19as Jornadas HITOS ONCOLÓGICOS: LO MEJOR DE 2024
MADRID 20 - 21 NOVIEMBRE 2024

Inmunoterapia en cáncer colorrectal

Prof. Jesús García-Foncillas López

Disclosures

- Honoraria: Advisory boards and/or speaker fees and/or research projects:
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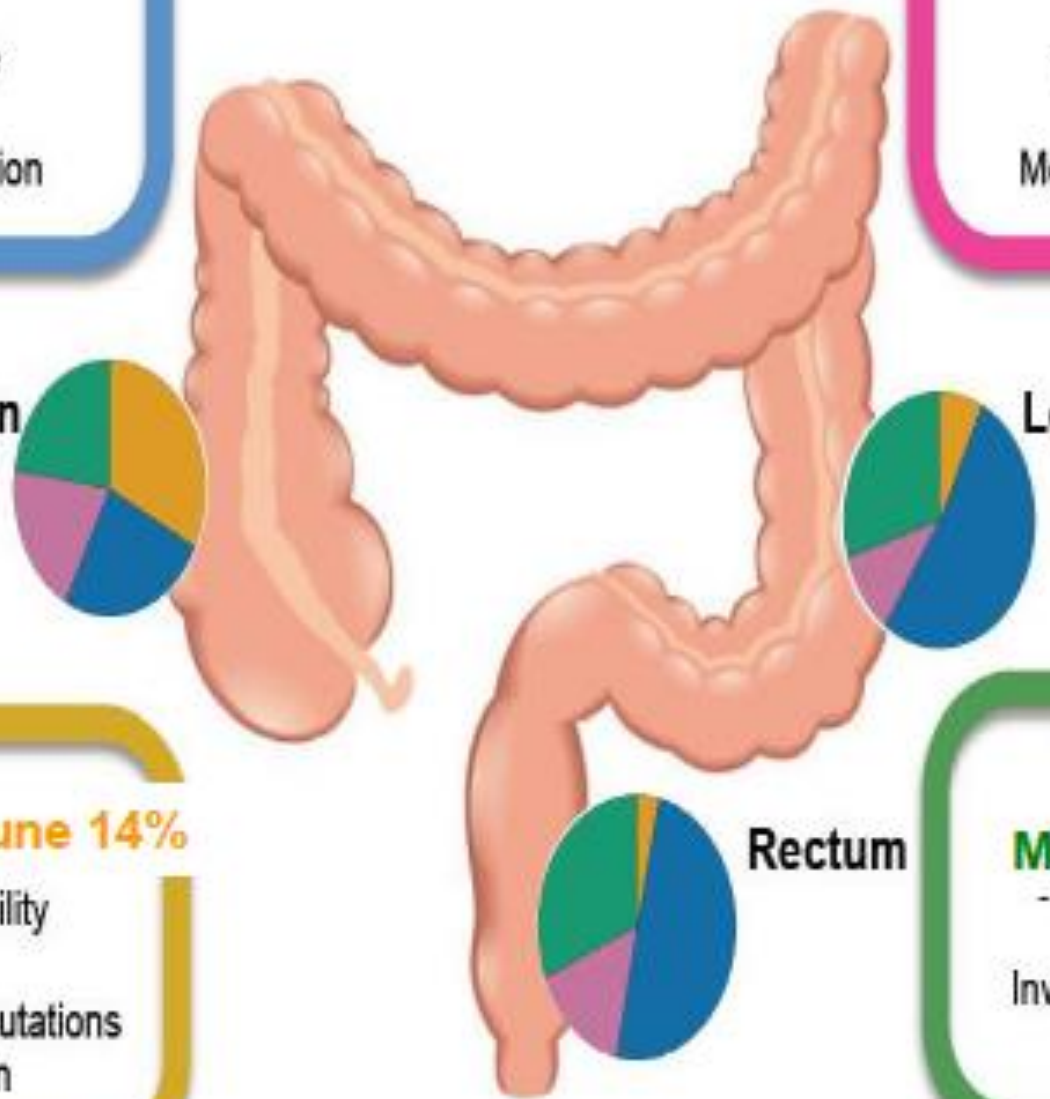
Immunotherapy in all CRC?

CMS2 – Canonical
37%

Microsatellite stable
CIMP negative
WNT and MYC activation

CMS3 – Metabolic
13%

microsatellite status
KRAS mutations
Metabolic reprogramming



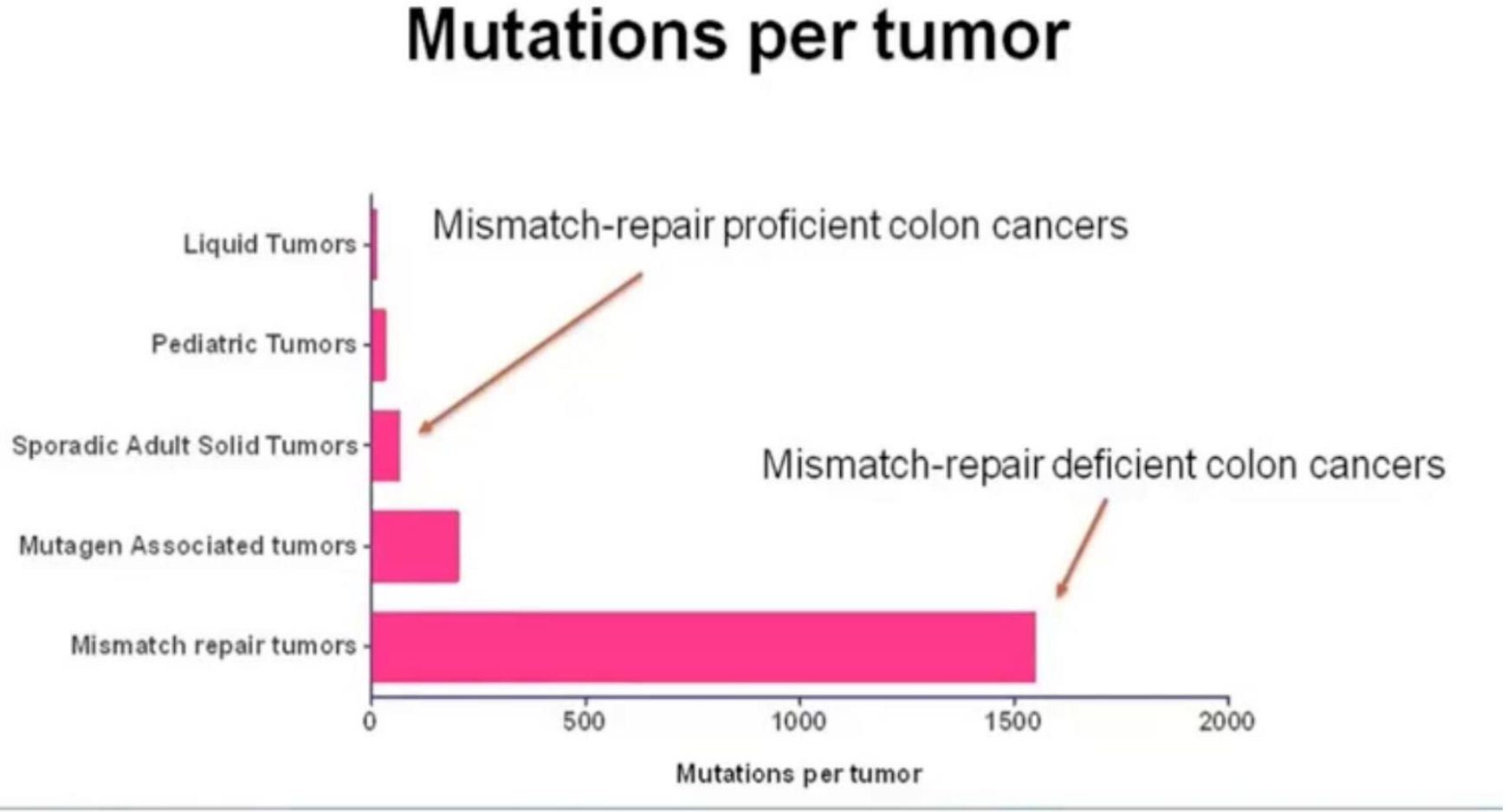
CMS1 - MSI – Immune 14%

Microsatellite instability
CIMP high
Hypermutation, *BRAF* mutations
Immune activation

CMS4–
Mesenchymal 23%

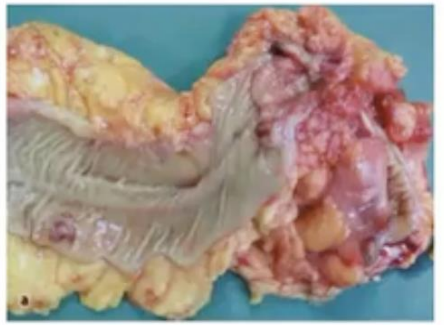
TGFb activation
Invasion, matrix remodeling
Angiogenesis

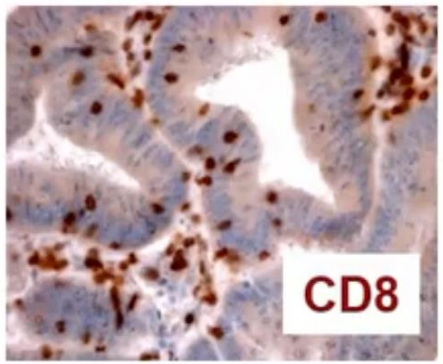
MSI-high tumors have more mutations



MSI causes high immunogenicity

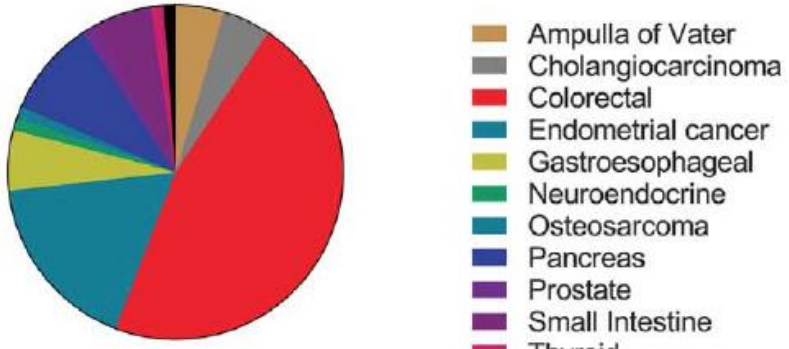
- Large local tumors
- Proximal localization
- Low frequency of distant metastases
- **Dense infiltration with activated cytotoxic lymphocytes**
- **Lymph follicles surrounding the tumor (Crohn‘s like reaction)**
- **Expression signatures indicative of immune cell activation**

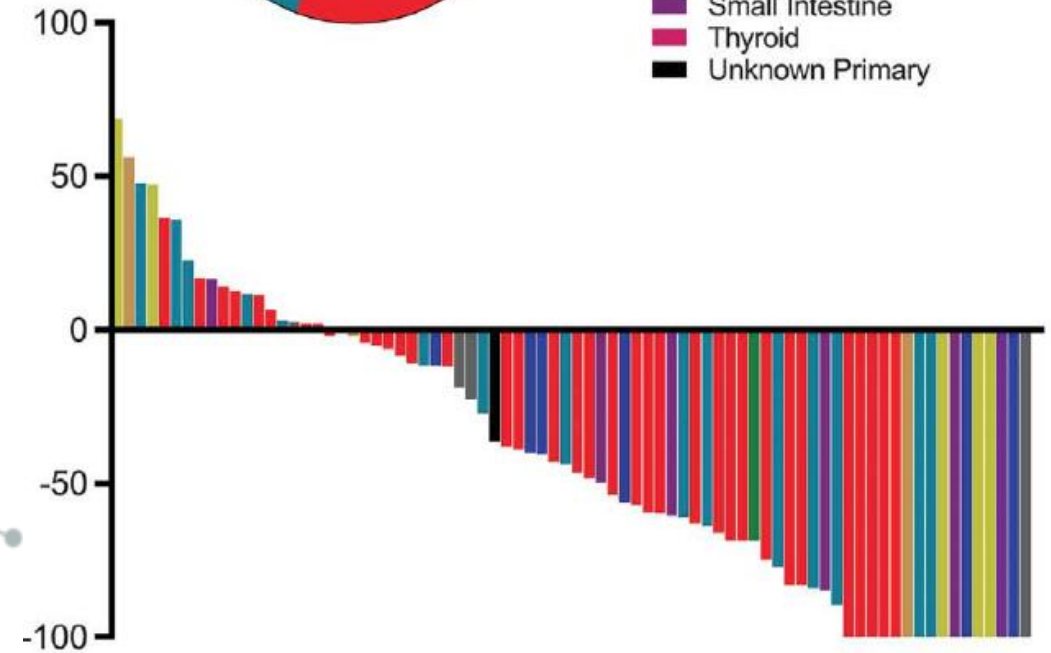




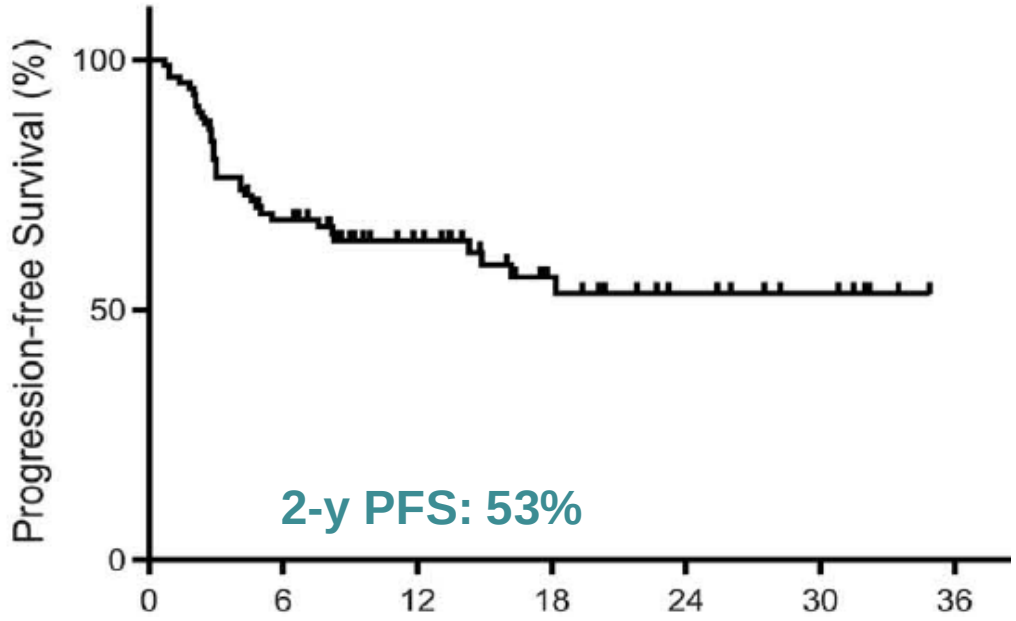
Buckowitz et al., *Br J Cancer* 2005, Marisa et al., *J Natl Cancer Inst* 2018

Pembrolizumab in MMRd: Keynote 028





Name of trial	Phase of trial	Drug and dose	Objective response rate in dMMR	Disease control rate >12 weeks in dMMR
KEYNOTE 028 Le *et al.*[28]	Phase II	Pembrolizumab 10 mg/kg every 14 days	40%	90%



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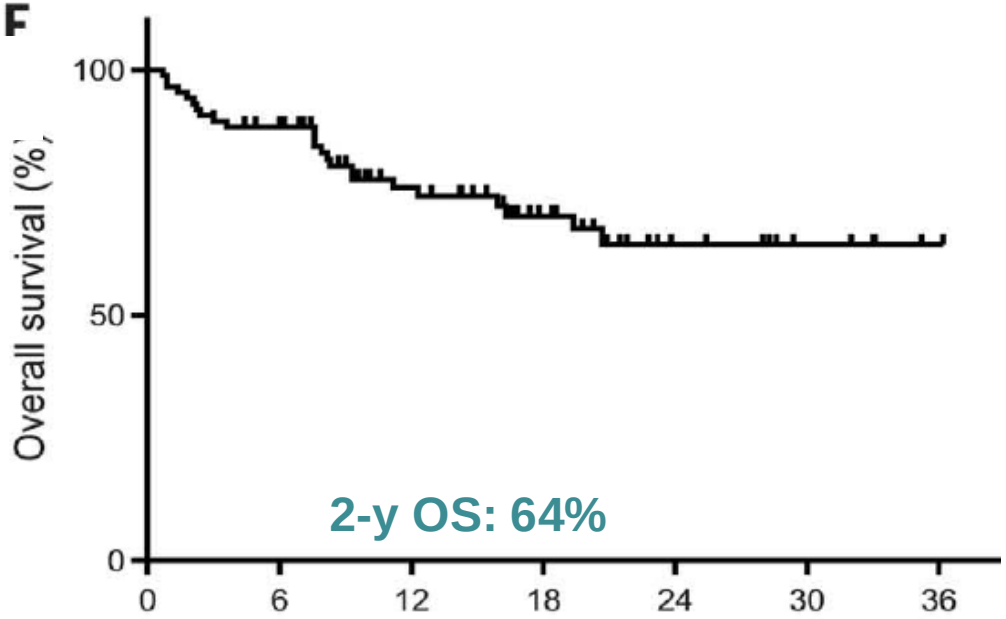

Le et al., Science 357, 409–413 (2017)

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KEYNOTE-164 Data

Key patient inclusion criteria
- Locally advanced, unresectable or metastatic CRC
- dMMR/MSI-H CRC by IHC/PCR
- ≥1 prior line of therapy
- ECOG PS 0 or 1

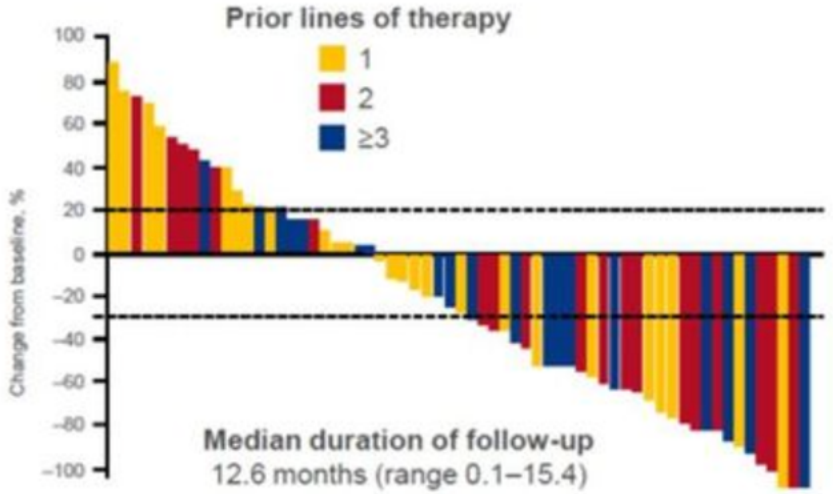
(n=63)

→ Pembrolizumab 200 mg q3w →

Treatment for approximately 2 years (35 cycles) or until PD/toxicity/ withdrawal

Primary Endpoint
- ORR

Secondary Endpoints
- DoR, PFS, OS, safety



Additional efficacy outcomes
- mDoR = NR
- mPFS = 4.1 mo
- 12-mo PFS = 41%

Le D, et al. *Ann Oncol*. 2018;29(suppl 5). Abstract O-021.

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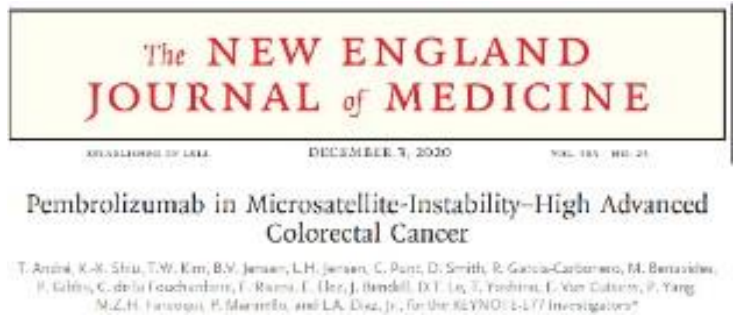
Contrasting Pembrolizumab With Standard Later-Line Therapies

Outcome	CORRECT Trial[a] (N = 753)		RECOURSE Trial[b] (N = 800)		KEYNOTE-164[c] (N = 63)
	Regorafenib (n = 500)	Placebo (n = 253)	TAS-102 (n = 534)	Placebo (n = 266)	Pembrolizumab
ORR, %	1.0	0.4	1.6	0.4	32
mPFS, mo	1.9	1.7	2.0	1.7	4.1
mOS, mo	6.4	5.0	7.1	5.3	NR*

*12.6 median duration of follow-up; 12-month OS rate was 76%.

a. Grothey A, et al. *Lancet*. 2013;381(9863):303-312.
b. Mayer RJ, et al. *N Engl J Med*. 2015;372(20):1909-1919.
c. Le D, et al. *Ann Oncol*. 2018;29(suppl 5). Abstract O-021.

KEYNOTE-177 Study Design NCT02563002



Key Eligibility Criteria

- Confirmed MSI-H/ dMMR Stage IV CRC
- Treatment naive
- ECOG PS 0 or 1
- Measurable disease

R (1:1)

Pembrolizumab 200 mg Q3W for up to 35 cycles

Investigator-Choice Chemotherapy[a]

mFOLFOX6 IV Q2W
OR mFOLFOX6 + Bevacizumab[b] IV Q2W OR mFOLFOX6 + Cetuximab[c] IV Q2W
OR FOLFIRI IV Q2W
OR FOLFIRI + Bevacizumab IV Q2W
OR FOLFIRI + Cetuximab IV Q2W

Optional crossover to pembrolizumab 200 mg Q3W for up to 35 cycles for patients with centrally verified PD by RECIST v1.1, central review

Until unacceptable toxicity, disease progression, or patient/physician withdrawal decision

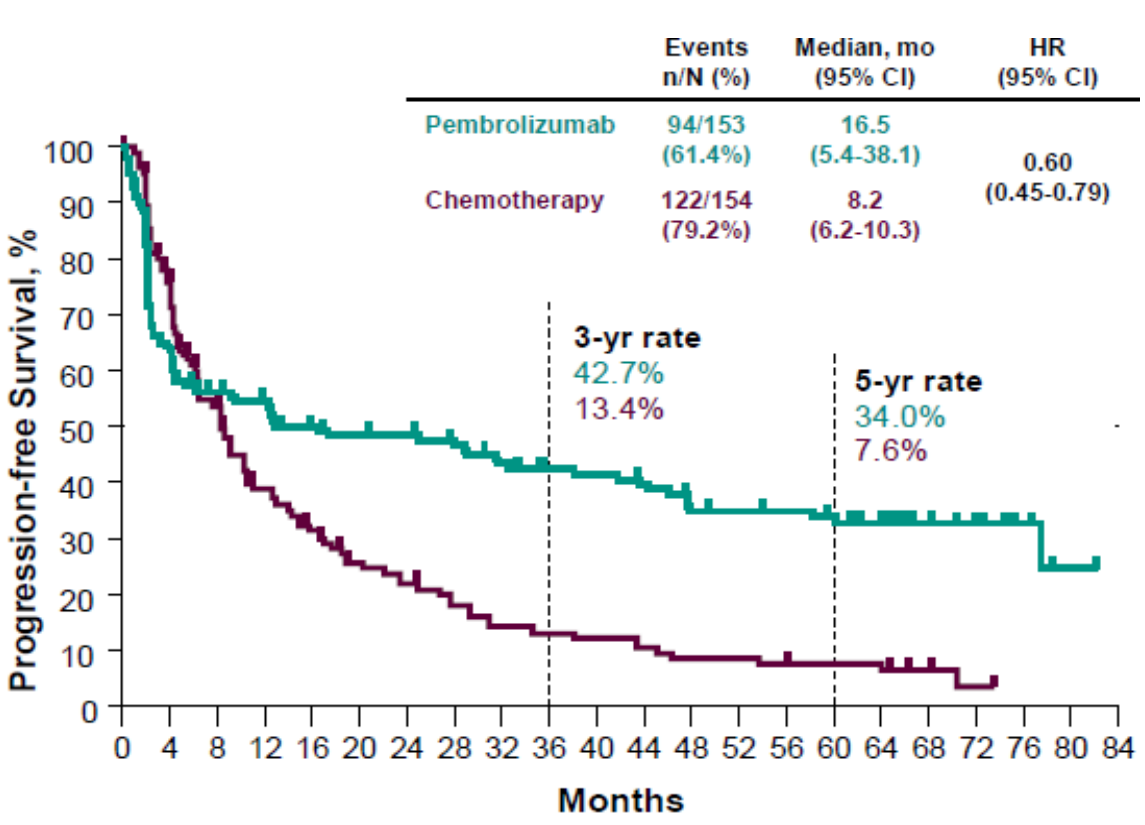
Safety and survival follow-up

- Co-primary endpoints: PFS per RECIST v1.1 by blinded independent central review (BICR) and OS
- Secondary endpoints: ORR per RECIST v1.1 by BICR, safety
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

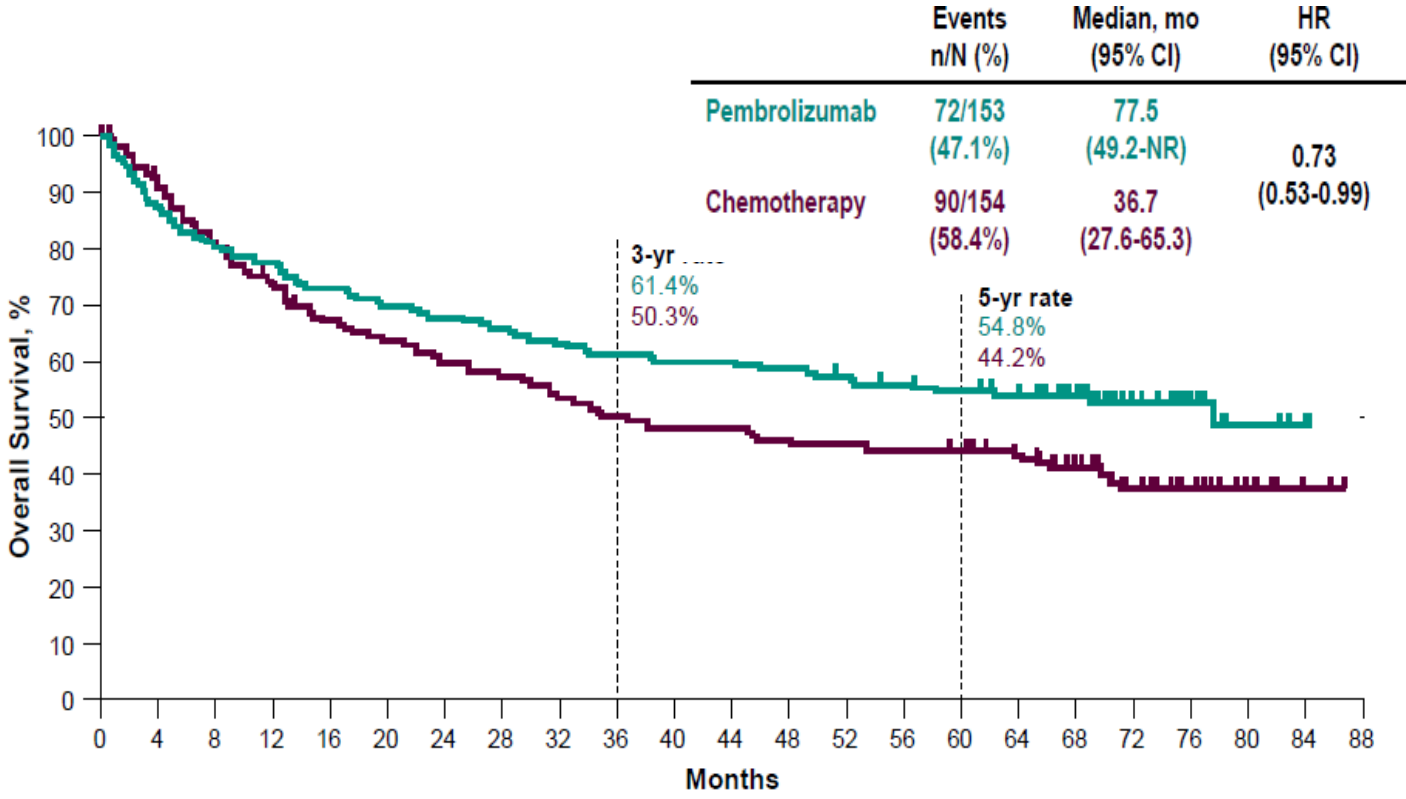
André T et al; N Eng J Med 2020
Diaz L, et al Lancet Oncol 2022
Shiu KK et al; LBA32; Ann of Oncol 2023

KEYNOTE-177: PFS and OS (5 year Follow up)

PFS



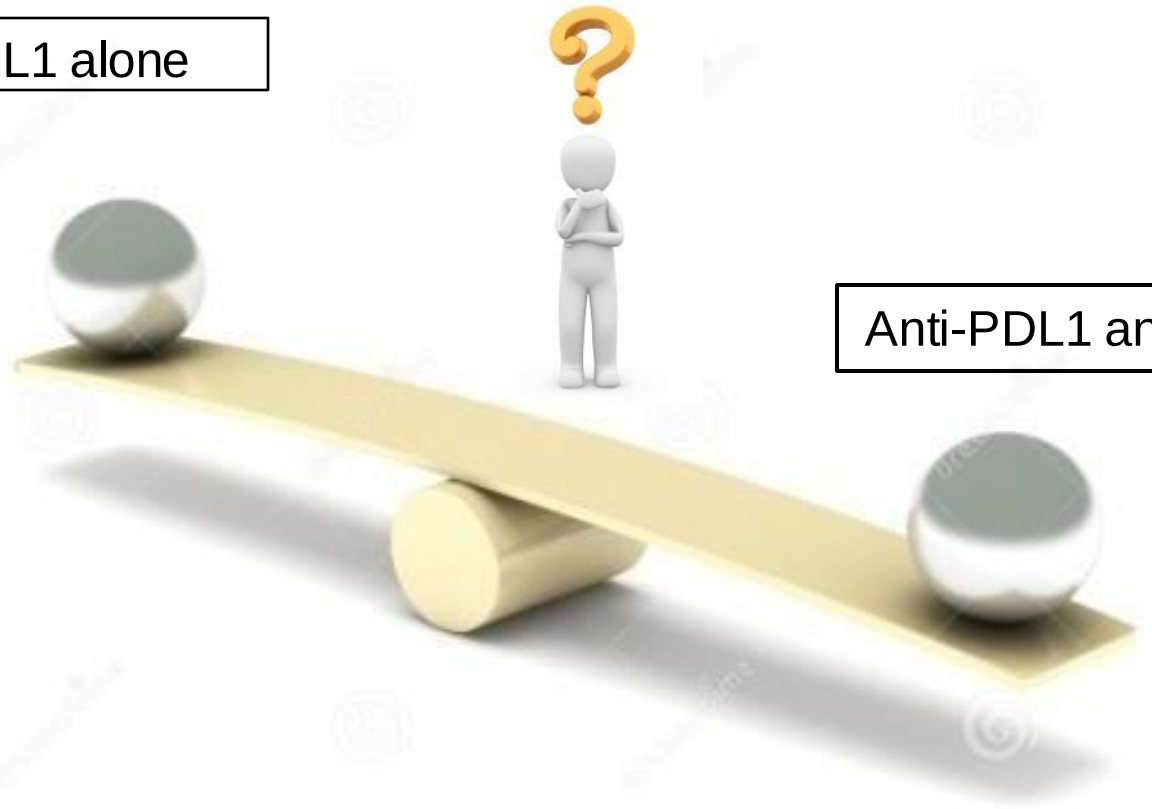
OS



Shiu KK et al; LBA32; Ann of Oncol 2023

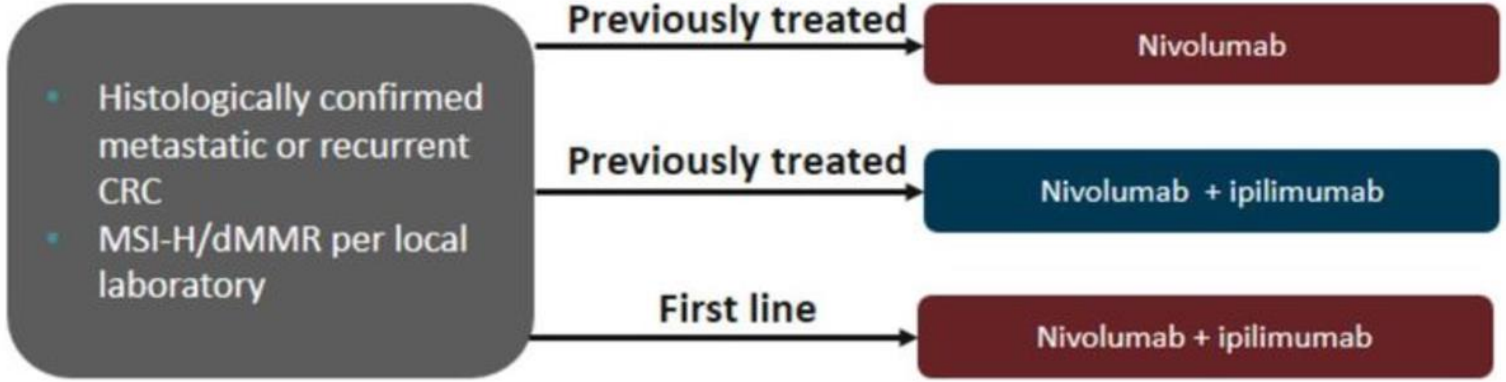
MSI-H/dMMR mCCR: Single or Double checkpont ihnibition[1] ?

Anti-PDL1 alone



Anti-PDL1 and anti-CTL4

CheckMate-142 Nivolumab-Ipilimumab Combination Results



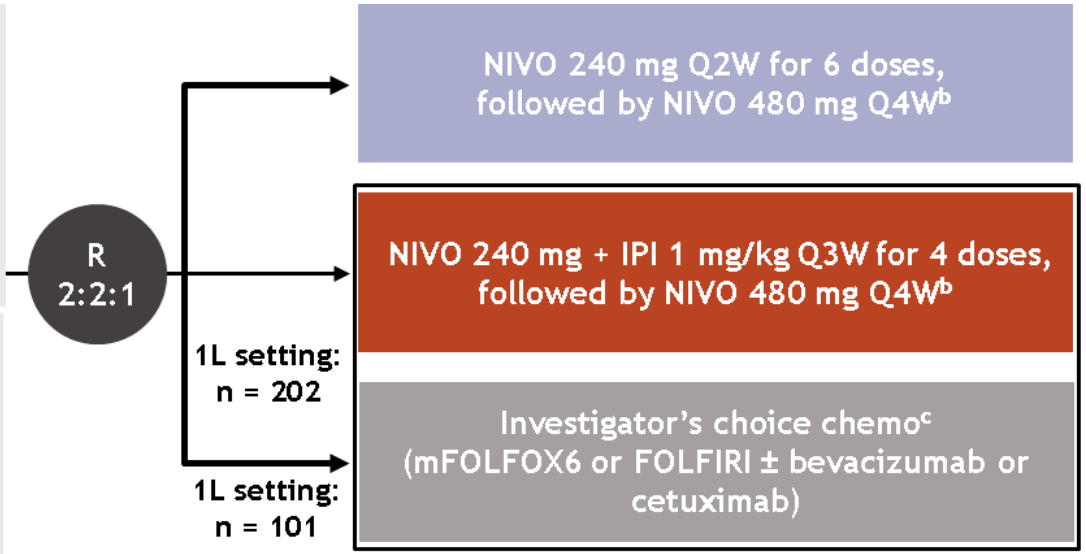
Endpoint	Nivolumab + ipilimumab (N = 119)
ORR, %	55
12-wk DCR, %	80
mDoR, mo	NR
6-mo DoR, %	83%

Overman MJ, et al. *J Clin Oncol.* 2018;36(8):773-779.

Nivolumab + ipilimumab vs chemo as first-line for MSI-H/dMMR mCRC: CheckMate 8HW study

Key eligibility criteria:
- Histologically confirmed unresectable or metastatic CRC
- MSI-H/dMMR status by local testing
- ECOG PS 0 or 1

Stratification factors:
- Prior lines of treatment (0 vs 1 vs ≥ 2)
- Primary tumor location (right vs left)



Treatment until disease progression, unacceptable toxicity, withdrawal of consent (all arms), or a maximum treatment duration of 2 years (NIVO and NIVO + IPI arms only)

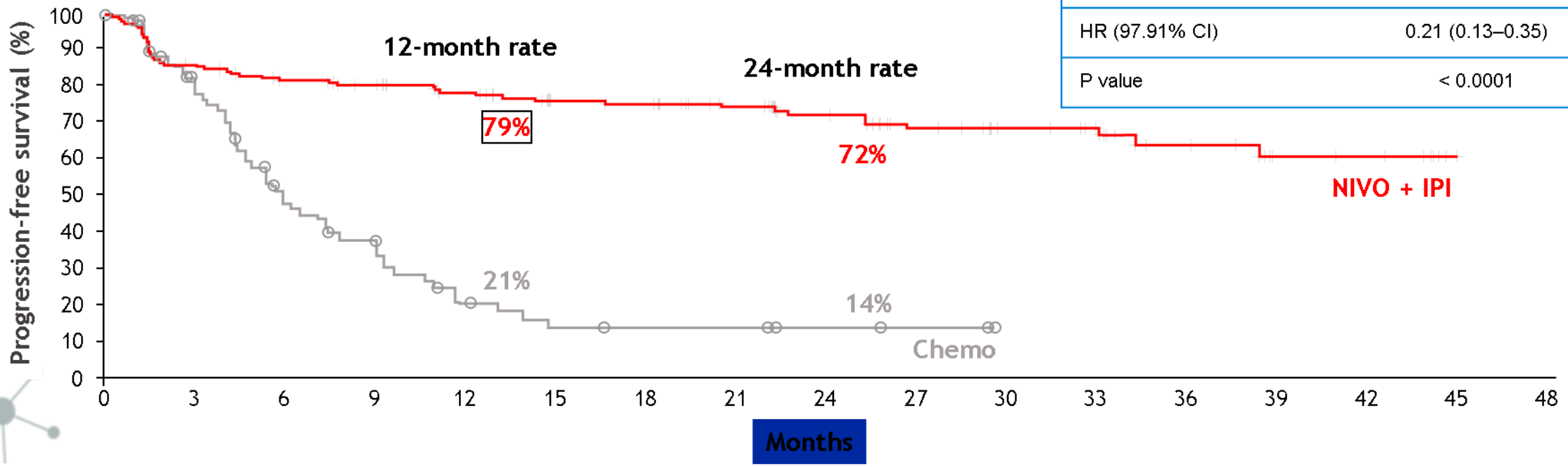
Dual primary endpoints in patients with centrally confirmed MSI-H/dMMR status[d]:
- PFS by BICR[e] (NIVO + IPI vs chemo in the 1L setting)
- PFS by BICR[e] (NIVO + IPI vs NIVO across all lines)

Other select endpoints:
- Safety
- OS; ORR by BICR[e]; PFS2 by BICR[e]; PROs

Andre T et al. Gastrointestinal Cancers Symposium 2024;Abst LBA768.
Lenz T et Al. ASCO 2024; Abst 3503

1st line for MSI-H/dMMR mCRC CheckMate 8HW: 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

- 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)

Andre T et al. Gastrointestinal Cancers Symposium 2024;Abst LBA768. Lenz T et Al. ASCO 2024; Abst 3503

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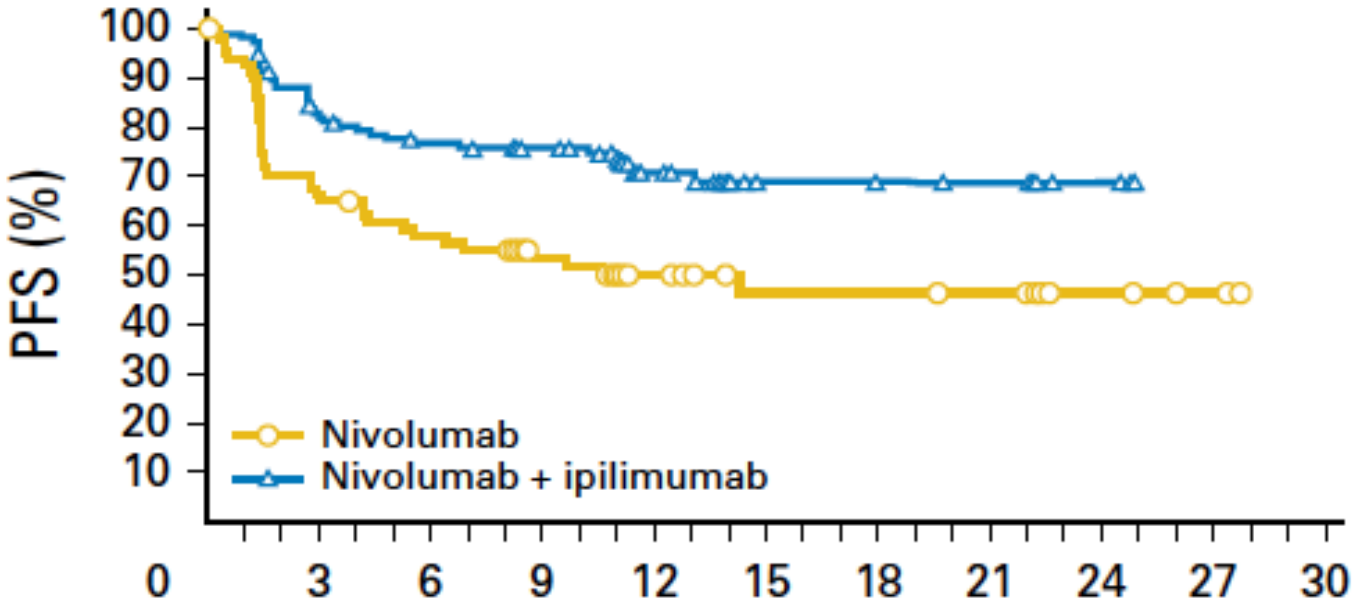
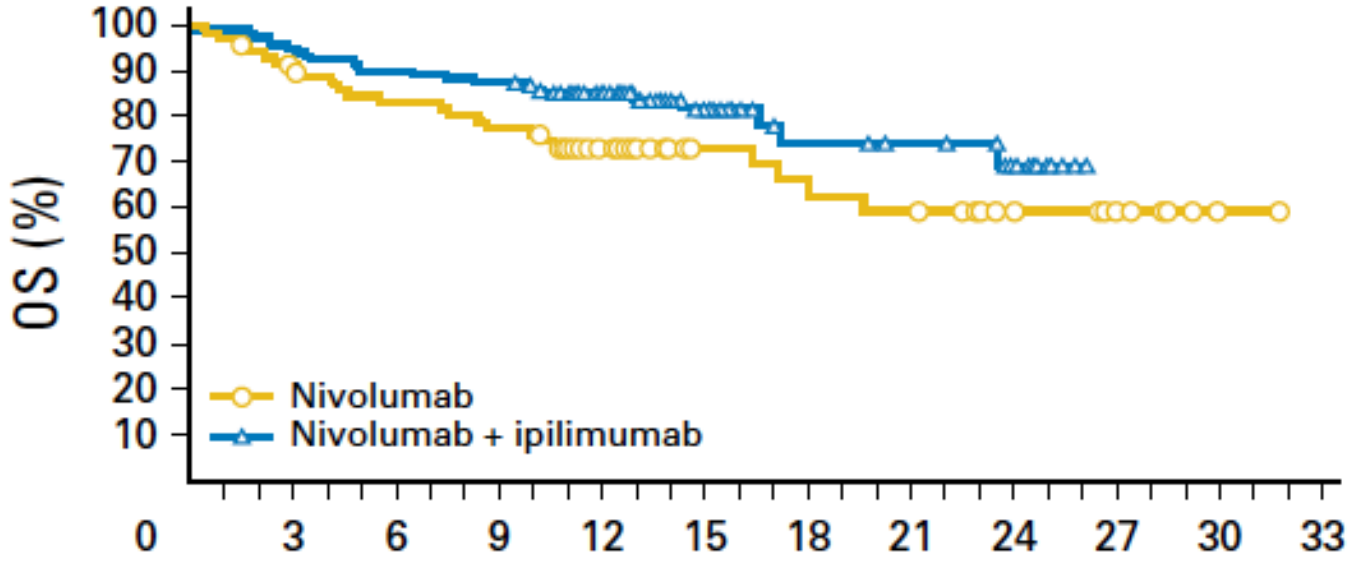
Nivolumab Plus Ipilimumab in DNA MMRd/MSI-H in mCRC





	12-m PFS	12-m OS
Pembro	34%	72%
Nivo	50%	73%
Nivo + Ipi	71%	85%

https://doi.org/10.1200/JCO.2017.76.9901

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First results of the CheckMate 8HW study

PFS subgroup analysis

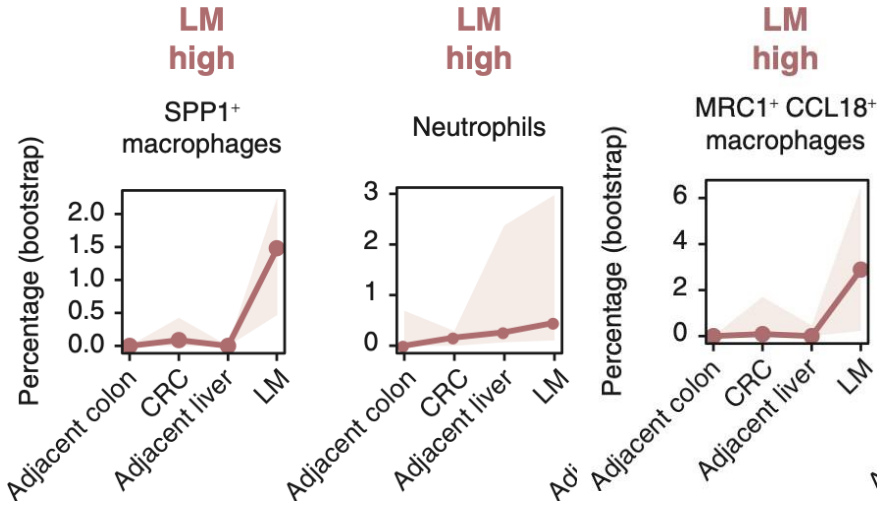
Category (1L centrally confirmed MSI-H/dMMR)	Subgroup	Median PFS,[a] mo		Unstratified HR	Unstratified HR (95% CI)
		NIVO + IPI	Chemo		
Overall (N = 255)		NR	5.9	0.21	
Age, years	< 65 (n = 138)	NR	5.7	0.19	
	≥ 65 (n = 117)	NR	5.9	0.24	
Sex	Male (n = 117)	NR	5.9	0.19	
	Female (n = 138)	NR	6.2	0.22	
Region	US/Canada/Europe (n = 167)	NR	5.7	0.27	
	Asia (n = 28)	NR	7.4	0.03	
	Rest of world (n = 60)	NR	6.2	0.16	
ECOG PS	0 (n = 142)	NR	9.0	0.22	
	≥ 1 (n = 113)	NR	4.2	0.20	
Tumor sidedness	Left (n = 70)	NR	4.4	0.22	
	Right (n = 185)	NR	7.1	0.21	
Liver metastases[a]	Yes (n = 87)	NR	5.9	0.11	
	No (n = 166)	NR	5.4	0.28	
Lung metastases[a]	Yes (n = 53)	13.2	4.9	0.40	
	No (n = 200)	NR	6.2	0.16	
Peritoneal metastases[a]	Yes (n = 115)	NR	4.4	0.19	
	No (n = 138)	NR	7.4	0.23	
Tumor cell PD-L1 expression	≥ 1% (n = 55)	NR	3.4	0.11	
	< 1% (n = 191)	NR	6.5	0.22	
BRAF/*KRAS*/*NRAS* mutation status	*BRAF*/*KRAS*/*NRAS* all wild type (n = 58)	34.3	5.4	0.08	
	BRAF mutant (n = 72)	NR	9.2	0.37	
	KRAS or *NRAS* mutant (n = 45)	NR	5.7	0.24	
	Unknown (n = 74)	NR	4.9	0.17	
Lynch syndrome	Yes (n = 31)	NR	7.4	0.28	
	No (n = 152)	NR	6.2	0.25	
	Unknown (n = 66)	NR	5.5	0.13	

[a]Per BICR.

Liver metastases in CRC

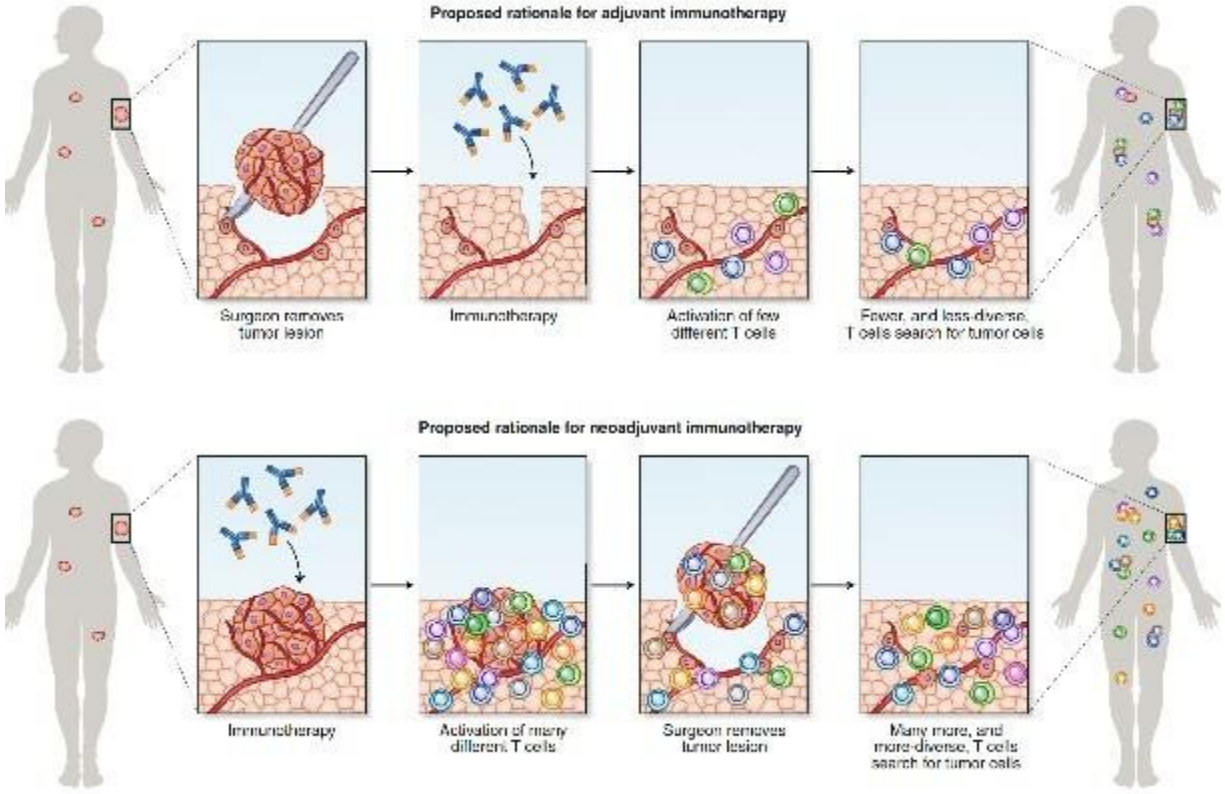
- Liver is the most common metastatic site for CRC
  - > 50% of pts develop liver mets
- Liver mets associated with worse prognosis and **non-response to current IO regimens**
- Immune evasion associated with liver mets poorly understood

CRC liver mets are high in immunosuppressive macrophages and neutrophils



Wu et al, Cancer Discov 2022

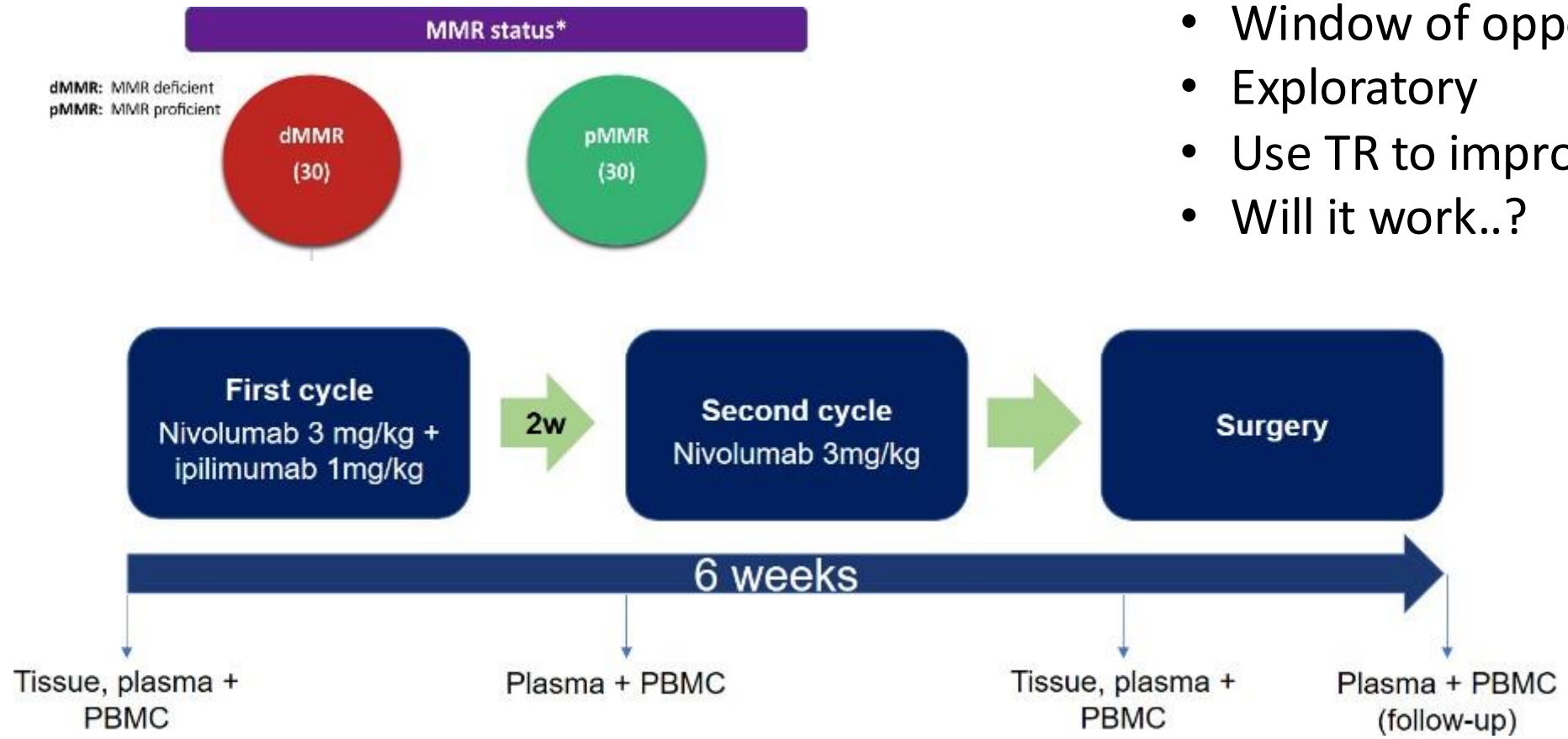
Improved antigenicity with neoadjuvant IO



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

Versluis et al, *Nat Med* 2020; Blank et al, *Nat Med*, 2018

How the NICHE study started

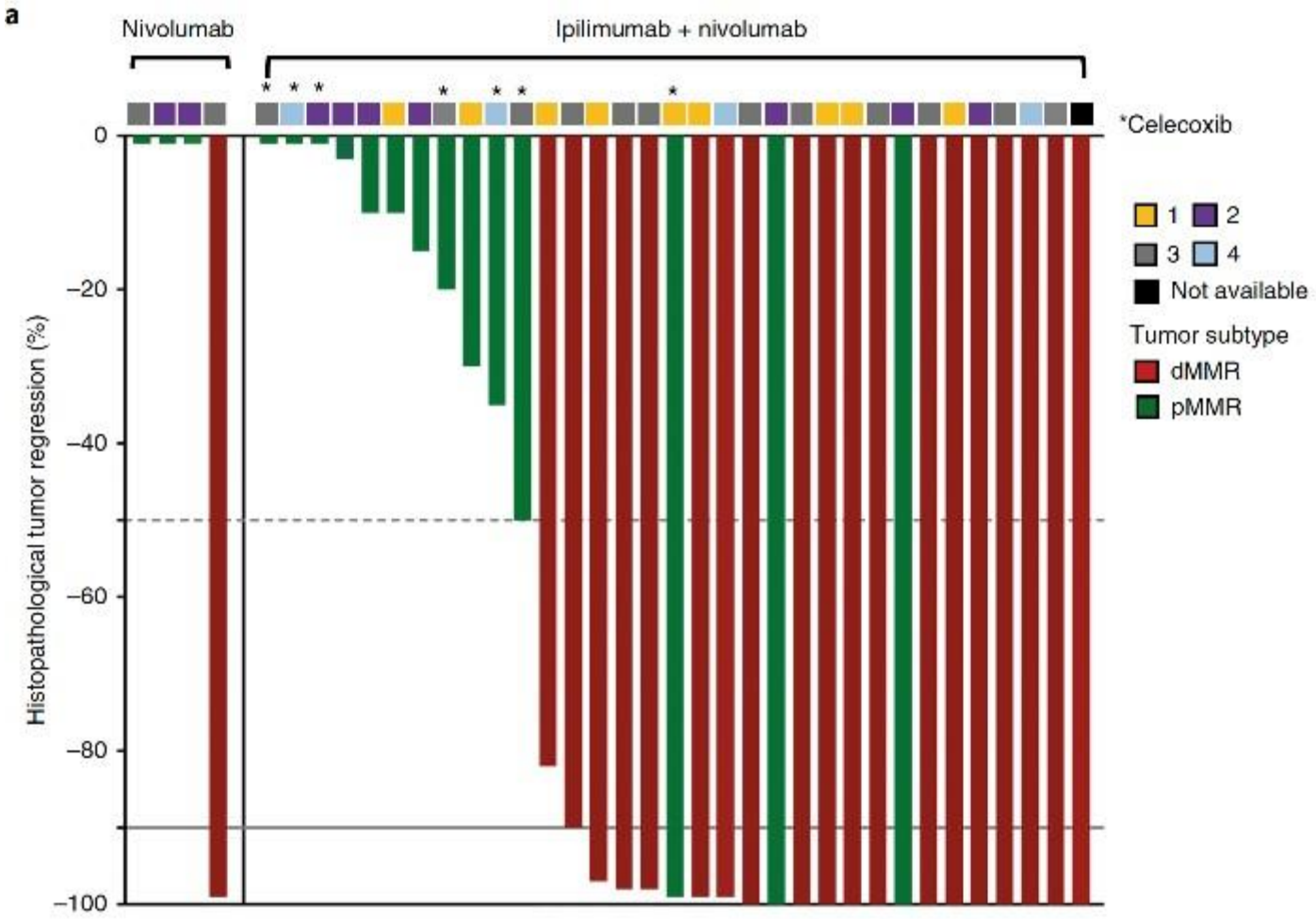


- Window of opportunity study
- Exploratory
- Use TR to improve IO for CRC
- Will it work..?

Chalabi et al, Nat Med 2020, ESMO 2022

Nivolumab = anti-PD1
Ipilimumab = anti-CTLA4

First results NICHE dMMR + pMMR cohorts



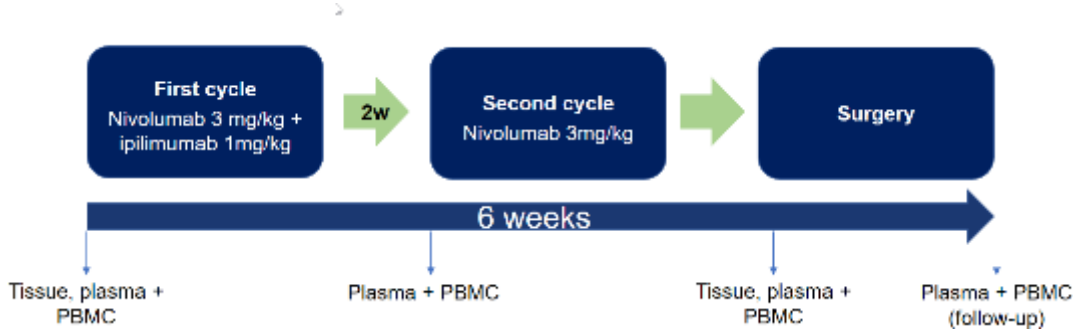
ARTICLES
https://doi.org/10.1038/s41591-020-0805-8
nature medicine
Check for updates

Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers

Myriam Chalabi[1,2,3], Lorenzo F. Fanchi[2,4,17], Krijn K. Dijkstra[2,4,17], José G. Van den Berg[5,17], Arend G. Aalbers[6], Karolina Sikorska[7], Marta Lopez-Yurda[7,8], Cecile Grootscholten[1], Geerard L. Beets[6,9], Petur Snaebjornsson[5], Monique Maas[10], Marjolijn Mertz[11], Vivien Veninga[2,4], Gergana Bounova[4,12], Annegien Broeks[13], Regina G. Beets-Tan[9,10], Thomas R. de Wijkerslooth[1], Anja U. van Lent[14], Hendrik A. Marsman[15], Elvira Nuijten[7], Niels F. Kok[6], Maria Kuiper[1], Wieke H. Verbeek[1], Marleen Kok[3,16], Monique E. Van Leerdam[1], Ton N. Schumacher[2,4], Emile E. Voest[1,2,4,17] and John B. Haanen[2,3,17]

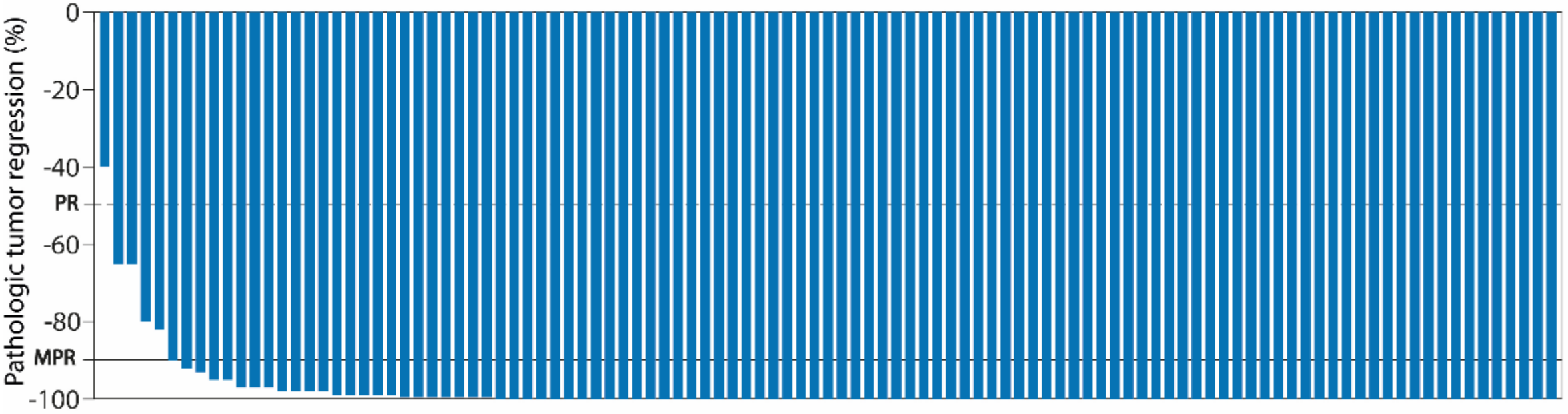
- dMMR cohort (*n*=21): 100% pathologic responses and 60% pathologic complete responses
- pMMR cohort (*n=15)*: 27% (4/15) pathologic responses

NICHE-2: Biomarker driven neoadjuvant IO



In locally advanced <u>MMR-deficient</u> colon cancers

- **95% MPR; 67% pCR**

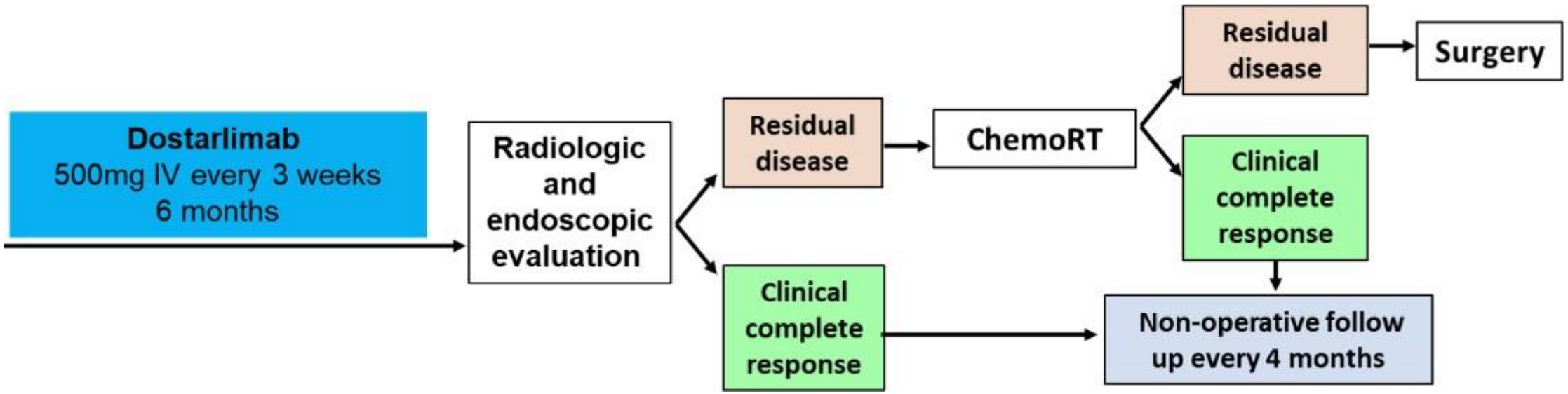


Only 3 patients received adjuvant chemotherapy. At the time of presentation, median follow-up of 13 months and 0 recurrences.

Chalabi et al, ESMO 2022

MPR = major pathologic response = ≤ 10% residual viable tumor

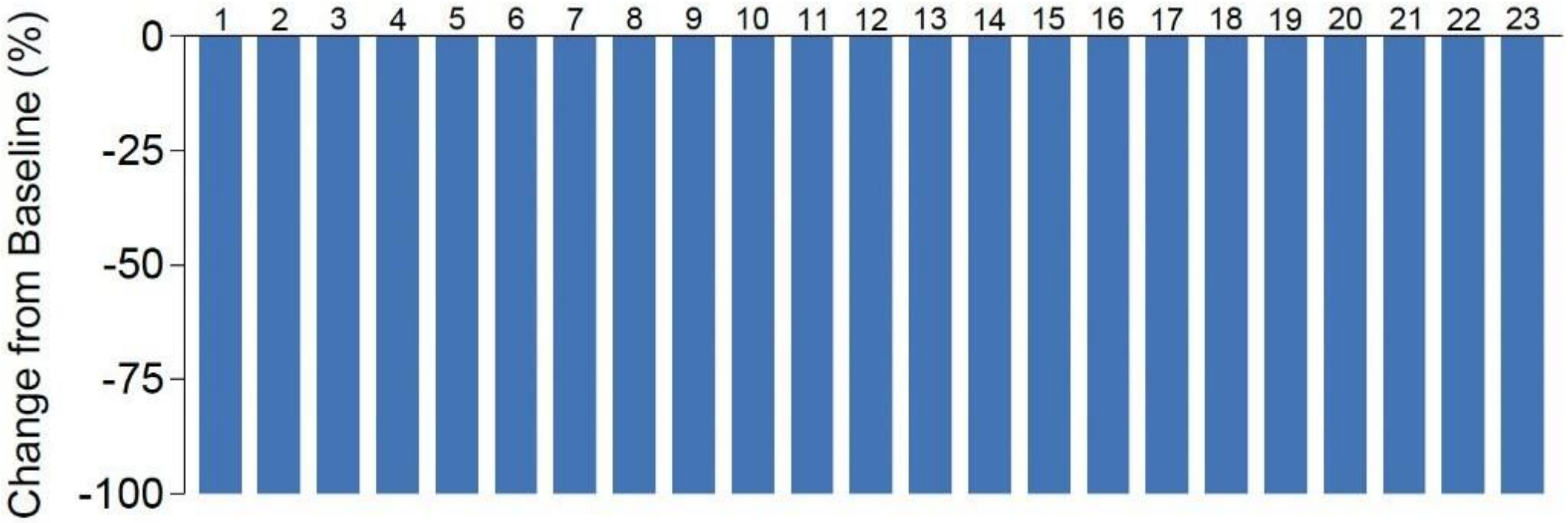
Neoadjuvant anti-PD1 in dMMR rectal cancer



Cercek et al, *NEJM* 2022, JSMO 2023

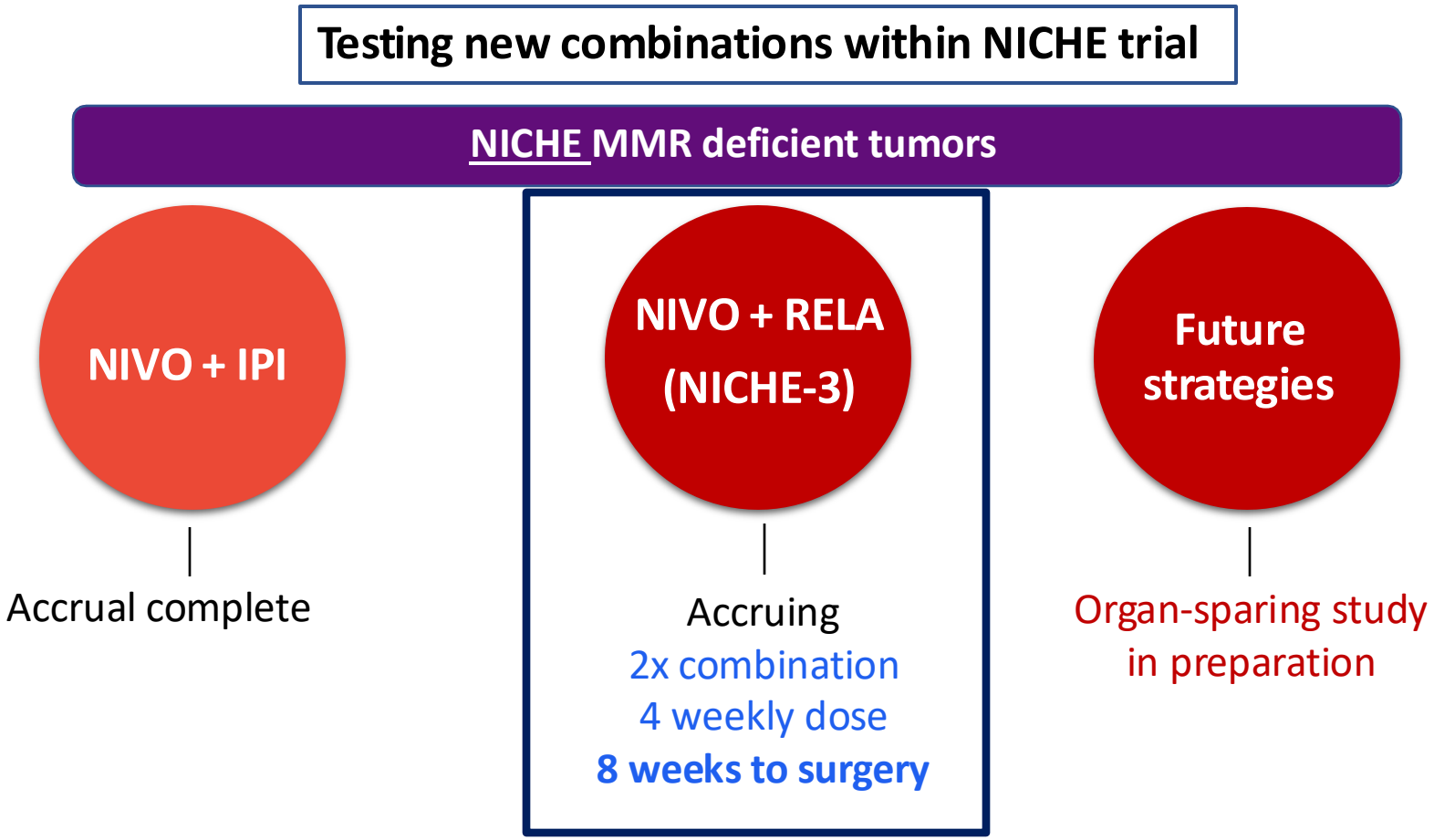
Neoadjuvant anti-PD1 in dMMR rectal cancer

-100% cCR with 6 months of dostarlimab monotherapy
- 0% underwent RT, CRTx and/or surgery



Cercek et al, *NEJM* 2023, JSMO 2023

What's next for dMMR tumors?



Ongoing translational research

Circulating tumor DNA dynamics

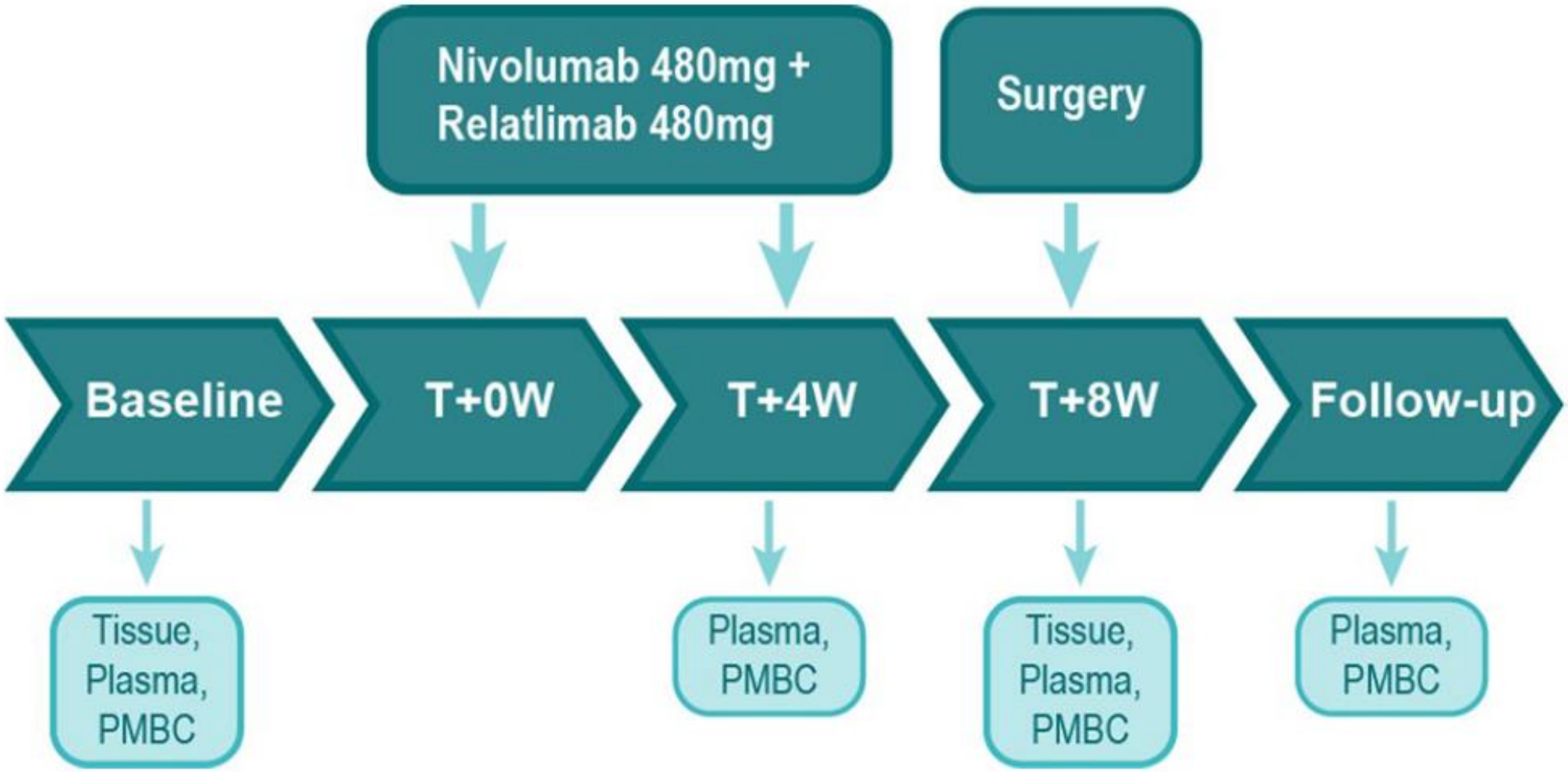
Response assessment using PET

organ preservation?

Interrogate responses in dMMR subsets

(BRAFmt, Lynch vs non-Lynch, type of dMMR)

NICHE-3: neoadjuvant nivo + rela in dMMR colon cancers

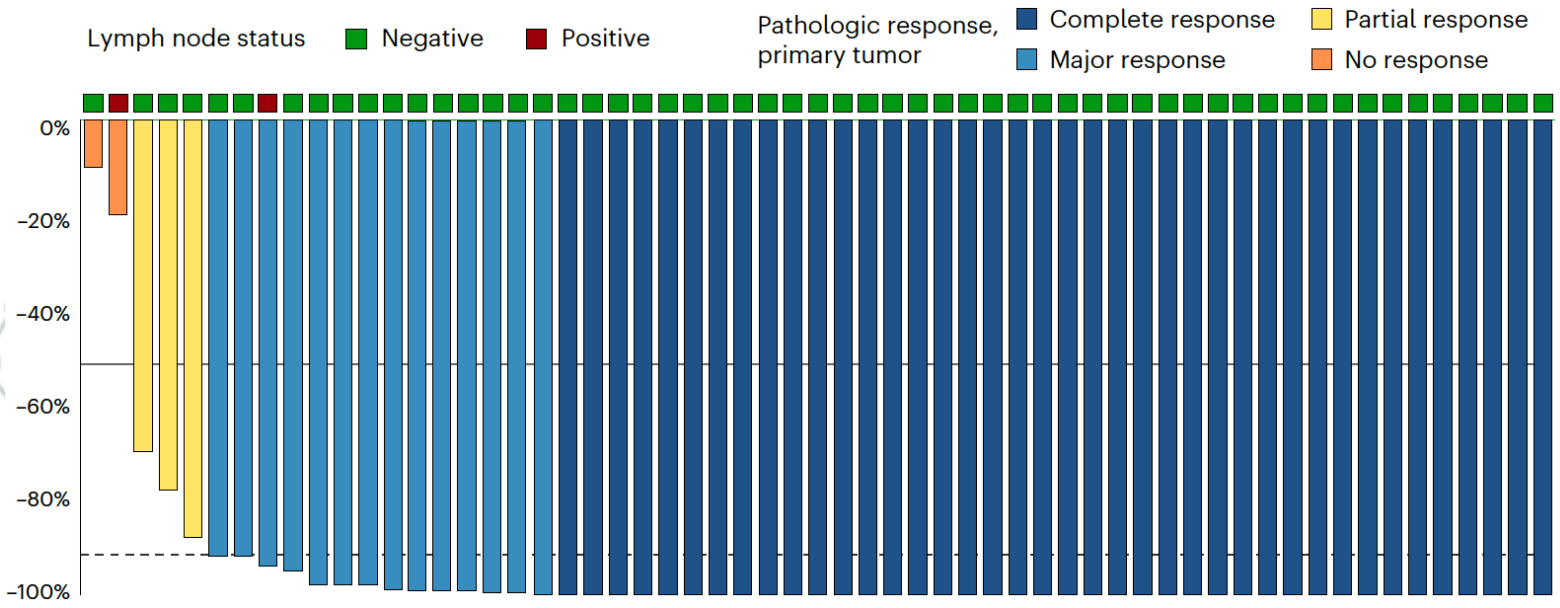


- Compared to NICHE-2 with nivo/ipi: difference in treatment doses, scheduling and timing of surgery
- Only 5% grade 3 irAE, yet 21% endocrinopathies requiring long-term supplementation

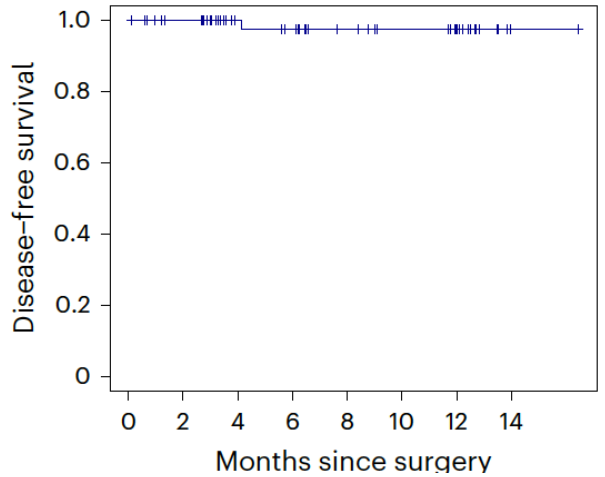
Nature Medicine | *Volume 30* | *November 2024* | *3284–3290*

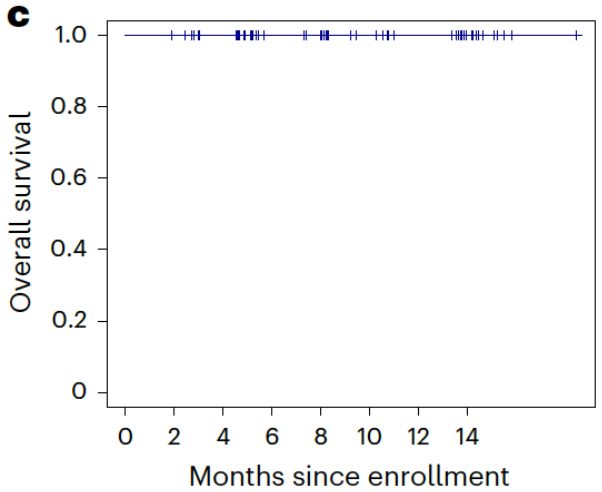
Neoadjuvant nivolumab and relatlimab in locally advanced MMR-deficient colon cancer: a phase 2 trial

nature medicine



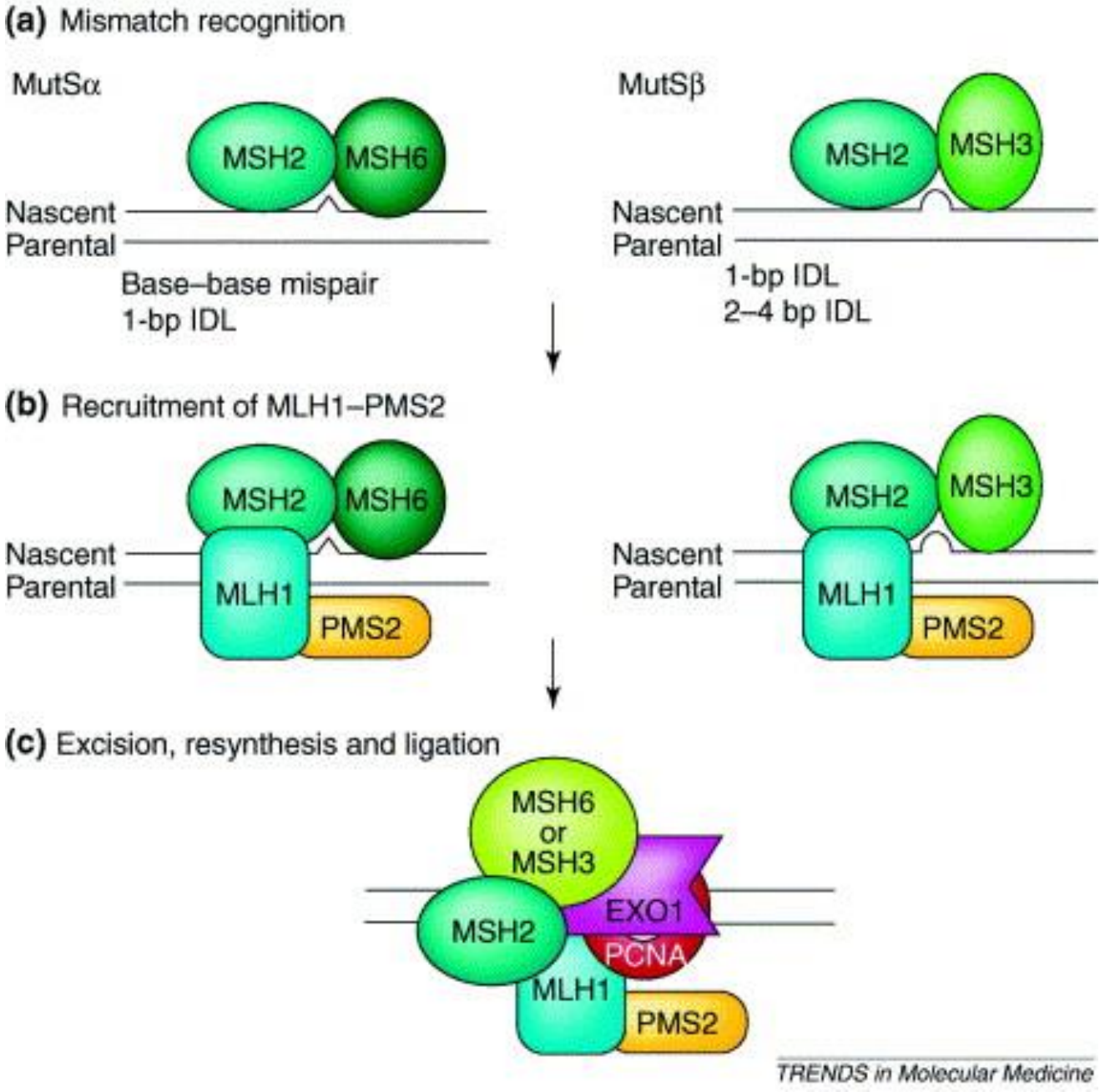
Pathologic response (RVT)	Full cohort *n*=59
Yes (≤50%)	57 (97%)
Major (≤10%)	54 (92%)
Complete (0%)	40 (68%)
Partial (11–50%)	3 (5%)
No (>50%)	2 (3%)





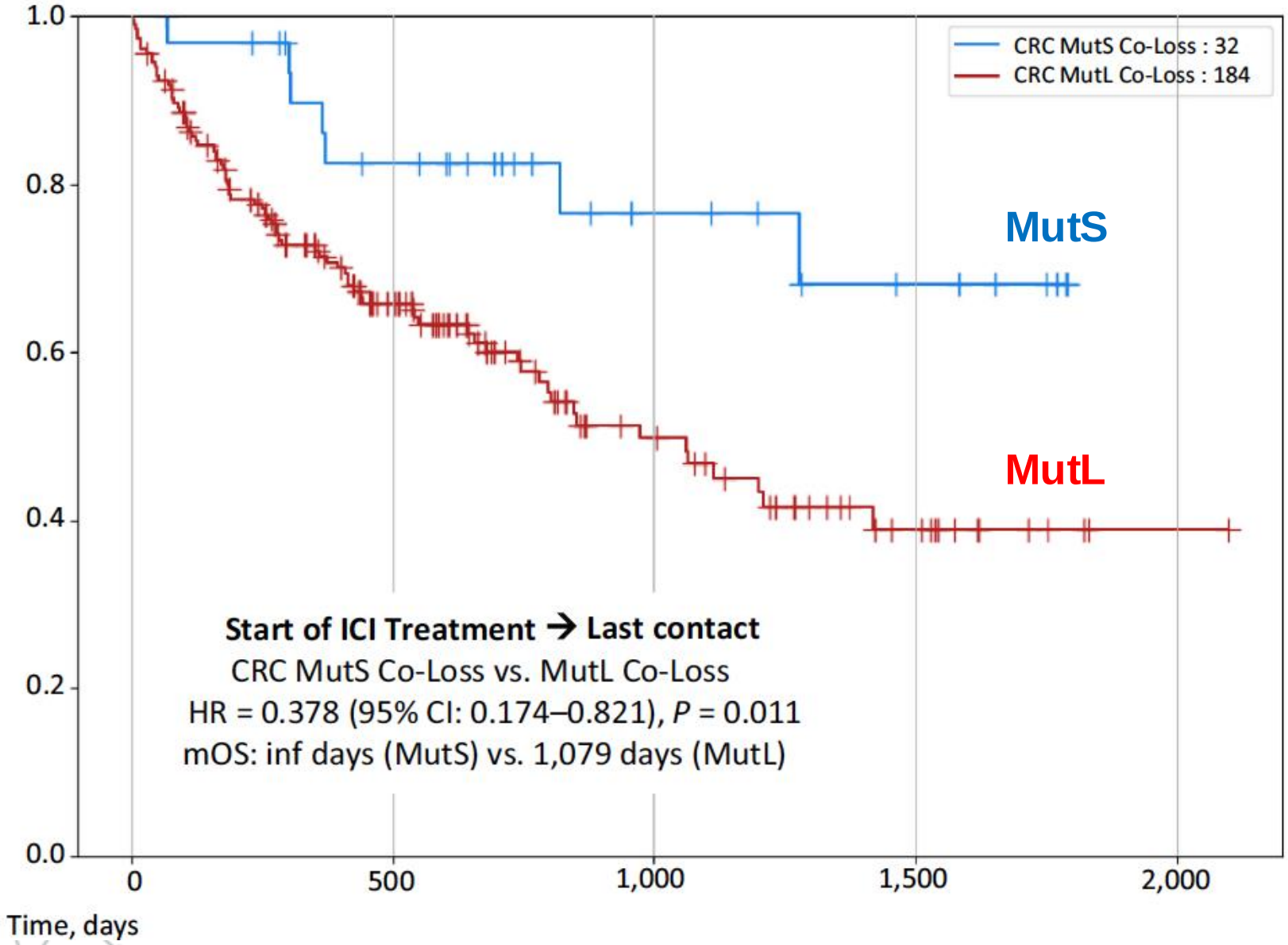
More insights in MSI-H?

Mismatch recognition and repair



MutS Homolog: MSH
MutL Homolog: MLH

Differential Responses to Immune Checkpoint Inhibitors are Governed by Diverse Mismatch Repair Gene Alterations



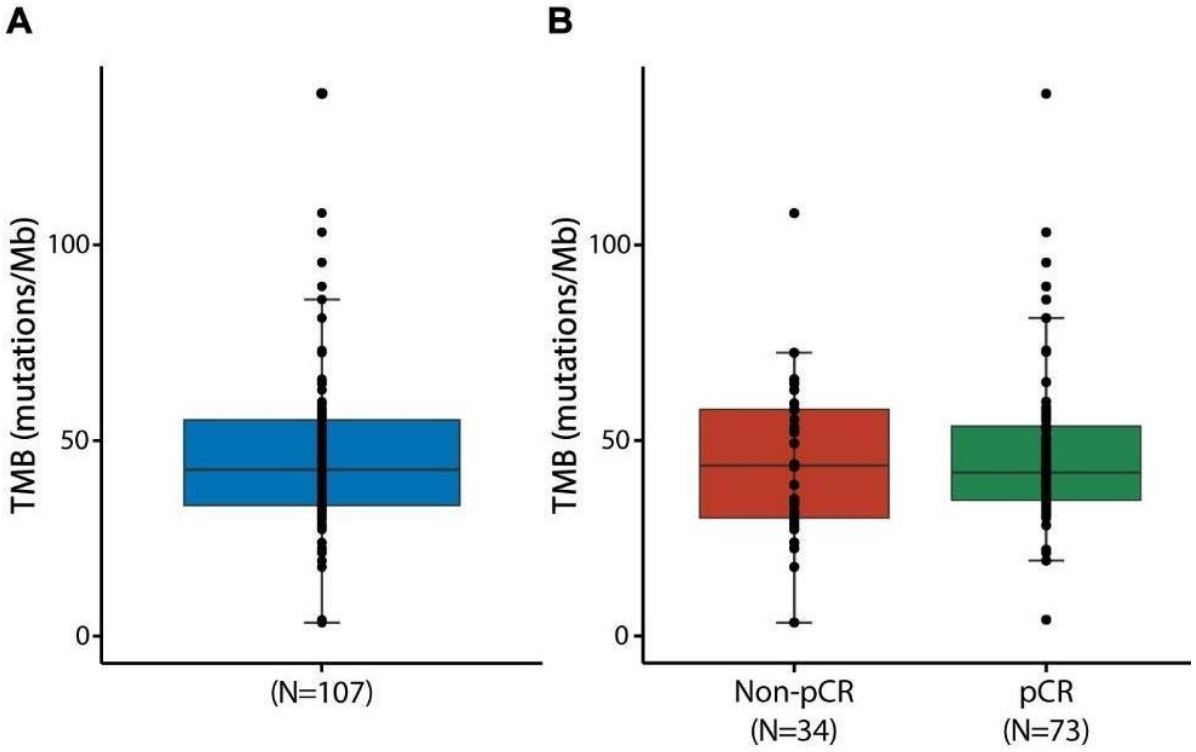
MutS: Recognition

MutL: Repair

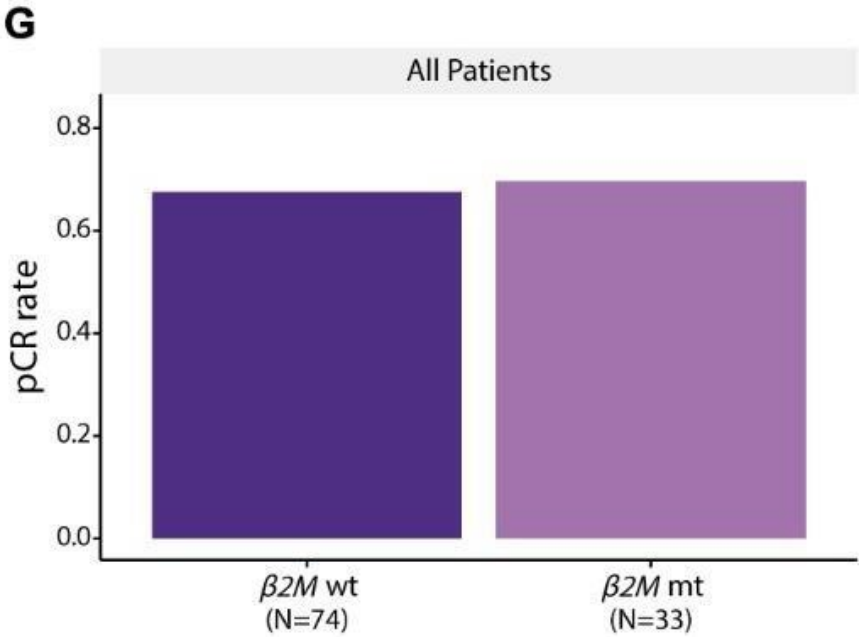
Clin Cancer Res 2024;30:1906–15

pCR in dMMR tumors: TMB and B2M

pCR not associated with TMB



Responses/pCR in B2Mmt dMMR tumors



Chalabi et al, NEJM 2024

MMR deficiency and antigen presentation defects

The role of gamma delta T cells

Article

γδ T cells are effectors of immunotherapy in cancers with HLA class I defects

https://doi.org/10.1038/s41586-022-05593-1
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Accepted: 24 November 2022
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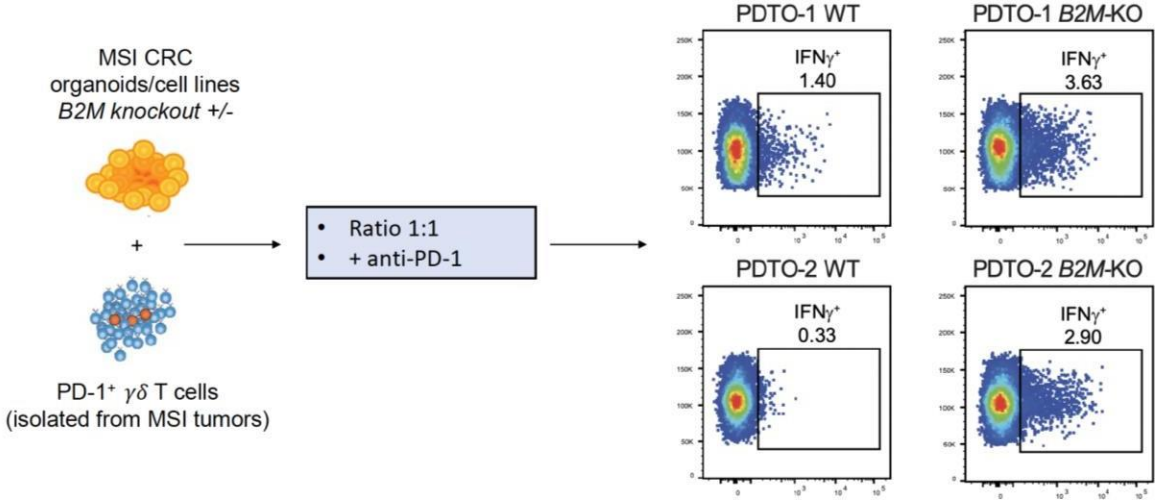
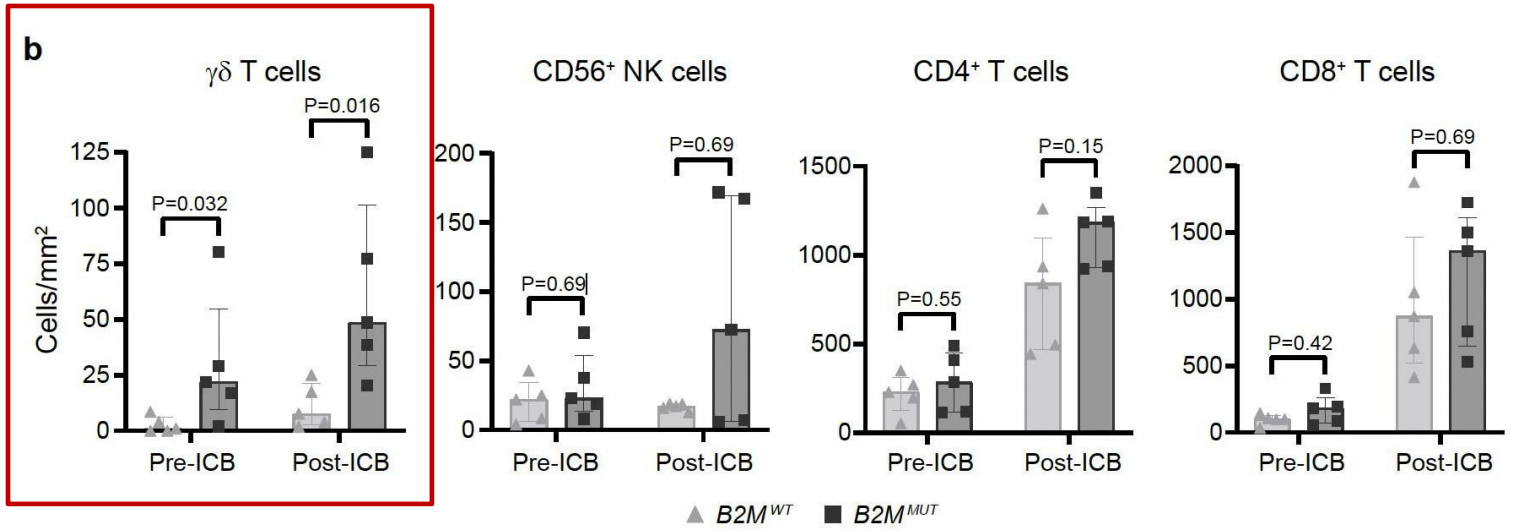
Natasja L. de Vries[1,2,13], Joris van de Haar[3,4,5,13], Vivien Veninga[3,4,13], Myriam Chalabi[3,6,7,13], Marieke E. Ijsselsteijn[1], Manon van der Ploeg[1], Jitske van den Bulk[1], Dina Ruano[1], Jose G. van den Berg[8], John B. Haanen[3,7], Laurien J. Zeverijn[3,4], Birgit S. Geurts[3,4], Gijs F. de Wit[3,4], Thomas W. Battaglia[3,4], Hans Gelderblom[9], Henk M. W. Verheul[10], Ton N. Schumacher[3,4,11], Lodewyk F. A. Wessels[4,5,12], Frits Koning[2,14], Noel F. C. C. de Miranda[1,14] ✉ & Emile E. Voest[3,4,14] ✉

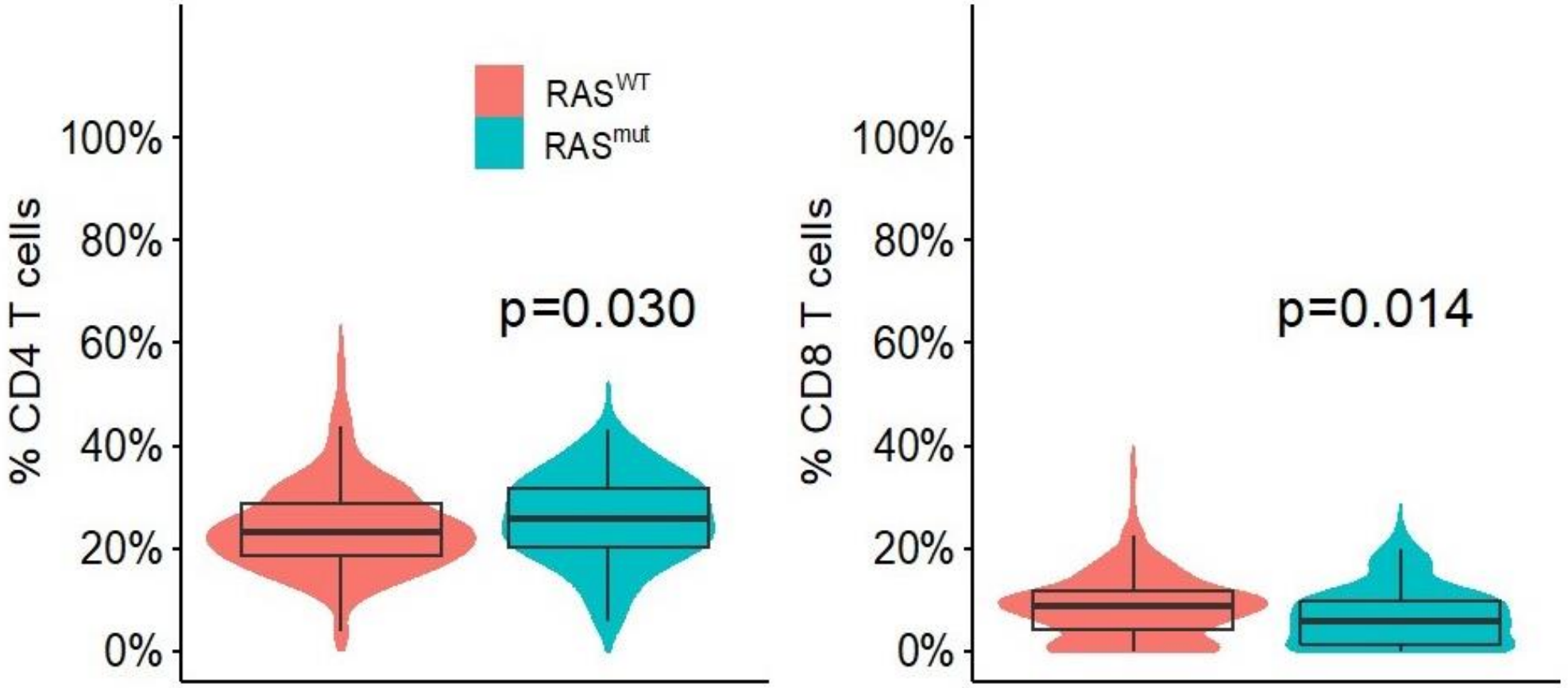
DNA mismatch repair-deficient (MMR-d) cancers present an abundance of neoantigens that is thought to explain their exceptional responsiveness to immune checkpoint blockade (ICB)[1,2]. Here, in contrast to other cancer types[3–5], we observed that 20 out of 21 (95%) MMR-d cancers with genomic inactivation of β2-microglobulin





De Vries, Van de Haar, Veninga, Chalabi et. al, Nature 2023

RAS^{mut} MSI-H CRC Tumors are Less Inflamed than *RAS*^{wt} Tumors



Salem M. et al ASCO 2022

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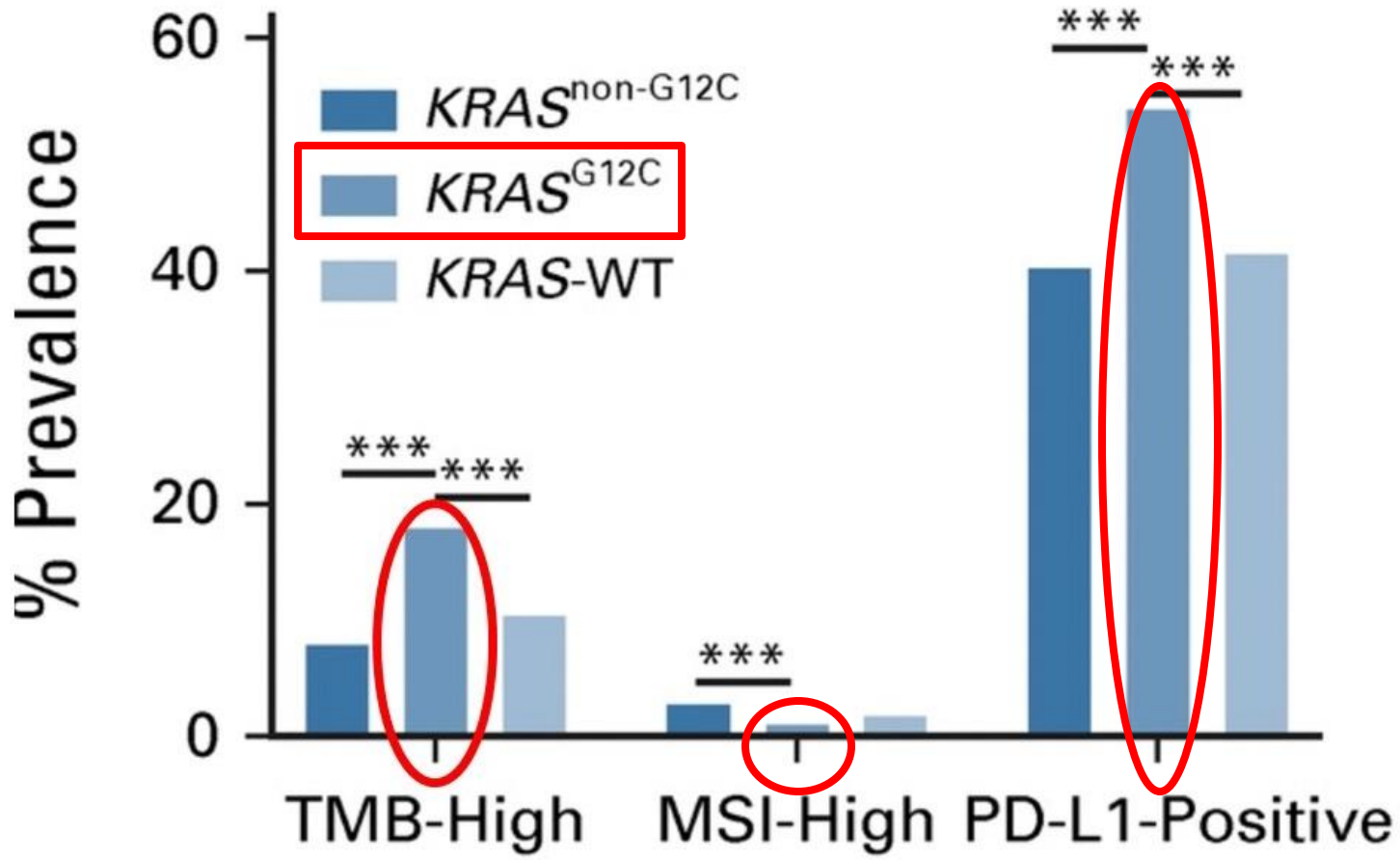
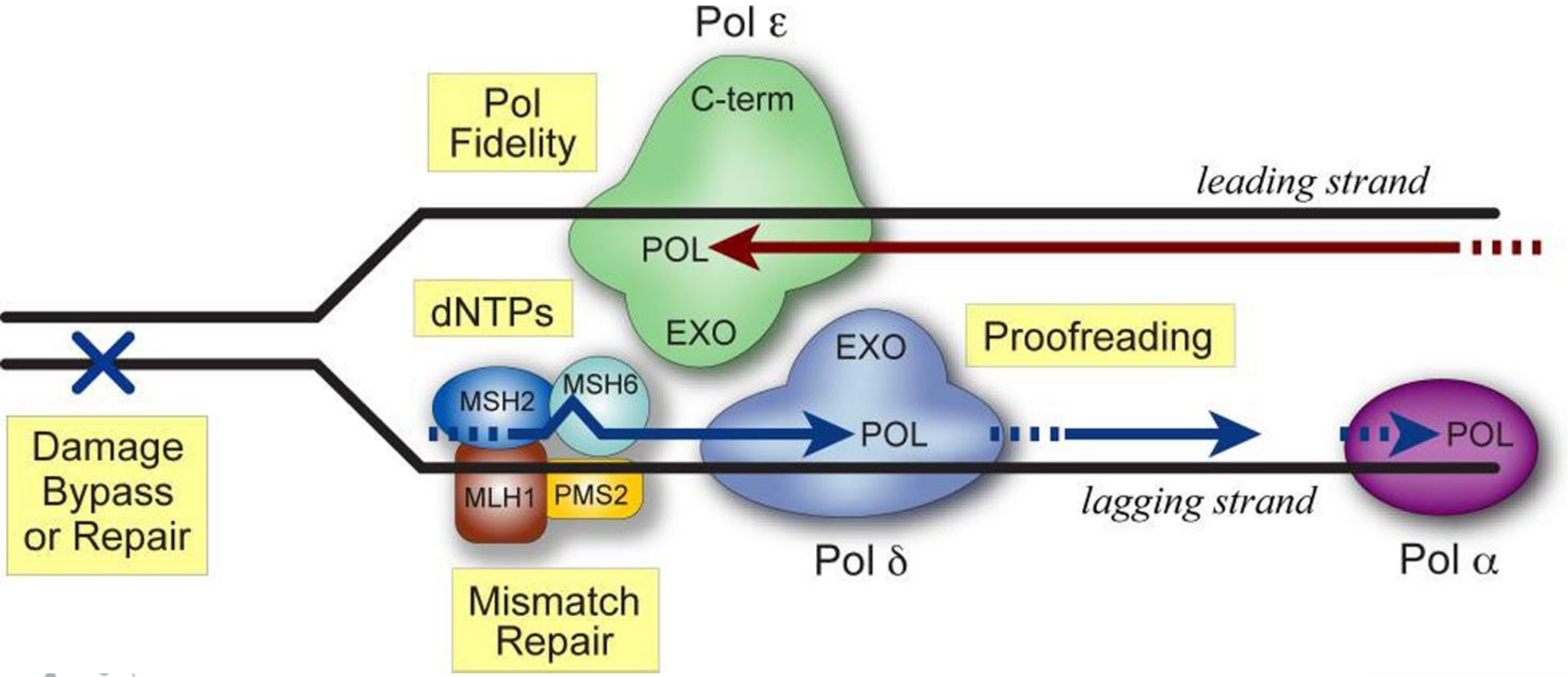
Association Between *KRAS*^{G12C} tumor mutational burden-high



Salem ME. et al. JCO Precis Oncol.2022

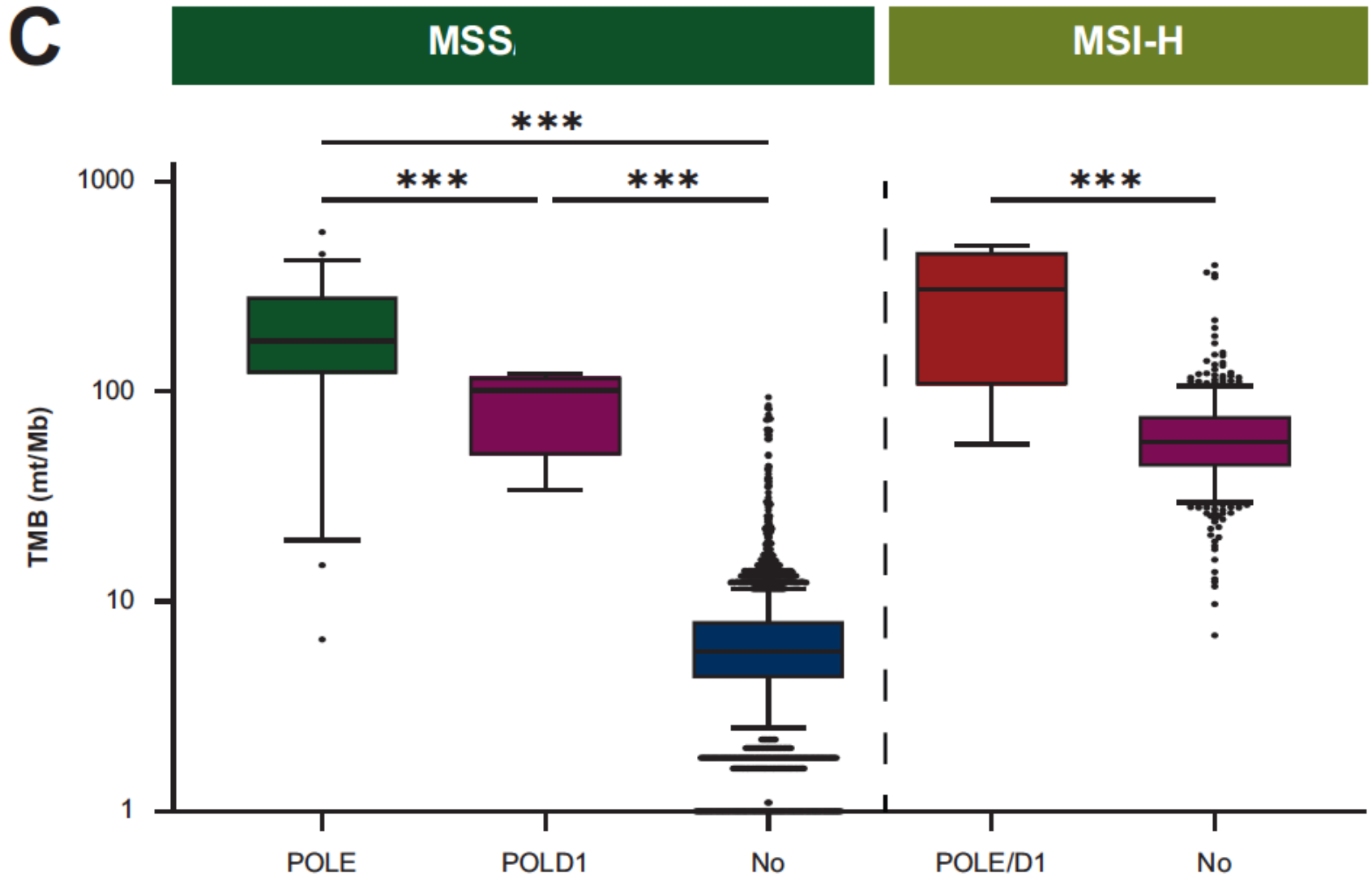
What happen in Polymerase-δ/ε mutant?

POL-ε & POL-δ



Seminars in Cancer Biology, 15 Oct 2010, 20(5):281-293

Immune checkpoint inhibitors for POLE or POLD1 proofreading-deficient metastatic colorectal cancer



https://doi.org/10.1016/j.annonc.2024.03.009

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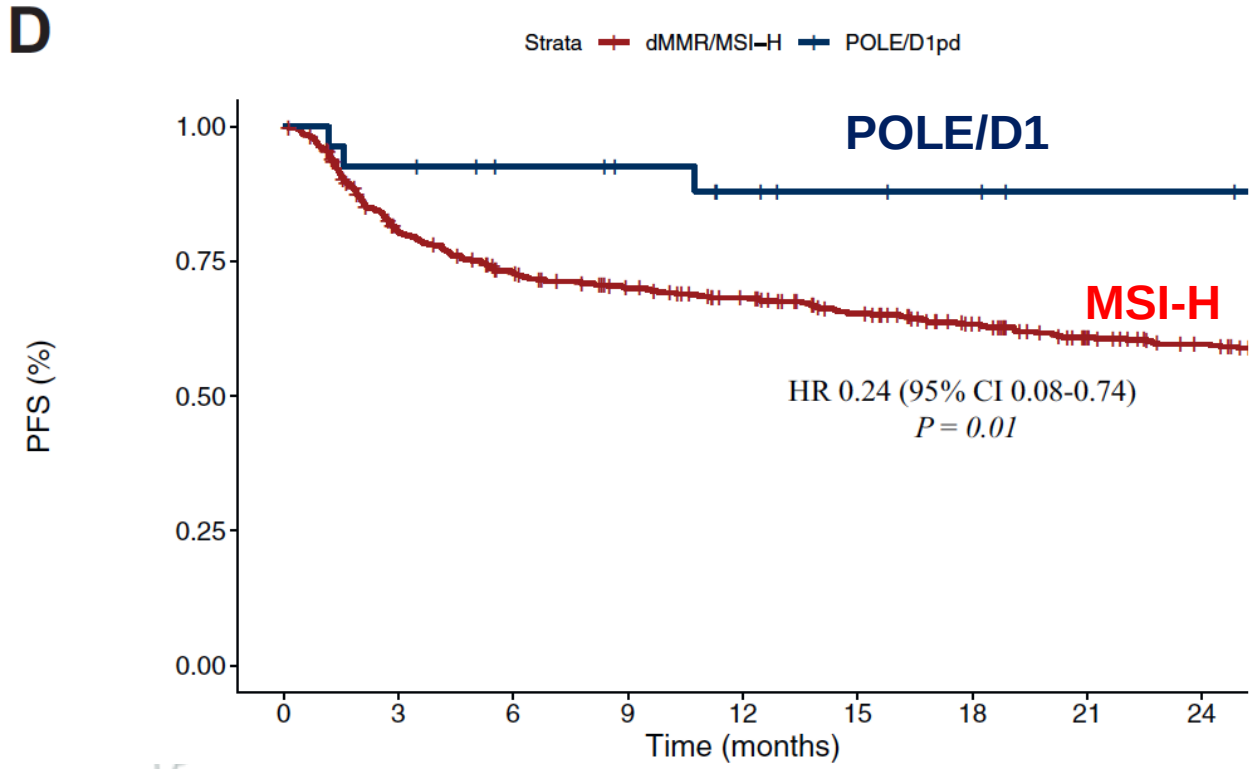
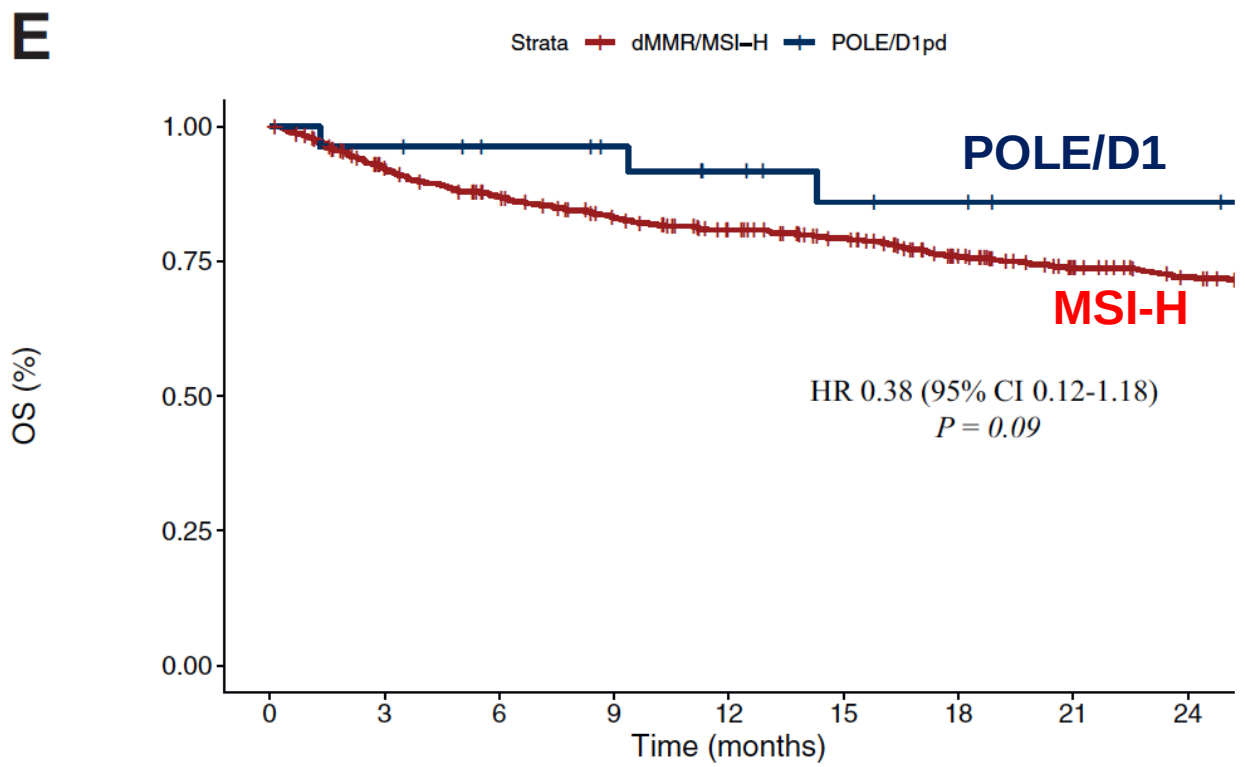
Immune checkpoint inhibitors for POLE or POLD1 proofreading-deficient metastatic colorectal cancer

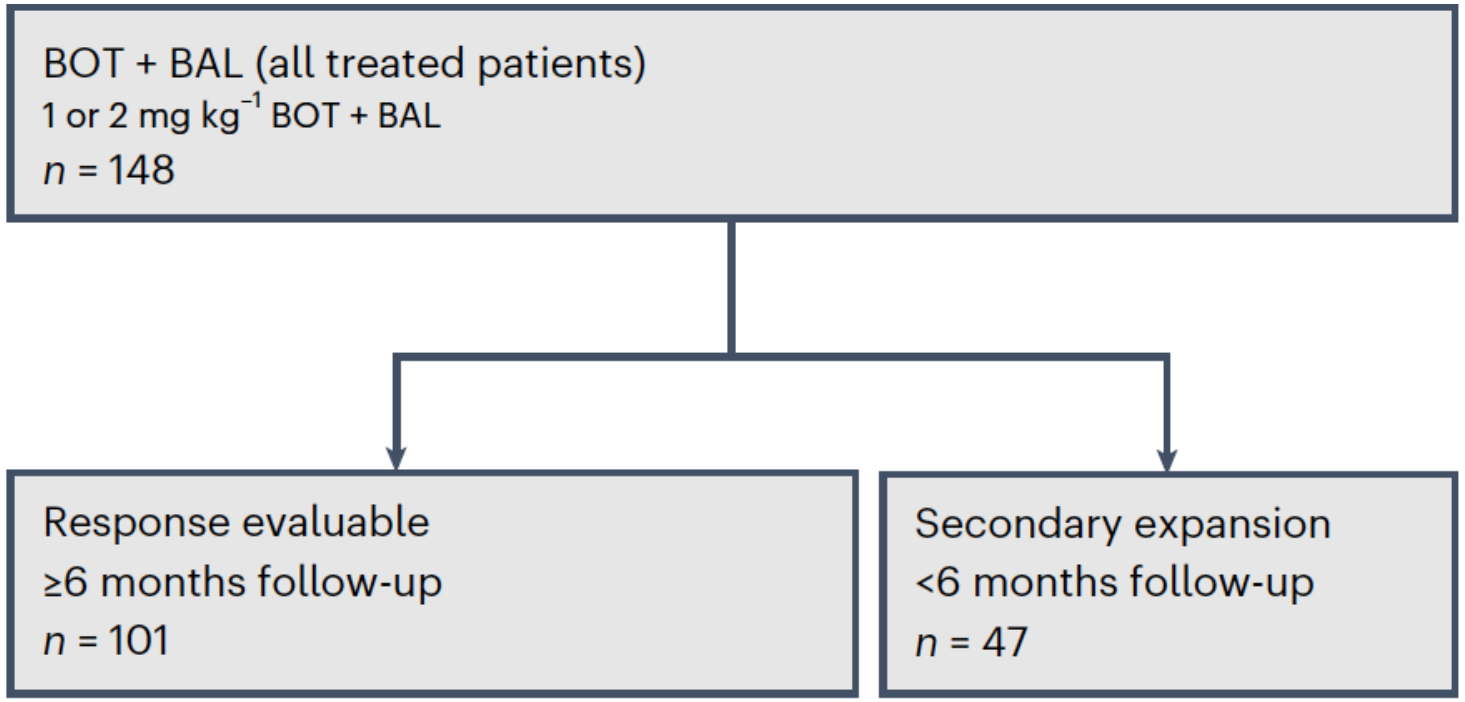




https://doi.org/10.1016/j.annonc.2024.03.009

Any option in CRC MSS?

New CTLA-4 & PD-L1 inhibitors: Botensilimab + Balstilimab

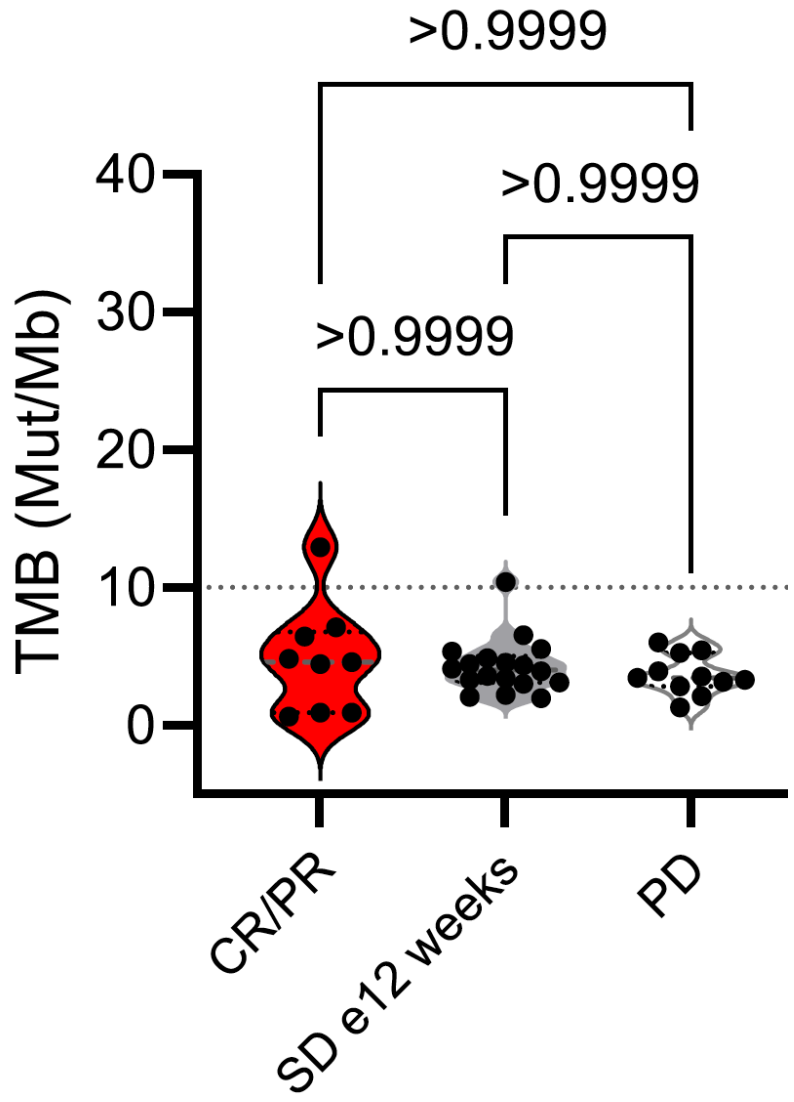


Prior regorafenib, *n* (%)	30 (20)
Prior trifluridine/tipiracil, *n* (%)	24 (16)
Prior regorafenib as well as trifluridine/ tipiracil, *n* (%)	43 (29)
Prior bevacizumab, *n* (%)	120 (81)
Prior bevacizumab/trifluridine/ tipiracil, *n* (%)	14 (9)
Prior radiotherapy, *n* (%)	64 (43)
Multiple metastatic sites, *n* (%)	100 (68)
Peritoneal disease, *n* (%)	62 (42)

nature medicine

New CTLA-4 & PD-L1 inhibitors: Botensilimab + Balstilimab

ORR[a], *n* (%)	2 (4)
95% CI	0.5–14.3
BOR[b], *n* (%)	
CR	1 (2)
PR	1 (2)
SD	17 (35)
PD	23 (48)
NE	6 (13)
DCR[c], *n* (%)	19 (40)



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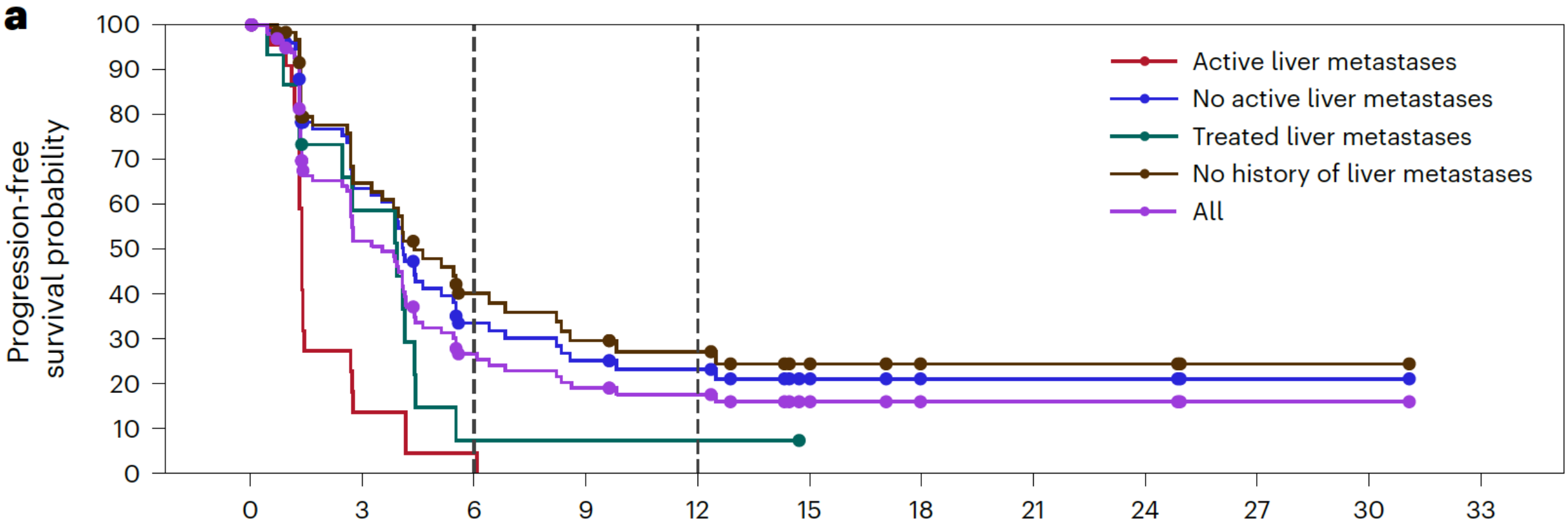
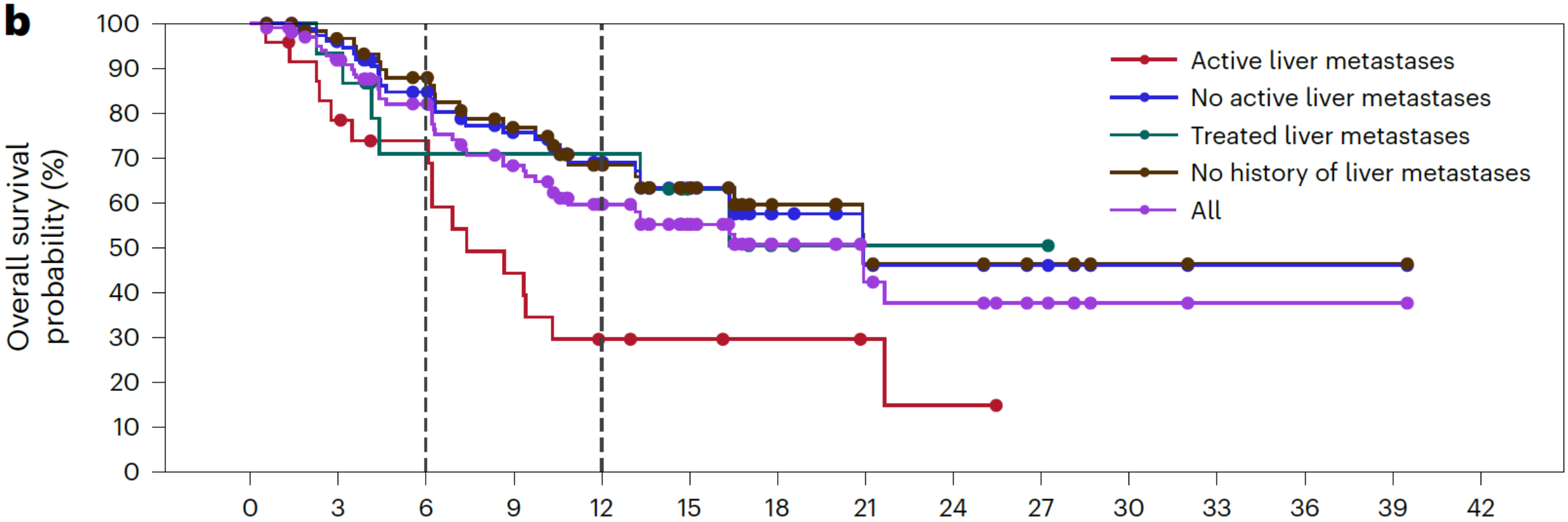
nature medicine

New CTLA-4 & PD-L1 inhibitors: Botensilimab + Balstilimab

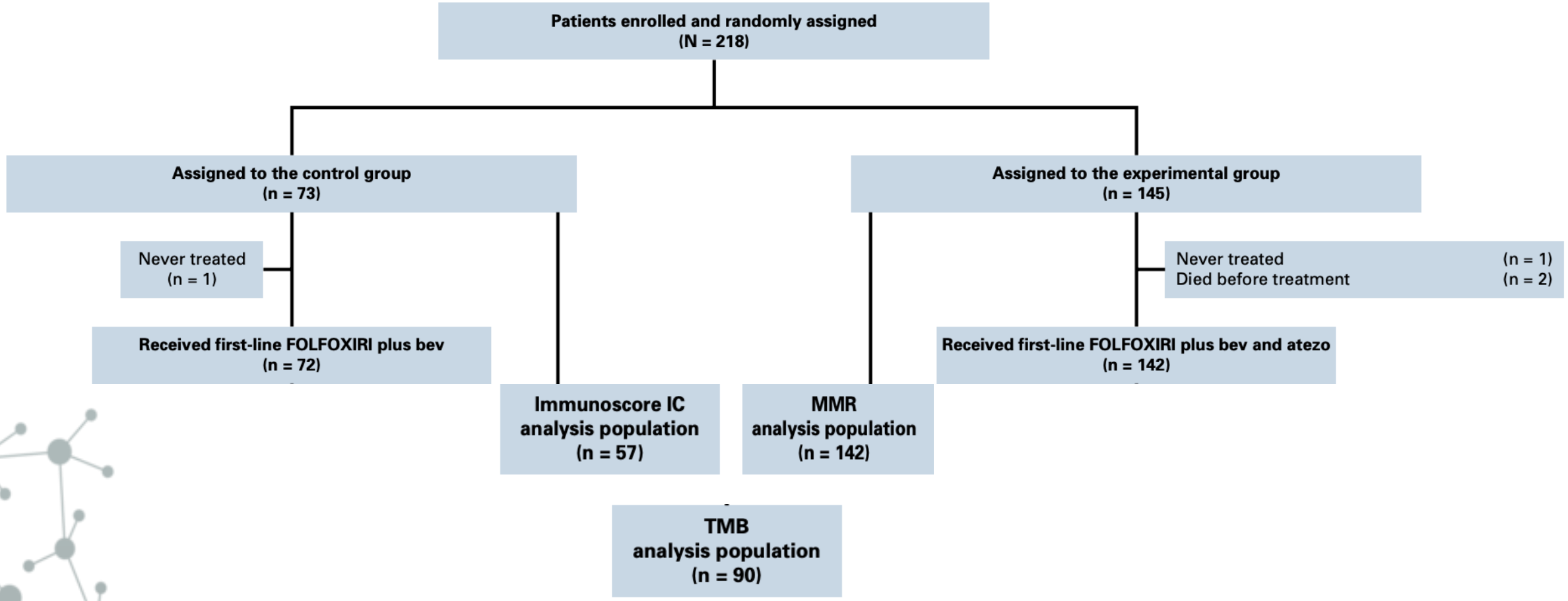


nature medicine

New CTLA-4 & PD-L1 inhibitors: Botensilimab + Balstilimab



ATEZOTRIBE: FOLFOXIRI + Beva + Atezo



J Clin Oncol 42:2637-2644

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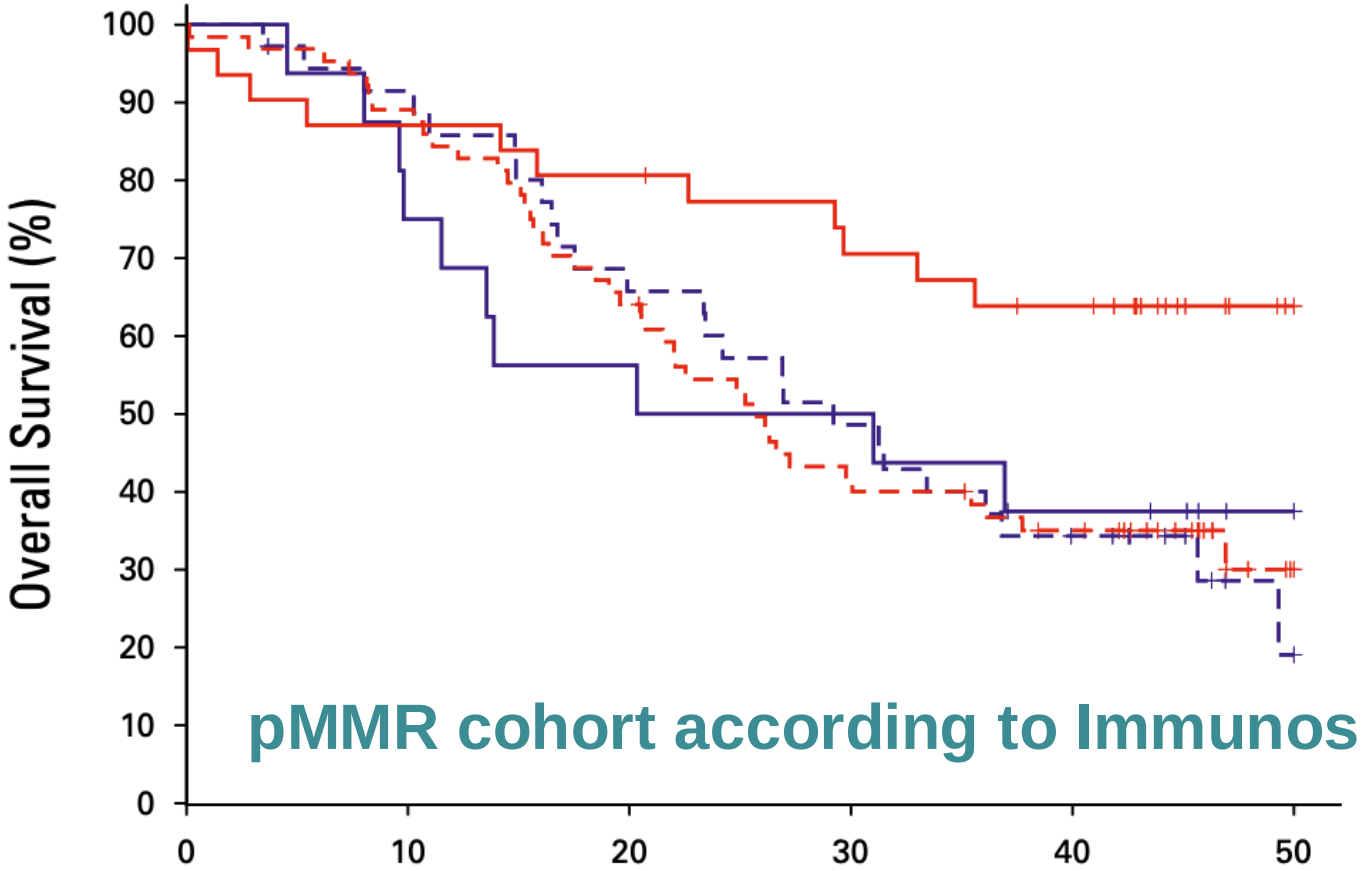
ATEZOTRIBE: FOLFOXIRI + Beva + Atezo

Group	HR (95% CI)	Events/Total	Median (95% CI)
Control Immunoscore IC high	1.00 (0.48 to 2.08)	10/16	25.7 (9.8 to NE)
Control Immunoscore IC low	Reference	25/36	29.2 (19.9 to 36.8)
Experimental Immunoscore IC high	0.42 (0.21 to 0.85)	11/31	NR (33.0 to NE)
Experimental Immunoscore IC low	0.99 (0.60 to 1.62)	42/64	25.7 (20.5 to 36.2)

Log-rank *P* value: .054

+ Censor



pMMR cohort according to Immunoscore IC status

J Clin Oncol 42:2637-2644

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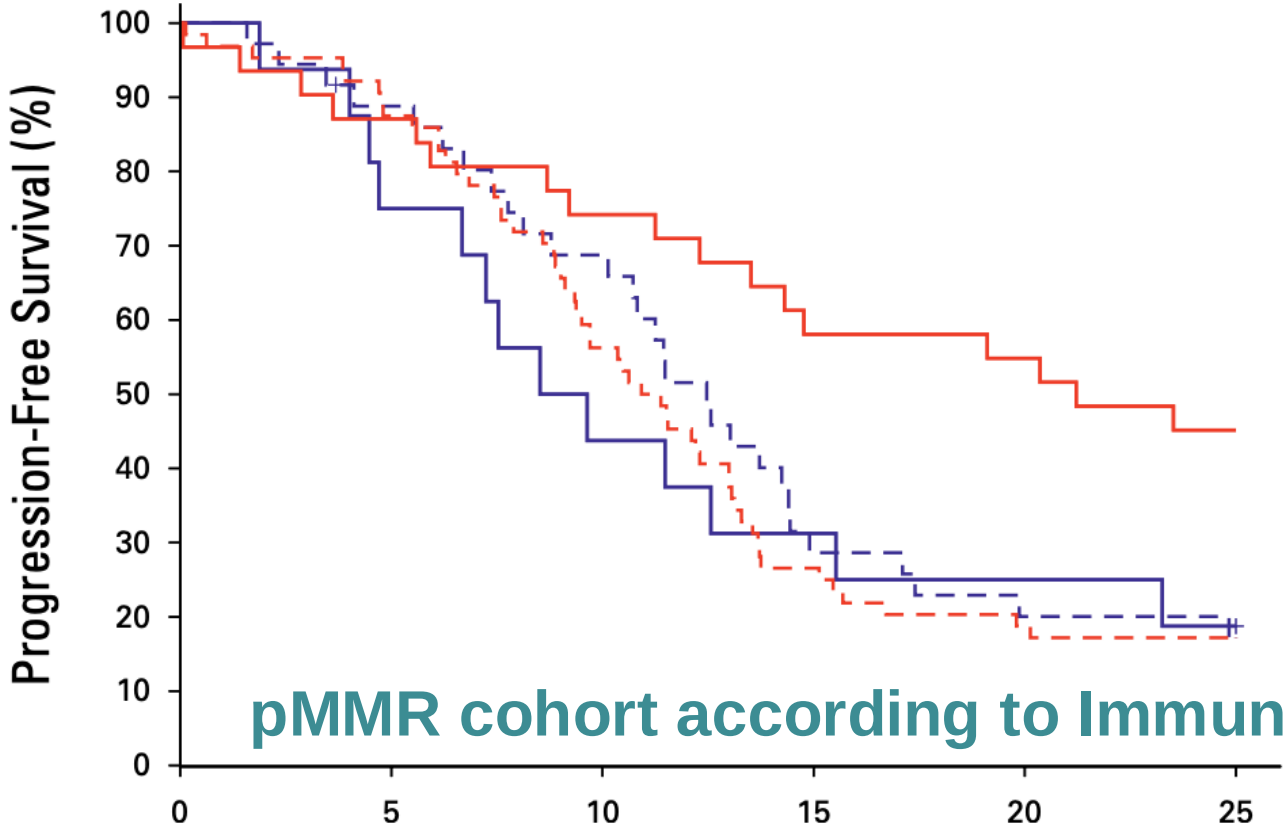
ATEZOTRIBE: FOLFOXIRI + Beva + Atezo

Group	HR (95% CI)	Events/Total	Median (95% CI)
Control Immunoscore IC high	1.06 (0.56 to 2.04)	13/16	9.1 (4.7 to 15.5)
Control Immunoscore IC low	Reference	31/36	12.5 (10.1 to 14.4)
Experimental Immunoscore IC high	0.54 (0.31 to 0.94)	21/31	21.2 (12.3 to 39.4)
Experimental Immunoscore IC low	1.09 (0.70 to 1.69)	56/64	11.2 (9.3 to 13.0)

Log-rank *P* value: .041

+ Censor



pMMR cohort according to Immunoscore IC status

J Clin Oncol 42:2637-2644

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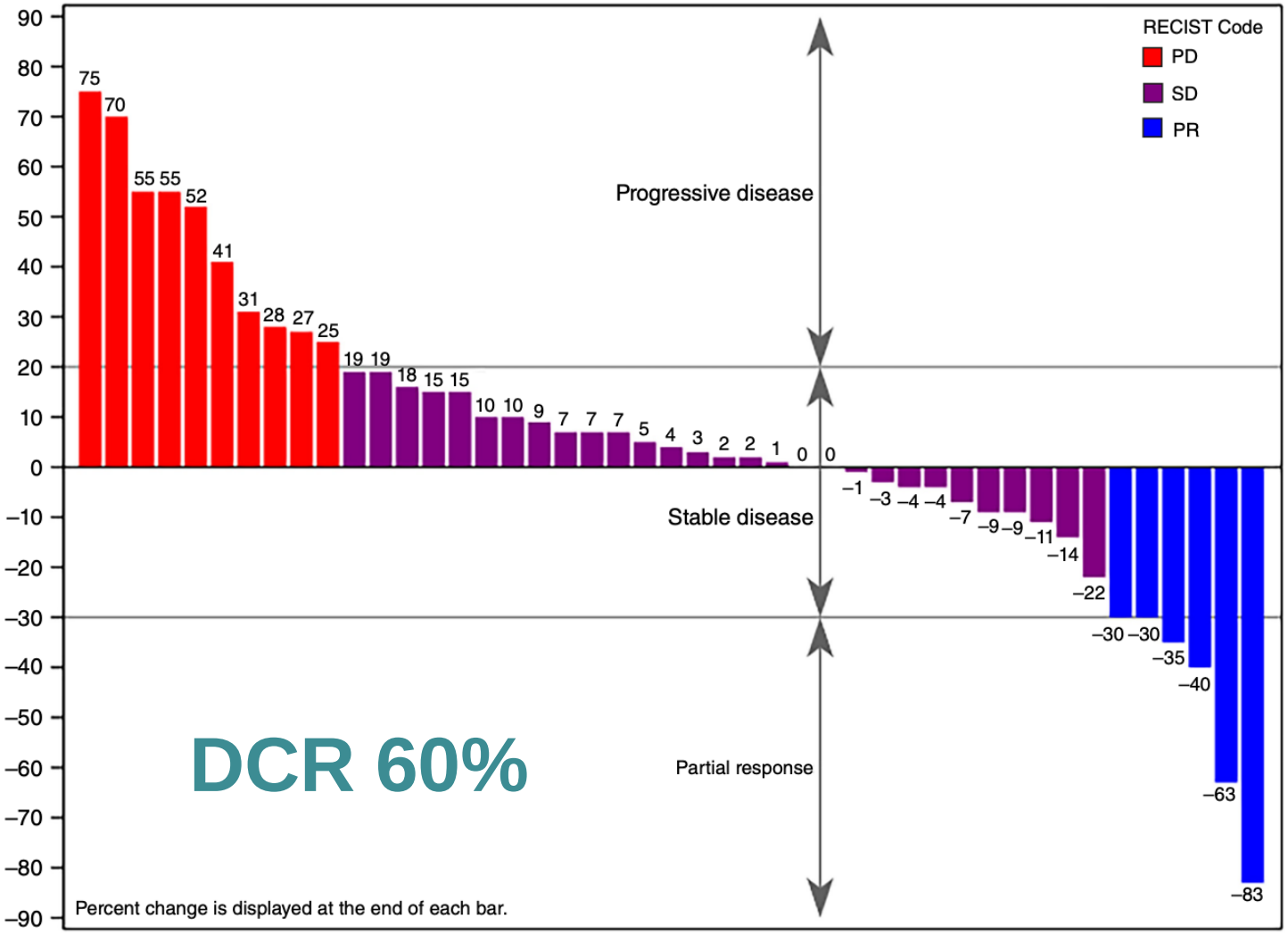
Pembrolizumab + Binimetinib + Bevacizumab



DCR 60%

Clin Cancer Res; 30(17) September 1, 2024

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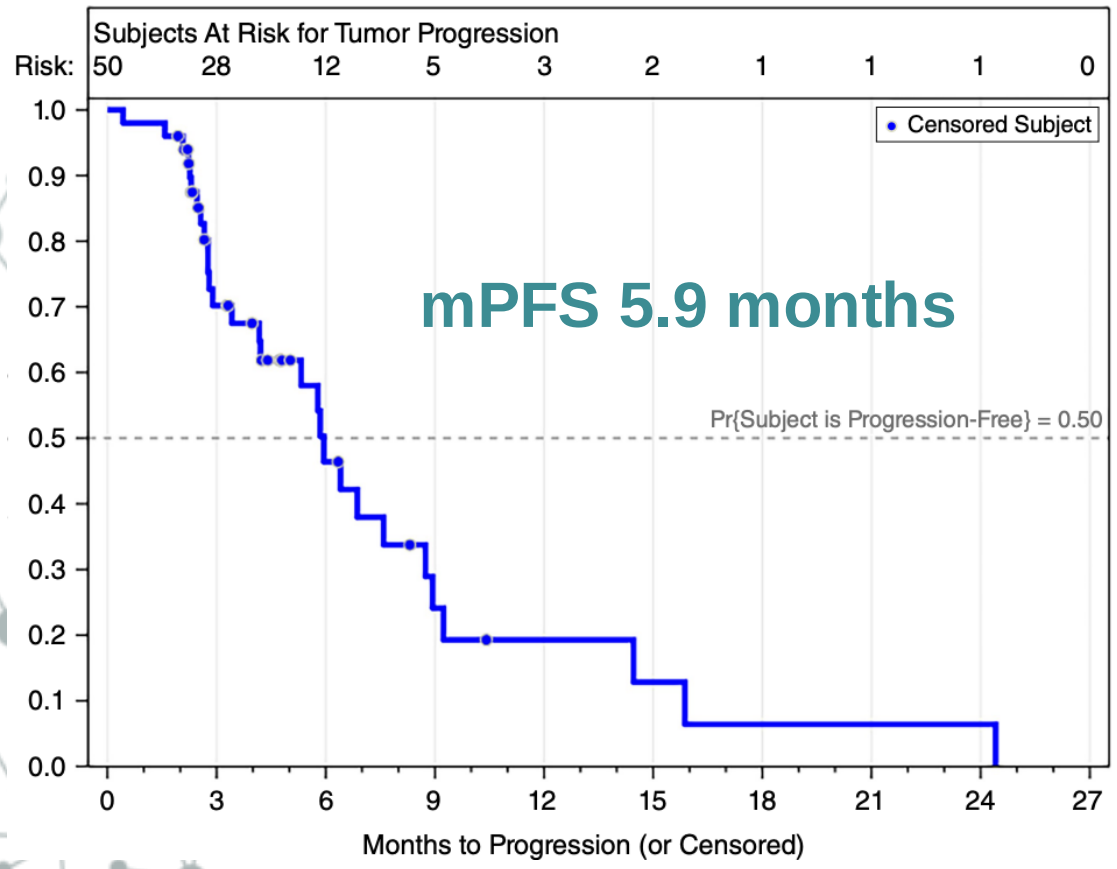
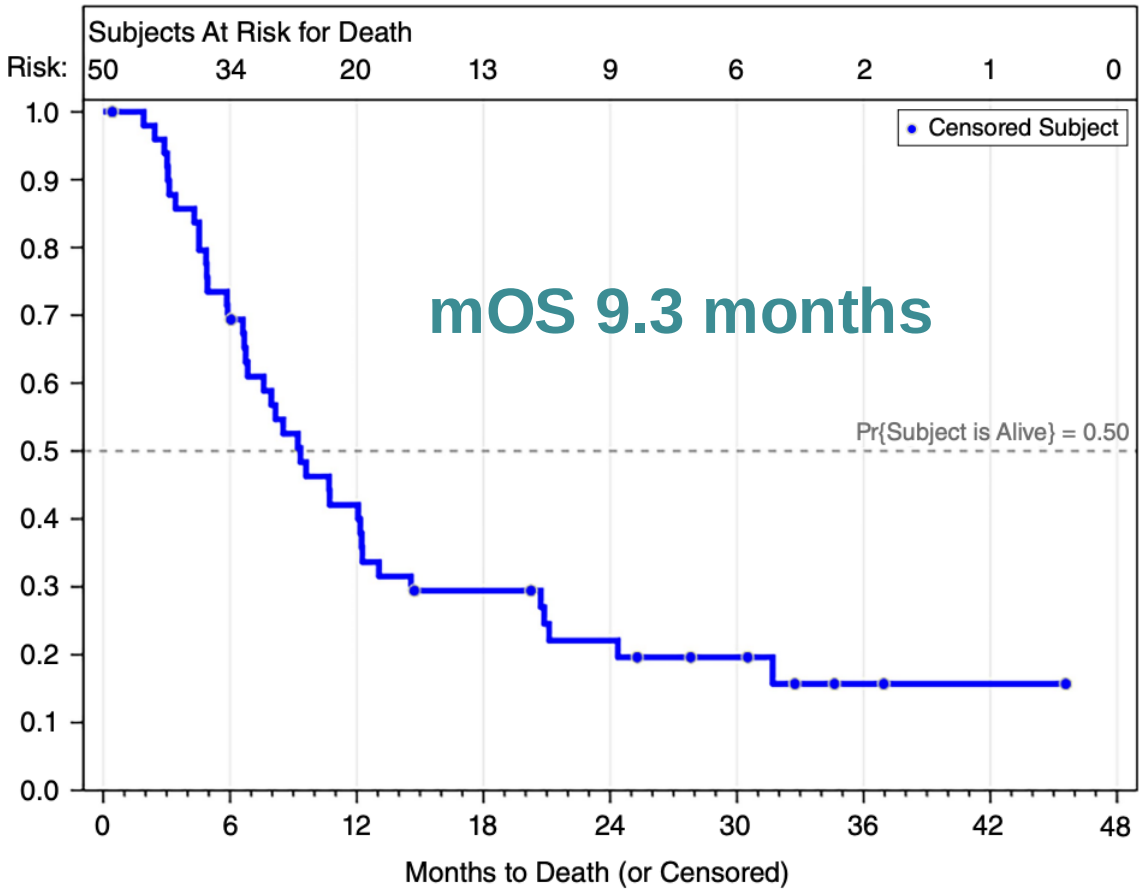
Pembrolizumab + Binimetinib + Bevacizumab





Clin Cancer Res; 30(17) September 1, 2024

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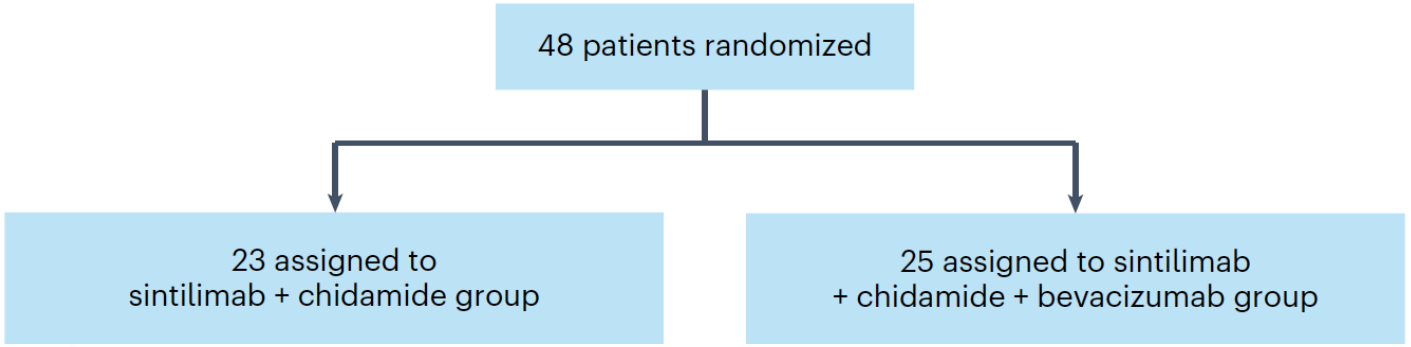
Anti-PD-1 (Sintilimab) + HDACi (Chidamide) + Bevacizumab in MSS CRC



Characteristics	Total (*n*=48)	Sintilimab +chidamide (*n*=23)	Sintilimab +chidamide +bevacizumab (*n*=25)
Primary site, *n* (%)			
Right half	13 (27.1)	7 (30.4)	6 (24.0)
Left half	35 (72.9)	16 (69.6)	19 (76.0)
Metastatic lesions, *n* (%)			
Liver	26 (54.2)	12(52.2)	14 (56.0)
Lung	33 (68.8)	16 (69.6)	17(68.0)
Lymph node	26 (54.2)	13 (56.5)	13(52.0)
Bone	7 (14.6)	2 (8.7)	5(20.0)
Others	17 (35.4)	10(43.5)	7(28.0)
RAS/*BRAF* status, *n* (%)			
RAS/*BRAF*^{V600E} wild-type	24 (50.0)	12(52.2)	12 (48.0)
RAS mutant	20 (41.7)	9 (39.1)	11 (44.0)
BRAF^{V600E} mutant	1 (2.1)	1 (4.3)	0 (0.0)
Prior therapeutic agents, *n* (%)			
Fluoropyrimidine	48 (100.0)	23 (100.0)	25 (100.0)
Oxaliplatin	45 (93.8)	21 (91.3)	24 (96.0)
Irinotecan	45 (93.8)	23 (100.0)	22 (88.0)
Bevacizumab	40 (83.3)	22 (95.7)	18 (72.0)
Cetuximab	22 (45.8)	13 (56.5)	9 (36.0)
Regorafenib	6 (12.5)	3 (13.0)	3 (12.0)
Fruquintinib	6 (12.5)	3 (13.0)	3 (12.0)

Nature Medicine | *Volume 30* | *April 2024* | *1035–1043*

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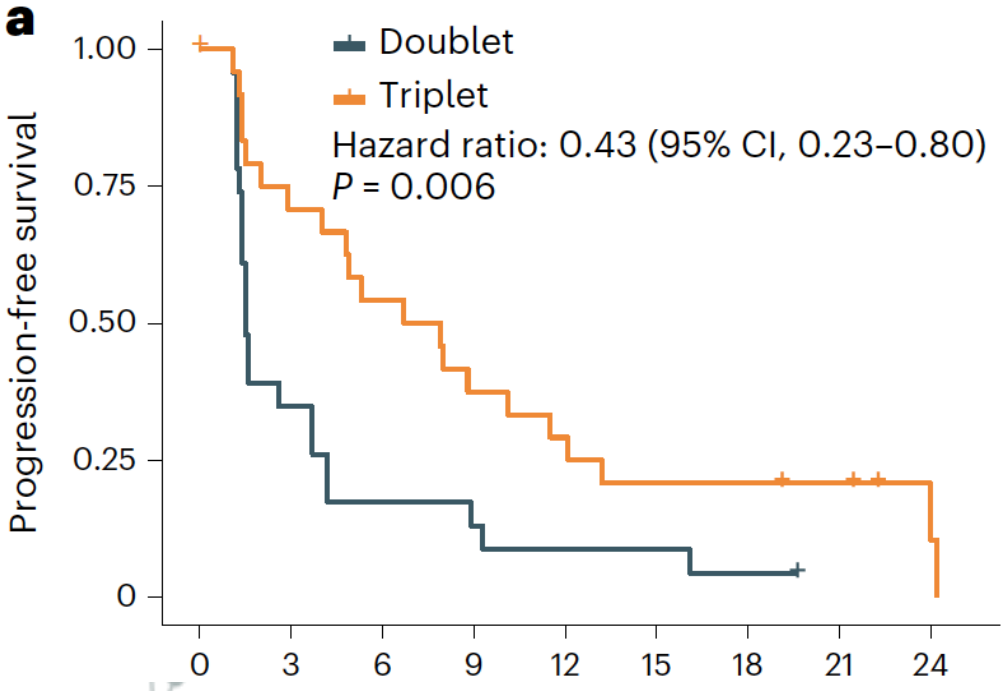
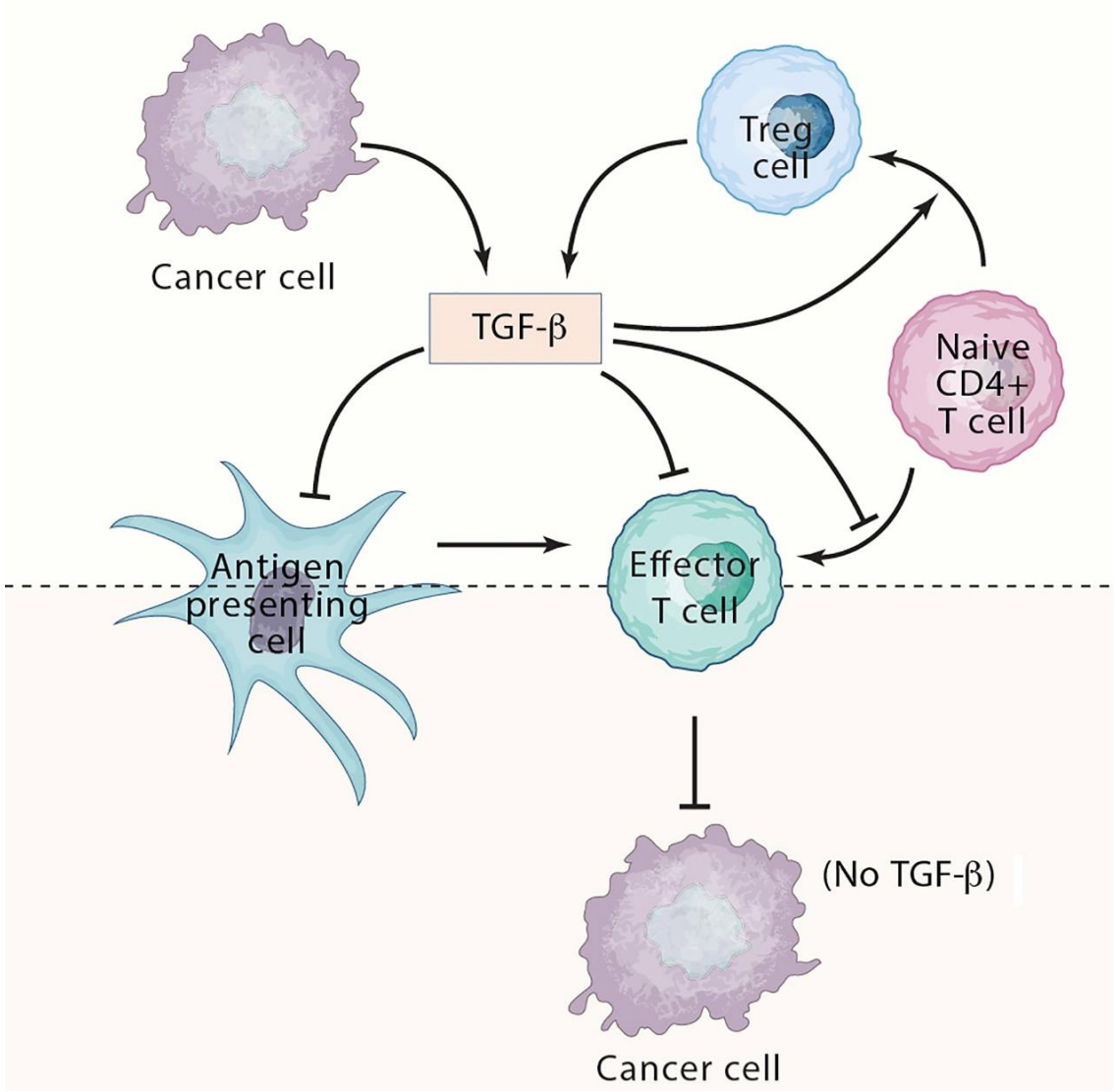
Anti-PD-1 (Sintilimab) + HDACi (Chidamide) + Bevacizumab in MSS CRC



Subgroup	mPFS (months)		Unstratified HR (95%CI)	*P* for interaction
	Triplet	Doublet		
Overall (*n* = 48)	**7.3**	**1.5**	**0.43 (0.23 – 0.80)**	0.083
Age, years				0.265
<55 (*n* = 23)	10.1	1.6	0.29 (0.11 – 0.78)	
≥55 (*n* = 25)	6.7	1.5	0.68 (0.30 – 1.57)	
Gender				0.034
Male (*n* = 32)	6.0	3.7	0.64 (0.30 – 1.40)	
Female (*n* = 16)	9.7	1.4	0.08 (0.01 – 0.62)	
ECOG				0.352
0 (*n* = 11)	6.7	4.2	0.67 (0.18 – 2.51)	
1 (*n* = 37)	7.9	1.5	0.35 (0.17 – 0.73)	
Primary site				0.003
Right half (*n* = 13)	NR	1.4	0.08 (0.01 – 0.70)	
Left half (*n* = 35)	5.1	3.1	0.66 (0.32 – 1.35)	
Liver metastases				0.154
Yes (*n* = 26)	7.3	1.4	0.24 (0.09 – 0.59)	
No (*n* = 22)	6.7	3.7	0.52 (0.20 – 1.39)	
Lung metastases				0.278
Yes (*n* = 33)	8.0	1.5	0.35 (0.16 – 0.78)	
No (*n* = 15)	2.9	1.5	0.85 (0.28 – 2.56)	
Lymph node metastases				0.396
Yes (*n* = 26)	8.4	1.5	0.32 (0.13 – 0.79)	
No (*n* = 22)	3.9	2.0	0.59 (0.24 – 1.44)	
RAS status[a]				0.381
RAS wild-type (*n* = 25)	5.1	2.1	0.58 (0.24 – 1.42)	
RAS mutant (*n* = 20)	8.8	1.5	0.20 (0.07 – 0.59)	
Bevacizumab previously used				0.989
Yes (*n* = 40)	8.4	1.5	0.39 (0.20 – 0.79)	
No (*n* = 8)	3.5	1.5	0.38 (0.03 – 4.28)	
Previous treatment lines				0.407
<3 (*n* = 25)	6.7	1.5	0.56 (0.23 – 1.35)	
≥3 (*n* = 23)	7.9	1.6	0.24 (0.09 – 0.65)	

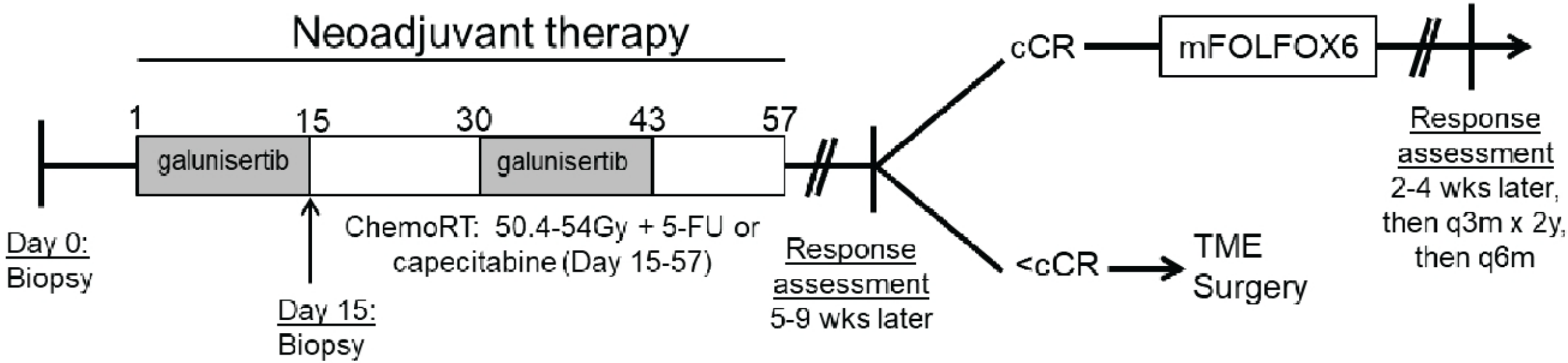
Nature Medicine | *Volume 30* | *April 2024* | *1035–1043*

Phase II trial of TGFß Type I Receptor Inhibitor, Galunisertib plus Neoadjuvant CHT-RT in LARC

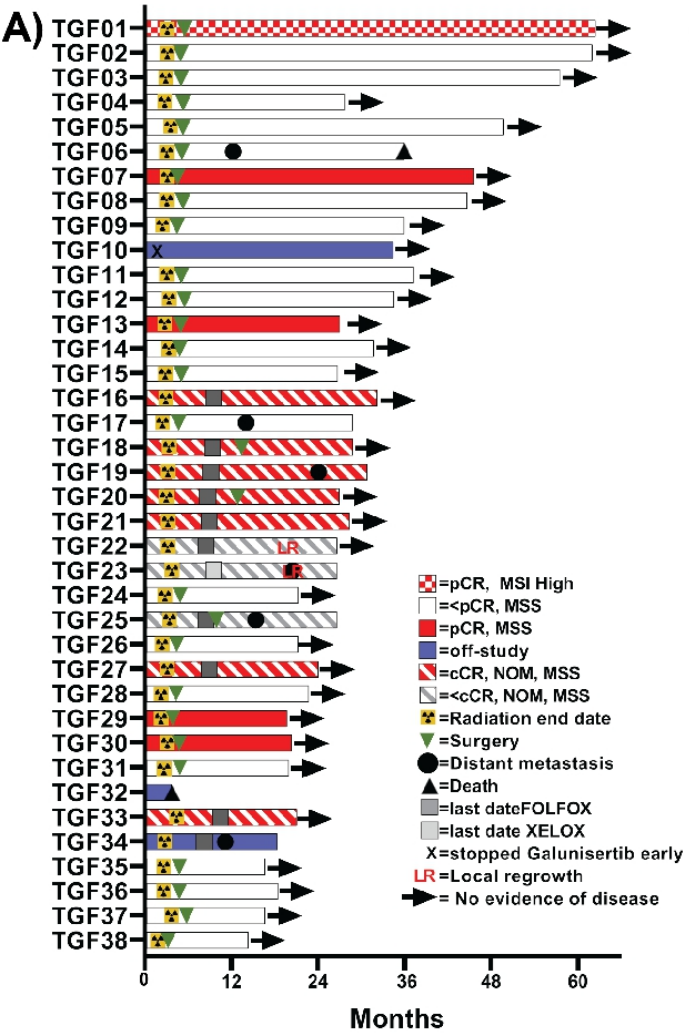


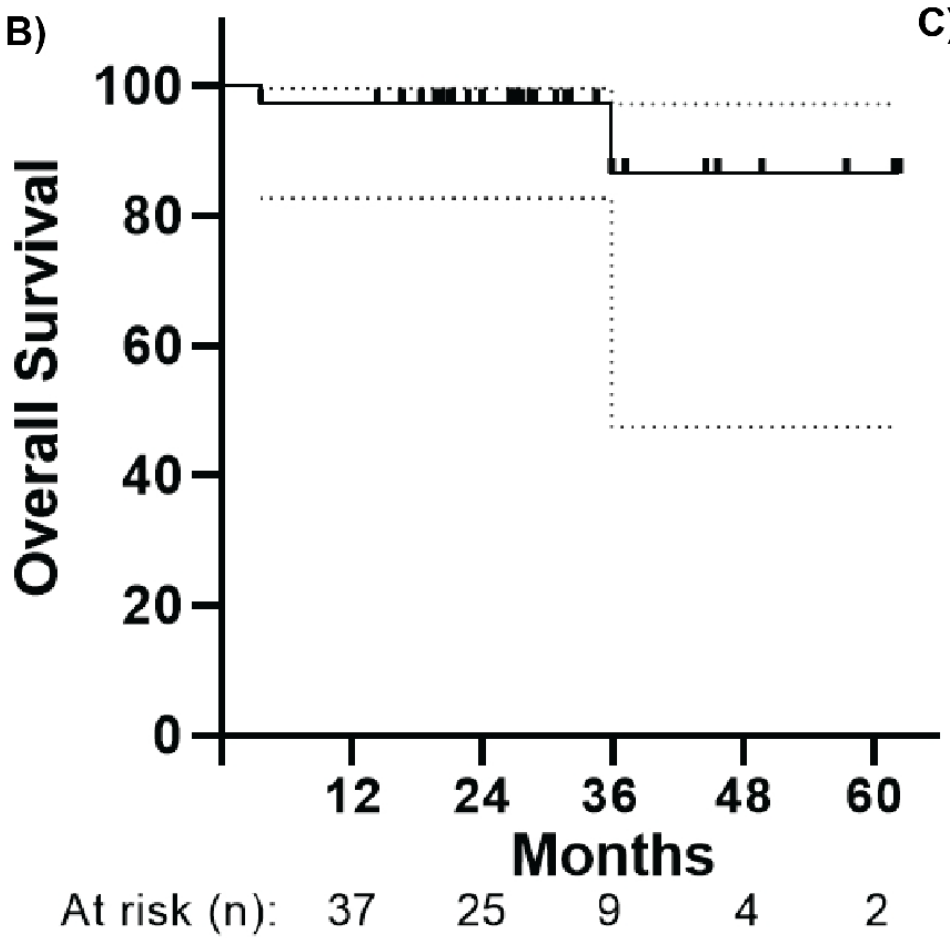
Abstract 2716, ASCO 2022

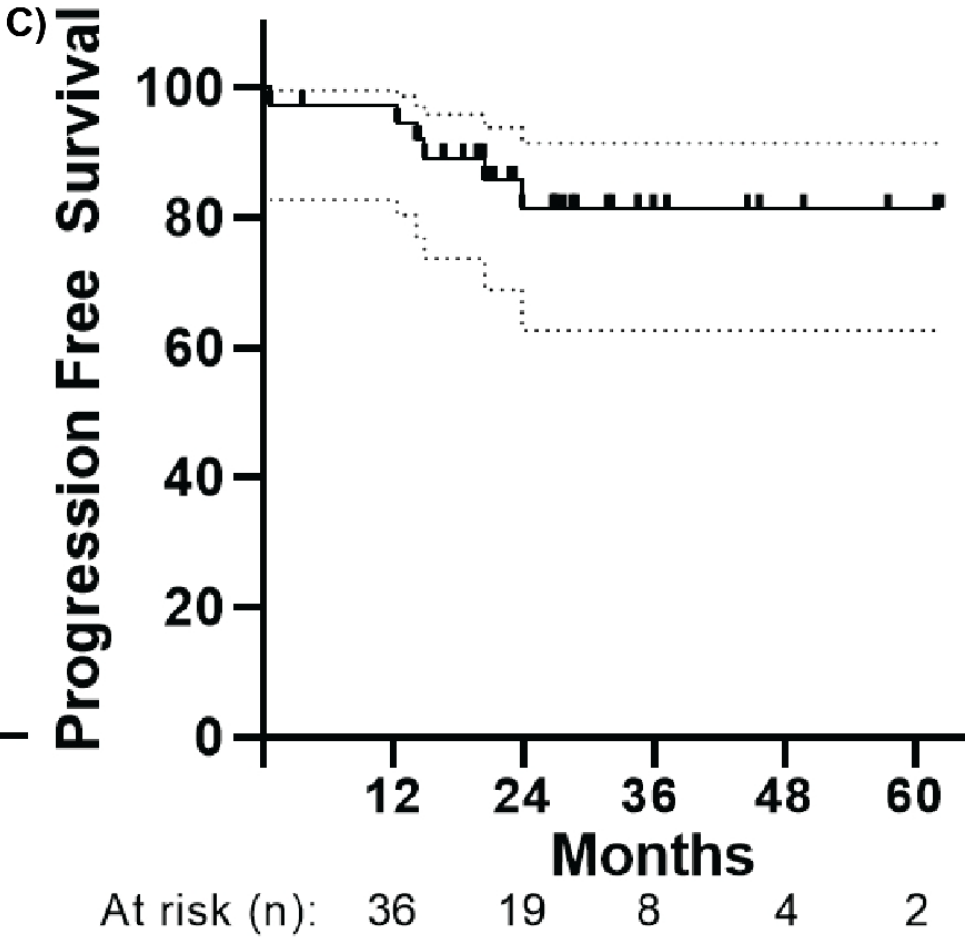
Phase II trial of TGFß Type I Receptor Inhibitor, Galunisertib plus Neoadjuvant CHT-RT in LARC



Phase II trial of TGFß Type I Receptor Inhibitor, Galunisertib plus Neoadjuvant CHT-RT in LARC







pCR & <pCR: 86%

2y PFS and OS: 81.5% and 97%

Abstract 2716, ASCO 2022

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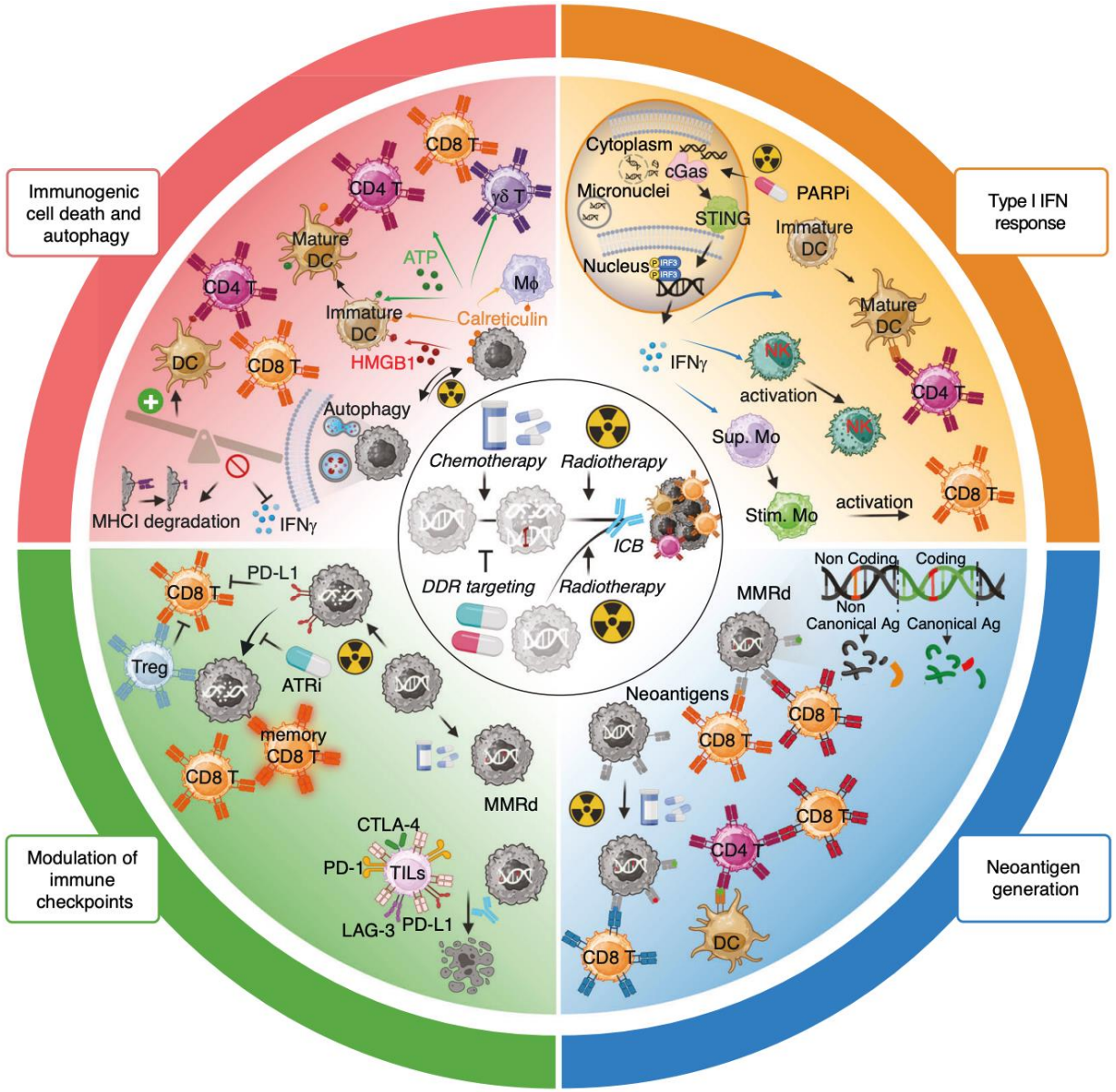
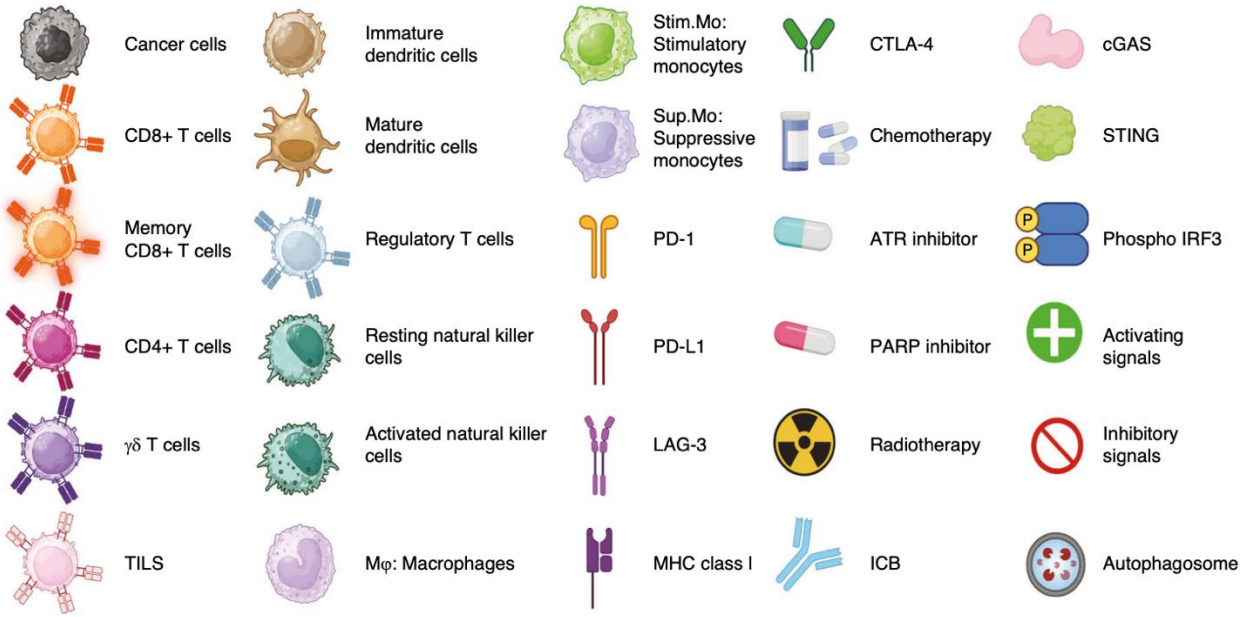
And in Homologous Recombination Deficiency (HRD)?

DNA repair-dependent immunogenic liabilities in mCRC: HRD





British Journal of Cancer (2024) 131:1576–1590

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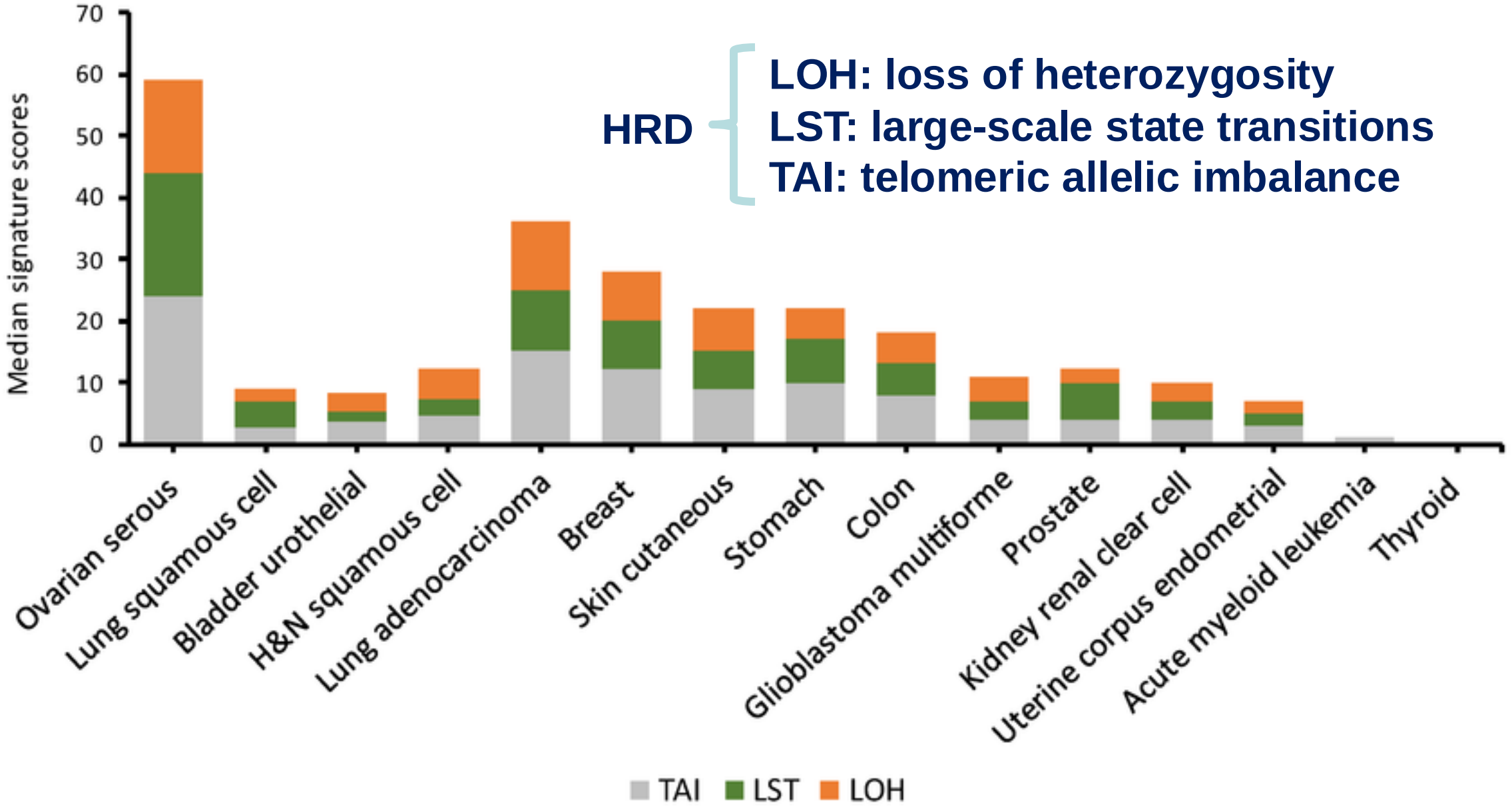

https://www.researchgate.net/figure/HRD-prevalence-across-different-tumor-types-Adapted-from-Marquard-et-al-21-copyright_fig3_361534738

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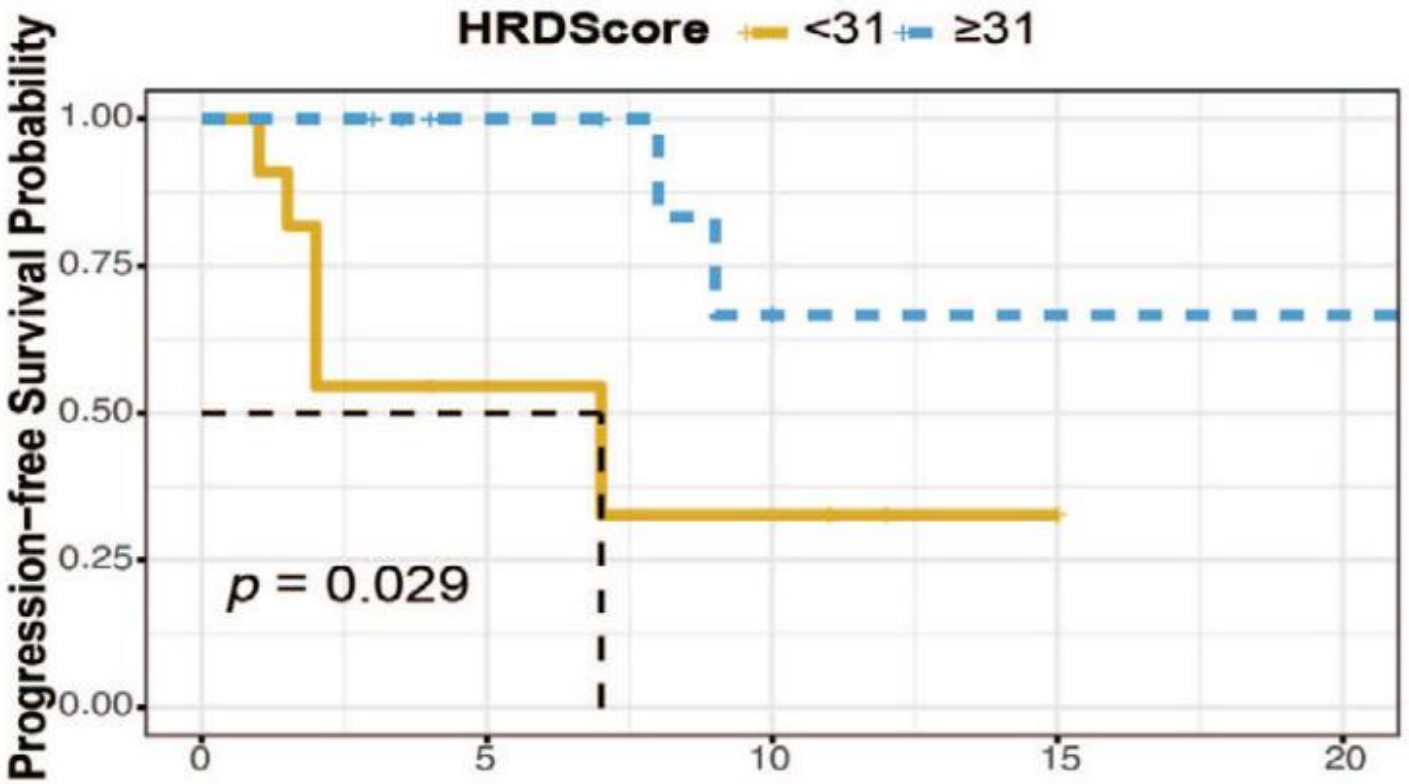
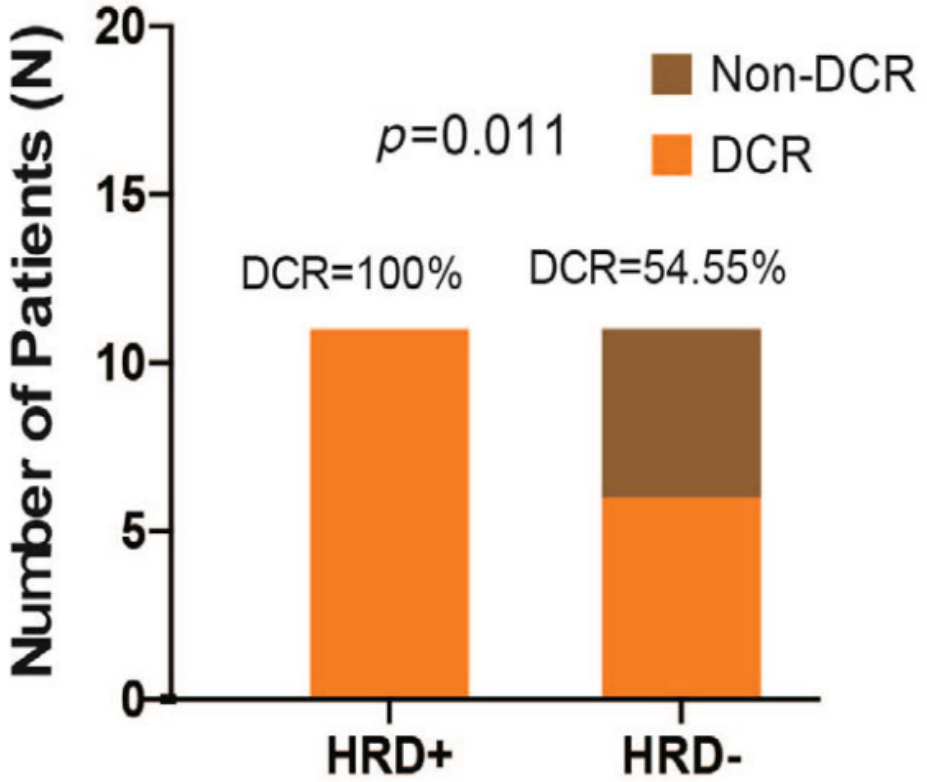
Response in HRD to IO





Thorac Cancer. 2024;15:1842–1853.

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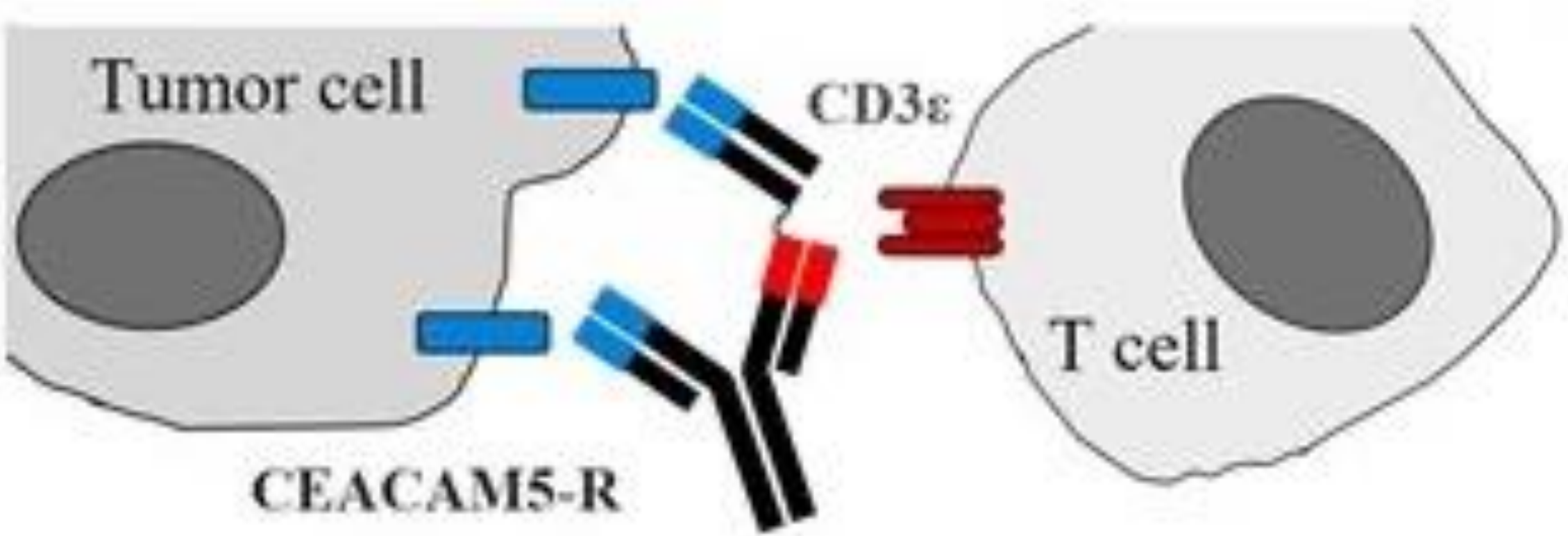
New IO directions in CRC

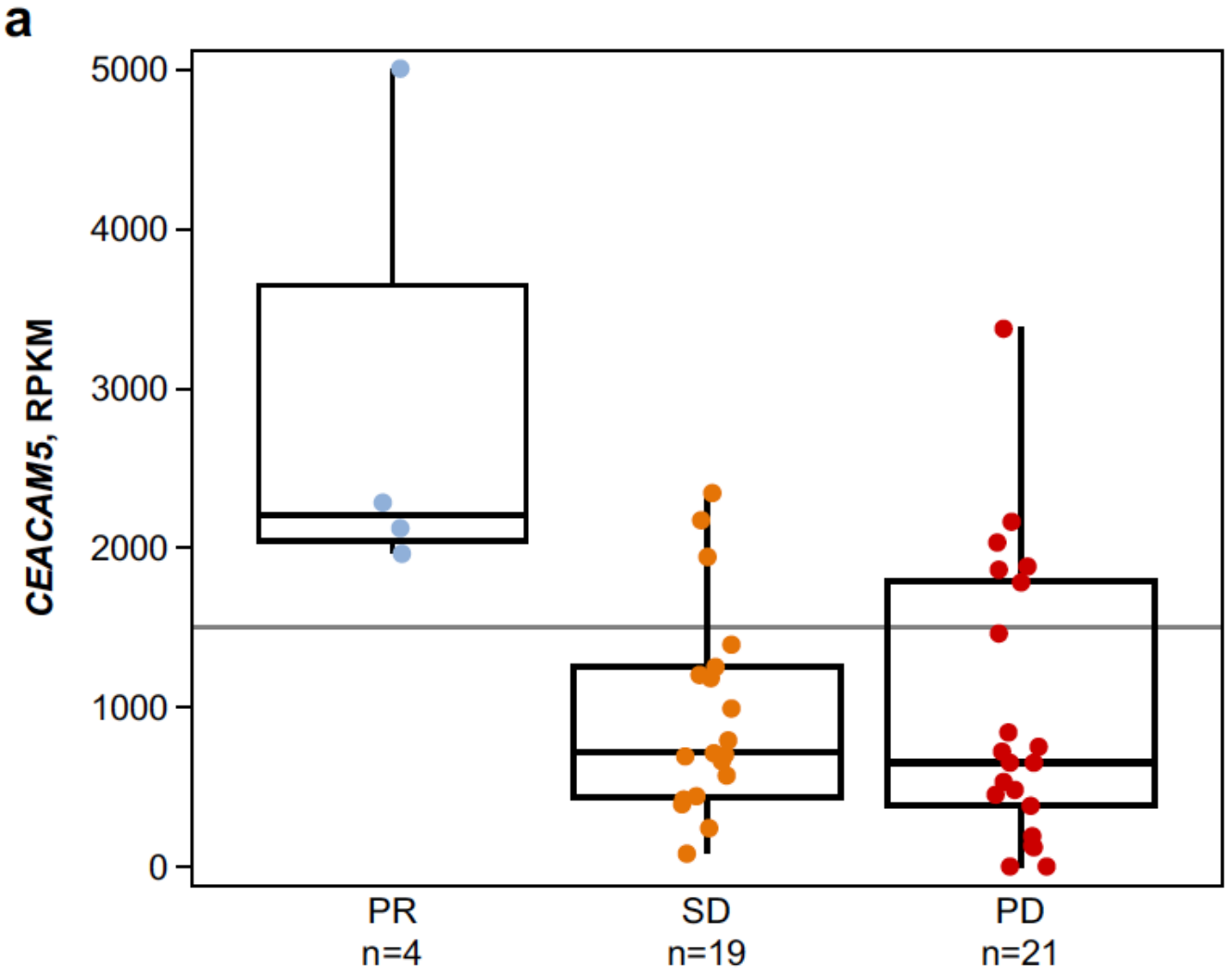
CEA-CD3 bispecific antibody cibisatamab with or without atezolizumab in patients with CEA-positive solid tumours



Nature Communications | (2024) 15:4091

CEA-CD3 bispecific antibody cibisatamab with or without atezolizumab in patients with CEA-positive solid tumours

	All MSS-CRC (*n* = 187)
ORR, *n* (%) 90% CI	13 (7.0) [4.2, 10.8)
CR, *n* (%) 90% CI	0 [0.0, 1.6]
PR, *n* (%) 90% CI	13 (7.0) [4.2, 10.8]
SD, *n* (%) 90% CI	68 (36.4) [30.5, 42.6]
PD, *n* (%) 90% CI	88 (47.1) [40.9, 53.3]
NE, *n* (%)	18 (9.6)
DCR, *n* (%) 90% CI	81 (43.3) [37.2, 49.6]



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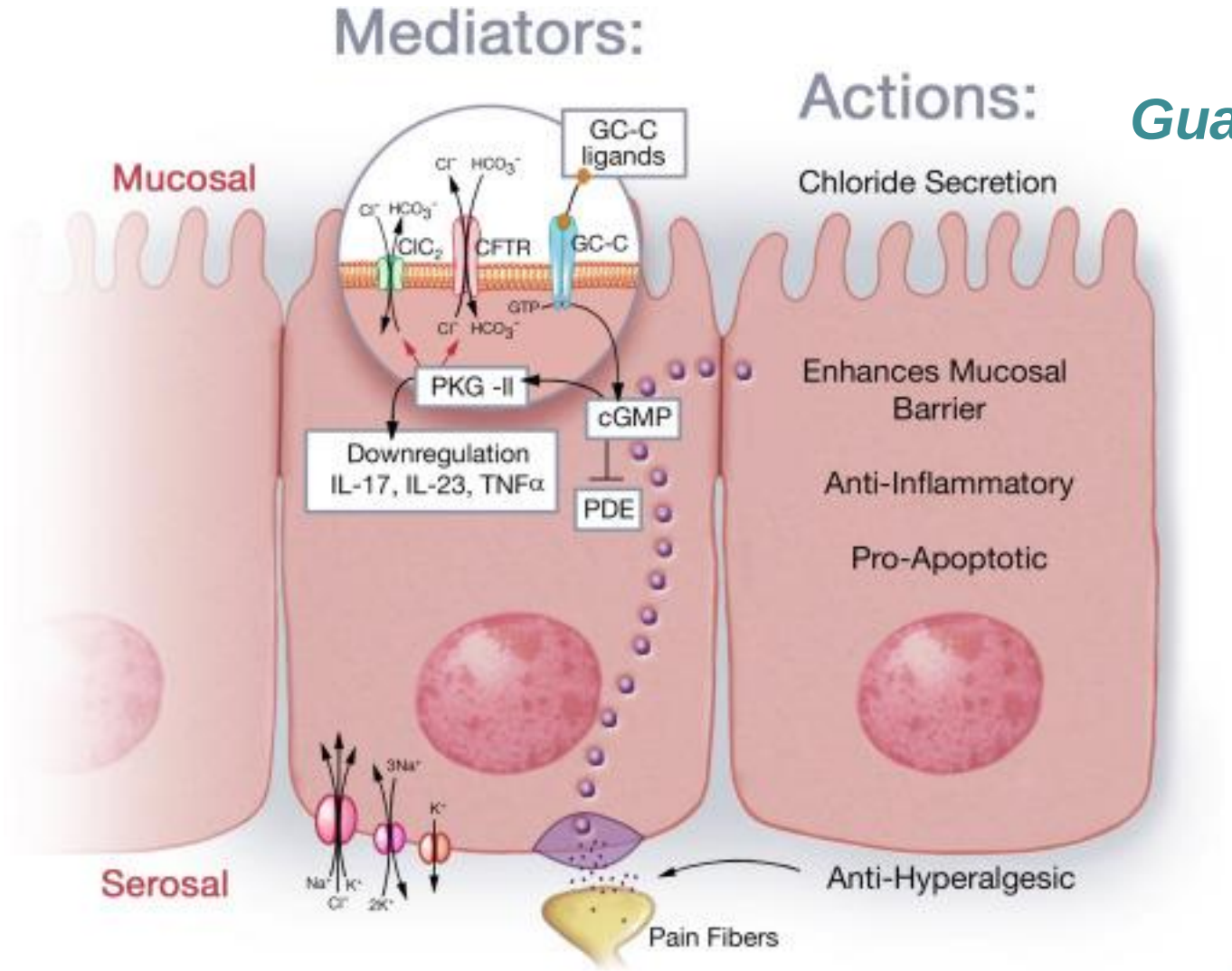
JAMA Oncology | Original Investigation

Chimeric Antigen Receptor T Cells Targeting CD19 and GCC in Metastatic Colorectal Cancer

A Nonrandomized Clinical Trial



JAMA Oncol. doi:10.1001/jamaoncol.2024.3891

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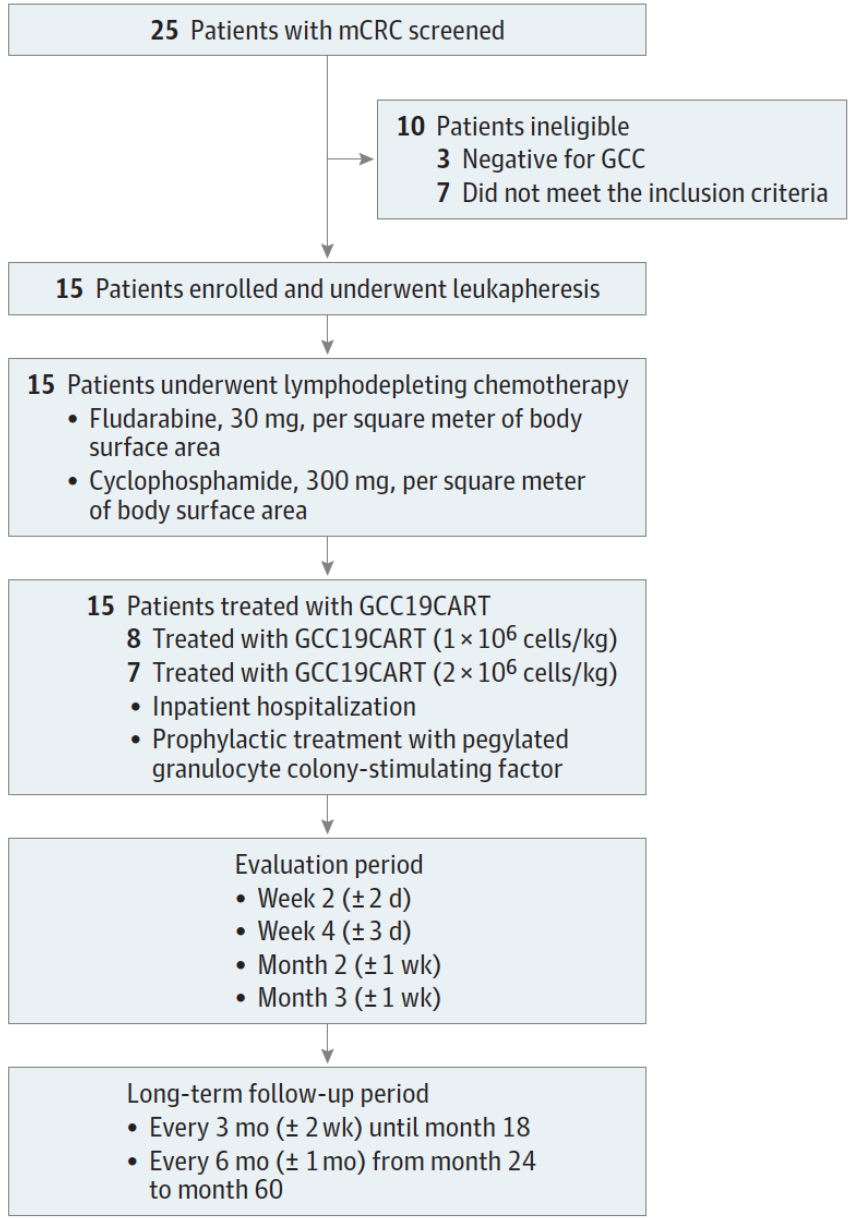

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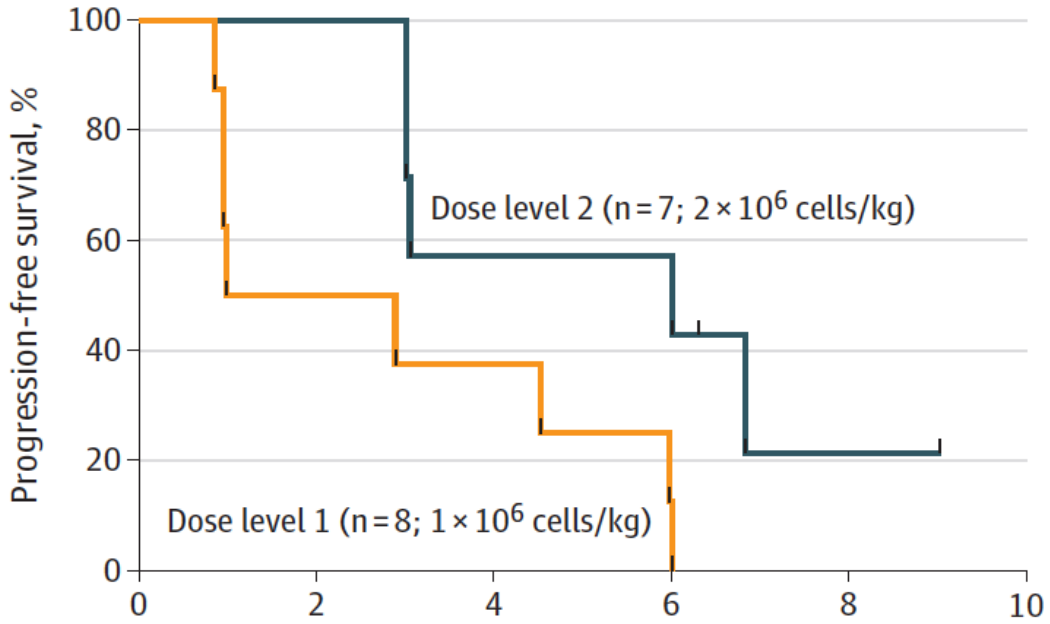
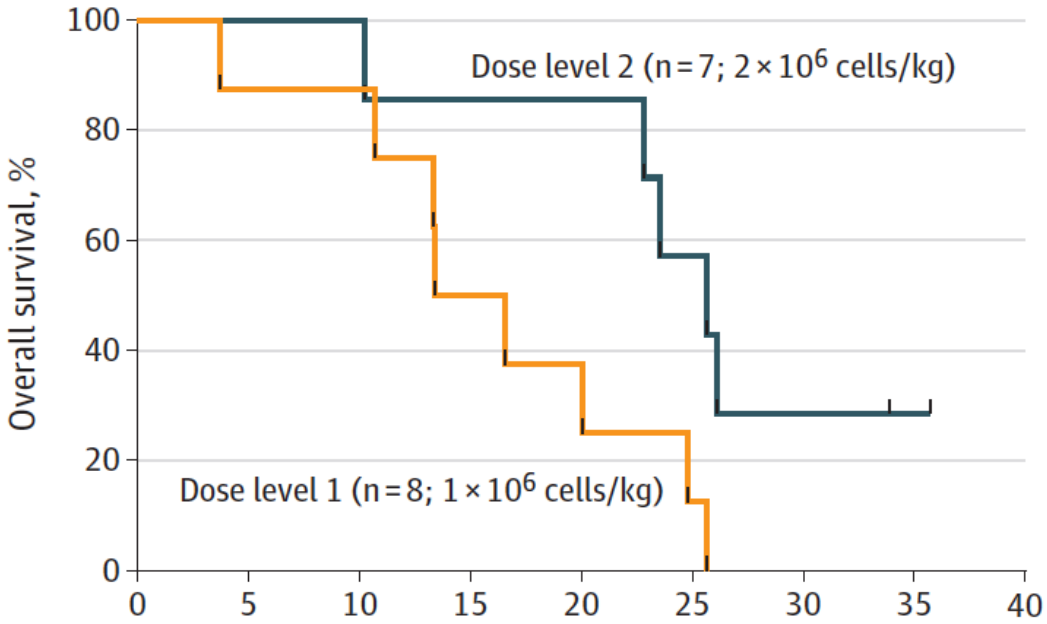
A Progression-free survival



B Overall survival



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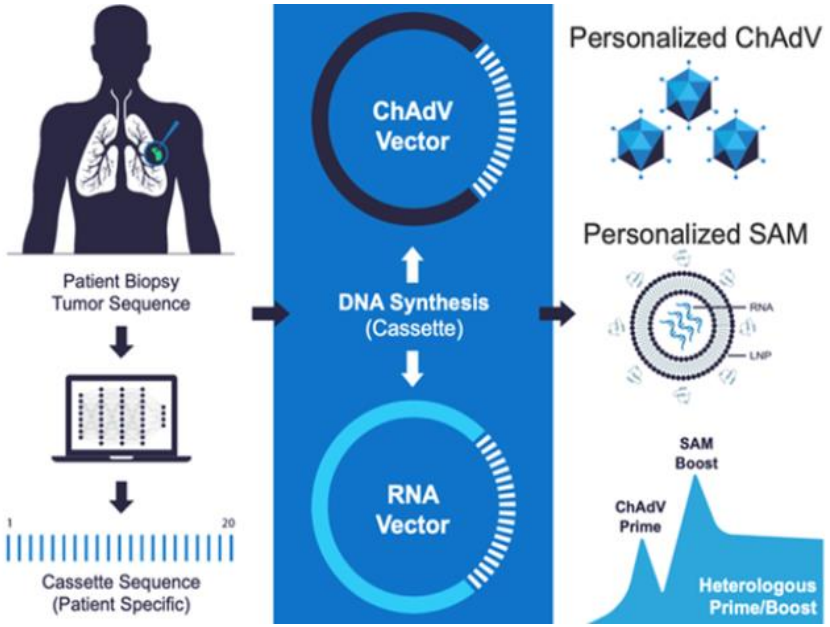
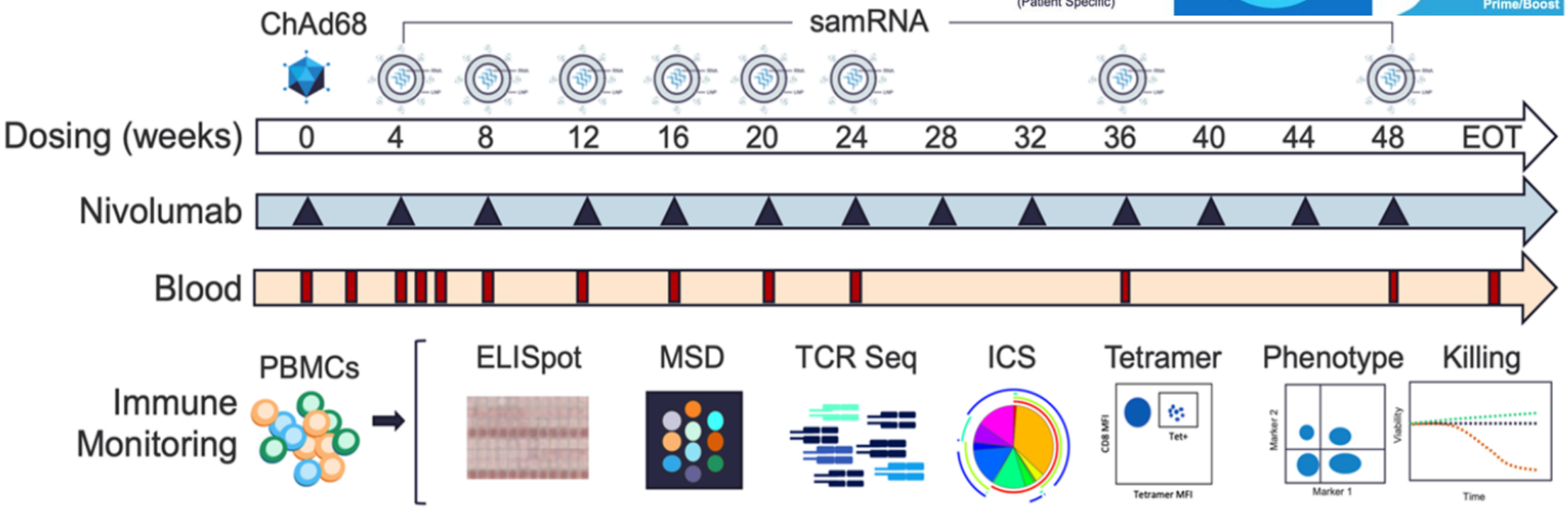
Individualized, heterologous chimpanzee adenovirus and self-amplifying mRNA neoantigen vaccine for advanced metastatic solid tumors: phase 1 trial interim results

nature medicine





Nature Medicine | *VOL 28* | *August 2022* | *1619–1629*

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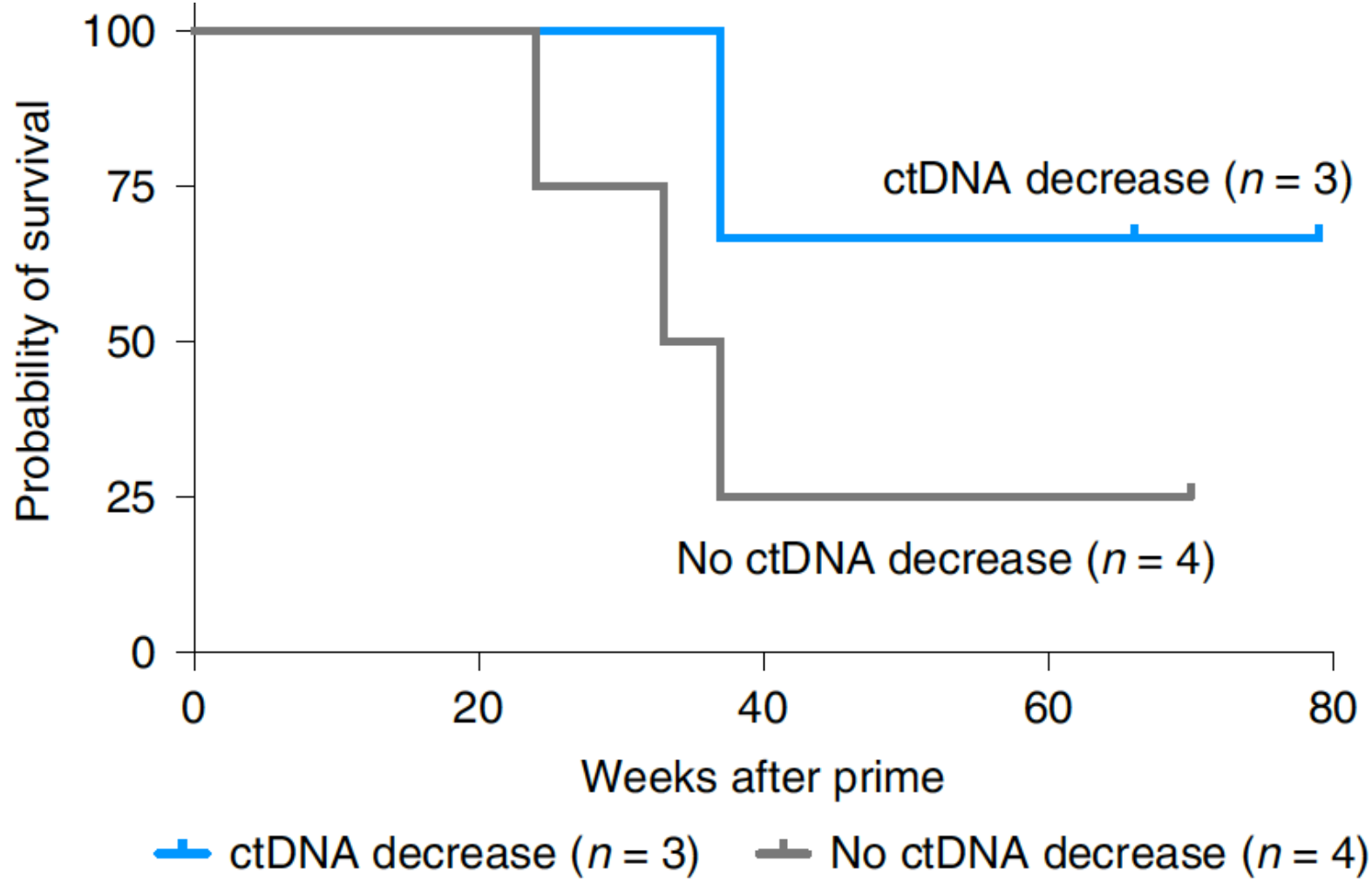

Nature Medicine | *VOL 28* | *August 2022* | *1619–1629*

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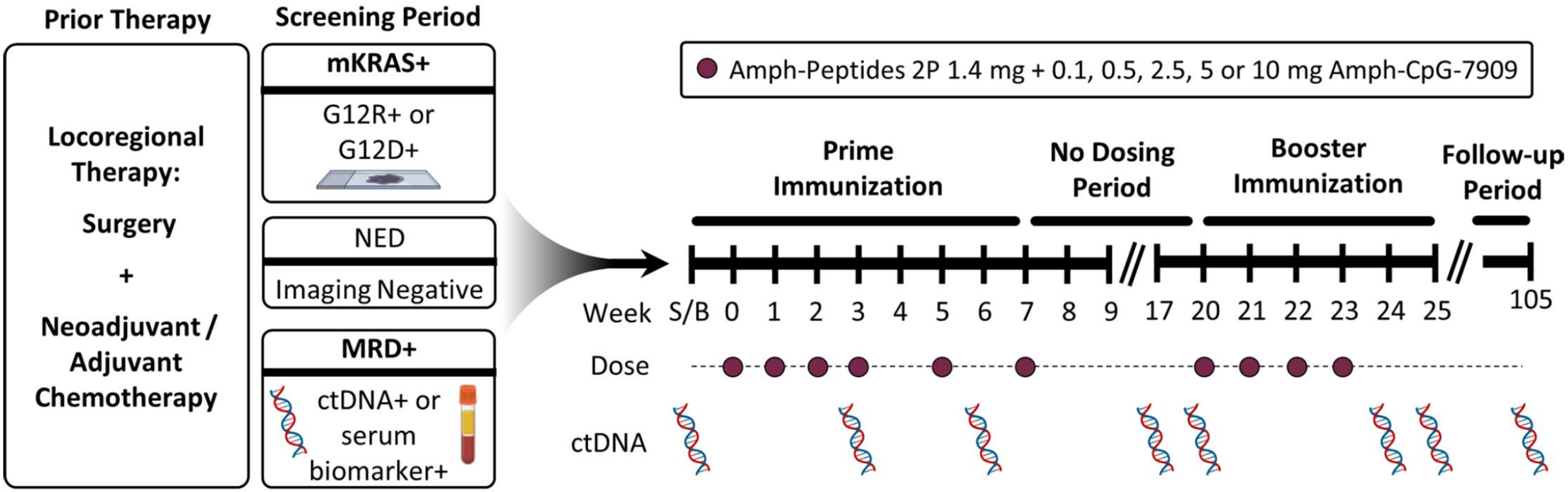
Lymph-node-targeted, mKRAS-specific amphiphile vaccine in pancreatic and colorectal cancer: the phase 1 AMPLIFY-201 trial

nature medicine



Nature Medicine
Volume 30 | February 2024 | 531–542

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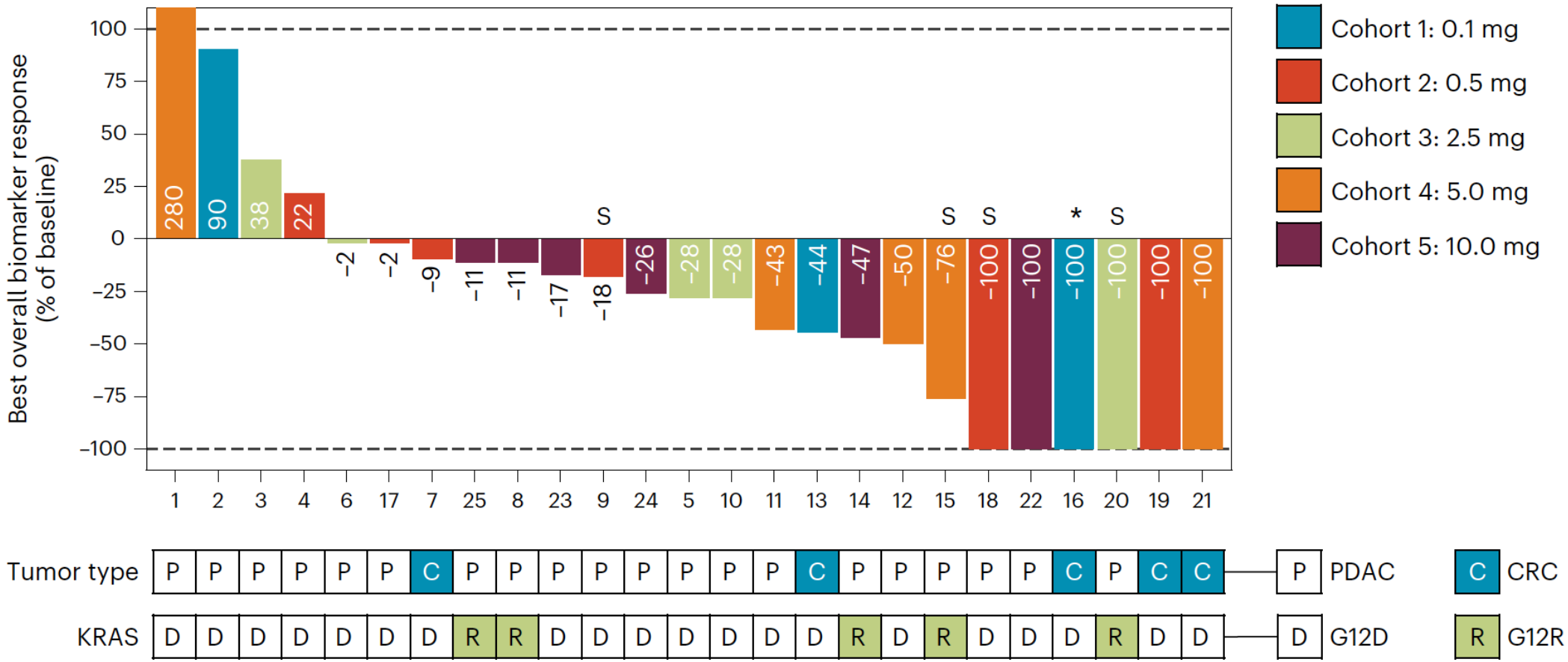

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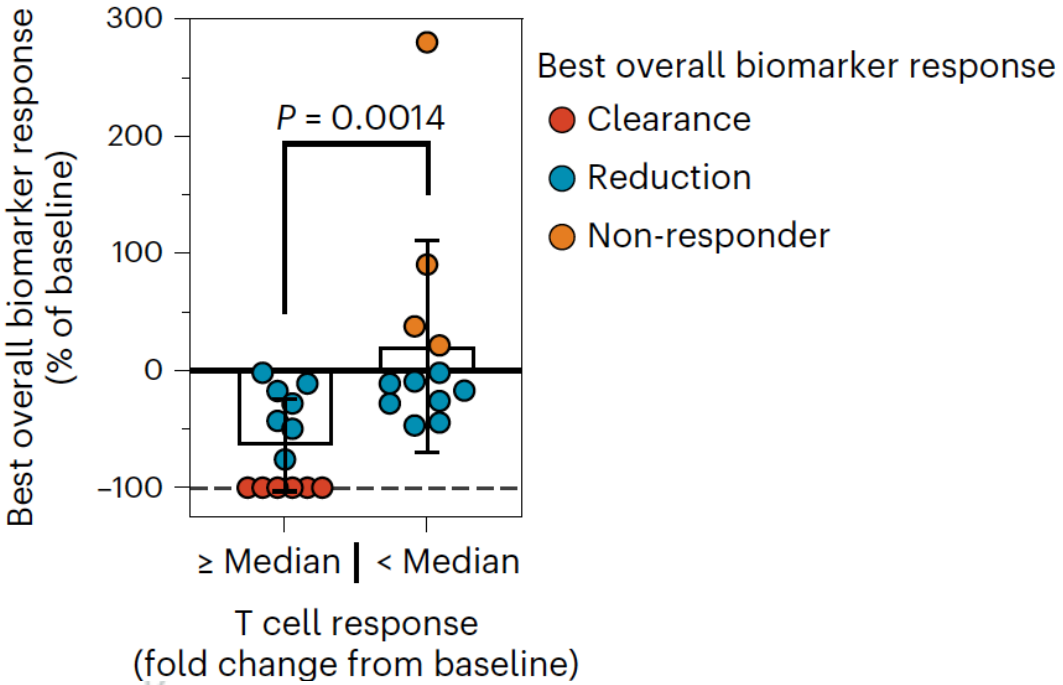

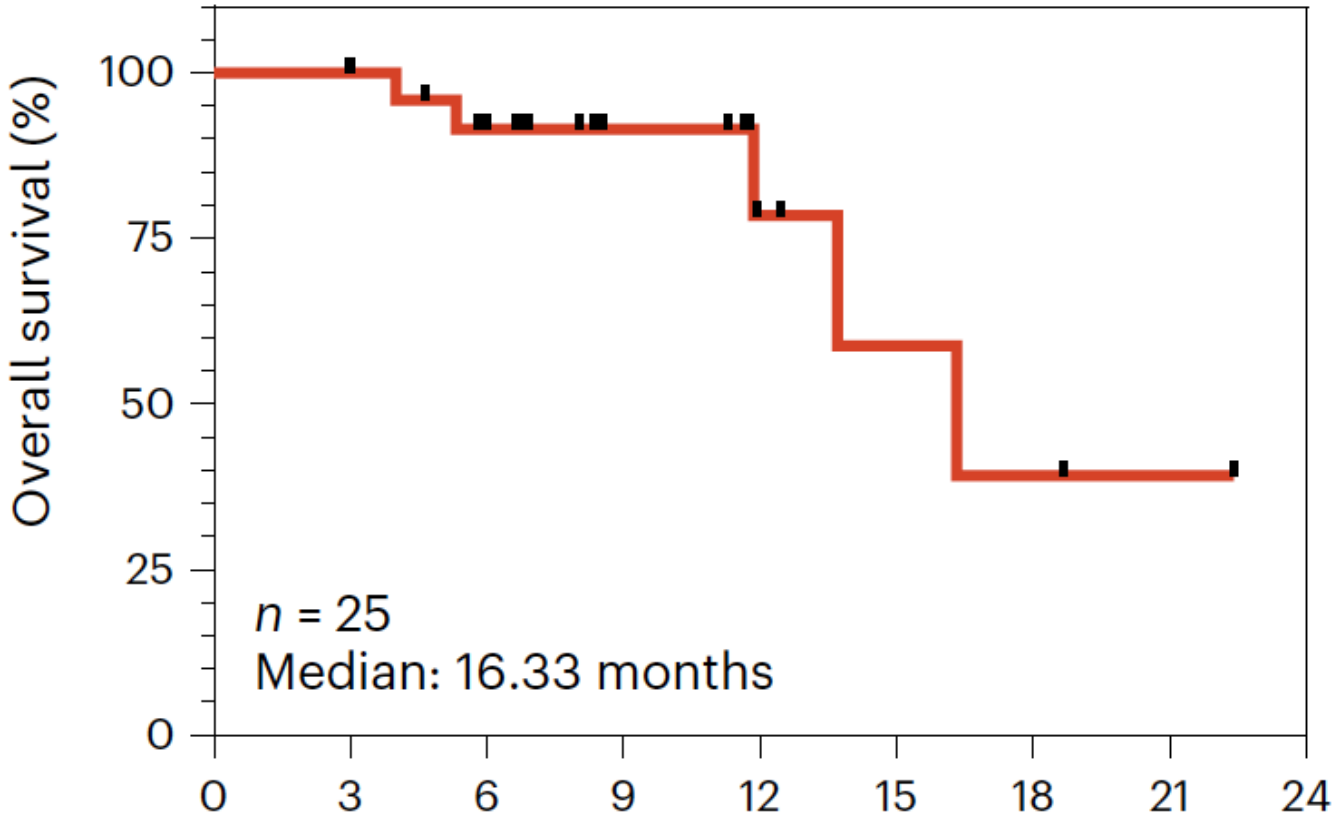

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CONCLUSIONS!

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- MSI-H
  - mCRC MSI-H:
    - anti-PD-1 (Pembrolizumab)
    - anti-PD-1 (Nivolumab) + anti-CTLA4 (Ipilimumab)
  - Rectal carcinoma MSI-H: anti-PD-1 +/- anti-LAG-3
- MSS
  - Not enough evidences yet
- POLE/D1
  - Significant benefit of IO
- HRD:
  - Potential benefit of IO

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