Targeting PD-1 and PD-L1 in T-cell Lymphoma

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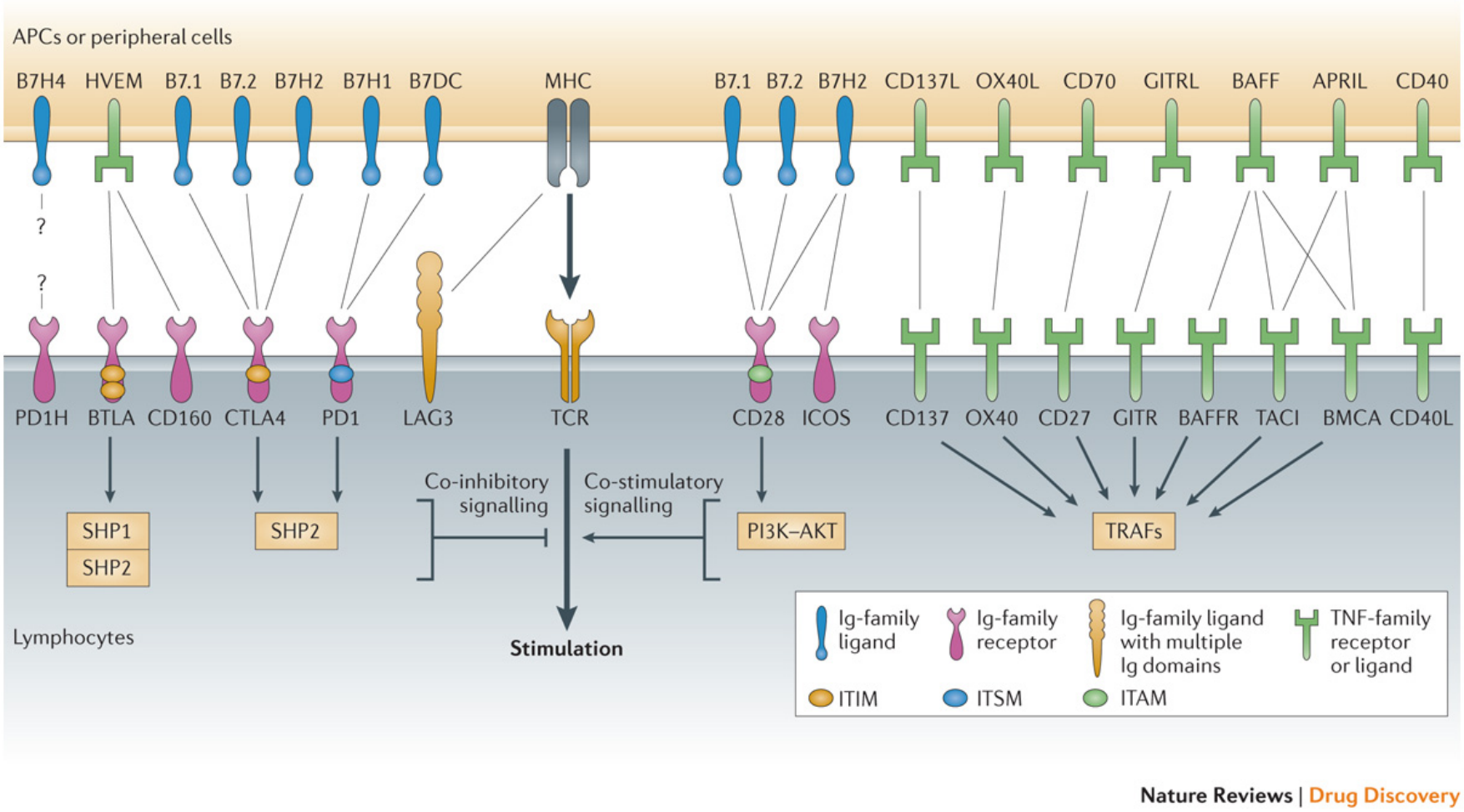
Conflicts of Interest

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

PD-1/PD-L1 Interaction in T-cell Lymphoma

- Preclinical data supporting the role of PD-1/PD-L1 interactions in T-cell lymphoma
- Clinical data with anti-PD-1 antibodies in PTCL.

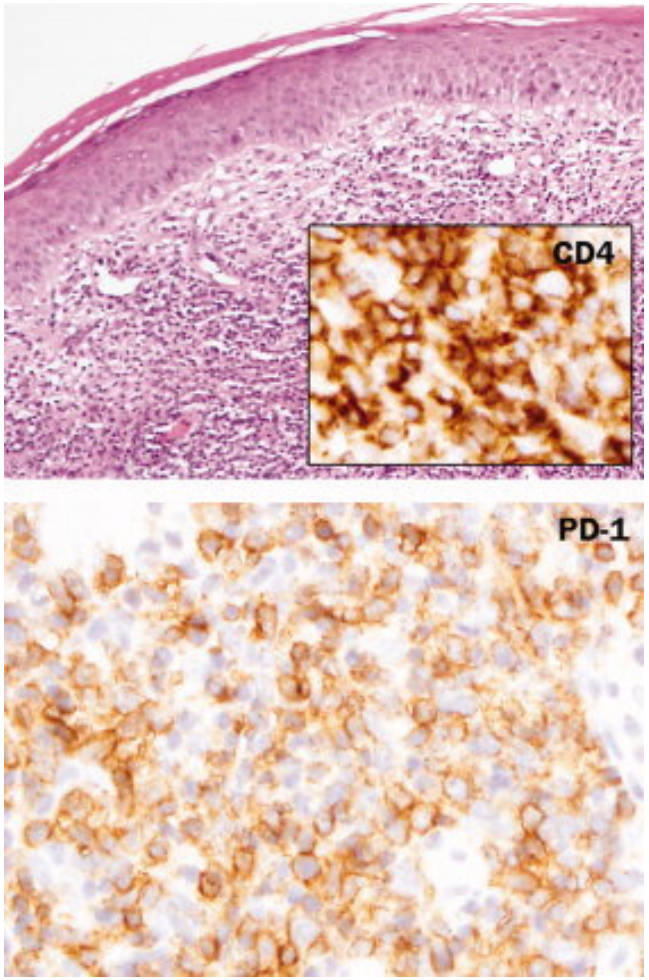
Targeting cell surface signaling molecules for immune modulation

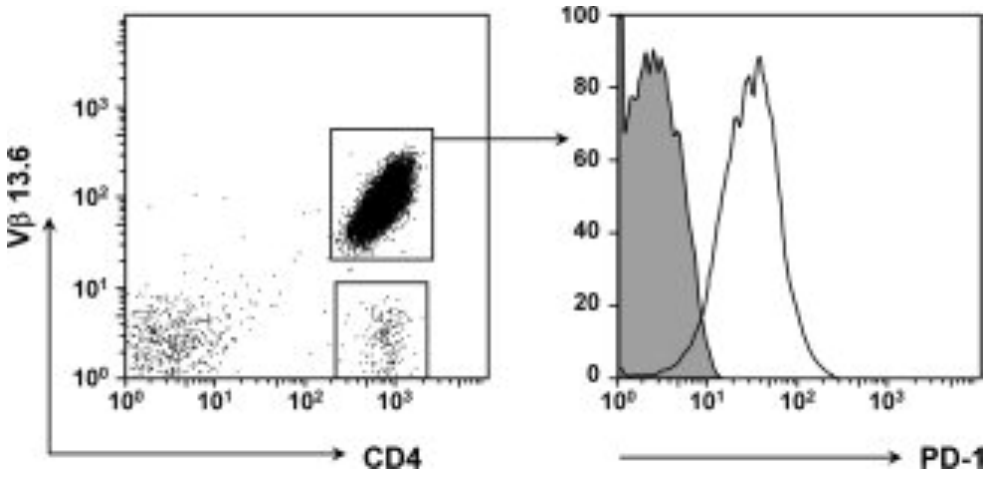


Nature Reviews | Drug Discovery

Yao et al. Nature Reviews Drug Discovery 2013; 12:130-146.

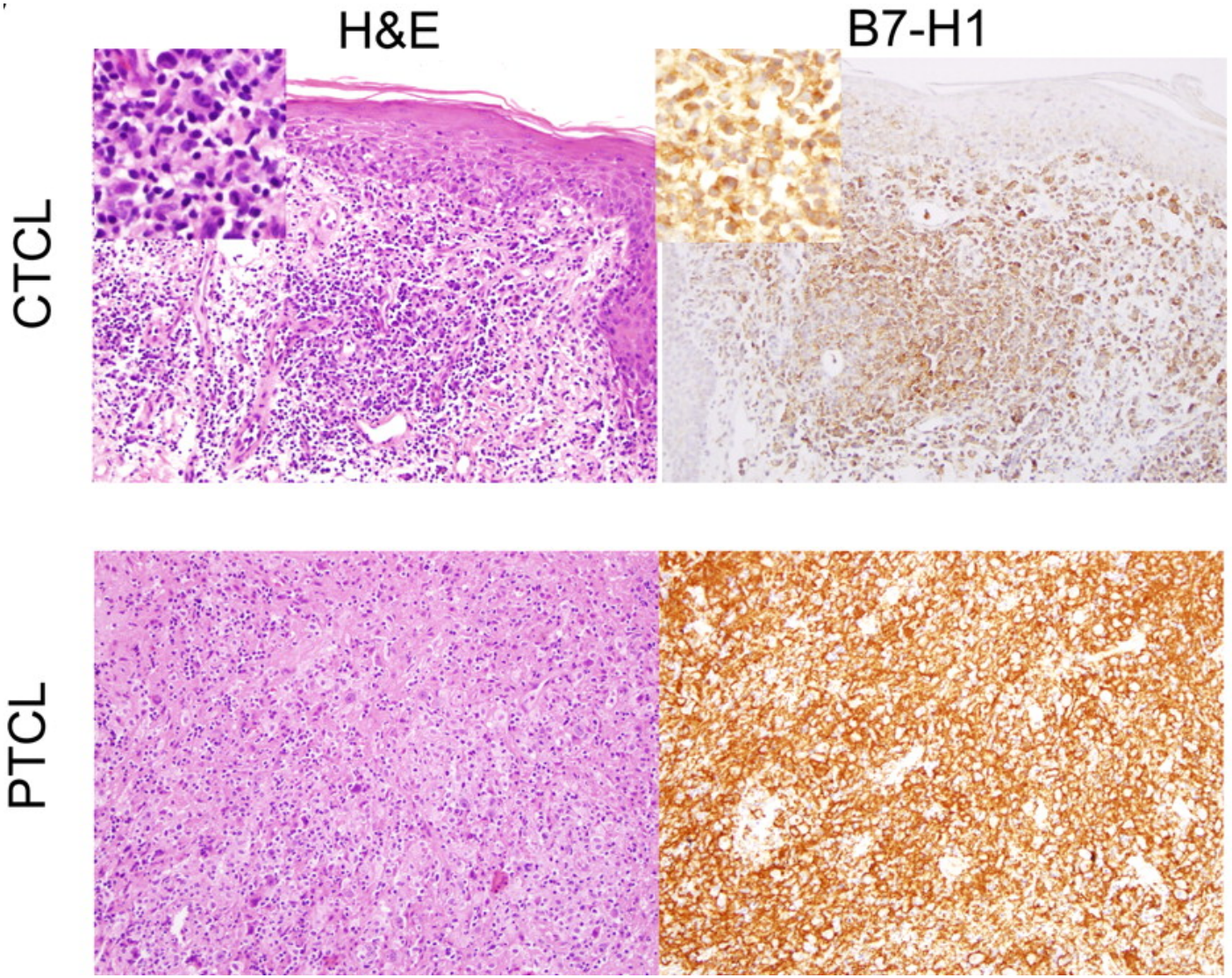
PD-1 is expressed in cutaneous infiltrates of mycosis fungoides and Sézary syndrome





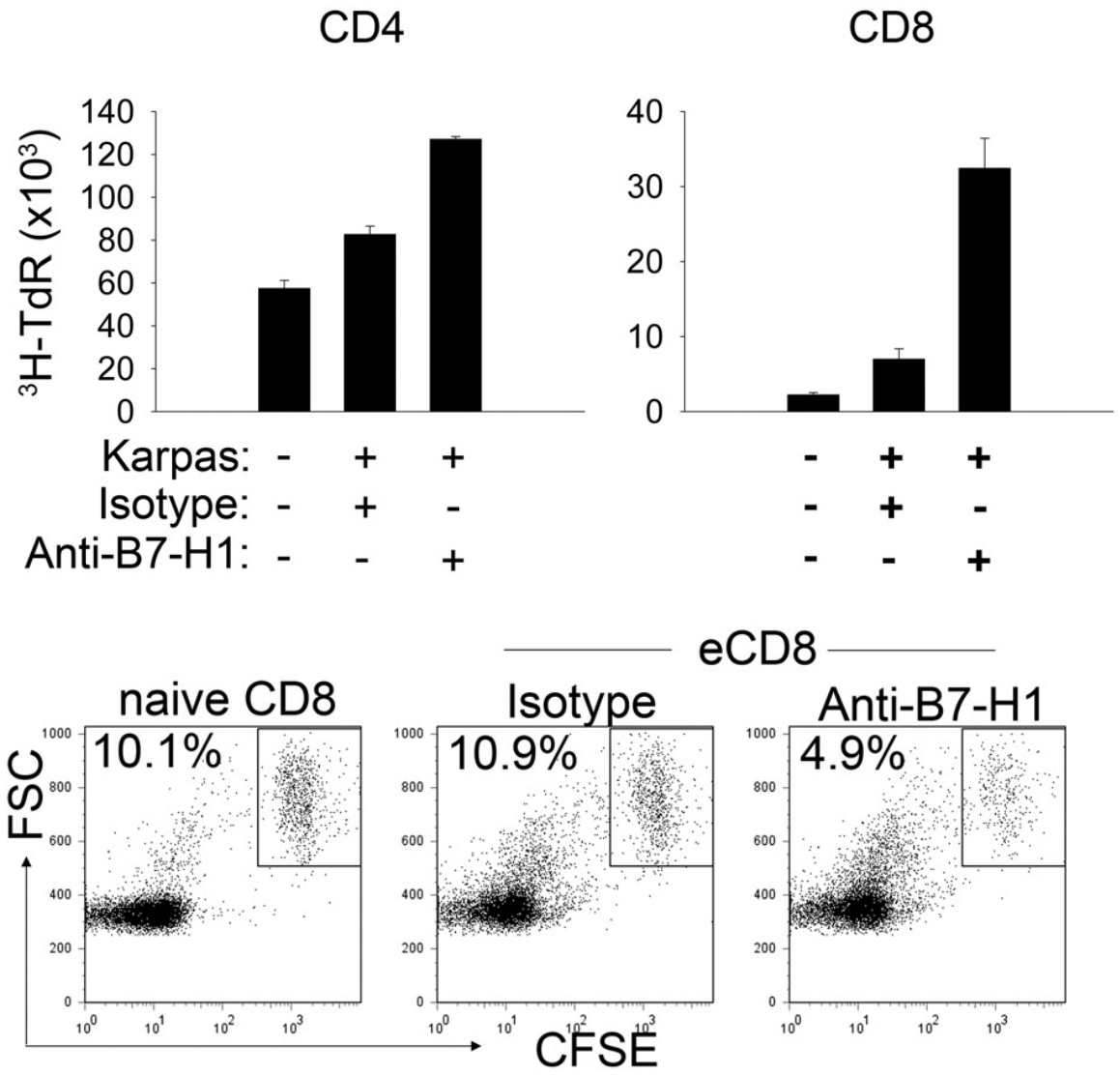
Wada DA, et al. Am J Hematol. 2011 Mar;86(3):325-7.

PD-L1 (B7-H1) is expressed in T-cell lymphomas



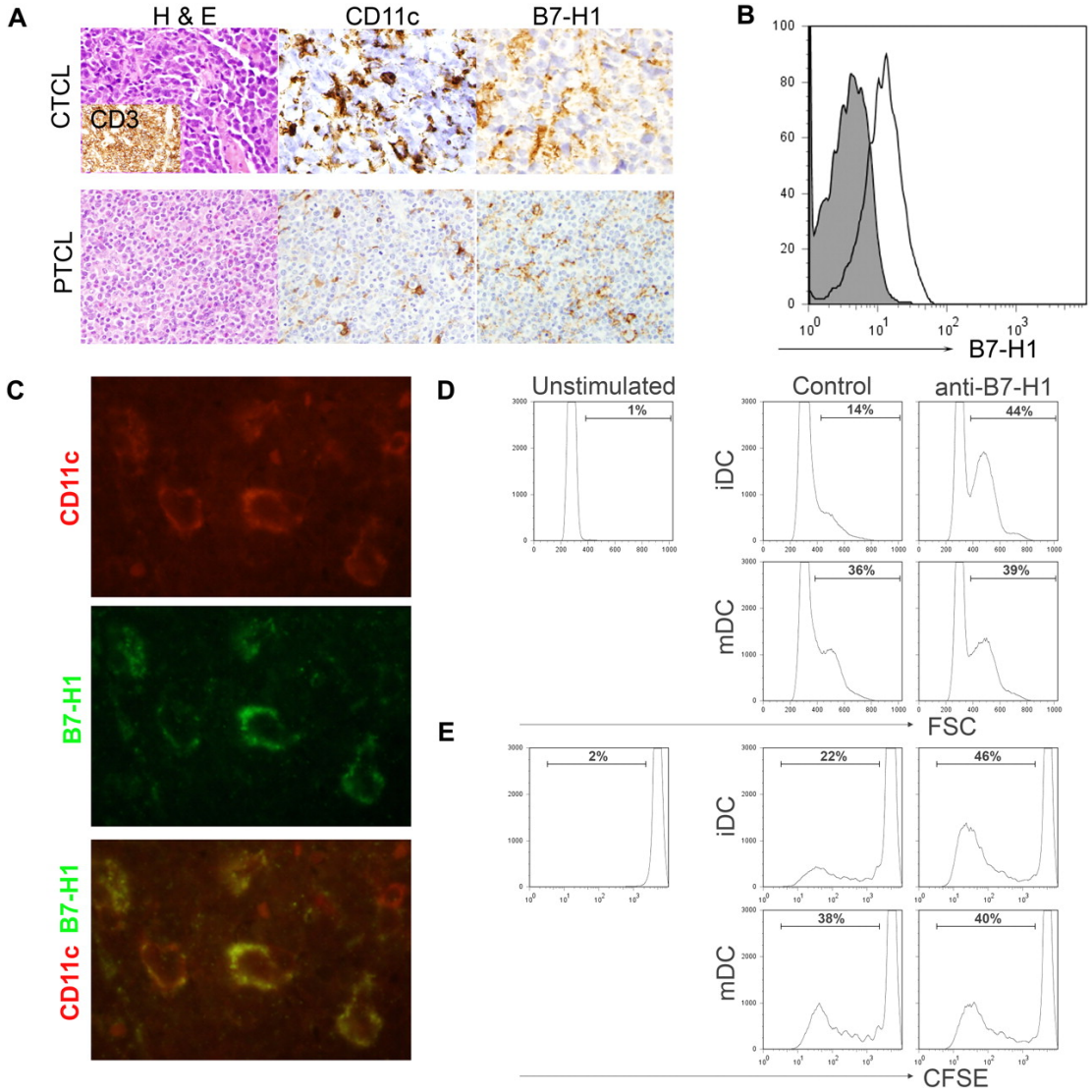
Wilcox et al. Blood 2009;114:2149-2158

Tumor-associated PD-L1 (B7-H1) inhibits T-cell immunity



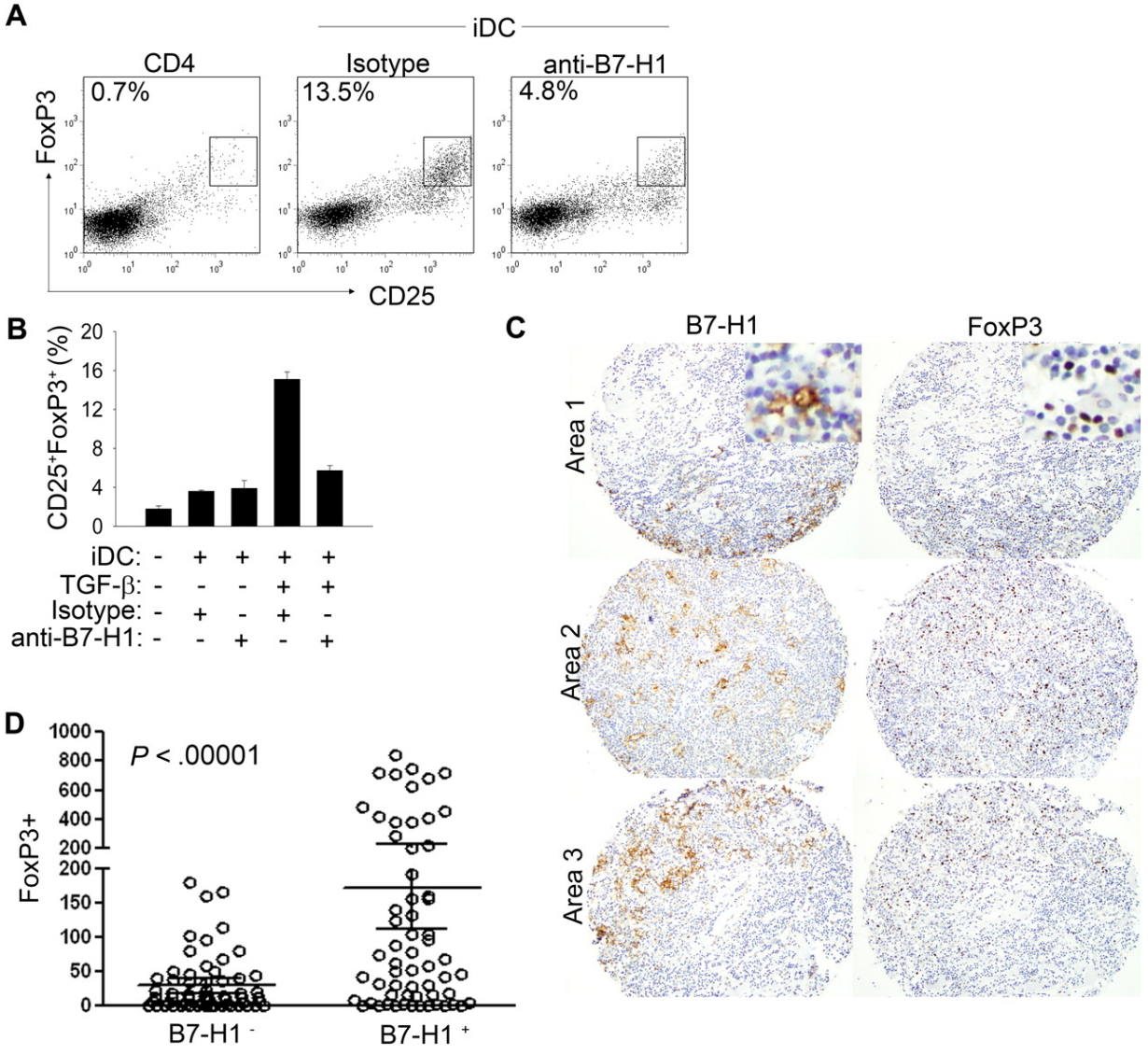
Wilcox et al. Blood 2009;114:2149-2158

PD-L1 (B7-H1) is expressed by tumor-associated DCs and inhibits T-cell proliferation.



Wilcox et al. Blood 2009;114:2149-2158

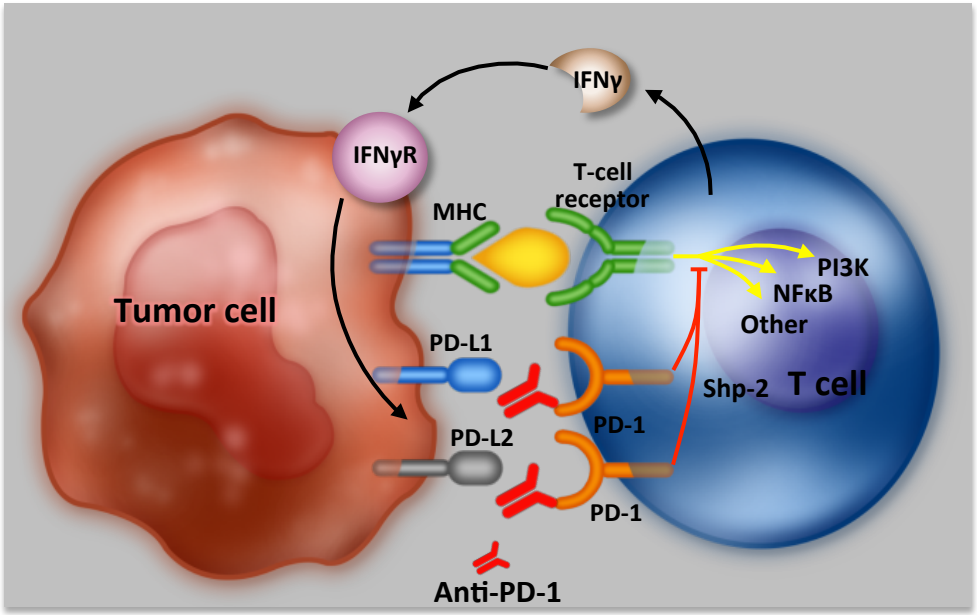
DC-associated PD-L1 (B7-H1) promotes the induction of FoxP3+ regulatory T cells.



Wilcox et al. Blood 2009;114:2149-2158

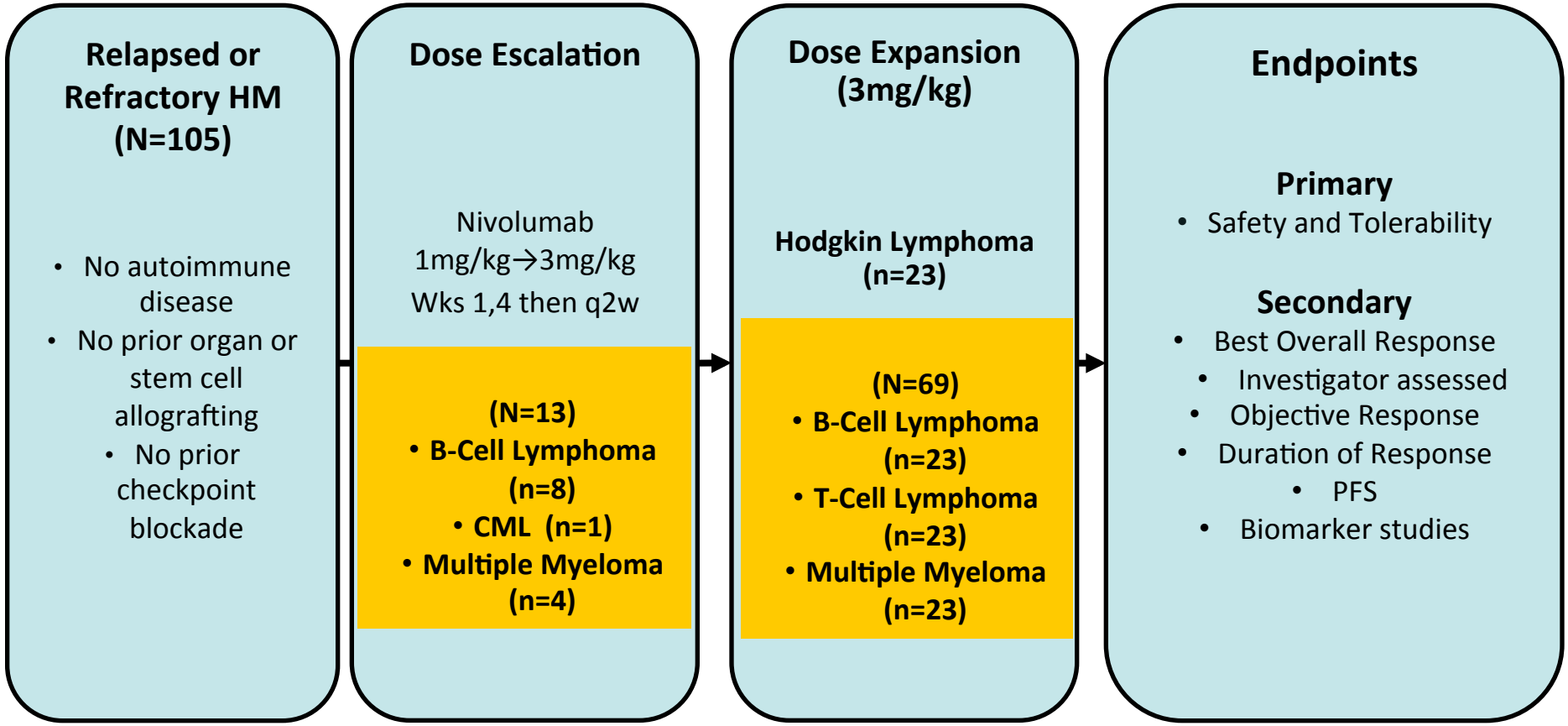
PD-1 Blockade

- 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 and interferes with host antitumor immunity.[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 – Phase I/II Study Design



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Baseline Characteristics By Tumor Type

Characteristic (N=82*)		B-Cell Lymphoma/ PMBL[†](n=31)			T-Cell Lymphoma[‡](n=23)			Multiple Myeloma (n=27)
		FL (n=10)	DLBCL (n=11)	Other (n=8)	MF (n=13)	PTL (n=5)	Other (n=3)	
Median age, y (range)		57 (37-69)	67 (37-74)	68 (61-74)	59 (30-78)	73 (47-81)	73 (51-76)	63 (32-81)
Prior autologous stem cell transplant, n (%)		2 (20)	2 (18)	0 (0)	0 (0)	2 (40)	0 (0)	15 (56)
No. prior systemic treatments, n (%)	2	1 (10)	2 (18)	2 (25)	0 (0)	2 (40)	0 (0)	8 (30)
	3	3 (30)	3 (27)	3 (38)	2 (15)	1 (20)	0 (0)	4 (15)
	4	1 (10)	3 (27)	0 (0)	4 (31)	1 (20)	1 (33)	6 (22)
	≥5	2 (20)	2 (18)	3 (38)	6 (46)	1 (20)	1 (33)	8 (30)

*A single patient had CML (data not shown)

[†]2 patients had PMBL (data not shown) [‡]2 patients had other non-cutaneous T-cell lymphomas (data not shown)

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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

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Drug-related Adverse Events

Drug-related Grade 3 Events		Drug-related Grade 4 Events		Drug-related Grade 5 Events	
Patients, n (%)	**15 (18)**	**Patients, n (%)**	**2 (2)**	**Patients, n (%)**	**1 (1)**
Anemia	3 (4)	Rash pustular	1 (1)	Pneumonitis	1 (1)
Leukopenia	2 (2)	Sepsis	1 (1)	ARDS	1 (1)
Lymphocyte count decreased	2 (2)				
Platelet count decreased	2 (2)				
Blood CPK increased	1 (1)				
Diplopia	1 (1)				
Eosinophilia	1 (1)				
Lipase increased	1 (1)				
Mucosal inflammation	1 (1)				
Neutropenia	1 (1)				
Pneumonia	1 (1)				
Pneumonitis	1 (1)				
Pulmonary embolism	1 (1)				
Rash	1 (1)				
Stomatitis	1 (1)				
WBC count decreased	1 (1)				

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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)

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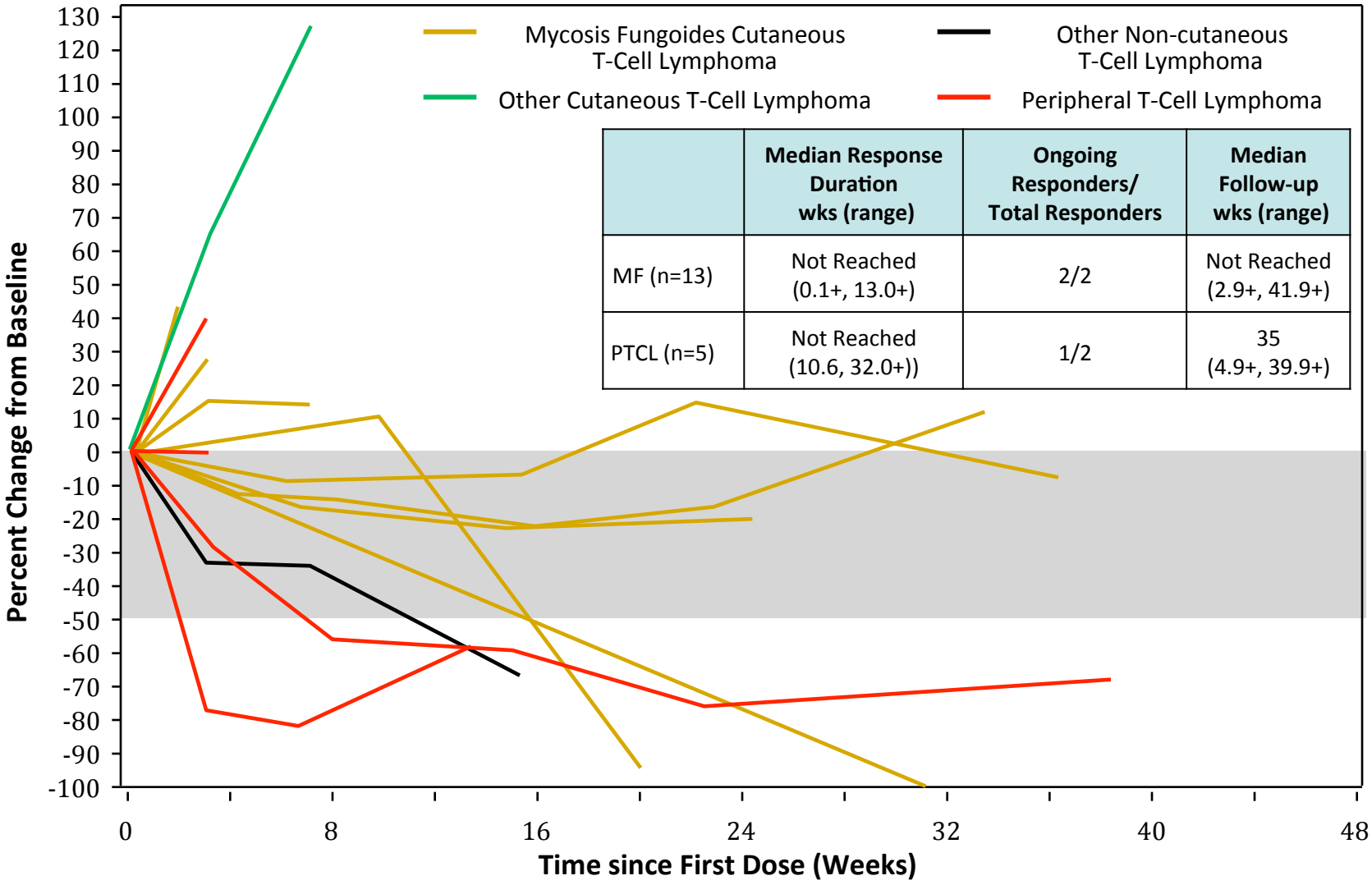
All T-Cell Lymphoma Patient Responses



	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+)

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Tumor Analysis

Tumor	Cytogenetics 9p Alteration	Immunohistochemistry PD-L1 Positive
Diffuse Large B-Cell (n=6)	1/6	1/6
Follicular (n=6)	1/6	1/5*
Other B-Cell Lymphoma (n=7)	0/7	1/7
Mycosis Fungoides (n=4)	1/4	1/4
Peripheral T-Cell (n=3)	0/3	0/3
T-Cell Lymphoma (n=2)	0/2	0/2
Unknown (n=2)	0/2	0/2

* No data for one patient

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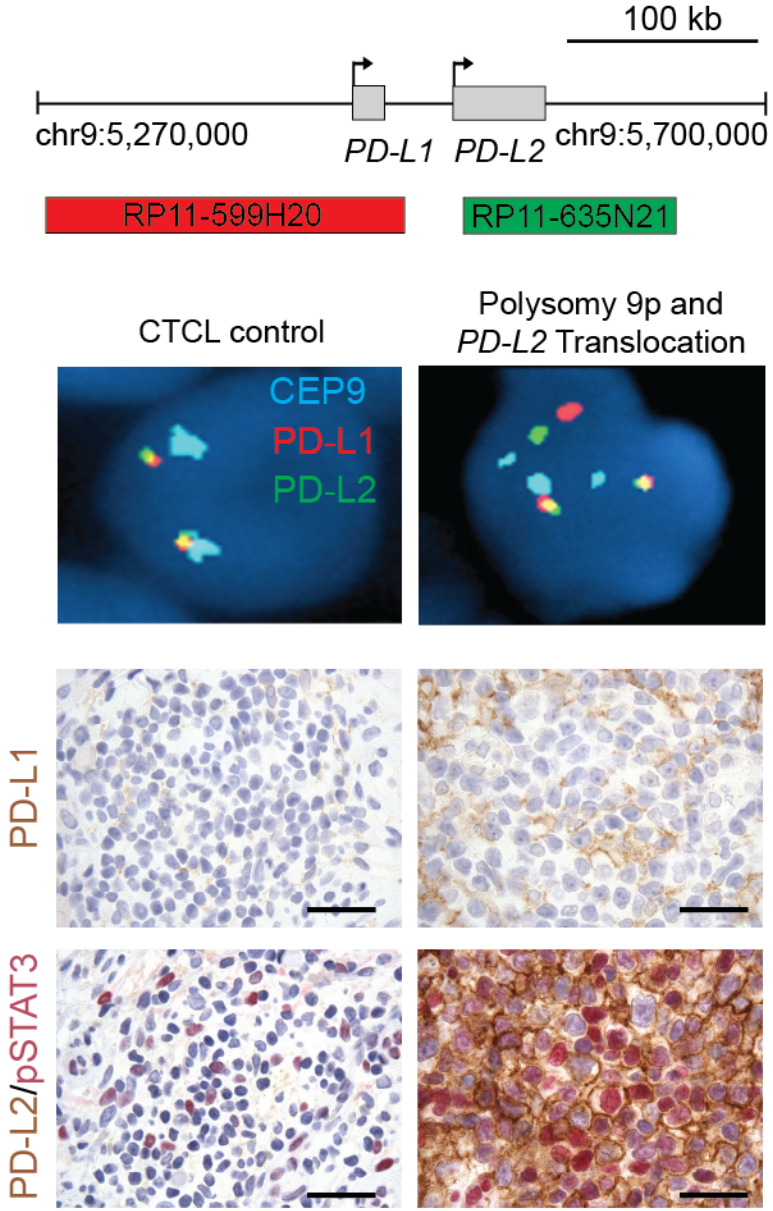
PD-L2 Translocation in a CTCL Patient



- Patient with the translocation had a partial response of 13 weeks duration.
- Translocation of *PD-L2* supports blockade of the receptor rather than the PD-L1 ligand.

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Conclusions

- Optimizing immune function is a new therapeutic "frontier" in T-cell lymphomas
- Immune checkpoint inhibitors hold real promise.
- 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.