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Emergency Medicine Pharmacotherapy with Resuscitation (EMPoweRx) Conference

Managing Cytokine Release Syndrome (CRS) Post CAR-T Cell Therapy

Brent C. Beckner PharmD, BCPS, BCCCP
Pharmacist Specialist – Emergency Medicine
Nebraska Medicine
Omaha, NE

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Disclosures

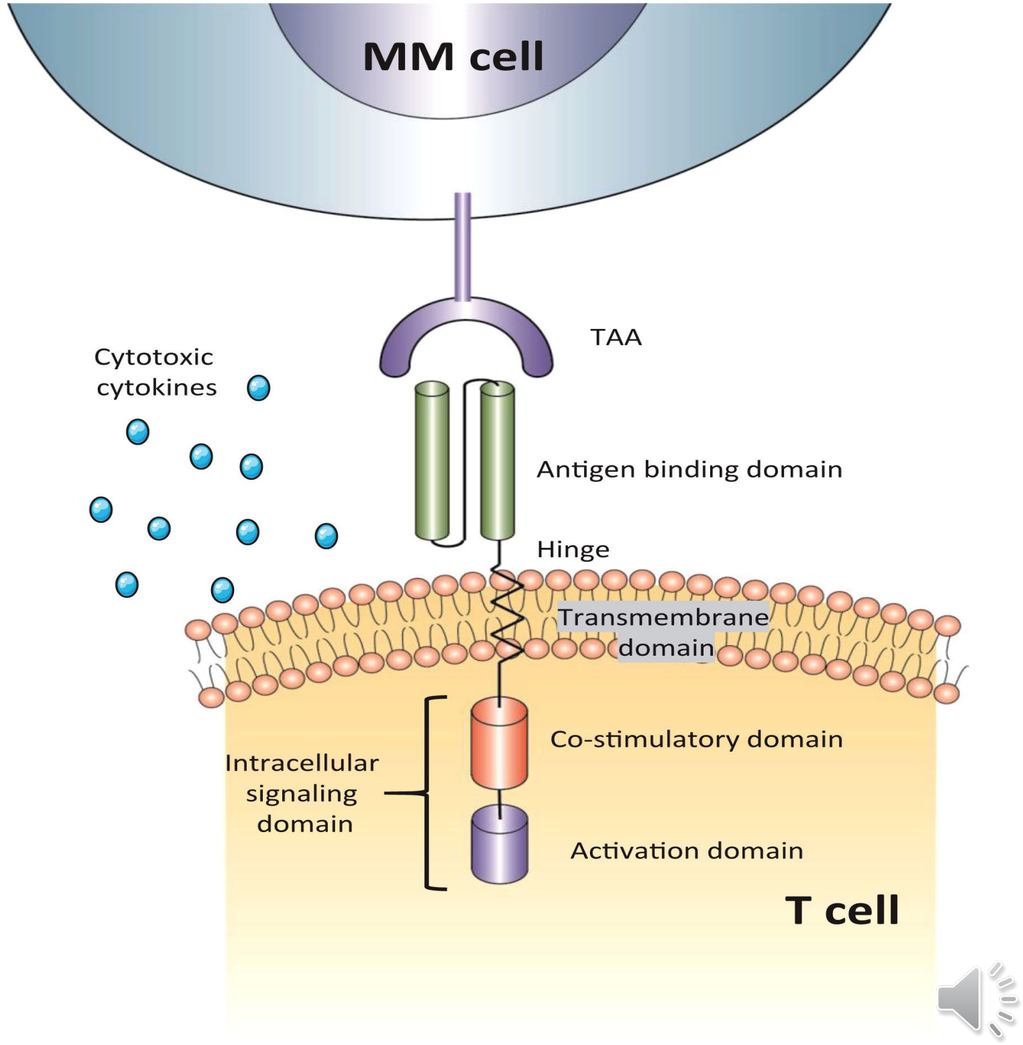
No one involved in the development of the educational content has a relevant financial relationship to disclose.

Objectives

- Evaluate clinical signs, laboratory data, and risk factors to accurately assess the severity of Cytokine Release Syndrome (CRS) in patients following CAR-T therapy.
- Apply evidence-based management strategies, including pharmacologic interventions and supportive care measures, to effectively treat CRS in the post–CAR-T setting.
- Develop a comprehensive, multidisciplinary management plan that addresses early recognition, intervention, and ongoing monitoring of CRS to optimize patient outcomes.

Chimeric Antigen Receptor (CAR) – T Cells

- Targets
  - CD19
  - B-Cell Maturation Antigen (BCMA)
- Components of CAR-T Cell
  1. Antigen Binding Domain
     - Target antigen specificity
  2. Hinge Region
     - Provides flexibility to facilitate binding
  3. Transmembrane Domain
     - Anchors the CAR to the T-Cell membrane
  4. Co-Stimulatory Domain
     - Increases T-Cell activation and cytolytic activity
  5. Intracellular Signaling Domain
     - Induces T-Cell Activation



Wang, Z. Front Immunol. 2022 Dec 22
Sterner RC and Sterner RM. Blood Cancer Journal. 2021;11:69.

FDA Approved Products

Generic Name	Abbreviated Name	Brand Name	Manufacturer	Antigen Target
Tisagenlecleucel	Tisa-cel	Kymriah	Novartis	CD19
Axicabtagene ciloleucel	Axi-cel	Yescarta	Kite Pharma	CD19
Brexucabtagene autoleucel	Brexu-cel	Tecartus	Kite Pharma	CD19
Lisocabtagene maraleucel	Liso-cel	Breyanzi	Juno Therapeutics	CD19
Idecabtagene vicleucel	Ide-cel	Abecma	Celegene (BMS)	BCMA*
Ciltacabtagene autoleucel	Cilta-cel	Carvykti	Janssen	BCMA*
Obecabtagene autoleucel	Obe-cel	Aucatzyl	Autolus	CD19

*BCMA: B-cell maturation antigen

Lexicomp Online. Waltham, MA: UpToDate, Inc. Accessed February 20, 2025.

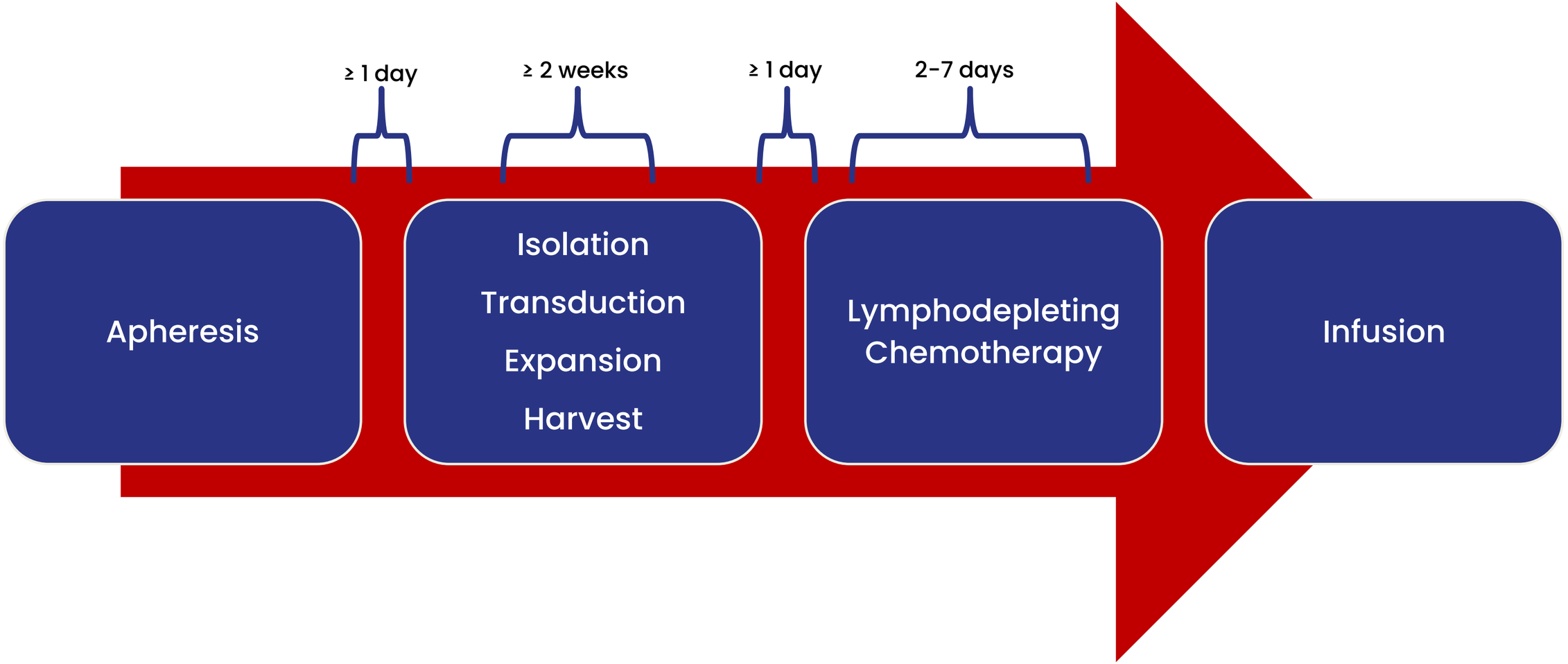
FDA Approved Indications

B-ALL	DLBCL	MCL	FL	MM
Tisa-cel	Tisa-cel	Brexu-cel	Axi-cel	Ide-cel
Brexu-cel	Axi-cel		Tisa-cel	Cilta-cel
Obe-cel	Liso-cel			

B-ALL = B-cell acute lymphoblastic leukemia
DLBCL = Diffuse Large B-cell lymphoma
MCL = Mantle cell lymphoma
FL = Follicular lymphoma
MM = Multiple myeloma

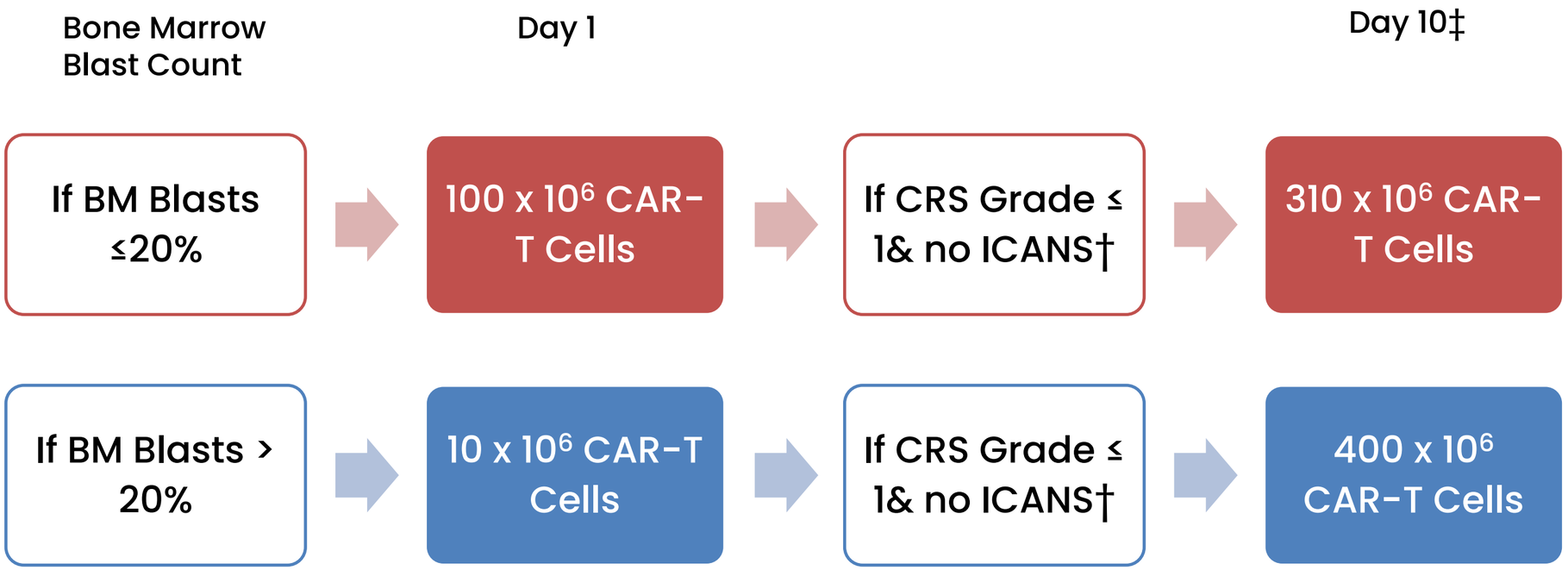
Kymriah [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2022.
Yescarta [package insert]. Santa Monica, CA: Kite Pharma, Inc; 2021.
Breyanzi [package insert]. Bothell, WA: Juno Therapeutics, Inc; 2021.
Tecartus [package insert]. Santa Monica, CA: Kite Pharma, Inc; 2021.
Abecma[package insert]. Summit, NJ: Celgene Corporation; 2021.
Carvykti [package insert]. Somerset, NJ: Janssen Biotech, Inc; 2022
Aucatzyl [package insert]. Gaithersburg, MD: Autolus, Inc; 2024

CAR-T Cell Therapy Process



Levine BL et al. MolTher Methods Clin Dev. 2017;4:92-101.

Obe-Cel Process



† If patient has Grade 2 CRS, consider postponing obe-cel infusion up to Day 21 to allow for the CRS to resolve to Grade ≤1. If patient has Grade 1 ICANS, consider postponing obe-cel infusion up to Day 21 to allow for the ICANS to completely resolve.

‡The second dose can be avoided or delayed if there are signs of severe immune toxicity.

ICANS = Immune effector cell-associated neurotoxicity syndrome

Aucatzyl [package insert]. Gaithersburg, MD: Autolus, Inc; 2024

Post Infusion

- Hospitalized for at least 10-14 days
- Discharged with REMS pocket card
- Advised to stay within 1h of hospital for 1 month
  - Should be with caregiver that can recognize signs/symptoms of CRS & ICANS

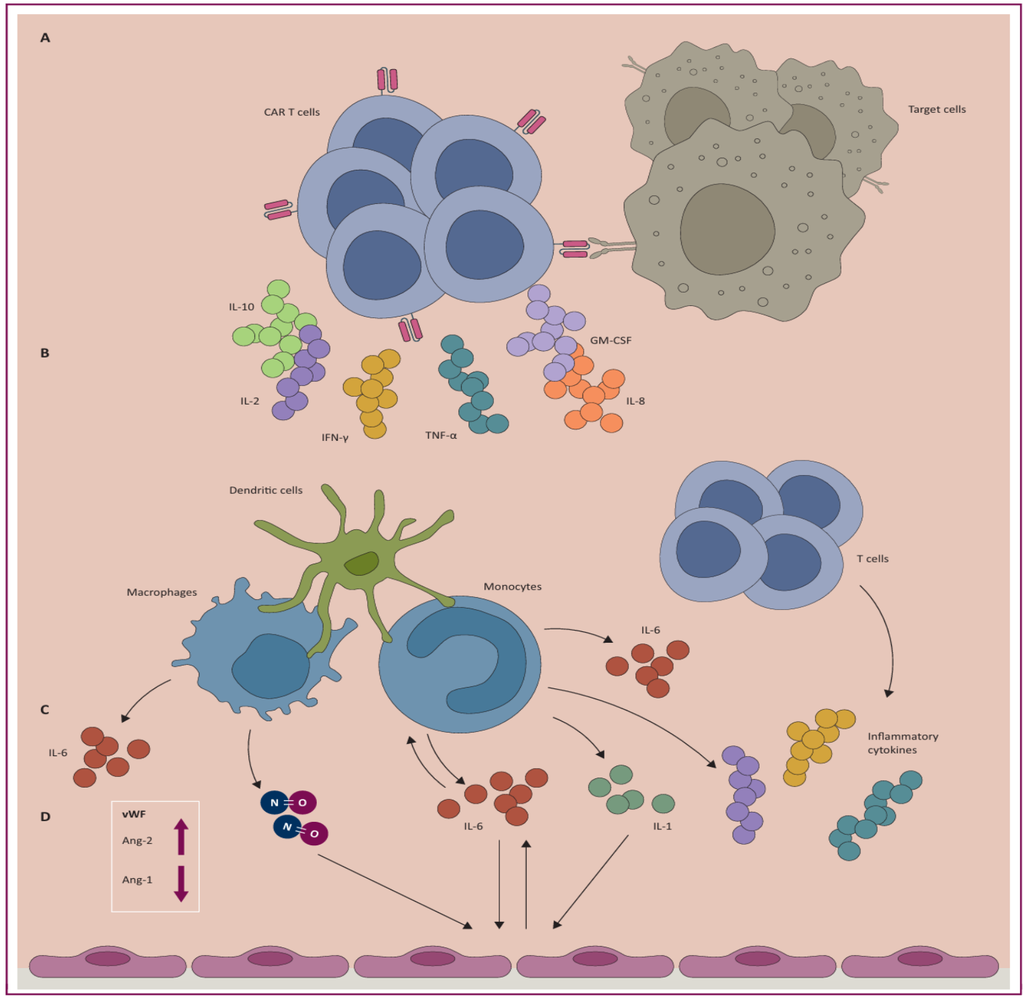
[CAR-T Product Name]

Carry this card with you at all times. SHOW THIS CARD to any healthcare professional involved in your care and if you go to the emergency room.

IMPORTANT SAFETY INFORMATION FOR PATIENTS RECEIVING TREATMENT WITH [CAR-T Product Name]

Cytokine Release Syndrome (CRS) Pathophysiology

- Supraphysiologic inflammation initiated by CAR-T Cells binding to Target
- Other cell types
  - Macrophages
  - other T cells
  - Monocytes
  - dendritic cells
- Inflammatory cytokines
  - IL-6, IL-2, interferon-γ, tumor necrosis factor-α, IL-8, IL-10, GM-CSF



Singh N, et al. Cytotherapy. 2017;19(7):867-880.
Teachey DT, et al. Cancer Discov. 2016;6(6):664-679.
Hay KA, et al. Blood. 2017;130(21):2295-2306.
Fitzgerald JC, et al. Crit Care Med. 2017;45(2):e124-e131.
Schubert, M-L. Ann Oncol . 2021 Jan;32(1):34-48

CRS Risk Factors

- High disease burden
- Concurrent infection
- ALL as underlying disease
- High number of administered CAR-T cells
- High peak of CAR-T Cell expansion
- Thrombocytopenia and endothelial activation before CAR-T cell treatment
- Lymphodepleting therapy with fludarabine and cyclophosphamide
- CD28 costimulatory domain

Hay KA, et al. Blood. 2017;130(21):2295-2306.
Turtle CJ, et al. J Clin Invest. 2016;126(6):2123-2138.
Frey NV, et al. J Clin Oncol. 2020;38(5):415-422.

CRS Clinical Presentation

- Fever is first sign
- Symptoms initially mild, gradually progress over hours to days
- Many cases can be self-limiting
- Can progress to
  - Hypotension
  - Tachycardia
  - Hypoxia
- Onset day 2-3 post infusion
- Duration 7-8 days

Organ System	Sings/Symptoms
Constitutional Symptoms	Fever, rigors, malaise, fatigue, anorexia, myalgias, arthralgias, headache
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Coagulation	Elevated D-dimer, hypofibrinogenemia +/bleeding

Lee DW, et al. Blood. 2014;124:188-195.

ASTCT Consensus CRS Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	>100.4 °F	>100.4 °F	>100.4 °F	>100.4 °F
		With Either:		
Hypotension	None	Fluid Responsive	Requiring 1 vasopressor (with or without vasopressin)	Requiring multiple Vasopressors (excluding vasopressin)
		And/Or		
Hypoxia	None	**Low-flow nasal cannula or blow-by	High-flow** nasal canula, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (CPAP, BiPAP, intubation and mechanical ventilation)

*Fever not attributable to any other cause. In patients who have CRS then receive antipyretics or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia. **Low flow oxygen: < 6 L/min, high flow oxygen: > 6 L/min

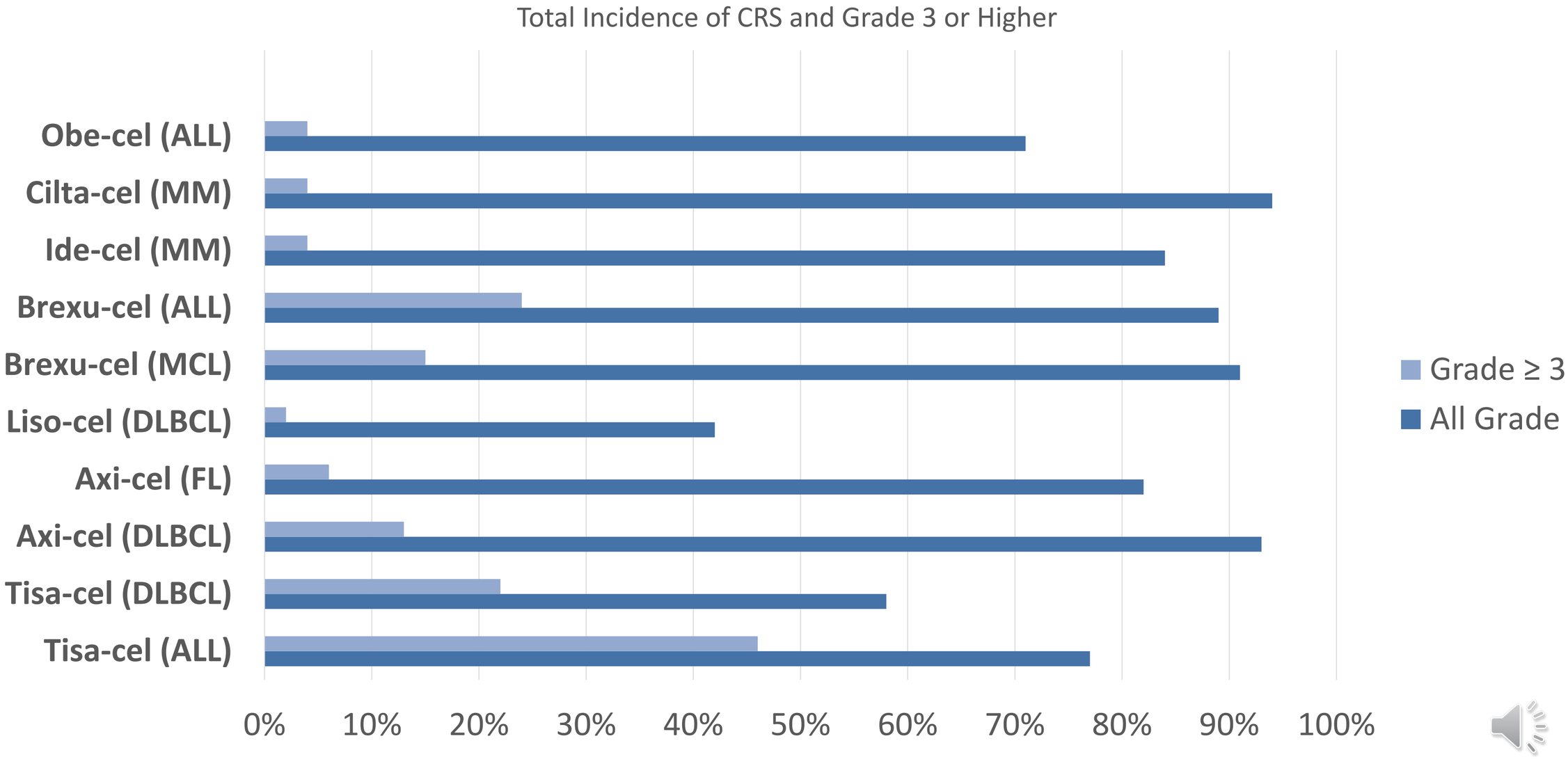
Lee DW, et al. Biol Blood Marrow Transplant. 2019; 25:625-638.

Onset of CRS

CAR-T Product	Median Days to Onset (range)
Tisa-cel	3 (1-22)
Axi-cel	2 (1-12)
Brexu-cel	2 (1-15)
Liso-cel	5 (1-14)
Ide-cel	1 (1-14)
Cilta-cel	7 (1-12)
Obe-cel	8 (1-23)

Kymriah [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2022.
Yescarta [package insert]. Santa Monica, CA: Kite Pharma, Inc; 2021.
Breyanzi [package insert]. Bothell, WA: Juno Therapeutics, Inc; 2021.
Tecartus [package insert]. Santa Monica, CA: Kite Pharma, Inc; 2021.
Abecma[package insert]. Summit, NJ: Celgene Corporation; 2021.
Carvykti [package insert]. Somerset, NJ: Janssen Biotech, Inc; 2022
Aucatzyl [package insert]. Gaithersburg, MD: Autolus, Inc; 2024

Incidence of CRS



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Tecartus [package insert]. Santa Monica, CA: Kite Pharma, Inc; 2021.
Abecma[package insert]. Summit, NJ: Celgene Corporation; 2021.
Carvykti [package insert]. Somerset, NJ: Janssen Biotech, Inc; 2022
Aucatzyl [package insert]. Gaithersburg, MD: Autolus, Inc; 2024

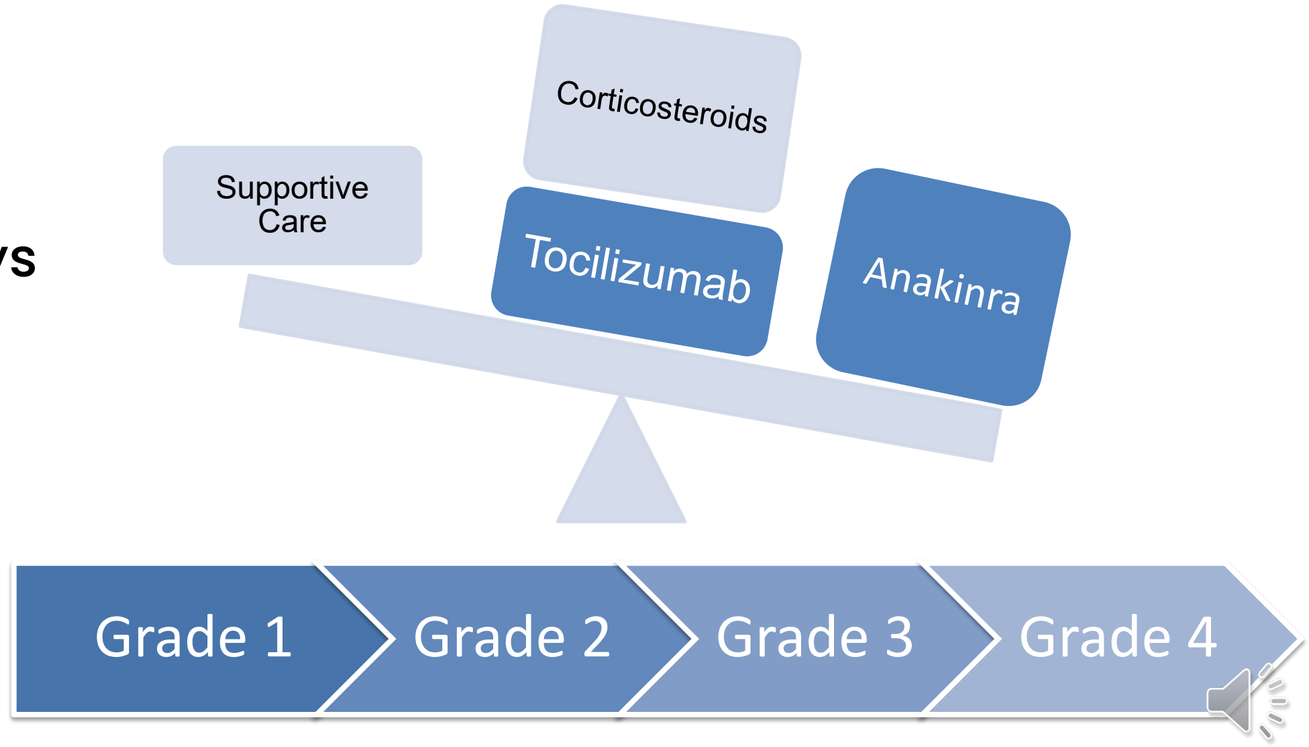
Learning Assessment

- KBB has been treated for refractory DLBCL with axi-cel and is post-infusion day 2
- He develops a fever of 103.6°F
- Initial blood pressure is 97/65 mmHg, improved to 108/72 with 1L 0.9% NaCl. O2 sat 98% on 2 L nasal cannula.
- Per the ASTCT grading scale, what grade of CRS is KBB experiencing?

A. Grade 1
B. Grade 2
C. Grade 3
D. Grade 4

Treatment of CRS - Overview

- Goal: prevent life-threatening toxicity but preserve antitumor efficacy
- Dependent on CAR-T Product
  - Each product has specific recommendations of management
- Dependent upon CRS Grade
- Expert and consensus guidelines
  - CARTOX, ASCO, SITC
- Move towards earlier intervention, consolidation of treatment pathways
  - May be institution specific
- General Supportive Care
- Tocilizumab
- Corticosteroids
- Anakinra (refractory CRS)



Supportive Care & Monitoring

- Workup and Evaluation (All Grades)
  - Labs: CBC, CMP, Magnesium, Phosphorus, CRP, LDH, Uric Acid, Fibrinogen, PT/PTT & Ferritin
  - Infectious Workup: Blood/Urine cultures, chest radiograph
- If patient is neutropenic follow institution specific guidelines
- Grade 2 CRS and higher
  - Continuous cardiac telemetry (or if clinically significant arrhythmia)
  - Continuous pulse oximetry
- Grade 3 CRS and higher
  - Should be managed in ICU
  - Obtain cardiac ECHO if not previously performed
  - Consider screening for cytomegalovirus & Epstein Barr
  - Consider chest & abdominal CT, brain MRI and/or lumbar puncture

Santomasso BD, et al. J Clin Oncol. 2021;39(35):3978-3992.
NCCN. Immunotherapy Toxicity Management. (Version1.2022).

ASCO Guideline Management

Grade	Supportive care	Tocilizumab 8 mg/kg IV over 1 hour (Max 800 mg/dose)	Corticosteroids
Grade 1 ● ▲	1) Antipyretics 2) IV fluid 3) Antibiotics (if neutropenic) ≥ grade 3 needs ICU transfer	Give tocilizumab if fever within 72 hours	Consider depending on CAR-T therapy
Grade 2 ⬢ ▲		Repeat tocilizumab q8h Max 3 doses/24 hours, 4 doses total for CRS treatment Once refractory to tocilizumab and steroid, consider other agents	Persistent hypotension after 1–2 doses tocilizumab – Give Dexamethasone 10 mg q12h (1-2 doses & reassess)
Grade 3			Recommended Dexamethasone 10 mg q6h (rapid taper once improvement)
Grade 4			Methylprednisolone 500 mg IV q12h then taper or 1000 mg q12h if unresponsive

Additional Considerations:

● Axi-cel

▲ Liso-cel

⬢ Ide-cel

Santomasso BD, et al. J Clin Oncol. 2021;39(35):3978-3992.
NCCN. Immunotherapy Toxicity Management. (Version1.2022).

ASCO Guideline Management

CAR-T Product	Prophylaxis	Grade 1	Grade 2
Axi-cel	Consider: Dexamethasone 10 mg oral once daily x 3 days (first dose pre-CAR T-Cell infusion)	Dexamethasone 10 mg IV q24h + Tocilizumab	-
Liso-cel	-	Consider dexamethasone 10 mg IV q24h if CRS < 72 hours since infusion	Consider dexamethasone 10 mg IV every 12-24h if < 72h since infusion
Ide-Cel	-	-	Consider dexamethasone 10 mg IV every 12-24h

Santomasso BD, et al. J Clin Oncol. 2021;39(35):3978-3992.
NCCN. Immunotherapy Toxicity Management. (Version1.2022).

Antimicrobial Prophylaxis

Pathogen	Standard Agent	Duration
Bacterial	Levofloxacin 500mg QD	ANC < 500
Viral	Acyclovir 400-800mg BID Valacyclovir 500mg QD	6-12 months
Pneumocystis jerovecii (PJP)	Sulfamethoxazole/Trimethoprim Pentamidine 300mg IV/INH Q30D Dapsone 100mg QD Atovaquone 1500mg QD	While CD4 < 200
Fungal (low risk)	Fluconazole 200-400mg QD	ANC < 500
Fungal (high risk) • 2 doses of tocilizumab • CRS/ICANS > grade 3 • High dose steroids > 3 days • Neutropenia > 14 days • Hx of invasive fungal infection	Posaconazole 300mg QD Voriconazole 200mg BID Isavuconazole 372mg QD	Continue for 1 month after steroids stopped or if ANC > 1000

Nebraska Medicine. CARTOX 2021.

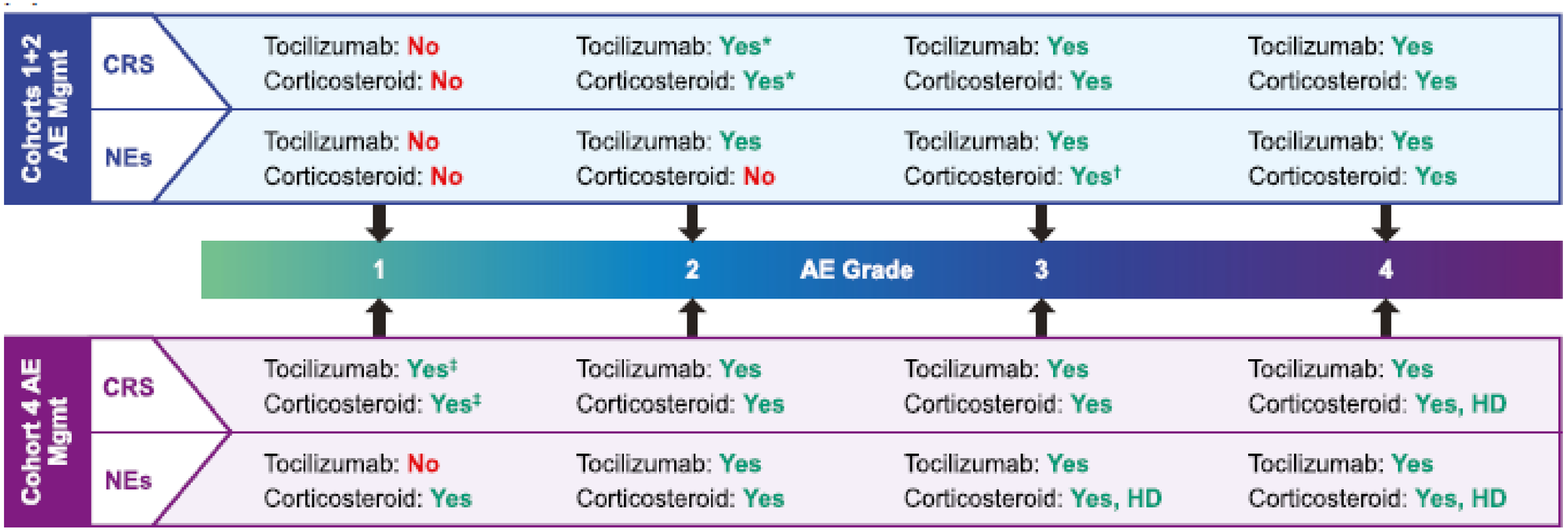
Learning Assessment

- KBB previously at grade 2 CRS has continued to worsen
- Blood pressure is now 100/63 mmHg, on 5 mcg/min of norepinephrine and is requiring 8 L/min of O2 via simple face mask to maintain saturations of 94% .
- He as previously received one dose of tocilizumab 8 mg/kg and 1 dose of dexamethasone 10 mg IV
- Per the ASTCT grading scale, what grade of CRS is KBB experiencing and what should his treatment be?

A. Grade 2; No further treatment
B. Grade 2 ; Anakinra 100 mg subcutaneously
C. Grade 3 ; schedule dexamethasone 10 mg q6h + tocilizumab 8 mg/kg for up to 3 more doses
D. Grade 4 ; Methylprednisolone 1g IV daily + tocilizumab 8 mg/kg up to 3 more doses

Early Intervention for CRS

- Comparison of cohorts 1+2 to cohort 4 of Zuma-1 trial using axi-cel in relapsing/refractory large B-cell lymphoma
- Primary endpoints of incidence and severity of CRS and neurological events (NEs)



Topp MS et al. Br J Haematol. 2021;195(3):388-398.

Early Intervention for CRS

CRS Grade	Tocilizumab Dose	Corticosteroid Dose
1	If no improvement after 3 days 8 mg/kg over 1 hour, repeat every 4-6h as needed	If no improvement after 3 days, dexamethasone 10 mg x 1
2	8 mg/kg over 1 hour, repeat every 4-6 hours as needed (max of 3 doses in 24h period)	Dexamethasone 10 mg x 1
3	Per Grade 2	Methylprednisolone 1 mg/kg IV twice daily or dexamethasone equivalent
4	Per Grade 2	Methylprednisolone 1000 mg IV x 3 days

Topp MS et al. Br J Haematol. 2021;195(3):388-398.

Early Intervention for CRS

Toxicity	Cohorts 1/2 (standard)	Cohort 4 (early toci/dex)
CRS (all grades)	93%	93%
Onset	2 days	2 days
Duration	8 days	7 days
Grade ≥3	13%	2%
ICANS (all grades)	64%	61%
Duration	12 days	9 days
Grade ≥3	28%	17%
Tocilizumab Use	43%	76%
Median Steroid Dose (MP)	5451mg	939mg

Topp MS et al. Br J Haematol. 2021;195(3):388-398.

Learning Assessment

- From the comparison of Zuma-1 cohorts 1&2 to cohort 4, the early use of tocilizumab and dexamethasone resulted in what clinical outcomes?

A. Reduction in all cause mortality
B. Reduction in total steroid dose
C. Reduction in Grade 3 CRS and ICANS
D. Both B & C

Product-Specific Early Intervention Recommendations

Axi-cel

- Dexamethasone IV x 1 for grade 1 CRS not improving after 3 days

Brexu-cel

- Tocilizumab for grade 1 CRS not improving after 24h

Liso-cel

- Consider tocilizumab for early onset (≤ 72h) grade 1 CRS
- Consider addition of dexamethasone

Ide-cel

- Consider tocilizumab for early onset (≤ 72h) grade 1 CRS

Cilta-cel

- Consider tocilizumab for early onset (≤ 72 hours) grade 1 CRS
- Consider addition of dexamethasone

Yescarta® (axicabtagene ciloleucel) [package insert]. Santa Monica, CA: Kite Pharma, Inc 2017.
Breyanzi® (lisocabtagene maraleucel) [package insert]. Bothwell, WA: Juno Therapeutics, a Bristol Myers Squibb company, Inc 2022.
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Carvykti® (ciltacabtagene autoleucel) [package insert]. Horsham, PA: Janssen Biotech, Inc. 2022

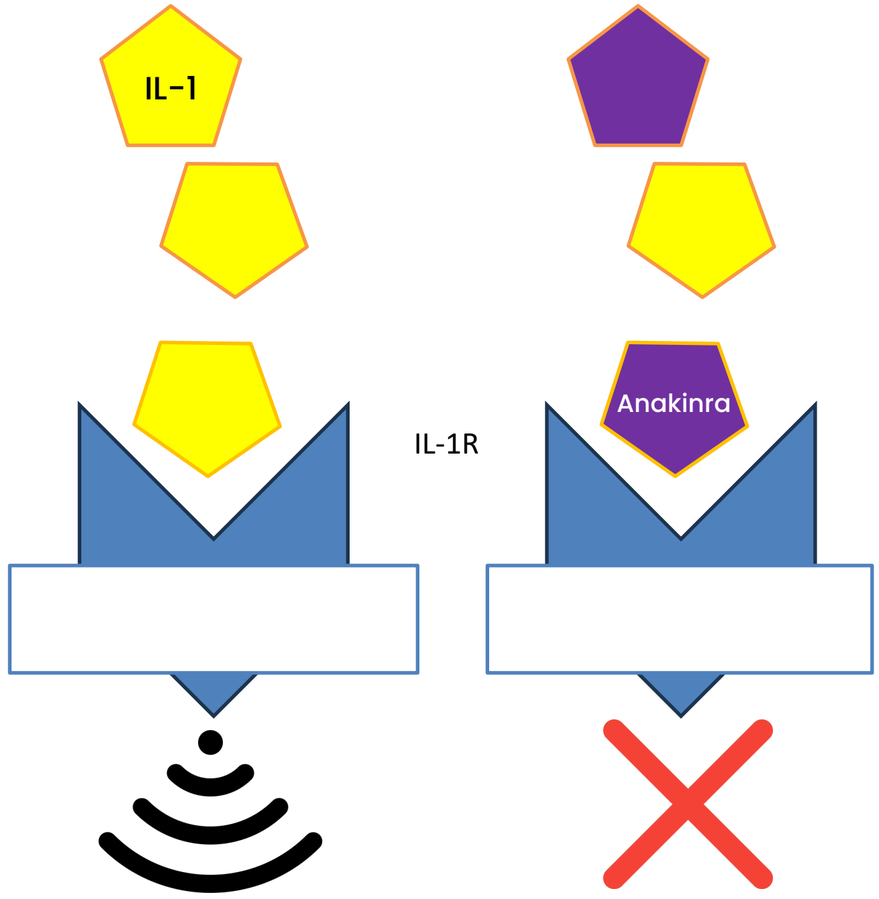
Management of Refractory CRS

Anakinra (IL-1 antagonist)	Siltuximab	Cyclophosphamide
Etanercept	Infliximab	Antithymocyte Globulin
Ruxolitinib	Dasatanib	ibrutinib

Jain, M. Blood . 2023 May 18;141(20)

Anakinra for Refractory CRS

- Mechanism: Inhibits IL-1 binding
- Dose: 100 -200 mg for 3-7 days
- Route: Subcutaneous or IV
- Half life: 4-6 hours (IV)
- Adverse Effects: Increased risk of thrombocytopenia
  - May require mold prophylaxis
- Currently no prospective studies but some are ongoing



Strati P, et al. Blood Adv. 2020;4(13):3123-3127.
Anakinra (Kineret) Image from Sobi, inc. 2022.

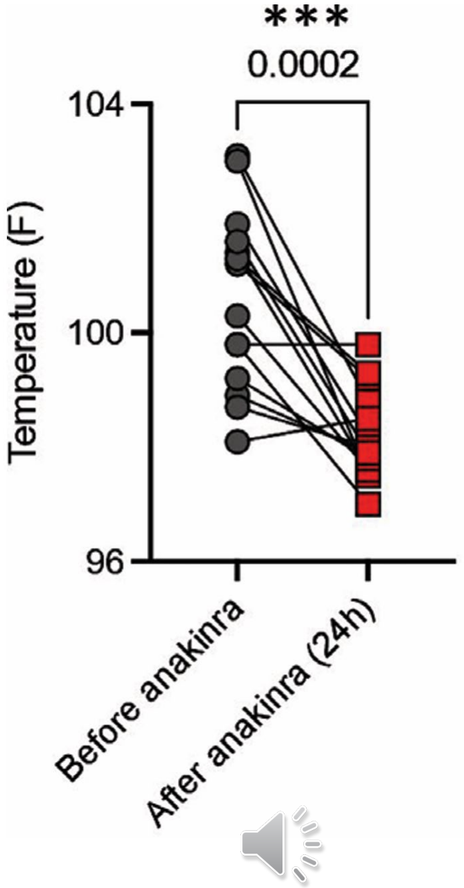
Anakinra for Refractory CRS

Wherli et al, 2021

- Population
  - 14 patients with refractory LBCL
  - 7 each on tisa-cel or axi-cel
  - Peak CRS Grade 2 (Range 1-4)
- Intervention
  - Anakinra 100 - 200 mg subcutaneous daily for up to 3 days (physician discretion)
- Other therapies
  - All patients got dexamethasone median 297 mg
  - 7/14 got tocilizumab median 2 doses

Outcomes

- Significant reduction in fever curve at 24h post dose
- Significant Reduction in inflammatory cytokines among grade 3 & 4 CRS/ICANS
  - IL-1, IL-6, IL-15, CCL-3, CCL-4, & CRP
- 55% overall reduction in neurotoxicity



Wehrli M, et al. J Immunother Cancer. 2022;10(1):e003847.

Helpful Resources

- CARTOX Guidelines (MD Anderson Cancer Center)
- Society of Clinical Oncology Guidelines
- Society for Immunotherapy of Cancer Guidelines (SITC)
- Institutional Guidelines

Summary

- CRS is a serious complication of CAR-T Cell Therapy
- Incidence and severity of CRS depends on several factors
  - The diversity of cancer types and CAR T-Cell products leads to a wide array of treatment variations
- Therapy is guided using consensus definitions of severity
- In general, moderate/severe cases require intervention with tocilizumab and steroids, respectively
- Optimal pharmacologic management of CRS remains to be determined, particularly for refractory cases
  - Anakinra remains the mainstay of refractory CRS

Santomasso BD, et al. J Clin Oncol. 2021;39(35):3978-3992.
NCCN. Immunotherapy Toxicity Management. (Version1.2022).

Questions?

Special Thanks to Jared Mataya
PharmD, BCOP