Myélome Multiple :
Le point sur les Immunothérapies Innovantes

DES Hématologie-26.11.2021

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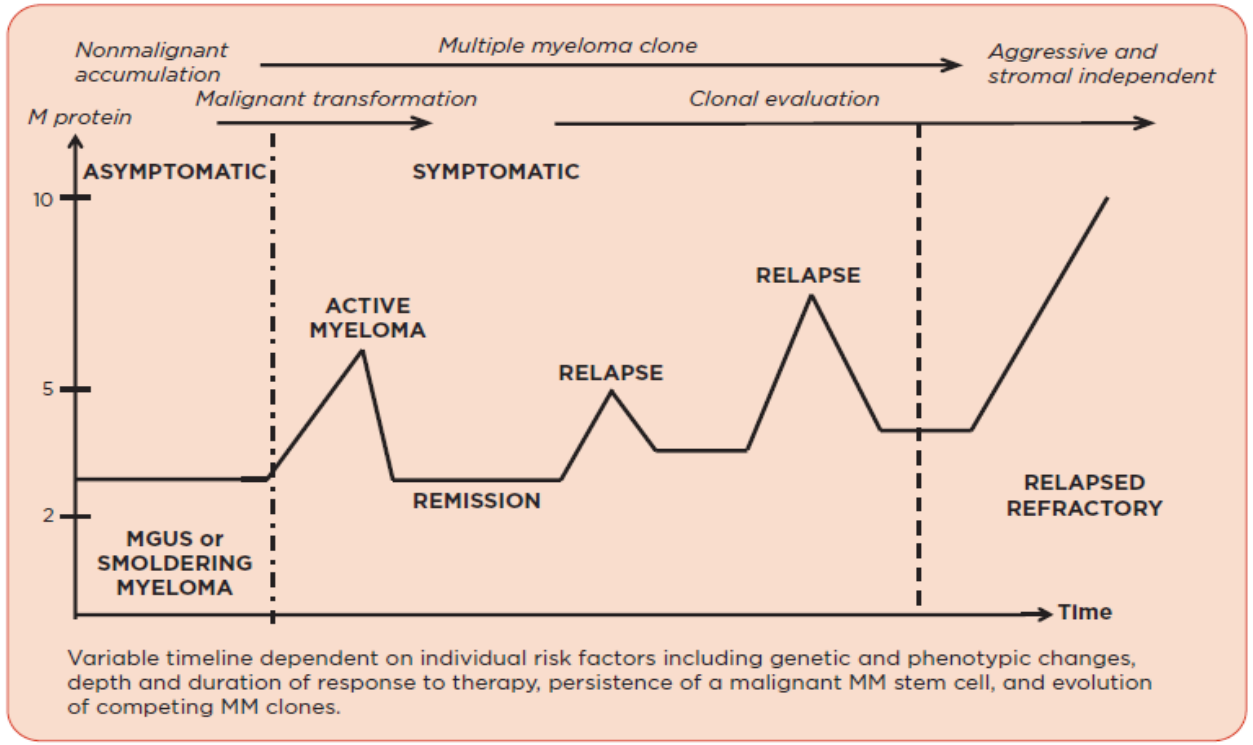
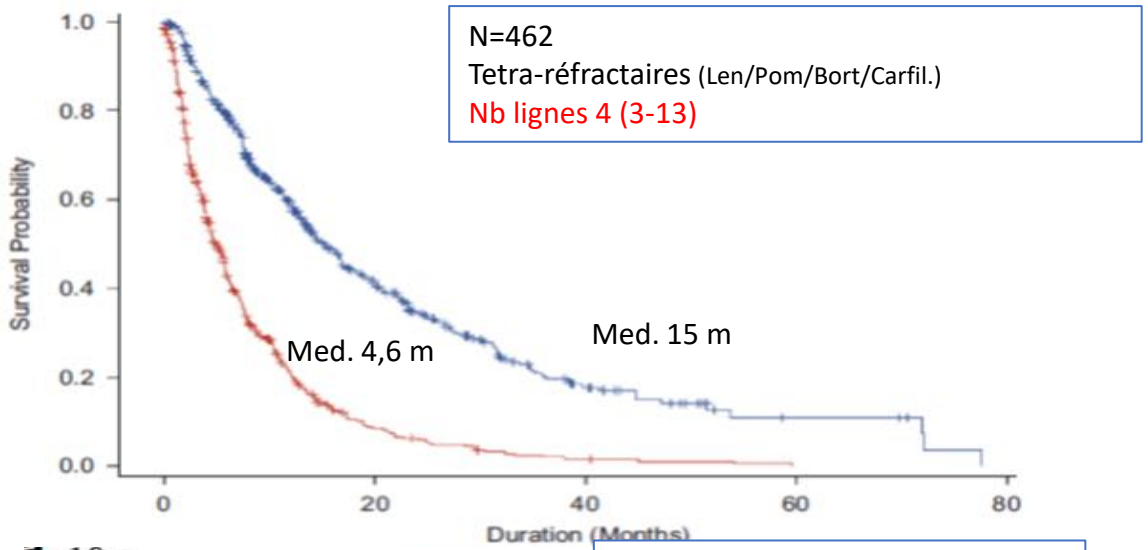
Myélome: Triple/penta voire Hexa exposés/réfractaires

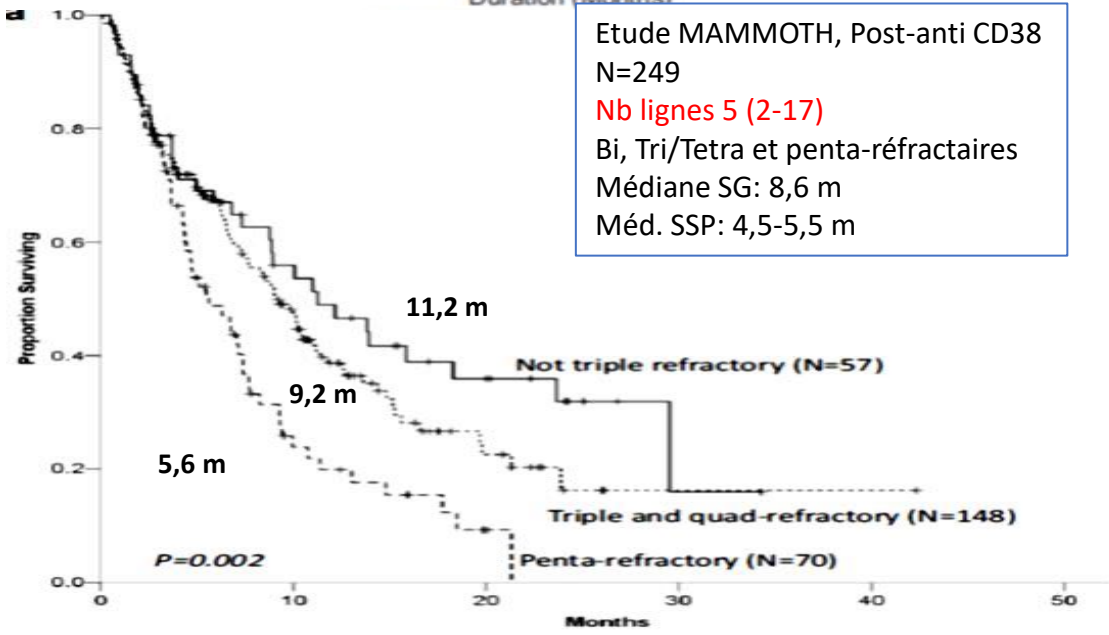


Progrès thérapeutiques: Imids, Inhibiteurs protéasome, anticorps Anti-CD38
Effets indésirables et coût élevé (#250 Ke/an)
Pas de Guérison: Maladie incurable avec rechute successives inexorables

➔ Développement Immunothérapies innovantes



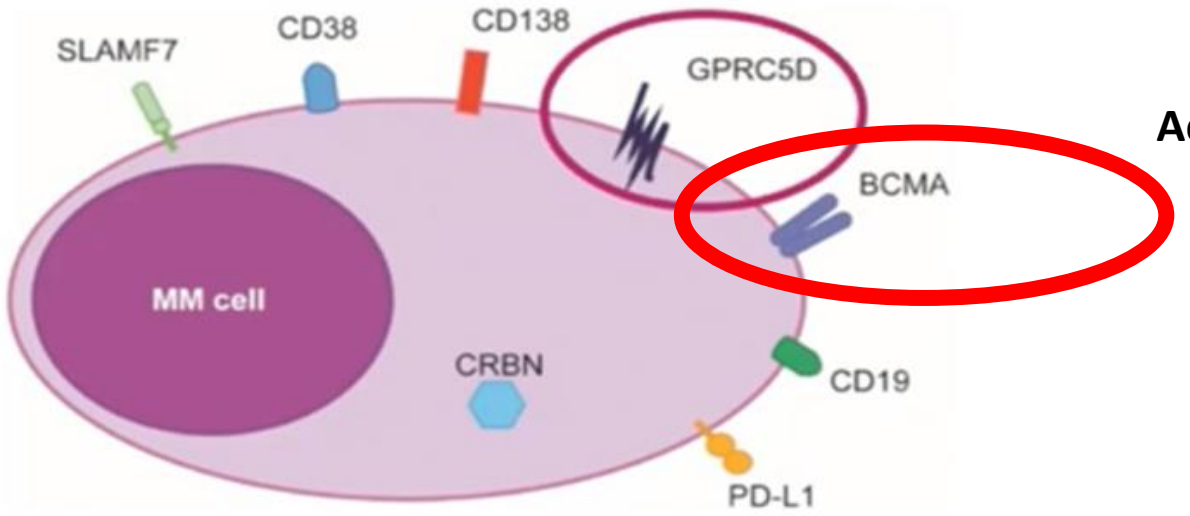
N=462
Tetra-réfractaires (Len/Pom/Bort/Carfil.)
Nb lignes 4 (3-13)

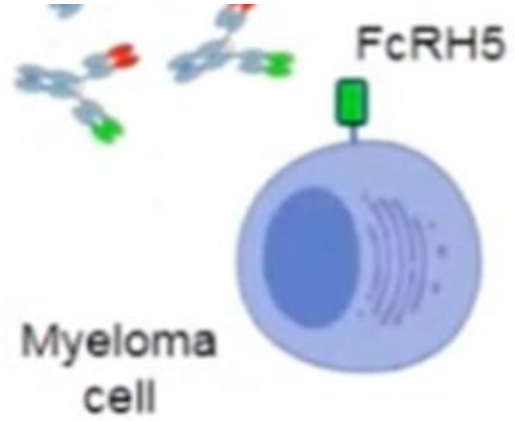


Etude MAMMOTH, Post-anti CD38
N=249
Nb lignes 5 (2-17)
Bi, Tri/Tetra et penta-réfractaires
Médiane SG: 8,6 m
Méd. SSP: 4,5-5,5 m

- Kumar SK, et al. Leukemia. 2017 ; Gandhi et al., Leukemia 2019; Ailawadhi et al., Cancer Med 2020

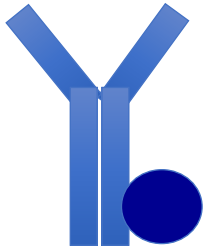
Myélome Multiple: Immunothérapies innovantes



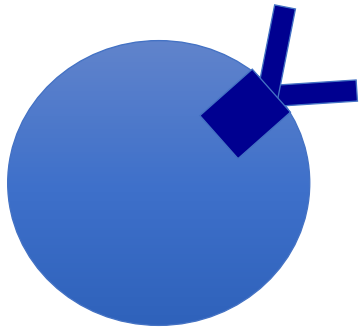


Immunothérapie Passive/adoptive

Ac monoclonaux couplés



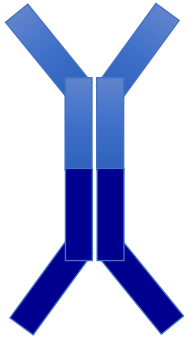
CAR-T/-NK



Immunothérapie active

Ac monoclonaux couplés

Ac Bispecific T/-NK



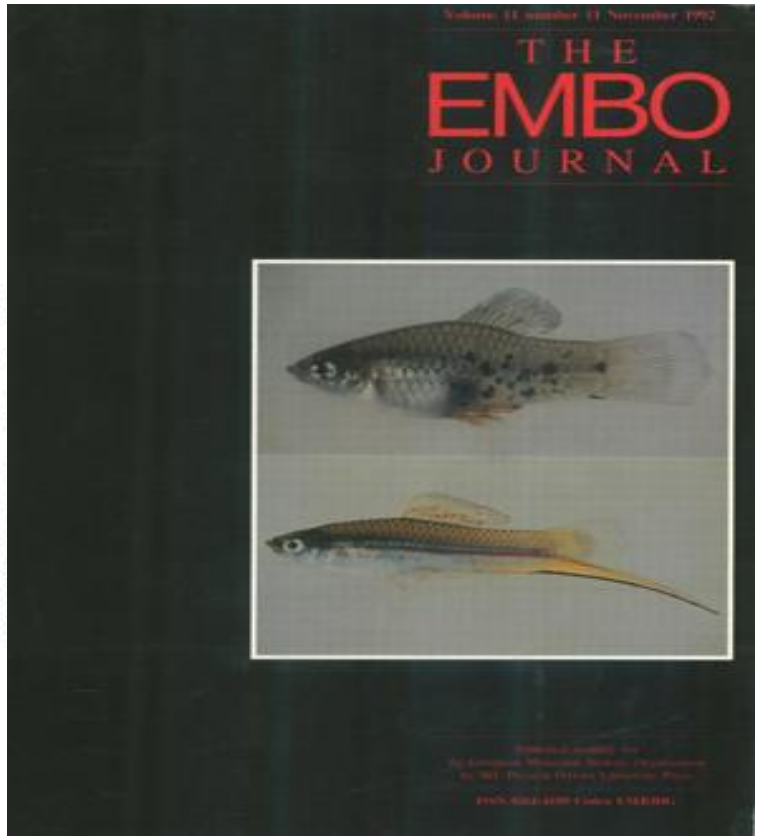
Principale Cible: BCMA

The EMBO Journal vol.11 no.11 pp.3897 – 3904, 1992

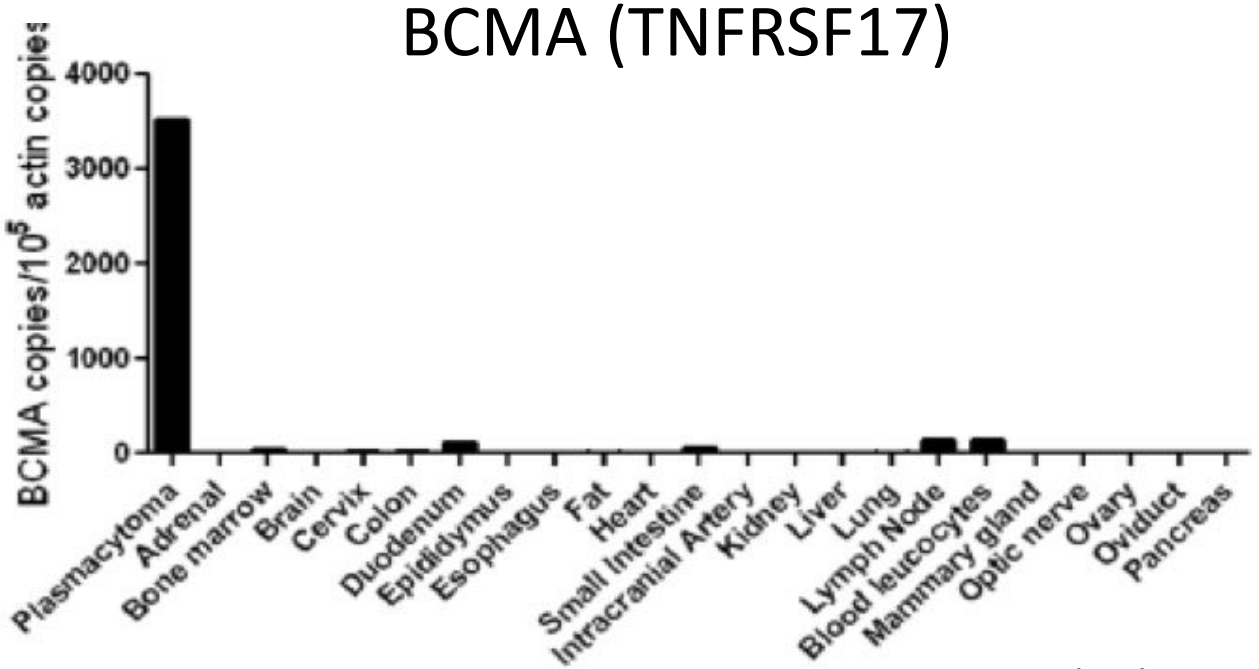
A new gene, BCM, on chromosome 16 is fused to the interleukin 2 gene by a t(4;16)(q26;p13) translocation in a malignant T cell lymphoma

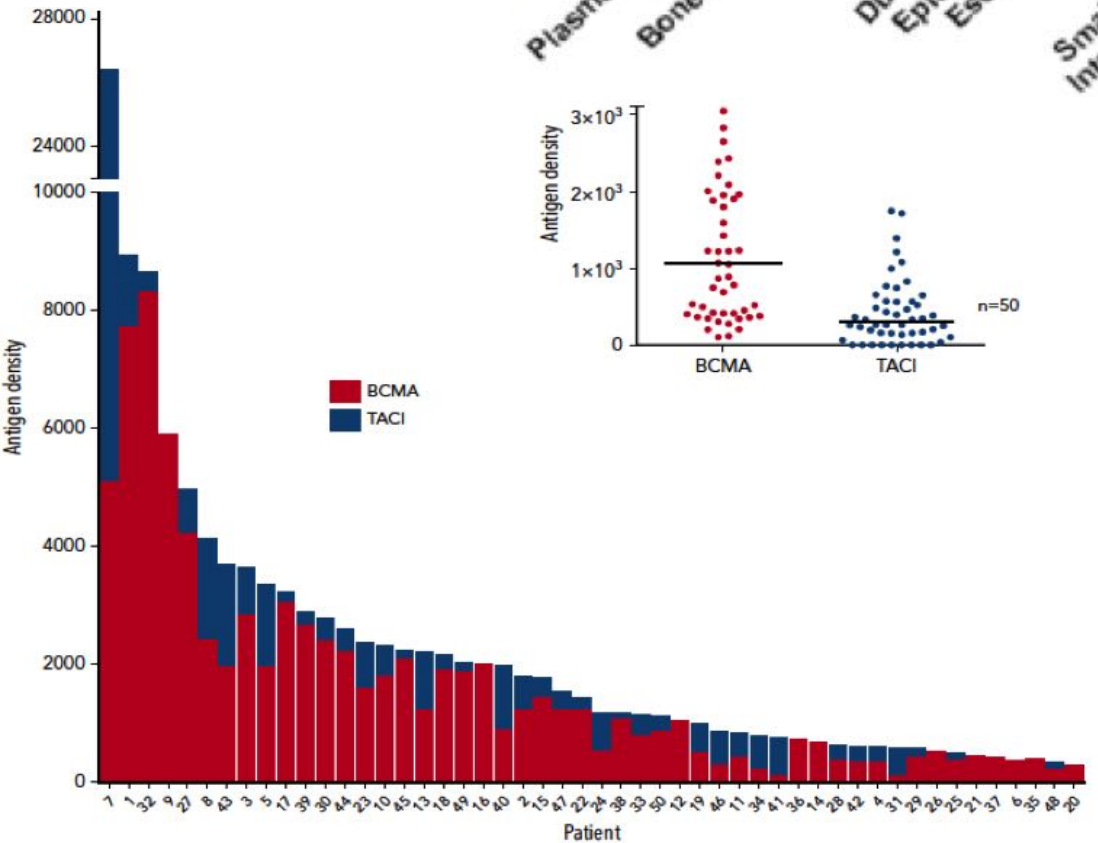
Y.Laâbi, M.P.Gras, F.Carbonnel[1], J.C.Brouet[2], R.Berger, C.J.Larsen and A.Tsapis[3]

Unité INSERM U 301 de Génétique Cellulaire et Moléculaire des Leucémies, Institut de Génétique Moléculaire, 27, rue J. Dodu, 75010 Paris, [1]Service de Gastro-Entérologie, Hôpital Saint Lazare, 75010 Paris and [2]Laboratoire d'Immunopathologie, Hôpital Saint Louis, 75010 Paris, France

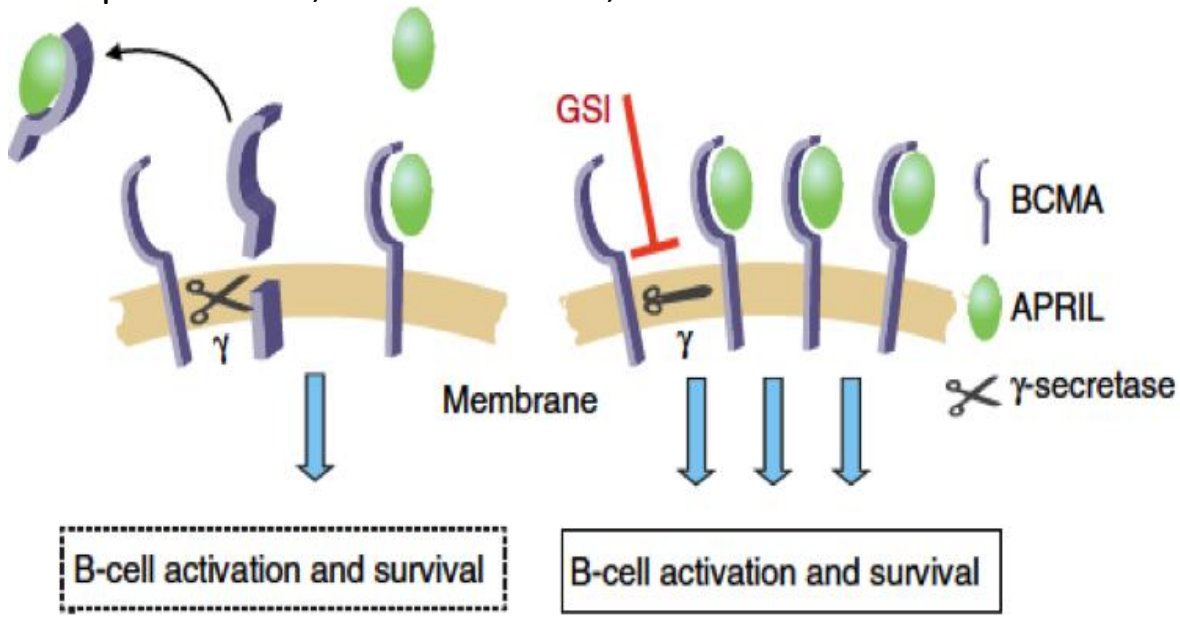


BCMA (TNFRSF17)





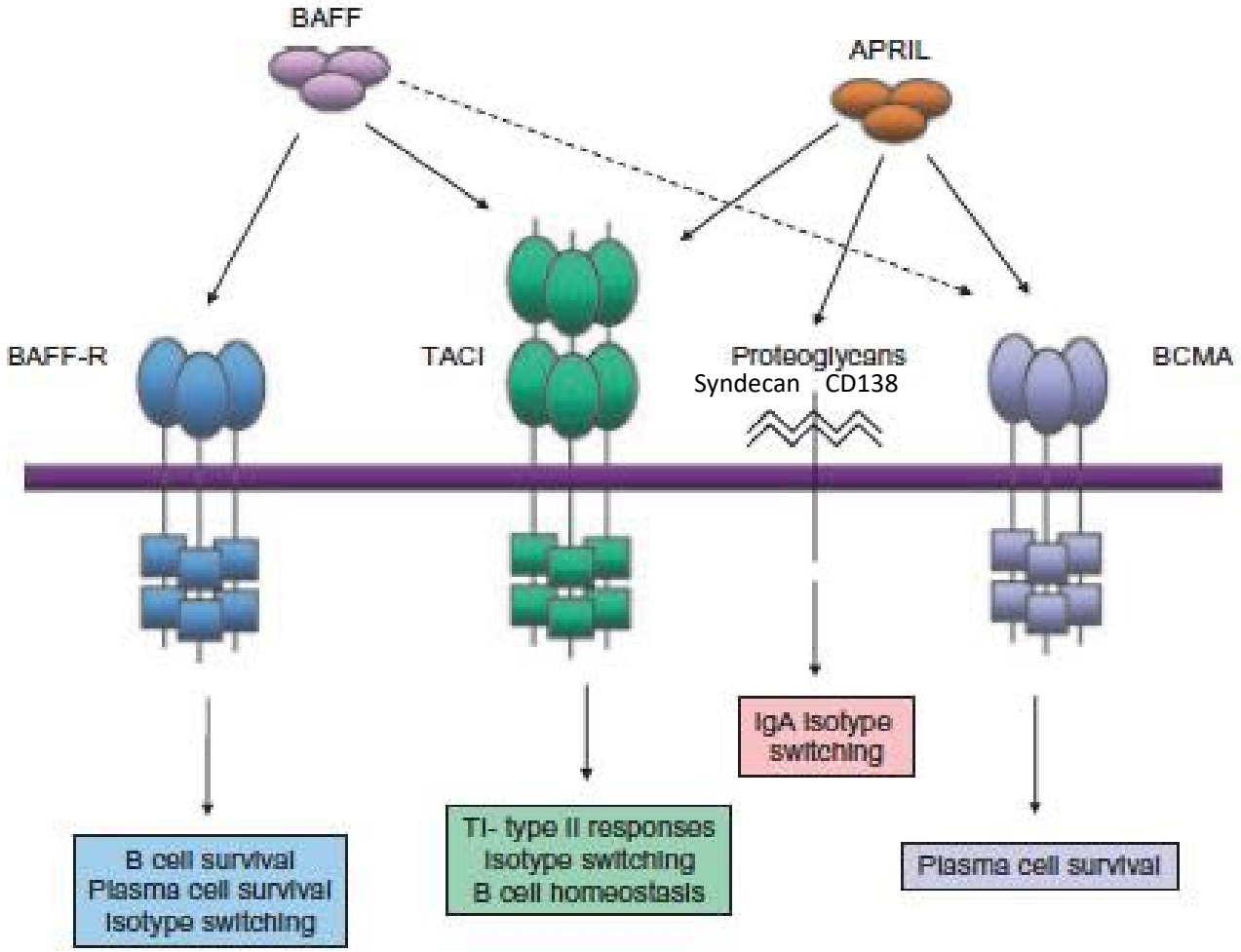
Carpenter et al., Clin Cancer Res., 2013

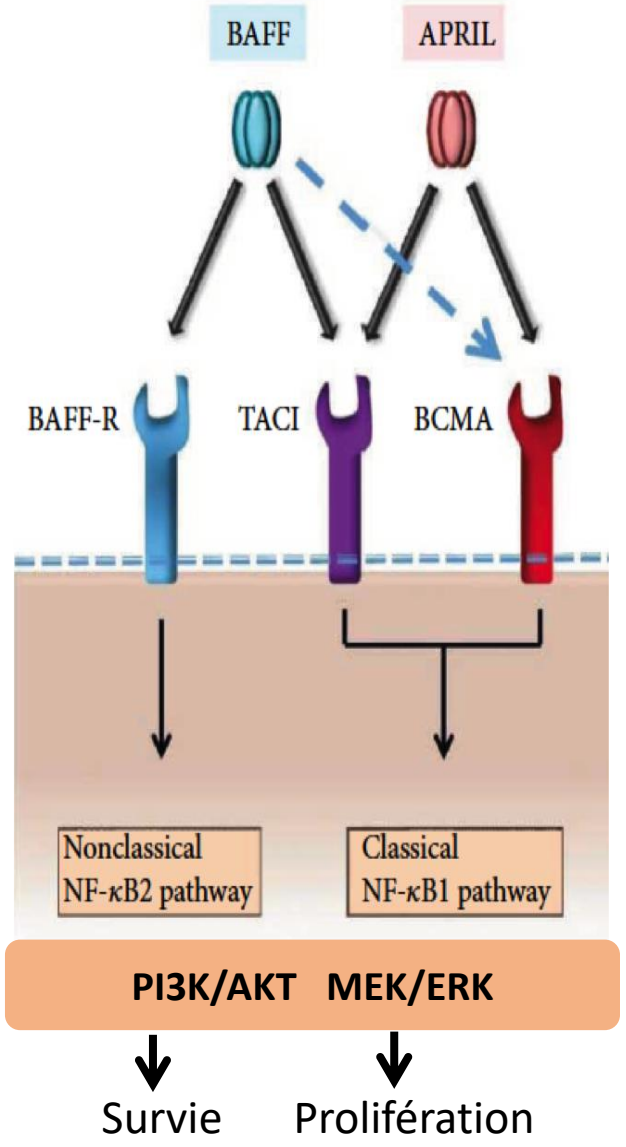


Lee et al., Blood 2018; Laurent et al., Nat Comm 2015

BCMA (TNFRSF17): Un membre de la famille des récepteur au TNF

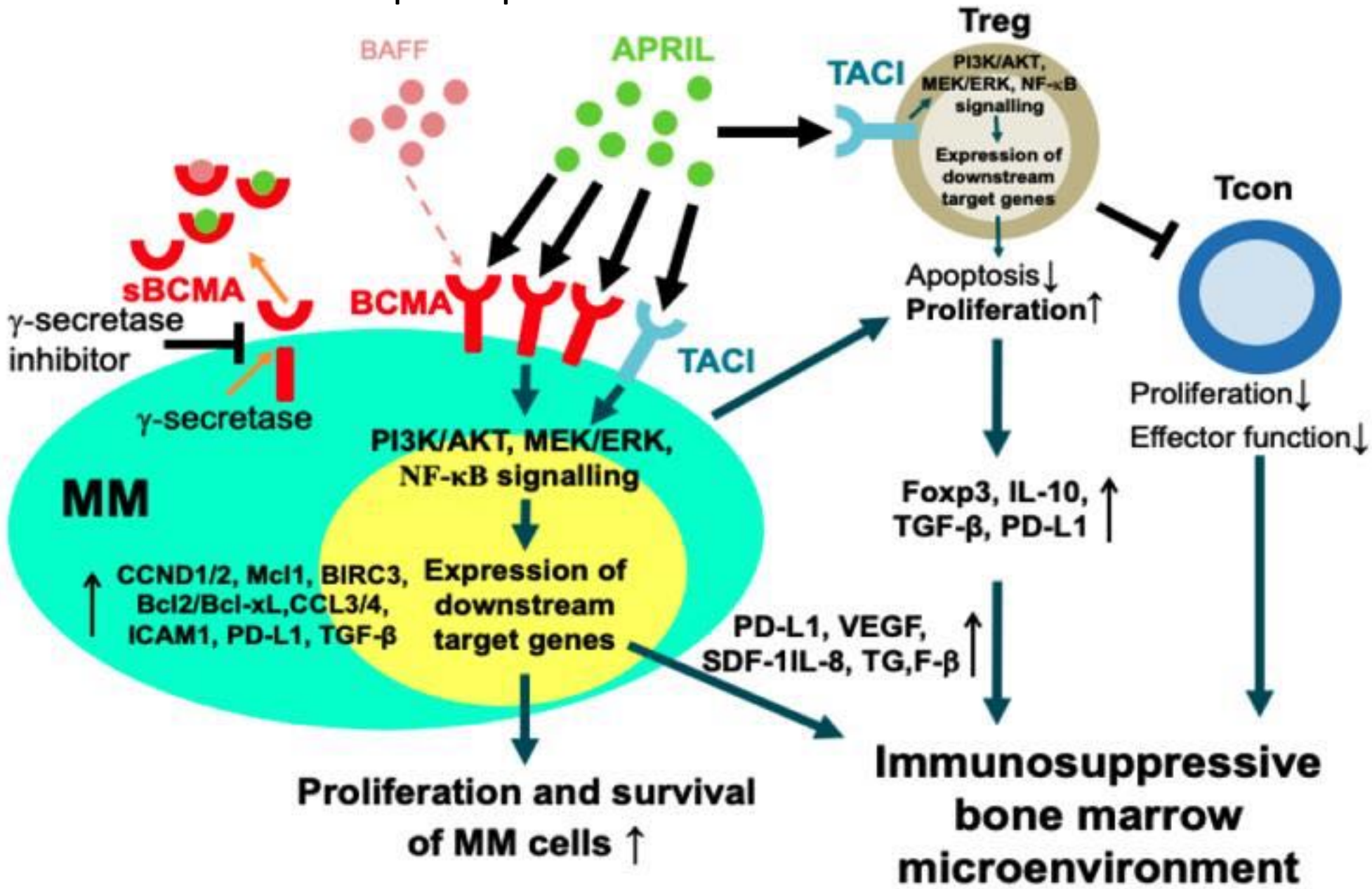
TRAF-interacting motif containing receptors	
TNF-R2	TNFRSF1B
CD40	TNFRSF5
CD30	TNFRSF8
CD27	TNFRSF7
LTβR	TNFRSF3
OX40	TNFRSF4
4-1BB	TNFRSF9
BAFFR	TNFRSF13C
BCMA	TNFRSF17
TACI	TNFRSF13B
RANK	TNFRSF11A
p75NTR/NGFR	TNFRSF16
HVEM	TNFRSF14
GITR	TNFRSF18
TROY	TNFRSF19
EDAR	EDA-A1R
XEDAR	EDA-A2R
RELT	TNFRSF19L
Fn14	TNFRSF12A





Bacheli et al., Clin exp Immunol 2007; Kampa et al., Frontiers Oncol. 2020

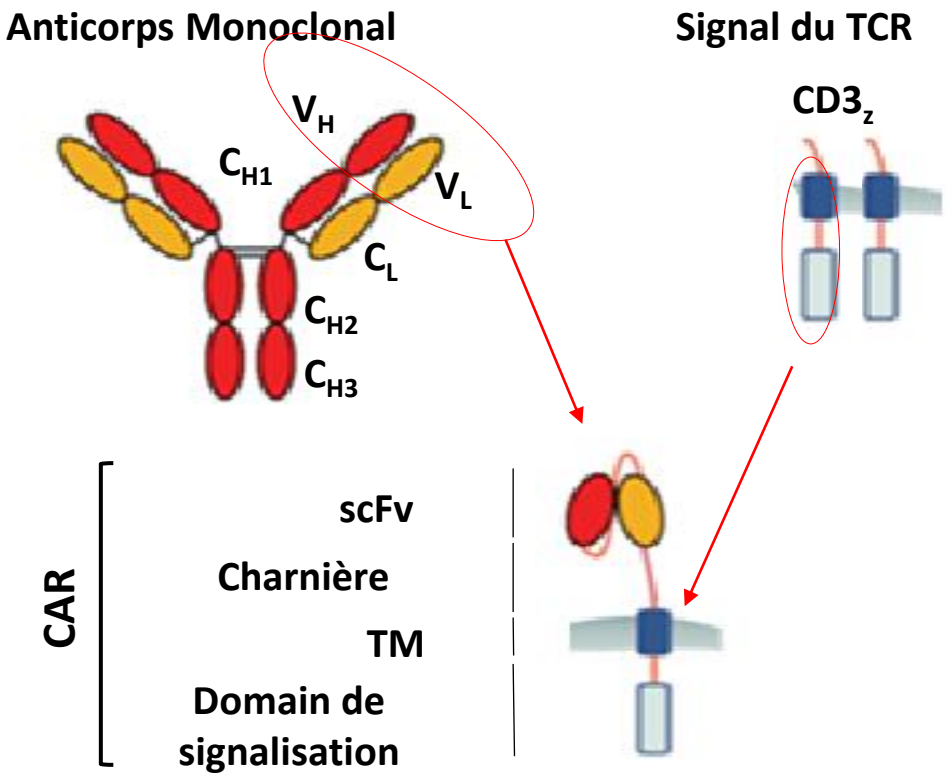
BCMA: Une nouvelle cible thérapeutique ?



Cho et al., Cancers 2020

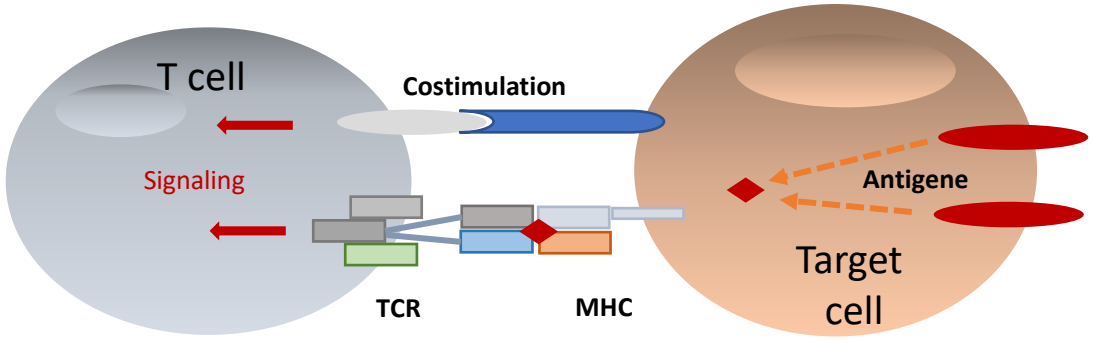
Structure et fonction des CAR

(revue Sadelain M. J Clin Invest. 2015)

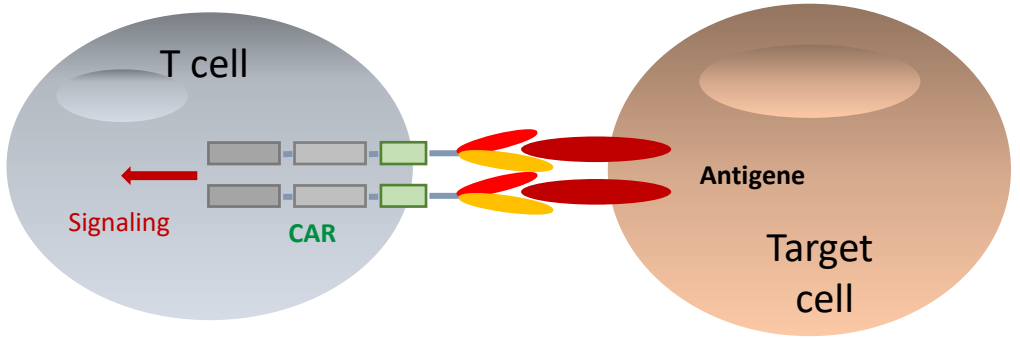


Structure des CARs de 1er génération

(Gross, G., and Z. Eshhar. 1992; Stancovski et al. 1993)



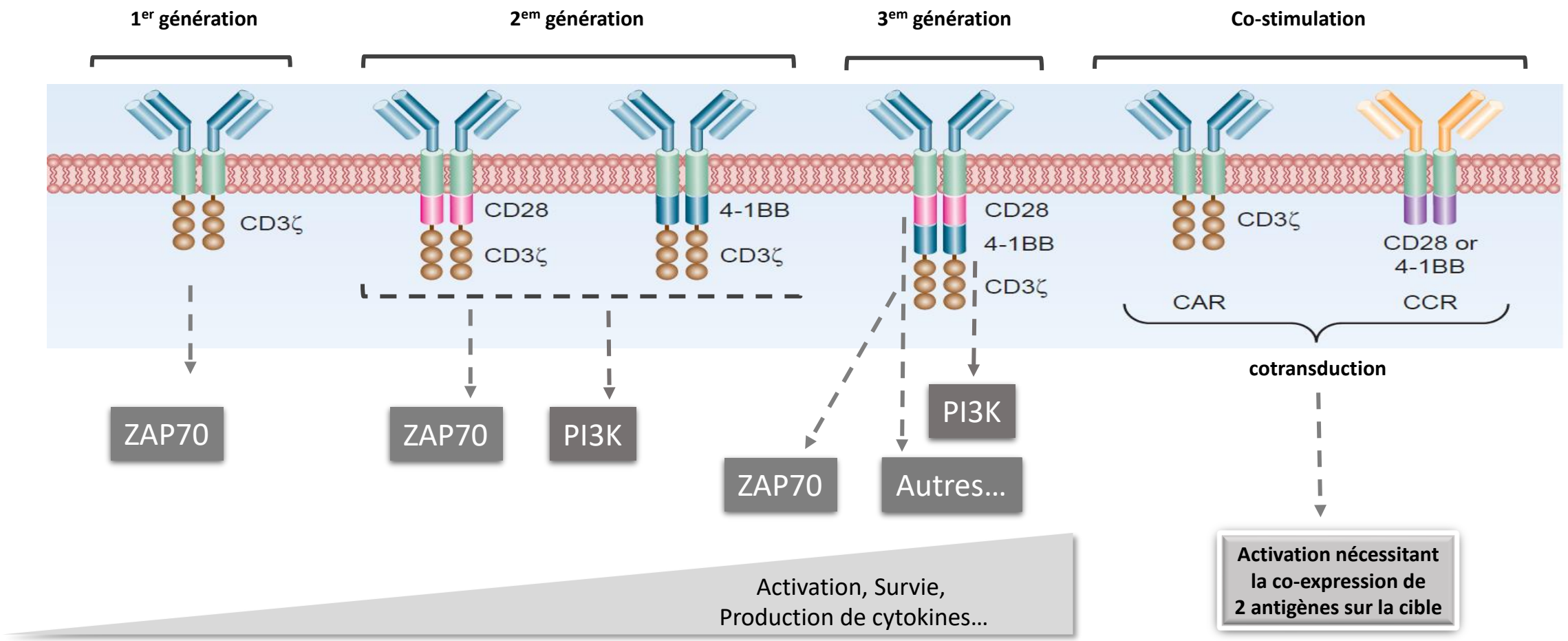
L'activation des T est dépendante du MHC



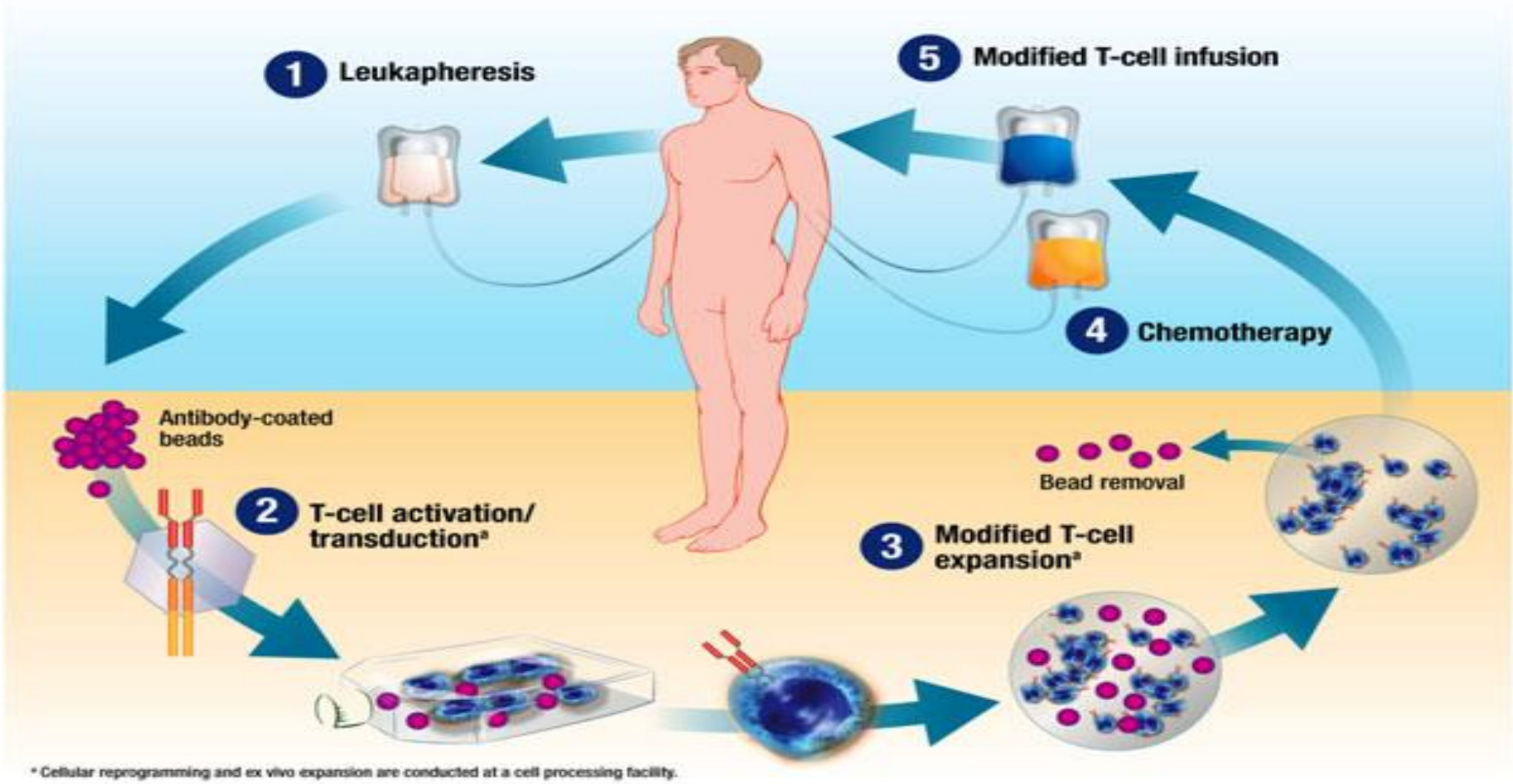
L'activation par les CARs est indépendante du MHC
mais dépend de la spécificité de l'anticorps d'origine

Structure et fonction des CARs

(from Maus et al 2014; Reviewed by Kershaw et al. 2013)

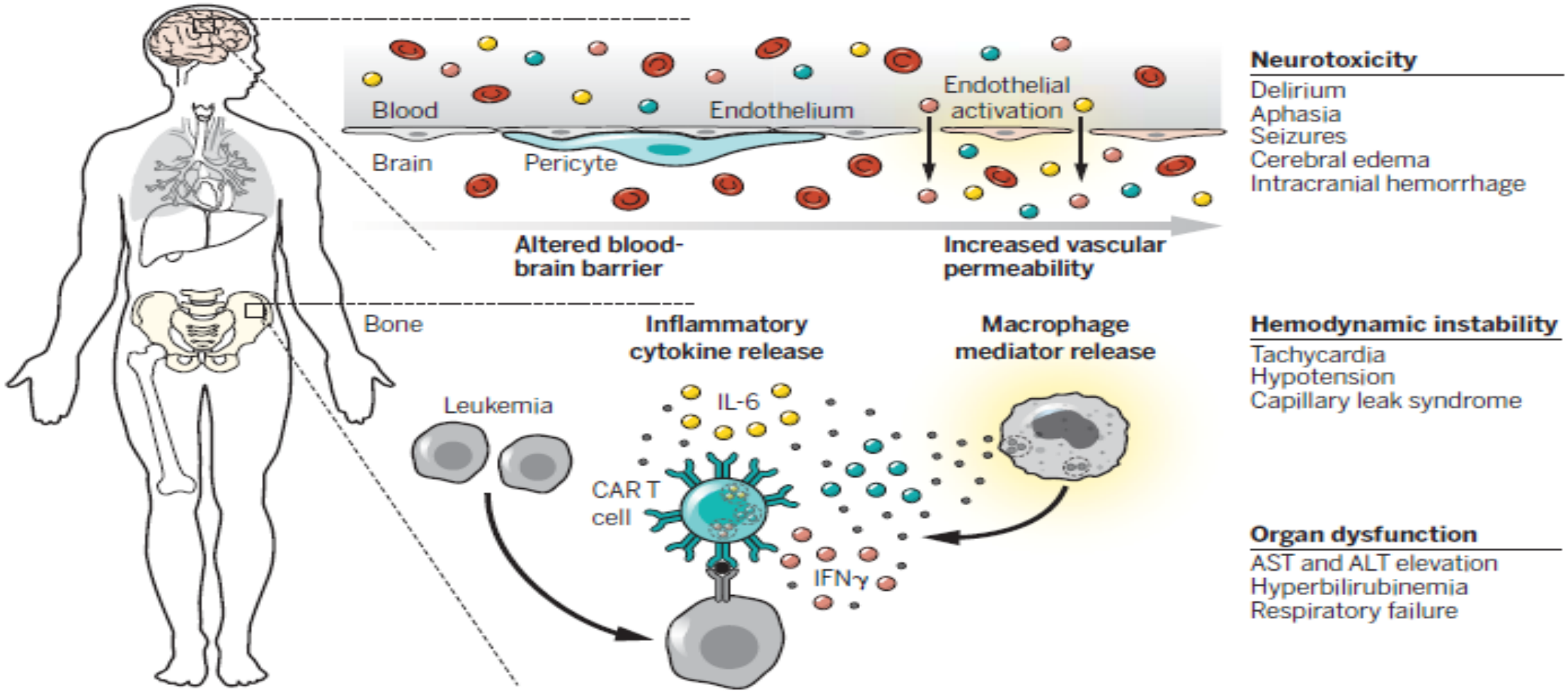


CAR T cells: Le circuit



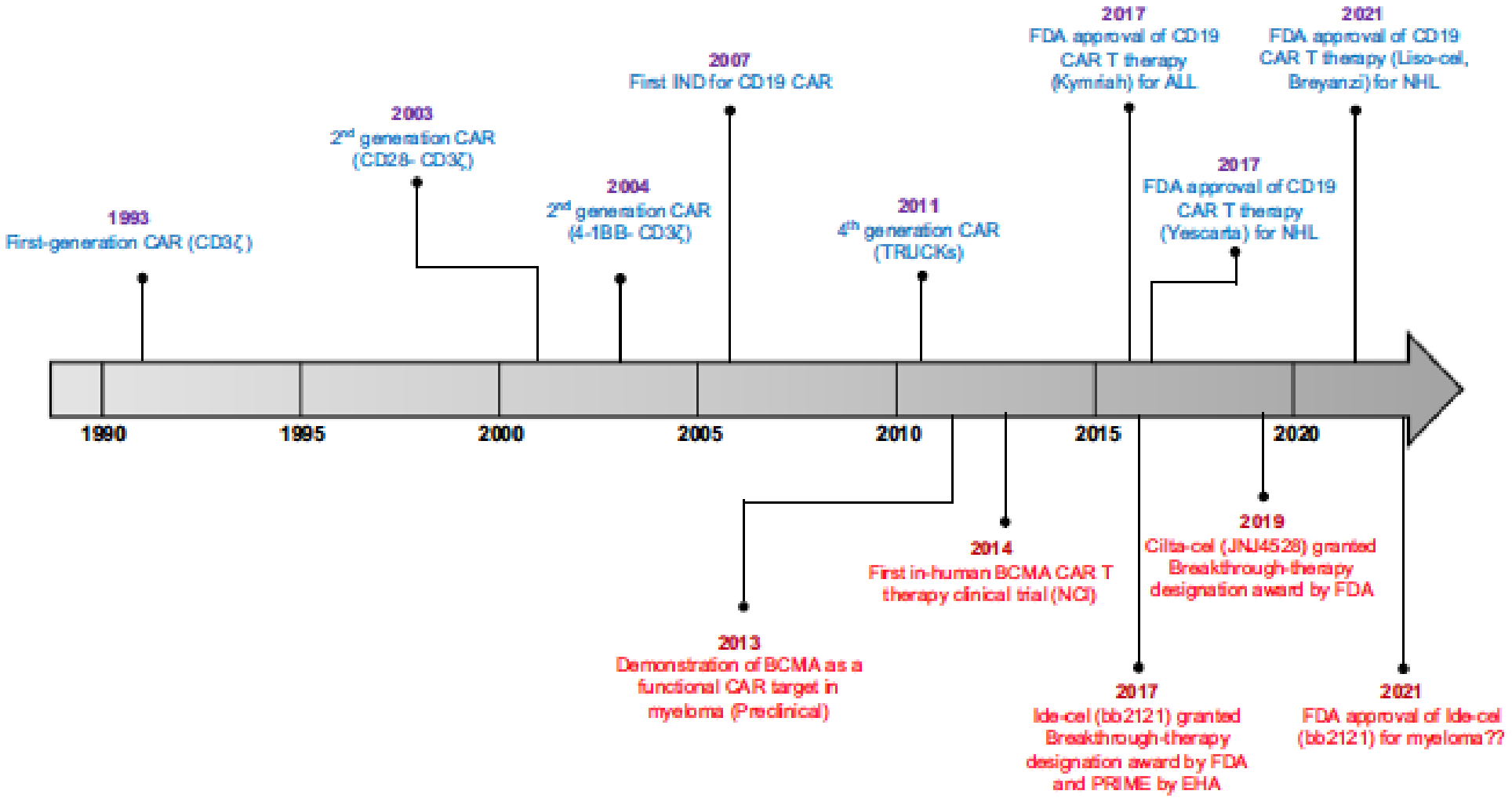
Wilcock and Webster, Nat Rev Drug Discov., 2019

CAR T cells: Les effets indésirables



June *et al.*, *Science* **359**, 1361–1365 (2018)

CAR T anti-BCMA

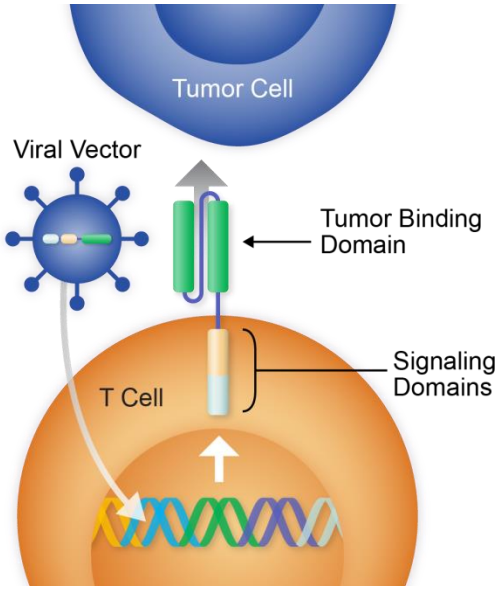


Teoh and Chng Blood Cancer Journal (2021)

CAR T-Cells anti BCMA dans le myélome multiple :

bb2121 : KarMMa-1

Idecabtagene Vicleucel (ide-cel)



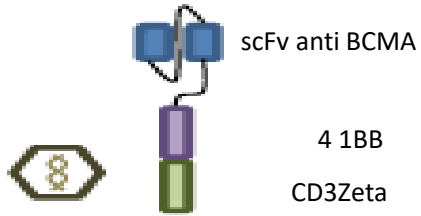
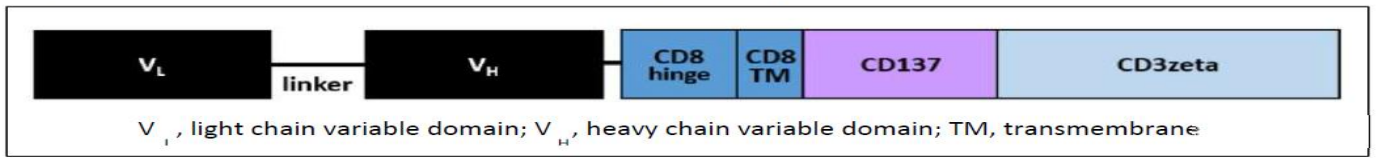
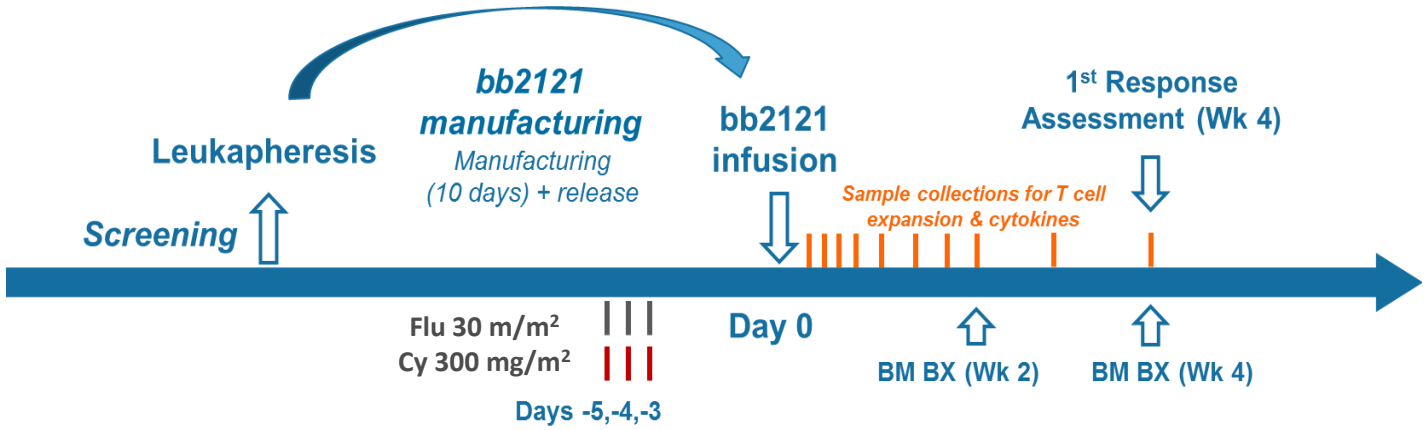


Figure 1: Anti-BCMA Chimeric Antigen Receptor





Dose Escalation (N=21)

≥50% BCMA expression

50 × 10^6 → 150 × 10^6 → 450 × 10^6 → 800 × 10^6

Dose Expansion (N=22)

< 50% BCMA expression (n=10)

≥ 50% BCMA expression (n=12)

Dose range: 150–450 × 10^6 CAR+ cells

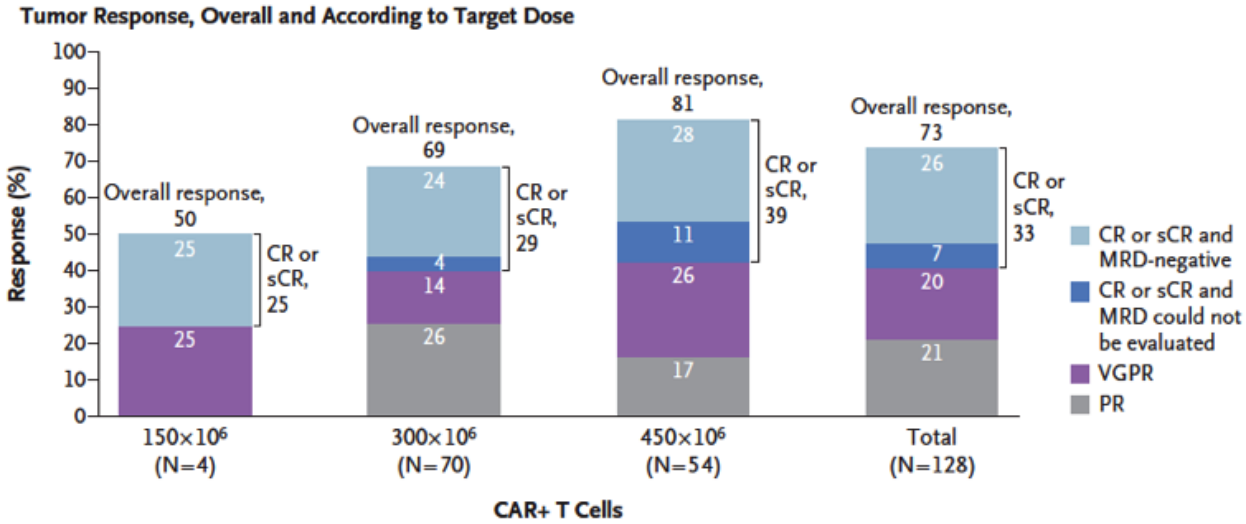
Ali SI, et al. Blood. 2016;128(13):1688-700; Raje et al. NEJM 2019

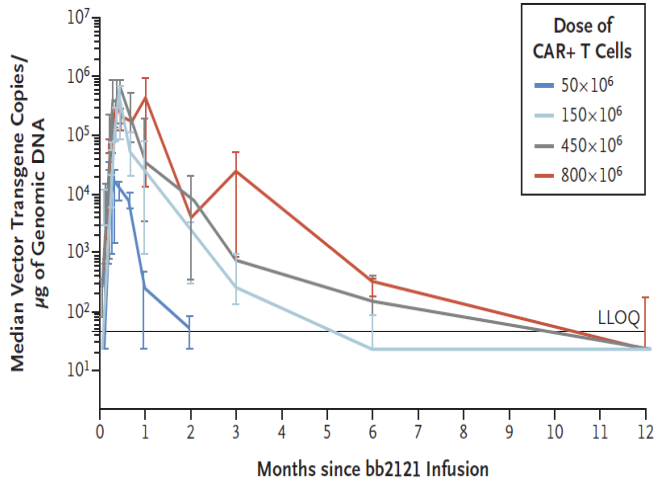
KarMMa-1: phase 1

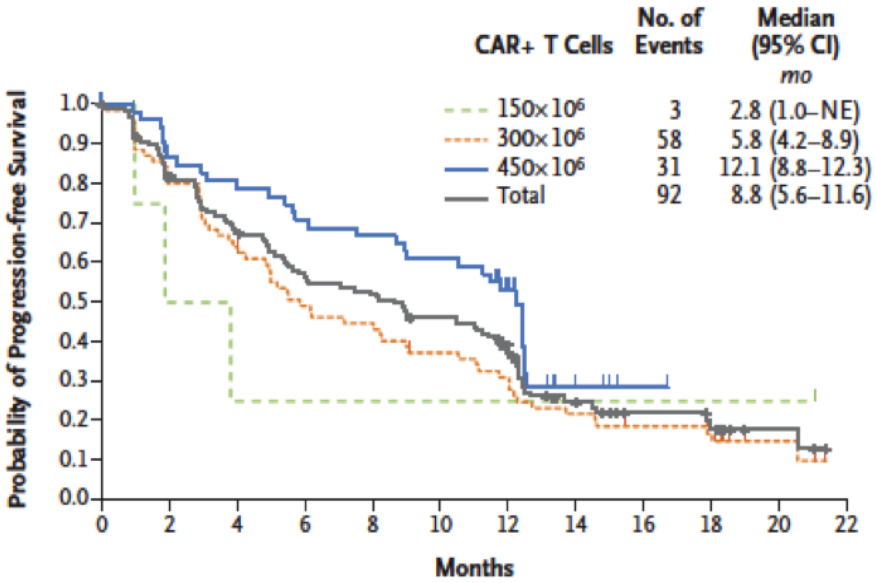
N=128
MM > 3 lignes (med.: **6** (3-21))
Réfractaires à derniere ligne

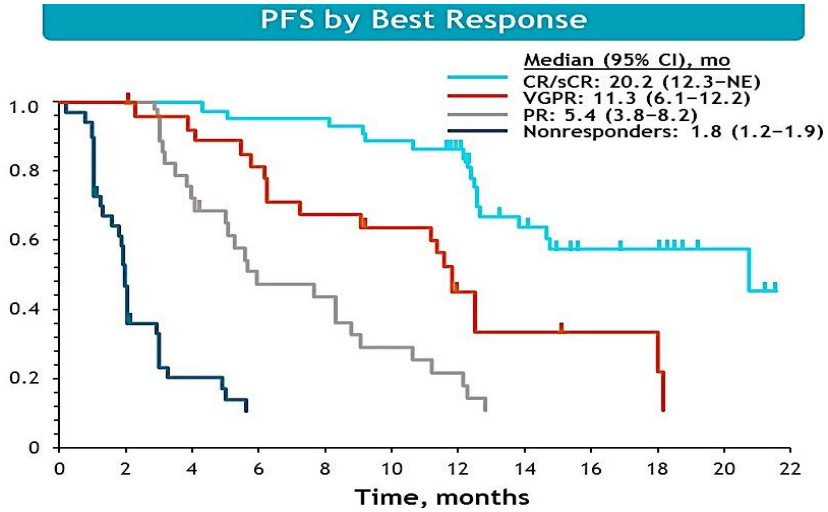
Triple réfractaires : 84%

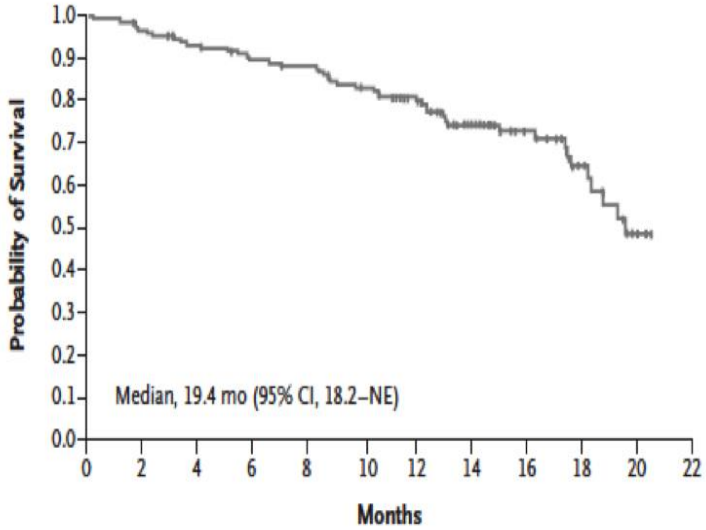
Penta réfractaires : 26 %









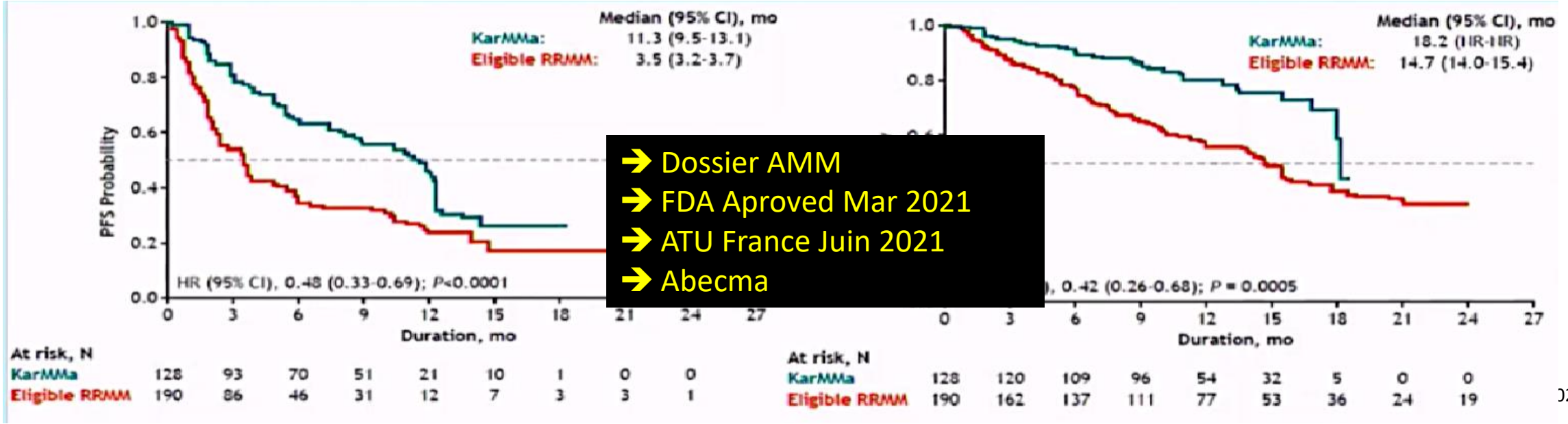


- Raje et al., NEJM 2019, Munshi et al., NEJM, 2021

Étude Ide-cel phase 2 pivotale: KarMMa-1

CRS, all / ≥G3, %	**84 / 6**
Med. time to CRS, day	1
Med duration CRS, day	5
Tocilizumab, %	52
ICANS, all, ≥G3, %	**18 / 3**
Neutropenia ≥G3, %	89
Thrombocytopenia ≥G3, %	52
Infection, all / ≥G3, %	69 / NA

5 décès:
2 progression
Aspergillose, CRS,hémorragie dig.
+1 DC à > 6 mois pneumopathie CMV



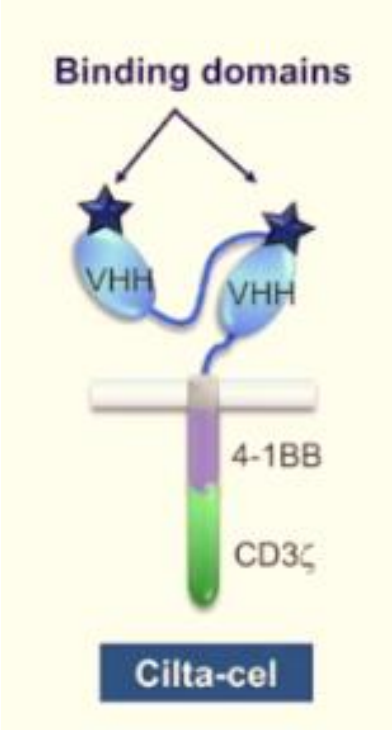
➔ Dossier AMM
➔ FDA Aproved Mar 2021
➔ ATU France Juin 2021
➔ Abecma

KarMMa RW

Martin et al.

020 ASCO 2020

CARTITUDE-1: Baseline Characteristics



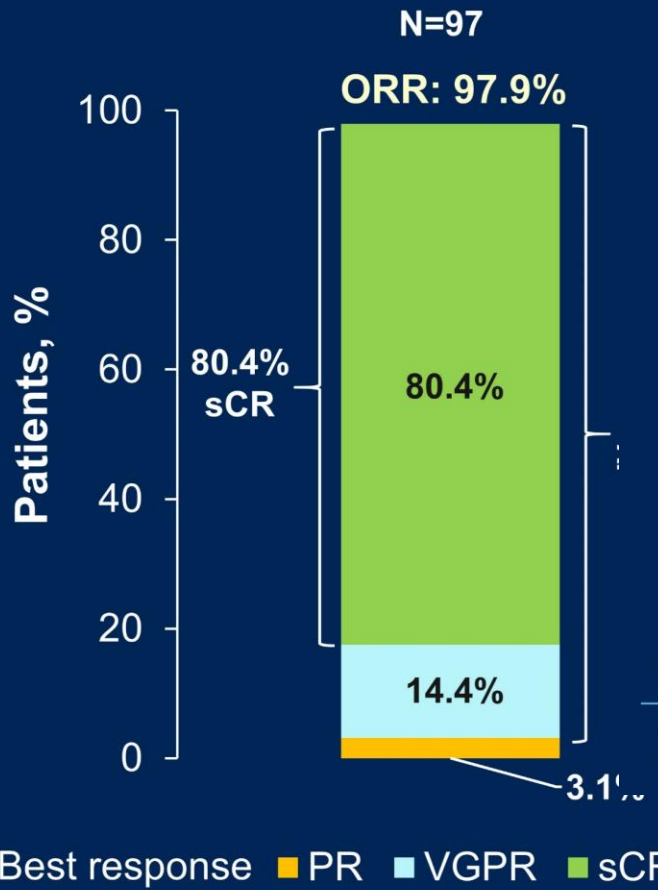
Characteristic	
Age, median (range) years	61.0 (43–78)
Male, n (%)	57 (58.8)
Black/African American, n (%)	17 (17.5)
All plasmacytomas,[a] n (%)	19 (19.6)
Extramedullary plasmacytomas, n (%)	13 (13.4)
Bone-based plasmacytomas, n (%)	6 (6.2)
Bone-marrow plasma cells ≥60%, n (%)	21 (21.9)
Years since diagnosis, median (range)	5.9 (1.6–18.2)
High-risk cytogenetic profile, n (%)	23 (23.7)
del17p	19 (19.6)
t(14;16)	2 (2.1)
t(4;14)	3 (3.1)
Tumor BCMA expression ≥50%, n (%)	57 (91.9)[b]

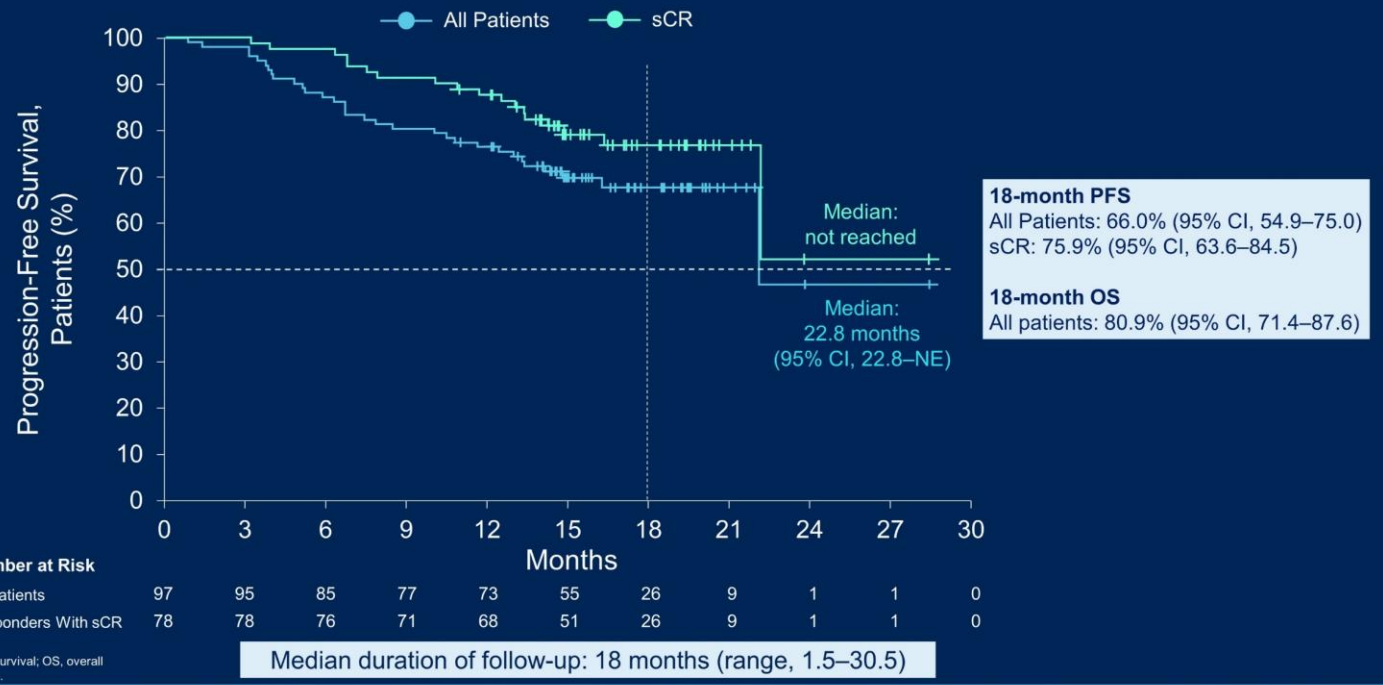
Characteristic	
Prior lines of therapy, median (range)	6.0 (3–18)
Prior lines of therapy, n (%)	
3	17 (17.5)
4	16 (16.5)
≥5	64 (66.0)
Previous stem-cell transplantation, n (%)	
Autologous	87 (89.7)
Allogeneic	8 (8.2)
Triple-class exposed,[c] n (%)	97 (100)
Penta-drug exposed,[d] n (%)	81 (83.5)
Triple-class refractory[c]	85 (87.6)
Penta-drug refractory[d]	41 (42.3)
Refractory status, n (%)	
Carfilzomib	63 (64.9)
Pomalidomide	81 (83.5)
Anti-CD38 antibody	96 (99.0)
Refractory to last line of therapy, n (%)	96 (99.0)

BCMA, B-cell maturation antigen; IMiD, immunomodulatory drug; PI, proteasome inhibitor.
[a]All plasmacytomas include extramedullary and bone-based plasmacytomas. [b]Denominator n=62, the number of evaluable samples; BCMA expression detected in all evaluable samples. [c]At least 1 PI, at least 1 IMiD, and 1 anti-CD38 antibody. [d]At least 2 PIs, at least 2 IMiDs, and 1 anti-CD38 antibody.

CARTITUDE-1:

CARTITUDE-1: Progression-Free Survival





18-month PFS
All Patients: 66.0% (95% CI, 54.9–75.0)
sCR: 75.9% (95% CI, 63.6–84.5)

18-month OS
All patients: 80.9% (95% CI, 71.4–87.6)

Median duration of follow-up: 18 months (range, 1.5–30.5)

NE, not estimable; PFS, progression-free survival; OS, overall survival; sCR, stringent complete response.

CR, complete response; ORR, overall response rate; sCR, stringent complete response; VGPR, very good partial response. ORR assessed by independent review committee. [a]Subgroups by number of prior lines of therapy (≤4, >4), refractoriness (triple-class, penta-drug), cytogenetic risk (high risk, standard risk), baseline bone marrow plasma cells (≤30%, >30 to <60%, ≥60%), baseline tumor BCMA expression (≥median, <median), and baseline plasmacytomas (including extramedullary and bone-based).

Presented By: Saad Z Usmani

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CARTITUDE-1: Safety

No new safety signals with longer follow-up

	N=97	
	Any grade	Grade 3/4
Hematologic AEs ≥25%, n (%)		
Neutropenia	93 (95.9)	92 (94.8)
Anemia	79 (81.4)	66 (68.0)
Thrombocytopenia	77 (79.4)	58 (59.8)
Leukopenia	60 (61.9)	59 (60.8)
Lymphopenia	51 (52.6)	48 (49.5)
Nonhematologic AEs ≥25%, n (%)		
Metabolism and nutrition disorders		
Hypocalcemia		3 (3.1)
Hypophosphatemia		7 (7.2)
Decreased appetite		
Hypoalbuminemia		
Gastrointestinal		
Diarrhea		
Nausea		
Other		
Fatigue		
Cough		
AST increas		
ALT increased		

CRS	N=97
Patients with a CRS event,[a] n (%)	92 (94.8)
Time to onset, median (range) days	7 (1–12)
Duration, median (range) days	4 (1–97)[b]

Of 92 patients with CRS, majority (94.6%) were grades 1/2
CRS resolved in 91 (98.9%) patients within 14 days of onset

	N=97
Total CAR T-cell neurotoxicities, n (%)	
Any Grade	20 (20.6)
Grade ≥3	10 (10.3)
ICANS, n (%)	
Any Grade	16 (16.5)
Grade ≥3	2 (2.1)
Other neurotoxicities,[c] n (%)	
Any Grade	12 (12.4)
Grade ≥3	9 (9.3)

Paralysie Faciale…
Syndromes parkinsoniens…
=====
Prévention par diminution masse tumorale avant injection CAR T et utilisation précoce du Tocilizumab

AE, adverse event; ALT, alan… and Cellular Therapy; CRS, cytokine release …drome: HLH, hemophagocytic lymphohistiocytosis.
[a]CRS was graded using Lee et a… alysis, Lee et al. criteria were mapped to ASTCT criteria for patients in the phase 1b portion.
[b]The patient with 97-day duration di… from CRS and/or ICANS).

CAR T cells anti-BCMA

	KarMMa[1] (n=128)	CARTITUDE-1[2] (n=97)
Nom	bb2121,ide-cel	JNJ-4528, cilta-cel
scfv	Chimeric mouse	Chimeric lama
Nb Cel. CAR T	450M	0.75M/kg
Nb de lignes ant.	6	5
HR/EMD, %	35/39	27/10
Triple/Penta-Ref	84/26	86/28
ORR/CR, %	82/39	97,9/89,4
MRD- (10^{-5}), %	28 at 450M	50
PFS/OS, med. , m	12.1 à 450M/19.4	> 22,8/NR
CRS, all / ≥G3, %	84 / 6	94,6 / 5,4
Délai app./durée	1j / 5j	7j / 4j
Tocilizumab, %	52	79
ICANS, all, ≥G3, %	18 / 3	20 / 10
Infection, all / ≥G3, %	69 / NA	NA / 19

[1] Munshi et al NEJM 2021, [2] Berdeja et al. ASCO 2020, [3] Mailankody et al. ASCO 2020, [4] Berdeja et al. ASH 2019

CAR T anti-BCMA: meta analyse

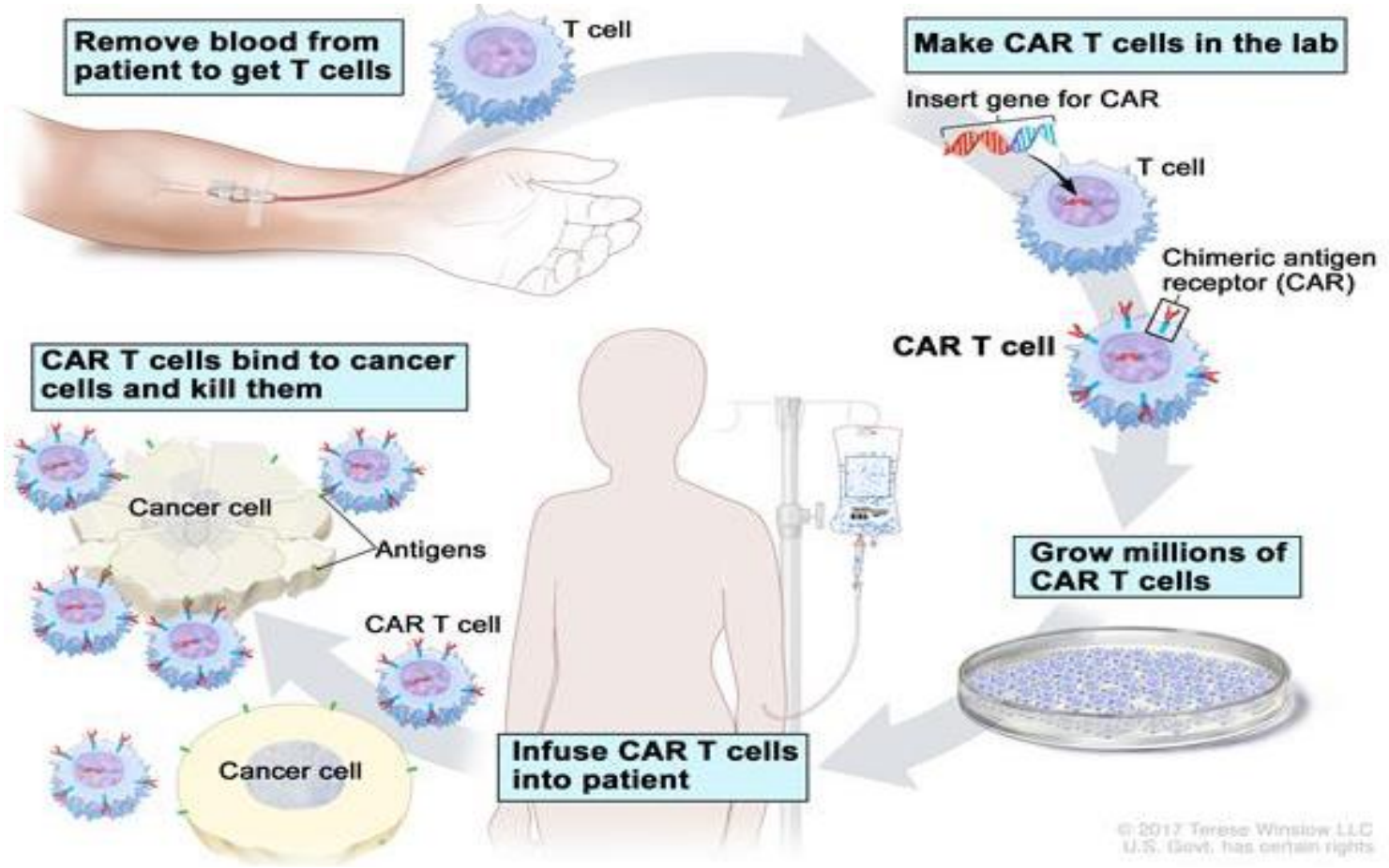
meta-analyse 23 differents anti BCMA-CAR T-cell chez 640 patients,
ORR of 80.5%, dont 44.8% CR
median PFS: 12.2 months

BCMA perte (# 5%) ou plus souvent diminution d'expression

CRS et neurotoxicité : 80.3% and 10.5%, respectivement

Roex, G. et al. J. Hematol. Oncol (2020); Teoh and Chng Blood Cancer Journal (2021)

CAR T Résistance/Perte d'efficacité et toxicité: Comment faire mieux ?



CAR T Résistance/Perte d'efficacité et toxicité: Comment faire mieux ?

- **Perte des CAR T**

- Quantitative (absence de persistance, de phénotype mémoire; immunogénicité)

- Fonctionnelle (exhaustion, perte cytotoxicité, micoenvironement)

- **Perte antigène/modulation antigénique**

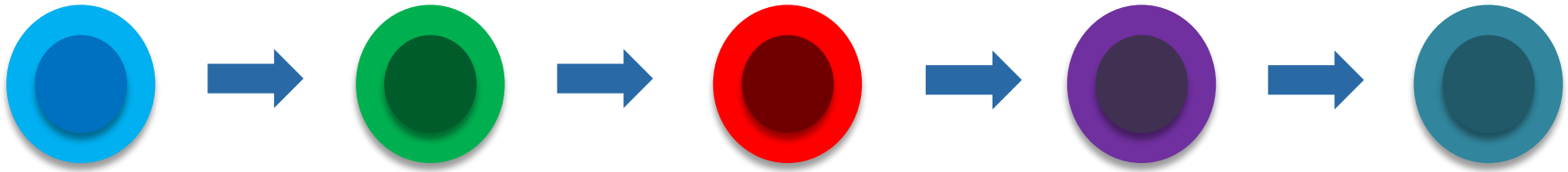
- Perte d'expression

- Modulation

- Clivage (gamma secretase)

Autre cible
GPRC5D, CD38, CS1
CAR reconnaissant
deux antigènes
BCMA/CS1
BCMA/GPRC5D
……

Différenciation des cellules T



Tn — *naive*

Tscm — *memory stem t cells*

Tcm — *central memory*

Tem — *effector memory*

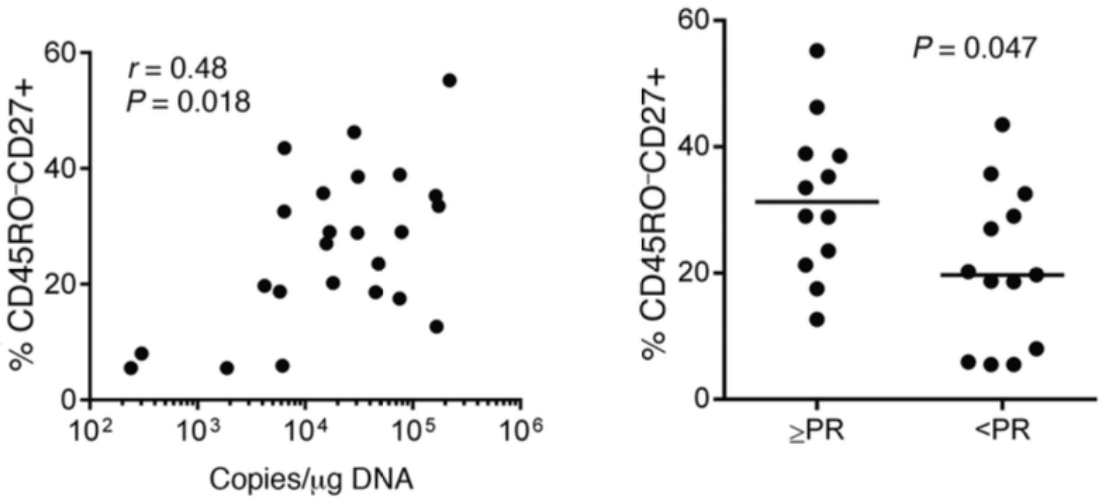
Temra — *terminally differentiated Teff*

Rôle pronostic des populations T à l'origine des CAR T

Qualité du Produit d'Aphérèse

CD45RA+/RO- CCR7+ CD27+ naive/early memory (stem-cell like)
faible expression of PD1, LAG3, Tim-3
CAR-T avec capacité proliferative et de persistance

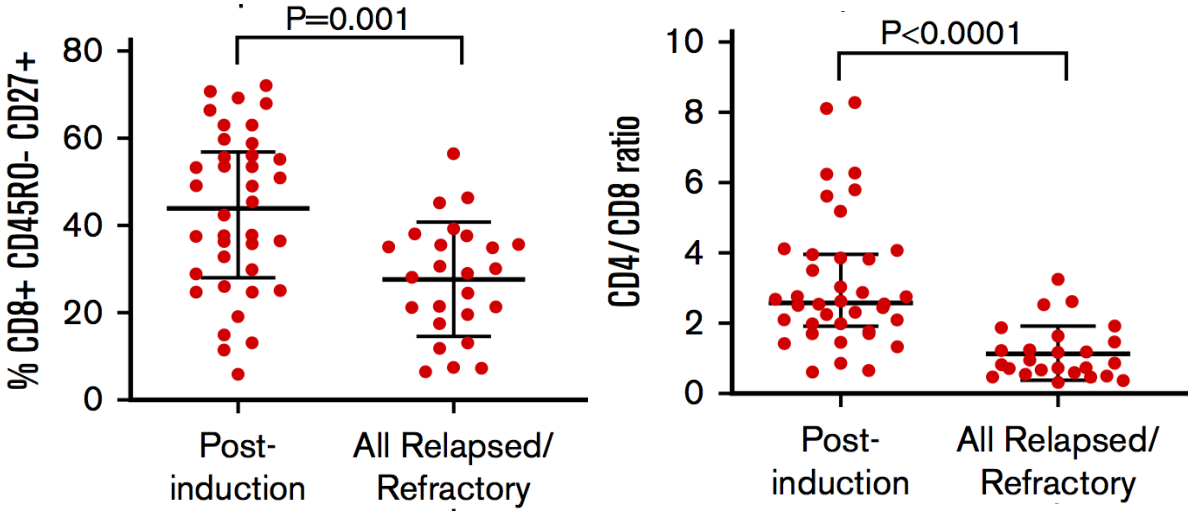
Fraietta Nat Med 2018



CD8⁺CD45RO⁻CD27⁺ memory phenotype

Cohen et al., JCI 2019

Impact des traitements préalables



Garfall et al., *Blood Advances* 2019

CAR T cell anti BCMA et myélome multiple : Perspectives

Essais en cours ou à venir :

MM > 3 lignes

KarMMa-1: pivotale
KarMMa-2 : Cohorte 1 phase Ib

➔ **ATU / AMM**
Abecma (Ide-Cel)

CARTITUDE-1: phase 1b

MM rechute précoce

KarMMa-3 : phase 3, 2 à 4 lignes ant.; exposé IP, IMID anti CD38: bb2121 *vs* triplet

KarMMa-2 :
Cohorte 1ere rechute précoce

CARTITUDE-4 : phase 3,
MM en rechute Lenalidomide réfractaire
JNJ4528 vs triplet

CARTITUDE-2 :
ph 2, Cohorte rechute précoce

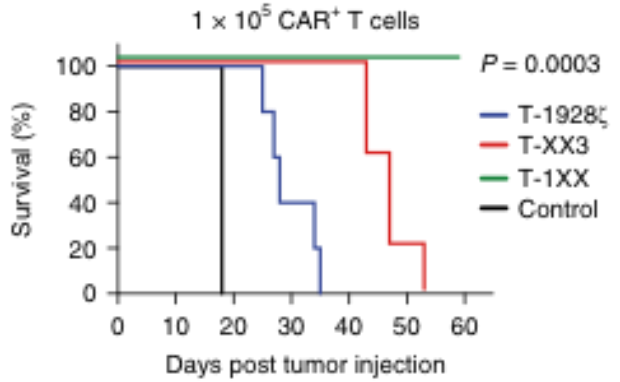
MM 1ère ligne

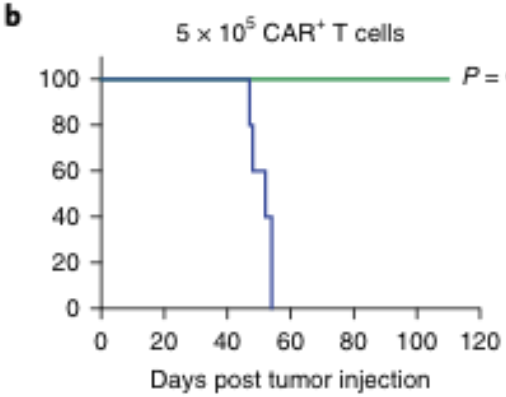
KarMMa-2 :
Cohorte 1ère ligne
non RC post autogreff

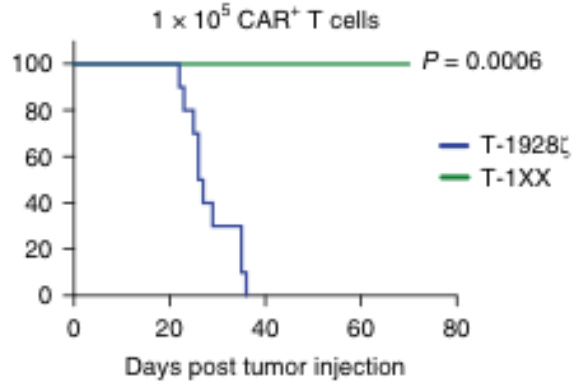
CARTITUDE-2 :
Cohorte 1e ligne
non RC post autogreffe

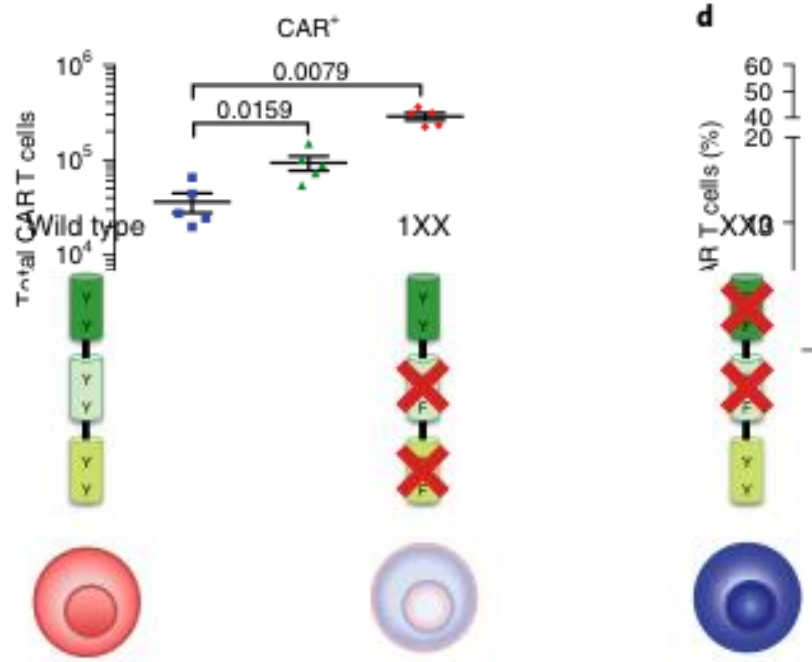
CARTITUDE 5:
VRD-RD vs VRD-Cilta cel

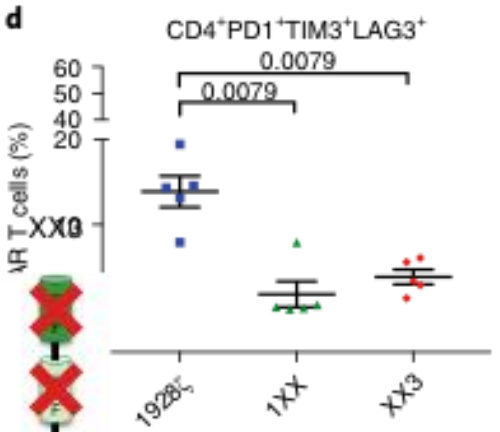
KarMMa 4 :
High risque première ligne à la place de l'autogreffe

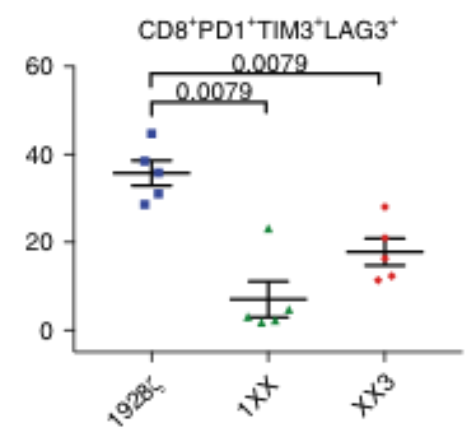


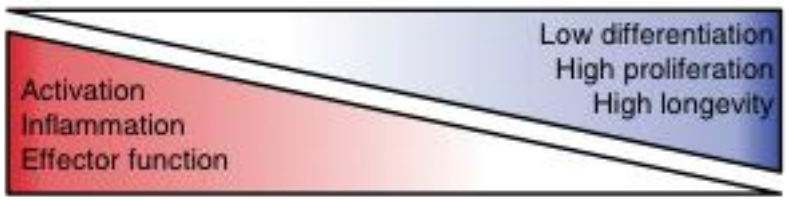












Moduler le signal de transduction du CD3
Pour plus de CAR T mémoires ….

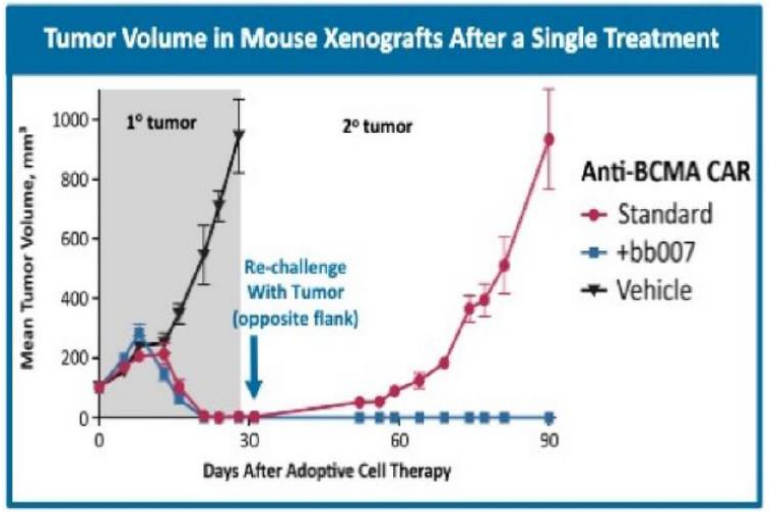
Feucht et al., Nat Med 2019

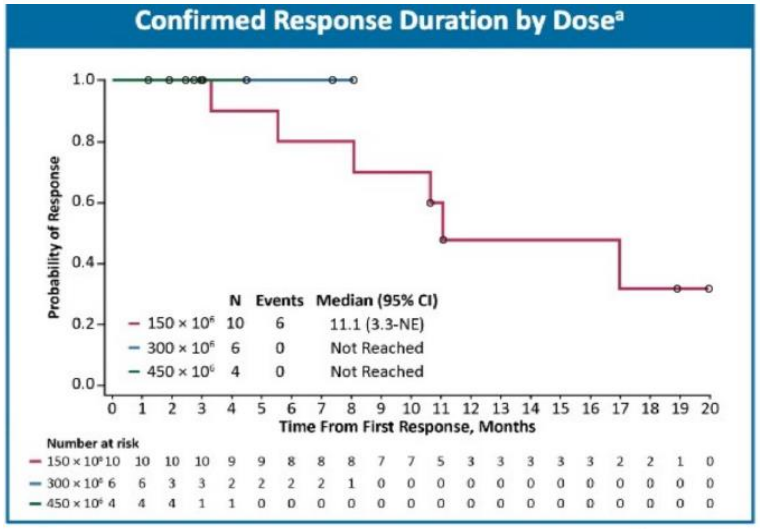
Comment améliorer la persistance des CAR T cell dans le myélome multiple ?

- Améliorer persistance des CAR T
  - Enrichissement en T CD8 mémoires (bb21217, JCARH125)
  - Humanisé (JCAR 125)

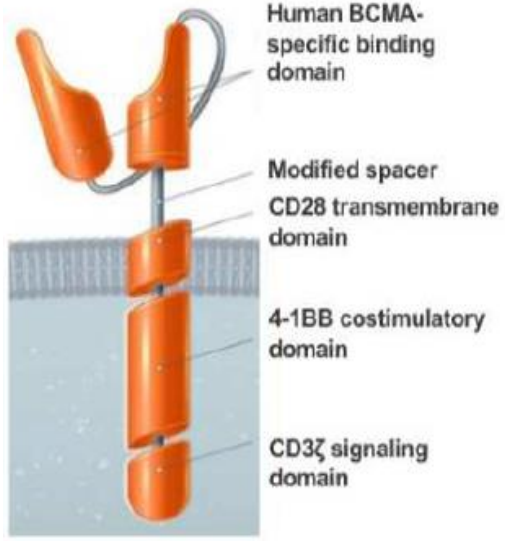
(Absence d'immunogénicité)

bb21217 Berdeja J et al. ASH2019

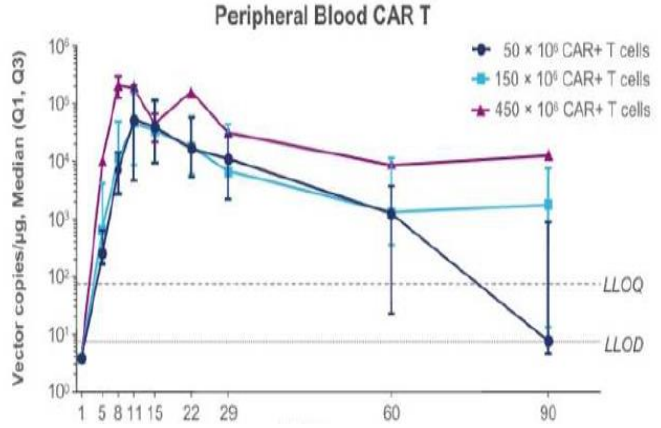




JCARH125
Mailankody S et al ASH2018



Ratio CD4:CD8
1



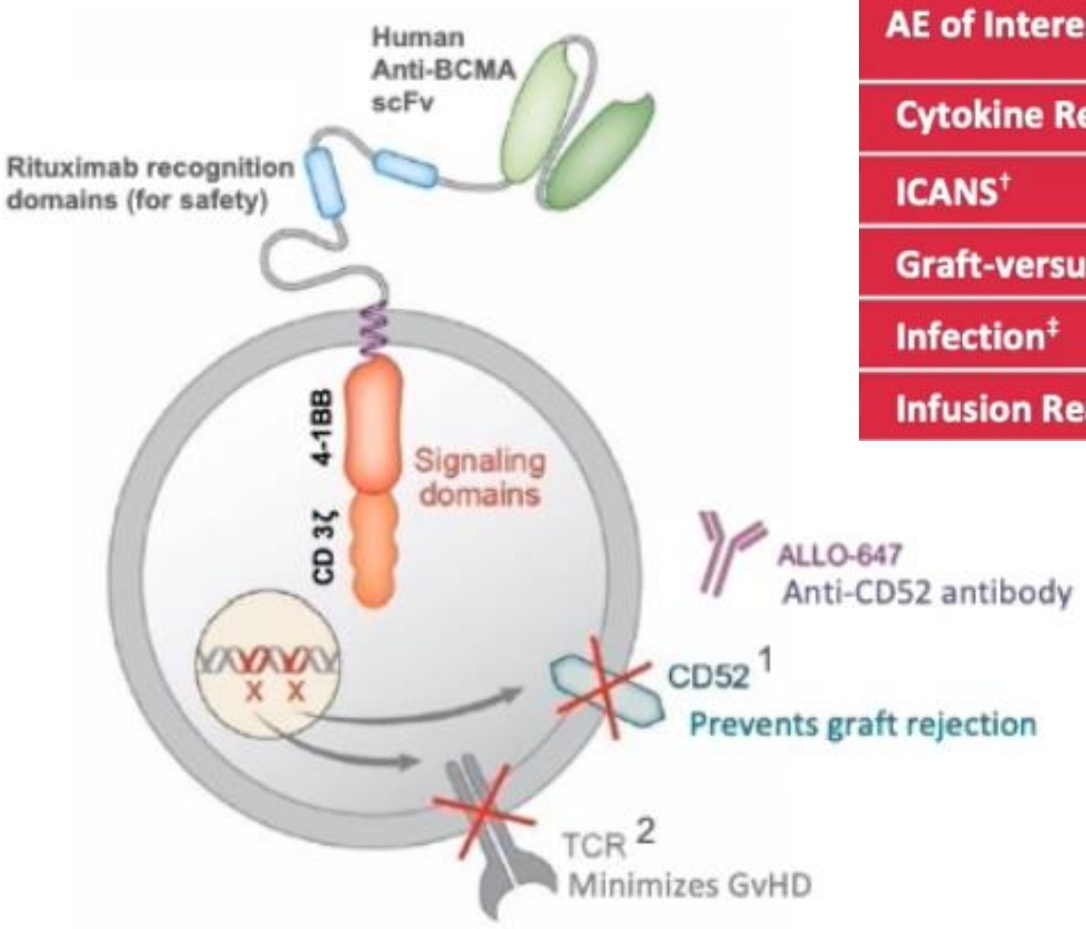
CAR T cells anti-BCMA

	KarMMa[1] (n=128)	CARTITUDE-1[2] (n=97)	EVOLVE[3] (n=62)	bb21217[4] (n=38)
Nom	bb2121,ide-cel	JNJ-4528	orva-cel (JCAR125)	bb2121 + bb007
scfv	Chimeric mouse	Chimeric lama	Human	Chimeric mouse
Nb Cel. CAR T	450M	0.75M/kg	600M	450M
Nb de lignes ant.	6	5	6	6
HR/EMD, %	35/39	27/10	41/23	34/NA
Triple/Penta-Ref	84/26	86/28	94/48	63/NA
ORR/CR, %	82/39	97,9/89,4	92/36	83/33
MRD- (10^{-5}), %	28 at 450M	50	NA	NA
PFS/OS, med. , m	12.1 à 450M/19.4	> 22,8/NR	NR/NR	17 m à 450 M
CRS, all / ≥G3, %	84 / 6	94,6 / 5,4	89 / 3	66 / 6
Délai app./durée	1j / 5j	7j / 4j	2j / 4j	3j / 4j
Tocilizumab, %	52	79	76	NA
ICANS, all, ≥G3, %	18 / 3	20 / 10	13 / 3	24 / 8
Infection, all / ≥G3, %	69 / NA	NA / 19	40 / 13	NA / 18

[1] Munshi et al. ASCO 2020, [2] Berdeja et al. ASCO 2020, [3] Mailankody et al. ASCO 2020, [4] Berdeja et al. ASH 2019

First-in-Human Study of the Allogeneic Anti-BCMA ALLO-715 CAR T cell Therapy and the Anti-CD52 Mab ALLO-647 in Relapsed/Refractory Multiple Myeloma (UNIVERSAL Study)

Sham Mailankody[1], Jeffrey Matous[2], Michaela Liedtke[3], Surbhi Sidana[4], Shahbaz Malik[5], Rajneesh Nath[6], Olalekan O. Oluwole[7], Erin E. Karski[8], Wade Lovelace[8], Xiangdong Zhou[8], Srinand Nandakumar[8], Arun Balakumaran[8], Parameswaran Hari[9]

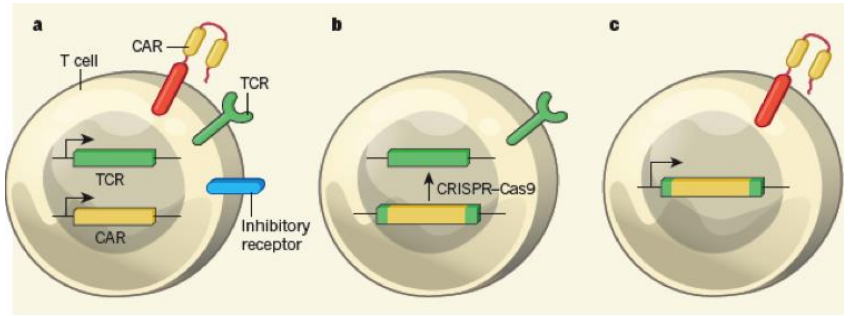


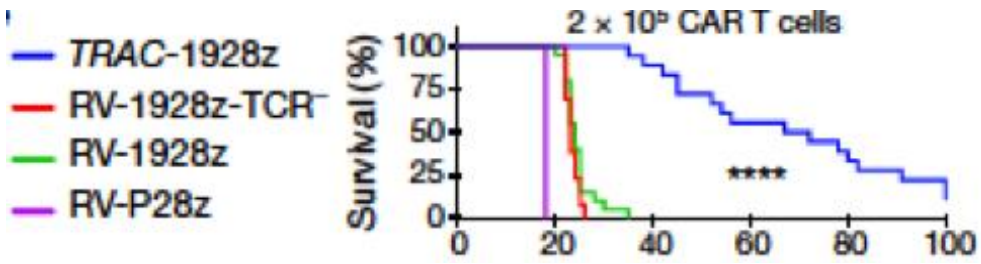
AE of Interest* (N=31)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All Grades
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Cytokine Release Syndrome†	5 (16)	9 (29)	–	–	–	14 (45)
ICANS†	–	–	–	–	–	–
Graft-versus-Host Disease	–	–	–	–	–	–
Infection‡	2 (7)	6 (19)	4 (13)	–	1 (3)	13 (42)
Infusion Reaction to ALLO-647	4 (13)	3 (10)	–	–	–	7 (23)

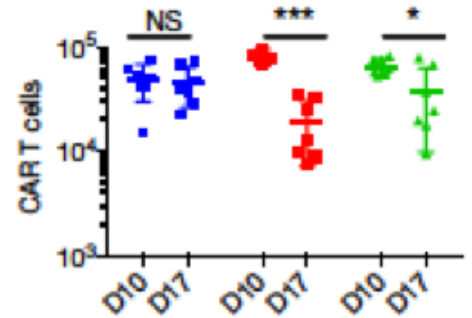
Cell Dose & LD Regimen	FCA						CA	
	DL1 (40M)	DL2 (160M)	DL3 (320M)			DL4 (480M)	DL2 (160M)	DL3 (320M)
	Low ALLO-647 (N=3)	Low ALLO-647 (N=4)	Low ALLO-647 (N=6)	High ALLO-647 (N=4)	ALL ALLO-647 (N=10)	Low ALLO-647 (N=3)	Low ALLO-647 (N=3)	Low ALLO-647 (N=3)
ORR†, n (%)	–	2 (50)	3 (50)	3 (75)	6 (60)	1 (33)	–	2 (67)
VGPR+ Rate†, n (%)	–	1 (25)	3 (50)	1 (25)	4 (40)	–	–	1 (33)

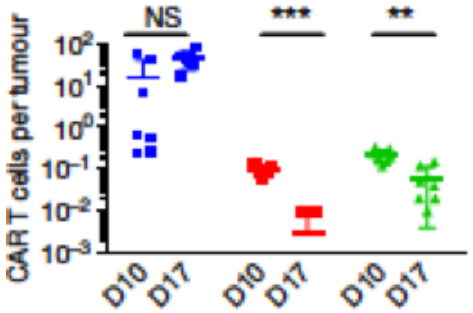
VGPR+ = sCR, CR, or VGPR

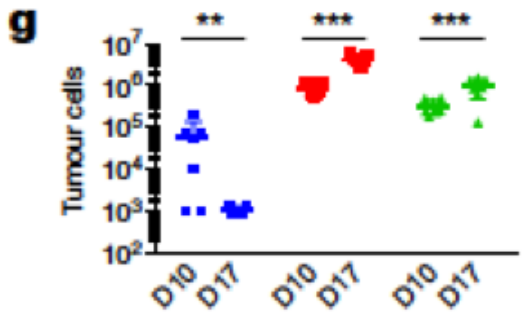
Allogenic CAR T

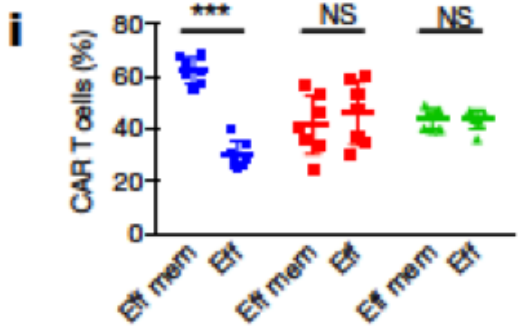


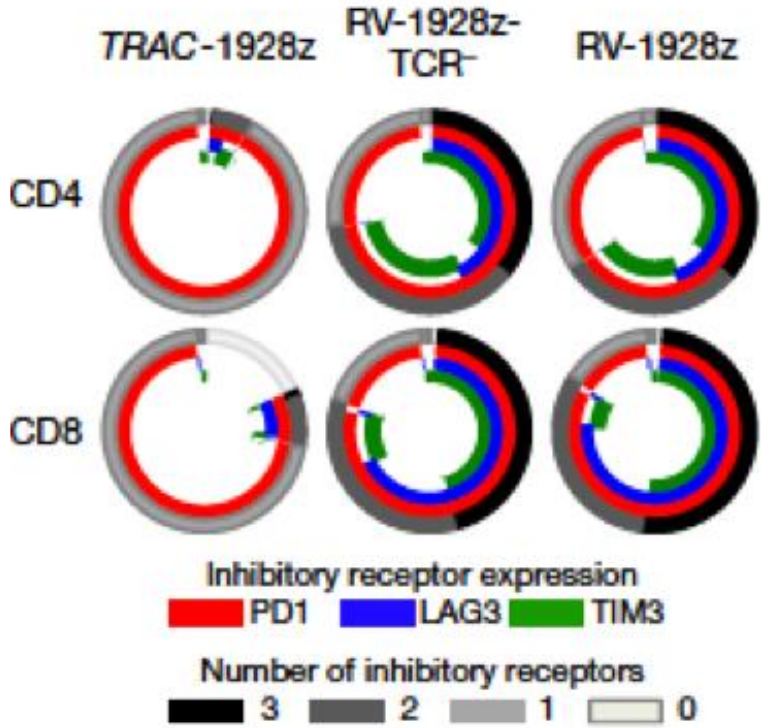












More efficient lysis, safe, « off-the-shelf »

Eyquem et al., Nature 2017

Etude cliniques CAR T MM (clinicaltrial.gov)

87 études dont 43 en Chine

CD8

Anti-BCMA CD8 (Descartes-08) **CARTESIAN**

Humanisé

CT 053 (LUMMICAR-2) **CARSGEN**
ARI 002h T « différenciés » **Academic** Espagne

T Allogénique/Insertion non lentivirale

Anti-CS1	UCAR T	MELANI-01
Anti-BCMACYAD-211	**CEYLAD**	
PBCAR 269A +/- Nirogacestat	**Precision Biosc** PBCMA-101/	
PBCMA allo1	**Precision Biosc**	

Ligand non scfv

CAR T-dd BCMA	**ArCellX**
Tripril	Boston

Autre cible

Anti CS1		NCI
Anti-CS1 CARAMBA	Europe	**Academic**
Anti-GPRC5D MCARH 109		MSK
Anti-CD38 CAR2		Mayo/UPen
Anti CD138 ATLCART	Caroline du Nord	
Anti- CD44v6		**MOLMED Italy**
Anti-TnMUC	**Tmunity Therap**	
Anti-kappa/CD28 T		**CHARKALL**

Double CAR T

Anti-BCMA/CD19: Fas T CAR GC012F **Gracell Bio ‘s (Chine)**

CD38/BCMA, CD38/CD19, CD38/CD56, CD38/CD138

Autre cellules

CAR NK

CAR T dans le myélome multiple
Conclusions et perspectives

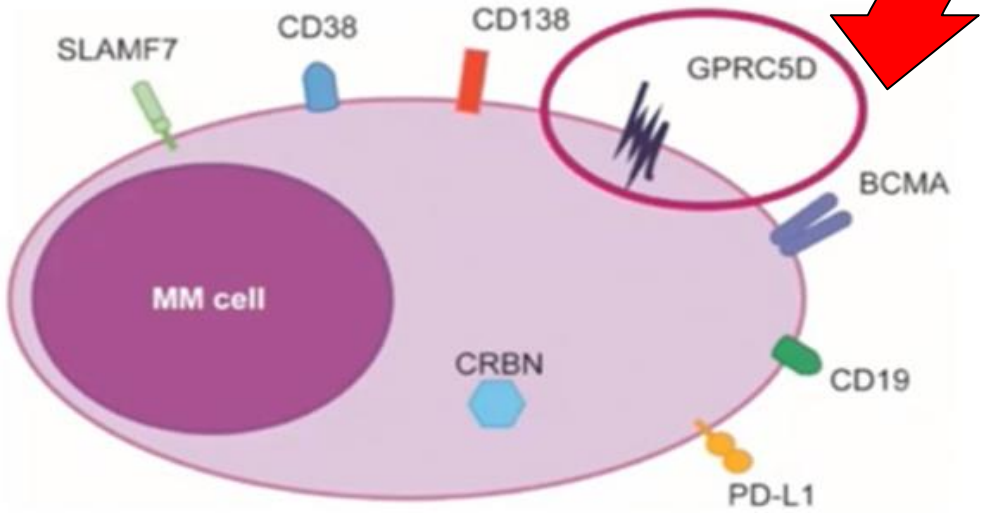
Taux de réponse et de RC impressionant pour des malades lourdement traités
1 seule injection, # 15-21 jours d'hospitalisation
Toxicité: CRS grade 3 et neurotoxicité limitée (mais à surveiller)
Durée de réponse améliorée si 2 épitopes; expansion in vivo (Cilta cel)?

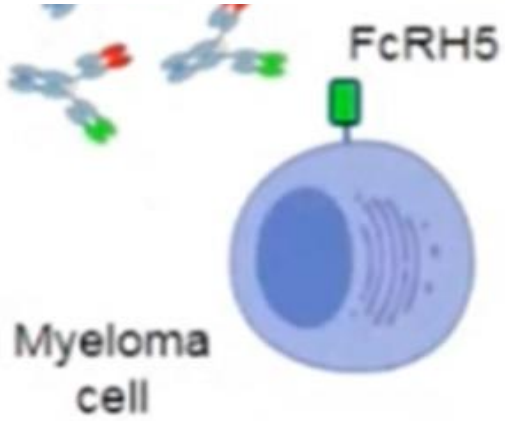
Mais: rechutes, toxicité, infections, coût et durée du manufacturing, nécessite infrastructure….

- ➔ A utiliser plus tôt dans l'histoire de la maladie, combinaisons ?
- ➔ A développer pour les malades de très haut risque (LPL, atteinte méningée….)
- ➔ Autres antigènes (CS1, CD38, GPRC5D….), double CAR ?
- ➔ Nouvelles constructions ? Intégrations non virale? CAR allo ? CAR NK ?
- ➔ Place par rapport aux bispécifiques (SC, toxicité faible, disponible…): non exclusif ?

Nécessité de développements académiques/partenariats ++++

Myélome Multiple: Immunothérapies



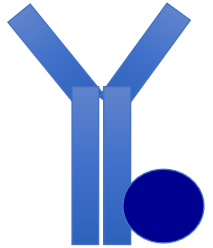


Immunothérapie Passive/adoptive

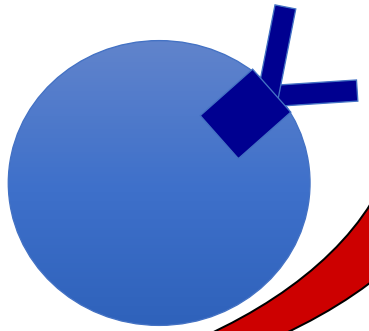
Immunothérapie active

Ac monoclonaux couplés

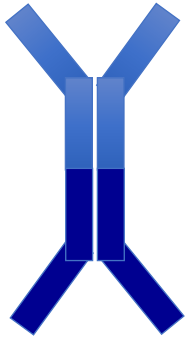
Ac monoclonaux couplés



CAR-T/-NK



Ac Bispecific T/-NK

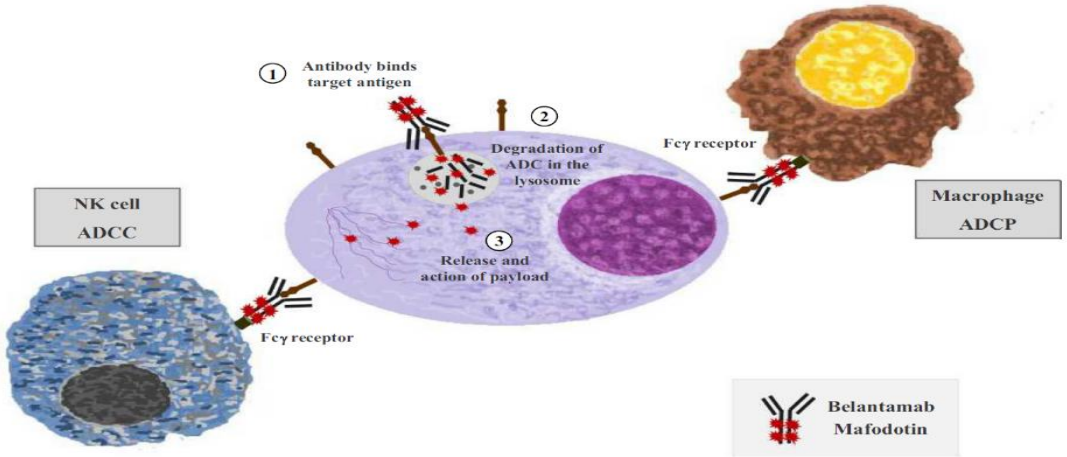


Belantamab Mafodotin

- IgG1 anti-BCMA lié au monomethyl auristatin F (MMAF) un poison des microtubules

Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study

Sagar Lonial, Hans C Lee, Ashraf Badros, Suzanne Trudel, Ajay K Nooka, Ajai Chari, Al-Ola Abdallah, Natalie Callander, Nikoletta Lendvai, Douglas Sborov, Attaya Suvannasankha, Katja Weisel, Lionel Karlin, Edward Libby, Bertrand Arnulf, Thierry Facon, Cyrille Hulin, K Martin Kortüm, Paula Rodríguez-Otero, Saad Z Usmani, Parameswaran Hari, Rachid Baz, Hang Quach, Philippe Moreau, Peter M Voorhees, Ira Gupta, Axel Hoos, Eric Zhi, January Baron, Trisha Piontek, Eric Lewis, Roxanne C Jewell, Elisha J Dettman, Rakesh Popat, Simona Degli Esposti, Joanna Opalinska, Paul Richardson, Adam D Cohen

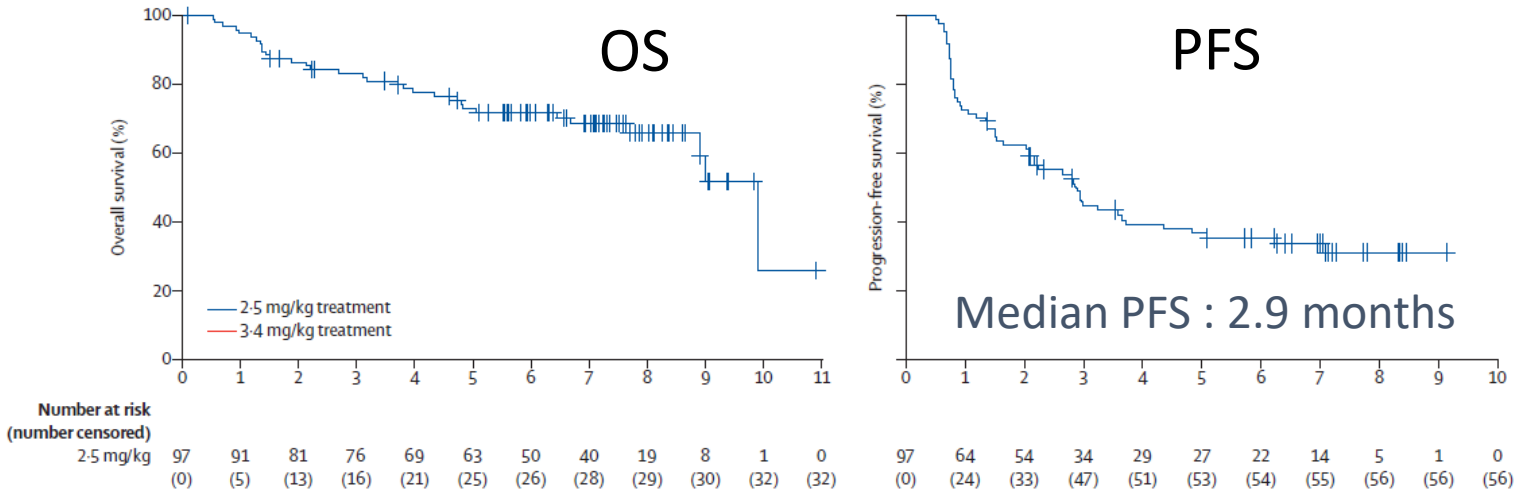


Belantamab Mafodotin

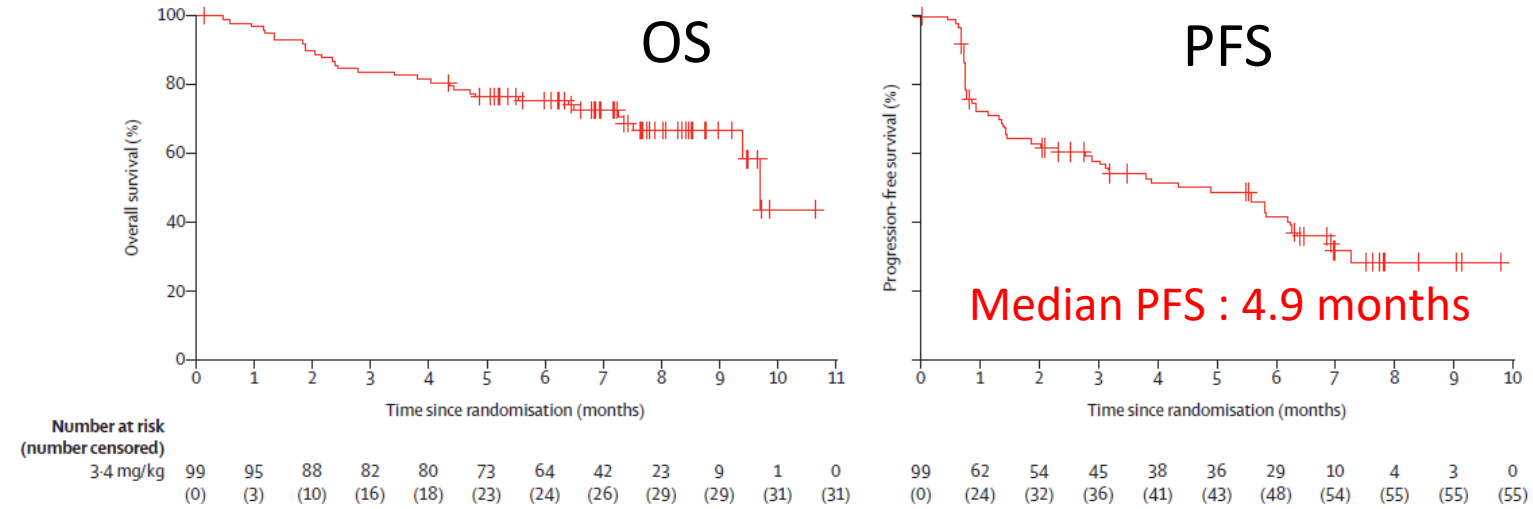
1 injection IV/3 semaines

N= 196	Belantamab mafodotin 2·5 mg/kg group (n=97)	Belantamab mafodotin 3·4 mg/kg group (n=99)
(Continued from previous column)		
Previous therapies received		
Proteasome inhibitor		
Bortezomib	95 (98%)	97 (98%)
Carfilzomib	74 (76%)	64 (65%)
Immunomodulatory drug		
Lenalidomide	97 (100%)	99 (100%)
Pomalidomide	89 (92%)	84 (85%)
Anti-CD38 monoclonal antibody		
Daratumumab	97 (100%)	96 (97%)
Isatuximab	3 (3%)	2 (2%)
Refractory to previous therapies‡		
Proteasome inhibitor		
Bortezomib	74 (76%)	74 (75%)
Carfilzomib	63 (65%)	57 (58%)
Immunomodulatory drug		
Lenalidomide	87 (90%)	88 (89%)
Pomalidomide	84 (87%)	77 (78%)
Anti-CD38 monoclonal antibody		
Daratumumab	97 (100%)	91 (92%)
Isatuximab	3 (3%)	1 (1%)

6 lignes antérieures



ORR : 31%
≥VGPR : 19%
CR/sCR : 3%



ORR : 34%
≥VGPR : 20%
CR/sCR : 3%

Median follow up : 6.5 months

Lonial et al. Lancet Oncology 2019

Belantamab Mafodotin

	Belantamab mafodotin 2·5 mg/kg group (n=95)				Belantamab mafodotin 3·4 mg/kg group (n=99)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Keratopathy or changes to corneal epithelium*	41 (43%)	26 (27%)	0	0	53 (54%)	20 (20%)	1 (1%)	0
Thrombocytopaenia†	14 (15%)	8 (8%)	11 (12%)	0	24 (24%)	11 (11%)	22 (22%)	1 (1%)
Anaemia	4 (4%)	19 (20%)	0	0	12 (12%)	22 (22%)	3 (3%)	0
Nausea‡	23 (24%)	0	0	0	31 (31%)	1 (1%)	0	0

	Belantamab mafodotin 2·5 mg/kg group (n=95)				Belantamab mafodotin 3·4 mg/kg group (n=99)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Keratopathy or changes to corneal epithelium*	41 (43%)	26 (27%)	0	0	53 (54%)	20 (20%)	1 (1%)	0
Thrombocytopaenia†	14 (15%)	8 (8%)	11 (12%)	0	24 (24%)	11 (11%)	22 (22%)	1 (1%)
Anaemia	4 (4%)	19 (20%)	0	0	12 (12%)	22 (22%)	3 (3%)	0
Nausea‡	23 (24%)	0	0	0	31 (31%)	1 (1%)	0	0
Pyrexia‡	18 (19%)	2 (2%)	1 (1%)	0	21 (21%)	4 (4%)	0	0
Blurred vision§	17 (18%)	4 (4%)	0	0	28 (28%)	2 (2%)	0	0
Infusion-related reactions¶	17 (18%)	3 (3%)	0	0	15 (15%)	1 (1%)	0	0
Increased aspartate aminotransferase	17 (18%)	2 (2%)	0	0	18 (18%)	6 (6%)	0	0
Fatigue‡	13 (14%)	2 (2%)	0	0	21 (21%)	5 (5%)	0	0
Dry eye‖	12 (13%)	1 (1%)	0	0	23 (23%)	0	0	0
Neutropenia**	4 (4%)	5 (5%)	4 (4%)	0	12 (12%)	12 (12%)	3 (3%)	0
Hypercalcaemia	6 (6%)	4 (4%)	3 (3%)	0	13 (13%)	3 (3%)	0	0
Decreased lymphocyte count	1 (1%)	8 (8%)	4 (4%)	0	4 (4%)	6 (6%)	2 (2%)	0
Diarrhoea‡	11 (12%)	1 (1%)	0	0	14 (14%)	1 (1%)	0	0
Constipation	12 (13%)	0	0	0	9 (9%)	0	0	0
Decreased appetite	11 (12%)	0	0	0	16 (16%)	2 (2%)	0	0

30% réponse
Chez triple réfractaires

3 mois médiane PFS

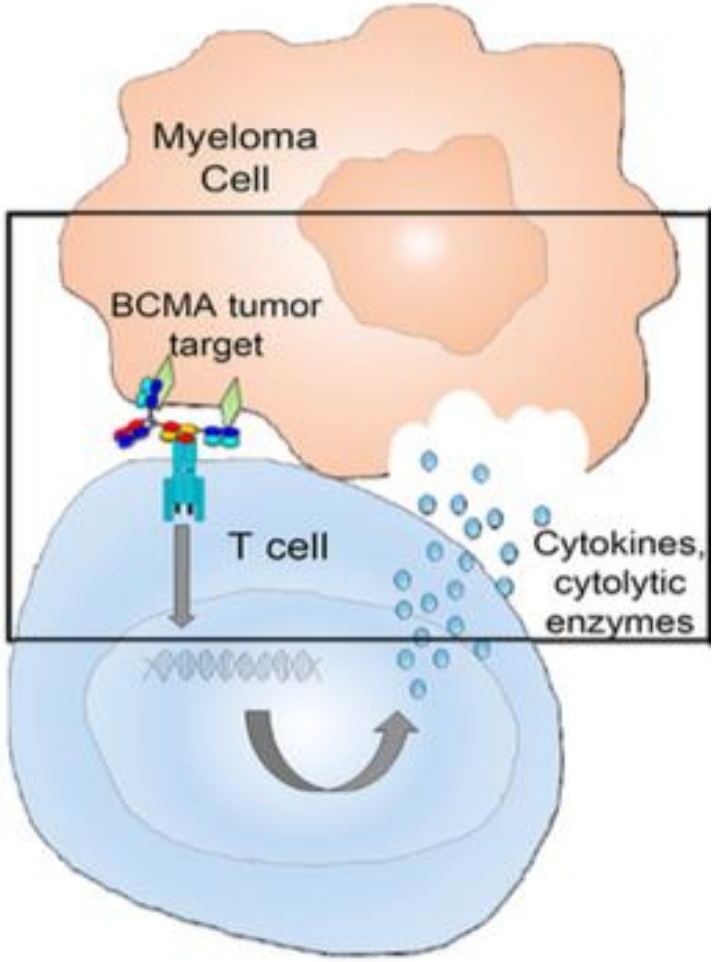
Non disponible depuis mi-octobre 2021
Arret du dévpment commercial en France

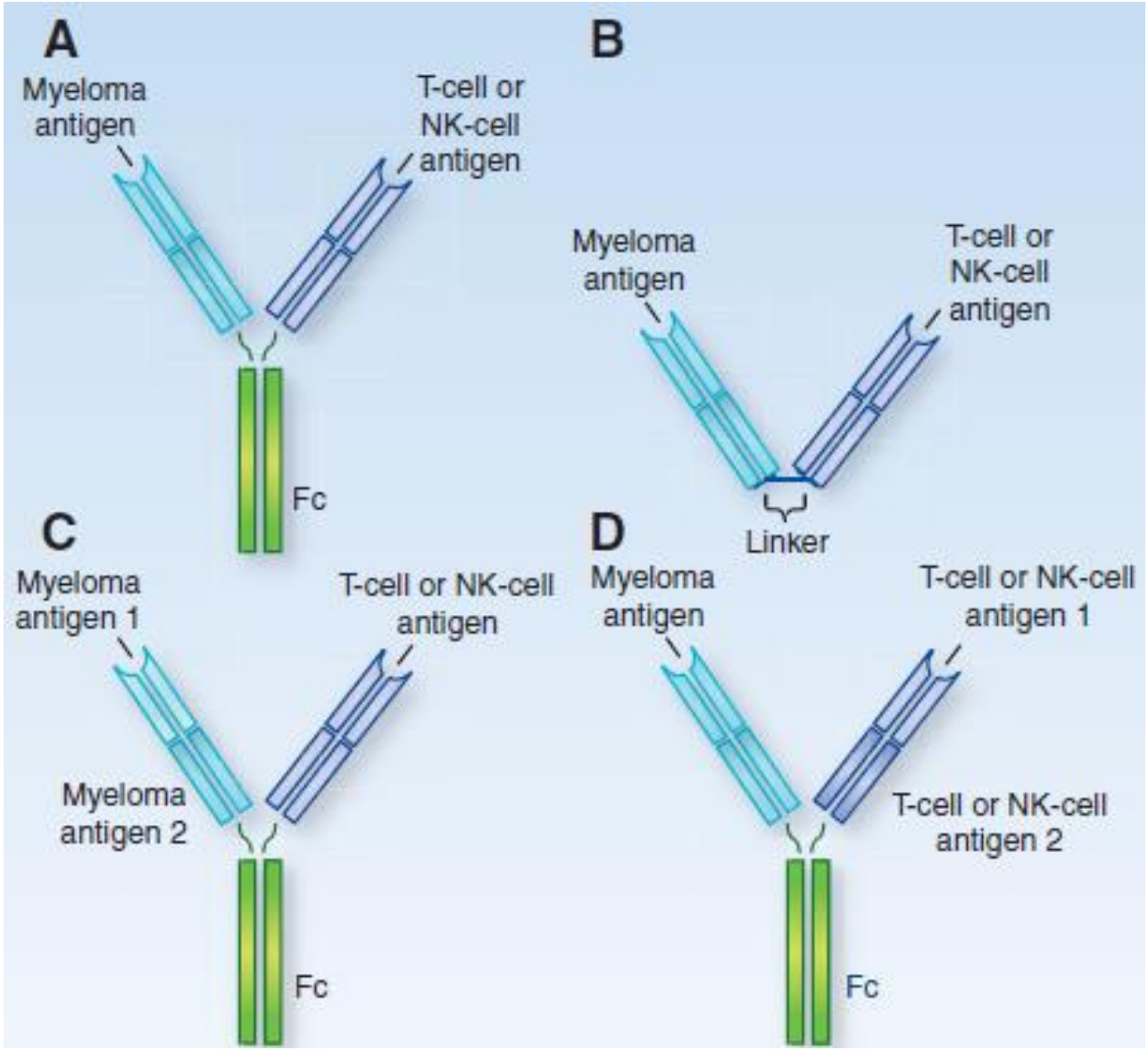
- Essais en cours :
  - DREAMM 6:
Phase ½, BM-Rd ou BM-Vd
  - DREAMM 9:
Phase 3, VRD+-BM
en L1 non éligible à la greffe

13 études ADC en cours: DREAMM (Belmaf); Anti CD138…..

Lonial et al. Lancet Oncology 2019

Anticorps bispécifiques et « Bispécific T-cell Engager (BiTe) »





Lancman et al., Blood Cancer Discovery, Sep 2021

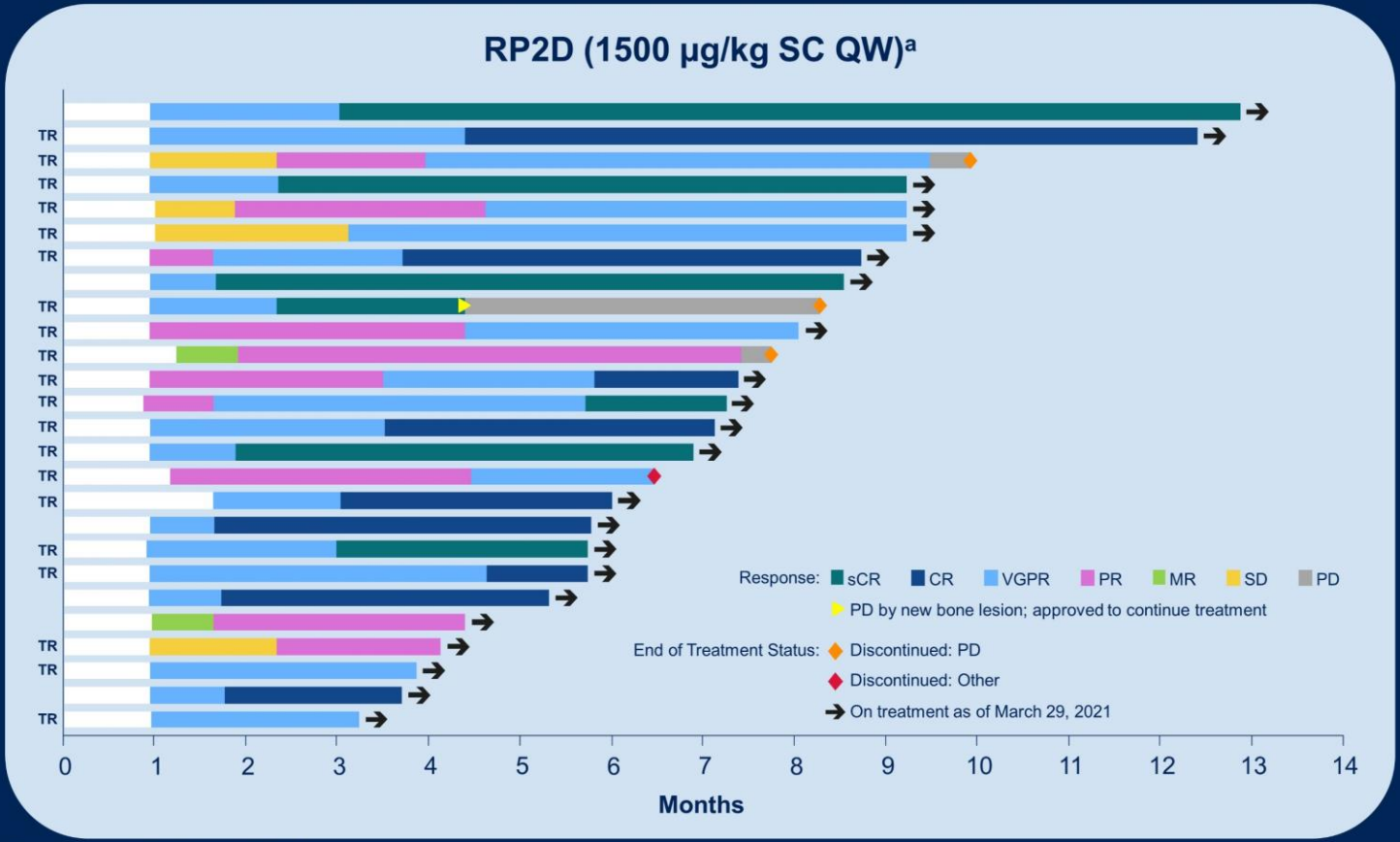
Anticorps bispécifiques anti-BCMA et anti-GPRC5D dans le MM

	CC93269 (n=30) 	Teclistamab (n=73)	AMG 701 (n=75)	PF-06863135 (n=30)	REGN5458 (n=45)	TNB-383B (n=38)	Talquetamab (n= 157)
Traitement	IV / sem	SC / sem	IV / sem	SC / sem	IV /sem	IV / 3 sem	IV ou SC/sem
Nb Lignes	5 (3-13)	5(2-14)	6	8	5	7	4.5
Triple/Penta Ref. %	66.7/NA	79/38	68/-	87/- 22% prior anti-BCMA	93/-	79/-	68/21
ORR %	89 (at 10mg)	65 (at >270 mg)	36 (16/45)	70/83 at RP2D	60	52 (12/23)	70
sCR/CR %	44 (at 10mg)	40 (at >270 mg)	-	30	-	-	39 ≥ VGPR
CRS, Gr1-2 (≥3)	90 (5)	60/70 (0)	61 (7)	57 (0)	38 (0)	21 (0)	50-60 (3)
Neurotox Gr1-2 (≥3)	-	1%	8 (0)	10%	-	-	6 40% Dysgueu.
PFS/durée réponse (m)	NA	85% à 7 mois Jusqu'à 21 m	NA/3,8 (14/17 ongoing)	92% à 6 mois	> 4 m 44%	NA	NA

Topp et al. ASCO 2019, [2]Costa et al. ASH 2019, [3]Usmani et al. ASCO 2020; Chiari et al., ASH 2020, Garfall et al ., ASH 2020, ASCO 2021; Bahlis et al., ASCO 2021

TECLISTAMAB

Duration of Response at RP2D



- At the RP2D of 1500 µg/kg SC QW:
  - Responses were durable and deepened over time
  - Median duration of response was not reached
  - 22/26 responders (85%), after median follow-up of 7.1 months (range: 3.0–12.2), were alive and continuing on treatment
- Across SC cohorts 36/45 responders (80%), after median follow-up of 9.3 months (range: 3.0–19.4), were alive and continuing on treatment
- Across IV cohorts 19/32 responders (59%), after median follow-up of 15.6 months (range: 5.4–29.6), were alive and continuing on treatment
  - 6 (19%) had ≥18 months of follow-up

[a]Step-up doses of 60 µg/kg and 300 µg/kg.

CR, complete response; IV, intravenous; MR, minimal response; PD, progressive disease; PR, partial response; QW, once weekly; RP2D, recommended phase 2 dose; SC, subcutaneous; sCR, stringent complete response; SD, stable disease; TR, triple-class refractory; VGPR, very good partial response.

Toxicité des Ac Bispécifiques

Agent	AMG701 (69)	CC-93269 (75)	PF-06863135 (76)	REGN5458 (73)	JNJ-64007957 (teclistamab) (72)	TNB-383B (70)	JNJ-64407564 (talquetamab) (74)	BFCR4350A (cevostamab) (71)
Target	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	GPRC5D	FcRH5
Patients (*N*)	65	19	30	49	149 (84 i.v., 65 s.c.)	58	157 (102 i.v., 55 s.c.)	53
CRS (grade ≥3)	65% (9%)	90% (5%)	73.3% (0%)	39% (0%)	55% (0%)	45% (0%)	54% (3%)	76% (2%)
Infection (grade ≥3)	(17%)	NR (26%)	NR (30%)	47% (18%)	52% (15%)	21% (14%)	38% (8%)	NR
Anemia (grade ≥3)	42%	NR (42%)	20% (16.7%)	37% (22%)	55% (32%)	21% (17%)	48% (27%)	28% (19%)
Neutropenia (grade ≥3)	25%	NR (53%)	33.3% (26.7%)	16% (14%)	57% (46%)	19% (16%)	47% (31%)	17% (15%)
Lymphopenia (grade ≥3)	NR	NR	16% (16%)	18% (12%)	NR	NR	40% (36%)	15% (15%)
Thrombocytopenia (grade ≥3)	21%	NR (21%)	8% (5%)	18% (6%)	40% (22%)	17% (14%)	32% (13%)	32% (25%)
Neurotoxicity (grade ≥3)	NR	NR	20%	12% (0%)	5% (1%)	NR	6% (2%)	28% (0%)
Other common SE (grade ≥3)	Diarrhea 31%, hypophosphatemia 31%	NR	NR	Fatigue 35% (6%), nausea 31% (0%), pyrexia 31% (2%), back pain 27% (4%)	Pyrexia 30% (0%), diarrhea 23% (1%), nausea 22% (1%), fatigue 22% (1%), headache 22% (0%), cough 21% (2%)	Fatigue 24% (2%), headache 22% (2%), nausea 21% (0%)	Skin-related disorder 45%, dysgeusia 38%, fatigue 29% (1%), headache 27% (1%), pyrexia 27% (1%), diarrhea 25% (3%), nail disorders 17%	Hypomagnesemia 28% (0%), diarrhea 28% (2%), hypokalemia 21% (4%)

69. Harrison SJ et al. Blood 2020;136:28–9.

70. Rodriguez C et al. Blood 2020;136:43–4.

71. Cohen AD et al. Blood 2020;136:42–3.

72. Garfall AL et al. Blood 2020;136:27.

74. Chari A et al. Blood 2020;136:40–1.

75. Costa L et al. EHA Library 2020;295025:S205.

76. Lesokhin AM et al. Blood 2020;136:8–9.

Bispecifics

Drug	Target	Med prior lines	Dosing	ORR	CRS %	Neurotox %	Notes
Teclistamab (n=68)	BCMA	6 (5@RP2D)	SC weekly for RP2D	69% (72% @RP2D)	55%, (64%)	5% (3%)	SC dosing!
Teneobio TNB-383B (n=58, 15)	BCMA	6	Q3 weeks	80% @higher doses, n=15	45%	0	Q 3 week, allowed for CrCl 30
REGN-5458 (n=49, 8)	BCMA	5	Q2 week	63% @highest does, n=8	39%	12%	
AMG-701 (n=85, 6)	BCMA	6	weekly	83% @highest does, n=6	64% (9% G3)	3.8%	
Talquetamab (n=157, 19)	**GPRC5D**	**6 (4.5)**	**Weekly or Q2 week, IV and SC**	**66% @ higher doses (n=50), 69% @ RP2D (n=13)**	**54% (68% @RP2D)**	**46% (5% @RP2D)**	**16% in RP2D with prior BCMA tx SC dosing! some G3 skin rash, oral toxicity, back pain**
Cevostamab (n=53, 34)	**FcRH5**	**6**	**Q3 weeks**	**53% in higher doses, 61% @ top dose (n=18); 63% in prior BCMA (n=8)**	**76% (2% G3**	**28%**	**21% with prior BCMA tx**

UCSF

Bispécifiques dans le myélome multiple
Conclusions et perspectives

Taux de réponse et de RC impressionnant pour des malades lourdement traités
1 injection sc hebdomadaire ! Et facile d'accès !
CRS grade 3 et neurotoxicité très limitée (mais à surveiller…..)➔ sujet agés +++

Mais: rechutes, infections, coût, durée du traitement ? Durée de réponse ? Biomarqueurs ?….

➔ A utiliser plus tôt dans l'histoire de la maladie, combinaisons (Imids, anti-CD38….) ?

➔ A développer pour les malades de très haut risque (LPL, atteinte méningée….)

➔ Autres antigènes (CS1, CD38, GPRC5D….), trispé CAR ?

➔ Nouvelles constructions Bi/Trispé NK ?

➔ Place par rapport aux CAR T (1 seule injection, toxicité, manufacture, coût…): pas exclusif ?

Ac Bi/Tri-spécifiques T/-NK

En développement préclinique….

En route pour le futur….

Target	Drug	Sponsor	Notes
BCMAxCD3	EM801	Bristol Myers Squibb	Active also in high-risk patients and non-cross-resistant with previous lines of treatment (14)
BCMAxCD3	AP163	Ampsource Biopharma Shanghai Inc.	Induces less cytokine secretion than other bispecifics *in vitro* (16)
BCMAxNKp30	CTX-8573	Compass Therapeutics	Antitumor effect in mice even with low BCMA expression (9)
BCMAxCD16a	AFM26	Affimed Therapeutics	NK-cell engager; may have superior safety profile over CD3 T-cell engagers (15)
BCMAxCD16a	RO7297089	Genentech	Has a favorable safety profile and represents a novel MOA among other BCMA-targeting modalities (10)
BCMAxMICA	2A9-MICA	China Pharmaceutical University	MICA binds NKG2D on NK cells to induce multiple myeloma cell death *in vitro* and in a mouse model (24)
BCMAxCD200xCD16a	Gantke et al.	Affimed Therapeutics	Results in increase in avidity leading to preferential lysis of antigen double-positive cells compared with antigen single-positive cells (7)
CD138xCD3	STL001	Jiangsu, China	Nanomolar-level affinity to recombinant human CD138 protein and shows more potent antitumor activity against RPMI-8226 cells than that of separate aCD3-ScFv-hIgFc and aCD138-ScFv-hIgFc, or the isotype mAb *in vitro* or *in vivo* (17)
CD138xCD3	h-STL002, m-STL002	Jiangsu, China	Shows potent cytotoxicity against multiple myeloma RPMI-8226 cell line through T-cell activation (18)
CD38xCD3xCD28	Wu et al.	Sanofi	Demonstrates *in vitro* multiple myeloma cell killing 3–4 log higher than daratumumab (12)
CD38xCD3	Sorrento CD38/CD3	Sorrento Therapeutics	Demonstrates more potent tumor cell killing than daratumumab (19)
CD38xCD3	Bi 38-3	Inserm	Kills multiple myeloma cells *in vitro* and in a mouse model with no toxicity to B, T, and NK cells (23)
SLAMF7xNKG2D	SLAMF7-NKG2D	Ohio State University	*In vivo*, survival was significantly prolonged using SLAMF7-NKG2D biAb in a xenograft NOD-SCID$^{IL2r\gamma c-/-}$ (NSG) mouse model engrafted with both human PBMCs and multiple myeloma cell lines (22)
GPRC5DxCD3	GPRC5DxCD3 TRAB	Chugai Pharmaceutical	Suppresses tumor growth of GPRC5D-positive myeloma cells through the activation of T cells *in vitro* and *in vivo* in xenograft models (20)
NY-ESO-1xCD3	ImmTAC-NYE	Immunocore	Produces lysis of multiple myeloma cell line *in vitro* (25)
A2/NY-ESO-1xCD3	Maruta et al.	Ehime University, Japan	Antimyeloma activity *in vitro* similar to CAR-T construct (26)

Lancman et al., Blood Cancer Discovery, Sep 2021

Merci pour votre attention !

Hôpitaux Universitaires SAINT-LOUIS LARIBOISIÈRE FERNAND-WIDAL

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2 cas cliniques…..

Mr C, 57 ans

MM IgA lambda, 50 g/l, t(4;14)

2016: Lesions osseuses, Hypercalcémie, anémie, Pu 2g/l

➔ VTD/Auto/VTD: VGPR

2019: Rechute avec plasmocytome sternal et pic 30g/l

➔ Dara/Len/Dex: RP

2020: Rechute+insuffisance rénale 250 micromol/l Créat.

➔ Carfil/Pom/Dex: VGPR avec normalisation créat.

Nov 2021: Rechute avec pic 25g/l et nouvelles lésions os.

Hb: 11g/dl, plq 120 G/L, Créat. 100micromol/l, Ca 2,8

➔ **Quel traitement ?**

Mme B, 76 ans

MM IgG kappa, 30 g/l, t(11;14)

2018: Tassement vertebraux D9-L1, anémie, Ca 2,9 mmol/l

➔ Len/Dex : RP

Juin 2019: 150 micromol/l Créat, Pu 2g/l (CLL)

➔ Dara/Bort/Dex: RP avec normalisation créat.

Dec 2019:Rechute avec lesion bassin

➔ Carfil/Dex: VGPR

Nov 2020: Rechute avec créat. 125 micromol/l, anémie

➔ Pom/Endoxan/Dex: RP

Oct. 2021: Rechute avec lésion D6, Hb: 8g/dl, plq 175 G/L

➔ **Quel traitement ?**