

# BCMA: Nouvelle cible thérapeutique dans le Myélome Multiple

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Liens d'intérêts

Honorarium: Celgene, Janssen, Amgen, Sanofi

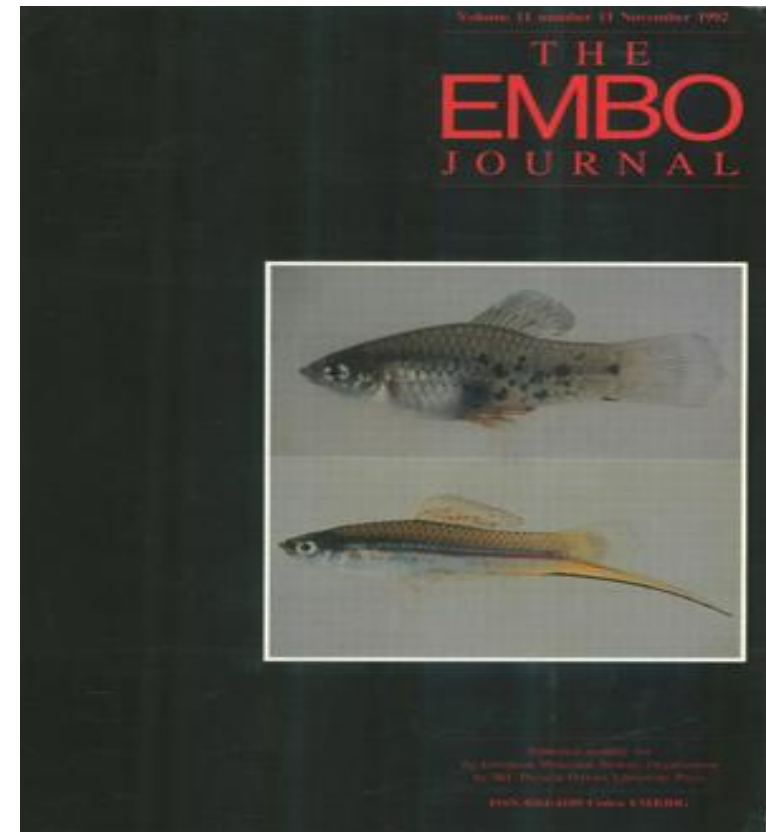
Board: Janssen, Celgene, Sanofi, GSK, Takeda

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<sup>1</sup>, J.C.Brouet<sup>2</sup>,  
R.Berger, C.J.Larsen and A.Tsapis<sup>3</sup>**

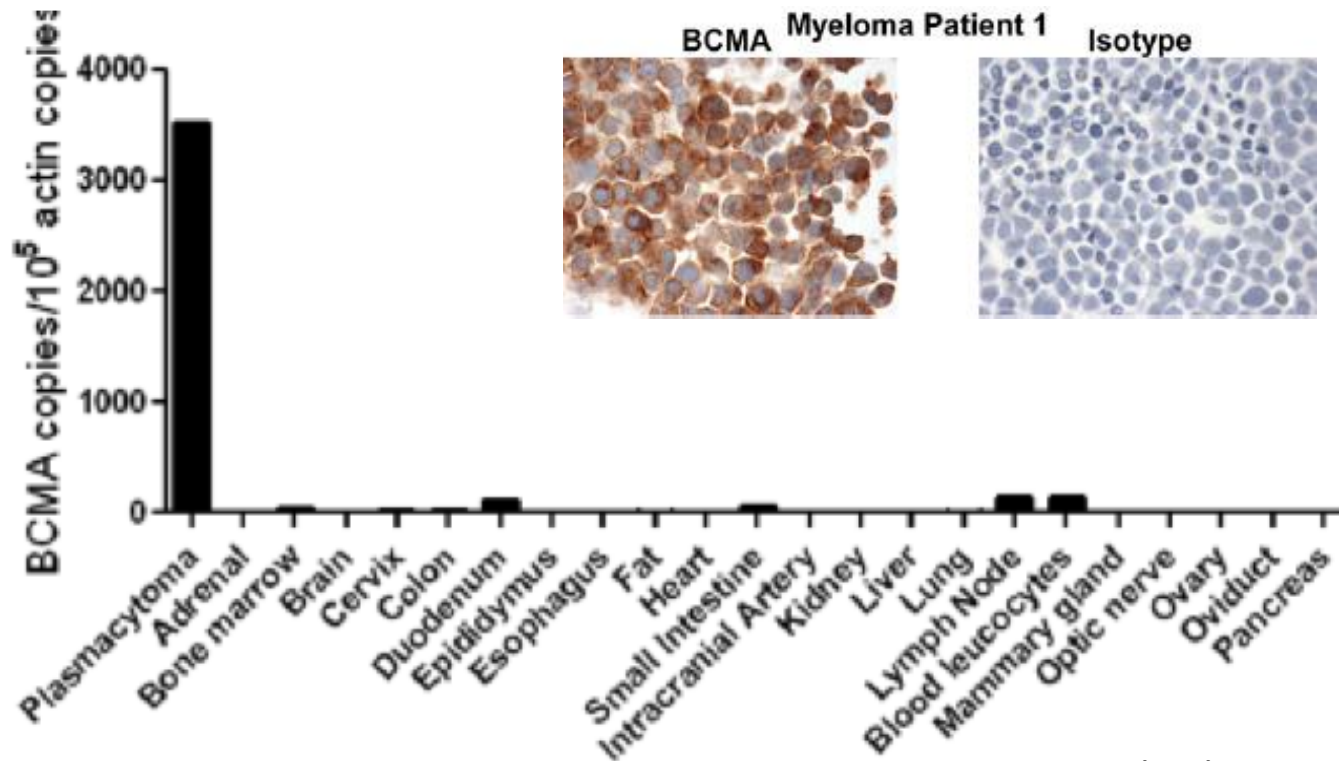
Unité INSERM U 301 de Génétique Cellulaire et Moléculaire des Leucémies, Institut de Génétique Moléculaire, 27, rue J. Dodu, 75010 Paris, <sup>1</sup>Service de Gastro-Entérologie, Hôpital Saint Lazare, 75010 Paris and <sup>2</sup>Laboratoire d'Immunopathologie, Hôpital Saint Louis, 75010 Paris, France



# The BCMA gene, preferentially expressed during B lymphoid maturation, is bidirectionally transcribed

Yacine Laabi, Marie-Pierre Gras, Jean-Claude Brouet<sup>1</sup>, Roland Berger, Christian-Jacques Larsen and Andréas Tsapis\*

INSERM U301 and SDI no. 16954 | CNRS, Institut de Génétique Moléculaire, 27 rue Juliette Dodu, 75010 Paris and <sup>1</sup>Laboratoire d'Immunopathologie, Université Paris VII, Institut d'Hématologie, Hôpital Saint Louis, Paris, France

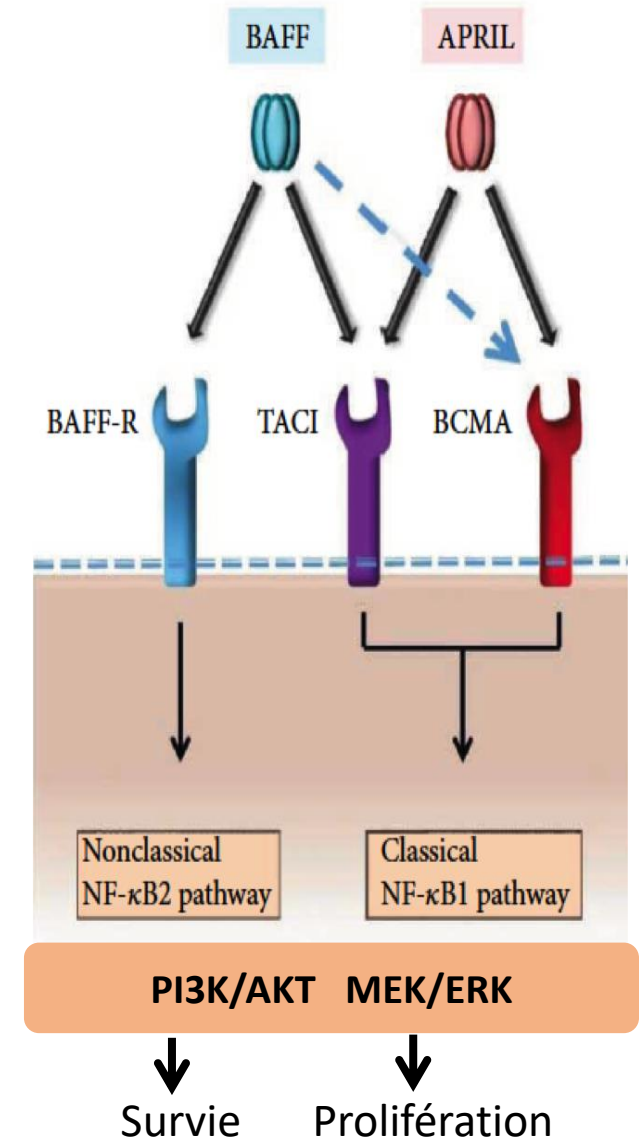
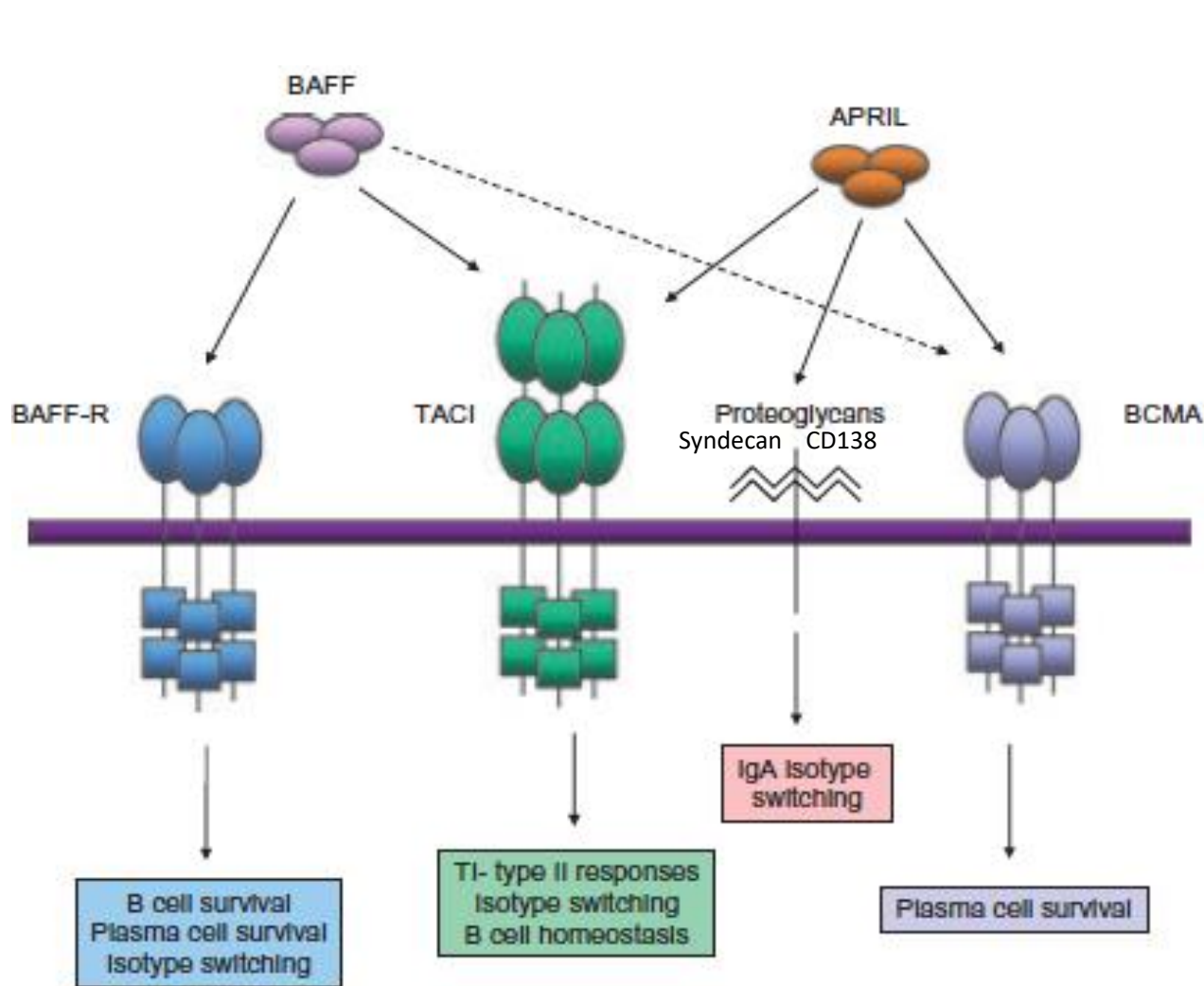


Carpenter et al., Clin Cancer Res., 2013

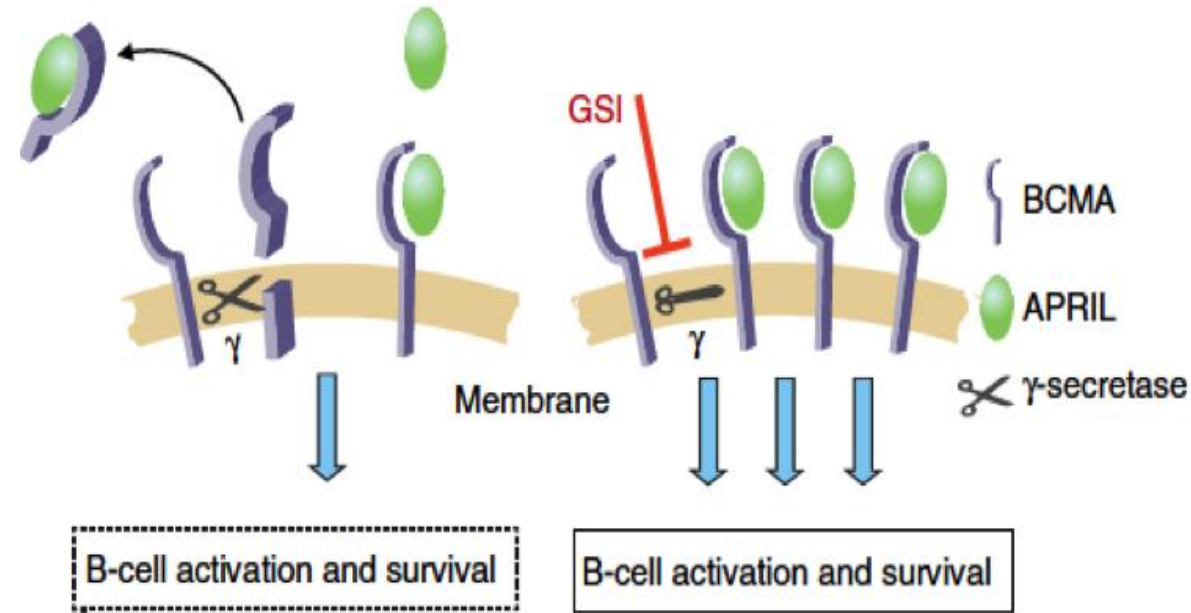
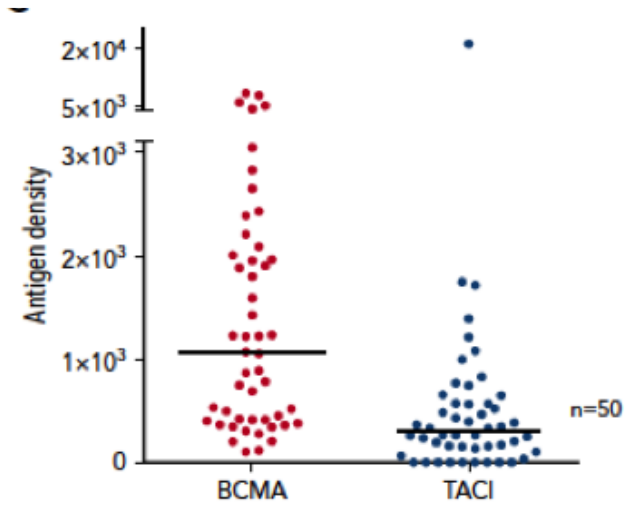
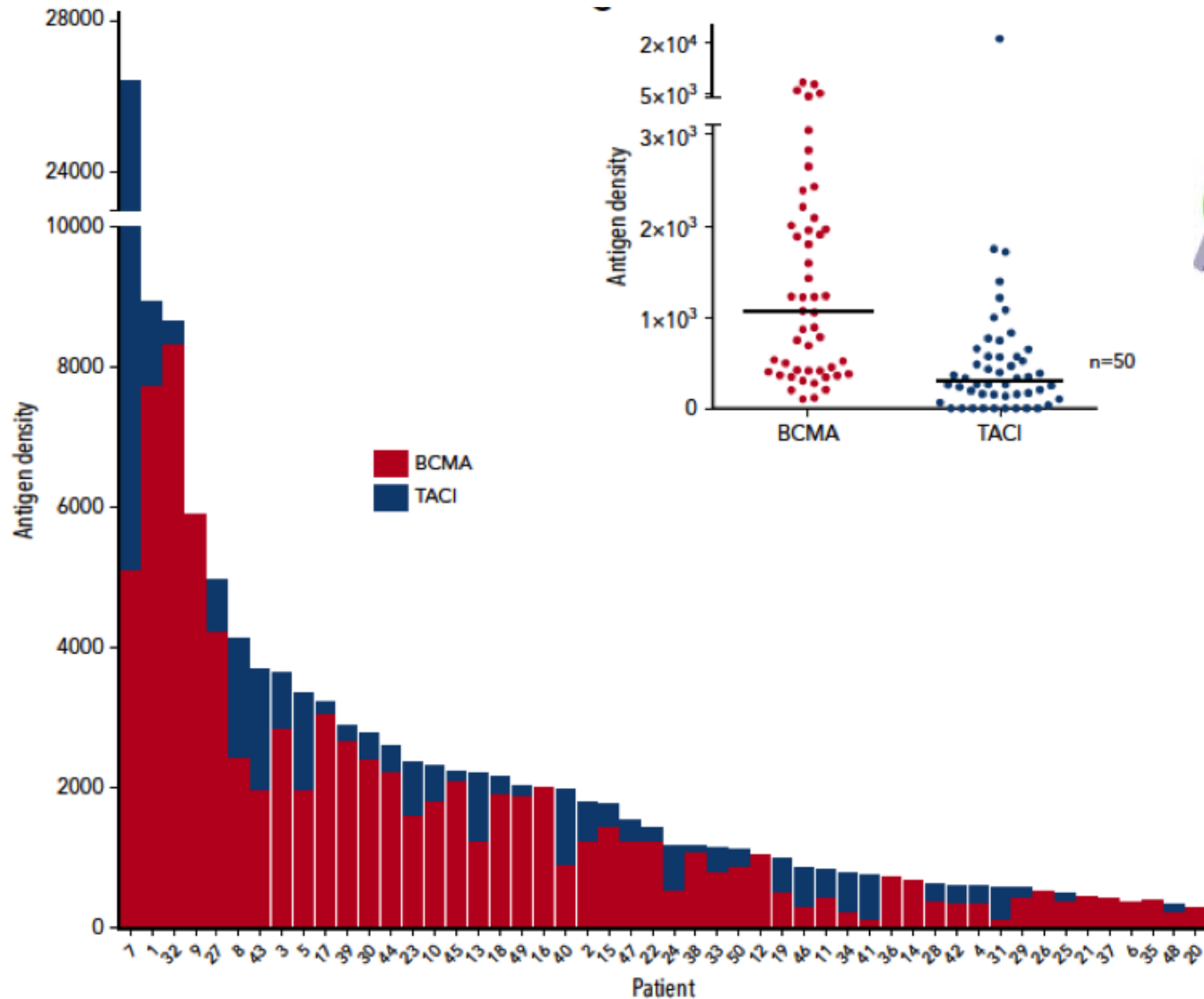
Cell type	Cell line	sense-RNA
Precursor lymphoid	KM3	-
Pre-B	REH	+
	JEA	+
B	Daudi	+
	Raji	+
	BL36	+
	LEF1	+
	167	+
	RPMI 8226	+
	U266B1	+
T	MOLT3	-
	MOLT4	-
	Jurkat	-
	Peer	-
	DU528	-
	HSB2	-
	HUT78	-
	SUPT1	-
	SUPT11	+
Myeloid	U937	-
	PMA-stim. U937	-
	NB4	-
Adult tissues	Brain	-
	Muscle	-
	Heart	-
	Adrenals	+
	Lung	-
	Liver	+
	Thyroid	-
	Kidney	-
	Uterus	-
	Bladder	-
	Spleen	+
	Lymph nodes	+
	Thymus	+
	Pancreas	-
	Testis	-
Placenta	-	

# 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
REL1	TNFRSF19L
Fn14	TNFRSF12A

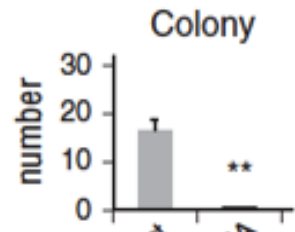
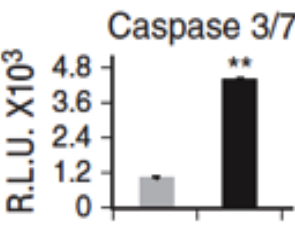
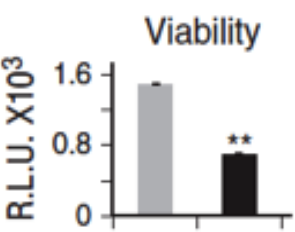


# BCMA (TNFRSF17): Expression hétérogène à la surface des plasmocytes tumoraux

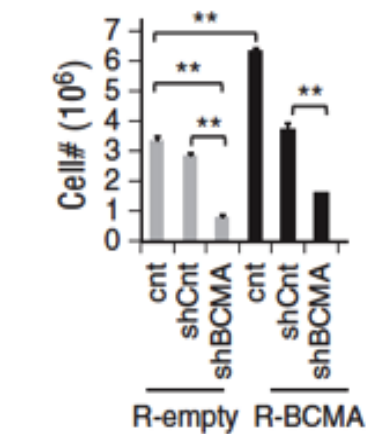
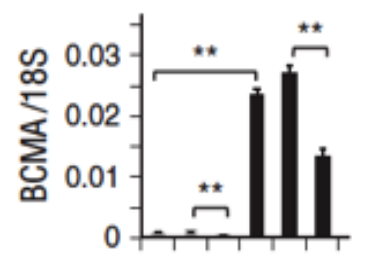




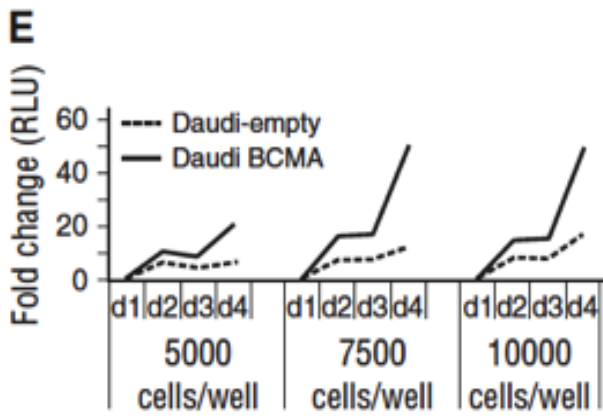
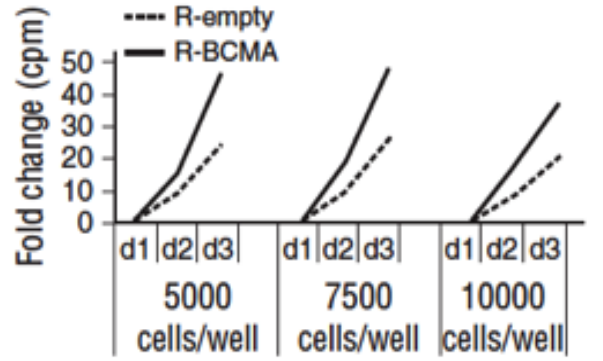
# BCMA (TNFRSF17): Rôle dans la survie et la prolifération des plasmocytes tumoraux



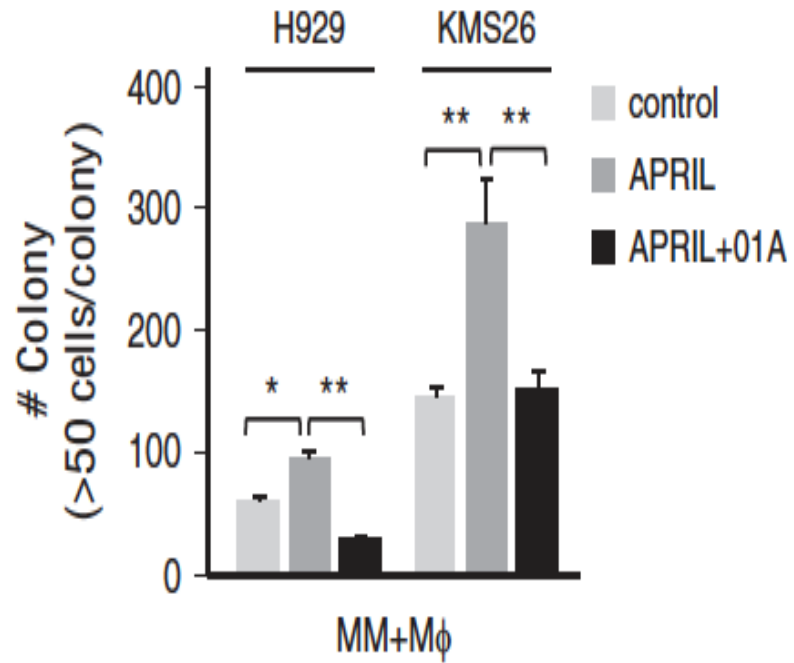
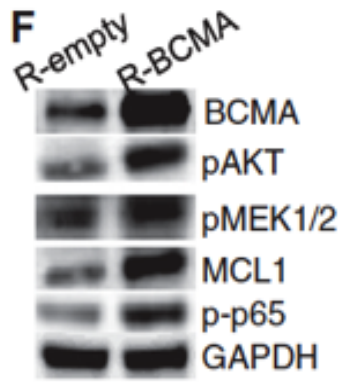
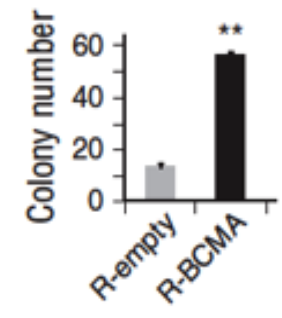
MM1R



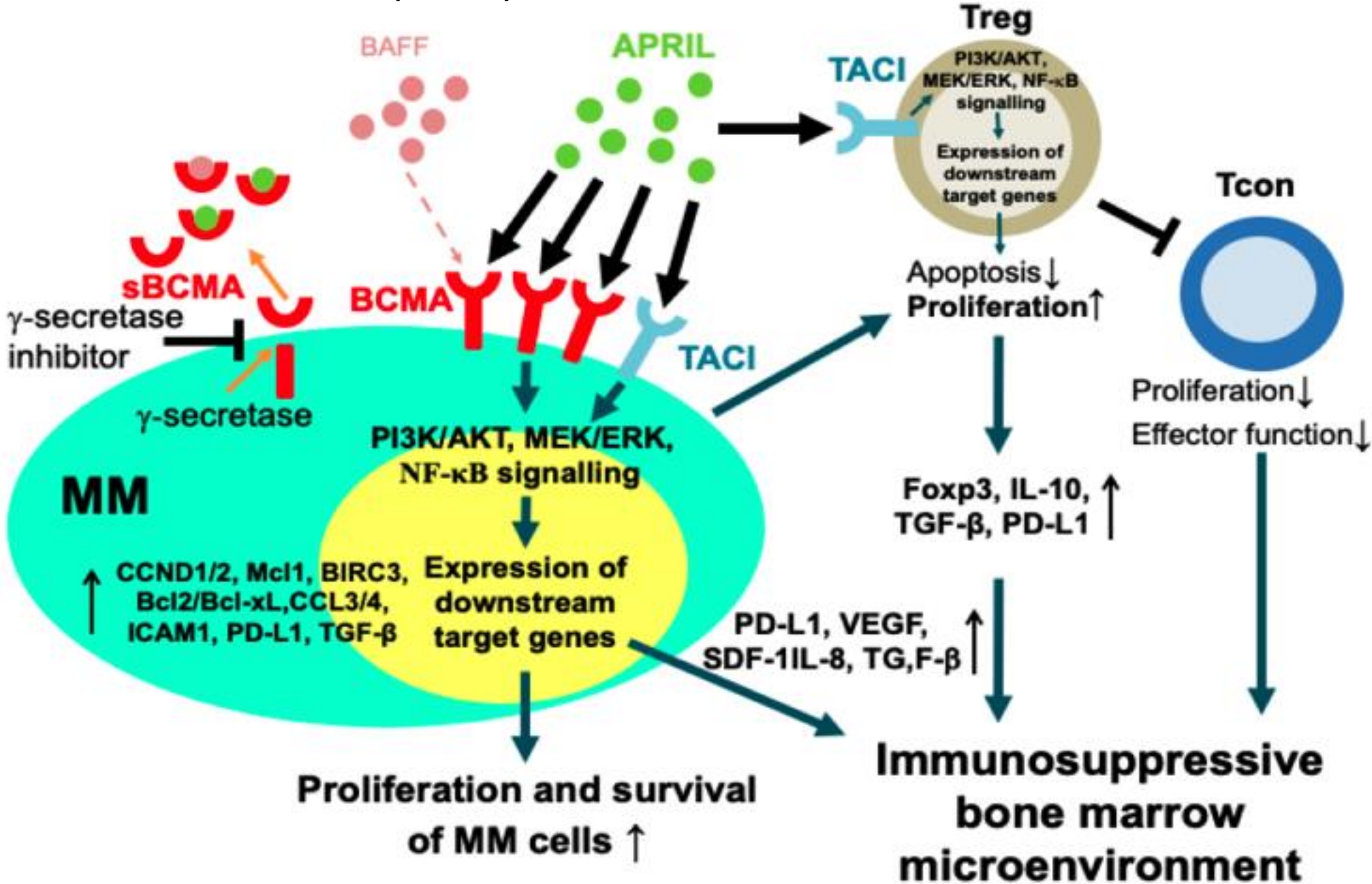
R-empty R-BCMA



Daudi-empty Daudi BCMA

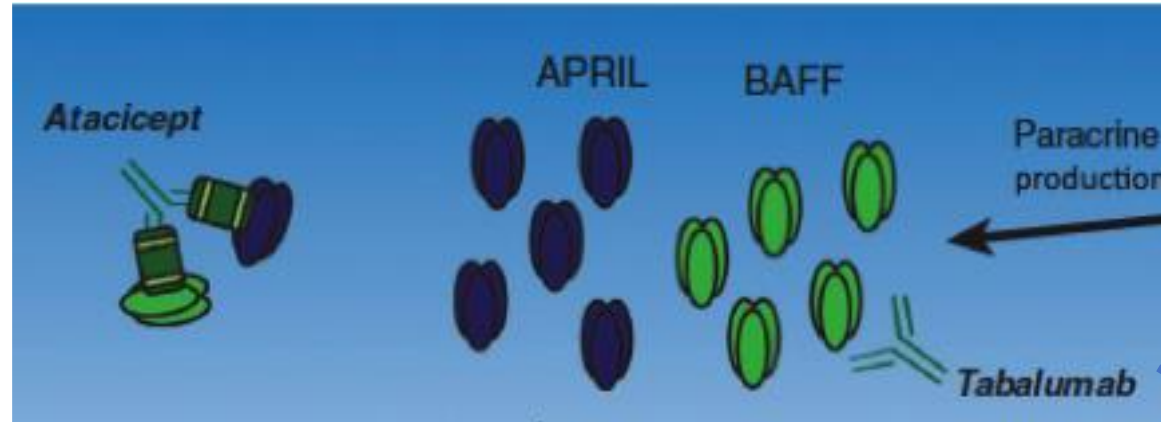


# BCMA: Une nouvelle cible thérapeutique ?





# BAFF et APRIL comme cibles thérapeutiques



Anticorps Mo anti-BAFF

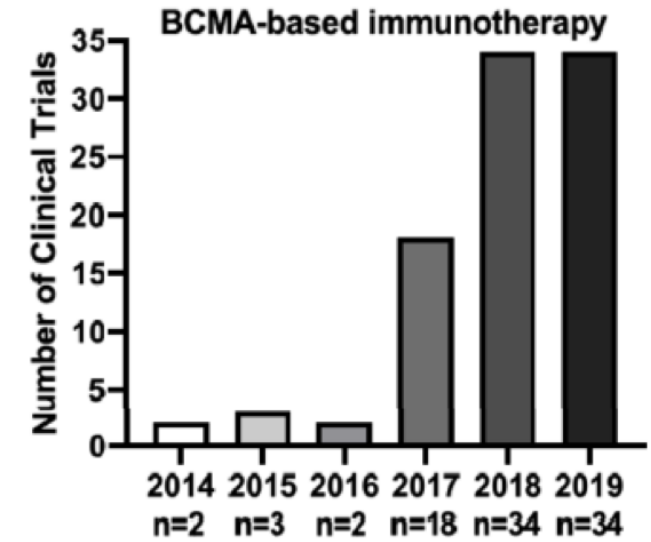
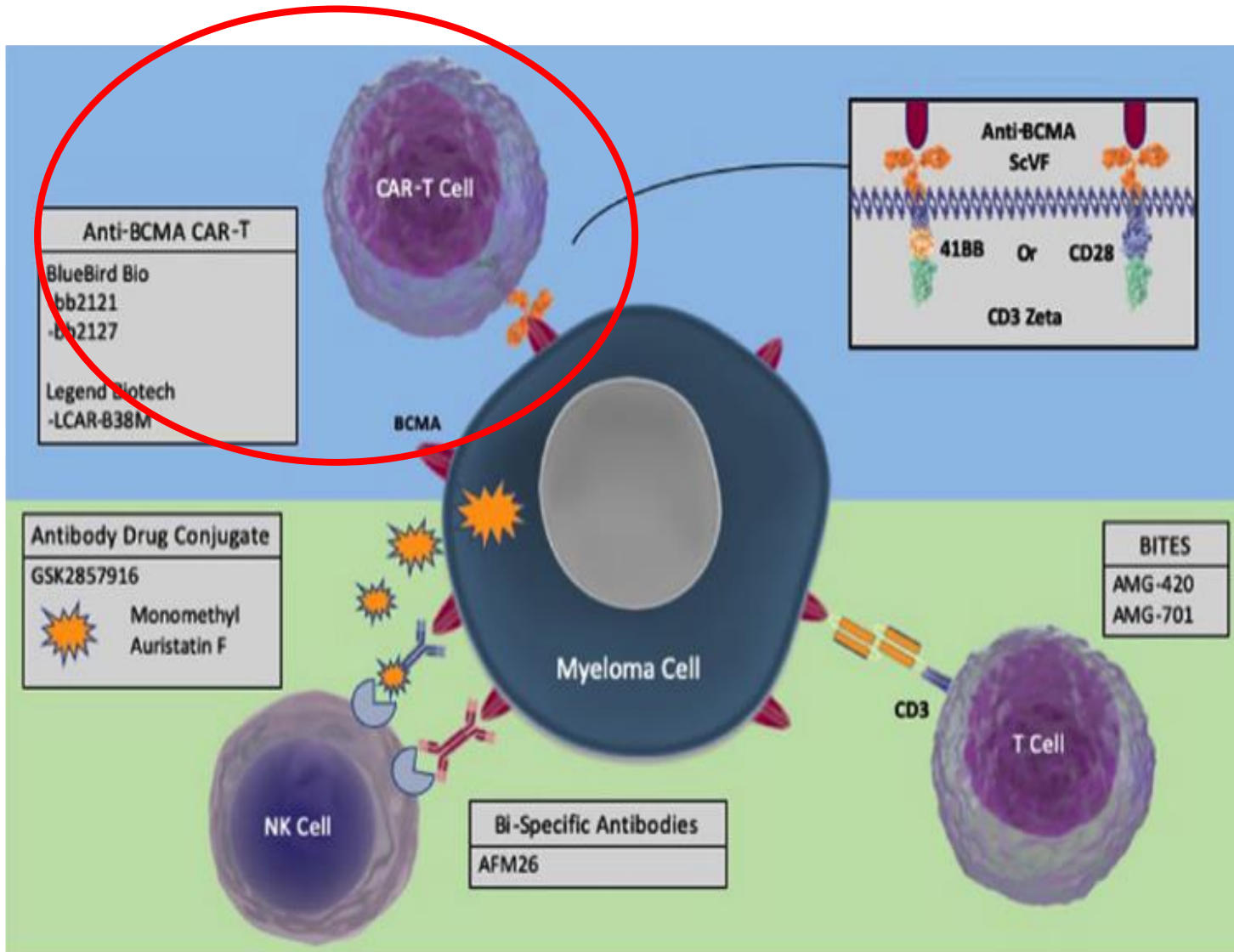
Tabalumab  
Belimumab (SLE)  
Blisublimab (SLE)

VD +

**Absence d'efficacité  
suffisante dans le  
MM**

Patient number	Dose mg kg <sup>-1</sup>	MM isotype	Cycle I	Stable disease	Progressive disease	Overall response rate (PR or better)	Quality of response*, Odds ratio versus placebo	Median time to next treatment (95% CI), months	Median time to first SRE† (95% CI), months	Tabalumab 100 mg (N = 74)	Tabalumab 300 mg (N = 74)	Placebo (N = 72)
<i>Patients with MM</i>												
1	2	IgG kappa IIIA	Progressive disease							66 (56, 85)	75 (58, 93)	76 (65, 93)
2	2	IgG lambda IIA	Stable disease							NA (NA, NA)	NA (19.1, NA)	NA (18.6, NA)
3	2	IgA lambda IIIA	Stable disease							0	1 (1-4)	2 (2-8)
5	4	IgD lambda IA	Progressive disease							4 (5-4)	10 (13-5)	4 (5-6)
7	7	IgG lambda IA	Progressive disease							16 (21-6)	10 (13-5)	9 (12-5)
8	7	IgA lambda IIIA	Progressive disease							23 (31-1)	23 (31-1)	29 (40-3)
11	10	IgG lambda IIA	Stable disease	Stable disease	Progressive disease					8 (10-8)	6 (8-1)	6 (8-3)
13	10	IgG kappa IIIA	Stable disease	Stable disease	Progressive disease					10 (13-5)	14 (18-9)	12 (16-7)
14	10	IgA kappa IIIA	Progressive disease							7 (9-5)	6 (8-1)	6 (8-3)
17	10	IgA kappa IIIA	Progressive disease							43 (58-1)	44 (59-5)	44 (61-1)
18	10	IgA kappa IIA	Stable disease	Stable disease	Progressive disease					1.98	1.84	NA
										10.1 (7.0, 11.9)	9.9 (6.8, 14.8)	11.7 (7.8, 17.5)
										NA (NA, NA)	NA (19.8, NA)	NA (NA, NA)

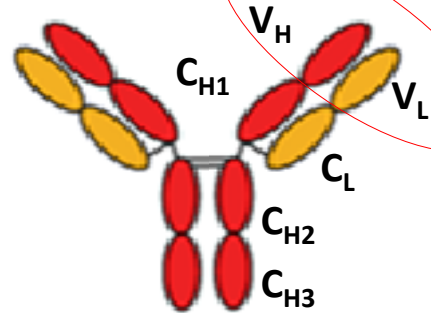
# BCMA: Une nouvelle cible thérapeutique



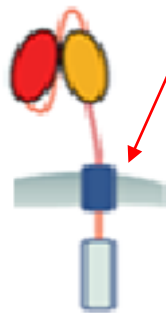
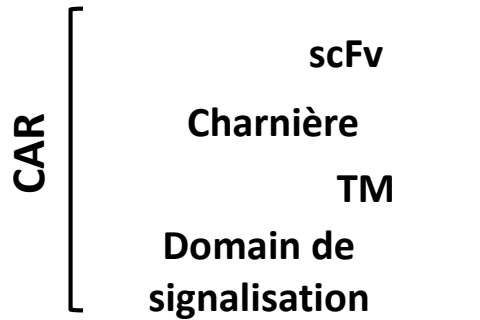
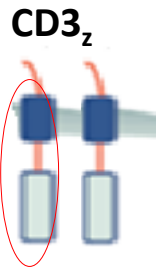
	(Year)					
	2014	2015	2016	2017	2018	2019
CAR T or NK	1	1	2	14	26	23
ADC	1	1		0	5	6
Bi or tri-specific Ab/BiTE		1		3	2	5
ACTR-T+ SEA-BCMA				1	1	0

# Structure et fonction des CAR

Anticorps Monoclonal



Signal du TCR



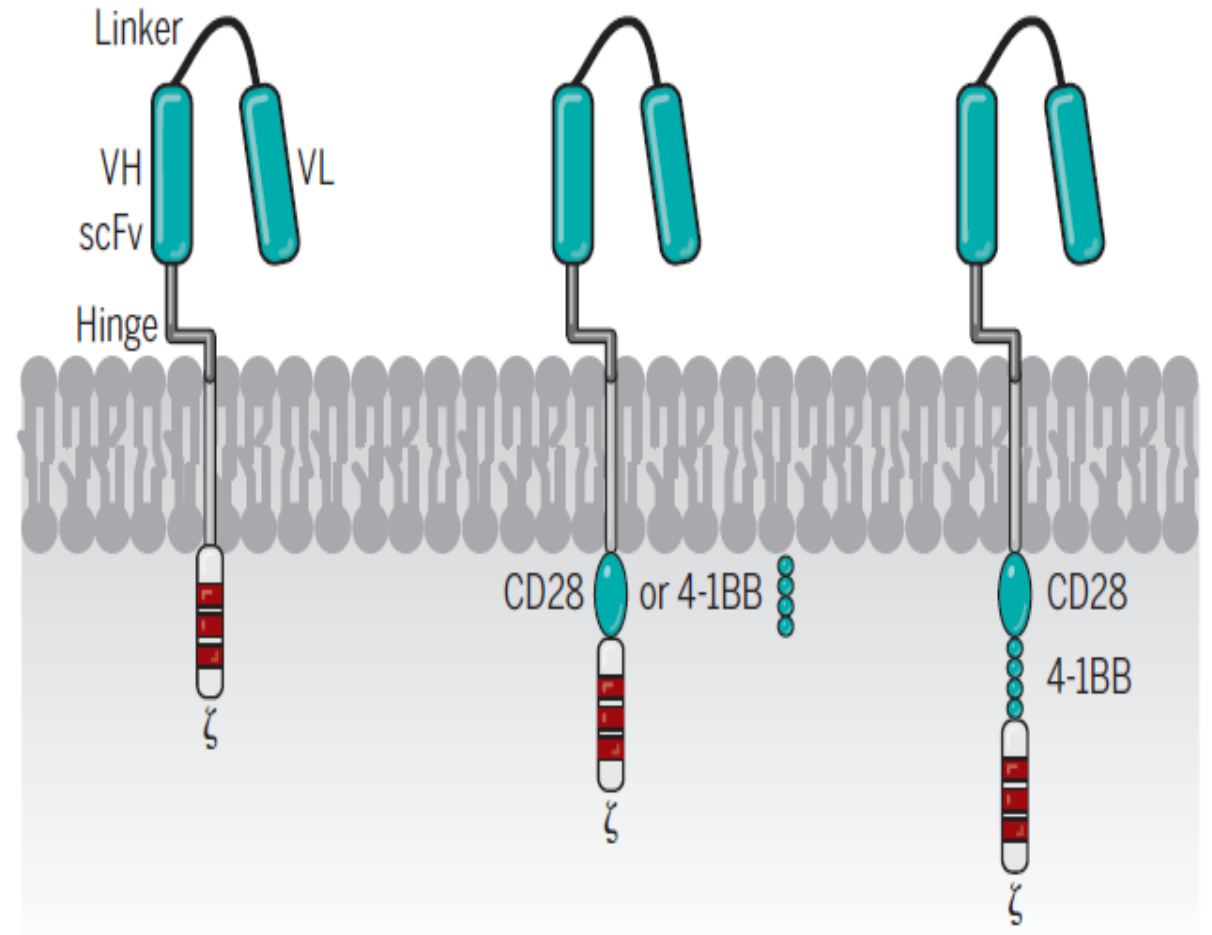
Structure des CARs de 1<sup>er</sup> génération

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

First generation CAR

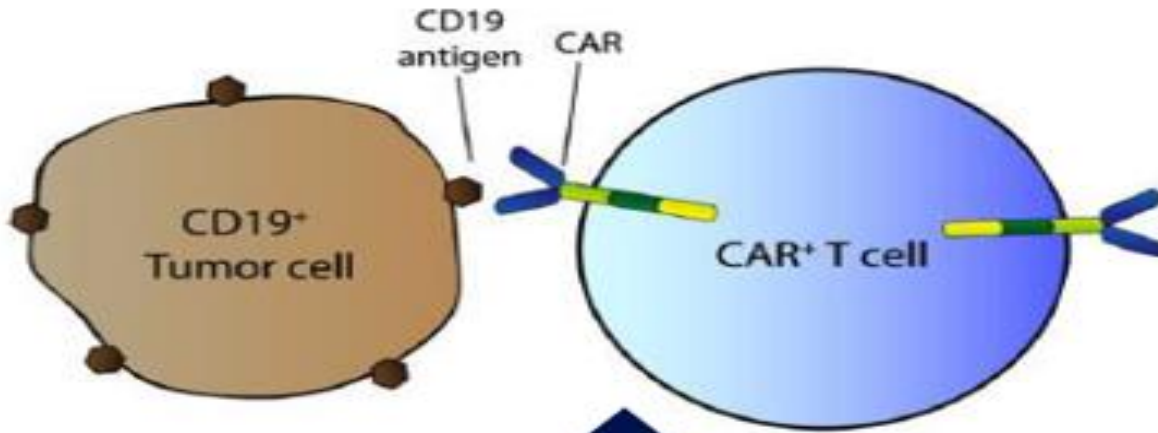
Second generation CAR

Third generation CAR

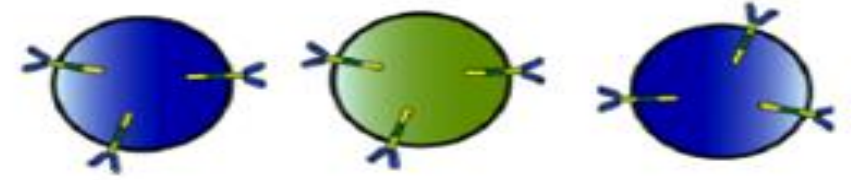


# CAR T: Mécanismes d'action

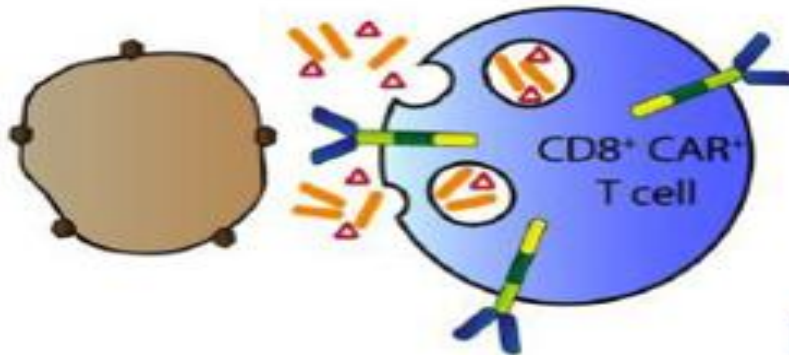
**Tumor cell recognition**  
CAR mediated T cell activation



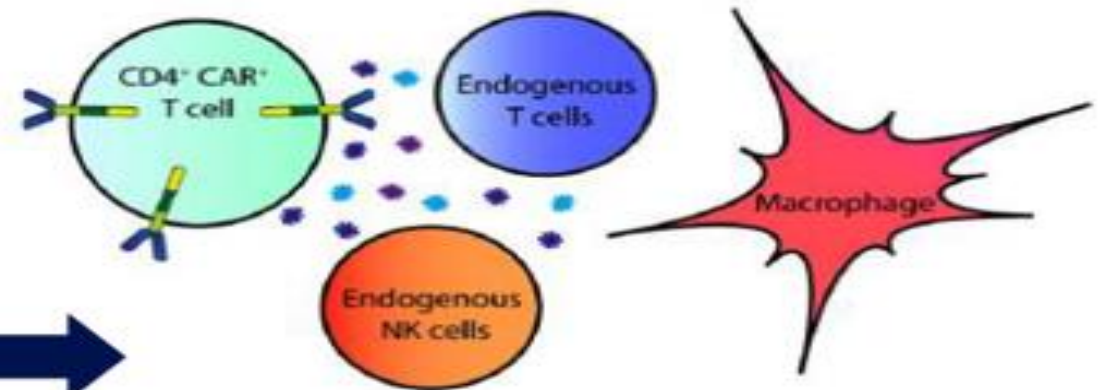
**Memory T cell formation**  
Long-lived tumor specific memory T cells remain



**Activation of Cytotoxic T cells**  
Release of Perforin (|) and Granzymes (Δ)

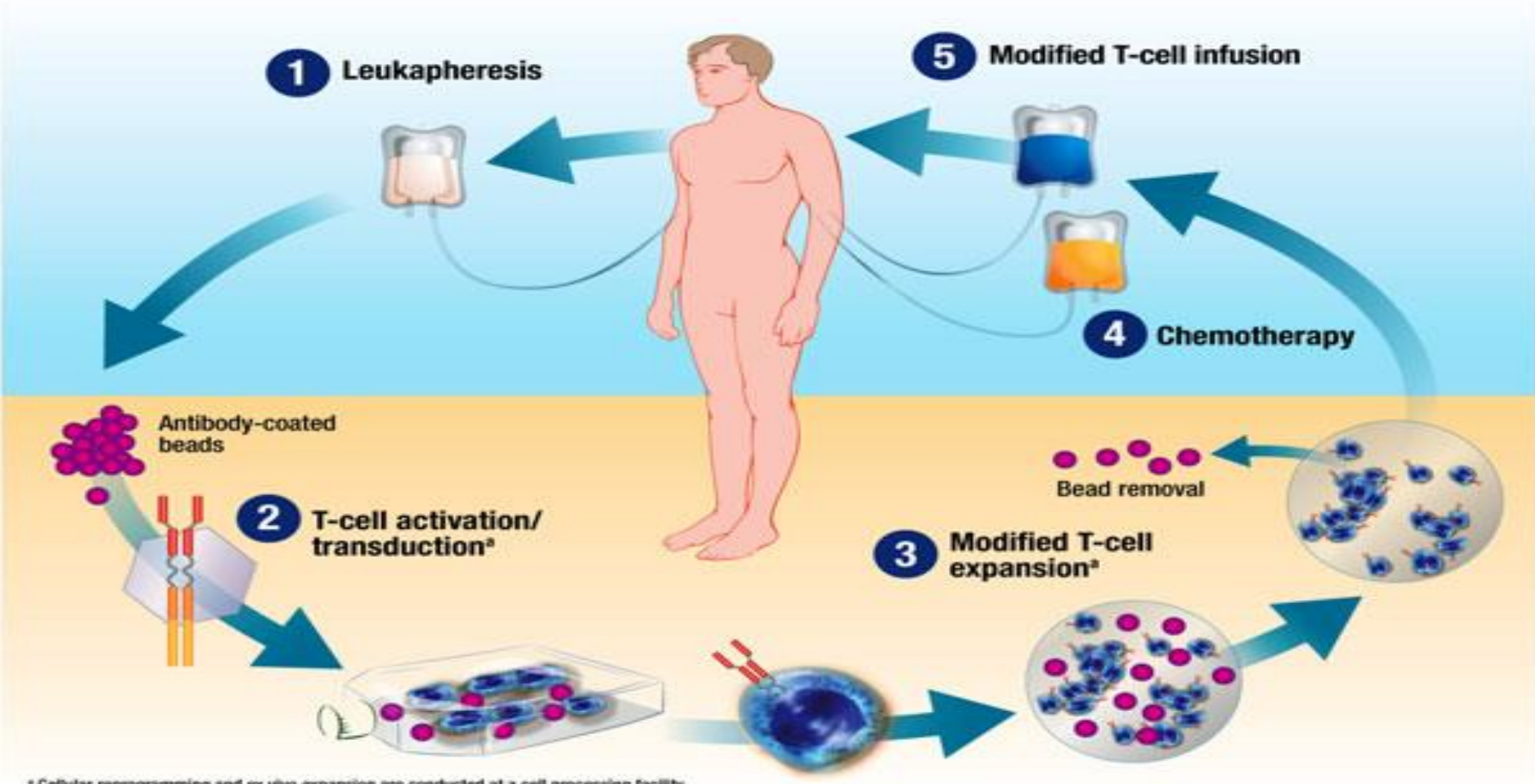


**Cytokine Release**  
Cytokines (•) recruit endogenous immune cells



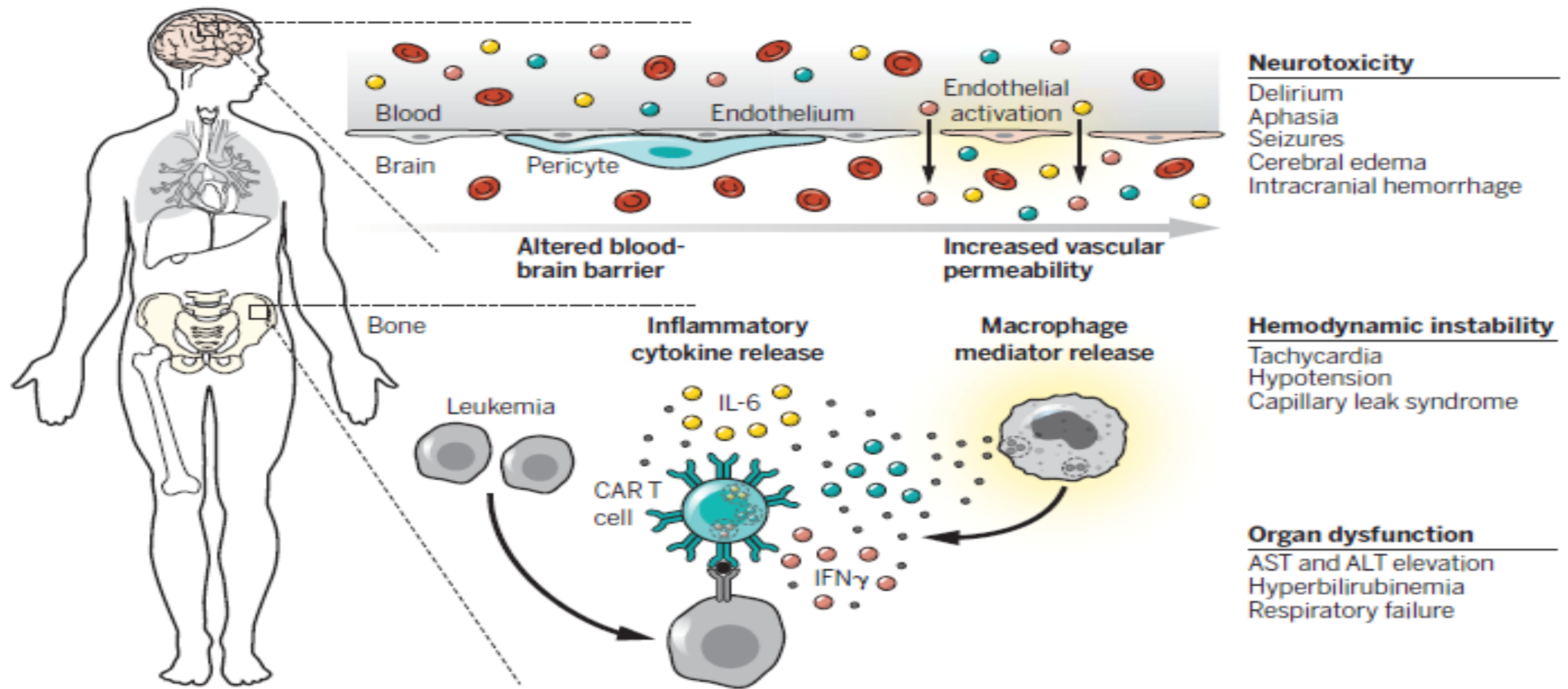


# CAR T cells: Le circuit





# CAR T cells: Les effets indésirables



# CAR T-Cells anti BCMA dans le myélome multiple :

bb2121 : CRB 401 phase 1

Idecabtagene Vicleucel (ide-cel)

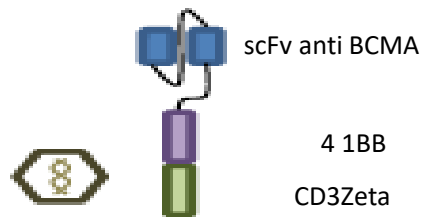
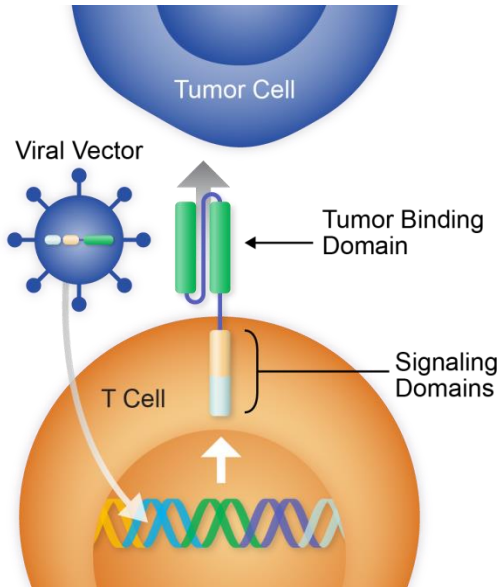
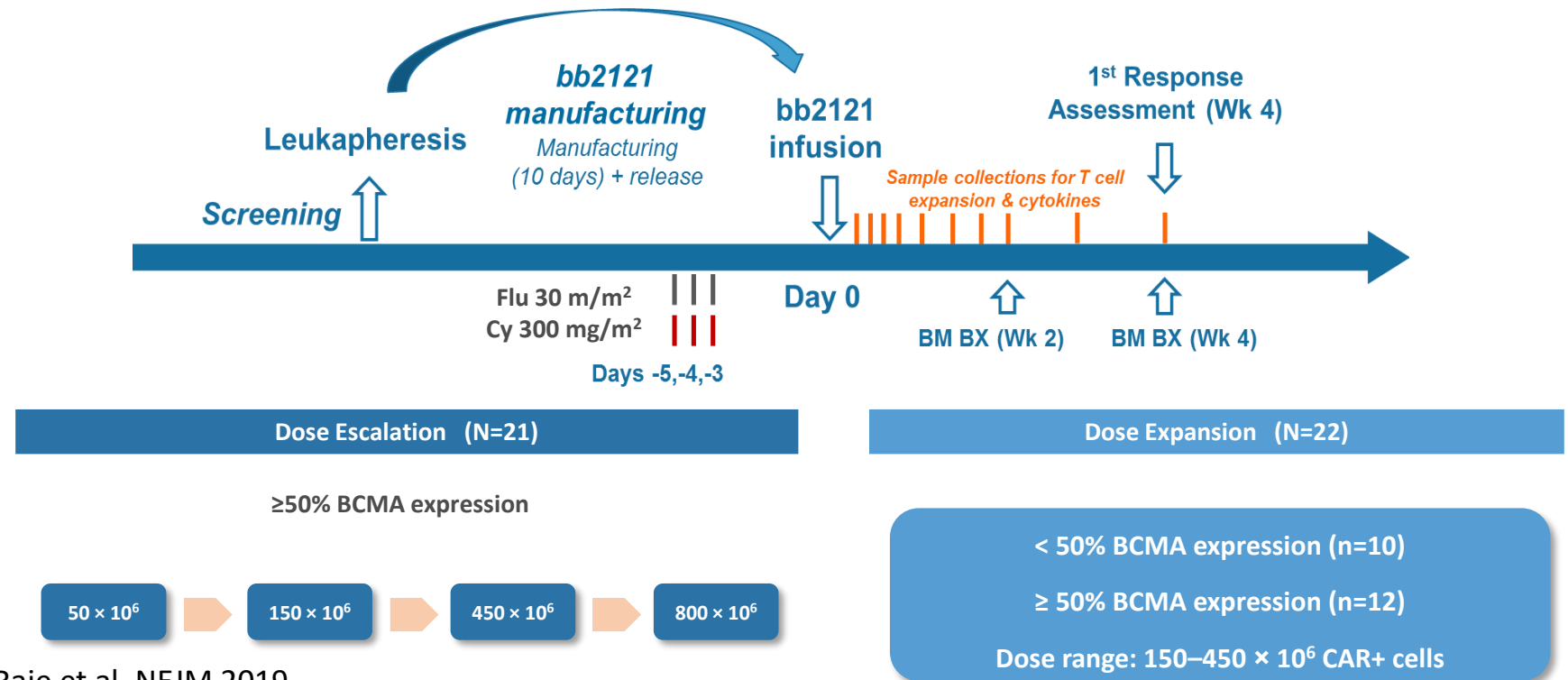


Figure 1: Anti-BCMA Chimeric Antigen Receptor



# bb2121 : CRB 401 phase 1

MM > 3 lignes (med.: 7 (3-21))

Réfractaires à dernière ligne

N=33

## Réfractaires :

Bz / Carfil 61% / 58%

Len / Pom 73% / 79%

Bort / Len 52%

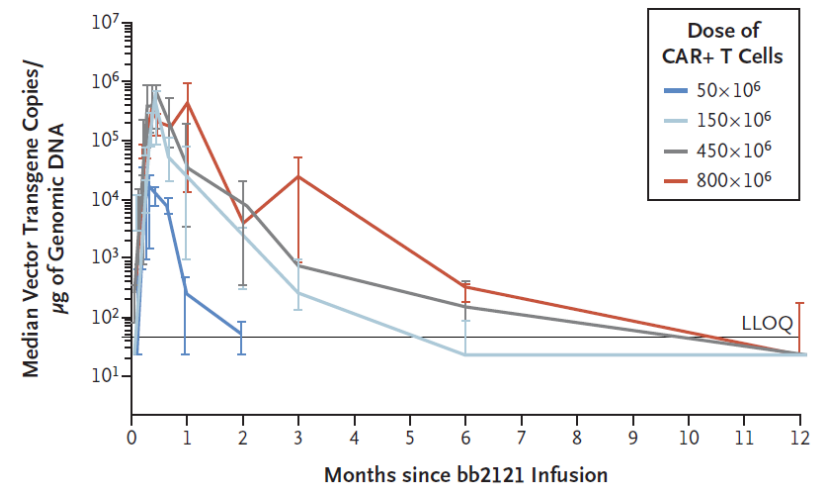
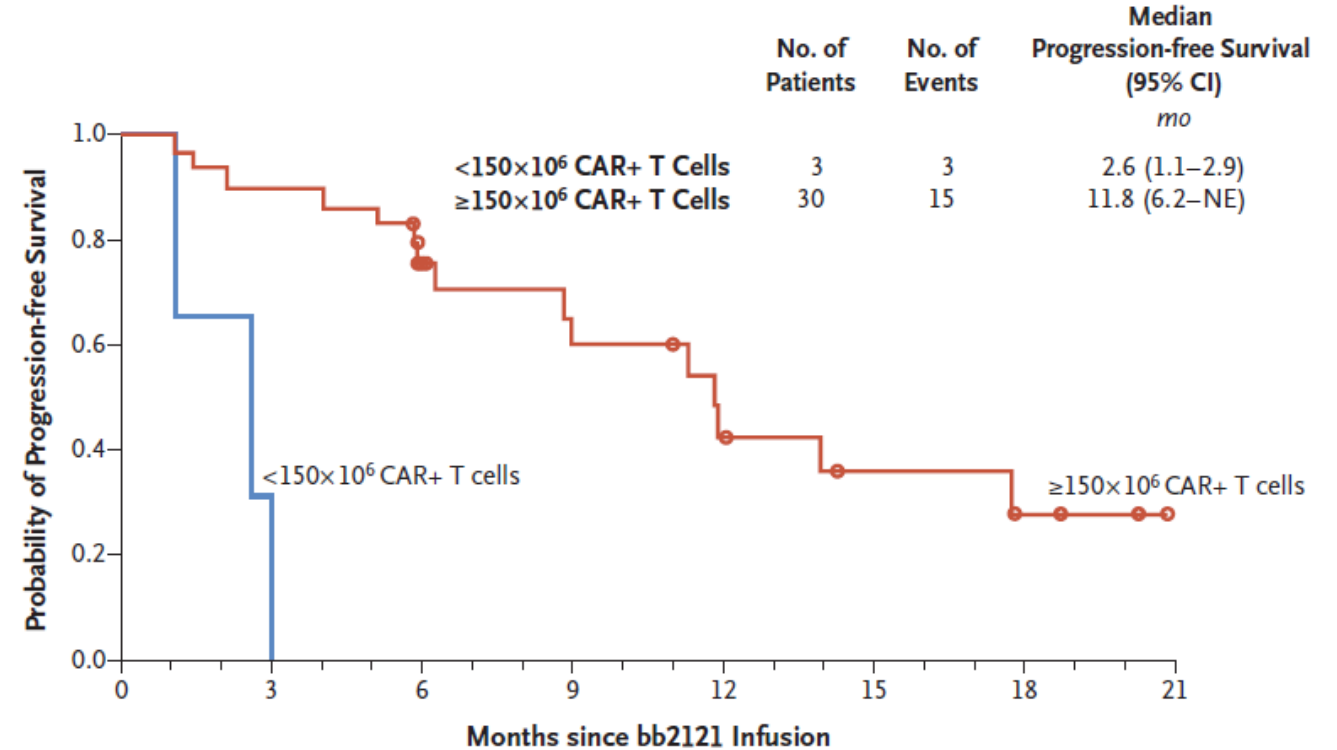
Dara 55%

**Penta réfractaires : 18 %**

- ORR 90% (50% CR)

- 16 / 16 MRD négative

- Raje et al., NEJM 2019

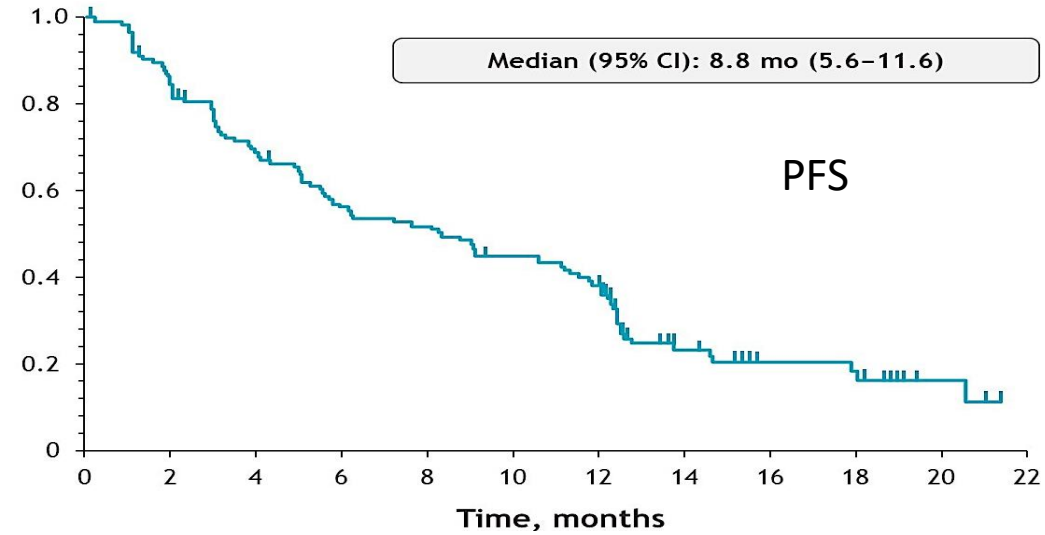
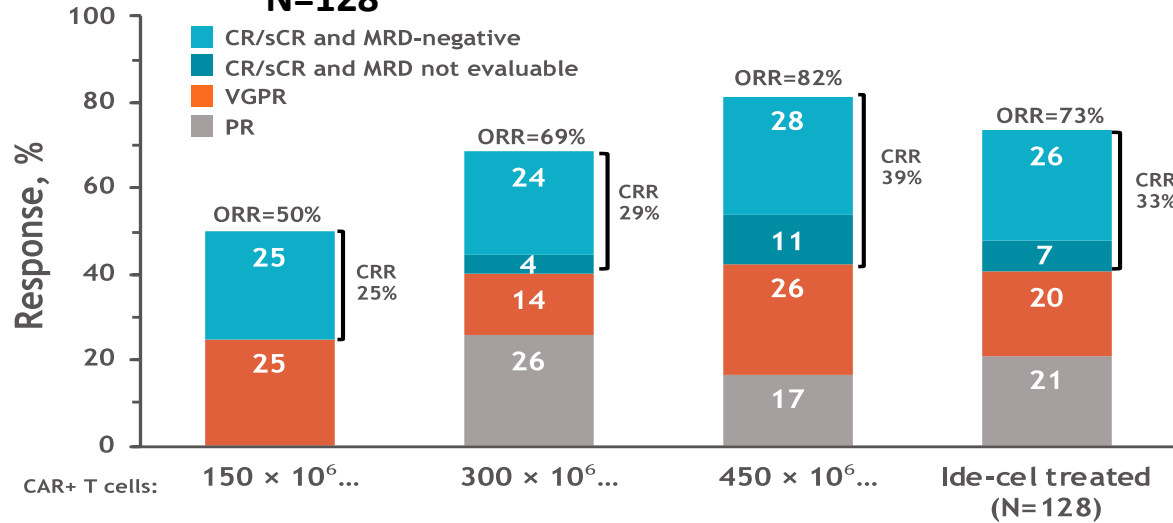


**CRS**  
92% (I-II); 0% (III)

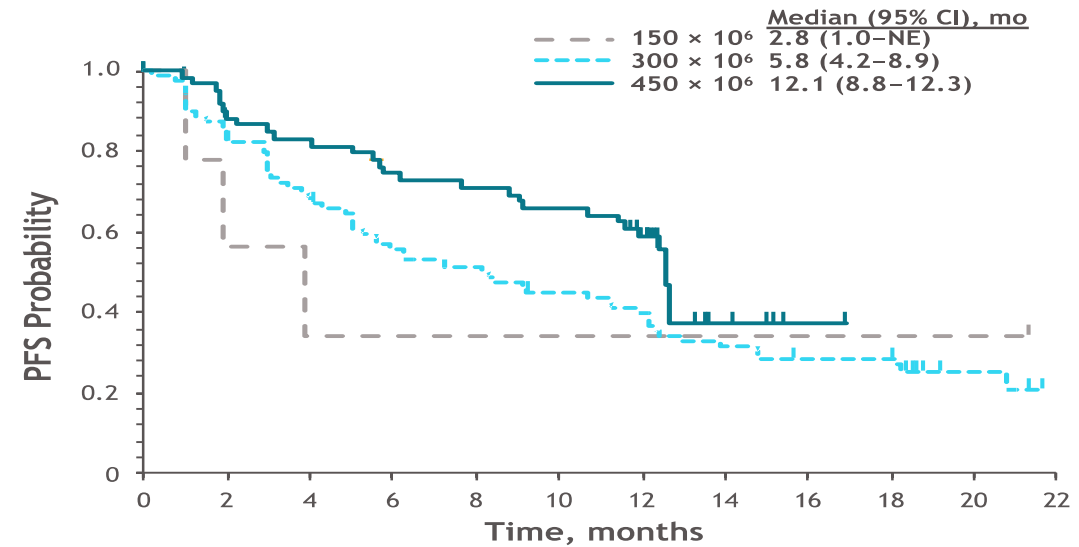
**ICAN**  
42% (I); 3% (III)

# Étude Ide-cel phase 2 pivotale: KarMMa-1

MM > 3 lignes (med.: 6)  
Réfractaires à dernière ligne  
N=128

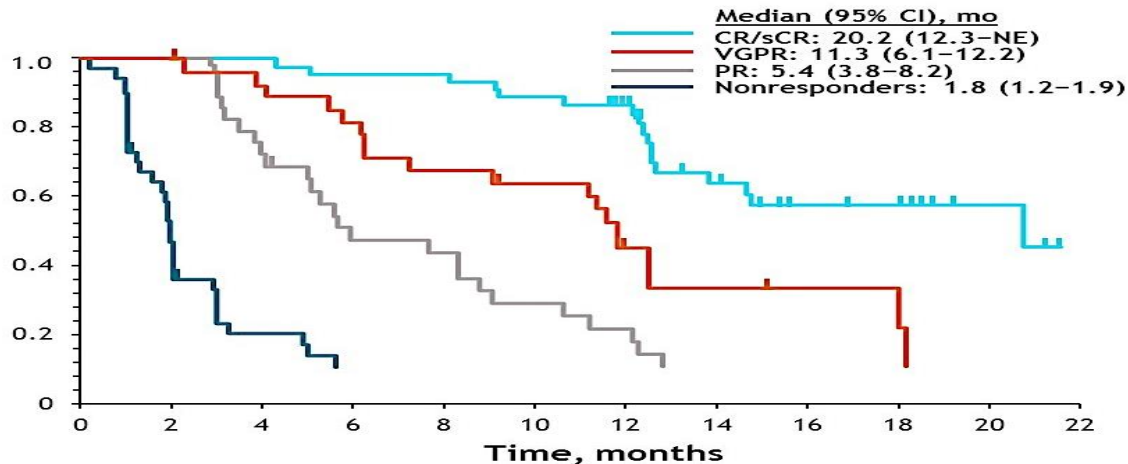


## PFS by Target Dose



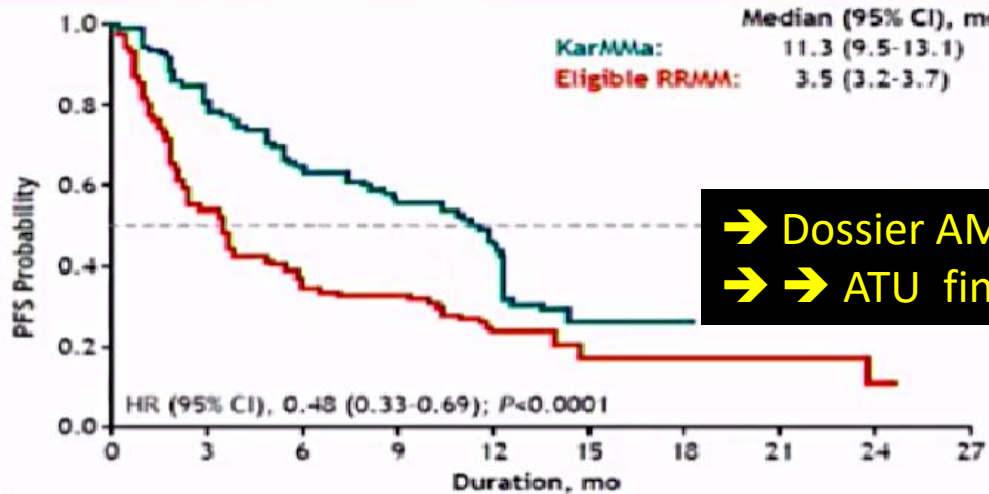
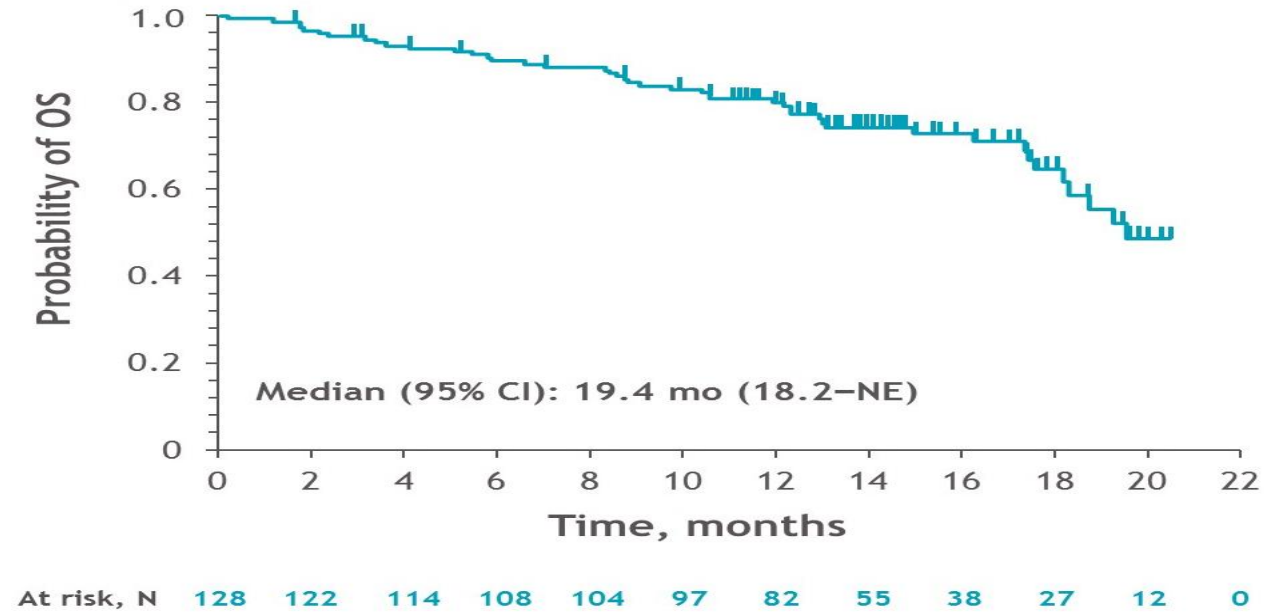
At risk, N	0	2	4	6	8	10	12	14	16	18	20	22
150 × 10 <sup>6</sup>	4	2	1	1	1	1	1	1	1	1	1	0
300 × 10 <sup>6</sup>	70	56	42	33	29	24	17	14	11	7	2	0
450 × 10 <sup>6</sup>	54	44	40	36	34	31	17	4	1	0	0	0

## PFS by Best Response

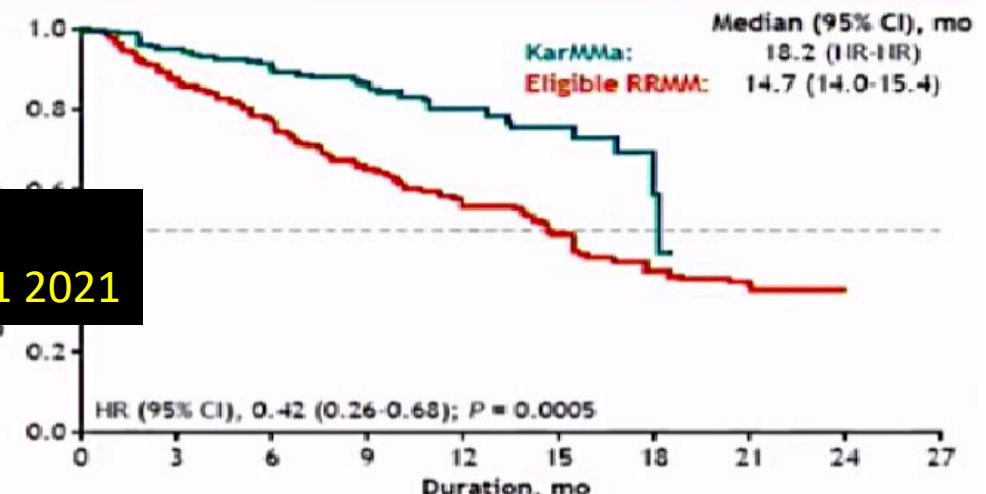


# Étude Ide-cel phase 2 pivotale: KarMMa-1

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



→ Dossier AMM  
 → → ATU fin 2020/Q1 2021



KarMMa  
RW

At risk, N	0	3	6	9	12	15	18	21	24	27
KarMMa	128	93	70	51	21	10	1	0	0	
Eligible RRMM	190	86	46	31	12	7	3	3	1	

At risk, N	0	3	6	9	12	15	18	21	24	27
KarMMa	128	120	109	96	54	32	5	0	0	
Eligible RRMM	190	162	137	111	77	53	36	24	19	

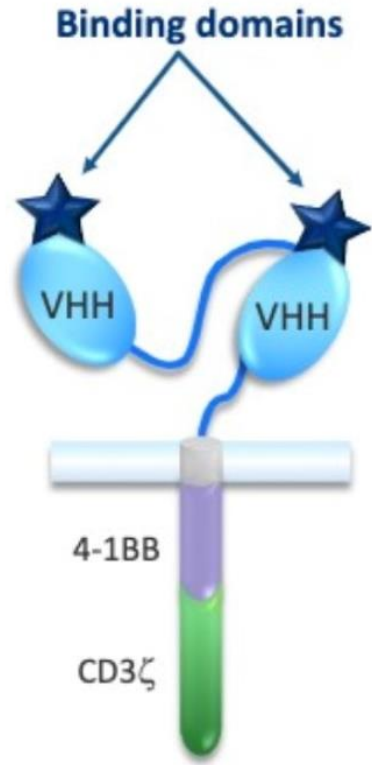
Martin et al.

J20 ASCO 2020



# CAR T anti BCMA : JNJ 4528- CARTITUDE-1

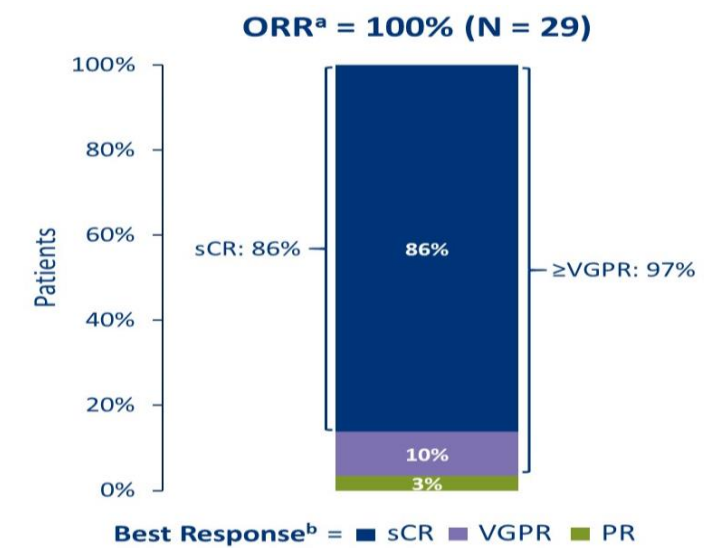
## JNJ-4528



- JNJ-4528 is a structurally differentiated BCMA-targeted CAR-T cell therapy
- 2 BCMA-targeting single domain antibodies designed to confer avidity
- Contains a CD3ζ signaling domain and 4-1BB costimulatory domain

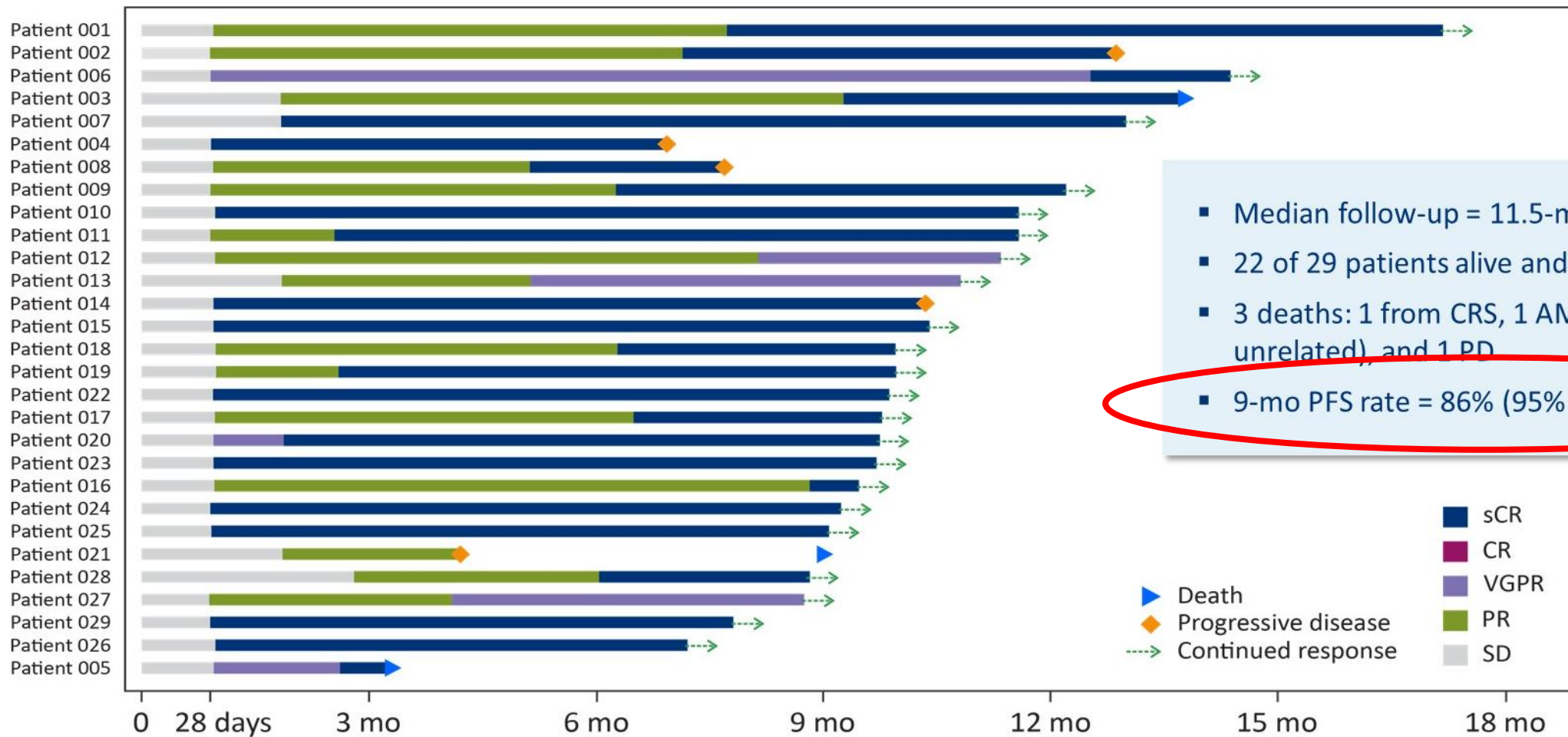
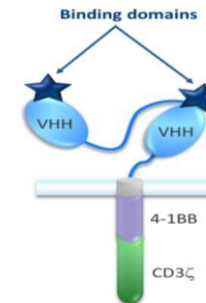
Patients	N= 29
Prior autologous transplantation, n (%)	25 (86)
Triple-exposed, <sup>c</sup> n (%)	29 (100)
Triple-refractory	25 (86)
Penta-exposed, <sup>d</sup> n (%)	21 (72)
Penta-refractory	9 (31)

Nb lignes ant. 5 (3-18)



• Madduri et al. ASH 2019; Berdeja et al., ASCO 2020

# CAR T anti BCMA : JNJ 4528- CARTITUDE-1



- Median follow-up = 11.5-mo (3 – 17)
- 22 of 29 patients alive and progression-free
- 3 deaths: 1 from CRS, 1 AML (treatment unrelated), and 1 PD
- 9-mo PFS rate = 86% (95% CI, 67 – 95)

▶ Death  
◆ Progressive disease  
- - - - -▶ Continued response  
■ sCR  
■ CR  
■ VGPR  
■ PR  
■ SD

<b>CRS, all / ≥G3, %</b>	<b>93 / 7</b>
Med. time to CRS, day	7
Med duration CRS, day	4
Tocilizumab, %	79

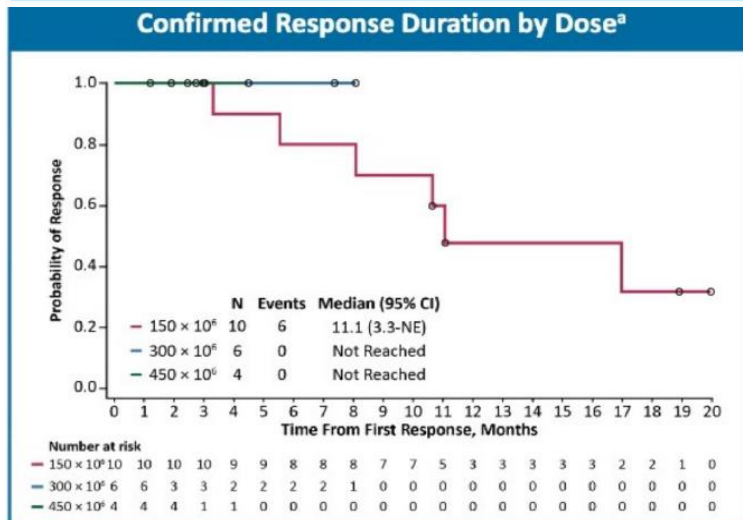
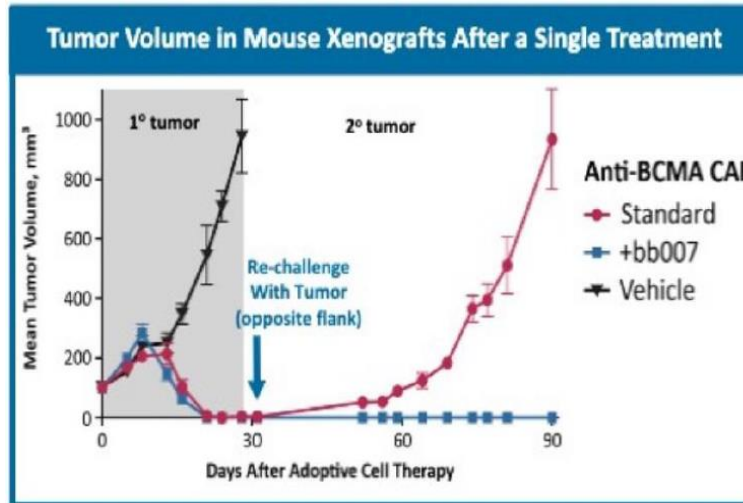
<b>ICANS, all, ≥G3, %</b>	<b>10 / 3</b>
Neutropenia ≥G3, %	100
Thrombocytopenia ≥G3, %	69
Infection, all / ≥G3, %	NA / 19

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

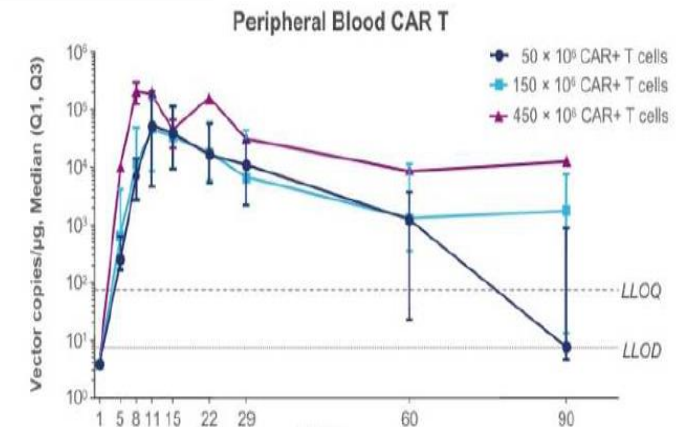
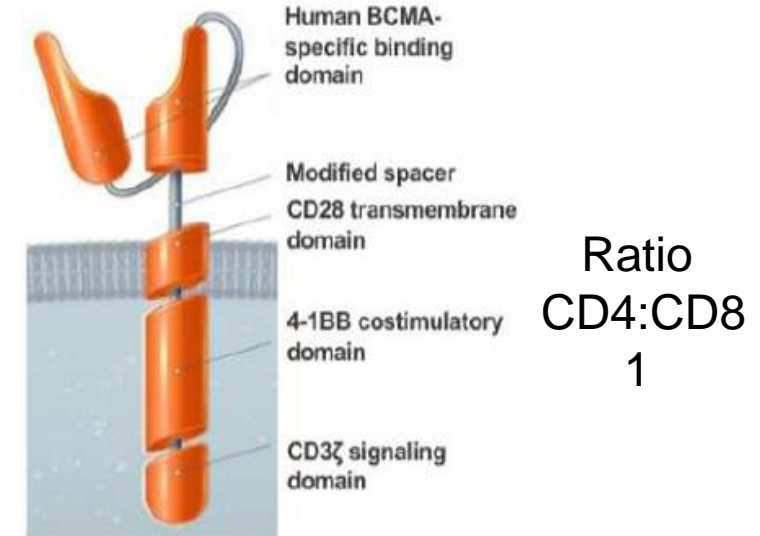
## • Améliorer persistance des CAR T

- 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

# CAR T cells anti-BCMA

	KarMMa <sup>1</sup> (n=128)	CARTITUDE-1 <sup>2</sup> (n=29)	EVOLVE <sup>3</sup> (n=62)	bb21217 <sup>4</sup> (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	100/86	92/36	83/33
MRD- ( $10^{-5}$ ), %	28 at 450M	50	NA	NA
PFS/OS, med. , m	12.1 à 450M/19.4	86% à 9 m/NR	NR/NR	NR/NR
CRS, all / $\geq$ G3, %	84 / 6	93 / 7	89 / 3	66 / 6
Delai app./durée	1j / 5j	7j / 4j	2j / 4j	3j / 4j
Tocilizumab, %	52	79	76	NA
ICANS, all, $\geq$ G3, %	18 / 3	10 / 3	13 / 3	24 / 8
Infection, all / $\geq$ G3, %	69 / NA	NA / 19	40 / 13	NA / 18

<sup>1</sup> Munshi et al. ASCO 2020, <sup>2</sup> Berdeja et al. ASCO 2020, <sup>3</sup> Mailankody et al. ASCO 2020, <sup>4</sup> Berdeja et al. ASH 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

CARTITUDE-1: phase 1b

→ **ATU / AMM**  
**Ide-Cel**

**Fin 2020 /début 2021**

### 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 1<sup>ère</sup> ligne

**KarMMa-2** :  
Cohorte 1<sup>ère</sup> ligne  
non RC post autogreffe

**CARTITUDE-2** :  
Cohorte 1<sup>e</sup> ligne  
non RC post autogreffe



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

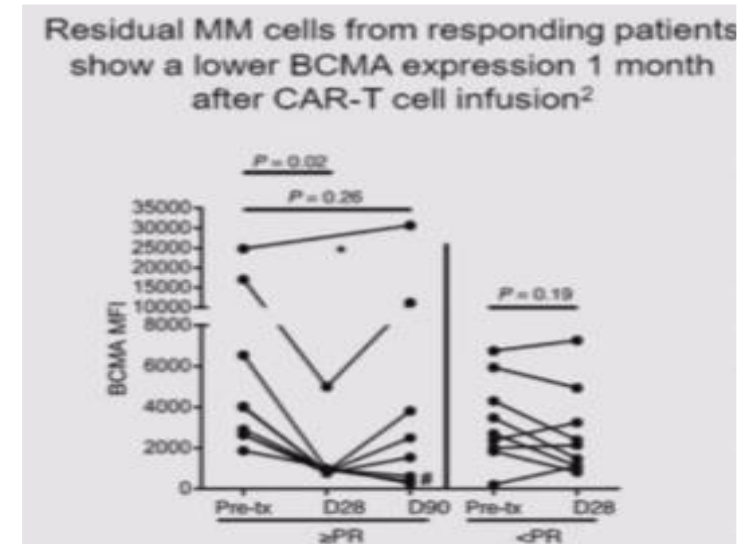
- **Perte des CAR T**

- Quantitative (absence de persistance, de phénotype mémoire; immunogénicité)
- Fonctionnelle (exhaustion, perte cytotoxicité, microenvironnement)

- **Perte antigène/modulation antigénique**

- Perte d'expression
- Modulation
- Clivage (gamma secretase)

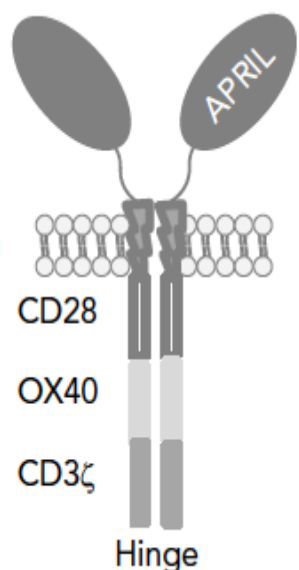
**CAR reconnaissant  
deux antigènes  
BCMA/CS1  
BCMA/GPRC5D  
.....**



# TACI et BCMA: cible thérapeutique ? : CAR T April

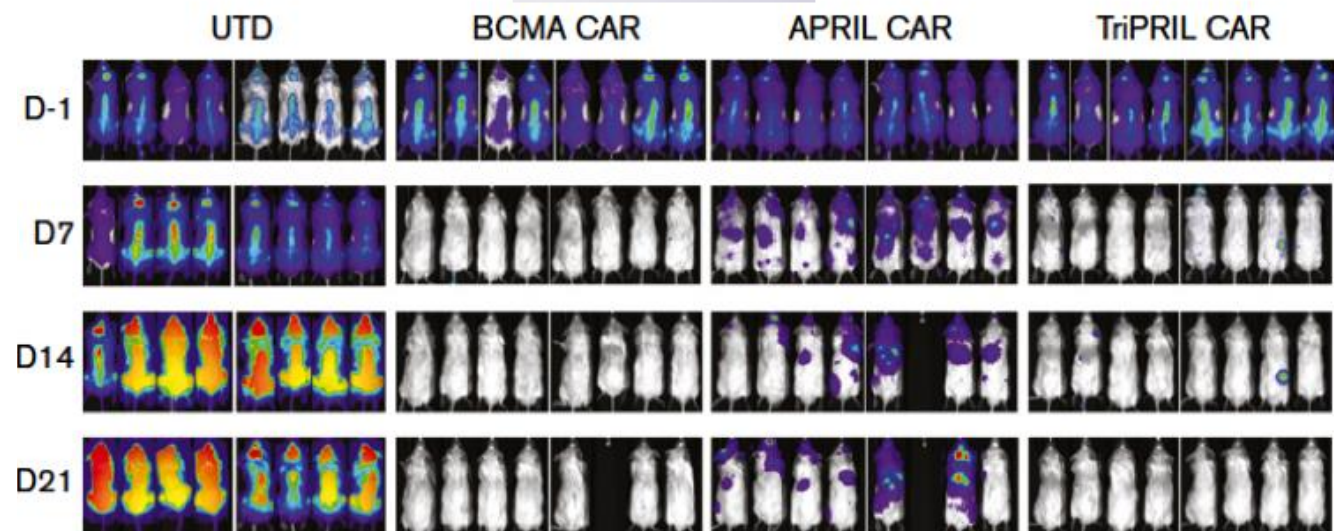
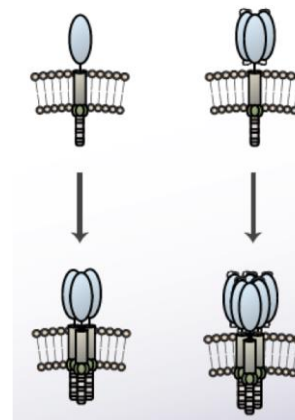
## CAR T April (AUTO-2)

### Phase 1 First-in-Human Study of AUTO2, the First Chimeric Antigen Receptor (CAR) T Cell Targeting APRIL for Patients with Relapsed/Refractory Multiple Myeloma (RRMM)



N=12  
 Med. Lignes ant. 5  
 80% Réfractaires à Imids et IP  
 45% réfractaire au Daratumumab  
 CRS 45% (Gr I)  
 Neurotox.=0  
 Dose 15 à 900x10e6  
 N=7 à ≥ 225x10e6  
 ORR 43% (28% PRs and 14% VGPRs)  
 PFS ?

## CAR T April (Tripril)



Schmidts et al., Blood Advances. 2019

# CAR T cell anti BCMA dans le myélome multiple : Perspectives

Place dans la stratégie  
thérapeutique ?  
Utilisation précoce  
Tous les Myélomes ?

Biomarqueurs de  
durée de réponse ?

Nouvelles cibles  
Nouveaux CARs

**Place par rapport aux  
autres Immunothérapies  
anti BCMA ?**

Coût / efficacité ?  
Réduction du coût  
Simplification circuit

Coopération  
Etudes académiques

## Electronic Certificate

**Version:** 1 . 0

**Document Number:** SE-FR-BLM-PPTX-200002

**Document Name:** BCMA: Nouvelle cible thérapeutique dans le Myélome Multiple

**Country:** France

**Product:** BLENREP

**Type:** Scientific Engagement

Role	Signature
Christophe Tessier - Medical Affairs (christophe.8.tessier@gsk.com)	It is approved that this material has been examined and is believed to be in accordance with the relevant Code of Practice and any other relevant regulations, policies and SOPs. Date: 10-Sep-2020 15:53:11 GMT+0000