Management of Patients After CAR-T Therapy

Adverse Reactions and Follow Up

Brigett Brandjes PA-C
Lead APP
TGH Cancer Institute

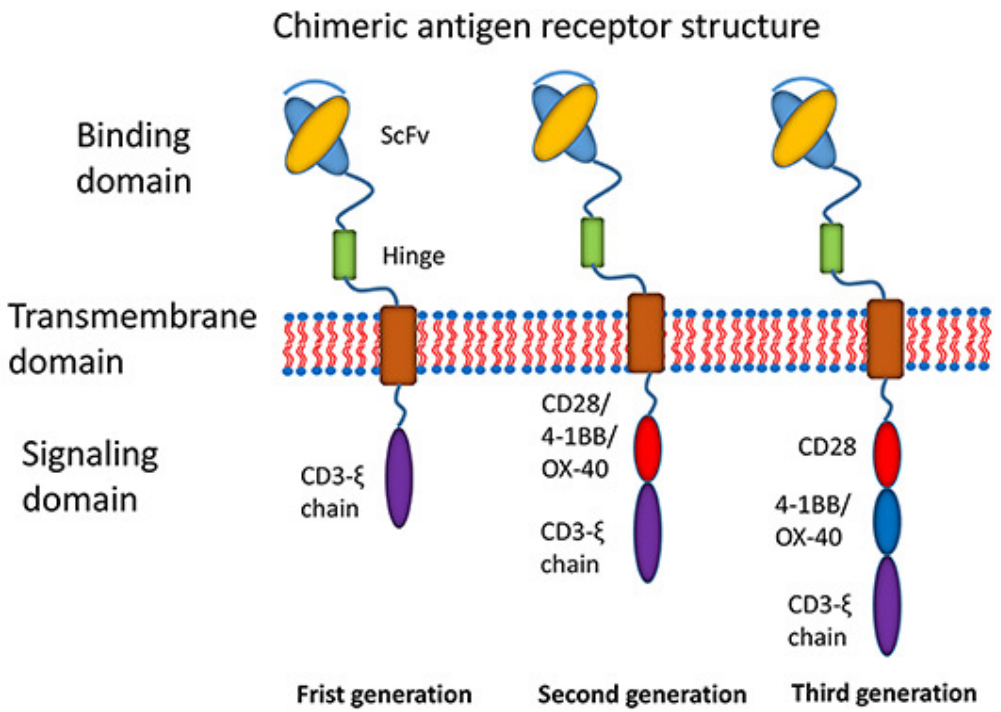
CAR T-cell Therapy

What is a CAR?

- Chimeric Antigen Receptor
  - “living drug”
  - Gene-engineered

What is CAR T-cell Therapy?

- Personalized targeted treatment
  - T cells are expanded ex vivo
  - After infusion cells proliferate
  - Degree of expansion in vivo associates with efficacy



https://www.frontiersin.org/articles/10.3389/fimmu.2019.00456/full

Maus et al. J. Immunother of Ca 2020;8 1511

FDA-Approved CD19-Targeted CAR T-cell Therapies

Therapy	Indications
Axicabtagene ciloleucel	Adults with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy, including DLBCL NOS, DLBCL arising from follicular lymphoma, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, follicular lymphoma Adults with LBCL refractory to first line or relapsed within 12 months of therapy
Brexucabtagene autoleucel	Adults with R/R MCL Adults with R/R B-cell precursor ALL
Lisocabtagene maraleucel	Adults with R/R **large B-cell lymphoma** including DLBCL NOS (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3 • R/R after ≥ 2 lines of systemic therapy • Refractory to first line or relapsed in <12 months or later if in ineligible for HSCT (d/t comorbidities or age)
Tisagenlecleucel	Patients < 25 yrs with B-cell precursor ALL that is refractory or in second or later relapse Adults with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy, including DLBCL NOS, DLBCL arising from follicular lymphoma, high-grade B-cell lymphoma Adults with R/R follicular lymphoma

FDA-Approved BCMA-Targeted CAR T-cell Therapies

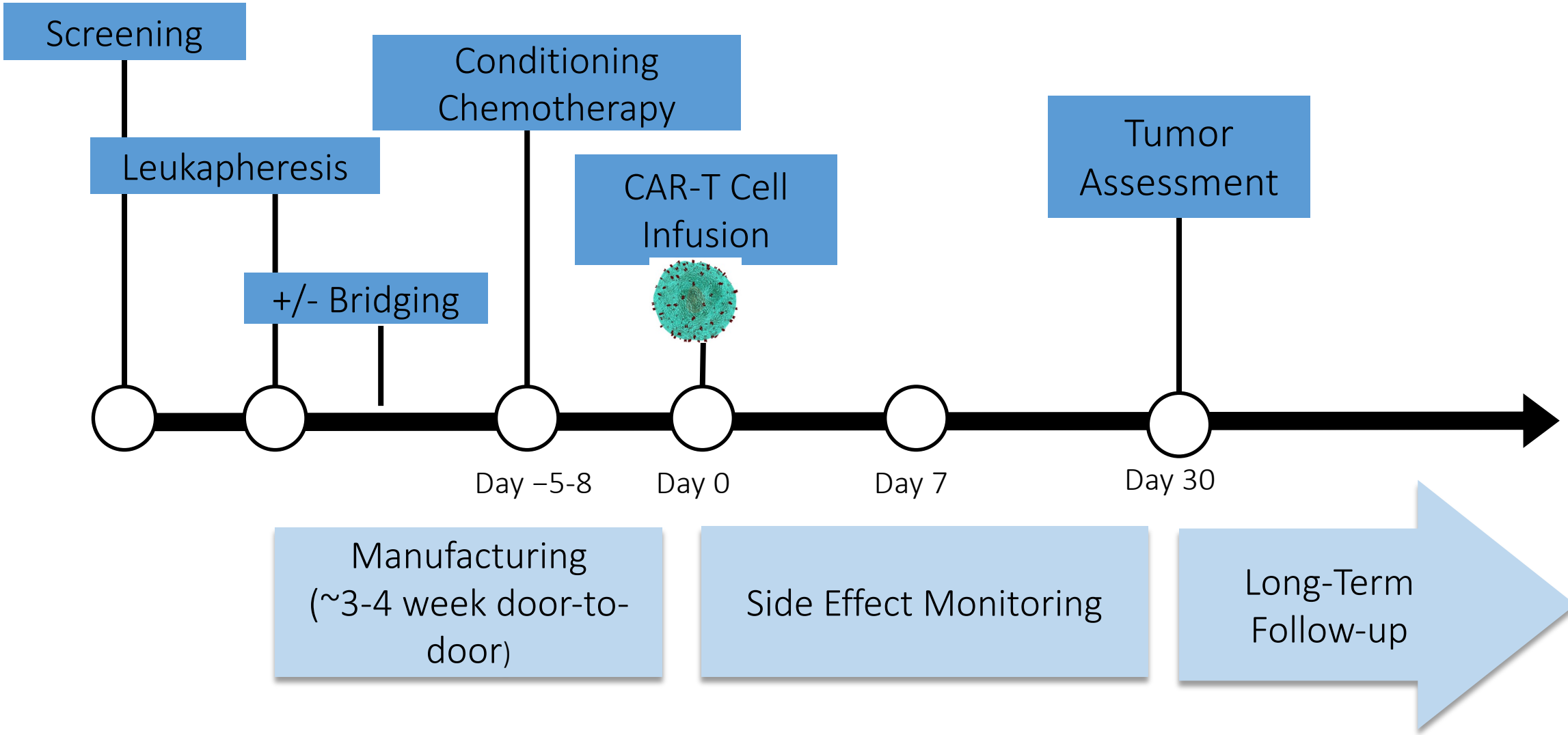
Therapy	Indications
Idecabtagene vicleucel	Adults with R/R multiple myeloma after ≥ 4 lines of systemic therapy, including an immunomodulary agent, proteasome inhibitor, and an anti-CD38 monoclonal antibody
Ciltacabtagene autoleucel	Adults with R/R multiple myeloma after ≥ 4 lines of systemic therapy, including an immunomodulary agent, proteasome inhibitor, and an anti-CD38 monoclonal antibody

CAR T-cell Therapy

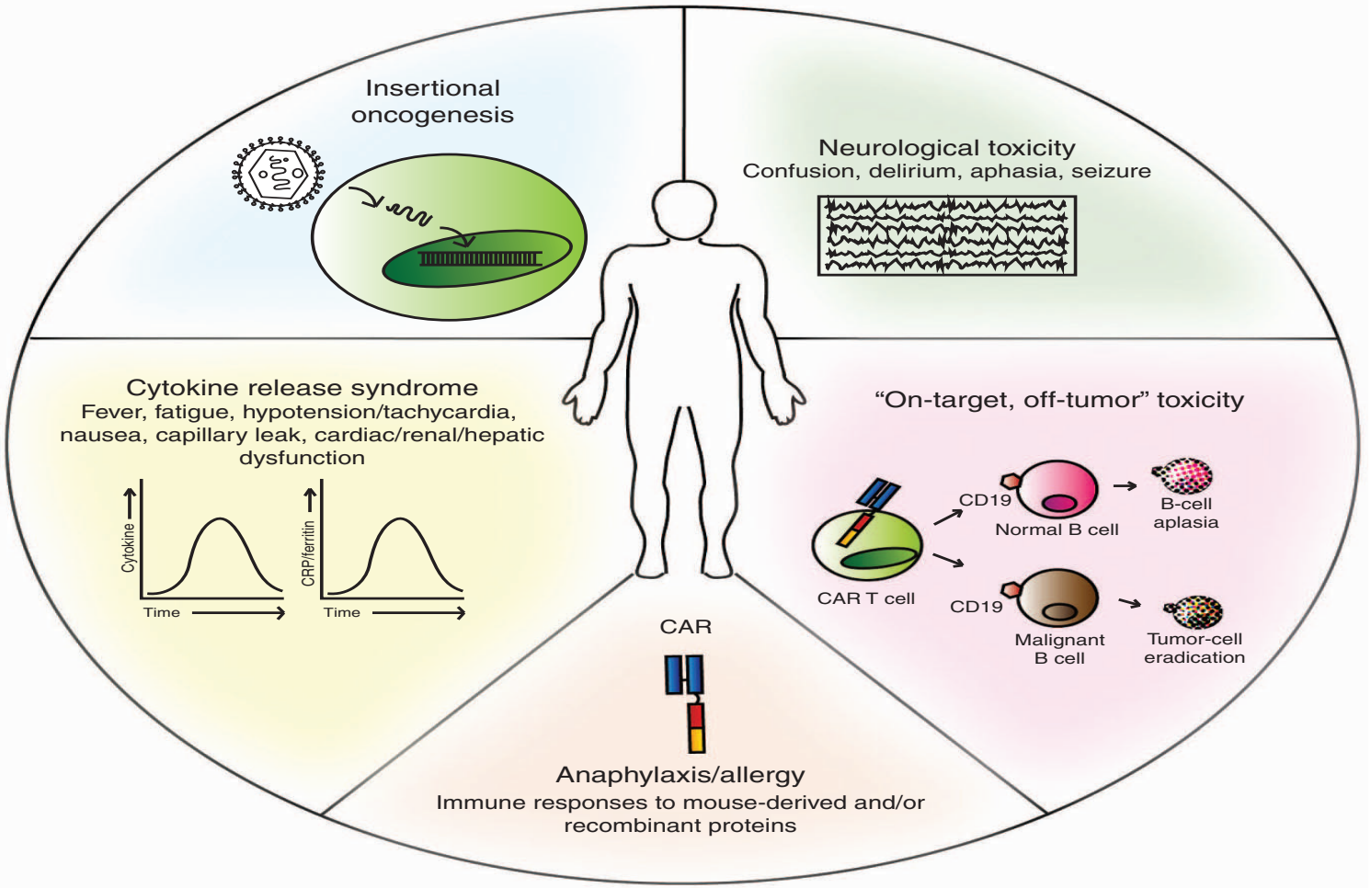
- Long term remissions can be achieved and even potentially curative in a subset of patients
  - Several factors are associated with response
    - Underlying malignancy type and characteristic
    - Deep initial response to treatment
    - Baseline tumor volume
    - Lymphodepletion chemotherapy
    - CAR-T peak level after Infusion
- Toxicities are notable
  - Can extend for several months to years following cell infusion

Cappell and Kockenderfer Nature Reviews Clin Onc 2023;20 359-371

CAR T-cell Treatment Schema



Spectrum of CAR T-cell related Toxicities



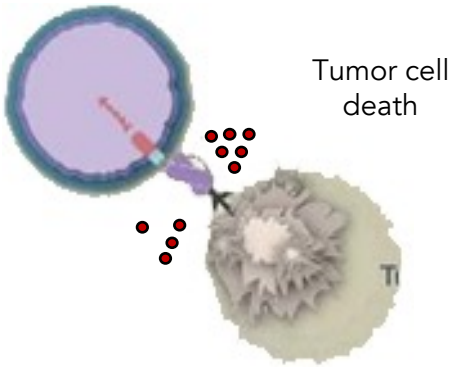
Bonifant et al. Molecular Therapy 2016;(3):16011

Early Adverse Effects:

Admission to Day +30

Tumor Lysis Syndrome

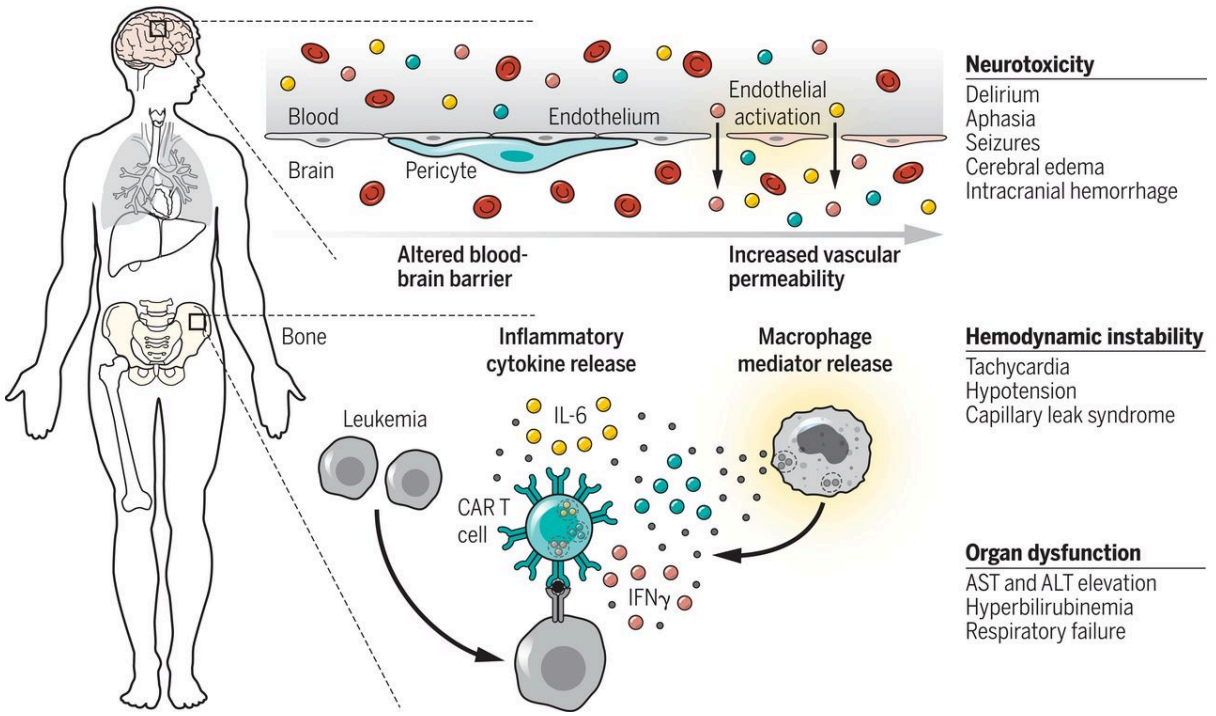
- Patients treated with CAR T-cell therapy often have high burden disease
  - Reported up 17% of patient treated with BCMA
- Etiology: Lysis of cells releasing intracellular components
  - Hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia
  - If untreated→ can progress to AKI/ARF, arrythmias, seizures, and death
- Treatment includes fluid hydration and allopurinol



Shimbabukuro-Vornhagen , et al. J Immunother Ca. 2018;6 56.

Cytokine Release Syndrome “CRS”

- Most common toxicity
  - Severe in 10-30%
- Characterized by elevated serum cytokines
  - Initiated by the activation of T- cells when engaged with the tumor
    - → Release of cytokines
    - → Recruitment and activation of other immune cells
    - IFN-γ, TNF-a, IL-6,IL-1, IL-2, IL-10, GM-CSF, and others

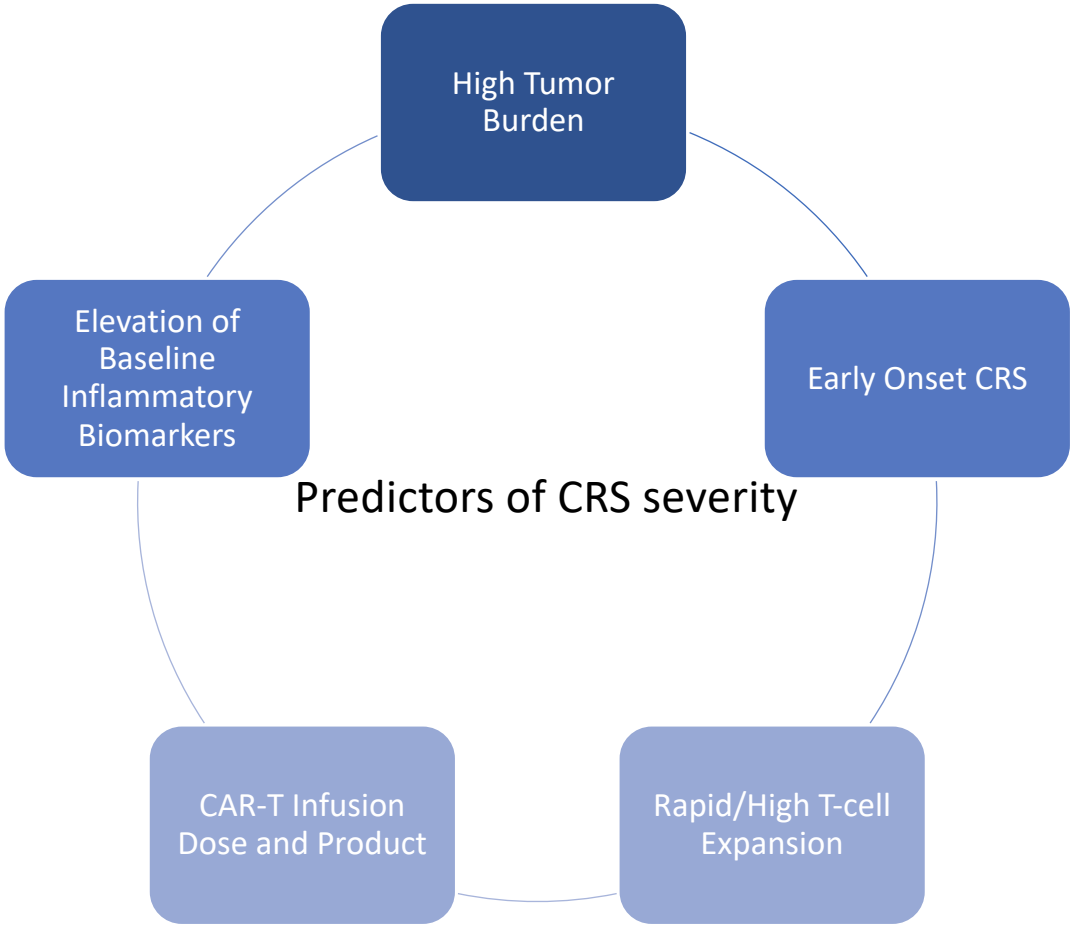


June et al. Science 2018

Lee DW et al. Biol BMT. 2019 Apr;25(4):625-638
Neelapu SS, et al. Nat Rev Clin Oncol. 2018; 15:47-62.

CRS: When & Why?

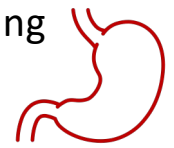
- Most common in **first 2 weeks**
  - Fever is the first sign
  - Duration ~7-10 days
  - Rarely presents beyond 14 days
- Onset can differ by product and disease state
  - Likely due to differences in pharmacokinetic profiles
    - CD28 vs 4-1BB



Lee DW, et al. Blood. 2014;124:188-195
Faramand et.al. Clinical Cancer Research 2020
Bonifant CL, et al. Oncolytics. 2016;3:16011
Hayden PJ; et al. Ann Onc 2022; 33: 259-275

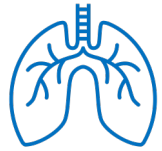
CRS Symptoms

Gastrointestinal
- Nausea/vomiting
- Diarrhea
- Anorexia



Skin
- Rash

Respiratory
- Tachypnea
- Hypoxia
- Pulmonary edema



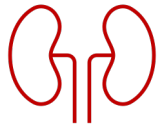
Constitutional
- Fever ± rigors
- Malaise/fatigue
- Myalgias
- Arthralgias
- Headache

Coagulation
- Elevated D-dimer
- Hypofibrinogenemia

Cardiovascular
- Tachycardia
- Hypotension
- Capillary leak
- Widened pulse pressure
- Cardiac output ⇅

Hepatic
- Transaminitis
- Hyperbilirubinemia

Renal
- Azotemia



Adapted from Lee DW et al. *Ther Clin Risk Manag*. 2019;15:323-335

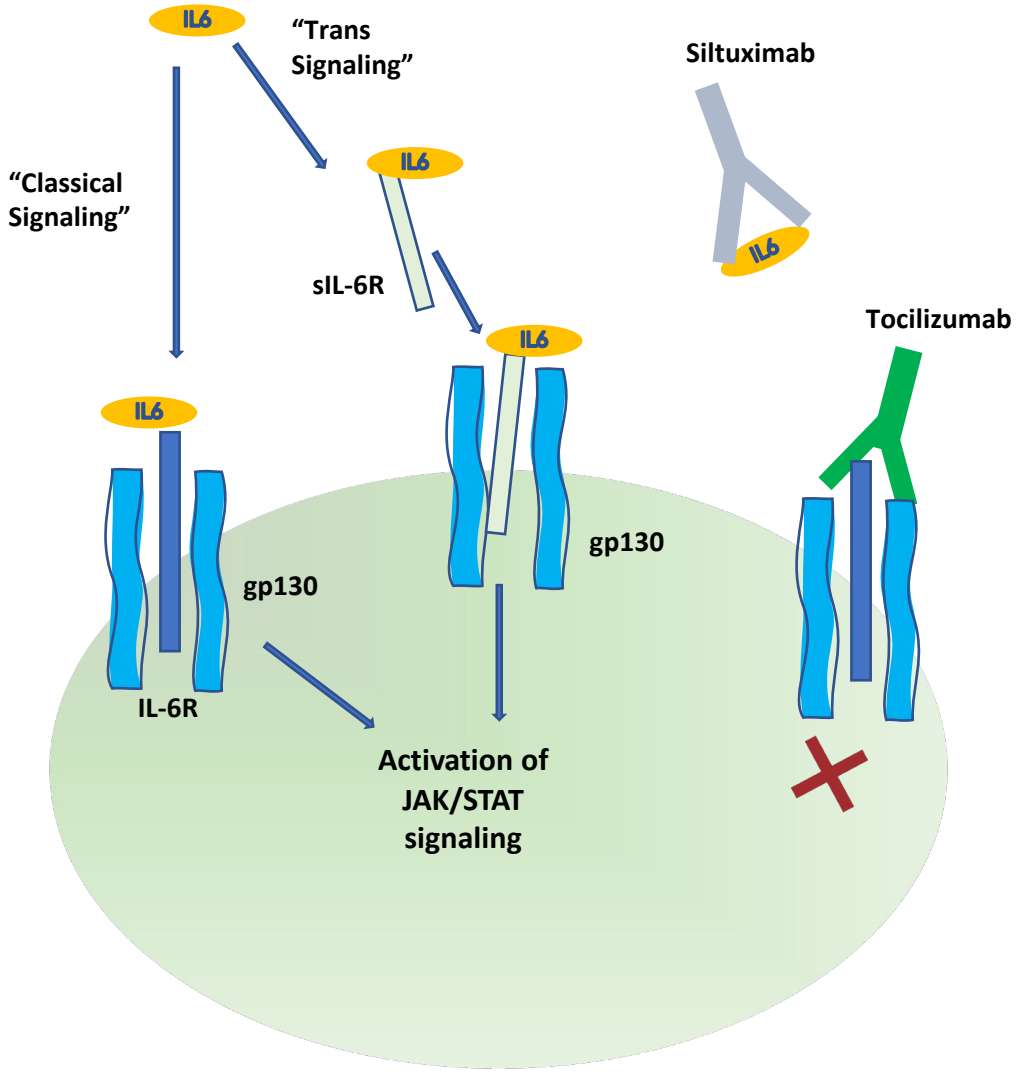
ASTCT Consensus Guidelines for CRS Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	$T_m \geq 38^oC$	$T_m \geq 38^oC$	$T_m \geq 38^oC$	$T_m \geq 38^oC$
With				
Hypotension	None	Responsive to fluids	Requiring 1 vasopressor (w/ or w/o vasopressin)	Requiring multiple vasopressor (excluding vasopressin)
And/or Hypoxia	None	Low-flow nasal cannula or blow-by (≤ 6L NC)	High-flow nasal canula, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (CPAP, BiPAP Intubation and mechanical ventilation)

Lee DW et al. Biol BMT. 2019 Apr;25(4):625-638

Management of CRS

- Supportive Care
  - IVF's, cooling blankets, acetaminophen
- IL-6 inhibition
  - Tocilizumab
    - Binds directly to the IL6R
    - FDA approved for severe CRS in August 2017
- Corticosteroids
  - Suppress immune response
  - Used when refractory to anti IL-6 or high-risk populations
    - Dexamethasone or Methylprednisolone
    - Taper rapidly



Adapted from Si S, et al. *Ther Clin Risk Manag*. 2020
Neelapu SS, et al. Nat Rev Clin Oncol. 2018; 15:47-62.

Refractory or Persistent CRS

- Persistent Grade 2 CRS despite repeat doses of tocilizumab and/or single dose corticosteroids or with progression to grade 3 CRS
  - Dexamethasone 10 mg IV every 6 hours
- Grade 4 CRS should be treated with methylprednisolone 1 g IV per day
  - Note after 2 doses of tocilizumab, repeat doses are generally not recommended
  - Consider alternative etiologies and additional therapies

Hayden PJ, et al. Ann Onc 2022; 33: 259-275
Jain M, et al. Blood 2023; 141 (20); 2430-2442

Additional Considerations

- Earlier or prophylactic treatment strategies have been reported
  - Aimed to reduce the incidence of severe CRS and/or ICANS
  - Could be considered for “High-Risk” Patients
    - Bulky disease, elderly, or medically frail patients
    - Larger studies are needed

Hayden PJ, et al. Ann Onc 2022; 33: 259-275
Jain M, et al. Blood 2023; 141 (20); 2430-2442

Hemophagocytic Lymphohistiocytosis

- HLH- like/IEC-HS toxicities are increasingly recognized a potential complication of CAR T-cell therapy
  - Association with CRS
  - High mortality rate ~80%
- Pathophysiology:
  - Hyperinflammation related to T cell and macrophage activation inducing cascading cytokine-mediated toxicities
- Characterized by:
  - Fever, splenomegaly, cytopenias, ↑ TGs, ↑Ferritin, ↑ sCD25, ↓Fibrinogen, organ failure

Hines MR, et al. Transplant Cell Ther. 2023. 29(7):438

Management of IEC-HS

- Systemic corticosteroids
  - Often initial therapy
- Anakinra
  - IL1-recptor antagonist
  - Relatively low toxicity agent with wide therapeutic dosing range and short half-life
- Ruxolitinib
  - Inhibits JAK1 AND JAK2
- Other agents: Etoposide, Emapalumab, Tocilizumab

Hines MR, et al. Transplant Cell Ther. 2023. 29(7):438

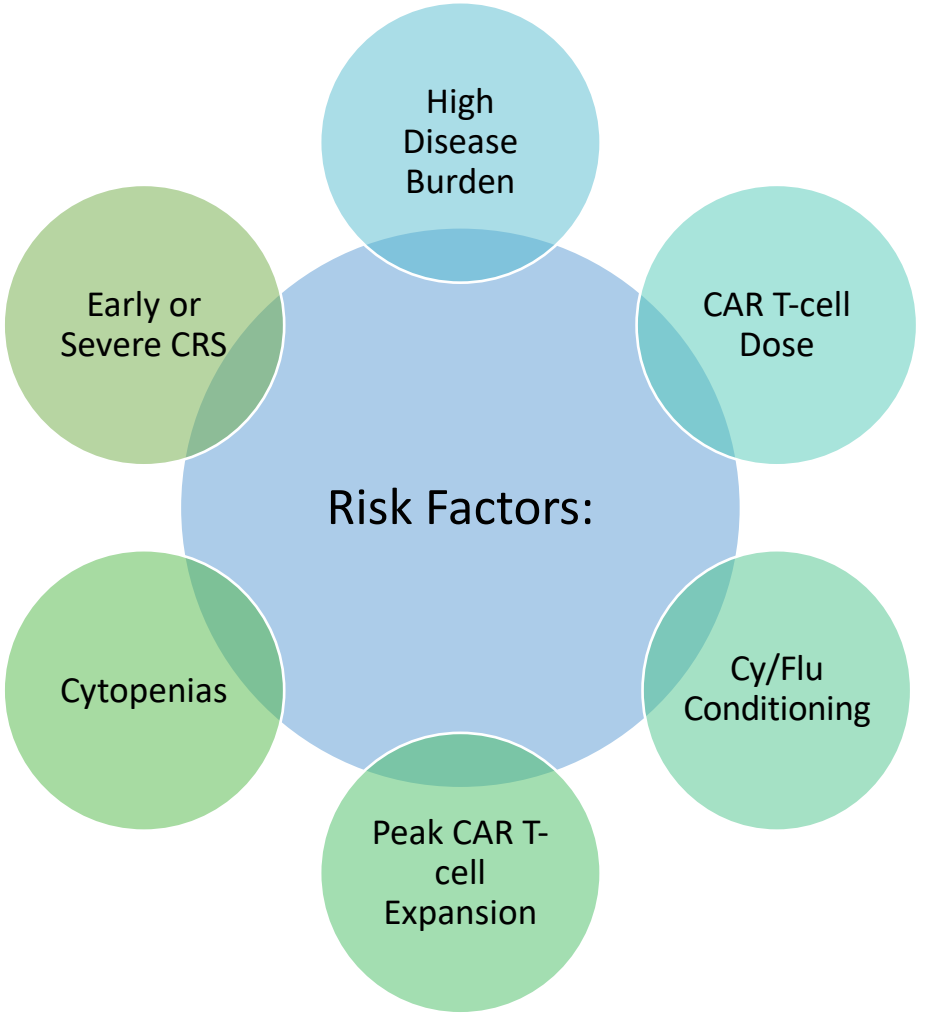
Immune Effector Cell-Associated Neurotoxicity Syndrome "ICANS"

- Second most common toxicity
  - Consistently reported regardless of CAR construct, patient population, or disease subtype
  - Incidence may vary between product and disease state
- Pathophysiology:
  - T-cell activation→ Cytokine mediated endothelial activation causing coagulopathy, capillary leak, and blood brain barrier (BBB) disruption
  - Several reports propose a role for pro-inflammatory cytokines and myeloid cells (such as macrophages) besides activated T-cells

Neelapu SS, et al. Nat Rev Clin Oncol. 2018; 124:188-195.

ICANS: When & Why?

- Onset usually **4-9 days** post infusion
  - Duration ~3- 8 weeks
- Timing can vary:
  - Occur concurrently with CRS
  - Shortly after CRS symptoms have resolved
  - Delayed onset 3-4 weeks after cell infusion



Santomasso BD, et al. Cancer Discov. 2018;8:958–71.
Gust J, et al. Cancer Discov. 2017;7:1404–19.

ICANS

- Diagnosis based on clinical symptoms
  - Baseline neurological status

- Clinical presentation:
  - **Common:** Confusion or delirium, aphasia (receptive and expressive), weakness, headaches, tremor, altered level on consciousness (somnolence, disorientation, agitation, coma)
  - **Rare:** Motor weakness, seizures, and cerebral edema
    - Handwriting changes or aphasia may serve as an early warning sign

Neelapu SS, et al. Nat Rev Clin Oncol. 2018; 124:188-195
.Maus et al. J. Immunother of Ca 2020;8 1511
Santomasso BD, et al. Cancer Discov. 2018;8:958–71.

Immune Effector Cell-Associated Encephalopathy (ICE) Score

ICE Score
How many of the following is the patient oriented to: year, month, city, hospital (4pts)
Name 3 objects: one point for each (3pts)
Follows a command: (1pt)
Write a standard sentence: (1pt)
Can count backwards from 100 by 10: (1pt)

Score 10: No impairment
Score 7-9: Grade 1
Score 3-6: Grade 2
Score 0-2: Grade 3

Lee DW et al. Biol BMT. 2019 Apr;25(4):625-638.

ASTCT Consensus Guidelines for ICANS Grading for Adults

	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score	7-9	3-6	0-2	0 (unable to perform)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient unarousable or requires vigorous repetitive tactile stimuli or stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly; or Non-convulsive seizure 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 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

Lee DW et al. Biol BMT. 2019 Apr;25(4):625-638

Management of ICANS

- Supportive care
- Corticosteroids are the main stay for treatment
  - Dexamethasone preferred agent
    - Taper rapidly with clinical improvement
    - Tocilizumab is not recommended unless concurrent CRS
  - Consider alternative agents if no improvement
    - Anakinra, Siltuximab

Maus et al. J. Immunother of Ca 2020;8 1511

Monitoring of Patients

- Laboratory analysis
  - CBC, CMP, CRP, Ferritin, LFT's, Fibrinogen
    - Major cost/technical difficulty in measuring "real time" cytokines
    - CRP is produced by the liver largely in response to IL-6
- Supportive Care
  - Aspiration precautions
  - Daily weights
- CNS imaging
  - MRI brain preferred
    - Consider CT head if unable
- EEG monitoring

Maus et al. J. Immunother of Ca 2020;8 1511

Monitoring continued…

- Lumbar puncture
  - Caution with coagulopathies
  - Opening pressure
    - CSF often with higher protein and WBC's→ BBB breakdown
- Consider ICU transfer for severe CRS/ICANS
  - May require intubation for airway protection
- Education
  - Both Patient and Caregiver
  - Instruct patients to remain within close proximity for first 4 weeks

Shimbabukuro-Vornhagen, et al. J Immunother Ca. 2018;6 56.
Neelapu SS, et al. Nat Rev Clin Oncol. 2018; 15:47-62.

Infections

- Occurs in ~27-36% of patients post CAR T-cell therapy
  - Bacterial is the most common < 30 days
  - Major factor for increased mortality
- Most common within the first 30 days
- **Risk Factors:** chemotherapy, advanced age, number of previous therapies, hypogammaglobinemia, and CRS
  - Difficult to distinguish sepsis from CRS
- ID screening, antimicrobial prophylaxis, and IVIG supplementation remain key

Maus et al. J. Immunother of Ca 2020;8 1511
Mikkilineni et al. Blood Nov 2019
Shimbabukuro-Vornhagen et al. J Immunother Ca 2018;6 56

Long- Term Adverse Effects

Day + 30 and Beyond

Hematotoxicity

- Cytopenia's can persist for several weeks to months following CAR-T cell infusion
- Occurrence is Biphasic:
  - *Early(<30 days): LD, chemotherapy, radiation*
  - *Prolonged(>30-90+days): Unclear etiology*
    - Occurs in upwards of 20-40% of patients with CD19 CAR-T
- **Risk Factors:** Prior HSCT, high disease burden, high grade CRS, number of prior therapies, bone marrow involvement, baseline cytopenias
- Transfusion support per institutional standards
  - Growth factor injections can be given
    - Consideration of other etiologies

Maus et al. J. Immunother of Ca 2020;8 1511
Sharma et al. Cancers (BASEL) 2022. 14 (6): 1501

CAR-HEMATOTOX Score

- Aimed to identify predictive biomarkers for cytopenias at Day+60
- Multicenter, retrospective, real-world analysis looked into 258 patients receiving axi-cel or tisa-cel for relapsed-refractory large B-cell lymphoma

Baseline Features	0 Point	1 Point	2 Points
Platelet Count	>175K	75-175K	<75K
ANC	>1200/ul	<1200/ul	-
Hemoglobin	>9.0g/dl	<9.0g/dl	-
CRP	<3.0mg/dl	>3.0mg/dl	-
Ferritin	<650ng/ml	650-2000ng/ml	>2000ng/ml
Low: 0-1		High: ≥ 2	

Rejeski et al. Blood 2021; Dec16. 138(24):2499-2513
Sharma et al. Cancers (BASEL) 2022. 14 (6): 1501

B-cell Aplasia

- Normal B cells contain CD19 "On Target, Off Tumor"
  - B cells → antibodies → hypogammaglobulinemia
- Occurs in ~18-74% of patients following CD 19 CAR T-cell therapy after Day +90
- Can persist for years despite lack of circulating CAR T-cell's
- Lack of consensus for management guidelines
  - Consider monthly IgG monitoring for first 6 months

Wat and Barmettler. J Allergy Clin Immunol Pract . 2022; 10(2):460-466

Infections

- Much less common >1 month after CAR infusion
- Incidence ranges from 9-29%
  - Viral infections are more prevalent
  - NCI conducted a long-term follow-up study involving 43 patients with B cell malignancies who received CD19-targeted CAR T cells
    - 4/43 (9%) required hospital admission for infections >6 months after CAR T-cell infusion
      - Median follow-up duration of 42 months

Cappell and Kockenderfer Nature Reviews Clin Onc 2023;20 359-371

Conclusions

- CAR T-cell therapy is associated with unique toxicities both acute and prolonged that require vigilant monitoring, aggressive supportive care, and specialized management
- Consensus guidelines for grading and management have provided the ability to facilitate the safe administration of CAR-T cells in medically frail patients
- Consider preemptive/earlier interventions for high-risk groups to prevent severe CRS and ICANS
- Improved understanding of prolonged cytopenias is needed
- Standardizing management for prolonged/refractory toxicities are needed

Questions???

- Email: Bbrandjes@tgh.org