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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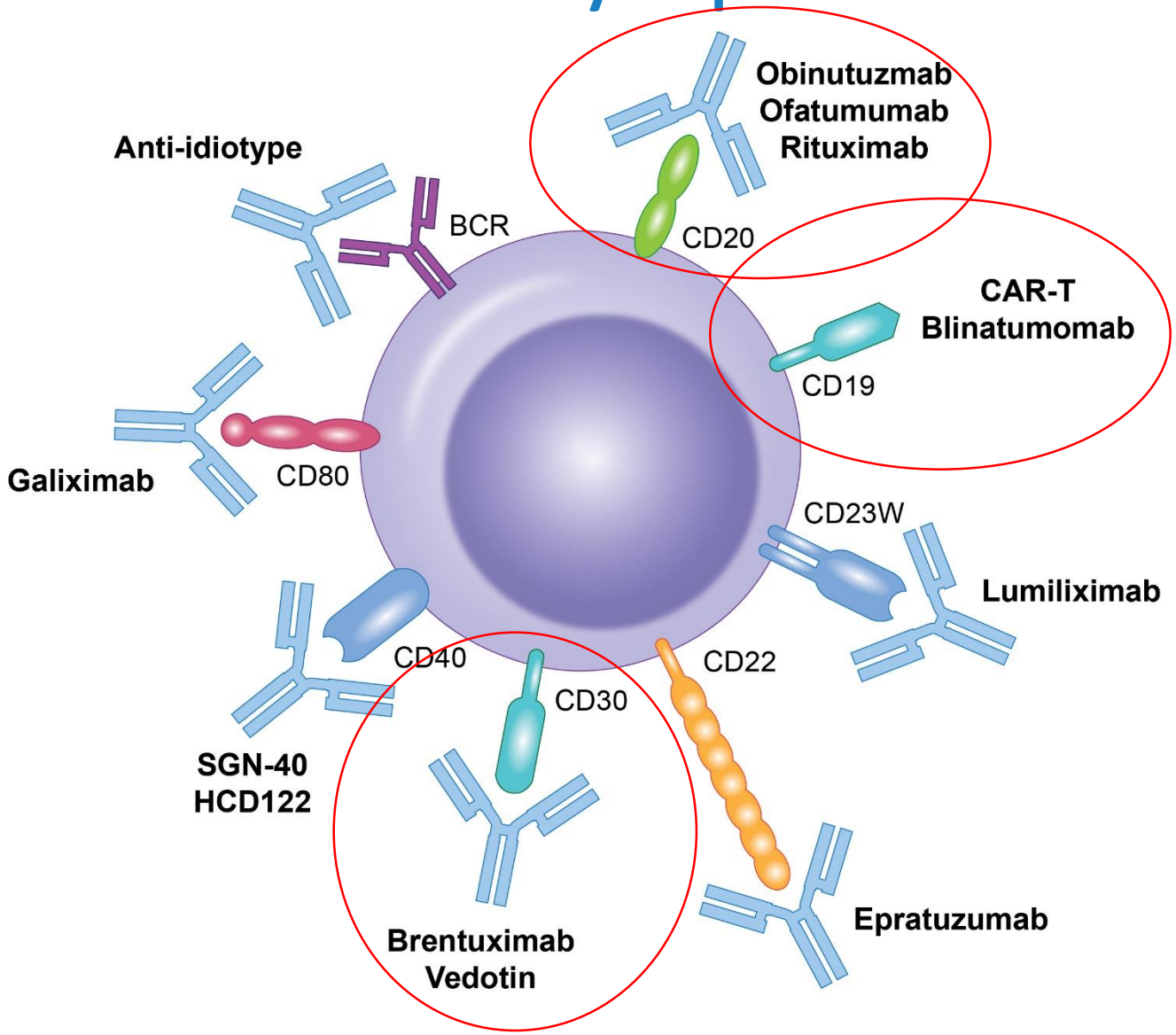
Disclosures

- Research Funding: Acerta, Gilead, Karyopharm
- Honoraria/Consulting: Genentech
- I will be discussing non-FDA approved indications during my presentation.

Presentation Outline

- **Monoclonal Antibodies**
- **Checkpoint Inhibitors**
  - Nivolumab
  - Pembrolizumab
- **BiTE Therapy**
  - Blinatumumab
- **CART Therapies**
  - Axicabtagene ciloleucel
  - Tisagenlecleucel
  - Toxicity
- **Future Indications for Immunotherapy**
  - Multiple Myeloma

Monoclonal Antibodies Targeting B Cell Lymphomas



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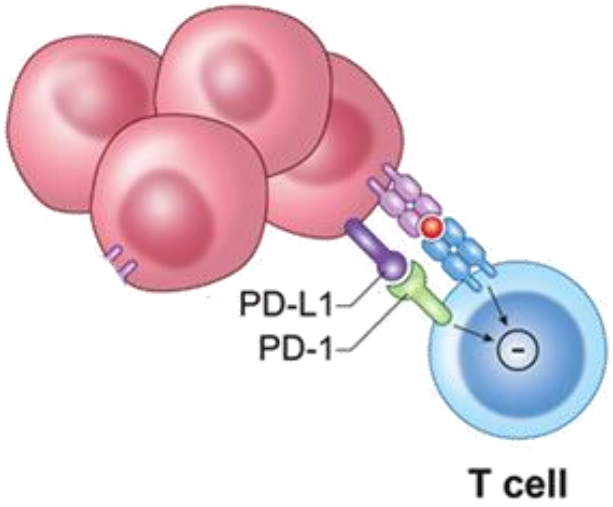
Checkpoint Inhibitors

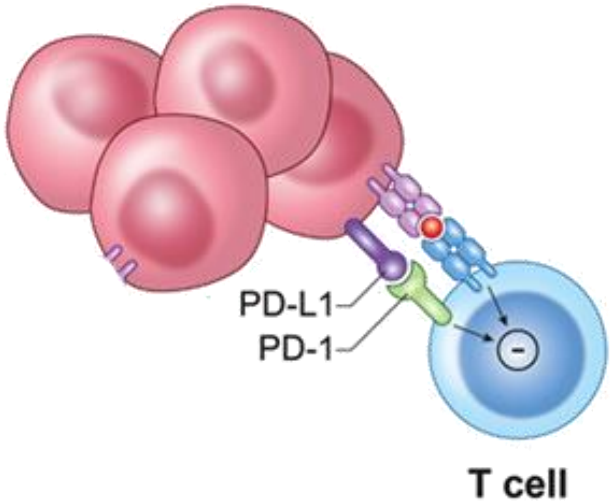
- PD-1 (T-cells) = looks for PD-L1 on other cells
- Once PD-1 and PD-L1 are bound = prevents T-cell induced apoptosis
- Tumor cells upregulate PD-L1 so they will not be killed by T-cells
- Blocking this interaction allows the tumor cells to be killed by the T-cells (and some normal cells)

- PD-1 = Passport control
- PD-L1 = Passport – if valid, can access and continue living in the country
- Tumor cells make fake passports
- Checkpoint inhibitors = border wall (don't allow interaction of passport and passport control)
- Blocks admission of tumor cells (and a lot of normal cells as well)



FDA-approved Checkpoint Inhibitors for Lymphomas

- Nivolumab (anti-PD-1)
  - CheckMate 205/039: R/R cHL following autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin
- Pembrolizumab (anti-PD-1)
  - KEYNOTE-087: Refractory cHL, or patients whose disease has relapsed after 3+ lines of therapy
  - KEYNOTE-170: Refractory primary mediastinal large B-cell lymphoma (PMBCL), or those who have relapsed after 2+ lines of therapy



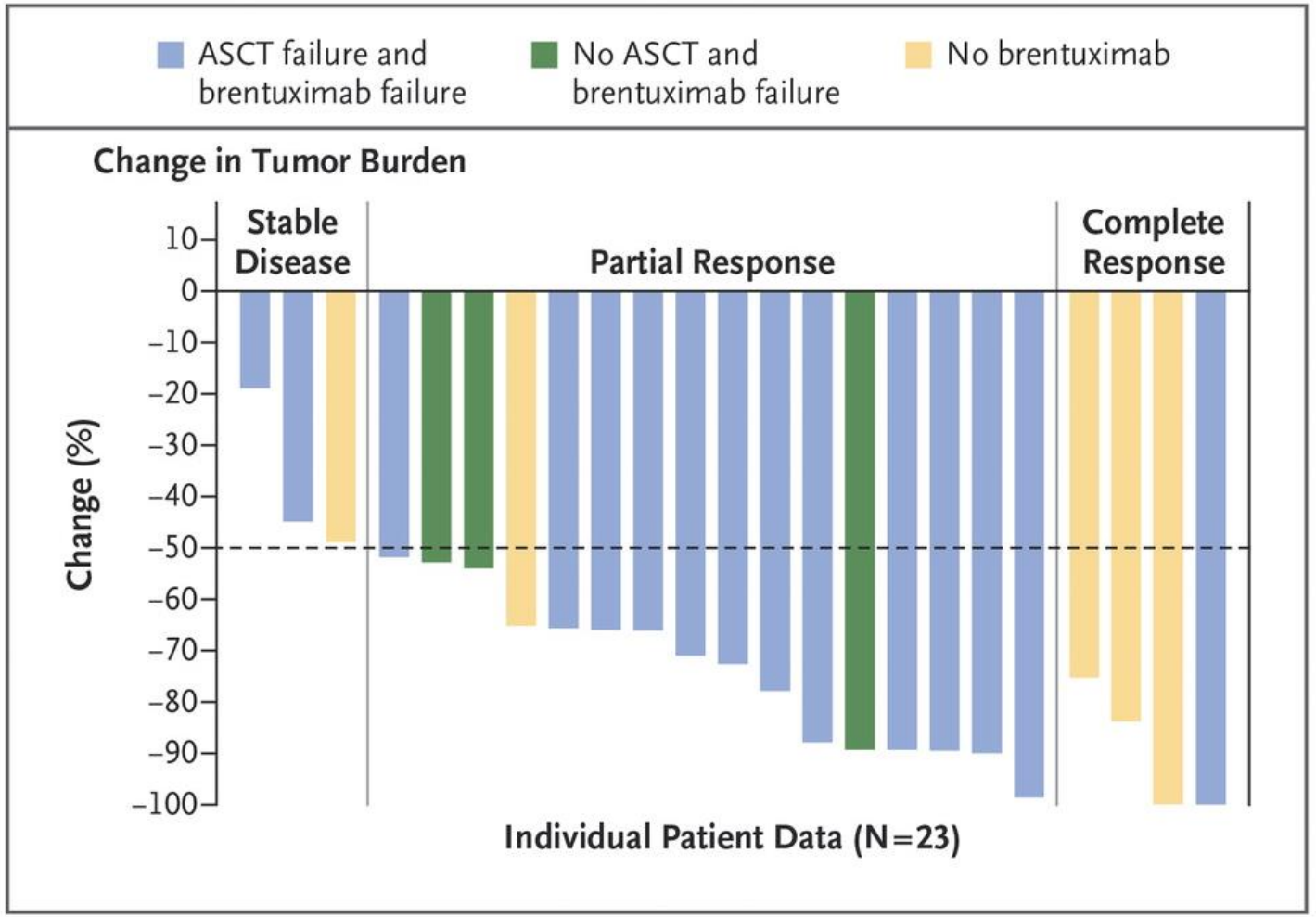
Nivolumab in Hodgkin Lymphoma

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

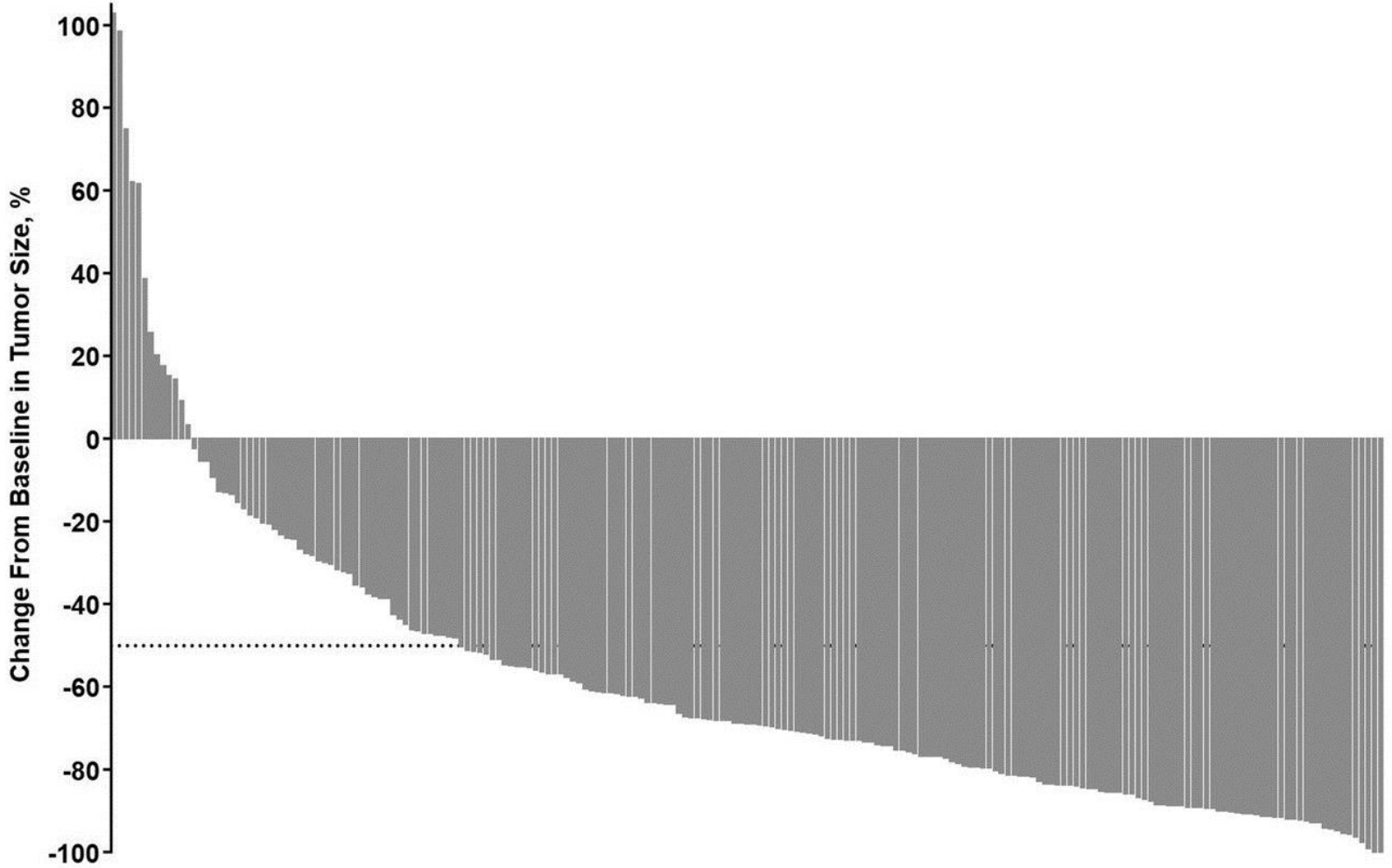
Ansell et al. NEJM 2015

Nivolumab in Hodgkin Lymphoma



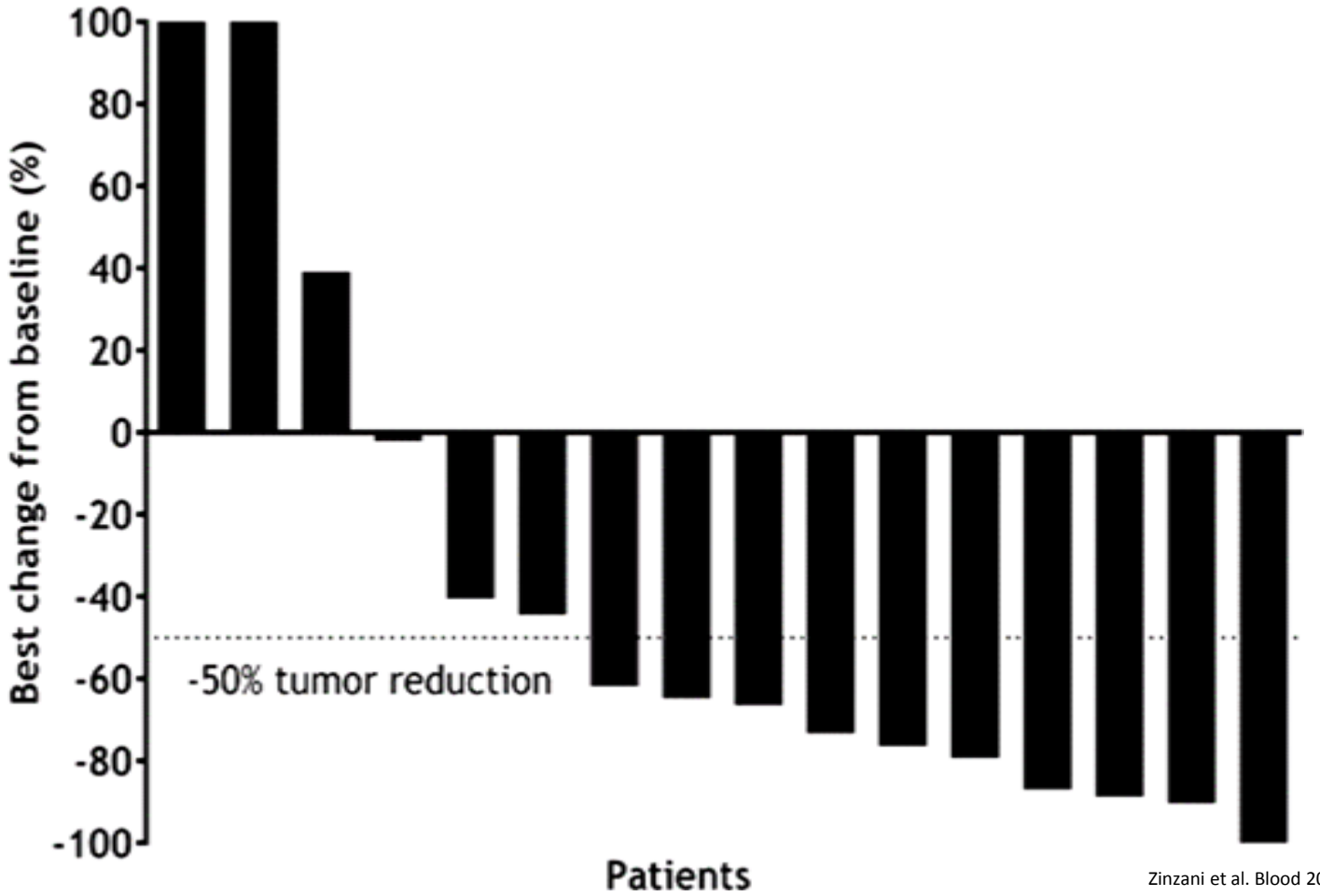
Ansell et al. NEJM 2015

Pembrolizumab in Hodgkin Lymphoma



Zinzani et al. Hematological Oncology 2017

Pembrolizumab in Primary Mediastinal Large B cell Lymphoma



Zinzani et al. Blood 2016

Checkpoint Inhibitor Toxicity

- **Autoimmune Manifestations**
- Colitis
- Hepatitis
- Pneumonitis
- Endocrinopathies
- Skin Rash
- Others

- **Management**
- Immune suppression
- High-dose steroids
- Mycophenolate or Infliximab

Zinzani et al. Blood 2016

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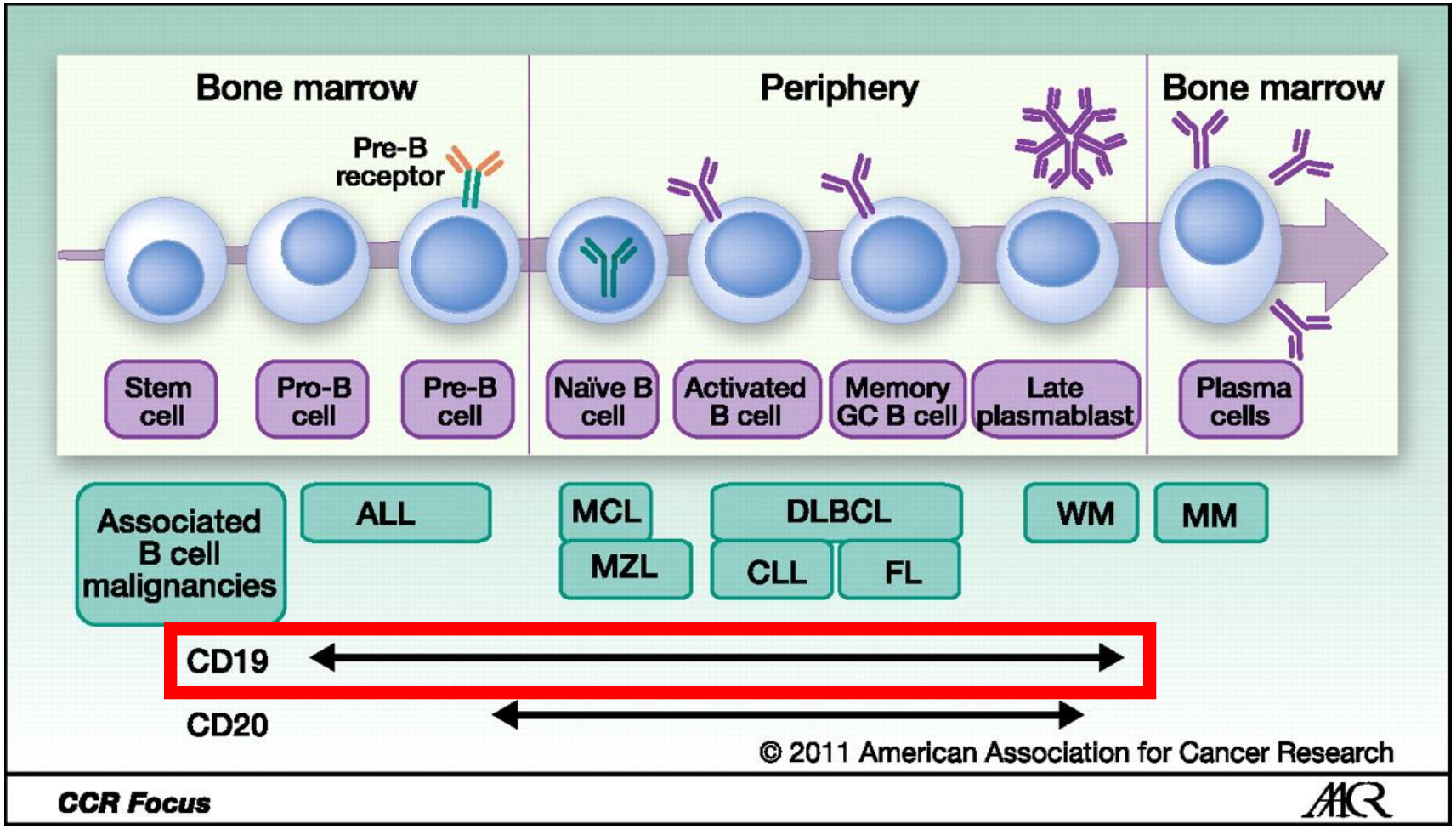
  - Nivolumab
  - Pembrolizumab
- **BiTE Therapy**
  - Blinatumumab

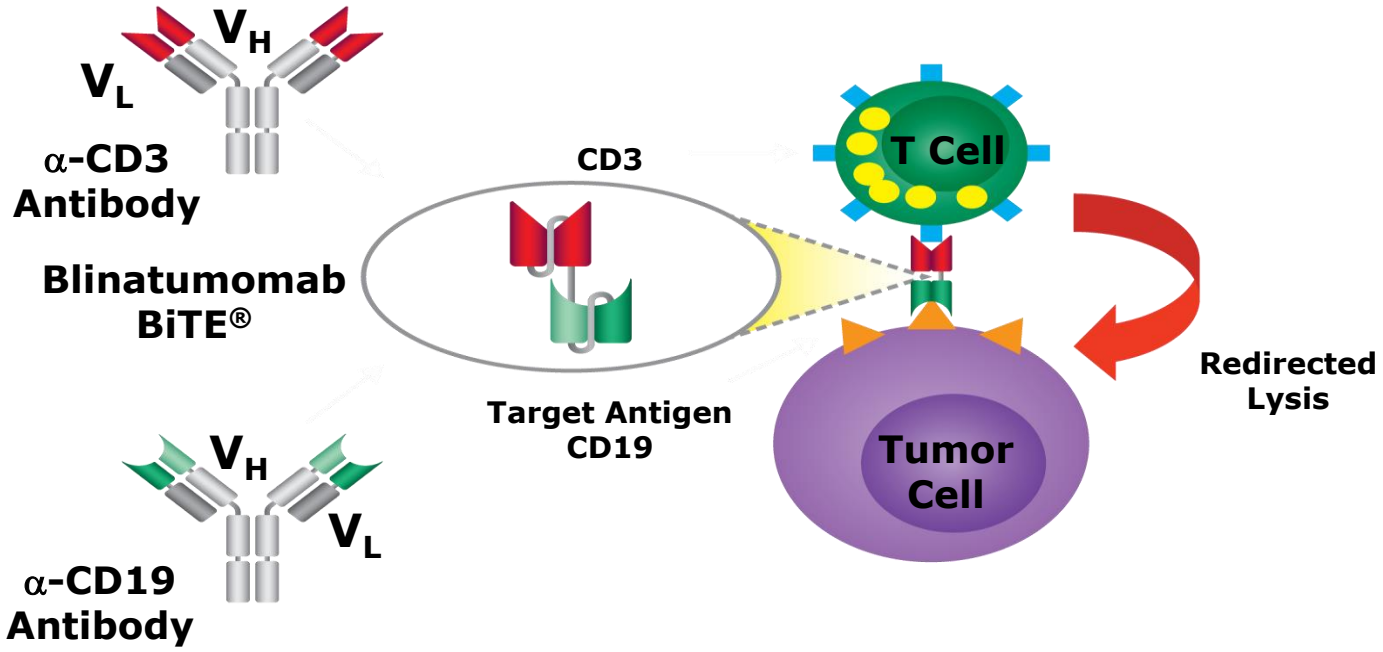
B Cell Malignancies are CD19+



Blanc et al. Clinical Cancer Research 2011

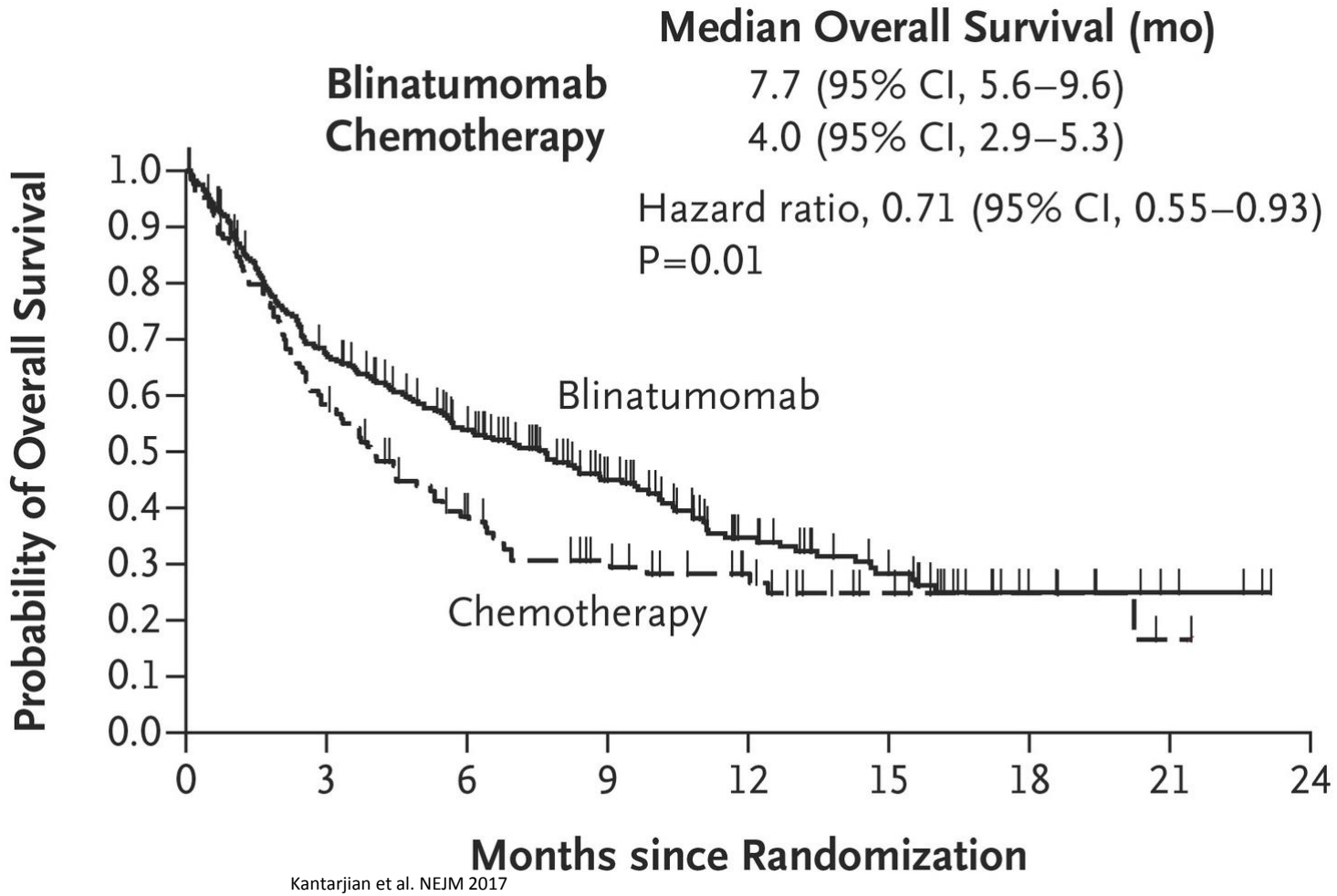
BiTE (Blinatumumab) Therapy

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



Bargou et al. Science 2008

Blinatumomab for B-ALL



Kantarjian et al. NEJM 2017

Challenges:

- Short half life = continuous infusion
- Hospital admission for 3 days with C1, 2 days with C2
- Toxicity = CRS

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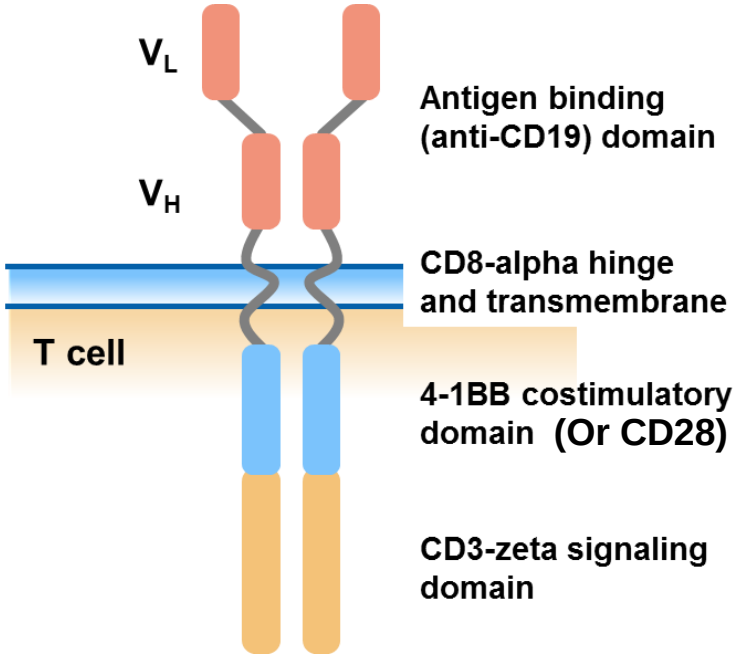
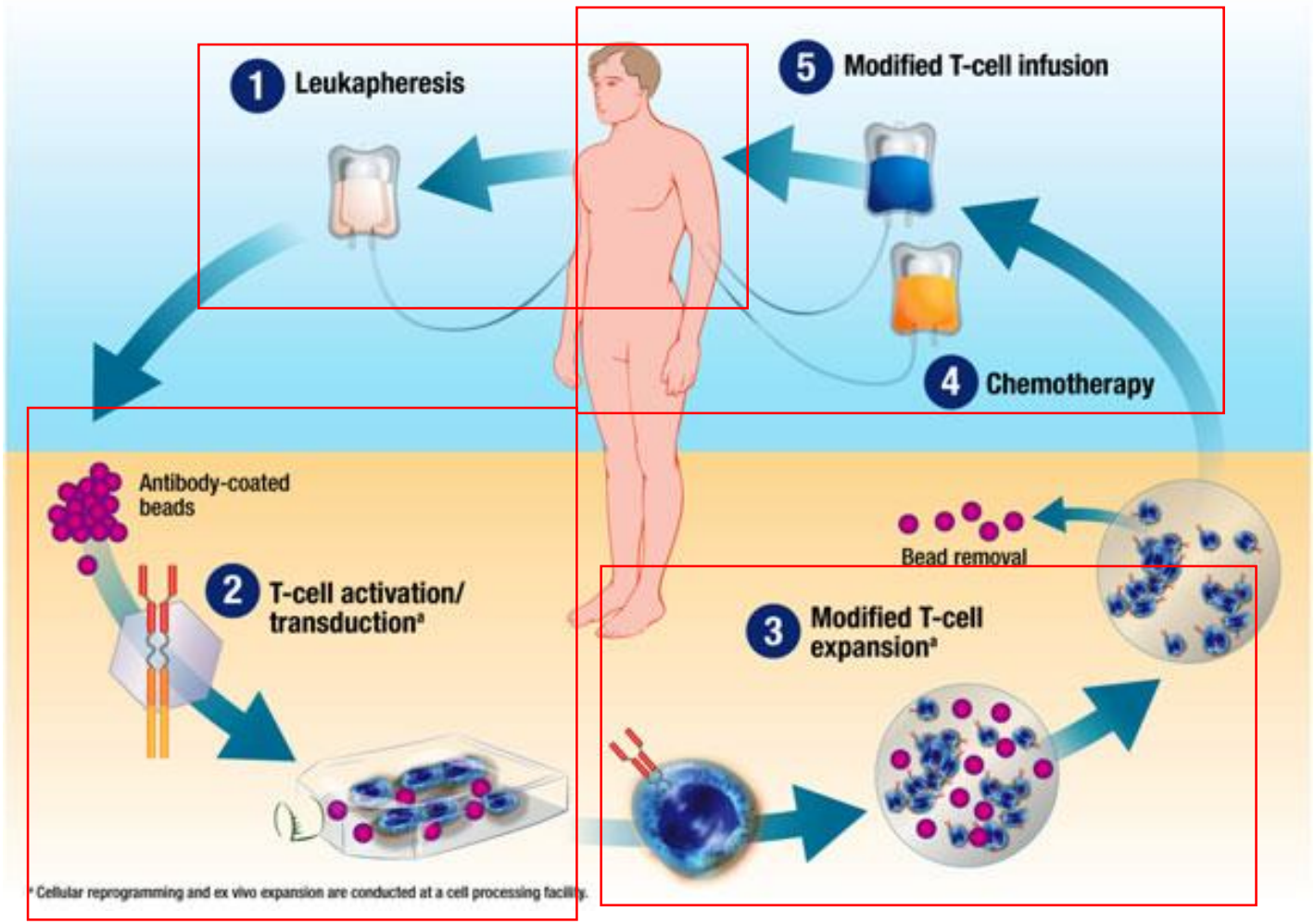
  - Tisagenlecleucel
  - Toxicity

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

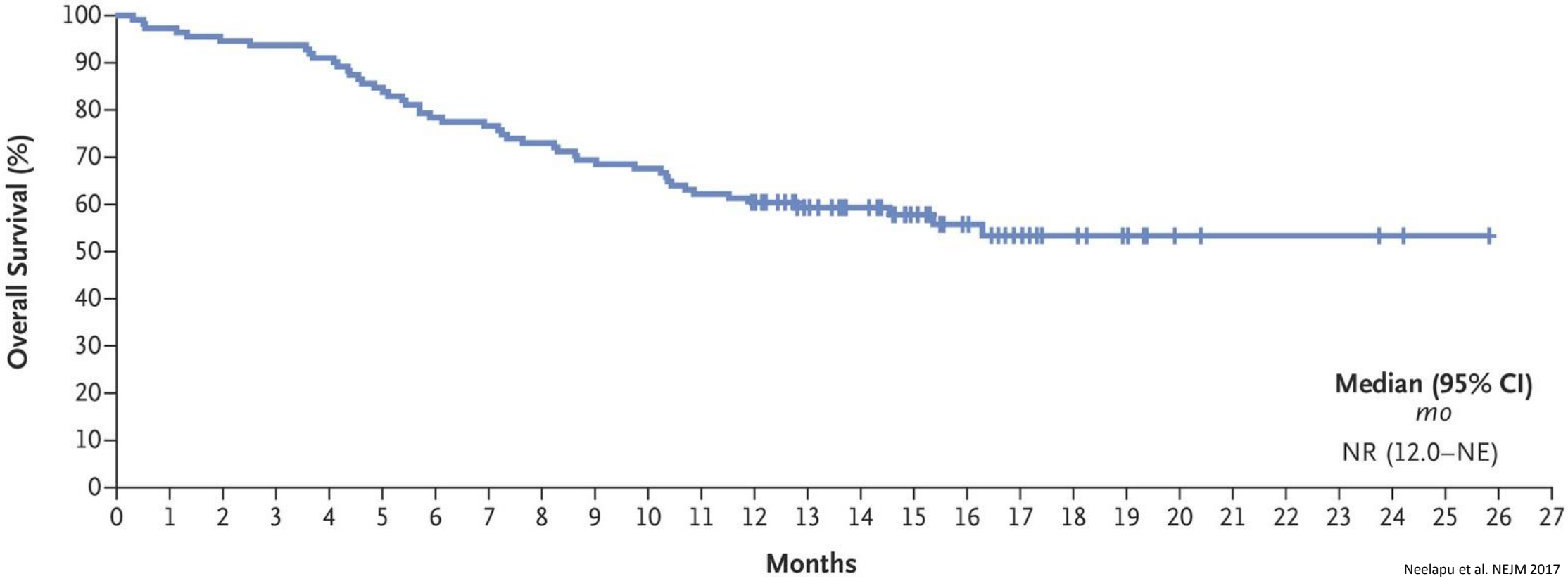
- Axicabtagene ciloleucel
  - ZUMA-1: Adult patients with R/R large B cell lymphoma after 2+ lines of systemic therapy, including diffuse large B cell lymphoma, high-grade B cell lymphoma, and DLBCL arising from follicular lymphoma
- Tisagenlecleucel
  - JULIET: adult patients with relapsed/refractory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

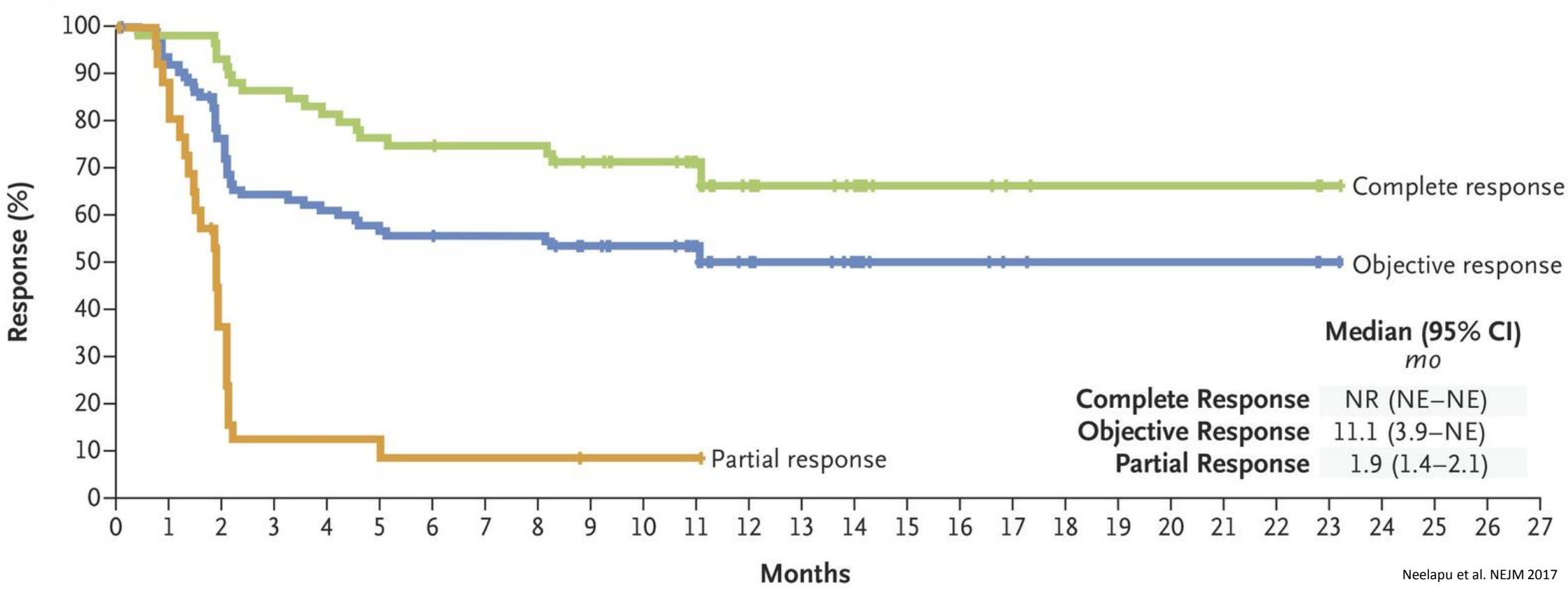
Overall Survival



Neelapu et al. NEJM 2017

Axicabtagene ciloleucel in B Cell Lymphoma

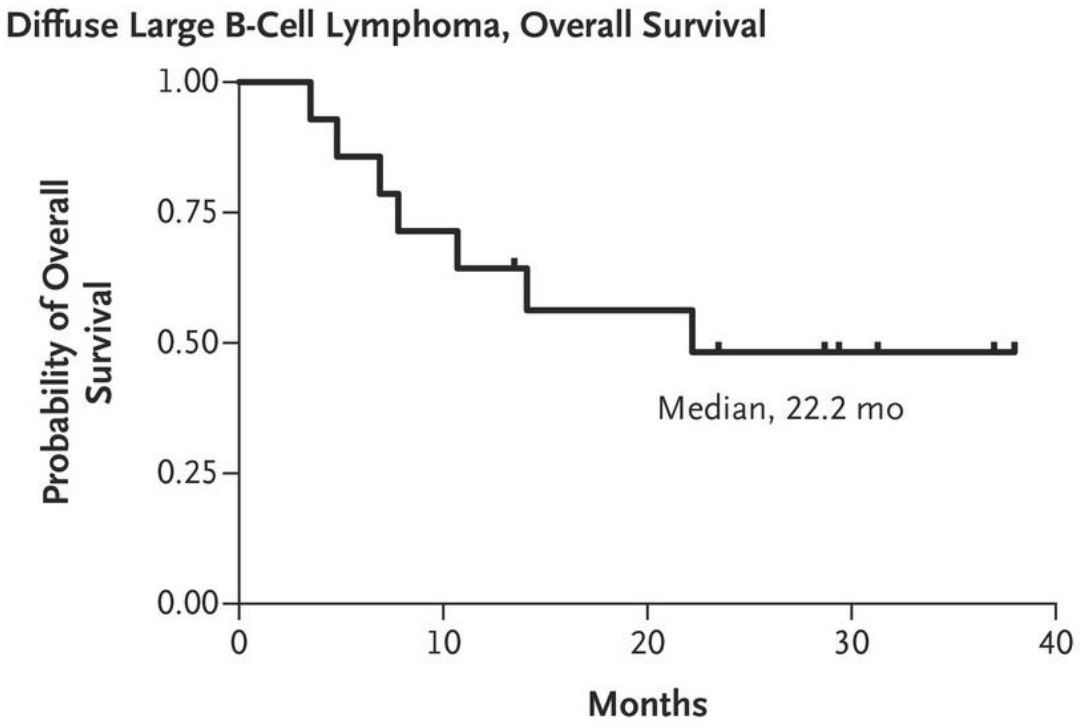
Duration of Response

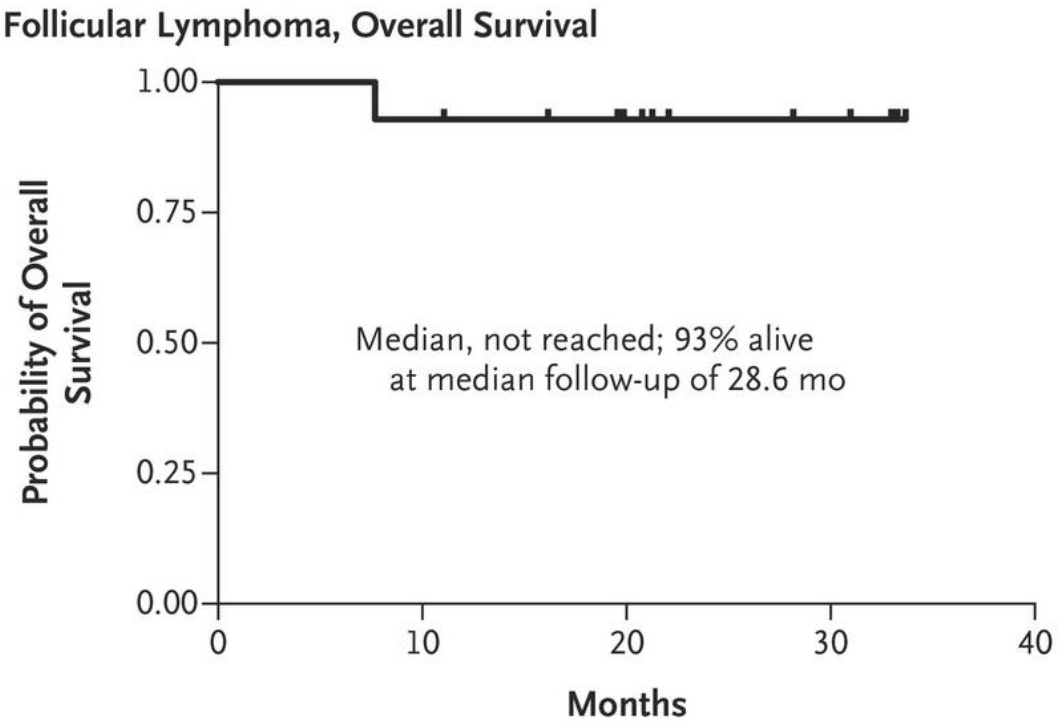


Neelapu et al. NEJM 2017

Tisagenlecleucel in B Cell Lymphoma

Overall Survival

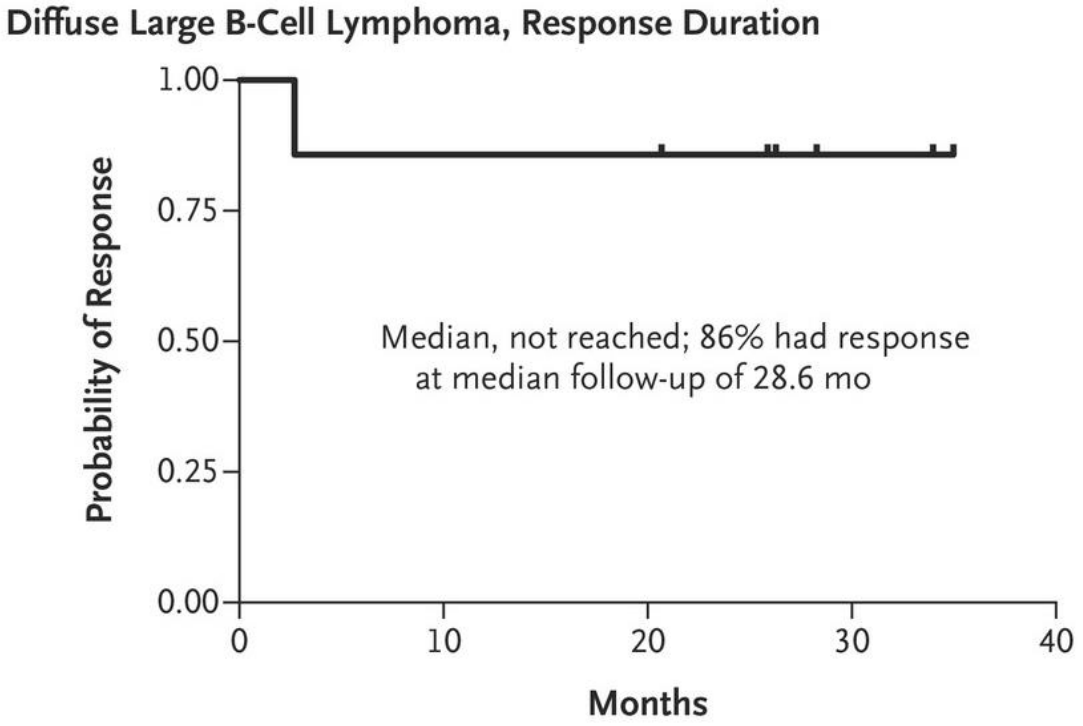


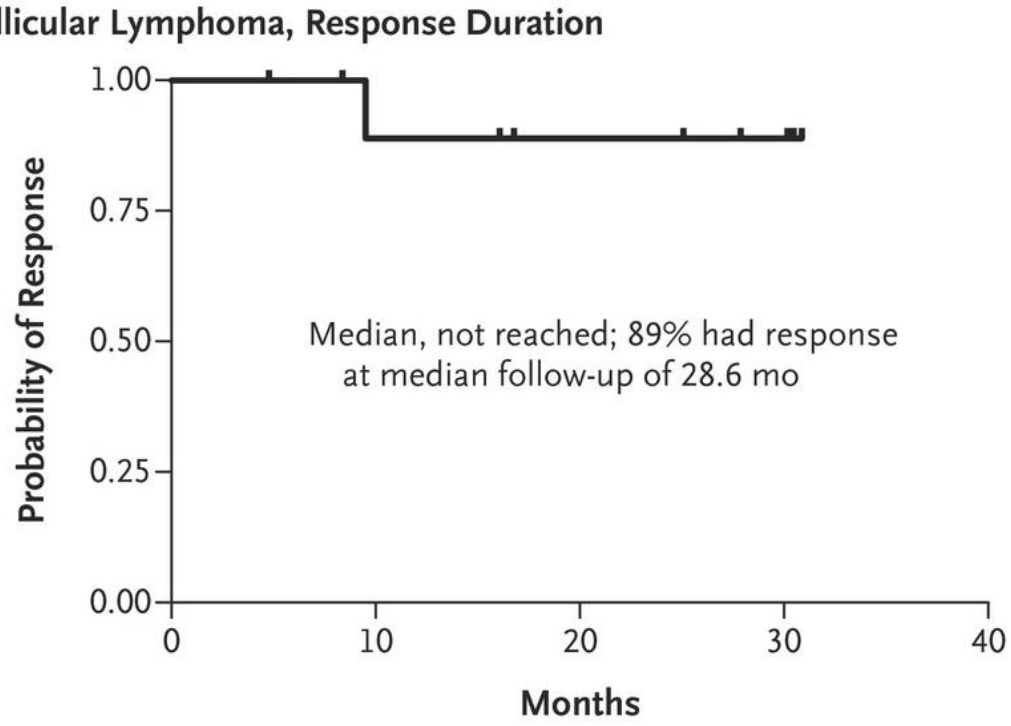


Schuster et al. NEJM 2017

Tisagenlecleucel in B Cell Lymphoma

Duration of Response



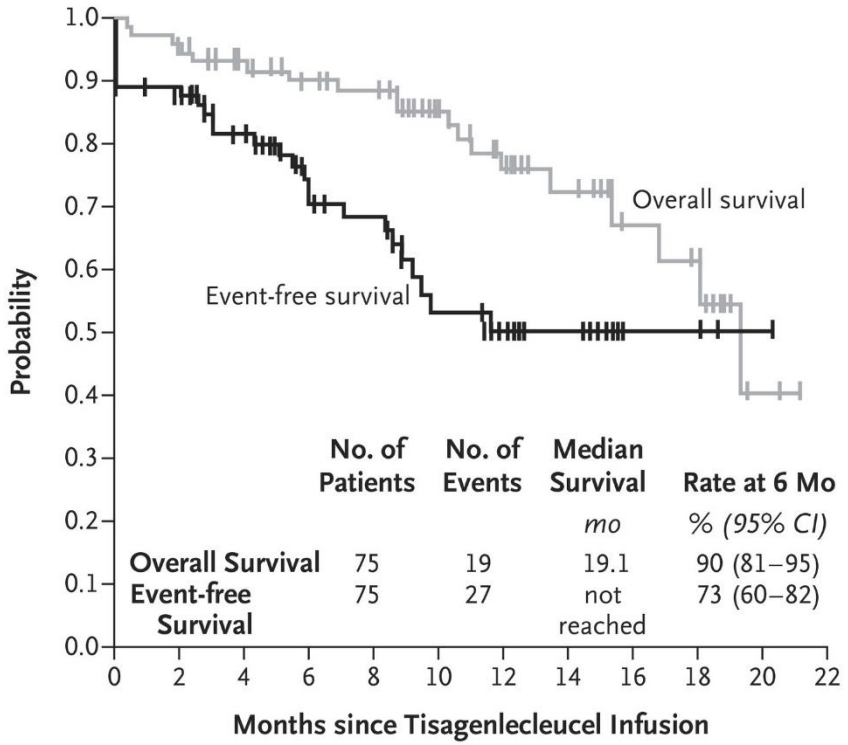


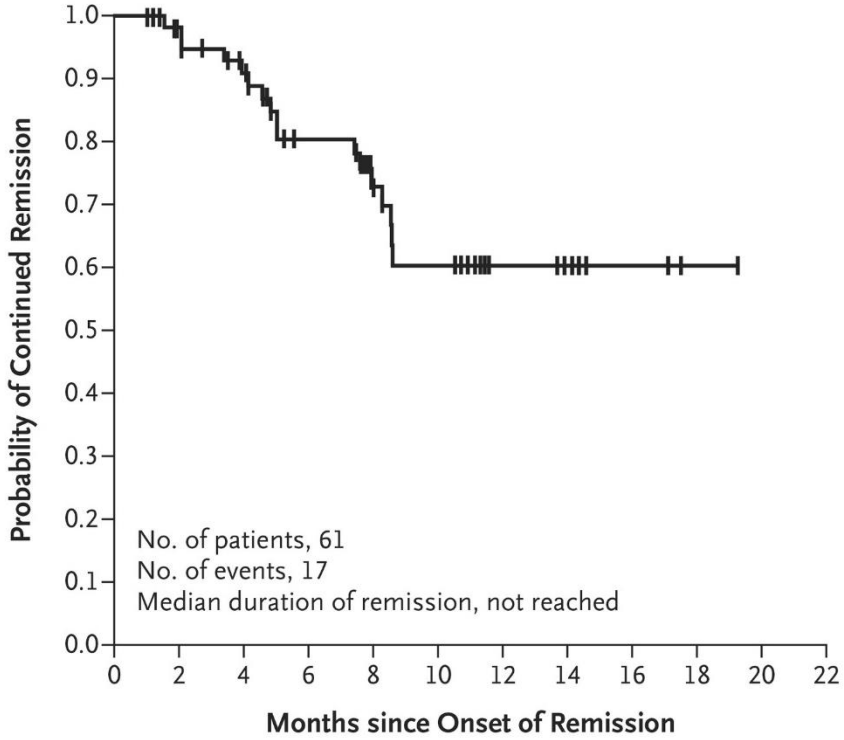
Schuster et al. NEJM 2017

FDA-approved CAR T Cell Therapies for Acute Leukemia

Tisagenlecleucel

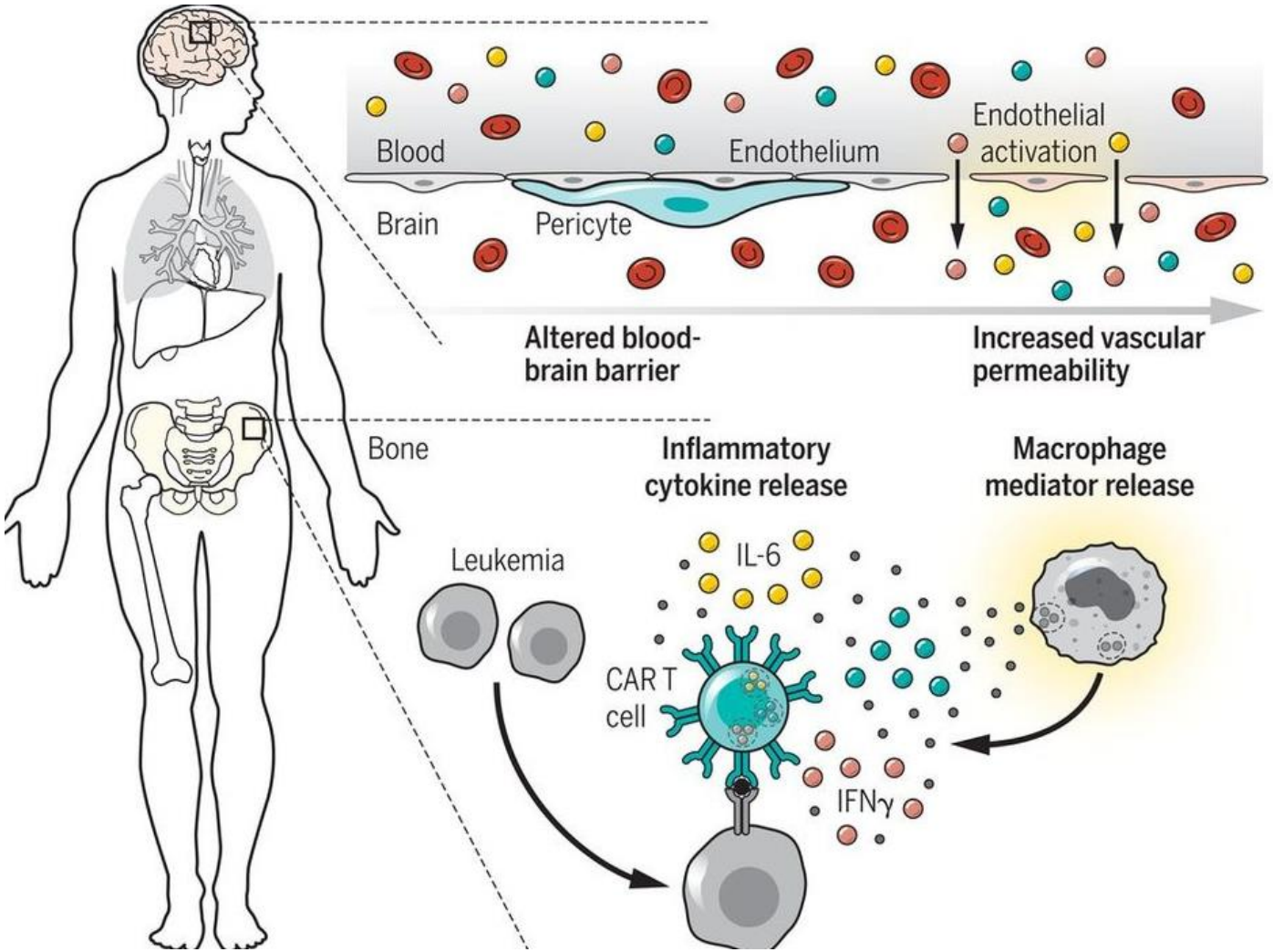
- ELIANA: patients up to age 25 years with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse





Maude et al. NEJM 2018

Cytokine Release Syndrome (CRS)



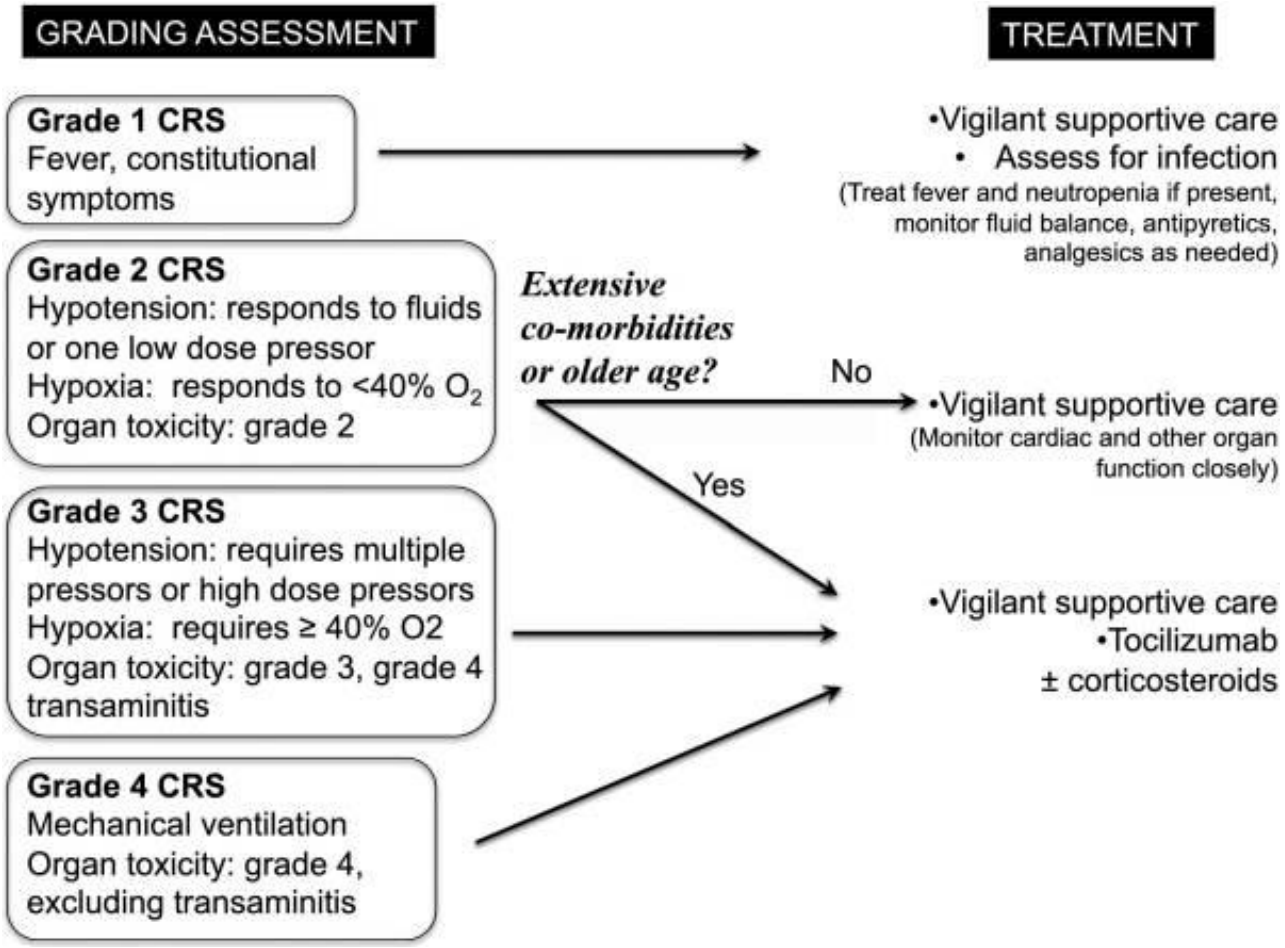
Neurotoxicity
Delirium
Aphasia
Seizures
Cerebral edema
Intracranial hemorrhage

Hemodynamic instability
Tachycardia
Hypotension
Capillary leak syndrome

Organ dysfunction
AST and ALT elevation
Hyperbilirubinemia
Respiratory failure

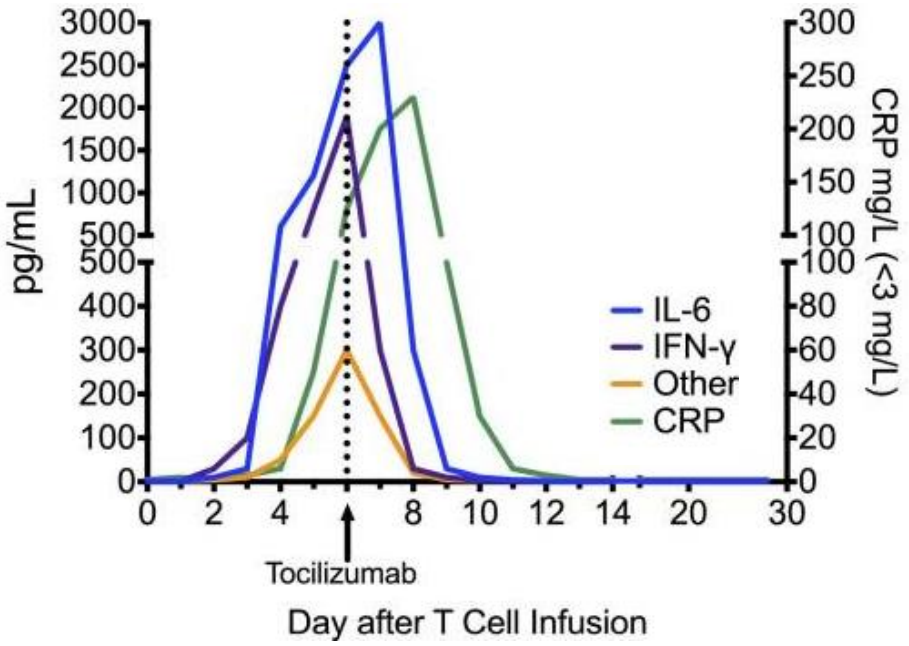
June et al. Science 2018

CRS management



Lee et al. Blood 2014

- Tocilizumab
  - Monoclonal antibody that blocks IL-6 signaling



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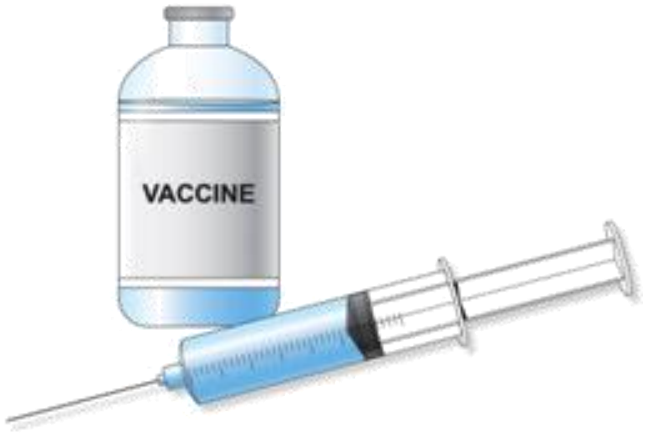
  - Multiple Myeloma

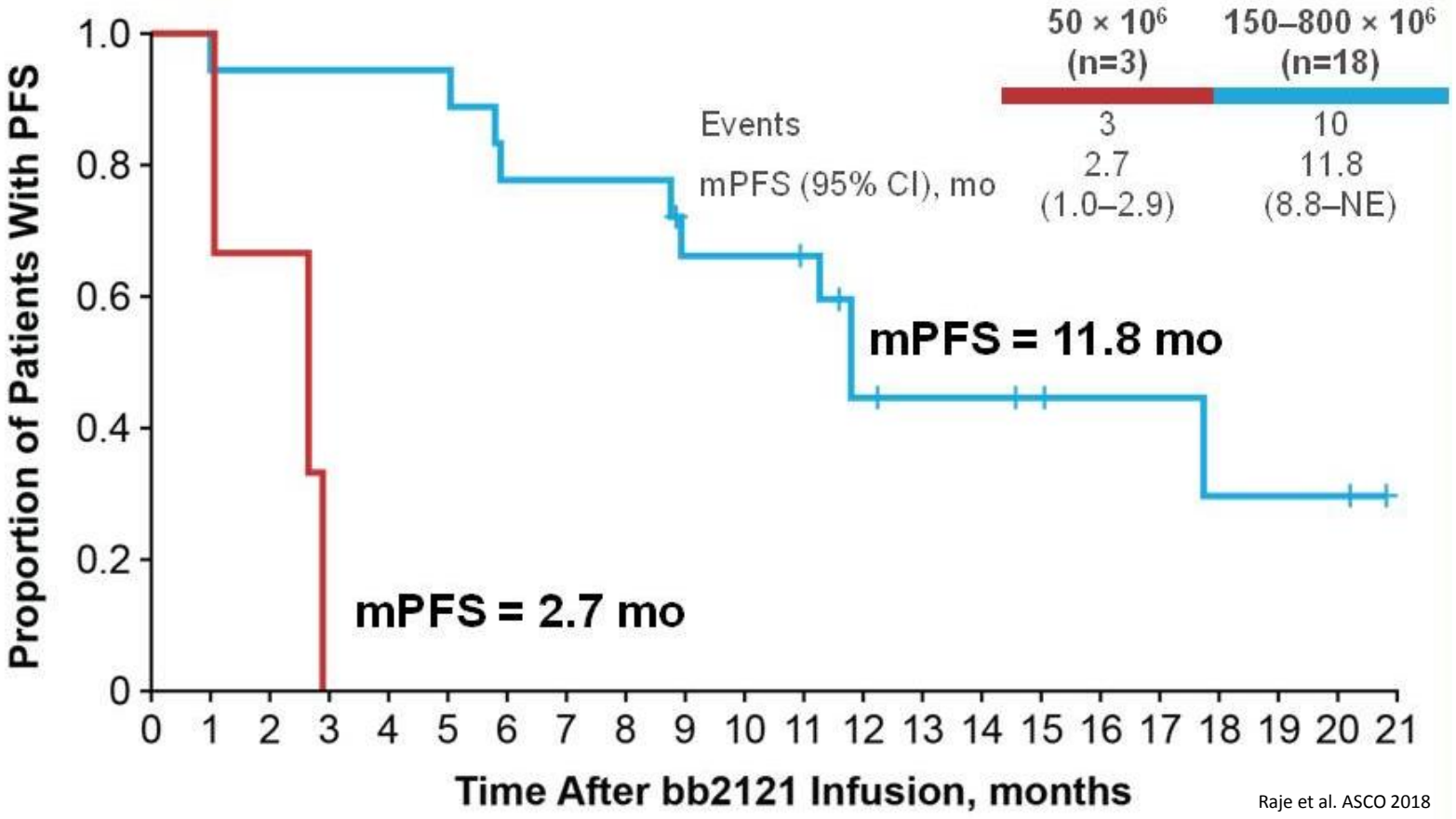
Immunotherapies for Multiple Myeloma

- 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

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*]

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Case Study 1

- 72M with follicular lymphoma originally diagnosed in 1993 and underwent: CHOP x 6, zevalin, fludarabine x 6, BR x 6, and multiple courses of rituximab
- Transformed to DLBCL and underwent: GemOx x 2, lenalidomide with no response
- Received one dose of nivolumab (off-label indication)
- Presented one week later with: fever, SOB, and skin rash
  - CXR normal, CT chest with diffuse ground glass opacities
  - Skin biopsy with “interface dermatitis with epidermal necrosis”
- What happened?

Case Study 1

- Rash:
  - 30-40% have derm complications with nivolumab
- Pneumonitis
  - ~5% develop pneumonitis
- What are next steps?
  - Hold further nivolumab
  - Steroids (0.5mg/kg prednisone)

Naidoo, Ann Oncol 2015; Naidoo, JCO 2017

Case Study 1

- Due to hypoxia- Patient admitted for observation
- Next day: Diffuse purple blistering rash, severe mucositis, conjunctivitis
- Consistent with Steven's Johnson syndrome (rare complication)
- What is the next step?
  - Increased steroids to methylprednisolone at 2mg/kg/day
- Did not improve after 3 days, what's next?
  - Infliximab 5mg/kg
  - Unique to this patient: Amniotic membrane transplants, feeding tube

Naidoo, Ann Oncol 2015; Naidoo, JCO 2017

Case Study 1

- Slow clinical improvement
- Discharged after a one month hospital stay on prednisone taper
- Returned one month later with sepsis related to pneumonia
- Transitioned to hospice and passed away
- Lessons learned:
  - Many
  - Checkpoint inhibitors are not benign drugs!
  - Even one dose can cause severe and life-threatening adverse effects!
  - Counsel patients and monitor closely

Naidoo, Ann Oncol 2015; Naidoo, JCO 2017

Case study 2

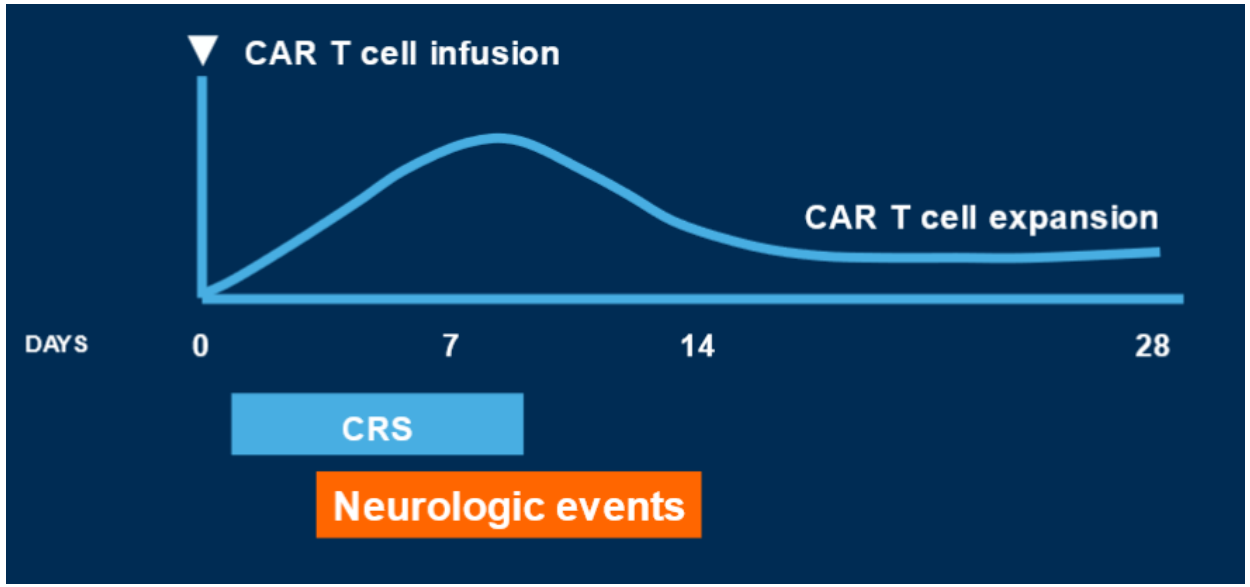
- 49M with DLBCL who was refractory to RCHOP, RDHAP, Nivolumab (off-label indication) presented with enlarging left groin node.
- Referred for CAR-T therapy and received CAR-T infusion on Day 0:
- Day 1 – Fevers – grade 1 CRS
- Day 2 – Hypotension – transferred to ICU
- Day 5 – Resolution of fevers and hypotension
- Day 6 – Mild confusion with waxing and waning mental status and significant headache – Grade 2 neurotoxicity
- What is the next step?
  - Dexamethasone 10mg IV q 6 hr

Case study 2

- Day 7 – No improvement of neurological symptoms after 24 hours – change to methylprednisolone 1mg/kg/day
- Day 8 – Worsened to grade 3 NT with disorientation and combative behavior, anomic aphasia
- What is the next step?
  - Siltuximab 11mg/kg (off label use)
- Day 12 – Rapid improvement of mental status to grade 1
- Day 13 – Complete resolution of all neurologic symptoms
- Day 14 – Discharged from the hospital with a rapid steroid taper

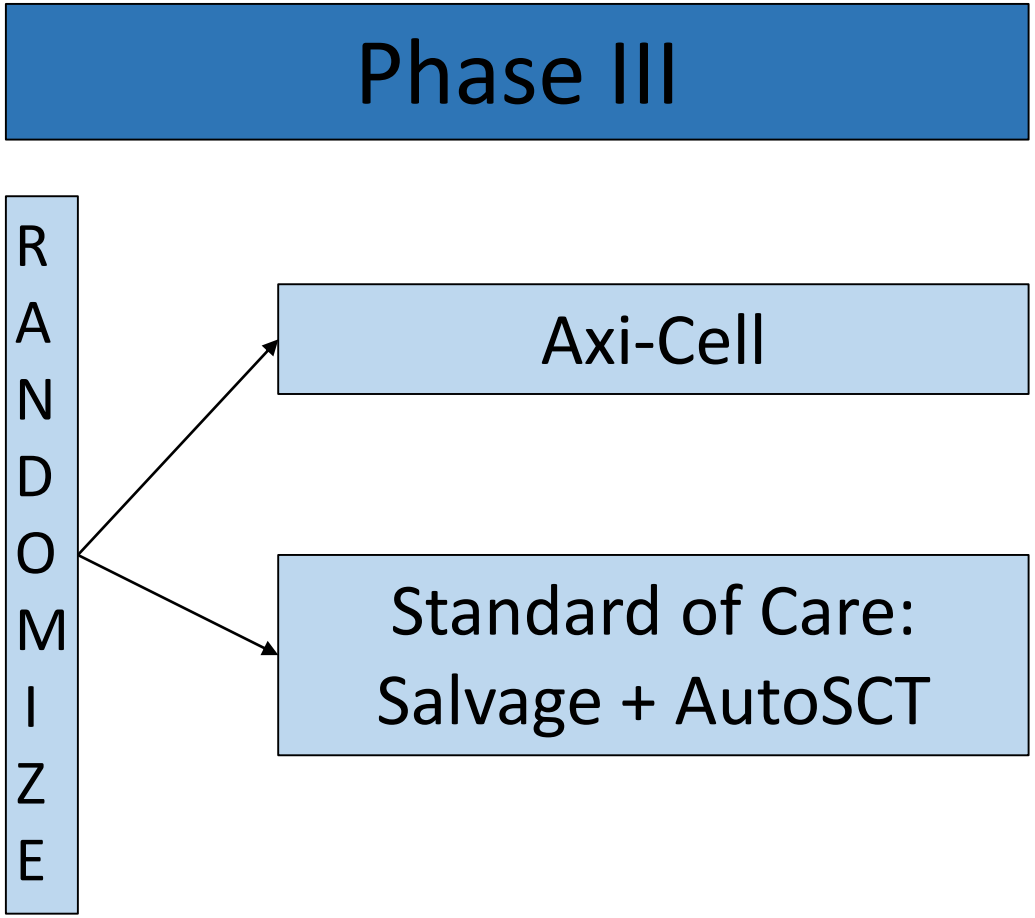
Case study 2

- Timing of adverse events post CART:
- No clear consensus on management of severe neurotoxicity
- Theoretical concern that tociluzumab may block IL6 receptors and cause a flare of IL6 levels
- Siltuximab blocks IL6 directly, so may be a good choice in this setting.



Lee, Blood 2014

Primary Refractory DLBCL

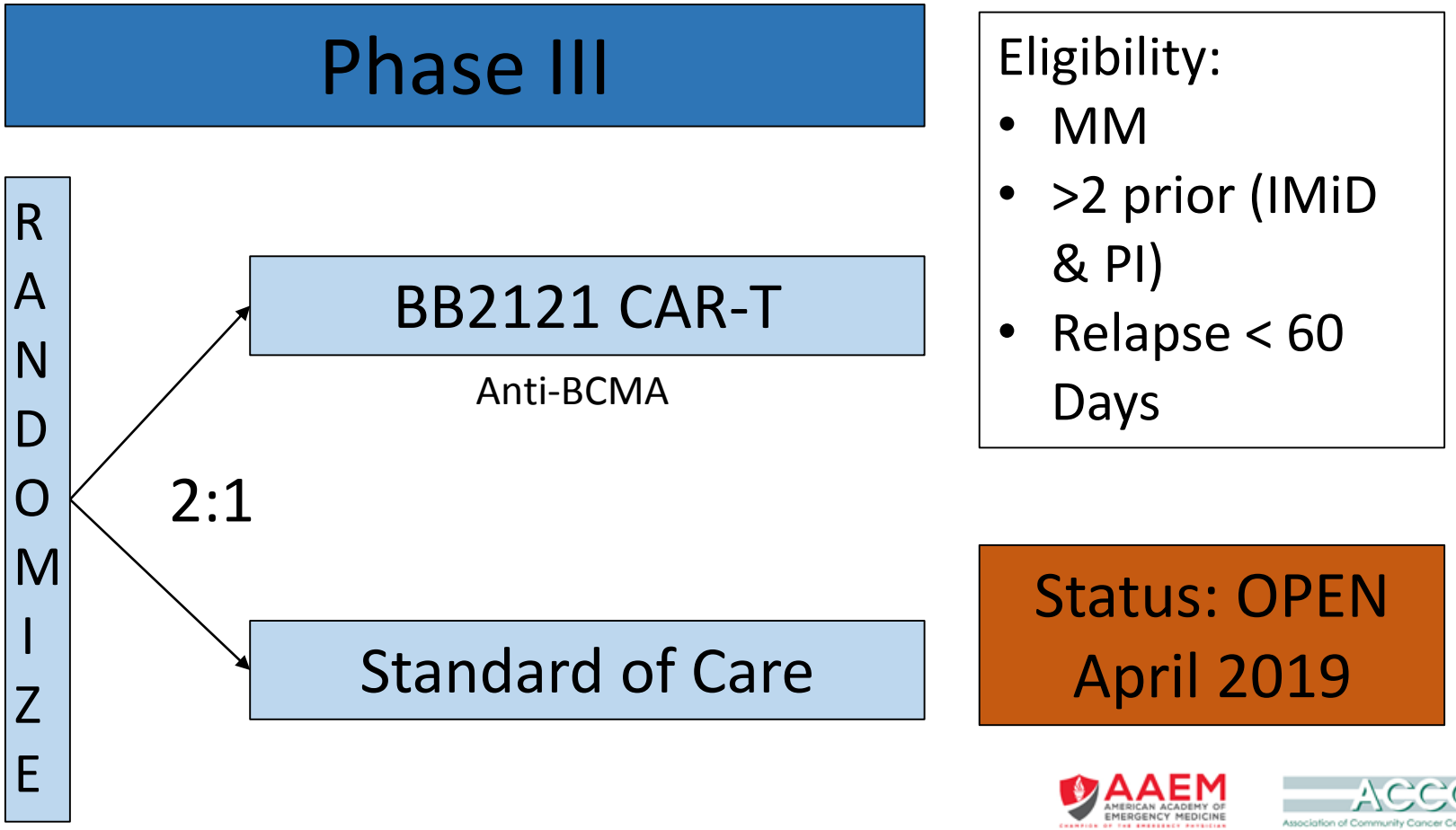


Eligibility:

- DLBCL (includes transformed FL)
- PD/SD/PR to induction Rx
- Relapse < 12 mos from induction Rx
- Candidate for autoSCT

Status: OPEN
Nov 2018

Multiple Myeloma



CLL/SLL

Phase I	Phase II
Monotherapy	JCAR017
JCAR+ibrutinib Cohort • Based on monotherapy dose • Open to pts on ibrutinib and progressing or on with <CR at 6 mos	JCAR + ibrutinib

Eligibility:
- CLL/SLL
- Failed/intolerant ibrutinib
- High-risk: > 2 prior
- Standard risk: > 3 prior

Status: OPEN to enrollment

Questions?

Co-Directors: CAR-T Program

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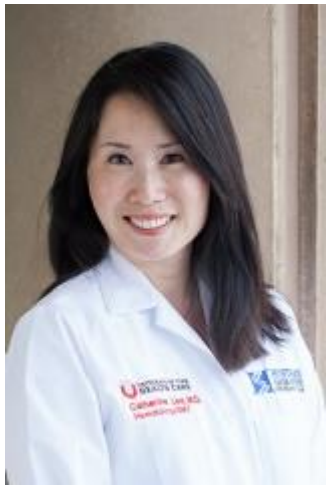
Dr. Catherine Lee
(catherine.lee@hci.utah.edu)



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