City of Hope®

Annual

Advances and Innovations in Endoscopic Oncology and Multidisciplinary Gastrointestinal Cancer Care

Immunotherapy for Localized GI Cancers

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Disclosures

- Grant/Research Support from Grant/Research Support from Agenus, CytoDyn, Inc., Haystack, Merck, and Novartis.
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This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon must contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- Differences among individuals in terms of response and access to some of the assays as well as immunotherapy treatments.

SECTIONS HOME SEARCH

The New York Times

WELL | LIVE

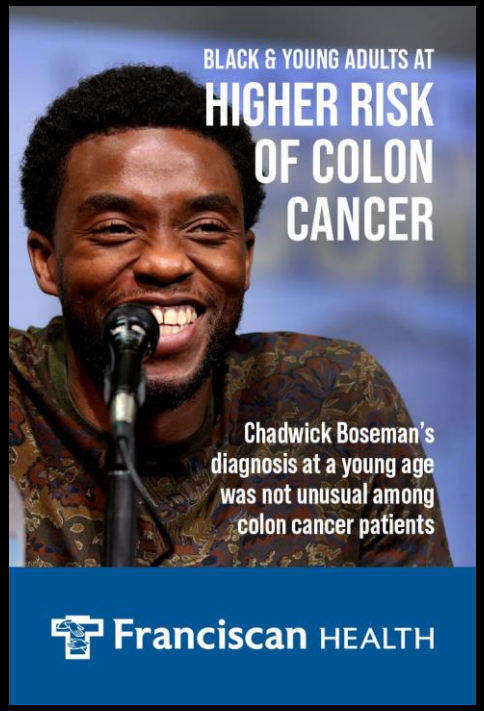
More Young People Are Dying of Colon Cancer















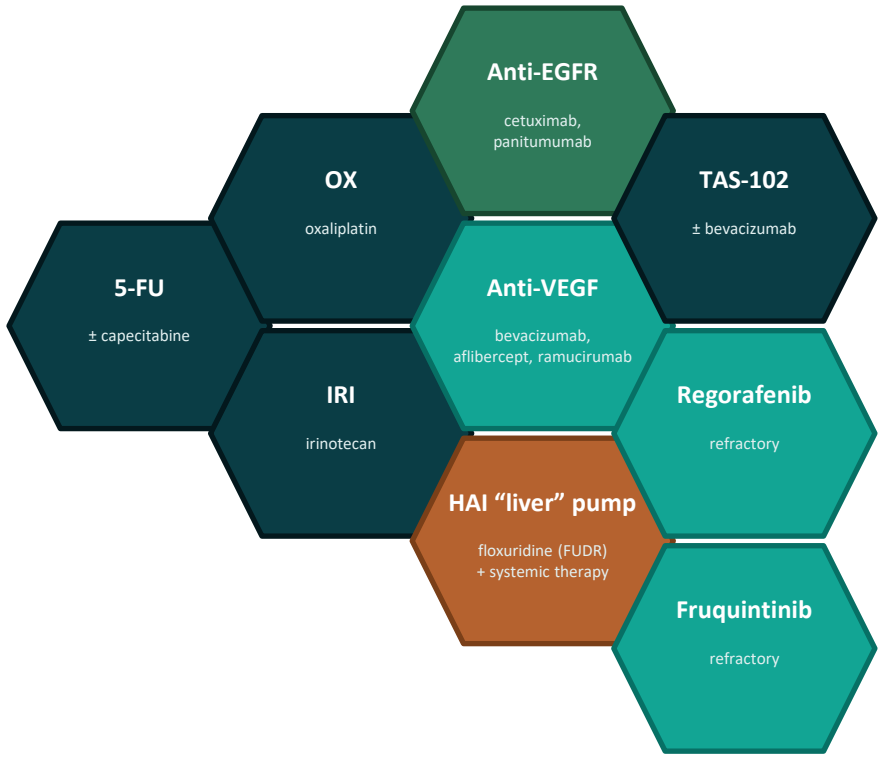


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THE LANDSCAPE ON ONE SLIDE

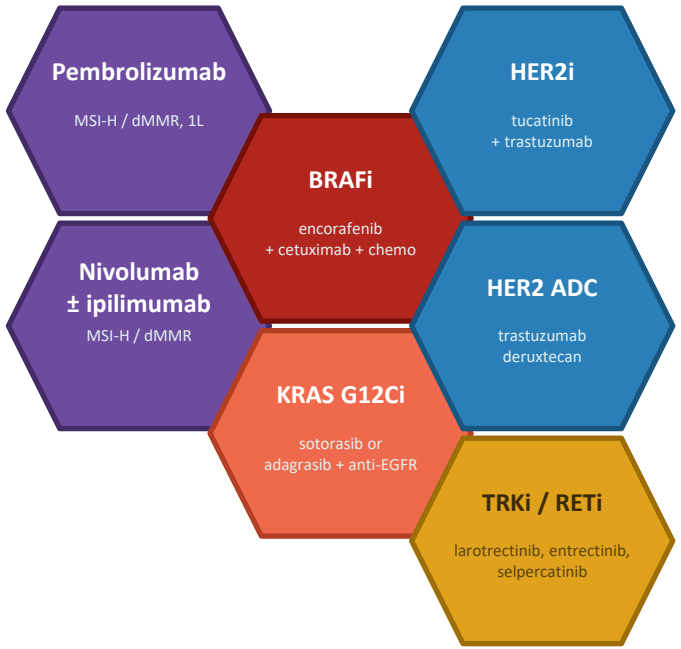
FDA-approved options in metastatic colorectal cancer, 2026

AVAILABLE TO EVERY PATIENT



Backbone + biologic partner and/or regional therapy → later lines

REQUIRES A BIOMARKER RESULT



Immunotherapy for dMMR/MSI-High versus targeted therapies driven by alteration

Legend

- Cytotoxic backbone
- Anti-EGFR
- Antiangiogenic
- Liver-directed
- Immunotherapy
- BRAF V600E
- KRAS G12C
- HER2 amplified
- NTRK / RET fusion

Red marks BRAF V600E — historically the poorest-prognosis subgroup in metastatic disease.

Biomarker required first

- MSI-H / dMMR → pembrolizumab, nivolumab ± ipilimumab
- BRAF V600E → encorafenib + cetuximab + chemotherapy
- HER2+ and RAS WT → tucatinib + trastuzumab, T-DXd
- KRAS G12C → G12C inhibitor + anti-EGFR
- NTRK / RET fusion → TRK or RET inhibitor
- RAS/BRAF WT and left-sided → anti-EGFR

Hepatic arterial infusion

Floxuridine via implanted pump with systemic therapy, for liver-limited or liver-dominant disease, at experienced centers.

FDA-approved options only; several carry accelerated approval. Concept adapted and updated from Kasi PM et al. Lancet 2019. Trastuzumab deruxtecan is approved tumor-agnostically for HER2 IHC 3+ solid tumors.

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FRAGMENTATION

Subsets of subsets: metastatic CRC in 2026

~25-30%

RAS/BRAF WT, left-sided, HER2-negative

Anti-EGFR 1L

~40-55%

RAS mutant, non-G12C

Chemo + bev; G12D in trials

~4-5%

dMMR / MSI-H

Nivo + ipi 1L, Pembrolizumab

8-10%

BRAF V600E

Enco + cetux + chemo

2-4%

HER2 amplified

Tuc + tras; T-DXd; higher in RAS/RAF-wild-type; rectal and left sided colorectal cancer

2-4%

KRAS G12C

G12Ci + anti-EGFR

<1%

NTRK / RET / ALK

TRK, RET inhibitors

<1%

POLE / POLD1, ?TMB-H

Checkpoint blockade

Each block is now a different first-line conversation. Together, the small orange subsets are ~15% of patients — you will see several per year.

Block width approximates prevalence; categories overlap (e.g., BRAF V600E enriched in dMMR). Frequencies are approximate and vary by cohort and by right- vs left-sided disease.

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Why move immunotherapy earlier?

1

Intact immunity

Treatment-naive T cells and draining lymph nodes are still in place

2

Antigen in situ

The primary tumor primes a broader, durable response before resection

3

Fast readout

Pathologic or clinical response in weeks, plus a path to organ preservation

dMMR / MSI-H (~15%)

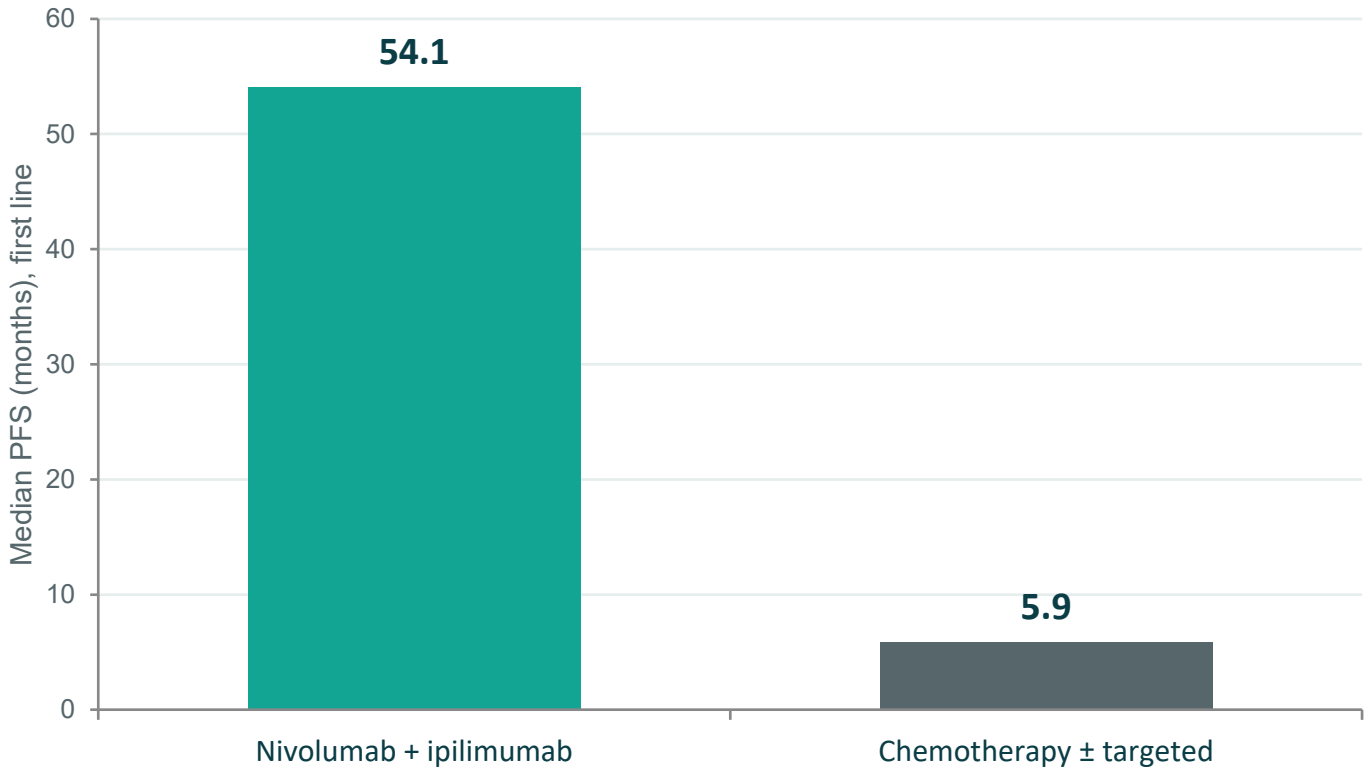
Practice-changing now

pMMR / MSS (~85%)

The frontier

MSI-H / DMMR, METASTATIC

CheckMate 8HW: chemotherapy is no longer the comparator



HR 0.21

79% reduction in progression or death

Doublet > mono

PFS benefit vs nivolumab alone at 50 mo follow-up (HR 0.69)

1L standard

FDA-approved first line for MSI-H/dMMR mCRC

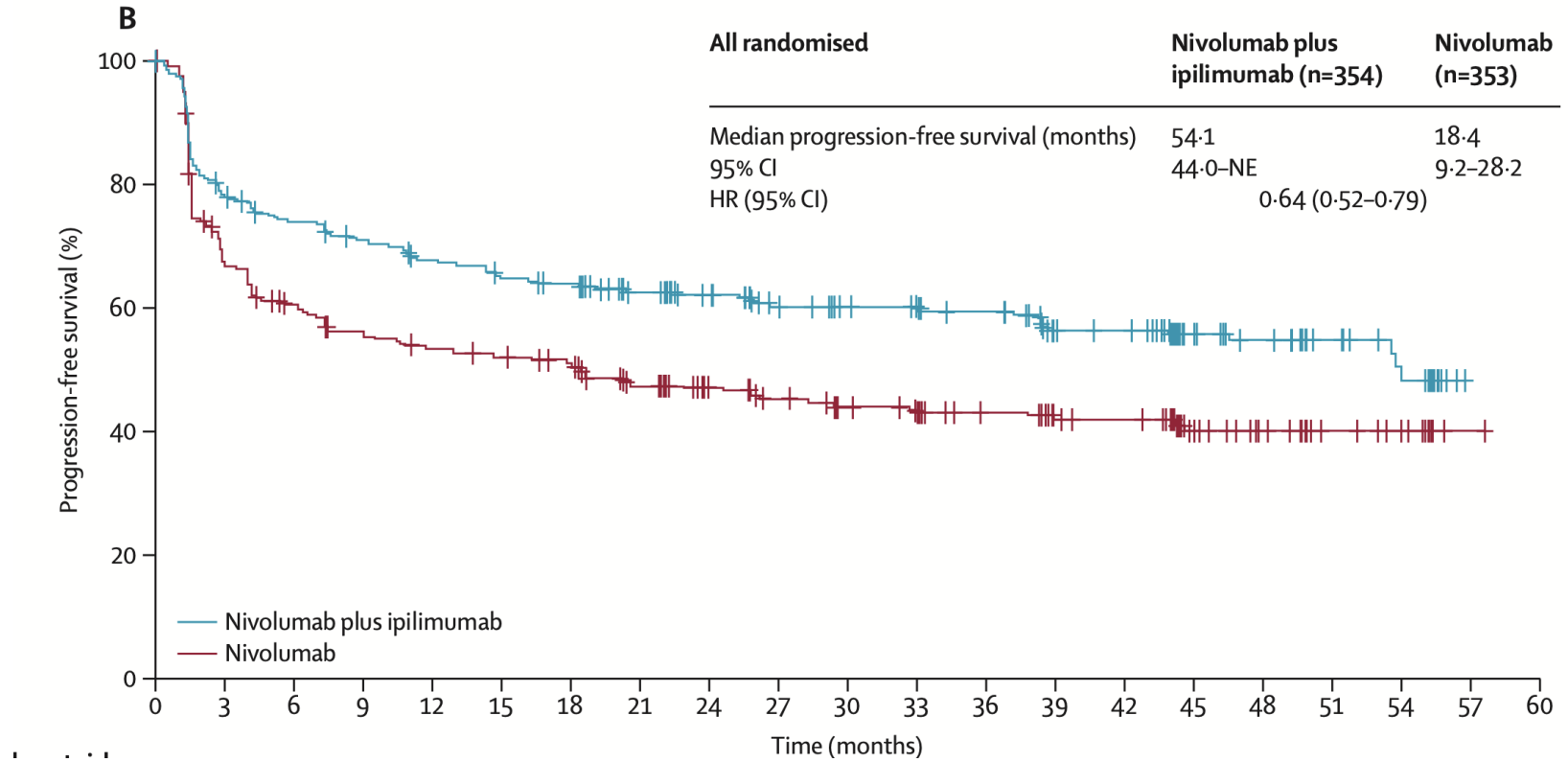
Practice point: a dMMR result that arrives after cycle 1 of FOLFOX has already cost the patient the best regimen.

CheckMate 8HW; Andre et al. Lancet 2025 and 2026 updated analyses. Median follow-up 47-50 months.

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MSI-H / DMMR, METASTATIC

CheckMate 8HW: chemotherapy is no longer the comparator

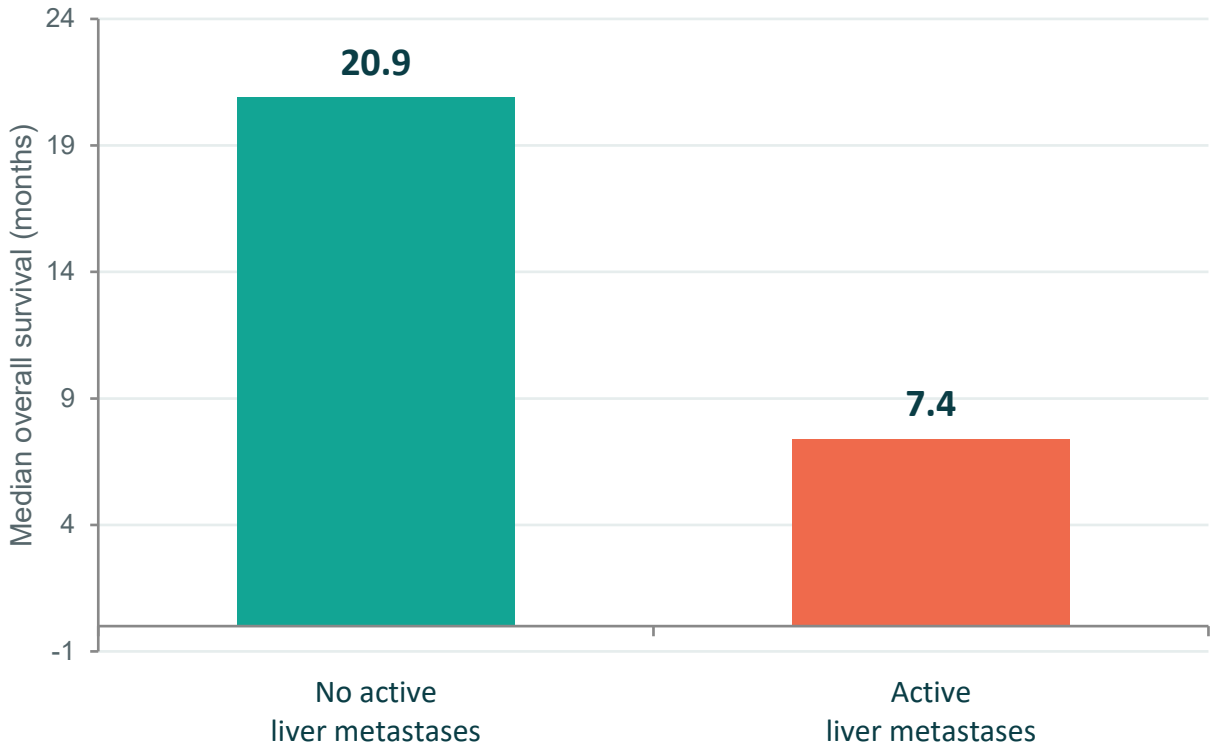


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André T, et al. Nivolumab plus ipilimumab versus nivolumab in microsatellite instability-high metastatic colorectal cancer (CheckMate 8HW): a randomised, open-label, phase 3 trial.
Lancet. 2025 Feb 1;405(10476):383-395.

NOVEL CTLA-4, RESULTS

Activity in refractory MSS disease — and a striking split – “NLM”



21%

confirmed ORR in patients without active liver metastases

21.2 mo

median OS in that population, heavily pretreated

33%

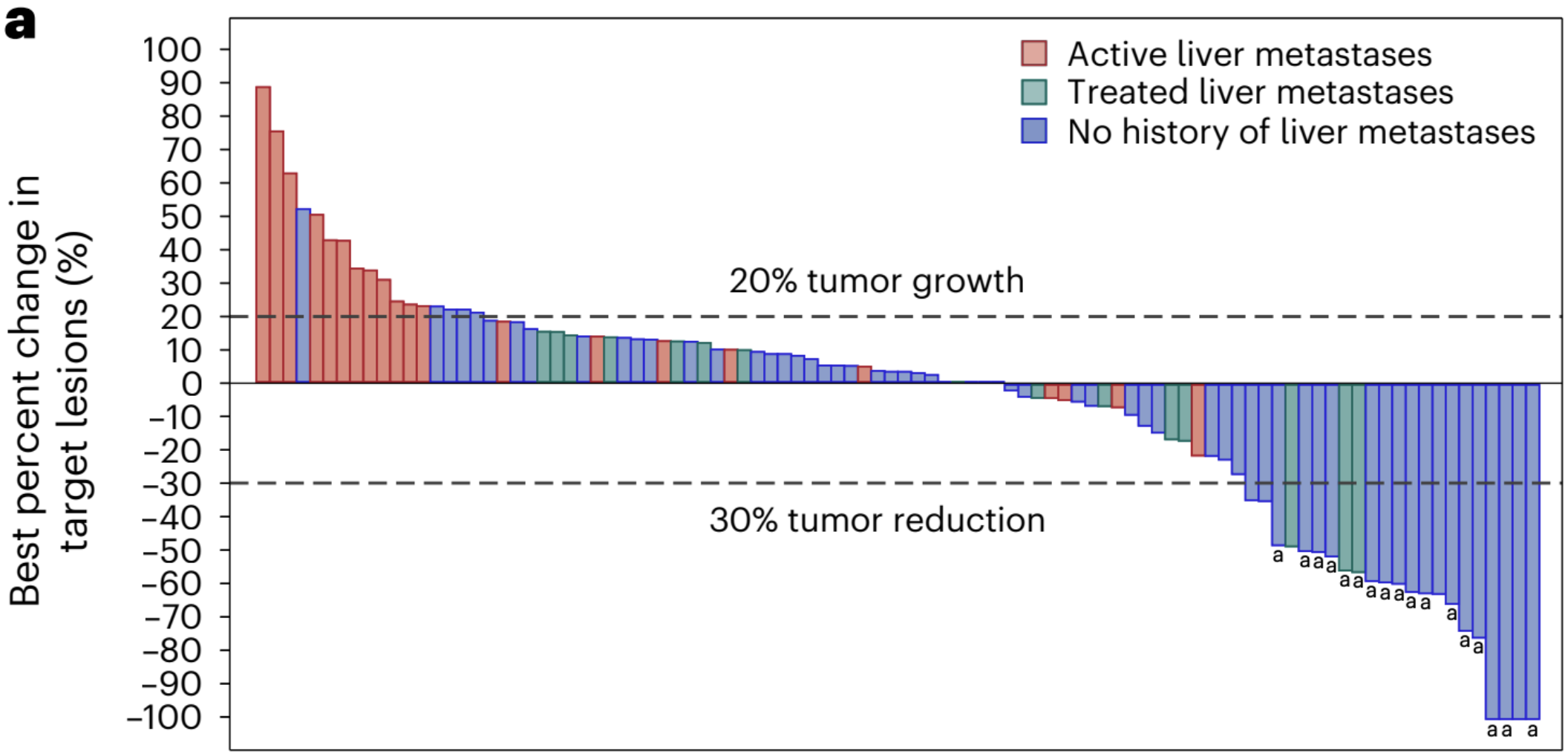
alive at 3 years — a tail, not a shift

In a disease where third-line survival is measured at 7 months, a 33% three-year survival rate in any subgroup is a different kind of result.

Phase 1 botensilimab + balstilimab, refractory MSS mCRC (Nat Med 2024) and subsequent updates; comparative analysis vs SUNLIGHT/FRESCO-2/RECOURSE/CORRECT, 2026. Investigational.

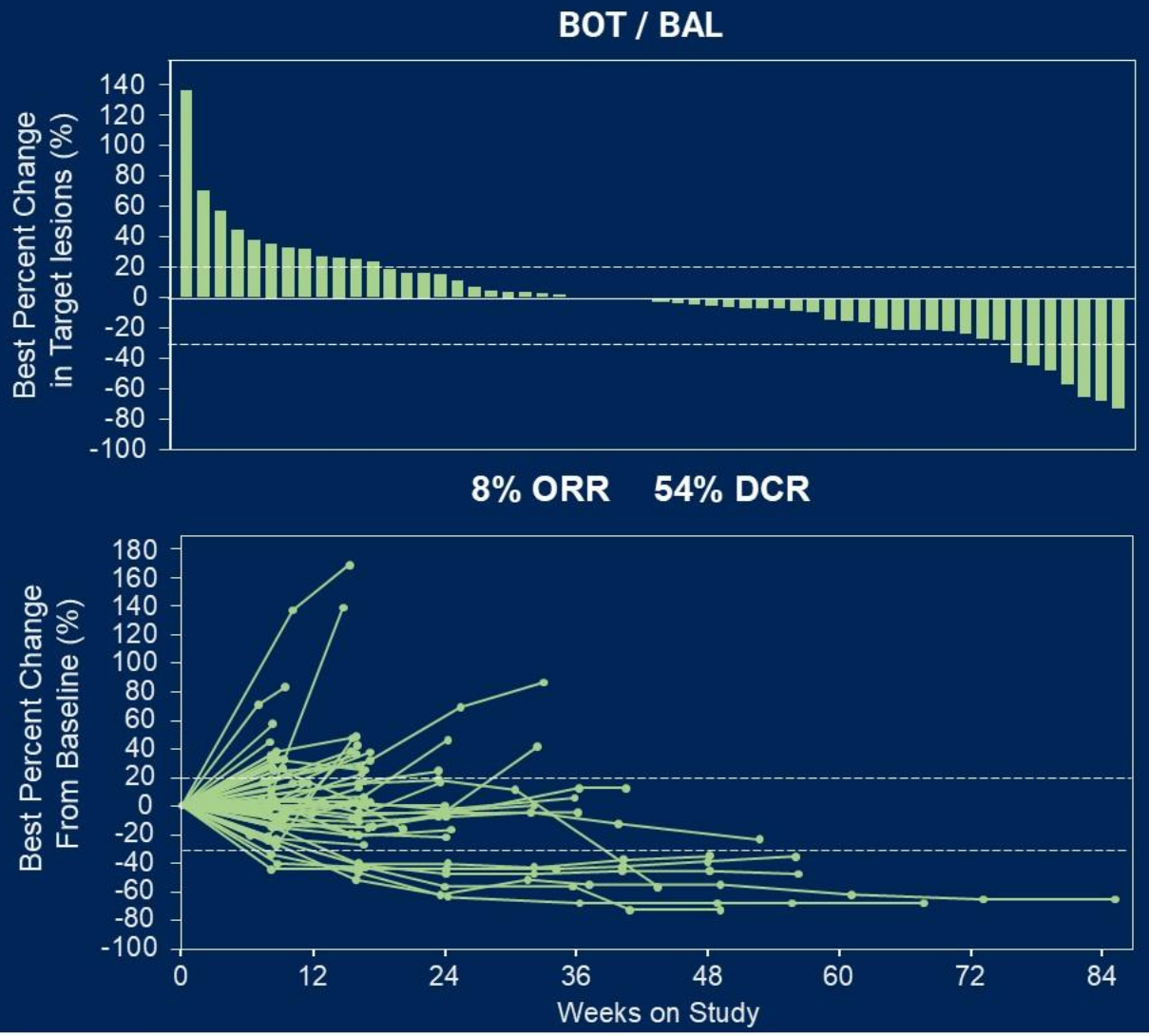
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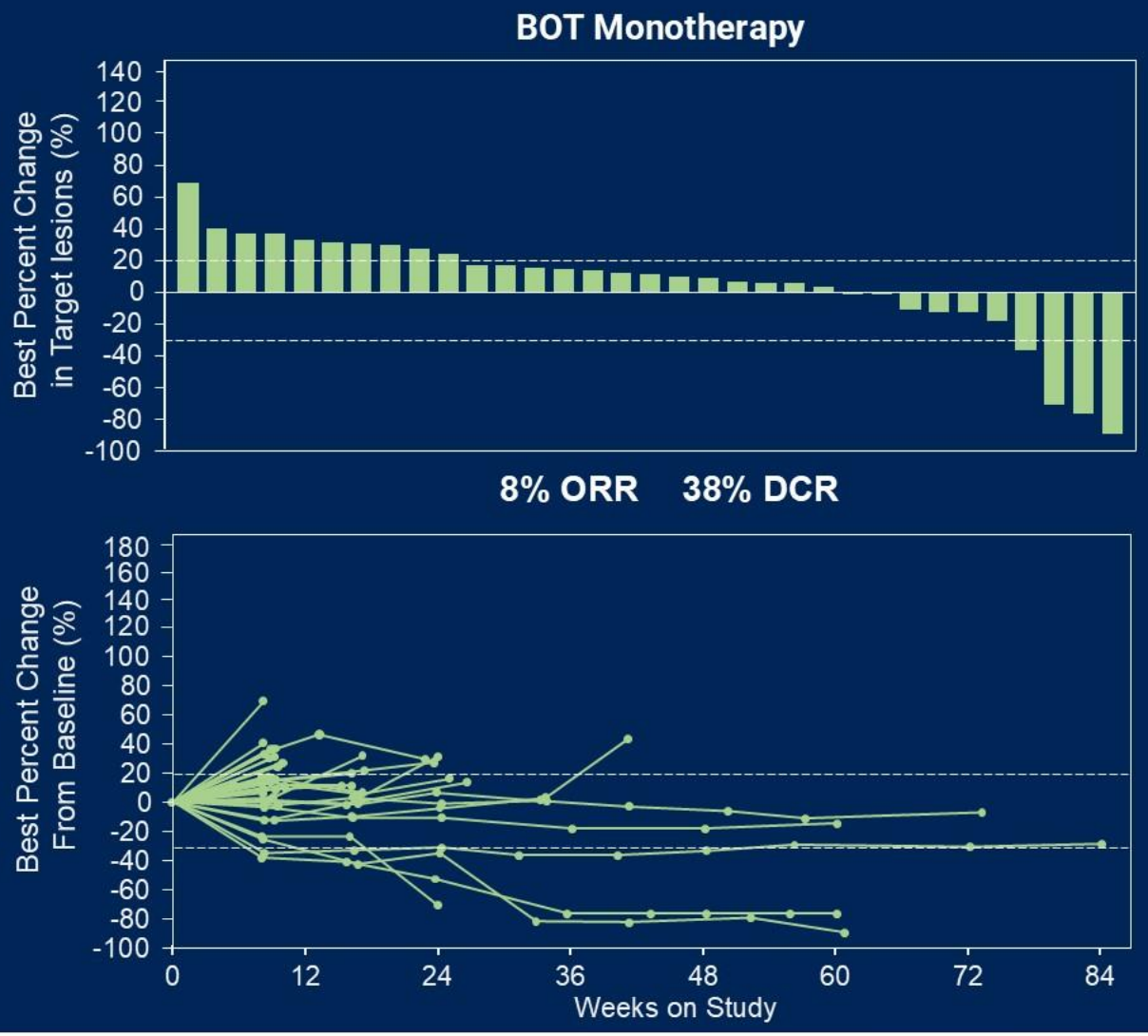
Activity in refractory MSS disease — and a striking split – “NLM”



Bullock AJ, et al. Botensilimab plus balstilimab in relapsed/refractory microsatellite stable metastatic colorectal cancer: a phase 1 trial. Nat Med. 2024 Sep;30(9):2558-2567.

Efficacy in BOT 150 mg Arms: Clinical Benefit Greater With BOT / BAL

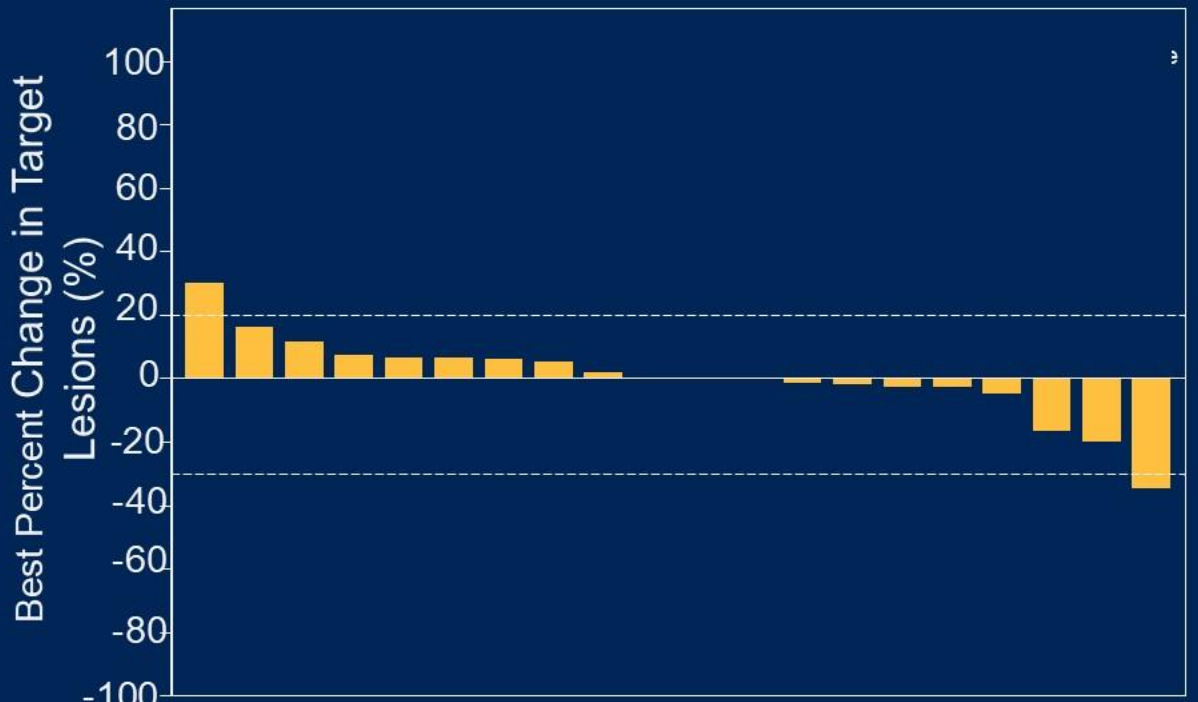


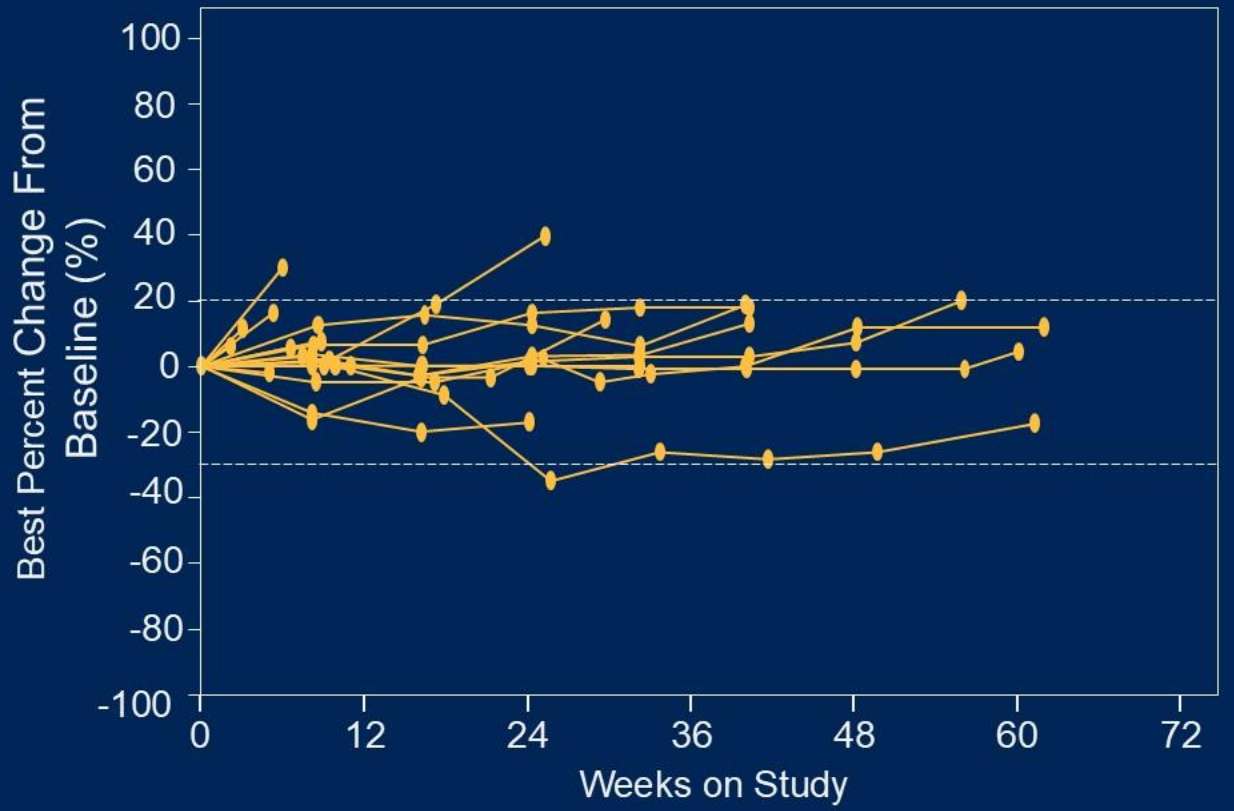


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No Objective Responses With SOC

Trifluridine/Tipiracil (n=13) or Regorafenib (n=8)





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MSI-H / DMMR, LOCALIZED — THE PARADIGM SHIFT

Immunotherapy before — or instead of — surgery

Rectal, dMMR

Dostarlimab x6 mo

100%

clinical complete response and organ preservation in the reported cohort

Colon, dMMR

Perioperative dostarlimab

AZUR-2

phase 3, randomized vs standard of care — the definitive trial

Colon, dMMR

Neoadjuvant checkpoint blockade

Major

pathologic responses in weeks, not months

What this means for the surgeon and the patient

For dMMR disease, resection is becoming a decision rather than an obligation — total mesorectal excision, permanent ostomy, and adjuvant chemotherapy can all potentially be avoided. The unresolved questions are durability, surveillance intensity, and who can safely enter a watch-and-wait pathway.

Cercek/Memorial Sloan Kettering dostarlimab experience in dMMR locally advanced rectal cancer; AZUR-1 (phase 2, rectal) and AZUR-2 (phase 3, perioperative, colon) study designs, Future Oncol 2026.

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Mismatch Repair Deficient Colorectal Cancers

Immunotherapy

Single-Agent Anti–PD-1 Therapy for Refractory Solid Tumors

Table 2. Treatment Characteristics and Clinical Response to Therapy

Dose (mg/kg)	No. of Patients	Total No. of Doses					Best Response (duration in months)*
		1	2	3	5	11	
0.3	6	6	0	0	0	0	N/A
1	6	3	1	1	1	0	1 MXR (1)
3	6	3	0	2	1	0	1 CR (21+)†
10	21	15	1	4	0	1	2 PR (3+, 16+)‡§ 1 MXR (1)
Total	39	27	2	7	2	1	1 CR, 2 PR, 2 MXR

Abbreviations: N/A, not applicable; MXR, mixed response defined as regression in some lesions but concomitant progression in others; CR, complete response; PR, partial response.

*CR and PR by Response Evaluation Criteria in Solid Tumors 1.0 criteria.

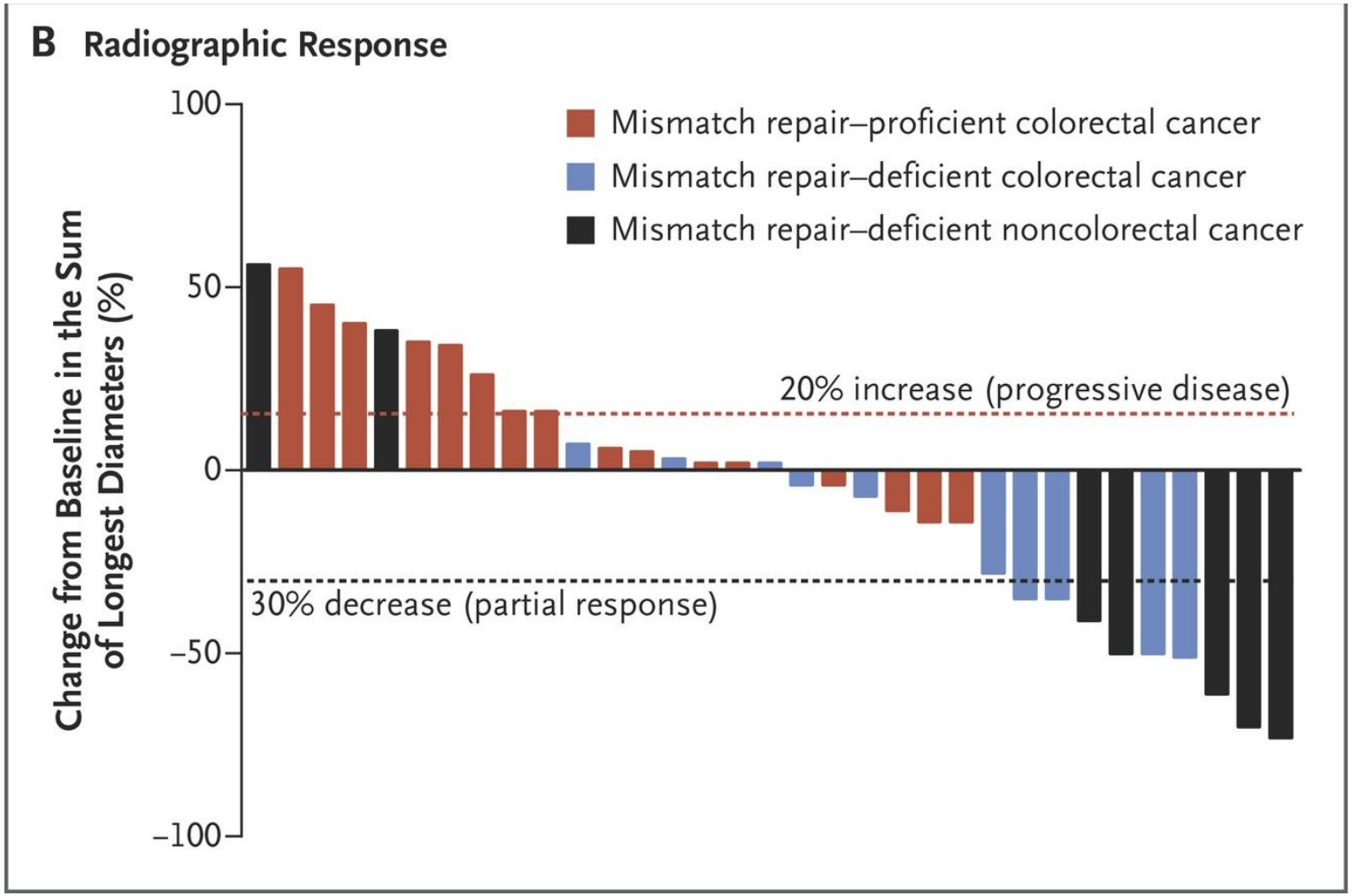
†This patient with stage IV colorectal cancer had previously shown progressive disease after receiving chemotherapy regimens including bevacizumab and cetuximab.

‡PR duration of 3+ months was preceded by an MXR in this patient with melanoma lasting 20 months. Previous therapies that were ineffective included high-dose interleukin-2 and temozolomide.

§PR duration of 16+ months was preceded by an MXR in this patient with renal cell carcinoma lasting 4 months. Previous therapies that were ineffective included sunitinib, sorafenib, and an experimental histone deacetylase inhibitor.

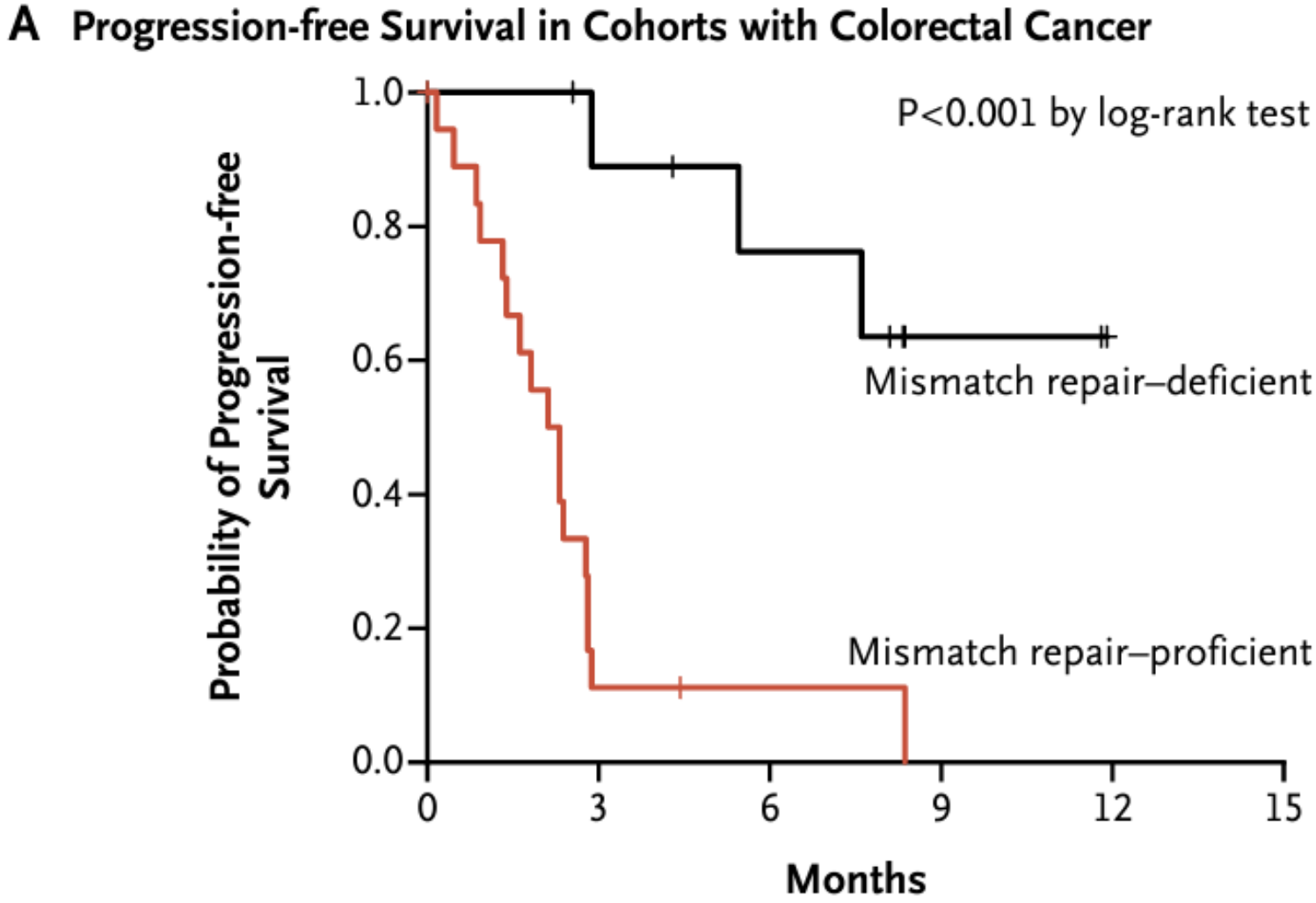
Brahmer JR. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol. 2010 Jul 1;28(19):3167-75. PMID: 20516446.

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency



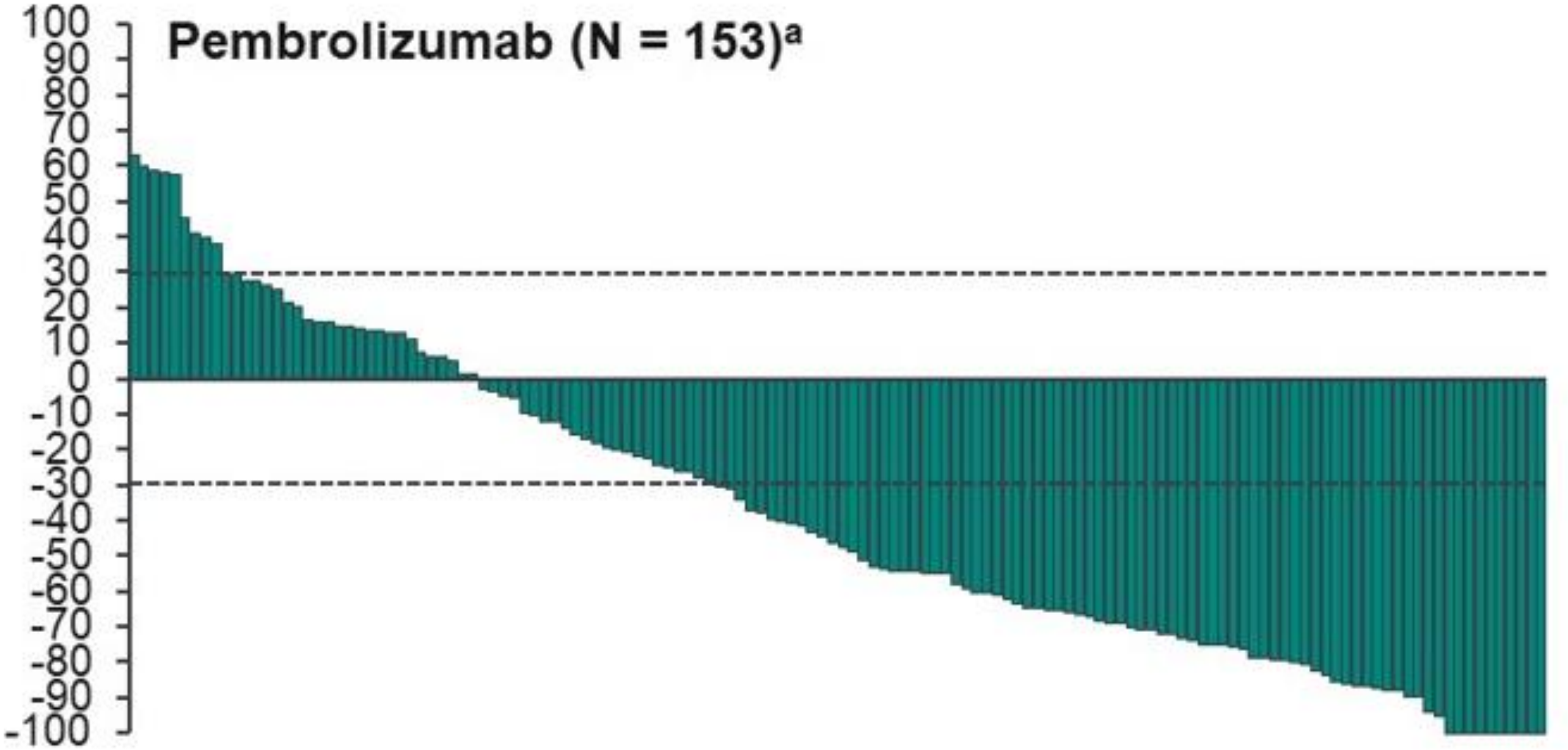
Le DT. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med. 2015 Jun 25;372(26):2509-20. PMID: 26028255.

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency



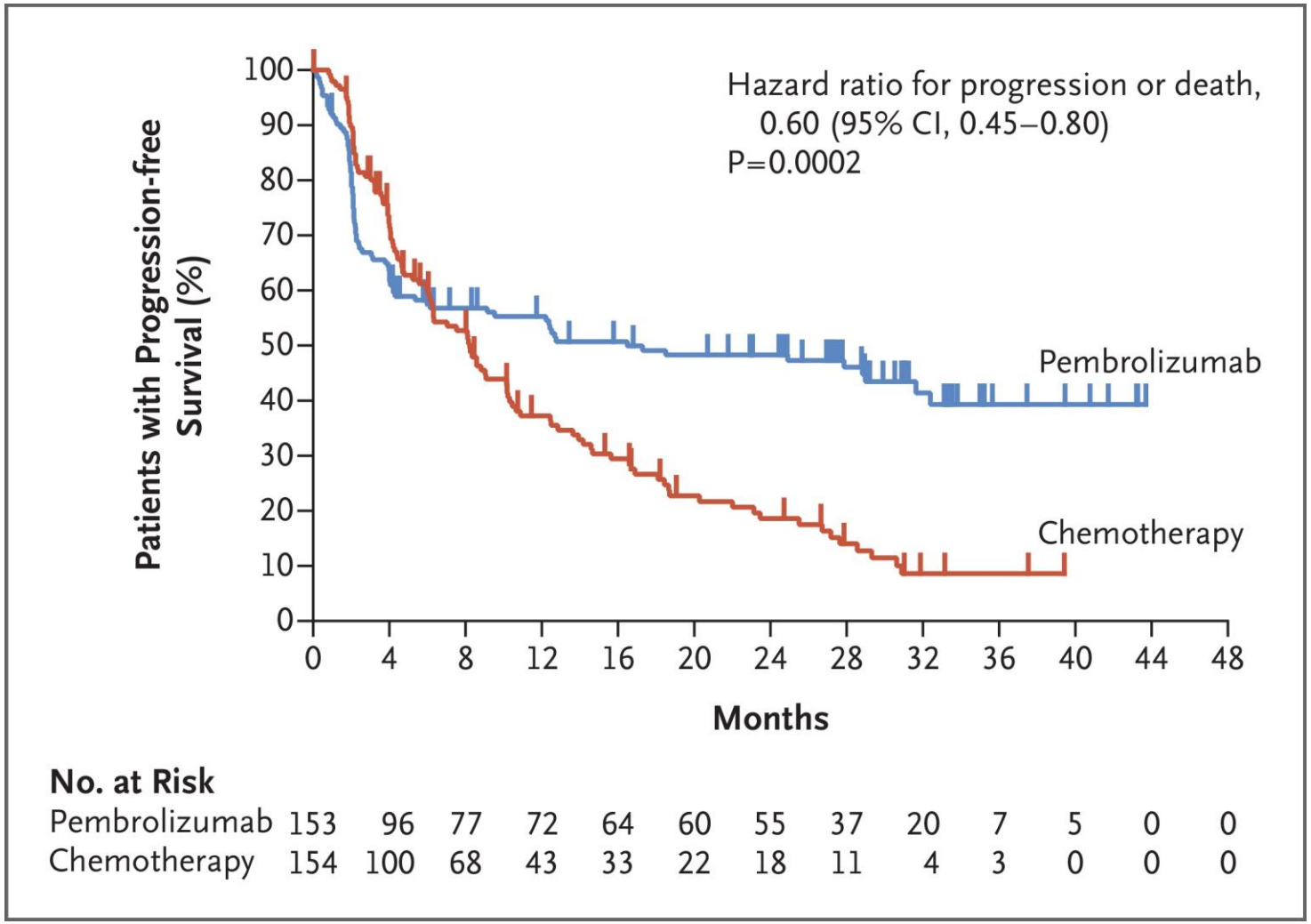
Le DT. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med. 2015 Jun 25;372(26):2509-20. PMID: 26028255.

Keynote 177: Pembrolizumab in metastatic setting



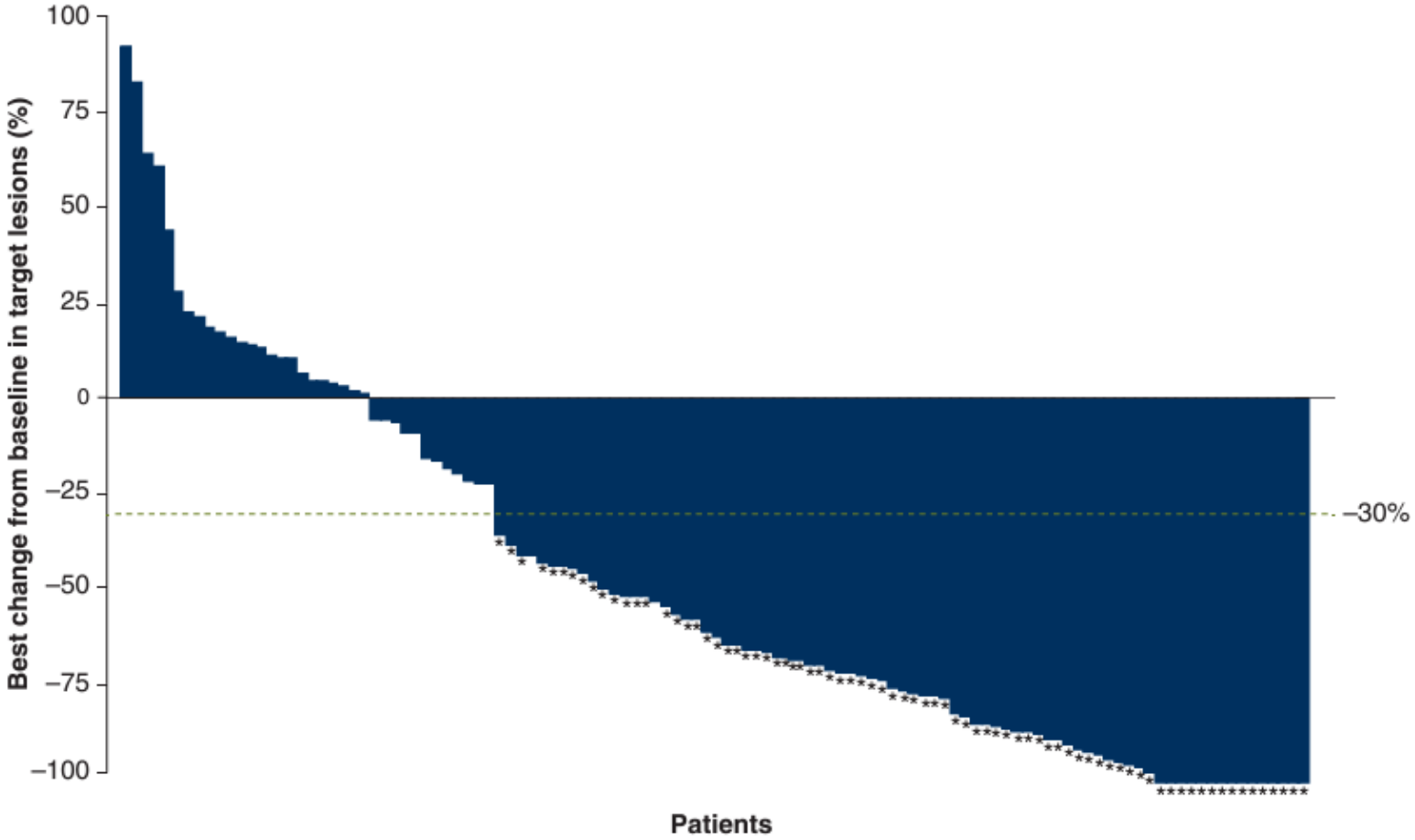
André T. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. N Engl J Med. 2020 Dec 3;383(23):2207-2218. PMID: 33264544.

Keynote 177: Pembrolizumab in metastatic setting



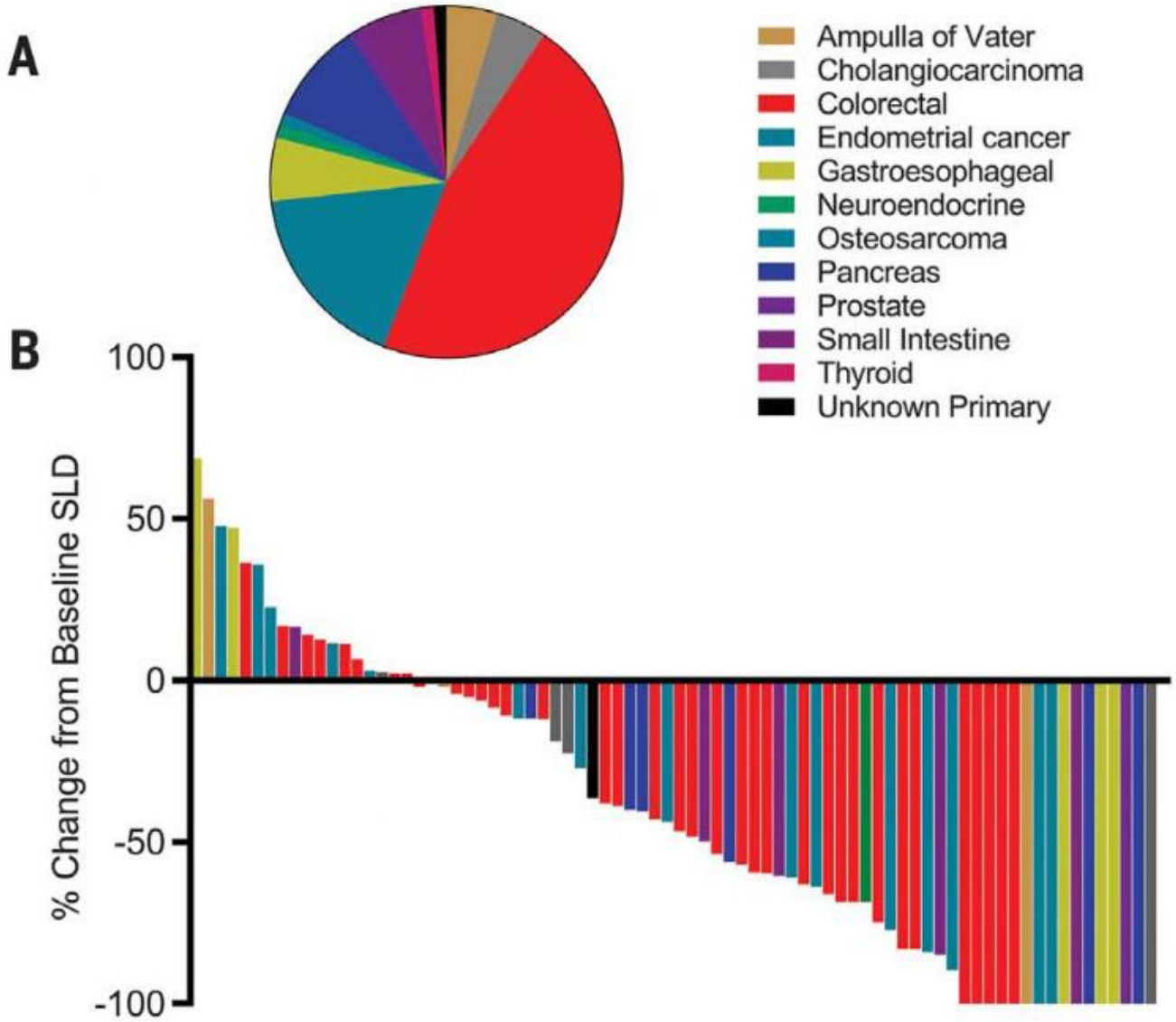
André T. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. N Engl J Med. 2020 Dec 3;383(23):2207-2218. PMID: 33264544.

CheckMate142: IPI/NIVO in previously treated metastatic colorectal cancer



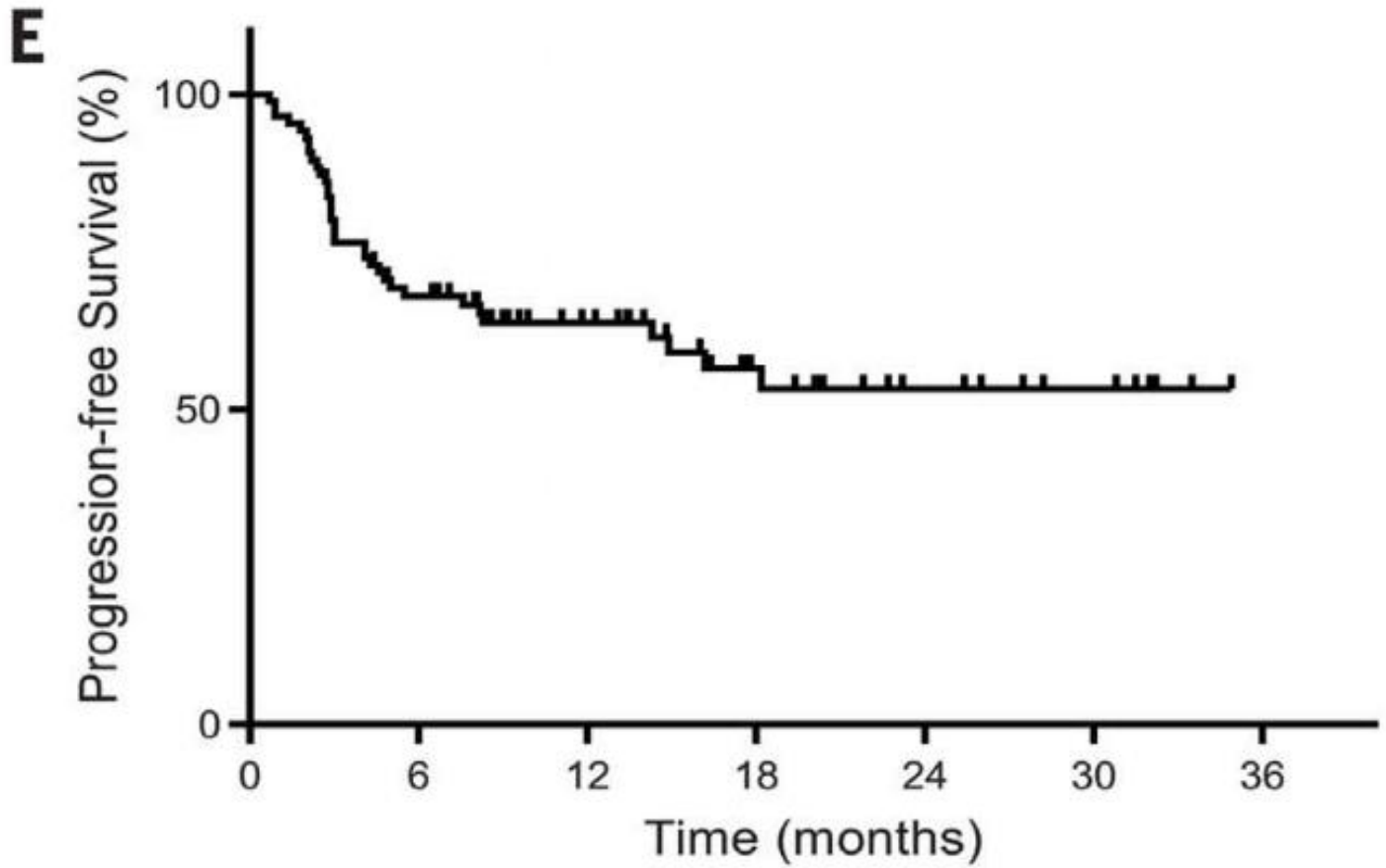
André T. Nivolumab plus low-dose ipilimumab in previously treated patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: 4-year follow-up from CheckMate 142. Ann Oncol. 2022 Oct;33(10):1052-1060PMID: 35764271.

Agnostic approval



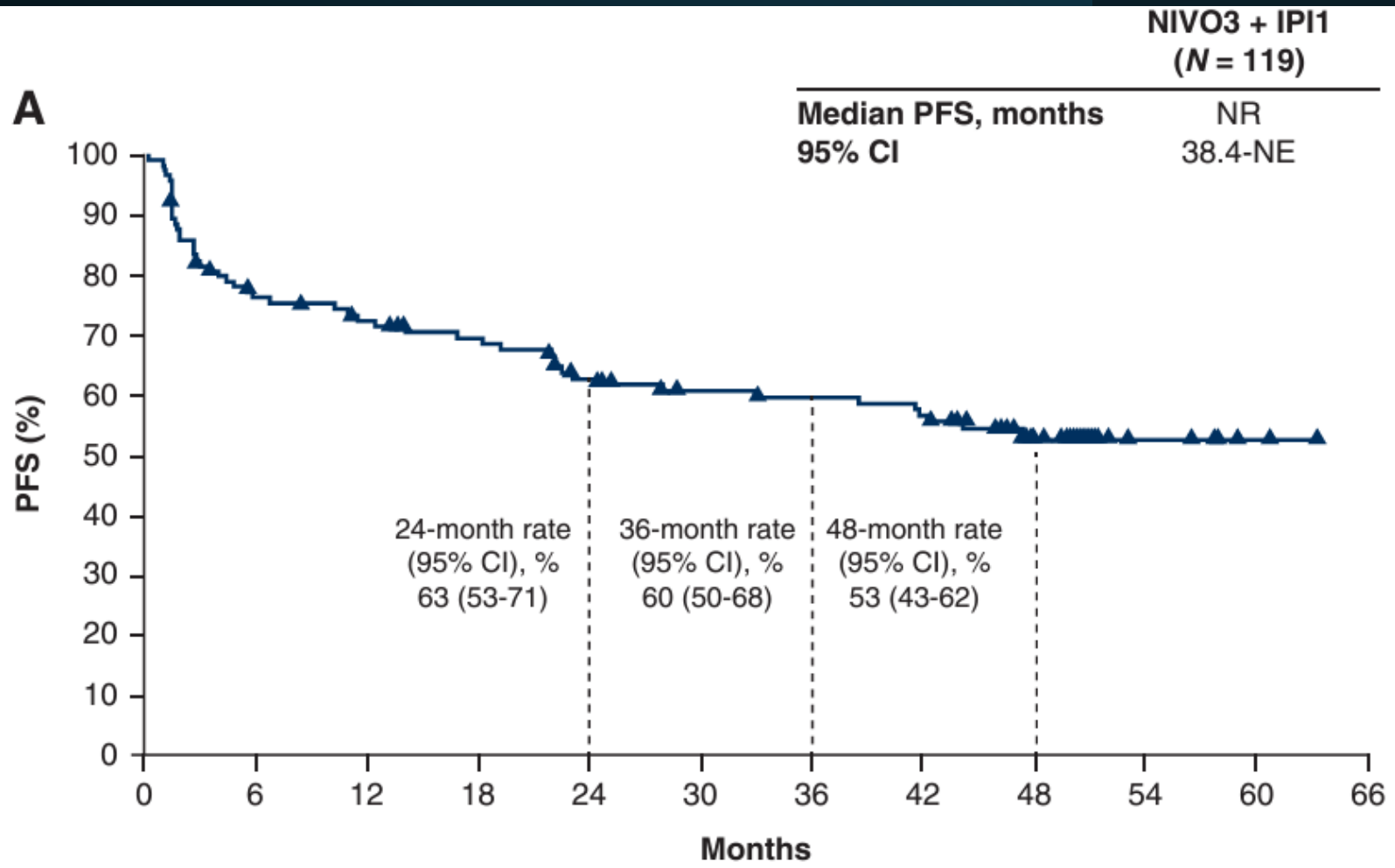
Le DT. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017. PMID: 28596308.

Agnostic Approval



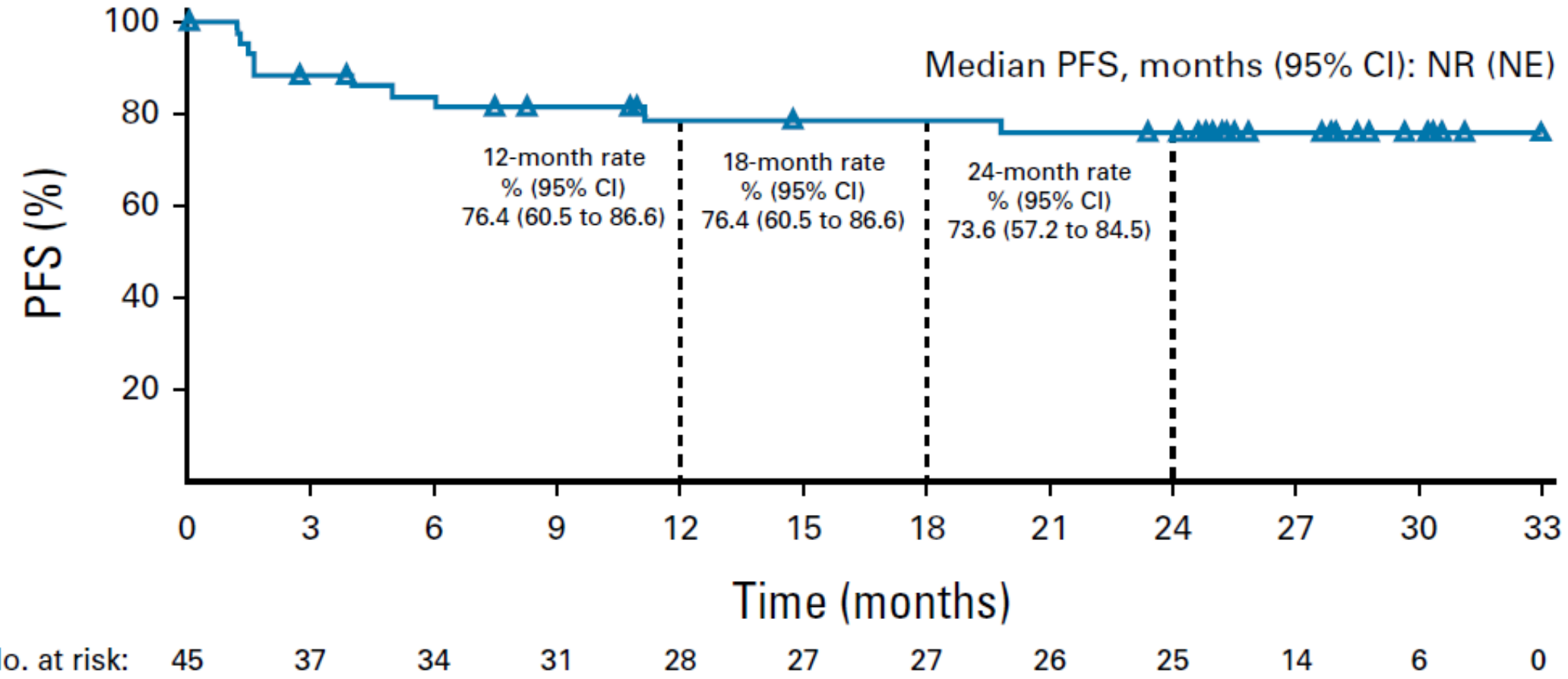
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CheckMate142: IPI/NIVO in previously treated metastatic colorectal cancer



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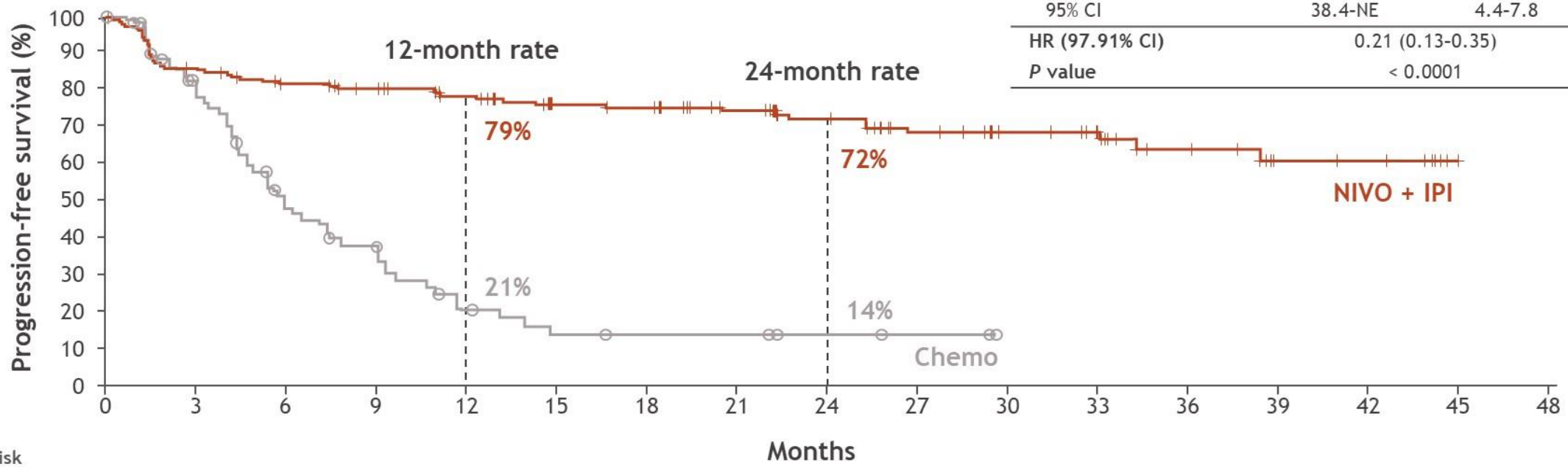
First-Line Nivolumab Plus Low-Dose Ipilimumab for Microsatellite Instability-High



Lenz HJ. First-Line Nivolumab Plus Low-Dose Ipilimumab for Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: The Phase II CheckMate 142 Study. J Clin Oncol. 2022 Jan 10;40(2):161-170. PMID: 34637336.

Progression-free survival

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

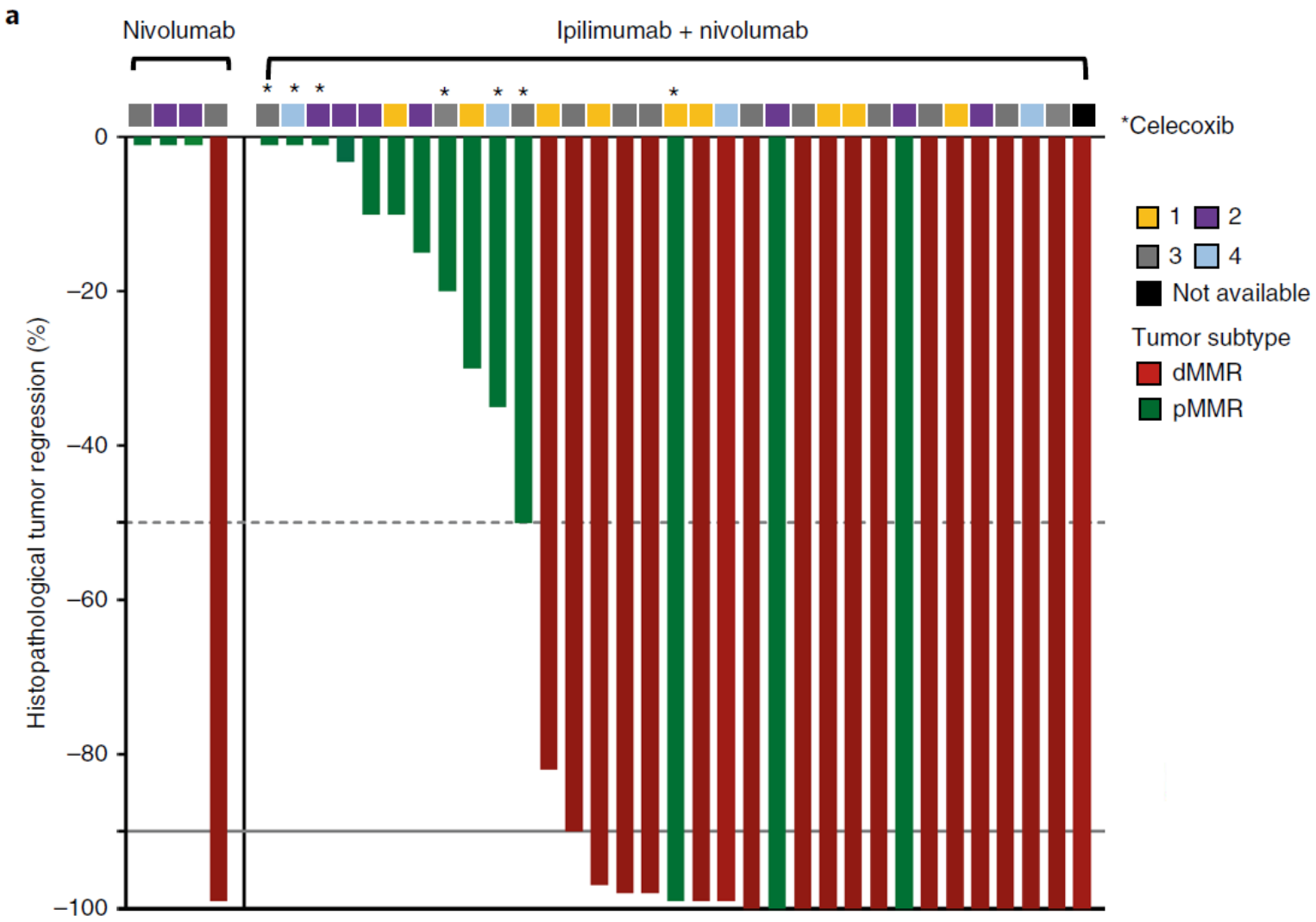
- PFS benefit with NIVO + IPI vs chemo was robust and consistent across the sensitivity and supportive analyses, including PFS by BICR in 1L all randomized patients (HR, 0.32; 95% CI, 0.23-0.46)

[a]Per BICR. [b]Median follow-up in patients with centrally confirmed MSI-H/dMMR, 31.6 months.

Mismatch repair deficient colorectal cancers

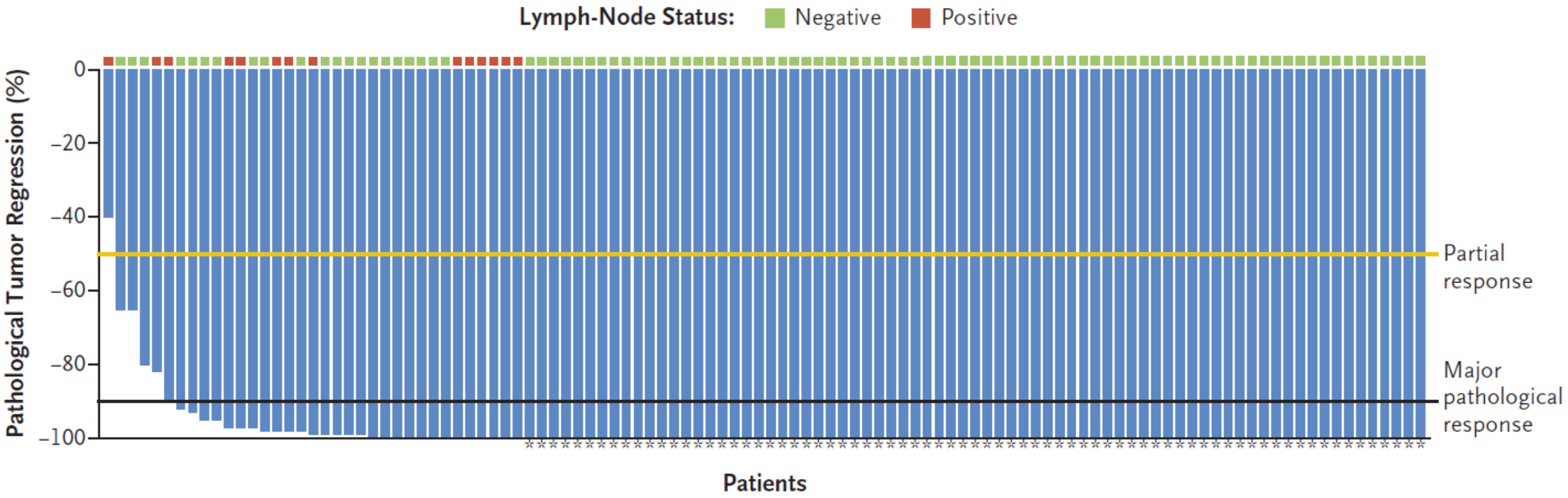
Neoadjuvant immunotherapy

NICHE-1



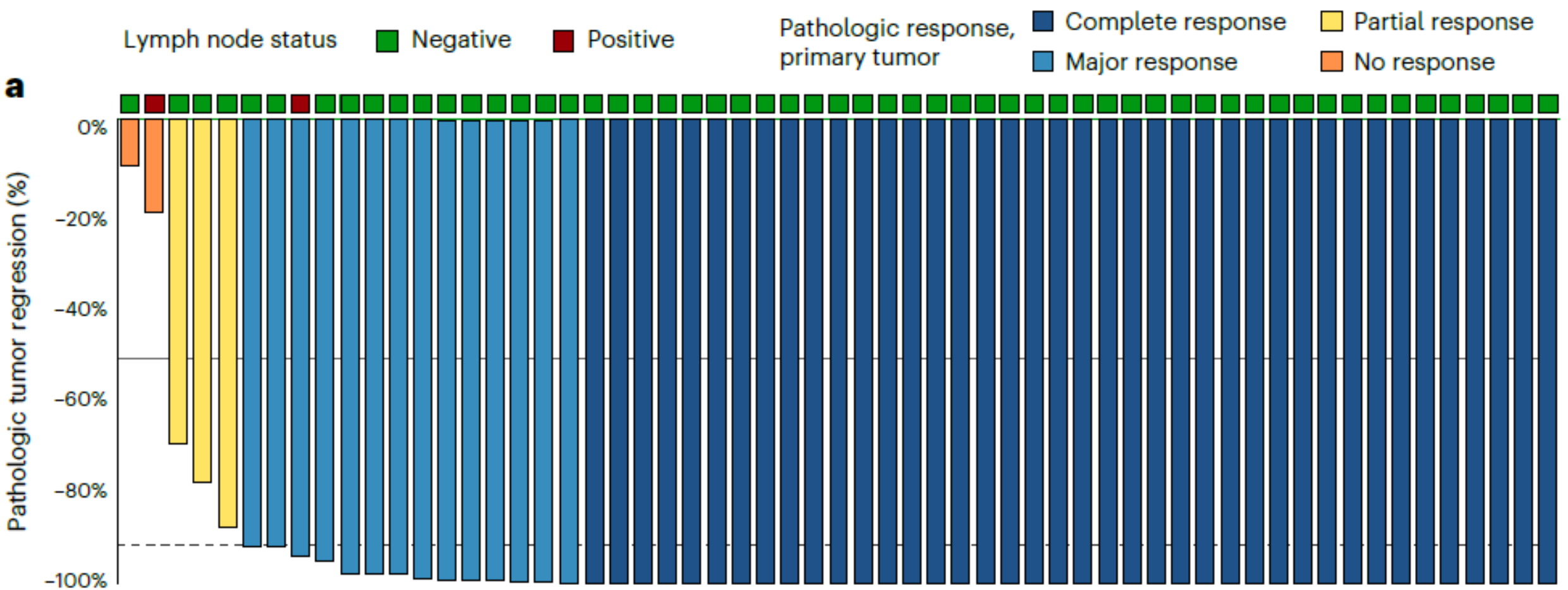
Chalabi M. Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. Nat Med. 2020 Apr;26(4):566-576. PMID: 32251400.

NICHE-2



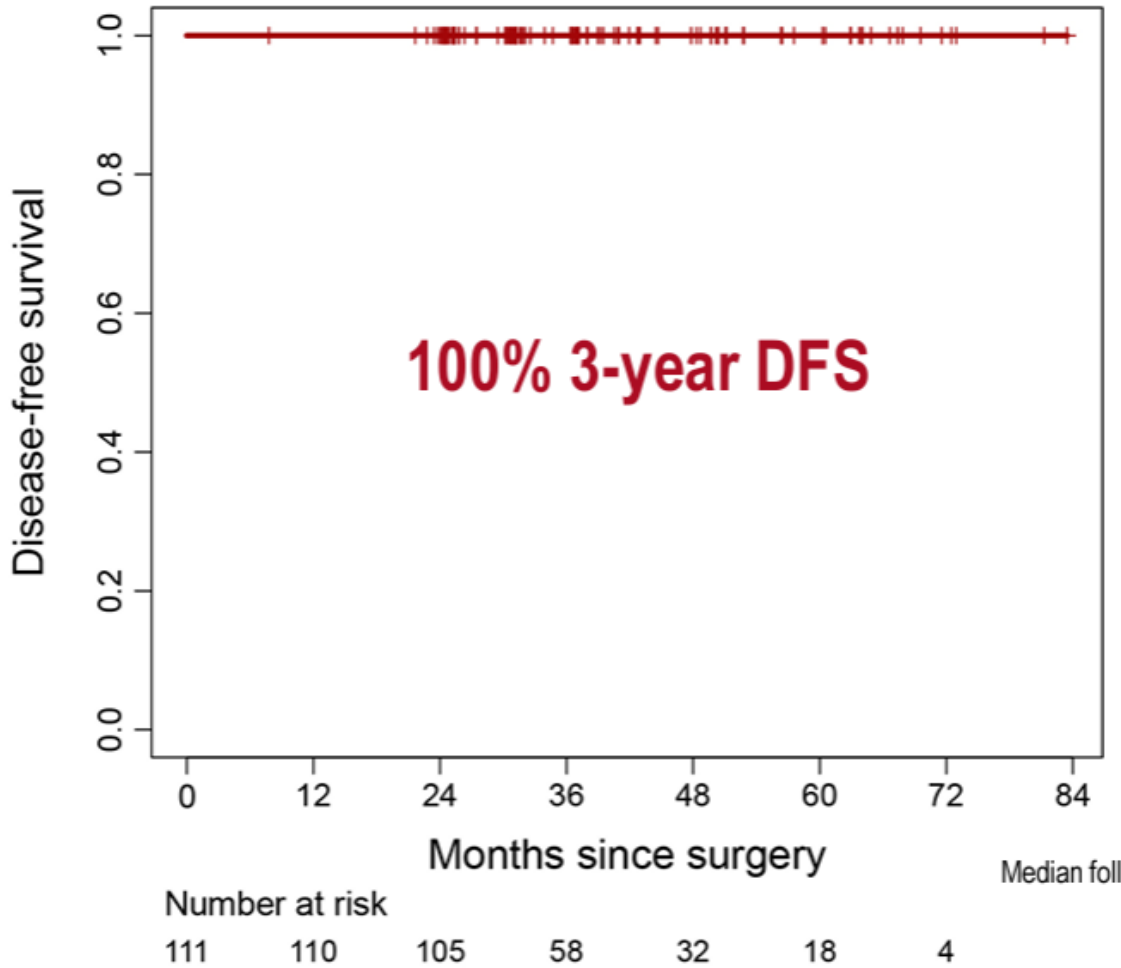
Chalabi M. Neoadjuvant Immunotherapy in Locally Advanced Mismatch Repair-Deficient Colon Cancer. N Engl J Med. 2024 Jun 6;390(21):1949-1958. PMID: 38838311.

NICHE-3



de Gooyer PGM Neoadjuvant nivolumab and relatlimab in locally advanced MMR-deficient colon cancer: a phase 2 trial. Nat Med. 2024 Nov;30(11):3284-3290. PMID: 39278994.

Results – 3-year disease-free survival 100%

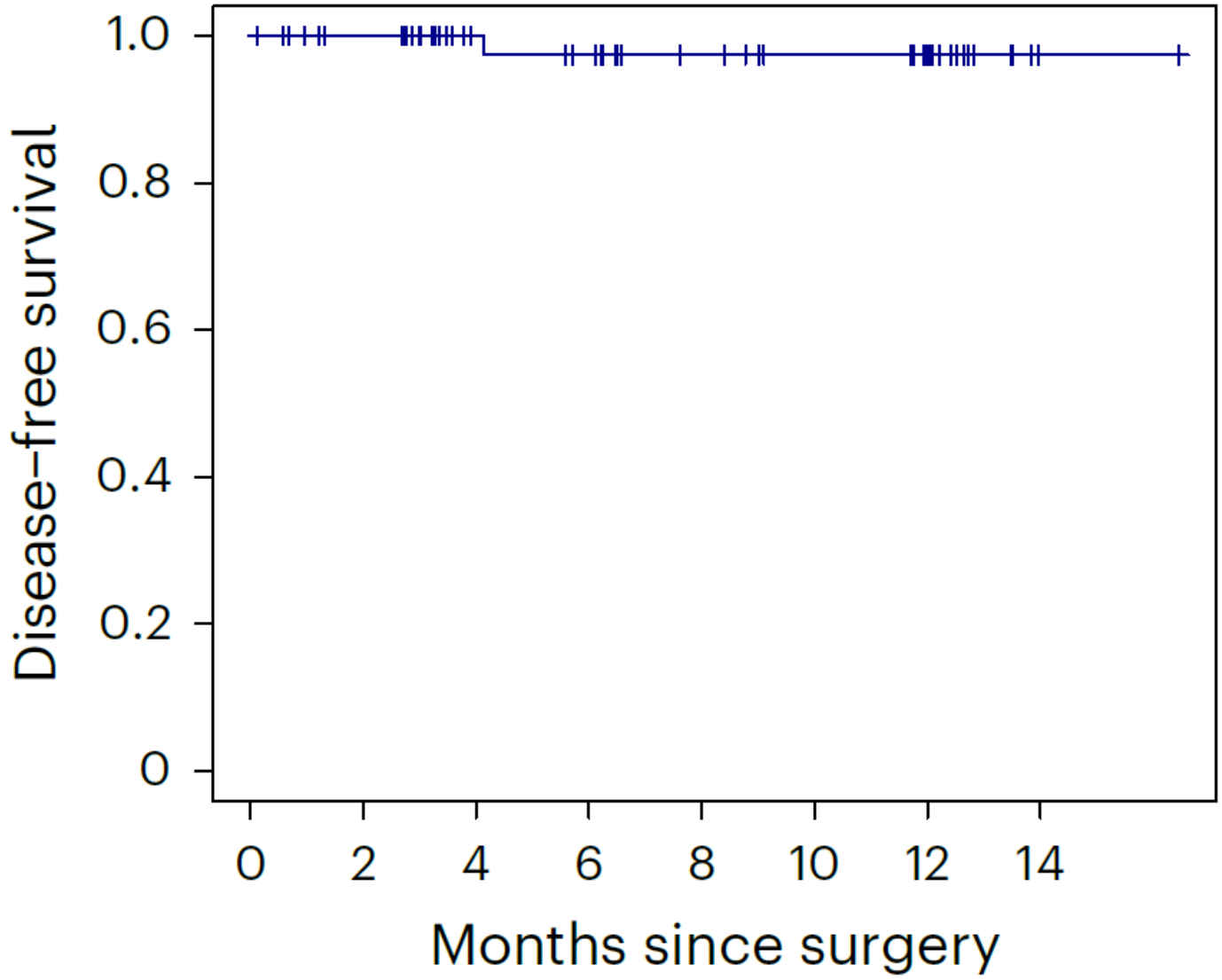


Median follow-up after surgery: 36.6 months (7.8 - 83.4)

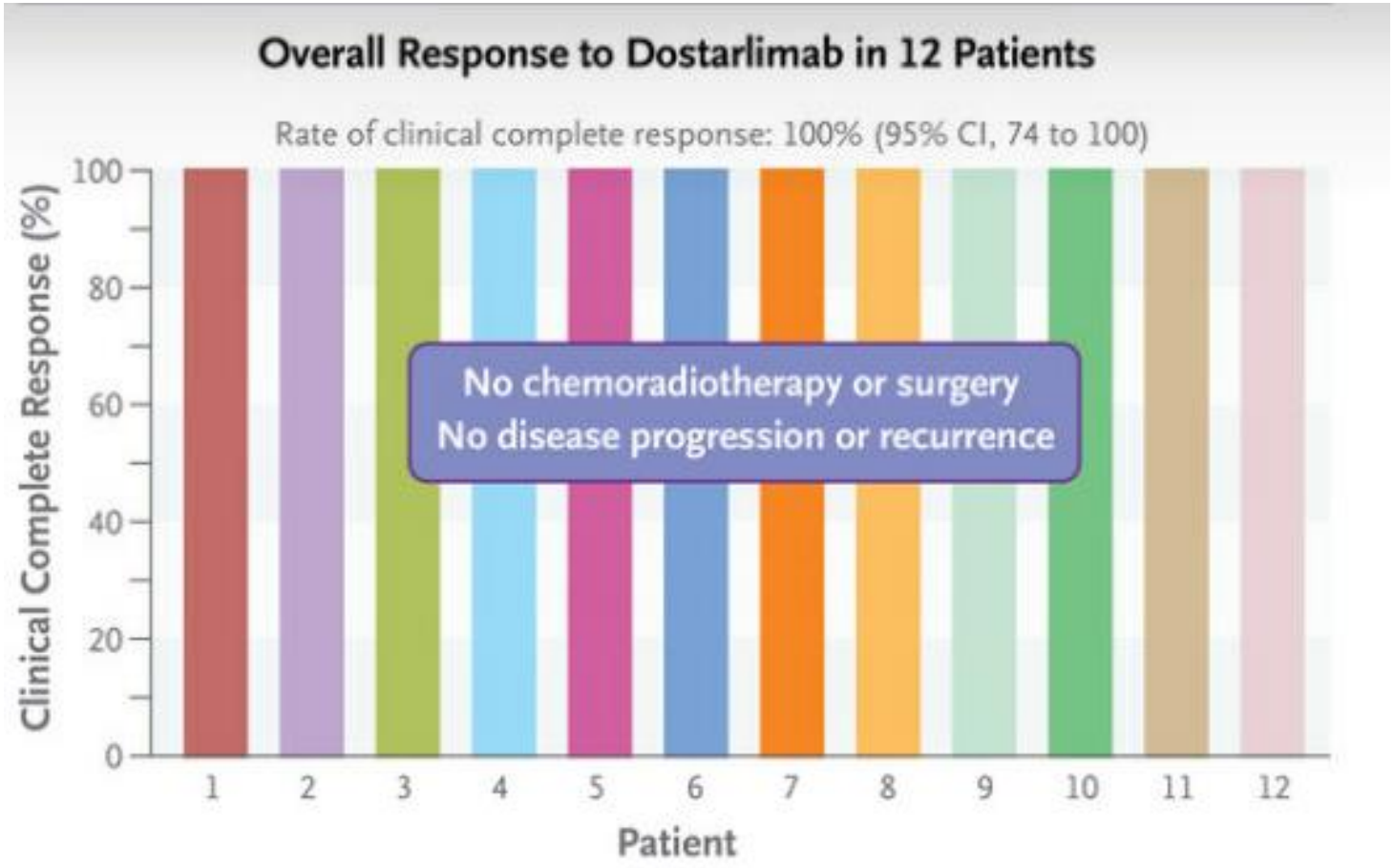
BARCELONA 2024 ESMO congress

Data cut-off: 11 September 2024

de Gooyer PGM Neoadjuvant nivolumab and relatlimab in locally advanced MMR-deficient colon cancer: a phase 2 trial. Nat Med. 2024 Nov;30(11):3284-3290. PMID: 39278994.



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

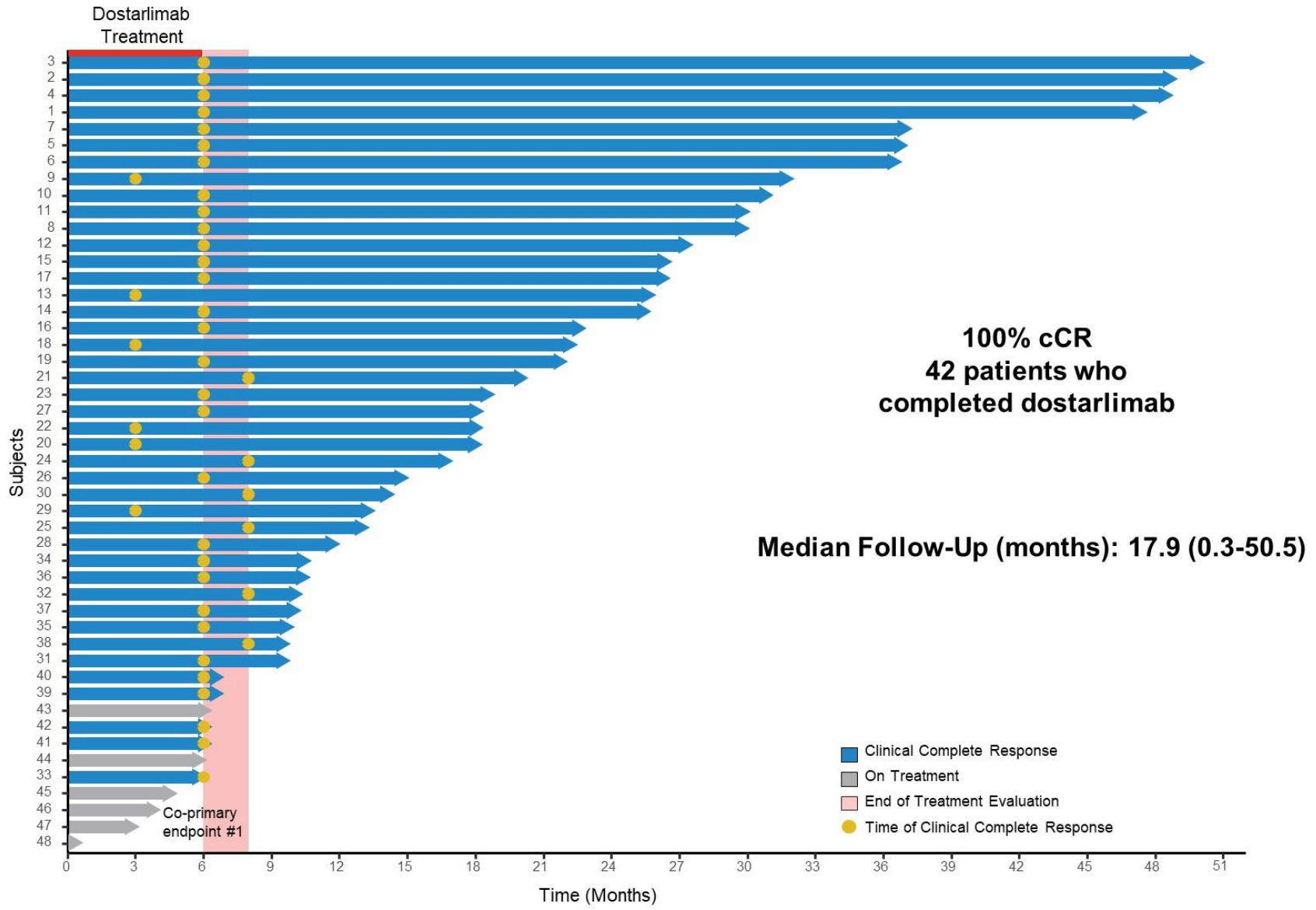


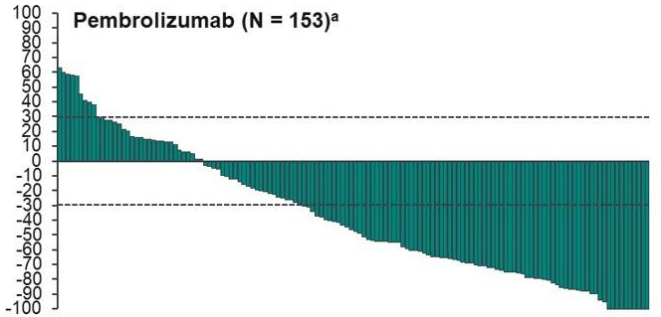
Cercek A. PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer. N Engl J Med. 2022 Jun 23;386(25):2363-2376. PMID: 35660797.

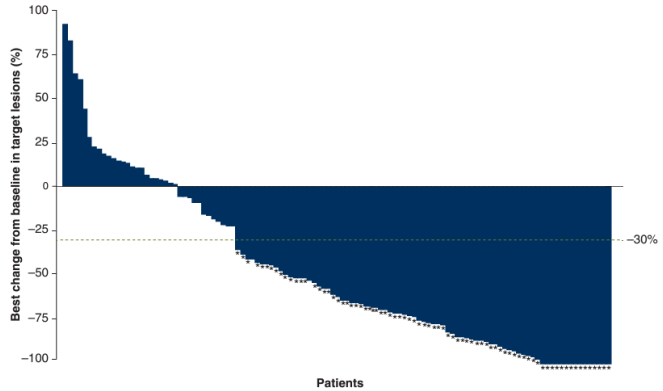
Individual responses to PD-1 blockade with dostarlimab

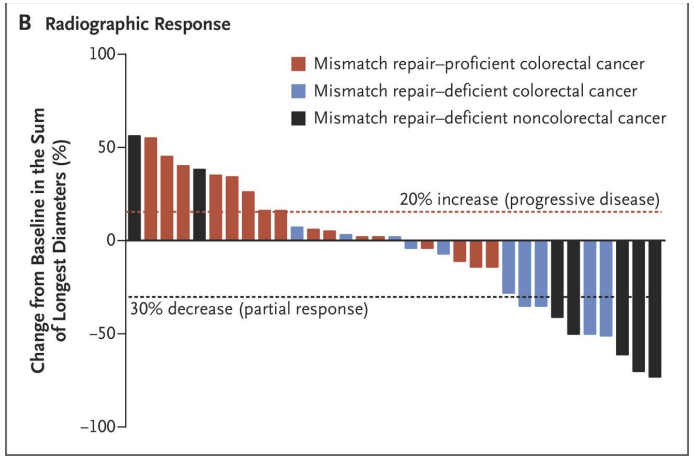
Patients who completed 6-months of dostarlimab

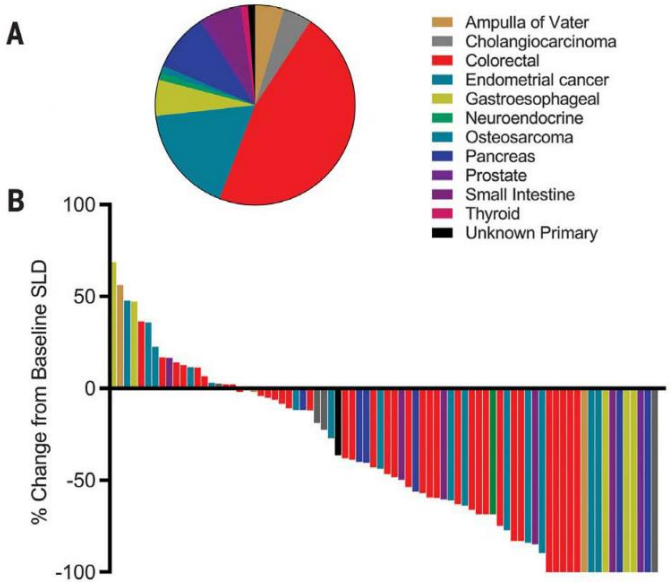
ID	Age	Stage T	Stage N	FU (months)	Digital rectal exam response	Endoscopic best response	Rectal MRI best response	Overall response 100%
1	38	T4	N+	23.8	CR	CR	CR	**cCR**
2	30	T3	N+	20.5	CR	CR	CR	**cCR**
3	61	T1/2	N+	20.6	CR	CR	CR	**cCR**
4	28	T4	N+	20.5	CR	CR	CR	**cCR**
5	53	T1/2	N+	9.1	CR	CR	CR	**cCR**
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**

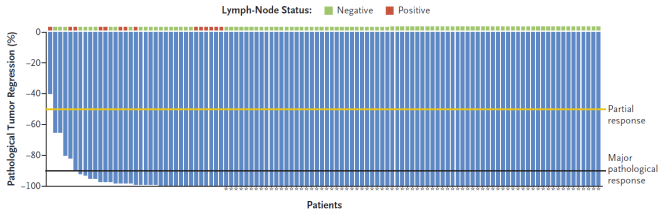

Dostarlimab
Treatment
Subjects
3
2
4
1
7
5
6
9
10
11
8
12
15
17
13
14
16
18
19
21
23
27
22
20
24
26
30
29
25
28
34
36
32
37
35
38
31
40
39
43
42
41
44
33
45
46
47
48
Co-primary
endpoint #1
0
3
6
9
12
15
18
21
24
27
30
33
36
39
42
45
48
51
Time (Months)
100% cCR
42 patients who
completed dostarlimab
Median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

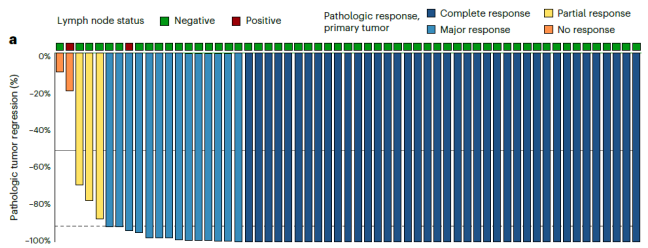

Pembrolizumab (N = 153)[a]
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100

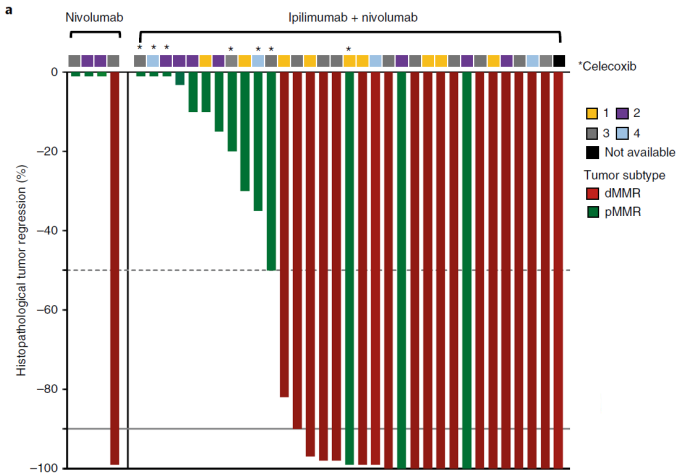

Best change from baseline in target lesions (%)
100
75
50
25
0
−25
−50
−75
−100
−30%
Patients

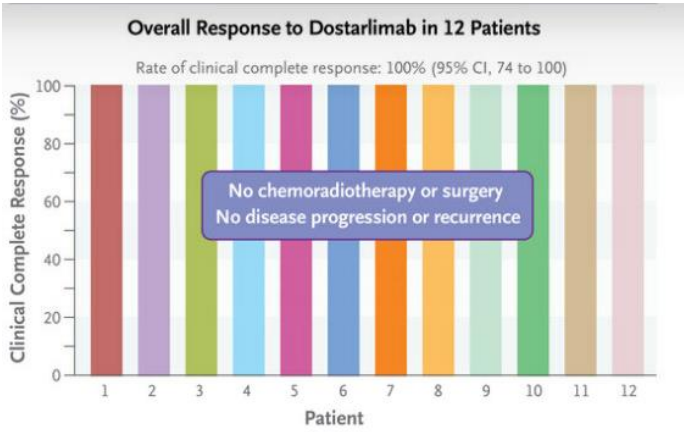

B Radiographic Response
Change from Baseline in the Sum of Longest Diameters (%)
100
50
0
−50
−100
Mismatch repair–proficient colorectal cancer
Mismatch repair–deficient colorectal cancer
Mismatch repair–deficient noncolorectal cancer
20% increase (progressive disease)
30% decrease (partial response)

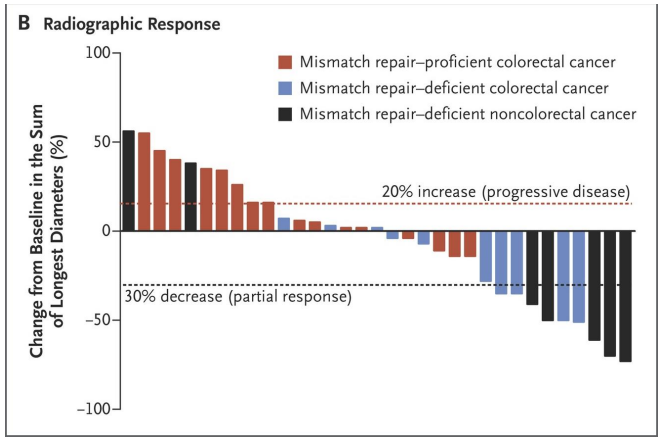

A
Ampulla of Vater
Cholangiocarcinoma
Colorectal
Endometrial cancer
Gastroesophageal
Neuroendocrine
Osteosarcoma
Pancreas
Prostate
Small Intestine
Thyroid
Unknown Primary
B
% Change from Baseline SLD
100
50
0
-50
-100

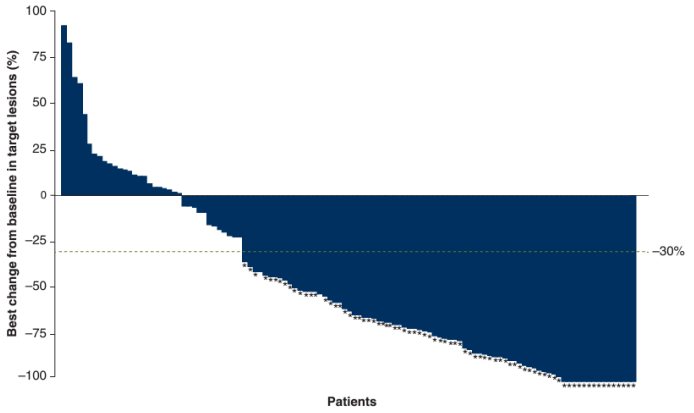

Lymph-Node Status: Negative Positive
Pathological Tumor Regression (%)
0
−20
−40
−60
−80
−100
Partial response
Major pathological response
Patients

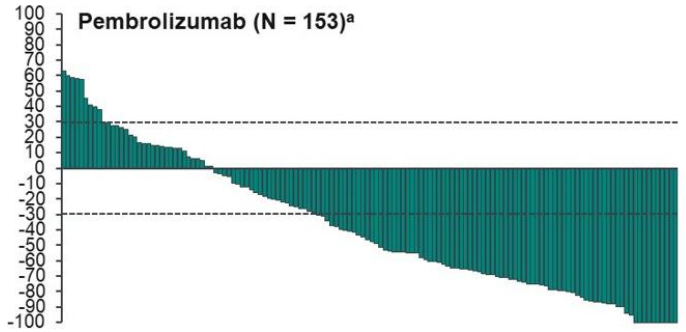

a
Lymph node status Negative Positive
Pathologic response, primary tumor Complete response Partial response Major response No response
Pathologic tumor regression (%)
0%
−20%
−40%
−60%
−80%
−100%

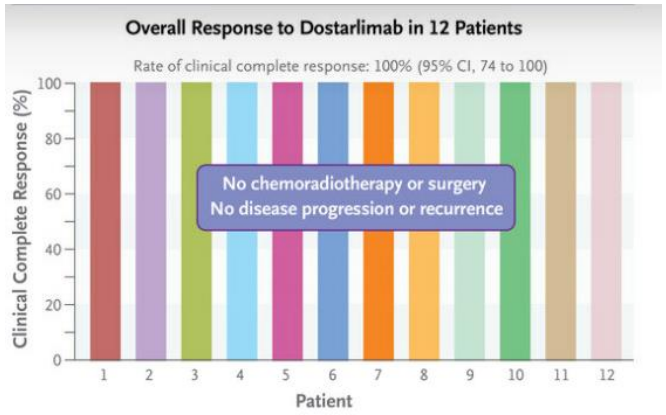

a
Nivolumab
Ipilimumab + nivolumab
*Celecoxib
1 2
3 4
Not available
Tumor subtype
dMMR
pMMR
Histopathological tumor regression (%)
0
−20
−40
−60
−80
−100

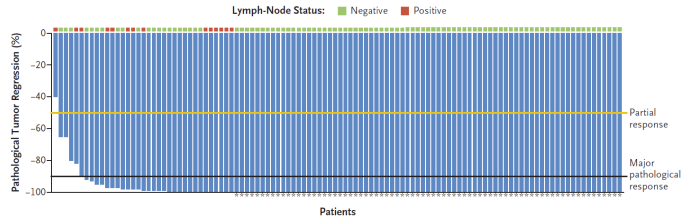

Overall Response to Dostarlimab in 12 Patients
Rate of clinical complete response: 100% (95% CI, 74 to 100)
Clinical Complete Response (%)
100
80
60
40
20
0
No chemoradiotherapy or surgery
No disease progression or recurrence
1 2 3 4 5 6 7 8 9 10 11 12
Patient

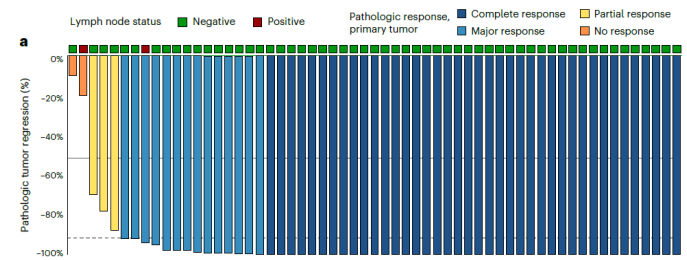

B Radiographic Response
Mismatch repair–proficient colorectal cancer
Mismatch repair–deficient colorectal cancer
Mismatch repair–deficient noncolorectal cancer
Change from Baseline in the Sum of Longest Diameters (%)
100
50
0
−50
−100
20% increase (progressive disease)
30% decrease (partial response)

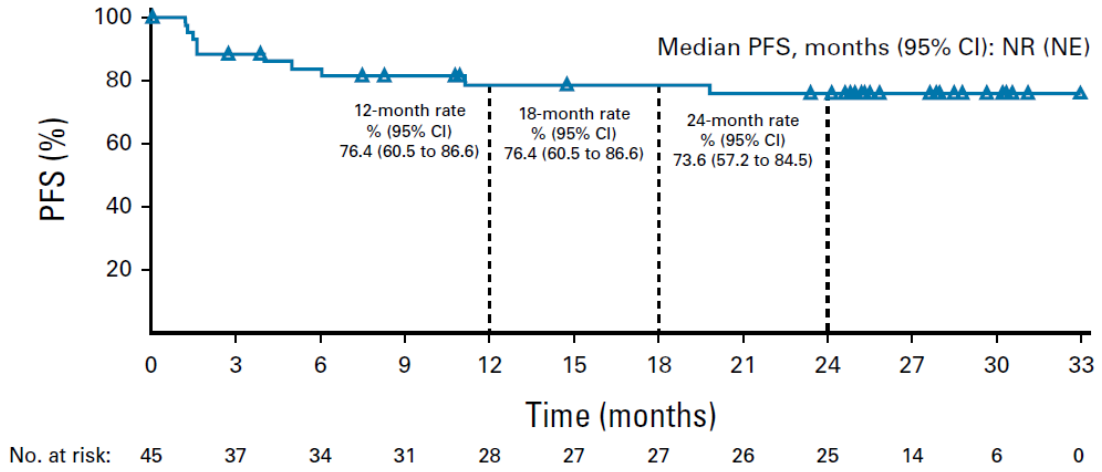

Best change from baseline in target lesions (%)
100
75
50
25
0
−25
−50
−75
−100
−30%
Patients

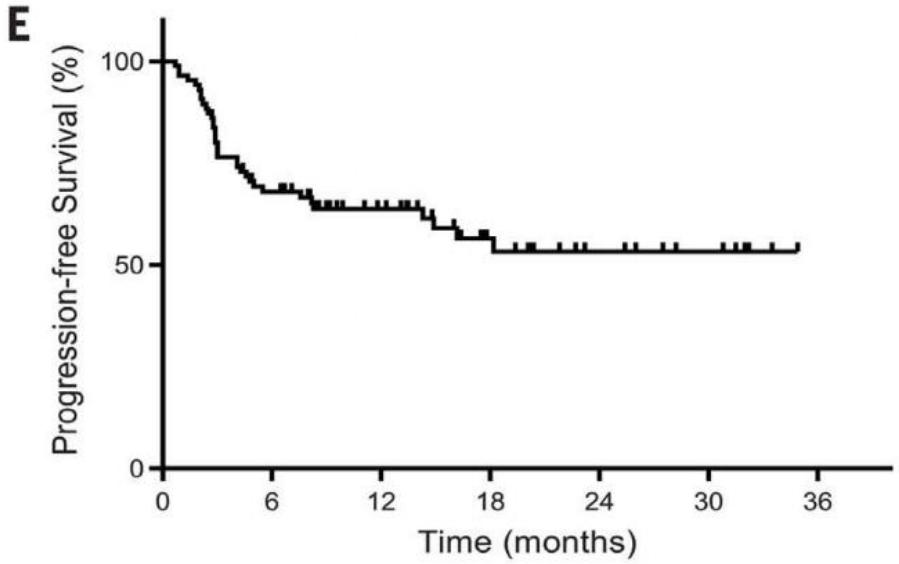

Pembrolizumab (N = 153)a
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100


Overall Response to Dostarlimab in 12 Patients
Rate of clinical complete response: 100% (95% CI, 74 to 100)
Clinical Complete Response (%)
100
80
60
40
20
0
No chemoradiotherapy or surgery
No disease progression or recurrence
1
2
3
4
5
6
7
8
9
10
11
12
Patient

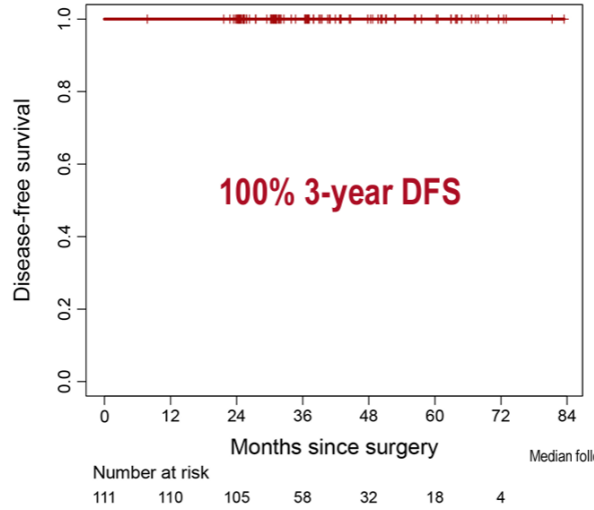

Lymph-Node Status: Negative Positive
Pathological Tumor Regression (%)
0
-20
-40
-60
-80
-100
Partial response
Major pathological response
Patients


Lymph node status Negative Positive
Pathologic response, primary tumor
Complete response
Major response
Partial response
No response
a
Pathologic tumor regression (%)
0%
-20%
-40%
-60%
-80%
-100%





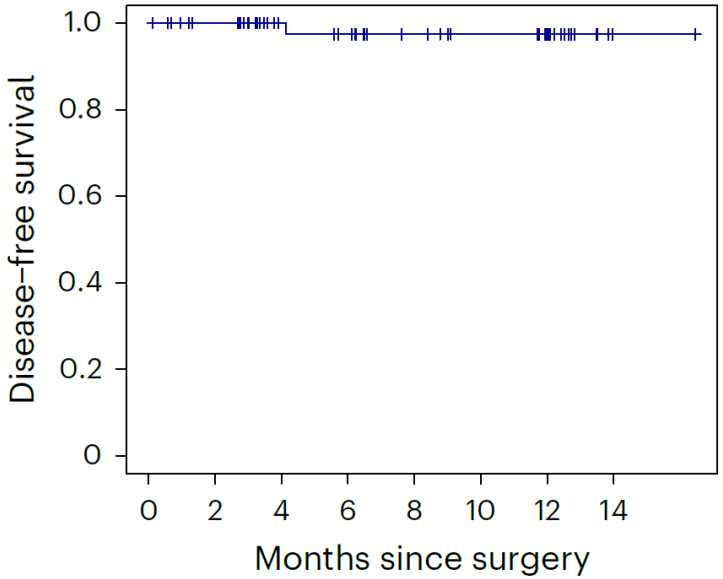
Results – 3-year disease-free survival 100%



Median follow-up after surgery: 36.6 months (7.8 - 83.4)

BARCELONA 2024 ESMO congress

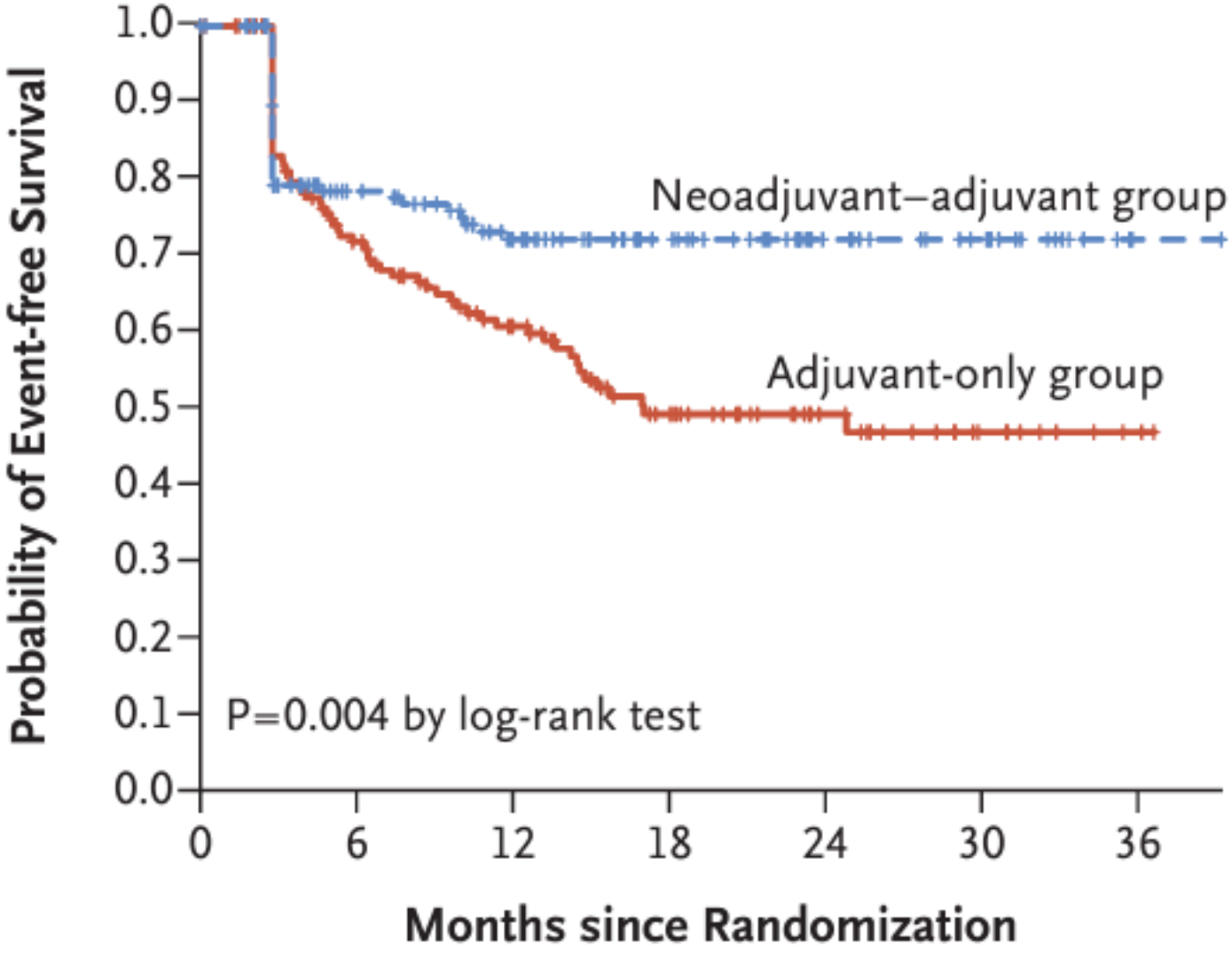
Data cut-off: 11 September 2024



Neoadjuvant Paradigm Shift

Additional data

Neoadjuvant–Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma



Patel SP. Neoadjuvant-Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma. N Engl J Med. 2023 Mar 2;388(9):813-823. PMID: 36856617.

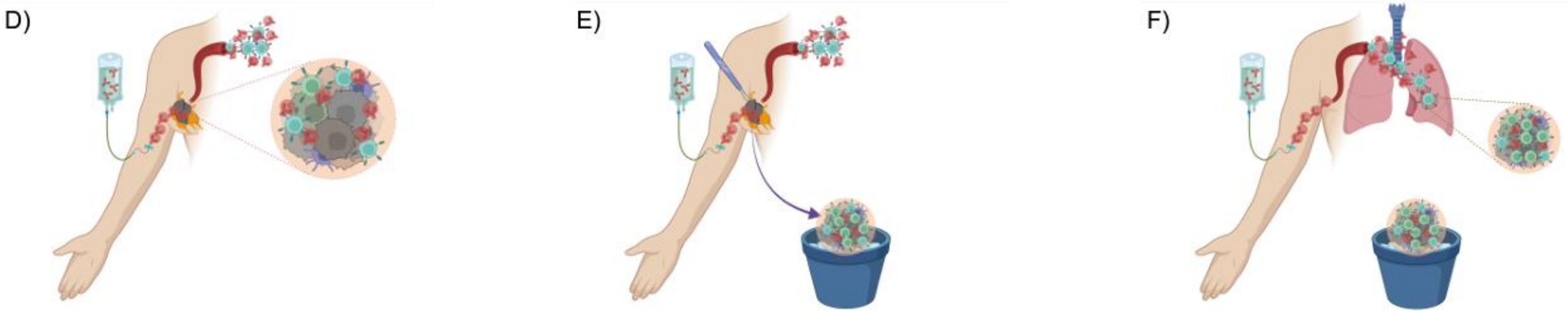
Mechanisms: Adjuvant Therapy



A, B and C) Adjuvant therapy. Before surgery, **the majority of antitumor T cells inhibited by PD-1 are located at the sites of locally advanced disease** (A), which are **resected** with surgery (B).

When giving adjuvant anti-PD-1, the therapy **relies on the existence of antitumor T cells inhibited by PD-1 at micrometastases sites** (C).

Mechanisms: Neoadjuvant Therapy

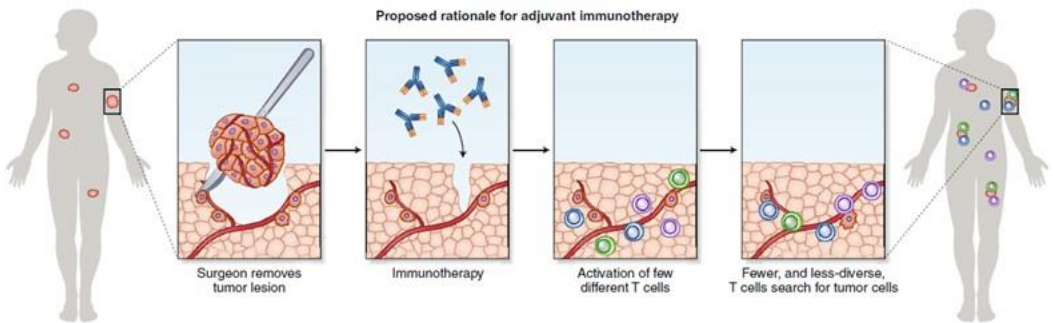


D, E and F) Neoadjuvant therapy. Administering neoadjuvant anti-PD-1 therapy is **intended to activate the large numbers of antitumor T cells at the tumor site** (D) **before the definitive surgery** (E).

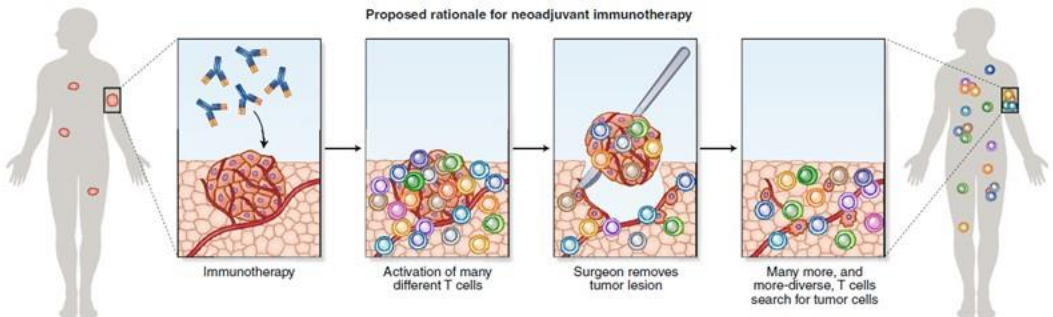
The locally-activated antitumor T cells then go onto induce a **systemic immune response** able to recognize distant micrometastatic sites (F)

Biological & Early Clinical Rationale for Neoadjuvant Immunotherapy

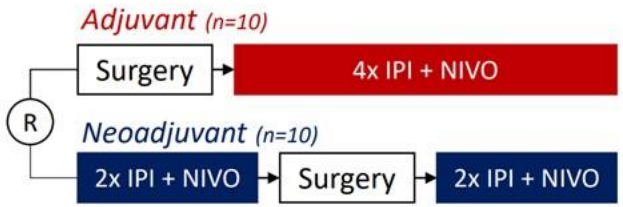
Adjuvant immunotherapy

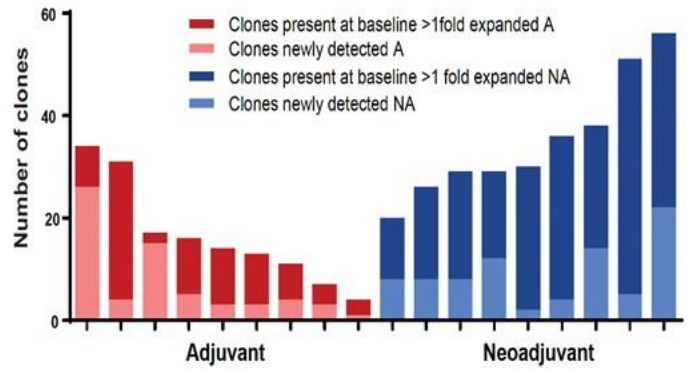


Neoadjuvant immunotherapy

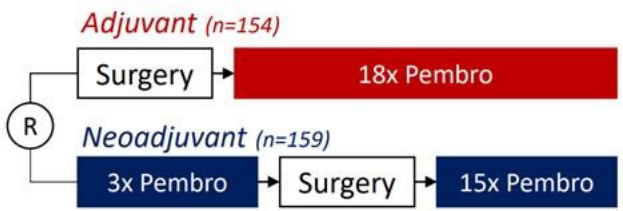


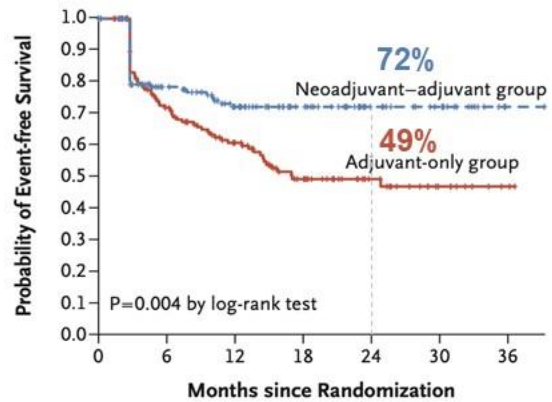
OpACIN (Phase1)
neoadjuvant ipilimumab + nivolumab





SWOG1801 (Phase 2)
neoadjuvant pembrolizumab

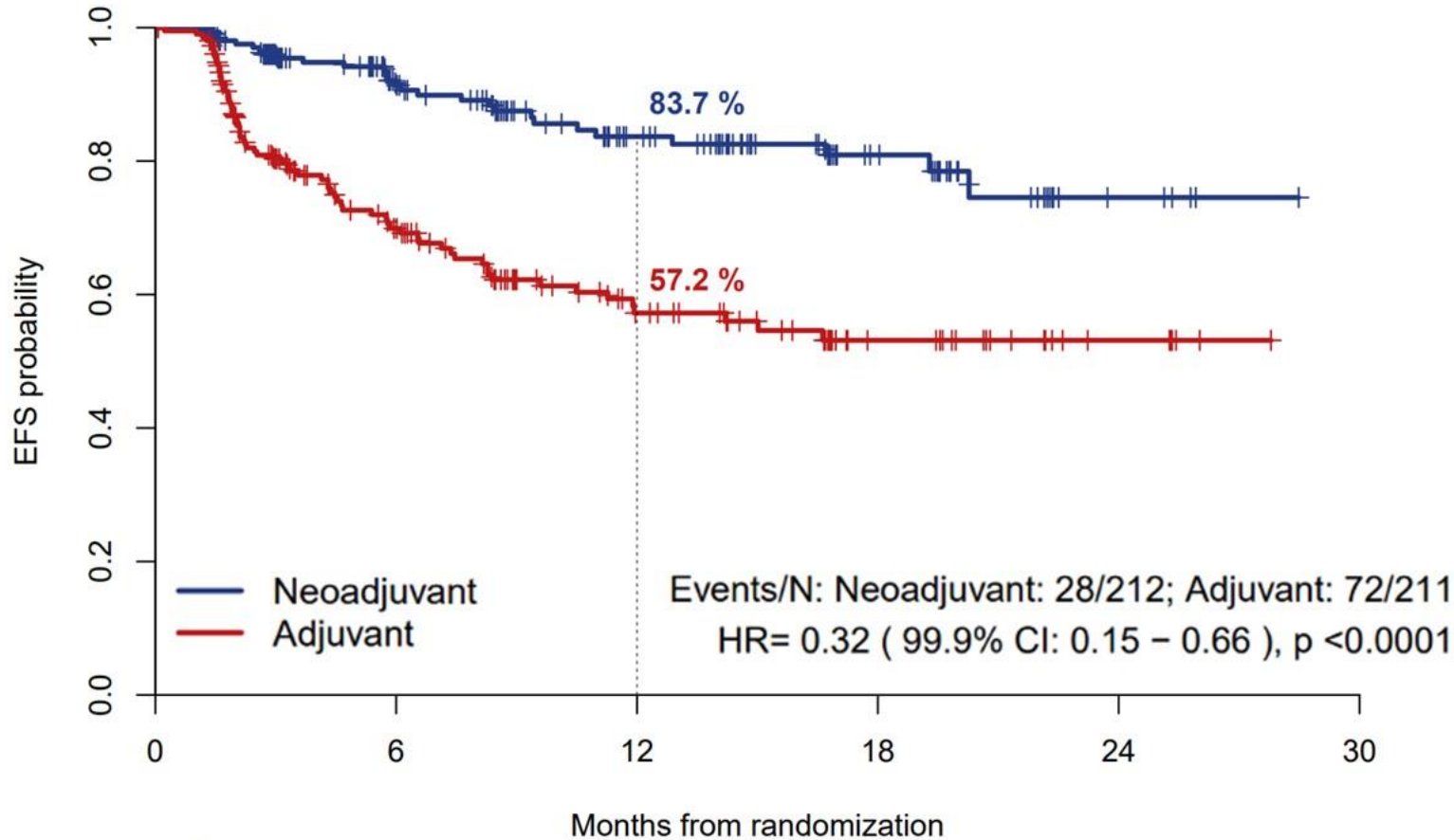




Versluis, Long and Blank, Nat Med 2020; Blank et al., Nat Med 2018; Patel et al., NEJM 2023

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NADINA – Primary Endpoint: Event-Free Survival (EFS)



# at risk (censored)										
Neoadjuvant	212	(0)	126	(71)	77	(111)	34	(152)	5	(179)
Adjuvant	211	(0)	100	(57)	53	(89)	23	(116)	6	(133)

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What about MSS (“cold”) tumors?

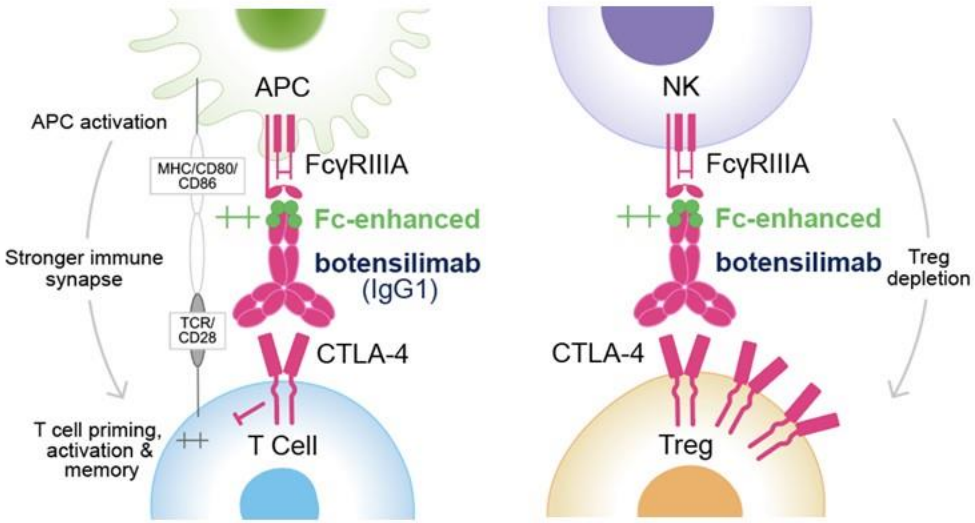
Microsatellite Stable/Mismatch Repair Proficient Colorectal Cancer

Background/Methods

- Effective therapies for colorectal cancer (CRC), particularly in those ~85-95% with **proficient mismatch repair/ microsatellite stable (pMMR/MSS)** cancer, are a critical unmet need.[1]
- **Botensilimab (BOT),** a multifunctional next-generation **anti-CTLA-4 antibody**, with balstilimab (BAL), an anti-PD-1 antibody, has a response rate of >20% in patients with heavily pretreated pMMR/MSS metastatic CRC.[2]
- NEST-1 (NCT05571293) is the first study to evaluate **neoadjuvant** BOT and BAL in CRC patients eligible for surgery.
- **Investigator-initiated trial supported by Agenus Inc.**

Botensilimab (BOT)[3]

Fc-enhanced CTLA-4 Inhibitor



- ↑ T cell priming, expansion, memory
- ↑ Frequency of activated APCs
- ↑ Treg depletion
- ↓ Complement mediated toxicity

Study Schema[1]



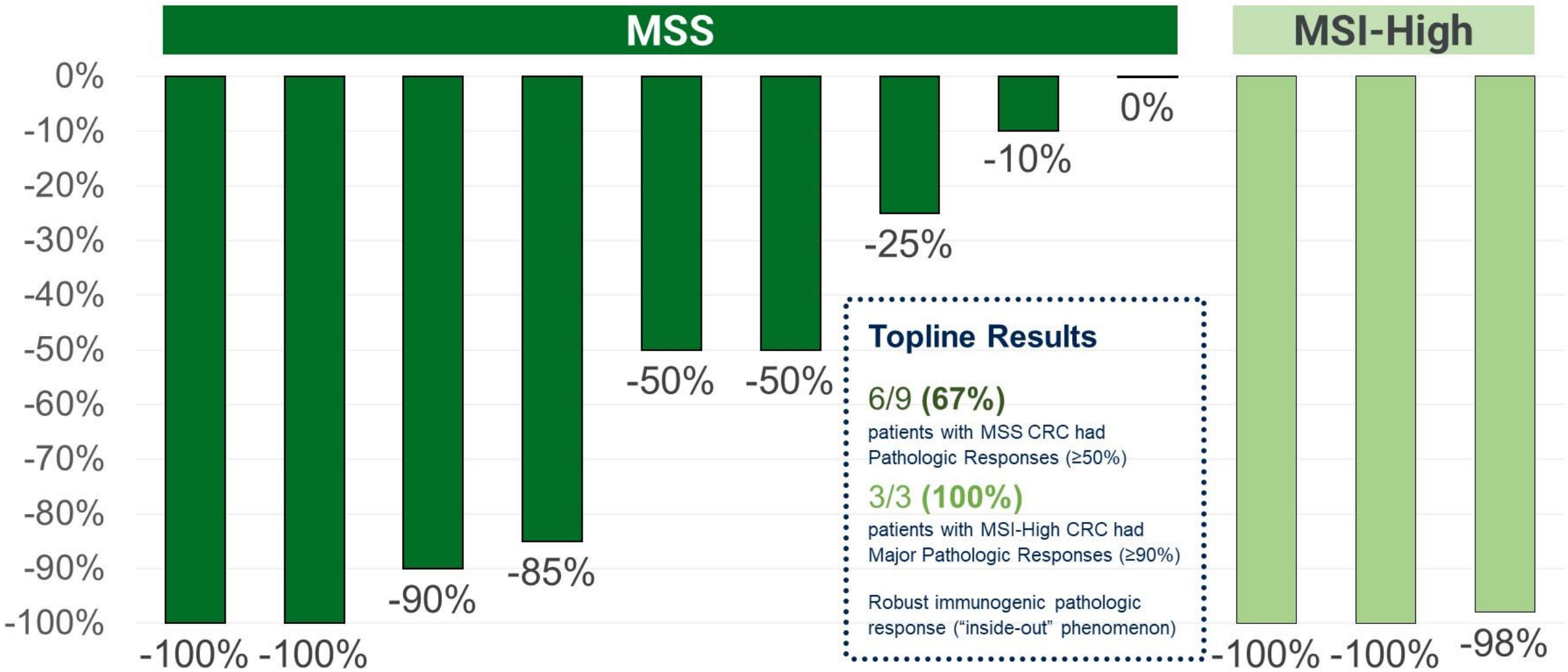
@pashtoonkasi

1. Kasi PM et al. Oncogene. 2023 Oct; 42 (44): 3252-3259.
2. El-Khoueiry AB. Journal of Clinical Oncology 2023 41:4_suppl, LBA8
3. Adapted from Wilky B, et al. Oral Presentation at CTOS 2023. Dublin, Ireland. Paper 31

PRESENTED BY: Pashtoon Kasi, MD, MS

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NEST-1 Clinical Trial: Pathologic Tumor Reductions (%) by Patient

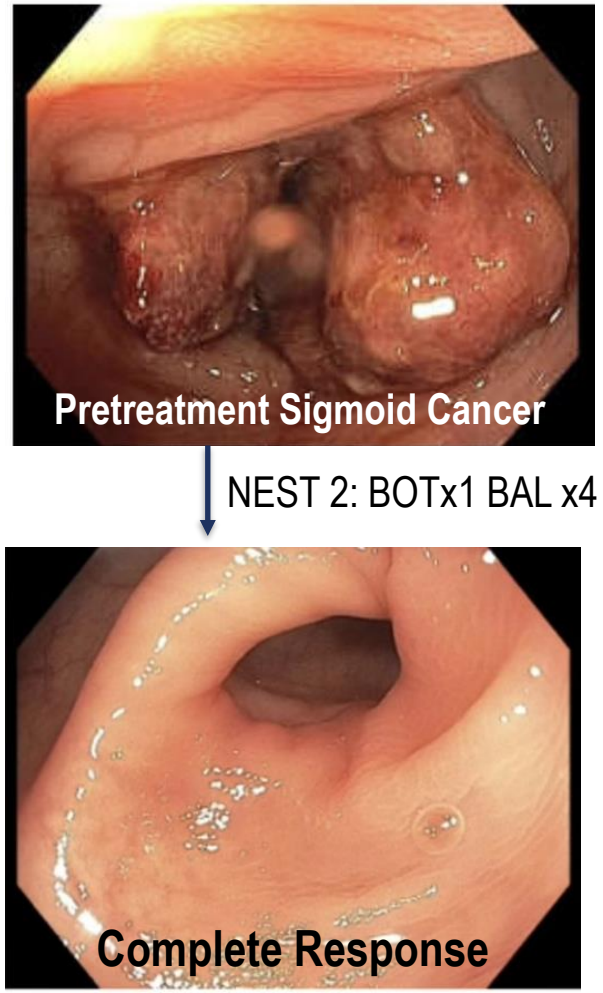


@pashtoonkasi

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CONCLUSIONS*

- Neoadjuvant BOT/BAL is a **safe** and **active** regimen in both pMMR/MSS and dMMR/MSI-H colon cancer.
- **Response rates increased with more doses of BAL in conjunction with increased interval to surgery** with up to 50% complete path response rate in pMMR colon cancer.
- **Downstaging and pathological response** may reduce reliance on surgery and/or adjuvant chemotherapy in future studies.



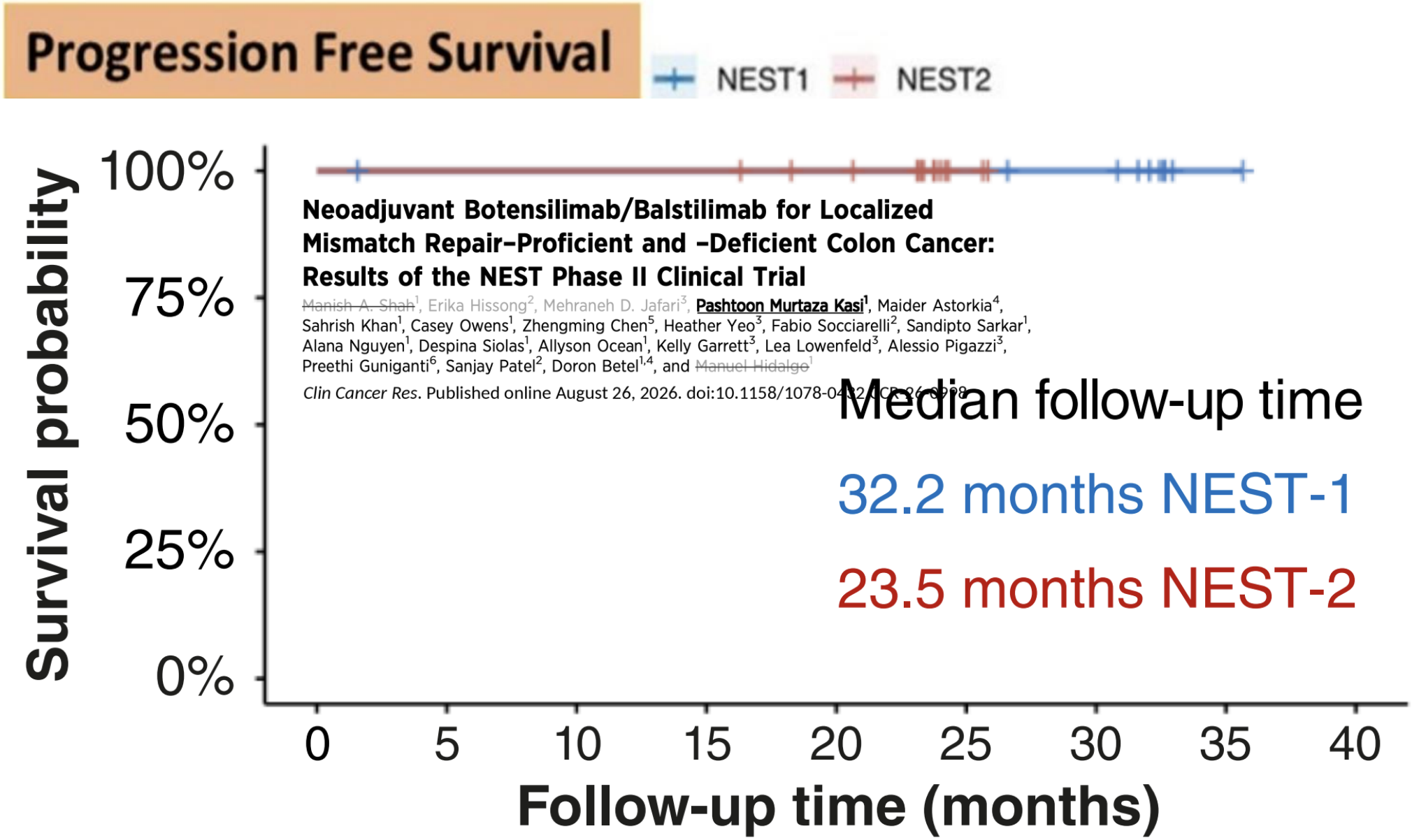
*This data is not final and under review by WCM.

*Final results are pending completion of the study analysis.

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Lesson 1

NEST 1/2 PFS



Neoadjuvant Botensilimab/Balstilimab for Localized Mismatch Repair–Proficient and –Deficient Colon Cancer: Results of the NEST Phase II Clinical Trial

~~Manish A. Shah~~[1], Erika Hissong[2], Mehraneh D. Jafari[3], **Pashtoon Murtaza Kasi**[1], Maider Astorkia[4], Sahrish Khan[1], Casey Owens[1], Zhengming Chen[5], Heather Yeo[3], Fabio Socciarelli[2], Sandipto Sarkar[1], Alana Nguyen[1], Despina Siolas[1], Allyson Ocean[1], Kelly Garrett[3], Lea Lowenfeld[3], Alessio Pigazzi[3], Preethi Guniganti[6], Sanjay Patel[2], Doron Betel[1,4], and ~~Manuel Hidalgo~~[1]

Clin Cancer Res. Published online August 26, 2026. doi:10.1158/1078-0432.CCR-26-0998

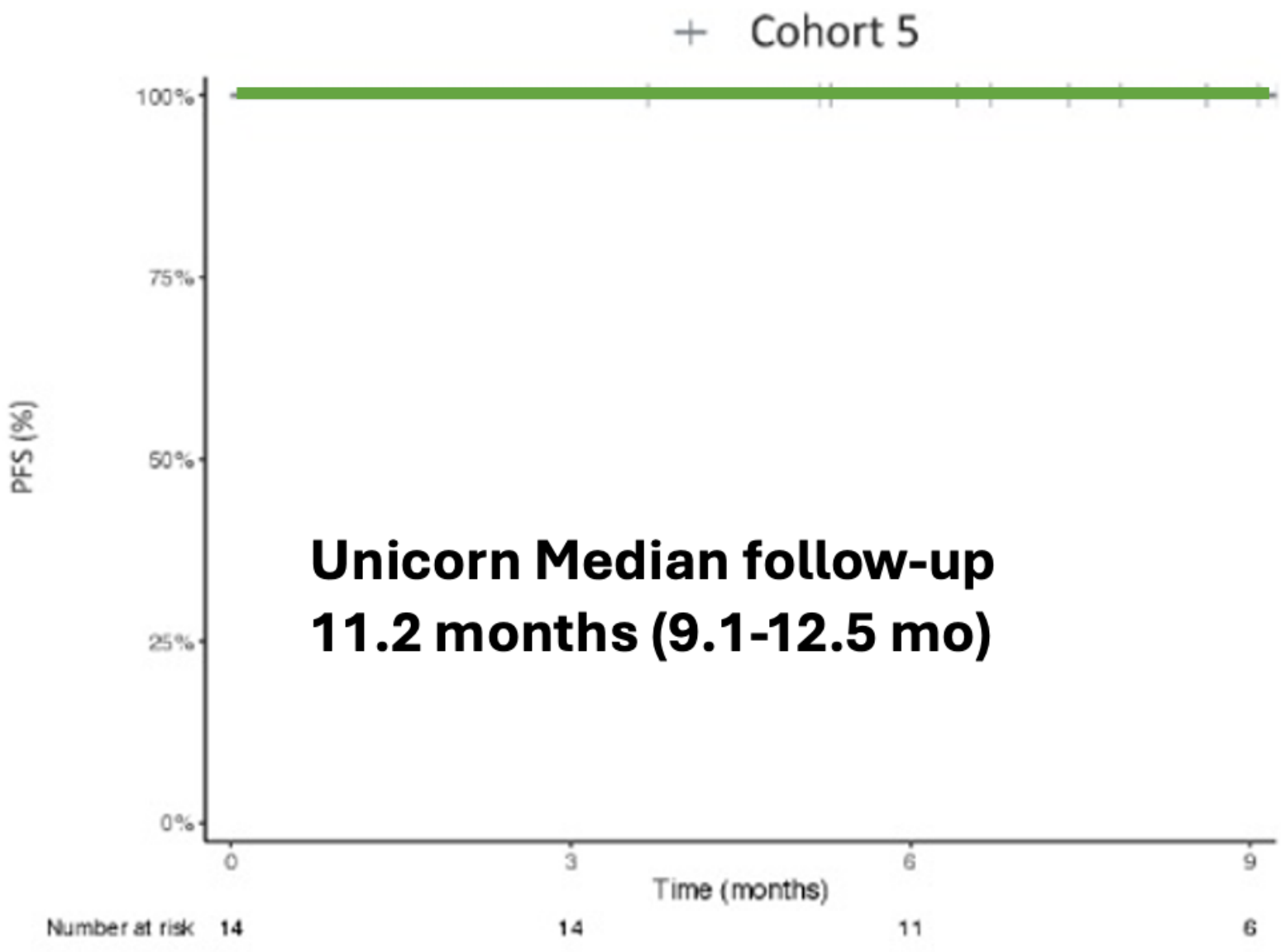
Median follow-up time

32.2 months NEST-1

23.5 months NEST-2

Lesson 2

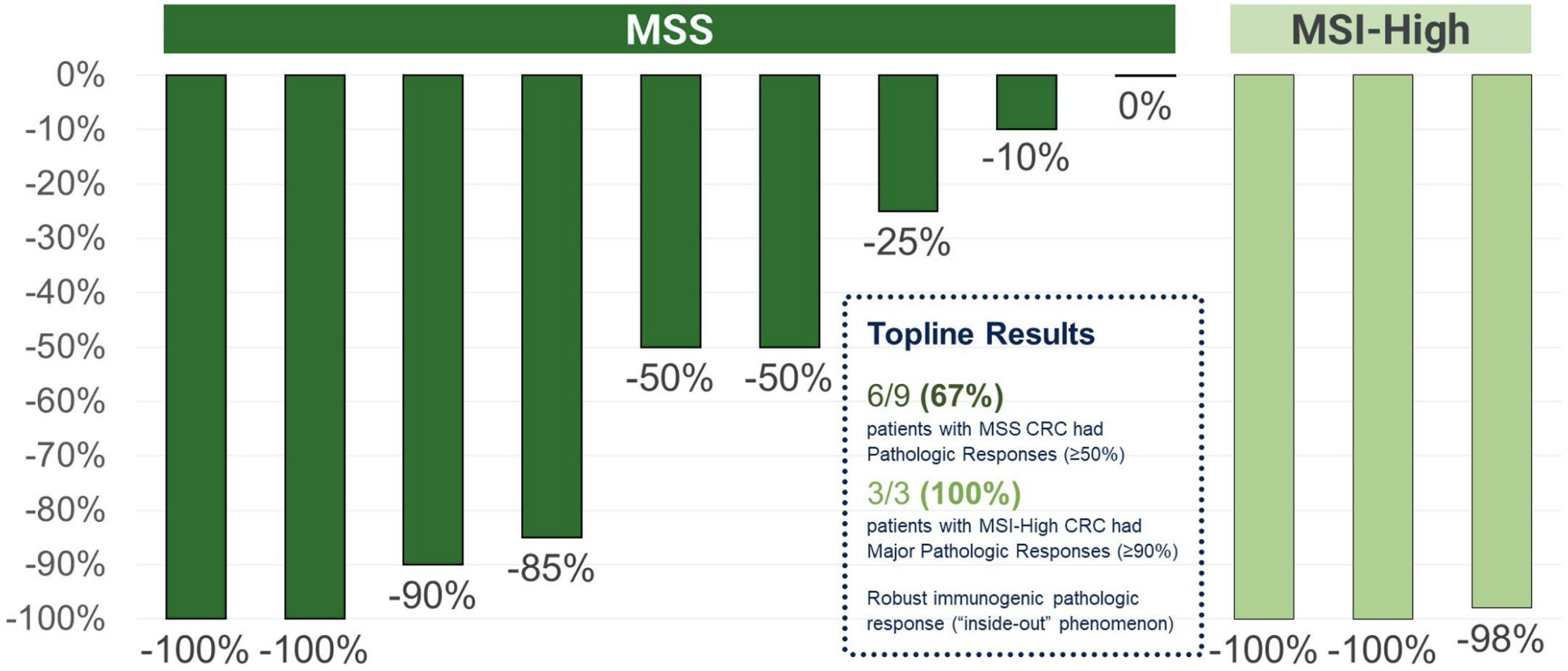
UNICORN PFS



Unicorn Median follow-up
11.2 months (9.1-12.5 mo)

Lesson 3

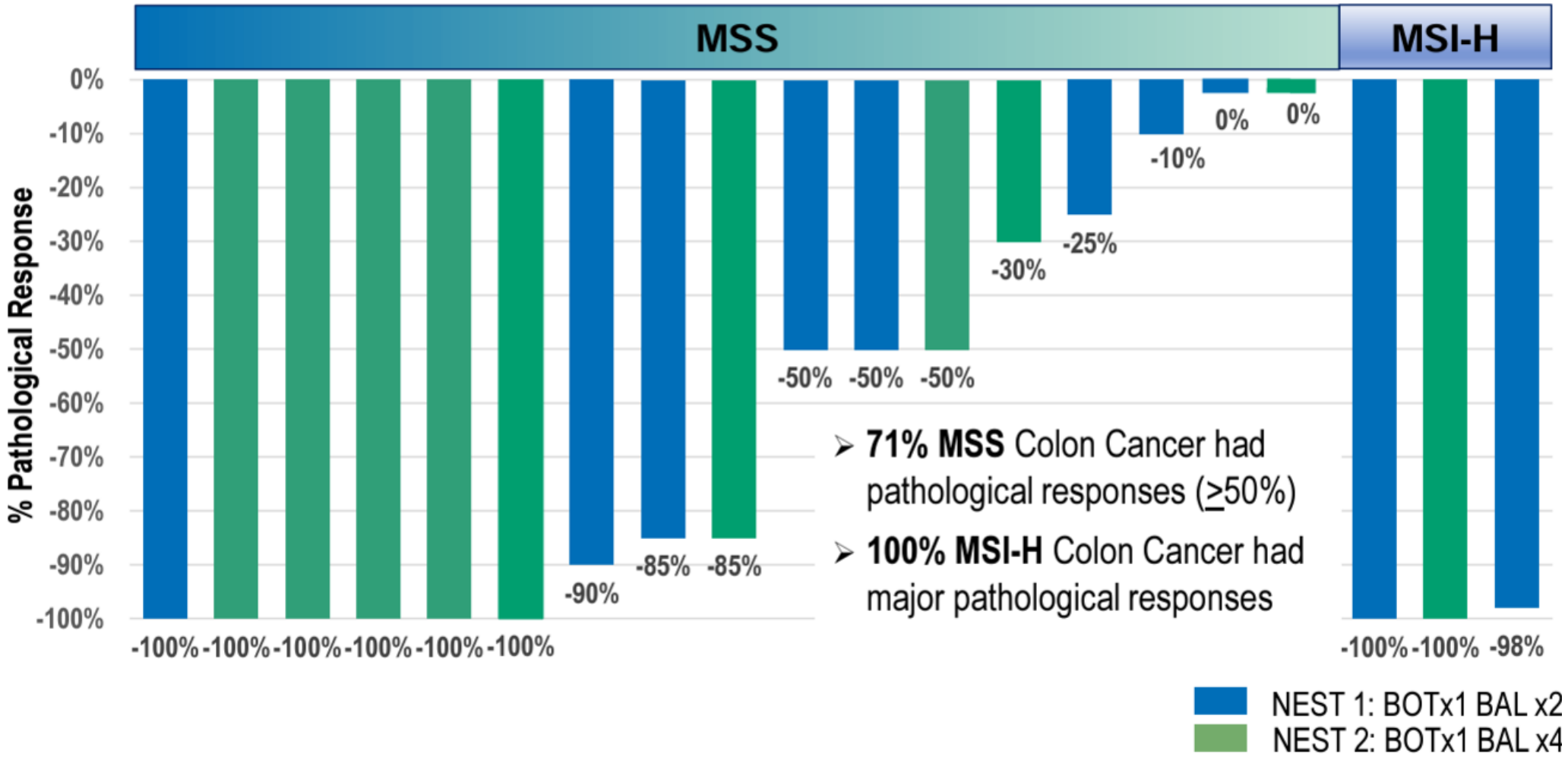
NEST-1 Clinical Trial: Pathologic Tumor Reductions (%) by Patient



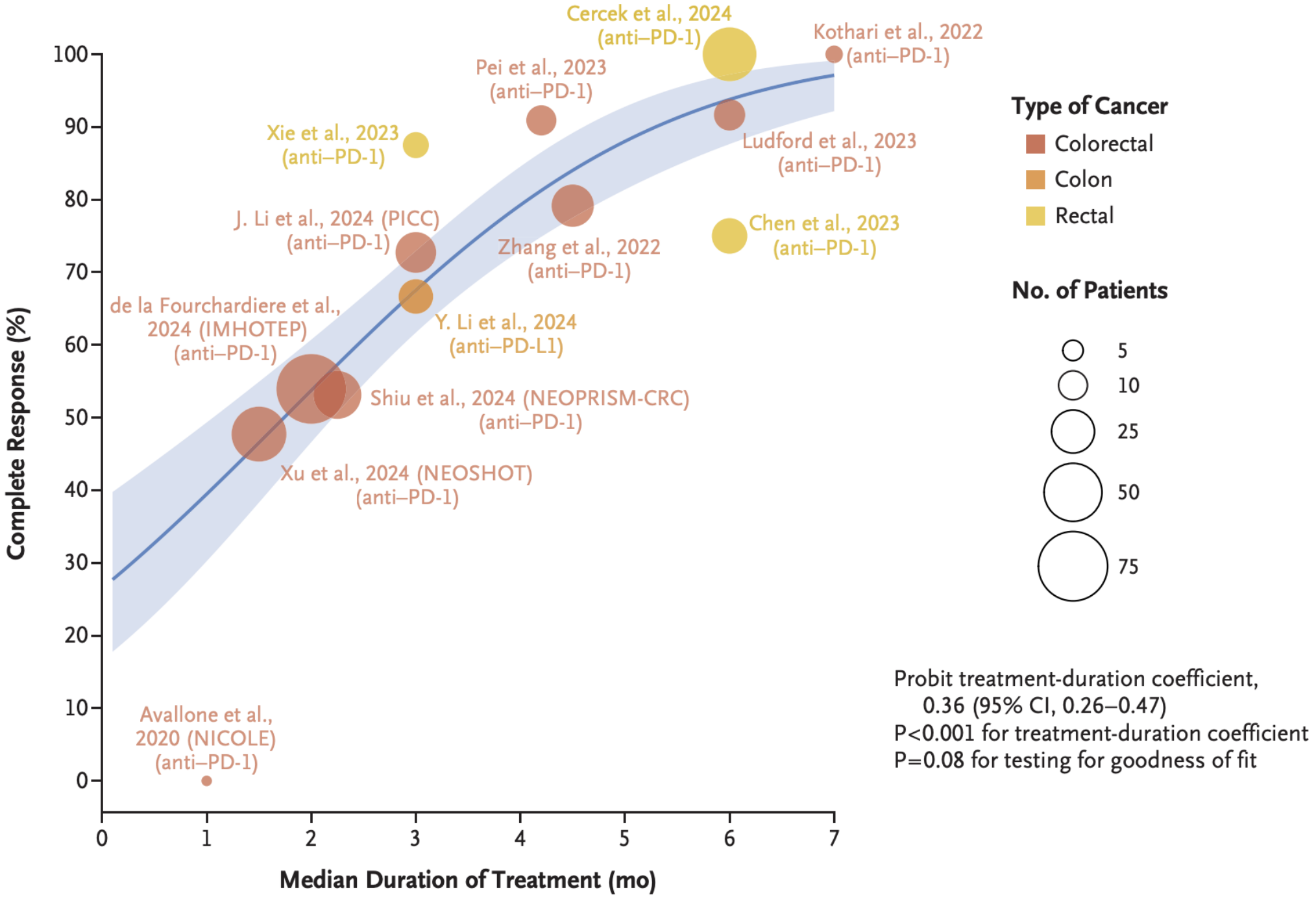
@pashtoonkasi

Lesson 4

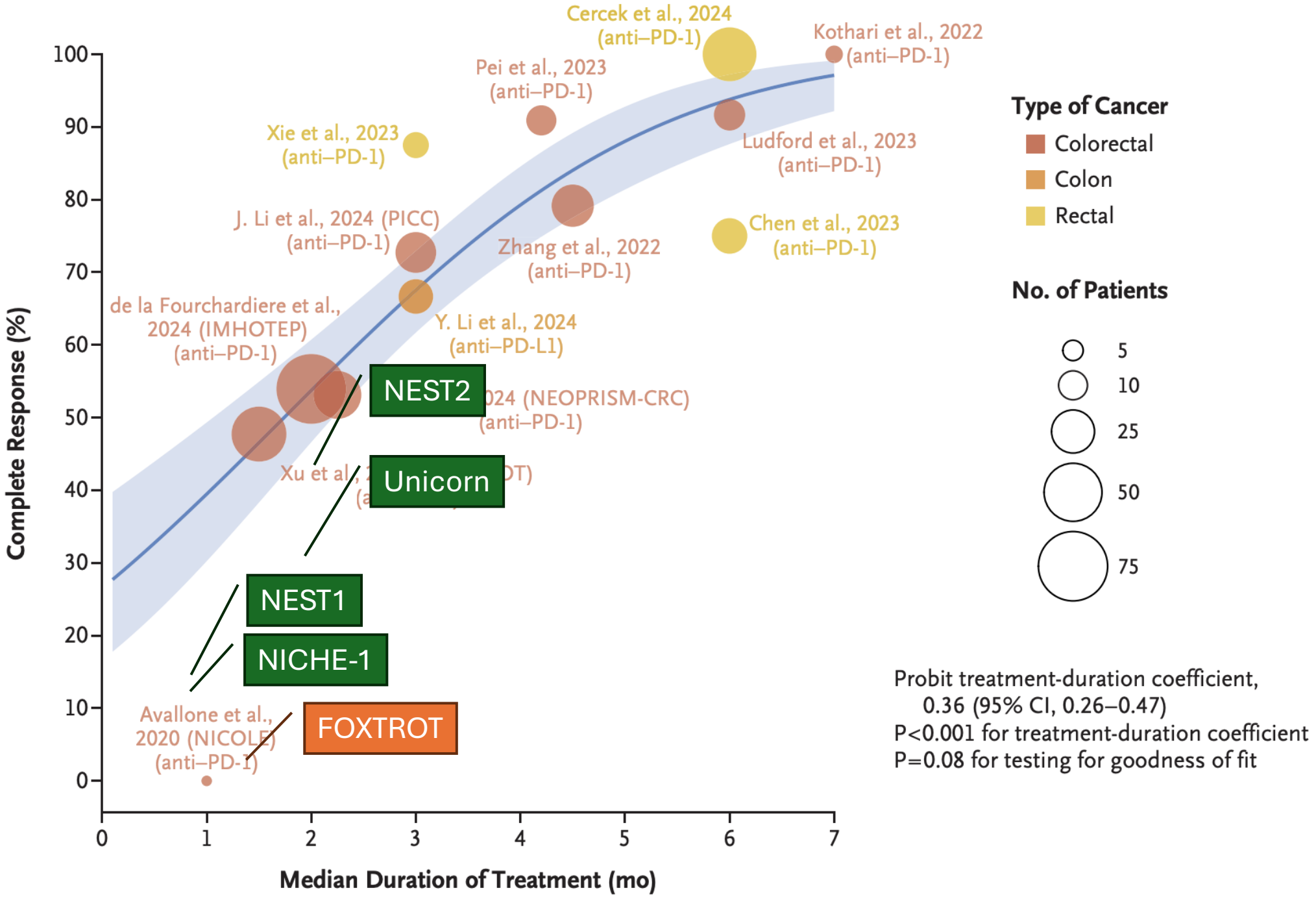
PATHOLOGICAL TUMOR REDUCTIONS (%) BY PATIENT



Lesson 4


Cercek et al., 2024 (anti–PD-1)
Kothari et al., 2022 (anti–PD-1)
Pei et al., 2023 (anti–PD-1)
Xie et al., 2023 (anti–PD-1)
Ludford et al., 2023 (anti–PD-1)
J. Li et al., 2024 (PICC) (anti–PD-1)
Chen et al., 2023 (anti–PD-1)
Zhang et al., 2022 (anti–PD-1)
de la Fourchardiere et al., 2024 (IMHOTEP) (anti–PD-1)
Y. Li et al., 2024 (anti–PD-L1)
Shiu et al., 2024 (NEOPRISM-CRC) (anti–PD-1)
Xu et al., 2024 (NEOSHOT) (anti–PD-1)
Avallone et al., 2020 (NICOLE) (anti–PD-1)
Complete Response (%)
Median Duration of Treatment (mo)
0
10
20
30
40
50
60
70
80
90
100
0
1
2
3
4
5
6
7
Type of Cancer
Colorectal
Colon
Rectal
No. of Patients
5
10
25
50
75
Probit treatment-duration coefficient, 0.36 (95% CI, 0.26–0.47)
P<0.001 for treatment-duration coefficient
P=0.08 for testing for goodness of fit

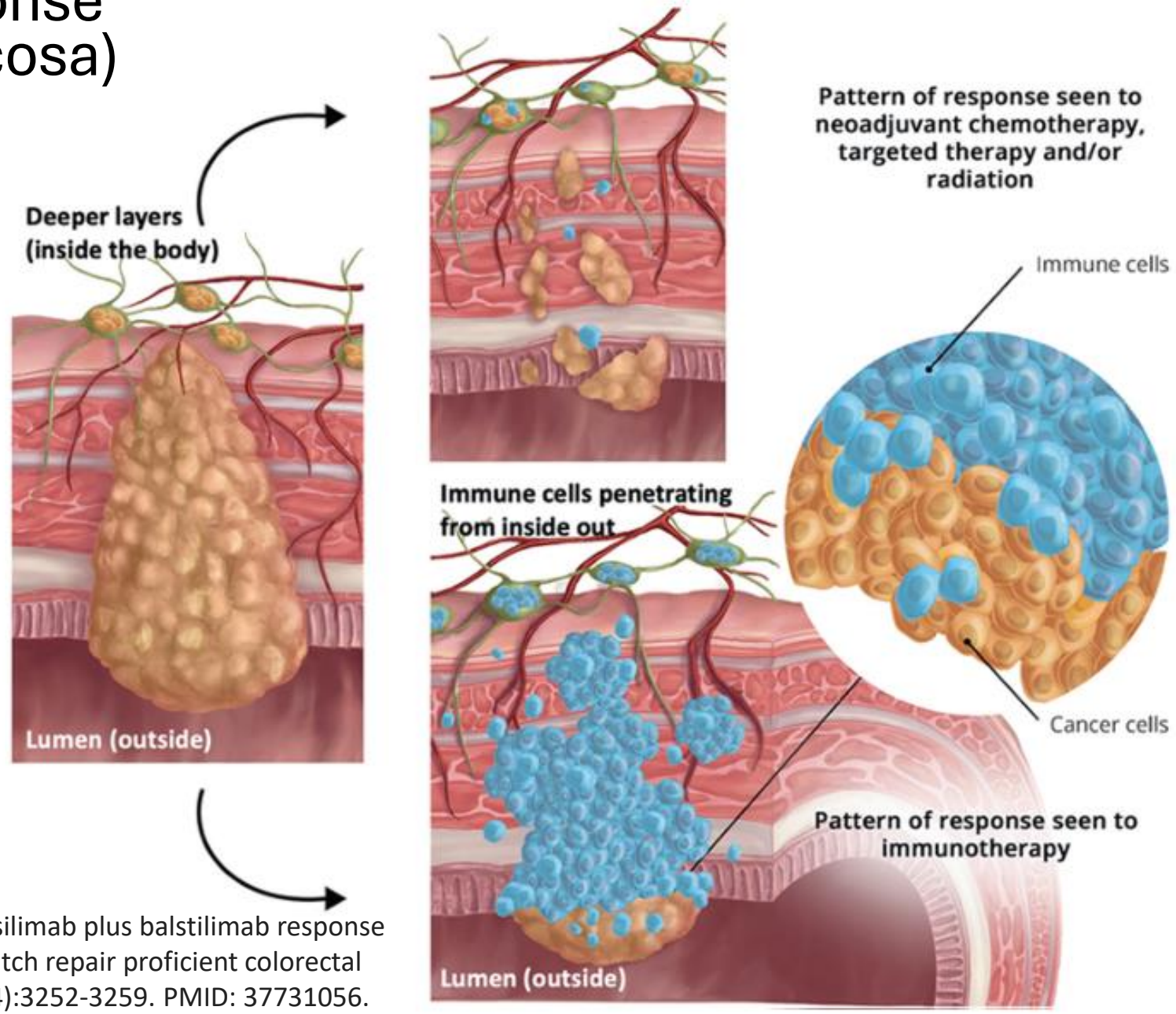
Lesson 4



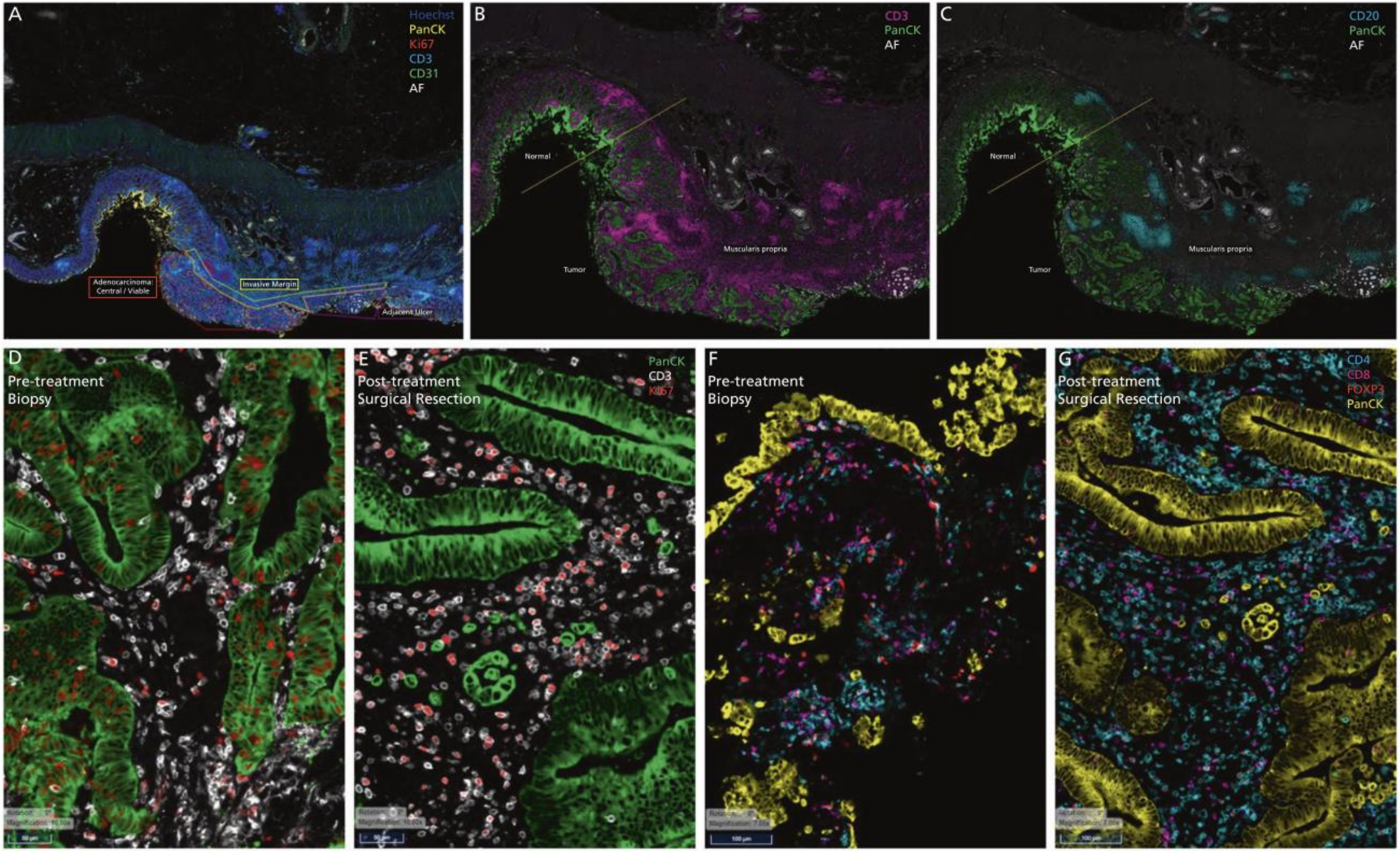
Probit treatment-duration coefficient,
0.36 (95% CI, 0.26–0.47)
P<0.001 for treatment-duration coefficient
P=0.08 for testing for goodness of fit

Lesson 5

“Inside-Out” Pattern of response (serosa-to-mucosa)



Kasi PM et al. Neoadjuvant botensilimab plus balstilimab response pattern in locally advanced mismatch repair proficient colorectal cancer. Oncogene. 2023 Oct;42(44):3252-3259. PMID: 37731056.


A
Hoechst
PanCK
Ki67
CD3
CD31
AF
Adenocarcinoma: Central / Viable
Invasive Margin
Adjacent Ulcer
B
CD3
PanCK
AF
Normal
Muscularis propria
Tumor
C
CD20
PanCK
AF
Normal
Muscularis propria
Tumor
D
Pre-treatment Biopsy
E
Post-treatment Surgical Resection
PanCK
CD3
Ki67
F
Pre-treatment Biopsy
G
Post-treatment Surgical Resection
CD4
CD8
FOXP3
PanCK

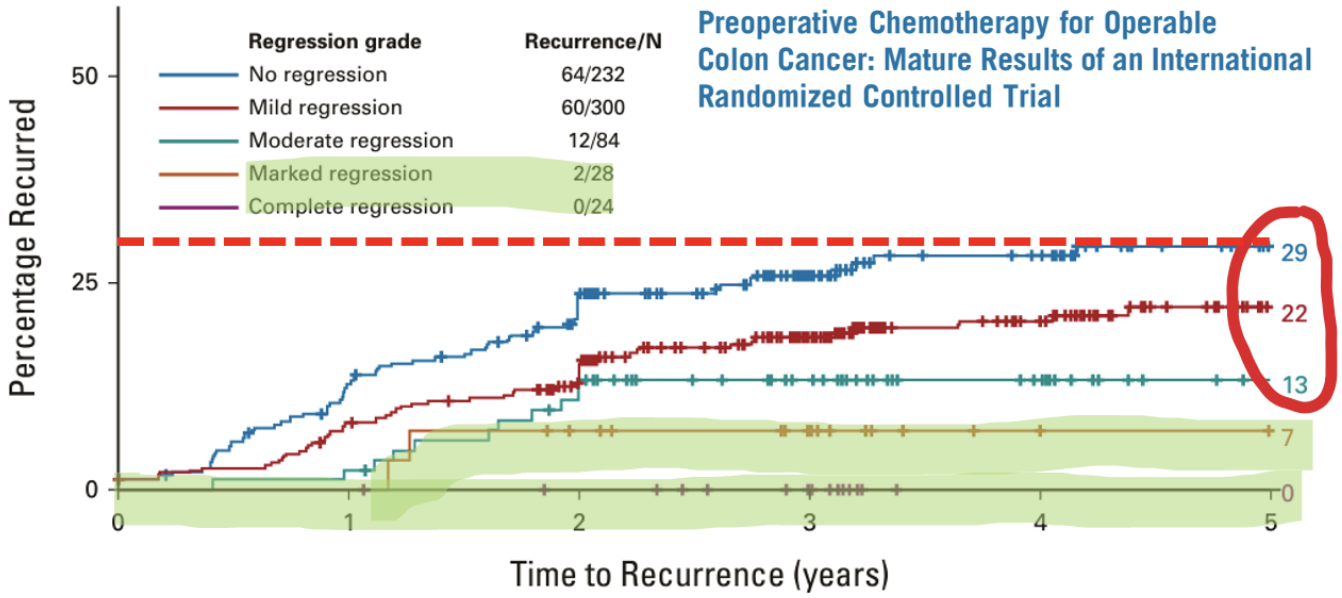
Lesson 6

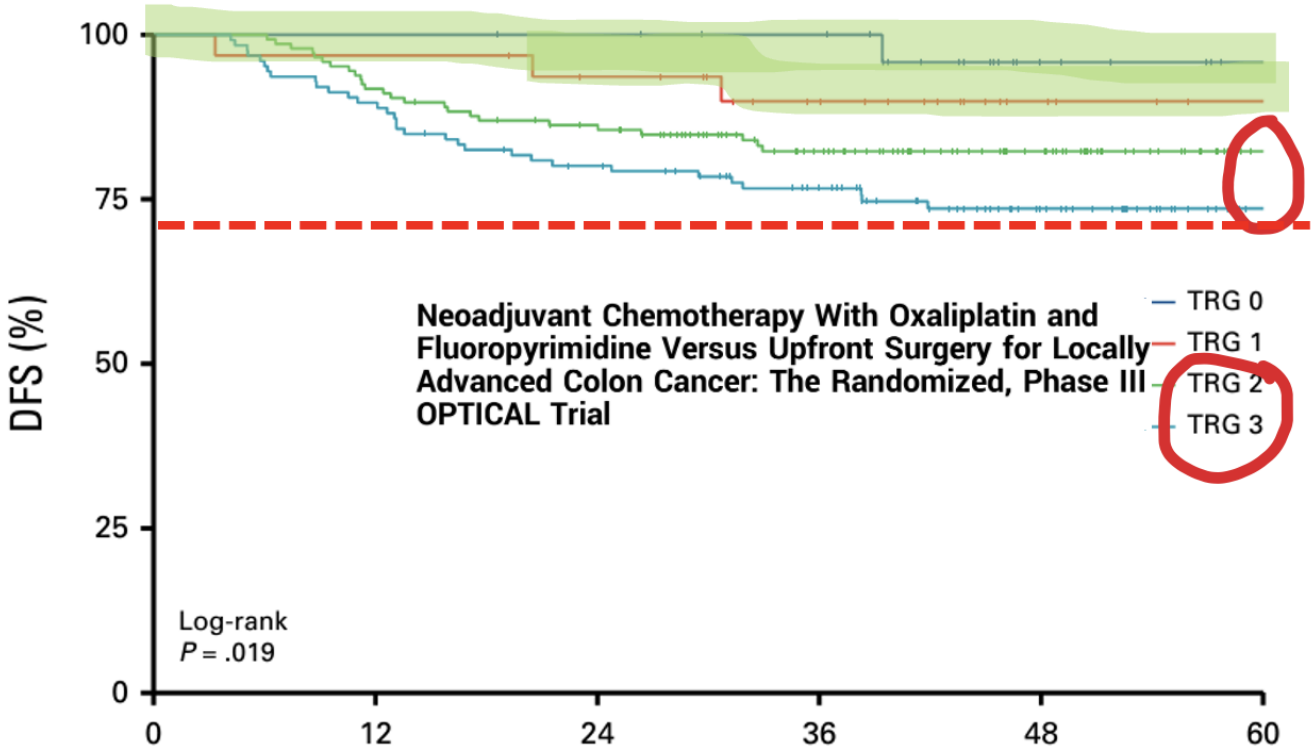
	FOxTROT results	NICHE results	NEST1	NEST2	UNICORN BOT	UNICORN BOT/BAL	Tumor Regression Score
No response	27%	71%	43%	40%	57%	29%	3
Mild response	50%						2
Moderate response	15%	6%	29%	13%	43%	36%	2
Marked response	5%	10%	14%	7%	0%	7%	1
Complete response	3%	13%	14%	40%	0%	29%	0
Major Pathologic Response	**8%**	**23%**	**28%**	**47%**	**0%**	**36%**	0+1

Lesson 6

What correlates with DFS?

Degree of major pathologic response.

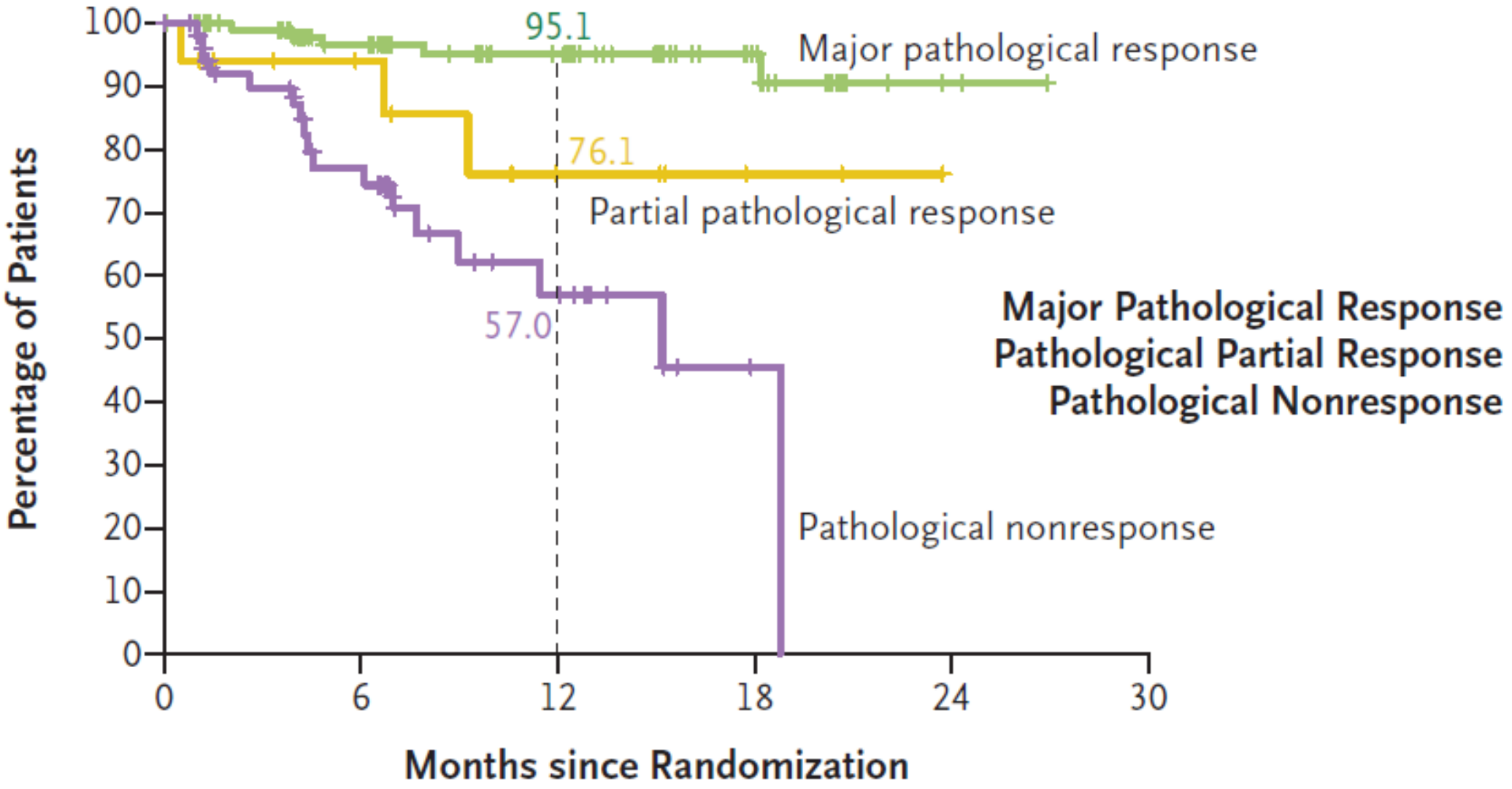




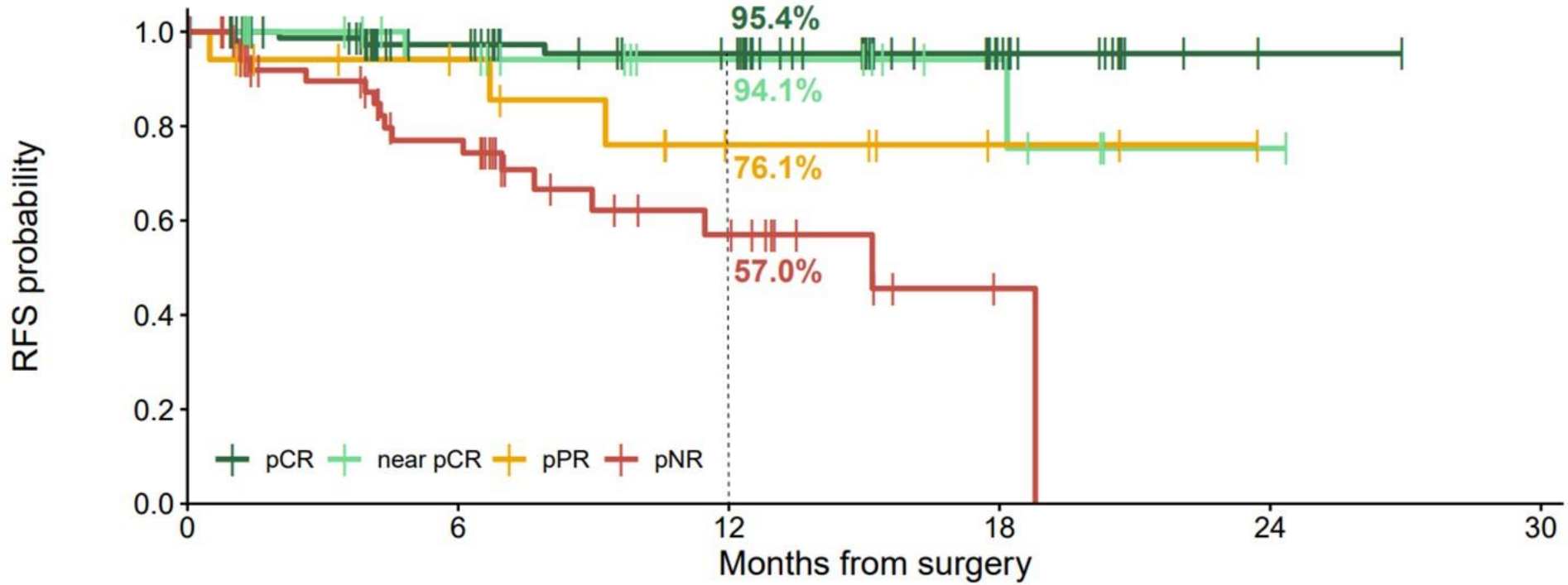
Lesson 6

What correlates with DFS?

Degree of major pathologic response.



NADINA – RFS According to Pathologic Response

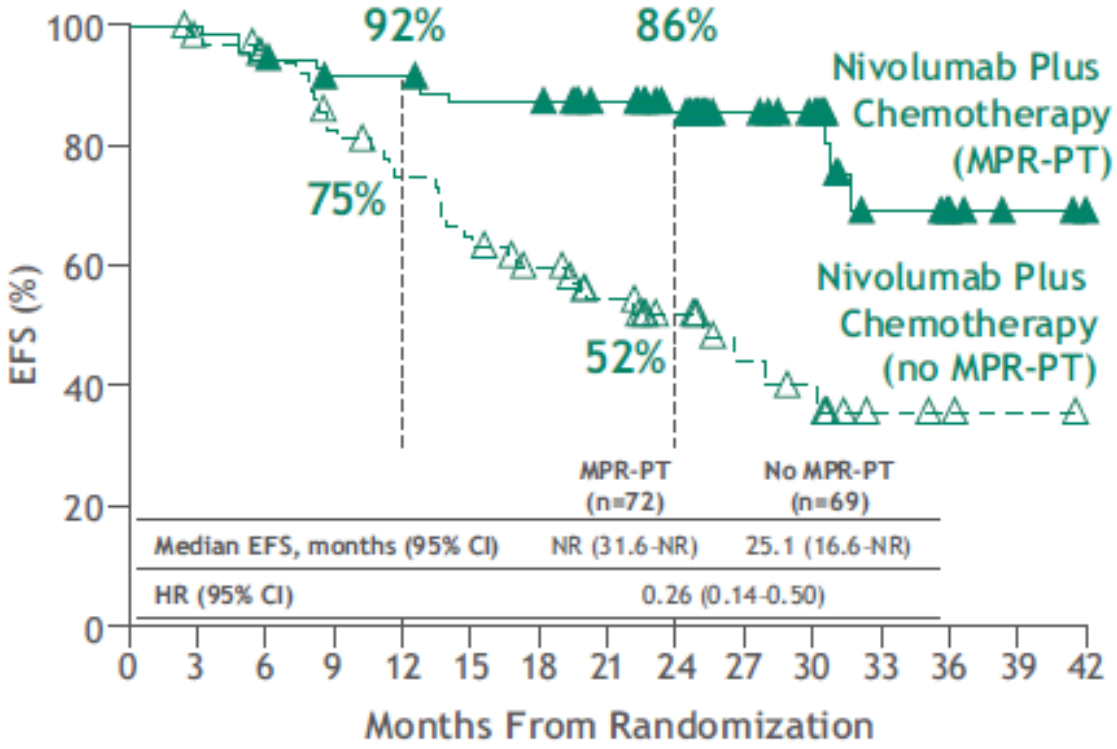


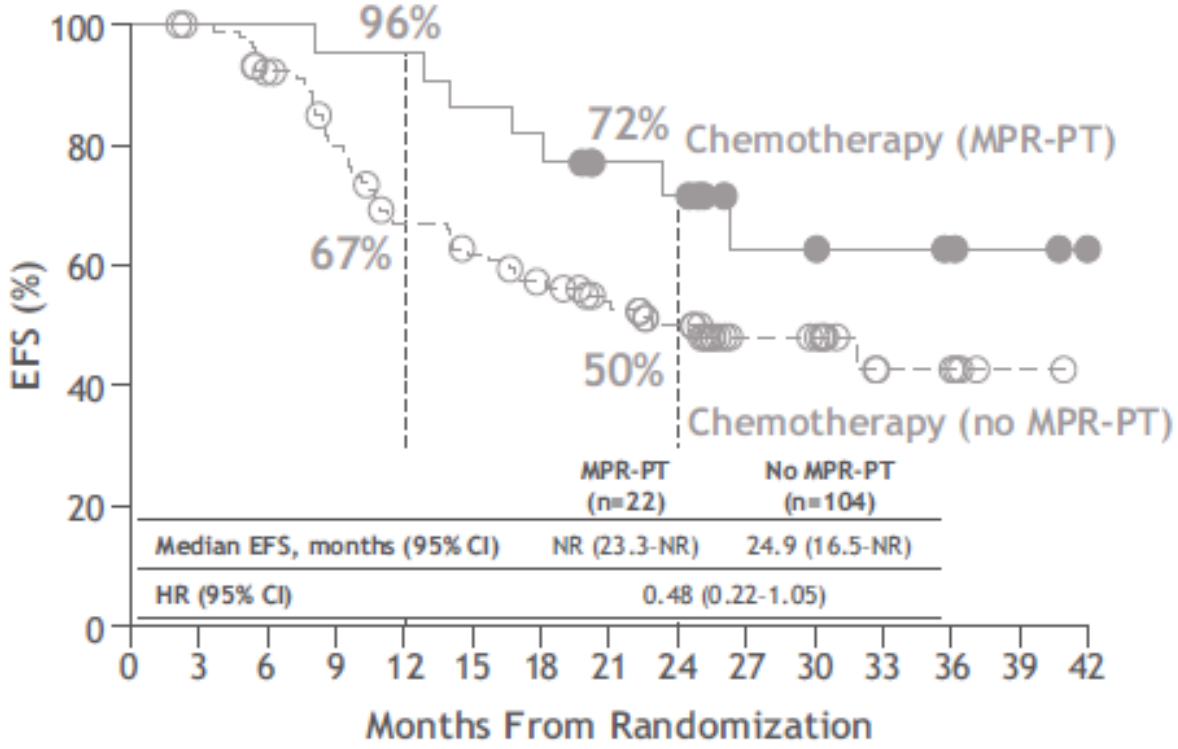
Number at risk

pCR	100	60	46	17	1	0
near pCR	25	16	9	5	1	0
pPR	17	11	5	2	0	0
pNR	56	29	11	1	0	0
	0	6	12	18	24	30

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Neoadjuvant chemo/immunotherapy in lung cancer



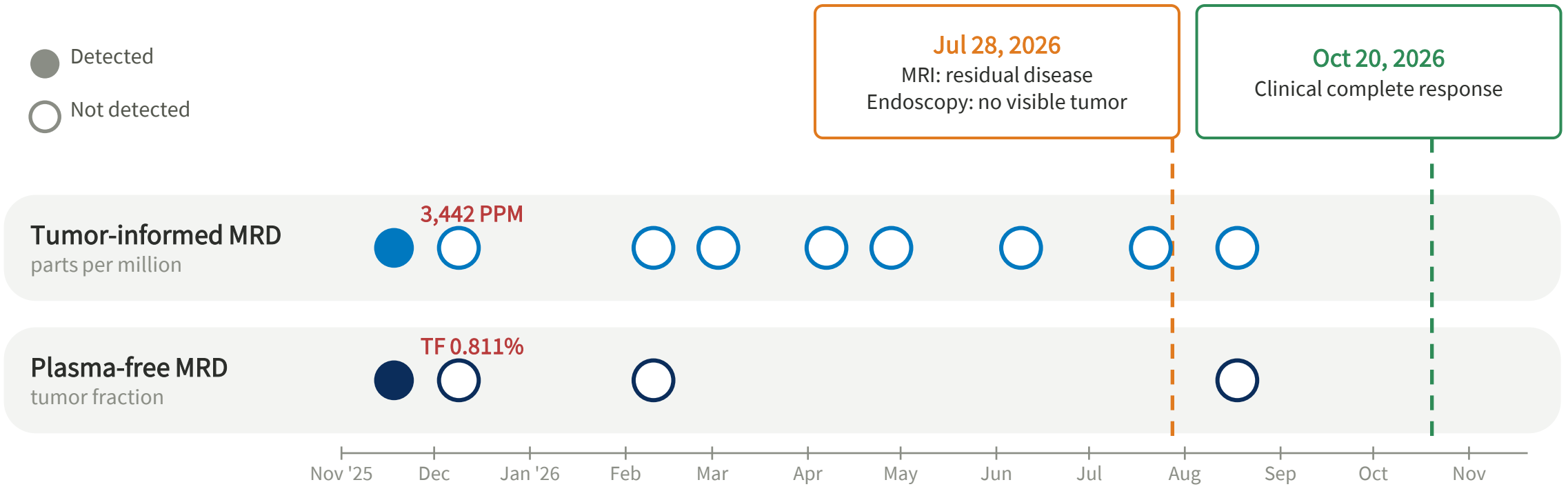


2-year EFS rates were 90%, 60%, 57% and 39% for patients with 0–5%, >5–30%, >30–80% and >80% RVT

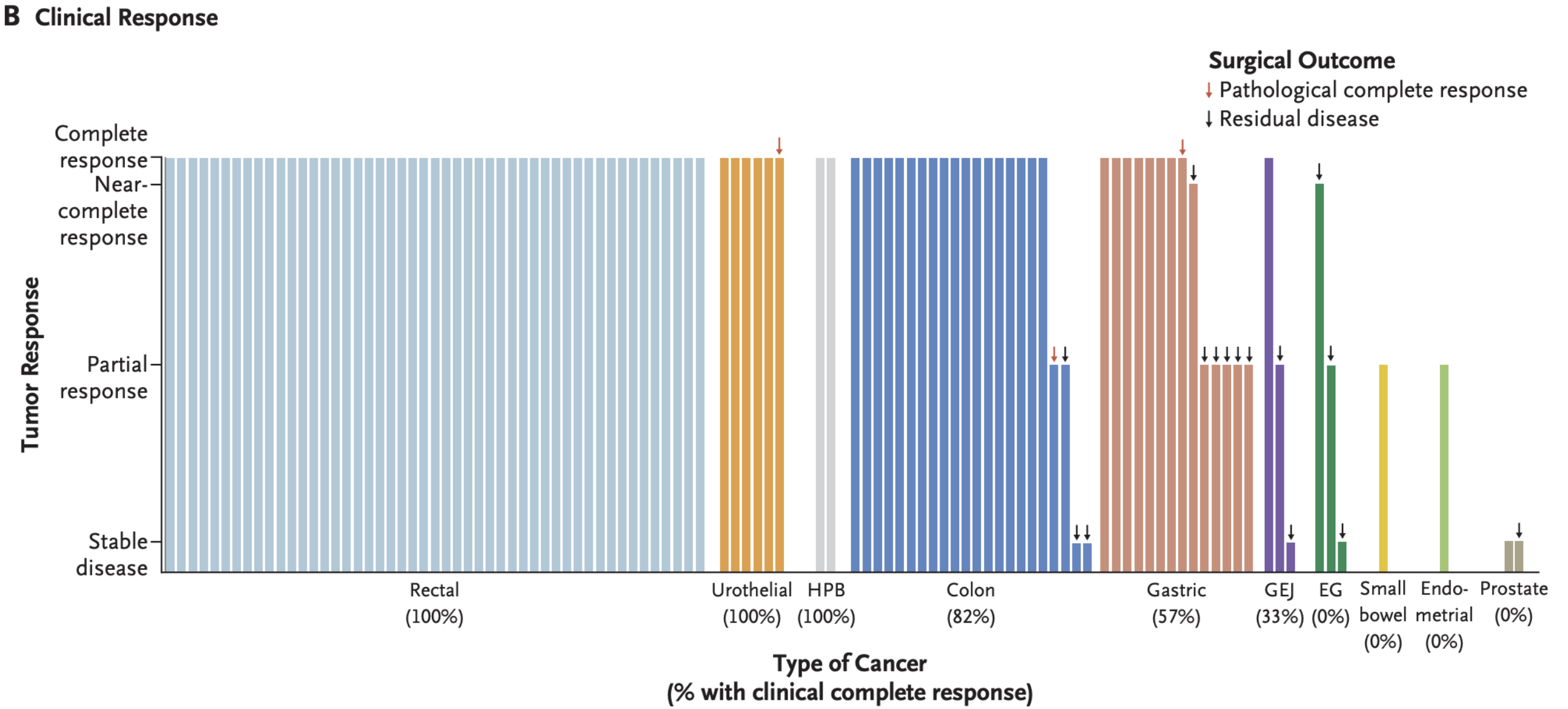
Each 1% RVT associated with a 0.017 hazard ratio increase for EFS

Deutsch JS. Association between pathologic response and survival after neoadjuvant therapy in lung cancer. Nat Med. 2024 Jan;30(1):218-228. PMID: 37903504.

Case: MSI-High rectal Cancer on immunotherapy ctDNA cleared before MRI



Cleared in 3 weeks; negative on 11 straight draws across 2 assays ~10 months before cCR



Cercek A, Foote MB, Rousseau B, et al. Nonoperative Management of Mismatch Repair-Deficient Tumors. *N Engl J Med*. 2025;392(23):2297-2308. doi:10.1056/NEJMoa2404512

NICHE 5-year results

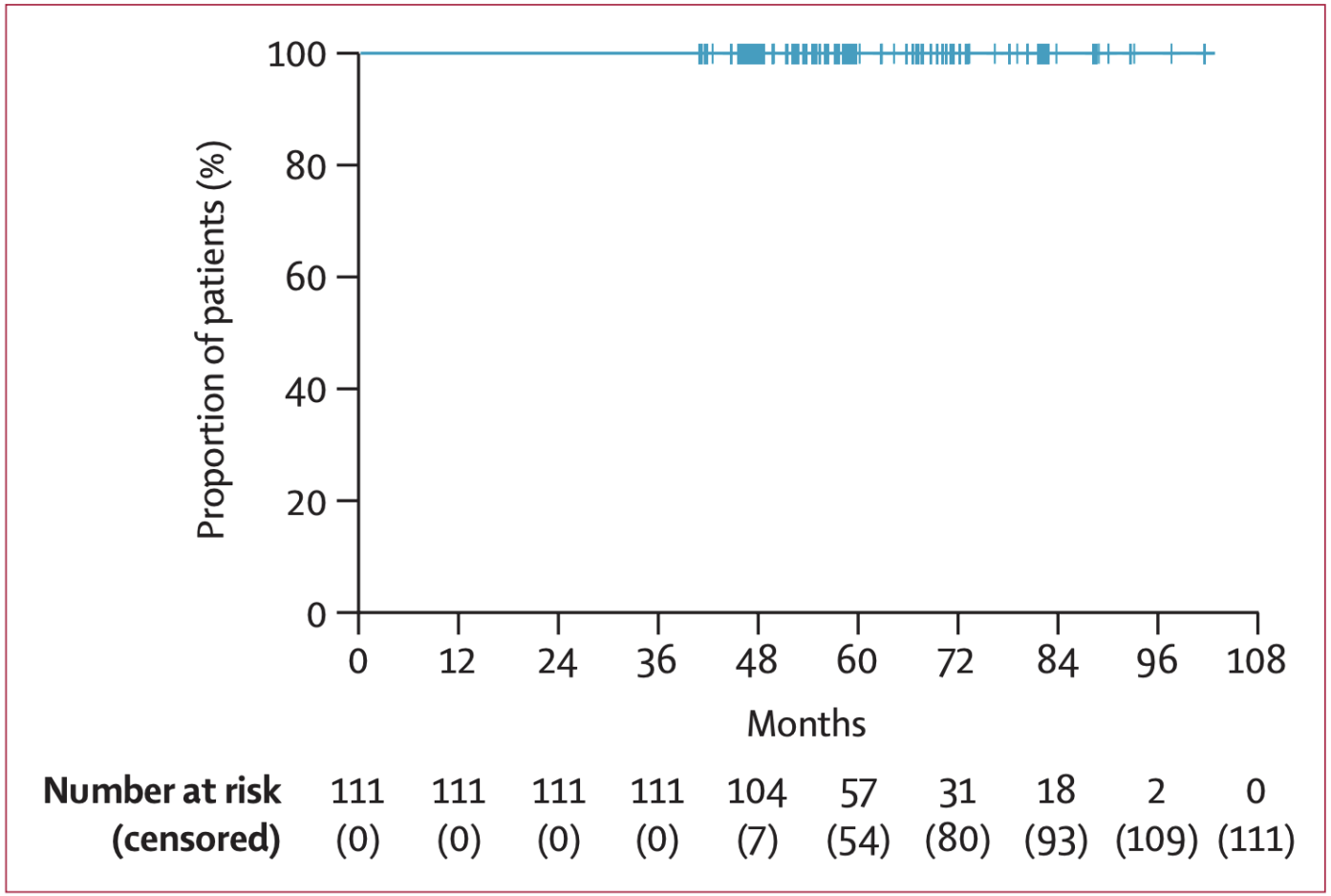
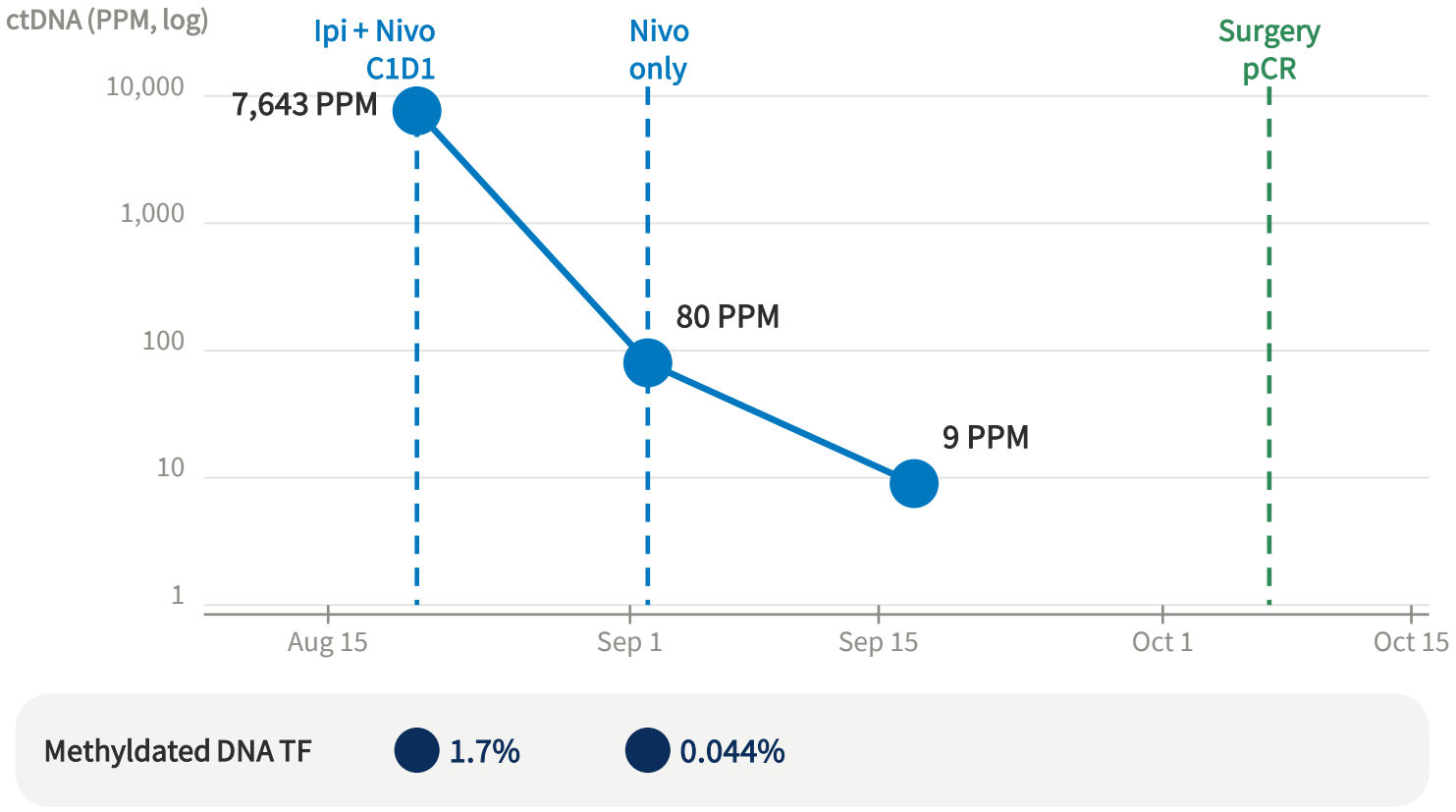


Figure 2: **Kaplan–Meier estimates of overall survival**

Time to event was measured from date of enrolment to date of death from any cause. Tick marks indicate data censored at the last moment the patient was known to be alive. 5-year overall survival was 100% (95% CI 100–100).

Chalabi M, et al. Disease-free survival and overall survival after neoadjuvant immunotherapy in mismatch repair-deficient colon cancer in the Netherlands: results of the single-arm, multicentre, phase 2, NICHE-2 trial. *Lancet*. Published online October 21, 2026. doi:10.1016/S0140-6736(26)01602-8

Case 2: kinetics foretell pCR



~850×

Drop in ctDNA

7,643 → 9 PPM in 4 weeks

~39×

Drop in tumor fraction

1.7% → 0.044% after one cycle

Oct 7, 2026 · surgery

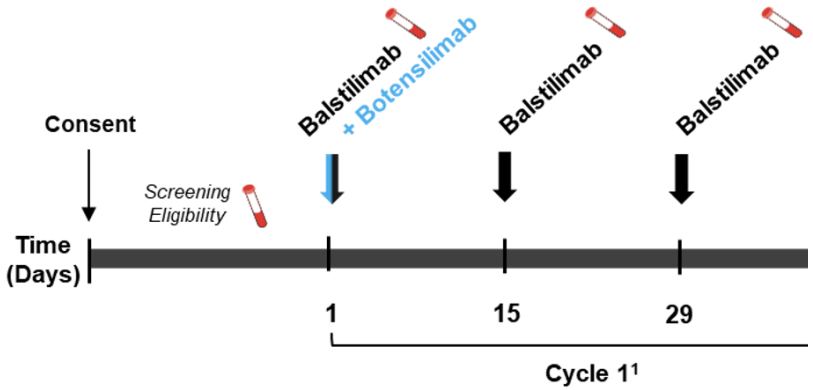
Pathologic complete response

Only acellular mucin pools

Still detectable at 9 PPM three weeks before surgery, yet pCR: read the slope, not a single low value.

NEST3

STUDY SCHEMA



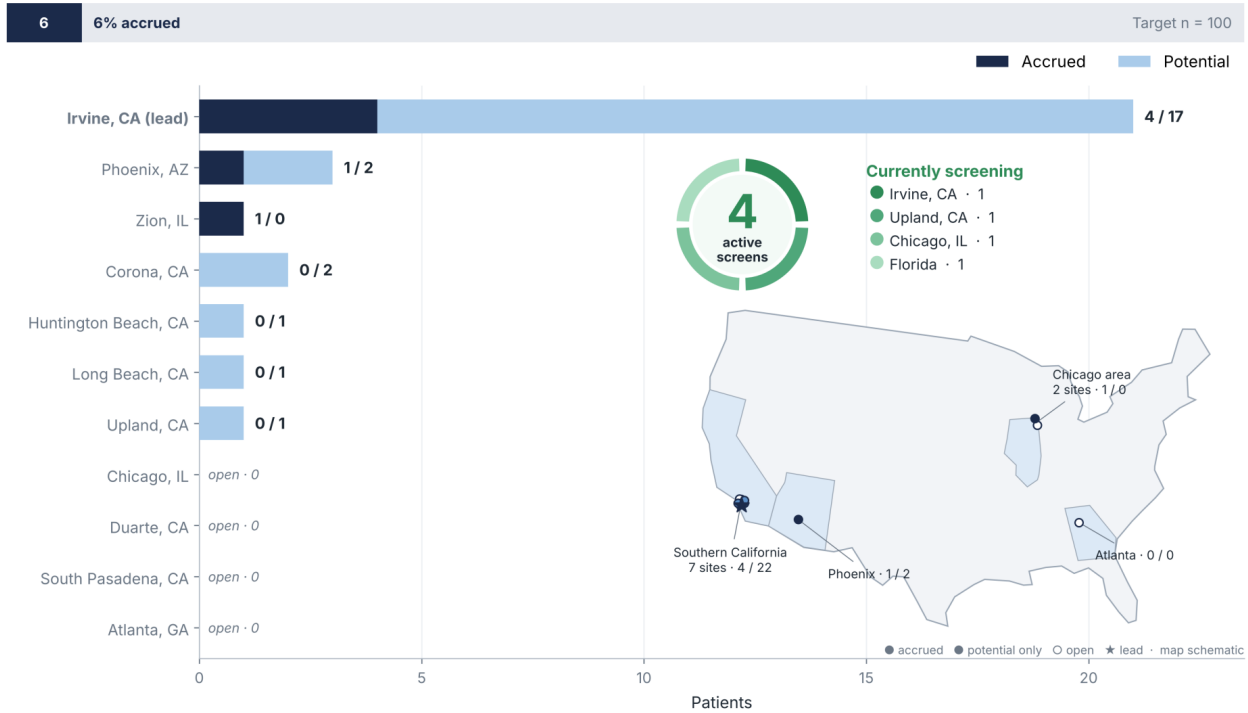
[1]: See Section 5.3 for treatment plan and dose escalation levels, ar

: ctDNA/cfDNA Research Samples

NEST3 accrual by site

As of October 23, 2026 · 11 open sites

6 of 100 accrued to date (6%) · 30 screened



NCT07595874 · City of Hope national trial model

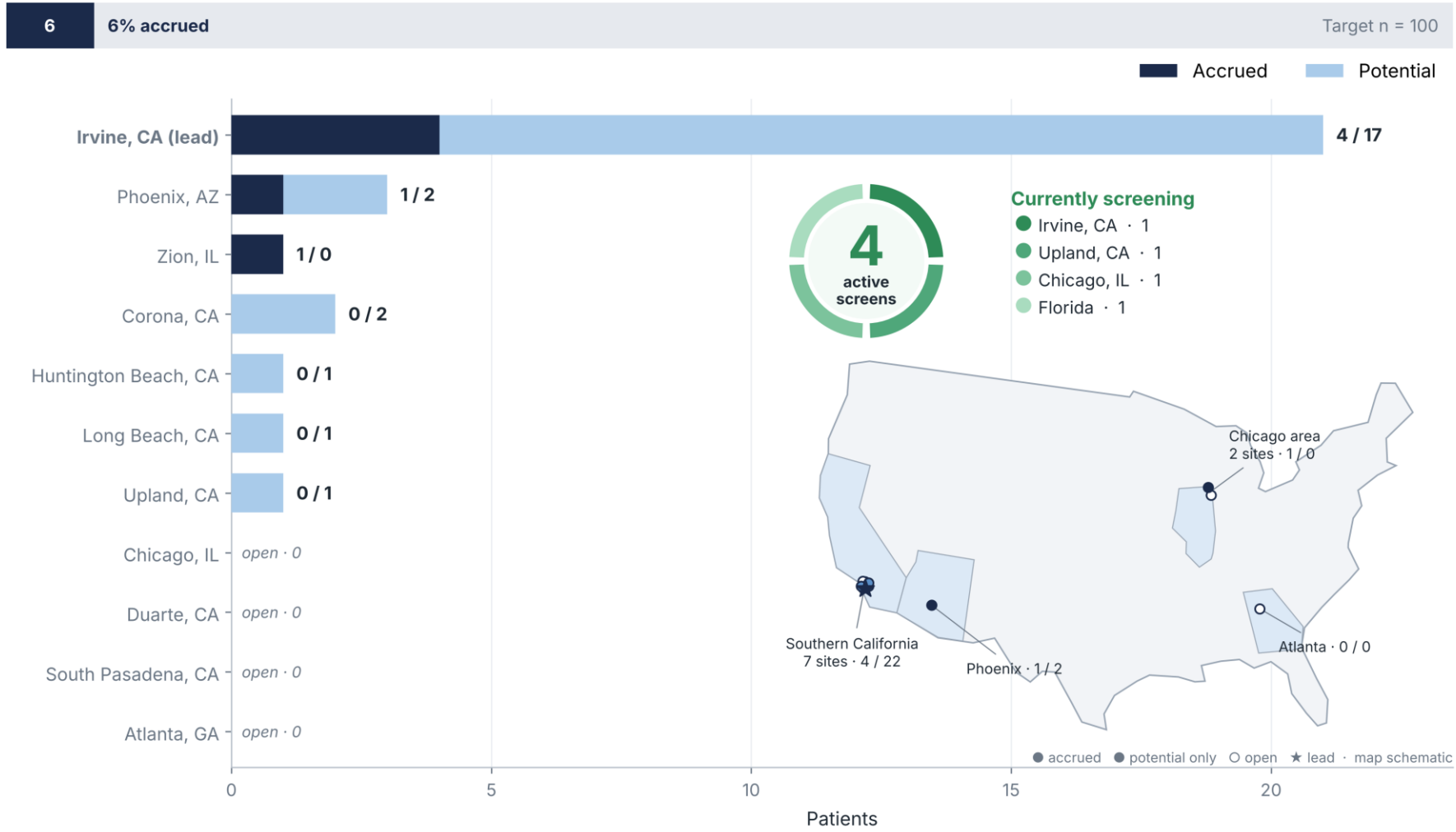
Labels show accrued / potential

Survival Follow Up

NEST3 accrual by site

As of October 23, 2026 · 11 open sites

6 of 100 accrued to date (6%) · 30 screened

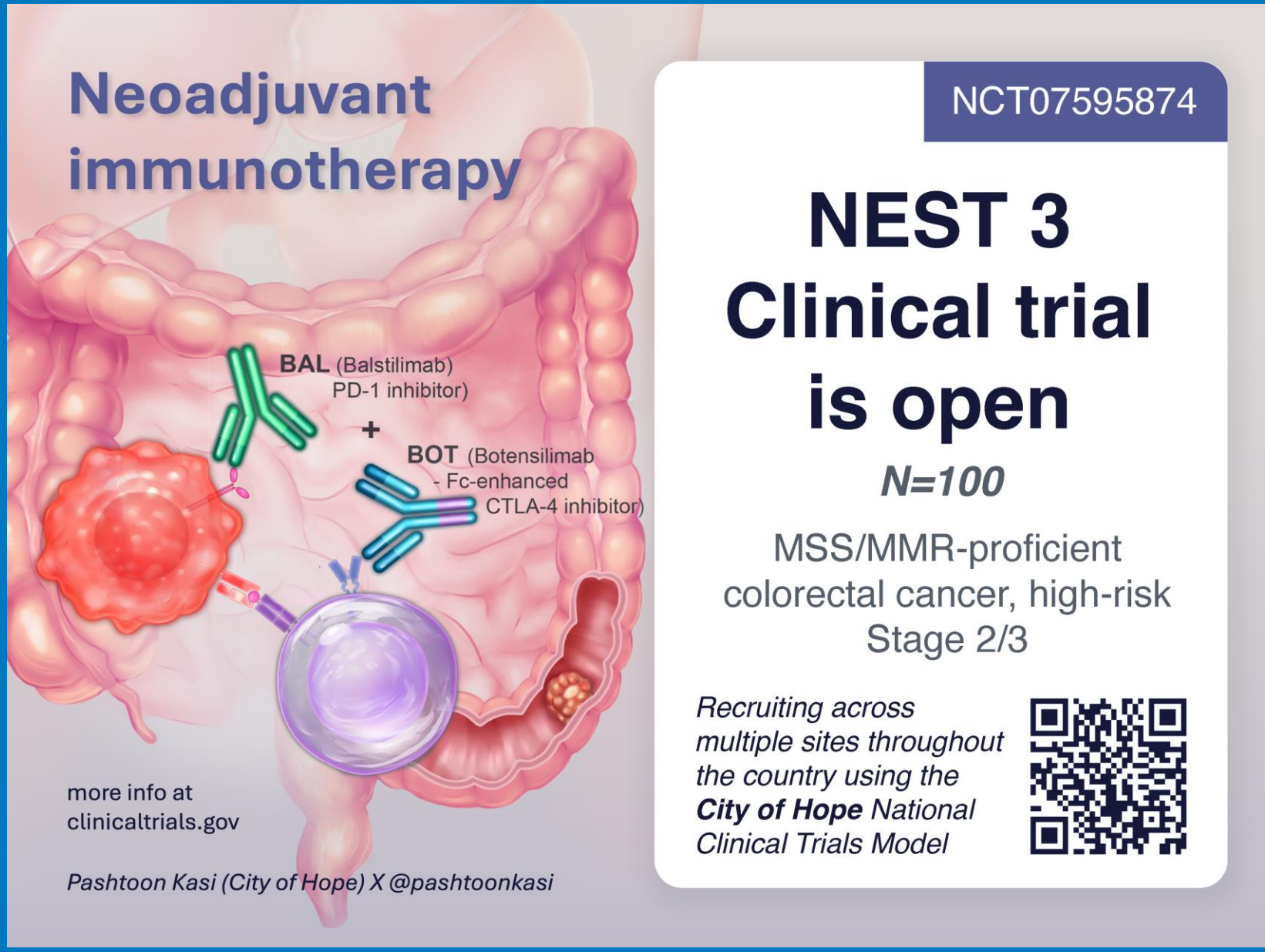


NCT07595874 · City of Hope national trial model

Labels show accrued / potential

Thank you!

kasi@coh.org;
X: @pashtoonkasi



City of Hope