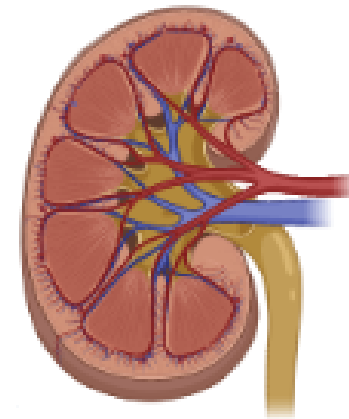
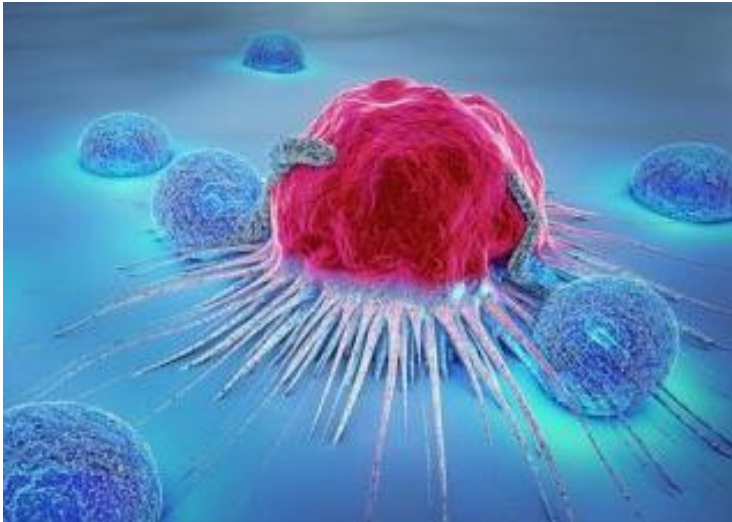




# Toxicité rénale des CAR-T cells



Lara Zafrani

Médecine Intensive Réanimation

Hôpital Saint-Louis

# Conflits d'intérêts

**Déclare les liens suivants :**

- **SANOFI : lecture**
- **MSD : lecture**

# Plan

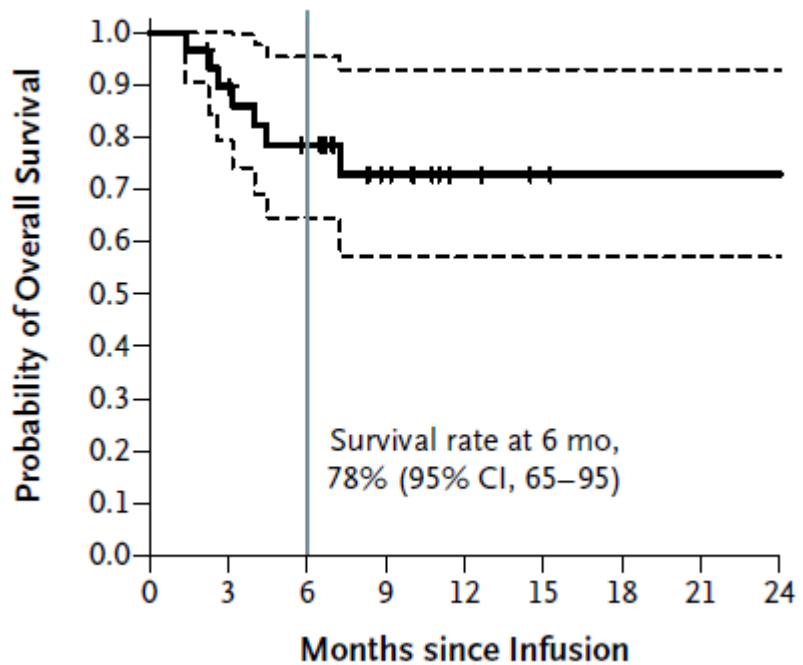
- CAR-T et hémopathies malignes
- IRA et CAR-T : épidémiologie
- IRA et CAR-T : physiopathologie
- Traitements spécifiques
- Pronostic

# Plan

- CAR-T et hémopathies malignes
- IRA et CAR-T : épidémiologie
- IRA et CAR-T : physiopathologie
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- Pronostic

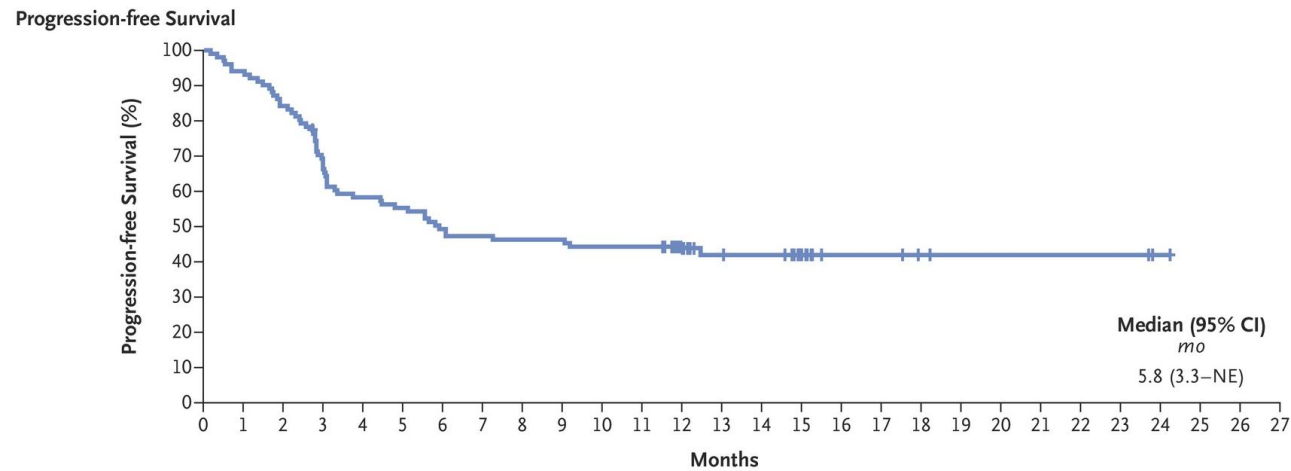
# CAR-T et hémopathies malignes

LAL



Maude et al. NEJM 2014

Lymphome



Neelapu et al. NEJM 2017

LAL

T cells expressing CD19 chimeric antigen receptor in acute lymphoblastic leukaemia in children and adolescents: a phase 1 dose-escalation trial

*Daniel W Lee, James N Kochenderfer, Maryalice Stetler-Stevenson, Yongzhi K Cui, Cindy Delbr, Marianna Sabatino, Nirali N Shah, Seth M Steinberg, Dave Stroncek, Nick Tschernia, Constar Alan S Wayne, Crystal L Mackall*

Lancet

ORIGINAL ARTICLE

Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia

Jae H. Park, M.D., Isabelle Rivière, Ph.D., Mithat Gonen, Ph.D.,

NEJM 2018

Lymphome

Lisocabtagene chimeric antigen receptor for relapsed or refractory large B-cell lymphoma: a multicentre phase 1b/2 trial

*Jeremy S Abramson, M Lia Palomb David G Maloney, Charalambos Ar Mary Mallaney, Ken Ogasawara, Kathryn Newhall, Yeonhee Kim, Daniel Li, Tan*

Tisagenlecleucel for Relapsed or Refractory Large B-Cell Lymphoma

Stephen J. Schuster, M.D.

Tisagenlecleucel in relapsed and refractory follicular lymphoma: a phase 1b/2 trial

Nathan Hale Fowler<sup>1,2</sup>✉, M

F.L. Locke, D.B. Mikl

ORIGINAL ARTICLE

NEJM 2020

KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma

M. Wang, J. Munoz, A. Goy, F.L. Locke, C.A. Jacobson, B.T. Hill,

Myélome

ORIGINAL ARTICLE

Ciltacabtagene autoleucel, a CD19-directed chimeric antigen receptor T-cell therapy with relapsed or refractory non-Hodgkin's lymphoma

(CARTITUDE-1): a phase 1b/2 trial

ORIGINAL ARTICLE

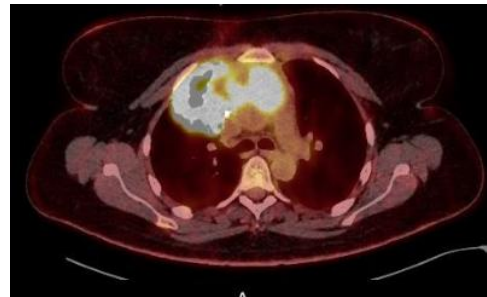
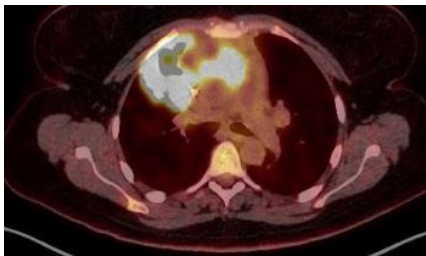
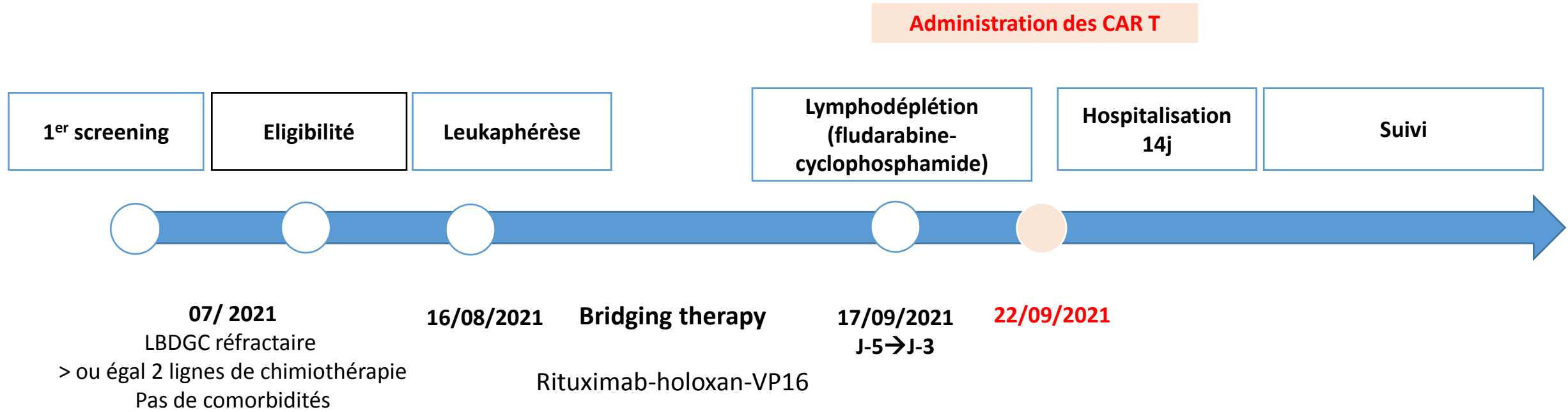
NEJM 2021

Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma

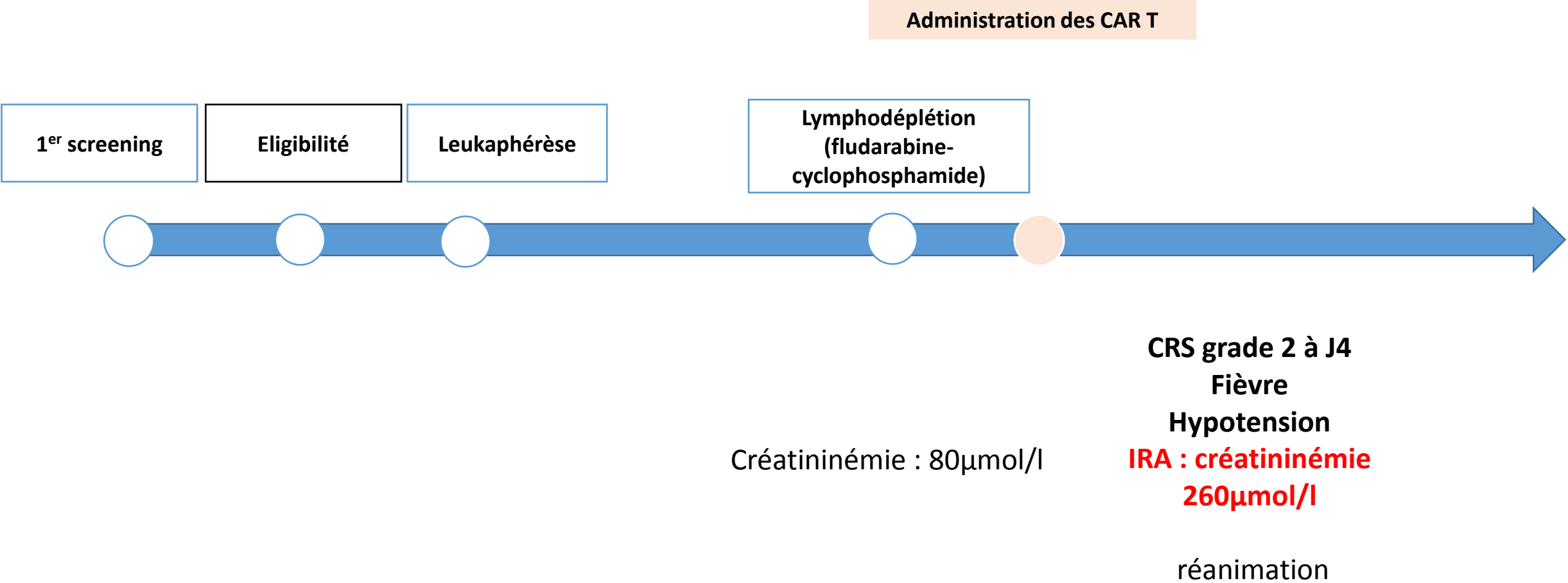
Noopur Raje, M.D., Jesus Berdeja, M.D., *Jesus G Berdeja\*, Deepu Madduri\*, Saad Z Usmani, Andrzej Jakubow*

Nikhil C. Munshi, M.D., Larry D. Anderson, Jr., M.D., Ph.D., Nina Shah, M.D.,

# Mr D, 75 ans



# Après les CAR-T

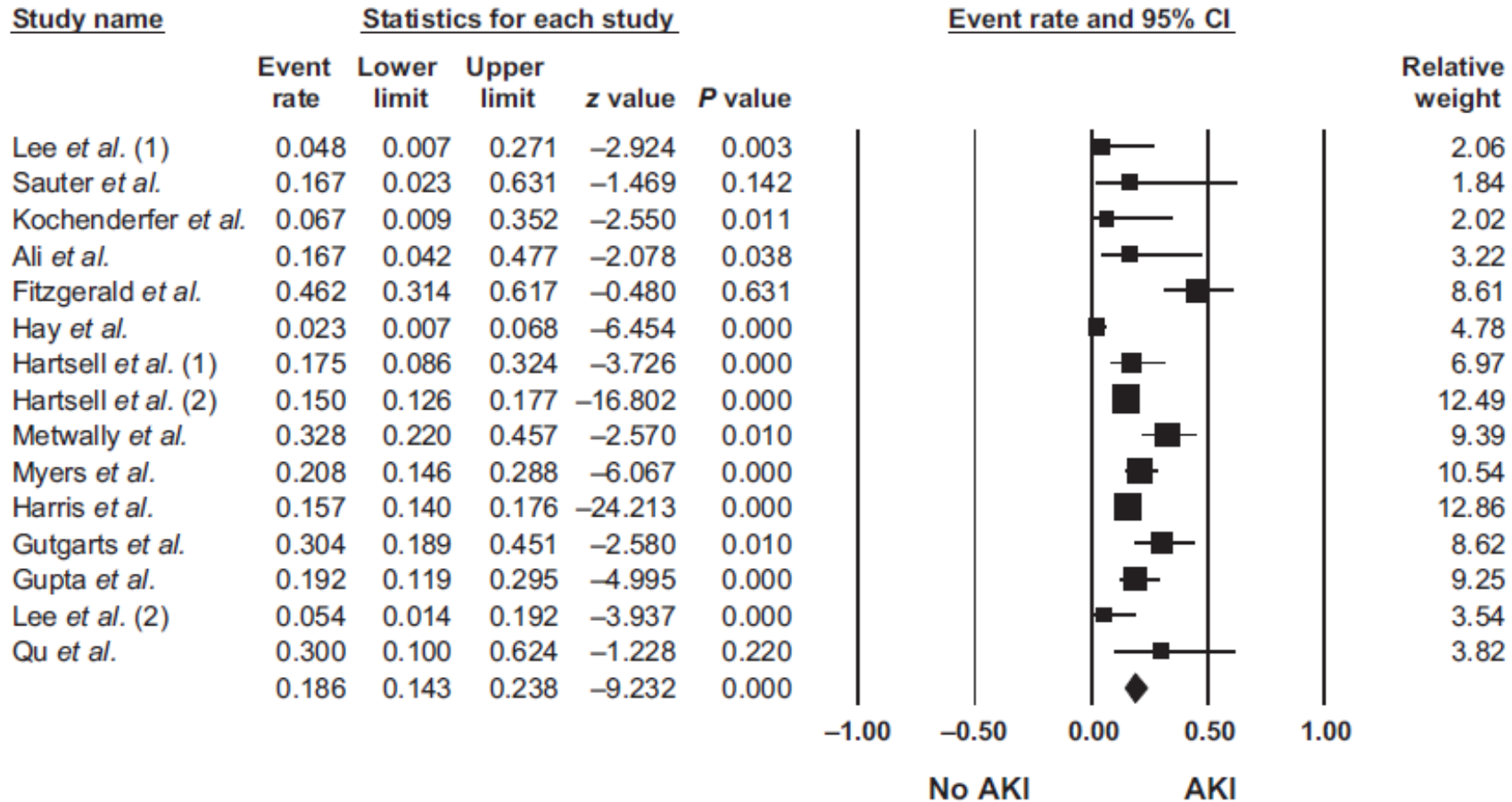




# Plan

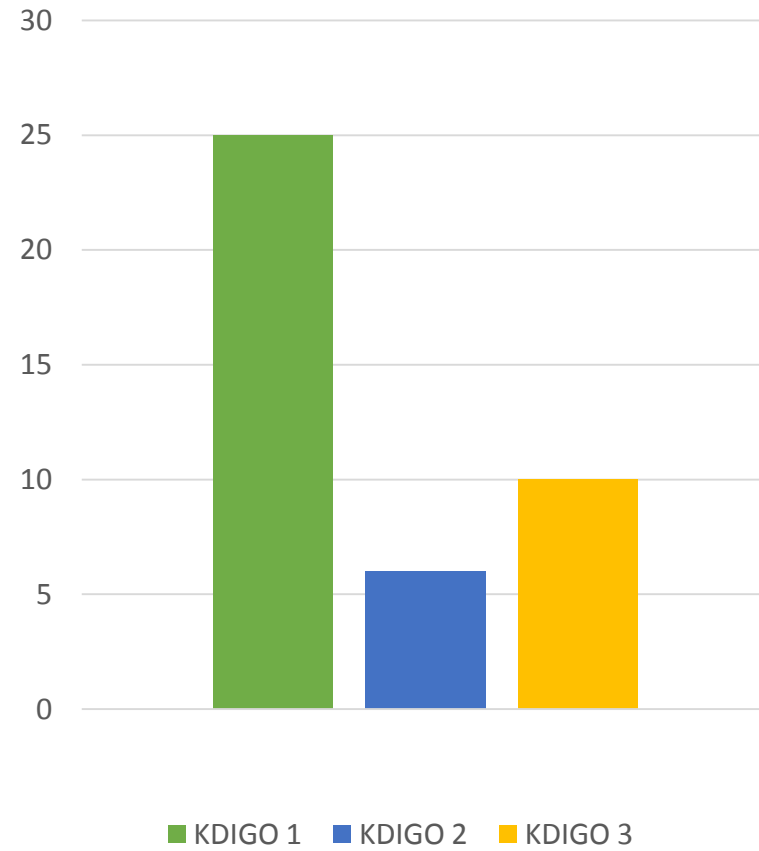
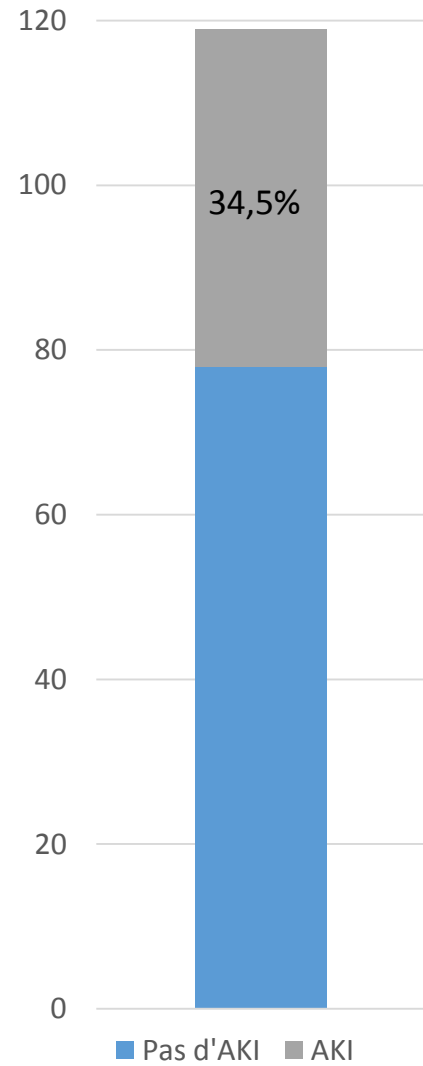
- CAR-T et hémopathies malignes
- **IRA et CAR-T : épidémiologie**
- IRA et CAR-T : physiopathologie
- Traitements spécifiques
- Pronostic

# Epidémiologie



Incidence IRA 18,9%  
Incidence RRT 4,4%

## Epidémiologie : en réanimation

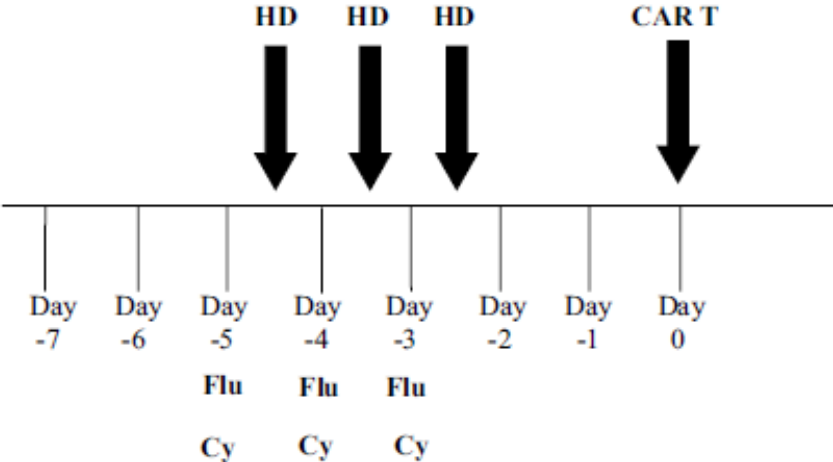
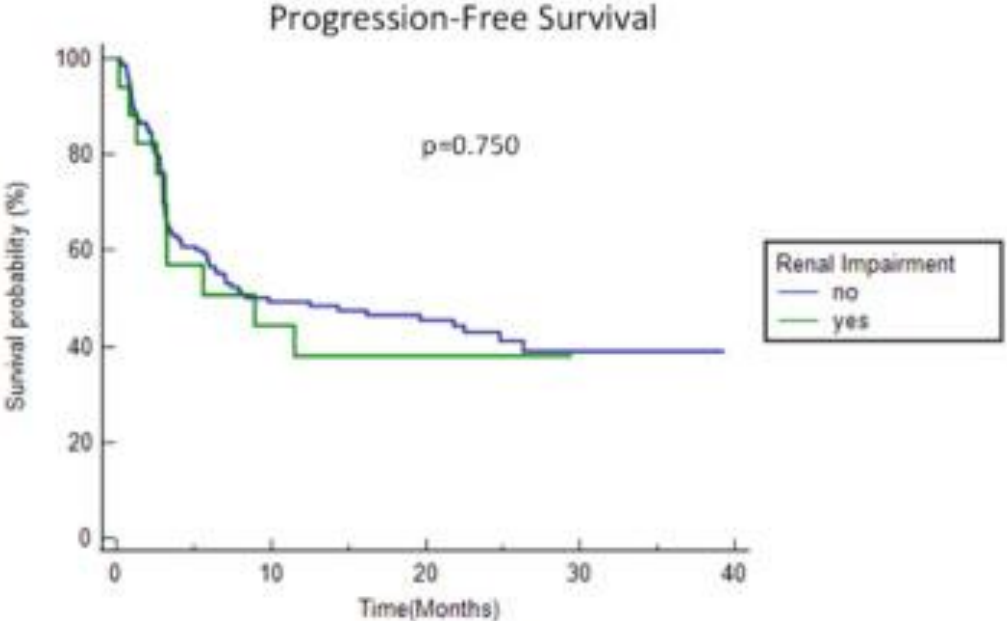


N=4 (9.8%)

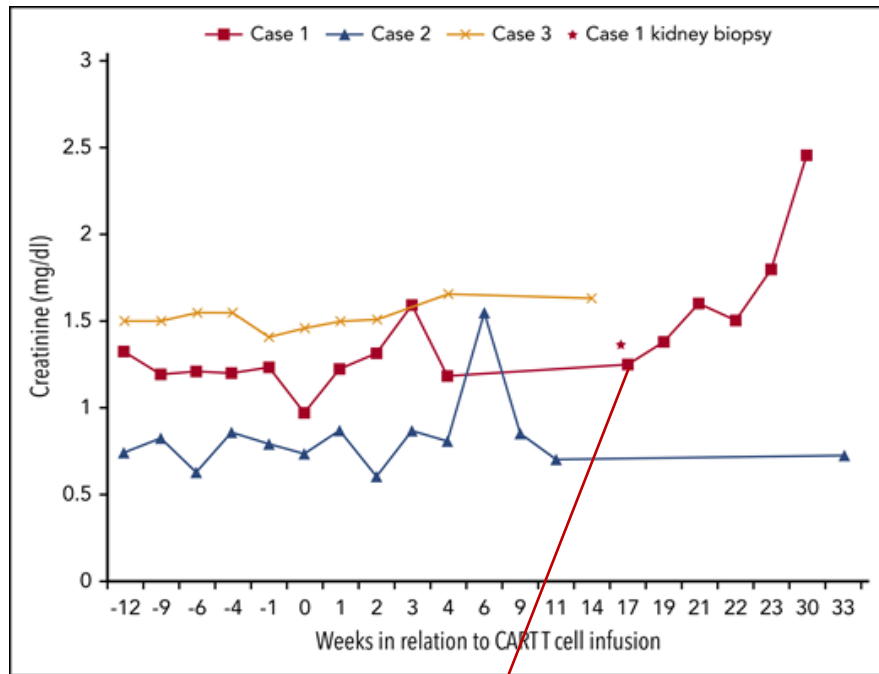
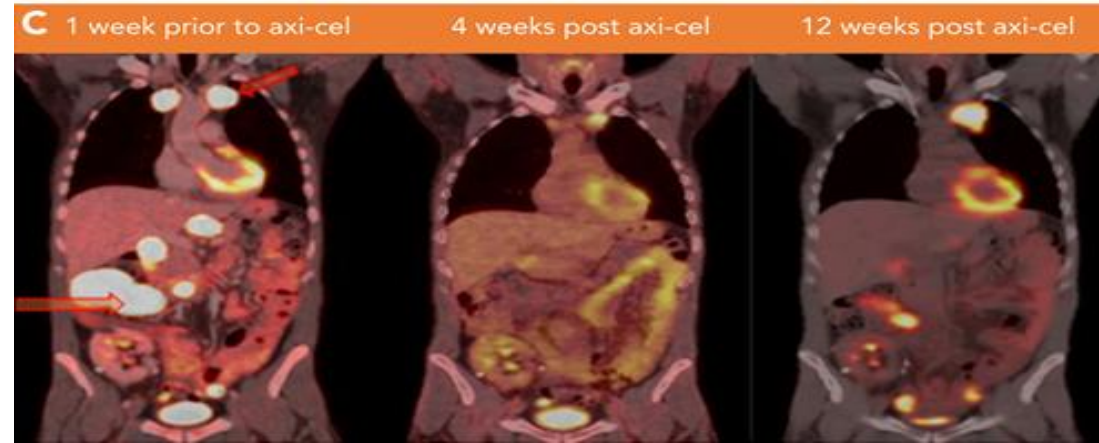
Et chez le patient insuffisant rénal chronique ?

Critère d'exclusion dans la plupart des essais...

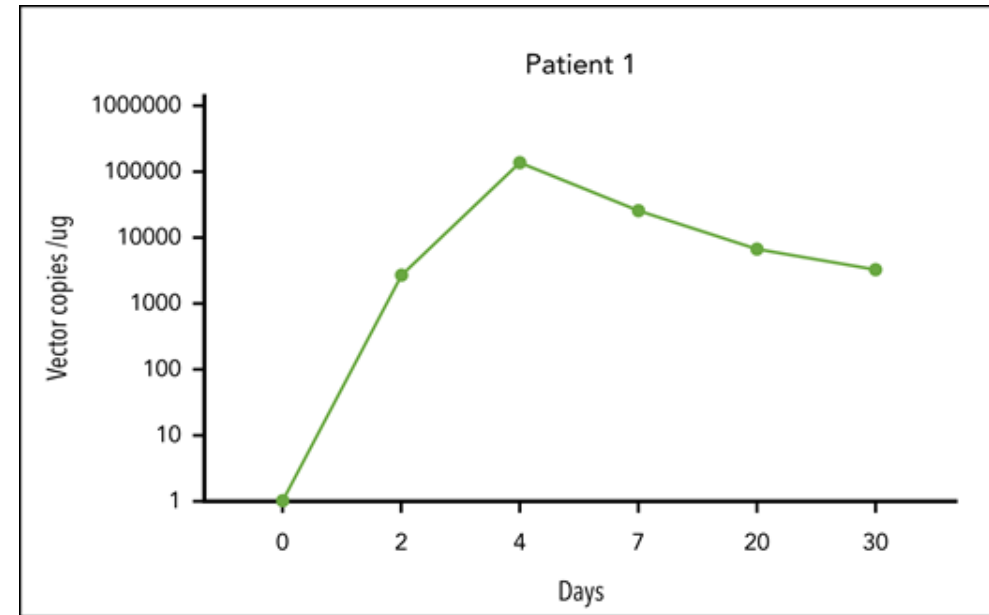
Clairance rénale de la Fludarabine → risque de neurotoxicité ?



# Et chez le patient transplanté rénal ?



Biopsie rénale ( patient 1)  
Acute graft rejection

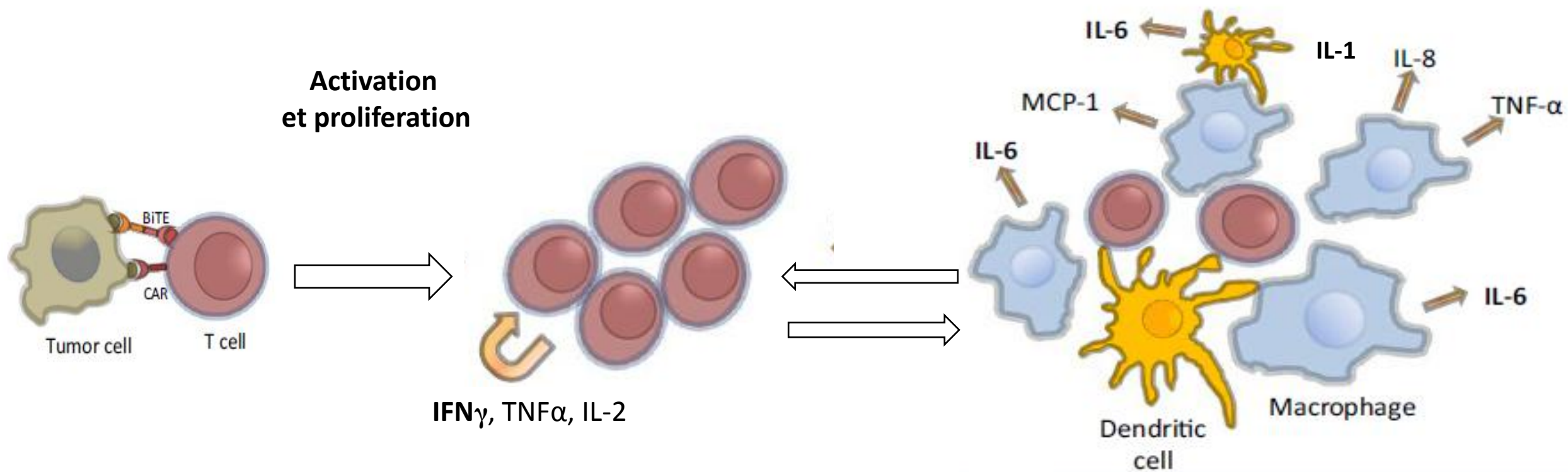


(Banff classification; i1,t1 v0, g0, ptc 0, c4d0, cg0, mm0, ah2, cv1, ci 0, and ct0).

# Plan

- CAR-T et hémopathies malignes
- IRA et CAR-T : épidémiologie
- **IRA et CAR-T : physiopathologie**
- Traitements spécifiques
- Pronostic

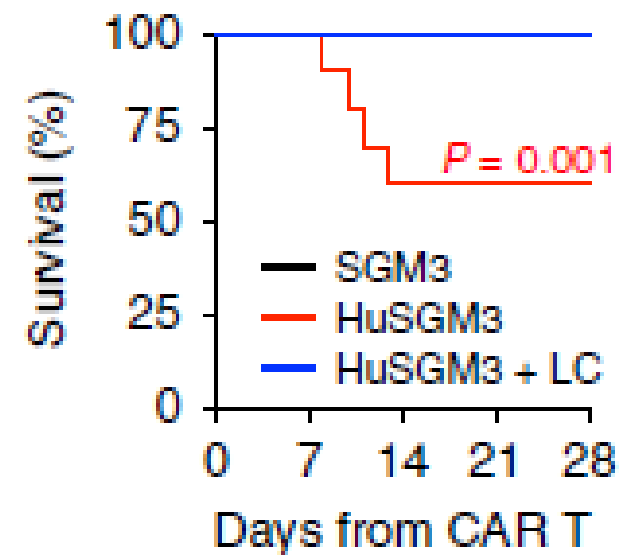
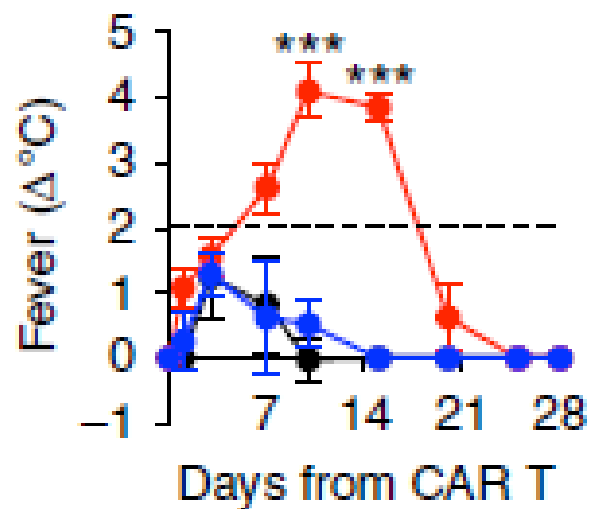
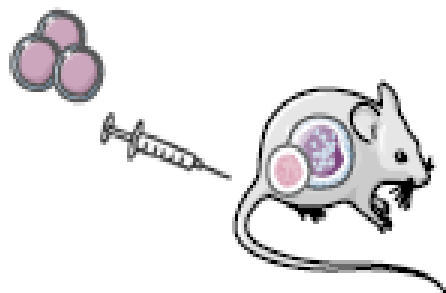
# Syndrôme de relargage cytokinique



# Syndrome de relargage cytokinique

Monocytes/macrophages : principales sources d'IL-6 et d'IL-1  
La déplétion en monocytes améliore la survie

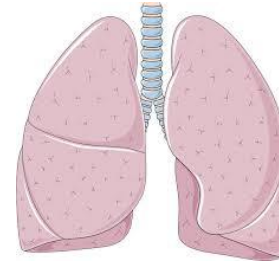
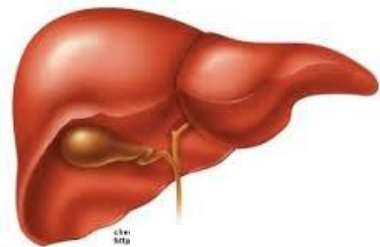
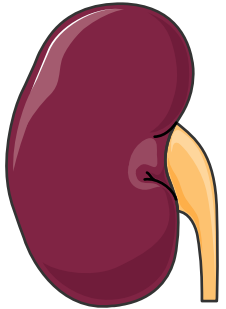
Ex vivo CAR-transduced  
HuSGM3 T cells



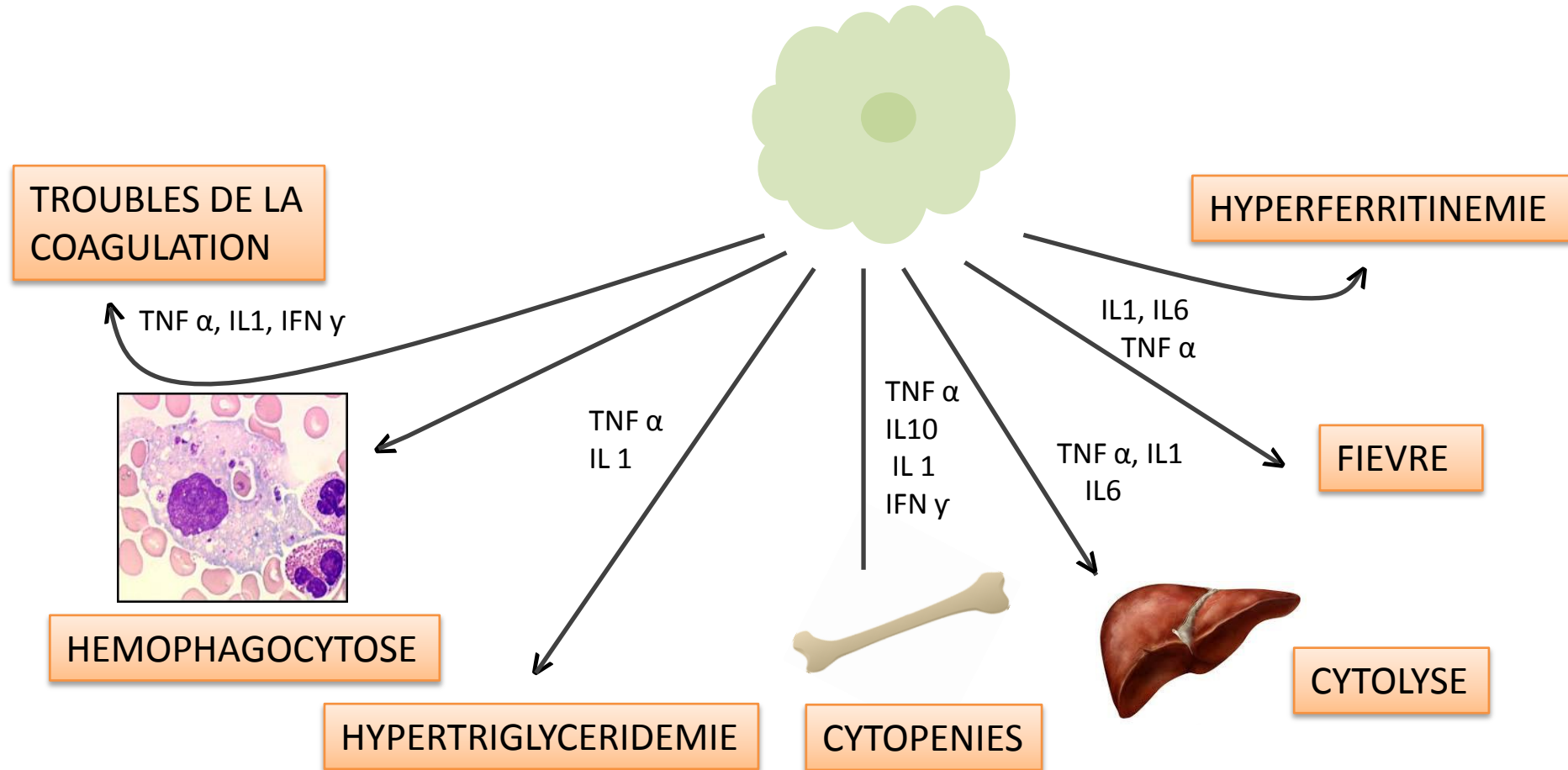


## Syndrome de relargage cytokinique

- Fièvre et hypotension
- +/- défaillances d'organes



# CRS/ Syndrome d'activation macrophagique « HLH-like syndrome »



## ASBMT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells

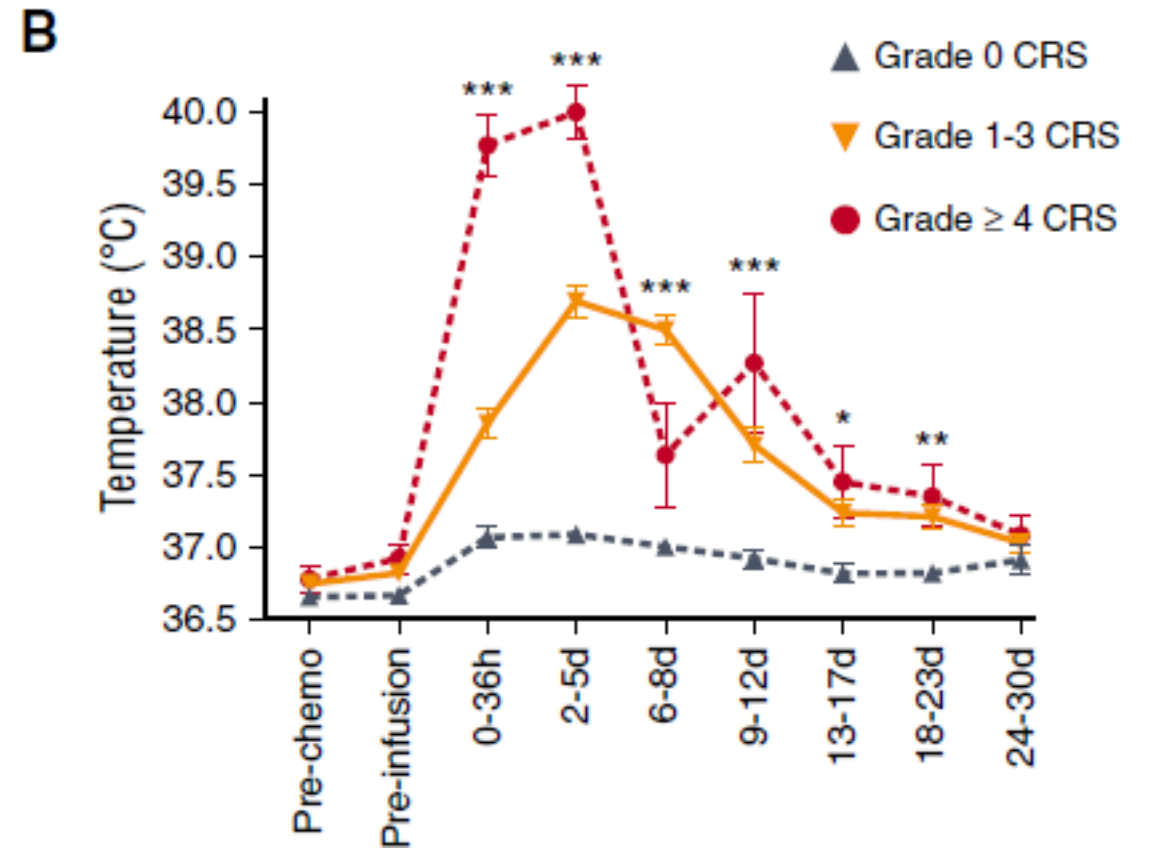
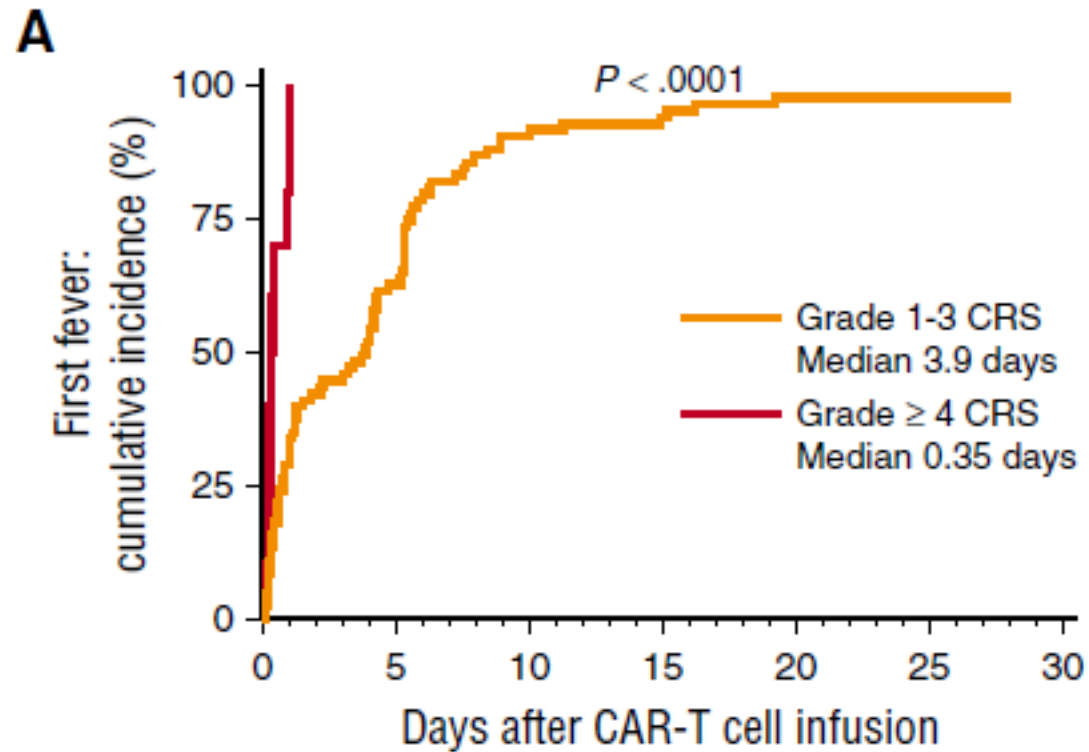
**Table 2**  
ASBMT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever <sup>a</sup>	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	Remplissage vasculaire	Vasopresseurs	Requiring multiple vasopressors (excluding vasopressin)
And/or <sup>b</sup> Hypoxia	None	Requiring low-flow nasal cannula <sup>c</sup> or blow-by	O <sub>2</sub> > 4l, Optiflow	VNI ou VM

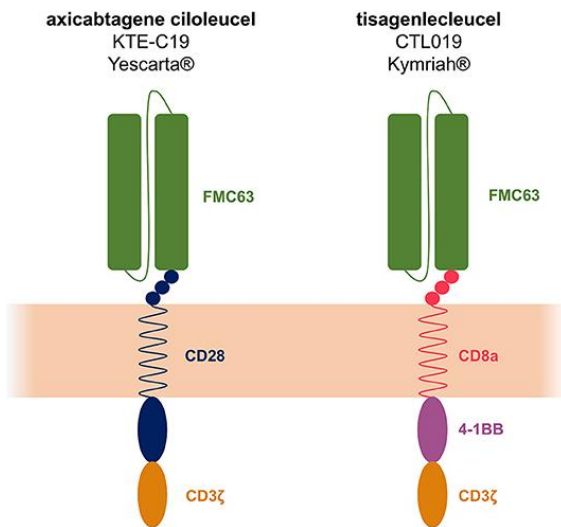
Jugement clinique ++++

## Délai d'apparition

- Survient entre J1 et J21
- Gravité des CRS précoces



# Facteurs de risque de CRS



	axi-cel		tisa-cel		P
	n	%	n	%	
CRS of any grade	180	(86.1%)	158	(75.6%)	0.006
Grade 1-2	169	(80.9%)	139	(66.5%)	<0.001
Grade ≥3	11	(5.3%)	19	(9.1%)	0.130



Masse tumorale



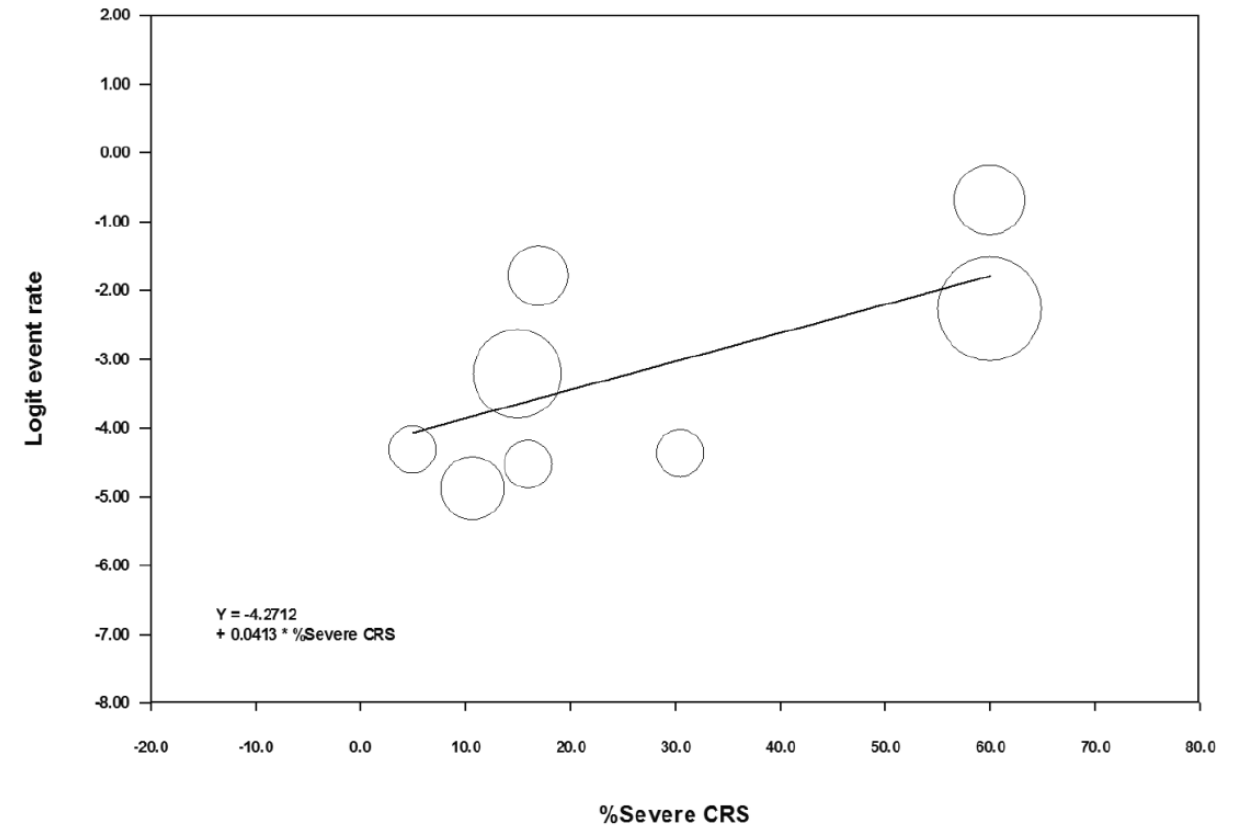
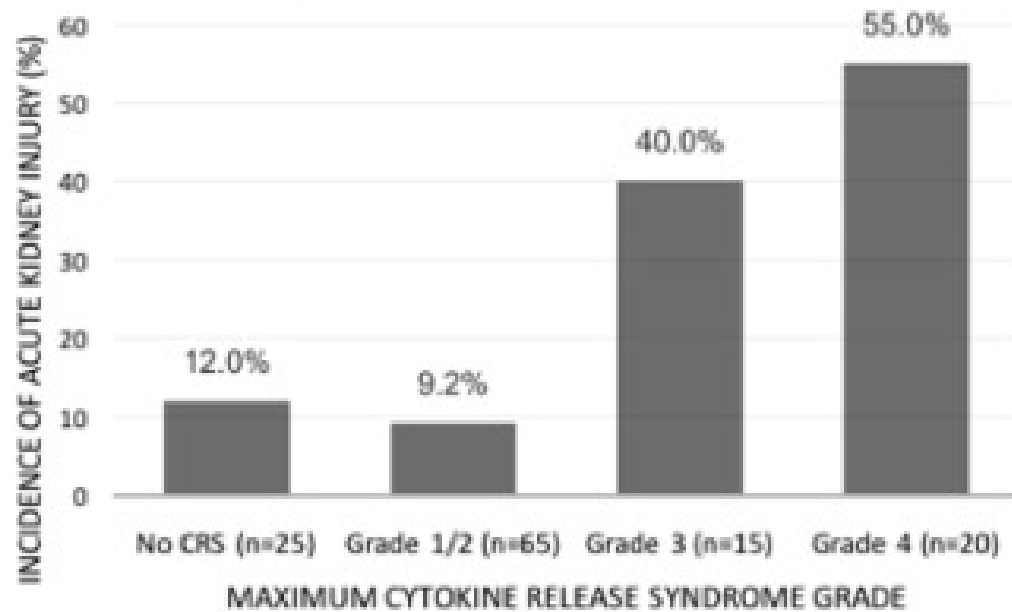
Conditionnement  
Fludarabine



Dose infusée  
CAR-T

# Syndrome de relargage cytokinique et IRA

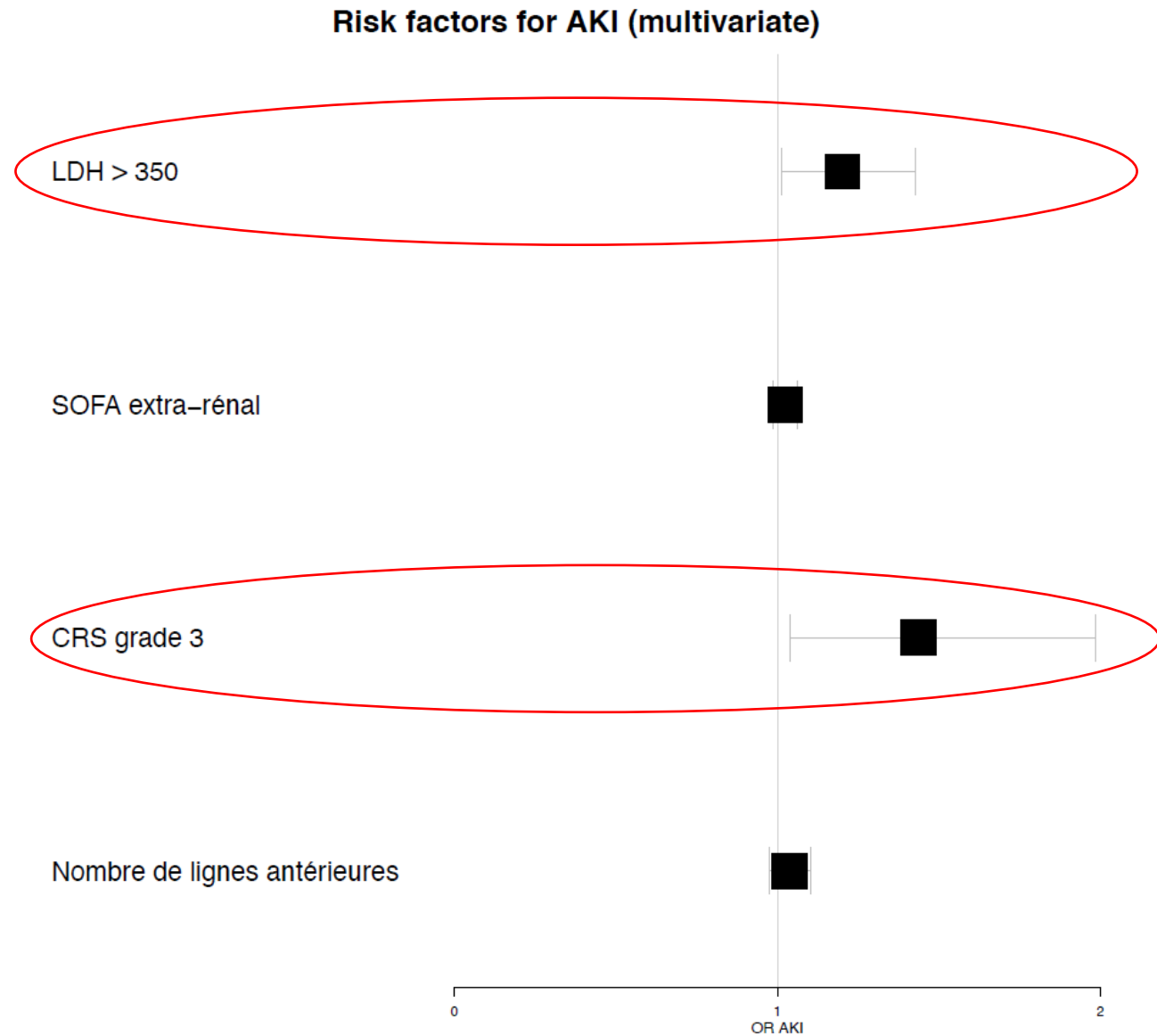
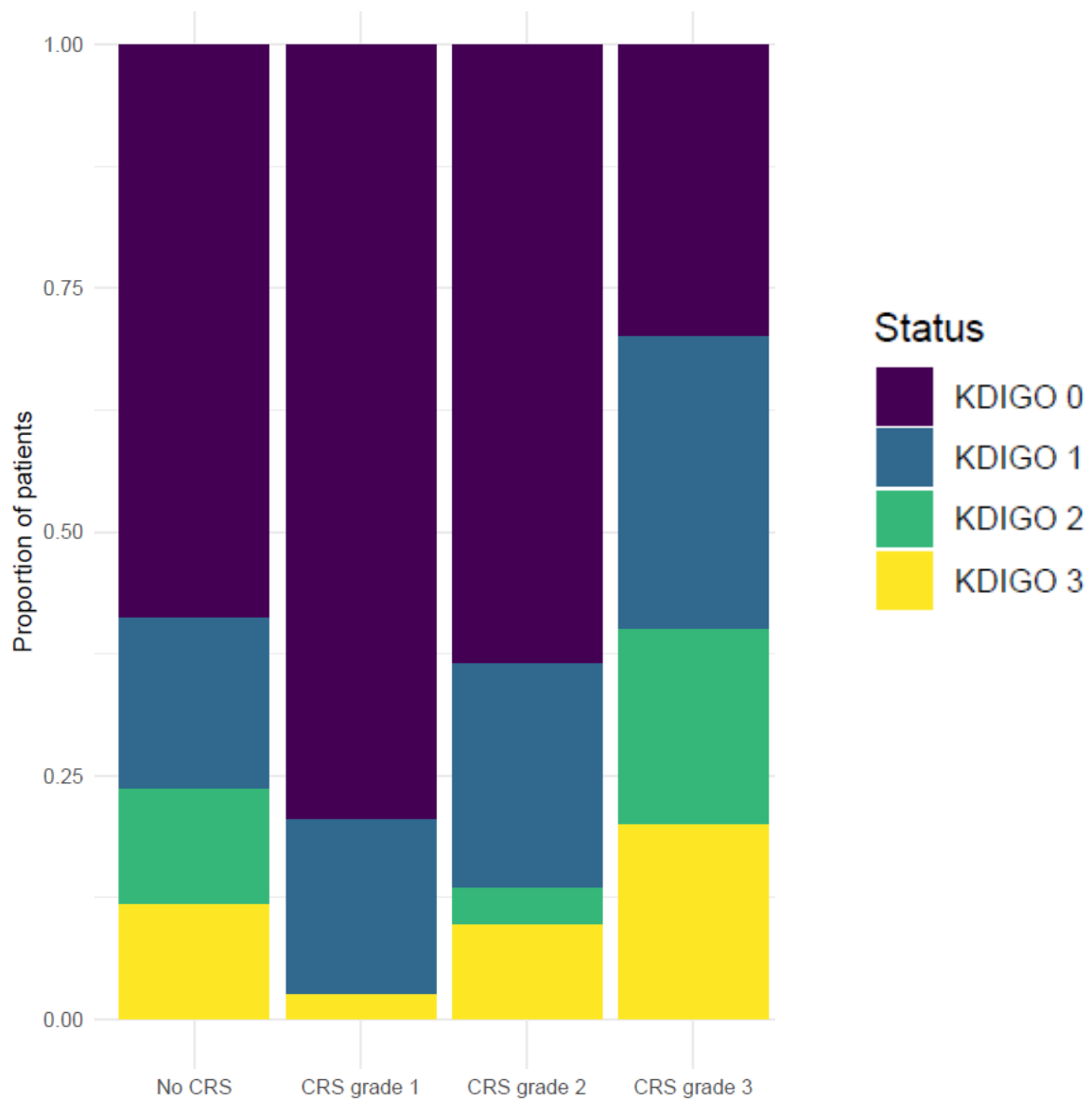
## A. Incidence of any acute kidney injury



Absence de corrélation avec les taux d'IL-6 et ferritine

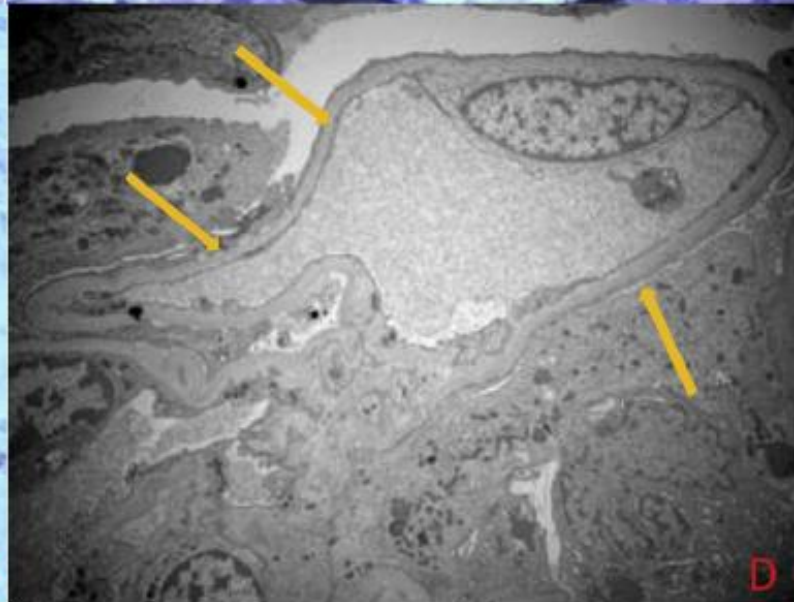
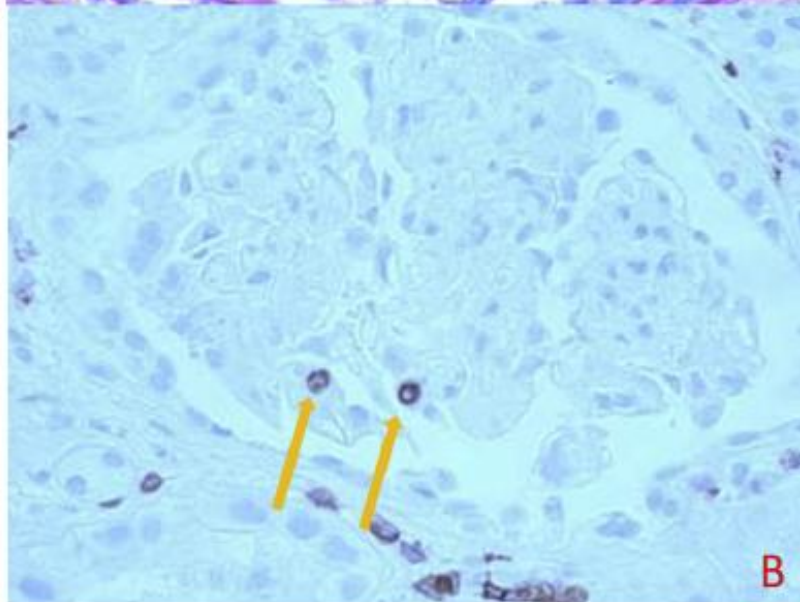
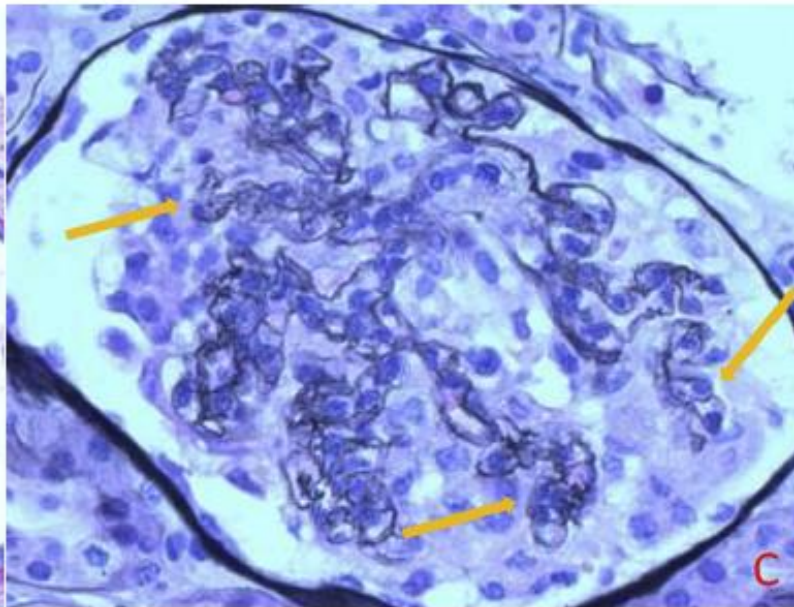
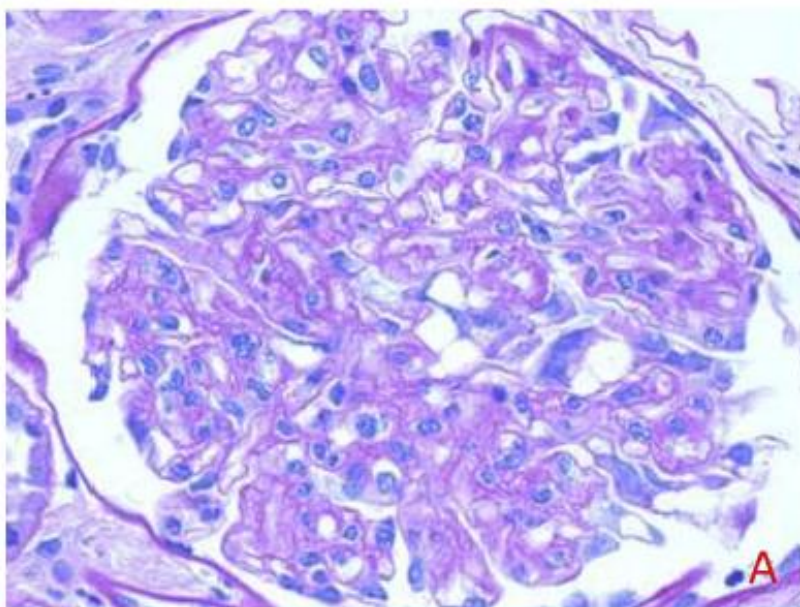
Plus d'AKI avec axi-cel versus tisa-cel

# Syndrome de relargage cytokinique et IRA



*Données Saint- Louis non publiées*

# Collapsing glomerulopathy

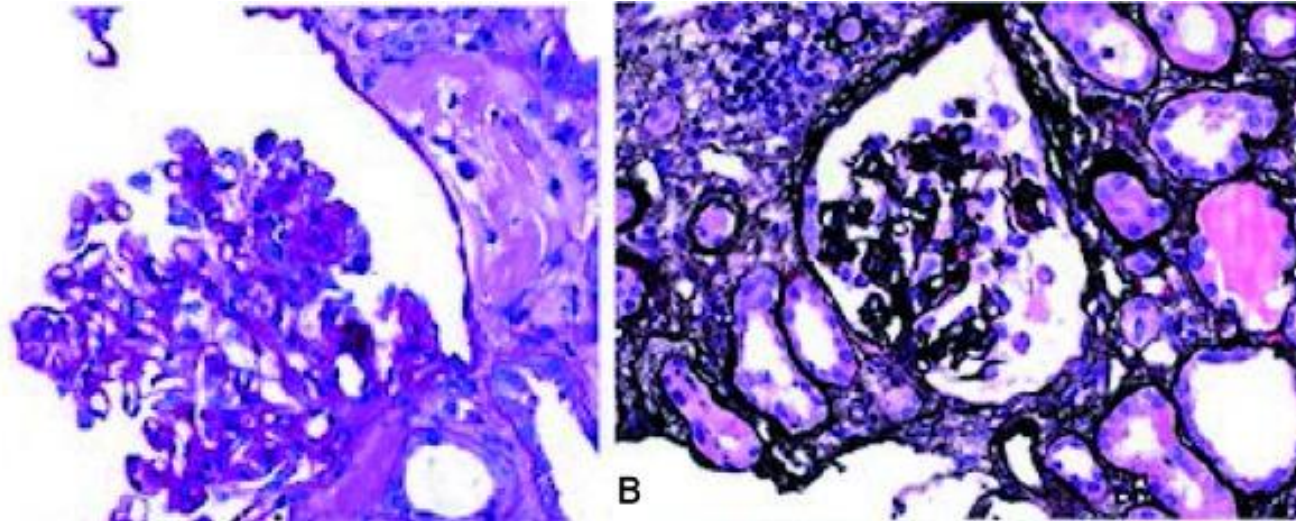




## Collapsing glomerulopathy et SAM

Série de 11 patients avec syndrome néphrotique et SAM : 5 patients avec CG

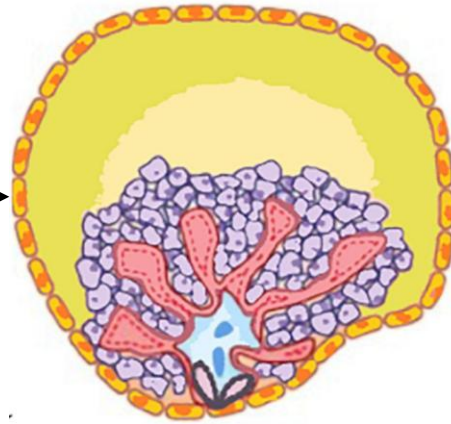
Lymphome T/NK  
SAM



# Collapsing glomerulopathy

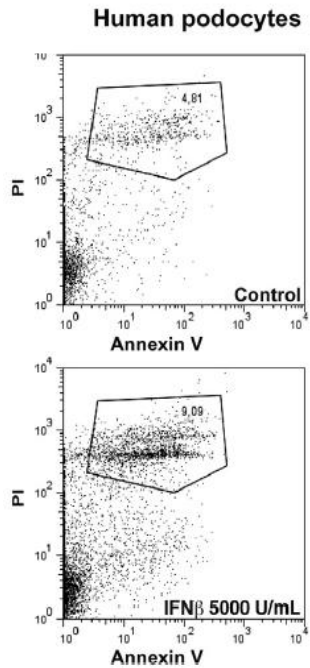
**IFN**

**Variants APOL1**



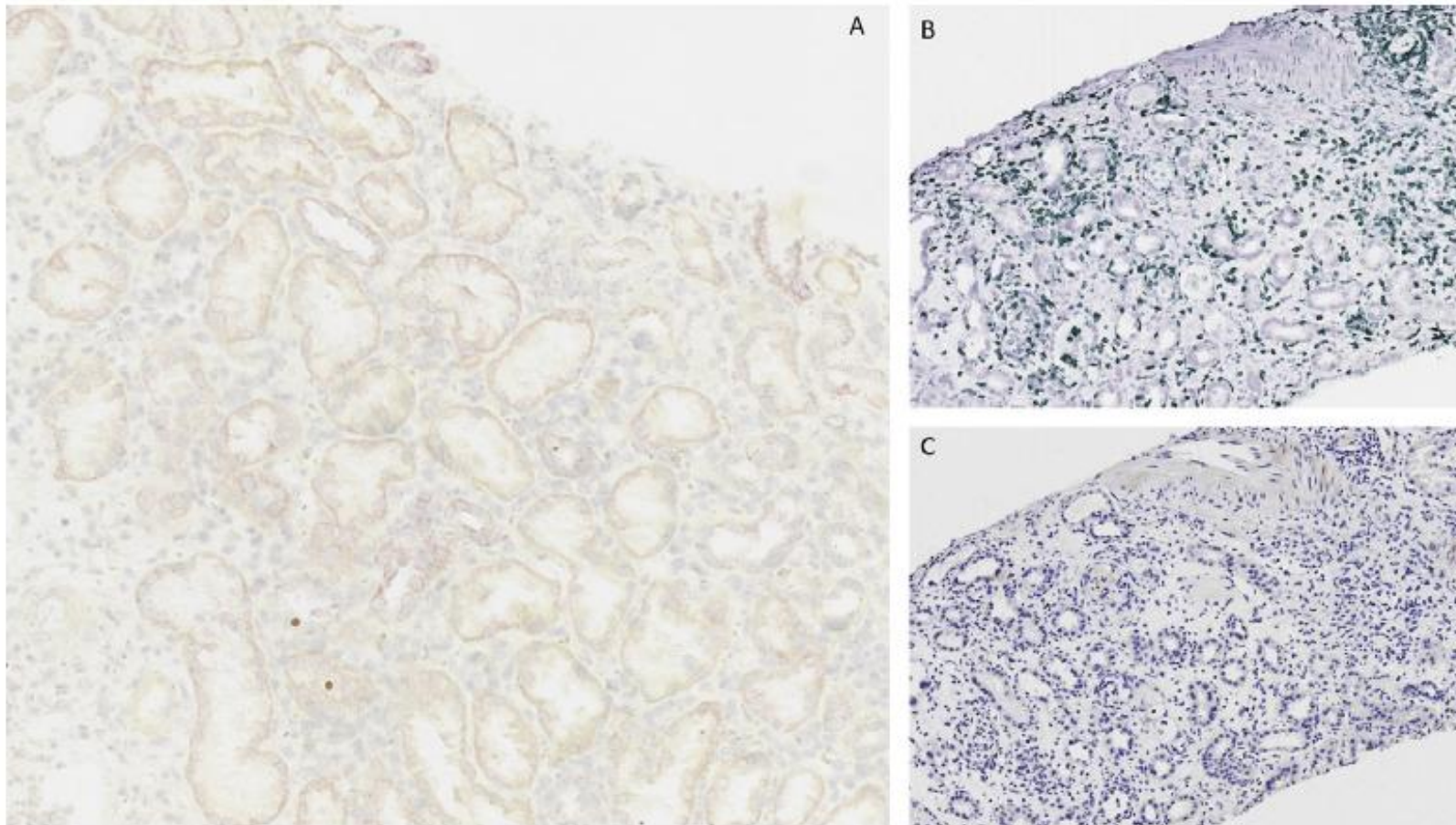
**Infections**  
HIV, CMV, ParvoB19, HBV, HCV, EBV, S  
ARS-COV-2  
Tuberculose, Leishmaniose, Paludisme

*Murilo Monteiro Cutrim, E et al. Frontiers Med 2022  
Migliorini, A et al. Am J Pathol 2013*



# Néphropathie tubulo-interstitielle

## Transplanté rénal-Lymphome BDGC



Mr D...

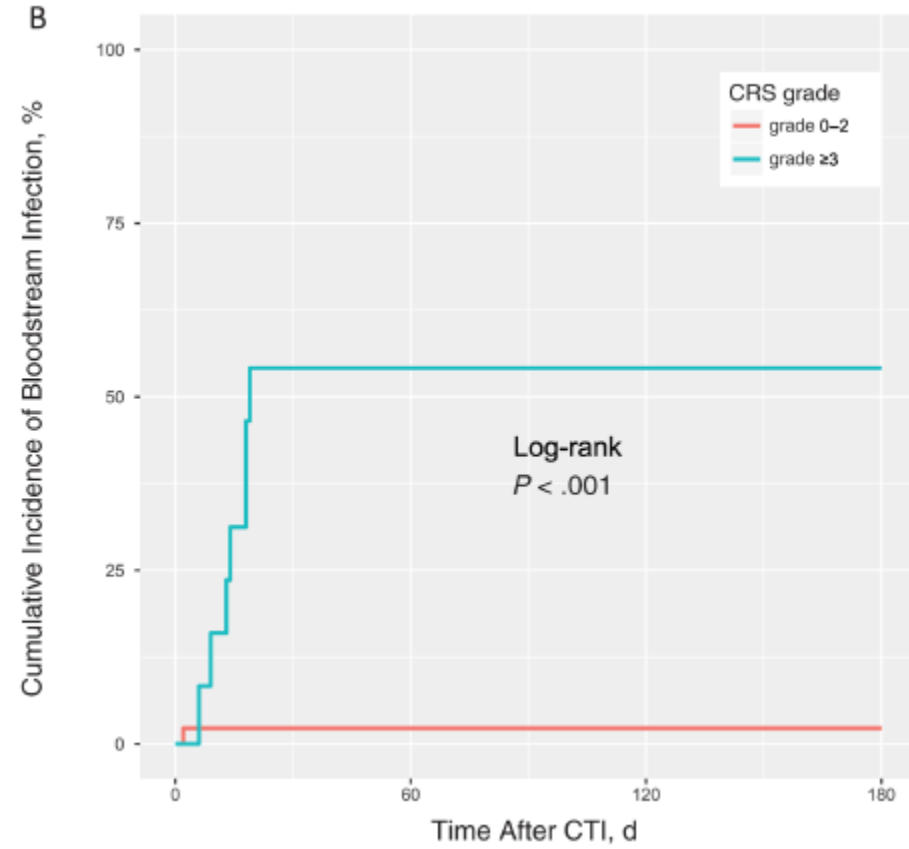
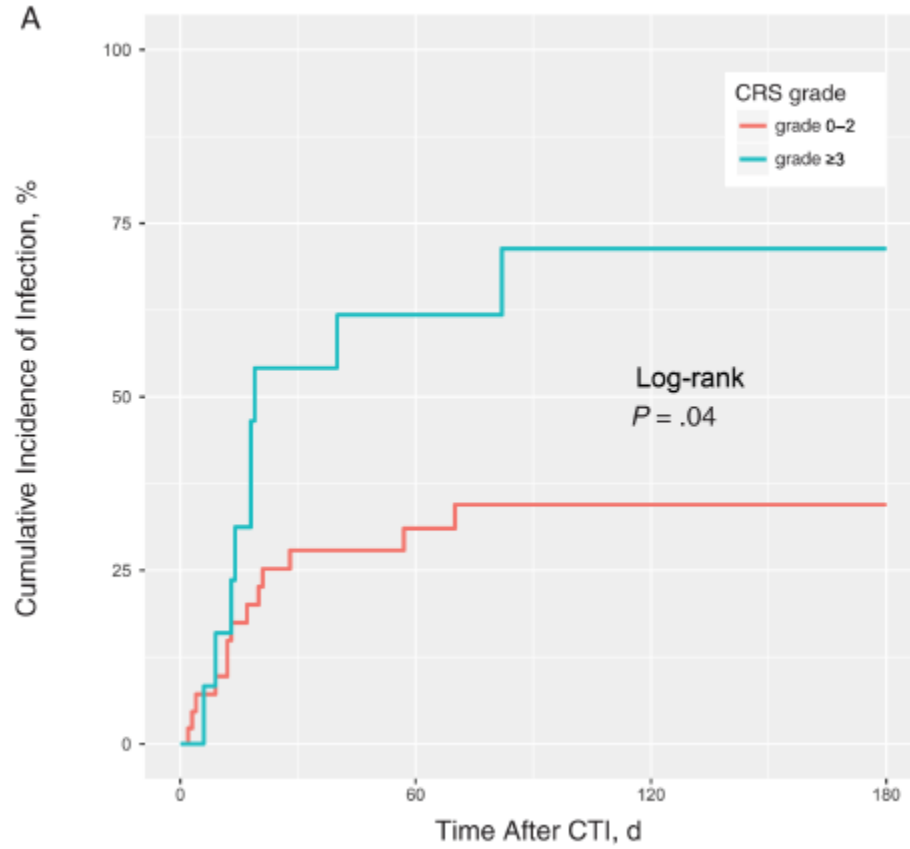
Administration des CAR T

Créatininémie : 260  $\mu\text{mol/l}$   
Echorénaie normale  
Ionogramme urinaire : Na/K > 1, Fe  
Na > 2%  
ECBU : leucocyturie sans germe  
Pu : 60mg/mmol

PCR dans les urines : 100 copies transgène/ml



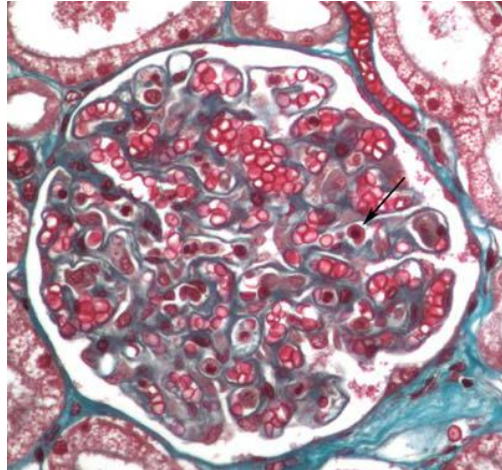
# CAR-T et sepsis



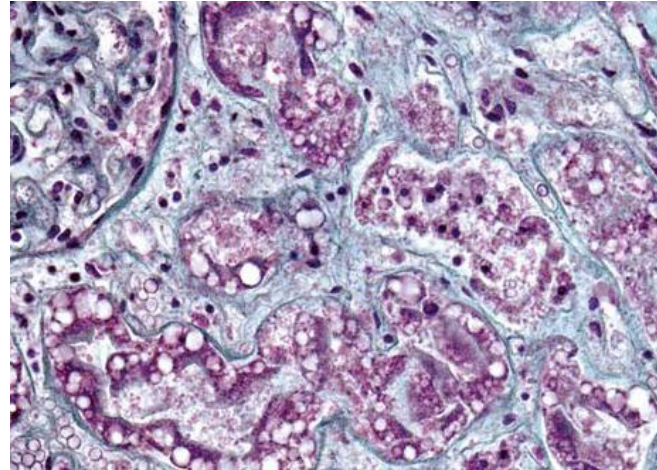
# IRA et sepsis

Pas que de la nécrose tubulaire +++

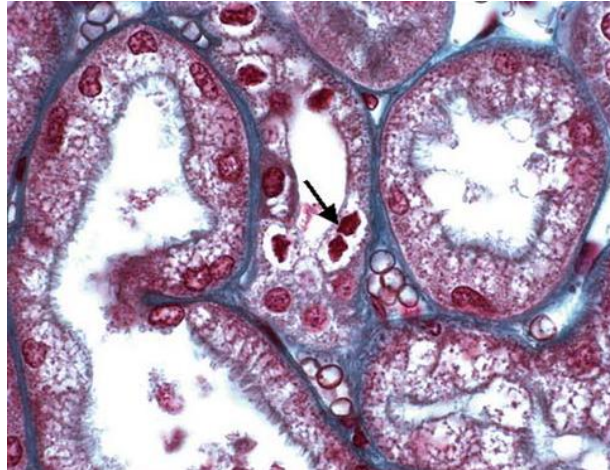
Infiltration  
PNN, monocytes,  
macrophages



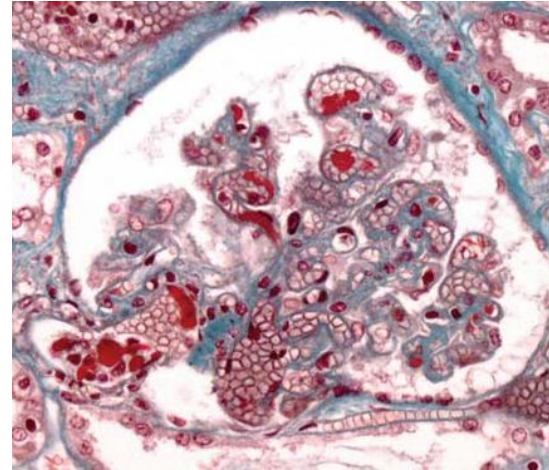
Lésions tubulaires  
aiguës ⇨ nécrose



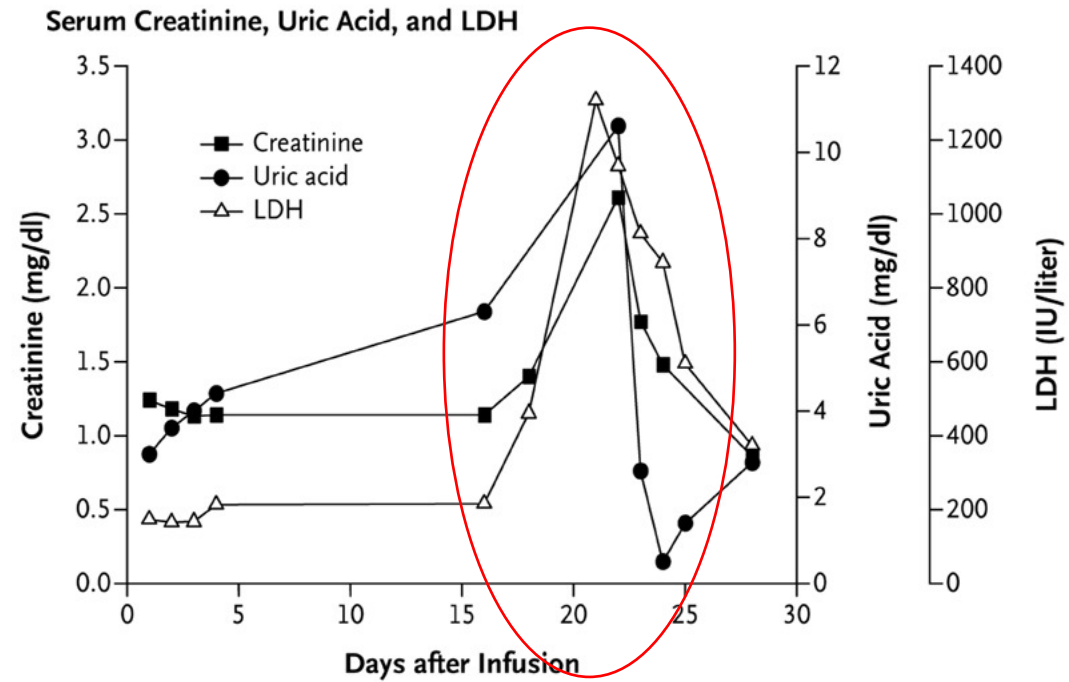
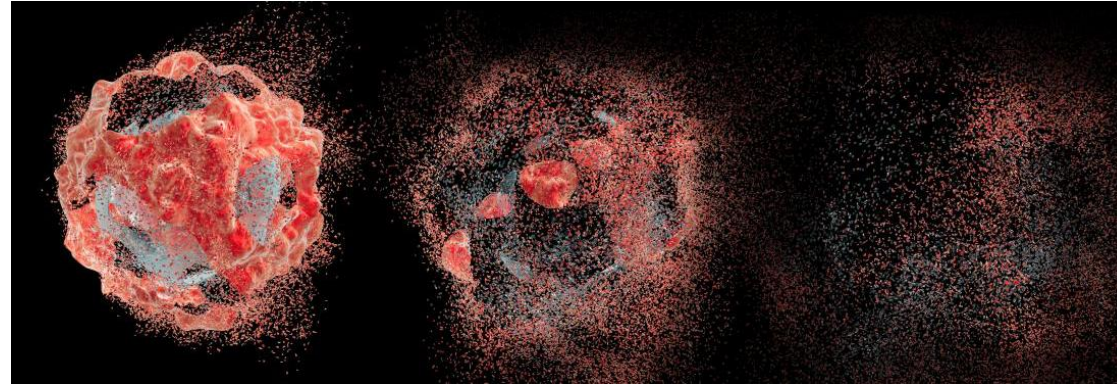
Apoptose  
cellulaire



Congestion  
vasculaire  
± thrombi



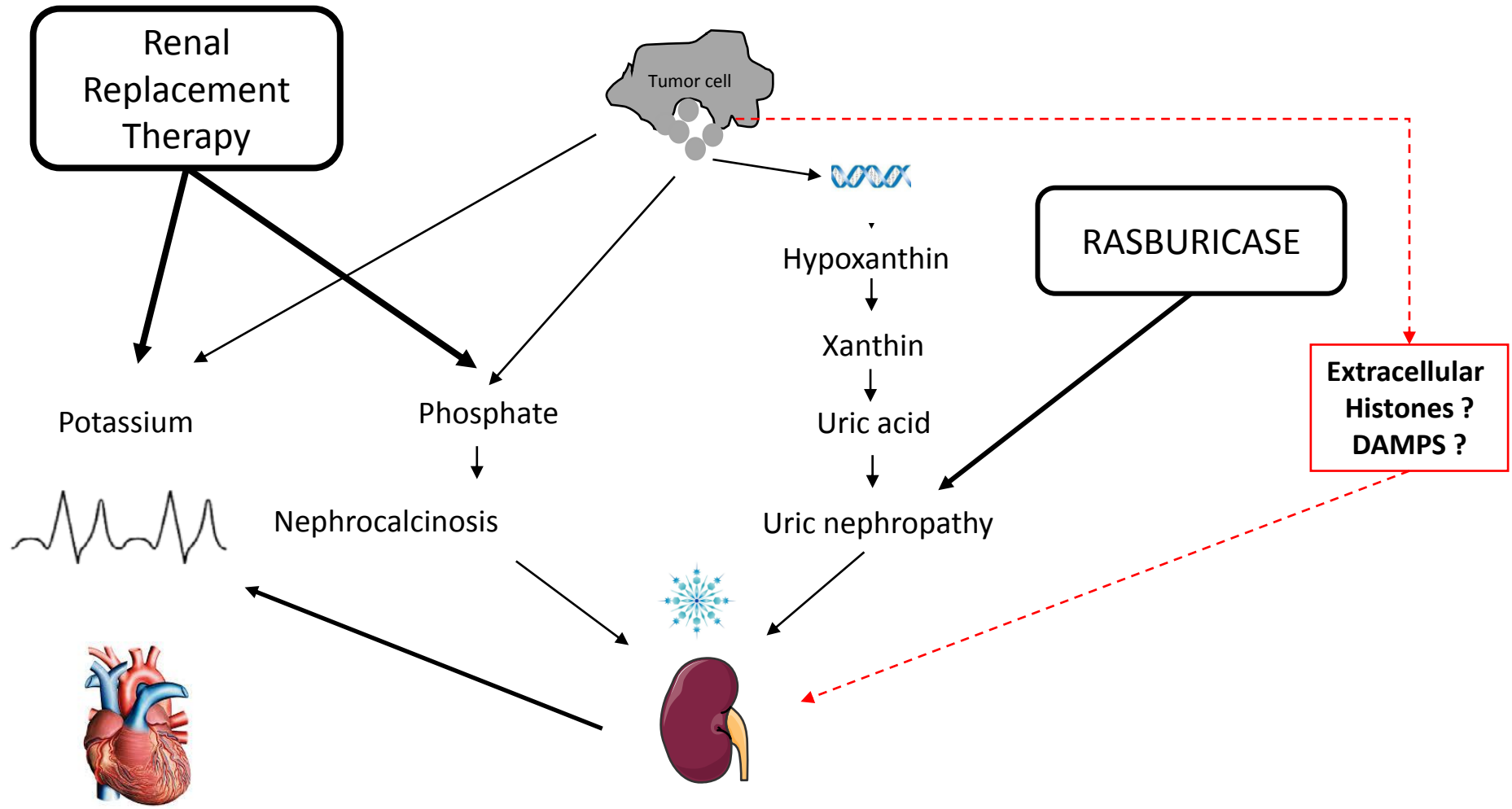
# CAR-T et syndrome de lyse tumorale



Porter, D NEJM 2011

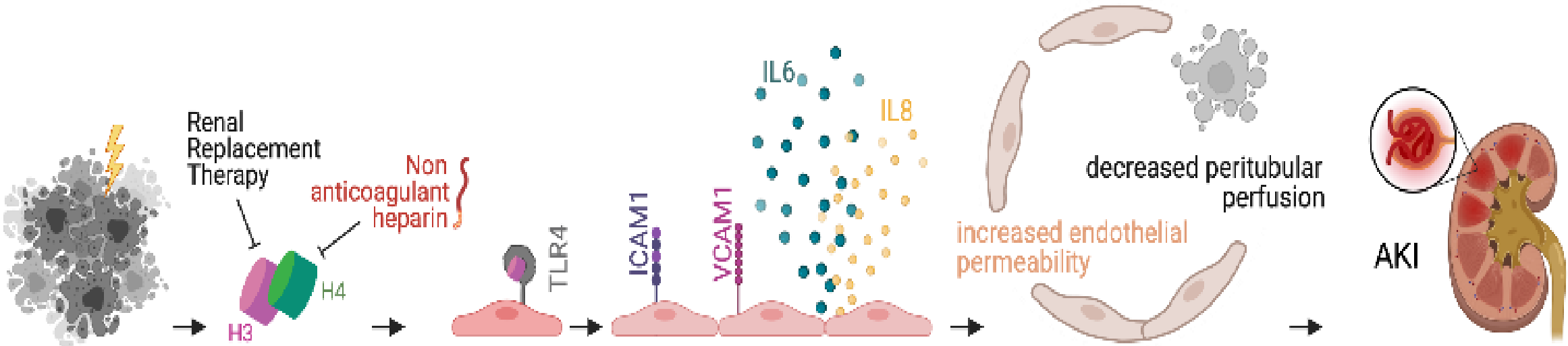
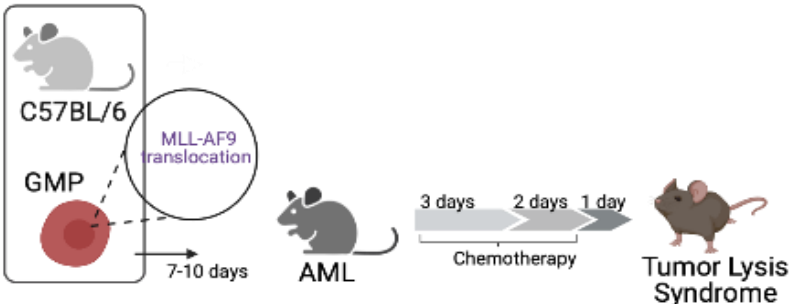
Grupp, SA NEJM 2013, Shank et al Pharmacotherapy 2017

IRA et syndrome de lyse tumorale

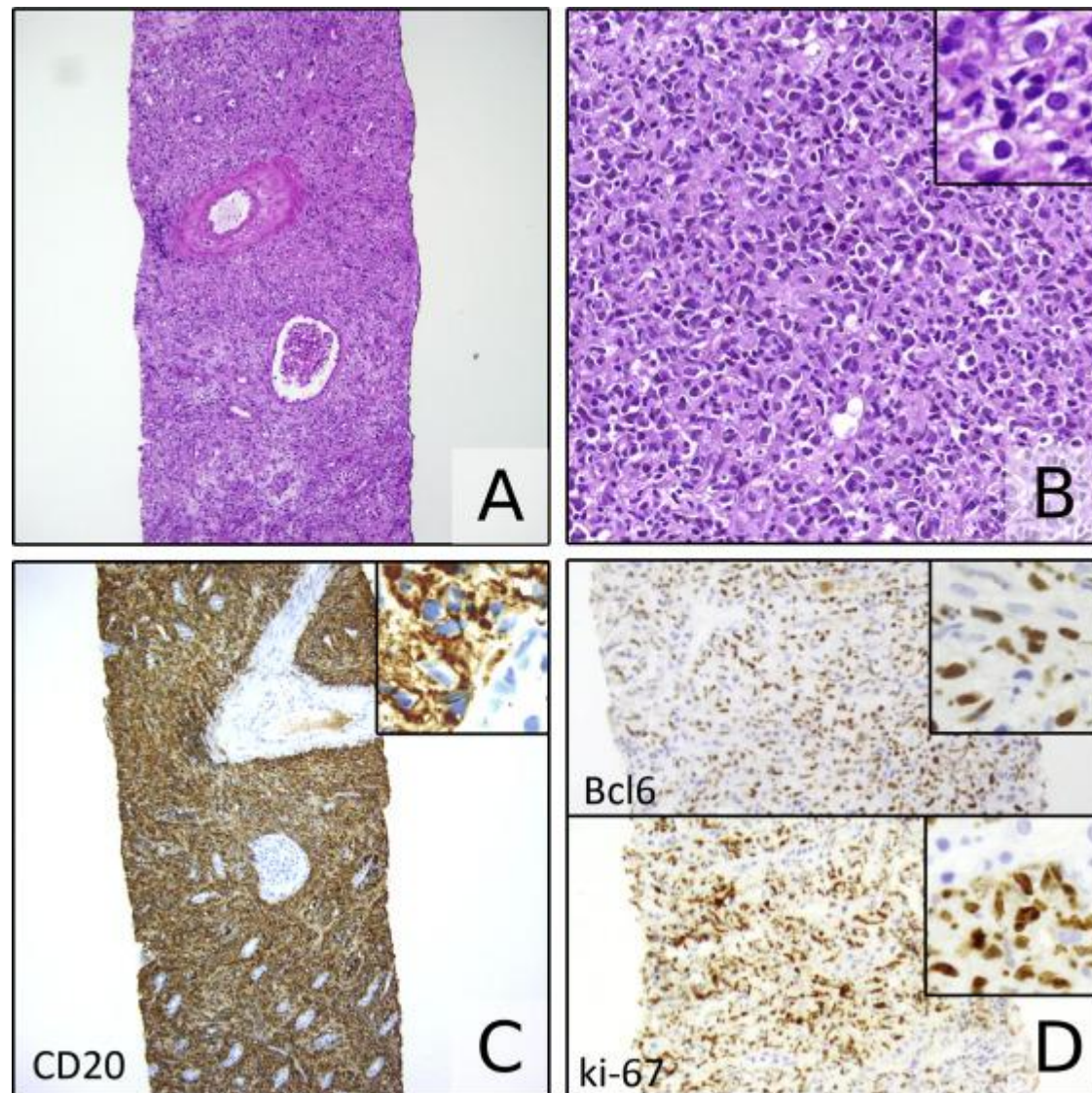


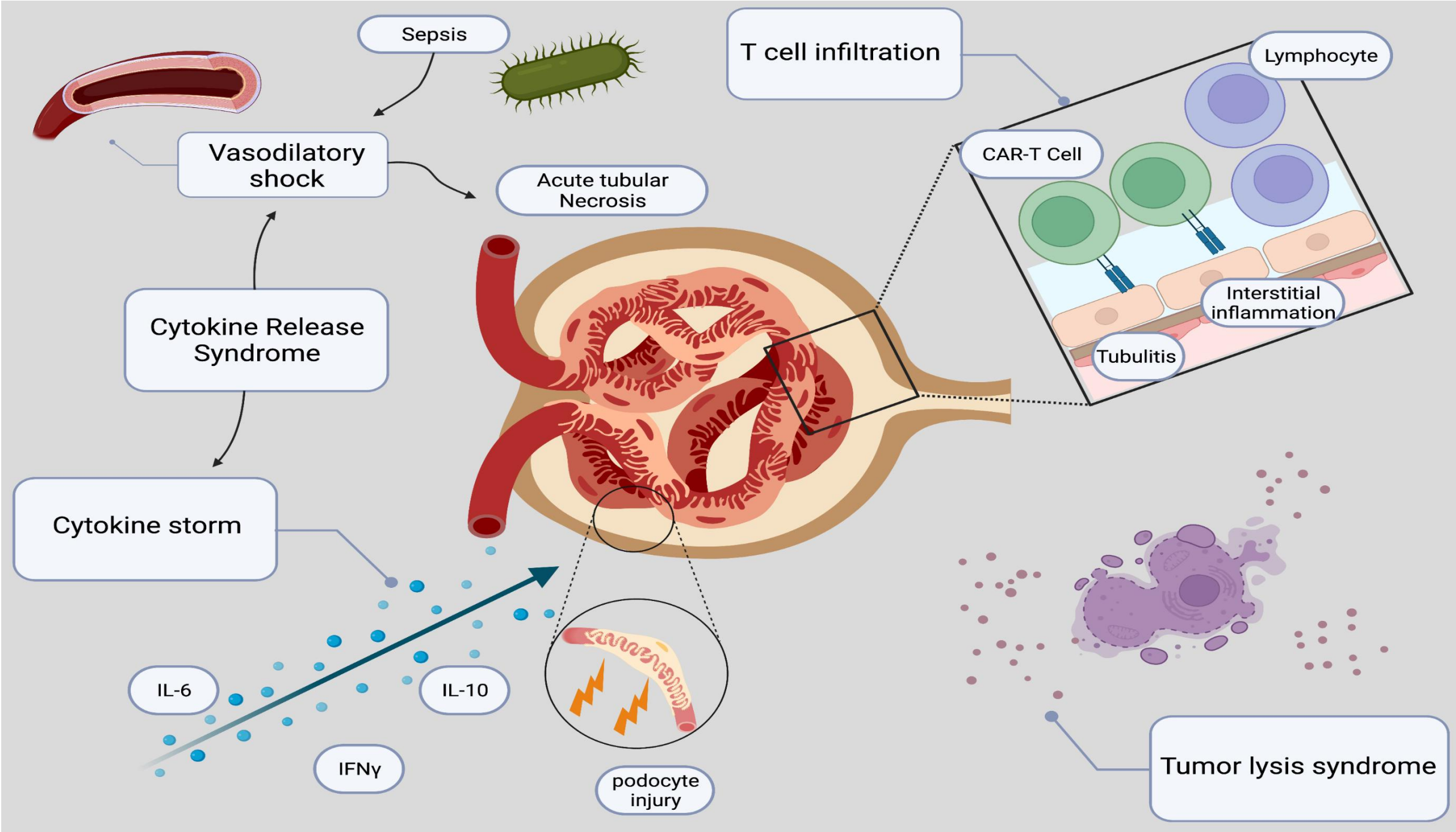


# IRA et syndrome de lyse tumorale



# Rôle de l'infiltration rénale spécifique ?





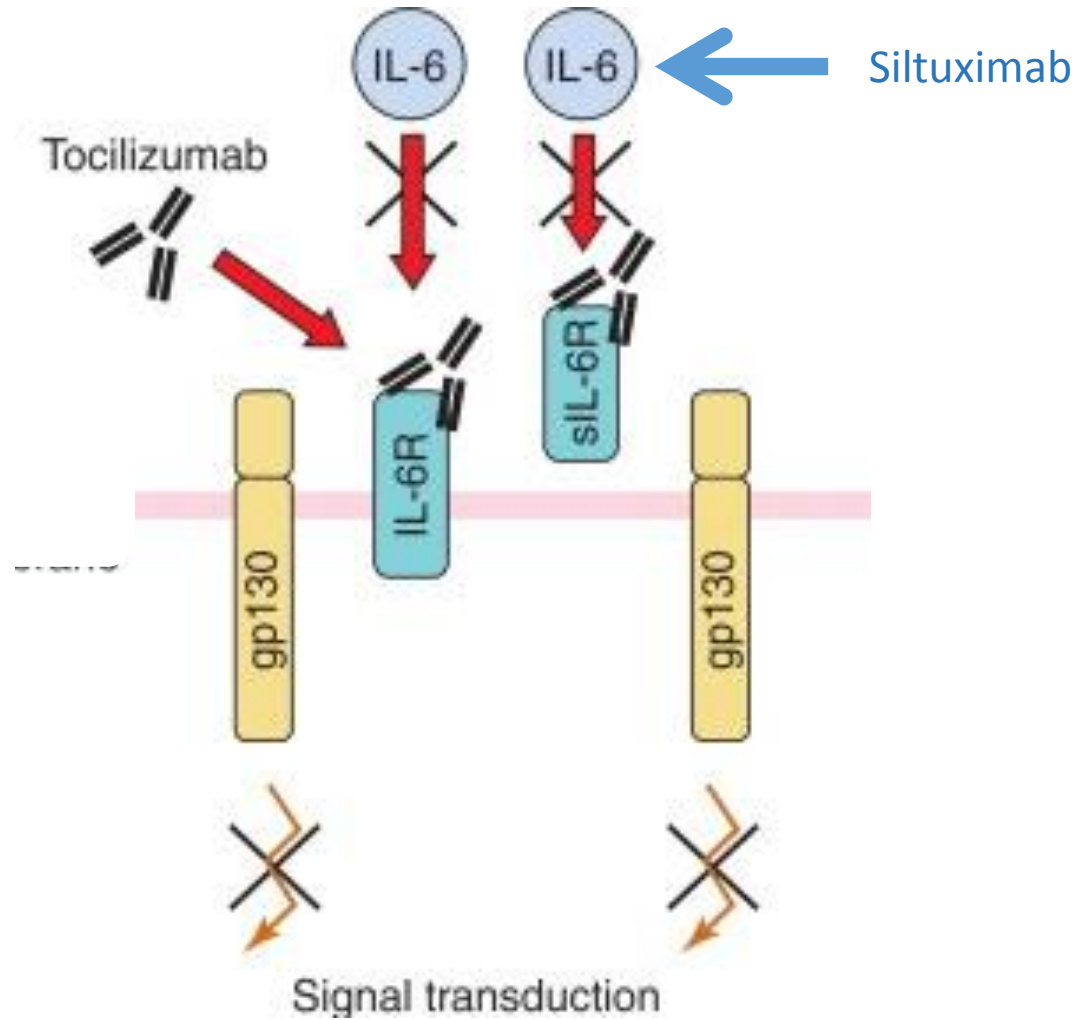
# Plan

- CAR-T et hémopathies malignes
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- **Traitements spécifiques**
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# Traitement du CRS

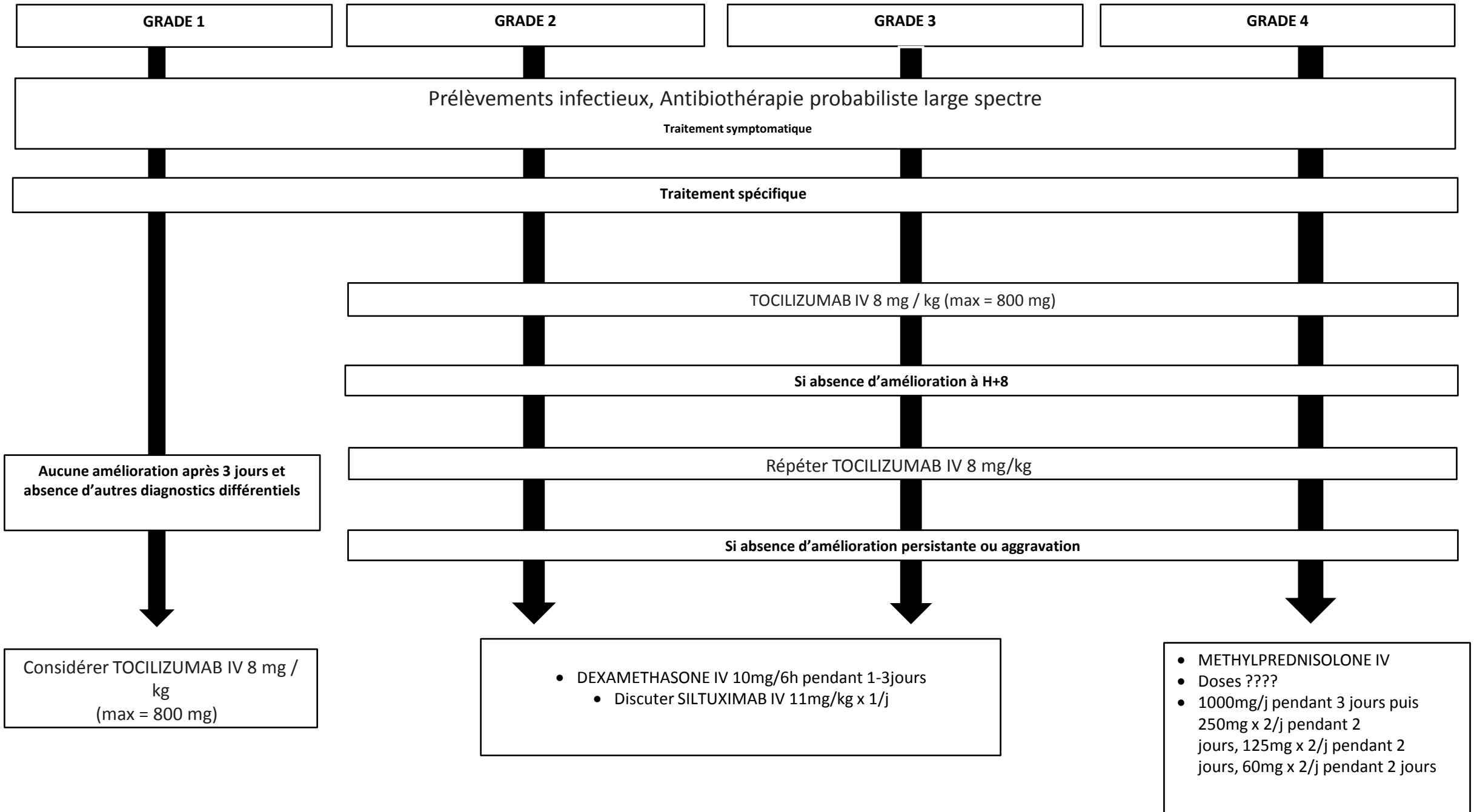
Anti-IL-6

Corticostéroïdes



Solumedrol

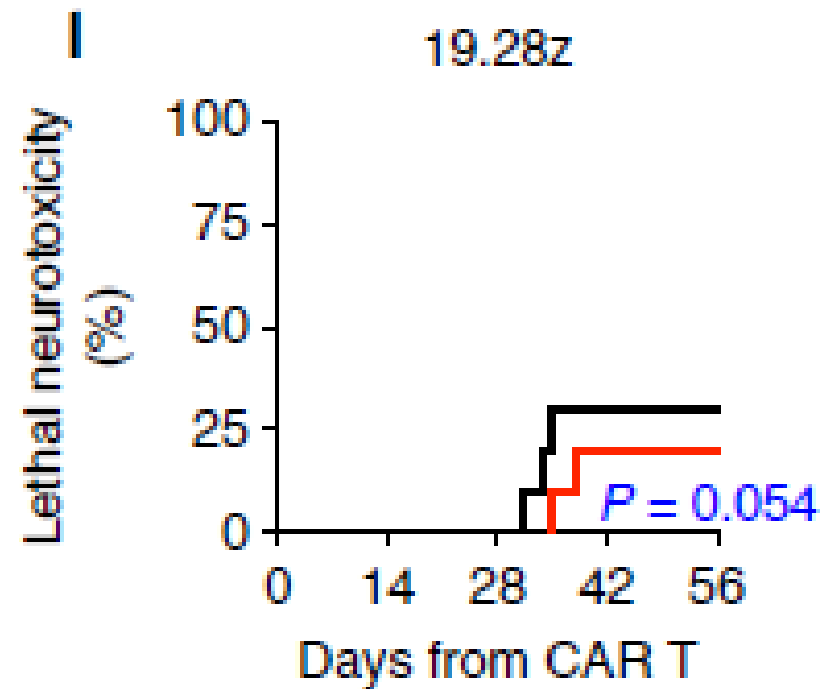
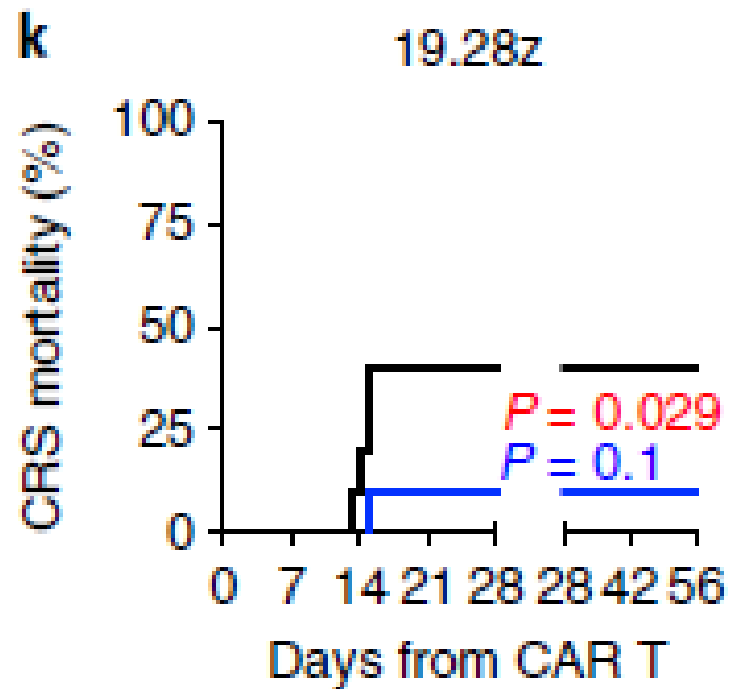
Dexamethasone



# Antagonistes de l'IL-1R ?

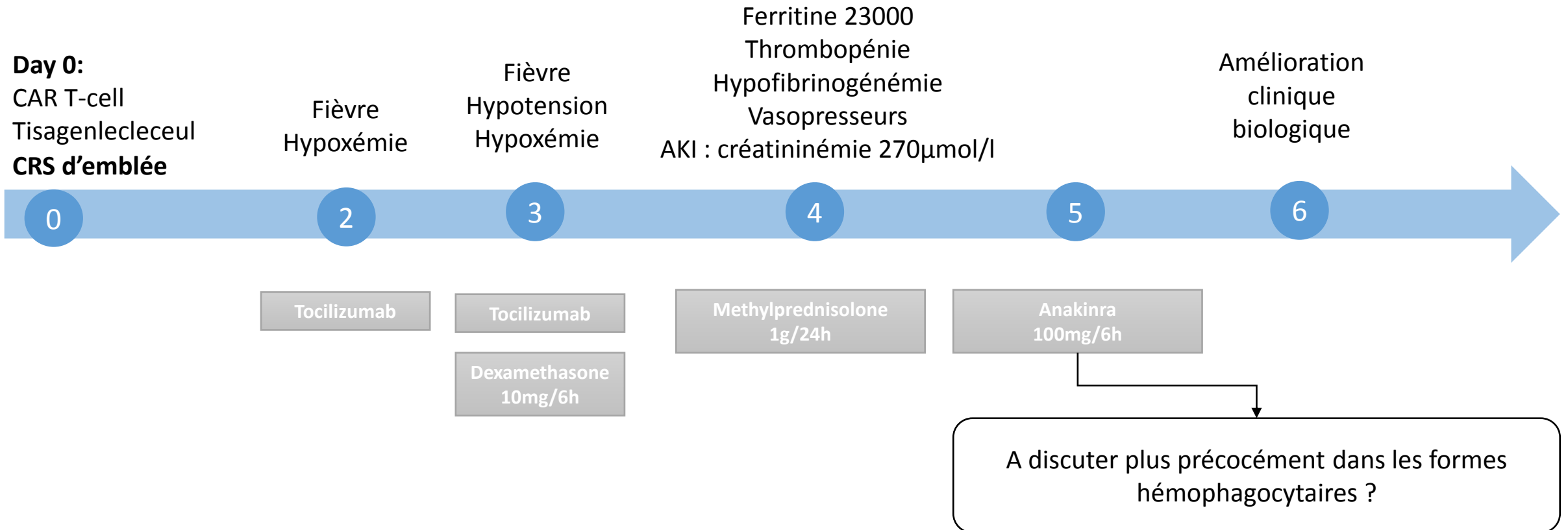
Anakinra et tocilizumab diminuent la mortalité liée au CRS

Anakinra diminue la neurotoxicité



## How I treat refractory CRS and ICANS following CAR T-cell Therapy

59 ans, DLBCL, masse bulky abdominale > 15 cm, 3 lignes de chimiothérapie

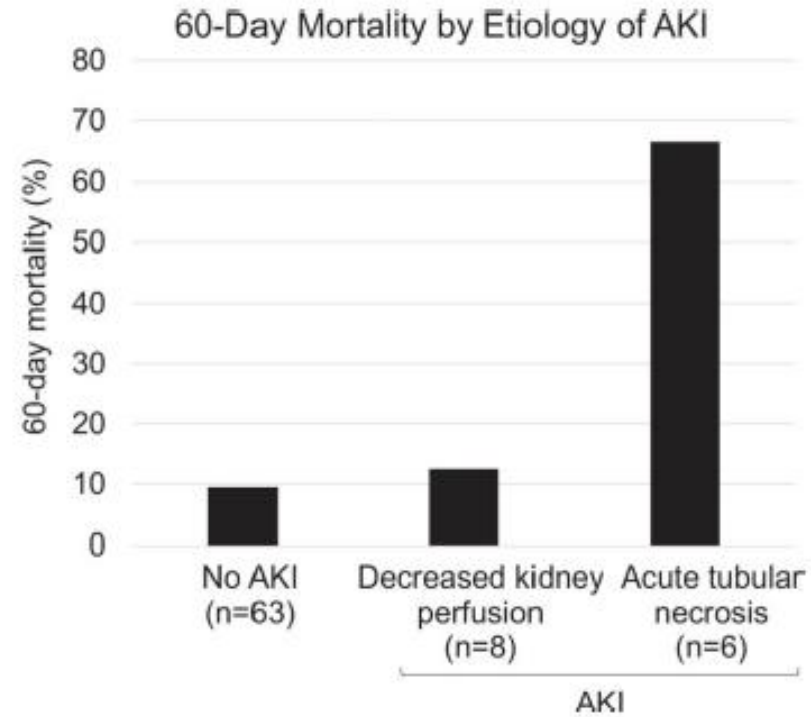
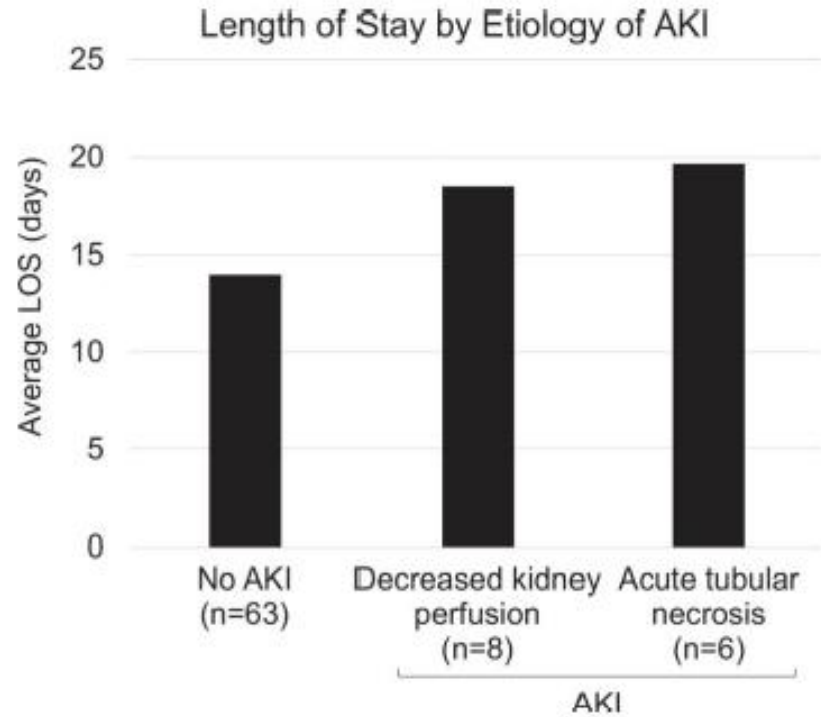




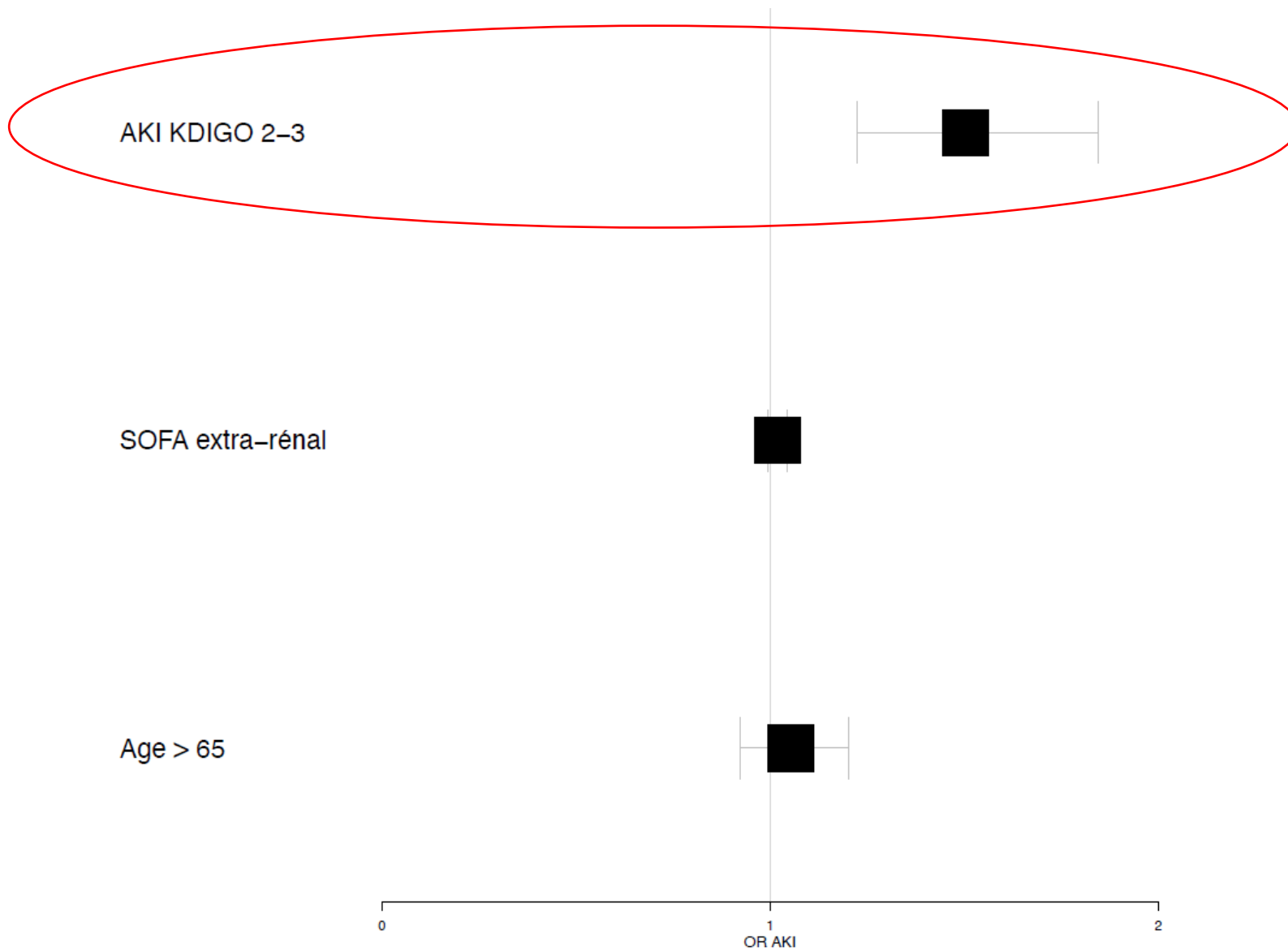
# Plan

- CAR-T et hémopathies malignes
- IRA et CAR-T : épidémiologie
- IRA et CAR-T : physiopathologie
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- **Pronostic**

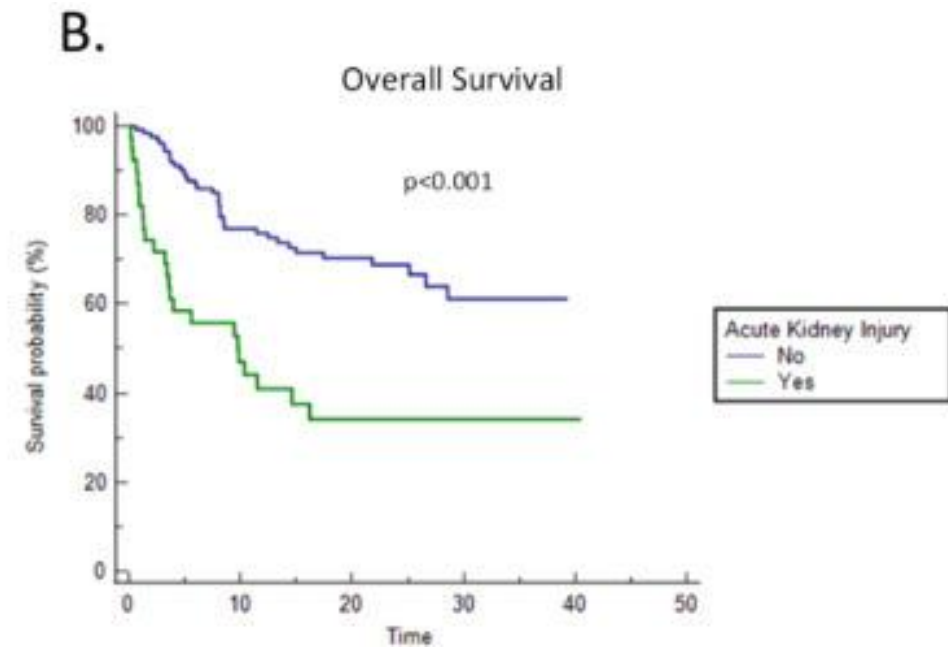
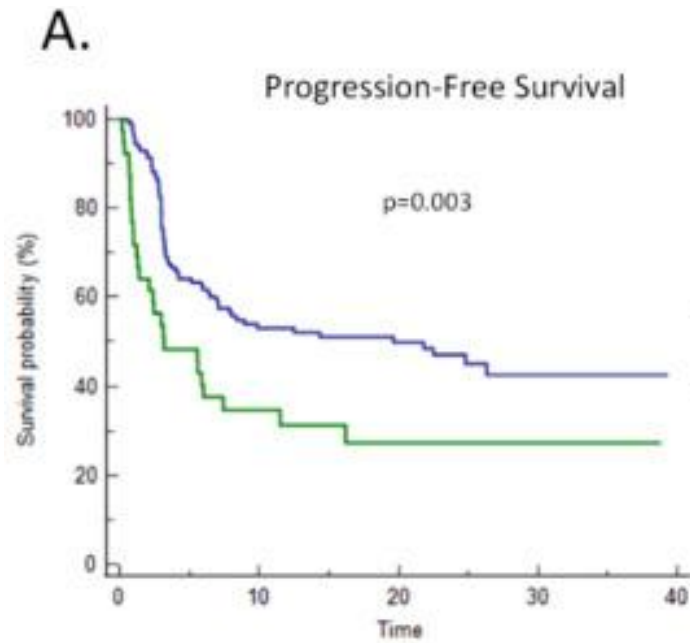
# Pronostic



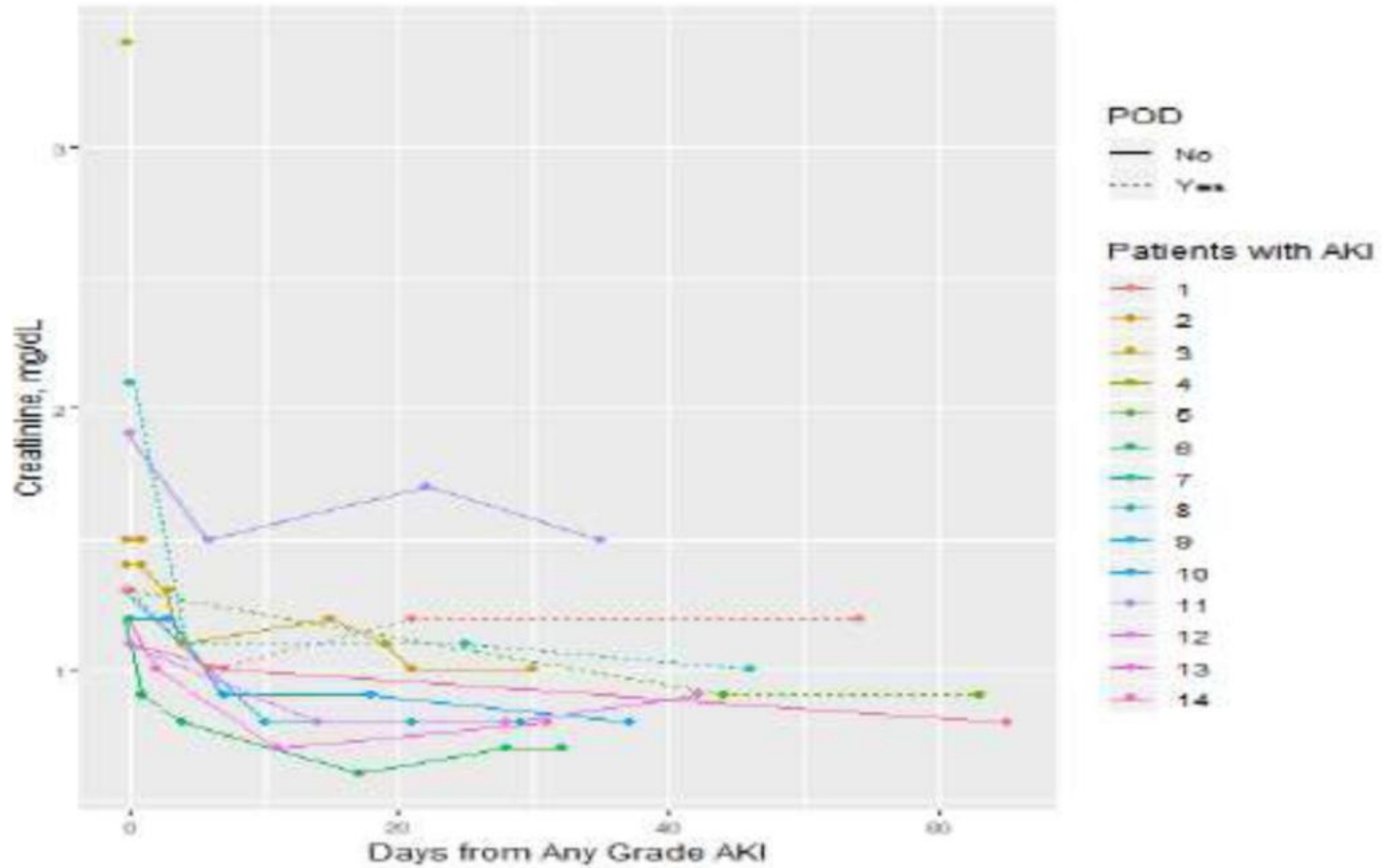
# Association AKI/mortalité



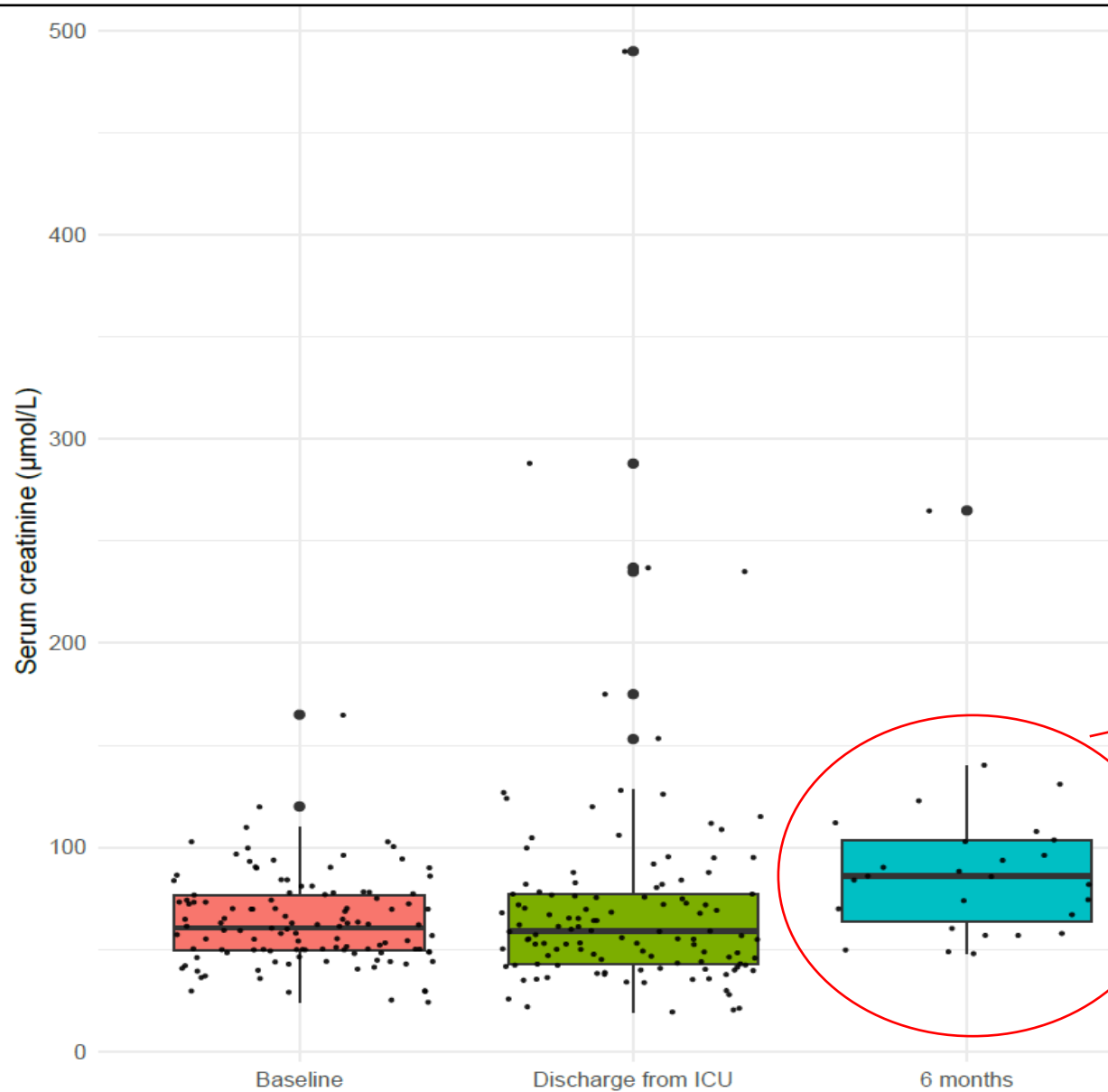
## Pronostic: rémission et survie



# Pronostic: récupération rénale

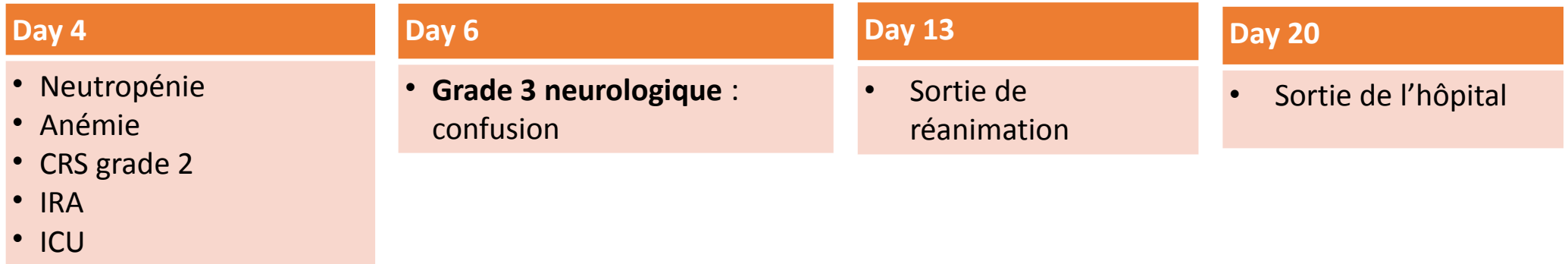


## Pronostic: récupération rénale



25,9% des survivants ont un DFG < 60ml/min

# Mr D...



**Day 0:**  
CAR T-cell

Tocilizumab

Corticoides

Antibiotiques

Créatininémie : 260  $\mu\text{mol/l}$   
Echorenale normale  
Ionogramme urinaire : Na/K > 1, Fe Na > 2%  
ECBU : leucocyturie sans germe  
Pu : 60mg/mmol  
CAR-T +++ dans les urines

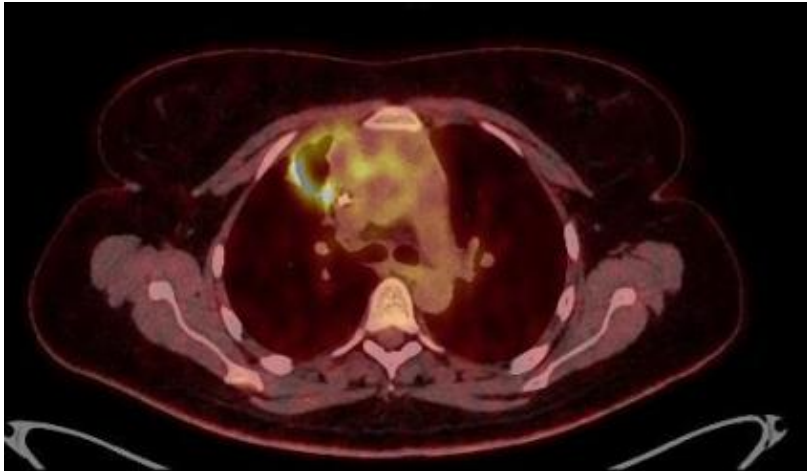
Créatininémie : 350 $\mu\text{mol/l}$

Créatininémie : 200  $\mu\text{mol/l}$

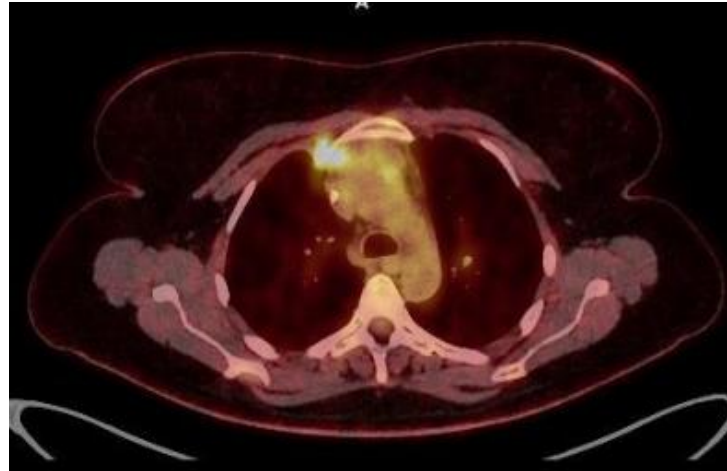
Créatininémie : 85  $\mu\text{mol/l}$

# Mr D...

Day 30



Day 90



6 mois

- Leukocyte: 1.5 /L
- Lymphocyte: 0.2 /L
- Haemoglobin: 130 g/L
- Platelets:  $173 \times 10^9/L$
- Gammaglobulines: 5 g/L
- Créatininémie :  $79 \mu\text{mol/l}$



## Conclusion

IRA : 15-20% des patients après injection de CAR-T

Données chez les patients avec tubulopathie myélomateuse ?

Causes très variées +++  
Importance du CRS

Rechercher syndrome néphrotique/NTIA  
CAR-T dans les urines ?

Impact des traitements spécifiques sur la fonction rénale ?