PARIS 2022 ESMO congress

Neoadjuvant immunotherapy in CRC

Where do we go from here?

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DECLARATION OF INTERESTS

All funding and honoraria are made to the institution

- Advisory role or expert testimony — BMS, MSD, NUMAB
- Honoraria — BMS, Roche
- Financing of scientific research — Roche, BMS, MSD

Neo- and adjuvant treatment in CRC

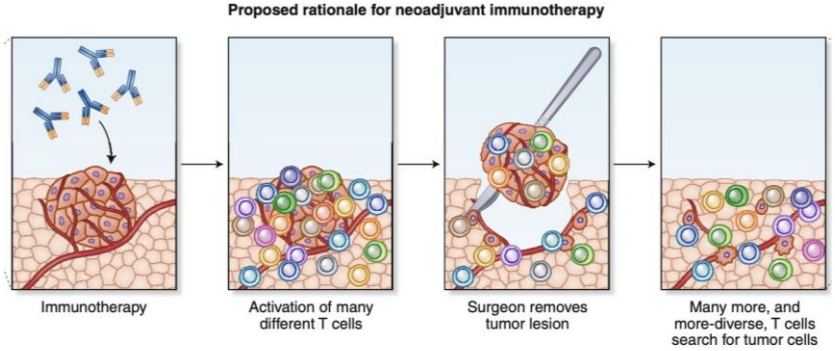
- Adjuvant chemotherapy = standard of care (SOC) for stage III and high-risk stage II (pMMR) colon cancers
- Neoadjuvant treatment (chemoradiation; TNT) SoC for rectal cancers
- Neoadjuvant chemotherapy: pathologic response in 20% of pMMR and 7% of dMMR tumors

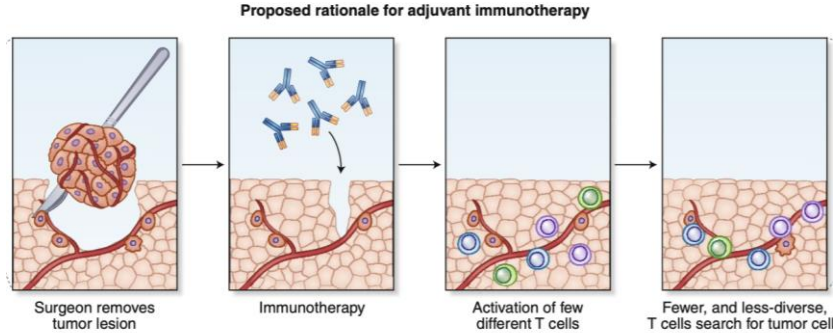
*Seligmann. J Clin Oncol, in press

Neoadjuvant *vs* adjuvant

Neoadjuvant
Improve surgical and survival outcomes
Treat micrometastases
Antigenicity (tumor in situ)
Organ-sparing treatment
Identify biomarkers

Adjuvant
Accurate staging
Patient perspective: “remove the tumor asap”
Diagnostics using the whole tumor specimen instead of biopsy





Conten ıse.

Adapted from: Versluis et al, Nat Med 2020 ; Rozeman et. Al, Nat med 2021

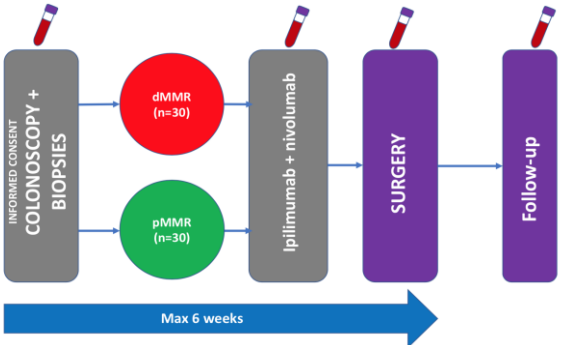
Neoadjuvant immunotherapy in colon cancers

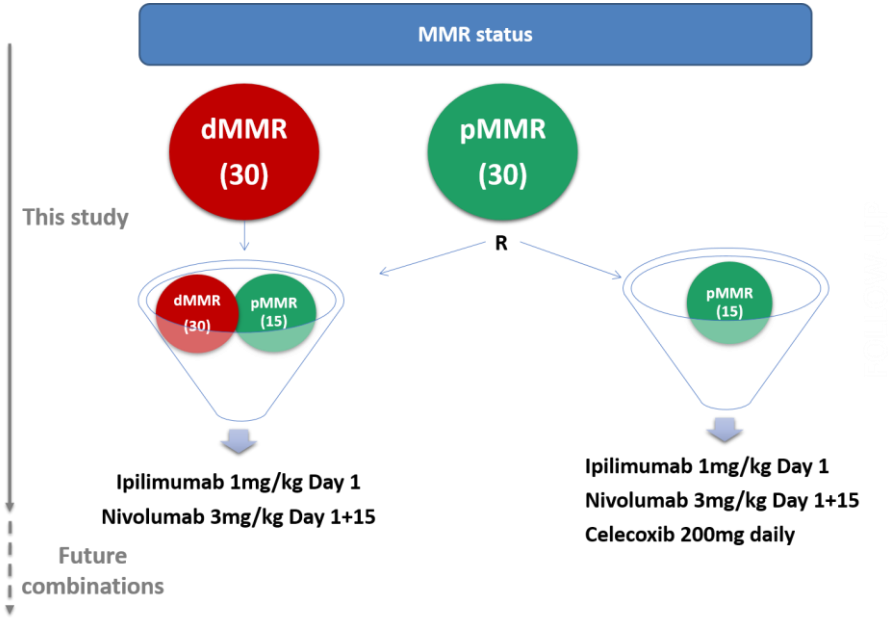
NICHE trial design and population

Neoadjuvant nivolumab (2x) + ipilimumab (1x) in patients with non-metastatic colon adenocarcinoma

primarily resectable disease (minor extension of the procedure is acceptable to achieve free margins, e.g. small bowel segment, abdominal wall)

no previous treatment with chemotherapy





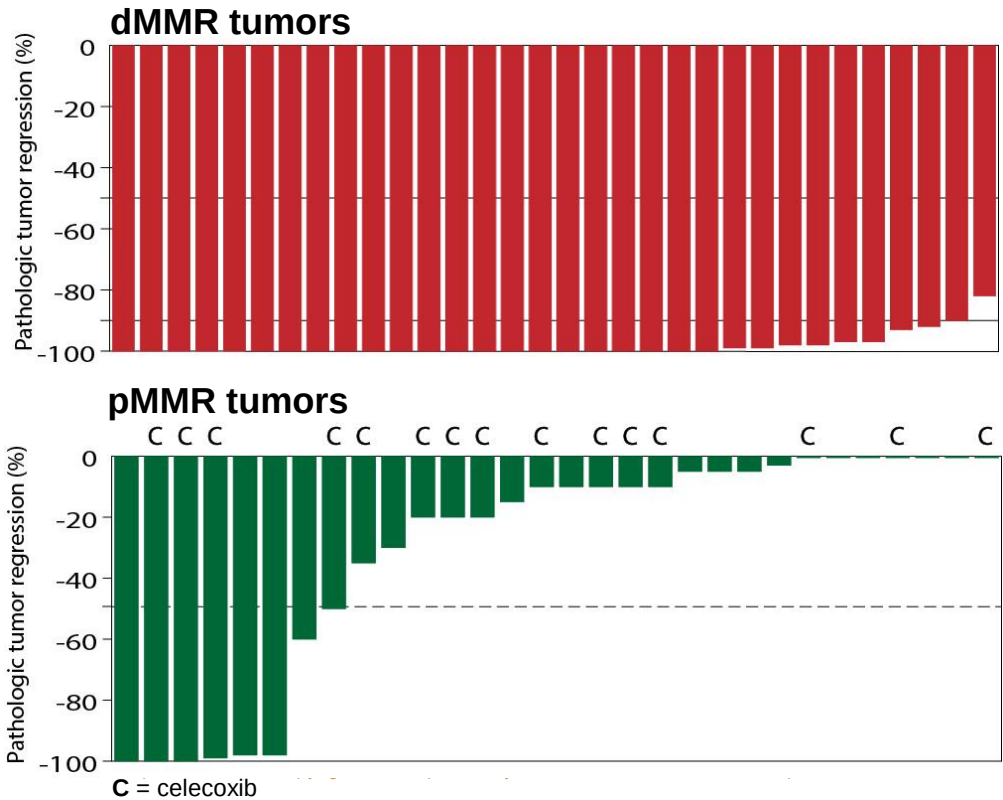
Final analysis of NICHE original cohorts

Pathologic response according to subtype

	dMMR *n*= 32	pMMR *n*= 31
Yes (≤50% VTR)	**100%**	**29%**
Major (≤10% VTR)	**31 (97%)**	**7 (23%)**
Complete (0% VTR)	**22 (69%)**	**4 (13%)**
Partial (≤50% VTR)	1 (3%)	2 (6%)
No (>50% VTR)	0 (0%)	22 (71%)

*1 patient has not undergone surgery, now 1 year after treatment completion and no longer evidence of intraluminal or radiological disease, incl neg biopsies

VTR= viable tumor rest; MPR = major pathologic response; pCR = pathologic complete response; PR= partial response



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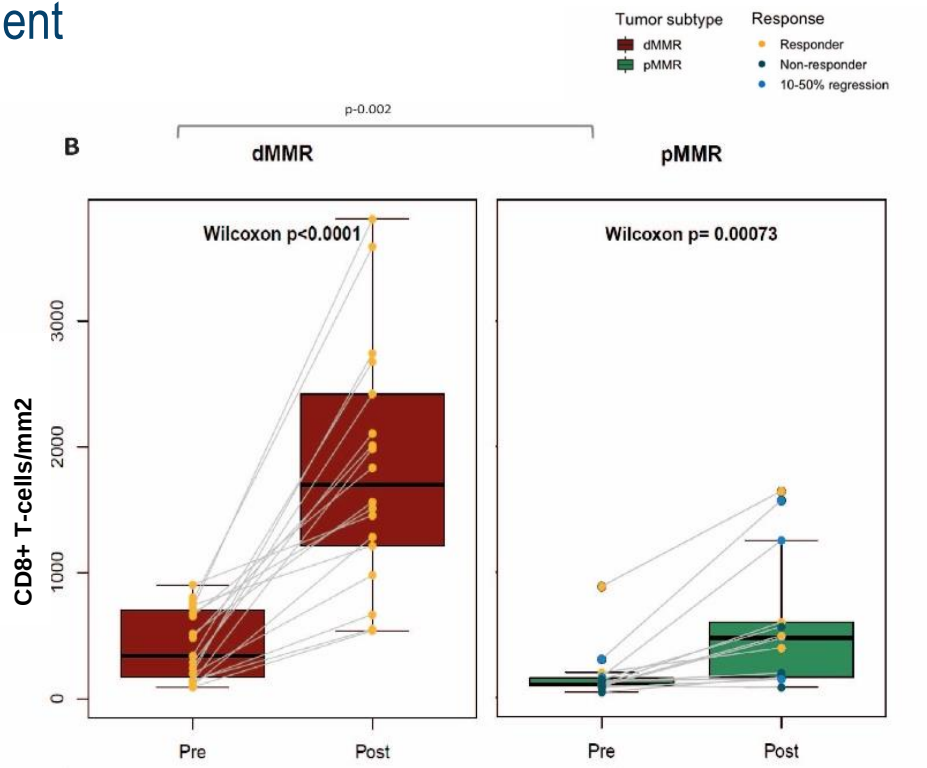
Dr. M. Chalabi

Verschoor et. al, ASCO 2022

Differences between dMMR and pMMR tumors

Changes in paired biopsies pre-/post-treatment

- Baseline CD8+ T-cells higher in dMMR tumors
  - Sign increase in dMMR + pMMR tumors



Chalabi et. al, Nat Med 2020

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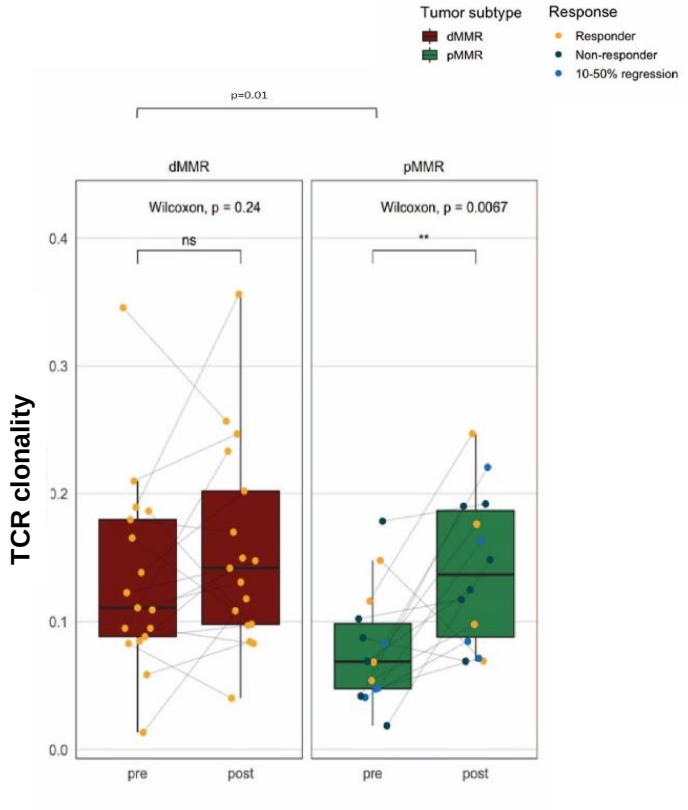
- TCR clonality higher in dMMR tumors at baseline
  - Sign increase only in pMMR tumors post-treatment



Chalabi et. al, Nat Med 2020

Differences between dMMR and pMMR tumors

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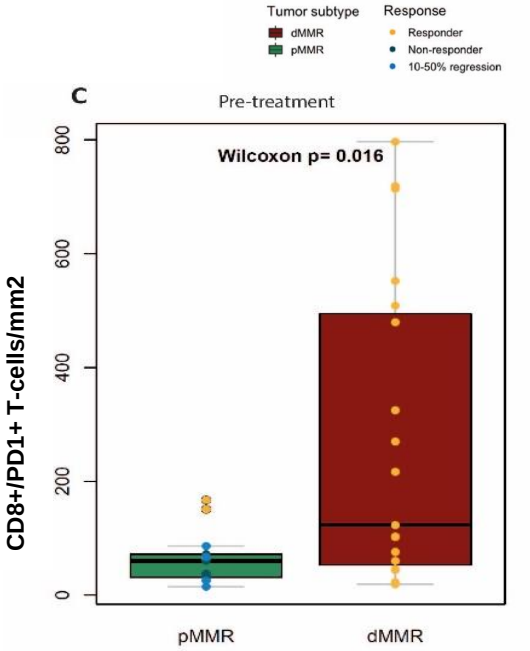
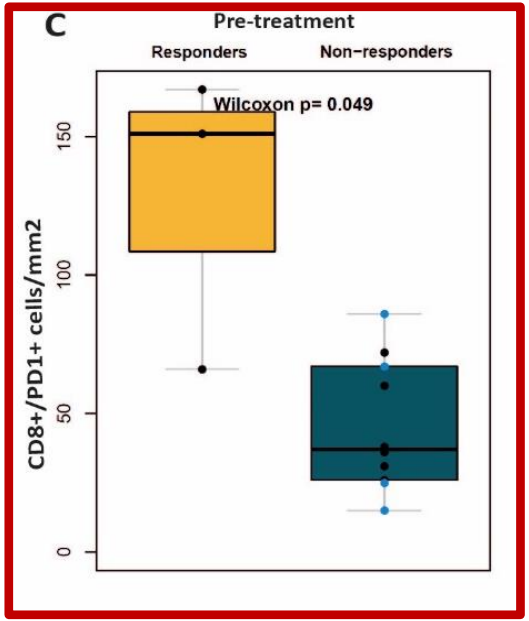
  - Sign increase only in pMMR tumors post-treatment
- CD8+/PD1+ T-cells sign. Higher in dMMR tumors at baseline

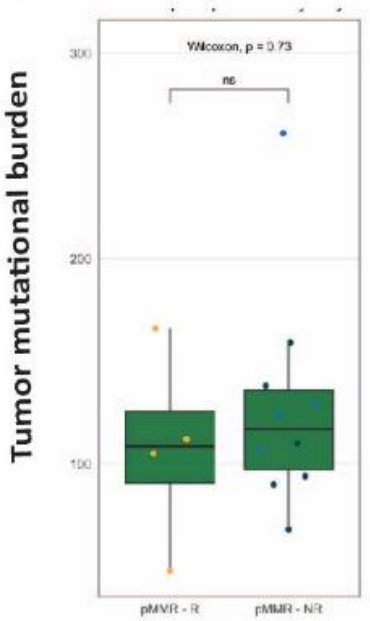


Chalabi et. al, Nat Med 2020

Predictors of response in pMMR tumors?

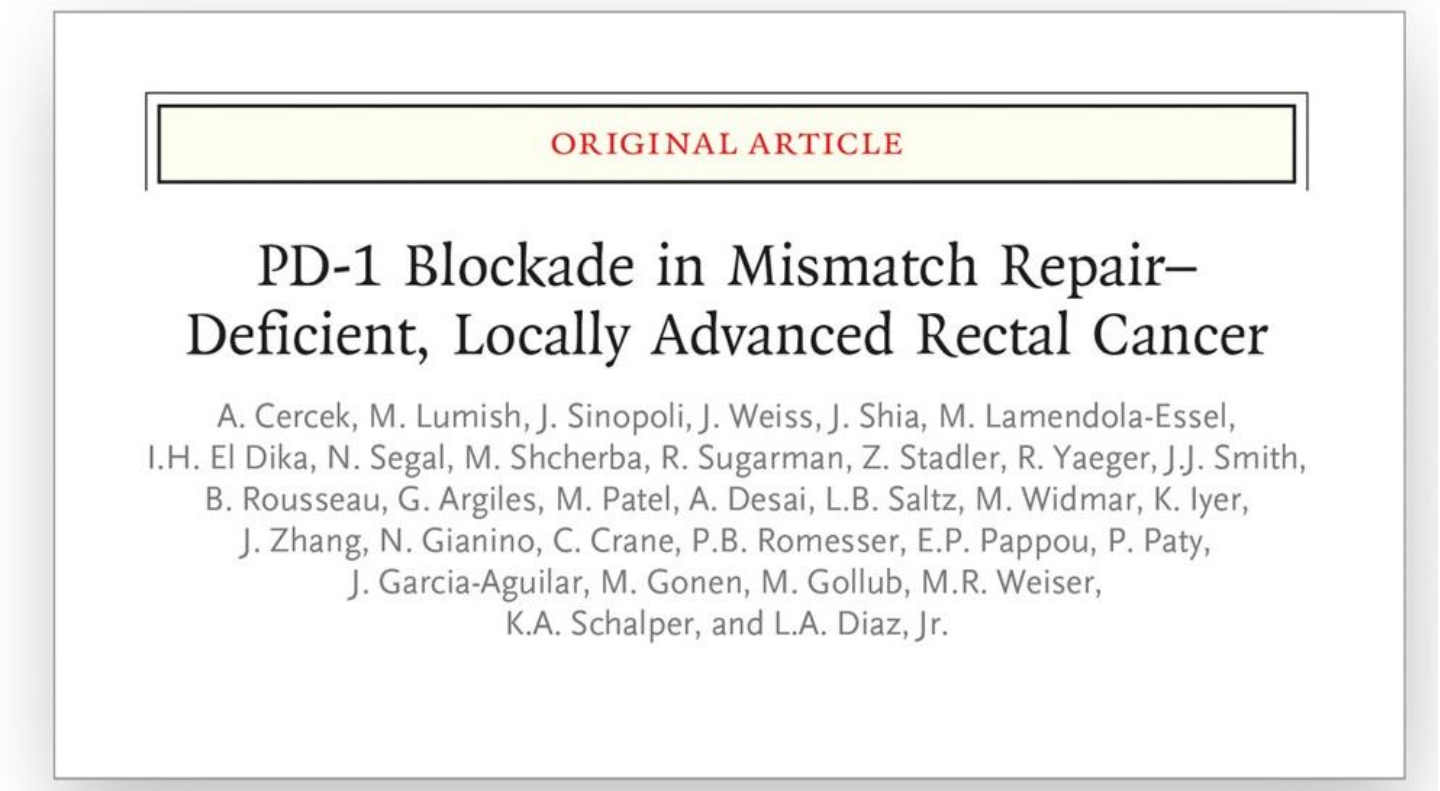
- Despite small cohort (*n*=15): CD8+/PD1+ T-cells seem predictive of response in pMMR tumors
- Validation for complete cohort ongoing
- TMB not predictive in this cohort





Chalabi et. al, Nat Med 2020

Immunotherapy in dMMR rectal cancer

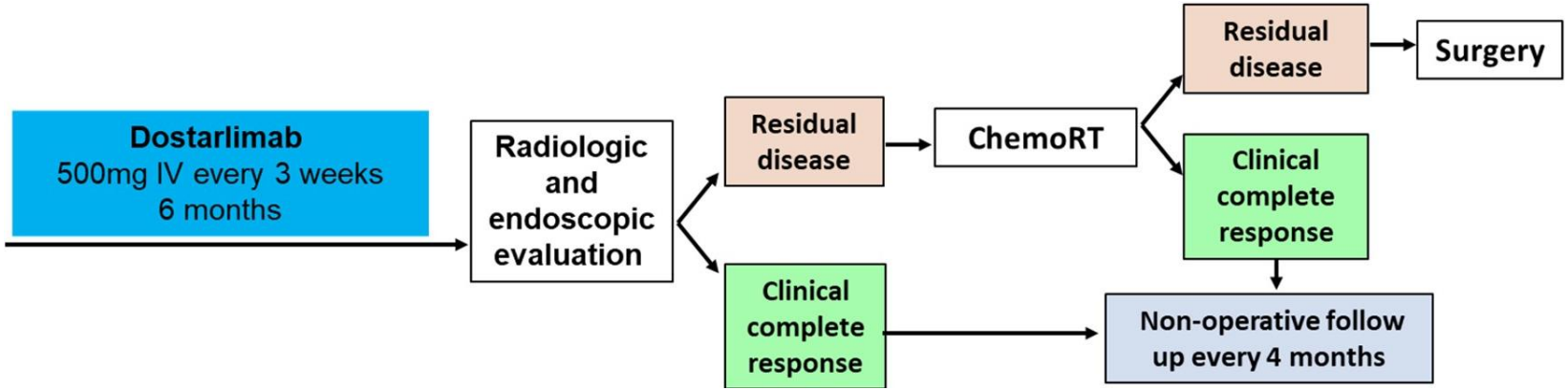


ORIGINAL ARTICLE

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

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

Study design



Patient population: stage 2 and 3 dMMR rectal cancer

Primary objectives:

- overall response rate
- pathologic or clinical complete response rate

Cercek et al, ASCO 2022

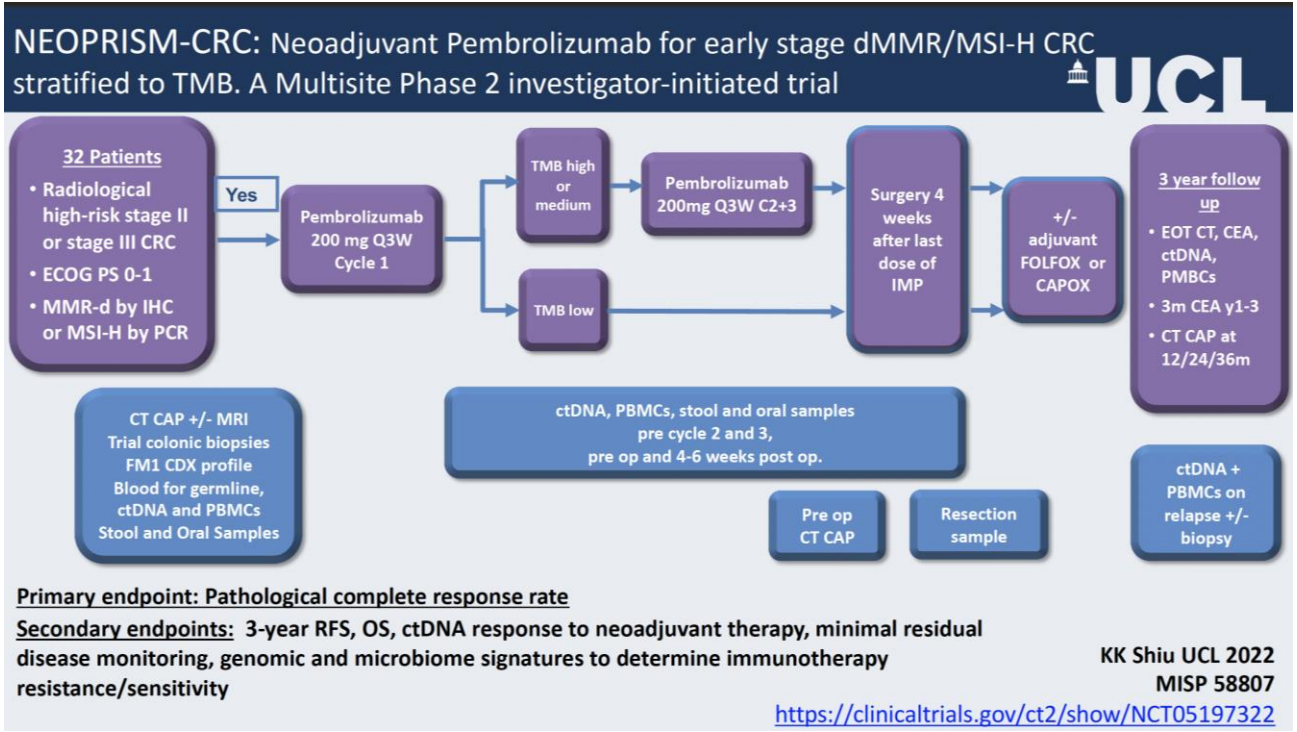
Individual responses to PD-1 blockade with dostarlimab

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**

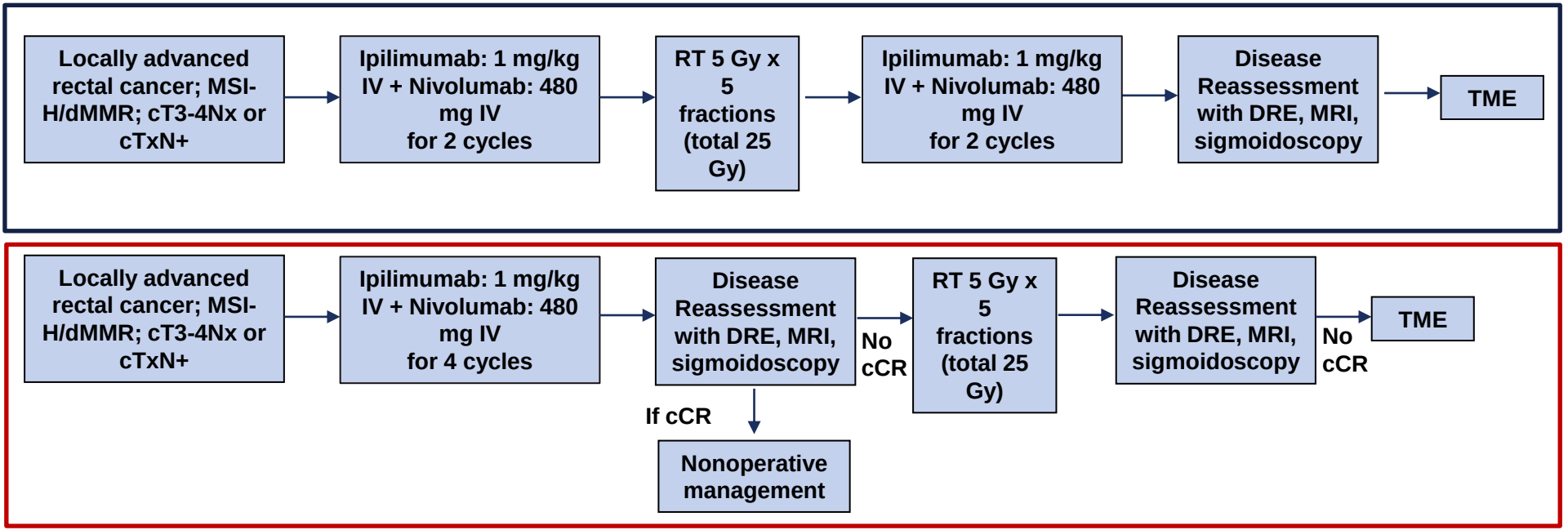
Cercek et al, ASCO 2022

Neoadjuvant pembrolizumab in dMMR colon cancer



Courtesy of dr. K. Shiu

Neoadjuvant IO in dMMR rectal cancer – EA2201



Current primary endpoint: Pathologic complete response rate (pCR)

Proposed primary endpoint: Clinical complete response rate (cCR)

Statistical design:

- Two-stage single-arm phase II study (n=31)

Courtesy of K. Ciombor

Immune Checkpoint Inhibition in dMMR mCRC

	Previous lines of treatment	No. of patients	Radiologic response rates
Andre et. al, 2020 (Keynote-177)			
Pembrolizumab	0	153	45 %
Overman et. al, 2017; Lenz et. al, 2022 (Checkmate-142)			
Nivolumab + ipilimumab	0	45	69 %
Nivolumab + ipilimumab	≥ 1	119	65 %
Nivolumab	≥ 1	74	33 %
Le et. al, 2018 (Keynote-164)			
Pembrolizumab	≥ 1 (cohort B)	63	33 %
Pembrolizumab	≥ 2 (cohort A)	61	33 %
Cohen et. al, 2022 (Nipicol)			
Nivolumab + ipilimumab	≥ 2	57	60 %
Andre et. al, 2021 (Garnet)			
Dostarlimab	≥ 1	69	36 %

Chalabi Cancer Cell 2022

Neoadjuvant immunotherapy in dMMR colorectal cancer

	Patient population	Treatment duration	No. of patients	Response rates
Verschoor et. al, 2022 (NICHE)				
Nivolumab + ipilimumab	Colon cancer Stage I-III	4 weeks	32	100% pathologic responses[1]
Cercek et. al, 2022				
Dostarlimab	Rectal cancer Stage II-III	6 months	12	100% clinical responses[2]
Overman et. al, 2021				
Pembrolizumab	Colorectal cancer Unresectable or high-risk	6 months – 1 year	31	74% radiologic responses[3]

[1]Pathologic responses include major pathologic response (97%), pathologic complete response (70%) and partial response (3%). [2]Clinical responses consisted of clinical complete responses (100%). [3]Radiologic responses include complete responses (26%) and partial responses (48%) according to RECIST 1.1.

Chalabi Cancer Cell 2022

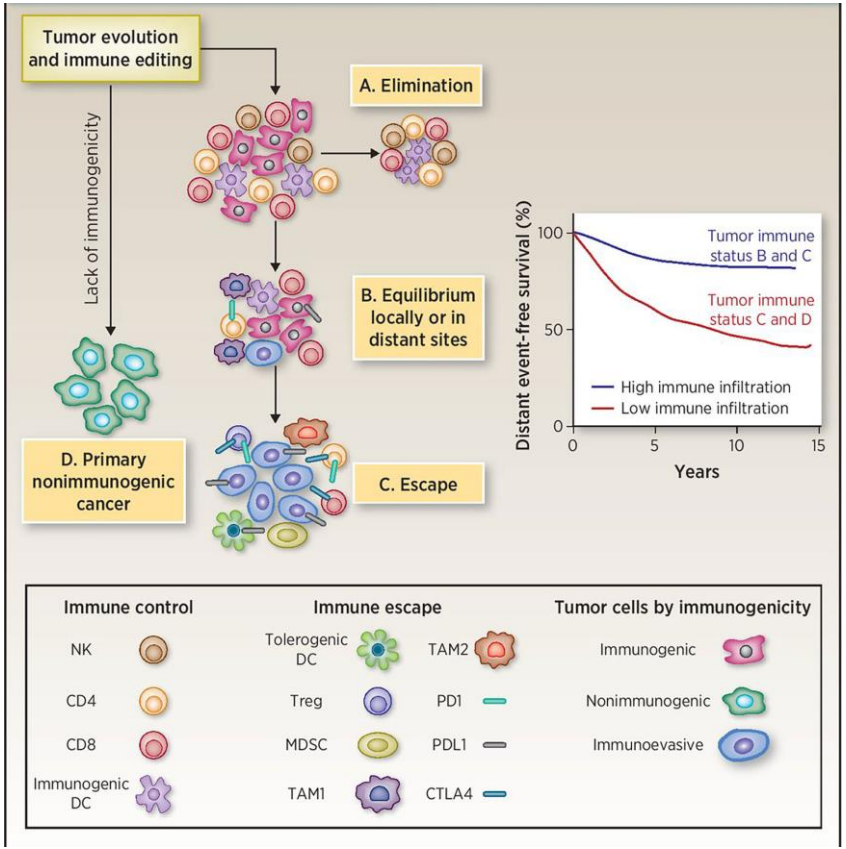
Weaker immune system in metastatic setting

What are the mechanisms behind the differences in response in metastatic *vs* neoadjuvant setting?

Metastasis formation = immune escape

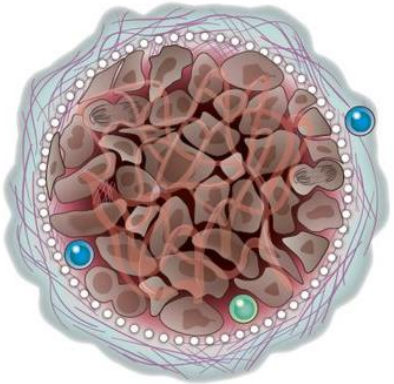
Chemotherapy and radiotherapy causes hematopoietic stress

Unlike neutrophils, NKs etc, T cells recover much slower



Zhang et al. Front Oncol 2021

How to turn cold tumors into hot tumors?
The holy grail for pMMR CRC



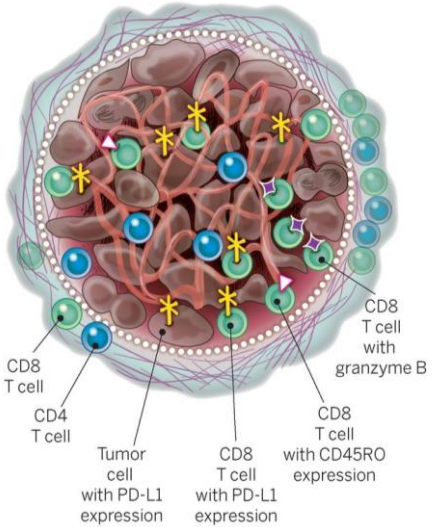
?

Radiation therapy?

Chemotherapy?

VEGF and TKI inhibitors?

COX-inhibition?



Non-inflamed

- Few T cells
- Non-clonal T cells
- Immunosuppressive tumor microenvironment
- Low number of antigens

Increase CD8+ T cell accumulation in tumors
Reduced immunosuppressive cells
Dendritic cell maturation

Inflamed

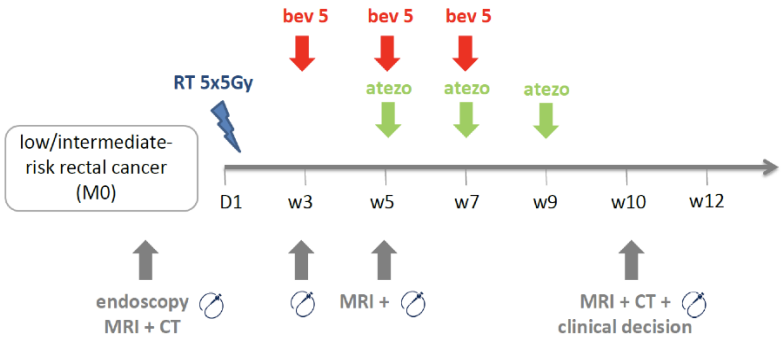
- Many T cells
- Clonal T cells
- No immunosuppression
- High number of antigens

Sharma P, Allison JP. *Science*. 2015;348(6230):56-61. 2. Hoff S et al. *Ann of Oncol*. 2017;28:v423. Abstract 2201; Hegde etl. Al, Clin Cancer Res 2016

TARZAN – neoadjuvant IO in rectal cancer

Neoadjuvant immunotherapy in rectal cancer - TARZAN study

- Phase II, single arm study
- Simon two-stage design



Primary objective: efficacy of neoadiuvant treatment in terms of ***complete and near-complete responses***

Secondary objectives:

- safety/tolerability
- relapse-free survival
- efficacy with regard to organ preservation
- translational research

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Simon two-stage design:

- Stage 1: 18 pts: continue to stage II if ≥3 responses
- Stage 2: 20 pts (currently ongoing)

Target population:

- Low-Intermediate risk rectal cancers

Where do we go from here? – pMMR tumors

- Promising early response data with dual anti-PD-1 + anti-LAG3 *or* anti-CTLA-4 in pMMR/MSS metastatic CRC
  - Higher response rates in the neoadjuvant setting?
- Learn from NICHE pMMR responders to inform future studies
- 2 new cohorts for pMMR tumors (anti-PD1+ anti-LAG3 or anti-IL8)
- Develop biomarker driven neoadjuvant study for pMMR CRC

Where do we go from here? – dMMR tumors

- Is neoadjuvant immunotherapy ready to become SoC in dMMR colorectal cancers?
  - Tune in for ESMO Presidential Symposium II: results of the NICHE-2 study
  - International validation of NICHE data could be helpful to achieve SoC status

- Organ preservation for colon cancer?
  - DFS data important
  - Better assessment of (near-)complete response

- Organ-sparing treatment for dMMR rectal cancer: more data and follow-up needed, but very promising without the need for chemo/radiotherapy or surgery!
  - Single *vs* dual checkpoint blockade

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THANK YOU!

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