

**GESTIONE DELLA TOSSICITÀ  
ASSOCIATA ALLE CAR-T**

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LE NUOVE FRONTIERE  
DELL'IMMUNOTERAPIA  
PER LA CURA DEL

**MIELOMA  
MULTIPLO**

*dalla teoria alla pratica*



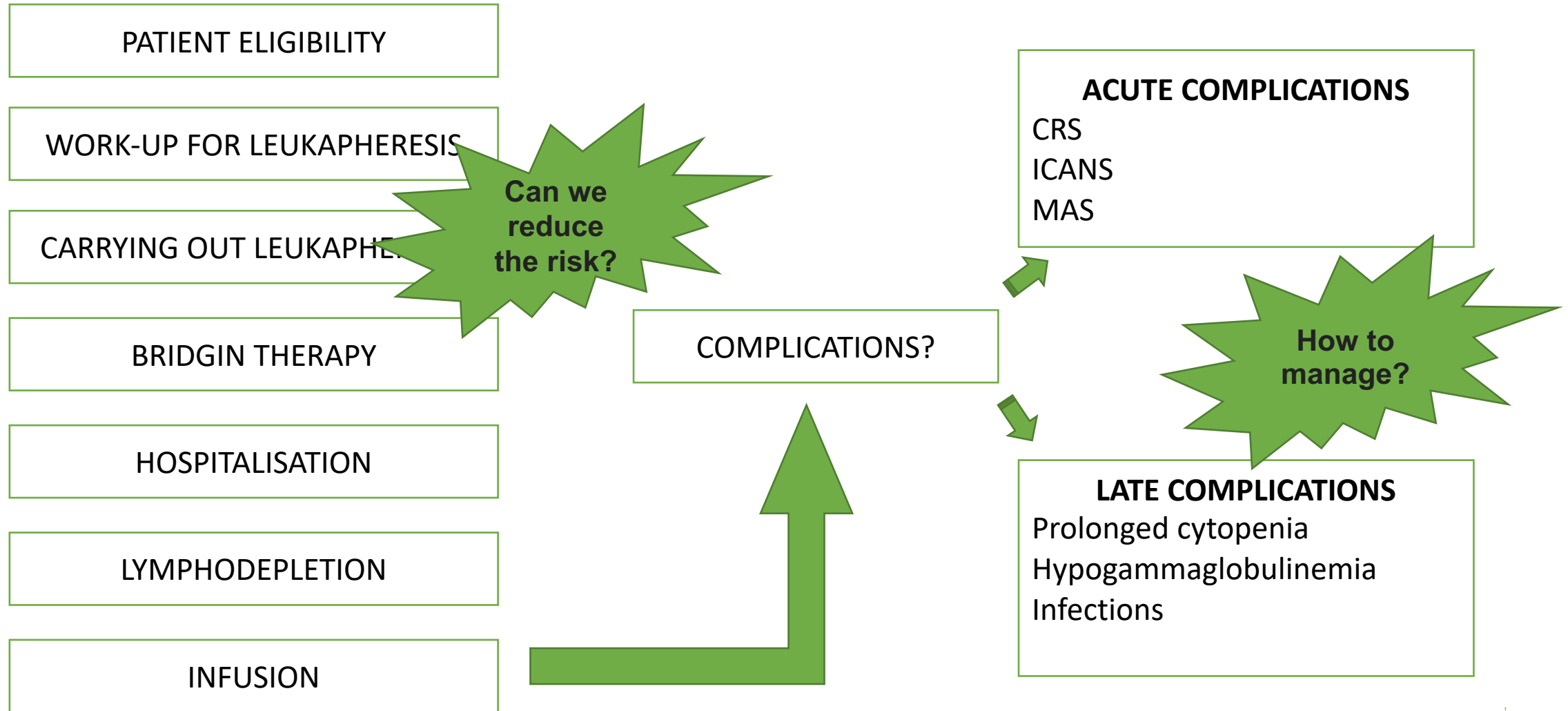
**TORINO 3-4 MARZO 2023**

## Disclosures of Francesca Gay

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janseen						x	x
Amgen						x	x
Pfizer						x	
BMS/Celgene						x	x
Roche						x	
Abbvie						x	x
Oncopeptides						x	
Adaptive						x	
Sanofi						x	x
Takeda						x	x
GSK						x	x



# CAR-T Cell Therapy

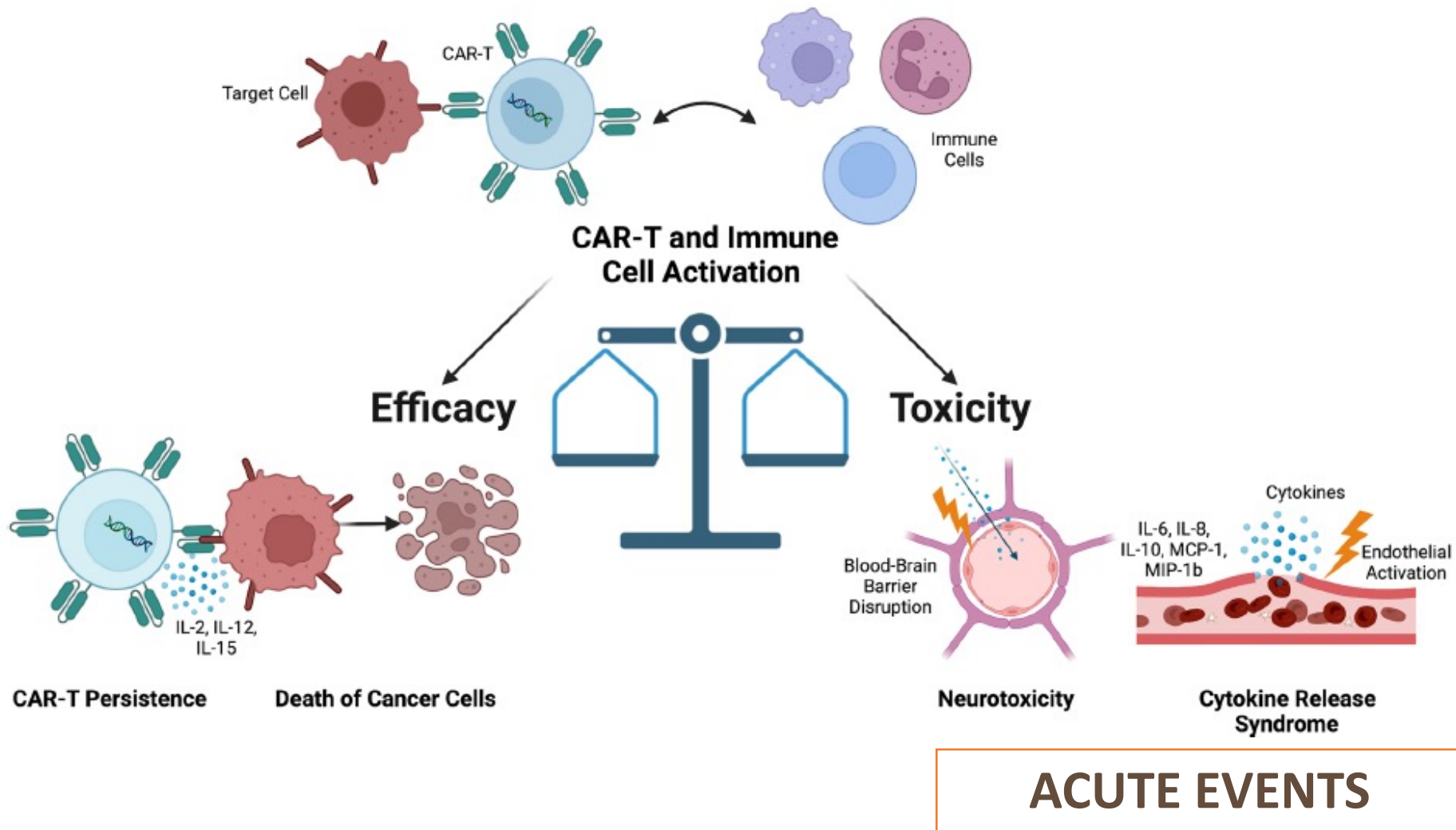


CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome;  
CAR: chimeric antigen receptor; MAS: macrophage activation syndrome

Hayden et al., Annals of Oncology 2022

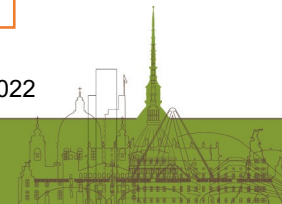


# CAR-T Cell Therapy: a balance between EFFICACY and TOXICITY

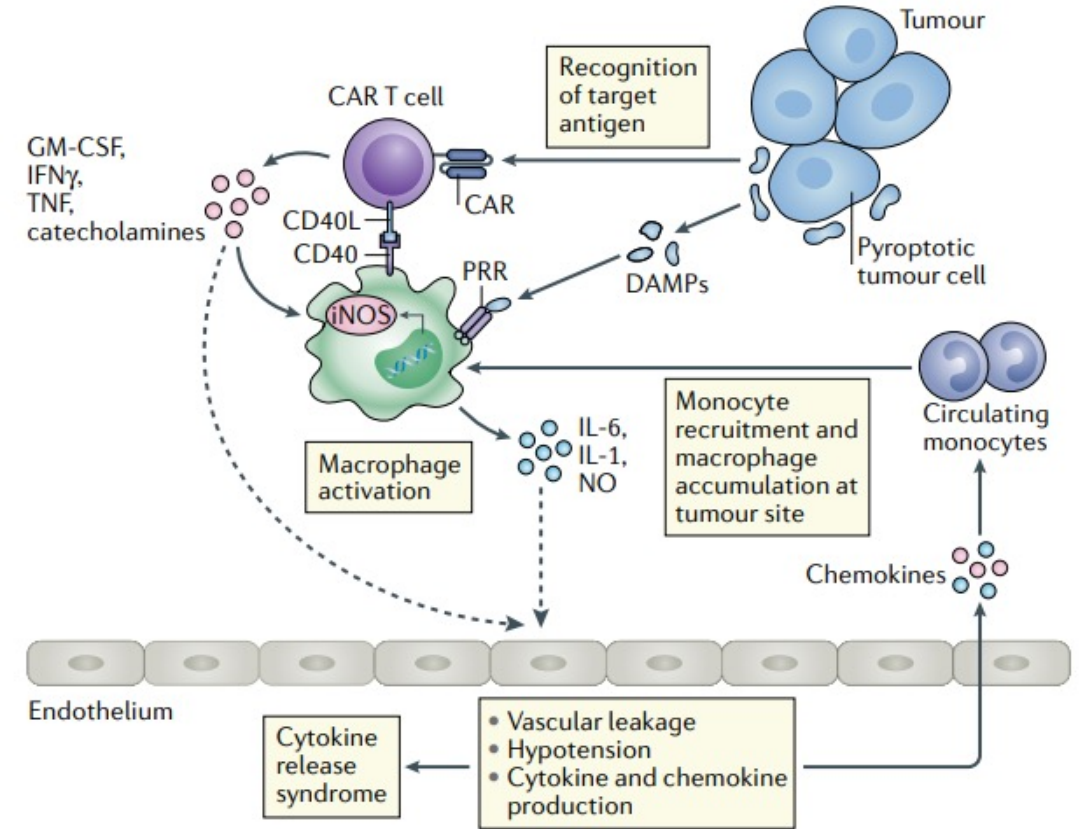
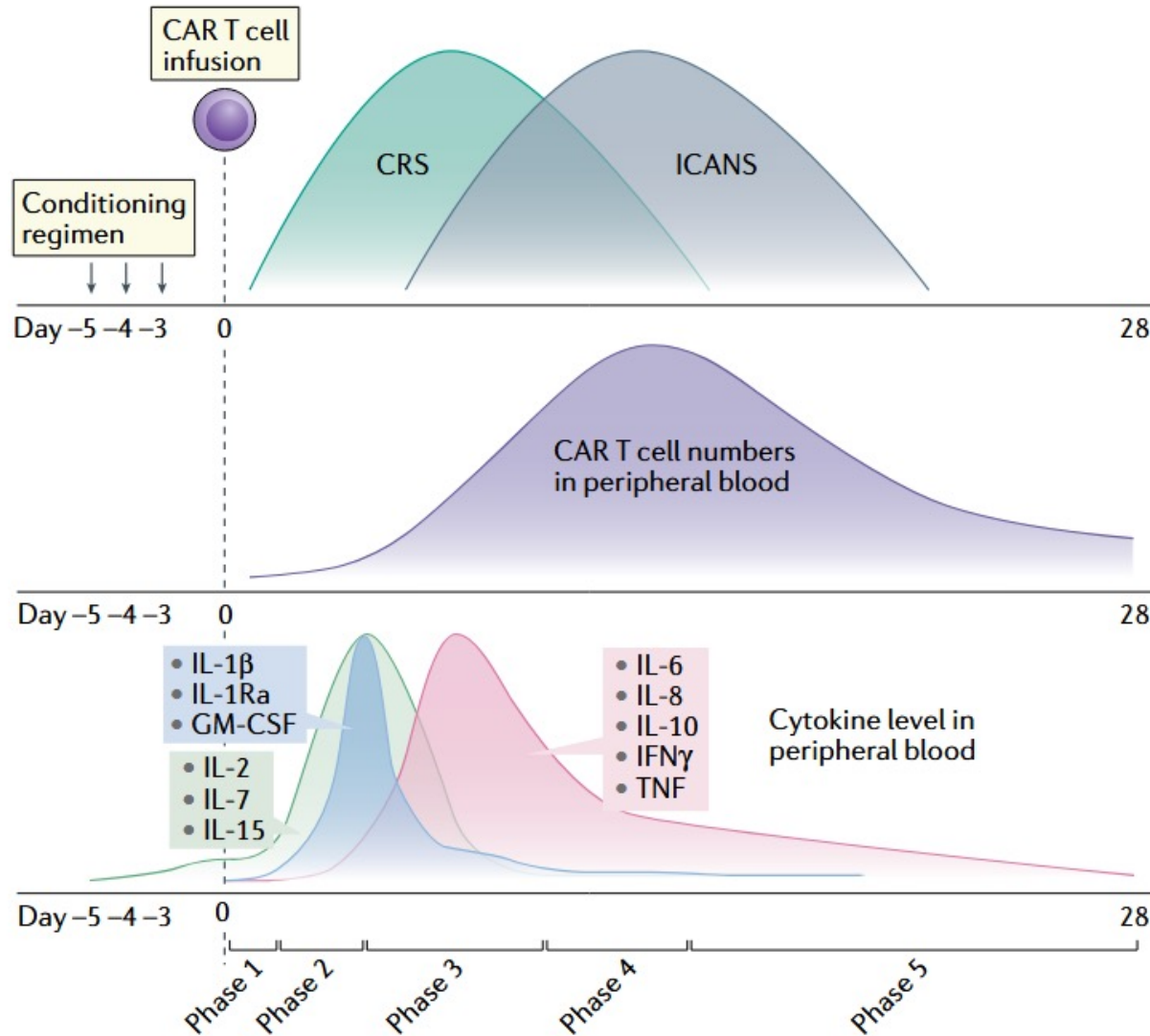


CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; CAR: chimeric antigen receptor;

Chohan et al., Current Hematologic Malignancy Reports, 2022



# PATHOPHYSIOLOGY OF CAR-T RELATED ACUTE TOXICITIES



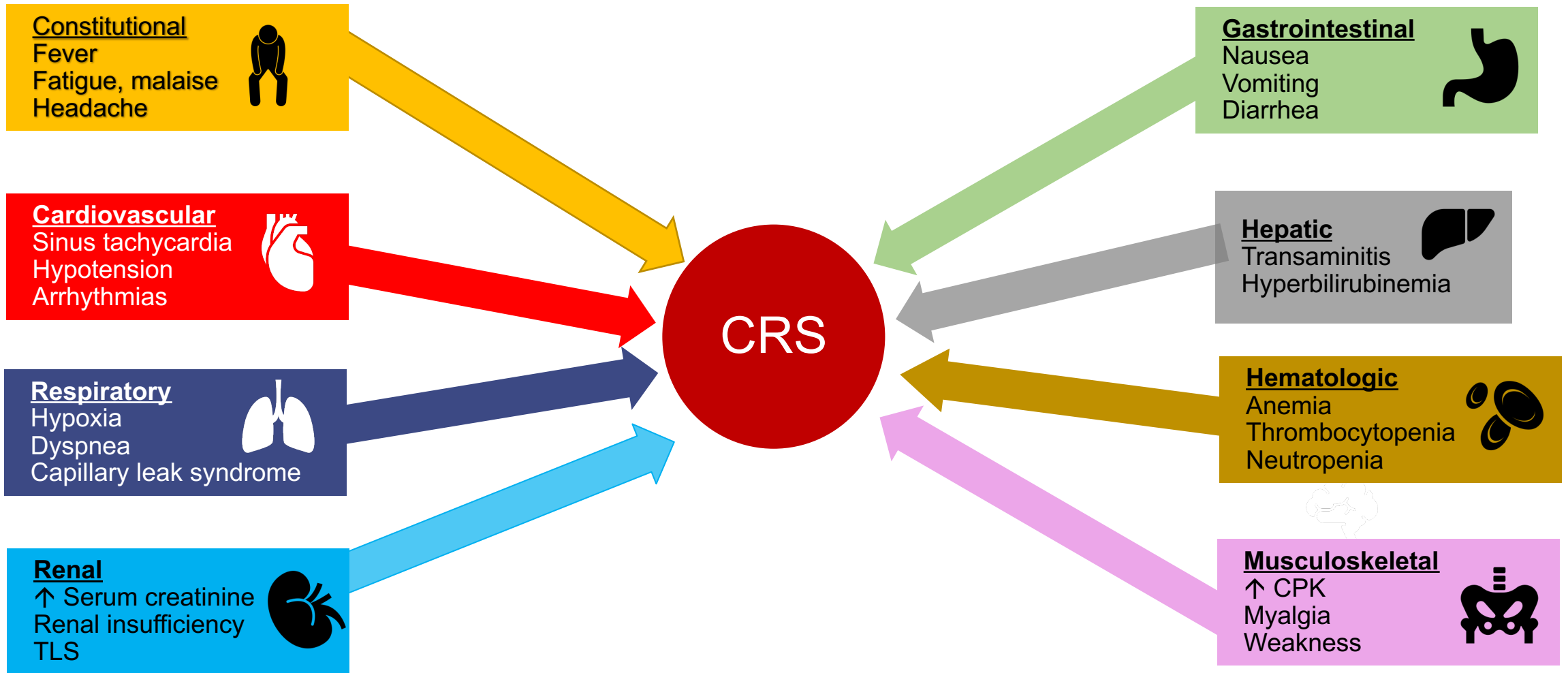
**Massive T cell activation and expansion, involving other immune cells**

CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; CAR: chimeric antigen receptor; IFN $\gamma$ : interferon- $\gamma$  (IFN $\gamma$ ); GM-CSF: granulocyte-macrophage colony-stimulating factor; TNF: tumour necrosis factor; DAMPs: damage-associated molecular patterns; NO: nitric oxide

Morris et al., Nature Reviews Immunology 2022



# SIGN AND SYMPTOMS OF CRS



CRS: cytokine release syndrome; TLS: tumor lysis syndrome; CPK: creatine phosphokinase

Brudno et al., Blood Reviews, 2019



# ASTCT Consensus Grading for CRS

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
<b>Fever</b>	≥ 38°C	≥ 38°C	≥ 38°C	≥ 38°C
<b>With hypotension</b>	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
<b>And/or hypoxia</b>	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)

CPAP: continuous airway pressure; ;BiPAP: bilevel positive airway pressure

Lee et al., ASTCT Consensus Grading, Biol Bone Marrow Transplant, 2019 Apr;25(4):625-638

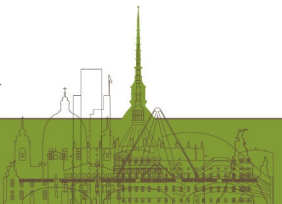


# SUPPORTIVE CARE AND MONITORING STRATEGIES

- **Baseline and routine monitoring of CRP, LDH, ferritin, electrolytes, uric acid, kidney / liver / coagulation function, triglycerides, NT-proBNP**
- Consider allopurinol for high disease burden, **aggressive hydration and rasburicase for confirmed TLS**
- Acetaminophen and/or cooling blankets for high fevers
- **Vital sign monitoring** every 2–4 hours in inpatient
- **Cardiac monitoring for tachycardia or hypotension**; judicious use of IV fluids to balance insensible losses; aggressive electrolyte repletion; consider early transition to vasopressors for hypotension to avoid worsening capillary leak due to fluid overload;
- **ECG and echocardiogram** for patients with persistent tachycardia or hypotension requiring vasopressors; Standard anti-arrhythmic therapy for arrhythmias; caution use of beta blockers in patients with hypotension
- **Continuous pulse oximetry** if changes in respiratory status; **Chest x-ray and/or chest CT** to evaluate new hypoxia

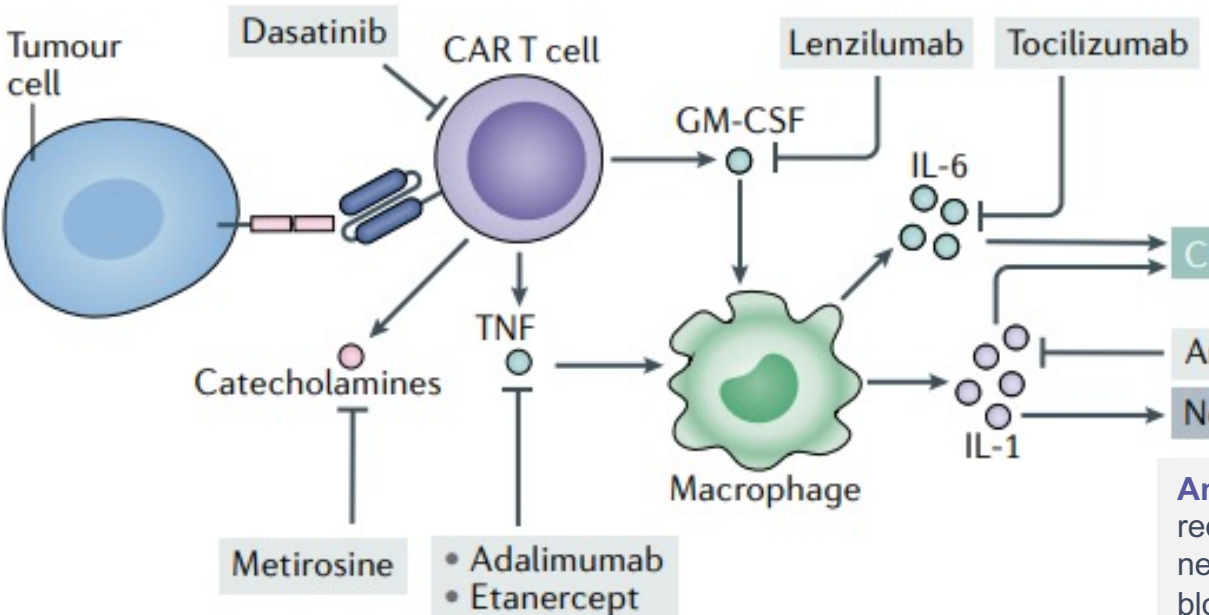
CRP: C-reactive protein, LDH: lactate dehydrogenase;  
NT-proBNP: TLS: tumor lysis syndrome

*Adapted from 2021 ASCO Educational Book*





# REPRESENTATION OF CURRENT AND POTENTIAL THERAPEUTIC INTERVENTIONS FOR CRS

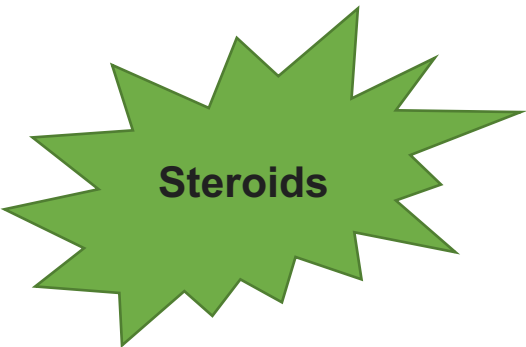


**Tocilizumab**, an IL-6 receptor antagonist to 3 additional doses of tocilizumab may be administered. The interval between consecutive doses should be at least 8 hours

**Siltuximab**, an anti-IL-6, has been used as a third-line therapy for CRS if tocilizumab and corticosteroid therapy fails

**Anakinra**, an anti-IL-1 receptor antagonist may reduce severity of CAR-T cell-related neurotoxicity, due to its ability to cross the blood-brain barrier

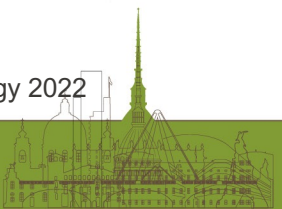
**TNF- $\alpha$  inhibitor** has been used in clinical trials in patients who are not responsive to tocilizumab and in whom TNF- $\alpha$  levels are elevated



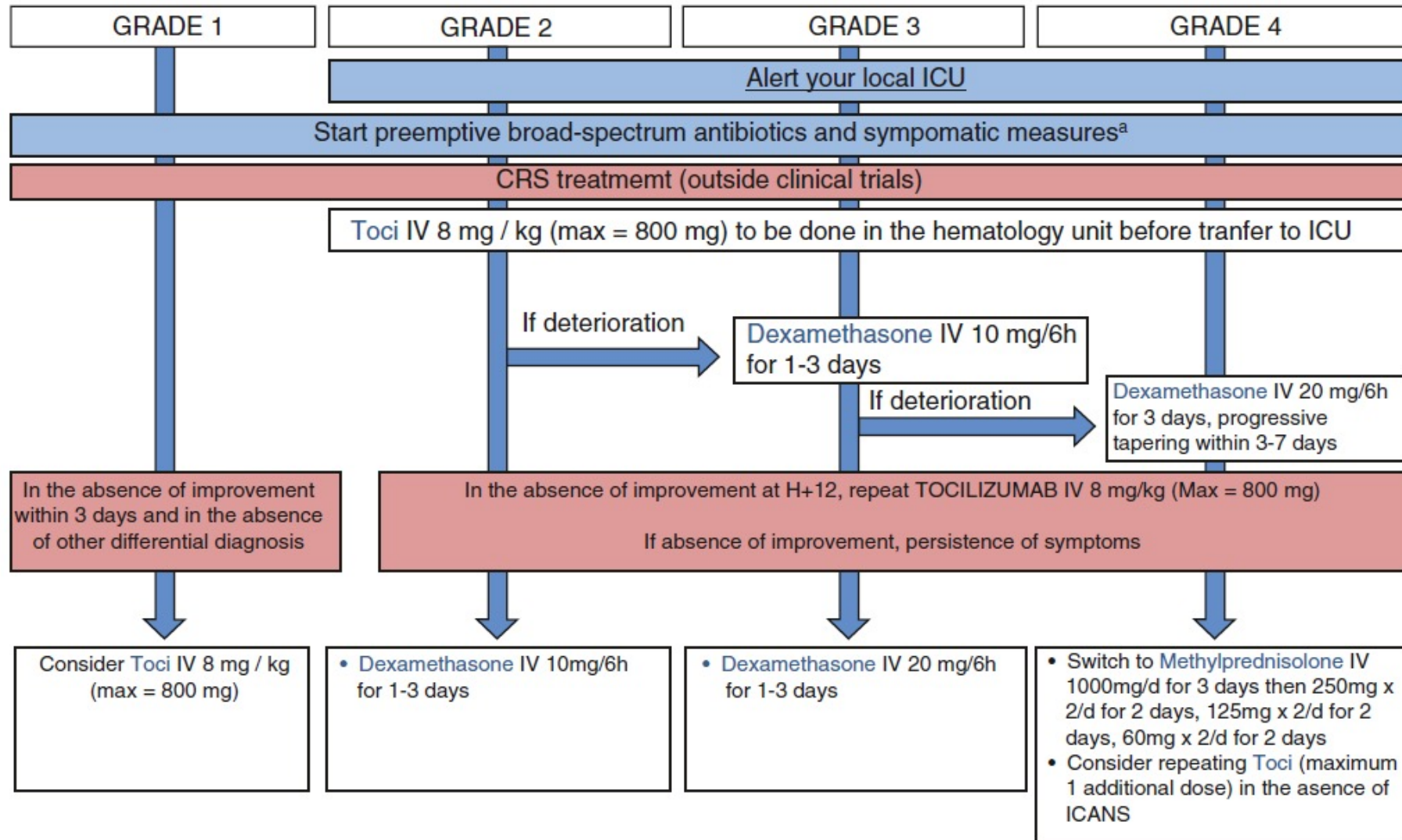
**Methylprednisolone** for CRS refractory to tocilizumab  
Administration: 1–2 mg/kg IV every 12 h

Ruxolitinib  
Ibrutinib → Inhibition of cytokine production → Future role in management of CRS?

Morris et al., Nature Reviews Immunology 2022

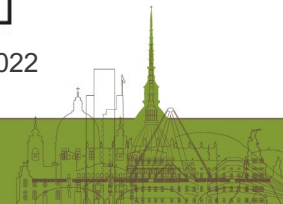


# ALGORITHM FOR MANAGEMENT OF CRS



ICU: intensive care unit; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; CAR: chimeric antigen receptor

Hayden et al., Annals of Oncology 2022



# CRS OCCURRENCE IN ANTI-BCMA CAR T-CELLS

Event	Idecabtagene Vicleucel (KarMMa trial) N=140	Ciltacabtagene Autoleucel (CARTITUDE-1 Trial) N=97	Ciltacabtagene Autoleucel (CARTITUDE-2 Trial – Cohort A) N=20	Ciltacabtagene Autoleucel (CARTITUDE-2 Trial – Cohort B) N=19
CRS event, n (%)				
Any grade	107 (84)	92 (95)	17 (85)	16 (84)
Grade ≥ 3	7 (5)	5 (4)	2 (10)	1 (5)
Median time to onset, days (range)	1 (1–12)	7 (1-12)	7 (5-9)	8 (5-11)
Median duration, days (range)	5 (1–63)	4 (1-97)	3.5 (2-11)	3.5 (1-7)
AE management, n (%)				
- Tocilizumab	67 (52)	67 (69)	14 (70)	11 (63)
- Corticosteroids	19 (15)	21 (22)	6 (30)	-
- Anakinra	2 (2)	18 (19)	1 (5)	-
- Siltuximab	1 (< 1)	-	-	-

AE: adverse events

CRS: cytokine release syndrome;

Munshi, NEJM 2021; Berdeja NEJM 2021, Martin et al., JCO 2023; Agha et al., A8013, JCO 2021; Agha et al., S185 EHA 2022



# RISK FACTORS FOR CRS

High Tumor burden (B2M, BMPCs)
Intensity of chemotherapy (lymphodepletion)
CAR-T cell dose
Concurrent infection

CRS: cytokine release syndrome;  
CAR: chimeric antigen receptor  
B2M: Beta-2- macroglobulin  
BMPCs: bone marrow plasma cells

Hay K.A. et al., Br J Haematol. 2018; Yan et al, Frontiers 2021



# CAR T-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

In case of persistent fever despite tocilizumab with...

## Manifestations of carHLH

Hyperferritinemia

Elevated LDH

Hyperbilirubinemia

Hypofibrinogenemia

Coagulopathy

Hypertriglyceridemia

Hemophagocytosis



In case of neurological involvement,  
consider intrathecal chemotherapy...

CRS/MAS

Dexamethasone i.v.: 10-20 mg × 4/day  
Anakinra s.c. or i.v. 100 mg × 2-4/day,  
(paediatric doses are often higher)

### Evaluation at 24-48 h

- Absence of clinical improvement
- Increase in serum ferritin level

- Switch to methylprednisolone i.v.  
1000 mg/day for 3 days then 250 mg × 2/day for 2 days, 125 mg × 2/day for 2 days, 60 mg × 2/day for 2 days
- Anakinra s.c. or i.v. 100 mg × 2-4/day

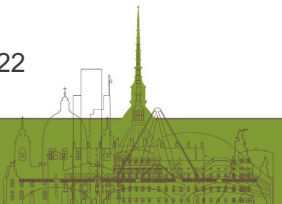
### Evaluation at 24-48 h

- Deterioration
- Increase in serum ferritin level

- Consider etoposide: 75 mg/m<sup>2</sup> i.v. at day 1 to repeat at day 4 and day 7 if needed

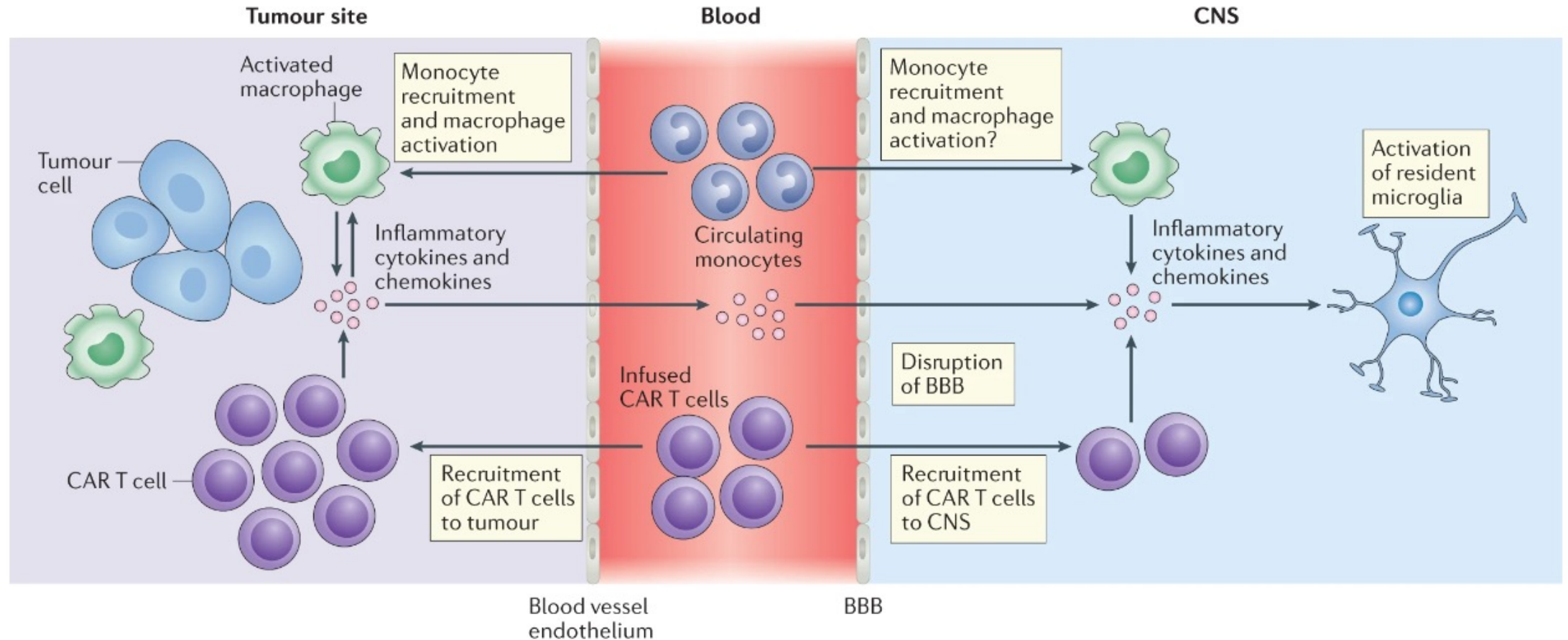
Hayden et al., Annals of Oncology 2022

CRS: cytokine release syndrome; CAR: chimeric antigen receptor; MAS: macrophage activate syndrome;



# PATHOPHYSIOLOGY OF CAR-T RELATED NEUROTOXICITY

A disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells.

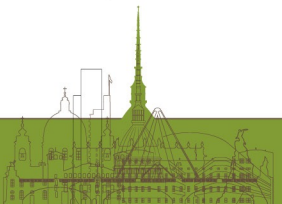
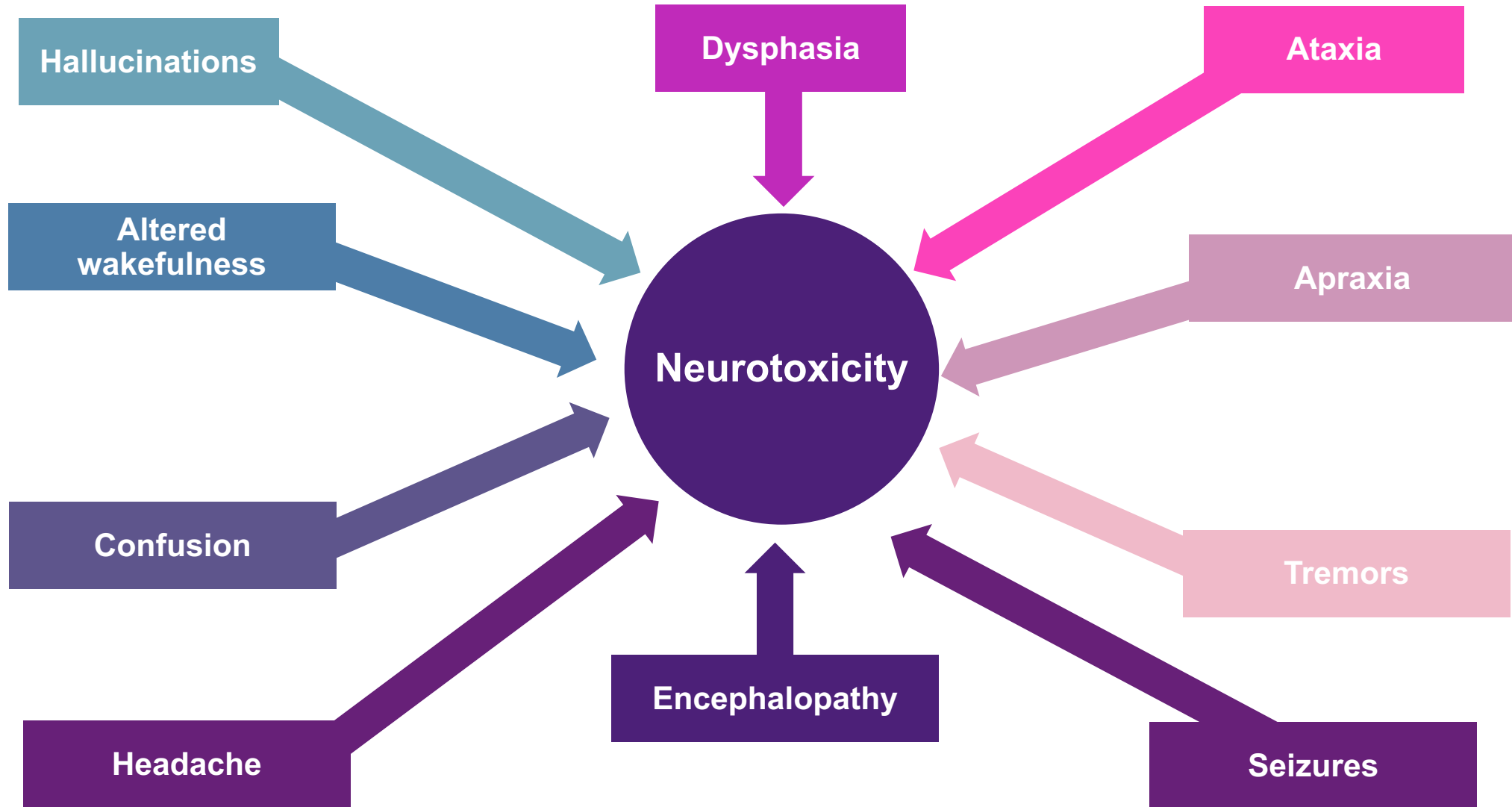


CNS: central nervous system; BBB: blood brain barrier

Morris et al., Nature Reviews Immunology 2022



# SIGN AND SYMPTOMS OF ICANS



# IMMUNE EFFECTOR CELL-ASSOCIATED ENCEPHALOPATHY (ICE) SCORE TO GRADE COGNITIVE FUNCTION

Domain	Definition	Points (max 10)
<b>Orientation</b>	Orientation to: year, month, city, hospital	4 total (1 point for each item)
<b>Naming</b>	Ability to name 3 objects (eg, point to clock, pen, button)	3 total (1 point for each item)
<b>Following commands</b>	Ability to follow simple commands (eg, “Show me 2 fingers” or “Close your eyes and stick out your tongue”)	1
<b>Writing</b>	Ability to write a standard sentence (eg, “Our national bird is the bald eagle”)	1
<b>Attention</b>	Ability to count backwards from 100 by 10	1

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





# ASTCT Consensus Grading for ICANS

ICANS Domain	Grade 1	Grade 2	Grade 3	Grade 4
<b>ICE score</b>	7-9	3-6	0-2	0 (unarousable and unable to perform ICE)
<b>Depressed level of consciousness</b>	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires vigorous/repetitive tactile stimuli to arouse. Stupor or coma
<b>Seizure</b>	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 min); or repetitive clinical or electrical seizures without return to baseline in between
<b>Motor findings</b>	N/A	N/A	N/A	Deep focal motor weakness (eg, hemiparesis or paraparesis)
<b>Elevated ICP / cerebral edema</b>	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

ICP, intracranial pressure; N/A, not applicable.  
 Lee DW et al. *Biol Blood Marrow Transplant.* 2019;25:625-638.



# ICANS OCCURRENCE IN ANTI-BCMA CAR T-CELLS

Event	Idecabtagene Vicleucel (KarMMa trial) N=140	Ciltacabtagene Autoleucel (CARTITUDE-1 Trial) N=97	Ciltacabtagene Autoleucel (CARTITUDE-2 Trial – Cohort A) N=20	Ciltacabtagene Autoleucel (CARTITUDE-2 Trial – Cohort B) N=19
ICANS event, n (%)				
Any grade	23 (18)	16 (17)	3 (15)	1
Grade ≥ 3	4 (3)	2 (2)	0	0
Median time to onset, days (range)	2 (1–10)	8 (IQR 6-8)	8 (7-10)	11
Median duration, days (range)	3 (1–26)	4 (IQR 3-6.5)	1 (1-2)	4
AE management, n (%)				
- Corticosteroids	10 (8)	9 (9)	-	-
- Tocilizumab	3 (2)	4 (4)	-	-
- Anakinra	1 (< 1)	3 (3)	-	-

AE: adverse events

Munshi, NEJM 2021; Berdeja NEJM 2021, Martin et al., JCO 2023; Agha et al., A8013, JCO 2021; Agha et al., S185 EHA 2022



# RISK FACTORS FOR ICANS

## CRS

Pre-existing neurologic comorbidities

High disease burden

High number of administered CAR T cells and high peak of CAR T-cell expansion

Elevated LDH, thrombocytopenia and endothelial activation before CAR T-cell treatment

Elevated ferritin concentration <72 h after CAR T-cell administration

CAR-design: CD28 costimulatory domain

Lymphodepleting therapy with fludarabine and cyclophosphamide

ALL as underlying disease



**...High fever ( $\geq 38.9$ ) and haemodynamic instability within 36h of CAR-T infusion (early CRS) predicts for severe ICANS!**

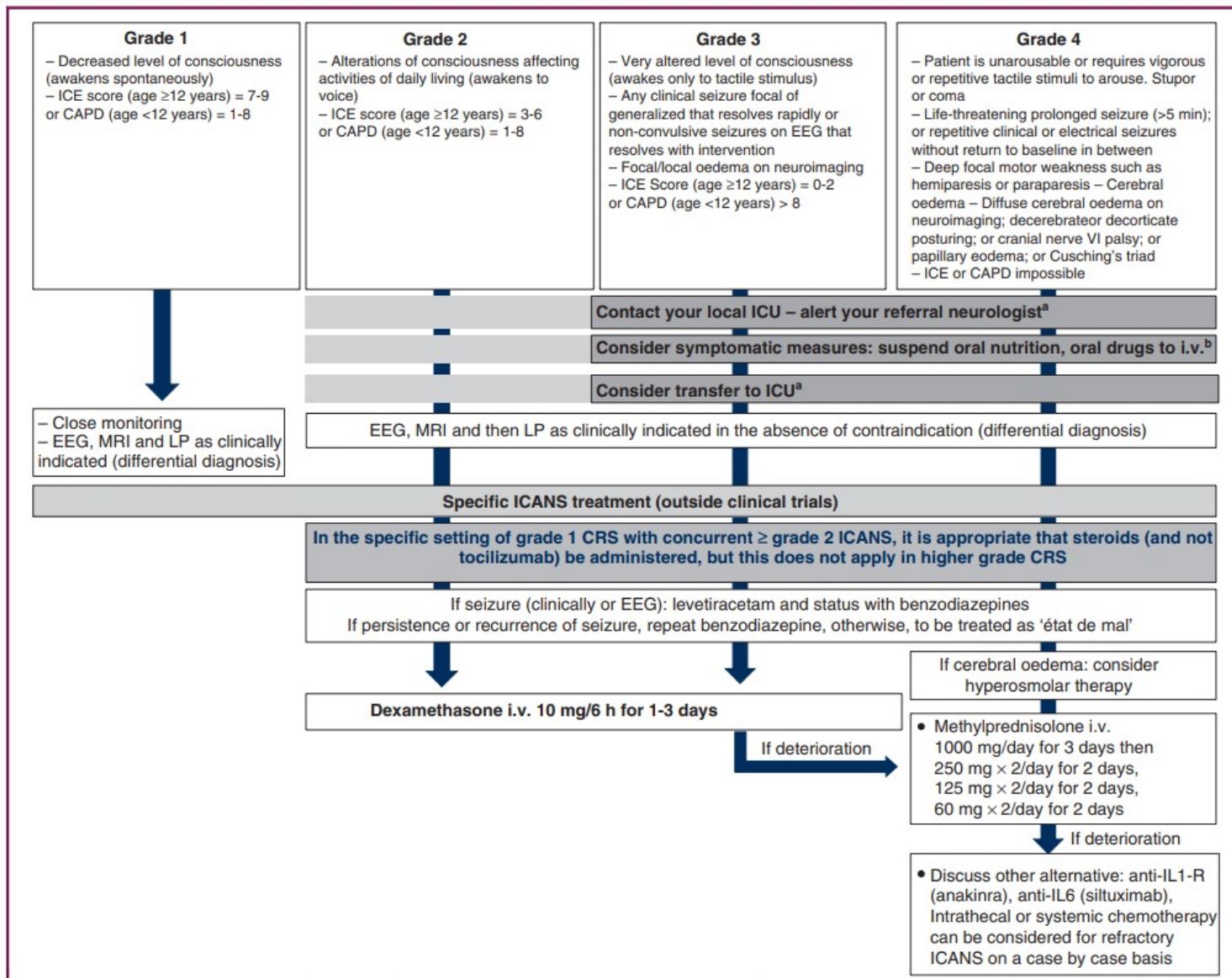


# SUPPORTIVE CARE AND MONITORING STRATEGIES

- **Baseline neurologic exam, ICE, brain MRI**
- Consider **prophylactic anti-epileptic medications** (levetiracetam), to be continued after discharge based on patient's risk to develop late neurologic-effects
- **Serial ICE score** at least daily, more frequently if NT present
- Consider **consultation with a neurologist** if ICANS present
- **MRI brain** to evaluate moderate to severe neurotoxicity (if feasible)
- **Lumbar puncture** to rule out infectious etiologies of altered mental status
- **EEG** if occult seizures suspected
- Consider prophylactic antiepileptic drugs (levetiracetam)



# ALGORITHM FOR MANAGEMENT OF ICANS



GRADE	TREATMENT
1	Levetiracetam (prophylaxis)
2	Steroids (dexamethasone)
3	Steroids (dexamethasone) <b>ICU critical care</b>
4	High dose steroids (methylprednisolone) <b>ICU critical care</b>

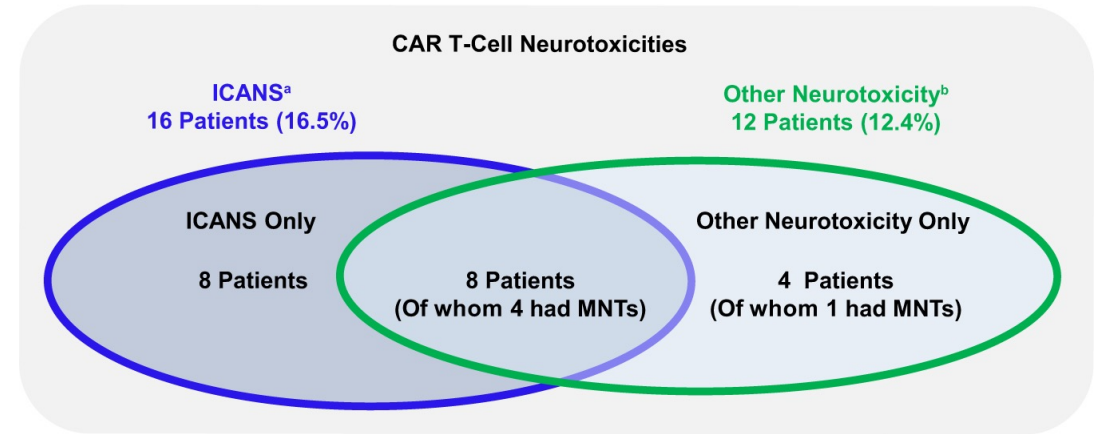
Hayden et al., Annals of Oncology 2022



# OTHER NEUROTOXICITIES AFTER CILTA-CEL INFUSION

Overall, 21 patients (21%) in CARTITUDE-1 experienced any grade neurotoxicity, including immune effector cell-associated neurotoxicity syndrome and other neurotoxicity (12%  $\geq 3$ ).

At 2-years follow-up, 6/97 had Parkinson-like symptoms (3 still alive)



Other Neurotoxicity	N (%)
Movement and neurocognitive treatment-emergent adverse events (MNTs)	6 (5)
Facial paralysis	1 (1)
Neurotoxicity	1 (1)
Concentration impairment	1 (1)
Diplopia	1 (1)
Cranial nerve palsy	1 (1)
Sensory loss, ataxia, peripheral motor neuropathy and peripheral sensory neuropathy	1 (1)
Altered mental status nystagmus	1 (1)

Cohen et al., Blood Cancer Journal 2022; Martin JCO 2023



# MOVEMENT AND NEUROCOGNITIVE TREATMENT-EMERGENT ADVERSE EVENTS (MNTs)

<b>Movement disorder</b>	Ataxia, cogwheel rigidity, dyskinesia, dysgraphia, dysmetria, gait disturbance, hand-eye coordination impaired, bradykinesia, micrography, myoclonus
<b>Cognitive impairment</b>	Amnesia, apraxia, bradyphrenia, confusional state, depressed level of consciousness, disturbance in attention, encephalopathy, psychomotor retardation
<b>Personality changes</b>	Flat affect, reduced facial expression

- Although the clinical presentation of MNTs overlaps with **Parkinson's disease**, neuropathology findings in the two patients with MNTs in CARTITUDE-1 for whom autopsies were available showed **intact substantia nigra** and a negative dopamine uptake scan in one patient and **lack of response to treatment with carbidopa/levodopa** in both patients;
- late onset (after a period of recovery from CRS and/or ICANS);
- insidious onset (normal to near ICE)
- generally non-responsive to steroids;
- often progressive;
- longer duration than ICANS.

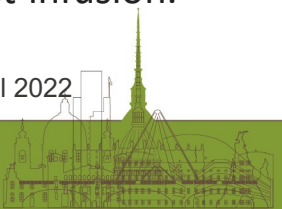
Risk factors for MNTs
High tumor burden
Grade ≥2 CRS or
Any grade ICANS
High CAR T-cell expansion/persistence

Strategies program to monitor and manage patients with MNTs



- Enhanced bridging therapy to reduce baseline tumor burden
- Early aggressive treatment of CRS and ICANS,
- Handwriting assessments for early symptom detection
- Extended monitoring/reporting time for neurotoxicity beyond 100 days post-infusion.

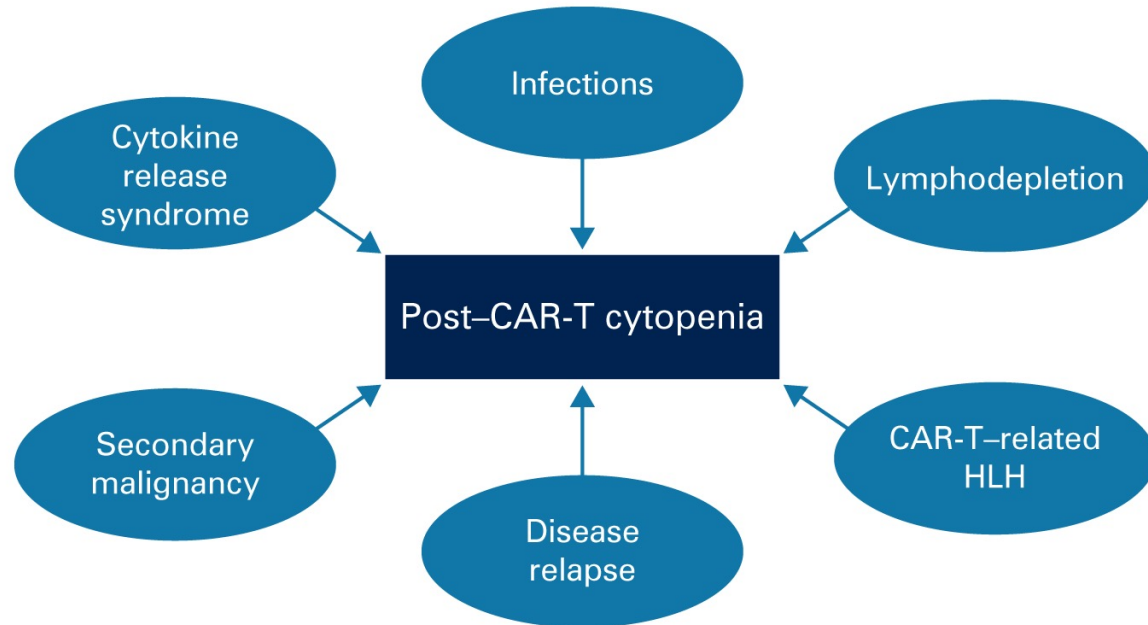
Cohen et al., Blood Cancer Journal 2022



# CYTOPENIAS IN ANTI-BCMA CAR T-CELLS

CYTOPENIAS (G $\geq$ 3)	KarMMa	CARTITUDE-1
Anemia	60%	68%
Thrombocytopenia	52%	60%
Neutropenia	90%	95%
Thrombocytopenia > 1 month	48%	25%
Neutropenia > 1 month	41%	10%

Median time to recovery from grade  $\geq$ 3 cytopenias after ide-cel and cilta-cel exposure was 1-4 months



→ LONG TERM PATHOGENESIS IS POORLY UNDERSTOOD

Munshi et al, NEJM 2021; Berdeja et al, Lancet 2021





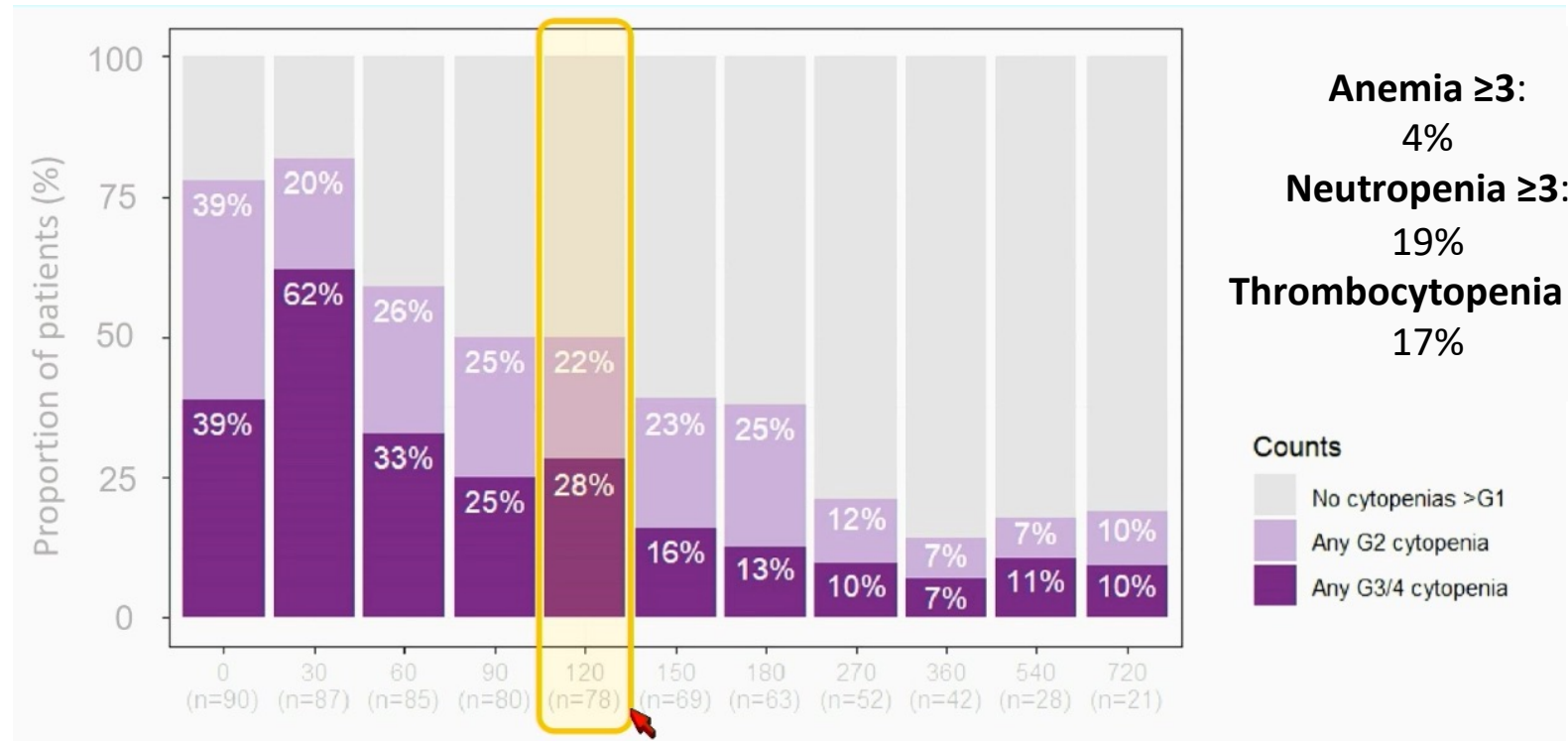
# CHARACTERIZATION OF PROLONGED CYTOPENIA

90 RRMM patients after BCMA CAR-T

78 patients evaluable at 4 months cutoff

**ADEQUATE  
HEMATOLOGIC  
RECOVERY**  
N=56 (72%)

**POOR  
HEMATOLOGIC  
RECOVERY**  
N=22 (28%)



**Anemia  $\geq 3$ :**  
4%

**Neutropenia  $\geq 3$ :**  
19%

**Thrombocytopenia  $\geq 3$ :**  
17%

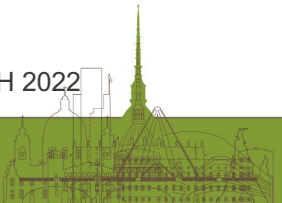
**Counts**

- No cytopenias >G1
- Any G2 cytopenia
- Any G3/4 cytopenia

- Older age
- Higher number of prior lines therapy
- Prior of  $\geq 1$  ASCT is significantly correlated with poor hematologic recovery

Reduced bone marrow reserve due to age and/or treatment-related toxicity may contribute to the decline of hematopoietic function by an unknown mechanism

Oral Abstract 249 ASH 2022



# POSSIBLE CLASSIFICATION AND MANAGEMENT OF POST-CAR-T CYTOPENIAS

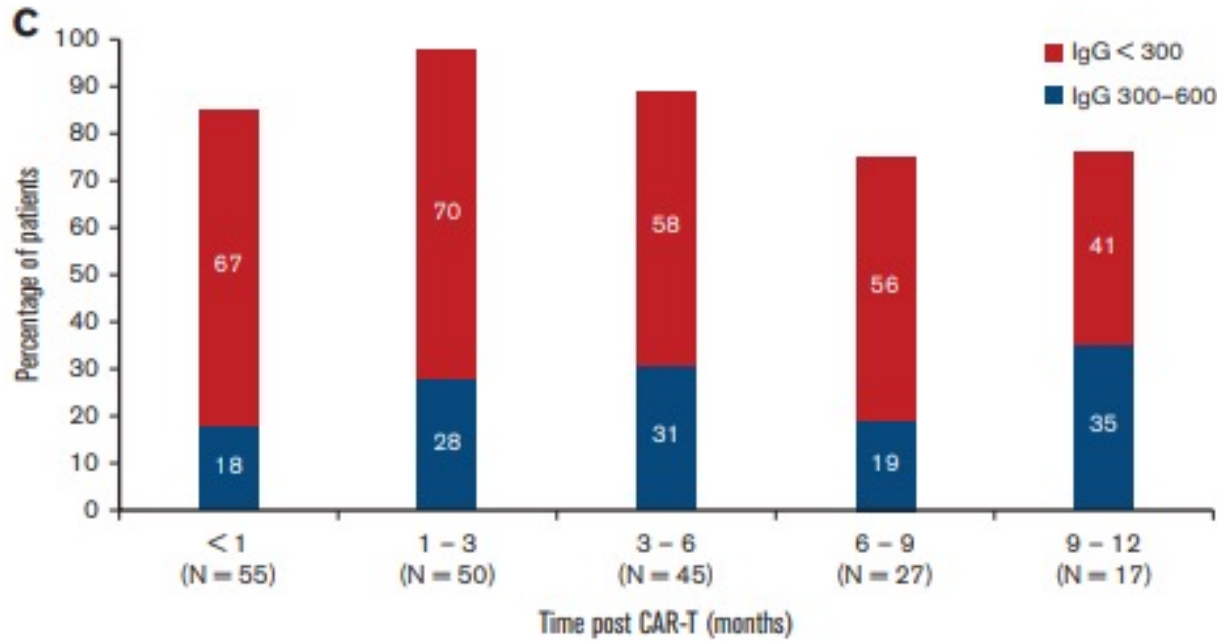
Timeline	Very Early	Early	Late
<b>Time</b>	<i>Up to 30 Days</i>	<i>Up to 90 days</i>	<i>&gt; 90 days</i>
<b>Causes</b>	Lymphodepleting regimens CRS	Delayed effects of CRS	Multiple factors
<b>Interventions</b>	<ul style="list-style-type: none"> <li>- Tocilizumab/dexamethasone</li> <li>- Transfusion support</li> <li>- (Empiric) Antibiotic prophylaxis</li> </ul>	<ul style="list-style-type: none"> <li>- Possible role for anti-inflammatory agents</li> <li>- G-CSF</li> <li>- TPO agonists</li> <li>- Transfusion support</li> </ul>	<ul style="list-style-type: none"> <li>- G-CSF</li> <li>- TPO agonists</li> <li>- Transfusion support</li> <li>- Consider bone marrow examination (MDS?)</li> <li>- Immunomodulatory therapy</li> <li>- Autologous stem cell rescue</li> </ul>

CRS: cytokine release syndrome; G-CSF: granulocyte cytokine stimulating factor; TPO: thrombopoietin; MDS: myelodysplastic syndrome

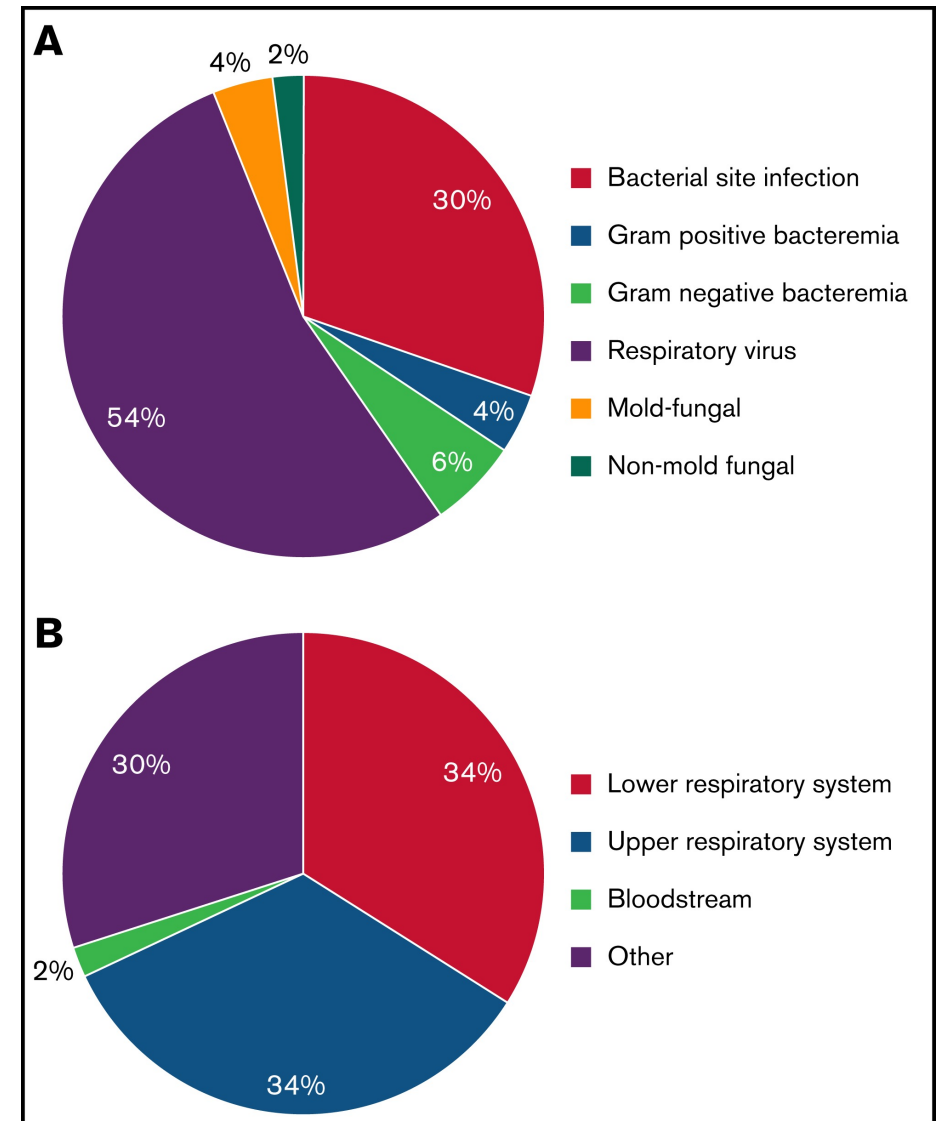
Sharma et al, Cancers 2022



# INFECTIONS AND HYPOGAMMAGLOBULINEMIA



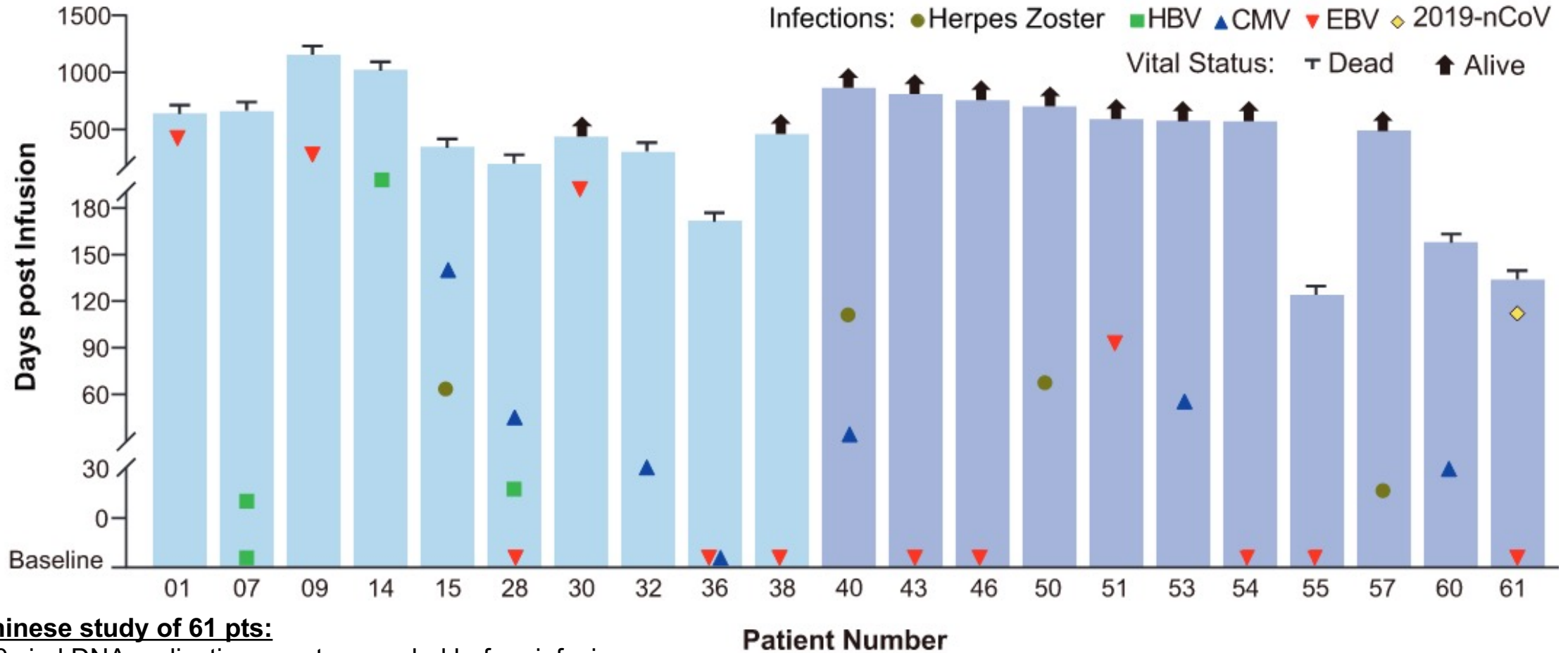
58% (32/55) patients received at least 1 dose of intravenous immunoglobulin (IVIg) within 12 months after CAR-T



Kambhampathi et al, Blood Advances 2022



# VIRAL REACTIVATION IN ANTI-BCMA CAR T-CELLS



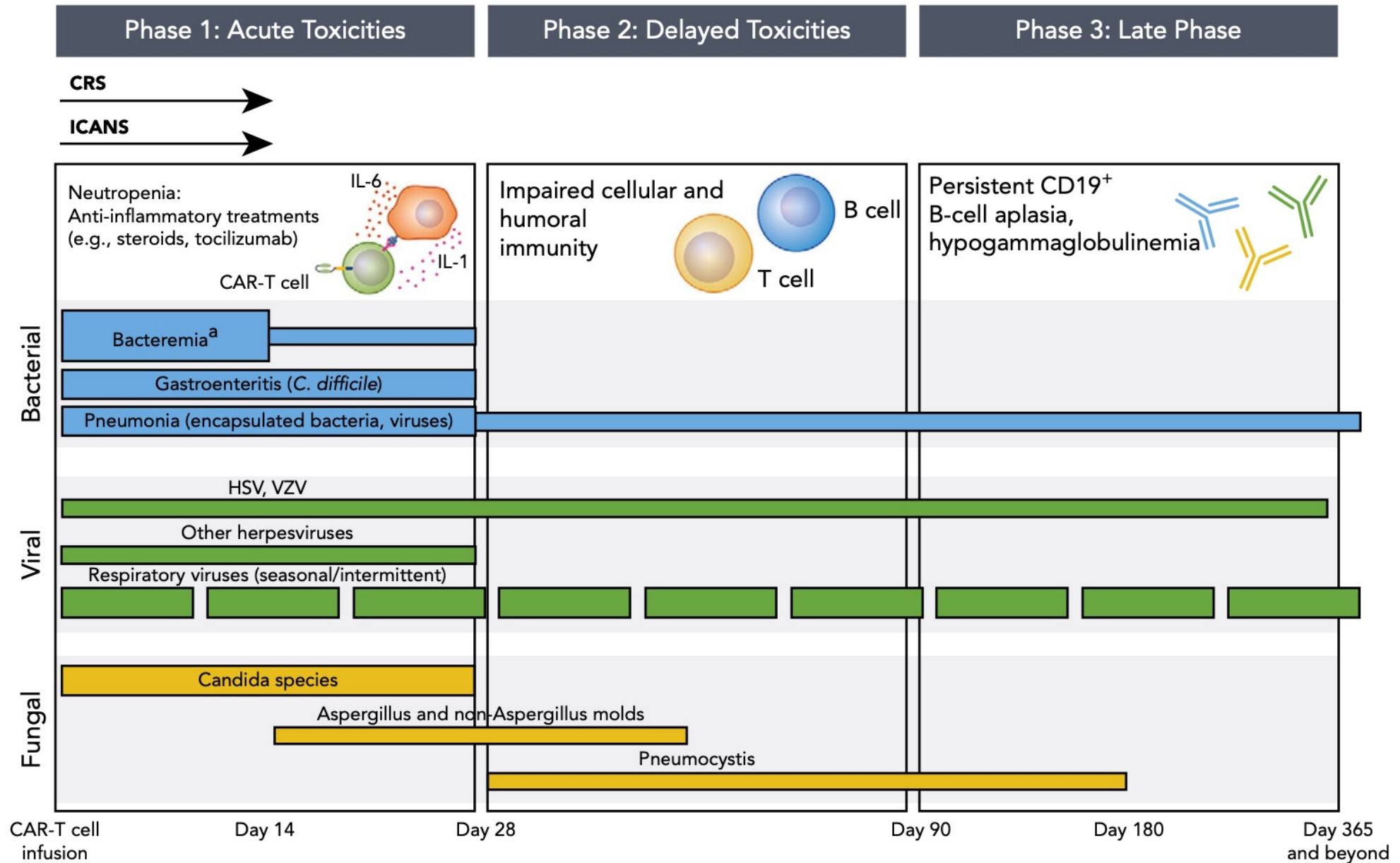
## Chinese study of 61 pts:

- 10 viral DNA replication events recorded before infusion
- 18 viral infection/reactivation events in 15 patients after infusion, including 4 EBV, 6 CMV, 3 HBV, 4 VZV, and 1 COVID-19

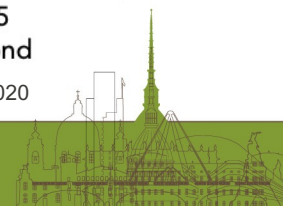
HBV: hepatitis B virus; CMV: cytomegalovirus;  
EBV: Epstein-Barr virus

Wang, Blood Cancer Journal 2021

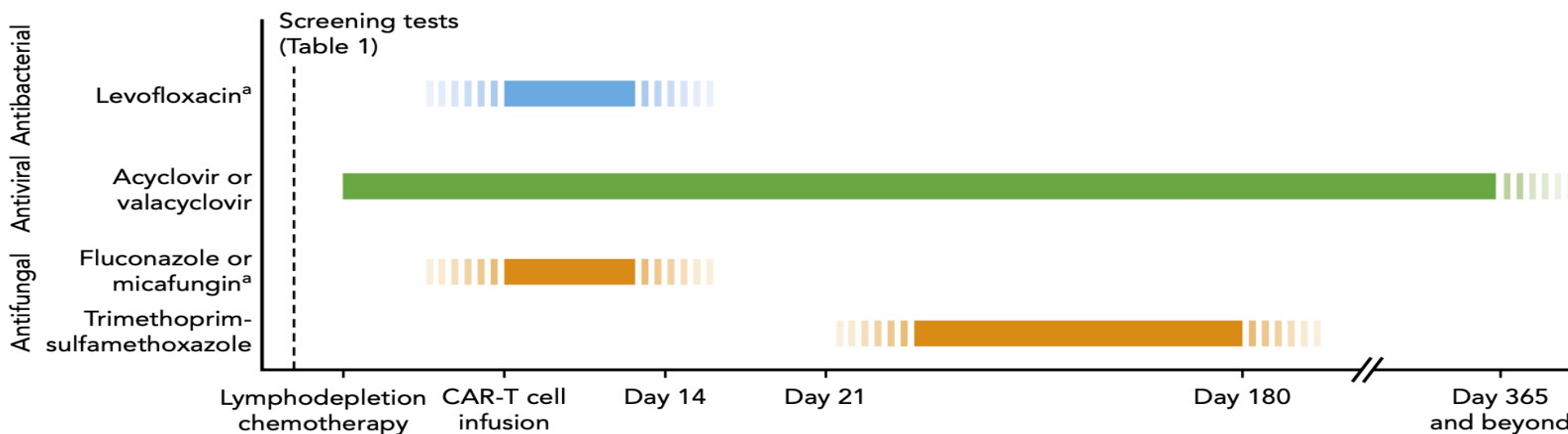
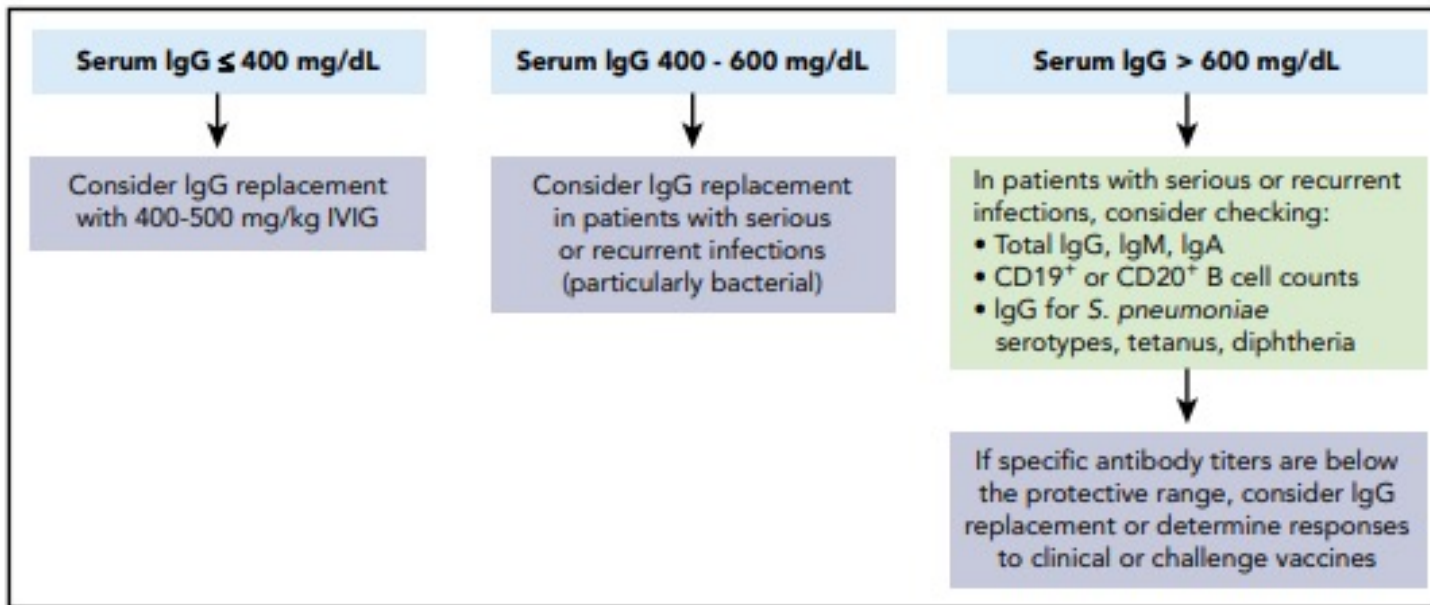




Hill & Seo, How I treat, Blood 2020



# PROPOSED TIMELINE FOR ANTIMICROBIAL PROPHYLAXIS AND IMMUNOGLOBULINS REPLACEMENT



Hill & Seo, How I treat, Blood 2020



# CONCLUSIONS

- Patients with triple-refractory multiple myeloma are **generally fragile**
- Acute toxicities are frequent and **can rarely be fatal**, therefore **accurate patients selection** in terms of age, fitness and comorbidities is warranted
- **Long term cytopenias** are poorly understood and often clinically challenging
- Triple-refractory multiple myeloma patients undergoing CAR T-cell therapies are exposed to **high risk of infections, especially late viral or opportunistic infections**:
  - Close monitoring, and aggressive screening/management of latent/symptomatic infections are recommended
  - Anti-infectious prophylaxis, IvIg replacement should be considered

Brudno JN, Kochenderfer JN. *Blood*. 2016;127(26):3321-3330. Brudno JN, Kochenderfer JN. *Blood Rev*. 2019;34:45-55  
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# GRAZIE PER L'ATTENZIONE



**EMN**



Università degli Studi  
di Torino



LE NUOVE FRONTIERE DELL'IMMUNOTERAPIA PER LA CURA DEL MIELOMA MULTIPLIO  
*dalla teoria alla pratica*

**TORINO**  
3-4 MARZO 2023

