Nuove frontiere nell'immunomodulazione

Dr. Daniele Vallisa

UO Ematologia e CTMO

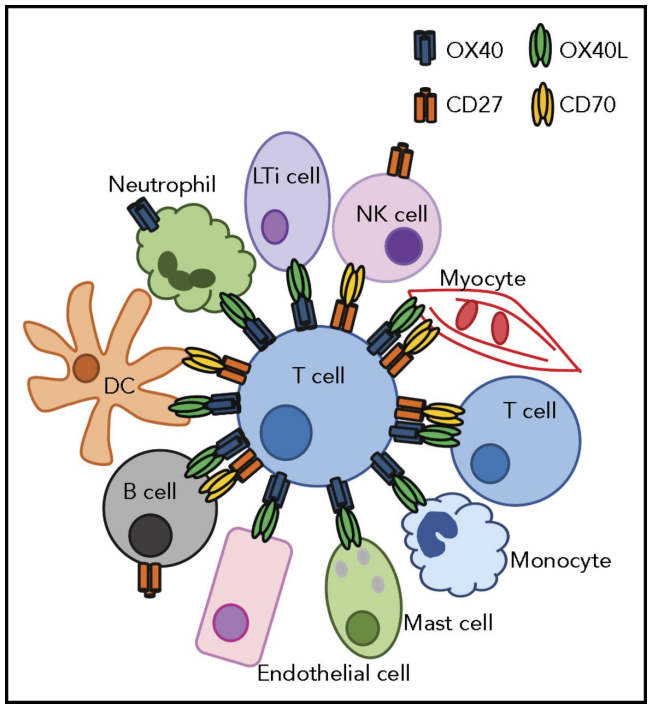
Ospedale Guglielmo da Saliceto di Piacenza

L’approccio immunoterapico nei linfomi

- Ab monoclonali con cellula tumorale quale target
  - Coniugati diretti sulla HRS
  - antiCD20
- Farmaci immunomodulanti
- “Check point inhibitors”
  - Monoclonali
  - (Farmaci)
- CAR-T cell
  - Linfociti ingegnerizzati
- Trapianto allogenico
- Vaccini

Linfociti T:
molecole stimolatorie ed inibitorie

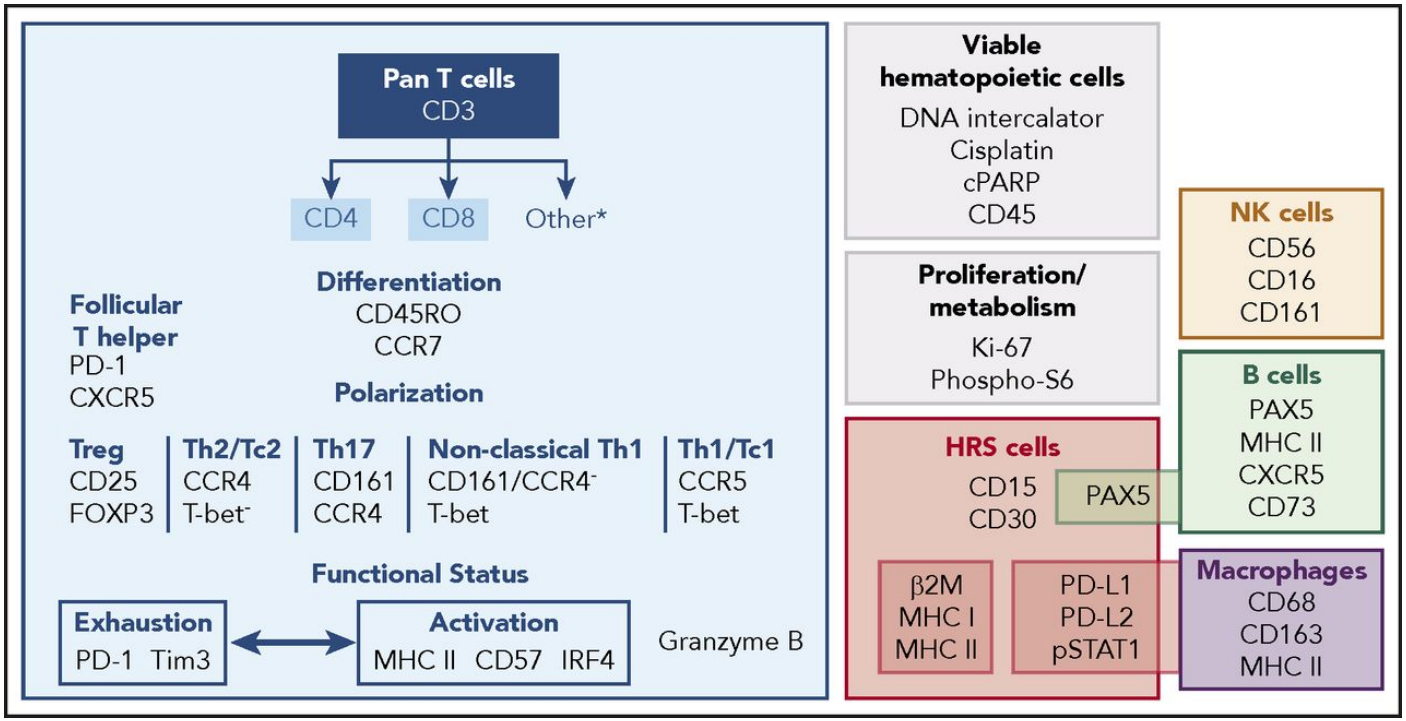
- Stimolazione
  - Molecole di superficie: OX40 e CD27
  - 2 dinamiche nei processi costimolatori
    - precoce
    - tardiva
- Inibizione
  - Intracitoplasmatico
  - Molecole di superficie: PD1, CXCR4



EXHAUSTED LINFOCITA T

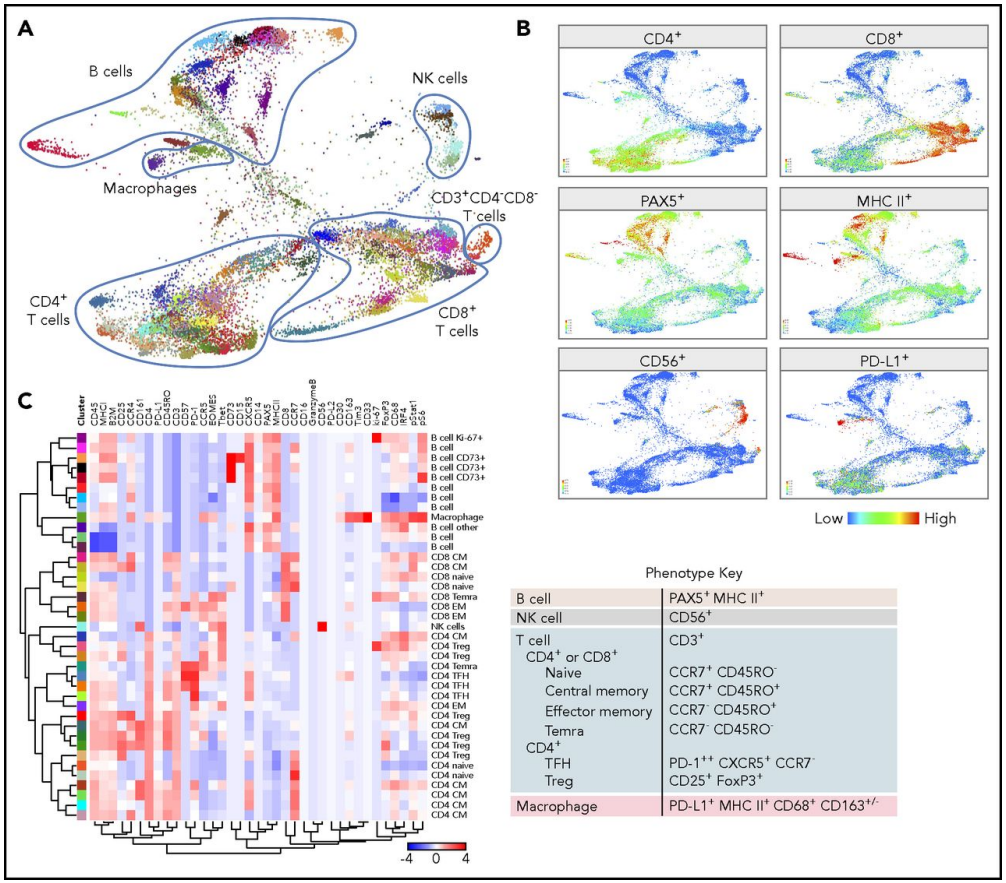
- Interazione del linfocita T CD8 con le cellule tumorali che esprimono contemporaneamente antigeni correlati alla classe prima del sistema maggiore di istocompatibilità (MHC I) e PDL-1. (exhausted linfocita T CD8).
- Interazione del linfocita T CD4 (effector cell) con le cellule tumorali che esprimono contemporaneamente antigeni correlati alla classe seconda del sistema maggiore di istocompatibilità (MHC II) e PDL-1. (exhausted linfocita T CD4) .

CyTOF panel for the simultaneous assessment of HRS cells and infiltrating immune cells.



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

CyTOF analyses of all viable cells.



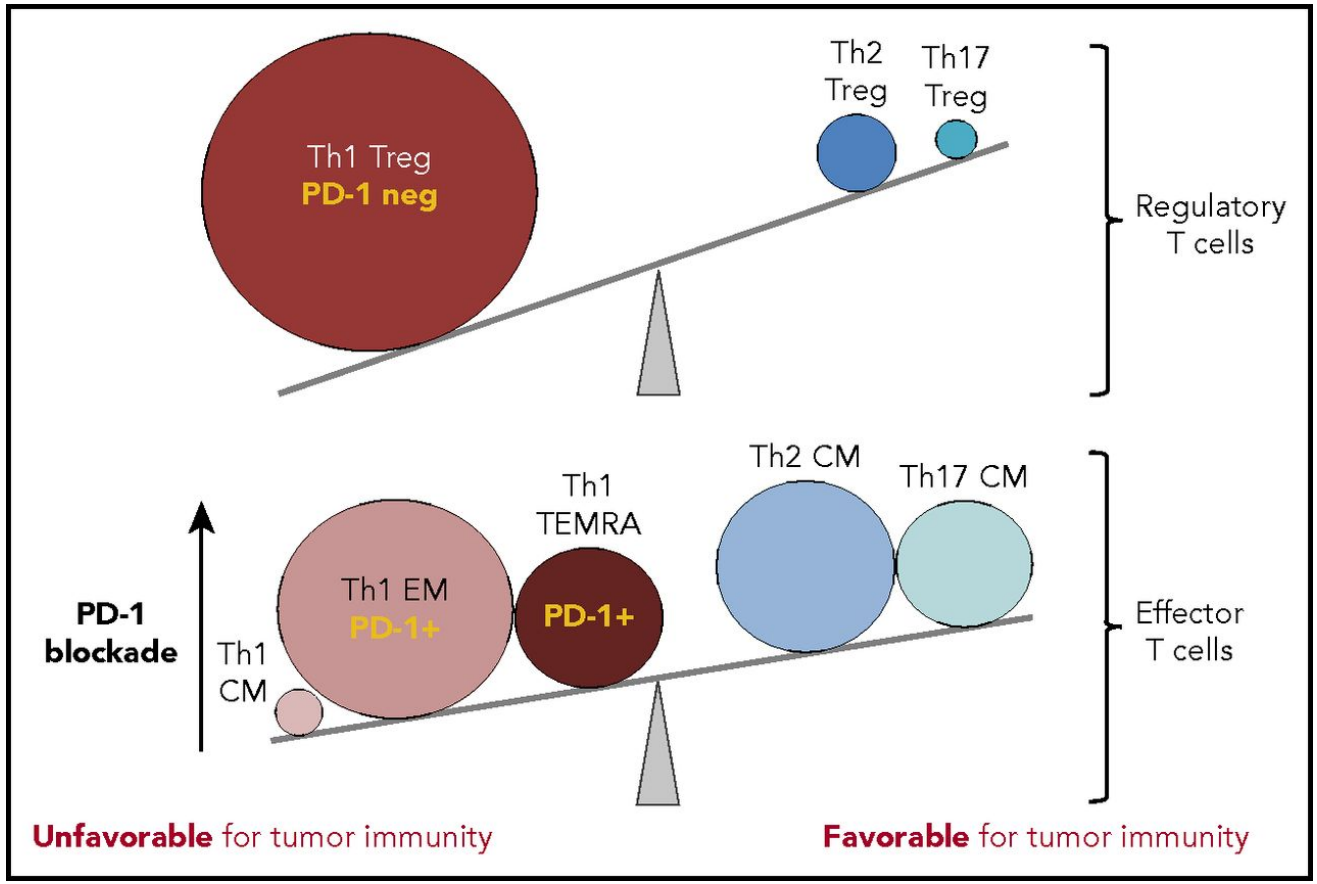
Fathima Zumla Cader et al. Blood 2018;132:825-836

Linfociti T effettori

- **CD4+ e CD8+**
  - **Naive**
  - **Central memory (CM)**
  - **Effector memory (EM)**
  - **Terminally differentiated effector memory (TEMRA)**

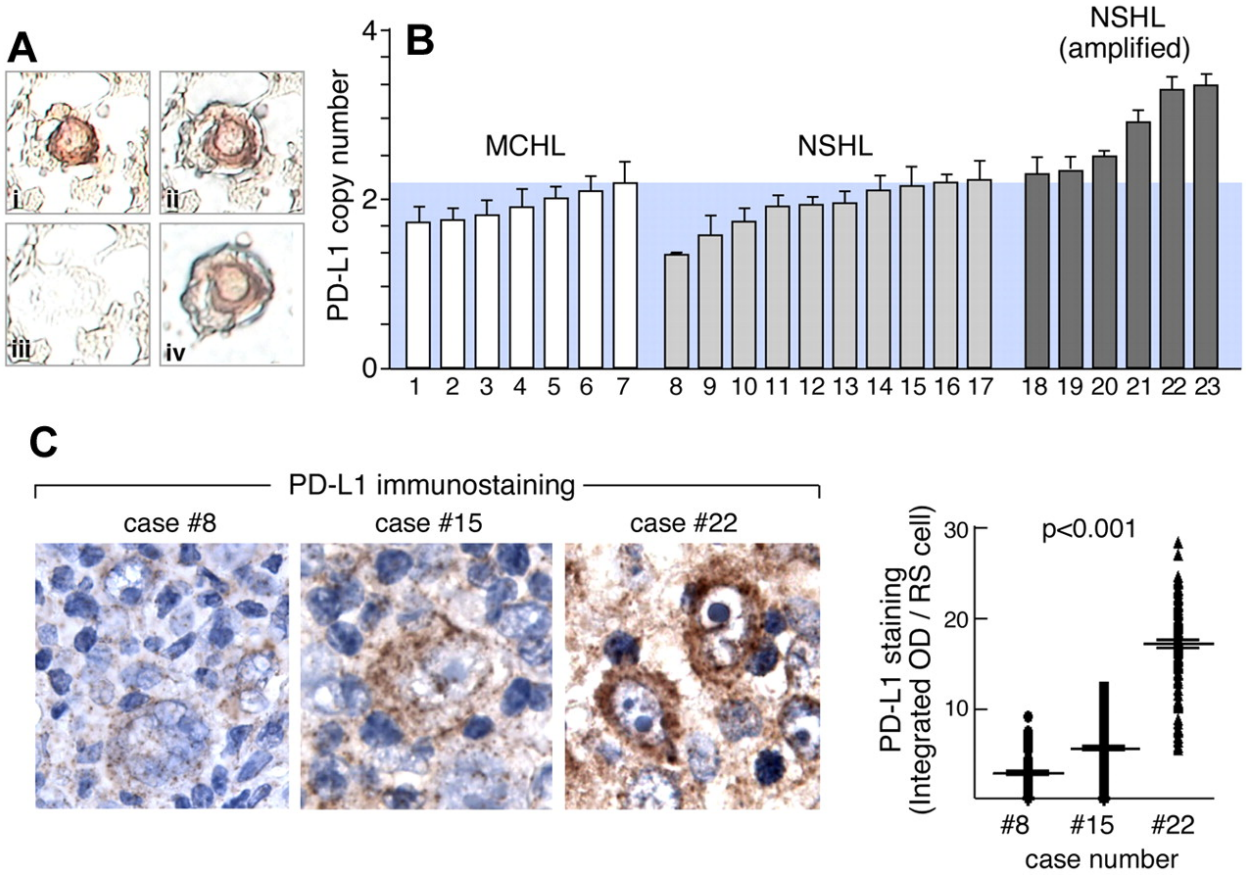
- CD4+ Th1 EM e TEMRA polarizzate e differenziate PD-1+
- CD4+ Th1 e Th2 e Th 17 CM meno differenziate e polarizzate PD-1-
- CD4+ Treg (FoxP3+ e CD25+) Th1 Th2 Th 17 polarizzate, PD-1-
- CD4 + TFH: PD-1++, CXCR5+, CCR7-

T-cell subsets within the Hodgkin lymphoma tumor microenvironment tip the balance away from tumor immunity.



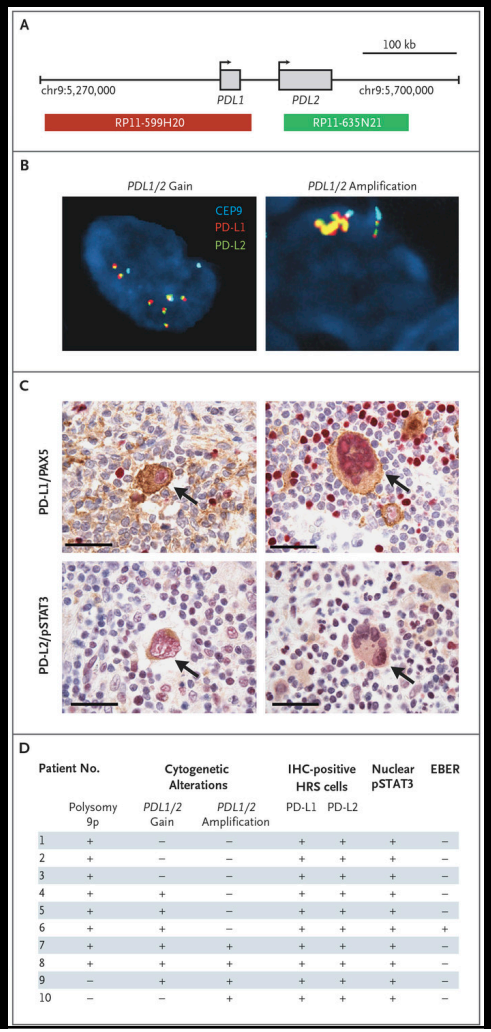
John Timmerman Blood 2018;132:770-771

PD-1 ligand amplification and overexpression in primary HL. (A) Laser-capture microdissection (LCM) of primary HL Reed-Sternberg RS cells.



Michael R. Green et al. Blood 2010;116:3268-3277

Genetic and Immunohistochemical Analyses of *PDL1* and *PDL2* Loci, PD-L1 and PD-L2 Protein Expression, and Epstein–Barr Virus Status in Patients with Hodgkin's Lymphoma.



Patient No.	Cytogenetic Alterations			IHC-positive HRS cells		Nuclear pSTAT3	EBER
	Polysomy 9p	*PDL1/2* Gain	*PDL1/2* Amplification	PD-L1	PD-L2		
1	+	–	–	+	+	+	–
2	+	–	–	+	+	+	–
3	+	–	–	+	+	+	–
4	+	+	–	+	+	+	–
5	+	+	–	+	+	+	–
6	+	+	–	+	+	+	+
7	+	+	+	+	+	+	–
8	+	+	+	+	+	+	–
9	–	+	+	+	+	+	–
10	–	–	+	+	+	+	–

Ansell SM et al. N Engl J Med 2015;372:311-319.

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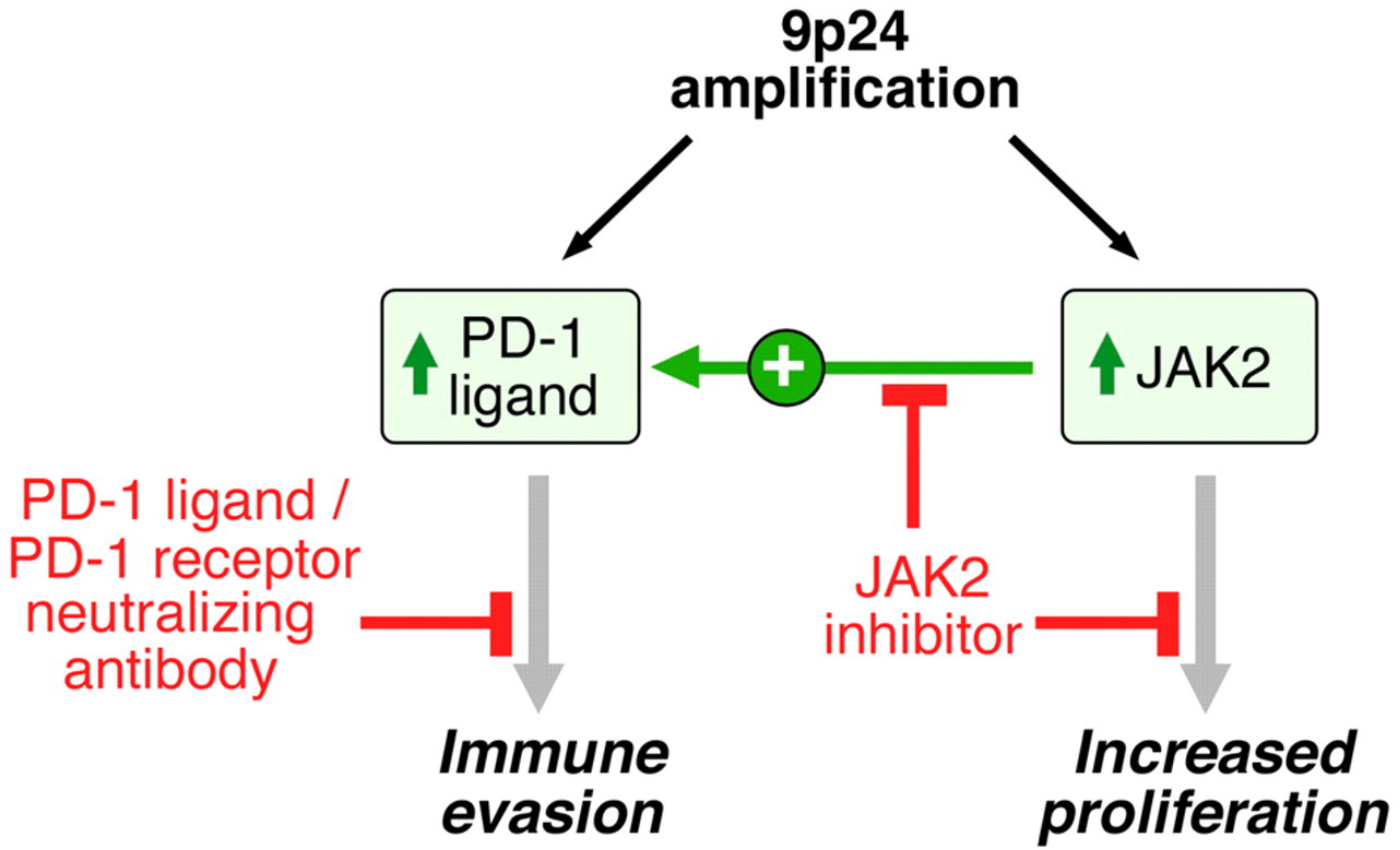
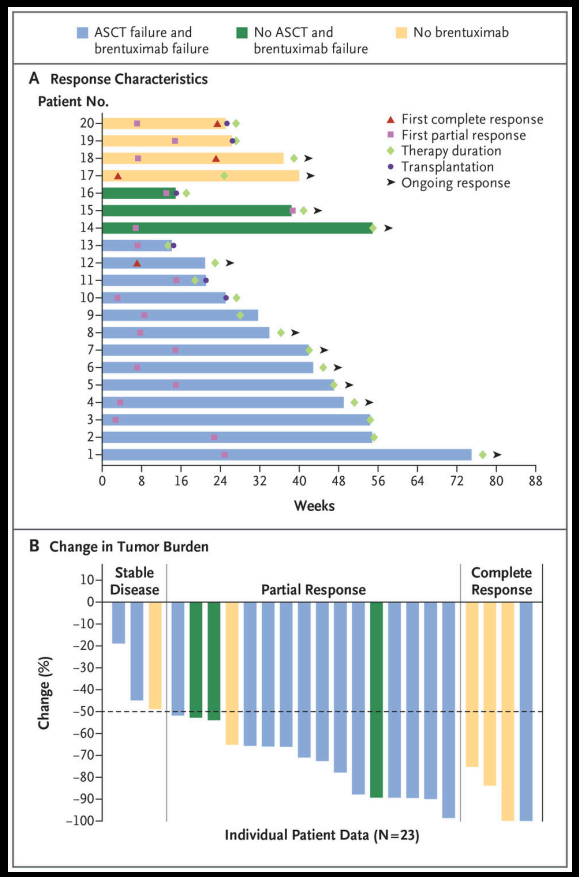
9p24.1 amplification targets, consequences, and associated treatment options. 9p24.1 amplification increases PD-1 ligand (PD-L1 and PD-L2) and JAK2 copy numbers, augments JAK2/STAT1 activity, induces PD-1 ligand expression, and stimulates HL proliferation.



Michael R. Green et al. Blood 2010;116:3268-3277

Response Characteristics and Changes in Tumor Burden in Patients with Hodgkin's Lymphoma Receiving Nivolumab.



Ansell SM et al. N Engl J Med 2015;372:311-319.

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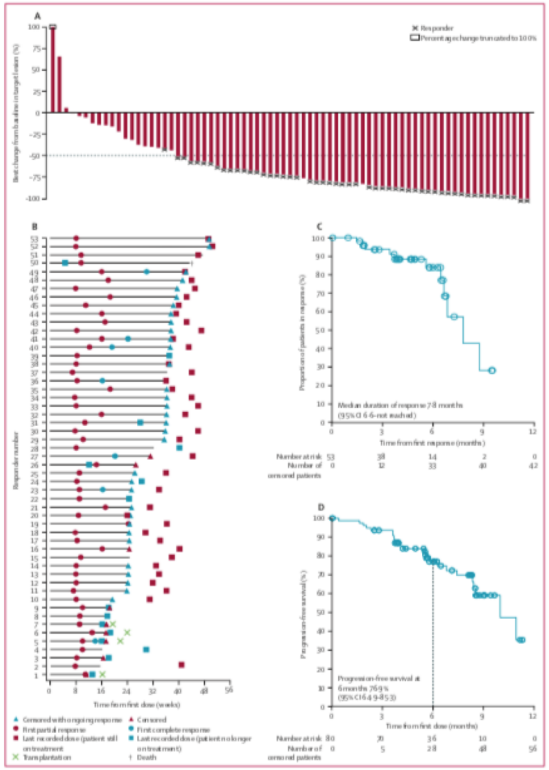
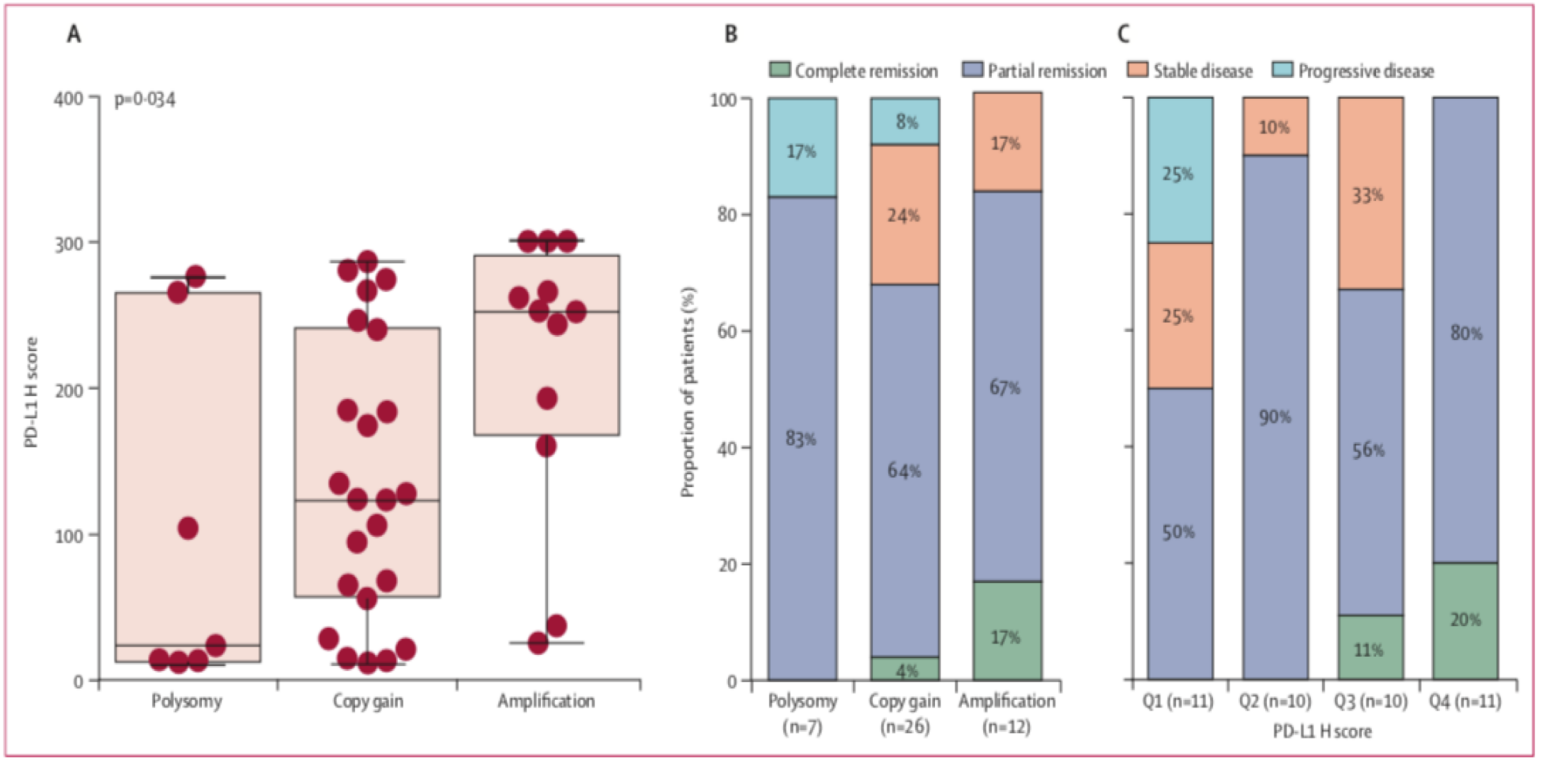
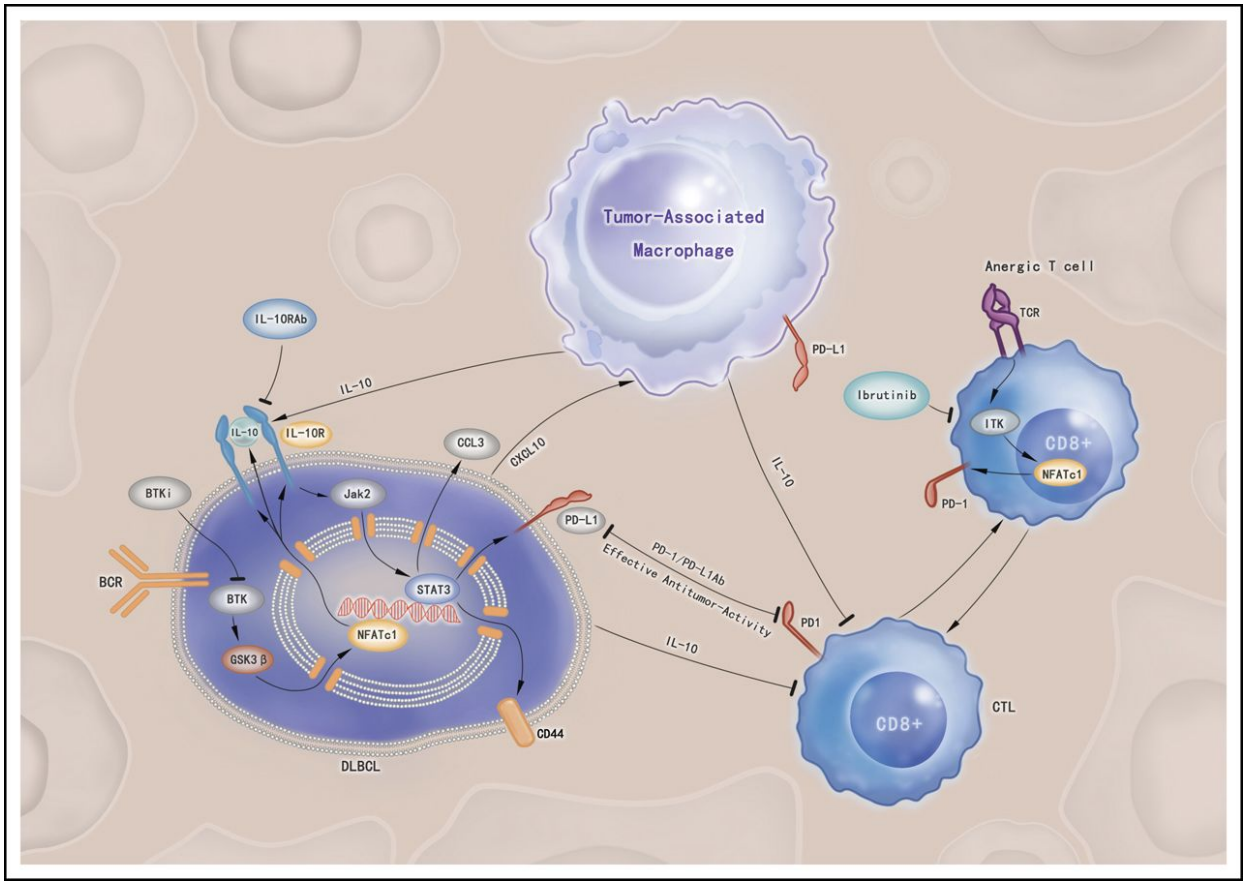



A
p=0·034
PD-L1 H score
400
300
200
100
0
Polysomy
Copy gain
Amplification
B
Complete remission
Partial remission
Stable disease
Progressive disease
Proportion of patients (%)
100
80
60
40
20
0
17%
83%
8%
24%
64%
4%
17%
67%
17%
Polysomy (n=7)
Copy gain (n=26)
Amplification (n=12)
C
25%
25%
50%
10%
90%
33%
56%
11%
80%
20%
Q1 (n=11)
Q2 (n=10)
Q3 (n=10)
Q4 (n=11)
PD-L1 H score



Li Li et al. Blood 2018;132:1805-1817

Brief Report

blood

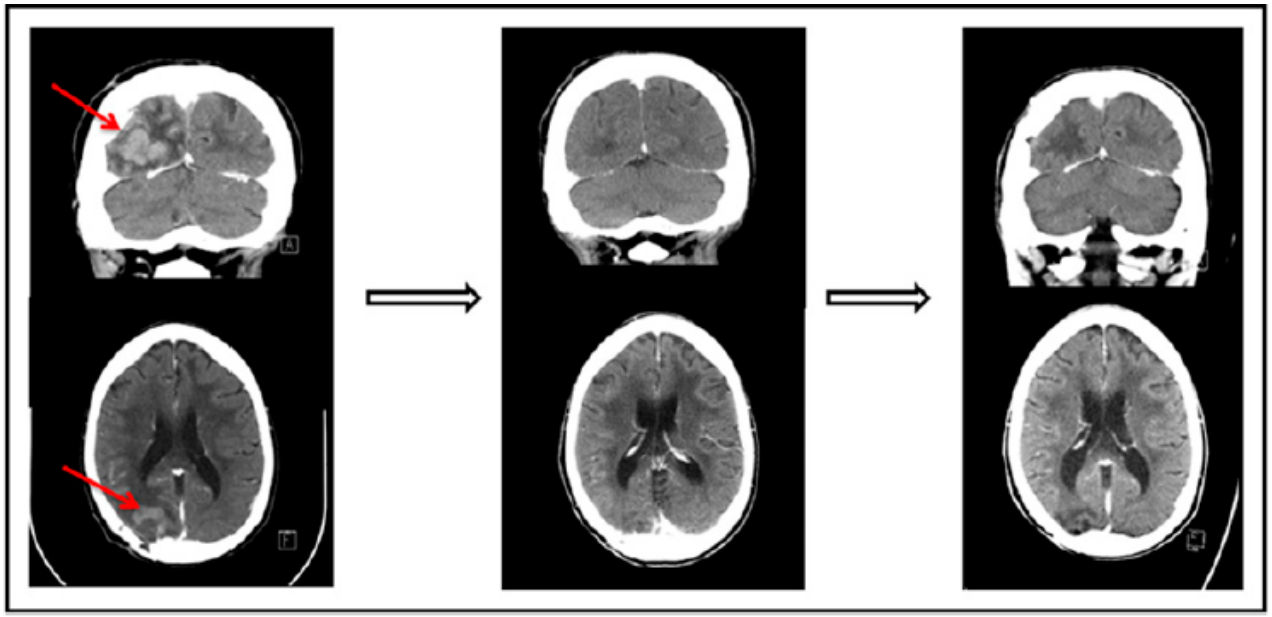
CLINICAL TRIALS AND OBSERVATIONS

PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma

Lakshmi Nayak,[1,2] Fabio M. Iwamoto,[3] Ann LaCasce,[1,2] Srinivasan Mukundan,[1,2] Margaretha G. M. Roemer,[1] Bjoern Chapuy,[1] Philippe Armand,[1,2] Scott J. Rodig,[1,2] and Margaret A. Shipp[1,2]

Key Points

- Genetic analysis reveals frequent 9p24.1/PD-L1/PD-L2 copy-number alterations and increased expression of the PD-1 ligands in PCNSL and PTL.
- PD-1 blockade with nivolumab demonstrated activity in patients with relapsed/refractory PCNSL and PTL.



Brief Report

blood

CLINICAL TRIALS AND OBSERVATIONS

Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma

Pier Luigi Zinzani,[1] Vincent Ribrag,[2] Craig H. Moskowitz,[3] Jean-Marie Michot,[2] John Kuruvilla,[4] Arun Balakumaran,[5] Yayan Zhang,[5] Sabine Chlosta,[5] Margaret A. Shipp,[6] and Philippe Armand[6]

Key Points

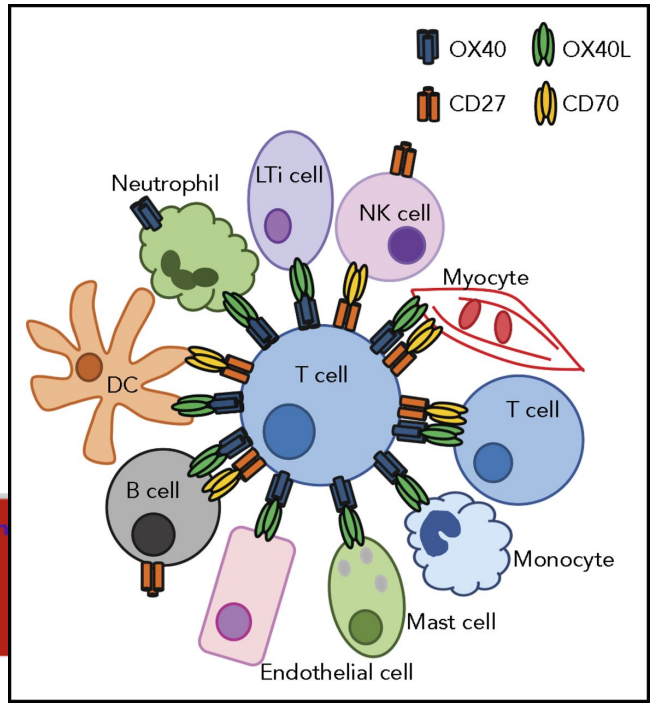
- Treatment options for relapsed/refractory PMBCL are limited, and prognosis is generally poor.
- Pembrolizumab had a manageable safety profile and promising antitumor activity in heavily pretreated rrPMBCL patients.

Table 1. Clinical outcomes in patients evaluated for efficacy: response to treatment

	n (%) (N = 17)	90% confidence interval
ORR	7 (41.2)	21.2, 63.6
CR	2 (11.8)	12.4, 52.2
Partial response	5 (29.4)	2.1, 32.6
Stable disease	6 (35.3)	16.6, 58.0
Progressive disease	3 (17.6)	5.0, 39.6
No assessment	1 (5.9)*	0.3, 25.0

Linfociti T:
molecole di superficie studiate

- CD27 (che interagisce con CD70)
- OX40 (che interagisce con OX40L)
- PD1
- CXCR4



blood
Review Series

THERAPEUTIC ANTIBODIES

The immunobiology of CD27 and OX40 and their potential as targets for cancer immunotherapy

Sarah L. Buchan, Anne Rogel, and Aymen Al-Shamkhani

Target	Agent	Delivered with	Trial number	Tumor type
OX40	MEDI6469 (9B12)	Vaccine or adjuvant	NCT01644968	Various advanced
		Surgical resection	NCT02274155	Head and neck
		Surgical resection	NCT02559024	Colorectal
		Radiation	NCT01862900	Breast
		Radiotherapy and cyclophosphamide	NCT01303705	Prostate
	MEDI0562	Monotherapy	NCT02318394	Solid tumors
		Anti-CTLA-4 or anti-PD-L1	NCT02705482	Solid tumors
	PF-04518600	Alone or with anti-4-1BB	NCT02315066	Solid tumors
		Anti-PD-L1 $^{+/-}$ anti-4-1BB	NCT02554812	Solid tumors
		Tyrosine-kinase inhibitor	NCT03092856	Renal
	INCAGN01949	Alone	NCT02923349	Solid tumors
	BMS-986178	Alone or with anti-PD-1/ anti-CTLA-4	NCT02737475	Solid tumors
	MOXR0916 (RG7888)	Alone	NCT02219724	Solid tumors
		Anti-PD-L1	NCT03029832	Urothelial
		Anti-PD-L1 $^{+/-}$ anti-VEGF	NCT02410512	Solid tumors
	GSK3174998	Alone or with anti-PD-1	NCT02528357	Solid tumors
	MEDI6383	Alone or with anti-PD-L1	NCT02221960	Solid tumors
CD27	Varlilumab (CDX-1127)	Alone	NCT01460134	Hematologic or solid
		Peptide vaccine and adjuvant	NCT02924038	Glioma
		Peptide vaccine	NCT02270372	Ovarian and breast
		Anti-PD-1	NCT02335918	Refractory
		Anti-PD-1	NCT03038672	B-cell lymphoma
		Antitumor mAb-drug conjugate	NCT02302339	Melanoma
CD70	SGN-CD70A	Alone	NCT02216890	$CD70^{+}$ renal or lymphoma
	SGN-75	Alone	NCT01015911	$CD70^{+}$ renal or NHL
	ARGX-110	Alone	NCT01813539	$CD70^{+}$ advanced tumors
		Alone or with chemotherapy	NCT02759250	Nasopharyngeal
	MDX-1203	Alone	NCT00944905	$CD70^{+}$ renal or NHL

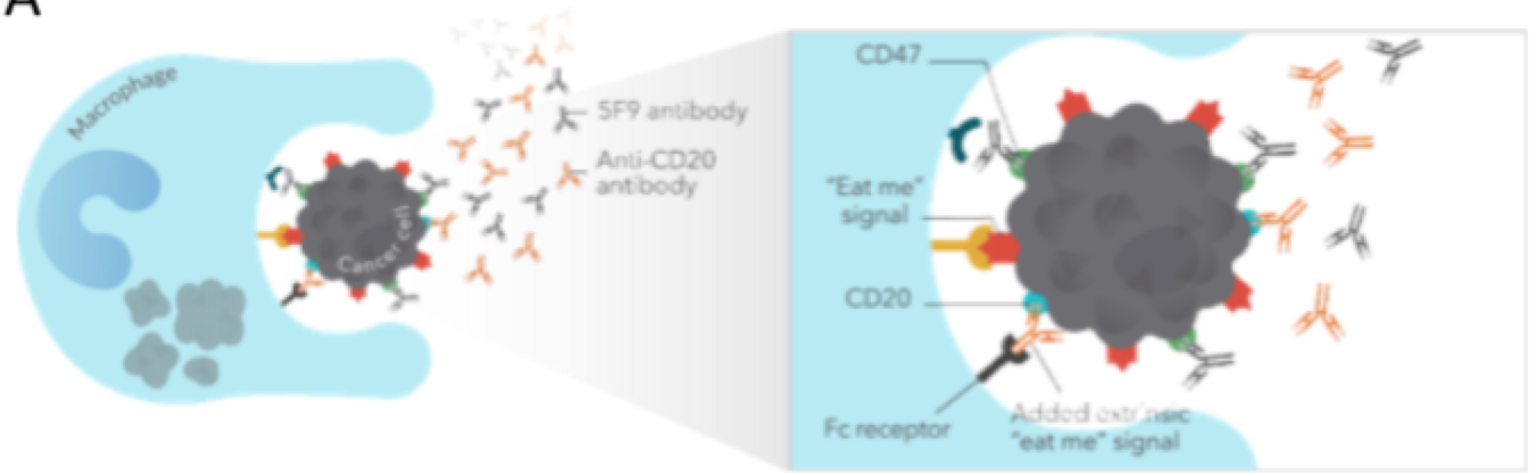
FARMACI

- Anti PD-1:
  - PEMBROLIZMAB, NIVOLUMAB
- Anti PDL-1:
  - AVELUMAB, ATEZOLIZUMAB
- Riduzione espressione PD-1:
  - PANOBINOSTAT
  - IBRUTINIB
- Incremento livelli di OX40:
  - ETINOSTAT (anti HDAc1)

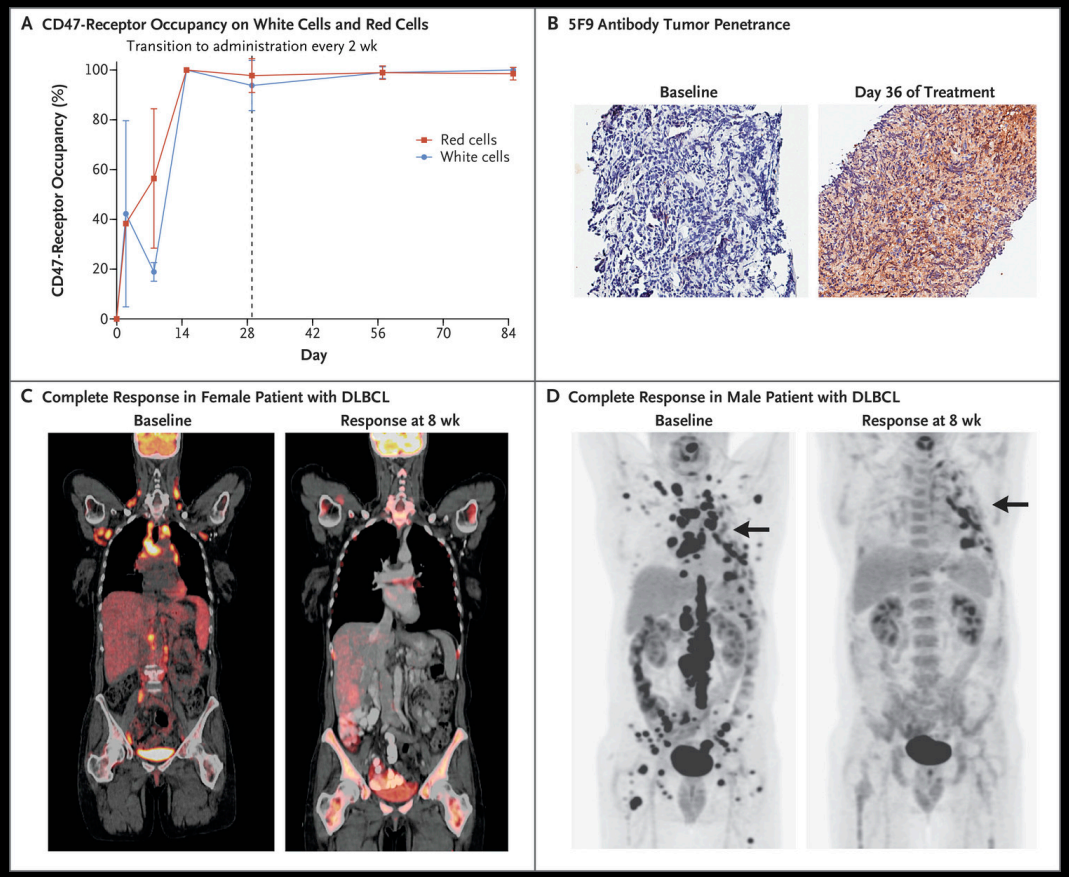
CHECK POINT

- PD-1
  - Linfociti T e linfociti B
- PD-1, TIM3, LAG-3
  - Linfociti T γδ
- IL-1R8
  - Cellule NK
- SIRPα–CD47
  - macrofagi

A


Macrophage
Cancer cell
SIRPα
5F9 antibody
Anti-CD20 antibody
CD47
"Eat me" signal
CD20
Fc receptor
Added extrinsic "eat me" signal

Pharmacodynamic Data on CD47-Receptor Occupancy, Tumor Penetrance, and Responses in Two Patients.



R Advani et al. N Engl J Med 2018;379:1711-1721.

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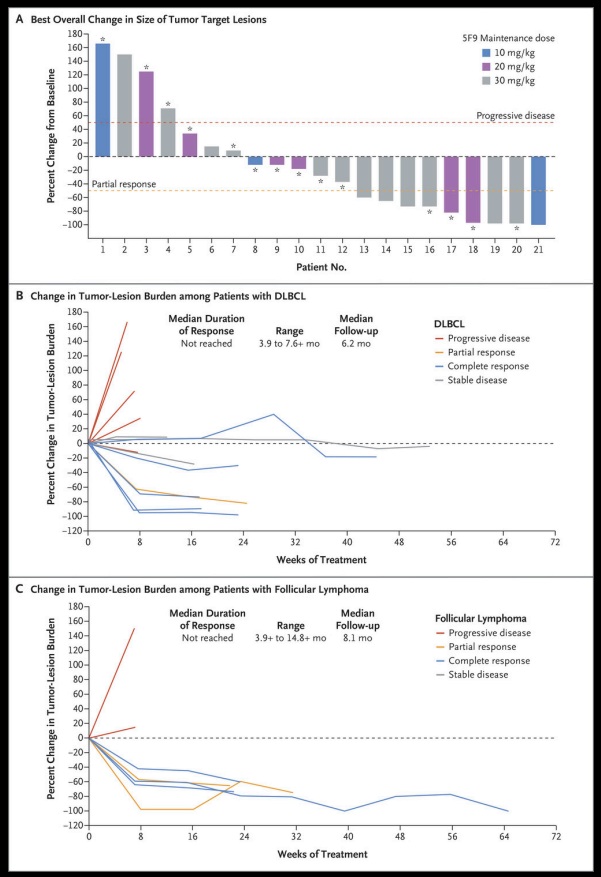
Change in Tumor-Lesion Size and Duration of Responses with 5F9 and Rituximab.



R Advani et al. N Engl J Med 2018;379:1711-1721.

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Clinical Responses to Combination Therapy with 5F9 and Rituximab.*

Table 2. Clinical Responses to Combination Therapy with 5F9 and Rituximab.*

Response	All Patients (N=22)	Patients with DLBCL (N=15)	Patients with Follicular Lymphoma (N=7)
Objective response	11 (50)	6 (40)	5 (71)
Complete response	8 (36)	5 (33)	3 (43)
Partial response	3 (14)	1 (7)	2 (29)
Stable disease	3 (14)	3 (20)	0
Progressive disease	8 (36)	6 (40)	2 (29)
Disease control	14 (64)	9 (60)	5 (71)

* Objective response was defined as a complete or partial response. Disease control was defined as a complete response, partial response, or stable disease.

R Advani et al. N Engl J Med 2018;379:1711-1721.

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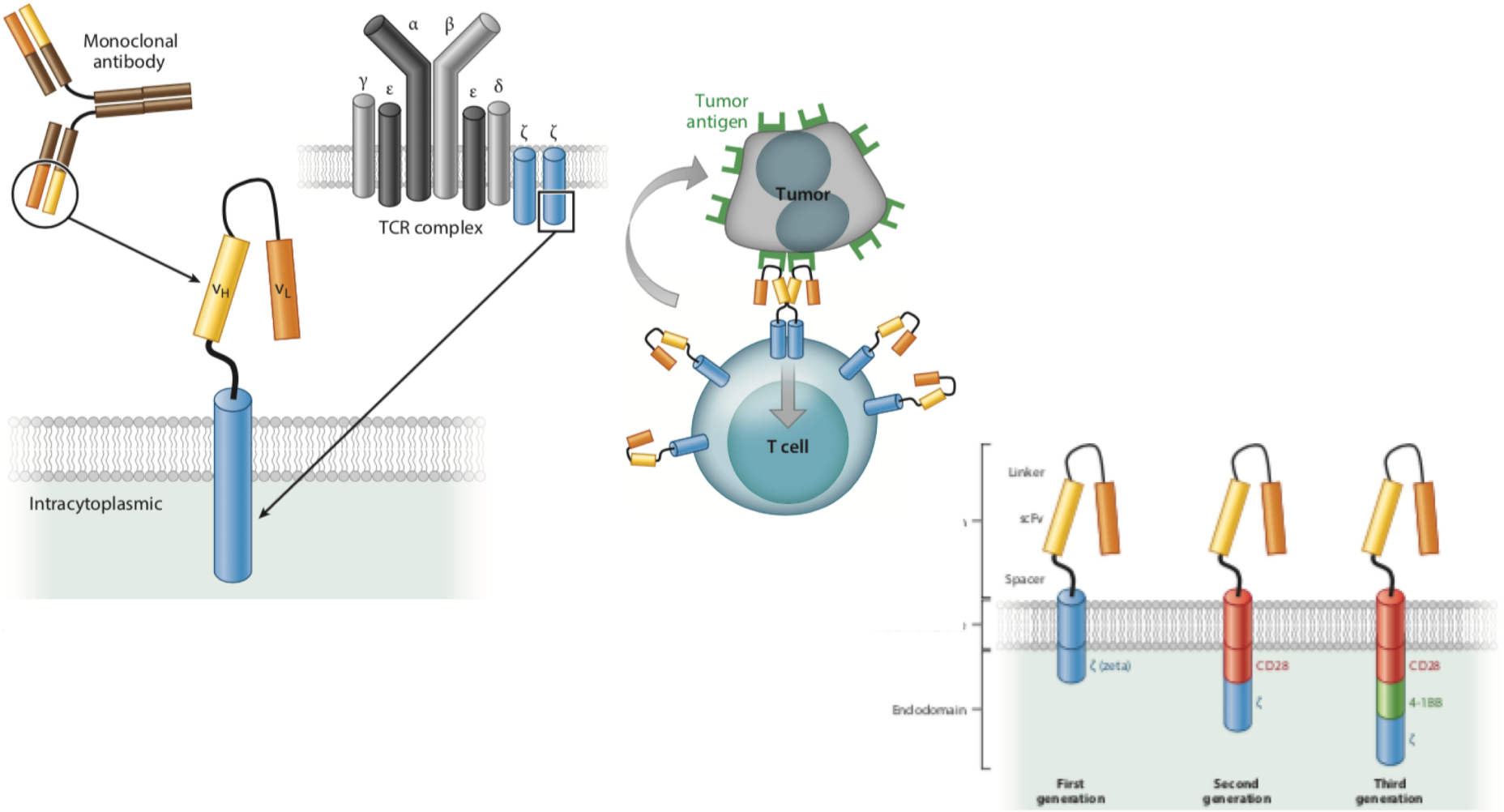
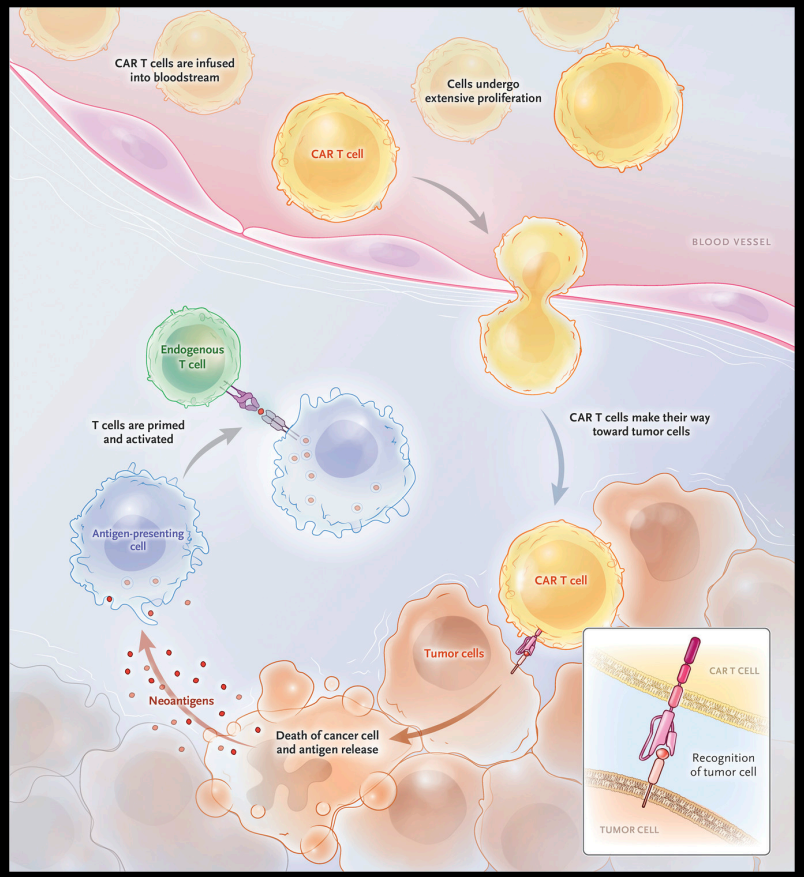

Monoclonal antibody
α
β
γ
ε
ε
δ
ζ
ζ
TCR complex
V_H
V_L
Intracytoplasmic
Tumor antigen
Tumor
T cell
Linker
scFv
Spacer
ζ (zeta)
CD28
ζ
CD28
4-1BB
ζ
Endodomain
First generation
Second generation
Third generation

Chimeric Antigen Receptor (CAR) T Cells Engrafting, Trafficking to Tumor, and Proliferating Extensively after Infusion.



CH June, M Sadelain. N Engl J Med 2018;379:64-73.

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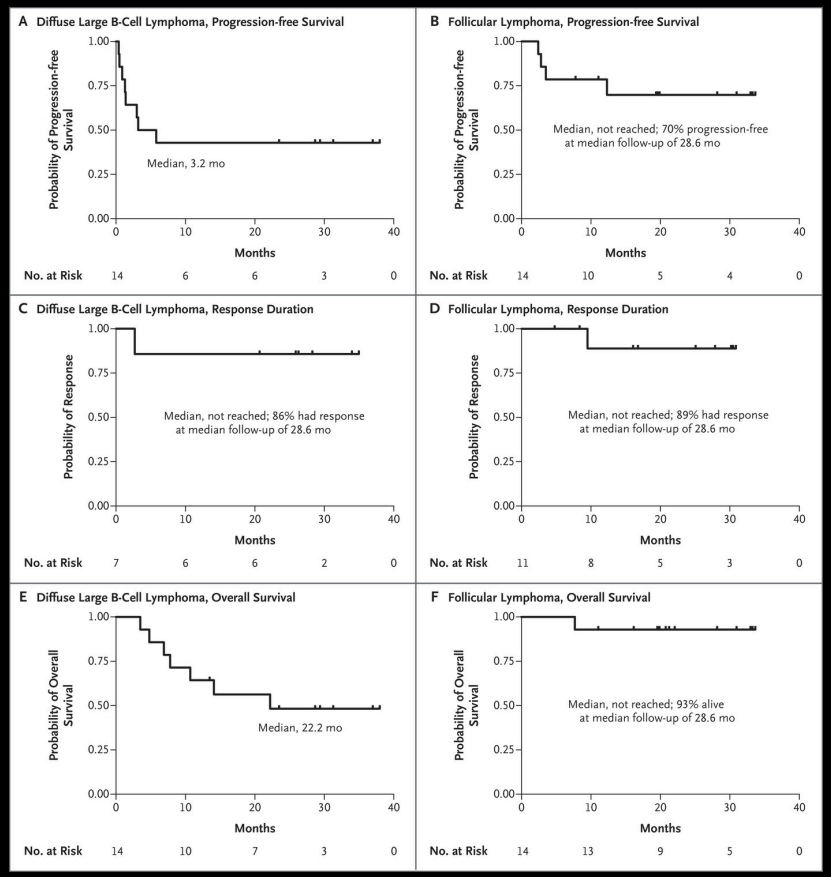
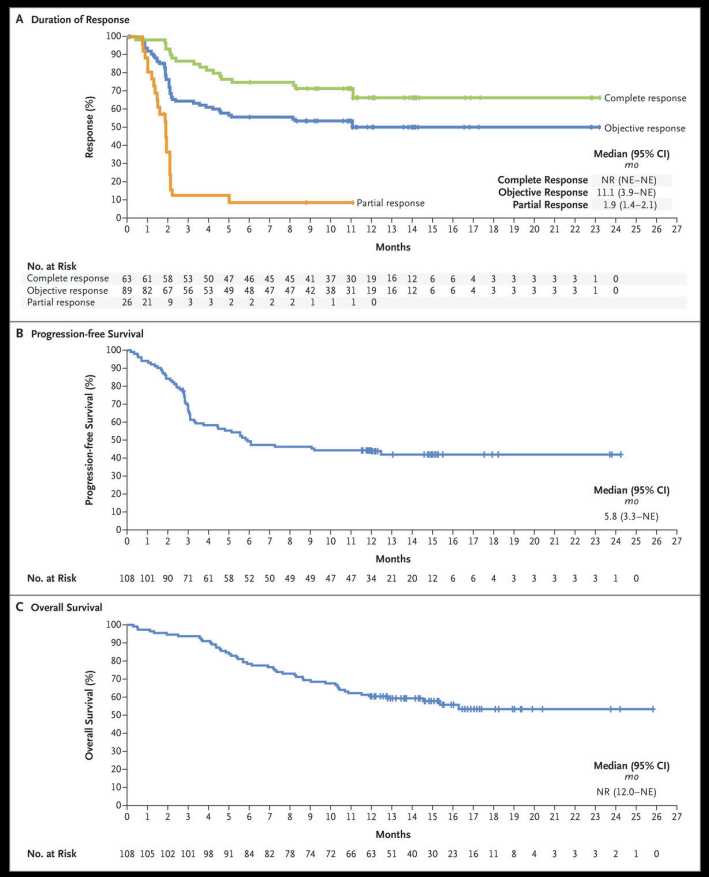
Progression-free Survival, Response Duration, and Overall Survival.



Schuster SJ et al. N Engl J Med 2017;377:2545-2554.

The NEW ENGLAND JOURNAL of MEDICINE

Kaplan–Meier Estimates of the Duration of Response, Progression-free Survival, and Overall Survival.



Neelapu SS et al. N Engl J Med 2017;377:2531-2544.

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Reported Toxic Effects of CAR T Cells.

Table 2. Reported Toxic Effects of CAR T Cells.

CAR Specificity and Adverse Effect	Reference
CD19 CAR	
B-cell aplasia and hypogammaglobulinemia	Kochenderfer et al.,[52] Kalos et al.[53]
Cytokine release syndrome	Davila et al.,[36] Lee et al.,[54] Teachey et al.[55]
Dermatitis	Rubin et al.[56]
Hematophagocytic lymphohistiocytosis and macrophage activation syndrome	Grupp et al.,[32] Porter et al.,[41] Teachey et al.[55]
Neurologic effects such as ataxia and aphasia	Brudno and Kochenderfer[57]
Cerebral edema	Gust et al.[58]
B-cell maturation antigen CAR: the cytokine release syndrome	Riches et al.[59]
Mesothelin CAR: anaphylaxis (antibody to murine single-chain variable fragments)	Maus et al.[60]
Carbonic anhydrase IX CAR: cholangitis (on-target)	Lamers et al.[61]
HER2/neu CAR: lethal cytokine release syndrome	Morgan et al.[62]
Carcinoembryonic antigen–related cell-adhesion molecule 5 (CEACAM5) CAR: hemorrhagic colitis (on-target)	Thistlethwaite et al.[63]

CH June, M Sadelain. N Engl J Med 2018;379:64-73.

The NEW ENGLAND JOURNAL of MEDICINE

Grazie per l’attenzione