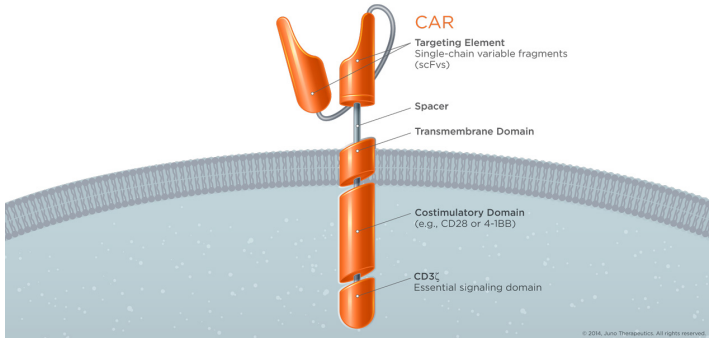


CAR T-cells

Données actualisées

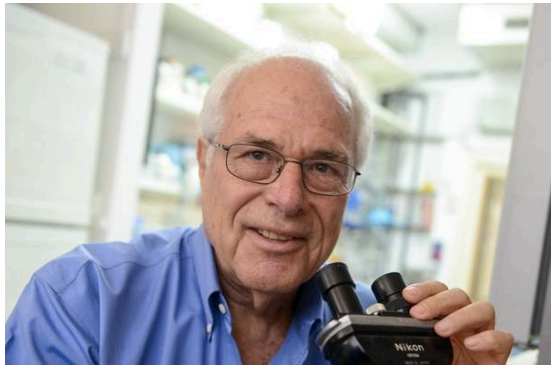
enseignements tirés de 3 ans de pratique clinique

SORBONNE UNIVERSITÉ
CRÉATEURS DE FUTURS DEPUIS 1257
HÔPITAUX UNIVERSITAIRES PITIÉ SALPÊTRIÈRE CHARLES FOIX

SFH
hemapherese.fr

L’histoire en 3 diapos

1° publication 1989



Proc. Natl. Acad. Sci. USA
Vol. 86, pp. 10024–10028, December 1989
Immunology

Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity

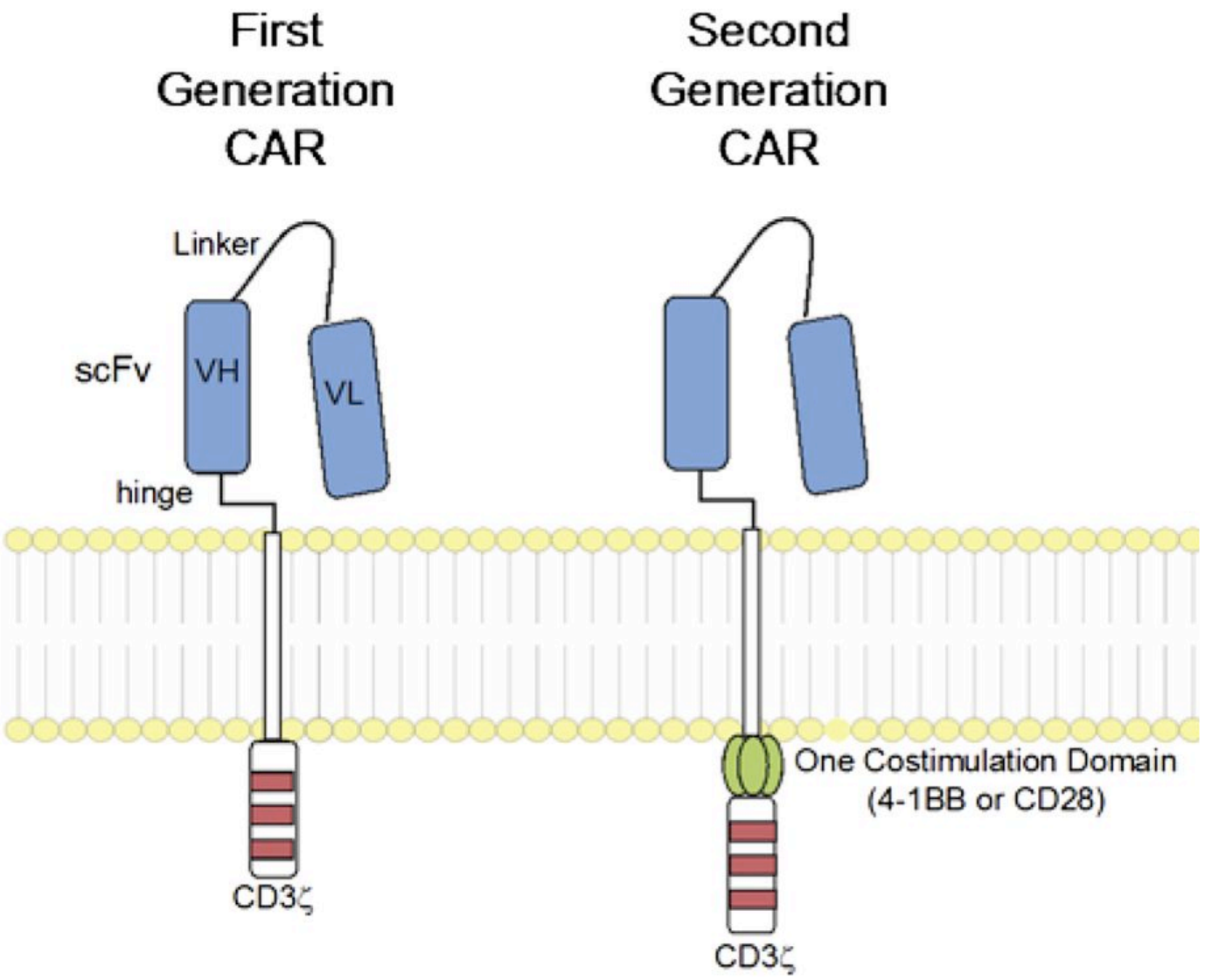
(chimeric genes/antibody variable region)

GIDEON GROSS, TOVA WAKS, AND ZELIG ESHHAR*

Department of Chemical Immunology, The Weizmann Institute of Science, Rehovot 76100, Israel

✓Affinité micromolaire ➔ nanomolaire
✓Indépendant du HLA

2° génération



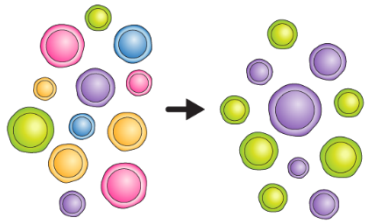
Le choc médiatique

2012

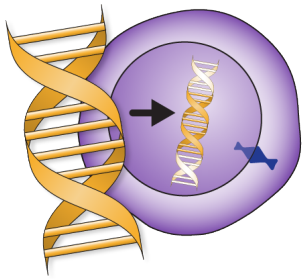
Fabrication

Apheresis Collection

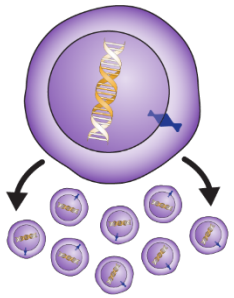
Lymphocyte Enrichment/T Cell Activation



Retroviral Transduction

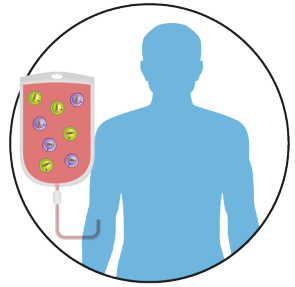


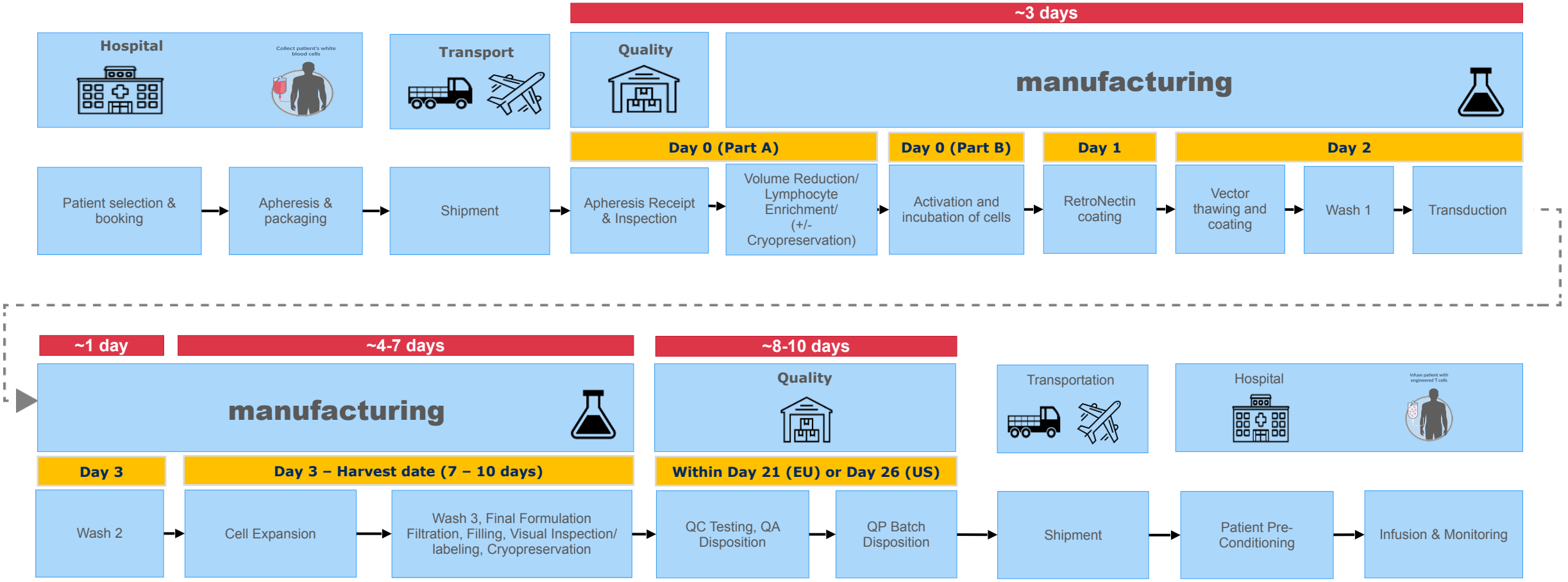
T Cell Expansion



Formulation & Cryopreservation

Patient Infusion





* Source interne Kite

Efficacité

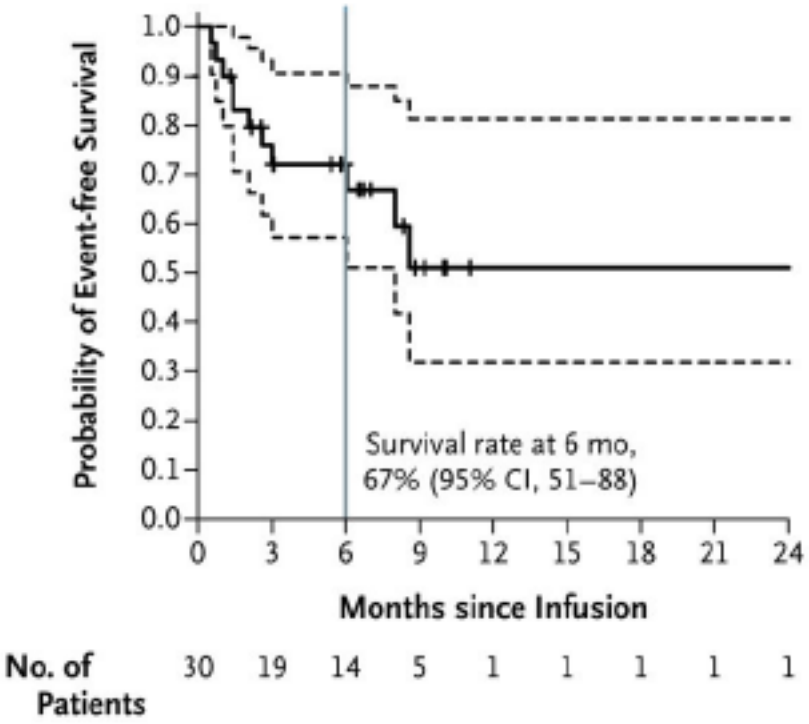
LAL de l’enfant/adolescent

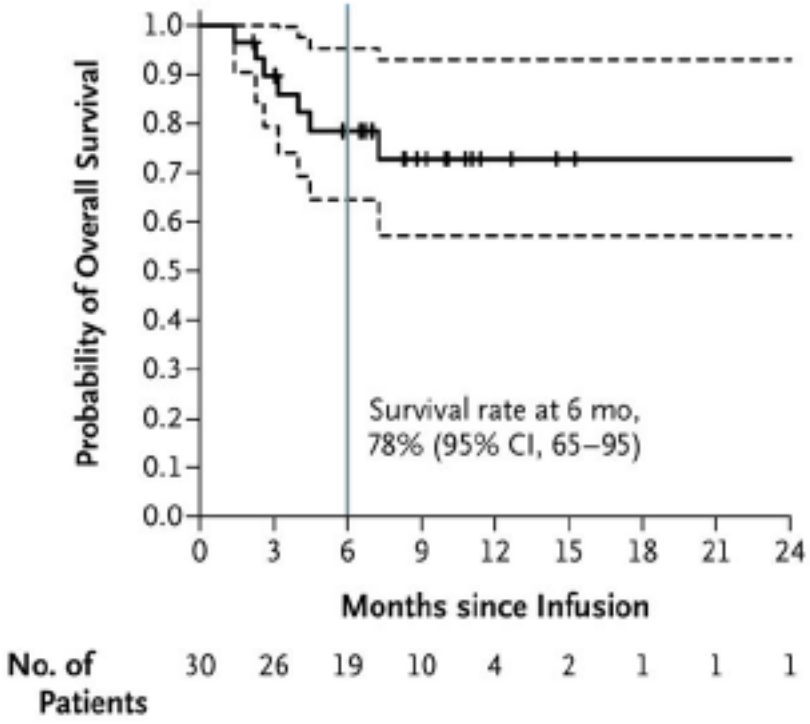
Published in final edited form as:
N Engl J Med. 2014 October 16; 371(16): 1507–1517. doi:10.1056/NEJMoa1407222.

Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia

Shannon L. Maude, M.D., Ph.D., Noelle Frey, M.D., Pamela A. Shaw, Ph.D., Richard Aplenc, M.D., Ph.D., David M. Barrett, M.D., Ph.D., Nancy J. Bunin, M.D., Anne Chew, Ph.D., Vanessa E. Gonzalez, M.B.A., Zhaohui Zheng, M.S., Simon F. Lacey, Ph.D., Yolanda D. Mahnke, Ph.D., Jan J. Melenhorst, Ph.D., Susan R. Rheingold, M.D., Angela Shen, M.D., David T. Teachey, M.D., Bruce L. Levine, Ph.D., Carl H. June, M.D., David L. Porter, M.D., and **Stephan A. Grupp, M.D., Ph.D.**

Réponse

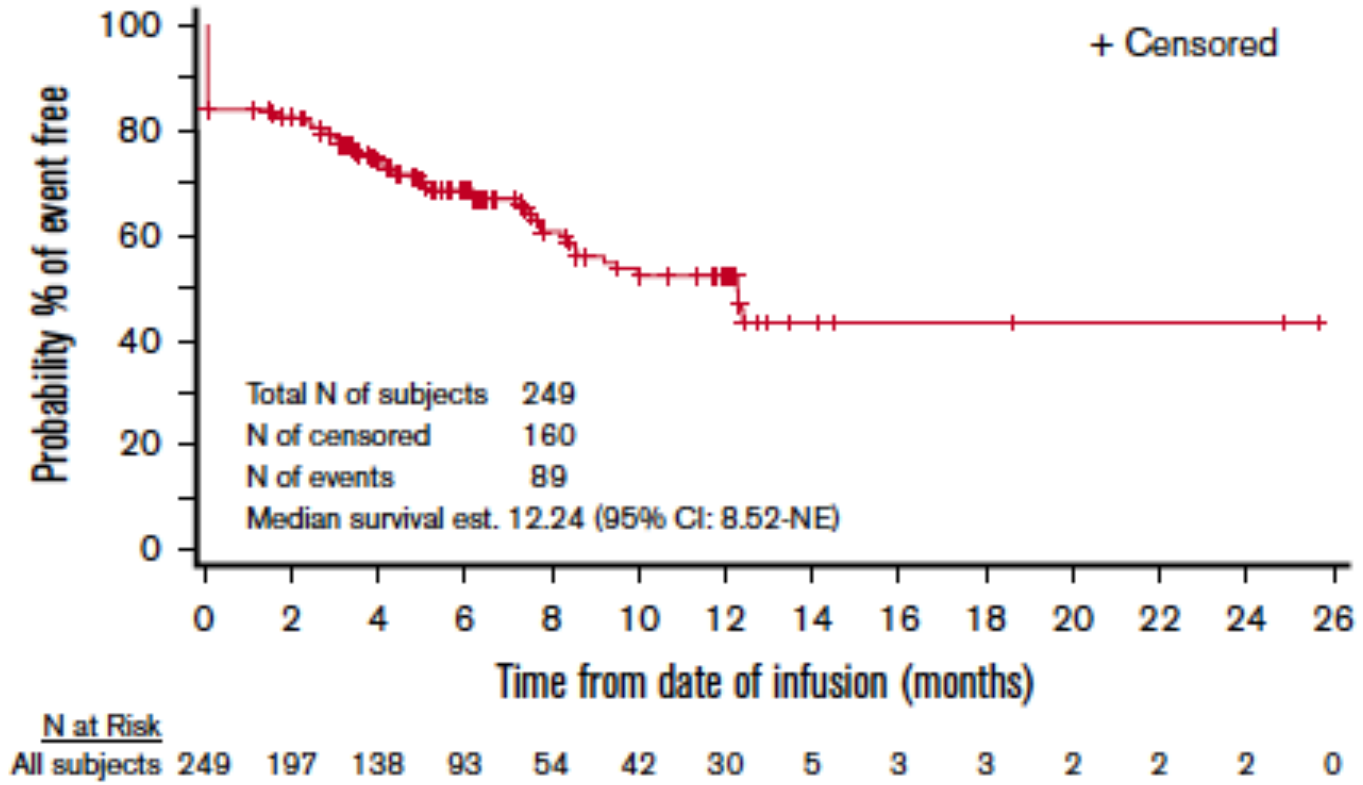




Maude SL et al. *NEJM* 2014

LAL vraie vie

Survie sans évènement



Pasquini MC *Blood Adv* 2020

LNH B diffus à grandes cellules (LBDGC)

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

The NEW ENGLAND JOURNAL of MEDICINE

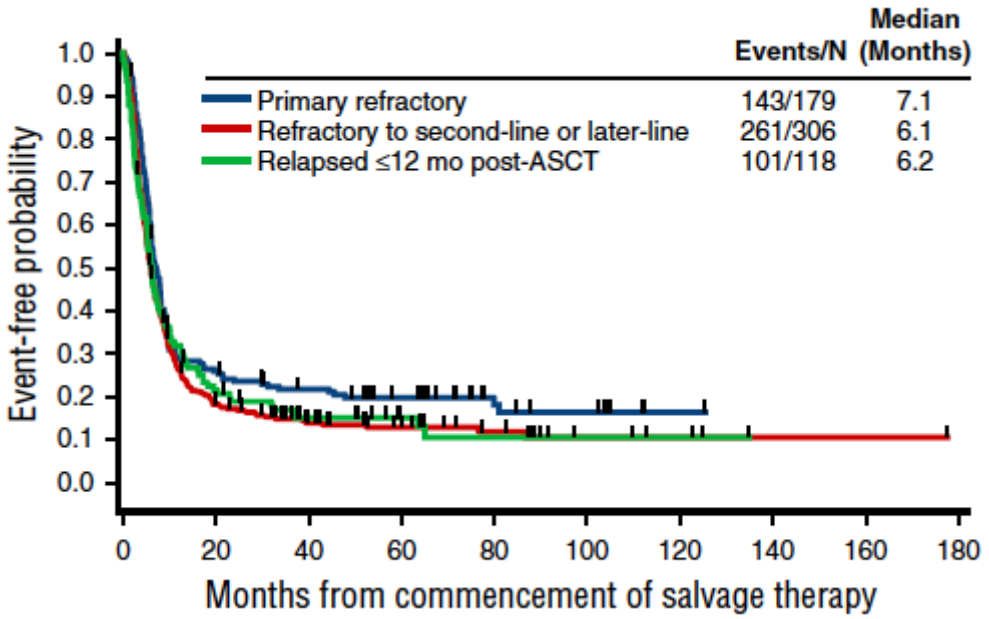
ORIGINAL ARTICLE

Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas

Stephen J. Schuster, M.D., Jakub Svoboda, M.D., Elise A. Chong, M.D., Sunita D. Nasta, M.D., Anthony R. Mato, M.D., Özlem Anak, M.D., Jennifer L. Brogdon, Ph.D., Iulian Pruteanu-Malinici, Ph.D., Vijay Bhoj, M.D., Ph.D., Daniel Landsburg, M.D., Mariusz Wasik, M.D., Bruce L. Levine, Ph.D., Simon F. Lacey, Ph.D., Jan J. Melenhorst, Ph.D., David L. Porter, M.D., and Carl H. June, M.D.

SSE avant les CAR-T cells

LNH B diffus à grandes C

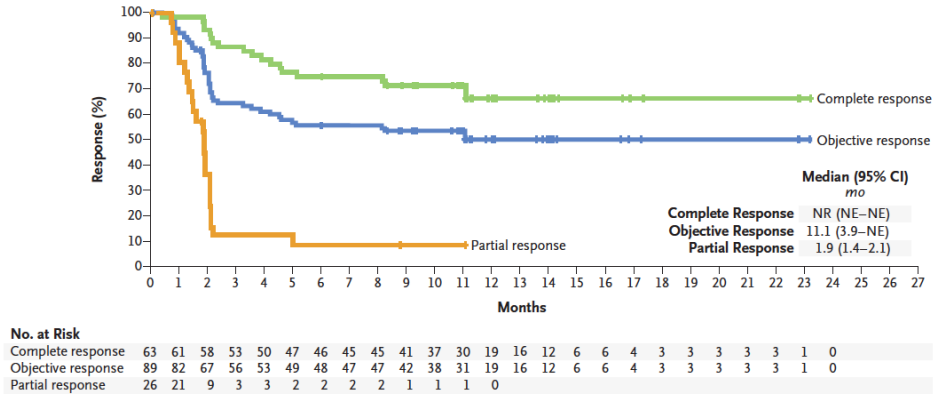


Scholar-1 (*Blood* 2017)

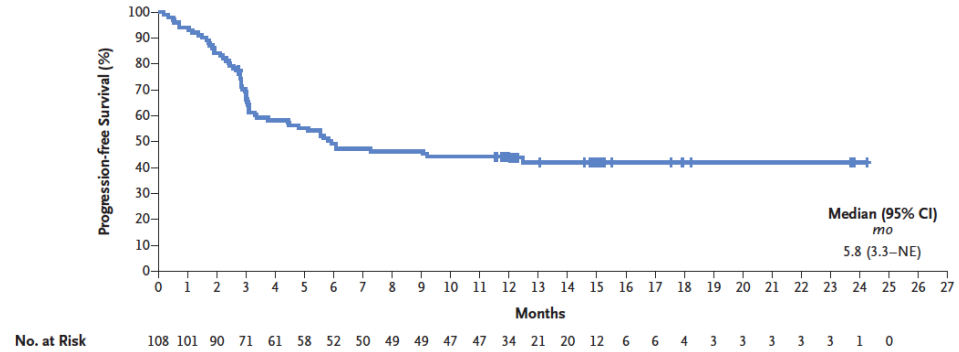
D'après Neelapu SS et al., New Engl J Med 2017; 377

Et Schuster SJ et al. New Engl J Med 2017; 377

ZUMA-1

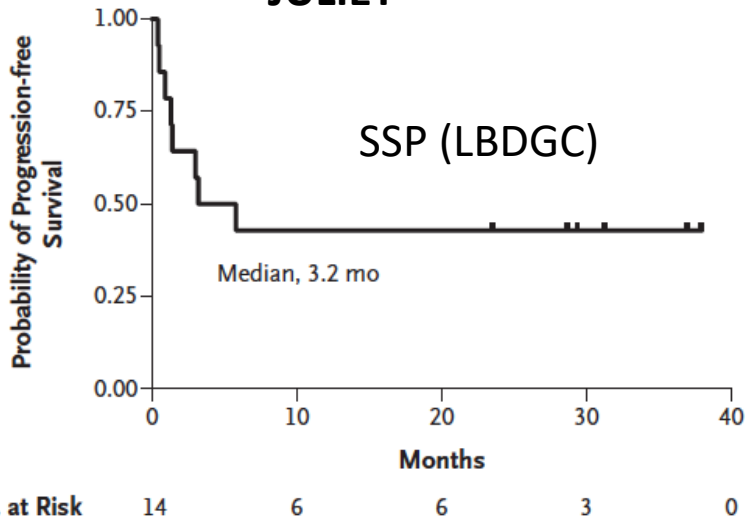


Durée de réponse



Survie sans progression

JULIET

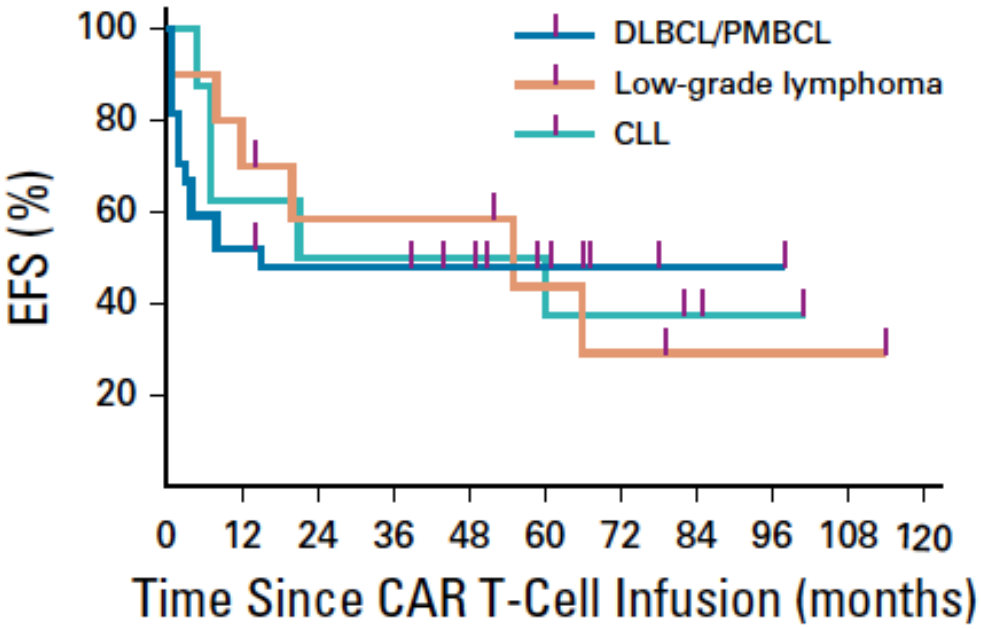


D'après Neelapu SS et al., New Engl J Med 2017; 377

Et Schuster SJ et al. New Engl J Med 2017; 377

LBDGC efficacité au long cours

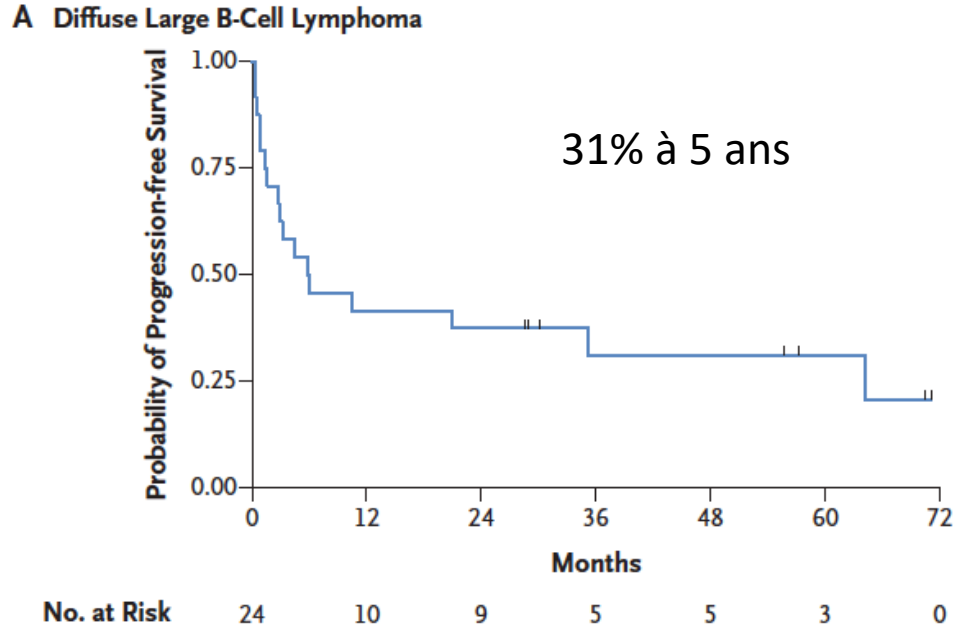
Médiane de SSE : 15 mois



No. at risk:

DLBCL/PMBCL	27	14	12	12	10	5	2	1		
Low-grade lymphoma	10	8	5	5	5	3	2	1	1	1
CLL	8	5	4	4	4	4	3	2	1	

Cappell KM *JCO* 2020

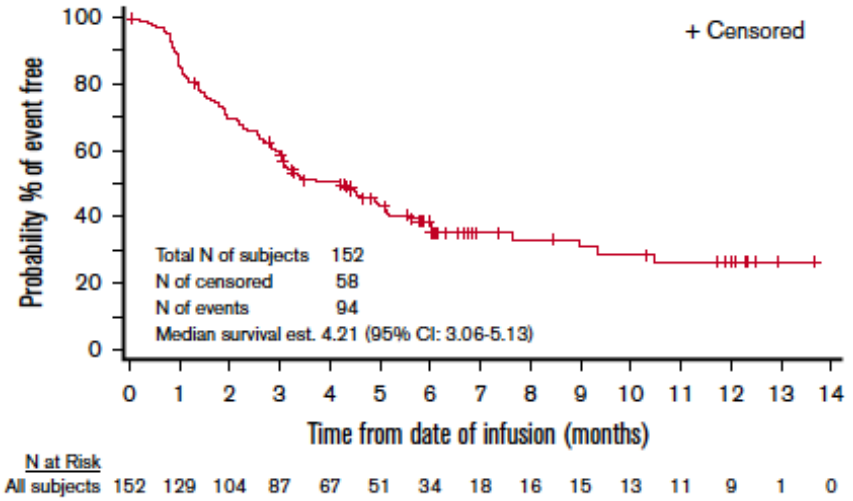


31% à 5 ans

Chong EA *NEJM* 2021

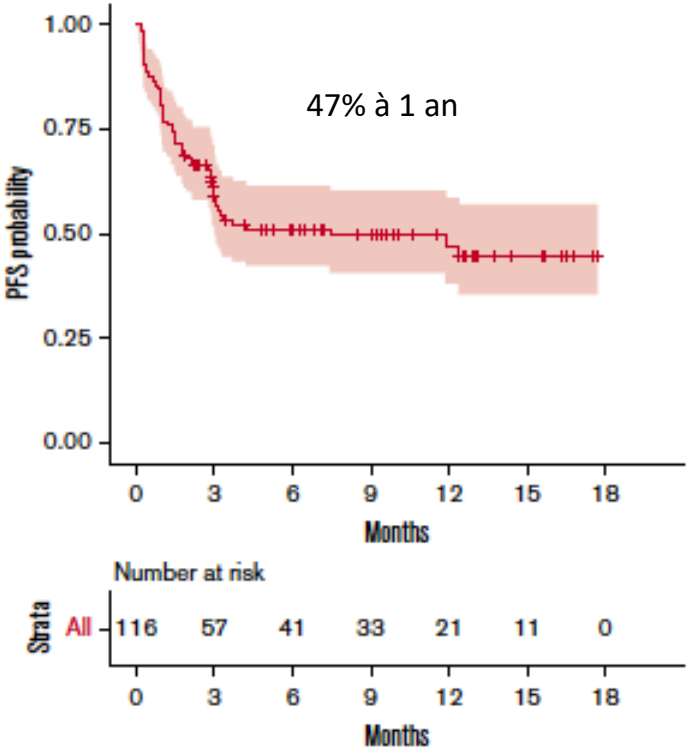
LBDGC vraie vie

Survie sans évènement



Pasquini MC *Blood Adv* 2020

Survie sans progression



Vercellino L *Blood Adv* 2020

LBDGC vraie vie : DESCAR-T

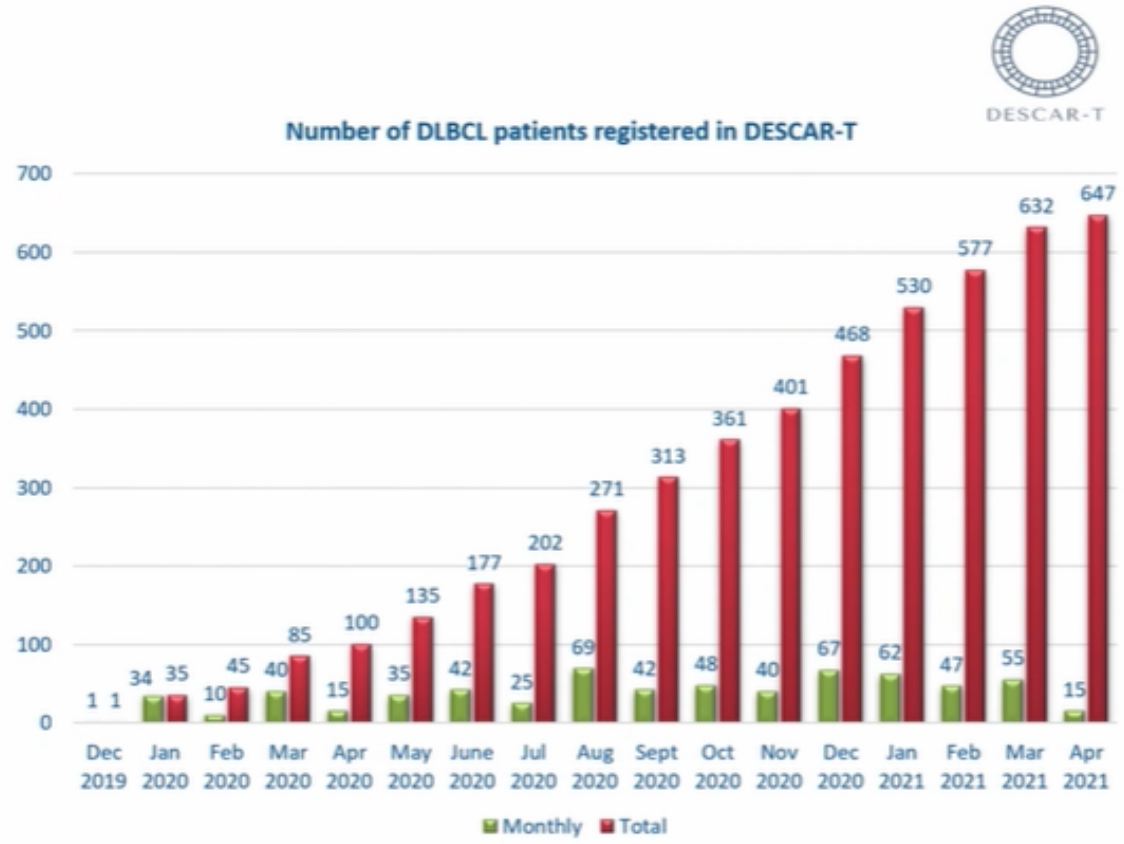
RESULTS: INCLUSIONS

Date: 12/04/2021

23 sites are qualified for CAR-T cells therapy and DESCAR-T

19 enrolling sites

Number of enrolled patients :
N = 647 DLBCL

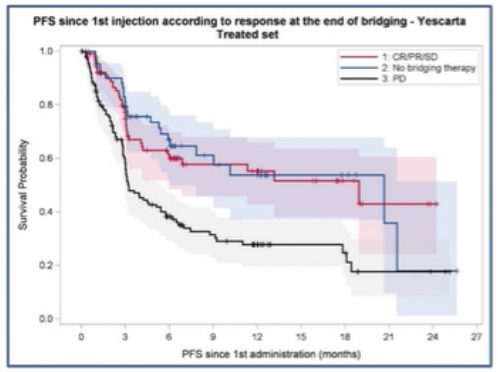


EHA 2021

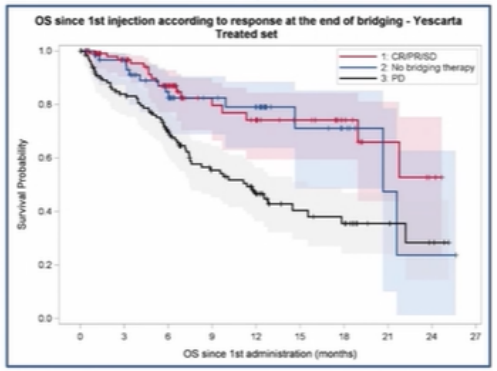
LBDGC vraie vie : DESCAR-T

PFS and OS ACCORDING TO DISEASE STATUS (Axicel; Yescarta®)

PFS at 6 months#:
- CR/PR/SD = 61.4% [50– 71] (n=116)
- No bridging = 66.9% [52.5 – 77.9] (n=75)
- PD = 38.2% [29.5 – 46.9] (n=139)

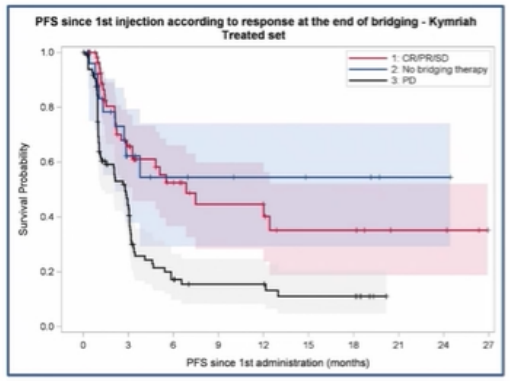


OS at 6 months#:
- CR/PR/SD = 87% [77 – 92.8] (n=116)
- No bridging = 84.7% [71.6 – 92.1] (n=75)
- PD = 69.7% [60.5 – 77.1] (n=139)

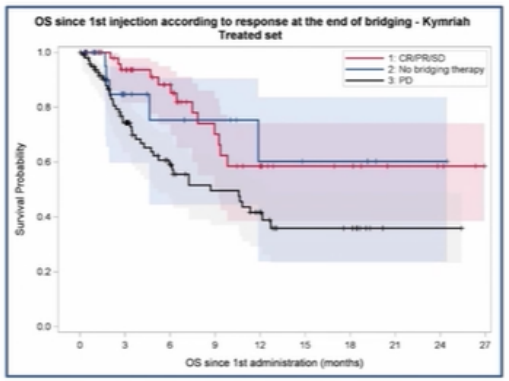


PFS and OS ACCORDING TO DISEASE STATUS (Tisacel; Kymriah®)

PFS at 6 months * :
- CR/PR/SD = 52.5% [36.7 – 66] (n=57)
- No Bridging = 54.4% [29.2 – 74.1] (n=34)
- PD = 17.1% [9.7 – 26.4] (n=100)



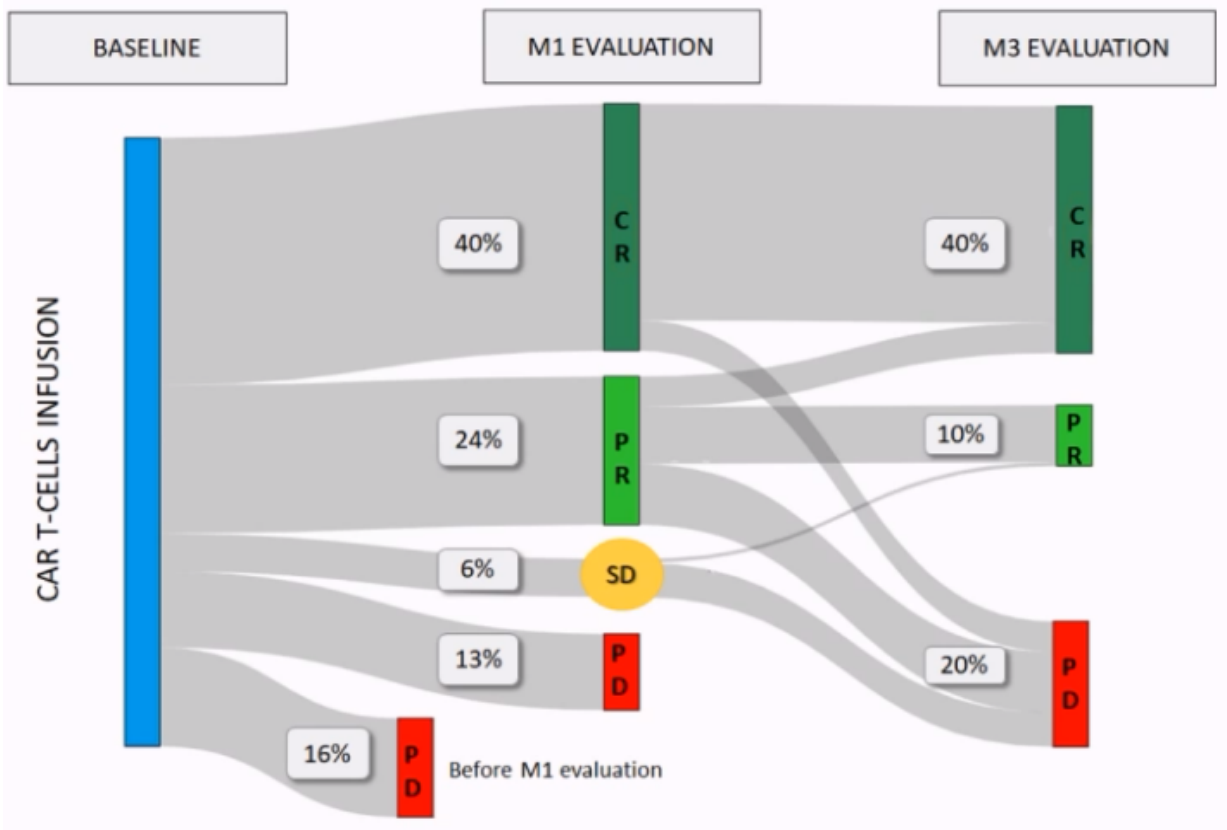
Os at 6 months * :
- CR/PR/SD = 88.2% [73.8 – 95] (n=57)
- No bridging = 75.3% [44.4 – 90.5] (n=34)
- PD = 59.1% [47 – 69.3] (n=100)



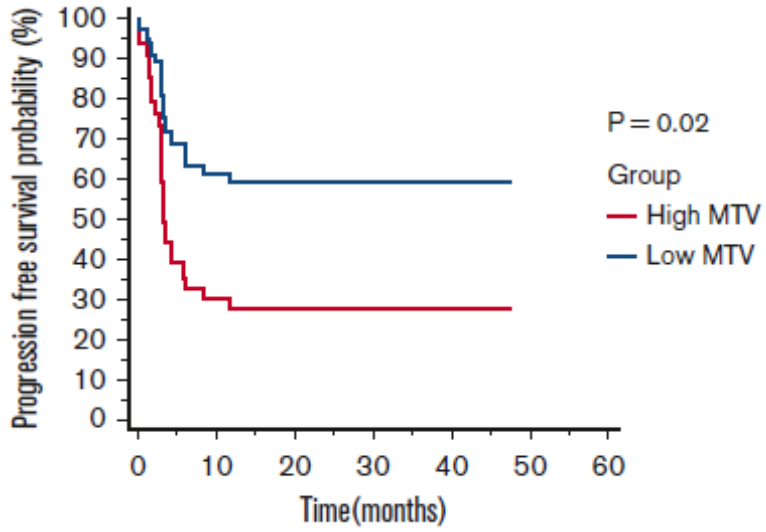
EHA 2021

Facteurs prédictifs de réponse

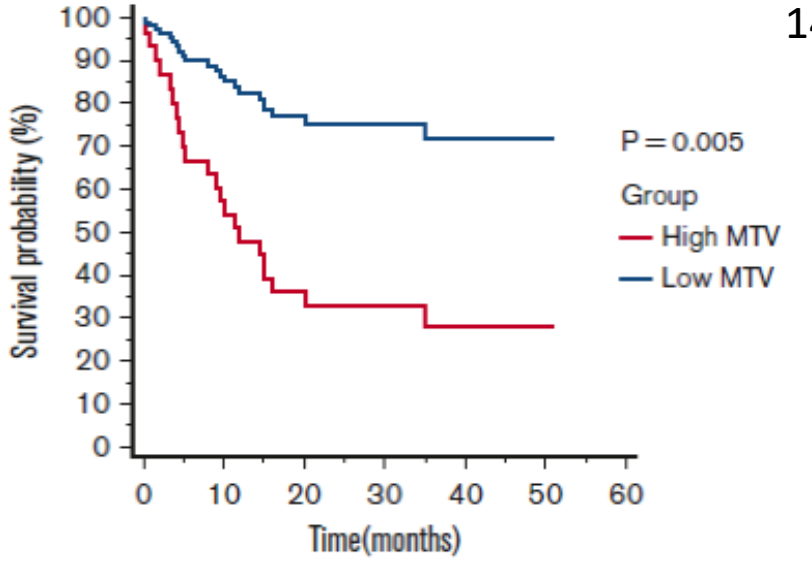
LBDGC : influence de la réponse à M1



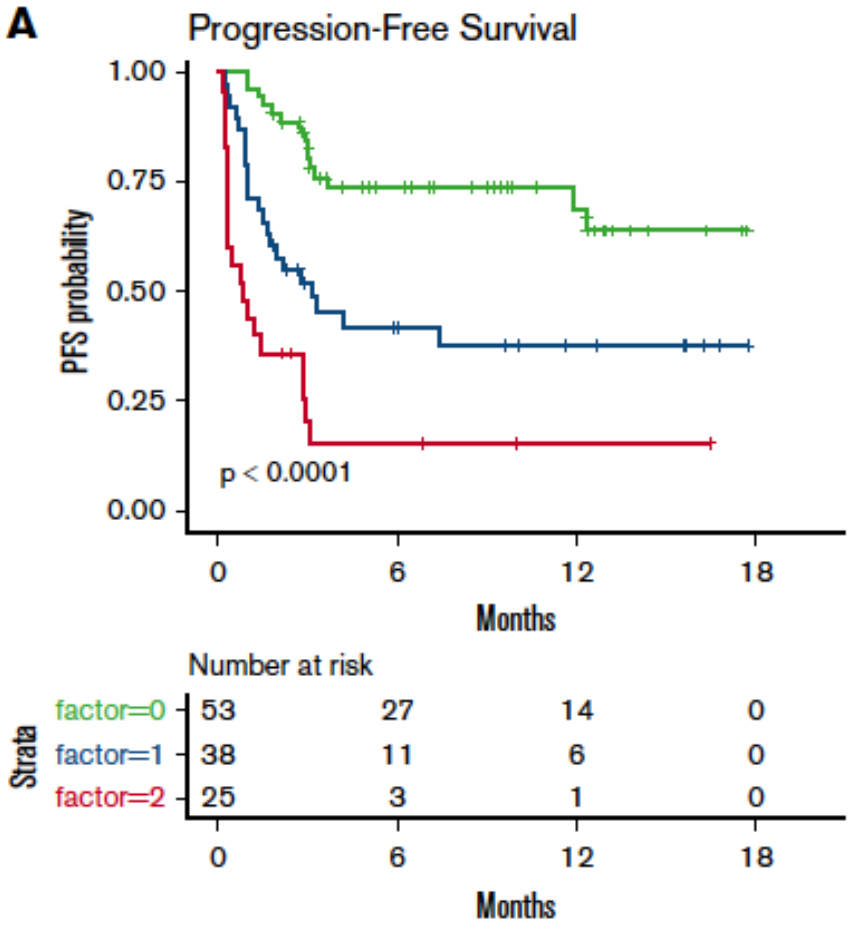
LBDGC : influence du TEP-scanner



147,5 mL



80 mL



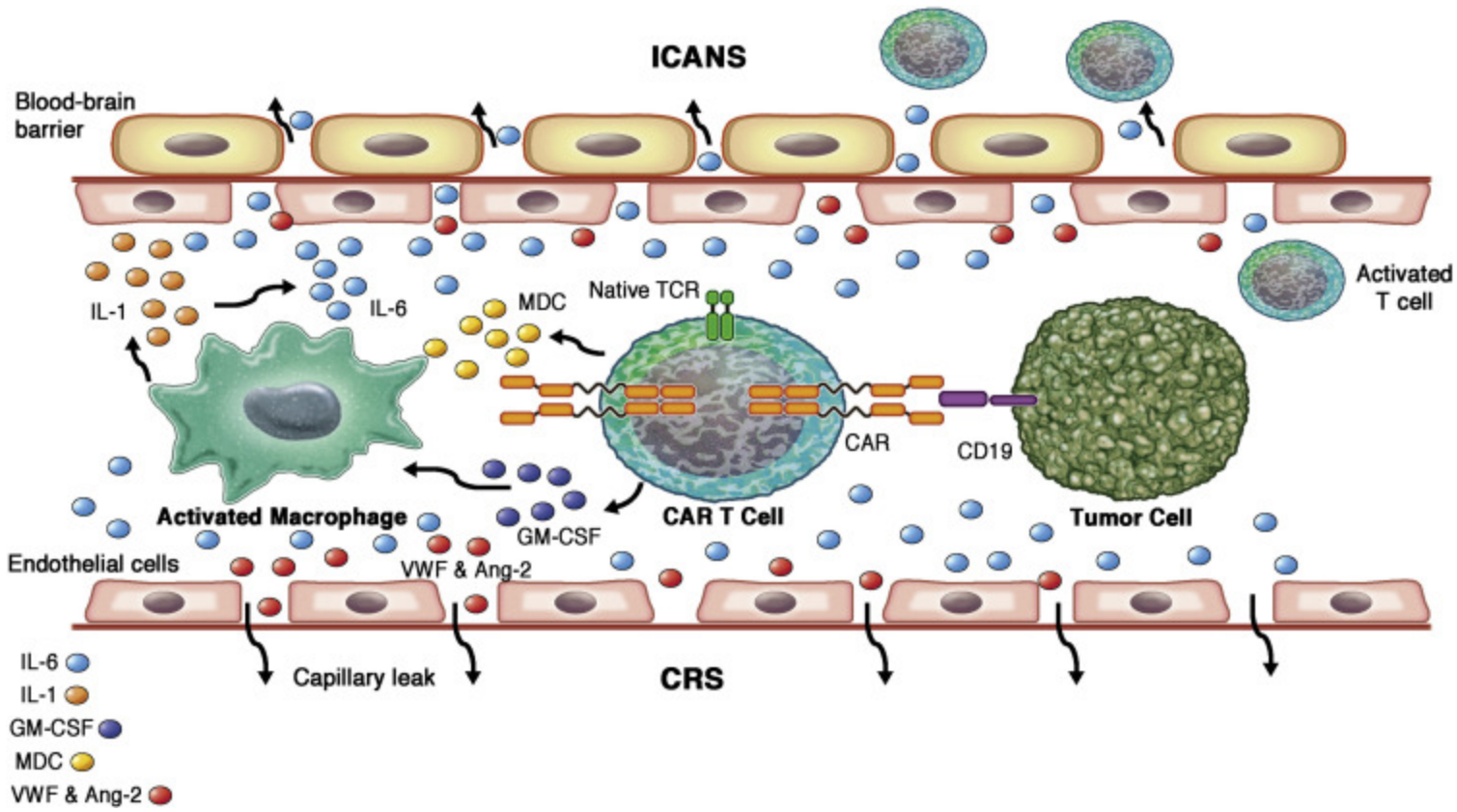
>=2 sites extra-ganglionnaires
TMTV > 80mL

Dean EA et al. *Blood Adv* 2020

Vercellino L *Blood Adv* 2020

Toxicité

Toxicité aiguë



Freyer CW et al. *J Allergy Clin Imm* 2020

Toxicité aiguë vraie vie (DESCAR-T)

EARLY CRS, NEUROTOXICITY AND INFECTIONS (Axicel; Yescarta®)

	Toxicities within 10d post CAR-T (data available in 322 pts)
CRS (all grades)	276 (85.7%)
grade 1-2	245
grade ≥ 3	30
missing	1
Neurotoxicity (all grades)	147 (45.7%)
grade 1-2	100
grade ≥ 3	47
missing	/
grade ≥ 3 opportunistic or medically significant infection	100 (31%)

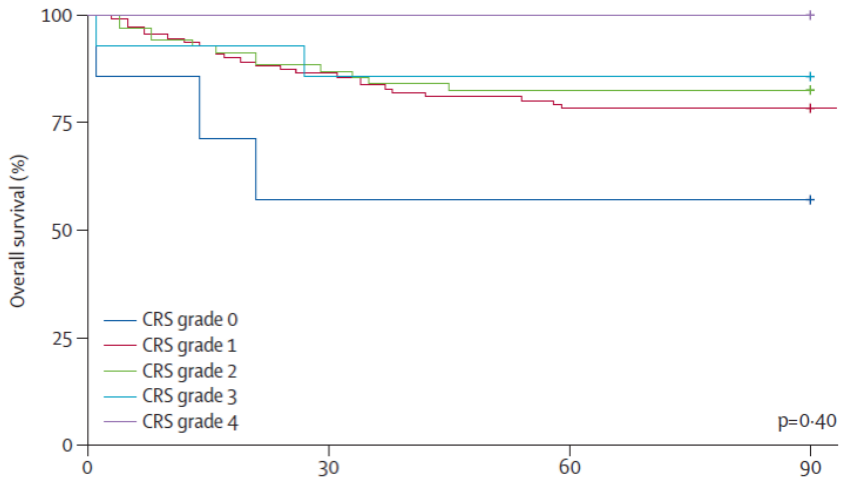
	Patients with at least one CAR-T specific toxicity within 10 days N=280
ICU hospitalization	102 (36.4%)
Treated for CAR-T specific tox	230 (82.1%)
Tocilizumab	194 (69.3%)
Siltuximab	12 (4.3%)
Corticosteroïds	135 (48.2%)

EARLY CRS, NEUROTOXICITY AND INFECTIONS (Tisacel; Kymriah®)

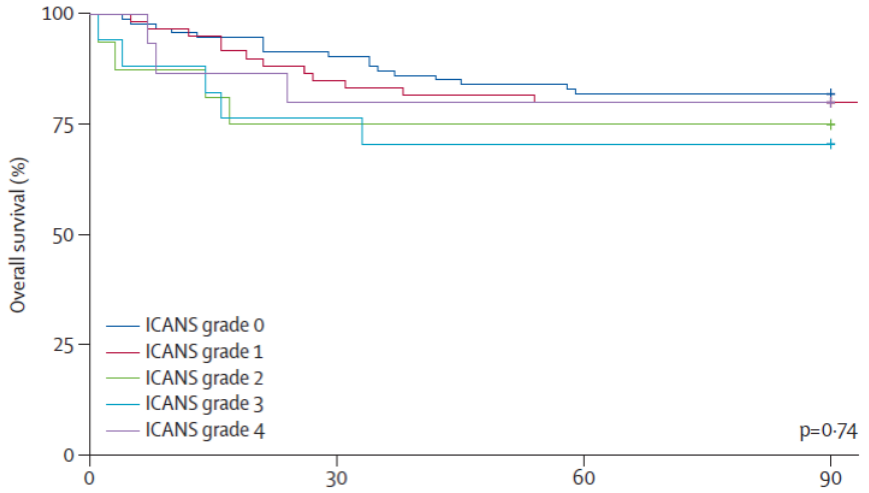
	Toxicities within 10d post CAR-T (data available in 193 pts)
CRS (all grades)	142 (73.6%)
grade 1-2	128
grade ≥ 3	14
missing	/
Neurotoxicity (all grades)	37 (19.2%)
grade 1-2	33
grade ≥ 3	3
missing	1
Grade ≥ 3 opportunistic or medically significant infection	63 (32.6%)

	Patients with at least one CAR-T specific toxicity within 10 days N=147
ICU hospitalization	37 (25.2%)
Treated for CAR-T specific tox	95 (64.6%)
Tocilizumab	84 (57.2%)
Siltuximab	1 (0.7%)
Corticosteroïds	41 (27.9%)

Toxicité aiguë vraie vie : réanimation



Number at risk				
CRS grade 0	7	4	4	4
CRS grade 1	111	96	87	87
CRS grade 2	69	60	57	57
CRS grade 3	14	12	12	12
CRS grade 4	1	1	1	1



Number at risk				
ICANS grade 0	94	85	77	77
ICANS grade 1	60	51	48	48
ICANS grade 2	16	12	12	12
ICANS grade 3	17	13	12	12
ICANS grade 4	15	12	12	12

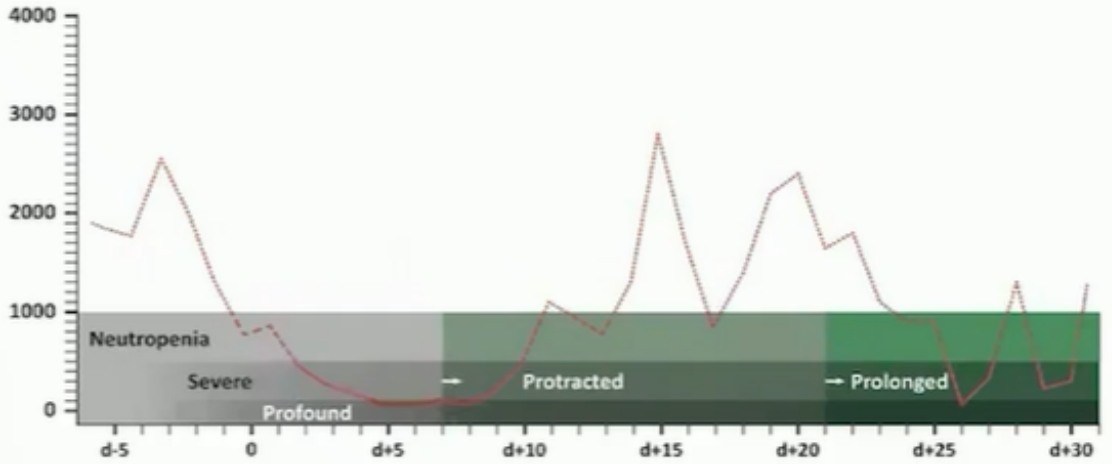
Azoulay E et a. *Lancet Haematol* 2021

Toxicité au long cours

Real-Life = High incidence of hematotoxicity

LMU KLINIKUM

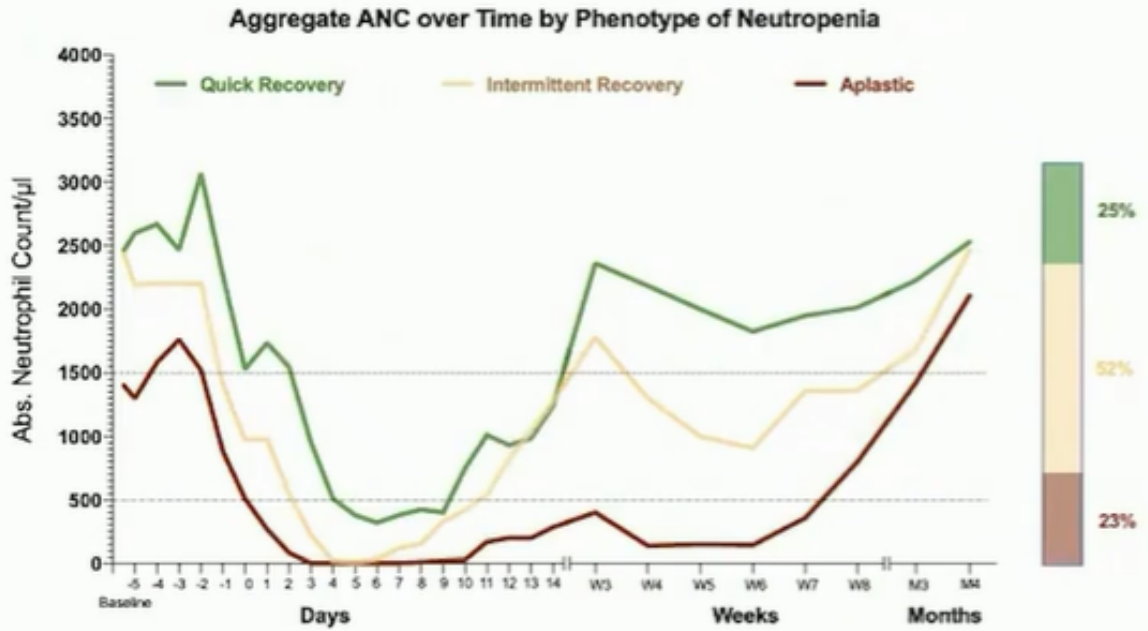
Clinical features: CAR T-cell mediated hematotoxicity	Pooled (n = 235)
Severe Thrombocytopenia (PLT Count < 50 G/l)	145 (62%)
Anemia (Hb <8 g/dl or requiring transfusion)	162 (69%)
Neutropenia	
Severe (ANC ≤ 500/µl)	213 (91%)
Profound (ANC ≤ 100/µl)	169 (72%)
Protracted, severe (ANC ≤ 500/µl, ≥ 7 days)	160 (68%)
Protracted, profound (ANC ≤ 100/µl, ≥ 7 days)	60 (26%)
Prolonged (ANC ≤ 1000/µl measured ≥ 21 days after CAR transfusion)	151 (64%)



Neutropenia	ANC < 1000/µl
Severe	ANC < 500/µl
Profound	ANC < 100/µl
Protracted	Neutropenia ≥ 7 days
Prolonged	ANC < 1000/µl measured ≥ 21 days after CAR infusion

Rejeski K et al. *Blood* 2021

Defining clinical phenotypes of neutrophil recovery



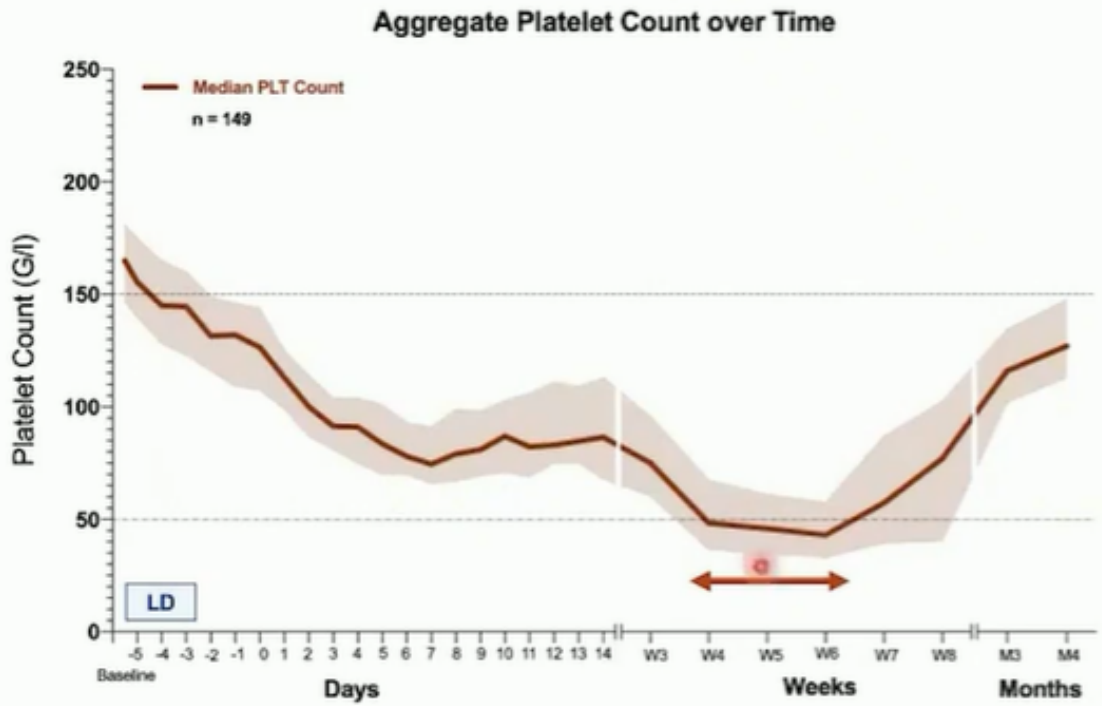
→ Dominant phenotype characterized by **2nd dip**

1. **"Quick Recovery"** = sustained neutrophil recovery without a second dip below an ANC < 1000/µl (n = 37)
2. **"Intermittent Recovery"** = neutrophil recovery (ANC > 1500/µl) followed by a second dip with an ANC < 1000/µl after day 21 (n = 78)
3. **"Aplastic"** = continuous severe neutropenia (ANC < 500/µl) ≥ 14 days (n = 34)

Training Cohort + European Validation Cohort (n = 149)

Rejeski et al, Blood 2021, in press

The thrombocytopenic nadir is delayed until after day 21 and independent of lymphodepletion in many patients

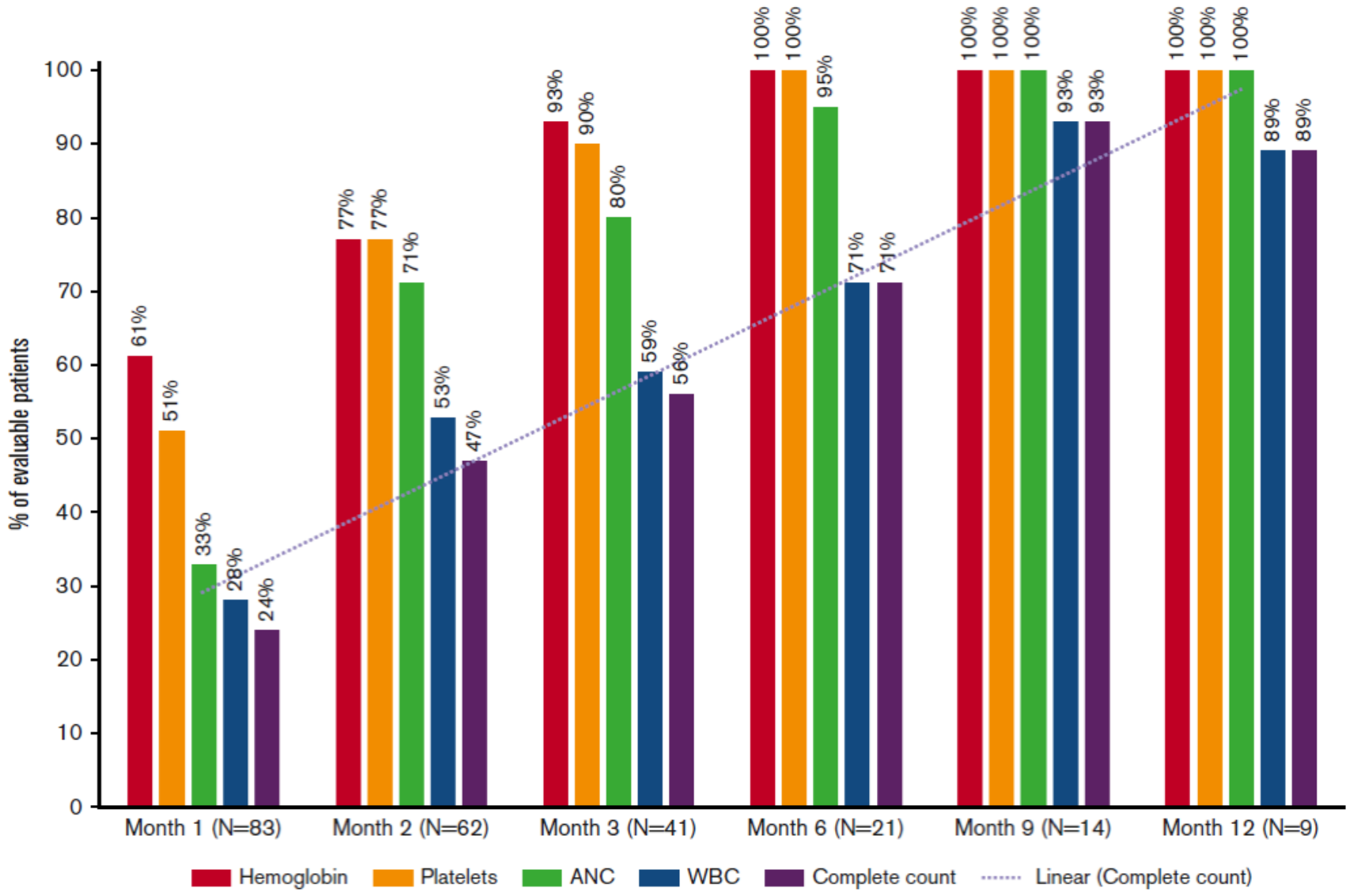


- Thrombocytopenic nadir: Day 21 - 60
- Delayed thrombocytopenia long after lymphodepletion and resolution of acute CRS → independent mechanism?
- Platelet count recovery by day 90 is achieved by most patients

Training Cohort + European Validation Cohort (n = 149)

Rejeski et al, Blood 2021, in press

Toxicité au long cours : récupération



Jain T et al. *Blood Adv* 2020

Nouvelles indications

LNH à cellules du manteau (LCM)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

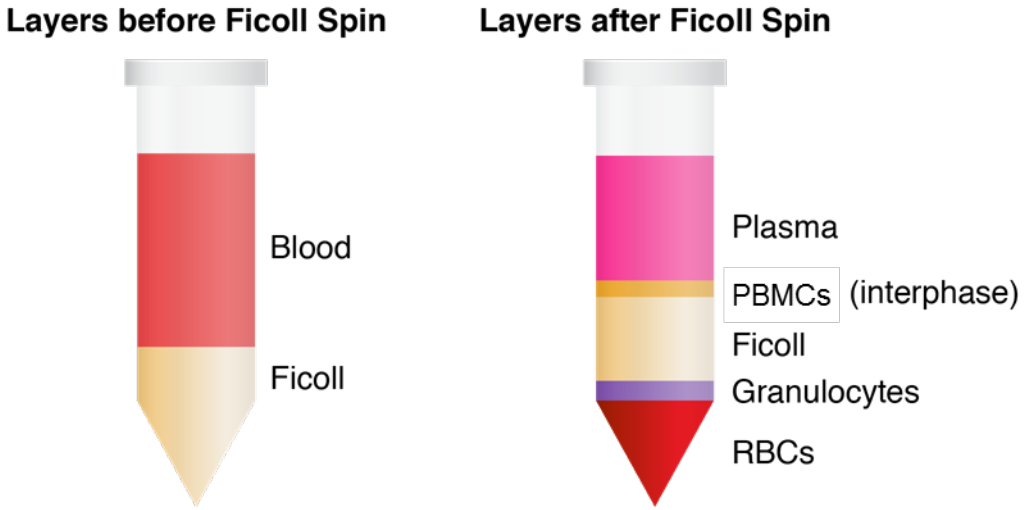
M. Wang, J. Munoz, A. Goy, F.L. Locke, C.A. Jacobson, B.T. Hill, J.M. Timmerman, H. Holmes, S. Jaglowski, I.W. Flinn, P.A. McSweeney, D.B. Miklos, J.M. Pagel, M.-J. Kersten, N. Milpied, H. Fung, M.S. Topp, R. Houot, A. Beitinjaneh, W. Peng, L. Zheng, J.M. Rossi, R.K. Jain, A.V. Rao, and P.M. Reagan

N Engl J Med 2020;382:1331-42.

Apheresis Collection → **Lymphocyte Enrichment/T Cell Activation** → Retroviral Transduction → T Cell Expansion → Formulation & Cryopreservation → Patient Infusion

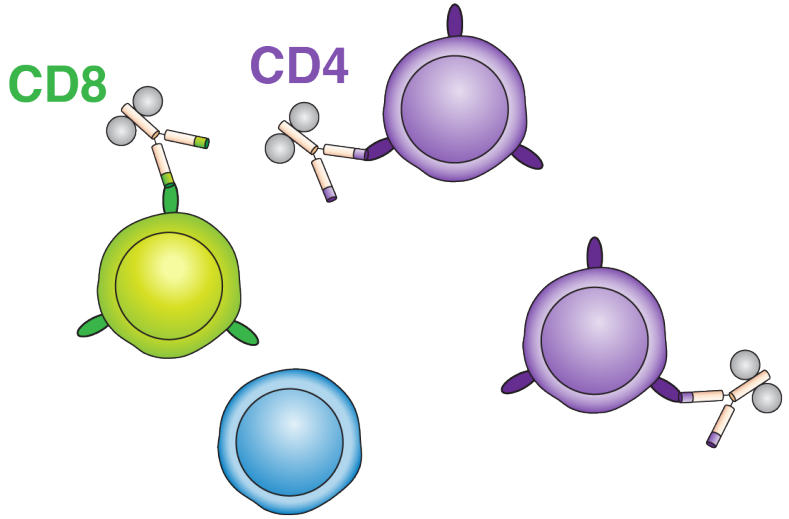
CLP Process

The T cell containing peripheral blood mononuclear cells (PBMC) fraction is enriched for mononuclear cells using Ficoll-based separation in a closed automated system[1]

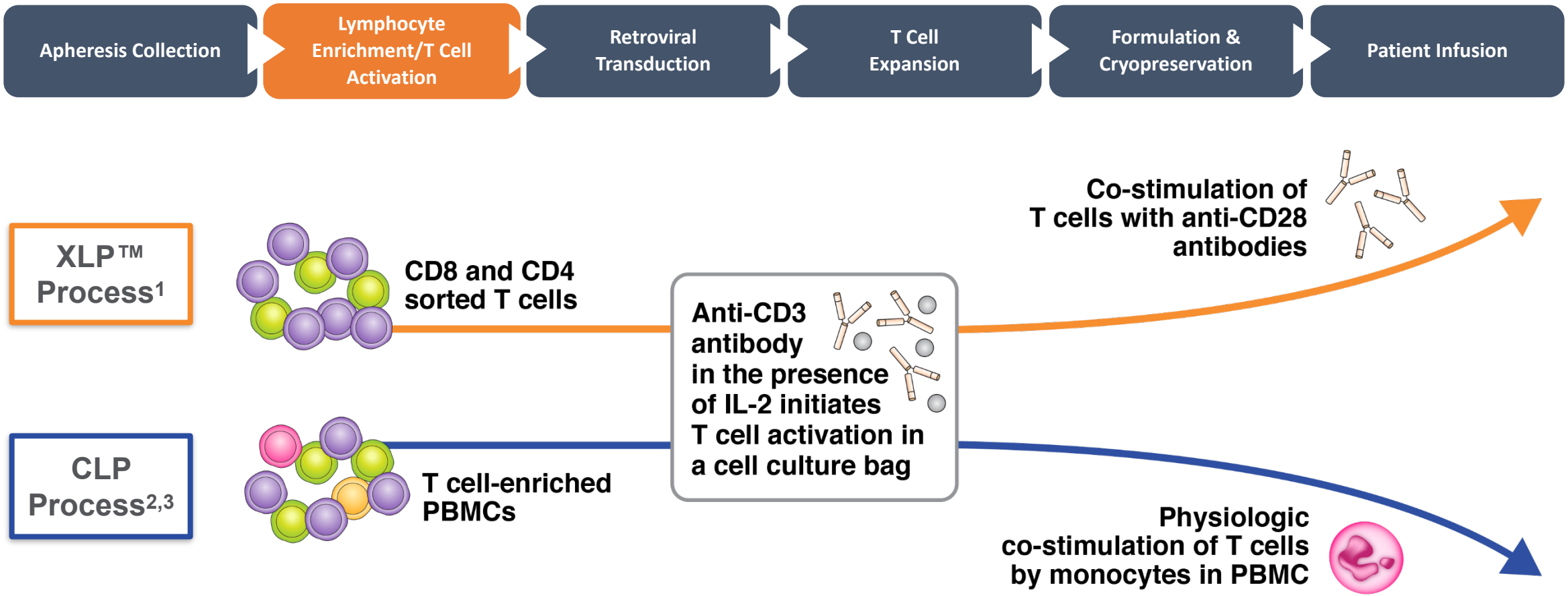


XLP™ Process

Enrichment of T cells by positive selection for CD4 and CD8 positive cells to remove blast and tumor cells[2,3]

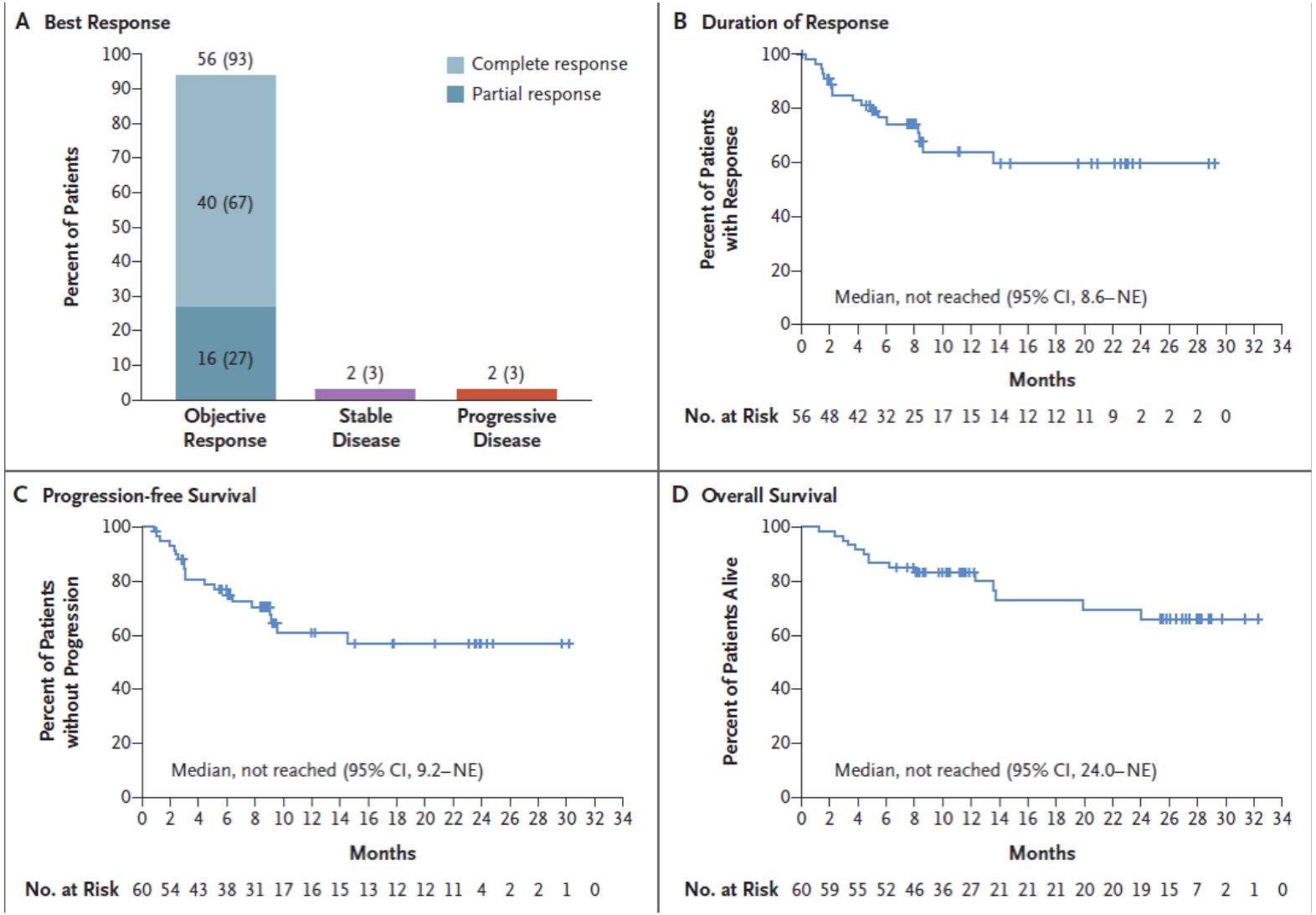


1. Better et al. AACR 2016. 2. Wang M et al. *N Engl J Med*. 2020;382:1331-1342. 3. Data on file.
RBC, red blood cell.



1. Data on File. 2. Better et al. AACR 2016. 3. Better et al. *CellWorld* 2017.
IL, interleukin; PBMC, peripheral blood mononuclear cell.

CAR-T et LCM



Wang M et al. *NEJM* 2020

LAL de l’adulte

blood®

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

KTE-X19 anti-CD19 CAR T-cell therapy in adult relapsed/refractory acute lymphoblastic leukemia: ZUMA-3 phase 1 results

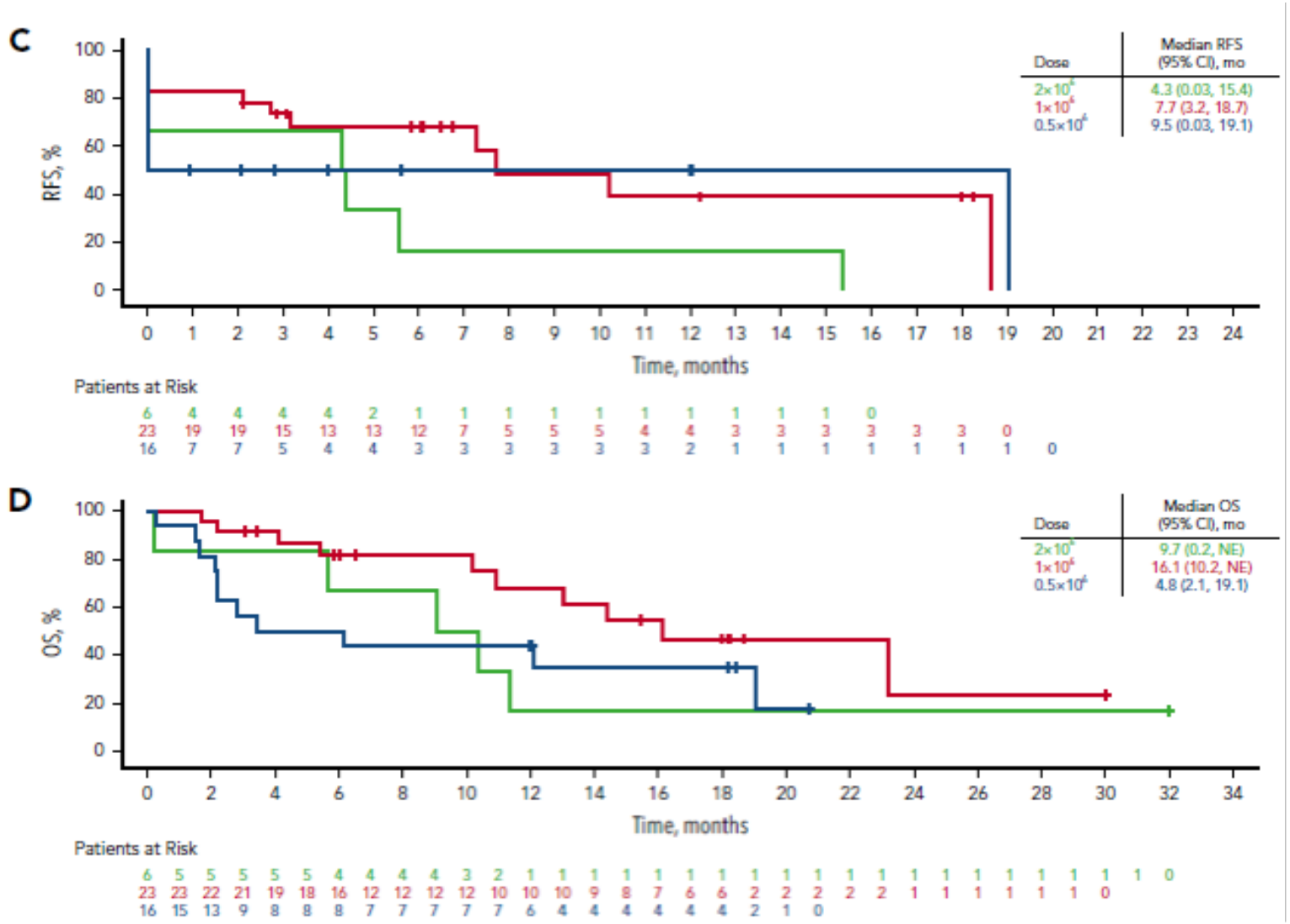
Bijal D. Shah,[1] Michael R. Bishop,[2] Olalekan O. Oluwole,[3] Aaron C. Logan,[4] Maria R. Baer,[5] William B. Donnellan,[6] Kristen M. O'Dwyer,[7] Houston Holmes,[8] Martha L. Arellano,[9] Armin Ghobadi,[10] John M. Pagel,[11] Yi Lin,[12] Ryan D. Cassaday,[13] Jae H. Park,[14] Mehrdad Abedi,[15] Januario E. Castro,[16] Daniel J. DeAngelo,[17] Adriana K. Malone,[18] Raya Mawad,[19] Gary J. Schiller,[20] John M. Rossi,[21] Adrian Bot,[21] Tong Shen,[21] Lovely Goyal,[21] Rajul K. Jain,[21] Remus Vezan,[21] and William G. Wierda[22]

blood® 8 JULY 2021 | VOLUME 138, NUMBER 1

Down

ǂ cette indication n'a pas l'AMM à ce jour

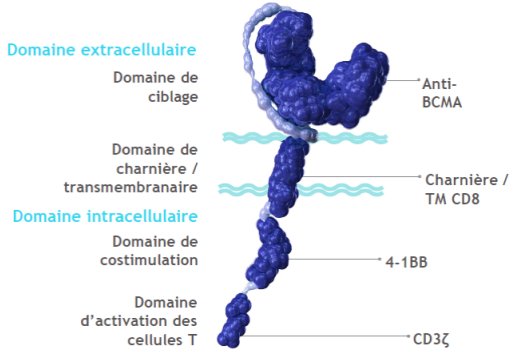
CAR-T et LAL de l'adulte



Shah BD et al. *Blood* 2021

ǂ cette indication n'a pas l'AMM à ce jour

Myélome



ORIGINAL ARTICLE

Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma

Noopur Raje, M.D., Jesus Berdeja, M.D., Yi Lin, M.D., Ph.D., David Siegel, M.D., Ph.D., Sundar Jagannath, M.D., Deepu Madduri, M.D., Michaela Liedtke, M.D., Jacalyn Rosenblatt, M.D., Marcela V. Maus, M.D., Ph.D., Ashley Turka, Lyh-Ping Lam, Pharm.D., Richard A. Morgan, Ph.D., Kevin Friedman, Ph.D., Monica Massaro, M.P.H., Julie Wang, Pharm.D., Ph.D., Greg Russotti, Ph.D., Zhihong Yang, Ph.D., Timothy Campbell, M.D., Ph.D., Kristen Hege, M.D., Fabio Petrocca, M.D., M. Travis Quigley, M.S., Nikhil Munshi, M.D., and James N. Kochenderfer, M.D.

N Engl J Med 2019;380:1726-37.

The NEW ENGLAND JOURNAL of MEDICINE

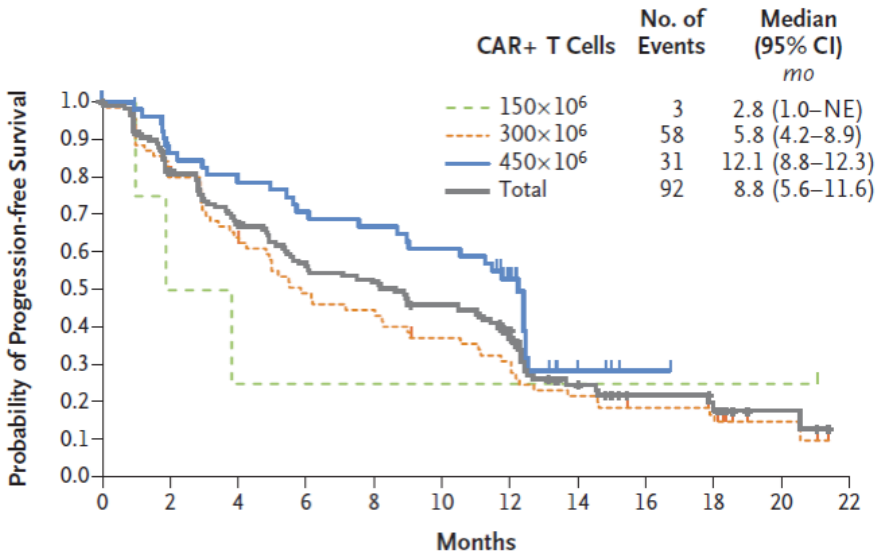
ORIGINAL ARTICLE

Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma

Nikhil C. Munshi, M.D., Larry D. Anderson, Jr., M.D., Ph.D., Nina Shah, M.D., Deepu Madduri, M.D., Jesús Berdeja, M.D., Sagar Lonial, M.D., Noopur Raje, M.D., Yi Lin, M.D., Ph.D., David Siegel, M.D., Ph.D., Albert Oriol, M.D., Philippe Moreau, M.D., Ibrahim Yakoub-Agha, M.D., Ph.D., Michel Delforge, M.D., Michele Cavo, M.D., Hermann Einsele, M.D., Hartmut Goldschmidt, M.D., Katja Weisel, M.D., Alessandro Rambaldi, M.D., Donna Reece, M.D., Fabio Petrocca, M.D., Monica Massaro, M.P.H., Jamie N. Connarn, Ph.D., Shari Kaiser, Ph.D., Payal Patel, Ph.D., Liping Huang, Ph.D., Timothy B. Campbell, M.D., Ph.D., Kristen Hege, M.D., and Jesús San-Miguel, M.D., Ph.D.

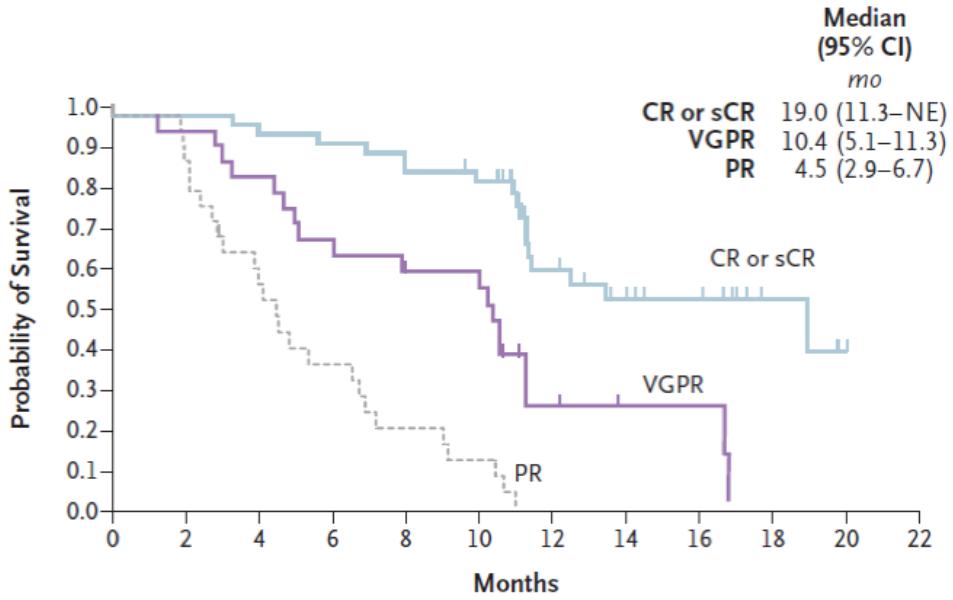
N Engl J Med 2021;384:705-16.

CAR-T et myélome



No. at Risk												
150×10⁶	4	2	1	1	1	1	1	1	1	1	1	0
300×10⁶	70	56	42	33	29	24	17	14	11	7	3	0
450×10⁶	54	44	40	36	34	31	17	4	1	0	0	
Total	128	102	83	70	64	56	35	19	13	8	4	0

Survie sans progression

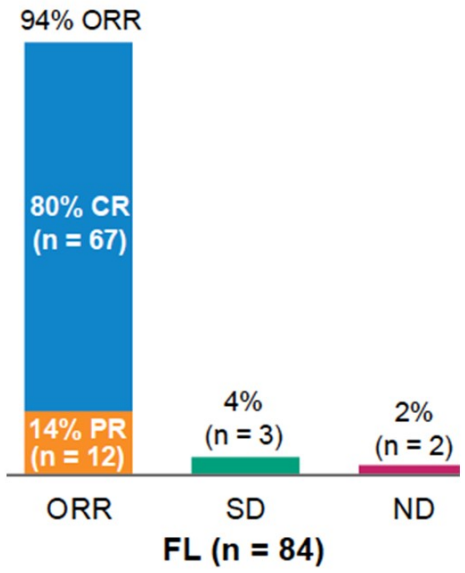


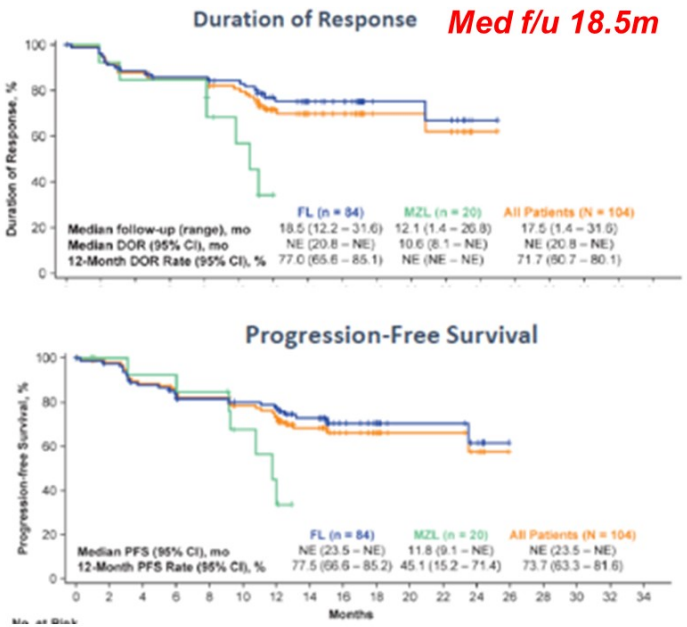
No. at Risk												
CR or sCR	42	42	40	39	36	34	18	13	10	4	1	0
VGPR	25	24	21	17	15	14	4	2	2	0	0	
PR	27	23	14	9	5	3	0	0	0	0	0	

Durée de réponse

Munshi NC et al. *NEJM* 2021

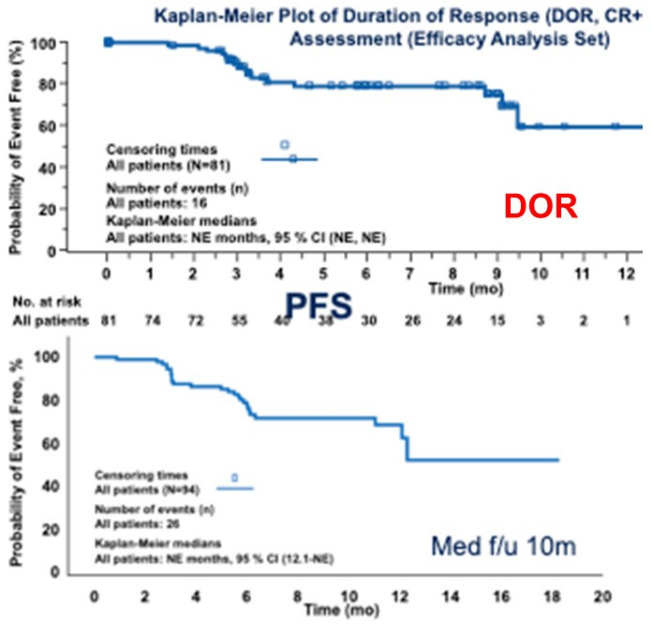
LNH Folliculaires





Response Rate, %	Patients Evaluable for Efficacy[b] (n=94)
CR	66.0[b]
PR	20.2
ORR (CR+PR)	86.2

Primary endpoint: CR

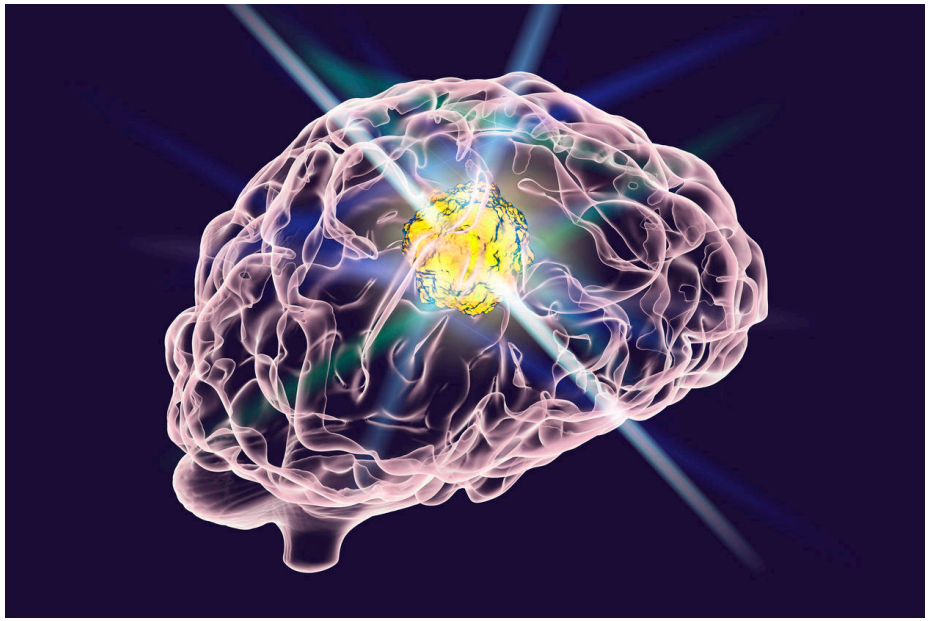


Axi-cel – ASCO 2021

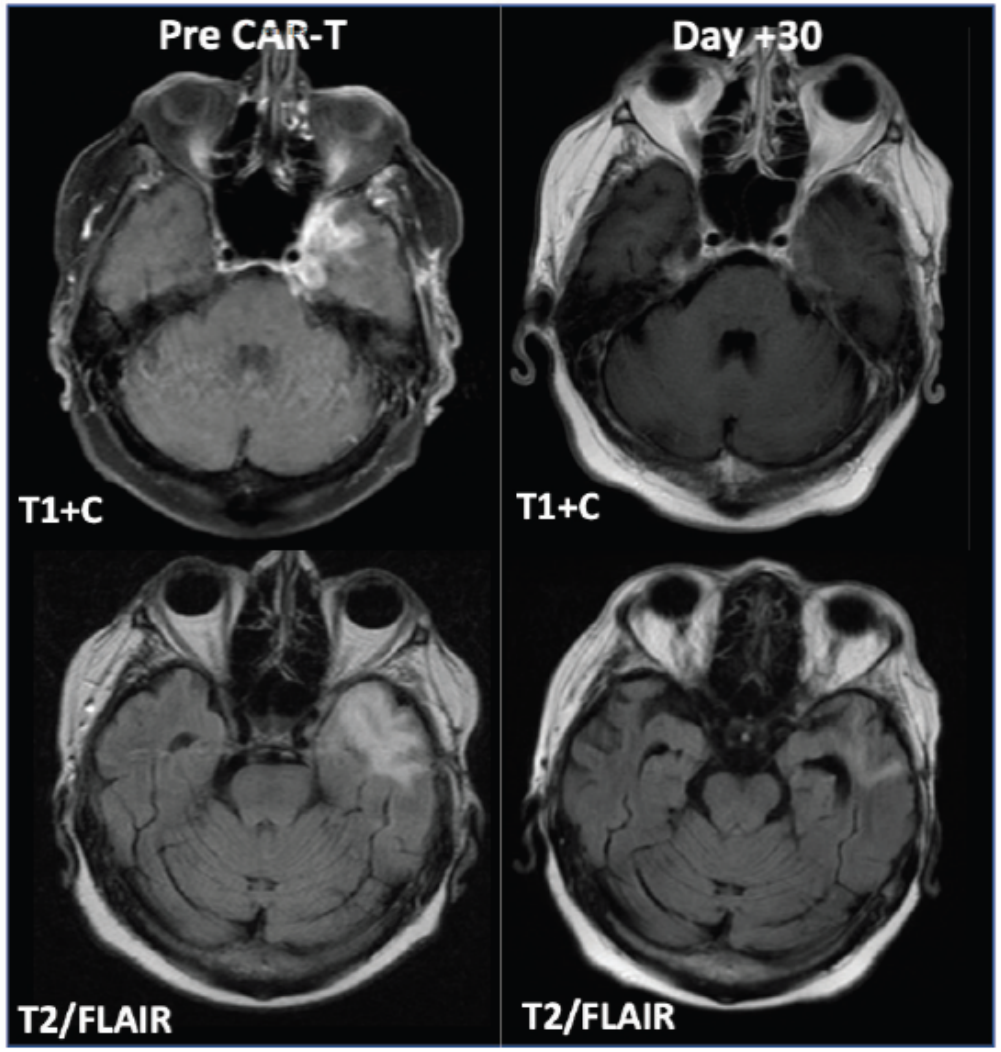
Tisa-cel – ASCO 2021

ǂ cette indication n'a pas l'AMM à ce jour

SNC

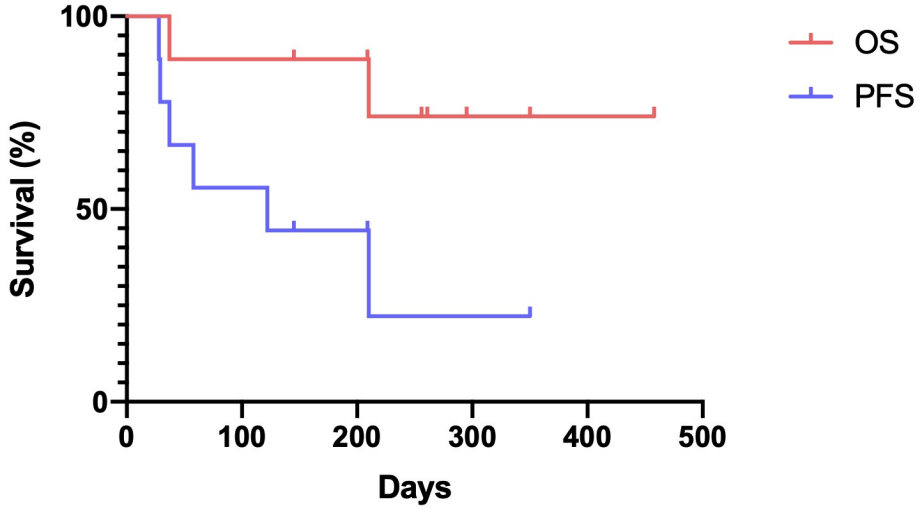


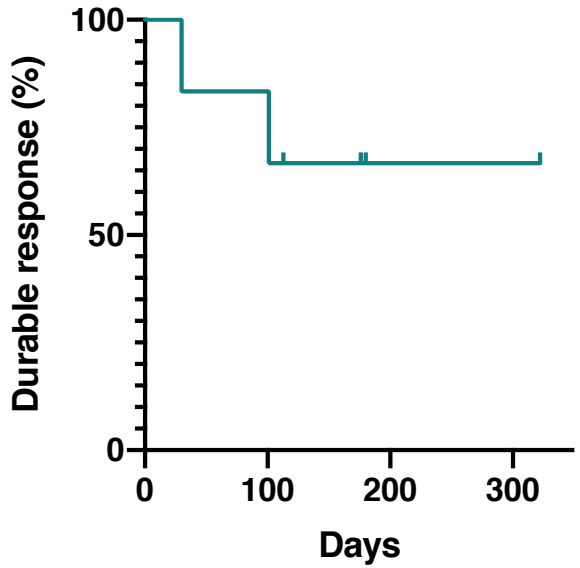
LNH SNC secondaires

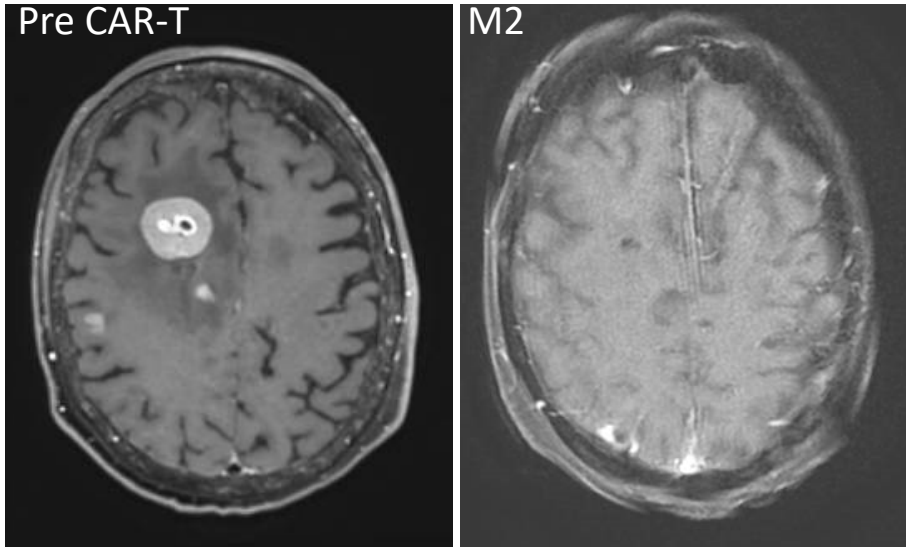


4 RC / 8 à J30

Frigault MJ *Blood* 2019



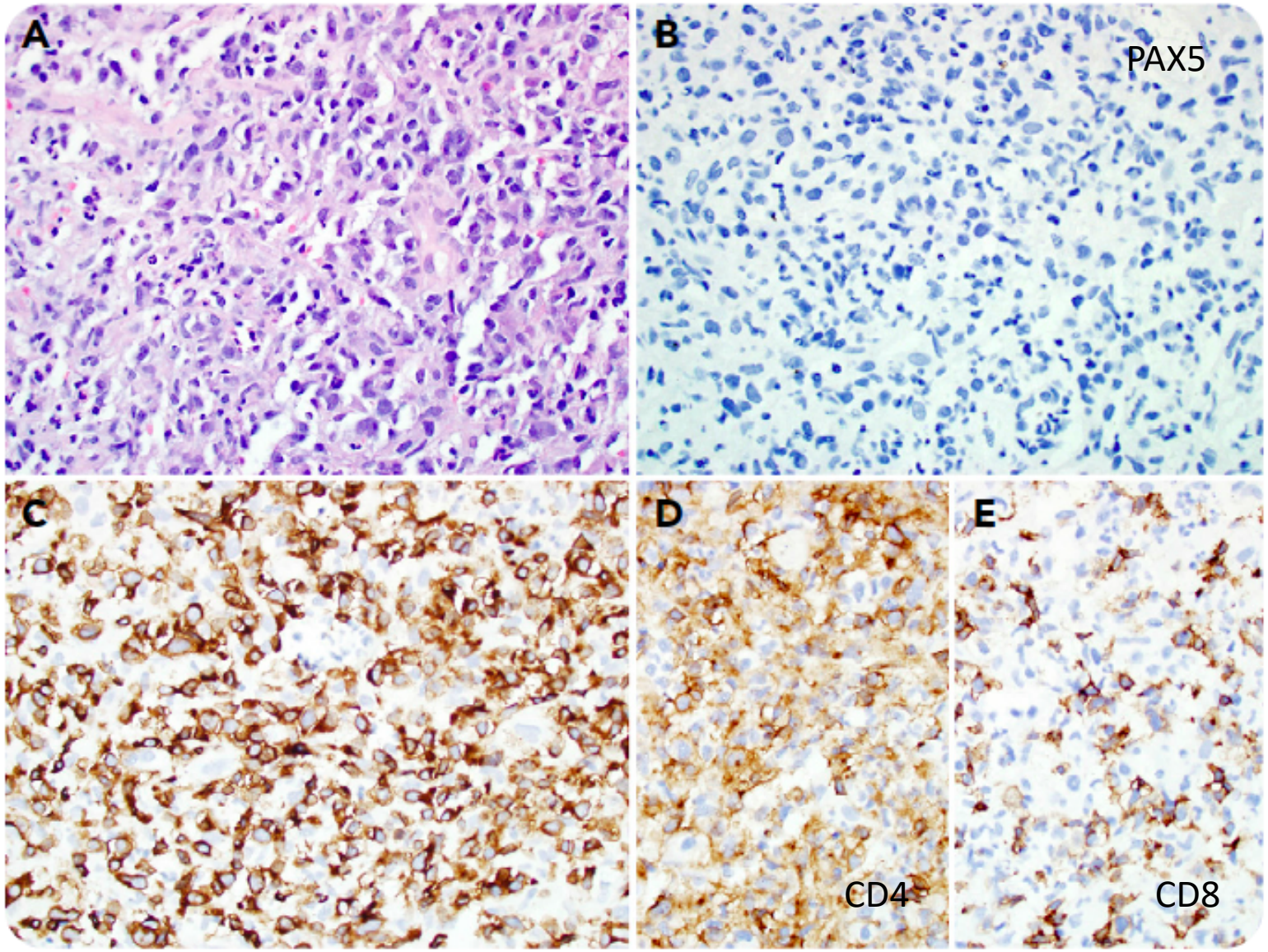




RC à 3 mois : 56%

Alcantara M et al. *Blood* 2021

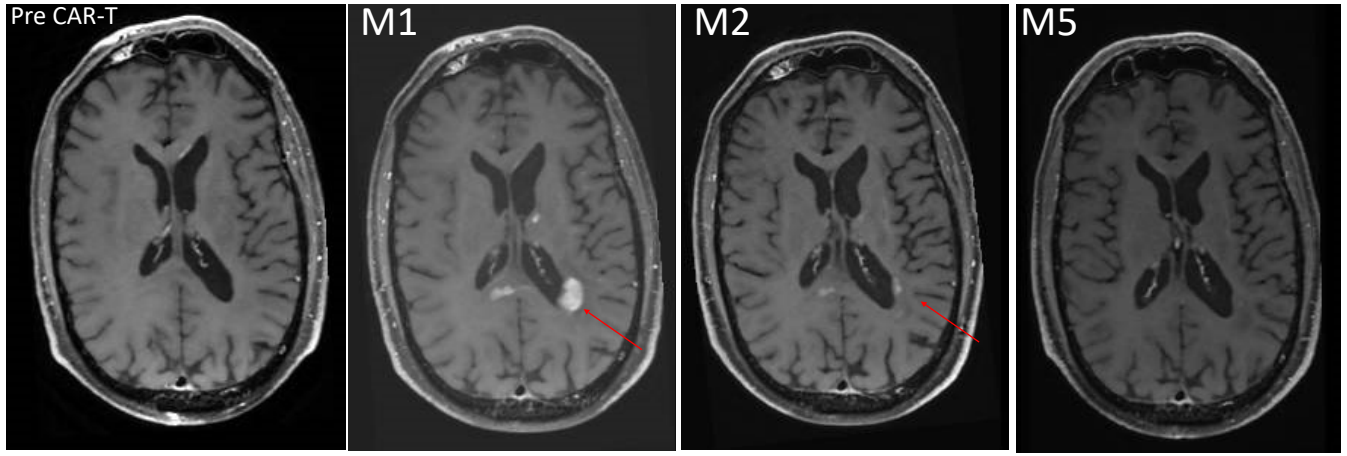
Effet « flare »



CD3

Song *Blood* 2019

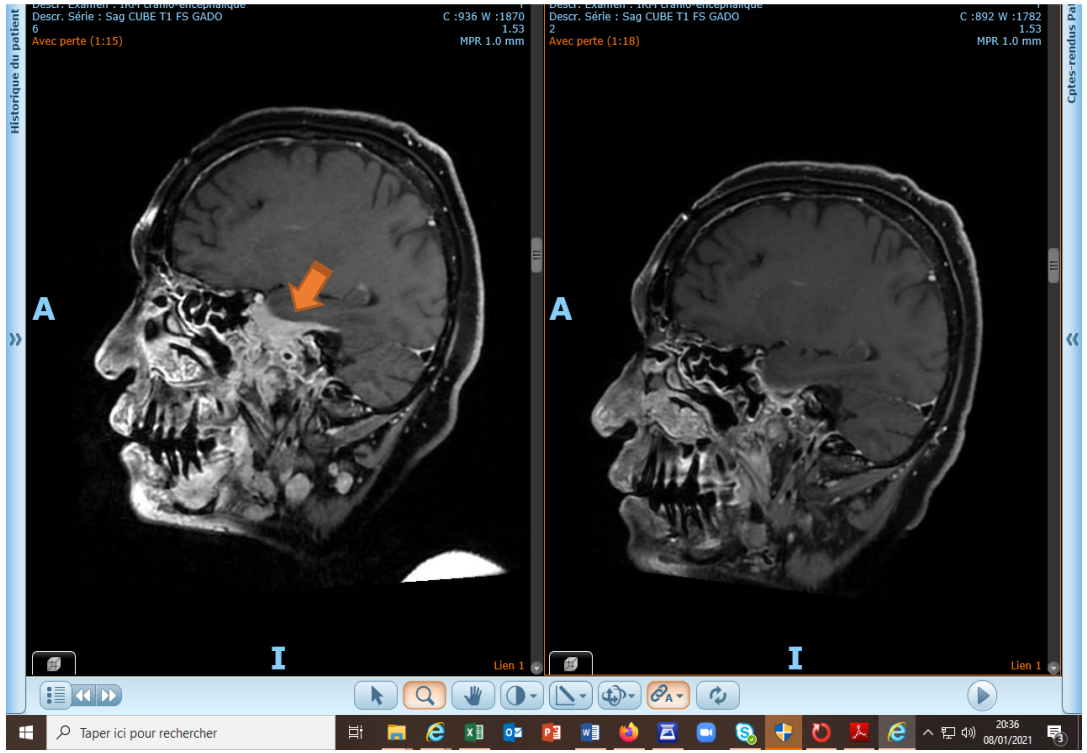
SNC : effet flare



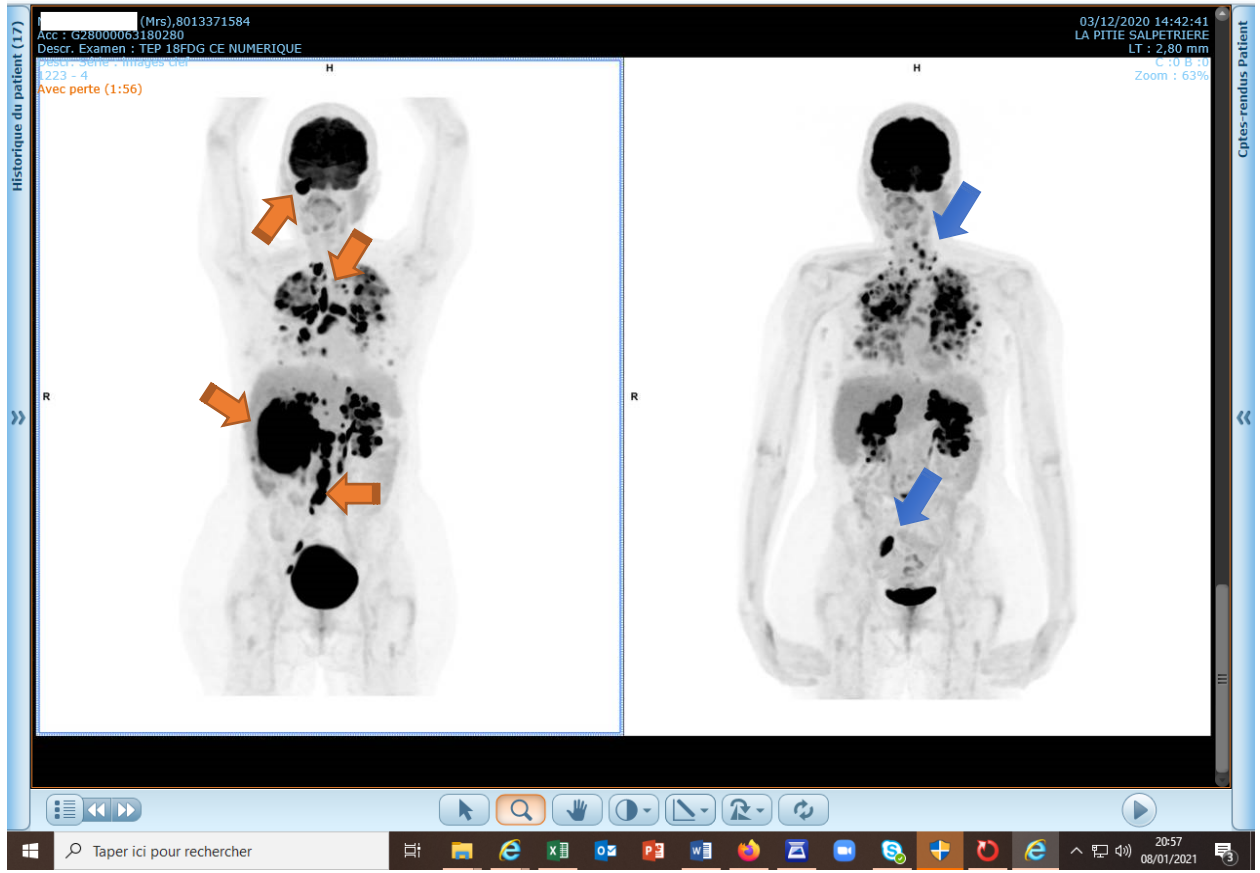
Alcantara M et al. *Blood* 2021

SNC / Systémique

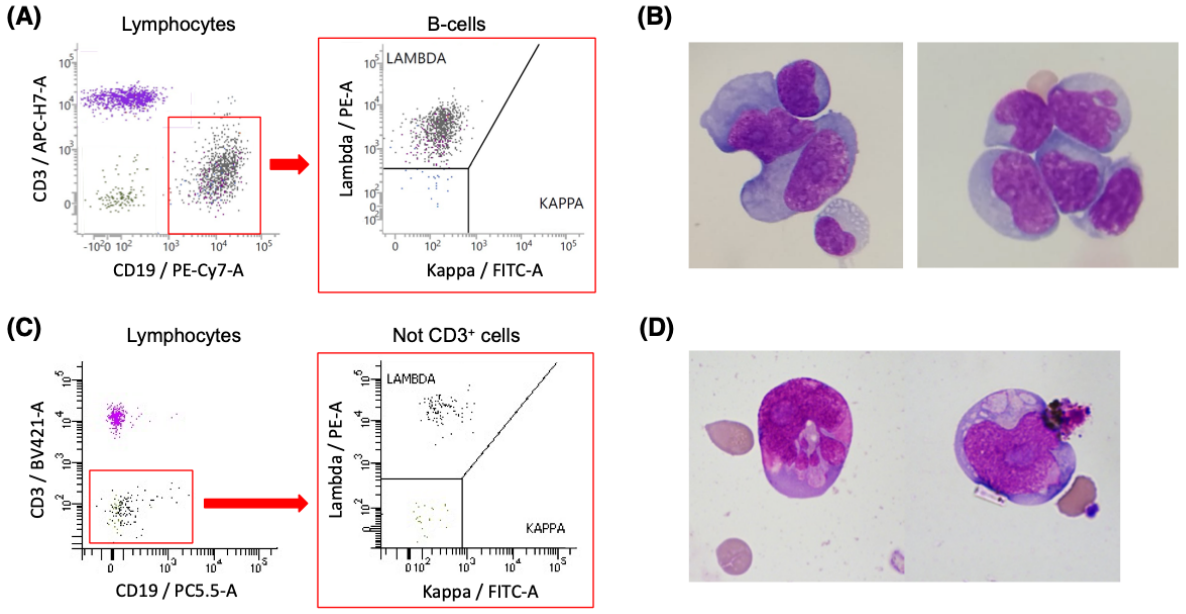
PS 4 → PS 1/2



Évaluation M4



SNC - échappement




The Future

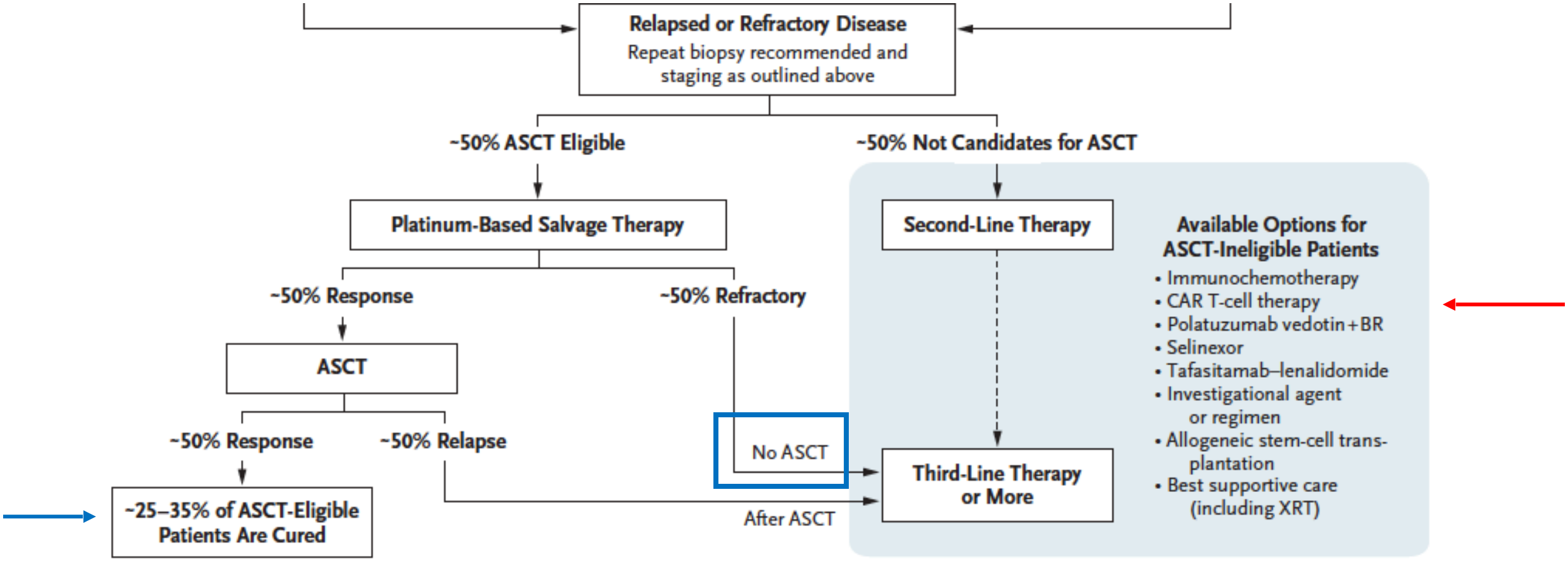
REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Diffuse Large B-Cell Lymphoma

Laurie H. Sehn, M.D., M.P.H., and Gilles Salles, M.D., Ph.D.

N Engl J Med 2021;384:842-58.



Future législation

Déclaration de l'établissement de santé prévue à l'article 2 de l'arrêté du 28 mars 2019 modifié par arrêté du 8 aout 2019 limitant l'utilisation de médicaments de thérapie innovante à base de lymphocytes T génétiquement modifiés dits CAR-T Cells autologues à certains établissements de santé

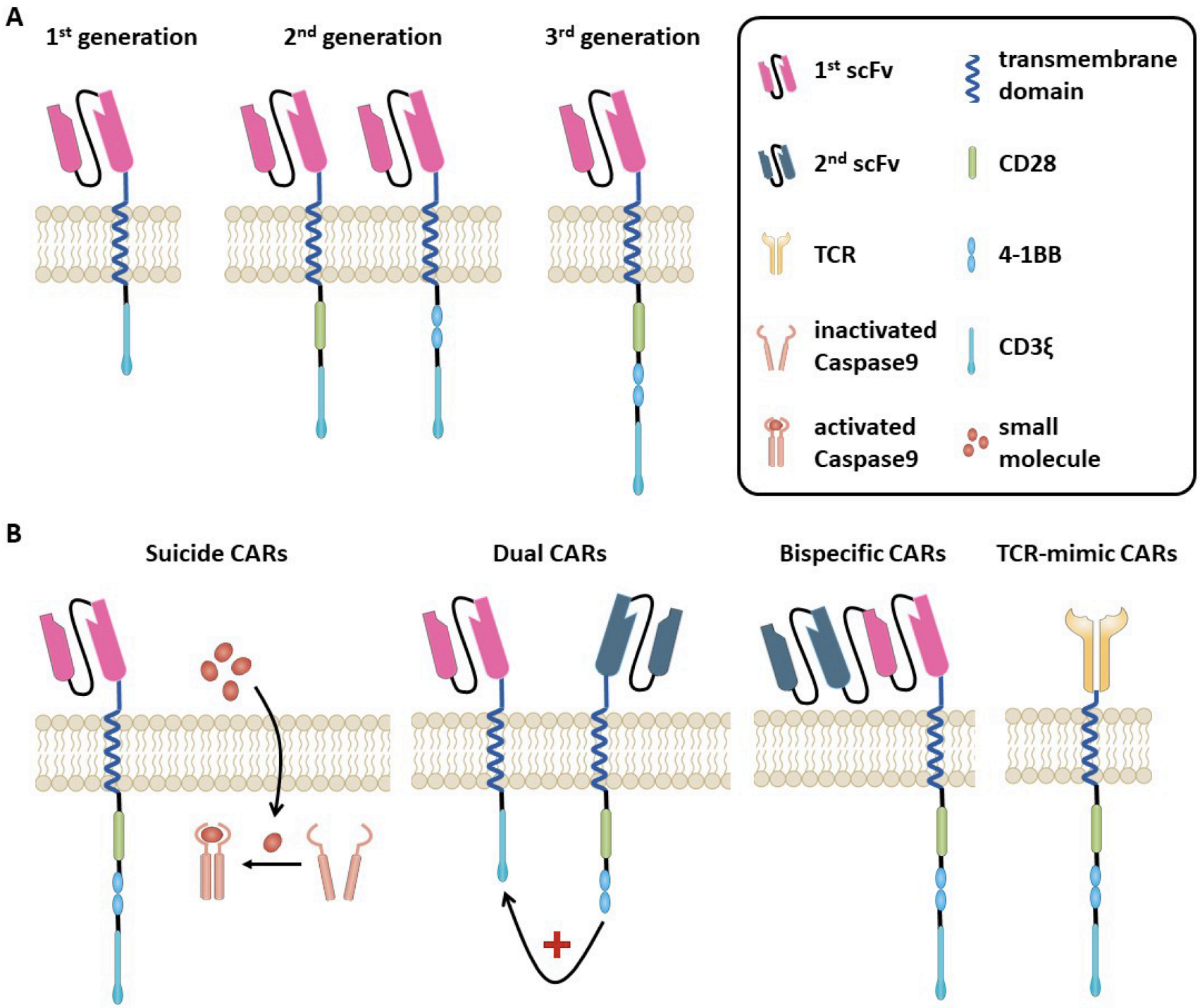
A adresser à : ars-idf-planif-autorisations@ars.sante.fr,
copie : daniele.simon@ars.sante.fr

Critères opposables à l'établissement de santé déclarant jusqu'au 31/12/2021 (voir arrêté pour le texte original)
1. dispose d'une autorisation à pratiquer les **allogreffes** de cellules souches hématopoïétiques (art. R. 6122-25 (8°) et R6123-75 du CSP)
2. dispose d'une **équipe pluridisciplinaire** pouvant organiser des réunions de concertation d'hémato-oncologie au sein de l'établissement de santé ayant pour but de confirmer l'éligibilité du patient au traitement par CAR-T Cells
3. dispose d'une Pharmacie à Usage Intérieur (PUI) autorisée à la reconstitution des médicaments de thérapie innovante ou exerçait déjà cette activité avant l'entrée en vigueur du décret du 21 mai 2019 (« décret PUI »)
Option 3a. la PUI assure la réception, la conservation et la reconstitution en vue de l'administration au patient ainsi que la dispensation des CAR-T Cells
Option 3b. La conservation et la reconstitution des CAR-T Cells est **organisée dans les conditions prévues à l'art. 5126-25 du CSP (donc par dérogation, dans une UTC)**

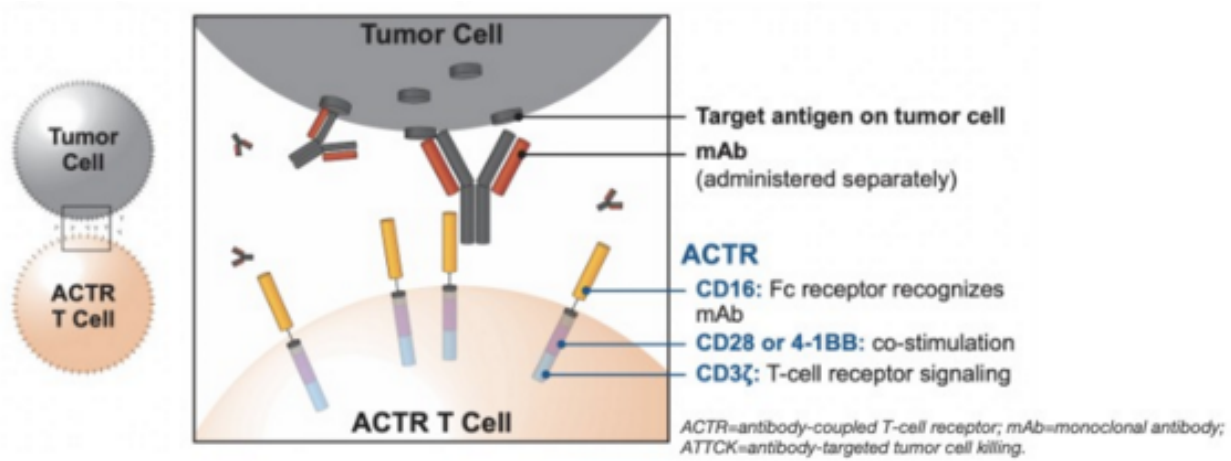
JACIE
Joint Accreditation Committee
ISCT | EBMT

AVANT

APRÈS


A
1st generation
2nd generation
3rd generation
1st scFv
transmembrane domain
2nd scFv
CD28
TCR
4-1BB
inactivated Caspase9
CD3ξ
activated Caspase9
small molecule
B
Suicide CARs
Dual CARs
Bispecific CARs
TCR-mimic CARs

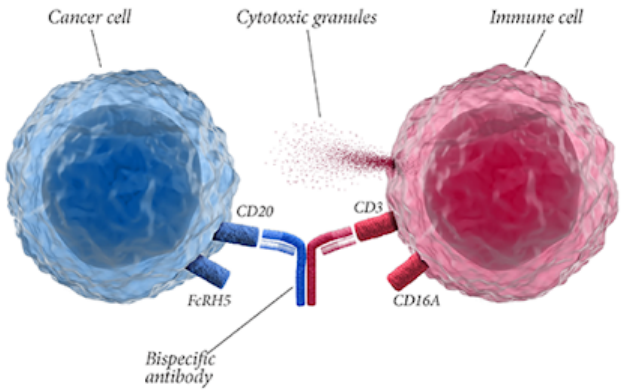
ACTR

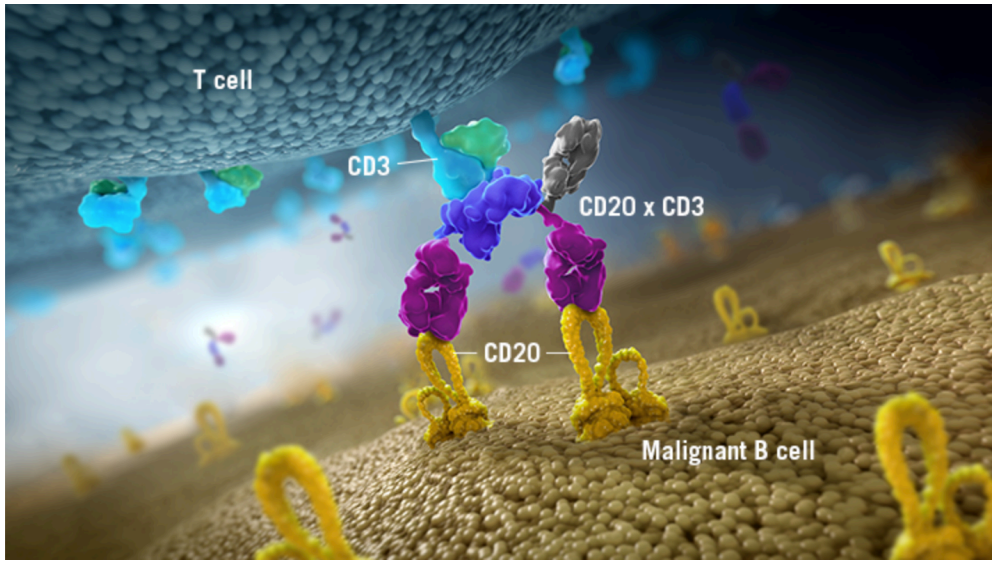


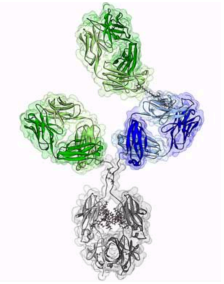
Autologue

« Engageurs » de lymphocytes T

Anticorps bispécifiques (engageurs de lymphocytes T)








C'EST FINI
MERCI DE VOTRE ATTENTION