sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Hematologic Malignancies

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE
CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

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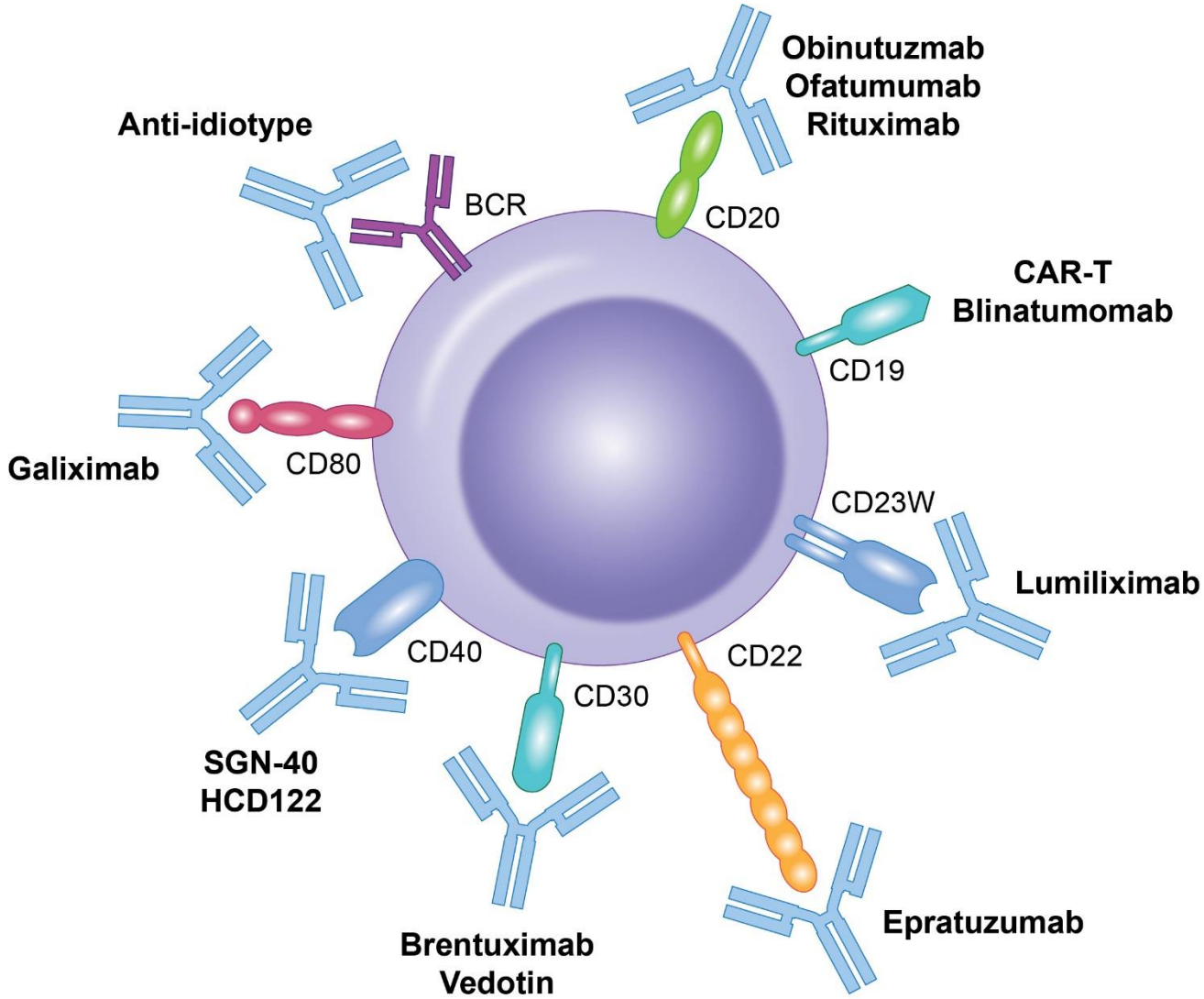
Disclosures

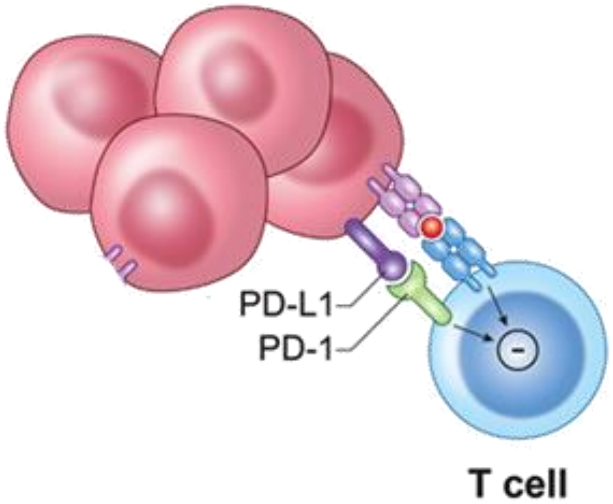
- No relevant financial relationships to disclose.
- I will not be discussing non-FDA approved indications during my presentation.

Monoclonal Antibodies Targeting B Cell Lymphomas



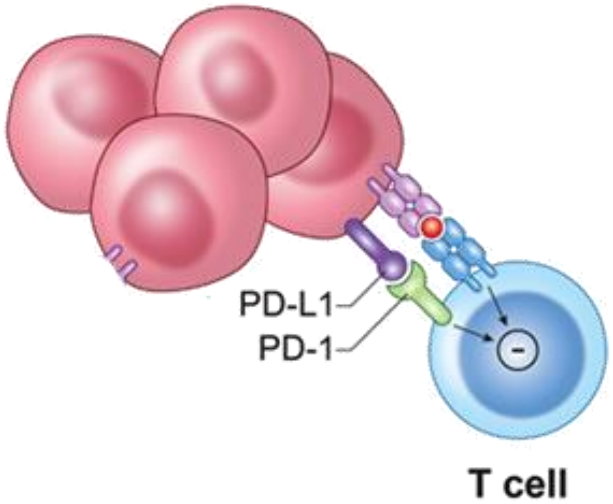
FDA-approved Checkpoint Inhibitors for Lymphomas

- 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



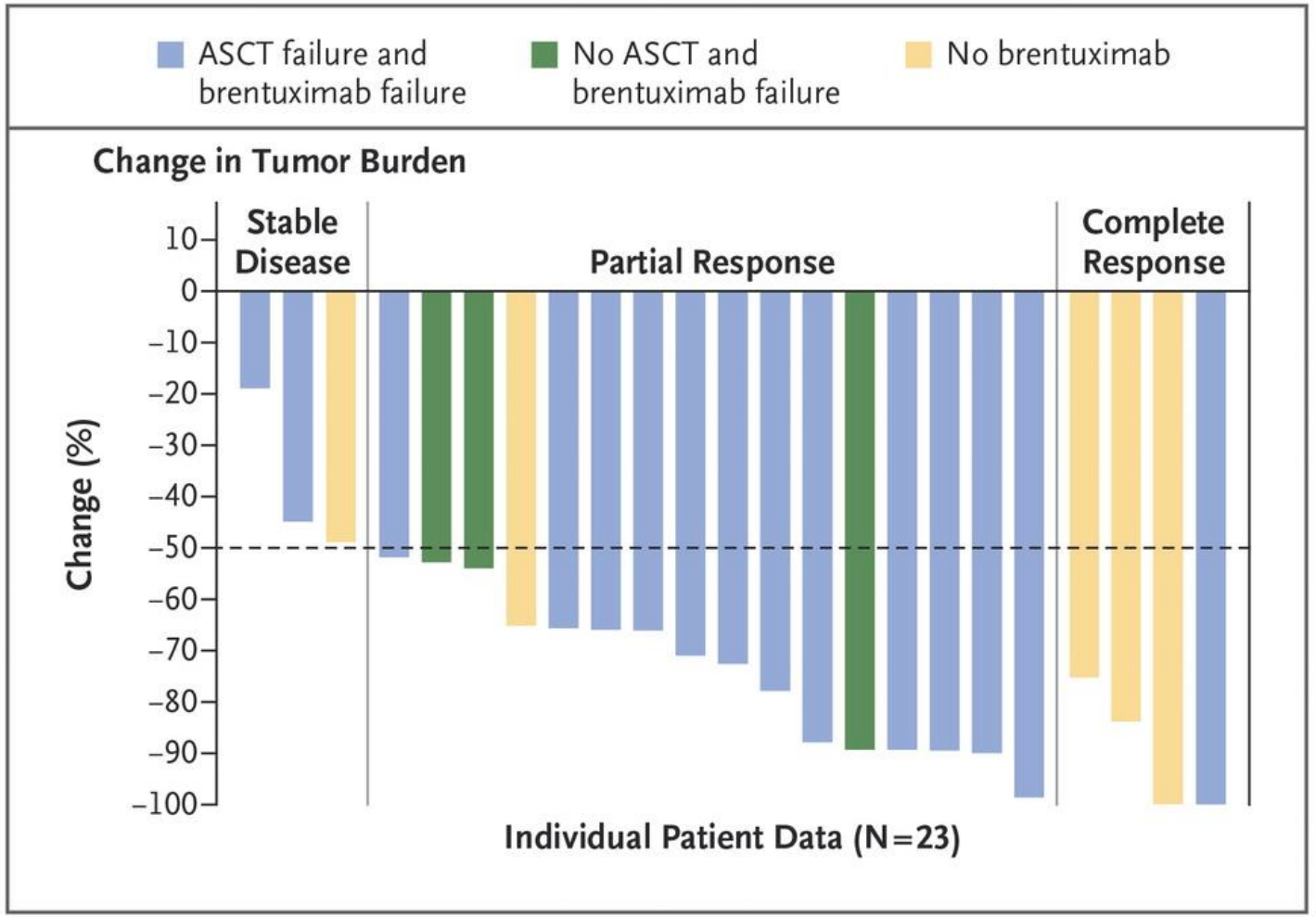
Nivolumab in Hodgkin Lymphoma

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

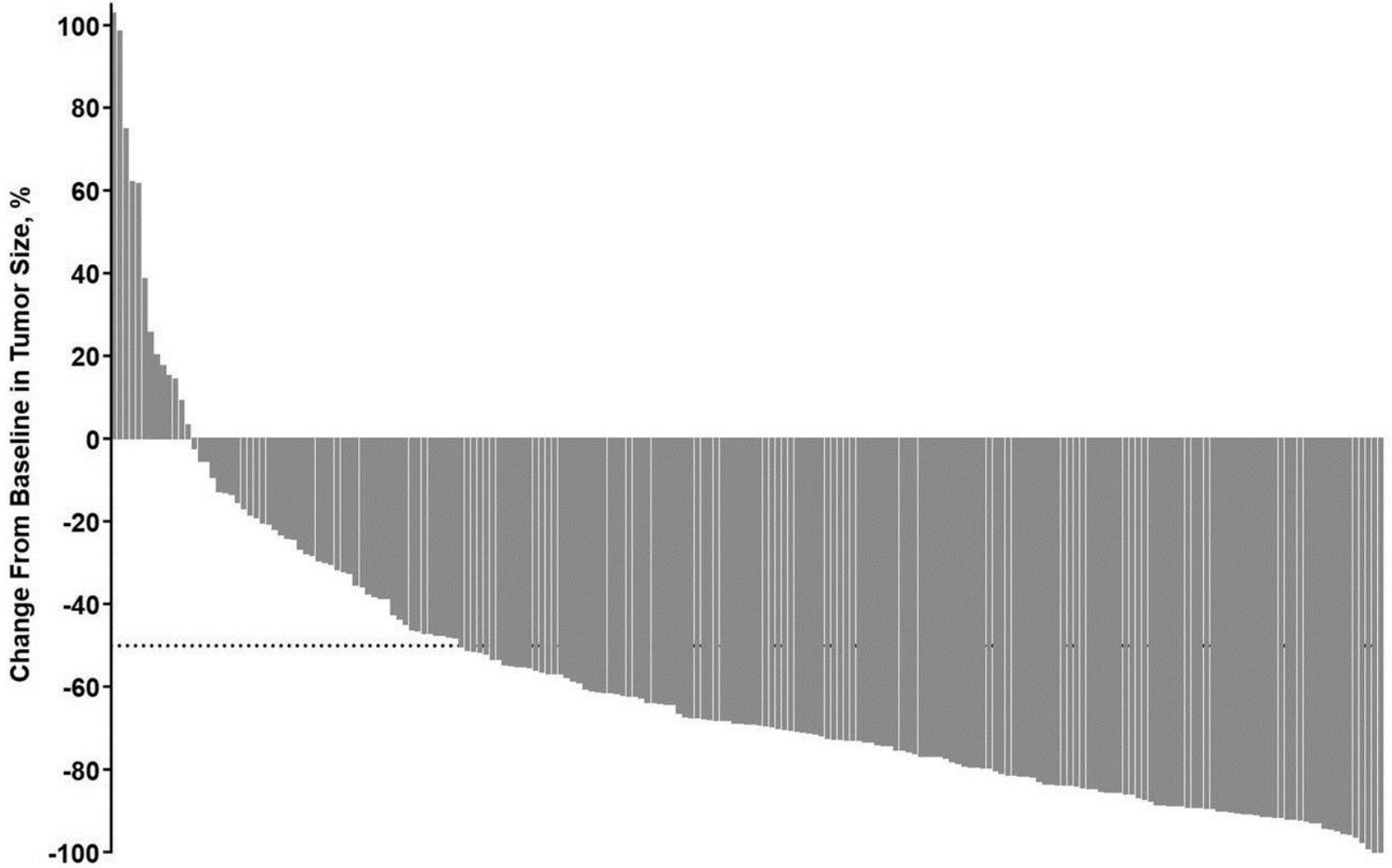
Ansell et al. NEJM 2015

Nivolumab in Hodgkin Lymphoma



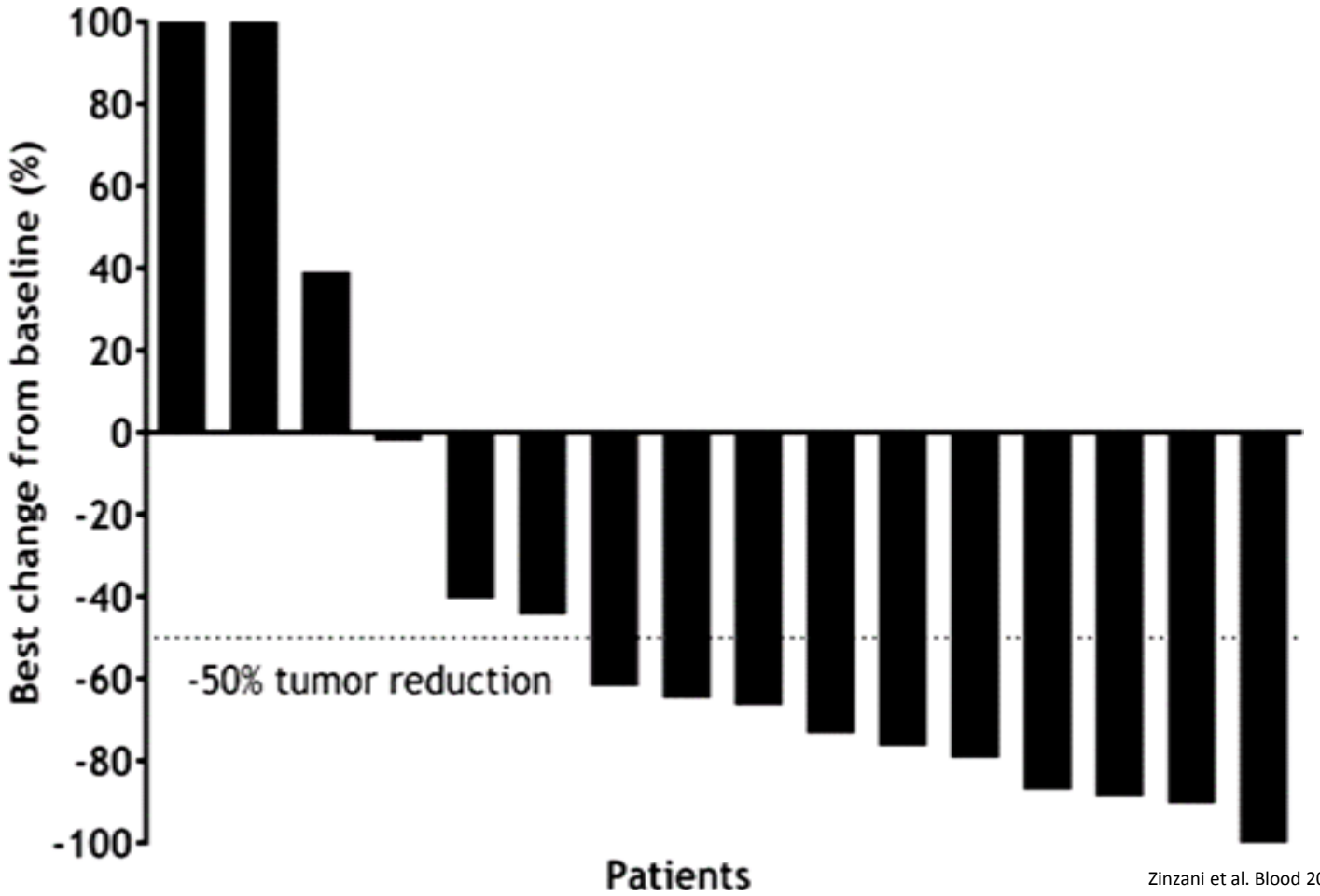
Ansell et al. NEJM 2015

Pembrolizumab in Hodgkin Lymphoma



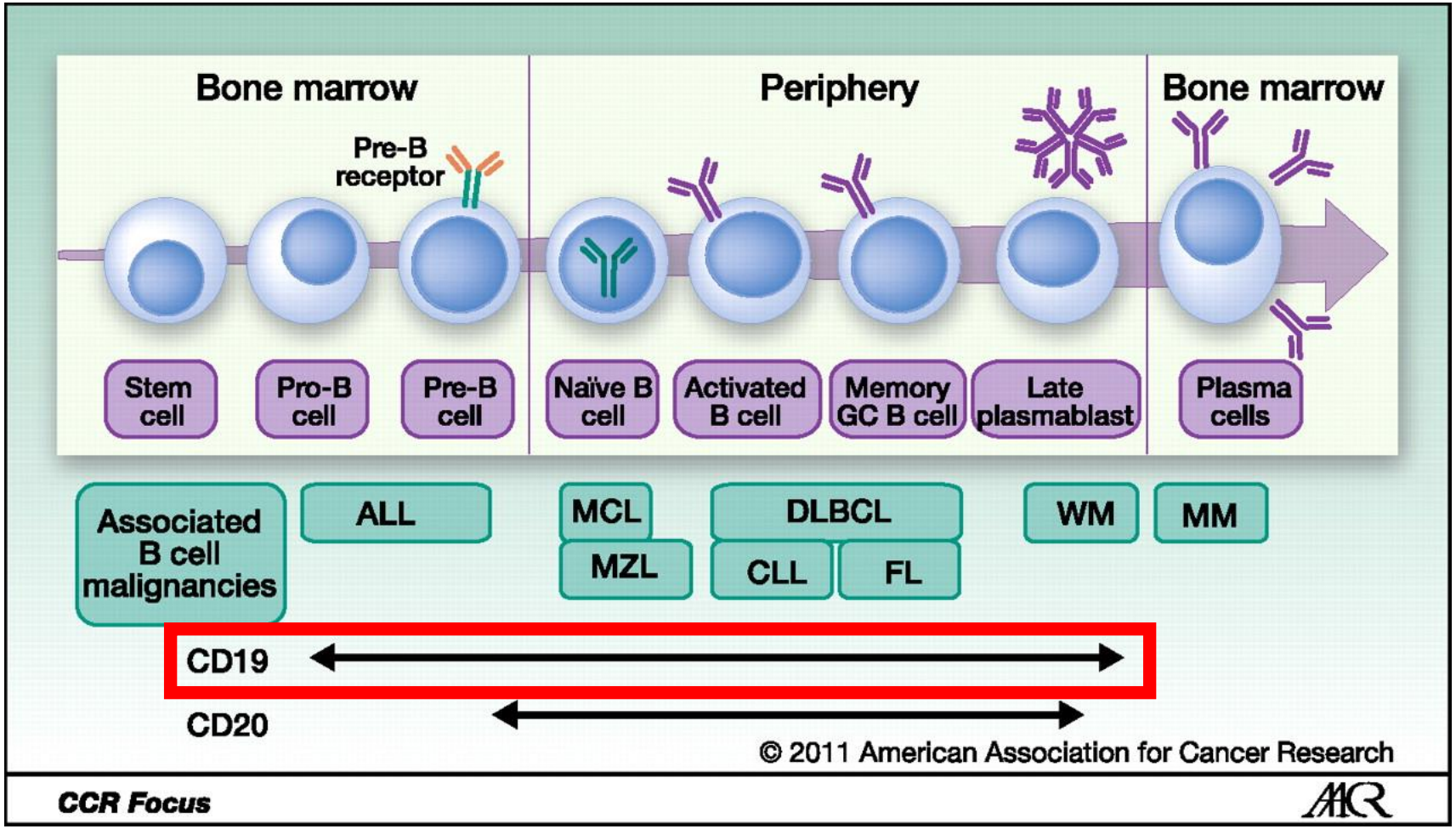
Zinzani et al. Hematological Oncology 2017

Pembrolizumab in Primary Mediastinal Large B cell Lymphoma



Zinzani et al. Blood 2016

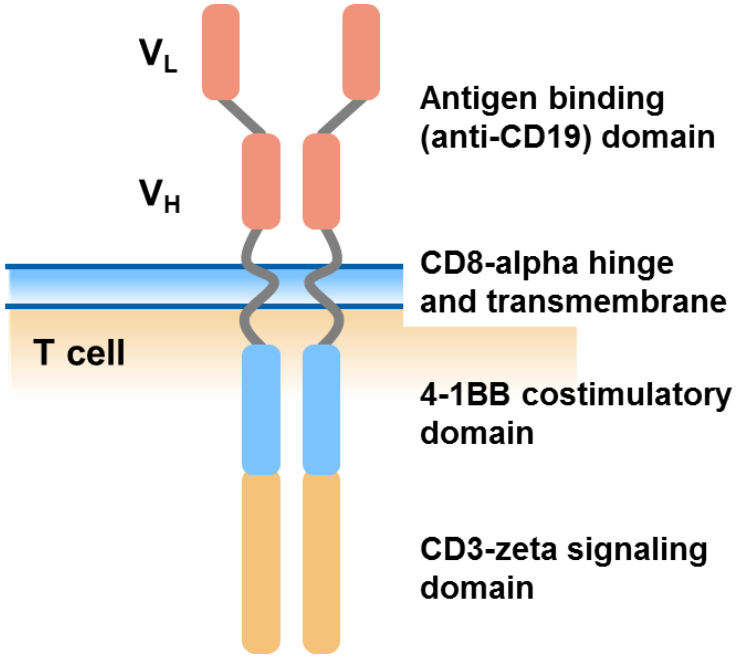
B Cell Malignancies are CD19+

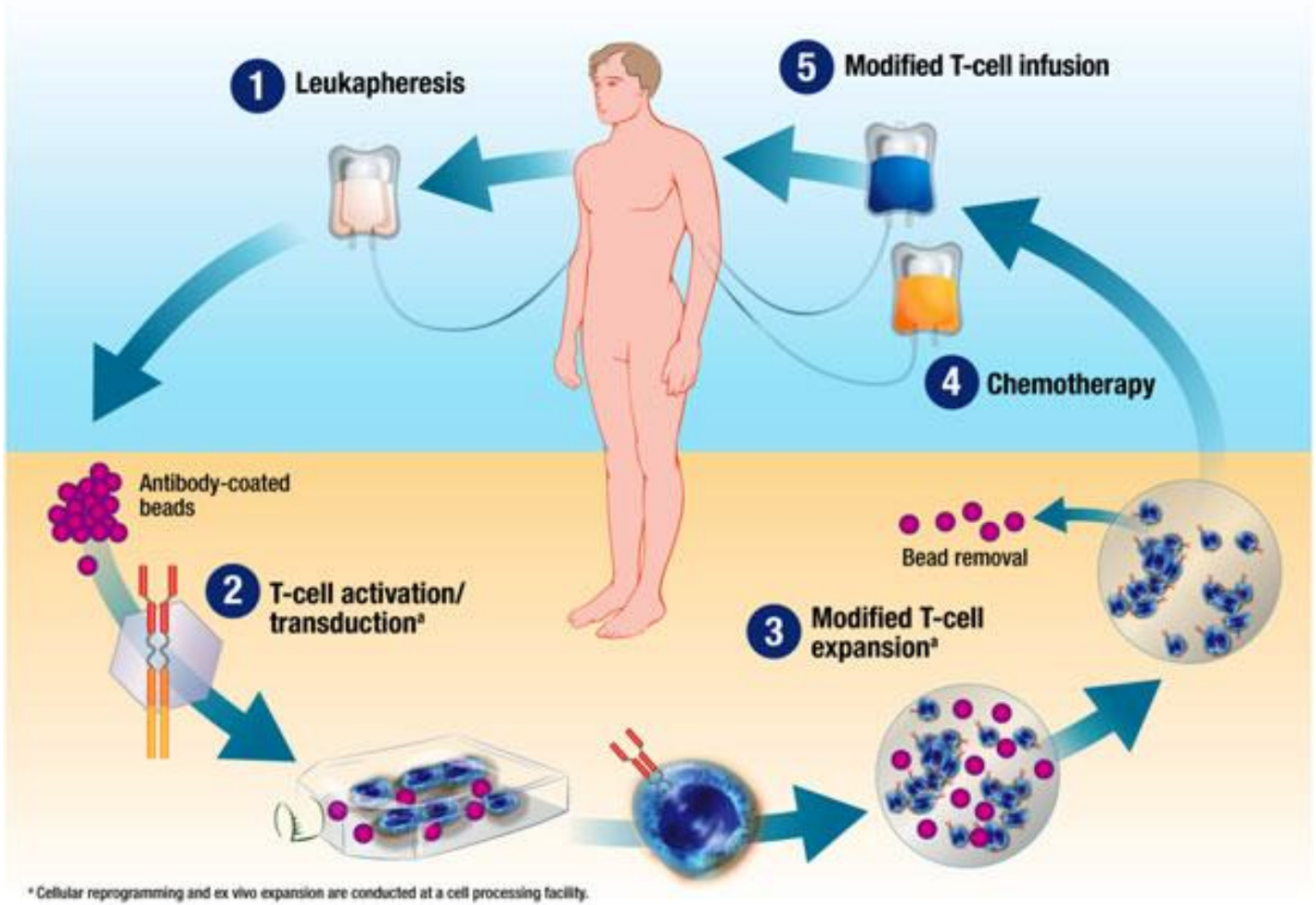


Blanc et al. Clinical Cancer Research 2011

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

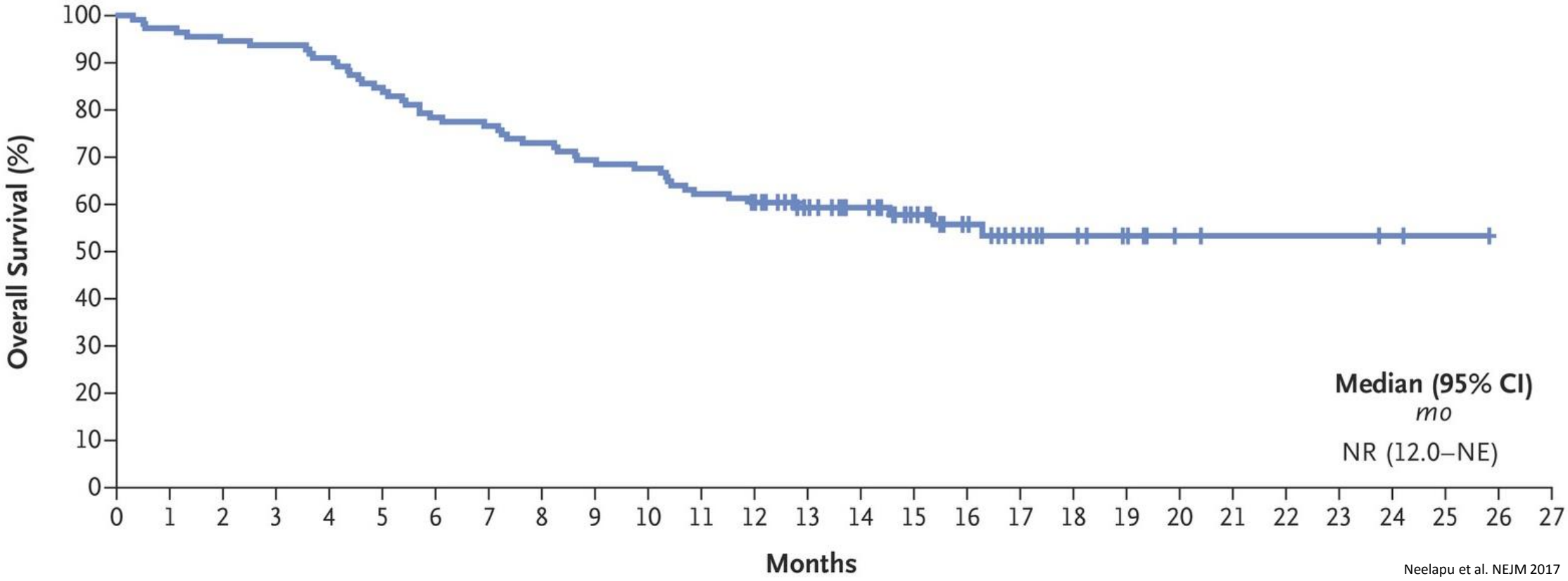
- Axicabtagene ciloleucel
  - ZUMA-1: Adult patients with relapsed or refractory large B cell lymphoma after two or more lines of systemic therapy, including diffuse large B cell lymphoma, high-grade B cell lymphoma, and DLBCL arising from follicular lymphoma
- Tisagenlecleucel
  - JULIET: adult patients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

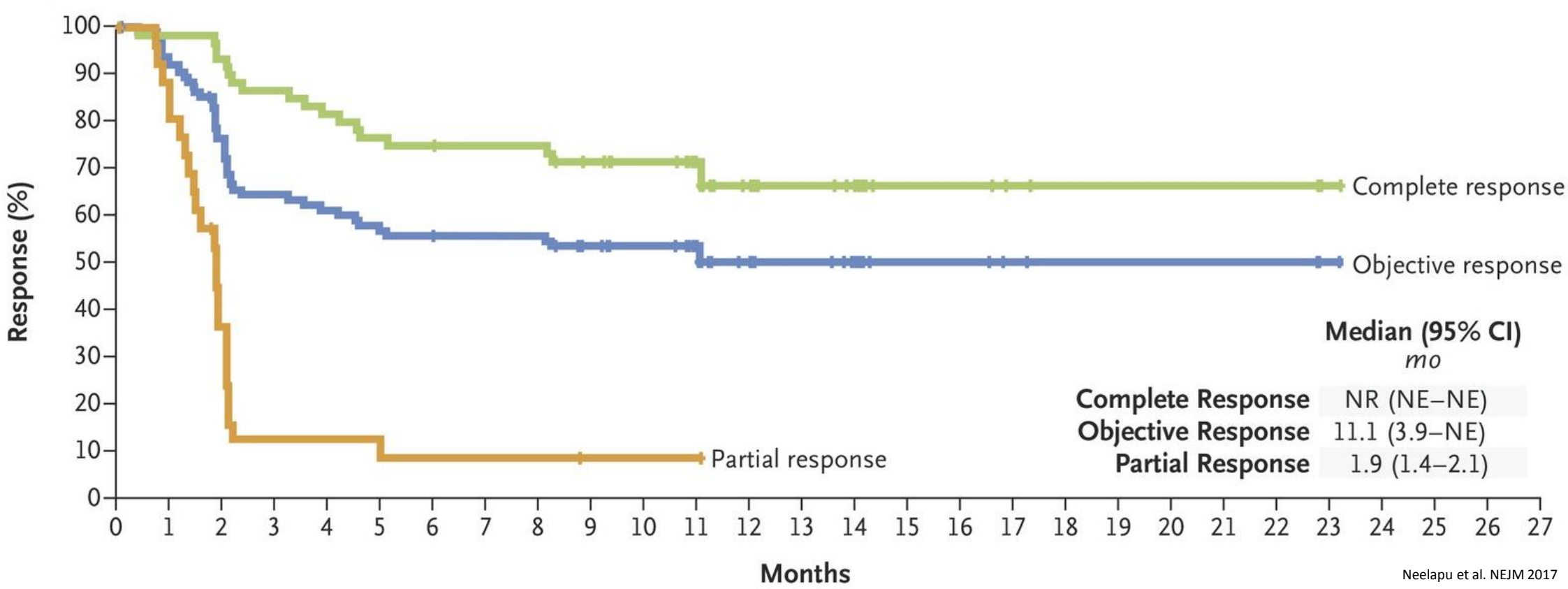
Overall Survival



Neelapu et al. NEJM 2017

Axicabtagene ciloleucel in B Cell Lymphoma

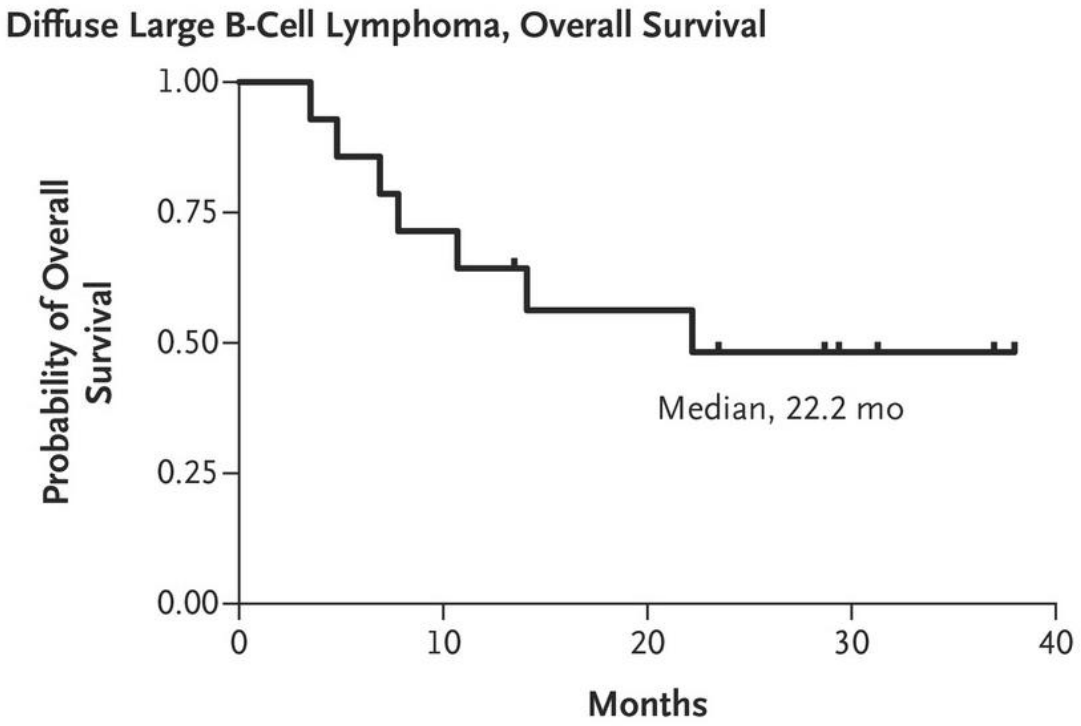
Duration of Response

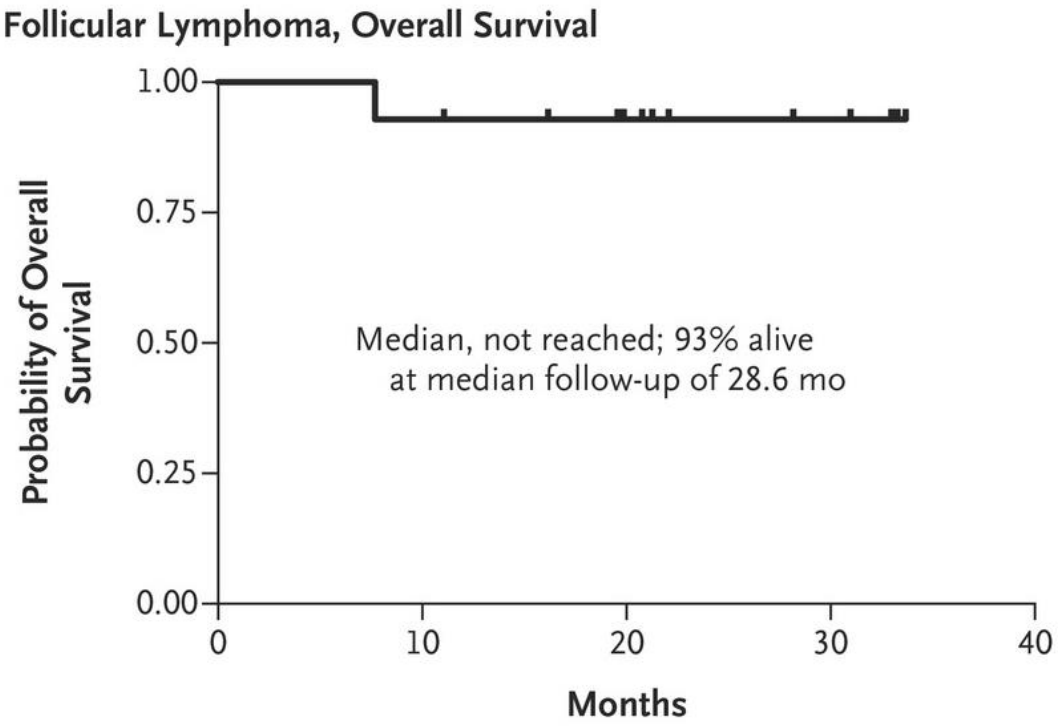


Neelapu et al. NEJM 2017

Tisagenlecleucel in B Cell Lymphoma

Overall Survival

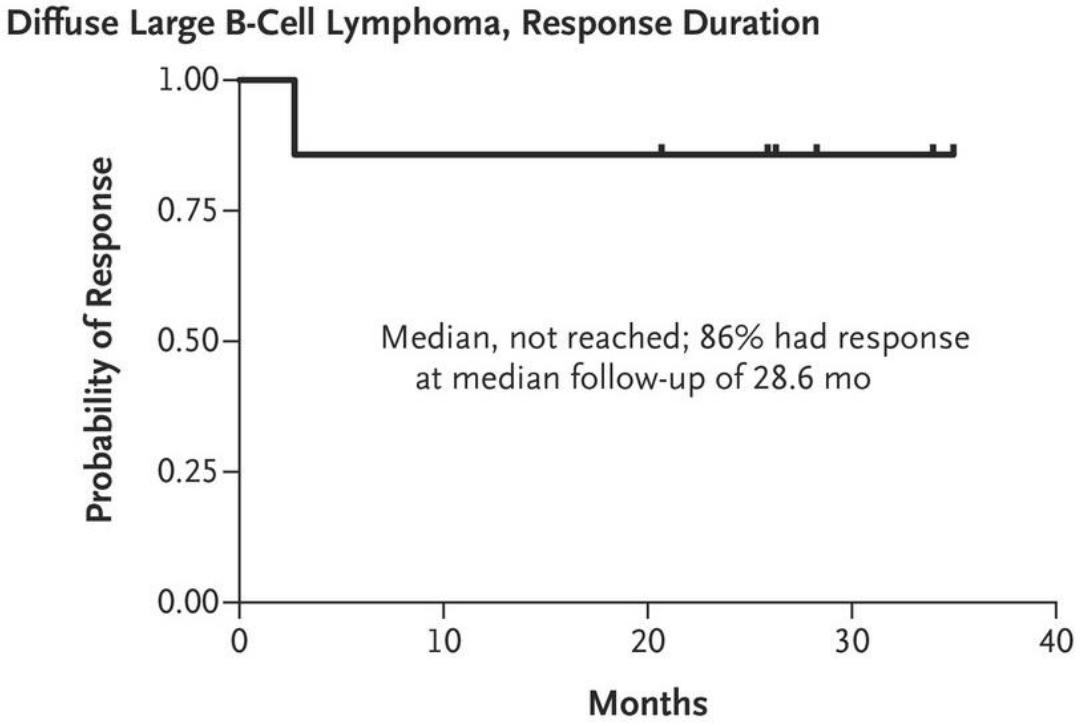


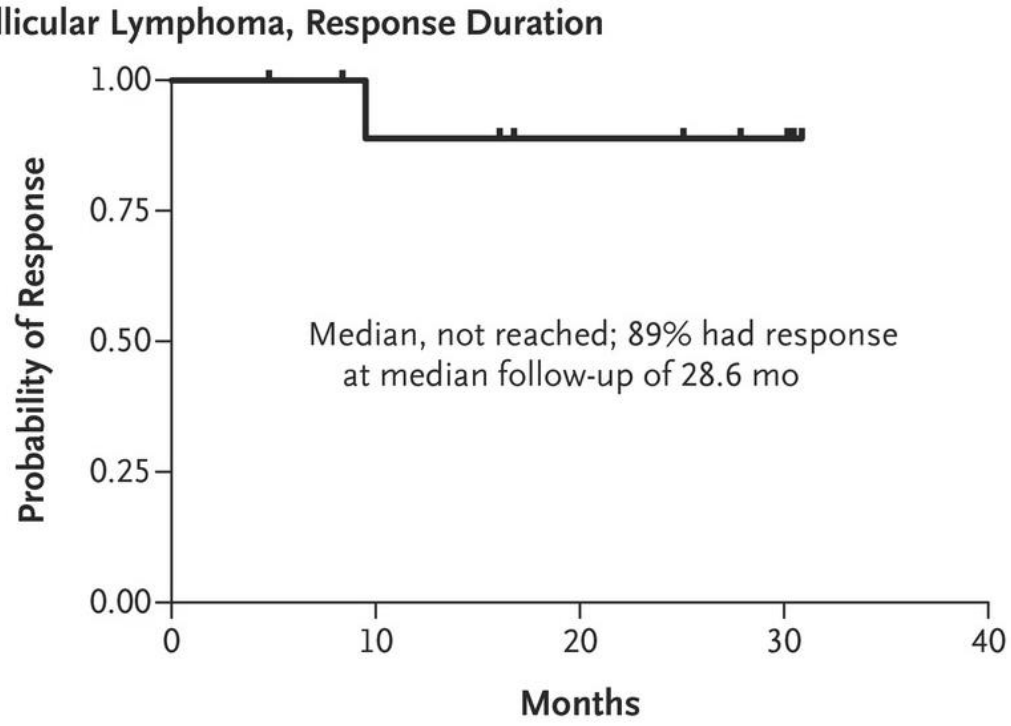


Schuster et al. NEJM 2017

Tisagenlecleucel in B Cell Lymphoma

Duration of Response



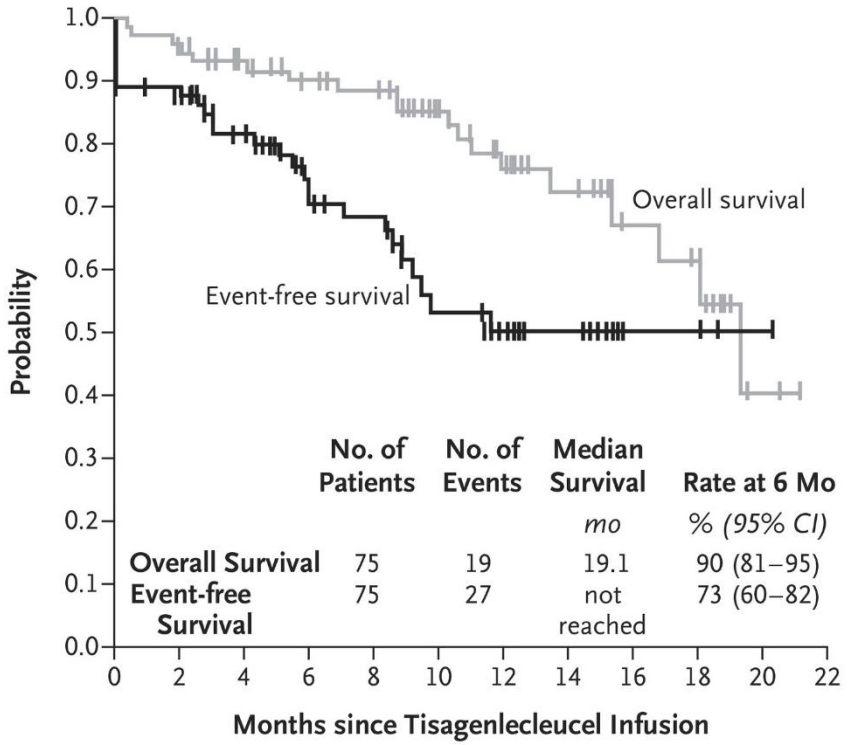


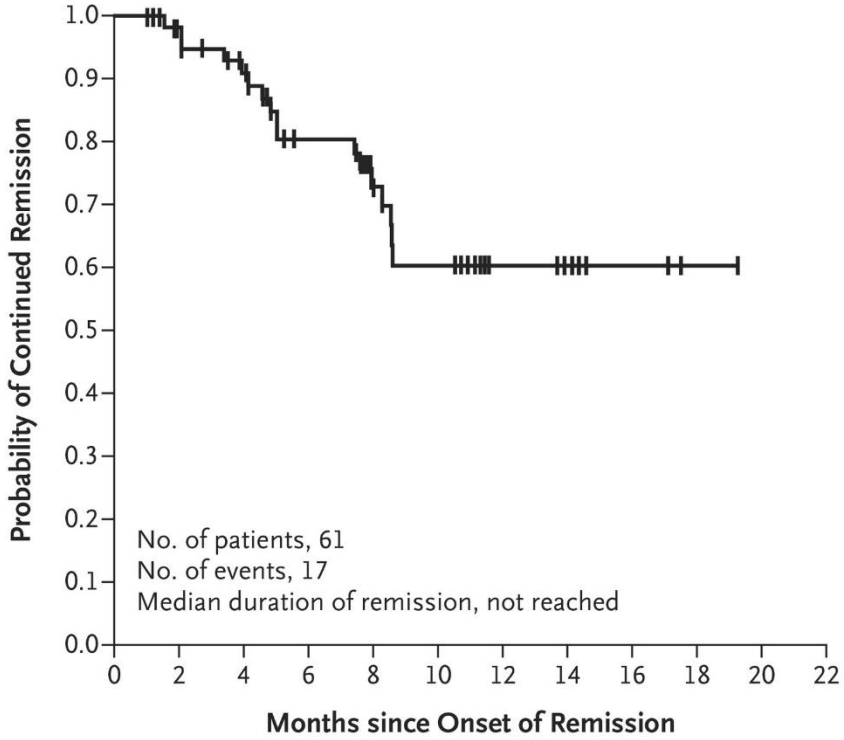
Schuster et al. NEJM 2017

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

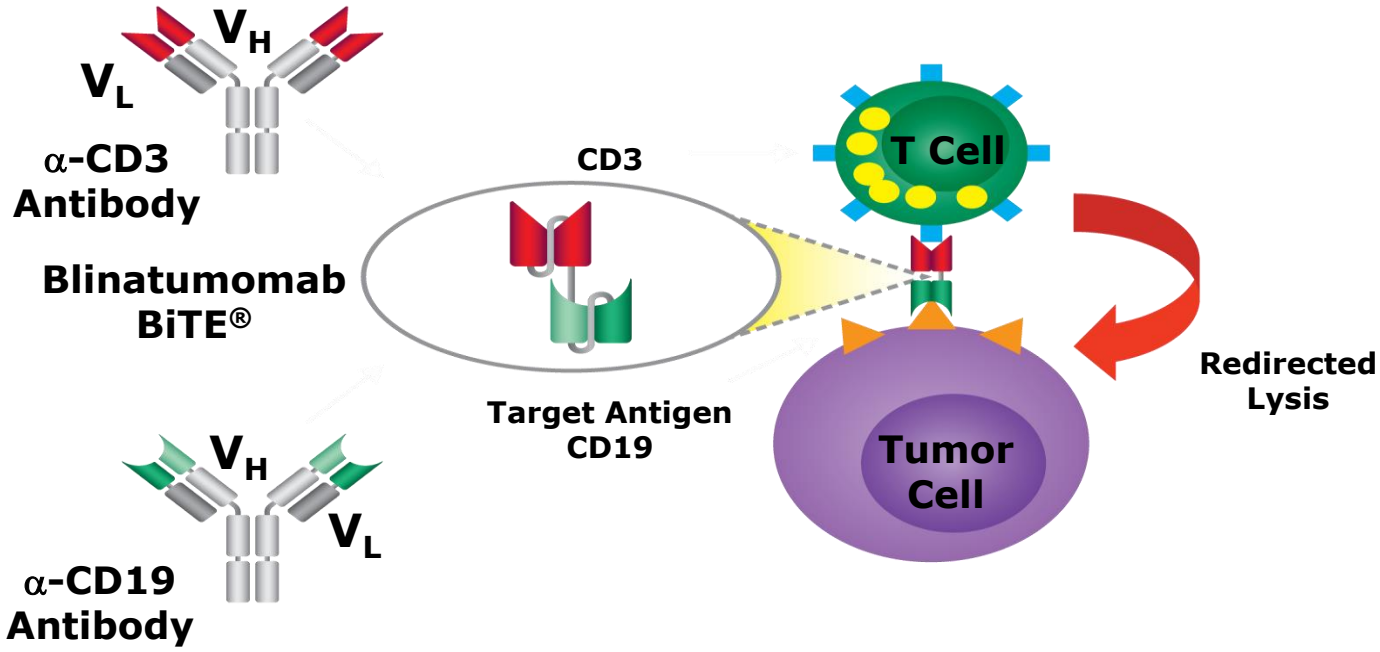




Maude et al. NEJM 2018

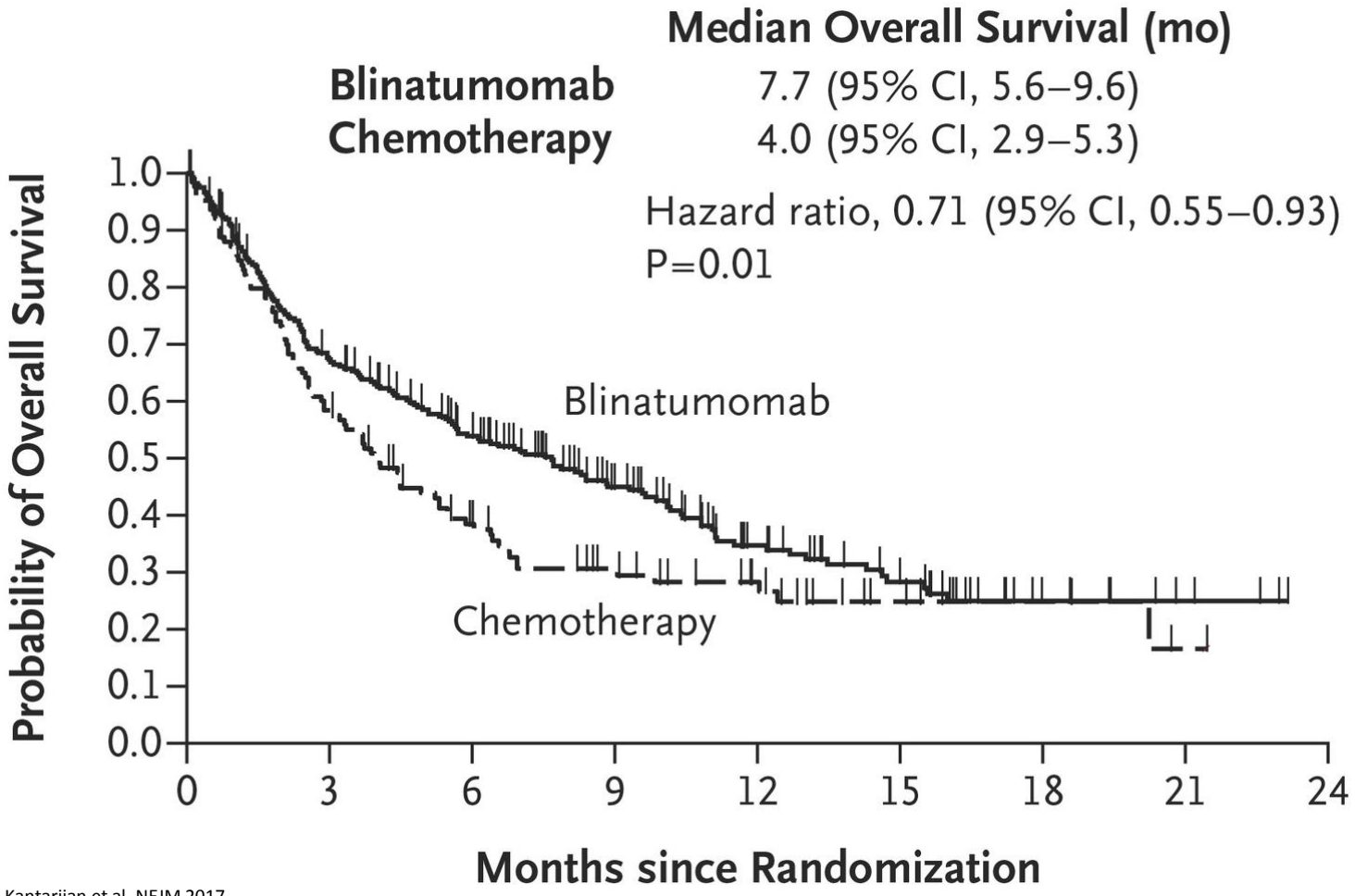
BiTE (Blinatumumab) Therapy

- 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

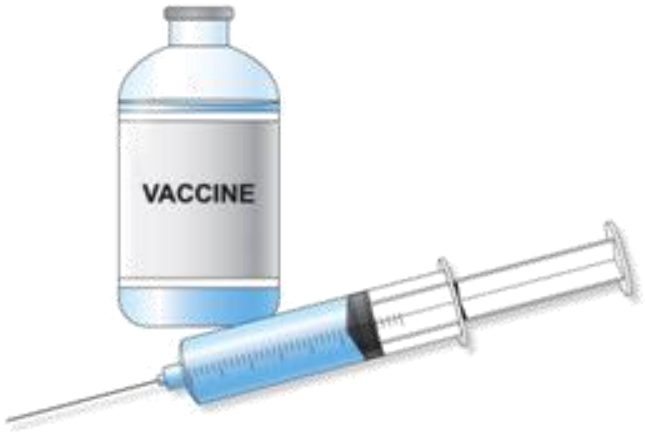
Blinatumomab for B-ALL



Kantarjian et al. NEJM 2017

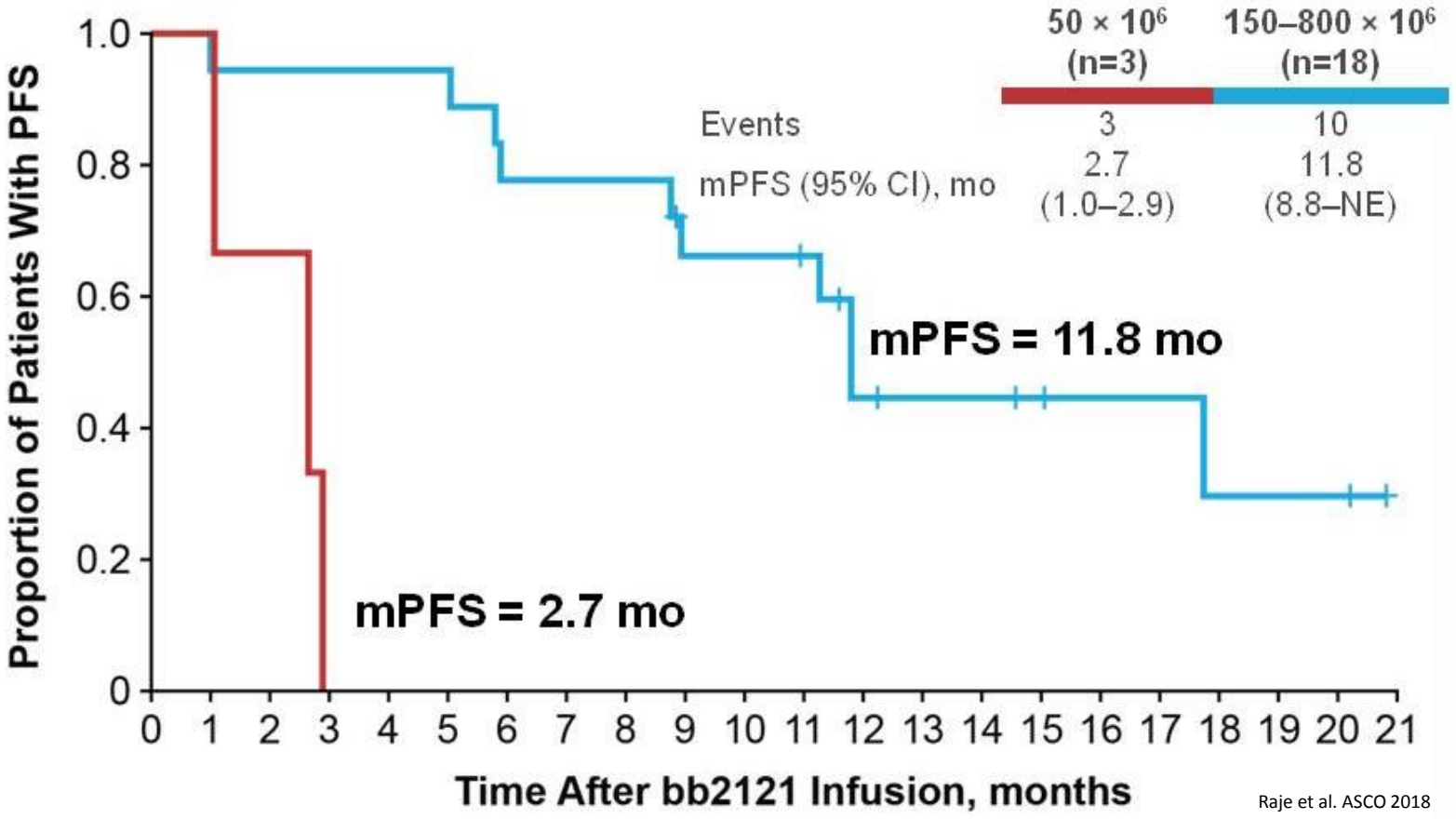
Immunotherapies for Multiple Myeloma

- 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



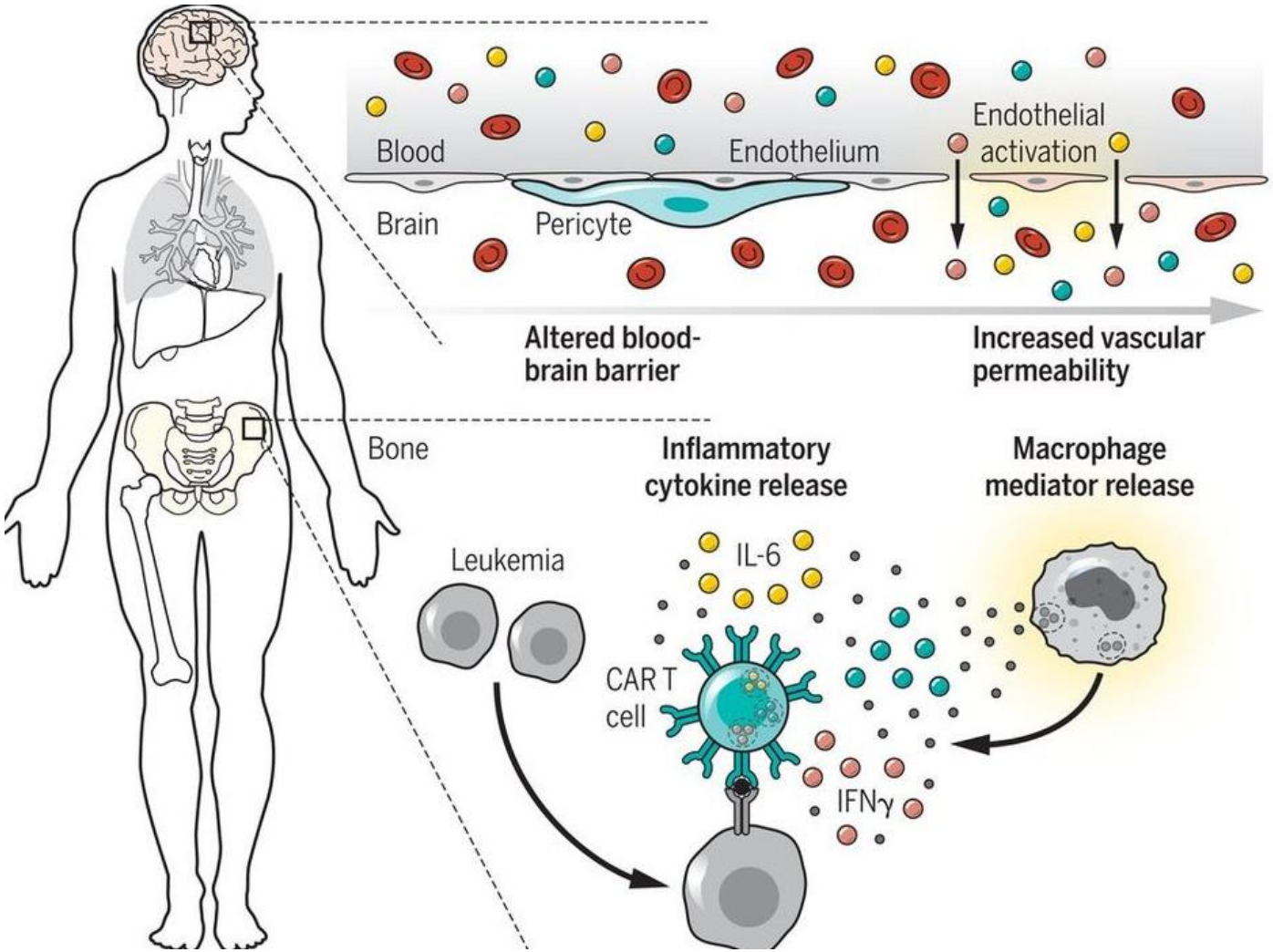
In Development: BCMA+ CAR T Therapy for Myeloma

- 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)



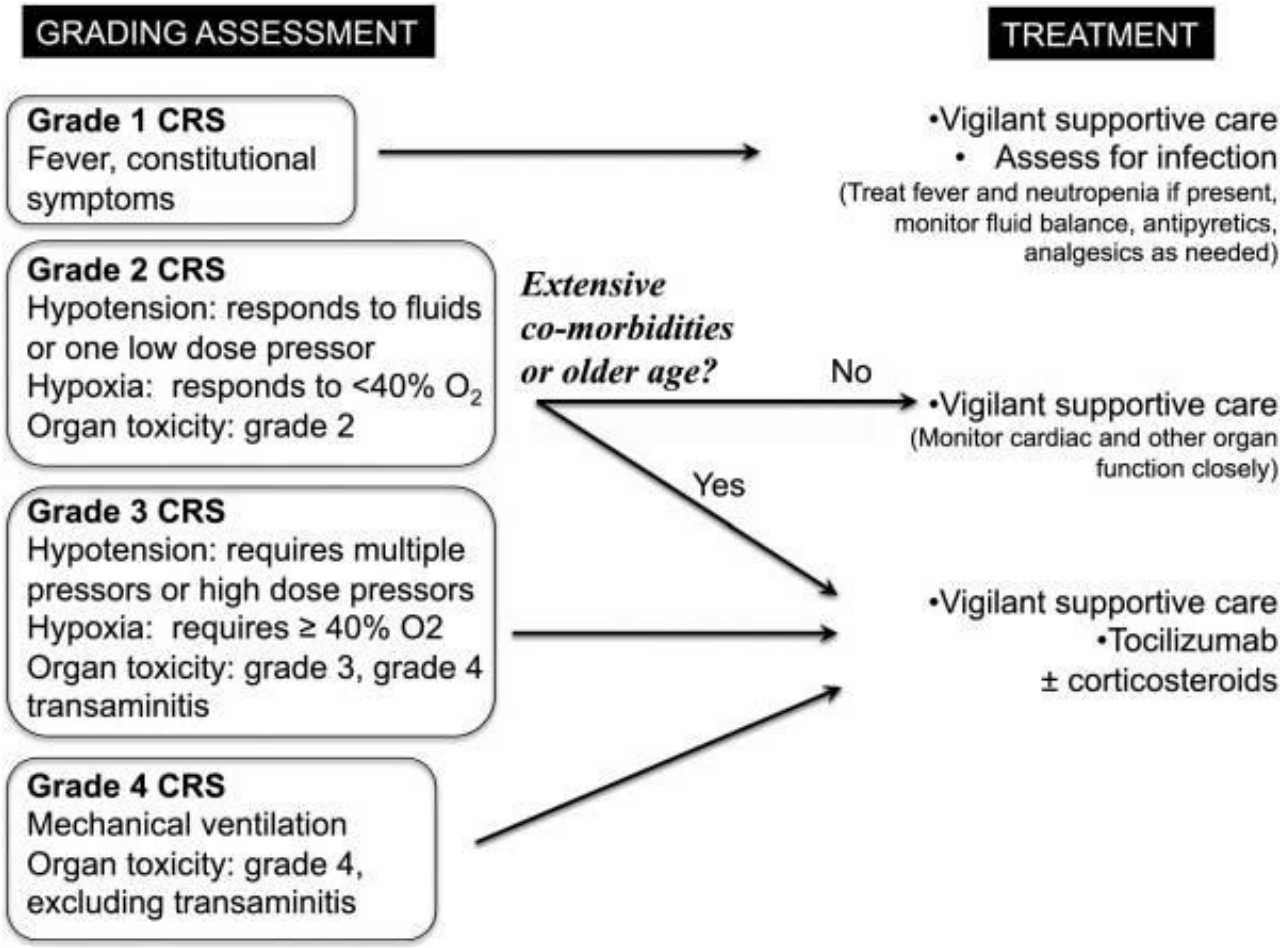
Neurotoxicity
Delirium
Aphasia
Seizures
Cerebral edema
Intracranial hemorrhage

Hemodynamic instability
Tachycardia
Hypotension
Capillary leak syndrome

Organ dysfunction
AST and ALT elevation
Hyperbilirubinemia
Respiratory failure

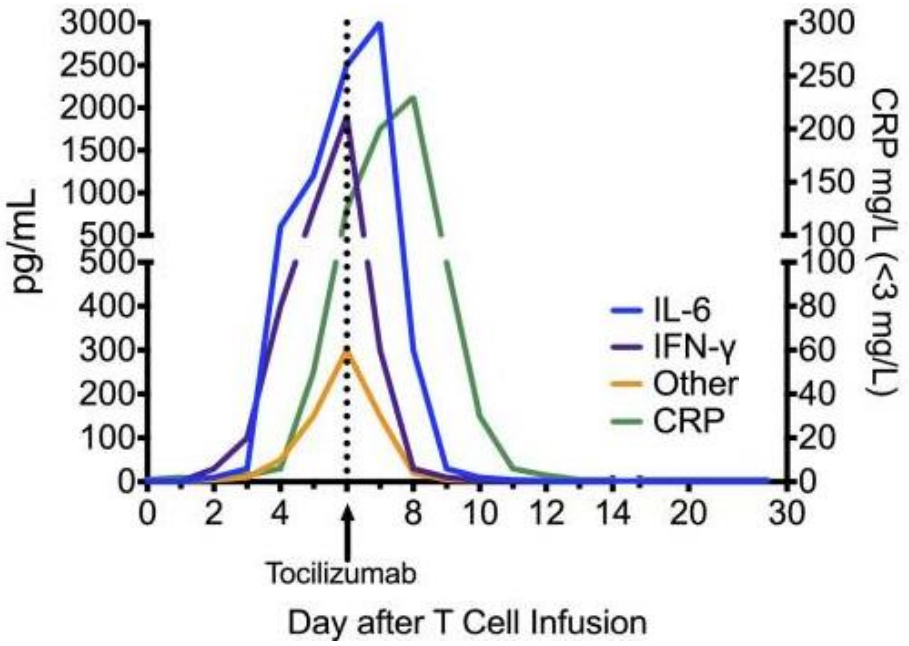
June et al. Science 2018

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 Study 1

- 32 y/o female with minimal pmh presenting with enlarging LN in the base of the R-neck. Non-tender, painless. Steady growth rate over ~3 months. Not responsive to anti-microbials.

- Lab testing:

  CBC: normal CMP: normal ESR: elevated at 25 mm/h

- Physical Exam:
  - LN 4.5 cm in size LN in the L-base of the neck and mild inspiratory wheezing
  - O/w physical exam is without any specific Findings

Case Study 1

Biopsy: Left cervical lymph node

- 2% large mono- or bi-nucleated blastoid giant cells and a plethora of reactive cells divided by sclerotic bands
- IHC: strong positivity of CD30 in tumor cells, positive staining of CD15 and a negative staining for CD20
- Diagnosis: diagnosis of classical Hodgkin, nodular sclerosing type

PET-CT Scan

- Large mediastinal tumor >1/3 of the thorax. Left-cervical and left-supraclavicular lymph nodes (up to 3.5 cm) and isolated lesions within the spleen. No uptake within the bone marrow.

Case Study 1

Treatment Course

- ABVD at standard dosing x 6 cycles wit PET-CR after after 2 cycles

Relapse

- 7 months after completion of therapy ➔ shortness of breath and night sweats
- Repeat PET-CT positive for mediastinal and splenic uptake.
- Biopsy of mediastinum with confirmed relapsed disease

Salvage:

- ICE chemotherapy at standard dosing x 2 cycles (stem cell mobilization and collection after c1) ➔ achieved PR with positive PET-by deuvile scoring
- Pembrlizumab x2 cycles with PET-CR and then went on to ASCT with BEAM conditioning regimen. Followed by radiation to the chest.

Case study 2

- 22 y/o female presented to the ED with abdominal pain, thought to be related to possible UTI. Imaging and UA consistent with pyelonephritis but also found to have a tWBC of 243 10*3/uL, 94% of which were atypical lymphocytes.
- CT Imaging with splenomegaly (17 cm). Bone marrow biopsy revealing preB-AL
  - 95% marrow cellularity
  - CD20 negative. CD19 positive.
  - NGS: MLL-AF1 fusion, *other abnormalities*
- LP: diagnostic CSF positive by flow and morphology (CNS3 status)

Case study 2

- Induction course:
  - Elected AYA treatment course as guided by CALGB 10403 Trial which includes: cytarabine, methotrexate, daunorubicin, vincristine, and peg-asparaginas
  - End of Induction Bone marrow biopsy: MRD positive 2.6% by flow cytometry
- Consolidation course:
  - HLA Typing with match search (siblings and registry)
  - Consolidation course agents: cyclophosphamide, cytarabine, mercaptopurine, IT-mtx, vincristine, peg-asparaginase
  - End of consolidation bone marrow biopsy: MRD 1.6% by flow cytometry

Case study 2: Question

- What treatment would recommend next?
  - Continue consolidation course
  - Move on to allogeneic stem cell transplant (assuming donor identified)
  - Blinotumumab
  - Liposomal vincristine
  - Nelarabine

Case study 2: Answer

- What treatment would recommend next?
  - Continue consolidation course
  - Move on to allogeneic stem cell transplant (assuming donor identified)
  - Blinatumomab
  - Liposomal vincristine
  - Nelarabine

Case study 2

- Salvage course:
  - One more course of consolidative chemotherapy with achievement of MRD followed by blinatumomab
  - Developed allergic reaction: fevers and neurologic toxicities with tremors

Case study 2: Question

- What do you do with this toxicity
  - Continue with agent and dose dexamethasone
  - Temporarily hold agent until resolution and then resume
  - Permanently discontinue agent

Case study 2: Answer

- What do you do with this toxicity
  - Continue with agent and dose dexamethasone
  - Temporarily hold agent until resolution and then resume
  - Permanently discontinue agent

Case study 2

- She was able to achieve MRD- status and is currently in midst of an allogeneic stem cell transplant