Les Transversales « by IFODS »

IFODS

on behalf of Cours St-Paul

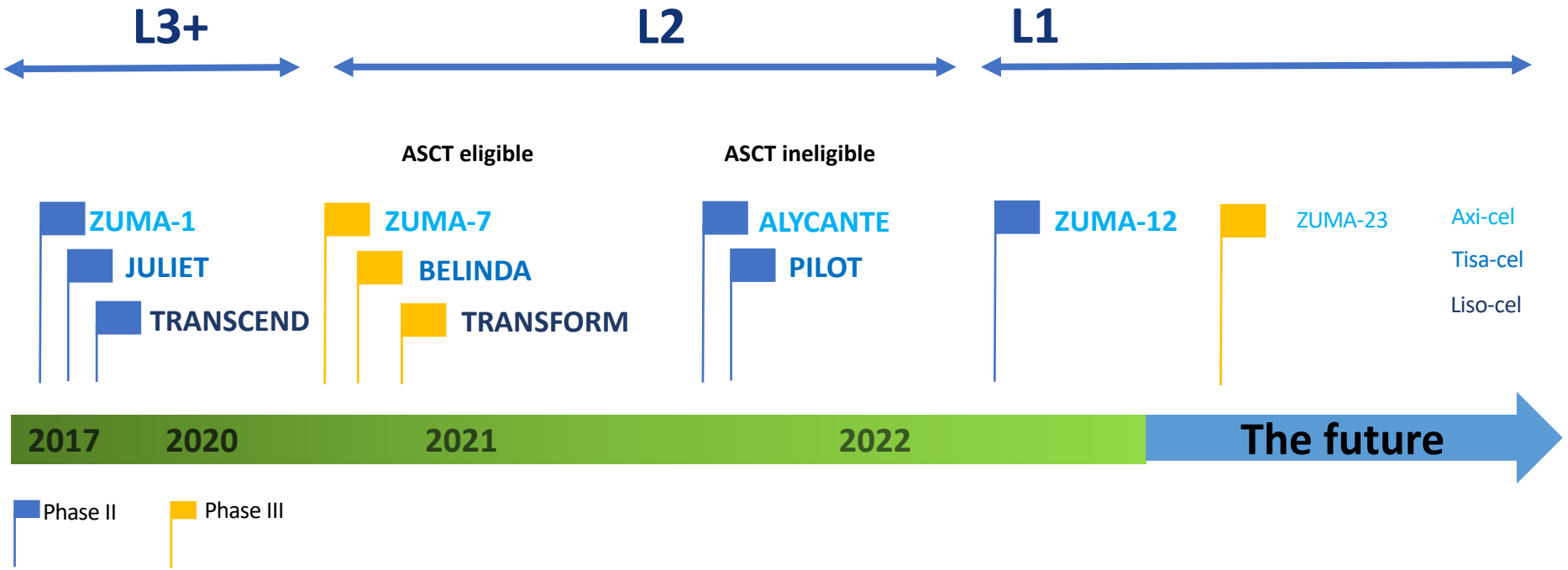
International and French Oncology Days

Journées Franco-Internationales d'Oncologie

CAR T-cells dans les lymphomes
Actualités en 2023

Catherine Thieblemont
Hôpital Saint-Louis, Paris

Trial landscape antiCD19 CART in aggressive B-cell lymphomas



Neelapu S et al .N *N Engl J Med 2017*
Locke FL, et al. Lancet Oncol. 2018
Schuster SJ, et al. *N Engl J Med.* 2019
Abramson JS, et al. *Lancet.* 2020

Locke FL, etal. N Engl J Med. 2021
Bishop MR, etal. N Engl J Med. 2021
Kamdar M, et al. ASH 2021; Abstract 91

Sehgal et al. Lancet Oncol 2022
Houot et al, Abstr #166, ASH 2022

Neelapu S. Nat Med. 2022 ;28:735-742

Line 3+

Efficacy : PFS and response rate in aggressive B-cell lymphoma

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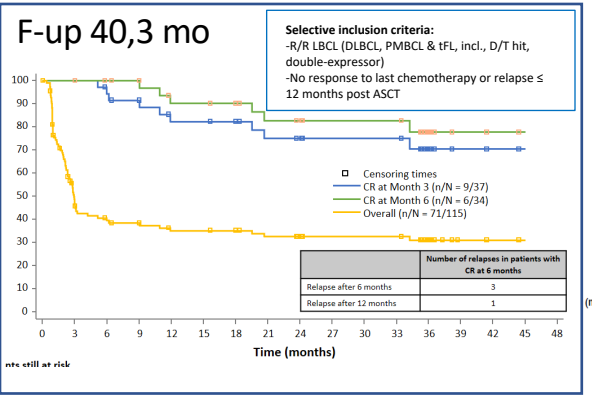
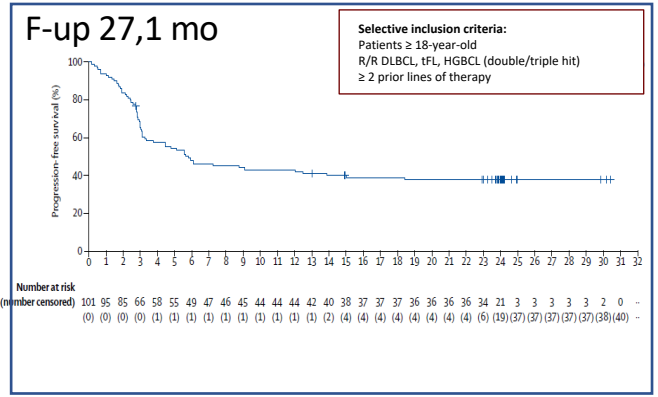
JULIET



Efficacy, %	n = 115
ORR[a], %	52%
CR[a], %	40%
Median DOR (95% CI), months	
PFS at 12 months (95% CI), %	83%
OS at 12 months (95% CI), %	49%

Schuster SJ, et al. *N Engl J Med.* 2019

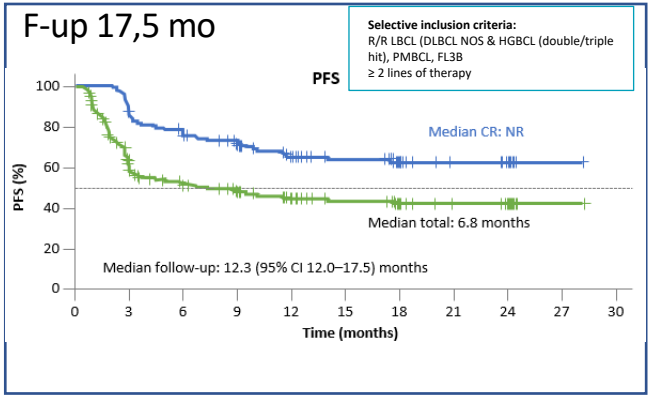
ZUMA-1



Efficacy, %	n = 101
ORR[2]	83%
CR[2]	58%
2-year PFS%	
Patients with CR at 3 months	72%
Patients with PR at 3 months	75%
Patients with SD at 3 months	22%
4-year OS[1]	44%

Locke FL, et al. Lancet Oncol. 2018

TRANSCEND-001



Efficacy, %[1]	n = 256
ORR	73%
CR	53%
2-year PFS	42%
2-year OS	45%

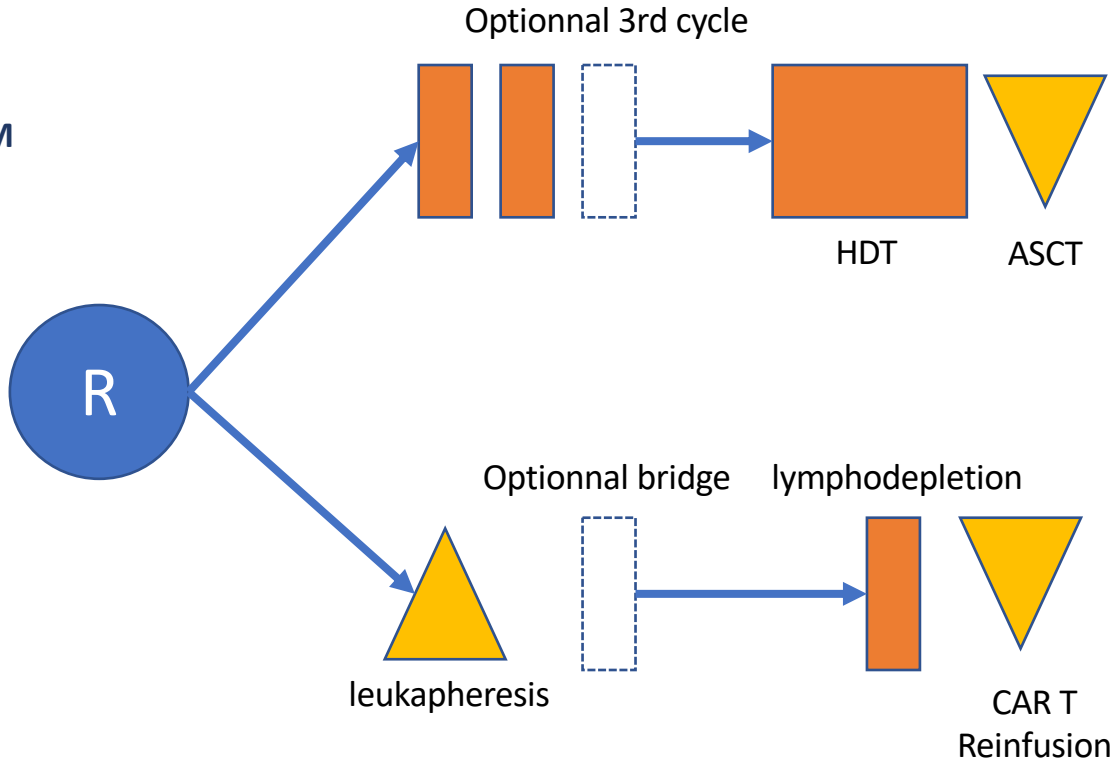
Abramson JS, et al. *Lancet.* 2020

Line 2

Axi-cel **ZUMA-7**

Tisa-cel **BELINDA**

Liso-cel **TRANSFORM**



Results

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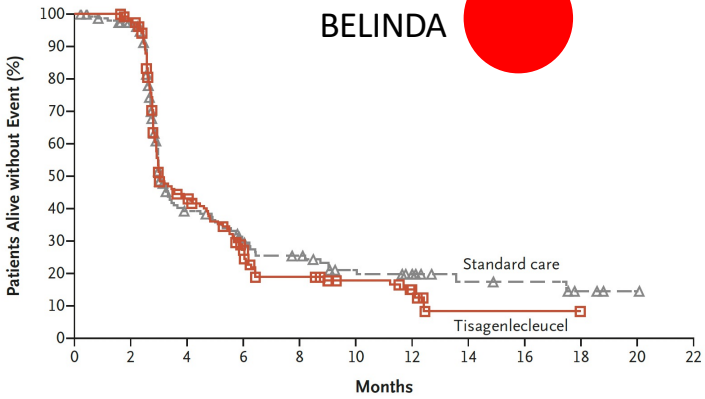
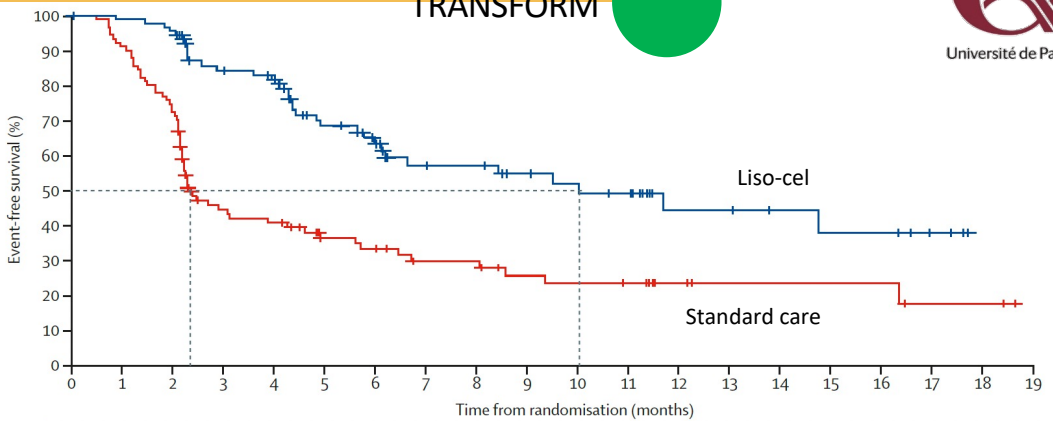
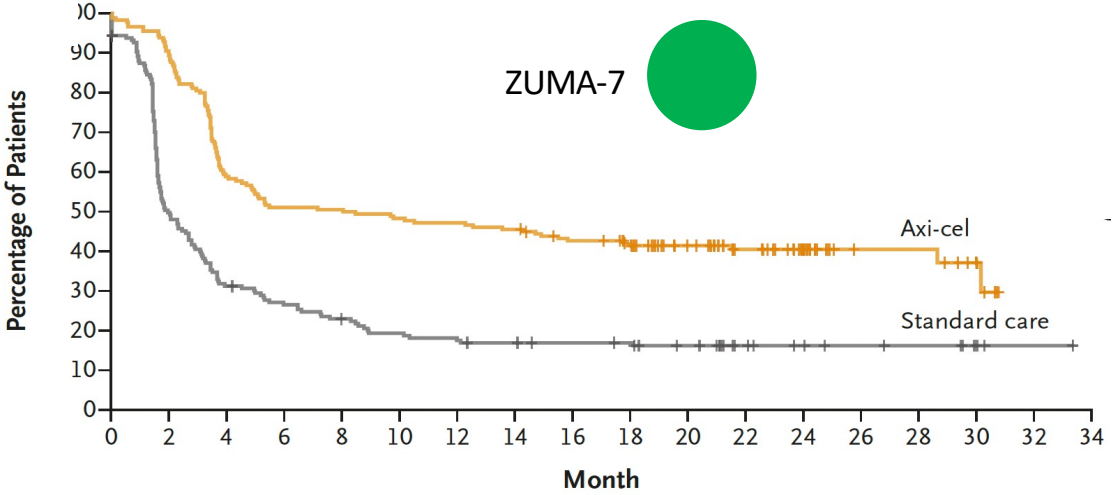
BELINDA



TRANSFORM



ZUMA-7



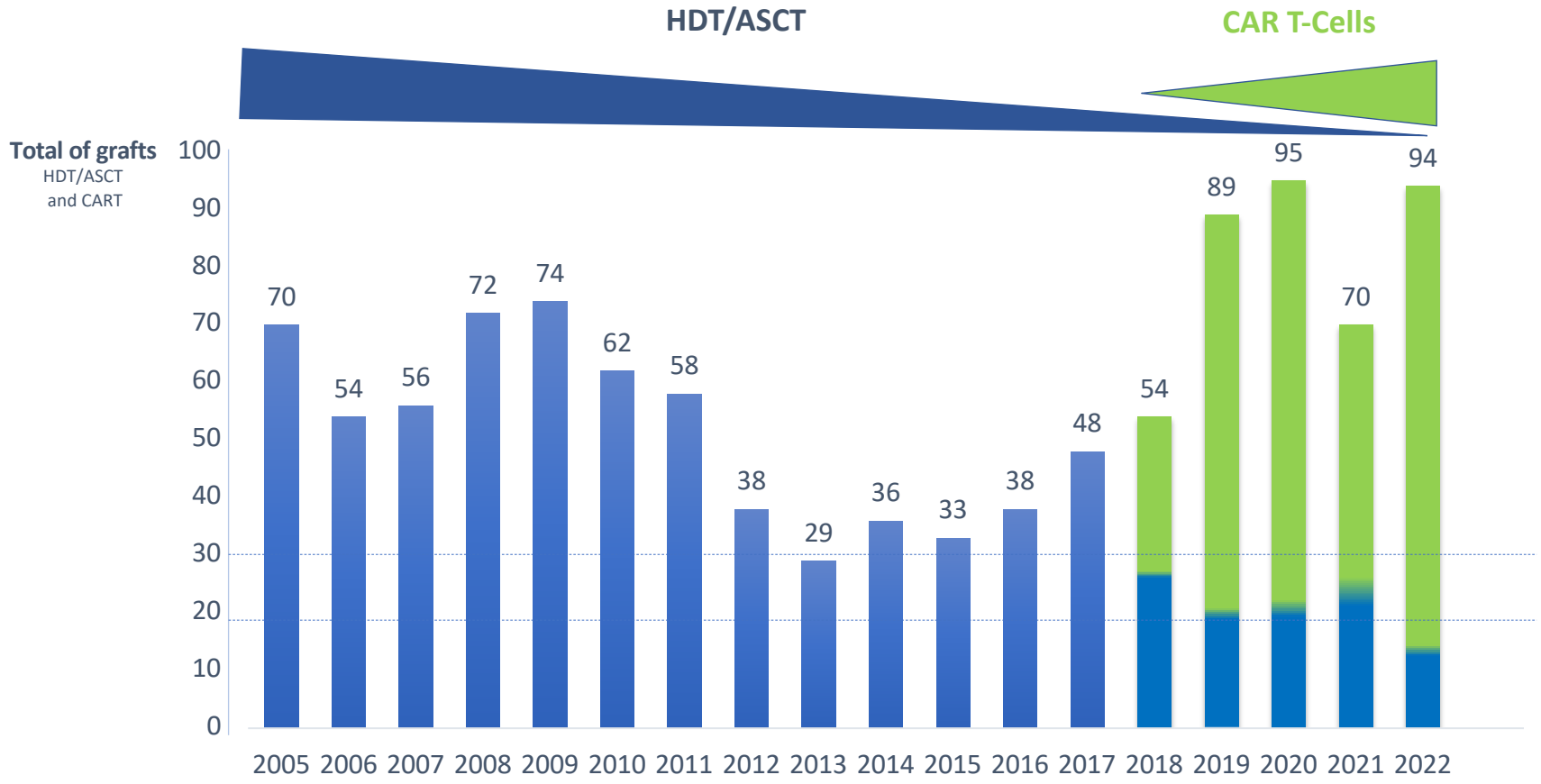
Bishop et al. NEJM 2022
Lock et al. NEJM 2022
Kamdar et al. Lancet 2022

Trial design differences

	# pts	Specific event definition	Bridging	Lympho depletion (Flu/EDX)	Dose of CAR T-cells	Crossover	FU
BELINDA	160+162	no	yes	Flu/Cy **25/250 mg/m2** for 3days or Bendamustine 90 mg/m2 for 2days	**0.6–6 x 10^8 Totale dose**	**yes**	-
ZUMA-7	179+180	Switch of salvage (eg R-DHAP → R-ICE)	No (steroids only)	Flu/Cy **30/500 mg/m2** for 3days	**2 x 10^6 /kg**	**no**	**24.9 mo**
TRANSFORM	92+92	no	yes	Flu/Cy **30/300 mg/m2** for 3days	**0.5–1.1 x 10^8 Totale dose**	**yes**	**6.2 mo**

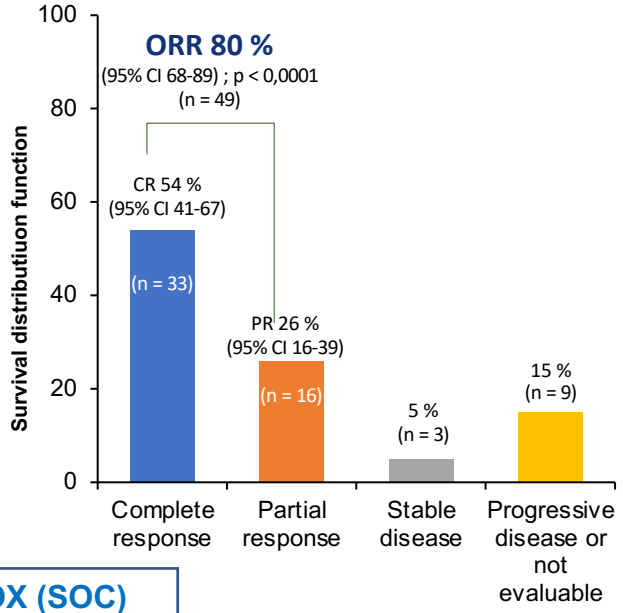
Bommier C et al. Comparing apples and oranges: The ZUMA-7, TRANSFORM and BELINDA trials. Hematological Oncology. 2022;1–4.

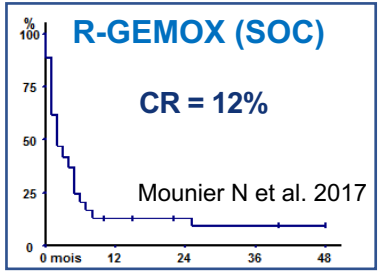
Intensification vs Imunotherapy



PILOT study

ASCT-ineligible





	Patients who received lisocabtagene maraleucel (n = 61)
Cytokine release syndrome, neurological events, or both	30 (49 %)
Cytokine release syndrome	
Any grade	23 (38 %)
Grade 1	11 (18 %)
Grade 2	11 (18 %)
Grade 3	1 (2 %)
Grade 4 or 5	0
Time to onset, days	4 (3-7)
Time to resolution, days	4 (2-5)
Neurological events	
Any grade	19 (31 %)
Grade 1	11 (18 %)
Grade 2	5 (8 %)
Grade 3	3 (5 %)
Grade 4 or 5	0
Time to onset, days	7 (5-12)
Time to resolution, days	6 (3-11)

Sehgal et al. Lancet Oncol 2022

Phase 2 ZUMA 12 : axi-cel in frontline in high-risk DLBCL

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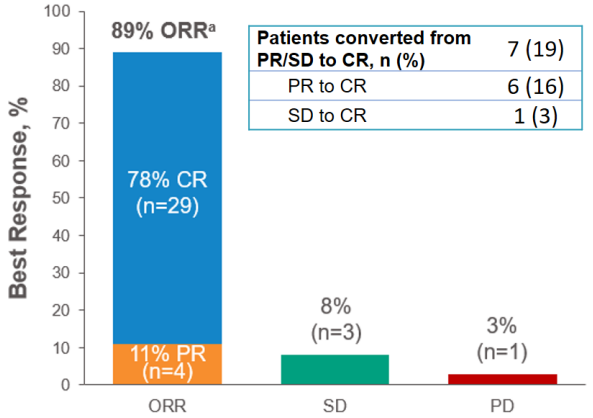
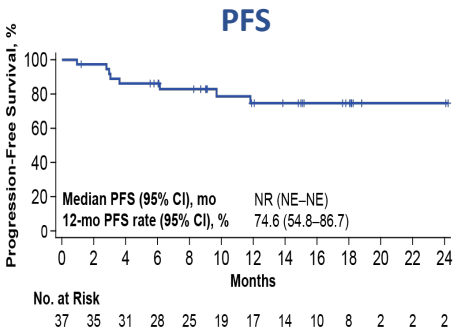
Inclusion criteria

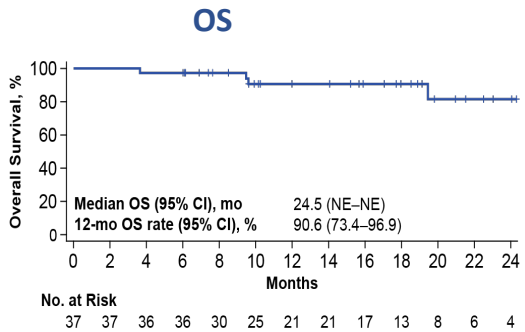
High-risk LBCL at baseline

- **High-grade BCL, with *MYC* and *BCL2* and/or *BCL6* translocations, or**
- **LBCL with IPI score ≥3 any time before enrollment**

***AND* Pos TEP** (DS 4 or 5) **after 2 cycles of R-Chemo dynamic Risk Assessment**







Neelapu S et al. Nat Medecine 2022

Novel algorithm in aggressive B-cell lymphomas

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LINE 1	LINE 2	LINE 3+

R-CHOP

CR

Eligible for transplant

- **Late relapse > 12mo after end of 1rst line**

  R-ICE, RDHAC/X, R- → **HDT/ASCT**

  CR

  No CR

- **Early relapse > 12mo after end of 1rst line**

  CAR T candidate
  R/R < 12 mo
  Liso-cel
  Axi-cel with bridging

Non eligible for transplant

R-GEMOX
Tafa-LEN
Pola-BR

Tisa-cel
Liso-cel
Axi-cel

Alternative
R-platin based chemo
Tafasitamab-Lenalidomide
Pola-BR

Clinical trials : bispecifics

3rd line approved
Selinexor
Loncastuximab tesirine

Supportive care

For Review : Westin & Sehn. Blood 2022; Frontzak et al .The Adv Hematol 2022; Ngu et al. Hematol malignancies 2022

Novel algorithm in aggressive B-cell lymphomas

Université de Paris

LINE 1	LINE 2	LINE 3+

CR

R-CHOP

Eligible for transplant

- **Late relapse > 12mo after end of 1rst line**

R-ICE, RDHAC/X, R- → **HDT/ASCT** → CR ↑ / No CR

- **Early relapse > 12mo after end of 1rst line**

CAR T candidate
R/R < 12 mo
Liso-cel
Axi-cel with bridging

Non eligible for transplant

R-GEMOX
Tafa-LEN
Pola-BR

Tisa-cel
Liso-cel
Axi-cel

Alternative
R-platin based chemo
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Supportive care

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CAR T-cells in B-cell lymphomas

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	Axi-cel	Tisa-cel	Liso-cel
Agressive B-cell lymphomas	• **≥ 2 Lines** DLBCL NOS , PMBL, HGBCL, Tr FL • **Line 2 – Transplant eligible** HIV infected pts	• **≥ 2 Lines** DLBCL NOS, PMBL, HGBCL	DLBCL NOS , HGBCL, PMBL, Transformed / indolent L., FL 3B • **Line 2 – Transplant eligible**
MCL	• **≥ 2 Lines**, including one with BTK inihbitor		
FL	• **≥ 2 Lines**	• **≥ 2 Lines**	

CAR T-cells in B-cell lymphomas in 2018

	Ligne 1	Ligne 2	Ligne 3+	Tox CRS,ICANS séjours SI
DLBCL				X
HGBCL				X
PMBL				x
Transf. FL				x
PCNSL				
Richter				
Transf. MZL/SLL				x
Aggressive BCL HIV+				
MCL				x
FL				x
FL 3B				x
MZL				
Hodgkin				X
CLL				X
T-cell lymphoma				

indication d'autogreffe

2018

- Kymriah (Tisa-cel) : Adult patients with R/R LBCL, L3+
  DLBCL NOS, PMBL, HGBCL
- Yescarta (Axi-cel) : Adult patients with R/R LBCL, L3+
  DLBCL NOS, PMBL, HGBCL Tr FL
  HIV infected pts

Indications CAR T-cells in B-cell lymphomas in 2023

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	Ligne 1	Ligne 2	Ligne 3+	Tox CRS,ICANS séjours SI
DLBCL				X
HGBCL				X
PMBL				x
Transf. FL				x
PCNSL				x
Richter				x
Transf. MZL/SLL				x
Aggressive BCL HIV+				x
MCL				x
FL				x
FL 3B				x
MZL				
Hodgkin				X
CLL				X
T-cell lymphoma				

+ 5 indications

indication d'autogreffe

2018

- Kymriah (Tisa-cel) : Adult patients with R/R LBCL, L3+ DLBCL NOS, PMBL, HGBCL
- Yescarta (Axi-cel) : Adult patients with R/R LBCL, L3+ DLBCL NOS, PMBL, HGBCL Tr FL - HIV infected pts

2020

- Tecartus (Axi-cel) : Adult patients with R/R MCL, L3+

2021

- Kymriah (Tisa-cel) : Adult patients with R/R FL, L3+

2022

- Breyanzi (Liso-cel) : Adult patients with R/R LBCL, L2 DLBCL NOS, PMBL, HGBCL, Tr indolents (except Richter)
- Yescarta (Axi-cel) : Adult patients with R/R LBCL, L2 DLBCL NOS, PMBL, HGBCL Tr indolents
- Yescarta (axi-cel) : Adult patients with R/R FL, L4+

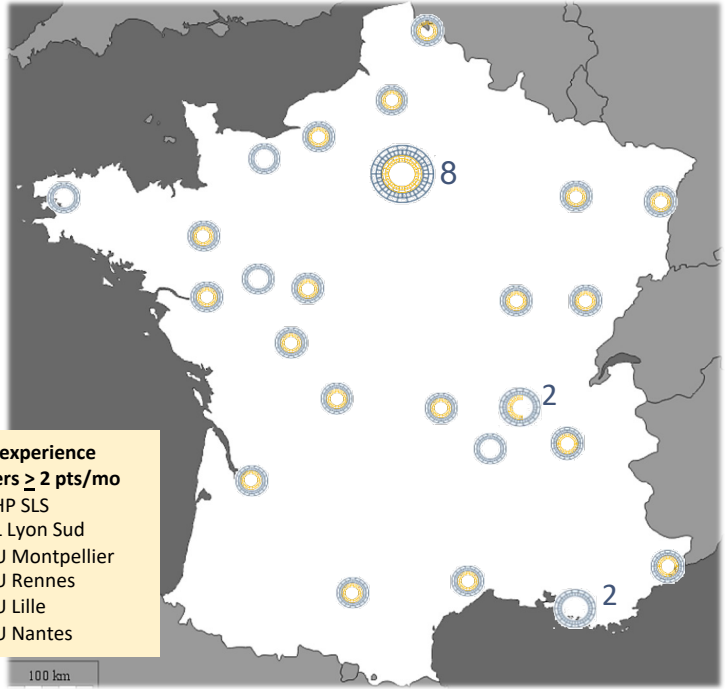
2023

- Clinical trials CAR T-cells and Bispecific T-cell engagers antibodies

➡ In first line

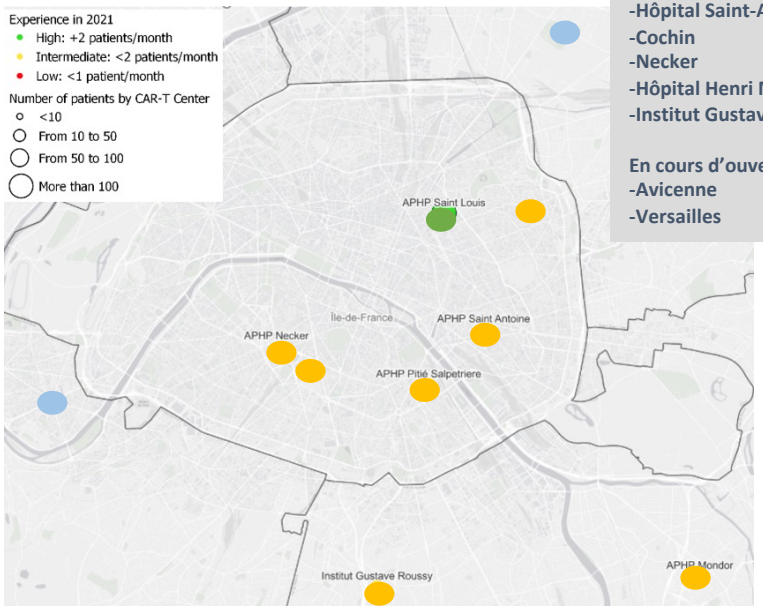
CAR T-cells sur le plan national

34 activated sites - 36 identified sites



High experience centers ≥ 2 pts/mo
- APHP SLS
- HCL Lyon Sud
- CHU Montpellier
- CHU Rennes
- CHU Lille
- CHU Nantes

Ile de France

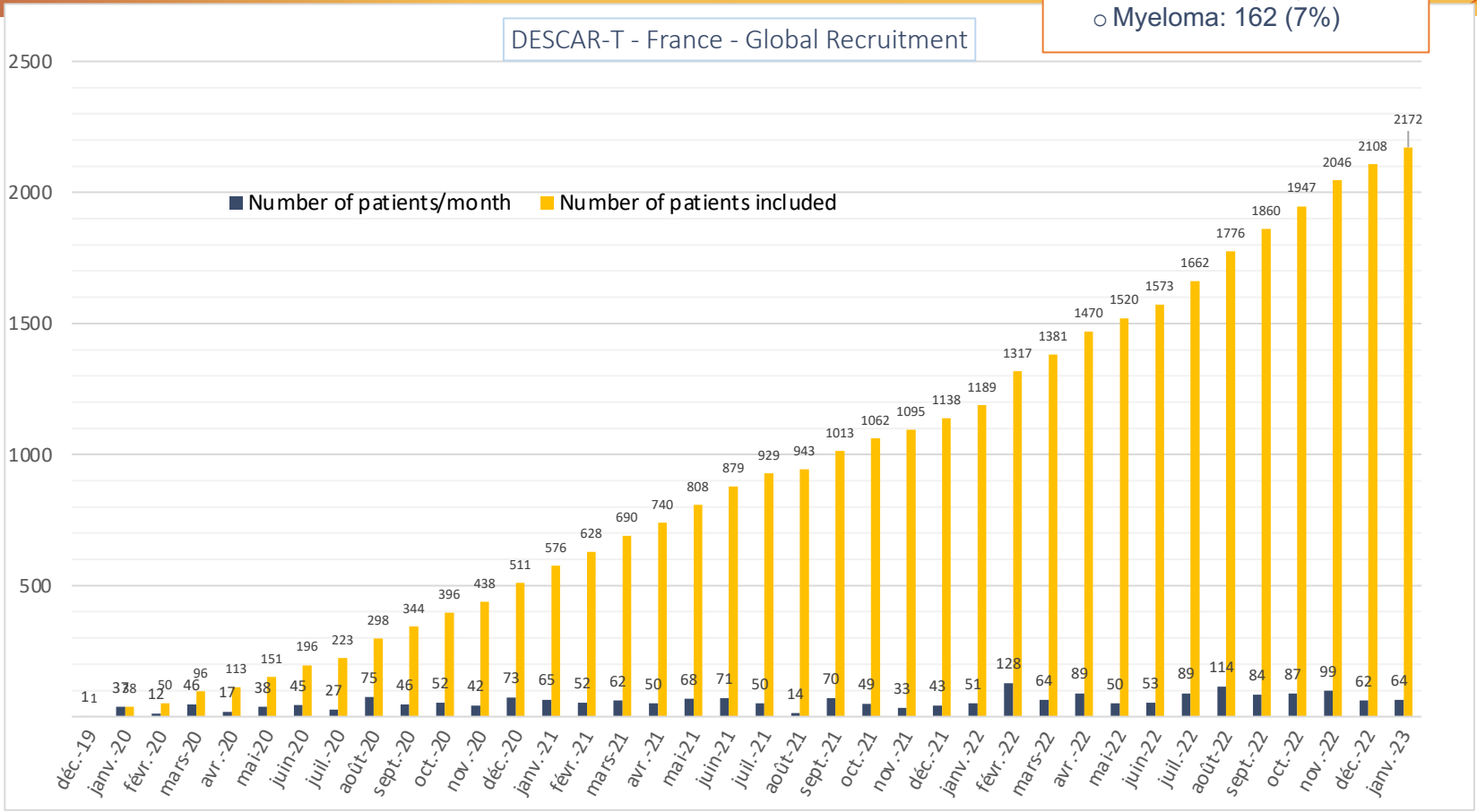


-Hôpital Saint-Louis
- Robert Debré
-La Pitié – Salpétrière
-Hôpital Saint-Antoine
-Cochin
-Necker
-Hôpital Henri Mondor
-Institut Gustave Roussy

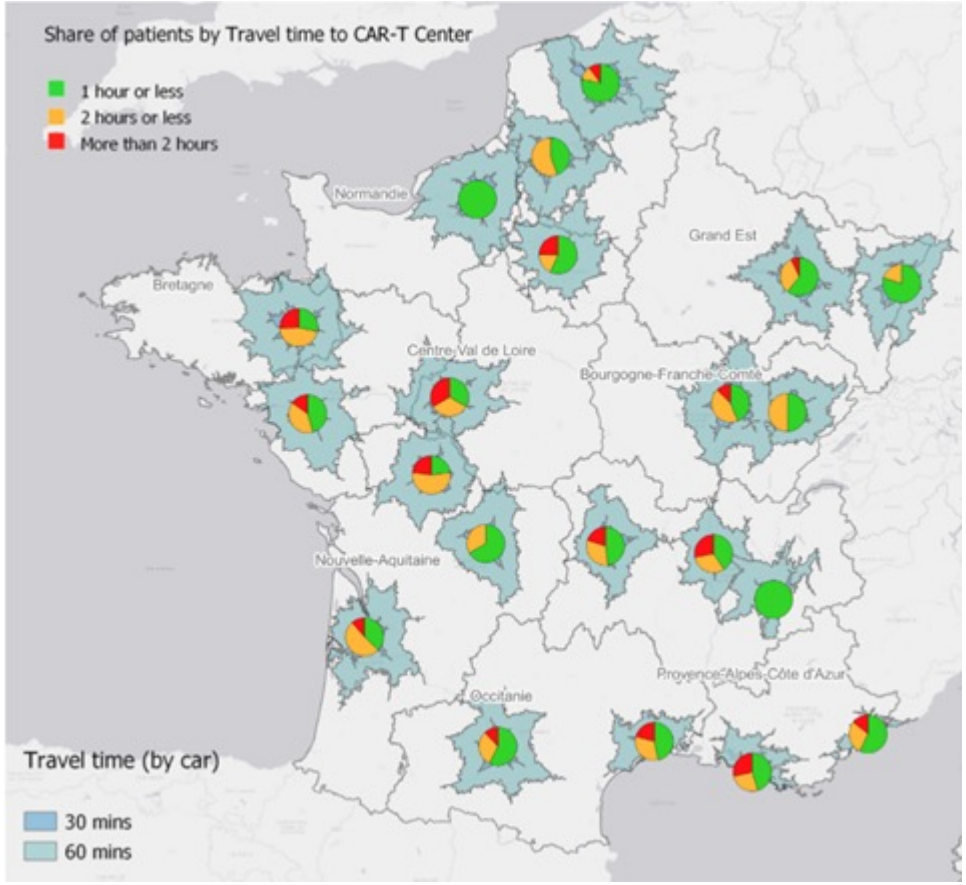
En cours d'ouverture
-Avicenne
-Versailles

The French DESCAR-T registry

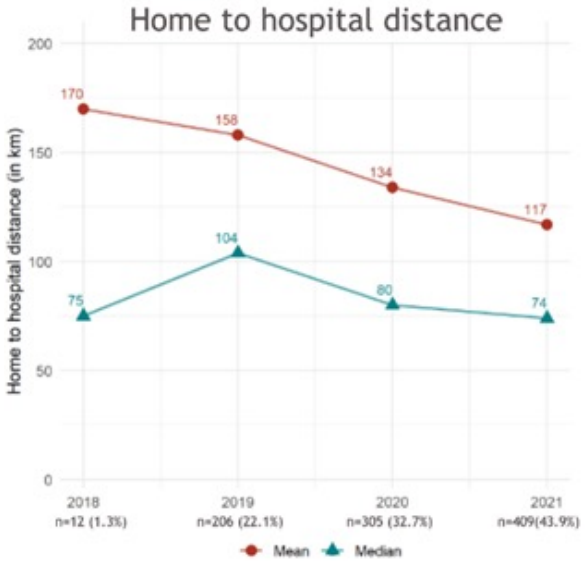
Inclusions: 2172 patients
- Lymphoma: 1835 (85%)
- B ALL: 175 (8%)
- Myeloma: 162 (7%)



Geographical distribution of the patients



- In Paris, CART centers catch a large majority of the patients leaving beyond 2 hours from the CAR T center
- 25% of the patients live at more than 2 hours



Huguet et al. 2021

Cell immunotherapy : to use our own immunity to treat cancer

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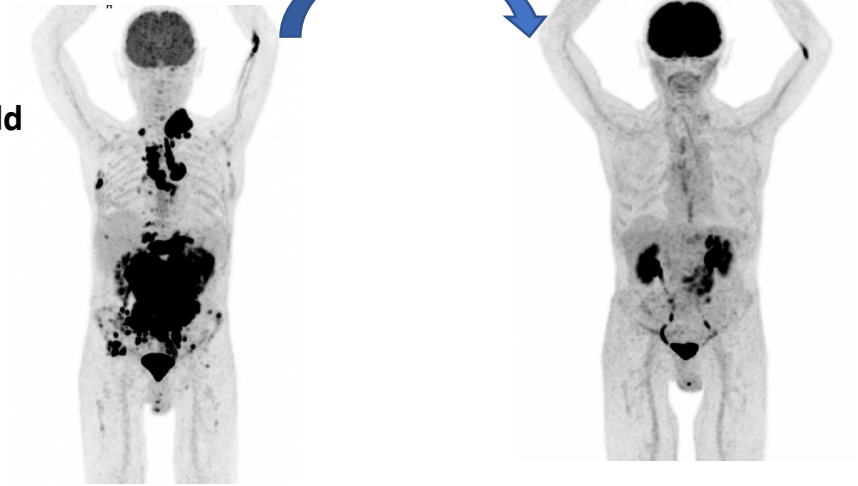
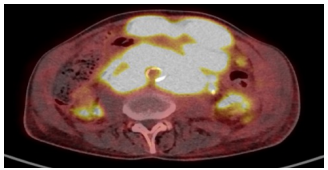
Case report . THE, male, 63 years old

- **R/R DLBCL**
- **3 prior lines**

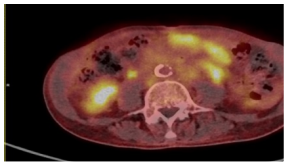
CAR T-cell



CURE



Metabolic tumoral volume 1200ml



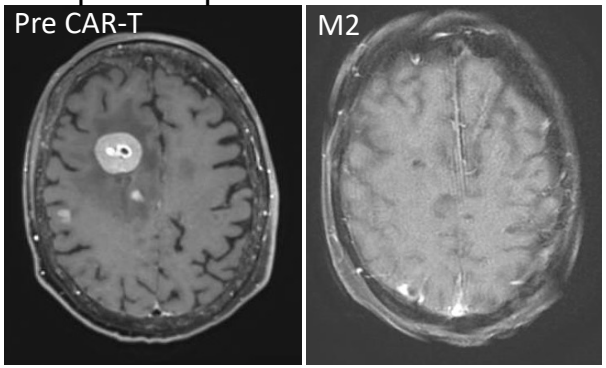
Primary CNS lymphoma

- Median follow-up: 8,5 mo

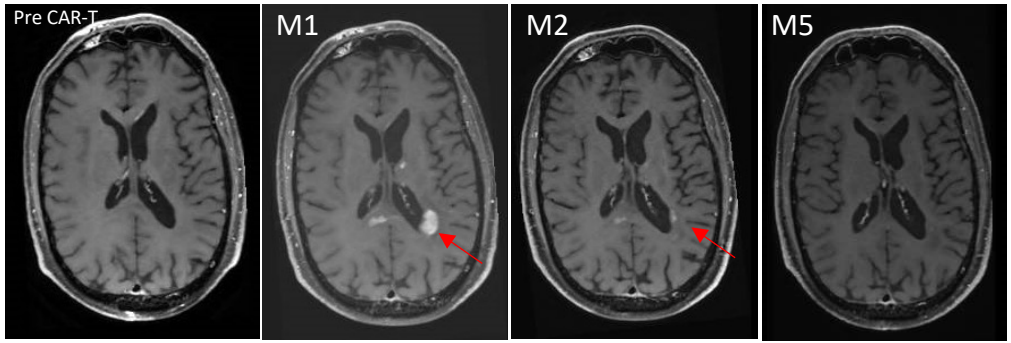
	LCP N = 9
Réponse à M1	
RG	6 (67%)
RC	3 (33%)
MP	2 (22%)
Réponse à M3	
RG	6 (67%)
RC	5 (56%)
MP	2 (22%)
Meilleure réponse	**5 (56%)**
RC	**1 (11%)**
RP	

Alcantara M., et al . Blood 2022

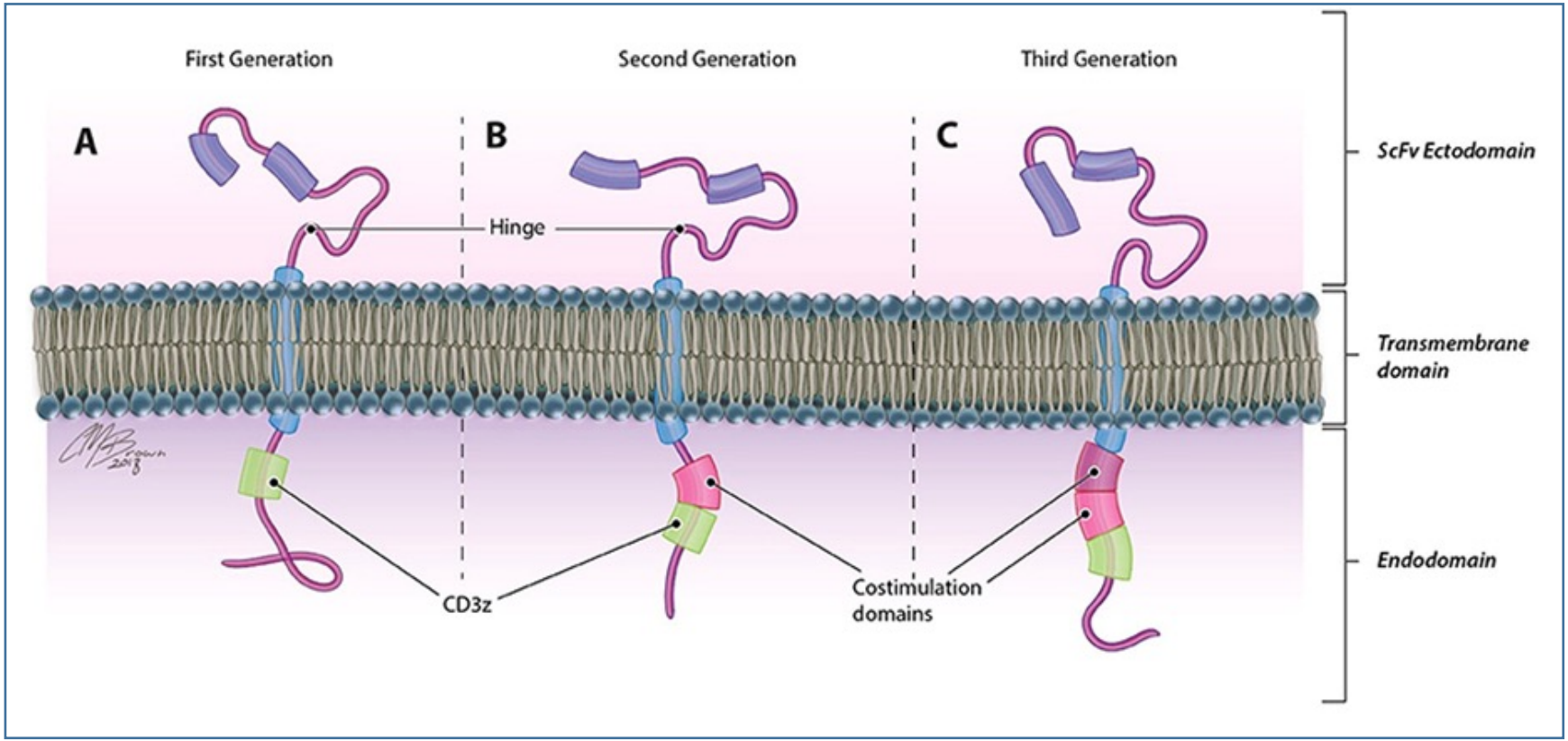
Complete response



Effet flare

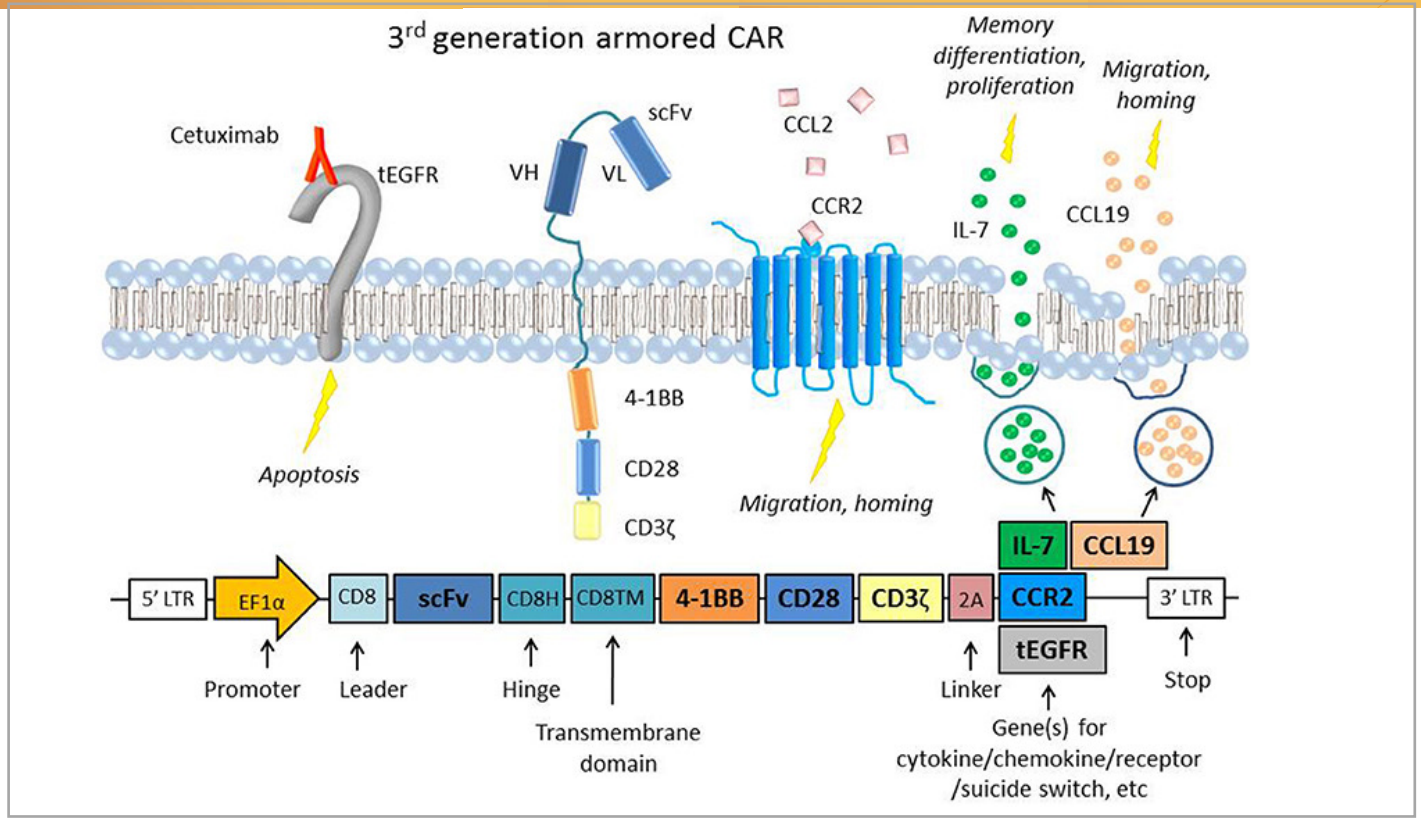


CAR T cells



Martinez *et al.* Frontier in Immunology - 2019

3rd and 4rd generation CAR T



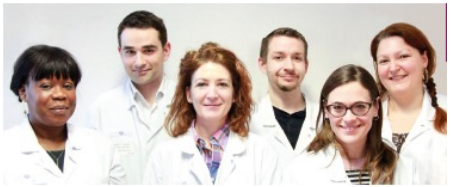
Martinez *et al.* Frontier in Immunology - 2019

CONCLUSION

- Cell immunotherapy is a revolution
- exhibit promising results with potential cure in 30-40% of the refractory LBCL
- Challenges are multiple
  - To offer personalized medecine based on pretreatment characteristics based on biology and functional imaging
  - To predict outcome
  - To overcome toxicities
  - To keep a good quality of life
  - Easy access to all the patients

APHP, Hôpital Saint-Louis, Paris, France

Cell ImmunoT program



Apheresis
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Actualités des CAR-T cells dans la Leucémie Aiguë Lymphoblastique B

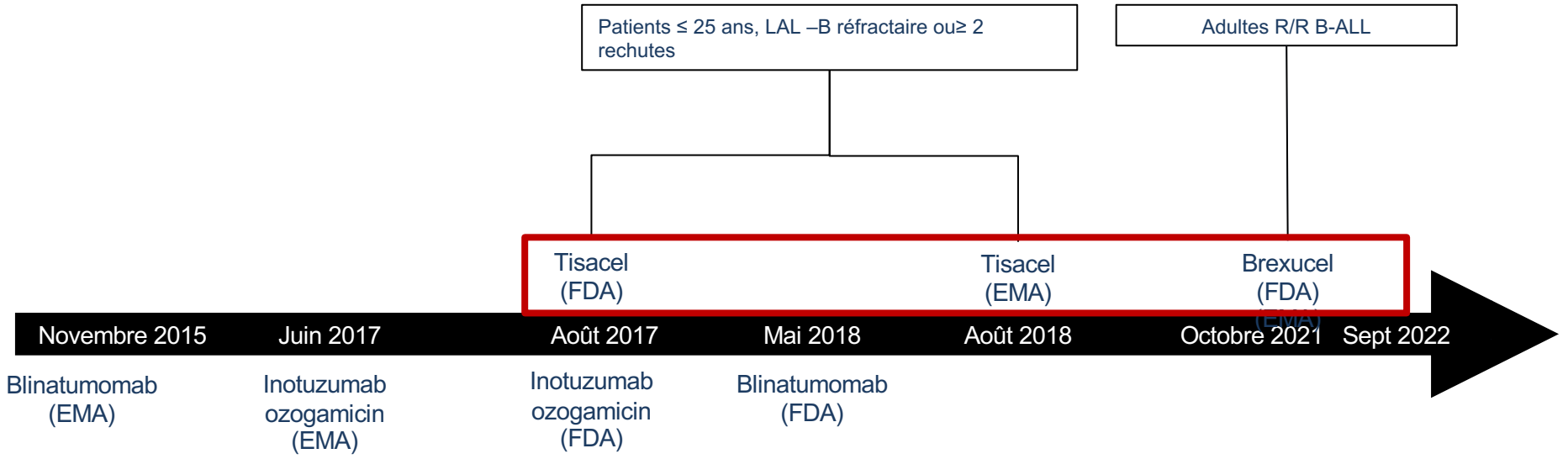
Dr. Eolia Brissot, MCU-PH

Service d'hématologie clinique et thérapie cellulaire

Hôpital Saint-Antoine, APHP, Paris

Liens d’intérêt : Research funding, honorarium, speaker’s fees and travel expenses from Novartis, Astellas, Alexion, Jazz Pharmaceuticals, Gilead, MSD, Keocyt, Amgen

CAR T-cell anti-CD19 pour LAL-B
calendrier des approbations FDA/EMA



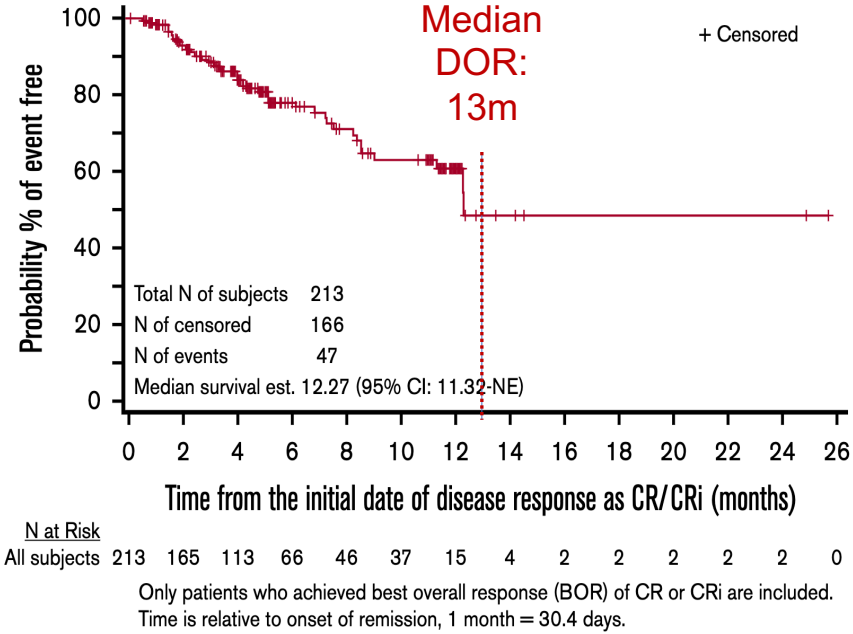
Tisacel, tisagenlecleucel
Brexucel, brexucabtagene autoleucel

Maude et al, NEJM, 2018; Shah et al, Blood, 2021; Shah et al The Lancet, 2021

Pasquini et al. Blood Advances. 2020

Enfants/AJA

Durée de réponse après tisacel

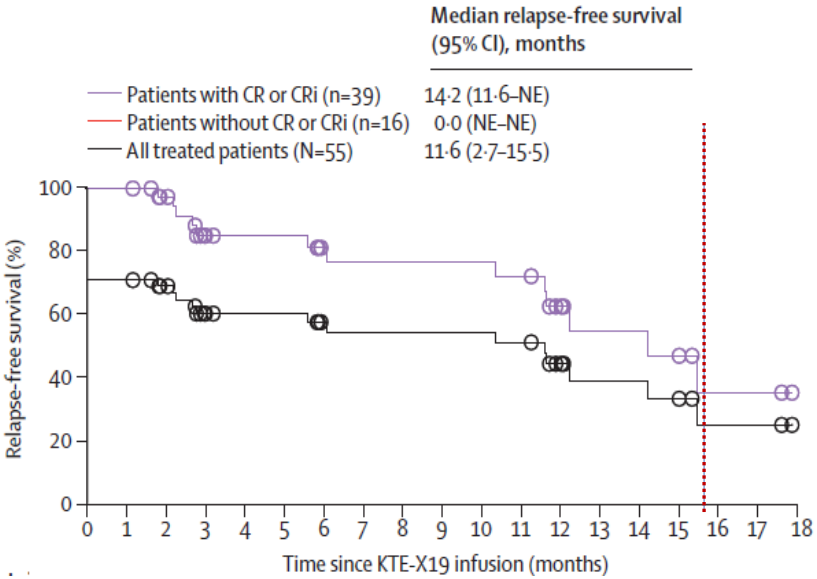


Only patients who achieved best overall response (BOR) of CR or CRi are included.
Time is relative to onset of remission, 1 month = 30.4 days.

Shah et al. JCO 2021 Zuma-3

Adultes

Durée de réponse après brexucel

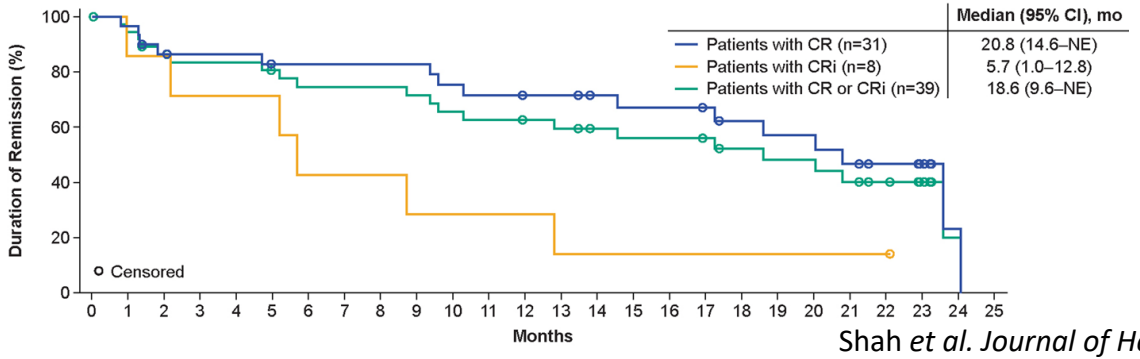


Two-year follow-up of KTE-X19 in patients with R/R B-ALL in ZUMA-3 and its contextualization with SCHOLAR-3, an external historical control study

Résultats actualisés sur l'efficacité et l'innocuité de l'étude ZUMA-3 sont rapportés chez les patients traités en phase 2 et dans analyse combinée des patients de phase 1 et 2 traités à la dose la dose pivot de KTE-X19 (1 × 106 cellules CAR T/kg)

score de propension: apparier les patients adultes atteints de LALB R/R et traités dans des essais cliniques historiques

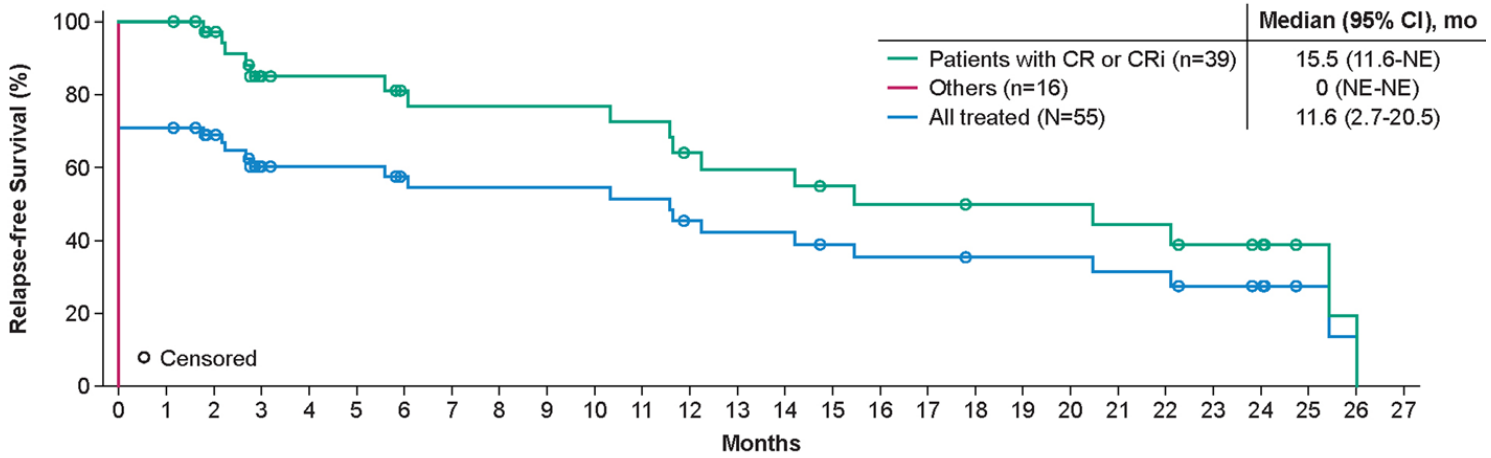
Mise à jour: suivi médian 27 mois- phase 2 traités (N = 55)
le taux de CR/Cri : 71%
11 pts ont été allogreffés- médiane de 100 j



Shah *et al. Journal of Hematology & Oncology (2022) 15:170*

Two-year follow-up of KTE-X19 in patients with R/R B-ALL in ZUMA-3 and its contextualization with SCHOLAR-3, an external historical control study

Survie sans rechute



Survie globale médiane: 25, 6 mois pour toute la population et non atteinte pour les patients en RC

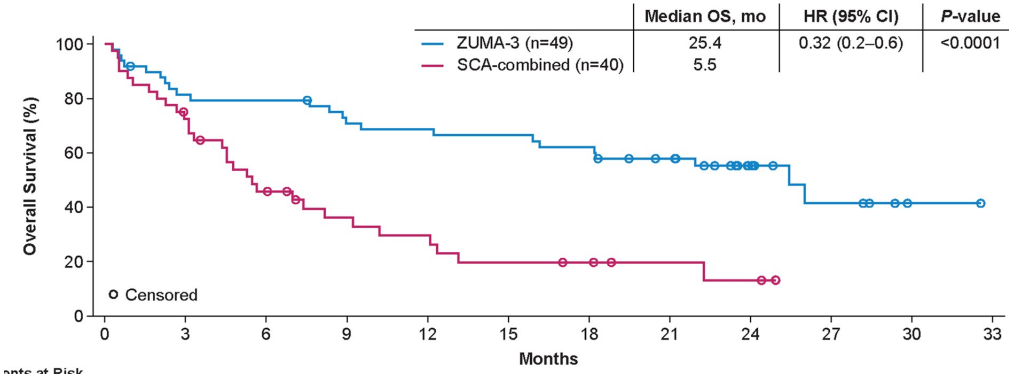
Shah *et al. Journal of Hematology & Oncology (2022) 15:170*

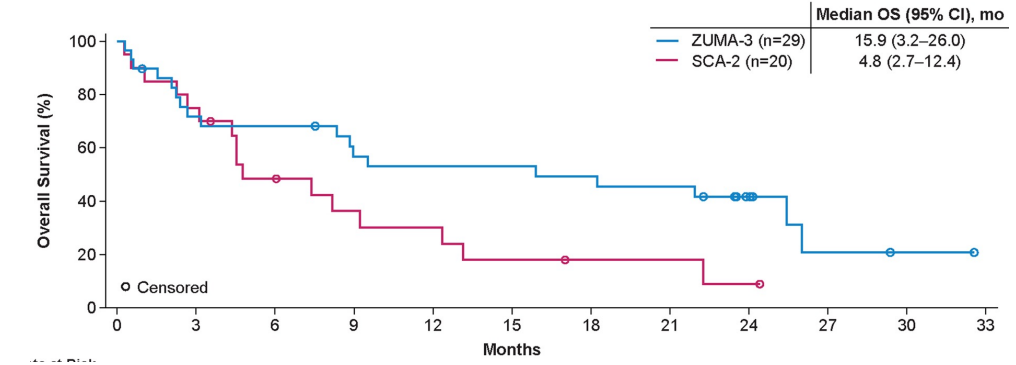
Two-year follow-up of KTE-X19 in patients with R/R B-ALL in ZUMA-3 and its contextualization with SCHOLAR-3, an external historical control study

Évènements indésirables: pas de nouveaux signaux

Pic d'expansion des CAR-T: Jour 15

À 6 mois, non détectable chez 79% des patients





Shah *et al. Journal of Hematology & Oncology (2022) 15:170*

LAL-B R/R: facteurs associés à la durée de la réponse après CAR T anti-CD19

Adult R/R B-ALL patients treated with defined-composition CD19 CAR T cells on phase I/II trial

Variable	Univariate HR (95% CI)	*P* value	Multivariable HR (95% CI)	*P* value
LDH (per 100 U/L, pre-lymphodepletion)	1.49 (1.22-1.80)	<.0001	1.39 (1.12-1.74)	.003
Bridging systemic therapy[a]	5.66 (2.56-12.5)	<.0001	-[b]	-
Platelet count (per 50,000/µL, pre-lymphodepletion)	0.57 (0.42-0.76)	.0002	0.65 (0.47-0.88)	.006
Extramedullary disease (Y)	3.57 (1.66-7.65)	.001	-	-
Fludarabine added to lymphodepletion (Y)	0.30 (0.13-0.66)	.003	0.34 (0.15-0.78)	.011
IL-6 (pg/mL, pre-lymphodepletion)	1.02 (1.01-1.03)	.005	-	-
Marrow blasts by flow cytometry (%)	1.01 (1.00-1.03)	.006	-	-
High-risk cytogenetics[d] (Y)	2.48 (1.12-5.50)	.03	-	-
Neutrophil count (1000/µL, pre-lymphodepletion)	0.73 (0.55-0.97)	.03	-	-
Soluble TNFRp55 (pg/mL, Day 0)	4.84 (1.07-21.8)	.04	-[c]	-
IL-2 (pg/mL, Day 0)	3.24 (1.05-10.0)	.04	-	-
IL-8 (pg/mL, pre-lymphodepletion)	1.78 (1.00-3.15)	.05	-	-
Soluble TIM-3 (ng/mL, pre-lymphodepletion)	1.05 (1.00-1.11)	.06	-	-
Dose level ($2x10^5$ vs $2x10^6$ CAR-T cells/kg)	0.51 (0.24-1.11)	.09	-	-
No. prior regimens (n)	1.13 (0.97-1.32)	.1	-	-
Prior allogeneic hematopoietic cell transplantation (Y)	1.65 (0.79-3.44)	.2	-	-
Prior blinatumomab therapy (Y)	1.27 (0.52-3.12)	.6		
ECOG performance status	1.18 (0.62-2.26)	.6	-	-
Age (years)	1.00 (0.98-1.01)	.7	-	-
Time from leukapheresis to lymphodepletion (days)	1.52 (0.64-3.62)	.3		
$CD4^+$:$CD8^+$ CAR-T cell ratio (peak expansion)	1.20 (0.86-1.68)	.3		
$CD4^+$:$CD8^+$ CAR-T cell ratio (AUC from day 0-28)	1.09 (0.76-1.55)	.6		
$CD4^+$:$CD8^+$ CAR-T cell ratio (fold change from infusion product to peak expansion)	1.21 (0.81-1.81)	.4		
CAR-T cell counts (transgene log_{10} copies/µg DNA, AUC28)	0.98 (0.56-1.71)	.9	-	-

Multivariable Cox model for EFS in patients in MRD-negative CR after CD19 CAR T-cell therapy (n=45)

Pediatric R/R B-ALL patients treated with SOC tisacel or investigational CD19 CAR T cells

Parameter	Parameter Estimate	SE	Chi-Square	*P*	Hazard Ratio	95% CI
Prior blina	**0.62**	**0.17**	**14.17**	**.0002**	**1.86**	**1.35 to 2.57**
Disease burden	0.93	0.15	35.90	< .0001	2.52	1.86 to 3.41
Primary refractory	–0.37	0.19	3.96	.047	0.69	0.48 to 0.99
CAR type[a]	0.65	0.18	13.42	.0002	1.93	1.36 to 2.74
Active EM	0.66	0.26	6.31	.01	1.94	1.16 to 3.25
PB blasts	0.77	0.17	20.57	< .0001	2.17	1.55 to 3.02

Multivariable Cox model for EFS (n=420)

Volume tumoral
Cinétique

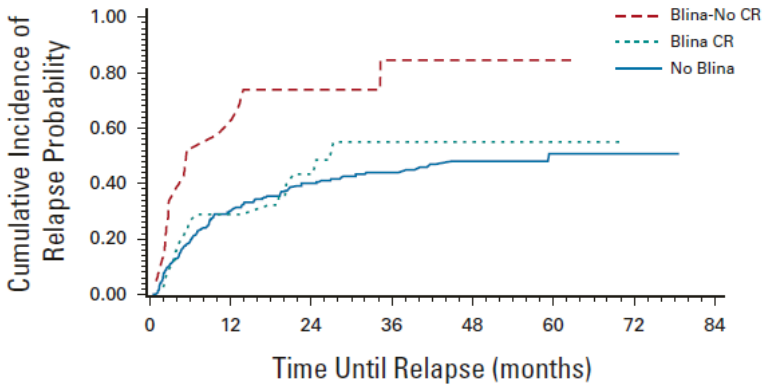
Persistance CAR T cell, fonctions

Hay K, Gauthier J et al. Blood 2019; Myers R et al. JCO 2021

L ‘absence de réponse au Blinatumomab et une masse tumorale importante sont associés à une moins bonne survie après CAR T- CELLS

- Etude rétrospectif multicentrique enfants et jeunes adultes atteints de LAL B R/R
- ayant reçu un CD19-CAR entre 2012 et 2019
- 420 patients : âge médian 12,7 ans
- tisagenlecleucel ou l'une des trois constructions CD19-CAR à l'étude entre 2012 et 2019
- 77 (18,3 %): blinatumomab au préalable.

Incidence cumulée de rechute



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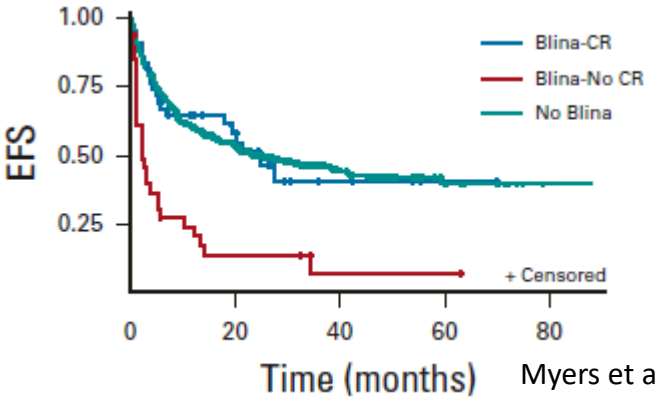


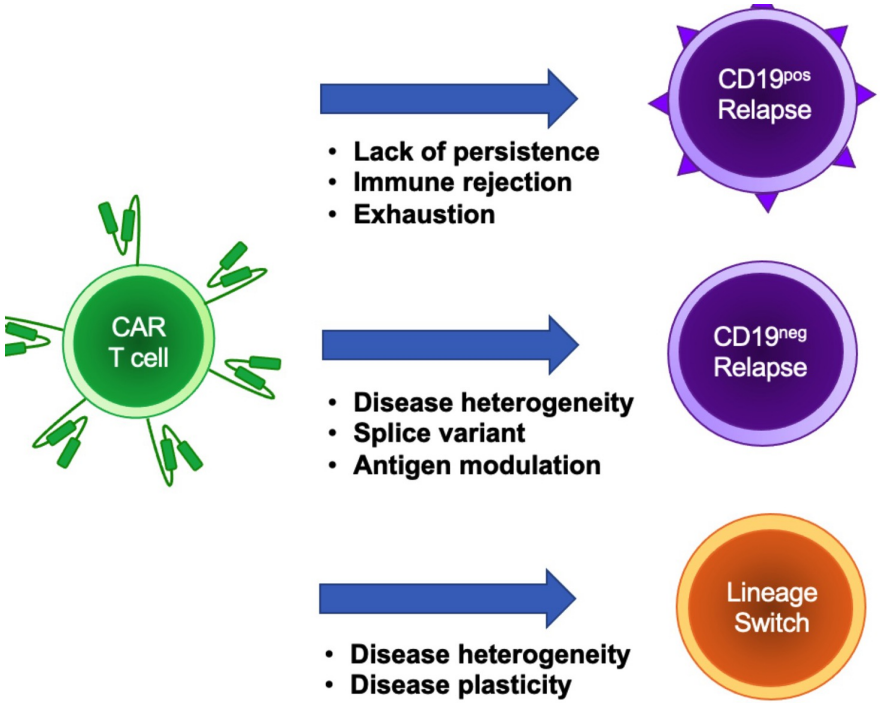
Myers et al. JCO 2022 Mar

Facteurs en pré-infusion ayant un impact sur l'immunophénotype de la rechute après l'utilisation de cellules T CAR CD19

- Trois principaux schémas de rechute prédominent :

- Cohorte : n= 420 - 163 rechutes
- Âge médian :12,7 ans

- Phénotype de rechute :
  - CD19 pos : 51%
  - CD19 négatif : 42 %.
  - Changement de lignée : 7%

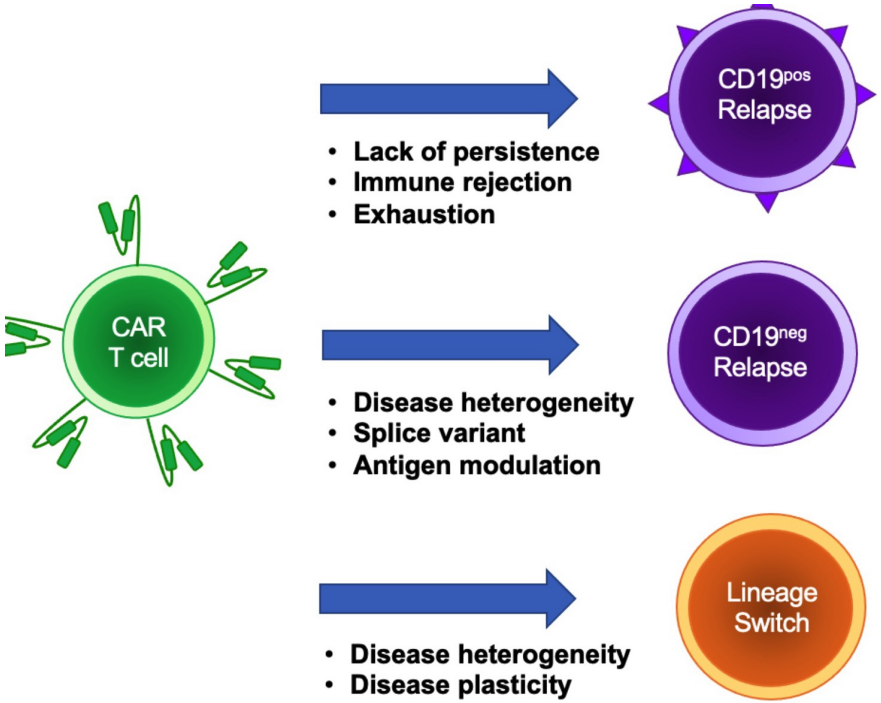


Lamble et al. Blood Adv. 2022

Facteurs en pré-infusion ayant un impact sur l'immunophénotype de la rechute après l'utilisation de cellules T CAR CD19

Analyse multivariée

- CD19 pos : 2 rémissions antérieures ou plus
- CD19 neg : moins de 7 ans, absence de KMT2Ar, type 4-1BB CAR, non-réponse antérieure au blinatumomab, charge de tumorale élevée (≥5% de blastes).
- Changement de lignage : KMT2Ar (HR : 32, p<0.0001)



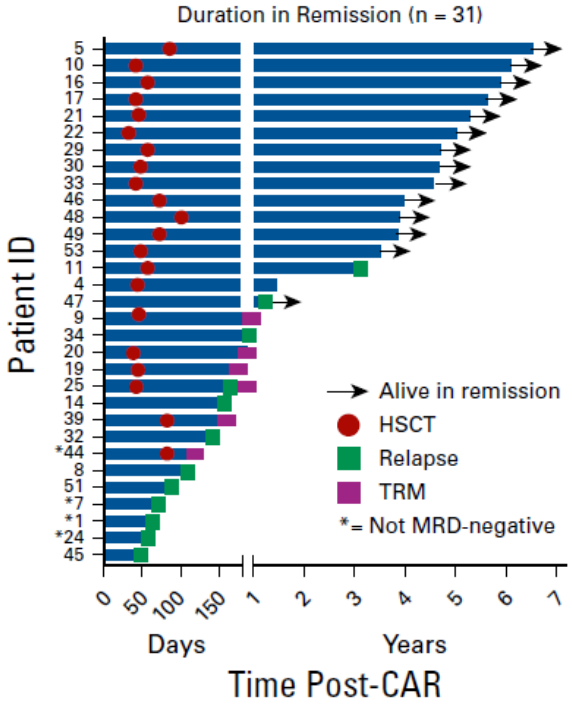
Lamble et al. Blood Adv. 2022

Allogreffe de CSH après CAR T cells

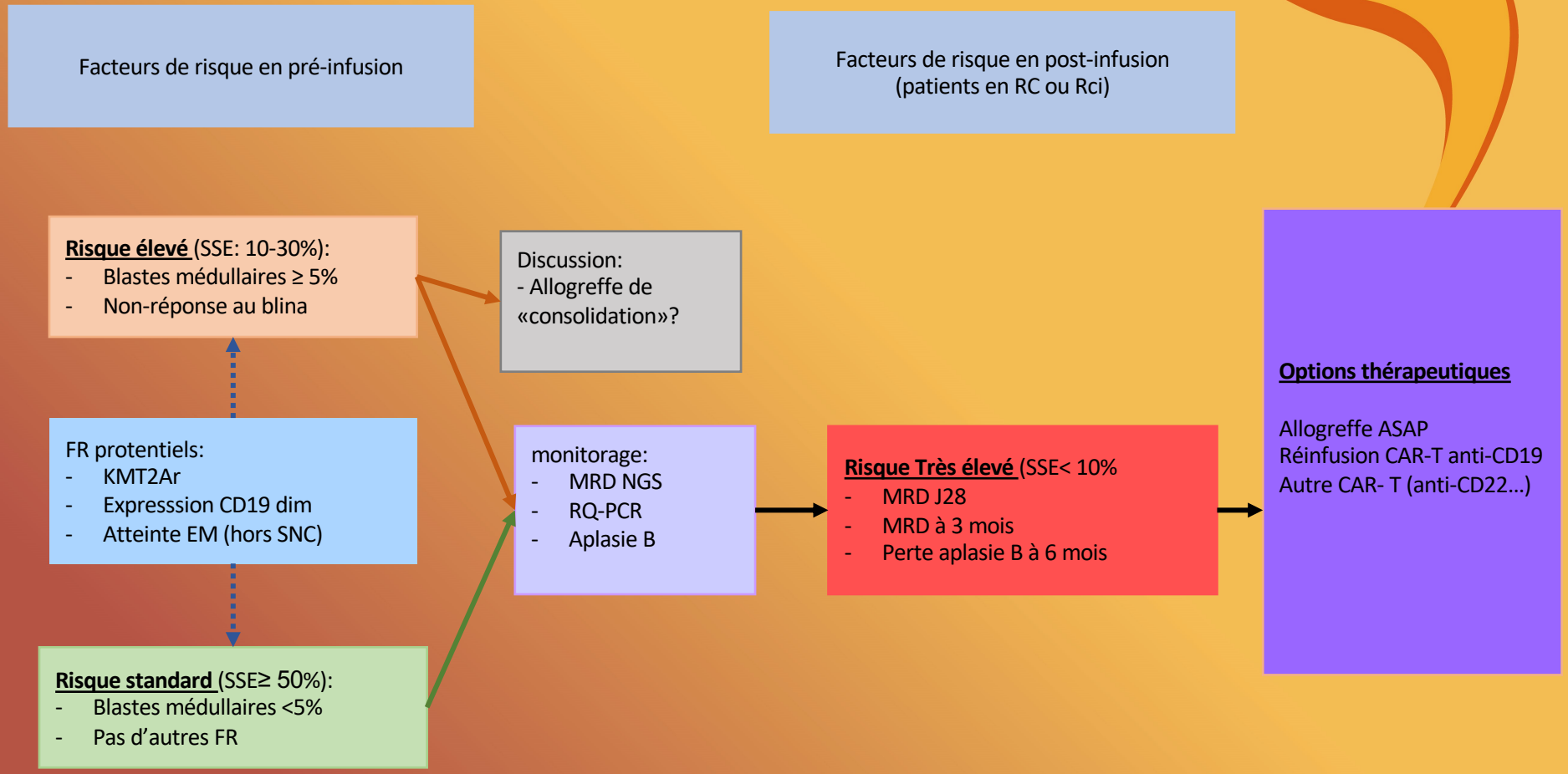
50 patients : âge médian de 13,5 ans (4,3-30,4)
62% ont obtenu une RC
21 des 28 (75,0 %) pts avec MRD négative ont été allogreffés

suivi médian de 4,8 ans
la SG médiane pour l'ensemble de la cohorte: 10,5 mois.
La SSE médiane :3,1 mois

La SG médiane à partir du J0 de l'allo-CSH: 5,8 ans
La SSE à 5 ans après l'allo-CSH était de 61,9 %
2 patients ont rechuté après allogreffe
L'incidence cumulée de la rechute après allogreffe était de 4,8% à 12 mois et de 9,5% à 24 mois.



Shah et al. JCO 2021



Selon Myers et al Blood 2023

Conclusion

La thérapie par CART cells est en train de transformer le traitement des LAL-B R/R, mais des défis importants restent à relever.

Bien que les CAR T cells anti-CD19 permettent l'obtention de taux élevés de MRD-négative chez 80 % des patients, les rechutes sont fréquentes.

Les stratégies actuelles visant à améliorer l'efficacité des CAR-T cells se concentrent sur l'amélioration des fonctions des CAR-T *in vivo*, les CAR-T multi-spécifiques (anti-CD19 et anti-CD22) et les nouveaux modèles de CAR.

L'accès à la thérapie par cellules CAR-T reste un défi majeur compte tenu du processus de fabrication et du coût.

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Dr Ramdane BELHOCINE
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Dr Laure RICARD
Dr Simona SESTILI
Dr Nicolas STOCKER
Dr Zoé VAN de WYNGAERT
Dr Anne VEKHOFF

“CAR-T cells dans le myélome multiple: actualités”

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I have the following relationships to disclose:

- Employment/leadership position/advisory role: No
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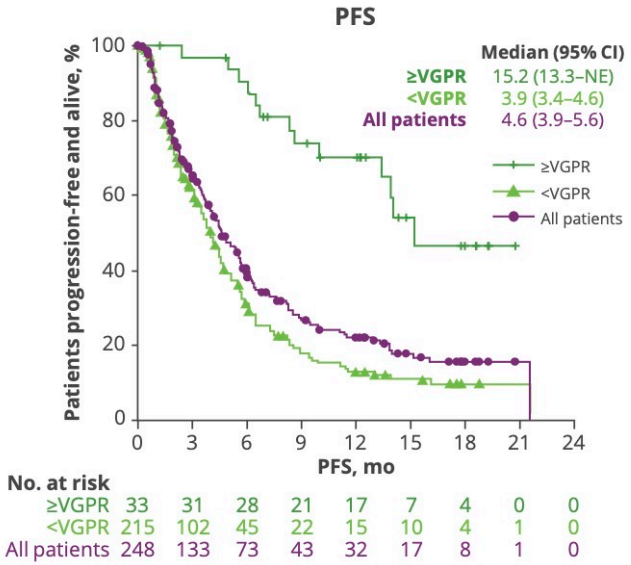
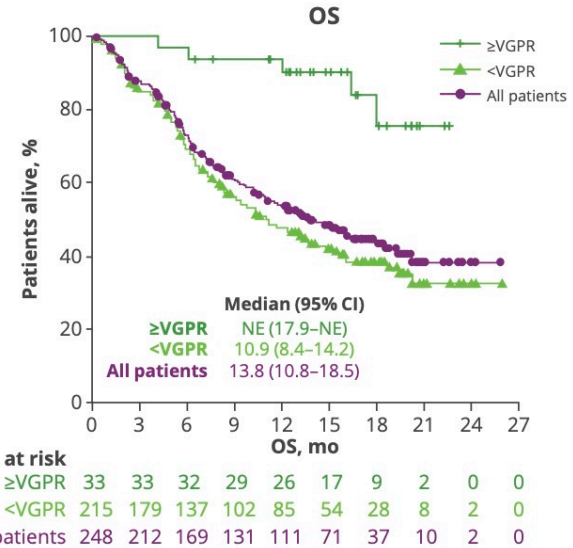
- Subsidies or donations: No
- Endowed departments by commercial entities: No
- Gifts and others: No

Triple-class exposed myeloma patients represent an unmet medical need population
Prospective observational LocoMMotion study (N=248)

- Median nº of PL: 4 (2-13)
- 73.4% were triple-class refractory

ORR 31.5% (95% CI: 25.7 – 37.6)





- Patients received 91 unique treatment regimens and 65.3% of patients received combinations of 3 drugs
- Drugs most frequently used were: Corticosteroids (89.5%), PI (54.0%), IMID (47.6%) and alkylating agents (43.1%)

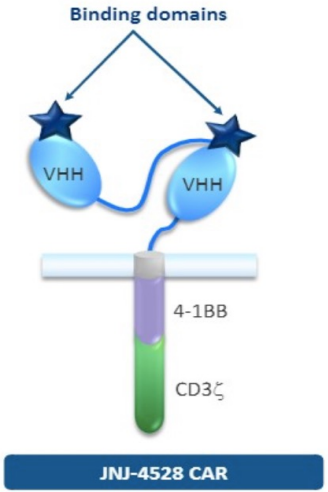
Novel agents with different mechanism of action are needed to overcome resistance in triple-class exposed RRMM

IMiD, immunomodulatory drug; mPFS, median progression-free survival; mOS, median overall survival; ORR, overall response rates; PI, proteasome inhibitor; PL, prior lines of therapy

Mateos MV et al. Leukemia 2022;36(5):1371-1376.

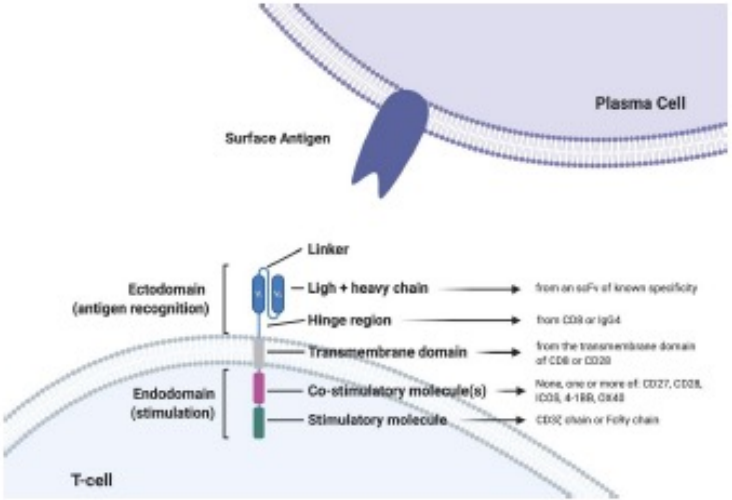
Two new *BCMA*-directed CAR T cell therapies are now approved for the treatment of triple-class exposed RRMM

Ciltacabtagene-autoleucel (cilta-cel)



Carvykti® is approved for the treatment of adults patients with RRMM who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and whose disease has worsened since the last treatment

Idecabtagene-vicleucel (ide-cel)



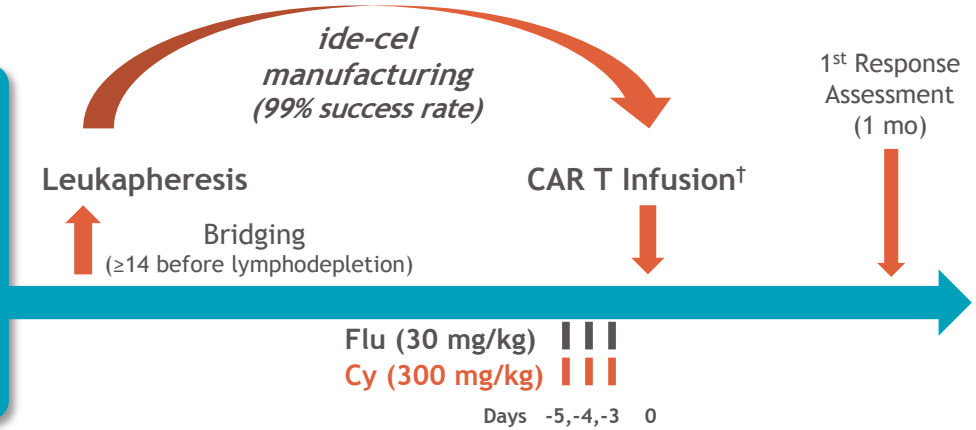
Abecma® is approved for the treatment of adult patients with RRMM who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and whose disease has worsened since the last treatment

https://www.ema.europa.eu/en/medicines/human/EPAR/carvykti

https://www.ema.europa.eu/en/medicines/human/EPAR/abecma

KarMMa
Ide-cel pivotal phase 2 single-arm study

- RRMM
- ≥3 prior regimens with ≥2 consecutive cycles each (or best response of PD)
- Previously exposed to:
  - IMiD agent
  - Proteasome inhibitor
  - Anti-CD38 antibody
- Refractory to last prior therapy per IMWG*



Study Status as of Jan 14, 2020

Screened N=158

Leukapheresed N=140

Treated N=128 (Target Dose CAR+ T cells)

150 × 10^6	n=4
300 × 10^6	n=70
450 × 10^6	n=54

Median Follow-up (mo)

150 × 10^6	18.0
300 × 10^6	15.8
450 × 10^6	12.4
Total	13.3

Endpoints

- **Primary**: ORR (null hypothesis ≤50%)
- **Secondary**: CRR (key secondary; null hypothesis ≤10%), Safety, DOR, PFS, OS, PK, MRD‡, QOL, HEOR
- **Exploratory**: Immunogenicity, BCMA expression/loss, cytokines, T cell immunophenotype, GEP in BM

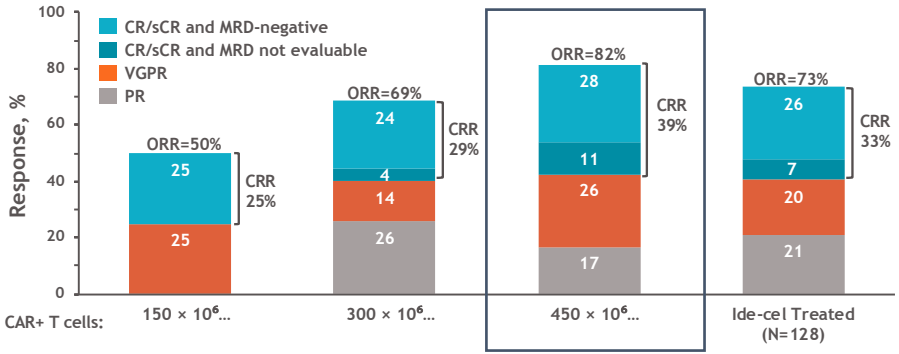
CRR, complete response rate; Cy, cyclophosphamide; DOR, duration of response; Flu, fludarabine; GEP in BM, gene expression profile in bone marrow; HEOR, health economics and outcomes research; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; QOL, quality of life.
*Defined as documented disease progression during or within 60 d from last dose of prior antimyeloma regimen. †Patients were required to be hospitalized for 14 d post-infusion. Ide-cel retreatment was allowed at disease progression for best response of at least stable disease. ‡By next-generation sequencing.

EudraCT: 2017-002245-29
ClinicalTrials.gov: NCT03361748

Munshi N et al. ASCO 2020;abstract 8503. Munshi N et al. N Eng J Med 2021;384(8):705-16

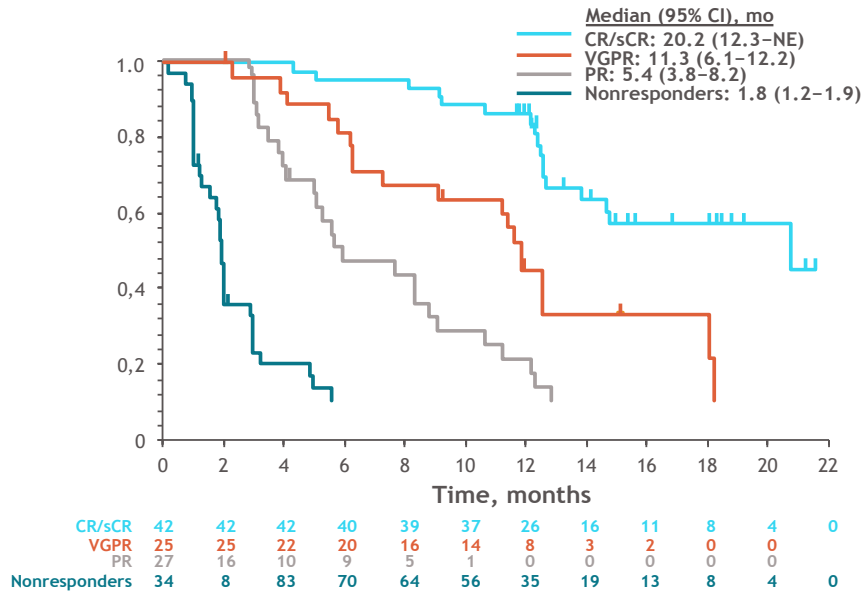
Ide-cel pivotal phase 2 single-arm study: Key efficacy data

- Median age 61 y. 39% had EMD and 35% HR CA
- Median nº of prior lines 6 (3 – 16)
  - 94% refractory to anti-CD38 MoAb
  - 84% triple-class refractory
  - 26% penta-refractory
- 88% patients received bridging therapy, only 4% responded



- **Median time to first response of 1.0 mo** (range, 0.5–8.8);
- Median time to CR of 2.8 mo (range, 1.0–11.8)
- Median follow-up of 13.3 mo across target dose levels

PFS by Best Response



- Median PFS was **8.8 months** across all dose ranges in all treated patients.
- PFS increased with higher target dose; median PFS was **12 mo** at 450 × 10^6 CAR+ T cells
- ***Median overall survival for all ide-cel treated patients: 24.8 m (19.9 – 31.2)***

CR, complete response; CRR, clinical response rate; EMD, extramedullary disease; HR CA high-risk cytogenetic abnormalities; MRD, minimal residual disease; PFS, progression-free survival; PR, partial response; sCR, stringent CR; VGPR, very good partial response

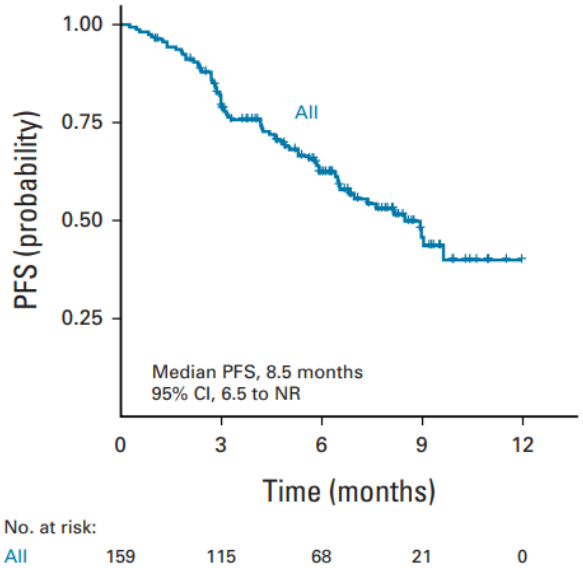
Munshi N et al. ASCO 2020;abstract 8503 (oral presentation).
Munshi N et al. N Eng J Med 2021;384(8):705-16

Idecabtagene vicleucel for relapsed/refractory multiple myeloma: Real-world experience from the US Myeloma CAR-T Consortium (n=159 infused)

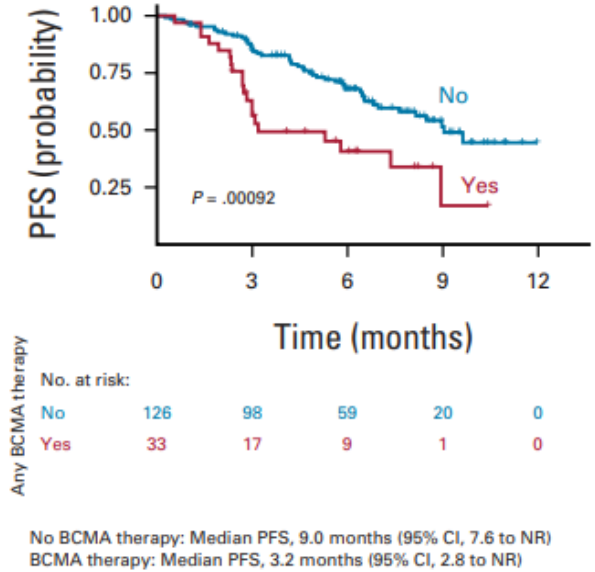
- Median age 64y (36-83). EMD 48%. HR-CA 35%.
- 75% did not meet KarMMa-1 inclusion criteria due to comorbidities
- Median nº PL: 7 (4-18). Prior BCMA (21%). Triple-Ref 84%, Penta-Ref 44%

BCMA, B-cell maturation antigen; CR, complete response; CRS, cytokine release syndrome; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; Ref, refractory; VGPR, very good partial response

Best ORR 84% (CR/sCR 42%)



Prior BCMA negatively impacts PFS



No BCMA therapy: Median PFS, 9.0 months (95% CI, 7.6 to NR)
BCMA therapy: Median PFS, 3.2 months (95% CI, 2.8 to NR)

Similar safety profile as in the KarMMa-1 trial
82% CRS [G ≥3: 3% (2 G5)]. NT 18% (G≥3 6%)

BCMA, B-cell maturation antigen; CRS, cytokine release syndrome; EMD, extramedullary disease; HR-CA, high-risk cytogenetic abnormalities; NT, neurotoxicity; ORR, overall response rate; PFS, progression-free survival; sCR, stringent complete response

Hansen DK et al. J Clin Oncol 2023;doi:10.1200/JCO.22.01365

Updated results from CARTITUDE-1: Ciltacabtagene autoleucel (cilta-cel) in RRMM (mITT n=97)

Primary objectives

- Phase 1b: Characterize the safety of cilta-cel and confirm the recommended phase 2 dose
- Phase 2: Evaluate the efficacy of cilta-cel

Key eligibility criteria

- Progressive MM per IMWG criteria
- ECOG PS ≤1
- Measurable disease
- ≥3 prior therapies or double refractory
- Prior PI, IMiD, anti-CD38 antibody exposure

Median administered dose:
0.71x10^6 (range 0.51–0.95x10^6) CAR+ viable T cells/kg

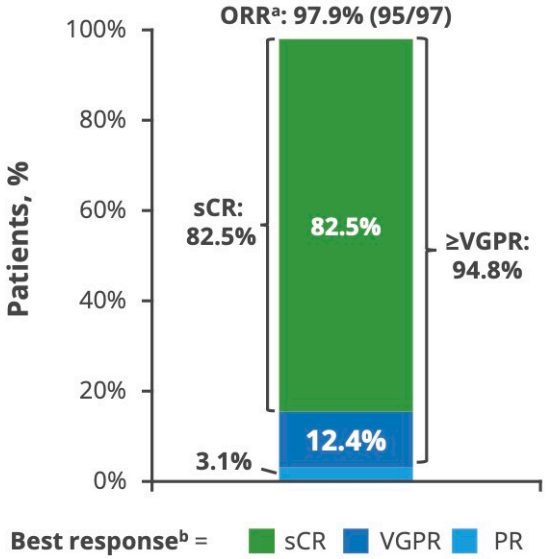
Cy, cyclophosphamide; Flu, fludarabine;
PD, pharmacodynamics; PK, pharmacokinetics

Cy, cyclophosphamide; ECOG, Eastern Cooperative Oncology Group; Flu, fludarabine; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; PI, proteasome inhibitor

Usmani S et al. ASCO 2022;abstract 8028 (poster presentation)

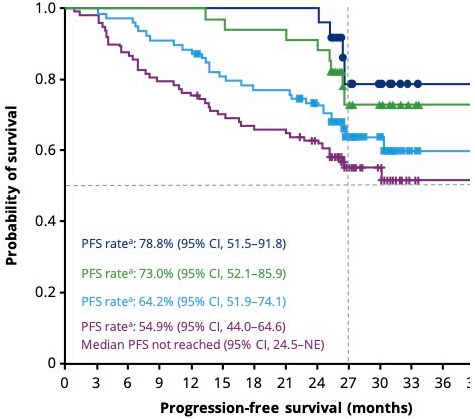
Updated results from CARTITUDE-1 (median FUP 27.7 m): Ciltacabtagene autoleucel (cilta-cel) in RRMM (mITT n=97) – Summary of efficacy

Key inclusion: Resistant to ≥ 3 prior lines or double refractory
Median number of prior lines: 6 (3–18)
Triple-class refractory 86.7%. Penta-Ref 42.3%



[a]ORR assessed by independent review committee. [b]No patient had CR or stable disease

Progression-Free Survival

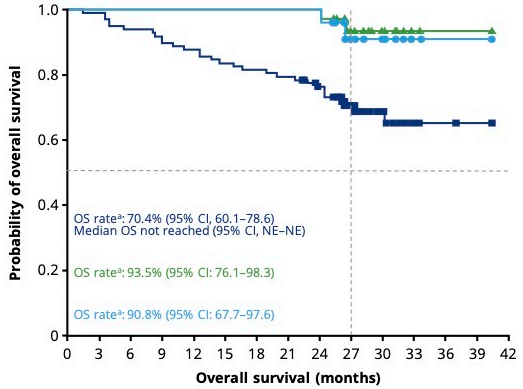


Patients at risk													
MRD negative ≥12 months	24	24	24	24	24	24	24	24	11	8	2	1	
MRD negative ≥6 months	34	34	34	34	34	33	32	32	31	13	10	3	1
sCR patients	80	80	78	73	71	64	62	61	55	27	17	3	1
All patients	97	95	85	77	74	67	64	63	57	27	17	3	1

MRD negative ≥12 months; MRD negative ≥6 m; sCR patients; All patients

[a]27-month PFS rate.

Overall survival



Patients at risk													
All patients	97	96	91	88	85	81	79	77	71	42	22	6	2	1	0
Sustained (≥6 mos) MRD neg	34	34	34	34	34	34	34	34	34	18	11	3	1	1	0
Sustained (≥12 mos) MRD neg	24	24	24	24	24	24	24	24	24	13	9	2	1	1	0

All patients; Sustained (≥6 mos) MRD neg patients; Sustained (≥12 mos) MRD neg patients

[a]27-month OS rate.

- Median time to first response was 1 m (range, 0.9–10.7)
- Median time to best response was 2.6 m (range, 0.9–17.8)
- Median time to ≥ CR was 2.9 m (range, 0.9–17.8)
- **Median duration of response was NE (21.8 m–NE)**
- **54.9% of patients are still progression-free at 27 m**

- Of the 61 patients evaluable for MRD, 91.8% were MRD-negative (at 10^{-5})
- 27m-PFS for patients with MRDneg ≥ 6m: 73% (95% CI, 52.1 – 85.9)
- 27m-PFS for patients with MRDneg ≥ 12m: 78.8% (95% CI, 51.5 – 91.8)

mITT, modified intent-to-treat; MRD, minimal residual disease; sCR, stringent complete response; PR, partial response; VGPR, very good partial response

LI Y et al. EHA 2022;abstract P961 (poster presentation)

Ide-cel (KarMMa) and cilta-cel (CARTITUDE-1): Safety

CARTITUDE-1 n=97	Any grade	Grade ≥5
Neutropenia[1]	**93 (95.9)**	**92 (94.8)**
CRS[2]	92 (94.8)	5.4%
Time to onset, median (range) days[3]	7 (1–12)	
Duration, median (range) days[3]	4 (1–97)	
Total CAR T-cell neurotoxicities, n (%)[2]	21 (21.6)	12 (12.3)
ICANS, n (%)[4]	16 (16)	2 (2.1)
MNT/neurocognitive[4]	5 (5.2)	4 (3.1)*
Infections-pathogen unspecified[5]	40 (41)	16 (17)
Viral infections[5]	22 (23)	7 (7)

Over the median 27 months of follow-up there were **20 secondary primary malignancies reported in 16 patients** (including 9 hematological malignancies, 6 MDS and 3 fatal AML and 1 low grade B-cell lymphoma), all were assessed by the investigator as unrelated to cilta-cel[2]

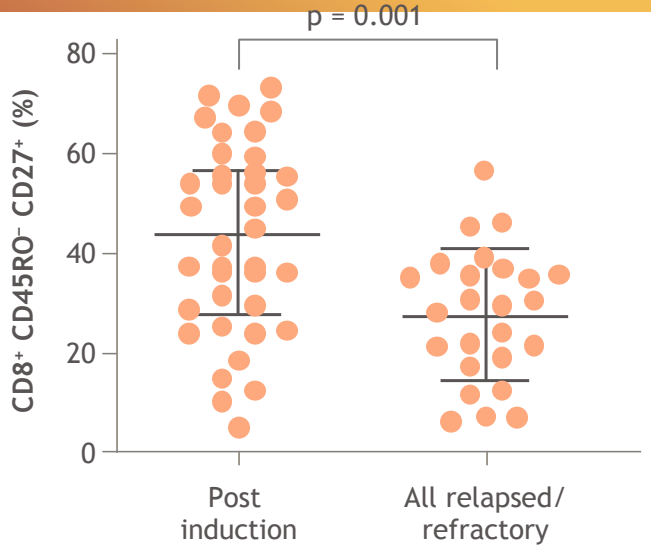
KarMMa n=128	Any grade	Grade 3-4
Neutropenia[6]	**117 (91)**	**114 (89)**
CRS[6]	**107 (84)** **450x10^6: 96%**	**7 (5)** **450x10^6: 6%**
Time to onset, median (range) days	1 (1–12)	
Duration, median (range) days	7 (1–63)	
Total CAR T-cell neurotoxicities, n (%)[7]	23 (18)	5 (4)
Infections-pathogen unspecified[8]	90 (70)	34 (27)
Viral infections[9]	NR	9%
Hypogammaglobulinemia[9]	52 (41)	--

*1 patient had grade 5 MNT. AML, CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; MDS, myelodysplastic syndromes; MNT, movement or neurocognitive adverse events.

1. Martin T et al. ASH 2021;abstract 549 (oral presentation); 2. Martin T et al. J Clin Oncol 2022;doi:10.1200/JCO.22.00842; 3. Madduri D et al. ASH 2020;abstract 177 (oral presentation); 4. Cohen AD et al. Blood Cancer J. 2022;12(2):32; 5. Carvykti. Prescribing information. Janssen Biotech, Inc; 2022.

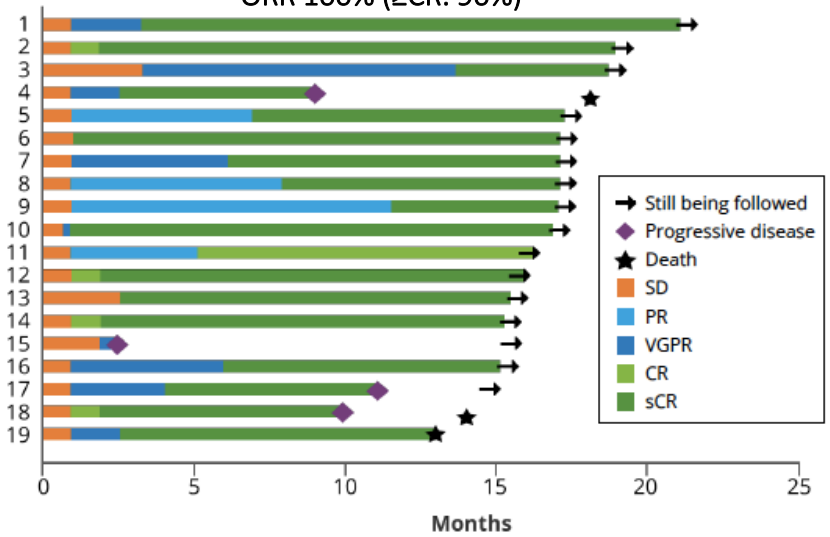
6. Munshi N et al. N Eng J Med 2021;384(8):705–16; 7. Munshi N et al. ASCO 2020;abstract 8503 (oral presentation); 8. Anderson L et al. ASCO 2021;abstract 8016 (poster presentation). 9. Abecma Prescribing Information. BMS 2022

Rationale for moving CAR-T to earlier lines of therapy
Higher proportion of memory T-cell in early disease settings



CARTITUDE-2 (1-3 PL, Len-Ref)[2]

ORR 100% (≥CR: 90%)



Previous treatment affects the percentage of memory T cells in the leukapheresis product (also affects the CD4/CD8 ratio)[1]

Median DOR was NR

15-month PFS rate was 70% (95% CI, 45.1–85.3)[2]

KarMMa-3 demonstrated significant improvement in PFS for ide-cel vs SoC (13.3m vs 4.4m; HR 0.49 [95% CI, 0.38-0.65]; P<0.0001)[3]

KarMMa-2 cohort 2c (<VGPR after ASCT): CR rate 74.2%. 24m PFS rate: 83.1%[4]

ASCT, autologous stem cell transplant; CR, complete response; DOR, duration of response; ORR, overall response rate; PL, prior lines of therapy; PFS, progression-free survival; sCR, stringent CR; SD, stable disease; VGPR, very good partial response

1. Garfall AL et al. Blood Adv. 2019;3:2812-15.

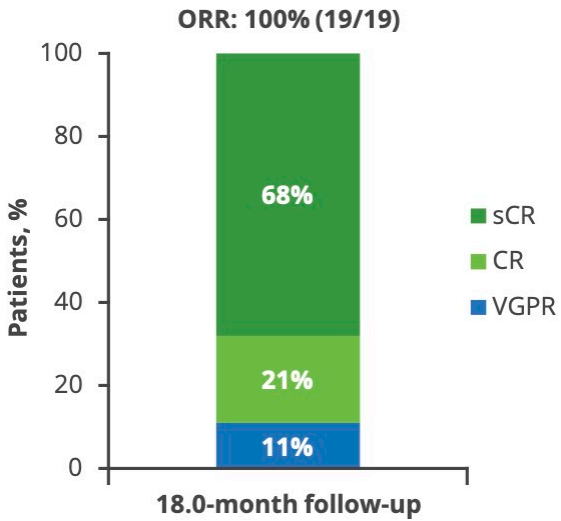
2. Agha M et al. IMS 2022;abstract OAB-043 (oral presentation);
3. Rodriguez-Otero P et al, NEJM Feb 2023; 4. Dhodapkar M et al. ASH 2022;abstract 3314 (poster presentation).

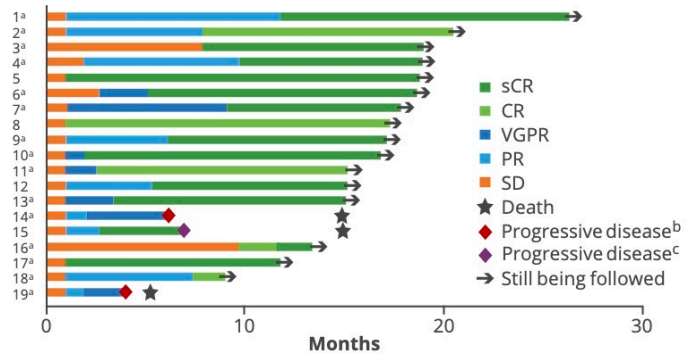
Use in earlier lines of therapy
Cilta-cel in patients with MM an early relapse after initial therapy

Patient population: early relapse after initial therapy with a PI and IMID ≤12 months after initiation of therapy in patients with NDMM

Characteristic	N=19
Age, median (range), y	58 (44–67)
Male, n (%)	14 (73.7)
Race, n (%)	
White	14 (73.7)
Black/African American	2 (10.5)
Asian	1 (5.3)
Not reported	2 (10.5)
Bone marrow plasma cells[a] ≥60%, n (%)	4 (21.1)
Extramedullary plasmacytomas, n (%)	3 (15.8)
High-risk cytogenetic profile,[b] n (%)	3 (20)
del17p	3 (20)
Years since initial diagnosis to enrollment, median (range)	1.15 (0.5–1.9)
Prior LOT, median (range)	1 (1–1)
Previous stem cell transplantation, n (%)	
Autologous	15 (78.9)
Allogeneic	0
Exposure status, n (%)	
Triple-class[c]	4 (21.1)
Penta-drug[d]	0
Refractory status, n (%)	
Triple-class[c]	3 (15.8)
Penta-drug[d]	0
To last line of therapy	15 (78.9)

[a]Maximum value from bone marrow biopsy and bone marrow aspirate is selected if both results are available. [b]4 patients had unknown cytogenetics; hence, cytogenetics was determined in 15 patients. [c]≥1 PI, ≥1 IMiD, and 1 anti-CD38 antibody. [d]≥2 PIs, ≥2 IMiDs, and 1 anti-CD38 antibody.





[a]Patients who received ASCT. [b]Progressive disease per International Myeloma Working Group criteria. [c]Progressive disease per investigator assessment based on a light chain escape. PR, partial response.

- Median duration of response was not reached
- 18-month PFS rate was 83% (95% CI, 55.9–94.3)
- 18-month OS rate was 83% (95% CI, 55.7–94.2)

- Safety was manageable and comparable to safety reported in CARTITUDE-1
- Grade 3/4 neutropenia and thrombocytopenia not recovered at day 60 was 11% and 16%, respectively
- CRS occurred in 16/19 patients (G3/4 1 patient). Tocilizumab used 63%. Median time to onset 8 days
- Neurotoxicity occurred in 5/19 patients (26%) (G3/4 1 patient). ICANS 1 patient (G1). MNT 1 patient onset at day 38 and still ongoing (G3)

CR, complete response; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; IMiD, immunomodulatory drug; LOT, line of therapy; MNT, movement and neurocognitive toxicities; PFS, progression-free survival; PI, proteasome inhibitor; PR, partial response; sCR, stringent CR; SCT, stem cell transplant; VGPR, very good partial response

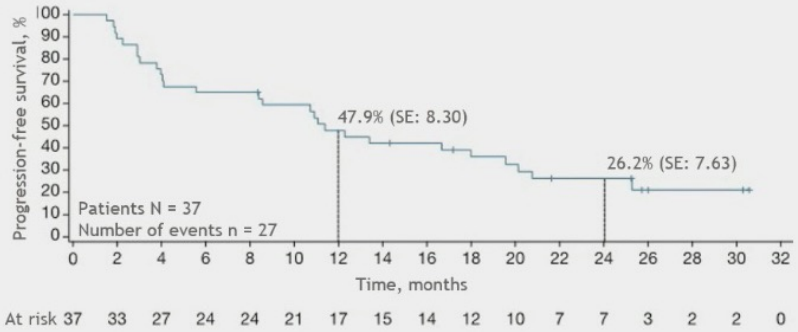
van de Donk N et al. ASH 2022;abstract 3354 (poster presentation)

KarMMa-2 cohort 2a:
Ide-cel in patients with early relapse after frontline therapy (n=39, 37 infused)

- 37 patients infused. Median dose: 425x10^6 CAR T+ cells (range 300.2 – 525.6)
- 33 pts had PD <12 m of ASCT. 86% IMID-Ref. 89% PI-Ref. 0% anti-CD38-Ref.
- Median follow-up 21.5 m (range 2-31)

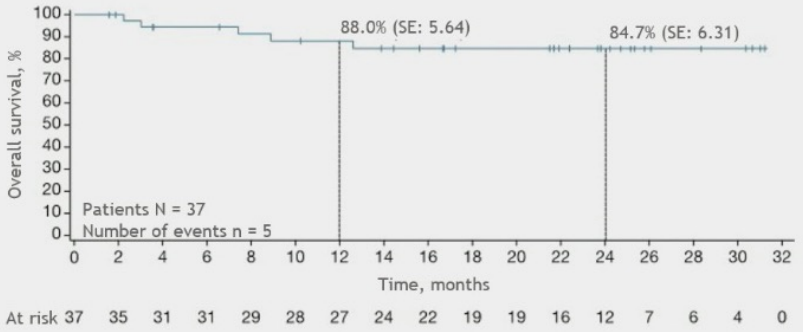
ORR 83.8%, CRR 45.9%, VGPR 21.6%

Progression-free survival[a]



- Median PFS was 11.4 months (95% CI 5.6-19.6)
  - Median follow-up was 21.5 months (range 2-31 months)

Overall survival



- Median OS was not reached; an OS event-free rate of 84.7% (SE: 6.31) was observed at 24 months

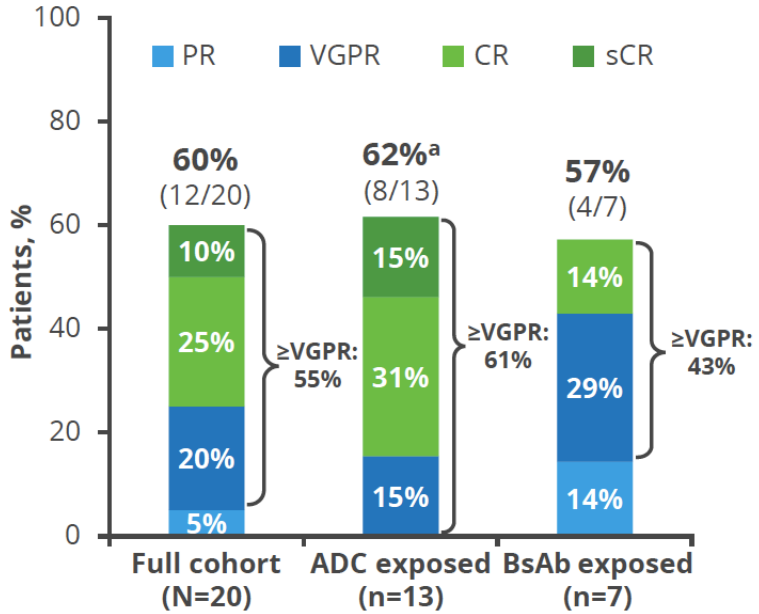
- Median DoR in all patients: 15.7 m (95% CI; 7.6 – 19.8)
- Median DoR in ≥CR patients: 23.5 m (95% CI; 10.2 – NE)
- Comparable safety profile as in KarMMa-1 pivotal trial

ASCT, autologous stem cell transplant; CR, complete response; CRR, clinical response rate; DoR, duration of response; IMiD, immunomodulatory drug; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; Ref, refractory; VGPR, very good partial response

Usmani S et al. ASH 2022;abstract 361 (oral presentation)

Prior anti-BCMA treatment: CARTITUDE-2 cohort C
Cilta-cel after prior BCMA-targeting ADC or bispecifics (n=15)

- **Factors likely associated with response:**
  - Shorter duration of prior BCMA therapy
  - Longer median time between prior BCMA and apheresis/ cilta-cel infusion



BsAb cohort (n=7), median follow-up 18 m

- Median nº LOT 8 (6-12), BCMA as last line in 2 pts. 5 pts BCMA-ref

ADC cohort (n=15), median follow-up 18 m

- Median nº LOT: 8 (4-13). BCMA as last line in 4 pts. 11 pts BCMA-ref

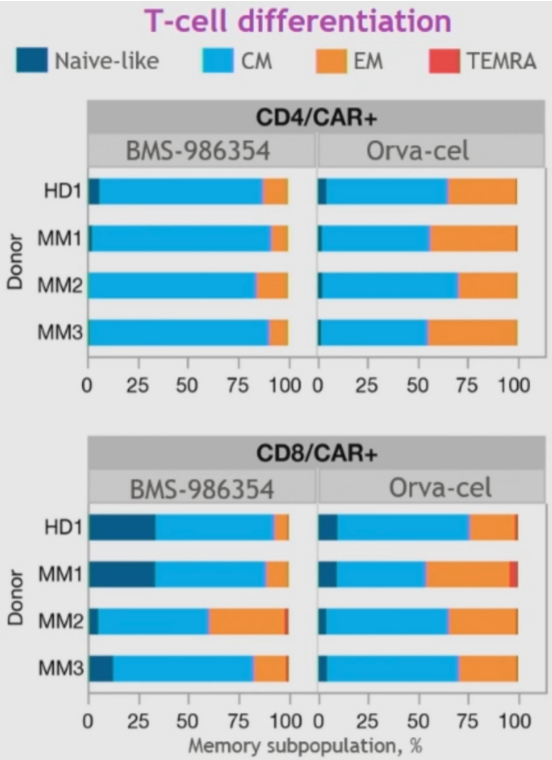
Estimate, months (95% CI)	Full cohort (N=20)	ADC exposed (n=13)	BsAb exposed (n=7)
DOR	12.3 (7.2–NE)	13.3 (7.2–NE)	8.2 (4.4–NE)
PFS	9.1 (1.5–13.2)	9.5 (1.0–15.2)	5.3 (0.6–NE)

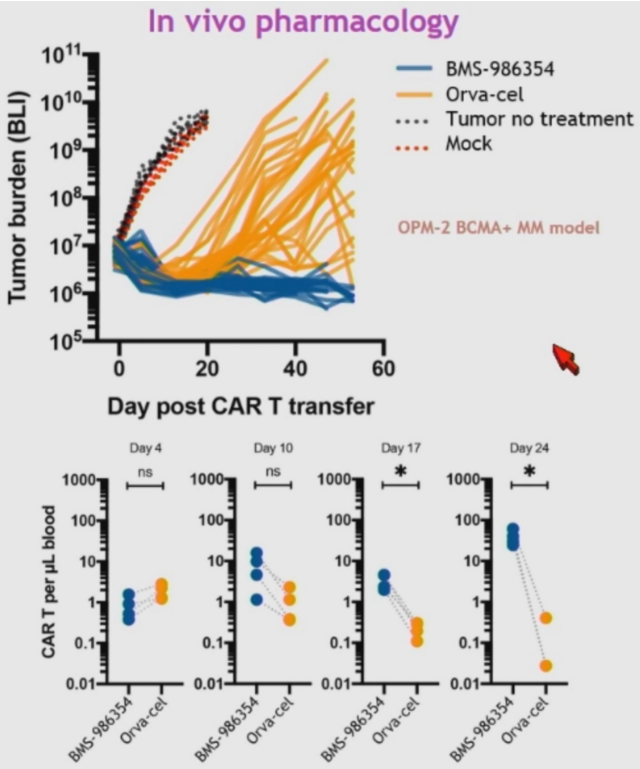
NE, not evaluable.

ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CR, complete response;; DoR, duration of response; LOT, line of therapy; PFS, progression-free survival; PR, partial response; Ref, refractory; sCR, stringent CR; VGPR, very good partial response

Cohen AD et al. ASH 2022;abstract 2028 (poster presentation)

Novel manufacturing process aiming to shorten vein-to-vein time
BMS-986354 – BCMA CAR-T manufactured using the NEX-T™ process (n=





Compared with orva-cel, BMS-986354, manufactured with the NEX-T process:

- is enriched in **less-differentiated** memory subtypes
- has ~10-fold **increased proliferative capacity**
- has **superior tumor control** at equivalent CAR T cell dose

Immune markers were: naïve-like, CCR7+CD45RA+; CM, CCR7+CD45RA-; EM, CCR7-CD45RA-; TEMRA, CD45RA+CCR7-.
*P<0.05.

BLI, bioluminescent imaging; CAR, chimeric antigen receptor; CM, central memory; EM, effector memory; HD, healthy donor; MM, multiple myeloma; TEMRA, effector memory RA

Costa L et al. ASH 2022;abstract 566 (oral presentation)

Closing remarks

- **BCMA-directed CAR T-cell therapies have demonstrated impressive clinical results in the context of advance triple-class exposed** RRMM leading to the approval of two different CAR T-cell products
- **Optimal and timely patient selection is critical for CAR T-cell treatment outcomes** since achievement of deep responses (CR and/or MRD negativity) is of utmost importance in the context of the “one-shot” treatment and is associated with prolonged duration of response and progression-free survival
- **New modalities are in development, including new targets (GPRC5d),** trying to overcome some of the current limitations of CAR T-cell therapy aiming to improve the outcomes, shorten vein-to-vein time and reduce toxicity
- **Further use of BCMA-directed CAR T-cell treatment in earlier lines** (including frontline therapy) may improve the outcomes and, hopefully, find the way to cure MM patients

BCMA, B-cell maturation antigen; CR, complete response; MRD, minimal residual disease

CANCERVIH
Réseau national de prise en charge des PVVIH atteintes de cancer

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CAR-T cells et Tumeurs solides

Pr. Jean-Philippe SPANO

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Disclosure form

JPS: Consultant or advisory role (fees) or meeting invitation from Roche, BMS, MSD, Pfizer, Lilly, PFO, Leo Pharma, Myriads, Biogaran, AZ, Novartis, Daichy-Sakyo, Exact-Sciences and Gilead

Grant: MSD Avenir

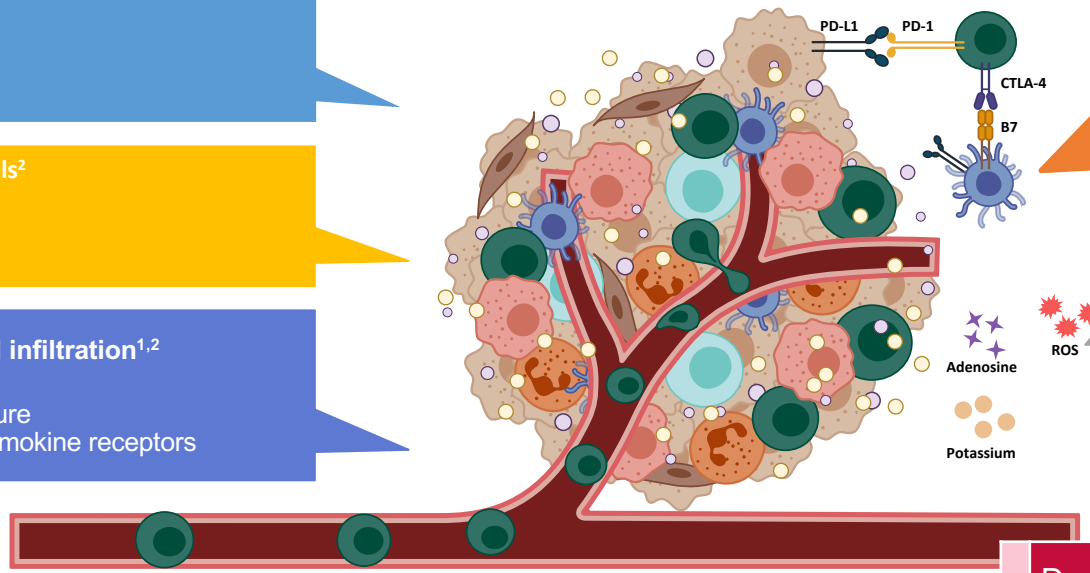
Quels sont les principaux défis ou obstacles dans le domaine des tumeurs solides?

Solid tumour microenvironment[1]

Antigen heterogeneity[1]
- Antigen presence
- Level of expression

Immunosuppressive cells[2]
- CAFs
- Tregs
- MDSCs

T-cell trafficking and infiltration[1,2]
- Physical barriers
- Aberrant vasculature
- Expression of chemokine receptors



T-cell dysfunction and exhaustion[2]
- Upregulated expression of inhibitory receptors such as PD-L1 and CTLA-4

Immunosuppressive factors[2]
- Reactive oxygen species
- High levels of adenosine
- Elevated extracellular potassium

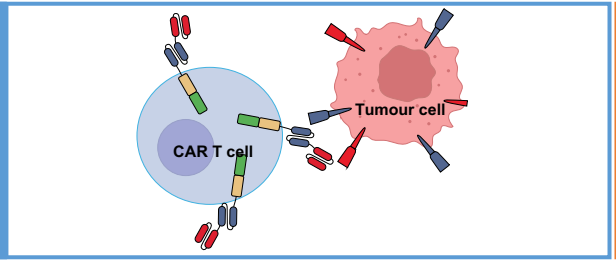
Despite success in haematological malignancies, CAR T-cell therapy in solid tumours is challenging[3]

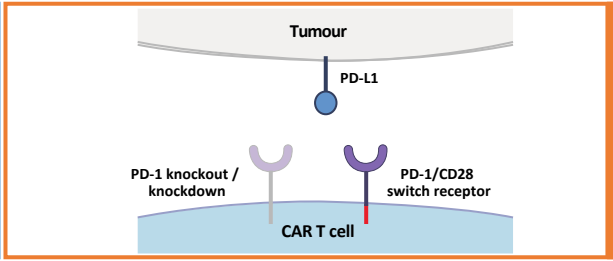
CAF: cancer-associated fibroblast; CAR: chimeric antigen receptor; CCL2: monocyte chemoattractant protein-1;
CTL2: cytotoxic T-lymphocyte-associated protein; CXCL8: CXC motif ligand 8; CXCL16: CXC motif ligand 16; L-10: interleukin -10; MDSC: myeloid-derived suppressor cell; PD-L1: programmed death ligand 1;
ROS: reactive oxygen species; TC1: type 1 CD8(+) T cell; TGFβ: transforming growth factor beta; TH1: T helper cell 1; Tregs: regulatory T cells;
1. Foeng J, et al. Cell Rep Med 2022; 3;100543. 2. Srivastava S & Riddell SR. J Immunol 2018; 200:459–468. 3. Andrea A, et al. Front Immunol 2022; 13:830292.

From JP SPANO, ESMO 2022, Kite Symposium, a Gilead company

,,,et quels sont les moyens pour les contourner: rôle du microenvironnement,,,,?

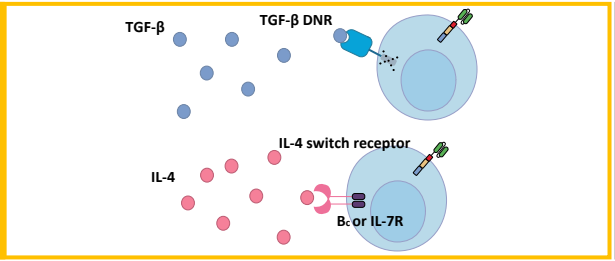
Improving tumour specificity
Dual-targeting CAR T cells[1]

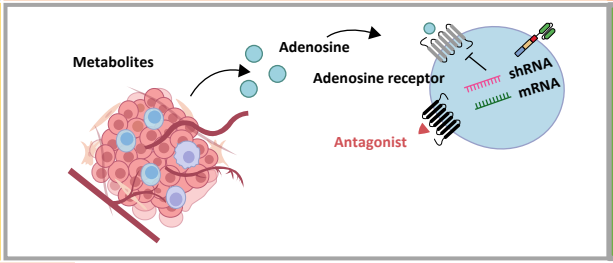




Preventing T-cell disruption
Altering PD-1/ PD-L1 axis[1]

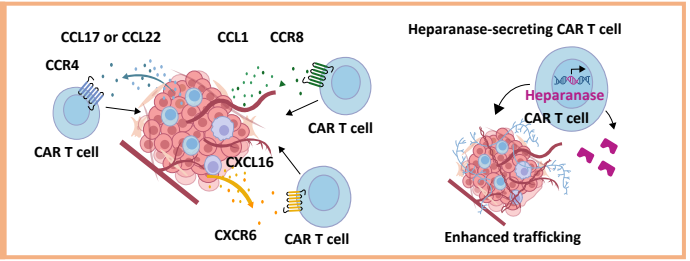
Resisting immunosuppression
Rewiring T-cell responses to immunosuppressive molecules[1]





Improving metabolic fitness
Blocking immunosuppressive metabolites that inhibit T-cell responses[1]

Improving T-cell trafficking
ECM degradation and chemokine signalling[1]



Designing new CAR T-cell products that address multiple barriers faced in solid tumours is a major focus of cancer research[2]

CCR8: CC chemokine receptor 8; DNR: dominant negative receptor; ECM: extracellular matrix; mRNA: messenger ribonucleic acid; shRNA:small hairpin RNA

1. Hupperetz C, et al. Immune Netw 2022; 22:e6. 2. Patel U, et al. EJHaem 2022; 3:24–31

From JP SPANO, ESMO 2022, Kite Symposium, a Gilead company

Quels sont les principaux antigènes et pour quels types de cancers ?

Targeted antigens in solid tumour CAR T-cell therapy (*in vitro* studies)[1]

Lung

MAGE-A1, CD32A, ROR, EGFRvIII

Liver

CEA, Glypican 3, AFP

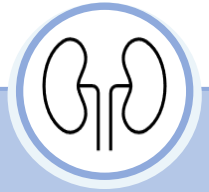
Stomach

Mesothelin, ANTXR1, MUC3A, Trop2, Claudin18.2, NKG2D, HER2, FR-α

Head and neck[a]

HER2

EGFRvIII, B7-H3, NKG2D, CAIX, αvβ3, IL13Rα2[a]



Kidneys

CAIX

The antigens and cancers shown on this slide are not exhaustive

Antitumour activity has been observed in several preclinical studies including CAR T cells expressing IL-7 and CD19[2] and negative TGF-βRII[3]

Increased understanding of the critical interactions between tumours and the immune response is key to improving the outcomes of CAR T-cell therapy in solid tumours[4]

a Head and neck cancer and glioblastoma grouped together
AFP: alpha-fetoprotein; ANTXR1: anthrax toxin receptor 1; AXL: anexeletkto receptor tyrosine kinase; CAIX: carbonic anhydrase IX;
CEA: carcinoembryonic antigen; EGFR: epidermal growth factor receptor; EpCAM: epithelial cell adhesion molecule; GD2: disiaganglioside;
HER2: human epidermal growth factor receptor 2; IL13Rα2: interleukin 13 receptor gamma 2; MUC1: mucin 1; MAGE: melanoma-associated antigen;
NK: natural killer; ROR: RAR-related orphan receptor; TGF-βRII: transforming growth factor beta receptor II

1. Marofi F, et al. Stem Cell Res Ther 2021; 12:81. 2. Pang N, et al. J Hematol Oncol 2021; 14:118.
3. Kloss C, et al. Mol Ther 2018; 26:1855–1866. 4. Guha P, et al. Biomedicines 2022; 10:655.

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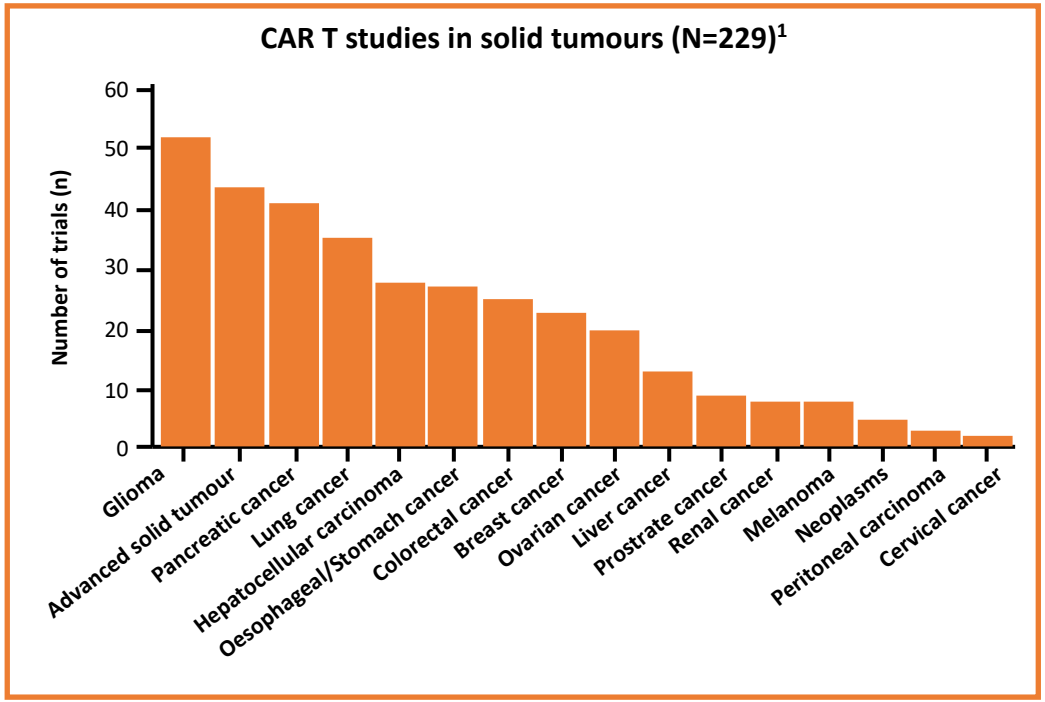
Essais thérapeutiques, des résultats prometteurs ?

Systematic review of CAR T studies in oncology worldwide using ClinicalTrials.gov in March 2022 (N=868)[1]



Most clinical trials are in Phase 1 with **persistence**, **safety** and **efficacy** as primary endpoints

Most trials investigate **single-target** CAR T cells

16% of studies are investigating CAR T in combination with other therapies including:

- Checkpoint inhibitors
- Cytokine administration
- Chemotherapy and small molecule inhibitors

An unprecedented number of clinical trials of CAR T cells in solid tumours are ongoing[2]

1. Barros L, et al. Cancers 2022; 14:2667. 2. Guha P, et al. Biomedicines 2022; 10:655.

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Another approach: NK cells

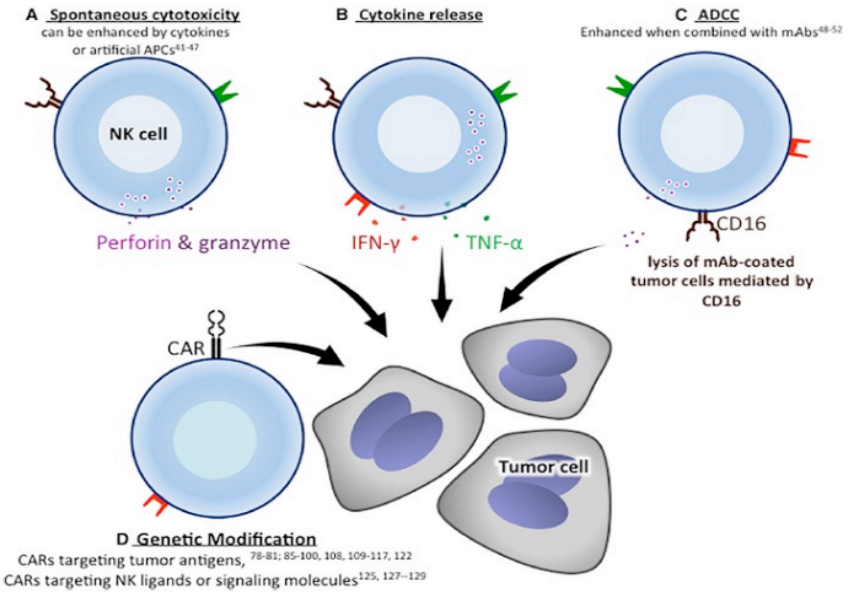


Figure 1. Mechanisms of NK-Mediated Cytotoxicity
(A) Spontaneous cytotoxicity. (B) Cytokine release. (C) ADCC. (D) Genetic modification. ADCC, antibody-dependent cell-mediated cytotoxicity; mAb, monoclonal antibody.

Rezvanika, Molecular Therapy 2017

NK cells and preclinic and perspectives

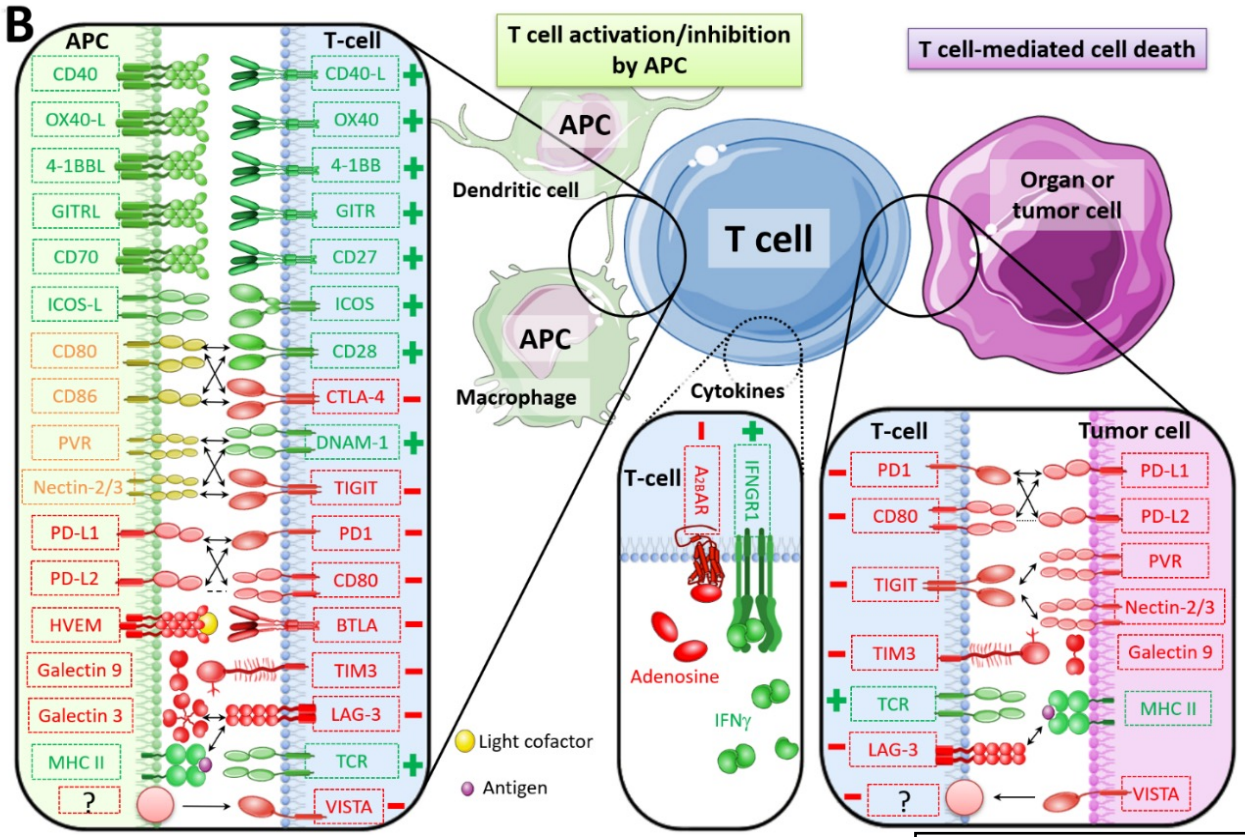
TABLE 1 | Preclinical studies with CAR-NK cells in brain cancer models.

Target	Antibody	Hinge	TM	Signaling	Effector cells	Gene transfer	Cancer type	*In vivo* model	Treatment	Reference
EGFRvIII	MR1-1	Myc-tag	DAP12	DAP12	YTS	Lentivirus	GB	s.c. xenografts in NMRI nude mice	i.v. injection	(82)
EGFRvIII	MR1-1	CD8α	CD28	CD28- CD3ζ	NK-92	Lentivirus	GB	orthotopic xenografts in NSG mice	i.t. injection	(71)
EGFRvIII	3C10	CD8α	CD28	CD28-CD137-CD3ζ	KHYG-1	Lentivirus	GB	–	–	(163)
EGFR	R1	CD8α	CD28	CD28- CD3ζ	NK-92	Lentivirus	GB	orthotopic xenografts in NSG mice	i.t. injection	(71)
EGFRvIII and EGFR	528	n.s.	CD28	CD28- CD3ζ	NK-92 NKL	Lentivirus	GB	orthotopic xenografts in NSG mice	i.t. injection	(160)
EGFRvIII and EGFR	Cetuximab (225)	CD8α	CD28	CD28- CD3ζ	NK-92	Lentivirus	GB	orthotopic xenografts in NSG mice	i.t. injection	(71)
ErbB2 (HER2)	FRP5	CD8α	CD3ζ	CD3ζ	NK-92	Retrovirus	Breast ca. brain metastasis	orthotopic xenografts in athymic nude rats	i.v. injection with FUS	(164, 165)
ErbB2 (HER2)	FRP5	CD8α	CD28	CD28- CD3ζ	NK-92	Lentivirus	GB	orthotopic xenografts in NSG mice	i.t. injection	(125)
ErbB2 (HER2)	FRP5	CD8α	CD28	CD28- CD3ζ	NK-92	Lentivirus	GB	syngeneic orthotopic tumors in C57BL/6 mice	i.t. injection	(15, 125)

TM, transmembrane domain; s.c., subcutaneous; i.v., intravenous; i.t., intratumoral; n.s., not specified; GB, glioblastoma; Breast ca., breast carcinoma; FUS, MRI-guided focused ultrasound.

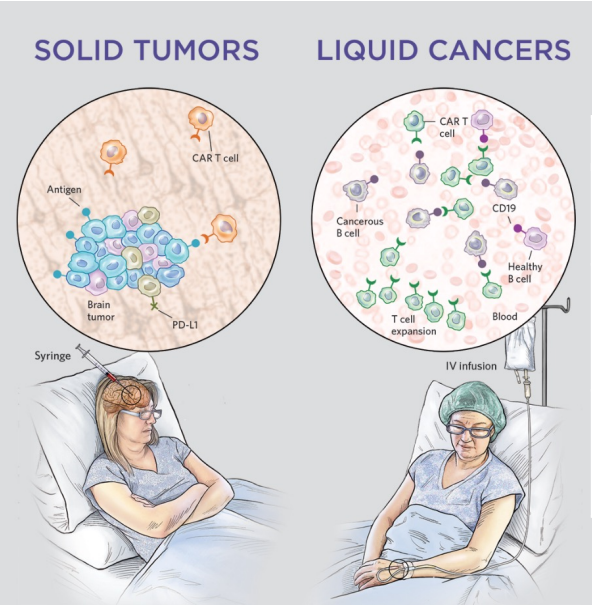
Burger MC, 2019

Perspectives: New ICIs ? New combinations ?



Geraud et al., Annu Rev Pharmacol Toxicol, 2020

CAR-T cell challenges in solid tumors



	Solid Tumors	Liquid Cancers
Heterogeneity	Antigens not present on all cells	CD19 present on all cancerous cells (but also on healthy cells
Microenvironment	PD-L1 and other immune checkpoint expression by tumor/stroma cells	Rapid expansion of CAR-T cells, but risk of cytokine release syndrome
Delivery	A solid mass is difficult to infiltrate. Intra-tumoral injection possible	Intraveinous injection allows easy access to cancer cells

https://www.the-scientist.com/features/the-next-frontier-of-car-t-cell-therapy--solid-tumors-65612

CAR-T cells pour les PVVIH atteintes d'hémopathies malignes

Un case report sur 2 patients traités à Boston par Yescarta® :

- Un patient avec DLBCL R/R initialement non observant pour son traitement ARV avec une CV VIH à 643 000 copies/mL et 52 CD4/mm^3, a développé un CRS grade 2 et une toxicité neurologique grade 3 (confusion, somnolence, aphasie) d'évolution favorable, à 1 mois aux scanners = réponse partielle, à 2 mois = réponse complète

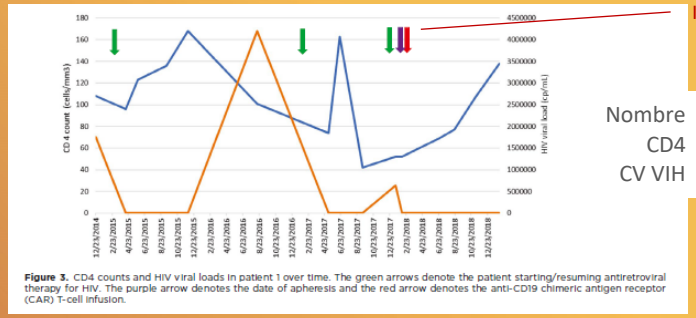


Figure 3. CD4 counts and HIV viral loads in patient 1 over time. The green arrows denote the patient starting/resuming antiretroviral therapy for HIV. The purple arrow denotes the date of apheresis and the red arrow denotes the anti-CD19 chimeric antigen receptor (CAR) T-cell infusion.

- Un patient avec DLBCL R/R EBV+ observant avec une CV indétectable et 127 CD4/mm^3, pas de toxicité, à 1 mois aux scanners = réponse complète

Successful anti-CD19 CAR T-Cell therapy in HIV-infected patients with refractory high-grade B-cell lymphoma - Abramson JS et al. Cancer 2019 Nov 1;125(21):3692-3698

Un article avec 10 patients traités à New-York par Yescarta® :

- Un patient VIH+ avec DLBCL R/R sous traitement ARV avec une CV indétectable et 127 CD4/mm^3 avec réponse complète

		21/12/2018	26/02/2019	10/06/2019	13/09/2019	14/10/2019
HIV Patient CAR-T infusion on 4/29/2019	HIV-1 Viral RNA Load (copies/ml)	0	0	0	116	683817
	CD4 count (cells/µl)	148	120	62	46	not tested

Vigilance +++

Axicabtagene ciloleucel CD19 CAR-T cell therapy results in high rates of systemic and neurologic remissions in ten patients with refractory large B cell lymphoma including two with HIV and viral hepatitis – Abbasi A et al. J Hematol Oncol. 2020 Jan 3;13(1):1

CAR-T cells pour les PVVIH atteintes d'hémopathies malignes : point sur la situation en France

qq cas en France :
Ex: Patiente avec LBDGC R/R traitée par CAR-T cells (Yescarta®) à l'Institut Paoli Calmettes le 05/08/2019 :

- Séjour de 48h en réa pour un CRS grade 1
- A J15, réactivation HHV6 traitée par Foscavir, sans complication à ce jour
- Quelques légers blips de la CV VIH après l'injection
- A S8 = en rémission métabolique complète au TEP-scanner
- Dosages des ARV normaux

Peu d'informations actuellement disponibles sur la tolérance immuno-virologique

- Elaboration d'un **monitoring immuno-virologique de soin** pour les PVVIH traitées par CAR-T cells pour leur cancer (réseau national CANCERVIH)
- Inclusion possible de ces patients dans la **cohorte ANRS CO24 ONCOVIHAC et la sous-étude ONCOVIRIM**

CAR-T cells pour les PVVIH atteintes de cancer

Un produit à base de CAR-T cells peut être fabriqué chez un patient infecté par le VIH qui reçoit des ARV ⇨ **longtemps remis en cause !!!**

Le produit à base de CAR-T cells peut être administré en toute sécurité en même temps qu'une thérapie ARV.

Les CAR-T cells peuvent induire une rémission durable chez les patients atteints d'un DLBCL R/R associé au VIH.

Bien que les patients séropositifs pour le VIH ne soient pas expressément exclus de l'étiquette de la FDA pour les produits à base de CAR-T cells approuvés pour le lymphome, ils ont été exclus des essais cliniques pivots qui ont établi leur sécurité et leur efficacité.

Pas d'essai spécifique en cours CAR-T cells pour les personnes vivant avec le VIH atteintes de cancer

⇨ **Il faut donc traiter les patients VIH comme la population générale (mais avec une surveillance accrue des données immuno-virologiques)**

CAR T-cell therapy for cancer and HIV through novel approaches to HIV-associated haematological malignancies Rust BJ, Kiem, HP, Uldrick TS (Lancet Haematol 2020 Sep;7(9)e690-696)

Les Transversales « by IFODS »

IFODS

on behalf of Cours St-Paul

International and French Oncology Days

Journées Franco-Internationales d'Oncologie