

# SITC 2019

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NATIONAL HARBOR, MARYLAND



Society for Immunotherapy of Cancer



# Lessons and Challenges from the Immunotherapy of Lymphoma

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Chair, Lymphoma Group

Mayo Clinic



Society for Immunotherapy of Cancer

#SITC2019

# Disclosures for Stephen Ansell, MD, PhD

*In compliance with ACCME policy, Mayo Clinic requires the following disclosures to the activity audience:*

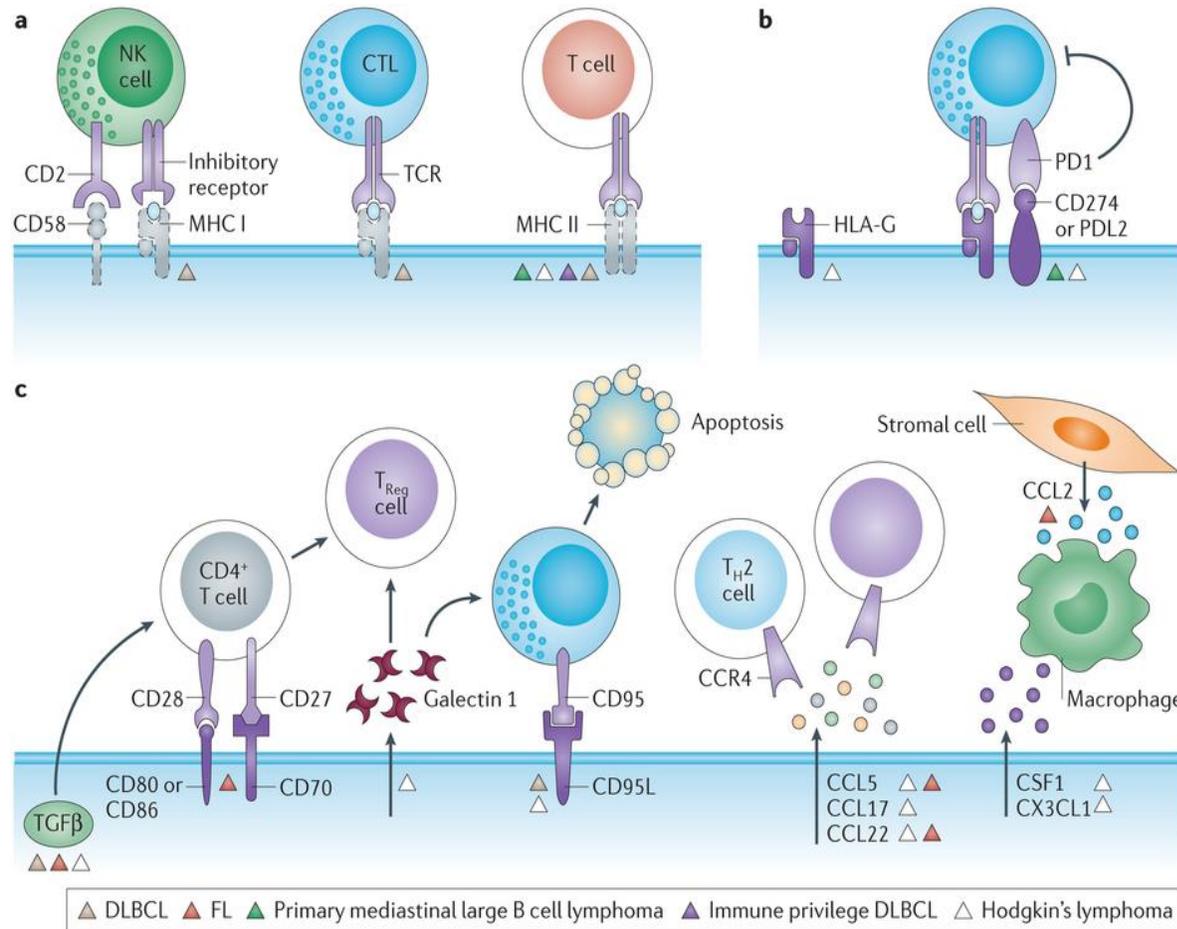
Research Support/P.I.	PI – Seattle Genetics, BMS, Affimed, Regeneron, Pfizer clinical trials
Employee	N/A
Consultant	N/A
Major Stockholder	N/A
Speakers' Bureau	N/A
Scientific Advisory Board	N/A

**N/A = Not Applicable (no conflicts listed)**

## Aims -

- Identify deficiencies in the Immune response in lymphoma.
- Describe strategies to overcome the immune deficiencies –
  - immune checkpoint blockade
  - combination approaches.
- Discuss complicating factors and limitations in what we know

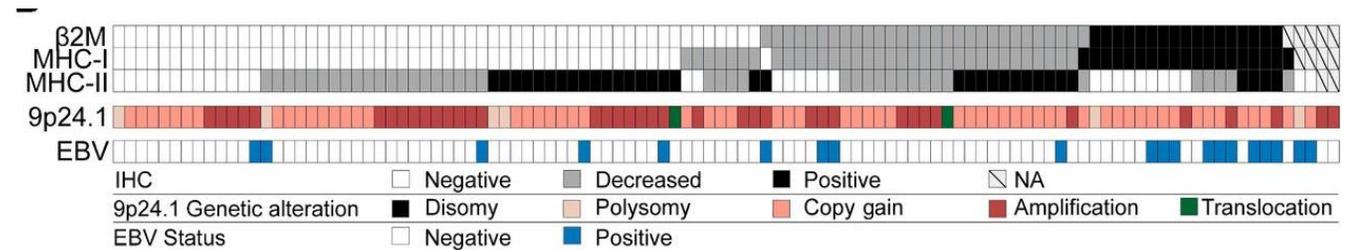
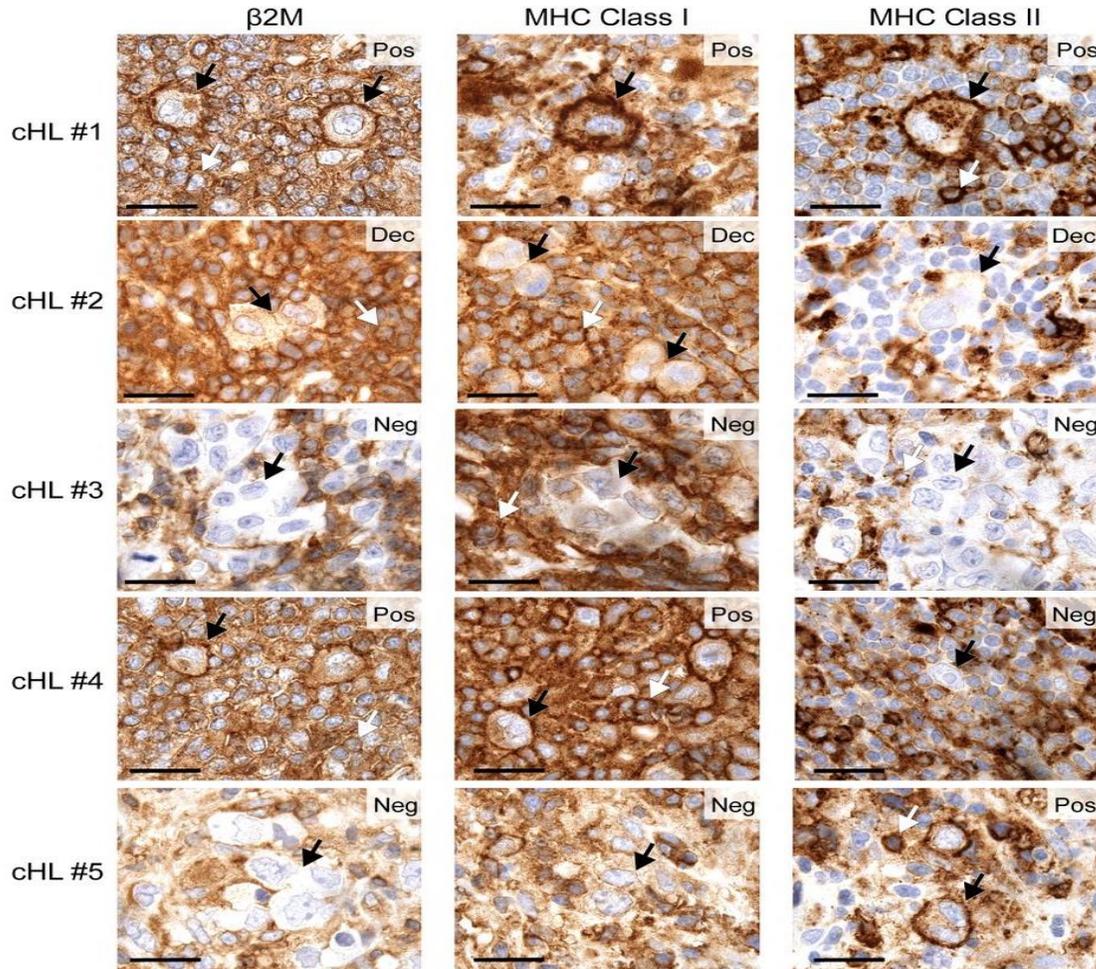
# Four Mechanisms accounting for an inadequate T-cell response in lymphoma



1. Loss of antigen presentation
2. Suppressive ligands
3. Suppressive cell populations
4. Suppressive cytokines

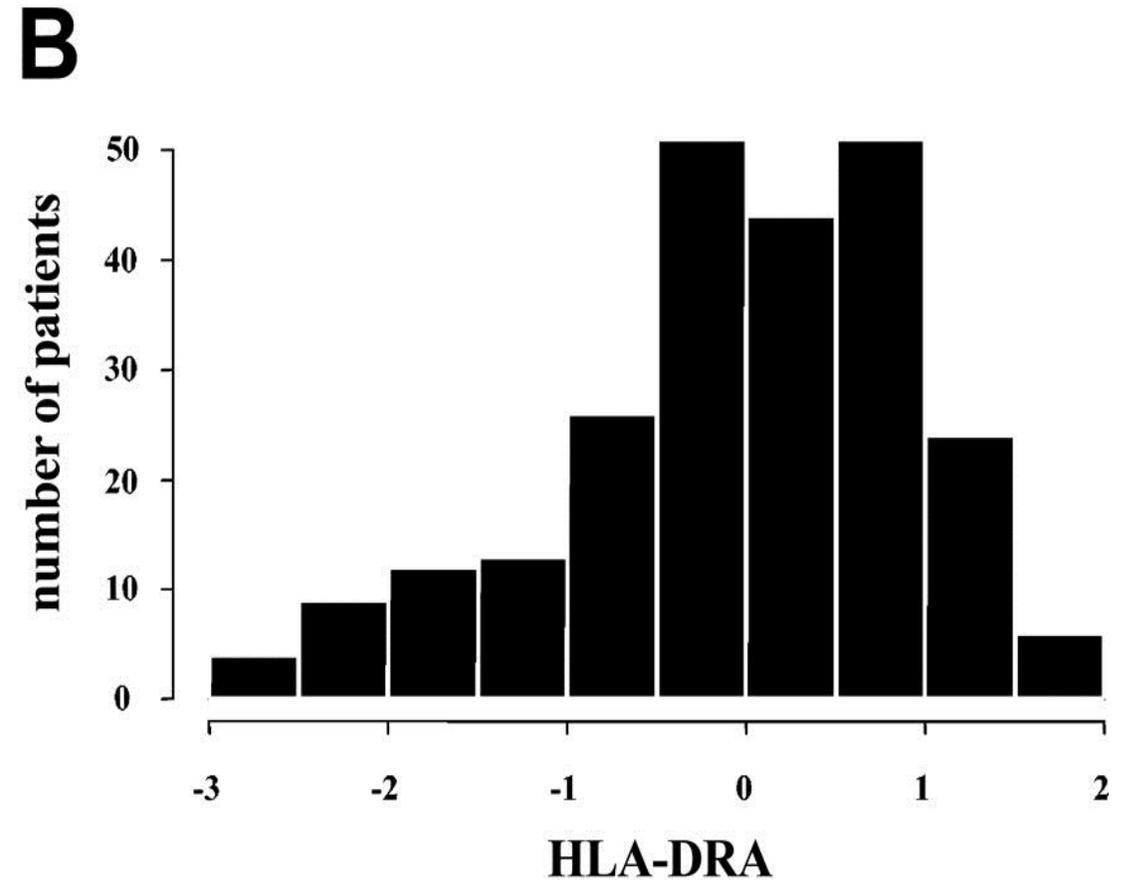
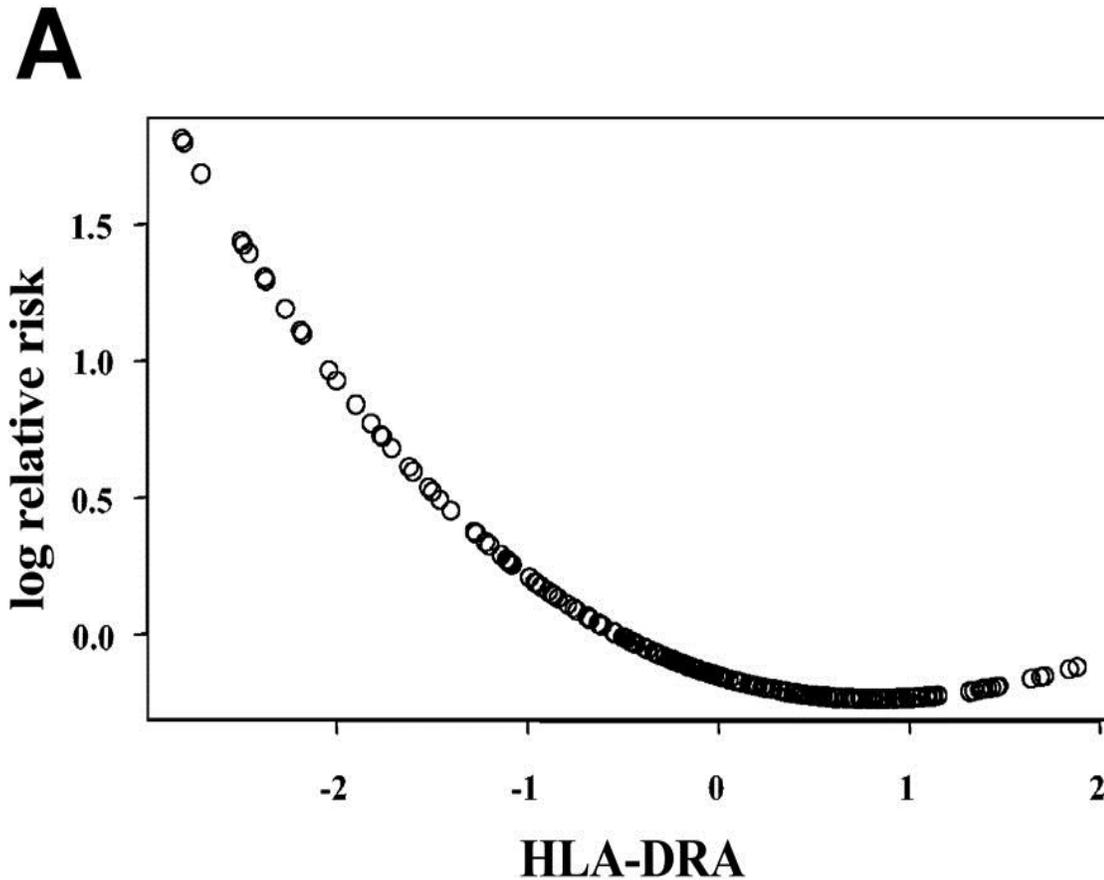
Scott et al. Nature Reviews Cancer 14, 517–534 (2014)

# 1. Loss of $\beta$ 2M, MHC class I and II expression in classical Hodgkin Lymphoma



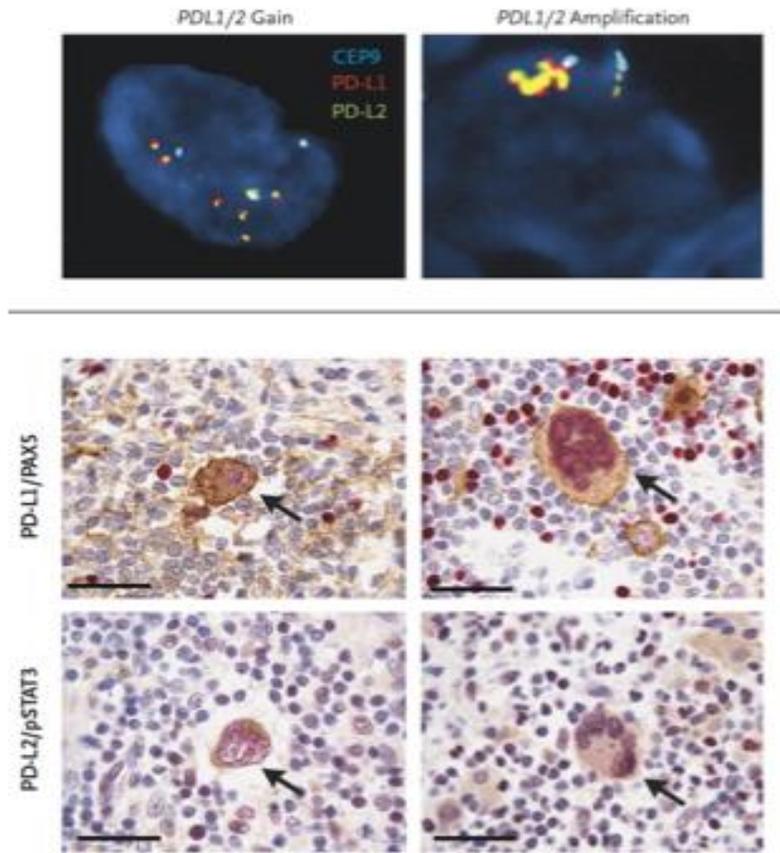
Roemer et al. Cancer Immunol Res 2016;4:910-916

# 1. Risk of death associated with loss of HLA-DRA expression in Diffuse Large B-cell lymphoma

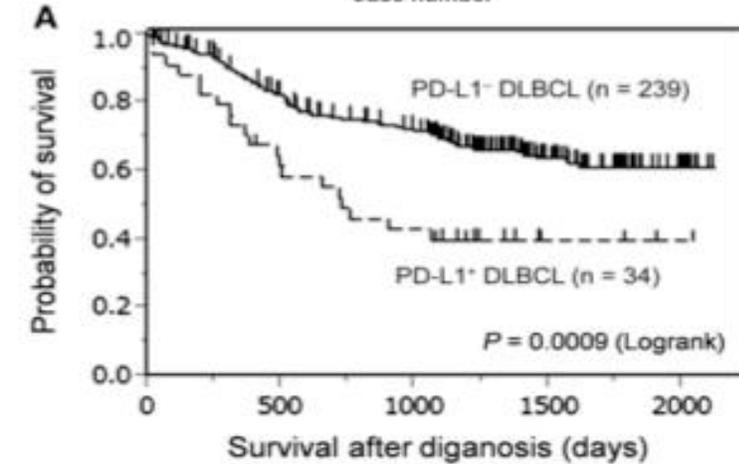
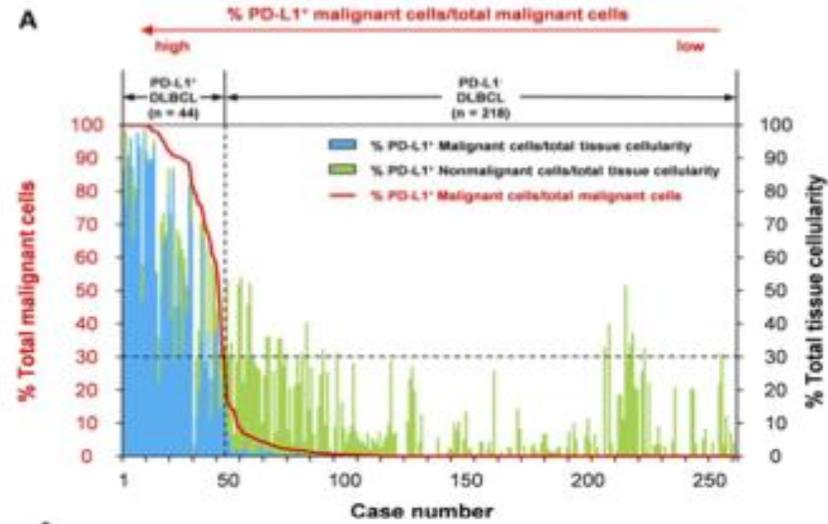


Rimsza et al. Blood 2004;103:4251-4258

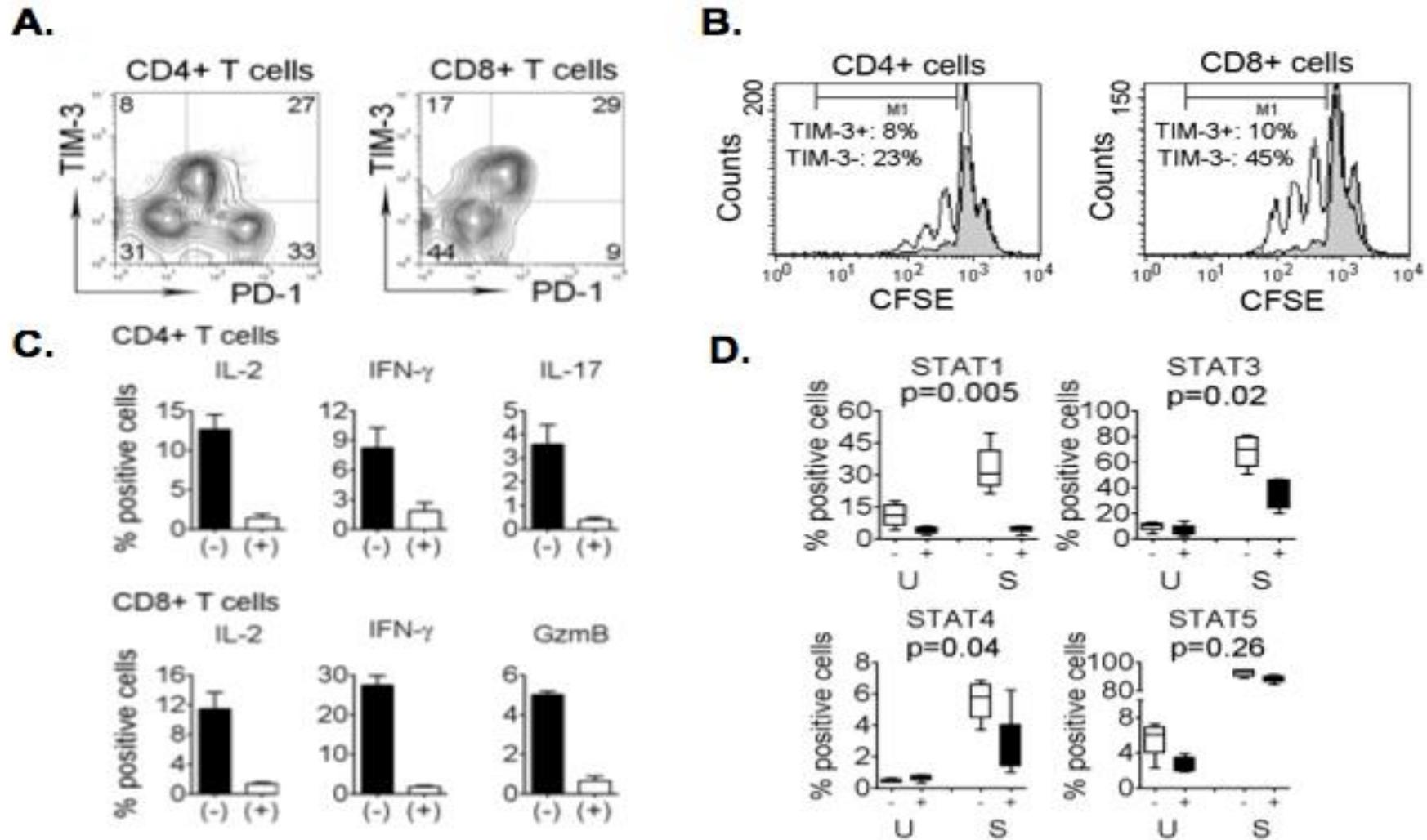
# 2. Increased Suppressive Ligands – PD-L1 and PD-L2 expression in Lymphoma



Ansell et al. N Engl J Med. 2015;372:311-319  
 Roemer et al. ASH 2015 abstract #176  
 Kiyasu et al. Blood 2015;126:2193-2201



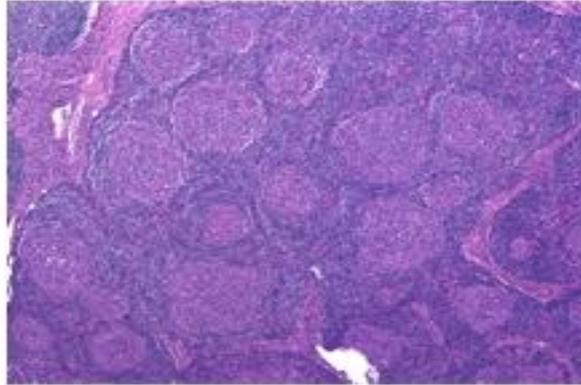
# 2. Exhausted T-cells in lymphoma are susceptible to suppression



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

### 3. Immune cells are prevalent at sites of lymphoma but do not eradicate it

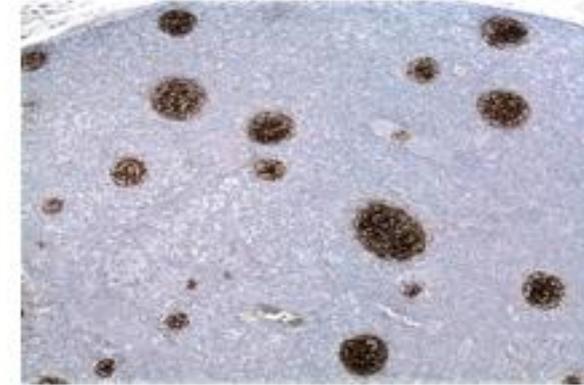
**H+E**



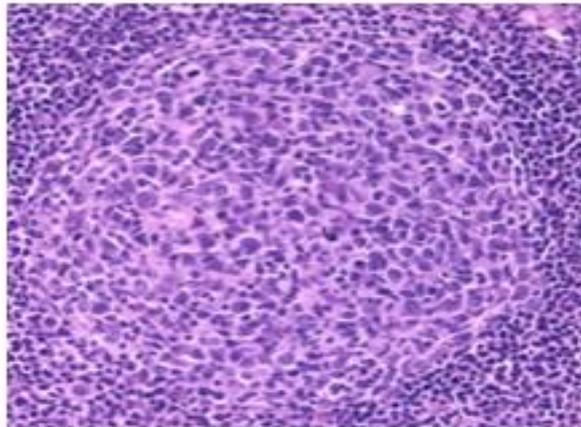
**CD3**



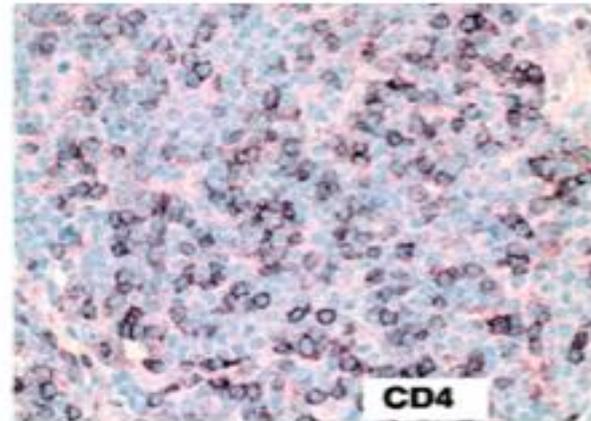
**CD21**



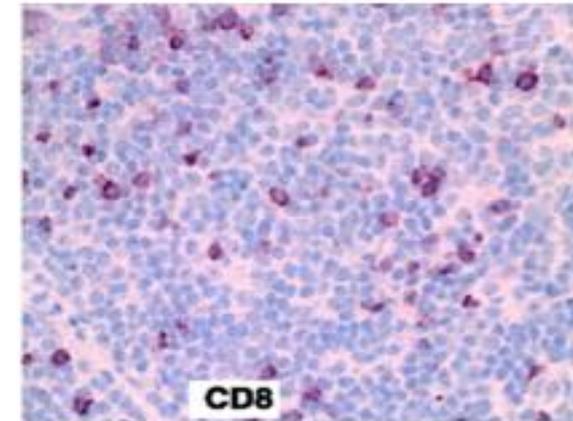
**H+E**



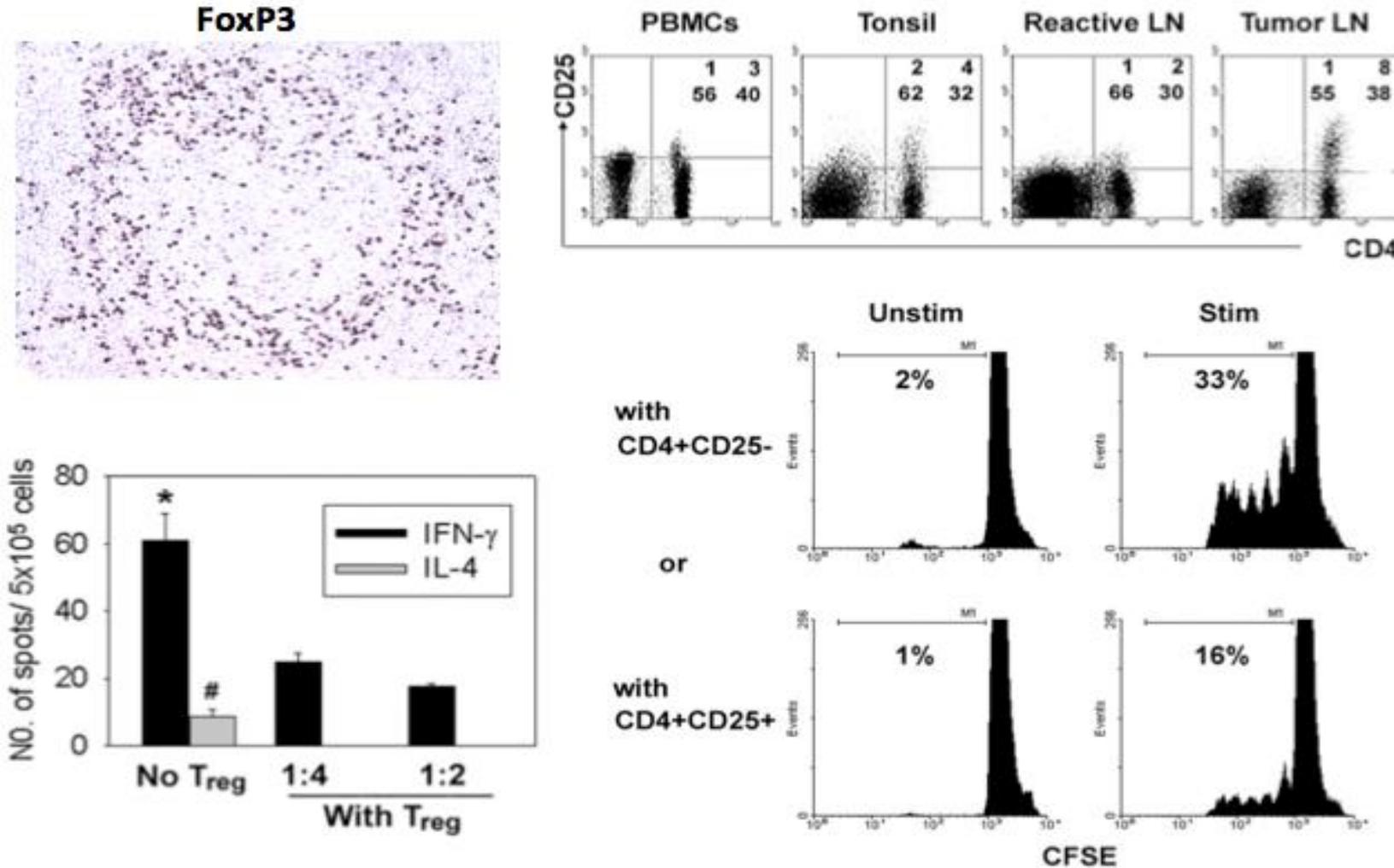
**CD4**



**CD8**

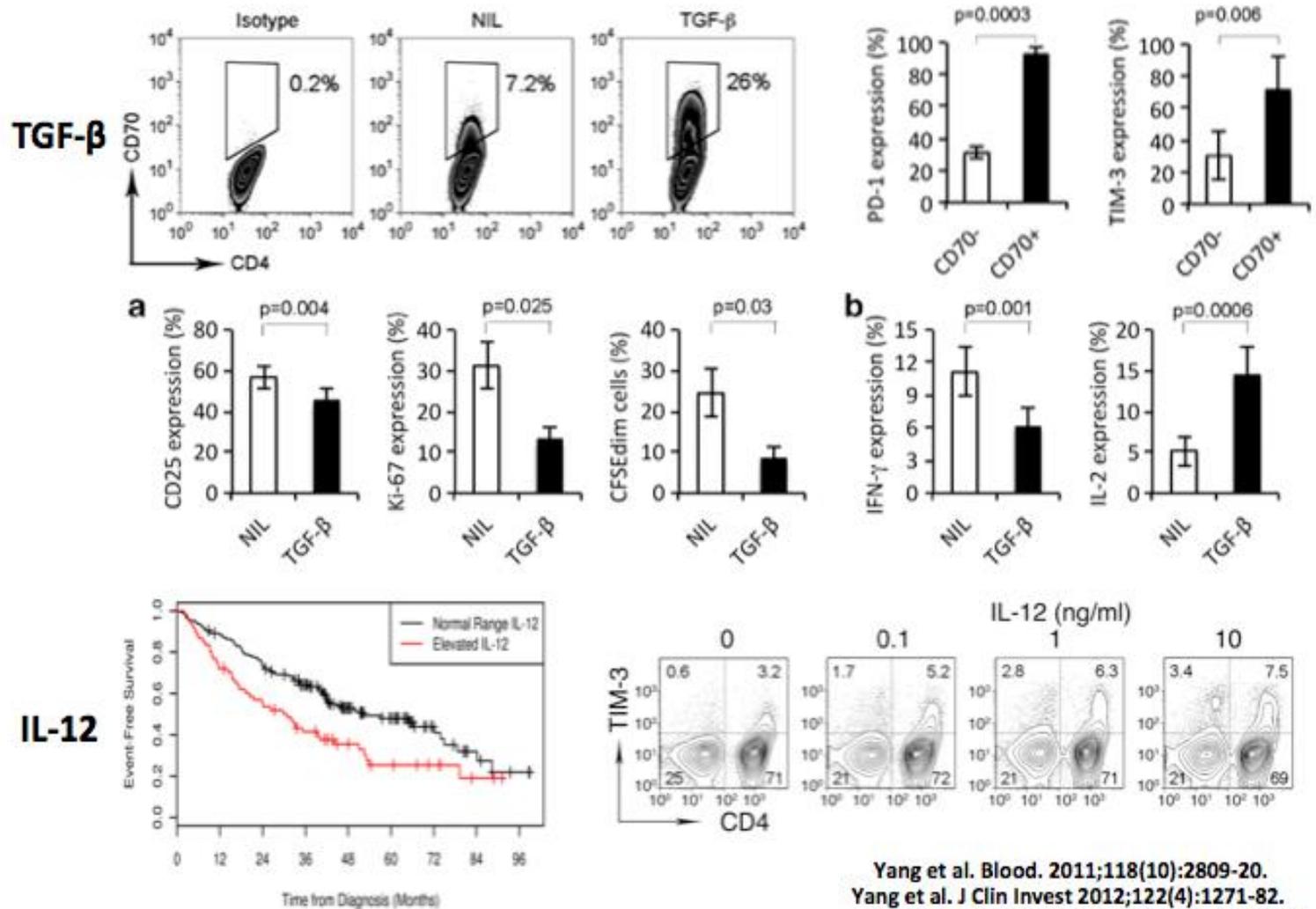


# 3. Increased regulatory T-cells in lymphoma



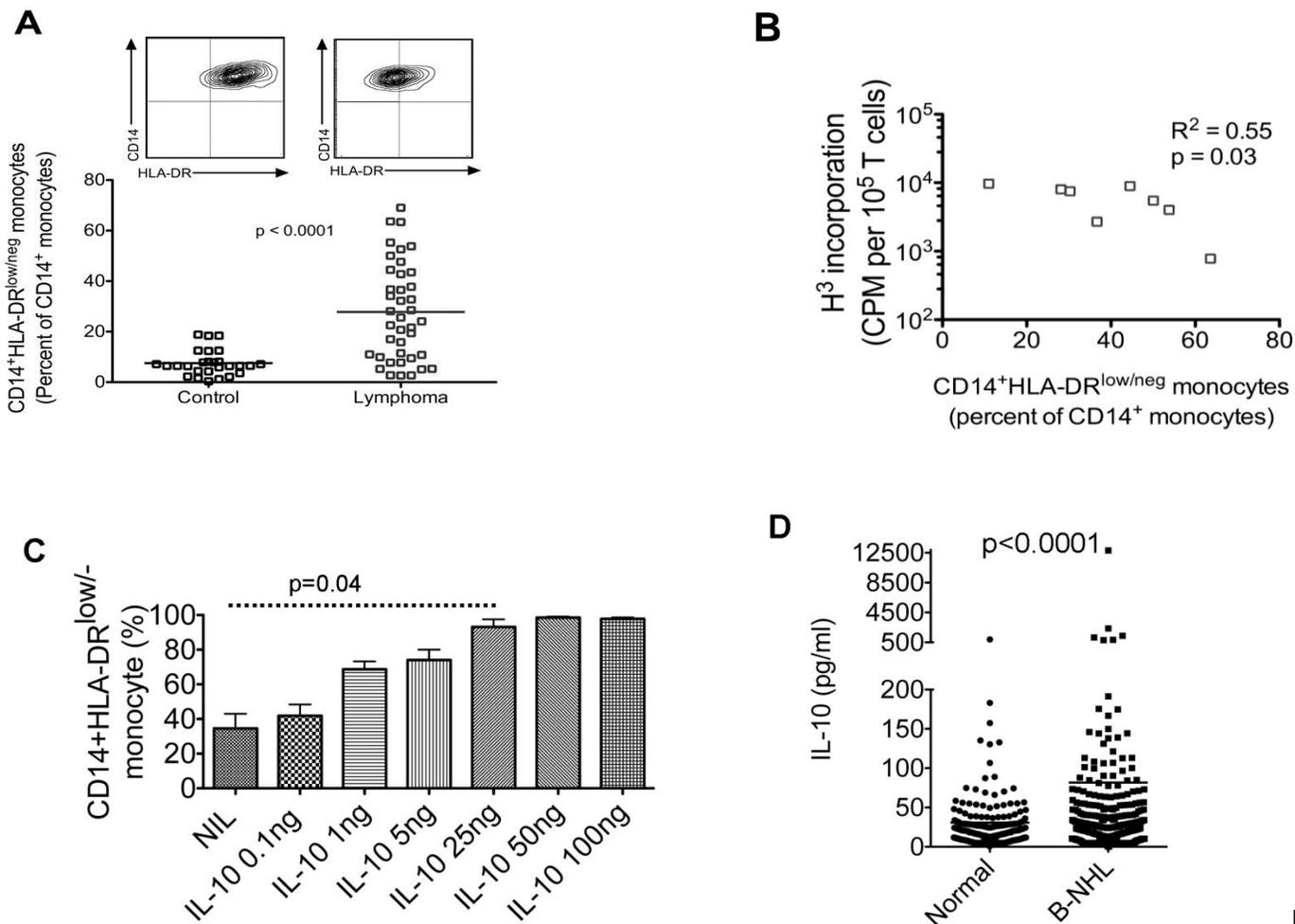
Yang et al. Blood 2006;107:3639-3646

# 4. Immunostimulatory cytokines induce T-cell exhaustion



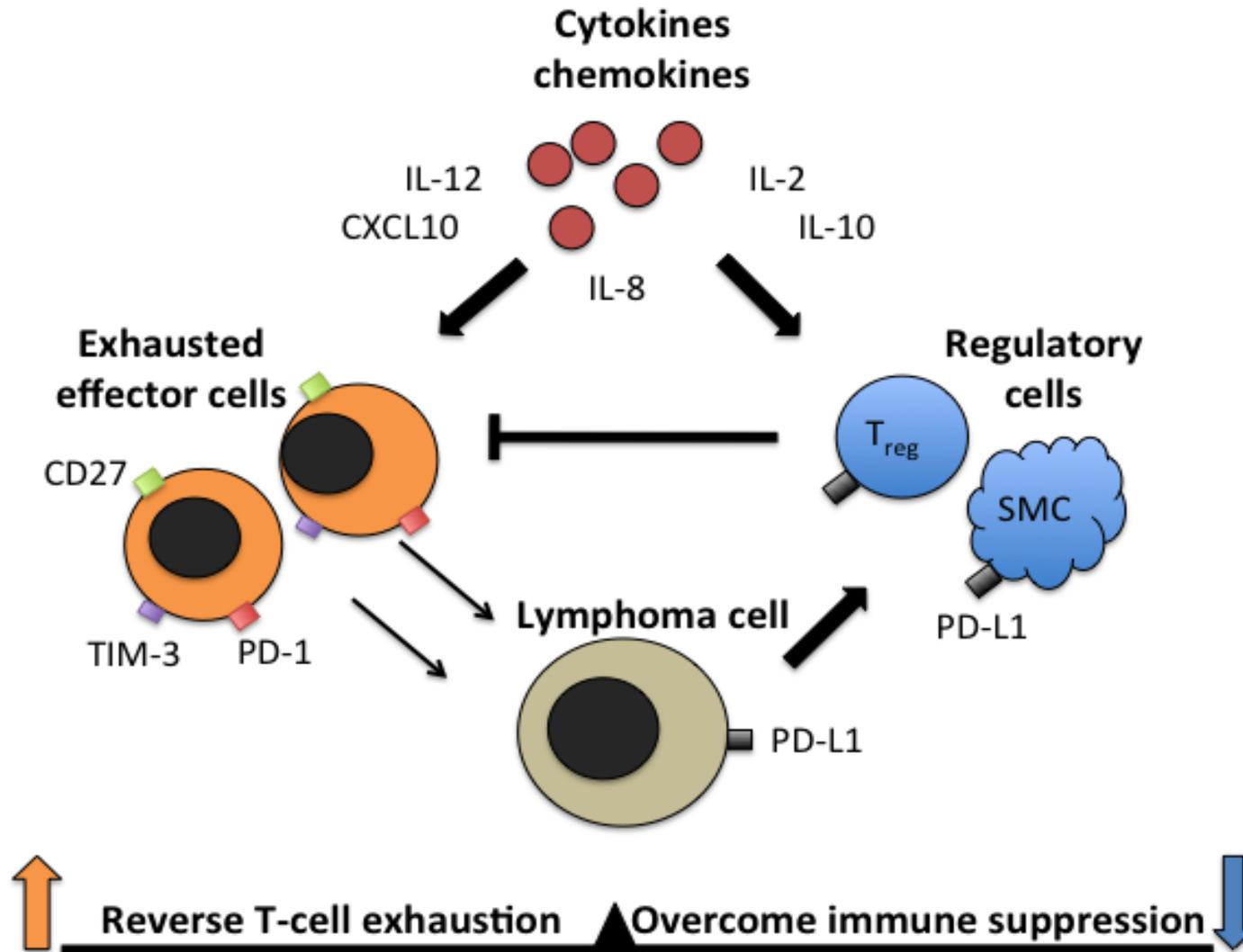
Yang et al. Blood. 2011;118(10):2809-20.  
Yang et al. J Clin Invest 2012;122(4):1271-82.  
Yang et al. Leukemia. 2014 Sep;28(9):1872-84.

# 4. Cytokines (IL-10) expand CD14+HLADR<sup>low</sup> monocytes that suppress T-cell function

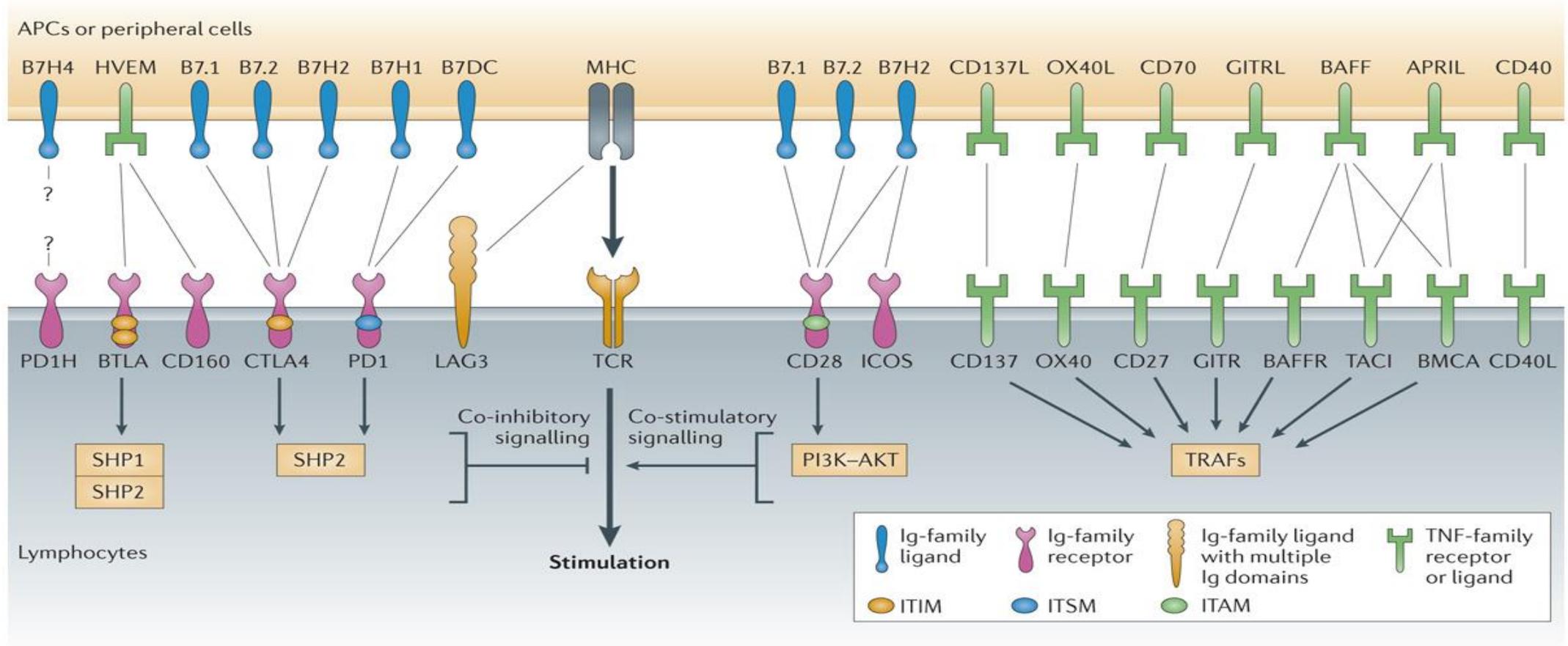


Lin et al. Blood. 2011 Jan 20;117(3):872-81.  
Xiu et al. Blood Cancer J. 2015 Jul 31;5:e328.

# How can we activate the anti-tumor immune response in lymphoma?



# Strategy 1: Target immune checkpoints – prevent immune suppression



Nature Reviews | Drug Discovery

# Strategy 1: Blocking PD-1 signaling

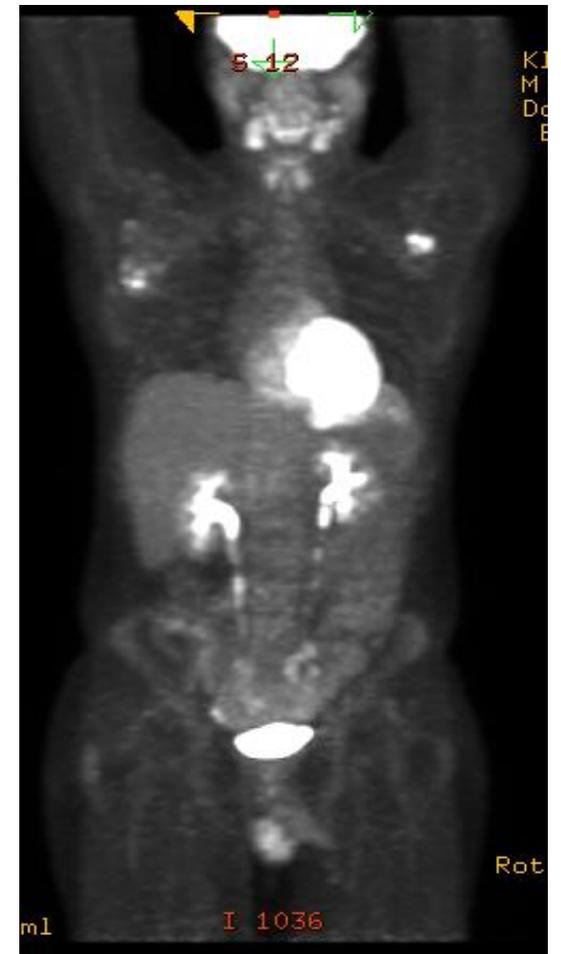
## Highly effective in Hodgkin lymphoma



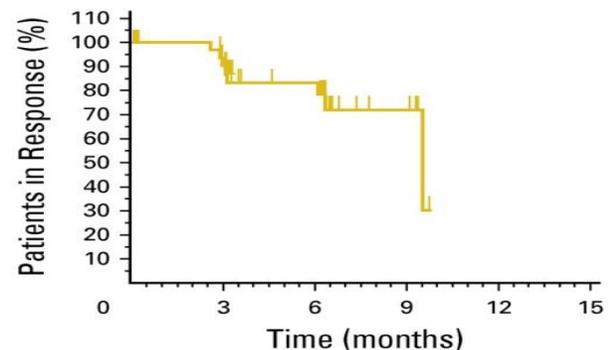
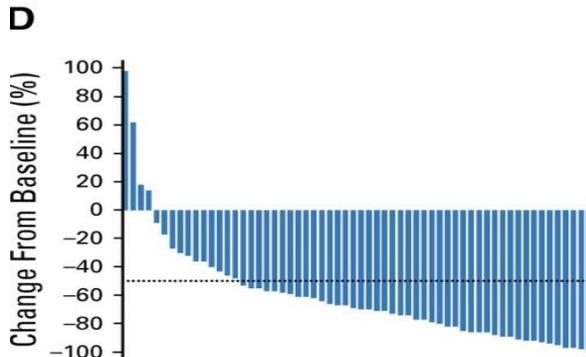
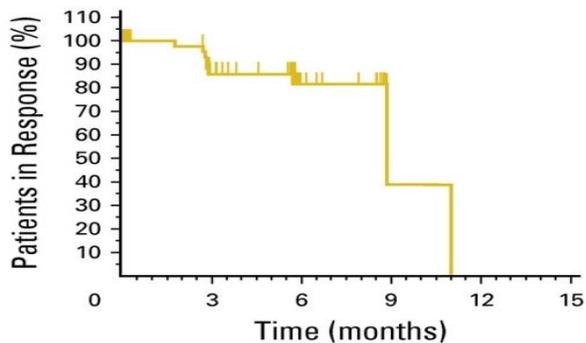
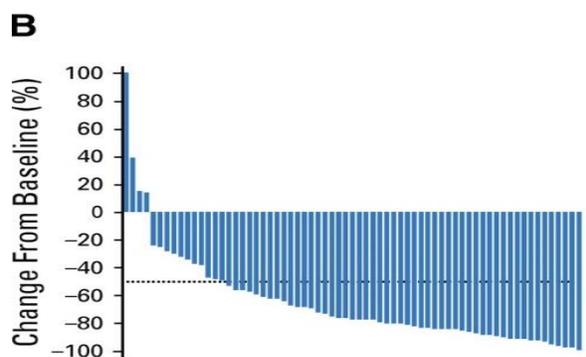
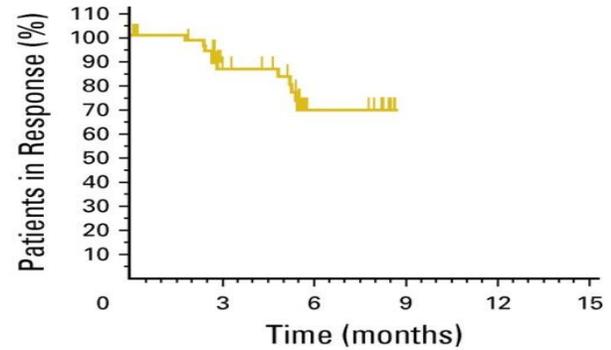
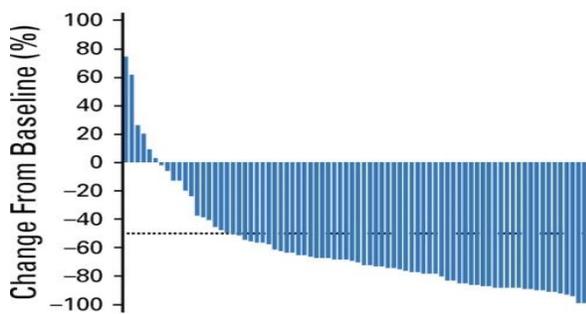
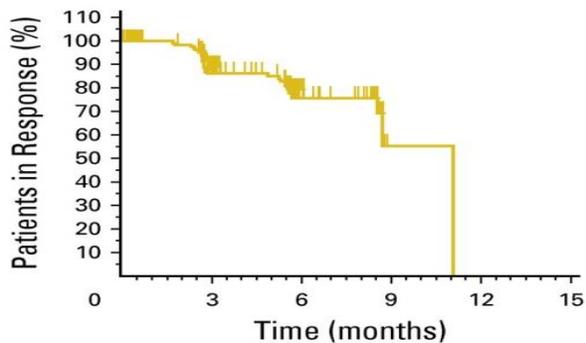
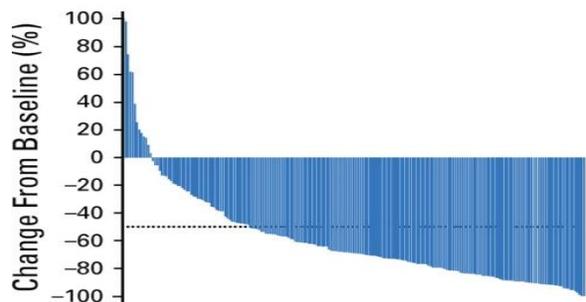
42 year old female – Hodgkin lymphoma



26 year old male – Hodgkin lymphoma

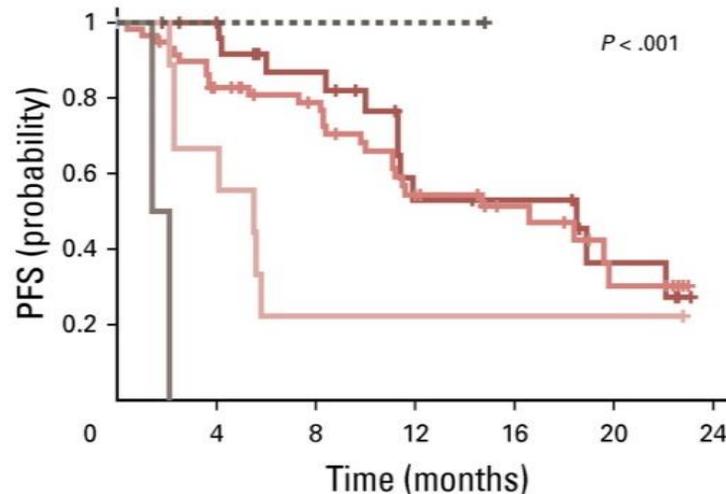
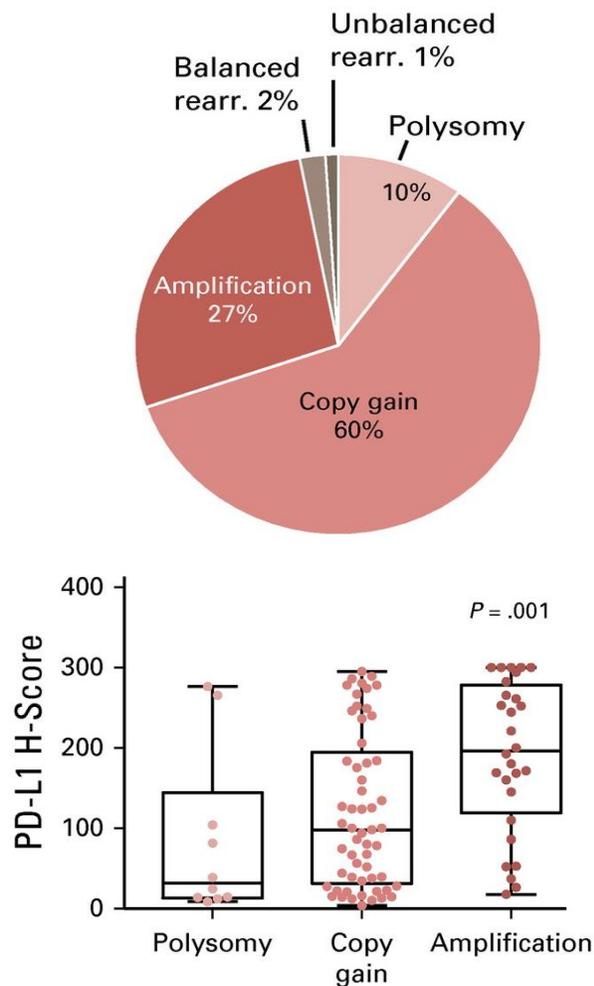


# Phase 2 Results in Hodgkin Lymphoma with Pembrolizumab

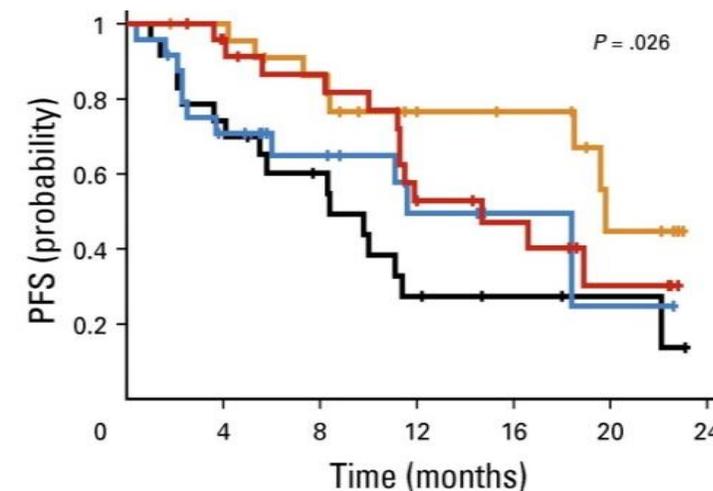


Chen et al. J Clin Oncol. 2017 Jul 1;35(19):2125-2132.

# Lessons Learned - PD-L1 Expression Predicts Outcome After PD-1 Blockade in cHL



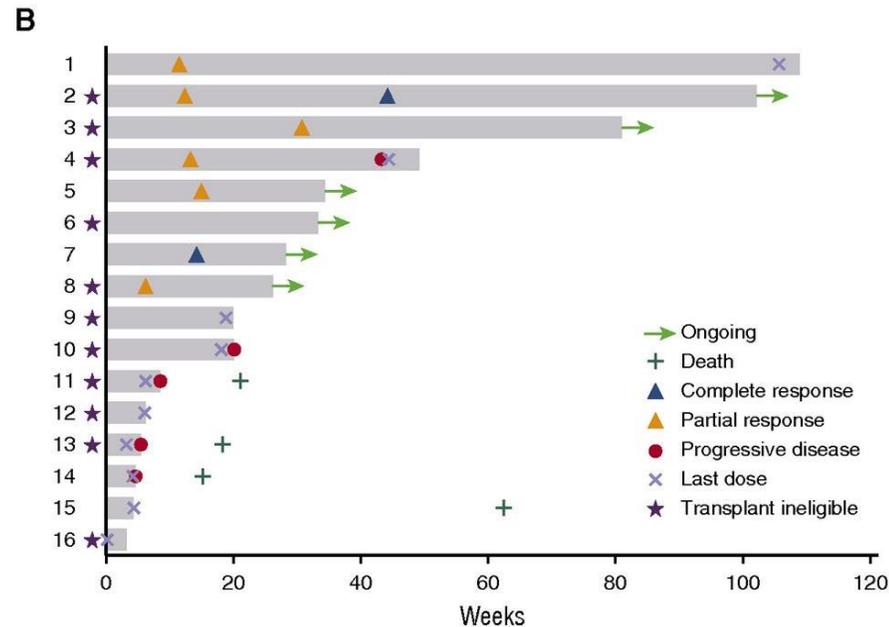
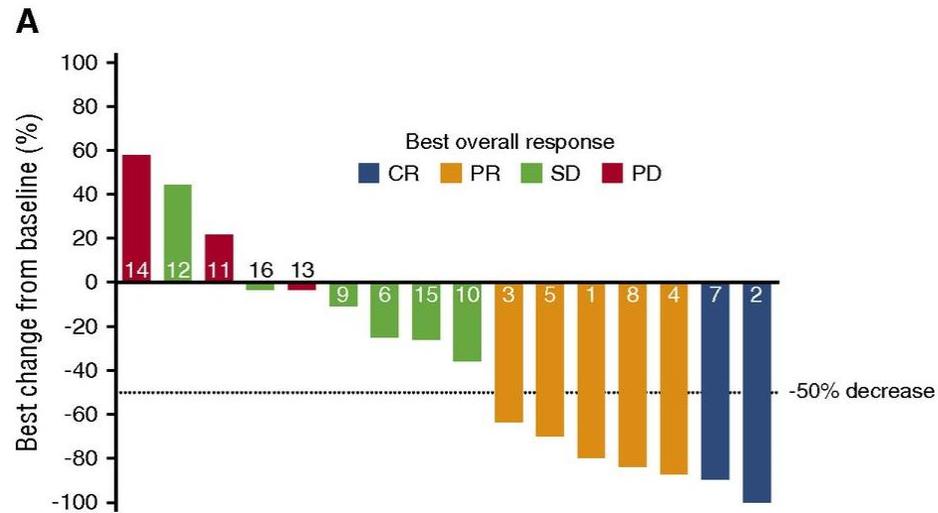
	No. at risk	0	4	8	12	16	20	24
Amplification	27	25	18	9	8	4		
Copy gain	59	45	38	22	12	5		
Polysomy	10	6	1	1	1	1		
Bal. rearr.	2							
Unbal. rearr.	1	1	1	1				



	No. at risk	0	4	8	12	16	20	24
Q1	25	17	11	5	3	2		
Q2	24	16	11	6	2	1		
Q3	23	22	18	11	9	4		
Q4	25	22	18	11	7	3		

Roemer et al. J Clin Oncol. 2018 Apr 1;36(10):942-950.

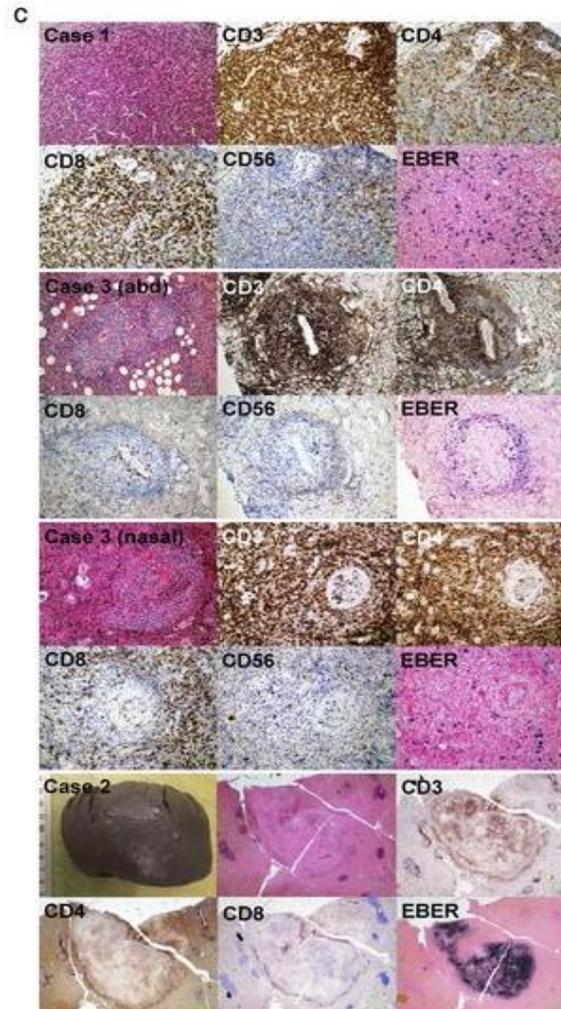
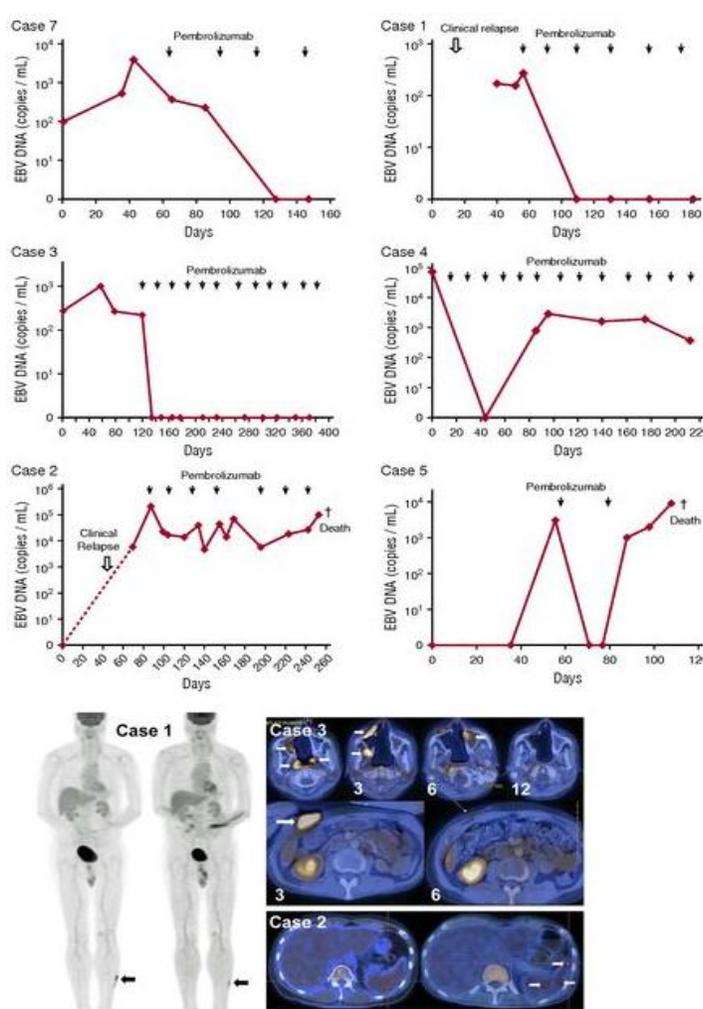
# Encouraging Treatment responses in pembrolizumab-treated patients with rrPMBCL



- Amplifications of 9p24.1 and overexpression of PD-L1/2 common in PMBCL
- ORR – 44% (7/16)

Zinzani et al. Blood 2017;130:267-270

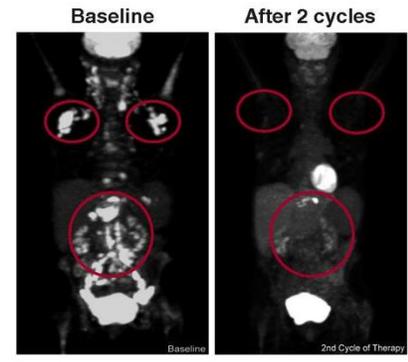
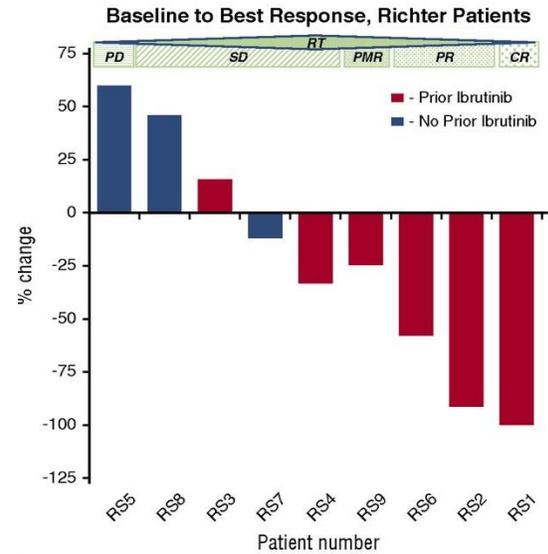
# Responses in patients with relapsed/refractory NK/T-cell lymphomas treated with pembrolizumab.



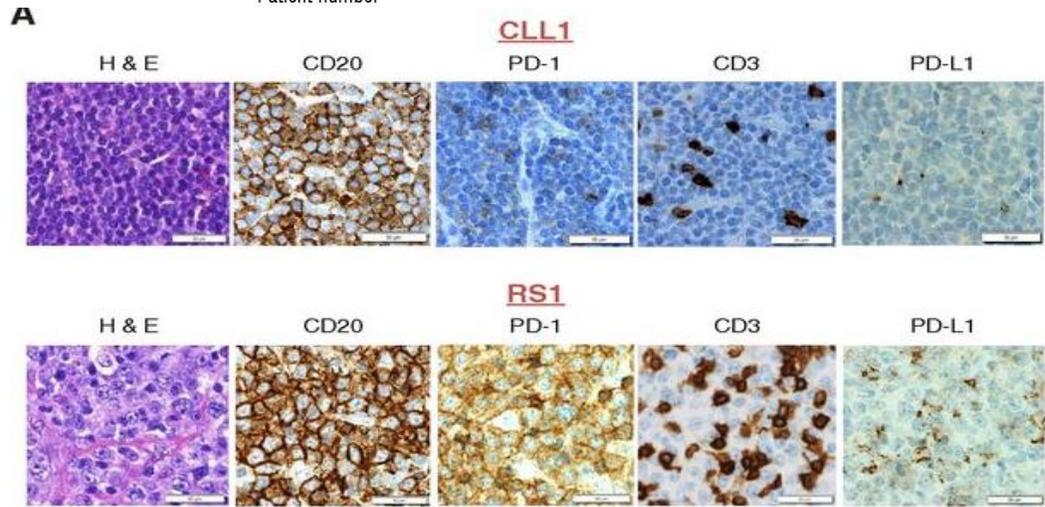
- 5/7 responses
- Decrease in circulating EBV in 3 patients
- Response seemed to be associated with PD-L1 expression

Kwong et al. Blood 2017;129:2437-2442

# Responses in CLL pts with Richter's Syndrome receiving pembrolizumab.

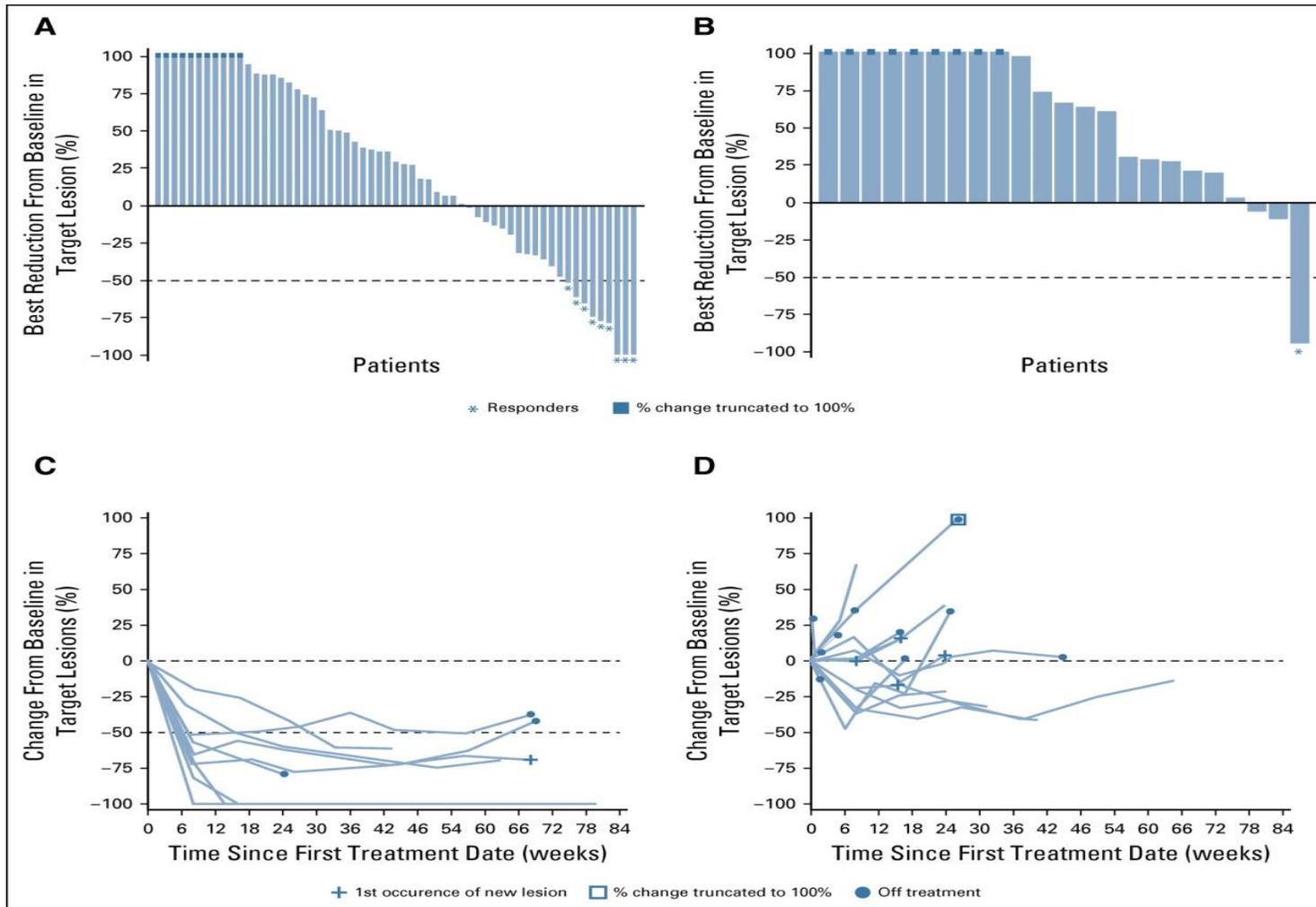


- ORR in RT patients – 44% (4/9)
- ORR in CLL patients – 0% (0/16)
- CLL progressed in responding RT patients
- 0/9 patients had copy number gain or amplification at 9p24.1



Ding et al. Blood 2017;129:3419-3427

# In Contrast: Nivolumab for Relapsed/Refractory Diffuse Large B-Cell Lymphoma

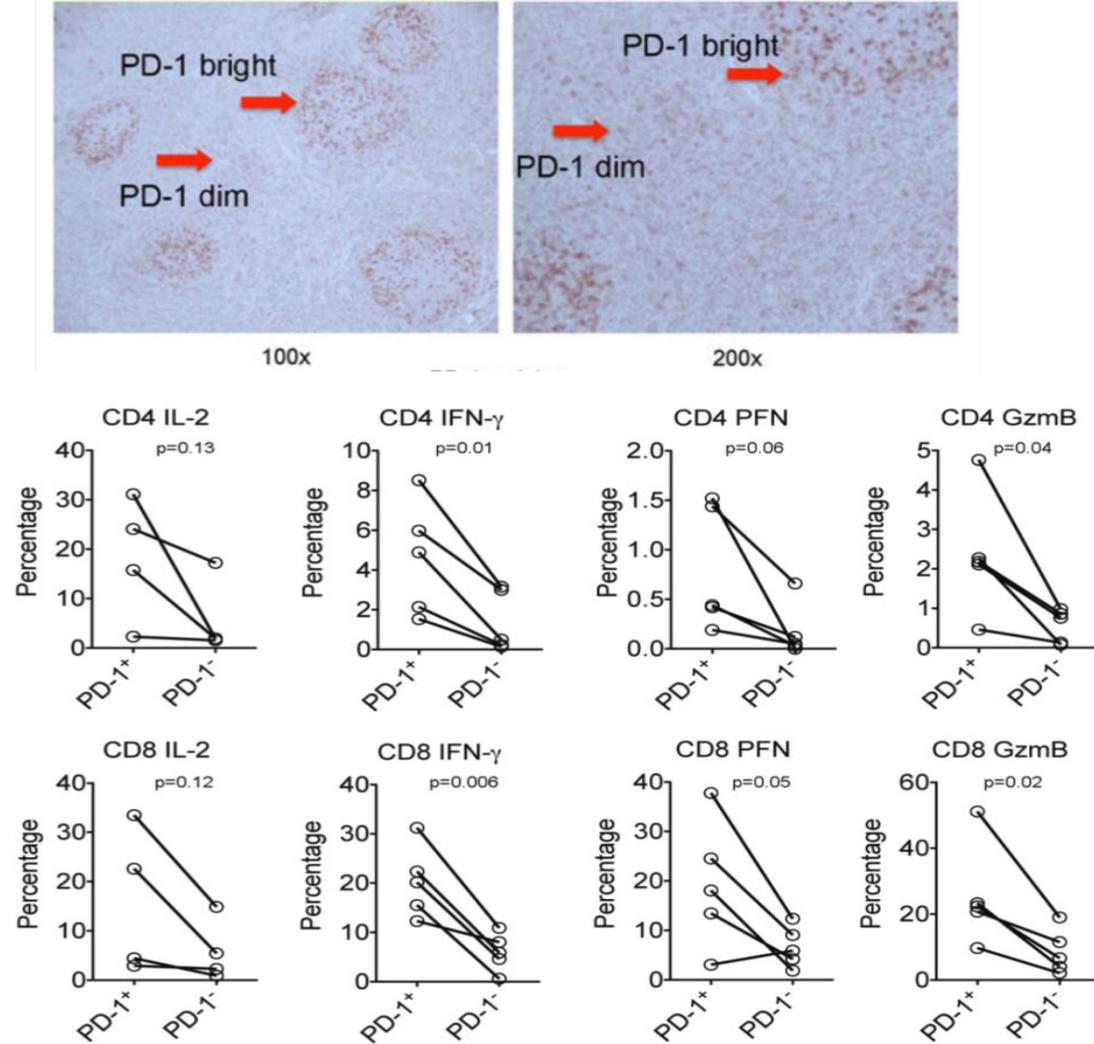


- 121 patients – 78 in the auto-HCT–failed cohort and 34 in the auto-HCT–ineligible cohort.
- ORR were 10% and 3%, and median durations of response were 11 and 8 months.
- Median PFS and OS were 1.9 and 12.2 months in the auto-HCT–failed and 1.4 and 5.8 months in the auto-HCT–ineligible cohorts.

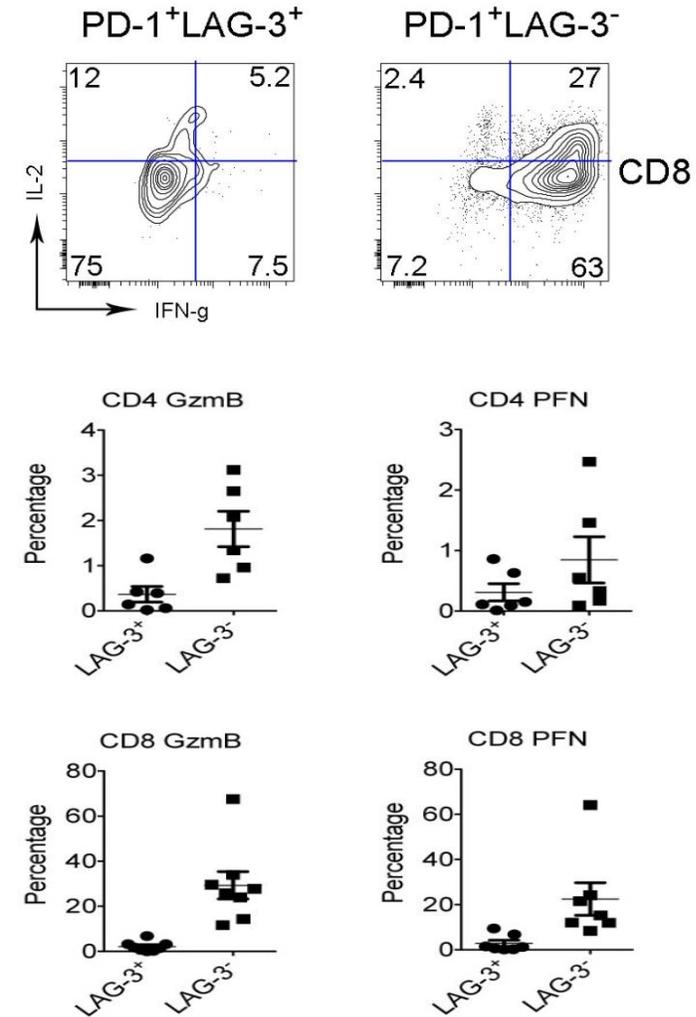
Ansell SM et al. J Clin Oncol. 2019 Jan 8;JCO1800766.

# Complicating Factor - Not all PD-1+ T-cells are inhibited or exhausted

A.



B.



Yang et al. Blood Cancer J. 2015 Feb 20;5:e281.  
Yang et al. Oncotarget. 2017, 8(37):61425-61439

# Complicating Factor - PD-1 may be expressed on malignant cells – Richter's Syndrome

## Richter's Syndrome

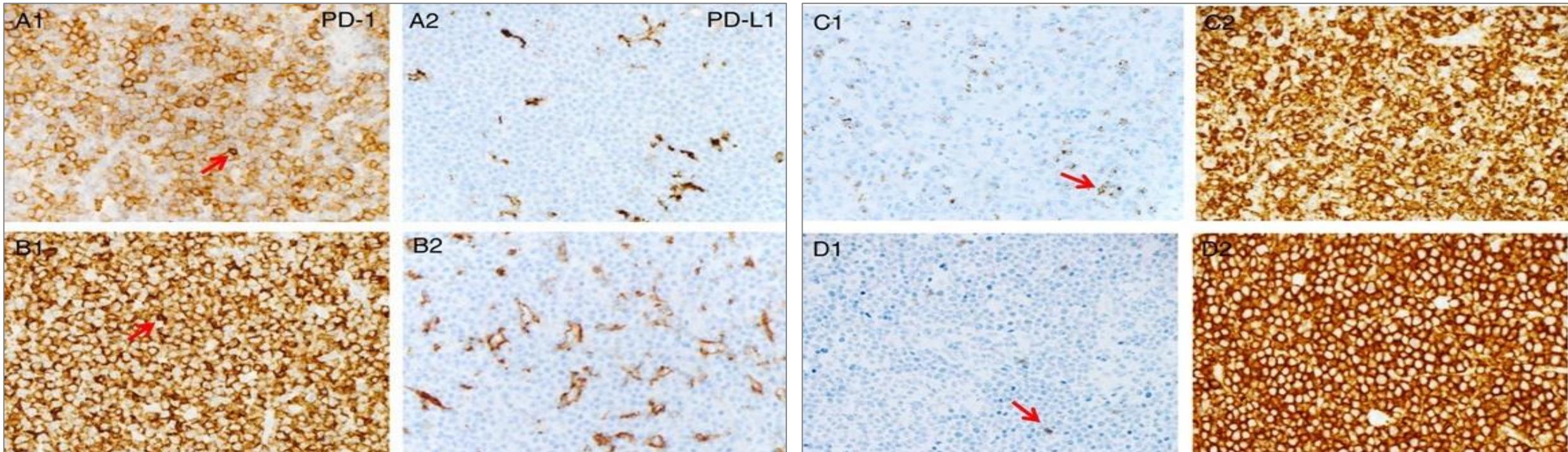
## DLBCL

PD-1

PD-L1

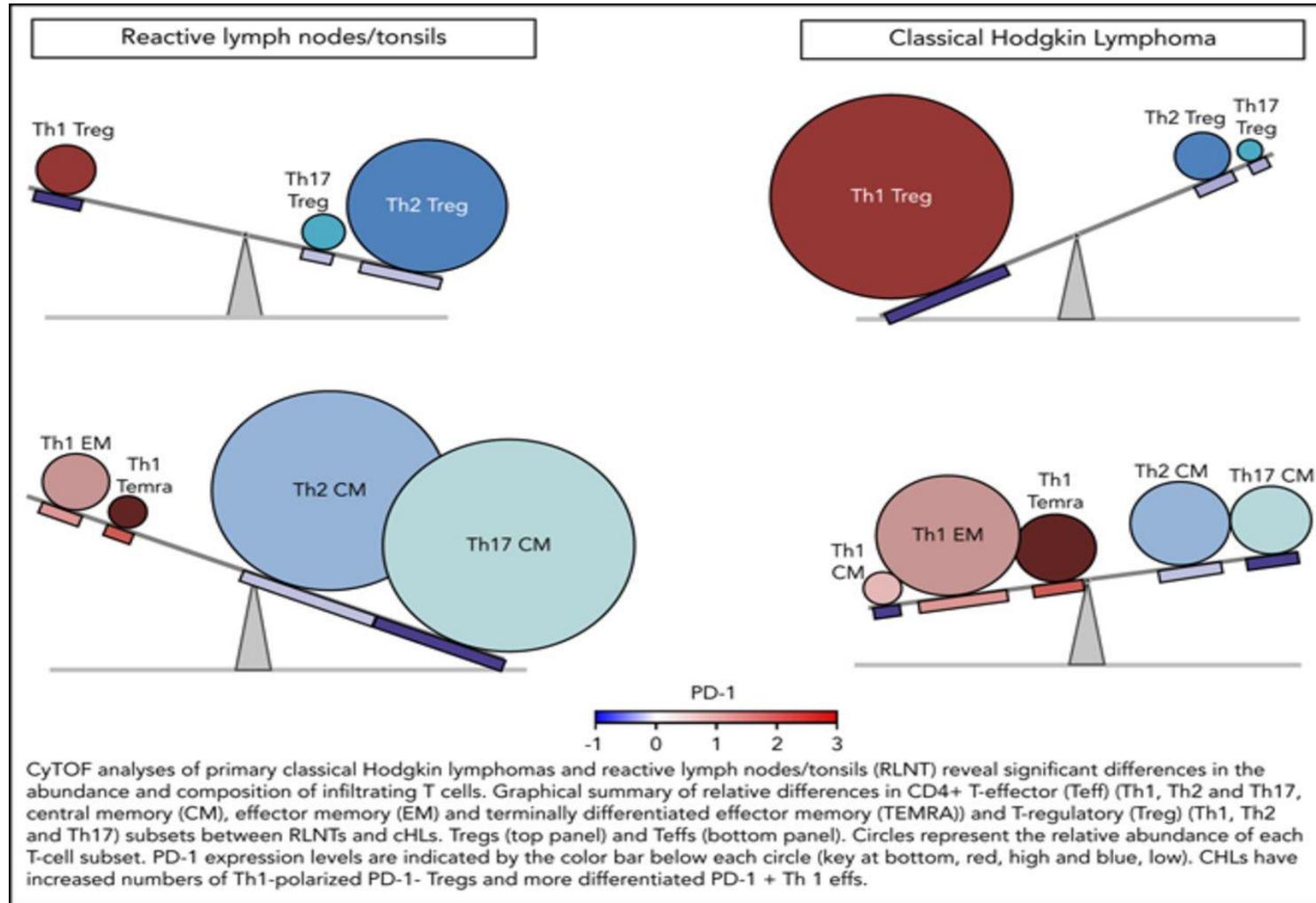
PD-1

PD-L1



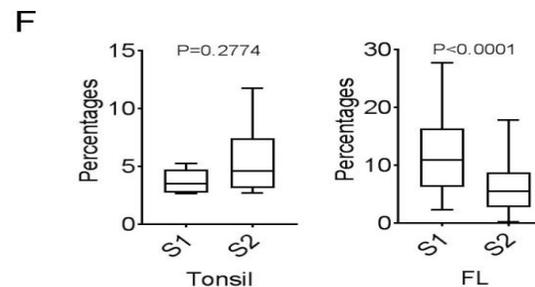
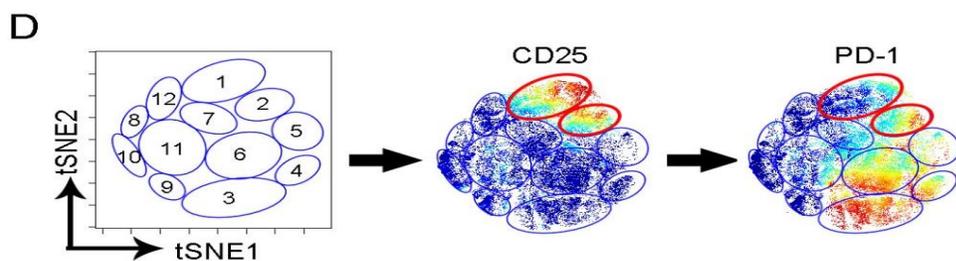
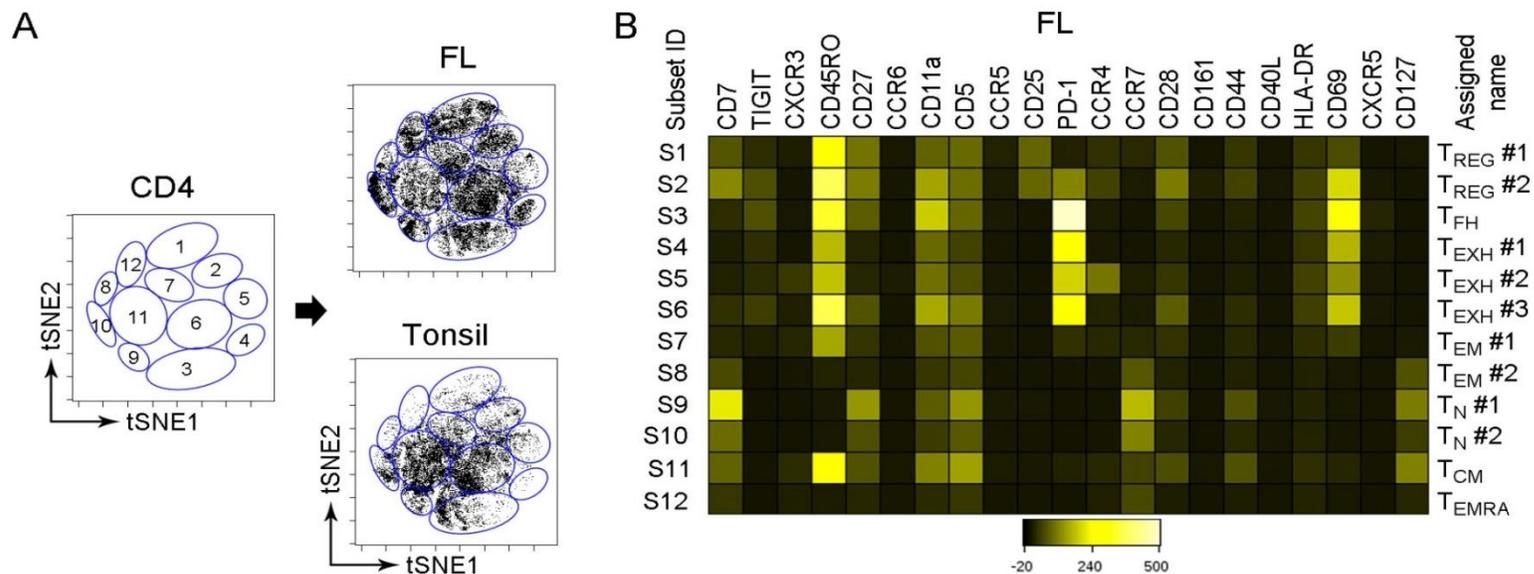
He et al. Am J Surg Pathol. 2018 Jul;42(7):843-854.

# Complicating Factor – In cHL Intratumoral CD4+ T-cells appear more relevant than CD8+ T-cells



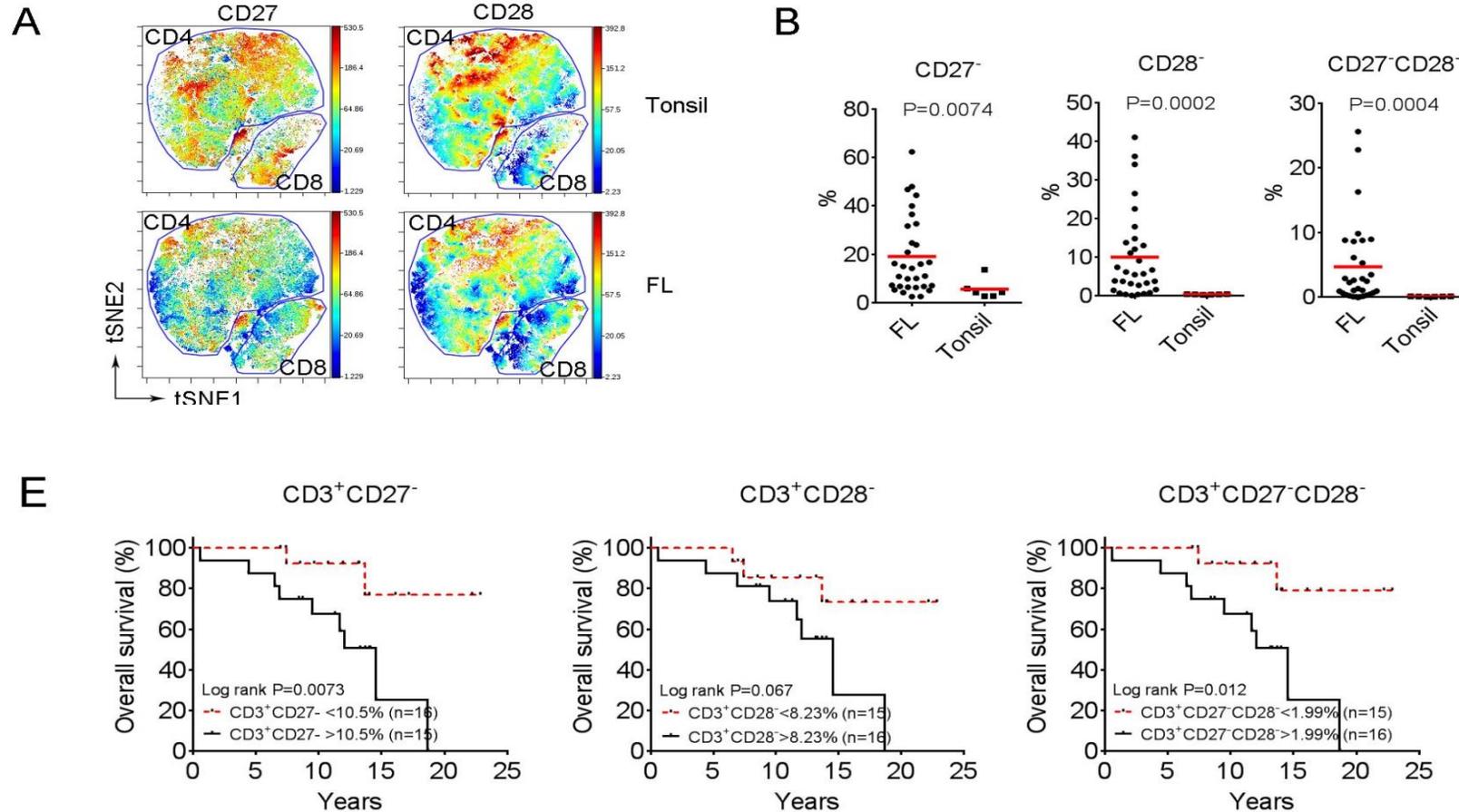
Cader et al. Blood 2018;132:825-836

# Complicating Factor – A similar population of PD-1+ Treg cells are seen In Follicular Lymphoma



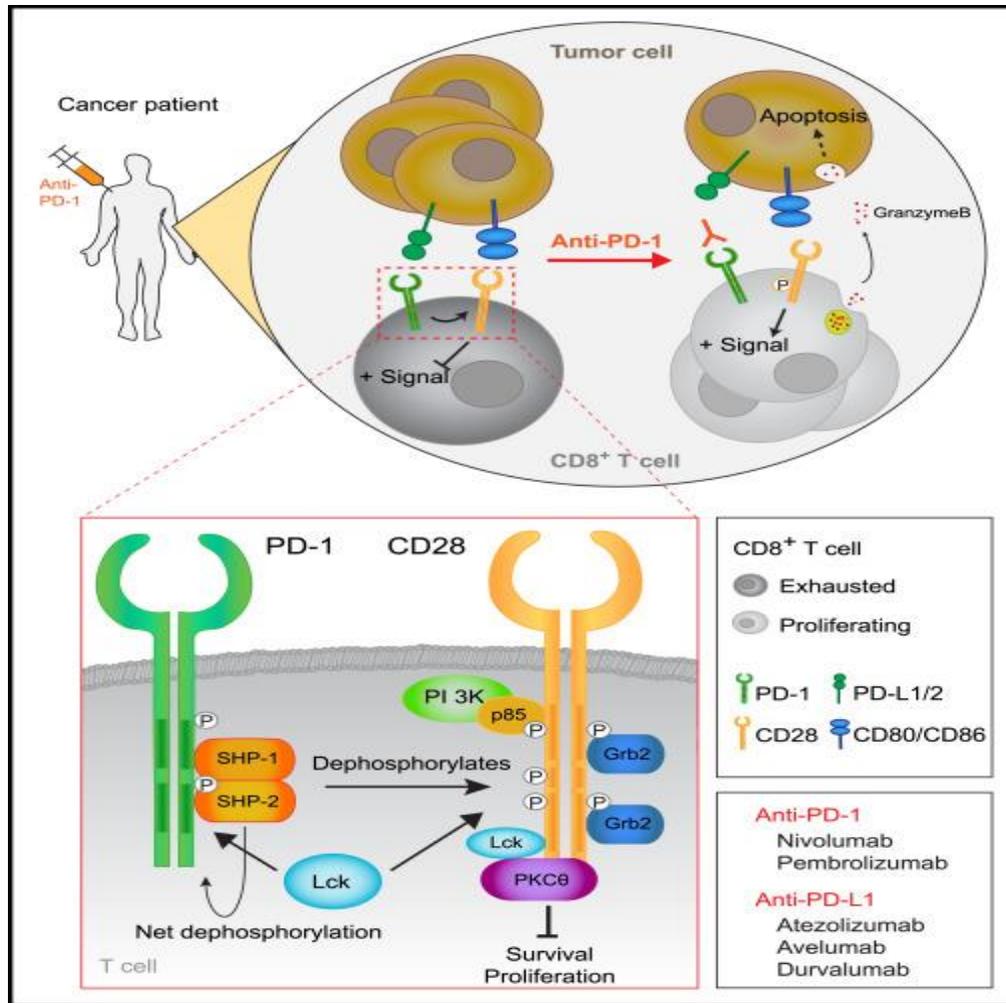
Yang et al. Cell Reports 2019; 26(8):2178-2193

# Complicating Factor: Intratumoral T-cells have downregulated co-stimulatory receptors



Yang et al. Cell Reports 2019; 26(8):2178-2193

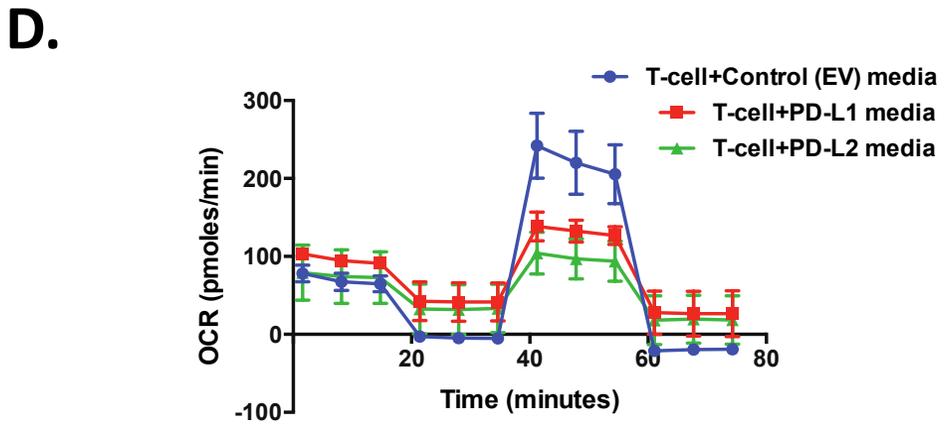
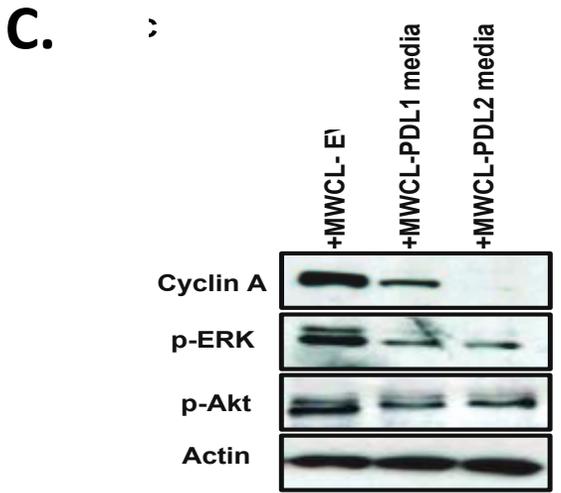
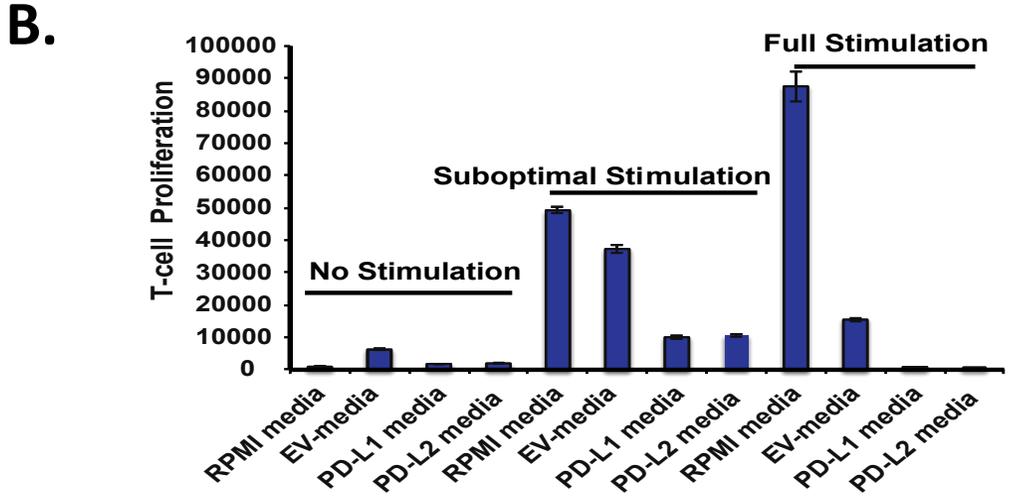
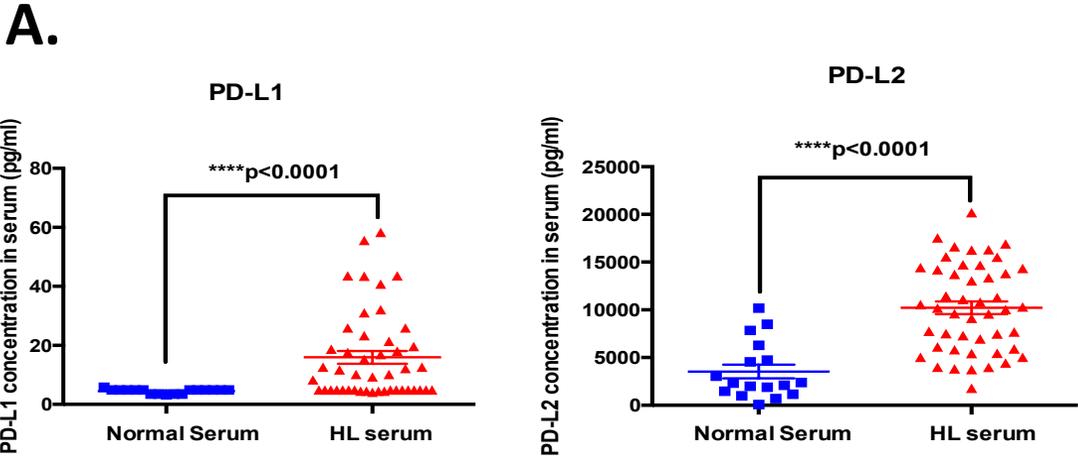
# Rescue of exhausted CD8 T cells by PD-1-targeted therapies is CD28-dependent



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.

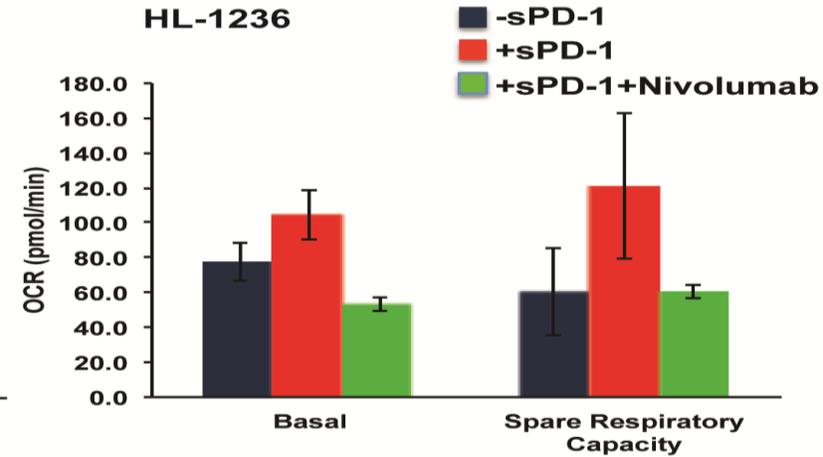
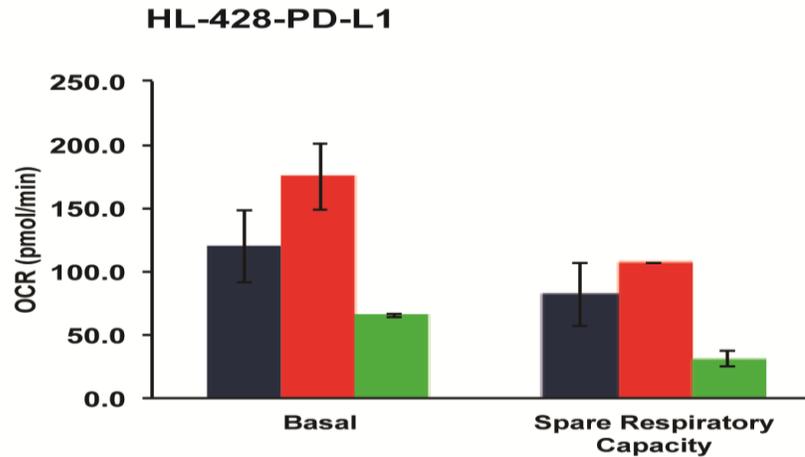
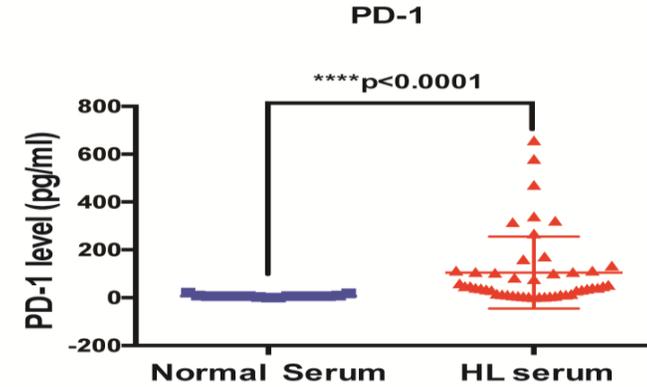
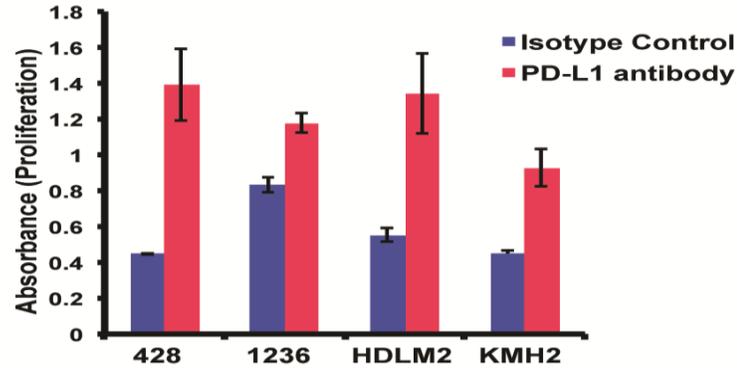
# Complicating Factor: Soluble PD-L1 inhibits T-cell Function at Remote

## Sites



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

# Complicating Factor: Reverse signaling via PD-L1 may promote RS cell growth and survival

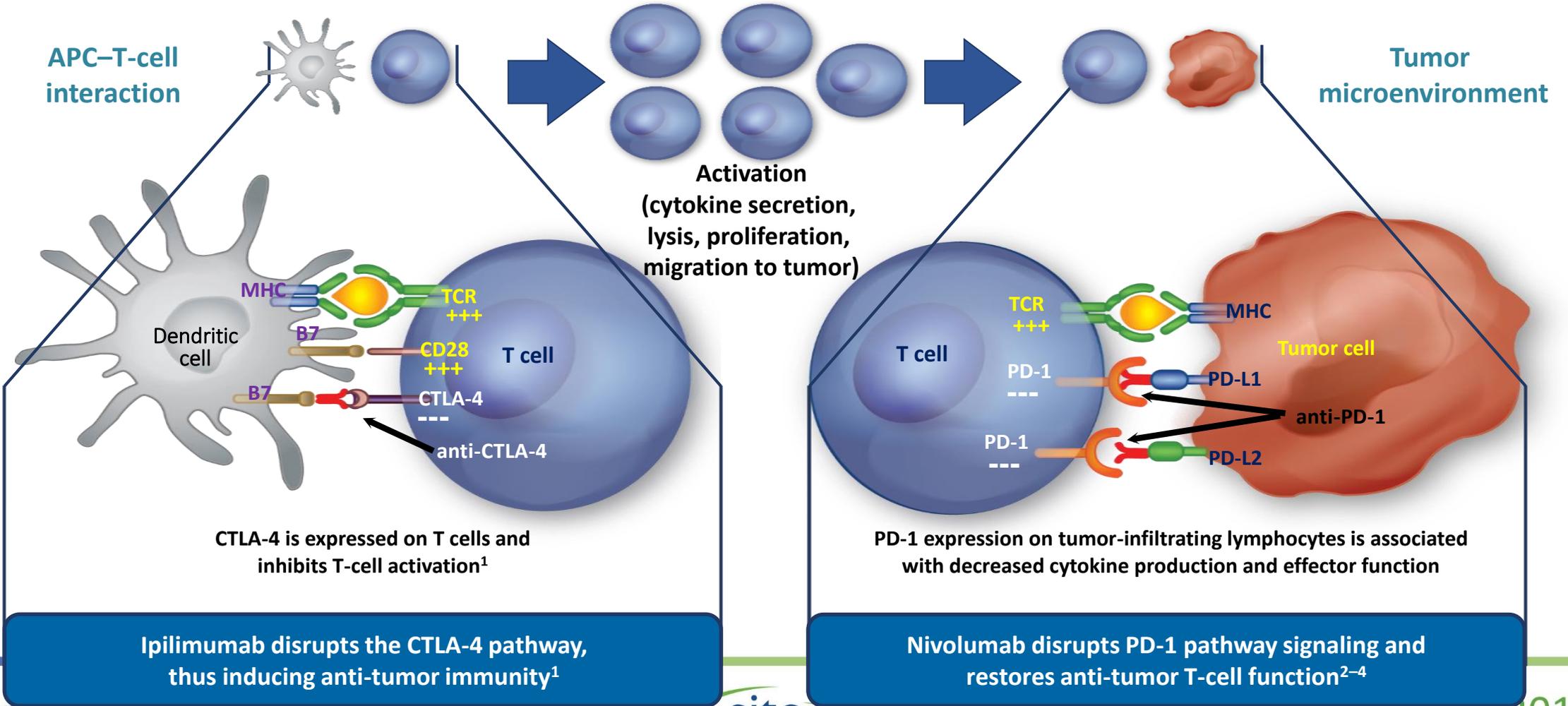


Jalali et al. Blood Cancer J. 2019 Feb 19;9(3):22

# Strategy #2: Combination Approaches – Nivolumab and Ipilimumab in cHL

## CTLA-4 blockade (ipilimumab)

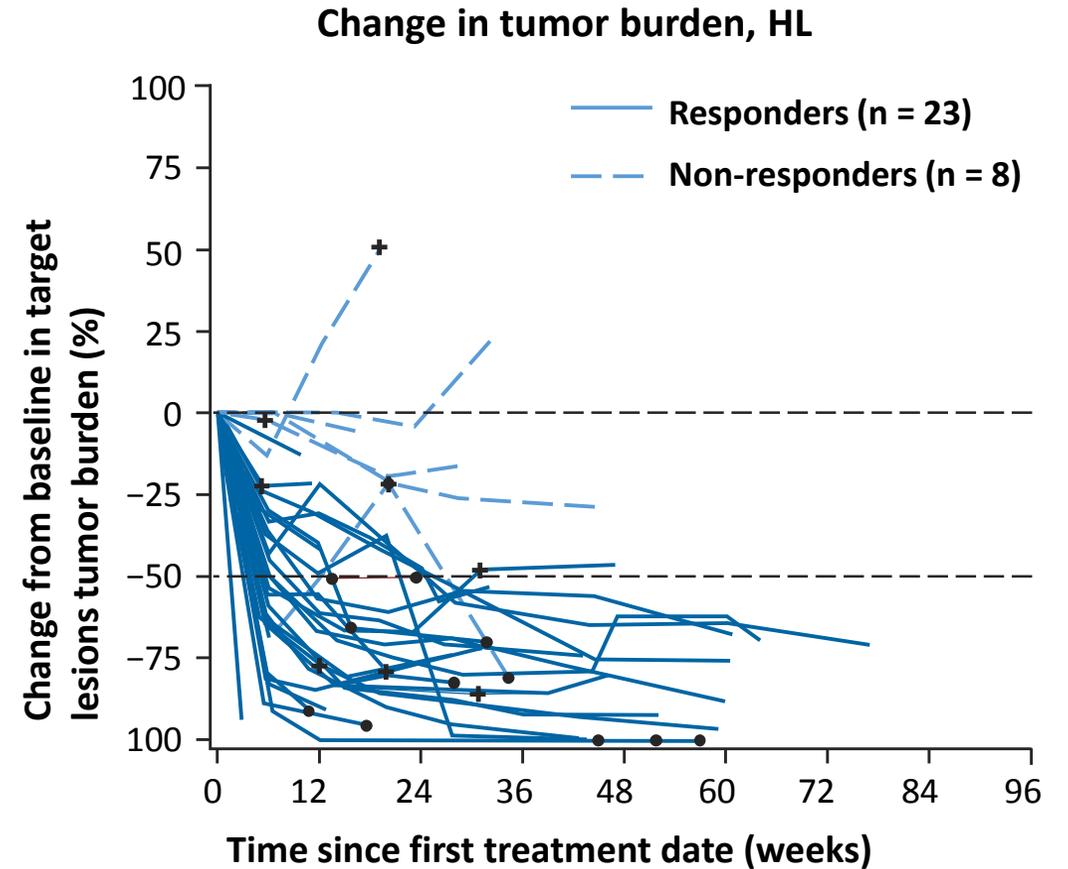
## PD-1 blockade (nivolumab)



# Combinations – Two Checkpoint Inhibitors

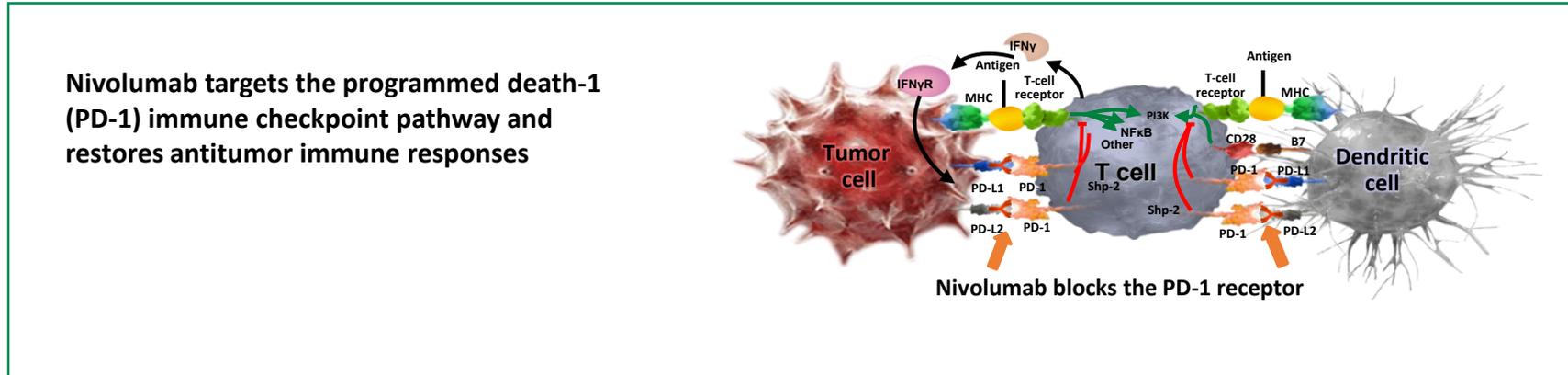
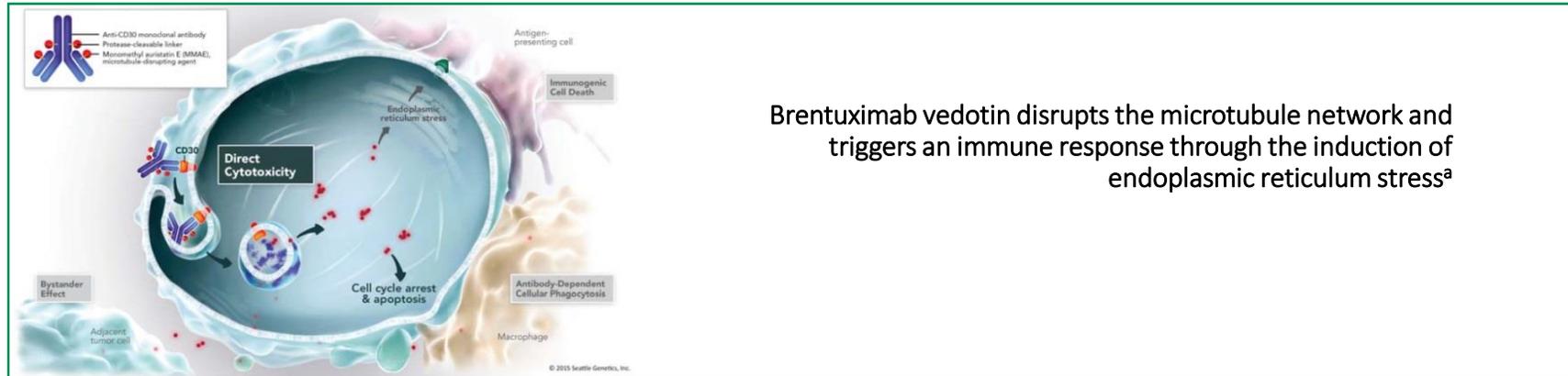
## Nivolumab and Ipilimumab in cHL

	HL (N = 31)
<b>ORR, n (%)<sup>a</sup></b>	23 (74)
Complete response	6 (19)
Partial response	17 (55)
Stable disease	3 (10)
Relapsed or progressive disease	3 (10)
Median duration of OR, months (range)	NR (0.0+, 13.4+)
	<b>Transplant naïve<sup>b</sup> (n = 18)</b>
<b>ORR, n (%)</b>	12 (67)



Ansell et al. ASH 2016 abstract #183

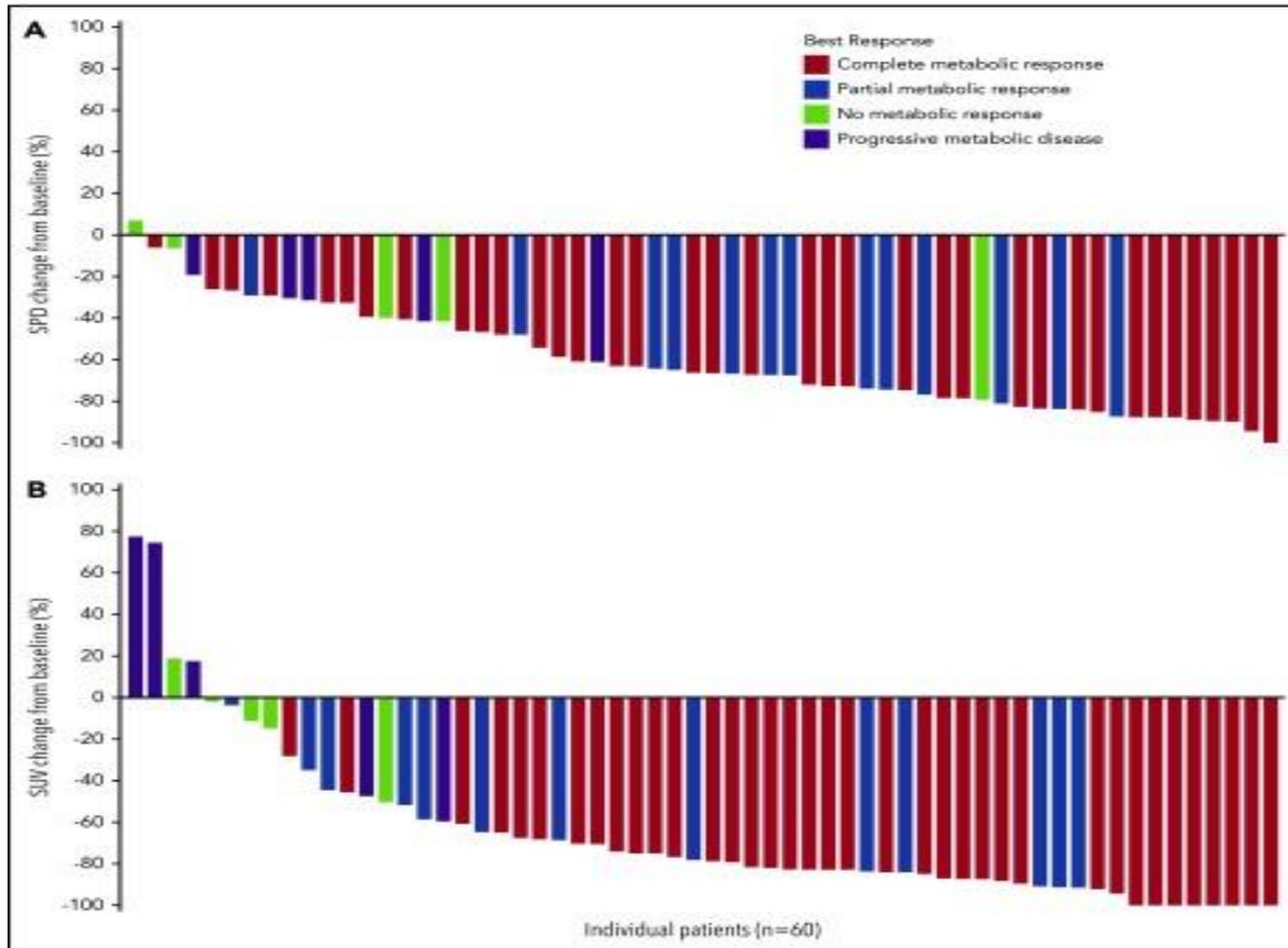
# Combinations - Brentuximab vedotin (BV) plus nivolumab as Salvage Therapy



- Both agents are well tolerated with high single-agent response rates in patients with R/R HL (BV=72% ORR, 33% CR; Nivo=73% ORR, 28% CR)
- Together, they could yield improved CR rates and improved durability of responses, and potentially lead to better long-term outcomes

Herrera et al. ASH 2016 abstract #1105

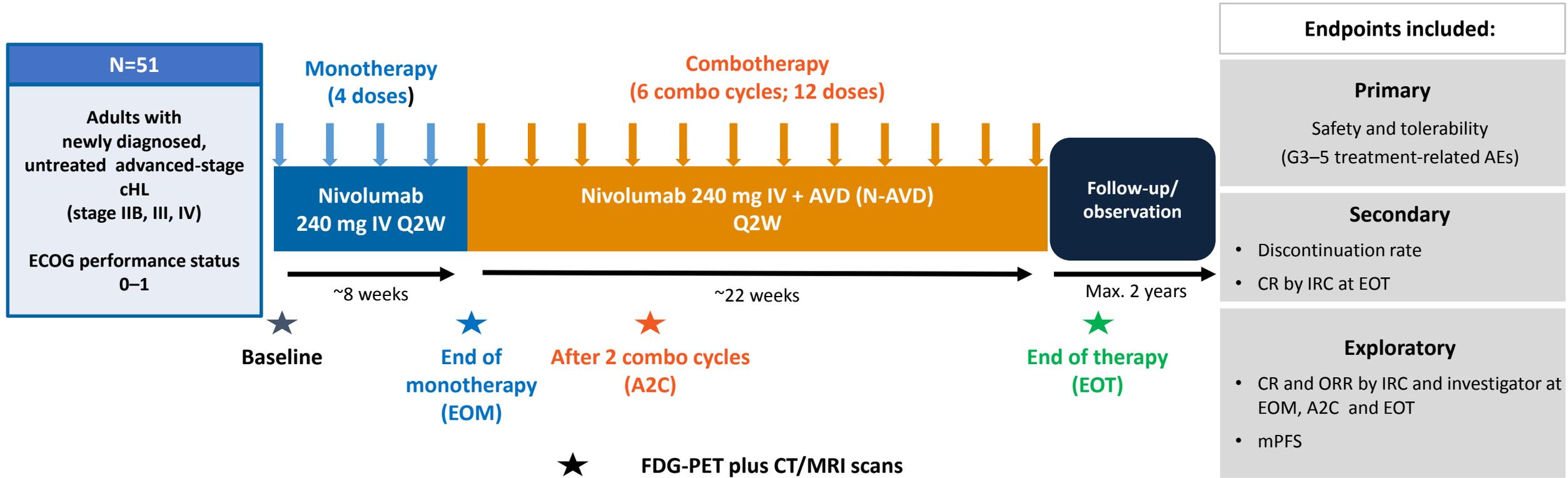
# Brentuximab vedotin plus nivolumab in patients with relapsed Hodgkin lymphoma



- 62 patients received 4 cycles of BV and nivolumab. Patients could proceed to ASCT.
- The CR rate (n = 61) was 61%, with an objective response rate of 82%.
- BV plus Nivo was an active and well-tolerated first salvage regimen, potentially providing patients with R/R HL an alternative to traditional chemotherapy.

Herrera et al. Blood. 2018 Mar 15;131(11):1183-1194.

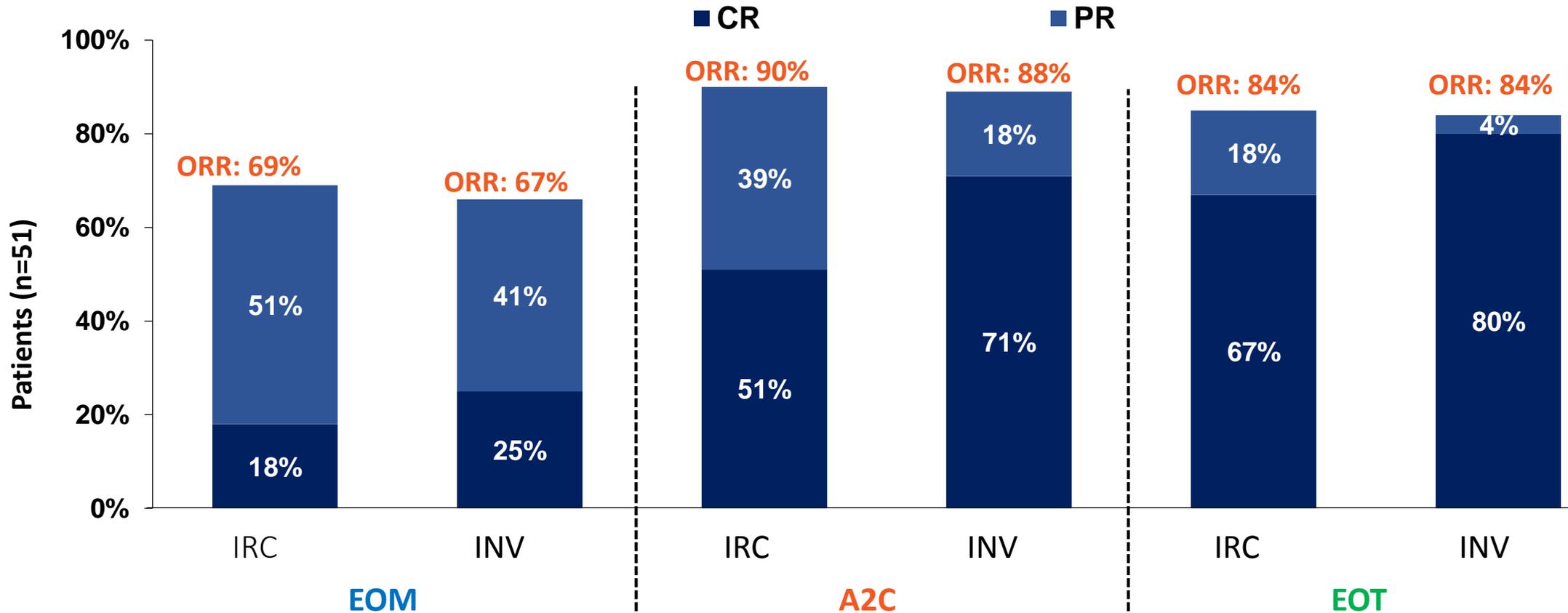
# Combination Approaches – PD-1 Blockade with Chemotherapy in cHL



- Responses were assessed using the IWG 2007 criteria
- Median duration of follow-up was 11.1 months (database lock: 12 October 2017)
- Bleomycin was excluded due to potential overlapping pulmonary toxicity

Ramchandren et al. J Clin Oncol. 2019 Aug 10;37(23):1997-2007.

# Combination Approaches – PD-1 Blockade with Chemotherapy in cHL

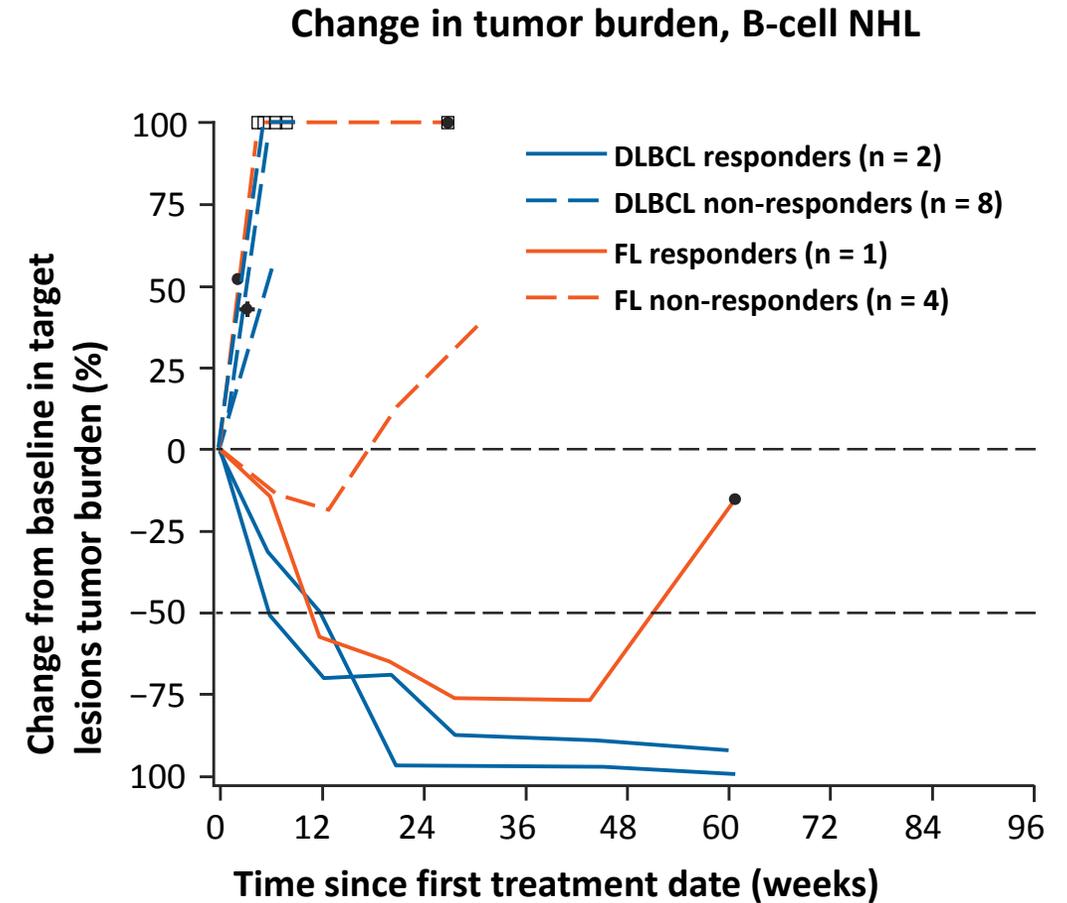


- At EOT, ORR per investigator in the ITT population was 84%, with 80% of patients achieving CR

Ramchandren et al. J Clin Oncol. 2019 Aug 10;37(23):1997-2007.

# Combining 2 checkpoint Inhibitors – Nivolumab and Ipilimumab in B-cell NHL

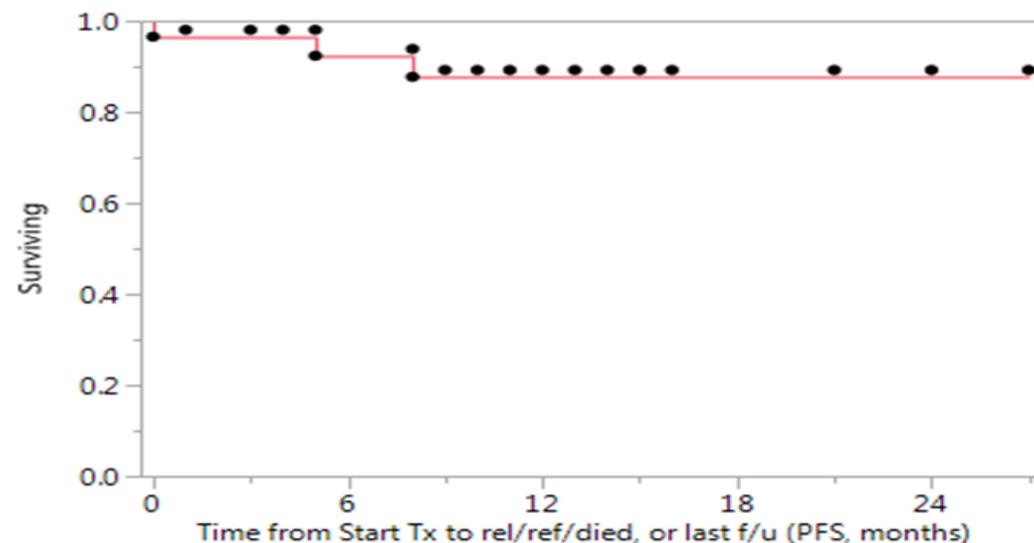
	B-cell NHL (N = 15)
<b>ORR, n (%)<sup>a</sup></b>	3 (20)
Complete response	0
Partial response	3 (20)
Stable disease	1 (7)
Relapsed or progressive disease	8 (53)
Median duration of PR, months (range)	NR (11.0+, 12.7+)



Ansell et al. ASH 2016 abstract #183

# Combining a checkpoint inhibitor with chemotherapy – Pembrolizumab plus RCHOP in diffuse large B-cell lymphoma

- Pembrolizumab 200mg IV every 3 weeks given with standard RCHOP.
- 29 patients treated. 11 non-GCB. 3 FL grade 3B. 2 EBV+. 1 double hit. 6/17 double expressors
- One patient died of a gastric bleed (Had stomach involvement by lymphoma).
- Toxicity appears similar to RCHOP alone.
- 18 CR (69%), 7 PR, and 1 primary refractory disease.



Smith et al. ASH 2018 abstract #1686.

# What does this teach us?

- Many immunological barriers to an effective anti-tumor response in lymphoma and the biology is complex
- Diseases with genetic alterations at chromosome 9p24.1 are more likely to respond to PD-1 blockade
- Blockade of PD-1 may affect T-cell populations differently
- Combinations (often including cytotoxic agents) are likely to be important in the future

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