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

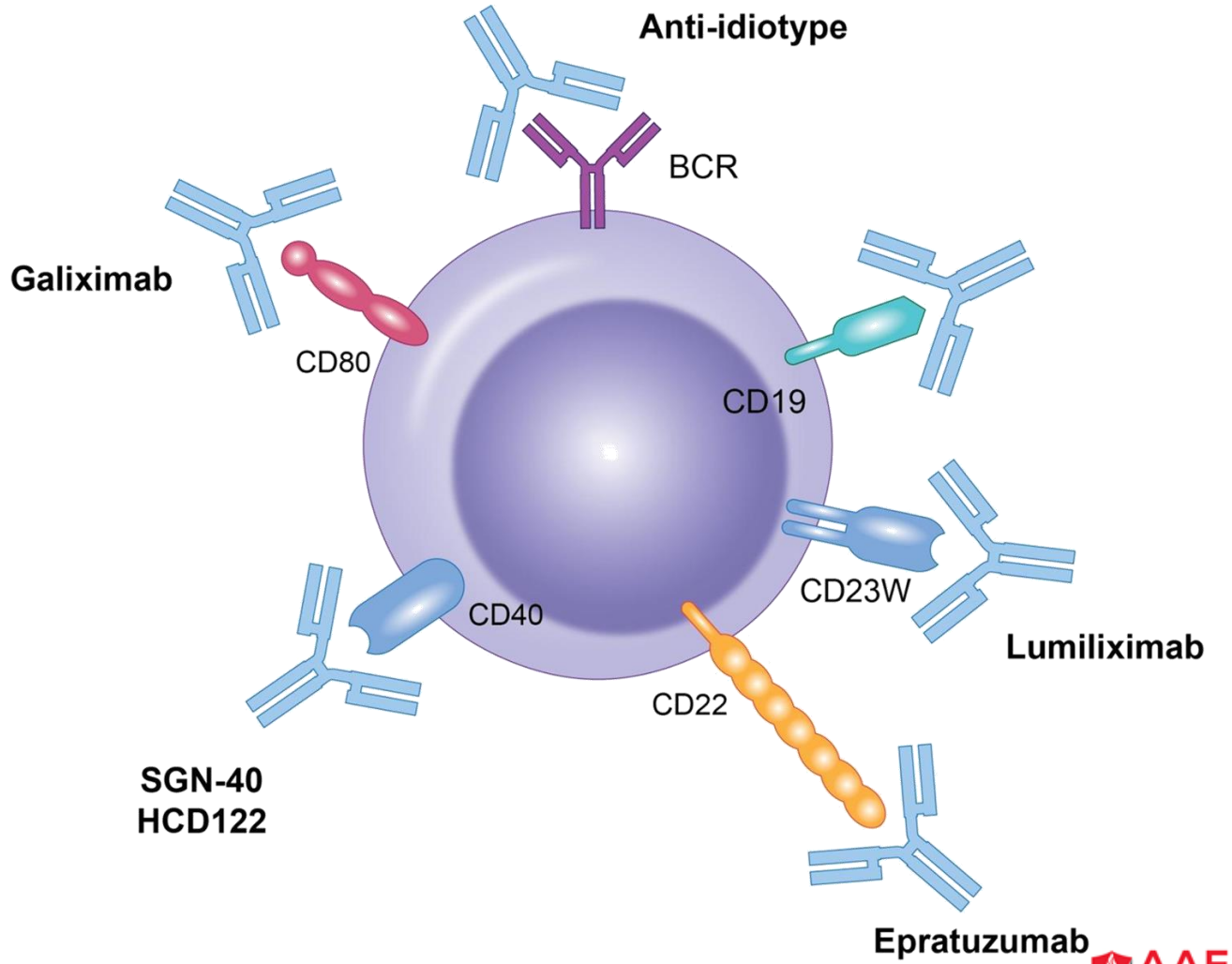
ACCC Association of Community Cancer Centers

Society for Immunotherapy of Cancer

Disclosures

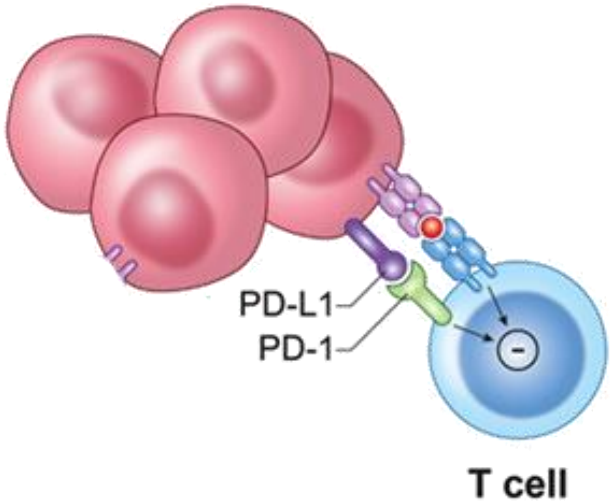
- I have no financial disclosures.
- I will not be discussing non-FDA approved indications during my presentation.

Monoclonal Antibodies Targeting B Cell Lymphomas



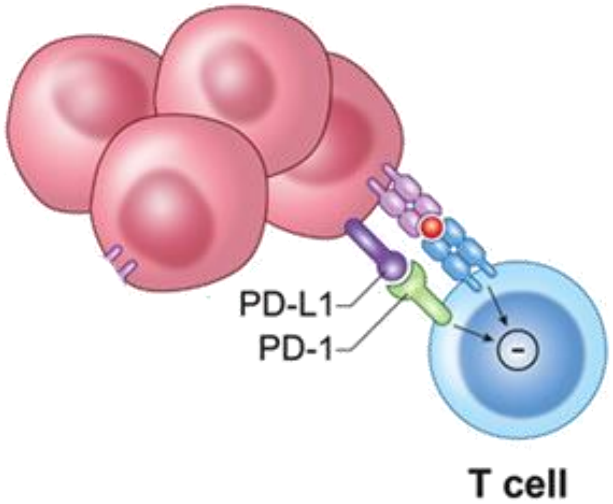
FDA-approved Checkpoint Inhibitors for Lymphomas

- 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



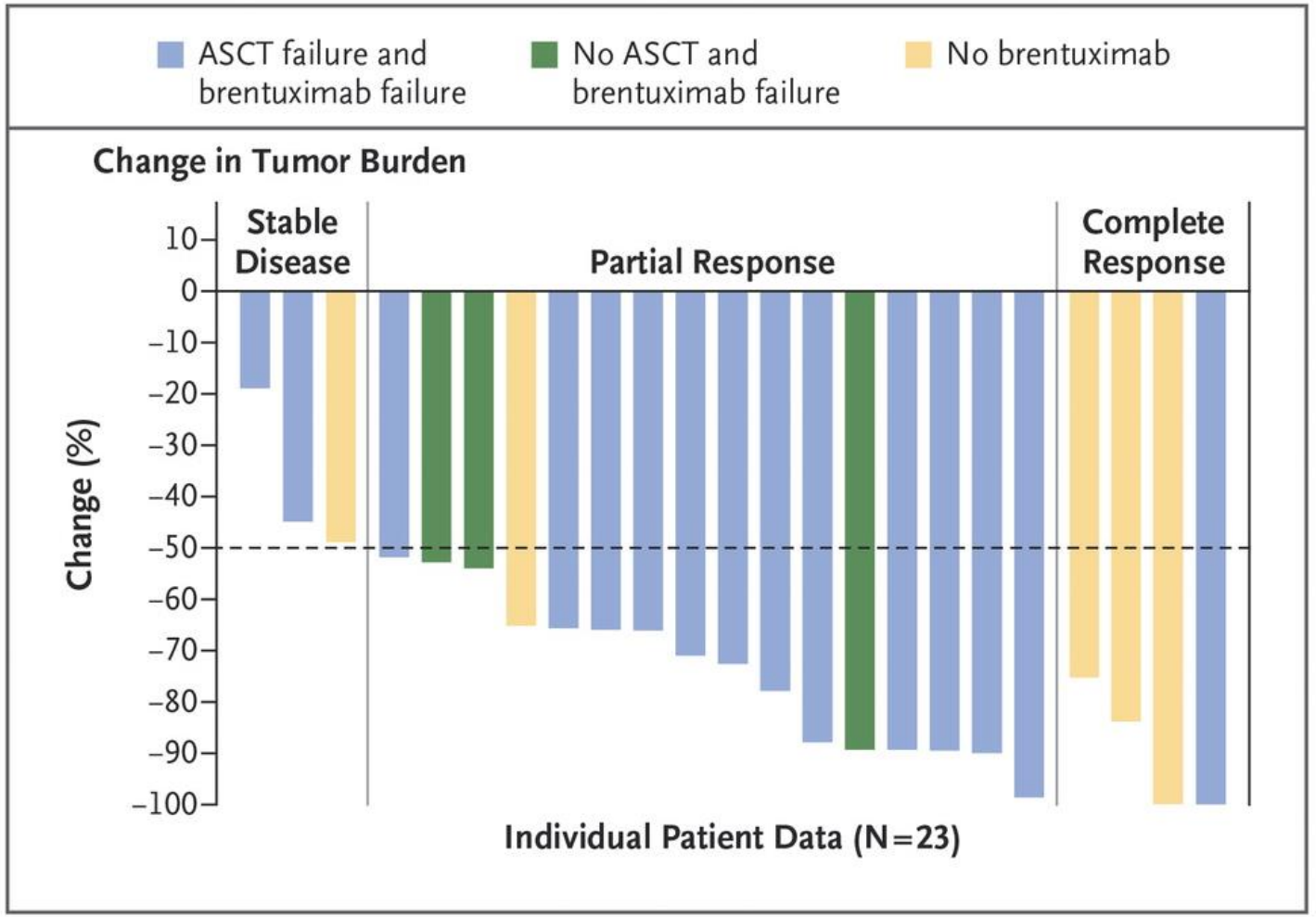
Nivolumab in Hodgkin Lymphoma

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

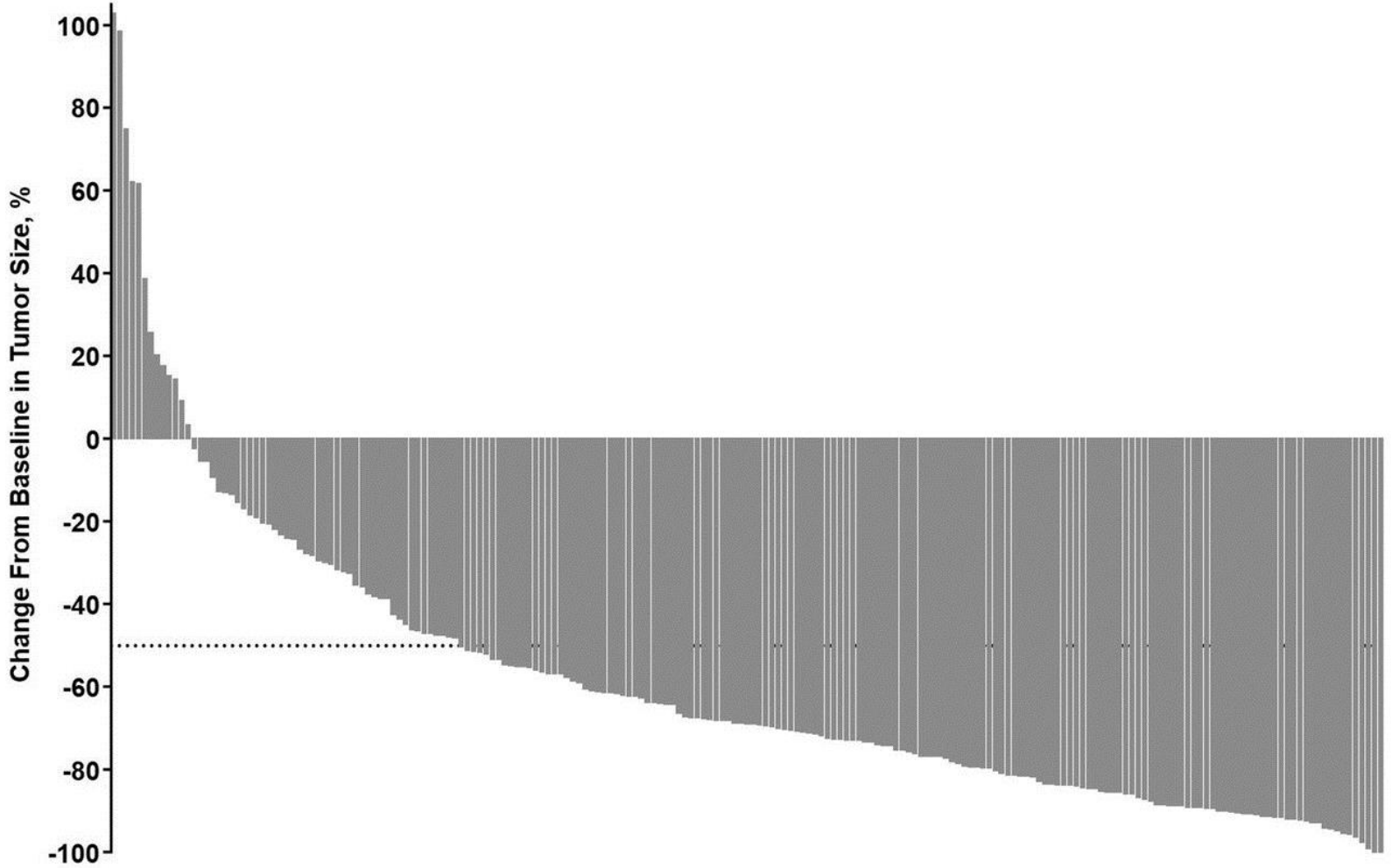
Ansell et al. NEJM 2015

Nivolumab in Hodgkin Lymphoma



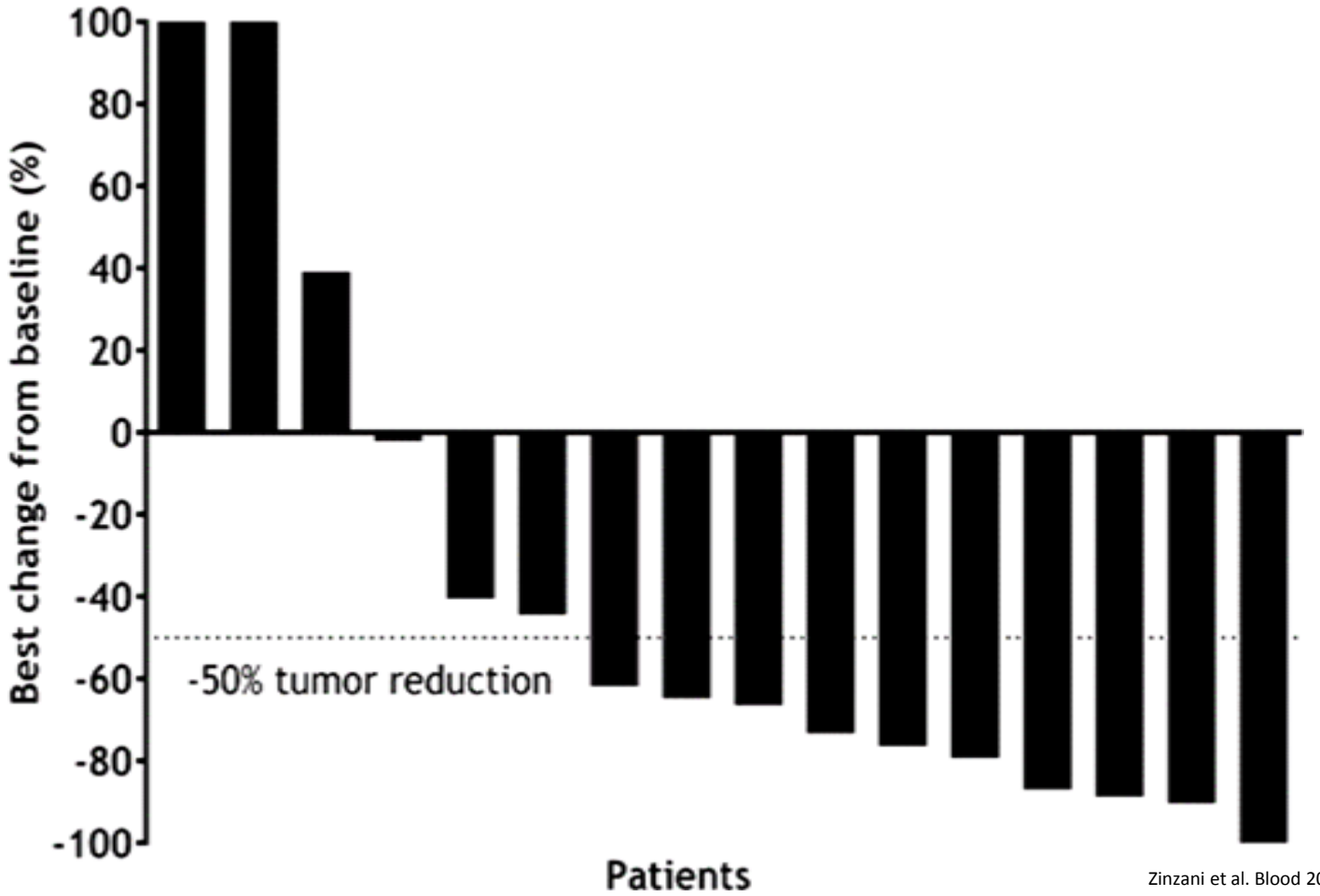
Ansell et al. NEJM 2015

Pembrolizumab in Hodgkin Lymphoma



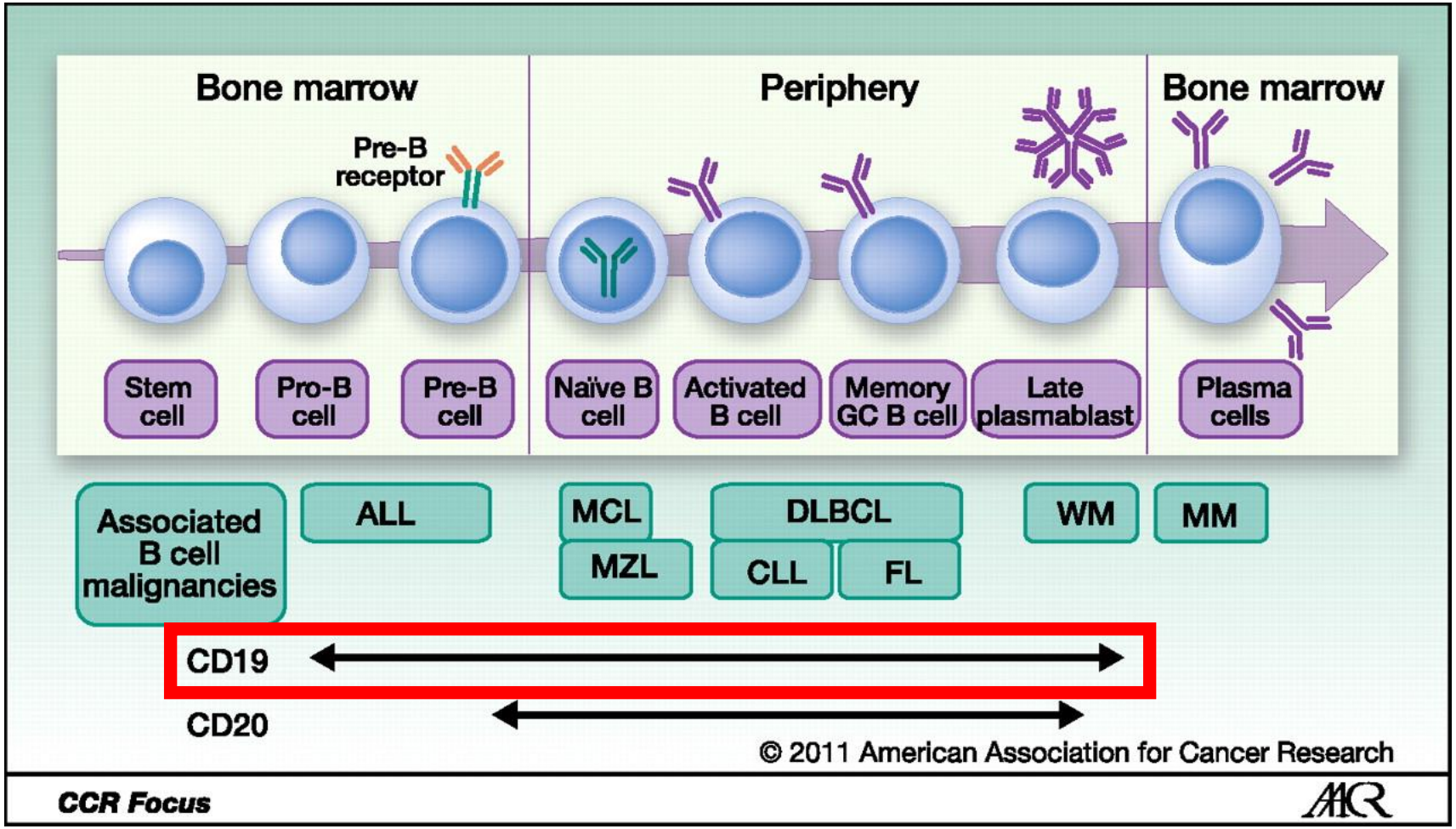
Zinzani et al. Hematological Oncology 2017

Pembrolizumab in Primary Mediastinal Large B cell Lymphoma



Zinzani et al. Blood 2016

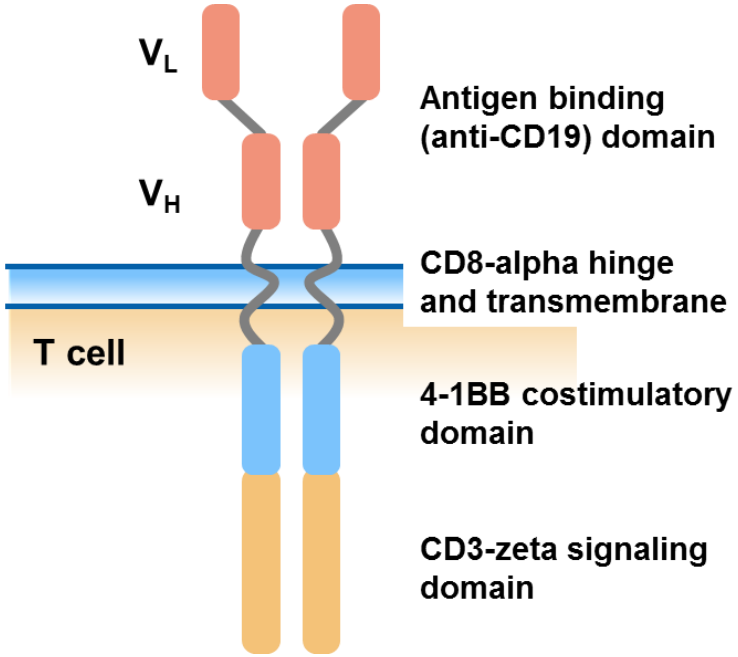
B Cell Malignancies are CD19+

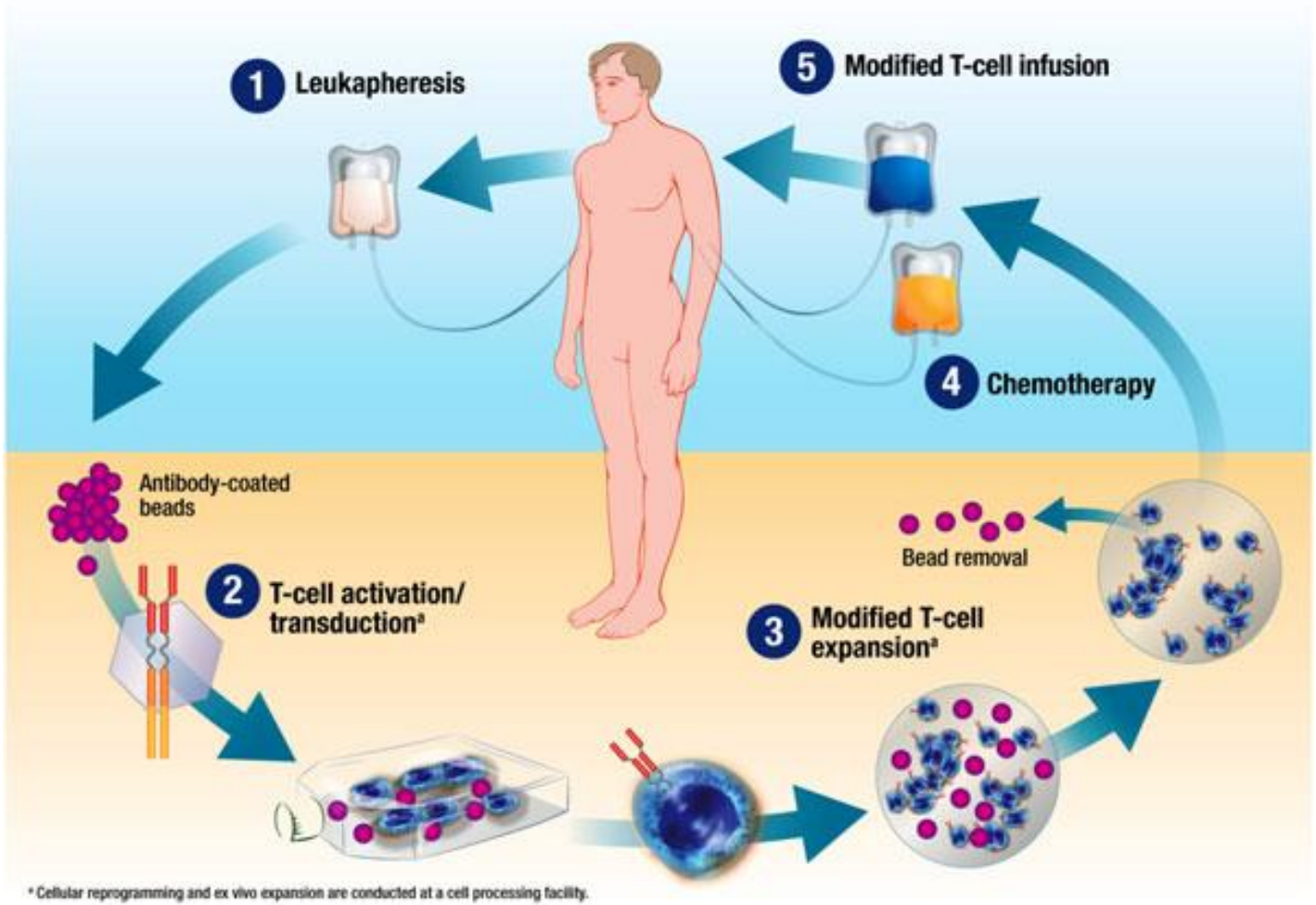


Blanc et al. Clinical Cancer Research 2011

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

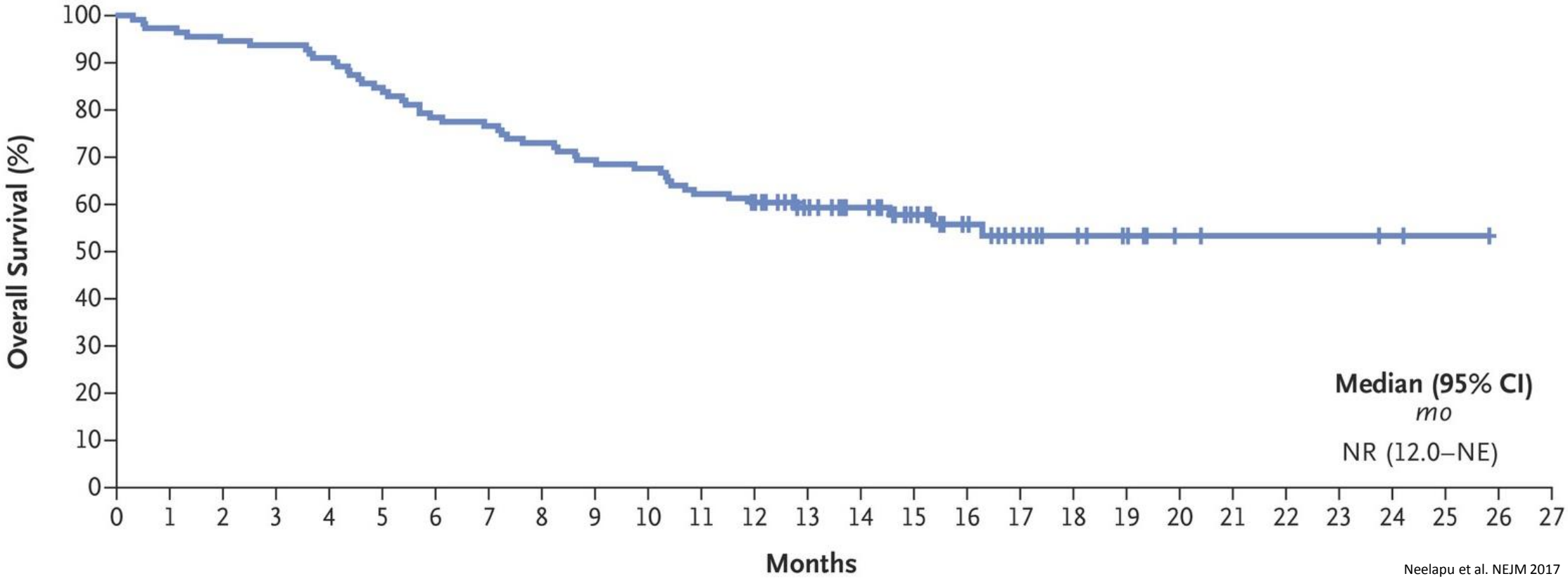
- Axicabtagene ciloleucel (Yescarta)
  - ZUMA-1: Adult patients with relapsed or refractory large B cell lymphoma after two or more lines of systemic therapy, including diffuse large B cell lymphoma, high-grade B cell lymphoma, and DLBCL arising from follicular lymphoma
- Tisagenlecleucel (Kymriah)
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

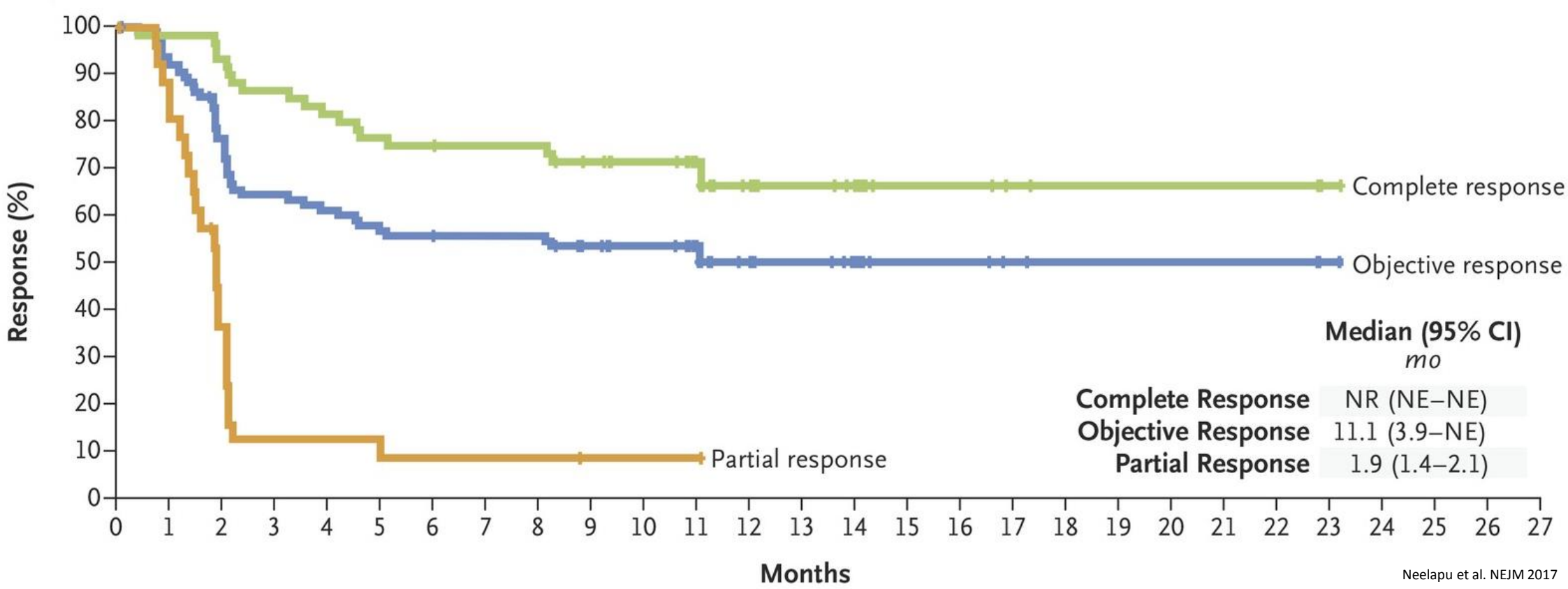
Overall Survival



Neelapu et al. NEJM 2017

Axicabtagene ciloleucel in B Cell Lymphoma

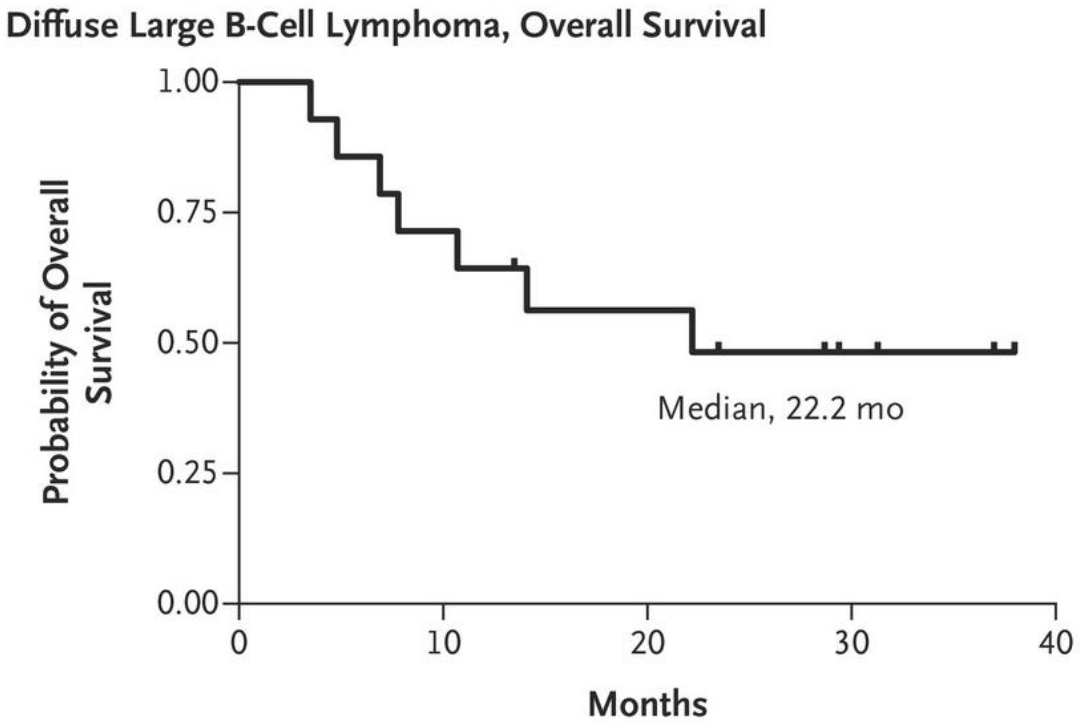
Duration of Response

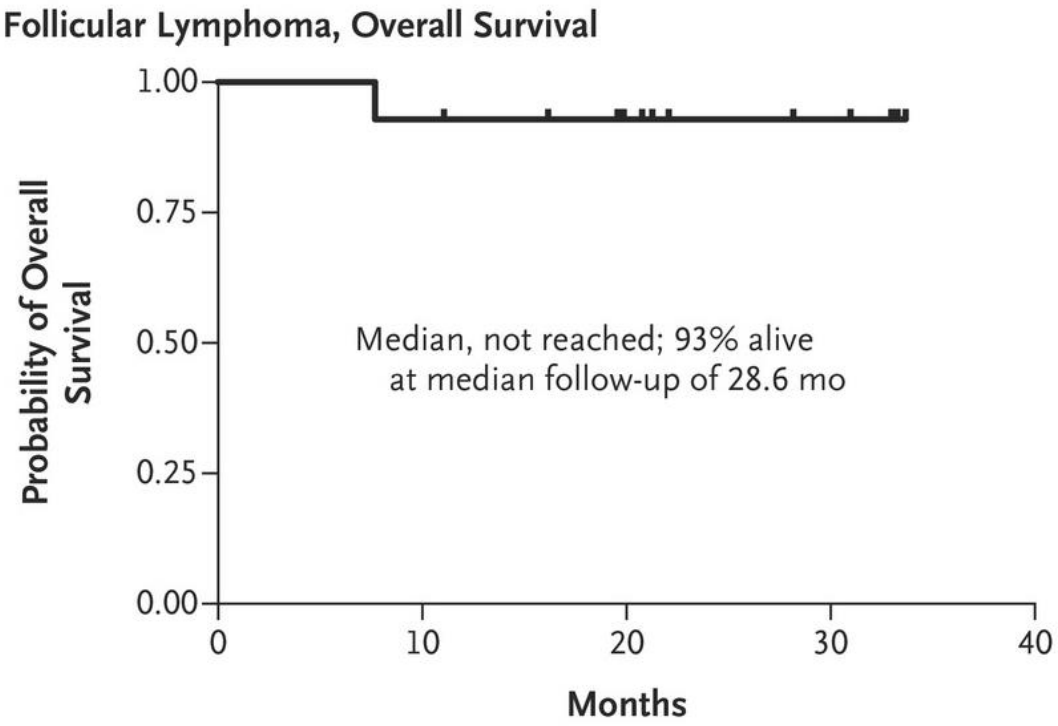


Neelapu et al. NEJM 2017

Tisagenlecleucel in B Cell Lymphoma

Overall Survival

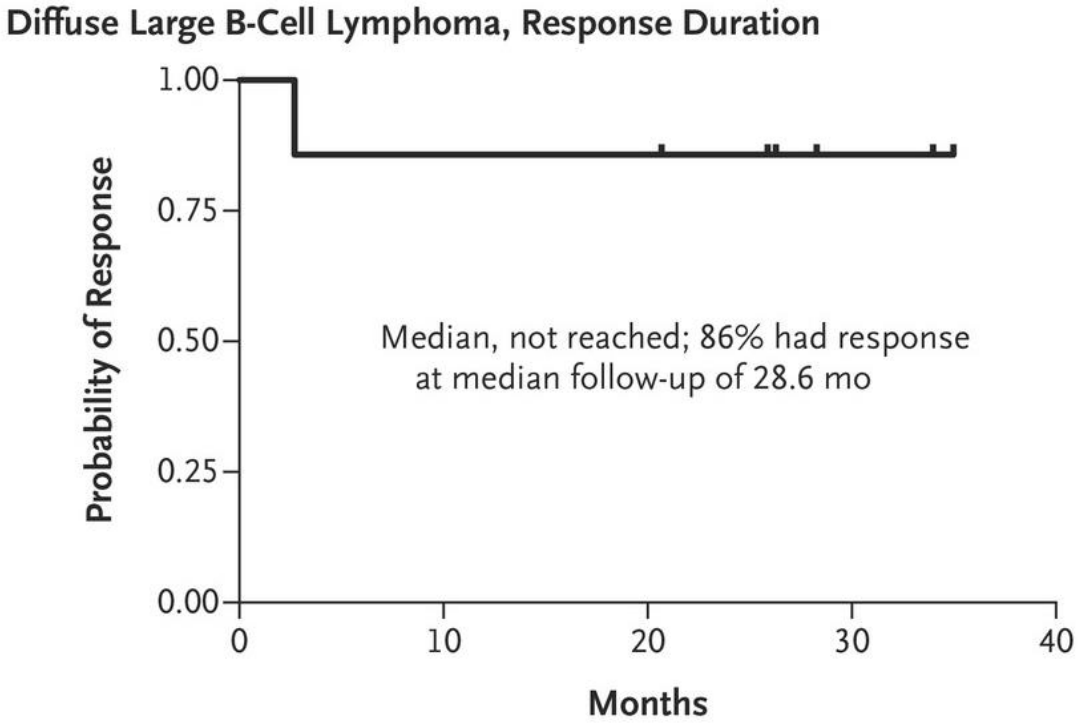


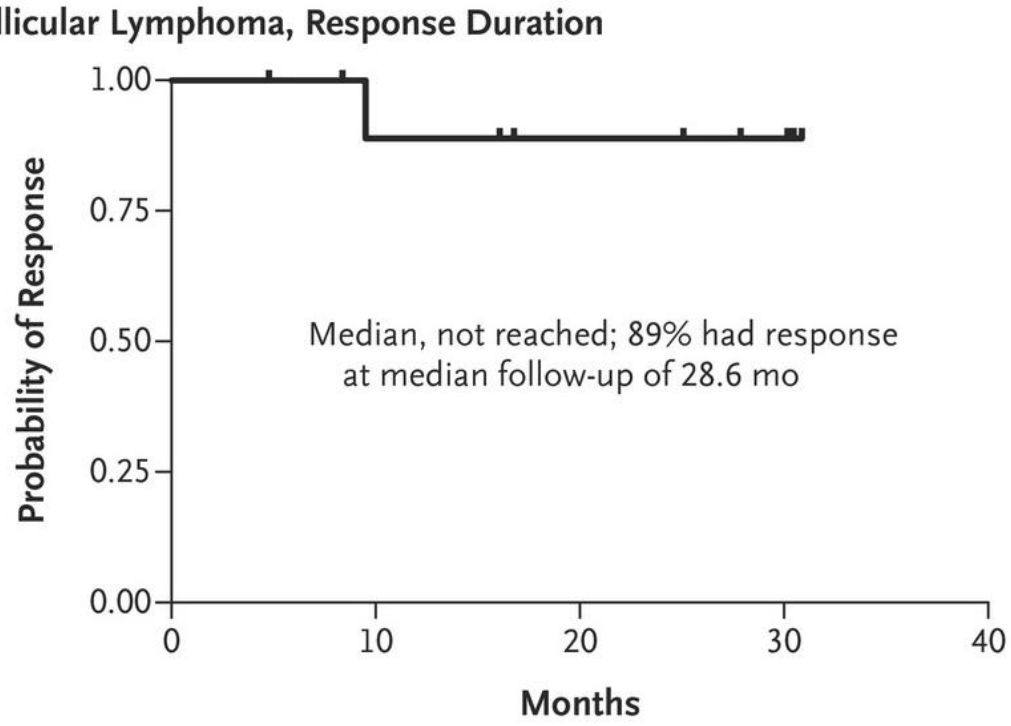


Schuster et al. NEJM 2017

Tisagenlecleucel in B Cell Lymphoma

Duration of Response



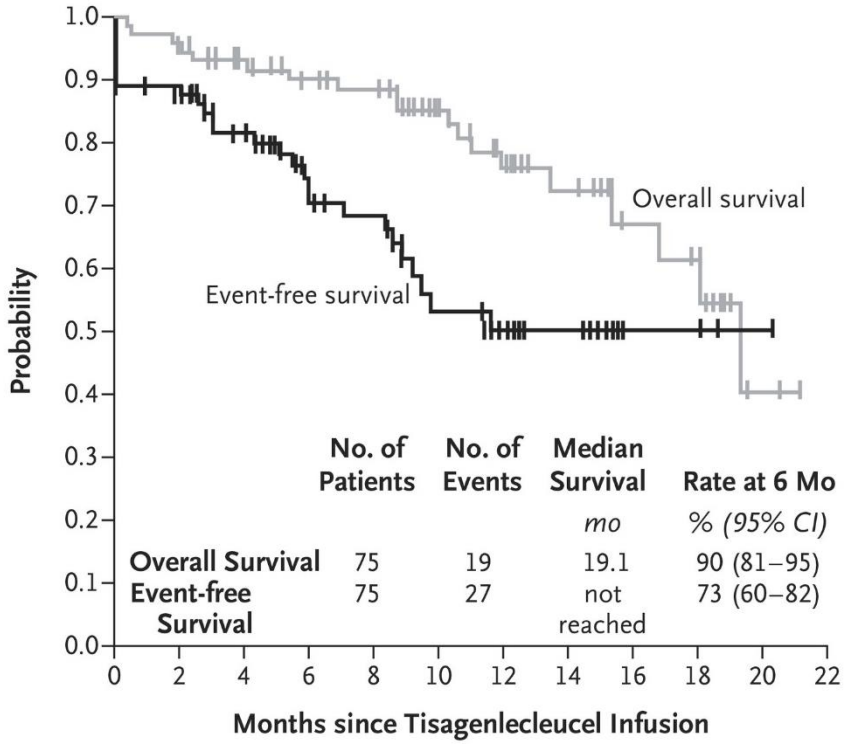


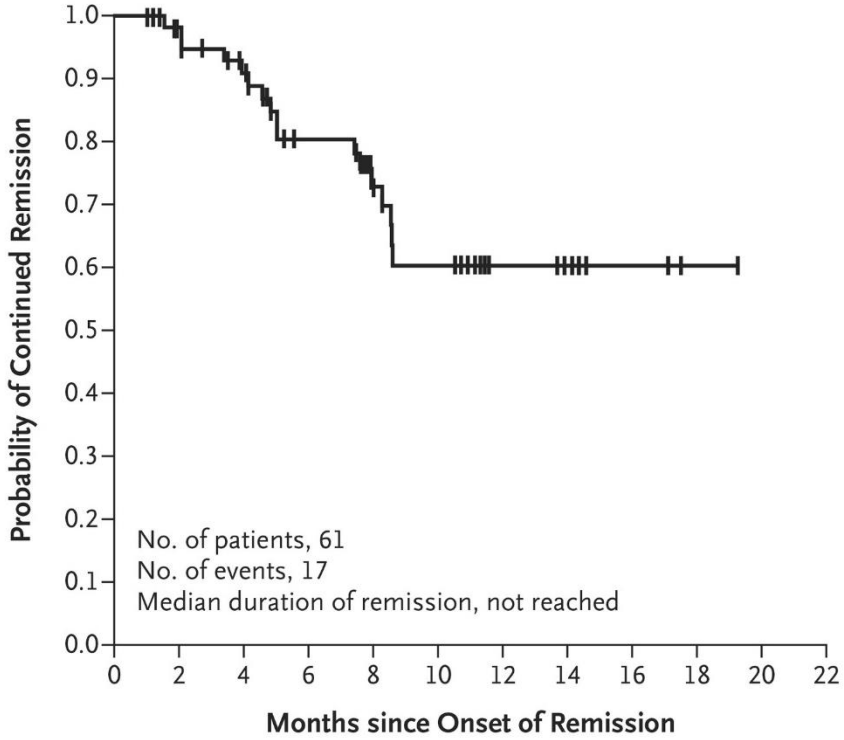
Schuster et al. NEJM 2017

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

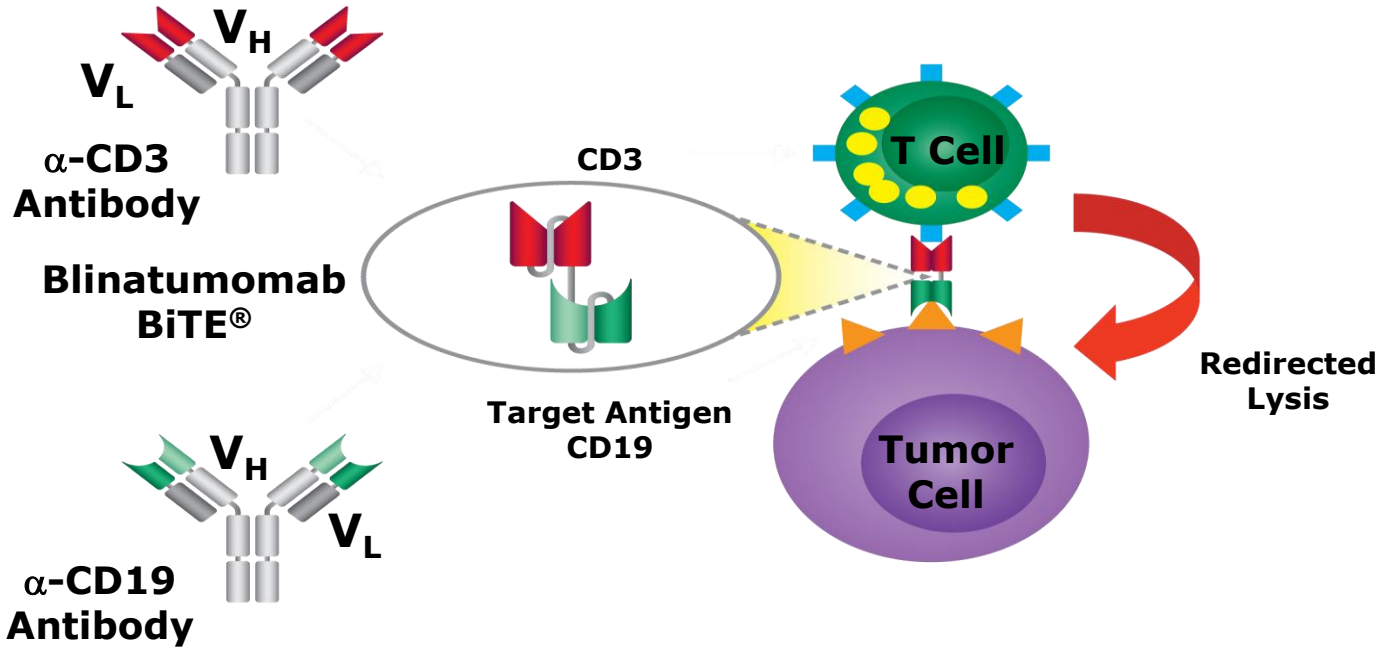




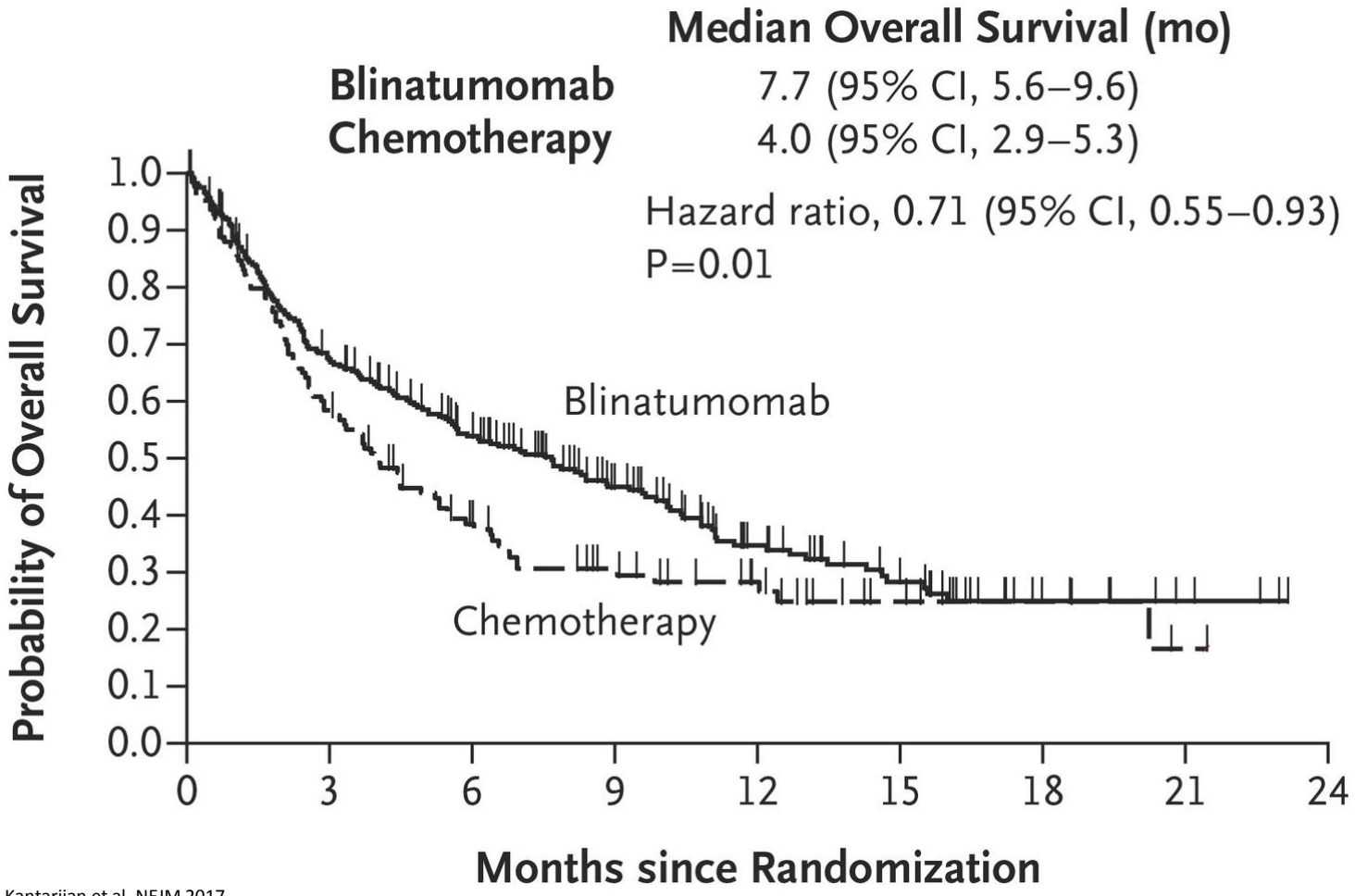
Maude et al. NEJM 2018

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



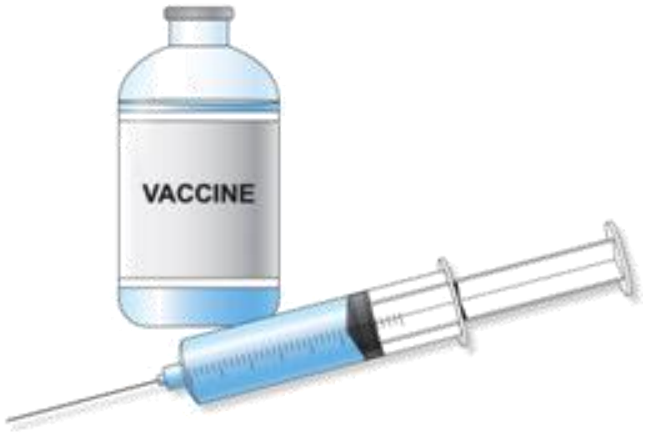
Blinatumomab for B-ALL



Kantarjian et al. NEJM 2017

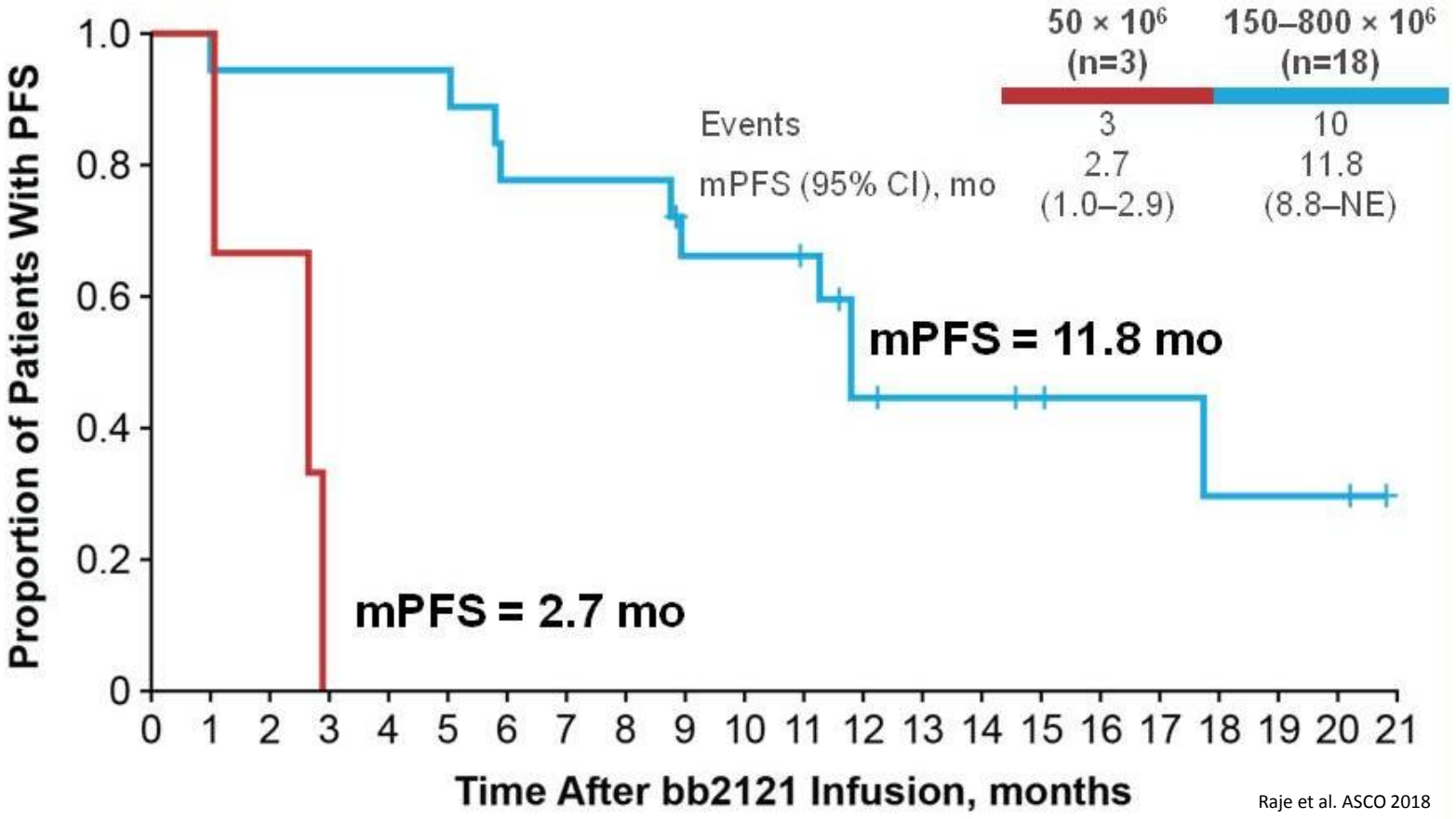
Immunotherapies for Multiple Myeloma

- 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



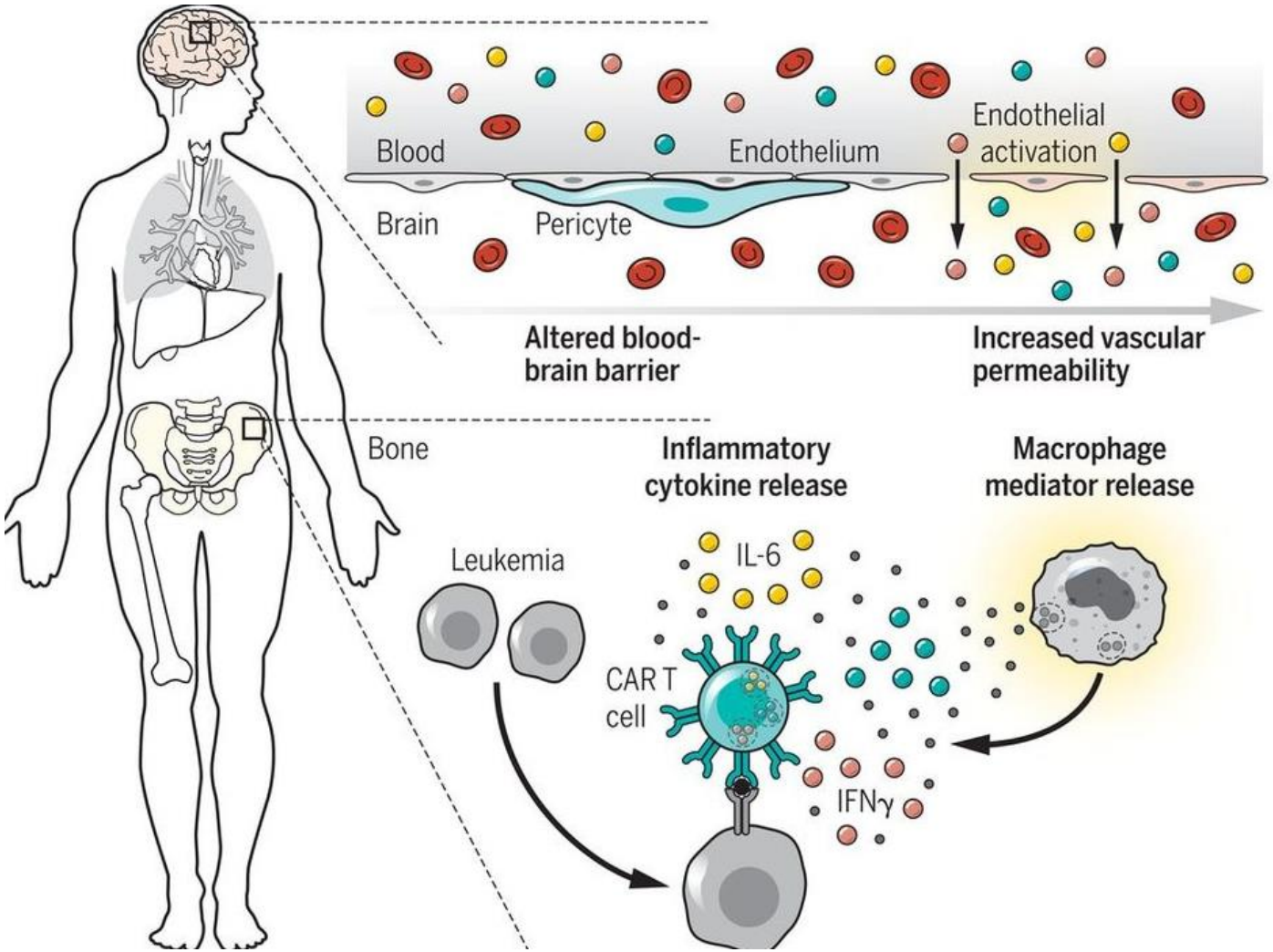
In Development: BCMA+ CAR T Therapy for Myeloma

- 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)



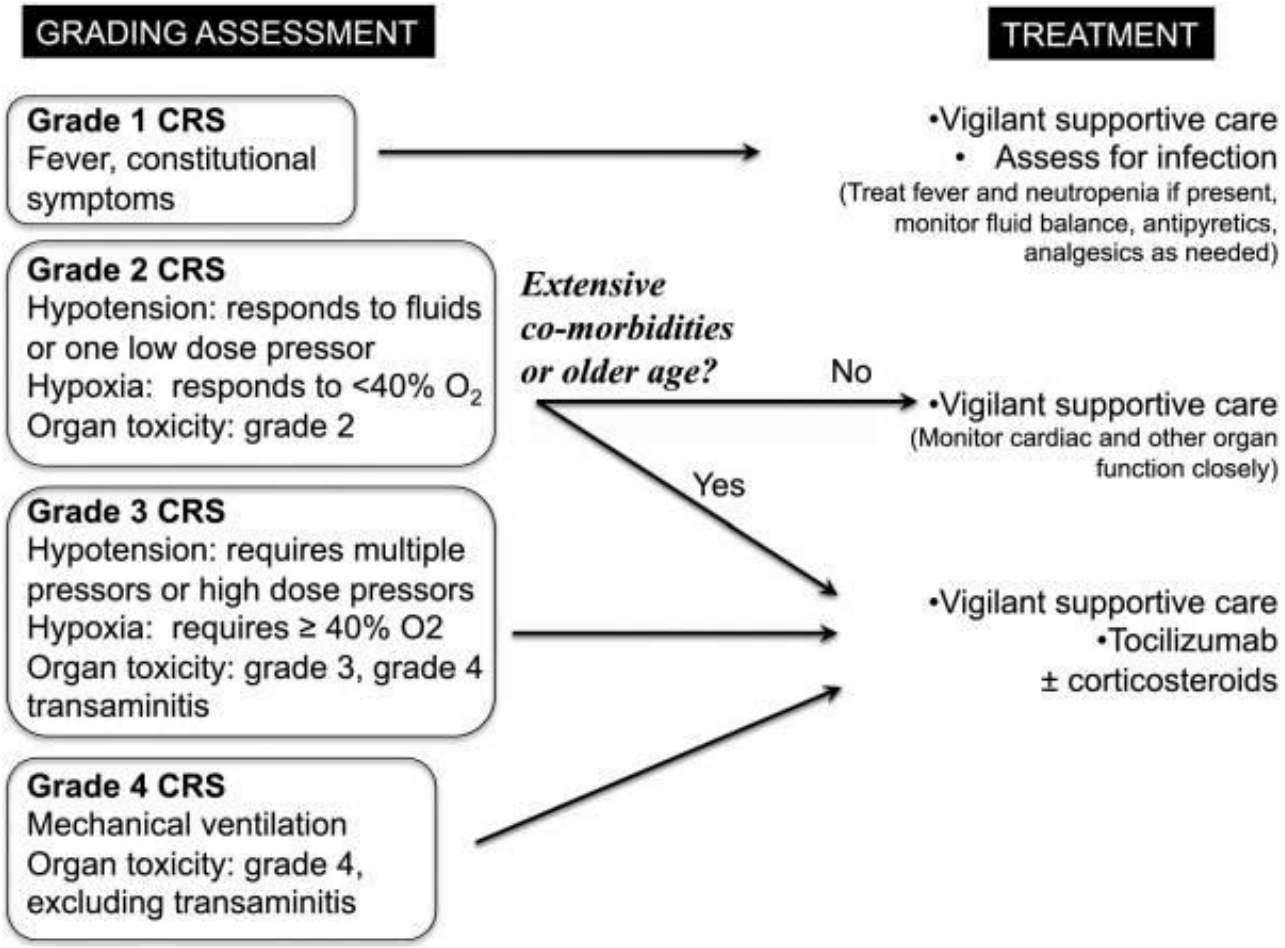
Neurotoxicity
Delirium
Aphasia
Seizures
Cerebral edema
Intracranial hemorrhage

Hemodynamic instability
Tachycardia
Hypotension
Capillary leak syndrome

Organ dysfunction
AST and ALT elevation
Hyperbilirubinemia
Respiratory failure

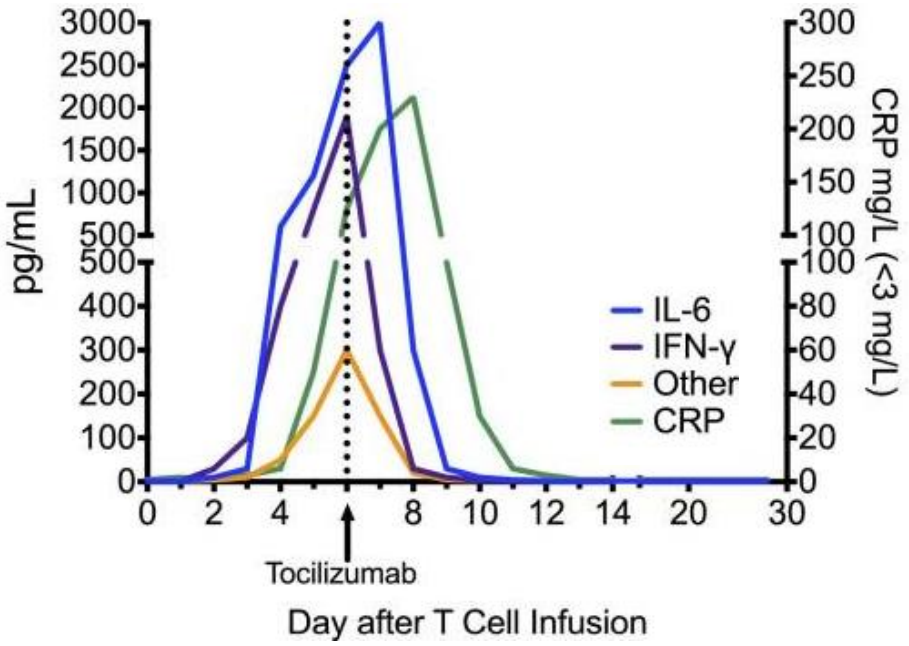
June et al. Science 2018

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 Studies

Case Study 1

- 72 year-old active, healthy female (ECOG 0) with no significant PMH diagnosed with bulky ABC subtype, p53 deleted *aggressive* DLBCL

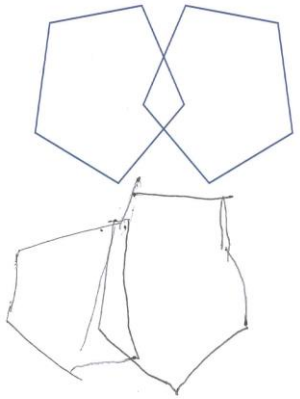
- <u>TREATMENT SUMMARY:</u>
  - 6 cycles DA-EPOCH-R (Feb - Jun 2016)→ Complete Response (CR)
  - Relapse 3 months later
  - 3 cycles Rituximab, Gemcitabine, and Cisplatin→ Progressive Disease (PD)
  - Enrolled on CAR T cell clinical trial

Timeline of CAR T Cell Therapy

T cell Apheresis

1 x 10^8 CAR T cell Infusion

Pre-Treatment



December

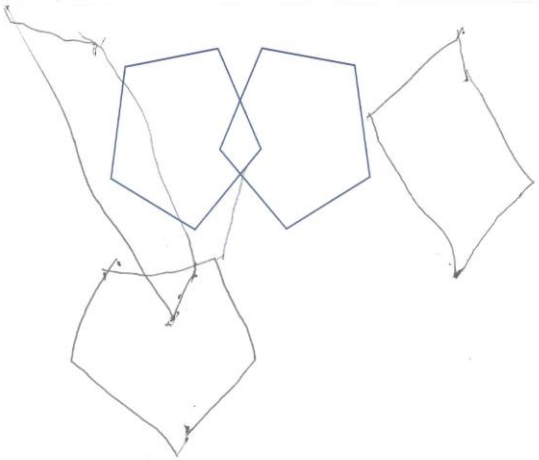
Day 0

March (3 days)

Fludarabine/ Cyclophosphamide lymphodepletion chemotherapy

Day 4

- Fatigue
- Gr 1 CRS
- CRP mildly elevated
- Changes in MMSE



Timeline of CAR T Cell Therapy

Day 6 → **Day 10**

- New headache with facial droop
- Grade 3 CRS (hypotension requiring 2 pressors and fever 101F)
- Ongoing difficulty with MMSE

- **Neurology Consult**
  - Non-contrast head CT normal
  - MRI brain
  - LP unrevealing
  - EEG: no seizure activity

- **Tocilizumab**
- **Steroids**
- **Anti-seizure**

Complete resolution of symptoms

Neurotoxicity

- 133 patients (ALL, NHL, CLL) treated with CD-19 CAR T cell with 4-1BB costimulatory domain
- 53 of 133 (40%) with neurotoxicity
- 48 of these 53 (91%) also had CRS
- The 5 without CRS had only grade 1 neurotoxicity
- All patients with grade 3 or higher neurotoxicity had an antecedent fever
- **Median 4.5 days (range 2-17 days) after CRS**
- Median time from onset of neurotoxicity to highest grade 1 day (range 0-19)
- Median duration of reversible neurotoxicity was 5 days (range 1-70 days)

Gust et al. Cancer Discovery. 2017

Neurotoxicity CTCAE grade		Grade 0[a]	Grade 1–2[a]	Grade 3–5[a]	Total	Univariate[b]	Multivariable[c]
Overall, *n* (%)		80 (60)	25 (19)	28 (21)	133 (100)		
Age, *n* (%)	<40 years	11 (41)	10 (37)	6 (22)	27	0.094	
	40–60 years	42 (66)	8 (13)	14 (22)	64		
	>60 years	27 (64)	7 (17)	8 (19)	42		
Sex, *n* (%)	Male	59 (63)	17 (18)	17 (18)	93	0.4	
	Female	21 (53)	8 (20)	11 (28)	40		
Diagnosis, *n* (%)	ALL	22 (47)	11 (23)	14 (30)	47	0.084	
	CLL	16 (67)	2 (8)	6 (25)	24		
	NHL	42 (68)	12 (19)	8 (13)	62		
Race, *n* (%)	White	62 (56)	22 (20)	26 (24)	110	0.17[d]	
	Not white	18 (78)	3 (13)	2 (9)	23		
Prior therapies	Median (range)	4 (1–11)	4 (1–10)	4 (1–11)	4 (1–11)	0.5	
Transplant history, *n* (%)	Auto	17 (68)	5 (20)	3 (12)	25	0.5	
	Allo	14 (50)	8 (29)	6 (21)	28		
Karnofsky score[e], *n* (%)	60–70	7 (50)	3 (21)	4 (29)	14	0.5	
	80–90	65 (61)	18 (17)	23 (22)	106		
	100	8 (62)	4 (31)	1 (8)	13		
Preexisting neurologic comorbidities, *n* (%)	Any	26 (45)	16 (28)	16 (28)	58	0.0059[g]	0.0023[g]
	PN[f]	14 (47)	7 (23)	9 (30)	30	0.2	
	CNS involvement	6 (43)	5 (36)	3 (21)	14	0.2	
	Headache disorder	6 (43)	5 (36)	3 (21)	14	0.2	
	Other	5 (50)	2 (20)	3 (30)	10	0.7	
	ICH[h]	4 (67)	1 (17)	1 (17)	6	1	
	Seizures	2 (33)	2 (33)	2 (33)	6	0.3	
	Cog impairment[i]	1 (25)	2 (50)	1 (25)	4	0.1	
	MTX CNS toxicity[j]	1 (50)	1 (50)	0	2	0.4	
Marrow disease, %	Median (range)	0.6 (0–97)	0.4 (0–93)	25.8 (0–97)	1.3 (0–97)	0.072	0.0165
Total CD19$^+$ cells in marrow, %	Median (range)	5.3 (0–99)	12.4 (0–93)	29.1 (0–97)	8.8 (0–99)	0.062	
CD8$^+$ central memory enriched CAR-T cells[k], *n* (%)	Selected	48 (67)	11 (15)	13 (18)	72 (54)	0.242	
Lymphodepletion regimen[l], *n* (%)	Cy/Flu	58 (56)	23 (22)	23 (22)	104	0.11	0.0259
	Non-Cy/Flu	22 (76)	2 (7)	5 (17)	29		
CAR-T cell dose, *n* (%)	2×10^5 cells/kg	20 (57)	10 (29)	5 (14)	35	<0.0001	0.0009
	2×10^6 cells/kg	55 (64)	15 (17)	16 (19)	86		
	2×10^7 cells/kg	5 (42)	0	7 (58)	12		
Cytokine release syndrome, *n* (%)	None (G 0)	35 (88)	5 (13)	0	40	<0.0001	n/a
	Mild (G 1–2)	44 (57)	19 (25)	14 (18)	77		
	Severe (G 3–5)	1 (6)	1 (6)	14 (88)	16		

Neelapu et al. Nature Review. 2016

Case Study 2

- 30 year-old male with no PMH diagnosed with Stage IV Hodgkin lymphoma

- *TREATMENT HISTORY:*
  - 6 cycles of ABVD → CR
  - Relapsed → ASCT
  - Relapsed → Anti-PD-1 blockade

Patient Develops New Symptoms

- Headache
- Fatigue
- Dizziness with standing

What is the differential?

A. ?

B. ?

C. ?

D. ?

What is the differential?

A. Progressive disease with CNS involvement
B. Hypophysitis
C. Adrenal insufficiency alone
D. Dehydration

What are you next steps?

What are you next steps?

- Vitals: Orthostatic hypotension
- Physical exam: Pale
  - ADMIT PATIENT

Work-Up Shows…

- Low TSH
- Low ACTH
- Low LH

- Brain MRI: a swollen pituitary gland is seen

- Now what should you do?

Management

- STOP immunotherapy
- Endocrine consult:
  - High-dose glucocorticoids, levothyroxine, and sex hormone replacement
- Almost all patients experienced resolution of acute symptoms within a few days

I can rechallenge patient with anti-PD-1 therapy

- True
- False

I can rechallenge patient with anti-PD-1 therapy

- True
- False