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
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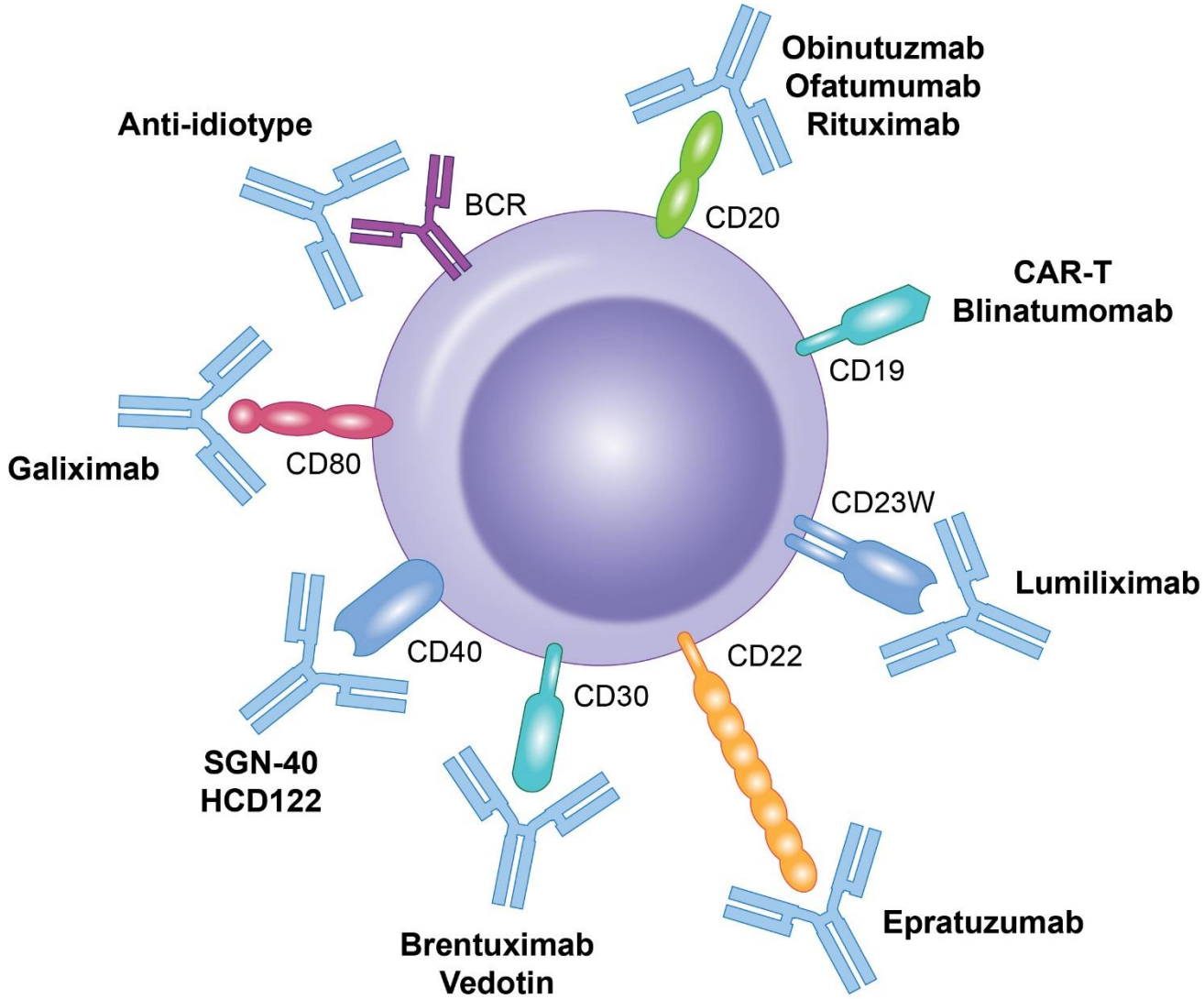
ACCC Association of Community Cancer Centers

Society for Immunotherapy of Cancer

Disclosures

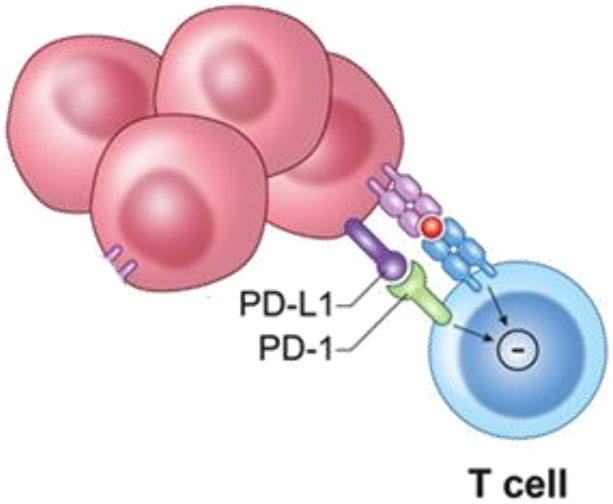
- Research funding: Genentech, Agenus, Inc.
- Consulting: Genentech, BMS, Celgene, Janssen
- I will be discussing non-FDA approved indications during my presentation.

Monoclonal Antibodies Targeting B Cell Lymphomas



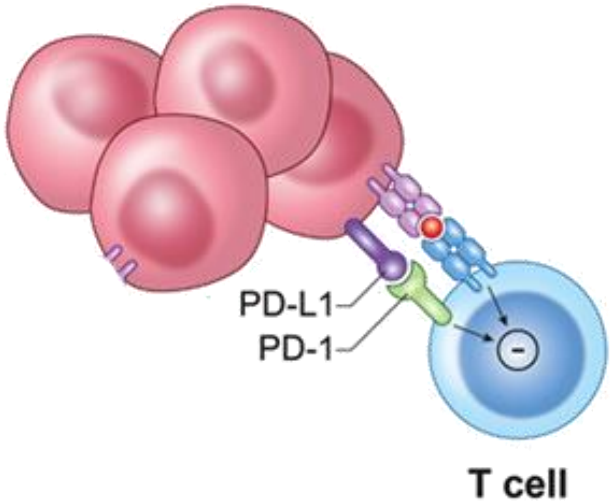
FDA-approved Checkpoint Inhibitors for Lymphomas

- 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



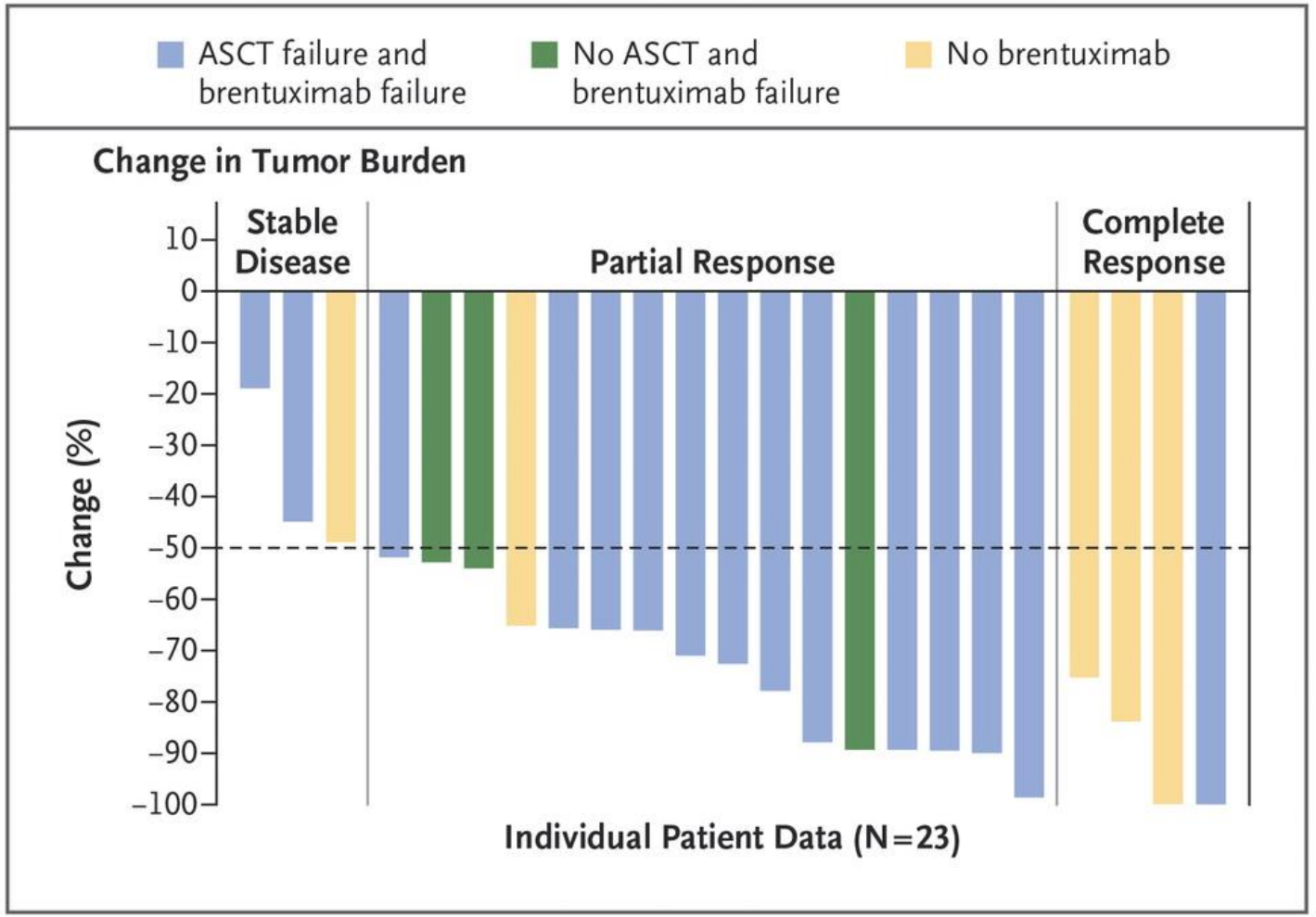
Nivolumab in Hodgkin Lymphoma

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

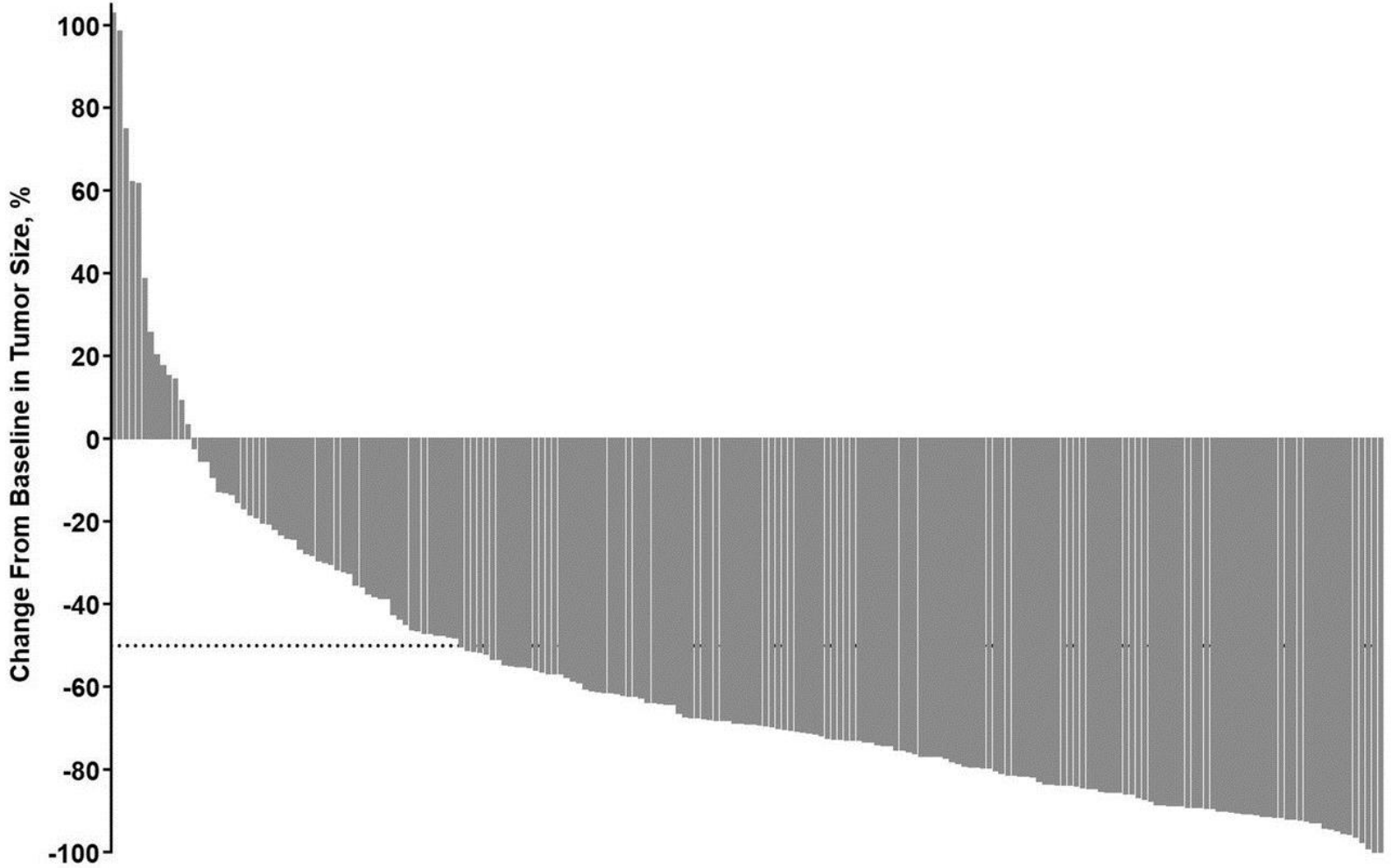
Ansell et al. NEJM 2015

Nivolumab in Hodgkin Lymphoma



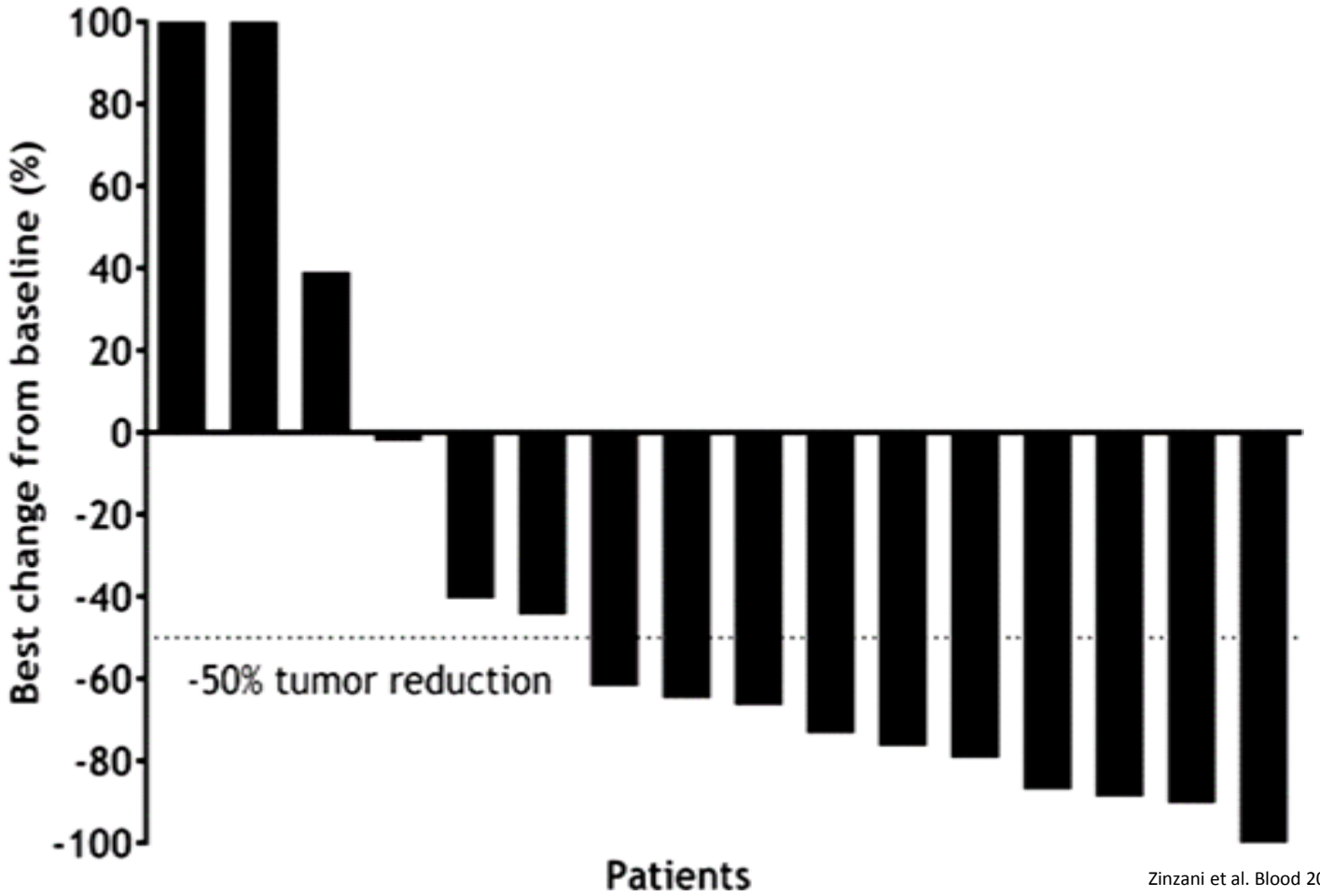
Ansell et al. NEJM 2015

Pembrolizumab in Hodgkin Lymphoma



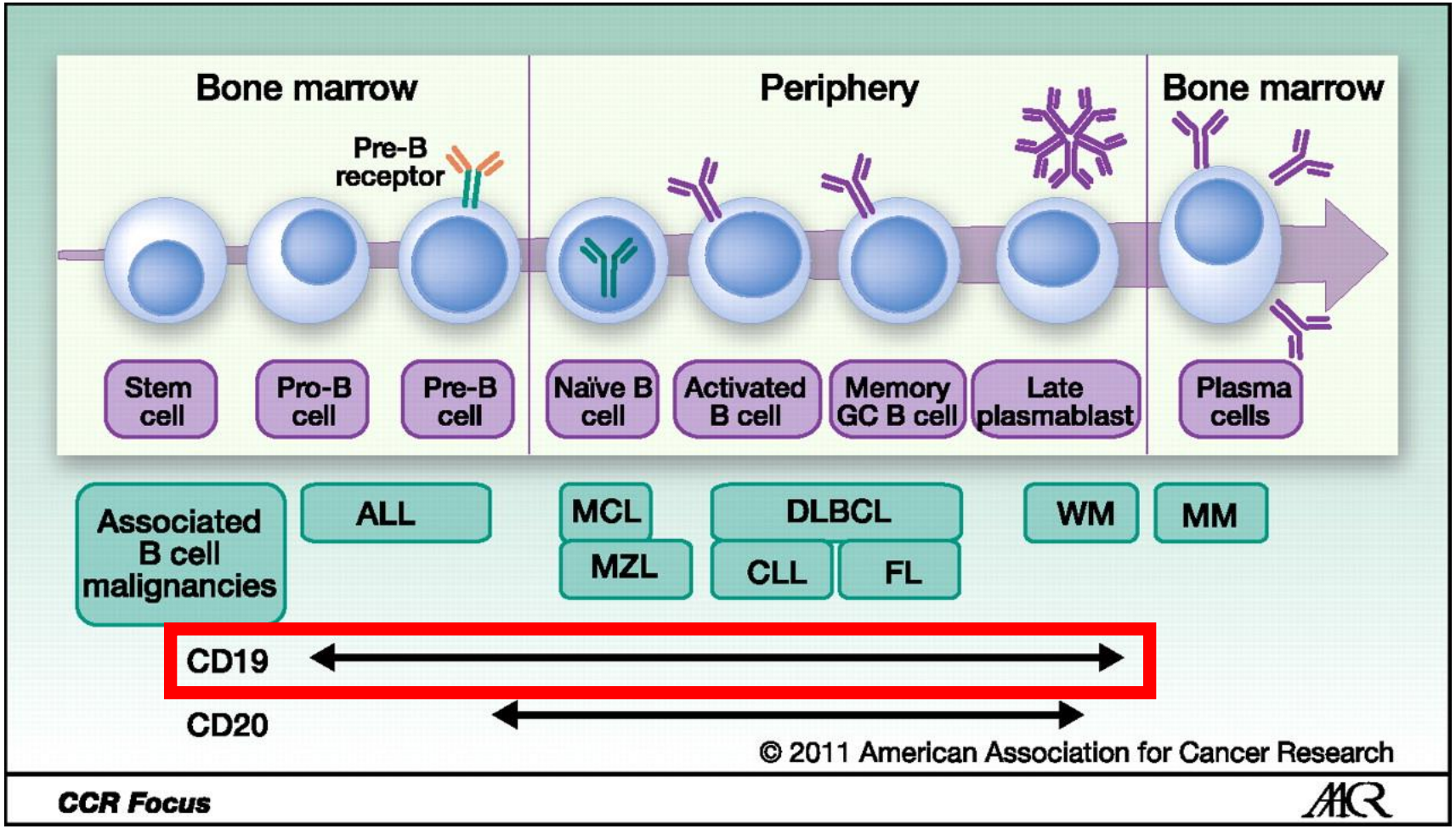
Zinzani et al. Hematological Oncology 2017

Pembrolizumab in Primary Mediastinal Large B cell Lymphoma



Zinzani et al. Blood 2016

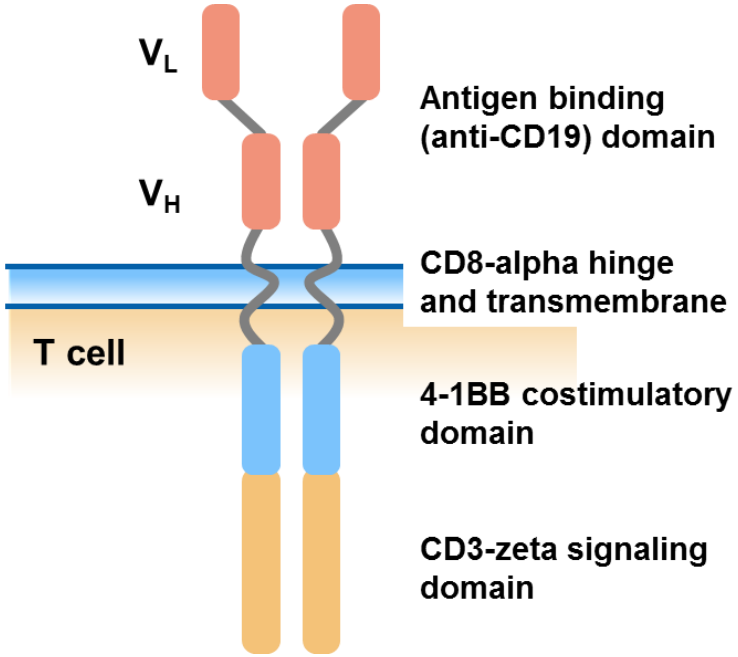
B Cell Malignancies are CD19+

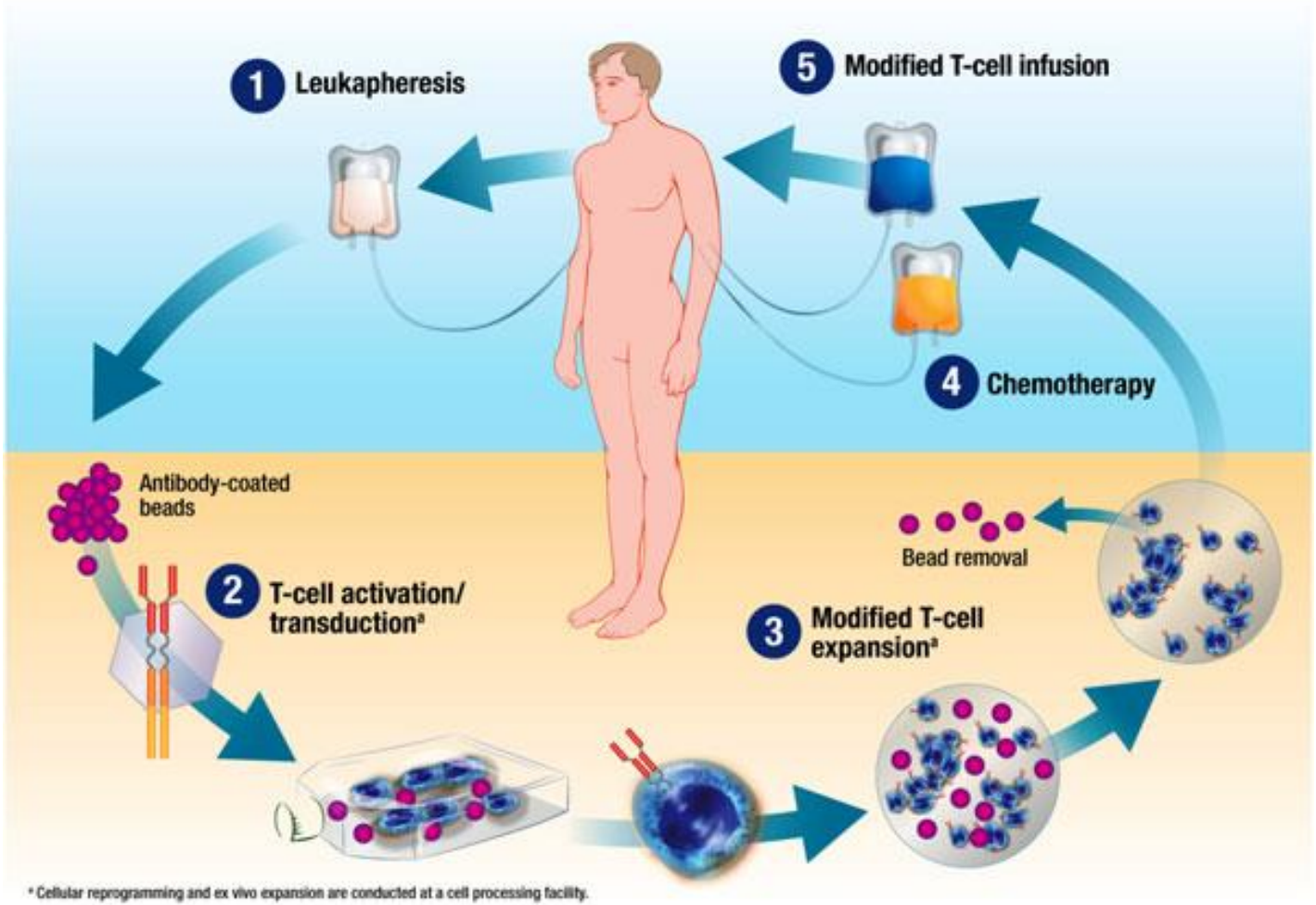


Blanc et al. Clinical Cancer Research 2011

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

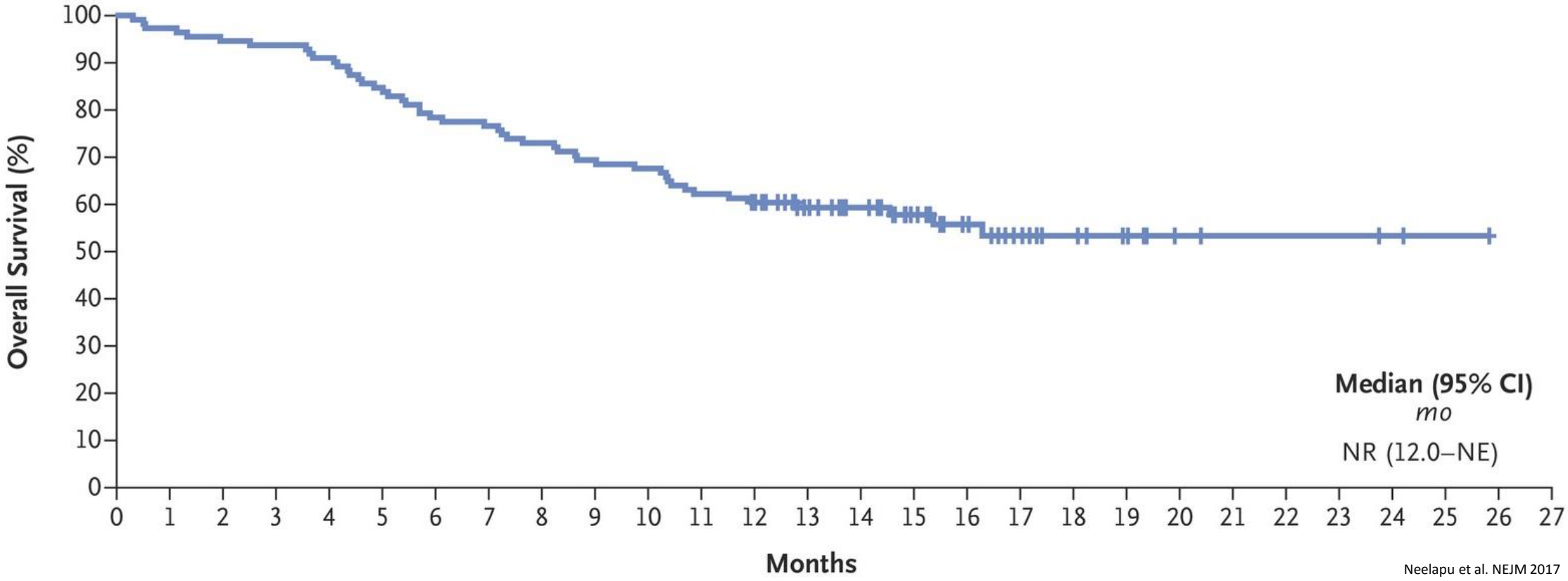
- Axicabtagene ciloleucel (Yescarta)
  - ZUMA-1: Adult patients with relapsed or refractory large B cell lymphoma after two or more lines of systemic therapy, including diffuse large B cell lymphoma, high-grade B cell lymphoma, and DLBCL arising from follicular lymphoma
- Tisagenlecleucel (Kymriah)
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

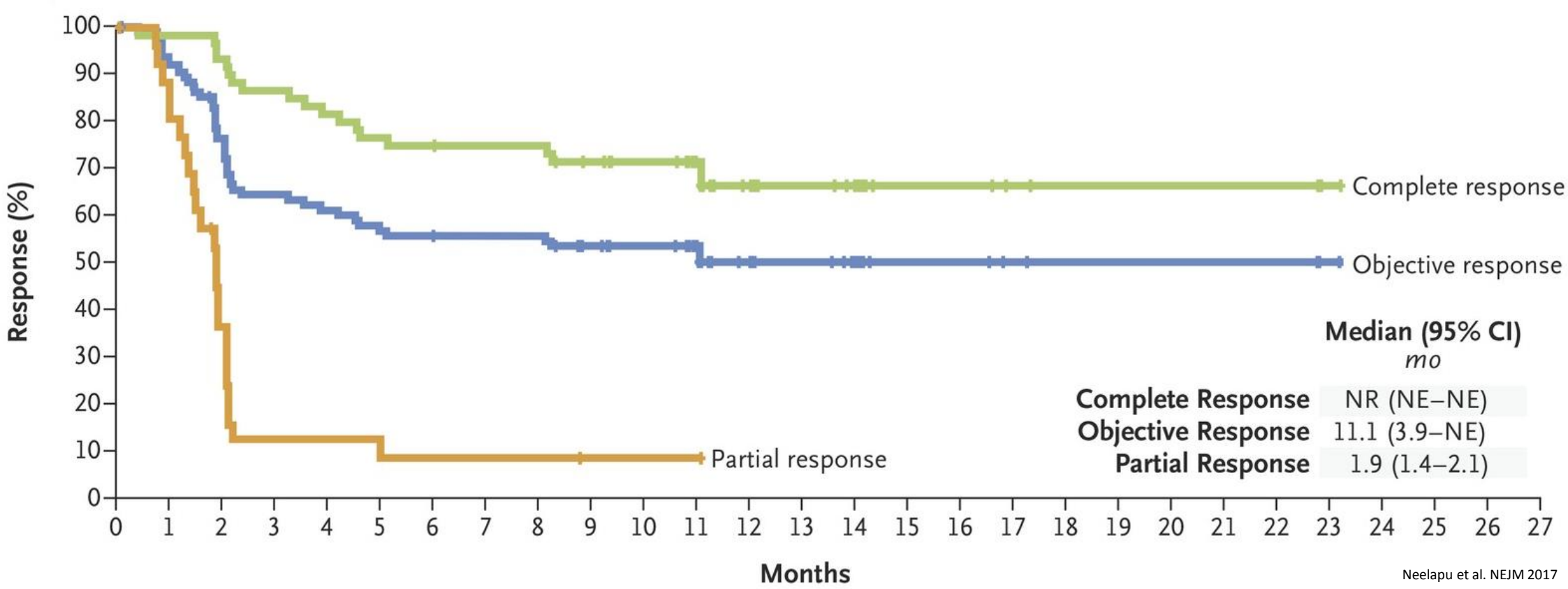
Overall Survival



Neelapu et al. NEJM 2017

Axicabtagene ciloleucel in B Cell Lymphoma

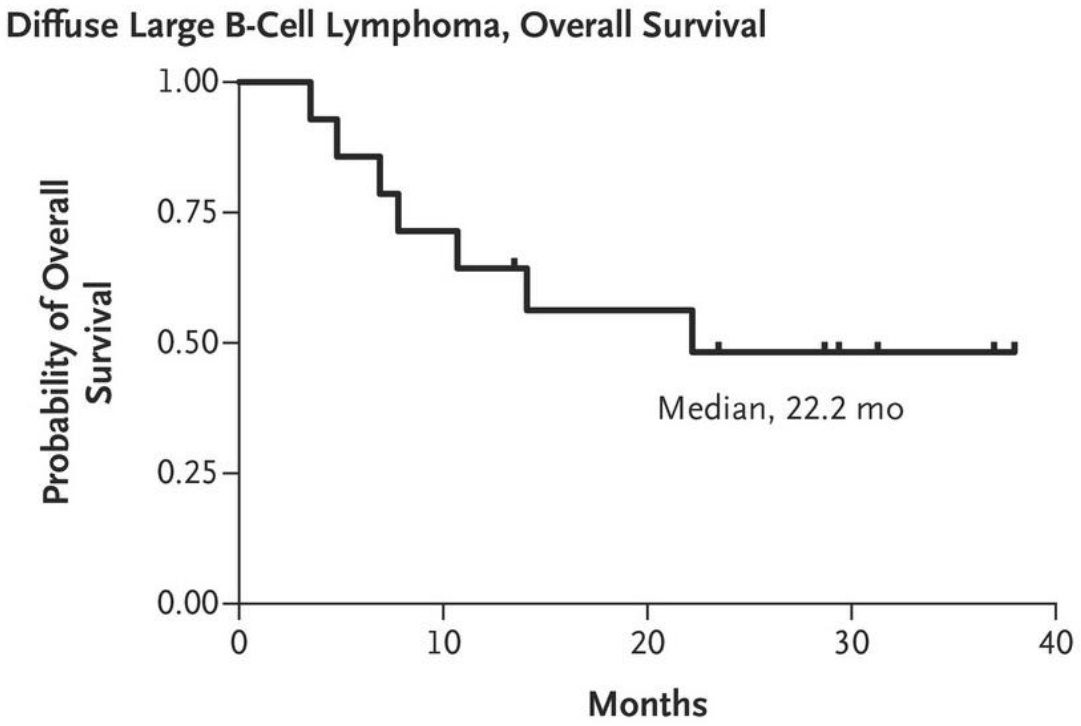
Duration of Response

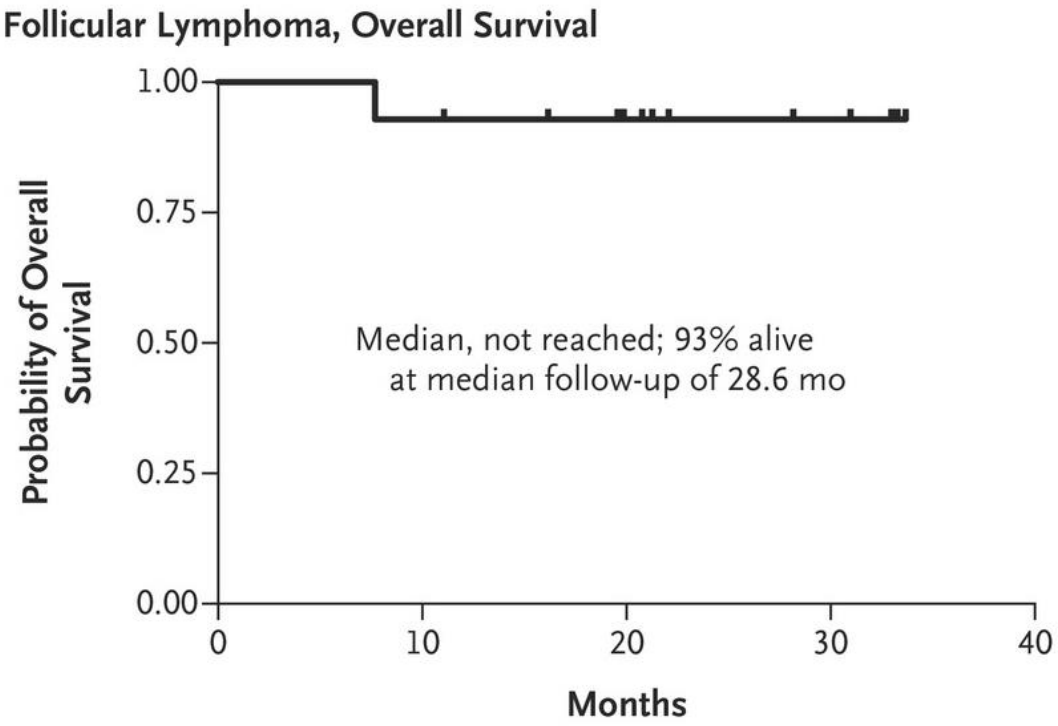


Neelapu et al. NEJM 2017

Tisagenlecleucel in B Cell Lymphoma

Overall Survival

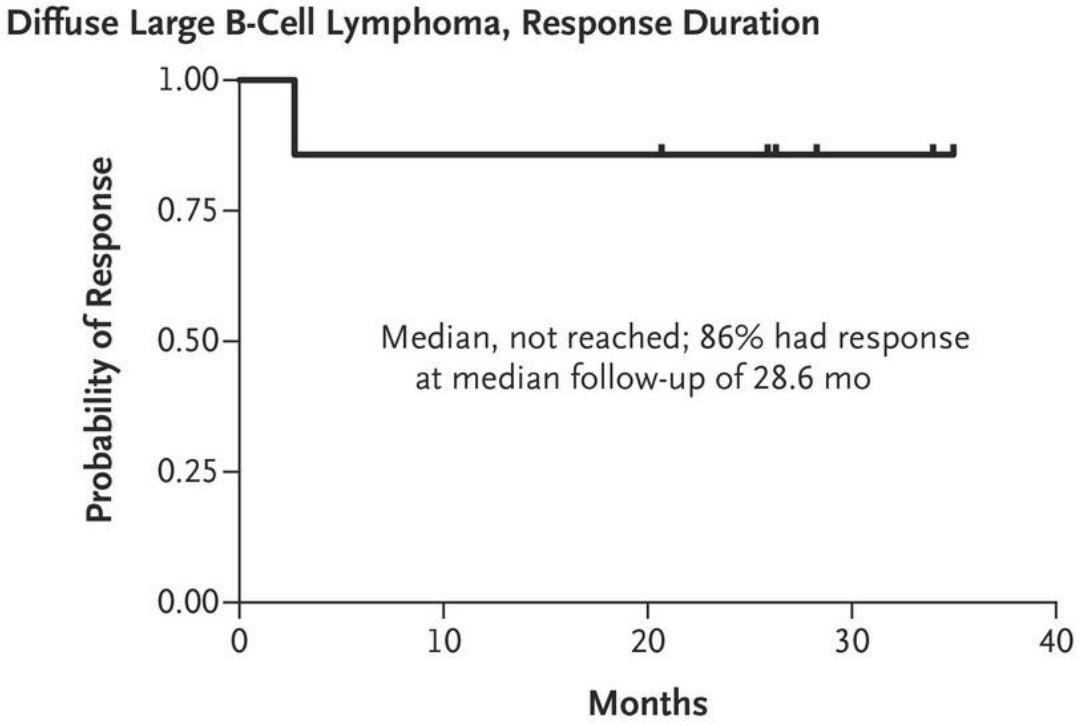


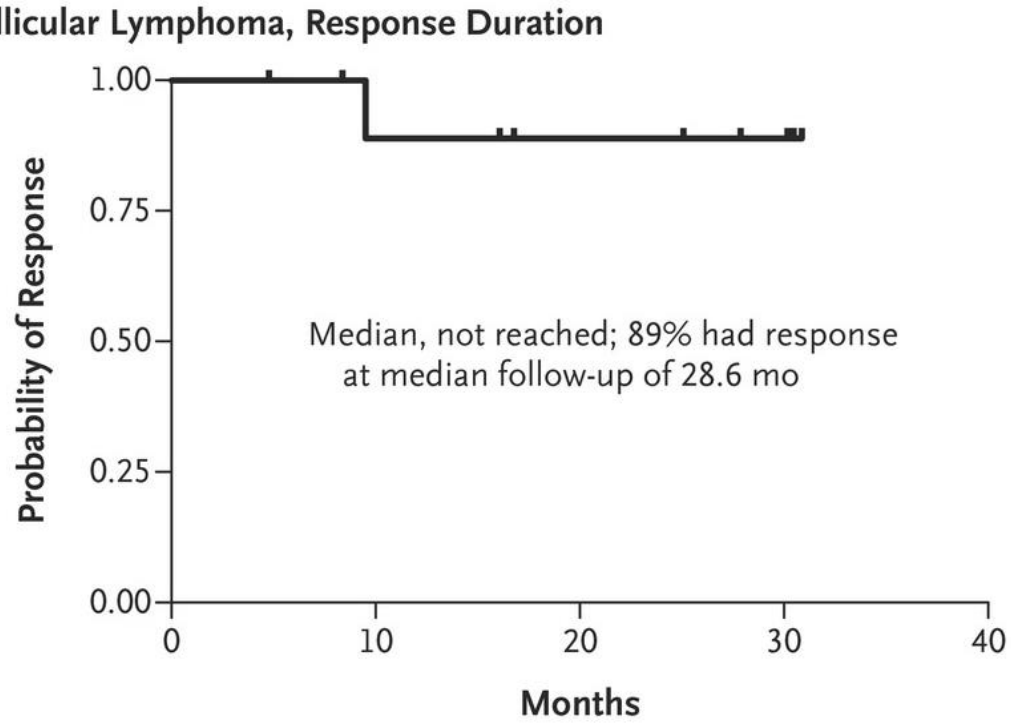


Schuster et al. NEJM 2017

Tisagenlecleucel in B Cell Lymphoma

Duration of Response



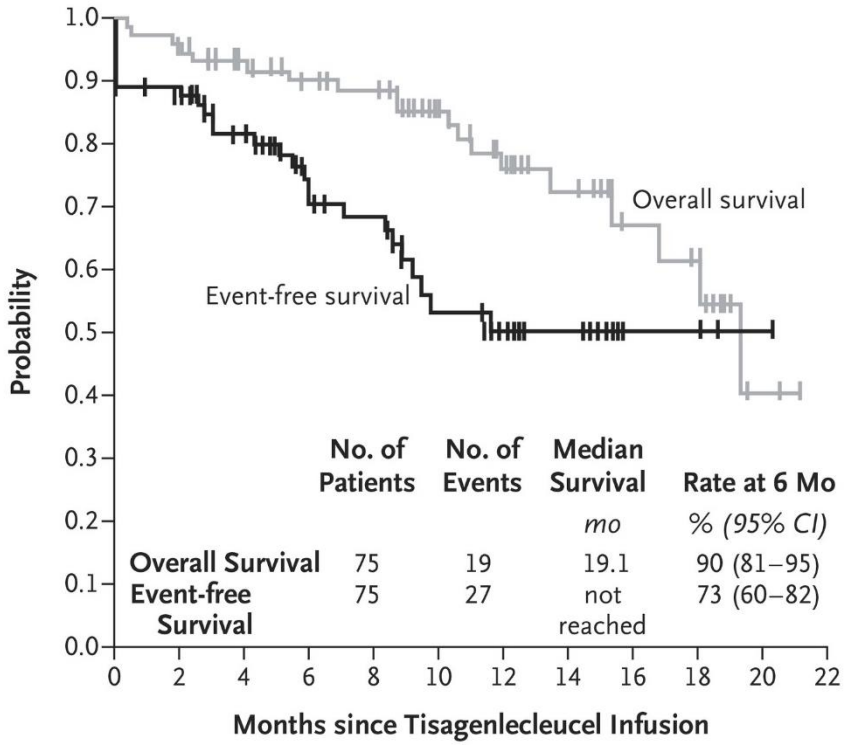


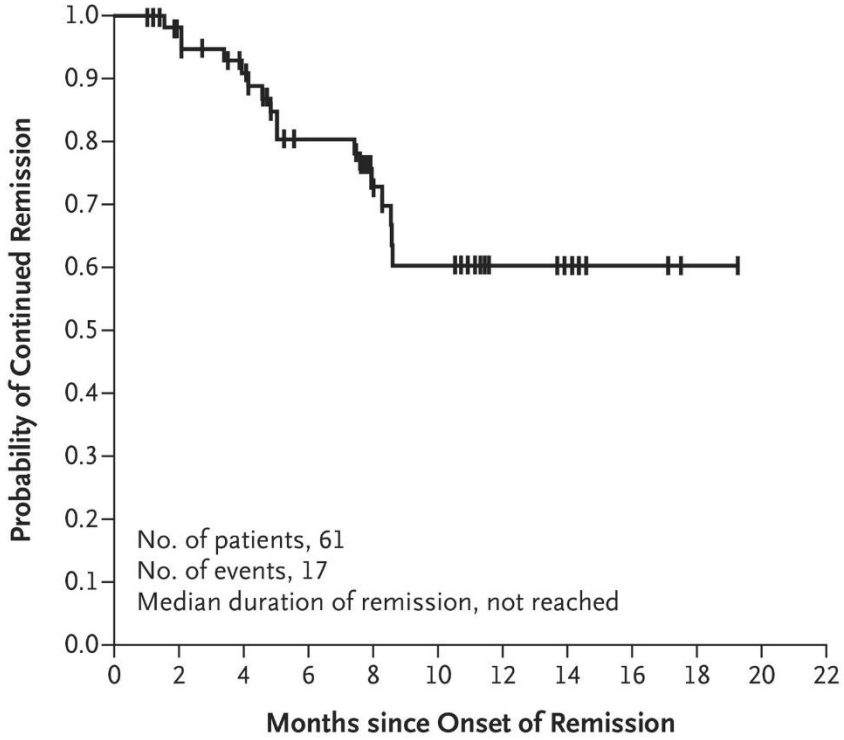
Schuster et al. NEJM 2017

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

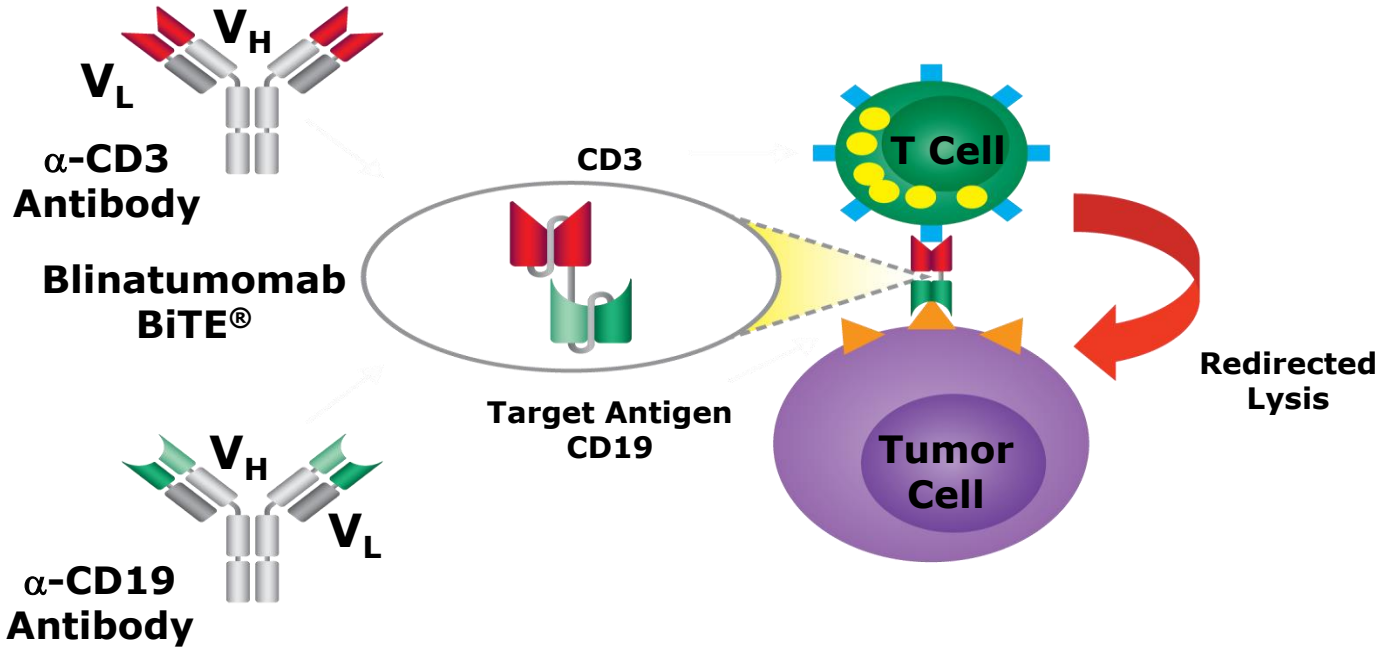




Maude et al. NEJM 2018

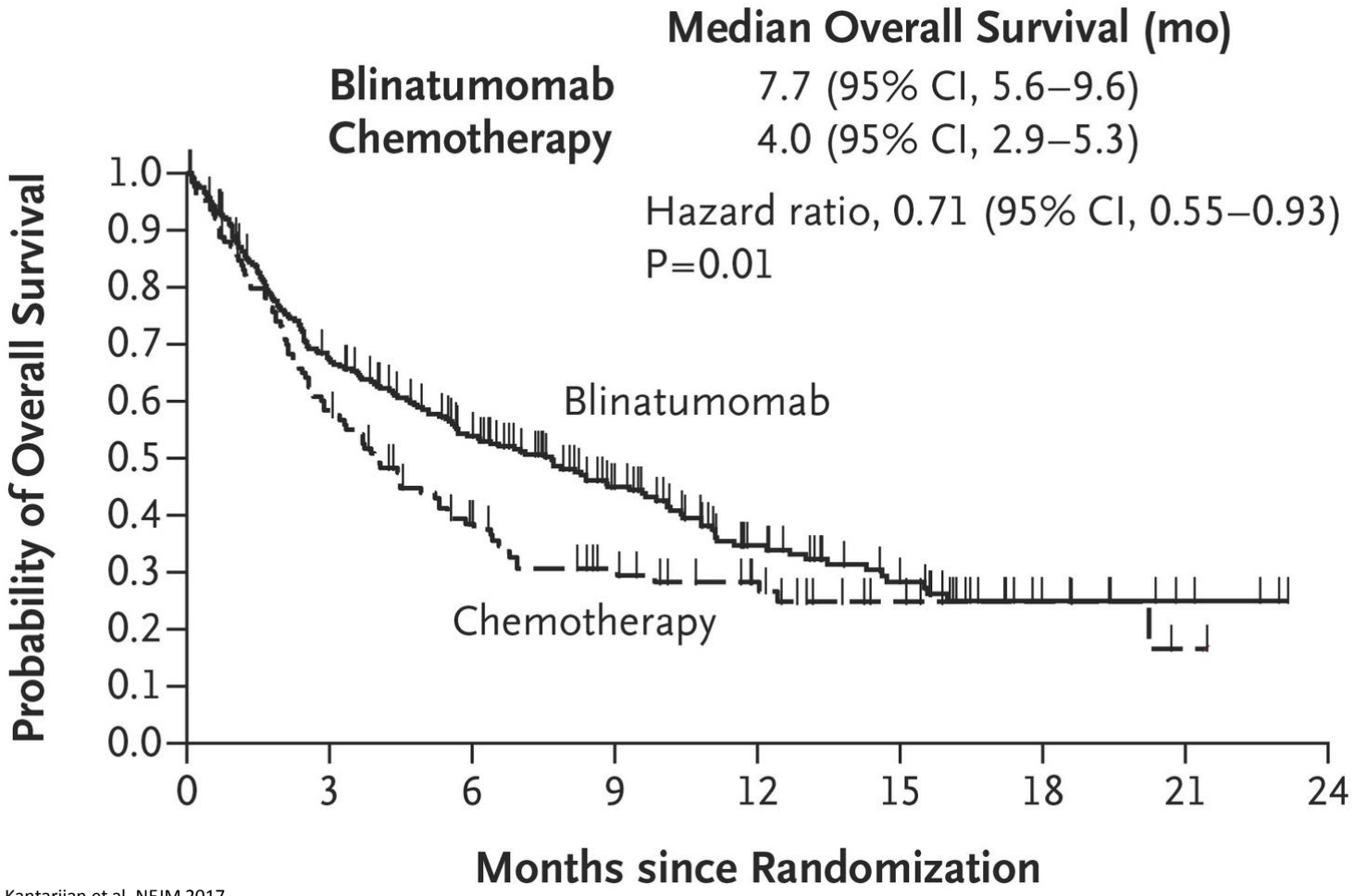
BiTE (Blinatumumab) Therapy

- 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



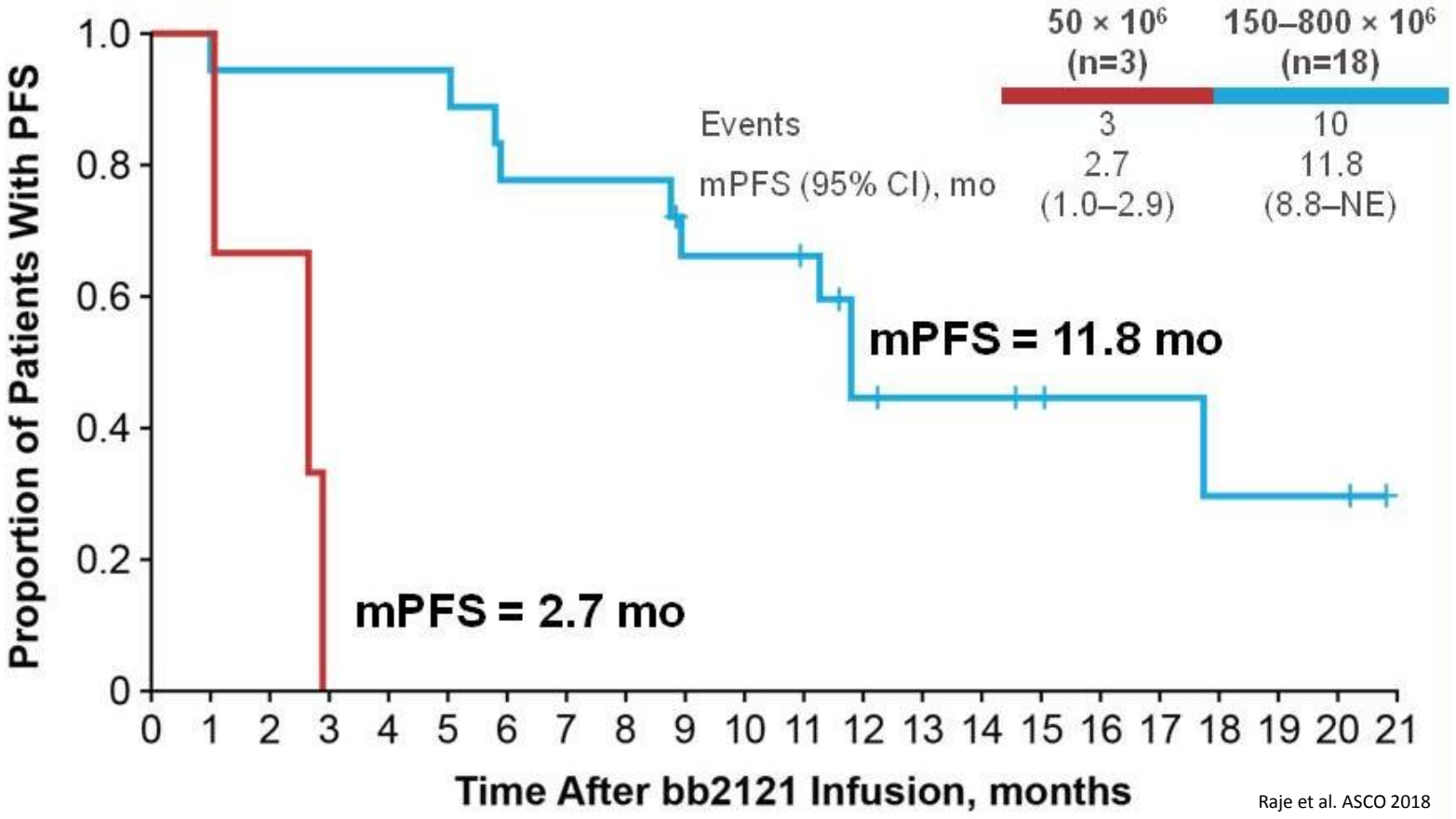
Kantarjian et al. NEJM 2017

Immunotherapies for Multiple Myeloma

- Monoclonal antibodies
  - Daratumumab (anti-CD38) monotherapy and in combination with lenalidomide, pomalidomide, or bortezomib
  - Elotuzumab (anti-SLAMF7) in combination with lenalidomide
- Immune checkpoint inhibitors (investigational)
  - KEYNOTE-183/185/023: Halted or discontinued due to risk/benefit profile
  - Other trials ongoing
- Vaccine-based approaches (investigational)
  - BMT-CTN 1401 DC-MM fusion vaccine for multiple myeloma
  - Other vaccine clinical trials
- Bi-specific and Ab-drug conjugates (investigational)
  - BCMA and GPRC5

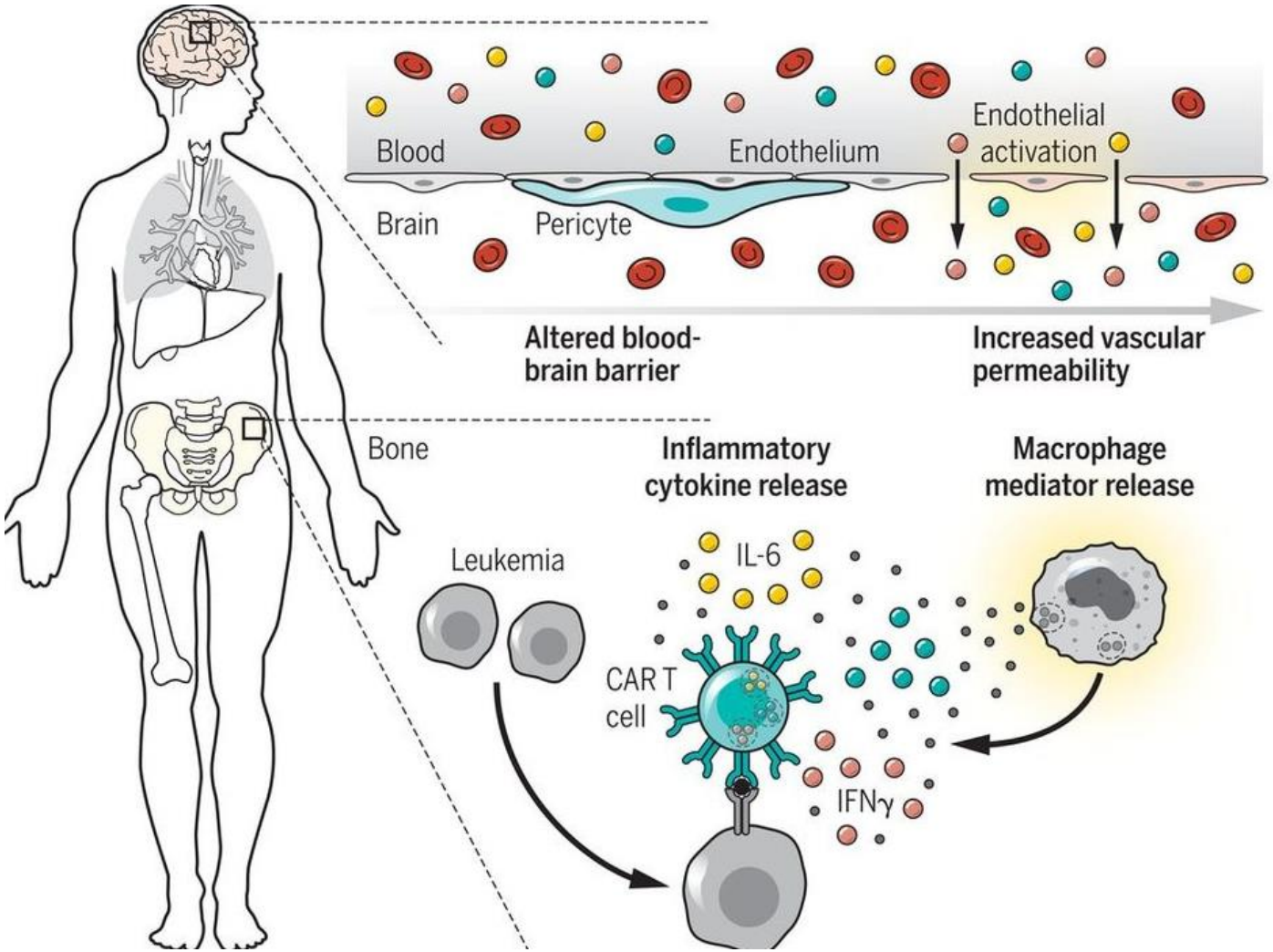
In Development: BCMA+ CAR T Therapy for Myeloma

- 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)



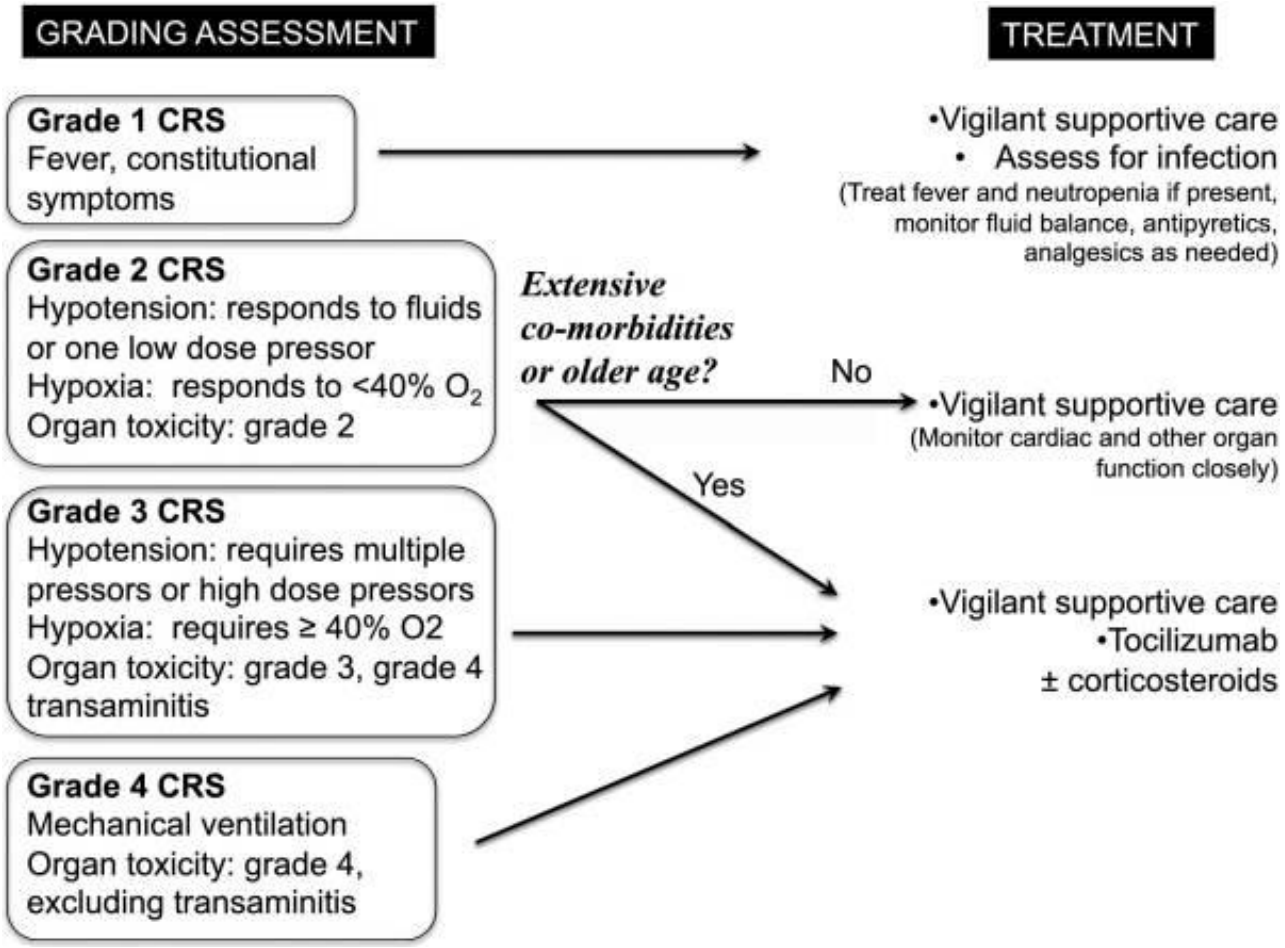
Neurotoxicity
Delirium
Aphasia
Seizures
Cerebral edema
Intracranial hemorrhage

Hemodynamic instability
Tachycardia
Hypotension
Capillary leak syndrome

Organ dysfunction
AST and ALT elevation
Hyperbilirubinemia
Respiratory failure

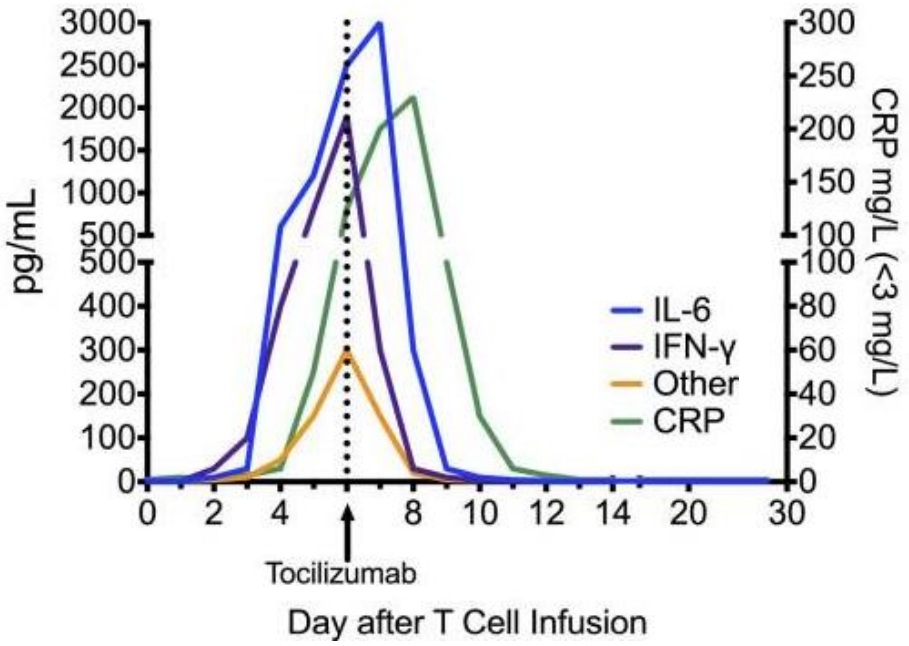
June et al. Science 2018

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: Lymphoma (I)

- A 25-year-old woman was diagnosed with classical, nodular-sclerosing Hodgkin's lymphoma stage IIIB after a 20 lb weight loss, night sweats, and mediastinal and retroperitoneal masses detected on PET/CT. She is otherwise in good health. WBC 6.8, Lymphocytes 20%, Hgb 10.1, Albumin 4.0. Pulmonary function tests indicate DLCO 98% predicted. Echocardiogram demonstrates LVEF = 60%. She received adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) for 2 cycles. PET2 demonstrated metabolic CR (Deauville 1) and she received another 4 cycles of AVD. She remained in remission for 18 months, then progression was noted by recurrent B symptoms and PET-avid lesions.
- What is the appropriate next treatment?
  - Salvage chemotherapy followed by autologous stem cell transplantation
  - Brentuximab vedotin
  - Anti-PD-1 checkpoint inhibitor (nivolumab or pembrolizumab)

Case Study: Multiple Myeloma (I)

- A 67-year-old woman with IgG kappa MM R-ISS stage 1 (alb 4, B2M 2.9, LDH 130, no HRCA) achieved >90% reduction in M-protein (VGPR) after four cycles of lenalidomide, bortezomib, dexamethasone (RVD) chemotherapy. She is referred for evaluation for high dose chemotherapy and stem cell transplant for consolidation therapy. The patient has grade 1 chronic renal insufficiency and well-controlled type 2 diabetes. Initial chemotherapy was complicated by grade 1 neuropathy.

Case Study: Multiple Myeloma (II)

- The patient underwent stem cell harvest followed by auto-transplant for consolidation. Re-staging assessment at day +90 post-transplant showed stringent complete remission (sCR). The patient started maintenance lenalidomide (10 mg daily 21/28 days). She completed two years of maintenance therapy then discontinued in agreement with he doctor. She remained in remission for four years after transplant. Four years after transplant, at age 71, the patient relapsed with rising IgG kappa M-spike and anemia. She started carfilzomib cyclophosphamide dex for salvage. She achieved a PR after 4 cycles but then demonstrated progression of disease.
- What is an appropriate next step for salvage therapy?
  - BCMA CAR-T clinical trial
  - Bortezomib doxil
  - Elotuzumab lenalidomide dex
  - Daratumumab pomalidomide dex