Toxicities associated with CAR-T therapy

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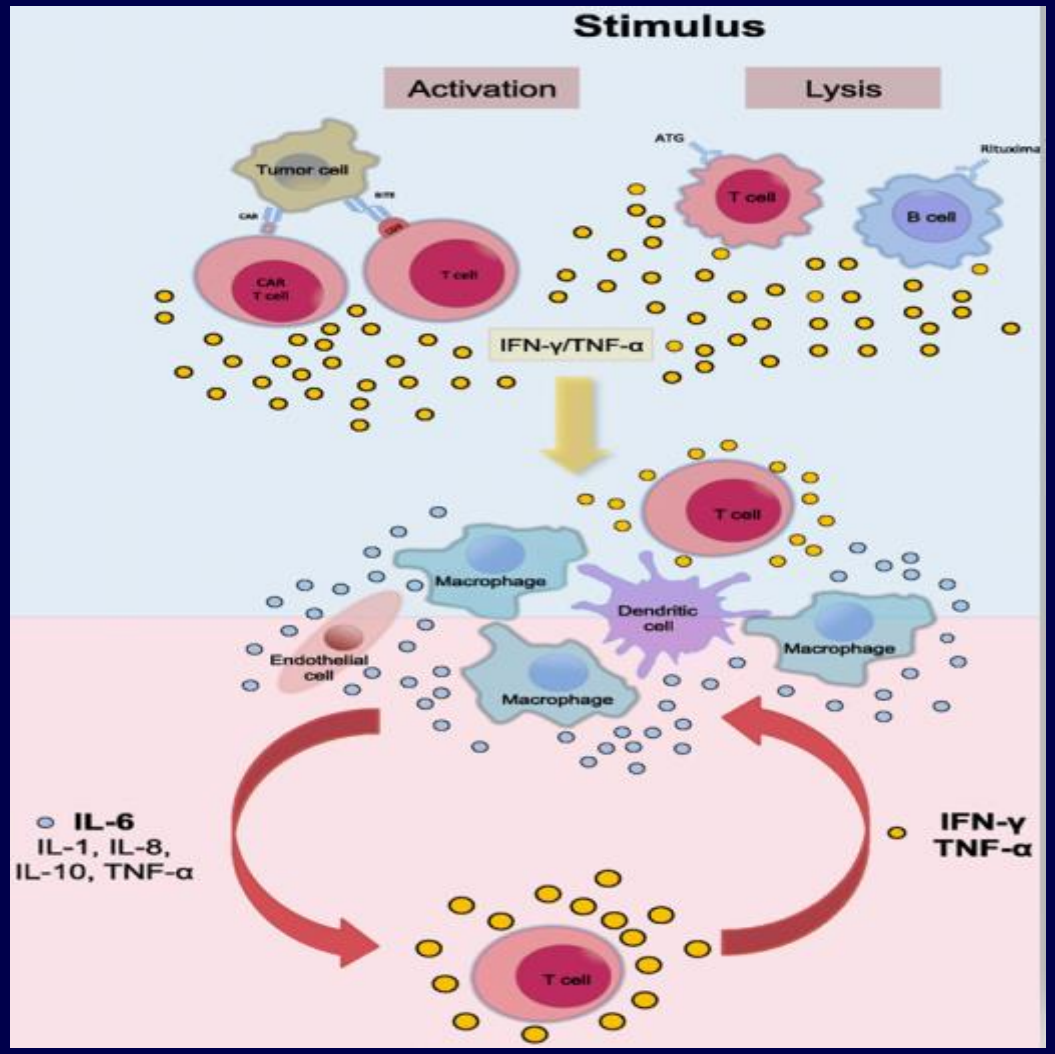
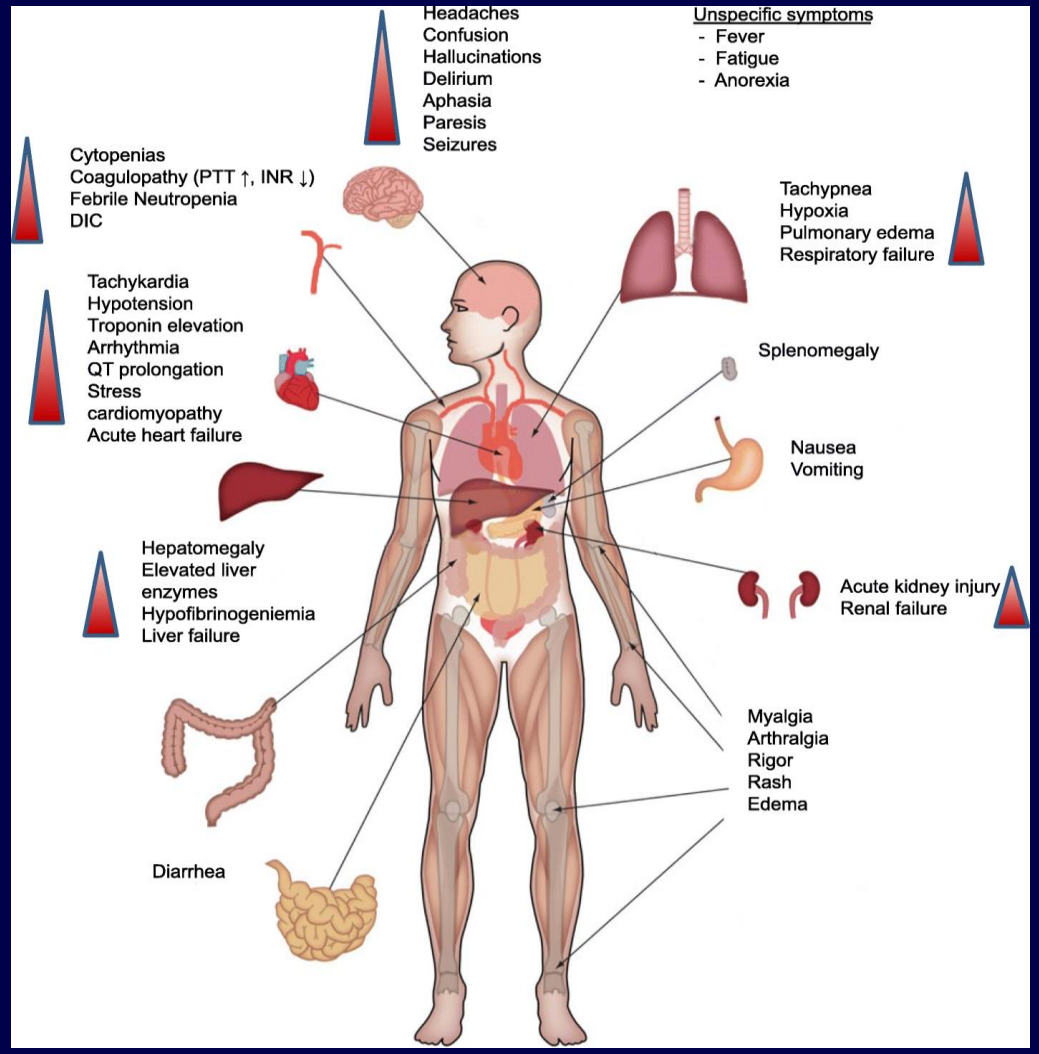
Effector cells and targets in cytokine release syndrome





CAR T-cell Toxicity

- Cytokine Release Syndrome (CRS)
  - Caused by activation/expansion of CAR T-cells and increased levels cytokines like IL-6, IL-15, INF-γ, GM-CSF and others
    - Monocytes and macrophages are a source of some of these cytokines
  - Onset: 1-3 days
  - Duration: 3-5 days
  - Risk variable but gr3+ up to 20-30%

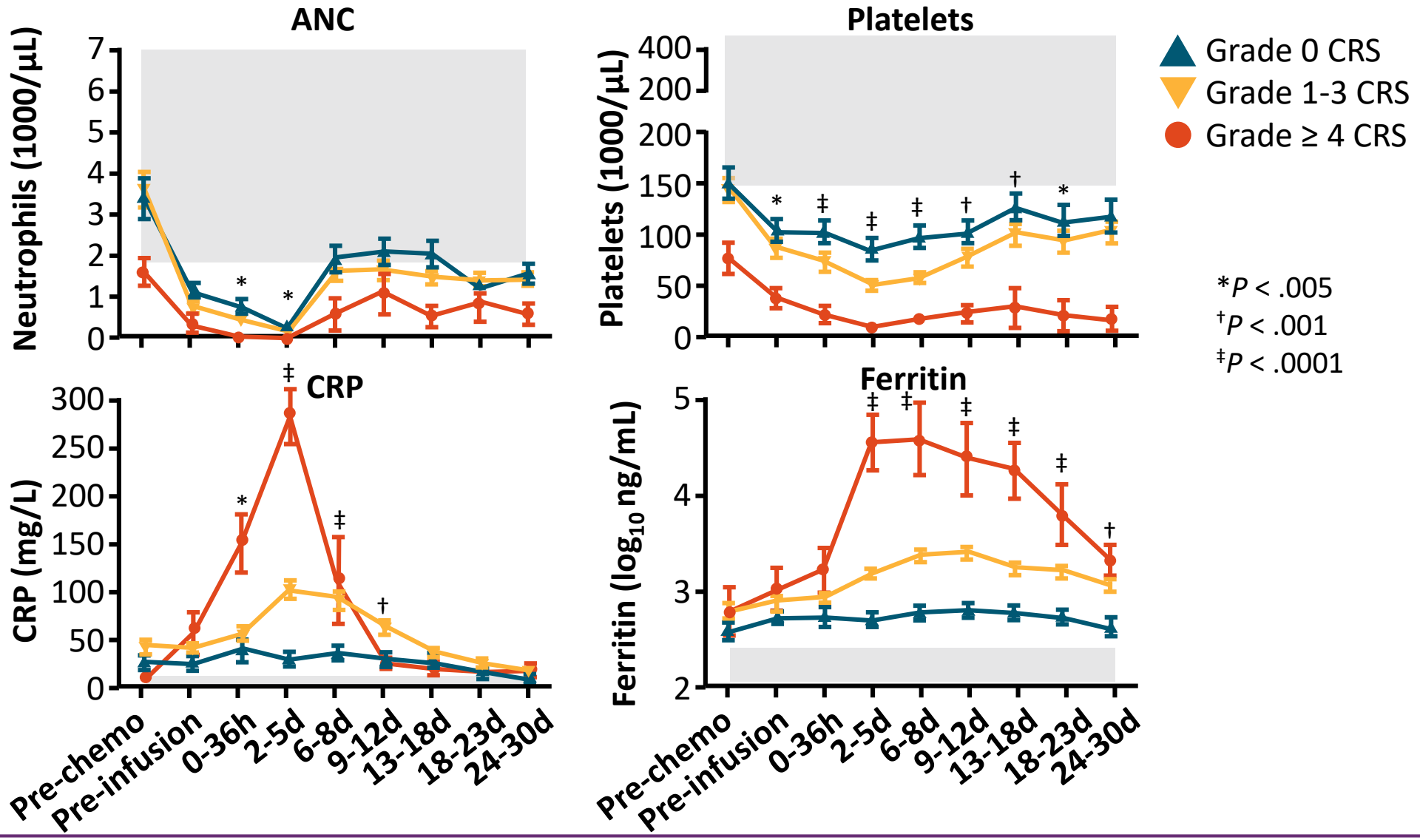
- Neurotoxicity
  - Mechanism less well understood
    - Clinically associated with tumor burden, CAR T-cell expansion, cytokine levels, early and high grade CRS
    - Biologically associated with markers of DIC, endothelial activation and breakdown of the blood brain barrier
      - CAR+ and CAR- T-cells and inflammatory cytokines are found in the CSF
  - Onset: 5-7 days
  - Duration: 5-10 days
    - Fully reversible except in cases of fatal cerebral edema
  - Risk variable but gr3+ in up to 30-40%

Predictors of Toxicity

Predictors of Increased Toxicity	
Pre treatment	▪ High tumor burden, pretreatment LDH, pretreatment inflammatory markers ▪ High pretreatment monocyte levels?
Post treatment	▪ High peak CAR T-cell, cytokine levels ▪ Markers of DIC (including fibrinogen levels) ▪ Early CRS (if product contains 41BB)

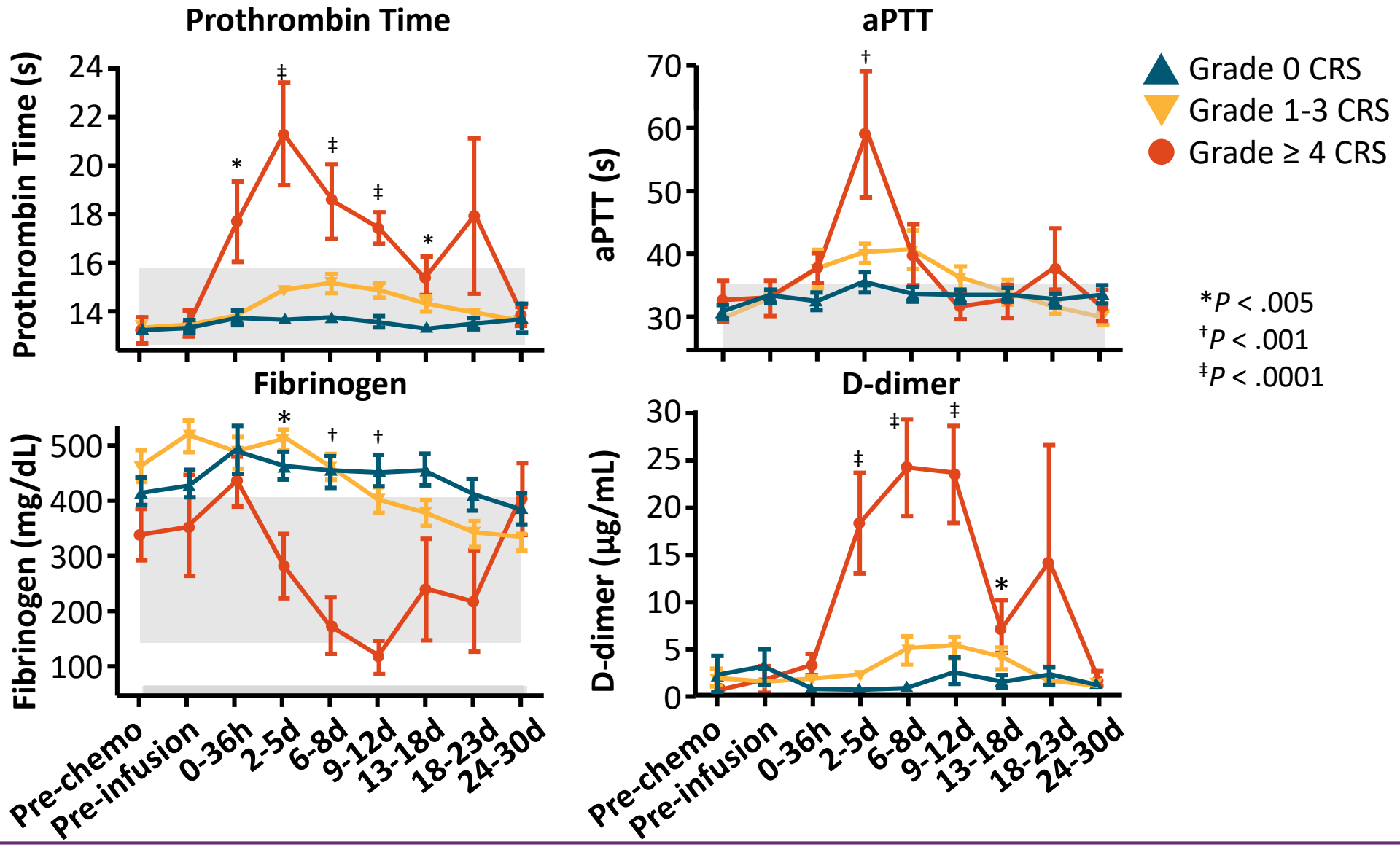
Nastoupil. JCO. 2020;38:3119. Locke. Blood Adv. 2020;4:4898. Du. Biomark Res. 2020;8:13.
Jaeger. ASH 2020. Abstr 1194. Majzner. ASH 2020. Abstr 556.

Biomarkers of CRS: Cytopenias and Inflammatory Markers



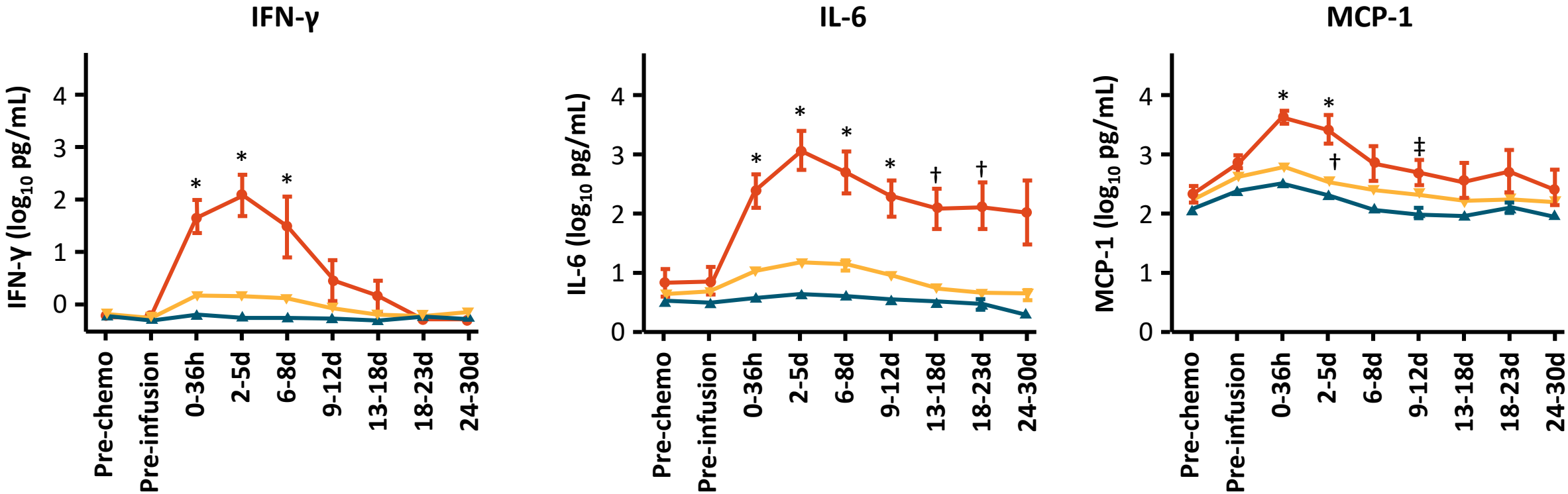
Hay. Blood. 2017;130:2295.

Biomarkers of CRS: Coagulopathy



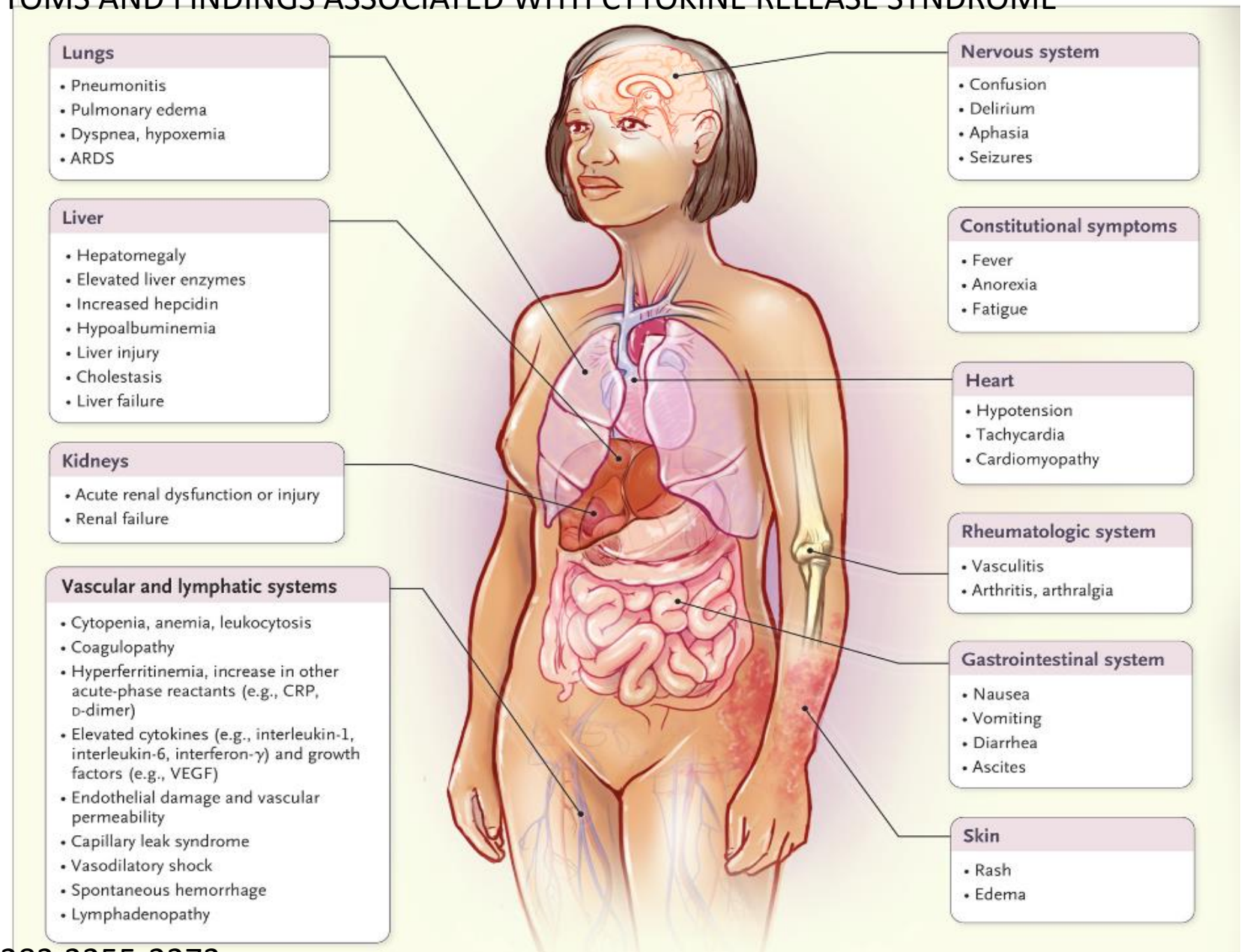
Hay. Blood. 2017;130:2295.

Biomarkers of CRS: Correlative Cytokines



Hay. Blood. 2017;130:2295.

SYMPTOMS AND FINDINGS ASSOCIATED WITH CYTOKINE RELEASE SYNDROME

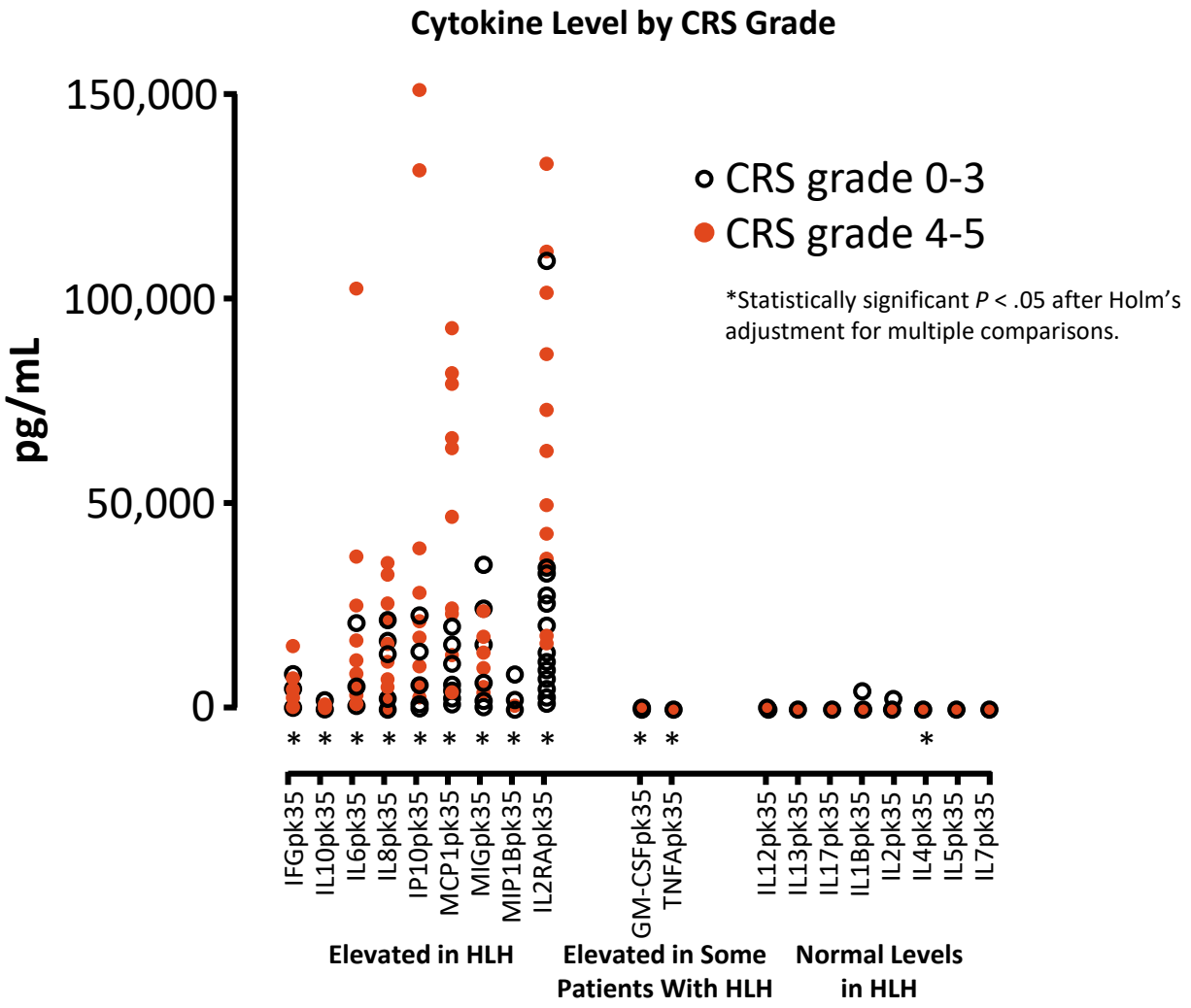


N Engl J Med 2020; 383:2255-2273

CRS: Macrophage Activation Syndrome (HLH): a life threatening consequence

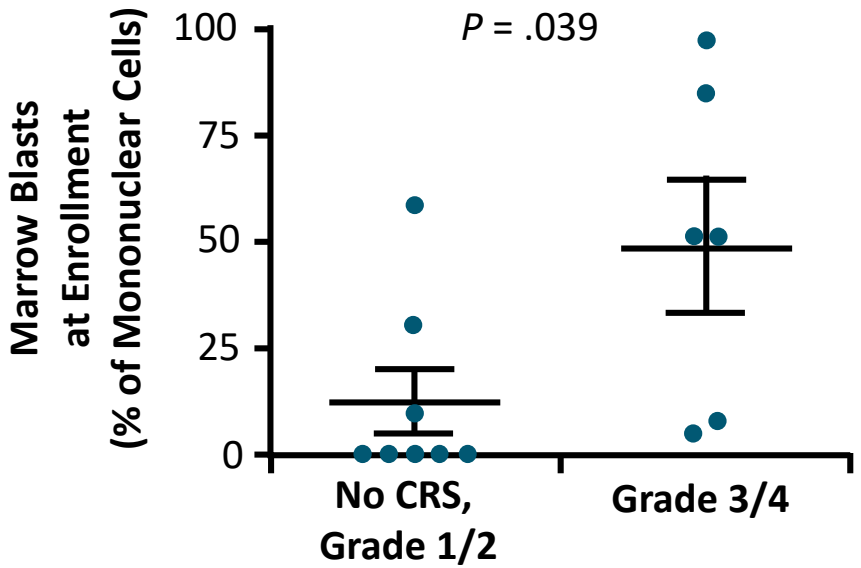
- MAS appears to accompany CRS in a subset of patients
- Characterized by high fevers, hepatosplenomegaly, liver dysfunction, renal failure, **coagulopathy**, hypofibrinogenemia, and profound hyperferritinemia
- Histologic evidence of hemophagocytosis noted on bone marrow biopsy at peak of CRS
- Similar cytokine profiles

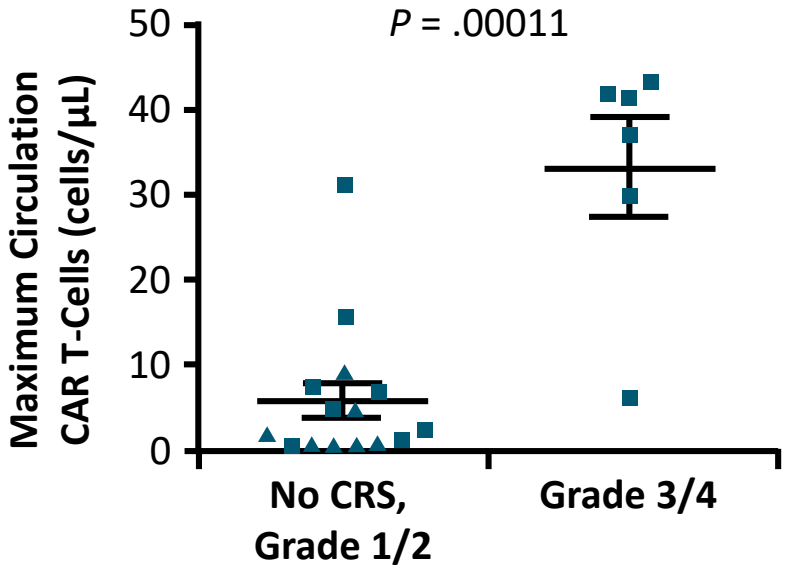
CRS → **MAS**

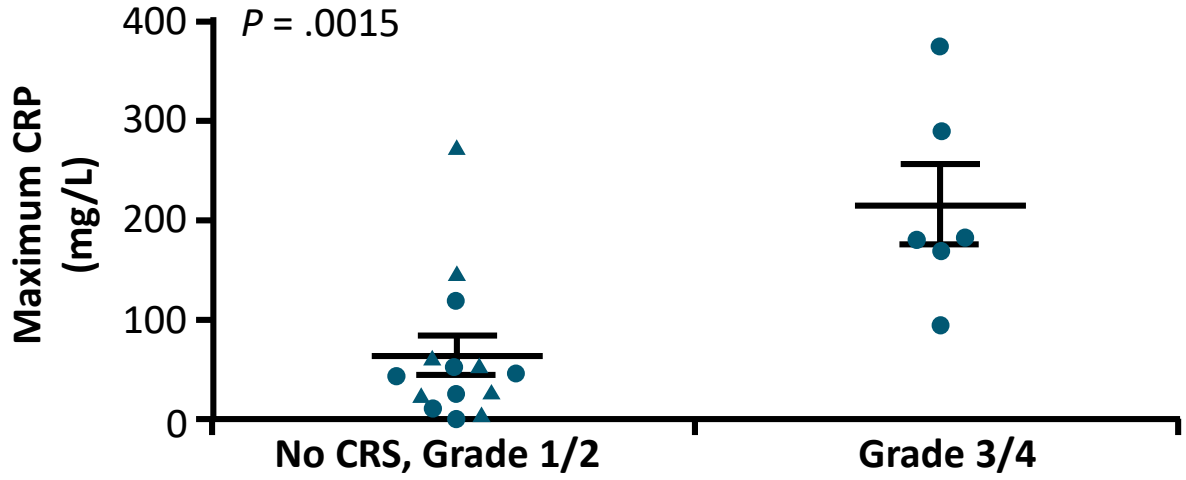


Teachey. Cancer Discov. 2016;6:664.

CAR T-Cell Number and Tumor Burden by Severity of CRS: May be related to tumor mass and CAR-T number







Lee. Lancet. 2015;385:517.

Slide credit: clinicaloptions.com

ASTCT Guidelines for Grading of CRS

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temp ≥ 38°C	Temp ≥ 38°C	Temp ≥ 38°C	Temp ≥ 38°C
with				
Hypotension	None	Not requiring vasopressors	Requiring a 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, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

*Fever defined as temperature ≥ 38°C not attributable to other causes. In patients with CRS who receive antipyretics or anticytokine therapy (eg, tocilizumab, steroids), fever no longer required to grade subsequent CRS severity; CRS grading driven by hypotension and/or hypoxia. †CRS grade determined by more severe event: hypotension or hypoxia not attributable other causes. Eg, temperature 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS. ‡Low-flow nasal cannula defined as oxygen delivered at ≤ 6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula defined as oxygen delivered at > 6 L/min.

Lee. Biol Blood Marrow Transplant. 2019;25:625.

ASTCT Guidelines for Grading of ICANS (Immune effector Cell Associated Neurotoxicity Syndrome): ICE Score

Parameter	Score (Points)
Orientation: year, month, city, hospital	4
Naming: ability to name 3 objects (eg, point to clock, pen, button)	3
Following commands: ability to follow simple commands (eg, “show me 2 fingers” or “close your eyes and stick out your tongue”)	1
Writing: ability to write a standard sentence (eg, “our national bird is the bald eagle”)	1
Attention: ability to count backwards from 100 by 10	1

Scoring:
10, no impairment
7-9, grade 1 ICANS
3-6, grade 2 ICANS
0-2, grade 3 ICANS
0 due to patient unarousable and unable to perform ICE assessment, grade 4 ICANS

Lee. Biol Blood Marrow Transplant. 2019;25:625.

New ASTCT Guidelines for Grading of 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; stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 mins) 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
Elevated ICP/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

*An ICE score of 0 may be classified as grade 3 ICANS if patient is awake with global aphasia; otherwise classified as grade 4 ICANS if unarousable. †Depressed level of consciousness not attributable to other cause. ‡Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading. §Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Lee. Biol Blood Marrow Transplant. 2019;25:625.

Toxicities associated with CAR-T products for NHL: variable rates of CRS >3

CAR T-Cell Product	Tisagenlecleucel, JULIET (N = 93); Lentivirus-41BB[4]	Axicabtagene Ciloleucel, ZUMA-1 (N = 108); Retrovirus-CD28[3]	Lisocabtagene Maraleucel, TRANSCEND (N = 102); Lentivirus-41BB[38]
Use of tocilizumab, %	15	45	17
Use of steroids, %	11	29	21
CRS all grades, %	58	93	37
CRS ≥ 3, %	23	12	1
Median time to CRS onset (range), days	3 (1–9)	2 (1–12)	5 (1–14)
Median duration CRS (range), days	7 (2–30)	8	NR
NT/ICANS all grades, %	NR	67	23
NT/ICANS ≥ 3, %	12	30	13
Median time to NT/ICANS onset (range), days			10 (3–23)
Nonrelapse fatal events, N	3 (4%) encephalitis; cerebral hemorrhage; mycosis (post-SCT)	3 (2.8%) cardiac arrests; HLH; pulmonary embolus	NR

Abbreviations: CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector cell–associated neurologic syndrome;

Santomasso ASCO Educational Book 2019

Cytokine-Release Syndrome

- Systemic inflammatory response that occurs as CAR T-cells activate and expand
- High levels of CRP, ferritin, IL-6, IL-10
- Flu-like symptoms with fever
- Can progress to life-threatening hypotension, hypoxia, and death
- High disease burden associated with more severe CRS

CRS With Products for MM	Cilta-cel	Ide-cel
Construct	BCMA-41BB	BCMA-41BB
Any-grade CRS, %	95	85
Grade ≥3 CRS, %	5	9
Median time to onset, d (range)	7 (1-12)	1 (1-23)
Median duration, d (range)	4 (1-40)	7 (1-63)

CRS graded per Lee 2014 scale.

Ciltacabtagene autoleucel PI. Idecabtagene vicleucel PI. Lee. Blood. 2014;124:188.

Slide credit: clinicaloptions.com

Immune Effector Cell–Associated Neurotoxicity Syndrome

- Symptoms can include:
  - Delirium
  - Encephalopathy
  - Aphasia
  - Lethargy
  - Difficulty concentrating
  - Agitation
  - Tremor
  - Seizures
  - Cerebral edema
  - Headache
- Pathophysiology
  - Endothelial activation → BBB disruption
  - Elevated levels of excitatory NMDA receptor agonists?
  - Activated T-cells and myeloid cells, proinflammatory cytokines

ICANS With Products for MM	Cilta-cel	Ide-cel
Construct	BCMA-41BB	BCMA-41BB
Any-grade ICANS, %	26	23
Grade ≥3 ICANS, %	11	4
Median time to onset, day (range)	8 (1-28)	2 (1-42)
Median duration, day (range)	8 (2-927)	6 (1-578)

Gust. Cancer Discov. 2017;7:1404. Cancer Discov. 2018;8:4. Lee. Biol Blood Marrow Transplant. 2019;25:625.
Ciltacabtagene autoleucel PI. Idecabtagene vicleucel PI.

Principles of Toxicity Management

- Appropriate screening per institutional standards
- Baseline labs
  - CRP, ferritin
  - CBC, CMP, coagulopathy
  - Tumor lysis syndrome labs
- Initiation of antiepileptic drugs if not used for prophylaxis
- Appropriate bacterial/fungal/viral prophylaxis per institutional standards
- Pre-infusion/LD chemo
- Monitor CBC, CMP, and coagulopathy
- Monitor for tumor lysis syndrome
- Monitor CRP and ferritin
- Daily assessments for at least 7 days
  - FDA requirement for axicabtagene ciloleucel
  - Fevers? Hypotension? Hypoxia?
  - Mental status

MD Anderson. CAR cell therapy toxicity assessment and management - adult. 2017.
Neelapu. Nat Rev Clin Oncol. 2018;15:47. Axicabtagene ciloleucel PI. Tisagenlecleucel PI.

Principles of Toxicity Management by Grade

Grade	CRS	Neurotoxicity	CRS + Neurotoxicity
1	Supportive care	Supportive care + AEDs	Supportive care + AEDs
2	Tocilizumab	Steroids (dexamethasone* or methylprednisolone†)	Tocilizumab + steroids (dexamethasone*)
3	Tocilizumab + steroids	Steroids (dexamethasone*)	Tocilizumab + steroids (dexamethasone*)
4	Tocilizumab + high-dose steroids/anakinra ICU/critical care	High-dose steroids (methylprednisolone‡) ICU/critical care/anakinra	Tocilizumab + high-dose steroids (methylprednisolone‡) ICU/critical care

*Dexamethasone 10-20 mg IV either as a one-time dose or Q6H. †Methylprednisolone 1 mg/kg IV Q12H. ‡High-dose methylprednisolone given at 500 mg IV Q12H for 3 days, then tapered over 2.5 wks.

- Always rule out/treat alternative causes
- If tocilizumab refractory, consider corticosteroids
- Patients with neurotoxicity should receive AEDs and appropriate CNS imaging, EEG monitoring
- Steroid dosing for neurotoxicity may vary between products
- Patients on steroids should receive appropriate fungal prophylaxis

MD Anderson. CAR cell therapy toxicity assessment and management - adult. 2017. Neelapu. Nat Rev Clin Oncol. 2018;15:47.

	LD	Day 0	Day 3	Day 4	Day 5	Day 6	Day 7			
WBC	3.6	1.5	0.4		0.2	0.3	0.3			
Hgb	8.2	7.6	8.3 (tx2)		9.3	8.8	8.5	5.3		
Platelets	35	28	11		8/11	5/6	7/7	39		
INR	1.1	1.2	1.2	1.4		2.4	2.0	1.8	2.3	
Ferritin	7519	9248	8345	29,604	80,577	170,478	175,725			
Creatinine	0.7		0.76	0.75	1.34	1.87	2.07			
AST			44	59	156	243	253			
ALT							375			
TG									262	
fibrinogen	>1000	893		261	185	155	136	63	56	
LDH	288	224	252	328			1140			

“H score”: calculates probability of HLH

H-Score

Metric	Result	Score
Known underlying immunosuppression (HIV positive or receiving long-term immunosuppressive therapy, i.e. glucocorticoids, ciclosporin, azathioprine)	No	0
	Yes	18
Temperature (°C)	<38.4	0
	38.4-39.4	33
	>39.4	49
Organomegaly	No	0
	Hepatomegaly or Splenomegaly	23
	Hepatomegaly and Splenomegaly	38
Number of Cytopenias (Haemoglobin <92g/l, White Cell Count ≤5.0x10^9/l, Platelets ≤110x10^9/l)	1	0
	2	24
	3	34
Ferritin (ug/l)	<2000	0
	2000-6000	35
	>6000	50
Triglyceride (mmol/l)	<1.5	0
	1.5-4	44
	>4	64
Fibrinogen (g/l)	>2.5	0
	≤2.5	30
AST (U/l)	<30	0
	≥30	19
Heamophagocytosis features on bone marrow aspirate	No	0
	Yes	35

CAR T-Cell Therapy: Toxicities

Acute Toxicities (Day 0-30)[1]

- Cytokine-release syndrome (CRS)
  - Hemophagocytic lymphohistiocytosis/ macrophage activation syndrome (MAS/HLH) a very rare and severe form
- Immune effector cell–associated neurotoxicity syndrome (ICANS)
- Cytopenias
- Disseminated intravascular coagulation (DIC)
- B-cell aplasia and hypogammaglobulinemia
- Tumor lysis syndrome

Generally managed by **treating center HCPs**

Delayed Toxicities (Day 30+)[2,3]

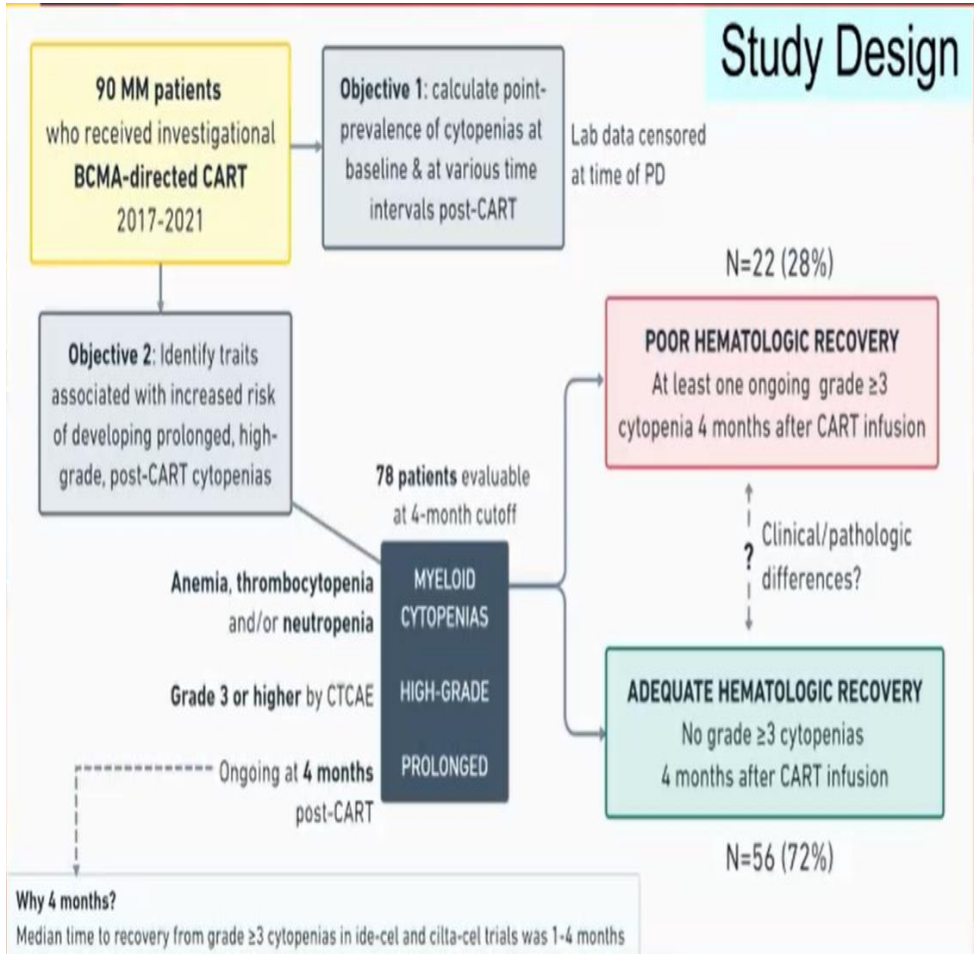
- B-cell aplasia and hypogammaglobulinemia
- Prolonged cytopenias
- T-cell deficiency
- Late infections
- Long-term neurologic events/ movement and neurocognitive treatment-emergent AEs (MNTs)
- Transient cardiac toxicities
- Secondary malignancies?

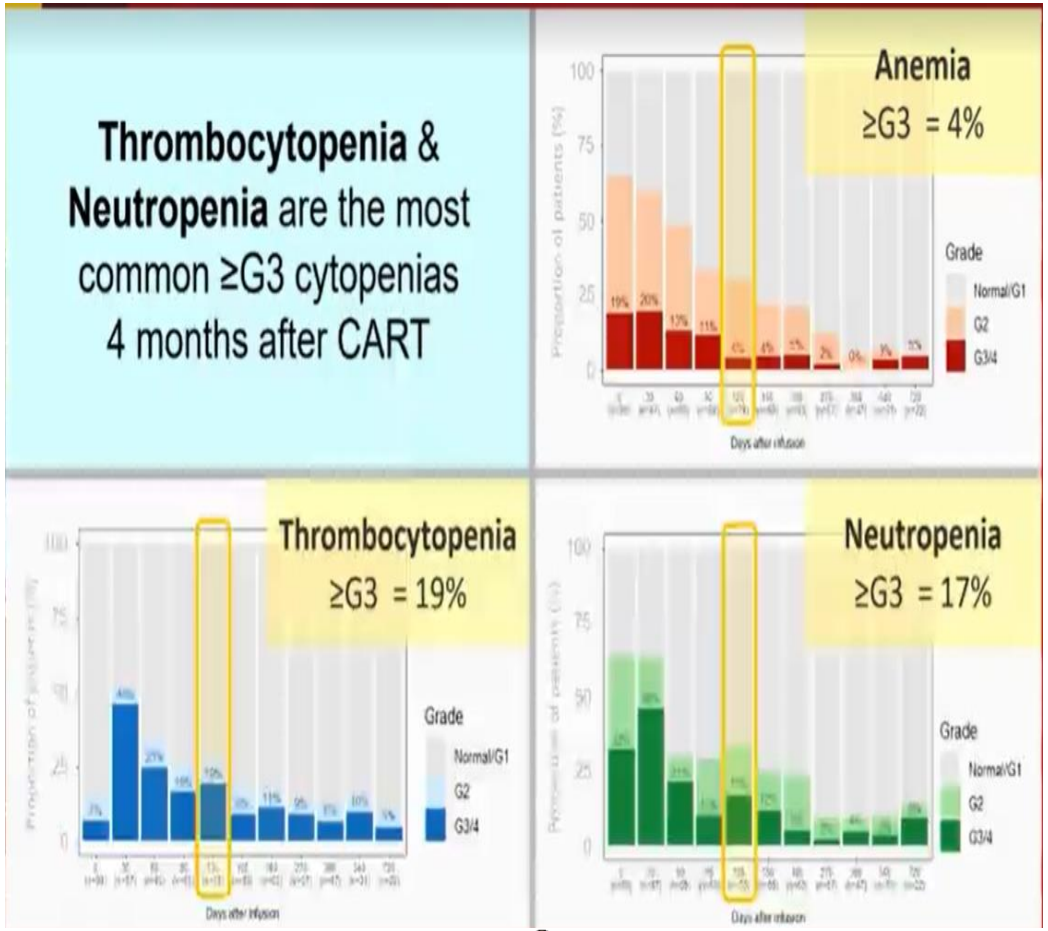
Generally managed by **primary oncologists** ***(can be treating center or community)***

1. Maus. J Immunother Cancer. 2020;8:e001511. 2. Cohen. Blood Cancer J. 2022;12:32. 3. Chakraborty. Transplant Cell Ther. 2021;27:222.

Slide credit: clinicaloptions.com

Cytopenias common after CAR-T, may limit options for future trial participation





Thibaud S ASH Abstract 165646 2022

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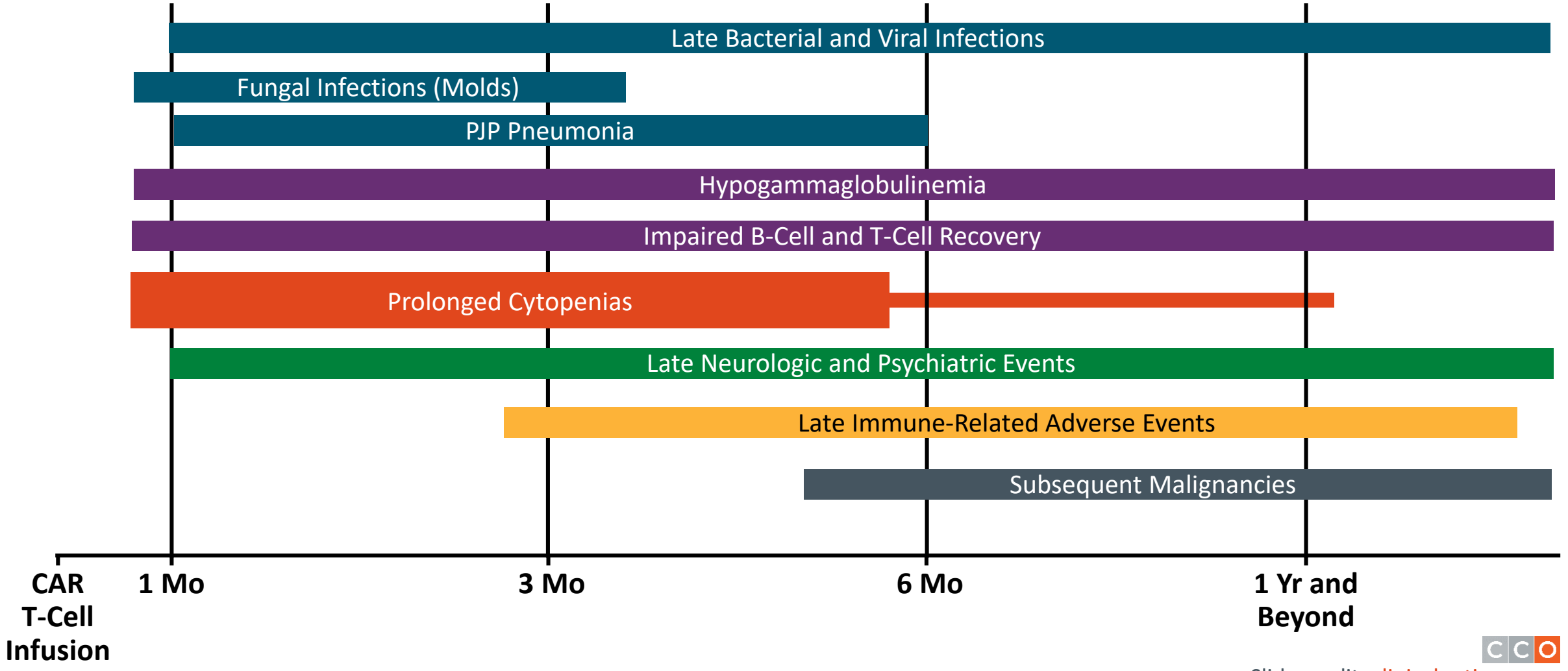
UNIVERSITY OF WISCONSIN-MADISON

Timeline for Delayed Toxicities With CAR T-Cells



Chakraborty. Transplant Cell Ther. 2021;27:222.

Slide credit: clinicaloptions.com

B-Cell Aplasia/Hypogammaglobulinemia in MM

- On-target/off-tumor effect of CAR T-cells targeting surface proteins on B-cells
  - Therefore, healthy B-cells expressing BCMA also will be affected by CAR T-cell therapy, thus causing B-cell aplasia
- Hypogammaglobulinemia is a result of B-cell aplasia and can increase infection risk
- Hypogammaglobulinemia common in clinical trials of CAR T-cells in MM
  - Cilta-cel (CARTITUDE-1): 94%
  - Ide-cel (KarMMa): 41%

Management

- Post CAR T-cell therapy, IgG levels should be monitored monthly for 6 mo and then Q3M until 1 yr
- Replace per institutional policy, usually when IgG levels <400 mg/dL
  - Criteria may be stricter due to IVIg shortages (eg, IgG <200 mg/dL or <400 mg/dL with severe infection)

Schubert. Ann Oncol. 2021;32:34. Chakraborty. Transplant Cell Ther. 2021;27:222. Sehgal. Lancet Oncol. 2022;23:1066. Locke. NEJM. 2022;386:640. Kamdar. Lancet. 2022;399:2294. Ciltacabtagene autoleucel PI. Idecabtagene vicleucel PI.

Patient Education on Acute Toxicities

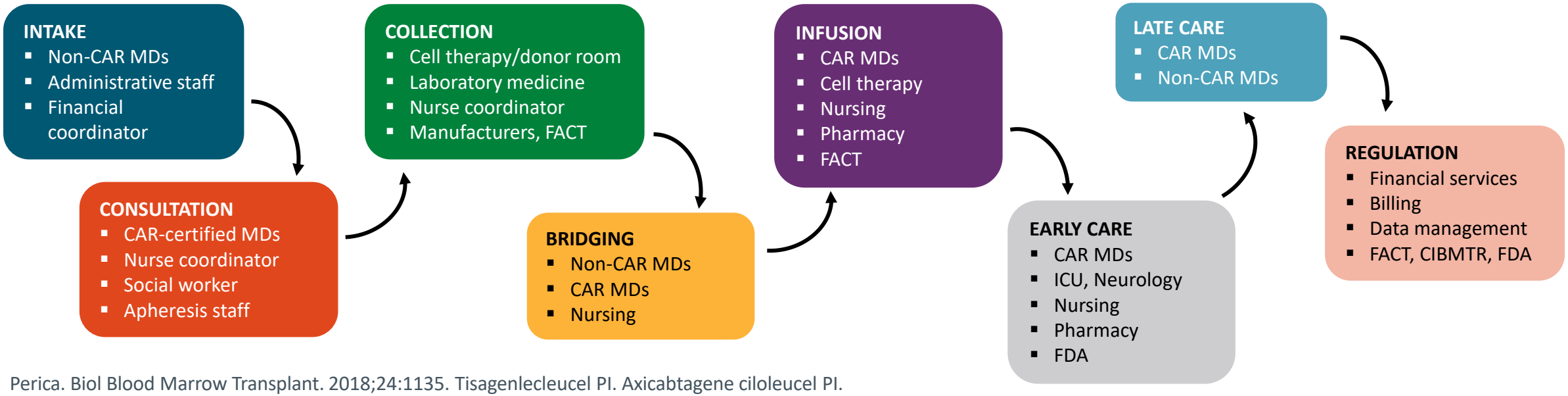
- CAR T-cell therapy is currently under a REMS program, which means treating centers must be enrolled in REMS program
- Under REMS, there is mandatory education that all patients must be given
  - Patients must refrain from driving for ≥8 wk after CAR T-cell therapy is given
  - Patients must remain within 2 hr of REMS-certified hospital for ≥4 wk after CAR T-cell therapy is given
  - Patients must be provided with wallet card (provided by manufacturer) with this information
- Patients should be given education on signs/symptoms of CRS and ICANS, and they should know when to seek emergency care and call their HCP
  - Fever ≥100.4°F, shortness of breath, chest pain

Slide credit: clinicaloptions.com

Multidisciplinary Team Roles in Delivering CAR T-Cell Therapies

- All physicians, pharmacists, nurses, and other midlevel providers interacting with patients receiving CAR T-cell therapy must have FDA-mandated training in management of CRS neurological toxicities
- Pharmacists and nurses serve vital roles in patient and caregiver education and in prevention, identification, and management of CAR T-cell–associated toxicities

Essential Steps and Required Personnel for a CAR T-Cell Program



Perica. Biol Blood Marrow Transplant. 2018;24:1135. Tisagenlecleucel PI. Axicabtagene ciloleucel PI.

Post-CAR T-cell Therapy Management and Concerns

- Patients remain within 2 hours of treating center for 4 weeks, and abstain from driving for 8 weeks, following CAR T-cell infusion due to a low risk of recurrent CRS and/or NT

- After this, patients should be monitored for:
  - Prolonged cytopenias – transfusions as indicated, G-CSF as needed for neutropenia
  - B cell aplasia (IgG levels) – replete with IVIg for levels <400
  - Relapse
  - Secondary malignancies

- Antibiotic (herpes virus and PJP) prophylaxis
  - Variable practices; we continue for at least 6m, at which time we measure the CD4 count and discontinue only if the CD4 count is >200

- Upon relapse, patients should be biopsied
  - Immunomodulatory therapies have had success in salvaging CAR T-cell relapses; can check for PDL1 on the tumor
  - Repeat CAR T-cell infusions have had limited testing in lymphoma and it is unclear if there is any role in this population

Conclusions:

- CAR-T therapy has become a mainstay of therapy in treating ALL, NHL and multiple myeloma
- Toxicities common and potentially life threatening
- Early Recognition of CAR-T related toxicity important
- Expect more information regarding long term side effects of CAR-T in the future