Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Hematologic Malignancies

Mehrdad Abedi MD

Professor of Medicine, UC Davis Medical Center

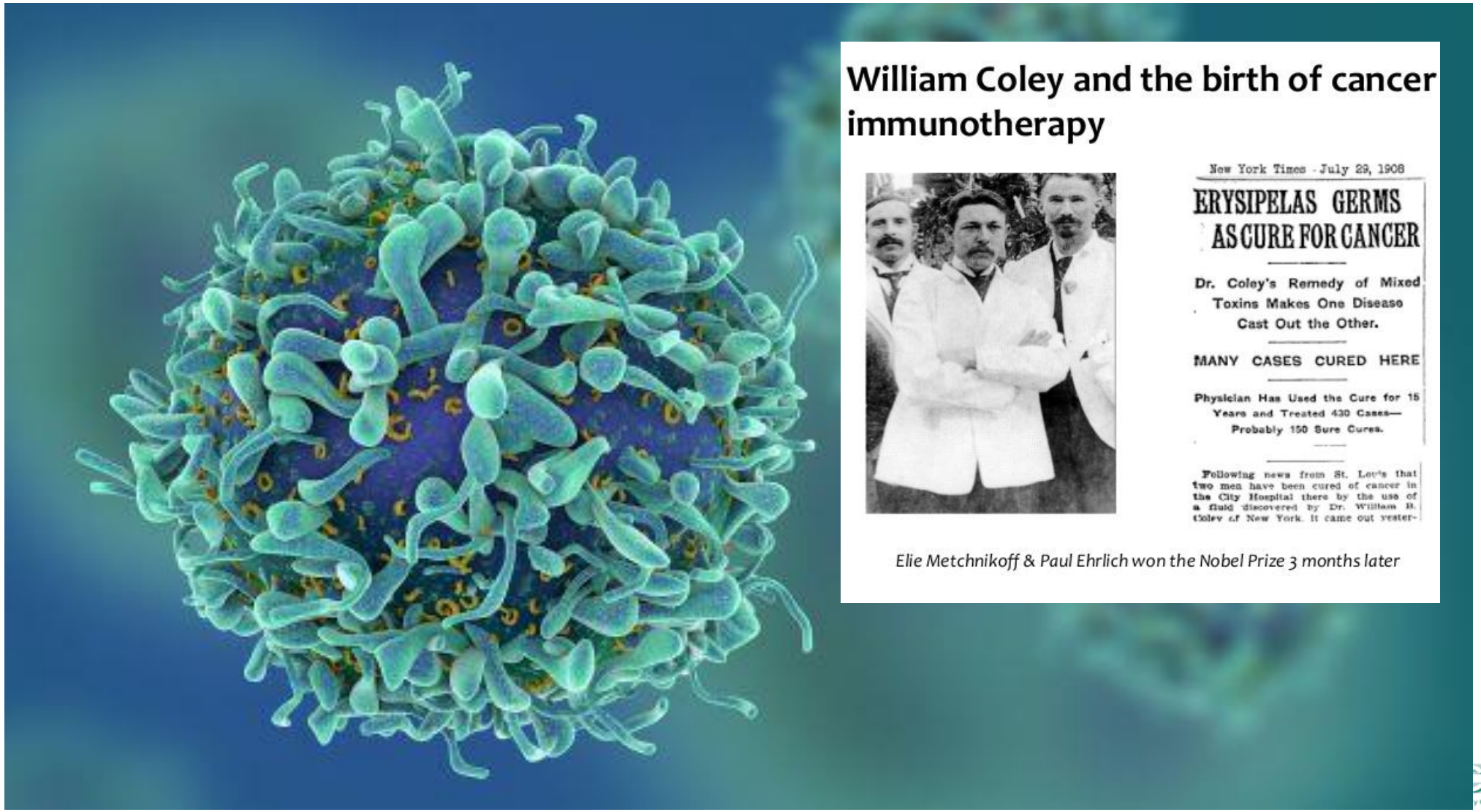
AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE
CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

Society for Immunotherapy of Cancer

Disclosures

- Speaker Panel: Celgene, Takeda, Gilead, BMS
- I will not be discussing non-FDA approved indications during my presentation.



William Coley and the birth of cancer immunotherapy

New York Times - July 29, 1908

ERYSIPELAS GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

Physician Has Used the Cure for 15 Years and Treated 430 Cases—Probably 150 Sure Cures.

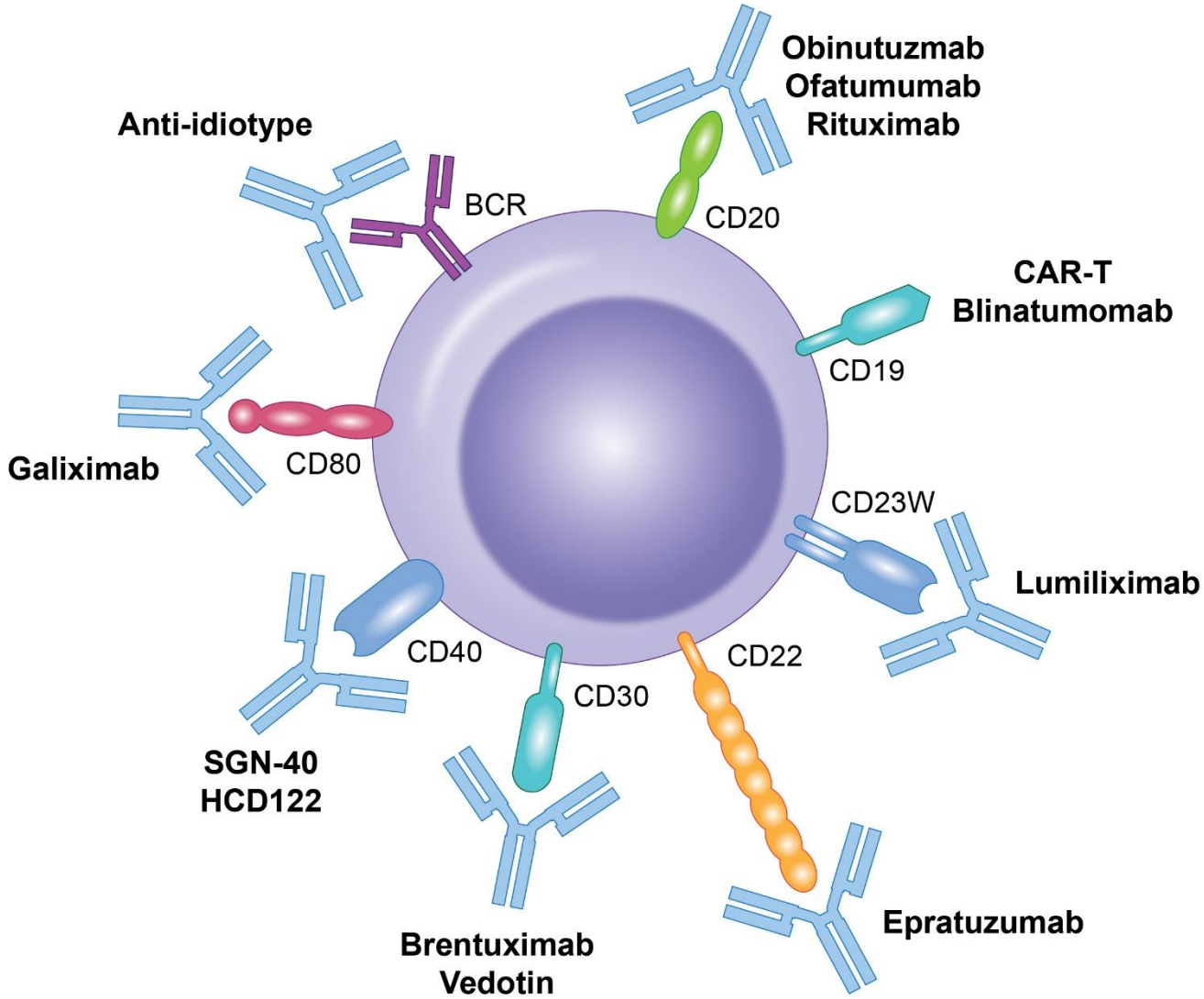
Following news from St. Louis that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York, it came out yester-

Elie Metchnikoff & Paul Ehrlich won the Nobel Prize 3 months later

Different Immunotherapy Approaches for Heme malignancies

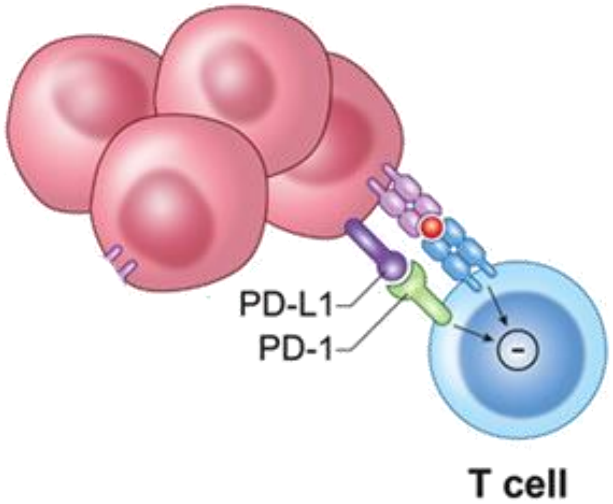
- Direct monoclonal antibodies against tumors (naked or armed with chemo or radioisotopes)
- Cytokine Therapies: GM-CSF, IL2, Il12, TNF-alpha, Interferon gamma …
- Costimulatory signal inhibitors
- Vaccine therapies
- Cellular therapy approaches: CAR T cells, TCRs, etc.

Monoclonal Antibodies Targeting B Cell Lymphomas



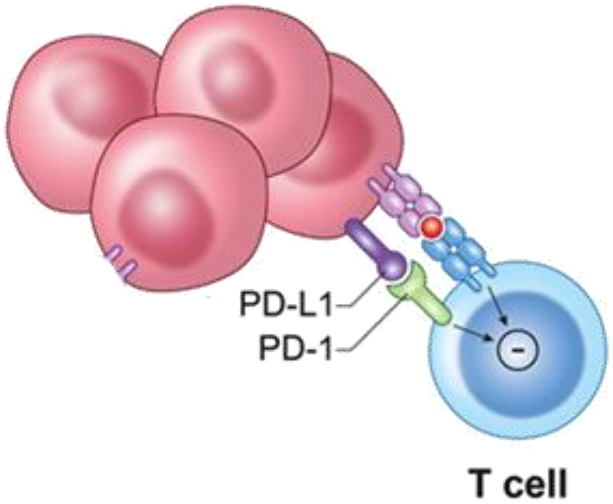
FDA-approved Checkpoint Inhibitors for Lymphomas

- 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



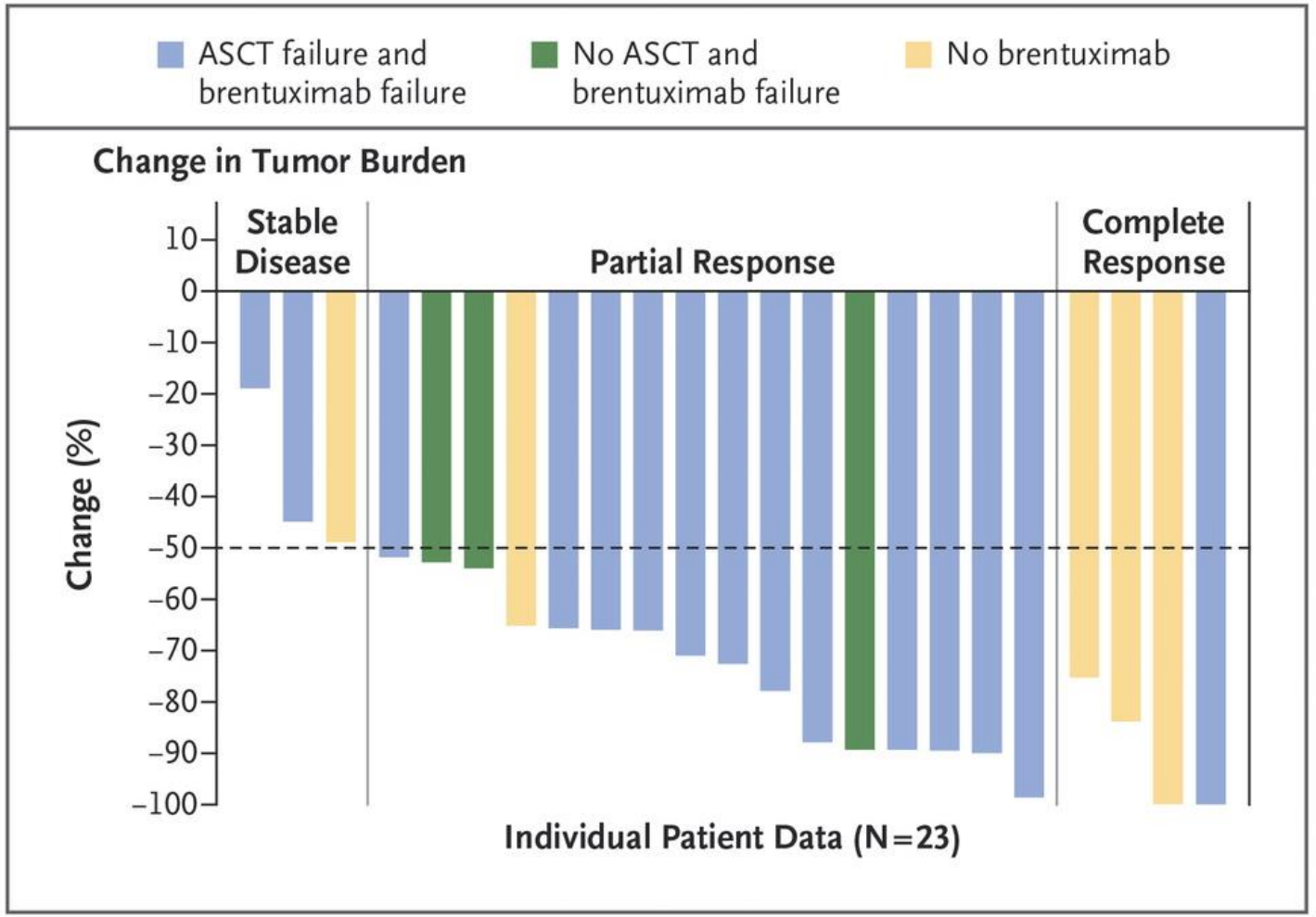
Nivolumab in Hodgkin Lymphoma

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

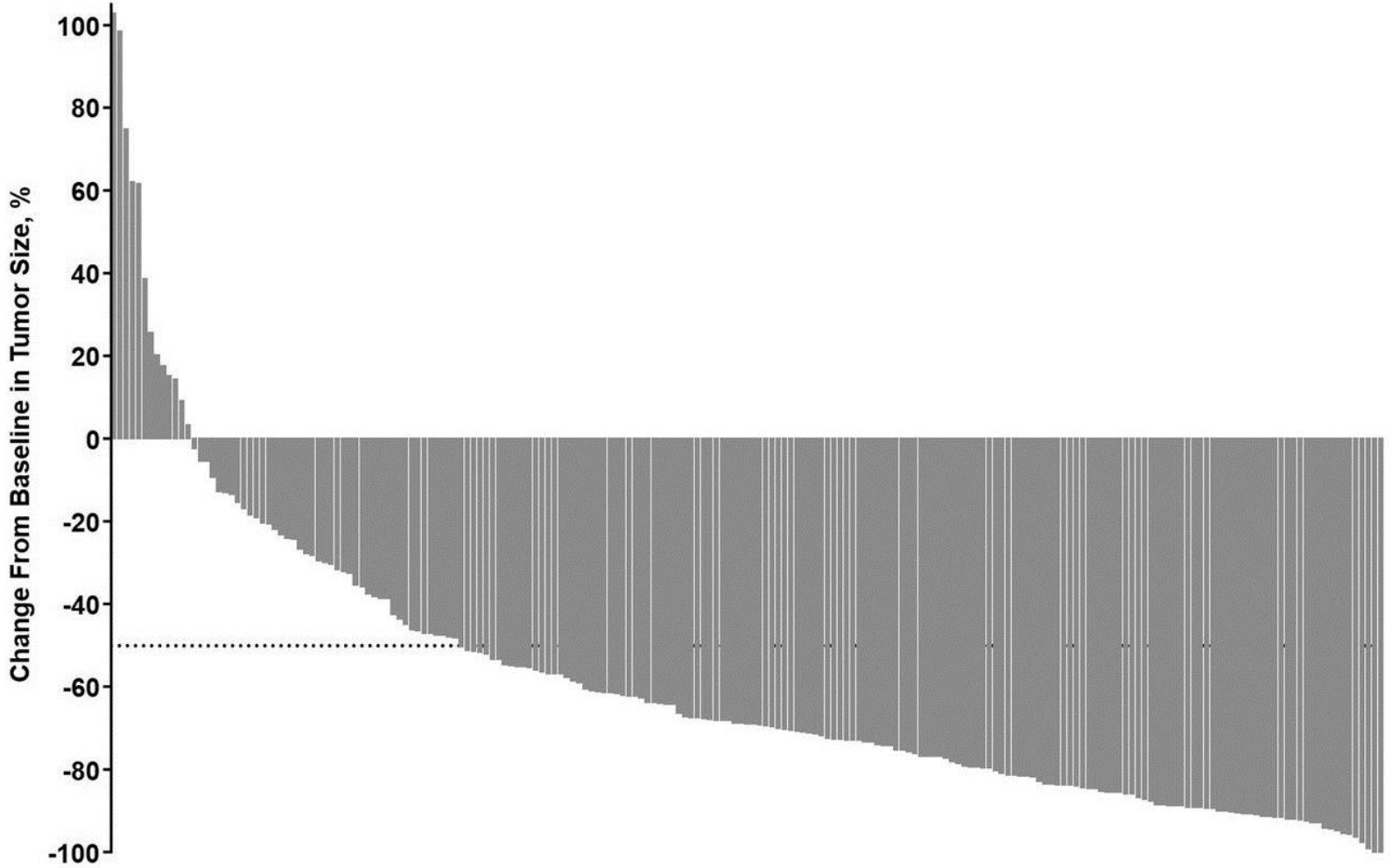
Ansell et al. NEJM 2015

Nivolumab in Hodgkin Lymphoma



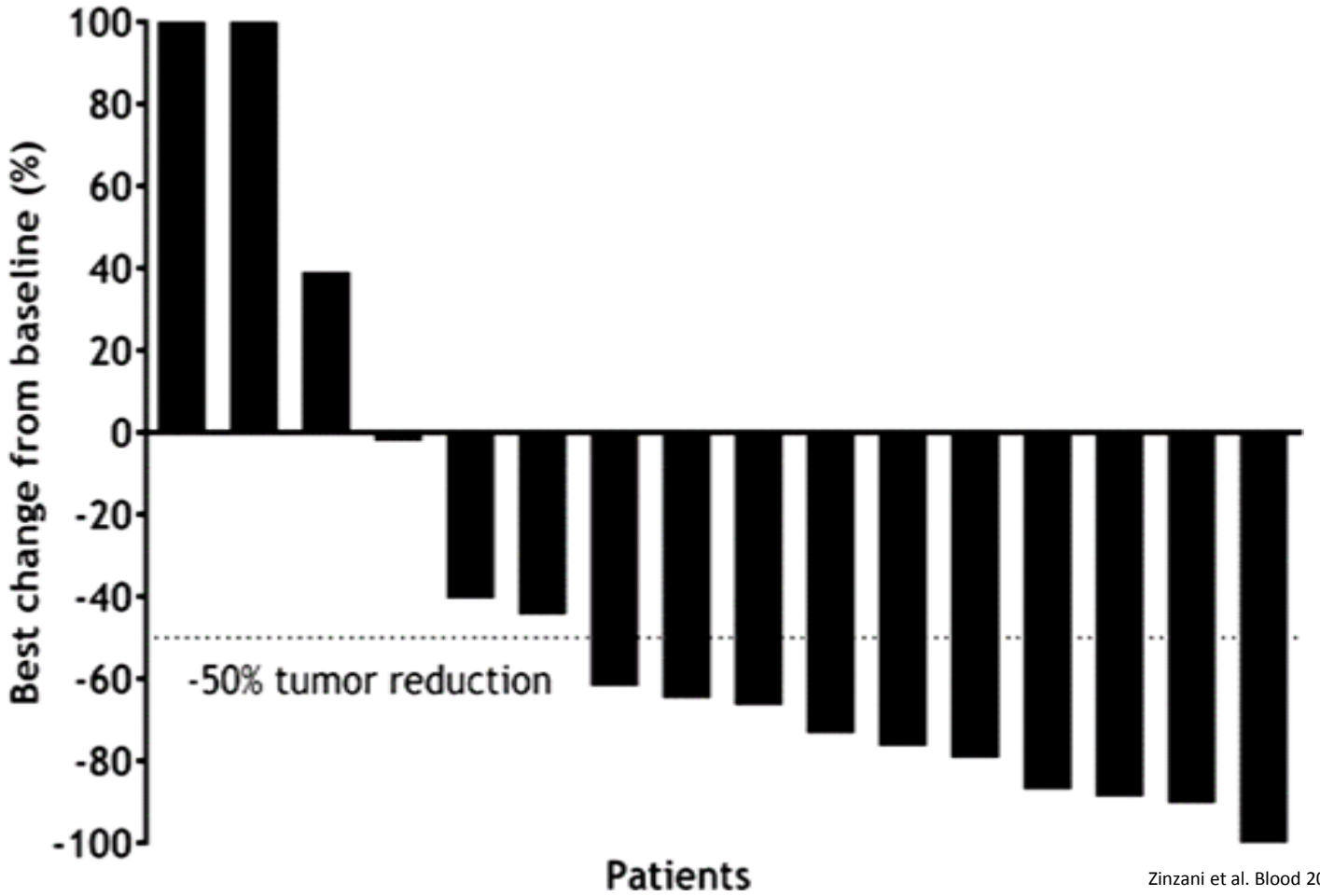
Ansell et al. NEJM 2015

Pembrolizumab in Hodgkin Lymphoma



Zinzani et al. Hematological Oncology 2017

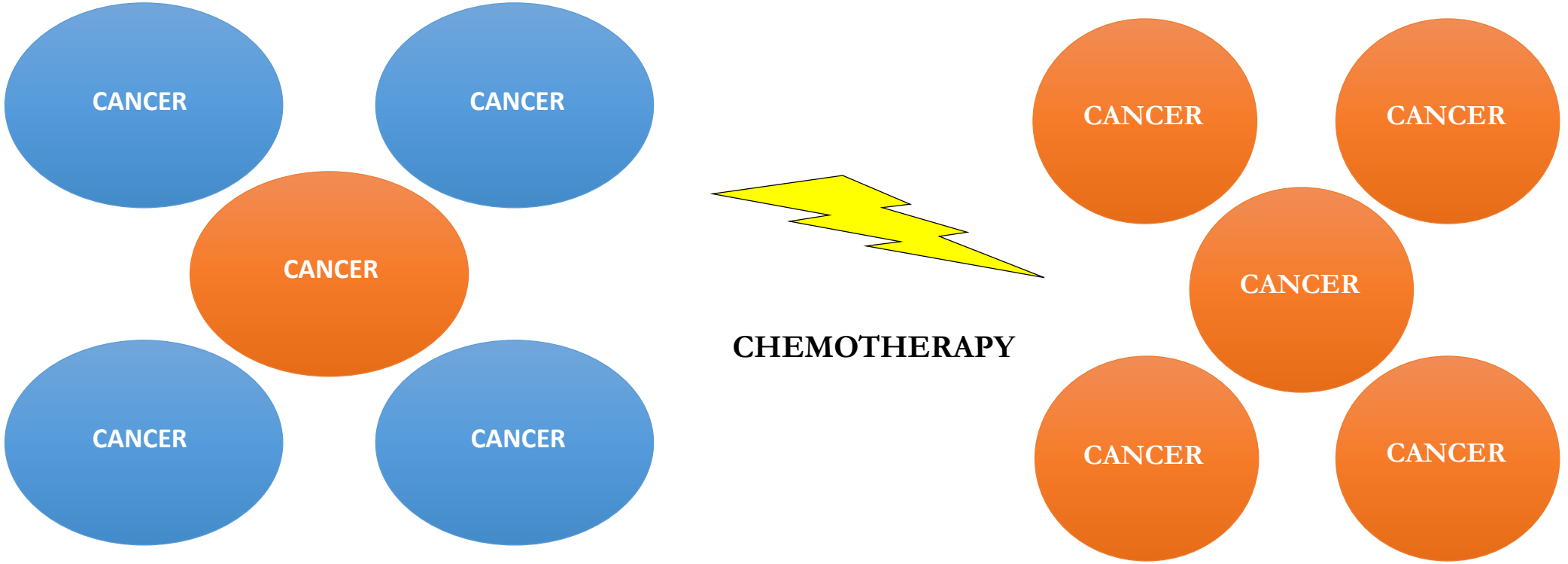
Pembrolizumab in Primary Mediastinal Large B cell Lymphoma



Zinzani et al. Blood 2016

Cellular Therapy for Heme Malignancies

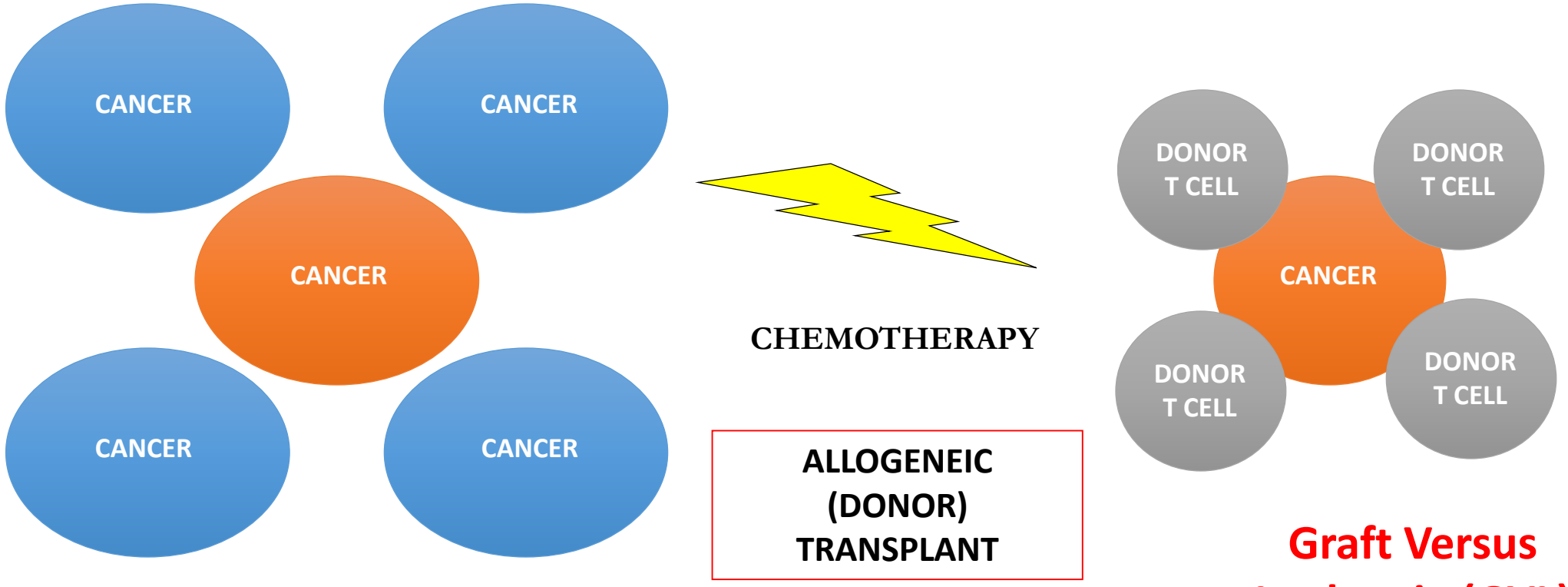
Why does leukemia relapse happen?



CHEMOTHERAPY SENSITIVE

CHEMOTHERAPY RESISTANT

Principles of Bone Marrow Transplant



ALLOGENEIC (DONOR) TRANSPLANT

Graft Versus Leukemia (GVL)

CHEMOTHERAPY SENSITIVE

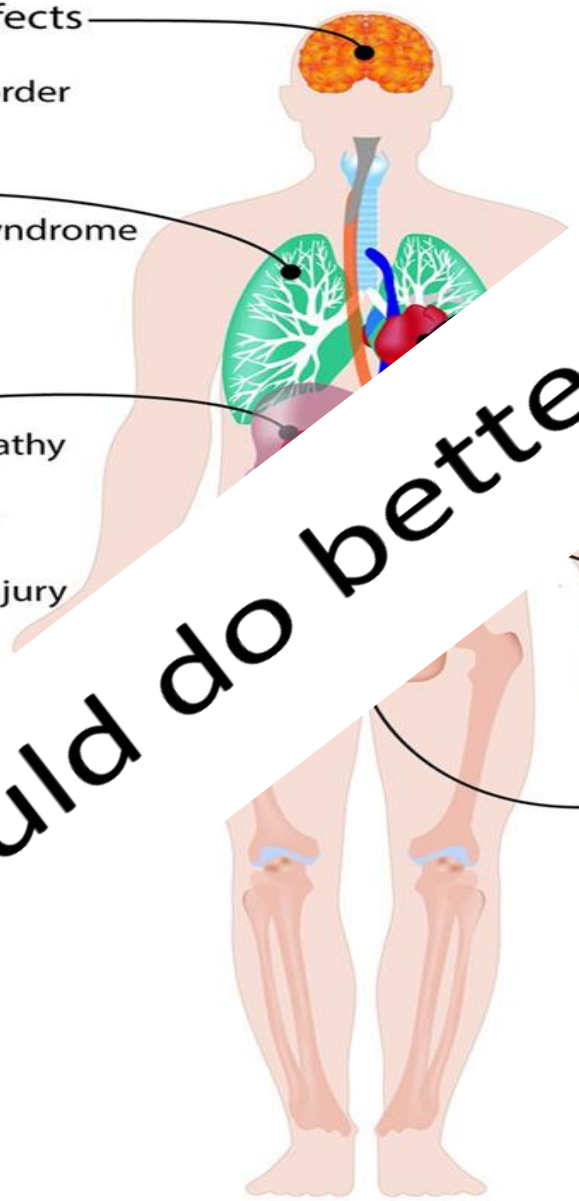
CHEMOTHERAPY RESISTANT

Donor Lymphocyte Infusion (DLI)

DLI is one of the earliest form of T cell therapy and proof of principal for GVL effect

DIAGNOSIS		INCIDENCES OF COMPLETE RESPONSES AFTER DLI
Chronic myeloid leukaemia:	Overall	60%[9]
	Chronic phase	76%
	Accelerated phase	33%
	Blastic phase	17%
Acute myeloid leukaemia/myelodysplastic syndrome		15-26%[9,18]
Acute lymphoblastic leukaemia		3-15%[9,18]
Chronic lymphocytic leukaemia		29%[60]
Multiple myeloma		5-29%[18,67]

Late effects of blood and marrow transplantation



Neuropsychological effects
- Depression, anxiety
- Post-traumatic stress disorder
- Neurocognitive deficits

Pulmonary diseases
- Bronchiolitis obliterans syndrome
- Cryptogenic organizing pneumonia
- Pulmonary hypertension

Kidney diseases
- Thrombotic microangiopathy
- Nephrotic syndrome
- Idiopathic chronic kidney disease
- Persistent acute kidney injury
- BK virus nephropathy

Iron overload

Bone diseases
- Osteopenia
- Osteoporosi
- Avascular

End
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estive heart failure
var dysfunction
Arrhythmia
- Pericarditis
- Coronary artery disease

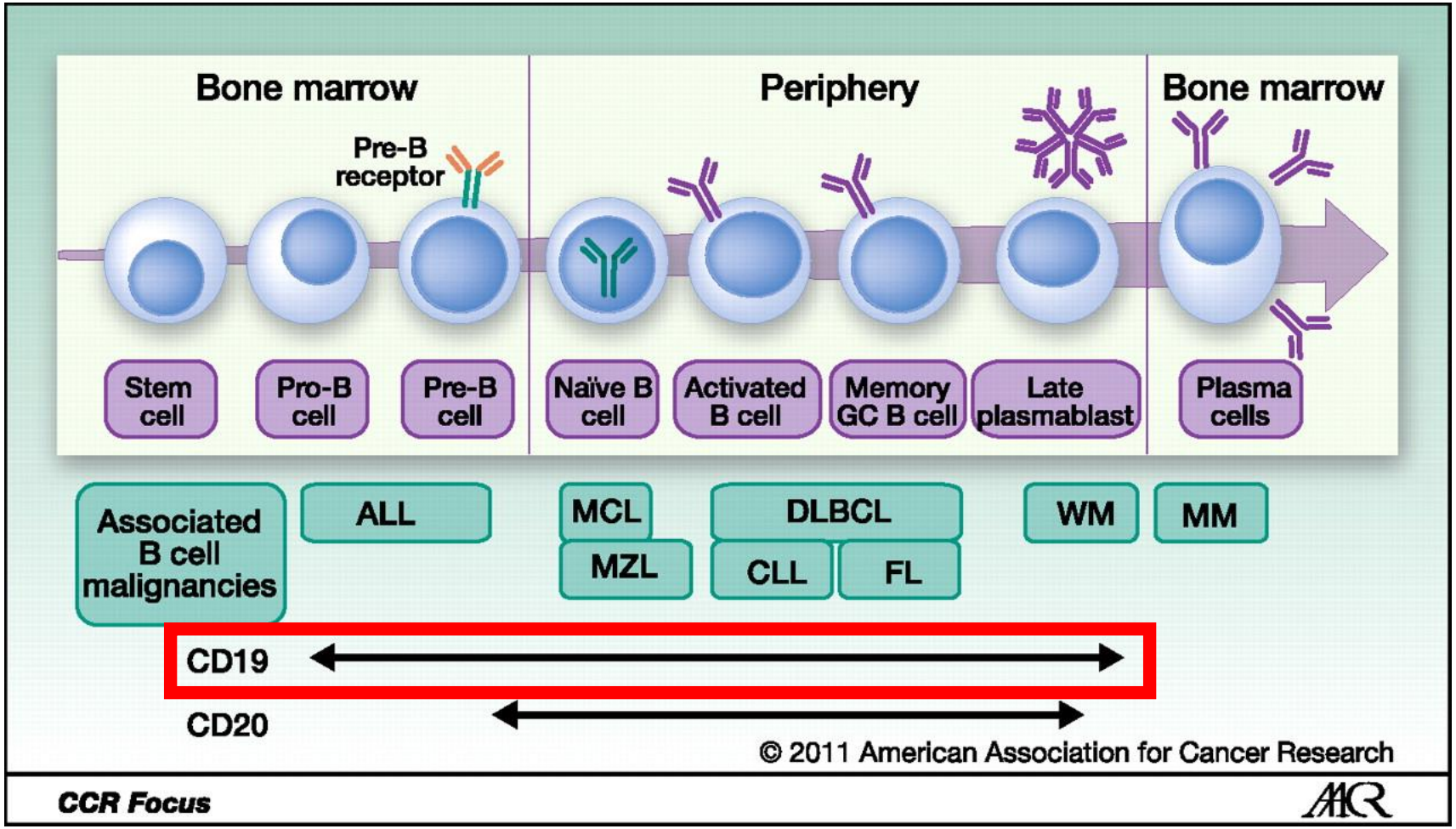
Liver diseases
- Hepatitis B, Hepatitis C, liver cirrhosis
- Nodular regenerative/focal nodular hyperplasia

Gonadal dysfunction/infertility

Infectious diseases
- *Pneumocystis jirovecci*
- Encapsulated bacteria
- Fungi
- Varicella-zoster virus
- Cytomegalovirus
- Respiratory syncytial virus
- Influenza virus
- Parainfluenza virus

We should do better than this!

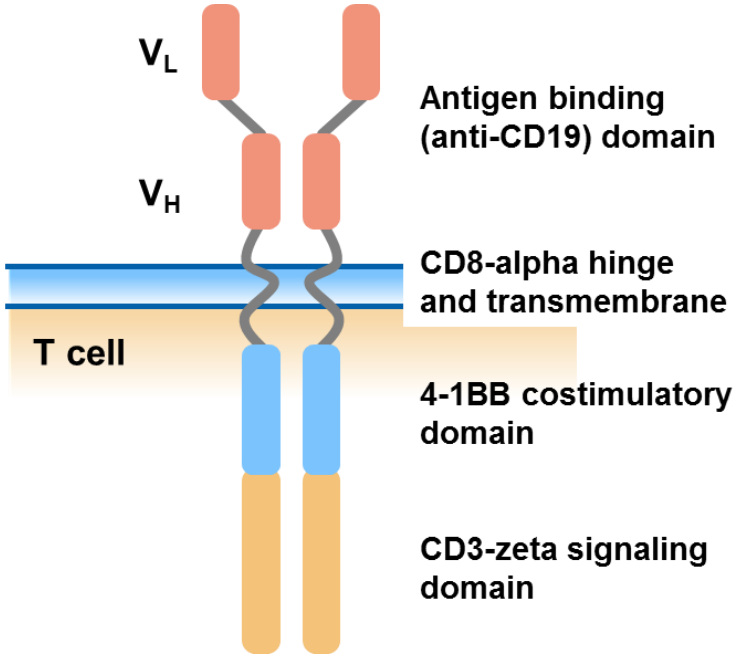
B Cell Malignancies are CD19+

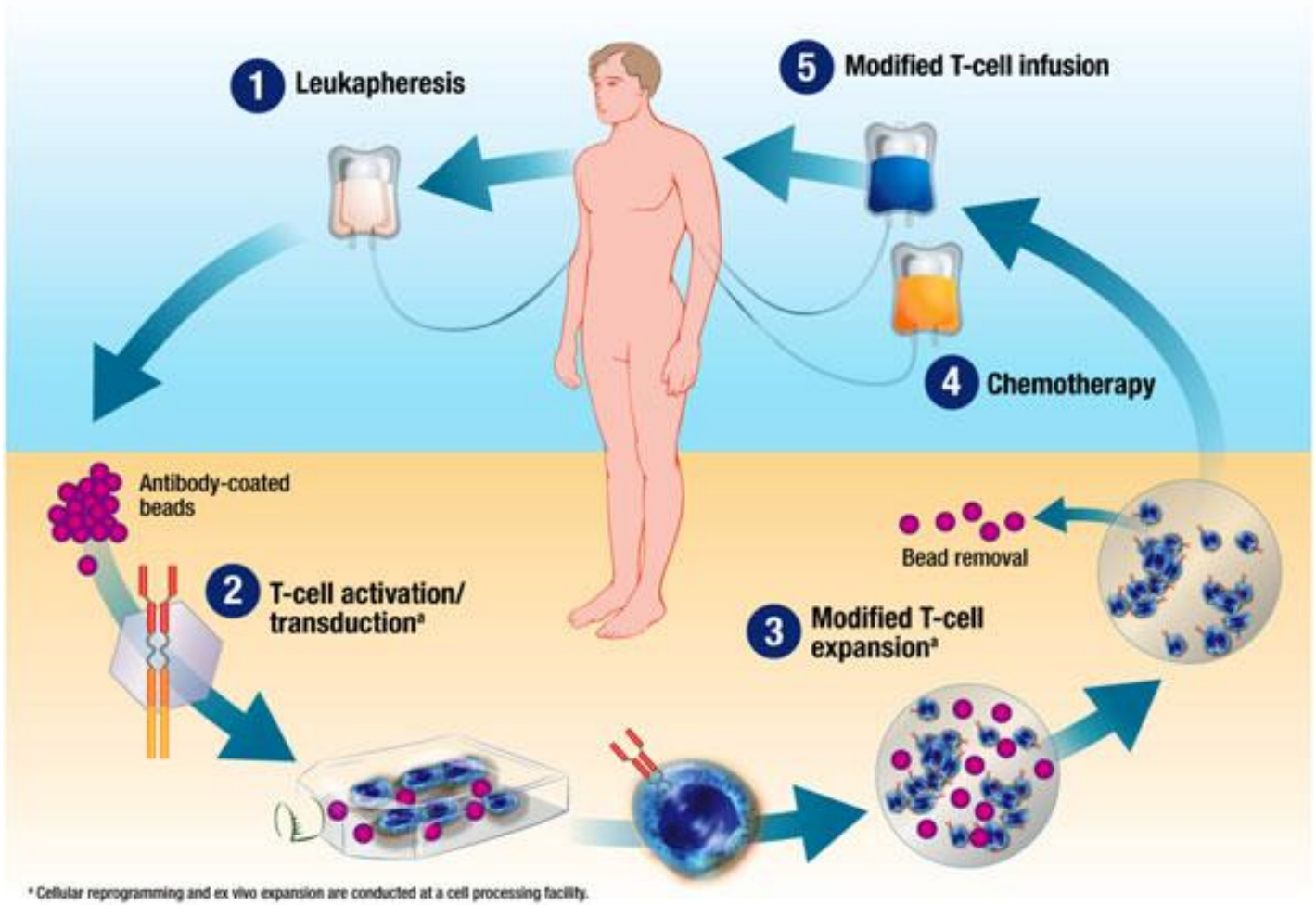


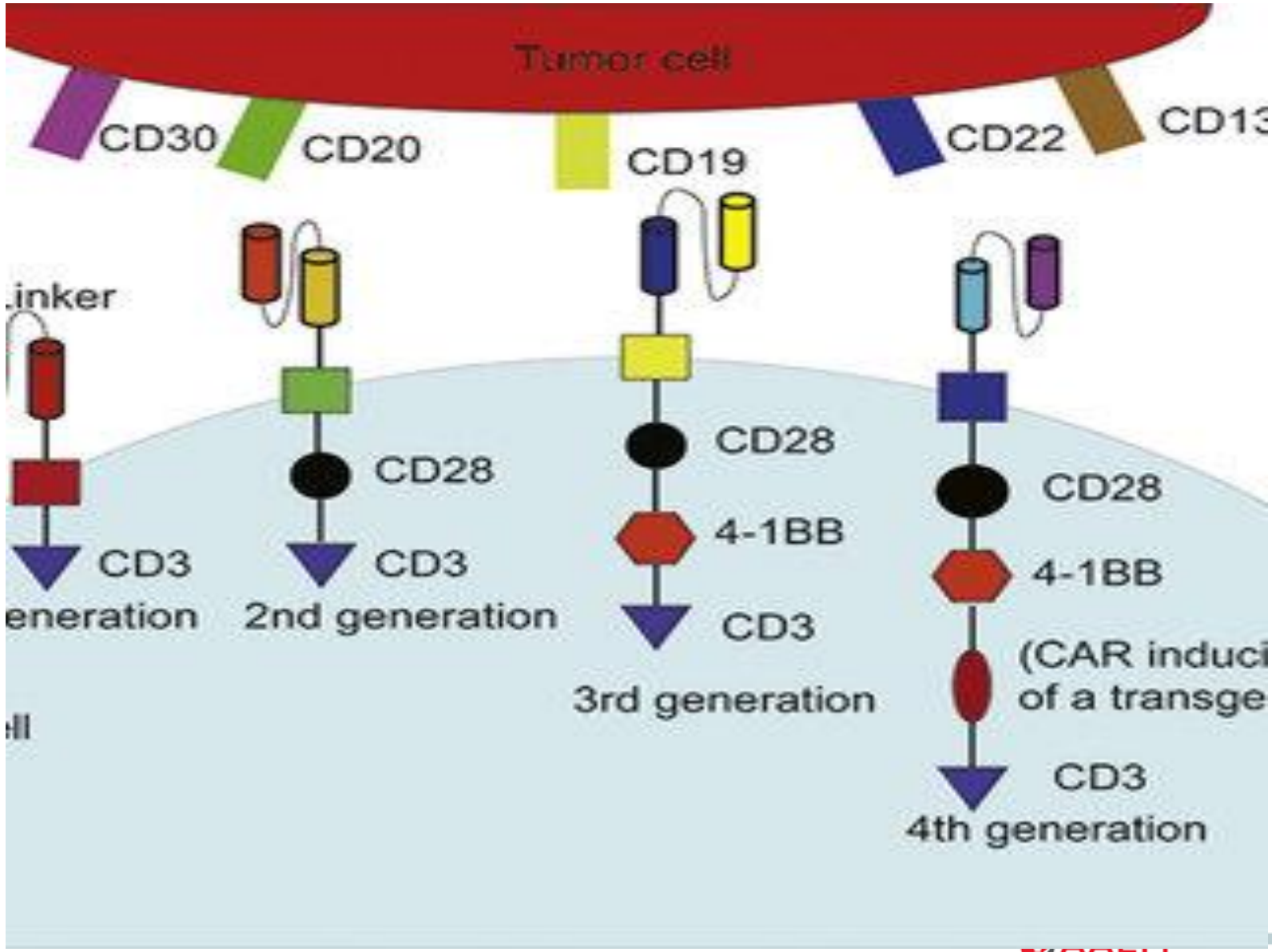
Blanc et al. Clinical Cancer Research 2011

Chimeric Antigen Receptor (CAR) T cell Therapy

- Engineering patient T cells to target and eliminate cells presenting specific antigens

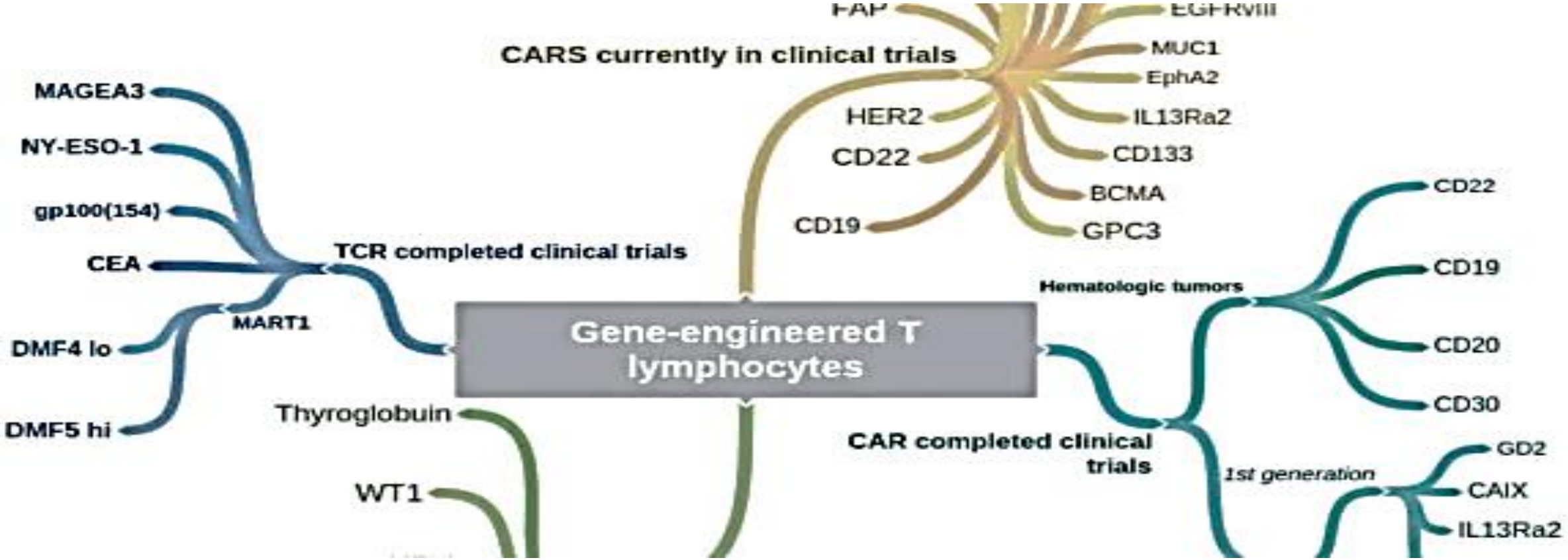






FDA-approved CAR T Cell Therapies for Lymphoma

- Axicabtagene ciloleucel
  - 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
  - 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.

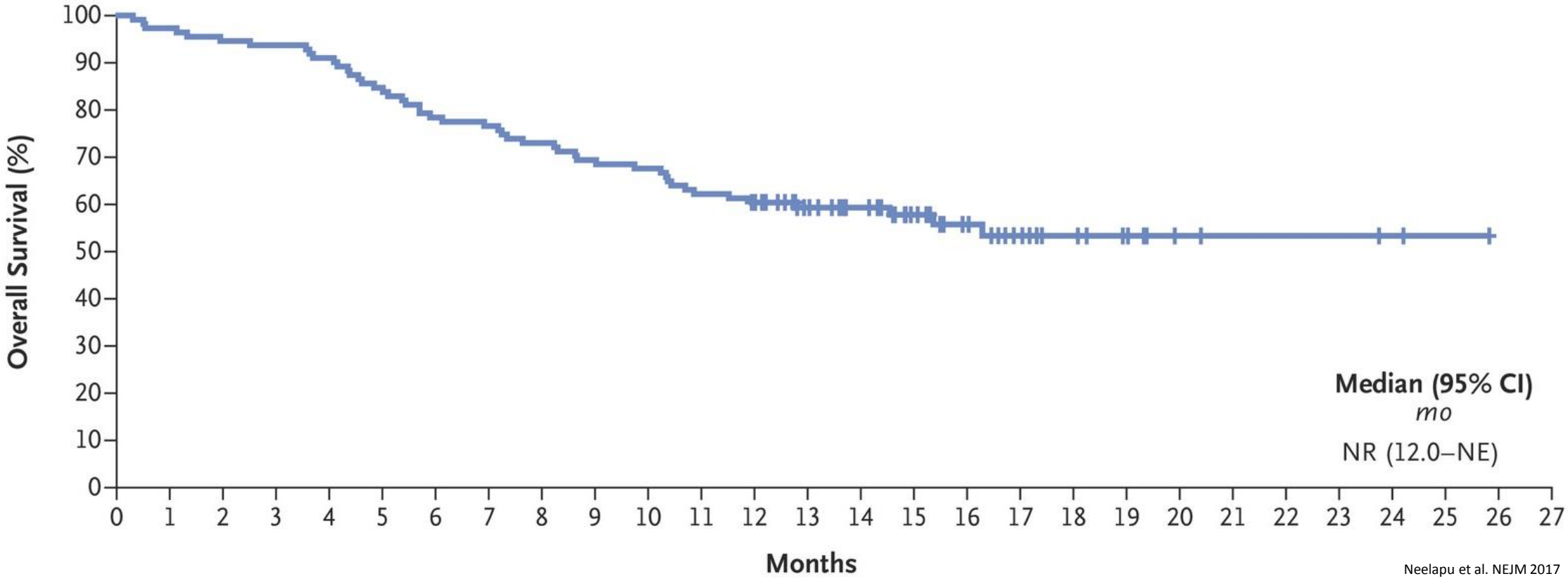


Patient Selection Criteria for CAR T Therapies

- 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

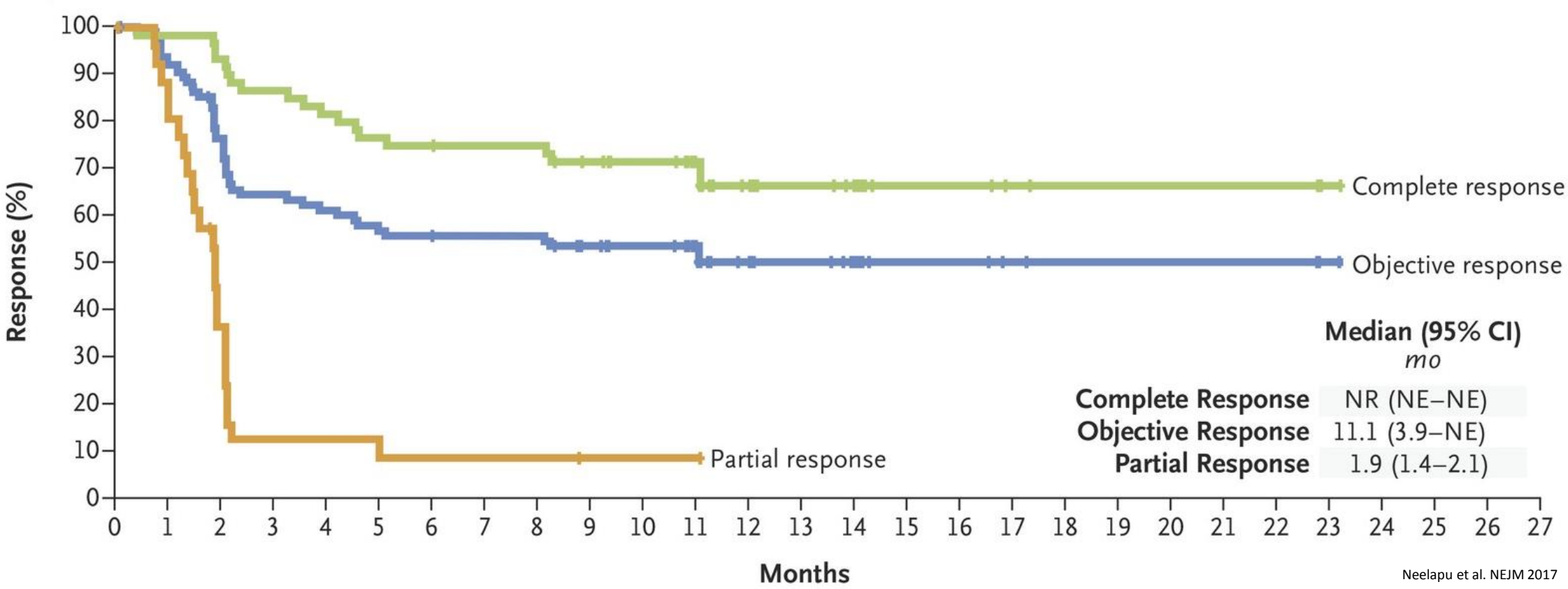
Overall Survival



Neelapu et al. NEJM 2017

Axicabtagene ciloleucel in B Cell Lymphoma

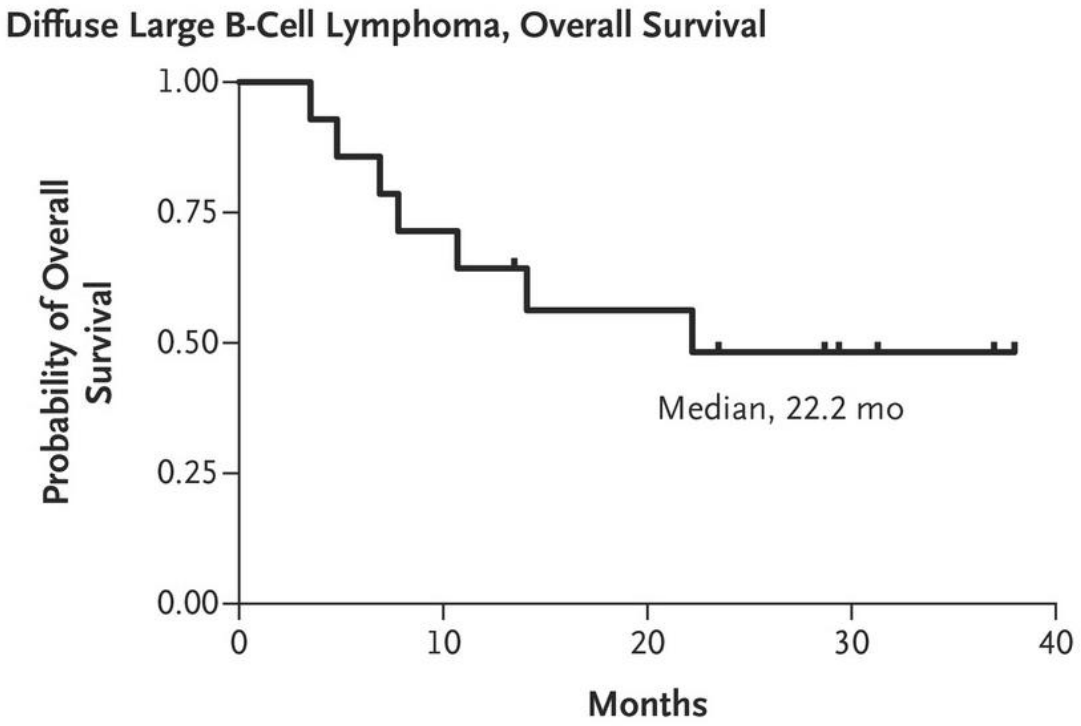
Duration of Response

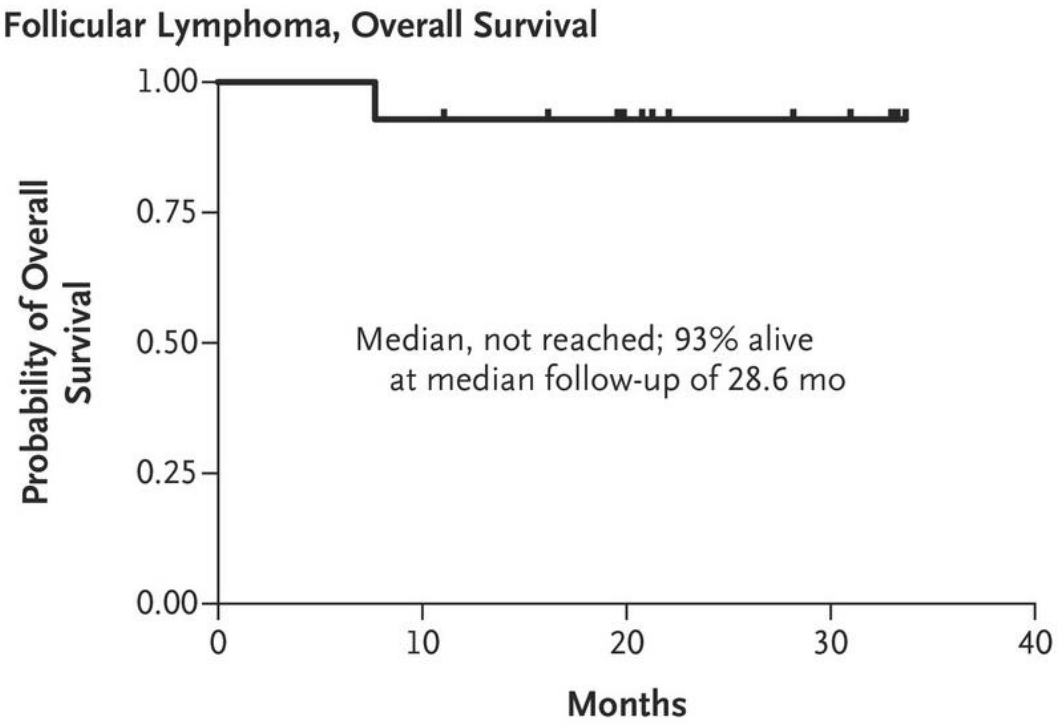


Neelapu et al. NEJM 2017

Tisagenlecleucel in B Cell Lymphoma

Overall Survival



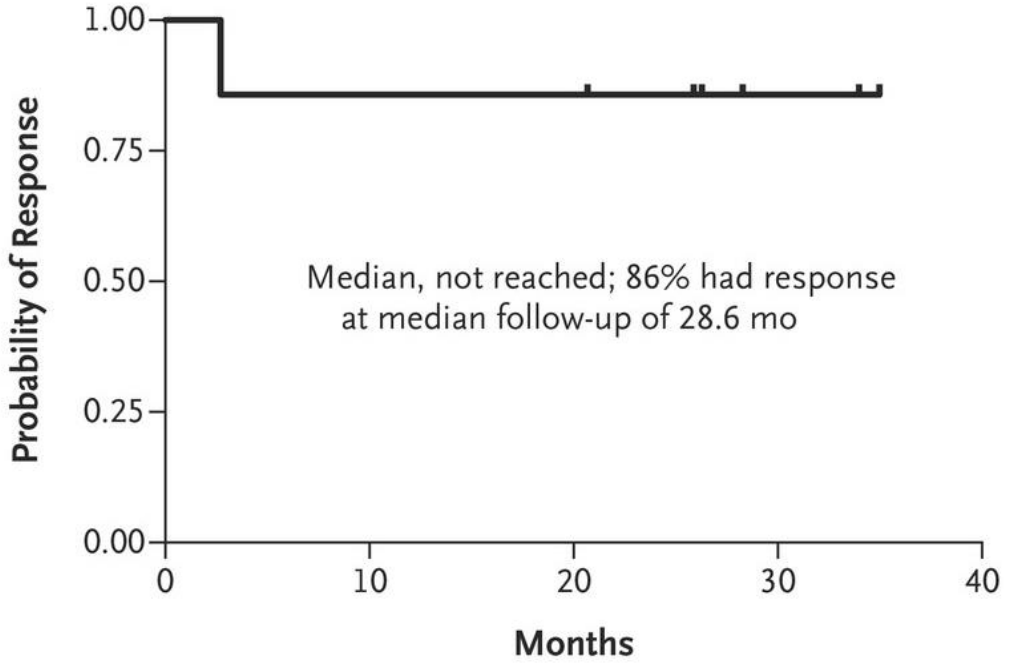


Schuster et al. NEJM 2017

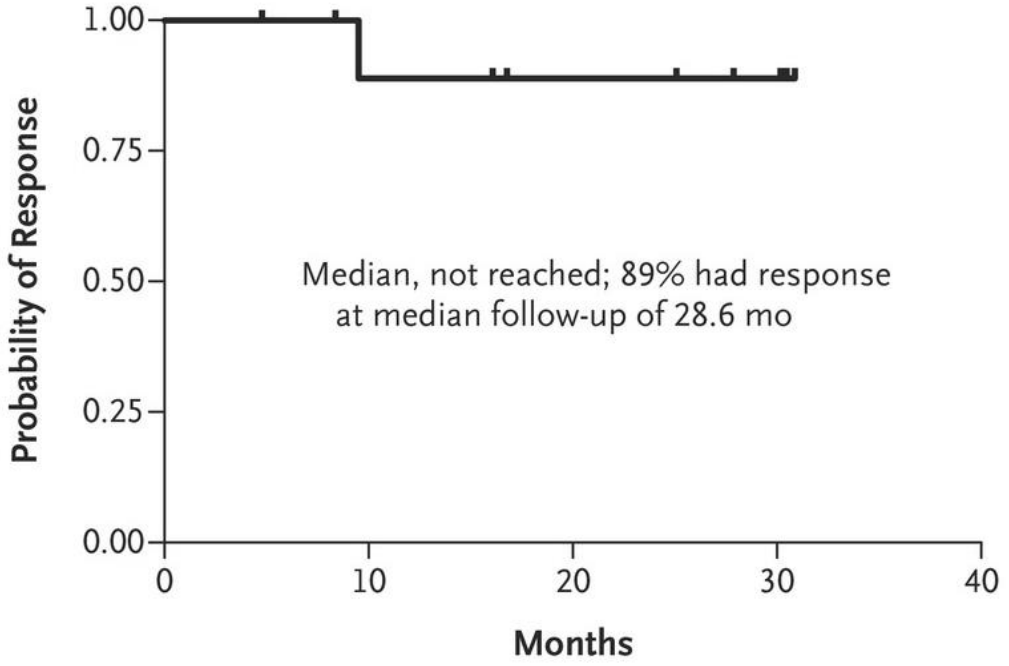
Tisagenlecleucel in B Cell **Lymphoma**

Duration of Response

Diffuse Large B-Cell Lymphoma, Response Duration



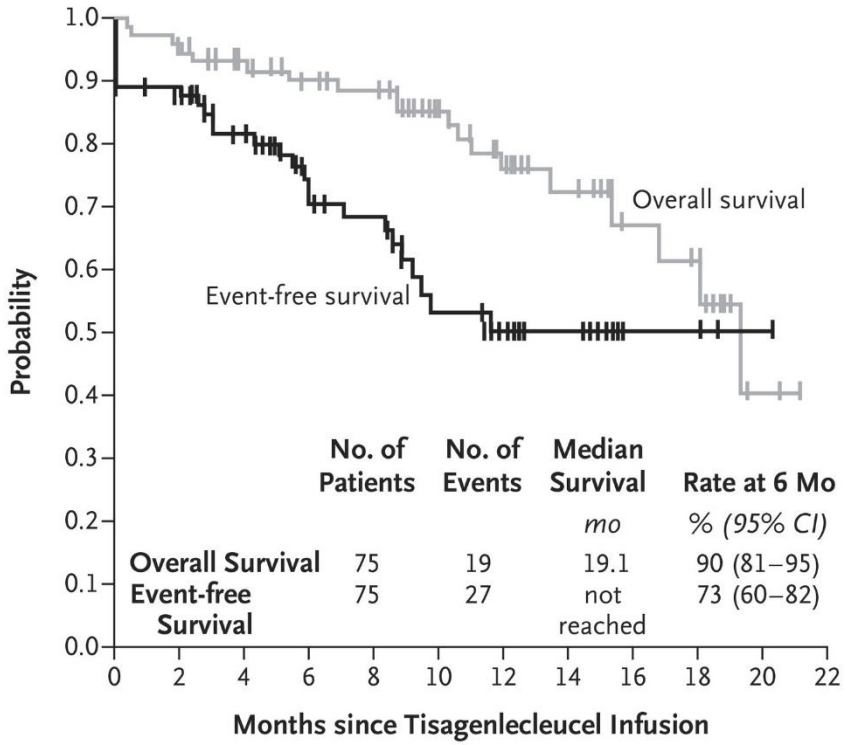
Follicular Lymphoma, Response Duration

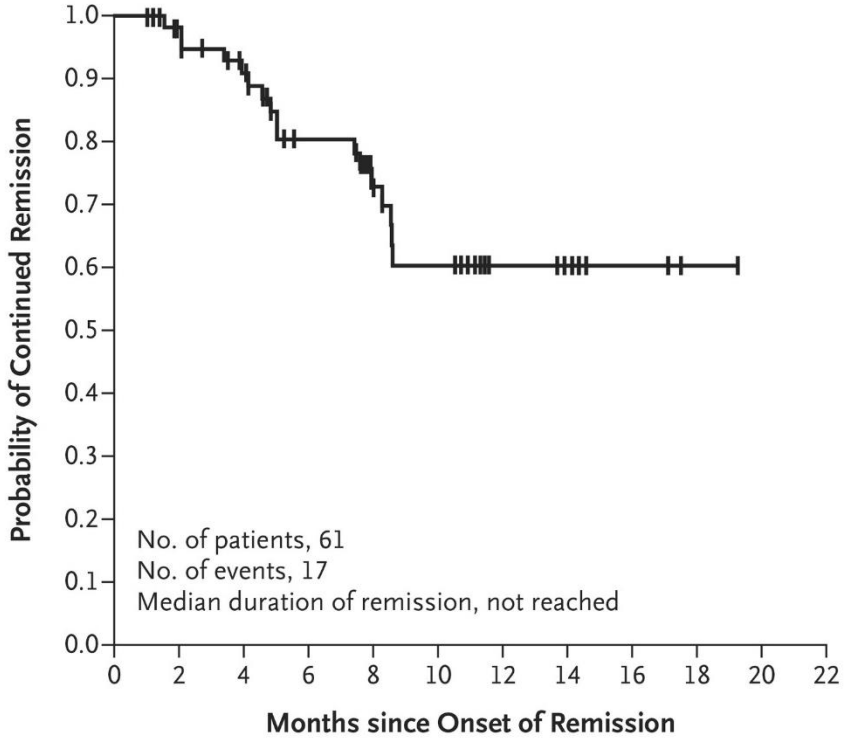


Schuster et al. NEJM 2017

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

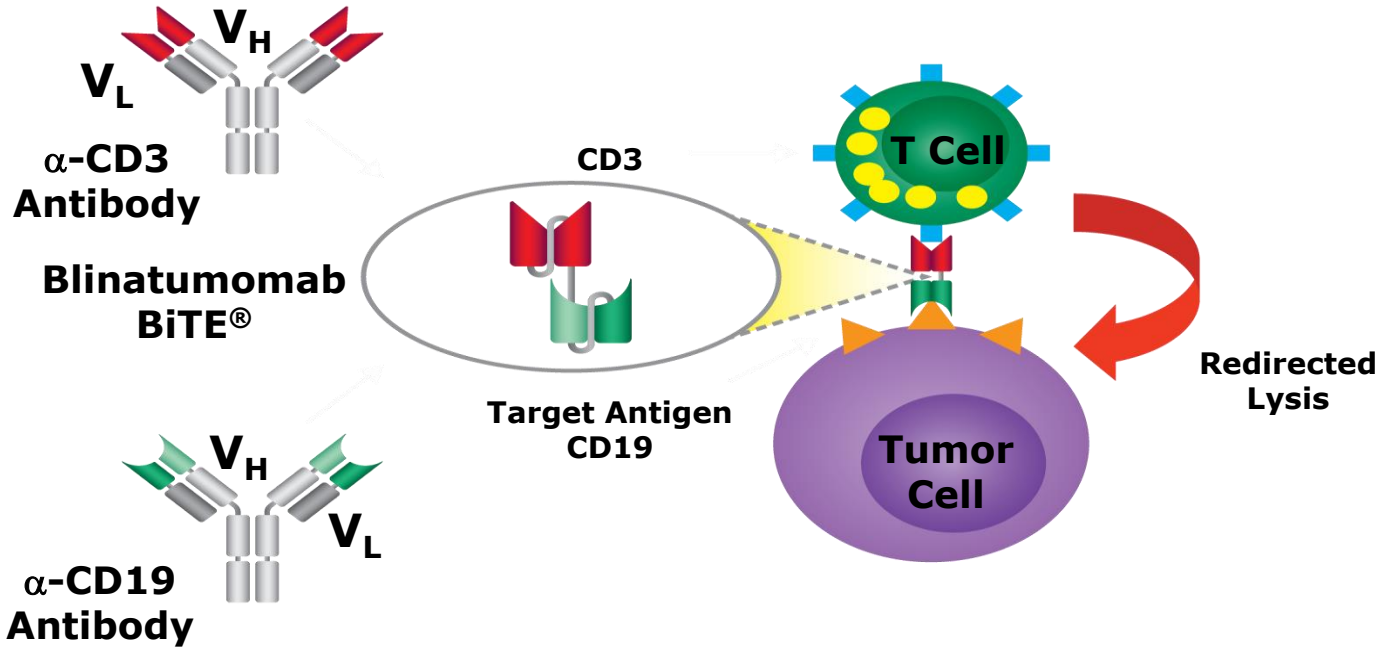




Maude et al. NEJM 2018

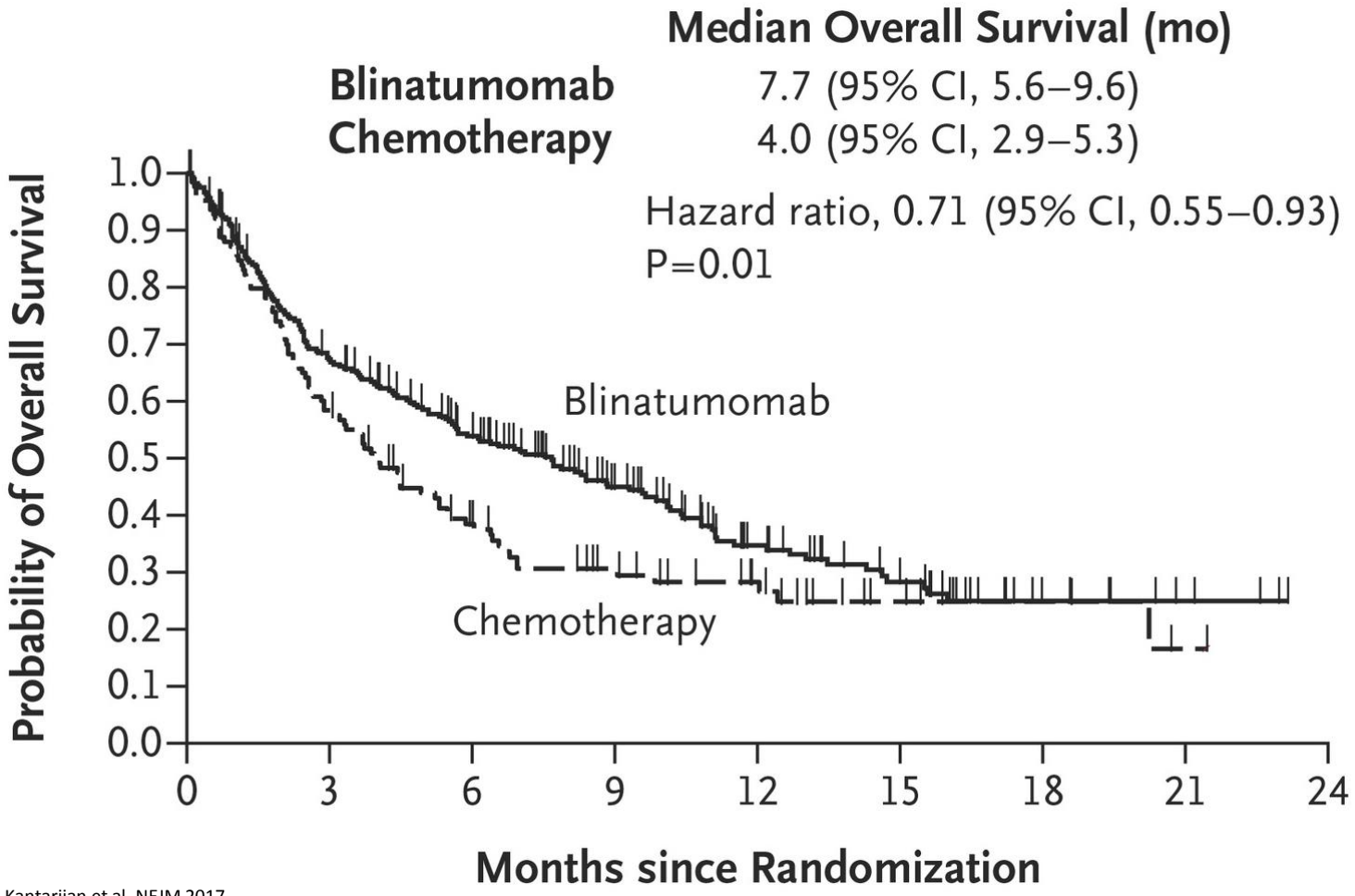
BiTE (Blinatumumab) Therapy

- 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

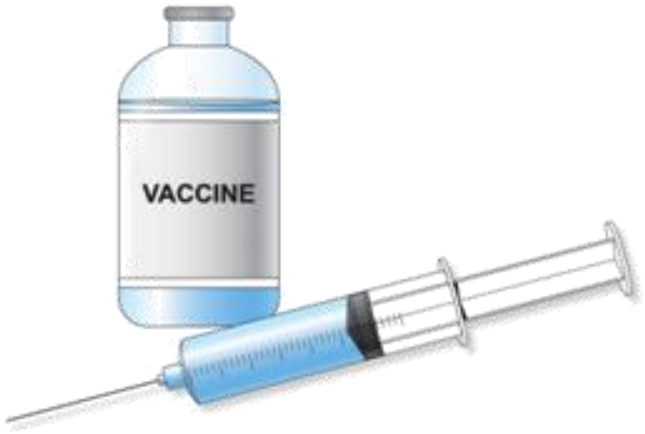
Blinatumomab for B-ALL



Kantarjian et al. NEJM 2017

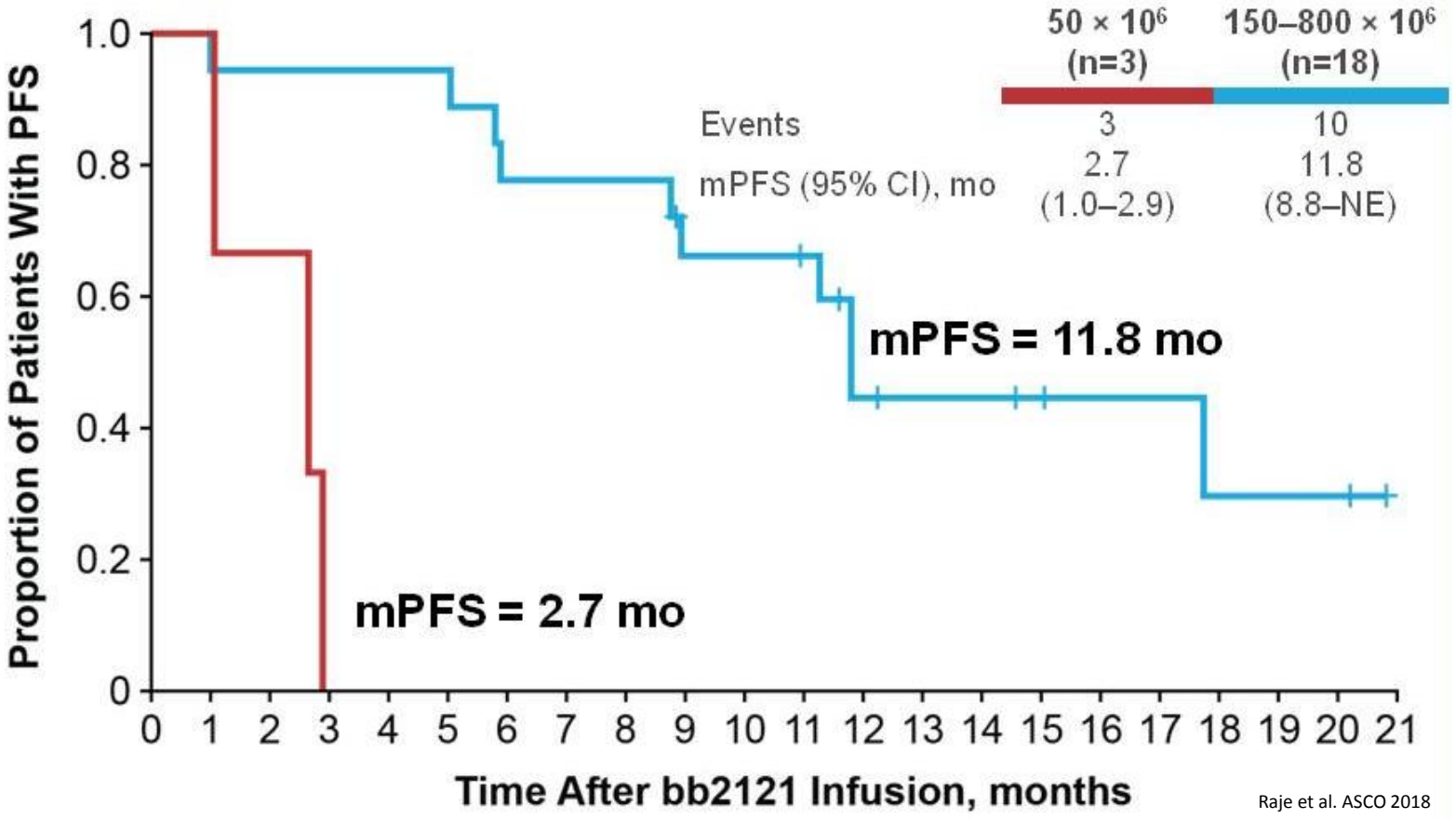
Immunotherapies for Multiple Myeloma

- 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



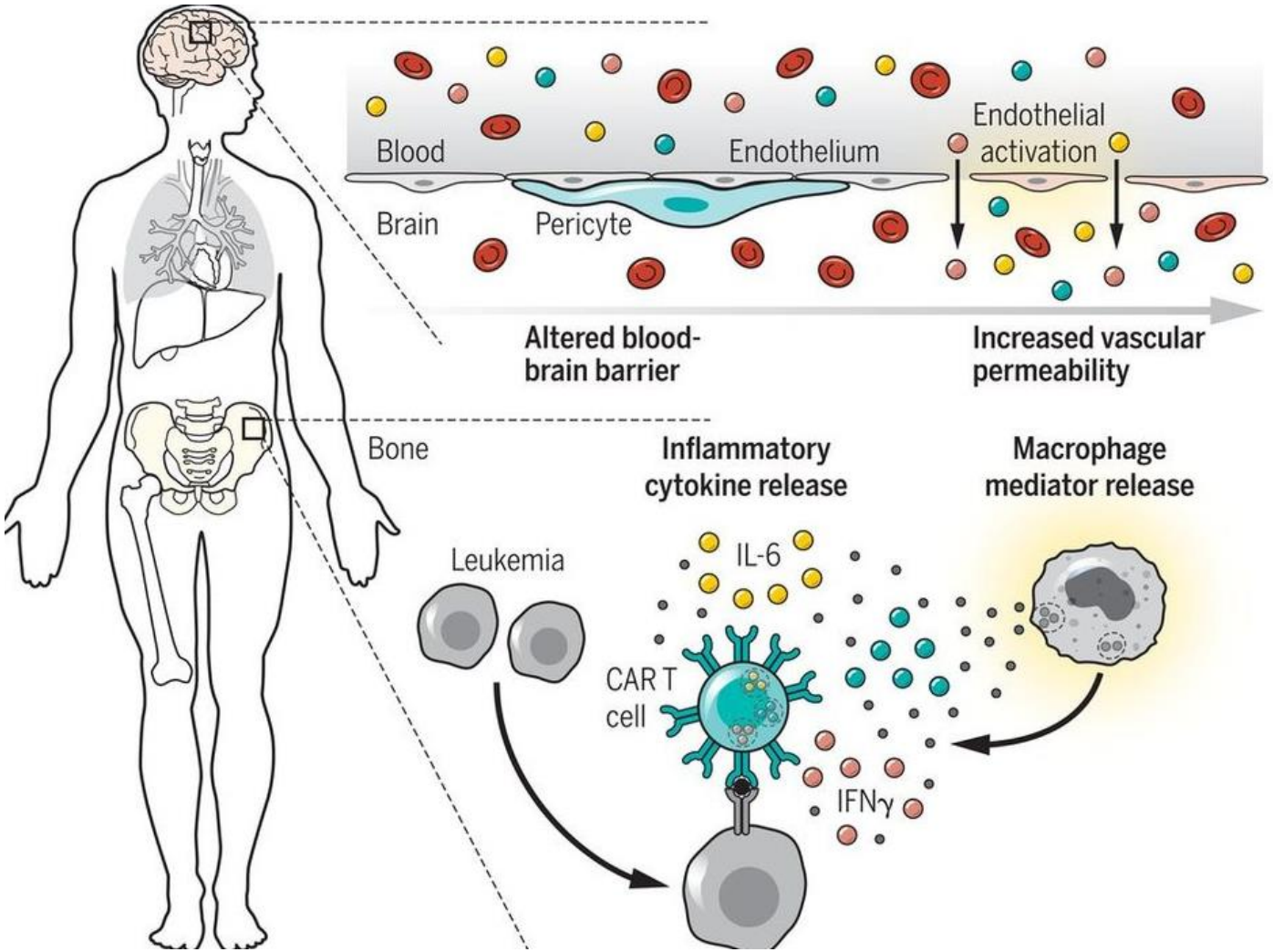
In Development: BCMA+ CAR T Therapy for Myeloma

- 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)



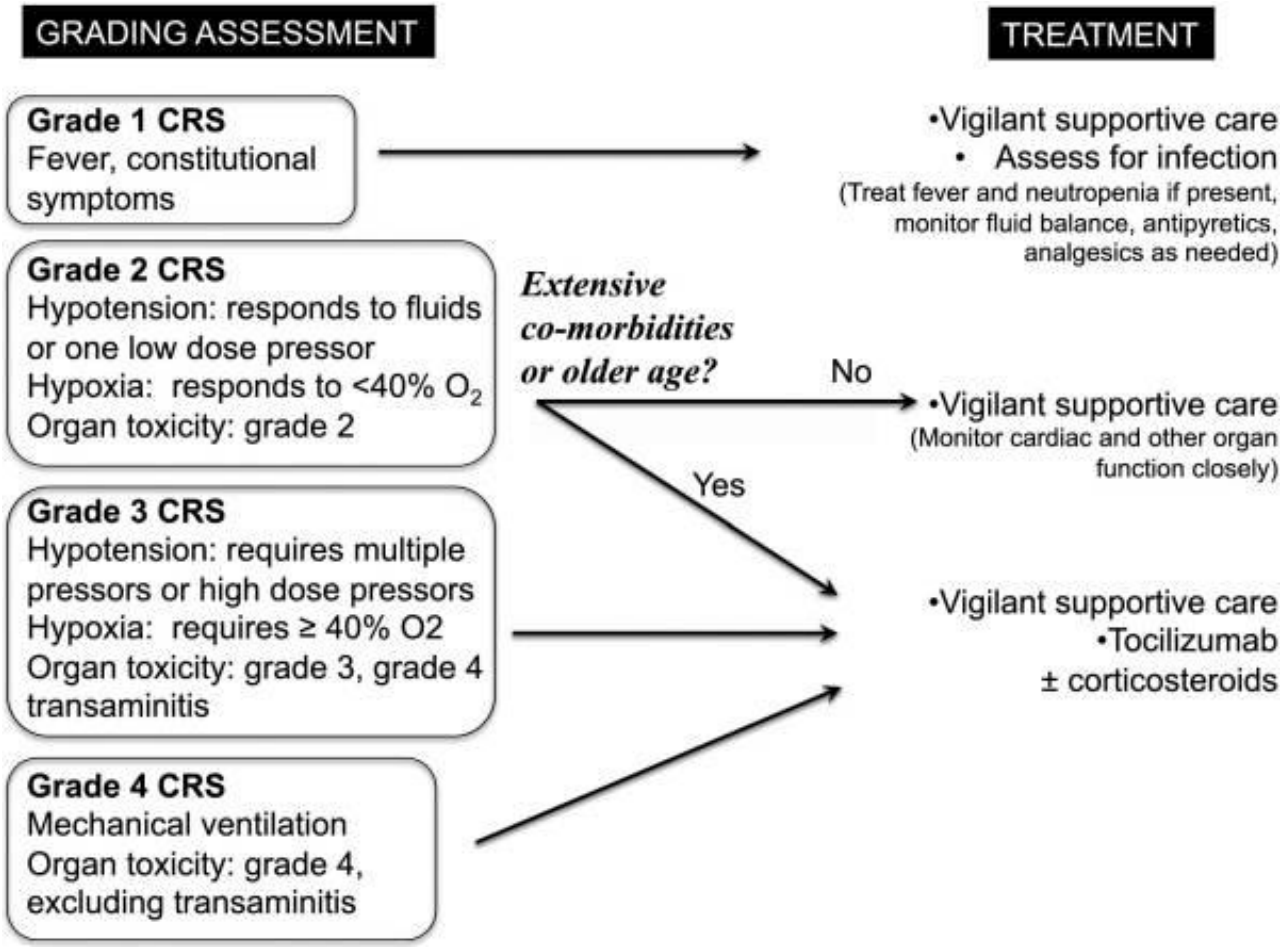
Neurotoxicity
Delirium
Aphasia
Seizures
Cerebral edema
Intracranial hemorrhage

Hemodynamic instability
Tachycardia
Hypotension
Capillary leak syndrome

Organ dysfunction
AST and ALT elevation
Hyperbilirubinemia
Respiratory failure

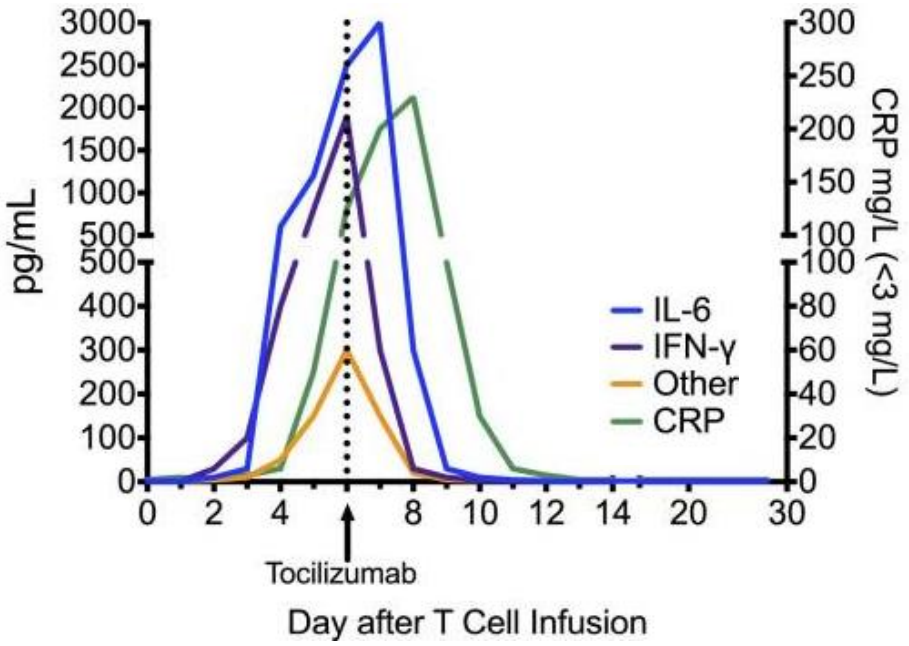
June et al. Science 2018

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

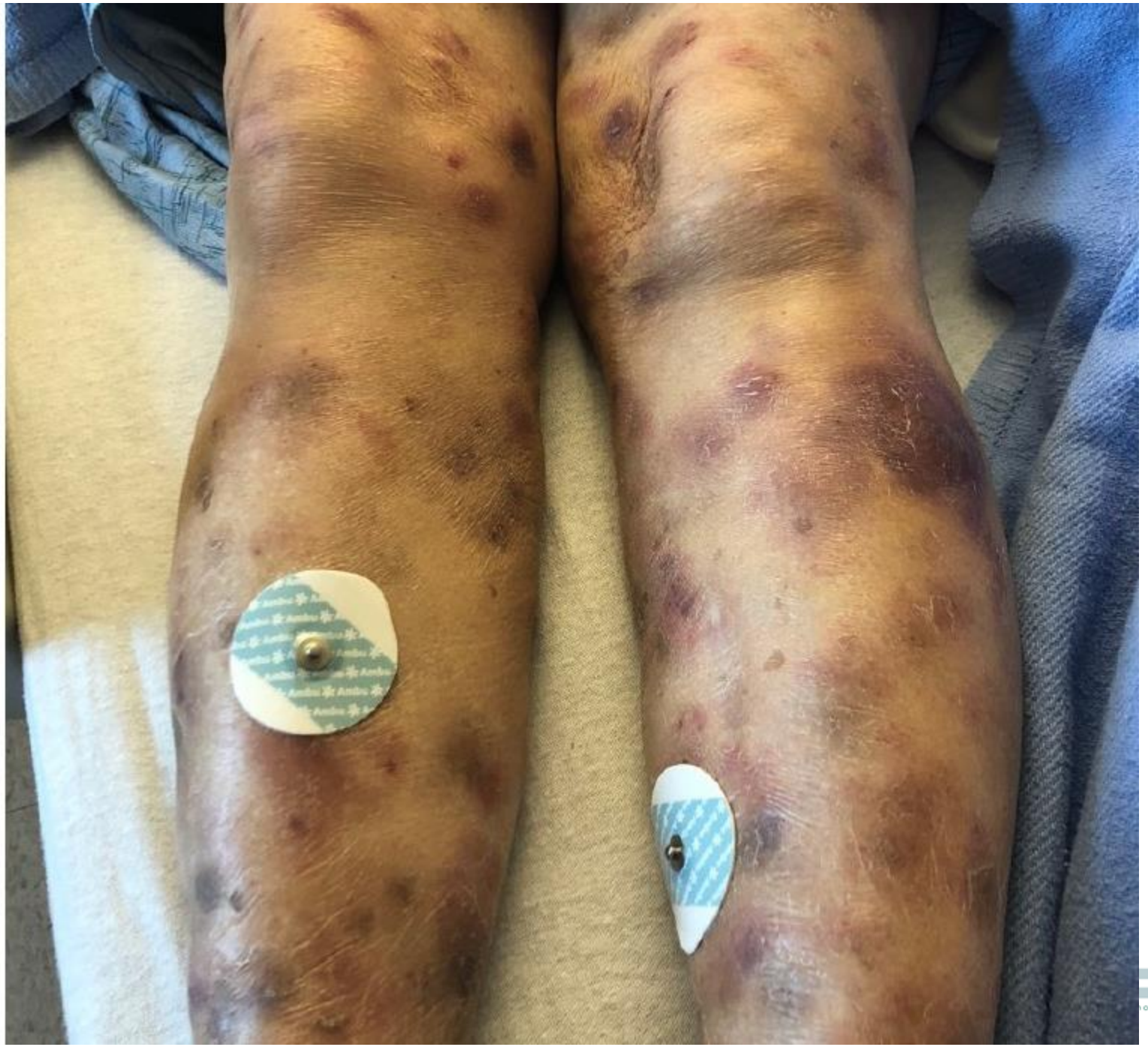
Michael Boyiadzis[1†], Michael R. Bishop[2†], Rafat Abonour[3], Kenneth C. Anderson[4], Stephen M. Ansell[5], David Avigan[6], Lisa Barbarotta[7], Austin John Barrett[8], Koen Van Besien[9], P. Leif Bergsagel[10], Ivan Borrello[11], Joshua Brody[12], Jill Brufsky[13], Mitchell Cairo[14], Ajai Chari[12], 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

- 80 year old lady who first began to notice raised, erythematous welt-like lesions on her feet and lower extremities in late July. She had had an upper respiratory illness ~1-2 months prior and was diagnosed with sinusitis for which she was prescribed Augmentin. She subsequently presented to the a local ED on 7/24/18 with complaints of continued sinus congestion and was noted to have nasal swelling and discharge as well as what was described in notes as a "generalized slightly violaceous/erythematous oval and round maculopapular rash on trunk and extremities

- She underwent CT sinus during this visit which showed "...enhancing lobulated polypoid soft tissue masses nasal cavity (left greater right)...".

- She was discharged with clindamycin PO, fluticasone nasal spray, mupirocin nasal ointment, and oral steroids for acute on chronic sinusitis with nasal polyps. Her nasal discharge subsequently resolved and she was seen for follow up with an ENT physician 9/4/18 who had some concern about a possible neoplasm and recommended surgery.



Picture taken with patient permission

- She represented to the ED on 9/11/18 with complaints of progressive nodular lesions, non-tender, non-pruritic. Dermatology was consulted and the patient underwent biopsy of two lesions--one on her arm and one on her R thigh.

- She was referred to Dermatology as an outpatient and was diagnosed with extranodal NK/T-cell lymphoma (nasal type) at both biopsied sites and was sent to a tertiary center in Bay area and was subsequently referred to us for further therapy.

- Patient blood work was relatively normal with mild anemia. Due to her pre-existing conditions she had a PS of 2-3 with very limited mobility.

- She has a history of diabetes, hypertension and previous cardiac issues.

- Due to her severe comorbidities, it was decided that she was not a good candidate of any chemotherapy.

- Patient was started on palliative PD1 inhibitors based on few case reports

- After the first cycles some of her skin lesions responded to therapy but others were stable. After the 3rd cycles, there was clear evidence that the most of her lesions were progressing again.

- She was started on UCD 271 study with intra-lesionsal CPG with concurrent radiation to the same lesion and systemic IDO inhibitors. After just two weeks almost all her lesions are responding to the therapy.

Case study 2

&1 years old gentleman in his usual state of health until he felt dizzy and SOB. He thought it was a side effect of metoprolol and sought advice from someone at his PCP's office, who recommended reducing his metoprolol dose until he followed up with his PCP.

A few days later his PCP drew a CBC which showed profound anemia and pancytopenia subsequently sent patient to the ED.

ED work up was concerning for leukemia (do not have labs from ED) and patient received 2 units pRBCs and 1 unit plts (9/9/15).

Patient was seen by a hematologist and bone marrow bx 9/10/15 showed BCR-ABL positive B-lymphoblastic leukemia and absent storage iron. Peripheral blood smear 9/10/15 showed pancytopenia and few circulating blasts (<5%). He was then referred to UCDMC for urgent evaluation.

- **9/17/15 - repeat BMBx at UCD shows B-ALL. CD20+. BCR-ABL qual positive. Cytogenetics failed. FISH shows complex t(9;22), +Myc, +17, -IgH.**
- 9/18/15 - C1A R-HyperCVAD plus Dasatinib 100mg days 1-14. IT chemo x2.
- 10/16/15 - C1B HyperCVAD plus Dasatinib. IT chemo x2. R was omitted this cycle. Complicated by FN and non-specific dermatitis.

- **10/28/15 - BMBx shows CR1. Cytogenetics 46,XY. FCM negative. B-cell gene rearrangement positive. BCR-ABL1 quant PCR positive at 0.081% (IS) consistent with 3.681 log reduction. Report notes mix of p210 (79%) and p190 (21%) isoforms.**

- 11/7/15 - C2A R-HyperCVAD plus Dasatinib. IT chemo x2. Complicated by FN.
- 12/3/15 - C2B R-HyperCVAD plus Dasatinib. IT chemo x1. Complicated by cerebellar toxicity, likely related to AraC. CNS work-up otherwise negative, including no ALL involvement, but did show small bilateral subdural hematomas.
- 1/13/16 - C3A R-HyperCVAD plus Dasatinib. 50% dose-reductions of Cytoxan/VCR for prior toxicity. Completed 8 doses of R and 8 doses of IT chemo this cycle.
- 2/10/16 - C3B R-HyperCVAD plus Dasatinib. Omit Ara-C due to prior toxicity.
- 3/16/16 - C4A R-HyperCVAD plus Dasatinib. 50% dose-reductions of Cytoxan/VCR for prior toxicity.
- 4/13/16 - C4B R-HyperCVAD plus Dasatinib.

- **5/11/16 - BMBx shows CR1. MRD by FCM and qPCR is negative. (PB p190 and p210 qPCR negative 5/17/16).**

- What do you suggest as maintenance:

1. Allogeneic stem cell transplant
2. Autologous stem cell transplant
3. POMP therapy (MTX-6MP-pred)
4. TKI (dasatinib or ponatinib)
5. POMP therapy + TKI

- 6/7/16 - C1 maintenance with Dasatinib 100mg daily, Vincristine 2mg IV day 1 and PSE 200mg PO days 1-5. 3/28/17 - C11 maintenance.
- 4/20/17 - BMBx showed relapsed Ph+ B-ALL. 13% blasts by aspirate, 25% by IHC and 9% by FCM. Positive FISH, normal cytogenetics and p190 qPCR positive (ratio 0.54614). ABL1 KD mutations negative.
- What would be your next treatment:

1. Liposomal vincristine
2. L-asparginase containing regimen (MOAP or MOpAD regimen)
3. Inotuzumab +/- mini-HyperCVAD
4. Blinatumumab
5. CAR T cells on a clinical trial
6. Switching TKIs to ponatinib

- 4/27/17 – Pt was started single agent ponatinib and a search was an allogeneic transplant was underway. Complicated by G3 elevations of lipase/amylase which resolved with temporary ponatinib cessation (5/4-5/8) and restart 5/9 at 30mg daily. Also complicated by mild HTN controlled with HCTZ started 5/22.
- 5/24/17 BMBx showed progressive Ph+ B-ALL. 26% blasts by aspirate, 25% by IHC and 19% by FCM. Positive FISH, normal cytogenetics and p190 qPCR positive (ratio 2.98927)
- What should we do next:

1. Hospice
2. Liposomal vincristine
3. L-asparginase containing regimen
4. Inutuzumab +/- mini-HyperCVAD
5. Blinatumumab
6. CAR T cells on a clinical trial

- 6/23/14 CAR-T cell infusion with fludarabine and cyclophosphamide conditioning. Complicated by fever, hypotension, and increased LFTs consistent with CRS grade 2 requiring an additional dose of tocilizumab, and C-diff. Bone marrow before the CAR T cell therapy showed 80% involvement despite one dose of liposomal vincristine. Post CAR T cell evaluation should complete response including molecular CR by BCR-ABL and MRD negativity by flow.
- 8/30/17 Patient underwent MUD allogeneic stem cell transplant with Bu2/Flu + ATG regimen
- 4/4/18 BMBx was positive for MRD and BCR-ABL
- 4/18/18 mobilized stem cell infusion with no effect.
- Are we done treating this patient?

1. Hospice
2. Second allo transplant from an unrelated donor
3. Re-treat with CAR T cells form the previously stored CAR T cells
4. Re-treat with CAR T cells after a new collection.