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ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Hematologic Malignancies

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Disclosures

- **Consultancy:** Abbvie, Genentech, Sound Biologics
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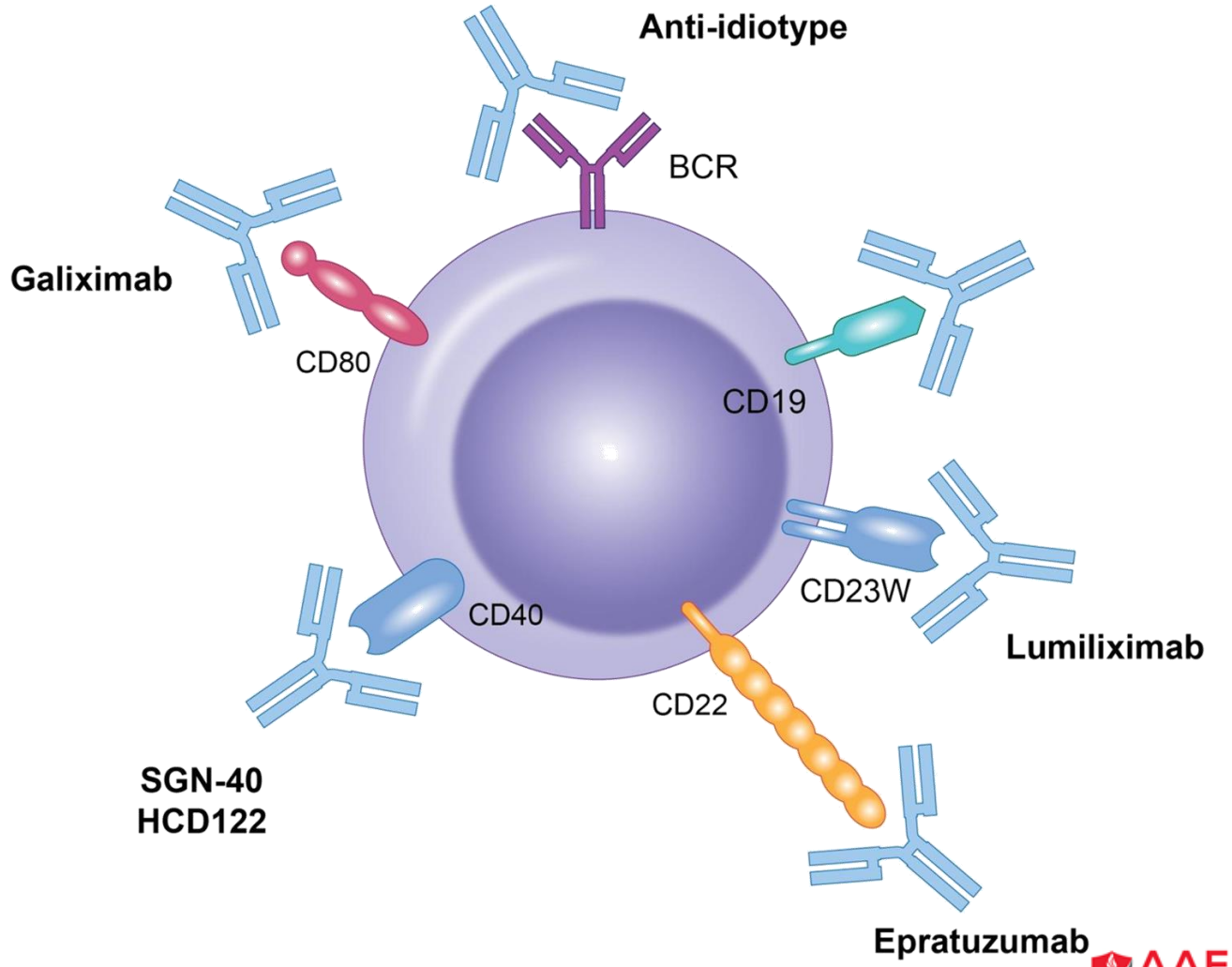
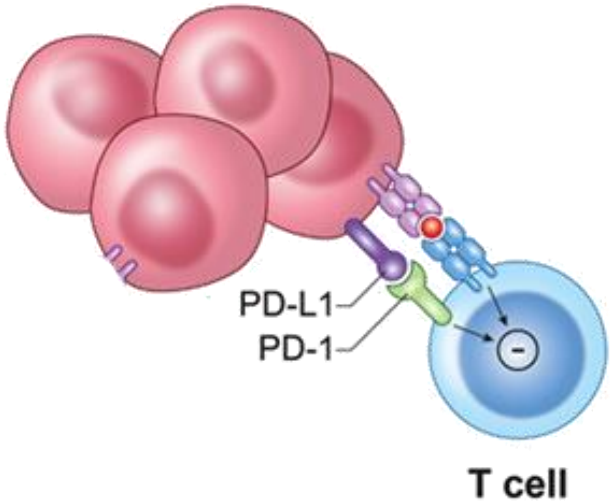
Monoclonal Antibodies Targeting B Cell Lymphomas



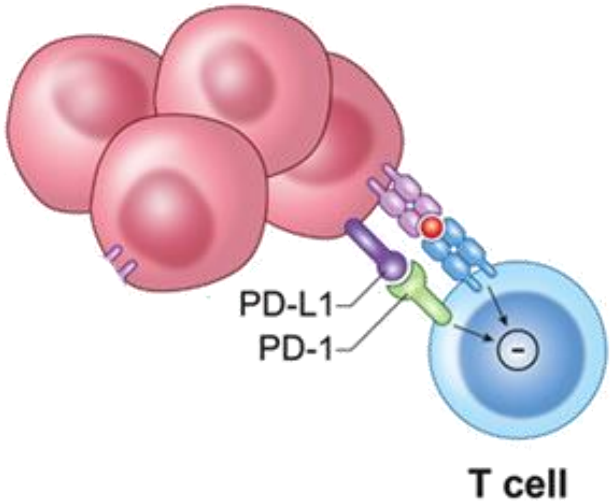
FDA-approved Checkpoint Inhibitors for Lymphomas

- 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



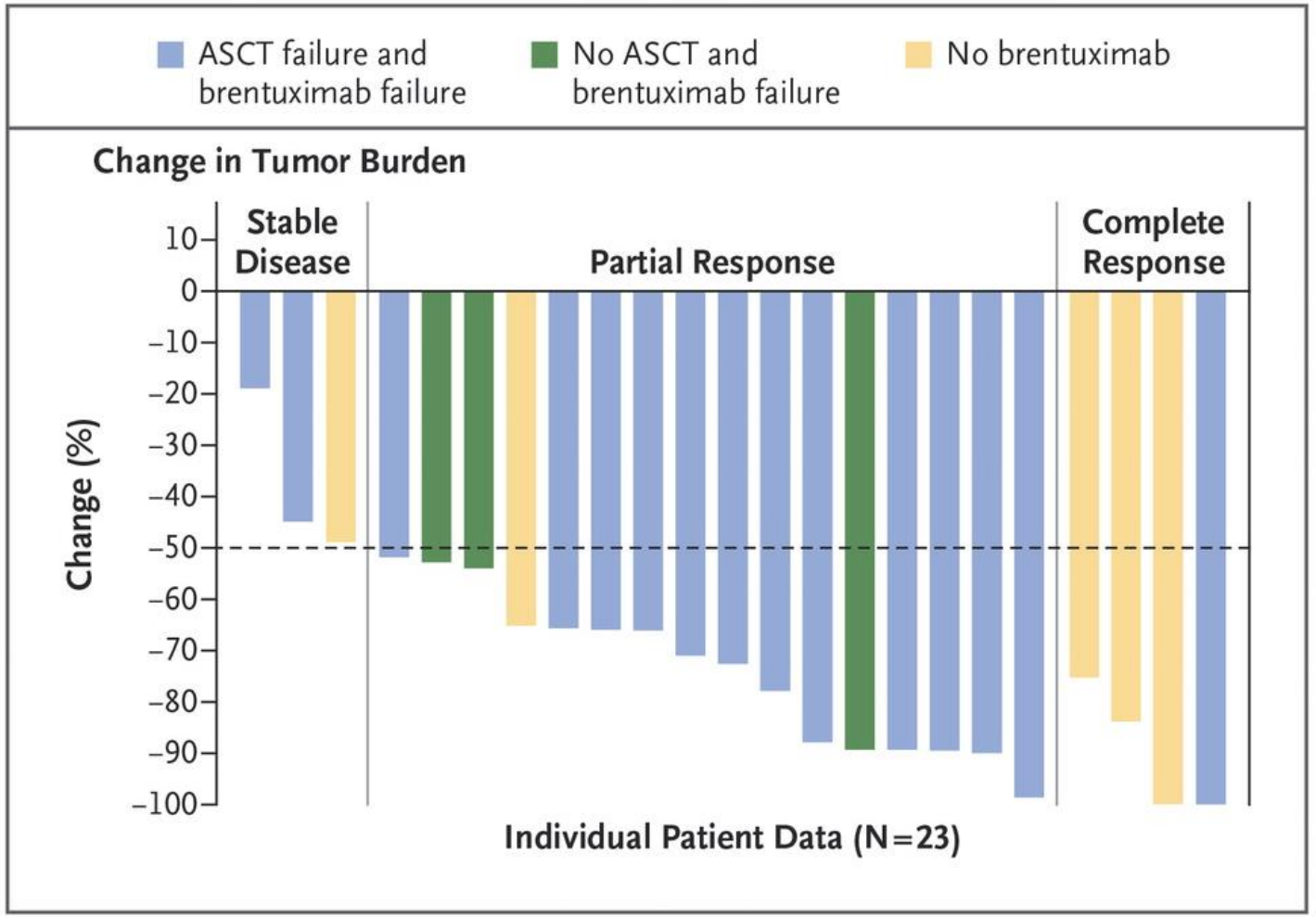
Nivolumab in Hodgkin Lymphoma

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

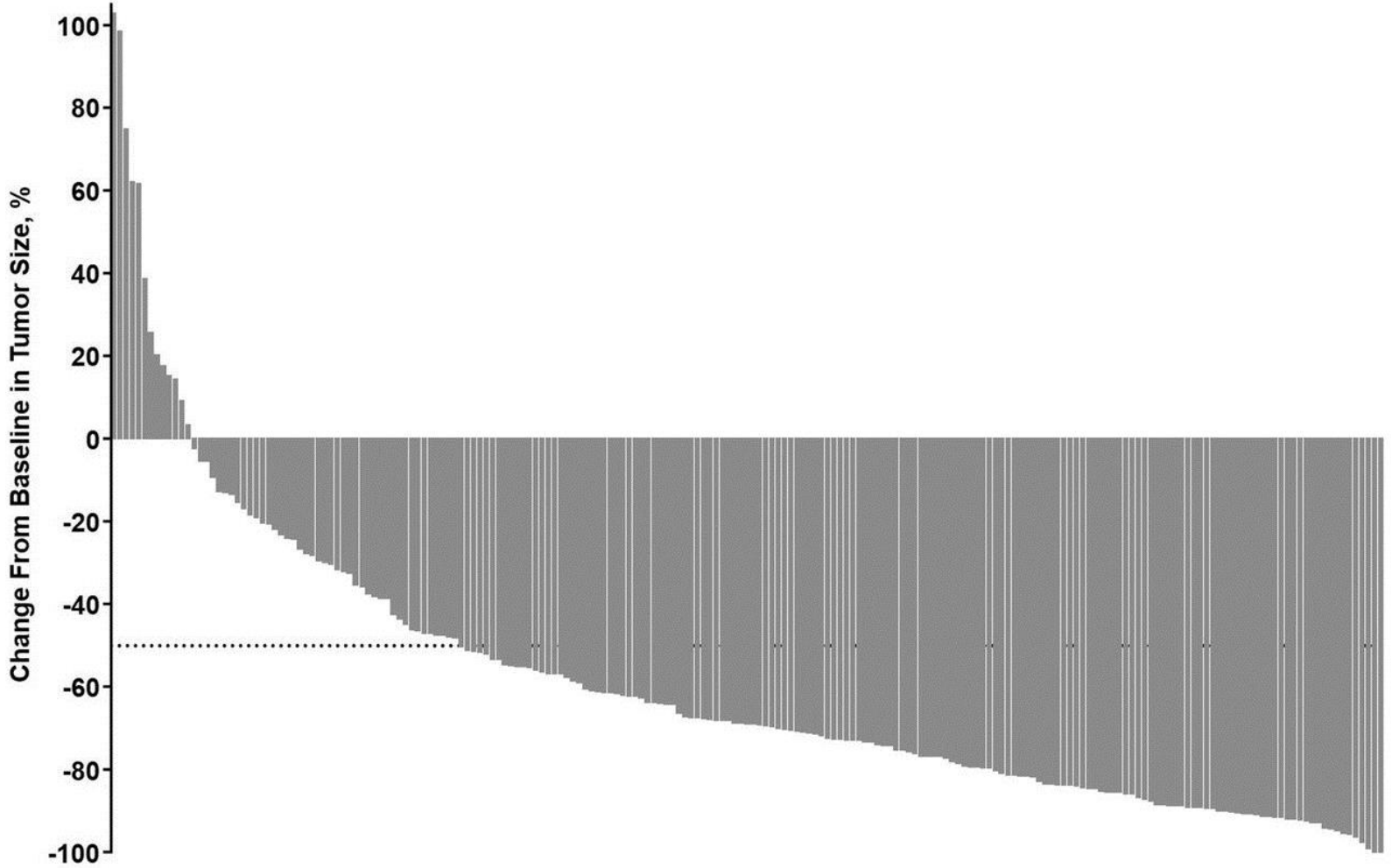
Ansell et al. NEJM 2015

Nivolumab in Hodgkin Lymphoma



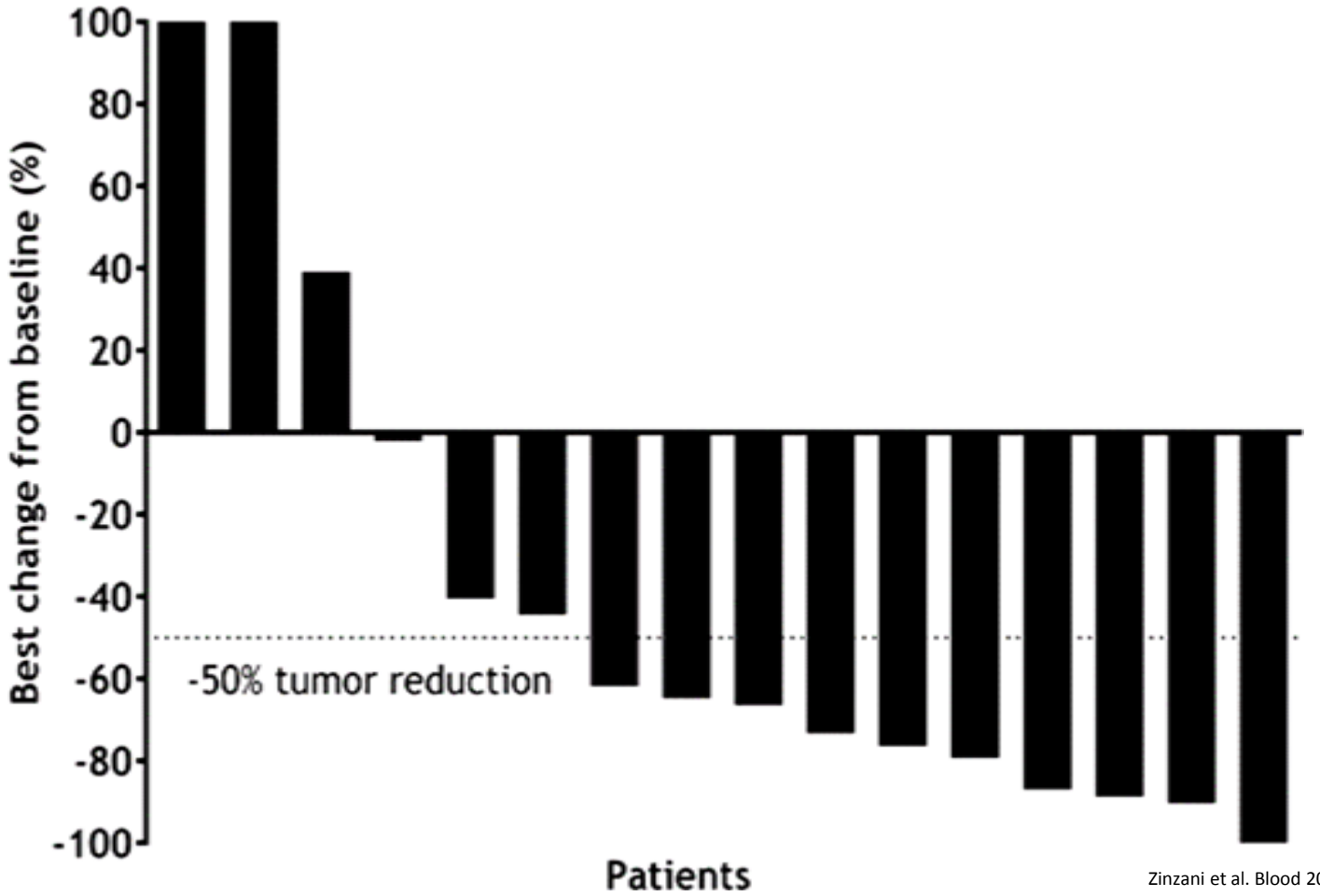
Ansell et al. NEJM 2015

Pembrolizumab in Hodgkin Lymphoma



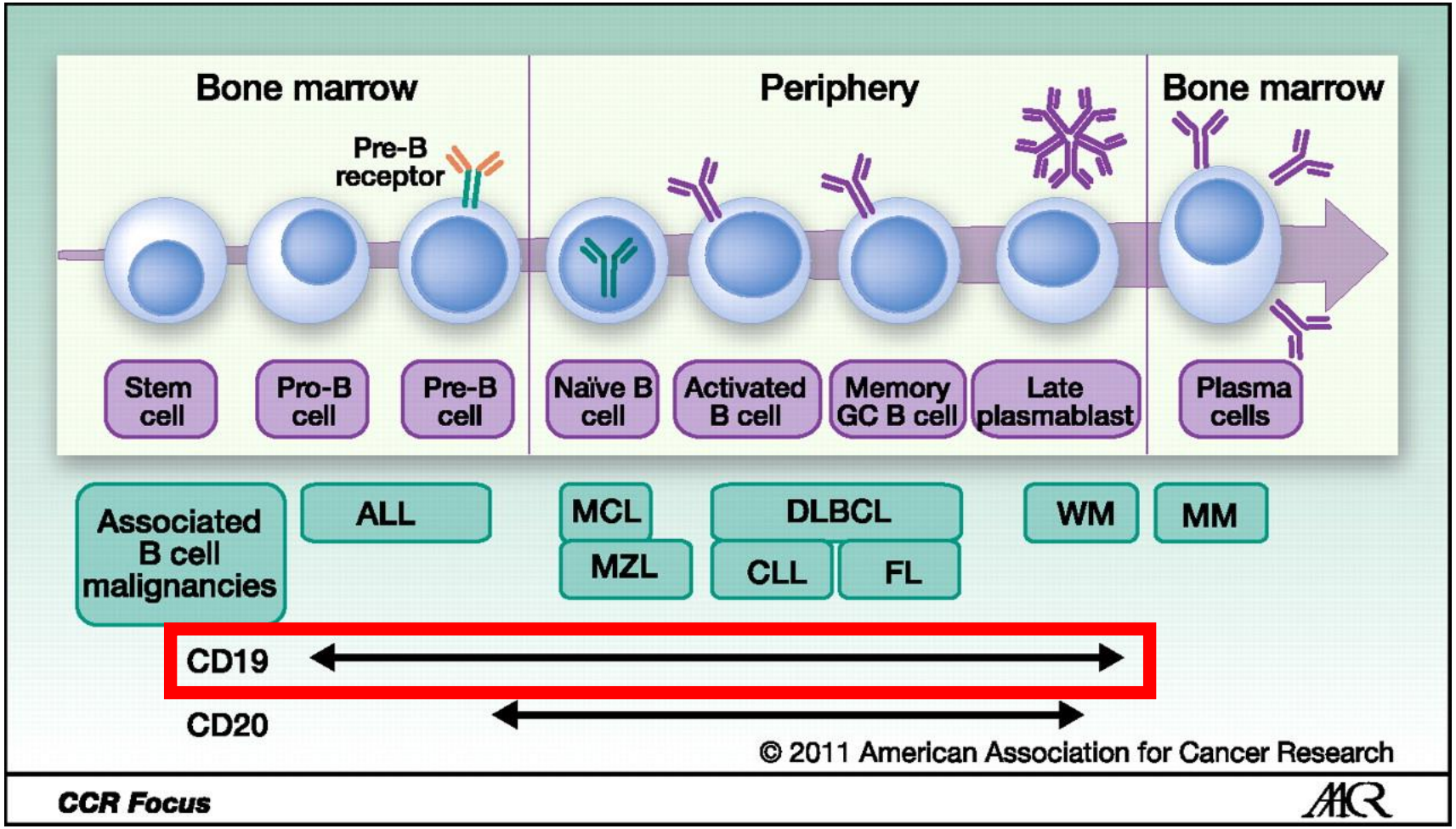
Zinzani et al. Hematological Oncology 2017

Pembrolizumab in Primary Mediastinal Large B cell Lymphoma



Zinzani et al. Blood 2016

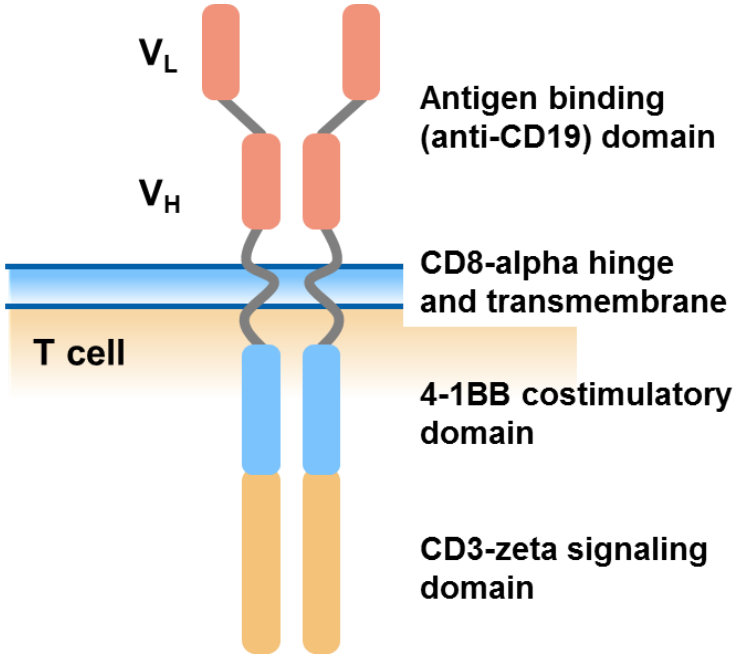
B Cell Malignancies are CD19+

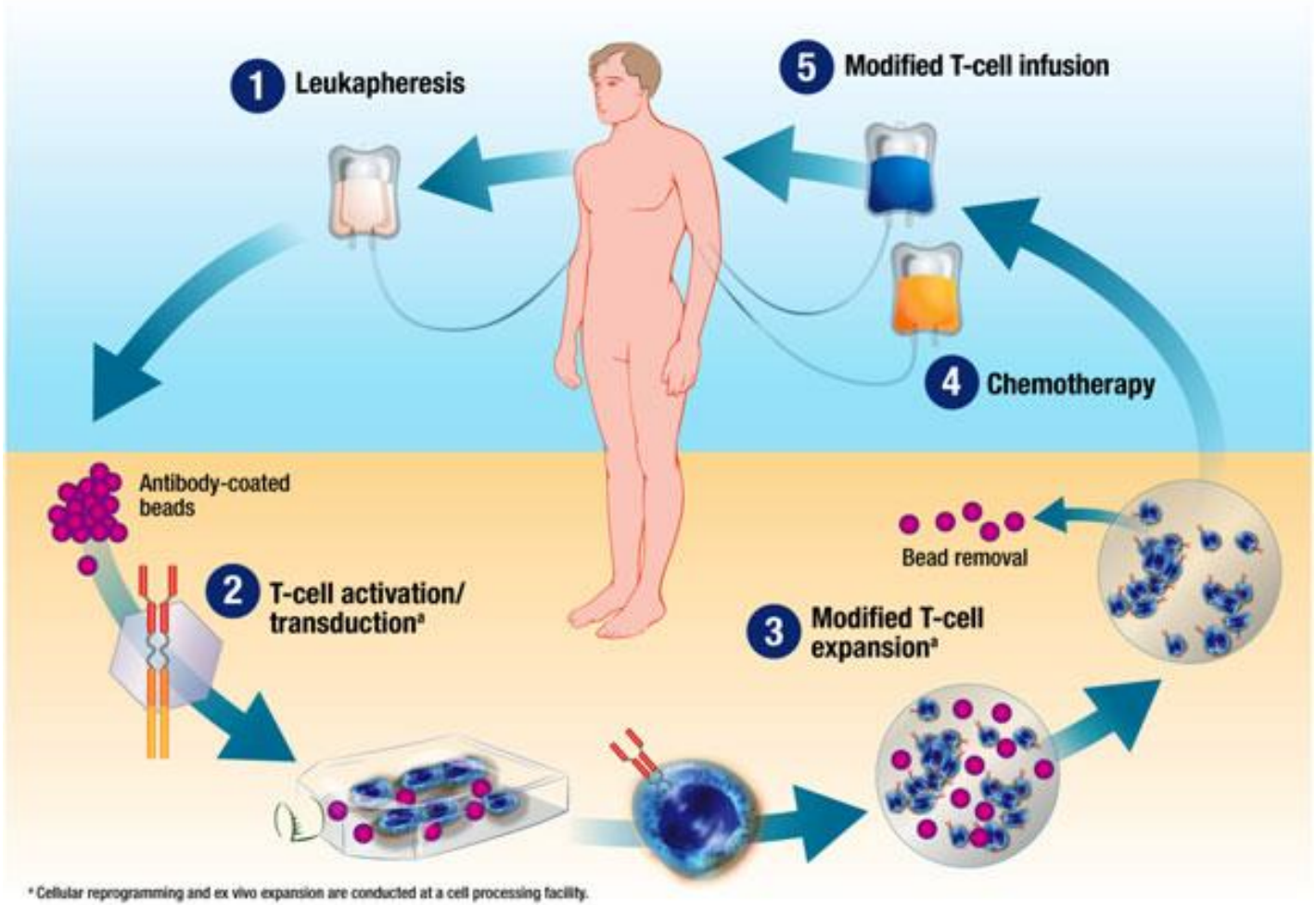


Blanc et al. Clinical Cancer Research 2011

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

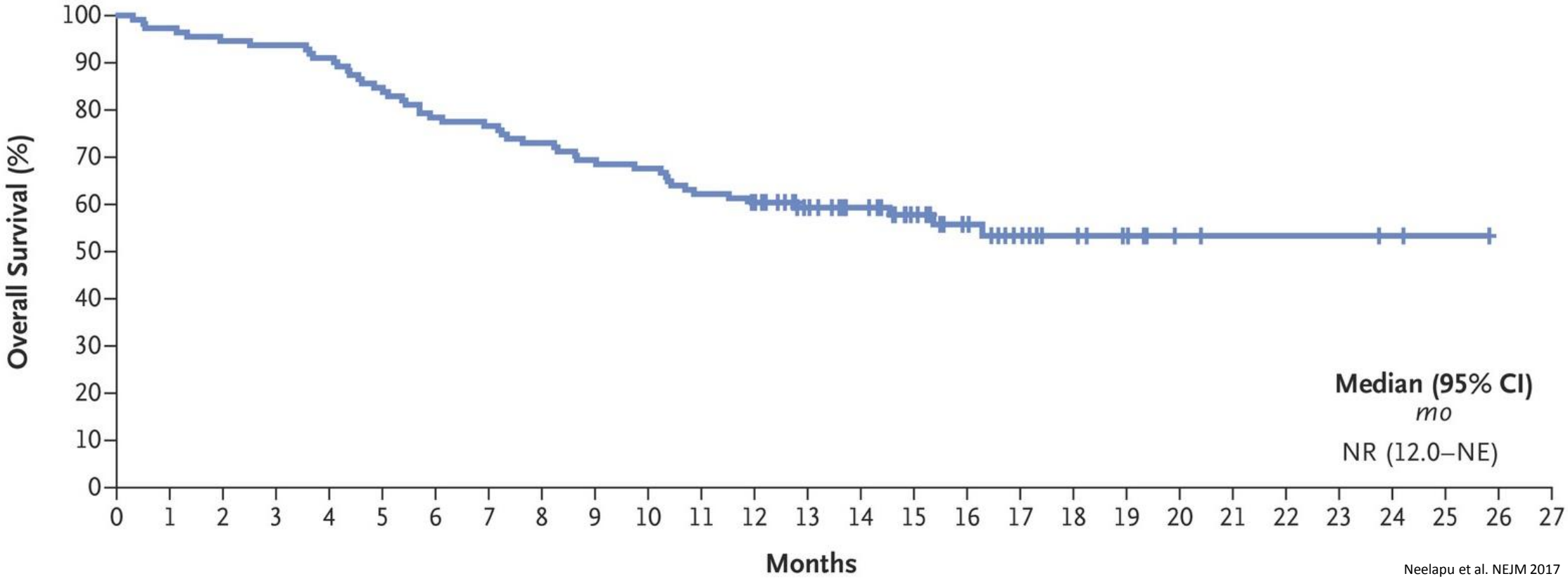
- Axicabtagene ciloleucel
  - ZUMA-1: Adult patients with relapsed or refractory large B cell lymphoma after two or more lines of systemic therapy, including diffuse large B cell lymphoma, high-grade B cell lymphoma, and DLBCL arising from follicular lymphoma
- Tisagenlecleucel
  - JULIET: adult patients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

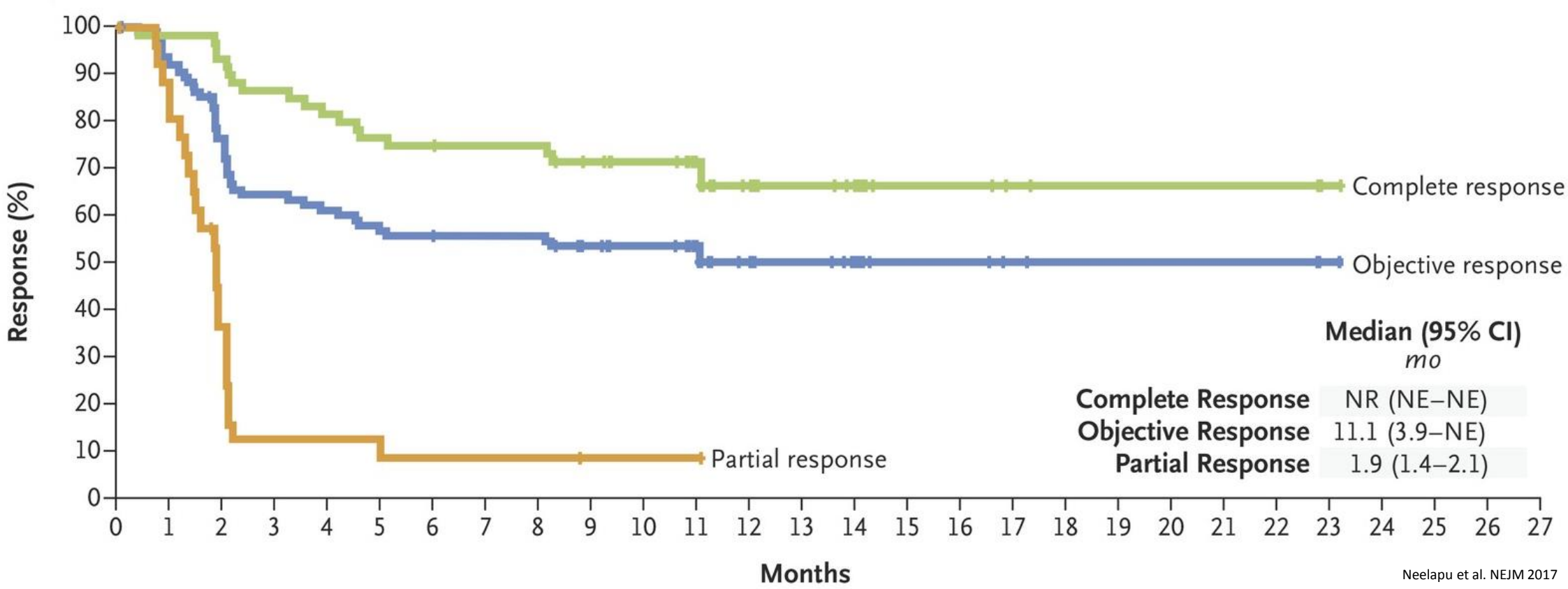
Overall Survival



Neelapu et al. NEJM 2017

Axicabtagene ciloleucel in B Cell Lymphoma

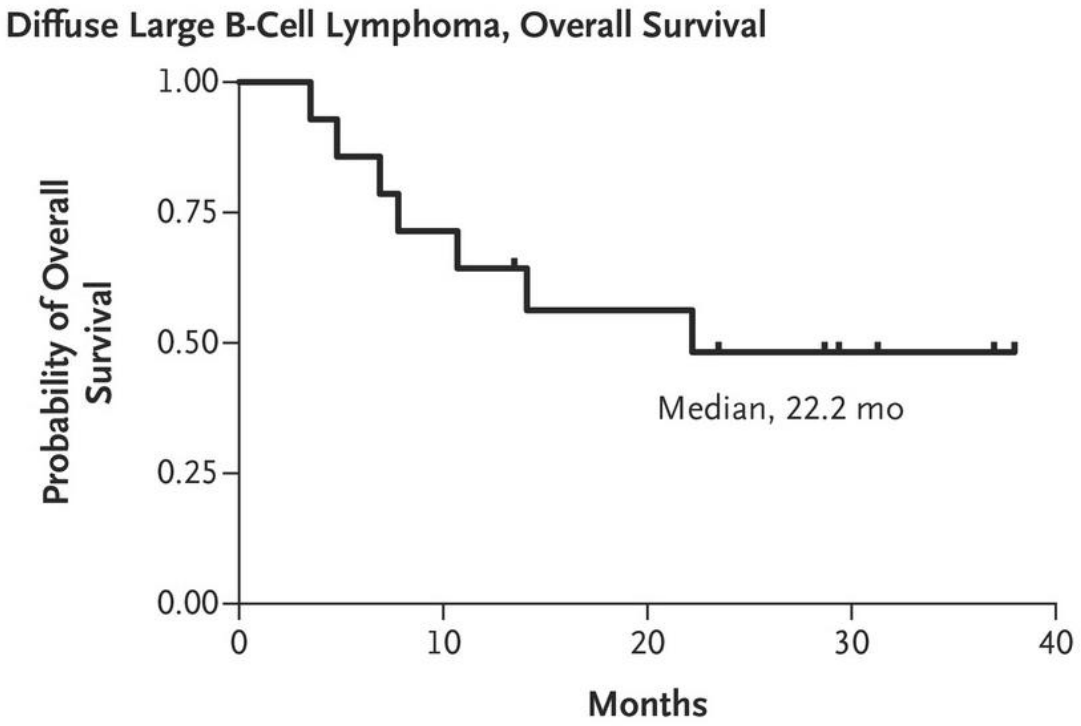
Duration of Response

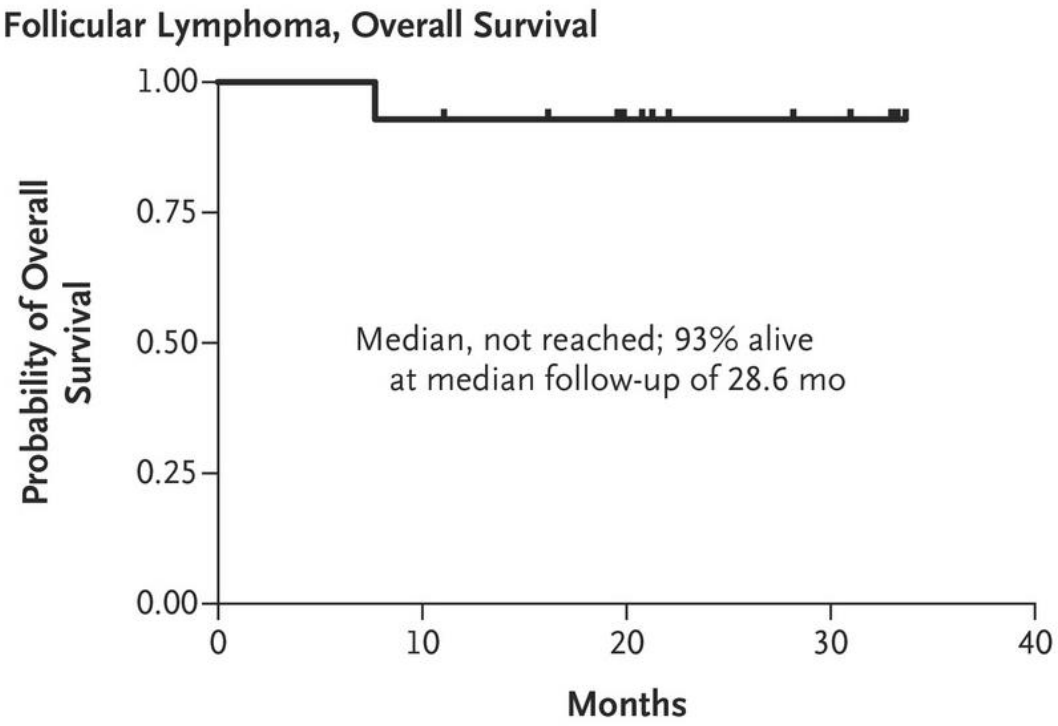


Neelapu et al. NEJM 2017

Tisagenlecleucel in B Cell Lymphoma

Overall Survival

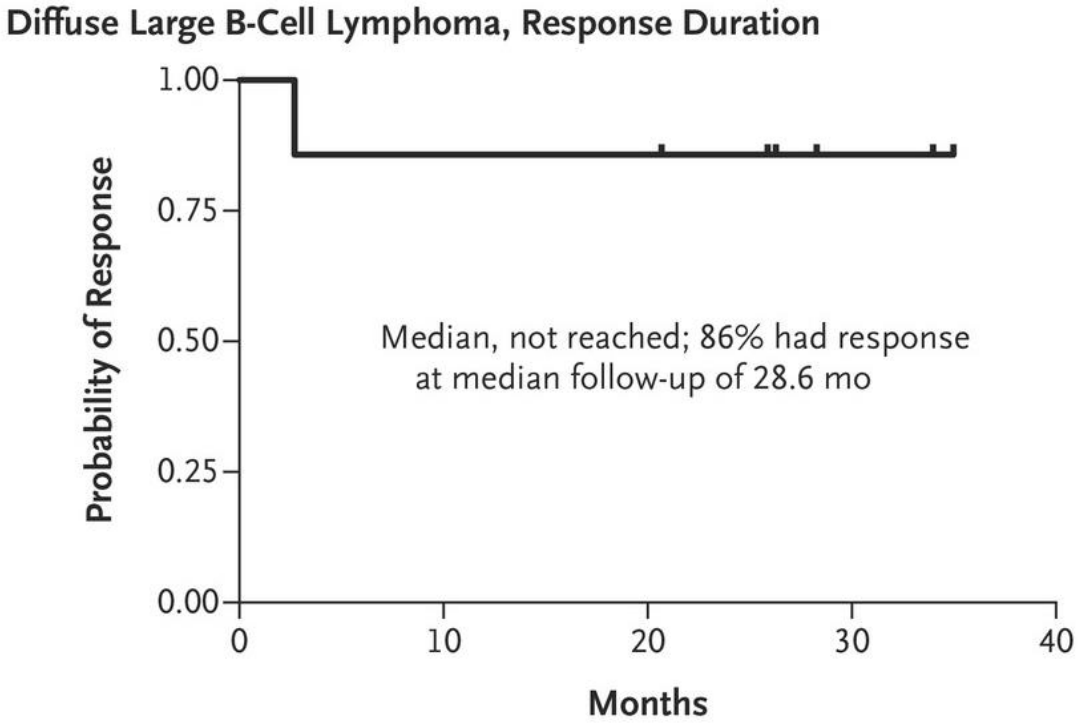


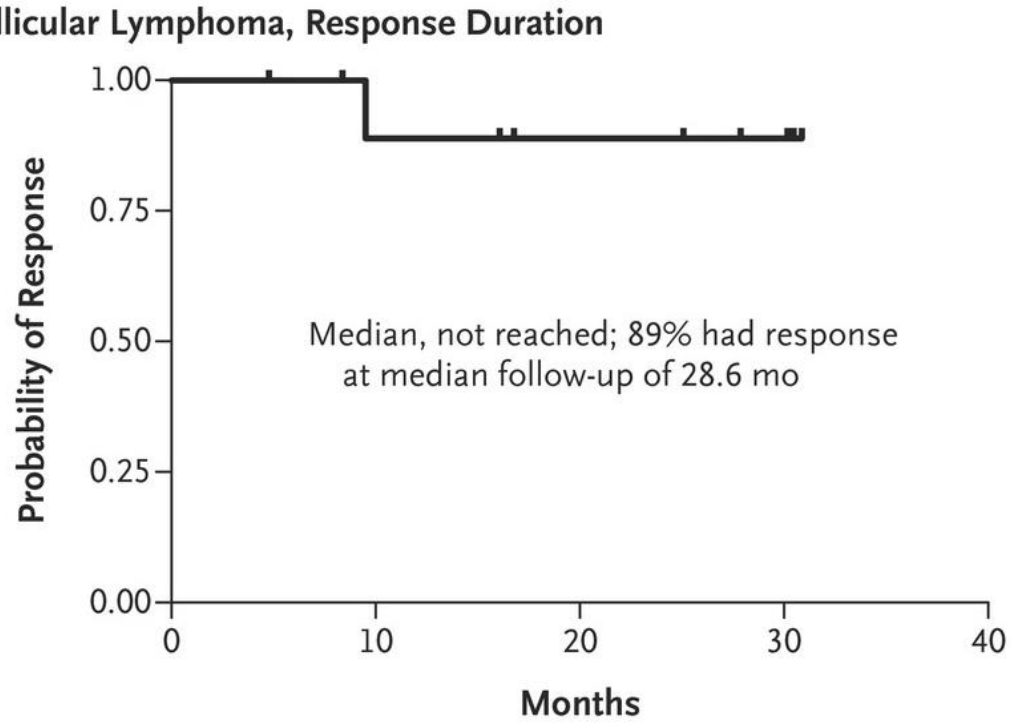


Schuster et al. NEJM 2017

Tisagenlecleucel in B Cell Lymphoma

Duration of Response



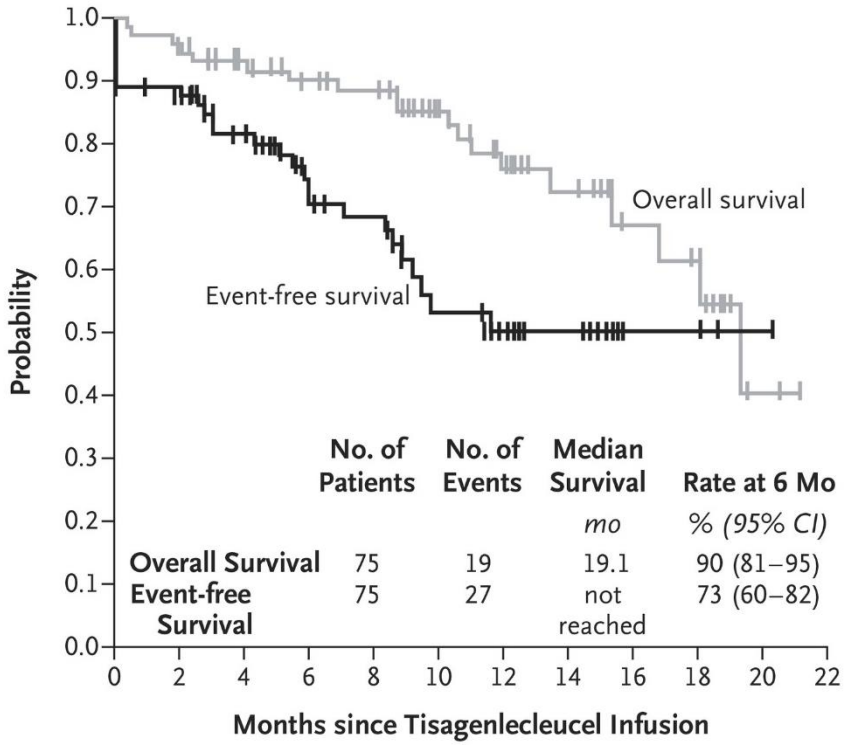


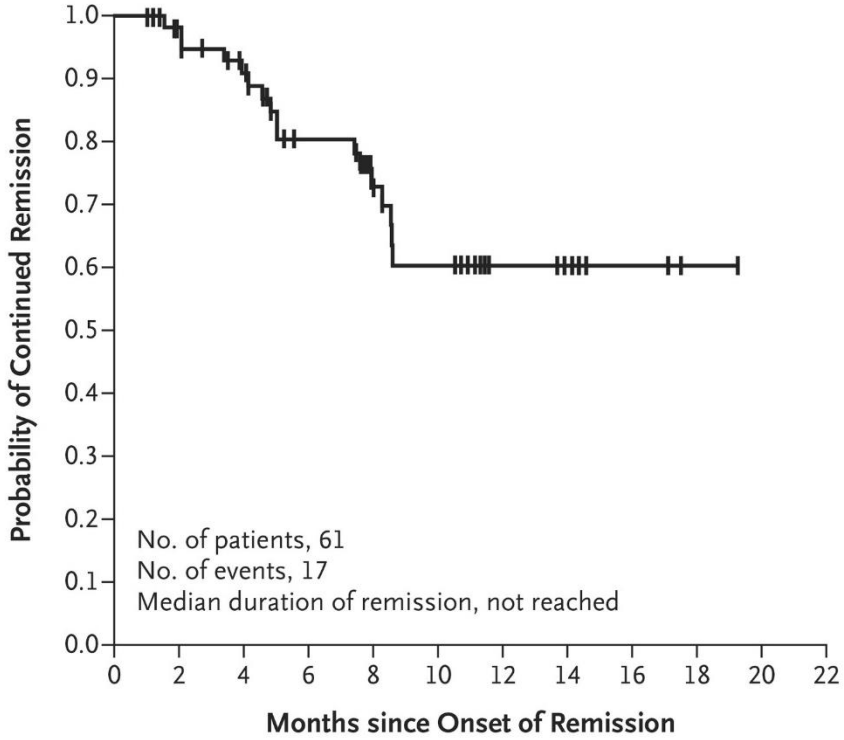
Schuster et al. NEJM 2017

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

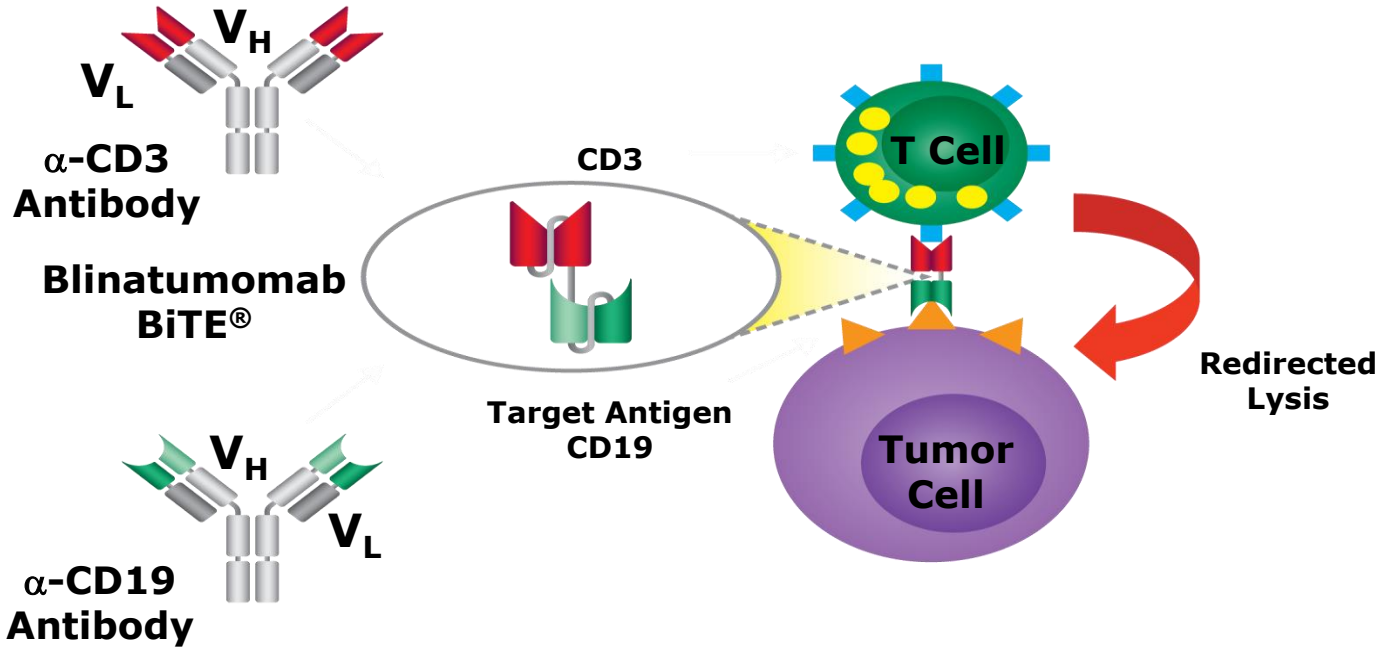




Maude et al. NEJM 2018

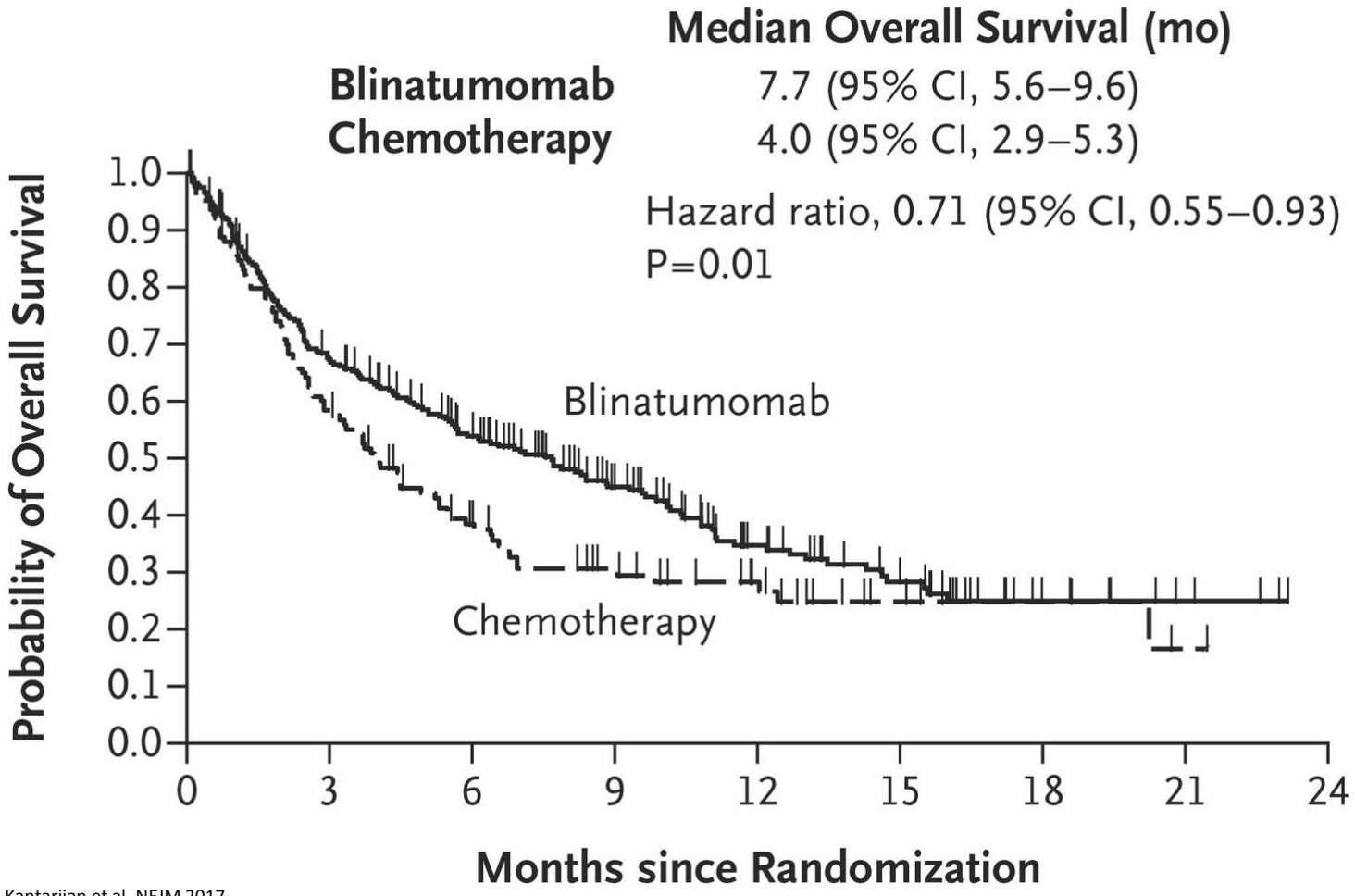
BiTE (Blinatumumab) Therapy

- 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

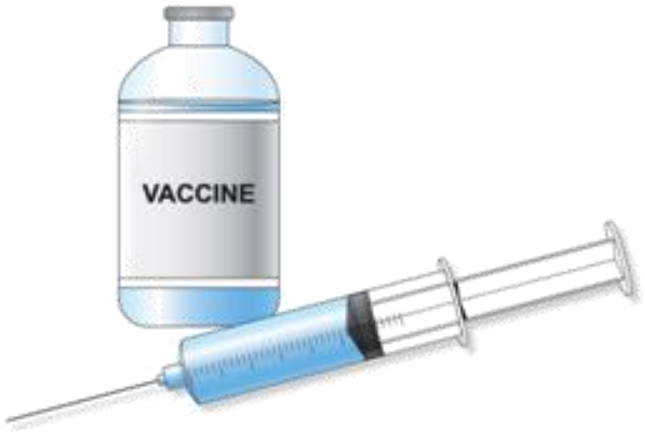
Blinatumomab for B-ALL



Kantarjian et al. NEJM 2017

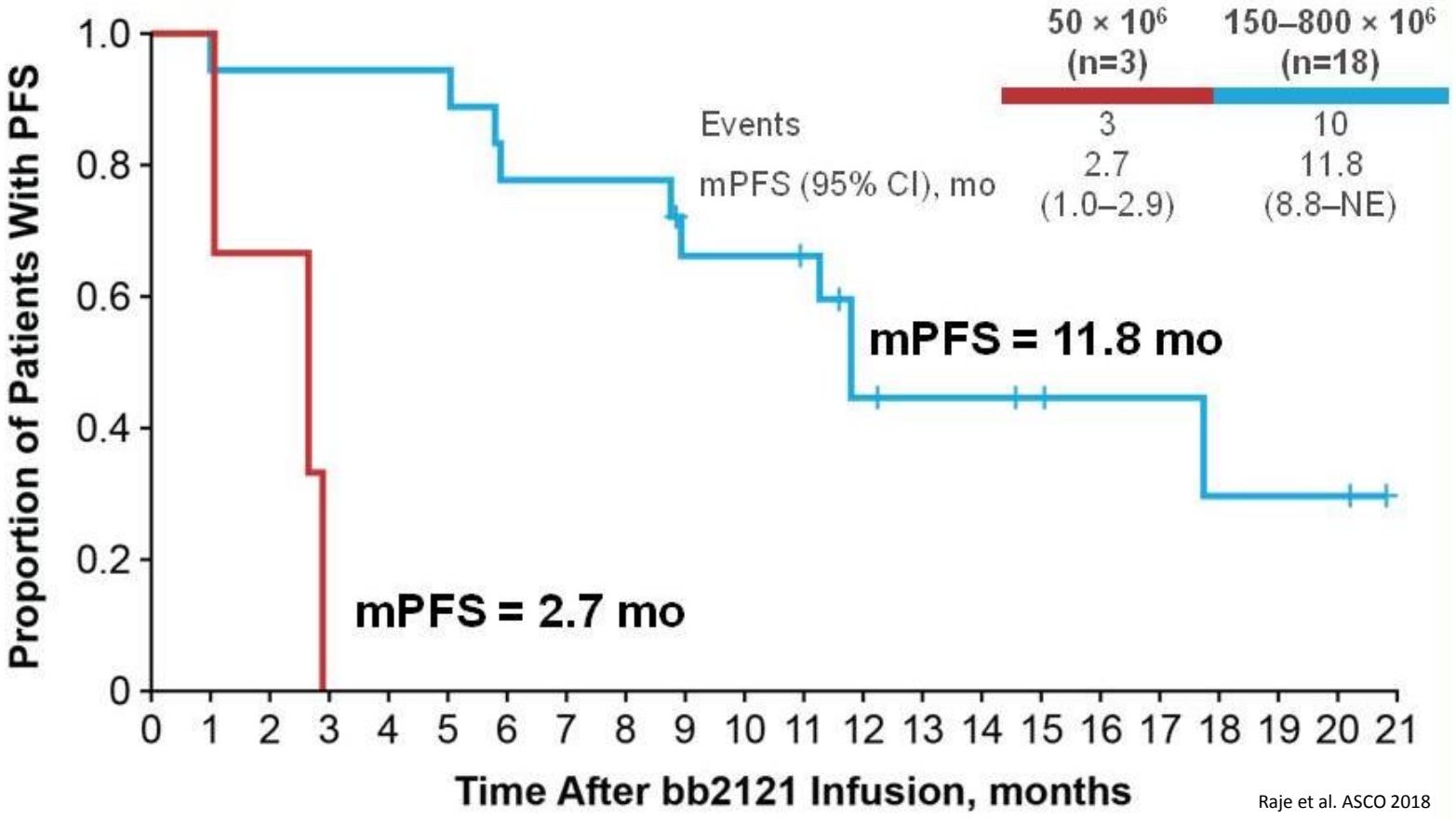
Immunotherapies for Multiple Myeloma

- 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
    - Idiotype: RNA < DNA, protein
    - Pulsed dendritic cells
    - Tumor-specific peptides



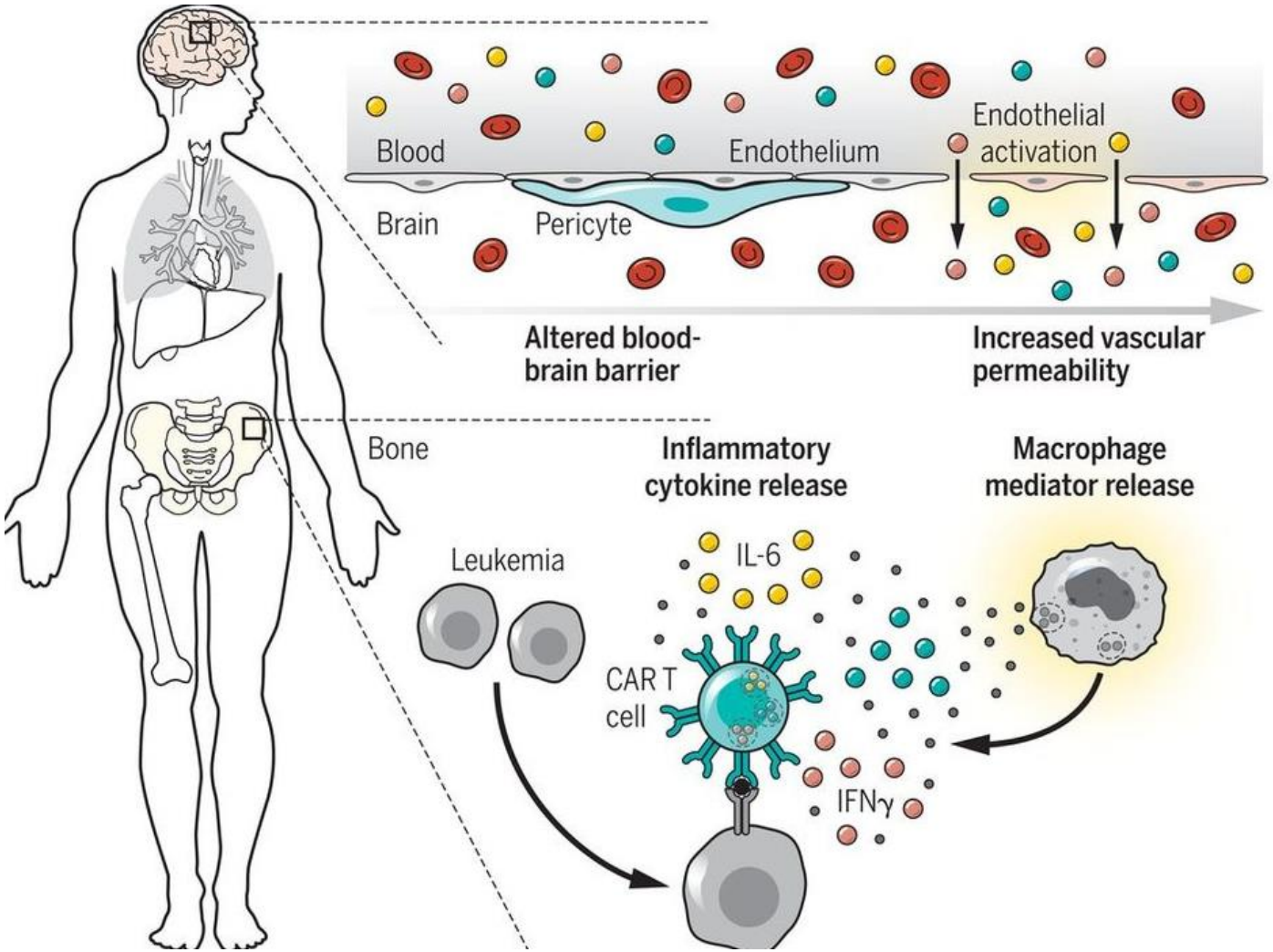
In Development: BCMA+ CAR T Therapy for Myeloma

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



Raje et al. ASCO 2018

Cytokine Release Syndrome (CRS)



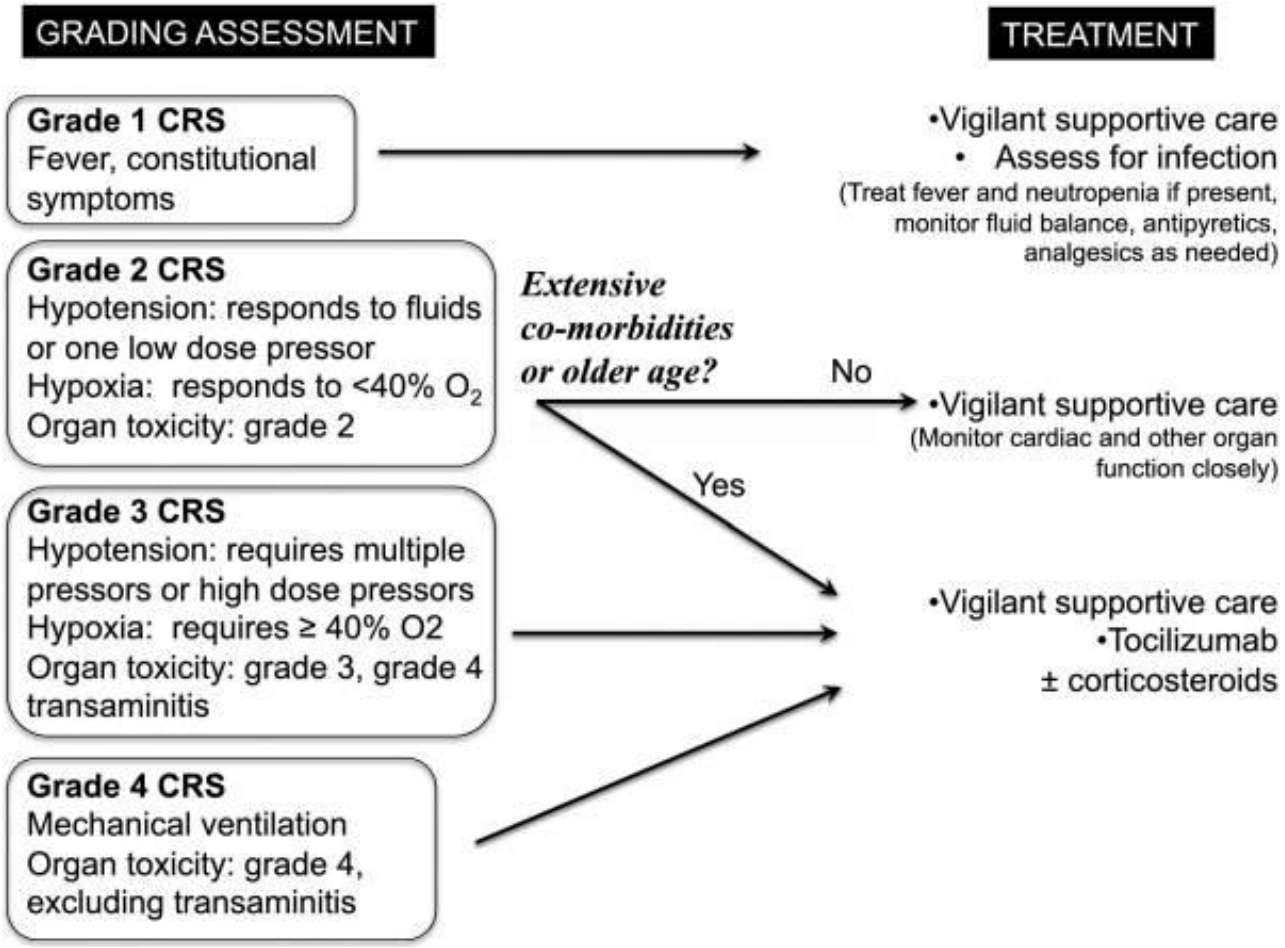
Neurotoxicity
Delirium
Aphasia
Seizures
Cerebral edema
Intracranial hemorrhage

Hemodynamic instability
Tachycardia
Hypotension
Capillary leak syndrome

Organ dysfunction
AST and ALT elevation
Hyperbilirubinemia
Respiratory failure

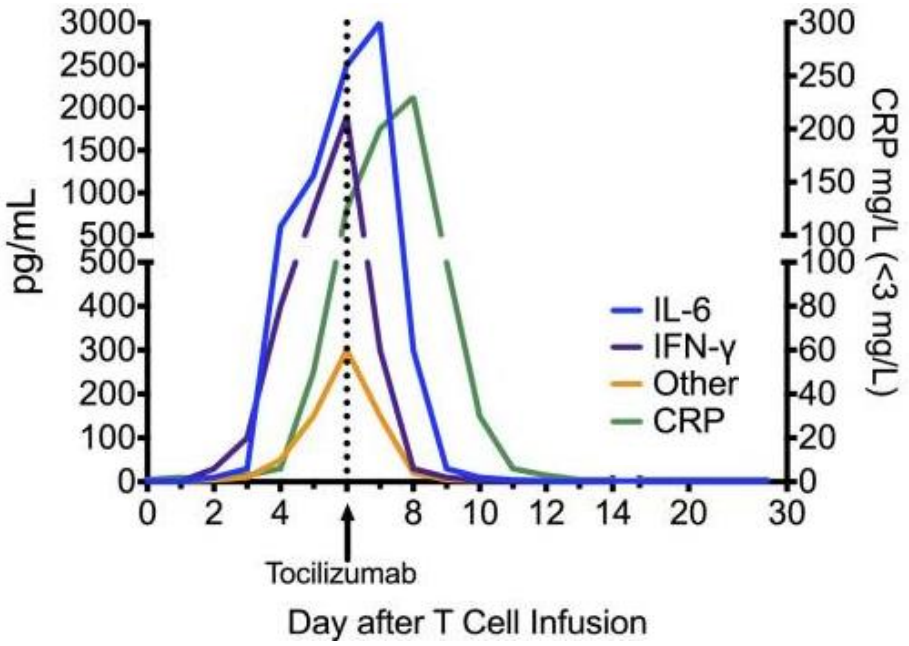
June et al. Science 2018

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 Abonour[3], Kenneth C. Anderson[4], Stephen M. Ansell[5], David Avigan[6], Lisa Barbarotta[7], Austin John Barrett[8], Koen Van Besien[9], P. Leif Bergsagel[10], Ivan Borrello[11], Joshua Brody[12], Jill Brufsky[13], Mitchell Cairo[14], Ajai Chari[12], Adam Cohen[15], Jorge Cortes[16], Stephen J. Forman[17], Jonathan W. Friedberg[18], Ephraim J. Fuchs[19], Steven D. Gore[20], Sundar Jagannath[12], Brad S. Kahl[21], Justin Kline[22], James N. Kochenderfer[23], Larry W. Kwak[24], Ronald Levy[25], Marcos de Lima[26], Mark R. Litzow[27], Anuj Mahindra[28], Jeffrey Miller[29], Nikhil C. Munshi[30], Robert Z. Orlowski[31], John M. Pagel[32], David L. Porter[33], Stephen J. Russell[5], Karl Schwartz[34], Margaret A. Shipp[35], David Siegel[36], Richard M. Stone[4], Martin S. Tallman[37], John M. Timmerman[38], Frits Van Rhee[39], Edmund K. Waller[40], Ann Welsh[41], Michael Werner[42], Peter H. Wiernik[43] and Madhav V. Dhodapkar[44*]

Case 1

A 64 year-old man with a diagnosis of Diffuse Large B-cell Lymphoma (DLBCL), Stage IV, NCCN-IPI 7 (high-risk), Double-hit (MYC and BCL2) presents for a second opinion. He was treated with 6 cycles of DA-R-EPOCH (reached level 4) and achieved a complete remission (CR by Lugano PET criteria). Six months later, noted an enlarging left cervical LN and an excisional biopsy was done and showed relapsed DLBCL (DH).

What is considered to be standard of care next step for this patient?

1. CAR-T therapy with Axicabtagene ciloleucel (axi-cel)
2. CAR-T therapy with Tisagenlecleucel (tisa-cel)
3. CAR-T therapy with lisocabtagene (liso-cel)
4. 1 or 2
5. Salvage chemotherapy treatment (R-ICE, R-GDP, etc)

Indications for CD 19 CAR-T for DLBCL

- **Axicabtagene ciloleucel (axi-cel ; Yescarta):** Treatment of relapsed or refractory large B-cell lymphoma **after 2 or more lines** of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma

- **Tisagenlecleucel (Tisa-cel; Kymriah):**Treatment of relapsed or refractory large B-cell lymphoma in adults (**after 2 or more lines of systemic therapy**), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

A 64 year-old man with a diagnosis of Diffuse Large B-cell Lymphoma (DLBCL), Stage IV, NCCN-IPI 7 (high-risk), Double-hit (MYC and BCL2) presents for a second opinion. He was treated with 6 cycles of DA-R-EPOCH (reached level 4) and achieved a complete remission (CR by Lugano PET criteria). Six months later, noted an enlarging left cervical LN and an excisional biopsy was done and showed relapsed DLBCL (DH).

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3. CAR-T therapy with lisocabtagene (liso-cel)
4. 1 or 2
5. Salvage chemotherapy treatment (R-ICE, R-GDP, etc)

Patient starts salvage treatment with R-ICE. After 2 cycles, a CT scan was done and showed progression of lymphadenopaty in multiple areas. Urgent referral was made for an transplant/immunotherapy consult.

Which one of the following is the most reasonable recommendation for this patient?

1. Axicabtagene ciloleucel (axi-cel)
2. Tisagenlecleucel (tisa-cel)
3. lisocabtagene (liso-cel)
4. 1 or 2
5. Start second salvage and achieve at least a partial response before considering a transplant or CAR-T therapy

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5. Start second salvage and achieve at least a partial response before considering a transplant or CAR-T therapy

When evaluating a patient for the FDA approved CAR-T cell products for DLBCL, which one of the following conditions is a major concern and can potentially exclude the patient for such treatment?

1. Primary CNS Lymphoma
2. HIV-associated lymphoma
3. Rheumatoid arthritis requiring active systemic treatment
4. High disease burden which may require chemotherapy between T-cell collection and lymphodepletion
5. 1,2,3
6. All of the above

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5. 1,2,3
6. All of the above

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Case 2

A 58 year-old man with DLBCL relapsed after autologous stem cell transplant is in hospital after receiving CAR-T cells (axicabtagene ciloleucel). His lymphodepletion included fludarabine (30 mg/m^2) and cyclophosphamide (500 mg/m^2) each given for 3 days.

On day +4, patient's wife noted speech changes and word finding difficulties. On further evaluation, he was found to be disoriented (time and location) and shortly becomes somnolent. His vital signs were all within normal range.

What intervention is recommended at this time?

1. Close observation, neurology consult
2. Close observation, neurology consult and transfer to the ICU
3. 1 &2 and Dexamethasone
4. 1 &2 and Tocilizumab (anti IL-6 receptor)
5. 1 &2 and Dexamethasone and Tocilizumab (anti IL-6 receptor)

A 58 year-old man with DLBCL relapsed after autologous stem cell transplant is in hospital after receiving CAR-T cells (axicabtagene ciloleucel). His lymphodepletion included fludarabine (30 mg/m^2) and cyclophosphamide (500 mg/m^2) each given for 3 days.

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What intervention is recommended at this time?

1. Close observation, neurology consult
2. Close observation, neurology consult and transfer to the ICU
3. 1 &2 and Dexamethasone
4. 1 &2 and Tocilizumab (anti IL-6 receptor)
5. 1 &2 and Dexamethasone and Tocilizumab (anti IL-6 receptor)

Patient was transferred the ICU and was started on dexamethasone (10 mg IV). Two hours later, he became hypoxic (SaO2 85% on RA) and hypotensive. He was placed on supplemental O2 (FiO2 = 30%) and IV fluids were initiated. Despite the fluid resuscitation, blood pressure remained soft and norepinephrine was started to keep the mean arterial pressure (MAP) in the safe range. On neurological assessment he remained disoriented (grade 2 NT).

What intervention is recommended at this time?

1. Continue dexamethasone
2. Stop dexamethasone and start tocilizumab
3. Add tocilizumab and continue dexamethasone

Patient was transferred the ICU and was started on dexamethasone (10 mg IV). Two hours later, he became hypoxic (SaO2 85% on RA) and hypotensive. He was placed on supplemental O2 (FiO2 = 30%) and IV fluids were initiated. Despite the fluid resuscitation, blood pressure remained soft and norepinephrine was started to keep the mean arterial pressure (MAP) in the safe range. On neurological assessment he remained disoriented (grade 2 NT).

What intervention is recommended at this time?

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3. Add tocilizumab and continue dexamethasone

Patient fully recovered from the CRS and NT and was discharged from hospital 8 days after CAR-T administration. On day 30, he underwent a restaging PET/CT which showed significant improvement (PR) in the diffuse lymphadenopathy but still had 2 small pelvic lymph nodes less than 3 cm and SUVs ~ 8.

Patient asks about the next treatment step. What would be the recommendation considering the current evidence?

1. Start salvage chemotherapy as soon as possible
2. Refer for allogeneic transplant
3. Repeat PET/CT in 2 months

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Patients who achieve less than a CR

- Active area of research
- ~ 1/3 of patients with PR at 1 month may convert to CR at 3 months [1]
- It is reasonable to follow the patient with repeat imaging
- Clinical trials are highly encouraged
- Other options (allogeneic HCT, etc) should be discussed

1-Locke, ASCO, 2018; #3003