CAR-T CELL THERAPY: FOCUS ON THE MAIN TOXICITY

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Timeline

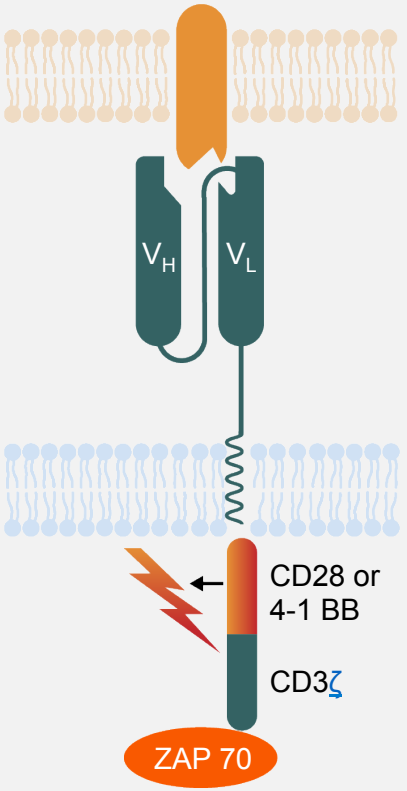
1. **Introduction**
2. **Main toxicity:**
   - Immune mediated toxicities
     - Cytokine release syndrome (CRS)
     - Immune effector cell-associated neurotoxicity syndrome (ICANS)
   - Cytopenia and hypogammaglobulinemia
3. **Conclusion:**
   - Future strategies to decrease adverse events related with CAR-T cell therapy

CD-19 targeting CAR-T cell

1. **Tisagenlecleucel** (Novartis):
   - Approved by AIFA on August 7th, 2019
   - Patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL), that is refractory or in second or later relapse (ELIANA trial)
   - Adult patients with large B-cell lymphoma relapsed/refractory after 2 or more line of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) NOS, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (JULIET trial).

2. **Axicabtagene ciloleucel** (Kite-Gilead):
   - Approved by AIFA on November 13th, 2019
   - Adult patients with large B-cell lymphoma relapsed/refractory after 2 or more line of systemic therapy, including DLBCL NOS, high grade B-cell lymphoma, primary mediastinal large B-cell lymphoma and DLBCL arising from follicular lymphoma (ZUMA-1 trial).

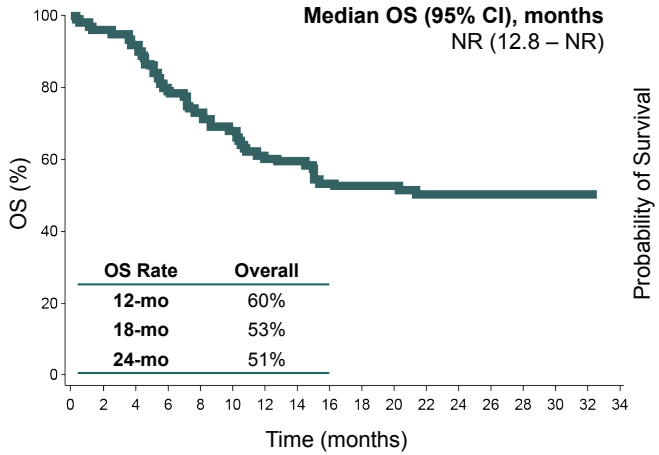
Early clinical data in follicular lymphoma, multiple myeloma and other malignant disease like glioblastoma are promising and new approvals are expected in the coming years.



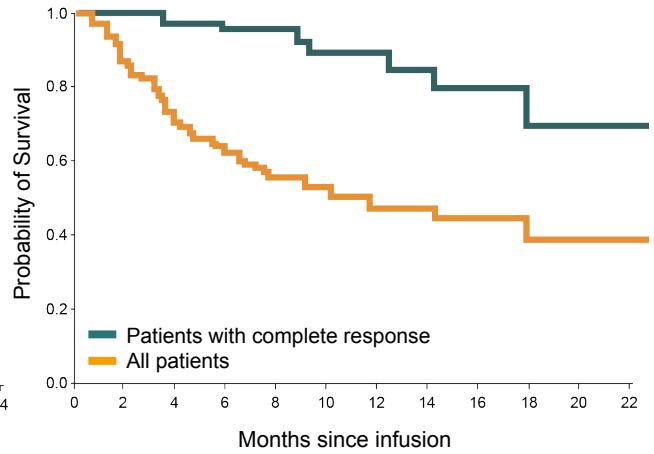
2nd generation
(dual signaling)

Introduction – Response rate

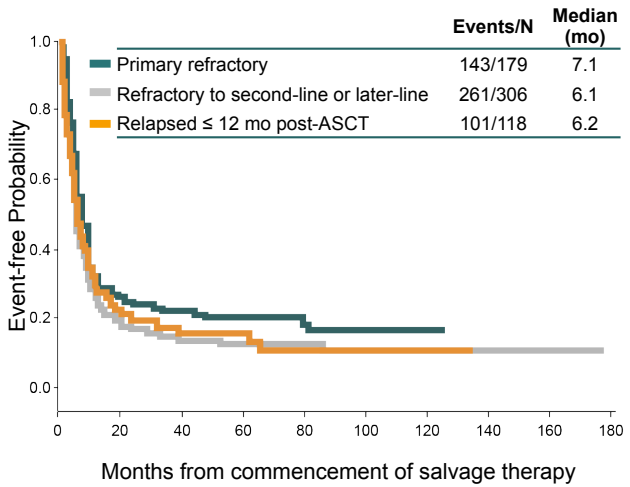
ZUMA-1, OS



JULIET, OS



SCHOLAR-1, OS



Prodotto CAR-T	Costrutto CAR	Indicazioni	ORR	CR	Median DoR	Median PFS	Median OS
Tisagenlecleucel (JULIET study)	CD19scFv/ 4-1BB/CD3ζ	DLBCL R/R LAL-B R/R (< 25 aa)	52%	40%	NR	4 mo	12 mo
Axicabtagene ciloleucel (ZUMA-1 study)	CD19scFv/ CD28/CD3ζ	DLBCL R/R PMBCL R/R	74%	54%	NR	5.9 mo	NR

Mod. da Schuster SJ, et al. NEJM 2019; 380: 45-56; Locke FL, et al. Lancet Oncol 2019; 20: 31-42; Crump M, et al. Blood 2017; 130: 1800-1808

Immune mediated toxicities - CRS

Cytokine release syndrome (CRS): immune-mediated toxicity characterized by an excessive immune reaction caused by immune-modulating drugs.

ZUMA-1 AE, n (%)	2-year analysis (N: 108)
Grade ≥ 3 AEs	106 (98%)
Grade ≥ 3 SAEs	52 (48%)
Any grade CRS	94 (93%)
Grade ≥ 3 CRS*	12 (11%)

- Median time to onset: 2 days (1-12)
- Median time to resolution: 7 days (2-29)

** grading by Lee et al. 2014*

JULIET AE, n (%)	2-year analysis (N: 111)
Grade ≥ 3 AEs	64 (58%)
Grade ≥ 3 SAEs	46 (41%)
Any grade CRS	64 (58 %)
Grade ≥ 3 CRS*	24 (22%)

- Median time to onset: 3 days (1-9)
- Median time to resolution: 7 days (2-30)

** grading by Porter et al. (UPenn)*

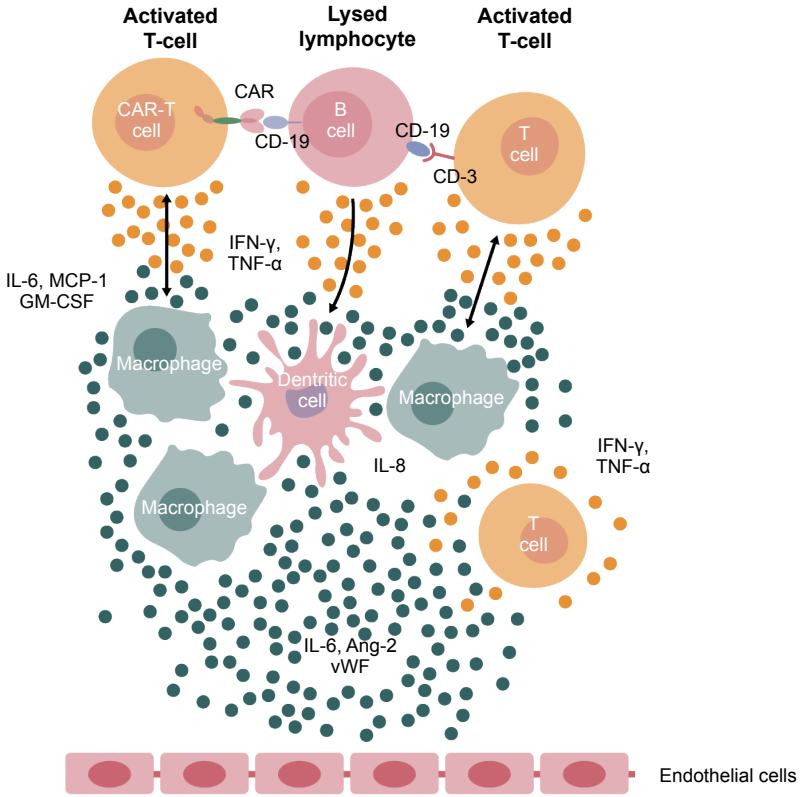
Mod. da Schuster SJ, et al. NEJM 2019; 380: 45-56; Locke FL, et al. Lancet Oncol 2019; 20: 31-42

CRS - Pathophysiology

Activated T cells, lysed B lymphocytes: IFN-γ, TNF-α
Macrophages: **IL-6**, TNF-α, IL-10, **IL-1**
Endothelial cells: Ang-2, vWF, **IL-6**

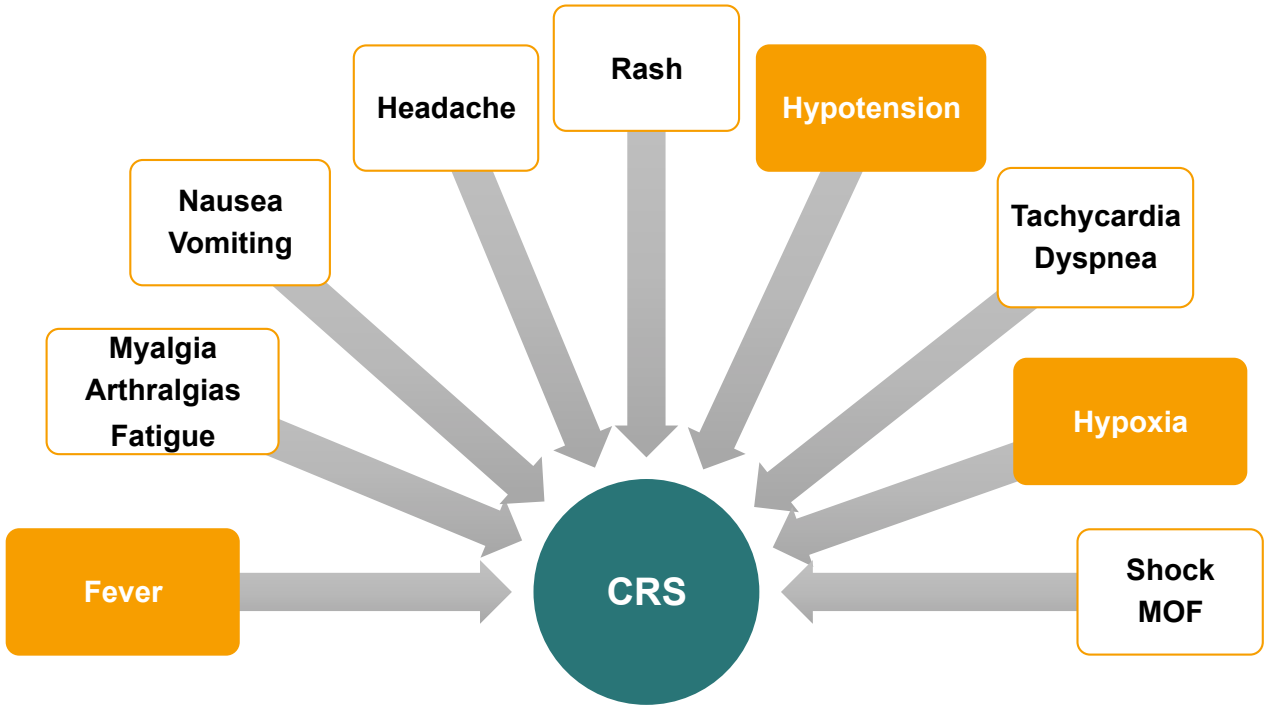
Early increase of IL-6 and angiopoietin2: angiopoietin1 ratio are associated with very severe CRS.

IL-6 has been implicated in key pathogenetic aspects of CRS like vascular leakage, CID, cardiomyopathy.



Mod. da Borrega JC. et al. Hemasphere 2019; 3: e191; Norelli M et al, Nat Med 2018; 24: 739-748; Faramand R, et al. Blood 2019; 132 (suppl_1): 95; Hunter CA, et al. Nat Immunol 2015; 16: 448-457

CRS – Clinical presentation



Blood test
Prolonged cytopenias
Coagulopathy
Electrolyte
Acute renal injury
Transaminitis
C-reactive protein
Ferritin elevations

Differential diagnosis:

- Sepsis: Severe CRS is associated with higher risk for infections (immune paralysis during CRS?)
- Hemophagocytic lymphohistiocytosis/macrophage activation syndrome
- TLS (can concur with CRS)

Mod. da Grupp SA, et al. NEJM 2013; 368: 1509-1518; Lee DW, et al. BBMT 2019; 25: 625-638

CRS grading and management

CRS grade 1	• temperature > 38°C • flu-like symptoms • nausea	• **infectious workup** • broad spectrum antibiotic • supportive measures (antipyretics)
CRS grade 2	• temperature > 38°C • hypotension not requiring vasopressors • hypoxia requiring low-flow nasal cannula or blow-by	• manage fever and symptoms as grade 1 • transfer to IMC/ICU • low dose vasopressor • tocilizumab 8 mg/kg i.v.
CRS grade 3	• temperature > 38°C • hypotension requiring one vasopressor with or without vasopressin • hypoxia requiring high-flow face mask	• manage fever and symptoms as grade 2 • repeat tocilizumab • low dose corticosteroids
CRS grade 4	• temperature > 38°C • hypoxia requiring positive airway pressure • hypotension requiring multiple vasopressors (excl. vasopressin)	• manage fever and symptoms as grade 2 • high dose corticosteroids • consider further individual treatment

- **The severity of CRS seems to be the only factor associated with infection.**
- **Patients with severe CRS present prolonged cytopenia and develop more frequent invasive mold infections.**

Mod. da Lee DW, et al. BBMT 2019; 25: 625-638

Immune mediated toxicities - ICANS

Immune effector cell-associated neurotoxicitity syndrome (ICANS)

ZUMA-1 AE, n (%)	2-year analysis (N: 108)
Grade ≥ 3 AEs	106 (98%)
Grade ≥ 3 SAEs	52 (48%)
Any grade NEs	65 (64%)
Grade ≥ 3 NEs**	35 (32%)

- Median time to onset: 5 days (1-17)
- Median time to resolution: 13 days (1-191)

*** grading by CTCAE ver 4.03*

JULIET AE, n (%)	2-year analysis (N: 111)
Grade ≥ 3 AEs	64 (58%)
Grade ≥ 3 SAEs	46 (41%)
Any grade NEs	23 (21%)
Grade ≥ 3 NEs**	13 (12%)

- Median time to onset: 6 days (1-17)
- Median time to resolution: 14 days

*** grading by CTCAE ver 4.03*

10% of patients experience CNS toxicity in the absence of CRS.
In the other 90% of patients CNS toxicity appears concurrent with CRS or following its resolution.

Mod. da Schuster SJ, et al. NEJM 2019; 380: 45-56; Locke FL, et al. Lancet Oncol 2019; 20: 31-42

ICANS - Pathophysiology

CAR-T cells, lysed B cells: IFN-γ, TNF-α

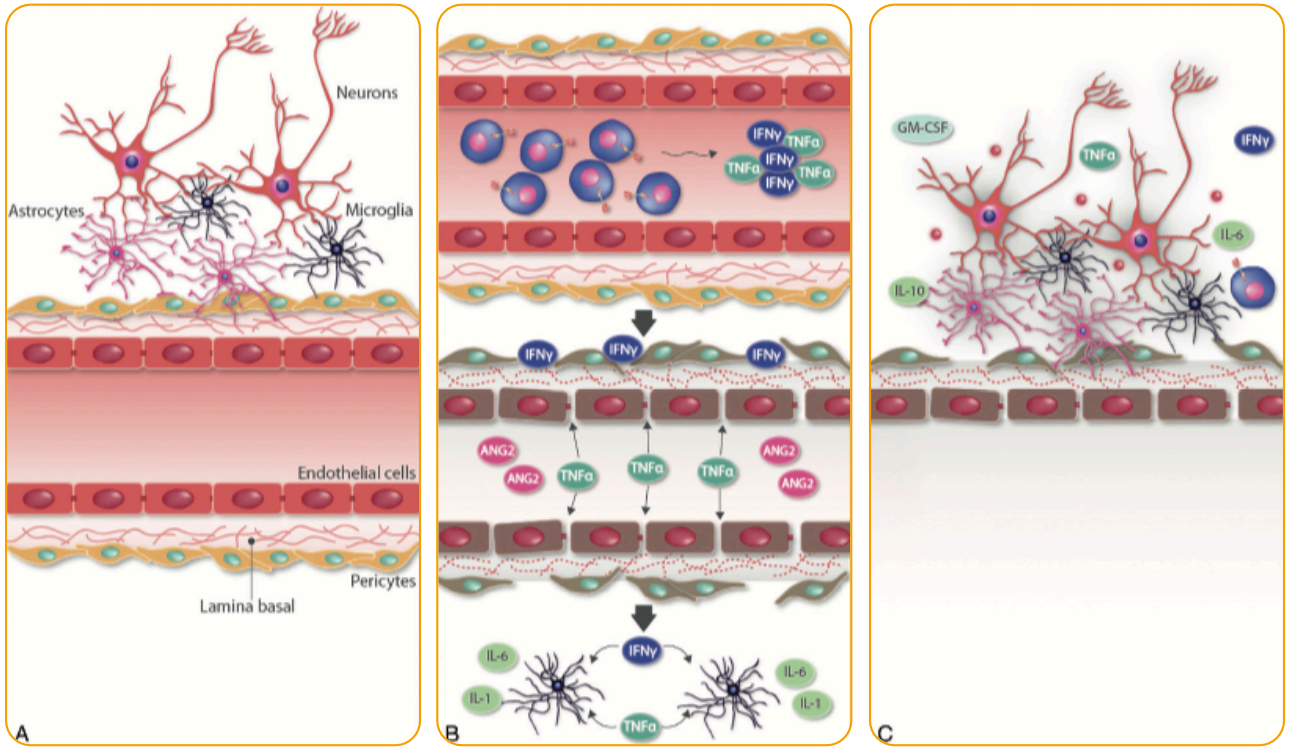
Macrophages: **IL-6**, TNF-α, IL-10, **IL-1**

Endothelial cells : Ang-2, vWF, **IL-6**

Disruption of BBB

Microglia activation

Intrathecal cytokines induce an inflammatory state and brain damage

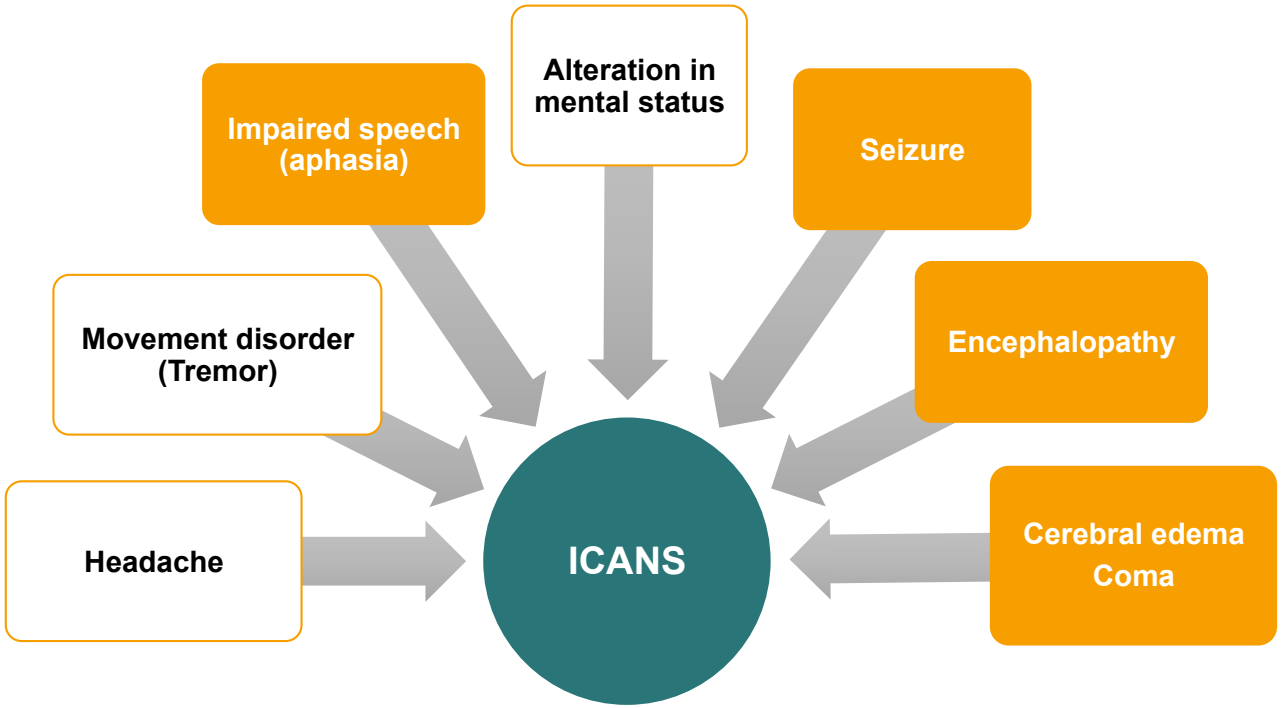


Mod. da Yañez L, et al. Hemasphere 2019; 3: e186; Gust J, et al. Cancer Discov 2017; 7: 1404-1419; Santomasso BD, et al. Cancer Discov 2018; 8: 958-971

ICANS – Clinical presentation

Risk factor for a severe ICANS:

- Severe CRS/systemic inflammation
- Tumour burden prior to CAR-T cell infusion
- Higher CAR-T cell doses
- Higher CAR-T cell peak expansion values
- Neurological comorbidities.



Mod. da Lee DW, et al. BBMT 2019; 25: 625-638

ICANS grading and management

ICANS grade 1	• awakens spontaneously • fatigue • ICE: 7-9 points	• supportive care • IV hydration • neurology consultation • EEG/MRI • consider antiepileptic drug
ICANS grade 2	• awakens to voice • delirius/somnolent • ICE: 3-6 points	• supportive care as grade 1 • consider ICU transfer • consider antiepileptic drug, if not started • low dose corticosteroids (i.e. dexamethasone 10 mg)
ICANS grade 3	• awakens to tactile stimulus • ICE: 0-2 points • local edema on imaging • seizure, that resolves with intervention	• supportive care as grade 2 • ICU trasfer • continous corticosteroids (i.e. dexamethasone 10 mg every 6 hours) and antiepileptic drugs • repeat MRI
ICANS grade 4	• comatose • ICE: 0 • cerebral edema • life-threatening (>5min) seizure • motor weakness	• supportive care as grade 3 • high dose corticosteroids specific neurointensive treatment (status epilecticus, brain edema) • consider further individual treatment

Mod. da Lee DW, et al. BBMT 2019; 25: 625-638

SCORE ICE: Immune Effector Cell-associated Encefaphalopathy

	Punteggio
Orientamento	Chiedere al paziente □ anno, □ mese, □ città e □ ospedale (totale 4 punti)
Denominazione	Chiedere al paziente di nominare 3 oggetti (es. □ penna, □ orologio □ bottone) (massimo 3 punti)
Compiti semplici su comando	Chiedere al paziente di eseguire compliti semplici (es. mostrare due dite o chiudere gli occhi □) (massimo 1 punto)
Scrittura	Chiedere al paziente di scrivere una frase semplice □ (massimo 1 punto)
Attenzione	Chiedere al paziente di contare all'indietro (es. partendo da 100 □) (massimo 1 punto)
Totale	……./10

ICANS + CRS - Management

Grado	Terapia di supporto	Tocilizumab	Steroidi	Follow-up
CRS grado 1				
+ ICANS grado 1	Standard of care	NO	NO	Stretta osservazione (vedi rispettive tabelle)
+ ICANS grado ≥2 (è il grado ICANS che guida la gestione della tossicità)	Trasferimento in ICU	NO	Si Desametasone 10 mg ev x 4 volte/die	Se migliora fino a tornare ICANS grado 1: tapering dello steroide in 3-4 giorni Se non migliora: prosegui steroide e supporto intensivo
CRS grado ≥ 2				
+ ICANS grado 1	Trasferimento in ICU se CRS grado 3-4, considera se grado 2	Si tratta solo la CRS a seconda del grading (vedi tabella sulla gestione della CRS)		
+ ICANS grado 2	Trasferimento in ICU			
+ ICANS grado 3	Trasferimento in ICU	Si tratta la CRS come da tabella 2 ma si inizia sempre metilprednisolone 1 mg/kg x 2 volte/die, anche se CRS grado 2		
+ ICANS grado 4	Trasferimento in ICU			

Cytopenia and hypogammaglobulinemia

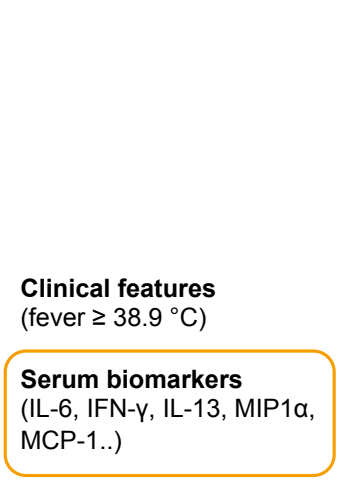
Cytopenia:

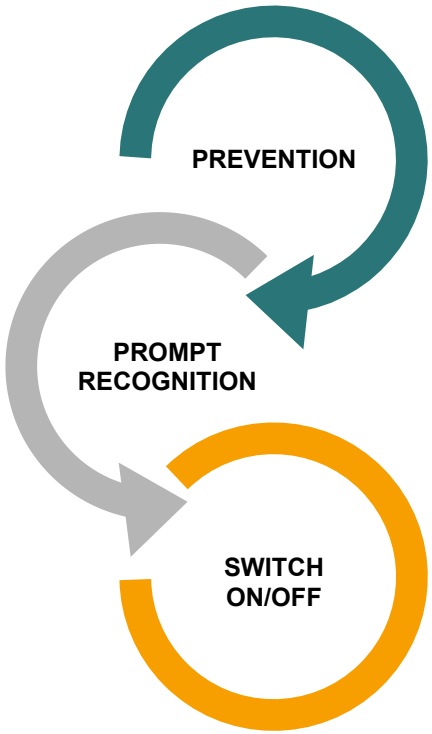
- Most common AE of grade ≥3
- Related to conditioning regimen, cytokine released during CRS, exposure to multiple prior chemotherapy treatment.
- Neutropenia is the most common cytopenia
  - 78% of patients in ZUMA-1 and 64% patients in JULIET trial developed PMN <1000/mm^3
  - GCSF is not recommended during the first 3 weeks after CAR-T cell infusion or until CRS has resolved
- Severe thrombocytopenia was seen in 38% of patients in ZUMA-1 and 11% of patients in JULIET trial

Hypogammaglobulinemia:

- Secondary to the persistence of CAR-T and subsequent development of B-cell aplasia
- Incidence: 15% of patients with DLBCL
- IgG levels usually fall 1 to 3 months after CAR-T infusion
- The presence of hypogamma is associated with the achievement of a complete response
- Replacement treatment is reserved to those patients with severe or recurrent infections

Conclusion - Strategies to mitigate toxicities





Prevention of CRS and neurotoxicity

- Risk adapted therapy
- Cytokine release prophylaxis

Prevention of "on-target/off tumor effect"

- Selective antigens (κ and γ light chain)
- Deleting the target antigen on normal HSC
- Optimizing the CAR (dual and affinity-tuned CAR)

Diminishing the activity of the CAR

- Suicide genes
- Destruction of the CAR-T cell by mAb
- Switch on/off CAR

Risk of CRS and ICANS is mainly related to: disease burden, CAR-T cell construct and dose infused, recipient factors

Conclusion – CAR-T cell team