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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

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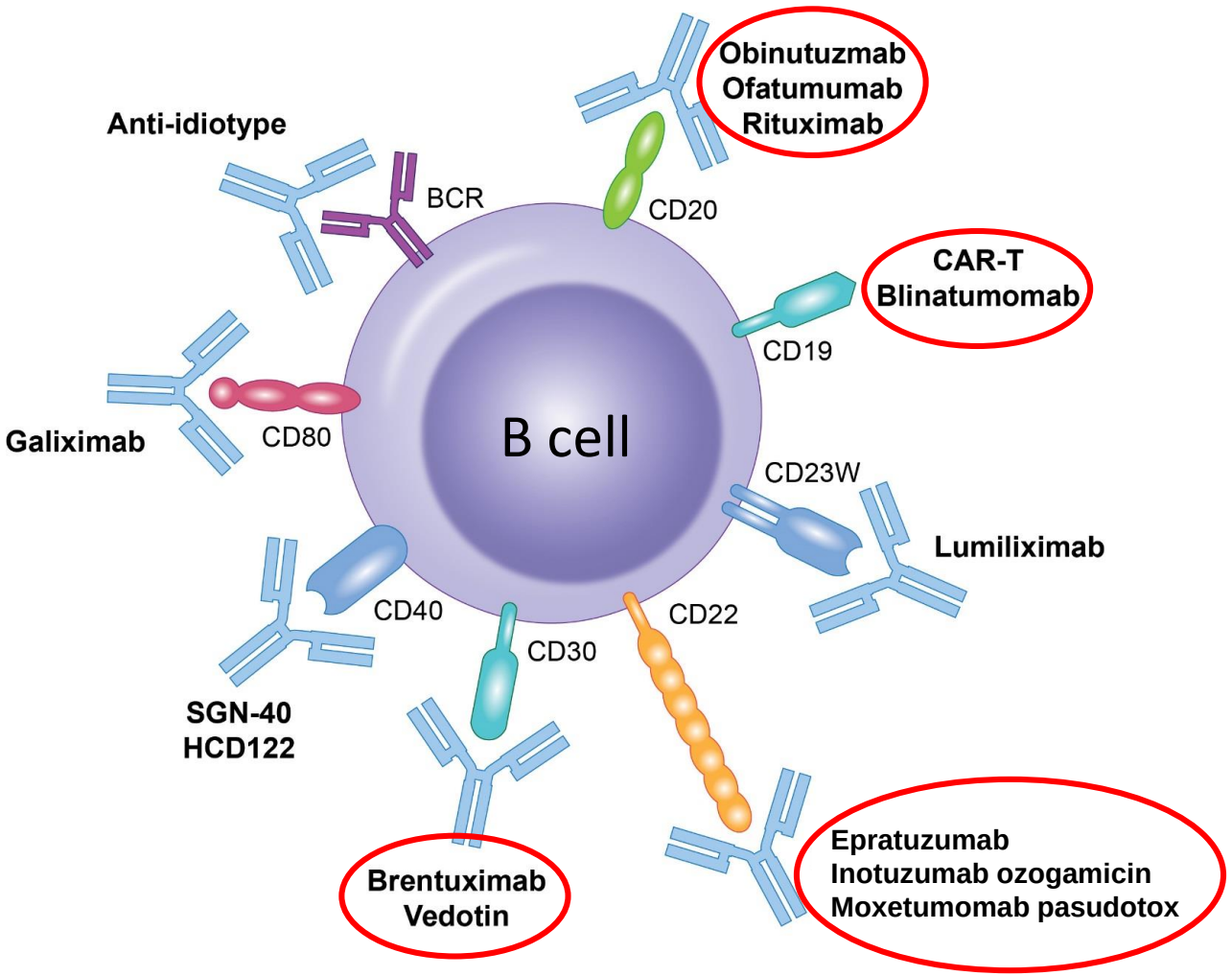
Disclosures

- Research support from Kite, Merck, BMS, Cellectis, Poseida, Karus, Acerta
- Advisory Board Member / Consultant for Kite, Merck, Celgene, Novartis, Unum Therapeutics, Pfizer, and CellMedica
- I will be discussing non-FDA approved indications during my presentation.

Monoclonal Antibodies Targeting B- and T-cell Lymphomas

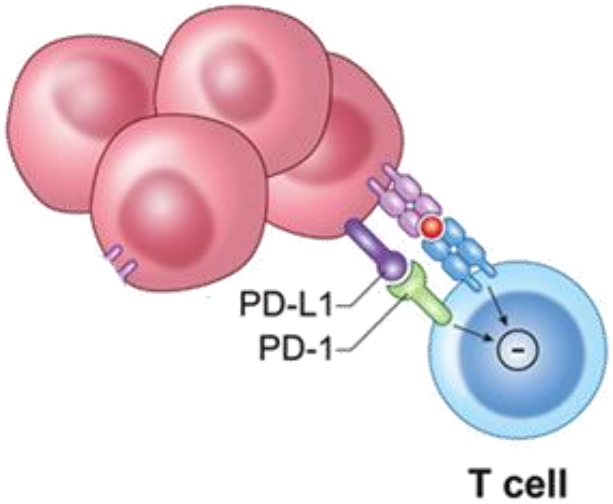


Myeloma
Daratumumab (CD38)
Elotuzumab (SLAM-F7)

T-cell lymphoma
Mogamulizumab (CCR4)

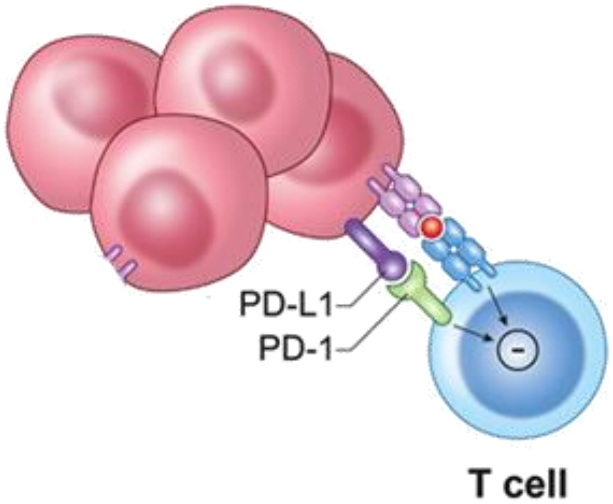
FDA-approved Checkpoint Inhibitors for Lymphomas

- Nivolumab (anti-PD-1)
  - CheckMate 205/039: Patients with cHL who have relapsed or progressed after ASCT 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

- Testing for PD-L1 expression not required
  - Upregulation of PD-L1 due to genetic aberrations is common in cHL and PMBCL
- 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

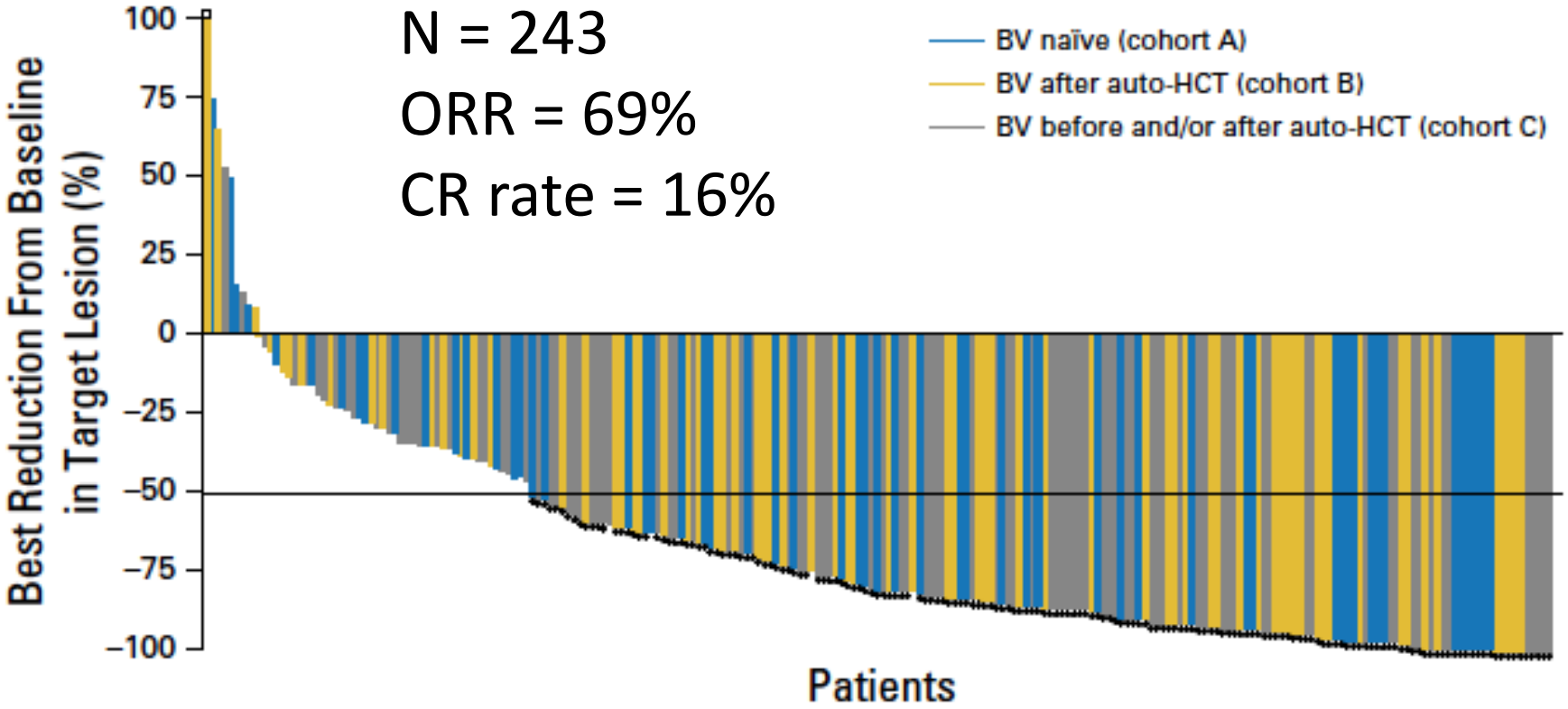


Checkmate 205: Nivolumab for r/r Hodgkin lymphoma

N = 243

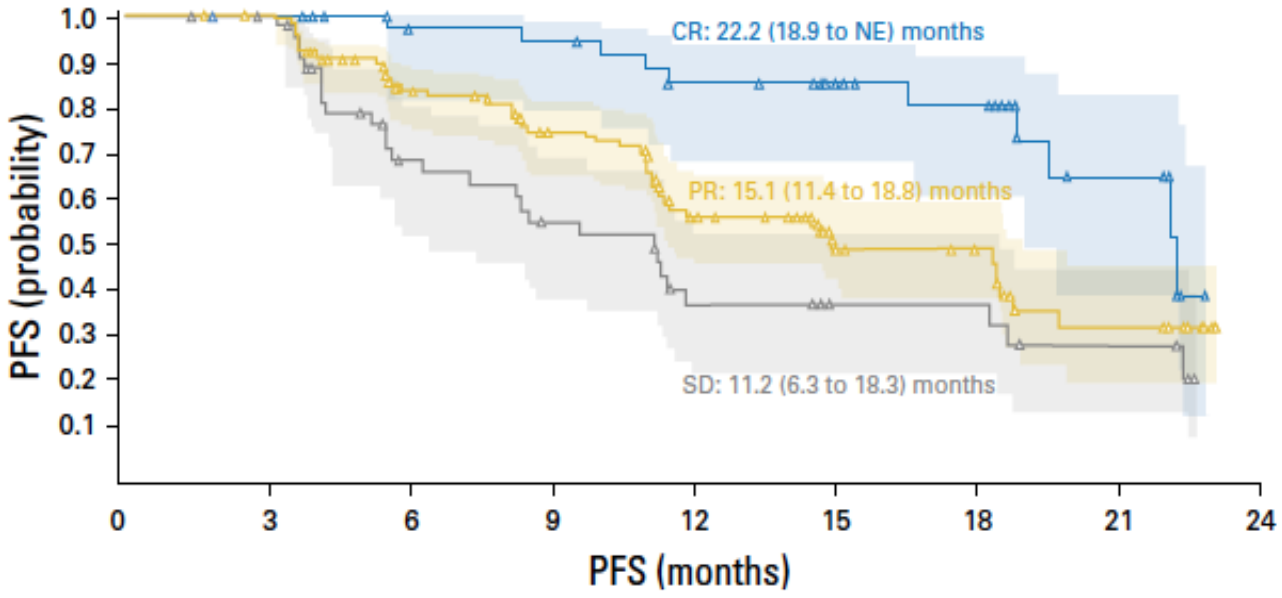
ORR = 69%

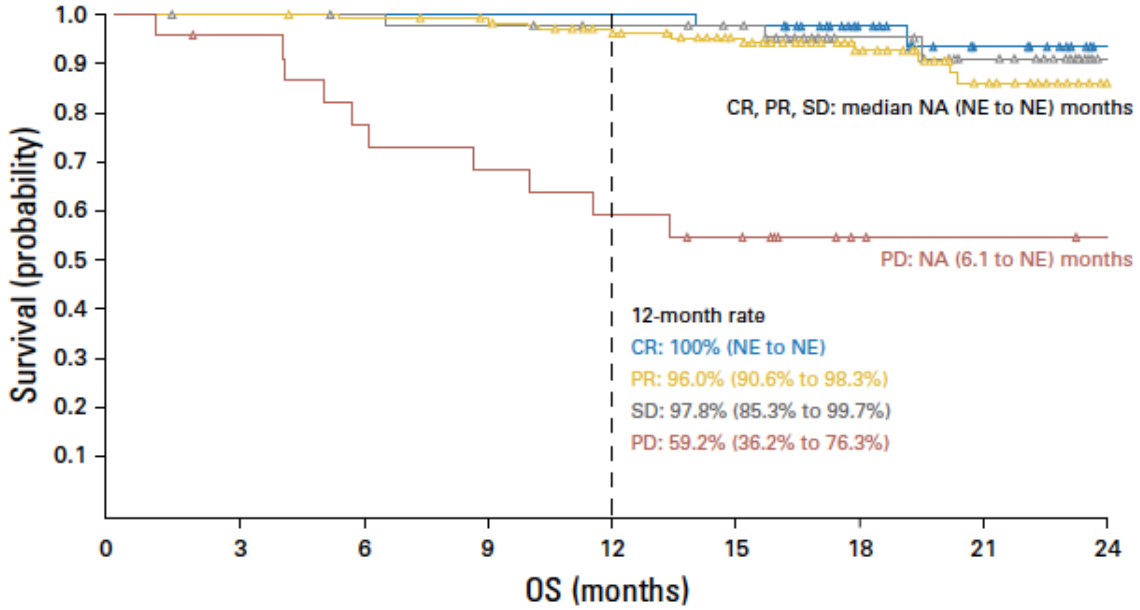
CR rate = 16%



Armand et al. J Clin Oncol 2018

Checkmate 205: Nivolumab for r/r Hodgkin lymphoma

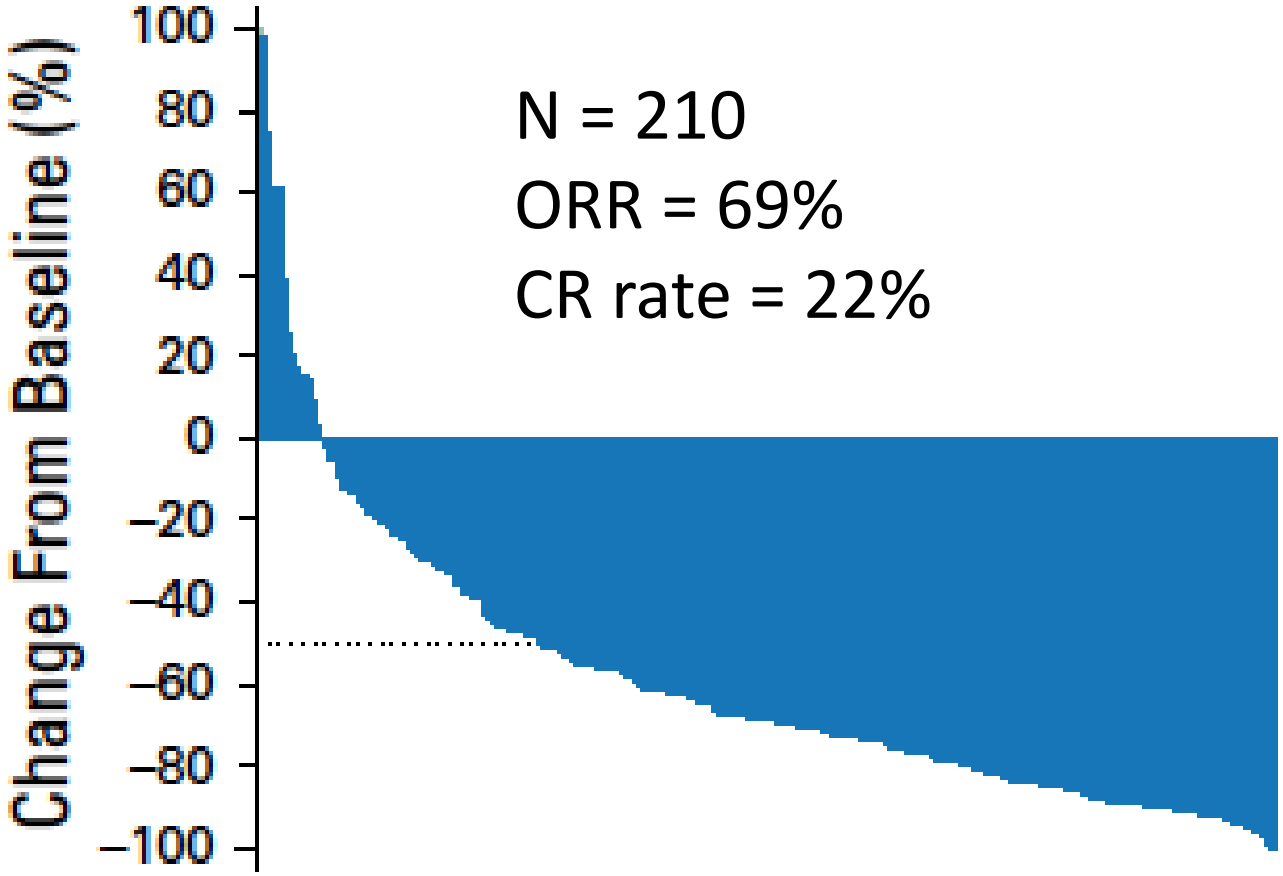




- PFS of nearly 1 year in patients with SD
- OS similar across response groups

Armand et al. J Clin Oncol 2018

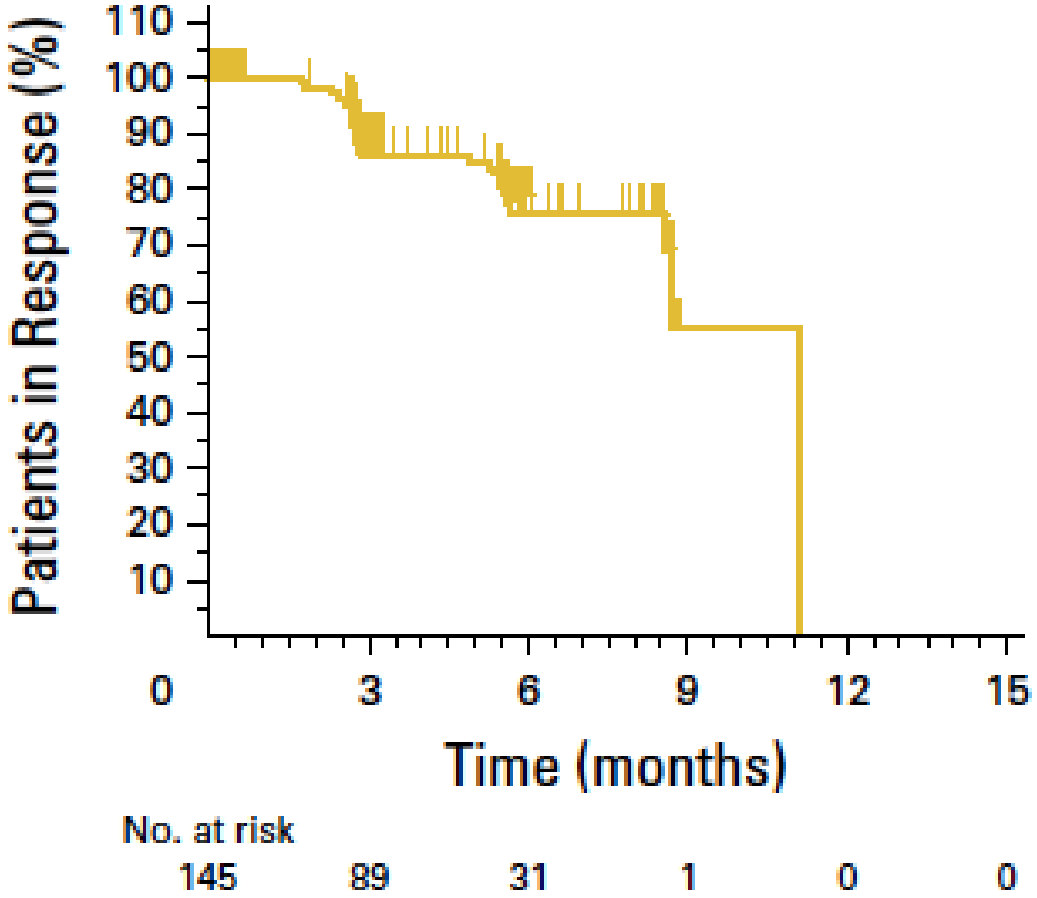
KEYNOTE-087: Pembrolizumab for r/r Hodgkin lymphoma



N = 210

ORR = 69%

CR rate = 22%

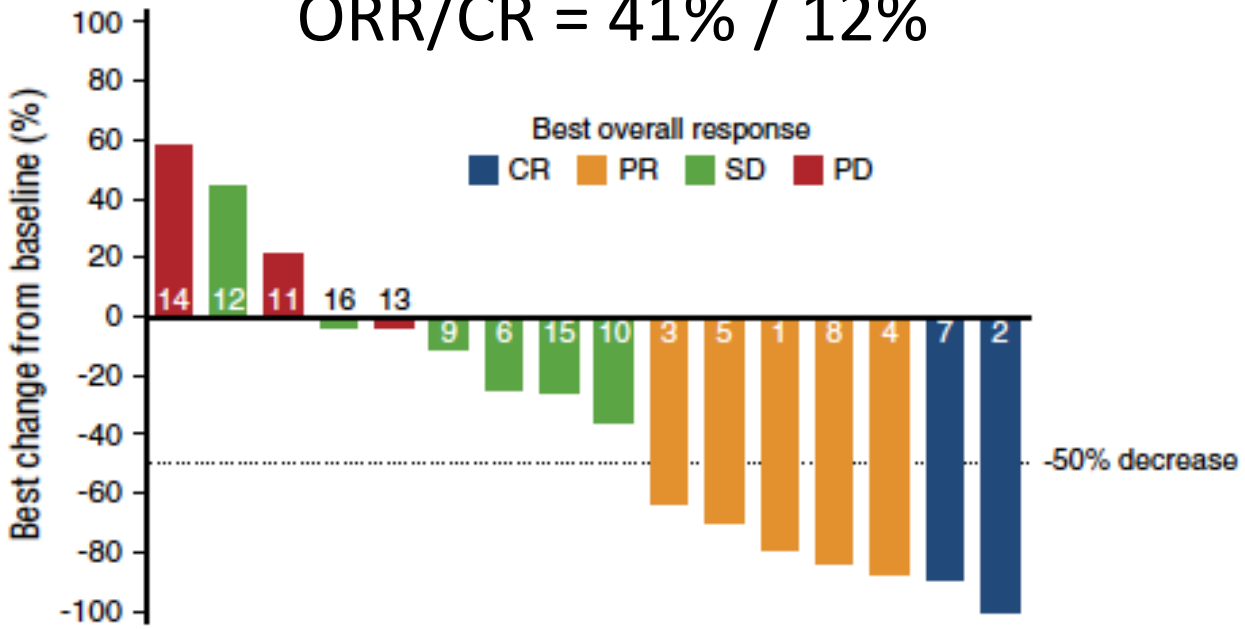


Chen et al. J Clin Oncol 2017

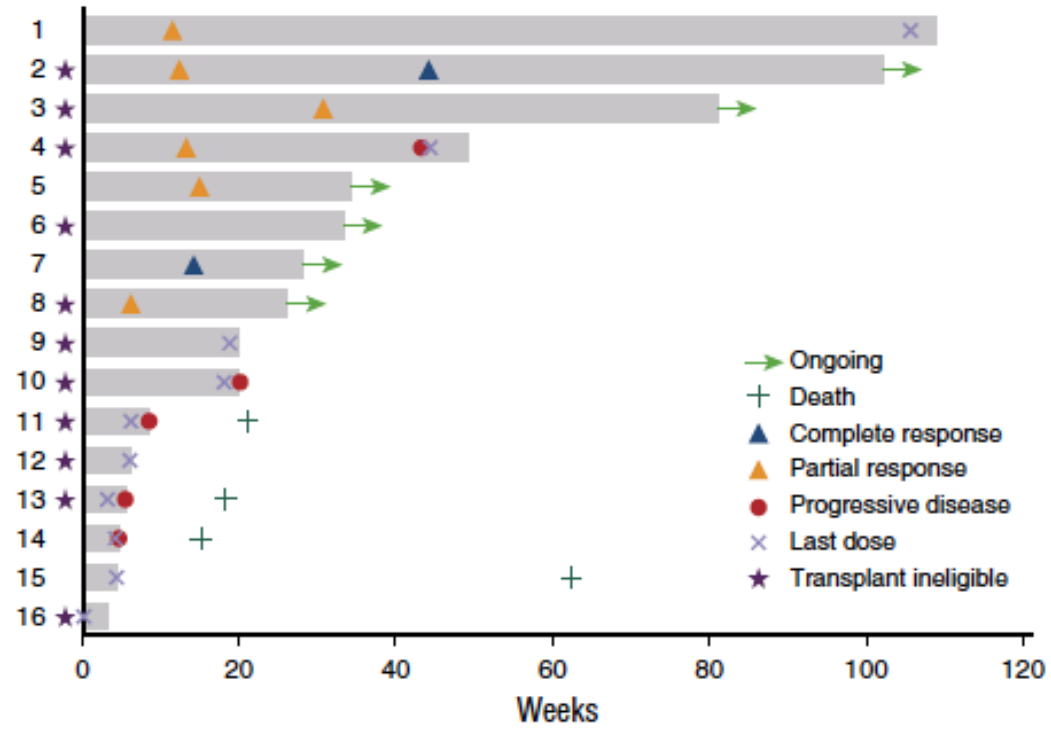
KEYNOTE-013: Pembrolizumab in r/r PMBCL

N = 17

ORR/CR = 41% / 12%



Zinzani et al. *Blood* 2017



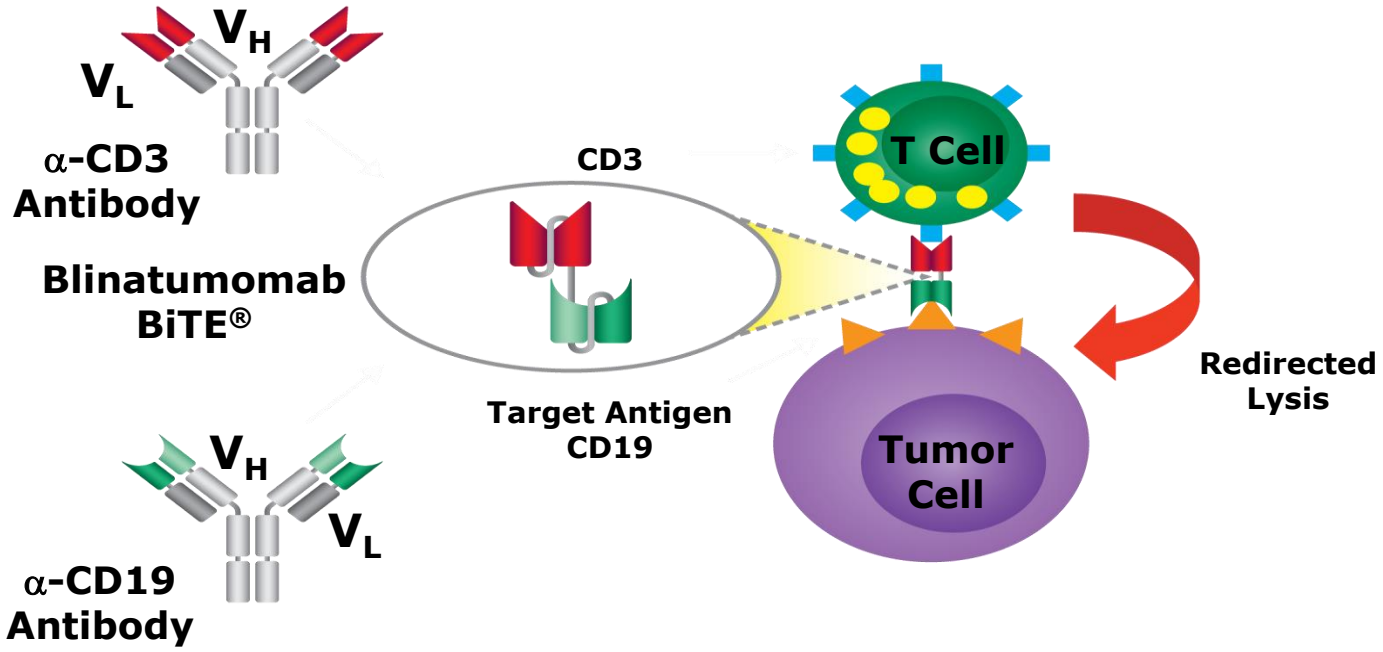
KEYNOTE-170

N = 53

ORR/CR = 45% / 11%

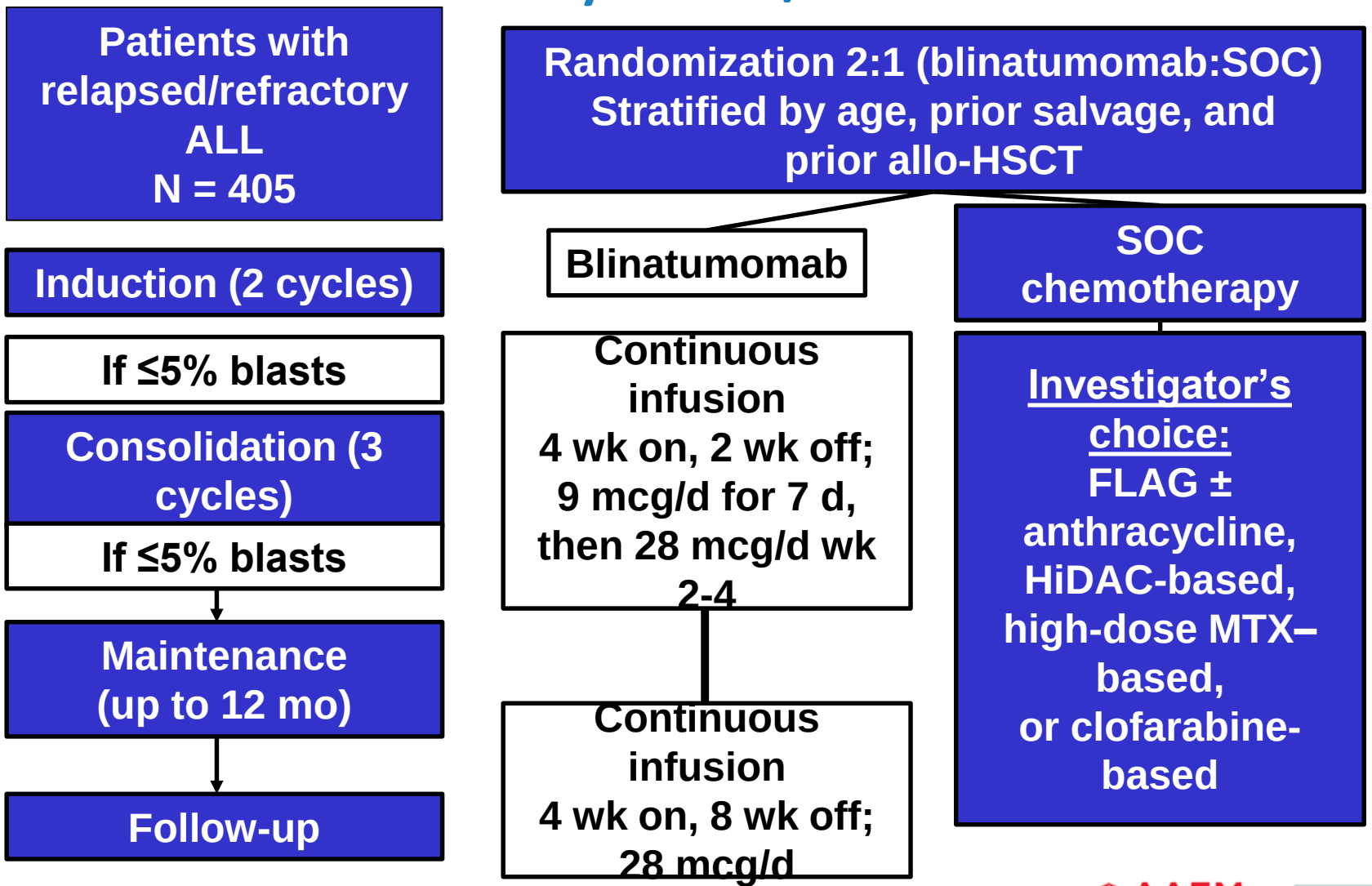
BiTE (Blinatumumab) Therapy

- 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: Phase 3 TOWER study for r/r B-ALL



Kantarjian et al. NEJM 2017

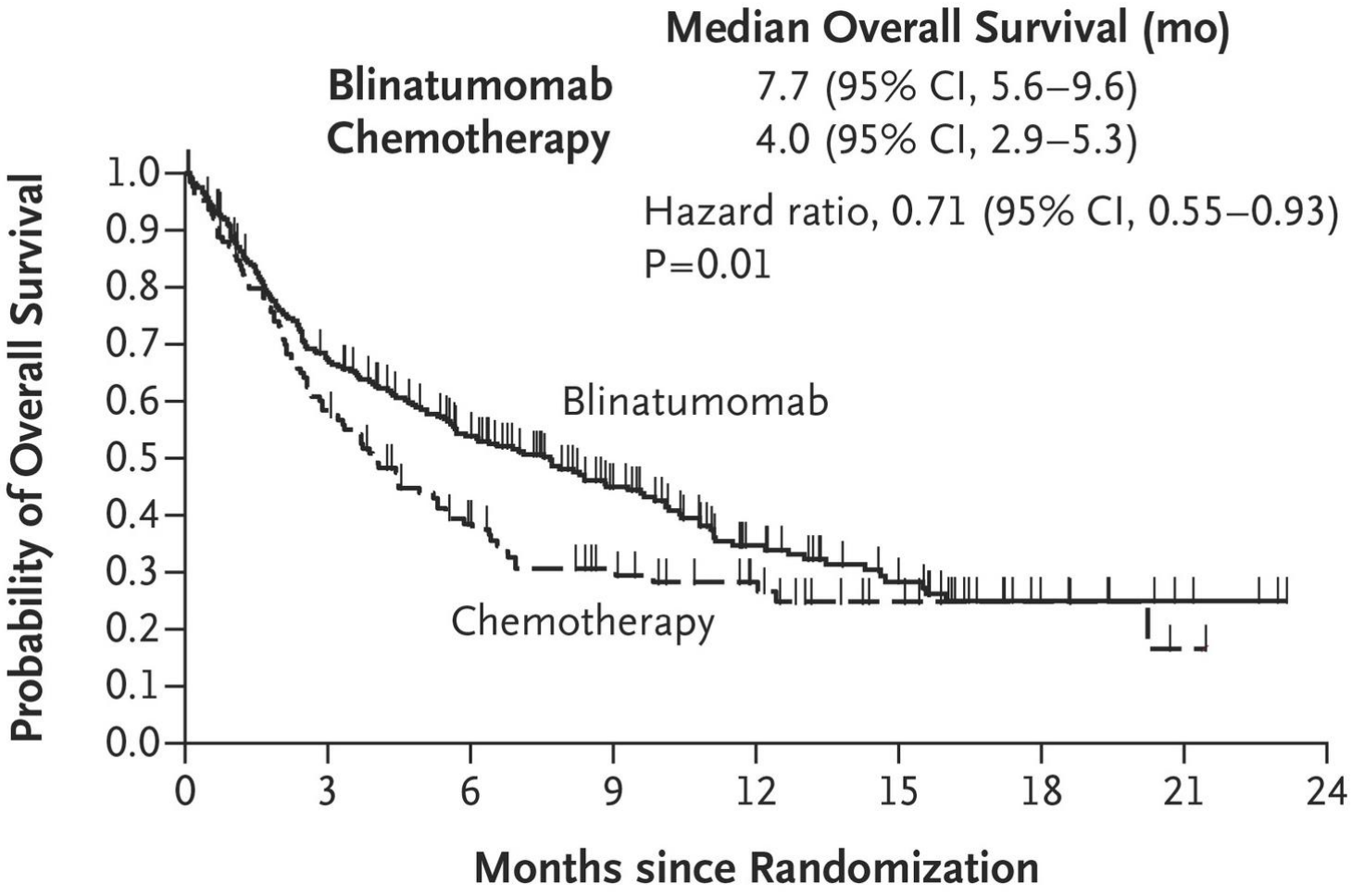
Blinatumomab: Efficacy on Phase 3 TOWER study for r/r B-ALL

Parameter	Blinatumomab	Chemo Rx	p value
% CR	34	16	<.001
% marrow CR	44	25	<.001
% MRD negative in CR	76	48	--
Median OS (mos)	7.7	4.0	.01

- 24% in each group had allo SCT subsequently

Kantarjian et al. NEJM 2017

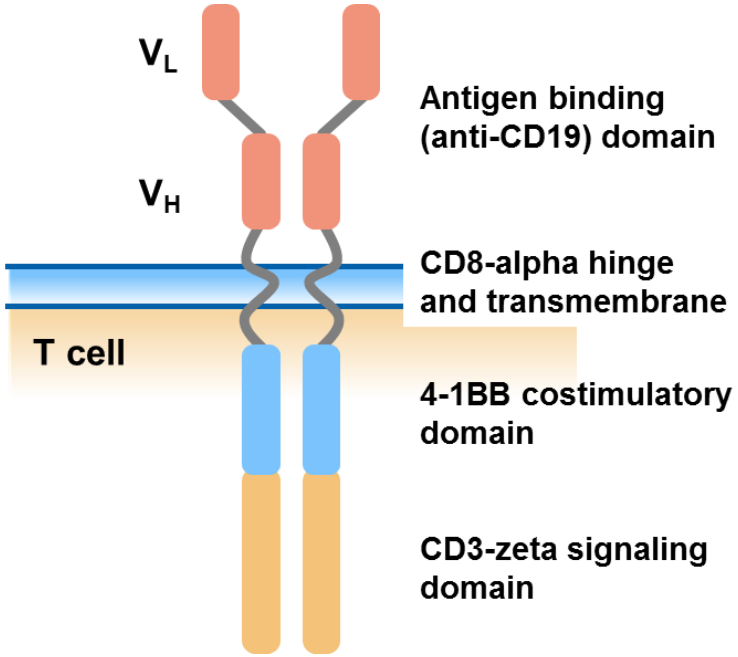
Blinatumomab: Efficacy on Phase 3 TOWER study for r/r B-ALL

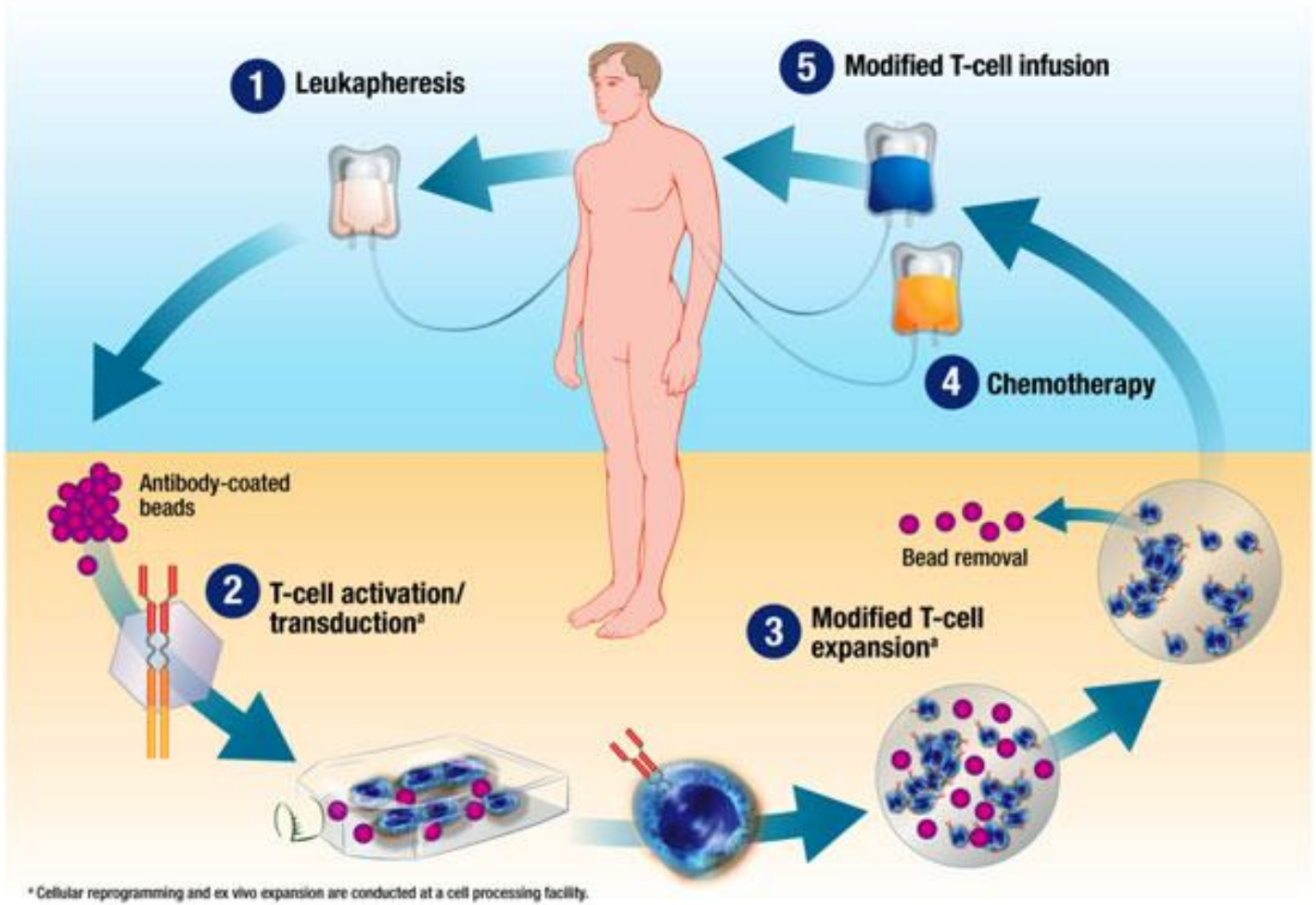


Kantarjian et al. NEJM 2017

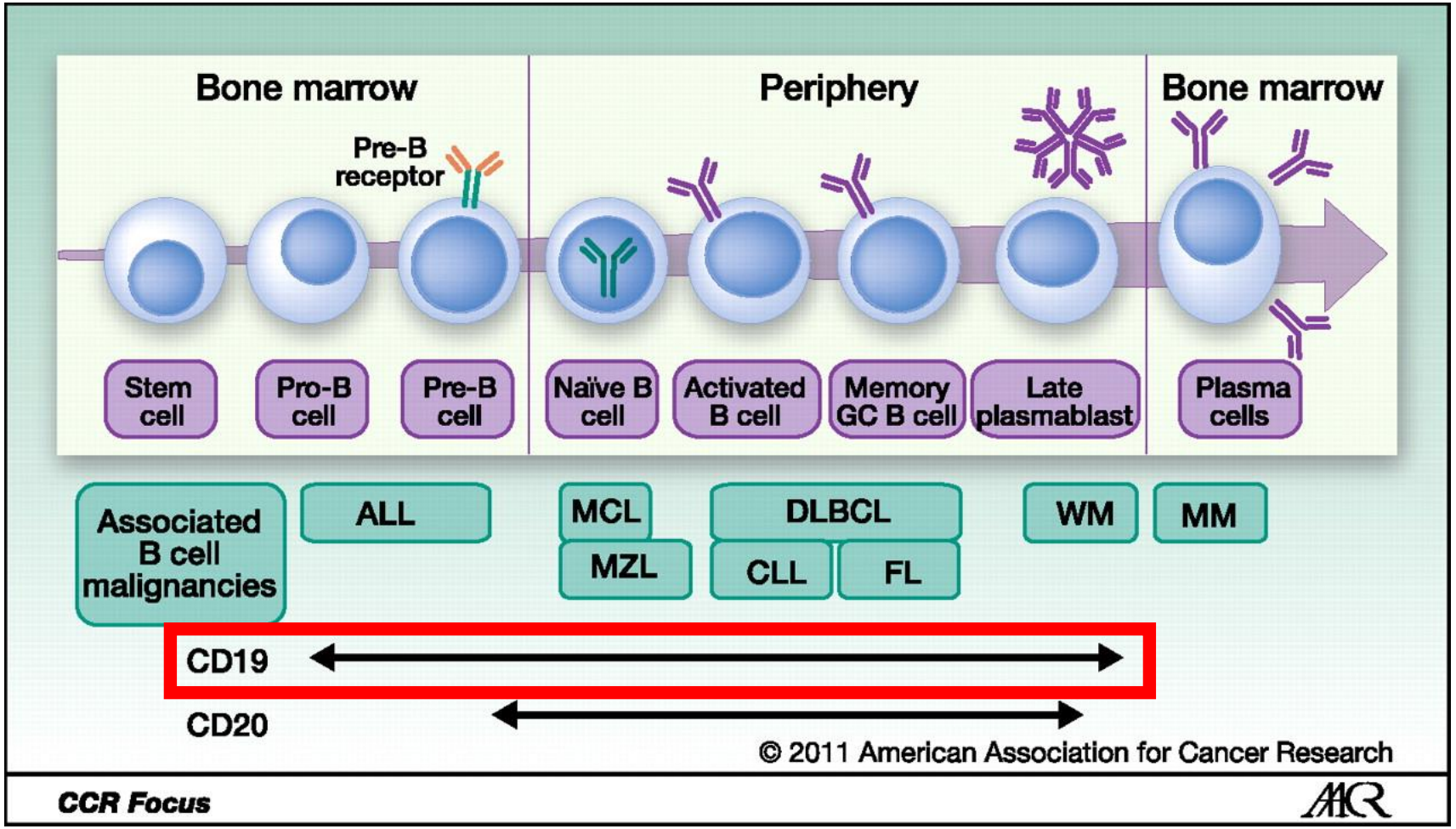
Chimeric Antigen Receptor (CAR) T cell Therapy

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





Rationale for CD19 as a CAR T target



Blanc et al. Clinical Cancer Research 2011

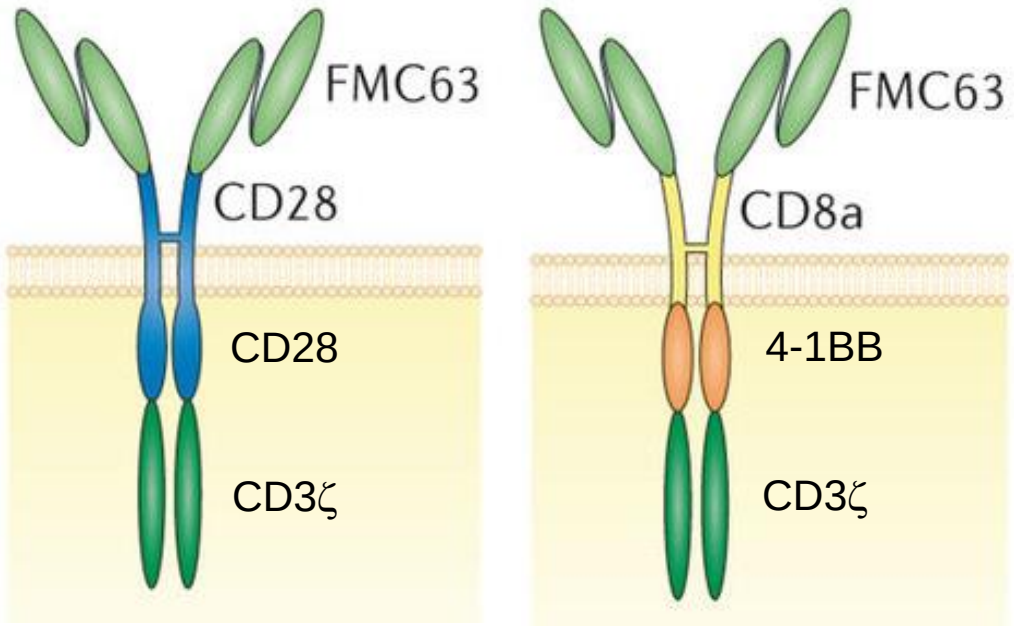
- CD19 is expressed on precursor and mature B cells
- Present on a wide range of B-cell malignancies
- Rarely lost during neoplastic transformation
- Not expressed on BM stem cells or other tissues

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 (DLBCL), high-grade B cell lymphoma, PMBCL, and DLBCL arising from follicular lymphoma
- Tisagenlecleucel
  - JULIET: adult patients with relapsed/refractory large B cell lymphoma—including diffuse large B cell lymphoma, high-grade B cell lymphoma and DLBCL arising from follicular lymphoma after 2 or more lines of systemic therapy.

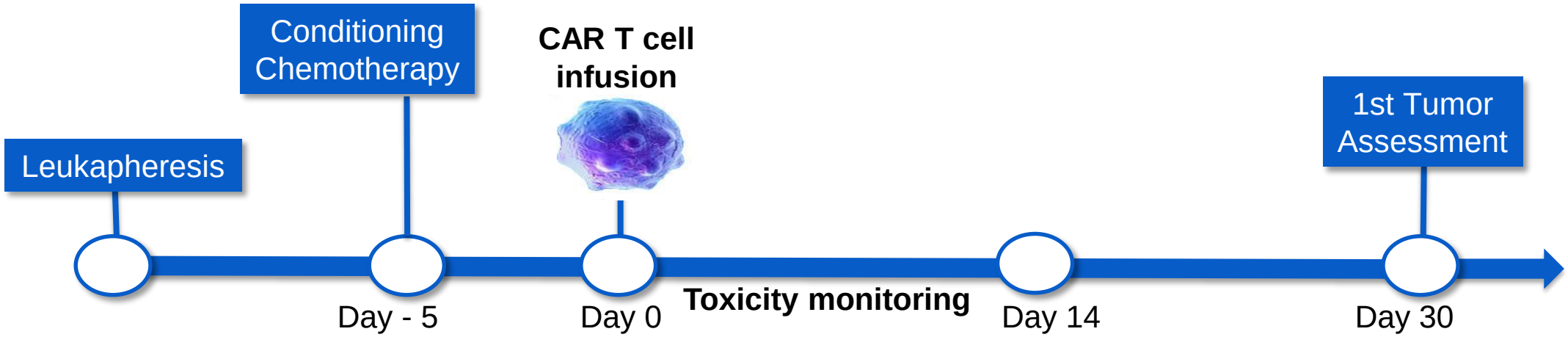
CD19 CAR T products approved for NHL and/or ALL

	NCI	U Penn
CD19 Ab	FMC63	FMC63
Hinge	CD28	CD8a
Transmembrane		
Signal 2	CD28	4-1BB
Signal 1	CD3ζ	CD3ζ
Gene transfer	Retrovirus	Lentivirus
	KTE-C19 **Axicabtagene ciloleucel** **Axi-cel**	**CTL-019** **Tisagenlecleucel**



Adapted from van der Steegen et al. Nat Rev Drug Discov, 2015

Treatment schema for CAR T-cell therapy



Multicenter CAR T-cell trials in aggressive B-cell NHL

Study	ZUMA1	JULIET
Reference	Neelapu et al. NEJM 2017	Schuster et al. NEJM2018
CAR T design	CD19/CD3ζ/CD28	CD19/CD3ζ/4-1BB
CAR T dose	2 x 10^6/kg	Up to 1-5 x 10^8
Conditioning therapy	Cy/Flu	Cy/Flu or Bendamustine
Lymphoma subtypes	DLBCL / PMBCL / TFL	DLBCL / TFL
Relapsed/Refractory	Refractory	Relapsed or refractory
Relapse post-ASCT	23%	49%
Bridging therapy	None	Allowed
Manufacturing success	99%	94%
Treated/Enrolled	108/119 (91%)	111/147 (76%)

Efficacy on ZUMA-1 and JULIET studies

Best response

Study/Sponsor	Product	N	Best ORR	Best CR rate
ZUMA1 / Kite	CD19/CD3ζ/ CD28	108	83%	58%
JULIET / Novartis	CD19/CD3ζ/ 4-1BB	93	52%	40%

Durability

Median F/U mo	N	Ongoing ORR	Ongoing CR rate	Ref
15.4	108	42%	40%	Neelapu et al, NEJM 2017
14	93	34%[#]	32%[#]	Schuster et al, NEJM 2018

[#]Calculated value from publication

PFS/OS

Study/Sponsor	Product	N	Median PFS	Median OS	OS at 12 mo
ZUMA1 / Kite	CD19/CD3ζ/ CD28	108	5.9 mo	Not reached @ 24 mo	59%
JULIET / Novartis	CD19/CD3ζ/ 4-1BB	93	2.9 mo	12 mo	50%

ZUMA-1 Update

Median f/u of 27.1 mo

Ongoing ORR – 39%
Ongoing CR – 37%

Neelapu et al [Locke], ASH 2018
Locke et al [Neelapu], Lancet Oncol 2018

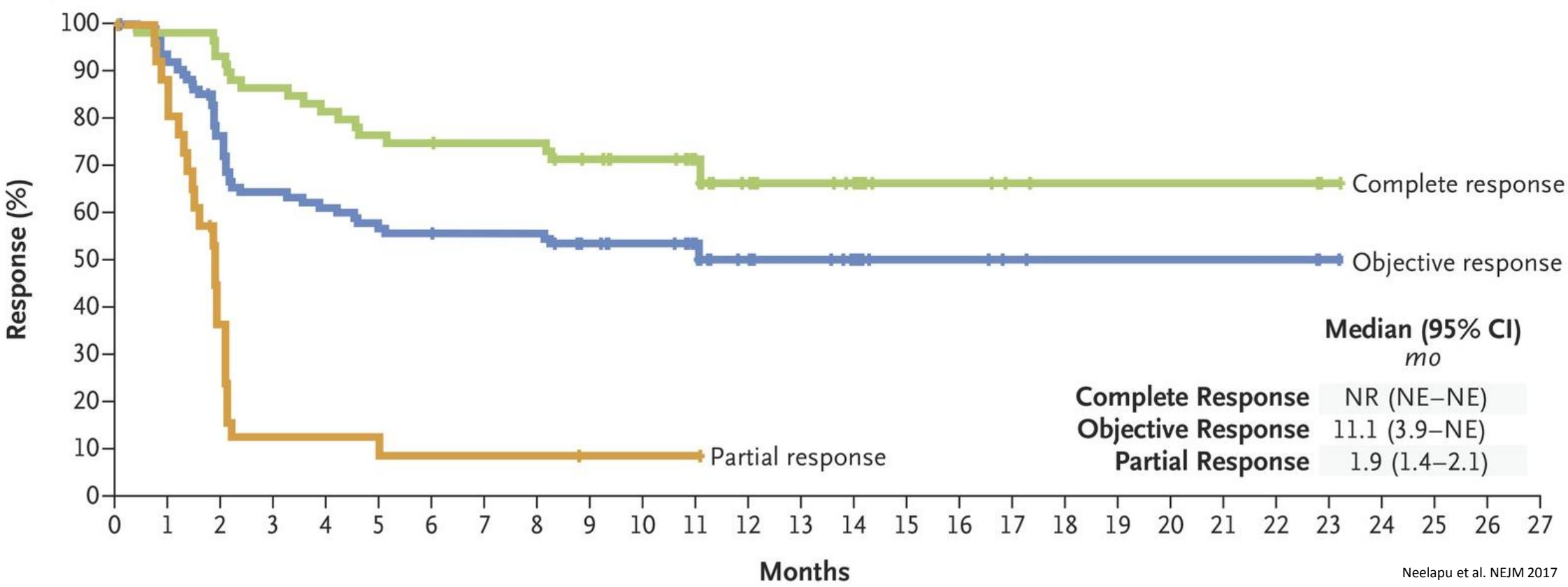
Safety on ZUMA-1 and JULIET studies

Study/Sponsor	Product	N	CRS All Grades	CRS Grade ≥3	NT All Grades	NT Grade ≥3	Toci usage	Steroid usage	Ref
ZUMA1 Kite	CD19/CD3ζ/ CD28	108	93%	13%	65%	31%	45%	29%	Neelapu et al, NEJM 2017
JULIET Novartis	CD19/CD3ζ/ 4-1BB	111	58%	22%	21%	12%	15%	11%	Schuster et al, NEJM 2018

- Lee criteria used for CRS grading on ZUMA1
- U Penn criteria used for CRS grading on JULIET
- Both trials used CTCAE criteria for neurotoxicity (NT) grading
- 3 deaths on ZUMA1 due to AEs – 1 cardiac arrest, 1 HLH, 1 pulmonary embolism

Axicabtagene ciloleucel in r/r Large B-Cell Lymphoma

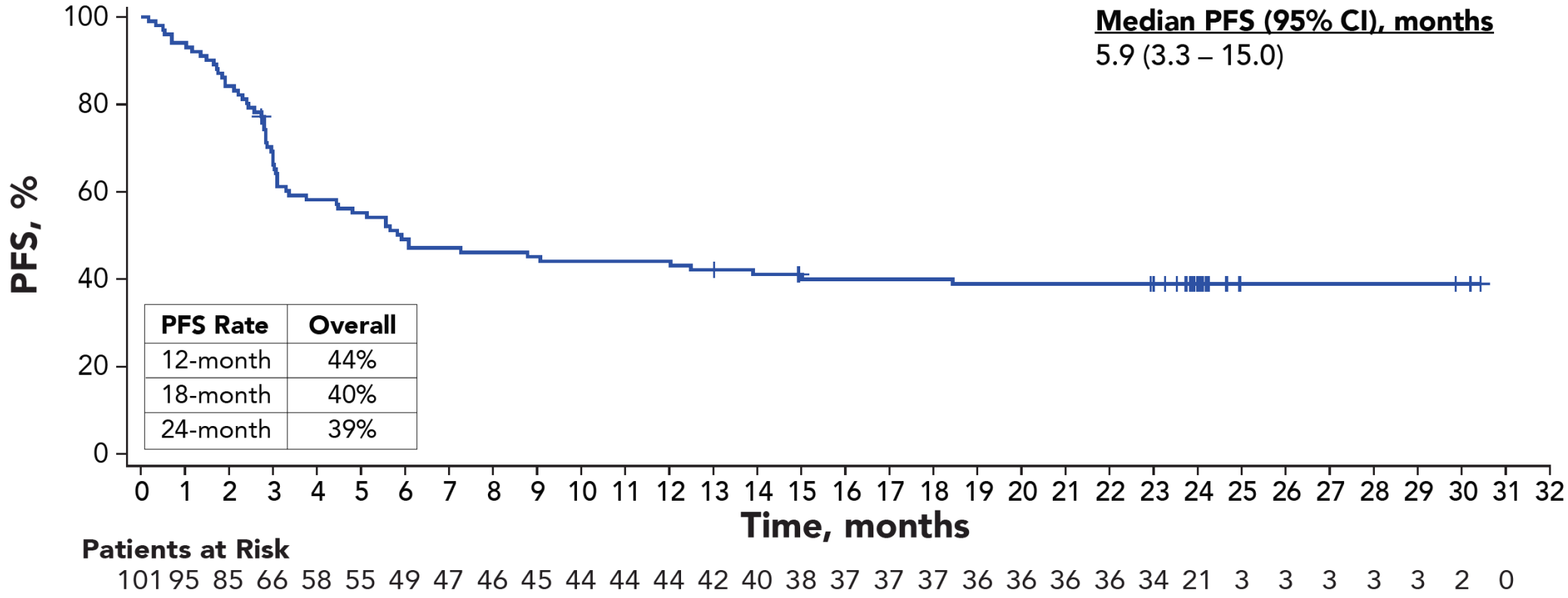
Duration of Response



Neelapu et al. NEJM 2017

ZUMA-1: 39% progression-free at 27.1 mo

Progression-free Survival

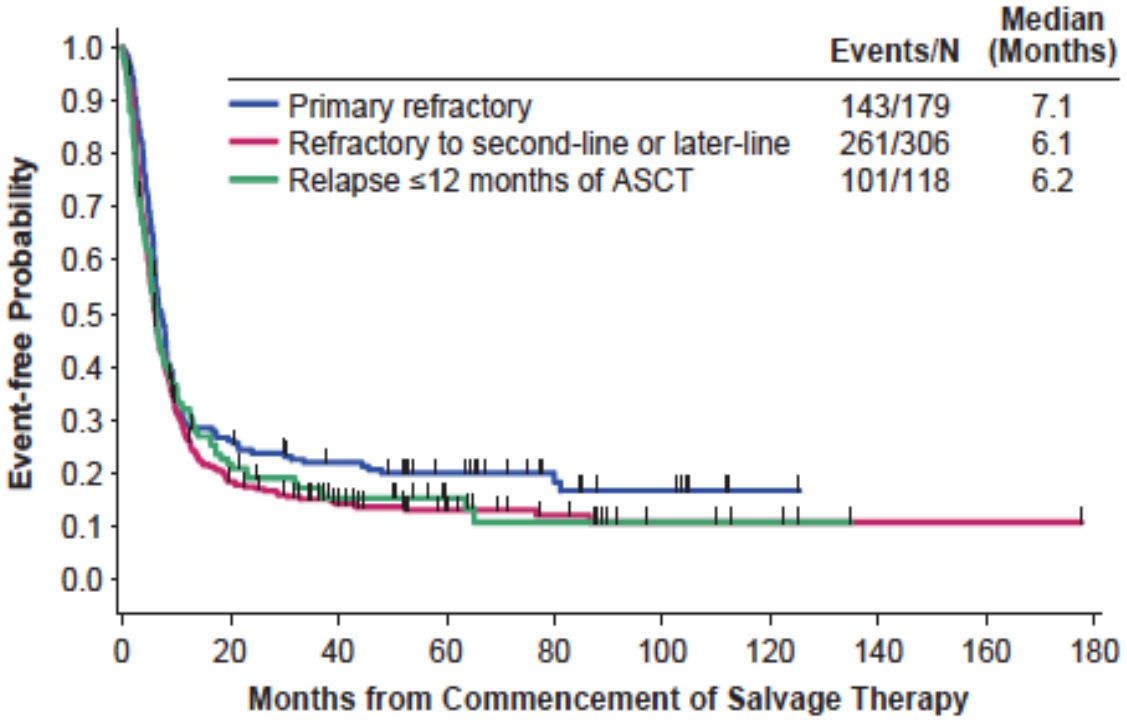


- The 6-month plateau was largely maintained, with only 10 patients progressing beyond the 6-month follow-up

Neelapu, Locke et al. N Eng J Med 2017
Locke et al Neelapu, Lancet Oncol 2019

Outcomes in refractory DLBCL: Historical vs. ZUMA-1

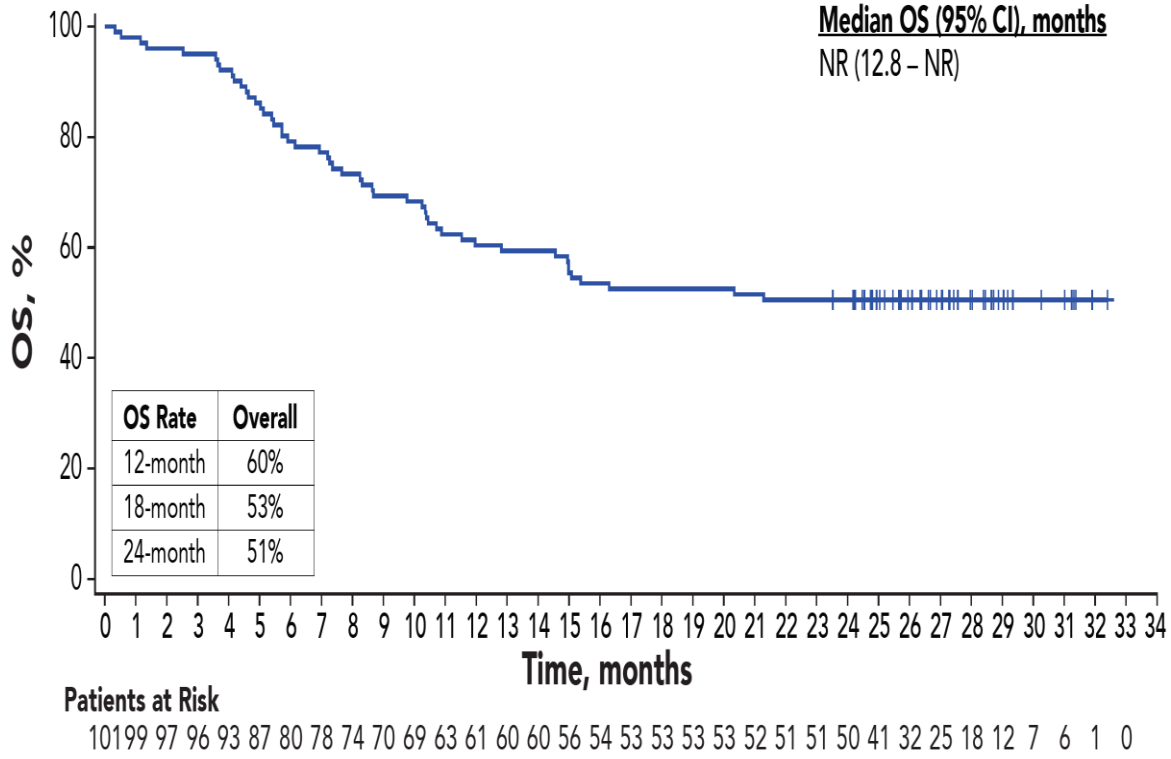
Overall survival: SCHOLAR-1



- N = 636
- ORR = 26%; CR rate = 7%
- Median OS = 6.3 months

Crump, Neelapu et al. *Blood* 2017

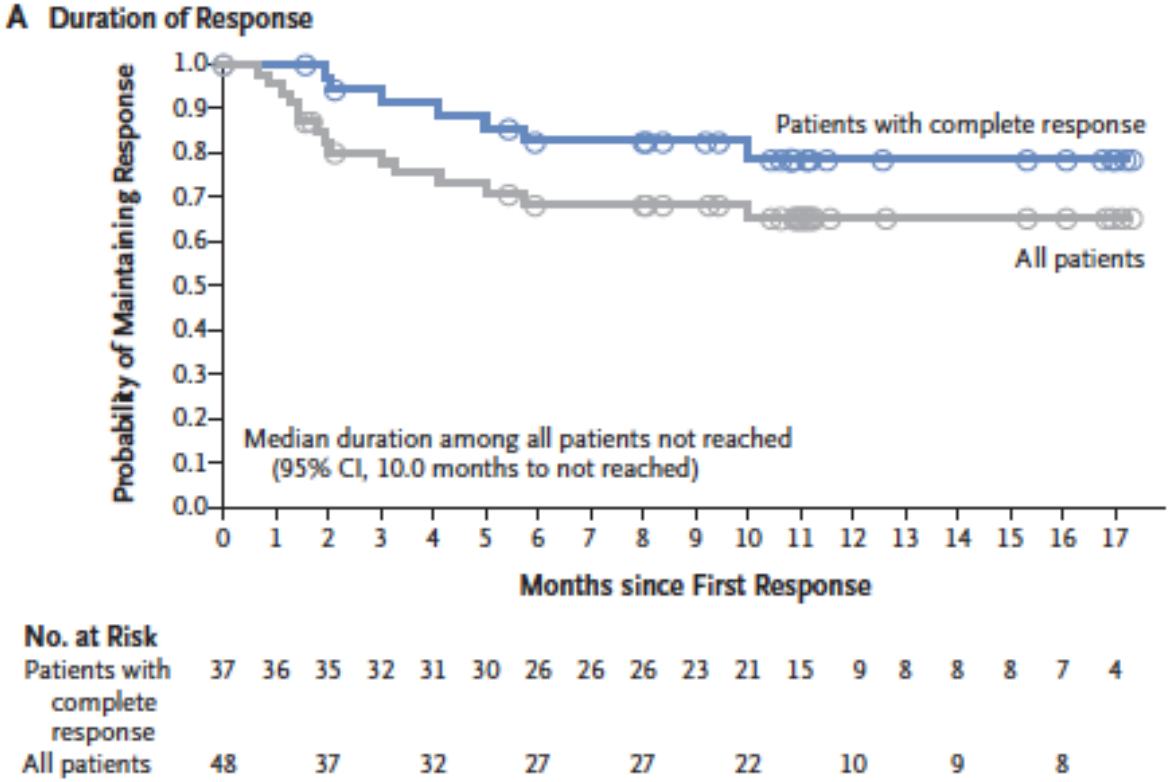
Overall survival: ZUMA1

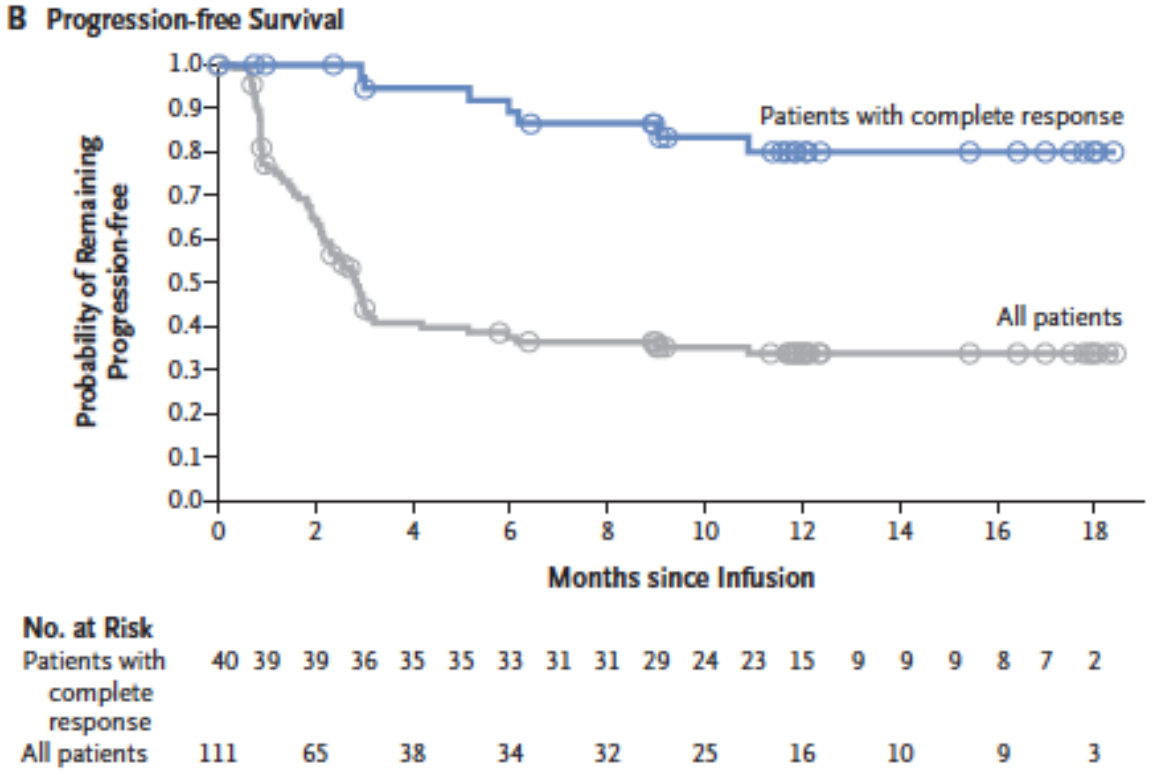


- N = 108
- ORR = 83%; CR rate = 58%
- Median OS = >24 months

Neelapu, Locke et al. *N Eng J Med* 2017
Locke et al Neelapu, *Lancet Oncol* 2019

JULIET: Tisagenlecleucel in r/r Large B-Cell Lymphoma





Schuster et al. *NEJM* 2018

ELIANA Trial: Efficacy of tisagenlecleucel in pediatric ALL

- ELIANA: patients up to age 25 years with B-cell precursor acute lymphoblastic leukemia (ALL) who are refractory or in second or later relapse (N = 75)

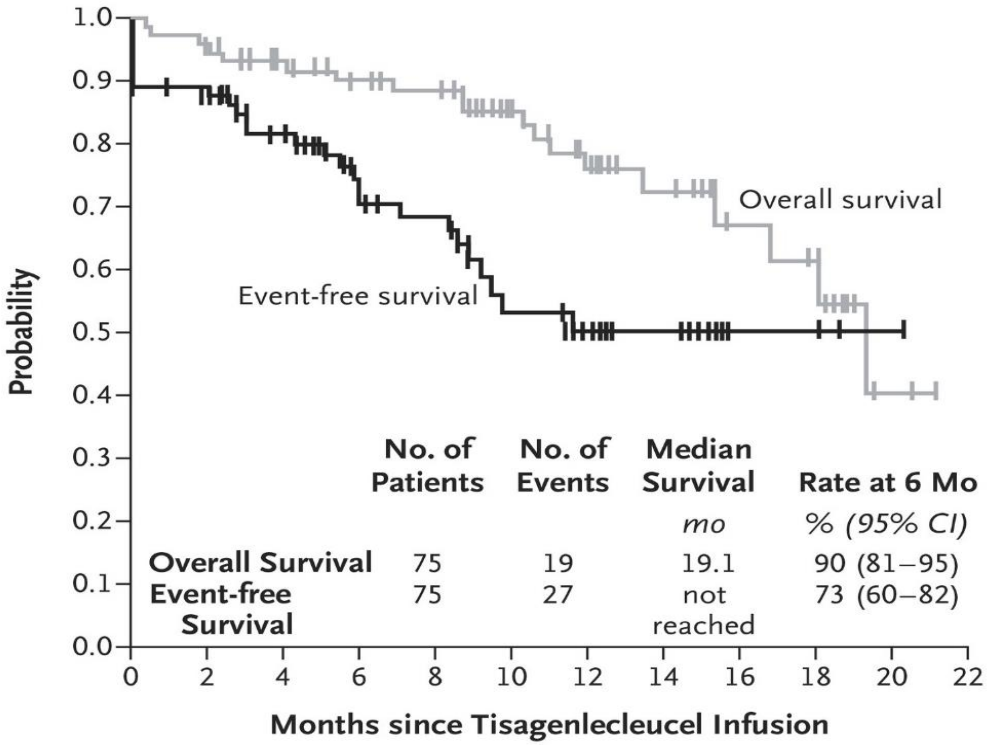
	N (%)
ORR (CR+CRi) within 3 months	61 (81)*
CR	45 (60)
CRi	16 (21)
Day 28 response	58 (95)
CR or CRi with MRD negative bone marrow	61 (81)*

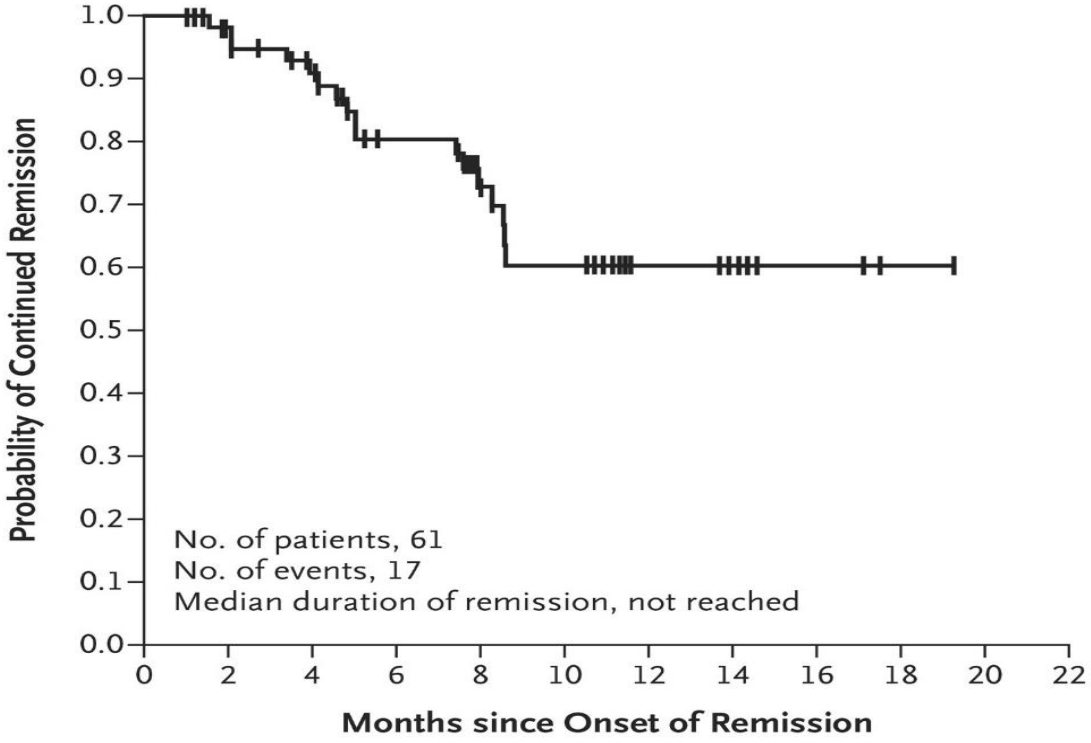
*$P < 0.0001$

- CR = Complete remission
- CRi = Complete remission with incomplete blood count recovery
- MRD negative = Flow cytometry of < 0.01%

Maude et al, *N Eng J Med* 2018

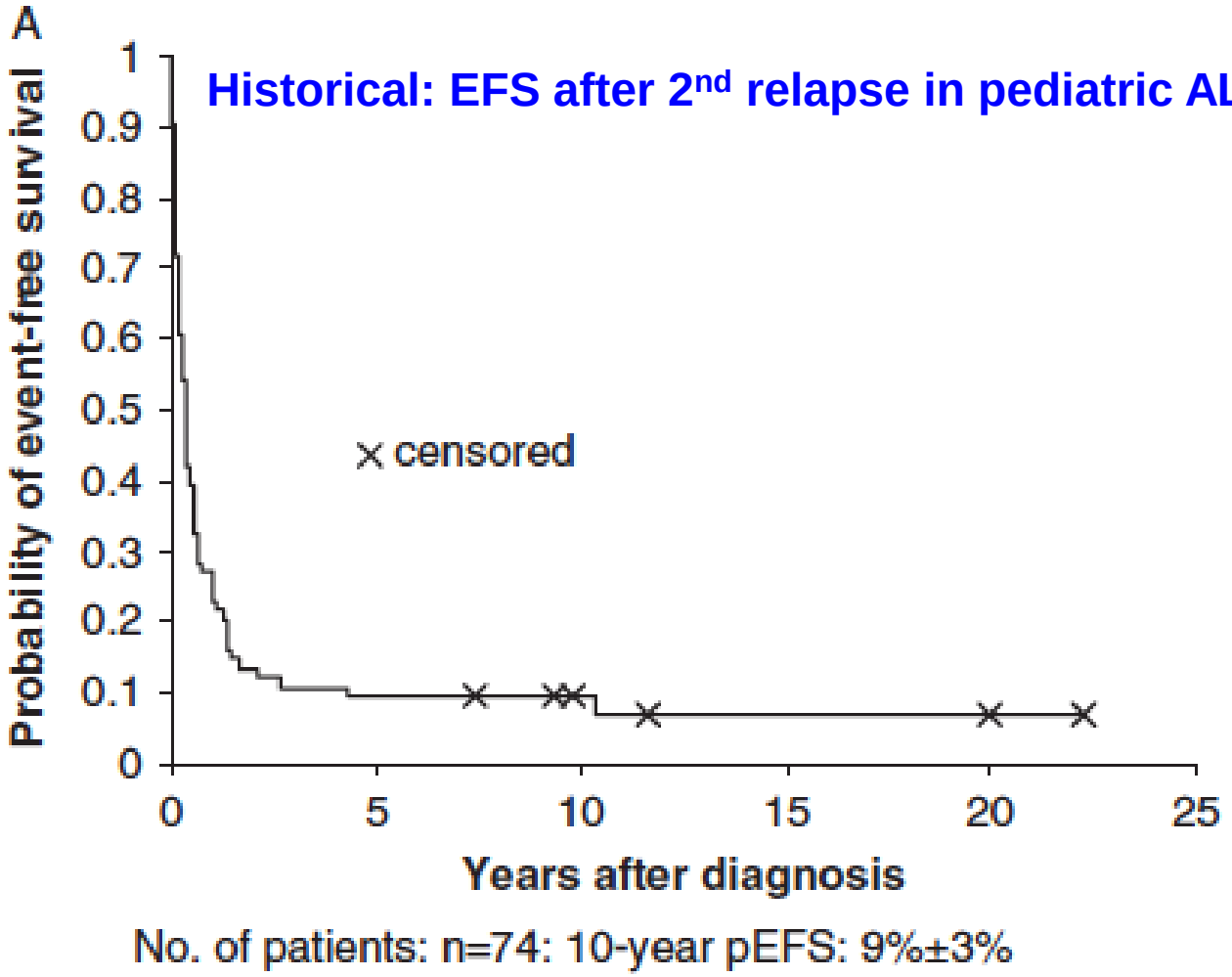
ELIANA Trial: Tisagenlecleucel for pediatric ALL – PFS and OS





Maude et al, *N Eng J Med* 2018

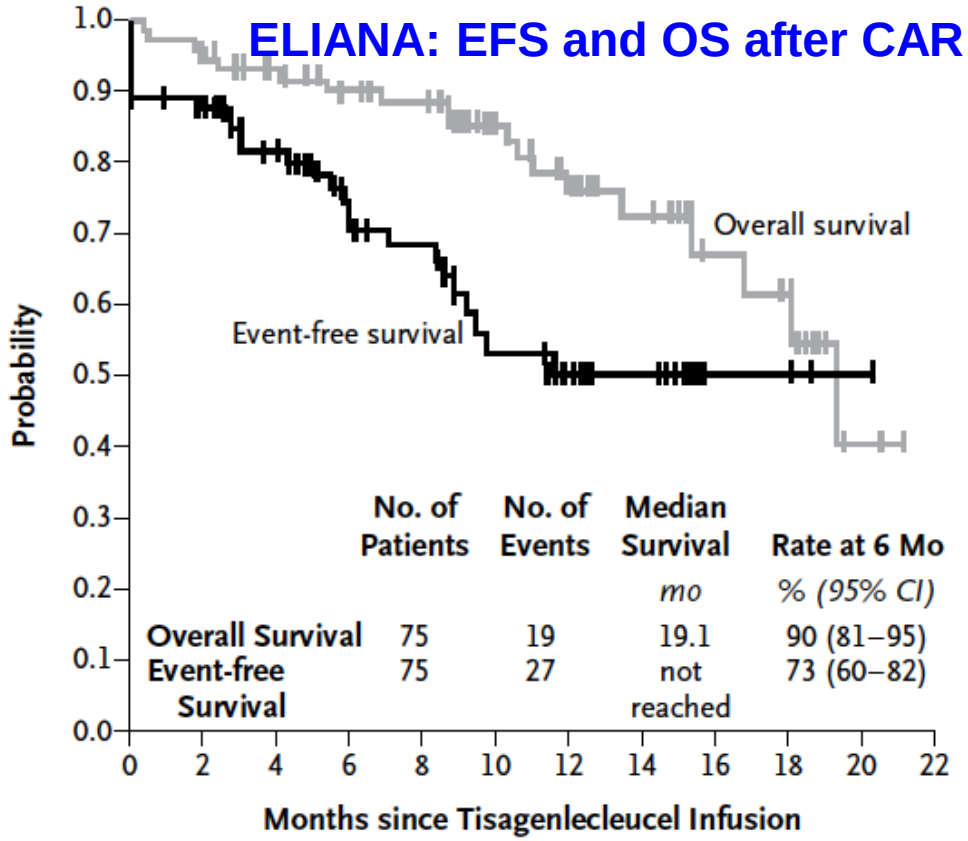
Outcomes in r/r pediatric ALL: Historical vs. ELIANA



Historical: EFS after 2nd relapse in pediatric ALL

Reismuller et al, J Pediatr Hematol Oncol 2013

ELIANA: EFS and OS after CAR T



	No. of Patients	No. of Events	Median Survival (mo)	Rate at 6 Mo % (95% CI)
Overall Survival	75	19	19.1	90 (81–95)
Event-free Survival	75	27	not reached	73 (60–82)

No. at Risk

Overall survival	75	72	64	58	55	40	30	20	12	8	2	0
Event-free survival	75	64	51	37	33	19	13	8	3	3	1	0

Maude et al, N Eng J Med 2018

ELIANA Trial: Safety of tisagenlecleucel in pediatric ALL

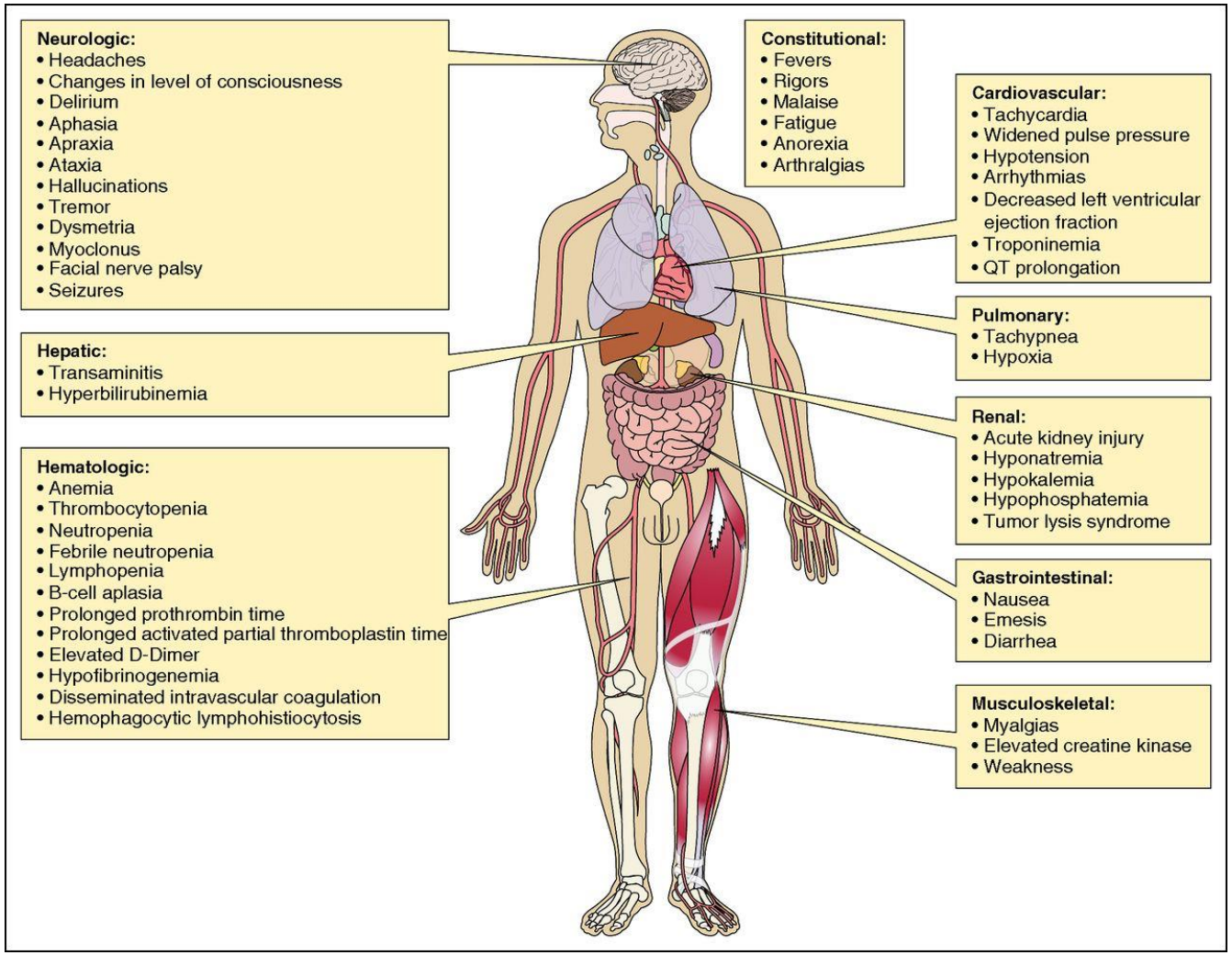
Adverse Events (within 8 wks post-CAR T)	All grades (%)	Grade ≥3 (%)
Cytokine release syndrome (CRS)	77	46
Neurological events	40	13
Infections	43	24
Cytopenias not resolved by day 28	37	32
Tumor lysis syndrome	4	4

- 2 deaths within 30 days of CTL019 (1 ALL, 1 cerebral hemorrhage)
- All patients who achieved CR/CRi developed B-cell aplasia and most received IVIG
- No deaths due to CRS
- No cases of cerebral edema

Maude et al, N Eng J Med 2018

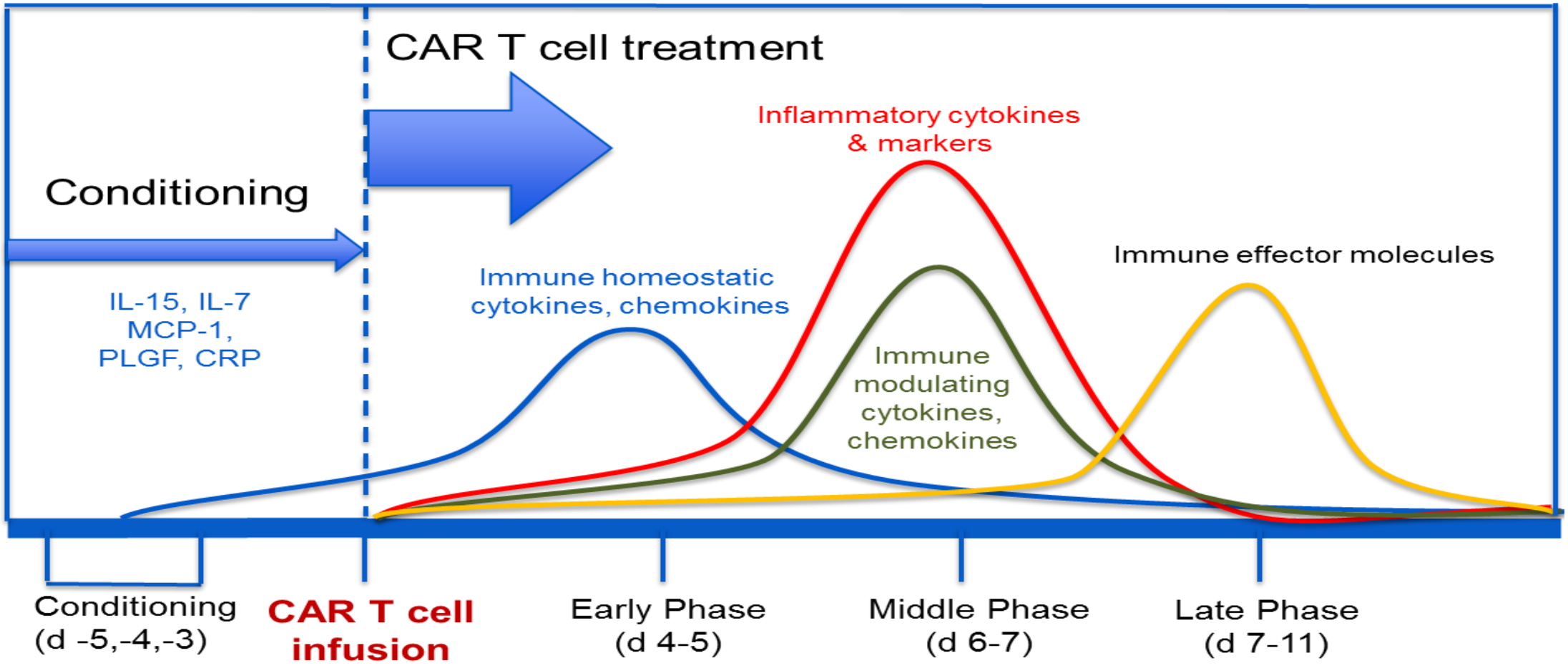
Cytokine Release Syndrome (CRS)

- Systemic inflammatory response caused by cytokines released by CAR T cells and other immune cells and results in reversible organ dysfunction



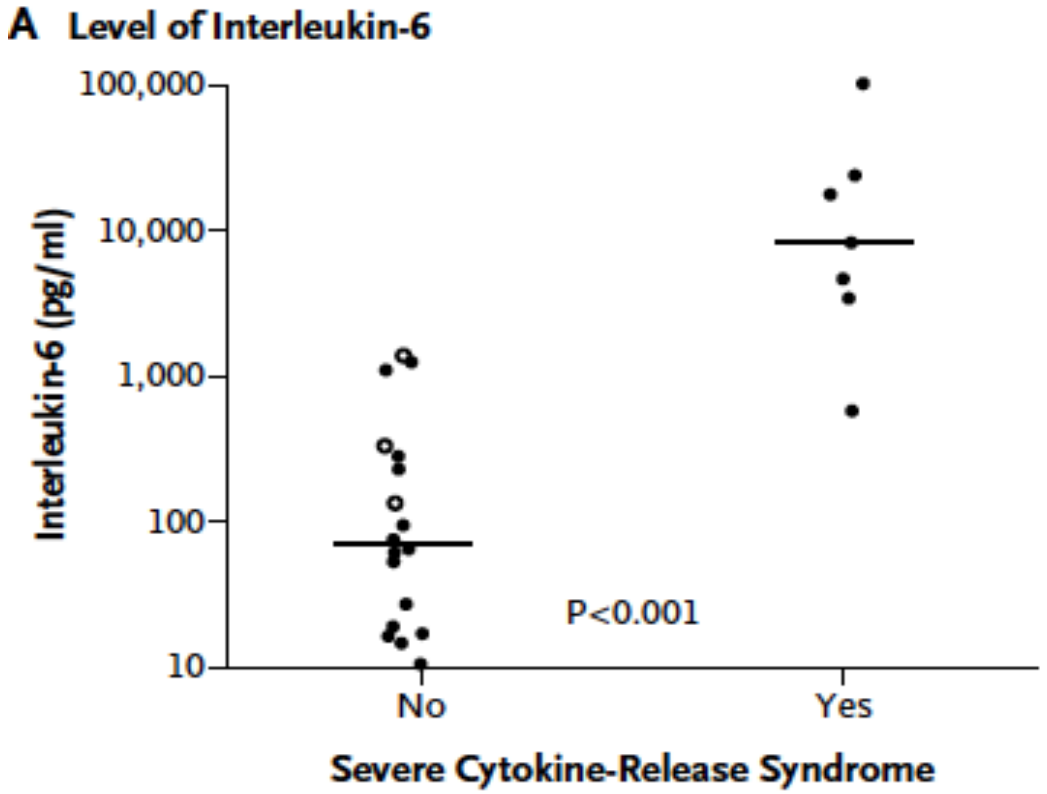
Brudno and Kochenderfer, *Blood 2016;* 127:3321-3330

CRS: Cytokine pattern



Perez, et al, ASH, 2015

IL-6 levels correlate with severity of CRS



Maude et al, *N Engl J Med*, 2014

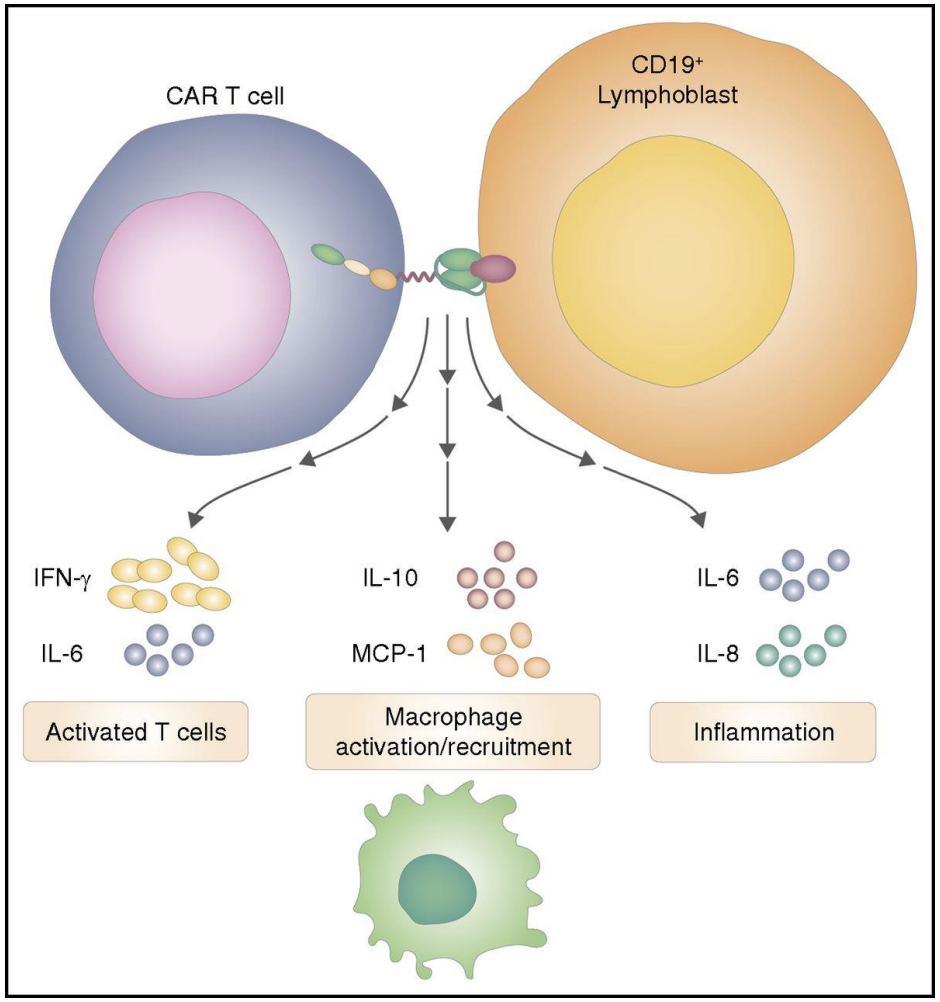
- Tocilizumab (anti-IL-6R Ab) is used for management of severe CRS
- Tocilizumab was FDA approved for management of CRS in 2017

Pathophysiology of CRS

blood®
2017 130: 2295-2306
doi:10.1182/blood-2017-06-793141 originally published online September 18, 2017

Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor–modified T-cell therapy

Kevin A. Hay, Laïla-Aïcha Hanafi, Daniel Li, Juliane Gust, W. Conrad Liles, Mark M. Wurfel, José A. López, Junmei Chen, Dominic Chung, Susanna Harju-Baker, Sindhu Cherian, Xueyan Chen, Stanley R. Riddell, David G. Maloney and Cameron J. Turtle



Shannon L. Maude. *Blood* 2017;130:2238-2240

ZUMA1: Tocilizumab/Steroid use did not impact clinical outcome

	Tocilizumab			Steroids		
	Without n = 58	With n = 43	*P* Value	Without n = 74	With n = 27	*P* Value
ORR, n (%)	47 (81.0)	36 (83.7)	.8	62 (83.8)	21 (77.8)	.56
CR, n (%)	33 (56.9)	22 (51.2)	.69	40 (54.1)	15 (55.6)	1
Ongoing, n (%)	28 (48.3)	16 (37.2)	.31	33 (44.6)	11 (40.7)	.82
Median peak CAR, cells/µL (range)	27 (1-1226)	61 (1-1514)	.0011	32 (1-1226)	50 (1-1514)	.0618
Median CAR AUC, cells/µL days (range)	290 (17-14329)	744 (5-11507)	.0022	408 (17-14329)	725 (5-11507)	.0967

Neelapu et al. *ICML 2017*, Abstract 8

Grading of CRS and Neurological Toxicity

Biology of Blood and Marrow Transplantation
Available online 25 December 2018
In Press, Accepted Manuscript

ASBMT Consensus Grading for Cytokine Release Syndrome and Neurological Toxicity Associated with Immune Effector Cells

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ASBMT Consensus Grading of CRS

CRS Parameter*	Grade 1	Grade 2	Grade 3	Grade 4
Fever#†	Temperature ≥38° C	Temperature ≥38° C	Temperature ≥38° C	Temperature ≥38° C
		With either:		
Hypotension#	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/ or‡		
Hypoxia#	None	Requiring low-flow nasal cannula^ or blow-by	Requiring high-flow nasal cannula^, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg: CPAP, BiPAP, intubation and mechanical ventilation)

#Not attributable to any other cause

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ASBMT Consensus Grading of Neurological Toxicity (ICANS)

Neurotoxicity Domain‡	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score^	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness❖	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse or stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly ; or Non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings§	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Raised intracranial pressure / Cerebral edema	N/A	N/A	Focal/local edema on neuroimaging#	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

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Further Resources

Boyiadzis *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:90
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Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES Open Access

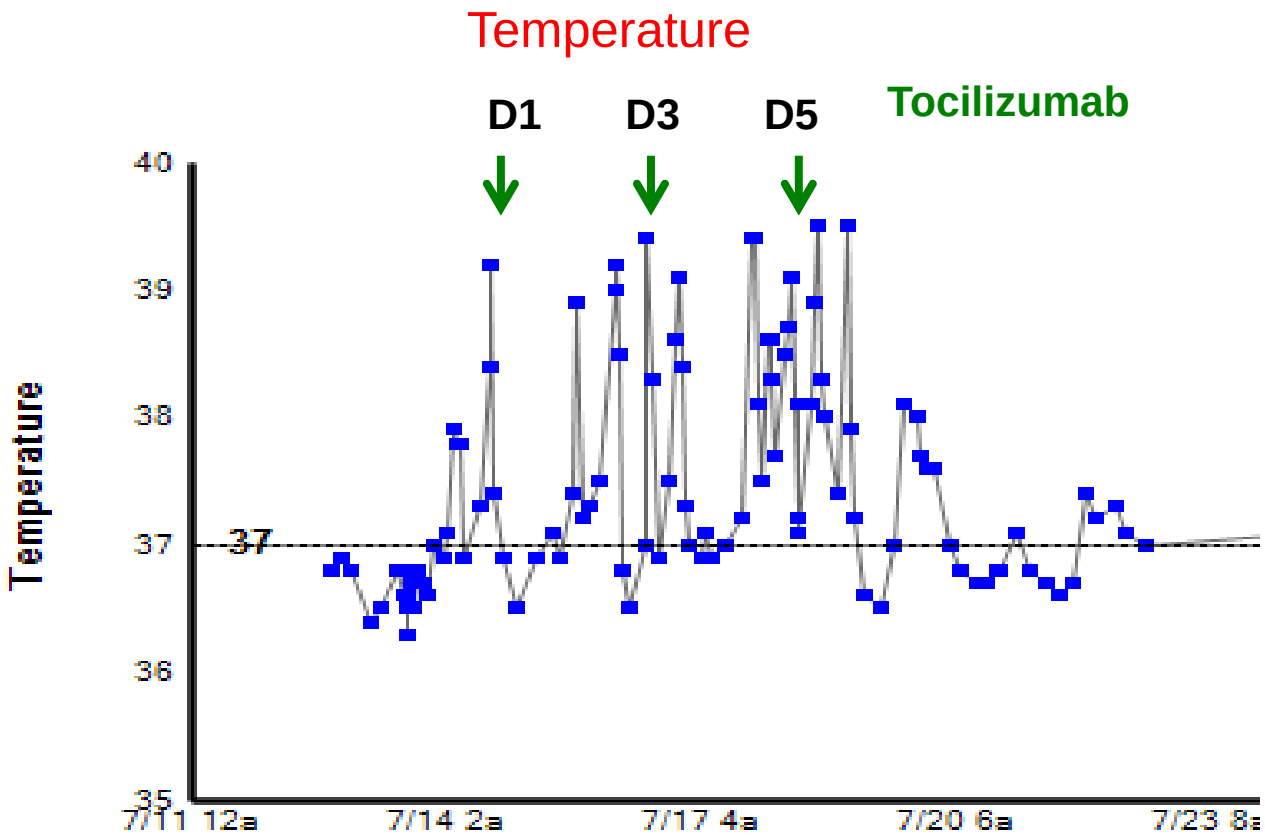
The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of hematologic malignancies: multiple myeloma, lymphoma, and acute leukemia

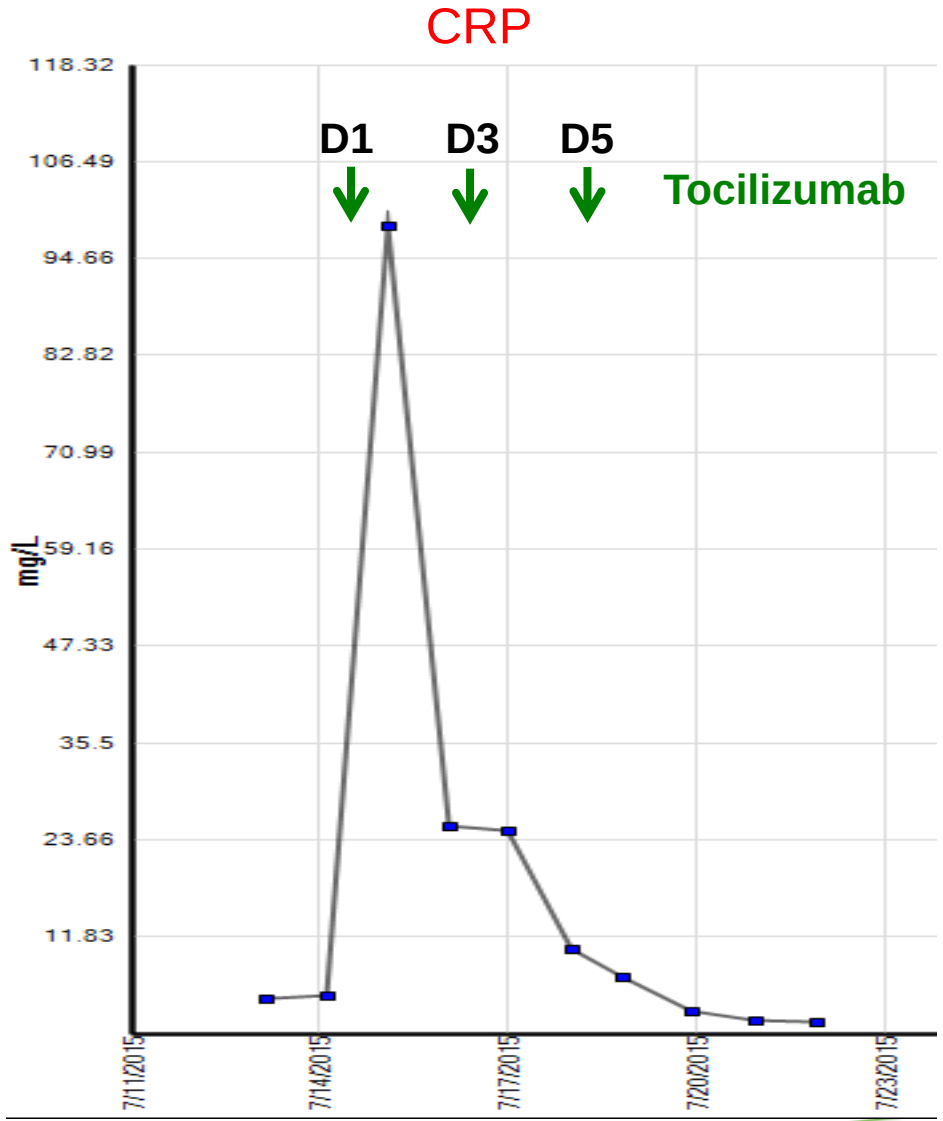
Michael Boyiadzis[1†], Michael R. Bishop[2†], Rafat Abonour[3], Kenneth C. Anderson[4], Stephen M. Ansell[5], David Avigan[6], Lisa Barbarotta[7], Austin John Barrett[8], Koen Van Besien[9], P. Leif Bergsagel[10], Ivan Borrello[11], Joshua Brody[12], Jill Brufsky[13], Mitchell Cairo[14], Ajai Chari[12],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

- 34 yo F diagnosed with with stage II DLBCL
- Achieved a CR after R-CHOP x 6.
- Relapsed 6 months later and was treated with R-ICE x 2 → CR
- Autologous stem cell transplant
- Relapsed 6 mo after ASCT
- Received axi-cel anti-CD19 CAR T cell therapy

Case Study 1: Hospital Course



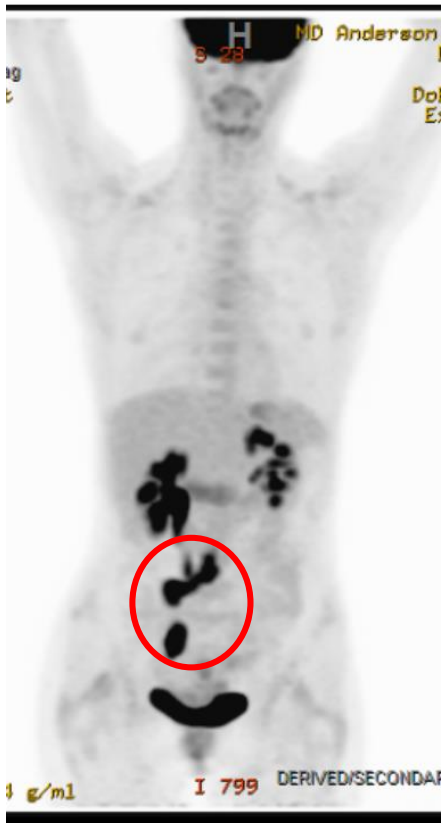


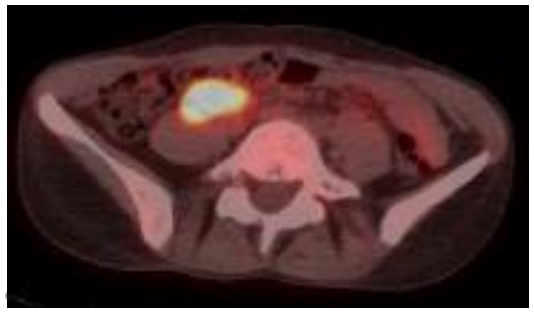
Case Study 1: Impaired handwriting is a sensitive sign of neurotoxicity

Day 4 9 am	I love Shawnee, KS.	MMSE score 29/30
Day 5 01:30 PM Toci 8 mg/kg		27/30
Day 5 03:30 PM		27/30
Day 6 9 am	I miss my kids.	29/30

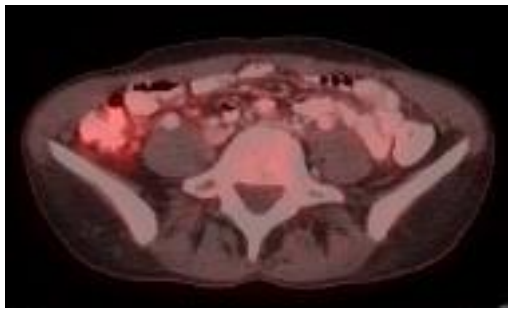
Case Study 1: Response to axi-cel

Baseline





Day 30



Remains in CR
3 years later

Case Study 2

- 47 yo male who presented with back pain and night sweats was found to have bulky retroperitoneal and iliac lymphadenopathy of up to 15 cm in size
- Biopsy revealed double-hit lymphoma (DHL) with bone marrow involvement suggesting Stage IVB disease
- He had partial response after 4 cycles of DA-EPOCH-R but progressed after cycle 6
- After 1 cycle of R-DHAP he had increasing back pain and a CT scan revealed progressive disease

Case Study 2

What treatment would you recommend next?

Option A: High-dose chemotherapy and stem cell transplant

Option B: CAR T-cell therapy

Option B: Axi-cel and tisagenlecleucel CAR T-cell therapies are approved for r/r large B-cell lymphoma after 2 lines of systemic therapy

Case Study 2

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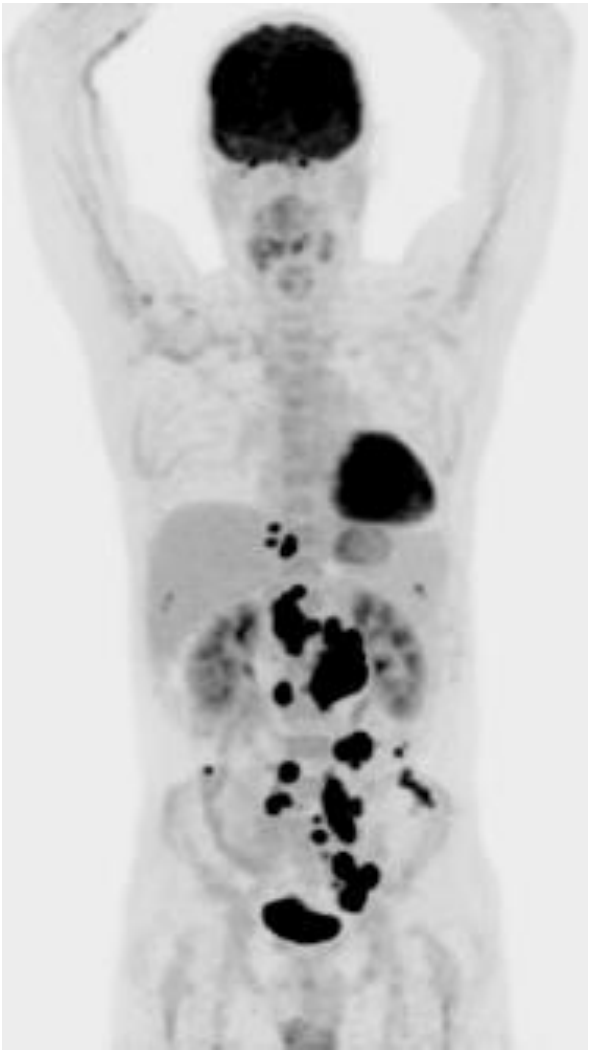
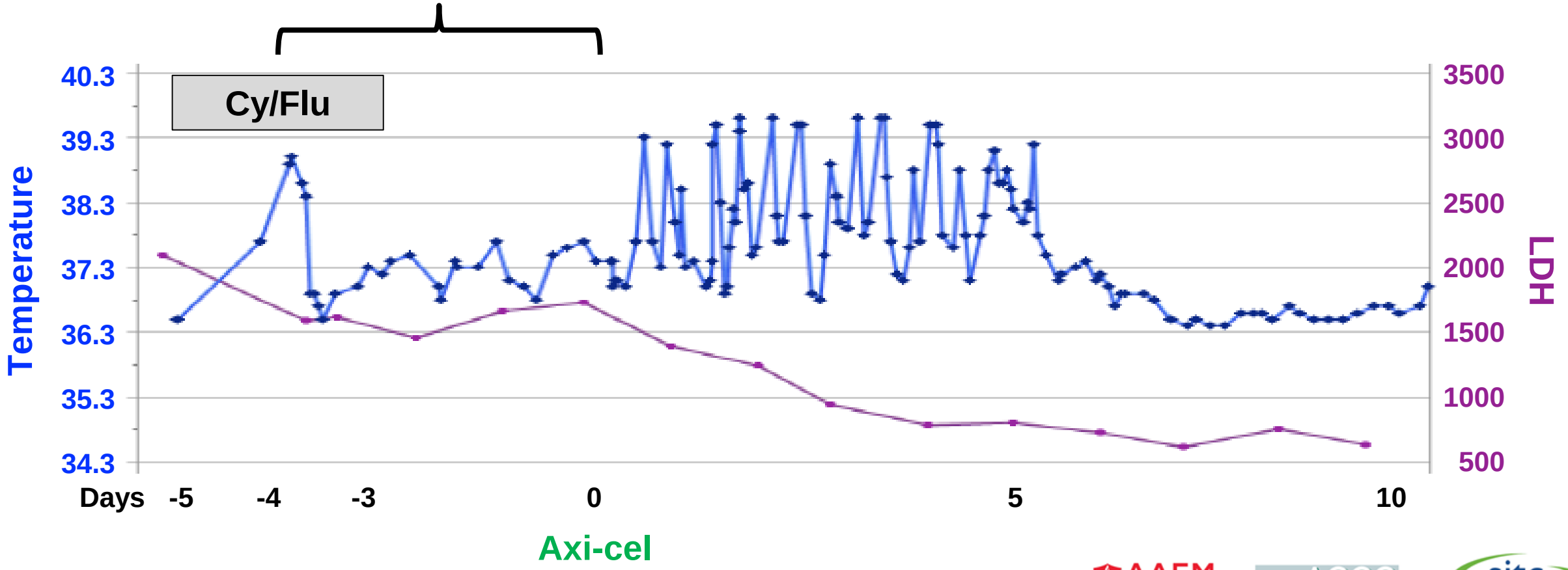
- Undergoes apheresis for axi-cel production



Case Study 2: Hospital Course

- **Infection work-up negative**



Case Study 2

Patient developed fever of 39 ^{o}C on day +1 after CAR T and is neutropenic. What would you do next?

Option A: Administer acetaminophen and continue to monitor

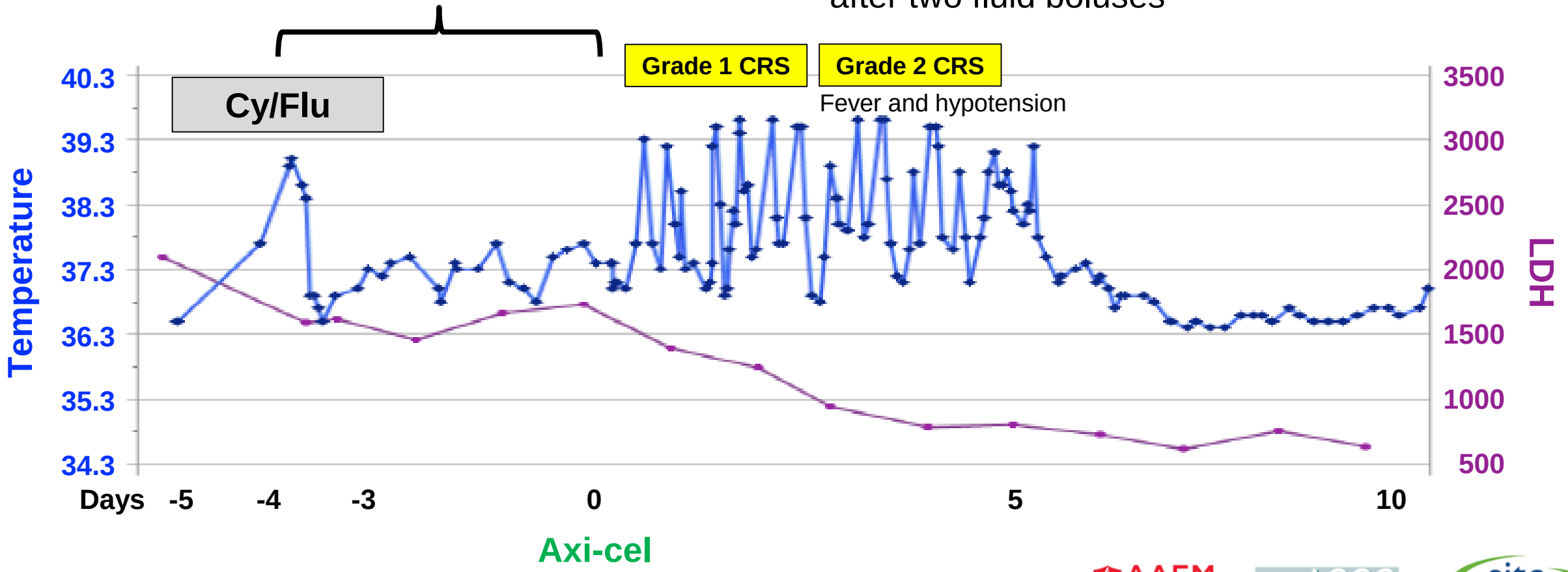
Option B: Administer acetaminophen, obtain blood cultures, chest x-ray, start antibiotics, and continue to monitor

Option B is the right answer as one cannot differentiate clinically whether fever is due to CRS vs. infection/neutropenic fever

Case Study 2: Hospital Course

- **Infection work-up negative**

Hypotension persists after two fluid boluses



Case Study 2

What is the next best step for persistent fever and hypotension?

Option A: Start vasopressors and administer tocilizumab

Option B: Start vasopressors

Option C: Consult Cardiology

Option A is the right answer as tocilizumab is generally indicated for grade 2 CRS and above

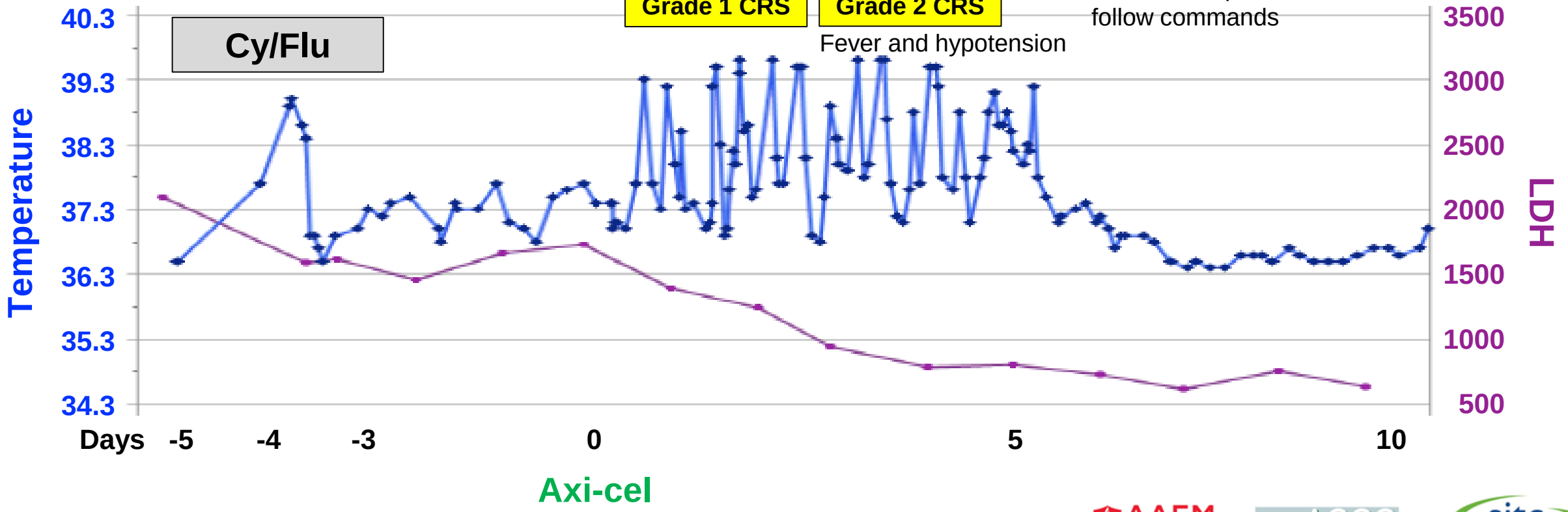
Case Study 2: Hospital Course

- **Infection work-up negative**

Tocilizumab

Grade 3 ICANS

Awake but aphasic, does not follow commands



Case Study 2

Patient developed grade 3 ICANS on day +6 after CAR T. What would you do next?

Option A: Obtain CT head and start dexamethasone 10 mg IV q6hrs

Option B: Obtain CT head but do not administer dexamethasone as corticosteroids are contraindicated and may eliminate CAR T cells permanently.

Option A is the right answer as corticosteroids may be used for the management of severe CAR T-related toxicities

Case Study 2: Hospital Course

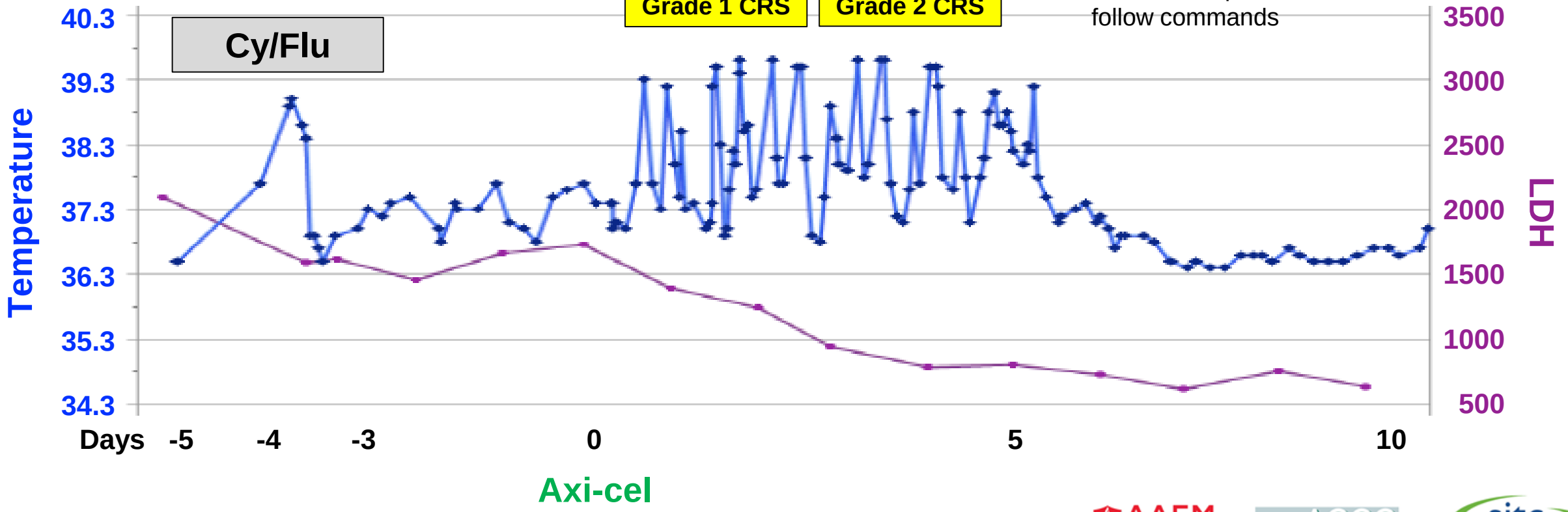
- **Infection work-up negative**

Dexamethasone

Tocilizumab

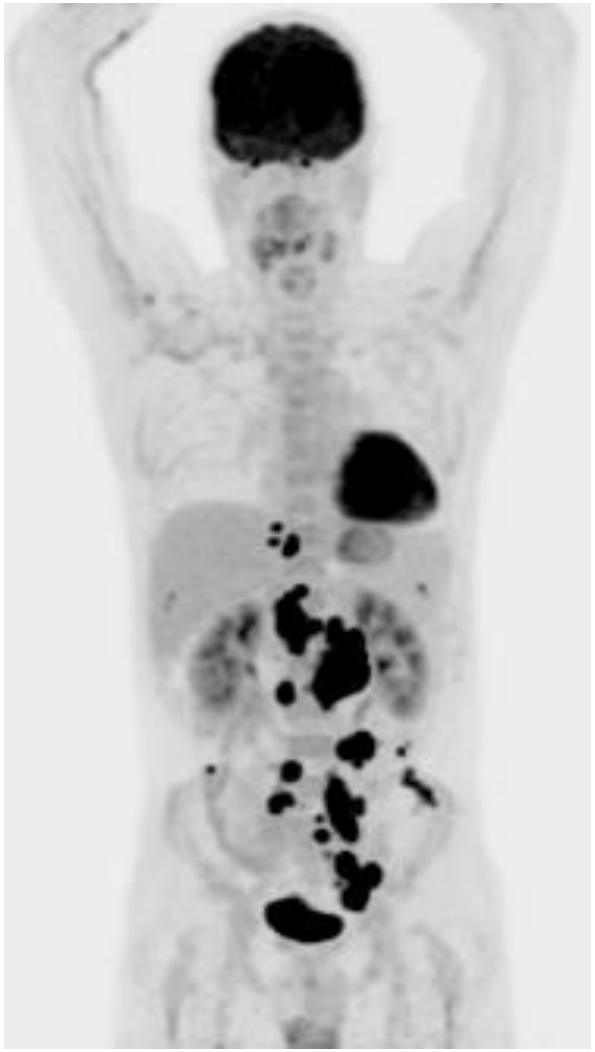
Grade 3 ICANS

Awake but aphasic, does not follow commands

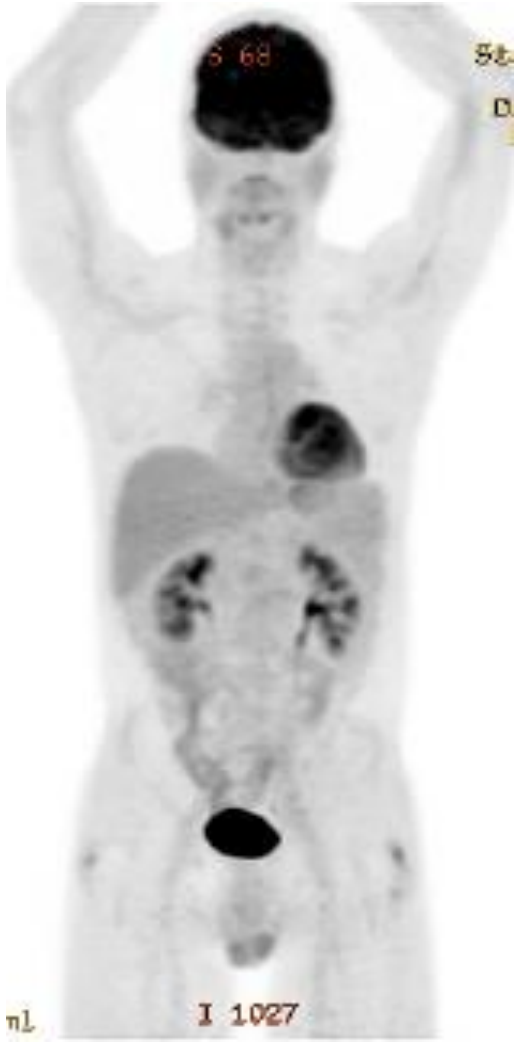


Case Study 2: Response to axi-cel

Baseline



Day 30



- Remains in CR 1 year later