

Immunotherapy for the Treatment of Hematologic Malignancies

Mohammad Abu Zaid, MD

Assistant Professor of Medicine

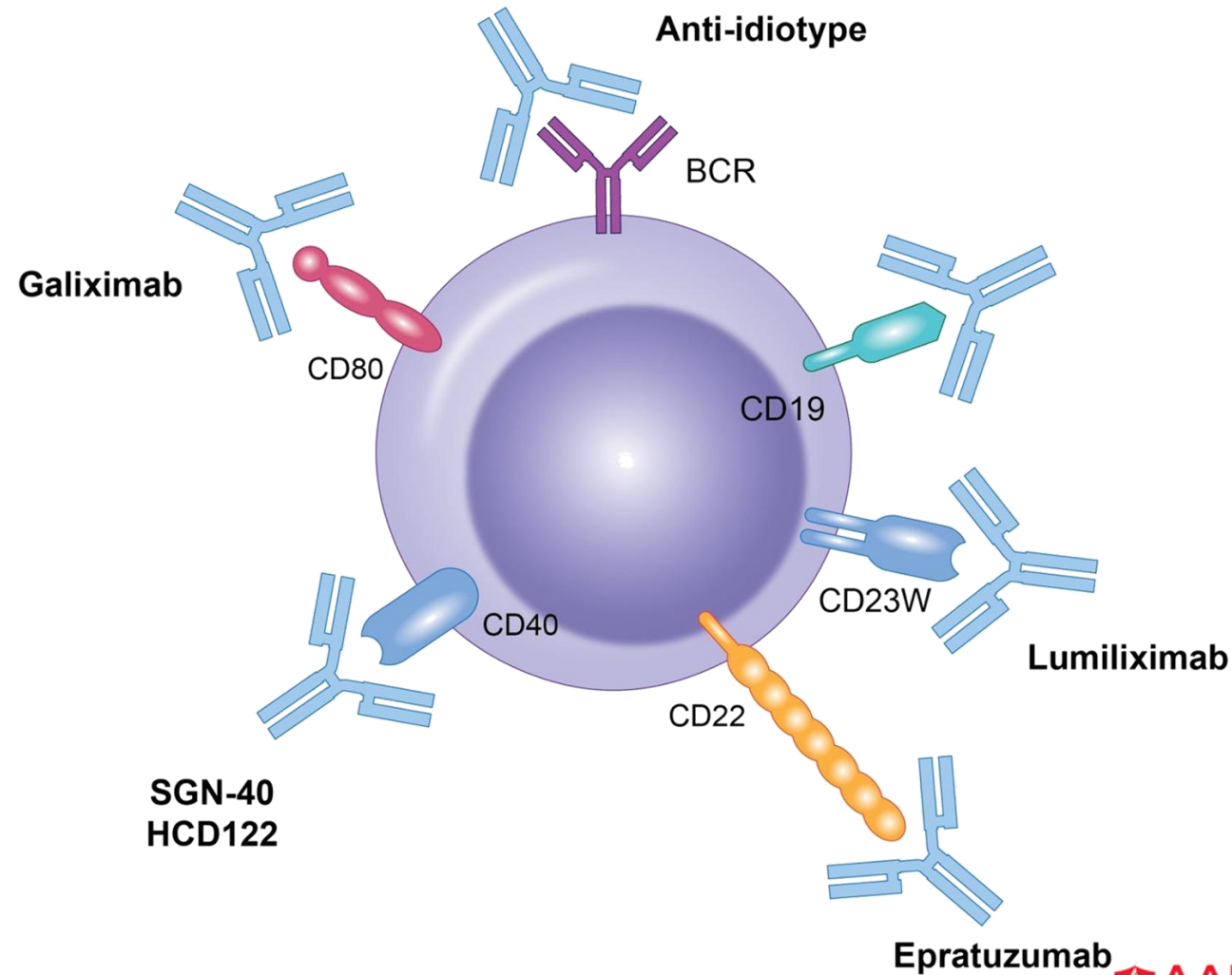
Indiana University Simon Cancer Center

10/25/2018

Disclosures

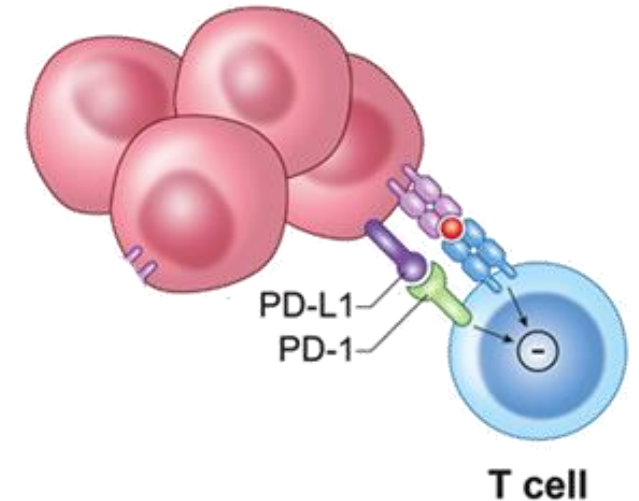
- Add disclosures here
- I will not be discussing non-FDA approved indications during my presentation.

Monoclonal Antibodies Targeting B Cell Lymphomas



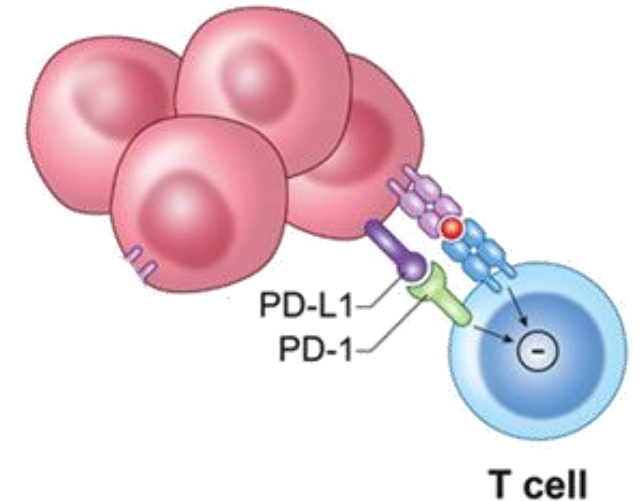
FDA-approved Checkpoint Inhibitors for Lymphomas

- Nivolumab (anti-PD-1)
 - CheckMate 205/039: Patients with cHL that has relapsed or progressed after autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin
- Pembrolizumab (anti-PD-1)
 - KEYNOTE-087: Adult and pediatric patients with refractory cHL, or patients whose disease has relapsed after three or more lines of therapy
 - KEYNOTE-170: Adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL), or those who have relapsed after 2 or more prior lines of therapy



Patient Selection Criteria for Checkpoint Inhibitor Therapies

- Expression of the ligand for checkpoint inhibition
 - e.g. PD-L1 expression for anti-PD-1 therapy
- Relapse or progression after previous therapies
 - Nivolumab: After prior HSCT and brentuximab therapy
 - Pembrolizumab: Relapse after three prior treatments, PMBCL
- Presence of co-morbidities
 - e.g. Presence of active autoimmune disease which could be worsened



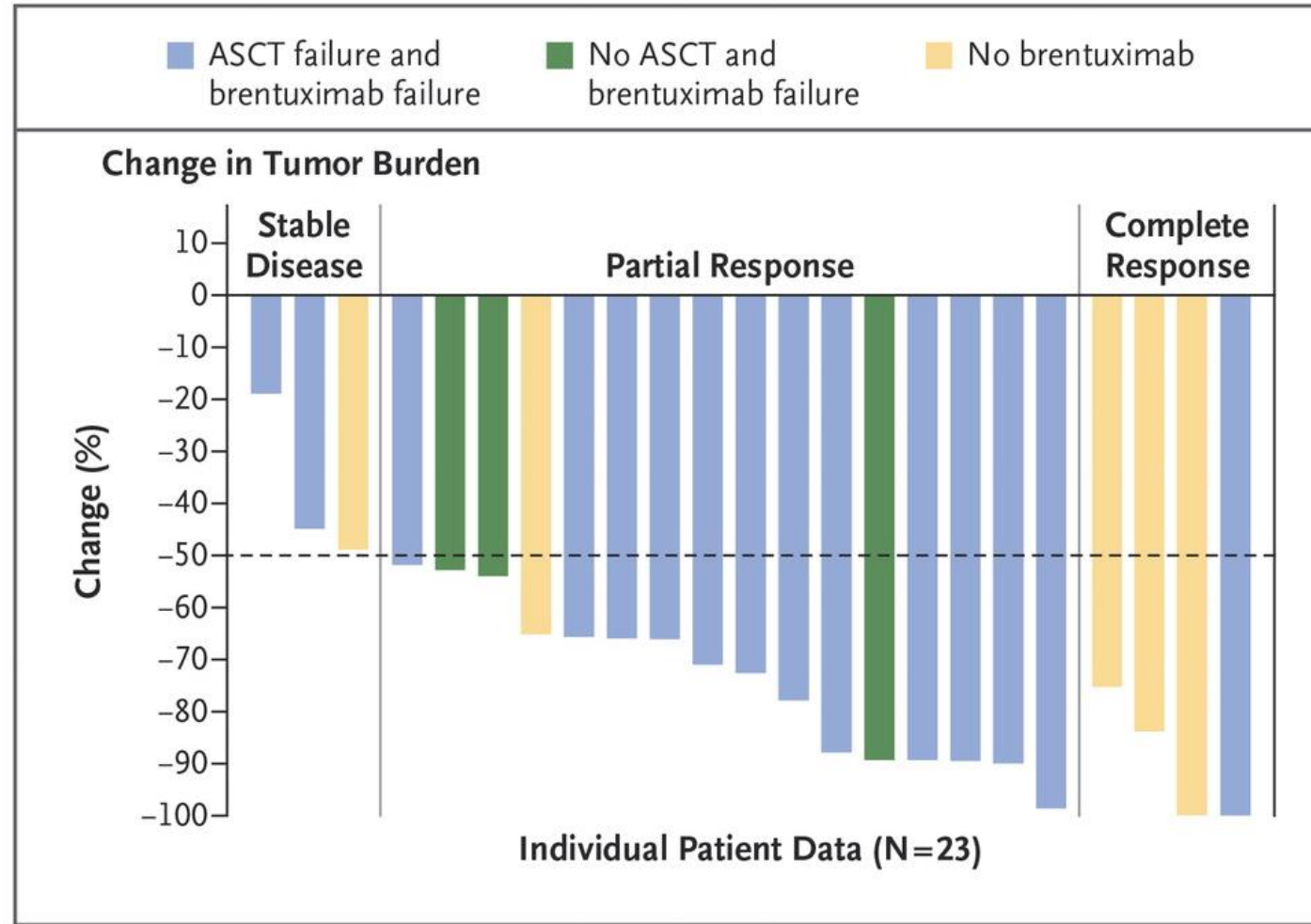
Nivolumab in Hodgkin Lymphoma

Table 3. Clinical Activity in Nivolumab-Treated Patients.*

Variable	All Patients (N=23)	Failure of Both Stem-Cell Transplantation and Brentuximab (N=15)	No Stem-Cell Transplantation and Failure of Brentuximab (N=3)	No Brentuximab Treatment (N=5)†
Best overall response — no. (%)				
Complete response	4 (17)	1 (7)	0	3 (60)
Partial response	16 (70)	12 (80)	3 (100)	1 (20)
Stable disease	3 (13)	2 (13)	0	1 (20)
Progressive disease	0	0	0	0
Objective response				
No. of patients	20	13	3	4
Percent of patients (95% CI)	87 (66–97)	87 (60–98)	100 (29–100)	80 (28–99)
Progression-free survival at 24 wk — % (95% CI)‡	86 (62–95)	85 (52–96)	NC§	80 (20–97)
Overall survival — wk				
Median	NR	NR	NR	NR
Range at data cutoff¶	21–75	21–75	32–55	30–50

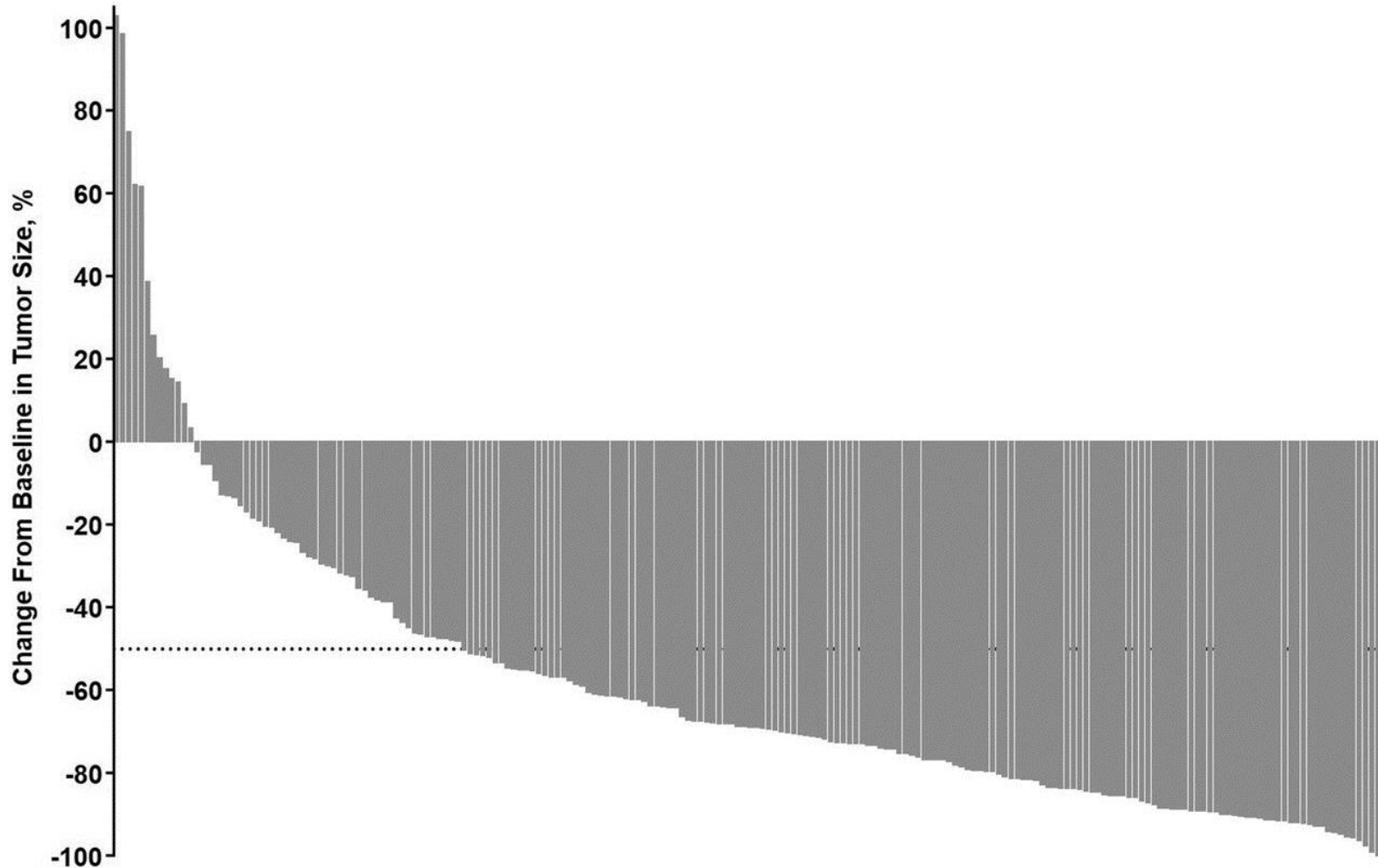
Ansell et al. NEJM 2015

Nivolumab in Hodgkin Lymphoma



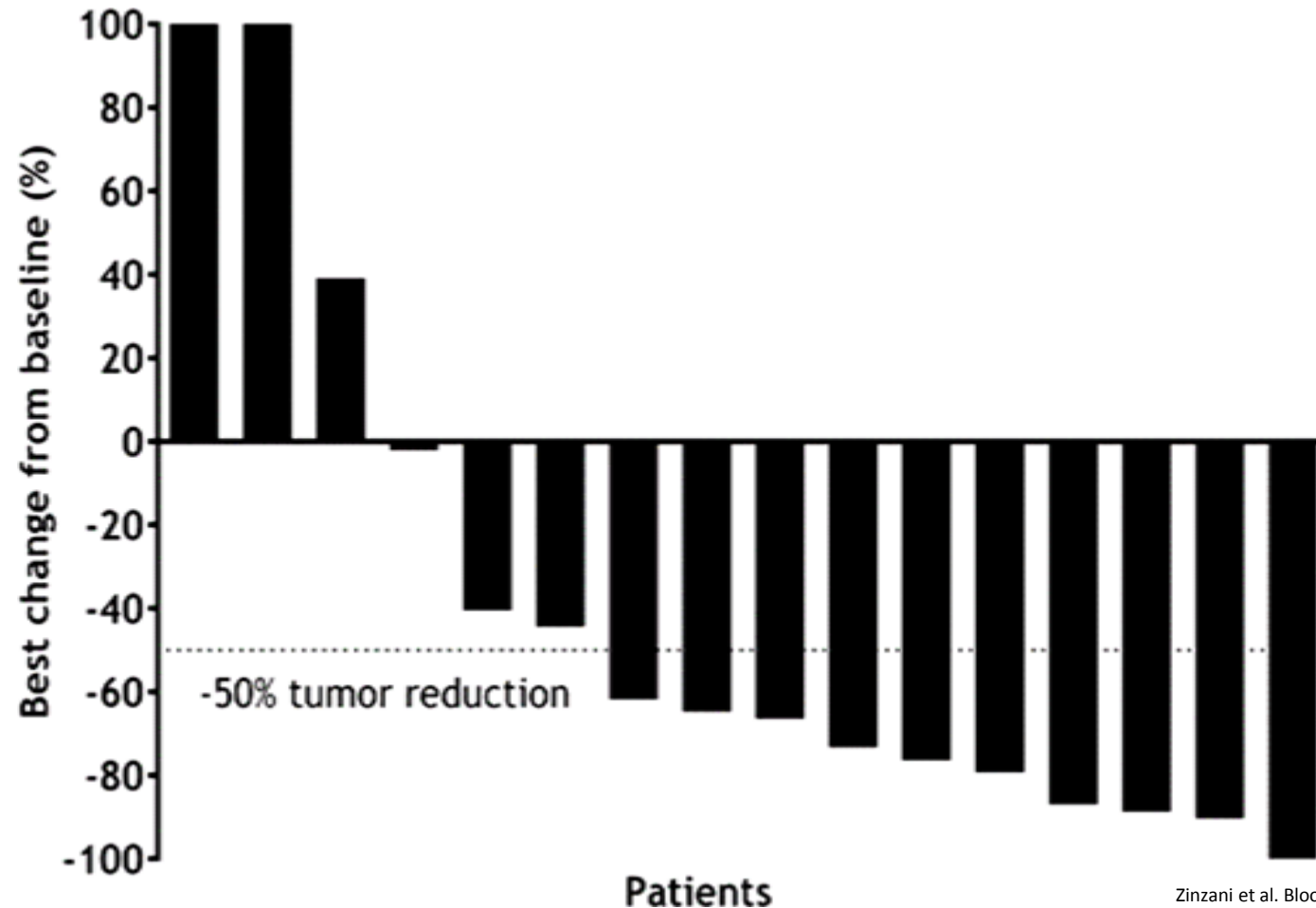
Ansell et al. NEJM 2015

Pembrolizumab in Hodgkin Lymphoma



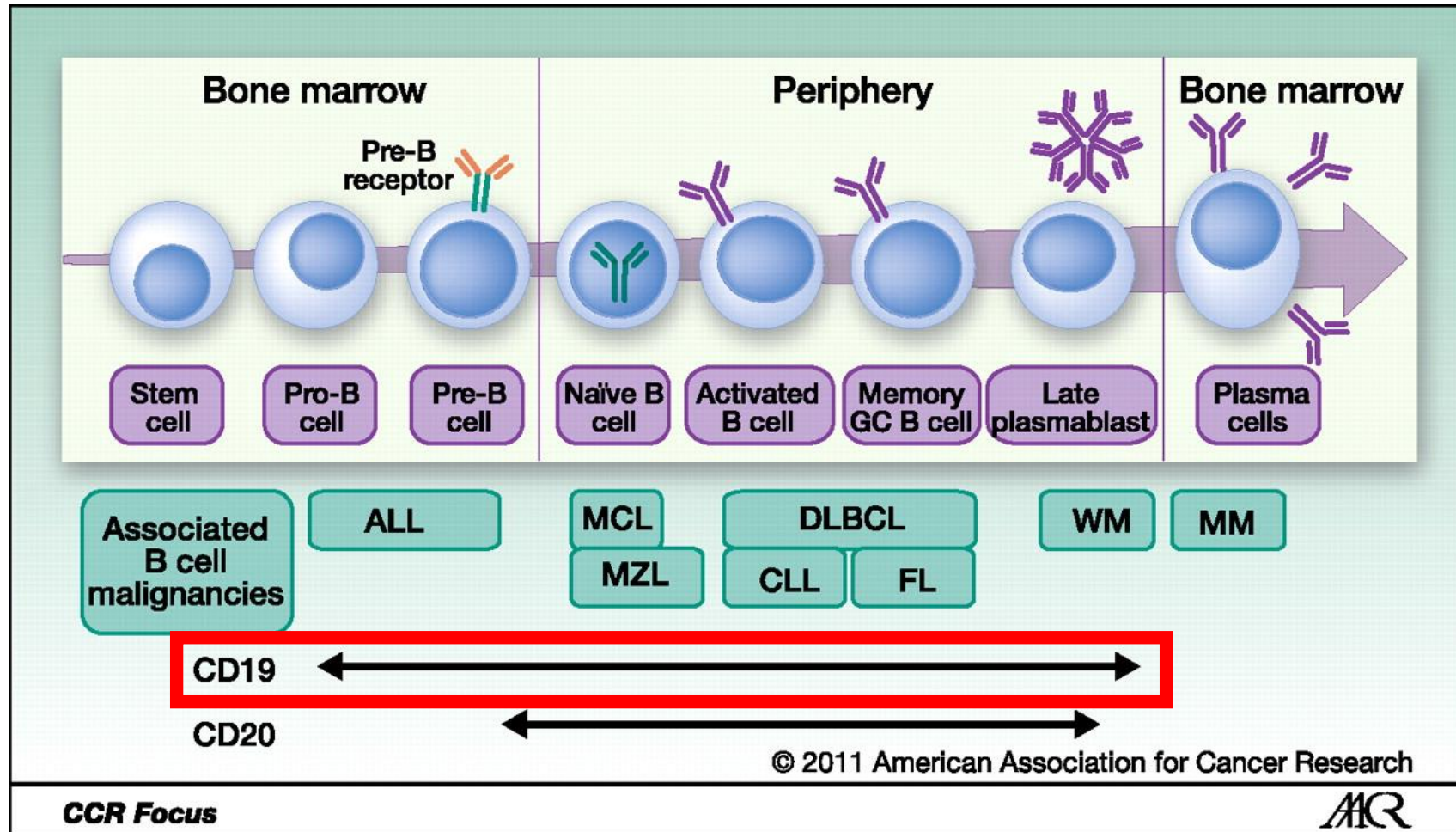
Zinzani et al. Hematological Oncology 2017

Pembrolizumab in Primary Mediastinal Large B cell Lymphoma



Zinzani et al. Blood 2016

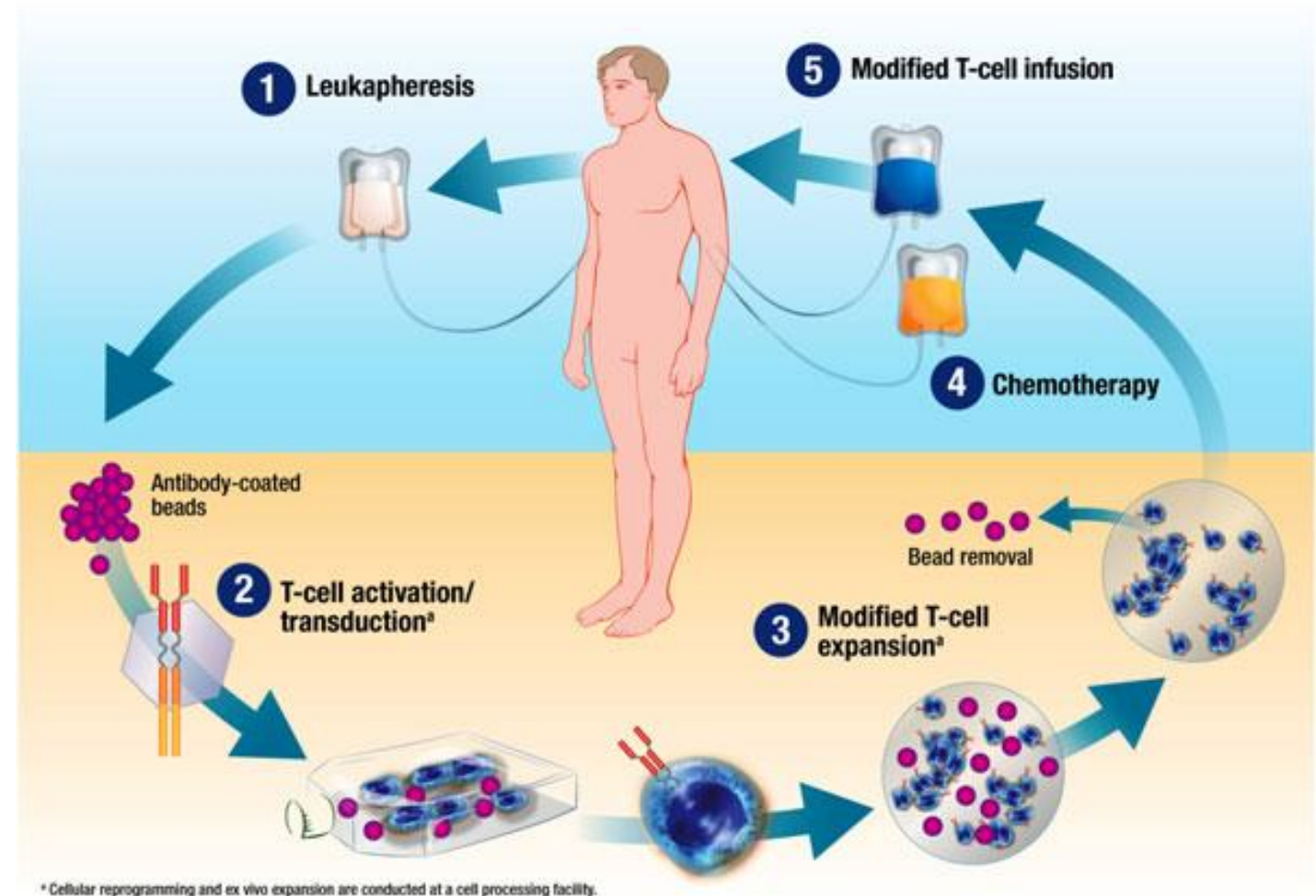
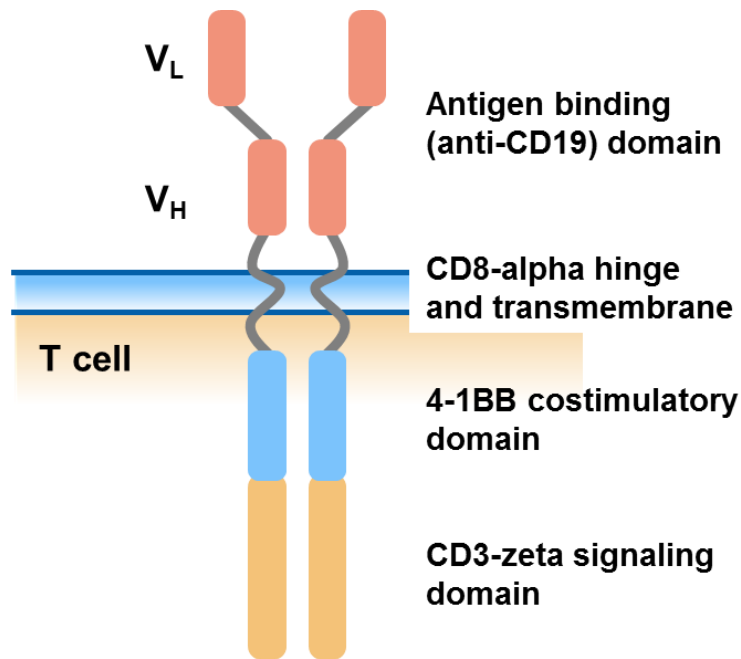
B Cell Malignancies are CD19+



Blanc et al. Clinical Cancer Research 2011

Chimeric Antigen Receptor (CAR) T cell Therapy

- Engineering patient T cells to target and eliminate cells presenting specific antigens



FDA-approved CAR T Cell Therapies for Lymphoma

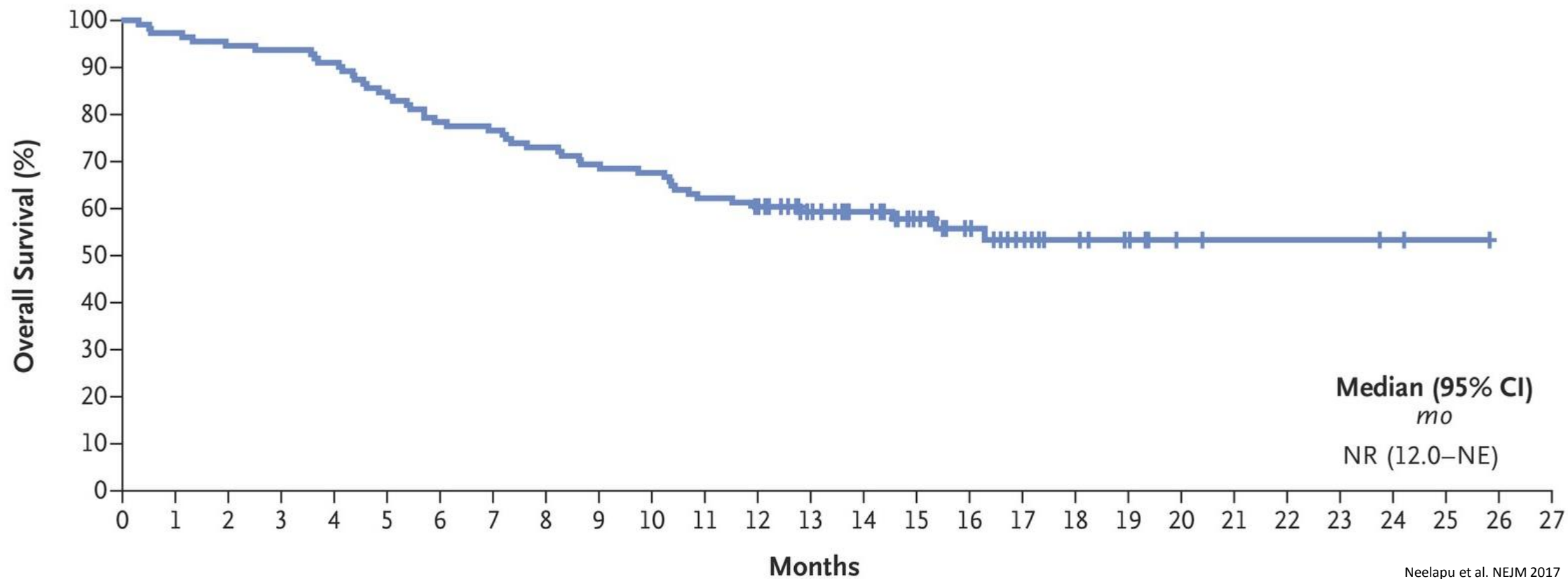
- Axicabtagene ciloleucel (Yescarta)
 - ZUMA-1: Adult patients with relapsed or refractory large B cell lymphoma after two or more lines of systemic therapy, including diffuse large B cell lymphoma, high-grade B cell lymphoma, and DLBCL arising from follicular lymphoma
- Tisagenlecleucel (Kymriah)
 - JULIET: adult patients with relapsed/refractory large B cell lymphoma—including diffuse large B cell lymphoma (DLBCL), high-grade B cell lymphoma and DLBCL arising from follicular lymphoma—after 2 or more lines of systemic therapy.

Patient Selection Criteria for CAR T Therapies

- Expression of the desired antigen for CAR T therapy
 - e.g. CD19
- Disease burden
 - CAR T trials: <30% to minimize the risk of cytokine release syndrome
- Presence of co-morbidities
 - e.g. Presence of active autoimmune diseases which could be worsened

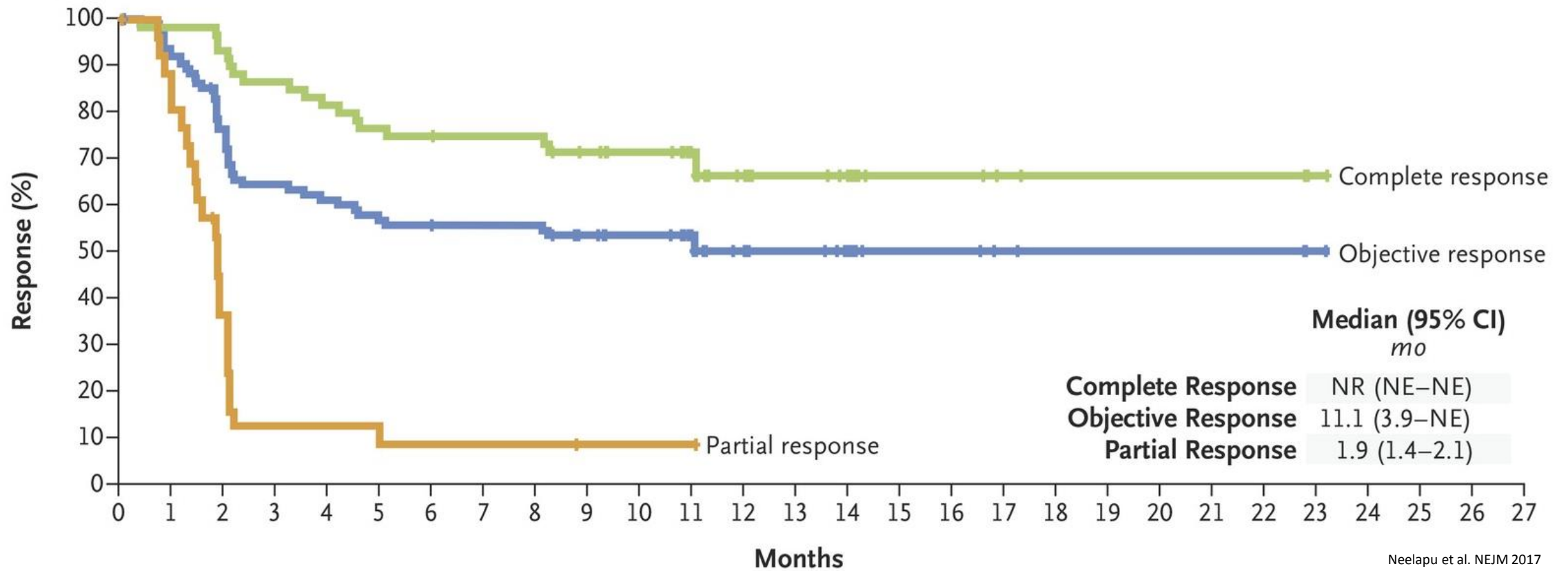
Axicabtagene ciloleucel in B Cell Lymphoma

Overall Survival



Axicabtagene ciloleucel in B Cell Lymphoma

Duration of Response

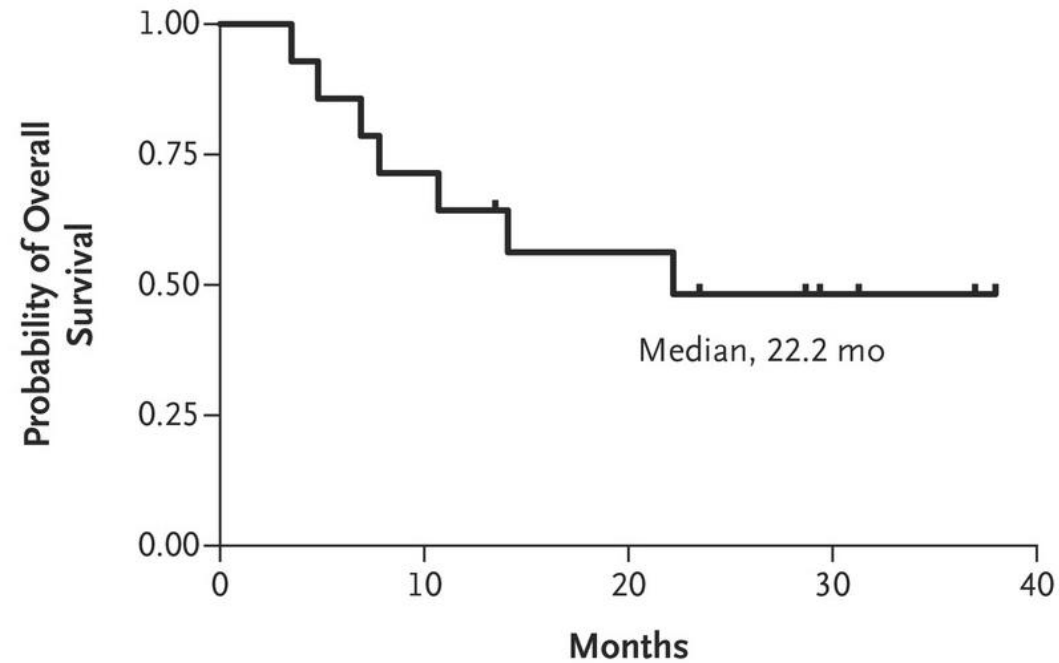


Neelapu et al. NEJM 2017

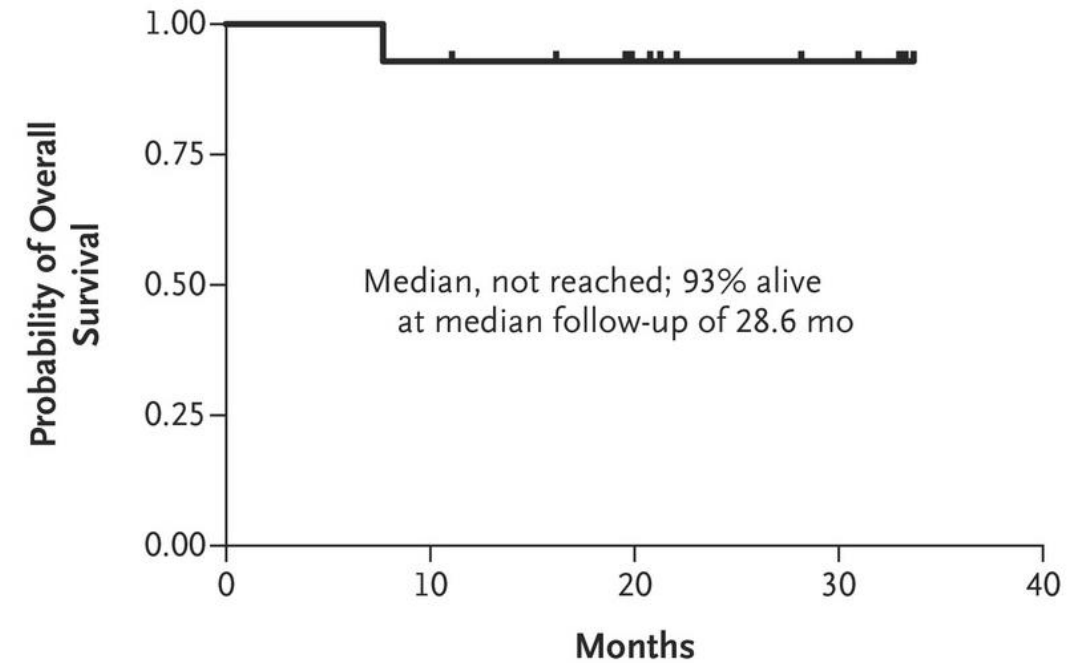
Tisagenlecleucel in B Cell Lymphoma

Overall Survival

Diffuse Large B-Cell Lymphoma, Overall Survival



Follicular Lymphoma, Overall Survival

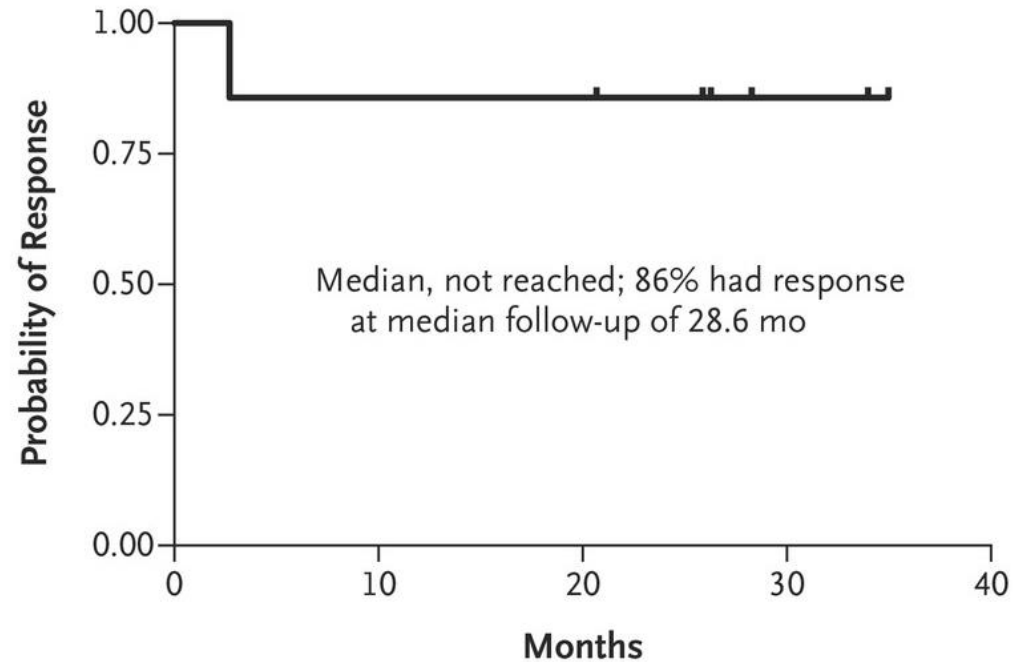


Schuster et al. NEJM 2017

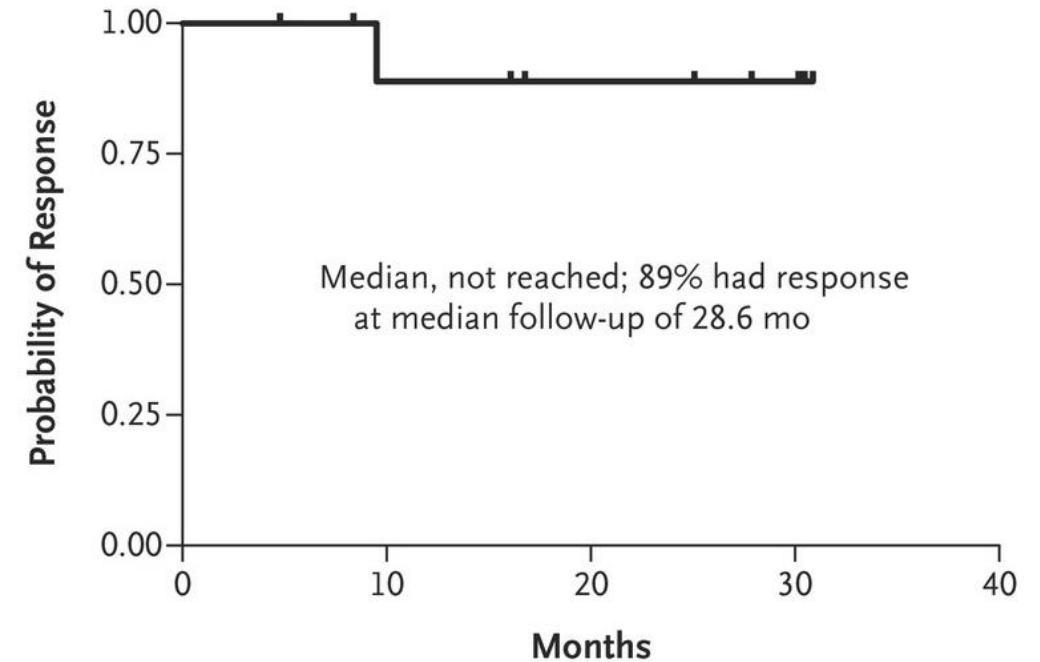
Tisagenlecleucel in B Cell Lymphoma

Duration of Response

Diffuse Large B-Cell Lymphoma, Response Duration



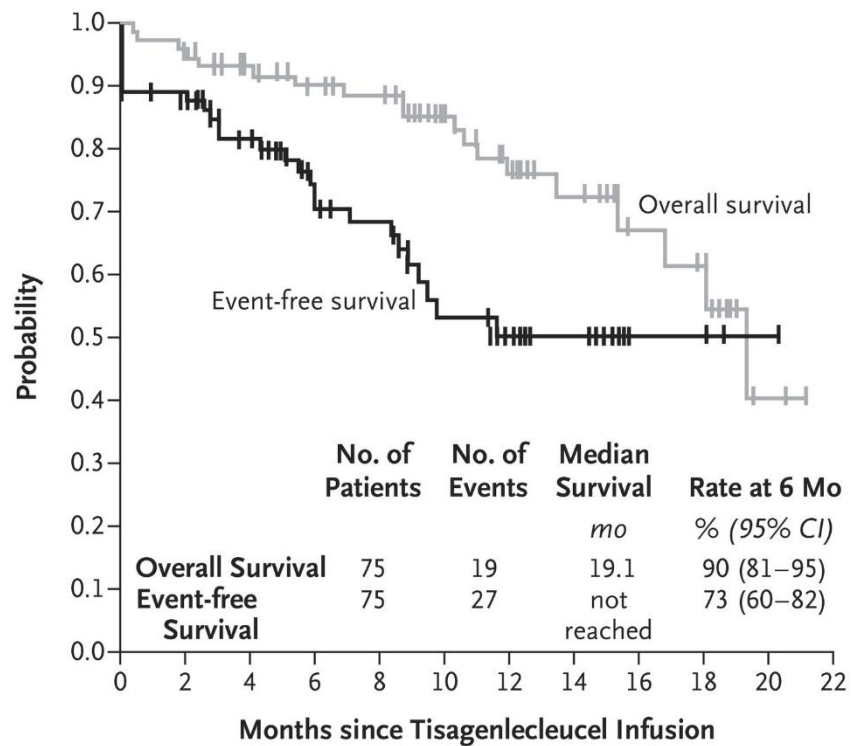
Follicular Lymphoma, Response Duration



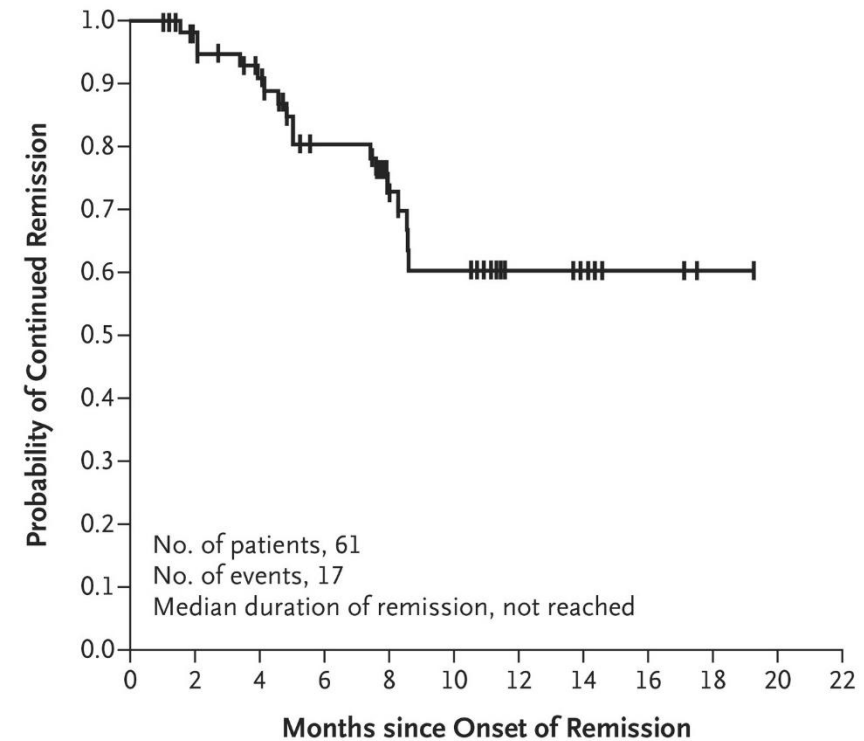
Schuster et al. NEJM 2017

FDA-approved CAR T Cell Therapies for Acute Leukemia Tisagenlecleucel

- ELIANA: patients up to age 25 years with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse

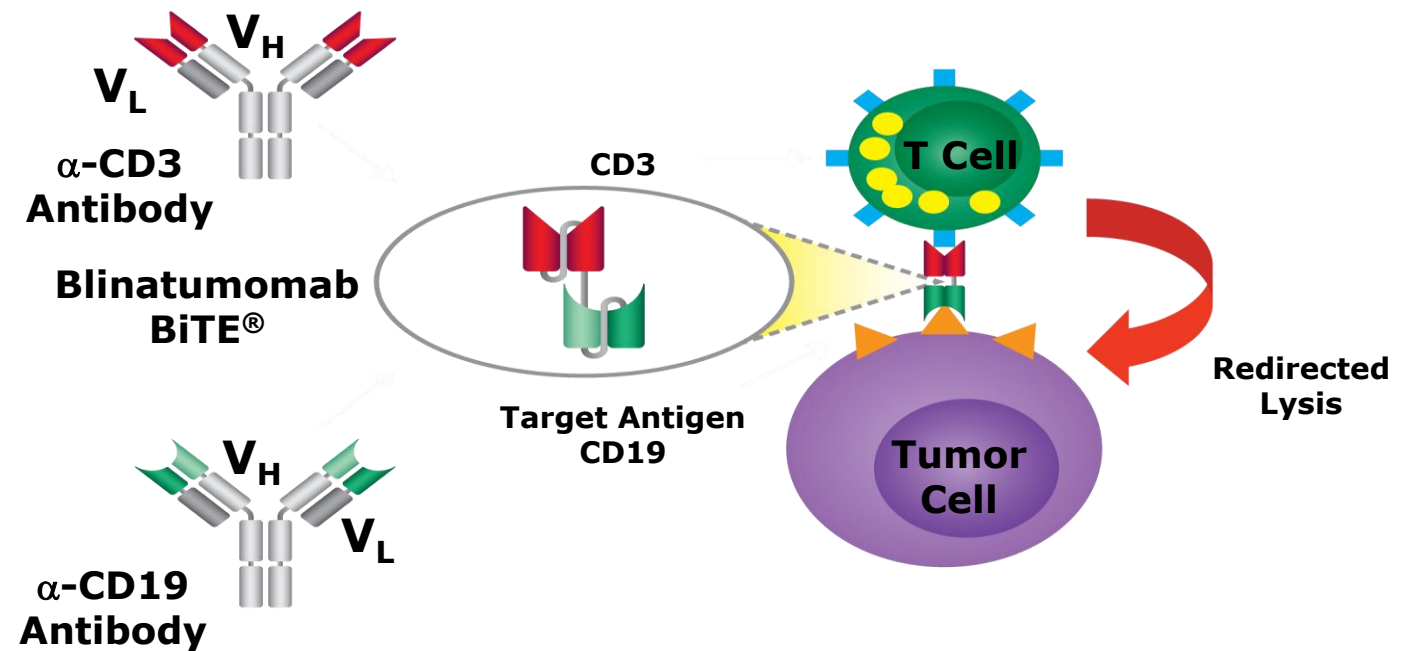


Maude et al. NEJM 2018



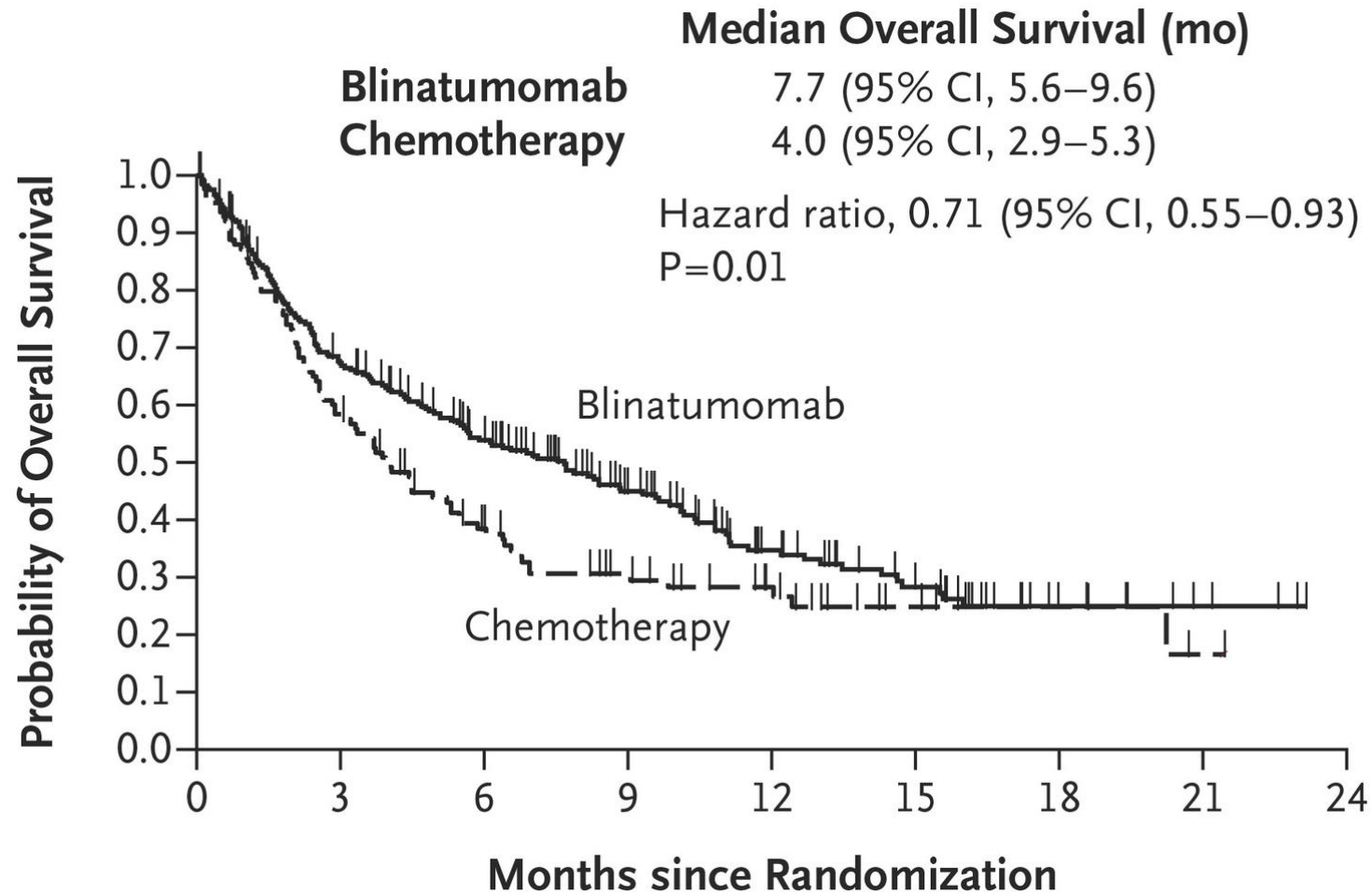
BiTE (Blinatumumab) Therapy

- Combines anti-CD19 F(ab) with anti-CD3 F(ab)
- Lacks the Fc region
- Facilitates T cell engagement with CD19+ tumor cells (Similar to CD19 CAR T)
- FDA approval: Patients with relapsed/refractory B cell precursor ALL



Bargou et al. Science 2008

Blinatumomab for B-ALL



Kantarjian et al. NEJM 2017

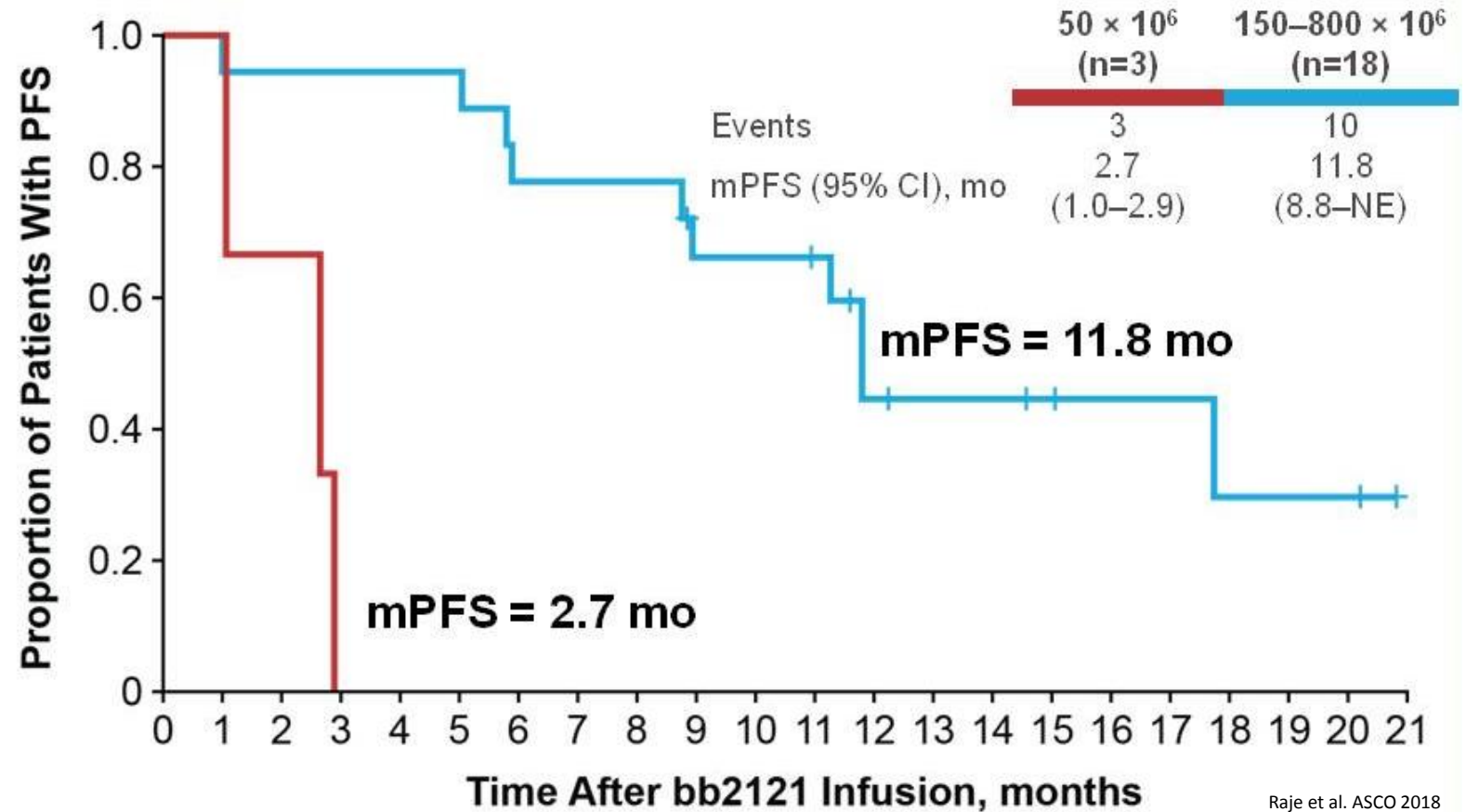
Immunotherapies for Multiple Myeloma

- No approved checkpoint inhibitors
 - KEYNOTE-183/185/023: Halted or discontinued due to risk/benefit profile
- Vaccine-based approaches
 - Non-antigen Specific
 - Attenuated measles
 - Whole cell – FM-CSF
 - Dendritic – tumor fusions
 - Antigen Specific
 - Idiotypic: RNA < DNA, protein
 - Pulsed dendritic cells
 - Tumor-specific peptides

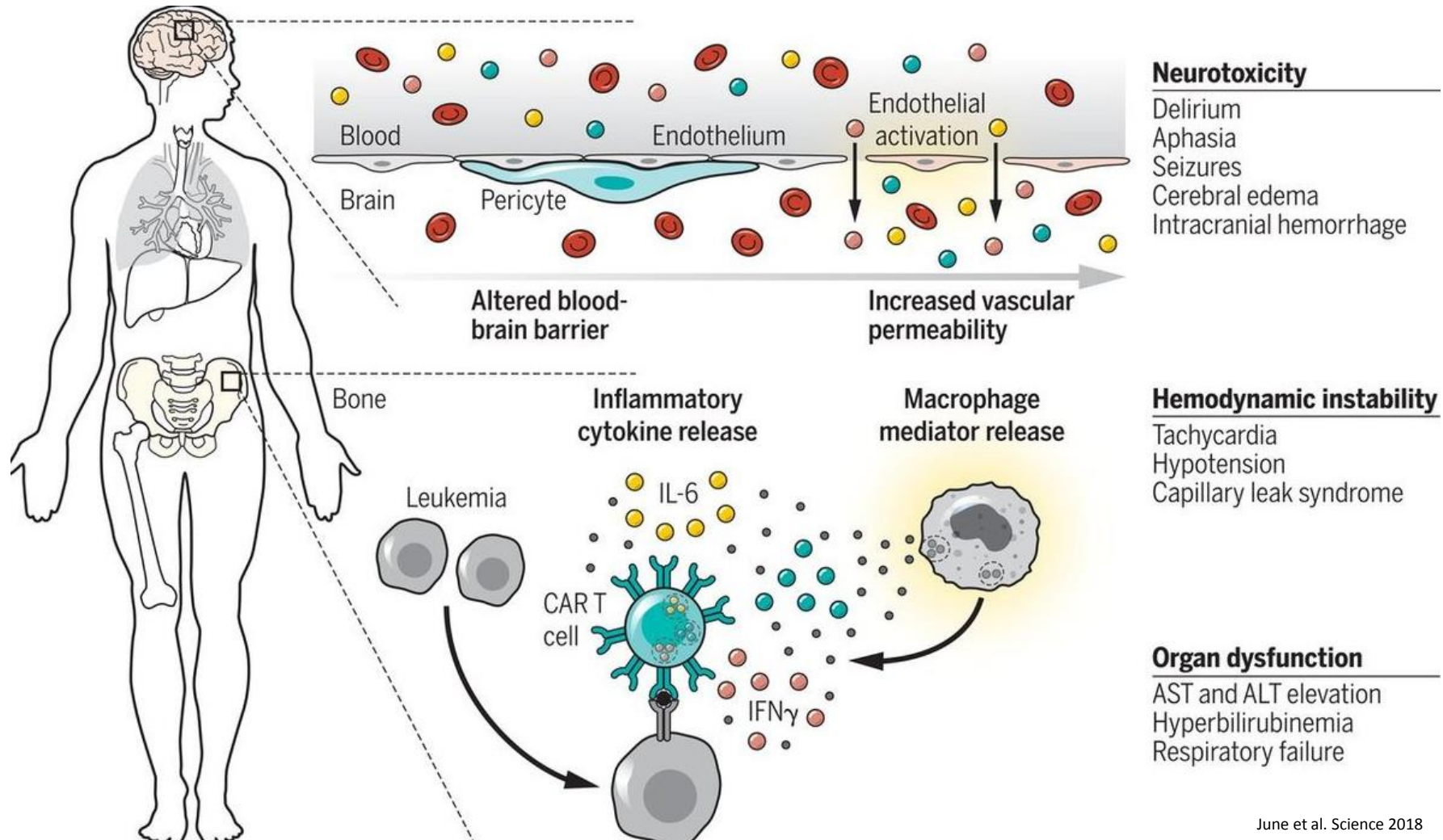


In Development: BCMA+ CAR T Therapy for Myeloma

- **bb2121**
 - B cell maturation antigen (BCMA)
 - Phase I CRB-401 study
 - Previously treated patients with relapsed/refractory multiple myeloma

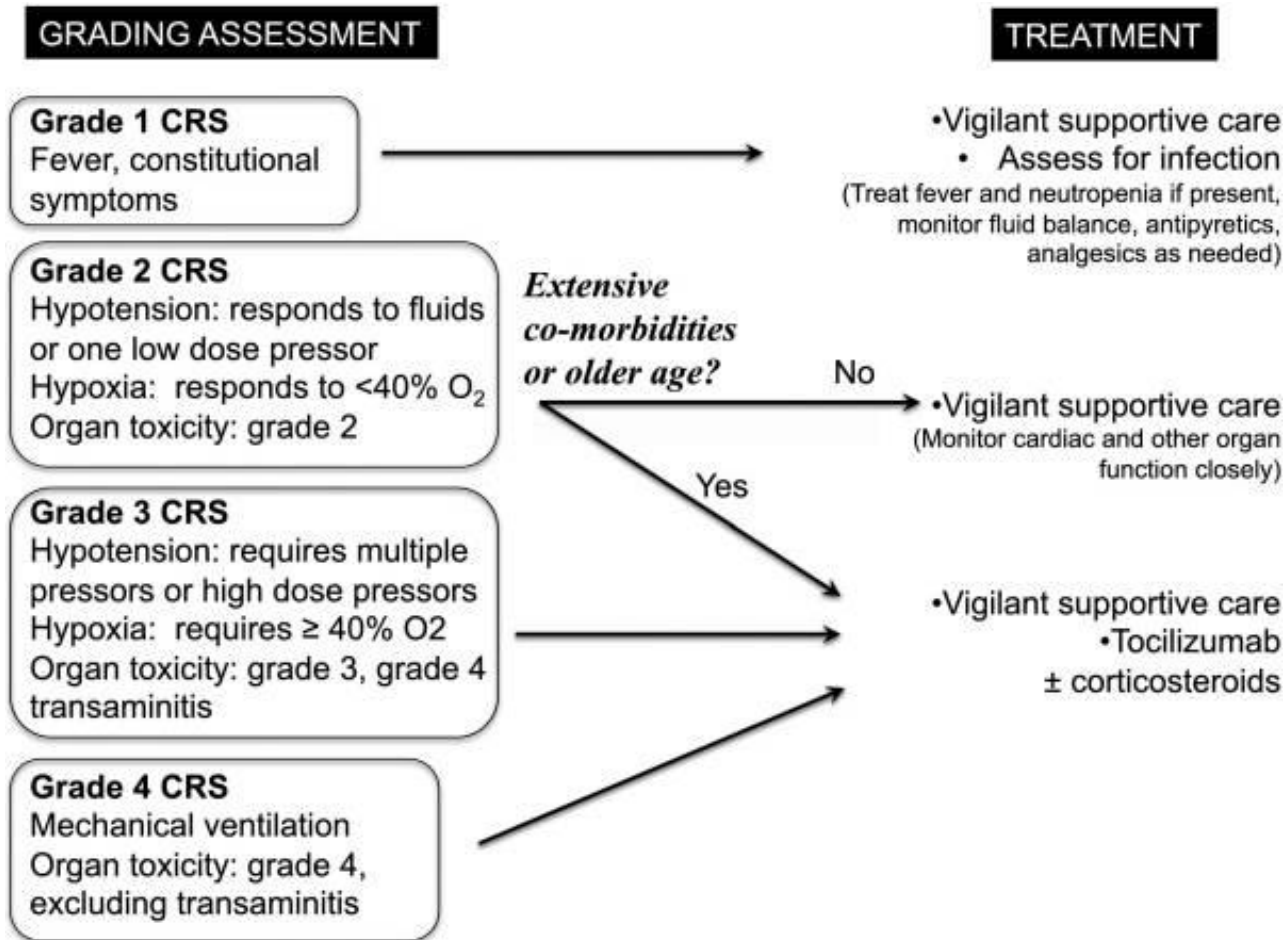


Cytokine Release Syndrome (CRS)



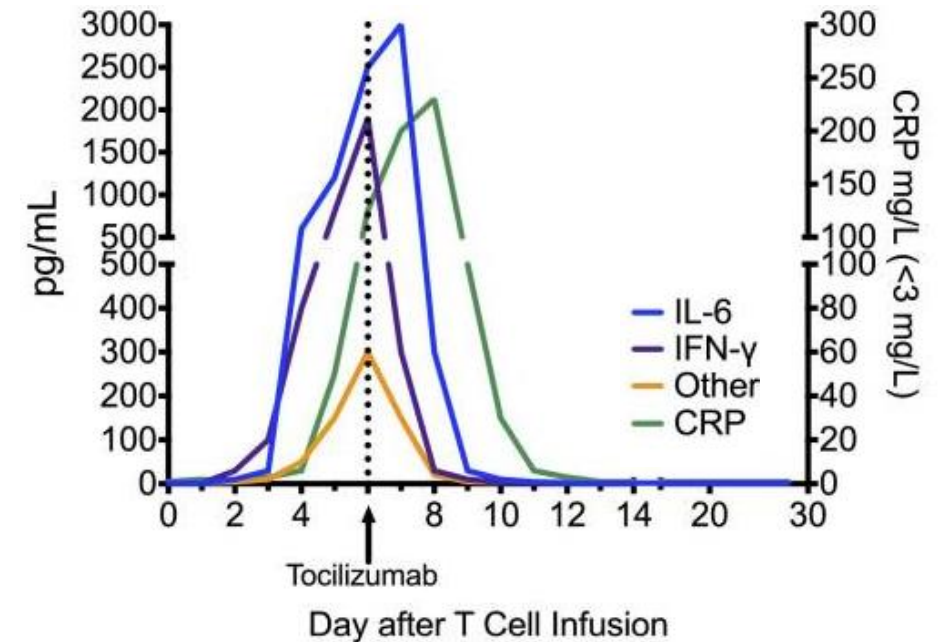
June et al. Science 2018

CRS management



Lee et al. Blood 2014

- Tocilizumab
- Monoclonal antibody that blocks IL-6 signaling



Further Resources

Boyiadzis et al. *Journal for Immunotherapy of Cancer* (2016) 4:90
DOI 10.1186/s40425-016-0188-z

Journal for Immunotherapy
of Cancer

POSITION ARTICLE AND GUIDELINES

Open Access



The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of hematologic malignancies: multiple myeloma, lymphoma, and acute leukemia

Michael Boyiadzis^{1†}, Michael R. Bishop^{2†}, Rafat Abonour³, Kenneth C. Anderson⁴, Stephen M. Ansell⁵, David Avigan⁶, Lisa Barbarotta⁷, Austin John Barrett⁸, Koen Van Besien⁹, P. Leif Bergsagel¹⁰, Ivan Borrello¹¹, Joshua Brody¹², Jill Brufsky¹³, Mitchell Cairo¹⁴, Ajai Chari¹², Adam Cohen¹⁵, Jorge Cortes¹⁶, Stephen J. Forman¹⁷, Jonathan W. Friedberg¹⁸, Ephraim J. Fuchs¹⁹, Steven D. Gore²⁰, Sundar Jagannath¹², Brad S. Kahl²¹, Justin Kline²², James N. Kochenderfer²³, Larry W. Kwak²⁴, Ronald Levy²⁵, Marcos de Lima²⁶, Mark R. Litzow²⁷, Anuj Mahindra²⁸, Jeffrey Miller²⁹, Nikhil C. Munshi³⁰, Robert Z. Orlowski³¹, John M. Pagel³², David L. Porter³³, Stephen J. Russell⁵, Karl Schwartz³⁴, Margaret A. Shipp³⁵, David Siegel³⁶, Richard M. Stone⁴, Martin S. Tallman³⁷, John M. Timmerman³⁸, Frits Van Rhee³⁹, Edmund K. Waller⁴⁰, Ann Welsh⁴¹, Michael Werner⁴², Peter H. Wiernik⁴³ and Madhav V. Dhodapkar^{44*}

Case Studies

Case Study 1

- 40 year old man with Aggressive DLBCL
 - R-CHOP → relapsed
 - R-GDP → auto transplant
 - Relapse 4 months later
- Admitted to receive anti-CD19 CAR T cells

Case Study 1

- On day 3, he developed fever, hypotension, and required oxygen through high flow nasal cannula. He received fluids, broad-spectrum antibiotics and tocilizumab.
- By day 5, he was doing much better.
- On day 8, he became aphasic and later on developed seizures.
- CT scan of head was normal.

Neurological Toxicity

- Onset: early, delayed, or without CRS
- 88% occur within the first 8 weeks
- Can include encephalopathy, delirium, anxiety, dizziness, headache, peripheral neuropathy, sleep disorders, seizures, mutism, and aphasia
- Neurological work up
- Supportive care +/- tocilizumab +/- steroids
- No driving or hazardous activities for 8 weeks

Case Study 2

- 30 year-old male with no MPH diagnosed with Stage IV Hodgkin lymphoma
- TREATMENT HISTORY
 - 6 cycles of ABVD → CR
 - Relapsed → ASCT
 - Relapsed → Anti-PD-1 blockade

Patient Develops New Symptoms

- Headache
- Fatigue
- Dizziness with standing

What is the differential?

- A. ?
- B. ?
- C. ?
- D. ?

What is the differential?

- A. Progressive disease with CNS involvement
- B. Hypophysitis
- C. Adrenal insufficiency alone
- D. Dehydration

What are your next steps?

What are your next steps?

- Vitals: Orthostatic hypotension
- Physical exam: Pale
 - ADMIT PATIENT

Work-Up Shows...

- Low TSH
- Low ACTH
- Low LH
- Brain MRI: a swollen pituitary gland is seen
- Now what should you do?

Management

- STOP immunotherapy
- Endocrine consult:
 - High-dose glucocorticoids, levothyroxine, and sex hormone replacement
- Almost all patients experienced resolution of acute symptoms within a few days

I can rechallenge patient with anti-PD-a therapy

- True
- False

I can rechallenge patient with anti-PD-a therapy

- True
- False