Anything you can do we can do better !!

Immune System vs.Hematologic Malignancies

Omid Hamid MD

ohamid@theangelesclinic.org

The Angeles Clinic and Research Institute

Disclosures

The more conflicts of interest for the speaker, the more balanced the talk . . . . . Hauschild 2015

- Pfizer
- Rinat
- Genentech
- Roche
- BMS
- Merck
- Merck Serano
- Immunocore
- Medimmune
- Astra Zeneca
- Novartis
- Celldex
- Incyte
- Esai

Strategies for Immune Manipulation of Hematologic Malignancies

- Monoclonal antibodies targeting tumor antigens
  - Unlabeled (rituximab etc)
  - Toxin conjugated (brentuximab vedotin)
- Tumor vaccines
  - Protein antigens (Ig Idiotype) – Tumor/DC vaccines
- Antibodies to manipulate inhibitory signals
  - PD-1/PD-L1 pathways
  - Others
- Bi-specific antibodies
  - Anti-CD3 x Anti-CD19 Bite
- CAR-T cells against CD19 for ALL, CLL and NHL

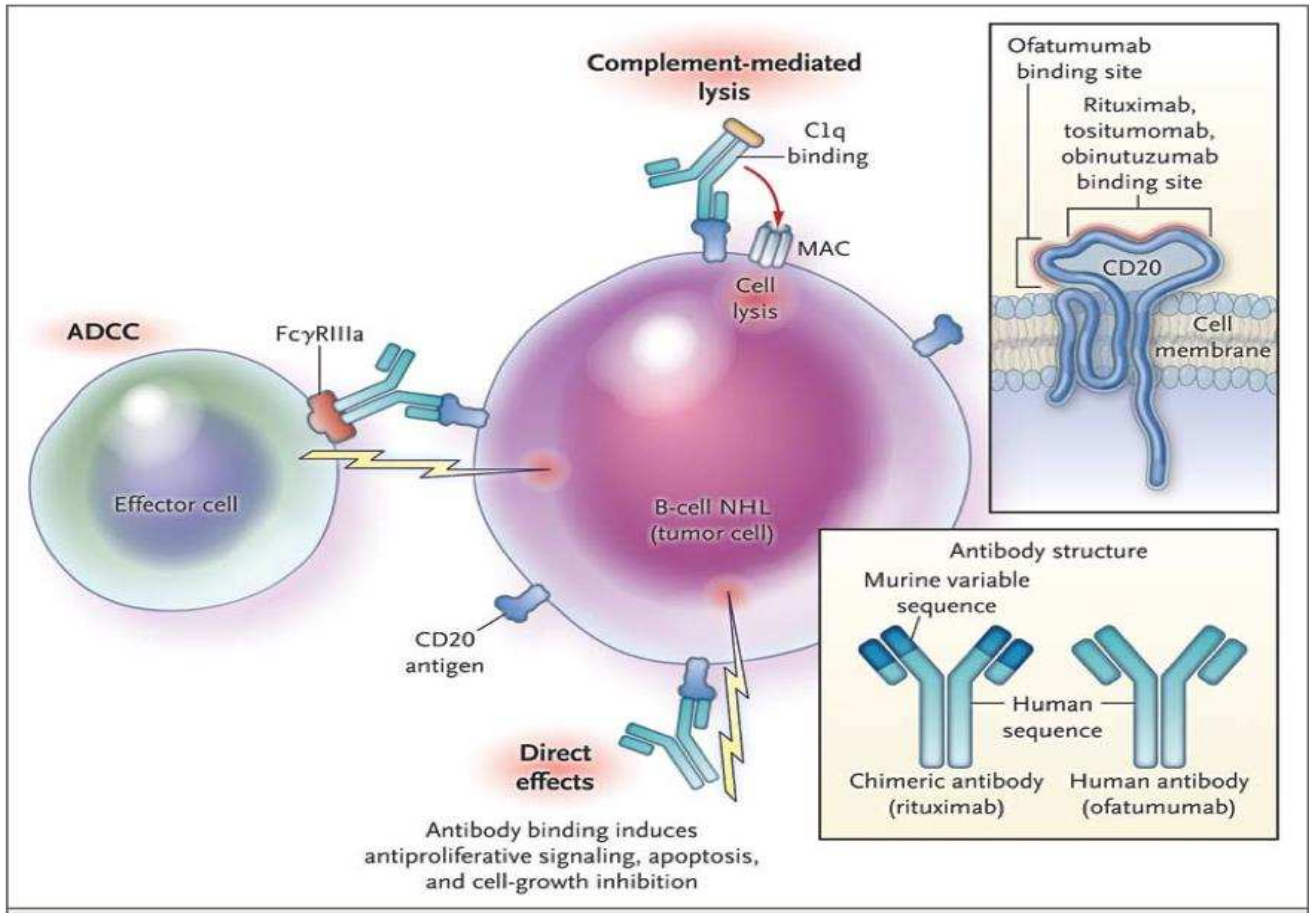
The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL THERAPEUTICS

Anti-CD20 Antibody Therapy for B-Cell Lymphomas

David G. Maloney, M.D., Ph.D.

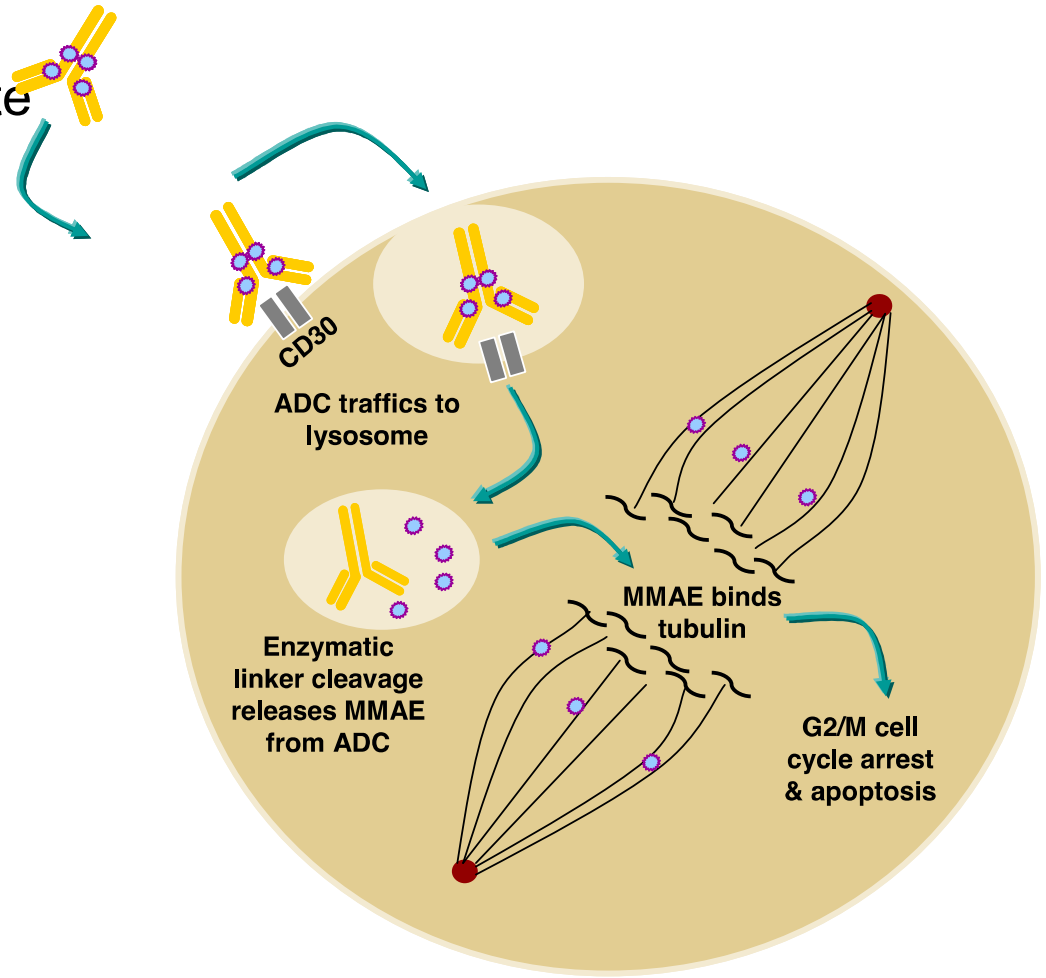
Monoclonal Antibodies: Rituximab



Maloney, DG NEJM 2012

Brentuximab Vedotin anti-CD30 drug conjugate: Mechanism of Action

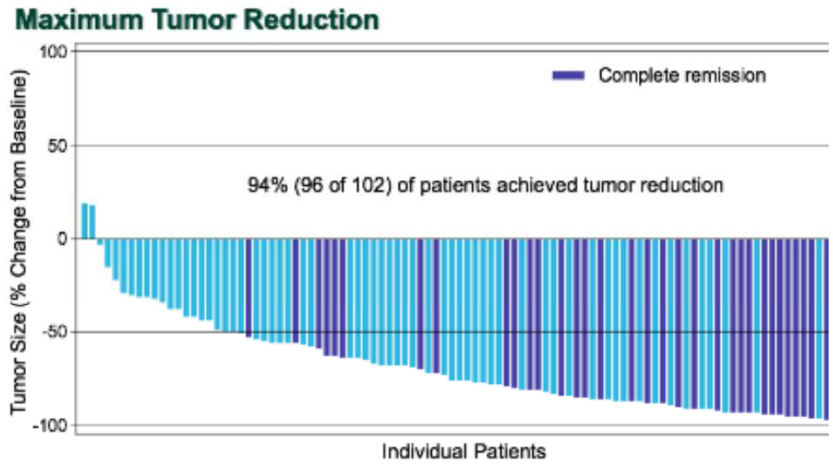
- SGN-35 antibody-drug conjugate
  - CD30-targeted antibody (cAC10) conjugated to an auristatin (MMAE), an anti-tubulin agent
- Selectively induces apoptosis in HL and ALCL cells:
  - Binds to CD30
  - Becomes internalized
  - Releases MMAE



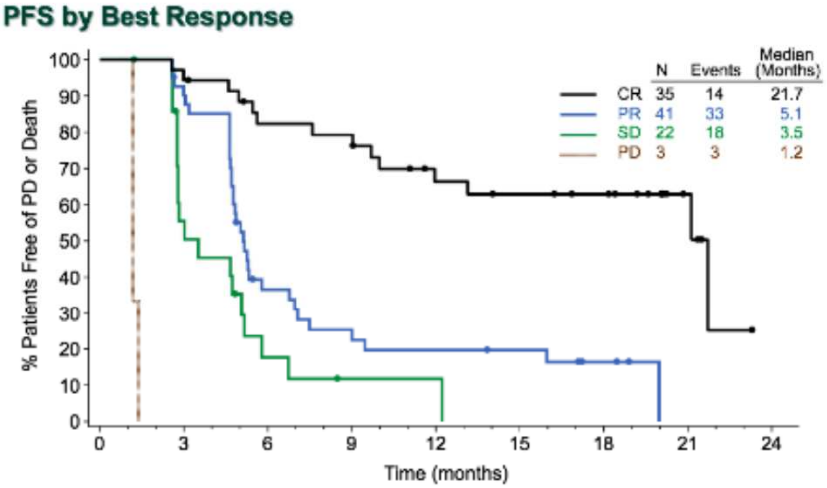
Brentuximab Vedotin Phase II Pivotal trial in Relapsed Hodgkin Lymphoma:

N=102, Patients heavily pretreated, failed prior ASCT,
94% of patients achieved tumor reductions
OR=75%, median duration of response 6.7 months
CR=34%, median duration of response 20.5 months

Maximum Tumor Reduction



PFS by Best Response



Led to FDA approval August, 2011

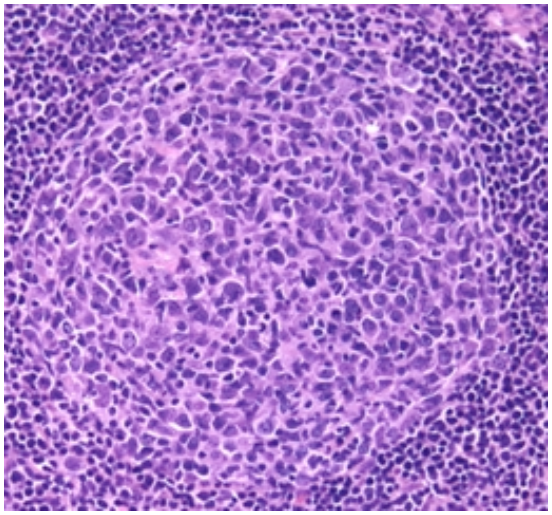
Chen ASCO 2011, Younes JCO 2012

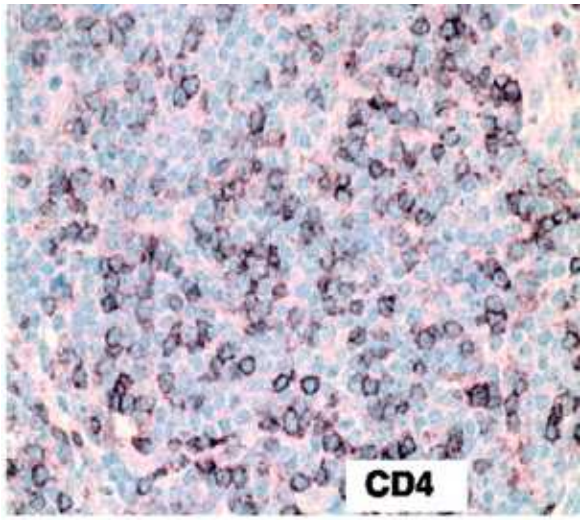
Immune Checkpoint Blockade in Lymphoma

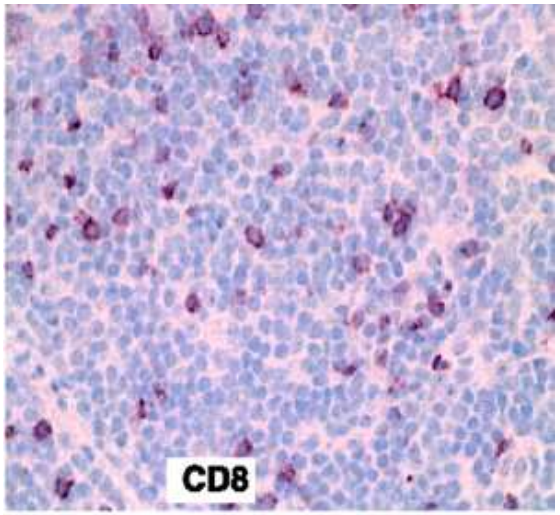
Stephen M. Ansell, MD, PhD Mayo Clinic
David Maloney, MD, PhD Fred Hutch
Phillipe Armand, MD Dana Farber
Holbrook Kohrt, MD, PhD Stanford
David Porter, MD Upenn

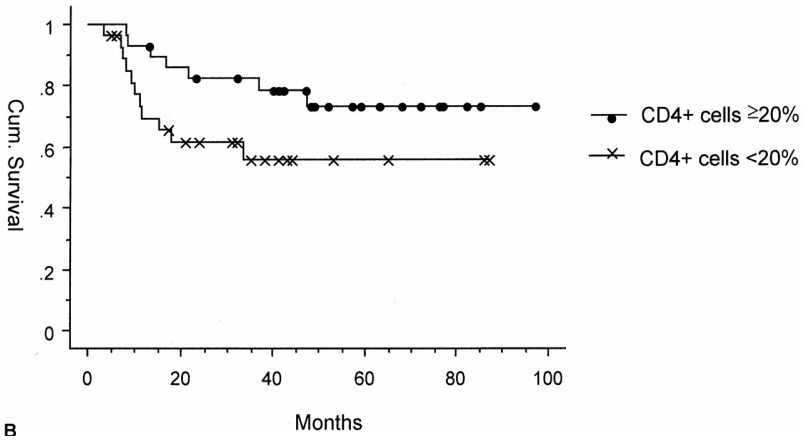
Intratumoral T-cells in Lymphoma – Are they good or bad?

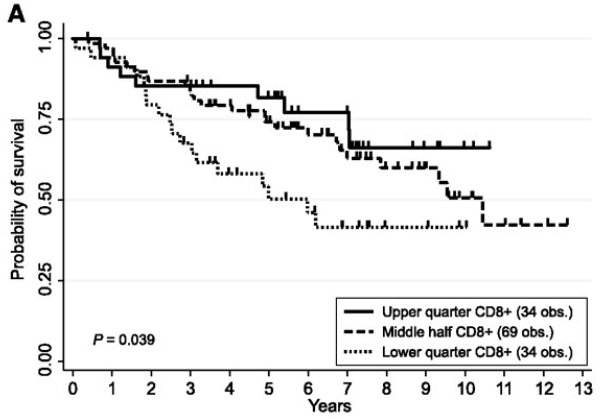
HE stain **CD4** **CD8**











Yang ZZ et al. Cancer Res 2006;66:10145-10152

Ansell SM et al. J Clin Oncol. 2001.

Wahlin BE et al. Clin Cancer Res 2007.

Why do intratumoral T-cells not eradicate the malignant B-cells?

- Greater % CD8+ T-cells or CD4+ T-cells correlated with a lower proliferative rate of the tumor.
- However, the increased numbers of immune cells did not result in clearance of the tumor cells
- Complete response rates were no different.

Can the immune response in lymphoma be activated by novel therapies?

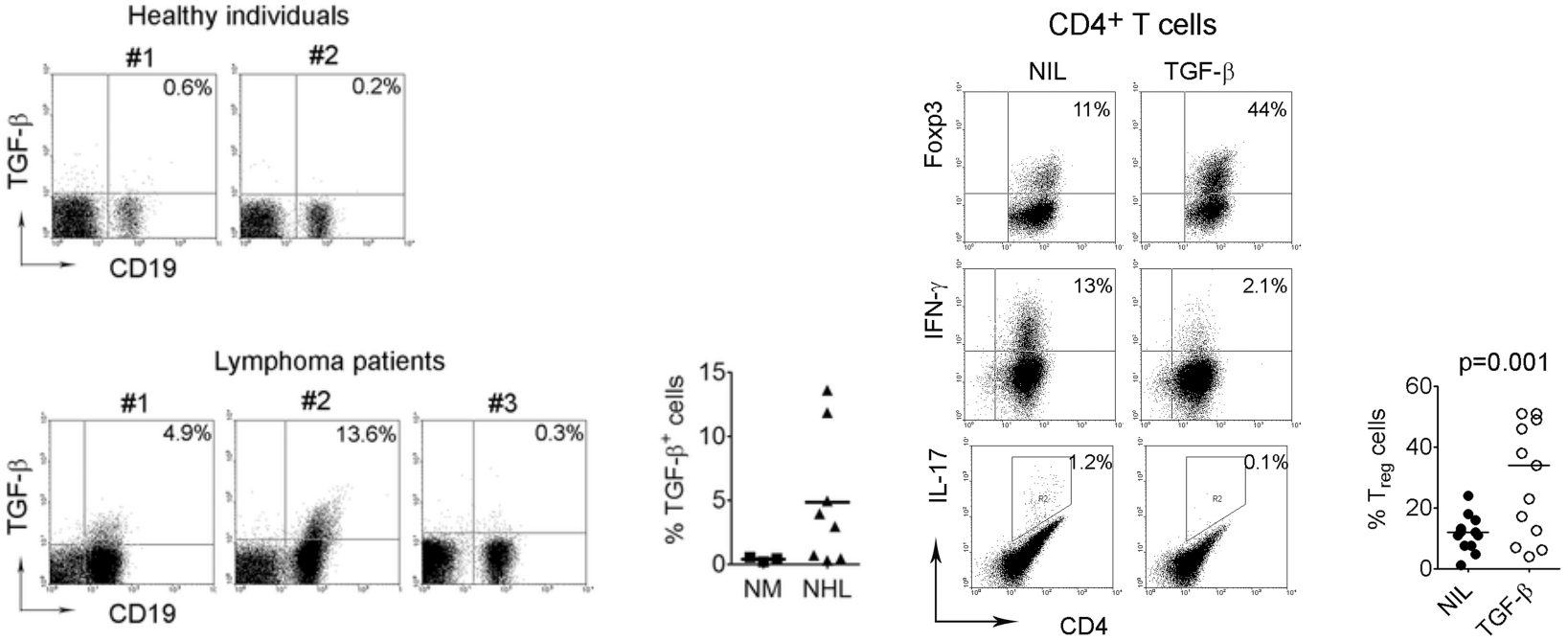
Ansell SM et al. J Clin Oncol. 2001.

Immunological Barriers to an effective Immune Response

- Increased regulatory T-cells in lymphoma
- Presence of exhausted T-cells
- Increased immunosuppressive ligands
- Presence of intratumoral monocytes and follicular dendritic cells

Presence of exhausted T-cells in Lymphoma

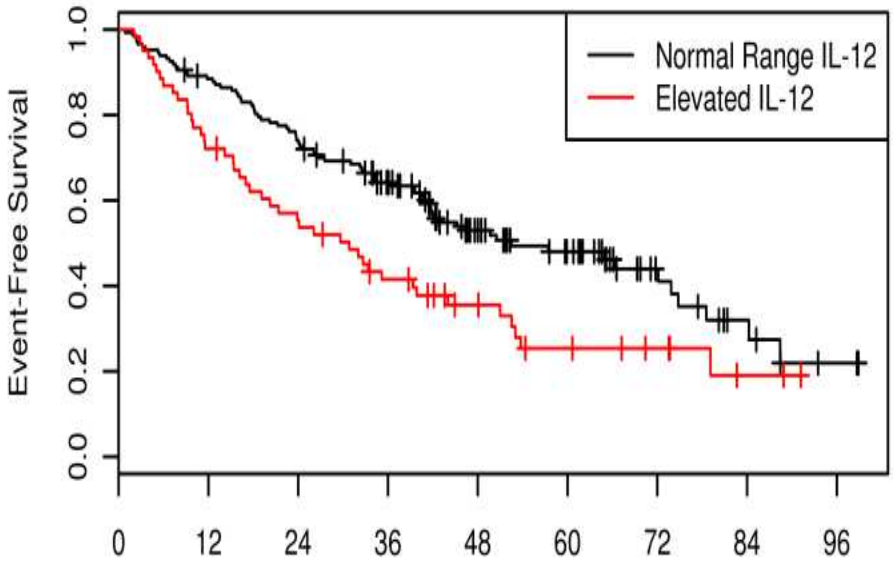
Membrane-Bound TGF-β on Lymphoma B-cells induces T_{reg} cells



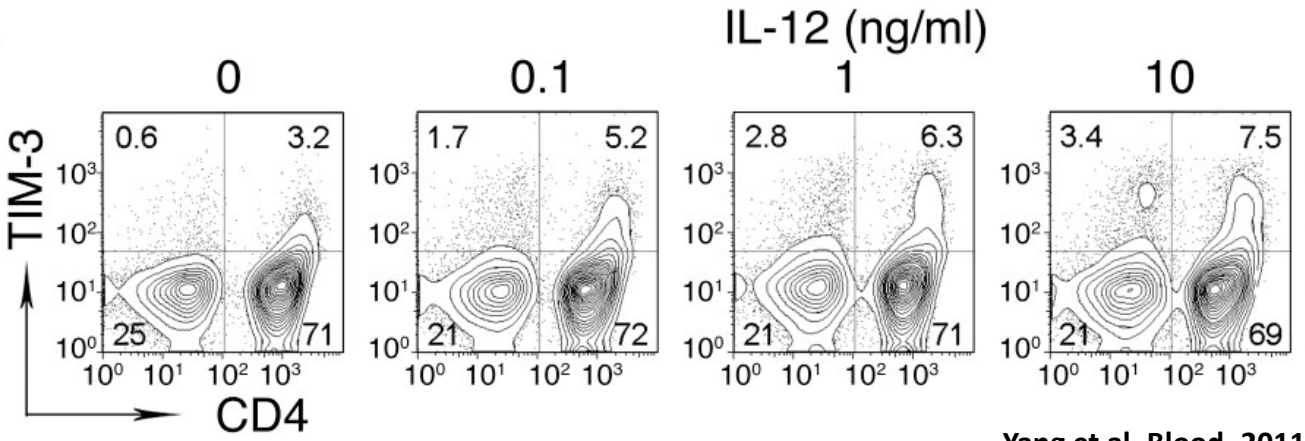
Yang, ZZ. et al. PLoS One. 2013;8(3):e59456.

Cytokines such as IL-12 promote T-cell exhaustion

A.

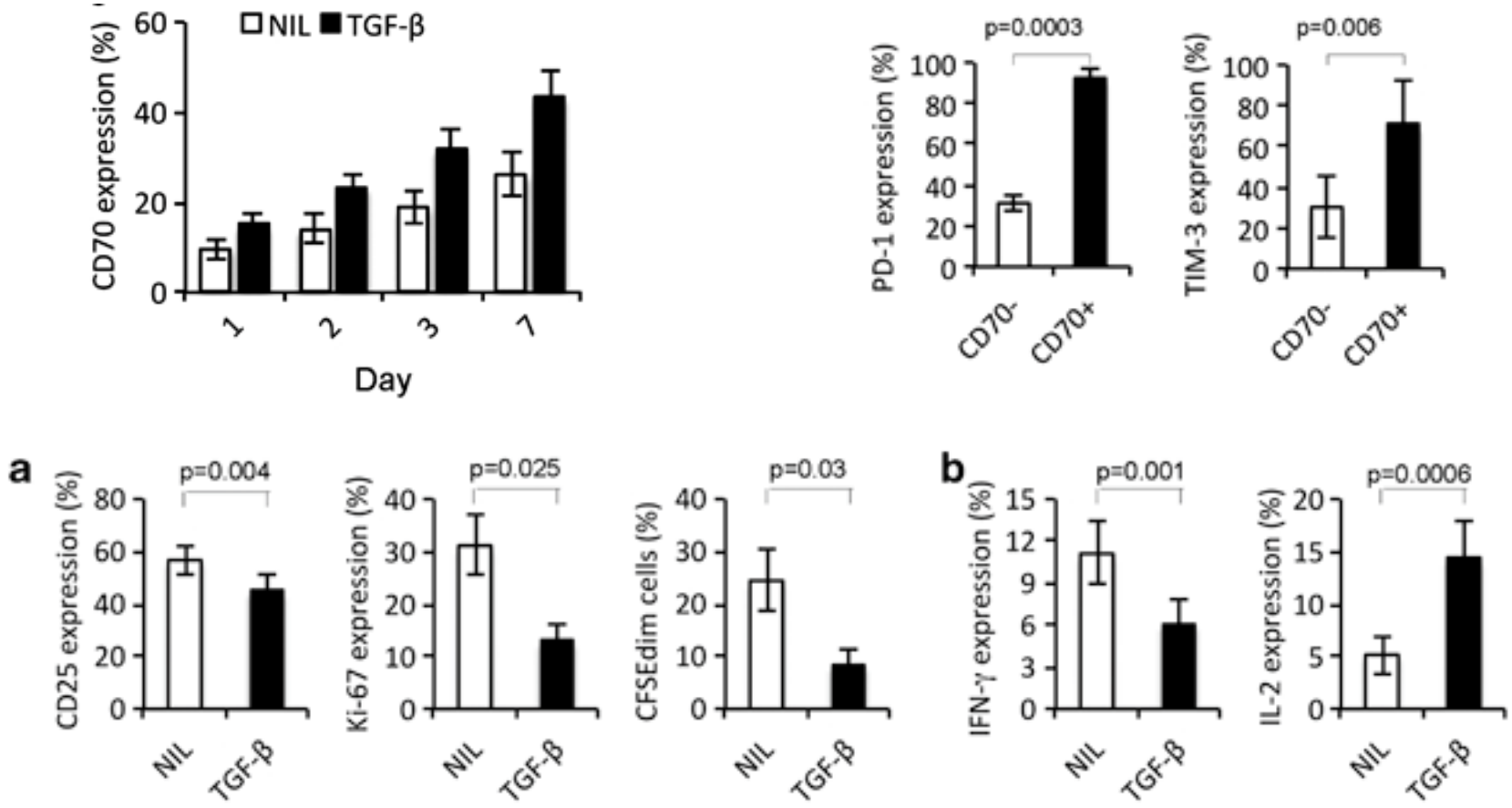


B.

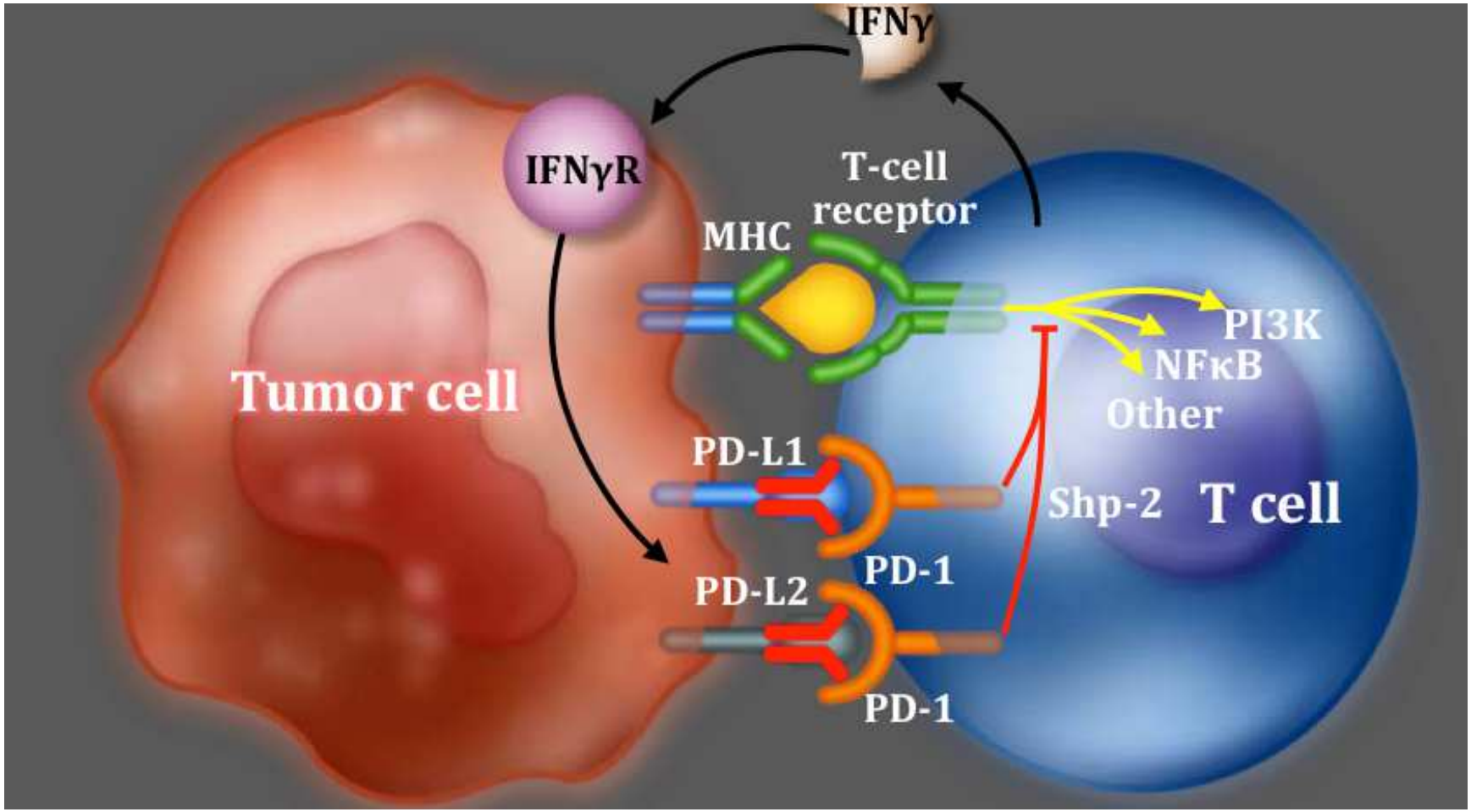


Yang et al. Blood. 2011;118(10):2809-20.
Yang et al. J Clin Invest 2012;122(4):1271-82.

TGF-β upregulates CD70 and Induces an exhausted T-cell phenotype

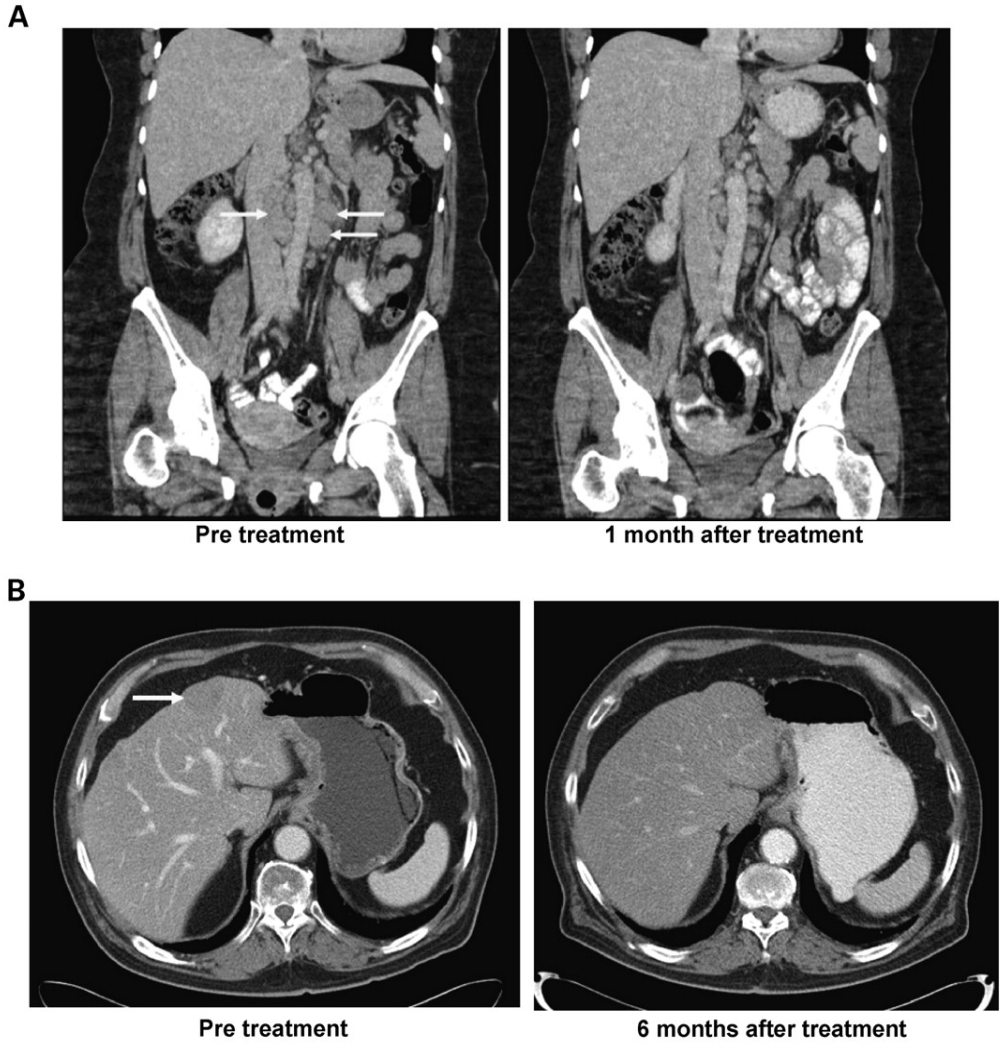


Yang ZZ et al. Leukemia. 2014 Sep;28(9):1872-84.


IFNγ
IFNγR
T-cell
receptor
MHC
PI3K
NFκB
Other
Tumor cell
PD-L1
Shp-2
T cell
PD-1
PD-L2
PD-1

Previous Experience with CTLA4 blockade (Ipilimumab) in lymphoma

- Treated 18 patients
- 1 CR (>31 months), and 1 PR (19 months)
- In 5 of 16 cases (31%), T-cell proliferation to recall antigens was increased >2-fold



Ansell et al. Clin Cancer Res 2009;15:6446-6453

Ipilimumab to treat relapse after allogeneic hematopoietic cell transplantation.

- 29 patients with relapsed hematologic disease.
- Three patients with lymphoid malignancy developed objective disease responses following ipilimumab:
  - CR in 2 patients with Hodgkin disease
  - PR in a patient with refractory mantle cell lymphoma.
- Ipilimumab did not induce or exacerbate clinical GVHD

Bashey et al. Blood. 2009;113(7):1581-8.

Pidilizumab post Autologous HCT for DLBCL

- Trial of autologous HCT for relapsed DLBCL
- Pidilizumab (Anti PD-1), 1.5 mg/kg q 42 days x 3 starting 1-3 mo post transplant
- Patients, n=66
  - Age 57 (19-80)
  - DLBCL 74%
  - PMBCL 6%
  - Transformed indolent 20%
  - Rituximab 85% 1st line, 82% salvage therapy
- PET response to salvage therapy (pre PBSCT)
  - Negative 47%
  - Positive 36%
  - Not done 17%

Armound, P JCO 31:4199, 2013

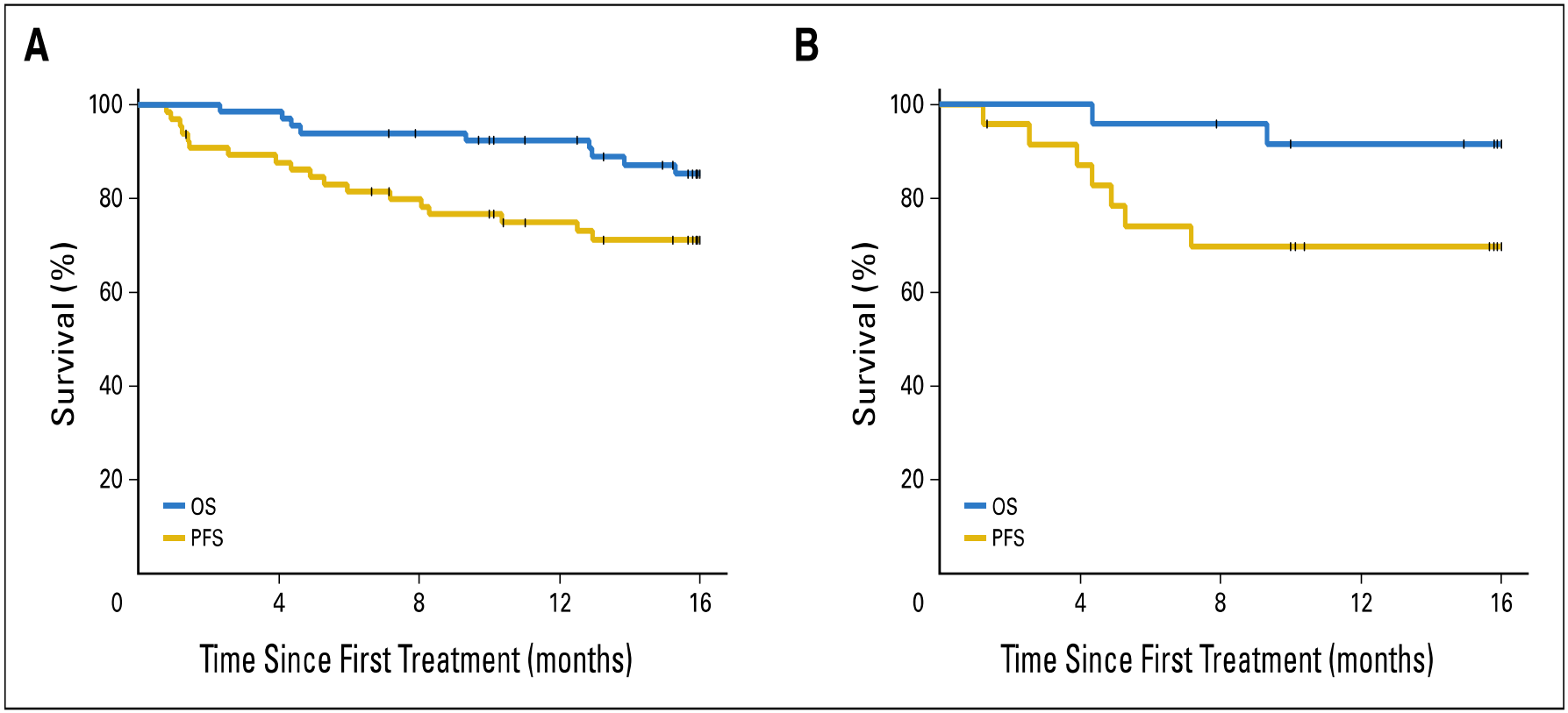
Pidilizumab post Autologous HCT for DLBCL

OUTCOMES

- N=66, all patients
  - PFS at 16 months 72%
- N=24, high risk- PET positive post salvage
  - PFS at 16 months 70%
- N=35, “measurable disease” post Auto
  - Not in CR due to CT scan (53%) or PET (18%)
  - OR 51%

Armound, P JCO 31:4199, 2013

Pidilizumab post Autologous HCT for DLBCL



OS/PFS all patients, n=66

OS/PFS 24 pts with PET + disease Pre HCT

Armound, P JCO 31:4199, 2013

Nivolumab in Patients with Relapsed or Refractory Hodgkin Lymphoma – Preliminary Safety, Efficacy and Biomarker Results of a Phase I Study

Philippe Armand[1], Stephen M. Ansell[2], Alexander M. Lesokhin[3], Ahmad Halwani[4], Michael M. Millenson[5], Stephen J. Schuster[6], John Timmerman[7], Ivan Borrello[8], Martin Gutierrez[9], Emma C. Scott[10], Deepika Cattry[3], Bjoern Chapuy[1], Azra H. Ligon[11], Scott J. Rodig[11], Lili Zhu[12], Joseph F. Grosso[12], Su Young Kim[12], and Margaret A. Shipp[1]

[1]Dana-Farber Cancer Institute, Boston, MA ; [2]Mayo Clinic, Rochester, MN; [3]Memorial Sloan Kettering Cancer Center, New York, NY; [4]University of Utah Huntsman Cancer Institute, Salt Lake City, UT; [5]Fox Chase Cancer Center, Philadelphia, PA; [6]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; [7]Jonsson Comprehensive Cancer Center, University of California, Los Angeles, CA; [8]Johns Hopkins University School of Medicine and the Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; [9]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ; [10]Oregon Health and Science University, Portland, Oregon; [11]Brigham and Women's Hospital, Boston, MA; [12]Bristol-Myers Squibb, Princeton, NJ

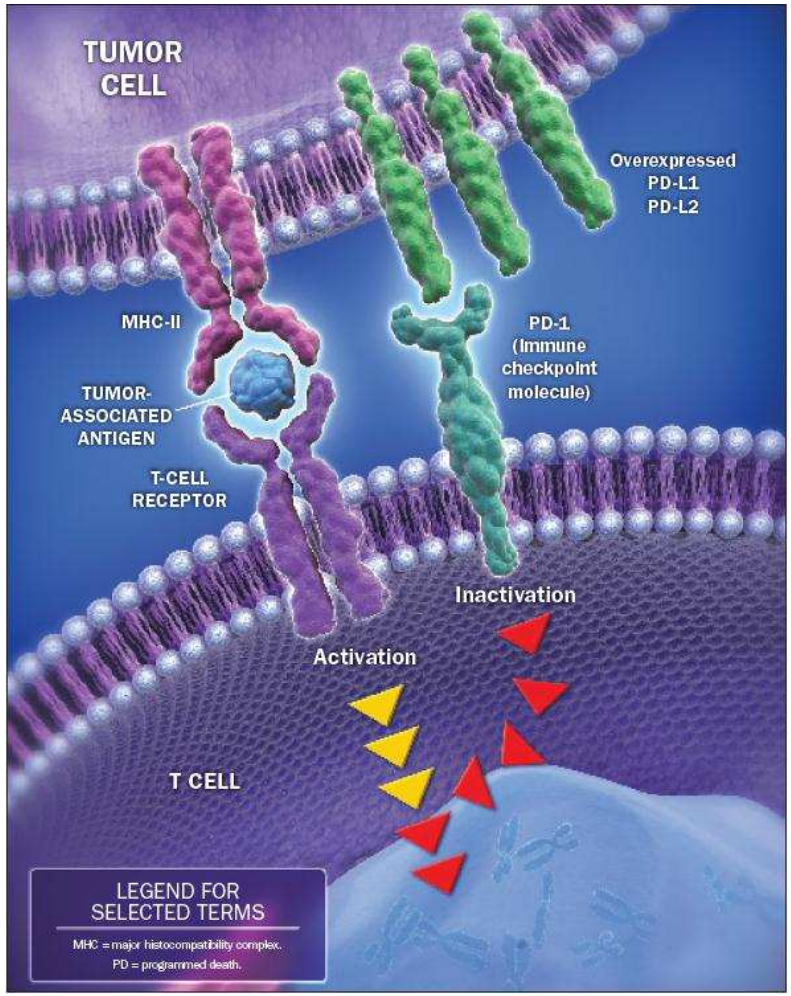
56TH ANNUAL ASH MEETING
DECEMBER 2014
SAN FRANCISCO, CA

PD-1 Blockade With the Monoclonal Antibody Pembrolizumab (MK-3475) in Patients With Classical Hodgkin Lymphoma After Brentuximab Vedotin Failure: Preliminary Results From a Phase 1b Study (KEYNOTE-013)

Craig H. Moskowitz,[1] Vincent Ribrag,[2] Jean-Marie Michot,[2] Giovanni Martinelli,[3] Pier Luigi Zinzani,[3] Martin Gutierrez,[4] Guadalupe De Maeyer,[5] Alexandra G. Jacob,[1] Karen Giallella,[6] Jennifer Weimer Anderson,[6] Martha Derosier,[6] Joy Wang,[6] Kenneth Emancipator,[6] Zijiang Yang,[6] Eric Rubin,[6] Arun Balakumaran,[6] Shelonitda Rose,[6] Margaret A. Shipp,[5] Philippe Armand[5]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Institut Gustave Roussy, Villejuif, France;
[3]Institute of Hematology "er àgnoli" University of Bologna, Bologna, Italy;
[4]Hackensack University Medical Center, Hackensack, NJ, USA;
[5]Dana-Farber Cancer Institute, Boston, MA, USA; [6]Merck & Co, Inc, Whitehouse Station, NJ, USA

PD-1 Pathway and Immune Surveillance

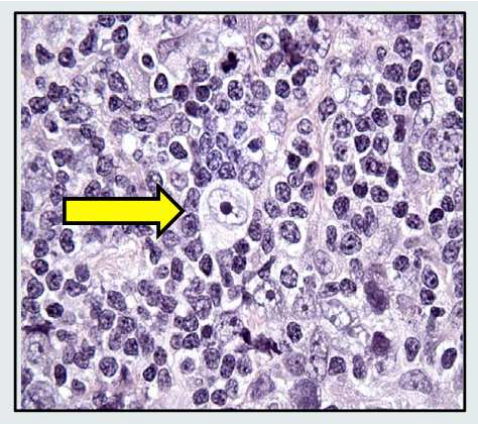


- PD-1 is expressed on the surface of activated T cells[1]
- Its ligands, PD-L1 and PD-L2, are overexpressed in certain tumor cells[1]
- Binding of PD-1 to its ligands inhibits T-cell activation, allowing tumors to evade the immune response[2]

1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252-264 .
2. Keir ME et al. *Annu Rev Immunol*. 2008;26:677-704.

cHL may have genetically driven dependance on PD-1

Role of the PD-1 Pathway in Classical Hodgkin Lymphoma

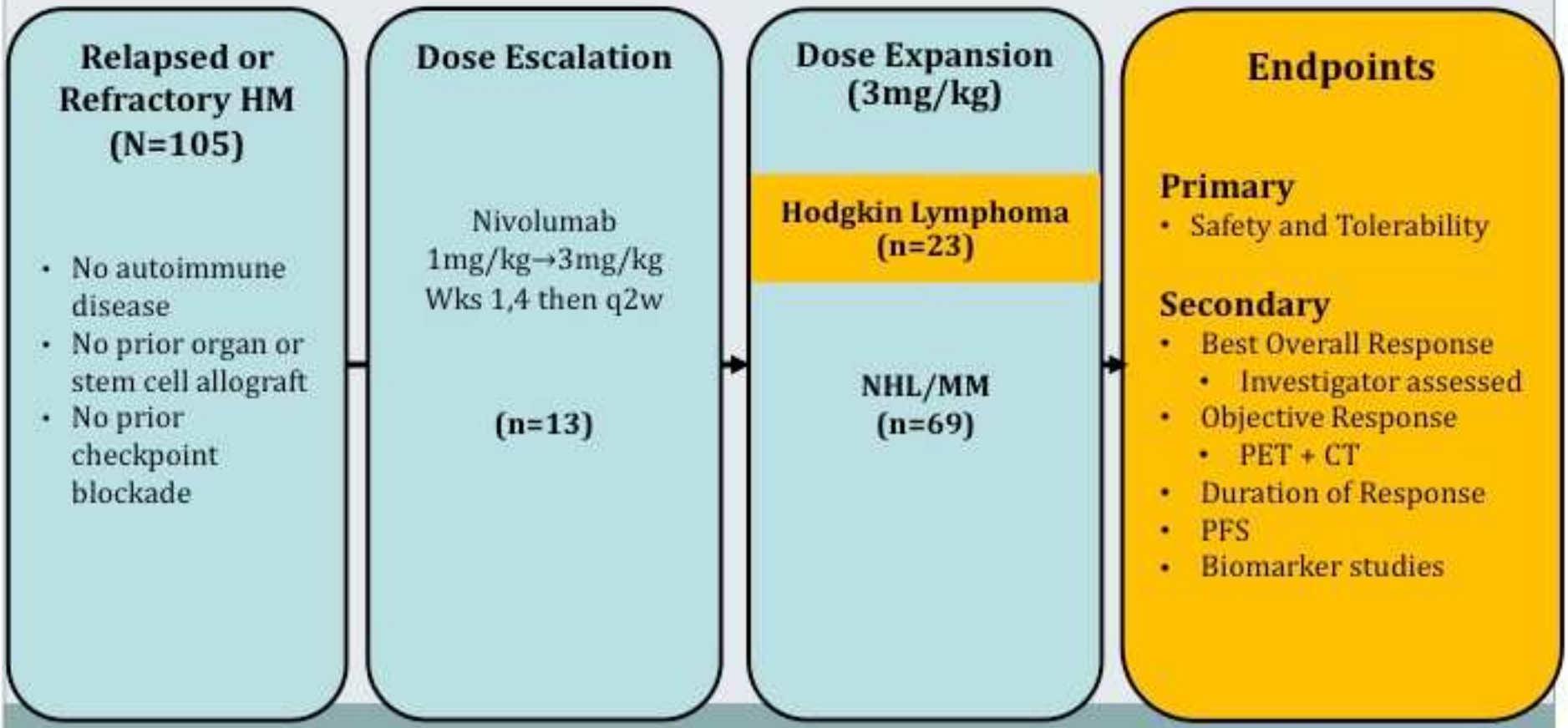


- cHL is characterized by rare malignant cells surrounded by ineffective immune infiltrating cells[1]
- PD-1 has an inhibitory role on T cells in cHL[2,3]
- Amplification of 9p24.1 is frequent in cHL and results in overexpression of PD-L1 and PD-L2[4]
- EBV infection also is associated with upregulation of PD-L1 and PD-L2[5]
- PD-L1 is over-expressed on the Reed-Sternberg cell surface in >85% of classical HL tumors[5]

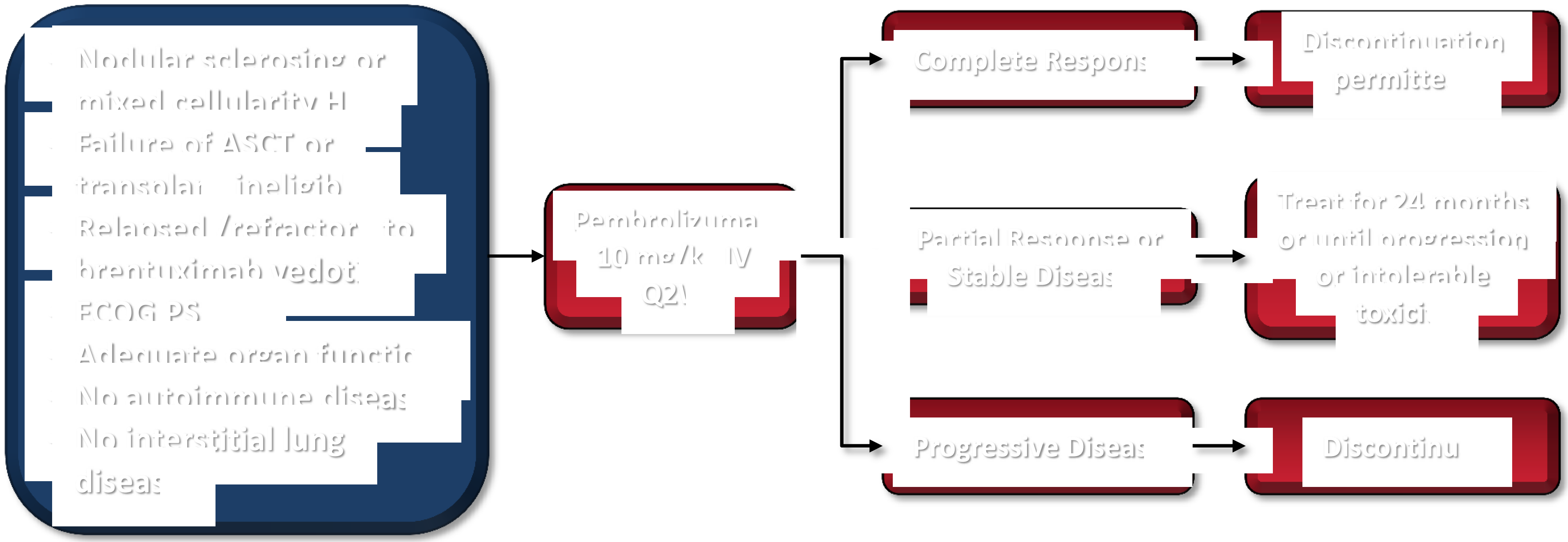
1. Green MR et al. *Clin Cancer Res*. 2012;18:1611-1618..
2. Chemnitz JM et al. *Blood*. 2007;110:3226-3233.
3. Yamamoto R et al. *Blood*. 2008;111:3220-4.
4. Green MR et al. *Blood*. 2010;116:3268-3277.
5. Chen B et al. *Clin Cancer Res*. 2013;19:3462-73.

Rationale and Design

- Based on potential vulnerability to PD-1 blockade, cHL included as independent expansion cohort in Phase 1b study of nivolumab in hematologic malignancies.



KEYNOTE-013: Hodgkin Lymphoma Cohort[a]



Patients enrolled: 31

Treatment: 10 mg/kg IV Q2W

Response assessment: At week 12 and every 8 weeks thereafter per International Harmonization Project response criteria[1]

[a]Other cohorts of KEYNOTE-013 included patients with myelodysplastic syndrome, mediastinal large B cell lymphoma, multiple myeloma, and Non-Hodgkin lymphoma.
[b]At [illegible] complete response may discontinue therapy. [c]Patients with radiographic disease progression at week 12 who are clinically stable may remain on therapy until a follow-up scan confirms disease progression.

1. Cheson BD et al. *J Clin Oncol*. 2007;25:579-586

Baseline Characteristics

Characteristic	N (%)
Total	23 (100)
Age	35 (20-54)
cHL histology	
Nodular sclerosis	22 (96)
Mixed cellularity	1 (4)
Prior ASCT	18 (78)
Prior Brentuximab Vedotin	18 (78)
Prior systemic therapies	
2 to 3	8 (35)
4 to 5	7 (30)
≥6	8 (35)

Baseline Characteristics

- Patients enrolled: **31**
- Analysis population: **29** patients with post-baseline efficacy assessment or who discontinued pembrolizumab before week 12

Characteristic	Total (N = 29)
Age, yr, median (range)	32 (20-67)
ECOG performance status, n (%)	
0	14 (48)
1	15 (52)
Bulky lymphadenopathy, n (%)	9 (31)
No. of prior therapies for advanced disease, n (%)	
2	1 (3)
3	8 (28)
4	5 (17)
[illegible]	15 (52)
Prior transplant failure, n (%)	20 (69)
Transplant ineligible, n (%)	8 (28)
Refused transplant, n (%)	1 (3)

Analysis cut-off date: November 17, 2014.

Treatment-Related Adverse Events of Any Grade Observed in [illegible]

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 [illegible] 1 treatment-related AE of any grade

[illegible] Related Adverse Events

Adverse Event, n (%)	N = 29
Axillary pain[a]	1 (3)
Hypoxia[a,b]	1 (3)
Joint swelling	1 (3)
Pneumonitis[b]	1 (3)

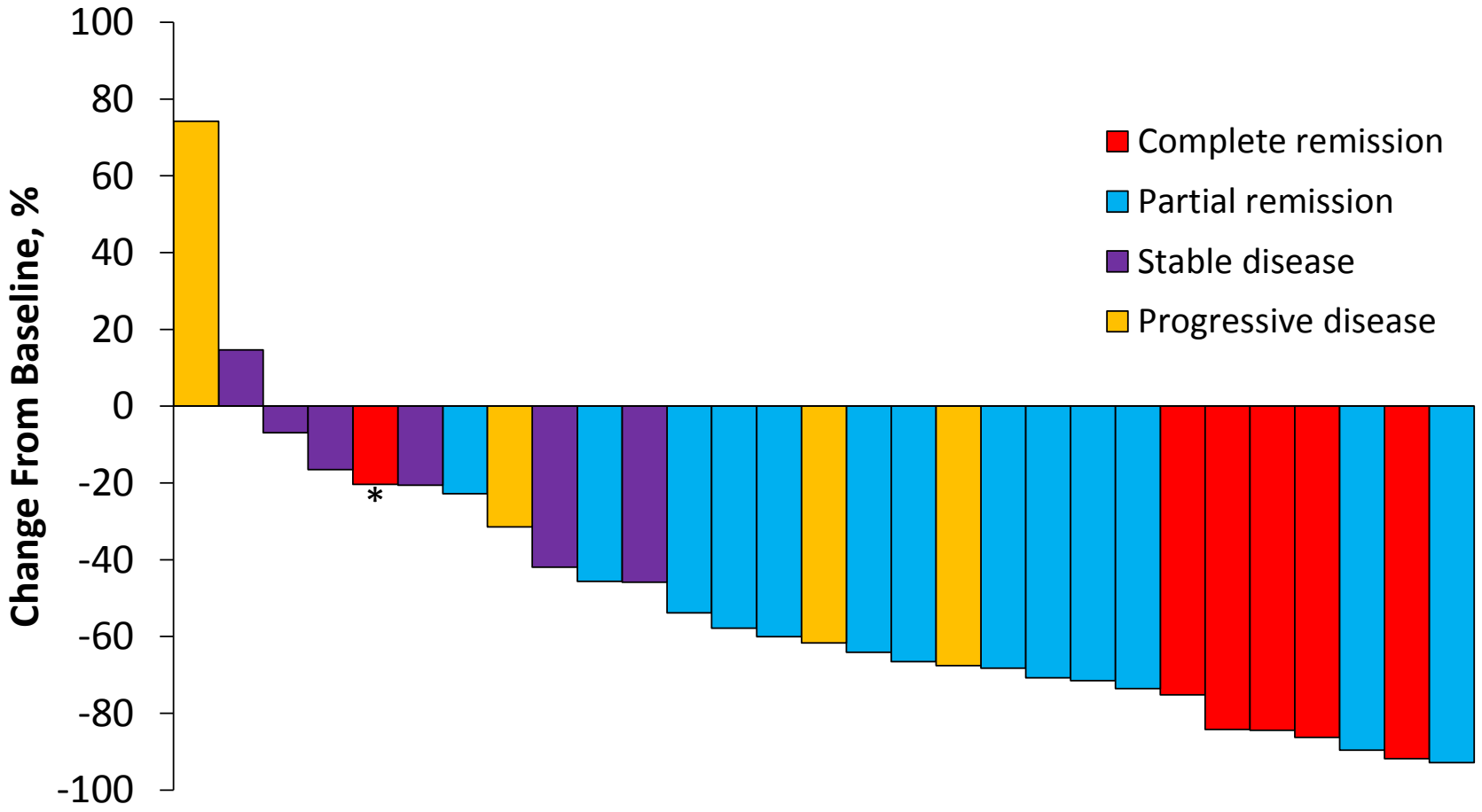
- 3 (10%) patients experienced a total of 4 grade [illegible] AEs
- No grade 4 treatment-related AEs or treatment-related deaths were observed

Adverse Events of Clinical Interest

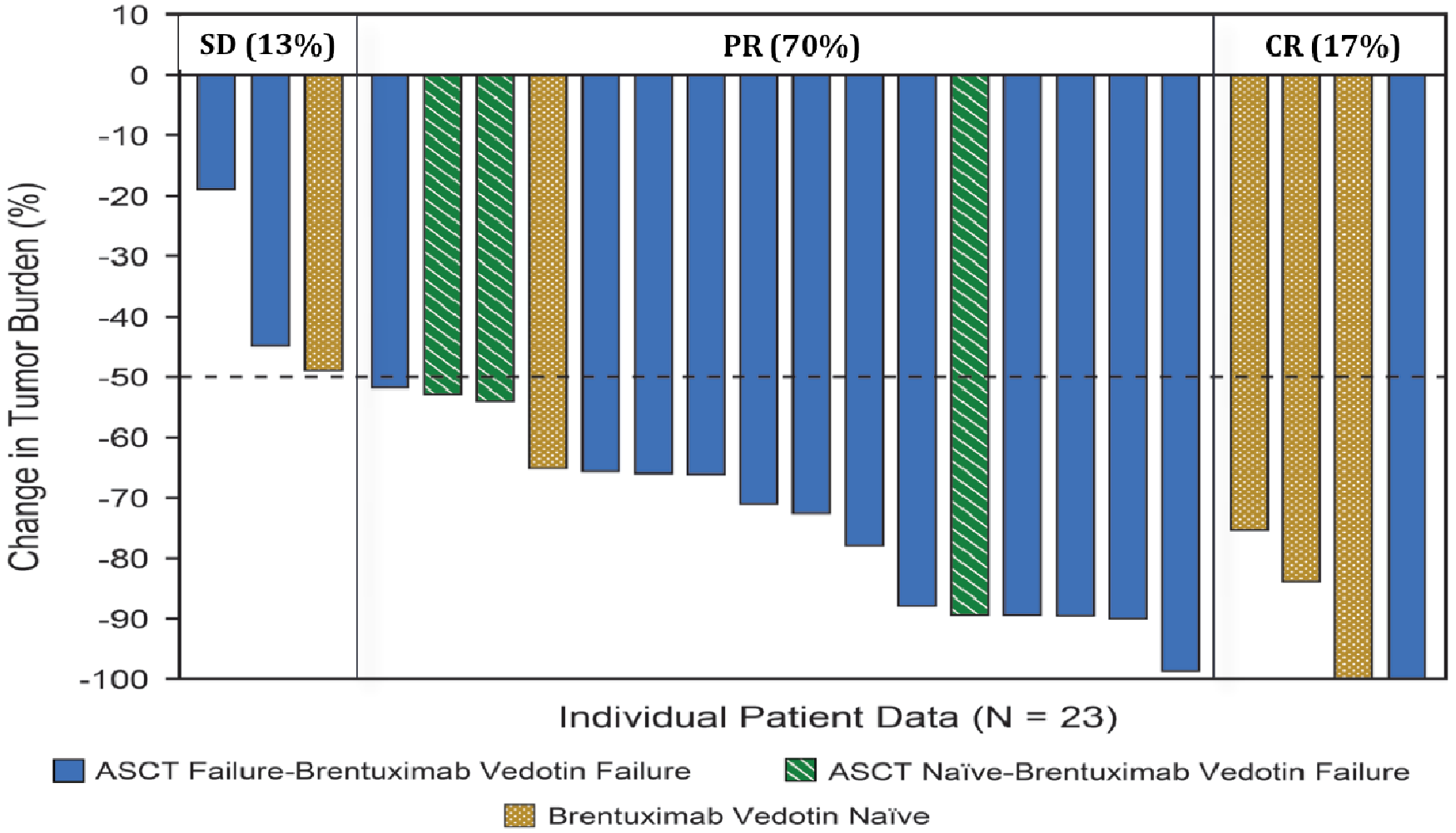
Adverse Event, n (%)	Any Grade N = 29	Grade 1-2 N = 29	Grade 3 N = 29	Grade 4 N = 29	Grade Not Reported N = 29
Hyperthyroidism	2 (7)[a]	2 (7)[a]	0	0	0
Hypothyroidism	3 (10)[b]	3 (10)[b]	0	0	0
Pneumonitis	3 (10)[b]	2 (7)[b]	1 (3)[b]	0	0
Colitis	2 (7)[a]	0	1 (3)	0	1 (3)[b]

- The following AEs of clinical interest were not observed: hepatitis, hypophysitis, nephritis, or uveitis

Maximum Percentage Change From Baseline in Target Lesions



Best Response



Antitumor Activity by Investigator Review

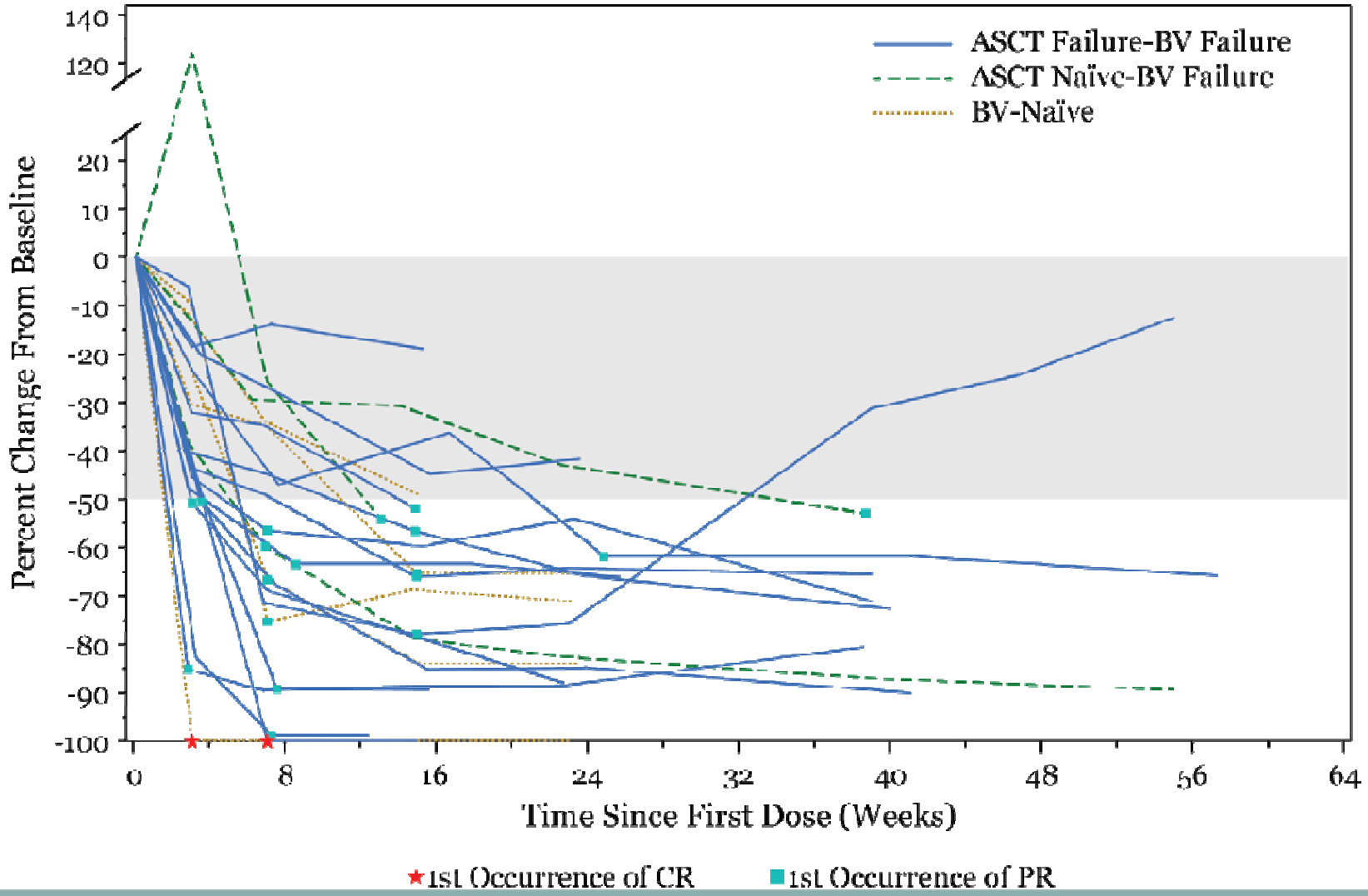
	Transplant Ineligible or Refused[a] n = 9	Transplant Failure n = 20	Total N = 29
Overall response rate	4 (44%)	15 (75%)	19 (66%)
Complete remission	2 (22%)	4 (20%)	6 (21%)
Partial remission	2 (22%)	11 (55%)	13 (45%)
Stable disease	3 (33%)	3 (15%)	6 (21%)
Progressive disease	2 (22%)	2 (10%)	4 (14%)

[a]8 patients were transplant ineligible, and 1 patient refused transplant. The patient who refused transplant experienced complete remission.
Analysis cut-off date: November 17, 2014.

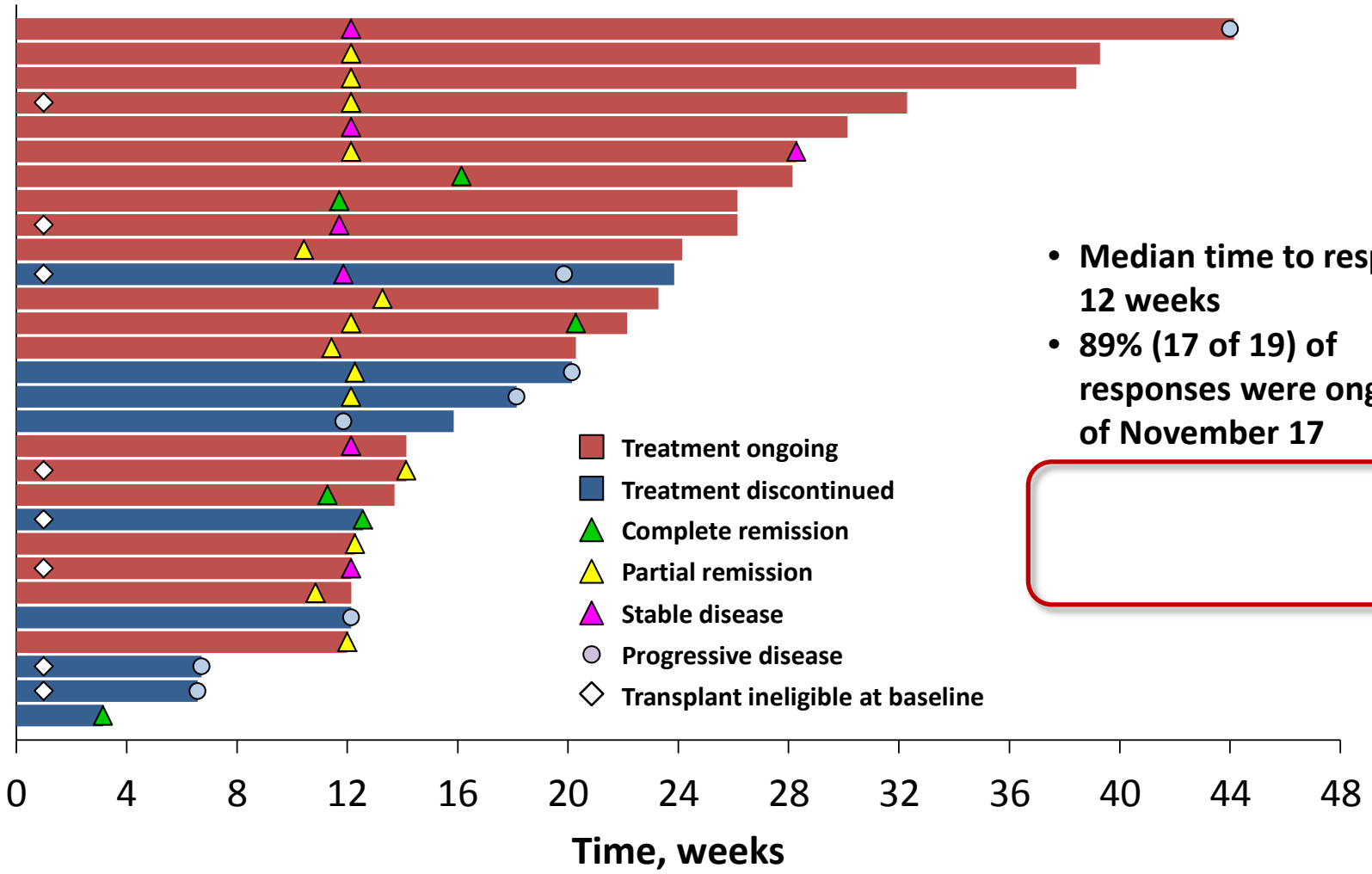
Efficacy

	Total (N = 23) n (%)	ASCT Failure Brentux Failure (N = 15) n (%)	ASCT-Naïve Brentux Failure (N = 3) n (%)	Brentux Naïve (N=5) n (%)
Overall Response	**20 (87)**	**13 (87)**	**3 (100)**	**4 (80)**
Best Response CR	**4 (17)**	1 (7)	0	3 (60)
PR	**16 (70)**	12 (80)	3 (100)	1 (20)
SD	**3 (13)**	2 (13)	0	1 (20)
PD	**0**	0	0	0
24-week PFS	**86%**	**85%**	n/c	**80%**

Response Kinetics



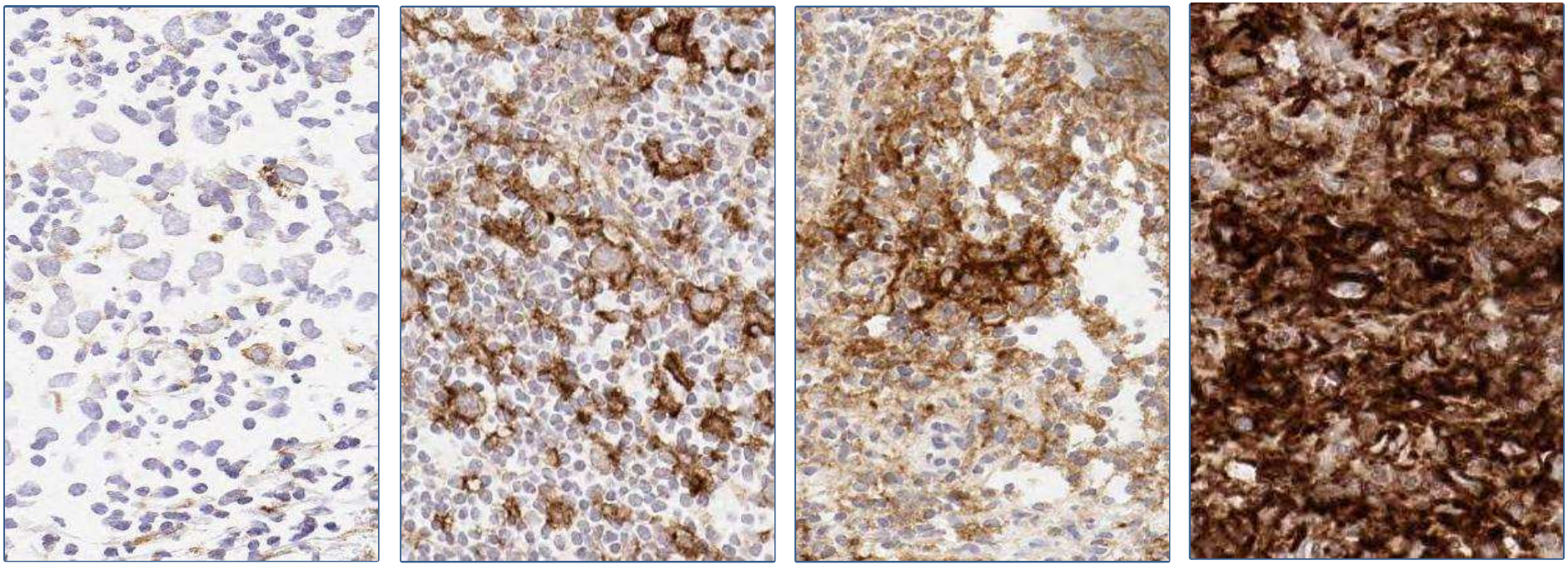
Treatment Exposure and Response Duration



- **Median time to response: 12 weeks**
- **89% (17 of 19) of responses were ongoing as of November 17**

Analysis cut-off date: November 17, 2014.

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.

Conclusions

- Nivolumab can be safely administered to patients with relapsed/refractory classical Hodgkin Lymphoma.
- **Response rate 87%** (20/23) in heavily pre-treated patients.
- All studied tumors harbored genetic abnormalities at 9p24.1 leading to over-expression of PD-1 ligands.
- Classical HL appears to be a tumor with genetically determined vulnerability to PD-1 blockade.
- FDA has granted nivolumab breakthrough therapy designation in Hodgkin Lymphoma.
- A Phase 2 study is ongoing in patients who relapsed after ASCT.
- PD-1 blockade could become an important part of the treatment of patients with cHL in the future.

Publication

The NEW ENGLAND JOURNAL of MEDICINE

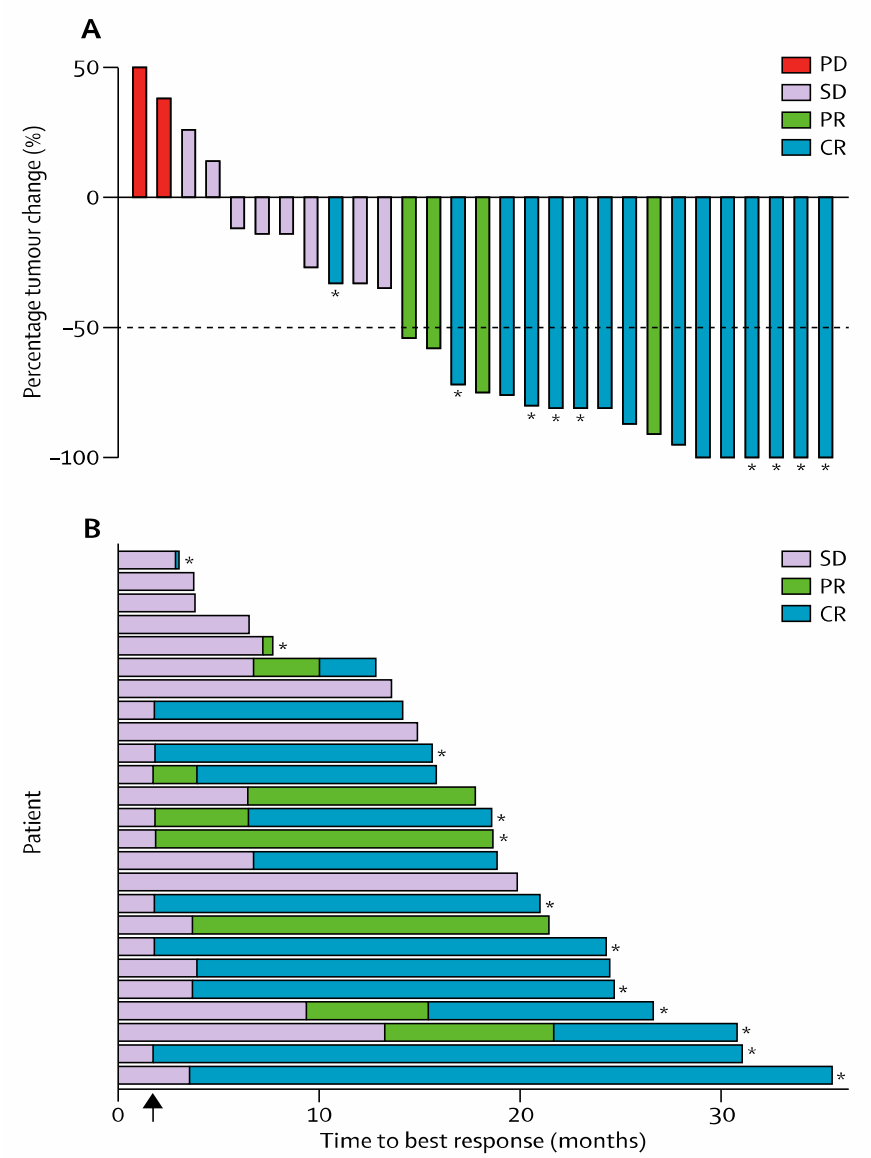
ORIGINAL ARTICLE

PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma

Stephen M. Ansell, M.D., Ph.D., Alexander M. Lesokhin, M.D., Ivan Borrello, M.D., Ahmad Halwani, M.D., Emma C. Scott, M.D., Martin Gutierrez, M.D., Stephen J. Schuster, M.D., Michael M. Millenson, M.D., Deepika Cattry, M.S., Gordon J. Freeman, Ph.D., Scott J. Rodig, M.D., Ph.D., Bjoern Chapuy, M.D., Ph.D., Azra H. Ligon, Ph.D., Lili Zhu, M.S., Joseph F. Grosso, Ph.D., Su Young Kim, M.D., Ph.D., John M. Timmerman, M.D., Margaret A. Shipp, M.D., and Philippe Armand, M.D., Ph.D.

- anti–PD-1 therapy will become the foundation for the treatment of Hodgkin’s lymphoma
- sparing patients both short- and long-termtoxic effects of combination chemotherapy

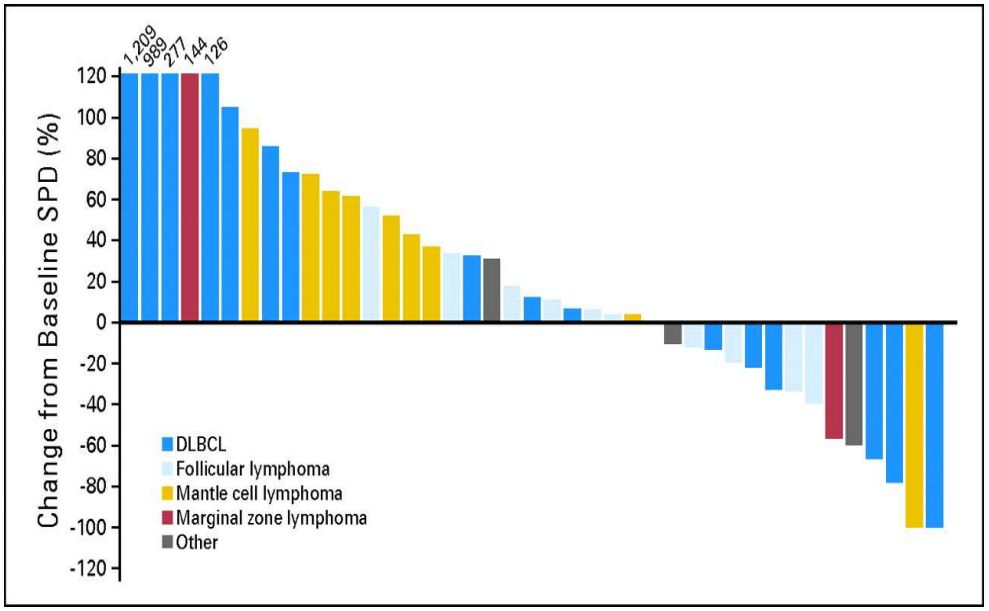
Pidilizumab and Rituximab for FL



Westin, JR Lancet Oncology 15:69, 2014

Phase I study of humanized anti-CD40 monoclonal antibody dacetuzumab in recurrent non-Hodgkin's lymphoma.

- 50 patients treated.
- Two DLTs: conjunctivitis and ALT elevation.
- Six objective responses (one complete response, five partial responses).
- Tumor size decreased in approximately one third of patients.

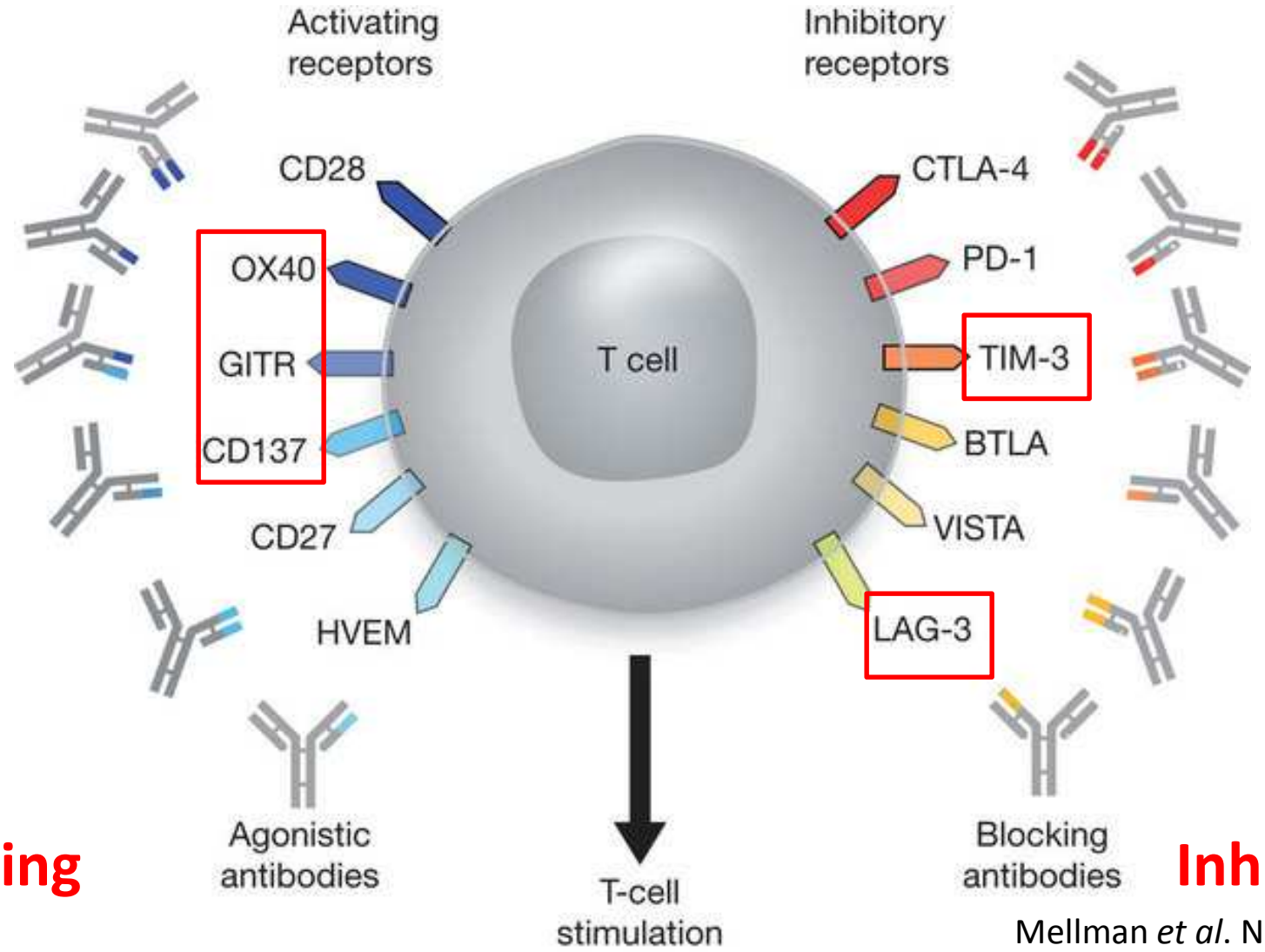


Advani et al. JCO 2009;27:4371-4377

Immune Modulatory Receptors

Turning up The Activating

Blocking the Inhibiting



Activating **Inhibiting**

Mellman *et al*. Nature, 2011

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.

Hypothesis

- Through gene-transfer techniques, T cells can be genetically modified to stably express antibodies on their surface, conferring new antigen specificity.
- Chimeric antigen receptors combine an antigen-recognition domain of a specific antibody with an intracellular domain of the CD3- zeta chain or FcγRI protein into a single chimeric protein.
- Chimeric antigen receptors can trigger T-cell activation in a manner similar to that of endogenous T-cell receptors,
  - a major impediment to the clinical application has been limited in vivo expansion of chimeric antigen receptor T cells and disappointing clinical activity.
- Chimeric antigen receptor–mediated T-cell responses can be further enhanced with the addition of a costimulatory domain

The NEW ENGLAND JOURNAL of MEDICINE

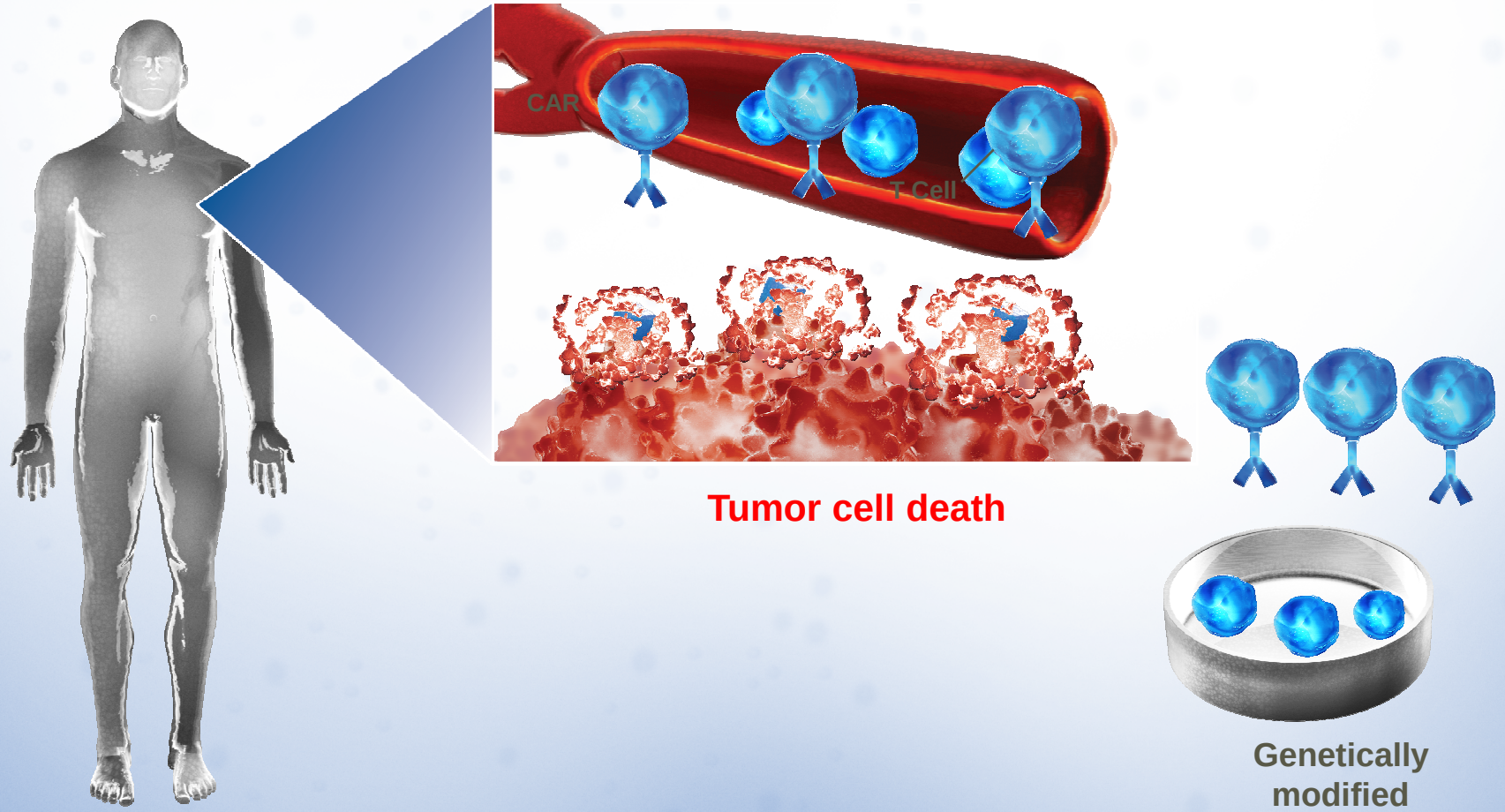
BRIEF REPORT

Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.

Genetically engineered T-cell receptors enable enhanced recognition of tumor cells

Main steps in T-cell receptor engineering



CAR=chimeric antigen receptor

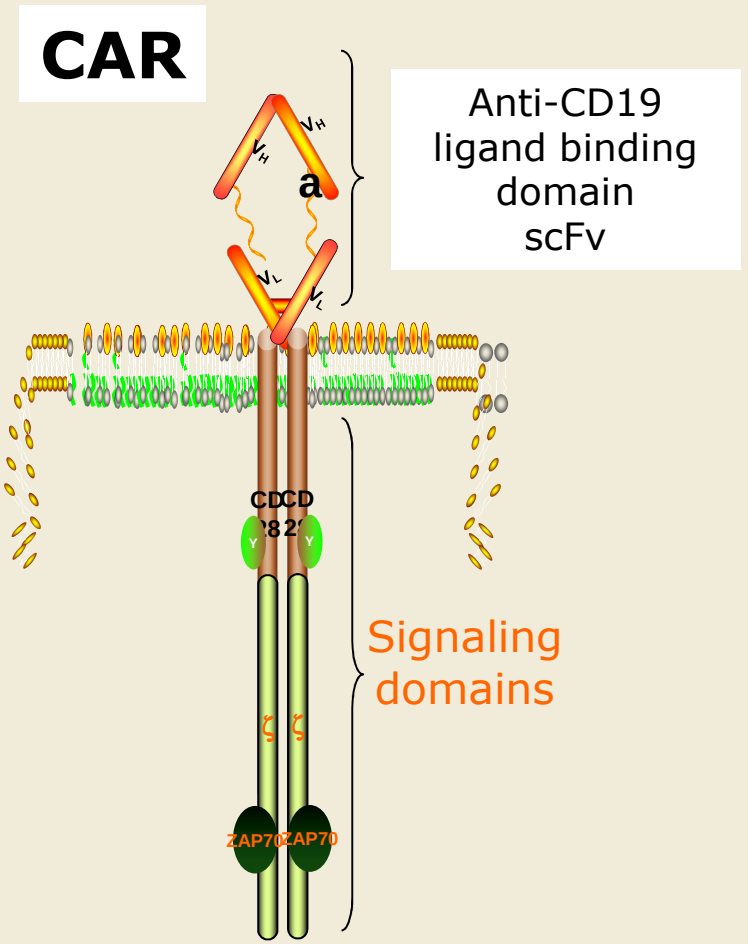
Study Design and Eligibility

- Single-center pilot trial of CTL019 (formally CART19) cells
- **Primary objective:**
  - Safety, feasibility and immunogenicity of CTL019 in patients with CD19-positive leukemia and lymphoma
- **Eligibility:**
  - CD19-positive B-cell malignancies with no available curative options (such as autologous or allogeneic stem cell transplant)
  - Failed ≥2 prior therapies, progression within 2 years of last treatment
  - Limited prognosis (<2 years) with available therapies

Porter DL et al. *Proc ASH* 2012;Abstract 717.

Treatment of Patients with CART19 Cells

- Autologous T cells collected by leuka-pheresis were transduced with a lentivirus encoding the anti-CD19 scFv linked to the 4-1BB (CD137) and CD3-z signaling domains.
- Gene-modified T cells were expanded and activated ex vivo by exposure to anti-CD3/CD28 beads.
- Ten patients received T-cell infusions con-taining a proportion of CART19 cells.
- Patients with CLL received lymphodepleting chemotherapy 4 to 7 days prior to infusion.
- Patients with ALL experienced chemo-refractory relapse, received 6 weeks of chemotherapy prior to infusion and did not require further lymphodepletion.



With permission from Porter DL et al. *Proc ASH* 2012;Abstract 717.

Clinical Response

Pt UPN#	Blood	Marrow	Nodes	Expansion	Comments	Max resp
01	NED	NED	NED	>3 log	MRD* neg	CR 28 mo+
02	NED	NED	NED	>3 log	MRD* neg	CR 27 mo+
03	PR	PR	PR	2 log		PR 4 mo
04	PR	PR	PR	2 log		PR 4 mo
05	NR	NR	NR	<2 log		NR
06	NR	NR	NR	<2 log		NR
09	NED	NED	NED	>3 log	MRD* neg	CR 7 mo+
10	NED	NED	PR	2 log	Bulky nodes	PR 3 mo+
12	NED	NED	PR	2 log	Bulky nodes	PR 2 mo+
14	ne	ne	ne			ne

NED = no evidence of disease; MRD = minimal residual disease; CR = complete response; PR = partial response; ne = not evaluated

Porter DL et al. *Proc ASH* 2012;Abstract 717.

** MRD assessed with deep sequencing analysis*

Toxicity Summary of CTL019 (CART19)

- No significant infusional toxicity
- Hepatotoxicity (Grade 3-4 in 5 responding patients)
- Renal toxicity (Grade 3 in 1 patient)
  - Related to tumor lysis syndrome, acute tubular necrosis from hypotension
  - Reversible
- B-cell aplasia and hypogammaglobulinemia in patients achieving complete response
  - Treated with intravenous immunoglobulin
  - No excessive or frequent infections
- Tumor lysis syndrome
- Cytokine release syndrome

Porter DL et al. *Proc ASH* 2012;Abstract 717.

Author Conclusions

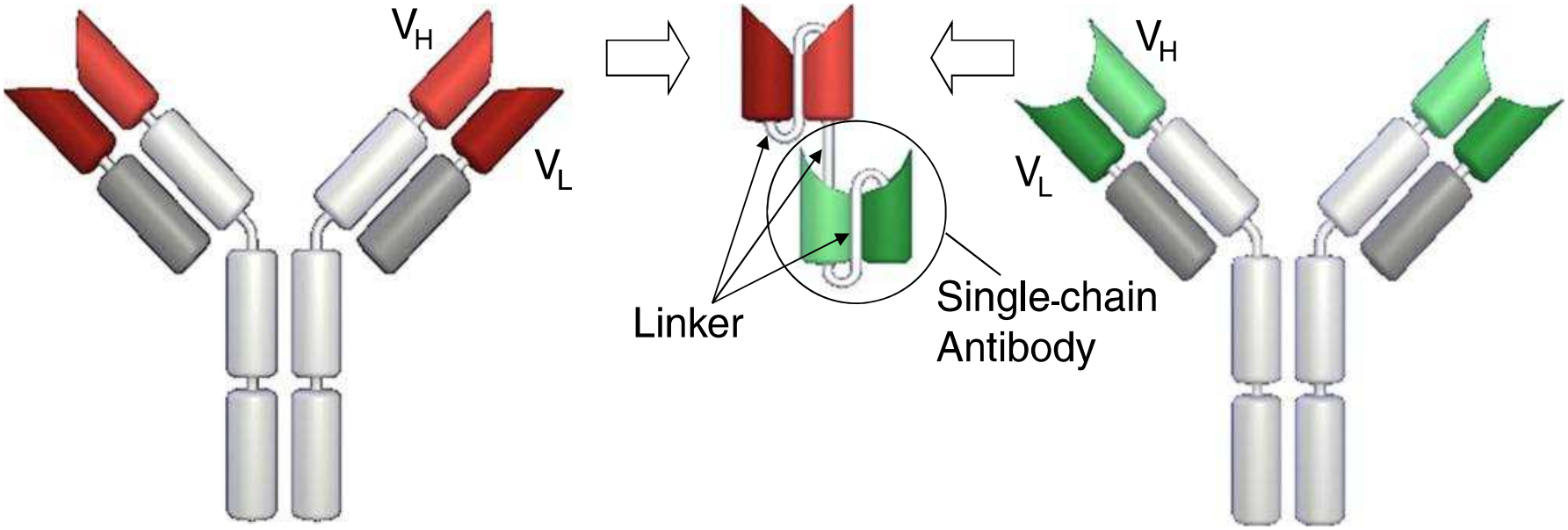
- Autologous T cells genetically engineered to express an anti-CD19 scFv coupled to 4-1BB/CD3-z signaling domains can undergo robust in vivo expansion and persist for more than 2 years.
- CART19 cells can induce an overall response rate of 78%.
  - 3/9 complete and 4/9 partial responses, including CR in 2/2 patients with ALL
- Responding patients develop cytokine release syndrome, which can be treated effectively with anticytokine therapy.

Porter DL et al. *Proc ASH* 2012;Abstract 717.

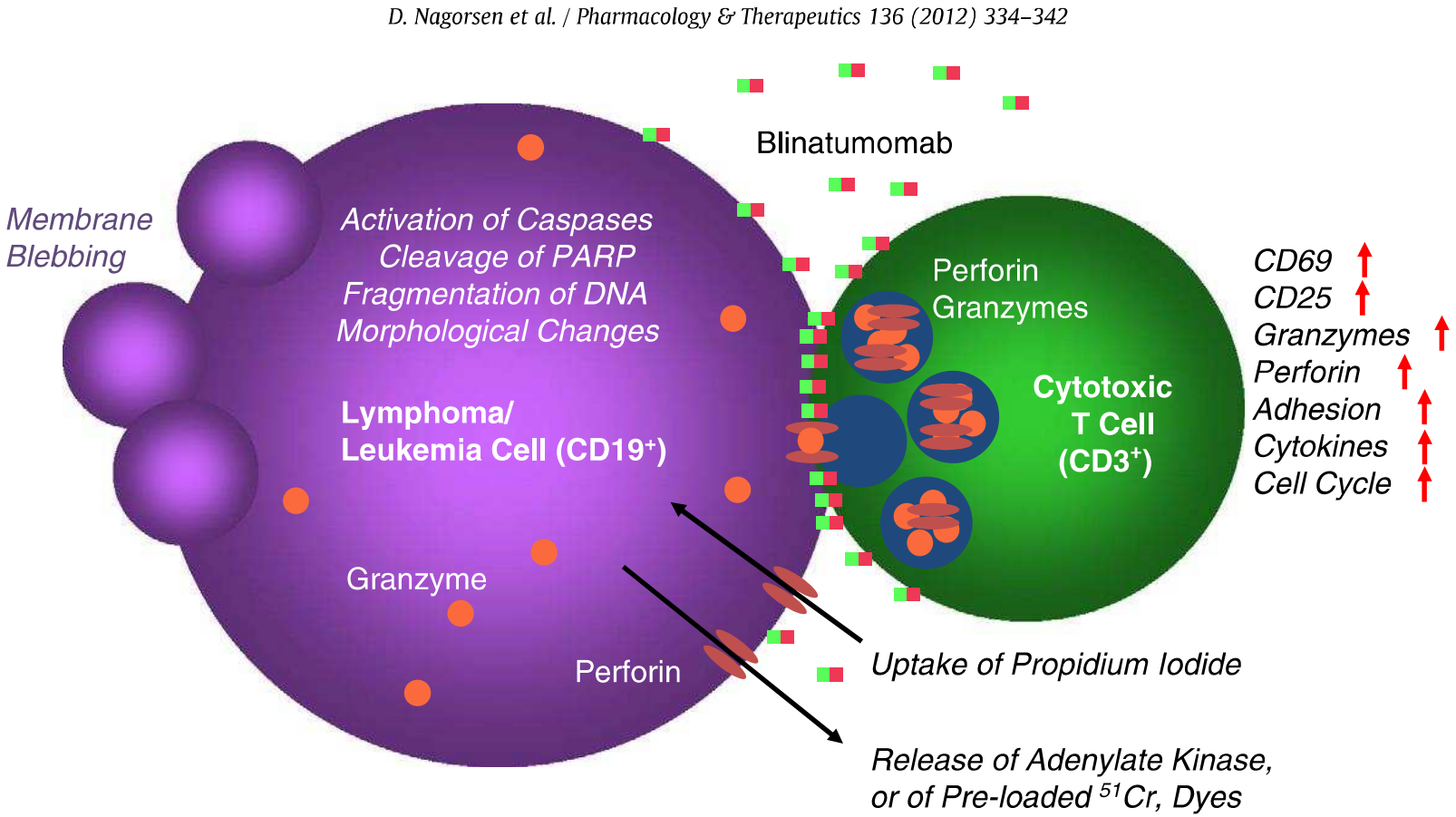
Anti-CD19 x CD3 Bi-specific Antibodies

D. Nagorsen et al. / Pharmacology & Therapeutics 136 (2012) 334–342

α-CD19 MAb **Blinatumomab** **α-CD3 MAb**

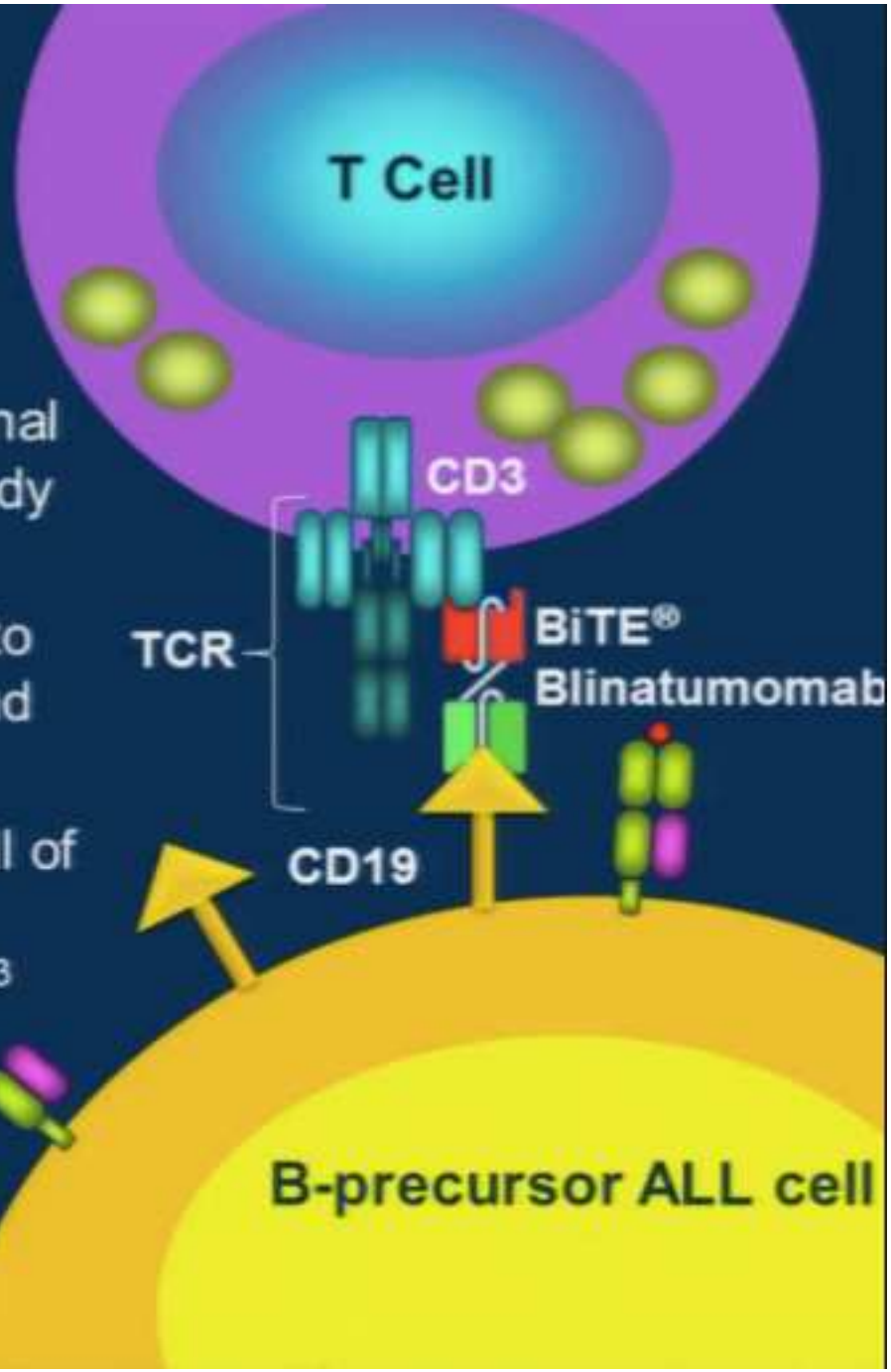


Anti-CD19 x CD3 Bi-specific Antibodies

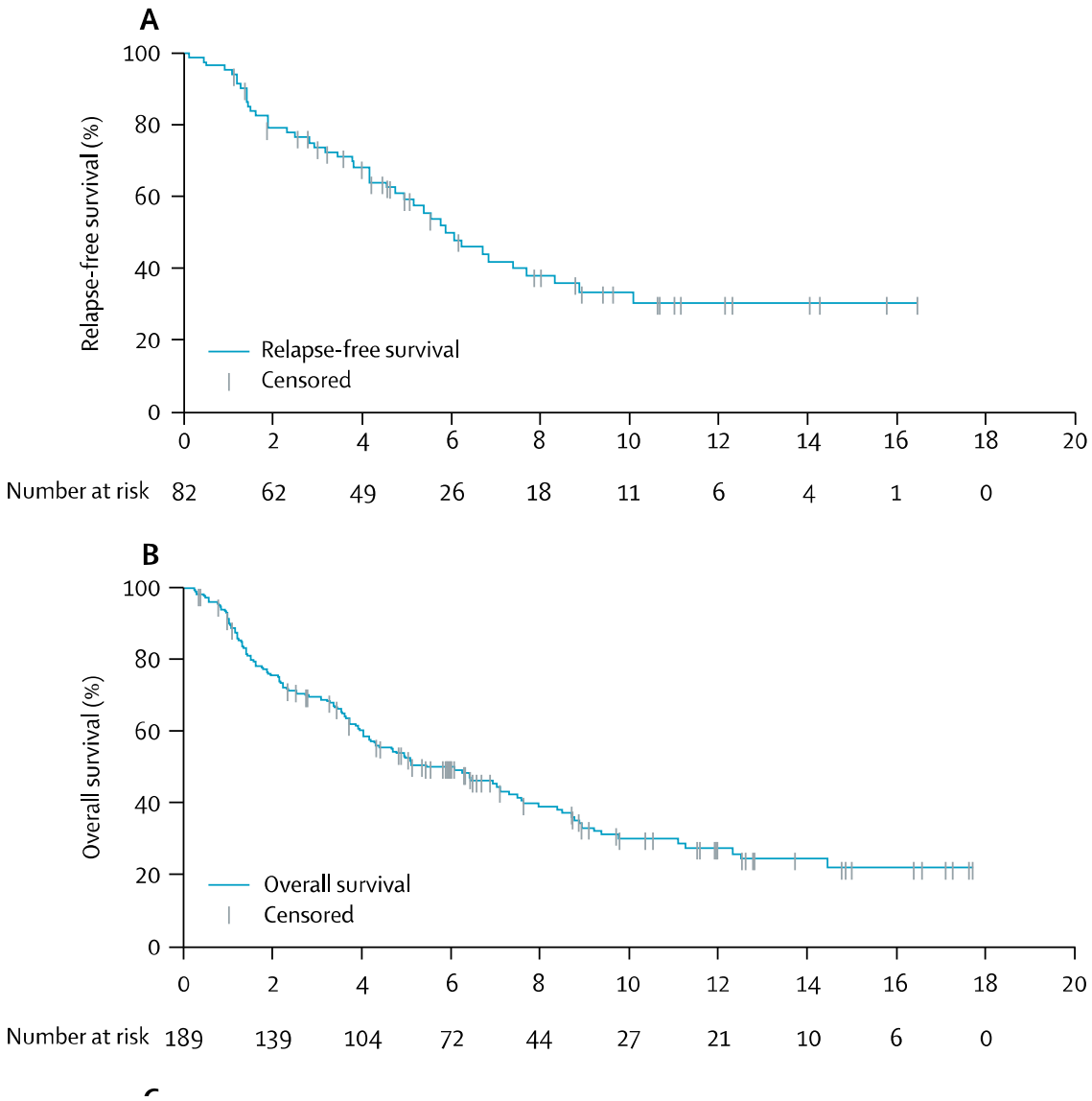


BiTE® Antibody, Blinatumomab

- Blinatumomab is an investigational bispecific T-cell engaging antibody (BiTE®)
- Blinatumomab redirects T cells to lyse CD19-positive malignant and nonmalignant B-cells[1]
- CD19 is expressed in virtually all of tested B-lineage ALL cells and throughout B-cell development[2,3]



1. Bargou R, et al. *Science*. 2008;321:974–977.
2. Raponi S, et al. *Leuk Lymphoma*. 2011;52:1098–1107.
3. Piccaluga P, et al. *Leuk Lymphoma*. 2011;52:325–327.



Topp, MS Lancet Oncology online 12/2014

Blinatumomab for Relapsed Adult ALL

- N= 189 enrolled (1/12 to 10/13)
  - – Age 39 (18-79)
  - – Prior Allogeneic HCT 34%, BM > 50% in 69%
- 81 pts post 2 cycles met the endpoint response
  - – CR 63 (33%) or CRh 18 (10%)
  - – No response 48%
  - – MRD anlaysis 60/73 < 10^{-4} by PCR
  - – 40 patients able to proceed to Allogeneic HCT
  - • Toxicity
  - – Fever/neutropenia 25%
  - – Neutropenia16%
  - – Anemia 14%
  - – Grade 3 cytokine release 2%
  - – Neurotoxicity grade III 11%, IV 2%
  - – 3 deaths due to sepsis

Topp, MS Lancet Oncology online 12/2014

In closing

- Future
  - Combinations
  - Biomarkers
  - First line therapies

  - Thank You