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

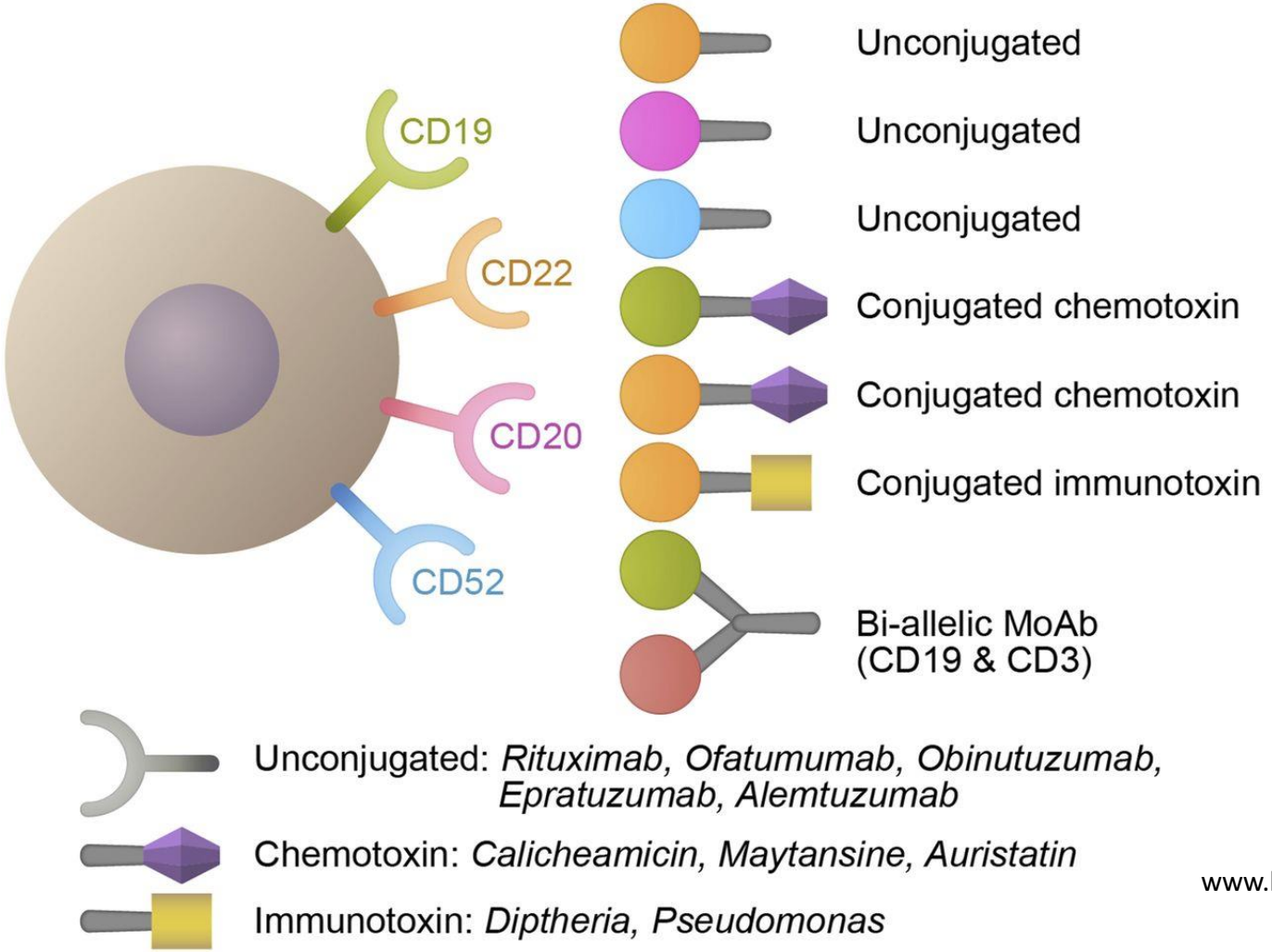
ACCC Association of Community Cancer Centers

Society for Immunotherapy of Cancer

Disclosures

- Advisory Board: Juno Pharmaceuticals
- Research/Travel Support: Lentigen Technology
- Personal Equity: Exelexis, Geron, Oncosec
- I will not be discussing non-FDA approved indications during my presentation.

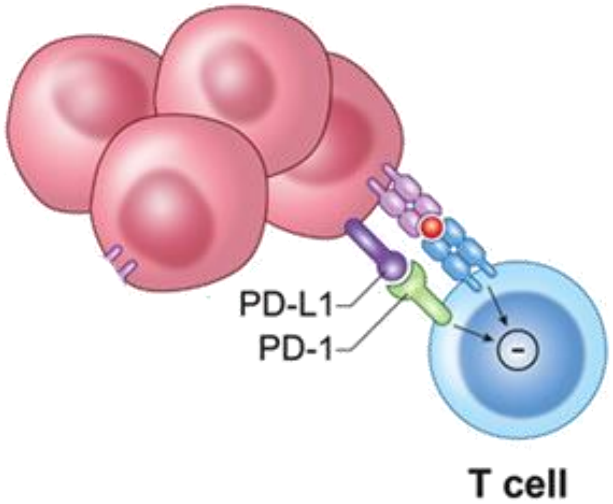
Monoclonal Antibodies Targeting B Cell Lymphomas



www.bloodjournal.org/content/125/26/4010

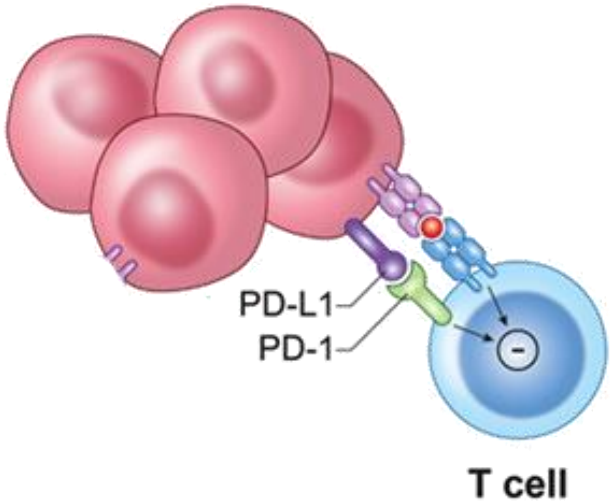
FDA-approved Checkpoint Inhibitors for Lymphomas

- 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



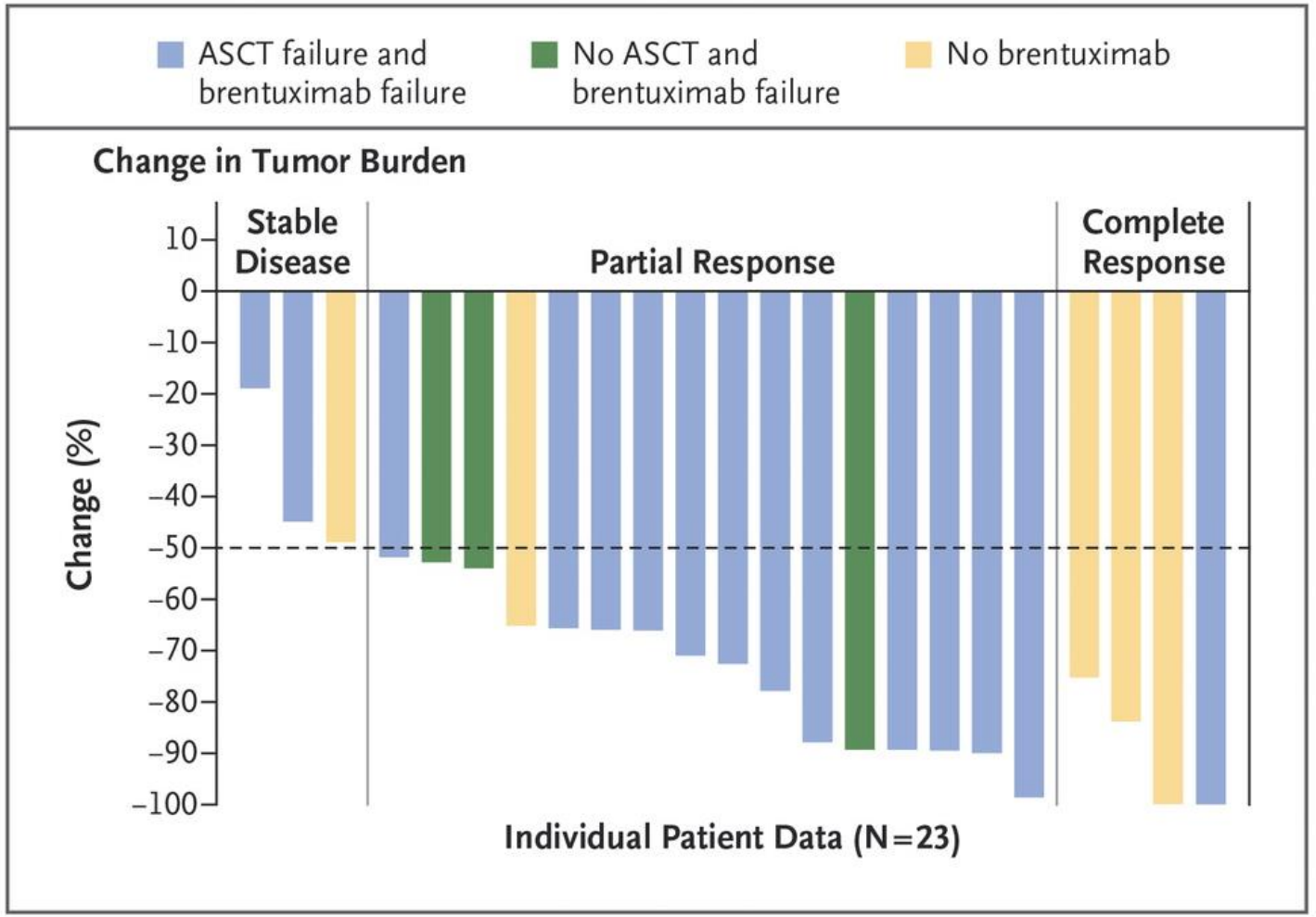
Nivolumab in Hodgkin Lymphoma

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

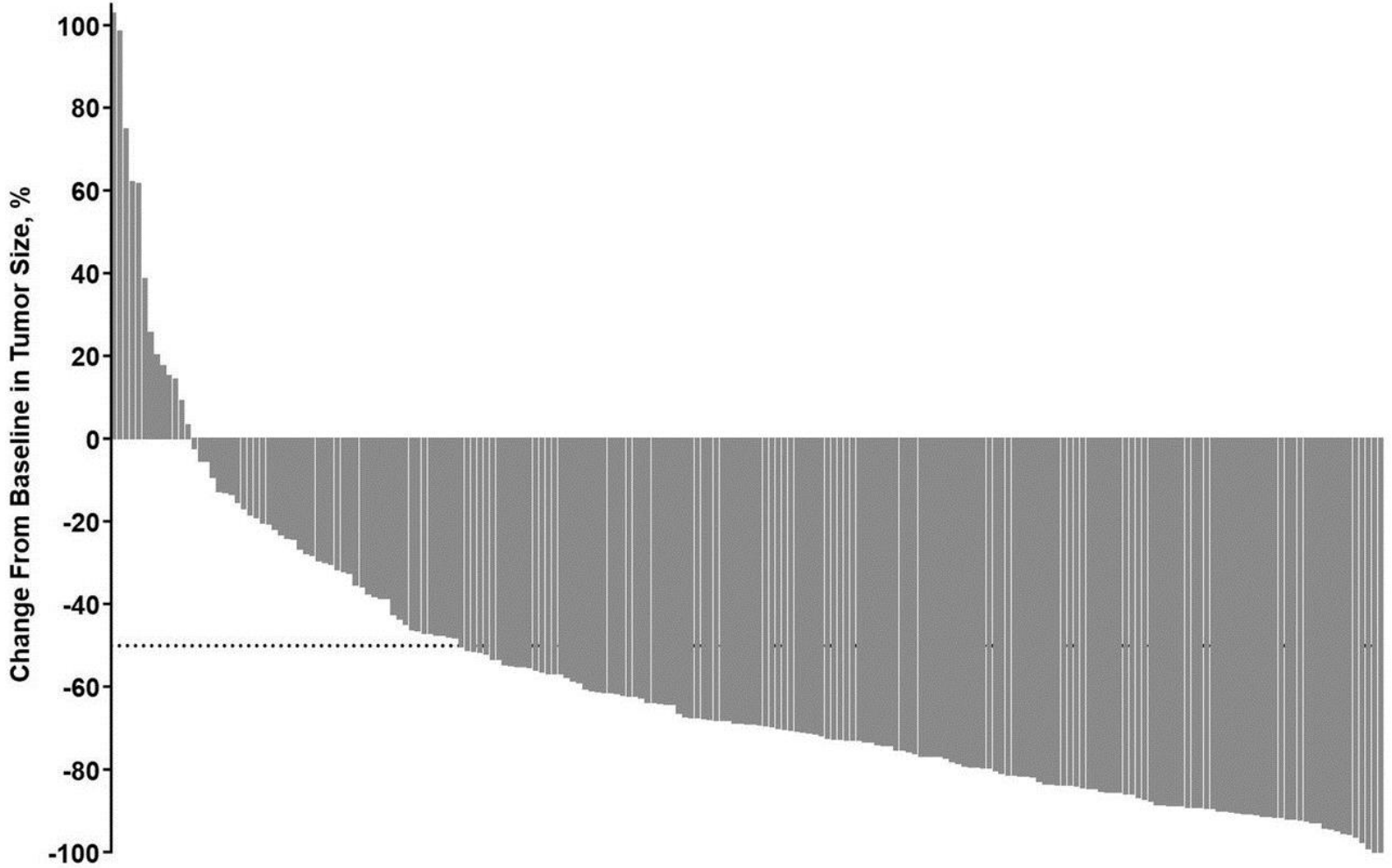
Ansell et al. NEJM 2015

Nivolumab in Hodgkin Lymphoma



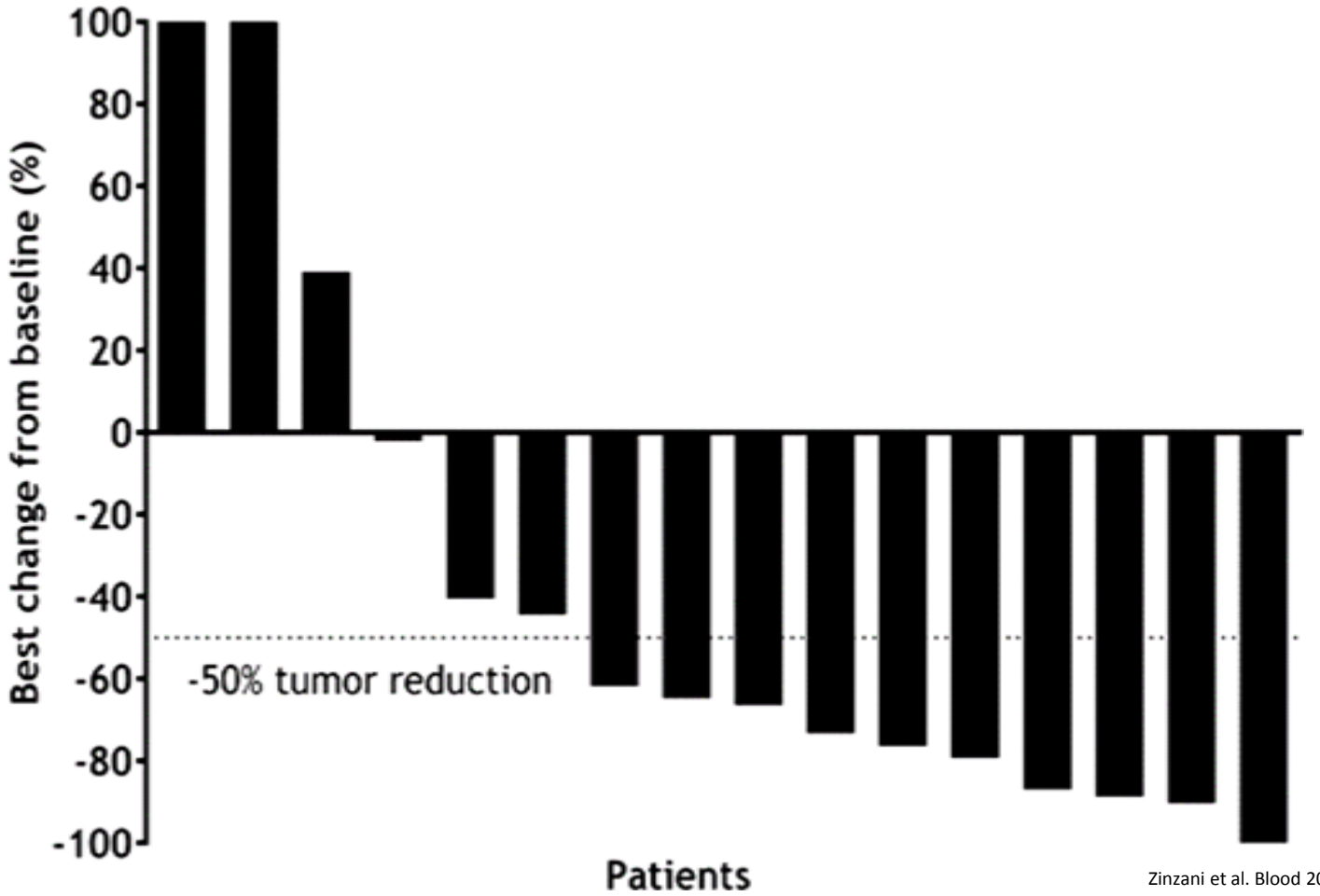
Ansell et al. NEJM 2015

Pembrolizumab in Hodgkin Lymphoma



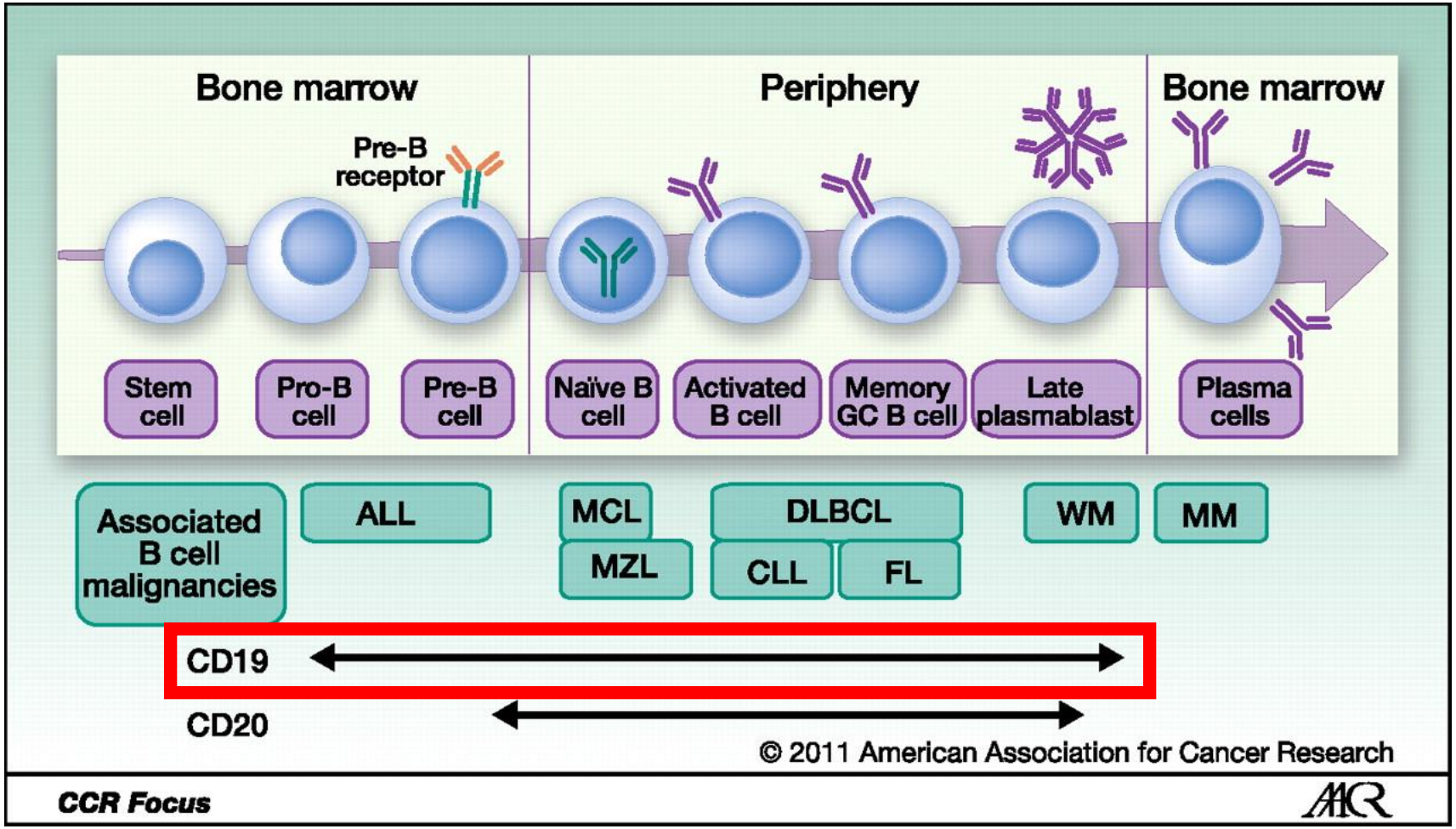
Zinzani et al. Hematological Oncology 2017

Pembrolizumab in Primary Mediastinal Large B cell Lymphoma



Zinzani et al. Blood 2016

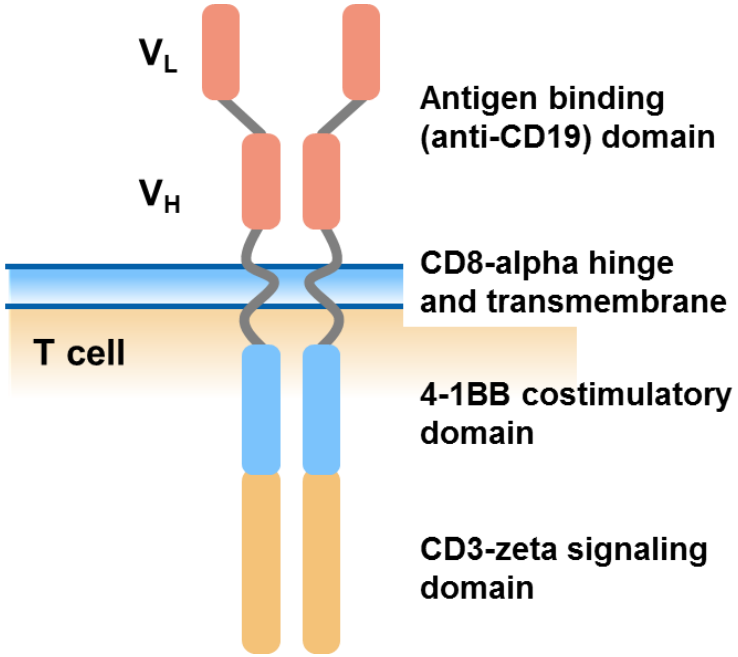
B Cell Malignancies are CD19+

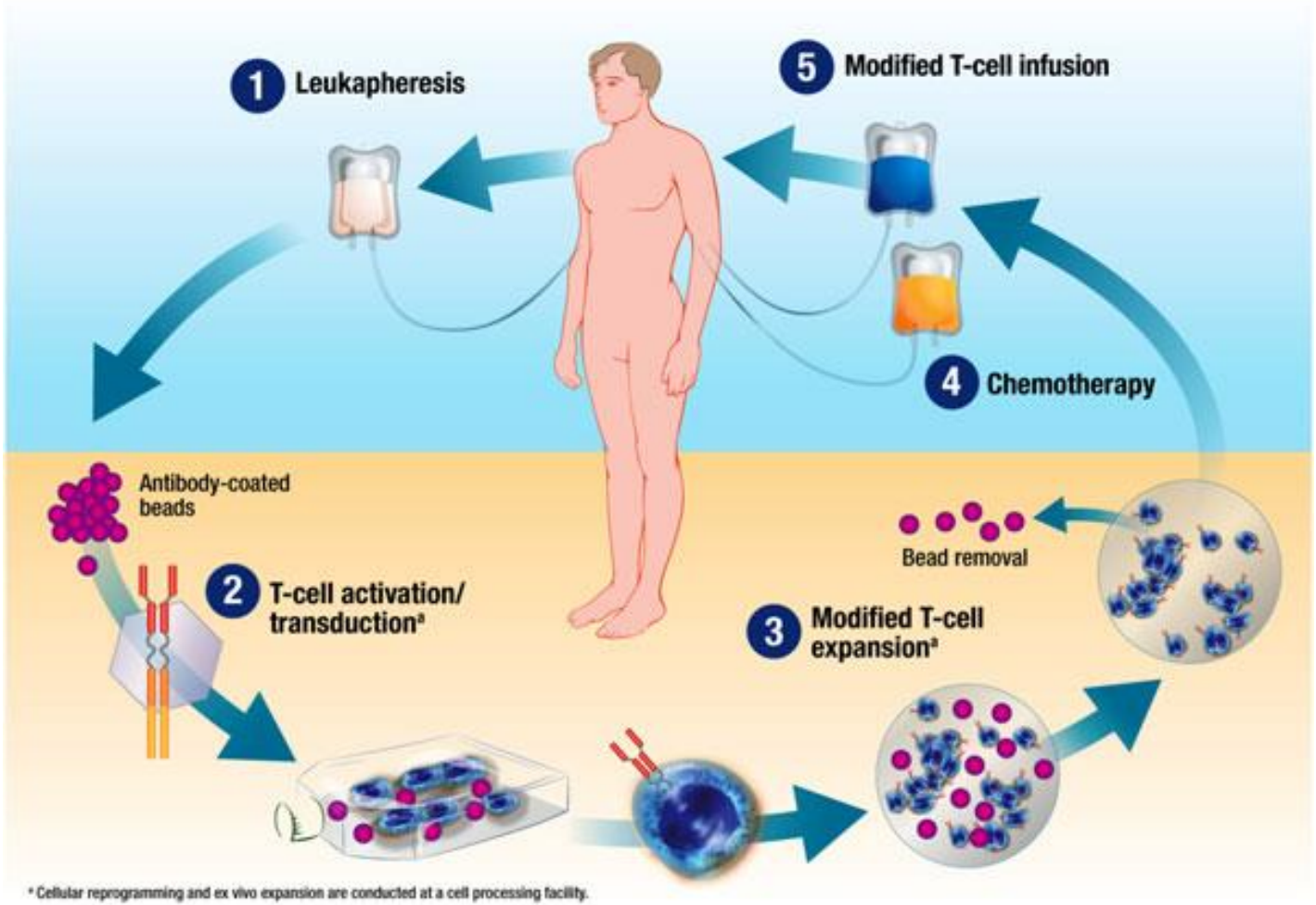


Blanc et al. Clinical Cancer Research 2011

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

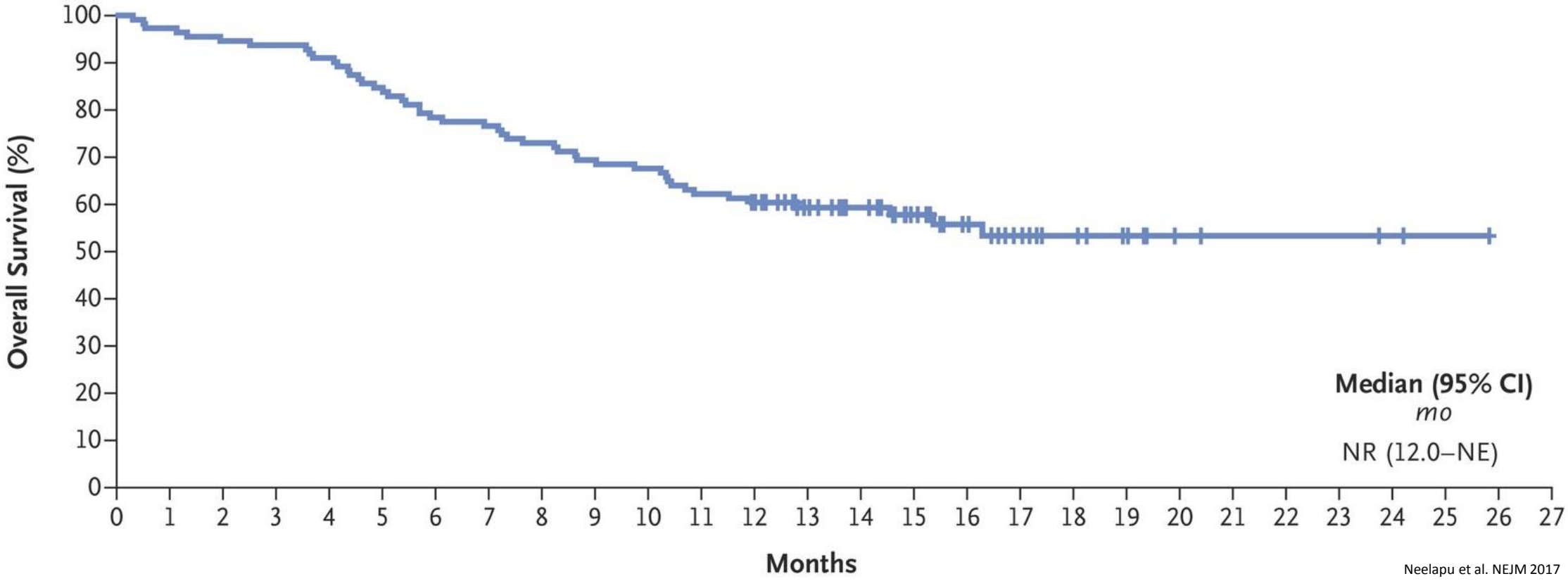
- Axicabtagene ciloleucel (Yescarta)
  - ZUMA-1: Adult patients with relapsed or refractory large B cell lymphoma after two or more lines of systemic therapy, including diffuse large B cell lymphoma, high-grade B cell lymphoma, and DLBCL arising from follicular lymphoma
- Tisagenlecleucel (Kymriah)
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

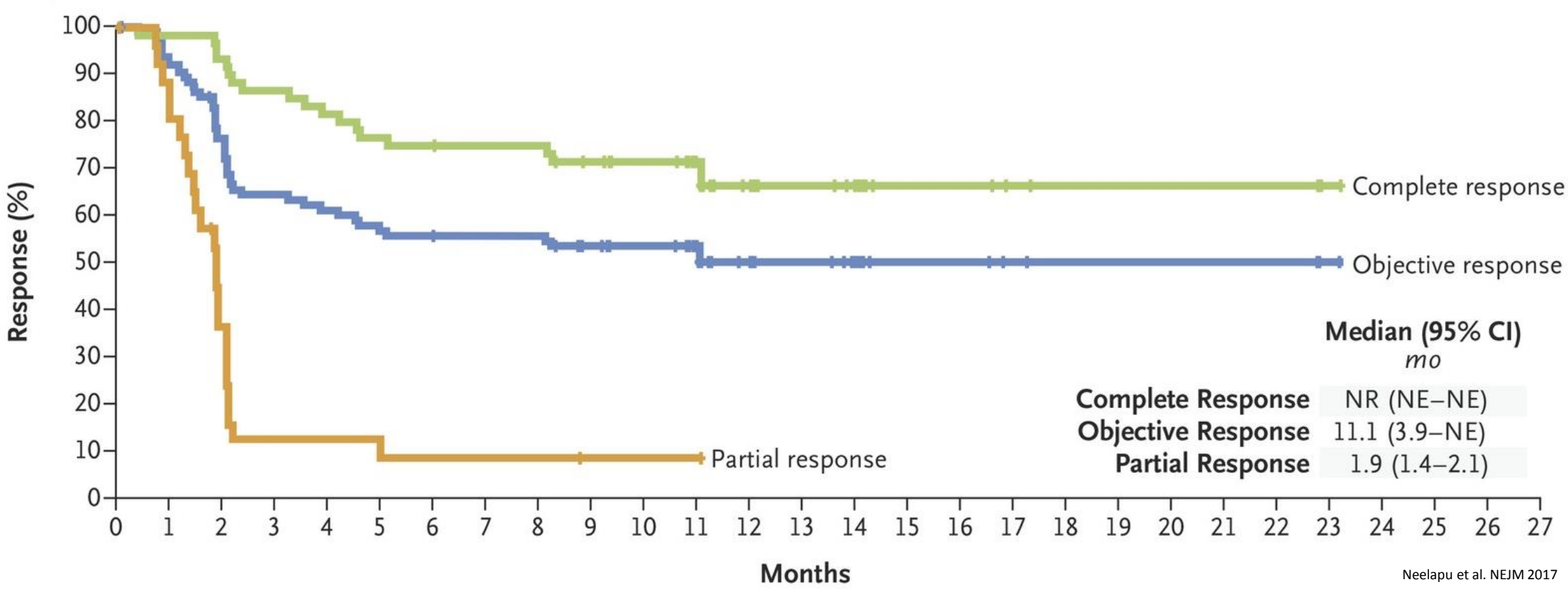
Overall Survival



Neelapu et al. NEJM 2017

Axicabtagene ciloleucel in B Cell Lymphoma

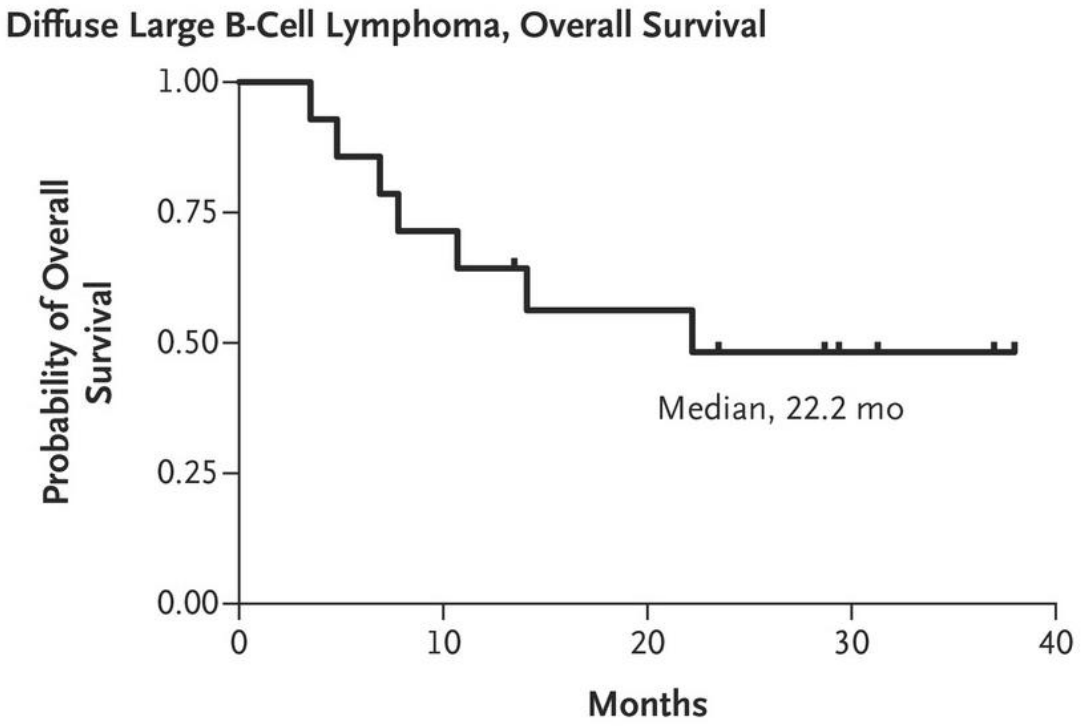
Duration of Response

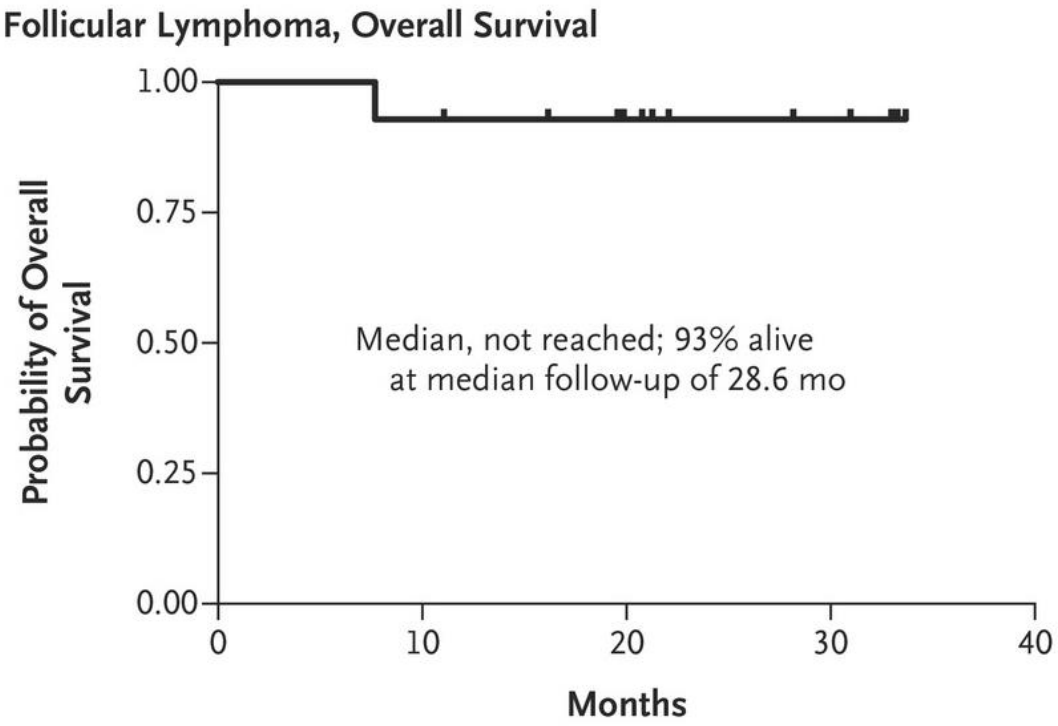


Neelapu et al. NEJM 2017

Tisagenlecleucel in B Cell Lymphoma

Overall Survival

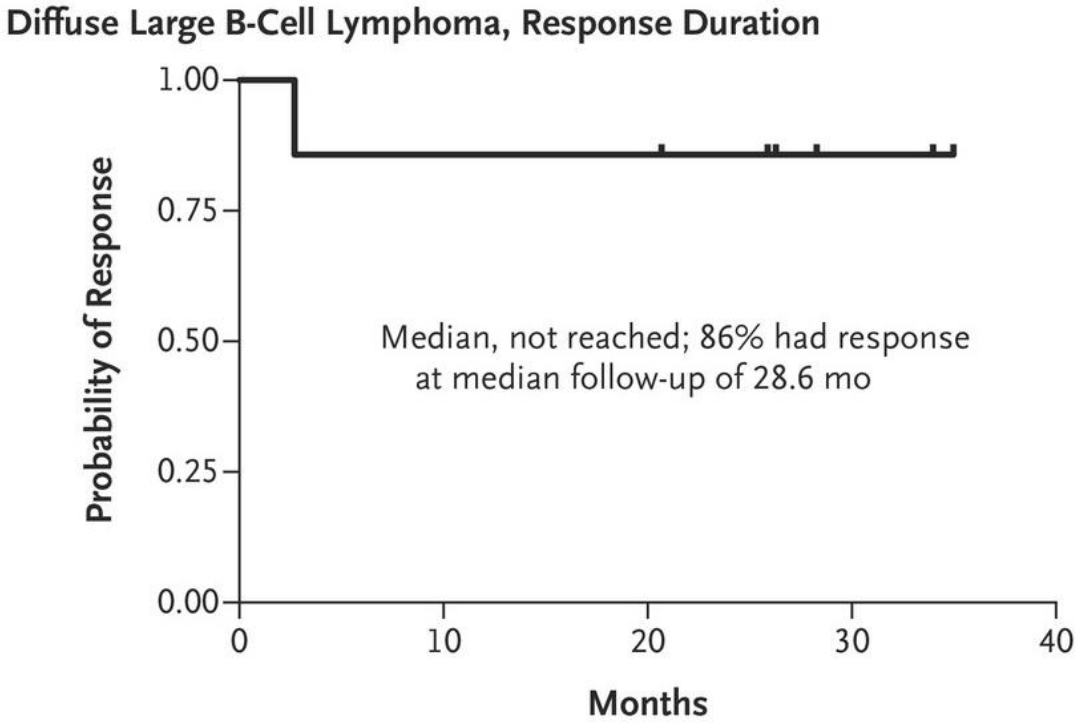


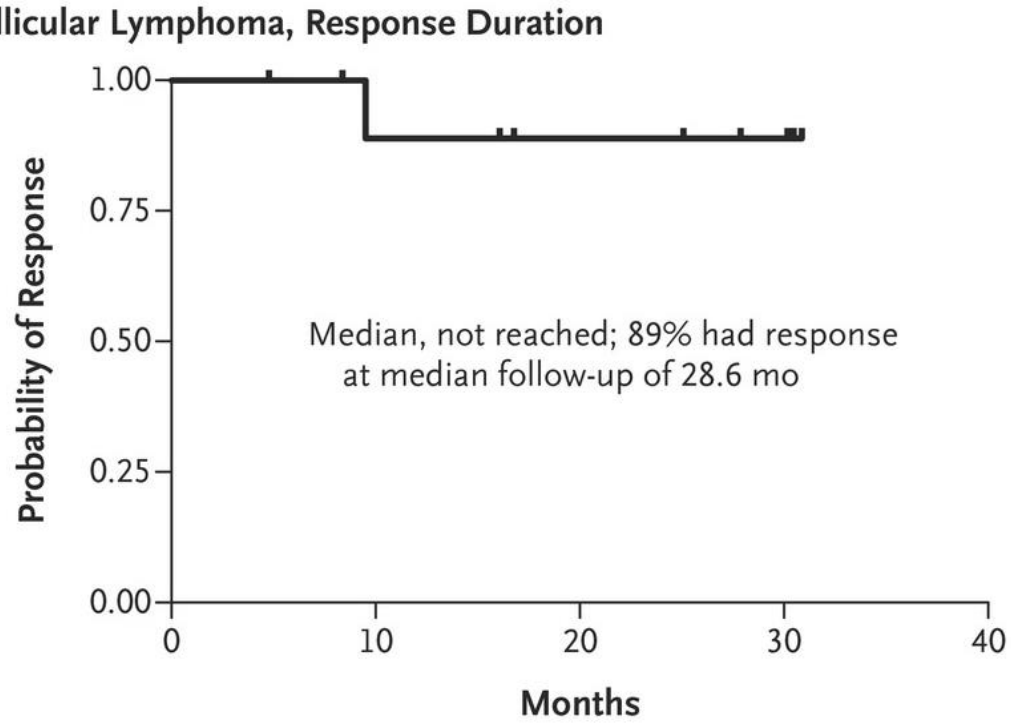


Schuster et al. NEJM 2017

Tisagenlecleucel in B Cell Lymphoma

Duration of Response



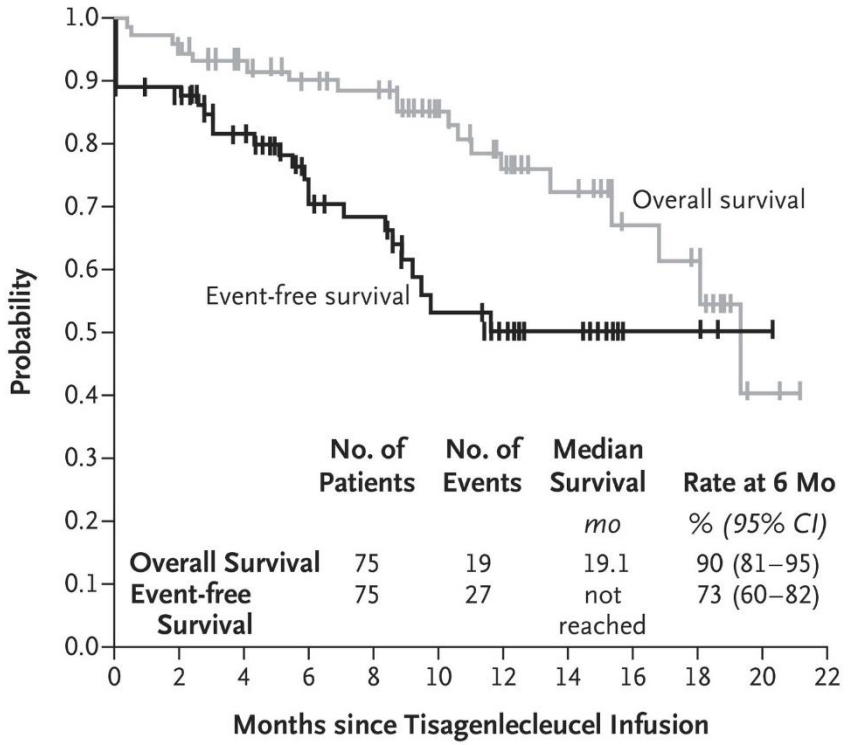


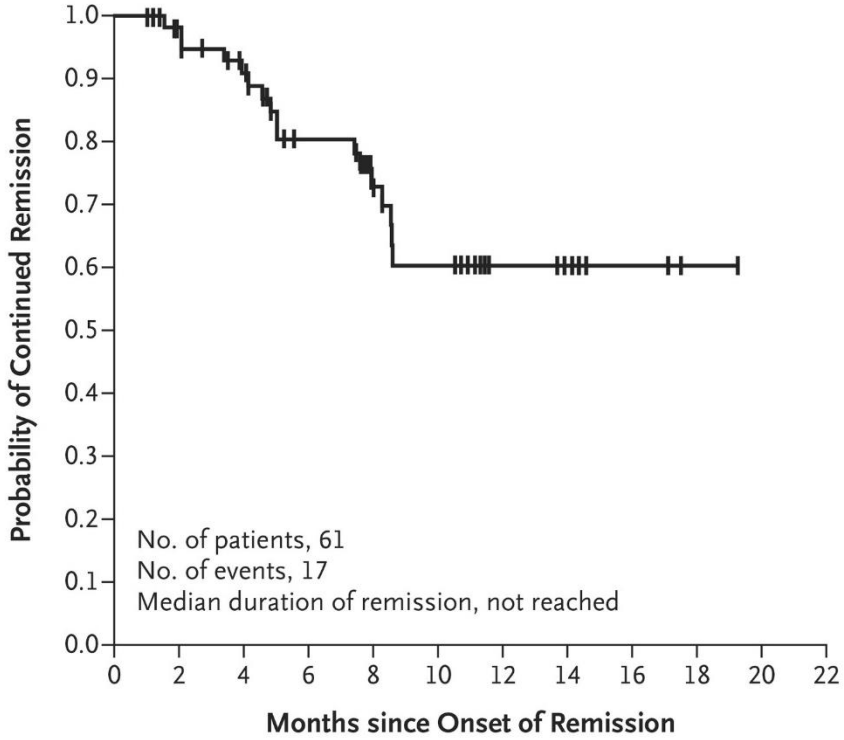
Schuster et al. NEJM 2017

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

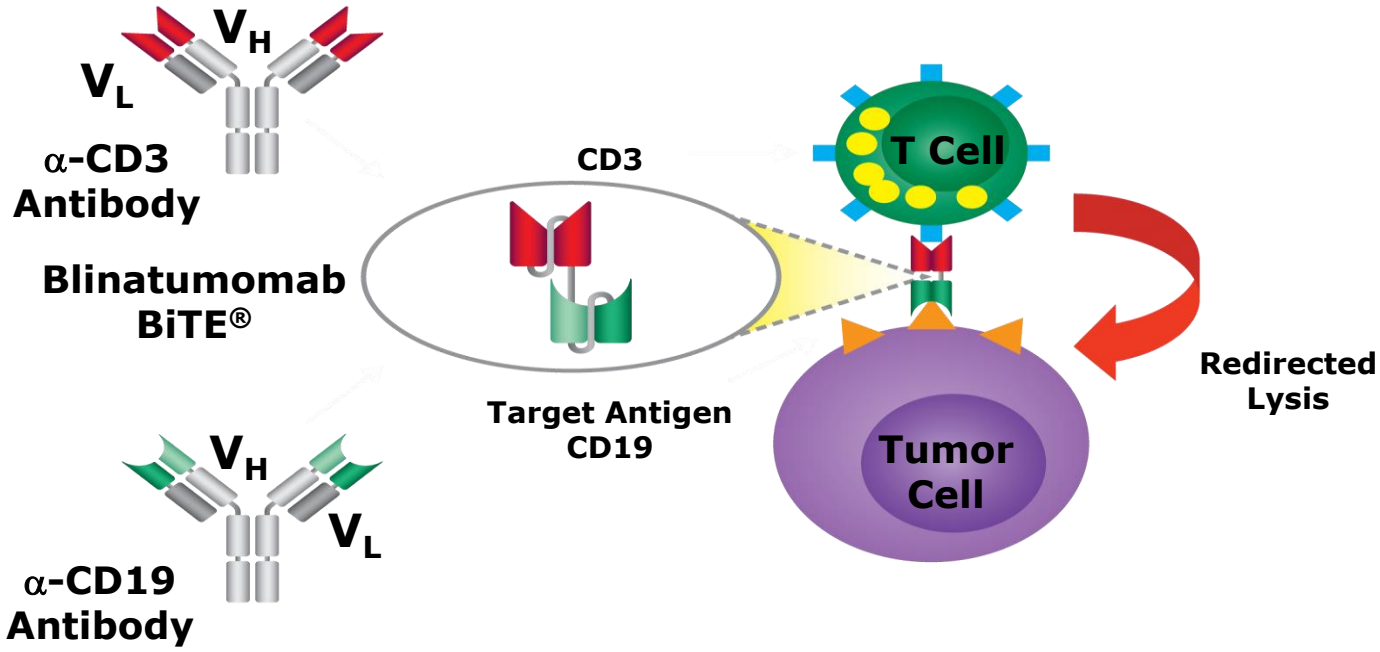




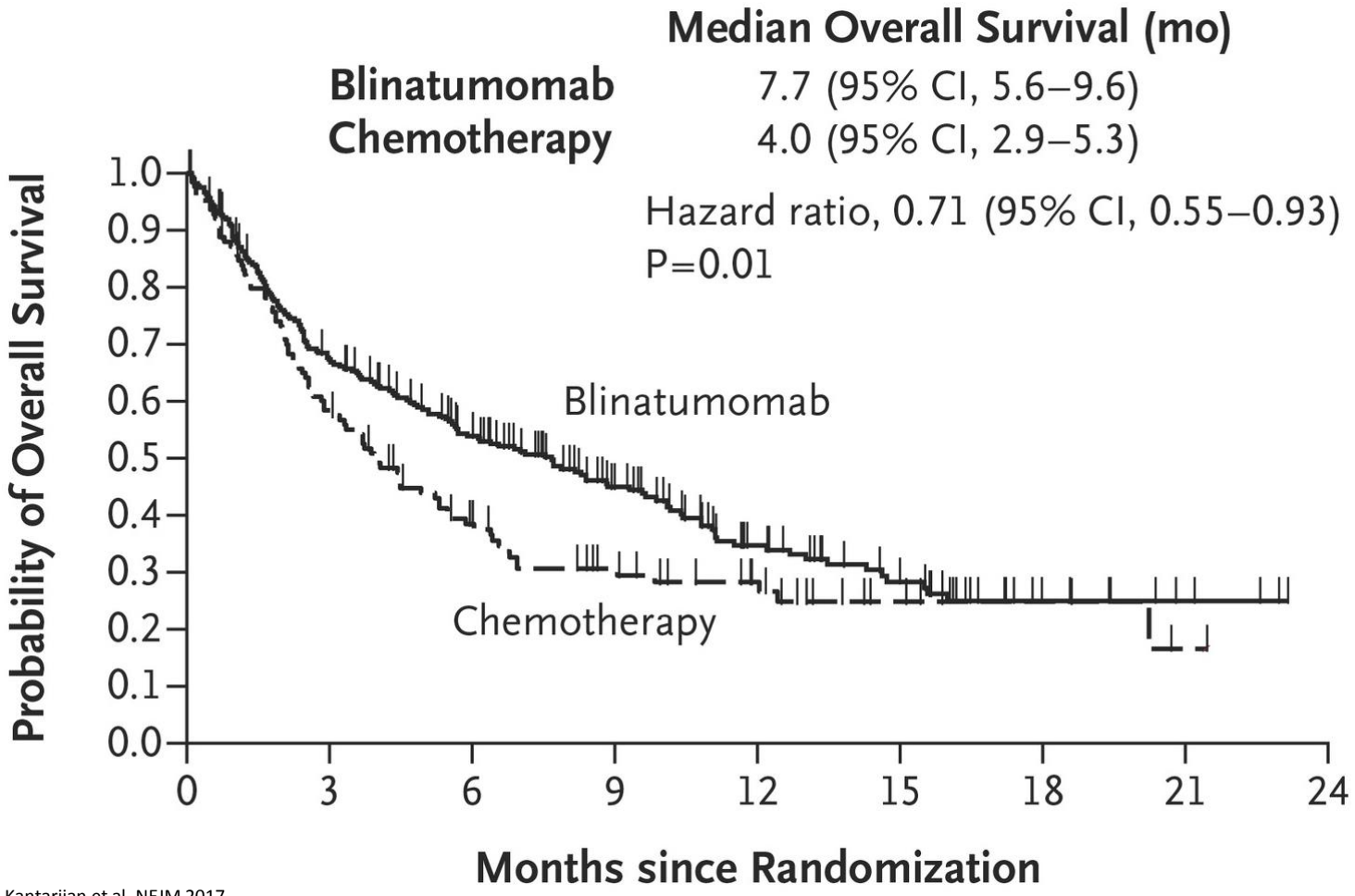
Maude et al. NEJM 2018

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



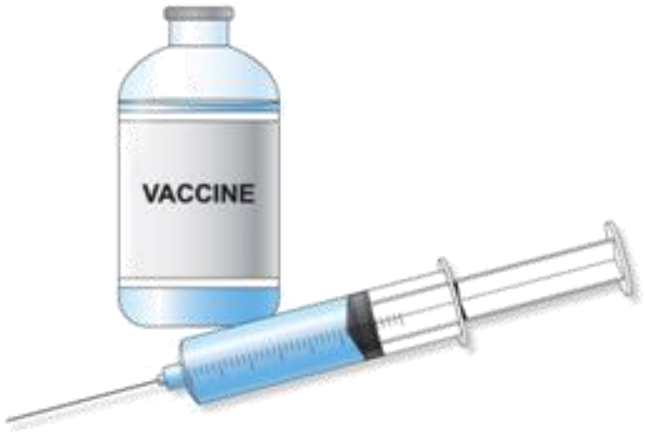
Blinatumomab for B-ALL



Kantarjian et al. NEJM 2017

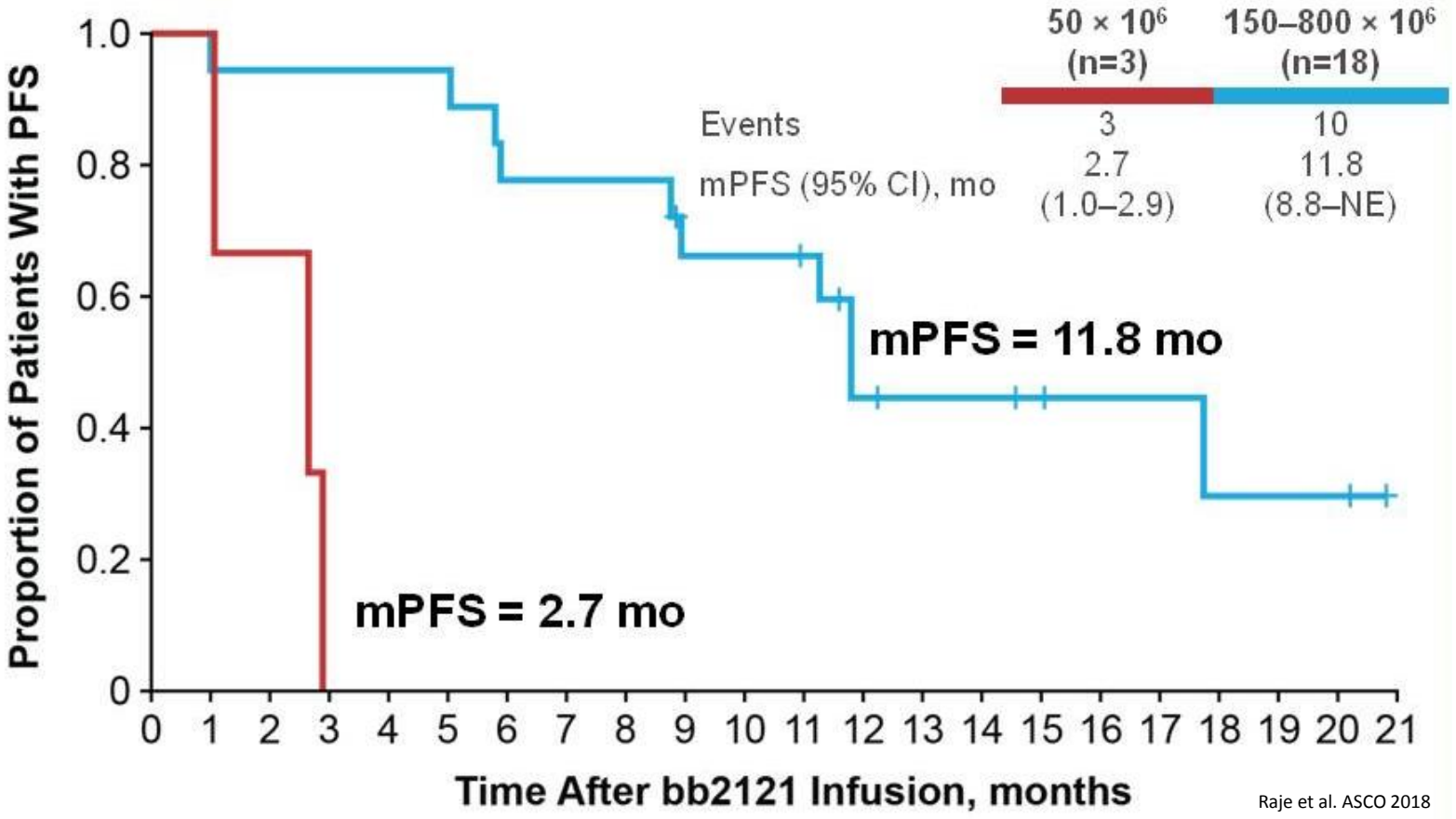
Immunotherapies for Multiple Myeloma

- 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



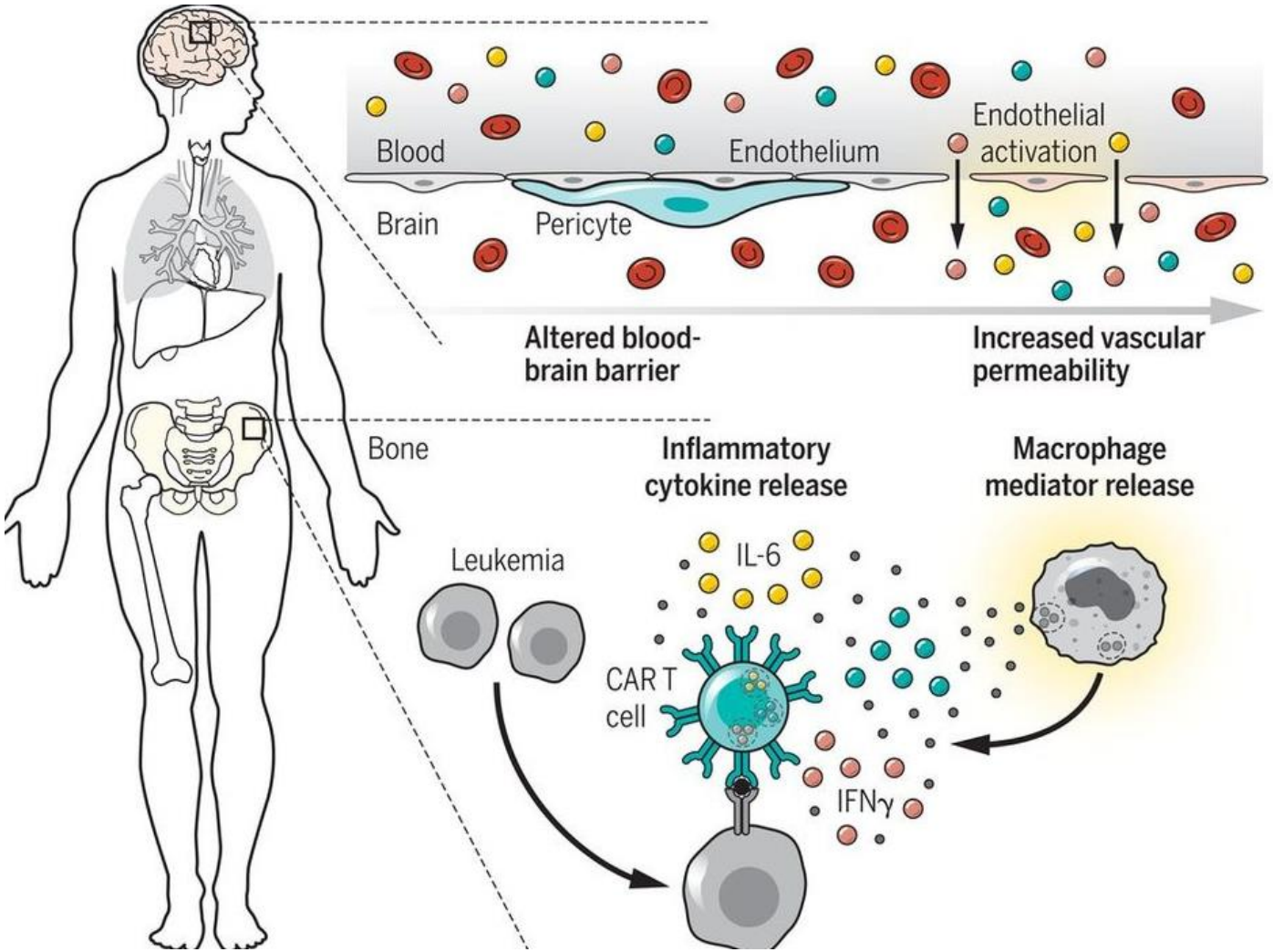
In Development: BCMA+ CAR T Therapy for Myeloma

- 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)



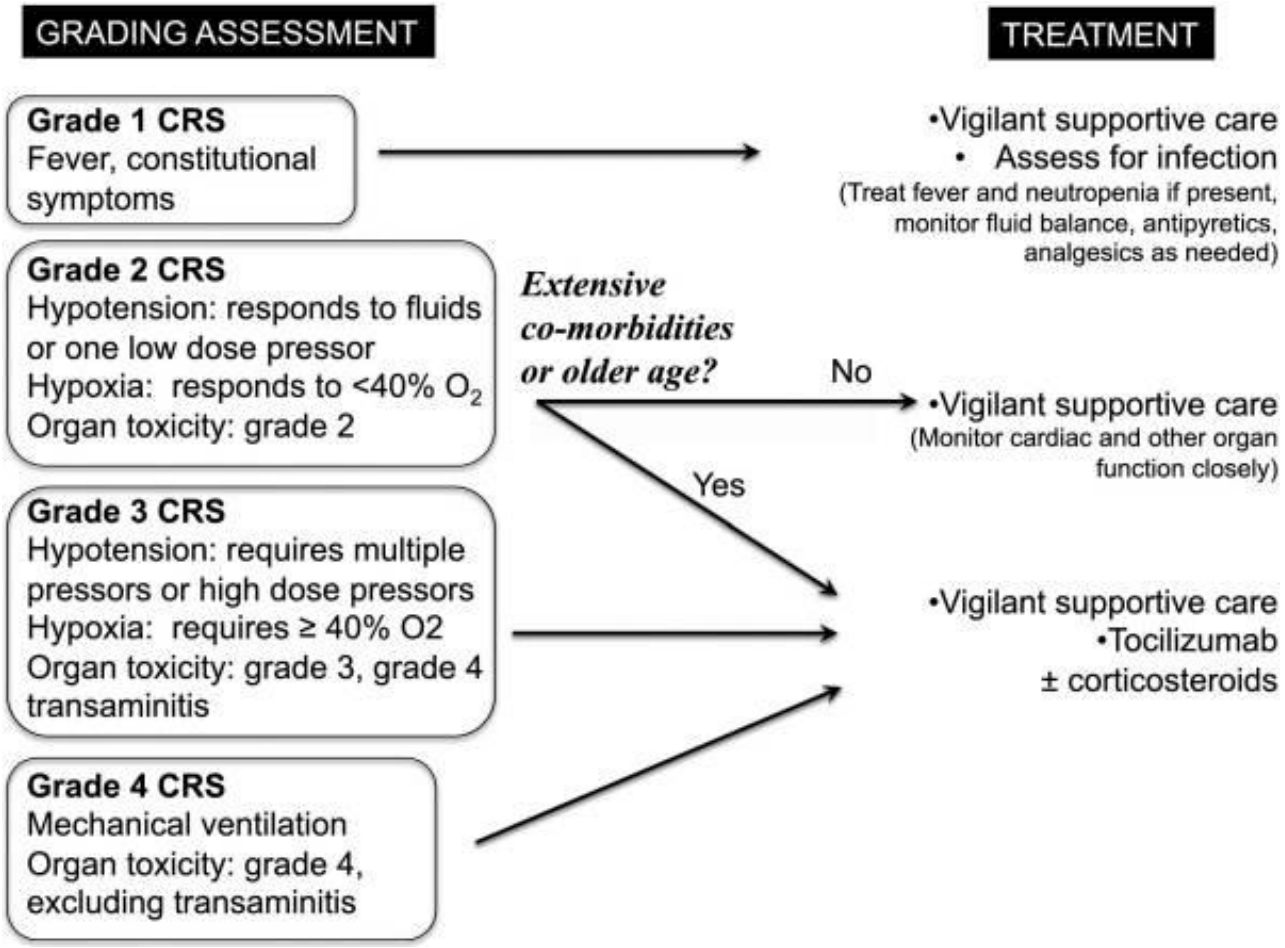
Neurotoxicity
Delirium
Aphasia
Seizures
Cerebral edema
Intracranial hemorrhage

Hemodynamic instability
Tachycardia
Hypotension
Capillary leak syndrome

Organ dysfunction
AST and ALT elevation
Hyperbilirubinemia
Respiratory failure

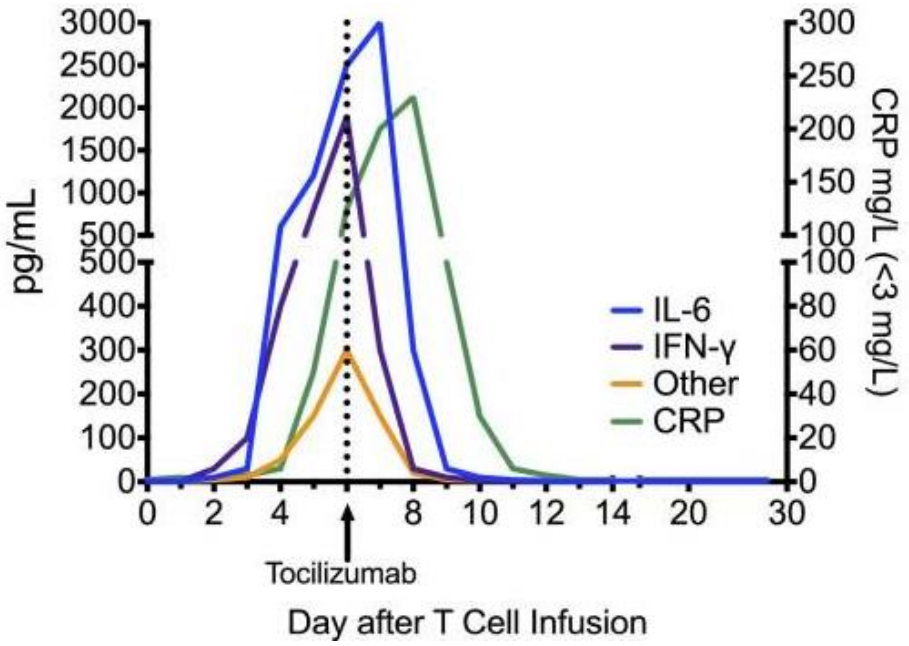
June et al. Science 2018

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*]

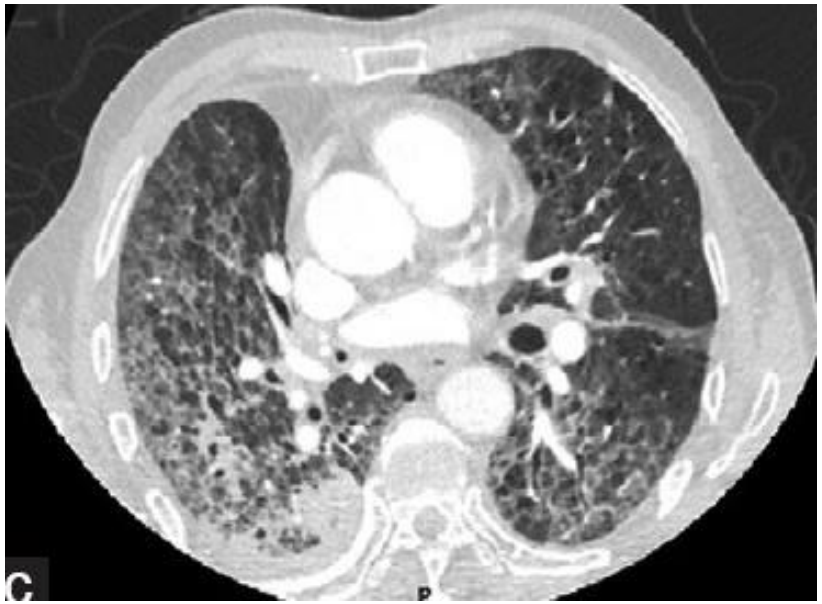
Case #1

- 25 year old female diagnosed with Stage IIIS Classical Hodgkin Lymphoma.
- Treated with 6-cycles of ABVD chemotherapy with residual disease at end of treatment
- Received ICE chemotherapy (ifosfamide, carboplatin, etoposide) x 2 cycles and achieved a complete response. Patient then proceeded with an autologous stem cell transplant
- Received 1 year of Brentuximab maintenance post-transplant
- Relapsed 18 months after transplant

Appropriate next treatment?

PD-1 Checkpoint Inhibitors

- Patient started on Nivolumab, PD-1 inhibitor, for relapse after auto-HCT and brentuximab failure. Patient has clinical improvement in disease burden but after 8 doses of Nivolumab patient develops shortness of breath and cough.



Management of anti-PD-1 toxicities

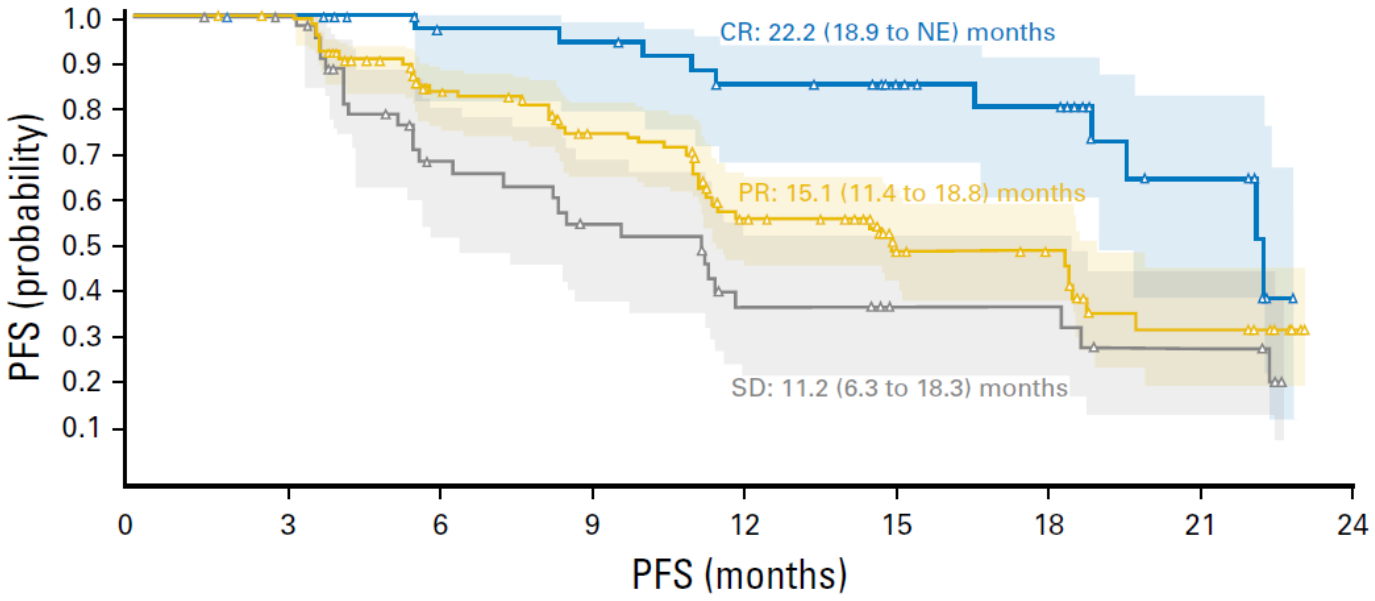
- Patient started on Prednisone 1 mg/kg/day with resolution of symptoms. Steroids tapered over 4-6 weeks. Therapy with PD-1 was resumed with radiographic and clinical improvement.

Grade of immune-related AE (CTCAE/equivalent)	Corticosteroid management	Additional notes
1	• Corticosteroids not usually indicated	• Continue immunotherapy
2	• If indicated, start oral prednisone 0.5-1 mg/kg/day if patient can take oral medication. • If IV required, start methylprednisolone 0.5-1 mg/kg/day IV • If no improvement in 2–3 days, increase corticosteroid dose to 2 mg/kg/day • Once improved to ≤grade 1 AE, start 4–6 week steroid taper	• Hold immunotherapy during corticosteroid use • Continue immunotherapy once resolved to ≤grade 1 and off corticosteroids • Start proton pump inhibitor for GI prophylaxis
3	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant • Once improved to ≤ grade 1, start 4–6-week steroid taper • Provide supportive treatment as needed	• Hold immunotherapy; if symptoms do not improve in 4–6 weeks, discontinue immunotherapy • Consider intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)
4	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant, e.g., infliximab • Provide supportive care as needed	• Discontinue immunotherapy • Continue intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)

Puzanov, I., A. et al, *Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer, 2017.* ***5(1): p. 95.***

Long-term Follow-up

- Patient proceeded with an allogeneic transplant while in remission with nivolumab



Updated results from Nivolumab in Classical HL after Failure of Autologous Transplant. Armand et al. 2018, JCO.

Case #2

- 55 year old male with Stage IV MYC+ DLBCL
  - Received R-CHOP x 6 cycles with end of treatment complete remission
  - Relapsed at 9 months post-treatment
  - Received R-ICE x 3 cycles with PET/CT CR after salvage chemotherapy
  - Underwent consolidative autologous transplant with BEAM conditioning
  - Day 100 PET/CT with evidence of disease recurrence

Which immunotherapy treatment is best next approach?

A: Pembrolizumab

B: Nivolumab

C: CAR-BCMA T cells

D: CAR-19 T cells

CAR-19 T Cell Treatment

- Patient underwent apheresis for T-cells. Product sent to central manufacturing site for axicabtagene ciloleucel manufacturing. Patient receives lymphodepletion with fludarabine and cyclophosphamide and received the modified CAR-T cells against CD19.
- Two days after infusion the patient develops high grade fevers to 102-103 and hypotension un-responsive to fluids.

What is the most likely diagnosis?

A: Graft-versus-host-disease

B: Cytokine release syndrome

C: Autoimmune toxicity

D: Bacterial Sepsis

Cytokine Release Syndrome

- A well established complication after CAR-T cell infusion. Felt to be due to engagement of the target antigen, activation of T-cells, and elevation of inflammatory cytokines.
- What is the appropriate next treatment:
  - A: Supportive care, IVF, anti-pyretics
  - B: Corticosteroids
  - C: Tocilizumab
  - D: Siltuximab

Management of CRS

- To date CRS management is product specific
  - **Tisagenlecleucel** and **axicabtagene ciloleucel** are different products with different toxicity profiles and different scales for grading toxicity. Separate algorithms are provided in respective package inserts
  - For **axicabtagene ciloleucel**: Tocilizumab is first line therapy for Grade 2-4 CRS per CRS grading system. If no improvement steroids are second line.
  - For **tisagenlecleucel** : Different grading scale. Tocilizumab is indicated for patients with “CRS requiring moderate to aggressive intervention”
    - Hemodynamic instability, worsening respiratory distress, mechanical ventilation, clinical deterioration.

Long-term Follow-up

- Post-CAR-T cell treatment patients can have persistent low blood counts.
- Disease assessment at 3 months tends to predict outcomes
- Monitoring for ongoing B-cell aplasia and hypogammaglobulinemia
- Monitoring for secondary malignancies
- Long-term toxicities not yet known