PD-1/PD-L1 Blockade in NHL

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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

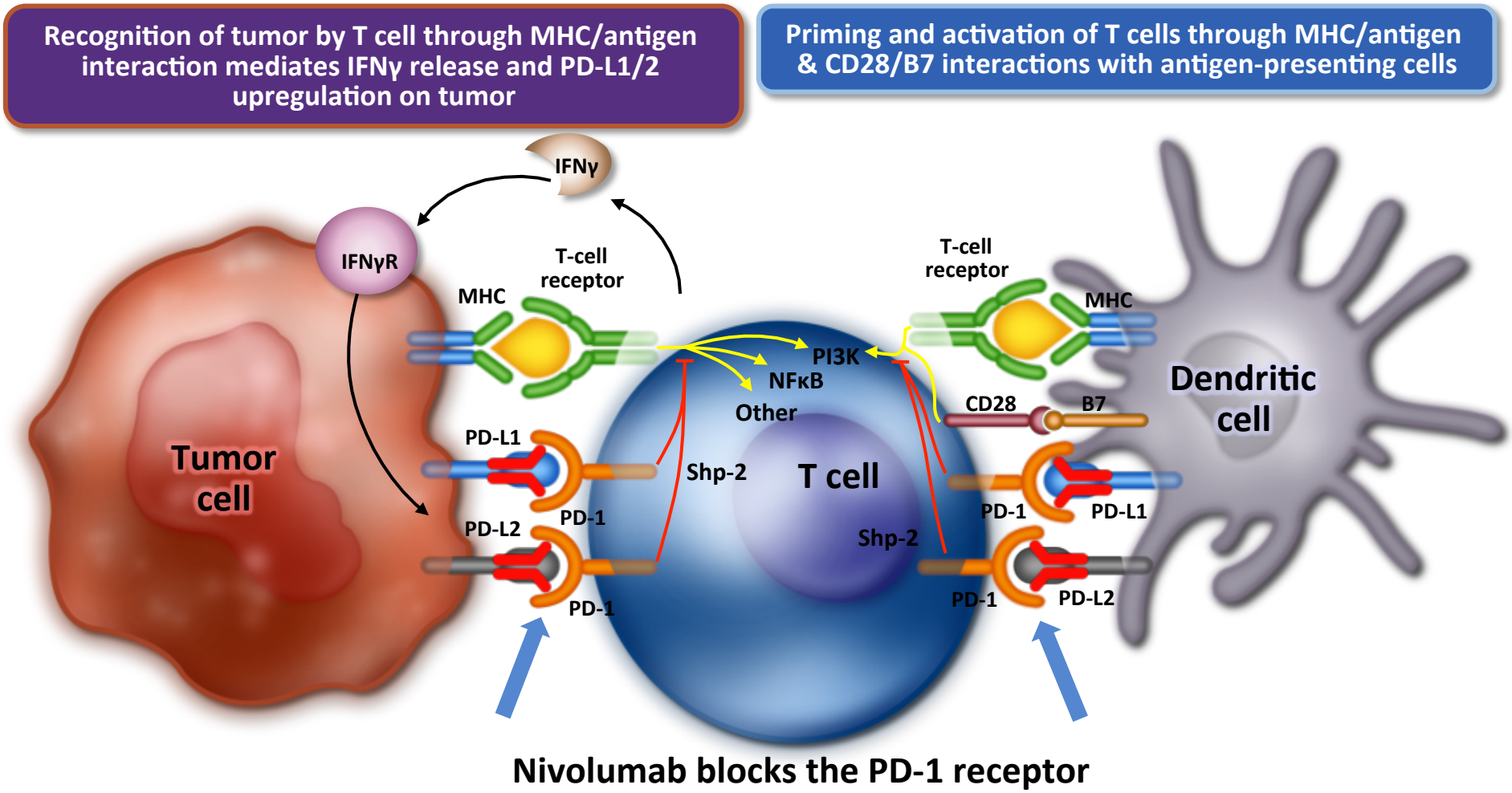
Combinations regimens with checkpoint inhibitors

>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**

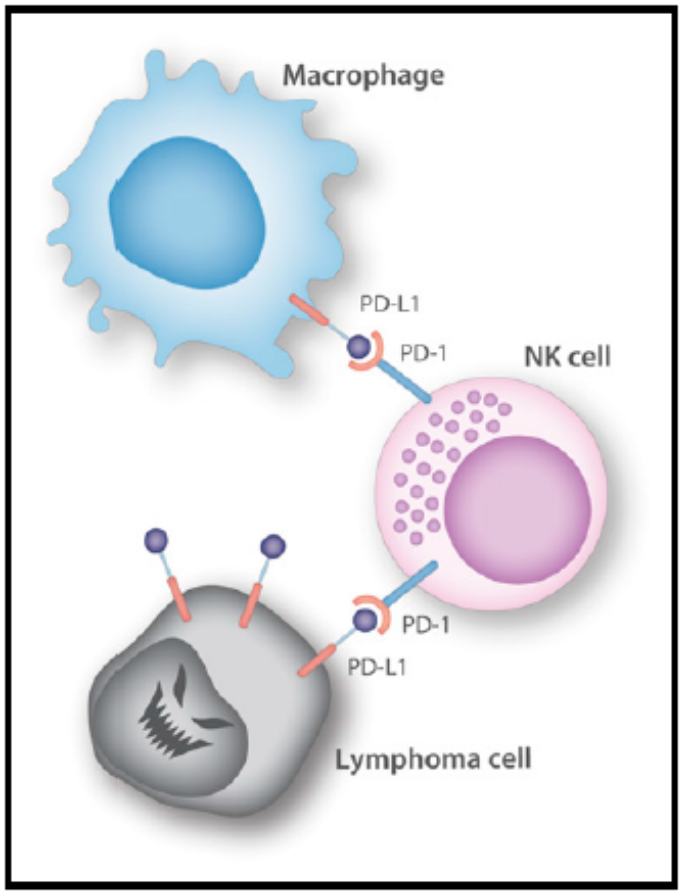
Anti-PD-1: Mechanism of Action



Checkpoint Blockade Therapy in NHL

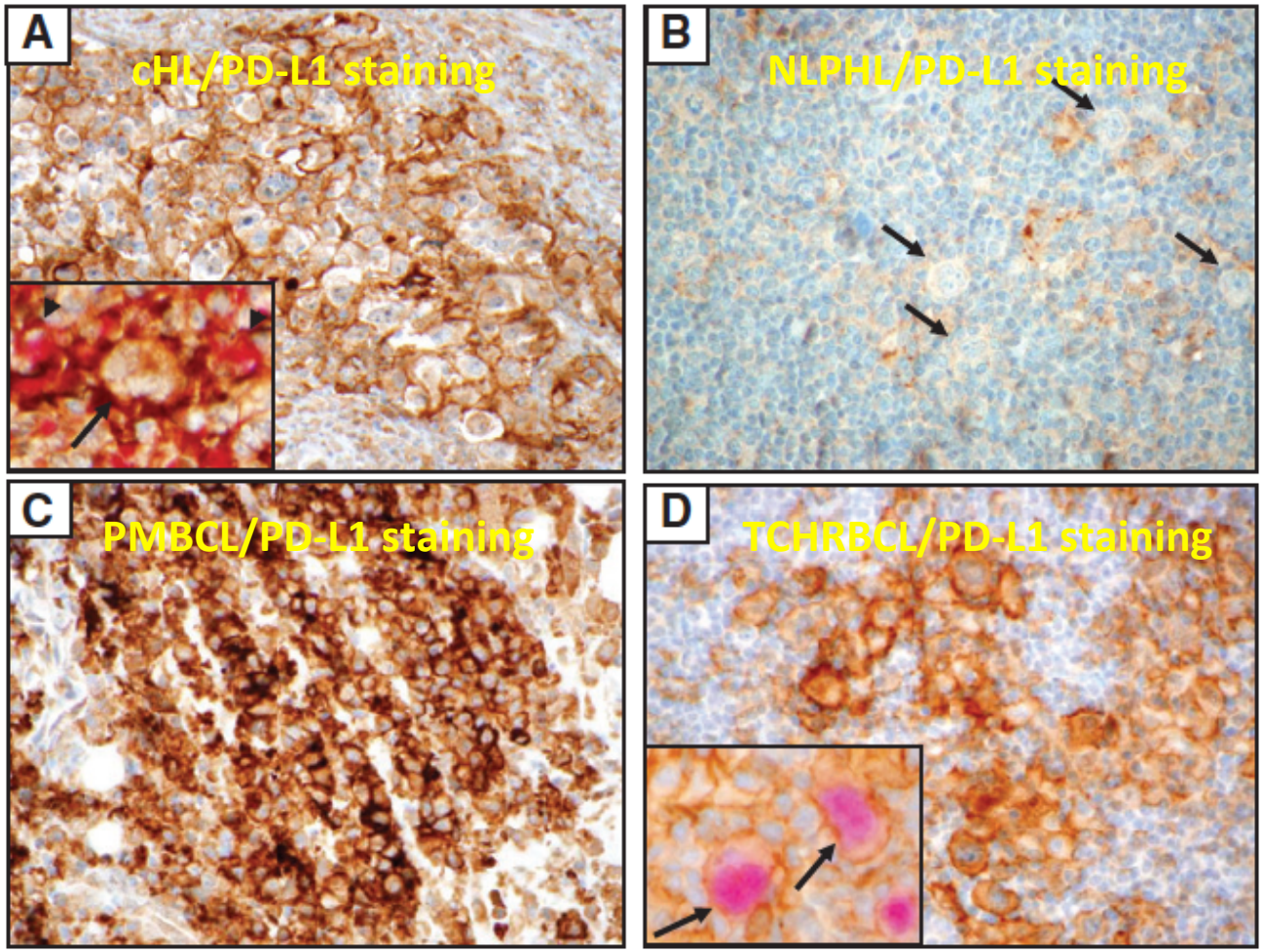
- Expansion of PD-1^{+}CD3^{-} CD56^{hi}CD16^{-ve} NK cells and PD-L1^{+} monocytes/macrophages is more prominent in cHL than DLBCL

- **PD-1 blockade reverses the immune evasion mediated by the interaction of PD-1^{+} NK cells and PD-L1^{+} monocytes/ macrophag**es



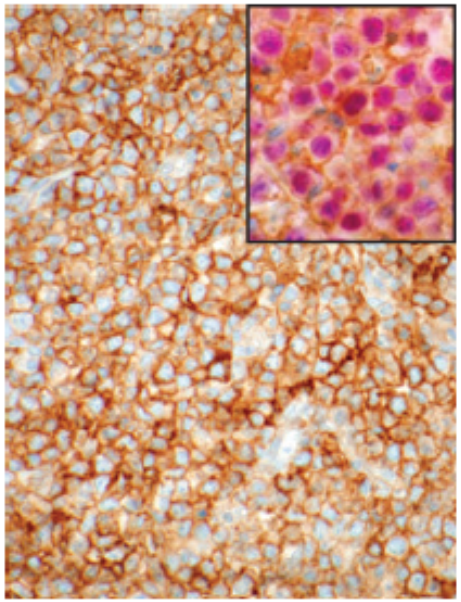
Vari F, Blood 131:1809-1819, 2018

PD-L1 Expression: Rationale for PD-1/PD-L1 Blockade

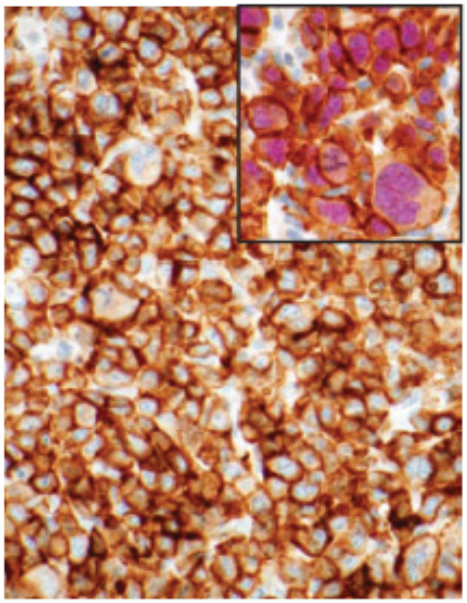


Chen B, Clin Cancer Res; 19:3462, 201

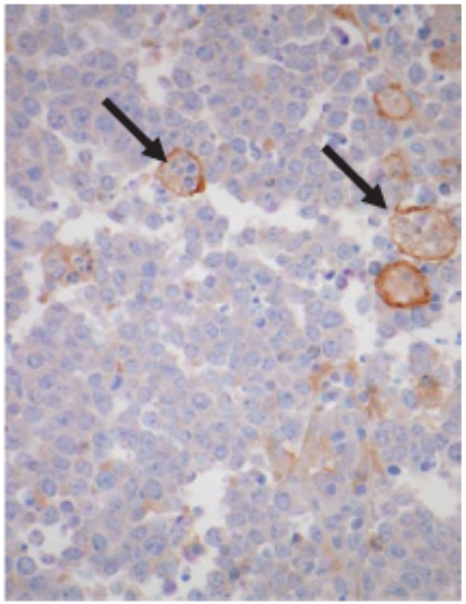
PD-L1 Expression: Rationale for PD-1/PD-L1 Blockade



EBV-pos BLBCL
PD-L1 staining



EBV-neg PTLD

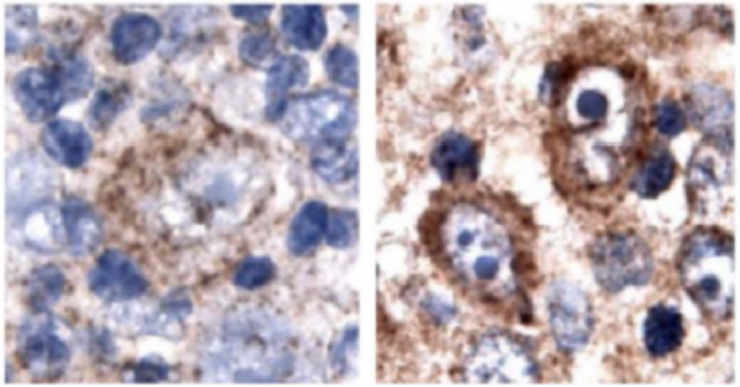


DLBCL-NOS

Chen B, Clin Cancer Res; 19:3462, 201

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

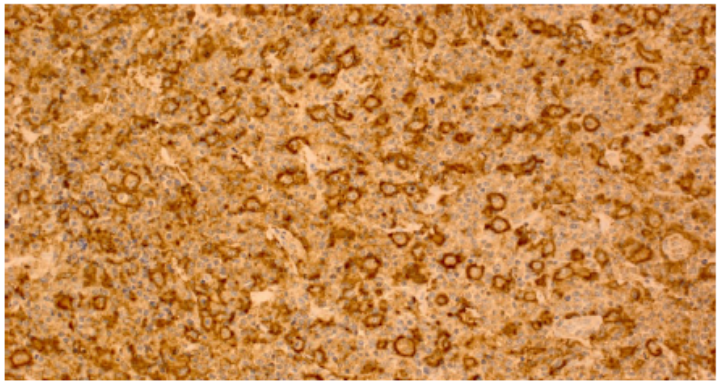
Hodgkin lymphoma



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

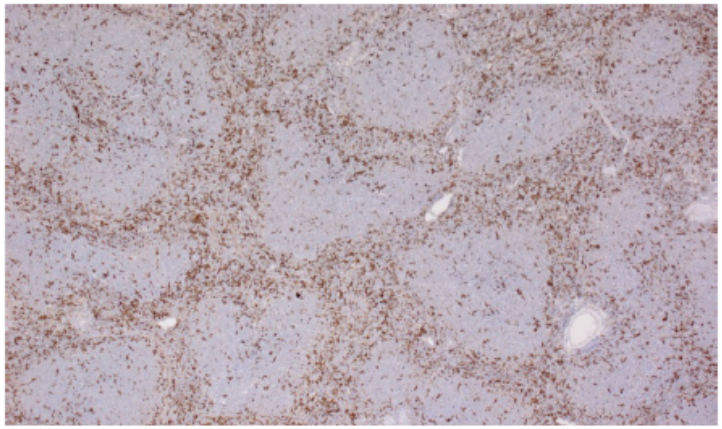
Green et al, Blood 2010

Diffuse large B cell lymphoma



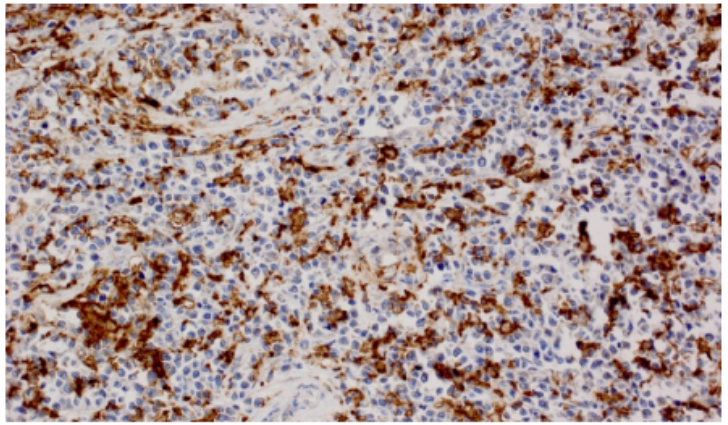
PD-L1 expression on tumor cells in some cases (ABC / non-GCB > GCB)

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

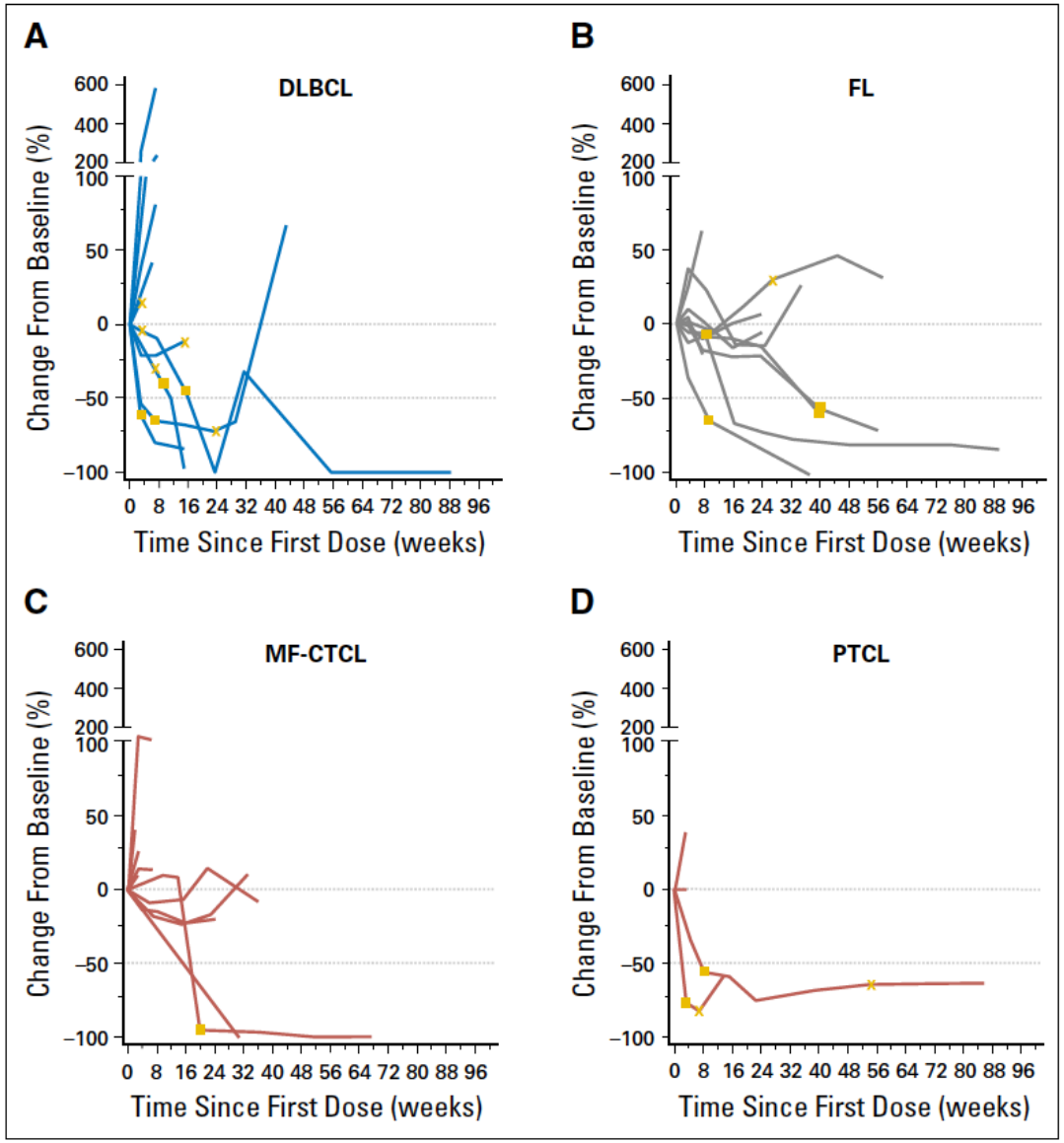
netic basis of *PD-L1* overexpression in diffuse large B-cell lymphom

tantinos Georgiou,[1] Longyun Chen,[1,2] Mattias Berglund,[3] Weicheng Ren,[1] Noel F. C. C. de Miranda,[4] Susana Lisb
o Fangazio,[6] Shida Zhu,[2] Yong Hou,[2] Kui Wu,[2] Wenfeng Fang,[7] Xianhuo Wang,[8] Bin Meng,[8] Li Zhang,[7] Yixin Ze
nd Bhagat,[9] Magnus Nordenskjöld,[10] Christer Sundström,[11] Gunilla Enblad,[11] Riccardo Dalla-Favera,[6] Huilai Zhan
el R. Teixeira,[5] Laura Pasqualucci,[6] Roujun Peng,[7] and Qiang Pan-Hammarström[1]

Georgiou K, Blood, 2016

- Translocations between PD-L1 and the IGH locus represent a genetic mechanism of PD-L1 overexpression in DLBCL
- Overall, gains (12%), amplifications (3%), and translocations (4%) of the PD-L1/PD-L2 locus were identified in nearly 20% of DLBCL
- Strong association between PD-L1 protein expression and alterations in the PD-L1/PD-L2 locus
- Genetic alterations in the PDL1/PDL-2 locus are mainly associated with the non-GCB subtype of DLBCL

Nivolumab in NHL

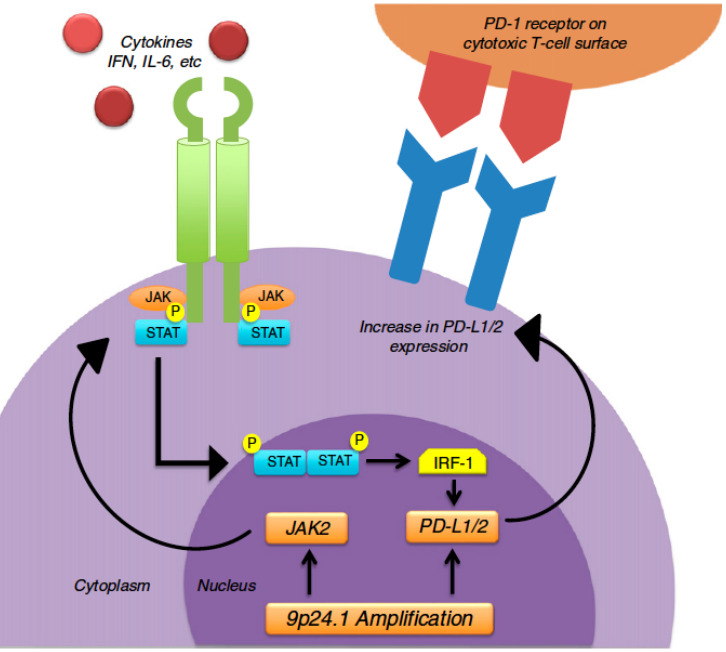


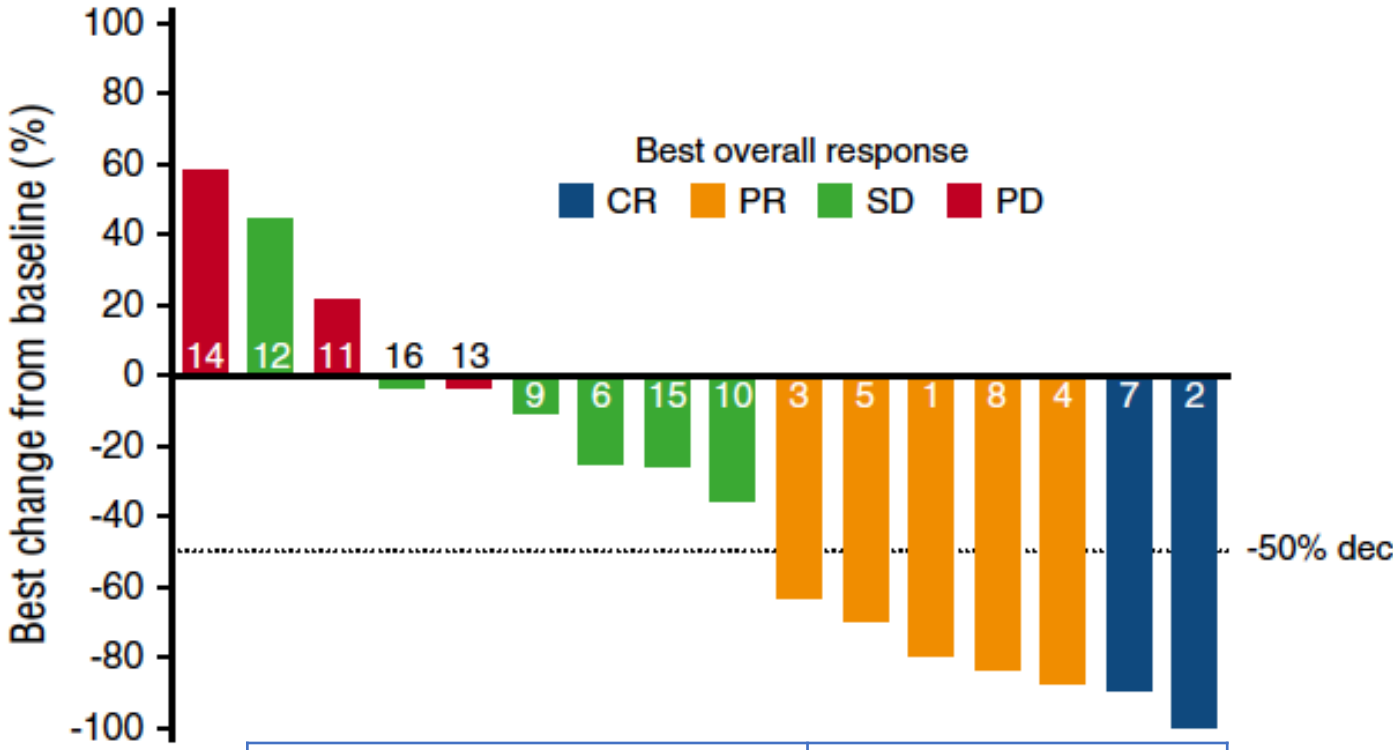
Lesokhin AM, JCO, 2016

PD-L1-Expressing Lymphomas

- PMLBCL, GZL, PCNSL, PTL (9p24.1 amplification)
- Richter transformation of CLL
- EBV & other virus-related lymphomas
  - BL HIV-related, EBV+ PTLD
  - Plasmablastic lymphomas
  - NK/T-cell lymphoma
  - Angioimmunoblastic T-cell lymphoma
  - HHV-8 PEL
  - Multicentric Castleman disease

Pembrolizumab in PMBCL

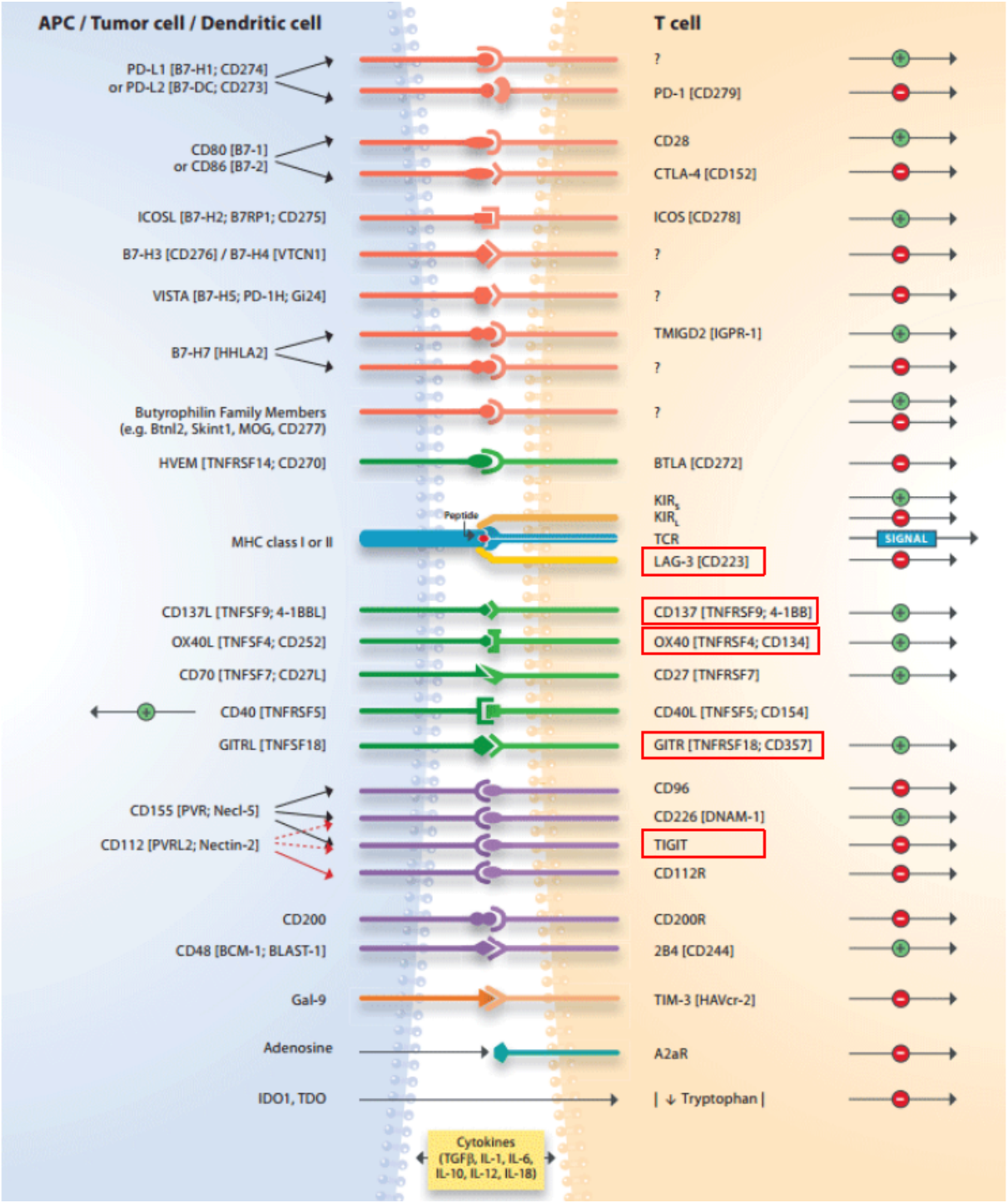




ORR	7/17 (41%)
CR	2/17 (12%)
Ongoing Responses	6/7 (86%)

ni et al, Blood 2017

Growing list of immune checkpoints



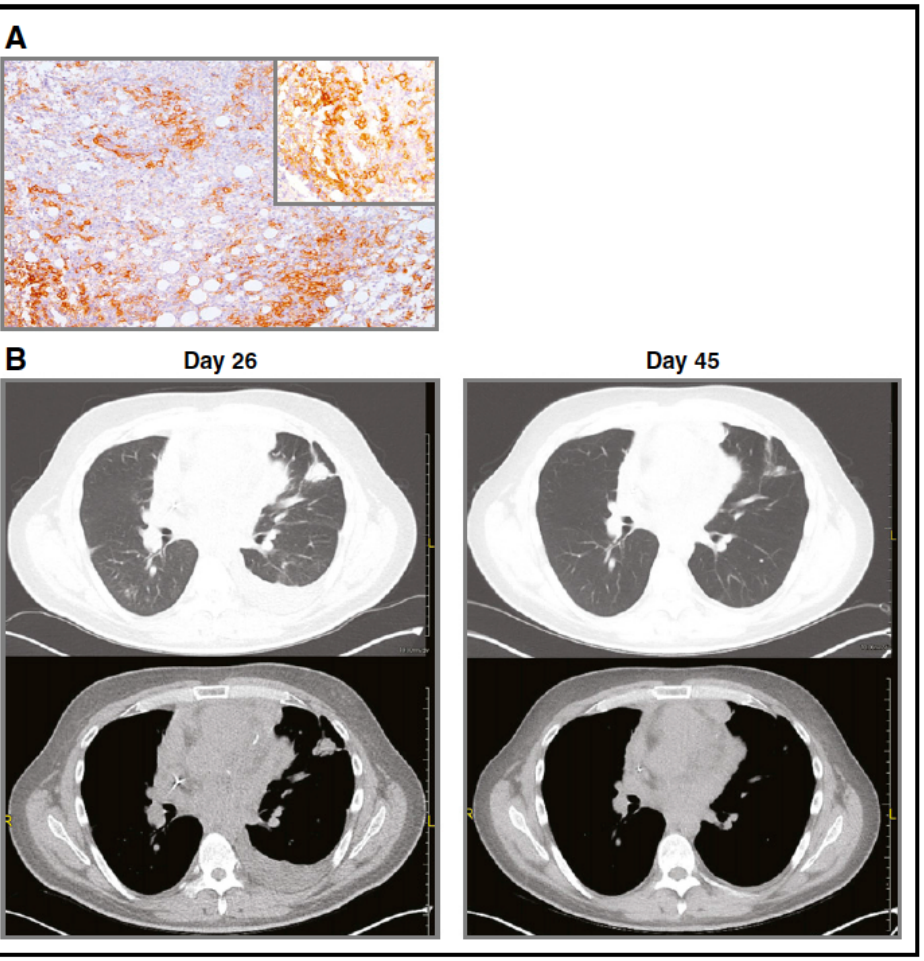
https://www.bio-connect.nl/immune-checkpoint-proteins-the-b7-cd28-

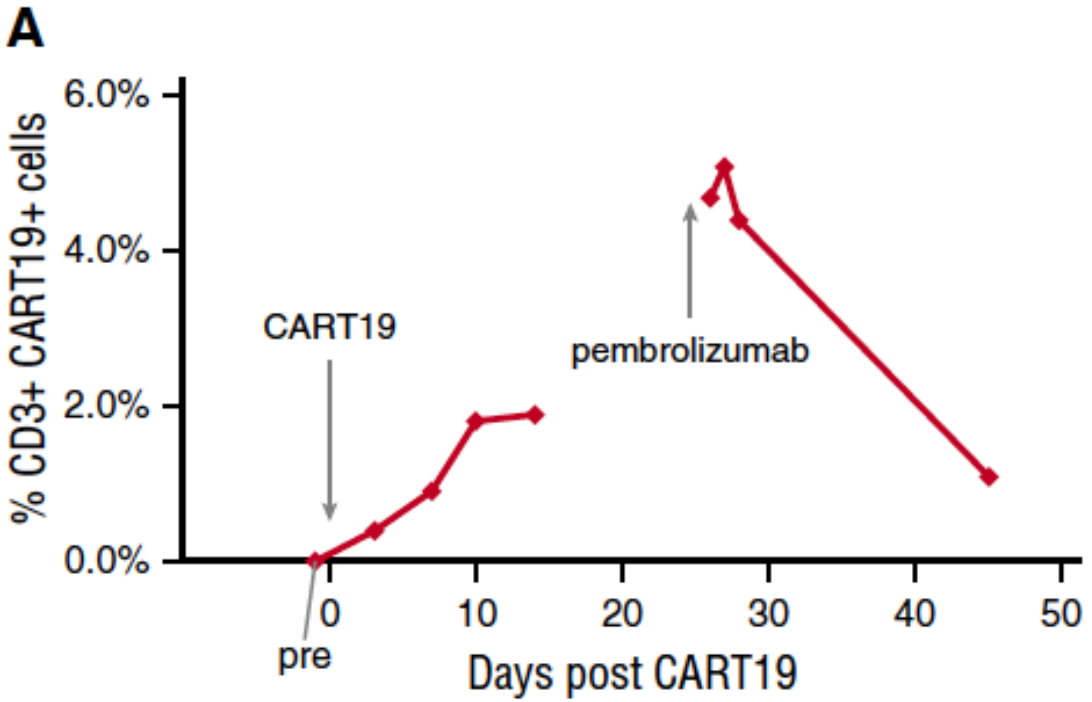
PD-1 blockade modulates chimeric antigen receptor (CAR)–modified T cells: refueling the CA

Elise A. Chong,[1] J. Joseph Melenhorst,[2] Simon F. Lacey,[2] David E. Ambrose,[2] Vanessa Gonzalez,[2] Bruce L. Levine,[2] Carl H. June,[2] and Stephen J. Schuster[1]

[1]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; and [2]Department of Pathology and Laboratory Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

Blood, 2017





Conclusions

- Therapeutic benefit of PD-1 blockade as a single agent is undoubtedly *much less in NHL then in cHL*
- However, distinct NHL subtypes may be attractive for CBT (i.e., PD-L1^{+} lymphomas)
- Building on evolving understanding of the molecular pathobiology of various NHL subtypes
- Combination partners for PD-1 blockade will extend the benefit of checkpoint blockade across a broad spectrum of NHLs

PD-L1 Expression

Diagnosis	Cases *n*	Cases with ≥5% malignant cells positive[a] *n* (%)	Cases with ≥20% total cellularity positive[b] *n* (%)
Classical Hodgkin lymphoma (CHL)	38	33 (87)	31 (82)
Nodular sclerosis CHL	25	21 (84)	19 (76)
Mixed cellularity CHL	8	7 (88)	7 (88)
CHL-not otherwise specified (NOS)	5	5 (100)	5 (100)
Nodular lymphocyte predominant Hodgkin lymphoma	15	2 (13)	1 (7)
Primary mediastinal large B-cell lymphoma	21	15 (71)	19 (90)
T-cell/histiocyte-rich large B-cell lymphoma	11	10 (91)	11 (100)
EBV+ diffuse large B-cell lymphoma (DLBCL)	16	16 (100)	16 (100)
EBV+ DLBCL of elderly	9	9 (100)	9 (100)
EBV+ immunodeficiency associated DLBCL	7	7 (100)	7 (100)
EBV+ posttransplant lymphoproliferative disorder (PTLD)	10	6 (60)	7 (70)
EBV-negative PTLD	7	4 (57)	4 (57)
DLBCL-NOS	66	7 (11)	9 (14)
Plasmablastic lymphoma	9	4 (44)	4 (44)
Primary effusion lymphoma	4	2 (50)	3 (75)
Extranodal NK/T-cell lymphoma	6	4 (67)	5 (83)
EBV+ Burkitt lymphoma	7	0 (0)	0 (0)
EBV+ nasopharyngeal carcinoma	18	16 (89)	nd
HHV8+ Kaposi sarcoma	9	0 (0)	nd

Chen B, Clin Cancer Res 19:3462, 20