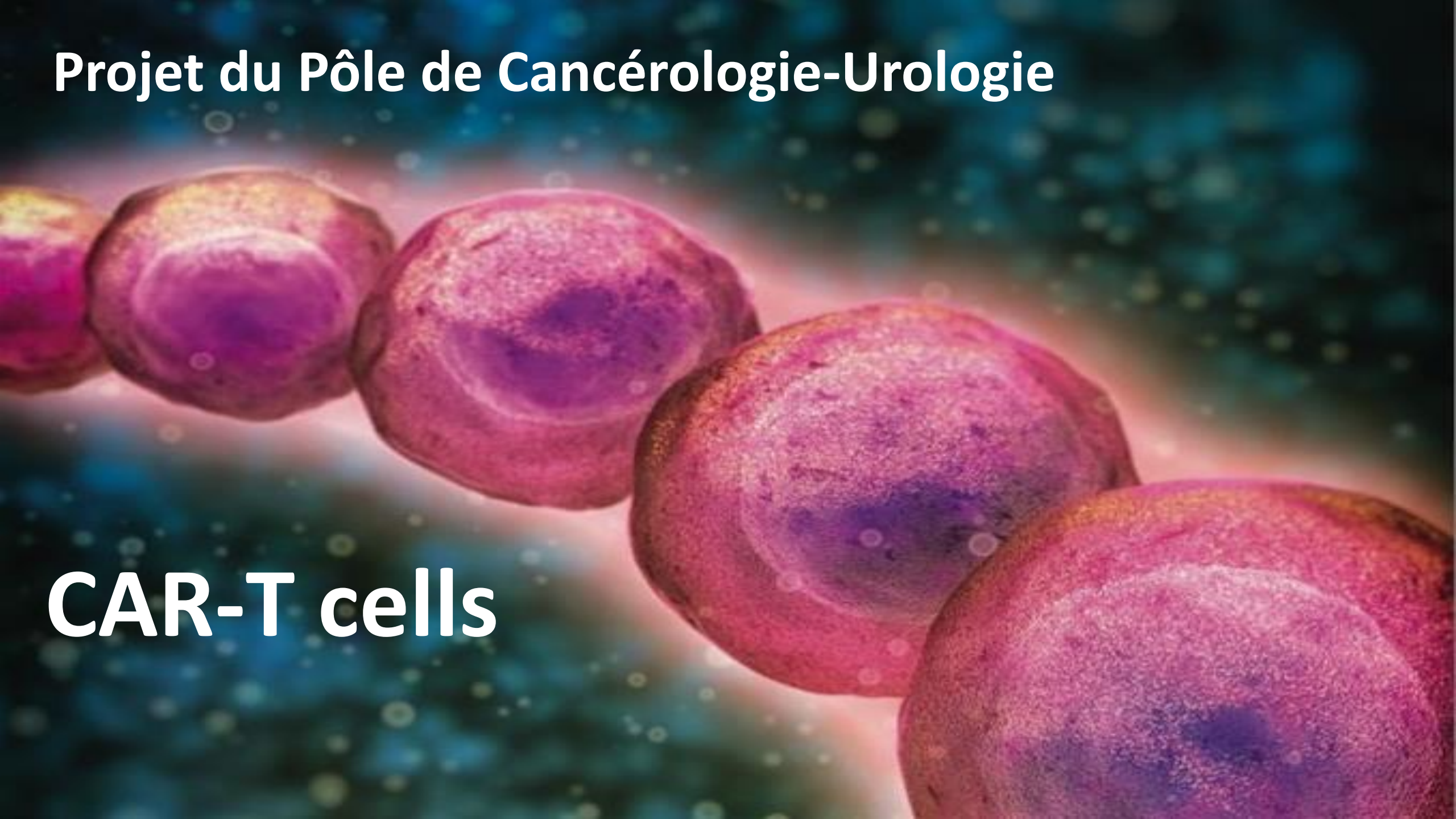
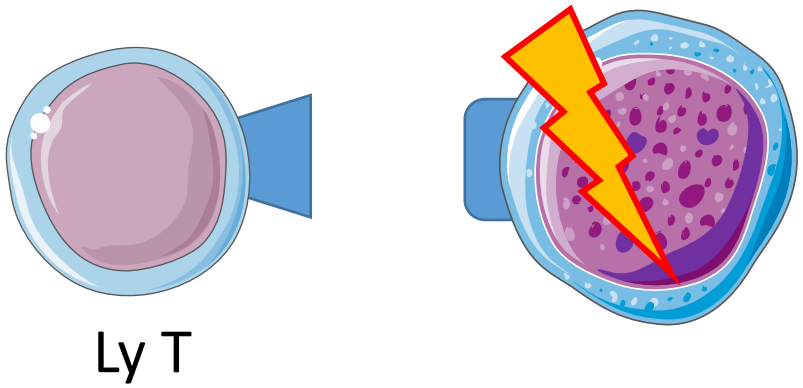
Projet du Pôle de Cancérologie-Urologie

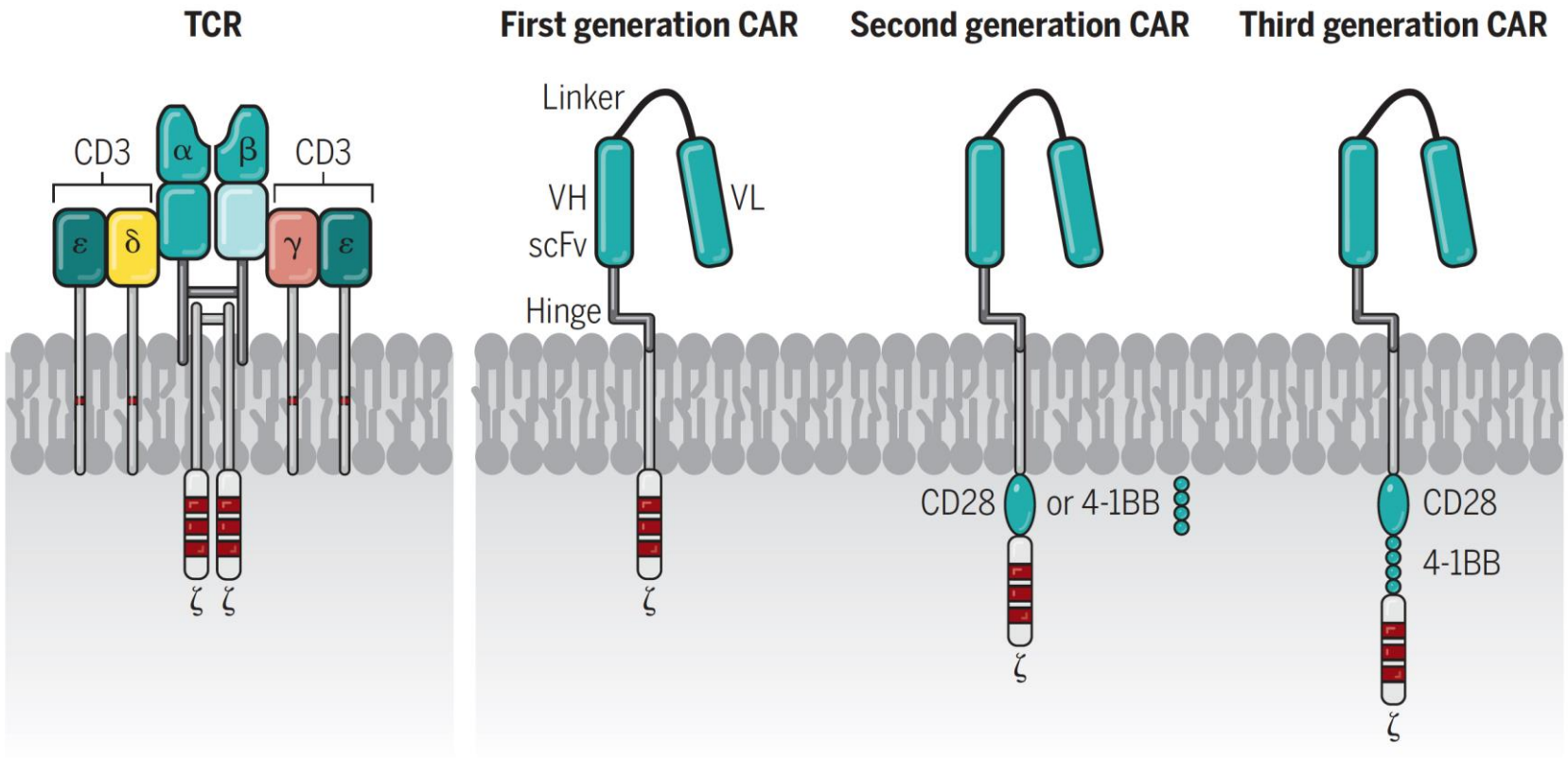


CAR-T cells

Principe des récepteurs chimériques

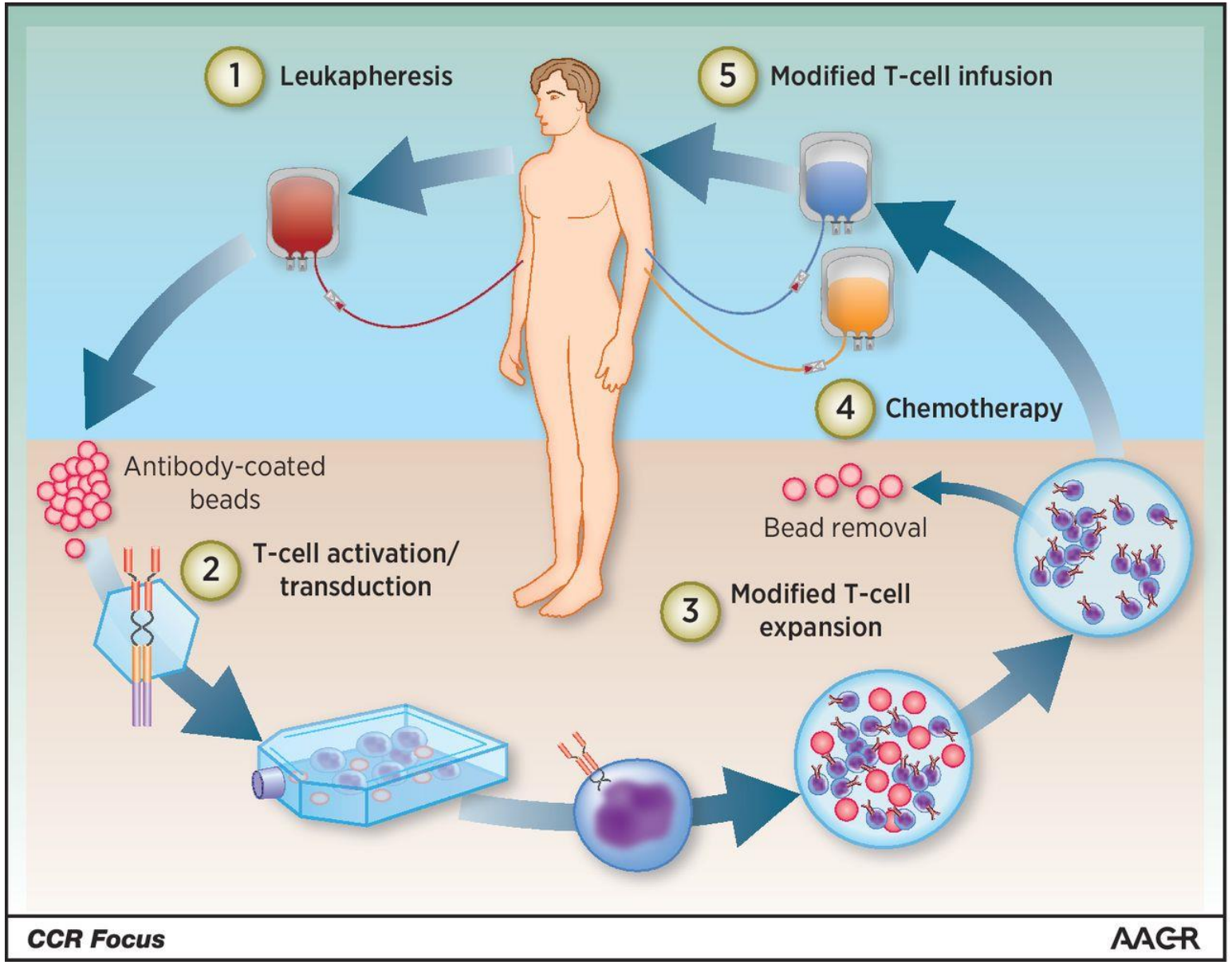


Structure des CAR-T-cells

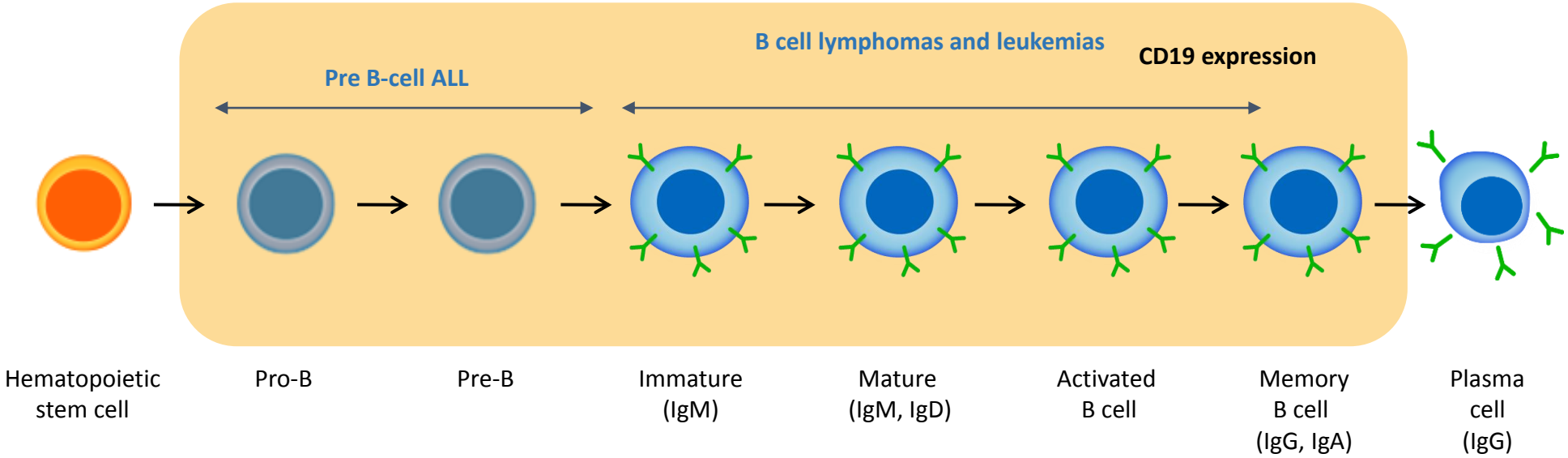


June et al., Science 2018

Fabrication des CAR-T-cells



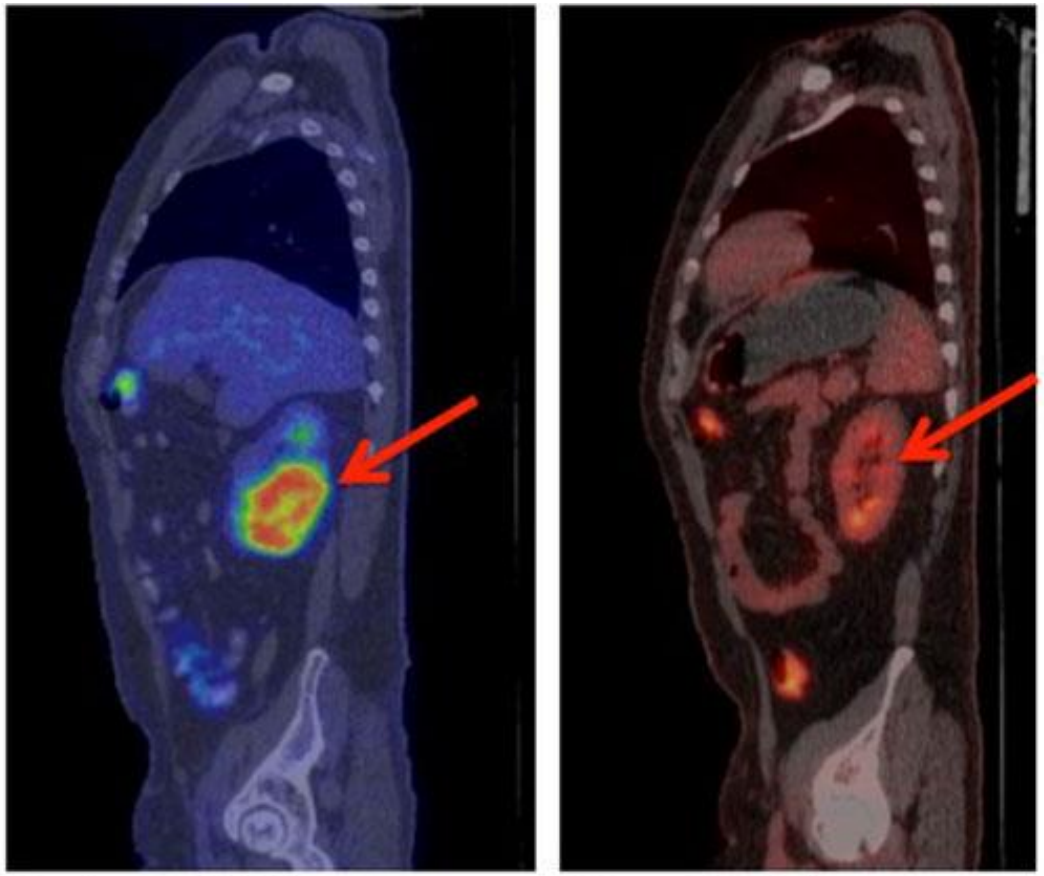
CD19 : Une cible idéale



Scheuermann et al. Leuk Lymphoma 1995

Résultats cliniques

Lymphome réfractaire



Before CAR-T treatment After CAR-T treatment

Phase II in 111 patients with R/R lymphoma

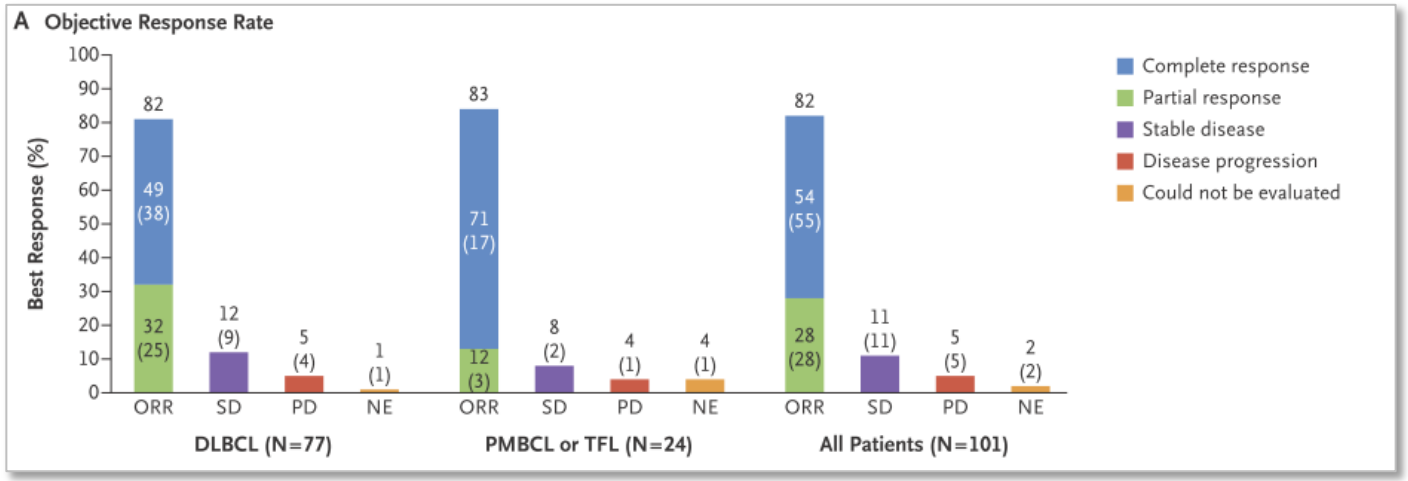
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

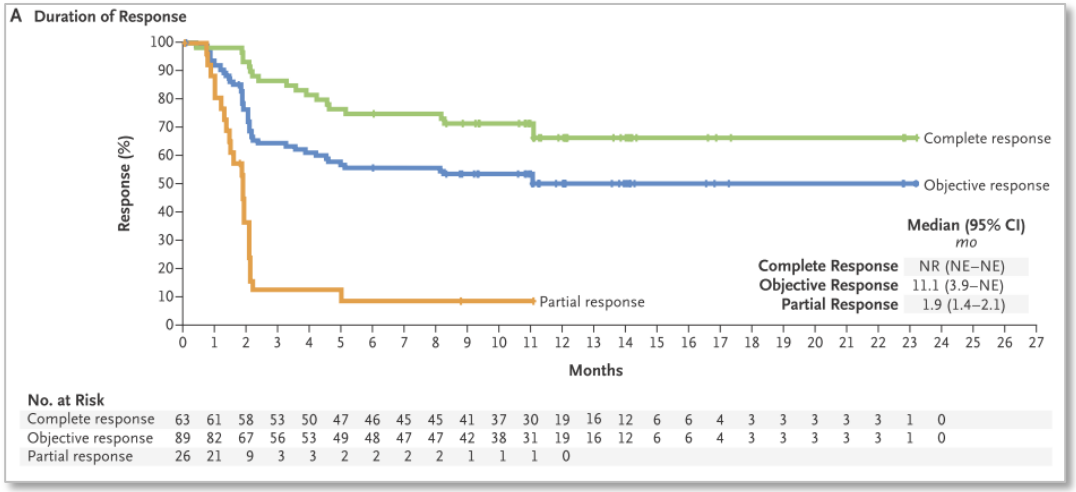
S.S. Neelapu, F.L. Locke, N.L. Bartlett, L.J. Lekakis, D.B. Miklos, C.A. Jacobson, I. Braunschweig, O.O. Oluwole, T. Siddiqi, Y. Lin, J.M. Timmerman, P.J. Stiff, J.W. Friedberg, I.W. Flinn, A. Goy, B.T. Hill, M.R. Smith, A. Deol, U. Farooq, P. McSweeney, J. Munoz, I. Avivi, J.E. Castro, J.R. Westin, J.C. Chavez, A. Ghobadi, K.V. Komanduri, R. Levy, E.D. Jacobsen, T.E. Witzig, P. Reagan, A. Bot, J. Rossi, L. Navale, Y. Jiang, J. Aycock, M. Elias, D. Chang, J. Wiezorek, and W.Y. Go

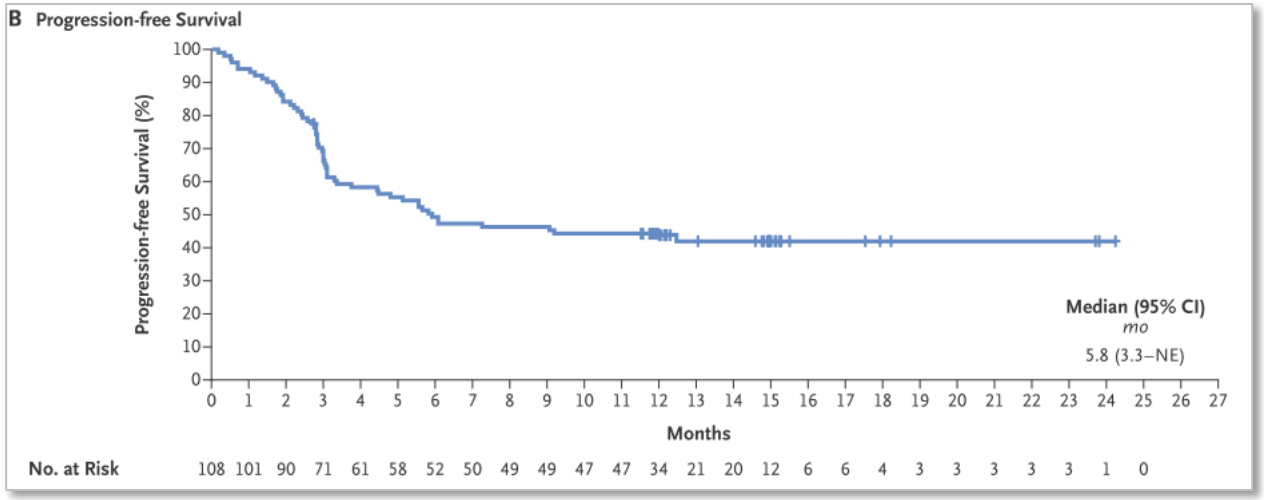
Variable	Patients with DLBCL	Patients with PMBCL or TFL	All Patients
Treatment disposition			
No. of patients enrolled	81	30	111
Prior therapies — no. (%)			
≥Three prior lines of therapy	49 (64)	21 (88)	70 (69)
History of primary refractory disease**	23 (30)	3 (12)	26 (26)
History of resistance to two consecutive lines	39 (51)	15 (62)	54 (53)
Refractory subgroup at study entry — no. (%)			
Primary refractory	2 (3)	0	2 (2)
Refractory to second-line or subsequent therapy	59 (77)	19 (79)	78 (77)
Relapse after autologous stem-cell transplantation	16 (21)	5 (21)	21 (21)

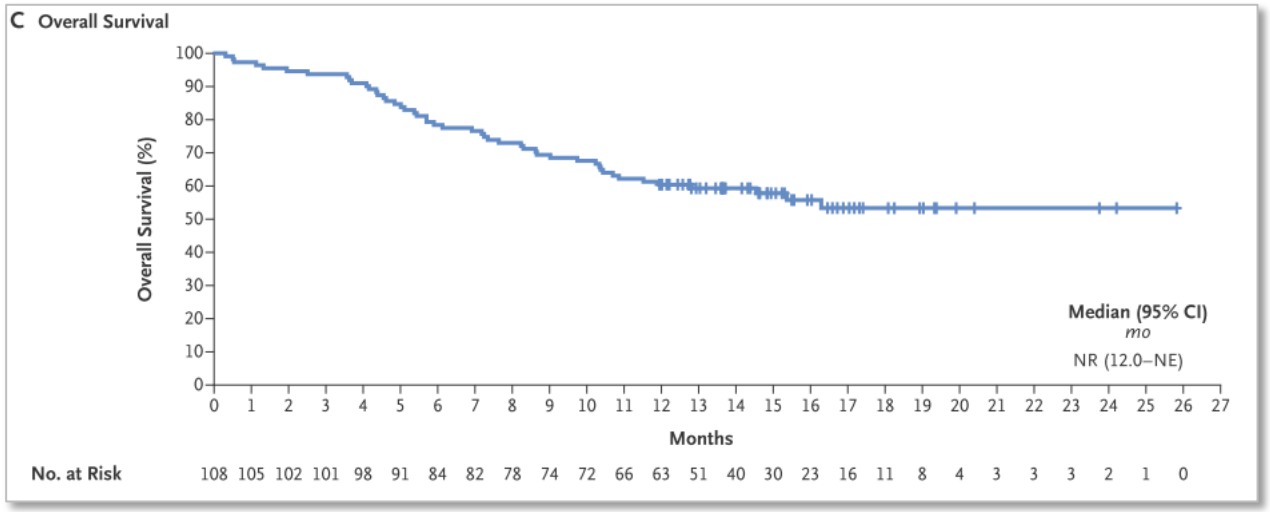


Neelapu et al., NEJM 2017;377:2531-44.

Durée de réponse



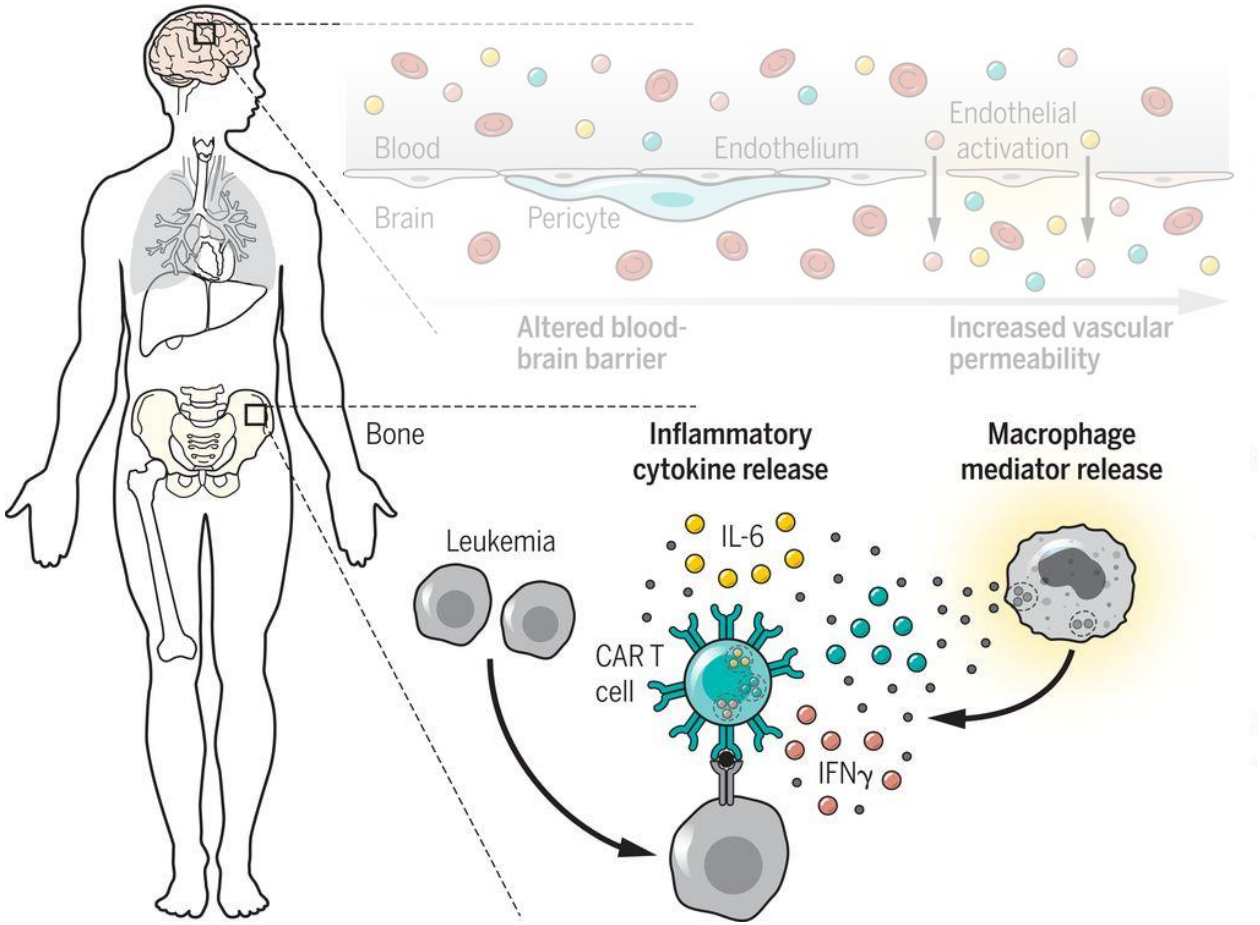




Quelques toxicités

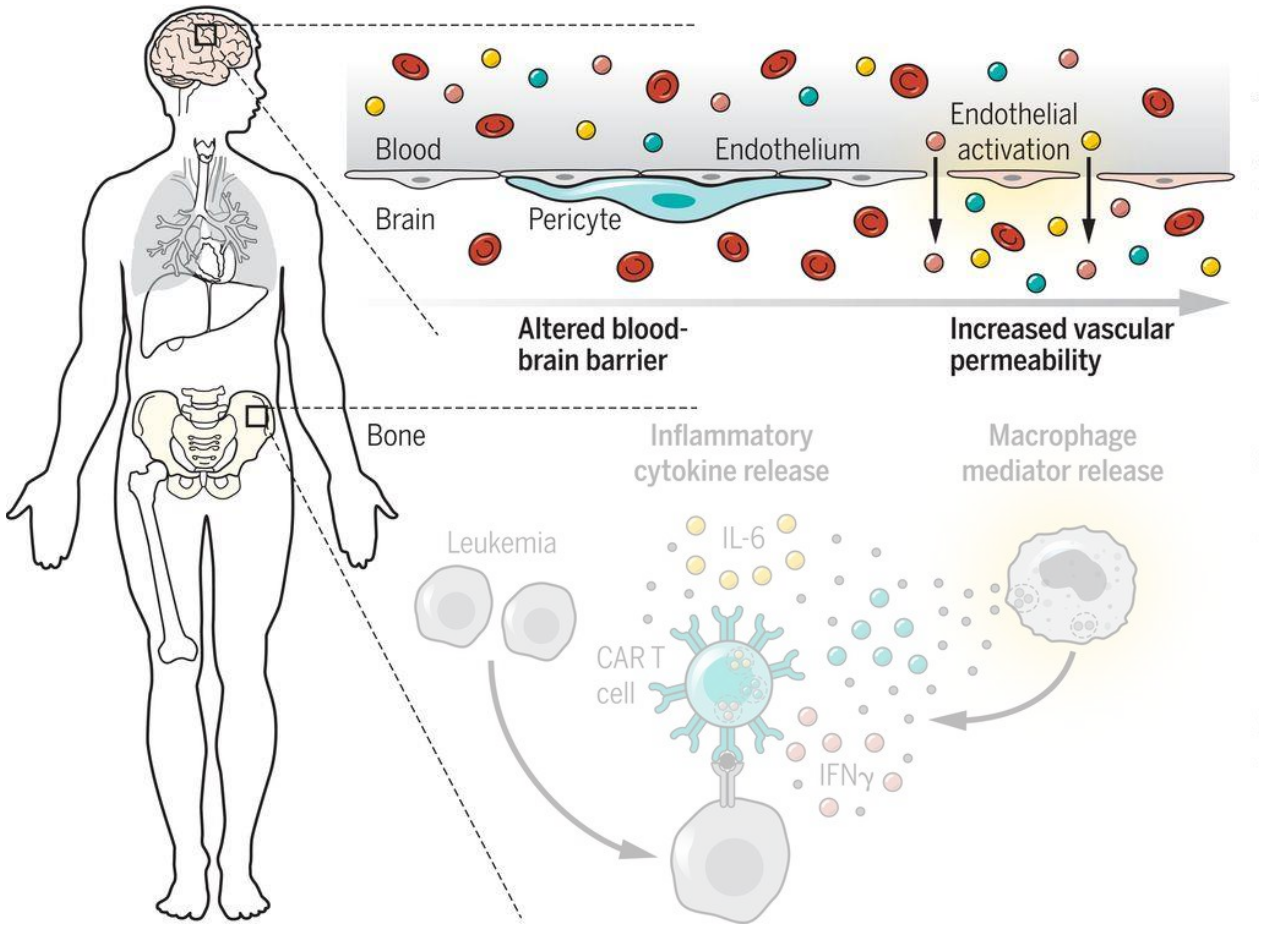
- CRS chez 93% of patients
- 17% des patients ont eu besoin de vasopresseurs
- 1 Syndrome d’activation macrophagique fatal
- 1 arrêt cardiaque fatal
- 64% de symptômes neurologiques
- 43% patients ont reçu du tocilizumab
- 27% ont reçu des corticosteroides

Potent… but toxic : cytokine releasing syndrome (CRS)



June et al., Science 2018

Potent… but toxic : CAR T-related encephalopathy syndrome (CRES)
Immune effector cells neurotoxicity syndrome (ICANS)



June et al., Science 2018

Time for consensus

Table 2
ASBMT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°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)

Lee et al., BBMT, 2018

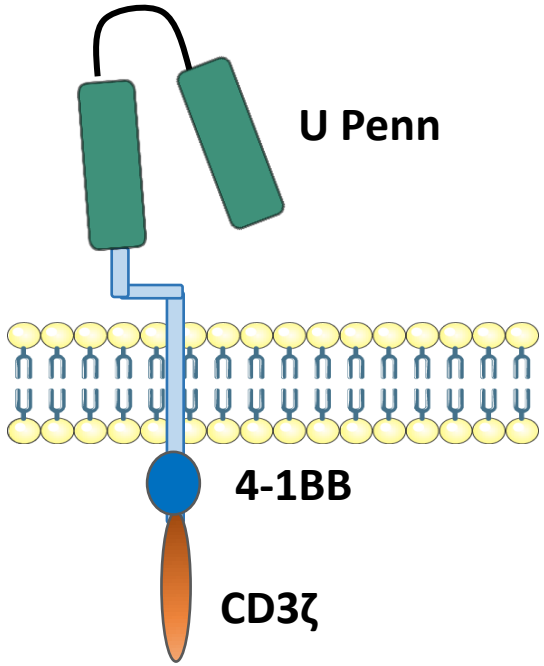
Time for consensus

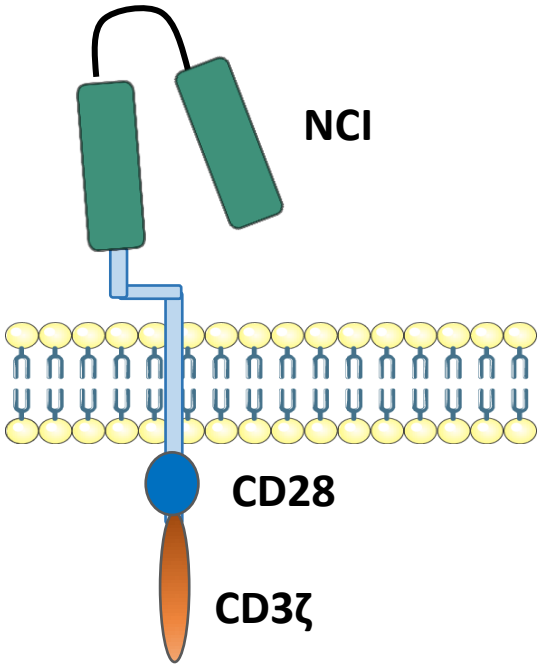
Table 6
ASBMT ICANS Consensus Grading for Adults

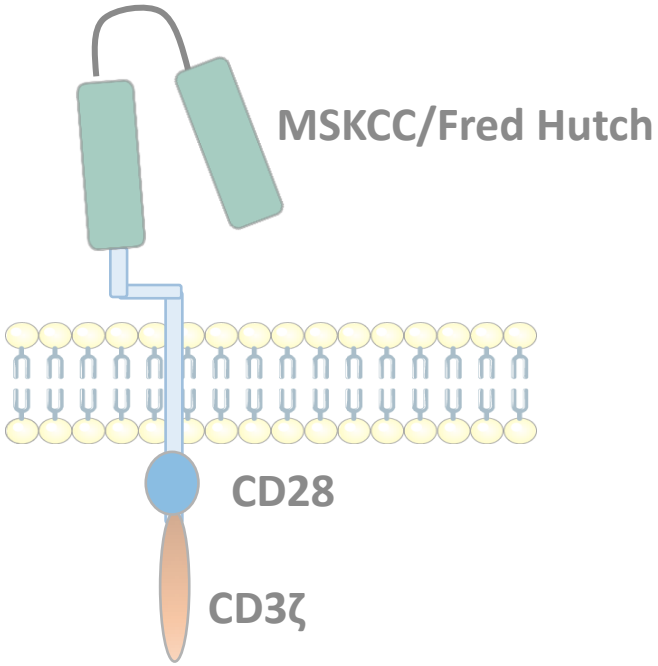
Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile 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

Lee et al., BBMT, 2018

3 ACTEURS MAJEURS, 3 TYPES DE CAR







Novartis CTL-019	Kite Gilead KTE-C19	Juno therapeutics JCAR Celgène
Lentivirus	**Retrovirus**	Retrovirus
Tisagenlecleucel	**Axicabtagene ciloleucel**	Lisocabtagene maraleucel
“tisa-cel”=Kymriah®	“axi-cel”=Yescarta®	“liso-cel”
JULIET	ZUMA	TRANSCEND

THE NATIONAL NETWORK

Centres ouverts aux études CAR-T cells en France
MAJ 21 février 2019

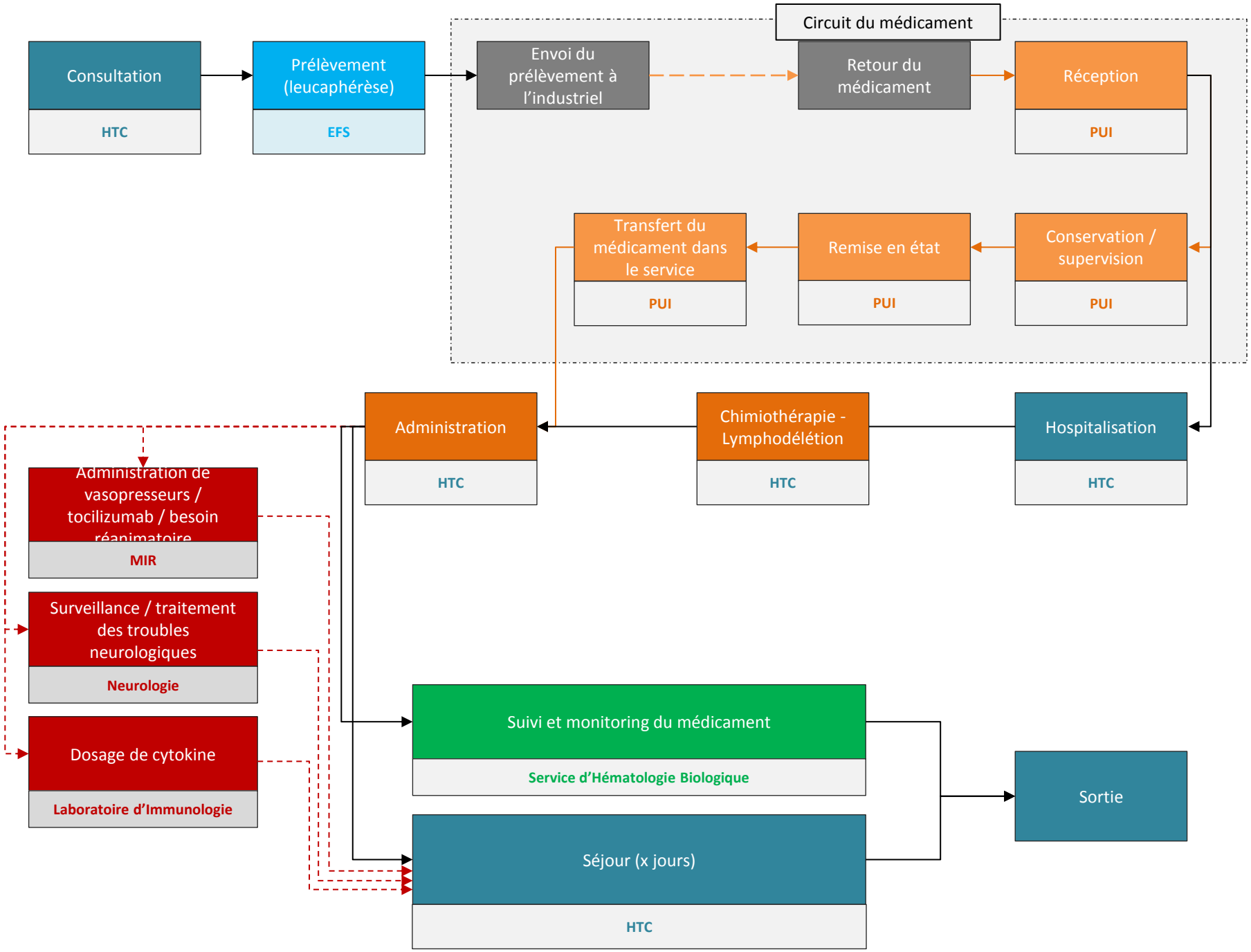
Lysa
THE LYMPHOMA STUDY ASSOCIATION

Mise en place des CAR-T *cells* au CHU de Tours

- Projet structurant – recours Régional
- Partenariat :
  - EFS (leucaphérèse)
  - Pharmacie à Usage intérieur (réception, conservation en azote liquide)
  - Service d'hématologie et thérapie cellulaire (coordination, injection)
  - Réanimation Médicale et Médecine Intensive (CRS, vasopresseurs, troubles neurologiques)
  - Service d'hématologie biologique (suivi en cytométrie/biologie moléculaire)
  - Imagerie (IRM disponible)
  - Neurologie (pour certains laboratoires)

Enjeux d’une mise en place de CAR-T expérimentaux (Recherche clinique)

- Organisation de l’accueil du produit expérimental en azote liquide
- Structuration d’une équipe transversale CAR-T
- Mise en place de procédures
- Partage d’expérience avec des centres déjà actifs
- Invitation des industriels à :
  - Visiter le centre
  - Prendre connaissance des organisations
  - Vérifier l’existence de procédures selon leur cahier des charges
  - Valider la structuration
  - Proposition d’essais cliniques


Circuit du médicament
Consultation
HTC
Prélèvement (leucaphérèse)
EFS
Envoi du prélèvement à l'industriel
Retour du médicament
Réception
PUI
Transfert du médicament dans le service
PUI
Remise en état
PUI
Conservation / supervision
PUI
Administration
HTC
Chimiothérapie - Lymphodélétion
HTC
Hospitalisation
HTC
Administration de vasopresseurs / tocilizumab / besoin réanimatoire
MIR
Surveillance / traitement des troubles neurologiques
Neurologie
Dosage de cytokine
Laboratoire d'Immunologie
Suivi et monitoring du médicament
Service d'Hématologie Biologique
Séjour (x jours)
HTC
Sortie

Composition GT1
"Circuit du médicament"

- PUI
  - Dr. H. BOURGOIN
  - Dr. V. ANDRE (UBCO)
- CRB
  - Pr. O. HERAULT
  - A. DECOCK
- Qualité/Direction de la Recherche
  - C. GADRAS
- EFS
  - I. DESBOIS
- HTC
  - Pr. E. GYAN
  - 1 ARC du service HTC
- Direction des Projets
  - T. BOUCHENOIRE

Composition GT2 "Processus global"

- PUI — Dr. V. ANDRE (UBCO)
- Service d'Hématologie Biologique — Pr. O. HERAULT
- Qualité/Direction de la Recherche — C. GADRAS
- EFS — I. DESBOIS ou délégué
- HTC — Pr. E. GYAN
- Neurologie — Pr. Ph. CORCIA
- Laboratoire d'Immunologie — Pr. H. WATIER
- MIR — Pr. P-F. DEQUIN
- Imagerie — Pr. J-P. COTTIER
- Direction des Projets — T. BOUCHENOIRE

Conclusions

- Les CAR-T cells sont une technologie de rupture dans les hémopathies lymphoïdes
- Toxicité nécessitant une coopération interservices
- La soutenabilité économique reste une question à traiter
- La place de ces stratégies est évolutive
- Un véritable espoir pour les patients