Les thérapies innovantes dans la prise
en charge thérapeutique des lymphomes

Comment l'immunothérapie bouleverse le traitement des **Lymphomes B diffus à grandes cellules**

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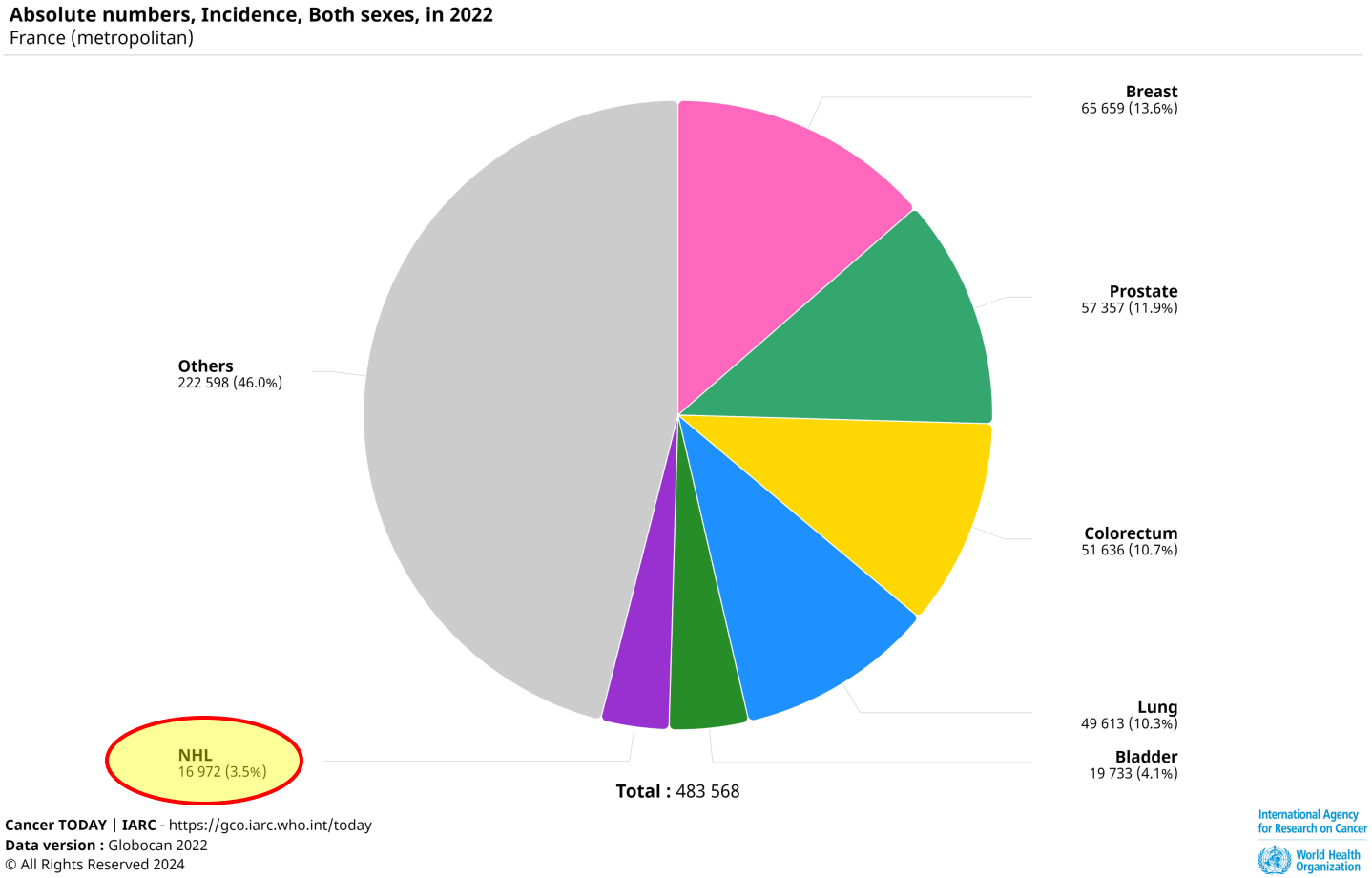
Colloque du CNCP 20 juin 2024

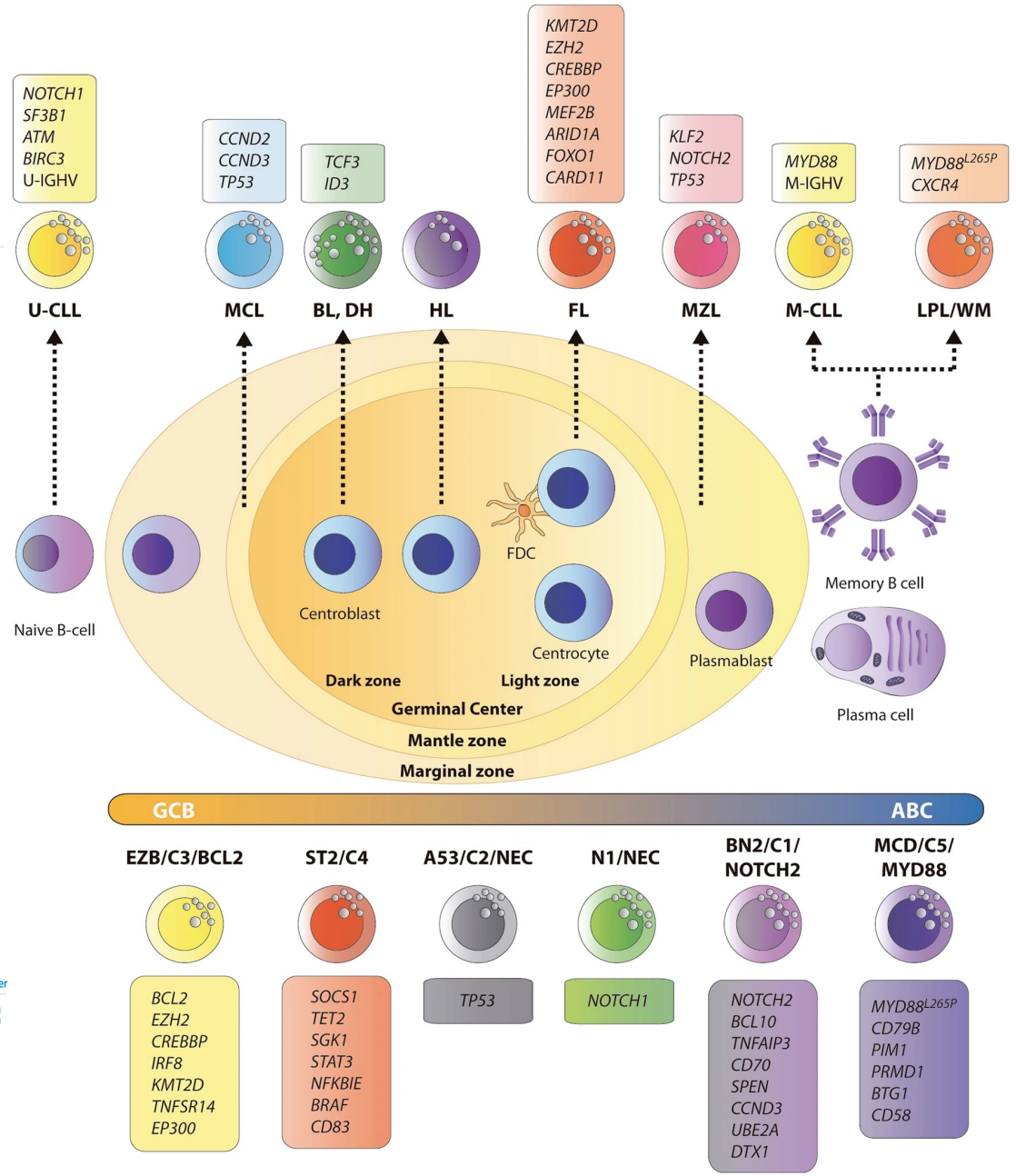
Liens d’intérêt

Dr Gabriel BRISOU	Board	Congress	Advsors / training
Incyte	x	x	x
Gilead	x	x	x
BMS	x	x	x
Novartis	x	x	x
Miltenyi Biomedicine			x

the opinions and thoughts expressed in this presentation reflect only the author's views

Les lymphomes qu'est-ce que c'est?

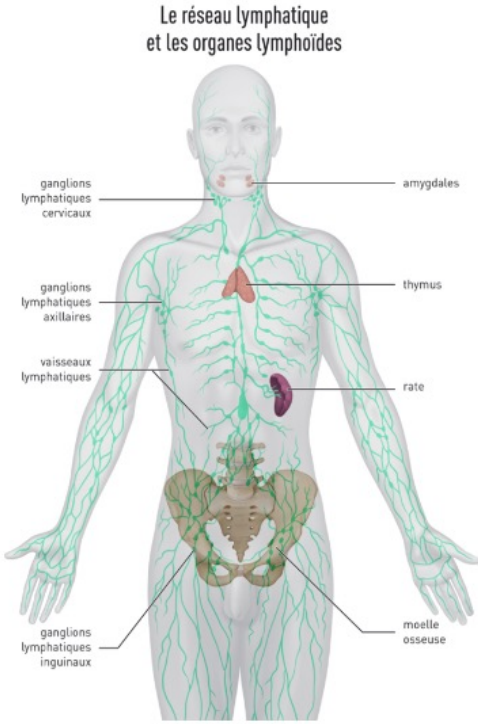


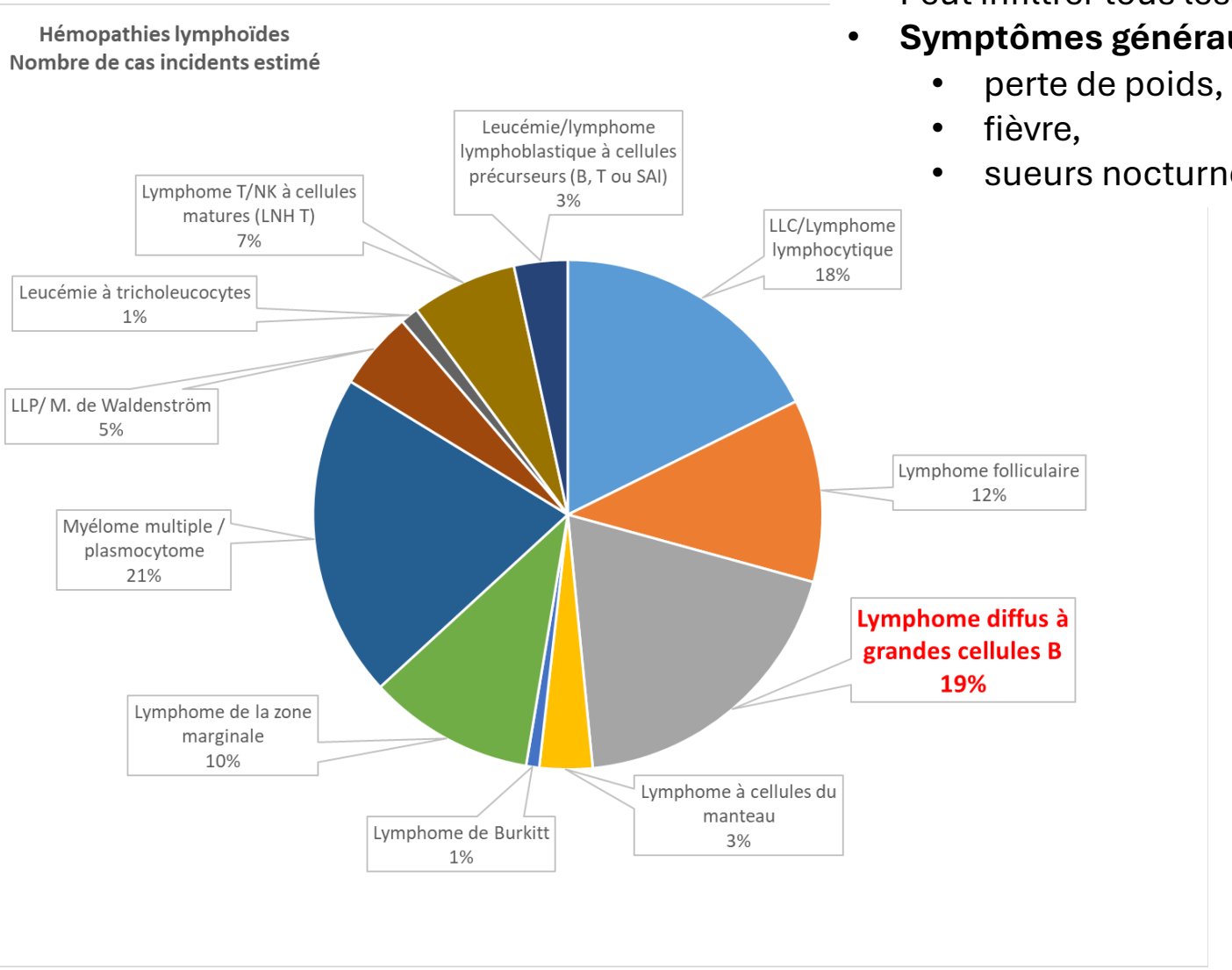


Sánchez-Beato, M. et al. A genetic profiling guideline to support diagnosis and clinical management of lymphomas. Clin Transl Oncol 26, 1043–1062 (2024).

Lymphome B diffus à grandes cellules

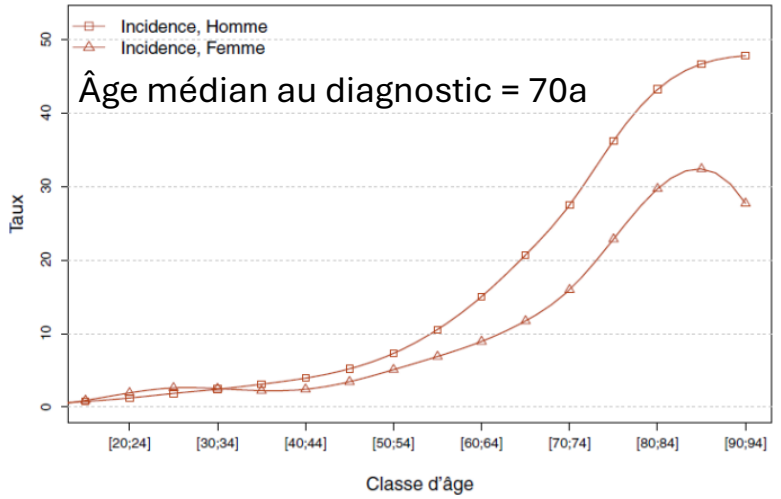
- **Lymphome agressif** = progression rapide
- Se développe majoritairement dans les **ganglions**
- Peut infiltrer tous les organes du corps humain
- **Symptômes généraux**:
  - perte de poids,
  - fièvre,
  - sueurs nocturnes profuses





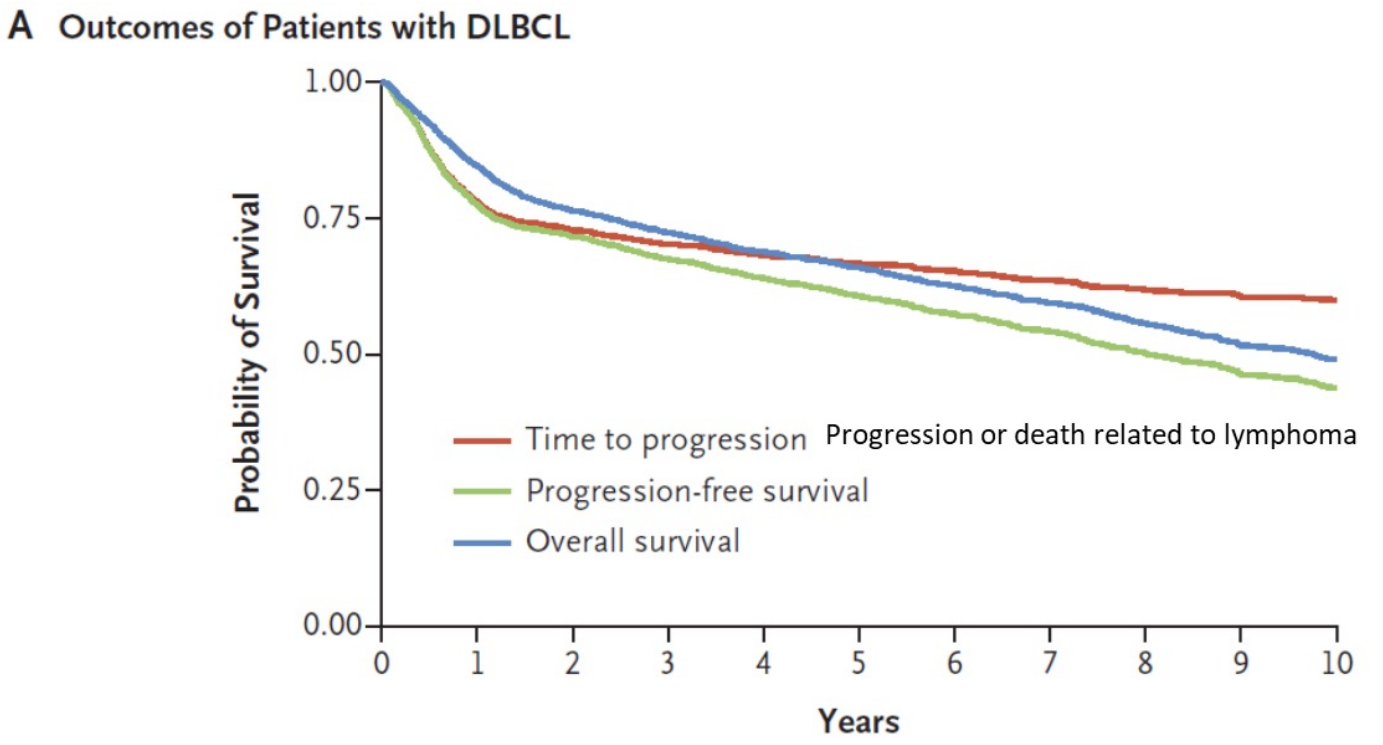
~5000 nouveau cas/an en France

Incidence des LBCLs selon l'âge



Le Guyader-Perou et al. Santé Public France 2019

R-CHOP = guérison pour 60% des patients



No. at Risk

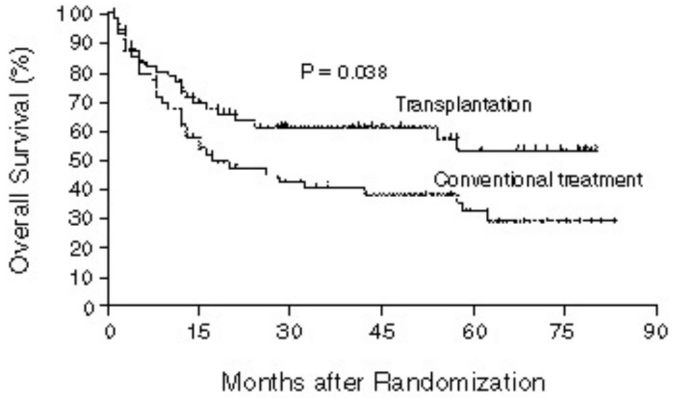
Time to progression	3082	2133	1775	1446	1236	1048	830	700	585	468	391
Progression-free survival	3082	2132	1774	1445	1235	1047	829	699	584	467	390
Overall survival	3082	2336	1900	1558	1338	1140	911	767	647	519	437

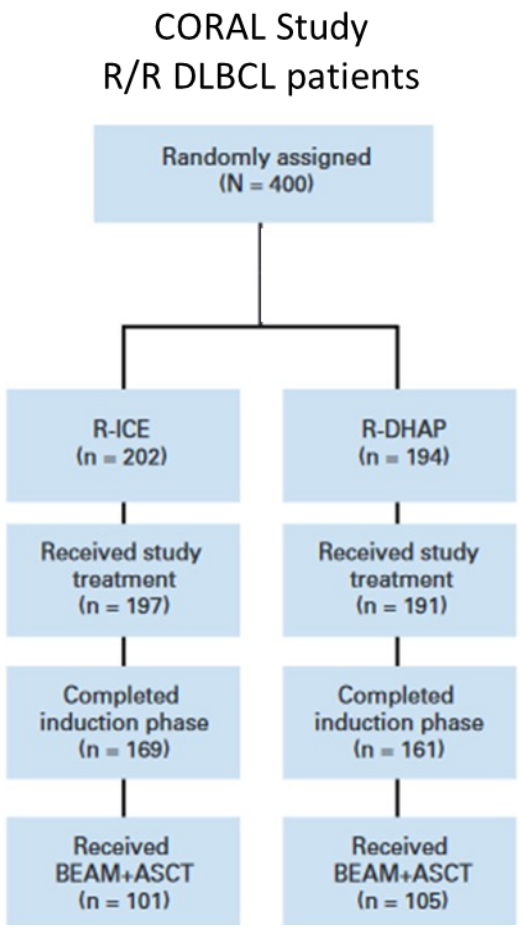
Sehn, Salles NEJM 2021

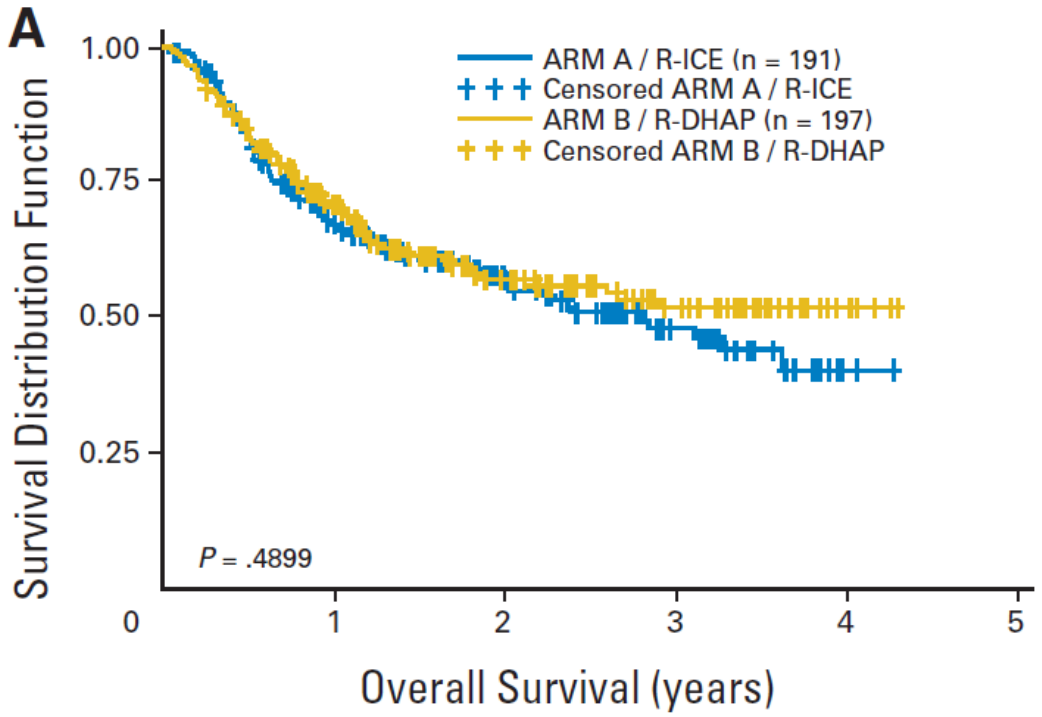
Rattrapage/autogreffe pour les patients avec LBCL R/R

Table 1. Base-Line Characteristics of the 109 Patients with Non-Hodgkin's Lymphoma Randomly Assigned to Autologous Bone Marrow Transplantation or Conventional Treatment.*

Characteristic	Transplantation (N = 55)	Conventional Treatment (N = 54)
	no. of patients	
Histologic type of lymphoma		
High-grade large-cell immunoblastic	10	12
High-grade lymphoblastic	0	2
High-grade, with small noncleaved cells	1	2
Intermediate-grade follicular, with predominantly large cells	3	3
Intermediate-grade diffuse, with small cleaved cells	0	3
Intermediate-grade diffuse, with mixed small and large cells	12	9
Intermediate-grade diffuse, with large cells	22	15
Other diffuse	7	8





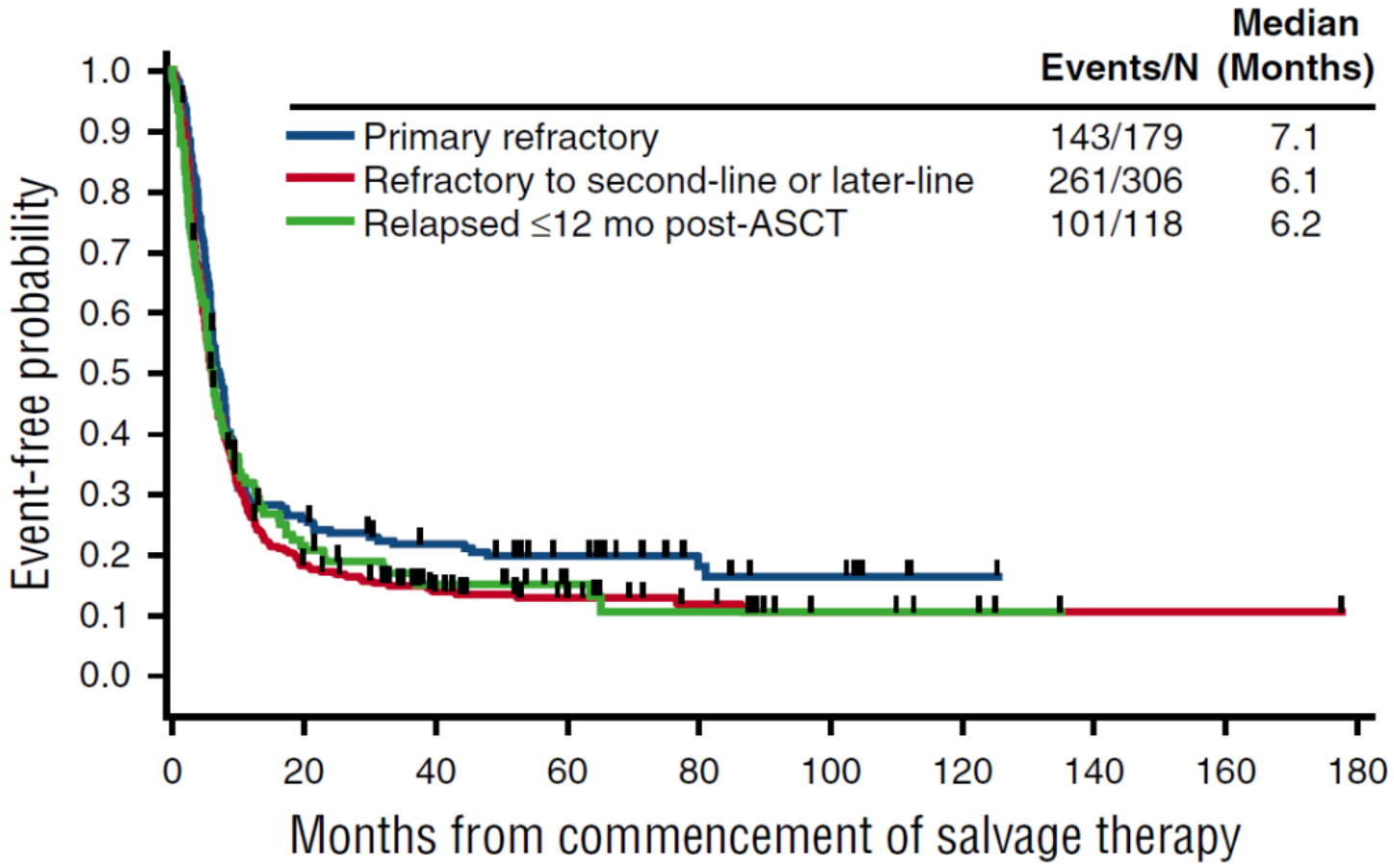


according to the first random assignment (intent to treat)

Philip et al. *NEJM* 1995

Gisselbrecht et al. *JCO* 2010

Pronostic défavorable des LBCLs réfractaires

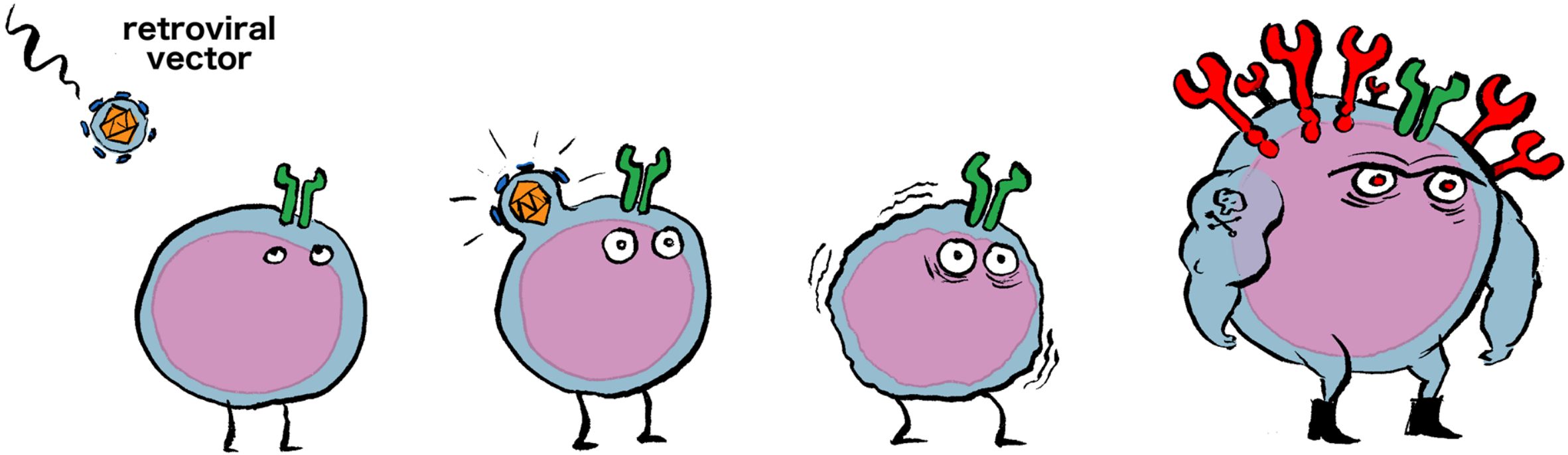


Crump et al. Blood 2017

Generating super-soldiers

the production of CAR-T cells

Chimeric Antigen Receptor



Développement des CAR T cells

1985 — 1989 — 1998 — 2003

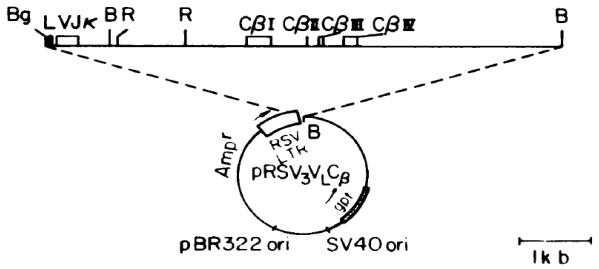
Rosenberg et al.
TILs stimulés in vitro par l'IL2
LAK: **lymphokine activated killer cells**
Preuve de concept

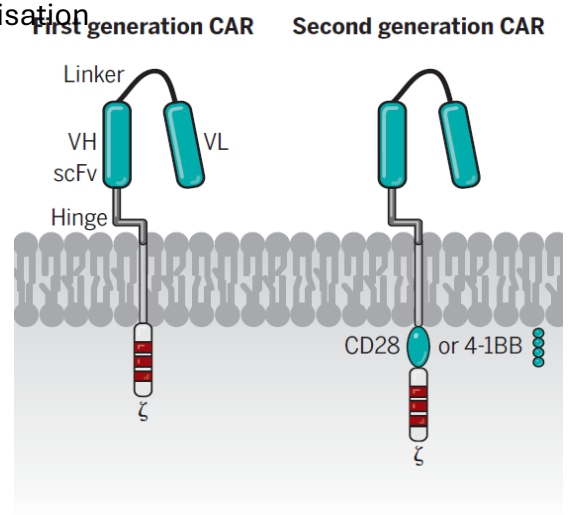
Gross, Waks, Eshhar
1st generation CAR

Sadelain / Finney
Introduction du domaine de co-stimulation CD28 au CAR
2nd generation CAR

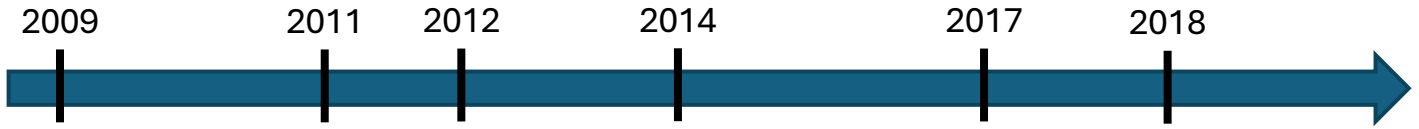
Brentjens et al
CAR T anti-CD19 efficace dans modèles murins

Ac monoclonaux: peu efficace pour tuer les cellules tumorales
Idée: combiner la spécificité des Ac monoclonaux avec la cytotoxicité des Ly T
Solution: associer la partie variable d'un Ac monoclonal au domaine de signalisation du TCR





L’essor des CAR T cells



Hollyman et al.
La « recette » publiée

FDA: **breakthrough therapy**

AMM européenne

FDA approval

Porter et al.
1re utilisation chez l’homme LLC

CAR T-CELL BIOTECH IPOs

Company	Date	Value
Kite Pharma	June 2014	$134.1 million
Bellicum	December 2014	$160 million
Juno	December 2014	$264.6 million
Cellectis	March 2015	$228 million

The New York Times

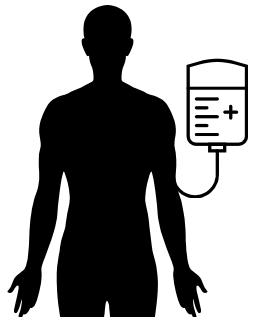
In Girl’s Last Hope, Altered Immune Cells Beat Leukemia

By DENISE GRADY DEC. 9, 2012

CAR T cells anti-CD19 autologue
Principes du traitement

Leucaphérèse

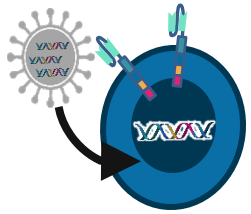
Prélèvement des lymphocytes



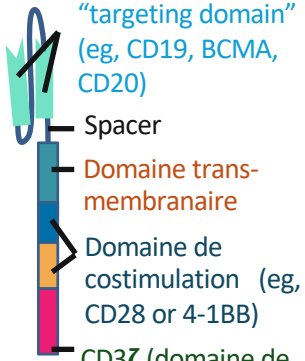
Production des CAR T cells

Tri/activation des Ly T

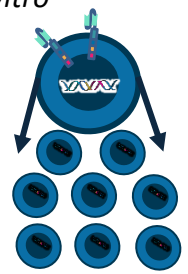
Infection retro ou lenti-virale



CAR-Tcell génétiquement modifiée

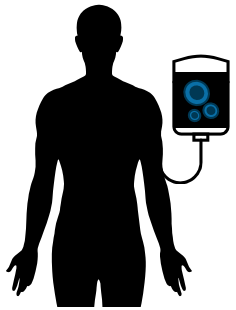


Expansion des CAR T cells *in vitro*



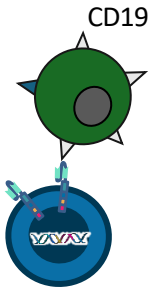
Infusion

Infusion des CAR-T autologues



In vivo

Activation
Expansion
Cytotoxicité
CRS/ICANS



Temps de production médian: 17-28 jours

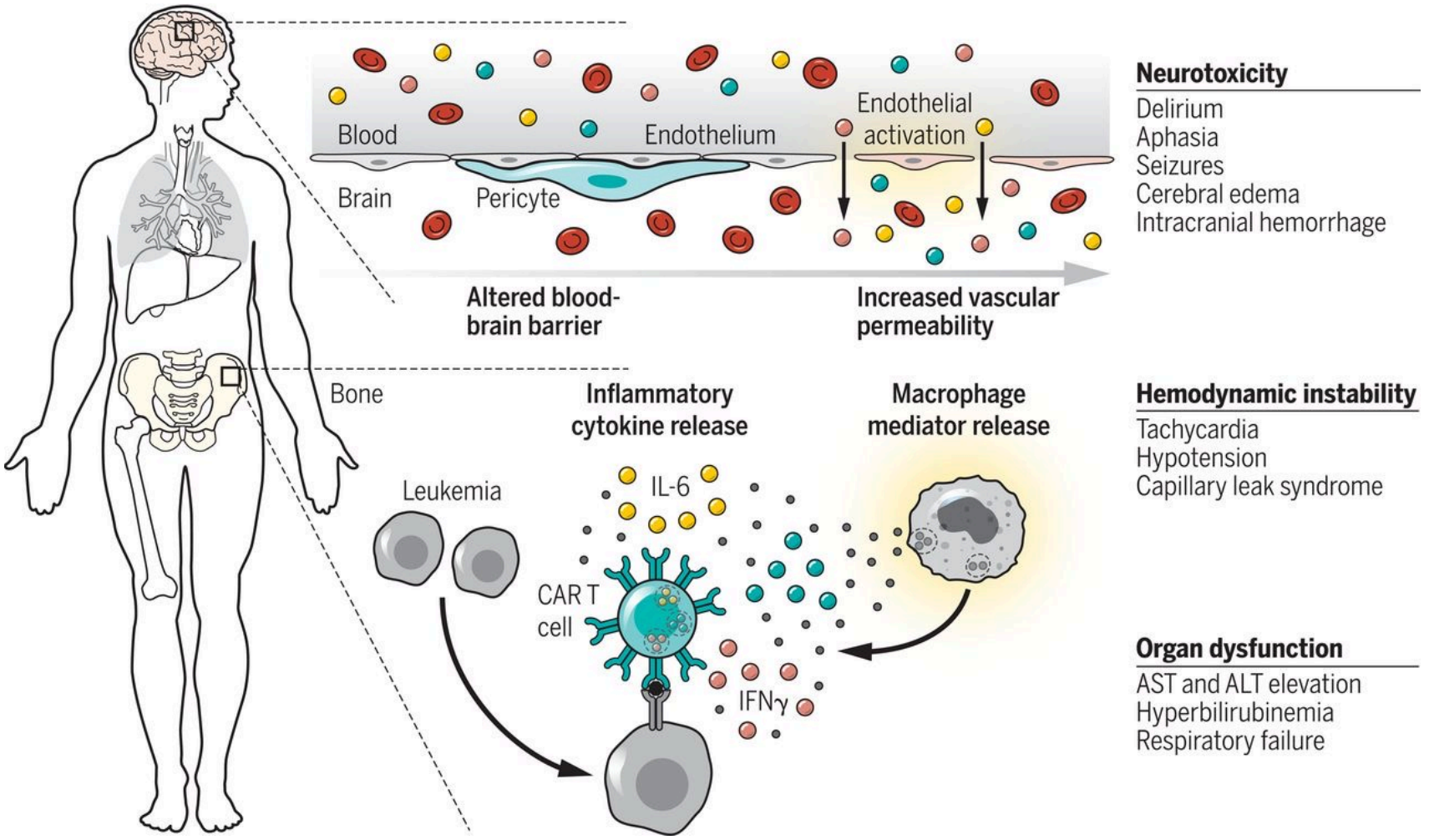
Traitement d'attente à considerer avant infusion

Chimiothérapie de lymphodepletion avant la ré-injection (Flu/Cy 3 jours)

Majors. EHA 2018. Abstr PS1156. Lim. Cell. 2017;168:724. Sadelain. Nat Rev Cancer. 2003;3:35.
Brentjens. Nat Med. 2003;9:279. Park. ASH 2015. Abstr 682.

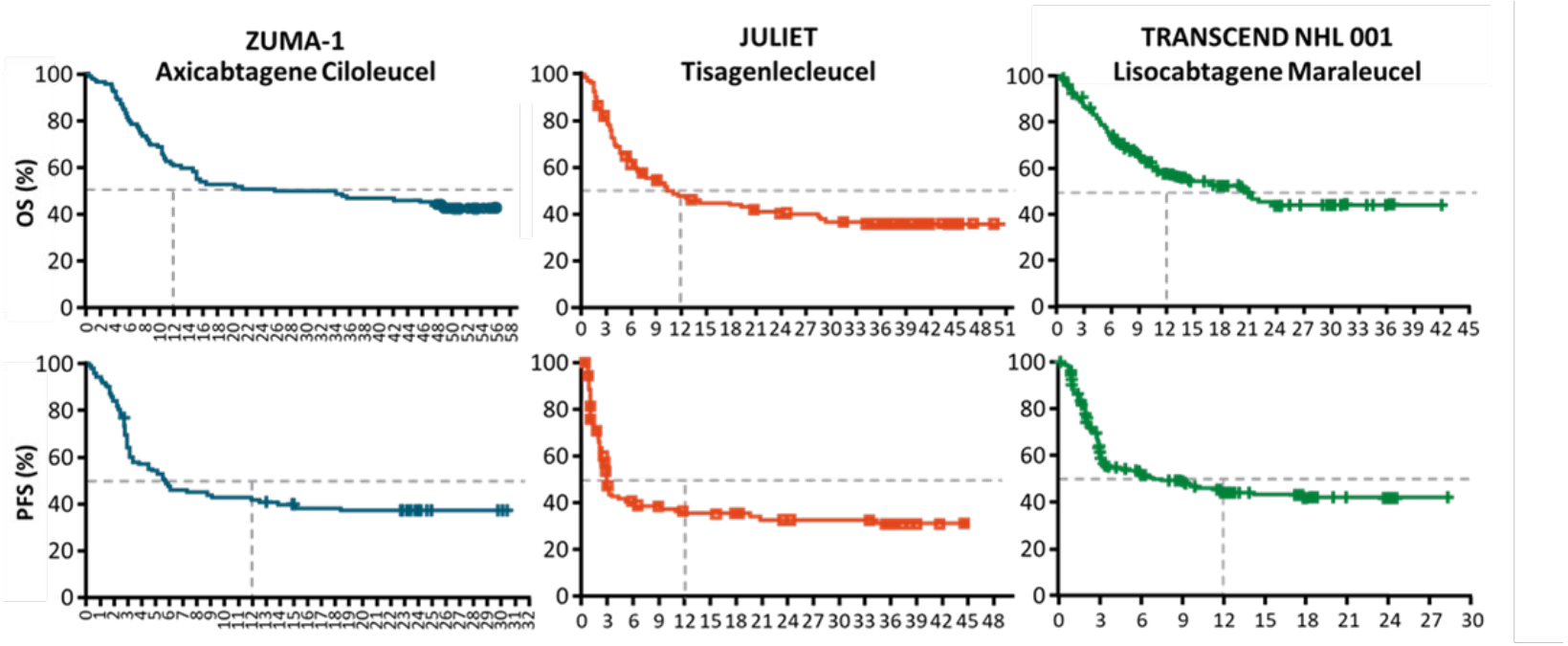
Slide credit: clinicaloptions.com

CRS (Cytokine Release Syndrome)
Neurotoxicité (Immune effector Cell Associated Neurotoxicity ICANS)



Carl H. June et al. Science 2018;359:1361-1365

CAR-T anti CD19 pour les LBCLs R/R en 3e ligne et plus



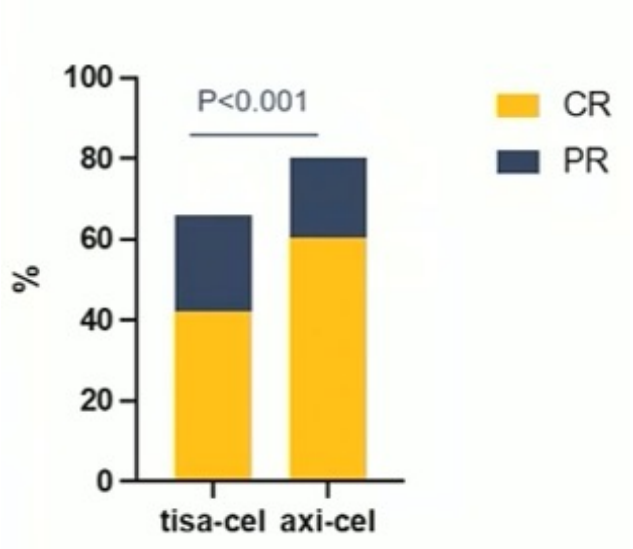
	ZUMA-1	JULIET	TRANSCEND NHL 001
CAR T	Axi-Cel	Tisa-Cel	Liso-Cel
leucapheresis / reinfusion (%)	111/101 (90%)	165/111 (67%)	344/269 (78%)
Bridging therapy(%)	Not possible	92%	59%
ORR, % CR, %	82% 54%	52% 40%	73% 53%

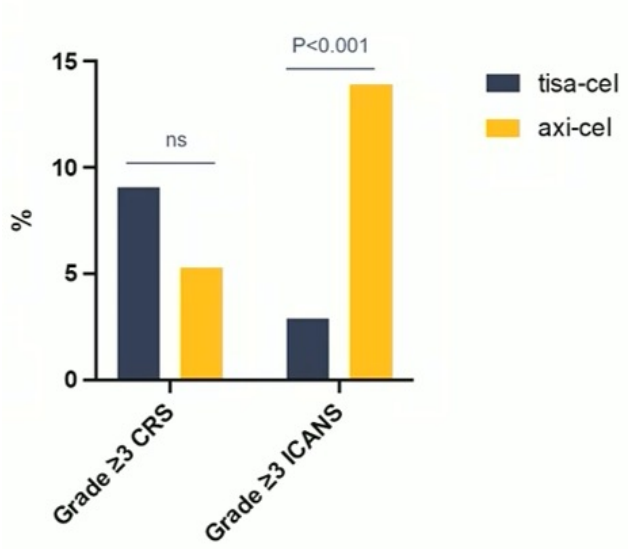
Les données ont été présentées à titre d'illustration comparative et aucunes comparaison directe des essais ne peut être faite.

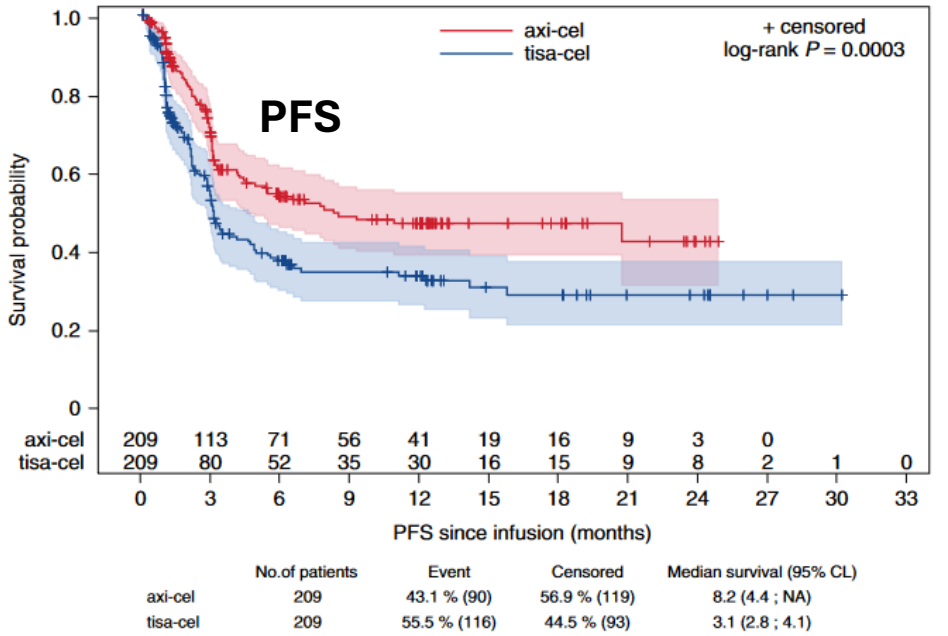
Locke et al. Lancet Oncol. 2019
Jacobson et al. ASH 2020. Abstr 1187
Jaeger. Et al. ASH 2020. Abstr 1194.
Abramson et al. Lancet. 2020

CAR anti-CD19 dans la vraie vie en France en 3e ligne et plus

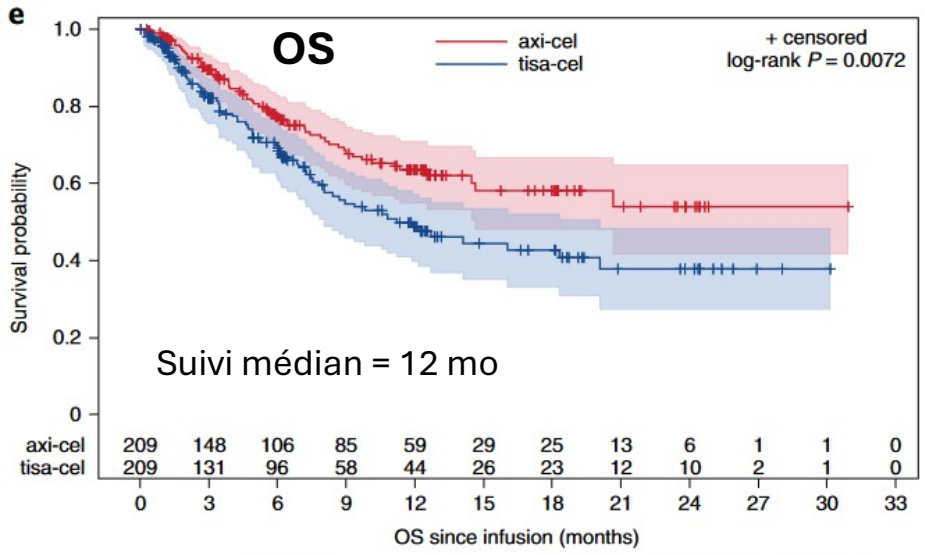
Registre DESCART > 1200 patients inclus







	No.of patients	Event	Censored	Median survival (95% CL)
axi-cel	209	43.1 % (90)	56.9 % (119)	8.2 (4.4 ; NA)
tisa-cel	209	55.5 % (116)	44.5 % (93)	3.1 (2.8 ; 4.1)



	No.of patients	Event	Censored	Median survival (95% CL)
axi-cel	209	28.2 % (59)	71.8 % (150)	Not reached (14.7 ; NA)
tisa-cel	209	37.8 % (79)	62.2 % (130)	11.2 (8 ; 20.1)

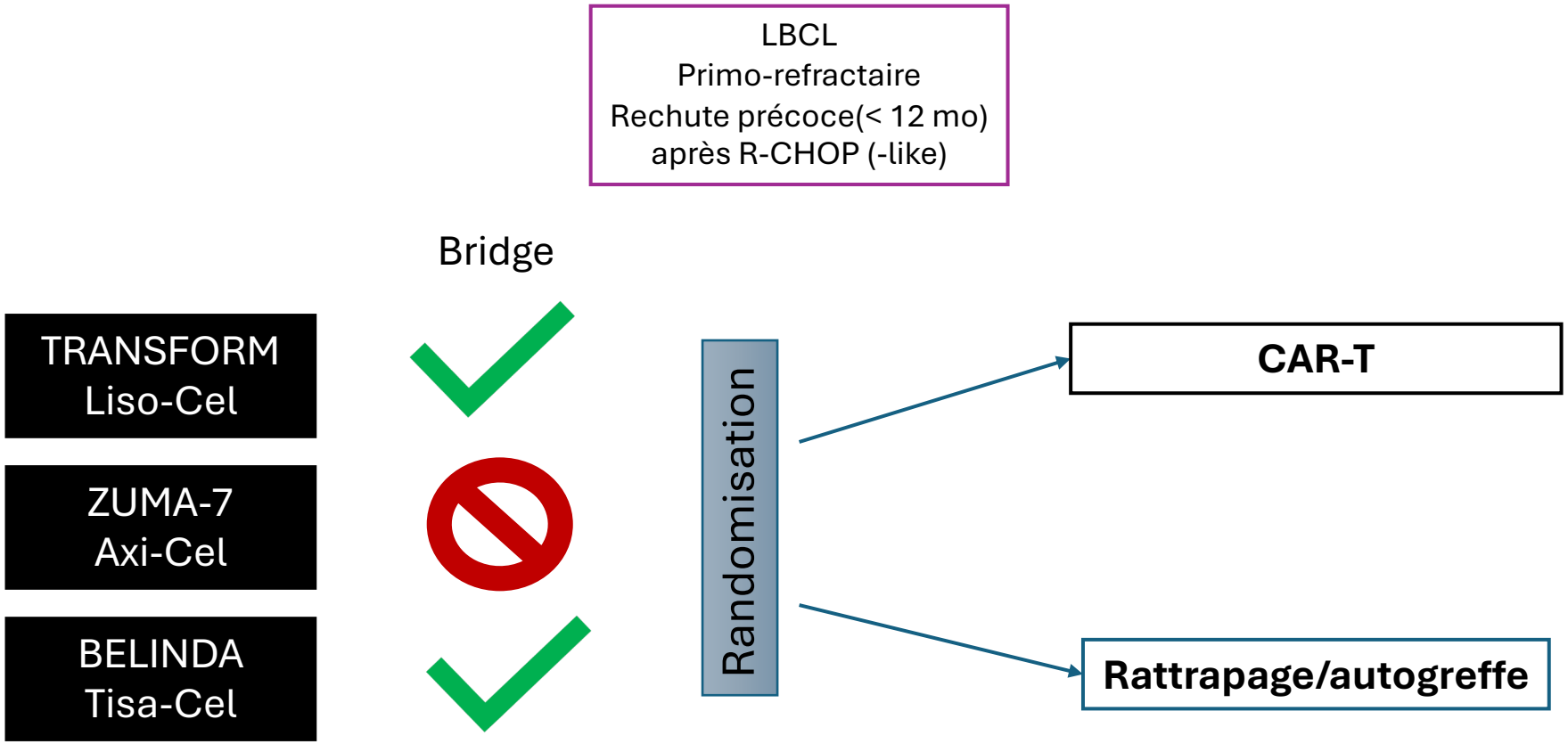
Bachy et al. ASH 2021 / EHA 2022

Bachy et al. Nat Med 2022

ASH 2021

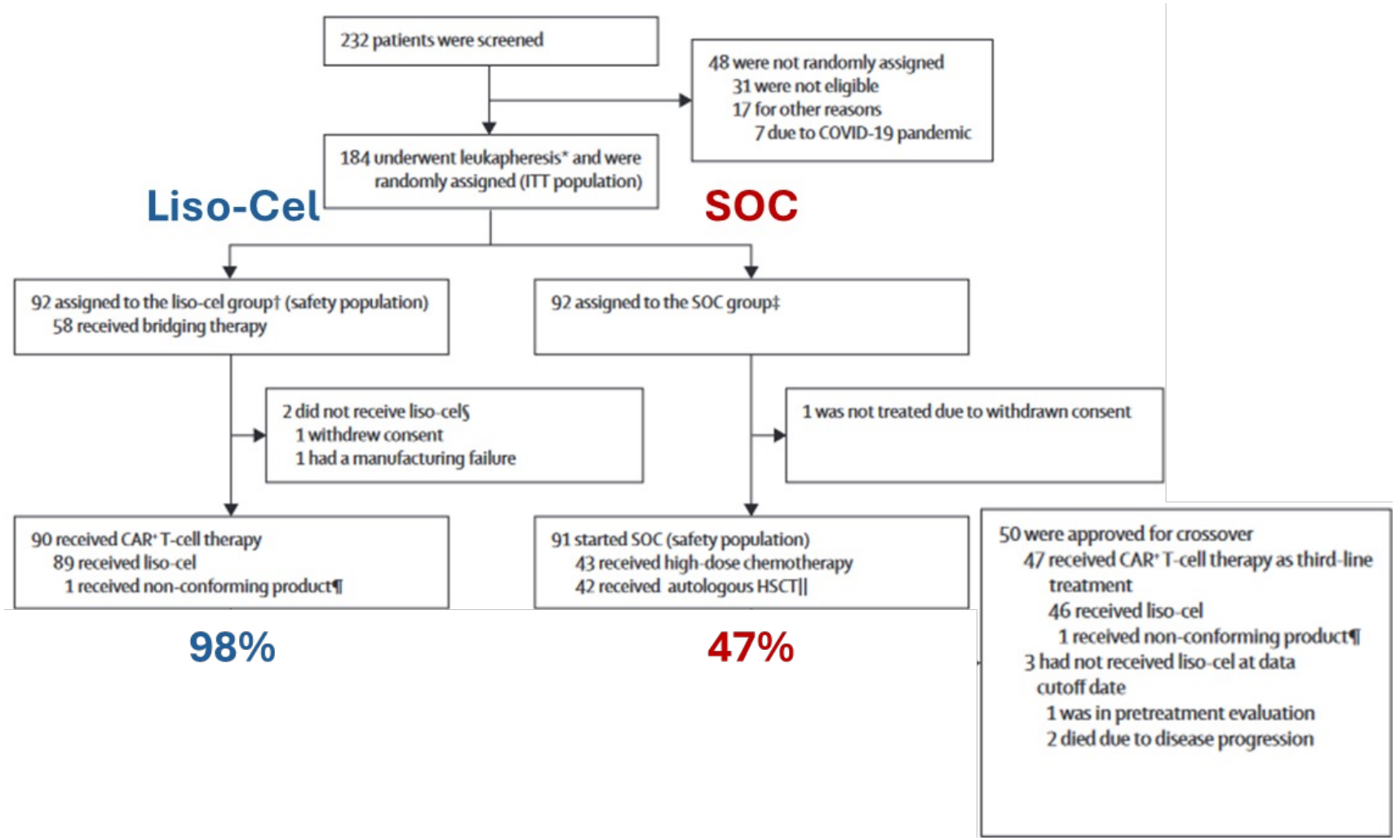
LBCL 2e ligne: CAR-T vs rattrapage/autogreffe

3 essais randomisés



TRANSFORM: Liso-Cel en 2e ligne vs autogreffe

Crossover et bridge autorisés
Suivi médian = **17,5 mois**



Kamdar et al. Lancet 2022; Abramson et al. Blood 2023

TRANSFORM: Liso-Cel en 2e ligne vs autogreffe

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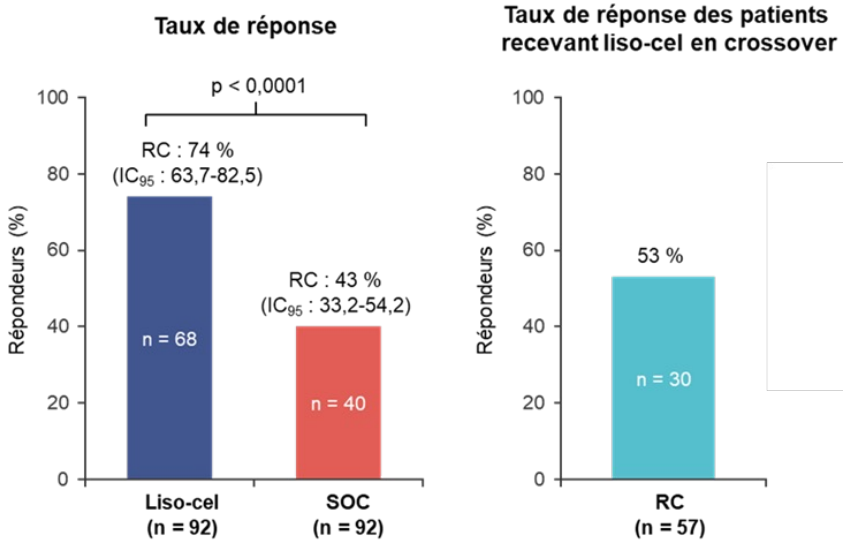
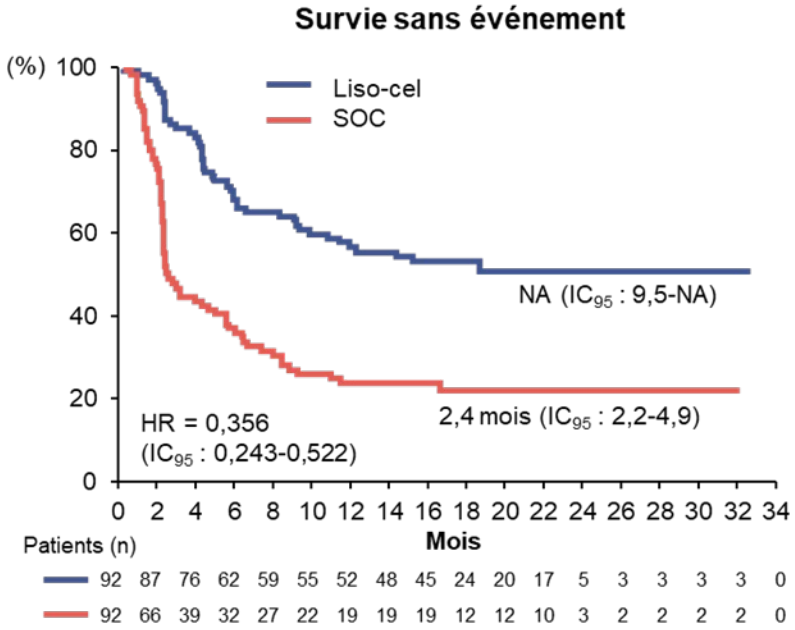
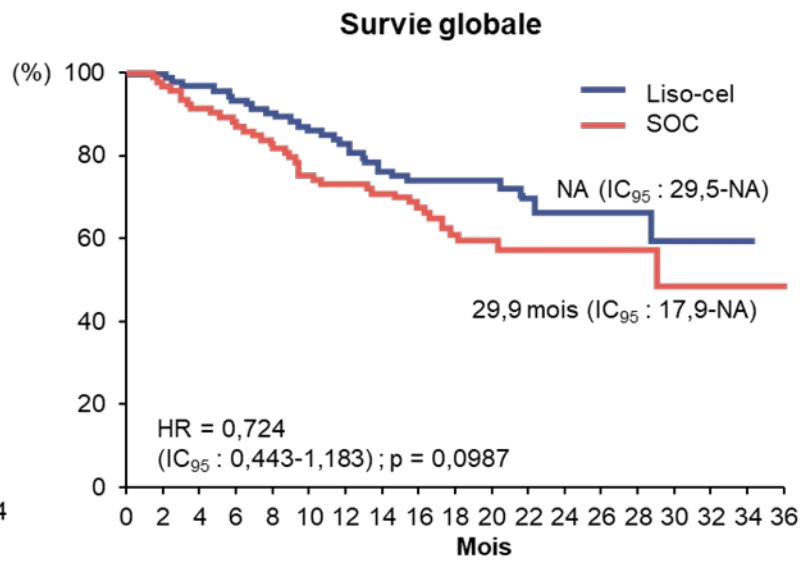






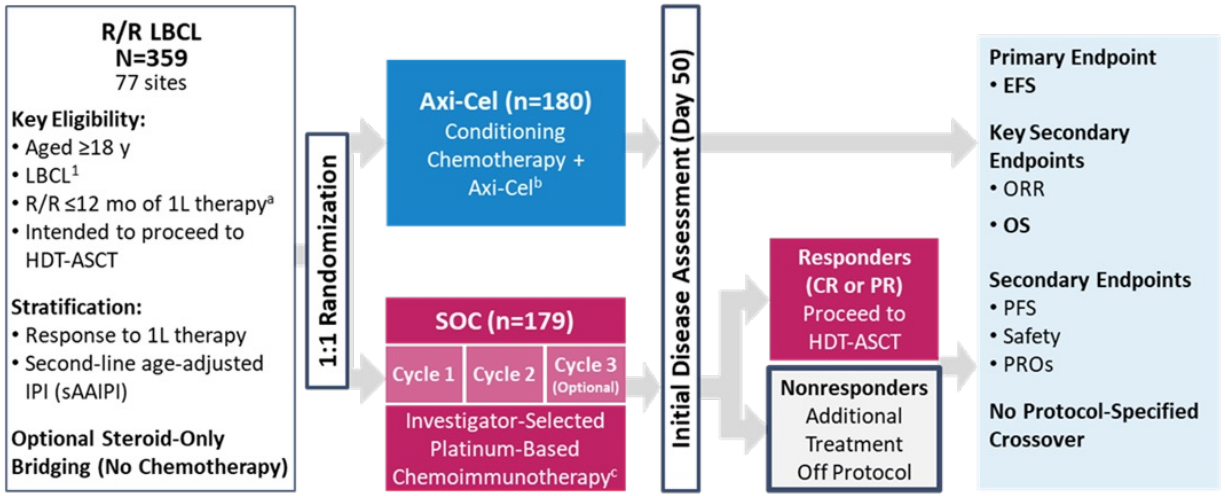
- **CRS**: 49%
  - Grade ≥ 3 : 1%
- **ICANS** : 11%
  - Grade ≥ 3 : 4%
- **Cytopénies prolongées** (> J+30) Grade ≥ 3: 43%

Liso-Cel: disponible en France en 2e ligne pour les LBCLs

Kamdar et al. Lancet 2022; Abramson et al. Blood 2023

ZUMA-7: Axi-Cel en 2e ligne vs autogreffe

Crossover et bridge NON autorisés
Suivi médian = **47,2 mois**



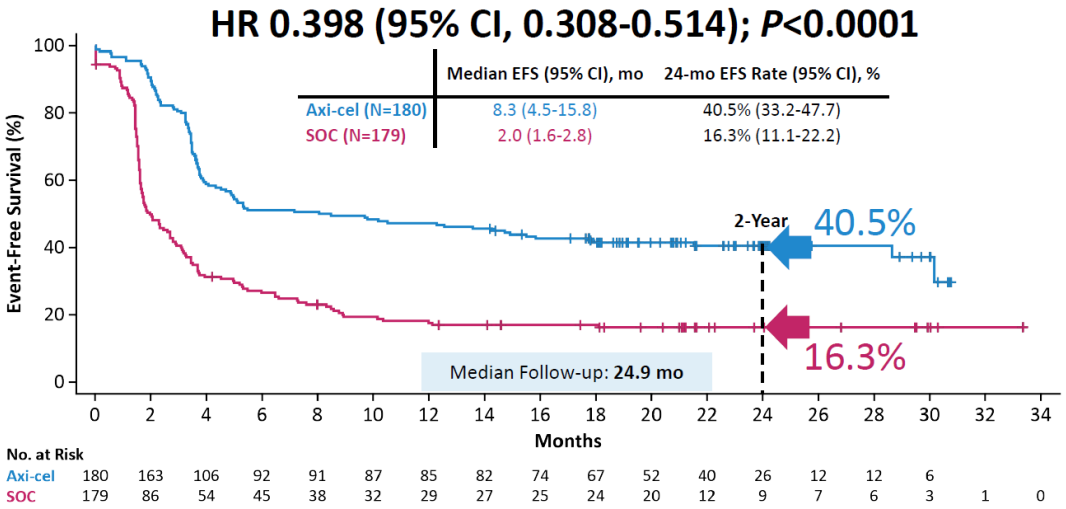
94% - ORR 83% - CR 65%

36% - ORR 50% - CR 32%

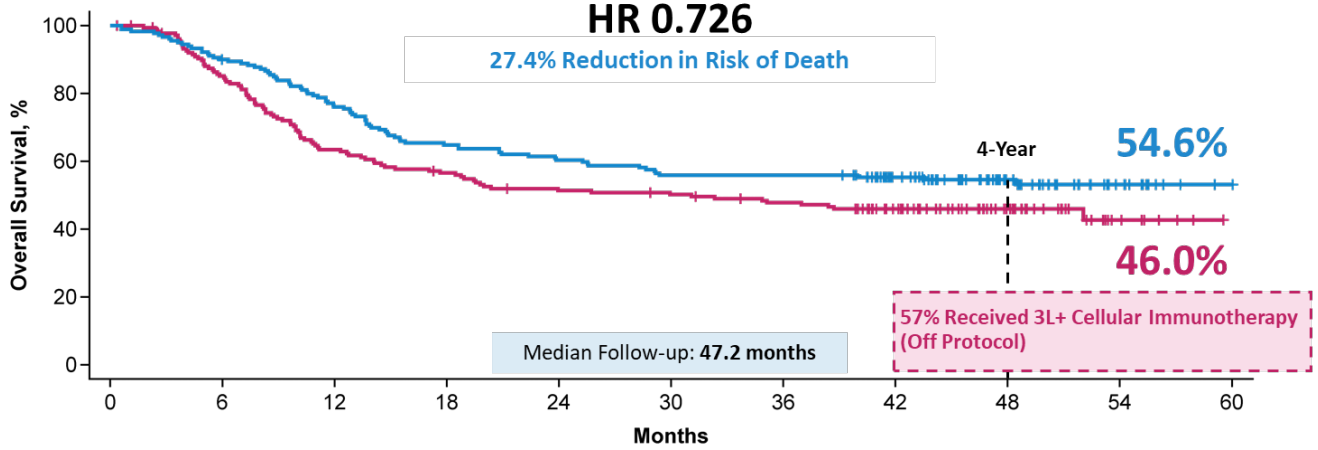
TOXICITE Axi-Cel

- **CRS**: 92%
  - Grade ≥ 3 : 6%
- **ICANS** : 60%
  - Grade ≥ 3 : 21%
- **Cytopénies prolongées** (> J+30)
  Grade ≥ 3: 29%

Survie sans évènements



Survie globale

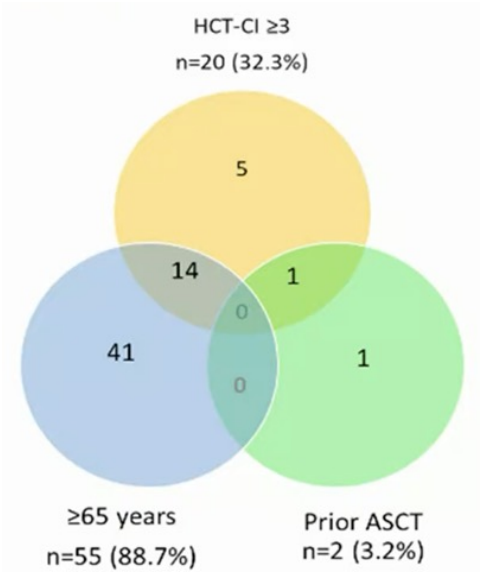


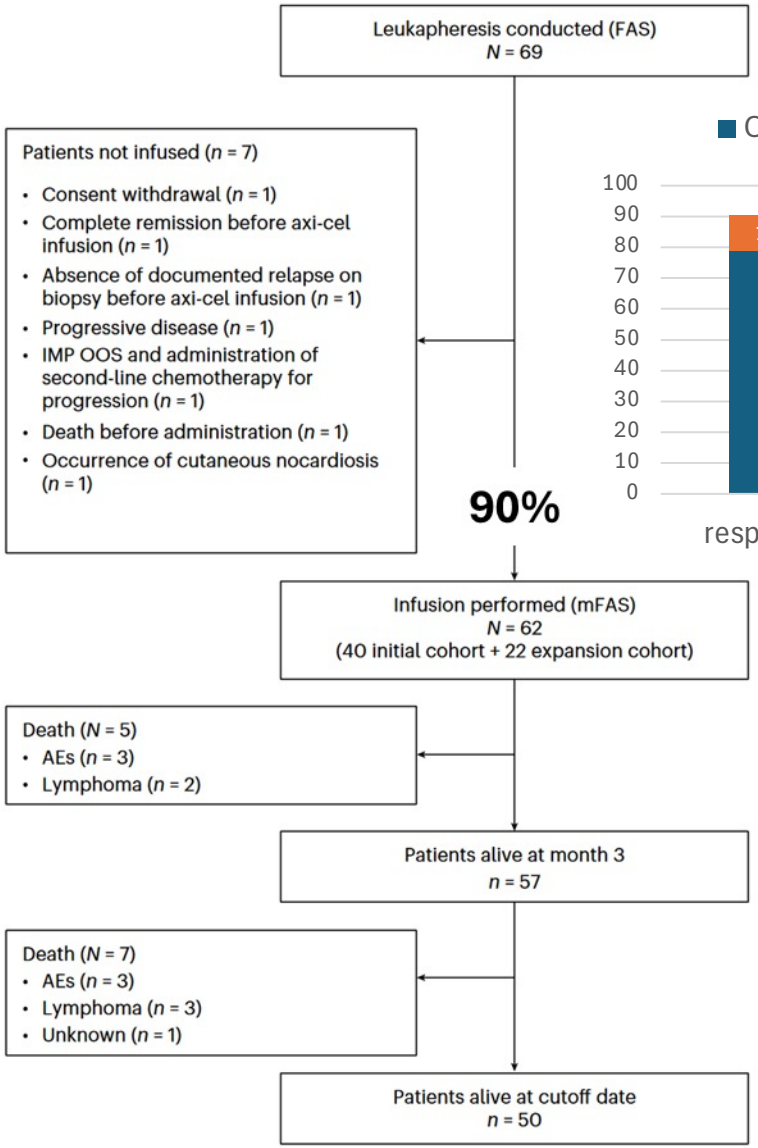
Locke et al. NEJM 2021 – Westin et al. NEJM 2023

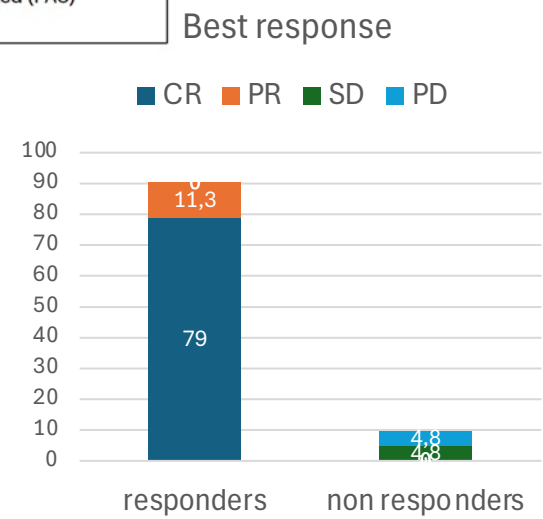
ALYCANTE: Axi-Cel en L2 pour les patients **inéligibles à l'autogreffe**

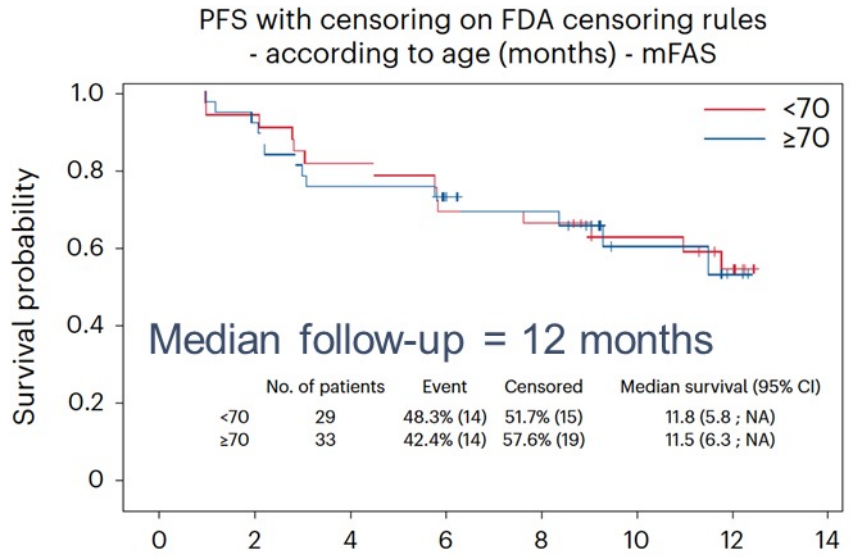
Suivi médian **12 mois**

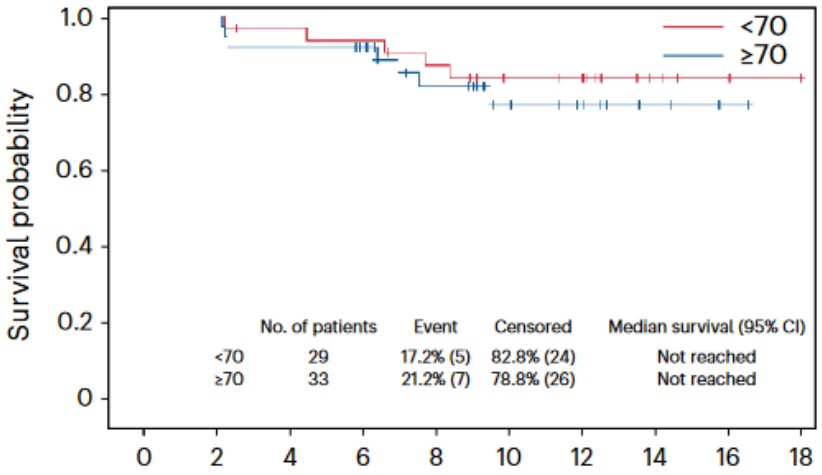
Critères d'inéligibilté à l'autoG







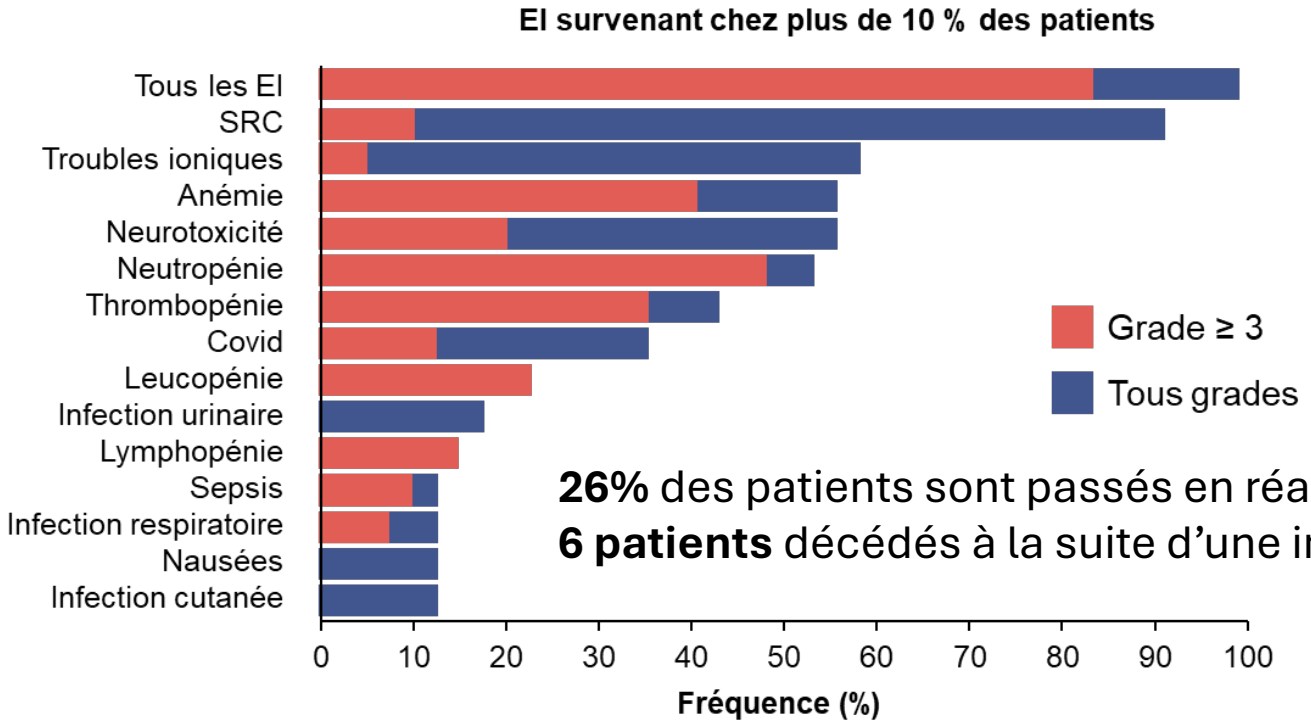




Houot et al. Nat Med 2023

ALYCANTE: Axi-Cel en L2 pour les patients **inéligibles à l'autogreffe**

TOXICITE



26% des patients sont passés en réanimation
6 patients décédés à la suite d'une infection

- **CRS**: 93,5%
  - Grade ≥ 3 : 8%
- **ICANS** : 51,6%
  - Grade ≥ 3 : 14,5%
- **Cytopénies prolongées** (> J+30) Grade ≥ 3: 37%

Axi-Cel disponible en France en AP en 2e ligne pour les LBCLs dans l'indication: traitement des patients adultes atteints de lymphome diffus à grandes cellules B, réfractaires ou en rechute dans les 12 mois après la fin d'un traitement de première ligne

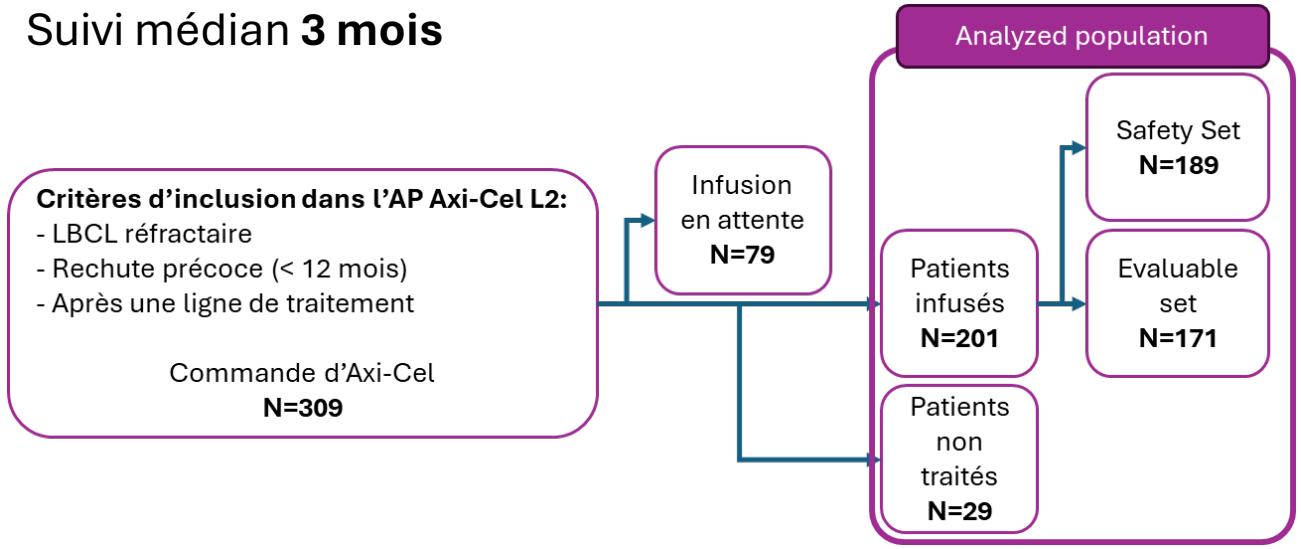
Houot et al. Nat Med 2023

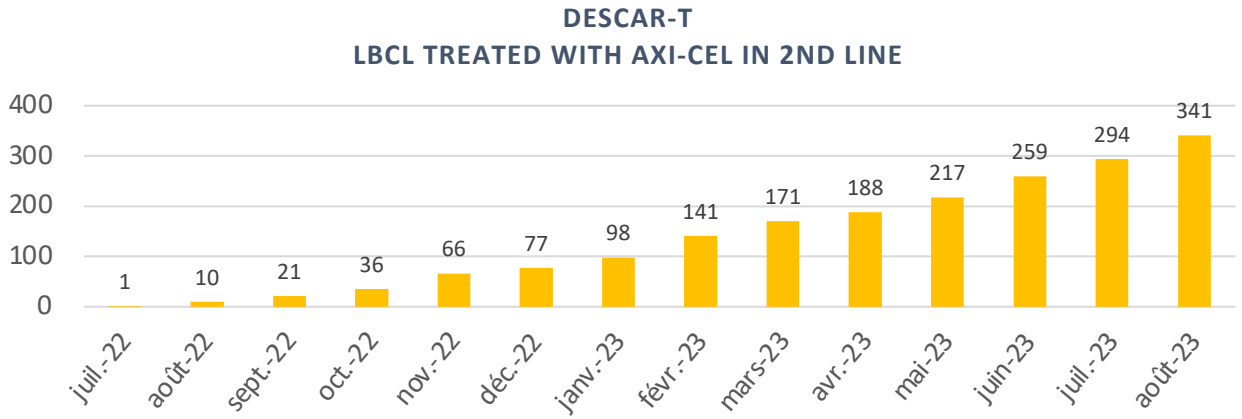
Axi-Cel dans la vraie vie en 2e ligne

Données du registre DESCAR-T

Patients inclus entre Jul 2022 et Aout 2023

Suivi médian **3 mois**





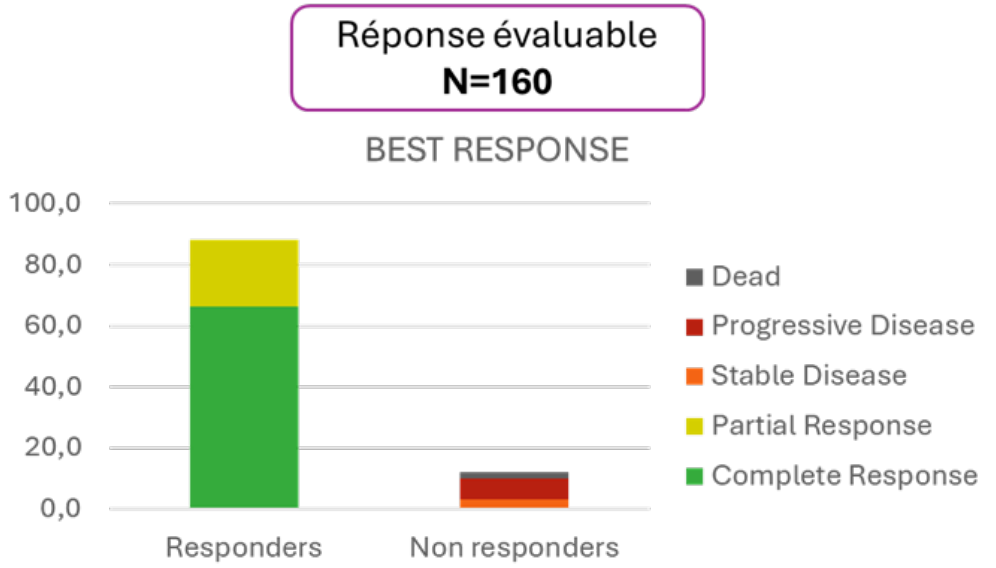
	Treated patients N=201 (87.4%)		Untreated patients N=29 (12.6%)	
Sex Male	122	(60.7%)	16	(55.2%)
Age (years)				
Median (min; max)	61 (21; 82)		65 (34;80)	
Age >= 65 years	**77**	**(38.3%)**	**15**	**(51.7%)**
Bridging therapy	**177**	**(88.1%)**	**18**	**(62.1%)**
ECOG				
0-1	164	(81.6%)	14	(48.3%)
>=2	10	(5.0%)	3	(10.3%)
Missing	27	(13.4%)	12	(41.4%)
LDH > Normal				
No	75	(37.3%)	16	(55.2%)
Yes	122	(60.7%)	12	(41.4%)
Missing	4	(2.0%)	1	(3.4%)
Ann Arbor Stage				
I-II	30	(14.9%)	4	(13.8%)
III-IV	149	(74.1%)	20	(69.0%)
Unknown	22	(10.9%)	5	(17.2%)
Histology				
DLBCL	149	(74.1%)	22	(75.9%)
Transformed indolent	28	(13.9%)	6	(20.7%)
PMBL	6	(3.0%)	0	(0.0%)
HGBL	8	(4.0%)	1	(3.4%)
Other#	10	(5.0%)	0	(0.0%)
Primary refractory disease	**149**	**(74.1%)**	23	(79.3%)

Brisou et al. ASH 2023

Axi-Cel dans la vraie vie en 2e ligne

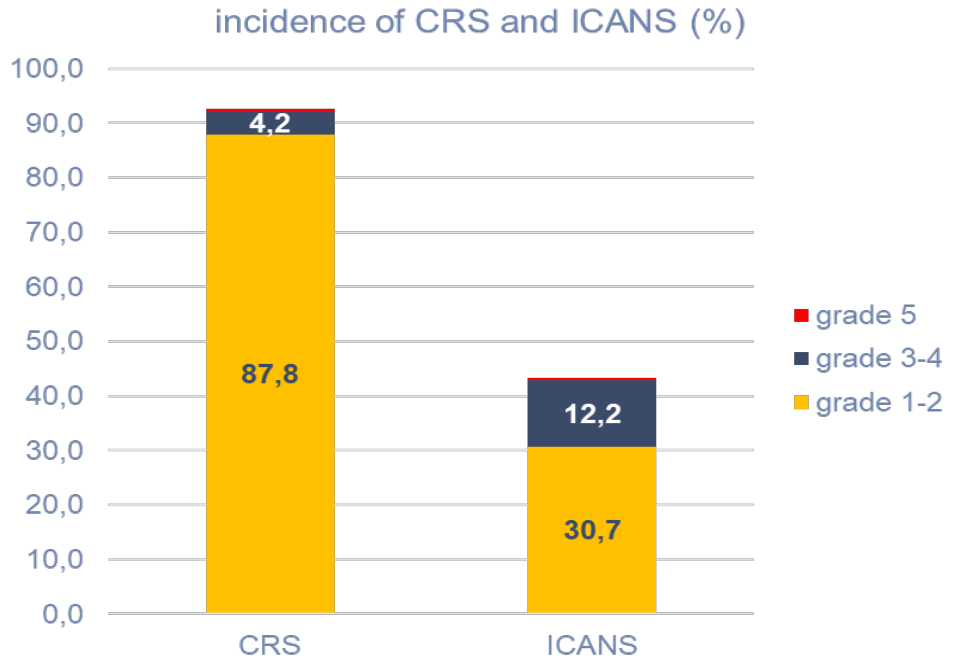
Données du registre DESCAR-T

Patients inclus entre Jul 2022 et Aout 2023
Suivi médian **3 mois**



	n	%
Réponse complète	**106**	**66.3**
Réponse partielle	**35**	**21.9**

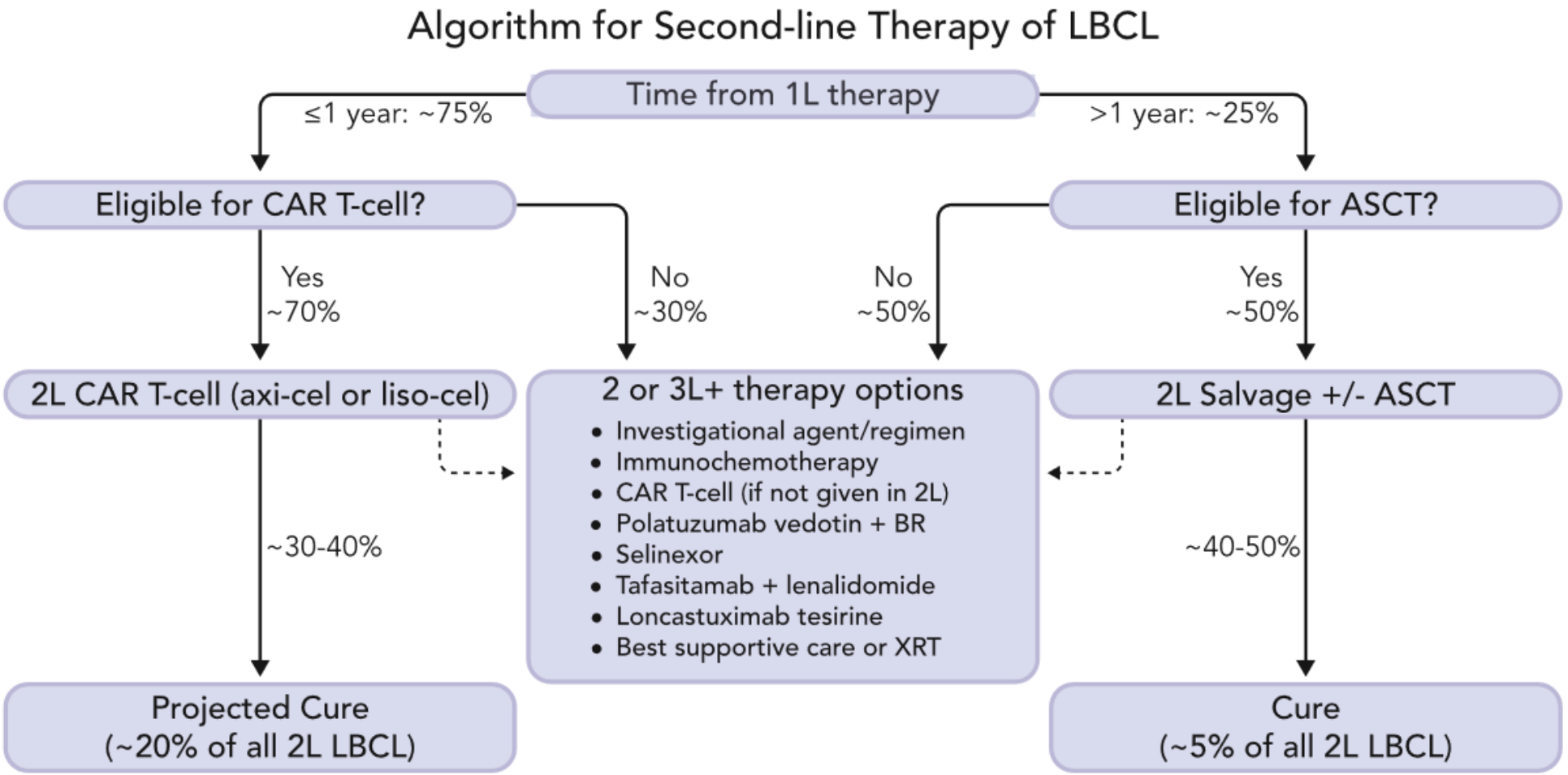
- **CRS**: 92%
  - Grade ≥ 3 : 5%
- **ICANS** : 43%
  - Grade ≥ 3 : 13%
- 7 patients (3,5%) décédés du fait de toxicités



Brisou et al. ASH 2023

CAR-T cells 2e ligne DLBCL :

standard de traitement y compris chez des patients > 65-70 ans moyennement fit

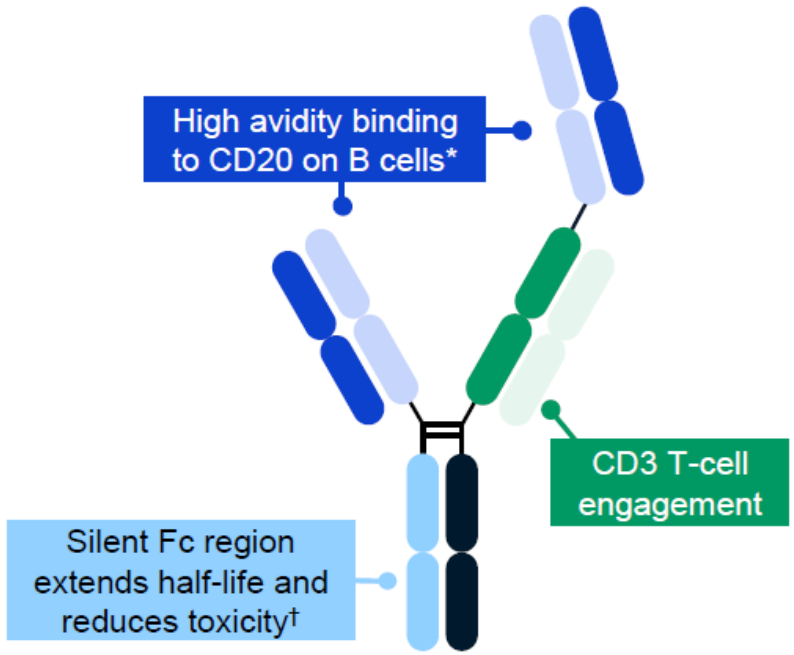


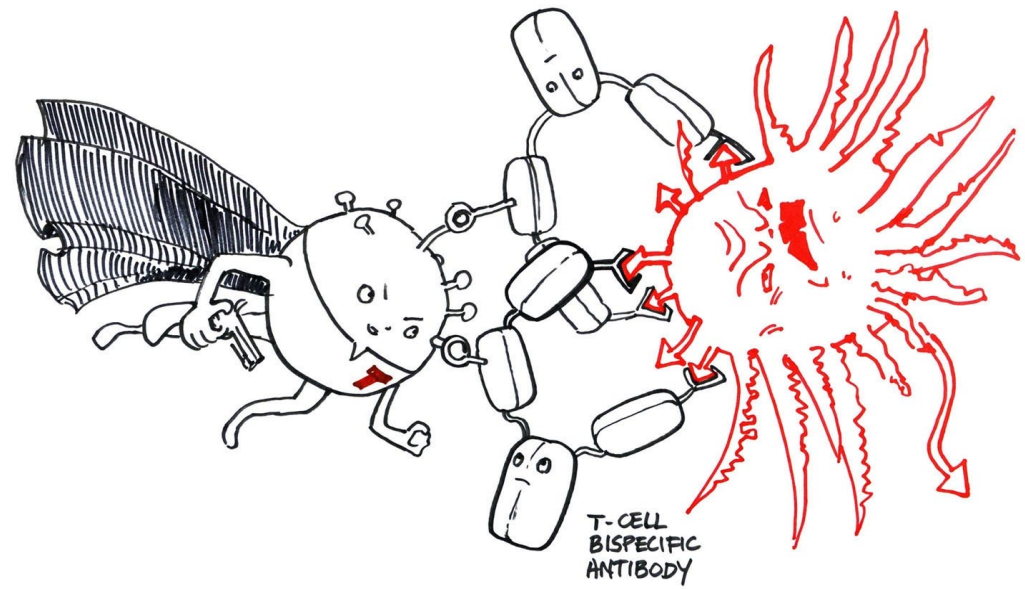
Westin and Sehn Blood 2022

Quels sont les patients inéligibles aux CAR-T cells ?

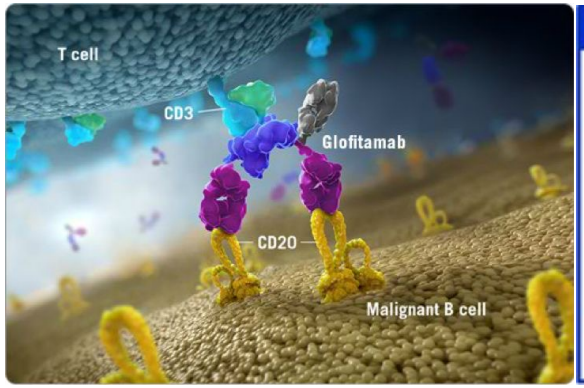
- **Grand âge ?**
- **Co-morbidités importantes**
- **Etat général altéré** (PS 3-4)
- **Progression rapide**
- **Manque d'accessibilité aux CAR-T**
- Rechute post CAR-T
- Refus du traitement par CAR-T

Glofitamab: *CD20xCD3 T-cell engaging bispecific antibody with 2:1 format*





Glofitamab DLBCL R/R



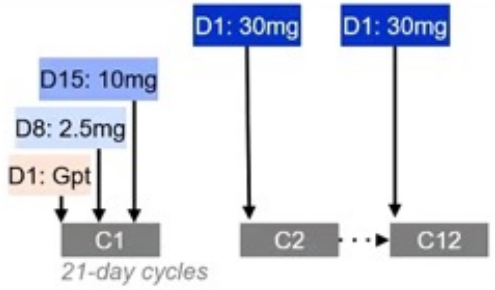
Glofitamab IV administration

Fixed-duration treatment

- max. 12 cycles

CRS mitigation:

- obinutuzumab pretreatment (1 x 1000mg)
- C1 step-up dosing
- monitoring after first dose (2.5mg)



n (%)*	N=154†
Median age, years (range)	66.0 (21–90)
Median no. of prior lines, n (range)	3 (2–7)
2 prior lines	62 (40.3)
≥3 prior lines	92 (59.7)
Prior CAR-T	51 (33.1)
Prior ASCT	28 (18.2)
Refractory to last prior therapy	132 (85.7)
Primary refractory	90 (58.4)
Refractory to prior CAR-T	46 (29.9)

ORR = 51 %

CR = 39,4 %

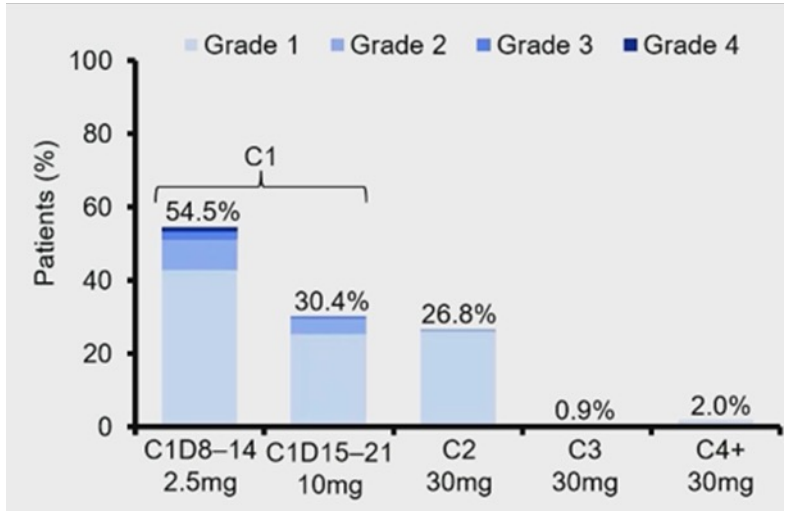
Suivi médian = 12,6 mois

Taux de survie sans rechute à 12 mois = 37%

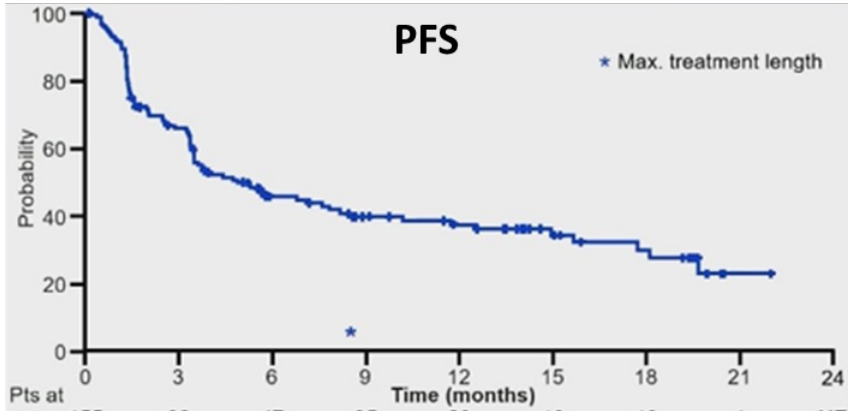
Survie médiane = 11,5 mois

Dickinson et al. EHA 2022

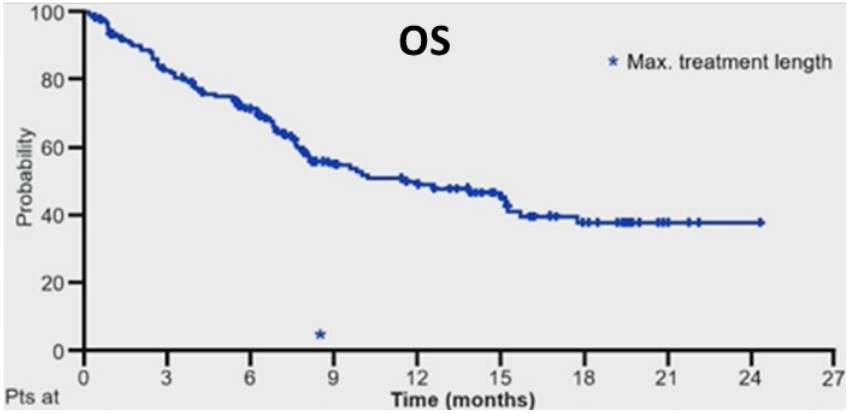
CRS



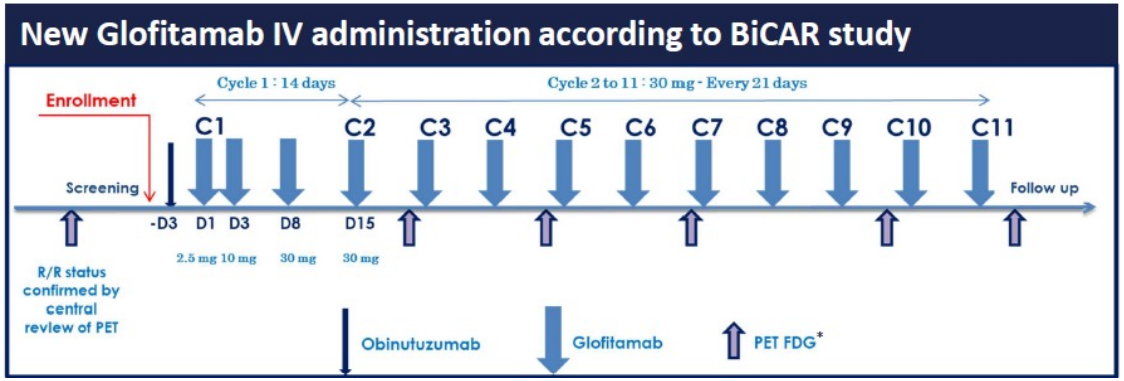
PFS

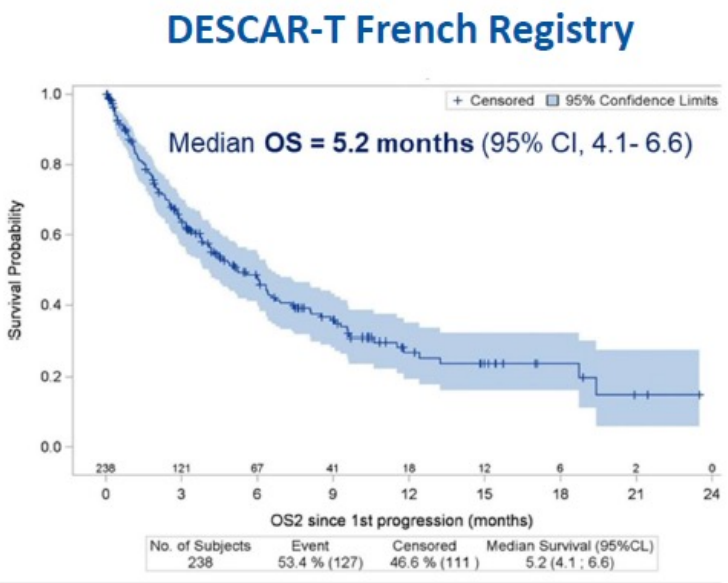


OS

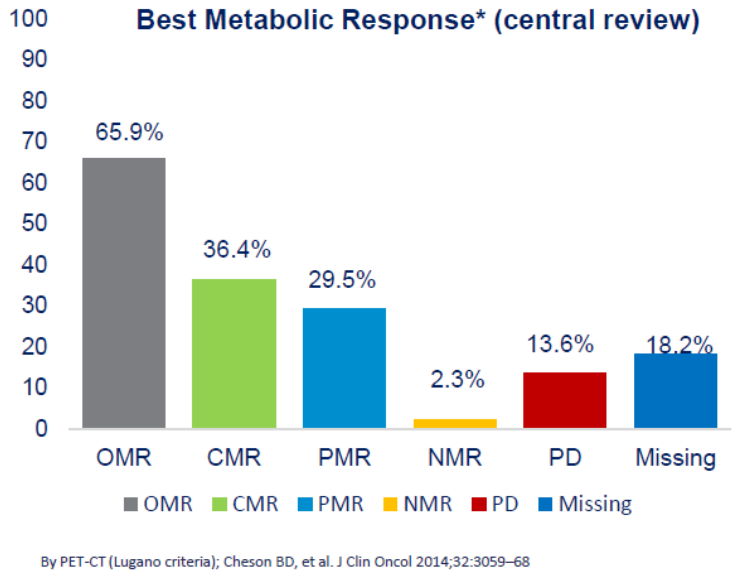


Glofitamab pour les patients ne répondant pas aux CAR-T - BICAR

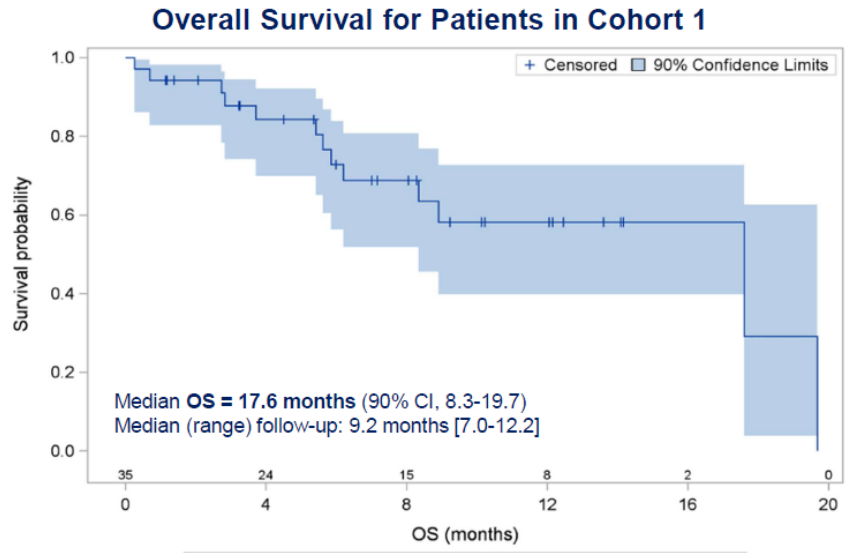




Di Blasi et al., Blood 2022

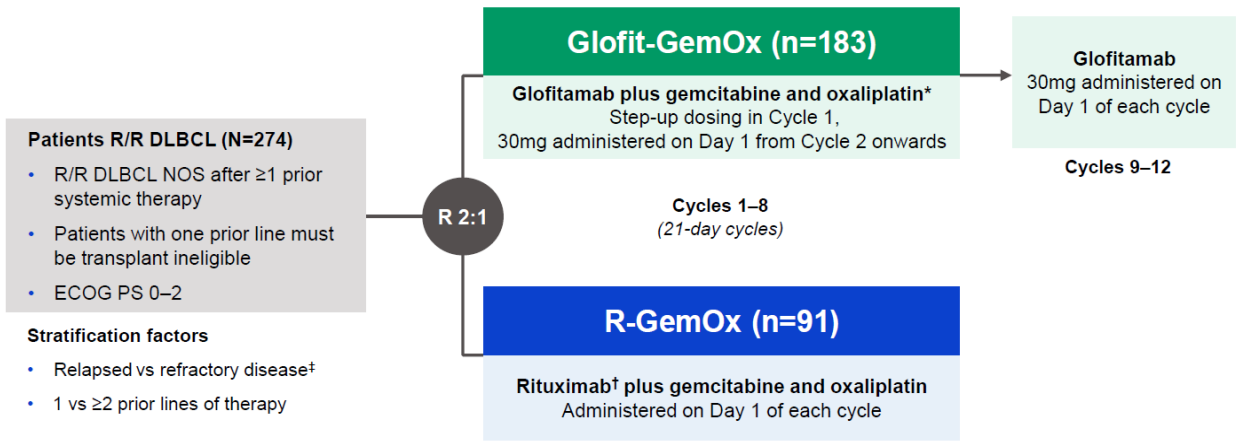


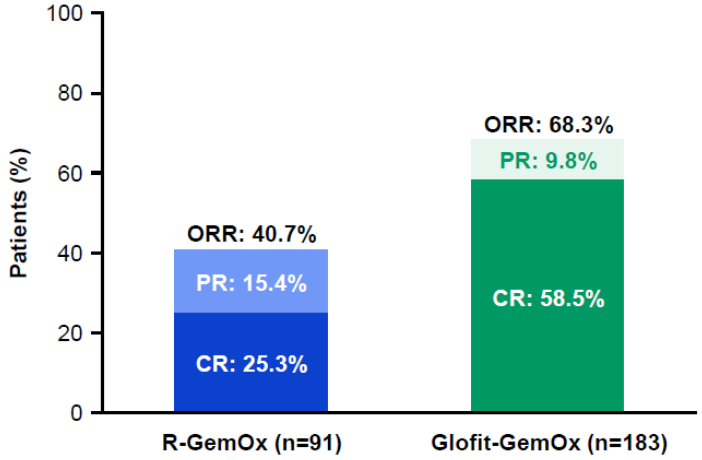
By PET-CT (Lugano criteria); Cheson BD, et al. J Clin Oncol 2014;32:3059–68



Sesques et al. ASH meeting 2023

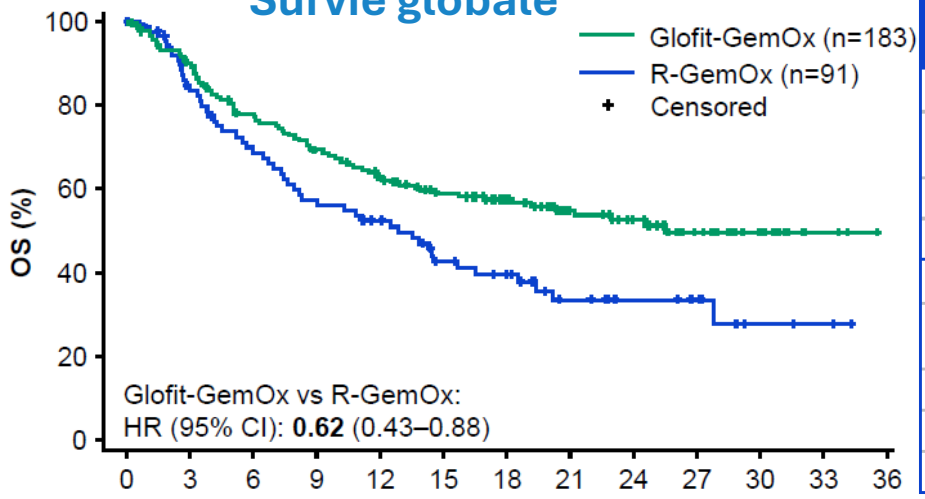
Glofitamab en 2e ligne – essai Starglo





Updated analysis

Survie globale



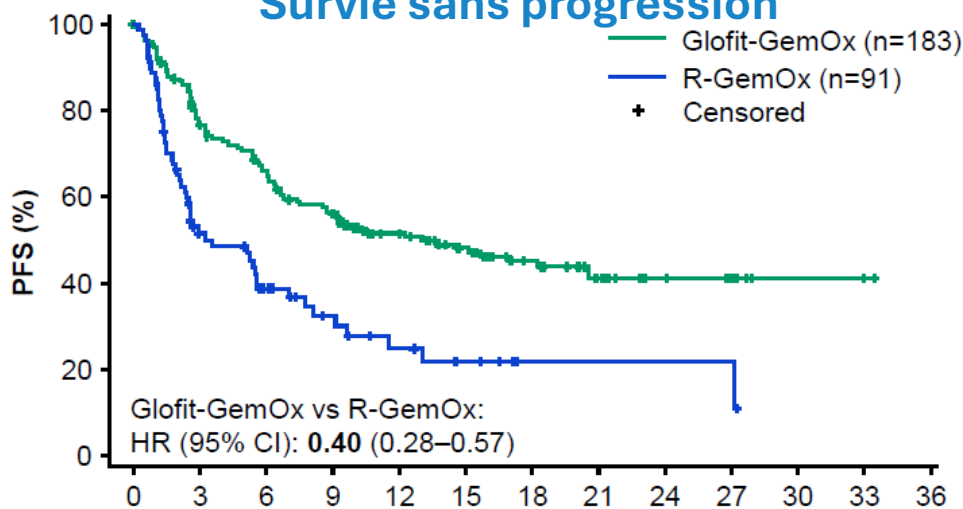
No. of patients at risk

Glofit-GemOx	183	159	135	119	104	86	71	51	40	26	11	3	NE
R-GemOx	91	68	55	46	40	29	23	14	10	8	3	2	NE

	R-GemOx (n=91)	Glofit-GemOx (n=183)
Primary analysis (median follow-up: 11.3 months)		
OS, median (95% CI); months	9 (7.3–14.4)	NE (13.8–NE)
HR (95% CI)	**0.59** (0.40–0.89)	
p-value*	0.011	
Updated analysis (median follow-up: 20.7 months)		
OS, median (95% CI); months	12.9 (7.9–18.5)	25.5 (18.3–NE)
HR (95% CI)	**0.62** (0.43–0.88)	
p-value*	0.006	
24-month OS (95% CI)	33.5% (22.2–44.9)	52.8% (44.8–60.7)

Updated analysis

Survie sans progression

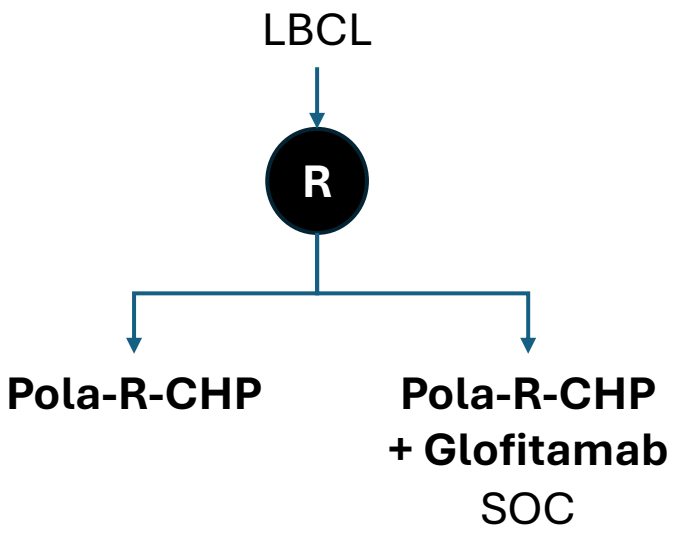


No. of patients at risk

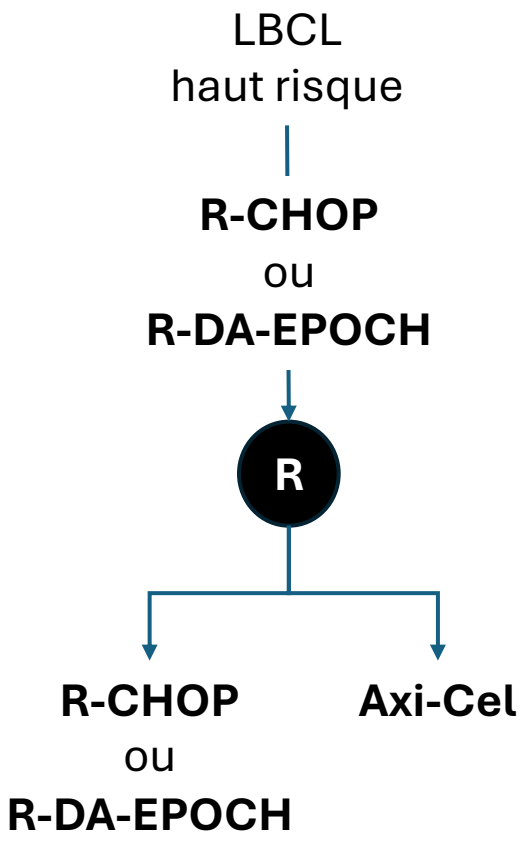
Glofit-GemOx	183	130	107	89	66	54	37	26	14	10	2	1	NE
R-GemOx	91	34	22	14	9	6	2	2	2	2	NE	NE	NE

Essais en cours et à venir

SKYGLO
Glofitamab en 1re ligne



ZUMA-23
Axi-Cel en 1re ligne



CARMOD
Association CAR-T + immunomodulateur

LBCL
Forte masse tumorale avant les CAR

CAR-T
+
Golcadomide

Messages clés et perspectives

- Les **CAR-T autologues anti-CD19** ont bouleversé la prise en charge des lymphomes B diffus à grandes cellules
  - Standard de traitement en 2e ligne = améliore la survie globale
  - Place en 1re ligne pour des patients à haut risque?
  - Difficile d'accès

- Les **anticorps bi-spécifiques antiCD3xCD20** représentent une nouvelle option de traitement efficace
  - Disponible à l'heure actuelle en 3e ligne y compris chez les patients ne répondant pas aux CAR-T
  - Bientôt en 2e et en 3e ligne?
  - Facile d'accès

- **Bispécifiques vs CAR-T** = quelle est la meilleure option? Faut-il les associer