Update on the Role of anti-PD1 and anti-PDL1

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Conflicts of Interest

- Research Funding from –
  - Bristol Myers Squibb
  - Celldex Therapeutics
  - Seattle Genetics

Immune checkpoint inhibitors in Hodgkin and non-Hodgkin Lymphoma

- What's the rationale for using them?
- Update on how well they work?
- Where will we use them?
  - Alone?
  - In combinations?

How do T cells become exhausted?

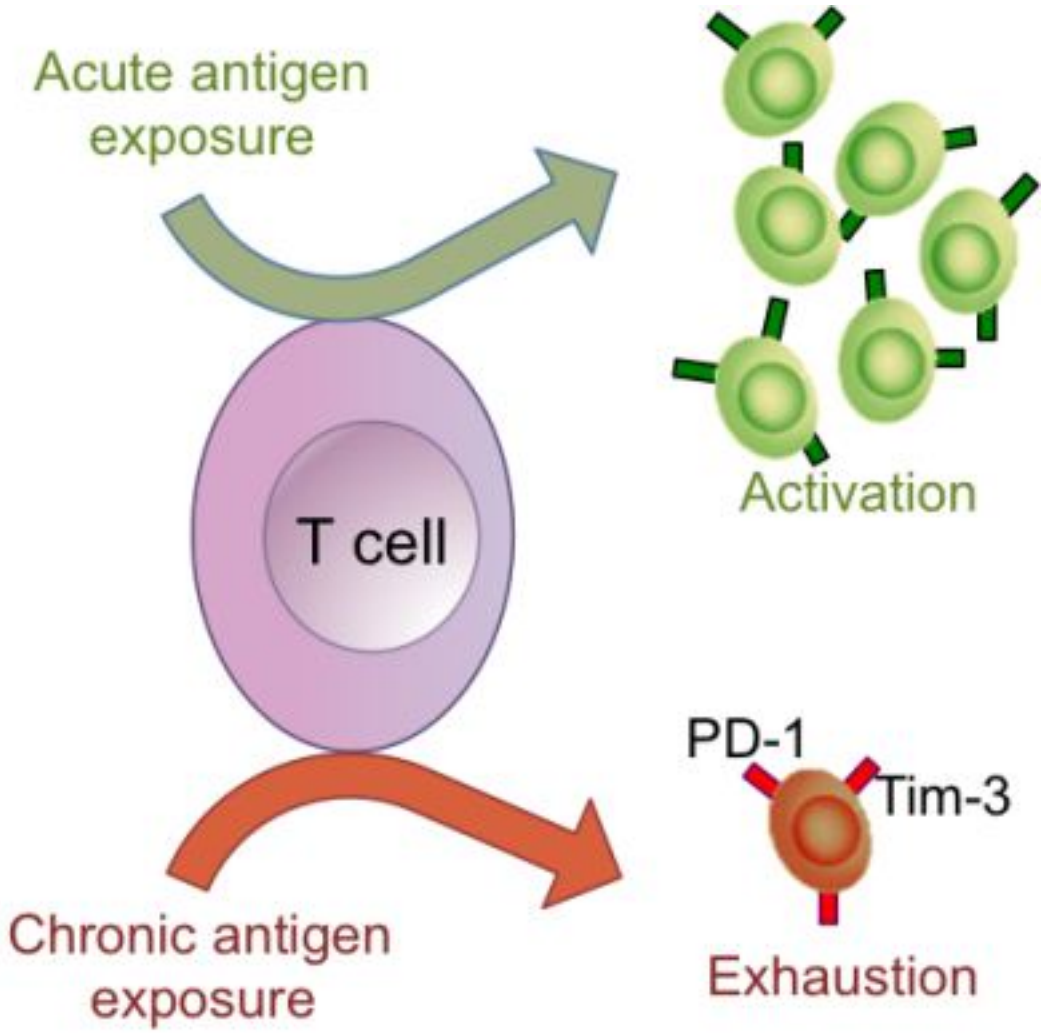
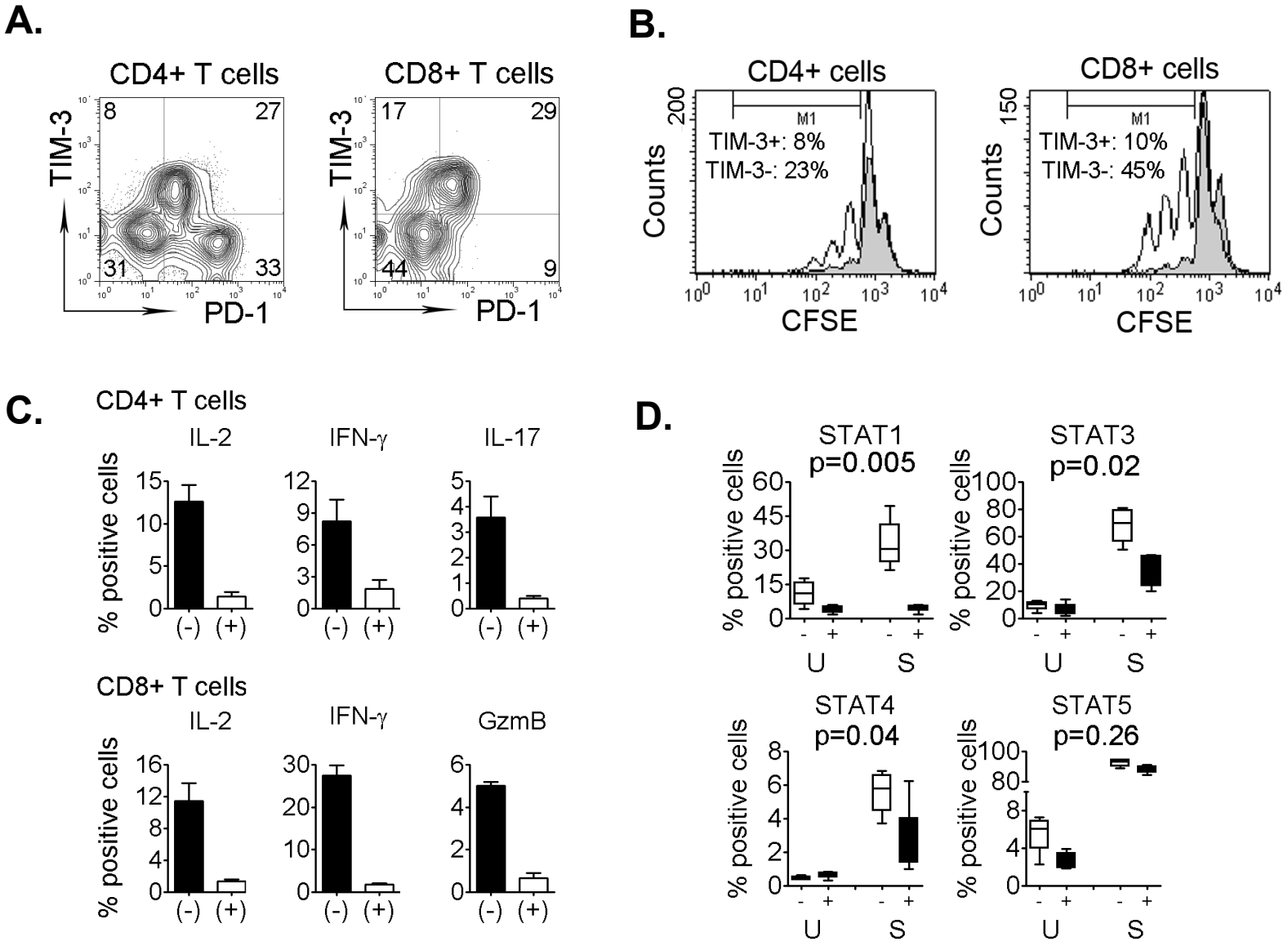


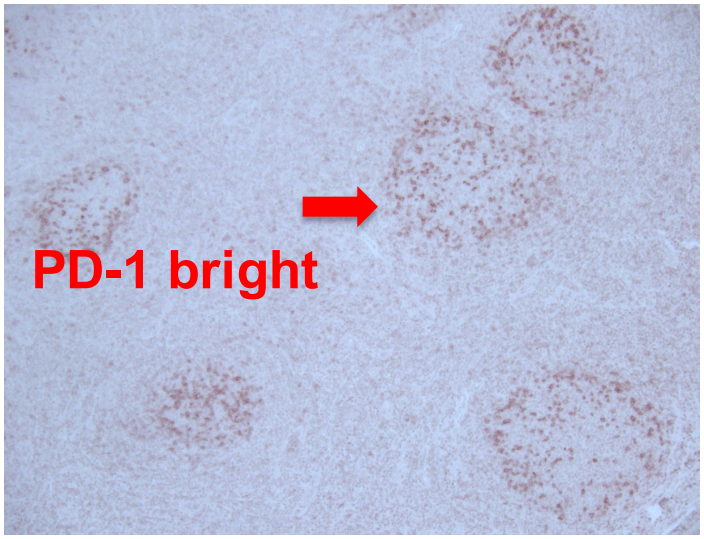
Image provided by Paul Nghiem (Fred Hutchinson Cancer Center)

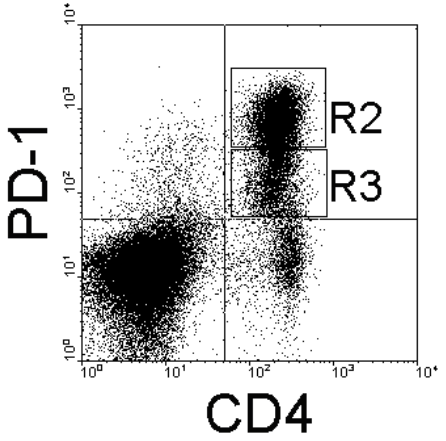
Are exhausted T-cells present in lymphoma?

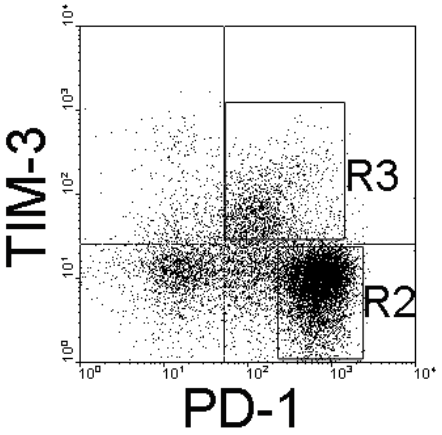


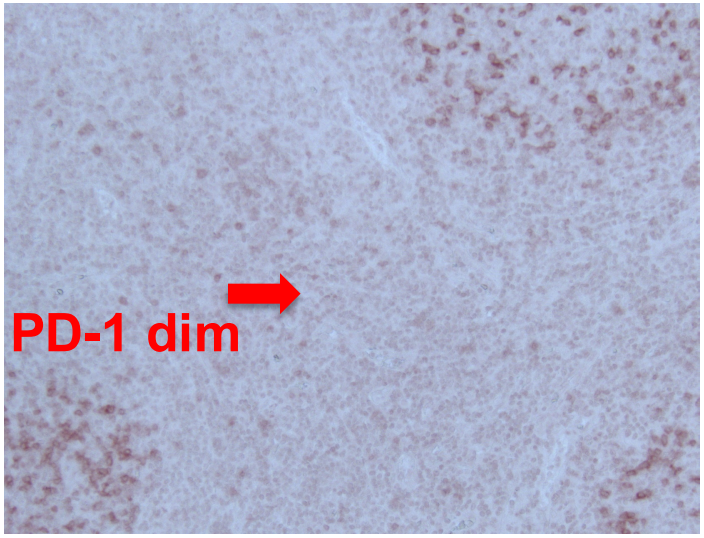
Yang et al. J Clin Invest 2012;122(4):1271-82.

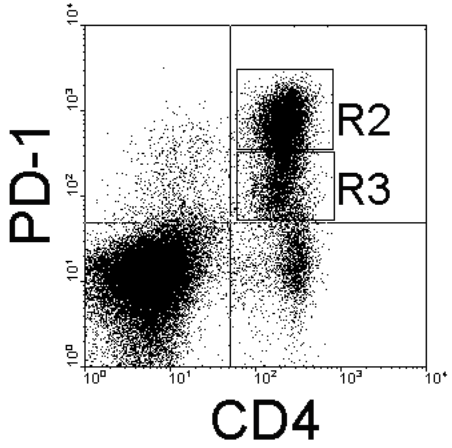
Not all PD-1+ cells are exhausted

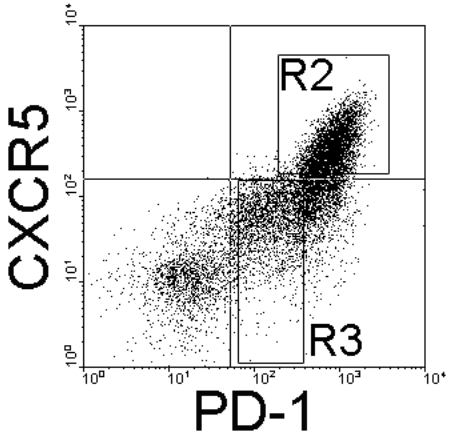






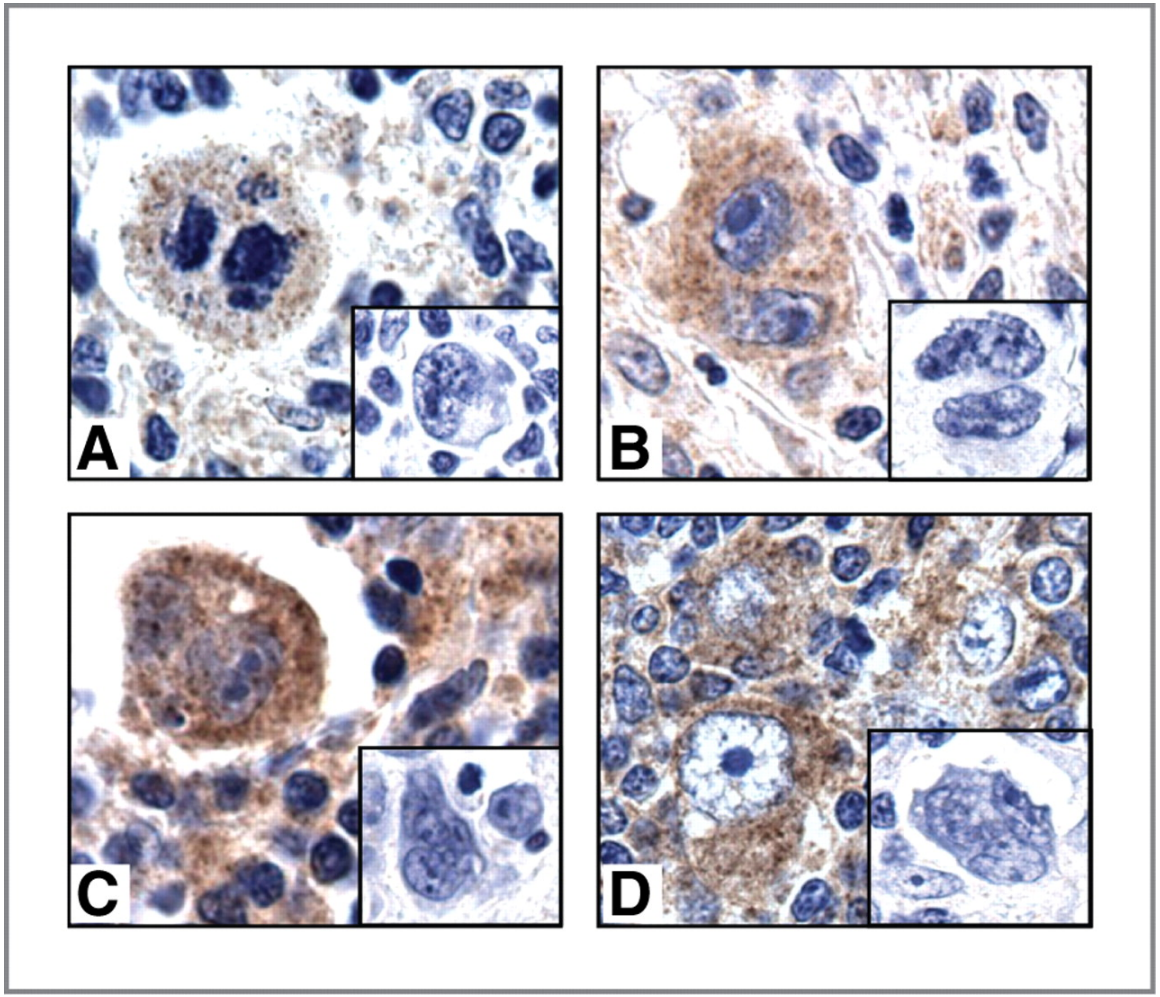






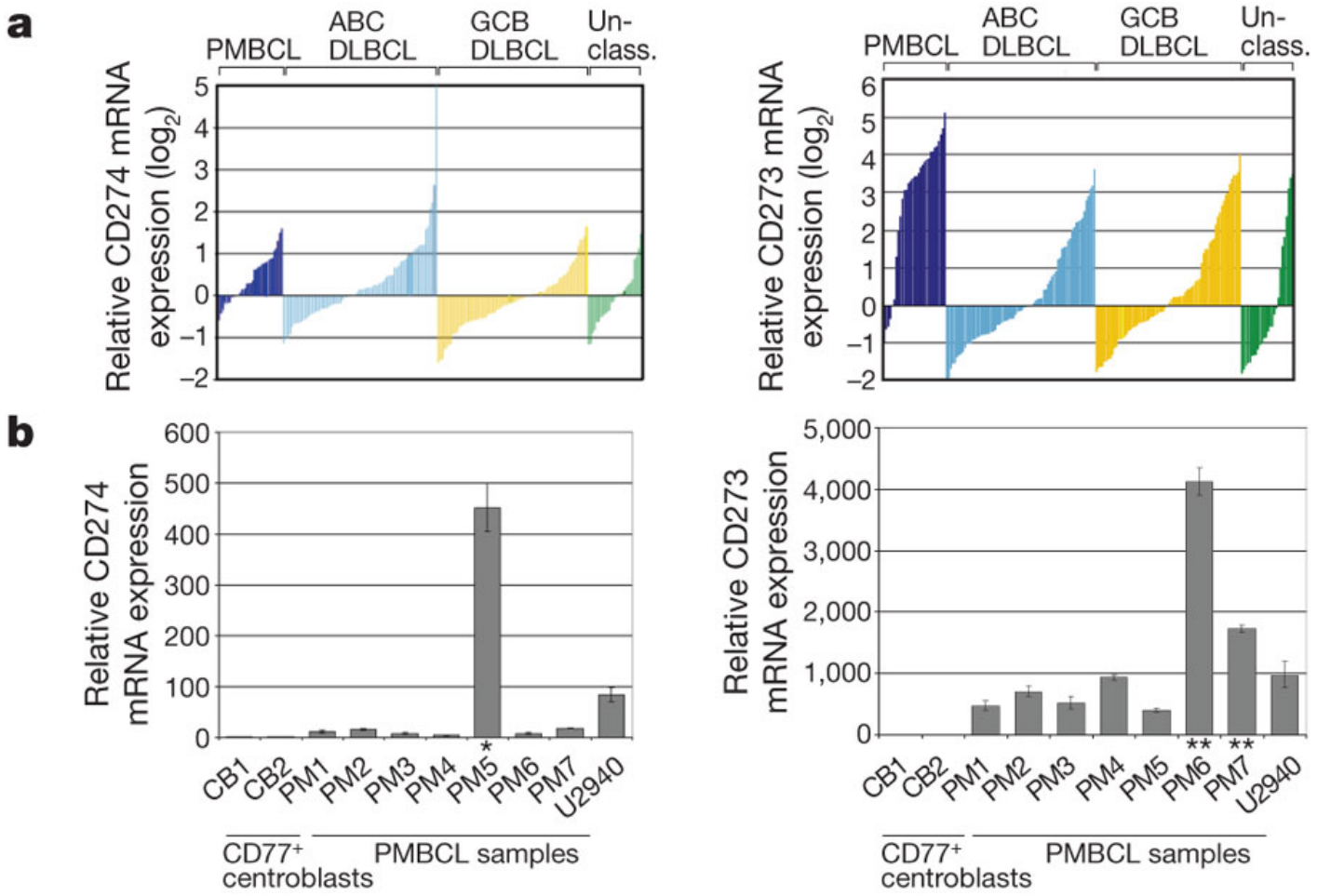
Yang et al. Blood Cancer J. 2015 Feb 20;5:e281.

PD-L1/2 is overexpressed in classical Hodgkin lymphoma and PMBCL due to EBV or CIITA translocations.



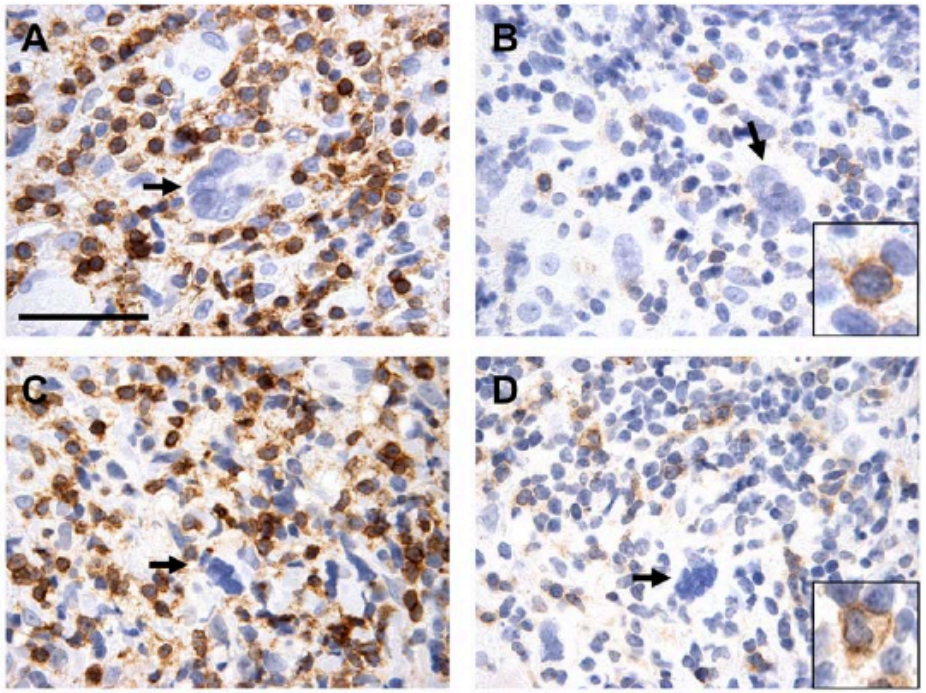
Green M R et al. Clin Cancer Res 2012;18:1611-1618

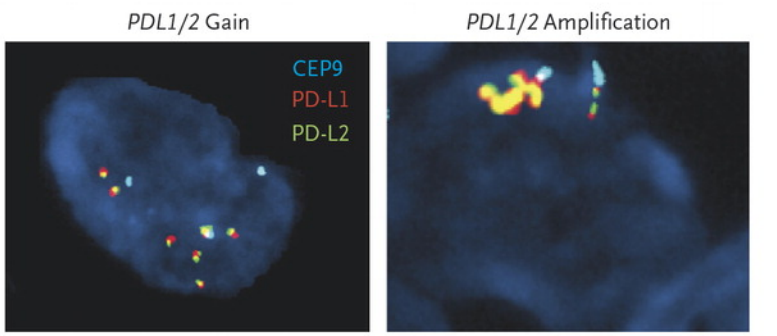
EBV or CIITA translocations increase PD-L1/2 expression in classical Hodgkin lymphoma and PMBCL.

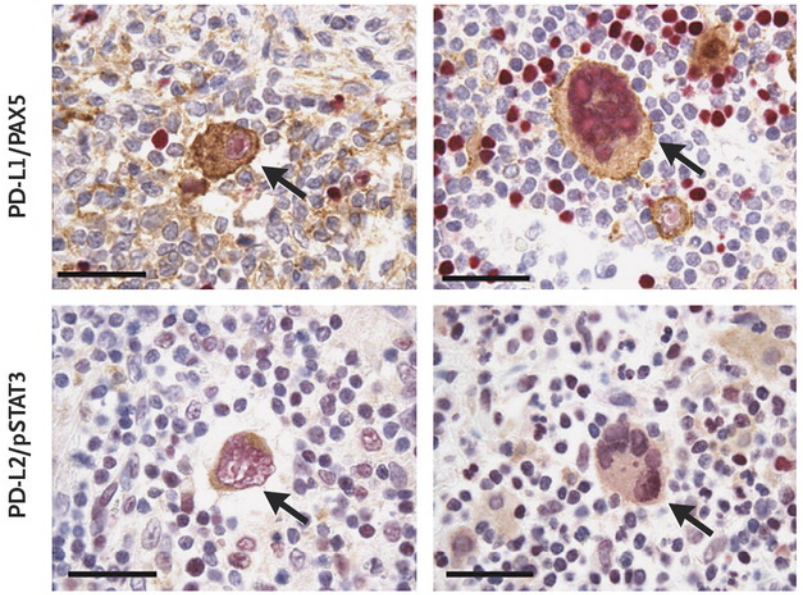


C Steidl et al. Nature 2011 Mar 17;471(7338):377-81.

Alterations in chromosome 9p24.1 increase PD-L1 and PD-L2 expression in classical Hodgkin Lymphoma

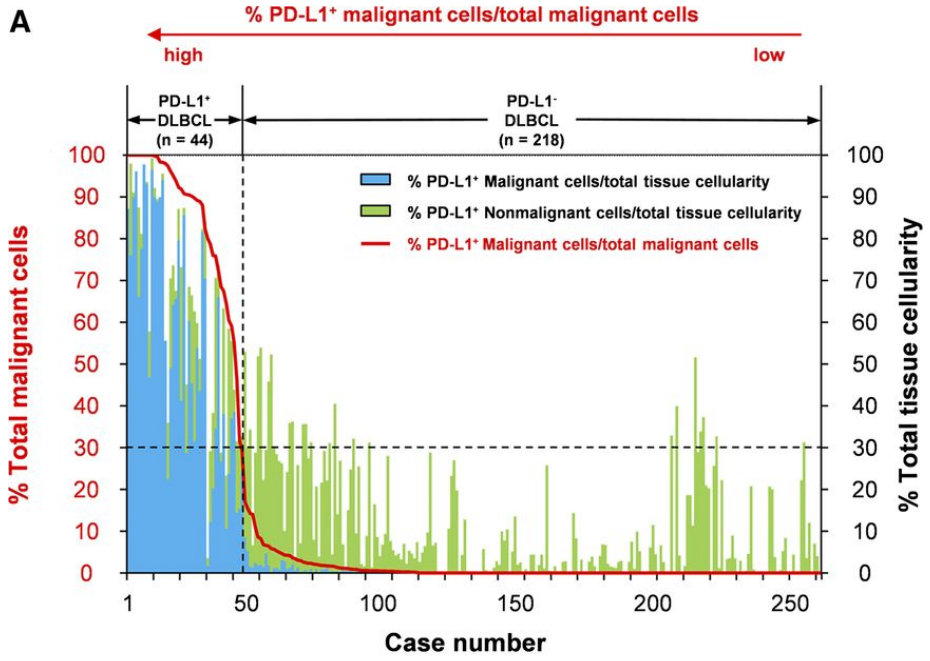


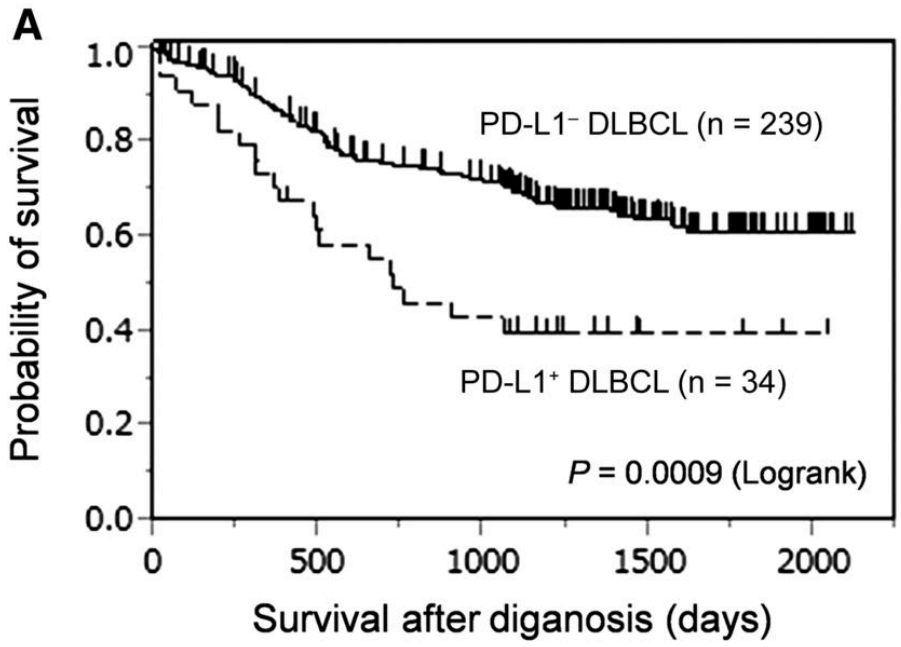




Ansell et al. N Engl J Med. 2015;372:311-319
Roemer et al. ASH 2015 abstract #176

PD-L1+ malignant and non-malignant cells within Diffuse Large B-cell Lymphoma samples - Association with Outcome



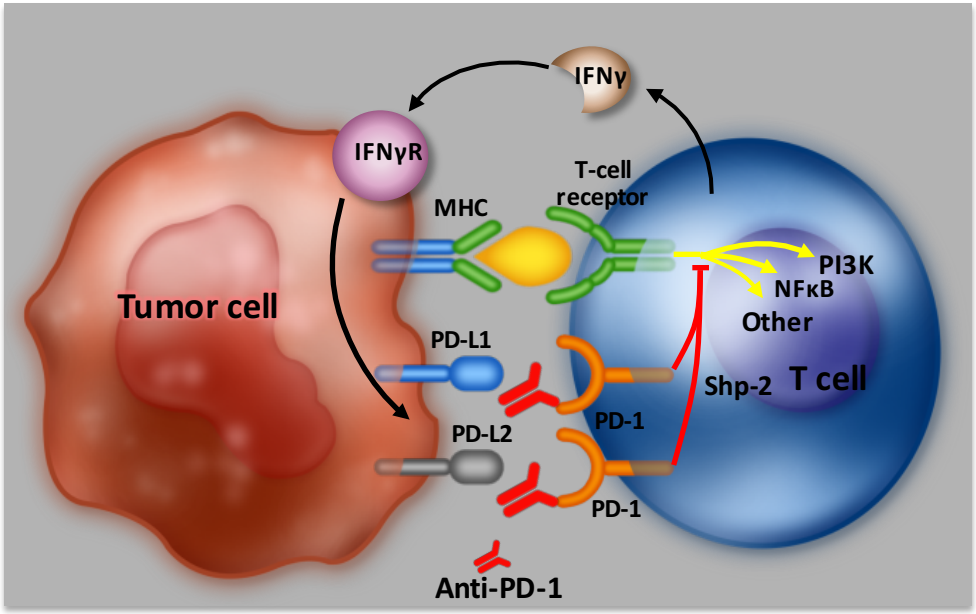


Junichi Kiyasu et al. Blood 2015;126:2193-2201

Does Immune Checkpoint Blockade work?

Blocking PD-1

- PD-1 ligands are overexpressed in inflammatory environments and attenuate the immune response via PD-1 on immune effector cells.[1]
- PD-L1 expressed on malignant cells and/or in the tumor microenvironment suppresses tumor infiltrating lymphocyte activity.[2]



[1]Francisco LM et al. J Exp Med 2009;206:3015-29.
[2]Andorsky DJ et al. Clin Cancer Res 2011;17:4232-44

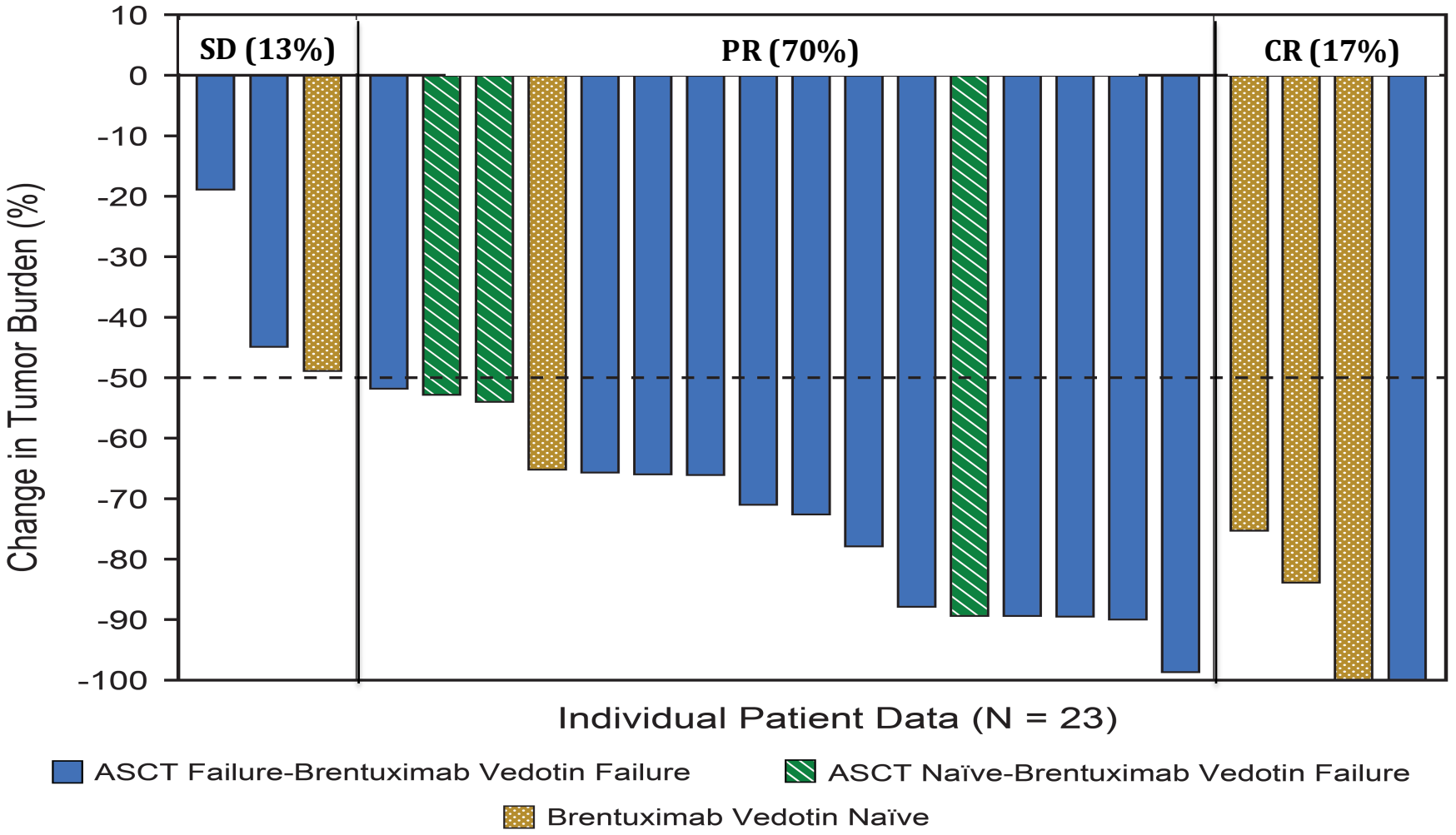
Nivolumab - Best Overall Response

	Objective Response Rate, n (%)	Complete Responses, n (%)	Partial Responses, n (%)	Stable Disease n (%)
B-Cell Lymphoma* (n=29)	8 (28)	2 (7)	6 (21)	14 (48)
Follicular Lymphoma (n=10)	4 (40)	1 (10)	3 (30)	6 (60)
Diffuse Large B-Cell Lymphoma (n=11)	4 (36)	1 (9)	3 (27)	3 (27)
T-Cell Lymphoma† (n=23)	4 (17)	0 (0)	4 (17)	10 (43)
Mycosis Fungoides (n=13)	2 (15)	0 (0)	2 (15)	9 (69)
Peripheral T-Cell Lymphoma (n=5)	2 (40)	0 (0)	2 (40)	0 (0)
Multiple Myeloma (n=27)	0 (0)	0 (0)	0 (0)	18 (67)
Primary Mediastinal B-Cell Lymphoma (n=2)	0 (0)	0 (0)	0 (0)	2 (100)

*includes other B-cell lymphoma (n=8)
†includes other cutaneous T-cell lymphoma (n=3) and other non-cutaneous T-cell lymphoma (n=2)

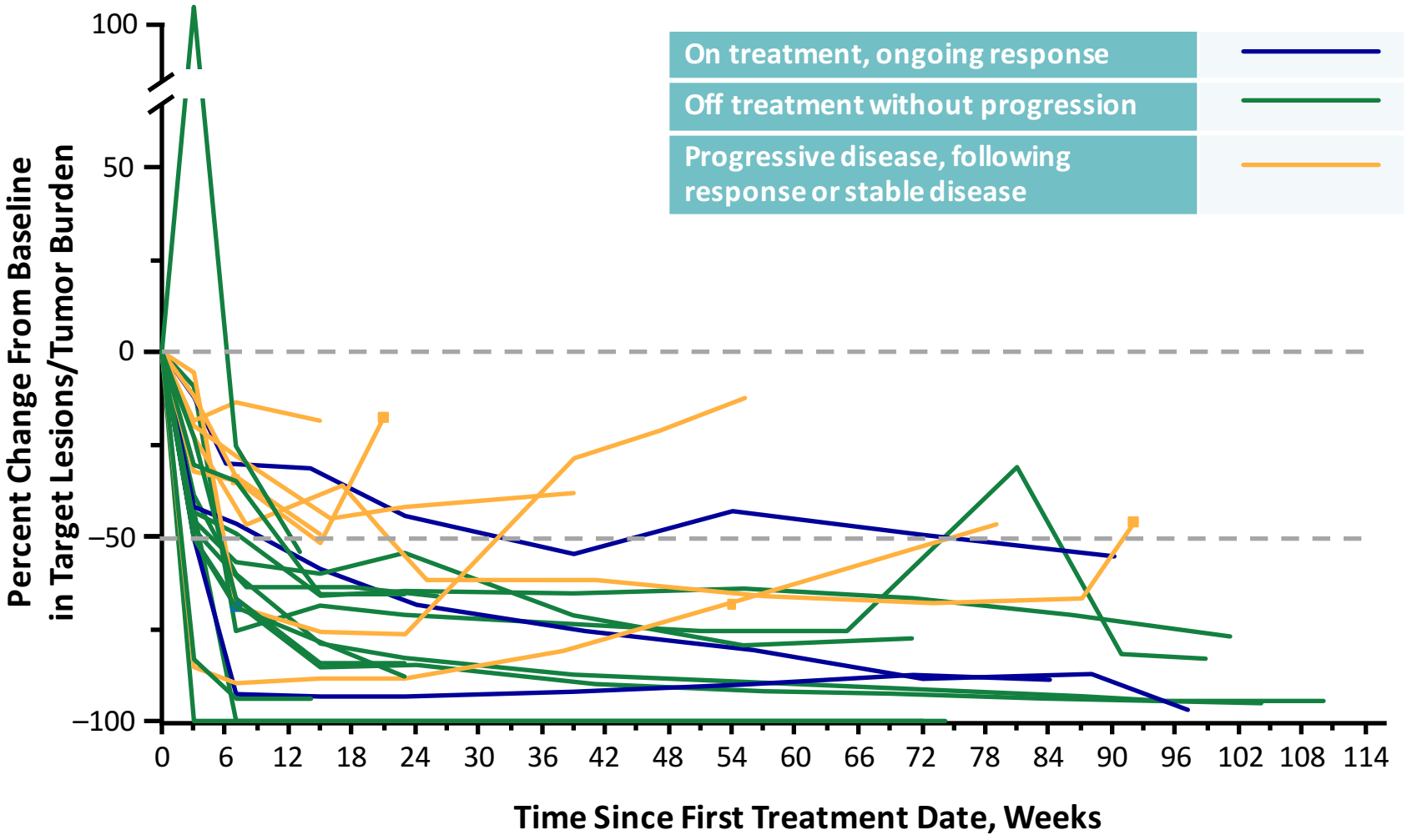
Lesokhin et al. ASH 2014, abstract 291

Hodgkin Lymphoma - Response to Nivolumab



Ansell et al. N Engl J Med. 2015;372(4):311-9.

Nivolumab - Durability of Response



■ First occurrence of new lesion

Ansell et al. ASH 2015, abstract 583

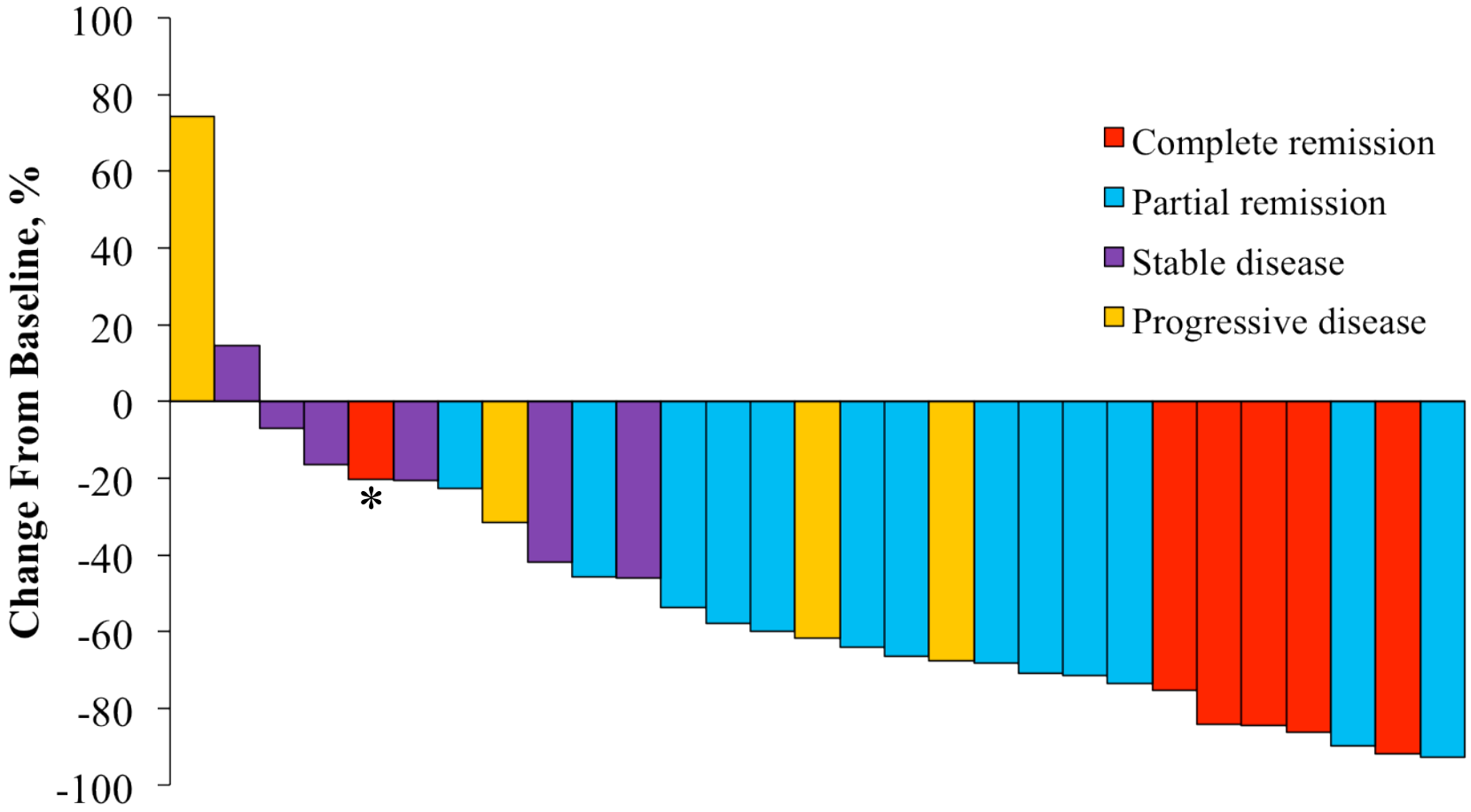
Nivolumab - Drug-related Adverse Events Overview

Nivolumab (N=82)	n (%)
Any Grade Related AE	51 (62)
Any Grade Drug-related AE Occurring in ≥ 5% of Patients	**n (%)**
Fatigue	11 (13)
Pneumonitis	9 (11)
Pruritus	7 (9)
Rash	7 (9)
Pyrexia	6 (7)
Anemia	5 (6)
Diarrhea	5 (6)
Decreased appetite	5 (6)
Hypocalcemia	5 (6)

- Safety profile similar to other nivolumab trials
- The majority of pneumonitis cases were Grade 1 or 2
- No clear association between pneumonitis and prior radiation (28 patients), brentuximab vedotin (9 patients) or gemcitabine

Lesokhin et al. ASH 2014, abstract 291

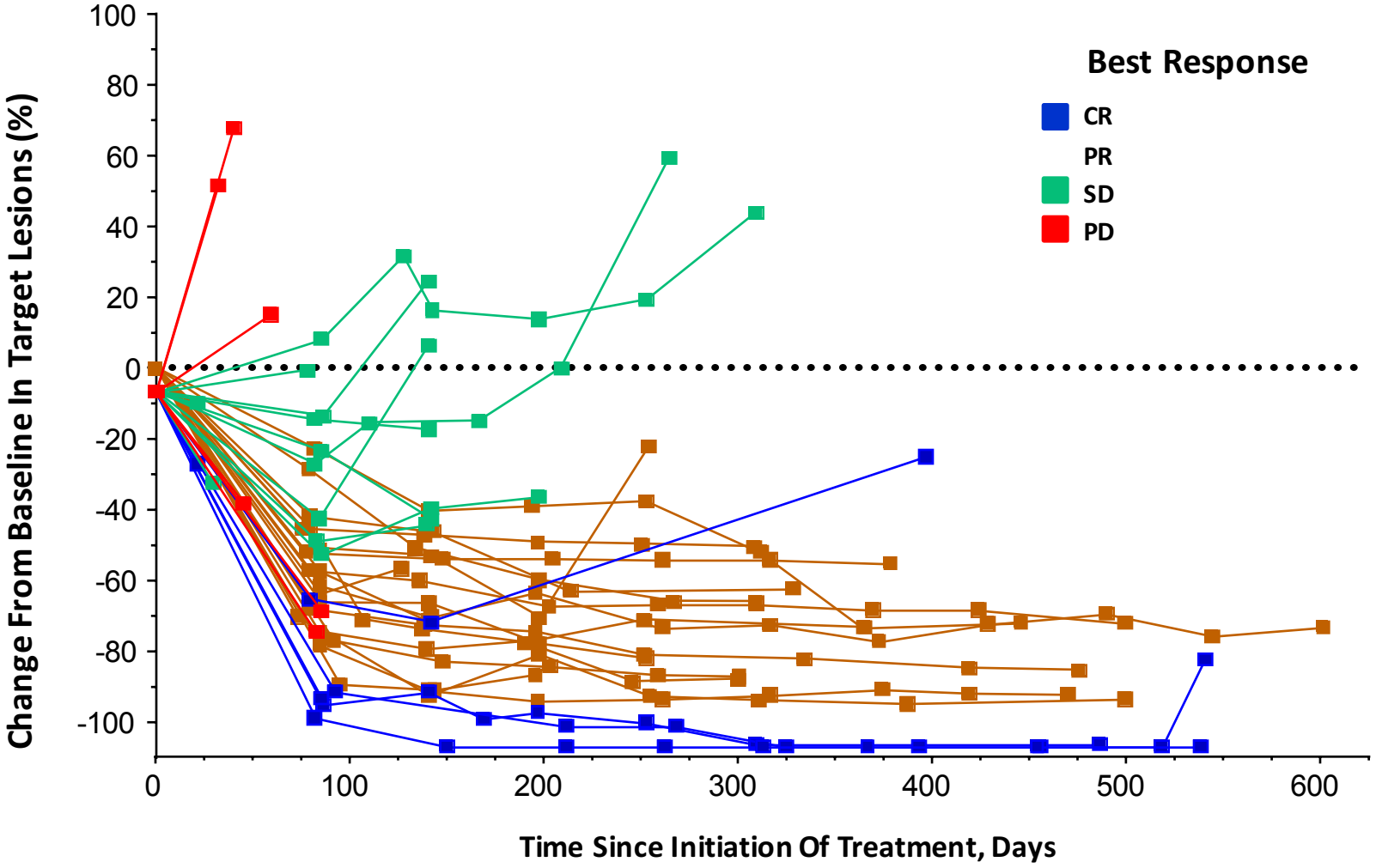
Hodgkin Lymphoma - Response to Pembrolizumab (n=29)



*Patient became PET negative and was therefore declared to be in complete remission.
Analysis cut-off date: November 17, 2014.

Moskowitz et al. ASH 2014, abstract 290

Pembrolizumab – Durability of Response



Armand et al. ASH 2015, abstract 583

Treatment-Related Adverse Events of Any Grade Observed in ≥2 Patients

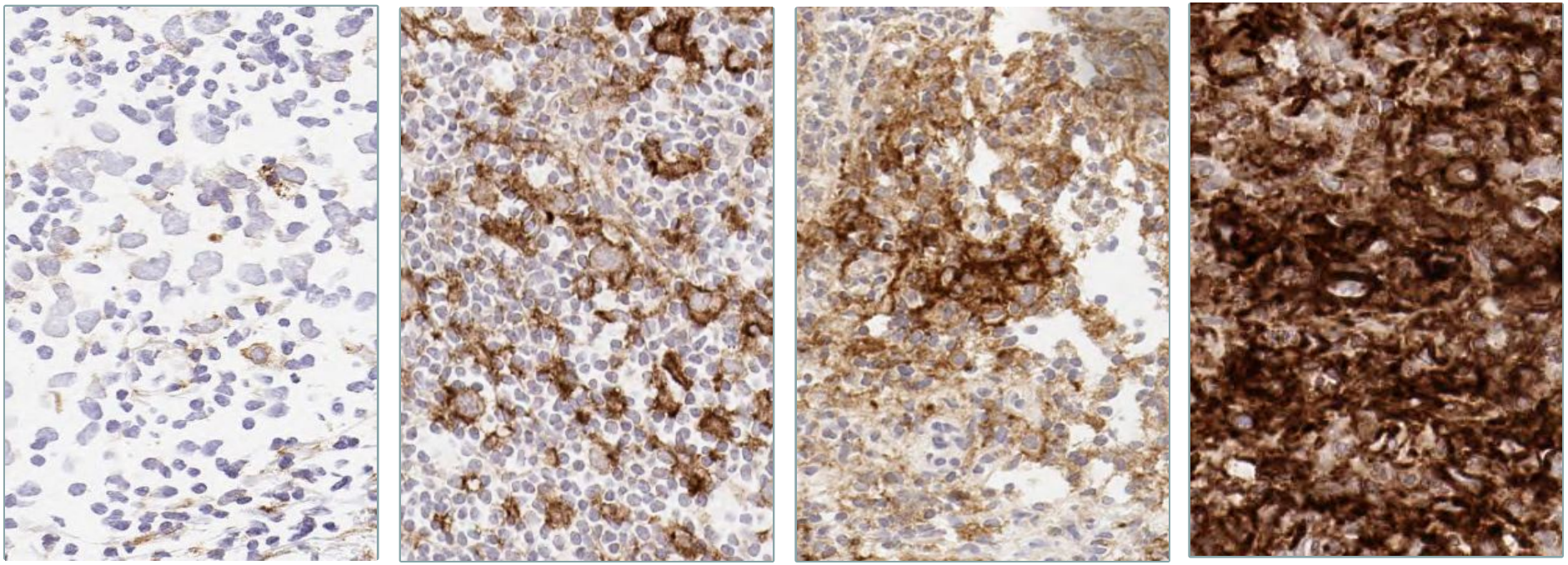
Adverse Event, n (%)	N = 29
Hypothyroidism	3 (10)
Pneumonitis	3 (10)
Constipation	2 (7)
Diarrhea	2 (7)
Nausea	2 (7)
Hypercholesterolemia	2 (7)
Hypertriglyceridemia	2 (7)
Hematuria	2 (7)

- 16 (55%) patients experienced ≥1 treatment-related AE of any grade

Analysis cut-off date: November 17, 2014.

Moskowitz et al. ASH 2014, abstract 290

PD-L1 Expression



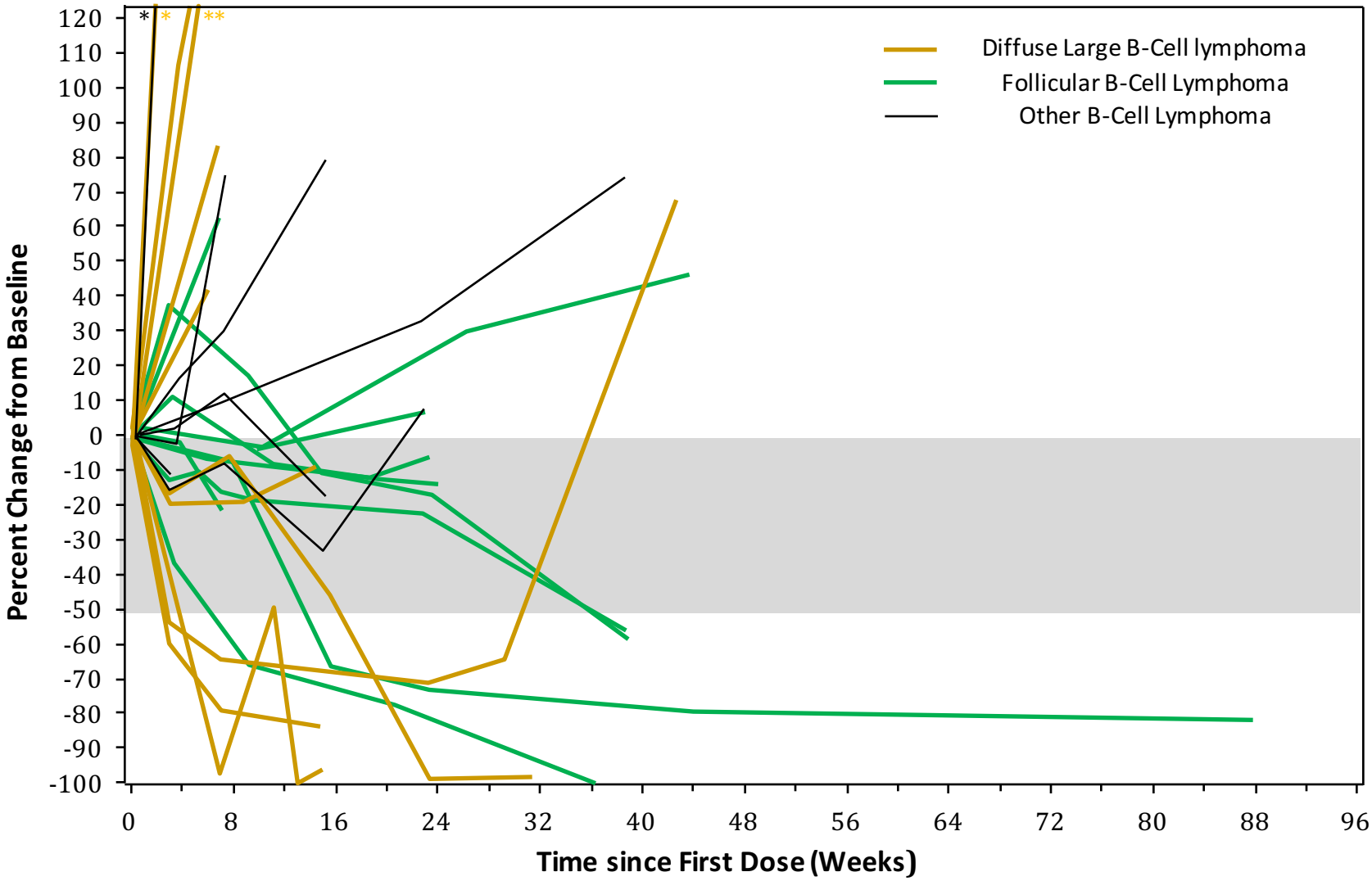
PD-L1 Negative ——— PD-L1 Positive

- Among the 10 enrolled patients who provided samples evaluable for PD-L1 expression, 100% were PD-L1 positive
- Best overall response in these 10 patients was CR in 1 patient, PR in 2 patients, SD in 4 patients, and PD in 3 patients

PD-L1 expression was assessed using a prototype immunohistochemistry assay and the 22C3 antibody. PD-L1 positivity was defined as Reed-Sternberg cell membrane staining with 2+ or greater intensity.
Analysis cut-off date: November 17, 2014.

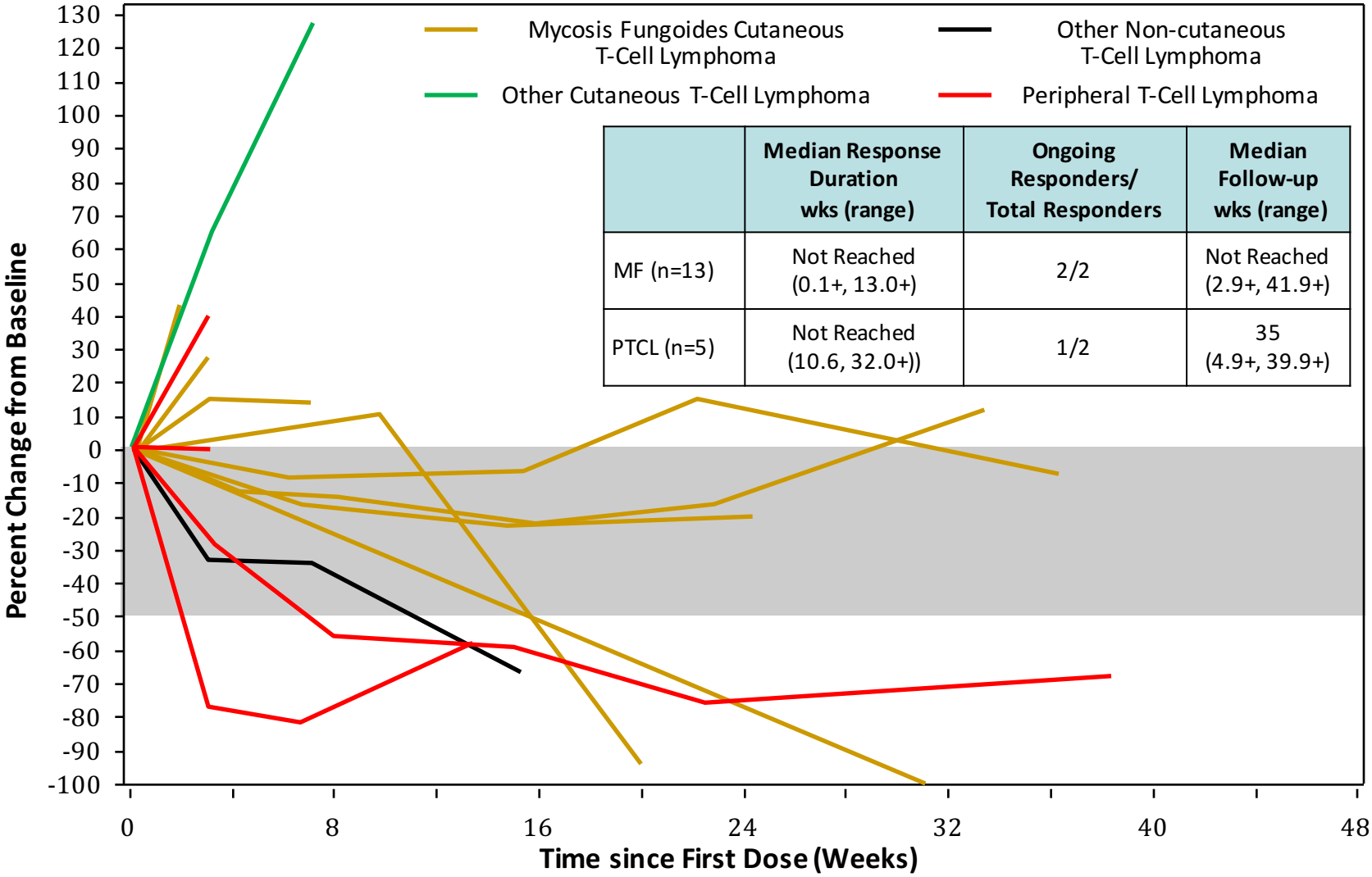
Moskowitz et al. ASH 2014, abstract 290

All B-Cell Lymphoma Patient Responses



Lesokhin et al. ASH 2014, abstract 291

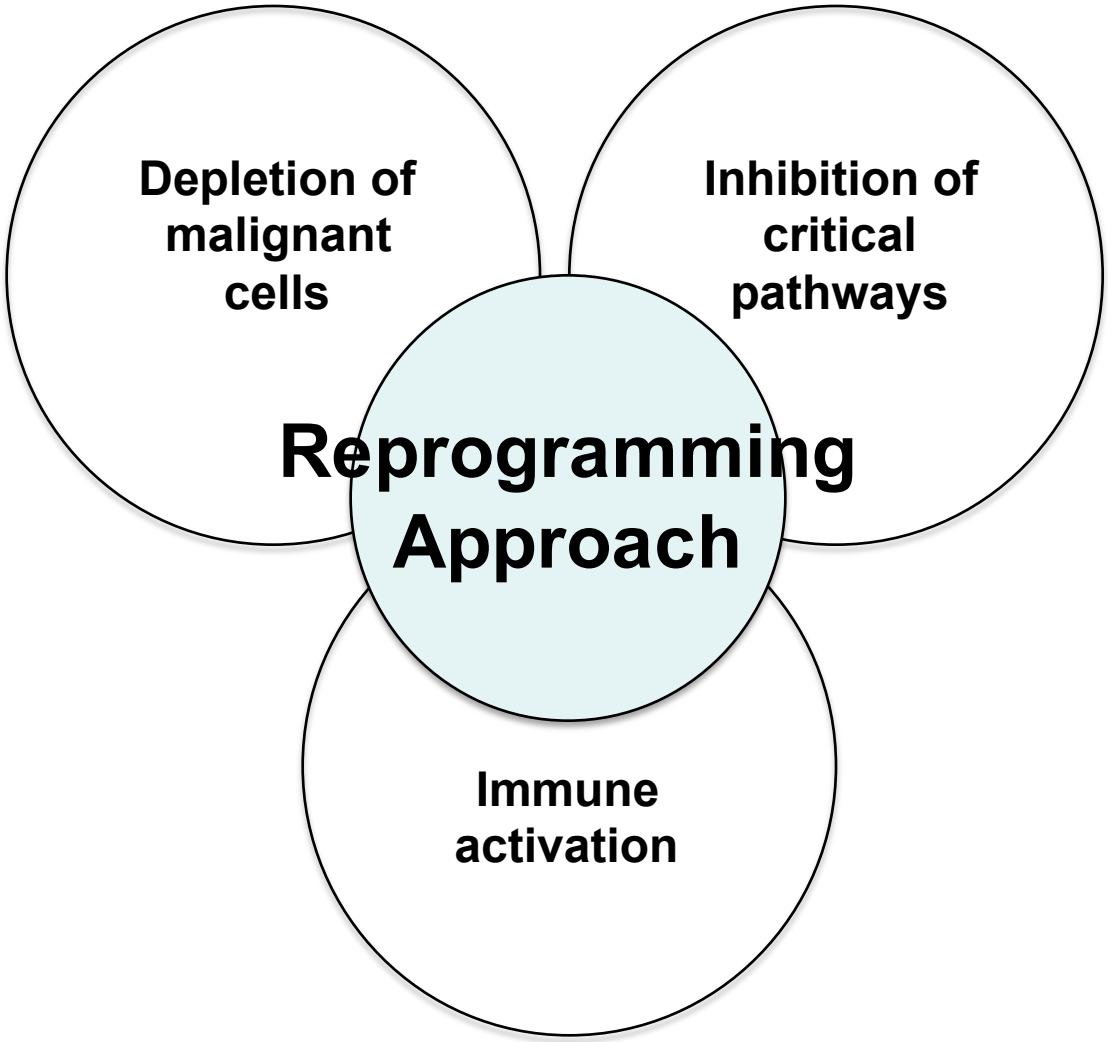
All T-Cell Lymphoma Patient Responses



	Median Response Duration wks (range)	Ongoing Responders/ Total Responders	Median Follow-up wks (range)
MF (n=13)	Not Reached (0.1+, 13.0+)	2/2	Not Reached (2.9+, 41.9+)
PTCL (n=5)	Not Reached (10.6, 32.0+))	1/2	35 (4.9+, 39.9+)

Lesokhin et al. ASH 2014, abstract 291

How will use Immune Checkpoint Inhibitors in the future? - Reprogramming Approach



How can the Depletion Approach be improved by Immune Checkpoint Blockade?

- Sequencing standard chemotherapy before or after immune checkpoint blockade
- Using antibody-drug conjugates for targeted killing – Brentuximab vedotin plus PD-1 blockade
- Giving immune checkpoint inhibition post transplant – pidilizumab

Brentuximab Vedotin and Ipilimumab is Highly Active in Relapsed Hodgkin Lymphoma

18 Response Eligible Patients

Evaluable Pts.	ORR	CR	PR	SD	PD
N = 18	13 (72%)	9 (50%)	4(28%)	2 (11%)	2 (11%)

Clinical Benefit 83%

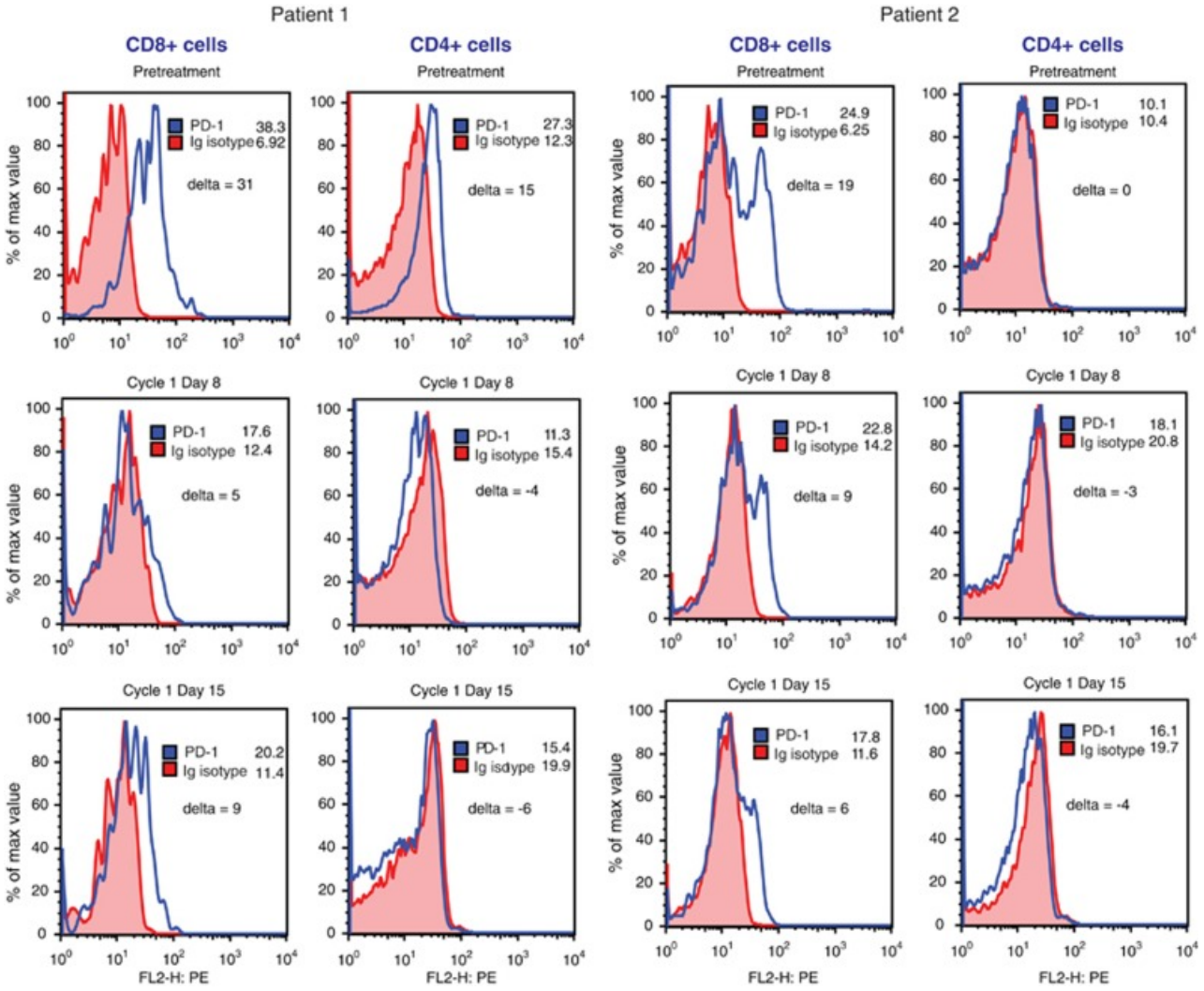
- Prior BV = 4/23 (17%)
- 2 patients were un-evaluable due to ineligibility
  - One, secondary to prior relapse on BV and on prior Nivo: SD
  - Second patient whose scan was out of window had CR which is ongoing
- 3 patients have not yet been assessed

Diefenbach et al. ASH 2015 abstract 585

How can the Pathway Inhibition Approach be improved by Immune Checkpoint Blockade?

- Use small molecule inhibitors that potentially modulate immune receptors/ligands – HDAC inhibitors
- Using inhibitors that have off target effects that promote immune (T-cell) function – ibrutinib, idelalisib
- Blocking downstream signaling induced by immune checkpoints – mTOR inhibitors, PI3 Kinase inhibitors

Immune regulatory effects of panobinostat in Hodgkin lymphoma through modulation of T-cell PD-1 expression

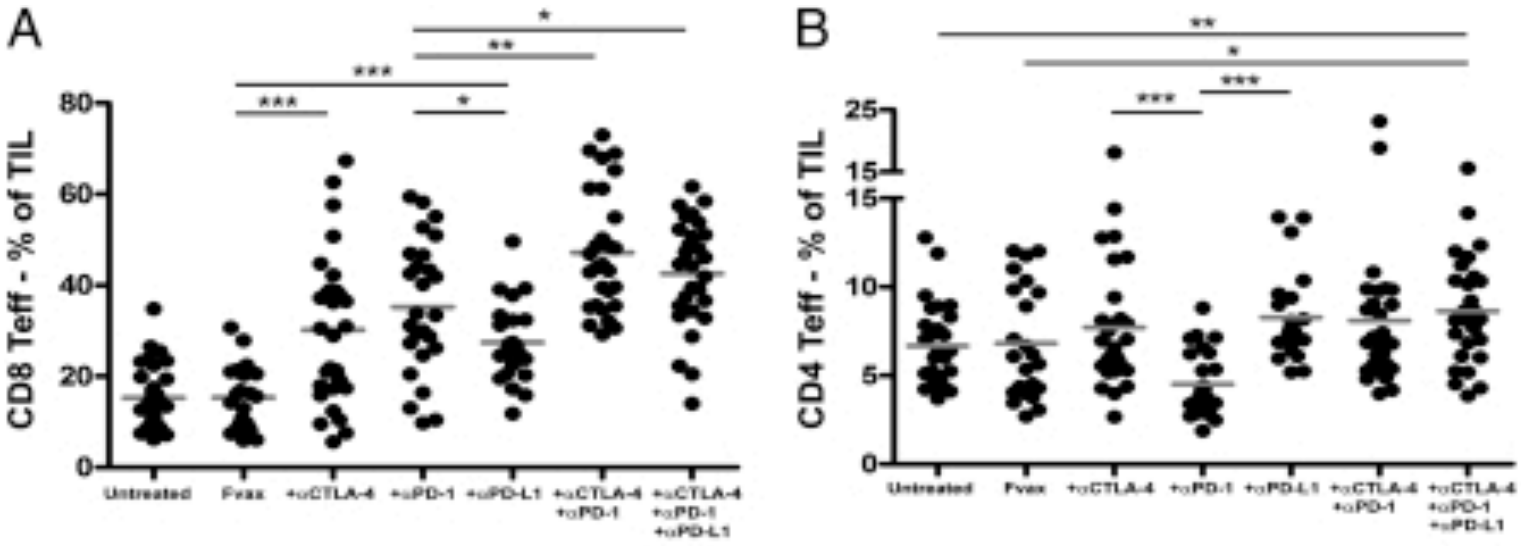


Oki et al. Blood Cancer J. 2014 Aug 8;4:e236.

How can the Immune Optimization Approach be improved by Immune Checkpoint Blockade?

- Inhibit more than one immune checkpoint – PD-1/PD-L1 and CTLA4/LAG-3/TIM-3
- Block an inhibitory signal and simultaneously give an activating signal – PD-1/PD-L1 and 4-1BB or OX-40
- Use a different immune activator – CART/bispecific antibody/BITE/viral therapy/vaccine in combination with an immune checkpoint inhibitor.

PD-1 and CTLA-4 blockade expands infiltrating T cells and reduces regulatory T and myeloid cells in the tumor



Curran et al. Proc Natl Acad Sci U S A. 2010 Mar 2;107(9):4275-80.

Conclusions

- Optimizing immune function is the new therapeutic "frontier" in B-cell lymphomas
- Immune checkpoint inhibitors hold real promise in Hodgkin and non-Hodgkin lymphoma.
- Multiple new agents (anti-PDL1, anti-LAG3, anti-TIM3) are in development to block immune suppression or induce immune stimulation.
- Incorporating promising immunologic agents into combination approaches will be the next clinical challenge.