Take a BiTE out of CRS

Practical tips for the diagnosis and management of cytokine release syndrome

Matthew Ulrickson, MD
Banner MD Anderson Cancer Center

TACOS
The Arizona
Clinical Oncology Society

Disclosures

- Advisory Board/Consultant – Gilead, Bristol Meyers Squibb, Stemline, Genentech
- Travel Support – Miltenyi

Case #1

- 68yo woman with IgG kappa myeloma since 2016
  - (hyperdiploid, del 13q and later *TP53* deletion)
- s/p 9 lines of therapy (including teclistamab x 4 doses) now with progression of disease
- PMHx: HTN, asthma, OA, AF

- WBC 1.3 Hb 7.9 Plt 109 Ca 8.7 Cr 1.0
- IgG 3272 with M spike 2.4g/dL; kappa 53, lambda <2
- Echo with LVEF 52%, Lytic bone lesions present

Case #1

- Treated with talquetamab with step up dosing.
- Baseline ferritin 4,000 CRP 30.6
  - Day 1 (0.01mg/kg)
  - Day 4 (0.06mg/kg)
  - Day 7 (0.4mg/kg)
  - Day 10 (0.8mg/kg)
- After day 1 dose: flushing and body aches; infectious workup sent
- No new symptoms after day 4 dose
- Day 5 – new oxygen requirement to 3-4L NC, CXR with bilateral interstitial prominence; some improvement with diuresis but stable O2 requirement. Sodium decrease to 123 (from 135). No fever. Stable BP. Ferritin 5,000 and CRP 47.8
- Day 7 talquetamab postponed due to O2; Sodium improved to 129, O2 improved to 2L NC. Afebrile
- Is this CRS? Would you restart dosing?

Cytokine release syndrome (CRS)

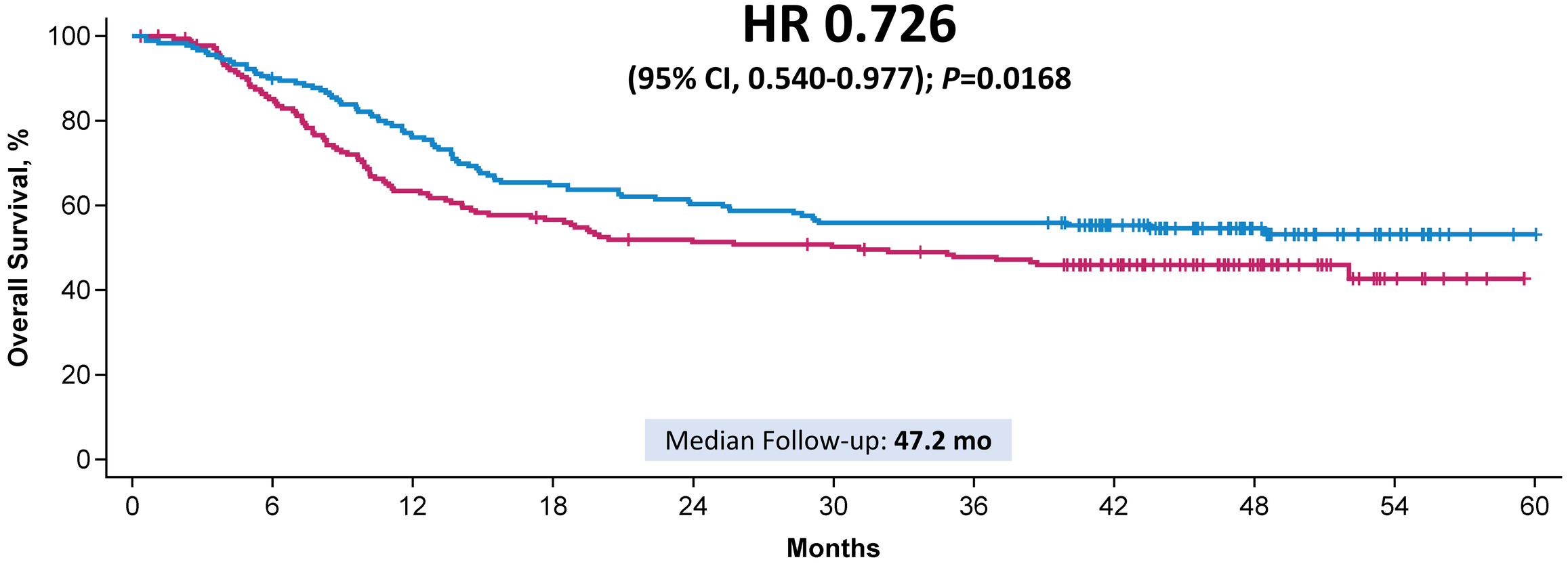
- Systemic inflammatory response to excessive antigen mediated immune stimulation
- Elevations in IL-6, IFN-gamma
- First described in the setting of CAR-T therapy

Primary Overall Survival Analysis of the Phase 3 Randomized ZUMA-7 Study of Axicabtagene Ciloleucel Versus Standard-of-Care Therapy in Relapsed/Refractory Large B-Cell Lymphoma

Jason R. Westin, MD, MS, FACP[1]; Olalekan O. Oluwole, MBBS, MPH[2]; Marie José Kersten MD, PhD[3]; David B. Miklos, MD, PhD[4]; Miguel-Angel Perales, MD[5]; Armin Ghobadi, MD[6]; Aaron P. Rapoport, MD[7]; Anna Sureda, MD, PhD[8]; Caron A. Jacobson, MD[9]; Umar Farooq, MD[10]; Tom van Meerten, MD, PhD[11]; Matthew L. Ulrickson, MD[12]; Mahmoud Elsawy, MD, MSc[13]; Lori A. Leslie, MD[14]; Sridhar Chaganti, MD[15]; Michael Dickinson, MBBS, D Med Sci, FRACP, FRCPA[16]; Yin Yang, MD[17]; Marco Schupp, MD[17]; Christina To, MD[17]; and Frederick L. Locke, MD[18]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [3]Amsterdam UMC, University of Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands; [4]Stanford University School of Medicine, Stanford, CA, USA; [5]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [6]Washington University School of Medicine, St Louis, MO, USA; [7]The Marlene and Stewart Greenebaum Cancer Center, University of Maryland School of Medicine, Baltimore, MD, USA; [8]Servei d'Hematologia Clínica, Institut Català d'Oncologia-Hospitalet, Institut de Recerca Biomèdica de Bellvitge (IDIBELL), Universitat de Barcelona, Barcelona, Spain; [9]Dana-Farber Cancer Institute, Boston, MA, USA; [10]University of Iowa, Iowa City, IA, USA; [11]University Medical Center Groningen, Groningen, The Netherlands; [12]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [13]Division of Hematology and Hematologic Oncology, Department of Medicine, Dalhousie University and QEII Health Sciences Center, Halifax, Nova Scotia, Canada; [14]John Theurer Cancer Center, Hackensack, NJ, USA; [15]Centre for Clinical Haematology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; [16]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and the University of Melbourne, Melbourne, Victoria, Australia; [17]Kite, a Gilead Company, Santa Monica, CA, USA; and [18]Moffitt Cancer Center, Tampa, FL, USA

Axi-Cel Resulted in a Significantly Longer Overall Survival Versus the SOC Arm



No. at Risk											
Axi-Cel	180	161	136	116	108	100	100	80	41	14	1
SOC	179	149	111	98	88	85	79	63	31	7	0

Axi-cel, axicabtagene ciloleucel; HR, hazard ratio; SOC, standard of care.

Key Safety Data[a] At Primary Overall Survival Analysis

- No changes in cumulative treatment-related serious AEs or fatal AEs occurred since the primary EFS analysis[1]

AEs of Interest, %	Axi-Cel n=170		SOC n=168	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
CRS	92%	6%	–	–
Neurologic event	61%	21%	20%	1%
Hypogammaglobulinemia	11%	0%	1%	0%
Cytopenia	80%	75%	80%	75%
Infections	45%	16%	32%	12%

Reported in the safety analysis set. [b] COVID-19 (n=2), sepsis (n=2), hepatitis B reactivation, myocardial infarction, pneumonia, and progressive multifocal leukoencephalopathy (n=1 each). [c] Acute respiratory distress syndrome and cardiac arrest (n=1 each). [d] One patient died of acute myeloid leukemia and one died of lung adenocarcinoma, both deemed unrelated to study treatment per investigator assessment. [e] Includes fatal AEs that occurred outside of the protocol-specified AE reporting window. COVID-19 (n=4), other infection/inflammation (n=3), neurologic organ failure (n=2), respiratory organ failure, cardiac organ failure, progressive disease, and unknown (n=1 each) in the axi-cel arm. Other infection/inflammation (n=7), unknown (n=5), COVID-19 (n=4), respiratory organ failure, and cardiopulmonary/neurologic organ failure (n=1 each) in the SOC arm [f] Hepatitis B reactivation. [g] Cardiac arrest and acute respiratory distress syndrome (n=1 each).

1. Locke FL, et al. *N Engl J Med*. 2022;386:640-654.

AE, adverse event; axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; EFS, event-free survival; SOC, standard of care.

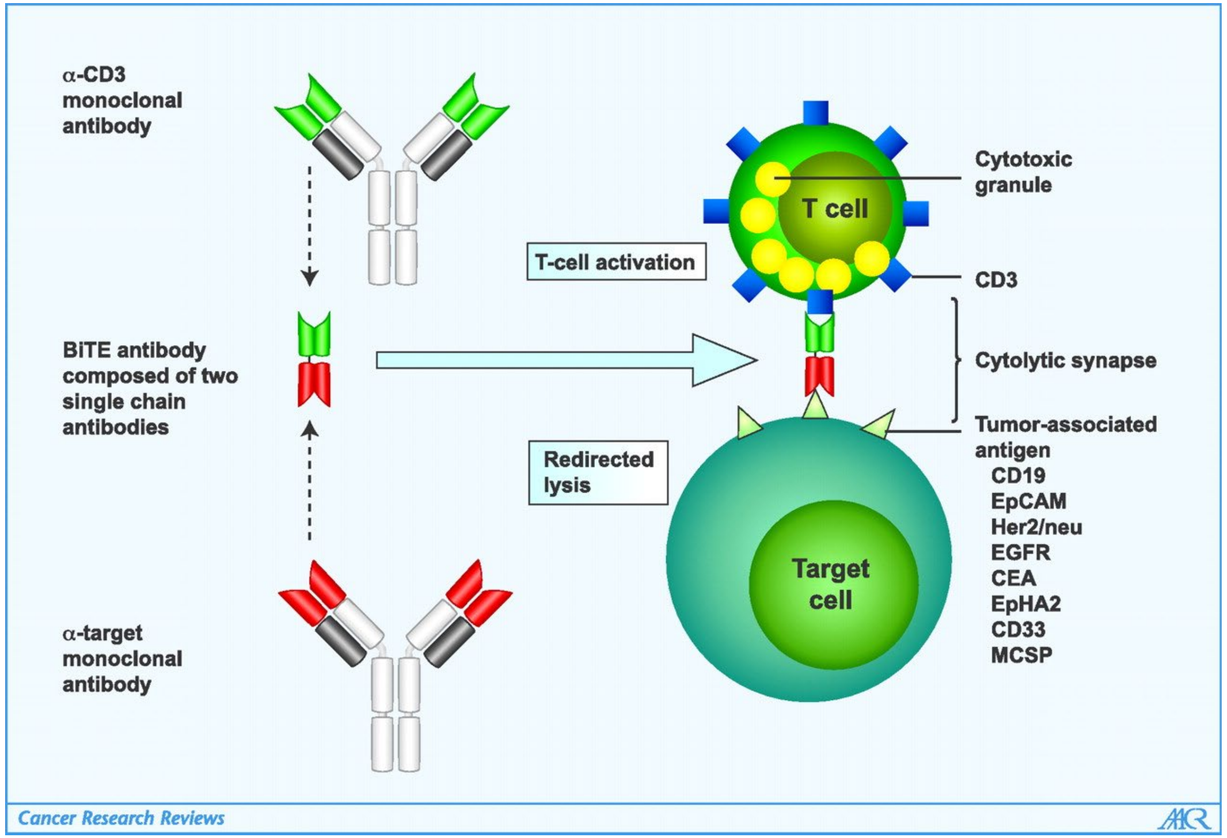
CD19-Targeted CAR Therapies Approved in the United States

Disease	CAR T therapy Approved	Date of Approval	Target	Costimulatory Domain	Pivotal Trial
Large B-cell Lymphoma	**Axicabtagene ciloleucel (Axi-cel)** **Tisagenlecleucel (Tisa-cel)** **Lisocabtagene maraleucel (Liso-cel)**	Oct 2017 May 2018 Feb 2021	CD19 CD19 CD19	CD28-CD3zeta 41BB-CD3zeta 41BB-CD3zeta	ZUMA-1[1,2] JULIET[3] TRANSCEND[4]
Mantle Cell Lymphoma	**Brexucabtagene autoleucel (Brexu-cel)**	July 2020	CD19	CD28-CD3zeta	ZUMA-2[5]
Follicular Lymphoma	**Axicabtagene ciloleucel (Axi-cel)** **Tisagenlecleucel (Tisa-cel)**	Mar 2021 May 2022	CD19 CD19	CD28-CD3zeta 41BB-CD3zeta	ZUMA-5[6] ELARA[11]
Multiple Myeloma	**Idecabtagene vicleucel (Ide-cel)** **Ciltacabtagene autoleucel (Cilta-cel)**	Mar 2021 Feb 2022	BCMA BCMA	41BB-CD3zeta 41BB-CD3zeta	KarMMa[7] CARTITUDE-1[10]
Pediatric ALL	**Tisagenlecleucel (Tisa-cel)**	Aug 2017	CD19	41BB-CD3zeta	ELIANA[8]
Adult ALL	**Brexucabtagene autoleucel (Brexu-cel)**	Oct 2021	CD19	CD28-CD3zeta	ZUMA-3[9]

1. Neelapu et al. NEJM 2017. 2. Locke et al. Lancet Oncol 2019. 3. Schuster et al. NEJM 2019. 4. Abramson et al. Lancet 2020. 5. Wang et al. NEJM 2020.
6. Jacobson et al. ASH 2020. 7. Munshi et al NEJM 2021. 8. Maude et al NEJM 2018.
9. Shah et al Lancet 2021. 10. Berdeja et al Lancet 2021. 11. Fowler et al Nat Med 2022.

BiTEs (Bispecific T-cell Engager)

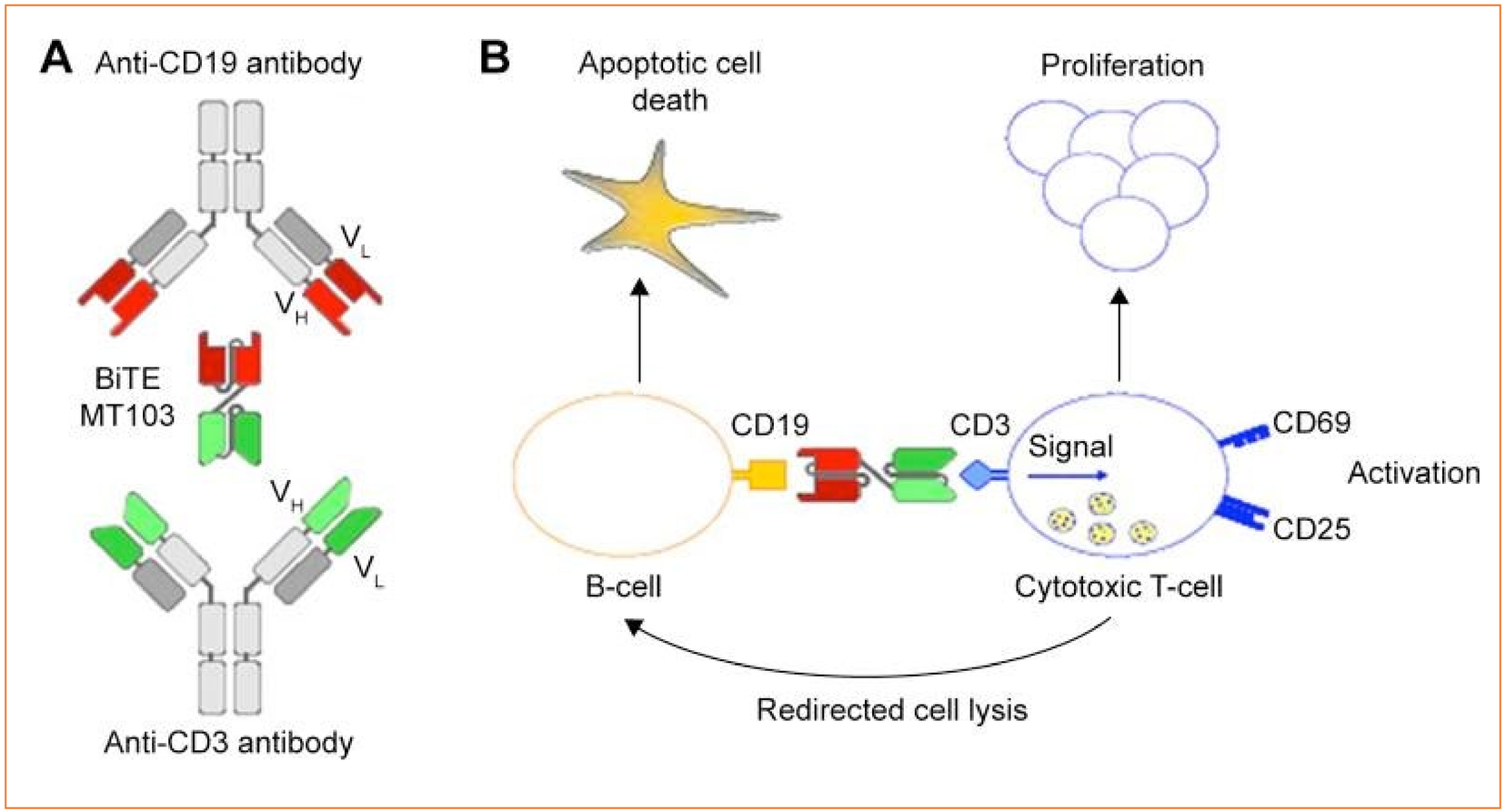
- BiTE antibodies are recombinant proteins with dual specificity for CD3 and a tumor antigen
- BiTE antibodies transiently induce a cytolytic synapse between the cytotoxic T cell and the cancer target cell
- BiTEs replace the need for antigen processing by replacing the MHC / Peptide / T-cell receptor complex
- BiTE-activated T cells proliferate, secrete granzymes and perforin, and engage multiple cancer cells



Baeuerle PA, Reinhardt C. *Cancer Res.* 2009;69(12):4941-4944.

Blinatumomab (B-Lineage-Antitumoral-MoAb)

- Blinatumomab engages the host's CD3+ T cells to cause direct lysis of CD19+ target / tumor cells
- This type of immunotherapy brings autologous effector cells into direct contact with the target and nothing else



Le Jeune C, Thomas X. *Drug Des Devel Ther.* 2016;10:757-765.

Blinatumomab

- Blinatumomab-activated T cells secrete inflammatory cytokines
  - Short half-life
    - $t_{1/2}$ ~2 hours
  - Delivered as a continuous infusion for 28-day cycles, then 2 weeks off

Le Jeune C, Thomas X. *Drug Des Devel Ther.* 2016;10:757-765.

BiTEs in Lymphoma and Myeloma

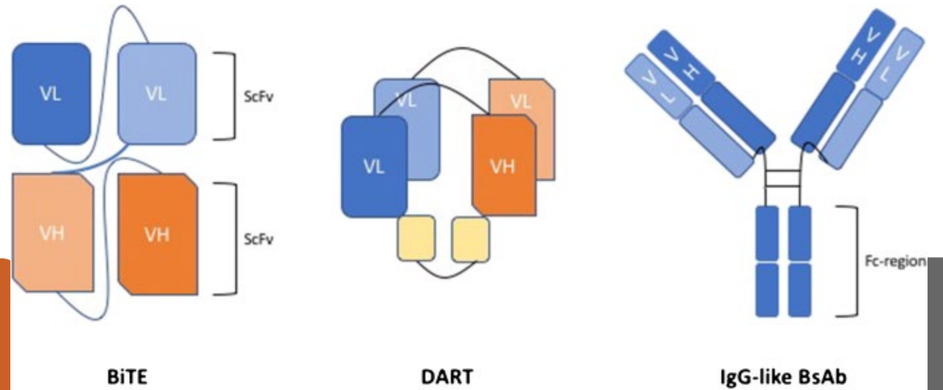
- Lymphoma (all CD3 x CD20)
  - Glofitamab (*NEJM* 12/15/22) (DLBCL)
  - Epcoritamab (*JCO* 12/22/22) (DLBCL)
  - Mosunetuzumab (*Lancet Onc* 8/23/22) (FL)

- Myeloma
  - Teclistamab (BCMA x CD3) – *NEJM* 8/11/22
  - Talquetamab (GPRC5D x CD3) *NEJM* 12/15/22
  - Elranatamab (BCMA x CD3) – *Nature Med* 8/15/23

CAR T Cells vs BiTE

- One-time infusion; CAR T-cell in vivo expansion 1,000- to 10,000-fold amplifies activity; CAR T cells persist – so not easy to start/stop
- Time to treatment of 10 to 28 days due to manufacturing
- CRS generally more frequent and higher grade

- Repeated infusions; in setting of toxicity, doses can be held and modified
- Time to treatment only depends on timing of authorization
- All products with some CRS, but less common and lower grade compared to CAR-T
- Monovalent CD3 binding enables longer t½ and less neurotoxicity
- Newer generations of BsAbs include the dual-affinity re-targeting antibody (DART) and tandem diabody (TandAb) platforms (A BiTE is a variable-fragment Fv based bispecific antibody (BsAb))



VH, heavy chain variable region; VL, light-chain variable region; ScFv, single-chain variable fragments; Fc, fragment crystallizable

Bock AM, et al. Bispecific Antibodies for Non-Hodgkin Lymphoma Treatment. Curr Treat Options Oncol. 2022 Feb;23(2):155-170. doi: 10.1007/s11864-021-00925-1. Epub 2022 Feb 19. PMID: 35182296.

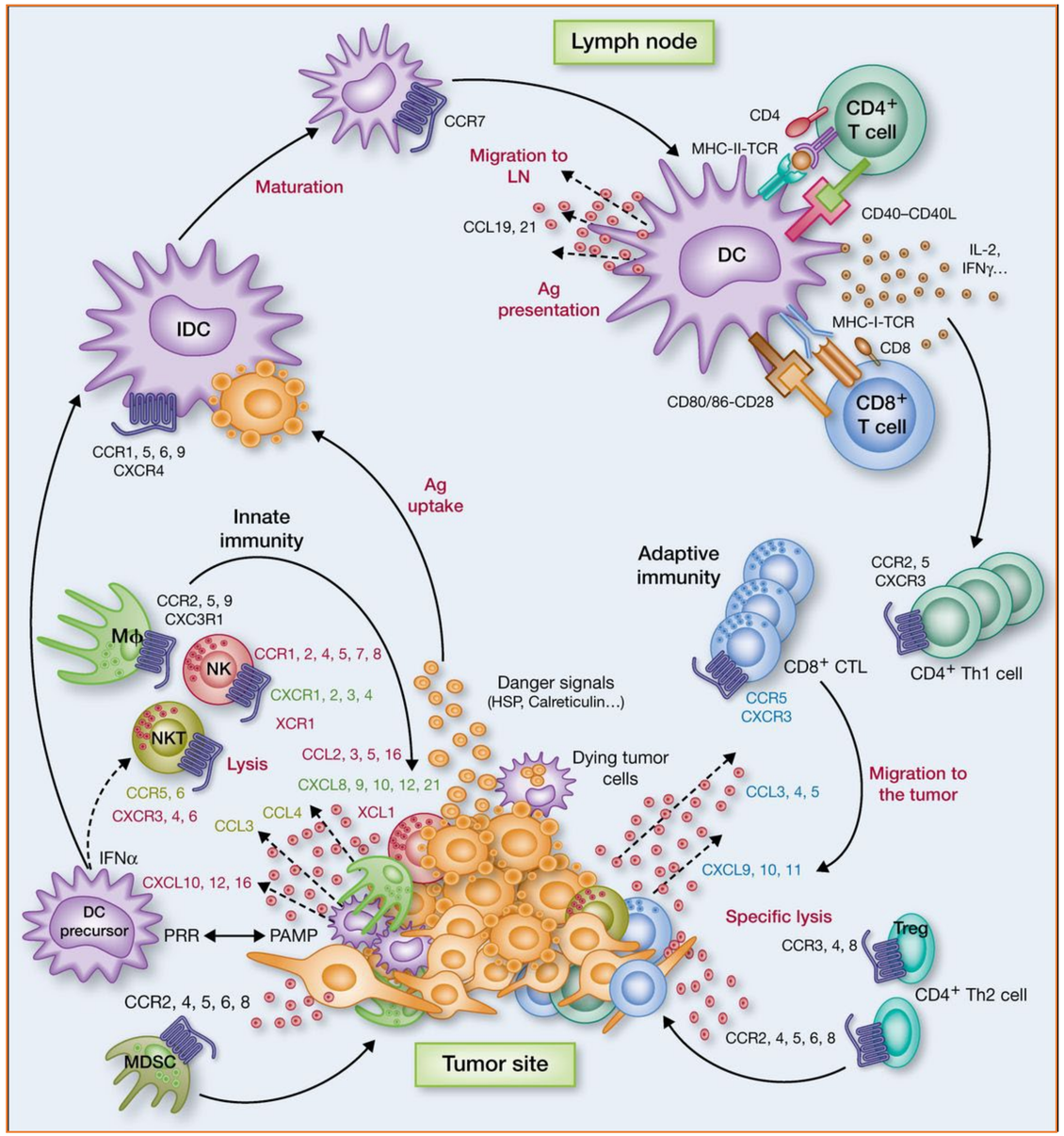
CRS: Clinical Signs and Symptoms

Organ System	Symptoms and Findings Can Include
Constitutional	**Fever** ± rigors, malaise, fatigue, anorexia, myalgias, arthralgias, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late),
Coagulation	Elevated D-dimer, hypofibrinogenemia ± bleeding, disseminated intravascular coagulation
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Headache, mental status changes, confusion, delirium, word-finding difficulty or frank aphasia, hallucinations, tremor, altered gait, seizures

CAR T, chimeric antigen receptor T cell; CRS, cytokine release syndrome.

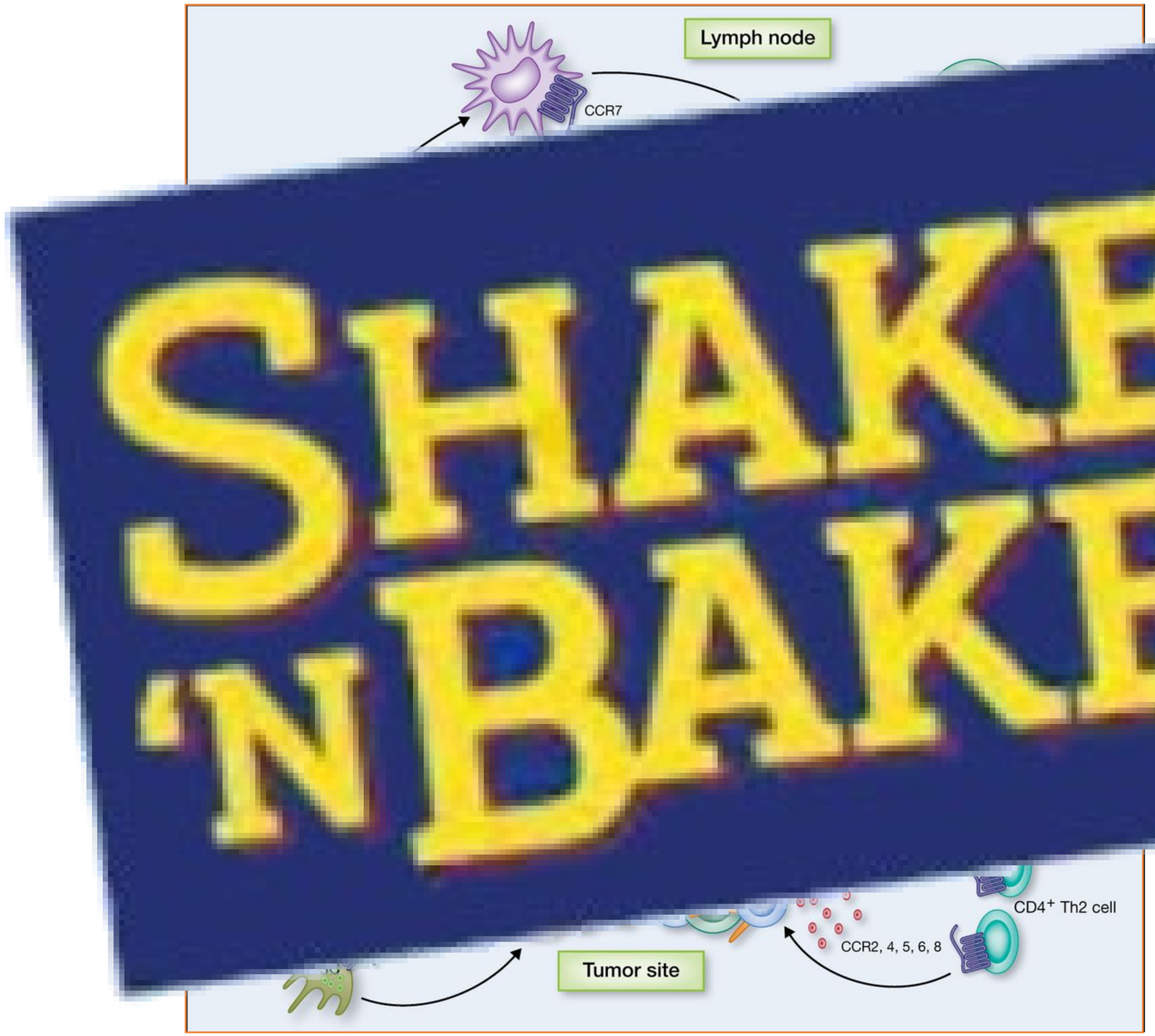
Lee DW, Gardner R, Porter DL, et al. *Blood*. 2014;124(2):188-195.

The Role of Cytokines in the Antitumor Immune Response



Franciszkiewicz K, et al. *Cancer Res.* 2012;72:6325-6332.

The Role of Cytokines in the Antitumor Immune Response



Franciszkiewicz K, et al. *Cancer Res.* 2012;72:6325-6332.

ASTCT Consensus Definition of CRS

- A supraphysiologic response following the activation or engagement of T cells and/or other immune effector cells for therapeutic intent. Symptoms **MUST** include fever at the onset and:
  - May include hypotension, capillary leak (hypoxia), and end organ dysfunction
- Symptoms must occur within a reasonable timeframe to the therapy
- CRS is **NOT** defined by cytokine levels or laboratory tests
- CRS applies to any immune effector cell activating/engaging therapy, not just CAR T cells
- As new immunotherapies (non–T cell) are developed, the definition may need to be altered

Although CTCAE v5.0's list of CRS-associated symptoms is more in line (relative to previous versions) with what is seen clinically during immune effector cell-associated CRS, this definition limits the cause to cytokines alone and is not contextually defined

ASTCT
American Society for Transplantation and Cellular Therapy
formerly ASBMT

CAR T, chimeric antigen receptor T cell; CRS, cytokine release syndrome.

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.

TACOS
The Arizona Clinical Oncology Society

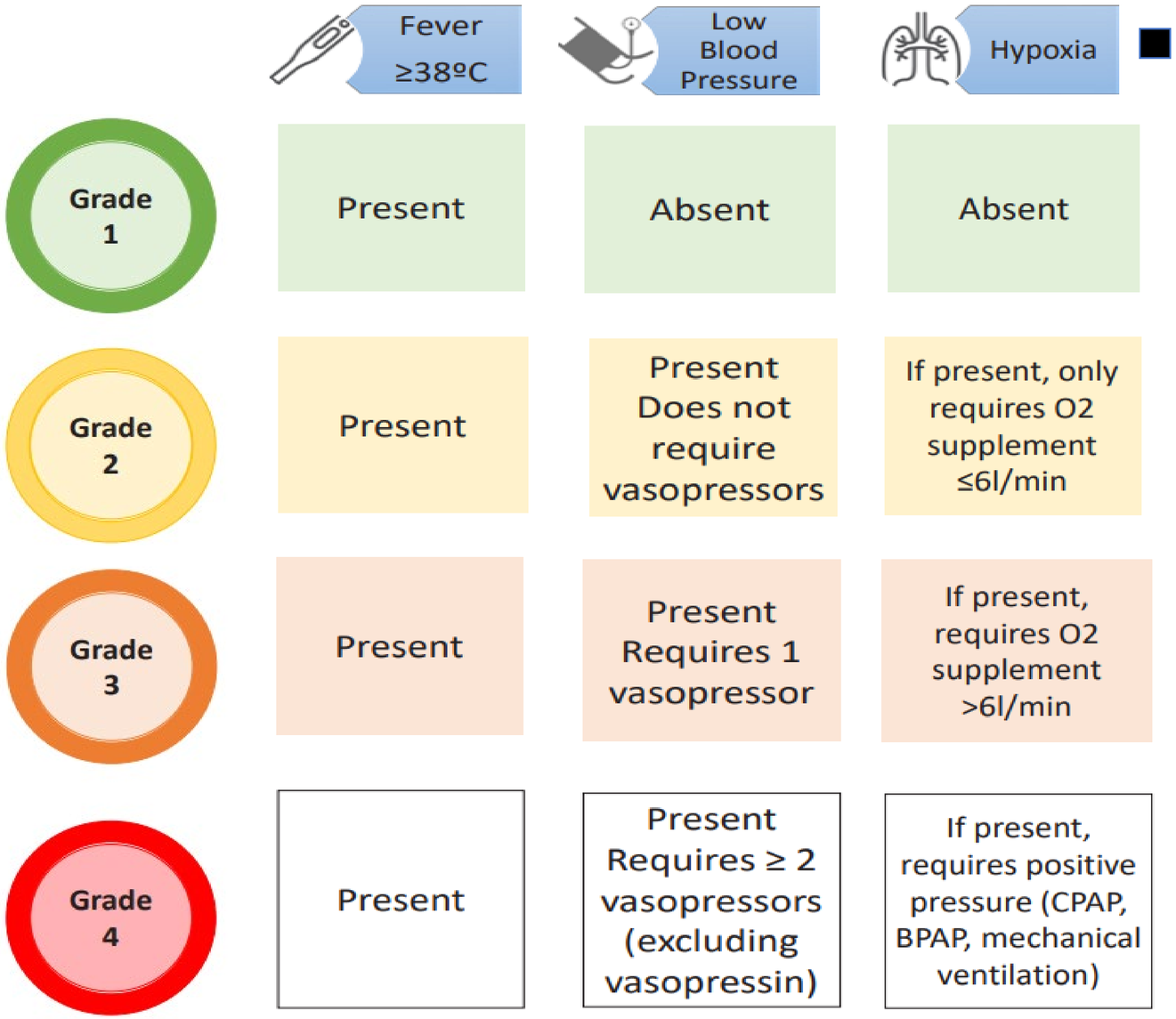
ASTCT Consensus Grading for CRS

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever not attributable to any other cause	Temperature ≥38°C with or without constitutional symptoms	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
With either:				
Hypotension not attributable to any other cause	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or				
Hypoxia not attributable to any other cause	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)

BiPAP, bilevel positive airway pressure; CAR T, chimeric antigen receptor T cell; CPAP, continuous positive airway pressure.

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.

ASTCT Consensus Grading for CRS



Adapted from Yáñez L, Alarcón A, Sánchez-Escamilla M, Perales MA. *ESMO Open*. 2020;4(Suppl 4):e000746.

ASTCT, American Society for Transplantation and Cellular Therapy; BPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome; ICU, intensive care unit.

CRS: Management

Case #2

•A 64-year-old woman is in the hospital after receiving glofitamab step up dose for relapsed diffuse large B-cell lymphoma. She underwent infusion two days ago, and you are called to her room due to onset of fever. She is uncomfortable but does not have any localizing symptoms.

On examination her temperature is 102.8 with a HR of 120 and a blood pressure of 118/62. O2 saturation is 96% on room air. She has palpable adenopathy in the cervical and supraclavicular regions.

Laboratory studies reveal:

Hemoglobin	10.1 g/dL
Leukocyte count	2,200/mm^3
Platelet count	104,000/mm^3
Ferritin	1245.mg/dL (baseline 450mg/dL)

Case #2

•A 64-year-old woman is in the hospital after receiving glofitamab step up dose for relapsed diffuse large B-cell lymphoma. She underwent infusion two days ago, and you are called to her room due to onset of fever. She is uncomfortable but does not have any localizing symptoms.

On examination her temperature is 102.8 with a HR of 120 and a blood pressure of 118/62. O2 saturation is 96% on room air. She has palpable adenopathy in the cervical and supraclavicular regions.

Laboratory studies reveal:

Hemoglobin	10.1 g/dL
Leukocyte count	2,200/mm^3
Platelet count	104,000/mm^3
Ferritin	1245.mg/dL (baseline 450mg/dL)

•Which of the following treatments do you suggest in this patient?

A.Acetaminophen

B.Tocilizumab

C.Dexamethasone

D.Anakinra

E.Emapalumab

Case #2

•A 64-year-old woman is in the hospital after receiving glofitamab step up dose for relapsed diffuse large B-cell lymphoma. She underwent infusion two days ago, and you are called to her room due to onset of fever. She is uncomfortable but does not have any localizing symptoms.

On examination her temperature is 102.8 with a HR of 120 and a blood pressure of 118/62. O2 saturation is 96% on room air. She has palpable adenopathy in the cervical and supraclavicular regions.

Laboratory studies reveal:

Hemoglobin	10.1 g/dL
Leukocyte count	2,200/mm^3
Platelet count	104,000/mm^3
Ferritin	1245.mg/dL (baseline 450mg/dL)

•Which of the following treatments do you suggest in this patient?

A.Acetaminophen

B.Tocilizumab

C.Dexamethasone

D.Anakinra

E.Emapalumab

Grade I CRS with fever, normal BP and O2 sat

General Considerations for CRS Management

- Management of CRS is based on clinical parameters, not laboratory values
  - Ferritin, CRP, serum cytokines should only be used to support the diagnosis
- CRS is managed with high level of clinical surveillance, fluids, and vasopressors
  - CRS requires continuous monitoring
- The IL-6 receptor antibody tocilizumab is indicated for 1L treatment of CRS
- 2L treatment for CRS varies by protocol and / or institutional guidelines
  - Steroids are effective for treating CRS
  - Other cytokine modulating agents for CRS include: anakinra, siltuximab, etc

1L, first line; 2L, second line; CAR T, chimeric antigen T cell; CRP, C-reactive protein; CRS, cytokine release syndrome; IL, interleukin.

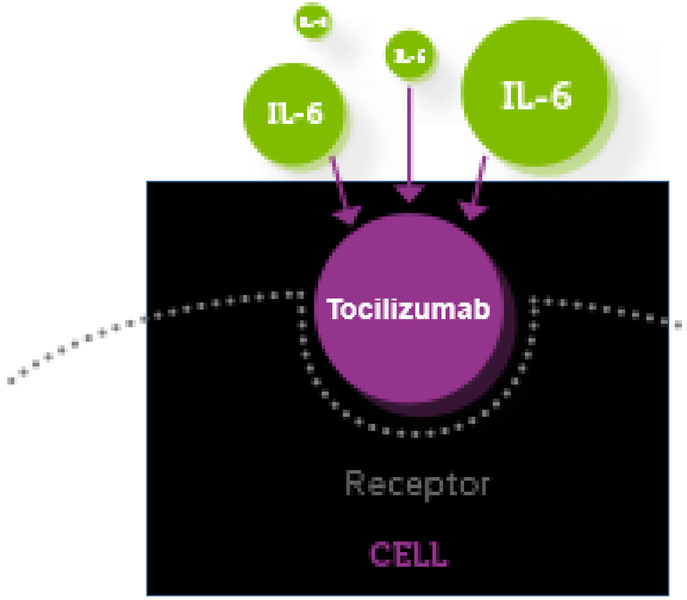
1. Neelapu SS, Tummala S, Kebriaei P, et al. *Nat Rev Clin Oncol*. 2018;15(1):47-62.
2. Brudno JN and Kochenderfer JN. *Blood*. 2016;127(26):3321-3330.

An approach to CRS in CAR-T (NCCN Nov 2023)

CRS Grade	Anti-IL-6 Therapy	Steroids[j,k,l]	Additional Supportive Care
Grade 1 Fever (≥38°C)	For prolonged CRS (>3 days)[h] in patients or those with significant symptoms, comorbidities, and/or are >65 years, consider 1 dose of IV tocilizumab 8 mg/kg over 1 hour (not to exceed 800 mg)[i,†,*]	For idecabtagene and lisocabtagene, consider IV dexamethasone 10 mg every 24 hours for early-onset CRS (<72 hours after infusion)[m]	• Sepsis screen and empiric broad-spectrum antibiotics, consider granulocyte colony-stimulating factor (G-CSF) if neutropenic[q] • Maintenance IV fluids for hydration • Symptomatic management of organ toxicities
Grade 2 Fever with hypotension not requiring vasopressors and/or hypoxia[f] requiring low-flow nasal cannula[g] or blow-by	IV tocilizumab 8 mg/kg over 1 hour (not to exceed 800 mg/dose).[j] Repeat in 8 hours if no improvement; no more than 3 doses in 24 hours, with a maximum of 4 doses total[†,*]	For persistent refractory hypotension after 1–2 doses of anti-IL-6 therapy: Consider IV dexamethasone 10 mg every 12–24 hours depending on product[a,m,n]	• IV fluid bolus as needed • For persistent refractory hypotension after two fluid boluses and anti-IL-6 therapy: Start vasopressors, consider transfer to ICU, consider echocardiogram, and initiate other methods of hemodynamic monitoring. Telemetry, ECG, troponin, and BNP if persistent tachycardia • Manage per Grade 3 if no improvement within 24 hours after starting anti-IL-6 therapy • Symptomatic management of organ toxicities
Grade 3 Fever with hypotension requiring a vasopressor with or without vasopressin and/or hypoxia requiring high-flow cannula,[g] face mask, nonrebreather mask, or Venturi mask	Anti-IL-6 therapy as per Grade 2[j] if maximum dose not reached within 24-hour period	IV dexamethasone 10 mg every 6–12 hours depending on the product.[a,m] If refractory, manage as grade 4	• Transfer to ICU, obtain echocardiogram, and perform hemodynamic monitoring • Supplemental oxygen • IV fluid bolus and vasopressors as needed • Symptomatic management of organ toxicities
Grade 4 Fever with hypotension requiring multiple vasopressors (excluding vasopressin) and/ or hypoxia requiring positive pressure (eg, continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, mechanical ventilation)	Anti-IL-6 therapy as per Grade 2[j] if maximum dose not reached within 24-hour period	IV dexamethasone 10 mg every 6 hours.[m] If refractory, consider 3 doses of IV methylprednisolone 1 - 2 g/day depending on the product.[a] If refractory, consider dosing every 12 hours.[o] Other lines of therapy may be considered[p]	• ICU care and hemodynamic monitoring • Mechanical ventilation as needed • IV fluid bolus and vasopressors as needed • Symptomatic management of organ toxicities

Tocilizumab

- IL-6 receptor inhibitor
- Blocks IL-6–mediated effects
- Monoclonal antibody with $t_{1/2}$ ~21 days
- Indicated for the treatment of rheumatologic disorders
- Indicated for the treatment of CRS



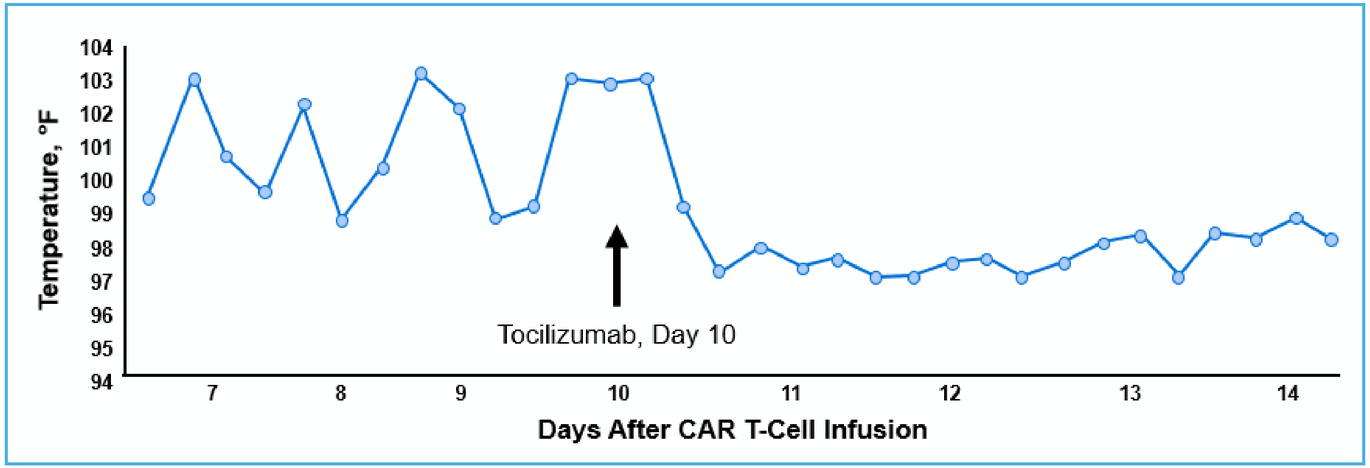
- Dosing for CRS management is based on clinical parameters
  - Dosing of tocilizumab varies by protocol and/or institutional guidelines
    - Most common doses: 4 mg/kg or 8 mg/kg
    - Maximum dose: 800 mg
  - Timing of second dose, if needed, varies by institutional guidelines
    - Range: every 6 to 24 hours
  - Typically, 1-3 doses are given based on clinical response

CAR T, chimeric antigen receptor T cell; CRS, cytokine release syndrome; IL, interleukin; $t_{1/2}$, half-life.

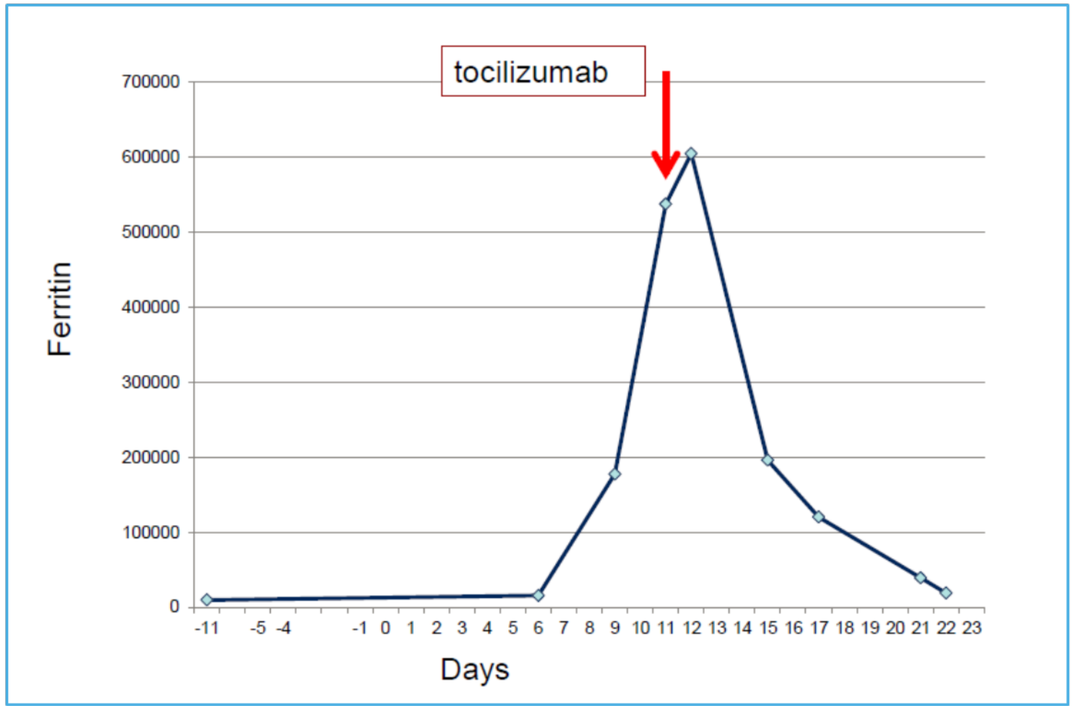
Tocilizumab [package insert] San Francisco, CA: Genentech, Inc.; 2022.

Response to Tocilizumab

Body Temperature

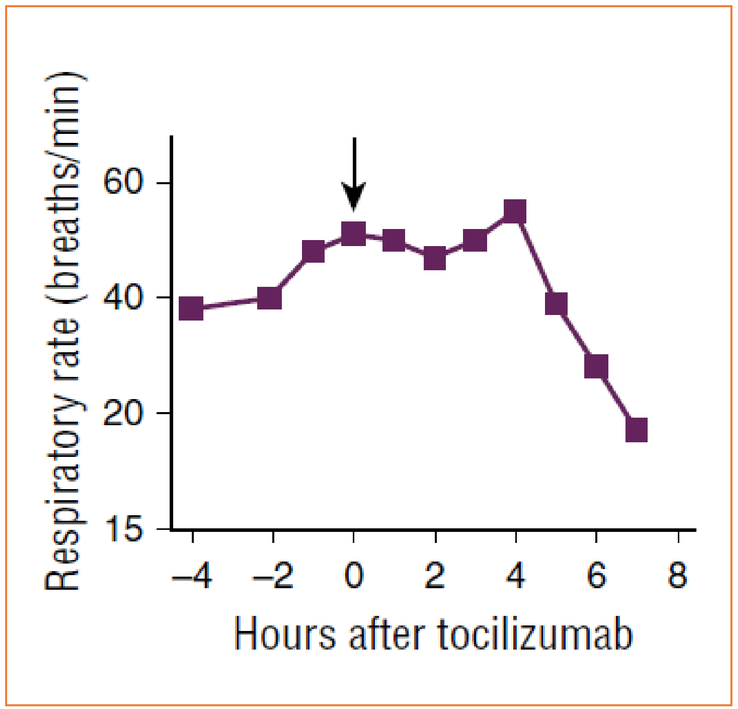


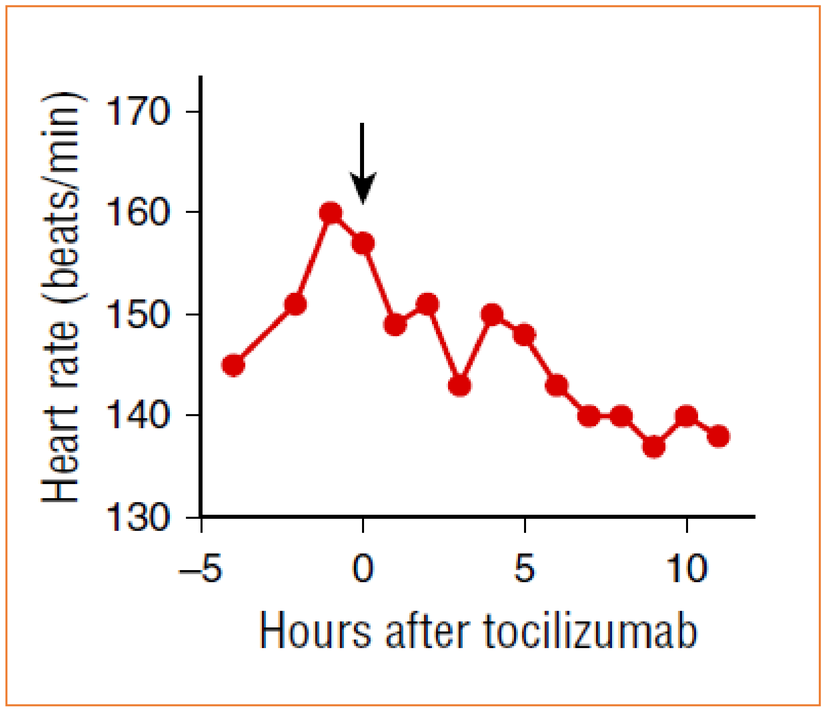
Ferritin

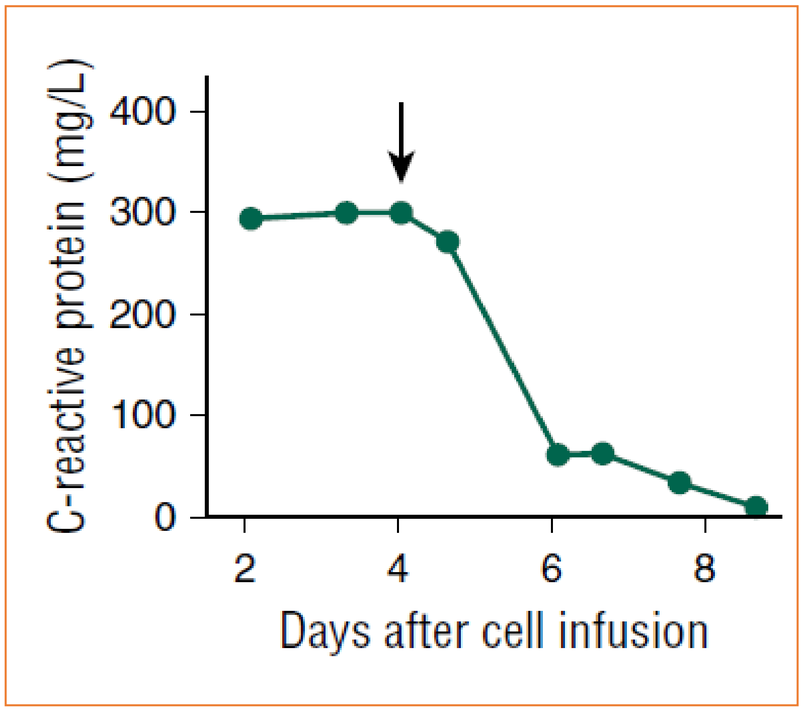


David L. Porter, unpublished.

Response to Tocilizumab







Patient is a 20-year-old woman with ALL. She experienced CRS toxicity with fevers, tachycardia, tachypnea, hypoxia, left ventricular systolic dysfunction, prolonged aPTT, and increased creatine kinase. She received tocilizumab on Day 4 following CAR T-cell infusion. Her respiratory rate and heart rate decreased following tocilizumab, and intubation was avoided. Following tocilizumab, CRP decreased over a period of days.

ALL, acute lymphoblastic leukemia; CAR T, chimeric antigen receptor T cell; CRP, C-reactive protein; CRS, cytokine release syndrome; PTT, partial thromboplastin time.

Brudno JN, Kochenderfer JN. *Blood.* 2016;127(26):3321-3330.

Earlier Intervention Steroid Use for Toxicities and CAR T Efficacy: ZUMA-1 Cohort 4 and 6 Data

The nonrandomized safety expansion cohorts of ZUMA-1 (Cohort 4 and 6) evaluated the impact of earlier steroid use on CRS and NE rates with primary end points of incidence and severity of CRS and NE rates.

Earlier use of steroids led to reductions in CRS and neurologic toxicity: Compared with the original management strategy, the **updated safety management strategy** resulted in a reduction in severe (Grade ≥3) CRS and neurologic toxicity associated with CAR T treatment.

Original cohorts (cohorts 1+2) (n=108)		Safety management cohort (cohort 4) (n=41)		Safety management cohort (cohort 6) (n=39)	
CRS Grade ≥3	13%	CRS Grade ≥3	2%	CRS Grade ≥3	0%
Neurologic Toxicity Grade ≥3	31%	Neurologic Toxicity Grade ≥3	20%	Neurologic Toxicity Grade ≥3	13%
CRS Median Duration	7 days	CRS Median Duration	7 days	CRS Grade Duration	4 days
Neurologic Toxicity Median Duration	17 days	Neurologic Toxicity Median Duration	8 days	Neurologic Toxicity Median Duration	12 days

Data from a safety management phase 2 multicenter, open-label study evaluating the safety and efficacy of Product X in subjects with relapsed or refractory large B cell lymphoma. In this cohort, 46 patients (cohort 4) and 39 patients (cohort 6) with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL after 2 or more lines of systemic therapy were enrolled and treated with Product X to assess the impact of early interventions on the rate and severity of cytokine release syndrome (CRS) and neurologic events.

1. Topp MS, et al. *Bio Blood Marrow Transplant.* 2020;20:S96-S255.
2. Locke FL, et al. *Lancet.* 2019;20(1):31-42.
3. YESCARTA. Package insert. Kite Pharma, Inc.; 2022.

CAR T, chimeric antigen receptor T cell; CRS, cytokine release syndrome; NE, neurologic event.

Earlier Intervention Steroid Use for Toxicities and CAR T Efficacy: ZUMA-1 Cohort 4 and 6 Data

The nonrandomized safety expansion cohorts of ZUMA-1 (Cohort 4 and 6) evaluated the impact of earlier steroid use on CRS and NE rates with primary end points of incidence and severity of CRS and NE rates.

Earlier use of steroids led to reductions in CRS and neurologic toxicity: Compared with the original management strategy, the **updated safety management strategy** resulted in a reduction in severe (Grade ≥3) CRS and neurologic toxicity associated with CAR T treatment.

Original cohorts (cohorts 1+2) (n=108)		Safety management cohort (cohort 4) (n=41)		Safety management cohort (cohort 6) (n=39)	
CRS Grade ≥3	**13%**	CRS Grade ≥3	**2%**	CRS Grade ≥3	**0%**
Neurologic Toxicity Grade ≥3	**31%**	Neurologic Toxicity Grade ≥3	**20%**	Neurologic Toxicity Grade ≥3	**13%**
CRS Median Duration	**7 days**	CRS Median Duration	**7 days**	CRS Grade Duration	**4 days**
Neurologic Toxicity Median Duration	**17 days**	Neurologic Toxicity Median Duration	**8 days**	Neurologic Toxicity Median Duration	**12 days**

But does more steroid decrease efficacy?

Data from a safety management phase 2 multicenter, open-label study evaluating the safety and efficacy of Product X in subjects with relapsed or refractory large B cell lymphoma. In this cohort, 46 patients (cohort 4) and 39 patients (cohort 6) with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL after 2 or more lines of systemic therapy were enrolled and treated with Product X to assess the impact of early interventions on the rate and severity of cytokine release syndrome (CRS) and neurologic events.

1. Topp MS, et al. *Bio Blood Marrow Transplant.* 2020;20:S96-S255.
2. Locke FL, et al. *Lancet.* 2019;20(1):31-42.
3. YESCARTA. Package insert. Kite Pharma, Inc.; 2022.

CAR T, chimeric antigen receptor T cell; CRS, cytokine release syndrome; NE, neurologic event.

Earlier Steroid Use for Toxicities and CAR T Efficacy: ZUMA-1 Cohort 4 and 6 Data

The nonrandomized safety expansion cohorts of ZUMA-1 (Cohorts 4 and 6) evaluated the impact of earlier steroid use on CRS and NE rates with primary end points of incidence and severity of CRS and NE rates.

Response rate and duration of response data

Cohorts 1+2	
ORR (CR rate)	72% (51%)
Median DOR, months	8.1
Patients with ongoing response	44%
6-month DOR rate	52%

Cohort 4	
ORR (CR rate)	73% (51%)
Median DOR, months	8.9
Patients with ongoing response	54%
6-month DOR rate	79%

Cohort 6	
ORR (CR rate)	95% (80%)
Median DOR, months	NR
Patients with ongoing response	62.5%
6-month DOR rate	62.4%

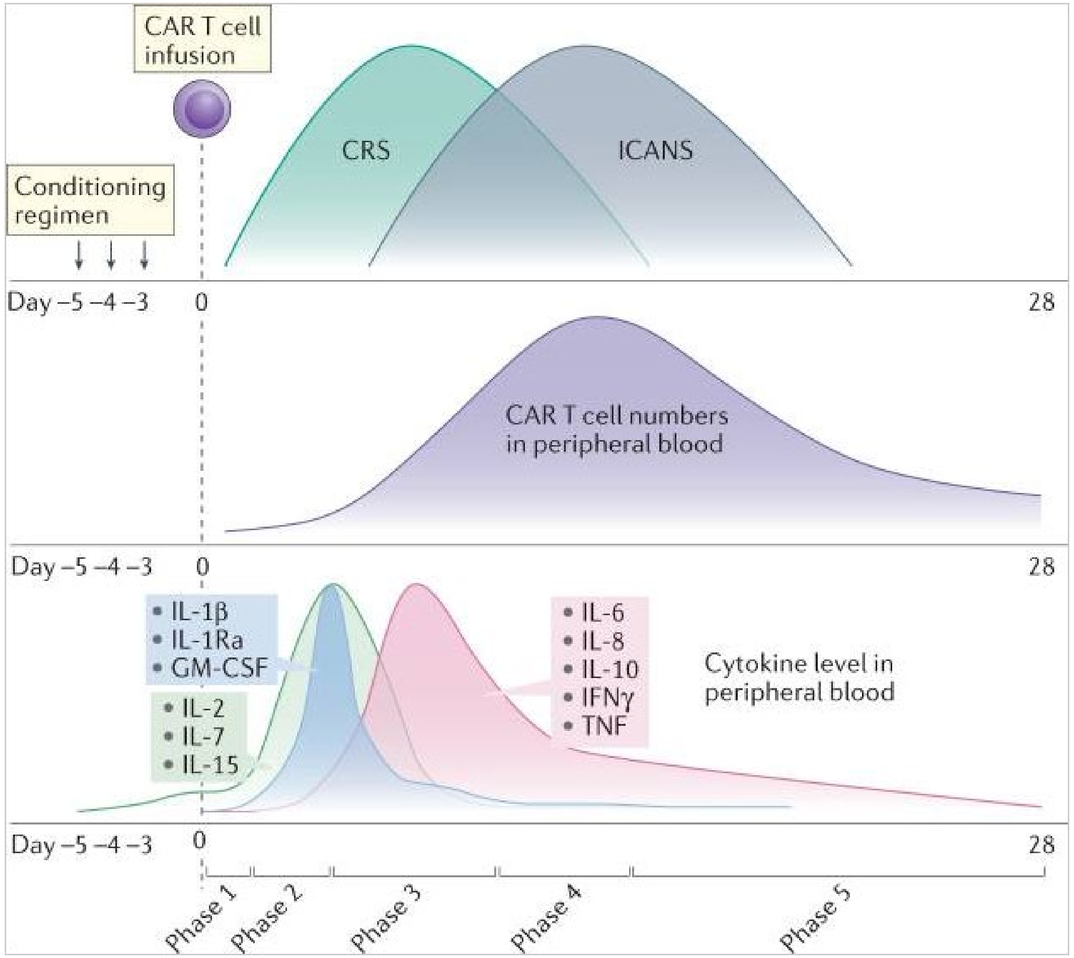
At least in this population in this study – preemptive steroid did not seem to decrease efficacy (though not randomized)

Differences in disease characteristics between Cohort 4, Cohorts 1 + 2, and Cohort 6 may have affected outcomes. In Cohort 4, bridging therapy was allowed, which may have resulted in lower tumor burden at baseline in Cohort 4. Response assessment is not confirmed by IRC. Cohort 4 analyses are descriptive, and no formal hypothesis testing was prespecified or conducted and these data are not included in the USPI.

1. Topp MS, et al. *Bio Blood Marrow Transplant.* 2020;20:S96-S255.
2. Locke FL, et al. *Lancet.* 2019;20(1):31-42.
3. Oluwole OO, et al. *BJH*. 2021.

CAR T, chimeric antigen receptor T cell; CR, complete response; CRS, cytokine release syndrome; DOR, duration of response; NE, neurologic event; ORR, objective response rate; OR, overall response; PFS, progression-free survival

Timeline for the onset and duration of CRS and ICANS CAR-T



CAR T, chimeric antigen receptor T cell; CRS, cytokine release syndrome; IFN, interferon; IL, interleukin.

Morris EC, et al. Nat Rev Immunol. 2022;22(2):85-96.

BiTES: Incidence and Timing of CRS

Drug	CRS rate all grade	CRS rate 3+	Onset (all grade)	Duration (all grade)	NeuroTox all grade	Neuro rate 3+	Onset (all grade)	Duration (all grade)
Epcoritamab	51%	2.5%	20-21h	2d	6.4%	0.6%	16.5d	3d
Glofitamab	66%	4%	14h	2d	8%	3%	Not reported	Not reported
Mosunetuzumab	39%	2.5%	5h	3d	39%	3%	Not reported	Not reported
Elranatamab	58%	0.5%	2d	2d	59%	7%	3d	2d
Teclistamab	72%	0.6%	2d	2d	57%	2.4%	4d	3d
Talquetamab	76%	1.5%	27h	17h	55%	6%	2.5d	2d

CRS Management in BiTE – An Approach

In addition to supportive care (also evaluate alternative causes such as sepsis

CRS Grade	Medications	BiTE modification
Grade 1	Acetaminophen	Hold next dose until resolves
Grade 2	IVF, O2, Acetaminophen, Steroids* If older/comorbidities consider Toci	Hold next dose until resolves >72hrs Consider adjusting rate/dose
Grade 3	Tocilizumab, Steroids	Hold until all CRS resolves Weigh risk/benefit of restart; if recurrent Gd 3, discontinue
Grade 4	Toci, Steroids, ICU	Discontinue

Who is at highest risk for CRS and Neurotoxicity?[1,2]

- **Patients with:**
  - High tumor/disease burden
  - ECOG PS ≥2[3]
  - With CAR-T: Products associated with rapid early expansion of CAR T-cells (CD28 costimulatory domain)

While advanced age had previously been considered a risk factor for CRS and ICANS, recent findings suggest otherwise.[3]

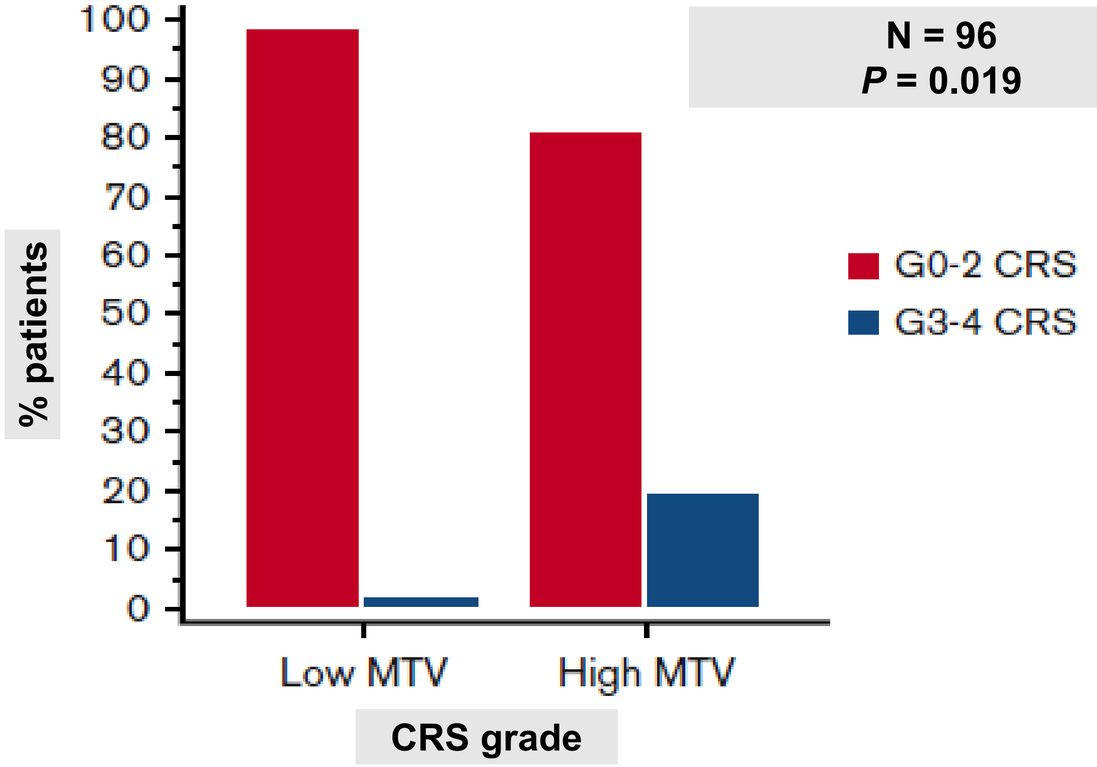
- **Primarily CRS predictors:**
  - Pre-existing systolic or diastolic cardiac dysfunction or baseline EKG abnormalities
  - High baseline CRP or IL-6 levels

Yañez L, et al. *ESMO Open*. 2020;4(Suppl 4):e000746.
Lee DW, et al. *Biol Blood Marrow Transplant.* 2019;25(4):625-638.

CAR T, chimeric antigen receptor T cell; CRP, C-reactive protein; CRS, cytokine release syndrome; ECOG PS, Eastern Cooperative Oncology Group performance score; EKG, electrocardiogram; ICANS, immune effector cell-associated neurotoxicity syndrome; IL, interleukin.

CRS by Low vs High Mean Tumor Volume (CAR-T data)

- High-grade tumor burden by MTV was associated with G3-4 CRS
  - Objective response = 12.4% (95% CI, 1.49-104.2); *P* = 0.019
- 90 out of 96 patients (93.7%) had any-grade CRS
- 9 out of 96 patients (9.3%) had G3-4 CRS



CAR T, chimeric antigen receptor T cell; CI, confidence interval; CRS, cytokine release syndrome; G, grade; MTV, mean tumor volume.

Dean EA, Mhaskar RS, Lu H, et al. *Blood Adv*. 2020;4(14):3268-3276.

Best Practices for CRS Management

Promote **open lines of communication** within the cross-functional team of HCPs

- ✓ Confirm regular and frequent assessment of patients
- ✓ Establish a process for escalation of care, increased monitoring, and relevant workups

Provide **guidelines for treating complications**, including the use of

- ✓ Anticytokine-directed therapy
- ✓ Corticosteroid administration

Ensure **rapid availability of treatment/evaluation**

- ✓ ICU support
- ✓ Neurology consult
- ✓ Infectious disease consult
- ✓ Anticytokine-directed therapy (aim for infusion within 1 hour of order)

HCP, health care professional; ICU, intensive care unit.

Best Practices of Experienced Centers: Building a Multidisciplinary Team

- Specialized, dedicated team of Immunotherapy physicians
  - There may be a designated clinical unit where immunotherapy is administered to focus expertise
- Dedicated coordinators and nurse navigators (for both commercial and research products)
- Dedicated Quality Managers to coordinate REMS for CRS trained staff
- Dedicated MICU physicians, neurologists, and other key subspecialists
  - Consider cardiologists, nephrologists, and infectious diseases experts
- Pharmacy
  - Tocilizumab must be kept in pharmacy (2 doses on admission) and added to hospital formulary
- Nursing
  - Inpatient/outpatient
- Emergency Department

Patients and Caregivers as Part of the Multidisciplinary Team

- Education is imperative, importance of presenting to a hospital (when needed) that is familiar with immunotherapy and has tocilizumab available
- Patients and caregivers should be educated about the common AEs of Immunotherapy, such as CRS and neurotoxicity, and when to seek care or treatment
  - Neurotoxicity may not be identified without a caregiver or proactive evaluation

AE, adverse event; CRS, cytokine release syndrome

Taylor L, et al. *Clin J Oncol Nurs*. 2019;23(2):20-26.

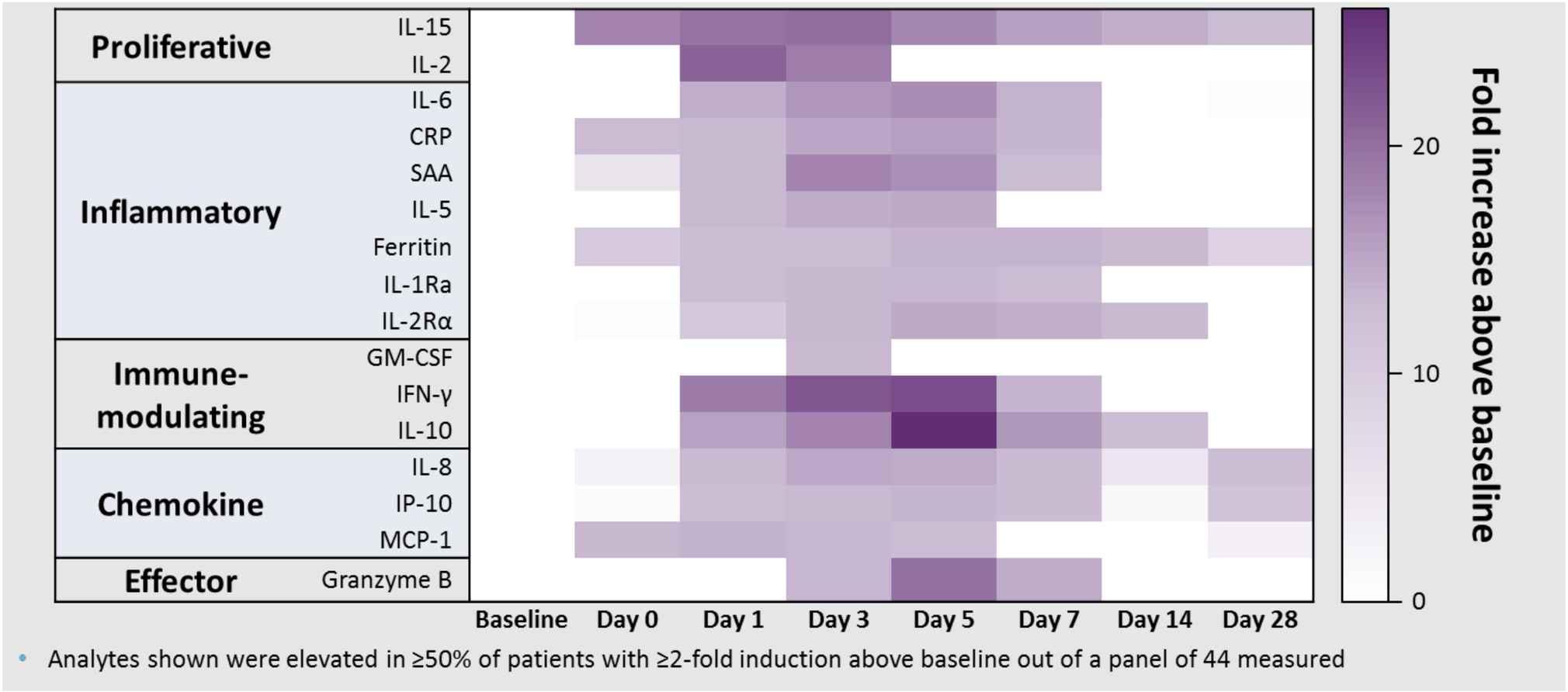
Questions?
Thank you!

Matthew.Ulrickson@bannerhealth.com

@MattUlricksonMD

The Arizona Clinical Oncology Society

Cytokine Profiles Observed in LBCL Patients Treated With CAR T Cells (Axi-Cel, Axicabtagene Ciloleucel)



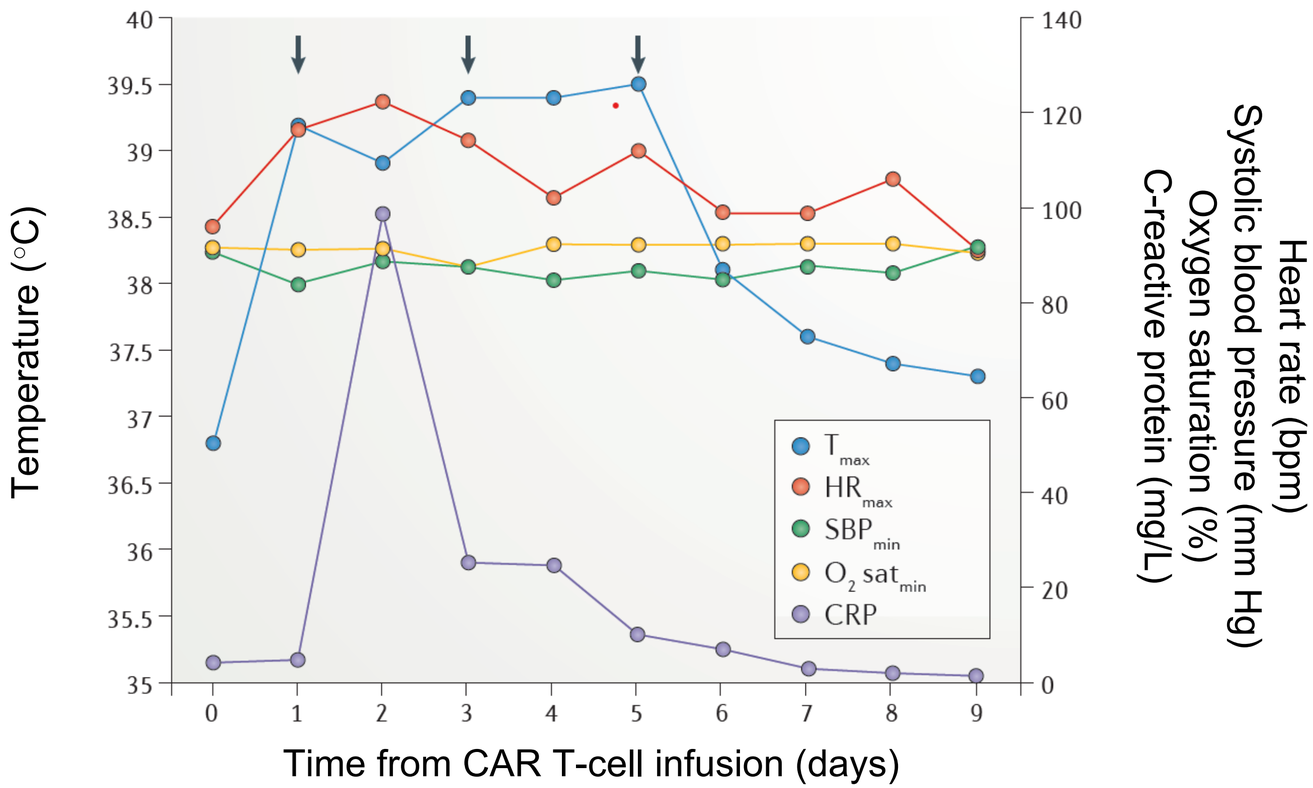
- Analytes shown were elevated in ≥50% of patients with ≥2-fold induction above baseline out of a panel of 44 measured

CAR, chimeric antigen receptor; CRP, C-reactive protein; GM-CSF; granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; LBCL, large B-cell lymphoma, MCP-1, monocyte chemoattractant protein-1; SAA, serum amyloid A.

Locke FL, Rossi J, Xue A, et al. Presented at 2017 American Association for Cancer Research Annual Meeting; April 1-5, 2017; Washington, DC. Abstract CT020.

CRS-Related Marker, C-Reactive Protein: Levels Post-CAR T-Cell Infusion

- Serum CRP level increased on day 2, a day after the onset of fever, and returned to baseline levels by the time fever subsided[1]
- Decreasing CRP may be an indicator of clinical improvement[2]

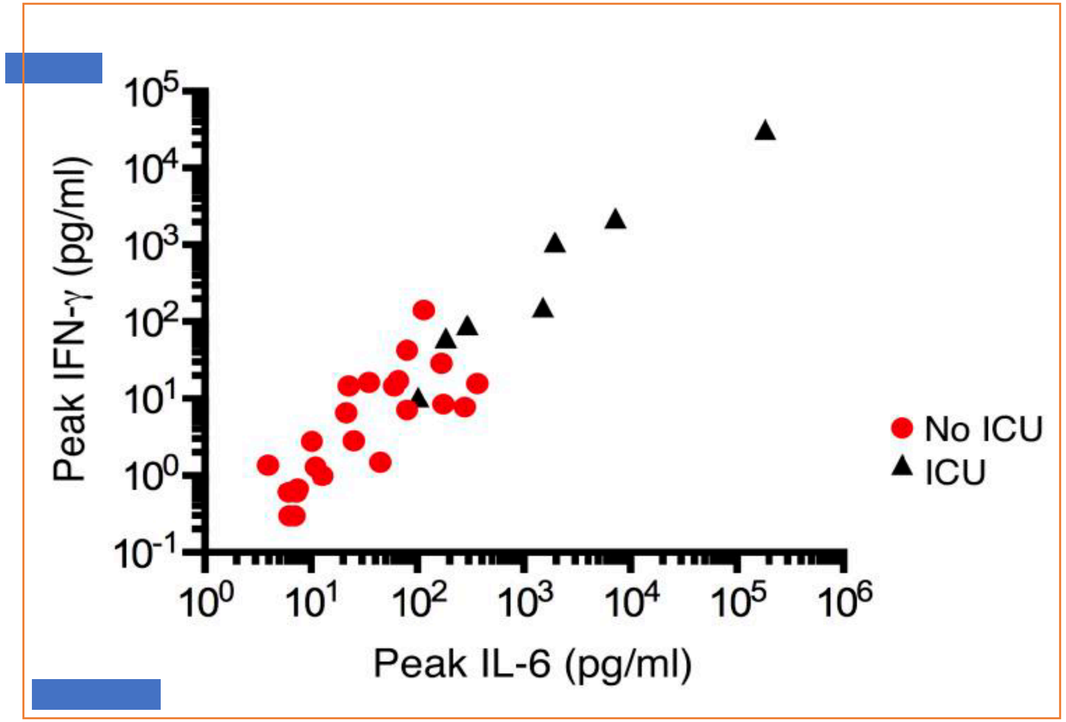


bpm, beats per minute; CAR, chimeric antigen receptor; CRP, C-reactive protein; CRS, cytokine release syndrome; HR, heart rate; O_2, oxygen; SBP, systolic blood pressure; T_{max}, maximum temperature.

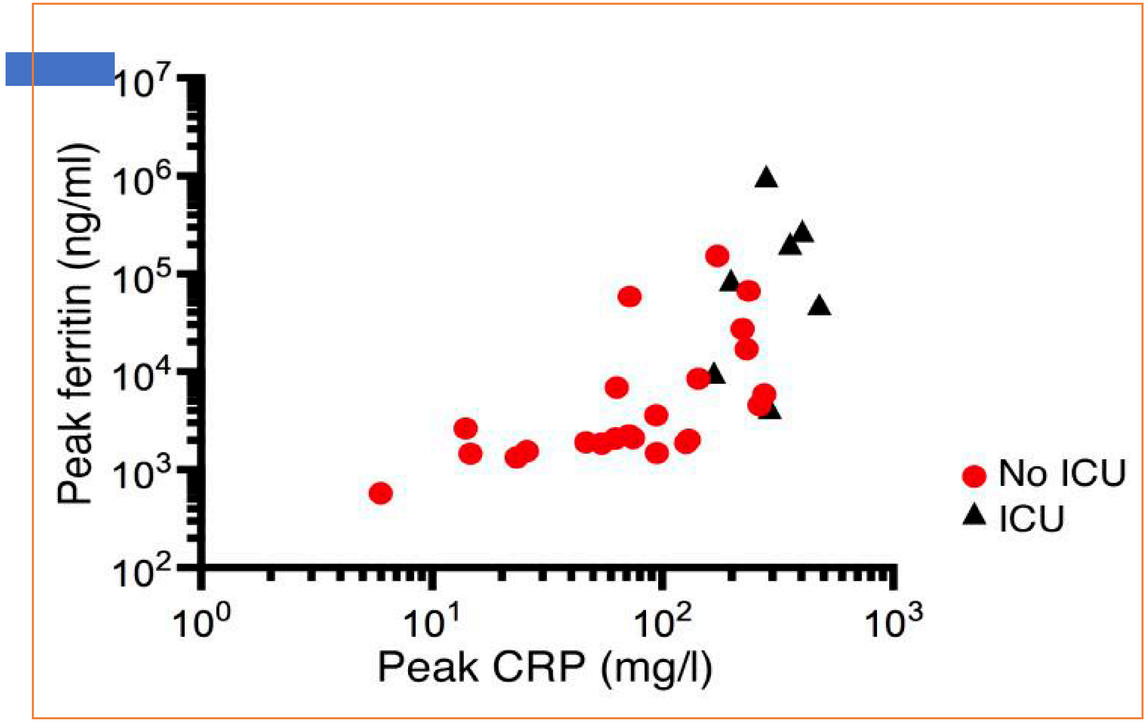
1. Neelapu SS, Tummala S, Kebriaei P, et al. *Nat Rev Clin Oncol*. 2018;15(1):47-62.
2. Lee DW, Kochenderfer JN, Stevenson MS, et al. *Lancet.* 2015;385(9967):517-528.

Peak Cytokine Levels Correlate With CRS Severity Requiring ICU Care

Higher peak IL-6 and IFN-γ levels are observed in patients requiring ICU care



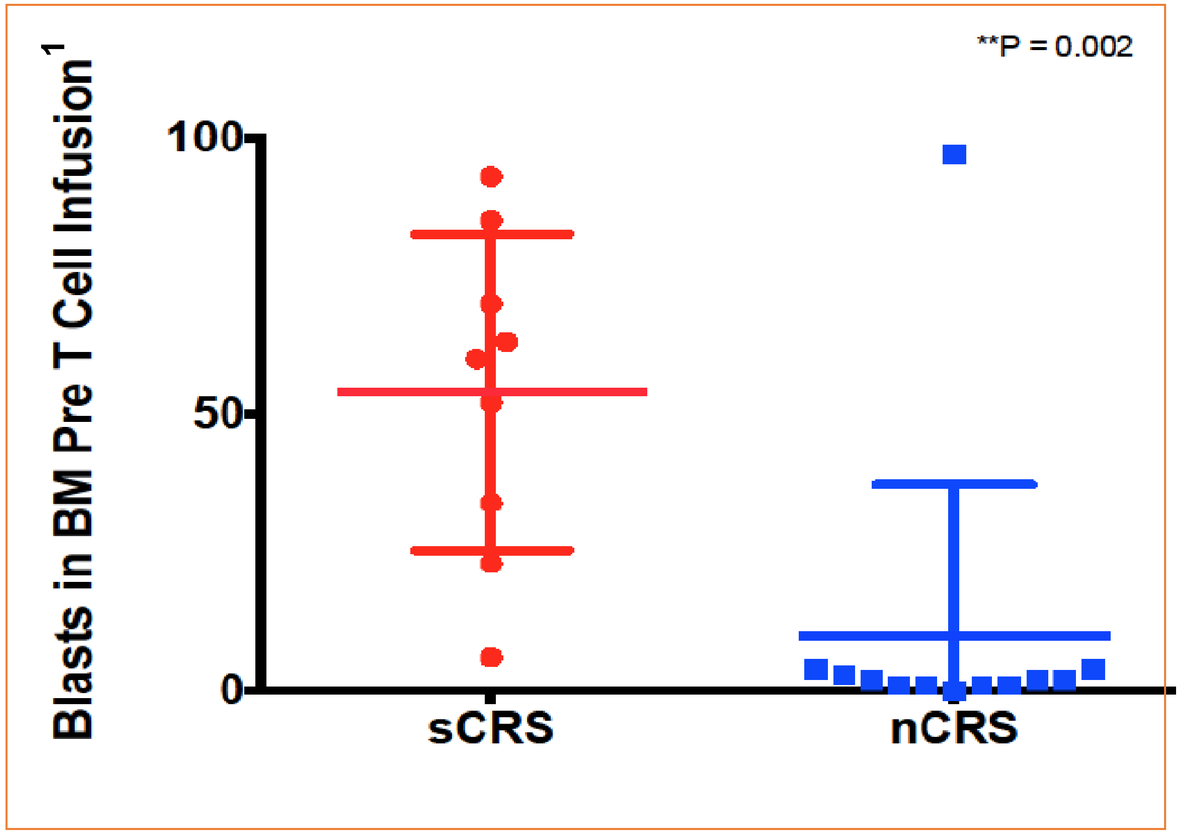
Elevations of CRP and ferritin correlate with the occurrence of severe CRS requiring ICU care



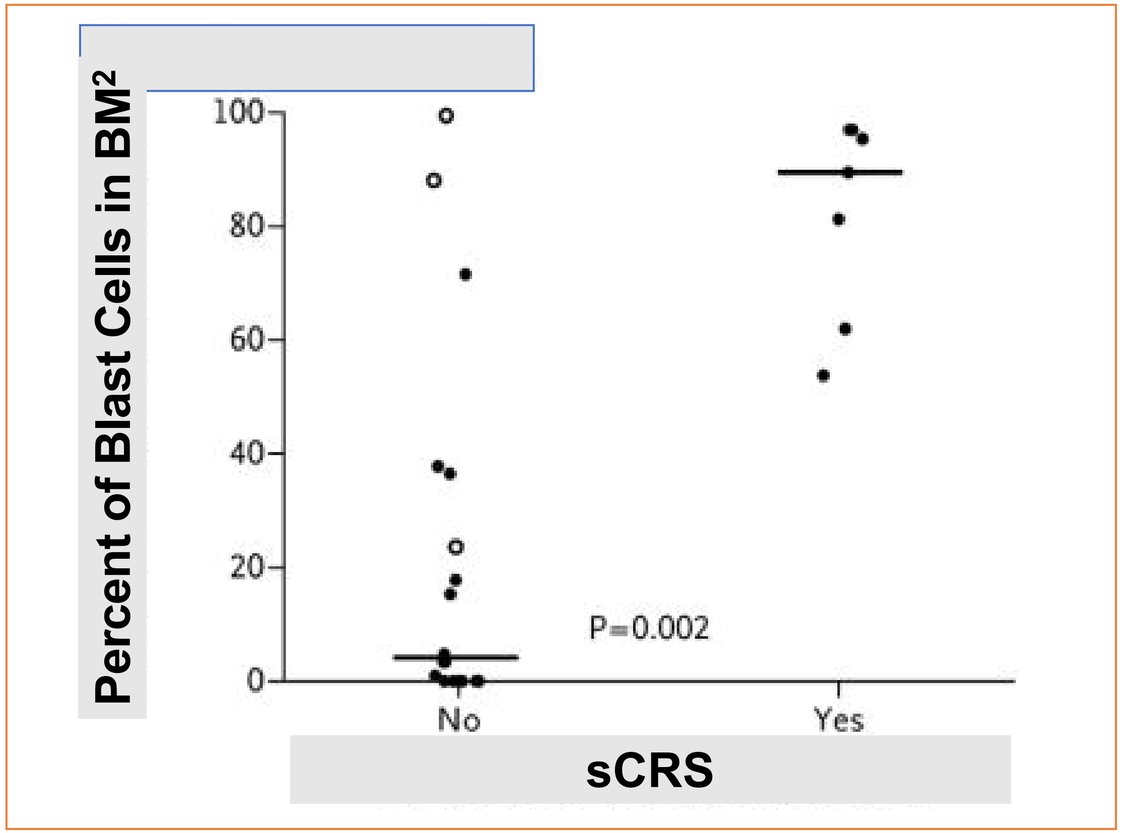
CAR T, chimeric antigen receptor T cell; CRP, C-reactive protein; CRS, cytokine release syndrome; ICU, intensive care unit; IFN, interferon; IL, interleukin.

Turtle CJ, Hanafi LA, Berger C, et al. *J Clin Invest*. 2016;126(6):2123-2138.

CRS Severity Correlates With Baseline Disease Burden and Peak Cytokine Levels in ALL



Baseline Disease Burden

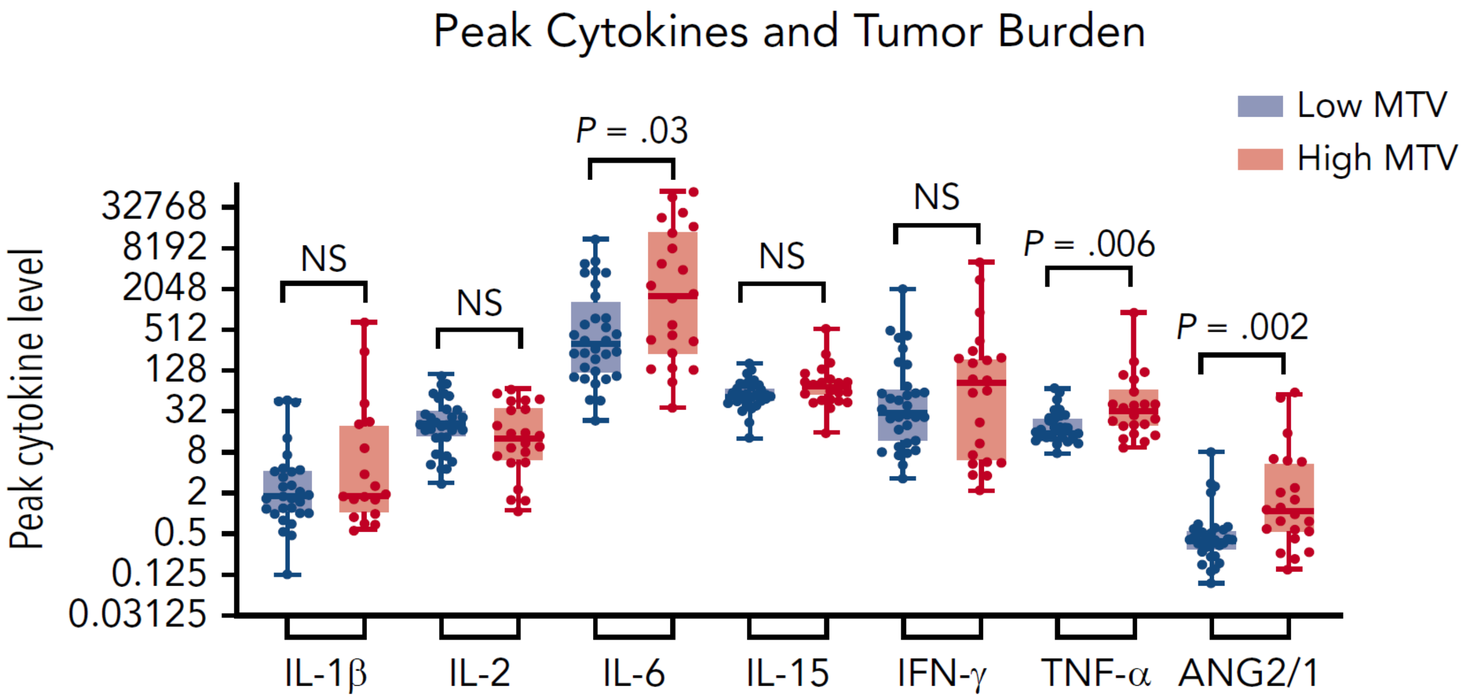


1. Davila M, et al. *Sci Transl Med.* 2014;6(224):224ra25.
2. Maude SL, Frey Noelle, Shaw PA, et al. *N Engl J Med*. 2014;371(16):1507-1517.

ALL, acute lymphoblastic leukemia; BM, bone marrow; nCRS, patients who only required routine observation and management; sCRS, severe cytokine release syndrome.

CRS Severity Correlates With Baseline Disease Burden and Peak Cytokine Levels in LBCL

- Expanded access trial for products outside of manufacturing specifications
- Samples were obtained from 105 patients treated with **axicabtagene ciloleucel (axi-cel)**;
  - 85 patients received standard of care therapy,
  - 14 patients as part of a clinical trial
  - 6 patients received axi-cel under the **ZUMA-9 (NCT03153462)**



Jain MD, et al. *Blood*. 2021;137(19):2621-2633.

CRS, cytokine release syndrome; LBCL, large B-cell lymphoma; MTV, metabolic tumor volume.

Characteristics and Outcomes of R/R LBCL Patients Who Did Not Develop CRS After Axi-Cel

Results from the US Lymphoma CAR T Consortium[1]

The Consortium includes 17 US academic centers that contribute data independently of manufacturers

24 out of 275 patients (9%) who received an axi-cel infusion did not develop CRS* (median follow-up = 12 months)

Baseline characteristics: ECOG score of 0-1 ($P < 0.001$) , IPI score of 4-5 ($P = 0.014$)

Safety outcomes for patients who did not develop CRS

- Lower rates of grade ≥3 neurotoxicity ($P = 0.002$)
- Lower rates of ICU admission ($P = 0.006$)
- Shorter length of hospital stay

(median 10 days vs 14 days for CRS group, $P < 0.001$)

Efficacy outcomes

- Durable responses were seen in patients who did not develop CRS
  - However, grade 1-2 CRS was associated with better outcomes
- Patients with severe grade 3 or higher CRS had lower rates of overall survival

*CRS was graded according to Lee criteria[2] or CARTOX.[3]

1. Jacobs MT, Jain MD, et al. *Blood*. 2021. In publication, ahead of print.
2. Lee DW, et al. *Blood*. 2014;124(2):188-195.
3. Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018;15:218.

CAR T, chimeric antigen receptor T cell; CRS, cytokine release syndrome; ECOG, Eastern Cooperative Oncology Group; IPI, international prognostic index; LBCL, large B-cell lymphoma; R/R, relapsed/refractory; US, United States.