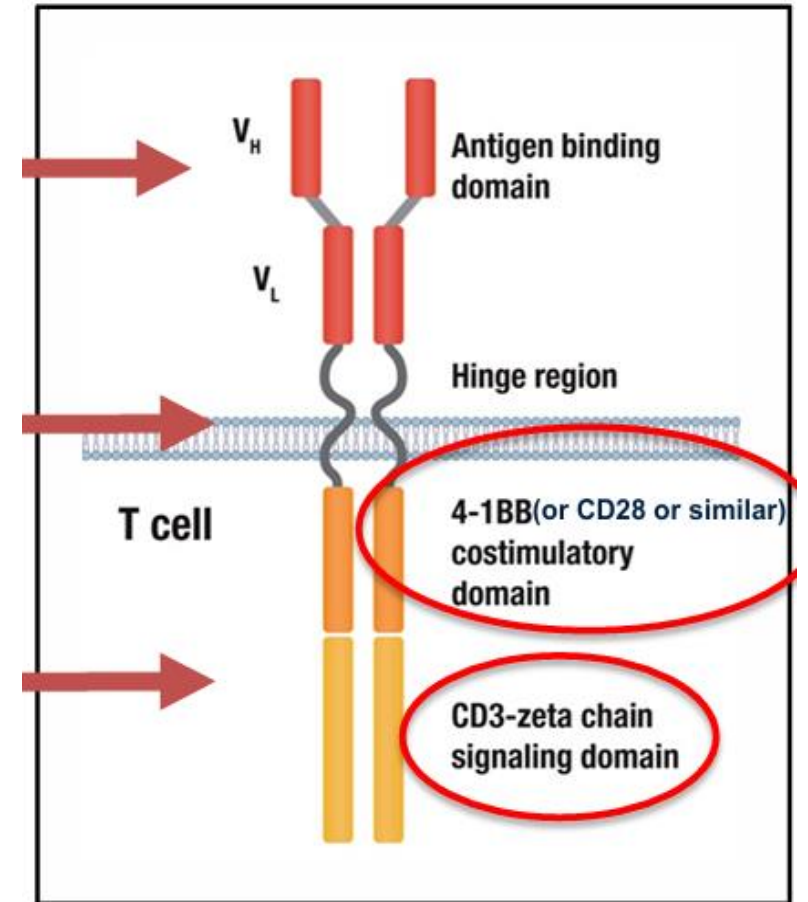
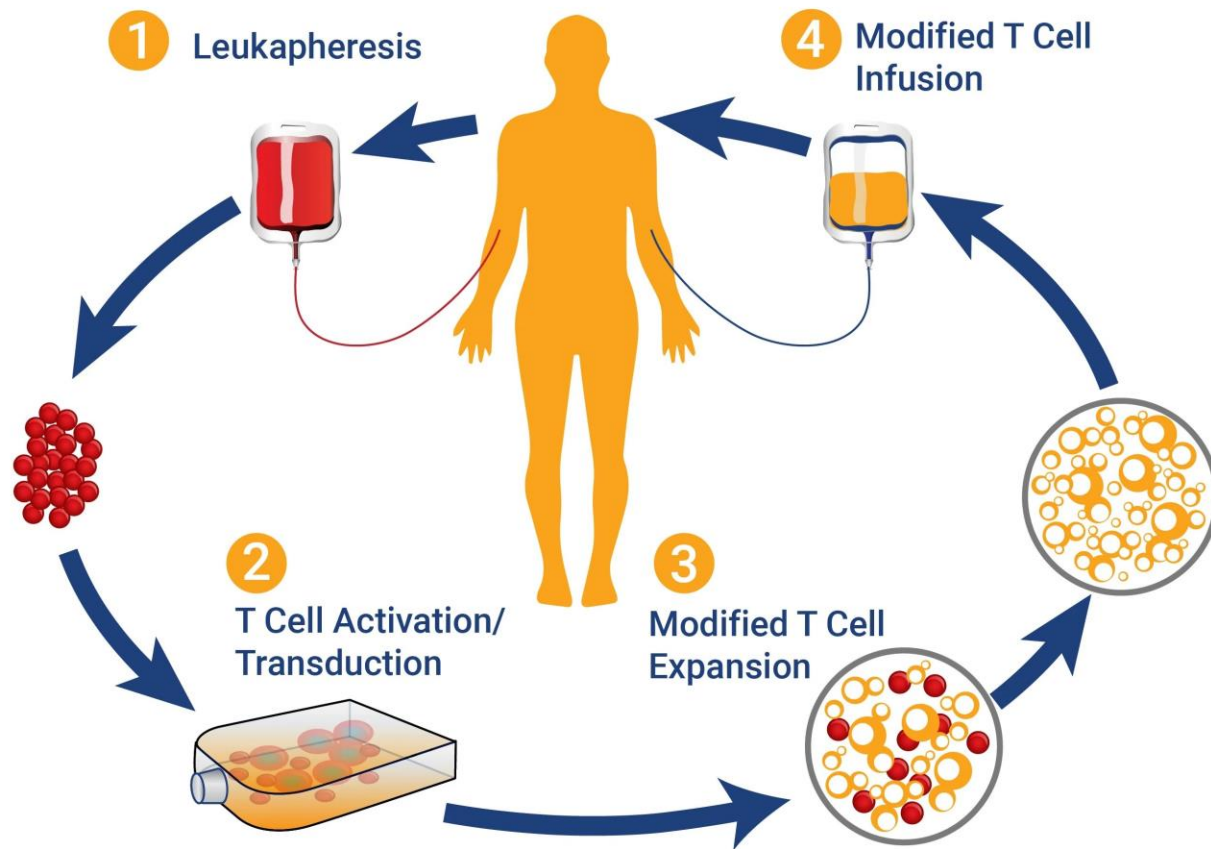


# How I monitor post CAR-T

ISBMT- 14<sup>th</sup> Dec 2025

Dr Narendra Agrawal

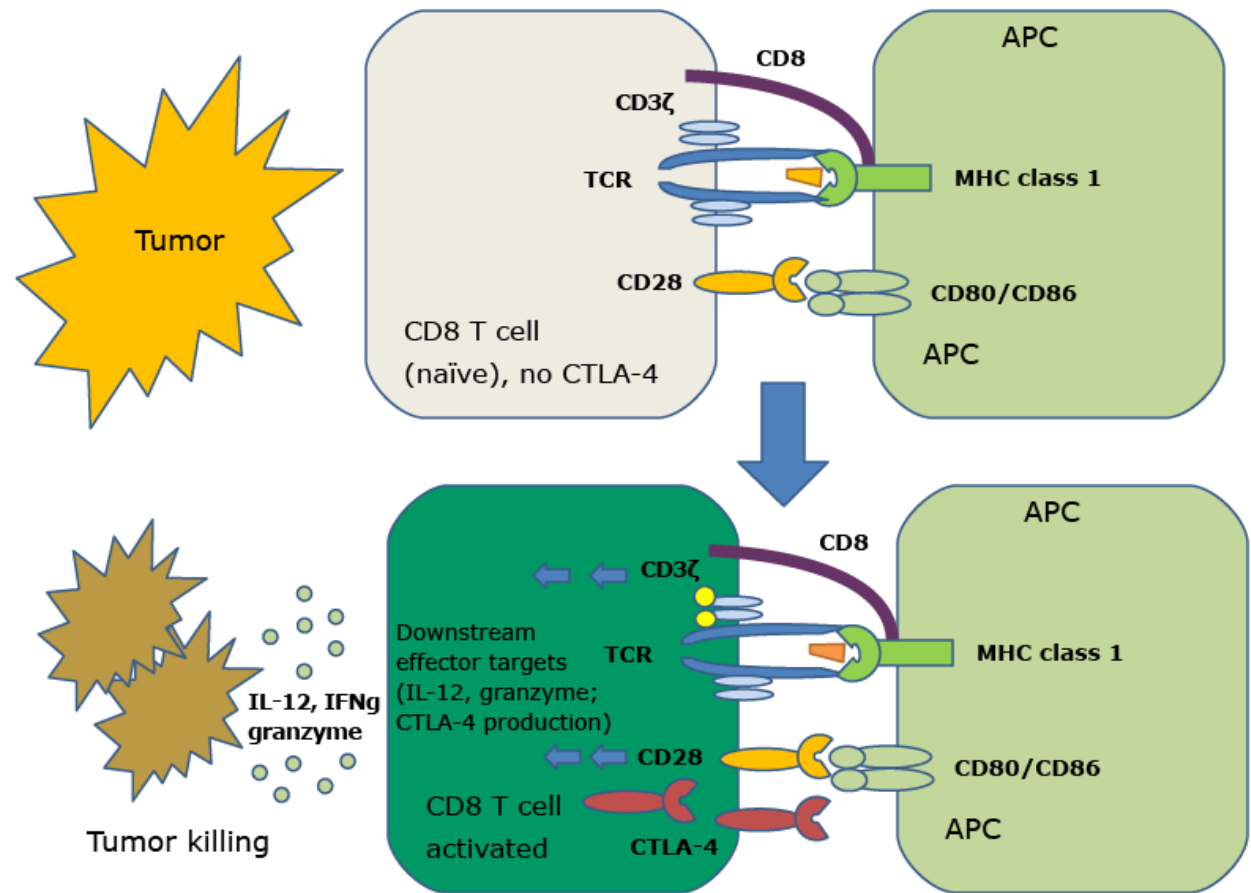
Rajiv Gandhi Cancer Institute &  
Research Centre Delhi



# Immune synapse: how T cells kills tumor

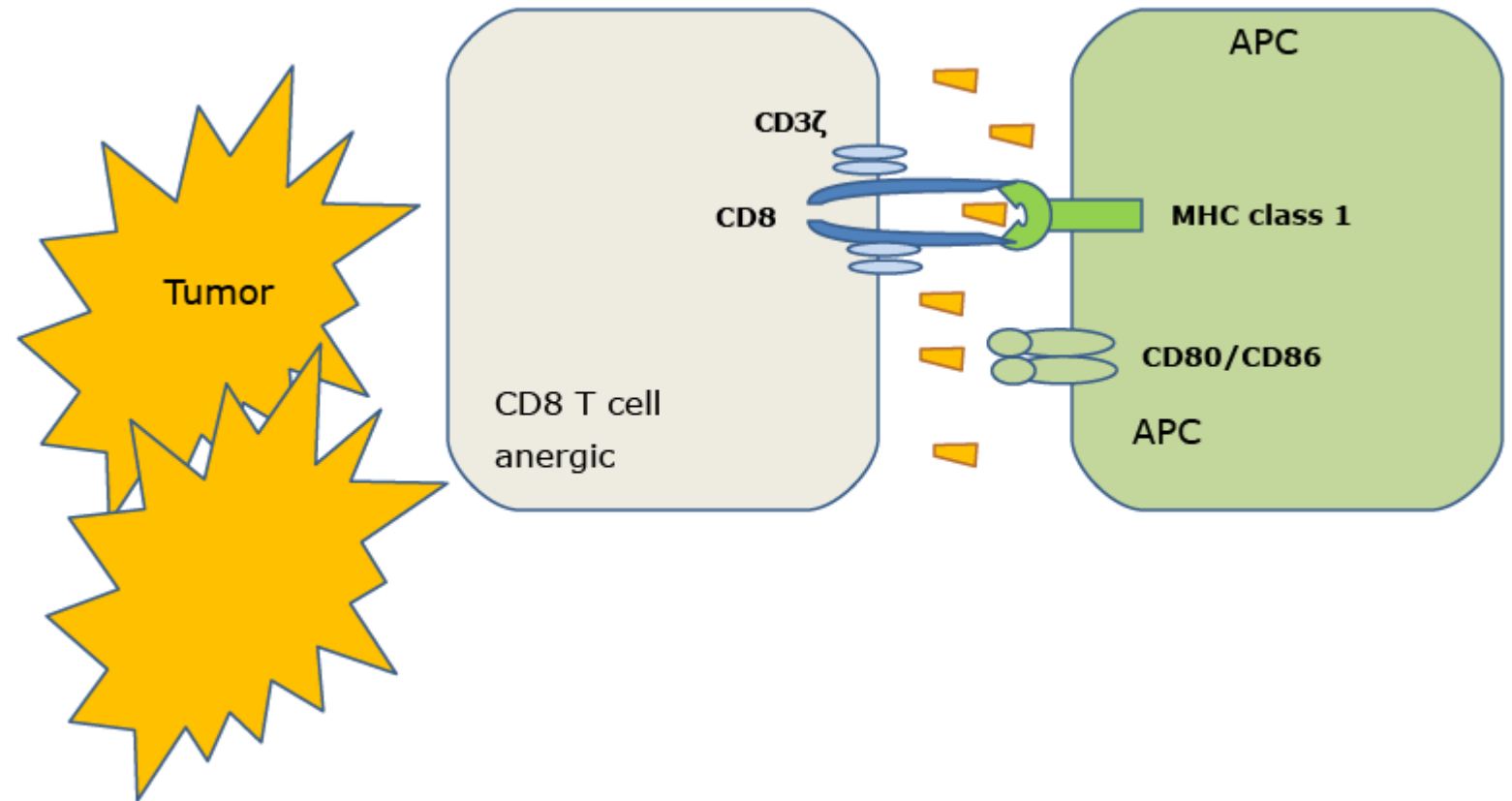
- **T cell mediated tumor killing needs**

- **APCs**
- **MHC-1**
- **Co-stimulatory molecules**
- **Cytokines**
- **No inhibitory signals/mechanisms**



# Immune tolerance

**Immune  
tolerance:  
anergy**



# Role of CAR T cell

- **Tumor specific**
- **Intense cytokine mediated tumor killing**

# Post CAR T: What to monitor

- We should keep in mind key post infusion outcomes
  - Toxicities- short term, long term
  - Immune-paresis/ recovery
  - Malignancy flares/ remission status

# Know the baseline factors

- Prior therapies
- Pre-treatment tumor burden (antigen load), aggressiveness of dis
- Intensity of lymphodepletion- CRS, prolonged cytopenias
- CAR construct: CD28 vs 4-1BB co-stimulation
- Every CAR is different- can have some differences in toxicity profile

# Phases of Post CAR T monitoring

CRS  
ICANS  
HLH/MAS  
TLS  
Tumor flare  
Cytopenias  
Infections

Delayed CRS, ICANS  
Infections  
IEC-HS  
IEC-Hematologic toxicity  
IEC-Cardiovascular toxicity  
CAR-T expansion/  
persistence

Immune monitoring,  
response/ relapse

B cell aplasia  
Immune monitoring

CAR-T persistence  
Monitoring for response/  
relapse

Secondary malignancies

Early phase-

Monitoring for response/  
relapse

Early phase- outpatient 8

Long-term- Hometown

# CRS symptoms

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

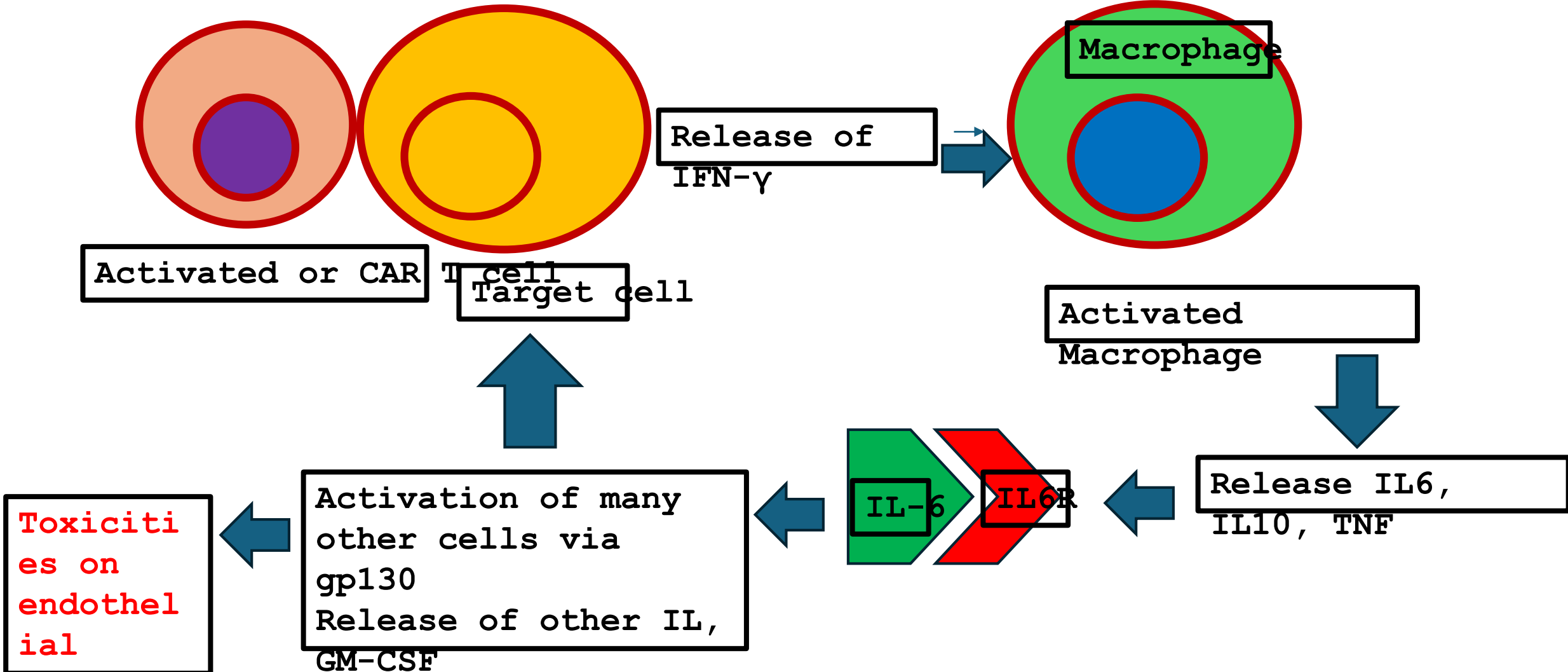
# ASTCT consensus grading- unique to CAR-T related CRS

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
<b>Fever*</b>	≥100.4°F (38.0°C)	≥100.4°F (38.0°C)	≥100.4°F (38.0°C)	≥100.4°F (38.0°C)
<b><i>With either:</i></b>				
<b>Hypotension</b>	None	Responsive to fluids	Requiring 1 vasopressor (w/ or w/o vasopressin)	Requiring multiple vasopressor (excluding vasopressin)
<b><i>And/or</i></b>				
<b>Hypoxia</b>	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)

# Diagnosis

- CRS is **a clinical diagnosis** (not based on a lab test)
- Must have fever ( $\geq 38.0^{\circ}\text{C}$ )
- The **temporal relationship** to the triggering immune therapy is important for establishing the diagnosis of CRS.
- **Laboratory studies are not required** to diagnose CRS, but required for monitoring

# Pathophysiology of CRS



# Key Survival and Mortality Data

Metric	Key Data	Notes
Incidence of any-grade CRS	~56% of patients	Varies by disease, product & grading system
Grade $\geq 3$ CRS	Up to ~22%	Higher risk in ALL, bulky disease etc.
CRS-related mortality	<1% (meta-analysis, 2,592 pts)	Very low in controlled trials
Real-world CAR-T + CRS mortality	~5%	Slightly higher than 2.5% baseline mortality
Non-relapse	~5% (registry	Only ~10-11% of

## D/D of CRS

- Sepsis- SIRS-MODS: cultures and other appropriate microbiologic tests can help
- **HLH/ MAS- these pts usually have organomegaly and evidence of hemophagocytosis. Both CRS and HS can co-occur**
- Tumor flare/ true progression- imaging/ blood or marrow immuno-phenotyping may help differentiate
- Thrombo-embolism

# Coming to neuro-toxicity- the ICANS

- Commonest initial symptoms (communication is the key)
  - Disorientation
  - Inattention
  - Language deficit
- Can rapidly progress within hours to severe symptoms
- Worsening signs of encephalopathy include
  - Decreased level of consciousness,
  - Slowness to respond
  - Disorientation to time and location
  - Language dysfunction or mutism
  - Seizures, coma

# ICE Scoring System: 5 components/ 10 score

- Orientation (Year, Month, City, Hospital): 4 points
- Naming (3 objects) - 3 points
- Following Commands - 1 point
- Writing a sentence - 1 point
- Attention (Count backwards by 10s) - 1 point
  
- Total = 10 points
  
- Interpretation:
  - **Normal = 10; Mild = 7-9; Moderate = 3-6; Severe = 0-2**
- May not be useful for pediatric patients <12 y age

# ICANS Grading Table (ASTCT 2019 Criteria)

Grade	ICE Score	Level of Consciousness	Seizure	Motor Findings	Raised ICP / Cerebral Edema
1	7-9	Awake	None	None	None
2	3-6	Awake	None	None	None
3	0-2	Arousable only to voice	Any seizure (brief, responsive)	Mild weakness	None
4	0	Unresponsive or coma	Prolonged / repetitive	Deep focal weakness	Signs of ↑ ICP or cerebral

D/D

- CNS malignancy
- Chemo induced neurotoxicity- specially with fludarabine
- PRES- usually with hypertension
- Progressive multifocal leuco-encephalopathy- JC virus

# Less common neurologic toxicities other than ICANS

- Syndrome of progressive parkinsonism and cognitive impairment
- Occur weeks to months after BCMA-targeted CAR-T cell therapies.
- Usually unresponsive to steroids
- Improved recovery with high-dose cyclophosphamide in severely affected patients who have evidence of persistent CAR-T cells in blood and/or cerebrospinal fluid.

# IEC-HS: Definition

- Hyperinflammatory syndrome that manifests with features of macrophage activation/HLH attributed to IEC therapy
- Along with
  - Progression or new onset of cytopenias
  - Hyper-ferritinemia
  - Coagulopathy with hypofibrinogenemia and/or transaminitis Independent from CRS and ICANS

# IEC-HS Diagnostic Criteria

Criteria for Identifying IEC-HS	Clinical/Laboratory Manifestations	
Required	Elevated ferritin (>2 x ULN or baseline at time of infusion) or rapidly rising per clinician assessment	
Common Manifestations	Onset with resolving CRS or worsening inflammation after initial improvement with CRS therapy	
	Hepatic transaminase elevation (>5 x ULN or baseline (if abnormal at baseline))	
	Hypofibrinogenemia (<150 mg/dL or < LLN)	
	Hemophagocytosis in bone marrow or other tissue	
	Cytopenia (new onset, worsening or refractory)	
Other Manifestations that may be present	LDH elevations	Neurotoxicity
	Other coagulation abnormalities	Pulmonary manifestations
	Direct hyperbilirubinemia	Renal insufficiency
	New-onset splenomegaly	Hypertriglyceridemia
	Fever (new or persistent, not attributable to CRS)	

# IEC-HS : Grading

Graded	1	2	3	4
IEC-HS	Asymptomatic Requires observation and evaluation Intervention not indicated	Mild-moderate symptoms with intervention indicated	Severe or medically significant but not immediately life threatening	Life-threatening consequences with urgent intervention indicated
Continuous	Evaluate alternative etiologies			
Initial therapy		Start anakinra 100-200 mg sc/IV every 6-12 hours And/or Dexamethasone 10-40 mg daily (eg-10 mg every 6 hours)		
Second-line Therapy		Increase anakinra to target dose, add corticosteroids (if not already on board), consider ruxolitinib 10-20 mg twice daily		
Third-line Therapy		Add ruxolitinib (if not started), consider alternative agents (eg-etoposide, emapalumab) if life threatening		

# Cytopenias: ICA-HT

- The term ICA-HT proposed by EHA/EBMT consensus panel to address cytopenia following novel T-cell immunotherapies
- Profound or prolonged cytopenia carry risks including
  - Infectious complications
  - Prolonged hospital stay, transfusions
  - Inability to initiate salvage therapy at relapse

# Risk factors of ICA-HT

- Baseline factors-
  - Heavily pretreated patients (>3 prior lines)
  - Prior HCT
  - Marrow replaced with tumor
  - Baseline cytopenias
  - Higher intensity of LD regime
- CAR-T specific factors
  - CD28 > 4-1BB constructs
- Post infusion correlates
  - Early and higher grade CRS
  - Higher peak CRP and ferritin levels

# CAR-HEMATOTOX- prediction model for HT

Features	0 Point	1 Point	2 Points
Platelet Count	> 175/ $\mu$ L	75 – 175/ $\mu$ L	< 75/ $\mu$ L
ANC	> 1200/ $\mu$ L	$\leq$ 1200/ $\mu$ L	—
Hemoglobin	> 9.0 g/dL	$\leq$ 9.0 g/dL	—
CRP	< 3.0 mg/dL	$\geq$ 3.0 mg/dL	—
Ferritin	< 650 ng/mL	650-2000 ng/mL	> 2000 ng/mL
Low: 0-1; High: $\geq$ 2			

- Scoring tool to evaluate cytopenia risk following CAR-T therapy

## Strengths

- Assessed at time of lymphodepletion with standard labs
- High negative predictive value

## Weaknesses

- Low positive predictive value
- Not validated prospectively
- Not validated in ALL

Rejeski K, et al. Blood. 2023;142(10):865-877.

Rejeski K, et al. Blood. 2021;138(24):2499-2513.

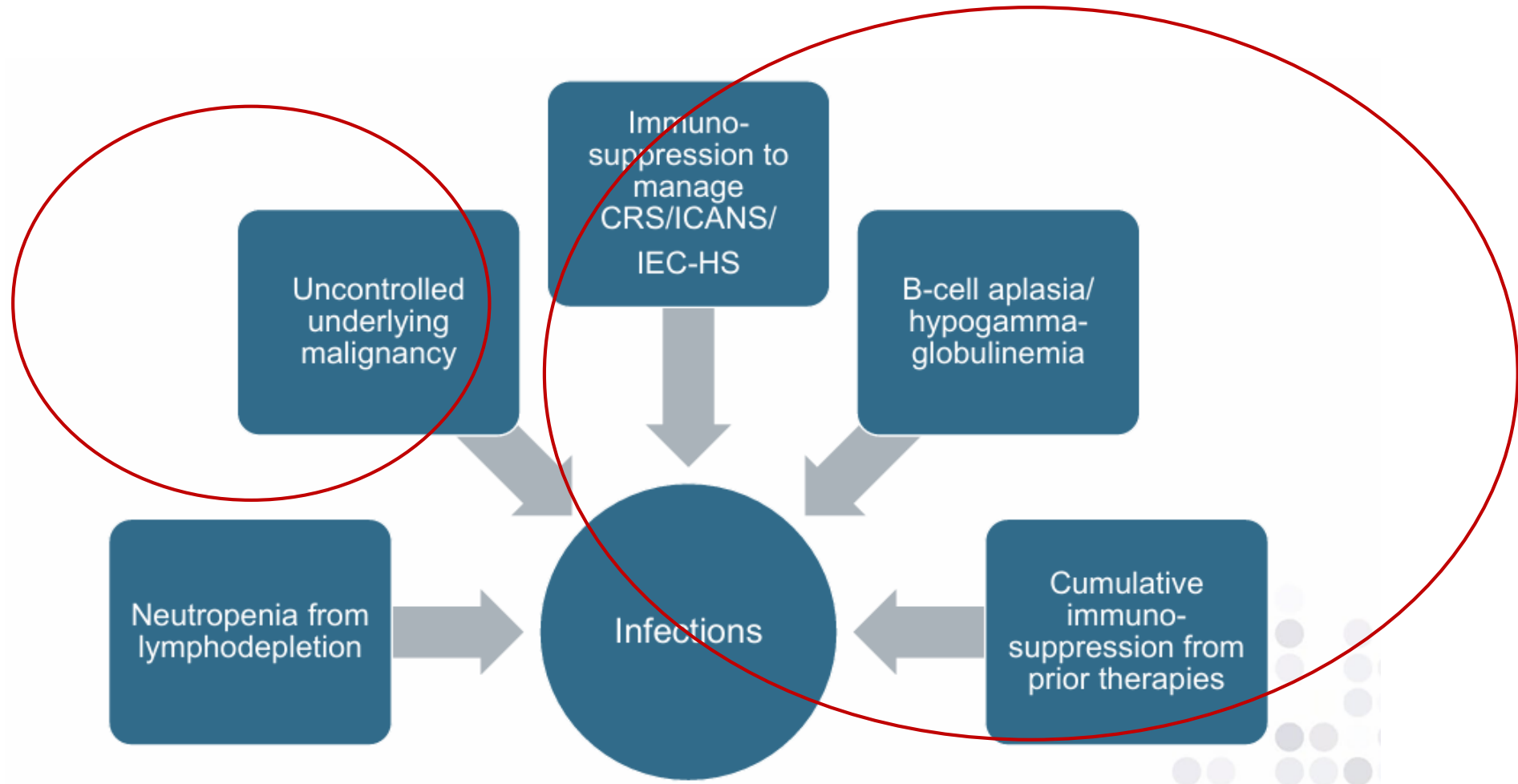
Rejeski K, et al. J Hematol Oncol. 2023;16(1):88

# EBMT/EHA ICA-HT Grading:

important to decide on use of G-CSF, stem cell boost or allo HCT

Grading	1	2	3	4
Early ICAHT (day 0-30)				
ANC $\leq$ 500/ $\mu$ L	<7 d	7-13 d	$\geq$ 14 d	Never above 500/ $\mu$ L
ANC $\leq$ 100/ $\mu$ L	-	-	$\geq$ 7 d	$\geq$ 14 d
Late ICAHT (after day+30)				
ANC	$\leq$ 1500/ $\mu$ L	$\leq$ 1000/ $\mu$ L	$\leq$ 500/ $\mu$ L	$\leq$ 100/ $\mu$ L

# Post CAR-T: Infections



# Timeline of infections

	Day 0-30	1-3 months	1-6 months
Overall Incidence	12% - 46%	14% - 23%	6% - 40%
Bacterial	32% - 68%	35% - 57%	33% - 51%
Viral	19% - 47%	44% - 58%	18% - 60%
Fungal	3% - 14%	0% - 9%	0% - 35%

Hill JA, et al. Blood. 2018;131(1):121-130.  
Kampouri E, et al. Transpl Infect Dis. 2023;25  
Suppl 1:e141157

# Risk factor for infections post CAR-T

## Host-related factors

- B-ALL and MM
- Prior HCT
- Prior lines of therapy
- CAR-HEMATOTOX > 2
- Infection within past 100 days
- Baseline performance status
- Baseline hypogammaglobulinemia
- Older age (IE-Adult)

## CAR T associated factors

- High CAR T dose and lymphodepletion intensity
- Severe CRS/ICANS
- ICAHT
- Corticosteroids dose/duration
- Neutropenia severity, duration
- Post-CAR T hypogammaglobulinemia
- IEC-HS

# Hypogamaglobulinemia

- A surrogate for B cell aplasia
- Monitor for IgG levels
- Look for indications of IVIg infusion
  - IgG  $\leq$  400 mg/dL AND severe or recurrent bacterial infections

How to monitor to identify  
these toxicities and outcomes

- Now we know “what to look for” (The spectrum of toxicities and possible outcomes post CAR T)
- Coming to “how to monitor”

# How to monitor

- Hearing patient and looking at him/her carefully
- Physical examination- at least twice a day
  - Cardiac- lung assessment: Look for pulm edema-ARDS,
  - Hemodynamic monitoring, Vitals, O<sub>2</sub> saturation- 2-4 hourly
  - LN, liver-spleen size

# How to monitor

- Labs every 1-3 days:
  - Basics- CBC, Chemistry, Ferritin, CRP, IL-6, Coagulation
  - If needed- NT-ProBNP, Fibrinogen, Cultures-infection screen, CMV monitoring

# How to monitor

- Careful Neurological assessment-
  - ICE score- twice a day
  - **Ask patient to write a new story/ event from his past- everyday**
  - look for confusion, anxiety, tremor, aphasia, delirium, seizures, or other findings that may be related to an associated ICANS
  - Fundus, CSF examination, EEG, Neuro-imaging if needed

# EEG

- Most patients with ICANS have an abnormal EEG
  - Some degree of encephalopathy
  - Electrographic seizures
- **Diffuse slowing** is the most commonly observed pattern
- Generalized periodic discharges (GPDs)
- Frank electrographic seizures and status epilepticus

# Neuro-imaging

- Normal MRI in most patients with ICANS
- In severe ICANS complicated by increased ICP: diffuse white matter changes and sulcal effacement (diffuse cerebral edema)
- Other abnormal findings cerebral infarctions, subarachnoid or subdural hemorrhage, and focal or diffuse white matter injury

# Immune Monitoring in CAR-T Cell Therapy: EBMT survey

EBMT Cellular Therapy & Immunobiology WP -  
Pagliuca et al., Blood Advances 2025

# Why Immune Monitoring Matters

- CAR-T therapy profoundly alters immune homeostasis.
- Monitoring **guides infection prophylaxis** & immune reconstitution.
- Supports **relapse prediction** and long-term survivorship planning.

# Common Immune Monitoring: EBMT recommendations

- Essential:
  - B-cell aplasia, Serum IgG
  - Lymphocyte subsets: CD4, CD8, CD19
- Recommended
  - CAR-T cell expansion (qPCR/flow cytometry)
  - CD4+ recovery for infection-prophylaxis decisions

# Suggested Immune Monitoring **Timeline**

- Baseline: Lymphocyte subsets, IgG
- Day 7–14: CAR-T expansion, B-cell aplasia
- Day 30: IgG, lymphocyte subsets
- Month 3: CD4 recovery evaluation, infection risk stratification
- Month 6–12: Long-term immune reconstitution, revaccination planning

Optimizing Post-CAR T  
Monitoring

(Ahmed et al., Blood Advances  
2024)

# Study Overview

- Optimizing Post-CAR T Monitoring (Ahmed et al., Blood Advances 2024)
- Multicenter real-world cohort (9 centers, N = 475) .
- CAR T products: Axi-cel, Tisa-cel, Liso-cel.
- Objective: characterize toxicity timing and propose optimized monitoring periods.

# CRS: Incidence & Timing

- Any-grade CRS: ~83%, **Grade  $\geq 3$  CRS: ~7–8%**
- Median onset: Day 2 (range 0–12)
- Median duration: 5 days
- **>90% of CRS events occurred in Days 1–7**
- Severe CRS extremely rare after Day 10; none new after Day 14

# IEC- HS (HLH-like Syndrome)

- Incidence: 3-4%
- **Median onset: Days 7-10- mostly in second week**
- Ferritin often  $>10,000$  ng/mL
- Occurs almost exclusively with high-grade CRS

# ICANS: Incidence & Timing

- Any-grade ICANS: 37–40%, **Grade  $\geq 3$  ICANS: 12–14%**.
- Median onset: Day 6 (range 2–16)
- Median duration: 4–6 days
- Severe ICANS peaked Days 4–9
- **>95% of all ICANS occurred before Day 14**

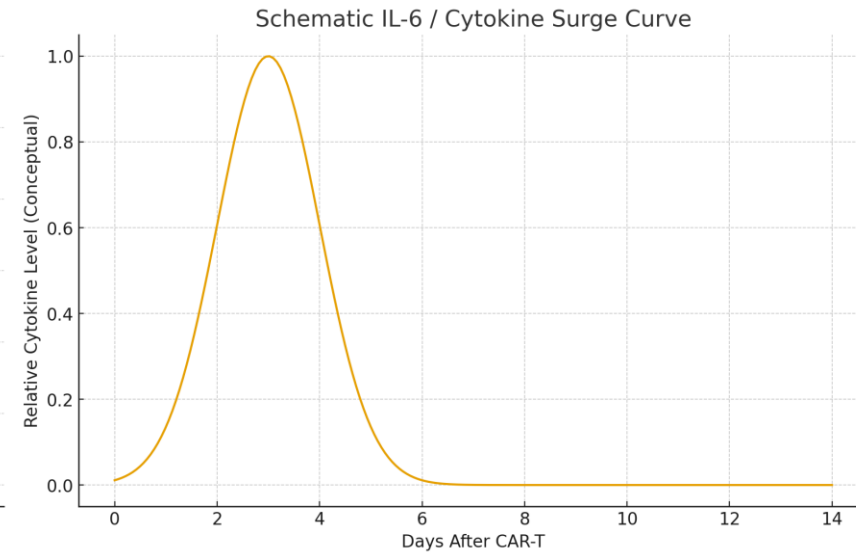
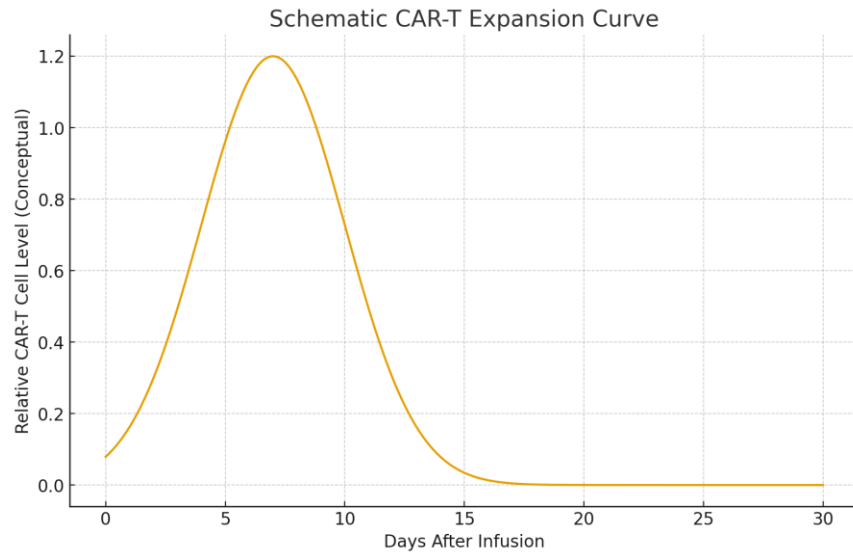
# Infections After CAR T

- Early infections ( $\leq 14$  days): ~16%
- Infections Days 15-28: rise to ~24%
- Bacterial infections: Days 7-21
- Viral infections: Days 14-28
- Late NRM primarily infection-driven

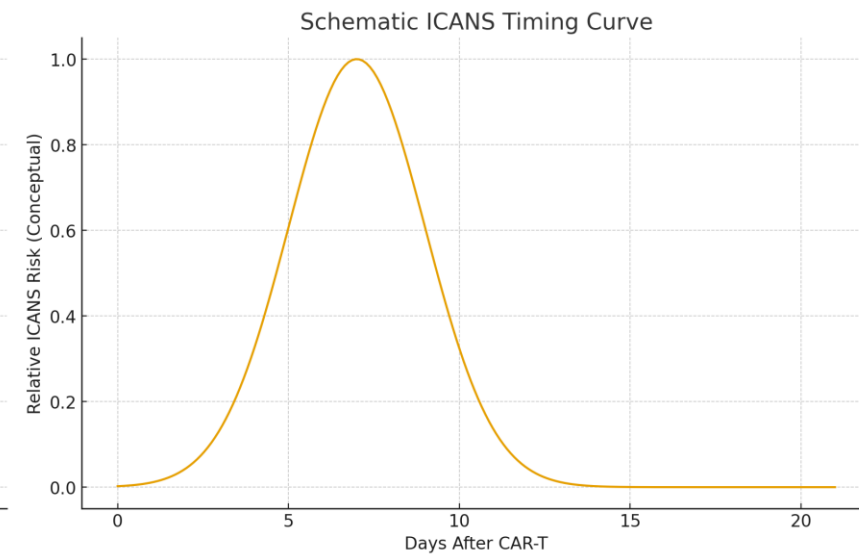
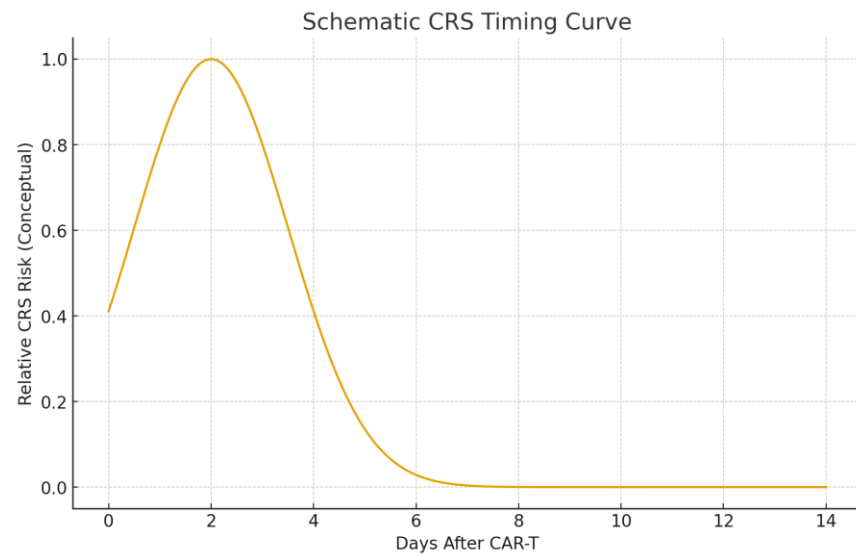
# Cytopenias- ICA-HT

- Can occur early to late phase and sometimes persists
- Grade  $\geq 3$  neutropenia: 78-82%
- Thrombocytopenia: 45-52%
- Anemia: 30-40%
- Median recovery: Days 14-21
- **Late prolonged cytopenias (>28 days): 20-25%**

# CAR-T Expansion and Cytokine Surge (Conceptual)



# CRS and ICANS Timing (Conceptual)



# Optimized Monitoring Period (Based on Data)

- Intensive monitoring recommended Days 0-14.
- Extend to Day 28 for high-risk patients:
  - High tumor burden
  - Early severe CRS/ICANS
  - Baseline frailty
- Post-Day 14 focus shifts to infection & cytopenia management.

# Tumor response

- Early tumor flares (Pseudoprogression) –
  - Rapid tumor enlargement, pain, fever and organ dysfunction
  - Usually due to inflammatory cells infiltrating tumor/ tissues. Coincide with CRS. Steroids can provide symptom relief
  - Important to differentiate from true progression
- Response assessment at 1 month, 3 months and then every 3 months
  - Marrow MRD
  - PET CT/ Other radiology
  - Look for monoclonal proteins– in myeloma

# Indian CAR T – Key Clinical Data (CD19)

Product (Brand) / Target	Indication & Study	Phase / Setting	N (treated / evaluable)	CRS any / ≥3	ICANS any / ≥3	Response (CR/CRi or ORR)	Overall Survival (OS)
Tallicabtagene autoleucel (NexCAR19) / CD19	r/r B-cell malignancies (B-ALL, B-NHL) – multicenter India	Phase 1/2 (Lancet Haematology 2025)	64 / 51 (efficacy)	≈5% ≥3 (any-grade NR)	0% (any-grade NR)	ORR 73% (51 pts)	NR at publication
Tallicabtagene autoleucel (NexCAR19) / CD19	Real-world India (multi-center)	Post-approval cohort (ASH 2024 poster)	89 infused / 77 evaluable	81% / 4%	6% / 3%	ORR 74% @ 3 mo (73% @ 6 mo)	NR

Notes: Variants are from peer-reviewed and accepted reports. NexCAR19 Phase 1/2 ORR and efficacy-evaluable any; safety ORR 91.7% are available. For Qartem, ORR and neurotoxicity drawn from ASH abstracts and regulatory/press summaries; full CRS breakdown NR.

Varenicabtagene

r/r B-cell

Phase 2 (primary

25 treated

NR / NR

NR any; ≥3: 0%

ORR 91.7% @ D+28:

NR

# Conclusion

- Monitoring for toxicities
  - Initial 2 weeks- CRS, ICANS, HS
  - Post 2 weeks- Infections, HT, Organ toxicities
- Monitoring for immune cells status
  - Less practised in India
  - Should be standardized across centres
- Monitoring for response in tumor
  - Functional imaging or marrow MRD tests at 1 month and then every 3 months

## Quiz: Question-1

- **Select one wrong statement for CAR-Ts anti-tumor effect**

- a. Works independent of MHC
- b. Requires APCs (antigen presenting cells) to identify the target
- c. Co-stimulatory molecule is not necessarily required in CAR-T constructs for CAR-Ts to kill target tumor cell
- d. There is no CTLA4 mediated feedback inhibition of T cells with CARs expressed on it

## Quiz: Question-2

- **Select one wrong statement for CAR-T toxicities**

- a. CRS occurs due to capillary leak mediated by IL6 : IL6-R complex
- b. Post CAR-T prolonged thrombocytopenia strongly correlate with high risk of relapse of tumor
- c. Diagnosis and ASTCT grading of CRS do not require testing for IL6 elevation
- d. Same criteria can be applied for grading of other immunotherapy mediated CRS

One more last question (no prize for it)

- **What co-stimulatory construct do Indian CARs have out of CD28 and 4-1BB**
  - Immuno-act
  - Immuneel
  - Vel-cart
  - Any other