



UZ  
LEUVEN

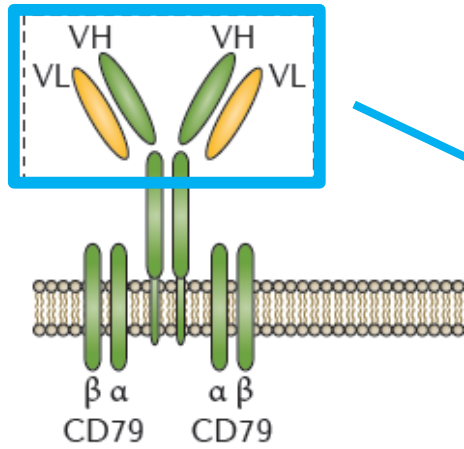


## CAR T vs bispecifics: how to manage toxicity and sequencing: Experience in lymphoma

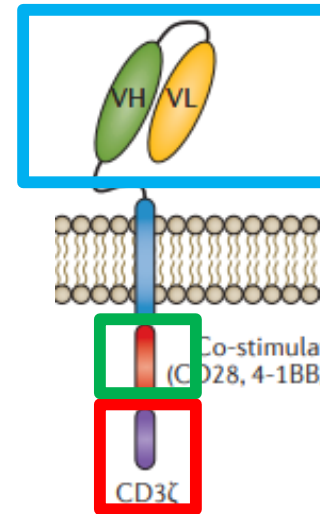
Peter Vandenberghe  
Head, Hematology department

# The Chimeric Antigen Receptor

BCR

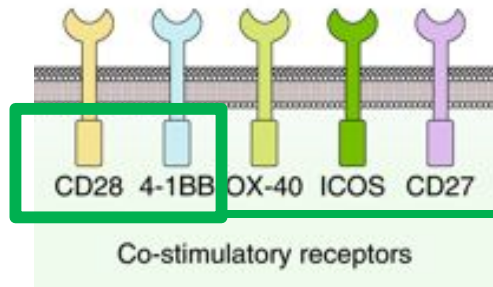


2nd generation CAR

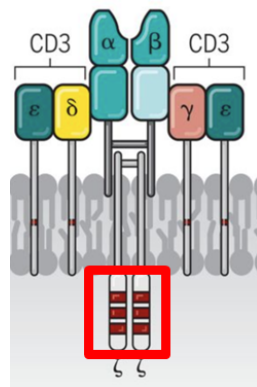


Anti-CD19: pan-B: DLBCL, B-ALL, MCL  
 Anti-BCMA / anti- GPRC5D:  
 multiple myeloma

Costimul  
 receptor  
 on T-cells



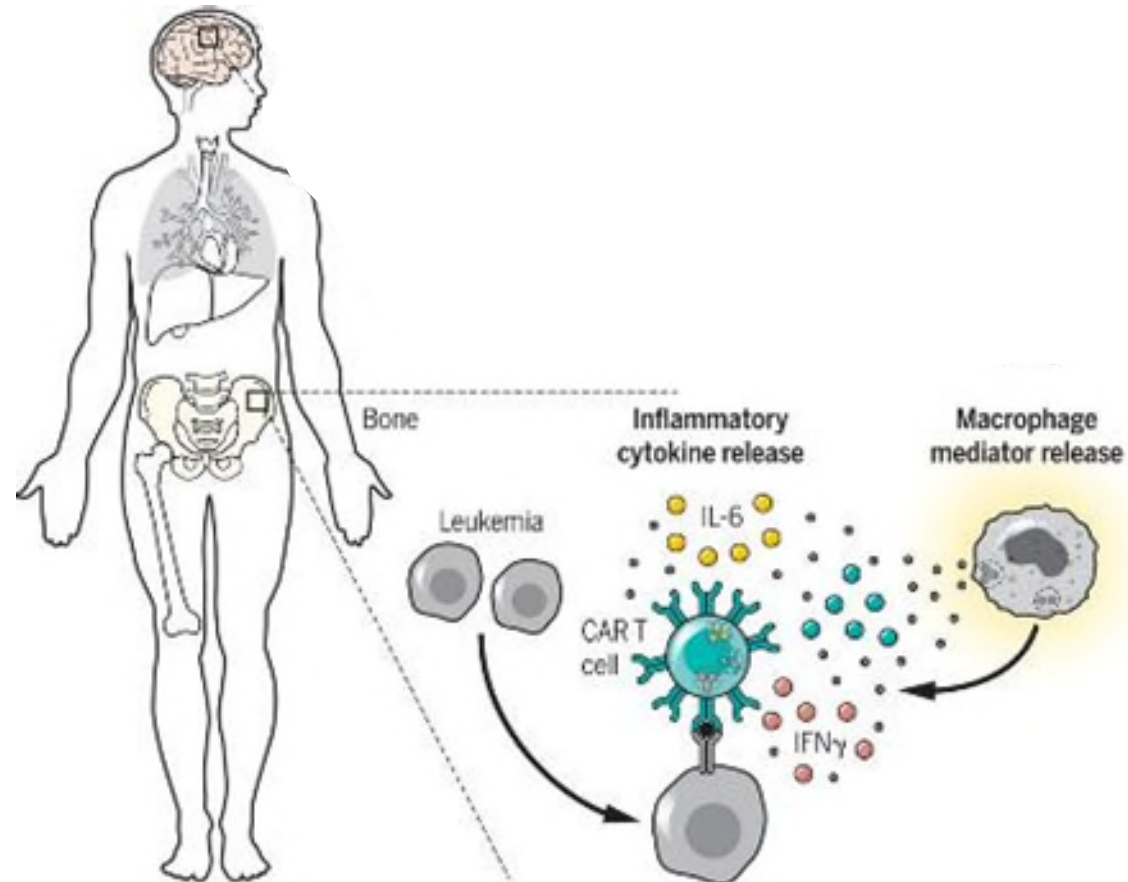
Co-stimulatory receptors



Adapted from Batlevi CL et al. Nature Reviews Clinical Oncology 2016; 13; 25-40,  
 Labanieh L et al. Nature Biomedical engineering. 2018;2; 377-391; June CH, et al.  
 Science. 2018;359(6382):1361-1365.

ALL, acute lymphocytic leukemia; BCMA, B cell maturation antigen; BCR, B cell receptor; CAR, chimeric antigen receptor; CD, cluster of differentiation; DLBCL, diffuse large B cell lymphoma; GPRC5D, G protein-coupled receptor class c group 5 member d; MCL, mantle cell lymphoma.

# Recognition of target antigen by the CAR induces T-cell activation, expansion and cell-mediated cytotoxicity



CRS, cytokine release syndrome; ICANS, immune cell-associated neurotoxicity syndrome; IEC-HLH, immune effector cell-associated hemophagocytic lymphohistiocytosis.

Adapted from June CH, et al. Science. 2018;359(6382):1361-1365.

## Pivotal CAR-T studies in R/R aggressive B-NHL >2L

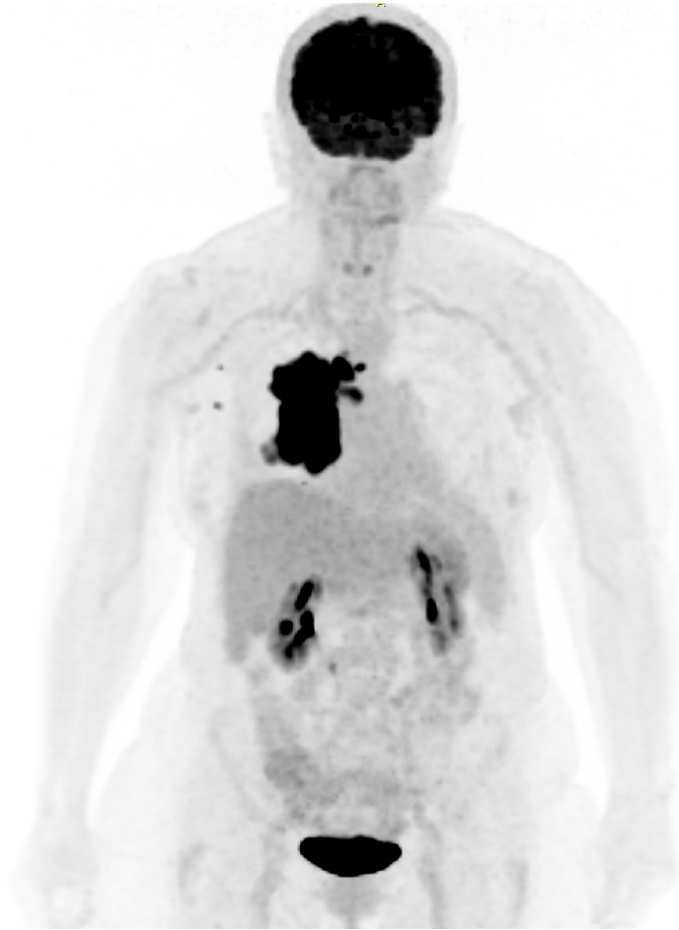
Study	NHL subtypes	N	Best ORR (%)	Best CR (%)	PFS 1y (%)	Median PFS (mo)	OS 1y (%)	Median OS (mo)
ZUMA1 <sup>1</sup> Axicabtagene ciloleucel (Axicel), Kite/Gilead	DLBCL / HGBCL / PMBCL / tFL	108	83	58	44	5,9	~60	NR
JULIET <sup>2</sup> Tisagenlecleucel (Tisacel), (Novartis)	DLBCL / HGBCL / tFL	111	52	40	~33	2,9	49	12
TRANSCEND NHL 001 <sup>3</sup> Lisocabtagen maraleucel (Lisocel), Juno/BMS	DLBCL / HGBCL / PMBCL / tFL / tiNHL / FL 3b	344	74	54	44	6,8	58	21,1

Cross trial comparisons cannot be inferred.

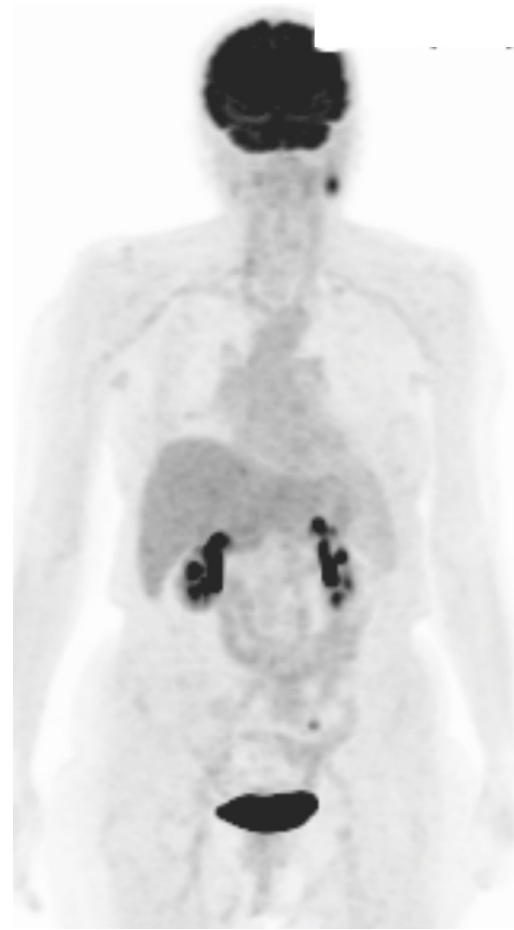
2L, second line; CAR; chimeric antigen receptor; CR, complete response; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; HGBCL, high-grade B cell lymphoma; mo, months; NHL, non-Hodgkin's lymphoma; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PMBCL, primary mediastinal large B-cell lymphoma; R/R, relapsed/refractory; tFL, testicular follicular lymphoma; y, year.

1. Neelapu SS et al, N Engl J Med. 2017; 377: 2531-2544; 2. Schuster S et al, N Engl J Med. 2019; 380: 45-56; 3. Abramson JS et al, Lancet 2020; 396: 839-8520.

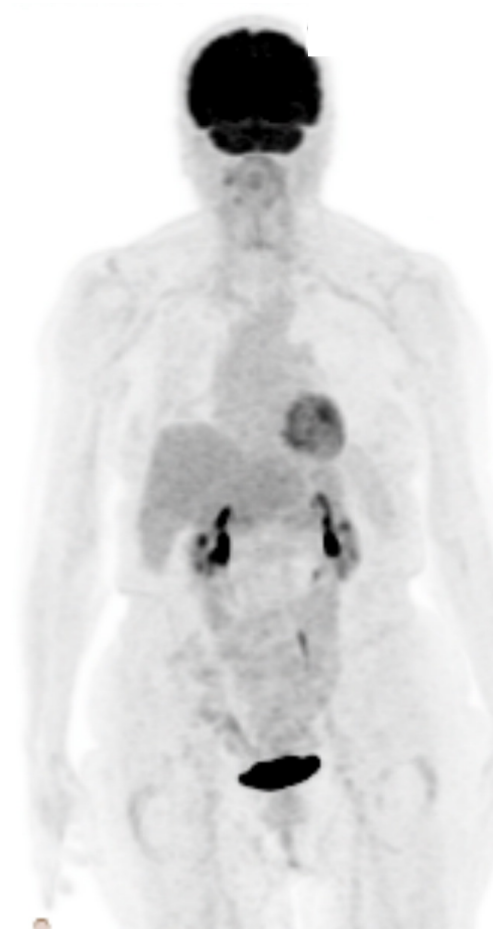
# DLBCL



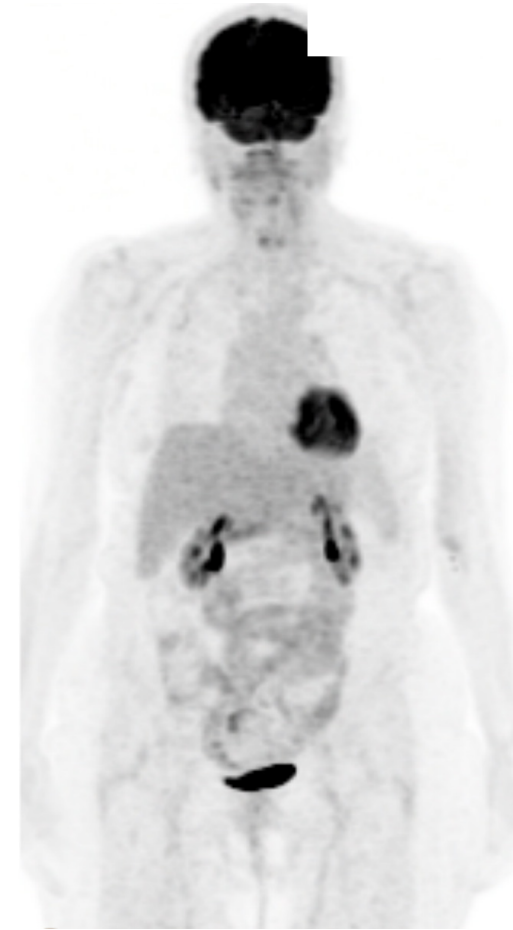
D -6



D 30



D 90

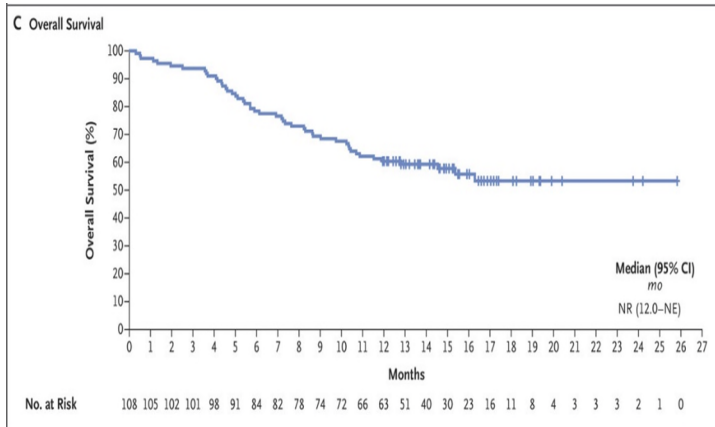


D 180  
Cured !

# Pivotal CAR-T studies in R/R aggressive B-NHL >2L

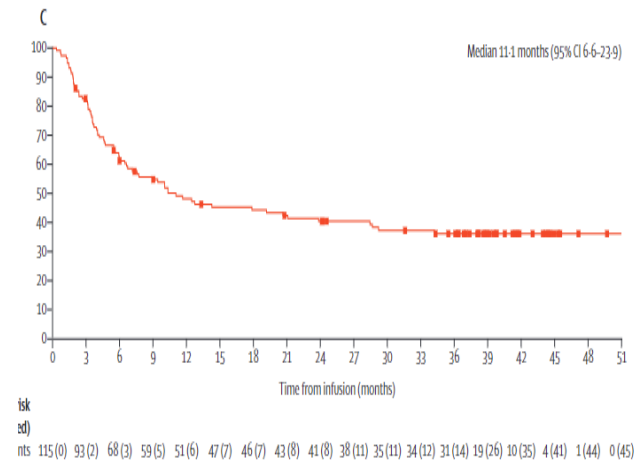
## Overall survival

ZUMA-1: axicel<sup>1,2</sup>



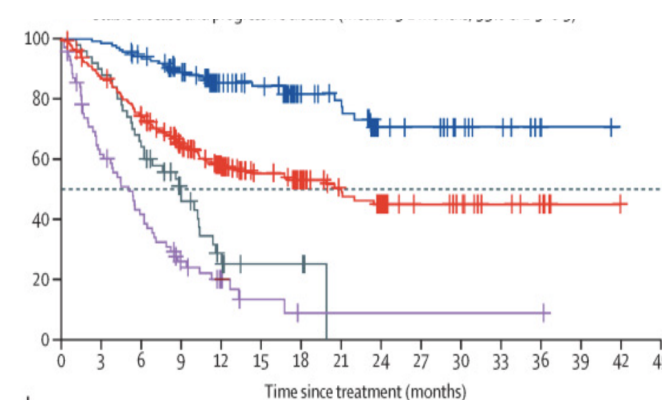
Median follow-up: 27,1 mo (from infusion)  
ORR 82%  
CR 54%  
Severe CRS 13%  
Severe ICANS 28%  
Median OS at 2y not reached

JULIET: tisacel<sup>3,4</sup>



Median follow-up 40,3 mo (from infusion)  
ORR 53%  
CR 39%  
Severe CRS 23%  
Severe ICANS 12%  
Median OS 11,1 months

TRANSCEND NHL 001: lisocel<sup>5</sup>



Median follow-up 17 mo (from infusion)  
ORR 73%  
CR 39%  
Severe CRS 2%  
Severe ICANS 9%  
Median OS 21 months

Cross trial comparisons cannot be inferred.

2L, second line; CAR; chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; ICANS, immune cell-associated neurotoxicity syndrome; mo, months; NHL, non-Hodgkin's lymphoma; ORR, overall response rate; OS, overall survival; R/R, relapsed/refractory; y, year.

1. Neelapu SS et al. N Engl J Med 2017;377:2531-2544. 2. Locke FL, et al. Lancet Oncol. 2019;20(1):31-42. 3. Schuster SJ, et al. N Engl J Med. 2019;380(1):45-56. 4. Schuster SJ, et al. Lancet Oncol. 2021 Oct;22(10):1403-1415. 5. Abramson JS, et al. Lancet. 2020 Sep 19;396(10254):839-852.



UZ  
LEUVEN



# Eligible B-NHL entities > 2L (Belgium)

WHO 2016	Tisacel	Axicef
<b>Diffuse large B-cell lymphoma NOS</b>	Green	Green
<b>Other lymphomas of large B-cells</b>		
T-cell/histiocyte-rich large B-cell lymphoma		
Primary diffuse large B-cell lymphoma of the CNS		
Primary cutaneous diffuse large B-cell lymphoma leg type		
EBV-positive diffuse large B cell lymphoma, NOS	Green	Green
Diffuse large B-cell lymphoma associated with chronic inflammation	Green	Green
Lymphomatoide granulomatosis		
Large B-cell lymphoma with IRF4 rearrangement		
Primary mediastinal (thymic) large B-cell lymphoma	Red X	Green
Intravascular large B-cell lymphoma		
ALK-positive large B-cell lymphoma		
Plasmablastic lymphoma		
HHV-8 positive diffuse large B-cell lymphoma	Green	Green
Primary effusion lymphoma		
High grade B-cell lymphoma with <i>MYC</i> and <i>BCL2</i> and/or <i>BCL6</i> rearrangements	Red	Green
High grade B-cell lymphoma NOS	Red	Green
<b>B-cell lymphoma, unclassifiable with features intermediate between DLBCL and classic Hodgkin lymphoma</b>		

2L, second line; ALK, anaplastic lymphoma kinase; BCL, B cell lymphoma; CNS, central nervous system; HHV, human herpes virus; IRF4, interferon regulatory factor 4; MYC, myelocytomatosis oncogene; NHL, non-Hodgkin's lymphoma; NOS, not otherwise specified; WHO, World Health Organization.

Leticia Quintanilla-Martinez. *Hematological Oncology*. 2017;35(S1):37-45 ; [www.riziv.fgov.be](http://www.riziv.fgov.be)



UZ  
LEUVEN



# CAR-T studies vs. SOC in R/R aggressive B-NHL in 2L

Study	NHL subtypes	N (Exp arm vs. SOC)	Bridging	Primary endpoint	
ZUMA-7 <sup>1,2</sup> Axicabtagene ciloleucel	DLBCL NOS/ HGBCL/ tFL	170 vs 168	Corticosteroids only	EFS	✓
BELINDA <sup>3</sup> Tisagenlecleucel	DLBCL NOS / HGBCL/ PMBCL/ FL3b	162 vs 160	Chemotherapy	PFS	✗
TRANSFORM study <sup>4</sup> Lisocabtagen maraleucel	DLBCL NOS/ HGBCL/ tiNHL/ PMBCL / FL 3b	92 vs 91	Chemotherapy	EFS	✓

2L, second line; CAR; chimeric antigen receptor; DLBCL, diffuse large B cell lymphoma; EFS, event-free survival; Exp, experimental; FL, follicular lymphoma; HGBCL, high-grade B cell lymphoma; NHL, non-Hodgkin's lymphoma; NOS, not otherwise specified; PFS, progression-free survival; PMBCL, primary mediastinal large B-cell lymphoma; R/R, relapsed/refractory; SOC, standard of care; tFL, testicular follicular lymphoma.

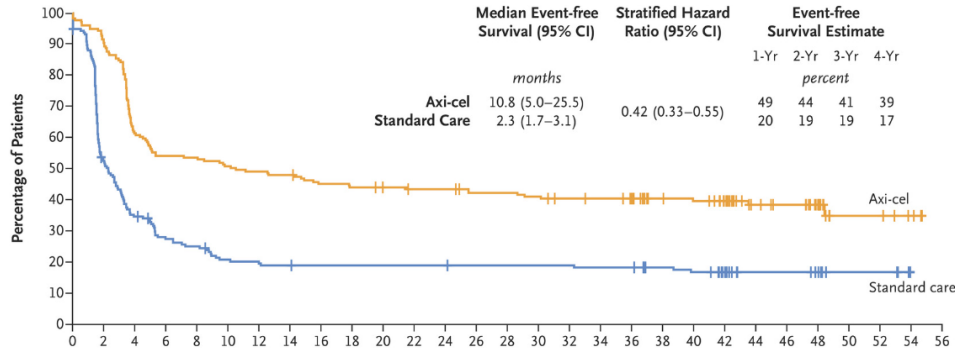
1. Locke FL, et al. N Engl J Med. 2022 386:640-654. 2. Westin JR, et al. N Engl J Med. 2023 389:148-157. 3. Bishop MR, et al. N Engl J Med 2022; 386:629-639. 4. Abramson JS, et al. Blood. 2023 141:1675-1684.



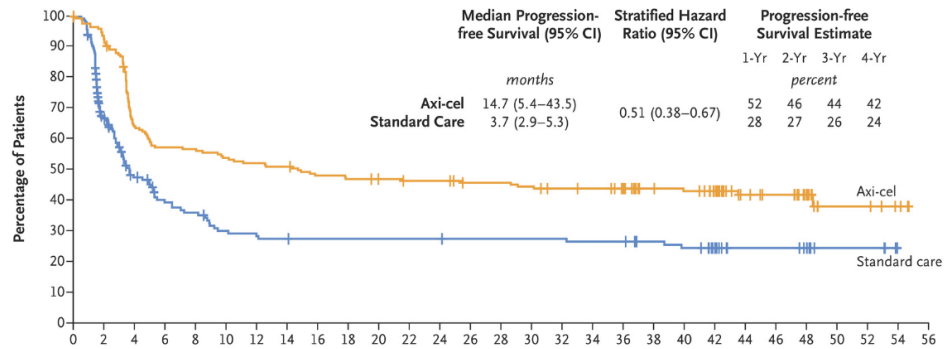
# CAR-T studies vs SOC in R/R aggressive B-NHL in 2L

Axi-cel<sup>1</sup>

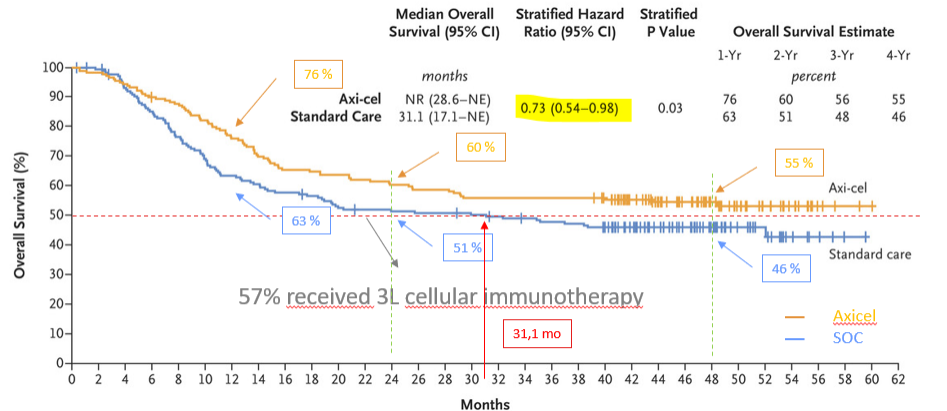
EFS



PFS

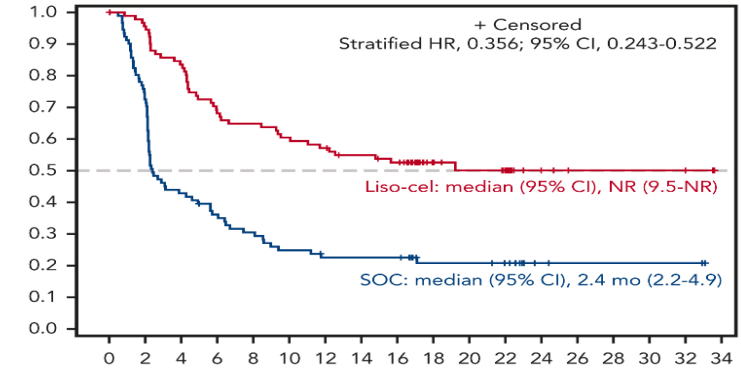


OS

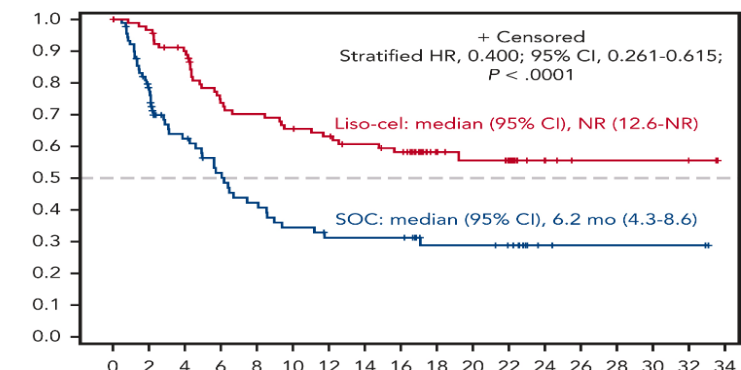


Liso-cel<sup>2</sup>

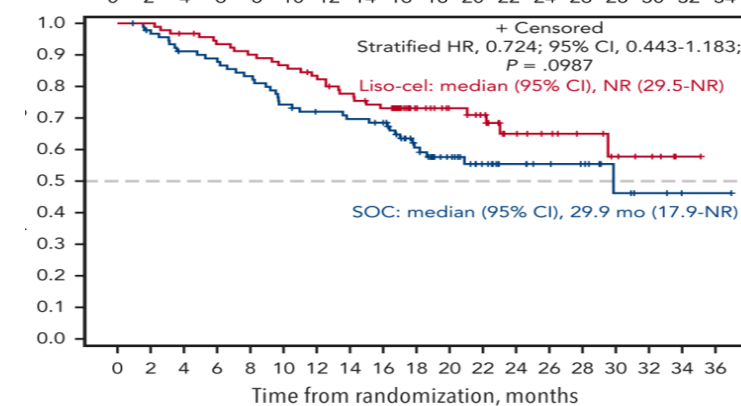
EFS



PFS



OS



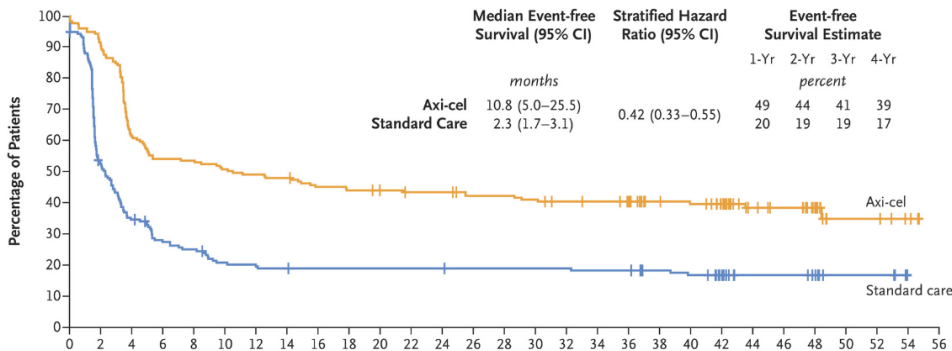
Cross trial comparisons cannot be inferred.

2L, second line; CAR, chimeric antigen receptor; EFS, event-free survival; NHL, non-Hodgkin's lymphoma; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; SoC, standard of care. 1. Westin JR, et al. N Engl J Med. 2023 389:148-157. 2. Abramson JS, et al. Blood. 2023 141:1675-1684.

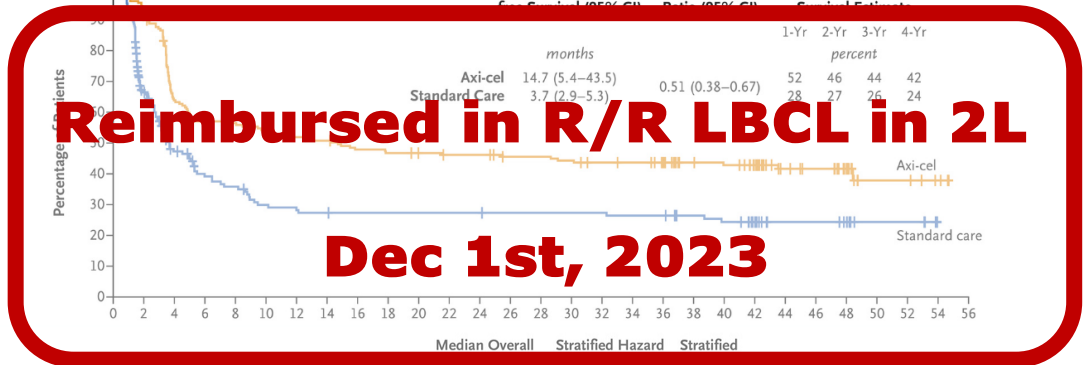
# CAR-T studies vs SOC in R/R aggressive B-NHL in 2L

Axi-cel<sup>1</sup>

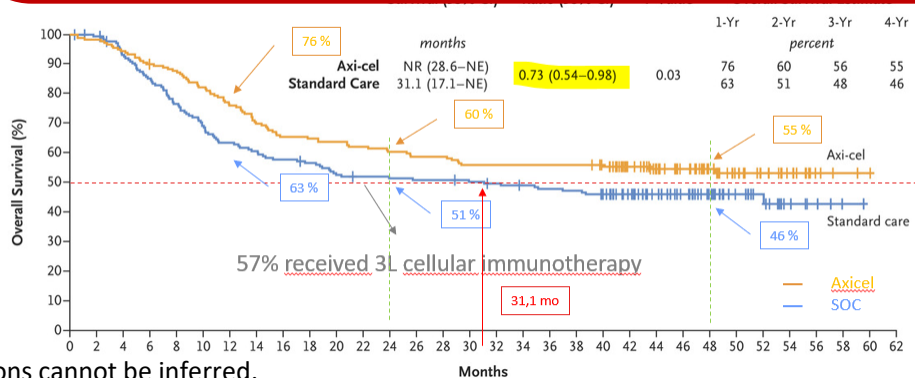
EFS



PFS

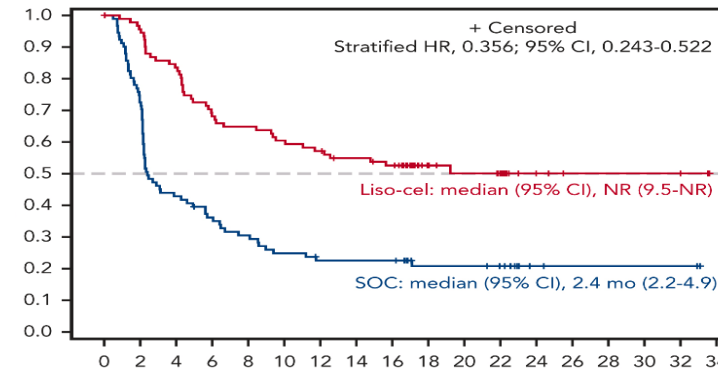


OS

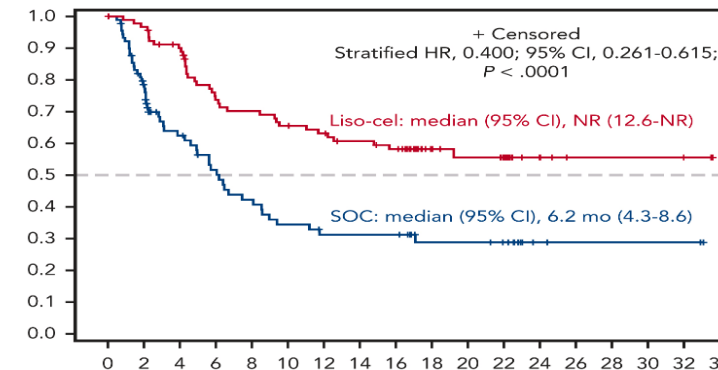


Liso-cel<sup>2</sup>

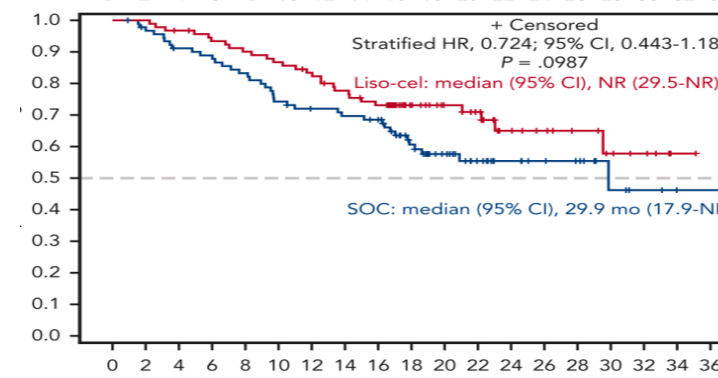
EFS



PFS



OS



Cross trial comparisons cannot be inferred.

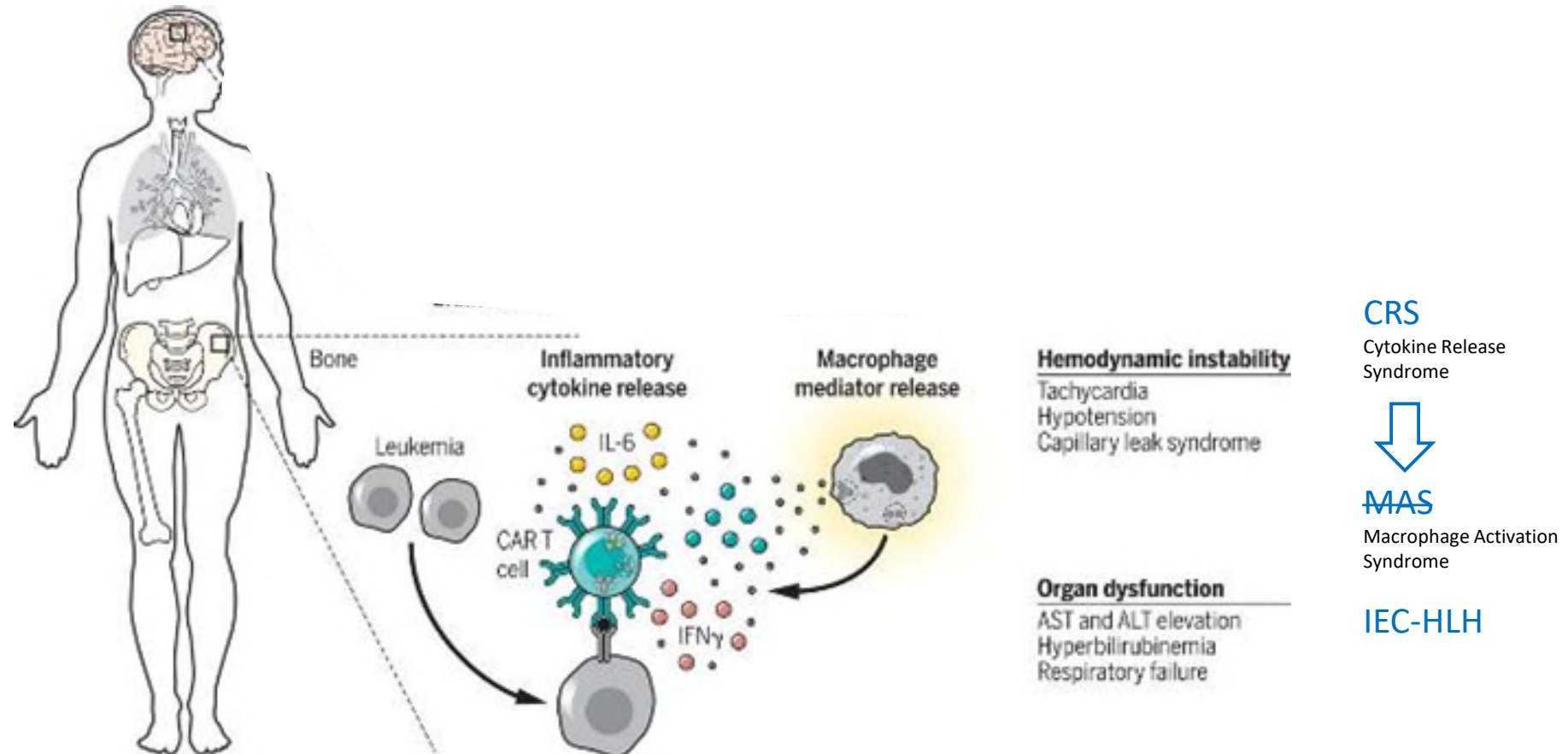
2L, second line; CAR, chimeric antigen receptor; EFS, event-free survival; LBCL, large B cell lymphoma; NHL, non-Hodgkin's lymphoma; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; SoC, standard of care. 1. Westin JR, et al. N Engl J Med. 2023 389:148-157. 2. Abramson JS, et al. Blood. 2023 141:1675-1684.



# CAR T-cells vs bispecific T-cell engagers

- One-time therapy versus therapy until progression
- How to sequence? Very limited data
- Today in Belgium: tafasitamab (CD19/CD3)  $\geq$  2L
  - Not eligible for autologous stem cell transplantation (ASCT) and not eligible for CD19-directed CAR-T cell therapy
  - Patients... previously treated with CD19-directed therapies... including... CD19-directed CAR-T cell therapy... are excluded
- Others
  - Glofitamab (CD20/CD3) (Dickinson MJ, et al. N Engl J Med. 2022 387:2220-2231)
  - Epcoritamab (CD20/CD3) (Hutchings M, et al. Lancet. 2021 398:1157-1169)

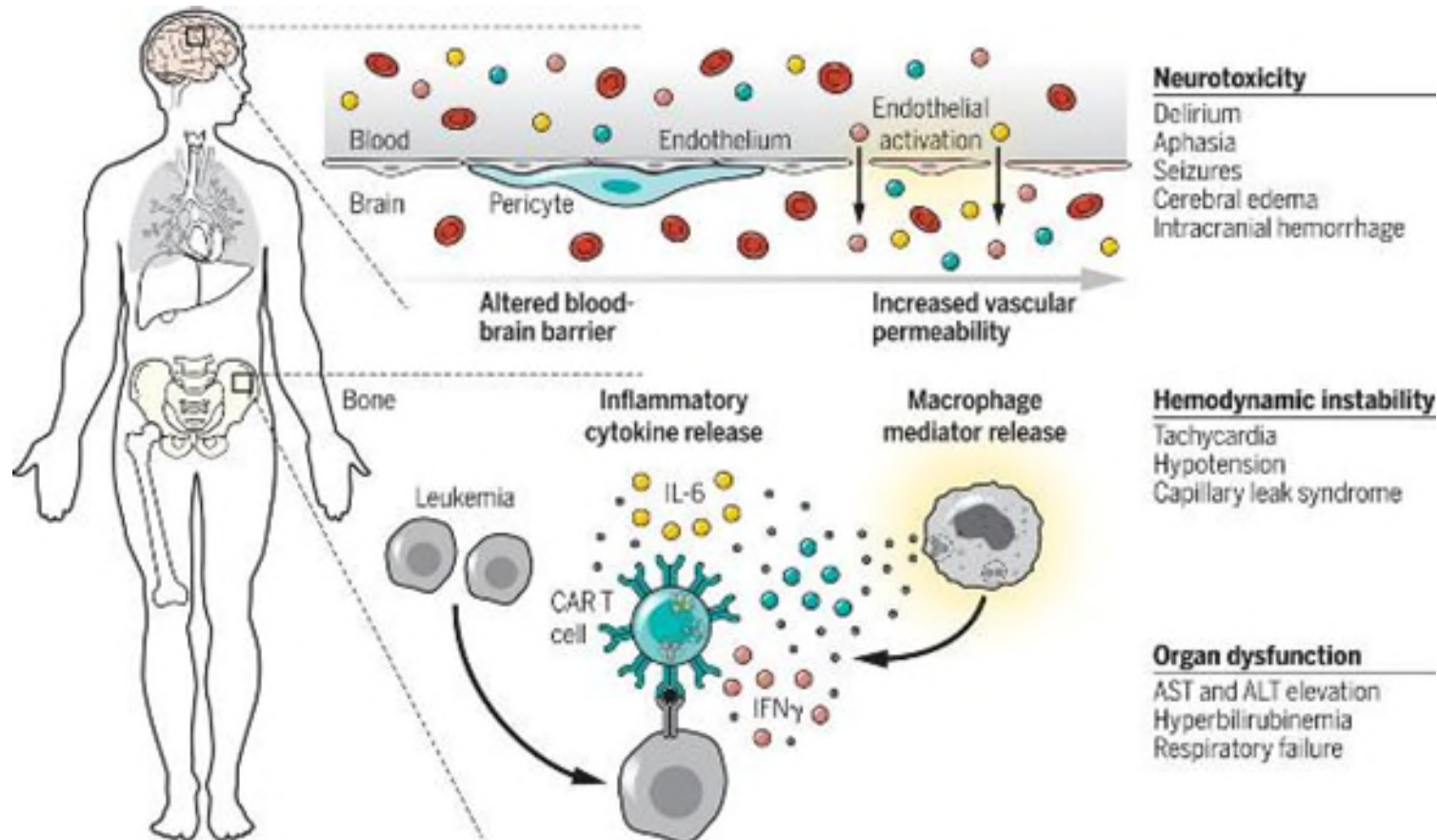
# CAR T-cell toxicities of special interest



CRS, cytokine release syndrome; ICANS, immune cell-associated neurotoxicity syndrome; IEC-HLH, immune effector cell-associated hemophagocytic lymphohistiocytosis.

Adapted from June CH, et al. Science. 2018;359(6382):1361-1365.

# CAR T-cell toxicities of special interest



## CRS

Cytokine Related Encephalopathy Syndrome

## ICANS

Immune Cell Associated Neurotoxicity Syndrome

## CRS

Cytokine Release Syndrome



## MAS

Macrophage Activation Syndrome

## IEC-HLH

CRS, cytokine release syndrome; ICANS, immune cell-associated neurotoxicity syndrome; IEC-HLH, immune effector cell-associated hemophagocytic lymphohistiocytosis.  
Adapted from June CH, et al. Science. 2018;359(6382):1361-1365.



UZ  
LEUVEN



## Pivotal CAR-T studies in R/R aggressive B-NHL: toxicity and safety issues

Beyond 2L	Axicel <sup>1</sup> n=108	Tisacel <sup>2</sup> n=111	Lisocel <sup>3</sup> n=344
Cytokine release syndrome all grades/ <b>grade 3-4</b> (%)	93/ <b>13</b>	58/ <b>22</b>	42/ <b>2</b>
Neurotoxicity all grades/ <b>grade 3-4</b> (%)	64/ <b>28</b>	21/ <b>12</b>	12/ <b>10</b>

As 2L therapy	Axicel <sup>4</sup> n=170	Tisacel <sup>5</sup> n=162	Lisocel <sup>3</sup> n=92
Cytokine release syndrome all grades/ <b>grade 3-4</b> (%)	92/ <b>6</b>	61/ <b>5</b>	49/ <b>1</b>
Neurotoxicity all grades/ <b>grade 3-4</b> (%)	60/ <b>21</b>	10/ <b>2</b>	11/ <b>4</b>

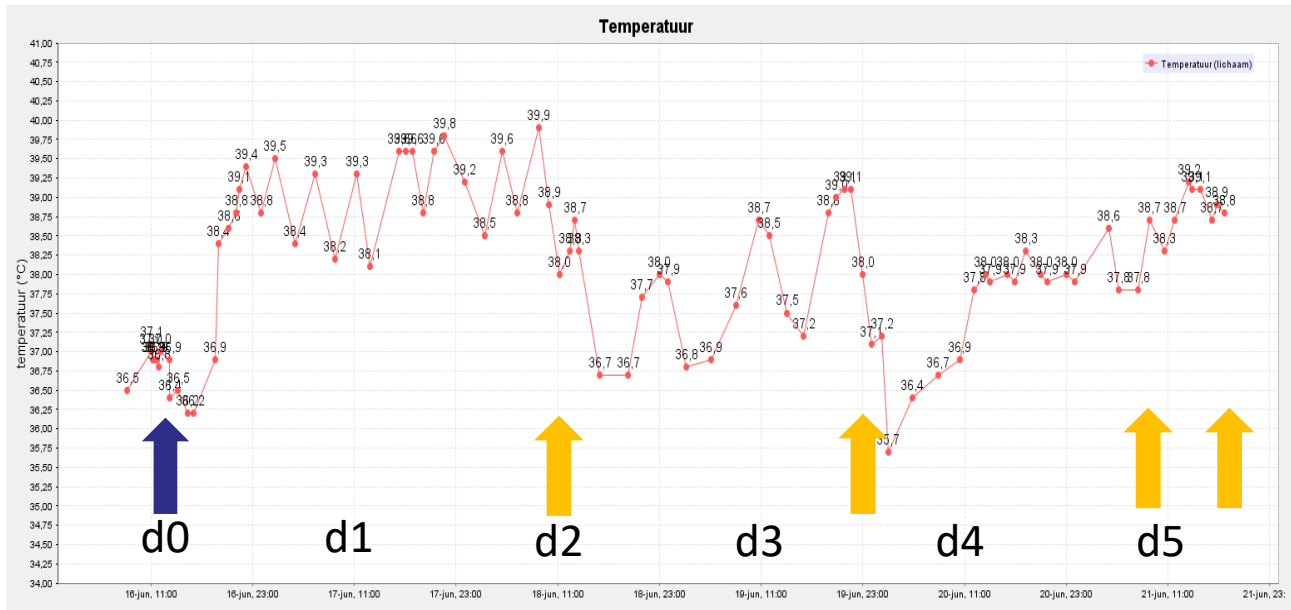
2L, second line; CAR; chimeric antigen receptor; NHL, non-Hodgkin's lymphoma; R/R, relapsed/refractory; SOC, standard of care.

1. Neelapu SS et al, N Engl J Med. 2017; 377: 2531-2544. 2. Schuster S et al, N Engl J Med. 2019; 380: 45-56. 3. Abramson JS et al, Lancet 2020; 396: 839-8520. 4. Locke FL, et al. N Engl J Med. 2022 386:640-654. 5. Bishop MR, et al. N Engl J Med 2022; 386:629-639.

# A complicated course

Male, 25y

B-ALL in second relapse after MUD Tx



Kymriah  
(CAR-T)

Tocilizumab  
Anti-IL6-R

Toci

Toci

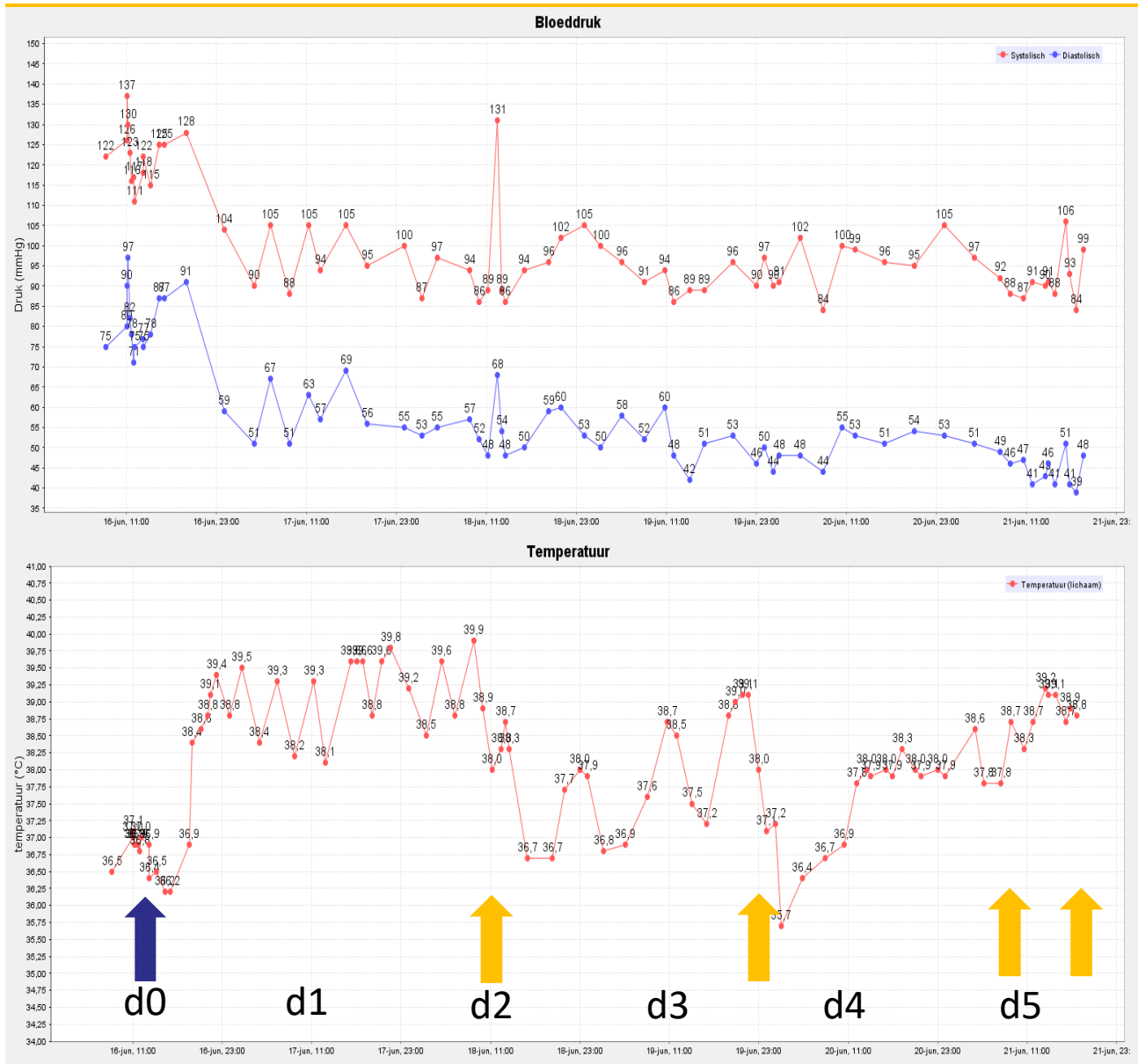
Toci

CRS gr 1

CRS gr 2

3

ALL, acute lymphocytic leukemia; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; d, day; IL, interleukin; MUD, matched unrelated donor; toci, tocilizumab; Tx, treatment; y, year. Case courtesy of Prof Vandenberghe.



# A complicated course

Male, 25y

B-ALL in second relapse after MUD Tx

Kymriah  
(CAR-T)

Tocilizumab  
Anti-IL6-R

Toci

Toci

Toci

CRS gr 1

CRS gr 2

3

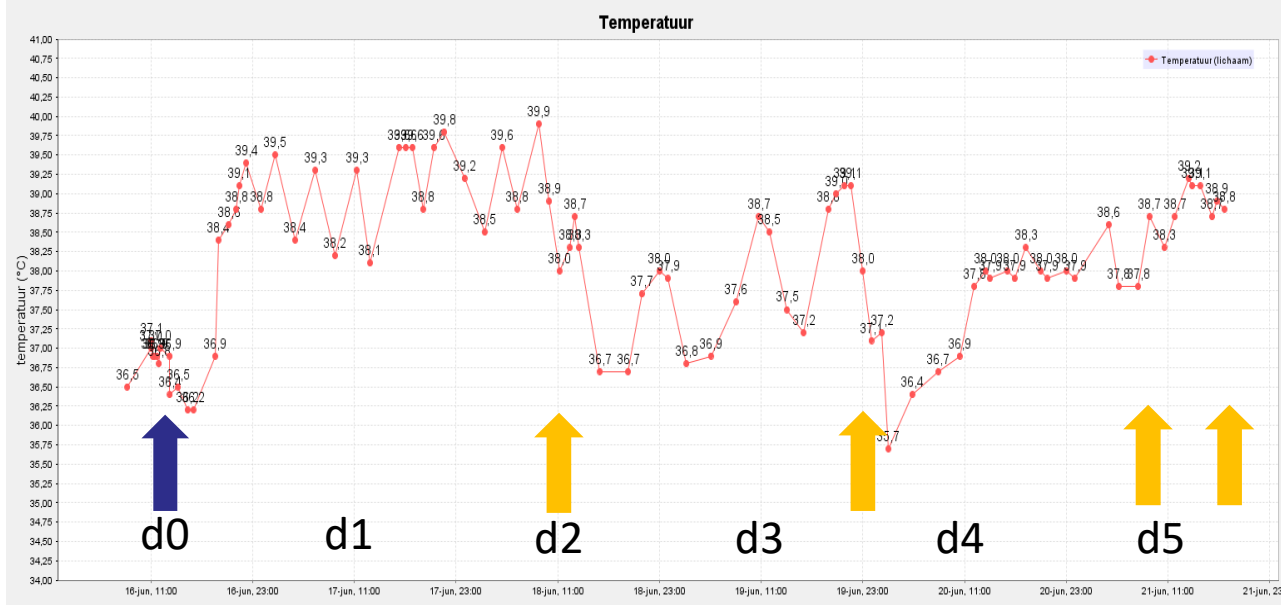
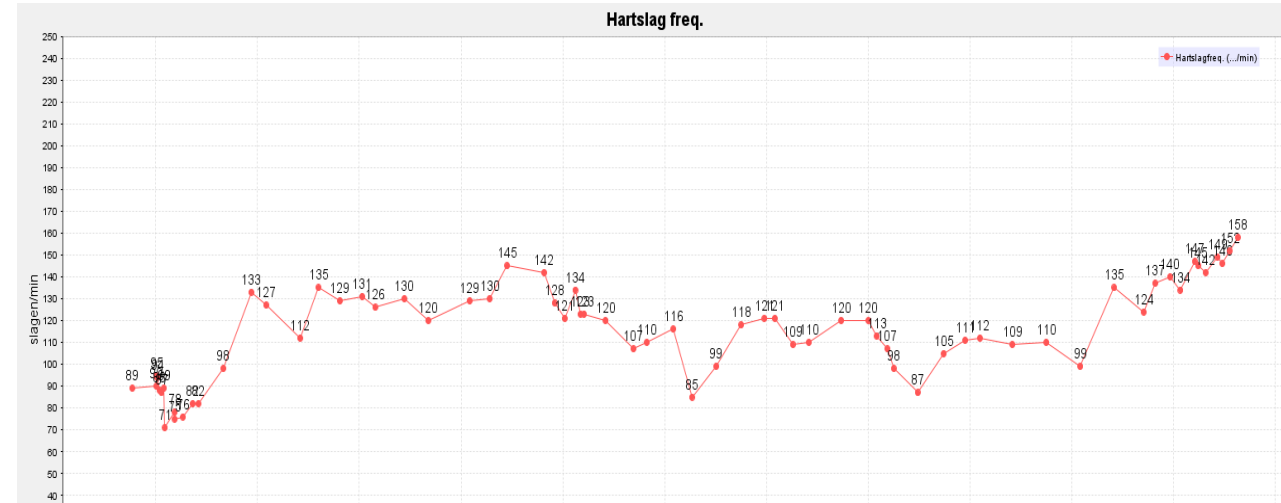
ALL, acute lymphocytic leukemia; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; d, day; IL, interleukin; MUD, matched unrelated donor; toci, tocilizumab; Tx, treatment; y, year. Case courtesy of Prof Vandenberghe.



# A complicated course

Male, 25y

B-ALL in second relapse after MUD Tx



Kymriah (CAR-T)

Tocilizumab Anti-IL6-R

Toci

Toci

Toci

CRS gr 1

CRS gr 2

3

ALL, acute lymphocytic leukemia; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; d, day; IL, interleukin; MUD, matched unrelated donor; toci, tocilizumab; Tx, treatment; y, year. Case courtesy of Prof Vandenberghe.

# A complicated course

D5

- urgent transfer to Medical Intensive Care in CRS grade 3
- precipitous evolution to grade 4 with multiple organ failure/MAS
  - respiratory failure
  - distributive shock
  - capillary leak
  - type 2 NSTEMI
  - acute kidney injury
  - rhabdomyolysis
  - MAS
  - presumed ICANS

D48 discharged from hospital

Now > d730 after CAR T: continuing remission, chronic kidney failure, hypogammaglobulinemia, resumed work

# Immune cell-associated neurotoxicity syndrome (ICANS)

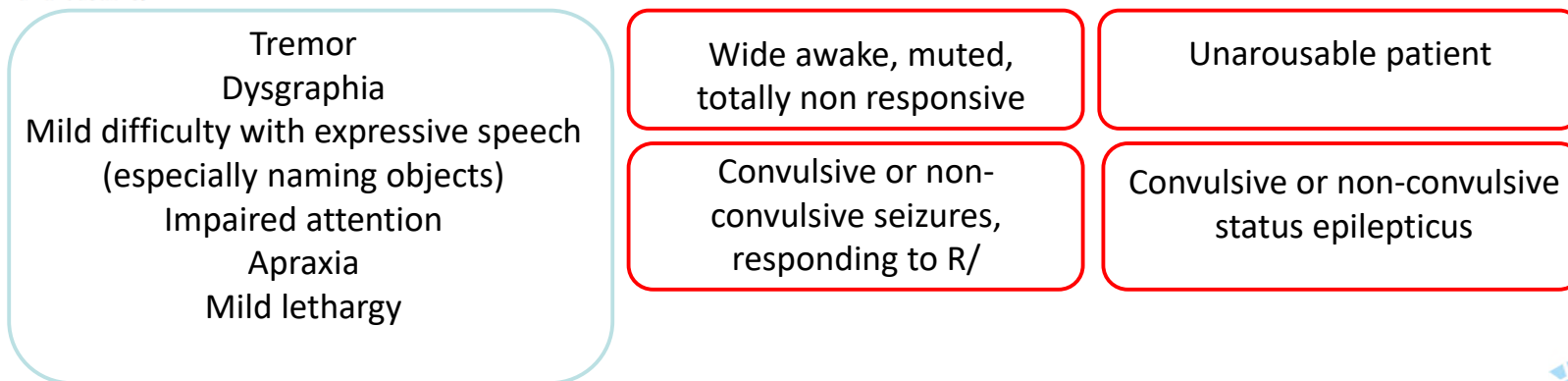
**Table 6**  
ASTCT ICANS Consensus Grading for Adults

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 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
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

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

N/A indicates not applicable.

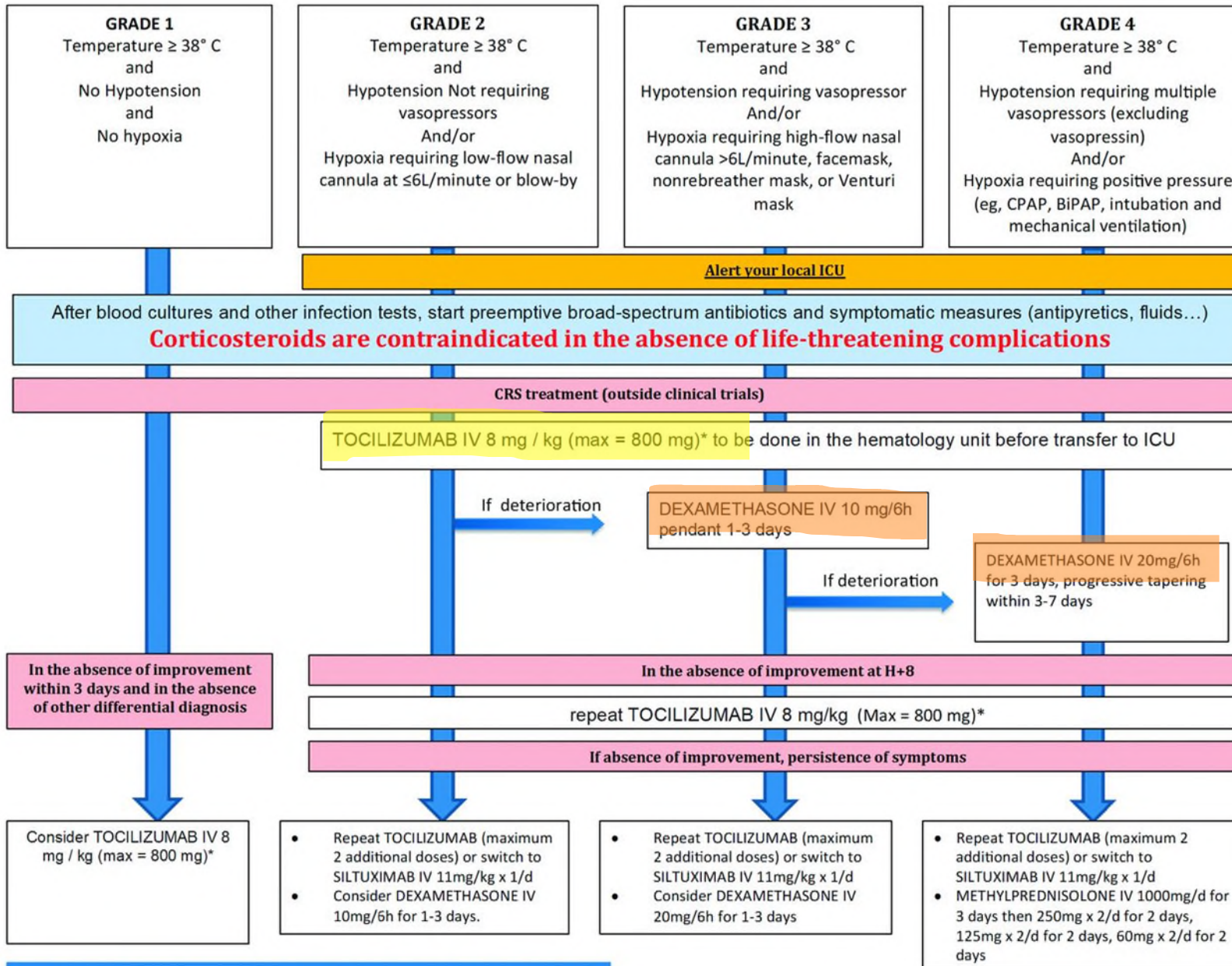
\* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.



# Risk management program

- Patient selection (ECOG 0-1)
- Patient monitoring (parameters, ICE-score)
- Differential diagnosis
  - CRS: neutropenic fever
  - ICANS: neurological complications in cytopenic and immunocompromised host
- Rapid escalation of therapy may be required
  - Imaging, neurology dept, ICU-department

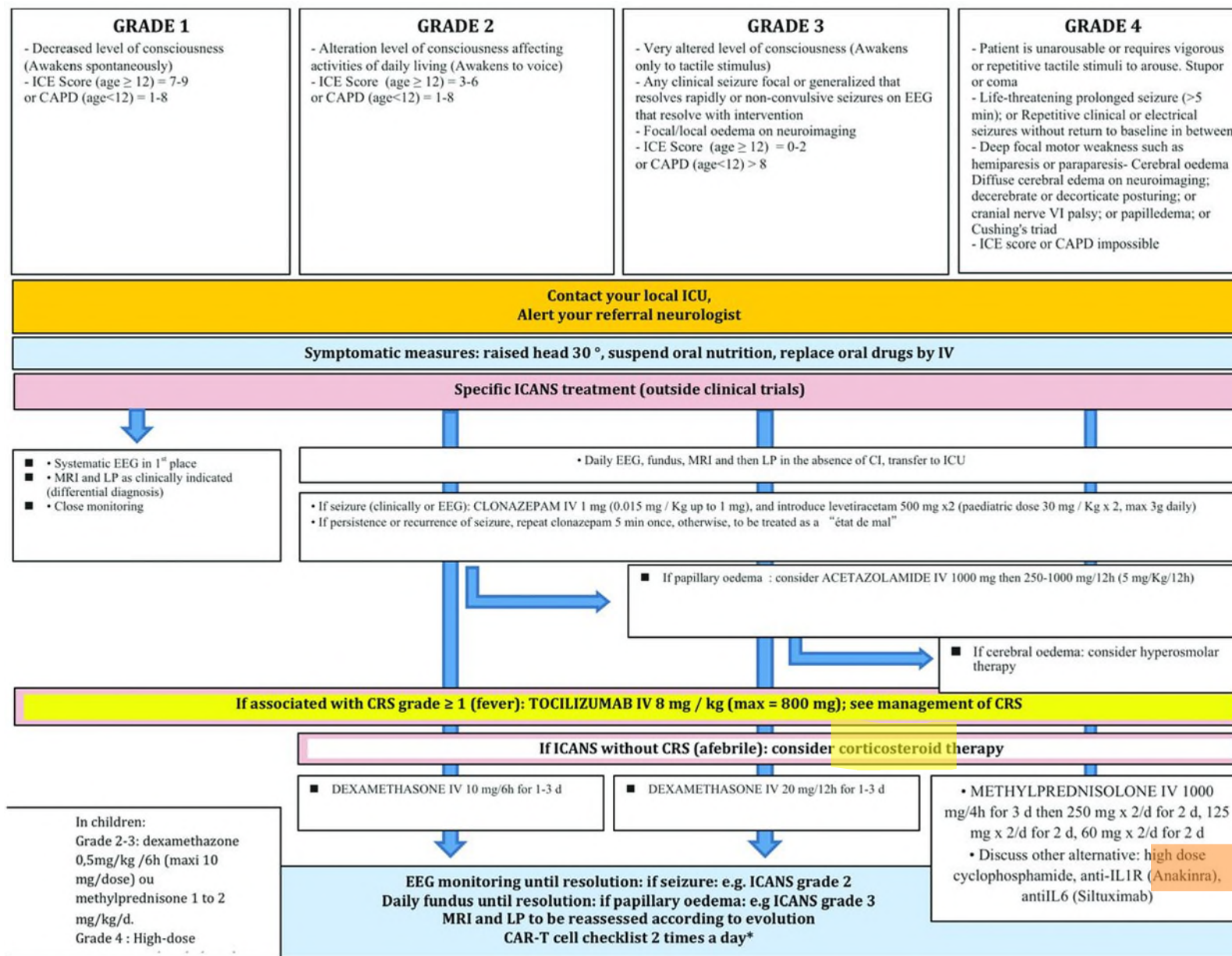
# CRS



CRS, cytokine release syndrome.  
Yacoub-Agha et al. Haematologica, 2020; 105: 297

\*In children less than 30 kg, TOCILIZUMAB is given at the dose of 12 mg/kg.

# ICANS

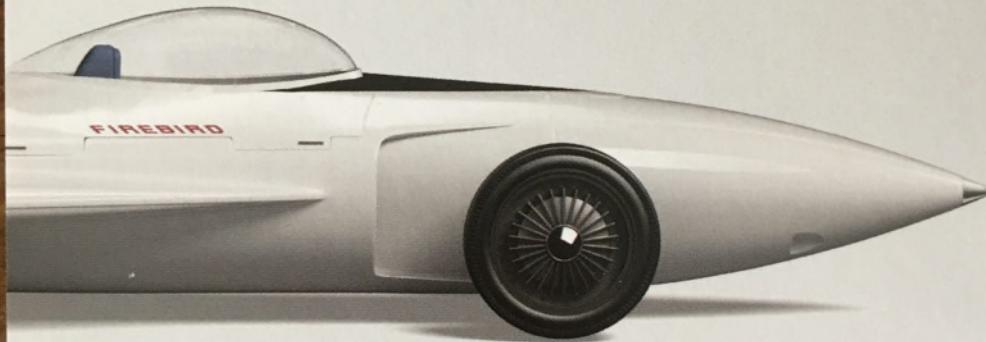


In children:  
 Grade 2-3: dexamethazone 0,5mg/kg /6h (maxi 10 mg/dose) ou methylprednisone 1 to 2 mg/kg/d.  
 Grade 4 : High-dose

ICANS, immune cell-associated neurotoxicity syndrome.  
 Yacoub-Agha et al. Haematologica, 2020; 105: 297

# V&A

23 November 2019 to 19 April 2020



# CARS

ACCELERATING THE MODERN WORLD

CAR T cells, accelerating  
medicine

Novel cellular medicine (ATMP)

Living drug

Targeted but “agnostic”

Expanding to other  
malignancies, autoimmunity,  
transplant rejection ...

Novel research domain

Novel biotech industry