Mechanisms of resistance to checkpoint inhibitors, novel checkpoints and novel combinations

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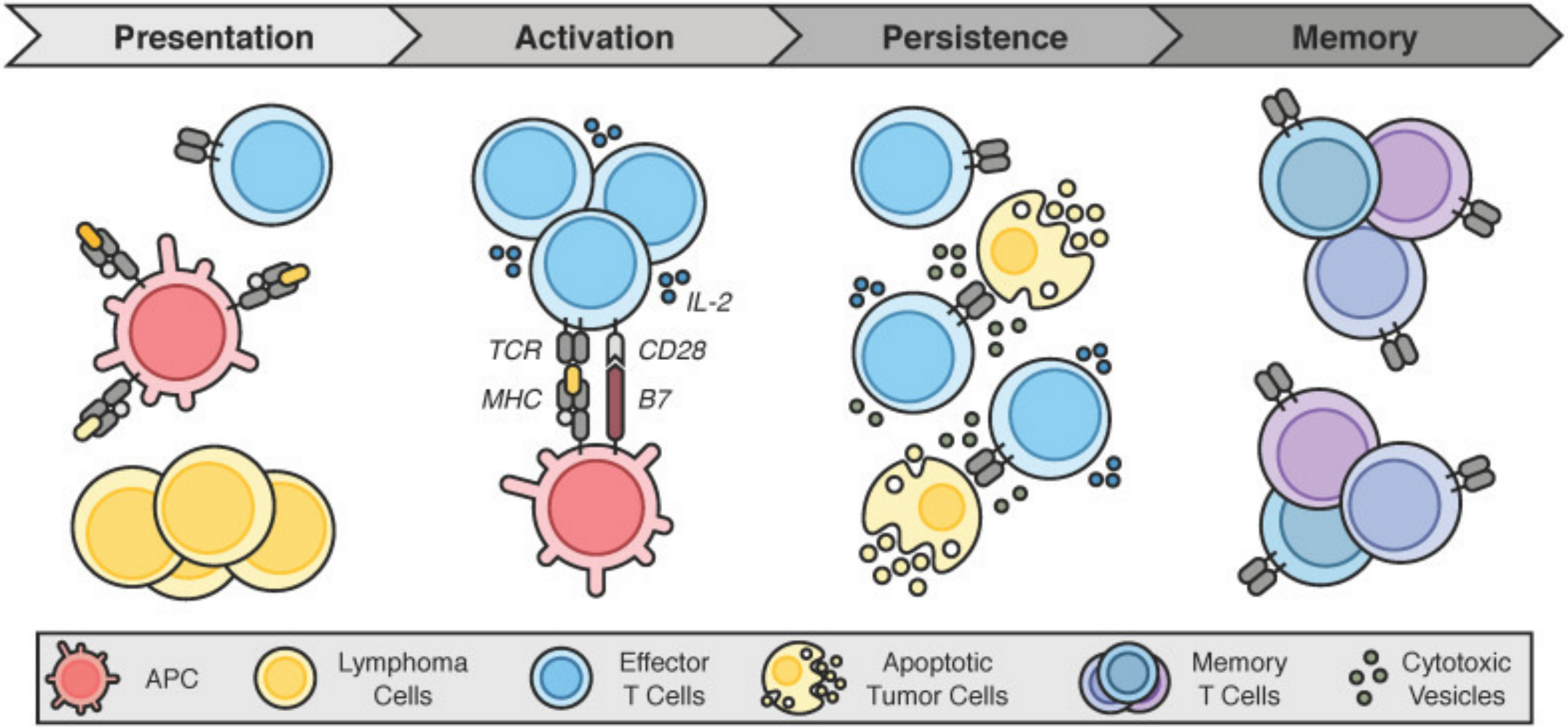
An Effective T-cell Response to Lymphoma



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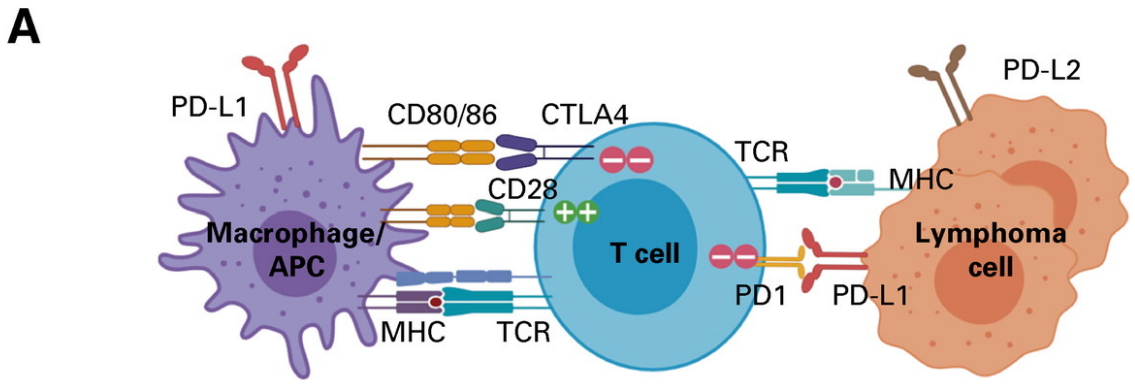
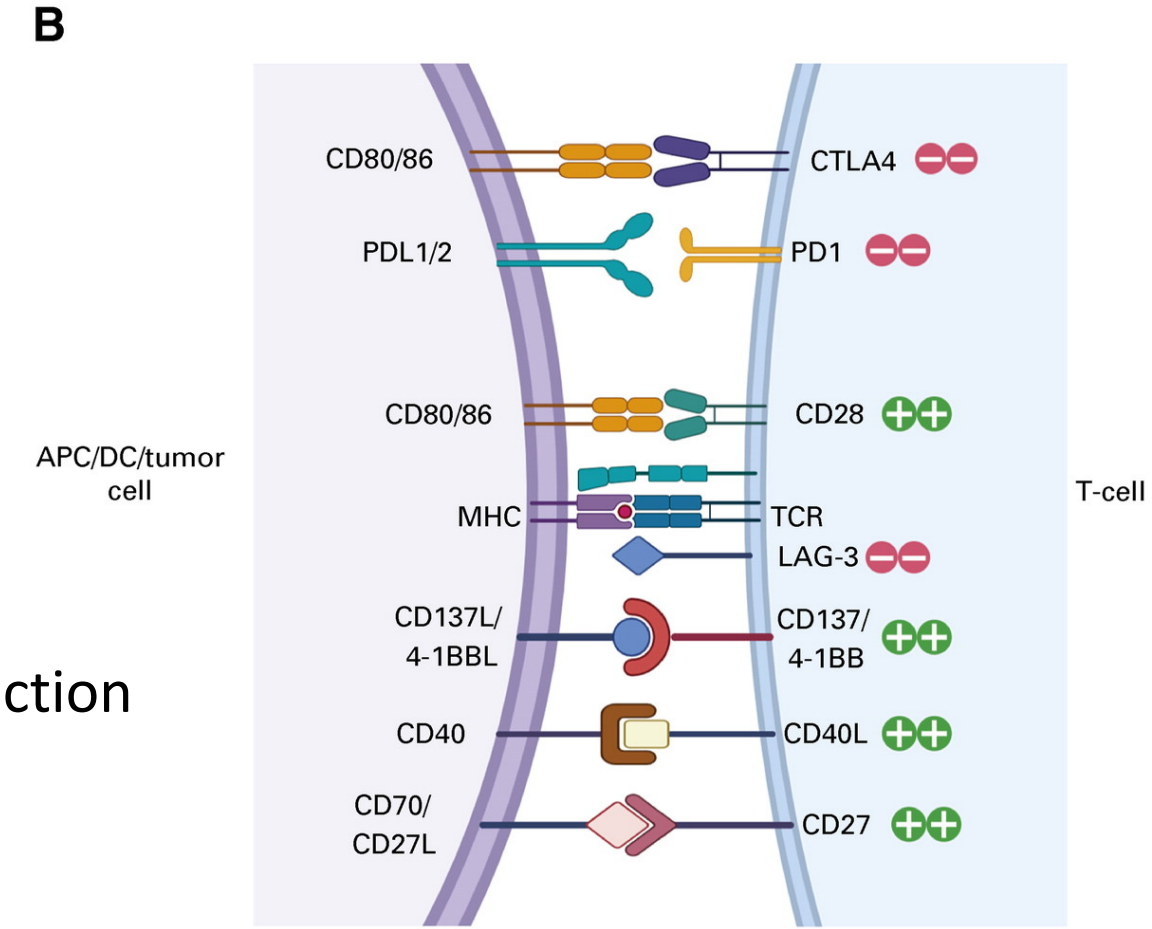
Immune checkpoints – Mechanisms of resistance

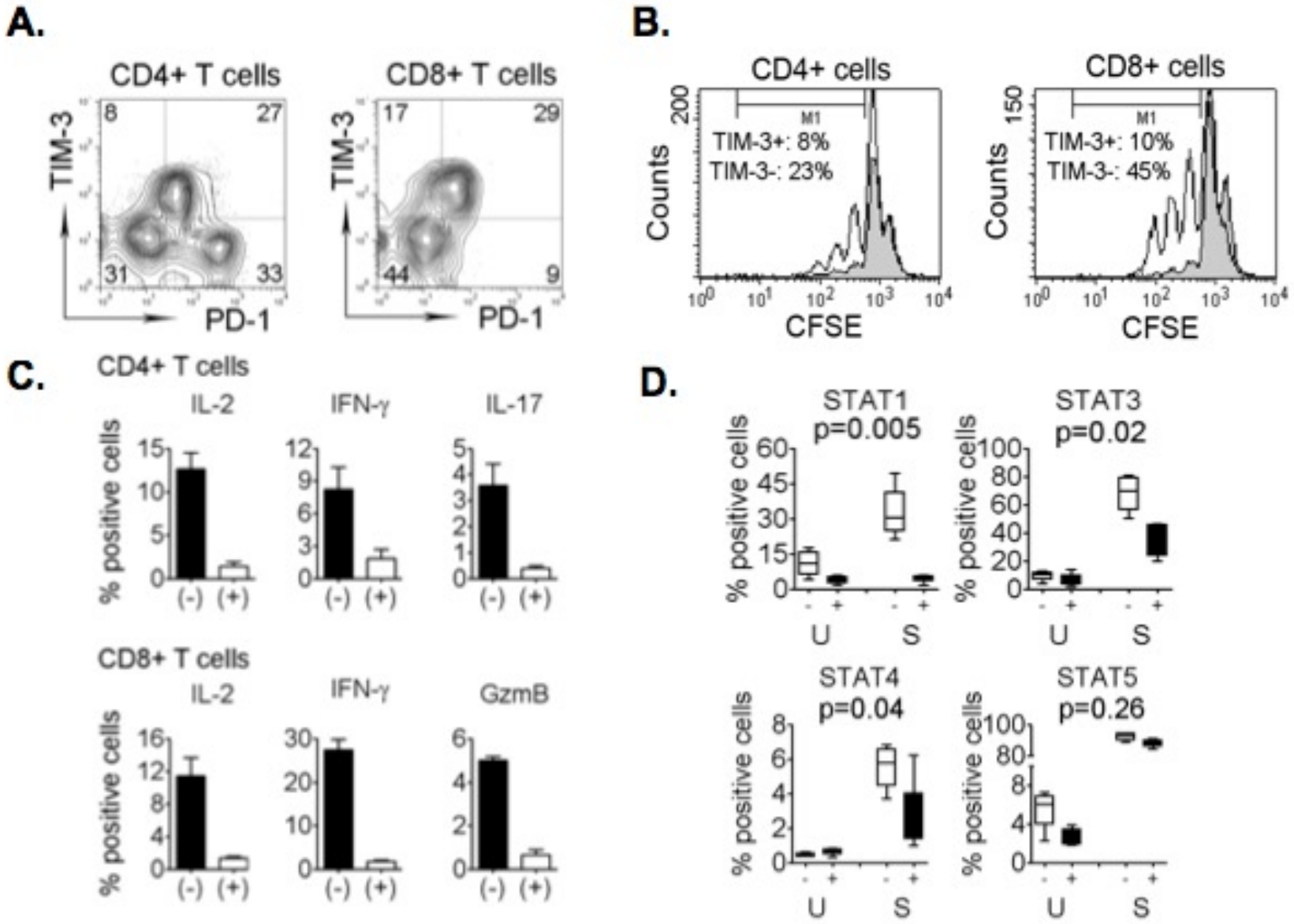




1. Other checkpoints involved
2. T-cell not activated/profound T-cell dysfunction
3. Tumor genetics
4. Tumor microenvironment/soluble ligands
5. Microbiome

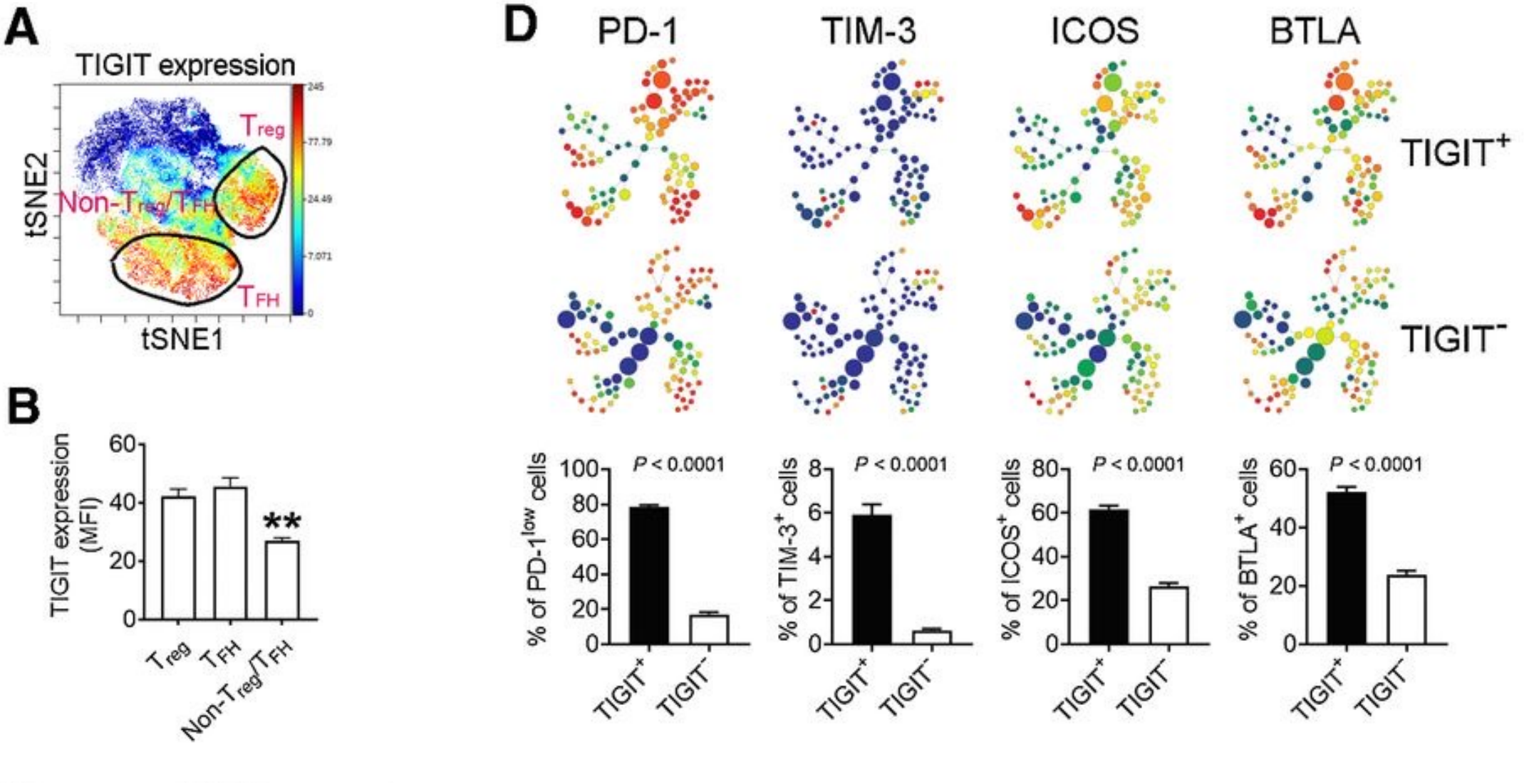
Ansell SM. J Clin Oncol. 2021 Feb 10;39(5):525-533.

1. Other checkpoints - Exhausted T-cells in lymphoma express TIM3



Yang et al. J Clin Invest 2012;122(4):1271-82.

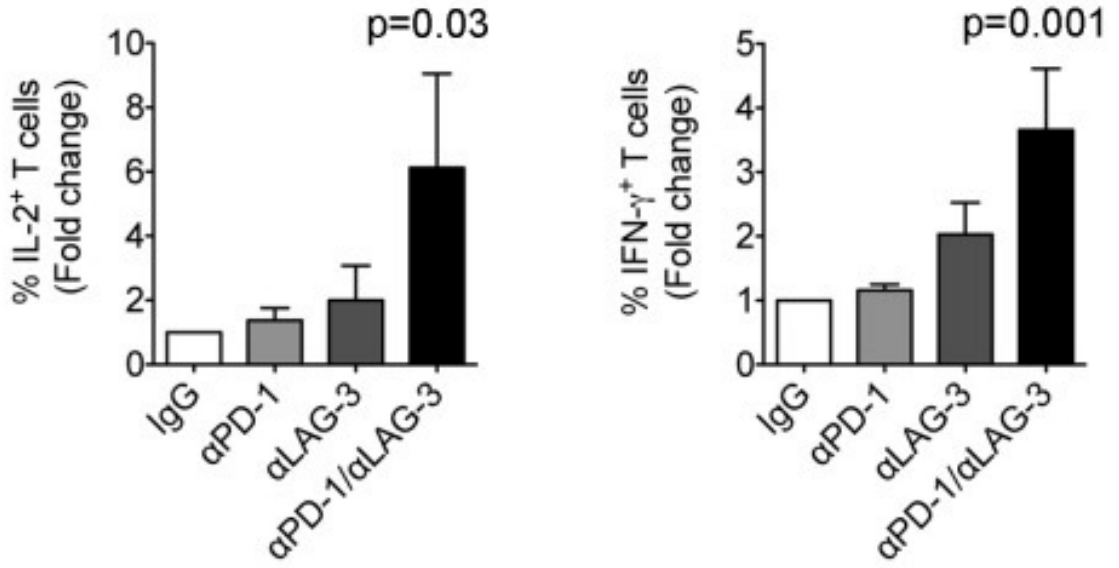
1. Other checkpoints - TIGIT expression defines intratumoral T-cells as exhausted



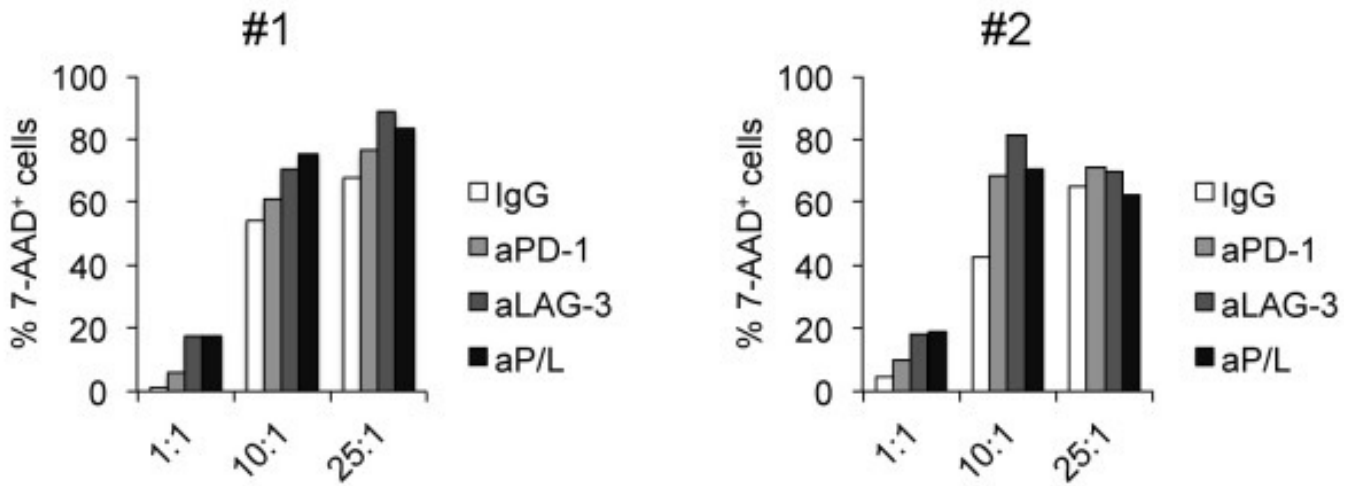
Yang ZZ, et al. Clin Cancer Res. 2020 Oct 1;26(19):5217-5231.

1. Other checkpoints - LAG-3 and PD-1 blockade reverses the dysfunction of T cells

Cytokines

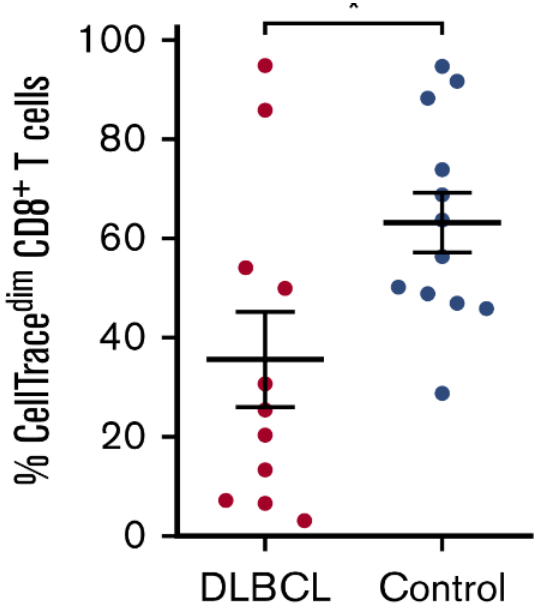


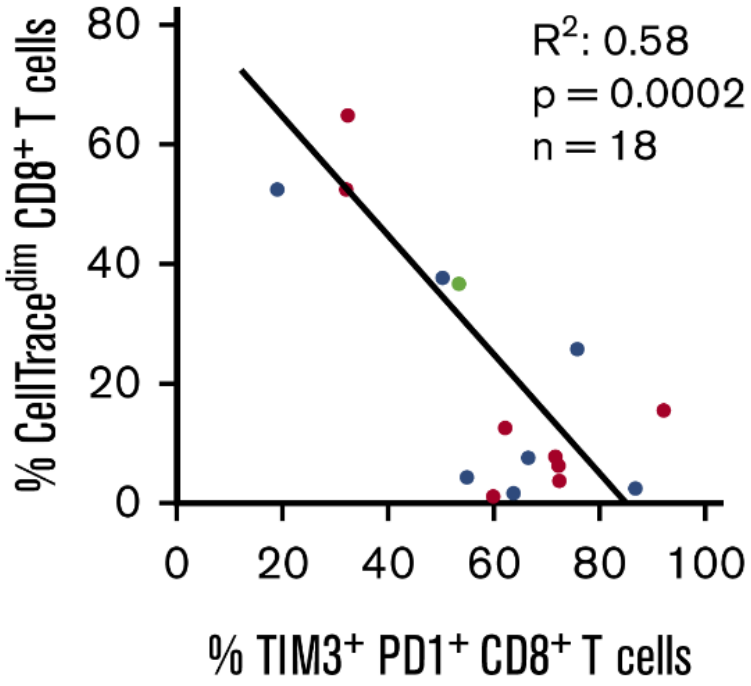
Cytotoxicity

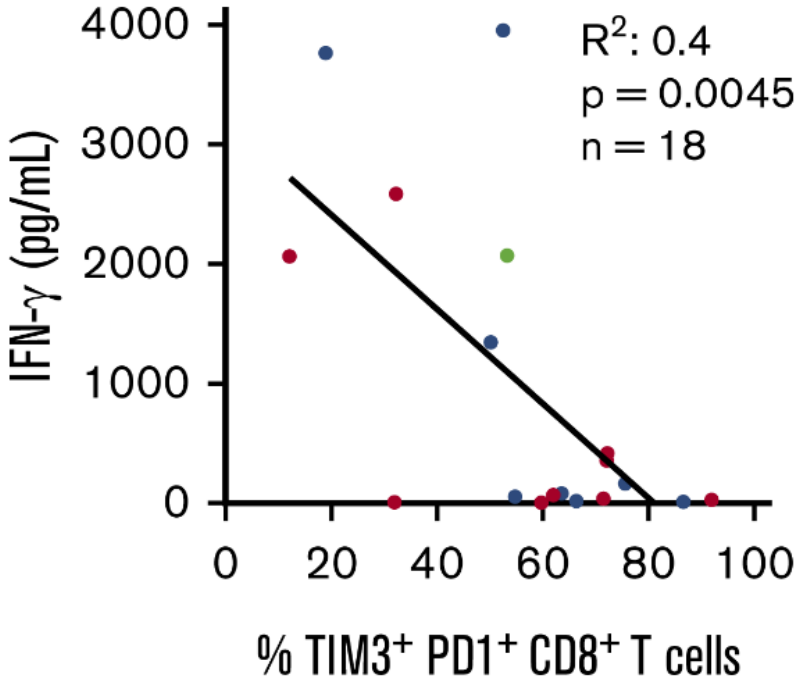


Yang et al. Oncotarget. 2017, 8(37):61425-61439

2. Profound T-cell dysfunction - Functional characterization of PD1^{+}TIM3^{+} tumor-infiltrating T cells in DLBCL

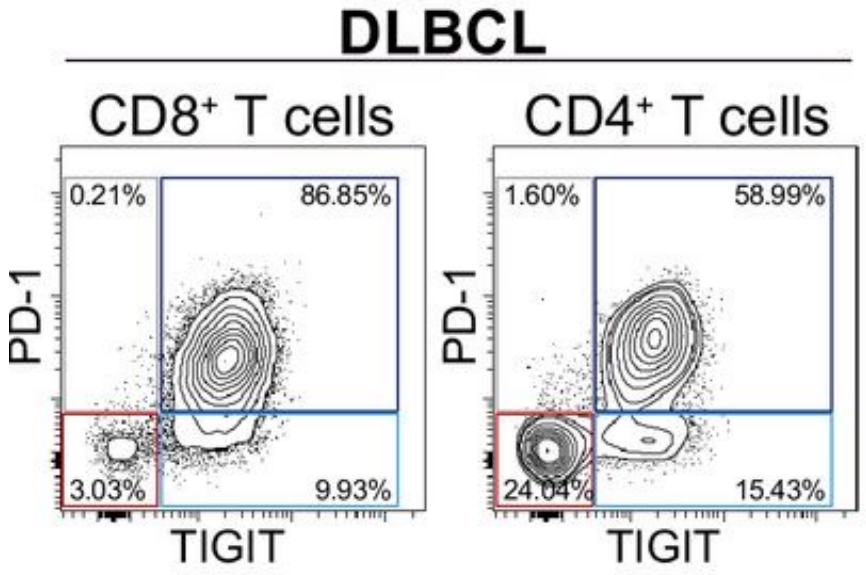


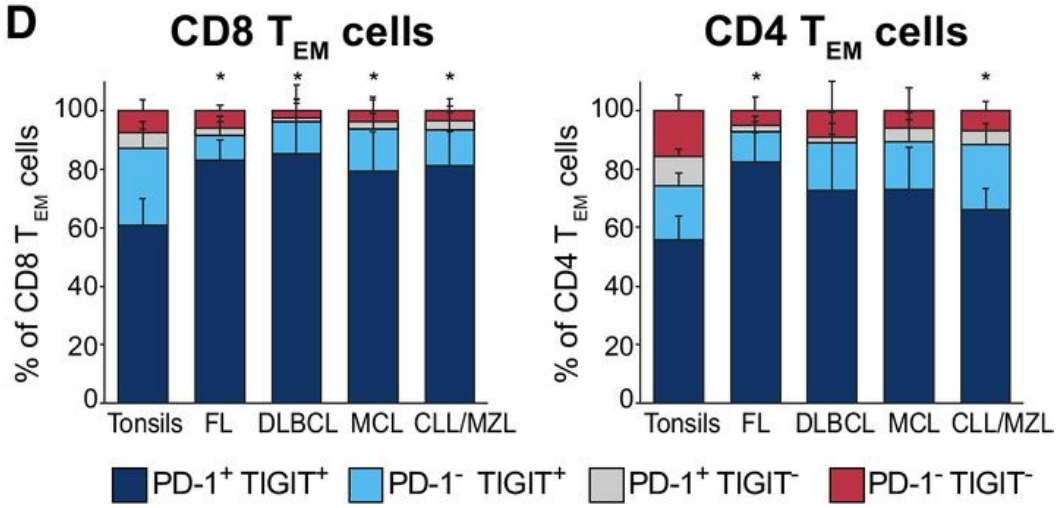


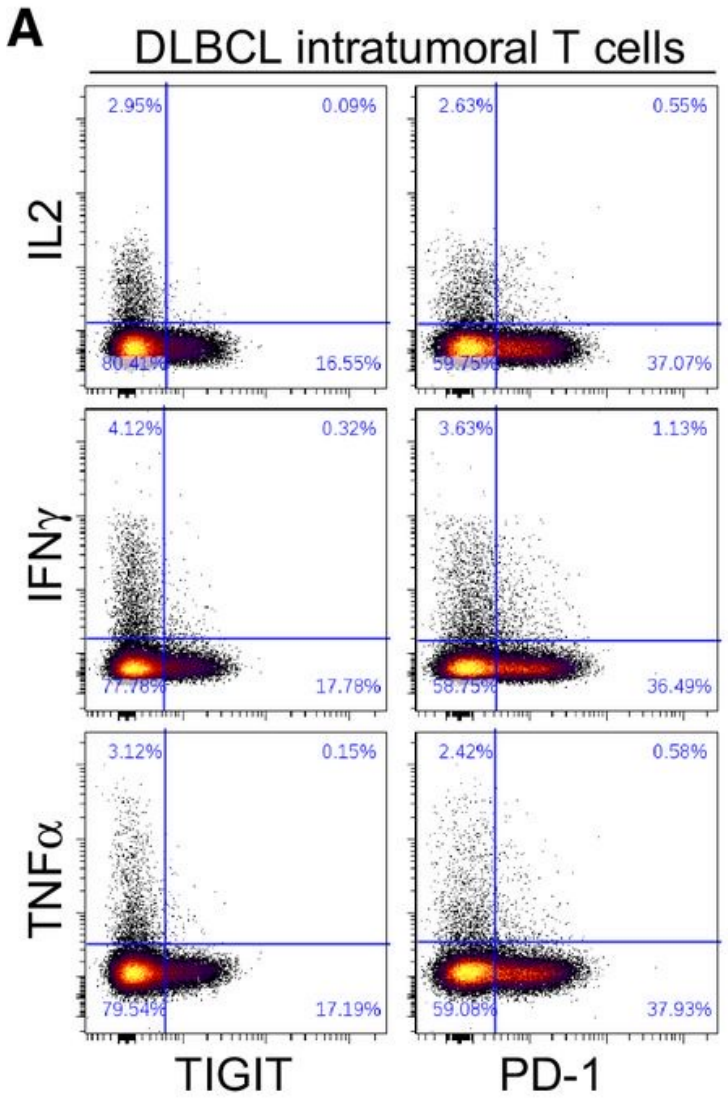


Roussel M, et al. Blood Adv. 2021 Apr 13;5(7):1816-1829.

2. Profound T-cell dysfunction - TIGIT and PD-1 Identify T-Cells with Reduced Effector Function

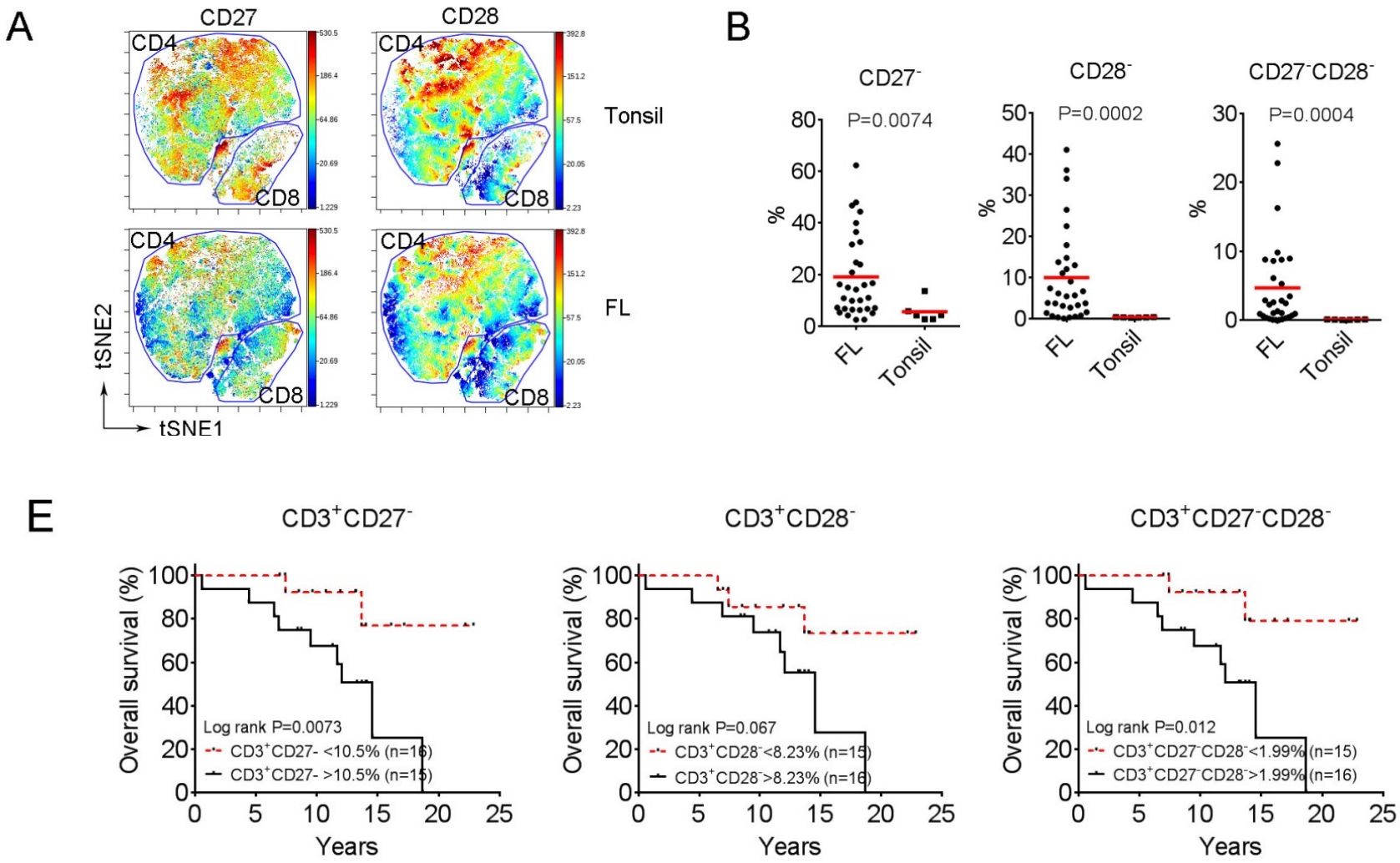






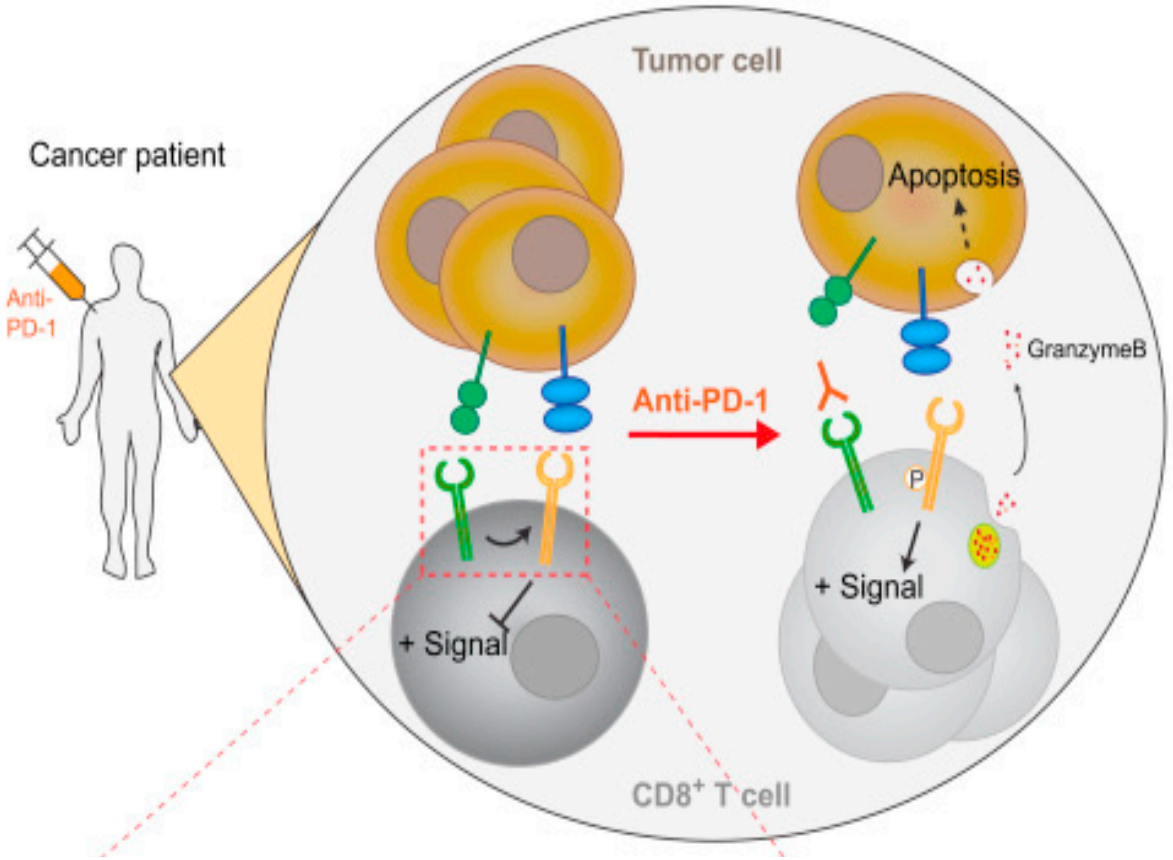
Josefsson SE, et al. Cancer Immunol Res. 2019 Mar;7(3):355-362.

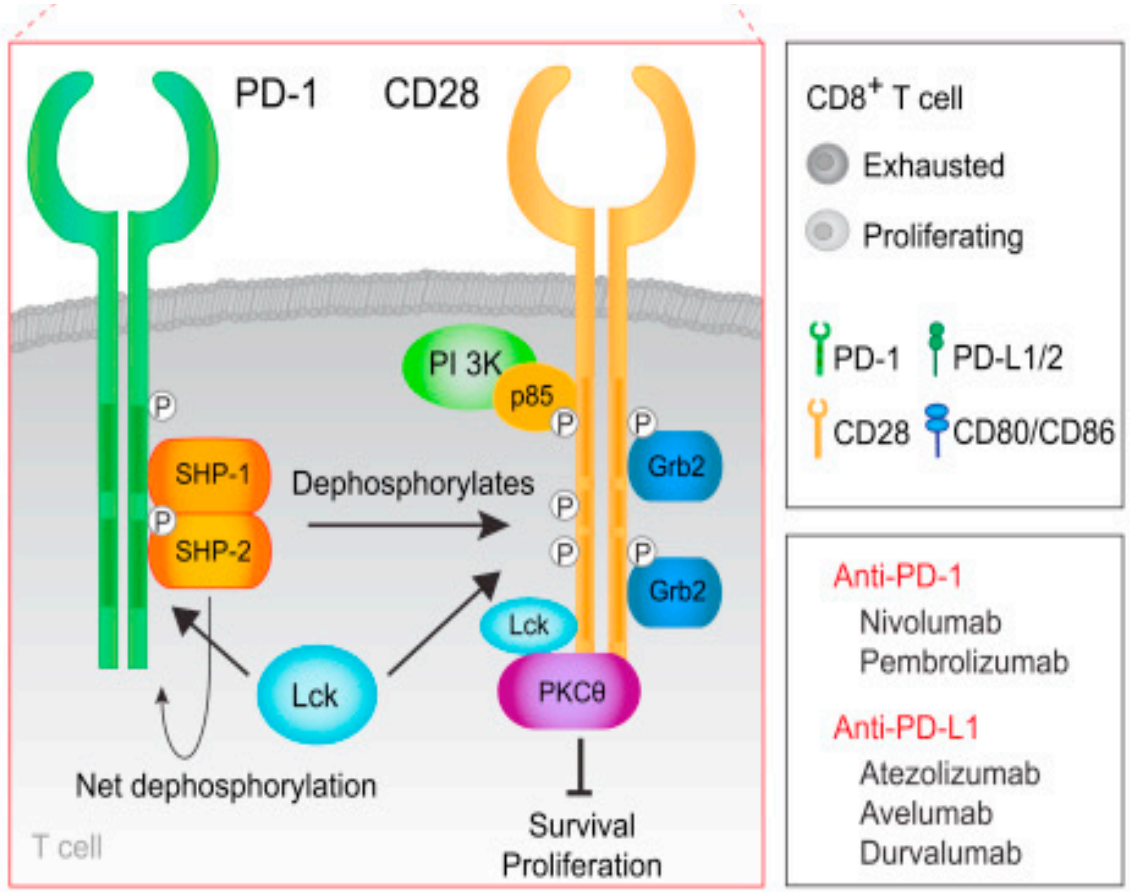
2. Profound T-cell dysfunction - Complicating Factor: Intratumoral T-cells have downregulated co-stimulatory receptors



Yang et al. Cell Rep. 2019 Feb 19;26(8):2178-2193.

2. Profound T-cell dysfunction - Rescue of exhausted CD8 T cells by PD-1-targeted therapies is CD28-dependent

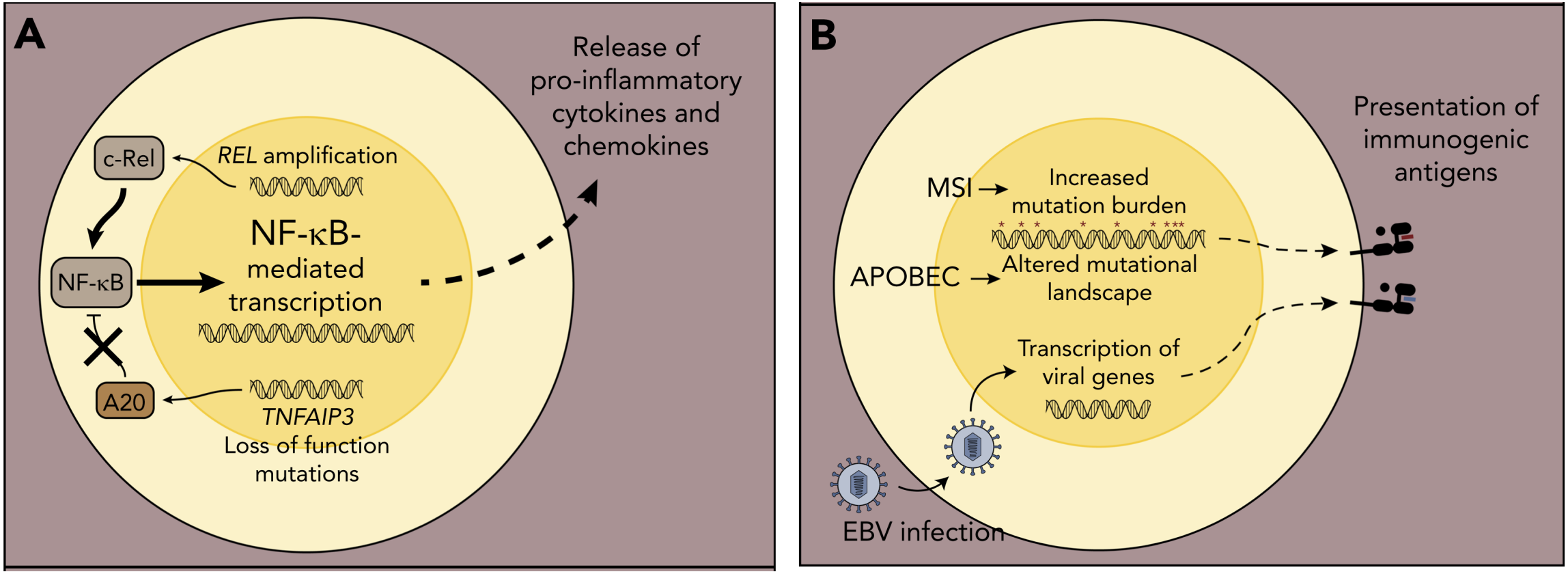




Kamphorst et al. Science. 2017 Mar 31;355(6332):1423-1427.
Hui et al. Science. 2017 Mar 31;355(6332):1428-1433.
Krueger., Rudd. Immunity. 2017 Apr 18;46(4):529-531.

3. Tumor genetics – "Hot vs Cold"

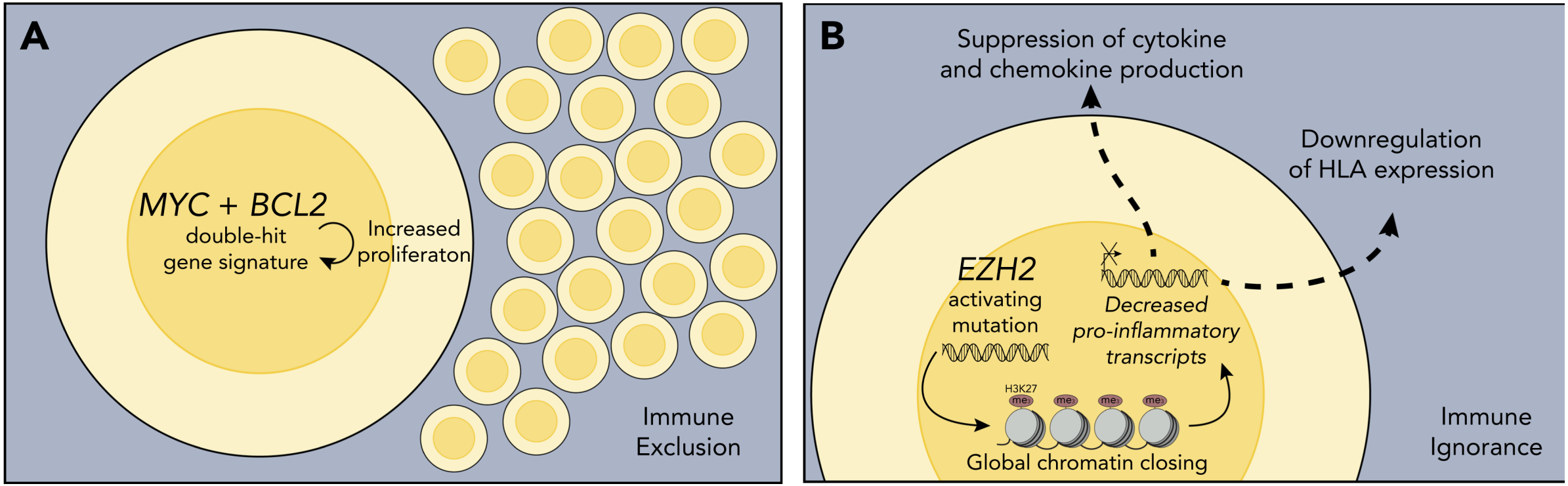
Mechanisms associated with inflamed lymphoma environments.



Kline J, et al. Blood. 2020 Feb 20;135(8):523-533.

3. Tumor genetics – "Hot vs. Cold"

Mechanisms associated with non-inflamed lymphoma environments.

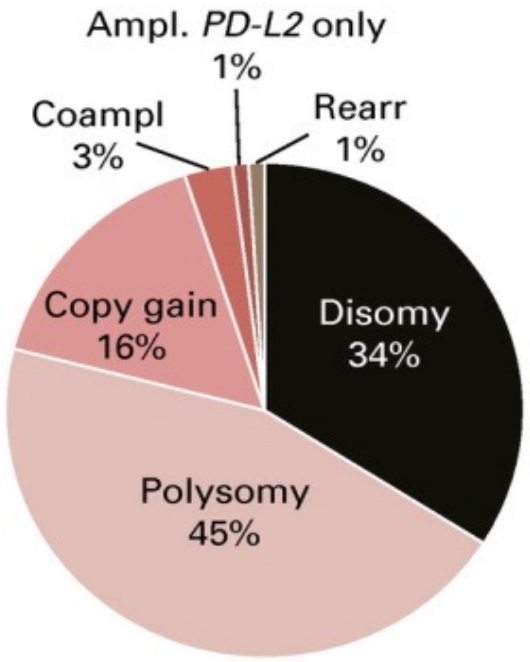


Kline J, et al. Blood. 2020 Feb 20;135(8):523-533.

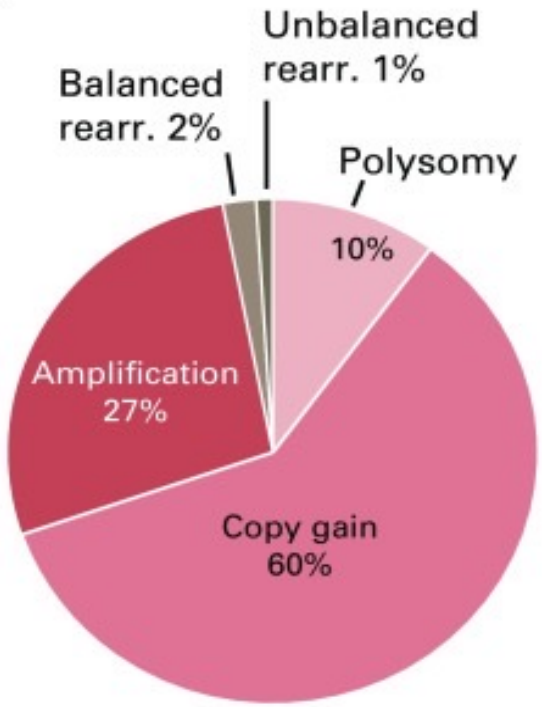
3. Tumor genetics – Reason for lack of response in FL/DLBCL - PD-L1/2 overexpression not commonly genetically driven

Copy number gain/amplification appears most important

DLBCL

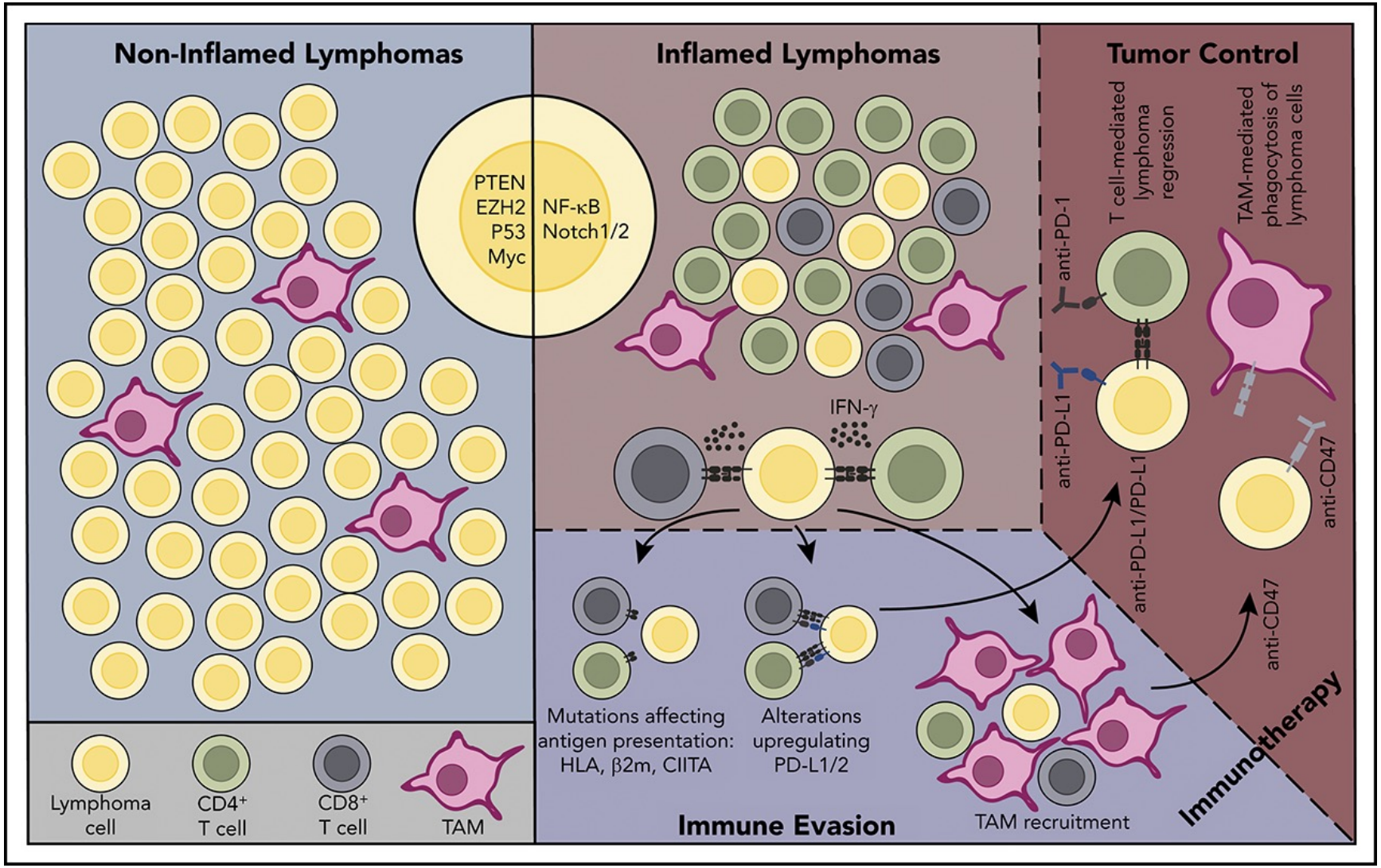


Hodgkin



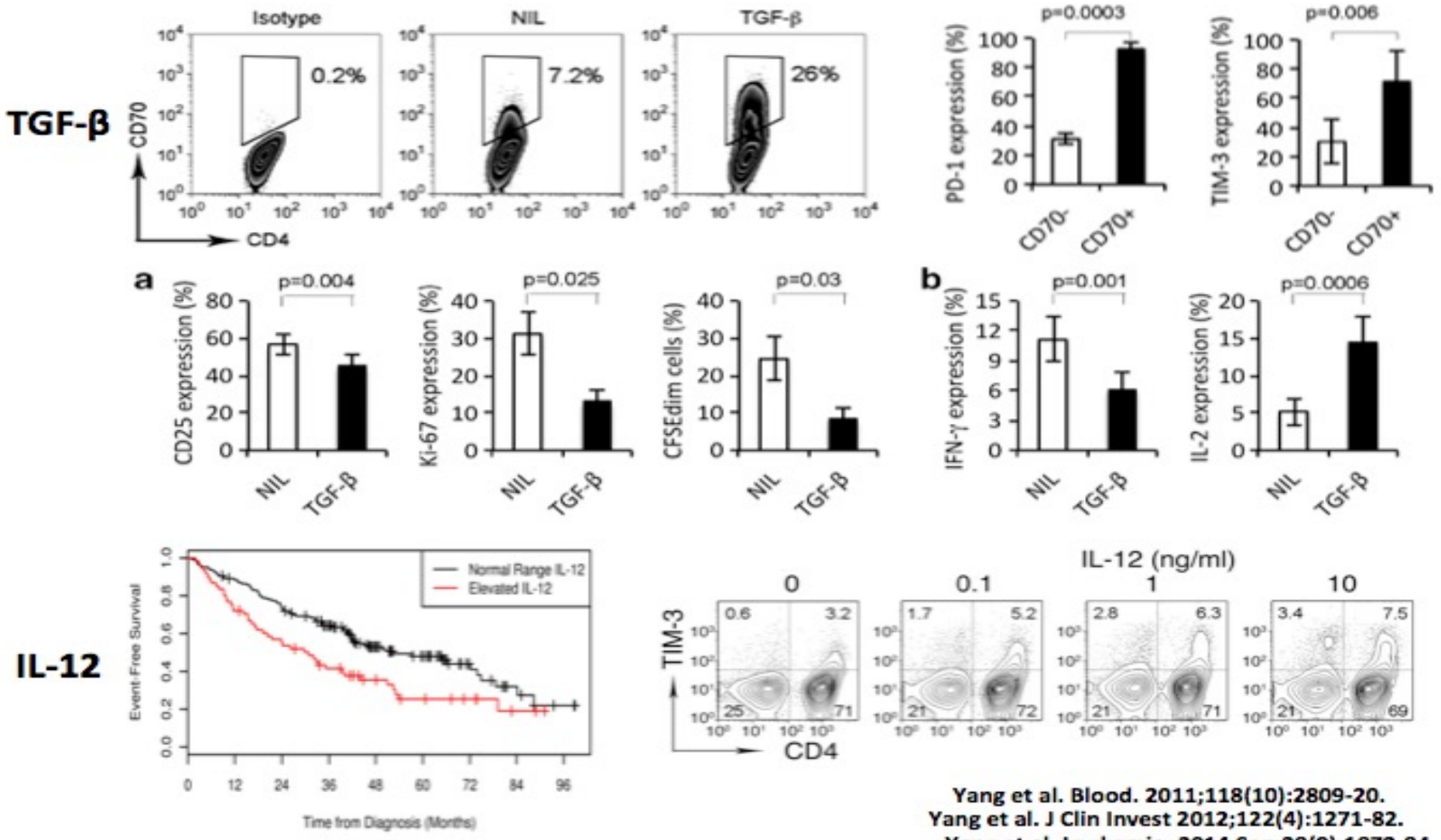
Roemer MGM, et al. J Clin Oncol. 2018 Apr 1;36(10):942-950.
Ansell SM et al. J Clin Oncol. 2019 Feb 20;37(6):481-489.

4. Tumor microenvironment and response to immune checkpoint blockade therapy in lymphoma



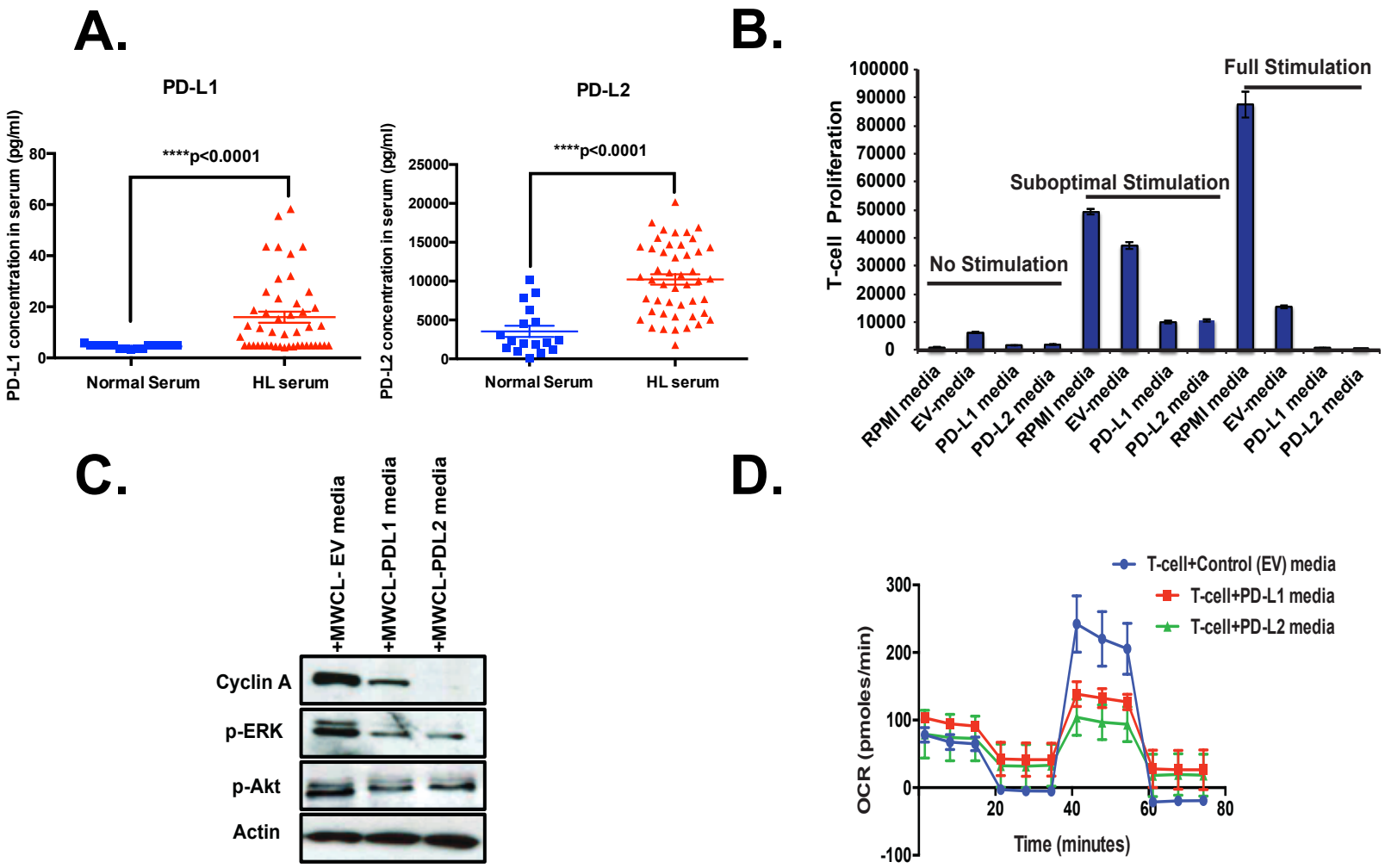
Kline J, et al. Blood. 2020 Feb 20;135(8):523-533.

4. Tumor microenvironment: Immunostimulatory cytokines induce T-cell exhaustion



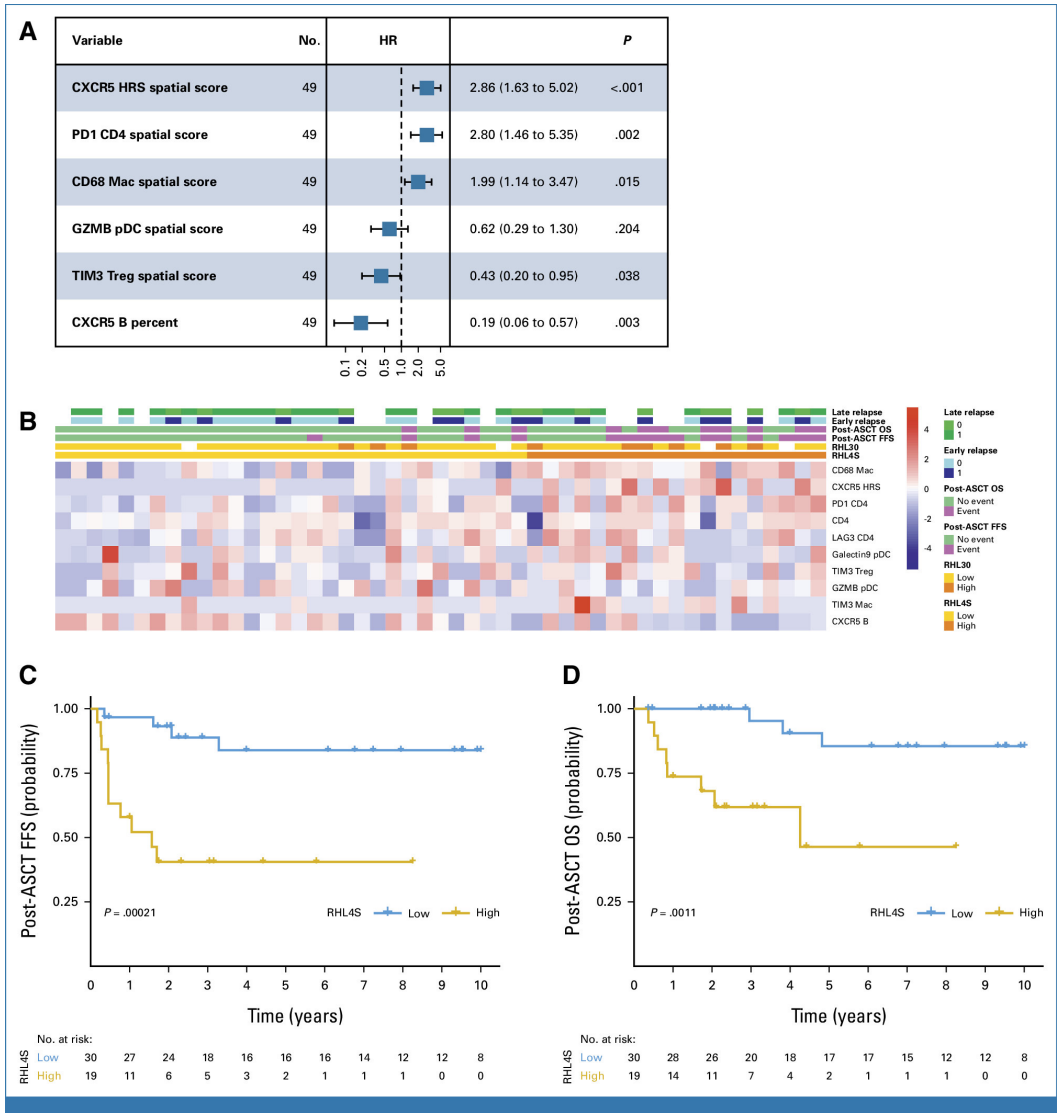
Yang et al. Blood. 2011;118(10):2809-20.
Yang et al. J Clin Invest 2012;122(4):1271-82.
Yang et al. Leukemia. 2014 Sep;28(9):1872-84.

4. Tumor microenvironment: Soluble PD-L1 inhibits T-cell Function at Remote Sites



Jalali et al. Blood Advances. 2018 Aug 14;2(15):1985-1997

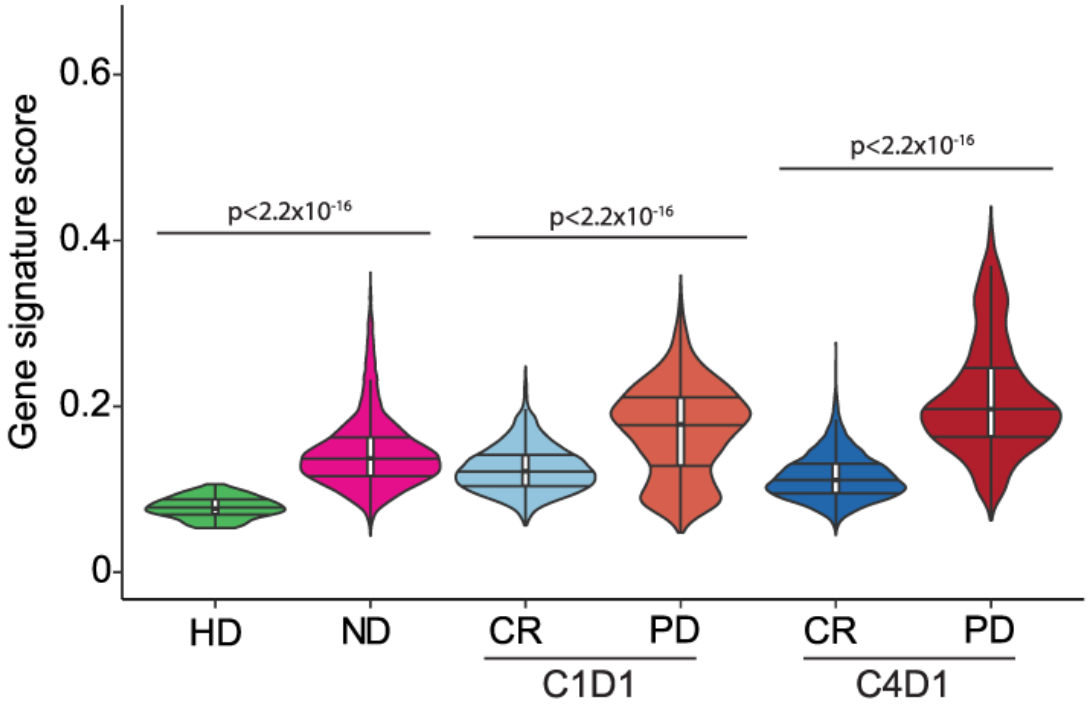
4. Tumor microenvironment - Interaction of CXCR5+ HRS cells with ligand-expressing CXCL13+ macrophages is prognostic



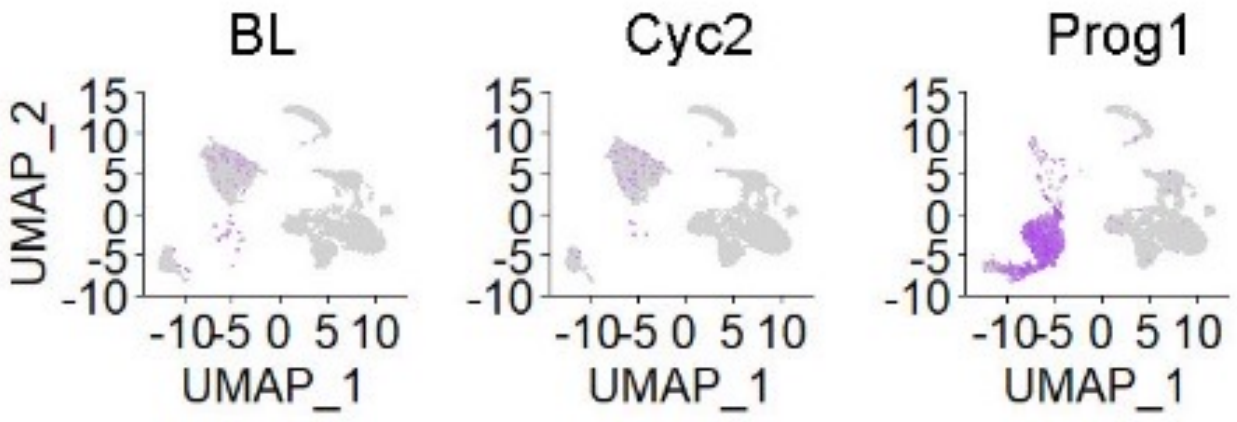
Aoki et al. J Clin Oncol. 2024 Mar 20;42(9):1077-1087.

4. Tumor microenvironment - IL1β⁺ monocytes are associated with lack of response to PD-1 blockade

Hodgkin lymphoma

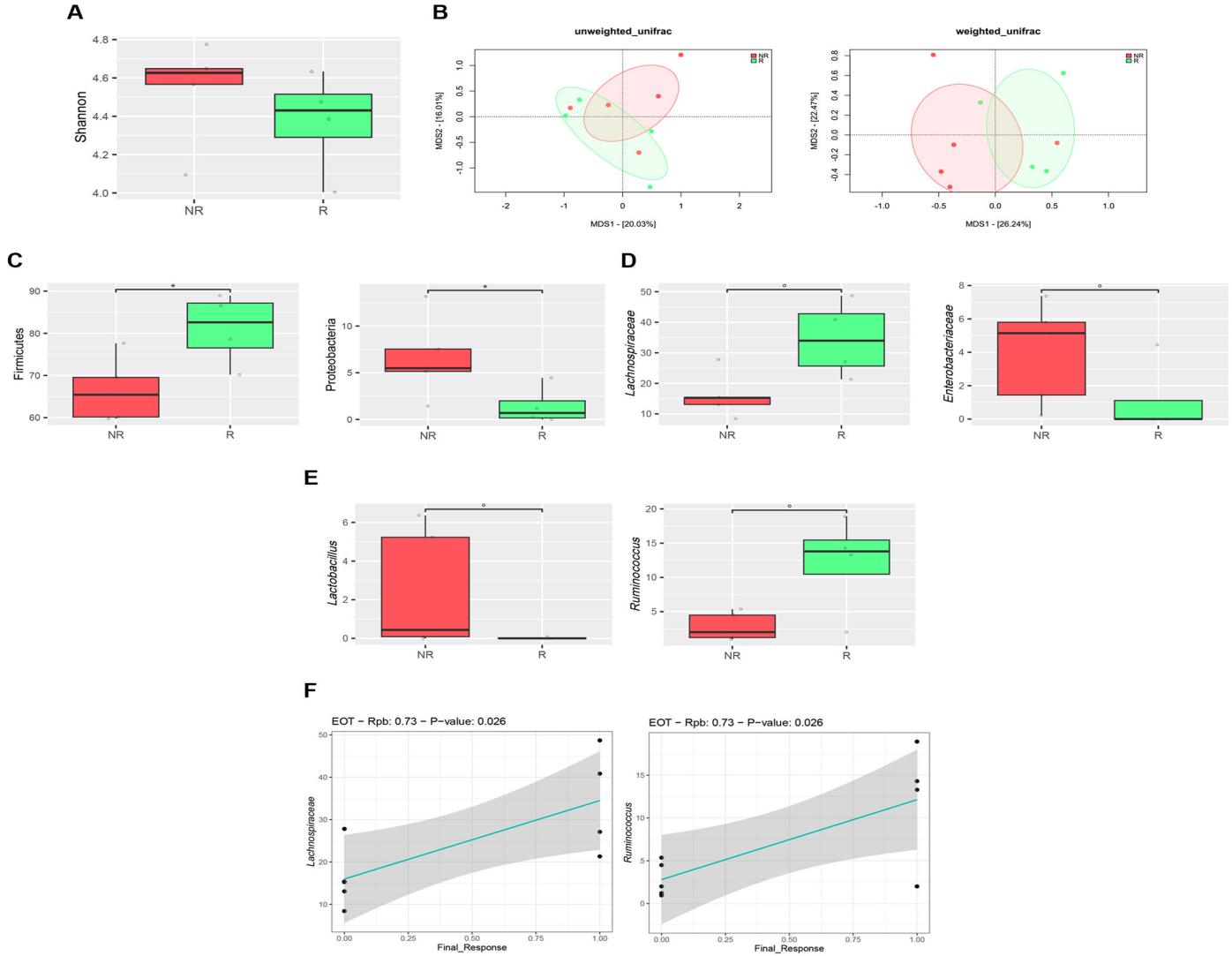


Follicular lymphoma



Paczkowska et al. Nat Commun. 2024 Dec 30;15(1):10740.
Yang et al. 2025 (submitted)

5. Role of gut microbiome in the outcome of lymphoma patients treated with checkpoint inhibitors—The MicroLinf Study

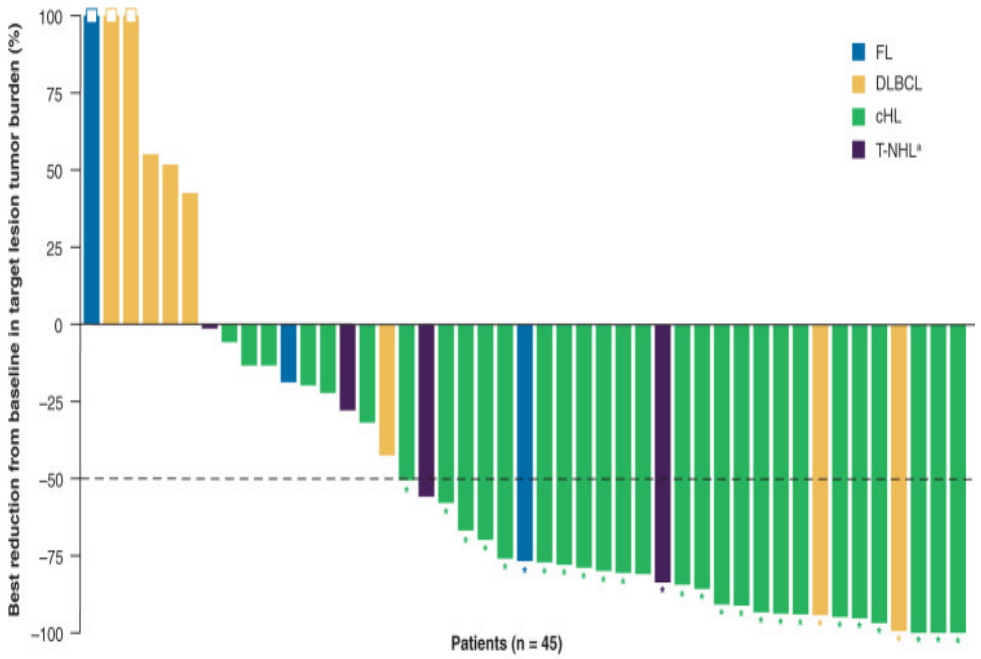


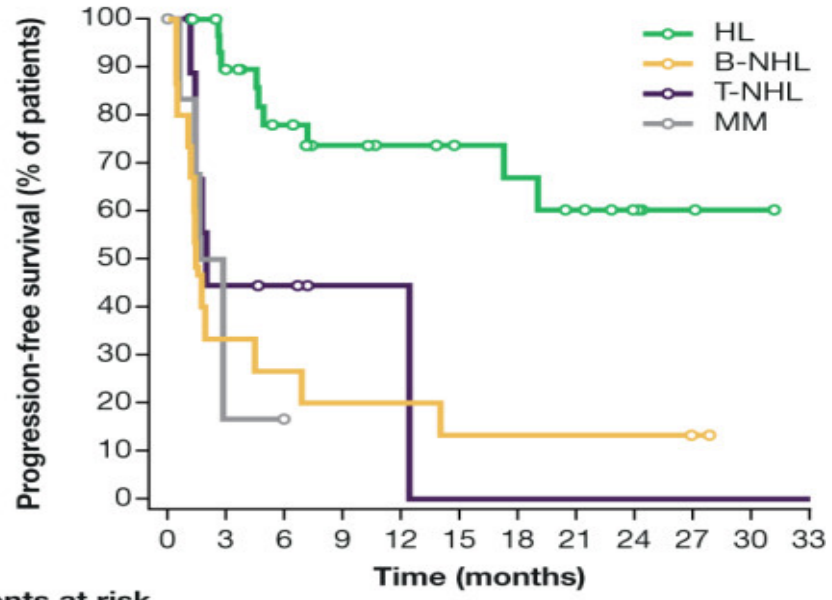
Responding patients showed a significant enrichment of *Lachnospira*

Non-responders showed higher presence of *Enterobacteriaceae*

Casadei et al. Hematol Oncol. 2024 Sep;42(5):e3301.

Strategy #1. Blocking other checkpoints – Nivolumab and Ipilimumab in classic Hodgkin Lymphoma





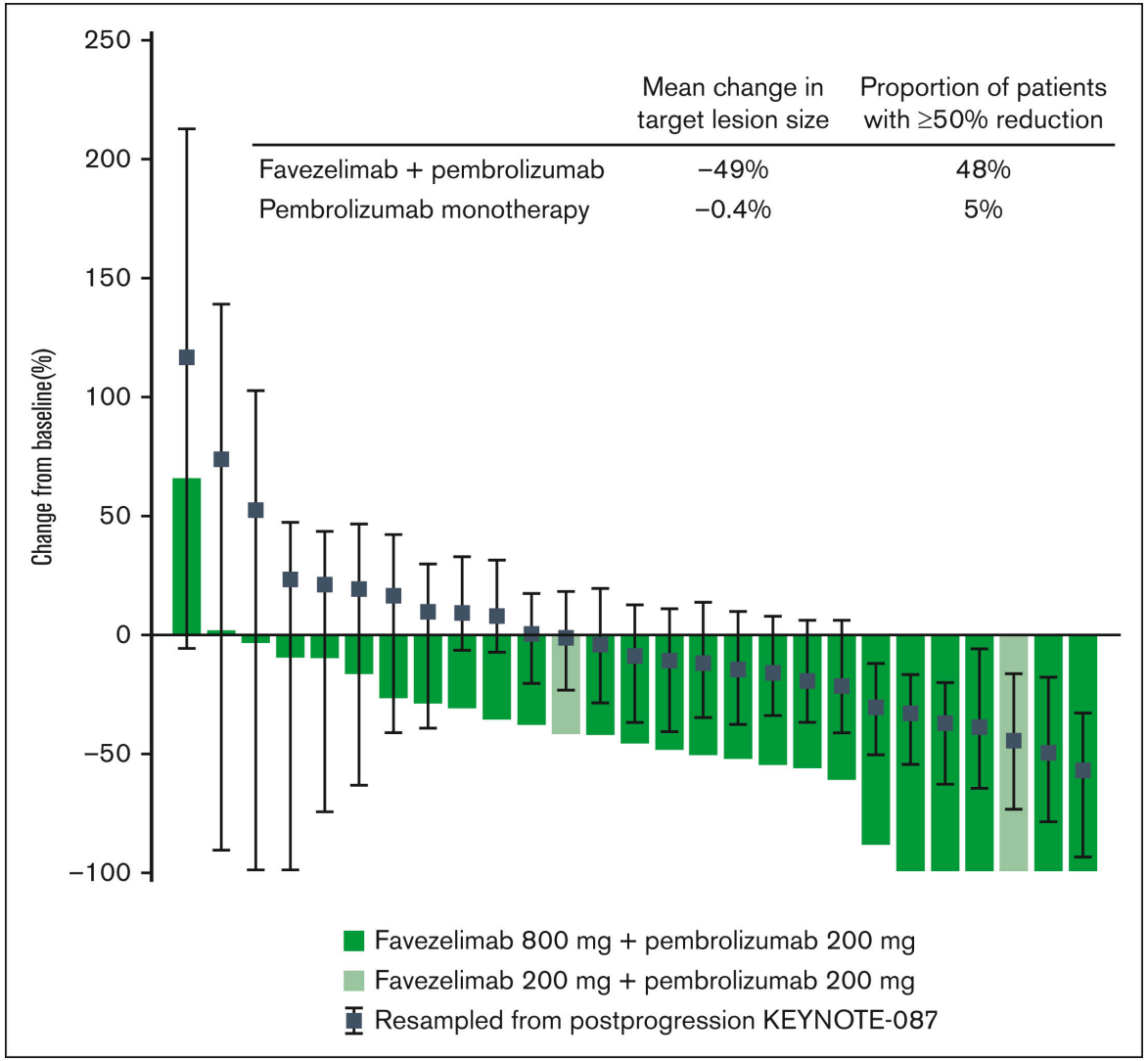
Number of patients at risk

Nivo + Ipi B-NHL	15	5	4	3	3	2	2	2	2	1	0	0
Nivo + Ipi HL	31	25	19	15	13	11	10	7	4	2	1	0
Nivo + Ipi MM	7	1	0	0	0	0	0	0	0	0	0	0
Nivo + Ipi T-NHL	11	4	3	1	1	0	0	0	0	0	0	0

In cHL, ORR was 74% for nivo/ipi, CRRs were 23%.

Armand P, et al. Leukemia. 2021 Mar;35(3):777-786.

Strategy #1. Blocking other checkpoints – Favezelimab (anti–LAG-3) and pembrolizumab in R/R Hodgkin lymphoma



34 patients

10 pts had objective response (ORR, 29%; CR 3 [9%]; PR 7 [21%]).

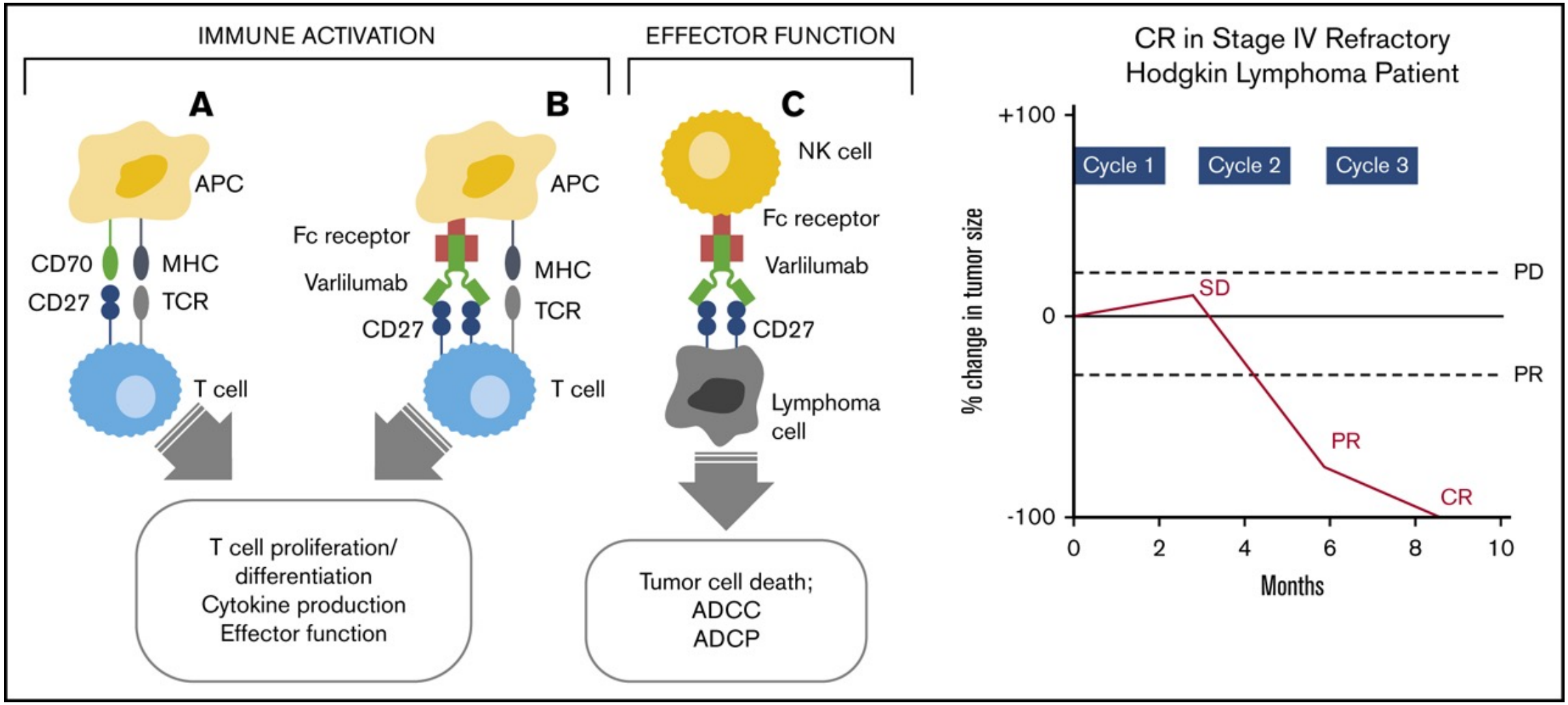
Median PFS was 9.7 months

Best percentage change from baseline in target lesion size shown for participants treated with favezelimab plus pembrolizumab compared with resampled data from participants who received postprogression pembrolizumab in KEYNOTE-087.

Favezelimab contributed substantially to efficacy

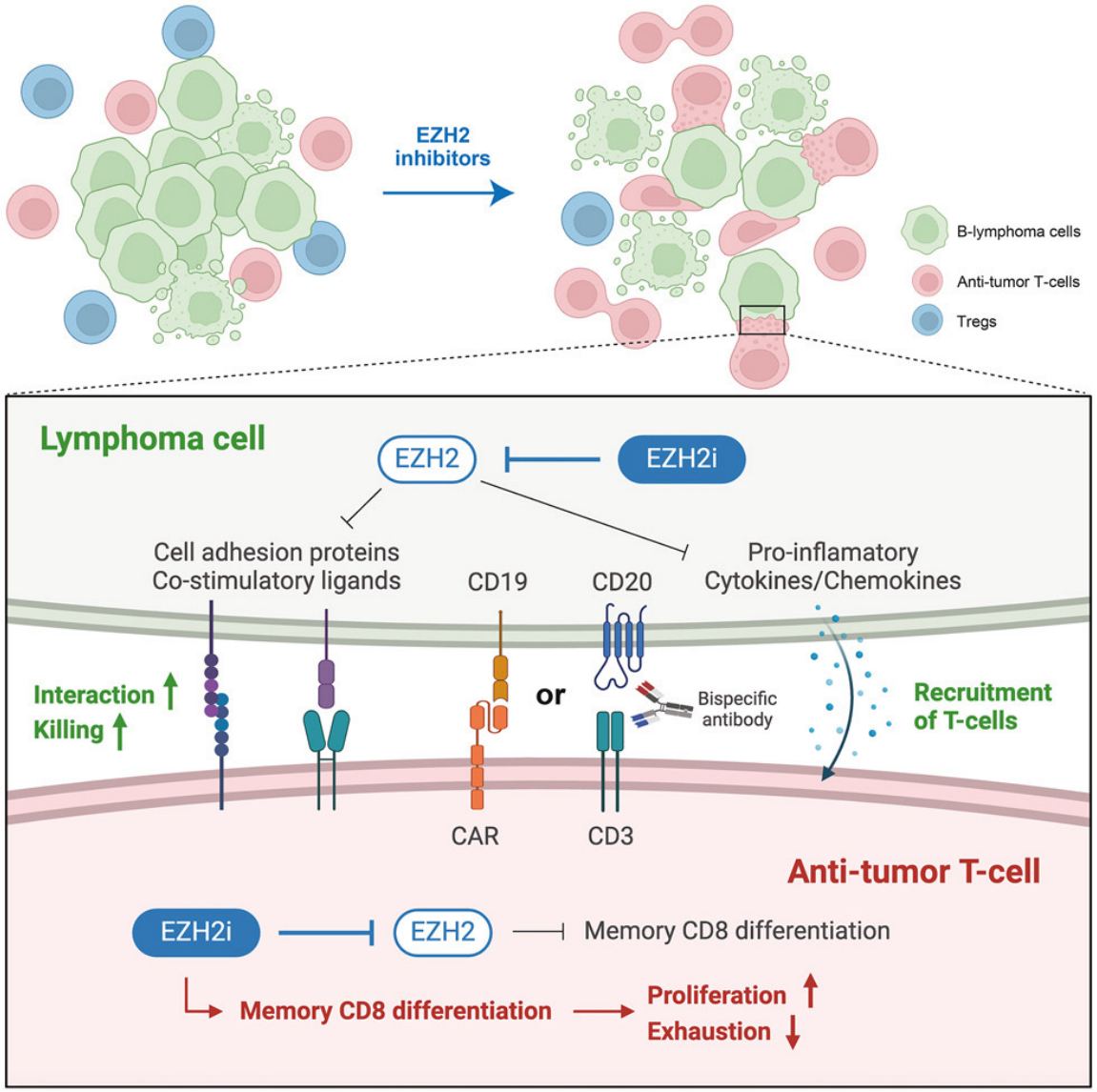
Armand et al. Blood Adv. 2025 Oct 14;9(19):4987-4995.

Strategy #2. Profound T-cell dysfunction - Varlilumab (agonist anti-CD27 antibody) for hematologic malignancies



Ansell SM et al. Blood Adv. 2020 May 12;4(9):1917-1926.

Strategy #3 -EZH2 inhibition enhances Bispecifics by inducing lymphoma immunogenicity and improving T cell function

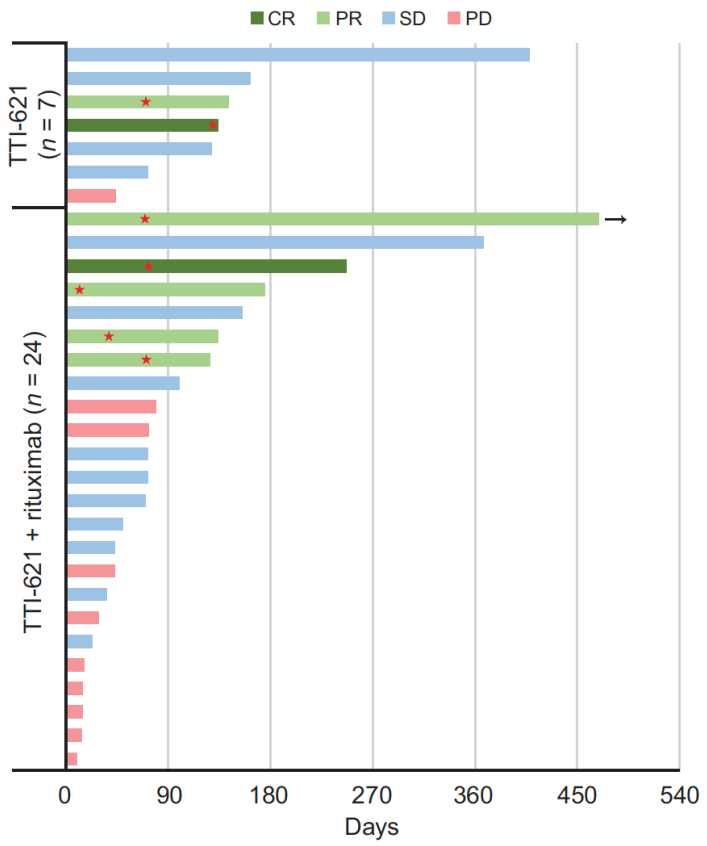


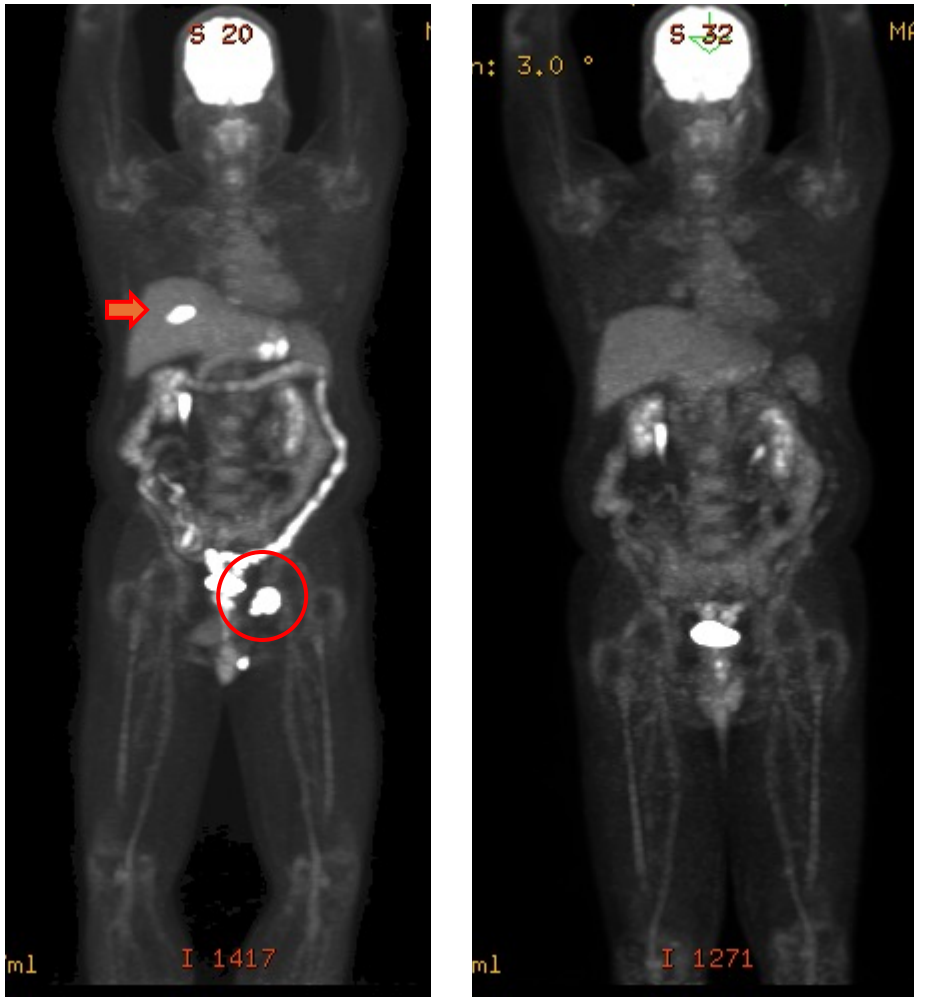
Isshiki et al. Cancer Cell. 2025 Jan 13;43(1):49-68.e9.

Strategy #4. Tumor microenvironment: Phase 1 trial of TTI-621, a novel immune checkpoint inhibitor targeting CD47

Best response in patients with DLBCL

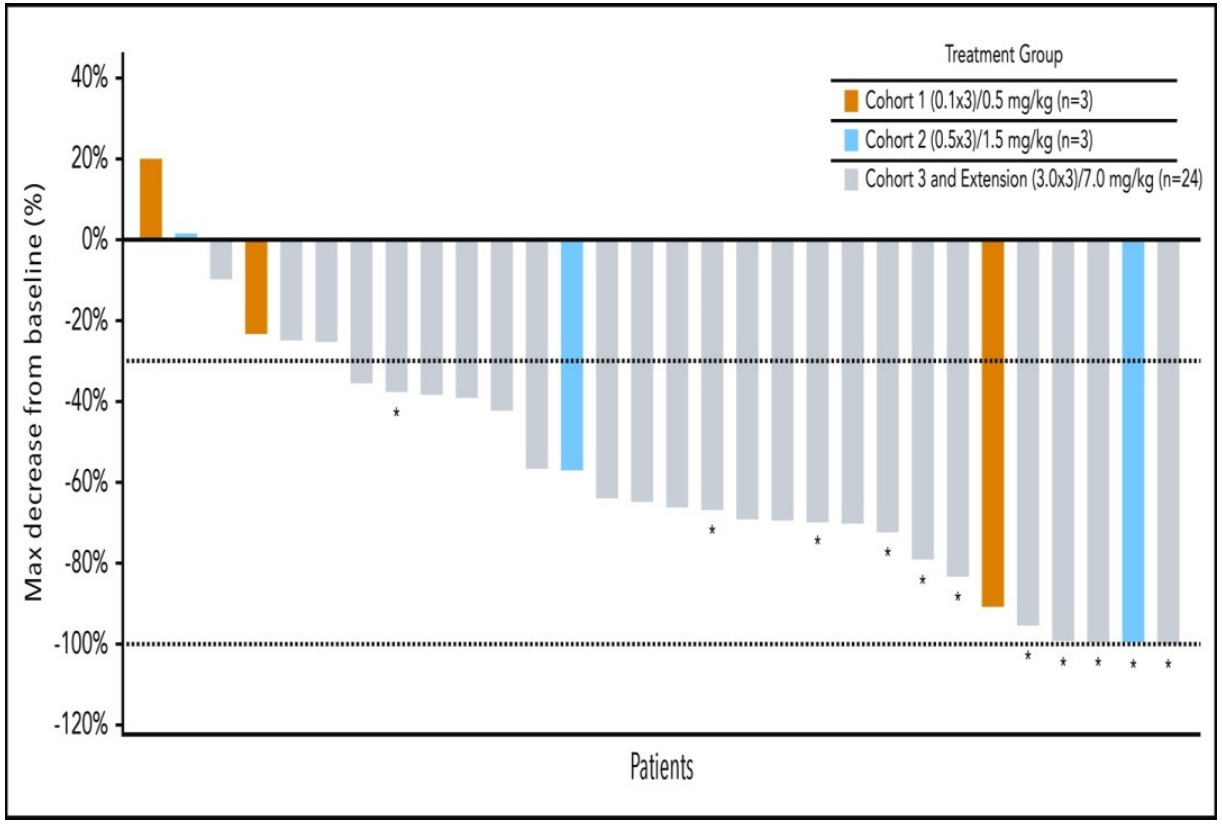
	n	Response, *n* (%)			Median (range) time to response, d	Median (range) treatment duration, d
		CR	PR	Total		
TTI-621	7	1 (14)	1 (14)	2 (29)	106 (78–133)	139 (134–143)
TTI-621 + R	24	1 (4)	4 (17)	5 (21)	77 (21–78)	175 (127–469)
Total	31	2 (6)	5 (16)	7 (23)	78 (21–133)	143 (127–469)

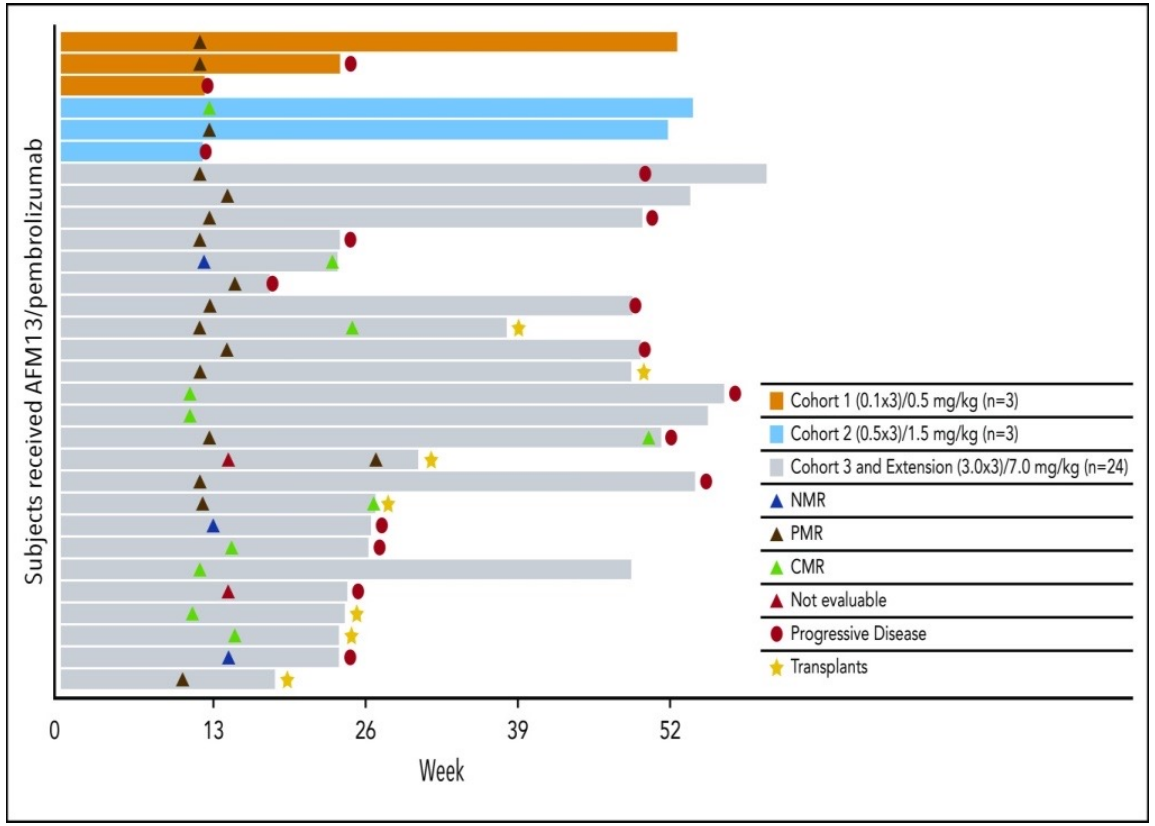




Ansell SM et al. Clin Cancer Res. 2021 Jan 15. doi: 10.1158/1078-0432.

Strategy #4. Tumor microenvironment: Bispecific antibody AFM13 + Pembrolizumab in cHL



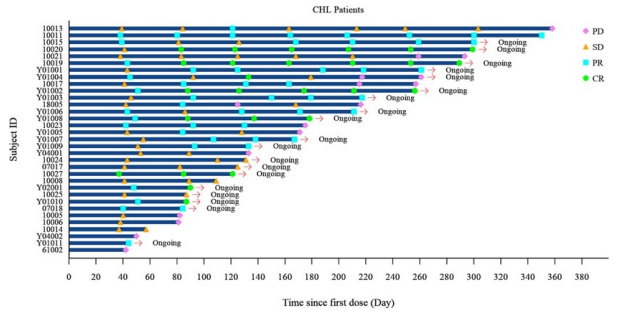


Bartlett NL, et al. Blood. 2020 Nov 19;136(21):2401-2409.

Strategy #4 – Adding Tislelizumab to Timdarpacept (SIRPa-Fc) in cHL patients failing anti-PD-1 therapy

Best Response	N=33
CR, n (%)	8 (24.2)
PR, n (%)	14 (42.4)
SD, n (%)	9 (27.3)
PD, n (%)	2 (6.1)
ORR, n (%)	**22 (66.7)**
DCR, n (%)	**31 (93.9)**

Duration of Response

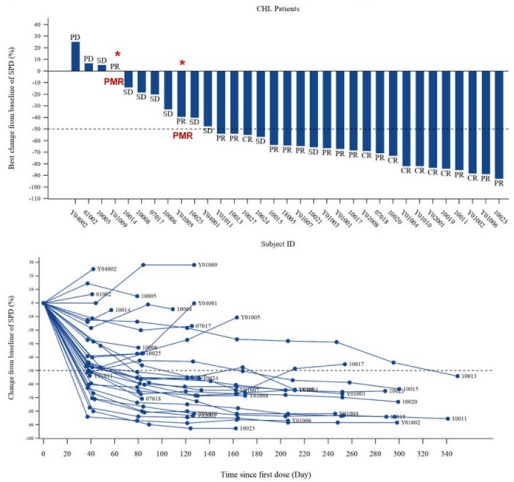


With the median follow-up time of 6.87 months:

- Median progression-free survival (mPFS) was not reached.
- Median duration of response (mDOR) was not reached.

Data cut-off date: March 01, 2024

Tumor Size Change after Treatment

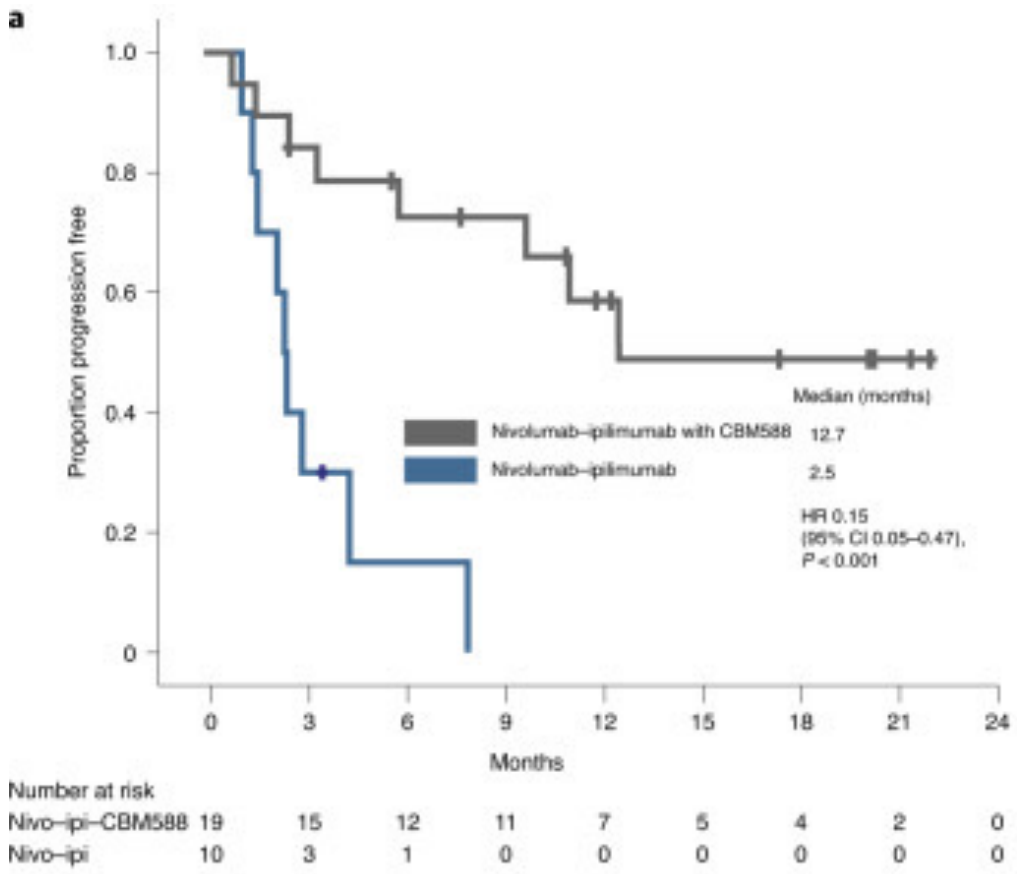


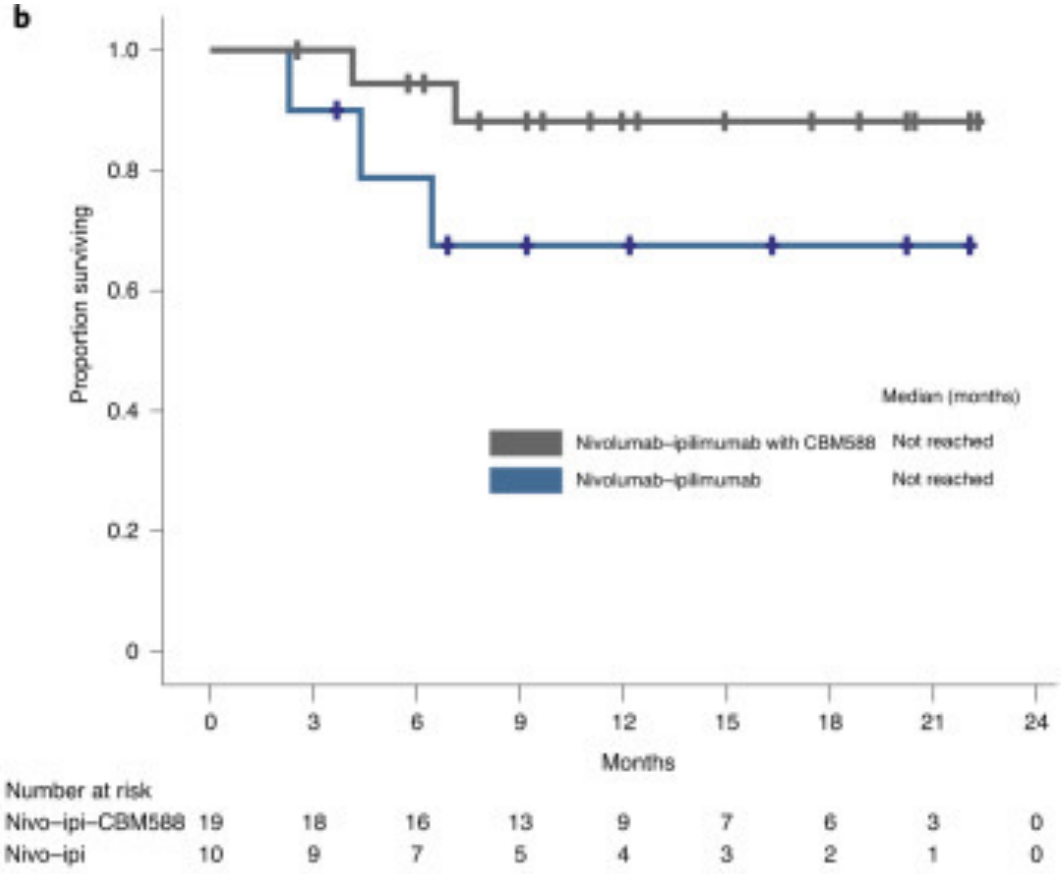
- 87.9% patients had target lesion size reduction.
- Two patients achieved PMR by PET-CT.

Data cut-off date: March 01, 2024

Song et al. J Clin Oncol 42, 2024 (suppl 16; abstr 7017)

Strategy #5 – Nivolumab plus ipilimumab with or without live bacterial supplementation in metastatic renal cell carcinoma





Dizman et al. Nat Med. 2022 Apr;28(4):704-712.

How to overcome resistance to immune checkpoints

1. Other checkpoints involved
    - Blocking multiple checkpoints has promise

2. T-cell not activated/profound T-cell dysfunction
    - May need to replace immune dysfunctional cells

3. Tumor genetics
    - Could be modulated by EZH2 inhibition

4. Tumor microenvironment/soluble ligands
    - Opportunity to engage the innate immune system

5. Microbiome
    - Could change the fecal (or skin) microbiome

Acknowledgements

Lab members -

Zhi-Zhang Yang

JC Villasboas

Patrizia Mondello

Xinyi Tang

Prithviraj Mukherjee

Hyo Jin Kim

Anne Novak

Grant funding –

National Institutes of Health, Lymphoma Research Foundation, International Waldenstrom Macroglobulinemia Foundation, Predolin Foundation.