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Immune Checkpoints Inhibitors to Treat Lymphomas

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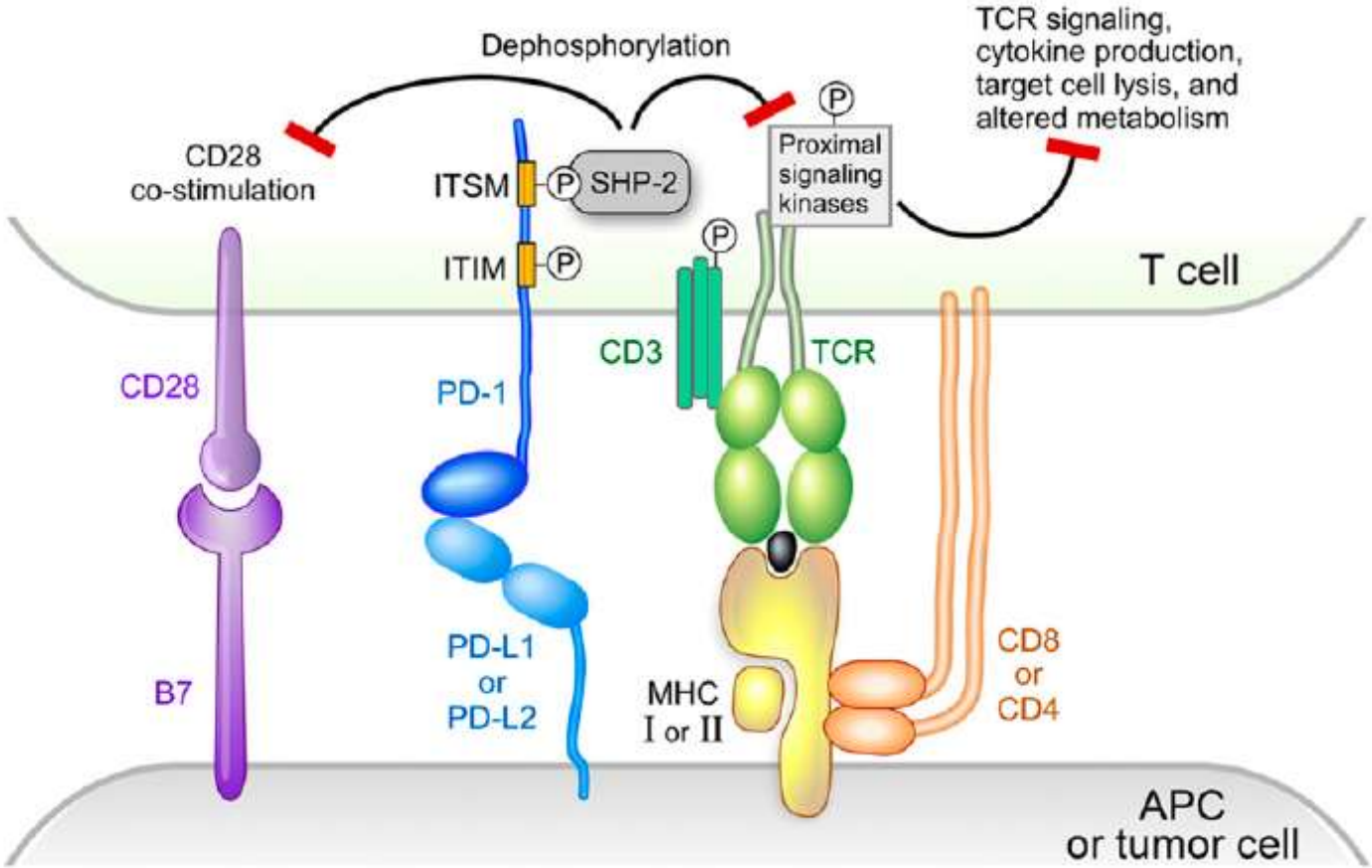
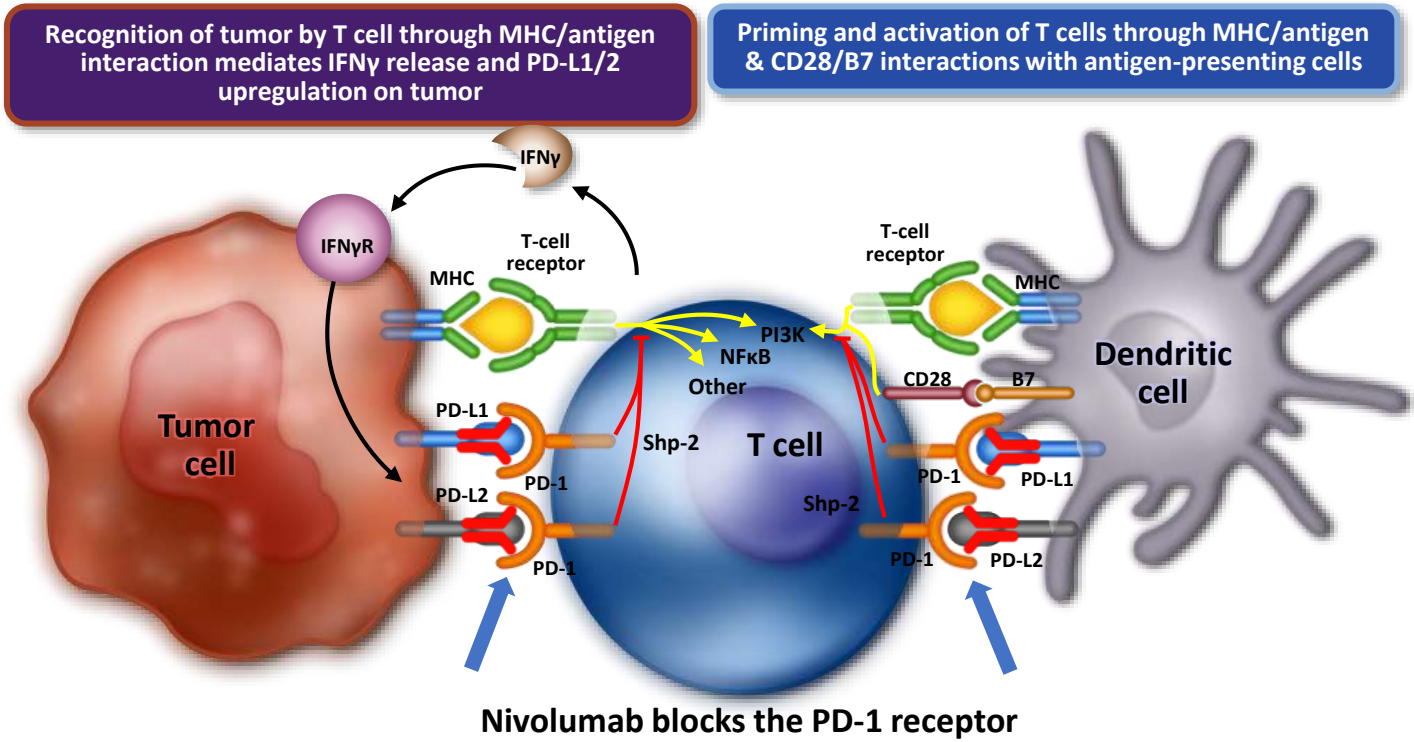
PD-1/PD-L1 Signaling



Anti-PD-1: Mechanism of Action

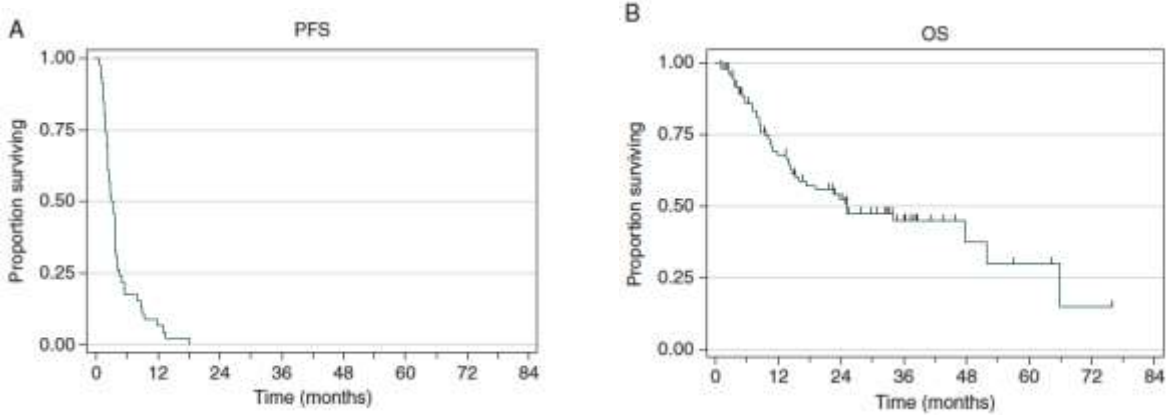


Unmet Medical Needs in Lymphomas

- Primary refractory / high-risk HL (20%-25%)
- Primary refractory / high-risk DLBCL (30%-40%)
- Primary refractory / high-risk T-NHL (30%-40%)

Patients with classical Hodgkin lymphoma experiencing disease progression after treatment with brentuximab vedotin have poor outcomes

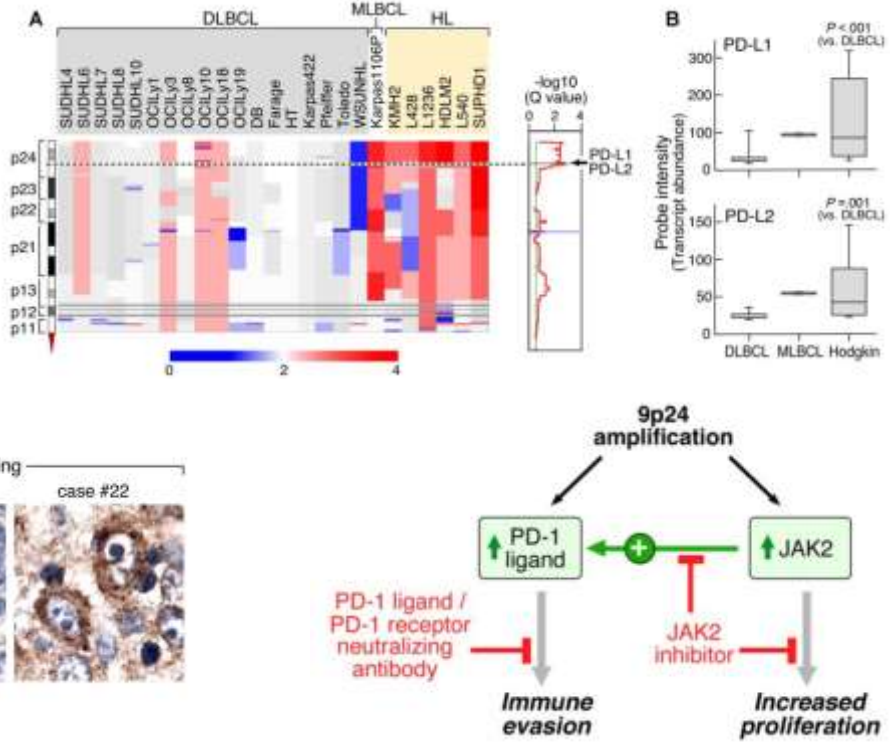
Cheah CI et al, Ann Oncol, 27:1317, 2016



Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma

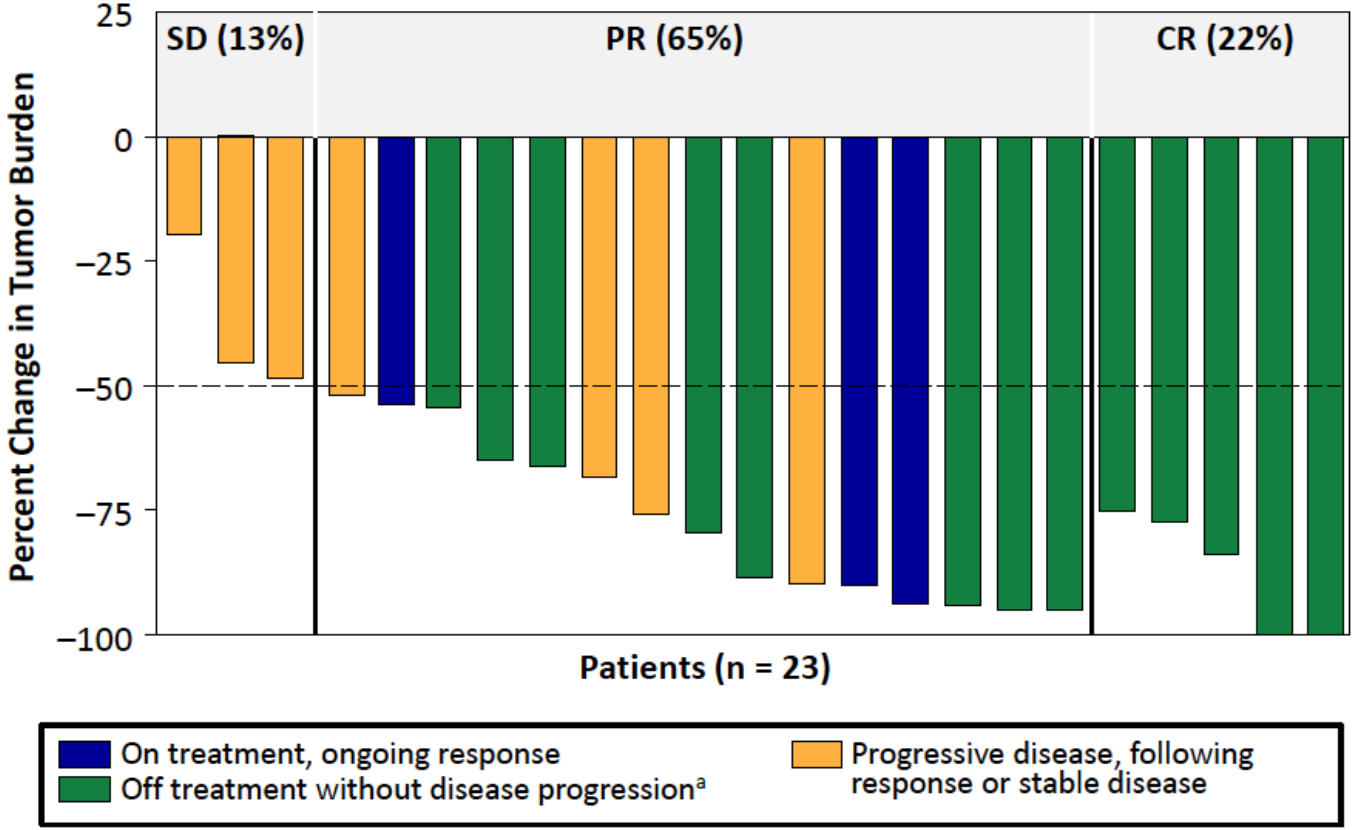
M Green, Blood, 2010

- Chromosome 9p24.1 amplification and increased expression of PD-L1 in HL and MLBCL cell lines



Nivolumab in Patients With Relapsed or Refractory Classical Hodgkin Lymphoma

Best Response (PR + CR =87%)



[a]Maximum clinical benefit, transplant, or toxicity

Ansell et al , ASH 2015

Select Treatment-Related Adverse Events

Adverse Event	cHL (n = 23)	
	Any Grade, n (%)	Resolved, %
Gastrointestinal	**4 (17)**	
Diarrhea	3 (13)	100
Colitis	1 (4)	100
Hepatic	**2 (9)**	
ALT increased	1 (4)	100
AST increased	1 (4)	100
Blood alkaline phosphatase increased	1 (4)	0
Pulmonary	**1 (4)**	
Pneumonitis	1 (4)	100
Skin	**5 (22)**	
Rash	4 (17)	100
Pruritus	3 (13)	100
Pruritic rash	1 (4)	100
Skin hypopigmentation	1 (4)	0
Endocrine disorders		
Hyperthyroidism	4 (17)	75
Hypersensitivity/infusion reaction	**2 (9)**	
Bronchospasm	1 (4)	100
Infusion-related reaction	1 (4)	100

- All AEs were Grade 1/2 except colitis and pneumonitis which were Grade 3
- There were no Grade 4 or Grade 5 AEs and no treatment-related deaths

Challenging Issues

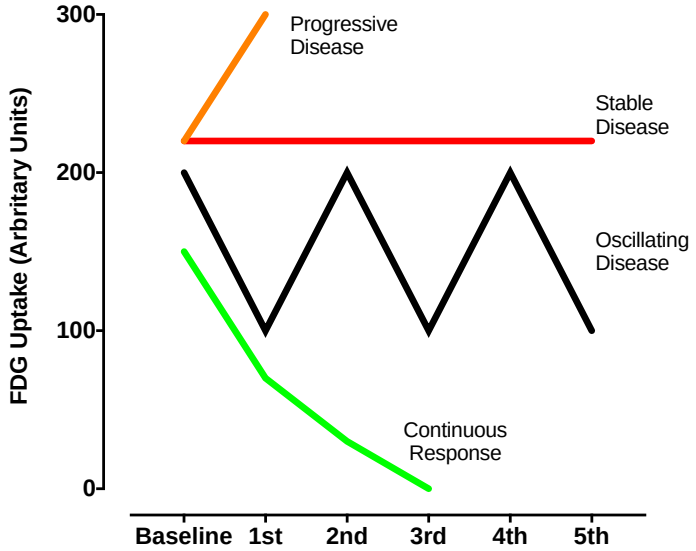
- Response assessment
- Mechanisms of acquired resistance to Nivo

Response Assessment

- Patients at risk of being prematurely removed from a treatment from which they actually stand to benefit

- Patients at risk of receiving a treatment from which they actually do not benefit

Types of PET Responses



Perspectives

blood

Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy

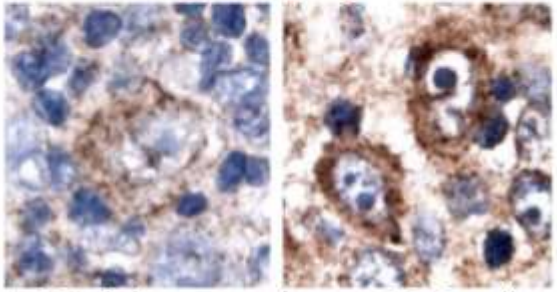
Bruce D. Cheson,[1] Stephen Ansell,[2] Larry Schwartz,[3] Leo I. Gordon,[4] Ranjana Advani,[5] Heather A. Jacene,[6] Axel Hoos,[7] Sally F. Barrington,[8] and Philippe Armand[6]

Blood, 128:2489, 2016

- Findings suggestive of Progressive Disease despite evidence of clinical benefit (eg, tumor flare or pseudo-progression)
- To reduce ambiguity in current trials and to enable the collection of accurate data in a consistent way

Pre-clinical rationale for PD-1/PD-L1 blockade

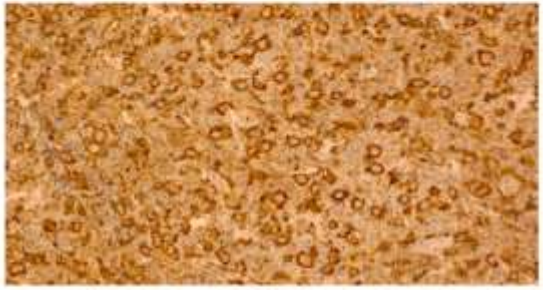
Hodgkin lymphoma



PD-L1 expression on R-S cells corresponds to 9p24.1 amplification

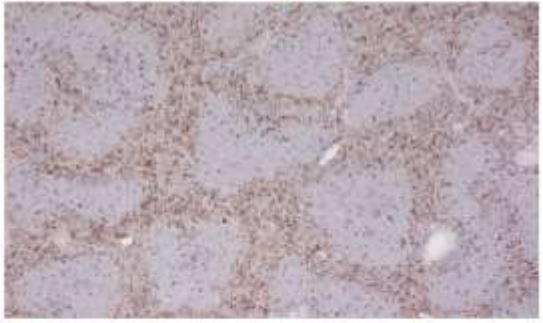
Green et al, Blood 2010

Diffuse large B cell lymphoma



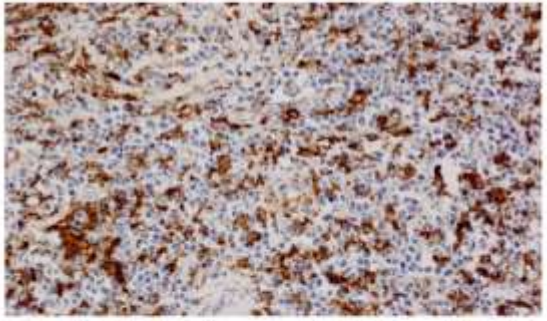
PD-L1 expression on tumor cells in some cases (ABC / non-GCB > GCB)

Follicular lymphoma



PD-L1 expression on infiltrating macrophages (interfollicular)

Diffuse large B cell lymphoma



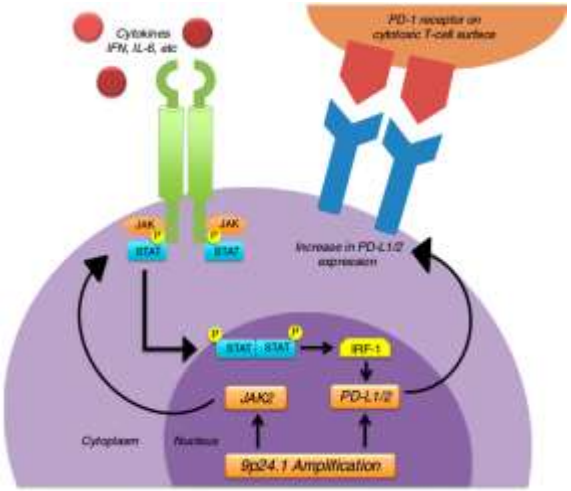
PD-L1 expression on infiltrating macrophages

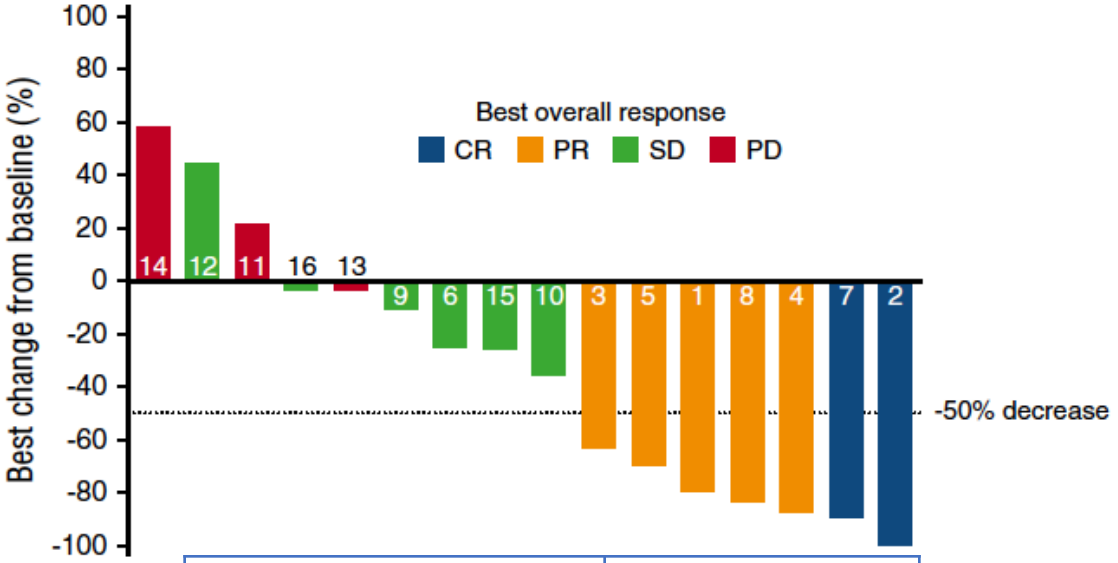
Andorsky et al, Clin Cancer Res 2011, Chen et al, Clin Cancer Res 2013

PD-L1-Expressing Lymphomas

- PMLBCL
- Mediastinal gray zone lymphomas
- Richter transformation of CLL
- EBV & virus-related Lymphomas
- Plasmablastic lymphomas
- NK/T-cell lymphoma
- Angioimmunoblastic T-cell lymphoma
- Multicentric Castleman disease

Pembrolizumab in PMLBCL (PD-L1^{+} Lymphoma)





ORR	7/17 (41%)
CR	2/17 (12%)
Ongoing Responses	6/7 (86%)

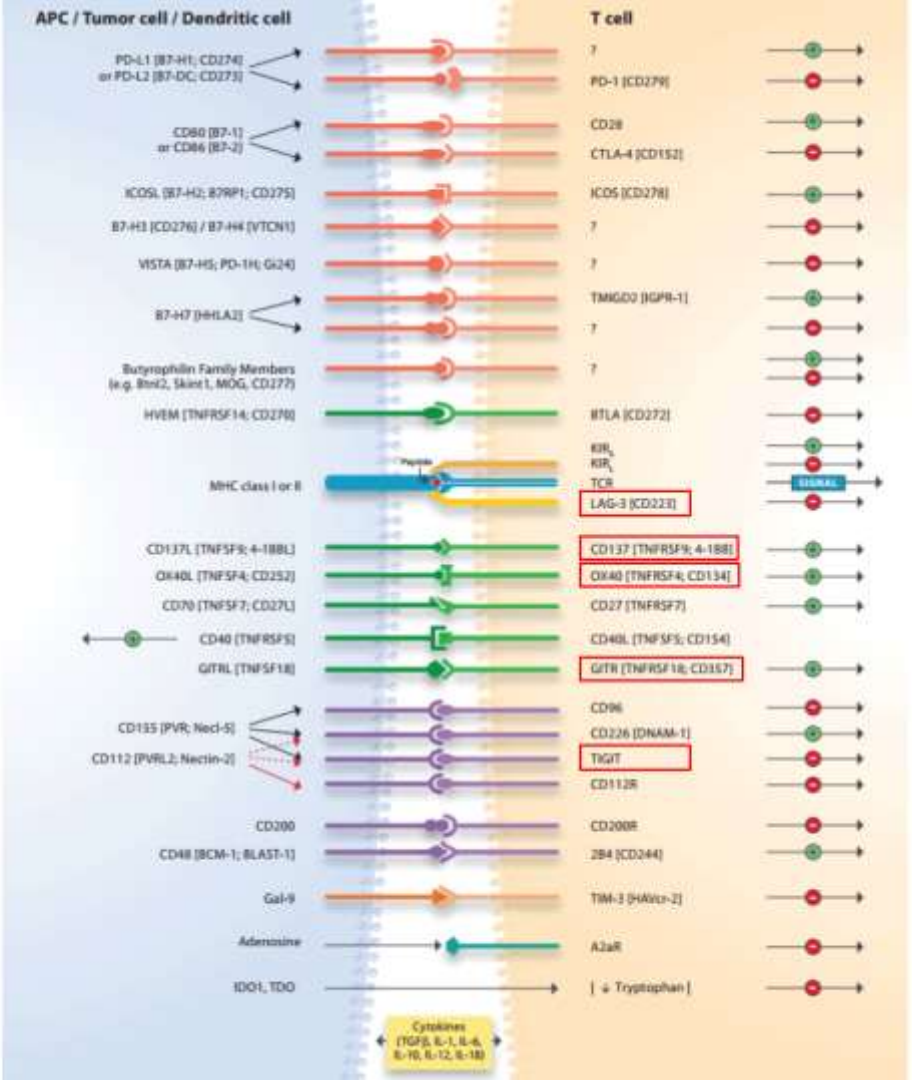
Zinzani et al, Blood 2017

Nivolumab in NHL: Best Response

Tumor Type	# pts	ORR	CR	PR	SD
Hodgkin Lymphoma	23	20 (87)	6 (26)	14 (61)	3 (13)
B-Cell Non-Hodgkin Lymphoma	**31**	**8 (26)**	**3 (10)**	5 (16)	16 (52)
Diffuse Large B-Cell	**11**	**4 (36)**	**2 (18)**	2 (18)	3 (27)
Follicular	**10**	**4 (40)**	**1 (10)**	3 (30)	6 (60)
Mantle Cell	**4**	**0**	**0**	0	3 (75)
Primary Mediastinal B-Cell	**2**	**0**	**0**	0	2 (100)
Other B-NHL (SLL n=3, MZL n=1)	**4**	**0**	**0**	0	2 (50)
T-Cell Non-Hodgkin Lymphoma	**23**	**4 (17)**	0	4 (17)	10 (43)
CTCL/MF	**13**	**2 (15)**	0	2 (15)	9 (69)
Peripheral T-Cell	**5**	**2 (40)**	0	2 (40)	0
Other T-NHL	5	0	0	0	1 (20)
Multiple Myeloma	27	1 (4)	1 (4)	0	17 (63)

S. Ansell et al, NEJM 2015, A. Lesokhin et al, JCO 2016

Growing list of immune checkpoints



https://www.bio-connect.nl/immune-checkpoint-proteins-the-b7-cd28-

Combinations regimens with checkpoint inhibitors

>100 combination trials underway in blood cancers using:
Anti-PD-1 (nivolumab, pembrolizumab)
Anti-PD-L1 (atezolizumab, durvalumab, avelumab)
Anti-CTLA-4 (ipilimumab, tremelimumab)

- Novel checkpoint inhibitors: LAG-3, KIR, others
- Costimulatory agonistic antibodies: 4-1BB, OX-40, others
- Tumor-targeting mAbs: CD20, CD30, CD38, others
- Antibody-drug conjugates
- Kinase inhibitors: BTK, PI3K, multikinase
- IMiDs
- TLR, STING agonists (interferon-inducers)
- DNA methylation inhibitors
- IDO inhibitors
- Tumor antigen vaccines
- CAR T cells

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