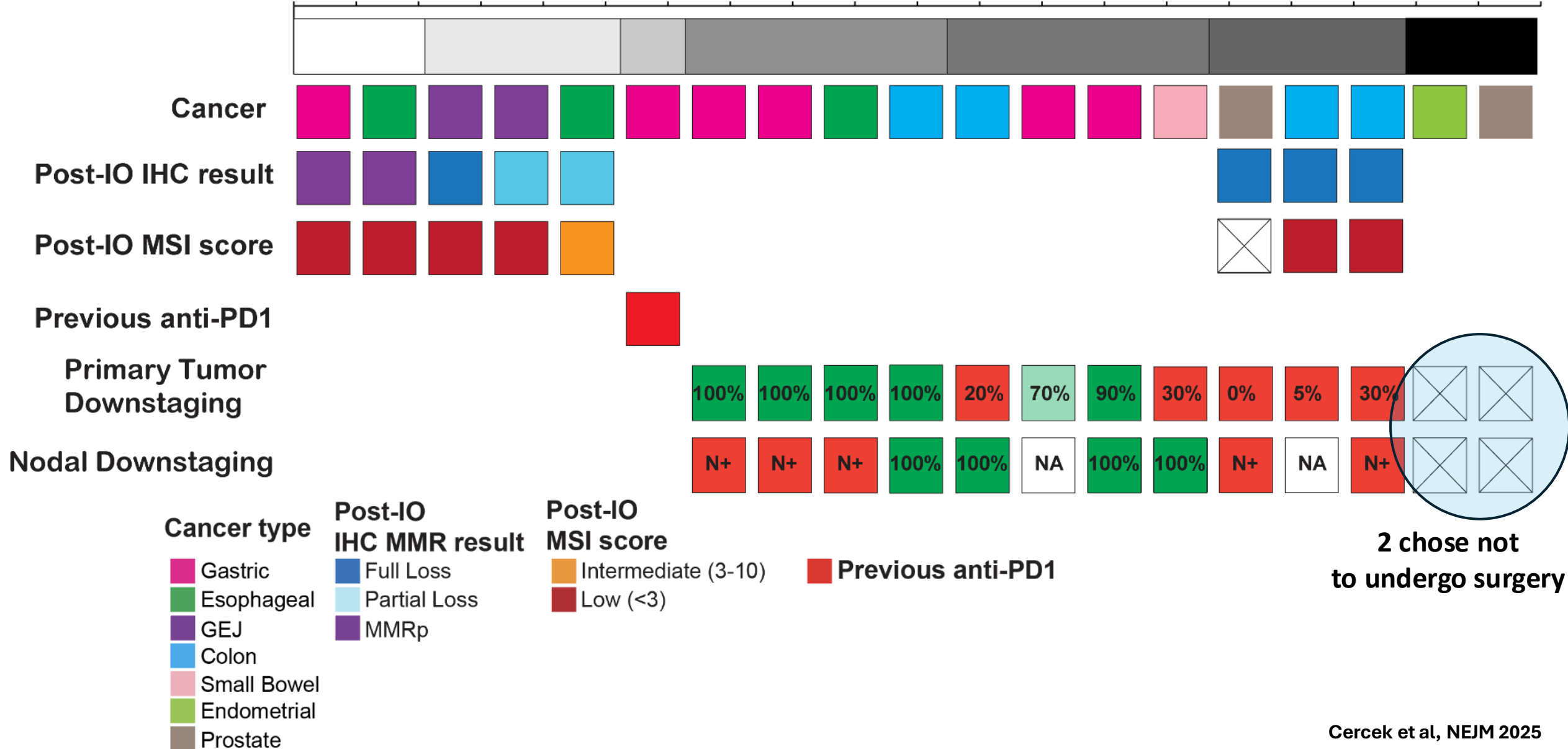


65% achieved a clinical complete response

Cohort 2 – Non-rectal cancer – Incomplete responses

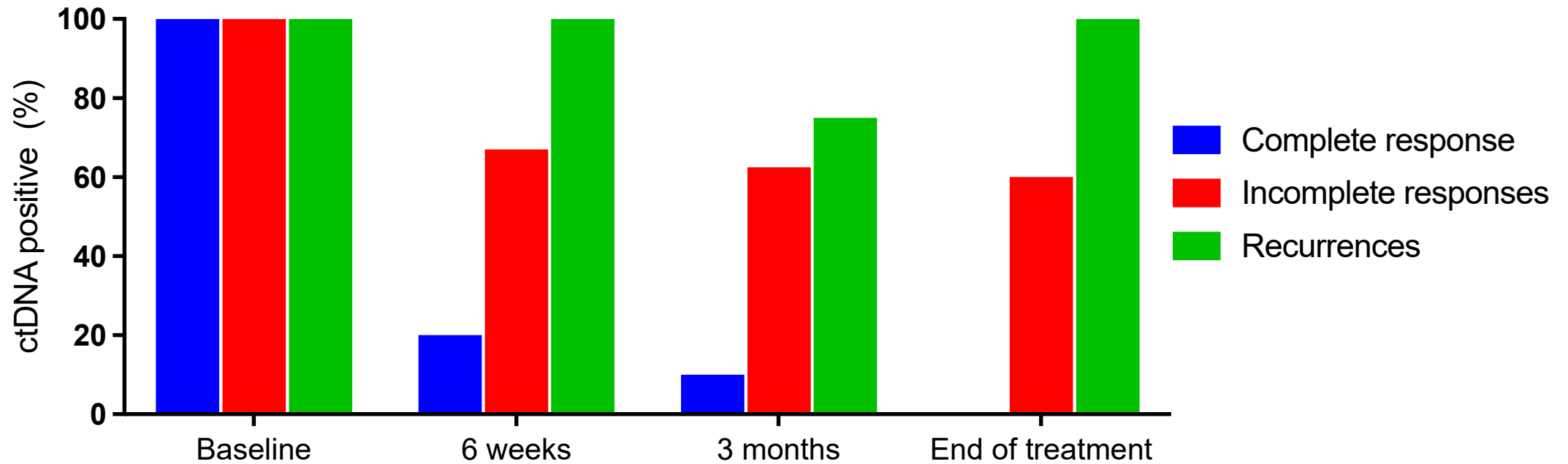
Proportion Total Incomplete Responders (%)

0 10 20 30 40 50 60 70 80 90 100

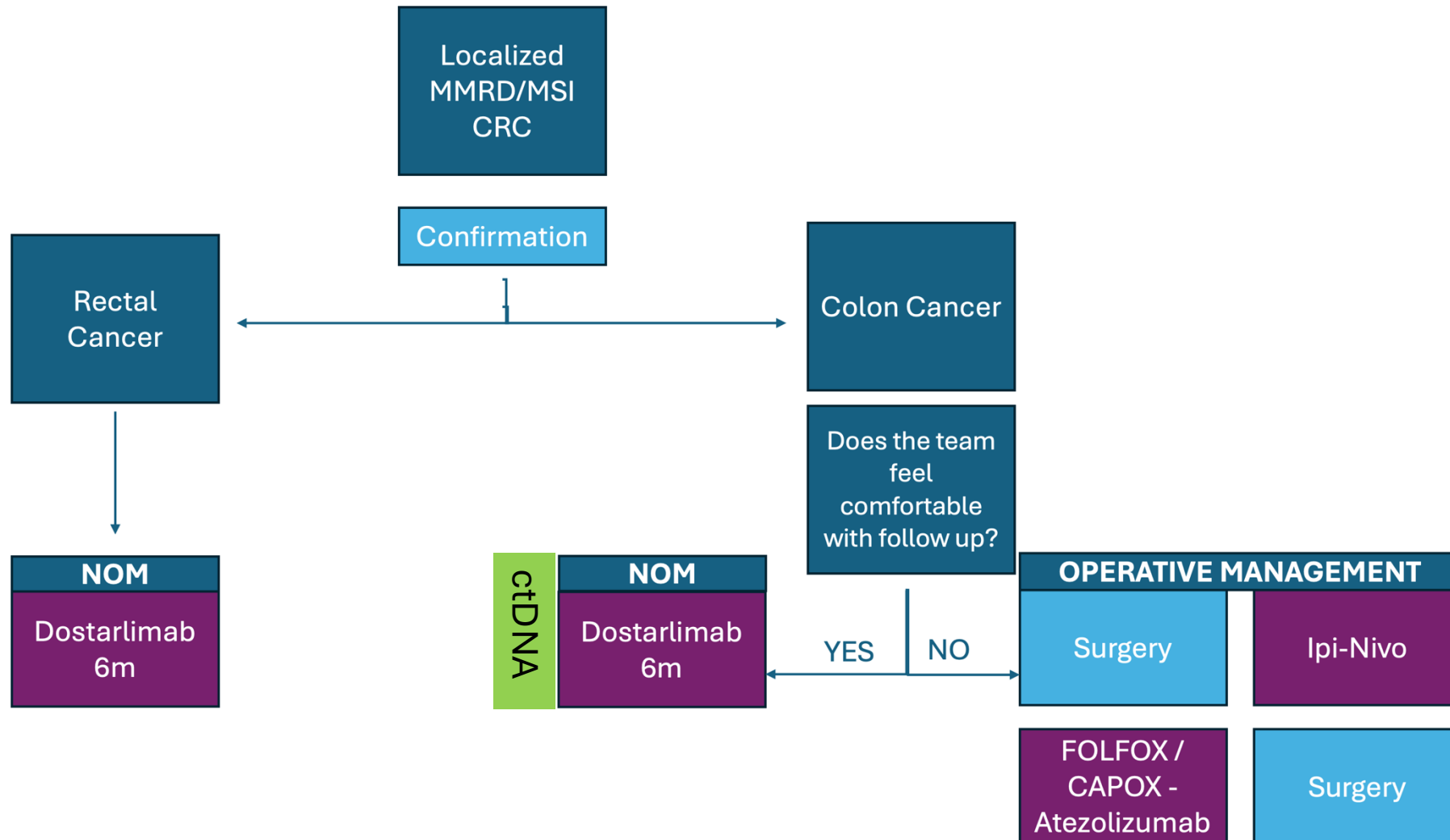


Trial	NCT number	N	Clinical stage III (%)	Regimen	Treatment duration (weeks)	pCR rate (%)	Median follow-up (months)	DFS rate/survival data
NEOPRISM-CRC	NCT05197322	31	81	pembrolizumab	6*	55*	6	No recurrences
RESET-C	NCT05662527	85	60	pembrolizumab	3	44	-	-
IMHOTEP	NCT04795661	77 [†]	79 [†]	pembrolizumab	6-12	46 (1 cycle) 68 (2 cycles) [†]	-	-
PICC	NCT03926338	17	95	toripalimab	12	65	14.9	1-y: 100%
Wang et al.	NCT05890742	45	81	sintilimab	6	43	21.4	only 1 TR-death
PICC	NCT03926338	17	84	toripalimab/celecoxib	12	88	14.9	1-y: 100%
NICHE-2	NCT03026140	115	67	ipilimumab/nivolumab	4	68 [‡]	36.5	3-y: 100%
NICHE-3	NCT03026140	59	63	nivolumab/relatlimab	8	68	8	98% disease-free
Wang et al.	NCT05890742	52	78	IBI310/sintilimab	6	77	21.4	only 1 postop. death
UNICORN	NCT05845450	14	-	botensilimab/balstilimab	4	93	5.9	1-y: 100%

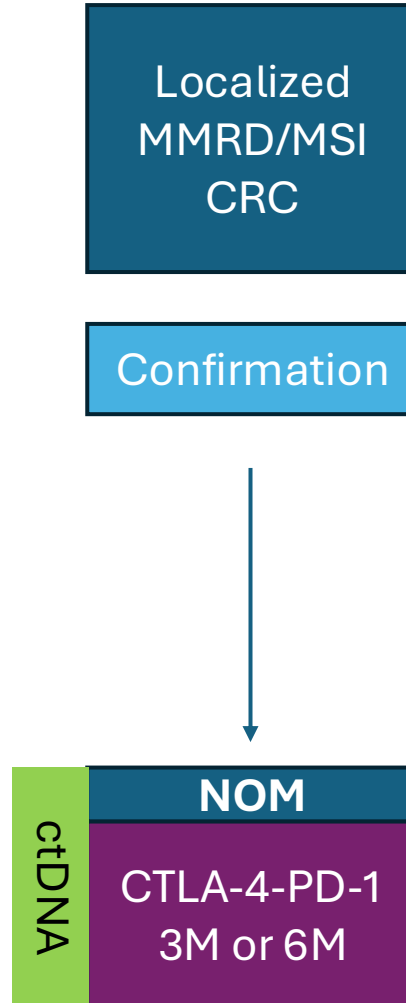
Detecting residual disease in the non-operative setting



Data-driven Algorithm:



Future directions:

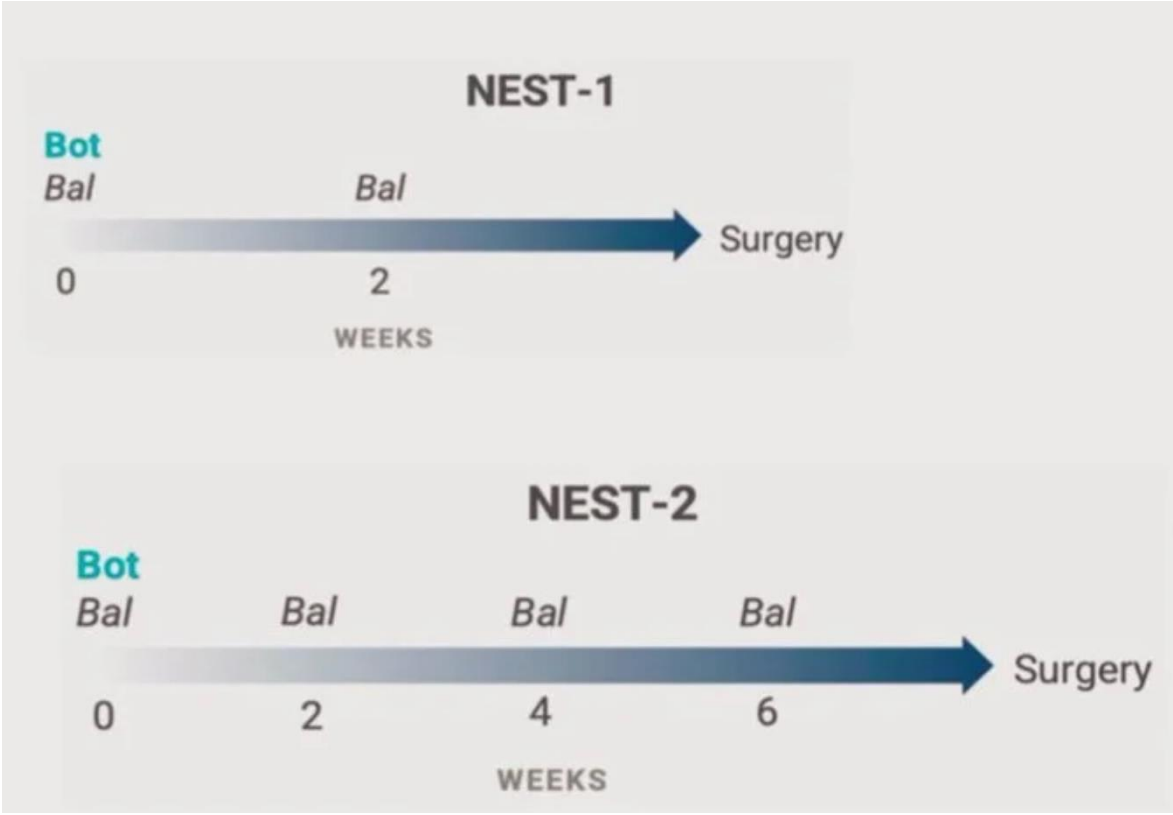


-There are some reports of resistance to 6m anti-PD1 in rectal'

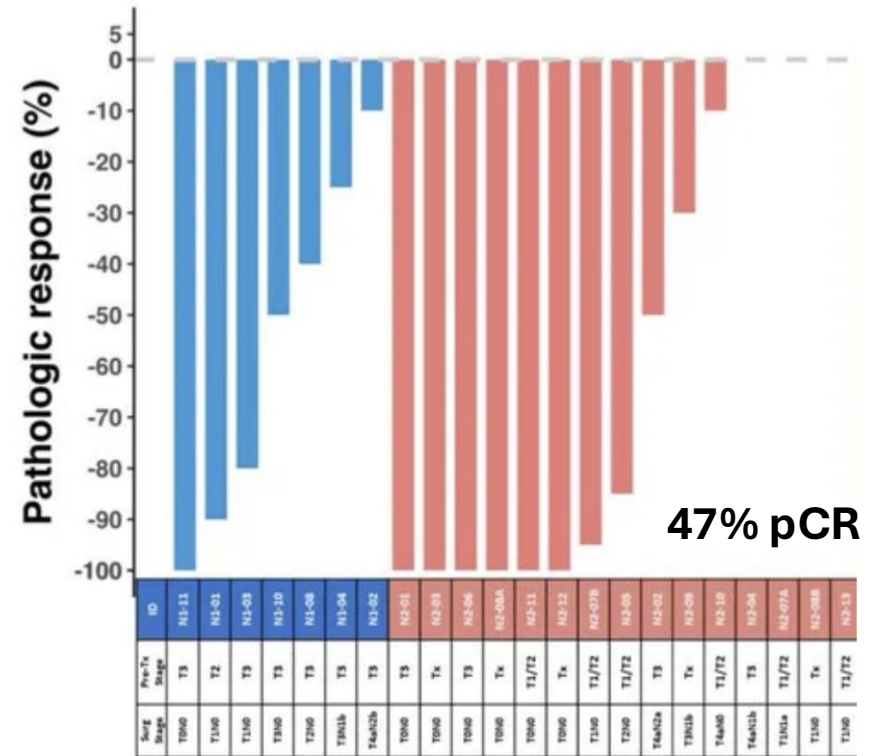
-No study has seen 100% cCR in colon with Anti-PD-1 s/a.

MSS:

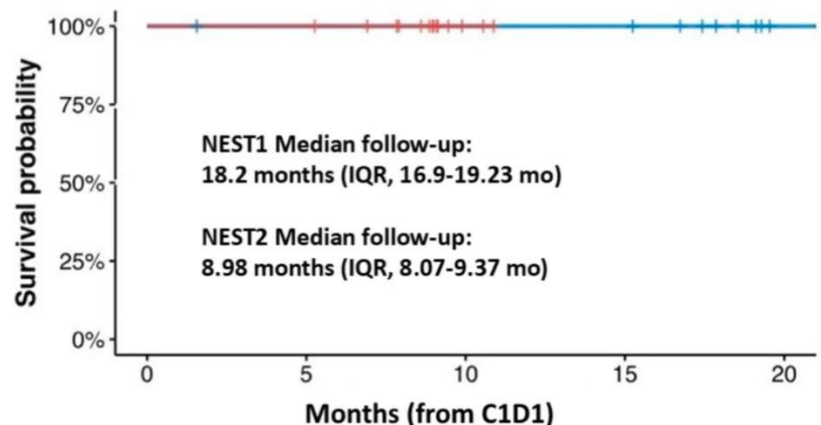
Bot-Bal neoadjuvant: MSS



Pathologic Response Group

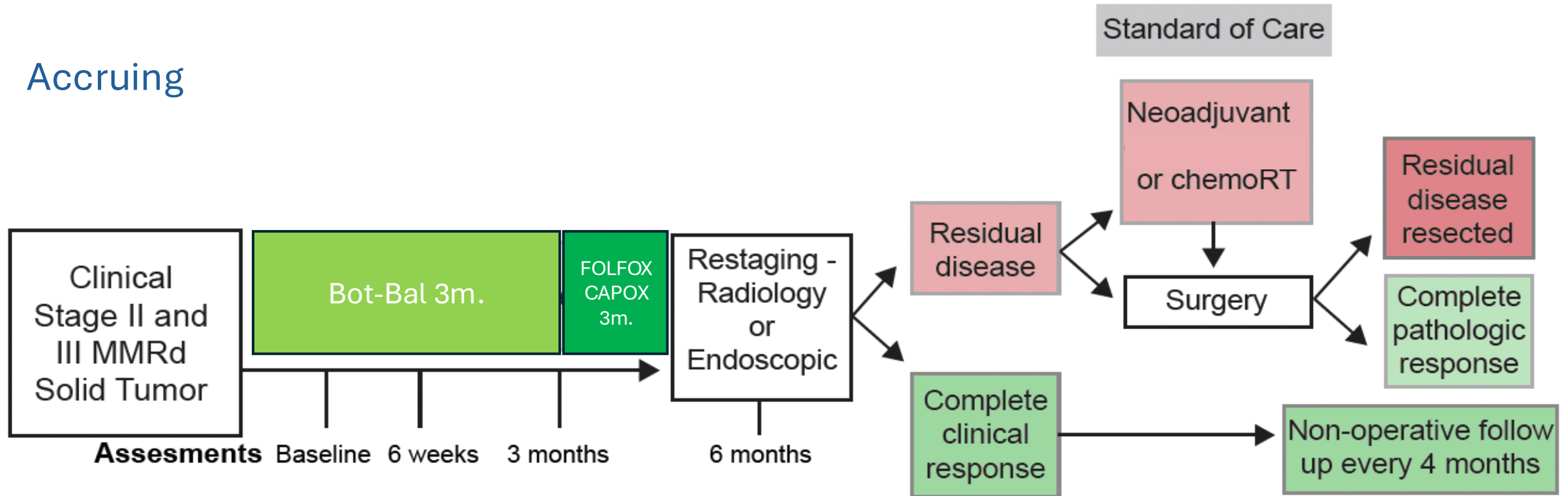


Progression Free Survival



Bot-Bal in NOM for Rectal MSS:

Accruing



Take Home Messages:

- IO should be the SOC on the adjuvant setting for **MSI-H**.
 - Next steps:
 - 1) Implementing neoadjuvant treatment
 - 2) Developing the anti-CTLA-4/PD-1 to maximize responses
 - 3) Figure out the optimal treatment length
- IO is not the SOC of **MSS** tumors however anti-CTLA-4/PD-1 seems promising.
- Current trials exploring combo **with longer treatments** are highly awaited to see the final role IO may play in MSS CRC.