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Microenvironment in HL and its relevance in response to therapy

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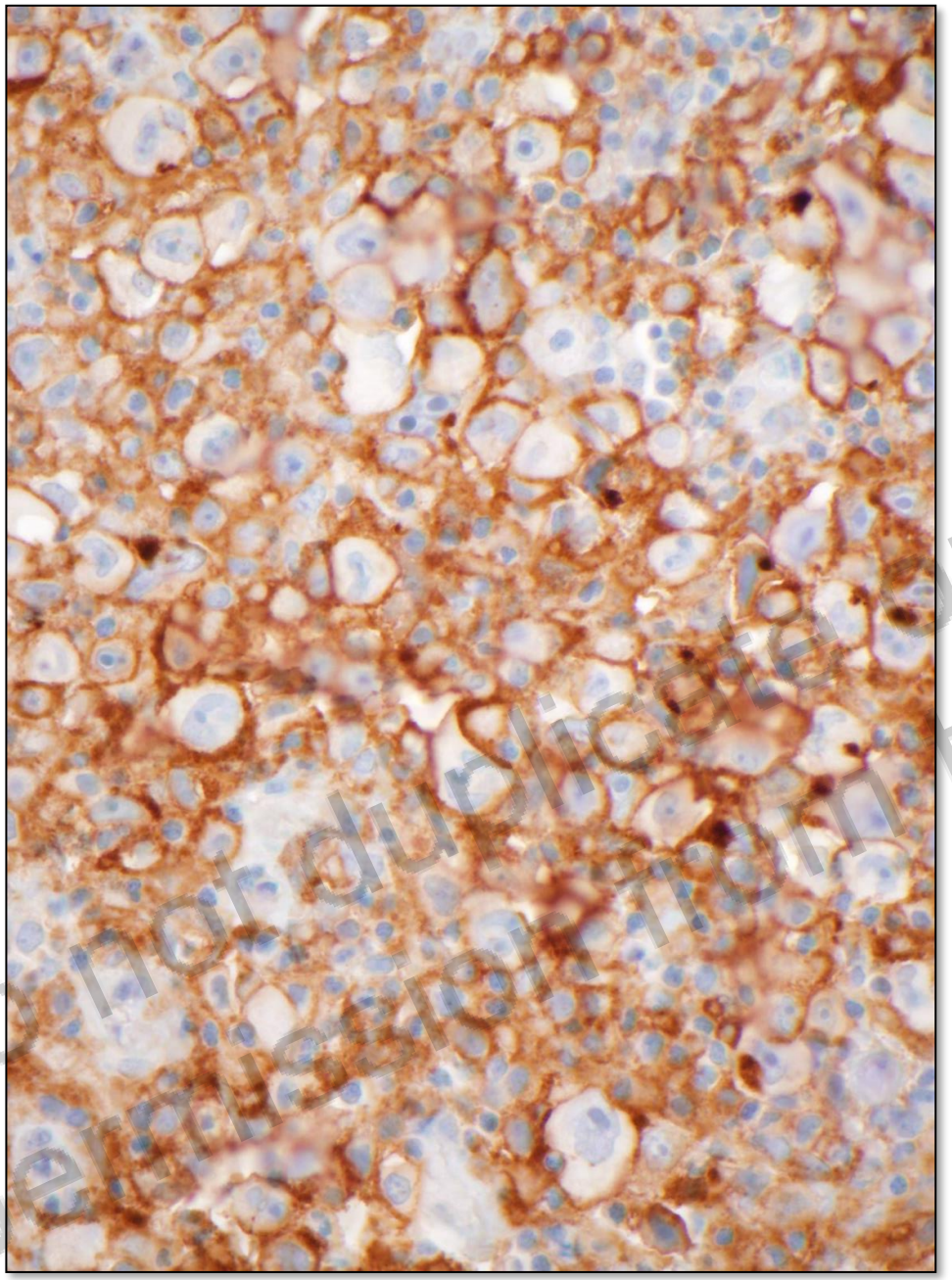
Discussant: **Dr Astrid Pavlovsky**, Clinical Research Center – FUNDALEU, Buenos Aires, Argentina



Microenvironment in HL and its Relevance to Therapy

Margaret Shipp

Dana-Farber Cancer Institute

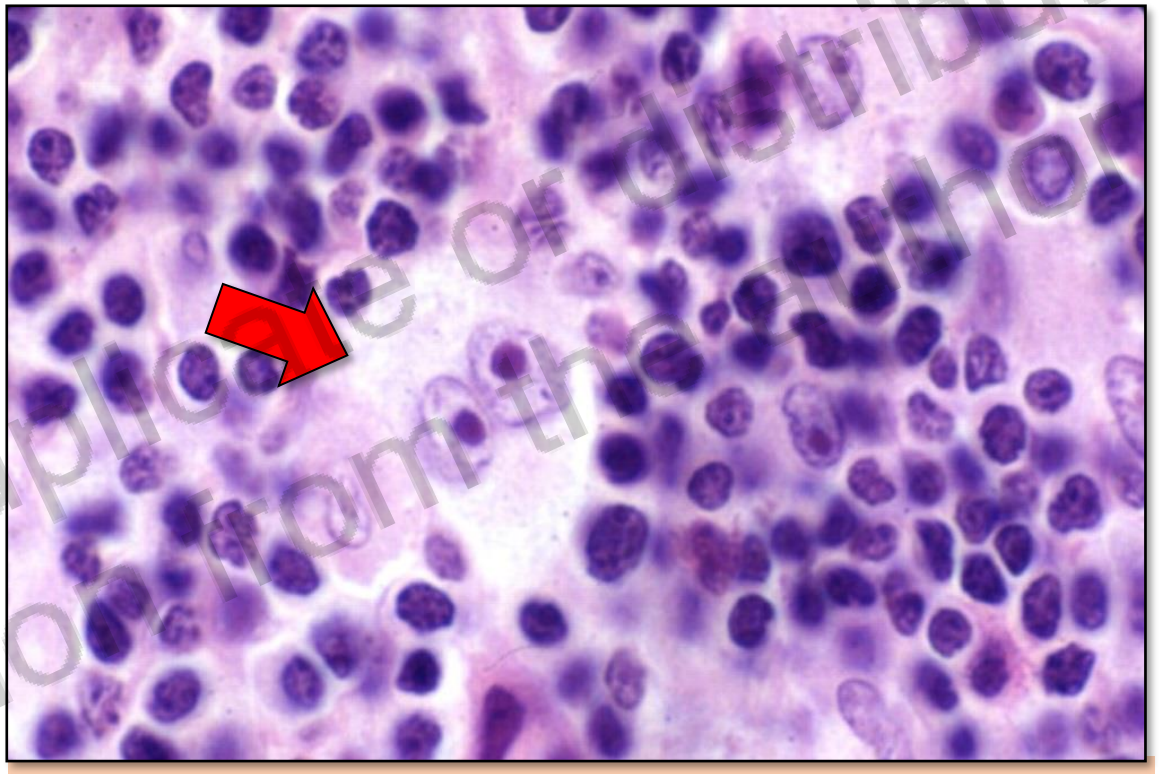
Harvard Medical School

DISCLOSURES

Name of Company	Research support	Consultant	Advisory Board
Bristol-Myers Squibb	X		X
Merck	X		
AstraZeneca	X		X
Immunitas		X	
Bayer	X (Institution)		
Abbvie	X (Institution)		

Classic Hodgkin Lymphoma

Primary tumors contain small numbers of malignant Reed-Sternberg cells within an extensive T-cell rich inflammatory/ immune cell infiltrate.

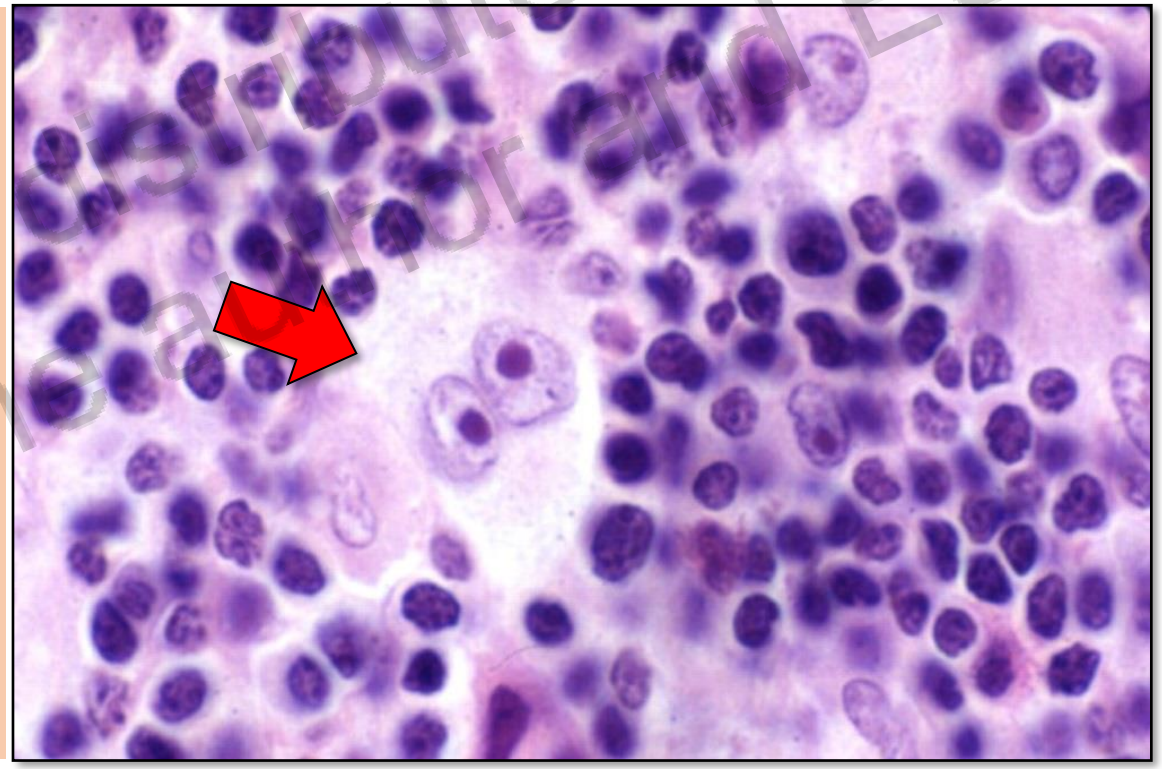


Until recently, there was no evidence of an effective anti-tumor immune response.

Kadin, *ASH Image Bank* 2002; 2002:100484

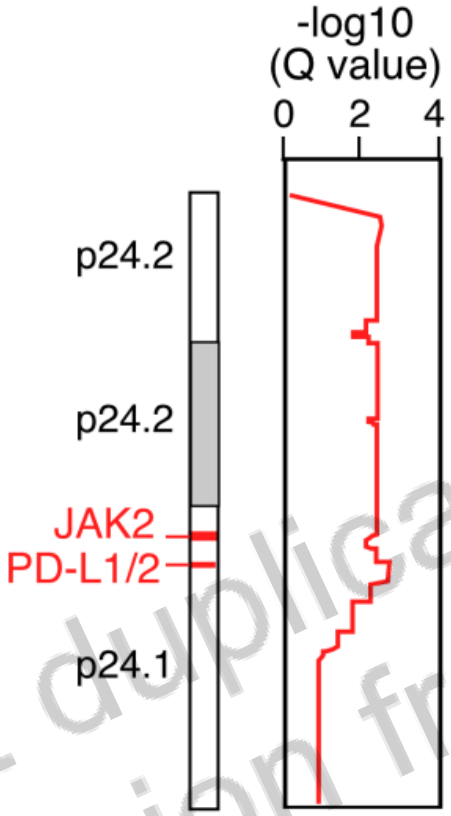
Classic Hodgkin Lymphoma

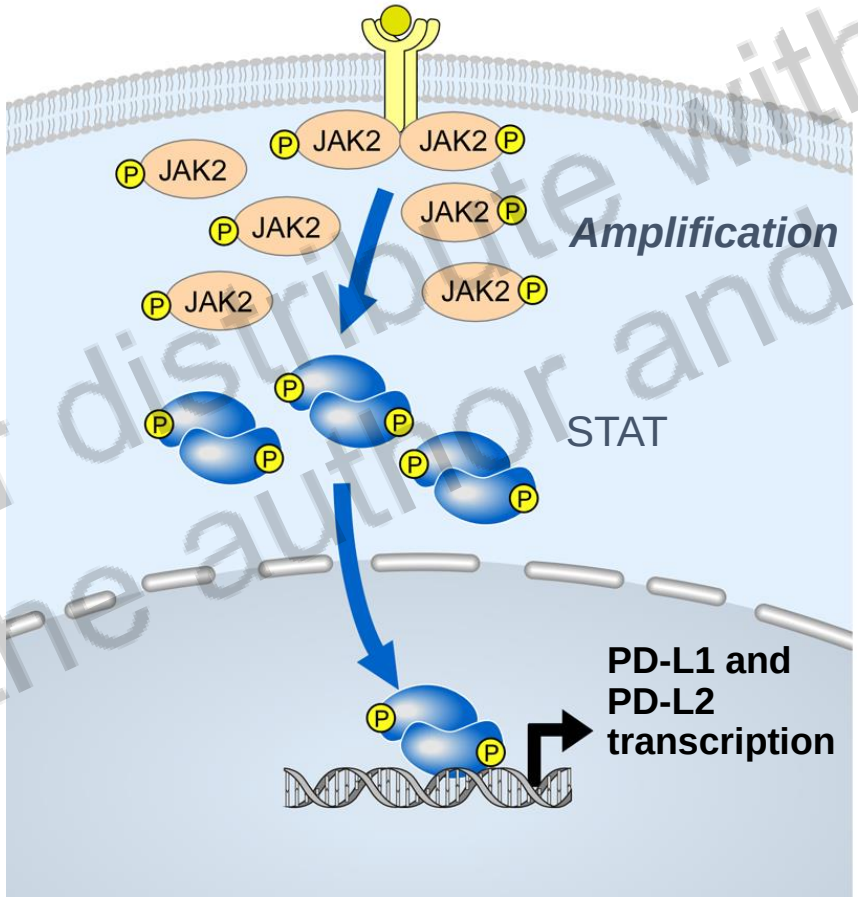
Our goal:
Review new insights into the genetics and tumor immune microenvironment of Hodgkin lymphoma that have transformed the treatment of patients with cHL



Kadin, *ASH Image Bank* 2002; 2002:100484

9p24.1 Amplicon Block in Hodgkin Lymphoma

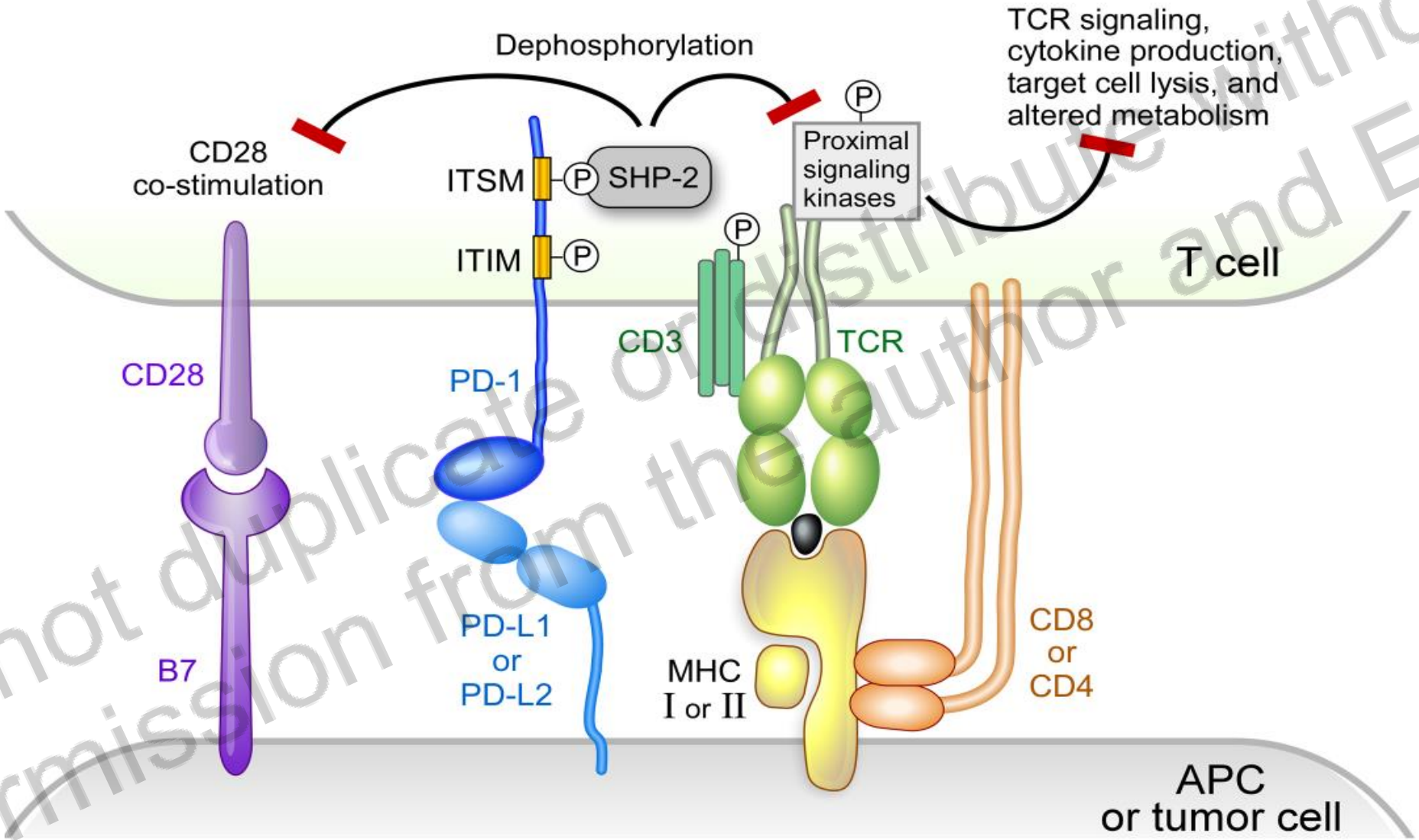




***PD–L1* and *PD-L2* copy gain and further induction via JAK2/STAT signaling**

Green et al., *Blood* 2010;116:3268
Hao et al., *Clin Cancer Res* 2014;20:2674

PD-1 Signaling



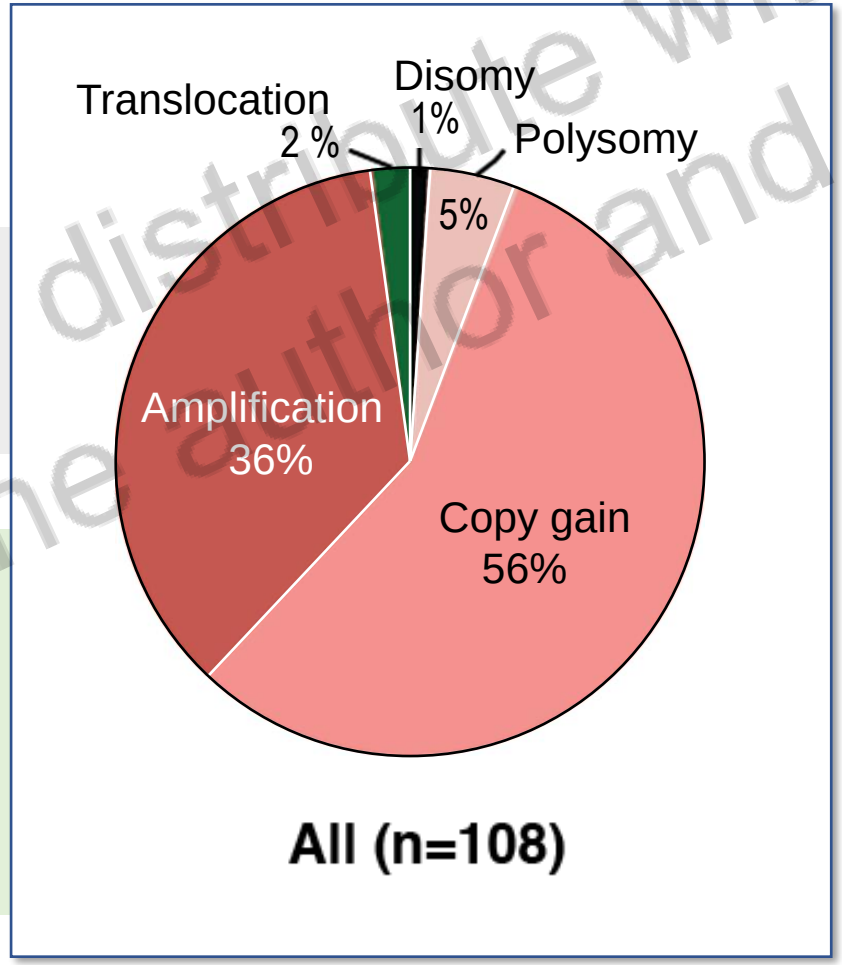
Modified from Baumeister et al., *Annu. Rev. Immunol* 2016;34:539-73

Chromosome *9p24.1/PD-L1/PD-L2* Copy Number Alterations a Defining Feature in Newly Diagnosed Hodgkin Lymphoma

Cases were classified by the highest observed level of 9p24.1 alteration

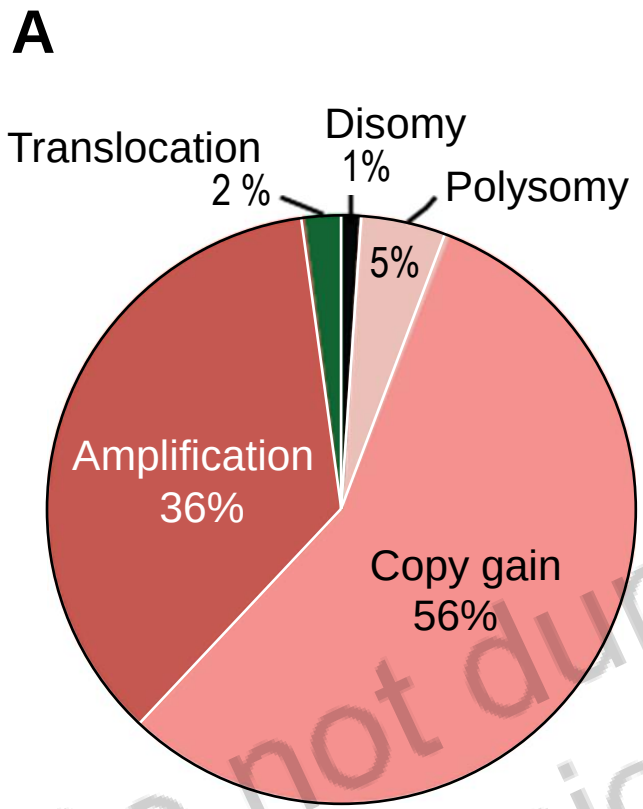
107/ 108 cases had 9p24.1 alterations

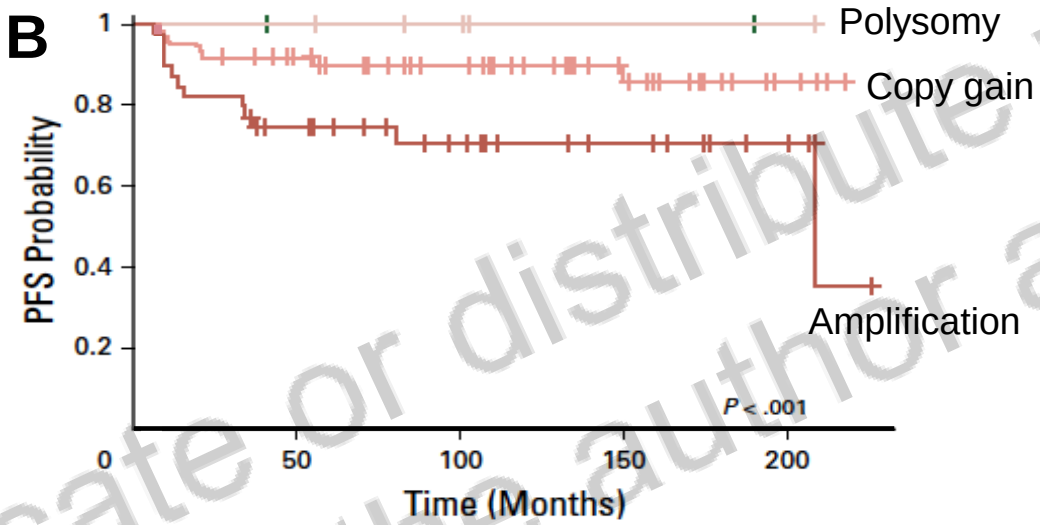
Genetic basis for sensitivity to PD-1 blockade?



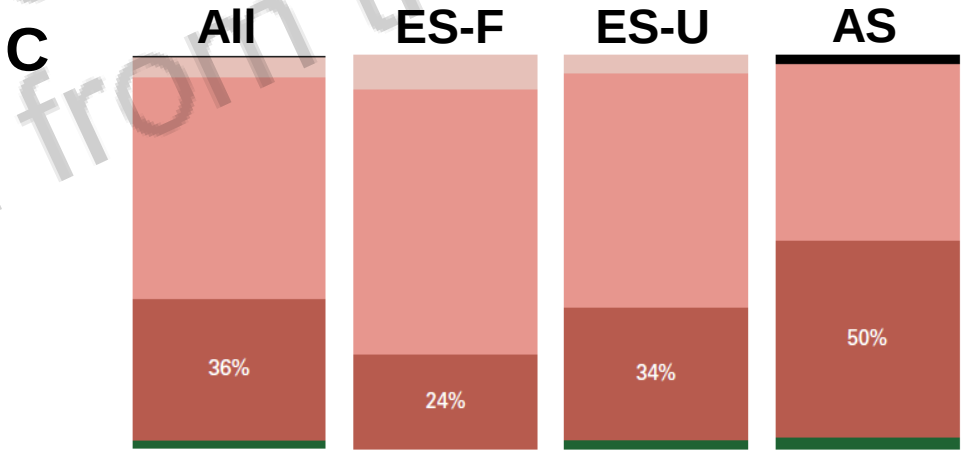
Roemer et al., *J Clin Oncol* 2016;34:2690-7

Chromosome 9p24.1 Amplification, Advanced Stage and Inferior Outcome Following Standard Induction Therapy





Chromosome 9p24.1 amplification associated with inferior PFS



Increased incidence of 9p24.1 amplification in patients with advanced stage disease

Roemer et al., *J Clin Oncol* 2016; 34:2690-7

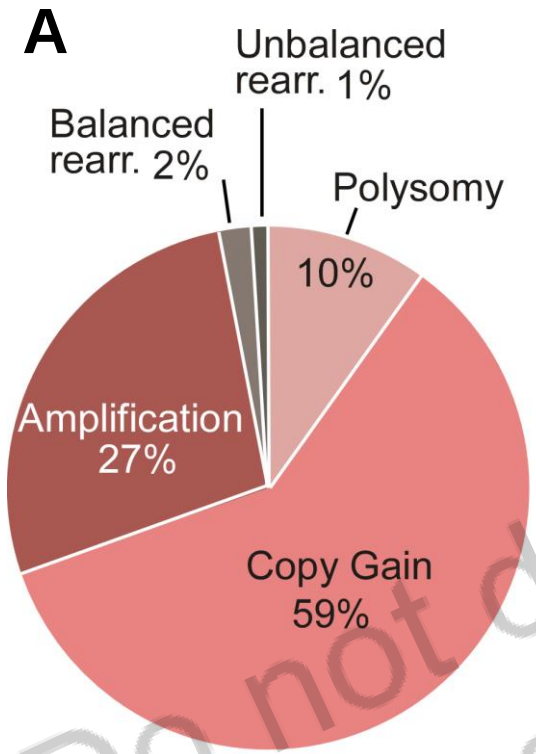
PD-1 Blockade in Patients with Relapsed/Refractory Hodgkin Lymphoma

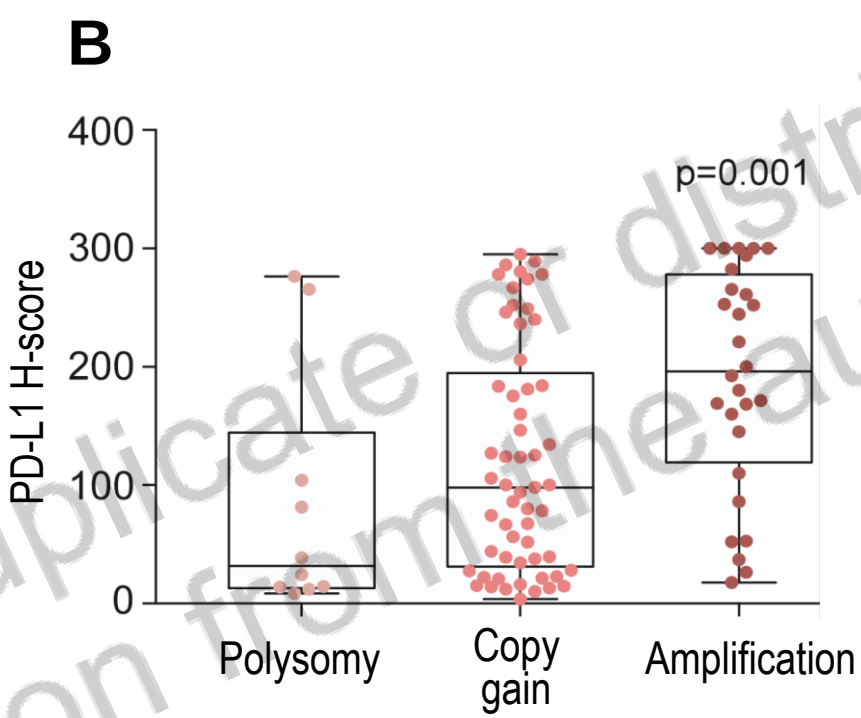
- Patients with R/R and otherwise incurable cHL who received PD-1 blockade had overall response rates of ~70% and median progression-free survivals of ~15 mos, with a subset of durable complete remissions.

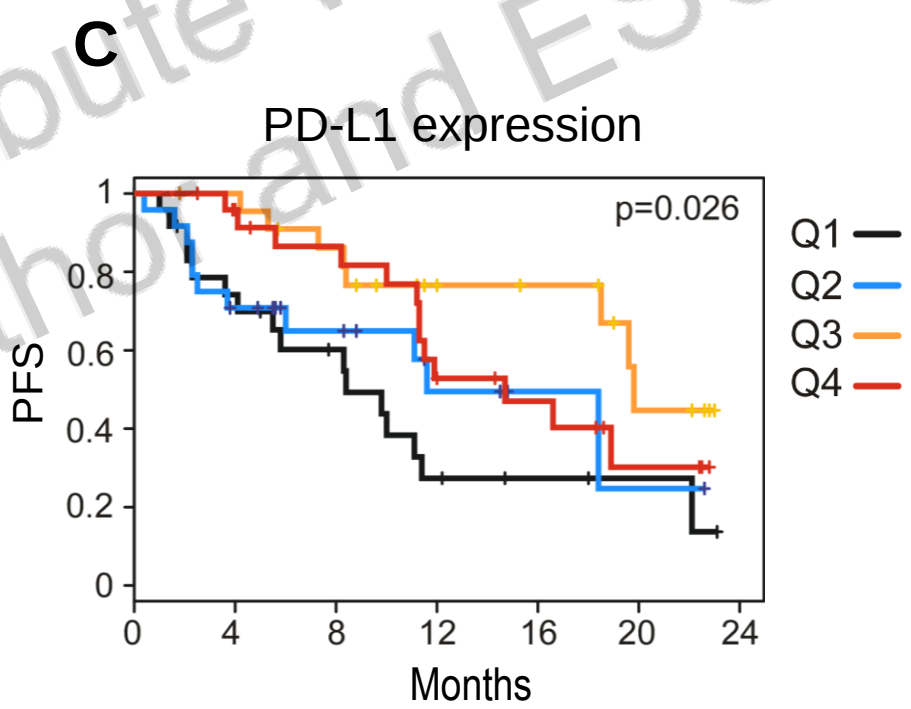
[1]Ansell et al., *N Engl J Med.* 2015
[2]Younes et al., *Lancet Oncol.* 2016
[3]Armand et al., *J Clin Oncol.* 2016
[4]Chen et al., *J Clin Oncol* 2017
[5]Armand et al., *J Clin Oncol.* 2018

- Findings led to promising trials of PD-1 blockade in combination and at earlier points in therapy – ASCT consolidation, first relapse, induction therapy.

Chromosome 9p24.1 Alterations, PD-L1 Expression and Outcome in Patients with Relapsed/refractory cHL Treated with Nivolumab (Checkmate 205)







- PD-1 ligand (PD-L1) expression associated with magnitude of 9p24 copy gain and progression-free survival

Roemer et al., *J Clin Oncol* 2018;36:942-950

PD-1 Blockade in Patients with Relapsed/Refractory Hodgkin Lymphoma

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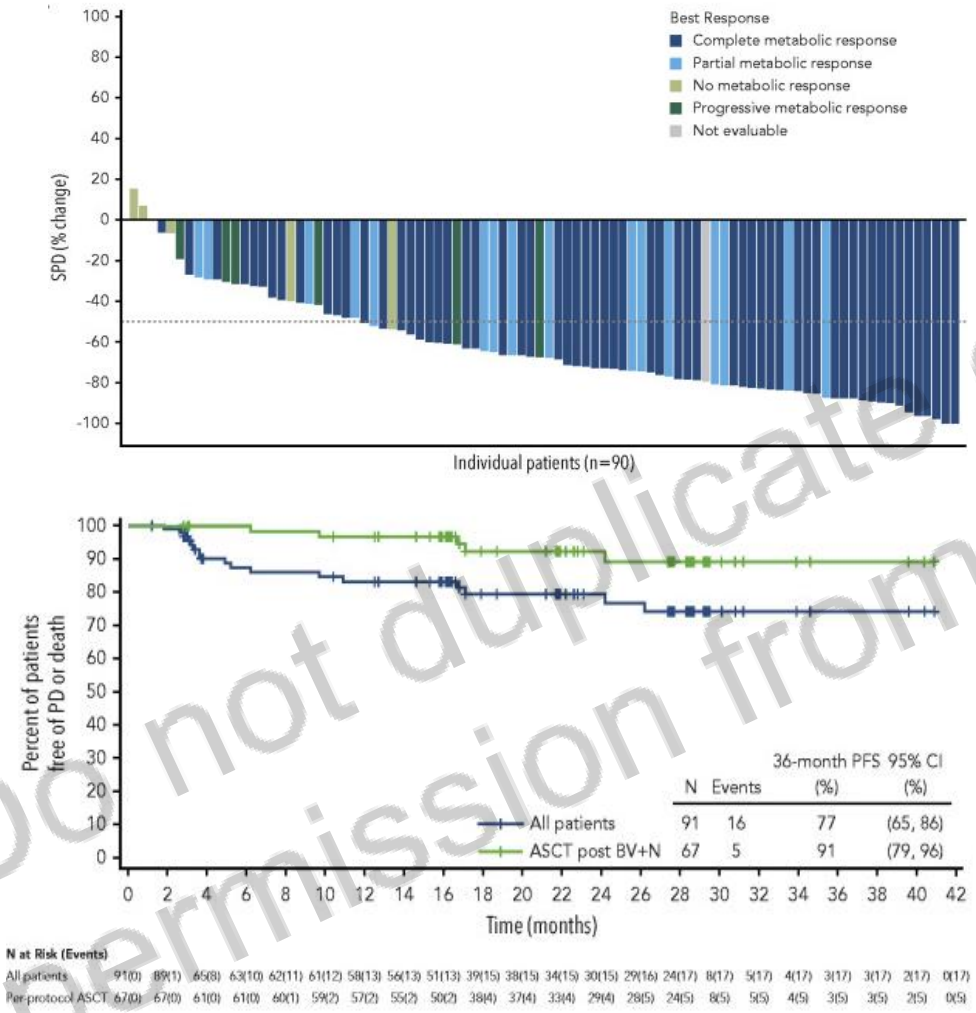
[1]Ansell *et al., N Engl J Med 2015;372:311-9*
[2]Younes *et al., Lancet Oncol 2016;17:1283-94*
[3]Armand *et al., J Clin Oncol 2016;34:3733-3739*
[4]Chen *et al., J Clin Oncol 2017;35:2125-32*
[5]Armand *et al., J Clin Oncol 2018;36:1428-1439*

- Findings led to promising trials of PD-1 blockade in combination and at earlier points in therapy – ASCT consolidation, first relapse, frontline treatment.

Nivolumab Plus Brentuximab Vedotin as Salvage Therapy in Relapsed Hodgkin Lymphoma



- Patients received 4 cycles of nivolumab and BV with option for subsequent ASCT.
- ORR 85% with 67% CRs.
- Estimated 3yr PFS rate 77% for all patients and 91% for patients undergoing ASCT.

Advani et al., *Blood* 2021;138:427-438

Pembrolizumab Plus GVD as Salvage Therapy for Relapsed or Refractory cHL

- Patients received pembro/GVD chemotherapy for 2- 4 cycles followed by ASCT.
- ORR 100% and CR rate 95%
- 95% of patients proceeded to HDT/ASCT.
- All transplanted patients remain in remission (med. post-tx follow up 13.5 mos).

Moskowitz et al., *J Clin Oncol* 2021;39:3109-3117

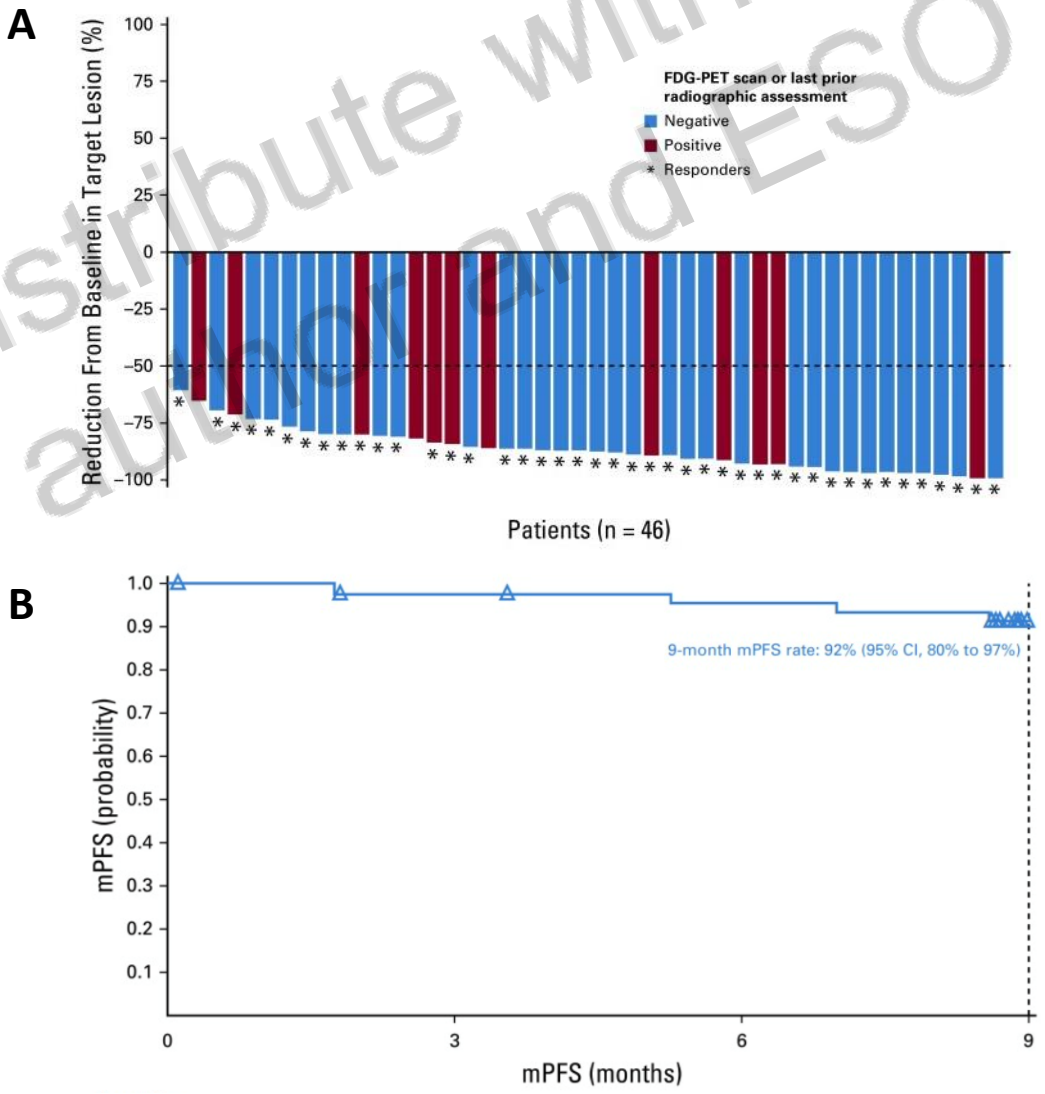
Rationale for Adding PD-1 Blockade to Induction Therapy

- Advanced stage associated with inferior outcome to standard induction therapy
- 9p24.1/*PD-L1/PD-L2* amplification associated with unfavorable outcome to standard induction therapy
- 9p24.1/*PD-L1/PD-L2* amplification more common in advanced stage patients
- More favorable responses to PD-1 blockade in patients with relapsed/ refractory cHL who have high-level 9p24.1 alterations and increased PD-L1 expression
- PD-1 blockade (nivolumab) and AVD as induction therapy for patients with advanced stage (and bulky IIB) disease

Roemer et al., *J Clin Oncol* 2016;34:2690-2697
Roemer et al., *J Clin Oncol* 2018;36:942-950
Ramchandren et al., *J Clin Oncol* 2019;37:1997-2007

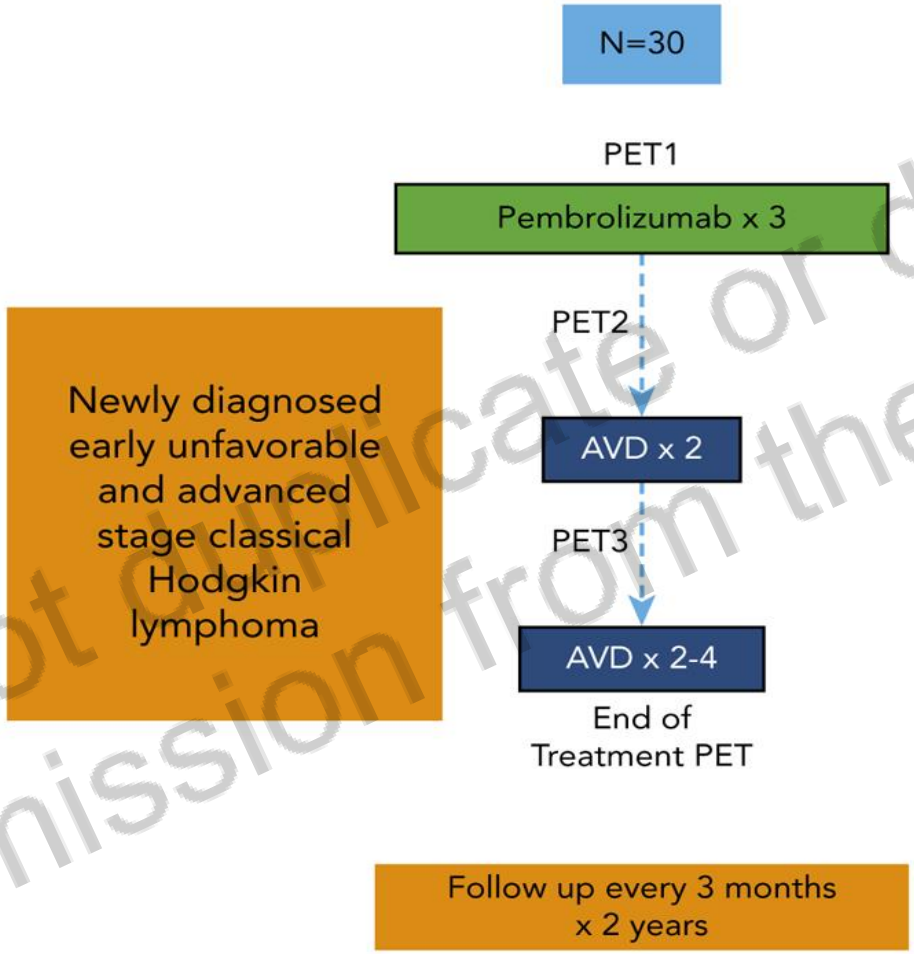
Nivolumab plus AVD for Newly Diagnosed Advanced Stage and Bulky IIB Hodgkin Lymphoma

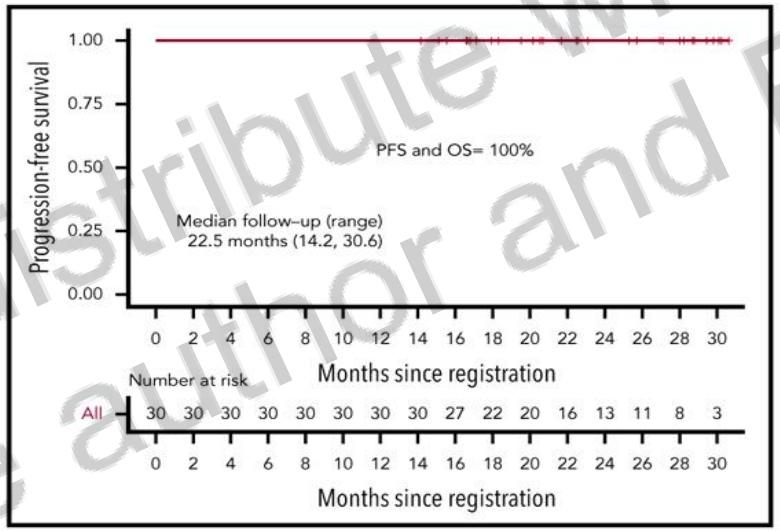
- Single-agent nivolumab (N, 4 doses) followed by N/AVD (6 cycles)
- ORR was 84% with 67% CRs
- 9-month modified progression-free survival 92%
- Patients with higher-level HRS cell expression of PD-L1 had more favorable responses to N/AVD (p=.04).

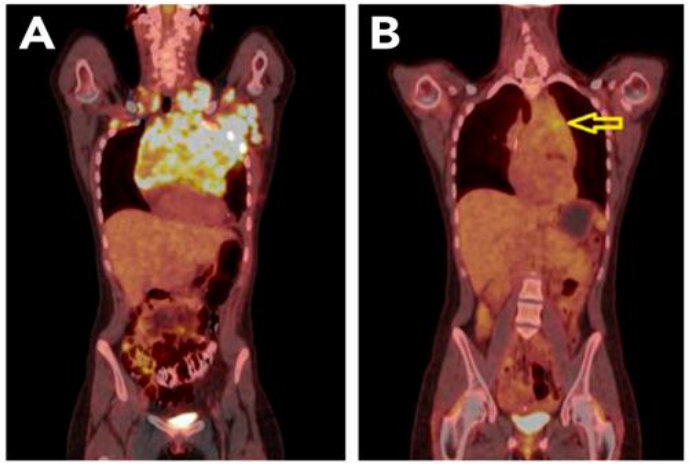


Ramchandren et al., *J Clin Oncol* 2019;37:1997-2007

Pembrolizumab Followed by AVD for Newly Diagnosed Early Stage Unfavorable and Advanced Stage Hodgkin Lymphoma





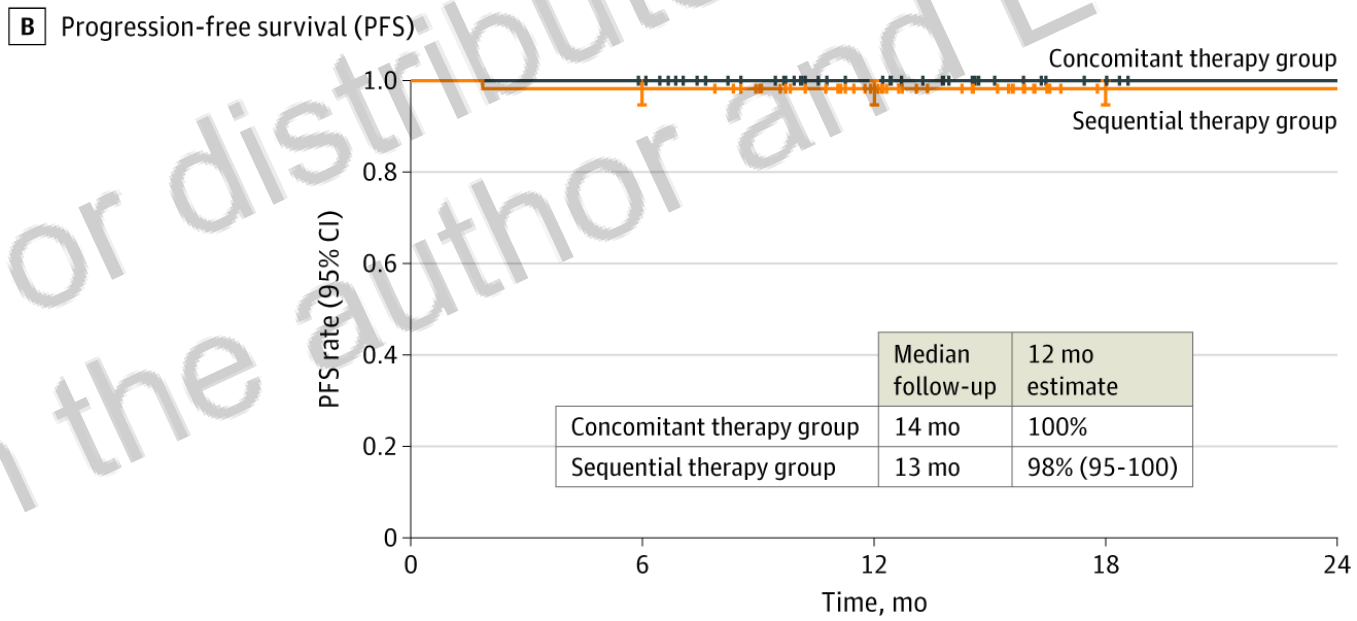


Response to single-agent pembrolizumab

Allen et al., *Blood* 2021;137:1318-1326

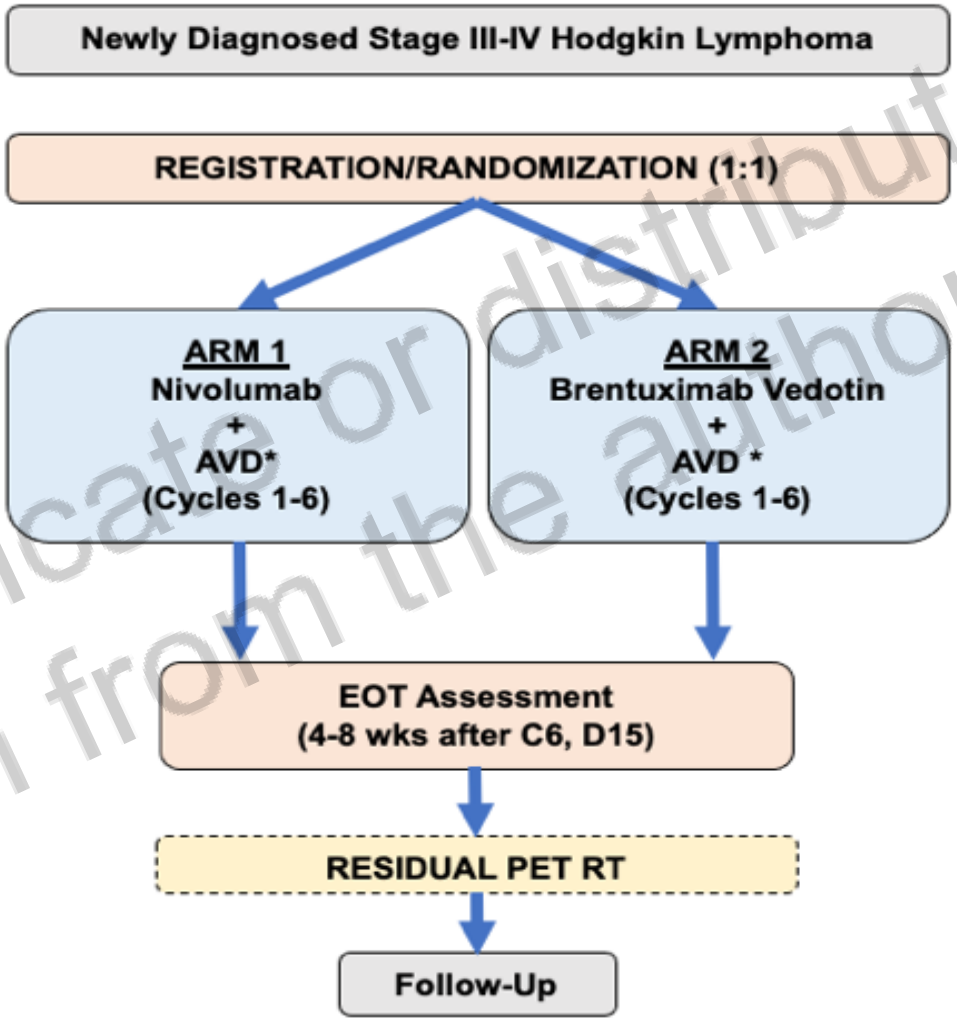
Nivolumab and AVD for Newly Diagnosed Early Stage Unfavorable Hodgkin Lymphoma

- Concomitant (4 cycles of N-AVD) or sequential (4 nivolumab, 2 N-AVD, 2 AVD) therapy followed by ISRT.
- Patients receiving concomitant therapy or sequential therapy had CR rates of 90% and 94%.
- Patients receiving concomitant or sequential therapy had 12 mo PFS of 100% and 98%.



Bröckelmann et al., *JAMA Oncol* 2020;6:872-880

Phase III Trial of Nivolumab/AVD versus Brentuximab/AVD in Newly Diagnosed Advanced Stage Hodgkin Lymphoma



*Doxorubicin, vinblastine, and dacarbazine.

SWOG S1826, NCT03907488 A. Herrera and J. Friedberg, PIs

Mechanisms of Response and Resistance to PD-1 Blockade in cHL

- Comprehensive genetic analyses of cHL
- Analyses of clinically annotated biopsies and peripheral immune cell signatures from patients treated with PD-1 blockade (nivolumab, CheckMate 205 registration trial)
- Analyses of the intact tumor microenvironment and primary tumor cell suspensions by multiplex imaging

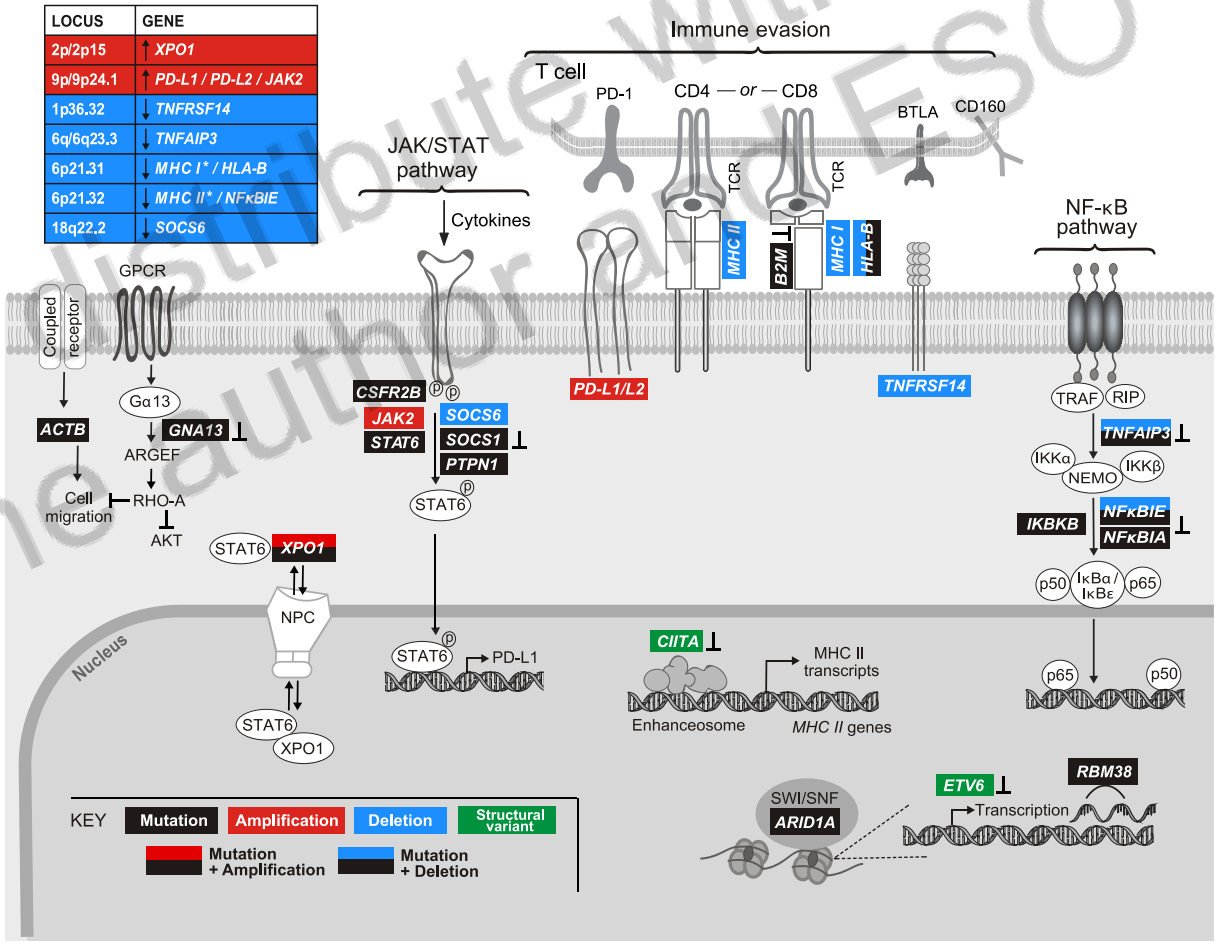
Genetic Bases of Immune Evasion in Hodgkin Lymphoma

1) Copy gain of 9p24.1/ *PD-L1, PD-L2* and *JAK2*

2) Additional genetic bases of increased JAK/STAT signaling - *STAT6* mutations, *SOCS1* mutations

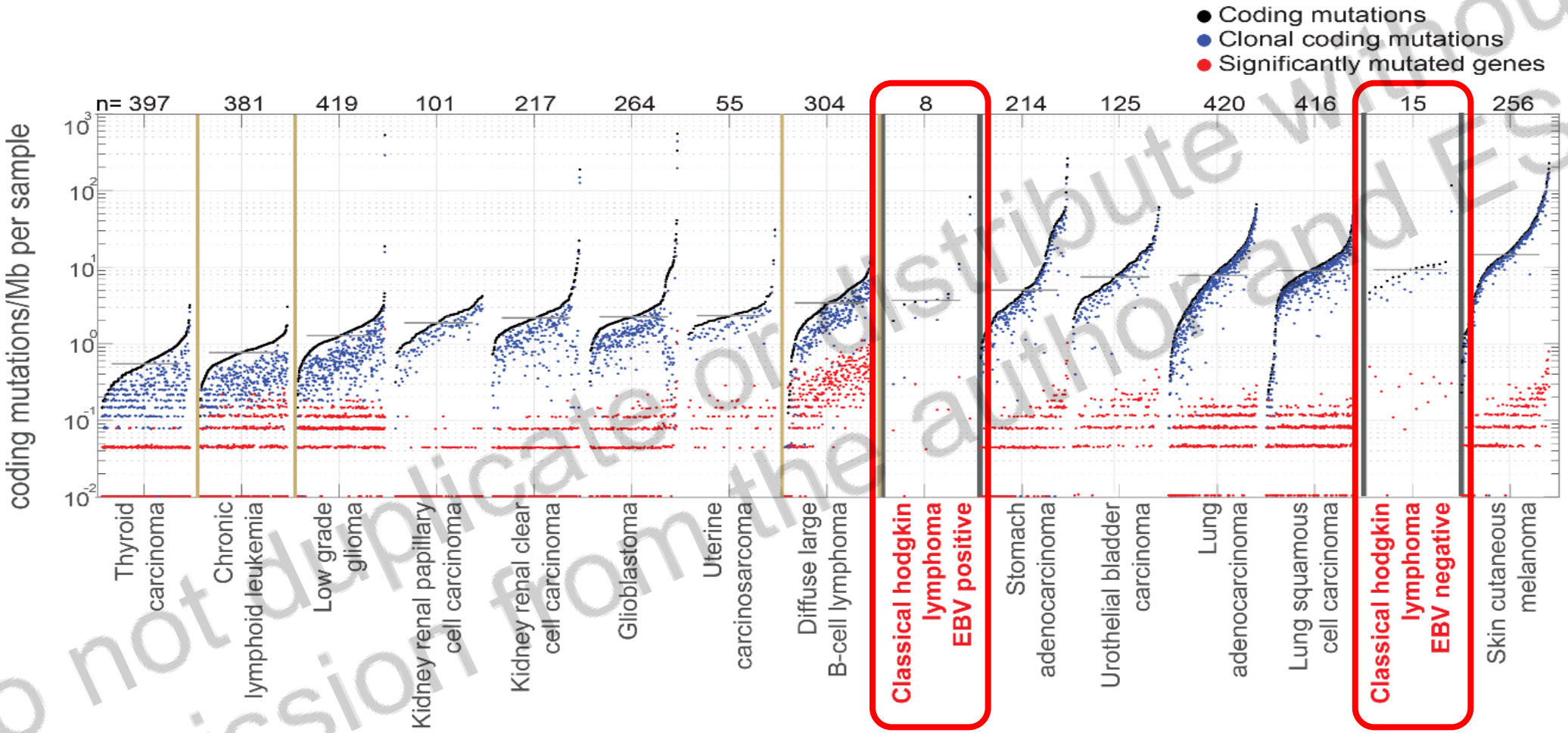
3) Alterations of antigen presentation machinery

- MHC class I (CD8$^+$ T cells)
  - *B2M* mutations and copy loss
  - *MHC-I* copy loss, *HLA-B* mutations
- MHC class II (CD4 $^+$ T cells)
  - *MHC II* copy loss
  - *CIITA* rearrangements
- Genetic bases of defective MHC class I antigen presentation more common in EBV- cHL



Wienand et al., *Blood Advances* 2019;3:4065-4080

High Mutational Burden in Hodgkin Lymphoma



- EBV-negative cHLs have an extremely high mutational burden.
- Increased incidence of microsatellite instability

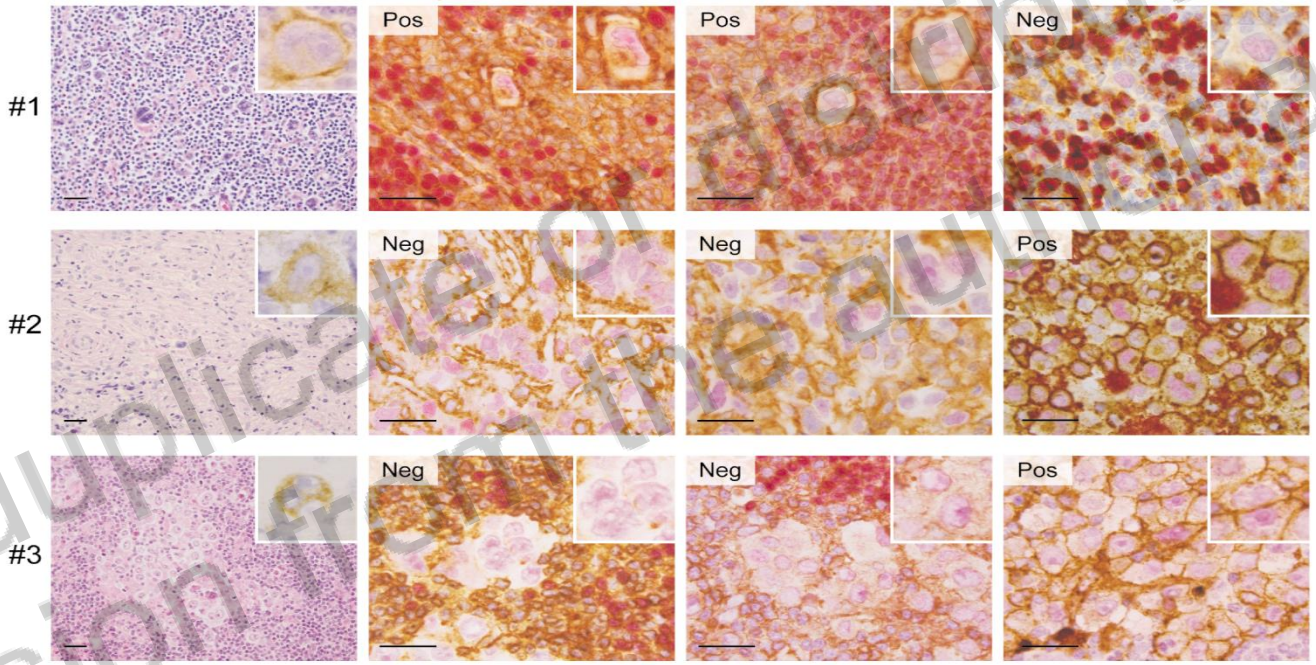
Wienand et al., *Blood Advances* 2019;3:4065-4080

Perturbed β2-Microglobulin, MHC Class I and II Expression in Hodgkin Lymphoma – Checkmate 205

A

	β2M	MHC class I	MHC class II
Negative	51 (71%)	46 (64%)	21 (29%)
Decreased	16 (22%)	21 (29%)	23 (32%)
Positive	5 (7%)	5 (7%)	28 (39%)

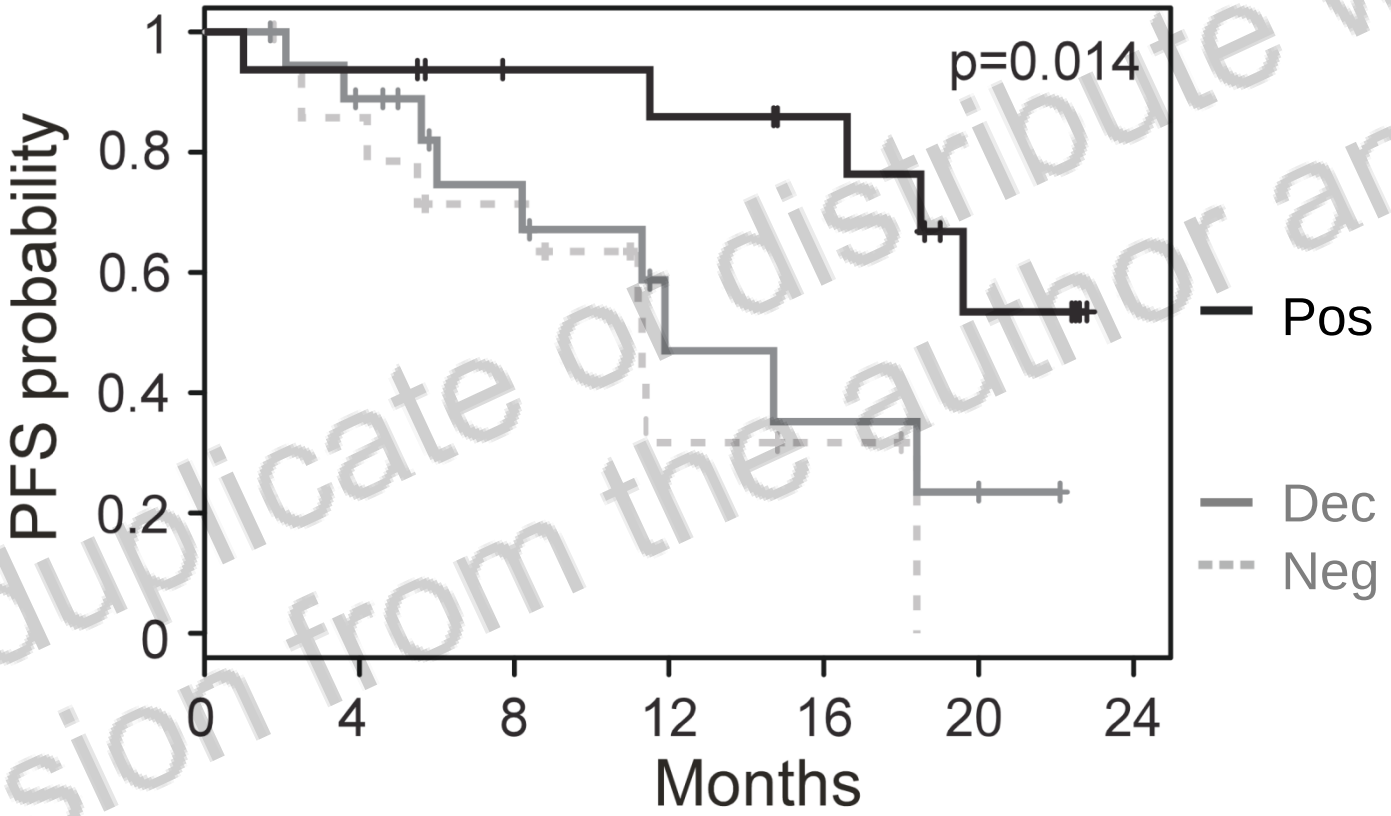
B



- Only 7% of cases positive for HRS cell expression of MHC class I.
- Tumor antigen presentation by MHC class I and CD8+ cytotoxic T cells unlikely to be playing a major role in the efficacy of PD-1 blockade in HL.

Roemer et al., *Cancer Immunol Res* 2016;4:910-916
Roemer et al., *J Clin Oncol* 2018;36:942-950

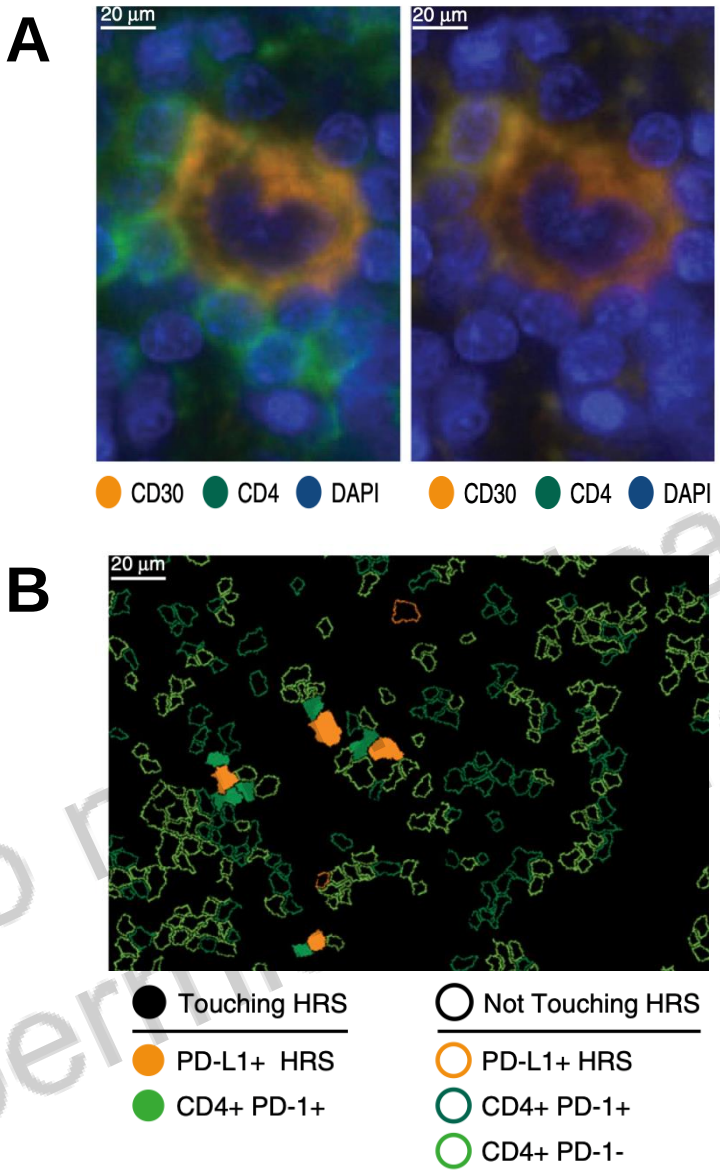
MHC Class II Expression is Predictive of Response to PD-1 Blockade - CheckMate 205

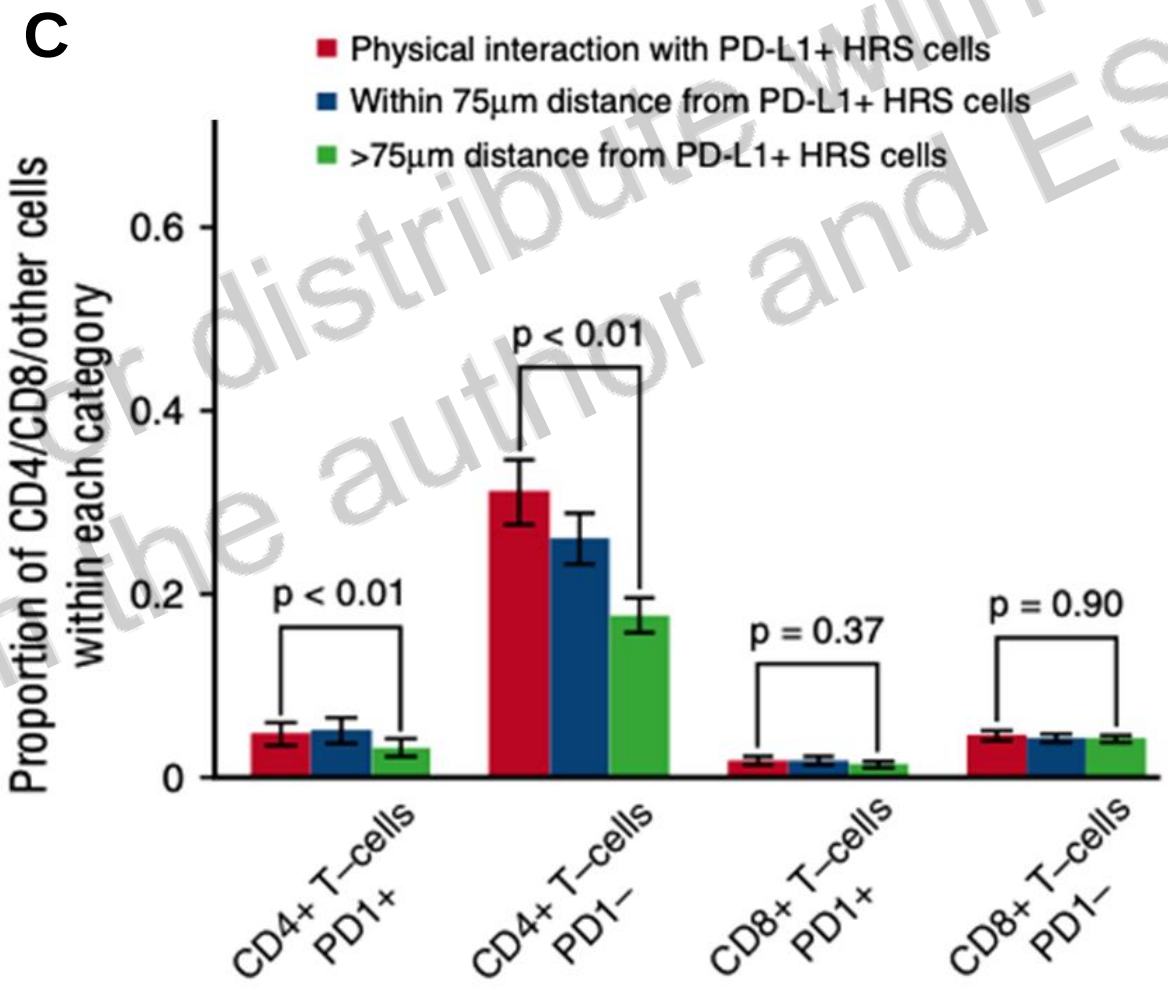


- Findings suggest a potential role of CD4+ T cells in the response to PD-1 blockade.

Roemer et al., *J Clin Oncol* 2018;36:942-950

PD-1^{+}CD4^{+} T-cells in Physical Proximity to HRS Cells

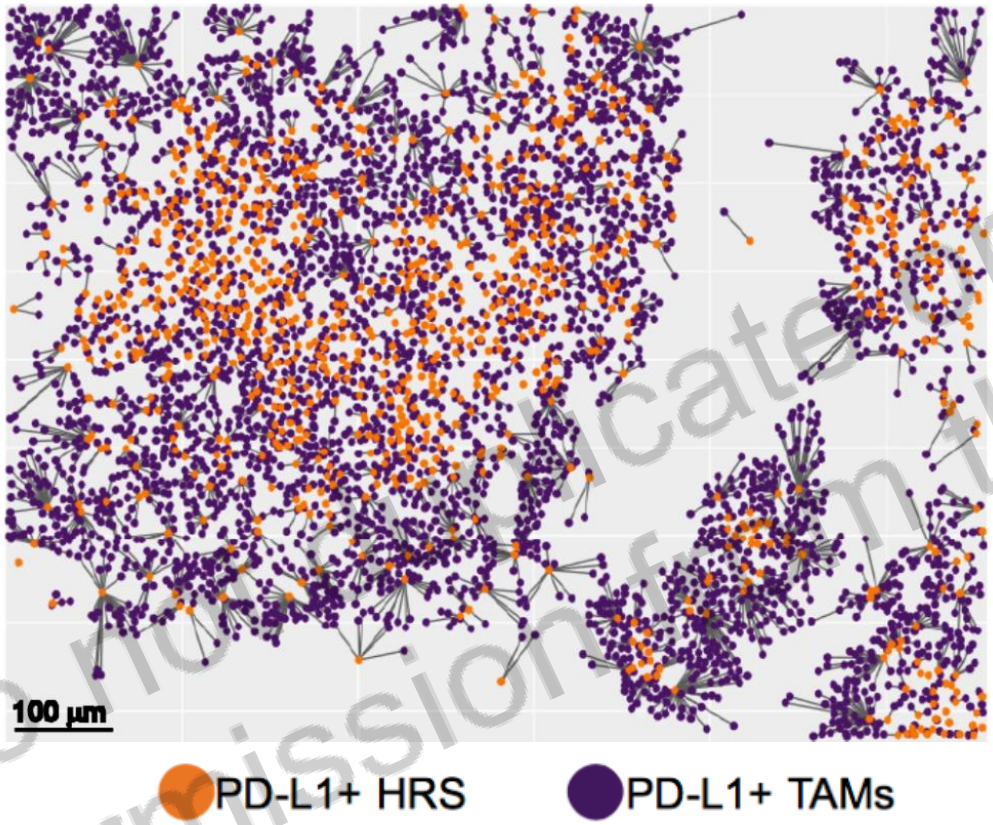




Carey et al., *Blood* 2017;130:2420-30

PD-L1+ HRS Cells Surrounded by PD-L1+ Tumor-associated Macrophages - "Castle and Moat"

A



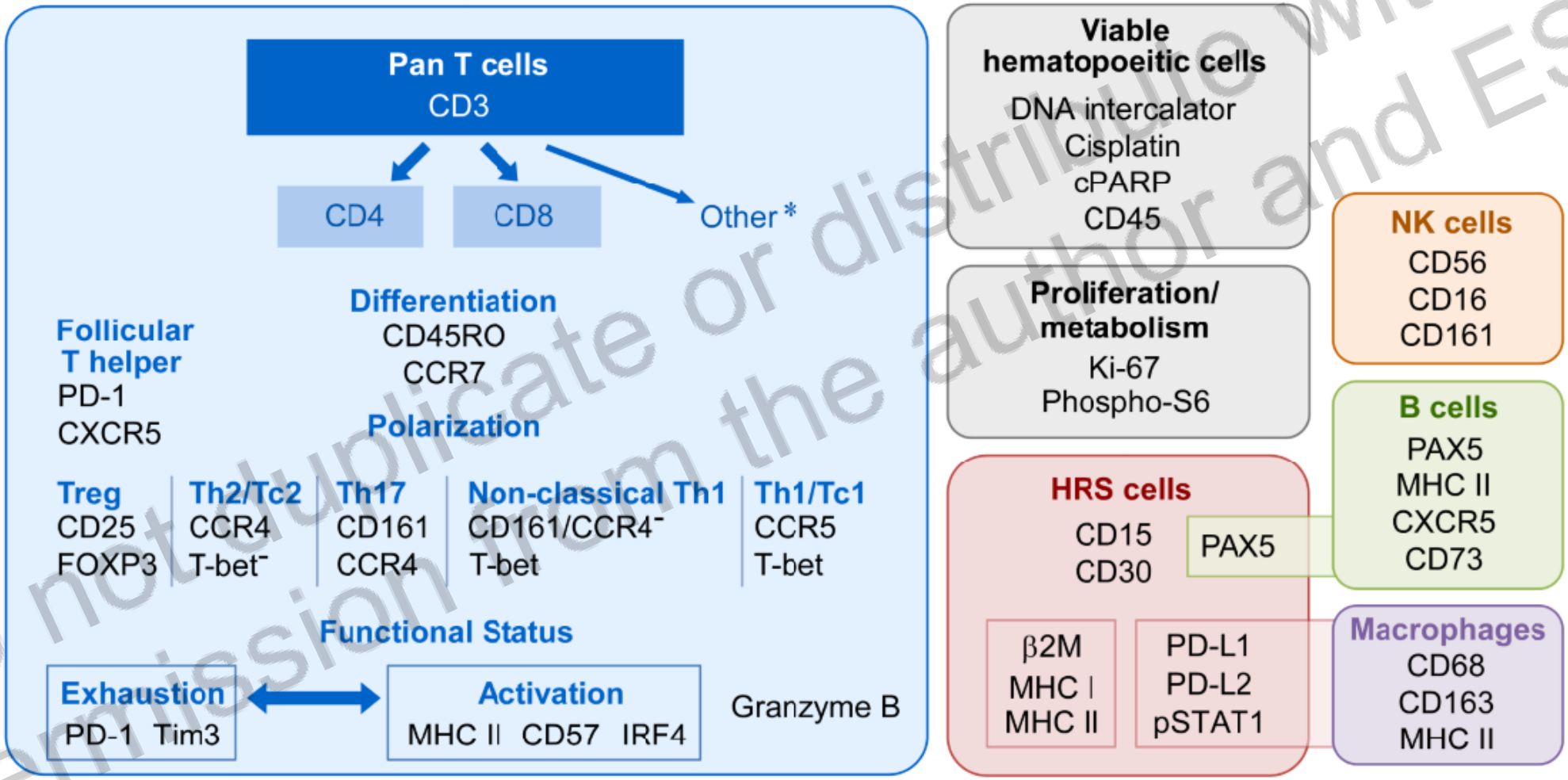
B

DiscoverBritain

- Identification of an immunosuppressive niche in cHL

Carey et al., *Blood* 2017;130:2420-30

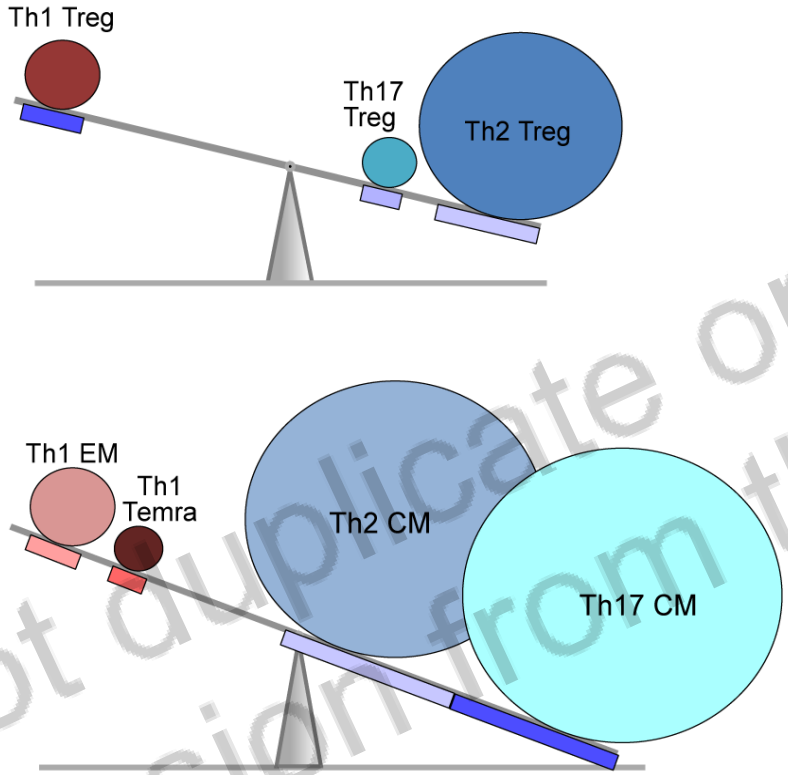
CyTOF Analysis of the Inflammatory/ Immune Cell Infiltrate in Hodgkin Lymphoma



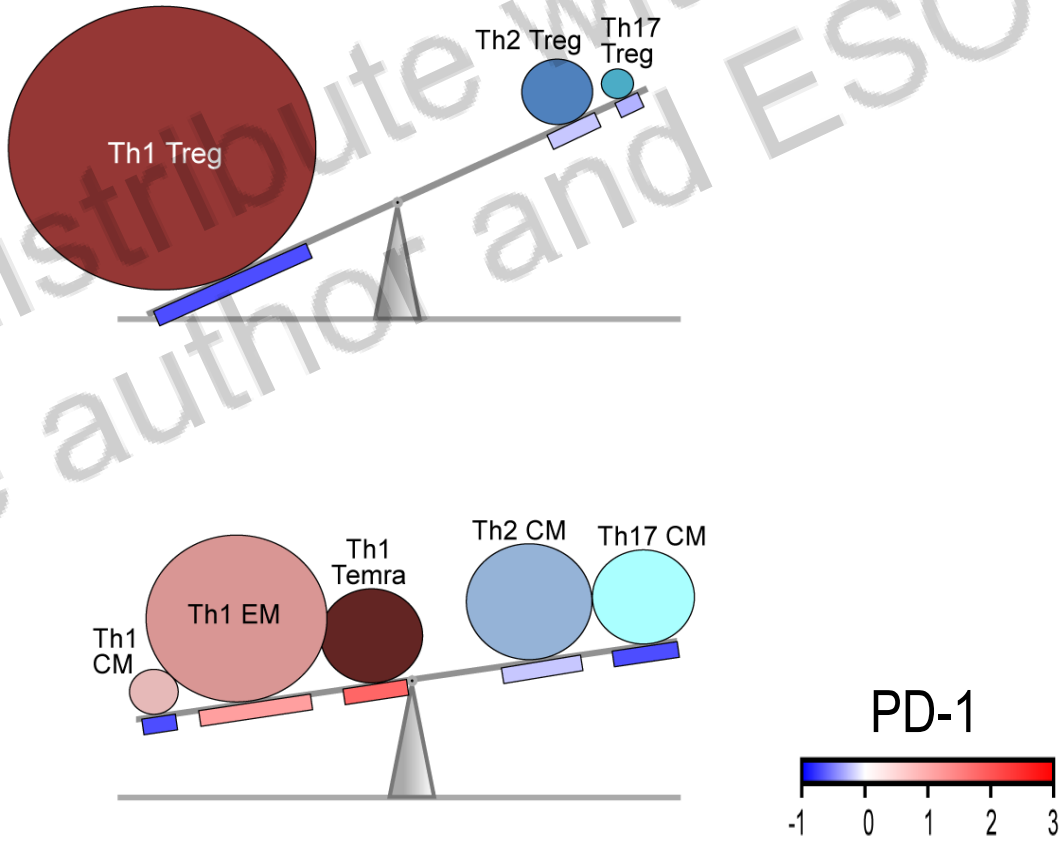
Cader et al., *Blood* 2018;132:825-836

Immune Infiltrates in:

Reactive lymph nodes/tonsils



Hodgkin lymphomas



- HLs have significantly increased CD4+Th1+PD-1+ exhausted T cell effectors and CD4+Th1+PD-1- functionally active T regulatory cells.
- Complementary bases for CD4+ T-cell dysfunction in HL.

Cader et al., *Blood* 2018;132:825-836

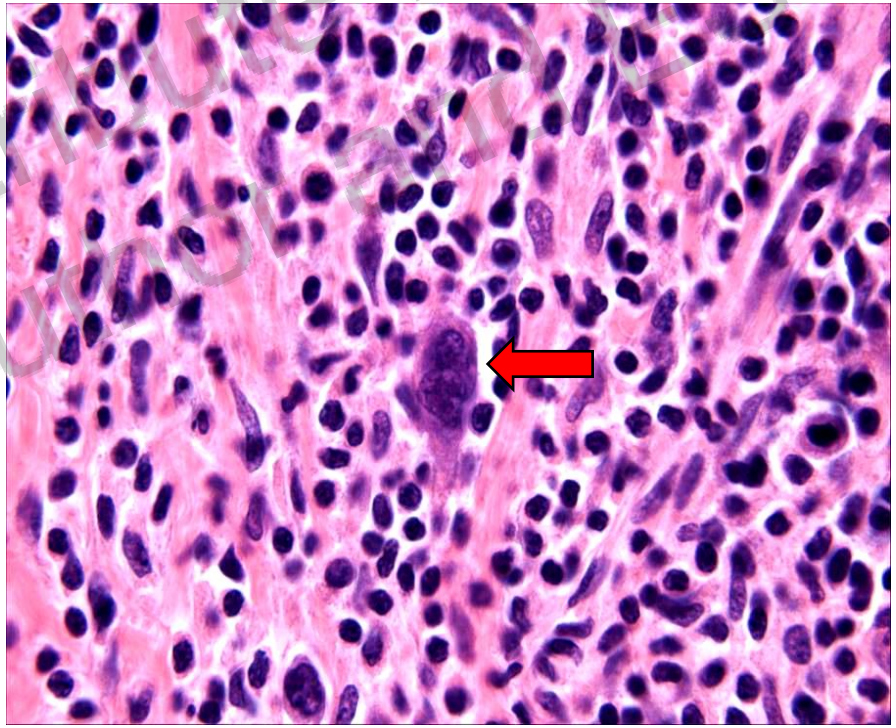
Conclusions- I

1. HRS cells are characterized by copy gains of 9p24.1/*PD-L1/PD-L2* which are associated with increased expression of the PD-1 ligands. CHLs highly susceptible to PD-1 blockade.

2. HRS cells are largely MHC class I- negative.

3. Efficacy of PD-1 blockade associated with HRS cell expression of MHC class II. Likely role for CD4+ T cells and innate immune cells in mediating anti-tumor responses.

4. HRS cells reside within a specialized CD4+ T-cell and PD-L1+ macrophage-rich microenvironmental niche to suppress anti-tumor immunity.

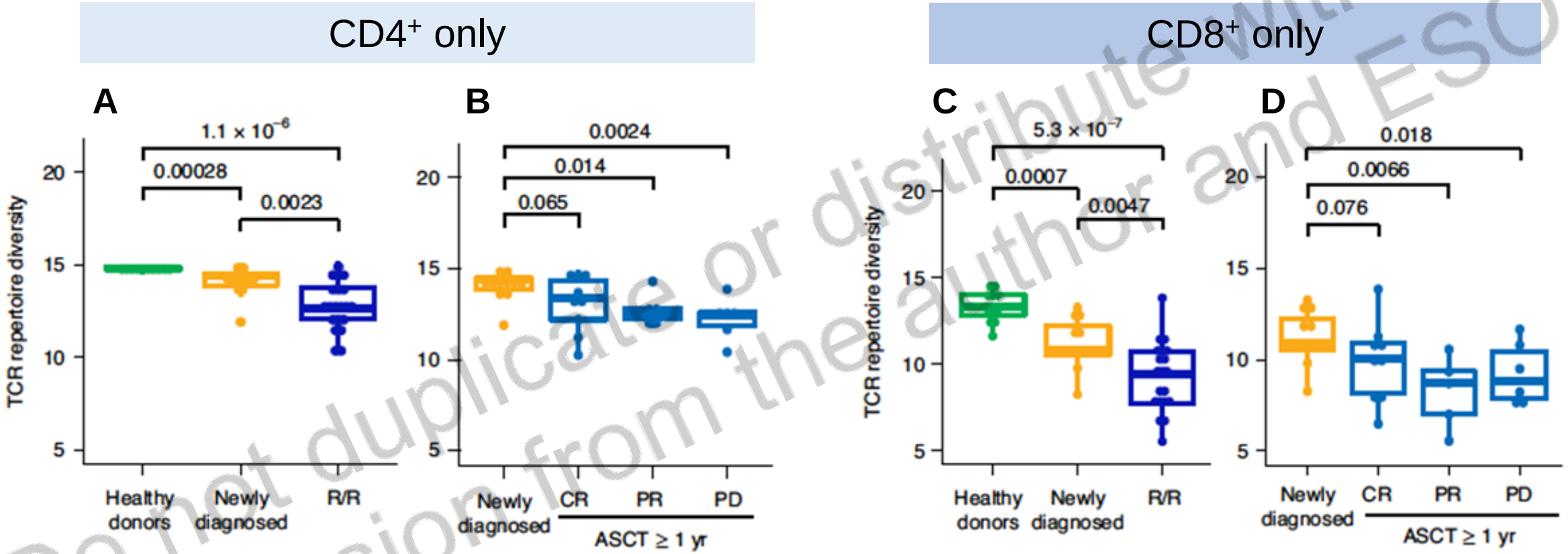


Peripheral Immune Signature of Responsiveness to PD-1 Blockade

- TCR sequencing of purified CD4+ and CD8+ T cells
- CyTOF analyses of CD3+ and CD3- immune cell subsets
- Patients with relapsed/ refractory HL treated with nivolumab on CheckMate 205
- Healthy donors and patients with newly diagnosed previously untreated Hodgkin lymphoma for comparison

Cader et al., *Nature Medicine* 2020;26:1468-1479

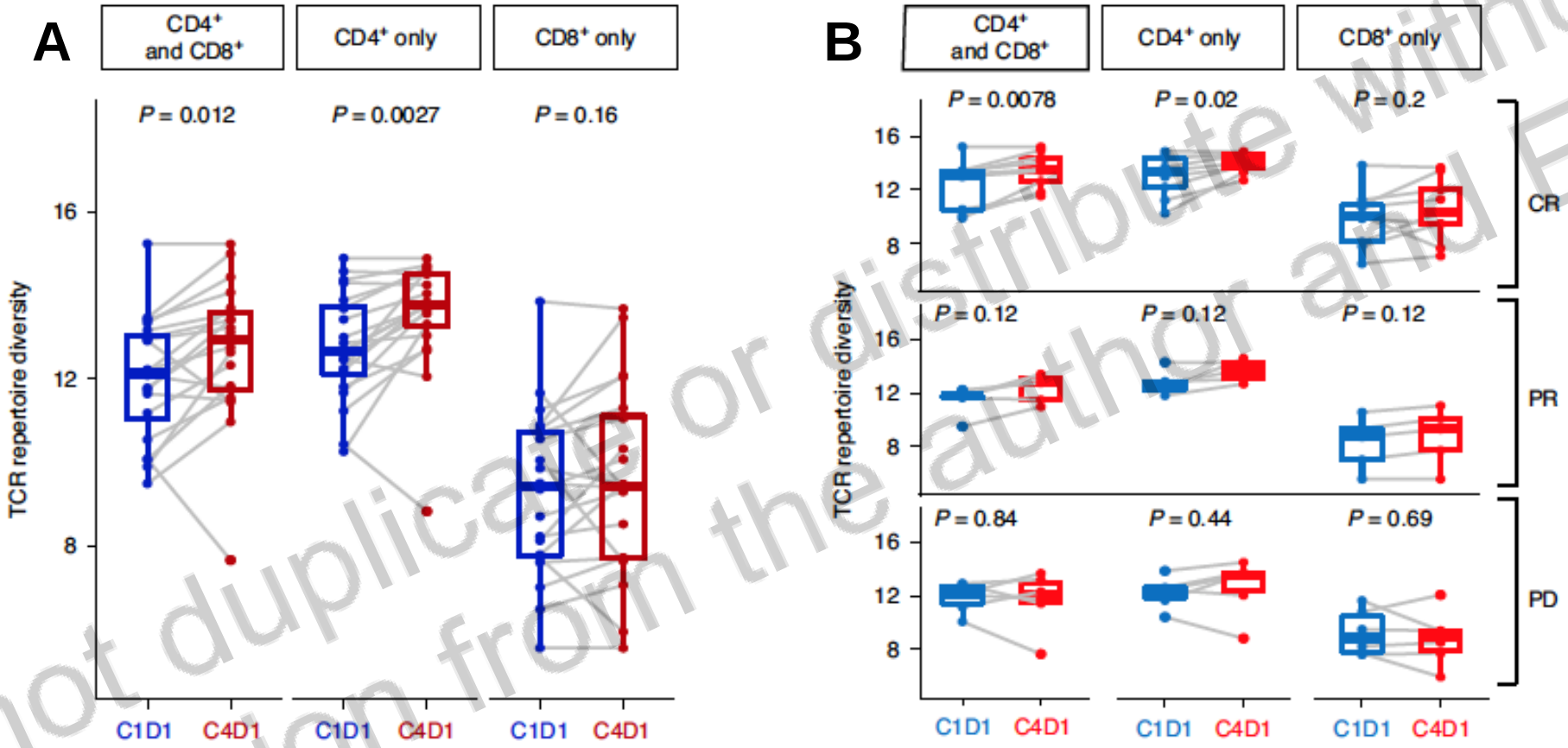
CD4+ and CD8+ Peripheral TCR Repertoire Diversity at Baseline



- T-cell receptor repertoire significantly decreased in patients with Hodgkin lymphoma
- T-cell receptor repertoire significantly decreased in patients with less favorable responses to PD-1 blockade

Cader et al., *Nature Medicine* 2020;26:1468-1479

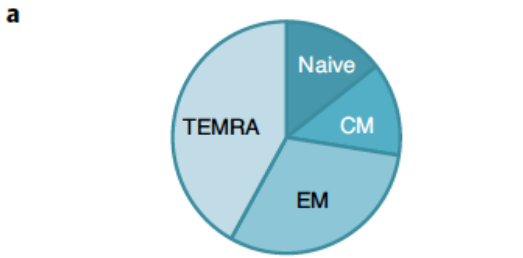
Changes in TCR Repertoire Diversity Following PD-1 Blockade



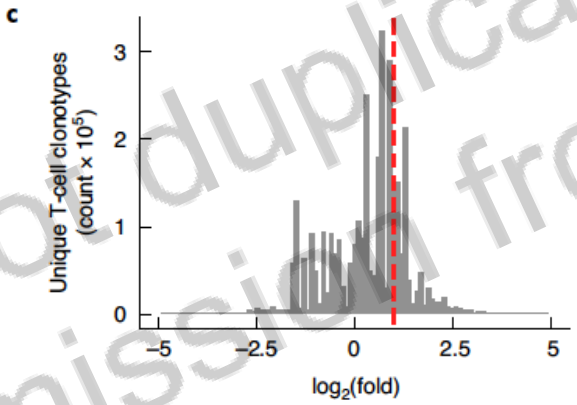
- Highly significant increase in CD4$^+$, but not CD8$^+$, TCR repertoire diversity with PD-1 blockade
- Increase in CD4$^+$ TCR diversity most striking in complete responders (CR)

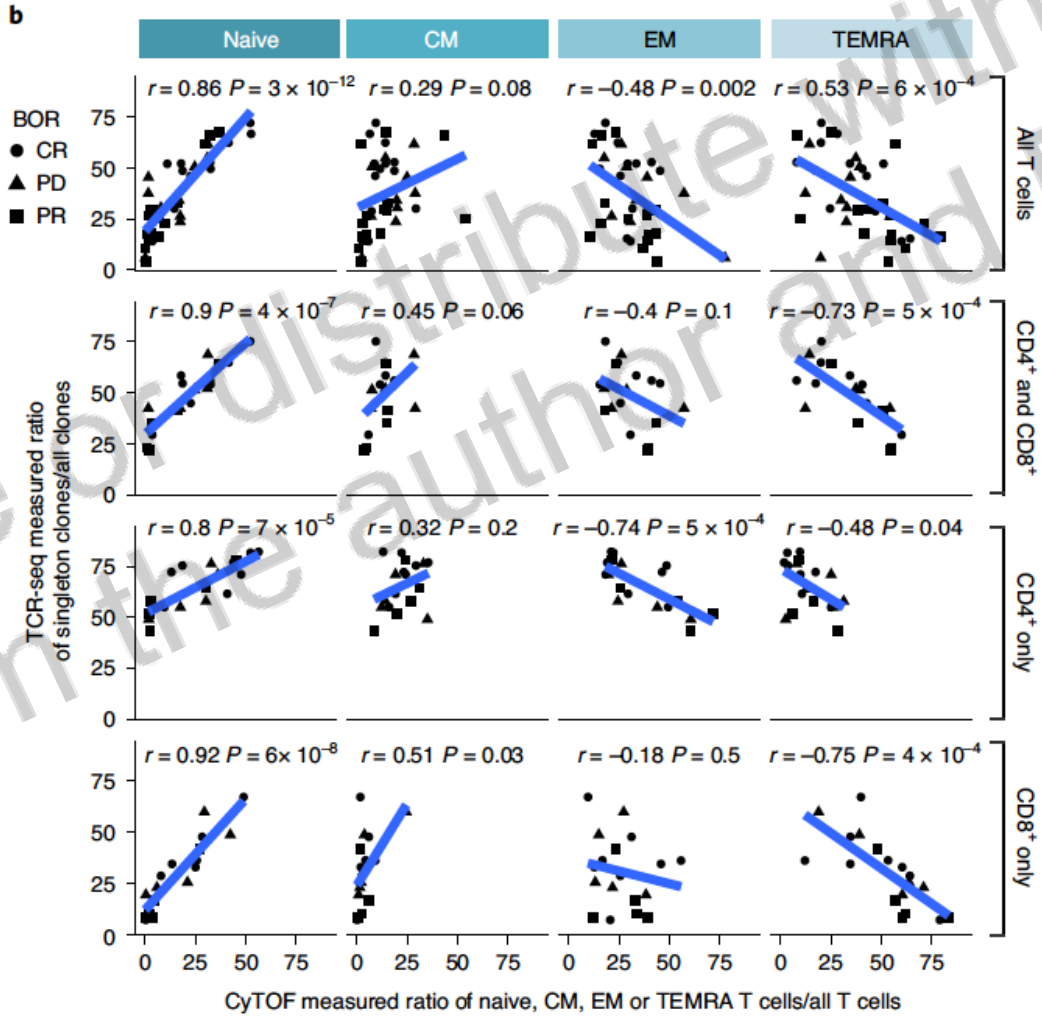
Cader et al., *Nature Medicine* 2020;26:1468-1479

TCR Singleton Clones and T-cell Differentiation



Differentiation status of CD3$^+$ cells	
Naive	CCR7$^+$CD45RO$^-$
CM	CCR7$^+$CD45RO$^+$
EM	CCR7$^-$CD45RO$^+$
TEMRA	CCR7$^-$CD45RO$^-$

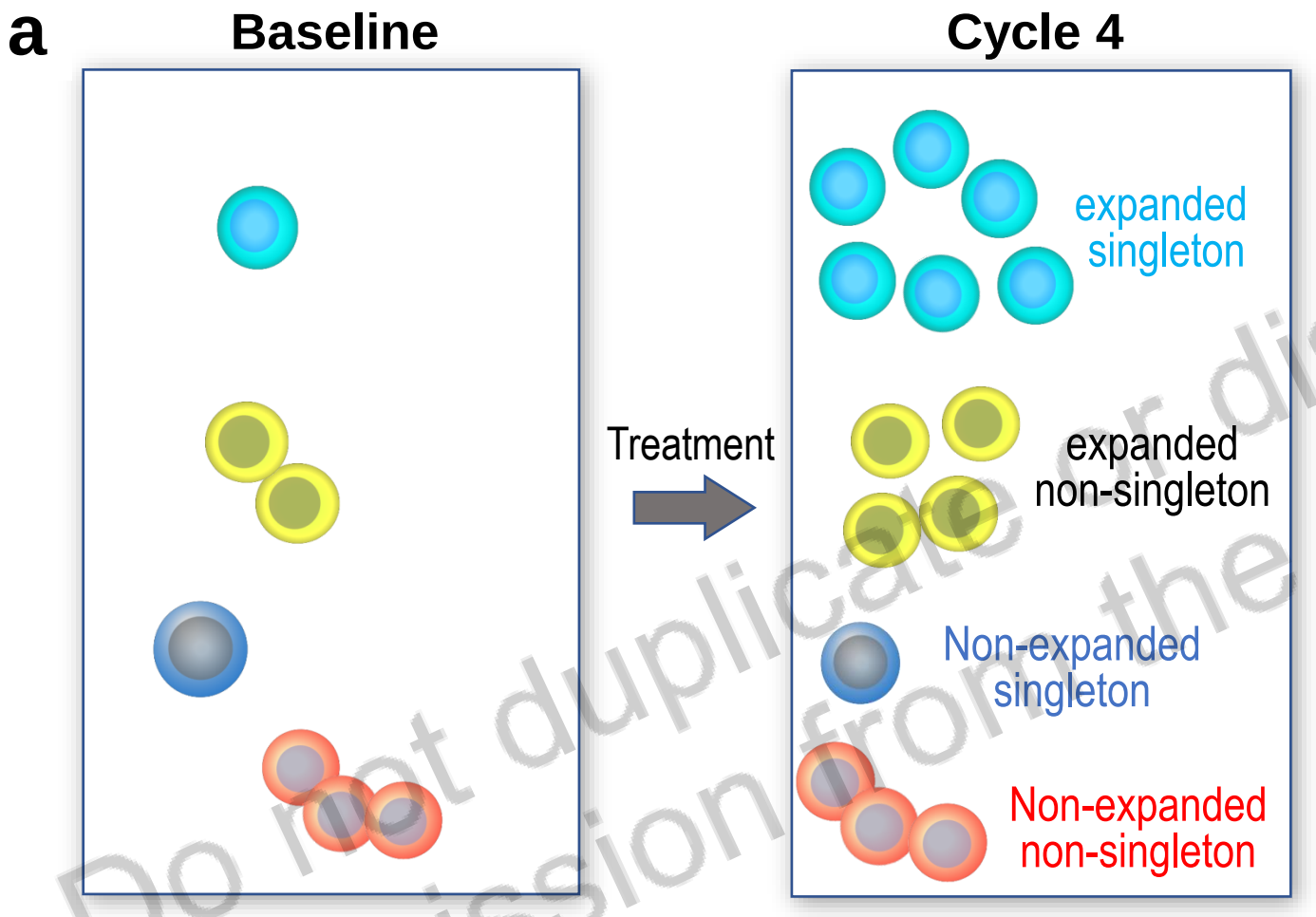


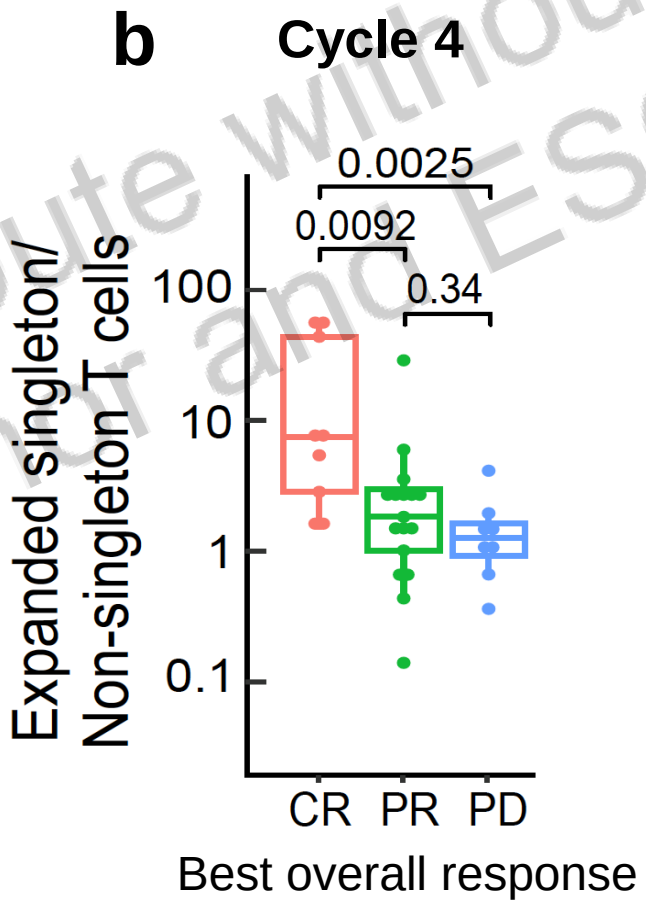


Cader et al *Nature Medicine 2020; 26: 1468-1479*

- T cells with singleton TCRs are less likely to be terminally differentiated.

Clonal Expansion Following PD-1 Blockade

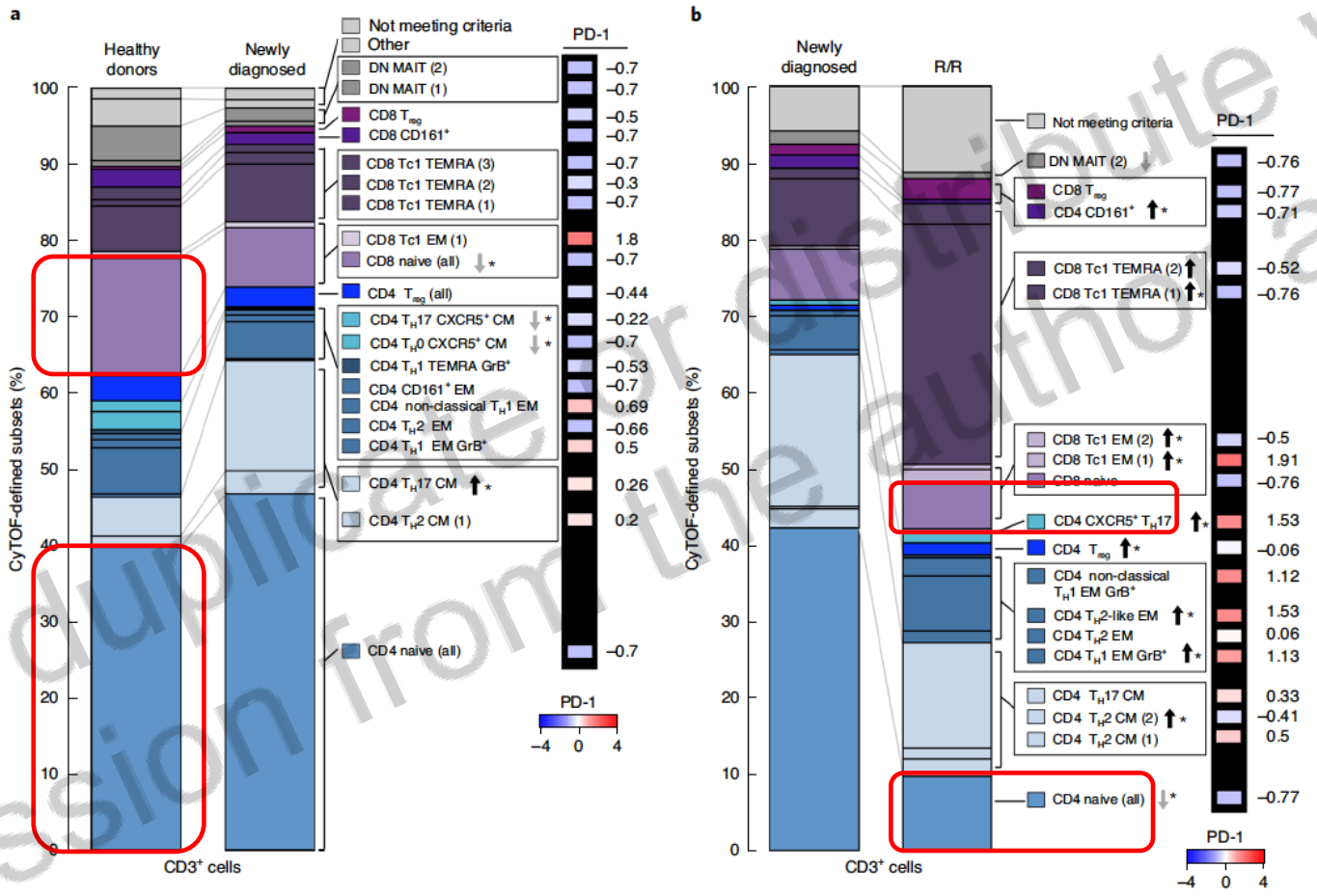




- 4,045,691 unique TCR sequences and 792,705 expanded at least 2-fold following PD-1 blockade
- Clonal expansion of less terminally differentiated singletons, rather than non-singletons, associated with a more favorable response to PD-1

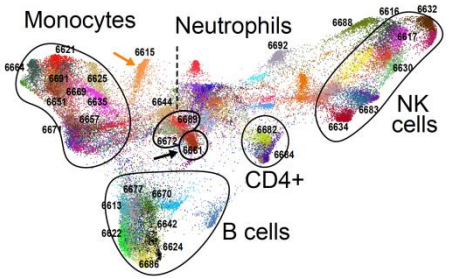
Cader et al., *Nature Medicine* 2020;26:1468-1479

Peripheral T-cell Signature in Healthy Donors and Patients with Newly Diagnosed or Relapsed/refractory Hodgkin Lymphoma

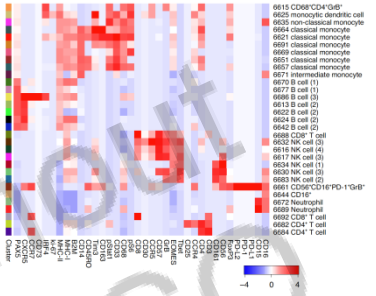


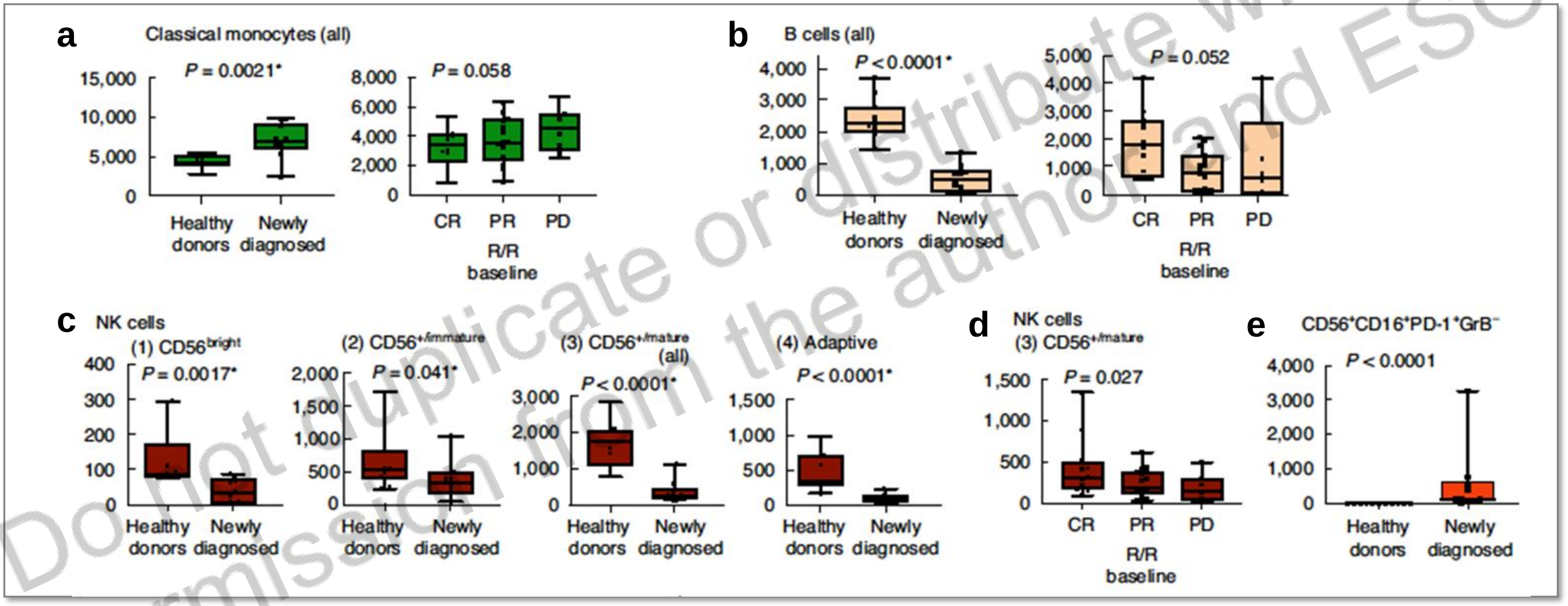
Cader et al., *Nature Medicine* 2020;26:1468-1479

- CD4+ and CD8+ naïve T cells decreased in patients with R/R cHL
- More terminally differentiated PD-1+ effectors increased in patients with R/R HL



CD3- Signature in Heathy Donors and Patients with Newly Diagnosed and Relapsed/ refractory Hodgkin Lymphoma

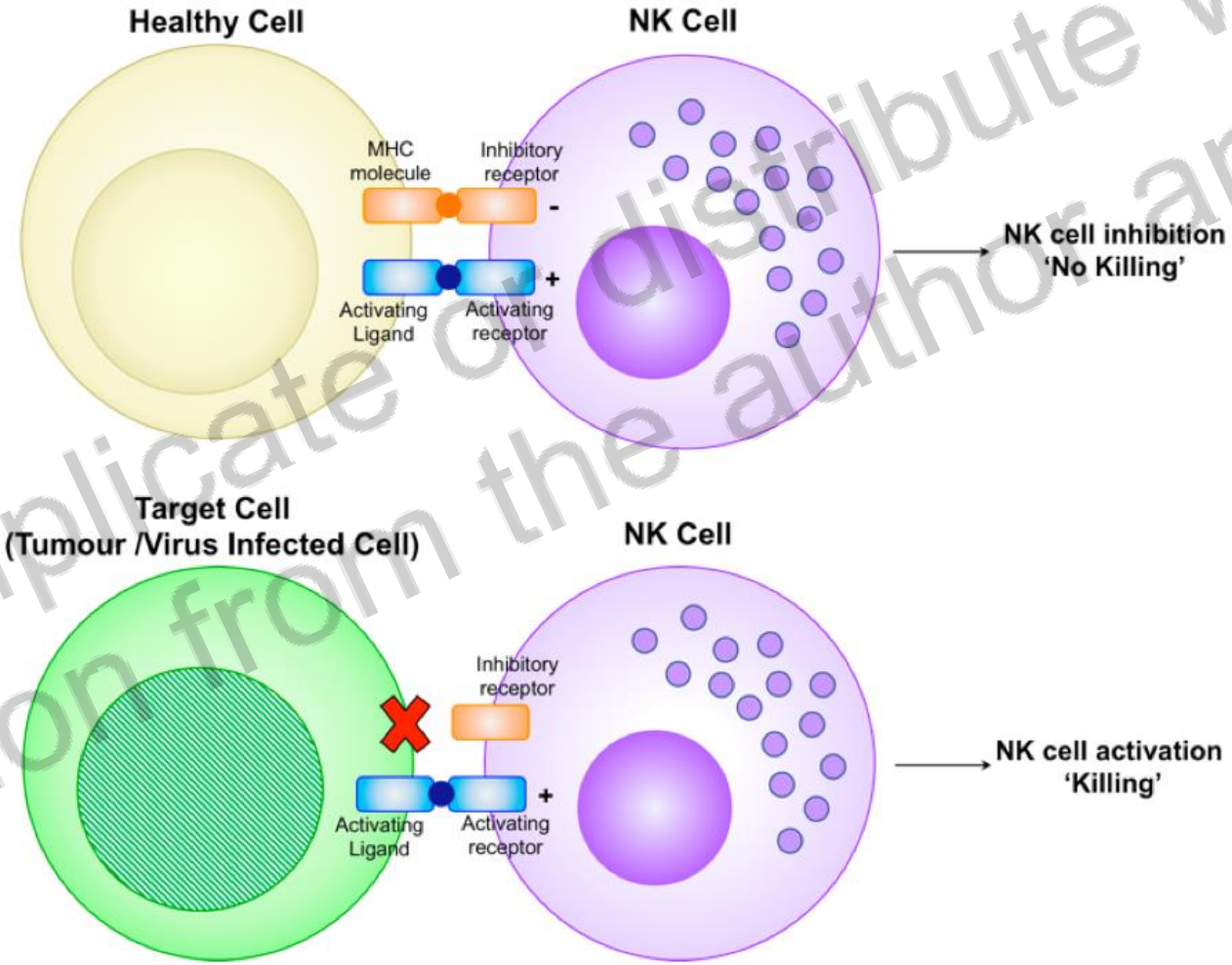




- CD3- peripheral immune signatures in complete responders (CR) more closely resembled those of healthy donors.

Cader et al., *Nature Medicine* 2020;26:1468-1479

Natural Killer Cells Preferentially Target MHC Class I-negative Tumors



https://www.elisagenie.com/blog/natural-killer-cells-and-their-role-in-immunometabolism/

Conclusions II - Lessons from the Periphery

- PD-1 blockade most effective in patients with a diverse baseline TCR repertoire and expansion of singleton clones during treatment
- CD4+, but not CD8+, TCR diversity significantly increased during therapy, most strikingly in patients who achieved CRs
- Findings suggest that a continued capacity to mount new CD4+ T-cell responses to tumor neoantigens important for the efficacy of PD-1 blockade
- Patients with the most favorable responses to PD-1 blockade had CD3- peripheral immune signatures - increased B cells and NK cells and decreased classical monocytes - more like those of healthy donors.
- Data highlights the likely complementary roles of newly expanded, clonally diverse CD4+ T cells, B cells and additional innate effectors

Cader et al., *Nature Medicine* 2020;26:1468-1479

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http://shipplab.dfci.harvard.edu

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will take place on 3rd November 2022, at the same time

Palliative medicine in paediatric oncology

Expert: **Dr Justin N. Baker**, St Jude Children's Research Hospital, Memphis, TN, USA

Discussant: **Dr Deena Levine**, St Jude Children's Research Hospital, Memphis, TN, USA

Thank you!

for participating in this
e-session
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