sitc 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

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Disclosures

Research Support	Canadian Cancer Society, Leukemia and Lymphoma Society Canada, Princess Margaret Cancer Foundation, Roche, Janssen
Consultant	Abbvie, BMS, Gilead, Janssen, Karyopharm, Merck, Roche, Seattle Genetics
Honoraria	Amgen, BMS, Celgene, Gilead, Janssen, Karyopharm, Lundbeck, Merck, Novartis, Roche, Seattle Genetics
Scientific Advisory Board	Lymphoma Canada (Chair)

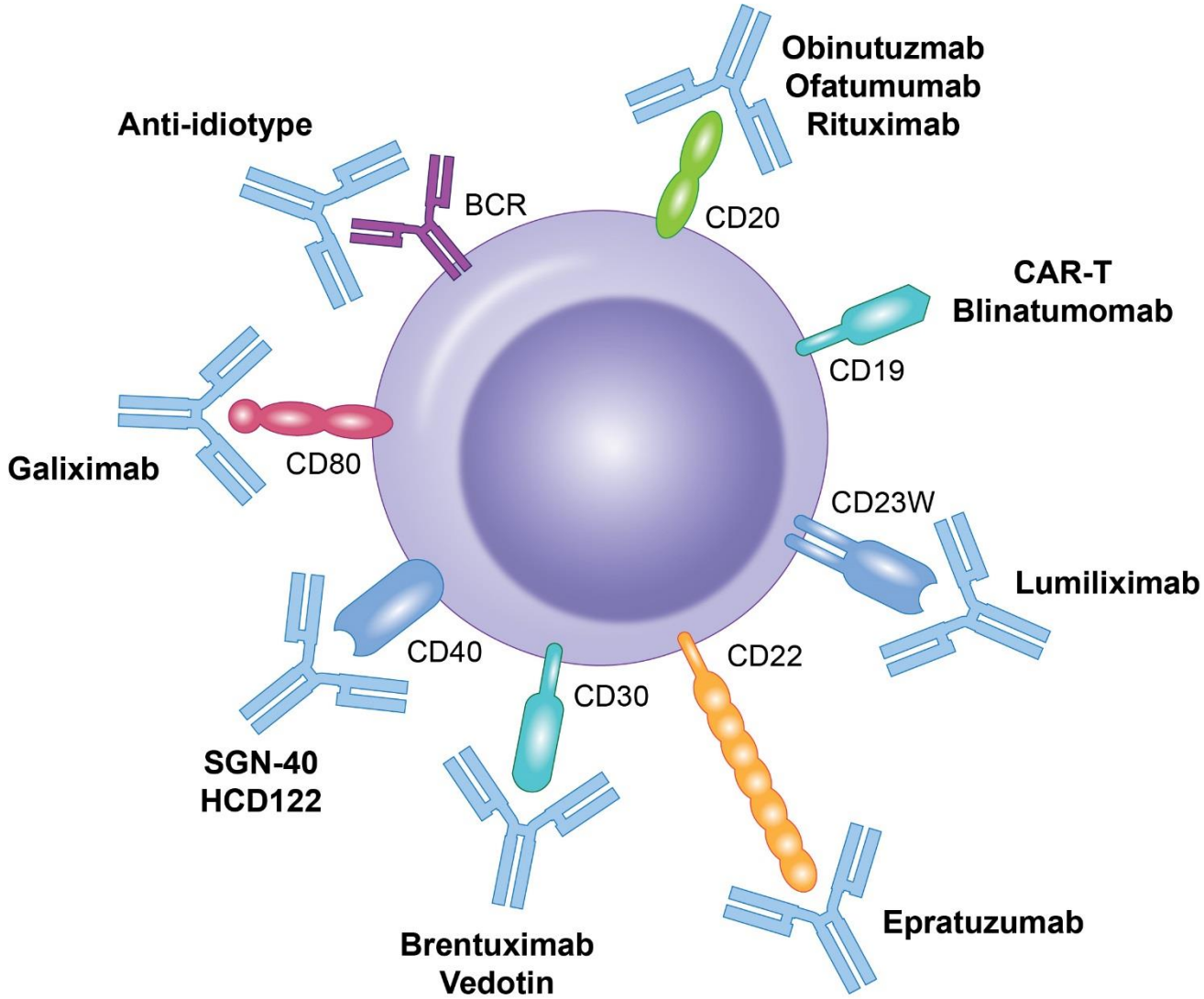
- I will be discussing non-FDA approved indications during my presentation.

- Data being presented concerns immunotherapies approved by the U.S Food and Drug Administration for marketing and usage in the United States

Immunotherapy and Hematology

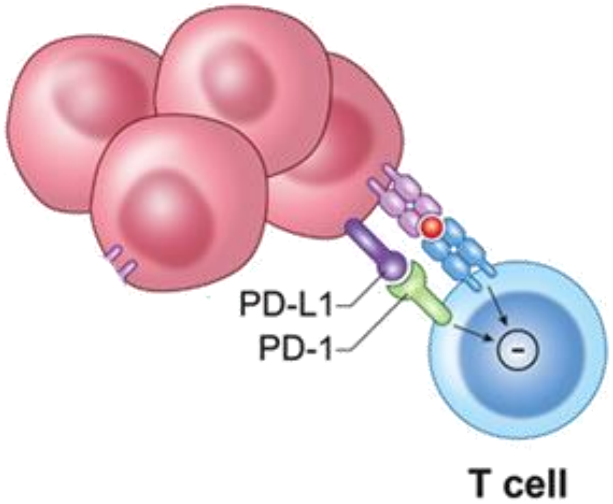
- Old school
  - Stem Cell transplantation
    - Graft-versus tumour effect (leukemia, lymphoma)
    - High dose chemotherapy (myeloablation and immune ablation)
  - Immuno-modulatory therapy
    - Alkylators and fludarabine
    - Antibodies – rituximab, alemtuzumab
- New School
  - Cell therapies
    - Chimeric Antigen Receptor T cells (CD19, other)
    - CTLs (viral specific)
  - Antibodies
    - New targets (immune checkpoint and others)
    - Antibody drug conjugates (CD30, CD19, CD33 and other)
    - Bispecific antibodies (T cell, NK)

Monoclonal Antibodies Targeting B Cell Lymphomas



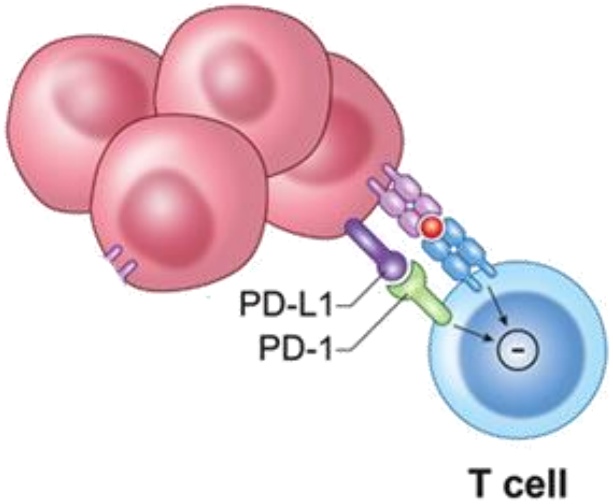
FDA-approved Checkpoint Inhibitors for Lymphomas

- 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

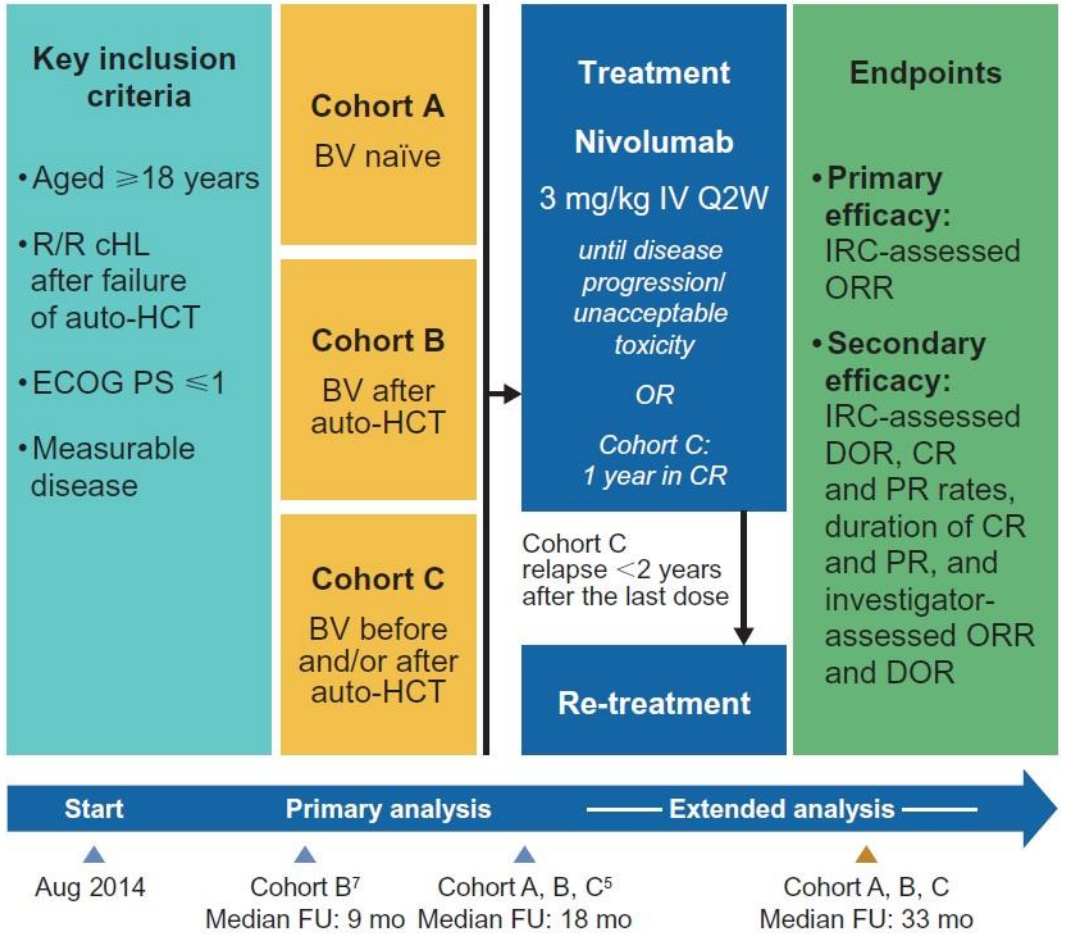


Patient Selection Criteria for Checkpoint Inhibitor Therapies

- 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

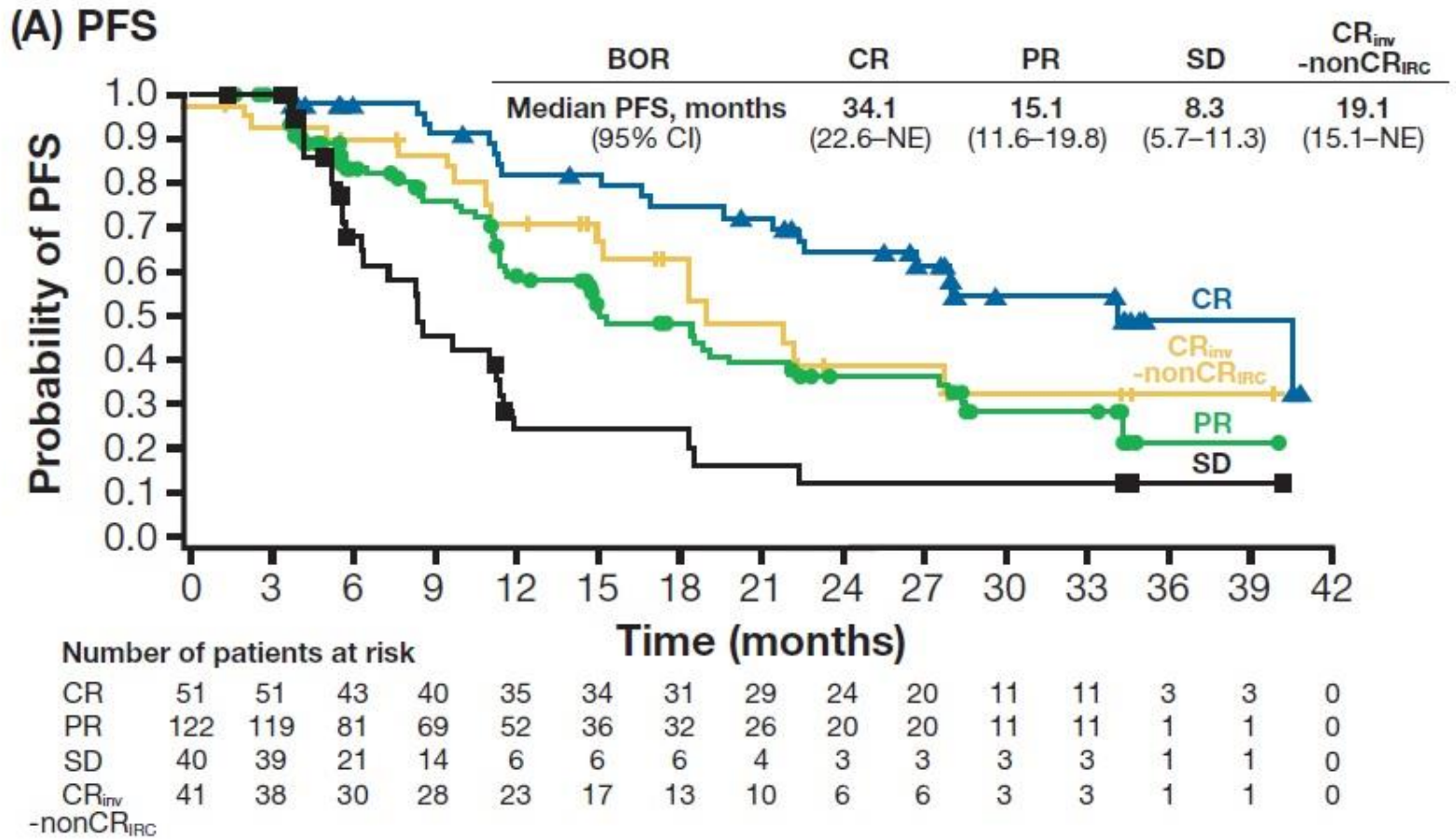


CheckMate 205 R/R cHL Study: ASH 2018



- BV, brentuximab vedotin; CR, complete remission; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FU, follow-up; PR, partial remission

Checkmate 205: PFS by BOR



- PFS and responses were per IRC unless noted otherwise

Checkmate 205: Most common TRAEs (≥10% any Grade or ≥3% Grade 3–4)

Event	All treated patients (N = 243)	
	Any grade	Grade 3–4
TRAEs	195 (80)	65 (27)
Frequent (⩾10%) or grade 3–4 (⩾3%) TRAEs		
Fatigue	59 (24)	2 (1)
Diarrhea	39 (16)	2 (1)
Infusion-related reaction	34 (14)	1 (<1)
Rash	29 (12)	2 (1)
Nausea	28 (12)	0
Pruritus	26 (11)	0
Increased lipase	22 (9)	14 (6)
Increased ALT	19 (8)	8 (3)
Neutropenia	16 (7)	9 (4)
AEs by categories		
IMAE (⩾5%)		
Rash	26 (11)	4 (2)
Hepatitis	13 (5)	10 (4)
Hypersensitivity	13 (5)	2 (1)
Pneumonitis	13 (5)	1 (<1)
Tx-related infections and infestations	36 (15)	6 (2)

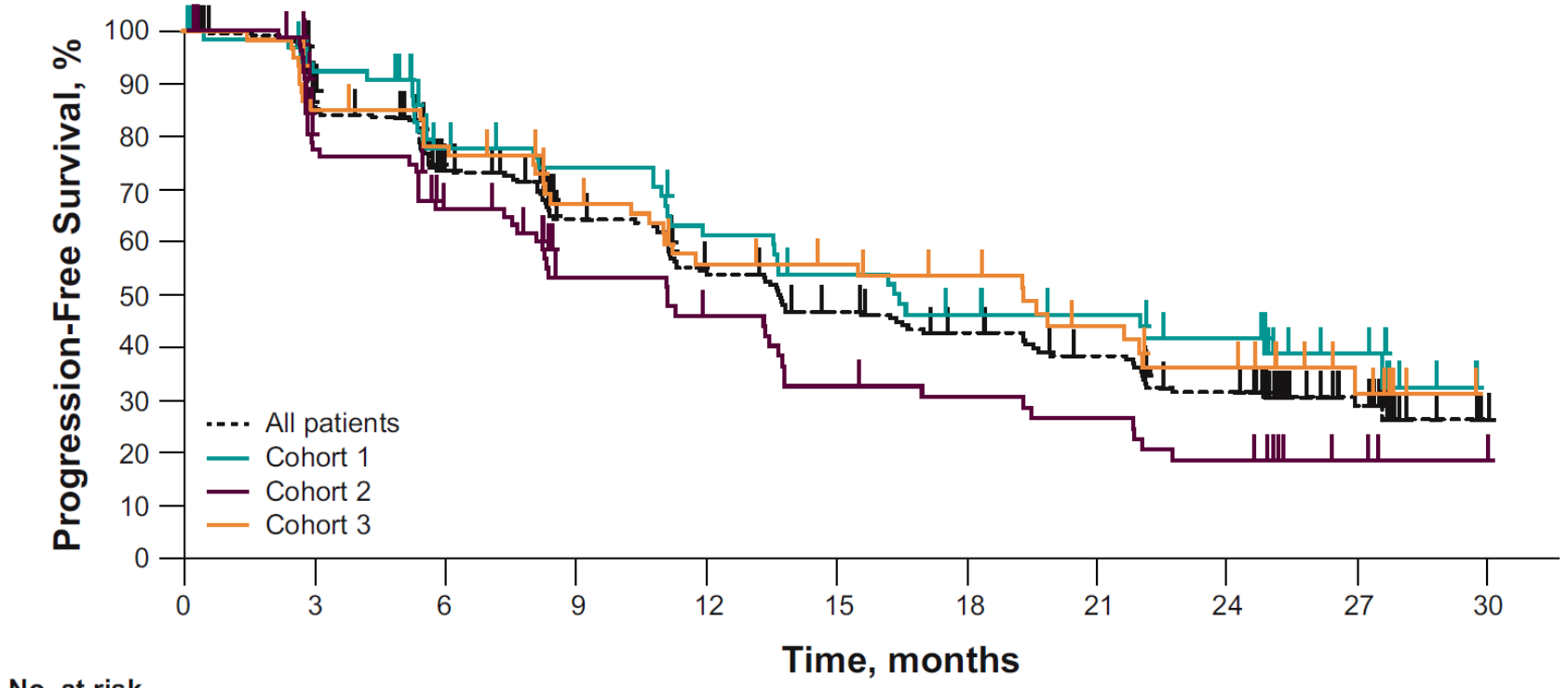
- Data are reported as n (%)
- ALT, alanine aminotransferase, Tx, treatment

Keynote 87 R/R-HL: ASH 2018

- The multicenter, single-arm, phase 2 KEYNOTE-087 study was conducted to evaluate pembrolizumab in 3 patient cohorts
  - Cohort 1: R/R cHL after ASCT and subsequent BV therapy
  - Cohort 2: ineligible for ASCT, no response to salvage chemotherapy, and unsuccessful BV therapy
  - Cohort 3: R/R cHL after ASCT but not treated with BV after ASCT
- Patients received 200 mg pembrolizumab every 3 weeks for a maximum of 24 months or until documented confirmed disease progression, intolerable toxicity, or study withdrawal
- Re-treatment with pembrolizumab was allowed in patients who experienced disease progression if the patient
  - Experienced complete response (CR), determined by investigator review, on first course
  - Stopped initial treatment after substantiation of CR by investigator assessment per International Working Group Revised Response Criteria for Malignant Lymphomas (RRCML) criteria1
  - Received pembrolizumab for ≥24 weeks before discontinuing treatment, received ≥2 pembrolizumab doses beyond the date when initial CR was declared, and continued to meet eligibility criteria
  - Patients received pembrolizumab 200 mg every 3 weeks for a maximum of 24 months or until documented confirmed disease progression, intolerable toxicity, or study withdrawal

1. Cheson BD et al. *J Clin Oncol.* 2007;25(5):579-586.

Kaplan-Meier Analysis of Progression-Free Survival[a] in All Patients and by Cohort



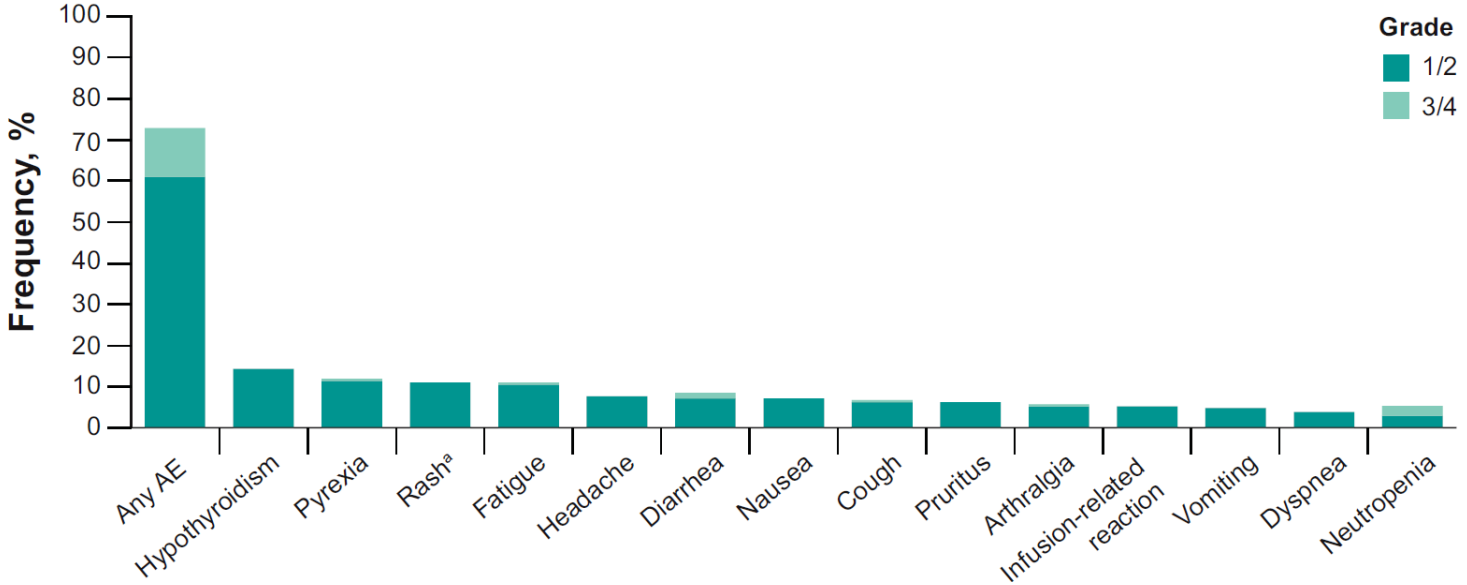
No. at risk

210	167	134	106	85	71	61	51	39	19	0
69	61	45	41	33	28	23	21	17	9	0
81	56	44	29	24	17	15	13	9	3	0
60	50	45	36	28	26	23	17	13	7	0

[a]From product limit (Kaplan-Meier) method for censored data.
Data cutoff: Mar 21, 2018

Treatment-Related Adverse Events Occurring in ≥2% of All Patients (N = 210)

Zinzani KN087 ASH 2018

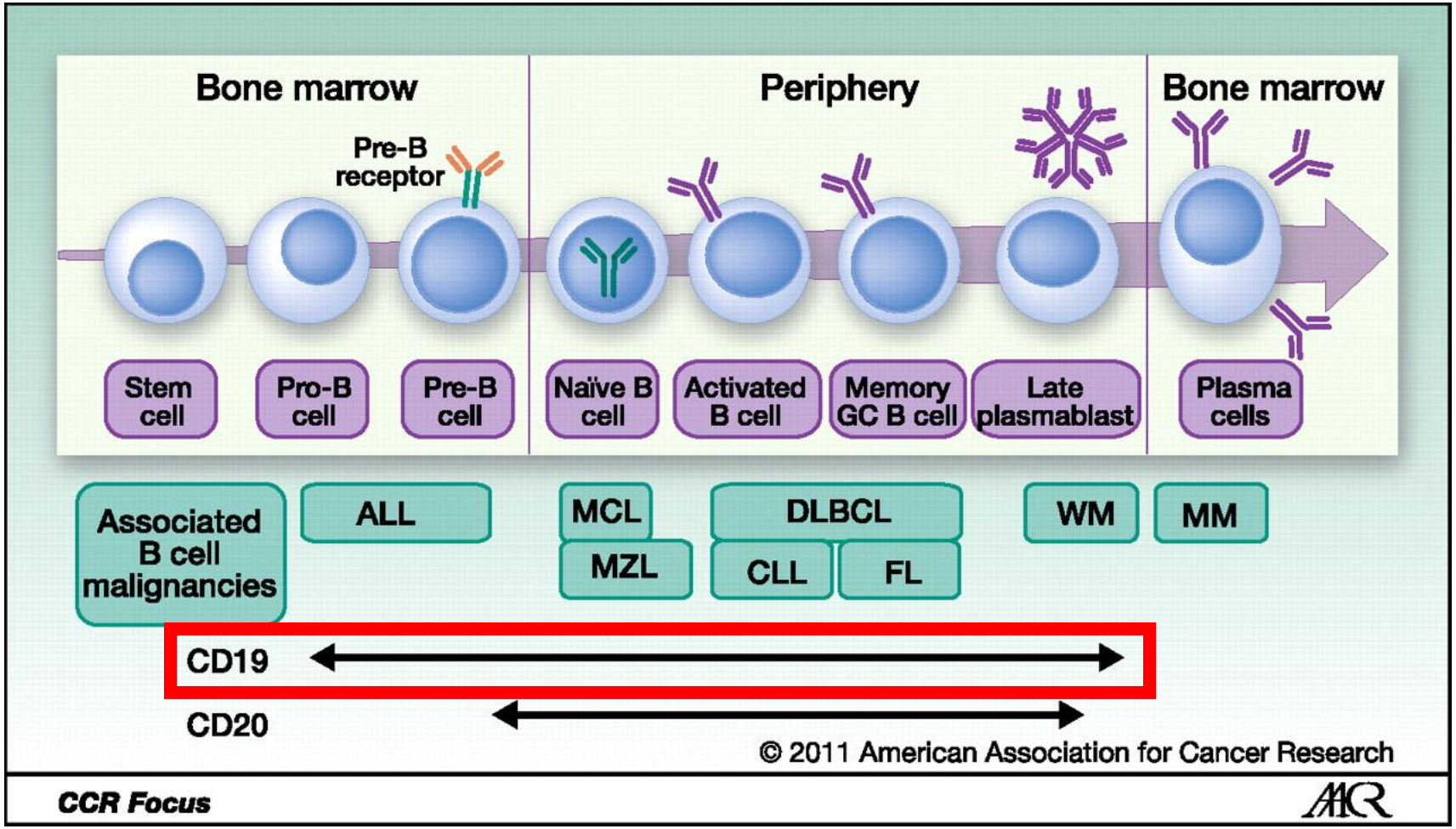


AE, adverse event.
[a]Excludes erythematous, macular, papular, and maculopapular rash.
Data cutoff: Mar 21, 2018.

Checkpoint inhibitors in Lymphoma

- Active agents in diseases where there is a biologic basis for activity
  - HL: amplification at 9p leads to upregulation of this pathway
  - NHL: activity in subsets with similar biology (PMBL) or where other mechanisms may support upregulation of checkpoint (EBV-driven lymphomas)
- Confirmatory RCTs underway in RR-HL to define superiority
  - Keynote 204 and Checkmate 812
- Multiple trials including second-line curative and front-line studies underway

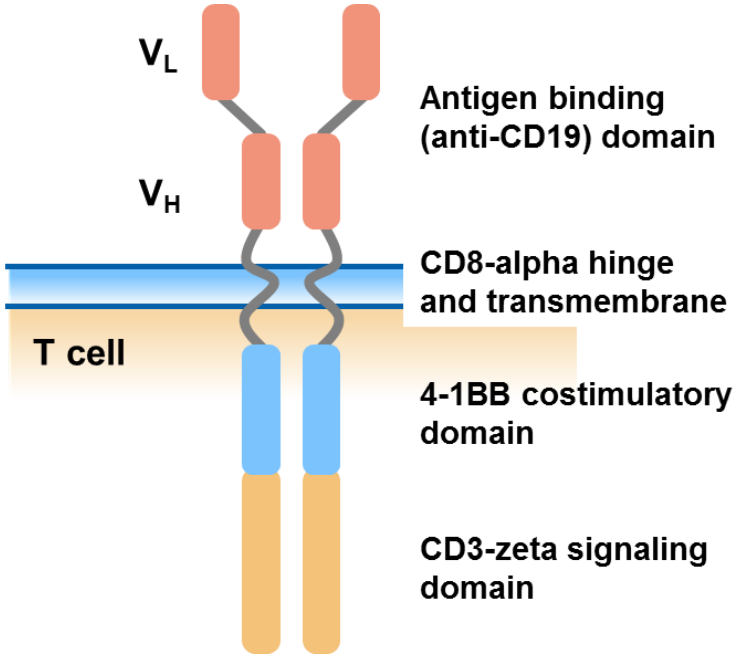
B Cell Malignancies are CD19+

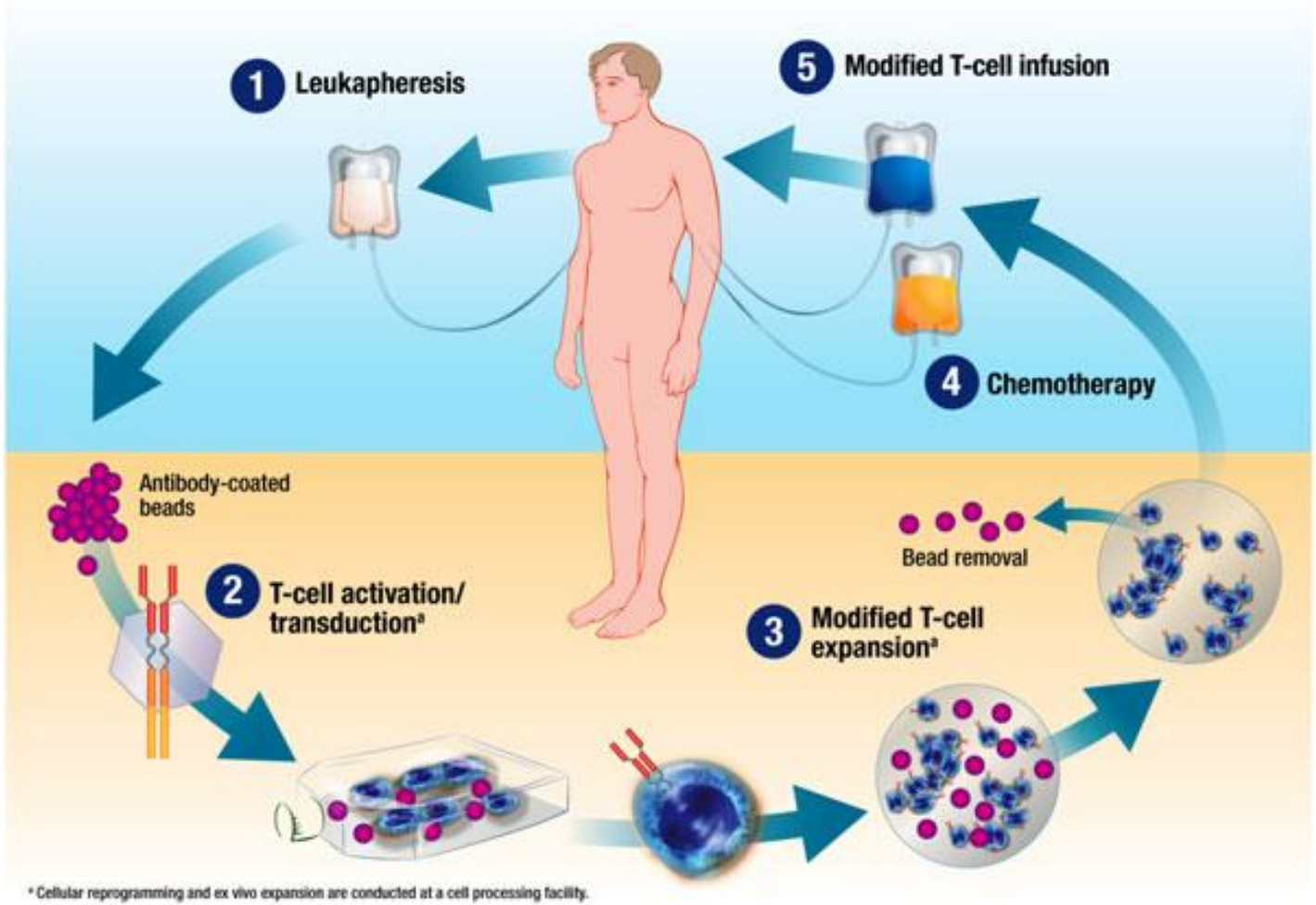


Blanc et al. Clinical Cancer Research 2011

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

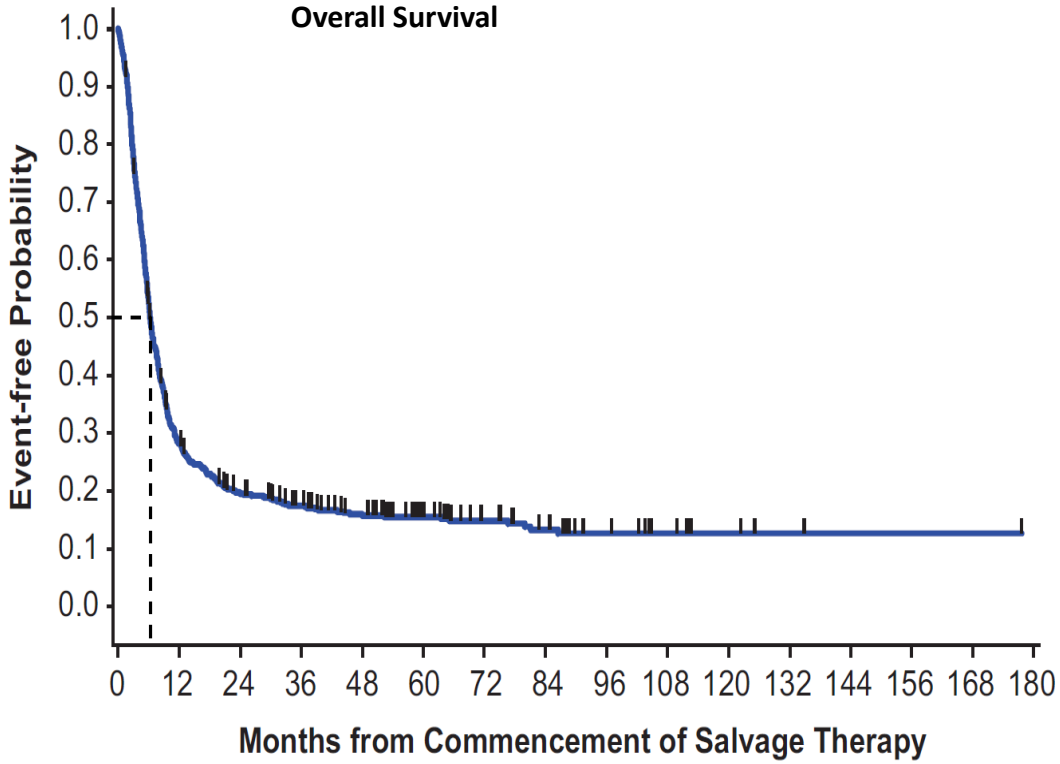
- Axicabtagene ciloleucel
  - ZUMA-1: Adult patients with relapsed or refractory large B cell lymphoma after two or more lines of systemic therapy, including diffuse large B cell lymphoma, high-grade B cell lymphoma, and DLBCL arising from follicular lymphoma
- Tisagenlecleucel
  - JULIET: adult patients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

SCHOLAR-1 (Retrospective Non-Hodgkin Lymphoma Research)

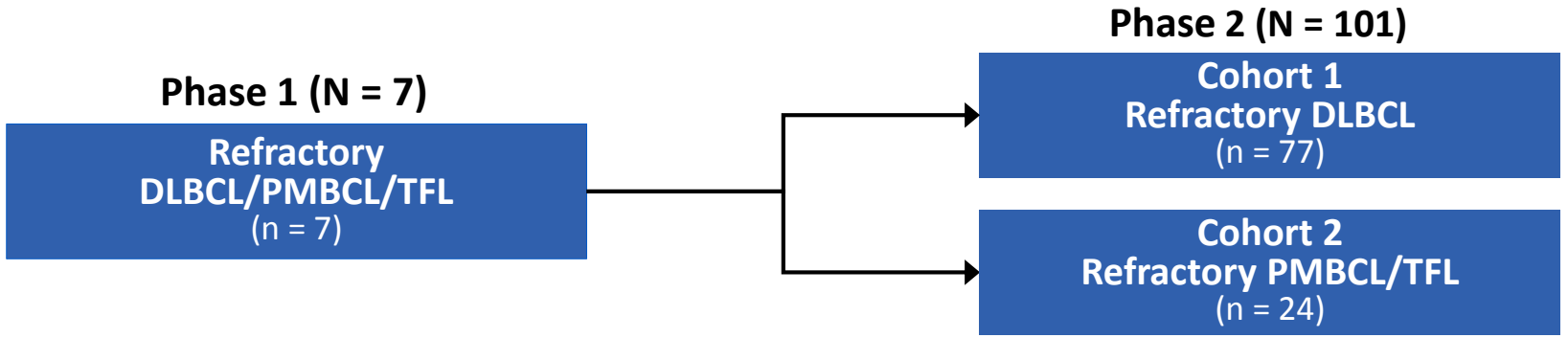
- SCHOLAR-1, a retrospective, international, patient-level, multi-institution study and the largest reported analysis of outcomes in patients with refractory large B cell lymphoma, demonstrated that these patients have a very poor prognosis[1]
  - N = 636 (post-rituximab era, 2000-2017)
  - ORR = 26%
  - CR rate = 7%
  - Median OS = 6.3 months
  - These results provided a benchmark for evaluation of new approaches



CR, complete response; ORR, objective response rate; OS, overall survival.

1. Crump M, et al. *Blood*. 2017;130:1800-1808..

ZUMA-1: Updated Analysis



Key eligibility criteria

- No response to last chemotherapy or relapse ≤ 12 mo post-ASCT
- Prior anti-CD20 monoclonal antibody and anthracycline

Conditioning regimen

- Cyclophosphamide 500 mg/m^2 + fludarabine 30 mg/m^2 for 3 days

Axi-cel: 2 × 10^6 CAR+ cells/kg

- 99% enrolled were successfully manufactured
- 91% enrolled were dosed

ASCT, autologous stem cell transplant.

Neelapu ASH 2018

Baseline Characteristics

Characteristic	DE/HGBCL (n = 37)	Overall (N = 108)
Median age (range), y	60 (28 – 76)	58 (23 – 76)
≥ 65, n (%)	9 (24)	27 (25)
Male, n (%)	25 (68)	73 (68)
ECOG 1, n (%)	22 (59)	62 (57)
Disease stage III/IV, n (%)	29 (78)	90 (83)
IPI score 3 – 4, n (%)	15 (41)	48 (44)
≥ 3 Prior therapies, n (%)	28 (76)	76 (70)
Refractory Subgroup Before Enrollment	**(n = 37)**	**(N = 108)**
Refractory to second- or later-line therapy, n (%) Best response as PD to last prior therapy	29 (78) 22 (59)	80 (74) 70 (65)
Relapse post-ASCT, n (%)	8 (22)	25 (23)

ASCT, autologous stem cell transplantation; DE/HBGCL, double-expressor or high-grade B cell lymphoma; ECOG, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; PD, progressive disease.

Neelapu ASH 2018

Objective and Ongoing Response Rates

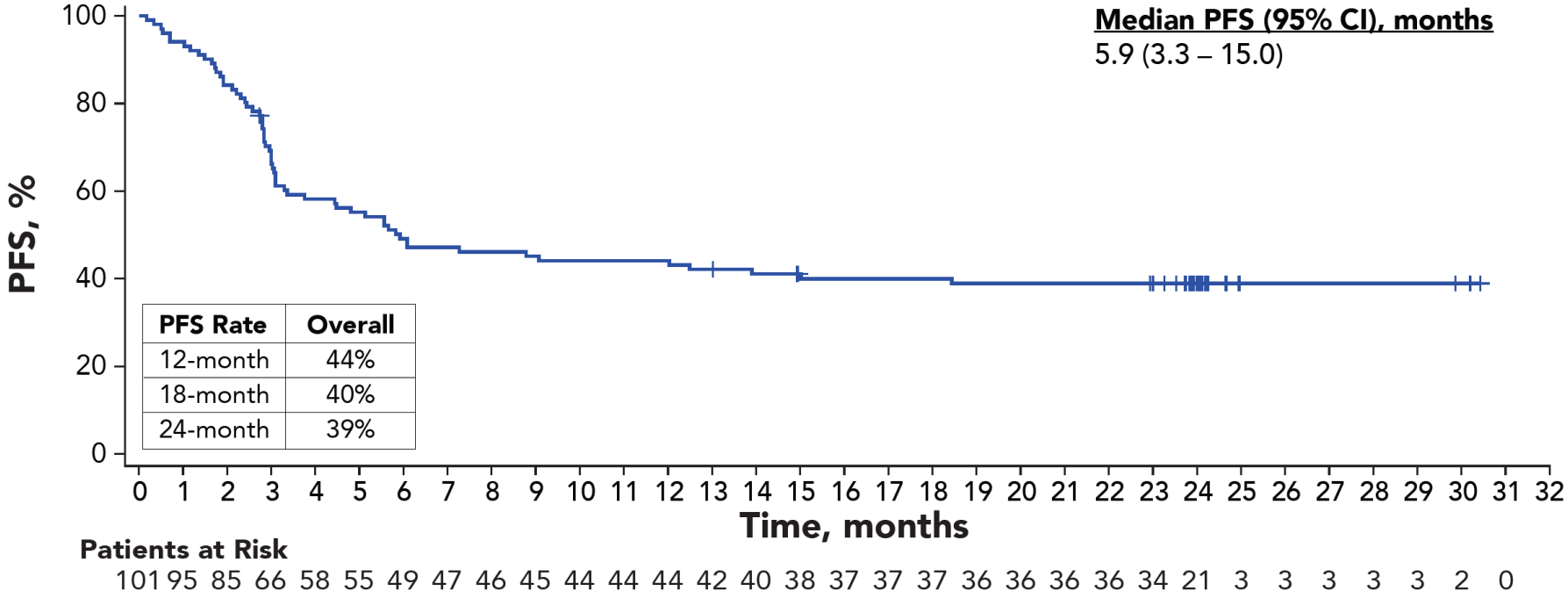
	Investigator-Assessed (n = 101)		Central Review (n = 101)	
	ORR	CR	ORR	CR
Best objective response, %	83	58	74	54
Ongoing, %[a]	39	37	36	35

- 93% of patients with ongoing response at 12 months remained in response at 24 months
- 81% concordance of ORR between investigator assessment and central review
- 91% ORR and 70% CR rate for the 33 Phase 2 patients with DE/HGBCL
  - 48% in ongoing response (all ongoing CR)
- Only 5% (2/39) ongoing responders underwent allogeneic SCT, and none received autologous SCT

[a]Three patients with ongoing response per investigator review were not ongoing responders per central review. Two of these patients underwent SCT prior to documented progression, which was considered a censor event per central review but not per investigator assessment. The third patient was deemed to have PD per central review after 10.9 months but was assessed to be in ongoing response at 23.4 mo per investigator.
DE/HBGCL, double-expressor or high-grade B cell lymphoma; SCT, stem cell transplantation.

Neelapu ASH 2018

Progression-Free Survival

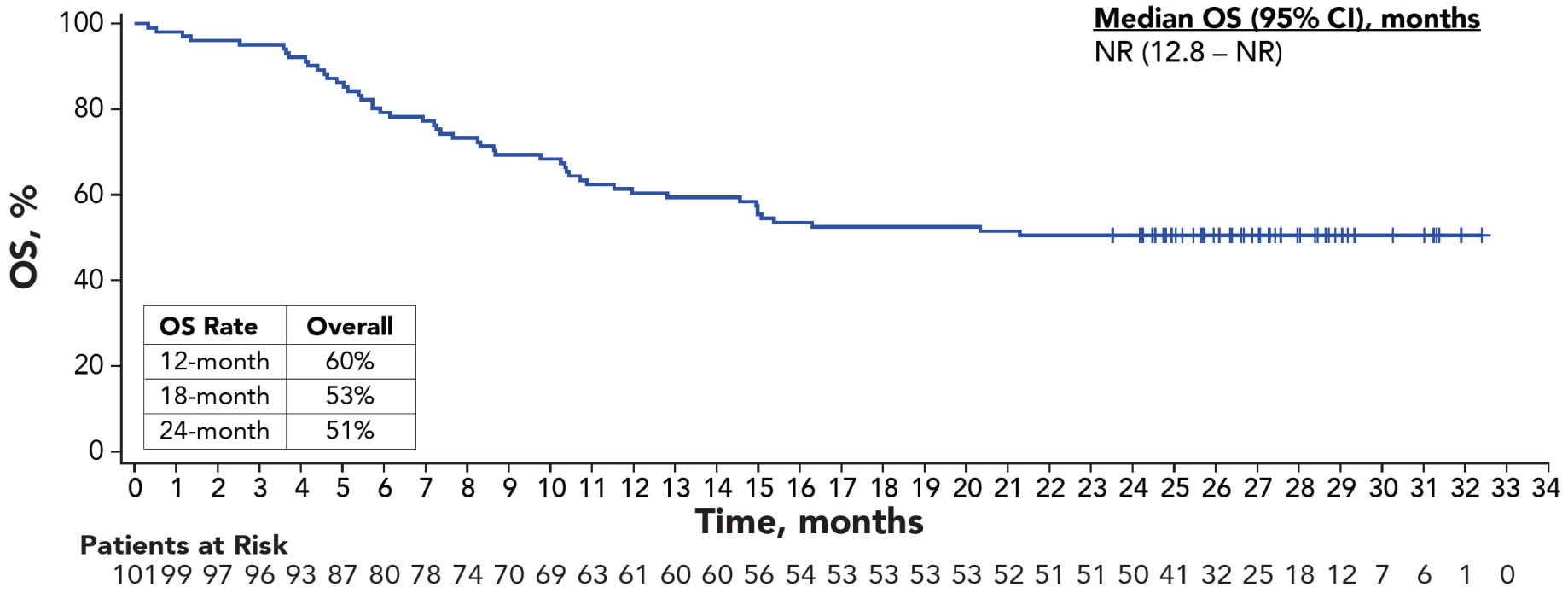


- The 6-month plateau was largely maintained, with only 10 patients progressing beyond the 6-month follow-up

NR, not reached; PFS, progression-free survival.

Neelapu ASH 2018

Overall Survival



- Median OS was not reached

NR, not reached; OS, overall survival.

Neelapu ASH 2018

Summary of Adverse Events

AE, n (%)	1-Year Analysis (N = 108)	2-Year Analysis (N = 108)
Grade ≥ 3 AEs	105 (97)	106 (98)
Grade ≥ 3 SAEs	50 (46)	52 (48)
Grade ≥ 3 CRS[a]	13 (12)	12 (11)
Grade ≥ 3 NEs[a]	33 (31)	35 (32)
Grade 5 AEs	4 (4)[b]	4 (4)

- No new axi-cel–related CRS, NEs, or Grade 5 AEs since the 1-year follow-up
- No cases of replication-competent retrovirus or axi-cel–related secondary cancers have been reported

[a]Differences in CRS and NE between the 1-year and 2-year analysis are due to revised coding following data audit. [b]As previously reported, Grade 5 AEs occurred in 4 patients.[1,2]

1. Neelapu SS, et al. *N Engl J Med.* 2017;377:2531-2544. 2. Locke FL, et al. *Mol Ther.* 2017;25:285-295.

SAE, serious AE.

Neelapu ASH 2018

Late-Onset Serious Adverse Events[a]

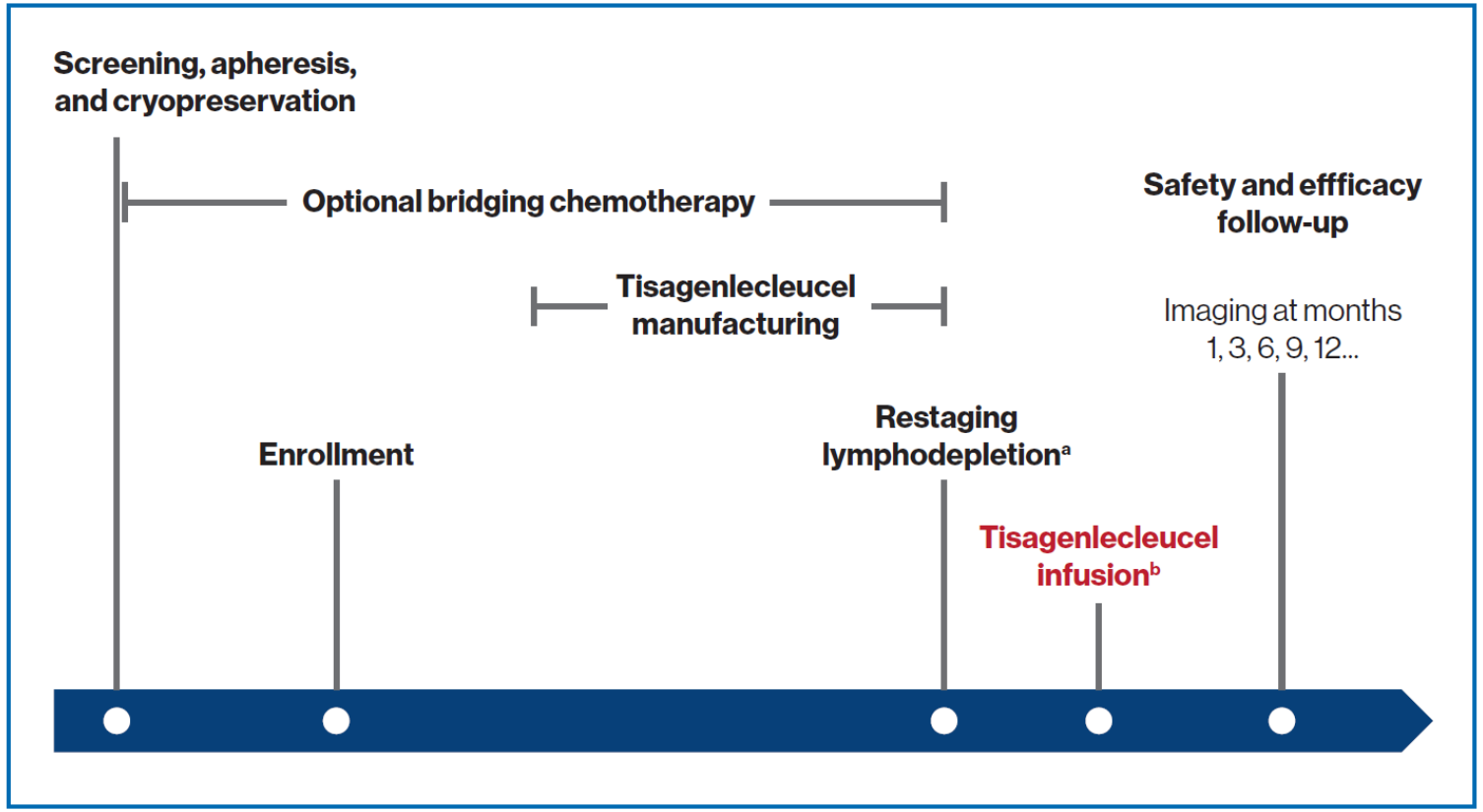
Patient No.	SAE Start Time After Axi-cel Infusion, mo	Grade	SAE	Attribution[b]
1	15.6	3	Mental status changes	Vasovagal episode in the context of hypovolemia unrelated to axi-cel
2	18.9	4	MDS	Prior chemotherapy unrelated to axi-cel
3	19.3	3	Lung infection	Unrelated to axi-cel
4	15.5	3	*Escherichia* bacteremia	Unrelated to axi-cel
	20.7	3	Bacteremia	Unrelated to axi-cel

[a]Late-onset event occurring since the previous data cutoff of August 11, 2017. [b]Per investigator.
MDS, myelodysplastic syndrome; SAE, serious adverse event.

Neelapu ASH 2018

Juliet Study: ASH 2018 Update

- JULIET is a single-arm open-label, global, phase 2 trial of tisagenlecleucel in adult patients with r/r DLBCL
- Patients received a single infusion with a target dose that ranged from 01. X 10^8 to 6 X 10^8 tisagenlecleucel CAR T cells



[a] To be completed 2 to 14 days prior to tisagenlecleucel infusion.
[b] Infusion conducted on an inpatient or outpatient basis at investigator discretion.

Schuster ASH 2018

Patient Demographics and Baseline Characteristics

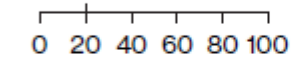
	Patients (N = 115)
Age, median (range), years	56 (22-76)
≥ 65 years, %	23
ECOG performance status 0/1, %	57/44
Central histology review	
Diffuse large B-cell lymphoma, %	80
Transformed follicular lymphoma, %	18
Double/triple hits in *CMYC/BCL2/BCL6* genes,[a] %	17
Cell of origin[b]	
Germinal/Nongerminal center B-cell type, %	55/43
Number of prior lines of antineoplastic therapy, %	
2/3/4-6	44/31/20
IPI ≥ 2 at study entry, %	73
Refractory/relapsed to last therapy, %	54/46
Prior ASCT, %	49

ASCT, autologous stem cell transplant; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic index.
[a] *CMYC* + *BCL2*, n = 10; *CMYC* + *BCL2* + *BCL6*, n = 5; *CMYC* + *BCL6*, n = 5.
[b] Determined by the Choi algorithm.

Schuster ASH 2018

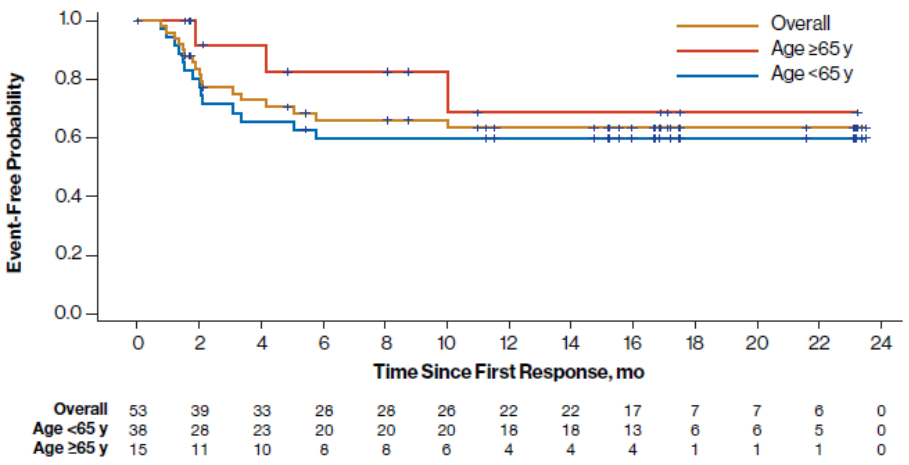
Overall Response Rate by IRC: Forest Plot

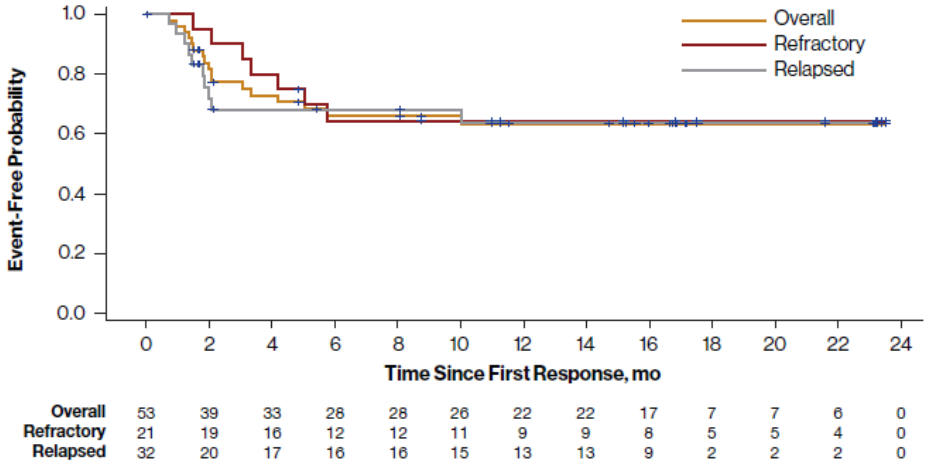
		N	ORR, n/N (%)	[95% CI]
All patients	All patients	99	53/99 (53.5)	[43.2-63.6]
Age	<65 years	75	38/75 (50.7)	[38.9-62.4]
	≥65 years	24	15/24 (62.5)	[40.6-81.2]
Sex	Female	36	22/36 (61.1)	[43.5-76.9]
	Male	63	31/63 (49.2)	[36.4-62.1]
Prior response status	Refractory to last line	50	21/50 (42.0)	[28.2-56.8]
	Relapsed to last line	49	32/49 (65.3)	[50.4-78.3]
IPI at enrollment	<2 risk factors	27	16/27 (59.3)	[38.8-77.6]
	≥2 risk factors	72	37/72 (51.4)	[39.3-63.3]
Prior anti-neoplastic therapy	≤2 lines	52	27/52 (51.9)	[37.6-66.0]
	3 lines	29	18/29 (62.1)	[42.3-79.3]
	≥4 lines	18	8/18 (44.4)	[21.5-69.2]
Molecular subtype	Activated B-cell	45	25/45 (55.6)	[40.0-70.4]
	Germinal center	51	25/51 (49.0)	[34.8-63.4]
Prior ASCT therapy	No	55	27/55 (49.1)	[35.4-62.9]
	Yes	44	26/44 (59.1)	[43.2-73.7]
Rearrangements in *MYC/BCL2/BCL6* genes	Double/triple hits	17	7/17 (41.2)	[18.4-67.1]
	Other	82	46/82 (56.1)	[44.7-67.0]
Tumor volume	<100 mL	50	28/50 (56.0)	[41.3-70.0]
	≥100 mL	31	11/31 (35.5)	[19.2-54.6]
	Unknown	18	14/18 (77.8)	[52.4-93.6]



Efficacy analysis set = All patients who received CTL019 infusion at least 3 months prior to data-cut date.
The area of each box is proportional to the number of patients in the particular grouping.
The 95% confidence intervals (CIs) are exact Clopper-Pearson CIs calculated for each subgroup.
ASCT, autologous stem cell transplantation; IPI, International Prognostic Index.

DOR by Age and Relapsed/Refractory Status





- The median DOR in the main cohort has not been reached
- No relapses were observed beyond 11 months after infusion
- 54% (15/28) of patients who had achieved a PR converted to CR
- DOR was similar by age group (≥ vs < 65 years) and by r/r status (**Figure 3**)

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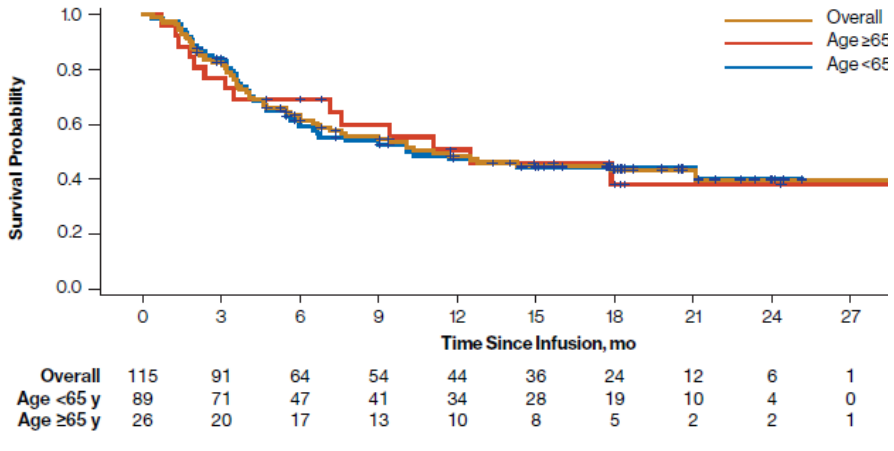
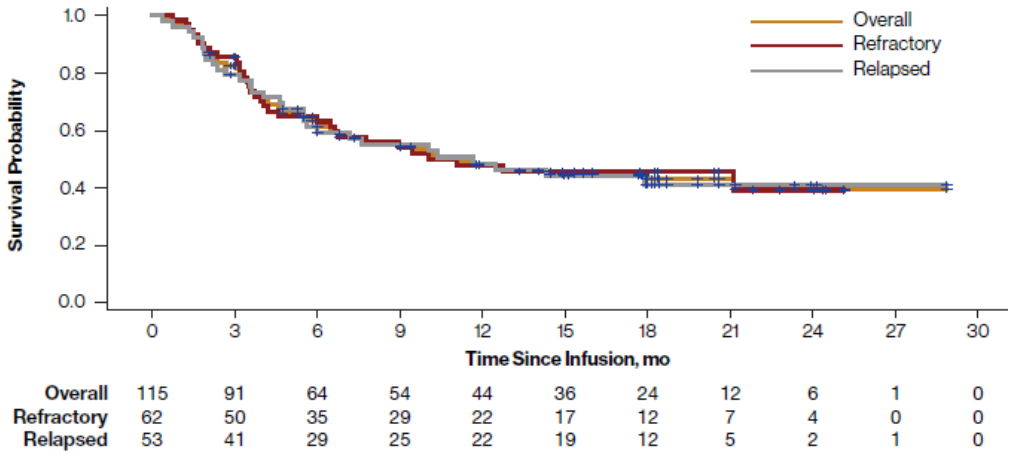
Overall Survival by Age and Relapsed/Refractory Status





- Median OS for all infused patients was 11.1 months (95% CI, 6.6 months-not evaluable [NE]) and was not reached (95% CI, 21 months-NE) for patients in CR
- The OS probability was 48% (95% CI, 38%-57%) at 12 months and 43% (95% CI, 33%-53%) at 18 months
- OS was similar by age group (≥ vs < 65 years) and by r/r status (**Figure 4**)
- No patients proceeded to allogeneic SCT or ASCT while in remission

Schuster ASH 2018

Adverse Events of Special Interest

AESI[a]	All Patients (N = 115)		
	All Grades, %	Grade 3, %	Grade 4, %
Cytokine release syndrome[b]	57	14	9
Prolonged cytopenia[c]	45	17	17
Infections	37	17	2
Neurological events[d]	20	7	4
Febrile neutropenia	15	13	2
Tumor lysis syndrome	2	1	1

AESI, adverse events of special interest.

[a] Occurring within 8 weeks of tisagenlecleucel infusion.

[b] Cytokine release syndrome was graded using the Penn scale.[12]

[c] Not resolved by day 28.

[d] A single case of grade 2 cerebral edema was reported as the finding of a CT scan without contrast and suboptimal quality. Repeat scanning with contrast 24 hours later showed no cerebral edema.

A retrospective analysis of CRS severity and neurological events was conducted using the Lee grading scale and mCRES scale, respectively.[13,14]

Schuster ASH 2018

CAR-T: Toxicity from phase II DLBCL trials

	Kite (n=101) (%)	Novartis (n=99) (%)	Juno (n=91) (%)
CRS – any	93	58	35 (25-46)
Grade 1/2 Grade 3/4	80 13	35 23	34 (24-45) 1 (0-6)
Neurotoxicity – any	64	21	19 (11-28)
Grade 1/2 Grade 3/4	37 28	9 12	7 (2-14) 12 (6-21)
Grade 5 AE	3 4*	0 3*	0 2*

- Not for direct comparison
- Note CRS definitions are different (Novartis – UPenn, not Lee)
- Patient populations not clearly similar

Neelapu ASH 2017, Schuster ASH 2017, Abramson ASH 2017

* Monograph and ASCO 2018 updates

CAR-T: Efficacy from phase II DLBCL trials

	Kite (n= 101) (%)	Novartis (n=99) (%)	Juno (n=73) (%)
ORR (Best) CR (Best)	74 54	54 40	79 55
ORR (ongoing) CR (ongoing)	36 35	37 30	47 41
PFS	39%	NR	NR
OS	51%	43%	~80%
Follow up	24 m	18 m	6m
Outpatient admin	0	16%	9%

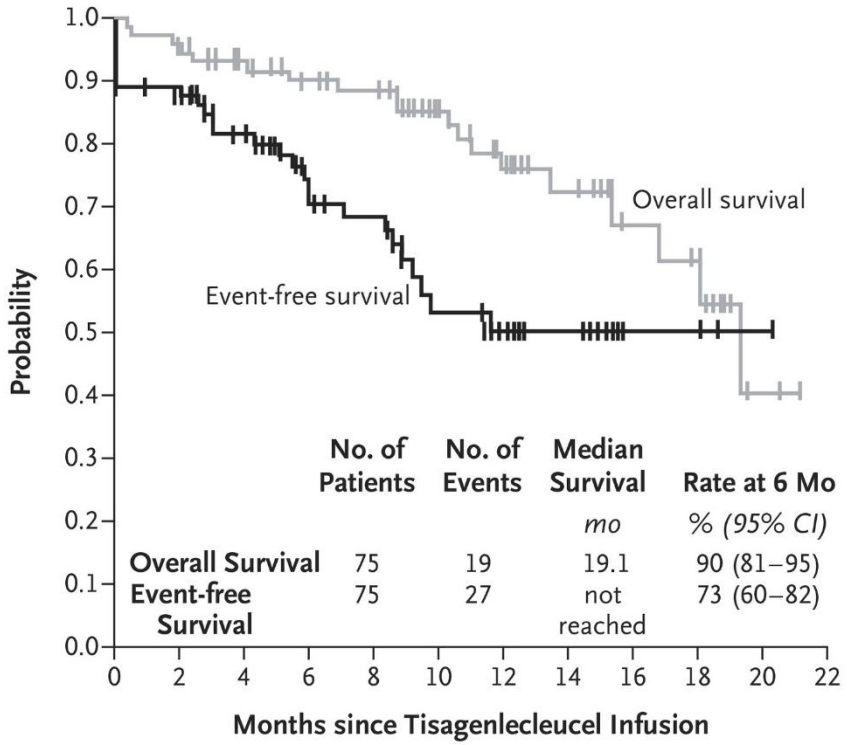
- Potentially curative approach in patients with limited effective options
- All platforms appear active although there are differences in constructs and practical administration
- Phase III trials underway in the curative setting

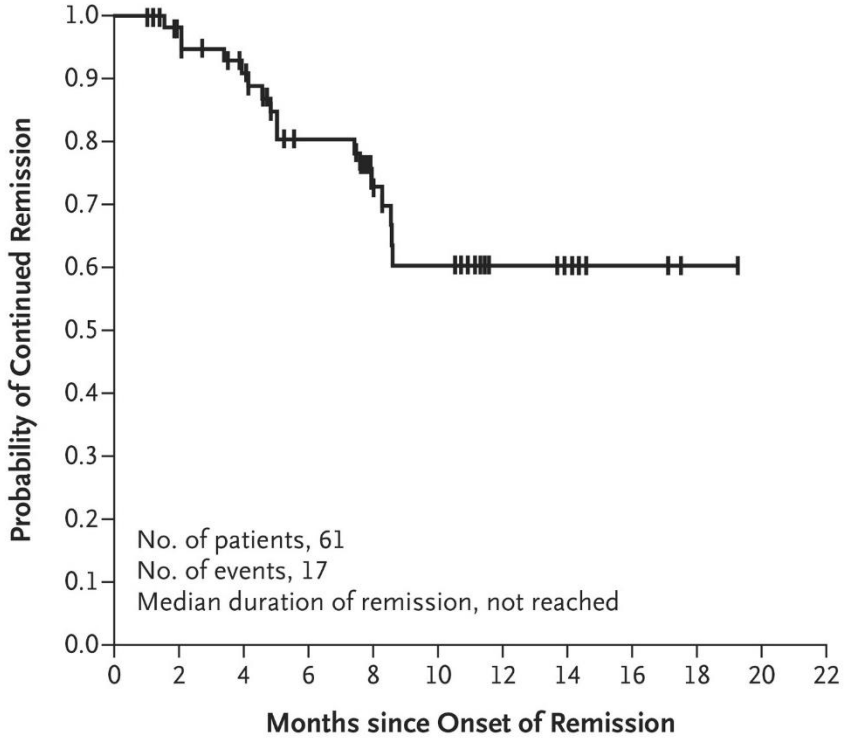
Neelapu ASH 2018, Schuster ASH 2018, Abramson ASCO 2018

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

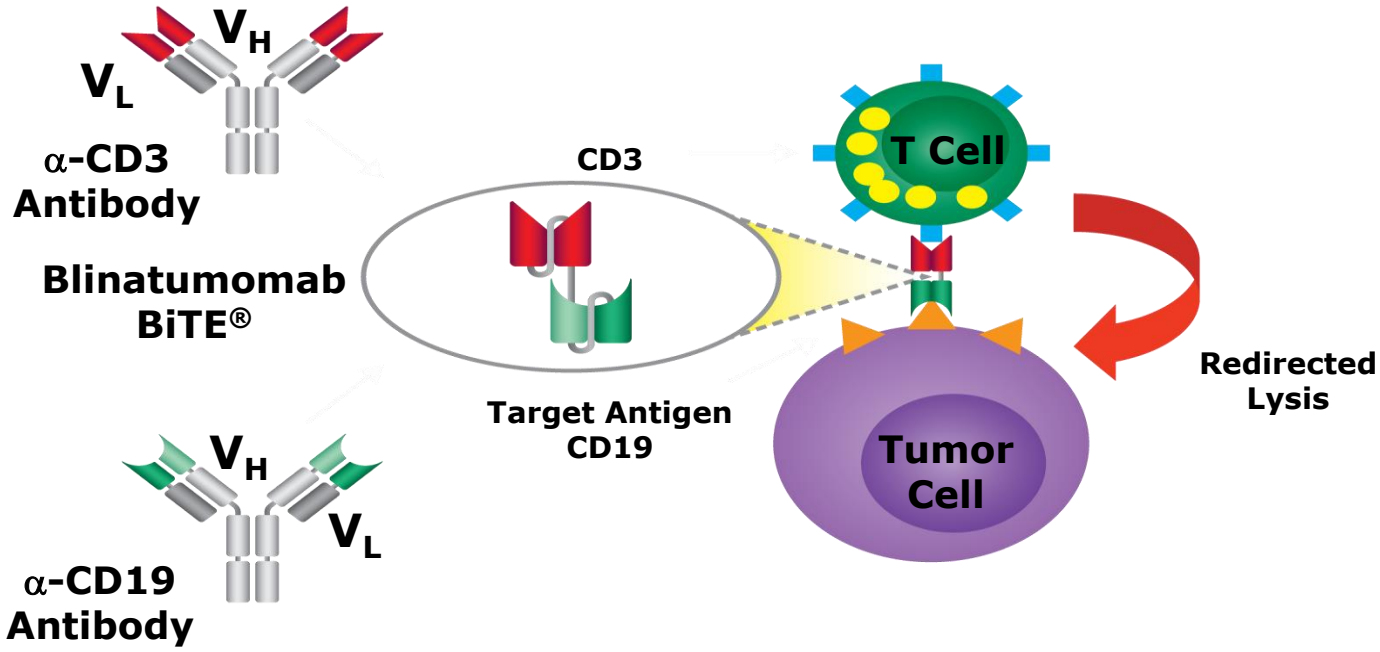




Maude et al. NEJM 2018

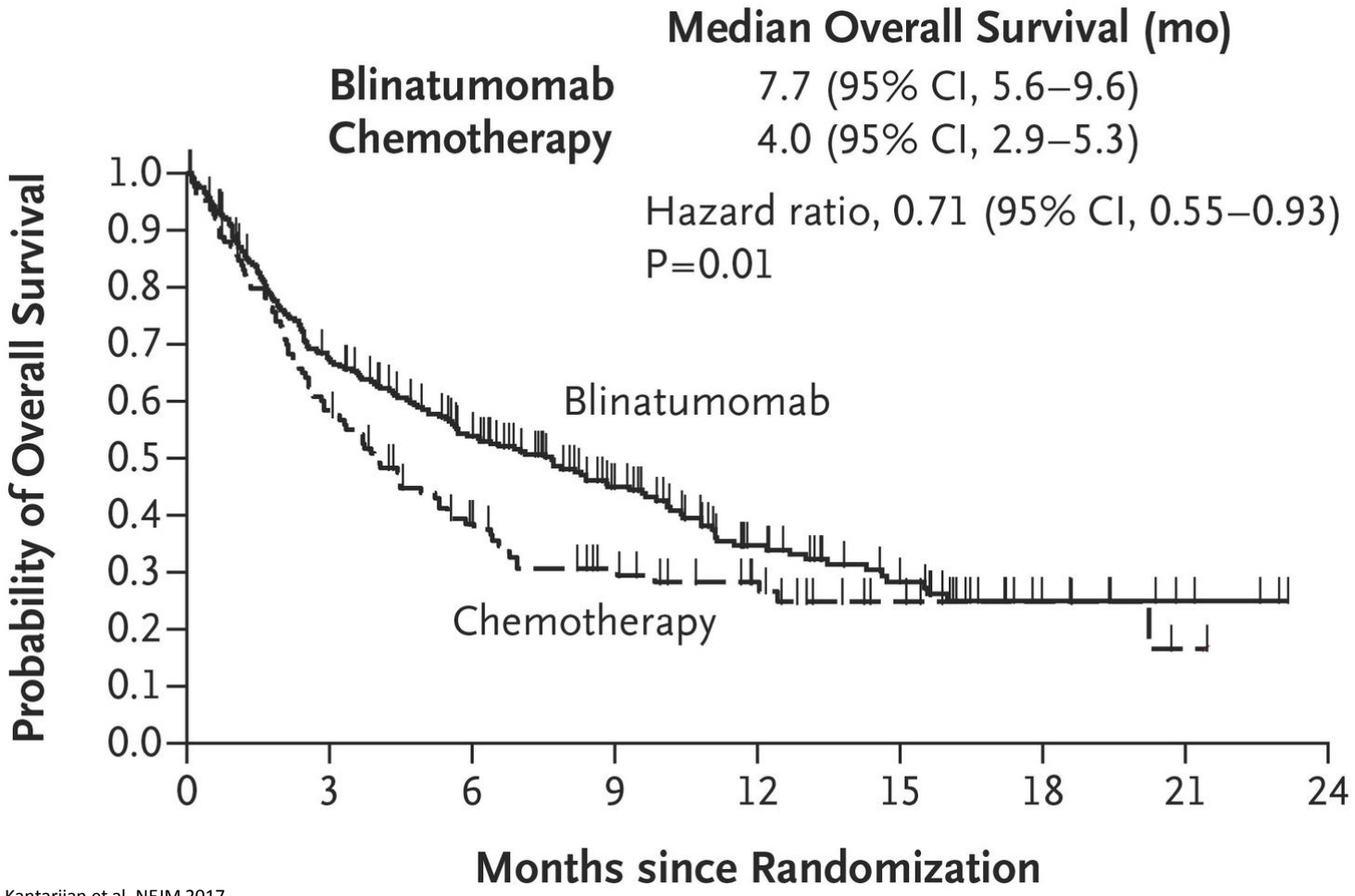
BiTE (Blinatumumab) Therapy

- 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

AEs (Regardless of Causality)

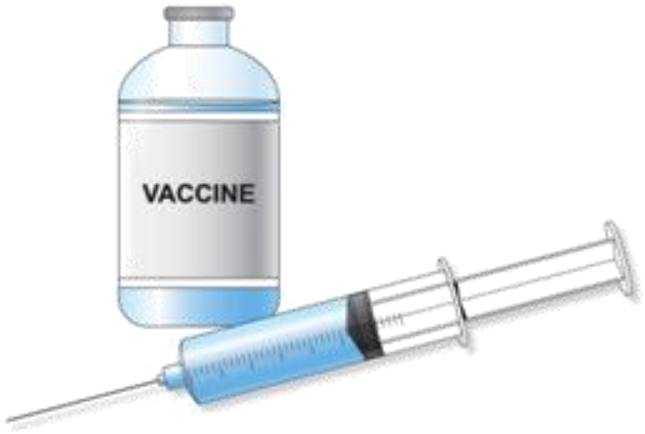
Event	Blinatumomab (n = 267) n (%)	SOC Chemotherapy (n = 109) n (%)
Any	263 (98.5)	108 (99.1)
Leading to discontinuation of study treatment	33 (12.4)	9 (8.3)
Serious AE	165 (61.8)	49 (45.0)
Fatal AE	51 (19.1)	19 (17.4)
Any grade ≥ 3 AE	231 (86.5)	100 (91.7)
Grade ≥ 3 AEs of interest categories reported for ≥ 3% of patients in either group		
Neutropenia	101 (37.8)	63 (57.8)
Infection	91 (34.1)	57 (52.3)
Elevated liver enzyme	34 (12.7)	16 (14.7)
Neurologic events	25 (9.4)	9 (8.3)
Cytokine release syndrome	13 (4.9)	0 (0)
Tumor lysis syndrome	8 (3.0)	1 (0.9)
Lymphopenia	4 (1.5)	4 (3.7)
Any decrease in platelets	17 (6.4)	13 (11.9)
Any decrease in white blood cells	14 (5.2)	6 (5.5)

AEs = adverse events; SOC = standard of care.

Kantarjian HM, et al. *N Engl J Med*. 2017; In press.

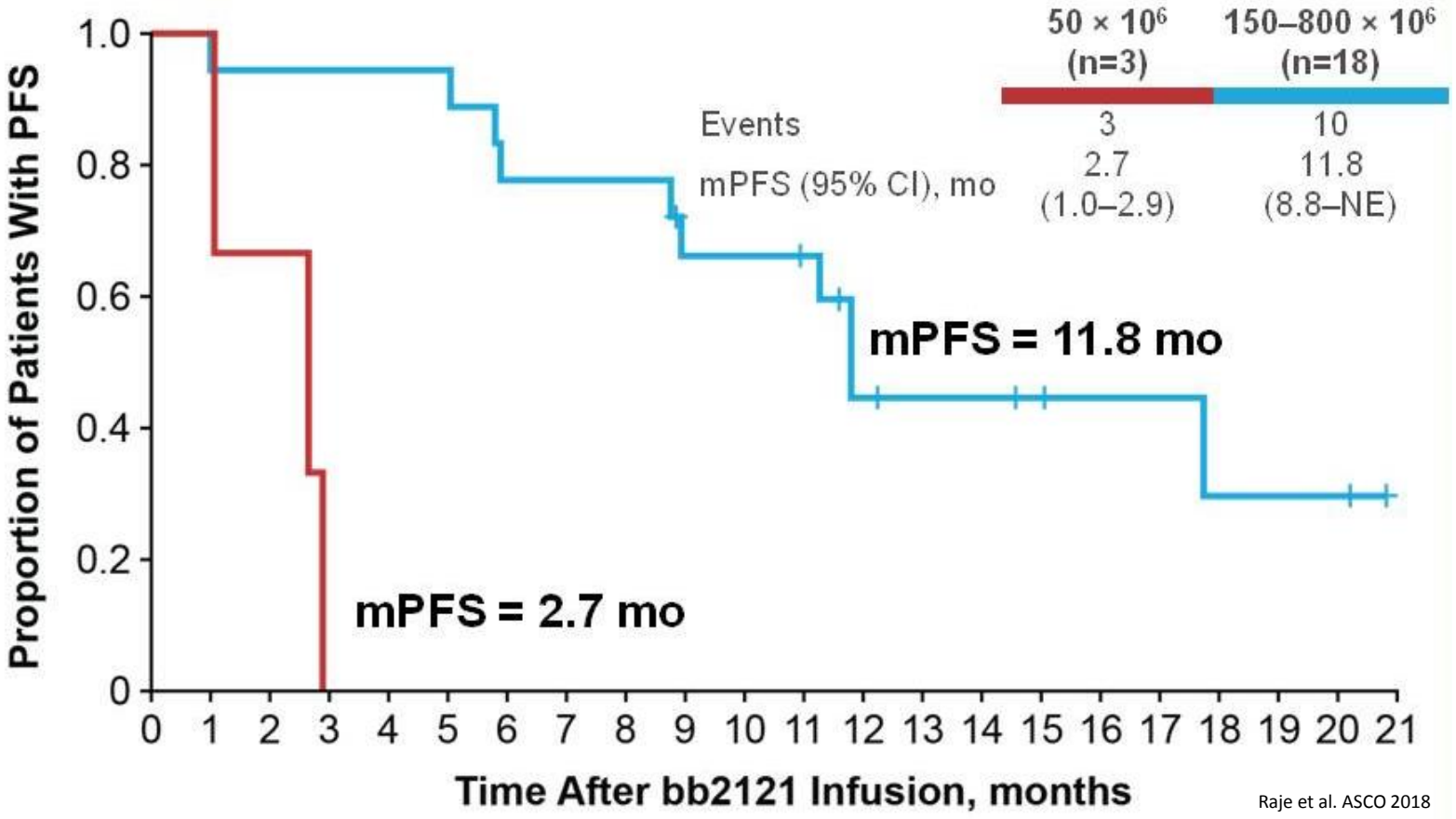
Immunotherapies for Multiple Myeloma

- 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
    - Bispecific antibodies (BCMA)



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



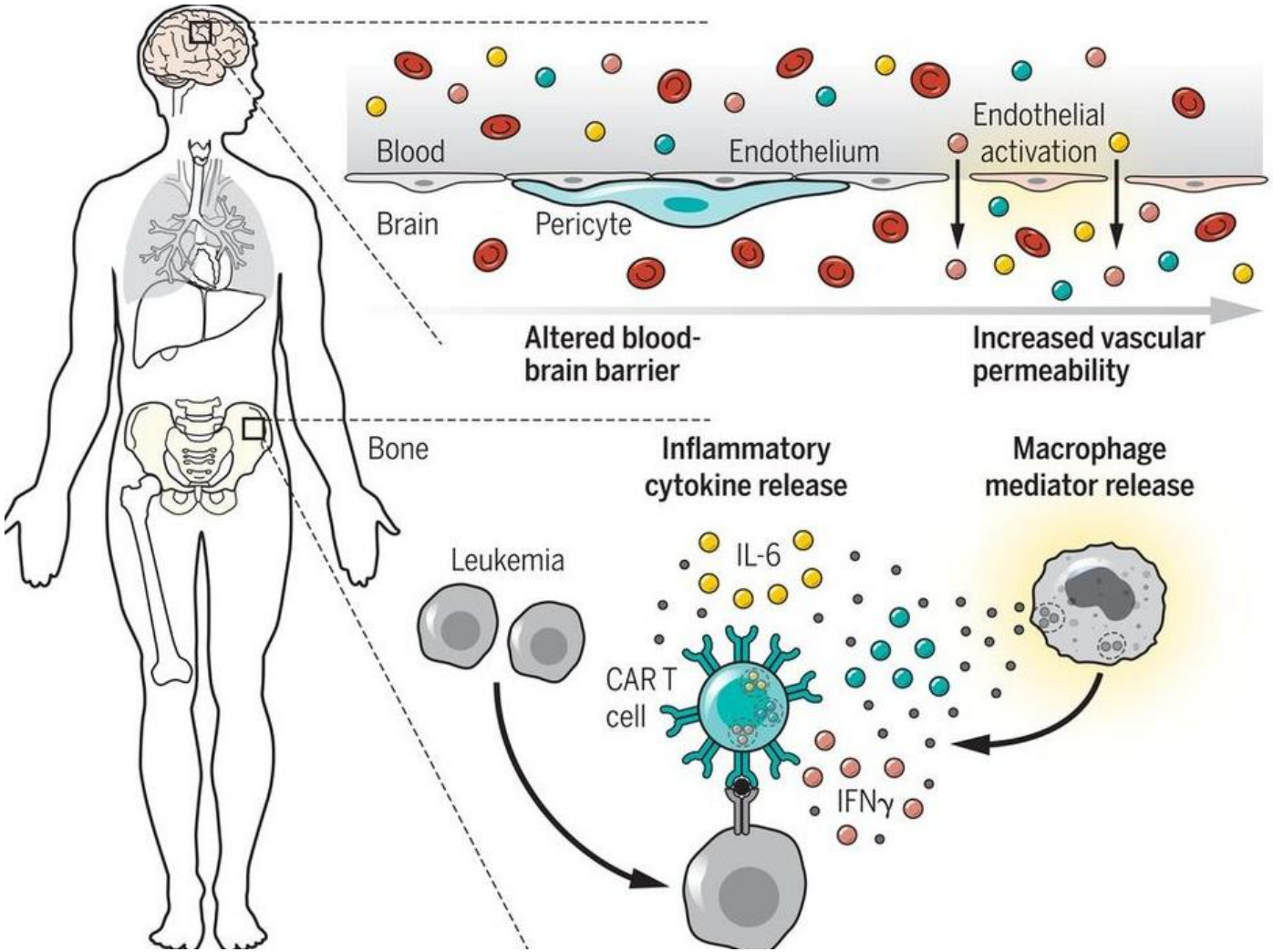
Raje et al. ASCO 2018

Immunotherapy in non-lymphoma indications

- ALL: approved indications for blinatumomab and tisagenlecleucel
  - Previously approaches had largely focused on allogeneic stem cell transplantation
- Multiple Myeloma
  - Early days but signals of promise with bispecific antibodies and CAR-T cell therapy

- Important to appreciate that immunology of tumour and microenvironment is different in all diseases and thus operating characteristics are likely to be very different

Cytokine Release Syndrome (CRS)



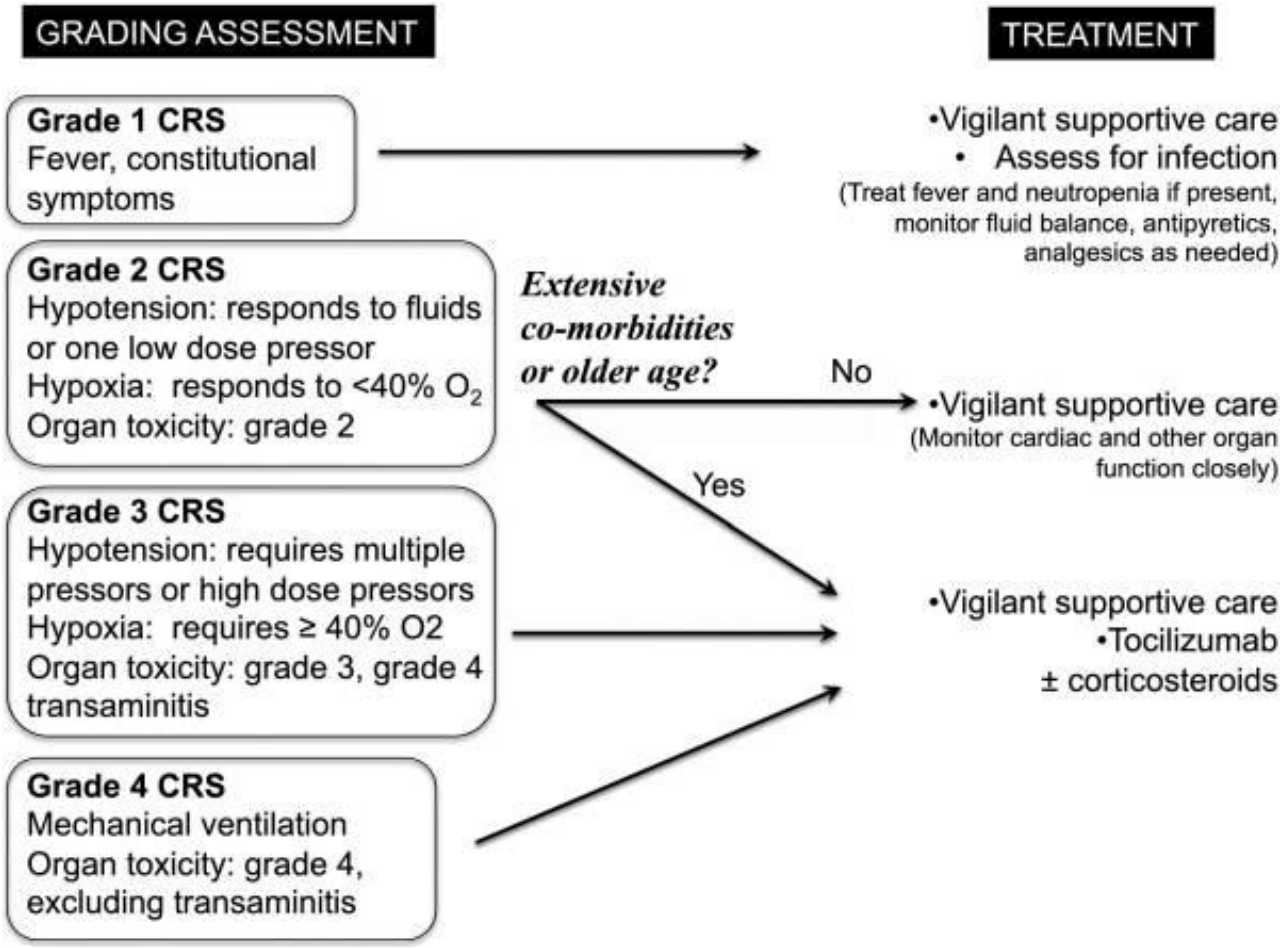
Neurotoxicity
Delirium
Aphasia
Seizures
Cerebral edema
Intracranial hemorrhage

Hemodynamic instability
Tachycardia
Hypotension
Capillary leak syndrome

Organ dysfunction
AST and ALT elevation
Hyperbilirubinemia
Respiratory failure

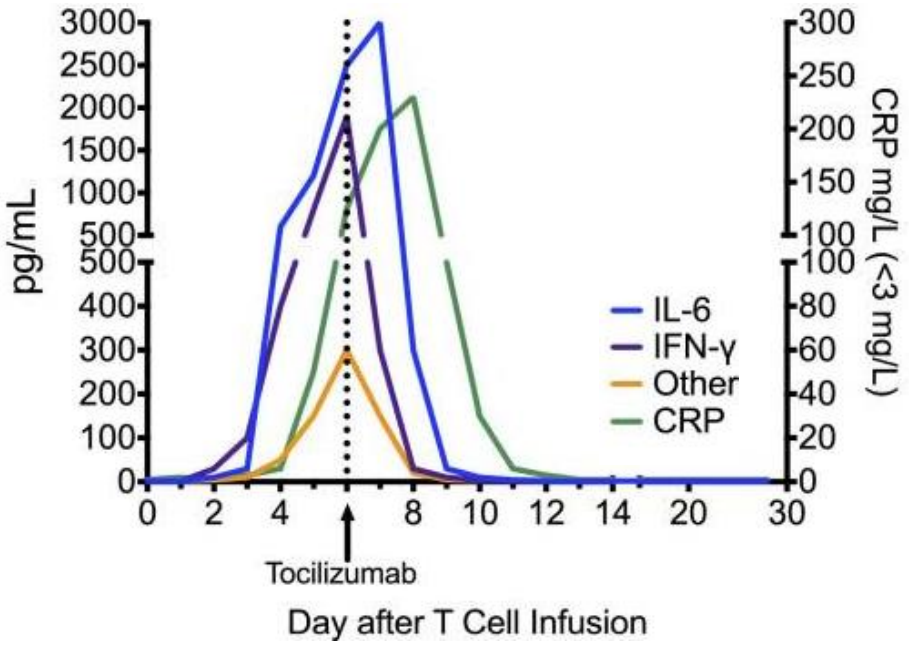
June et al. Science 2018

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*]

JT – Relapsed / Refractory HL

- 36 year old woman with Hodgkin's lymphoma
  - Initial therapy with ABVD X 6 cycles for Stage II disease
  - Radiation therapy not given due to concern of late effects and achievement of CR at end of chemotherapy
  - Disease relapse confirmed on core biopsy approximately nine months later with mediastinal disease and some splenic involvement (stage III)
  - Undergoes salvage chemotherapy (GDP) with partial remission followed by autologous stem cell transplantation
  - Relapse post ASCT at 6 months
  - Is there an optimal next choice?

JT – post-ASCT Brentuximab and then?

- Treatment post ASCT is by definition palliative
- Started on brentuximab vedotin
  - Achieves PR after 4 doses but then developed PD after 6 months
- Next choice?

JT – post-brentuximab

- Treatment post ASCT is by definition palliative
- Started on brentuximab vedotin
  - Achieves PR after 4 doses but then developed PD after 6 months
- Referred to Princess Margaret
  - Enrolled on Checkmate 205 – nivolumab for RR-HL
  - Achieves initial PR after 12 weeks
  - Noted to have PET+ growth in lymph nodes although clinically well at approximately 9 months

- What next?

JT – what is PD on a checkpoint inhibitor?

- Referred to Princess Margaret
  - Enrolled on Checkmate 205 – nivolumab for RR-HL
  - Achieves initial PR after 12 weeks
  - Noted to have PET+ growth in lymph nodes although clinically well at approximately 9 months
    - After serial imaging – demonstrates criteria for PD, remains well and thus met criteria for treatment beyond progression
  - Nivolumab discontinued due to clear PD after approximately 12 months of treatment beyond initial PD

- Starting to run out of things…

JT – post-Nivolumab failure

- Received radiation therapy
  - ? Abscopal effect
- Subsequent disease progression – repeat biopsy confirms persistent HL
  - Referral to PMH
- Enrolled on clinical trial of nivolumab + relatlimab (anti-LAG3)
  - Initial response assessment shows stable disease
  - Continues on with no toxicity

Case study 2 - CB

- 61 year old woman presents with Stage IIE diffuse large B cell lymphoma (DLBCL) with bulky iliac bone based lesion, regional lymph nodes, elevated LDH and ECOG PS 1 (IPI=2).
  - Initially started on R-CHOP for initial cycle, FISH reveals t(14;18) and t t(8;14) – MYC and BCL2
  - Treatment switched to DA-EPOCH-R for double hit lymphoma
  - End of treatment PET scan remains PET avid though patient had good CT response
  - Core biopsy confirms residual disease
- Undergoes salvage therapy (obinutuzumab + GDP) on clinical trial with PR and subsequent autologous stem cell transplant.
  - Consolidative radiation given to iliac site of disease
- Disease progression < 6 months post ASCT

What is the optimal management of patients who have relapsed after ASCT?

- Allogeneic transplant
- Palliation
- CAR-T cells
  - On a clinical trial
  - SOC
- A different clinical trial approach

Case study 2 - CB

- Patient enrolled onto phase II trial of tazemetostat (EZH2 inhibitor) after screening identifies EZH2 mutation
  - Initial PR on treatment but then PD after 3-4 months.
- ZUMA-1 clinical trial (axicabtagene ciloleucel) opens at PMH
  - Enrolled onto cohort assessing toxicity management
  - 4 days of high dose steroids as “bridging” after apheresis and during cell manufacturing process
  - Developed grade 2 cytokine release syndrome (CRS) requiring brief ICU stay and support but quick response to tocilizumab and corticosteroids
  - FDG PET scan 30 days post infusion demonstrates good cross-sectional response with residual mild FDG PET avidity
  - FDG PET scan 90 days post infusion confirms good response with very mild FDG avidity

Is there a best approach around “bridging” therapy prior to lymphodepletion and CAR-T infusion?

- Corticosteroids
- Radiation therapy
- Chemotherapy (bendamustine, R-Gem-OX, salvage)
- Novel agents

Case study 2 - CB

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  - Enrolled onto cohort assessing toxicity management with early corticosteroid intervention
  - 4 days of high dose steroids as “bridging” after apheresis and during cell manufacturing process
  - Developed grade 2 cytokine release syndrome (CRS) requiring ICU transfer

What is the best current management for CRS?

- Corticosteroids
- Tocilizumab
- Combination therapy with corticosteroids and tocilizumab depending on the scenario

Case study 2 - CB

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How do you interpret FDG PET scans in patients post immunotherapy such as CAR-T cell therapy?

- A negative PET scan is always a good thing
- A positive PET scan 30 days after CAR-T is a bad thing
- A positive PET scan 30 days after CAR-T isn't necessarily a bad thing
- The predictive value of a positive PET scan post immunotherapy is not optimal

Case study 2 - CB

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Summary and Conclusions

- Multiple immunotherapy approaches now available (and increasingly standard of care)
  - Checkpoint inhibitors (excellent single agent activity in HL)
  - Anti-CD19 CAR-T cells (potentially curative therapy)
  - Bispecific antibodies (improvement over conventional chemotherapy)
- Hematologic malignancies have some of the most impressive results for immunotherapy approaches
  - Novel immunotherapies are now being evaluated in the curative setting against established standards