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Immunotherapy for the Treatment of Hematologic Malignancies

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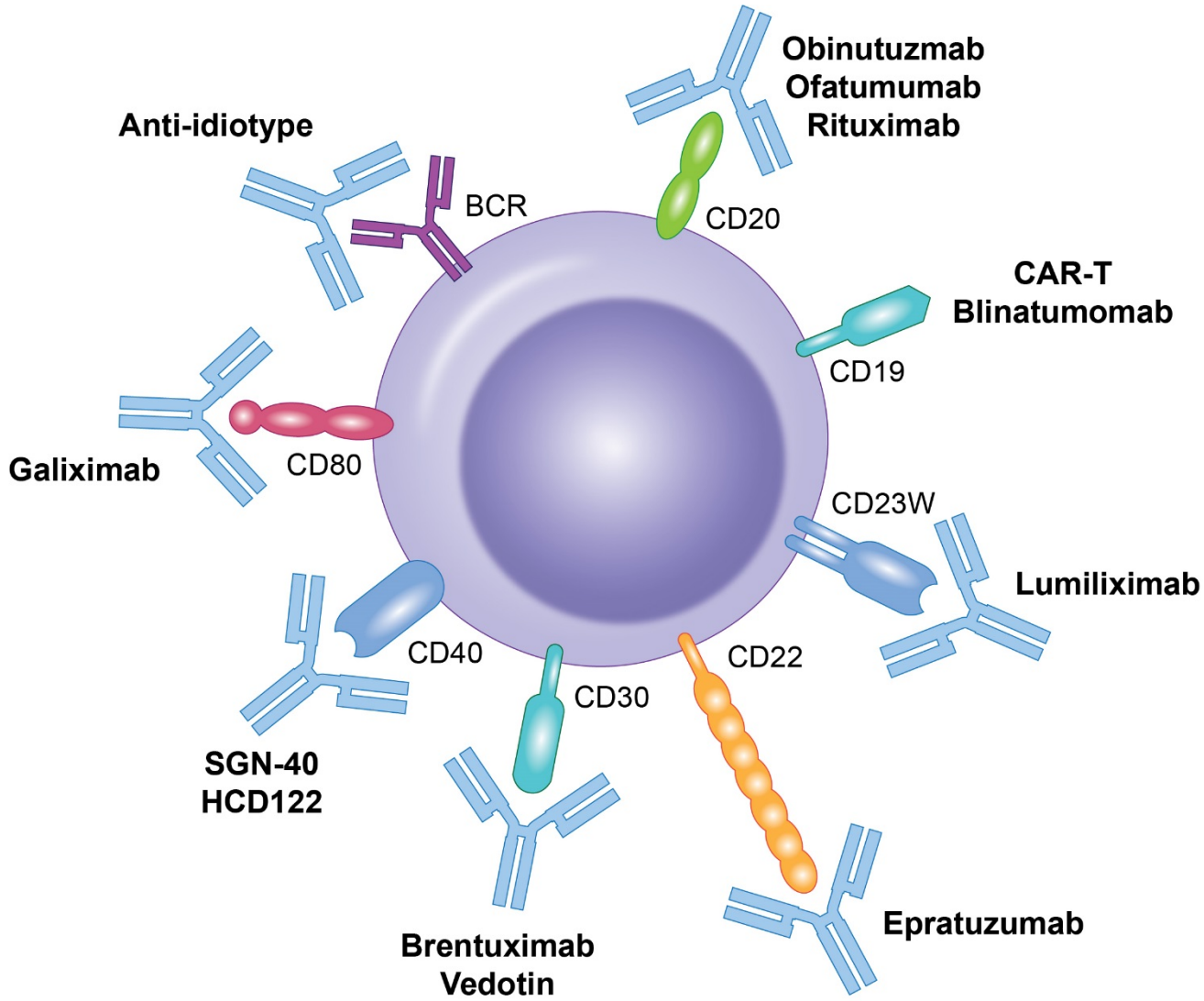
Disclosures

- No disclosures to report
- I will 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

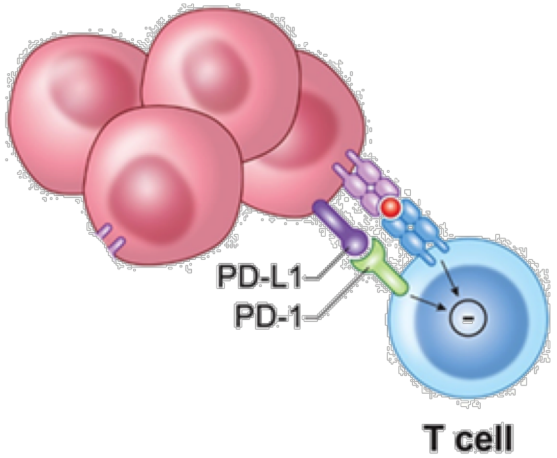
- Pembrolizumab (anti-PD-1)

  KEYNOTE-087:

  - Adult and pediatric patients with refractory cHL, or,
  - patients whose disease has relapsed after three or more lines of therapy

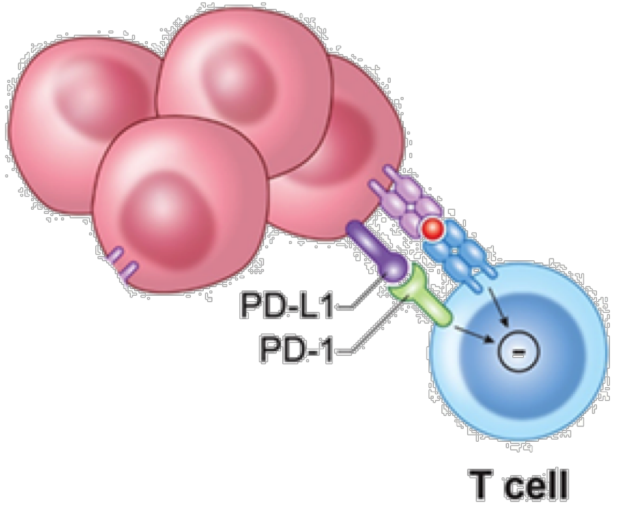
  KEYNOTE-170:

  - 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 or MSI status for anti-PD-1 therapy (in solid tumors)
- 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



Rationale for CPI in Hodgkin Lymphoma

- cHL is characterized by malignant Hodgkin Reed-Sternberg (HRS) cells dispersed within an extensive inflammatory/immune cell infiltrate
- HRS cells frequently harbor alterations in chromosome 9p24.1, leading to overexpression of programmed death-ligand 1 (PD-L1) and PD-L2, ligands of the programmed death 1 (PD-1) immune checkpoint receptor.
- rrHL may thus be genetically susceptible to blockade of the PD-1 pathway.

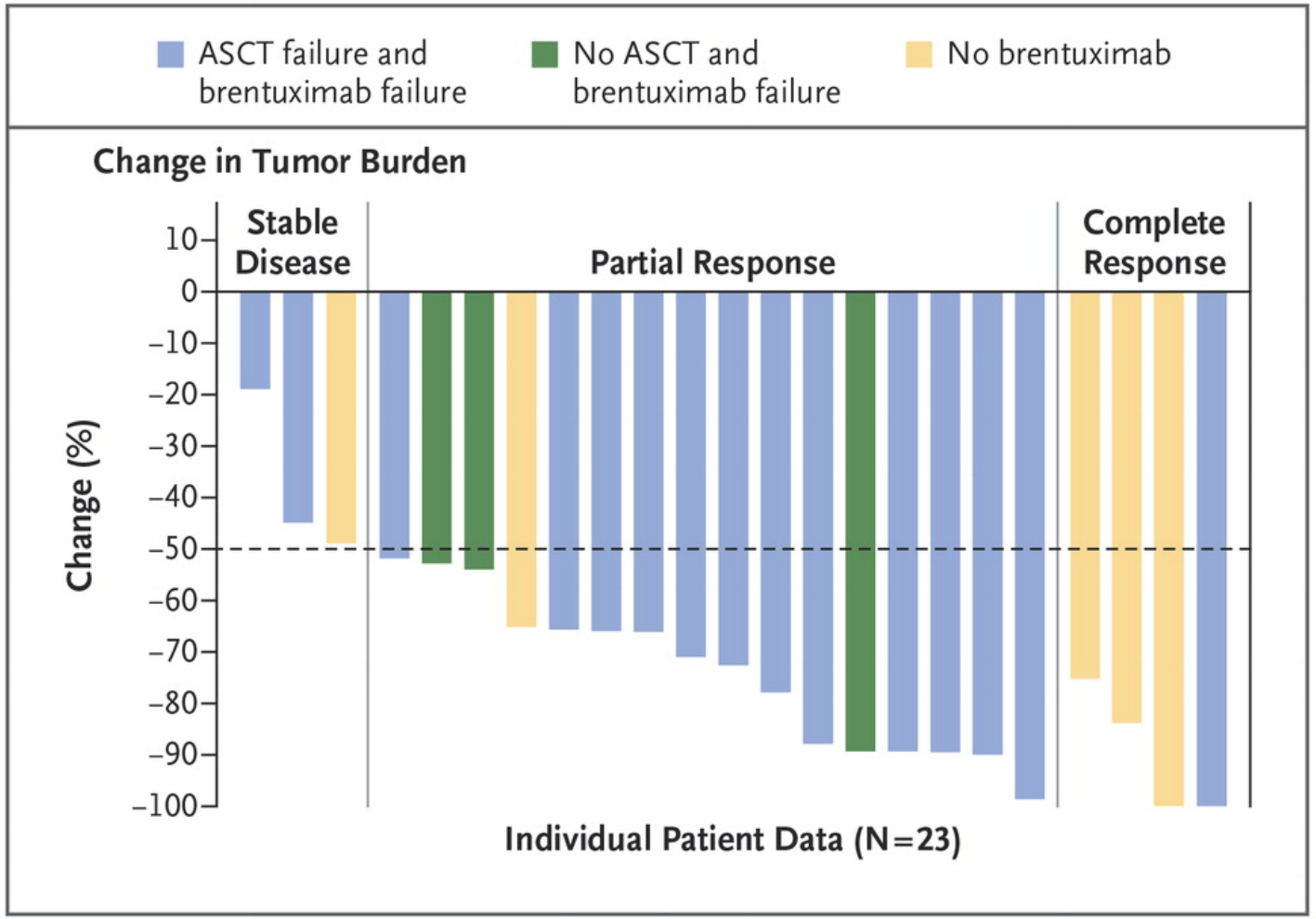
Nivolumab in Hodgkin Lymphoma- phase 1 study

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-phase 1 data

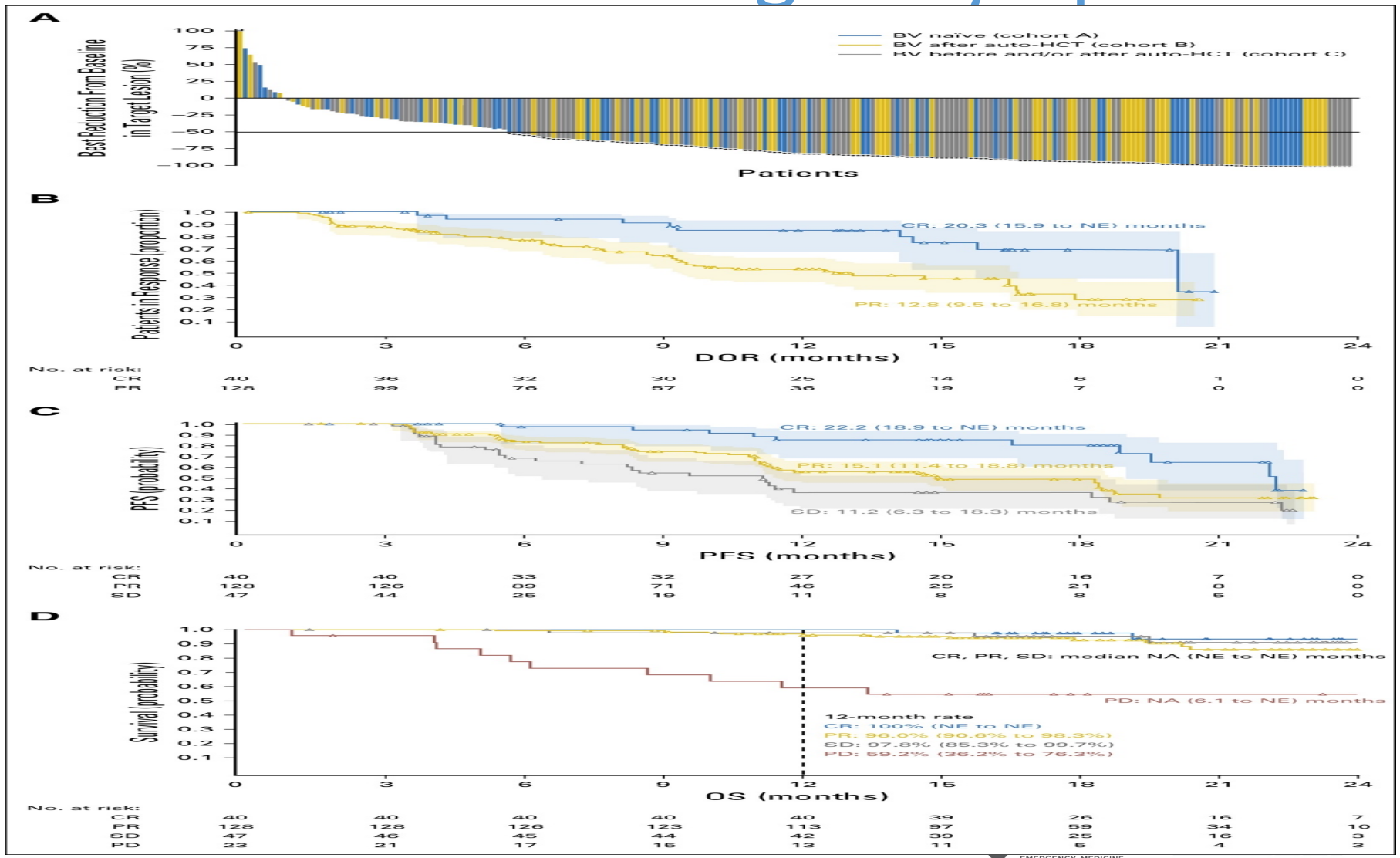


Ansell et al. NEJM 2015

Extended follow up of Checkmate205:single arm, phase 2 study

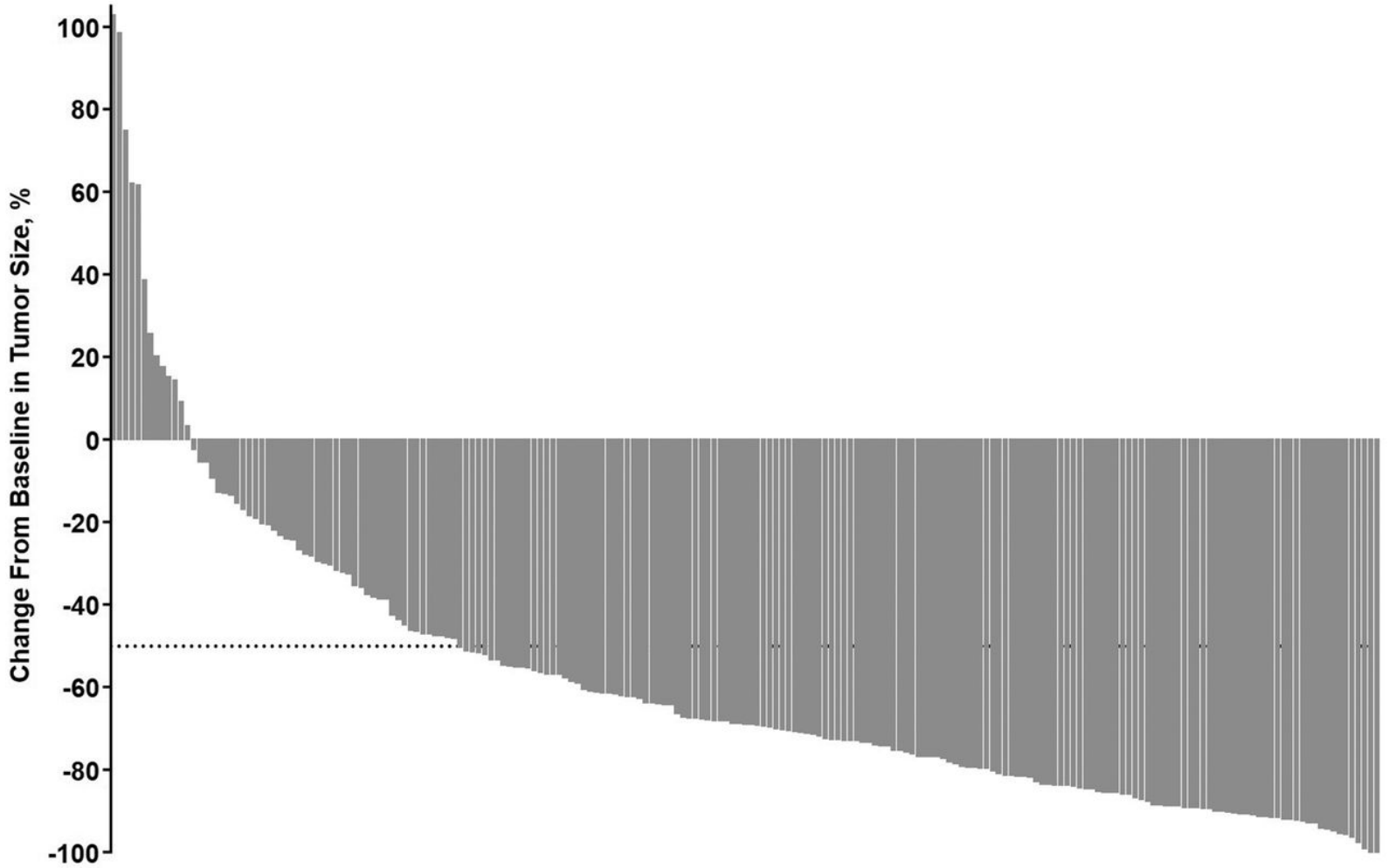
- 243 patients were treated
- 63 BV naive, 80 BV post auto, and 100 BV pre and post auto.
- After a median follow-up of 18 months, 40% continued to receive treatment.
- The ORR was 69% (95% CI, 63% to 75%) overall and 65% to 73% in each cohort.
- Overall, the median duration of response was 16.6 months (95% CI, 13.2 to 20.3 months), and median PFS was 14.7 months (95% CI, 11.3 to 18.5 months).
- Of 70 patients treated past conventional disease progression, 61% of those evaluable had stable or further reduced target tumor burdens.
- The most common grade 3 to 4 drug-related adverse events were lipase increases (5%), neutropenia (3%), and ALT increases (3%).

Nivolumab in Hodgkin Lymphoma



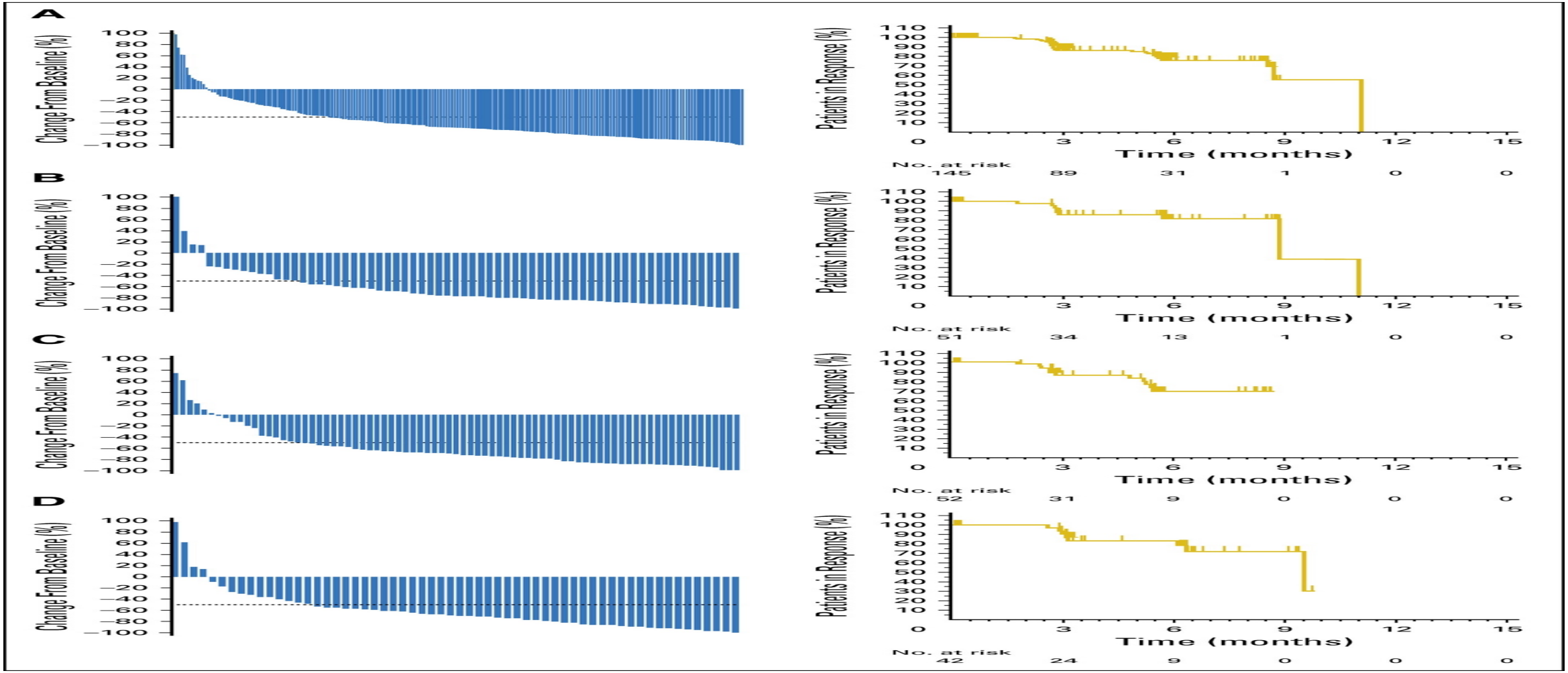
P Armand et al. JCO May 10 2018

Pembrolizumab in Hodgkin Lymphoma



Zinzani et al. Hematological Oncology 2017

Pembrolizumab in HL-KEYNOTE 087



R Chen et al. JCO July 1 2017

Pembrolizumab in HL-KEYNOTE 087

- Phase 2, multi-center, single arm study of Pembrolizumabin rr HL
- 3 cohorts defined

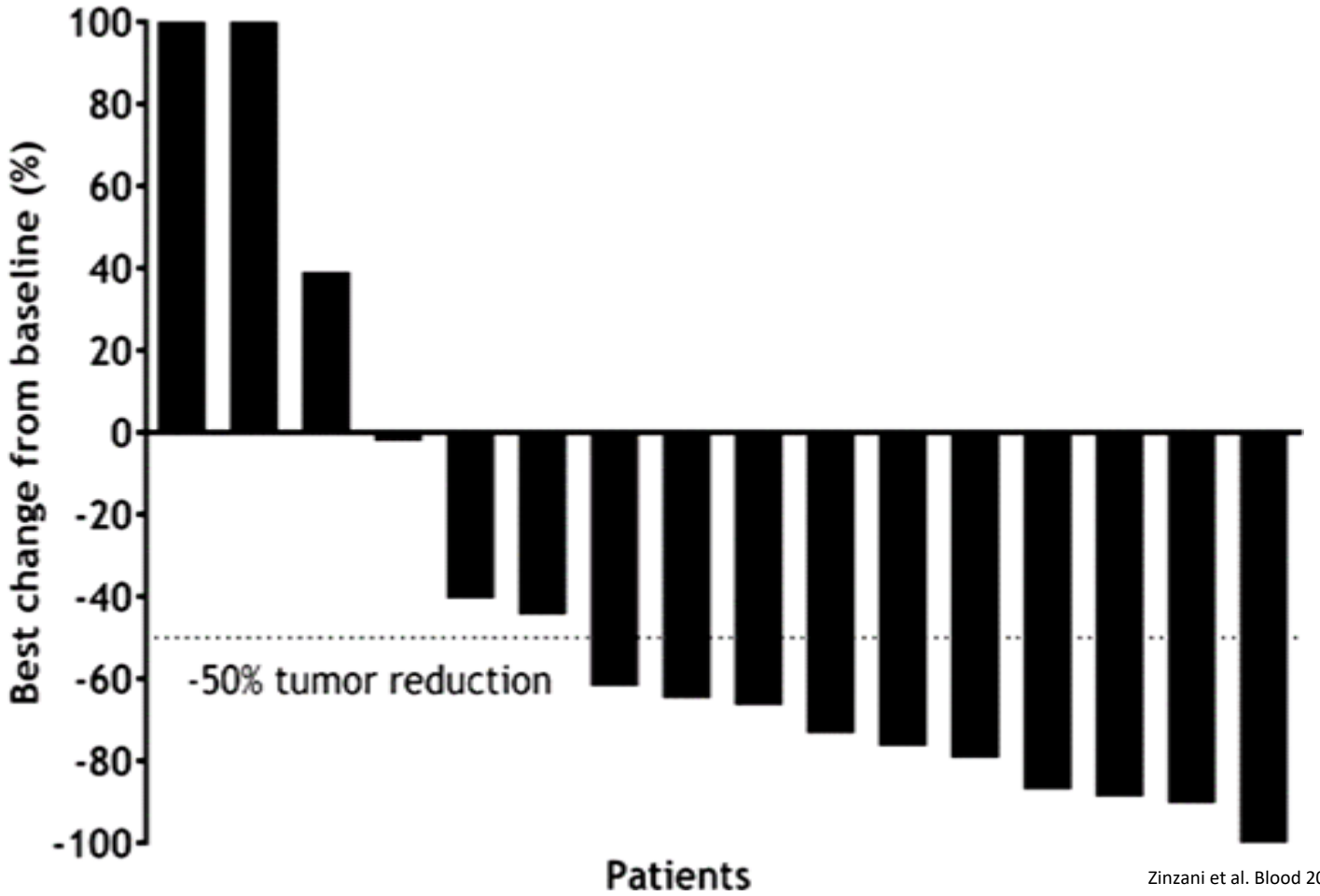
--progression after SCT and subsequent BV

--progression after salvage chemotherapy and BV, and thus ineligible for ASCT because of chemoresistant disease and

--progression after ASCT but had not received BV after transplantation

- Median DOR was not reached in all cohorts
- At 6 months, the OS rate was 99.5%, and the PFS rate was 72.4%.
- Thirty-one patients (75.6%) had a response ≥ 6 months.
- Median OS was not reached, with only four deaths occurring.

Pembrolizumab in Primary Mediastinal Large B cell Lymphoma

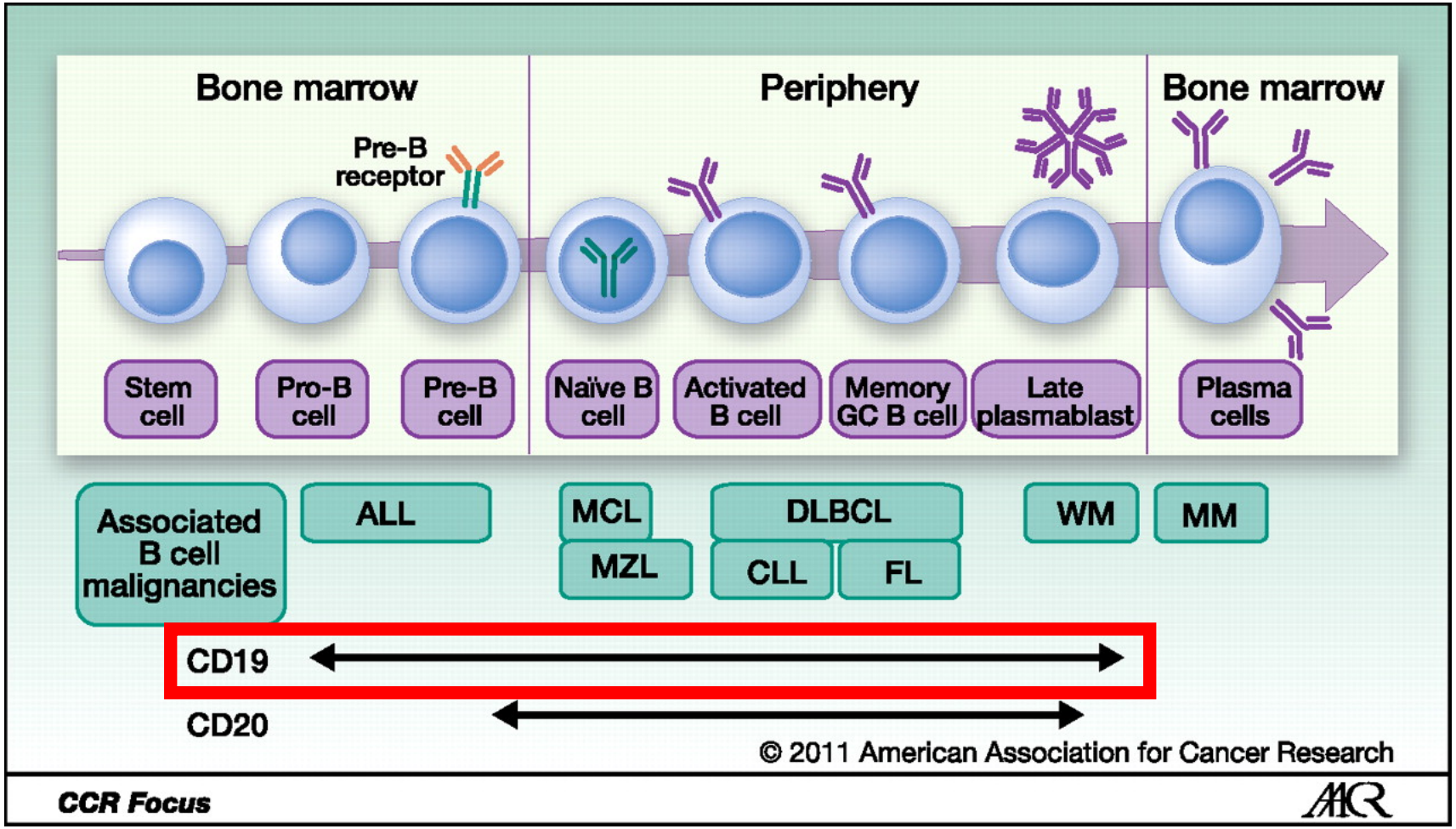


Zinzani et al. Blood 2016

Pembrolizumab in PMBCL-KEYNOTE 013

- 18 patients (median age 30 years; median 3 prior lines of therapy) enrolled and treated
- 17 were included in the efficacy analyses.
- ORR was 41% (7/17)
- 6 additional patients (35%) had stable disease.
- Of patients evaluable by imaging, 13 out of 16 (81%) had decreases in target lesions.
- With a median follow-up of 11.3 months, median duration of response was not reached.

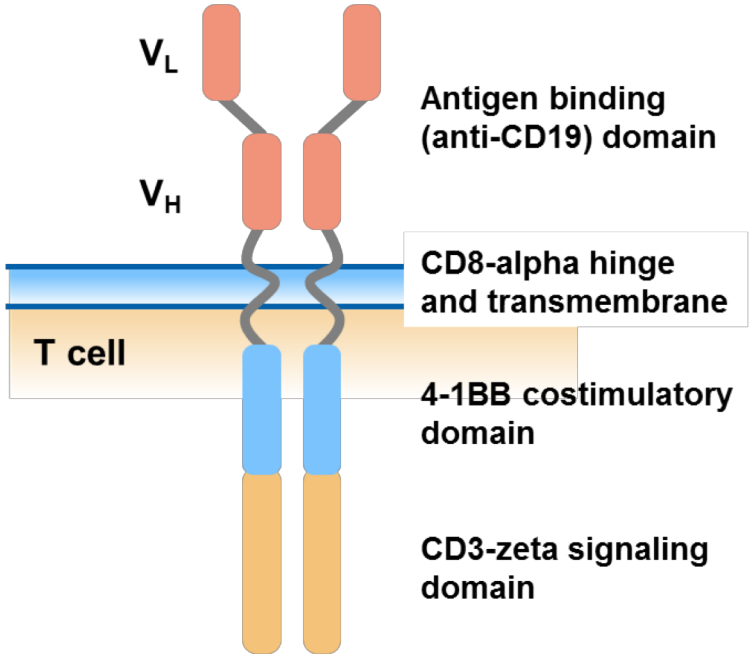
B Cell Malignancies are CD19+

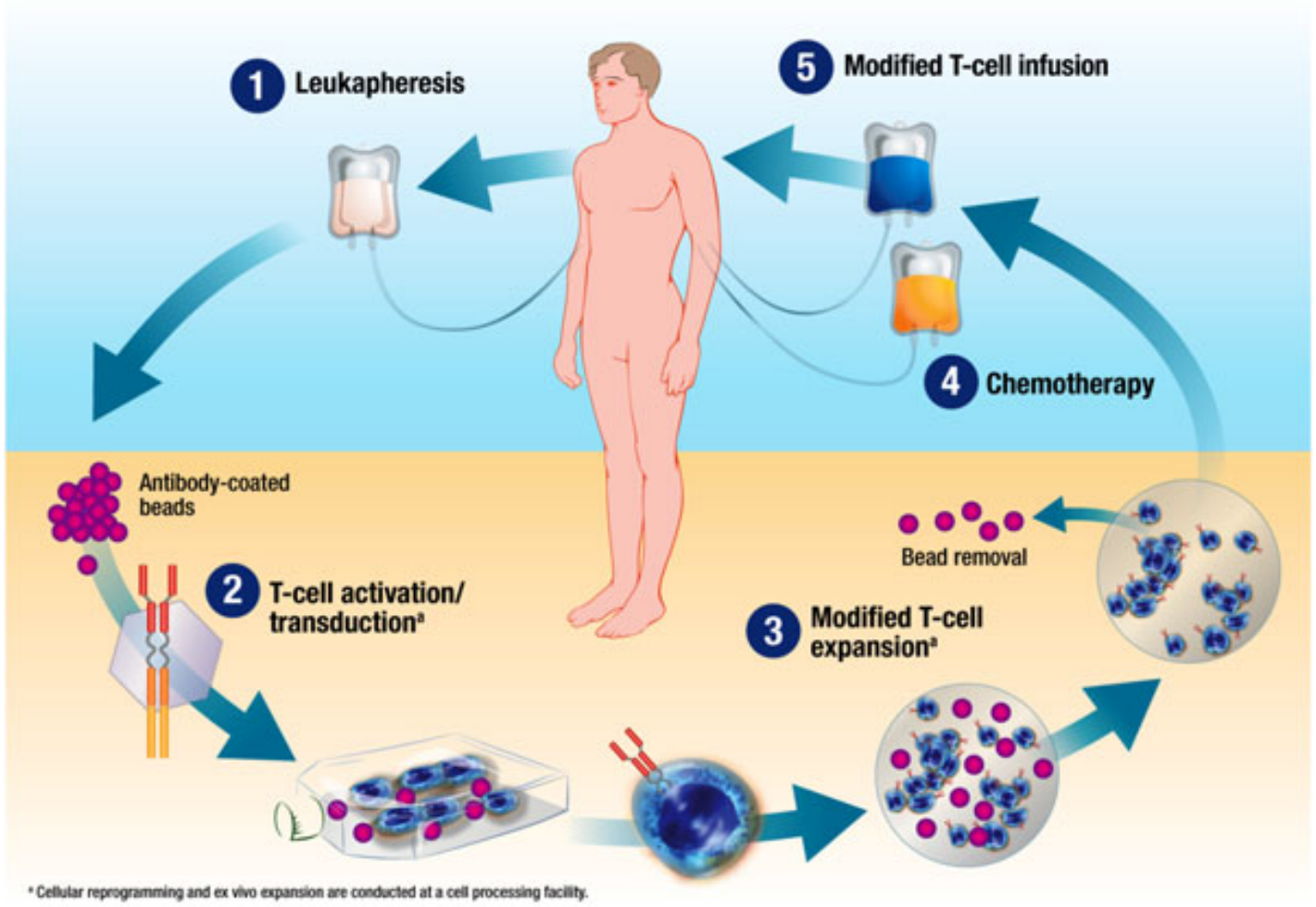


Blanc et al. Clinical Cancer Research 2011

Chimeric Antigen Receptor (CAR) T cell Therapy

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





What is CAR ?

- CAR is a hybrid antigen receptor
- It is composed of the intracellular signaling and activation domains of the T cell receptor (TCR) and extracellular antigen-binding domain, or single-chain variable fragment (scFv), derived from an antibody

Role of T cells in immunotherapy

- T cells have a specific inhibitory effect on the implantation and growth of cancer cells
- Fully competent activation requires three signals including T-cell receptor engagement (signal 1), co-stimulation (signal 2) and cytokine stimulus (signal 3)
- However, B-lineage malignancies, for example B-ALL, generally lack signal 2 by absence of ligands of two major T-cell co-stimulatory molecules CD28 or 4-1BB.
- The lack of these ligands leads to rapid apoptosis of T cells after stimulation and immune escape of B-ALL cells
- Integration of signals 1 and 2 into a kind of functional proteins (such as chimeric antigen receptor (CAR)) expressed on T cells by gene engineering contributes to resolve these problems for B-ALL (and DLBCL), and hence the advent of CAR-T therapy

CAR T

- Involves genetic modification of patient's autologous (or allogeneic) T-cells to express a CAR specific for a tumor antigen
- Followed by ex vivo cell expansion and re-infusion back to the patient.
- CARs are fusion proteins of a selected single-chain fragment variable from a specific monoclonal antibody and one or more T-cell receptor intracellular signaling domains.
- This T-cell genetic modification may occur either via viral-based gene transfer methods or nonviral methods, such as CRISPR/Cas9 technology

CAR T :Why CD 19 target

- Uniformly expressed on malignant B cells
- Expressed in the B-cell lineage,
- Not expressed in other lineages or other tissues.

CAR T

- Anti-CD19 CAR is a recombinant molecule consisting of three parts:

(i) a single-chain variable domain (scFv) derived from an anti-CD19 monoclonal antibody,

(ii) a transmembrane domain, and

(iii) the signal transduction domain of T-cell receptor (TCR) (CD3ζ

- When a CAR-T recognizes a specific antigen, the cell is activated via the intracellular signal transduction domain and exerts target cell toxicity.
- First-generation CAR-T showed limited expansion and antitumor efficacy because the CAR-T expansion was dependent on interleukin (IL)-2 production

CAR T

- Physiological *in vivo* T-cell activation is caused by interaction between antigen-presenting cells via T-cell receptor and several costimulatory receptors such as CD28 and 4-1BB
- To improve CAR-T-cell expansion capacity and antitumor activity, second-generation CAR contains a costimulatory domain, such as CD28 or 4-1BB
- With the additional costimulatory domain, second-generation CAR-T therapy shows better *in vivo* expansion.
- The most recent clinical trials of CAR-T therapy have used second-generation CAR-T.

FDA-approved CAR T Cell Therapies for Lymphoma

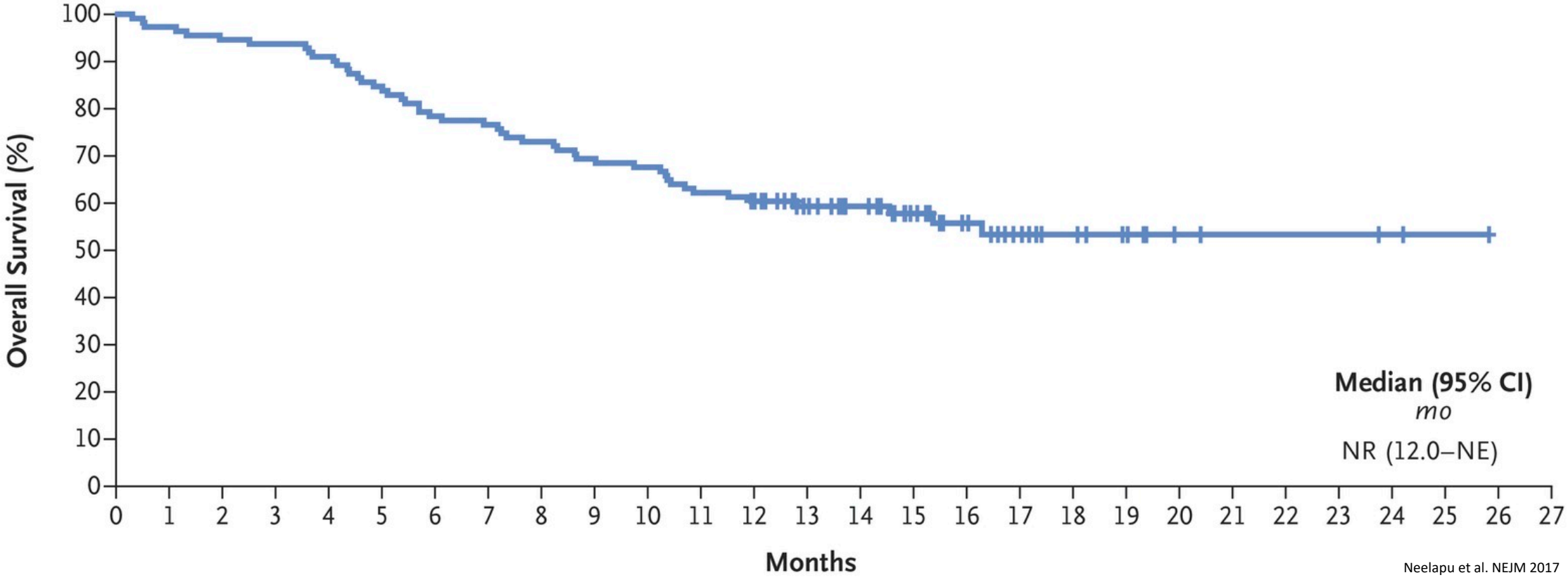
- Axicabtagene ciloleucel
  - ZUMA-1: Adult patients with relapsed or refractory large B cell lymphoma after two or more lines of systemic therapy, including diffuse large B cell lymphoma, high-grade B cell lymphoma, and DLBCL arising from follicular lymphoma
- Tisagenlecleucel
  - JULIET: adult patients 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
  - Low disease burden also correlated with better survival in some studies
- Presence of co-morbidities
  - e.g. Presence of active autoimmune diseases which could be worsened

Axicabtagene ciloleucel in B Cell Lymphoma

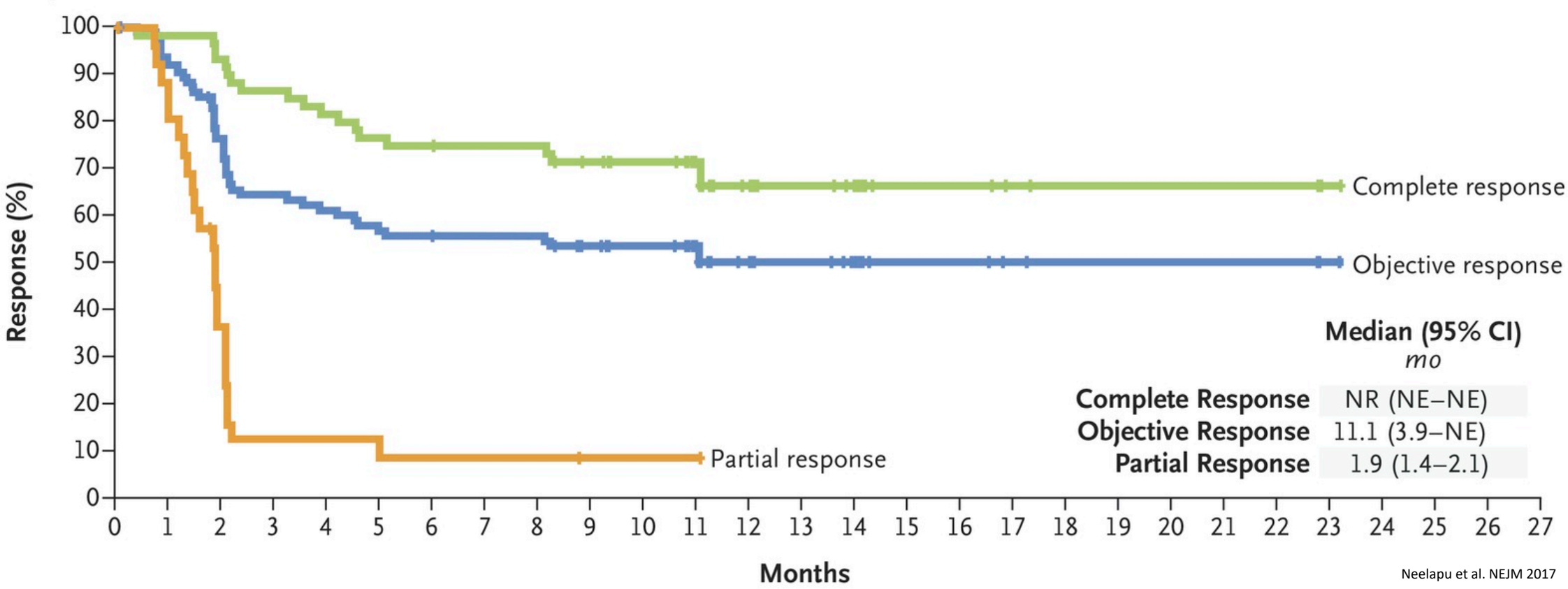
Overall Survival



Neelapu et al. NEJM 2017

Axicabtagene ciloleucel in B Cell Lymphoma

Duration of Response



Neelapu et al. NEJM 2017

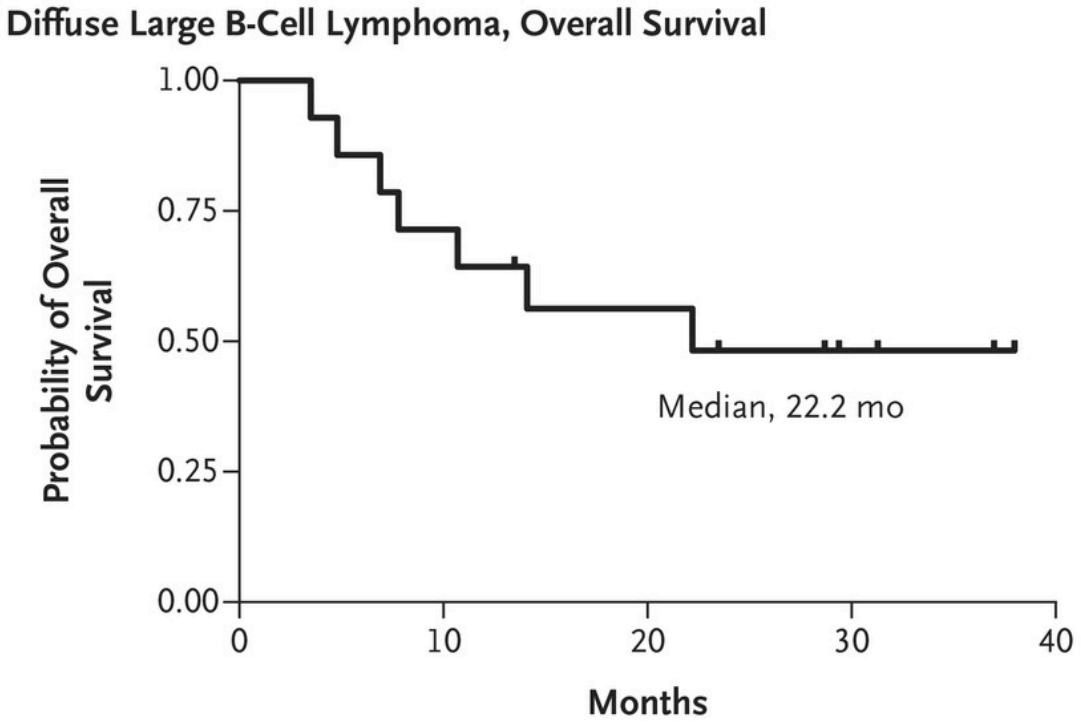
Axicabtagene cioleucel :updated analysis in DLBCL

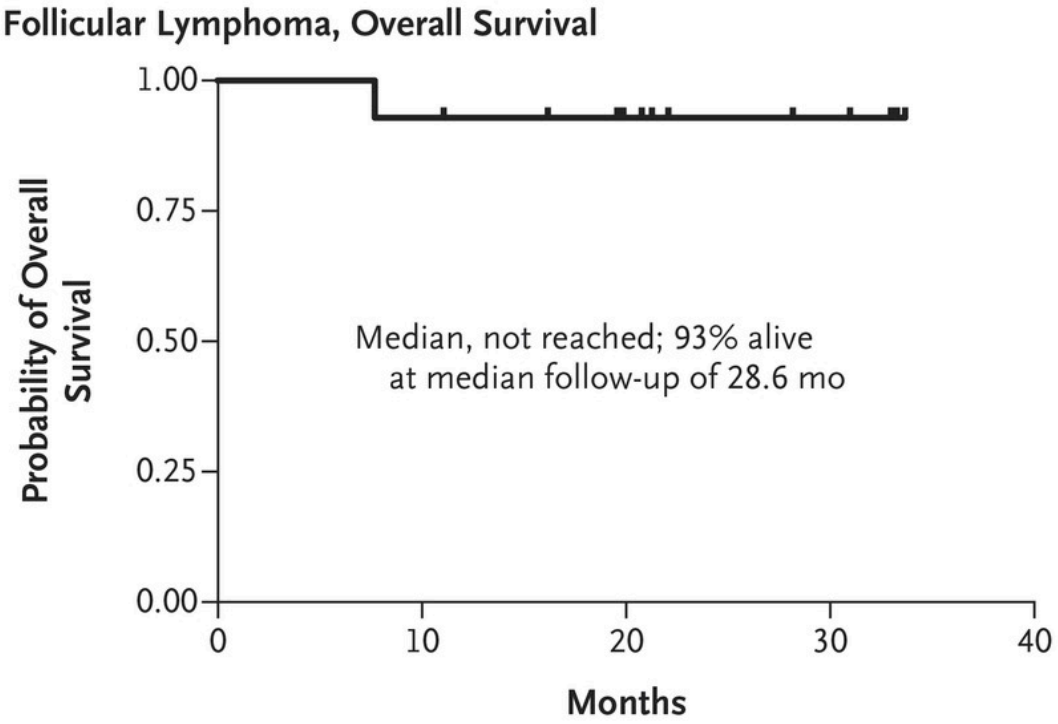
- With median follow-up of 27.1 months for 101 patients enrolled in phase II of the trial, the study found that 83% of patients had an objective response and 58% had a complete response.
- The median duration of response was 11.1 months (4.2–not estimable).
- The median overall survival was not reached (12.8 months–not estimable)
- The median progression-free survival was 5.9 months (95% confidence interval [CI] = 3.3–15.0 months).
- No new treatment-related deaths occurred during the additional follow-up.

ASH2018 abstract 2967

Tisagenlecleucel in B Cell Lymphoma

Overall Survival

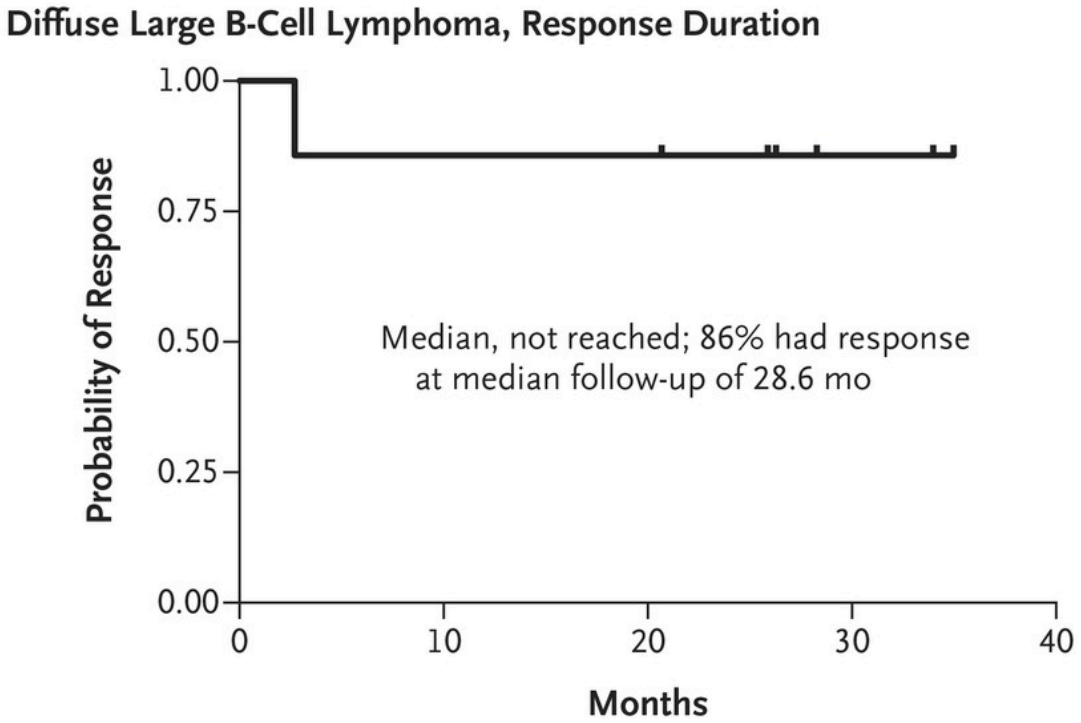


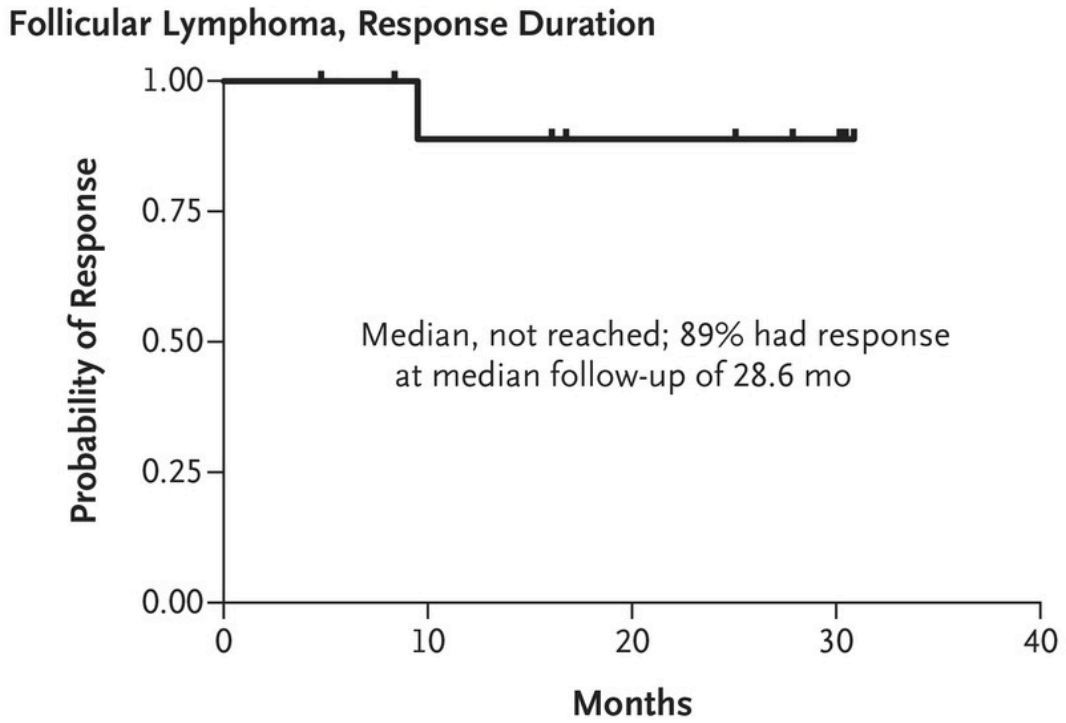


Schuster et al. NEJM 2017

Tisagenlecleucel in B Cell Lymphoma

Duration of Response





Schuster et al. NEJM 2017

Tisagenlecleucel in r/r DLBCL: updated analysis

- A total of 93 patients received an infusion and were included in the evaluation of efficacy.
- The median time from infusion to data cutoff was 14 months (range, 0.1 to 26).
- The best overall response rate was 52% (95% CI , 41 to 62)
- 40% of the patients had complete responses, and 12% had partial responses.
- At 12 months after the initial response, the rate of relapse-free survival was estimated to be 65% (79% among patients with a complete response).

Schuster et al. N Engl J Med 2019; 380:45-56

Tisagenlecleucel in r/r DLBCL: updated analysis

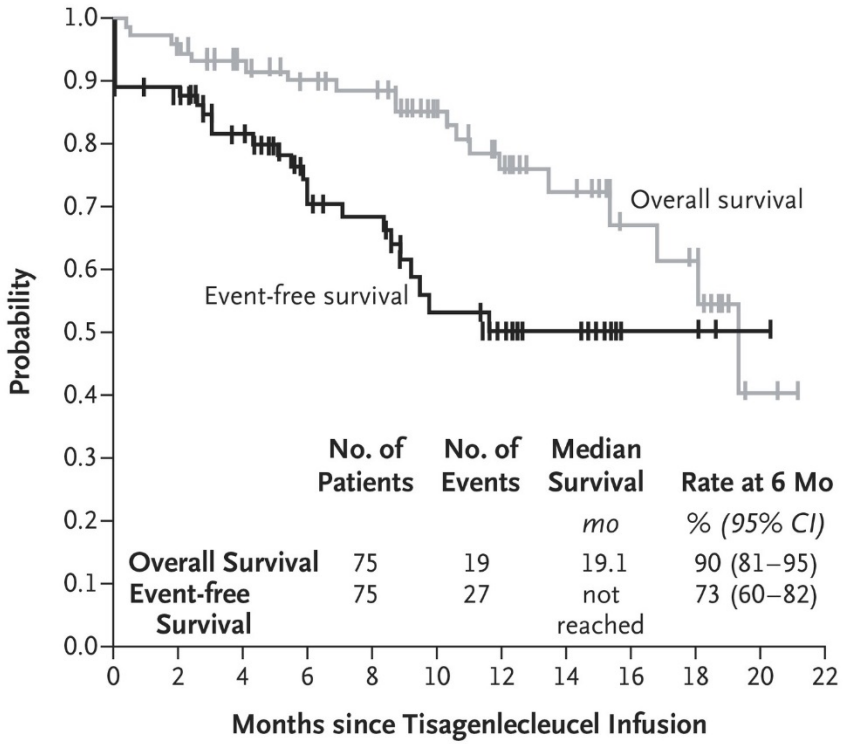
- The most common grade 3 or 4 adverse events of special interest included cytokine release syndrome (22%), neurologic events (12%), cytopenias lasting more than 28 days (32%), infections (20%), and febrile neutropenia (14%).
- Three patients died from disease progression within 30 days after infusion.
- No deaths were attributed to tisagenlecleucel, cytokine release syndrome, or cerebral edema.
- No differences between response groups in tumor expression of CD19 or immune checkpoint–related proteins were found

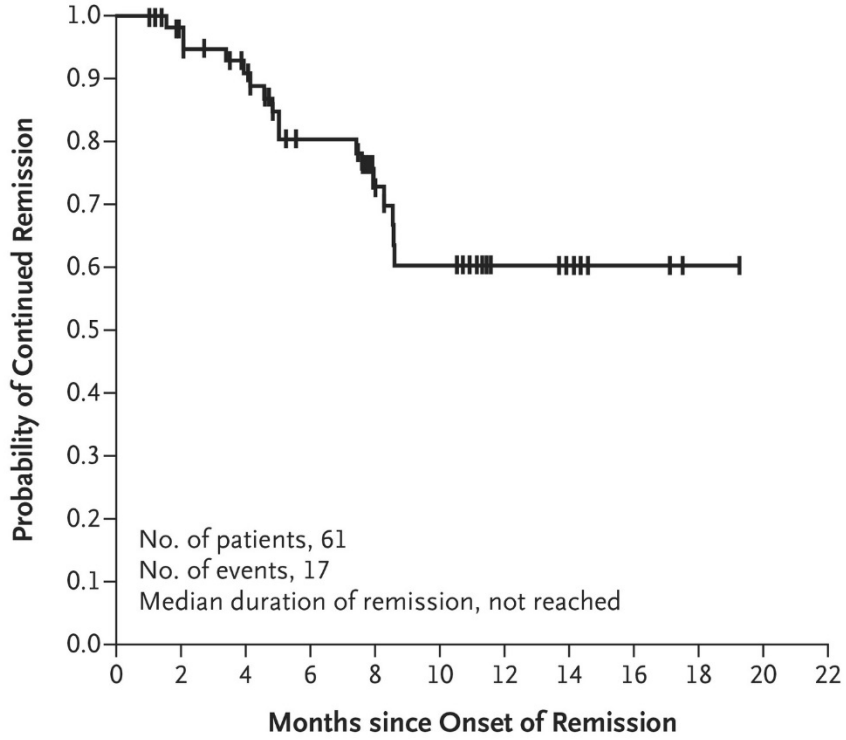
Schuster et al. N Engl J Med 2019; 380:45-56

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





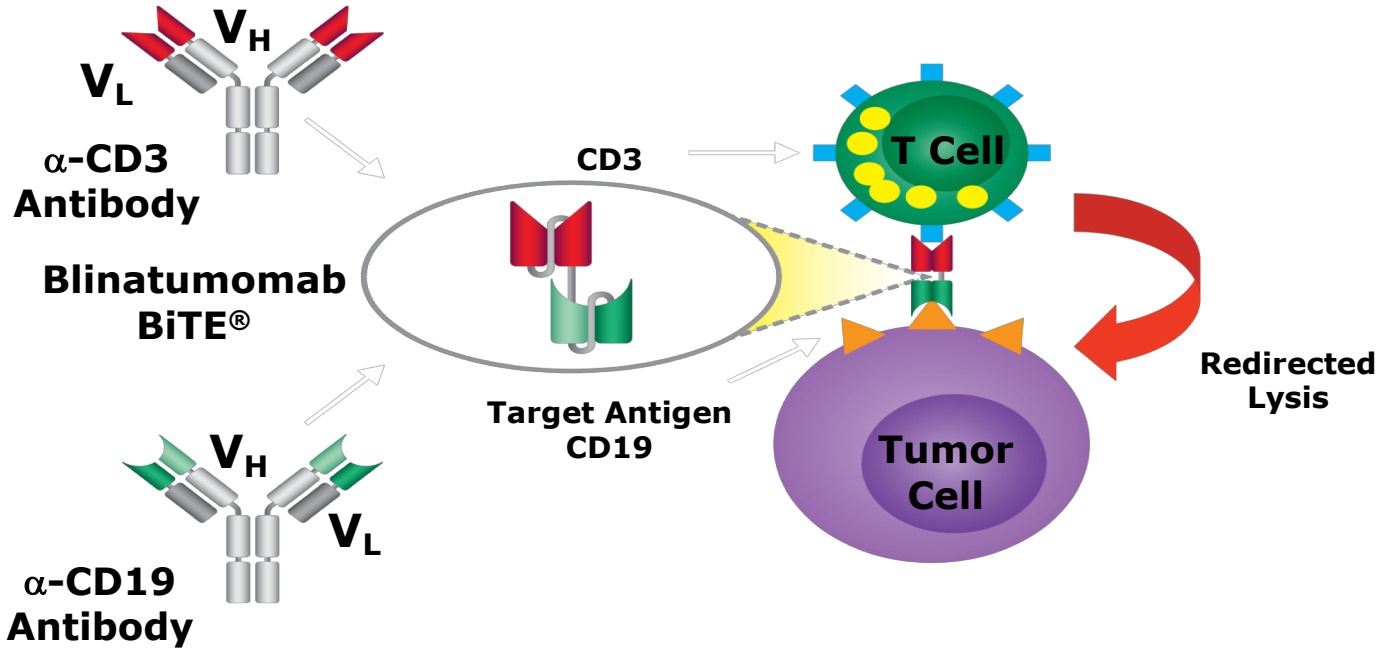
Maude et al. NEJM 2018

ELIANA update ASH 2018

- Median overall survival (OS) and median duration of response had not yet been reached (maximum duration of response = 29 months and ongoing).
- Responses remained ongoing in 29 patients.
- A total of 19 patients relapsed prior to receiving additional anti-cancer therapy, with 13 subsequent deaths.
- At 18 months, relapse-free survival was 66% (95% confidence interval 52%–77%), and OS was 70% (95% confidence interval 58%–79%).
- Of the 65 patients who achieved complete response, 64 patients (98%) were major residual disease negative within 3 months.

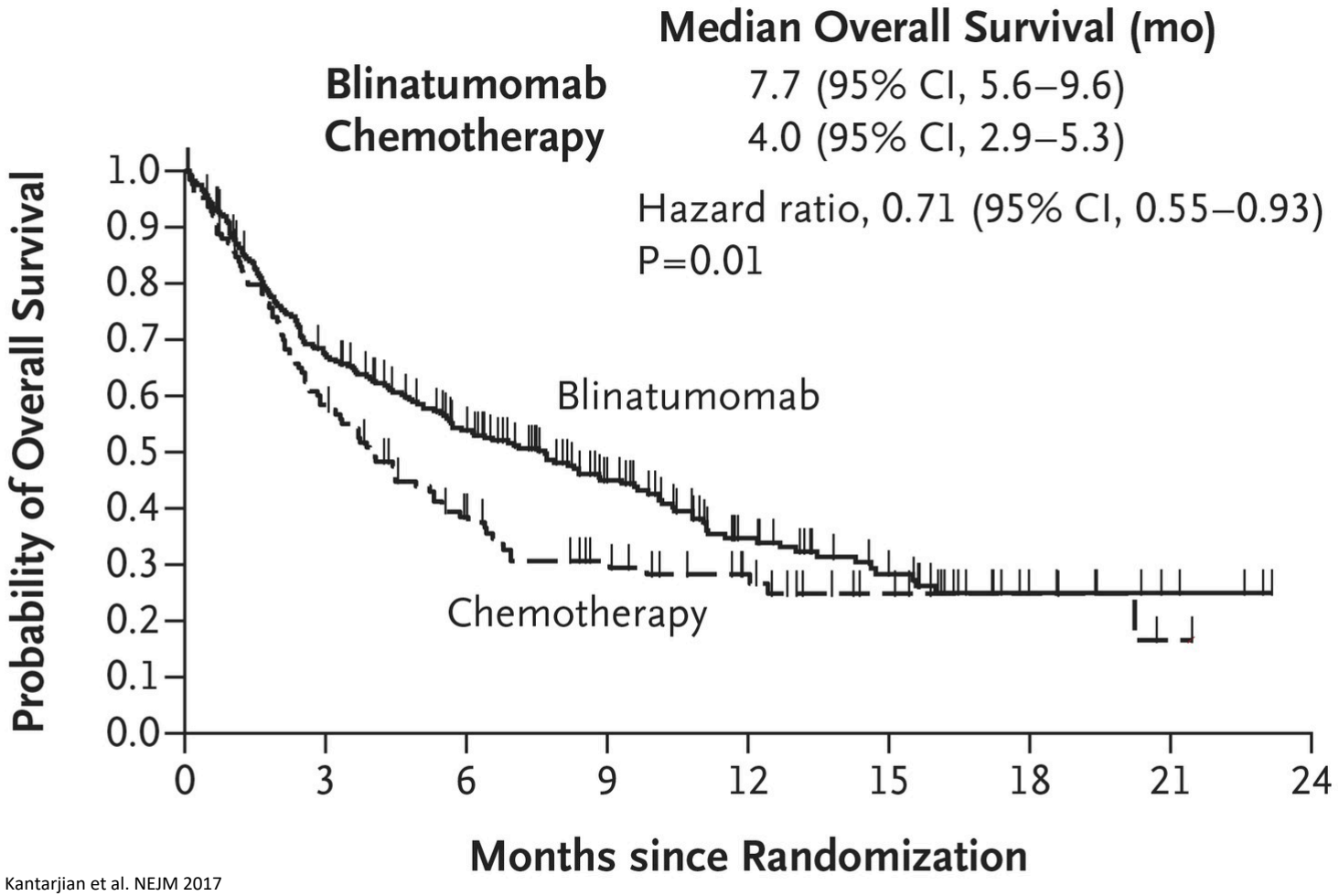
BiTE (Blinatumumab) Therapy

- 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

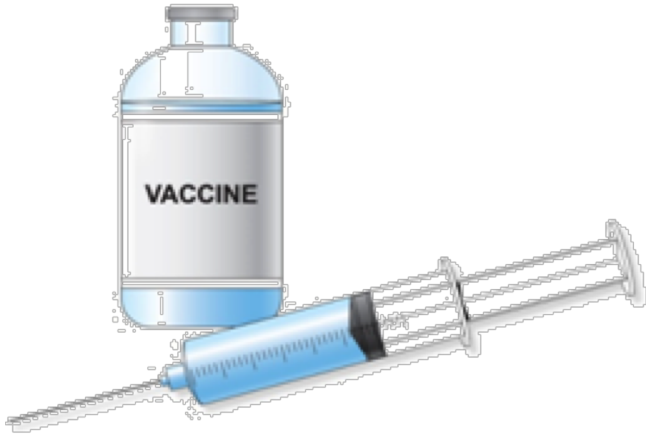
Blinatumomab for B-ALL



Kantarjian et al. NEJM 2017

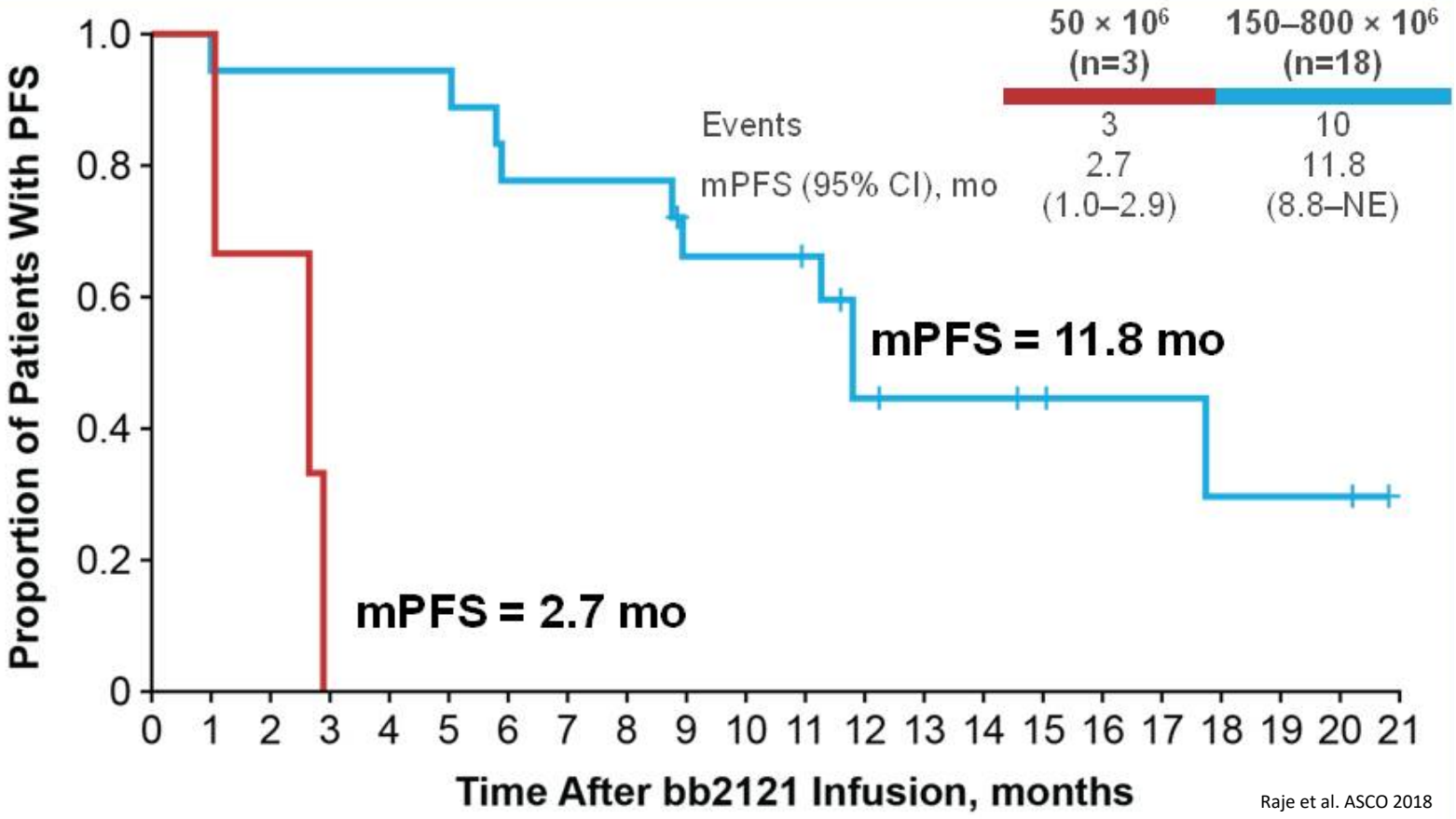
Immunotherapies for Multiple Myeloma

- 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

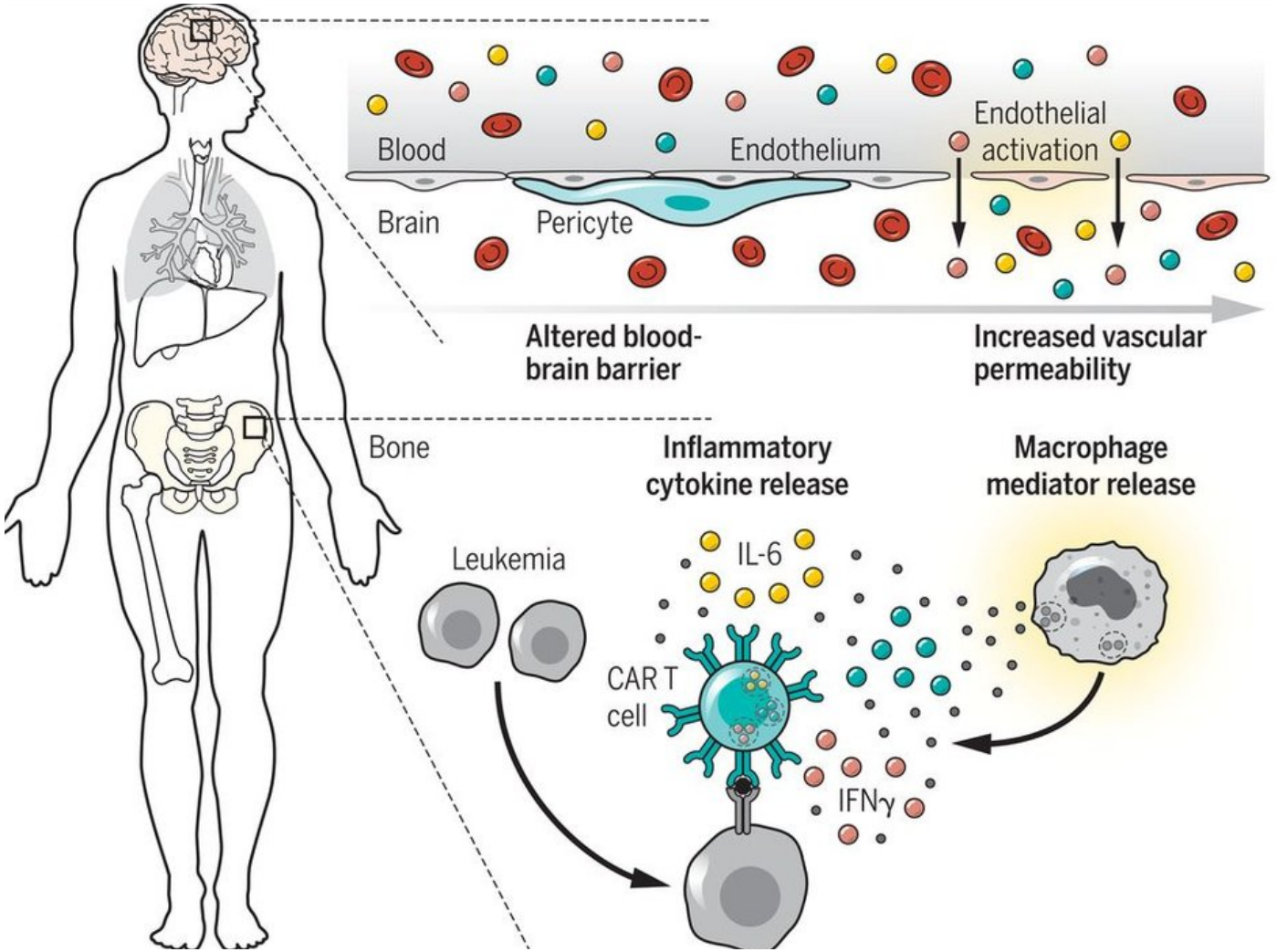


Raje et al. ASCO 2018

CAR T treatment

- LEGEND-2 study : rr MM pts treated with bispecific CAR T-cells targeting BCMA.
- ASH 2017: results reported on 19 patients, with 100 % response rate.
- ASH 2018: updated analysis included 57 patients.
- Ninety percent of patients experienced CRS but only one patient was reported to have neurotoxicity.
- The best overall response rate was 88 percent with a median duration of response of 16 months.
- The median progression free survival was 15 months.
- For patients who achieved very deep responses, as assessed by minimal residual disease (MRD) testing, the median progression free survival was 24 months.

Cytokine Release Syndrome (CRS)



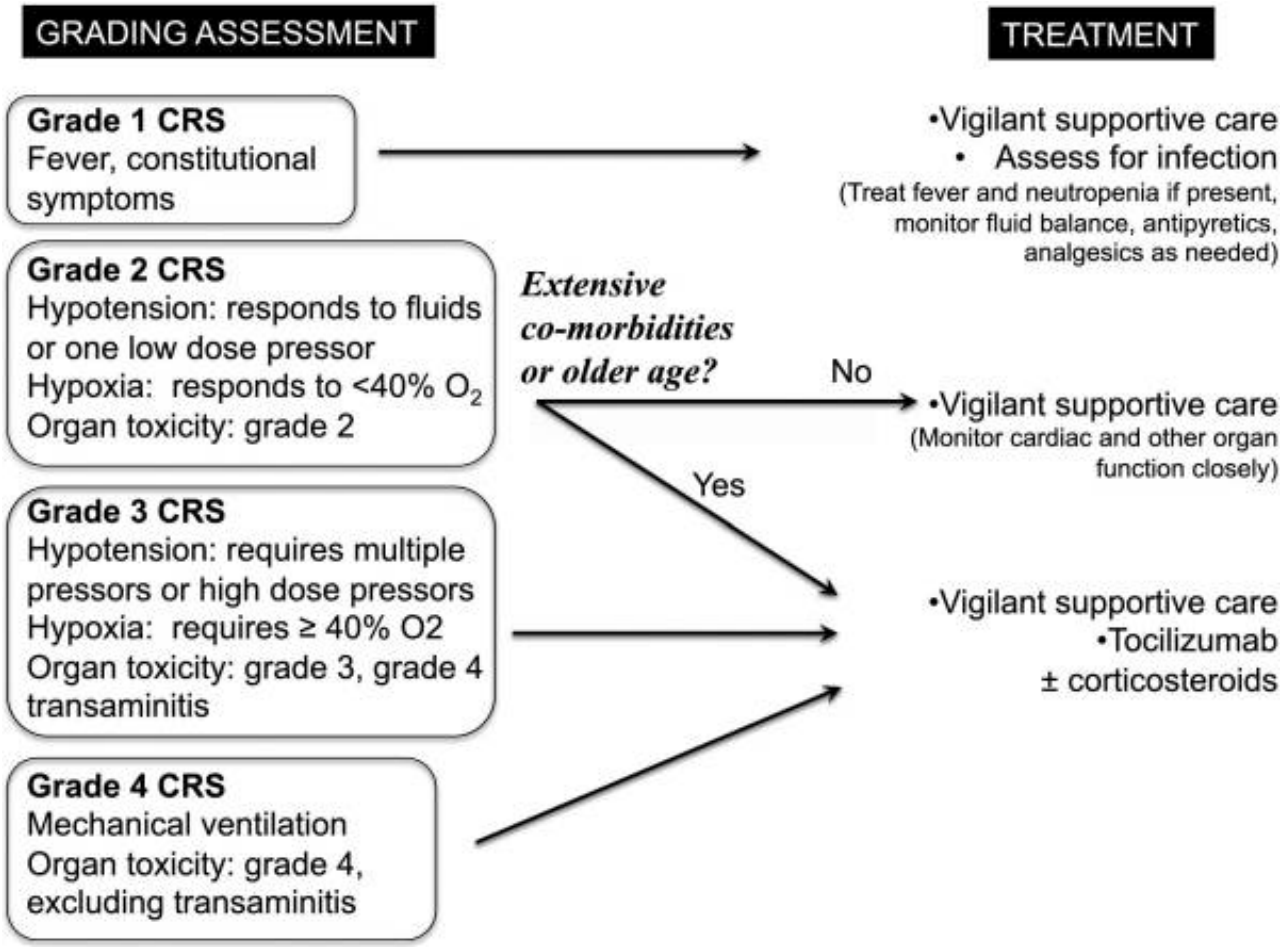
Neurotoxicity
Delirium
Aphasia
Seizures
Cerebral edema
Intracranial hemorrhage

Hemodynamic instability
Tachycardia
Hypotension
Capillary leak syndrome

Organ dysfunction
AST and ALT elevation
Hyperbilirubinemia
Respiratory failure

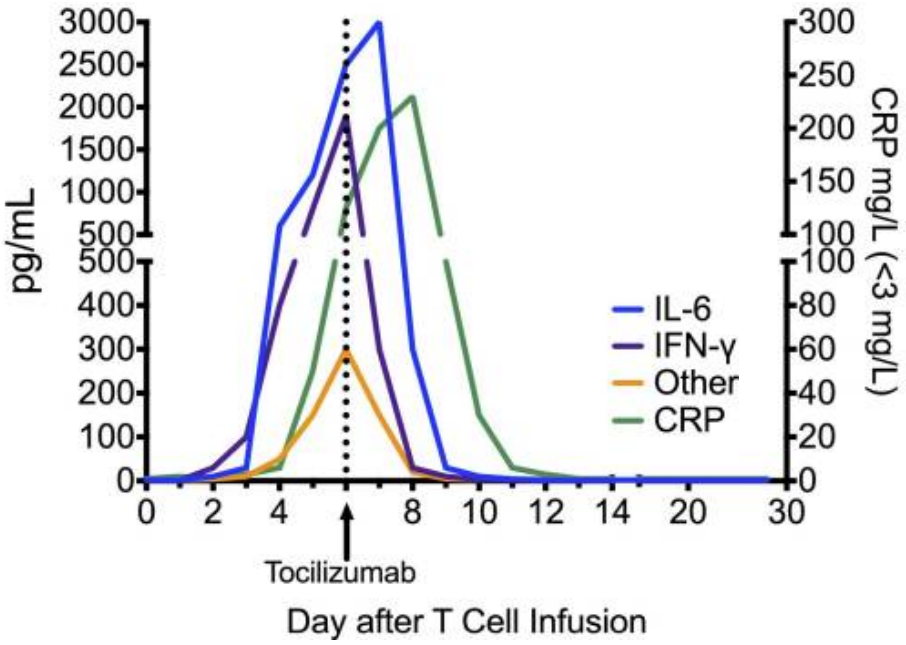
June et al. Science 2018

CRS management



Lee et al. Blood 2014

- Tocilizumab
  - Monoclonal antibody that blocks IL-6 signaling



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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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ACCC Association of Community Cancer Centers
sitc Society for Immunotherapy of Cancer

Case Study 1

- 63y/o lady diagnosed with acute mixed phenotypic Ph+ (p210) leukemia
- She had good performance status, with multiple siblings, and 1 sister was 10/10 match
- Initial plan was for allogeneic stem cell transplant in first CR
- Initial induction treatment was with Hyper CVAD
- She received Hyper CVAD cycles 1A, 1B, 2A with IT chemotherapy and Dasatinib
- There was no CNS involvement
- Bone marrow biopsy after 3 cycles demonstrated complete morphologic response.

Case Study 1

- She was on maintenance Dasatinib
- Developed cardio-respiratory complications ,Dasatinib was held
- She was off of ALL treatments for about 5 months
- No evidence of relapse in peripheral blood
- Refused follow up bone marrow biopsy

Case Study 1

- 5 months later, she presented with increasing WBC counts
- Repeat bone marrow biopsy demonstrated r**elapsed disease**, morphologically similar to initial diagnosis and was Ph +
- She was treated with Hyper CVAD again and completed 3 cycles again
- She however, refused TKI due to complications previously
- CNS involvement was still absent

Case Study 1

- She eventually presented with increasing WBC count, of > 100k
- A repeat bone marrow biopsy again demonstrated relapsed acute bi-phenotypic leukemia , Ph +
- Blasts were mostly positive for lymphoid lineage markers, with very scant myeloid markers
- No CNS disease
- She received 1 cycle Blinatumomab
- No CRS
- However, continued to have persistently high WBC count after C1
- Treatment changed to Clofarabine

Case study 2

- 62y/o male presented with several weeks back pain, weight loss
- Imaging showed pathologic rib fractures, retro peritoneal adenopathy
- Bone biopsy revealed grade 2 /admixed with grade 3a follicular lymphoma
- Initially treated with Rituximab-Bendamustine, with no response after 3 cycles
- Treatment changed to Ofatumumab – CHOP
- Minimal response by PET after 3 cycles
- PS= ECOG 1

Case Study 2

What is the next course of action?

1. Continue the current treatment
2. Biopsy and change treatment to EPOCH if transformed to DLBCL
3. Biopsy and change treatment to ICE if transformed to DLBCL
4. Autologous stem cell transplantation
5. Clinical trial
6. CAR-T

Case Study 2

- Biopsy of mass showed CD 20+ large cell lymphoma
- Treatment changed to R-ICE
- Repeat imaging after 2 cycles shows mixed response, with areas of decreased PET avidity and areas of increased avidity
- His performance status has declined slightly but still ECOG 1

Case Study 2

What is the next course of action?

1. Continue the current treatment and re-image after 2 more cycles
2. Autologous stem cell transplantation
3. Allogeneic stem cell transplantation
4. Clinical trial
5. CAR-T therapy