

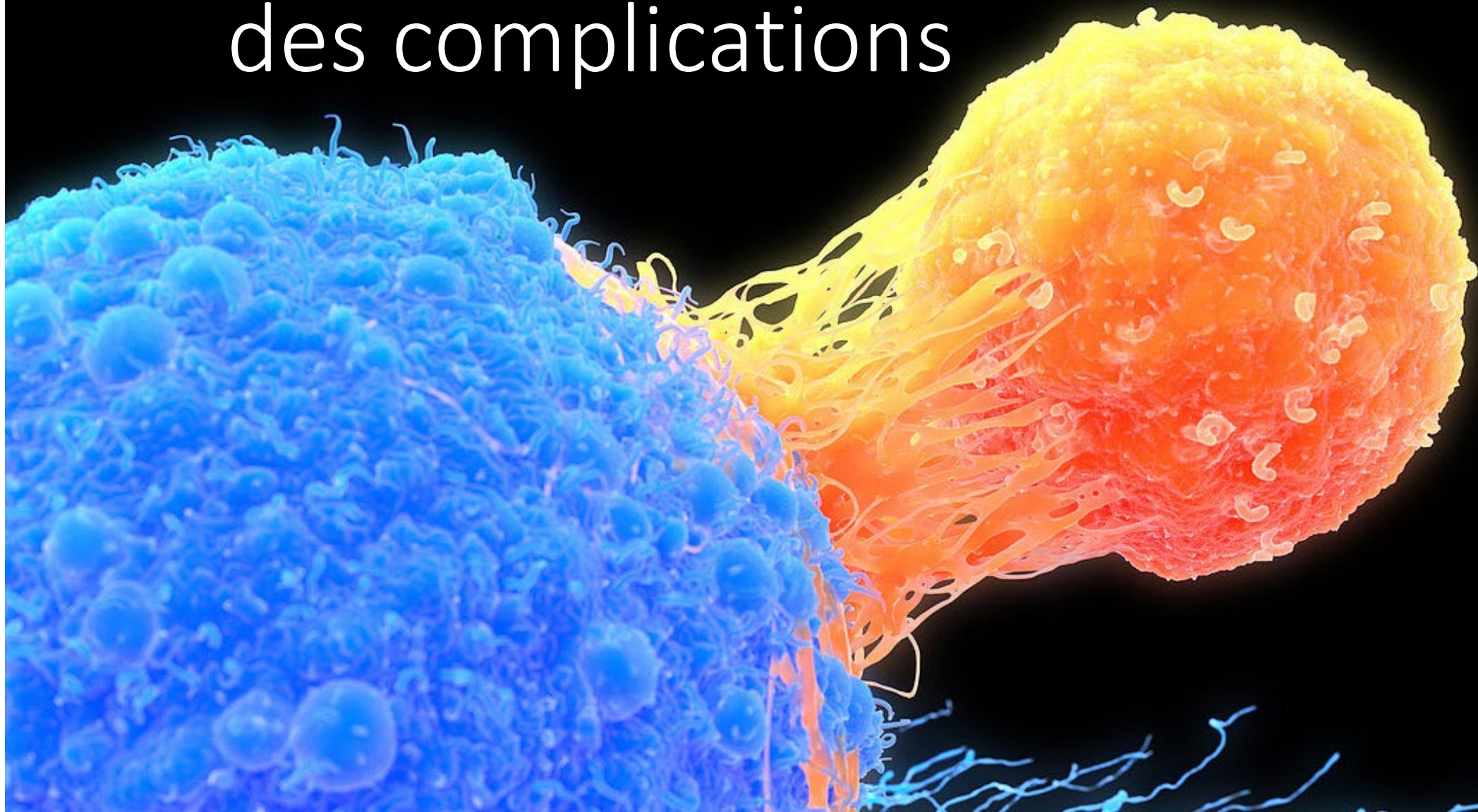
Florent Wallet

Service de réanimation
Médicale

CHU Lyon Sud

CAR-T : Prise en charge des complications

Congrès SFH
10 Novembre 2021



2-(3) grandes complications

- **Cytokine release syndrome (CRS)**

- Fièvre élevée
- Hypotension
- Hypoxie
- Défaillance multiviscérale

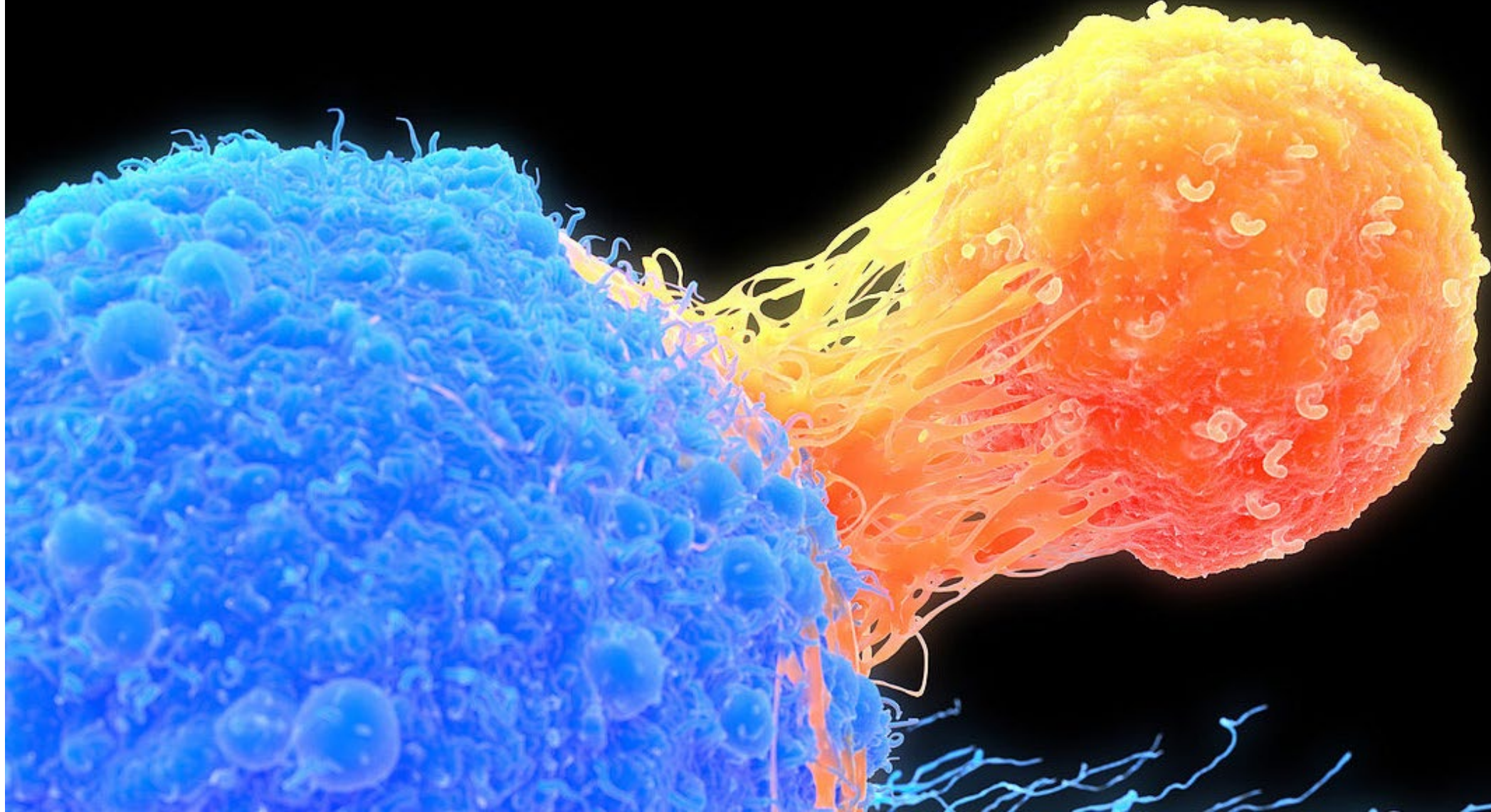
- **Immune Cells Associated Neurologic Syndrome**

- Encéphalopathie toxique
 - Confusion
 - Délirium
 - convulsions
 - Œdème cérébral



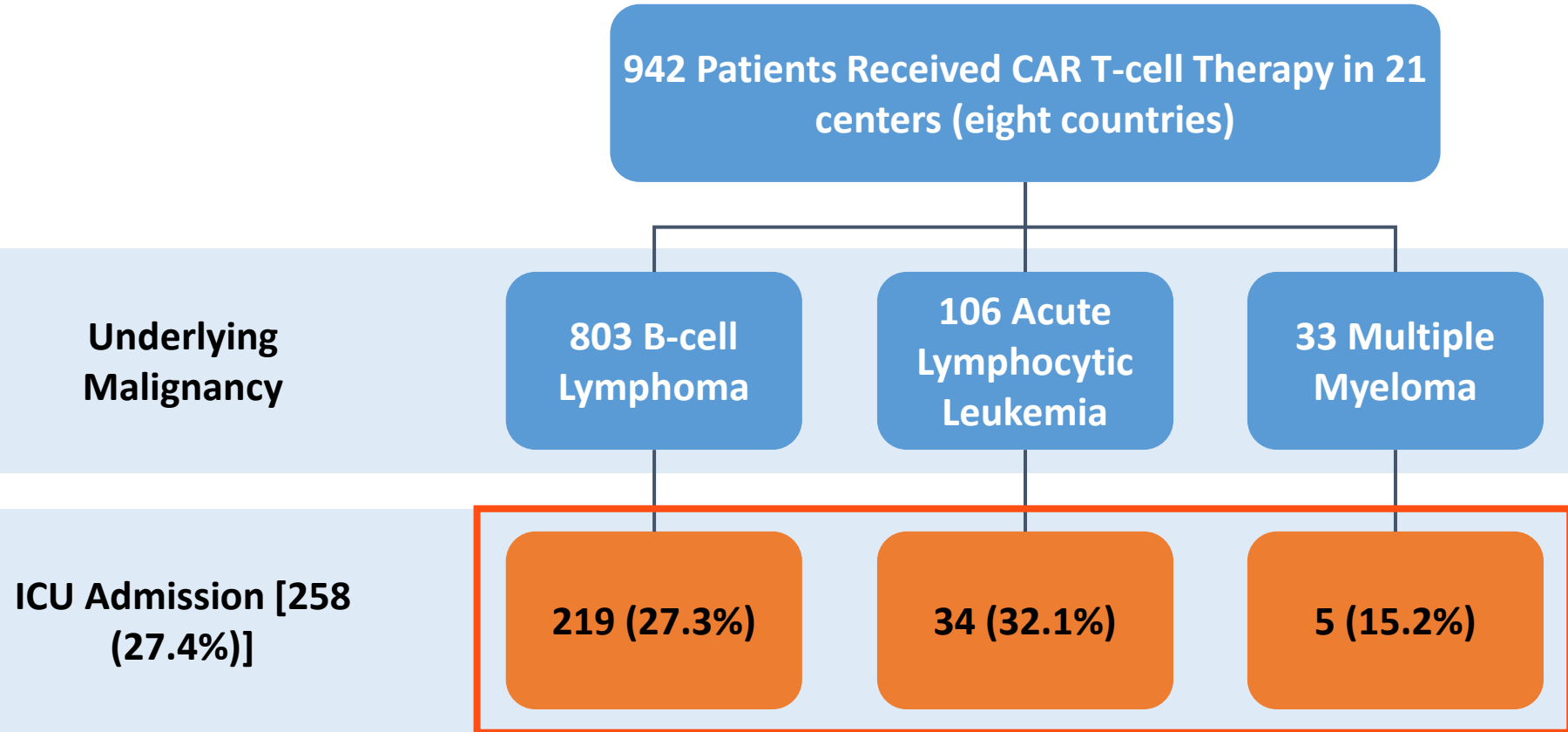
- **HLH/MAS**
 - Hypofibrinogénémie
 - Ferritine
 - Thrombopénie
 - TCA augmenté
 - TP diminué

Incidence

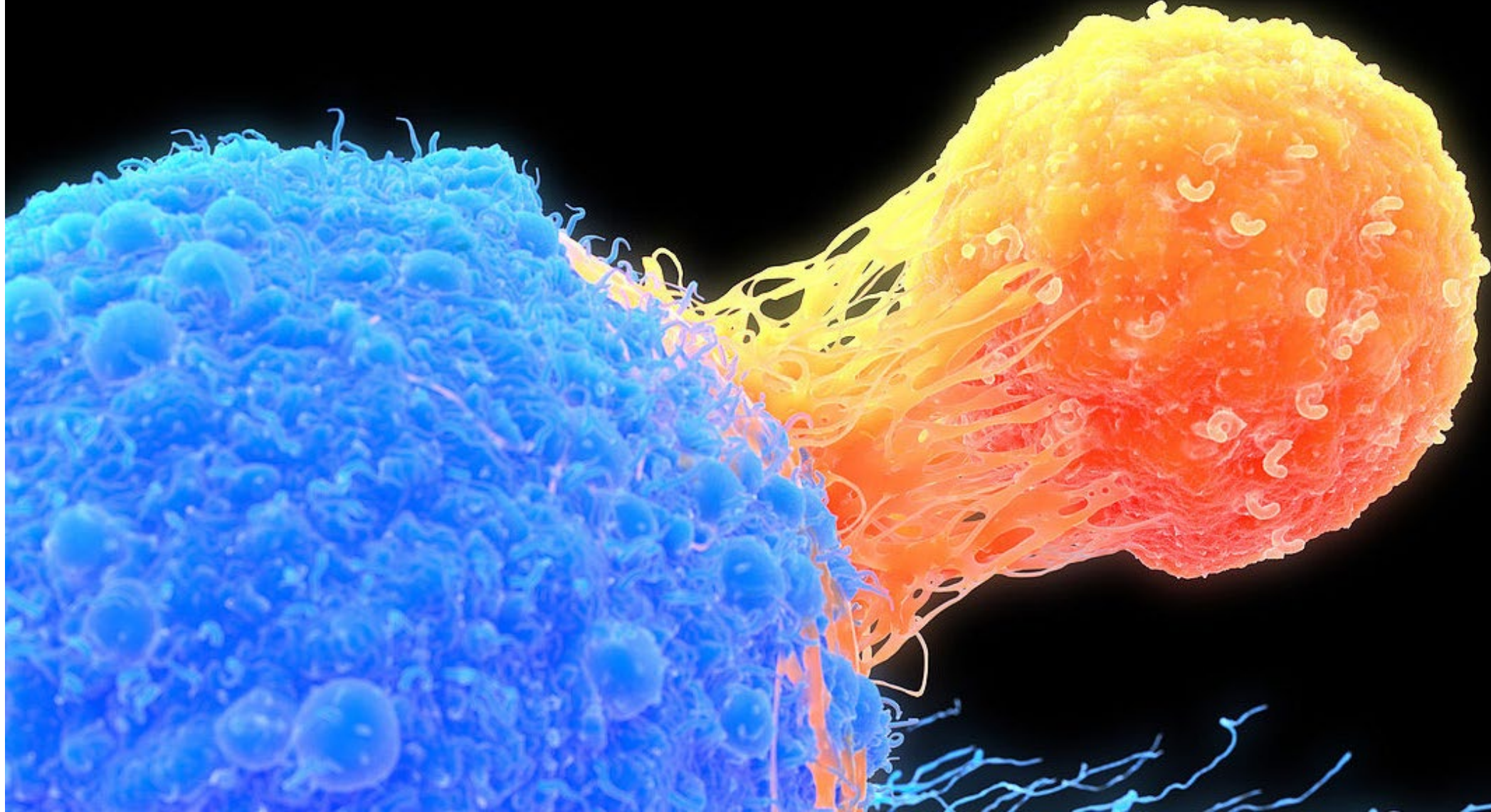


Target antigen	Disease	CAR	Clinical trial identifier	Sponsor	Number of patients analysed	Median age (years)	Response	Patients with CRS (%)	Patients with neurotoxicity (%)
CD19	B-ALL (paediatric) ^a	Tisagenlecleucel; 4-1BB co-stimulation; CTL019	NCT02435849 (REFS ^{53,199})	Novartis Pharmaceuticals	75	11	6-month relapse-free survival rate of 80%	77	40
CD19	Relapsed or refractory DLBCL ^a	Axicabtagene ciloleucel; CD28 co-stimulation; KTE-X19	NCT02348216 ZUMA-1 (REFS ^{52,200,201})	Kite Pharma (a Gilead Sciences company)	101	58	83% objective response; 58% complete response	93	67
CD19	Refractory B cell lymphomas ^a	Tisagenlecleucel; 4-1BB co-stimulation; CTL019	NCT02030834 (REFS ^{202,203})	UPenn	28	58.5	64% overall response; 43% complete remission	57	39
CD19	Mantle cell lymphoma ^a	Axicabtagene ciloleucel; CD28 co-stimulation; KTE-X19	NCT02601313 ZUMA-2 (REFS ^{204,205})	Kite Pharma	68	65	93% objective response rate; 67% complete response	91	63
CD19	B-ALL	CD28 co-stimulation	NCT01044069 (REFS ^{206,207})	MSKCC	53	44	83% complete remission; median overall survival 12.9 months	85	44
CD22	Relapsed or refractory pre-B-ALL	4-1BB co-stimulation	NCT02315612 (REFS ^{106,208})	NCI	21	19	73% complete remission treated with higher dose	76	Unreported
BCMA	Relapsed or refractory multiple myeloma	Idecaptagene cicleucel; 4-1BB co-stimulation; bb2121	NCT02658929 (REFS ^{137,209})	Celgene	33	60	85% objective response rate; 45% complete response rate	76	42
BCMA	Multiple myeloma	4-1BB co-stimulation	NCT02546167 (REFS ^{138,210})	UPenn	25	58	48% overall response rate	88	32

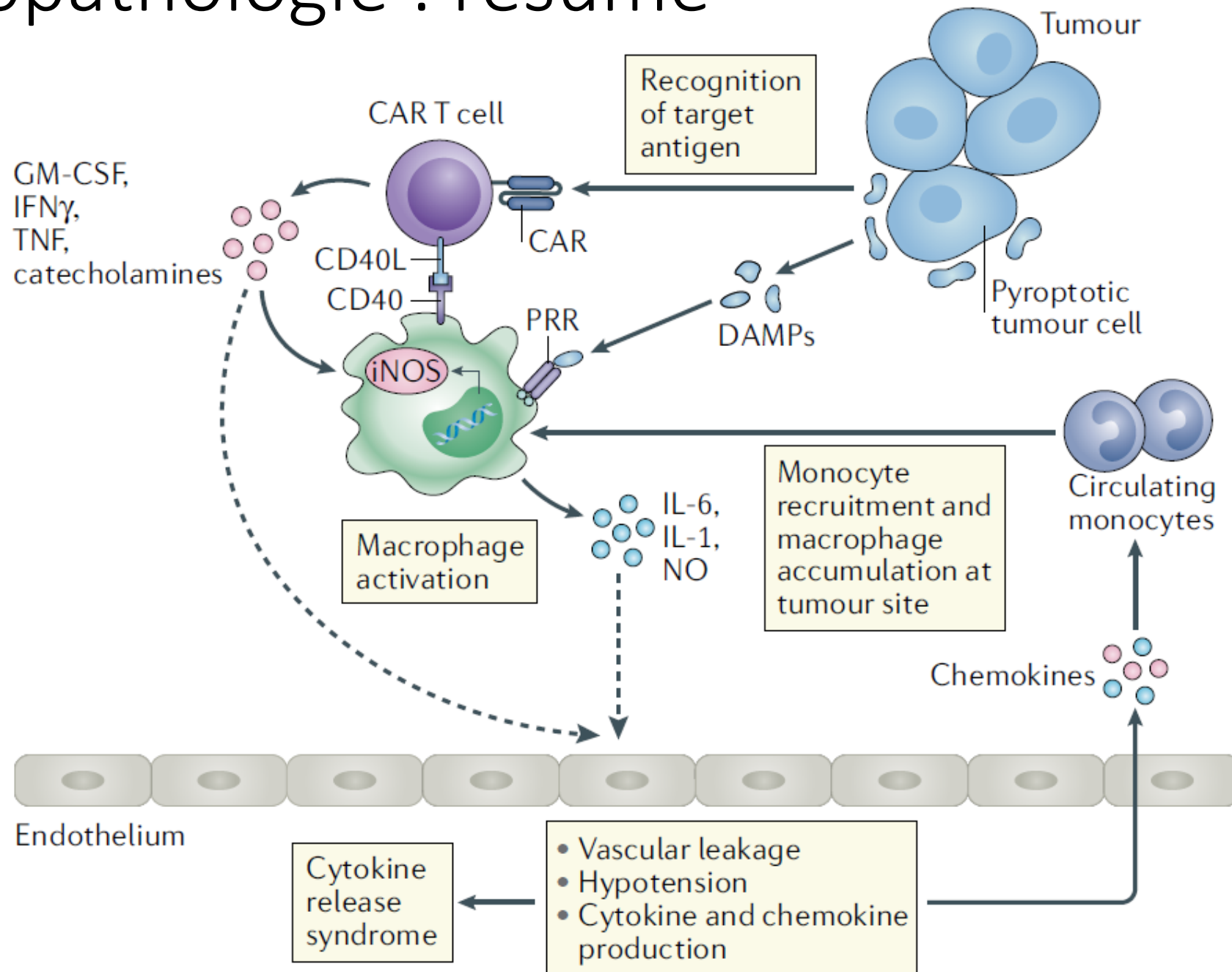
The CARTTAS Study



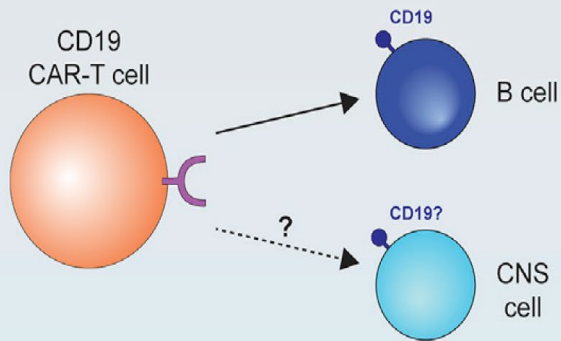
Physiopathologie



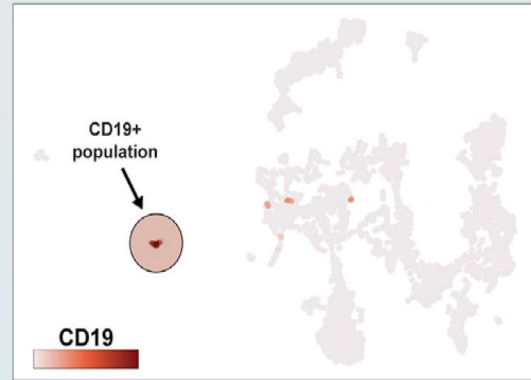
Physiopathologie : résumé



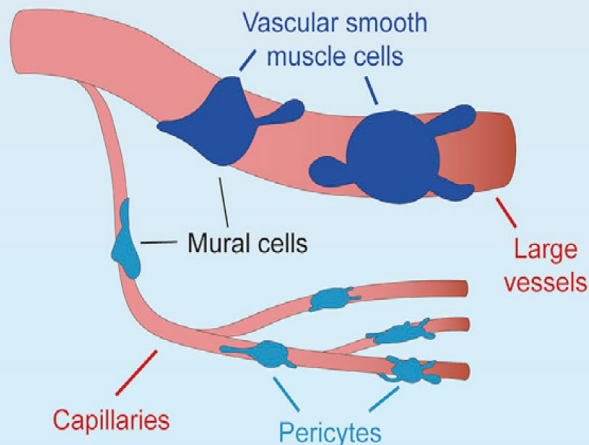
CD19 CAR-T therapy is associated with neurotoxicity



CD19 is expressed by cells in the human brain

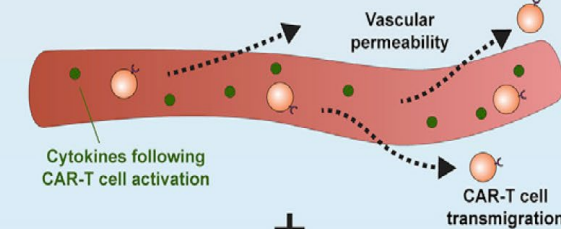


CD19+ cells are mural cells, which wrap and support the vasculature

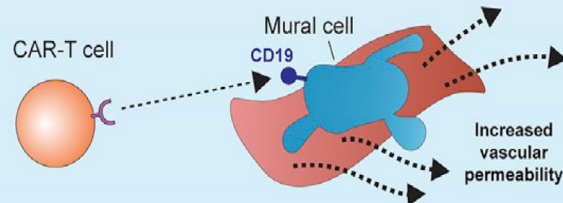


Potential mechanism:

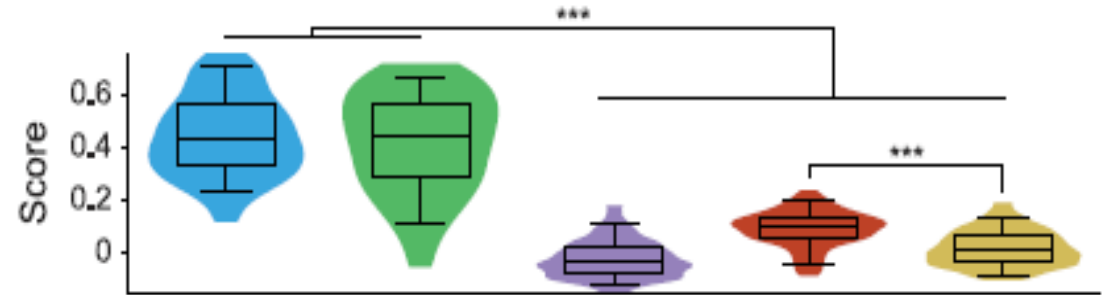
Blood brain barrier leakiness following cytokine release syndrome



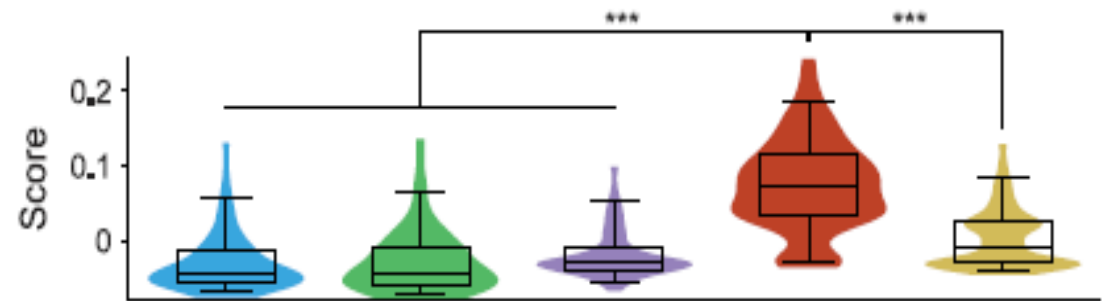
CAR-T cell recognition of CD19+ mural cells causing increased BBB leakiness



CD19 Gene Score

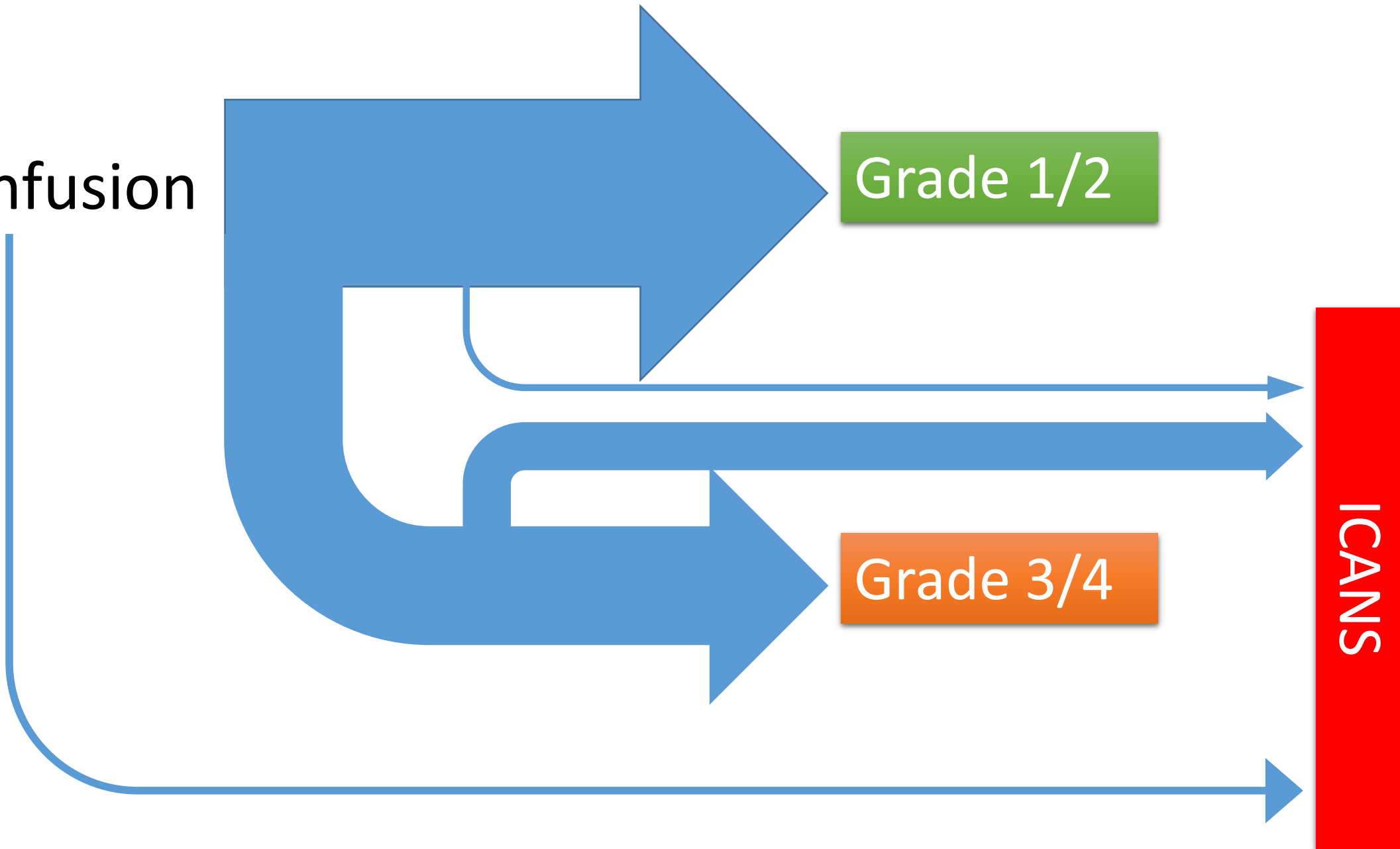


CD22 Gene Score



Pericytes Endothelial Cells Other Brain B Cells (PBMC) Other PBMC

CAR-T infusion

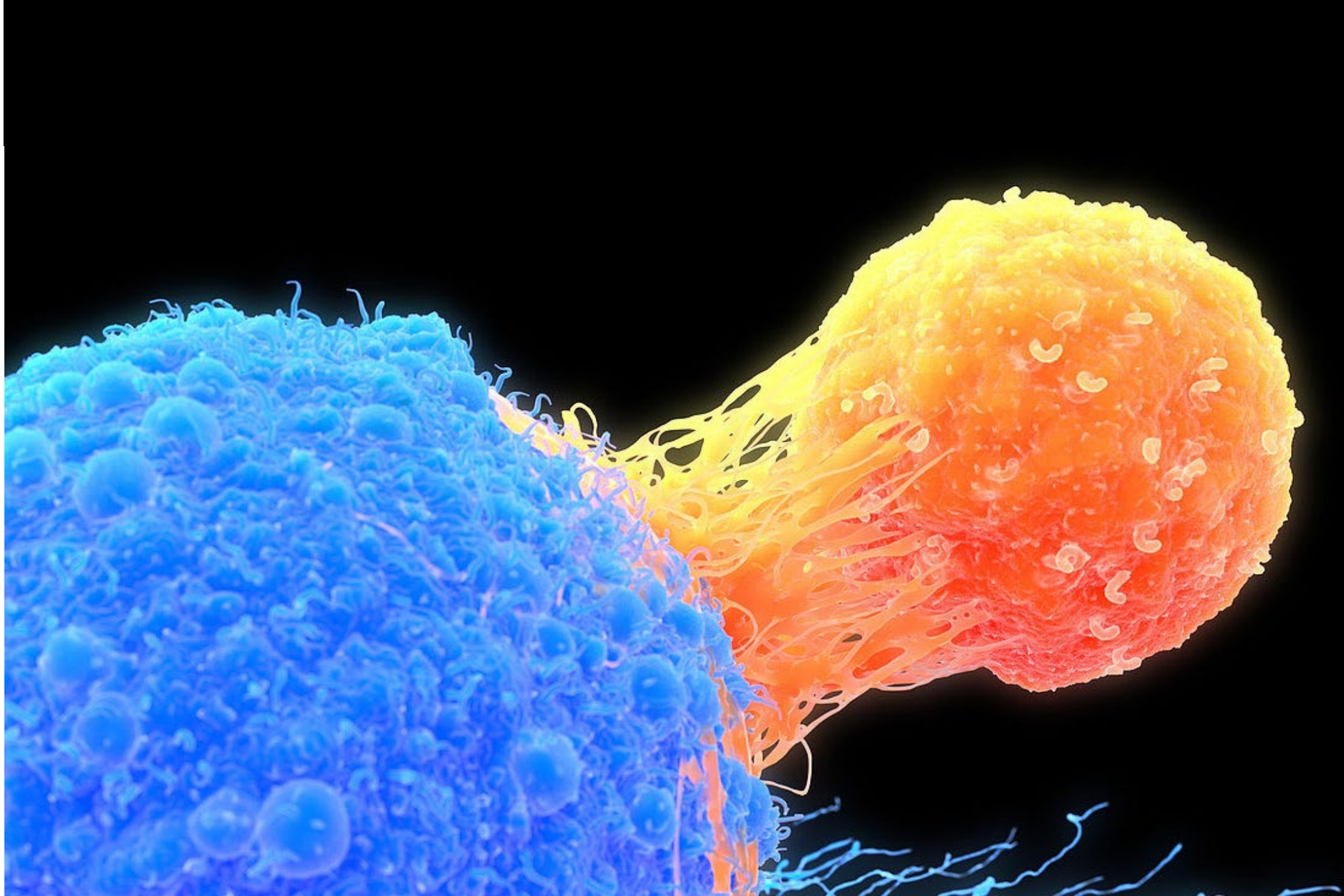


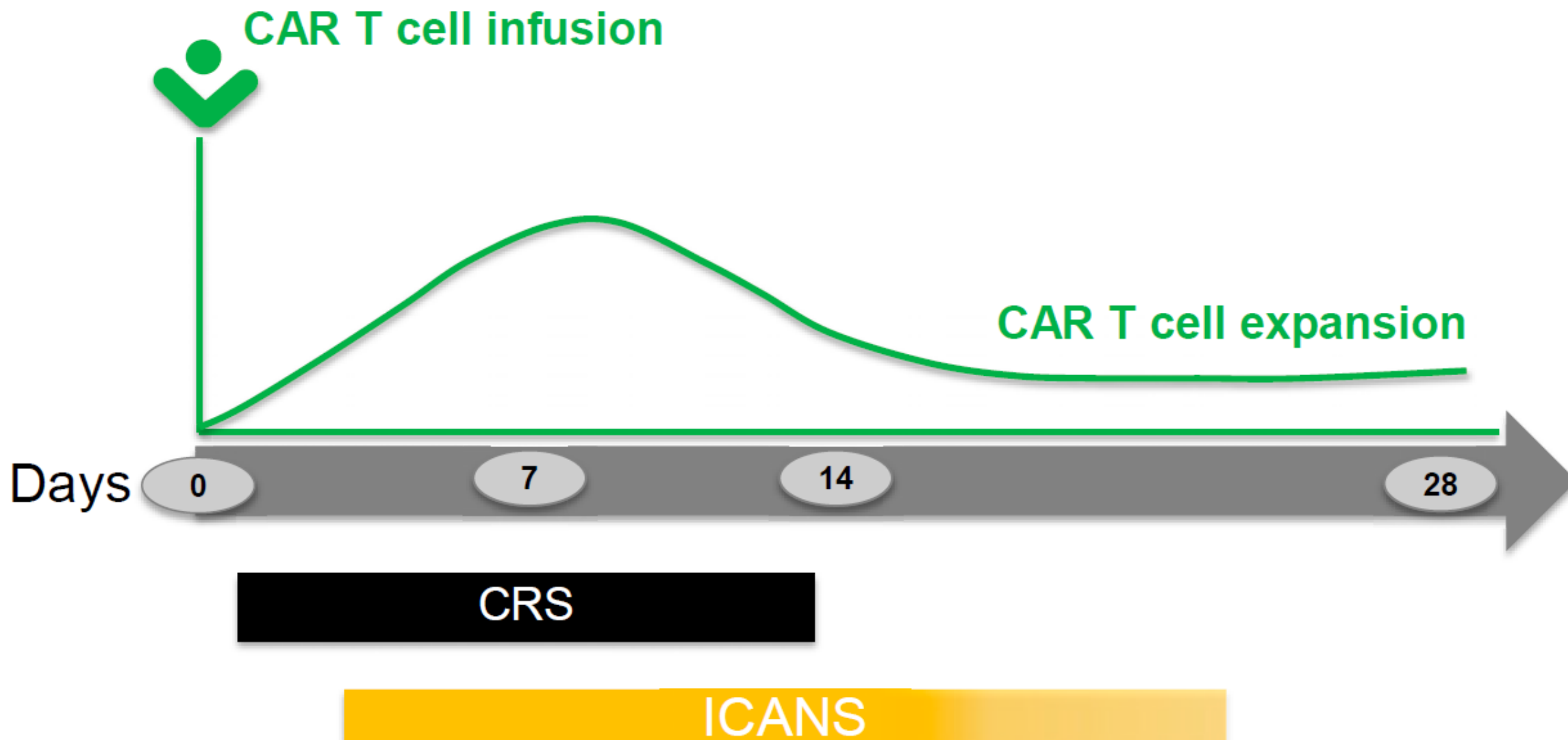
Grade 1/2

Grade 3/4

ICANS

CRS

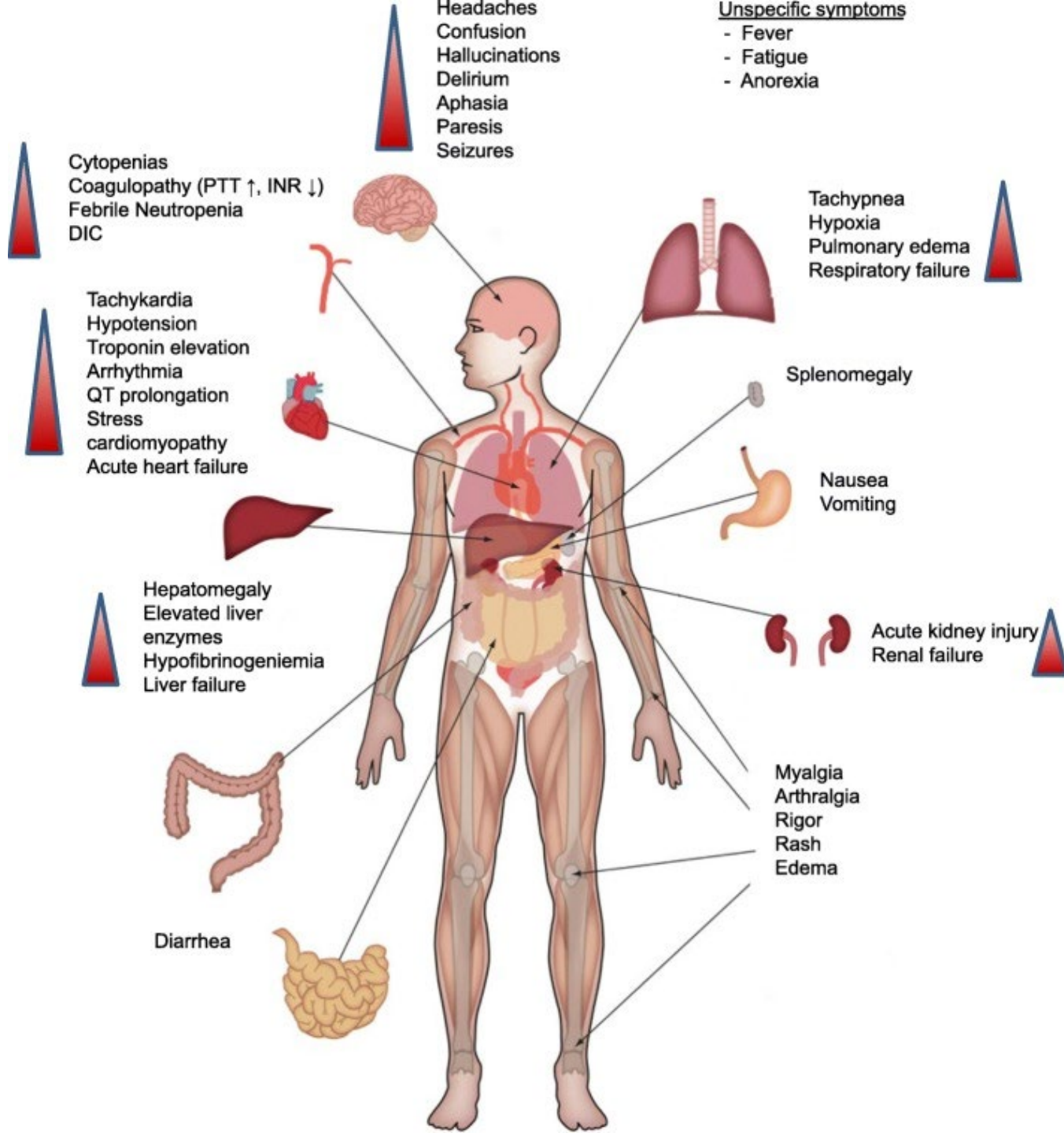




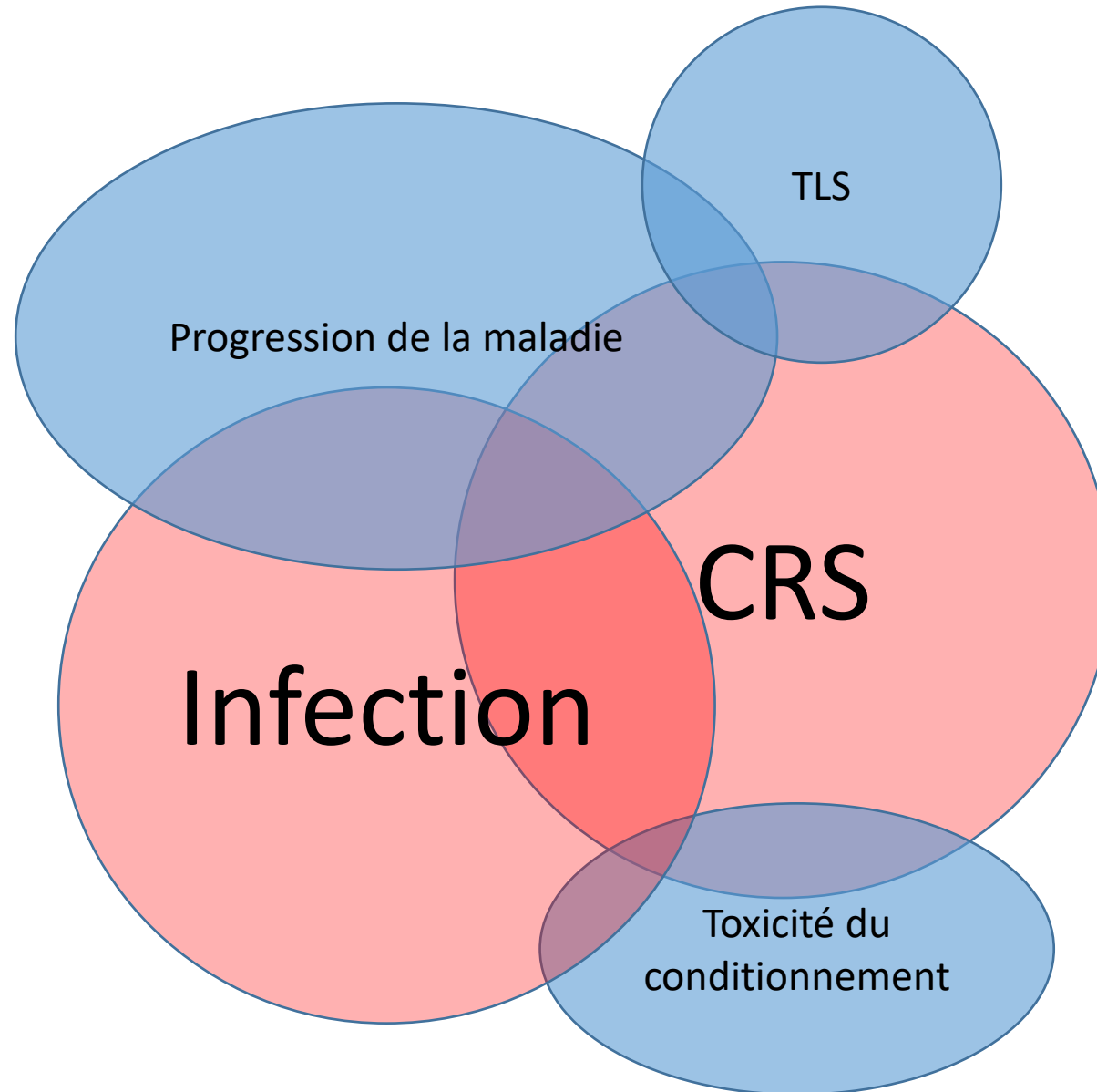
Diagnostic clinique : CRS

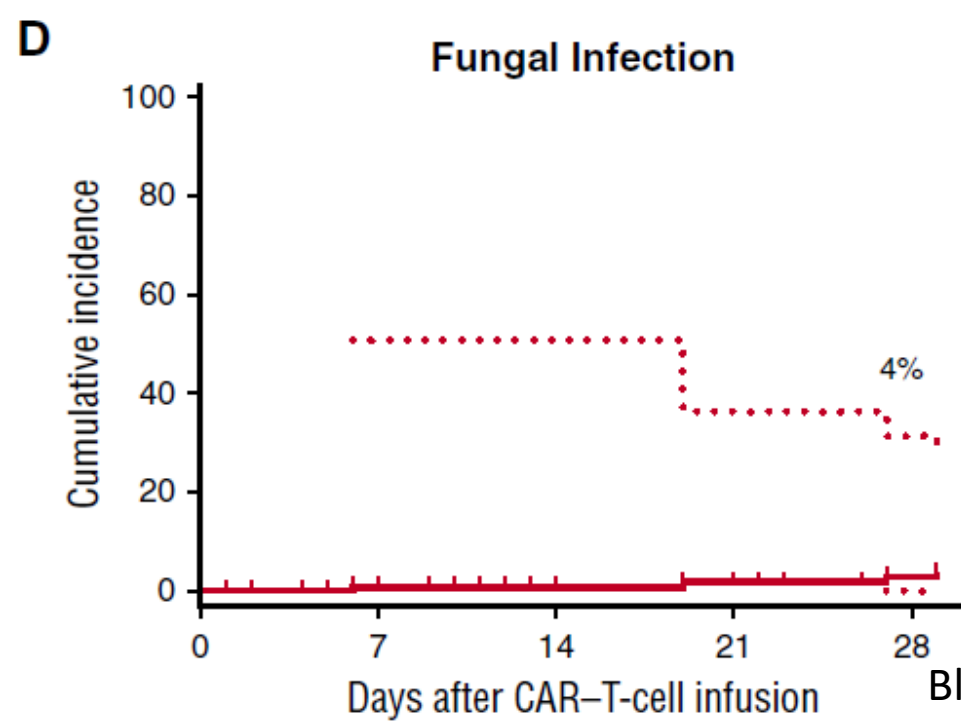
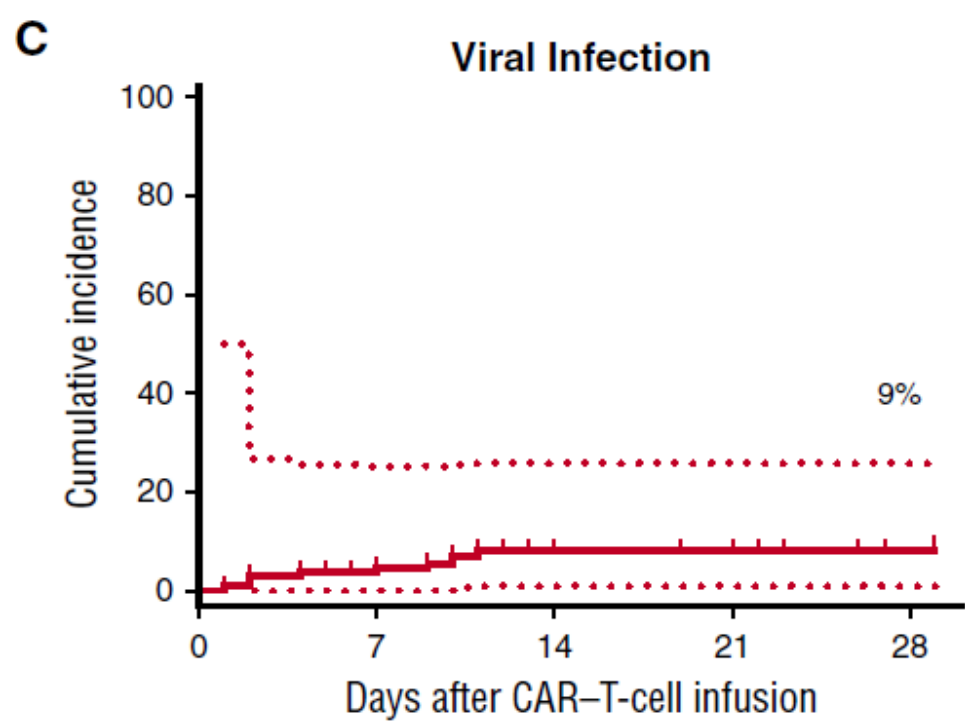
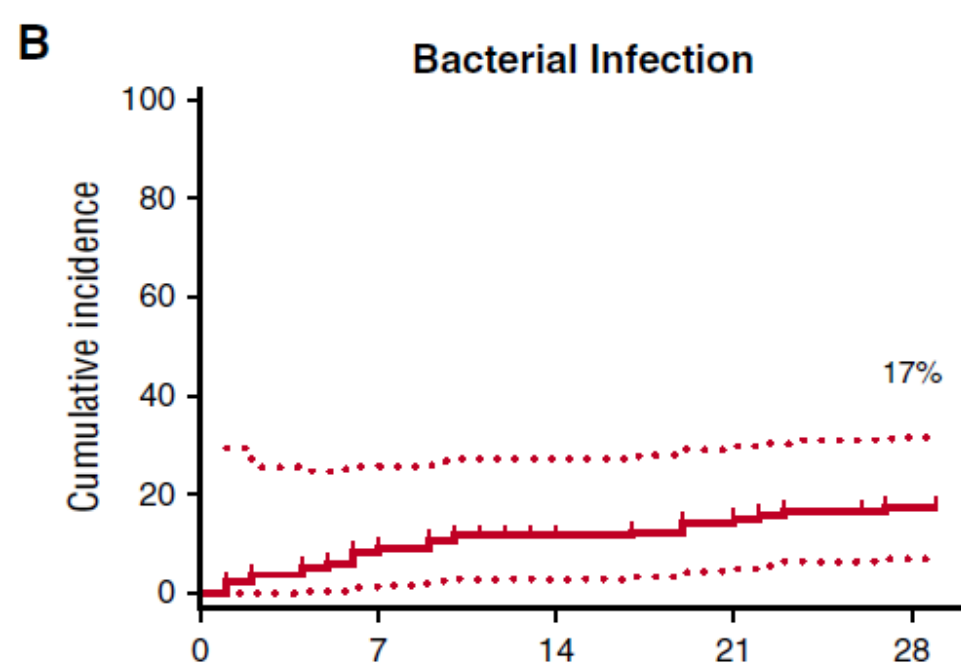
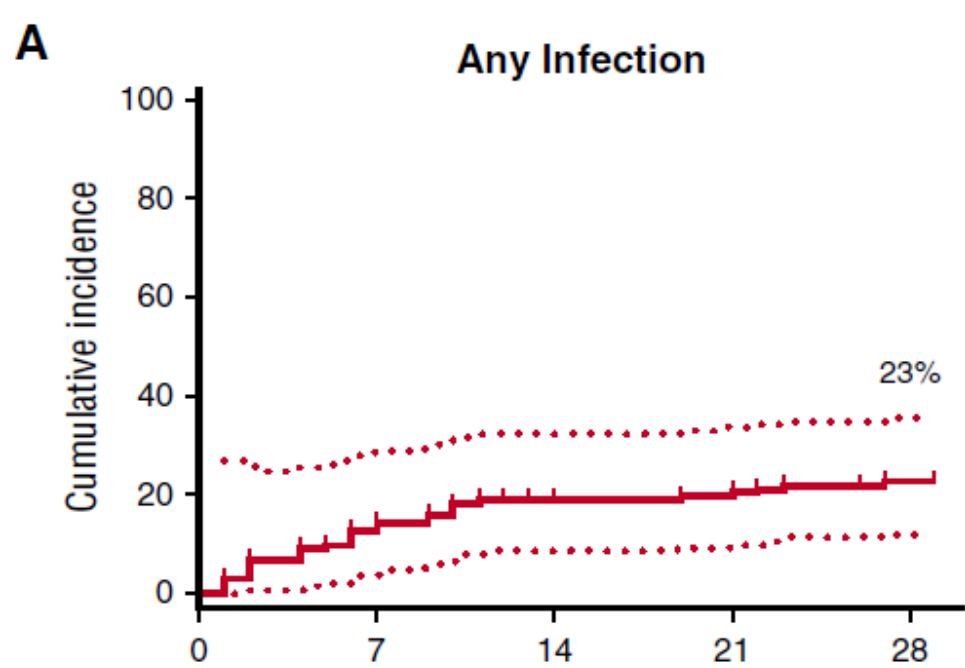
- SIRS = systemic inflammatory response syndrome
- N'étant pas d'origine infectieuse
- Associant des signes généraux
 - **Fièvre > 38,5**, malaise, maux de tête, myalgies, nausées, asthénie
- Une hypotension plus ou moins marquée
- Une atteinte respiratoire plus ou moins marquée
- Possiblement des défaillances d'organes

GRAVITE



Diagnostic différentiel du CRS

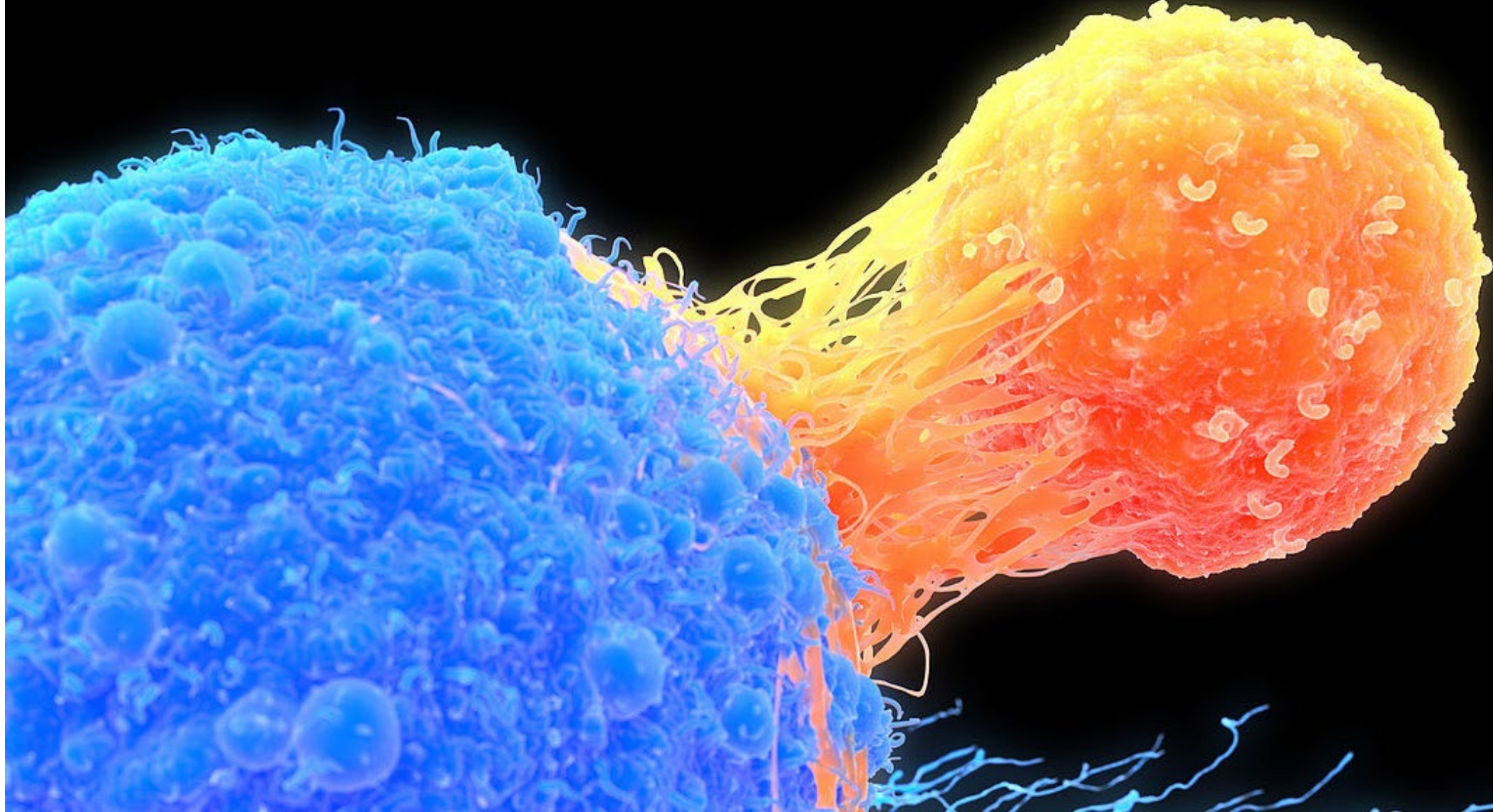


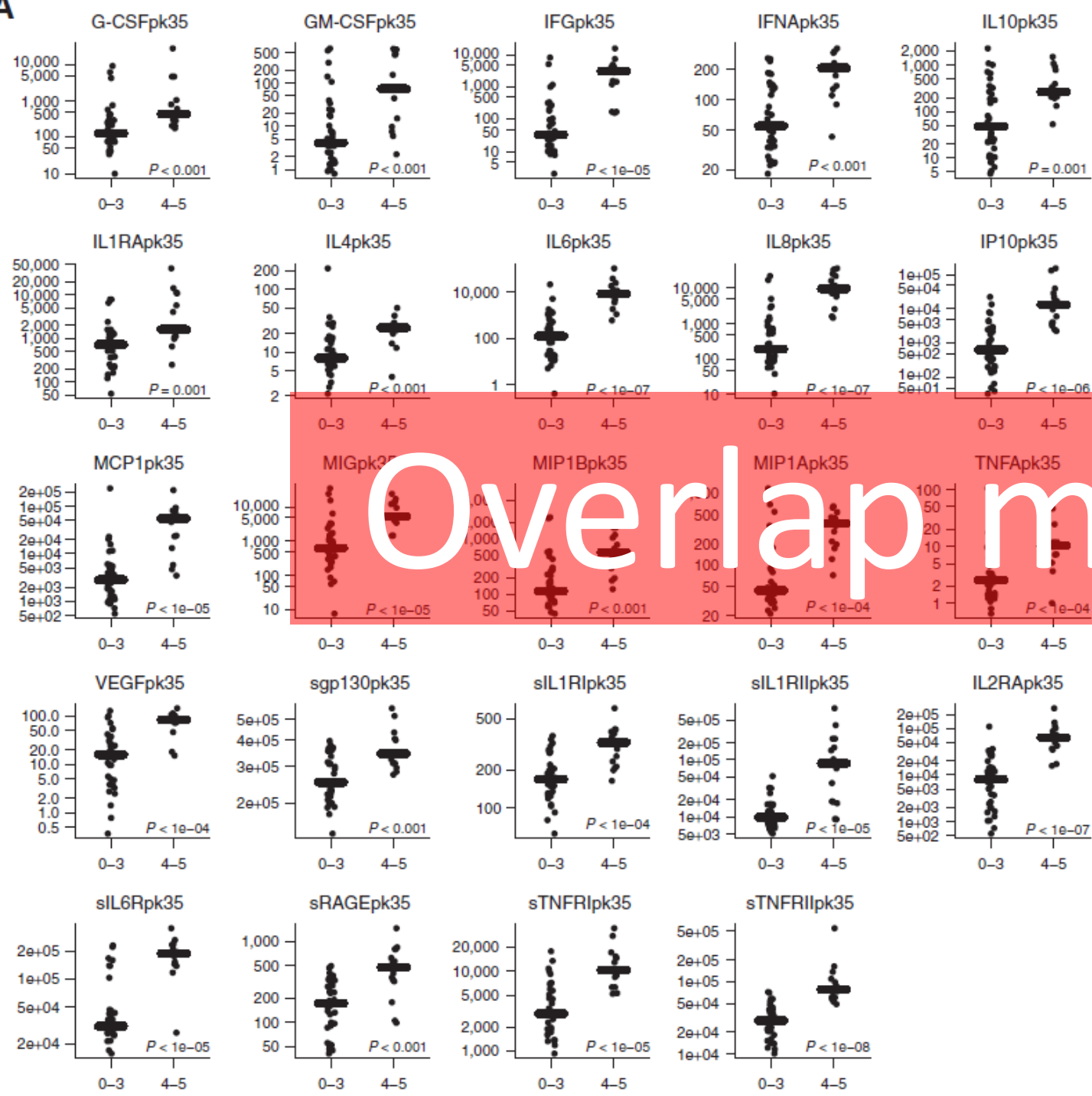


CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$
			With	
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
			And/or [†]	
Hypoxia	None	Requiring low-flow nasal cannula [†] or blow-by	Requiring high-flow nasal cannula [†] , facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

ASTCT CRS Consensus Grading

Biologie





Overlap majeur

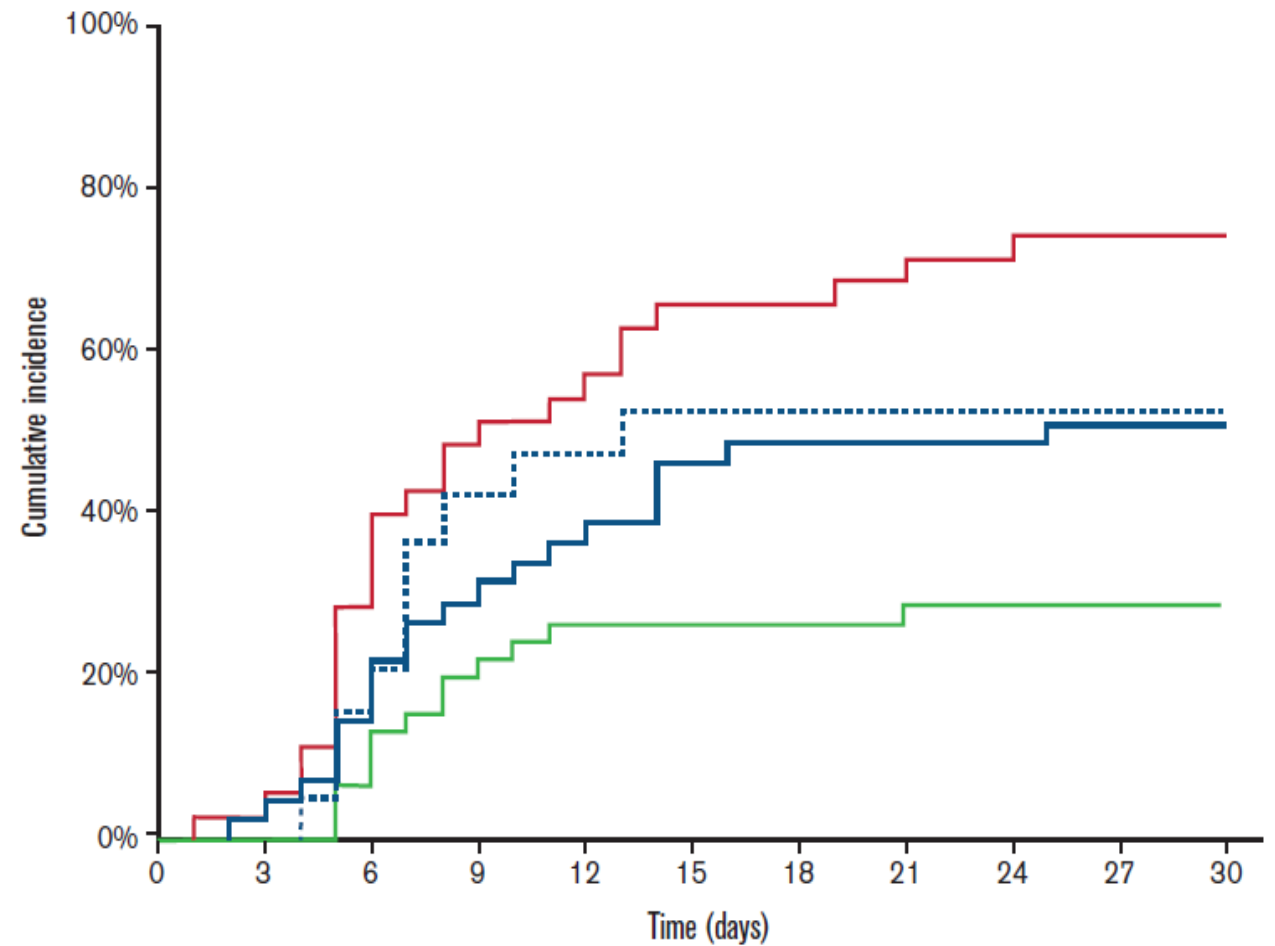
Valeur maximale sur M1

$$\text{EASIX} = \frac{\text{LDH [UI/L]} \times \text{creatinine [mg/dL]}}{\text{Plaquettes [10}^9 \text{ cells/L]}}$$

Ferritine

CRP

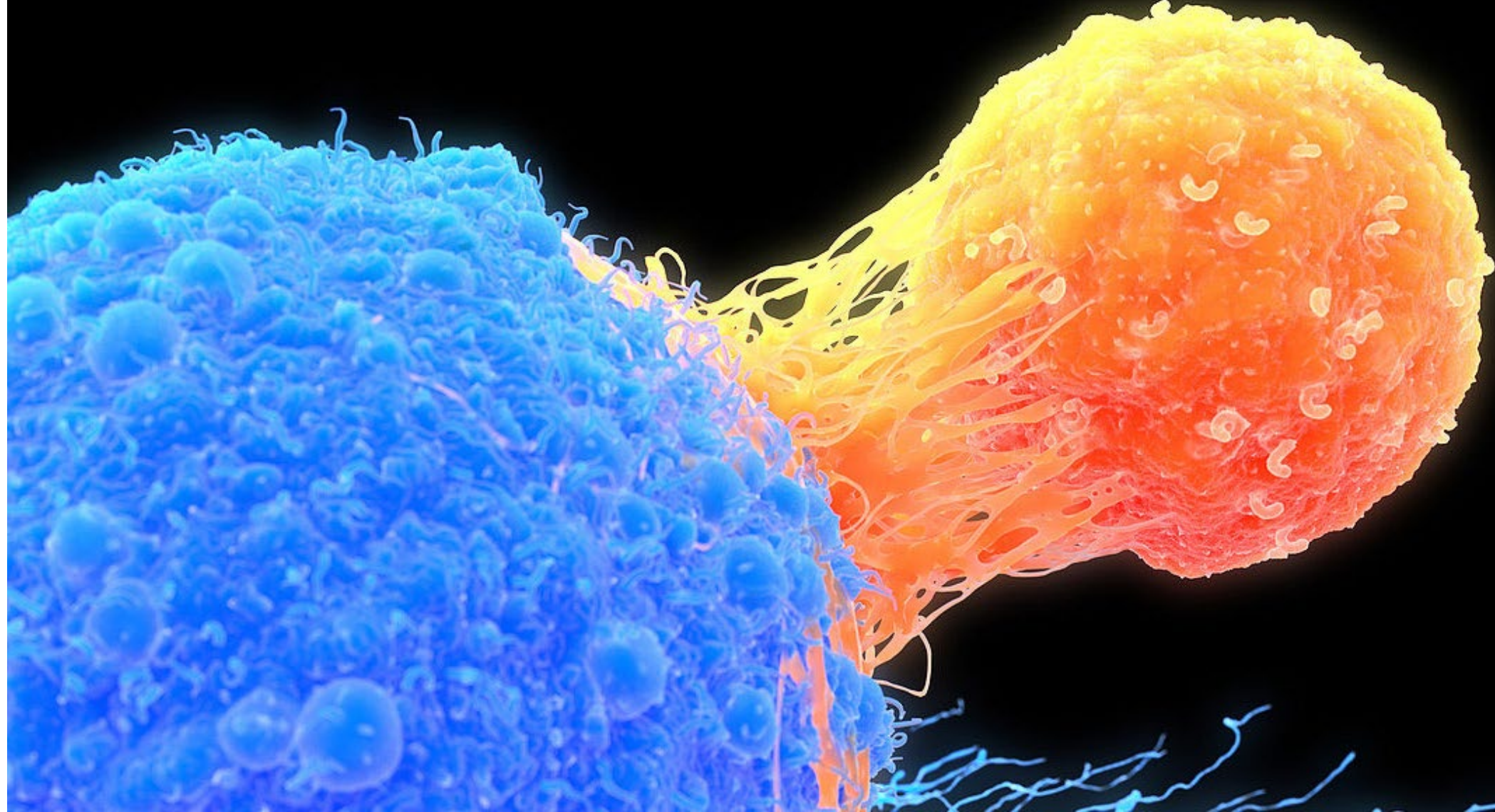
$$\text{m-EASIX} = \frac{\text{LDH [UI/L]} \times \text{CRP [mg/dL]}}{\text{Plaquettes [10}^9 \text{ cells/L]}}$$



Risk strata

- High risk: high (>1583 ng/mL) ferritin; HR=3.6, p<0.001
- Intermediate risk 1: low ferritin, high (>2.1) EASIX; HR=2.0, p=0.04
- ⋯ Intermediate risk 2: low ferritin, low EASIX, and high (>21) CRP; HR=2.2, p=0.06
- Low risk: low ferritin, low EASIX, and low CRP; reference

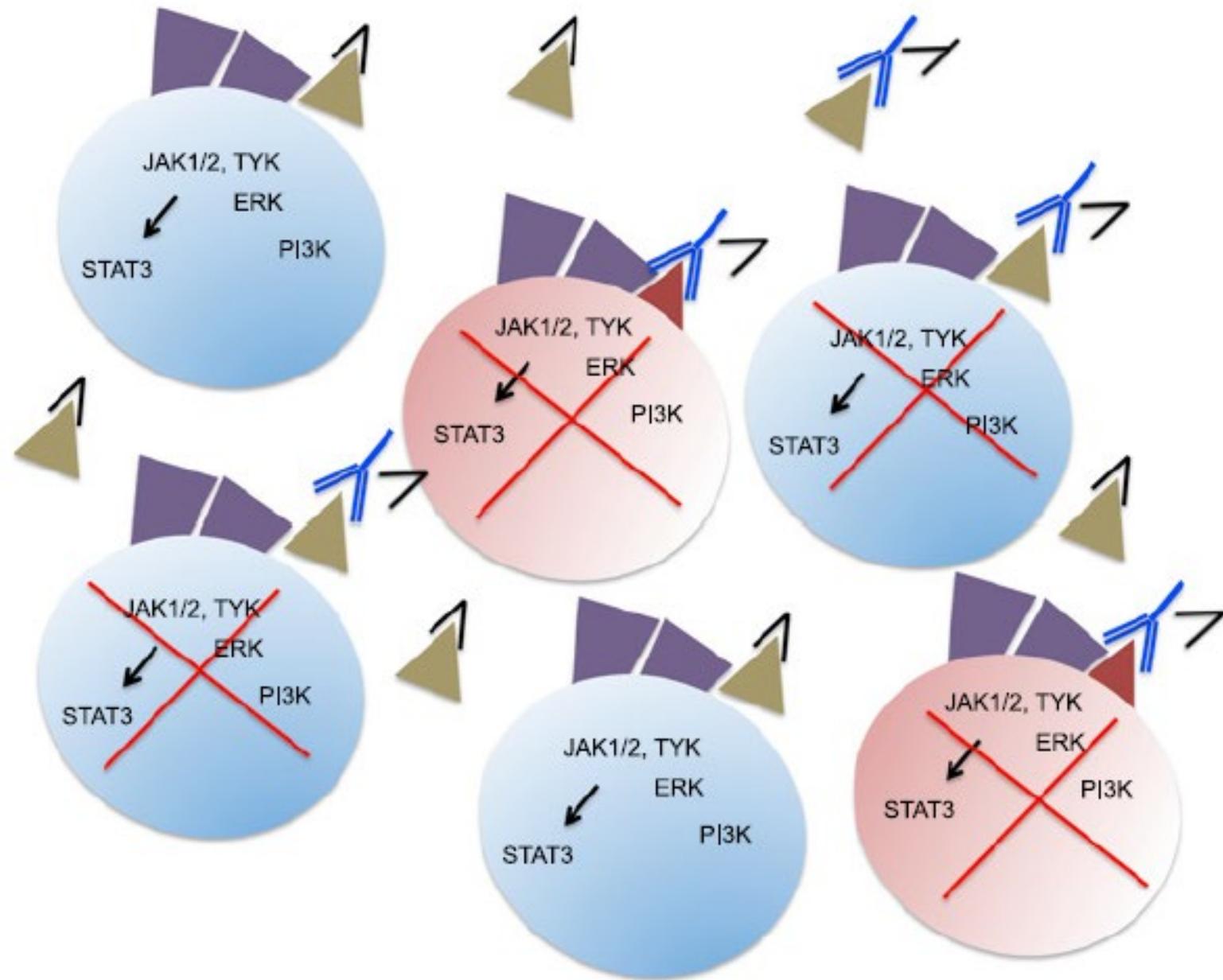
Traitement



Principe de la réanimation : prophylaxie infectieuse

- Prophylaxie virale → Valaciclovir
- Prophylaxie fongique ? → TMP-SMX (oui), Fluconazole, Posaconazole ?
- Pas de prophylaxie bactérienne, mais traitement préemptif par BL large spectre couvrant les BGN-NF (pip-taz, Cefepime) précoce
- CRS = Choc septique sans germe (retrouvé)

Tocilizumab

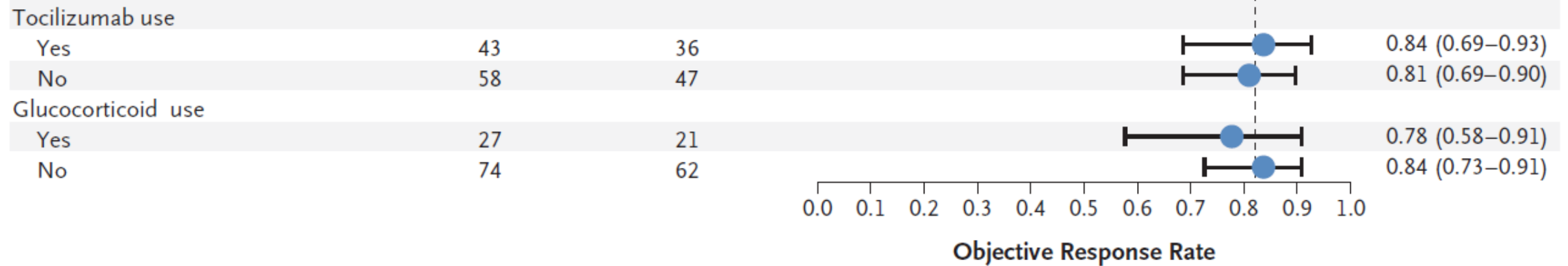


Corticoïdes

Plutôt à partir du grade 3, dès grade 2 si facteurs de risques associés → de plus en plus précoce

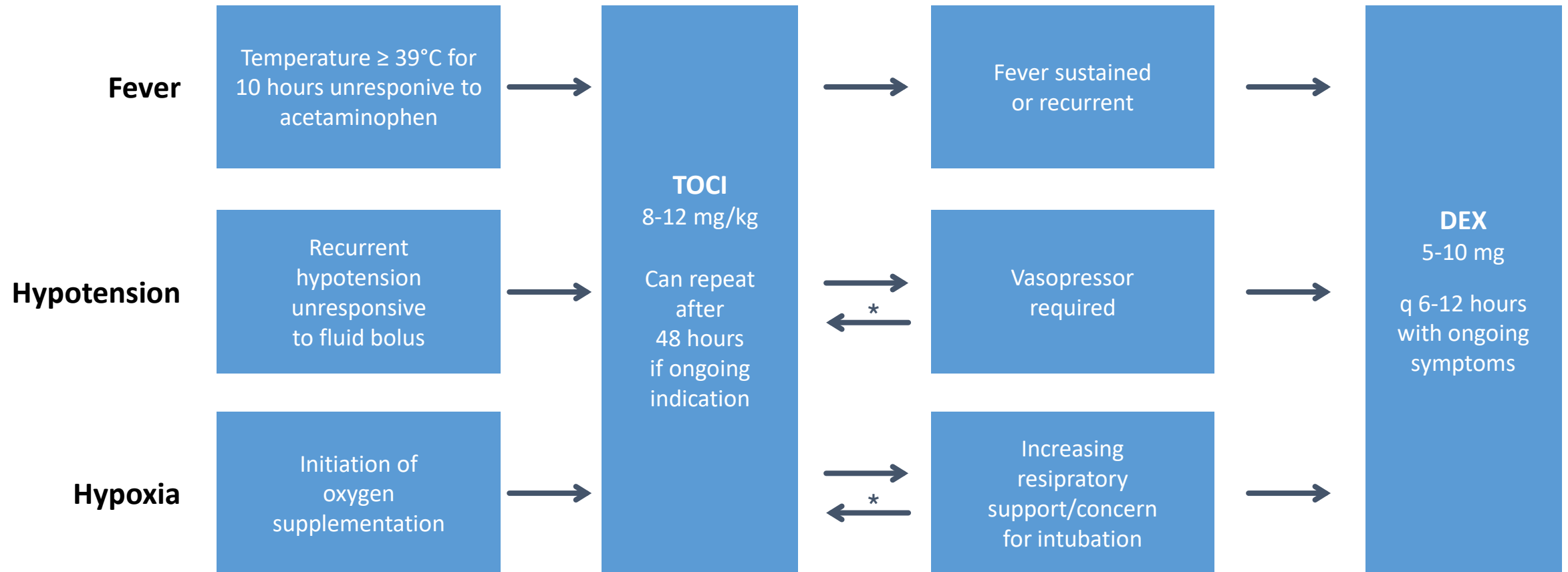
La dexaméthasone est à prioriser surtout pour la neurotox, car sa diffusion cérébrale est supérieure

Br J Haematol. 2005 Jun;129(6):734-45.



N Engl J Med 2017;377:2531-44

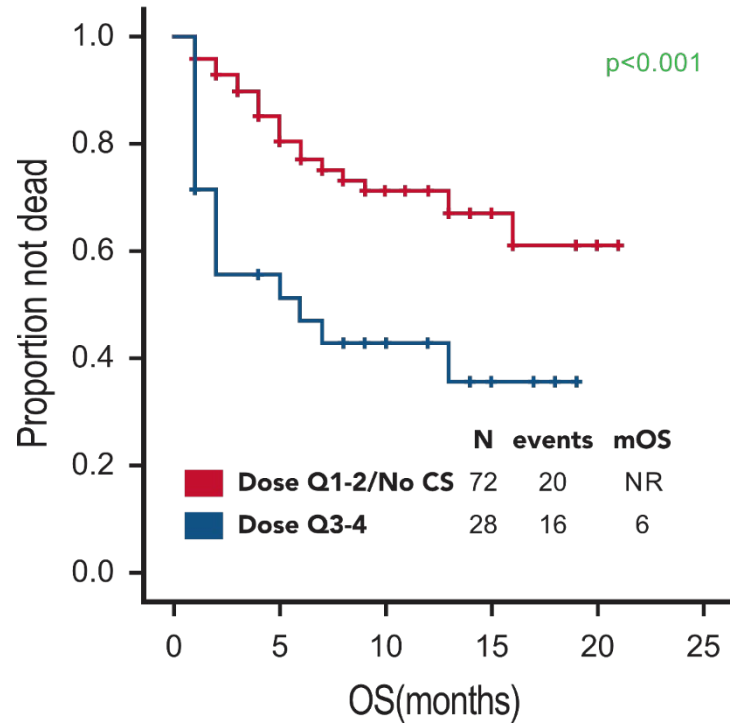
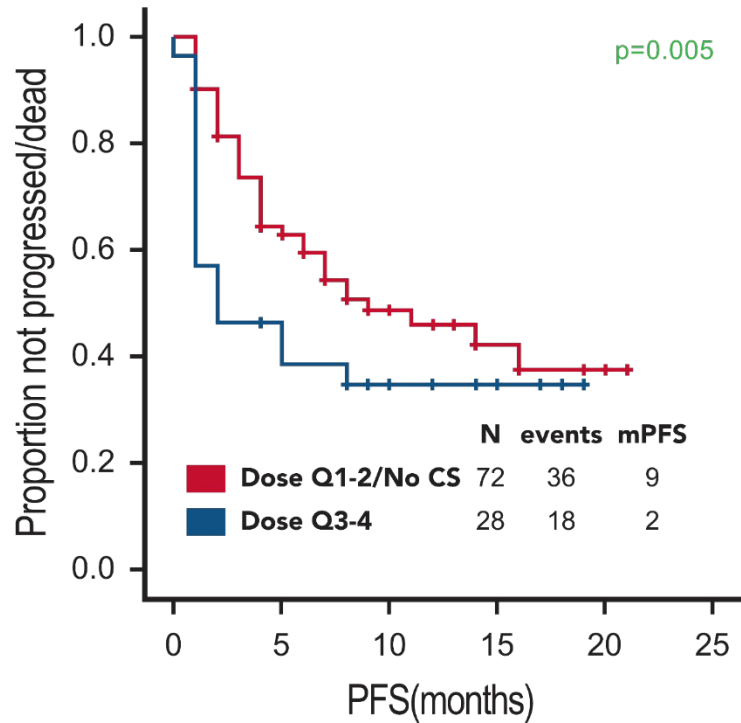
Timing thérapeutique



Prognostic Impact of Dose, Duration and Timing of Corticosteroid Therapy in Patients with Large B-cell Lymphoma Treated with Standard of Care Axicabtagene Ciloleucel (Axi-cel)

Paoto Strati, Fateeha Furquan, Jason Westin, Luis E Fayad, Sairah Ahmed, Hun J Lee, Swaminathan P Iyer, Ranjit Nair, Loretta J Nastoupil, Simrit Parmar, Maria A Rodriguez, Felipe Samaniego, Raphael E Steiner, Michael Wang, Chelsea C Pinnix, Christopher R Flowers, Sandra B Horowitz, Catherine M Claussen, Haleigh Mistry, Sattva S Neelapu

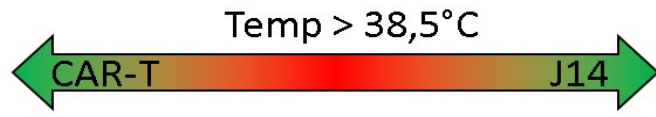
Department of Lymphoma and Myetoma, The University of Texas MD Anderson Cancer Center, Houston, TX.



Conclusions

- Early and higher cumulative dose of corticosteroids was associated with early progression and death in patients with LBCL treated with axi-cel.
- The association between high cumulative dose of corticosteroids and survival was confirmed also in patients with high tumor burden (elevated LDH)
- Patients who received corticosteroids had a higher CAR T-cell expansion
- Additional evaluation is needed to determine whether corticosteroids affect CAR T-cell function and impact durability of responses

Reconnaître le CRS / ICANS



Hypotension, détresse respiratoire, insuffisance rénale

Mesures générales:

Eliminer un sepsis (cf. infra)
Débuter une antibiothérapie
Discuter antifongiques
Bilan biologique

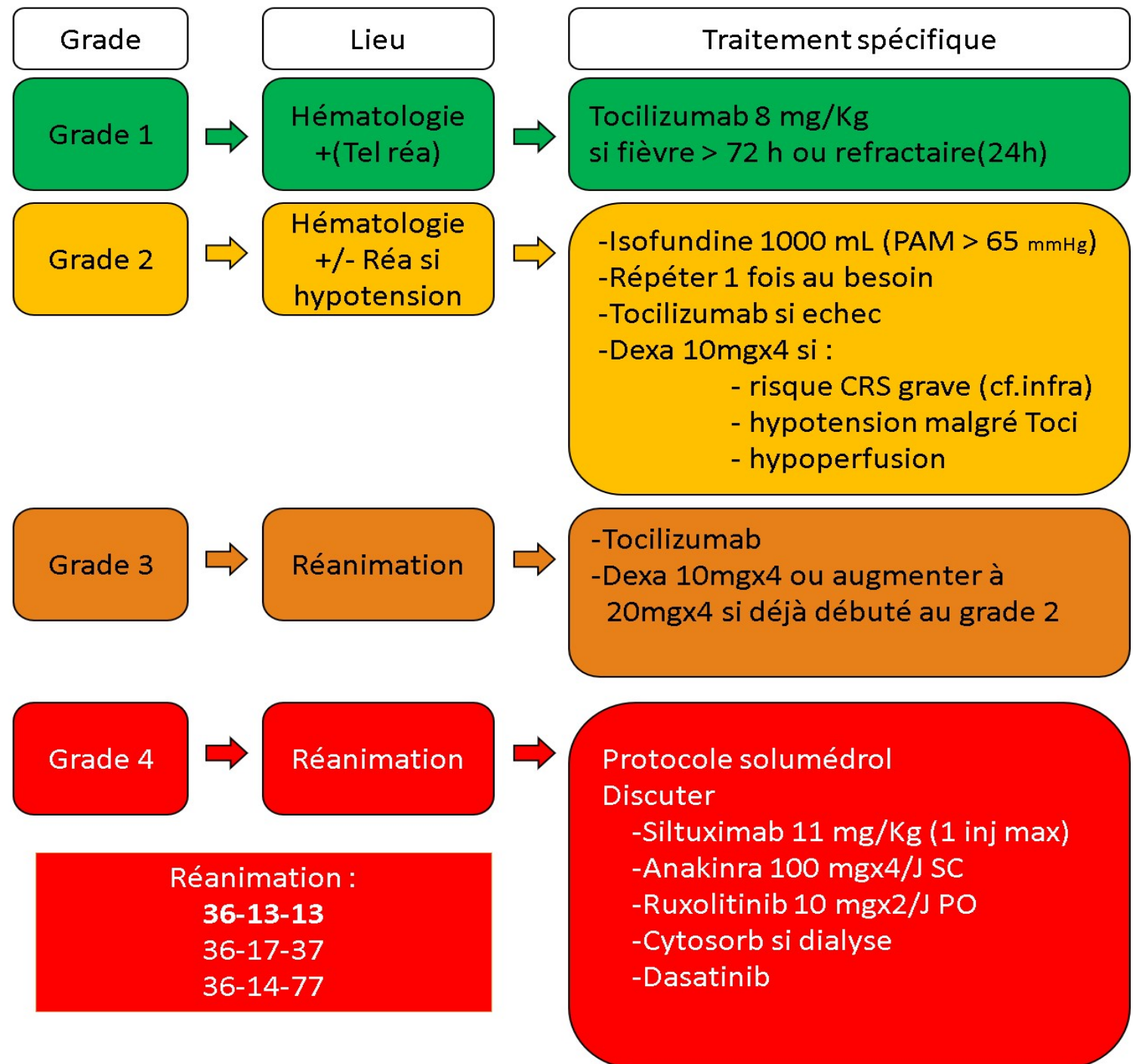
Signes de bas débit:

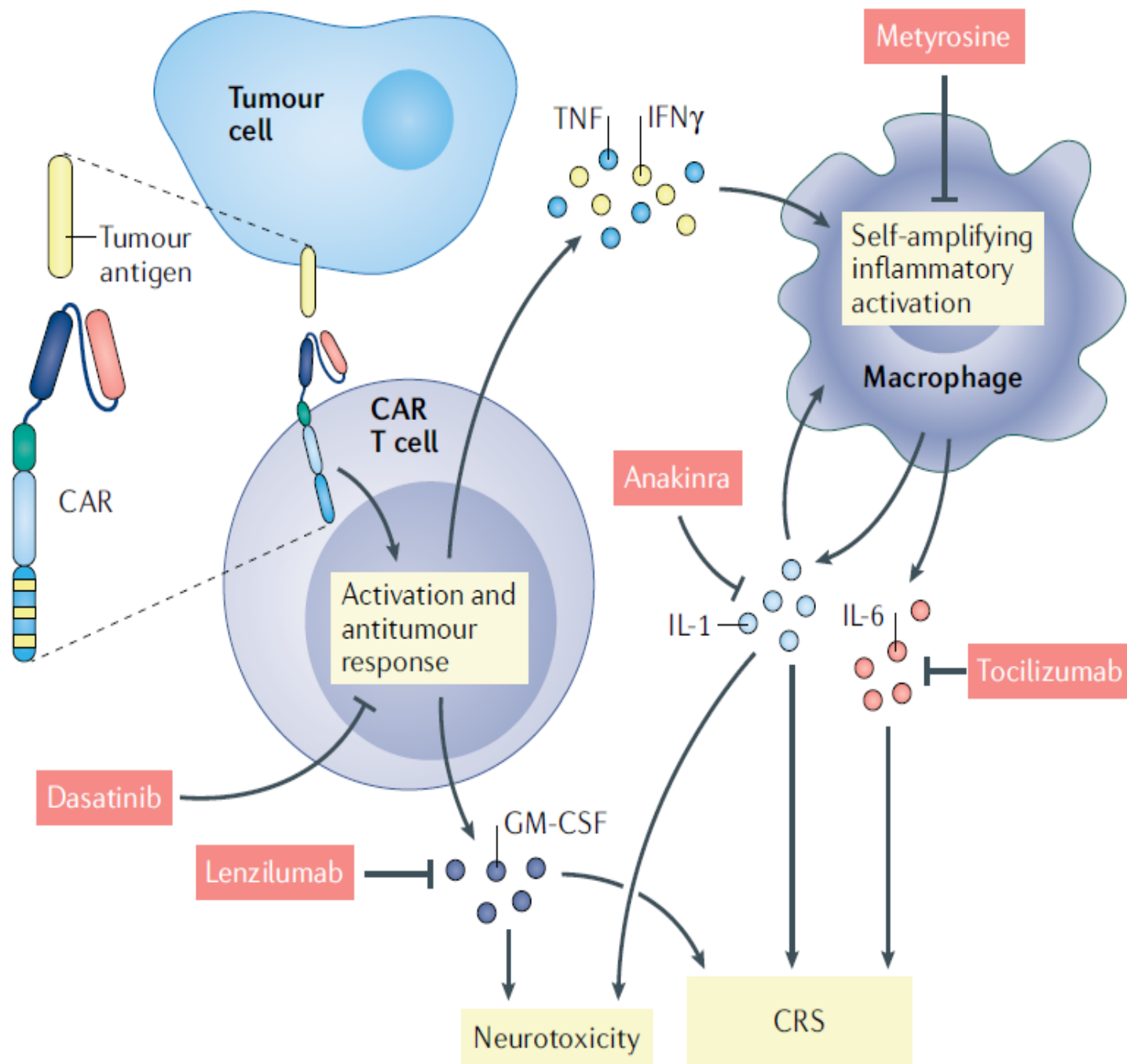
Oligurie (<0,5 ml/Kg/h)
Lactacidémie > 4 mM ou hausse malgré remplissage

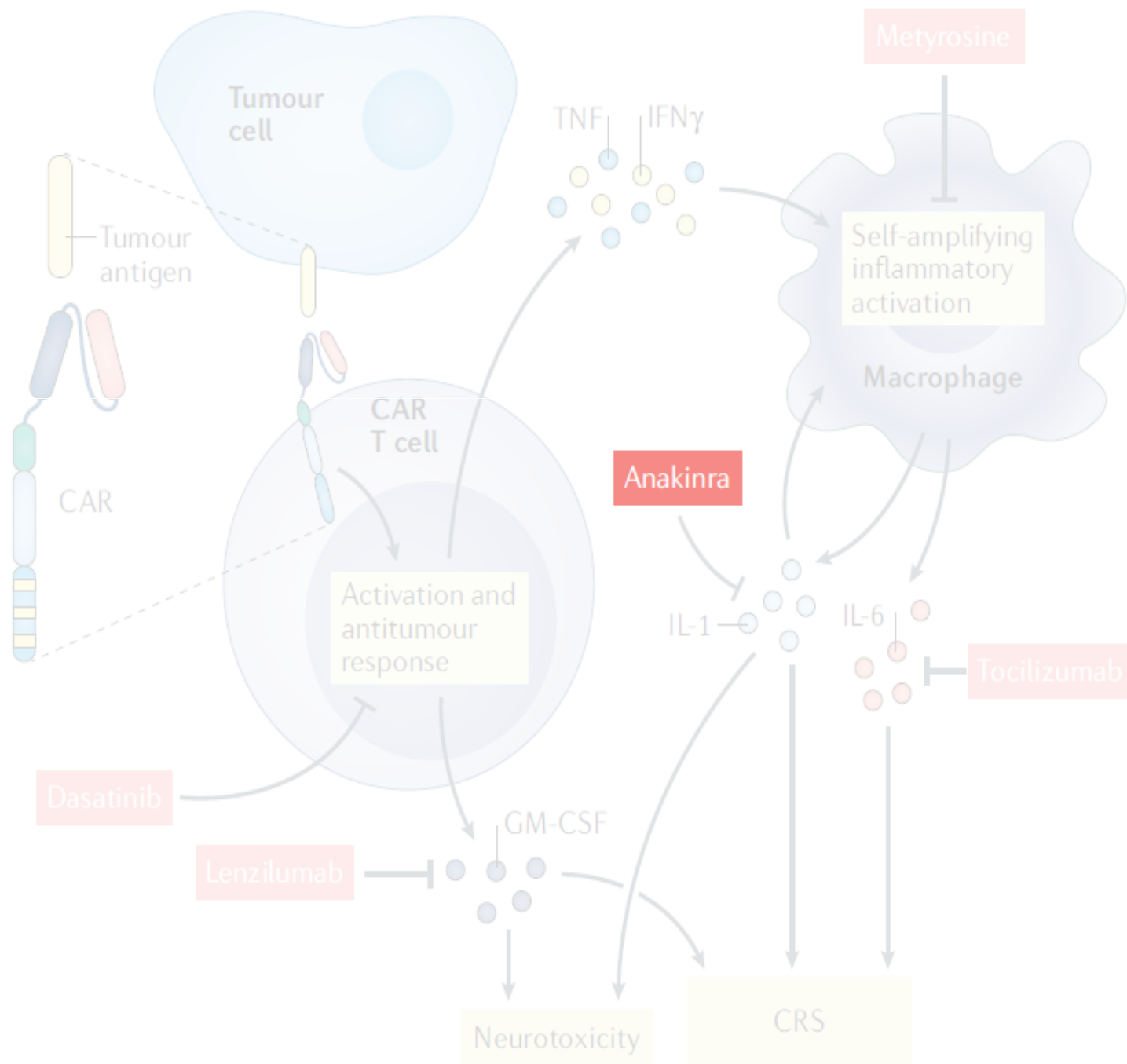
Risque de CRS grave

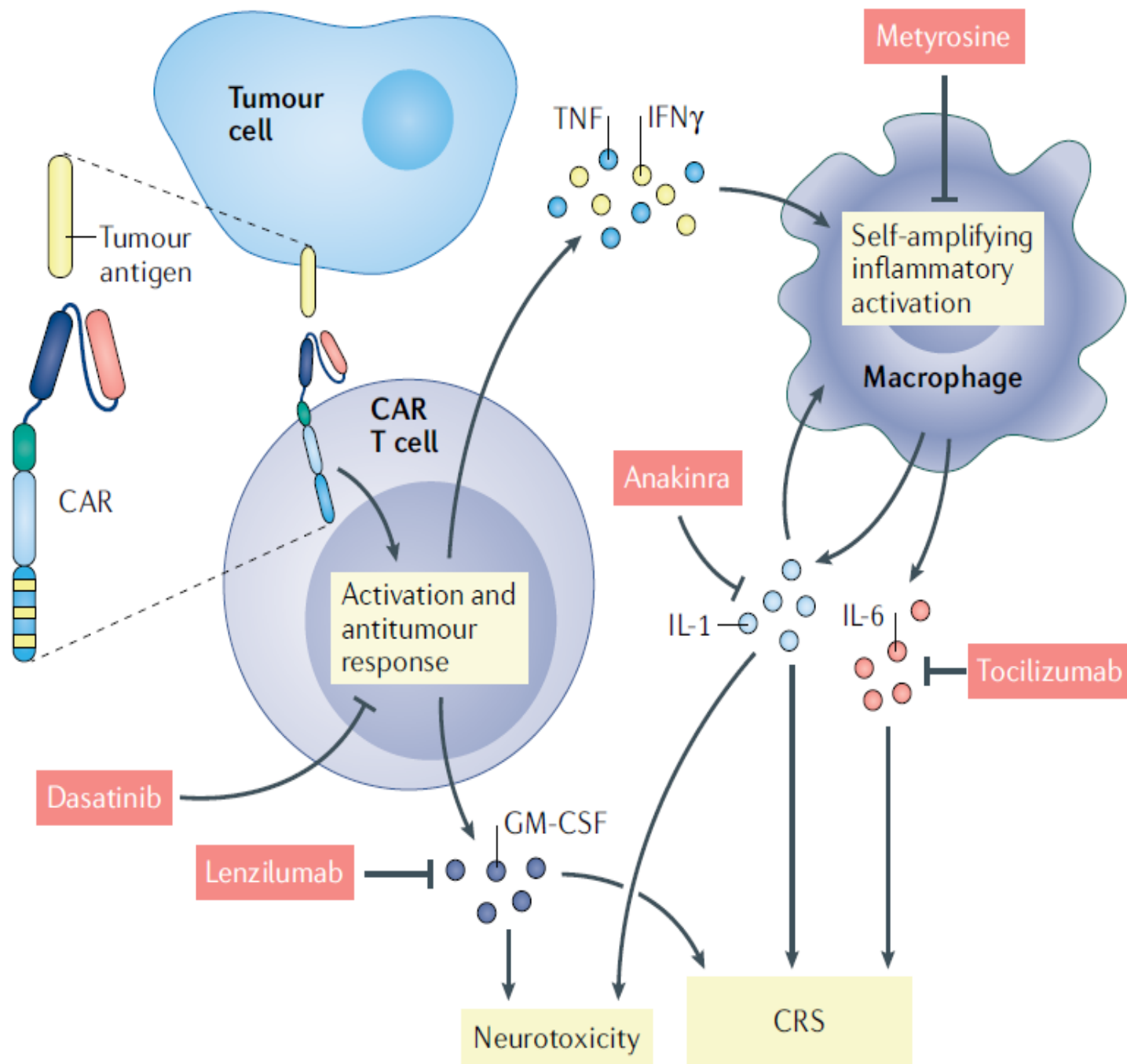
Masse tumorale élevée
CRS avant J3
comorbidités

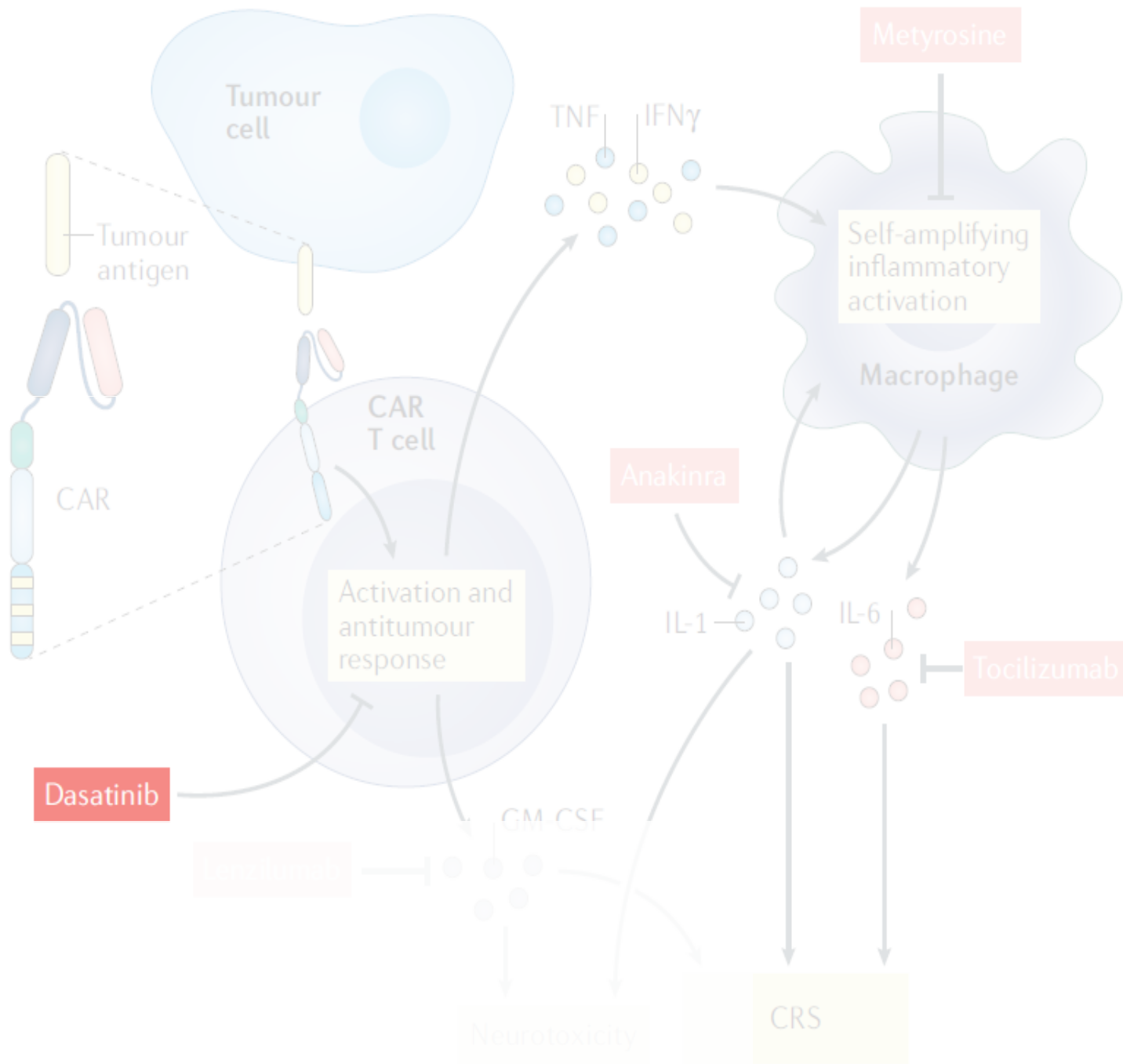
Prévenir la réa dès le grade 1 (même si le patient reste en hématologie)

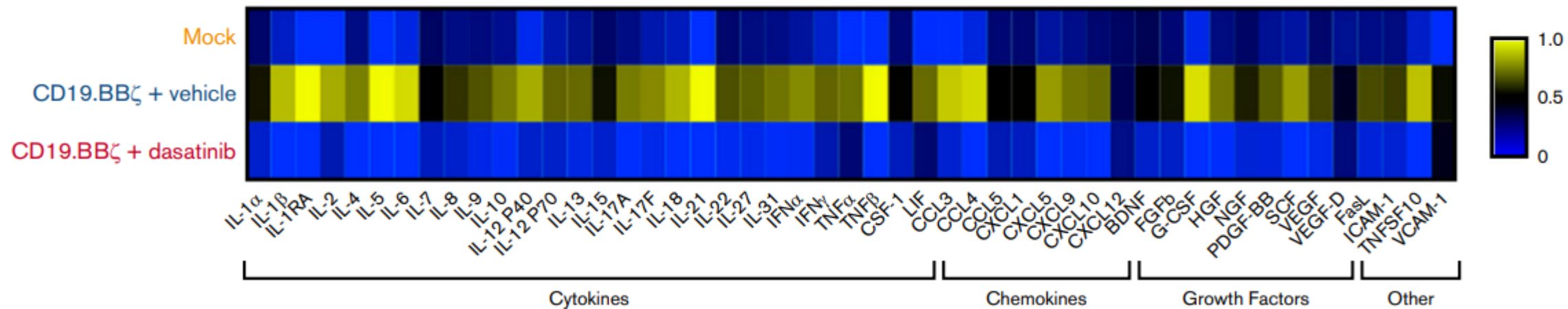
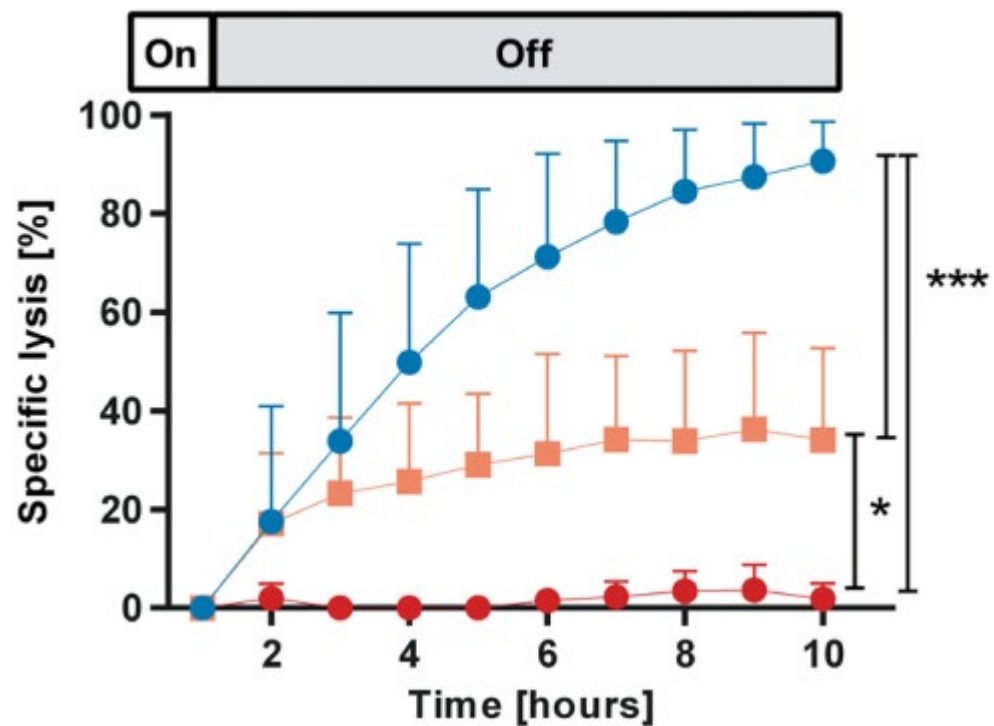


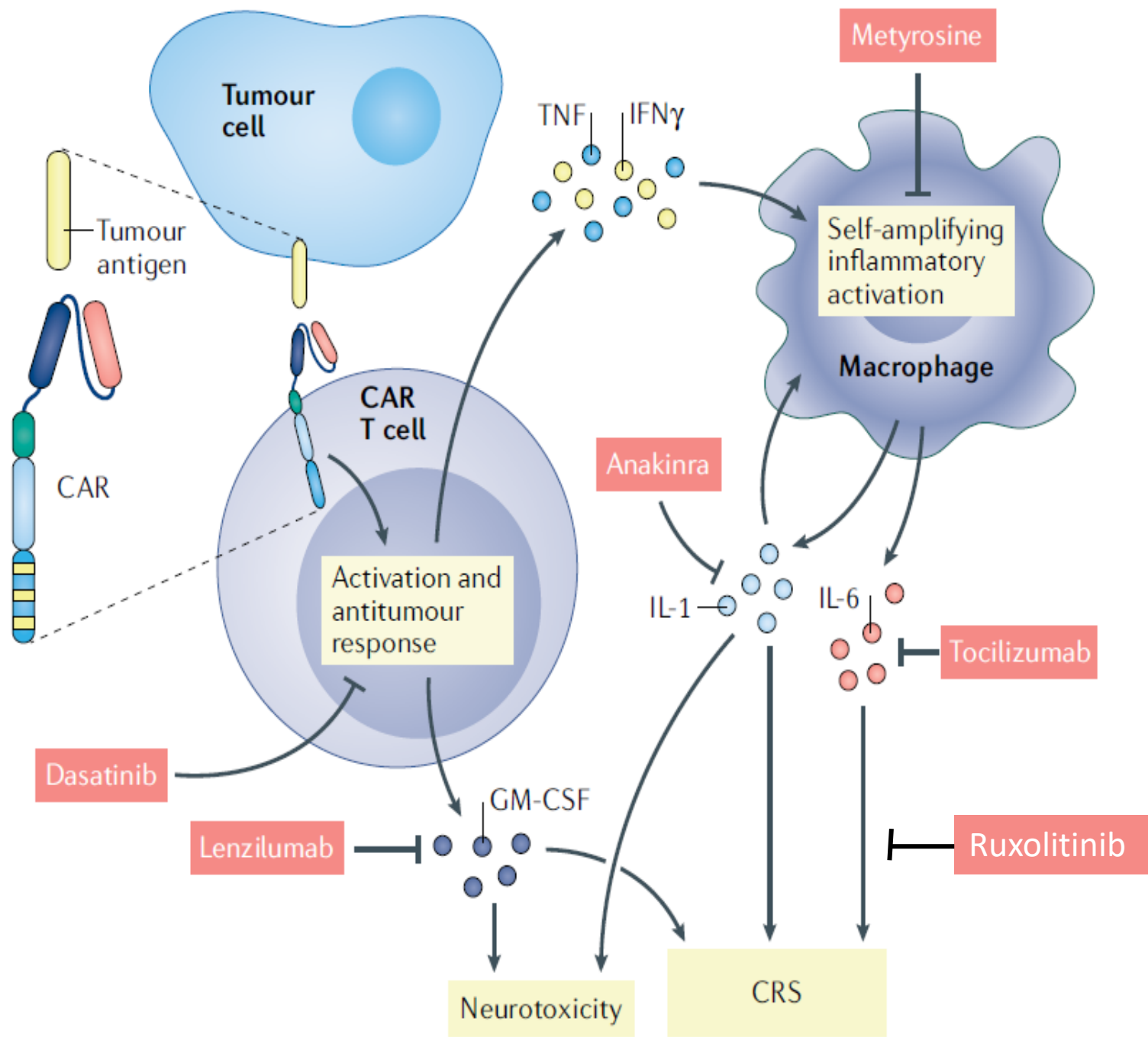


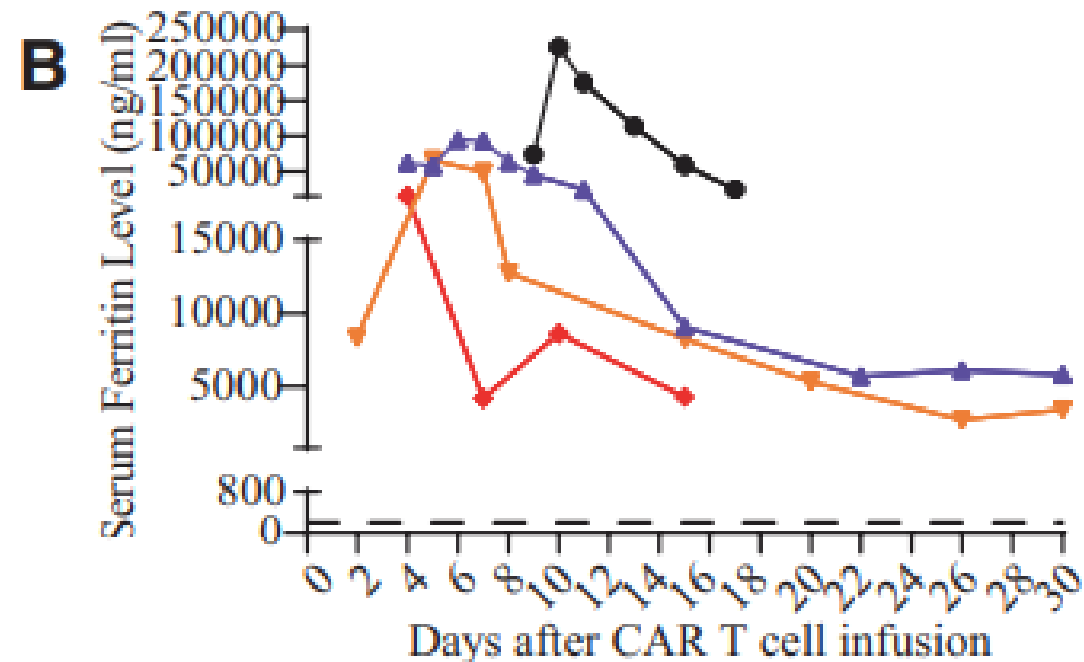
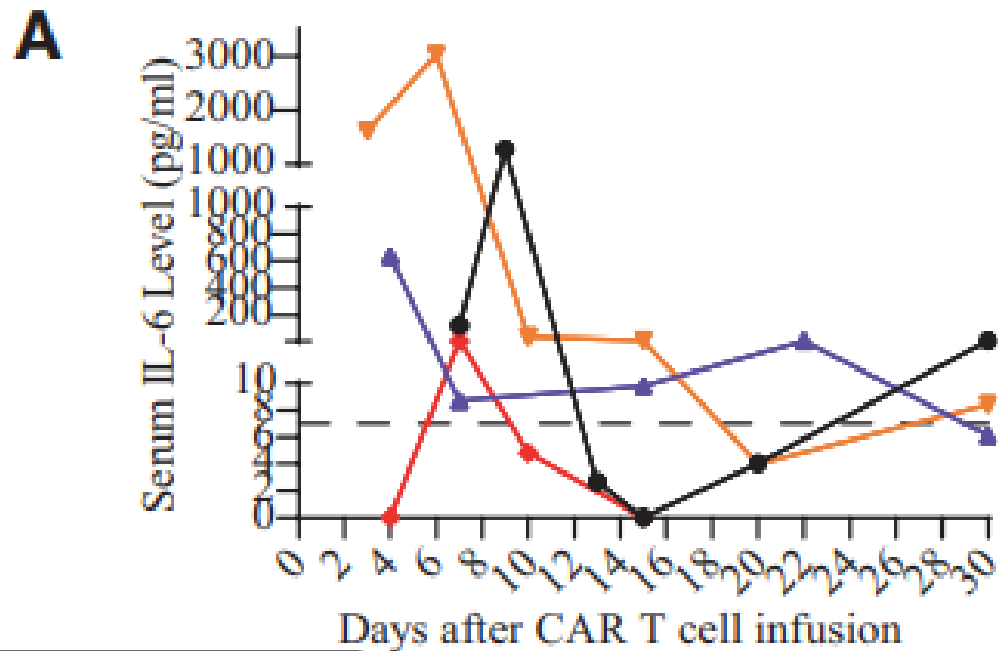




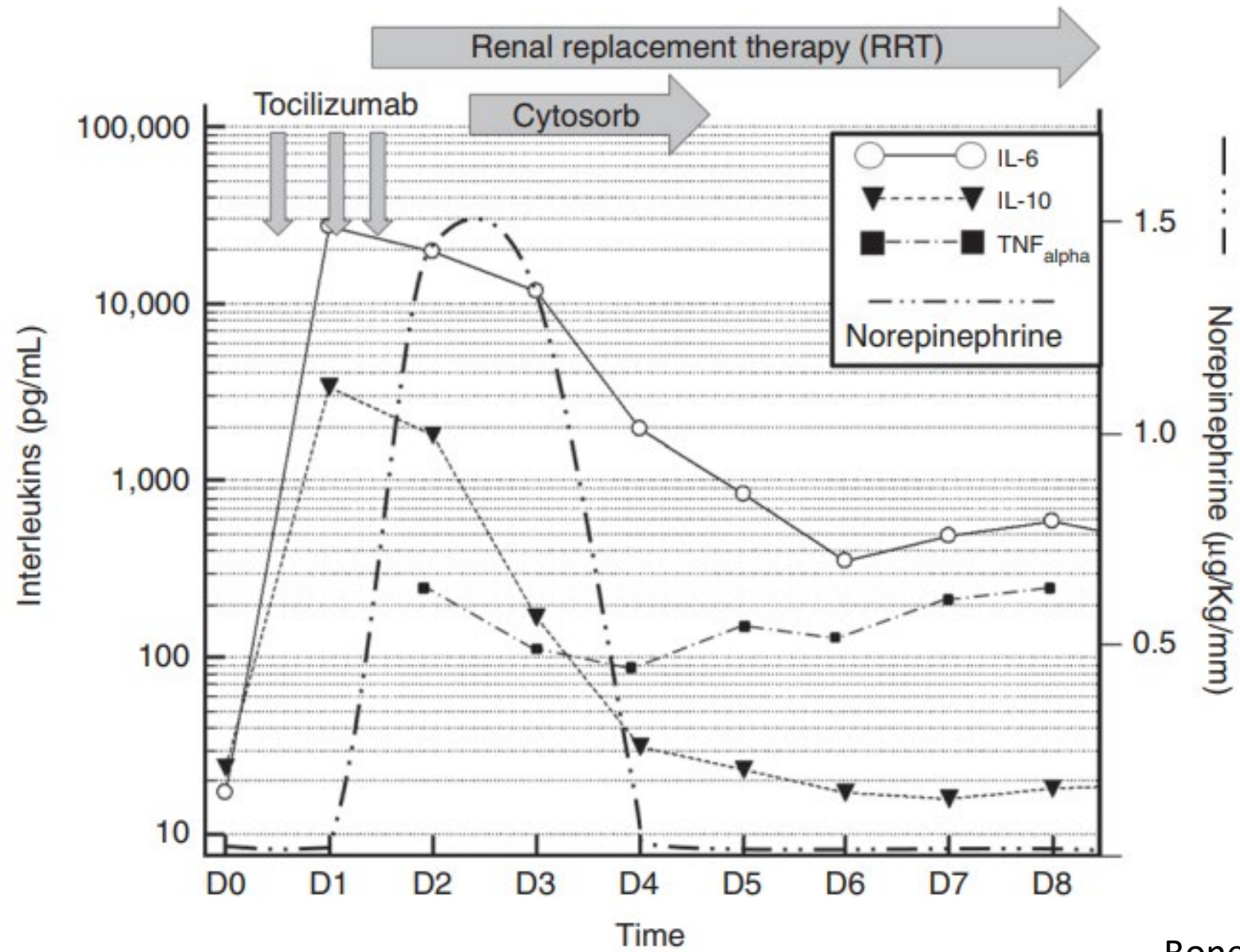


G**A** ● Untreated ● Dasa ■ Dasa + 1 hour

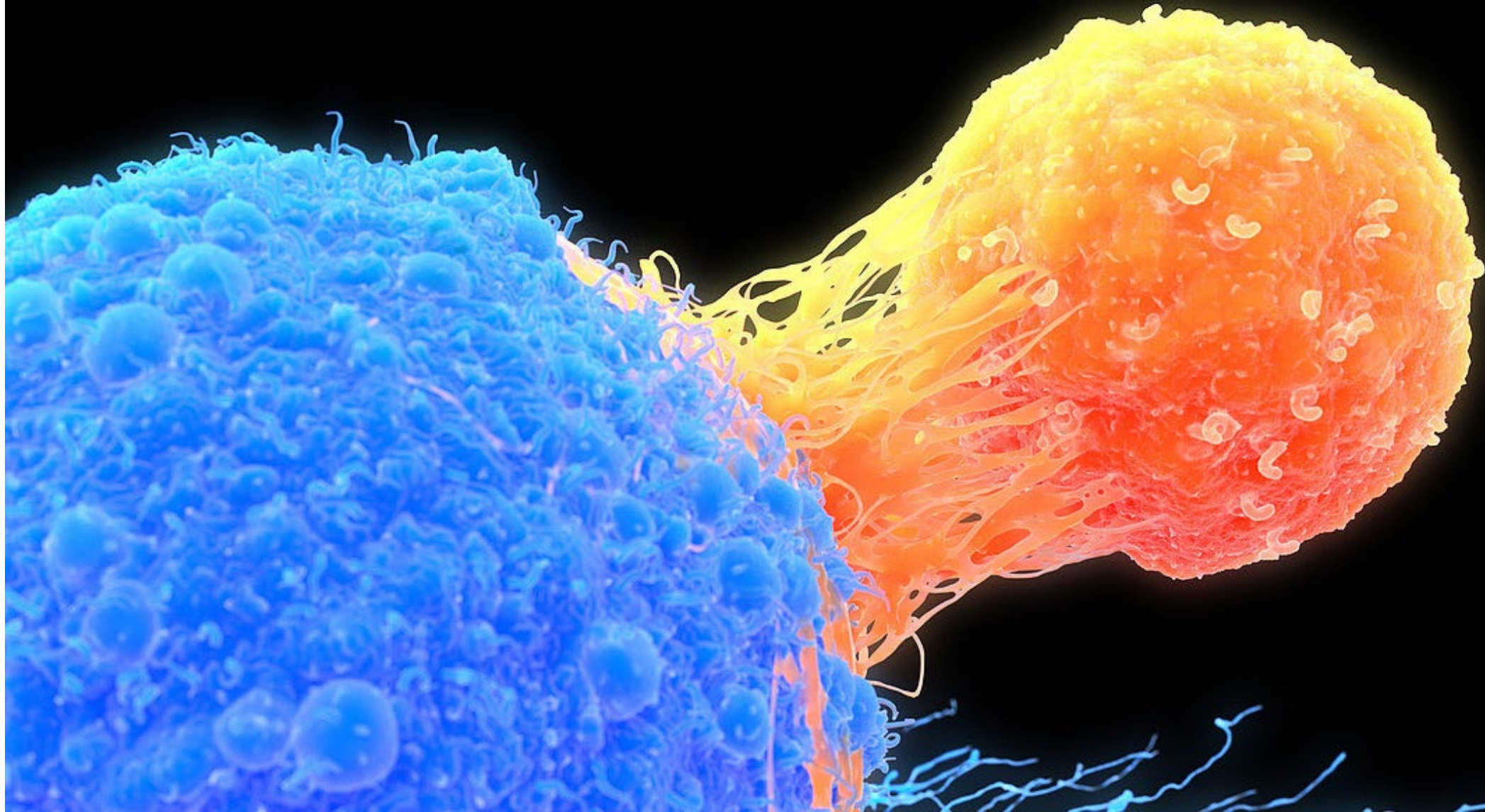




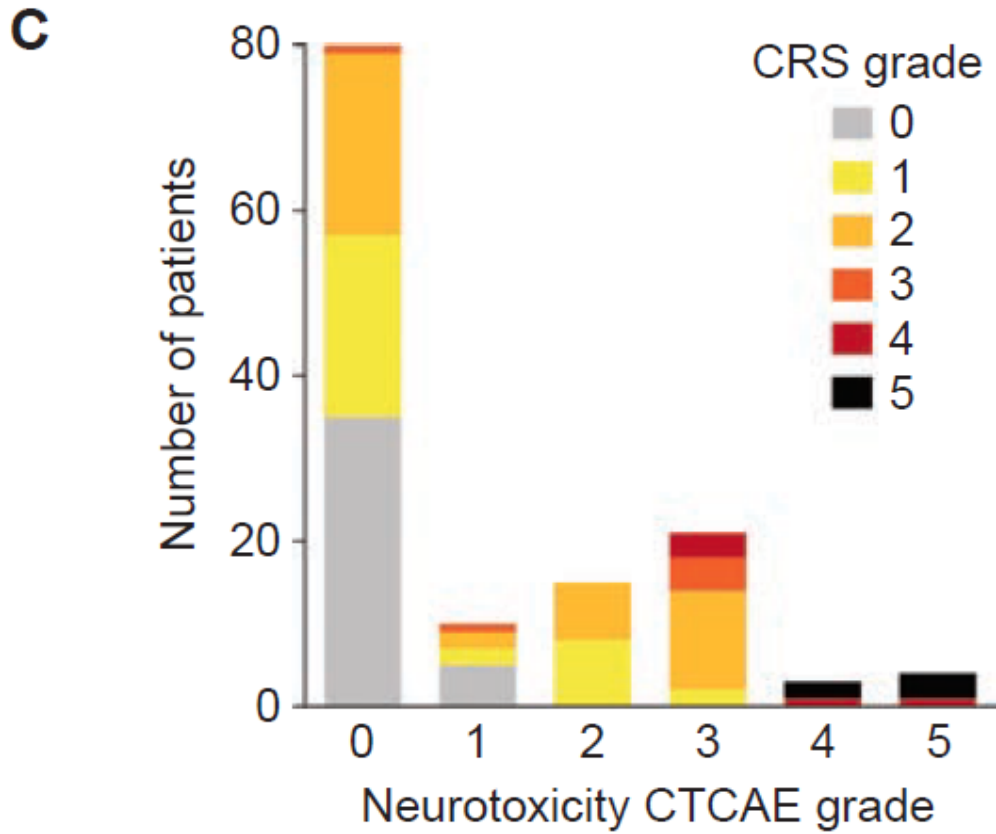
Cytosorb



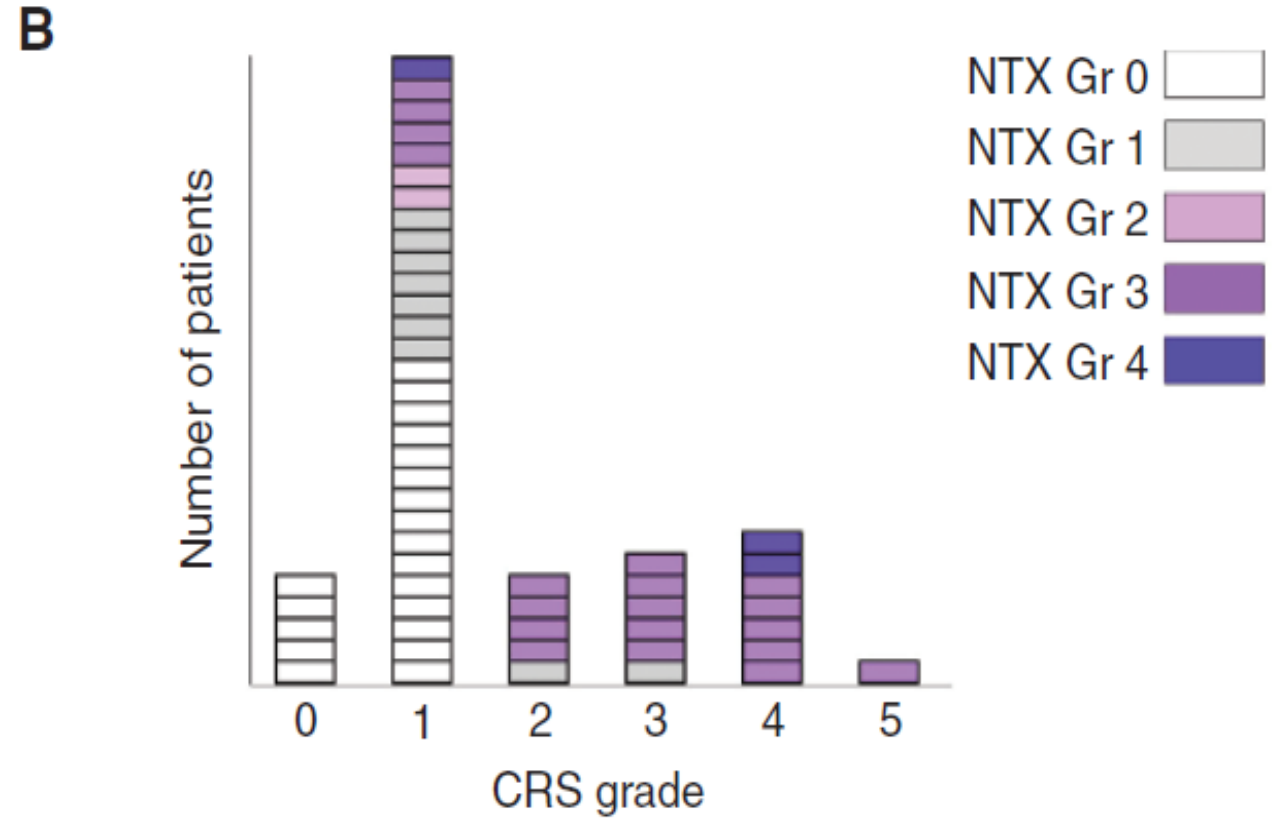
ICANS



Neurotoxicité : ICANS



4-1BB- ζ



CD28- ζ

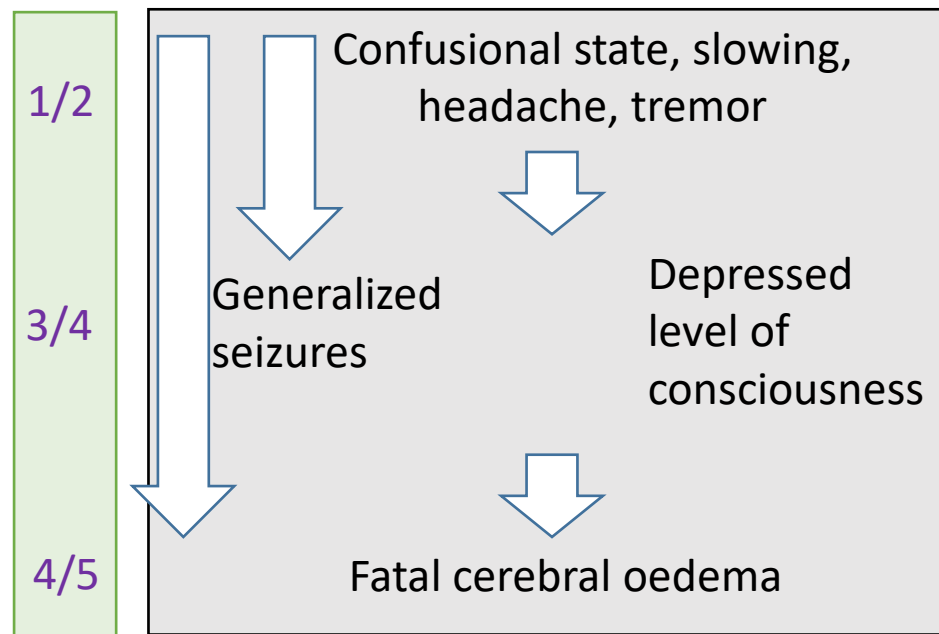
Neurotoxicité

- 71 % Confusion
- 49 % somnolence coma
- 34 % aphasie
- 20 % agraphie
- 13 % tremblements
- 13 % epilepsie
- 10 % céphalées
- 6 % déficit focal
- 5 % dyscalculie



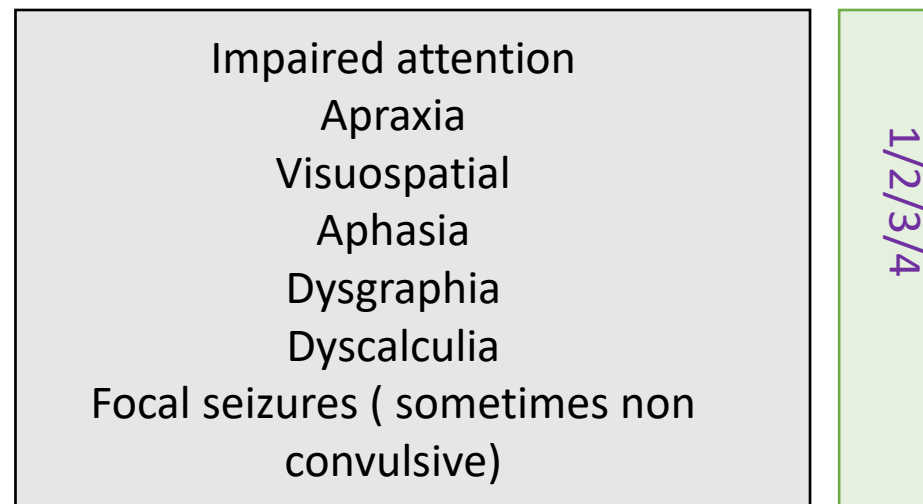
ICANS
GRADE

DIFFUSE LESIONS



FOCAL LESIONS

ICANS
GRADE



17/10 matin

Je m'appelle Rodolphe

17/10 soir

Je m'appelle Rodolphe

18/10 matin

Je m'appelle Rodolphe

18/10 AM

Je m'appelle Rodolphe

22/10/2018 matin 9^h

Je m'appelle Rodolphe

22/10/2018 : Soir

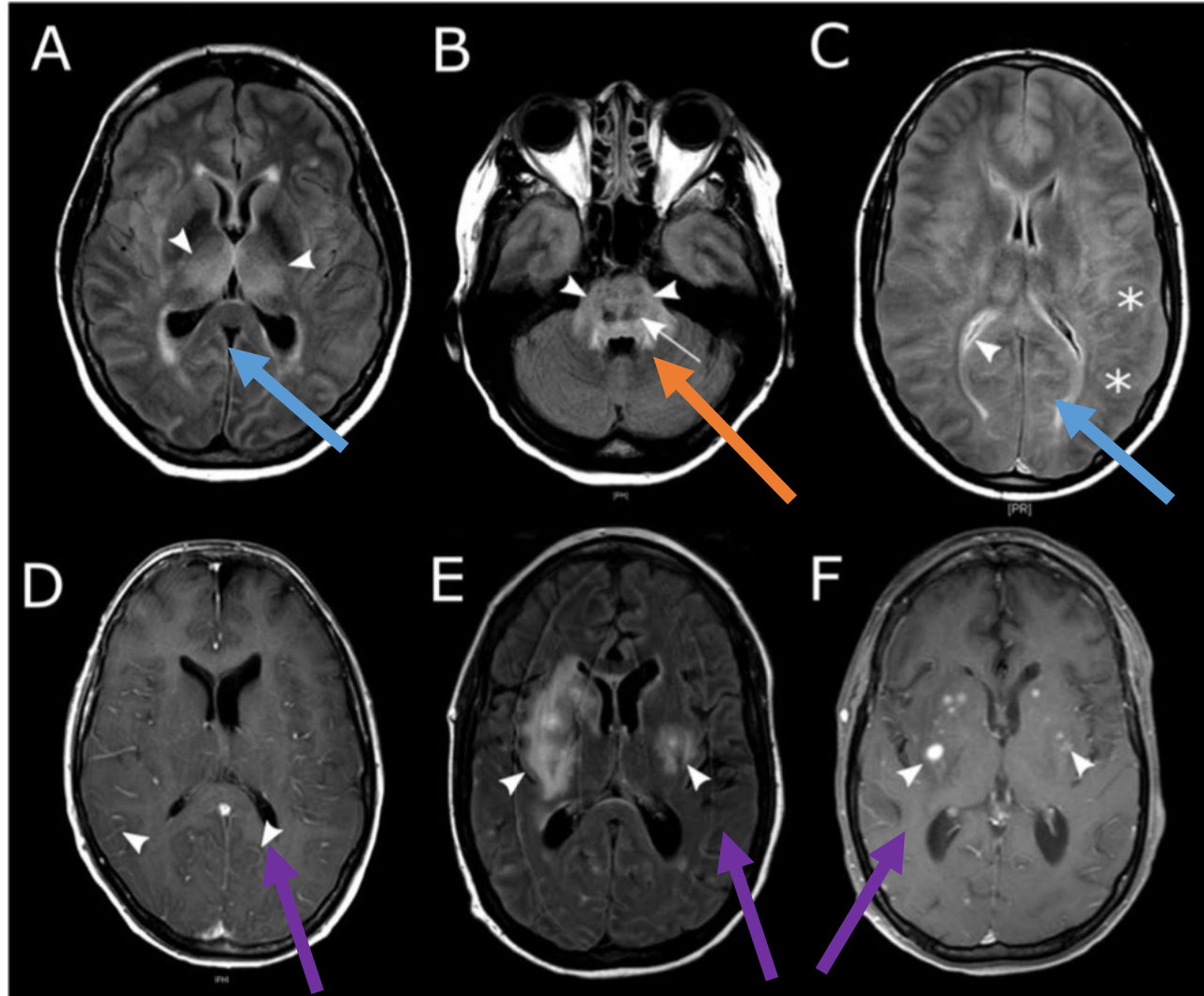
Je m'appelle Rodolphe

23/10/2018 matin 10^h

Je m'appelle Rodolphe.

MRI is neither Sensitive nor Specific

Cortical oedema



Metabolic pattern

!! Normal in 60-80% of ICANS!!



rule out alternative diagnosis

Contrast enhancement

Protocole ICANS 2019 – Lyon SUD

Grade 1:

- Seizure prophylaxis with levetiracetam (750*2)
- Neurologic examination with MOCA scale
- EEG monitoring/48-72H
- Imaging of brain +/- CSF
- Consider anti-IL-6 therapy if there is concurrent CRS

Grade 2:

- Same as grade 1 +
- Start dexamethasone 10mg 2 to 4 times daily
- Start anti-IL-6 therapy if CRS
- Seizure prophylaxis with levetiracetam
- EEG monitoring (1/24-48h)
- Admission to ICU if CRS >1

Grade 3:

- Admission to ICU
- Consider increasing dexamethasone 10 to 20 mg every 6 hours, up to methylprednisolone 100 mg/day
- BDZ for short term seizures control if needed
- Traitements de sauvetage * ?

Grade 4:

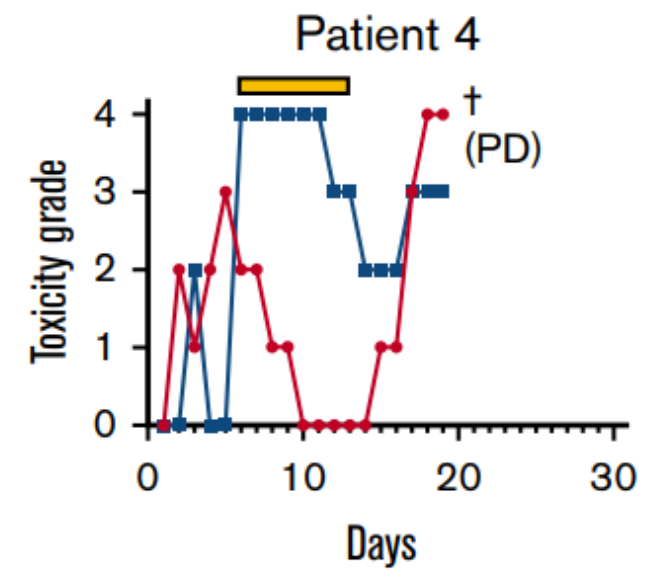
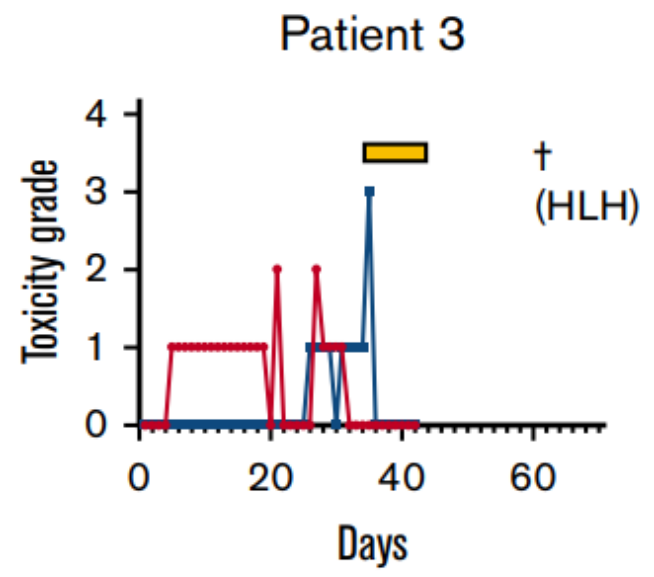
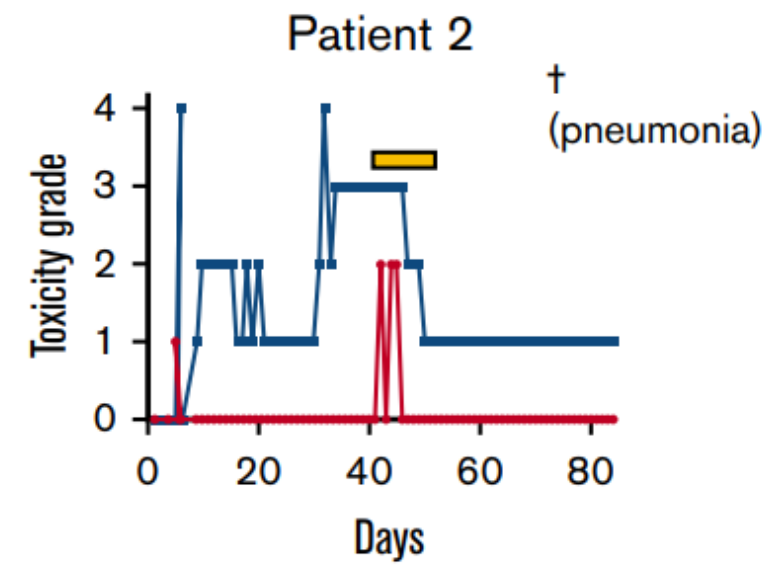
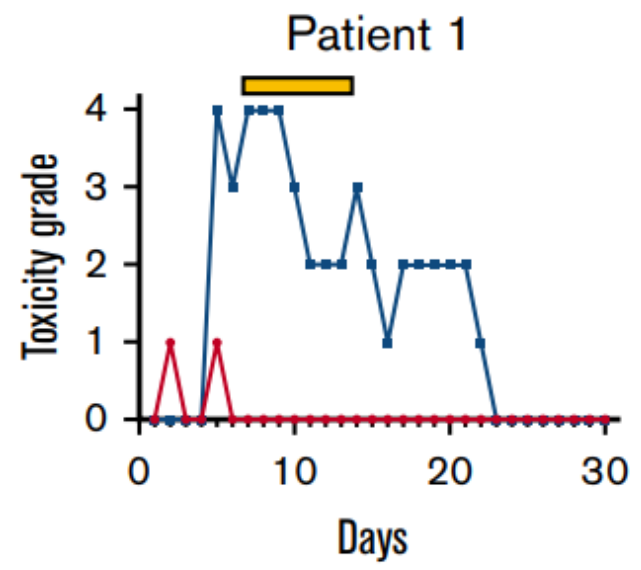
- Same as in grade 3 with HD methylprednisolone
- Management of cerebral edema if needed, up to craniectomy based on local consensus
- Traitements de sauvetage* ?

* Ce traitement n'a pas l'AMM dans cette indication

A

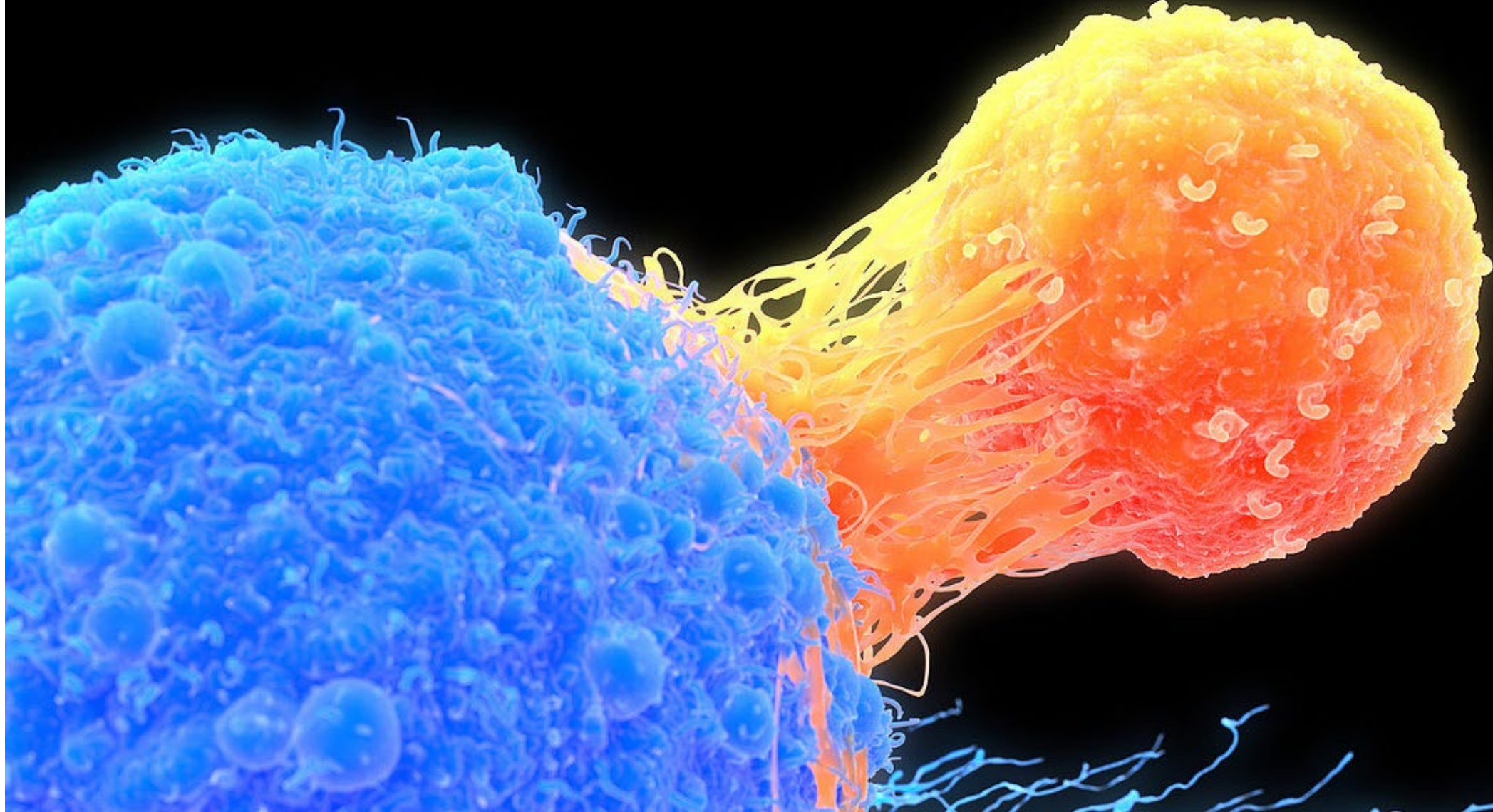
● CRS
■ ICANS
Anakinra

RESPONDERS

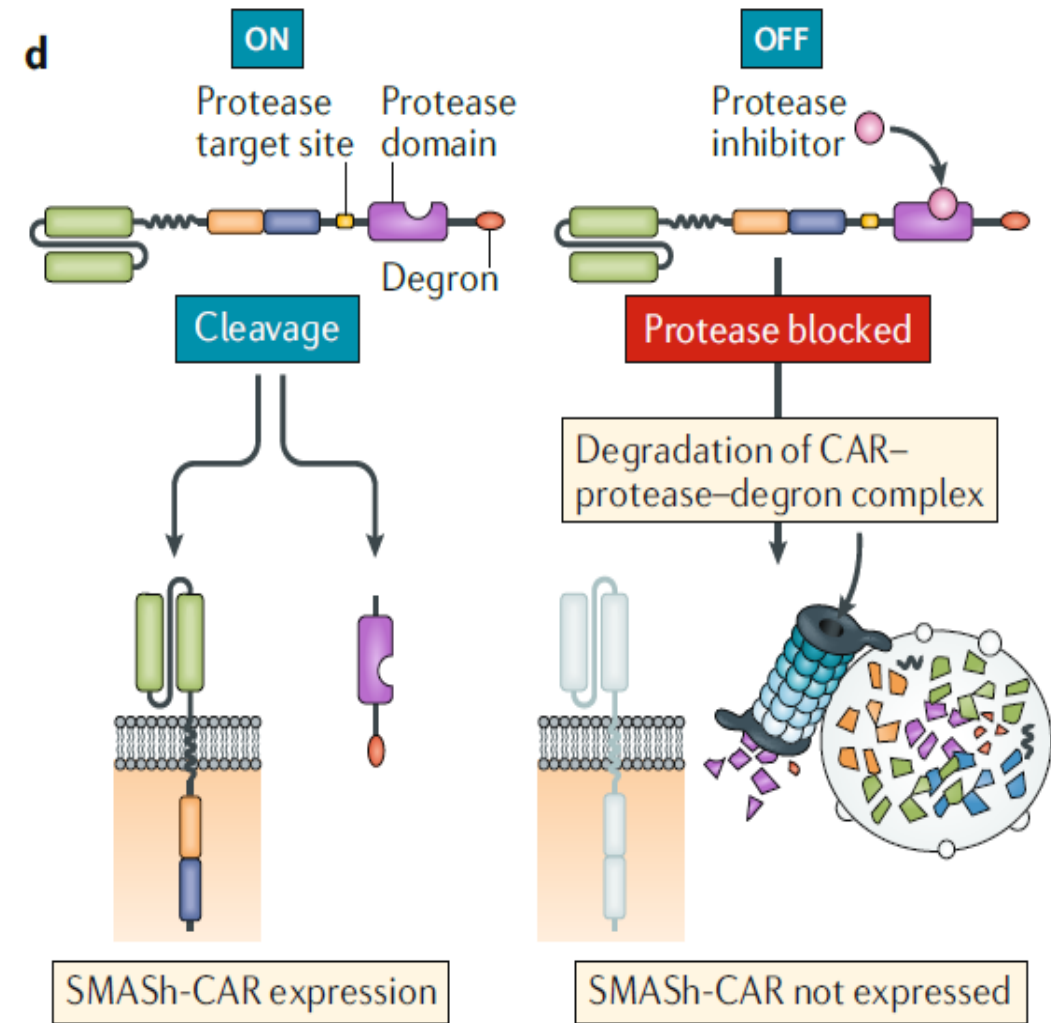
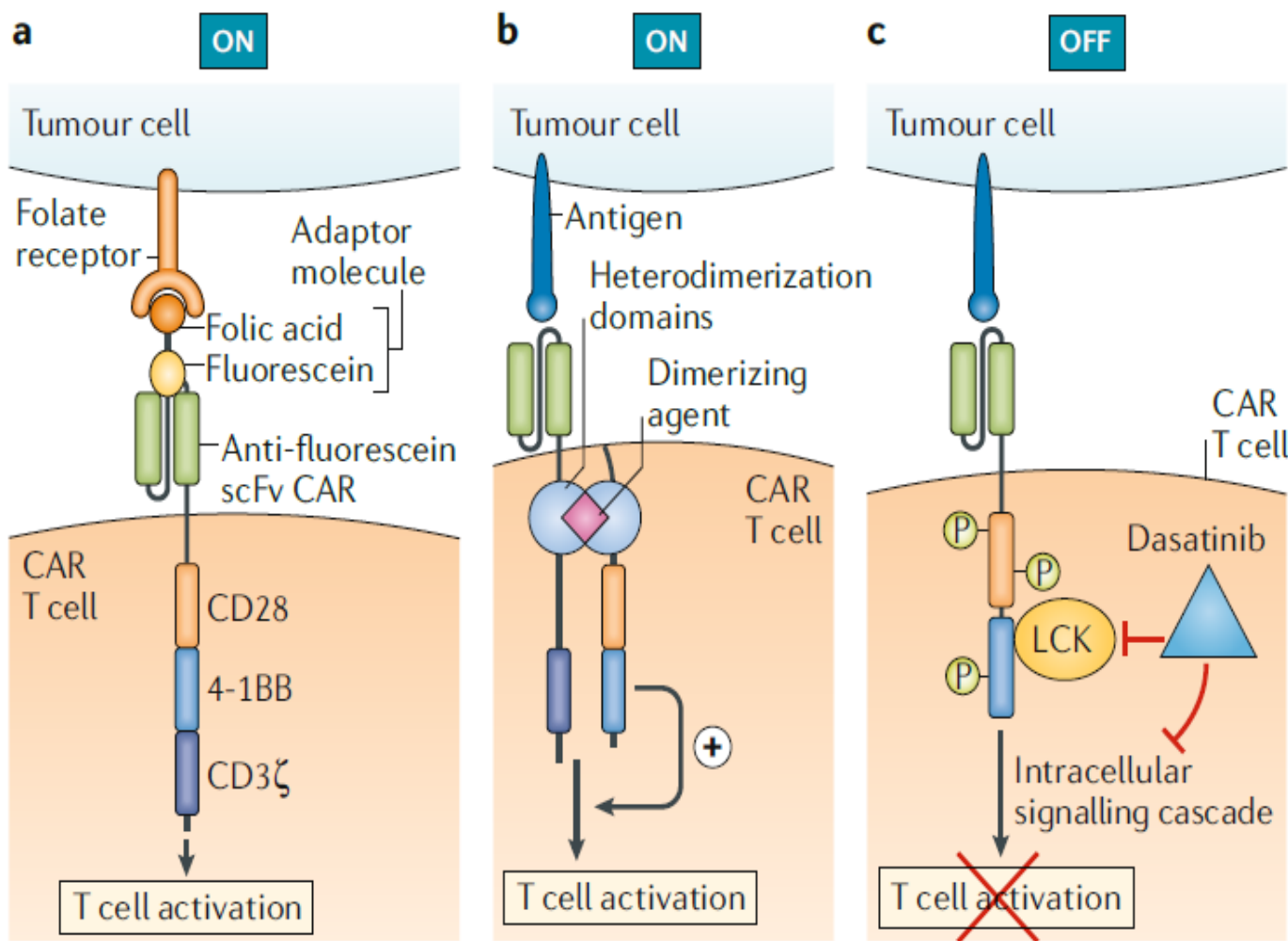


A Phase 2 Trial of Anakinra for the Prevention of CAR-T Cell Mediated Neurotoxicity

Et après...

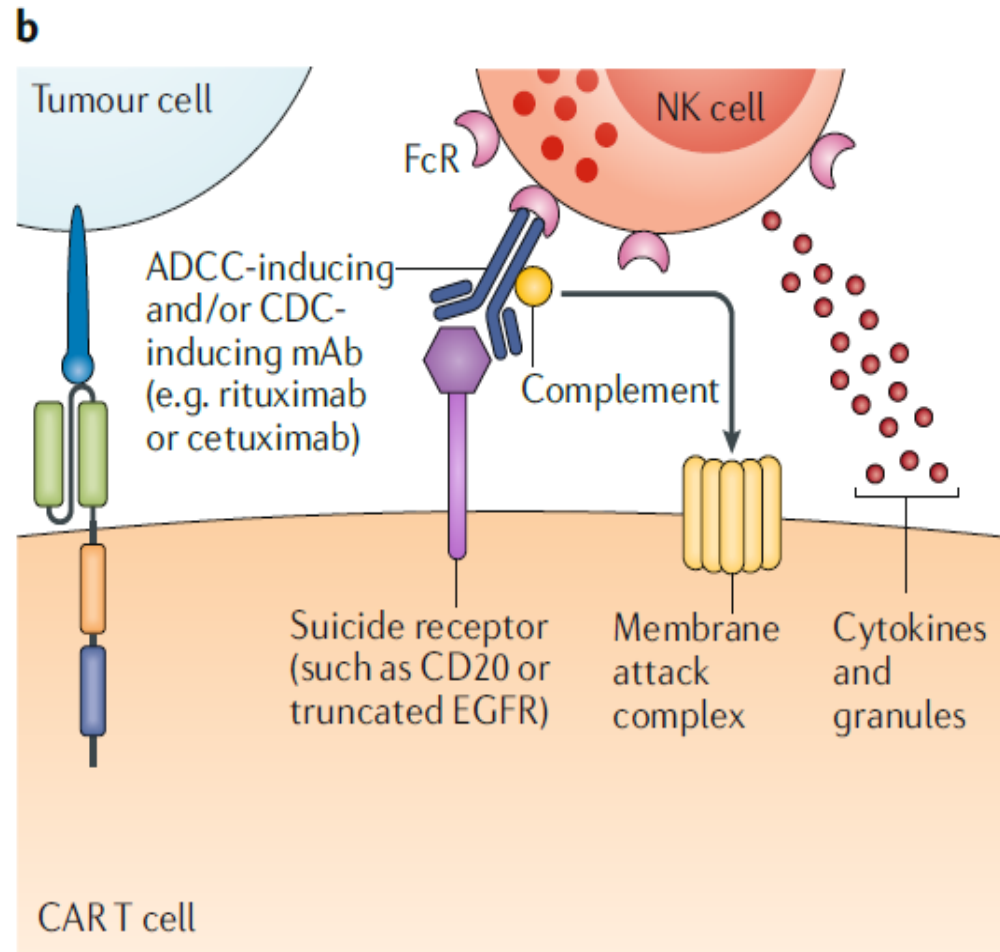
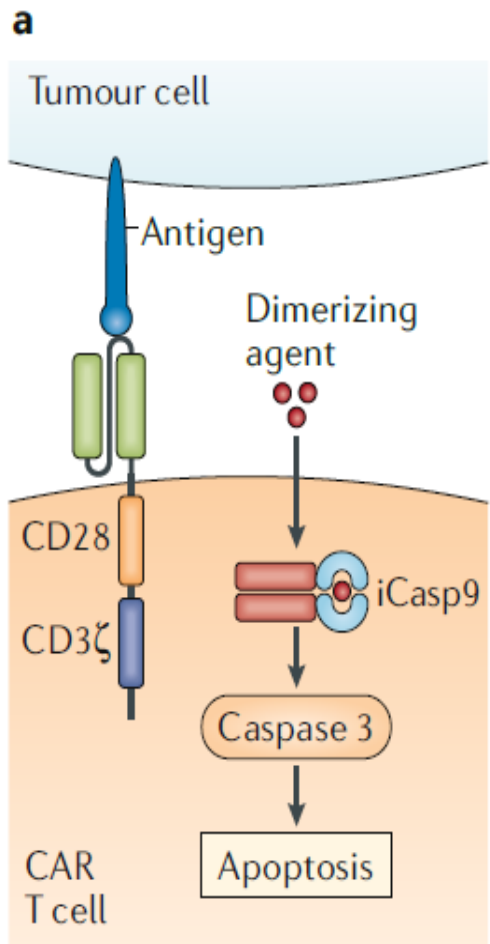


A 'On/off switches' predicated on administration of small-molecule agents

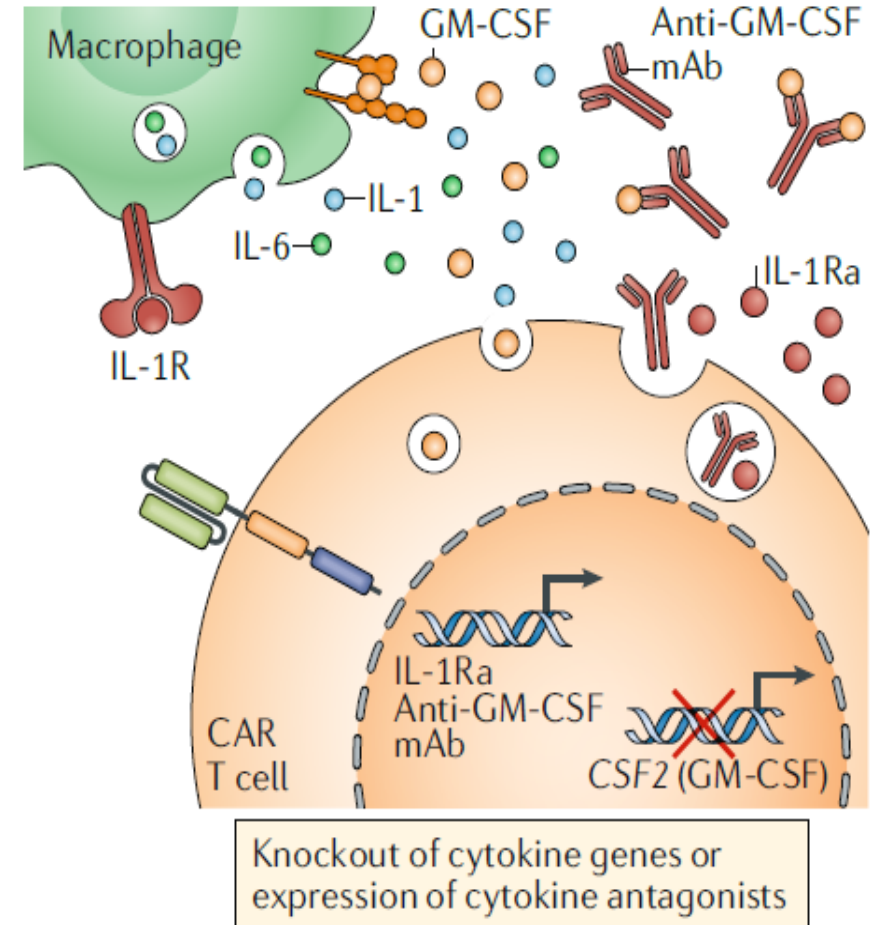


* Ces traitements ne disposent pas d'AMM en Europe

B Suicide gene systems



C Direct antagonism of systemic cytokines



* Ces traitements ne disposent pas d'AMM en Europe



Merci de votre attention