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

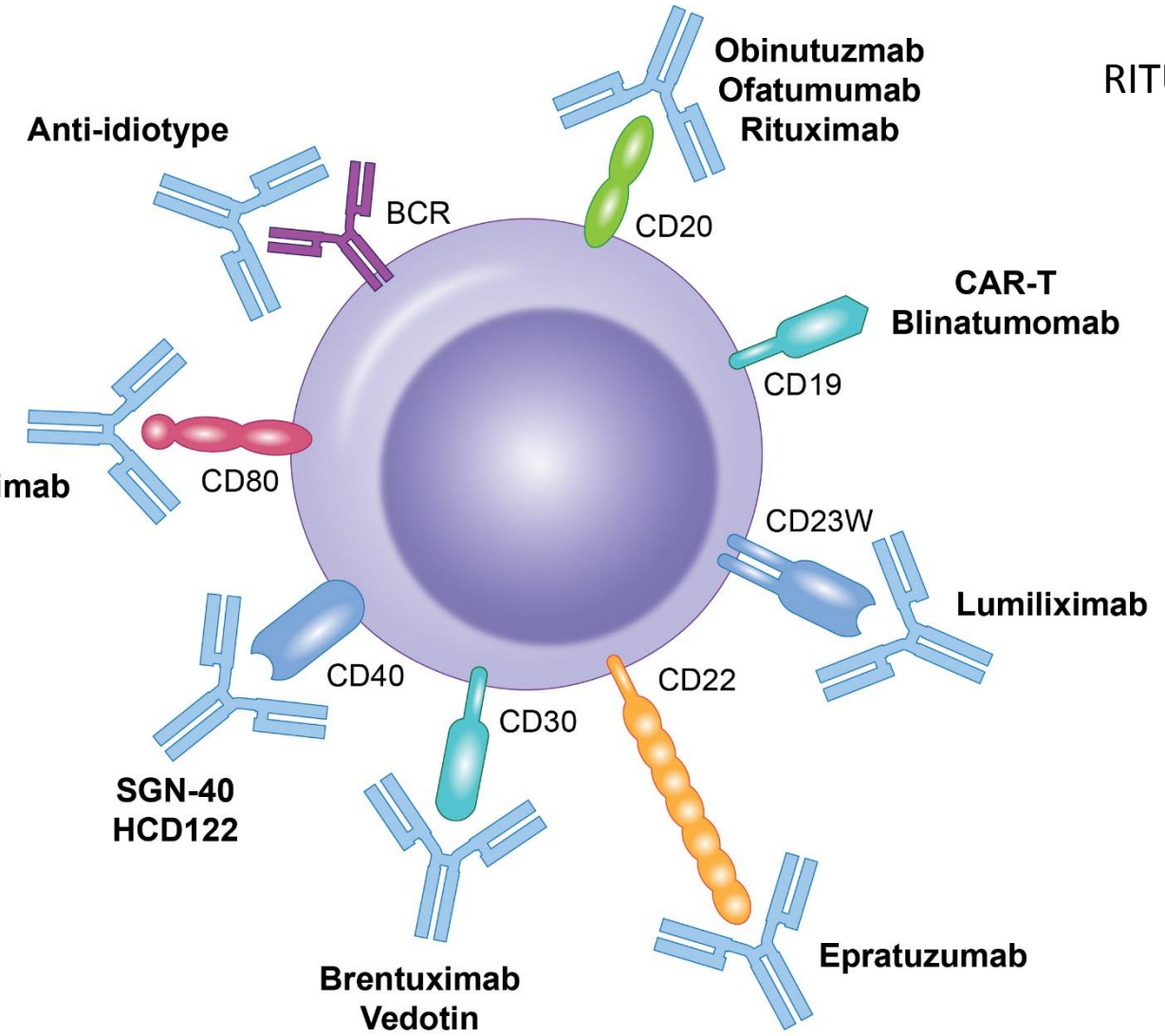
ACCC Association of Community Cancer Centers

Society for Immunotherapy of Cancer

Disclosures

- Add disclosures here
- I will be discussing non-FDA approved indications during my presentation- in the context of a clinical trial.

Monoclonal Antibodies Targeting B Cell Lymphomas



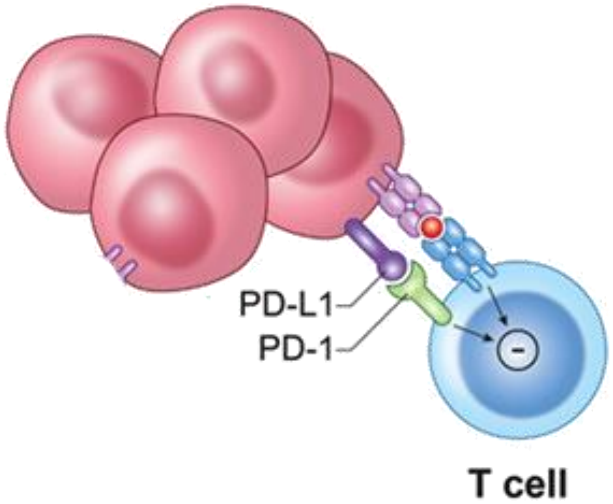
RITUXimab-

Galiximab
Not FDA approved
No NCI open clinical trials 2/02/19

Lumiliximab
Not FDA approved
5 NCI completed clinical trials in CLL - 2/02/19

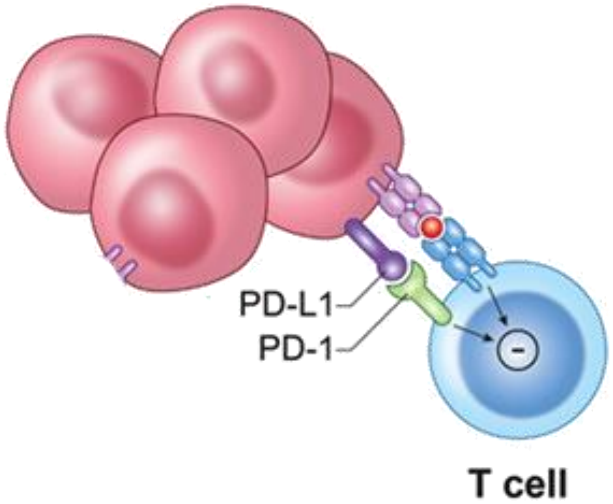
FDA-approved Checkpoint Inhibitors for Lymphomas- Hodgkin and PMBCL

- 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



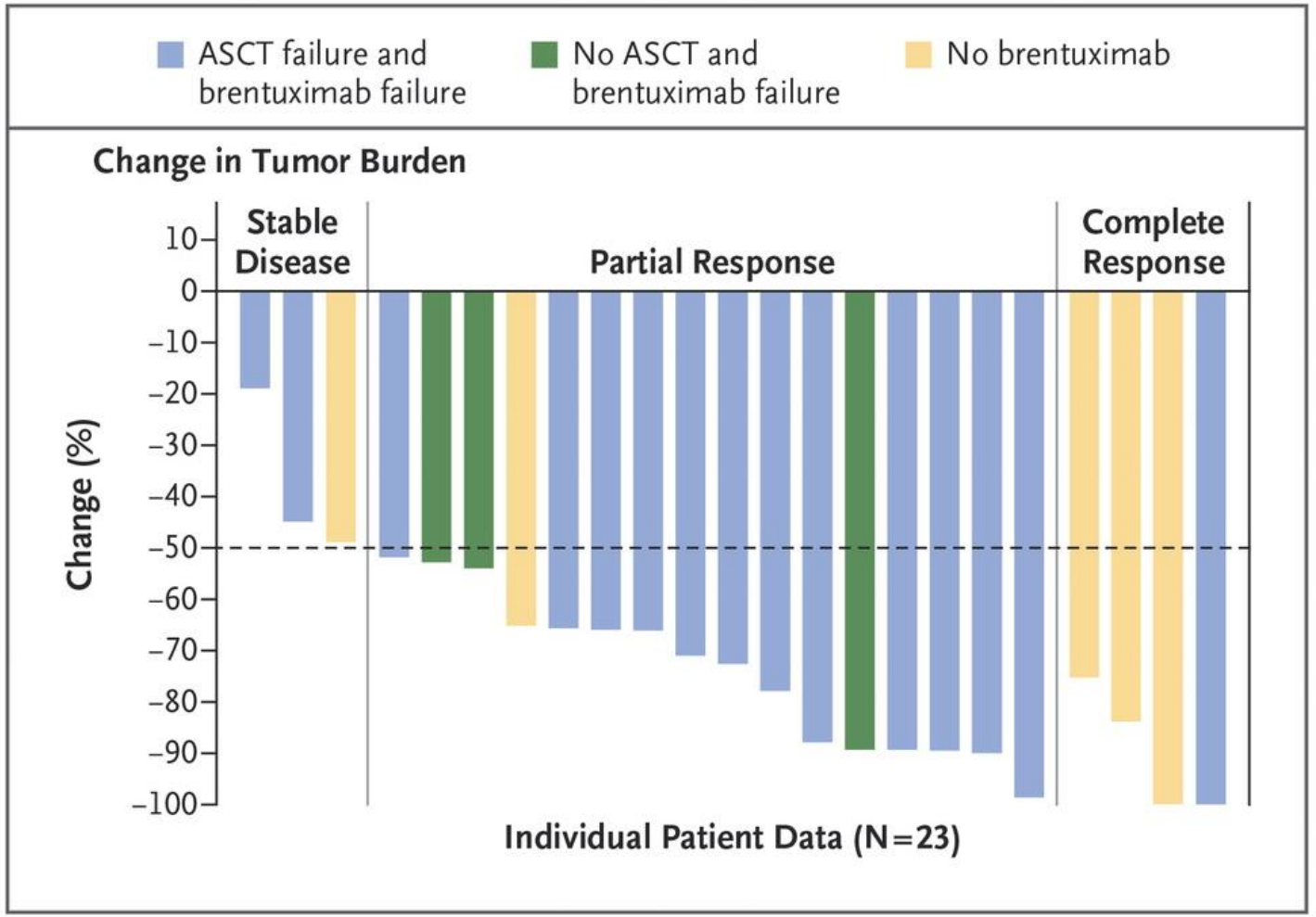
Nivolumab in Hodgkin Lymphoma

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

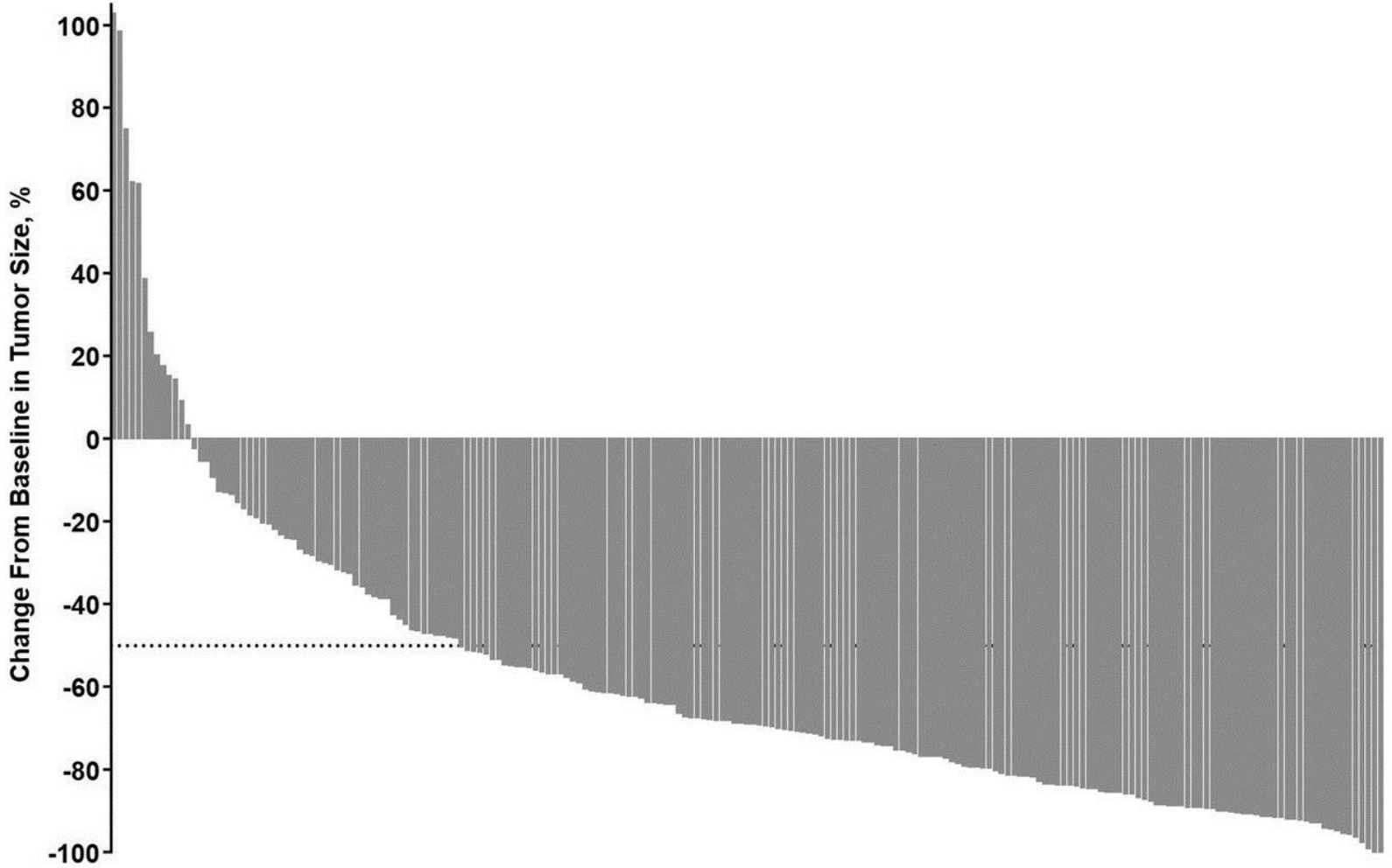
Ansell et al. NEJM 2015

Nivolumab in Hodgkin Lymphoma



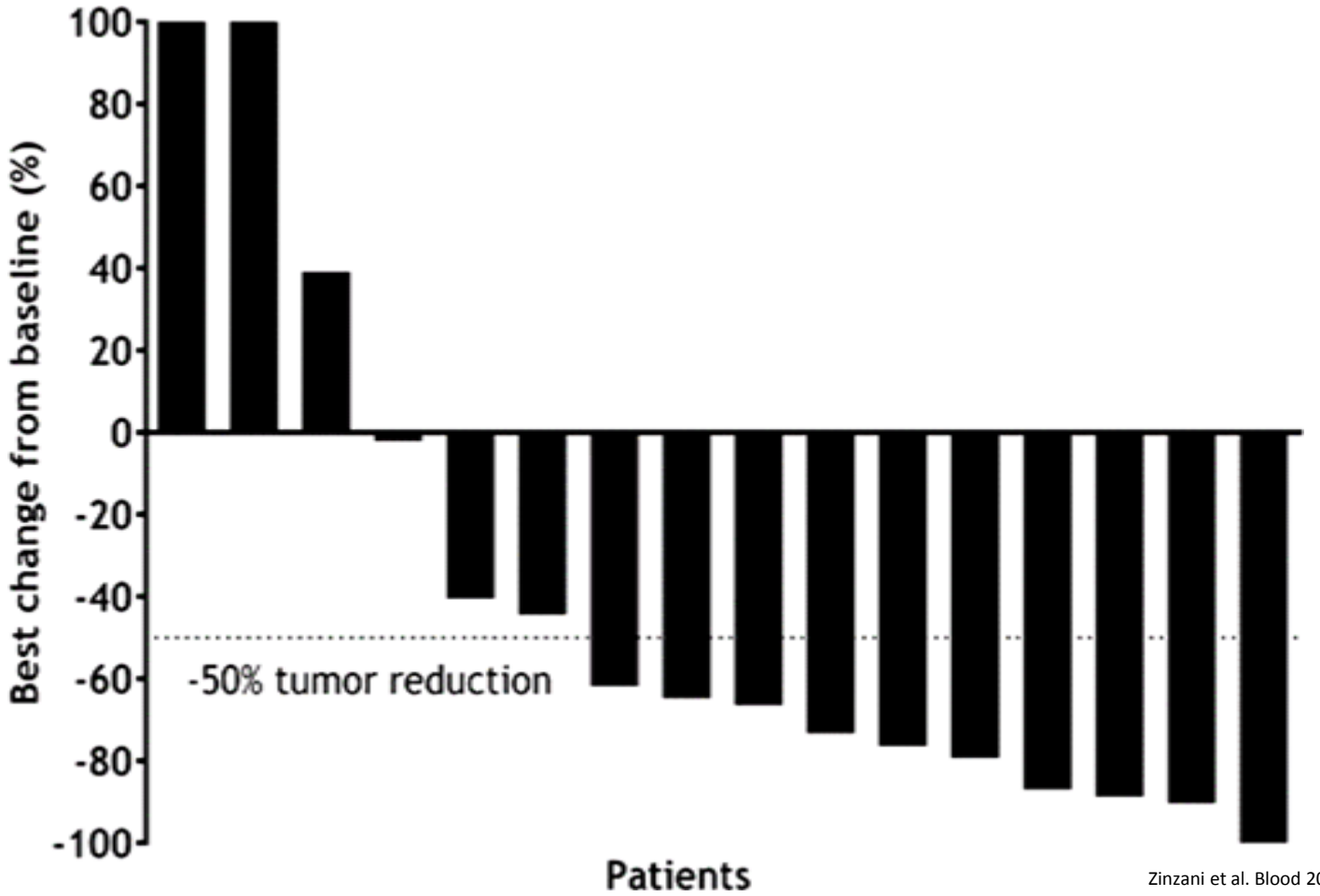
Ansell et al. NEJM 2015

Pembrolizumab in Hodgkin Lymphoma



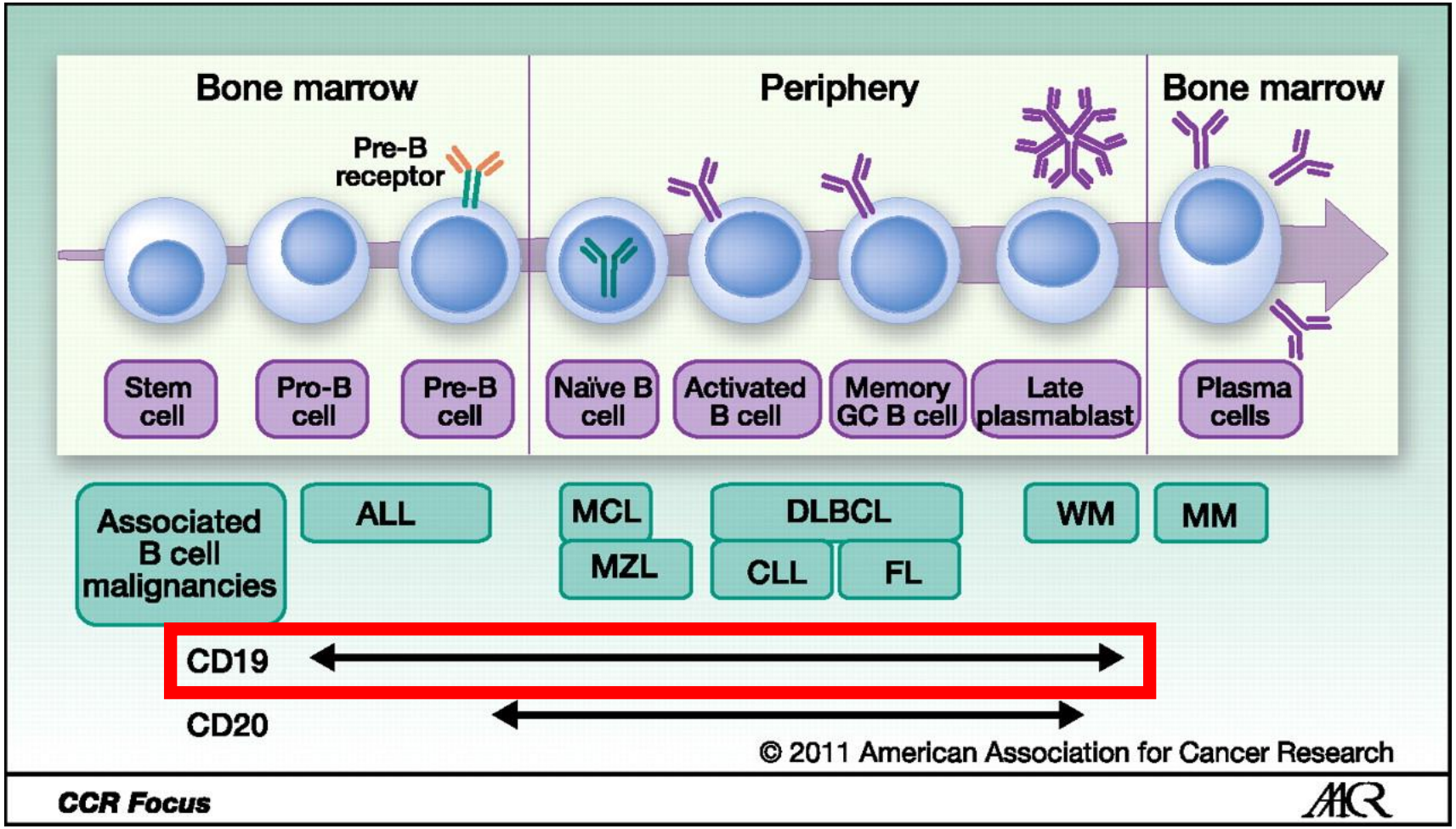
Zinzani et al. Hematological Oncology 2017

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

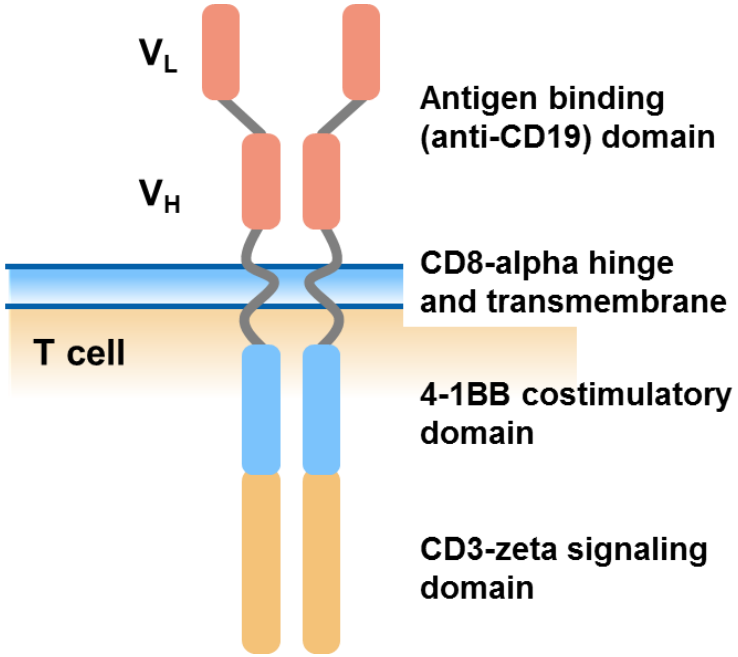
T Cell Cancer Therapies

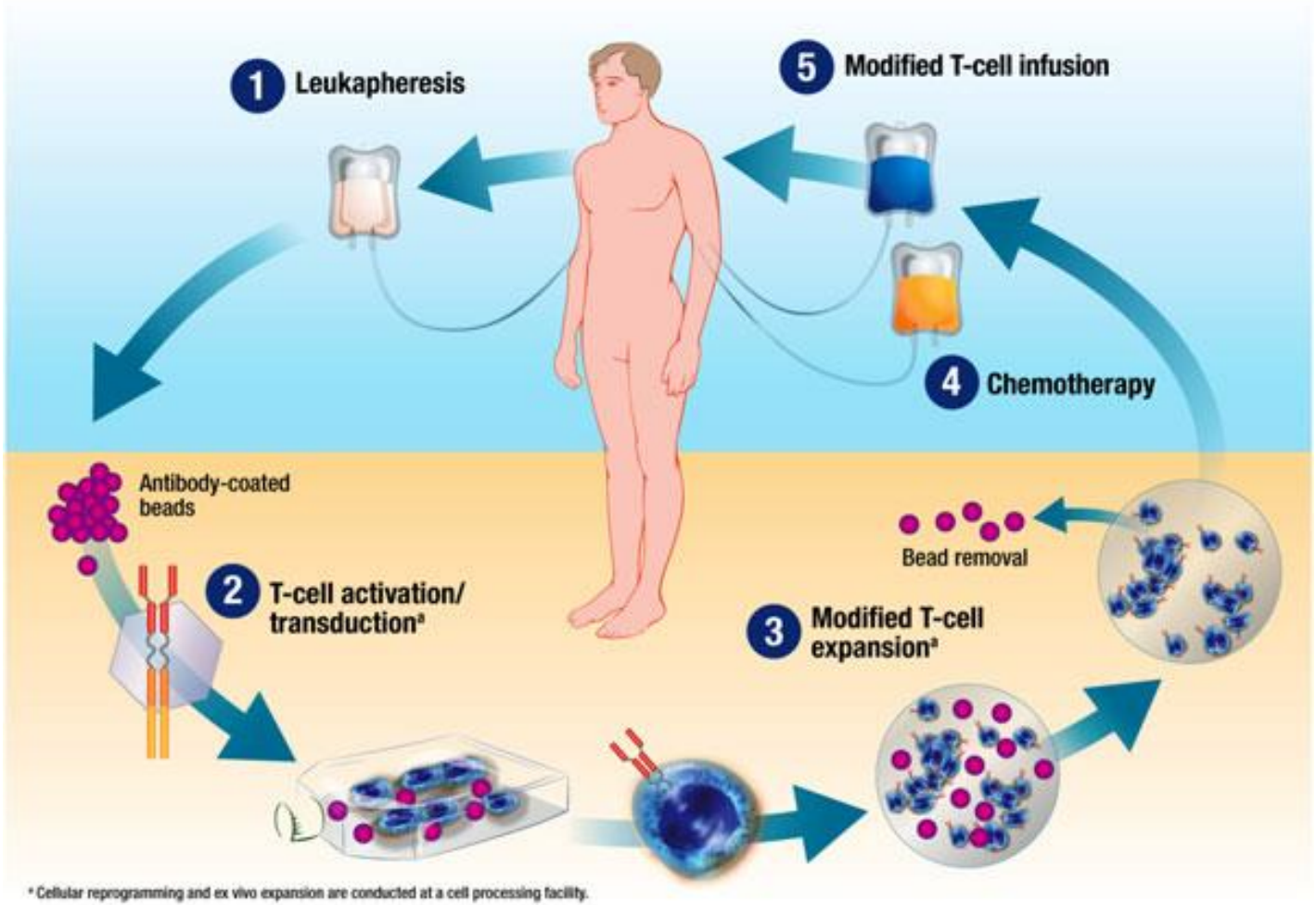
- Check point inhibitors
- “Unleash” Immune response
- Immune reaction already present

- T Cell Engagers
- Create a Productive Immune Response

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

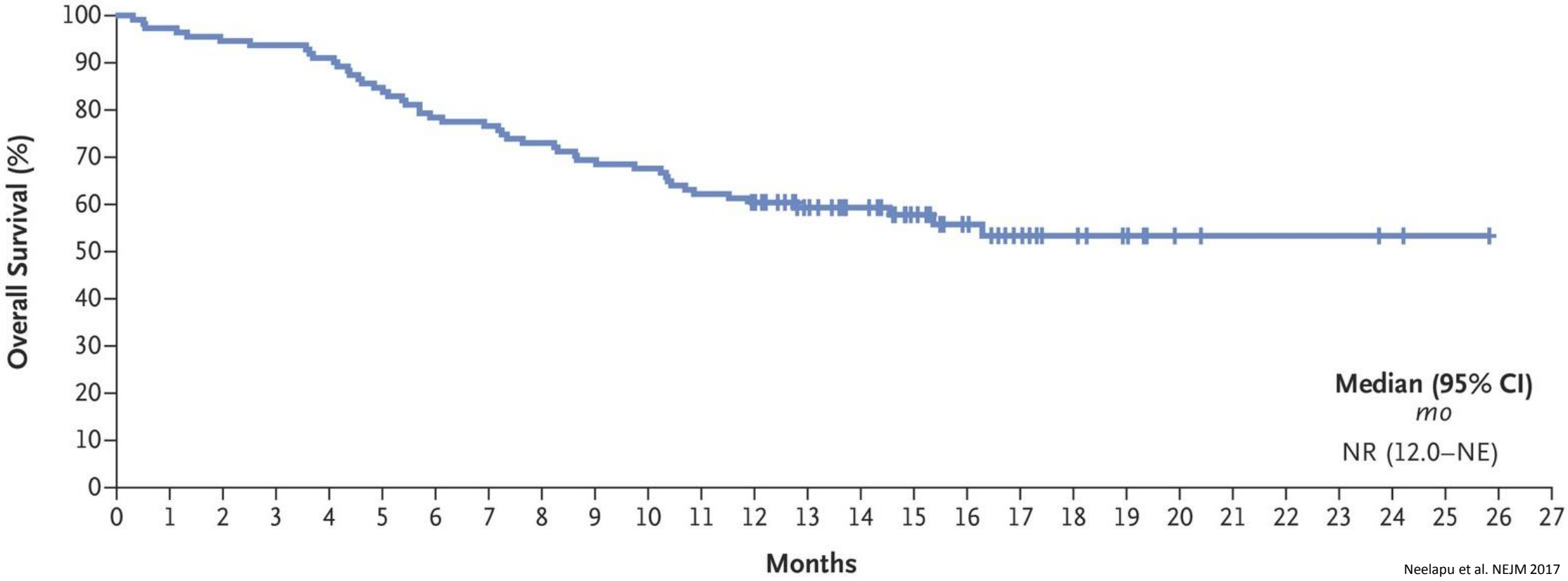
- Axicabtagene ciloleucel - Yescarta
  - ZUMA-1: Adult patients with relapsed or refractory large B cell lymphoma after two or more lines of systemic therapy, including diffuse large B cell lymphoma, high-grade B cell lymphoma, and DLBCL arising from follicular lymphoma
- Tisagenlecleucel - Kymriah
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

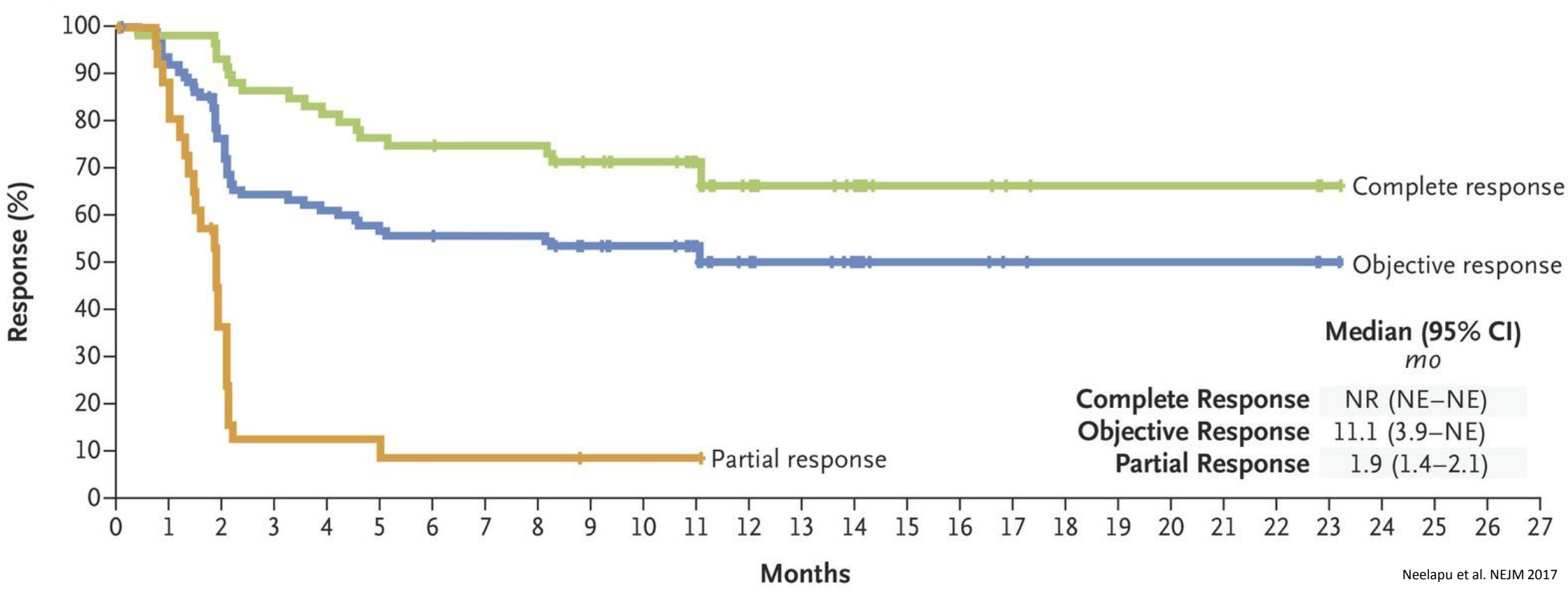
Overall Survival



Neelapu et al. NEJM 2017

Axicabtagene ciloleucel in B Cell Lymphoma

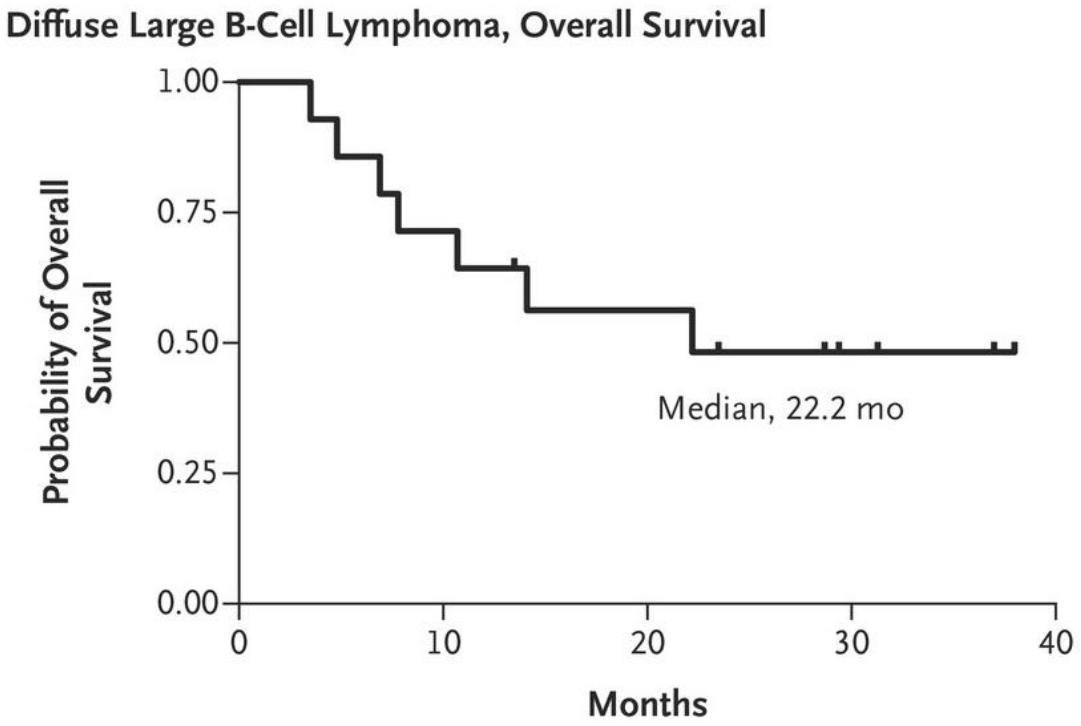
Duration of Response

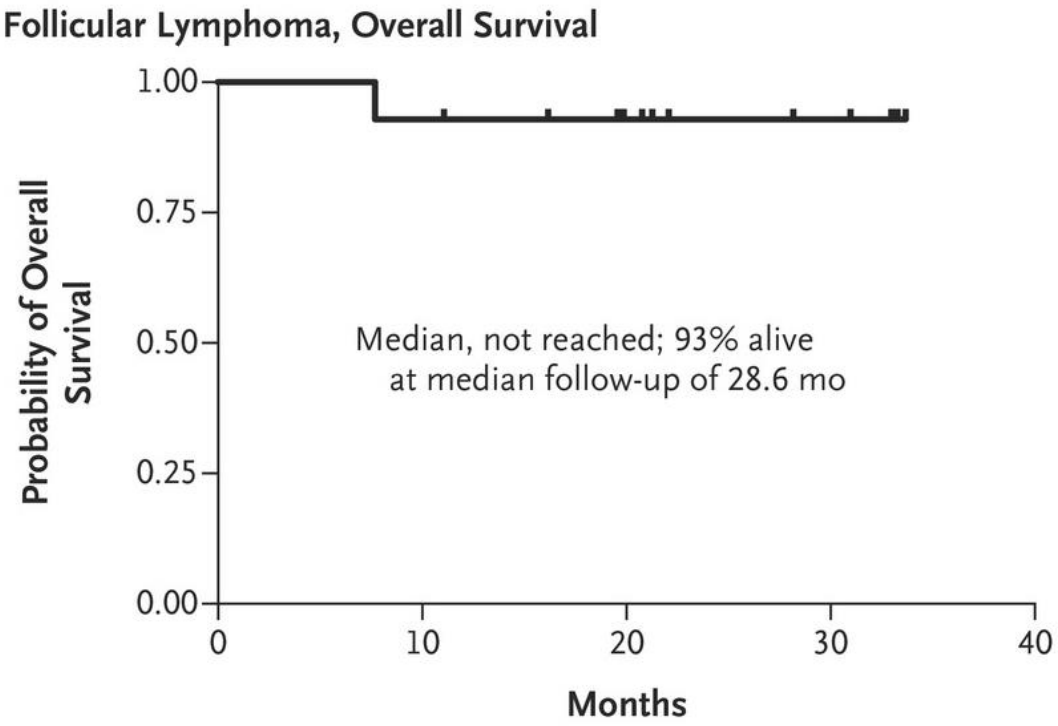


Neelapu et al. NEJM 2017

Tisagenlecleucel in B Cell Lymphoma

Overall Survival

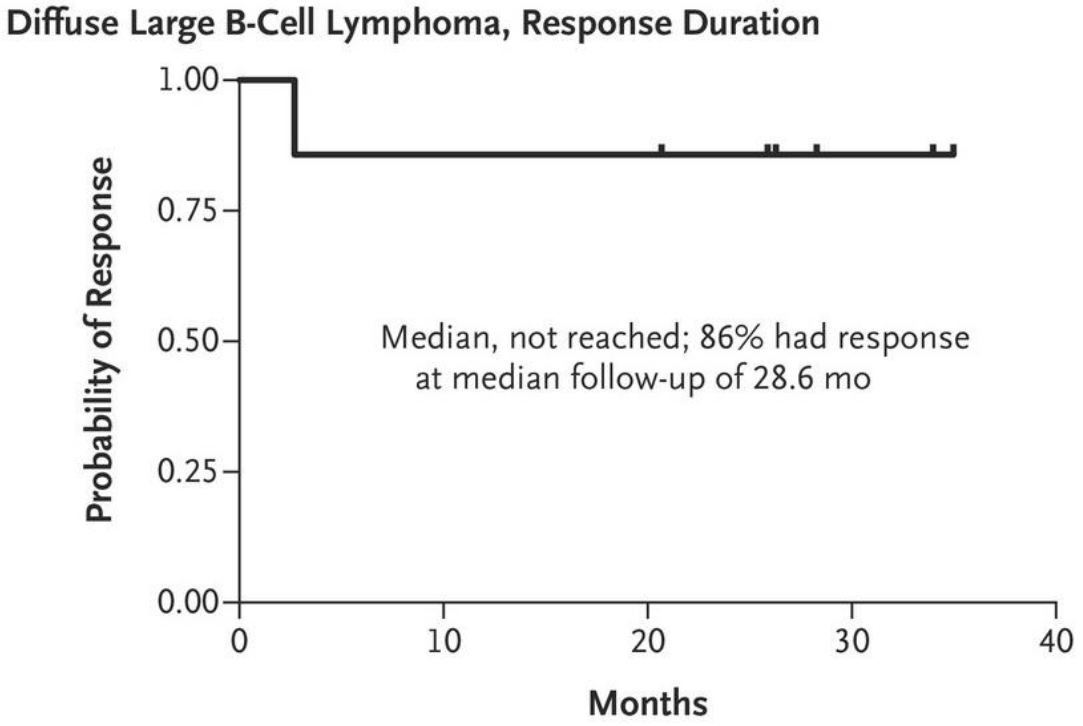


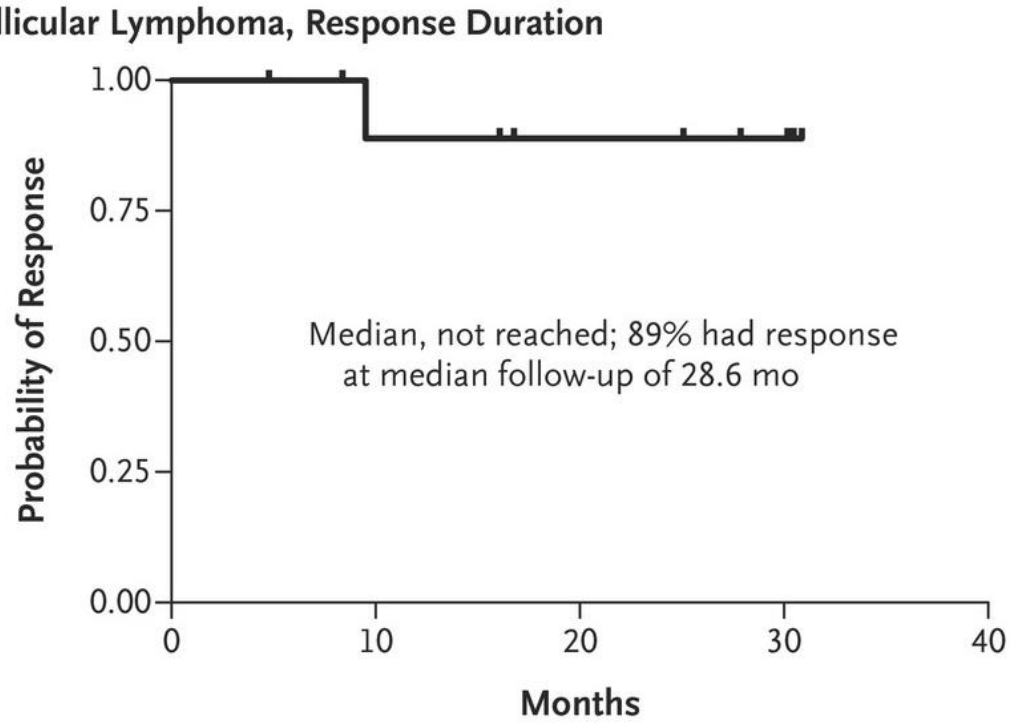


Schuster et al. NEJM 2017

Tisagenlecleucel in B Cell Lymphoma

Duration of Response



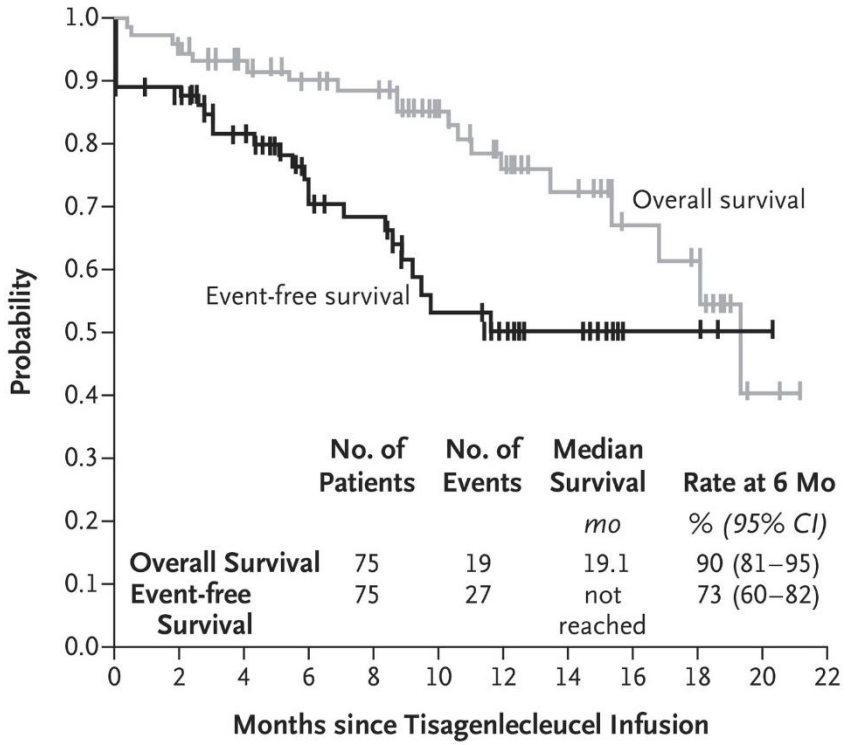


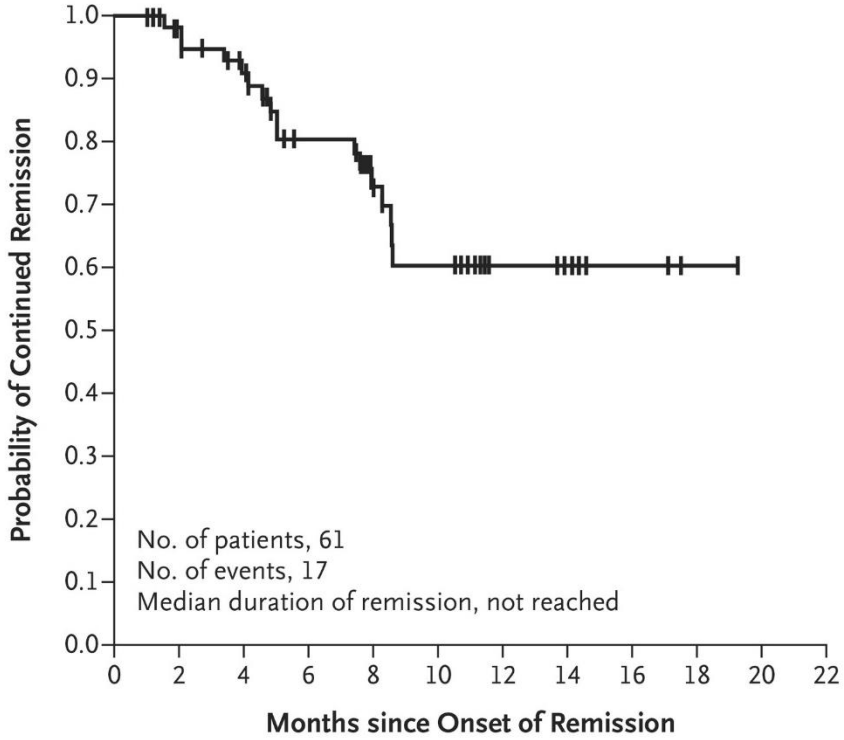
Schuster et al. NEJM 2017

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

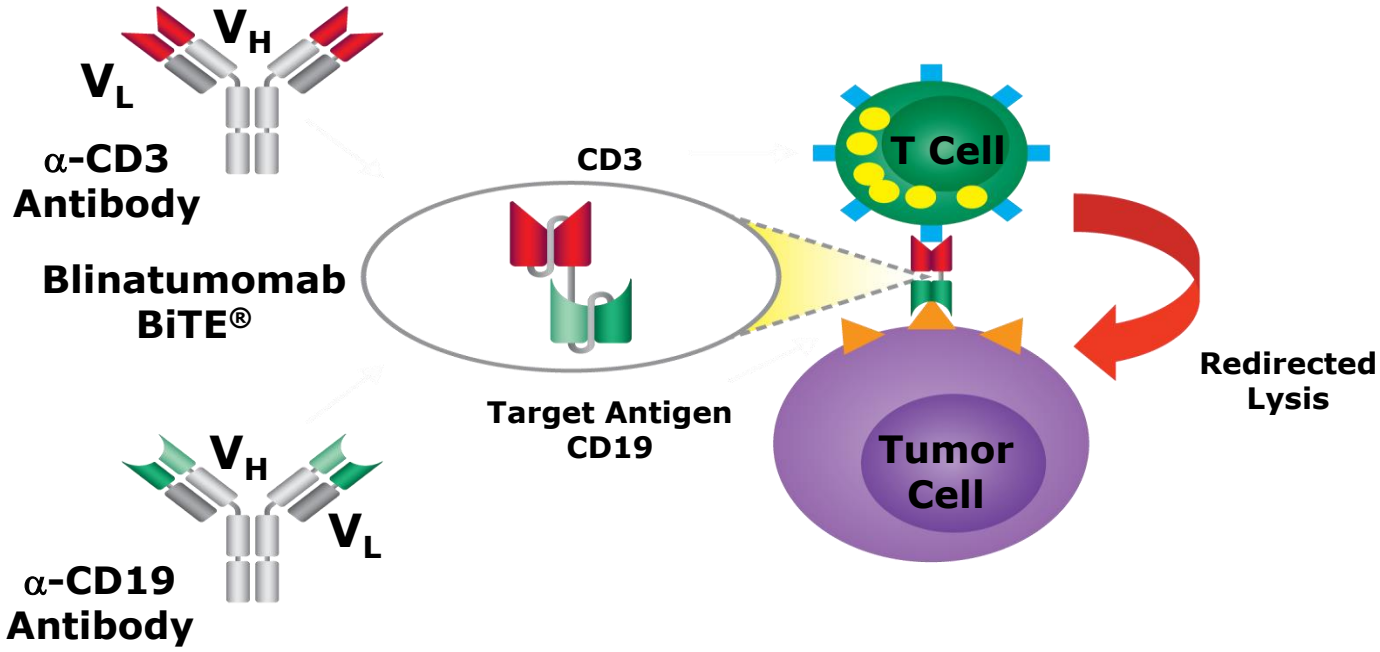




Maude et al. NEJM 2018

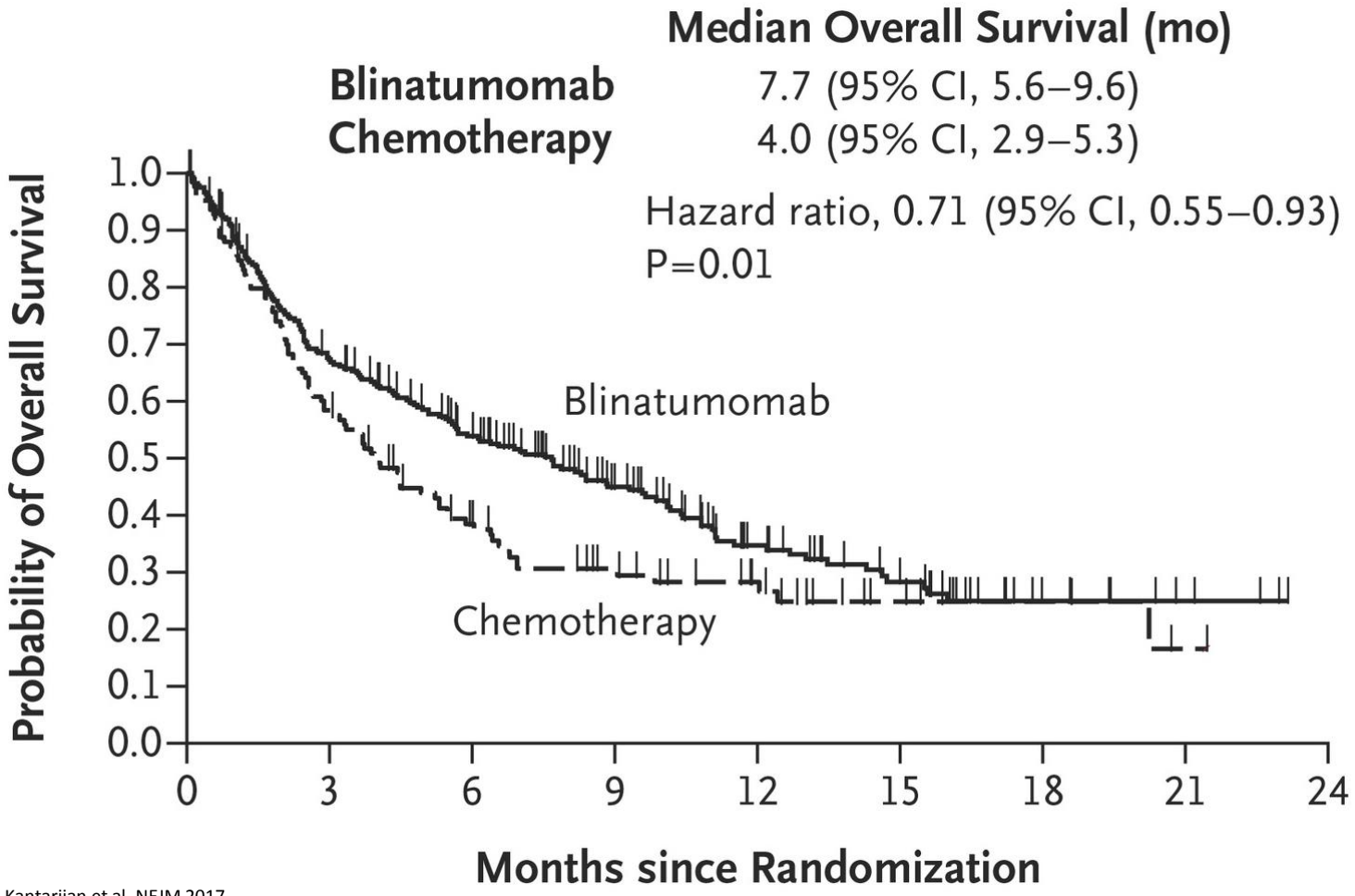
BiTE (Blinatumumab) Therapy

- 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
- And recently for MRD (> 0.1%) positive B-ALL



Bargou et al. Science 2008

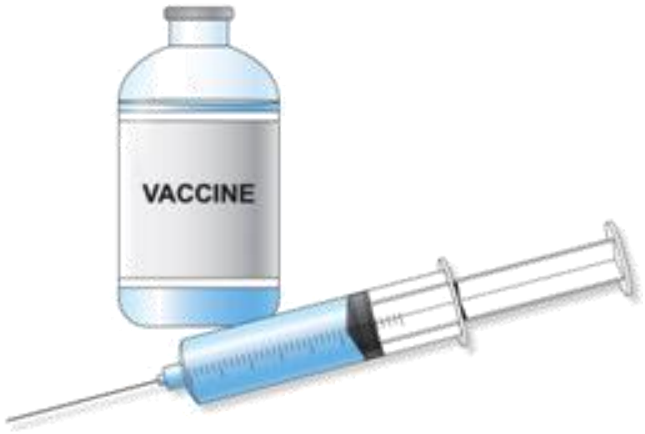
Blinatumomab for B-ALL



Kantarjian et al. NEJM 2017

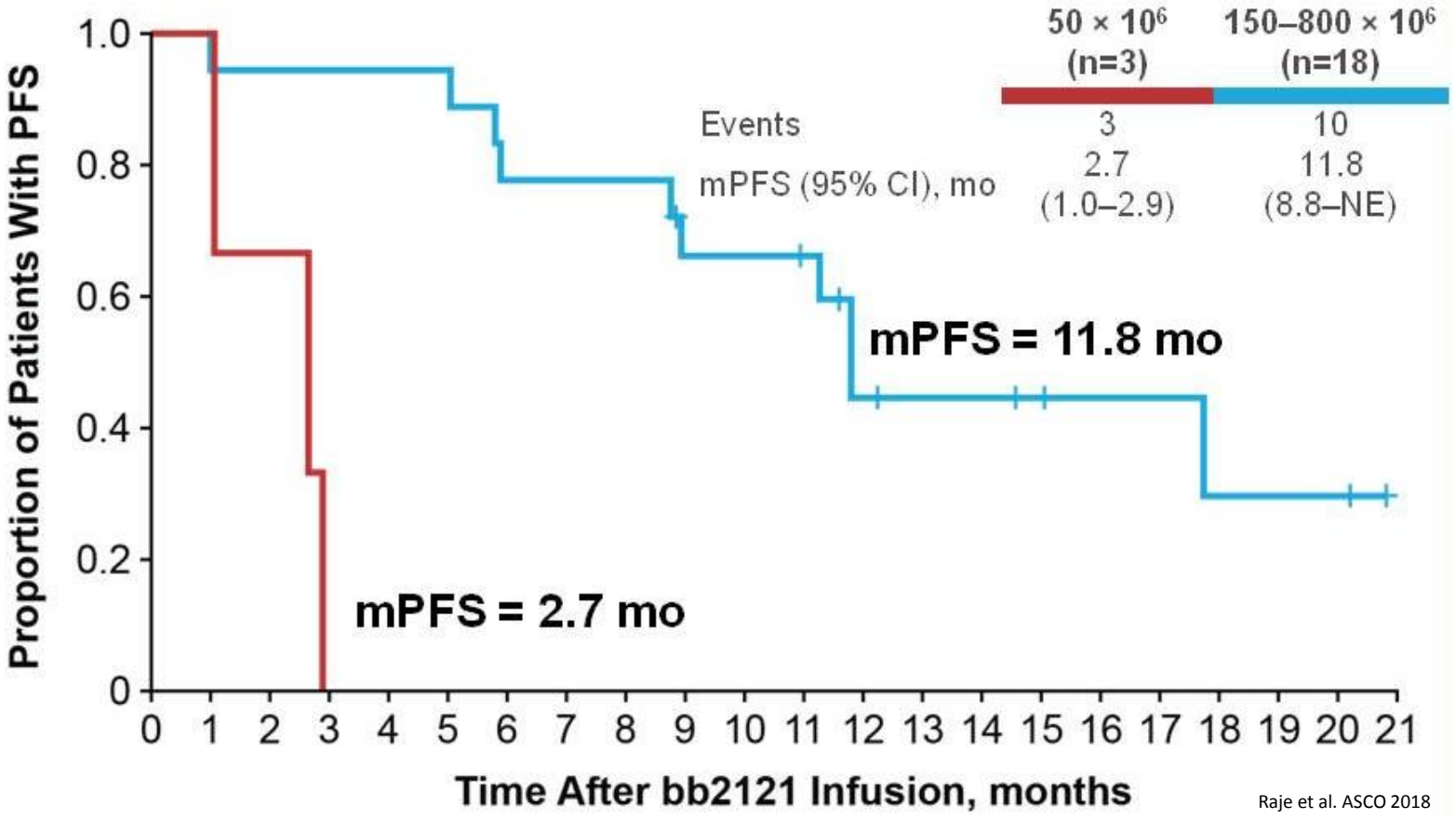
Immunotherapies for Multiple Myeloma

- 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



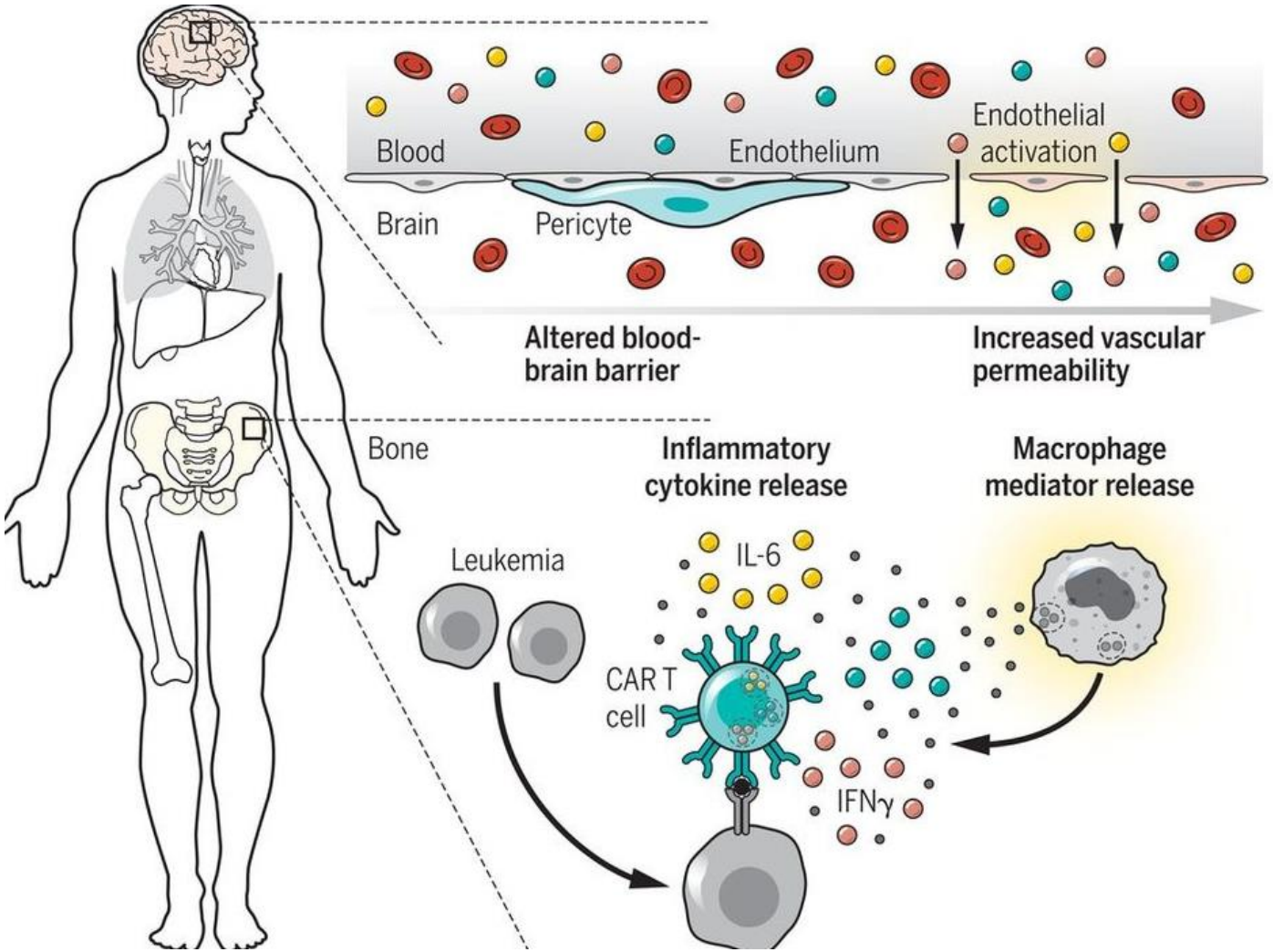
In Development: BCMA+ CAR T Therapy for Myeloma

- 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)



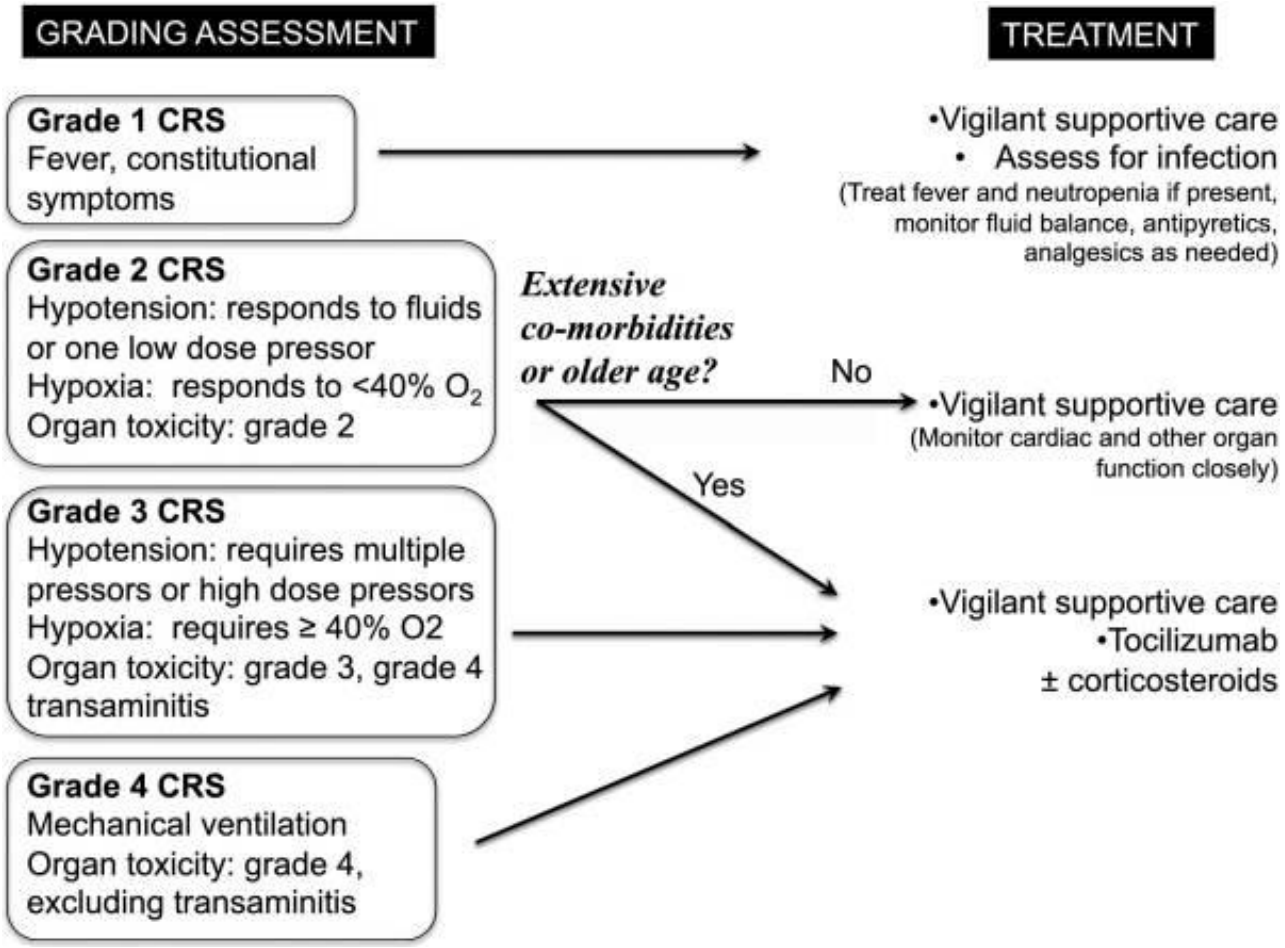
Neurotoxicity
Delirium
Aphasia
Seizures
Cerebral edema
Intracranial hemorrhage

Hemodynamic instability
Tachycardia
Hypotension
Capillary leak syndrome

Organ dysfunction
AST and ALT elevation
Hyperbilirubinemia
Respiratory failure

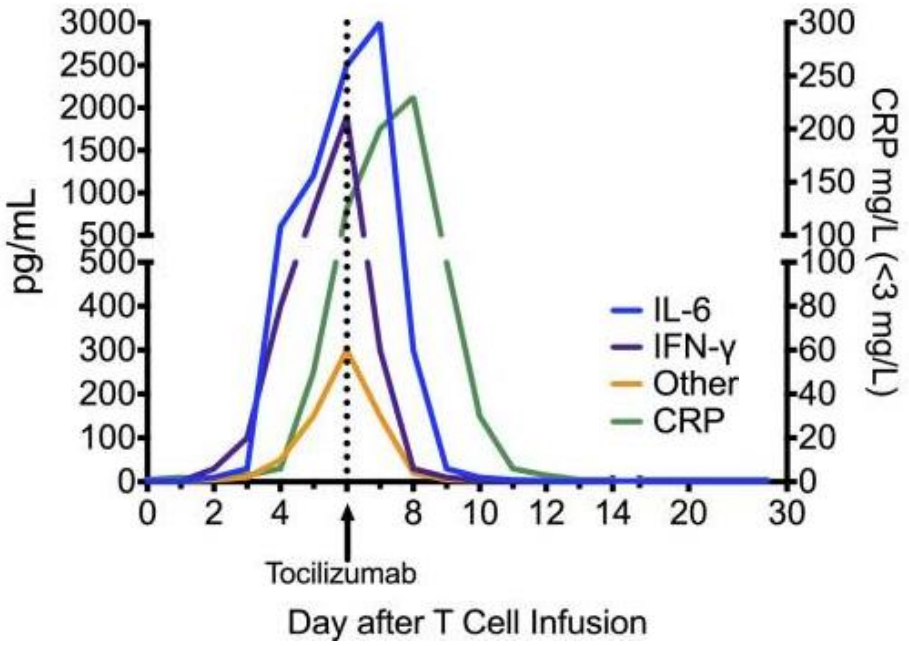
June et al. Science 2018

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

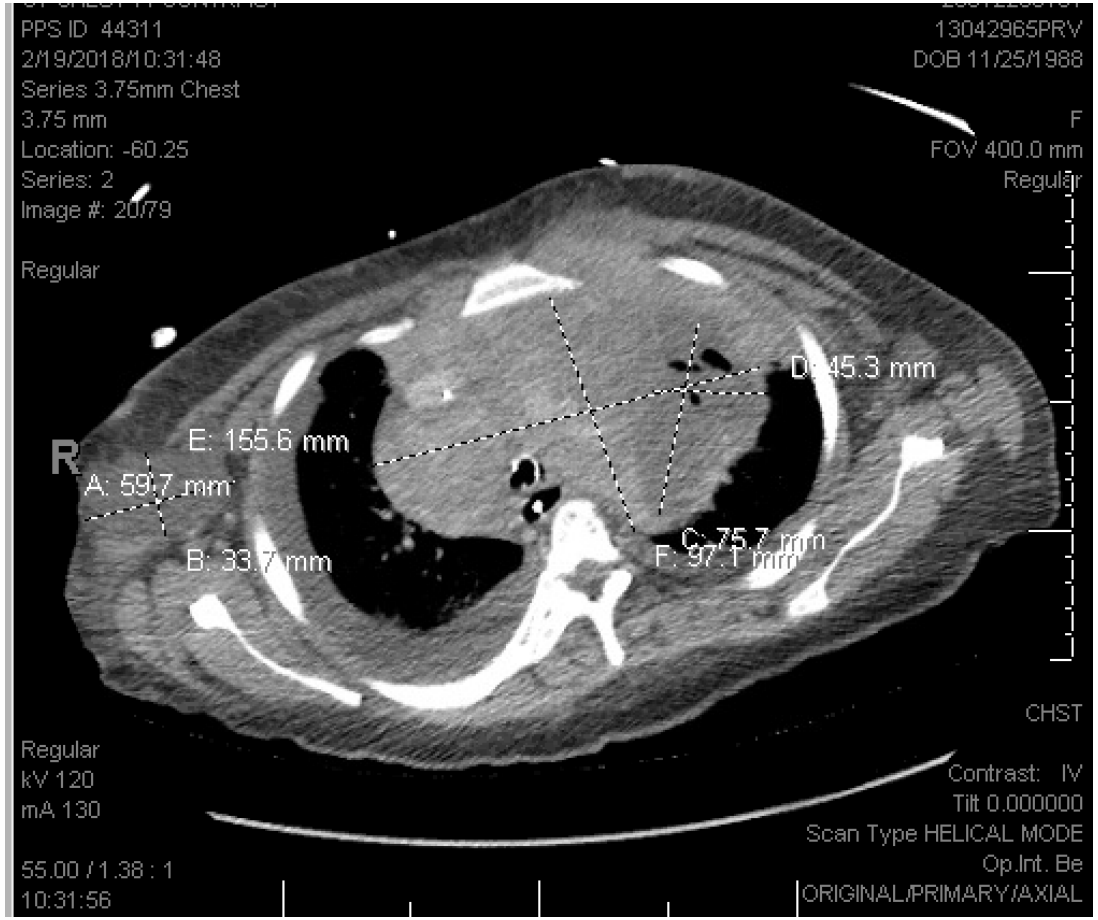
POSITION ARTICLE AND GUIDELINES Open Access

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*]

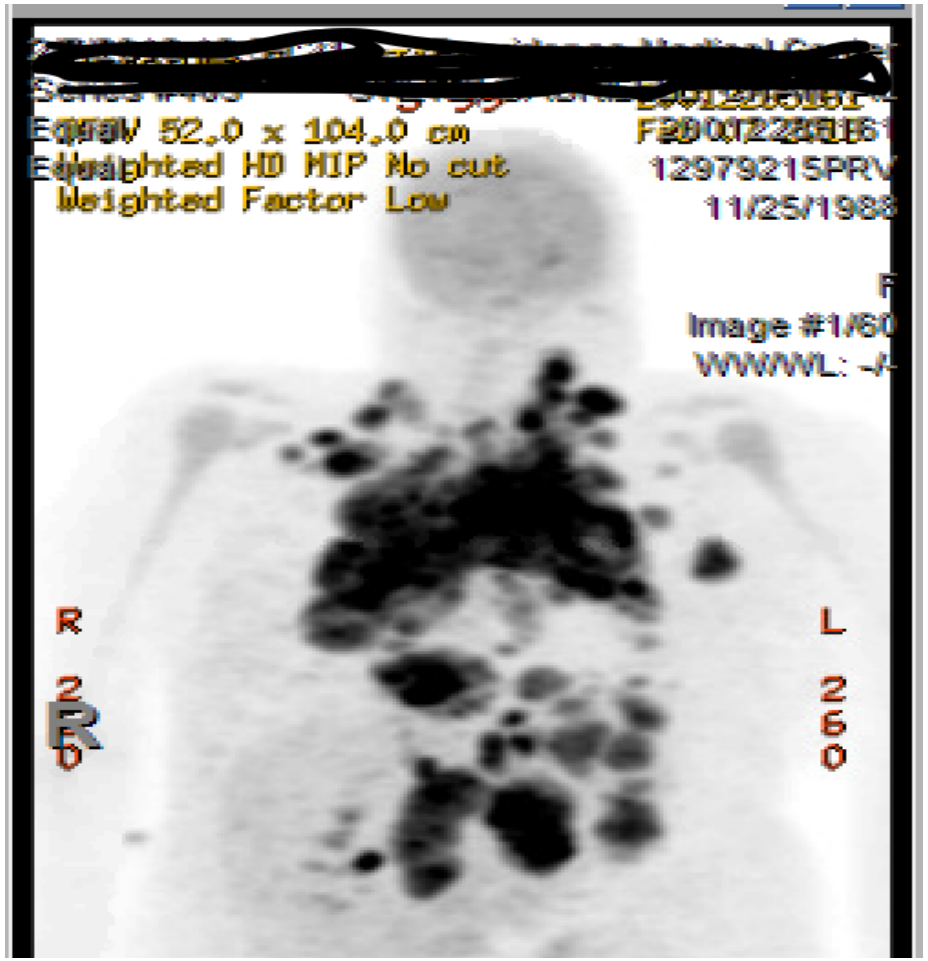
Case Study 1
Hodgkin Lymphoma

- 29 y.o. presented to Providence Seaside Hospital on 2/6/18 with a 9 month history of progressive weight loss, diffuse swelling, and dyspnea on exertion
- Upon transfer to PPMC, she required urgent endotracheal intubation and mechanical ventilation for acute hypoxic respiratory failure due to bulky mediastinal lymphadenopathy and tracheal compression



Case Study 1
Hodgkin Lymphoma

- PET showed large bilateral hilar and mediastinal hypermetabolic masses compatible with tumor extending into the neck, subpectoral area, left axilla and chest wall with maximum SUV of 14.8. There were multiple hypermetabolic foci are present in the spleen, porta hepatis and retroperitoneum with maximum SUV of 12.9.
- Axillary biopsy showed cHL-nodular sclerosis



Case Study 1

Hodgkin Lymphoma

- She was treated with radiation, and AVD (bleomycin not given as she was on ventilator w high flow oxygen.
- She was extubated and discharged to outpt for cycle 3 AVD.
- Then changed to ABVD for cycles 4 thru 8

- Post cycle 8 - PET showed residual disease-1**0/10/2018-**
- Biopsy proven refractory disease - 10/19/18- cHL
- **salvage regimen ICE-** X 2 cycles
- Repeat PET after cycle 2 done on **12/17/18**- disease progression

Case Study 1
Hodgkin Lymphoma

- What are your next treatment options after primary disease resistance?
- 1- Brentuximab Vedotin (anti-CD30 immunoconjugate)
- 2- anti-PD-1 treatment -Pembrolizumab (anti-PD-1)
- 3- Clinical trial

Case Study 1

- What are your next treatment options ? ALL 3 options correct-
- 1- Brentuximab Vedotin (anti-CD30 immunoconjugate)
  - FDA Indication - Classical Hodgkin lymphoma (cHL) after failure of auto-HSCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates
  - NIVO- adult patients with classical Hodgkin lymphoma that has relapsed or progressed afterb: (1.6)
    • autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or • 3 or more lines of systemic therapy that includes autologous HSCT.
- 2- anti-PD-1 treatment -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
- 3- Clinical trial
- Phase II Study of the Combinations of Ipilimumab, Nivolumab and Brentuximab Vedotin in Patients with Relapsed/Refractory Hodgkin Lymphoma

Case study 2

- 60 yr male with diagnosis of DLBCL, primary lymphoma of bone with PET CT showing widespread skeletal lesions R parietal skull; T7, central sacral lesion, L olecranon, L iliac bone, R iliac wing, R pubic rams, and R femoral shaft lesion.
- Treated with RCHOP x 6.
- Interim scan was performed after 4 cycles of chemotherapy.
  - This showed persistent abnormal finding. Other areas now negative.
- Patient completed 6 cycles of RCHOP and a post treatment scan was performed.
  - This also showed persistent finding.

Case study 2

Question :

What is the best way to assess response in DLBCL ? What are the Lugano criteria ?

What do you do with the post treatment response assessment in this patient ?

Case study 2

- Answer: PET CT is the standard of care- should be used for response assessment in FDG-avid histologies, using the 5-point scale; CT is preferred for low or variable FDG avidity lymphomas. Lugano Classification.
- http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.54.8800
- the Deauville scale:
  - 5PS: 1, no uptake above background; 2, uptake mediastinum; 3, uptake mediastinum but liver; 4, uptake moderately liver; 5, uptake markedly higher than liver and/or new lesions
- In aggressive NHL, studies have reported a negative predictive value of 80% to 100% but a lower positive predictive value, ranging from 50%to 100%.
- Interim PET showed persistent R hilar disease- Deauville 4
- Post treatment showed persistent R hilar disease – Deauville 4 , even though lower than the interim PET

Case study 2

- What do you do with the post treatment response assessment in this patient ?

- At the end of treatment, residual metabolic disease with a score of 4 or 5 represents treatment failure even if uptake has reduced from baseline.
- Unfortunately his treating oncologist did not act but scanned again in 2 mos
- The latest PET CT showed Deauville 5 –"new disease" sites.
- The patient may be a candidate for CAR T therapy- but will require a salvage therapy attempt –3RD Line.
  - CAR T INDICATION – "refractory large B cell lymphoma after two or more lines of systemic therapy"