Séance d'actualité Myélome multiple

Développement attendu des CAR-T et autres approches immunologiques

Cyrille Touzeau
CHU Nantes

Paris, 10 septembre 2020

ifm

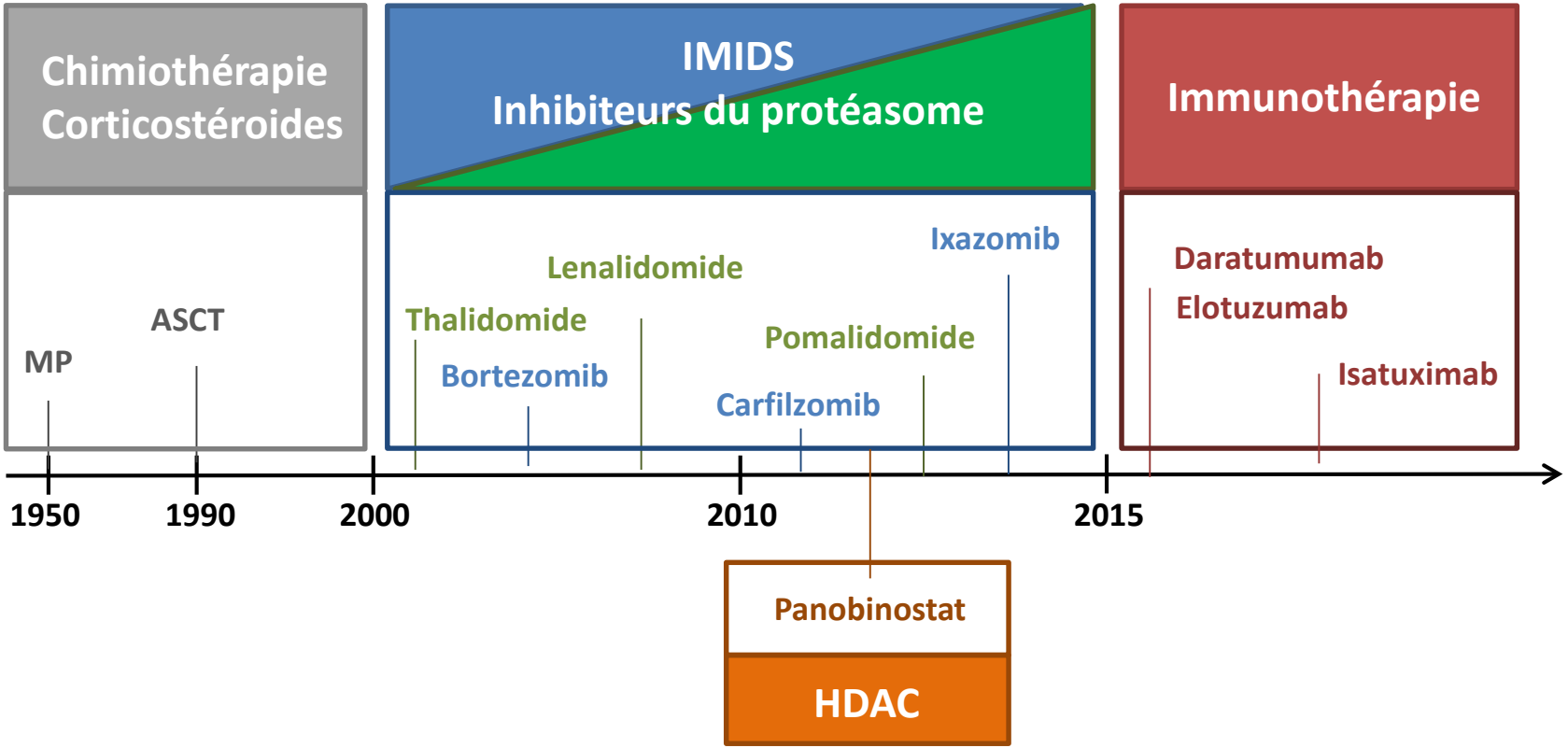
CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

Inserm

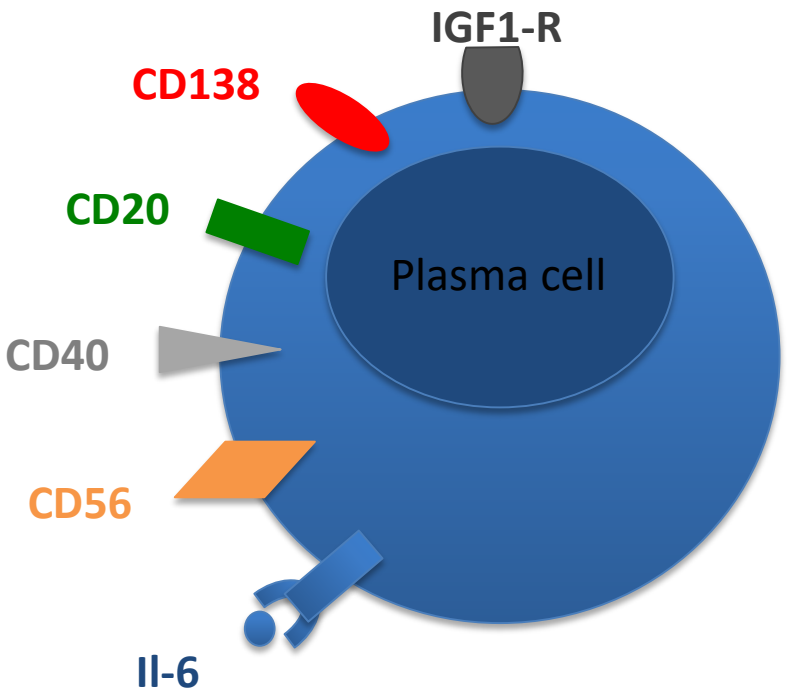
Liens d’intérêt

- Board : Amgen, Celgene, Janssen, Takeda, Abbvie
- Fonds de recherche : Abbvie, GSK, Sanofi

Myélome multiple : le paysage thérapeutique



Les cibles antigéniques plasmocytaires



Touzeau et al, Leukemia 2017. Review

Les cibles antigéniques plasmocytaires

AVE1642

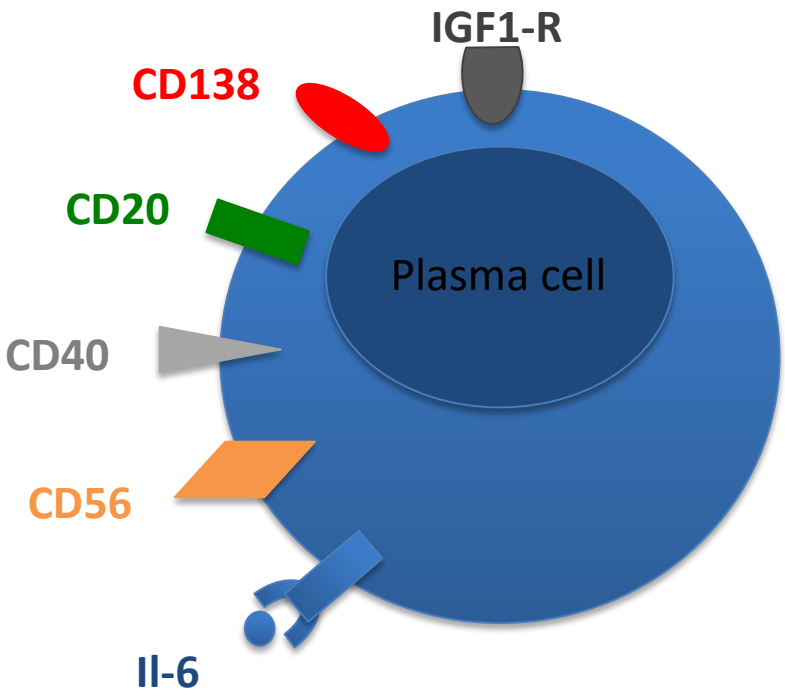
indatuximab ravtansine

Rituximab

Lucatumumab, Dacetuzumab

Lorvotuzumab

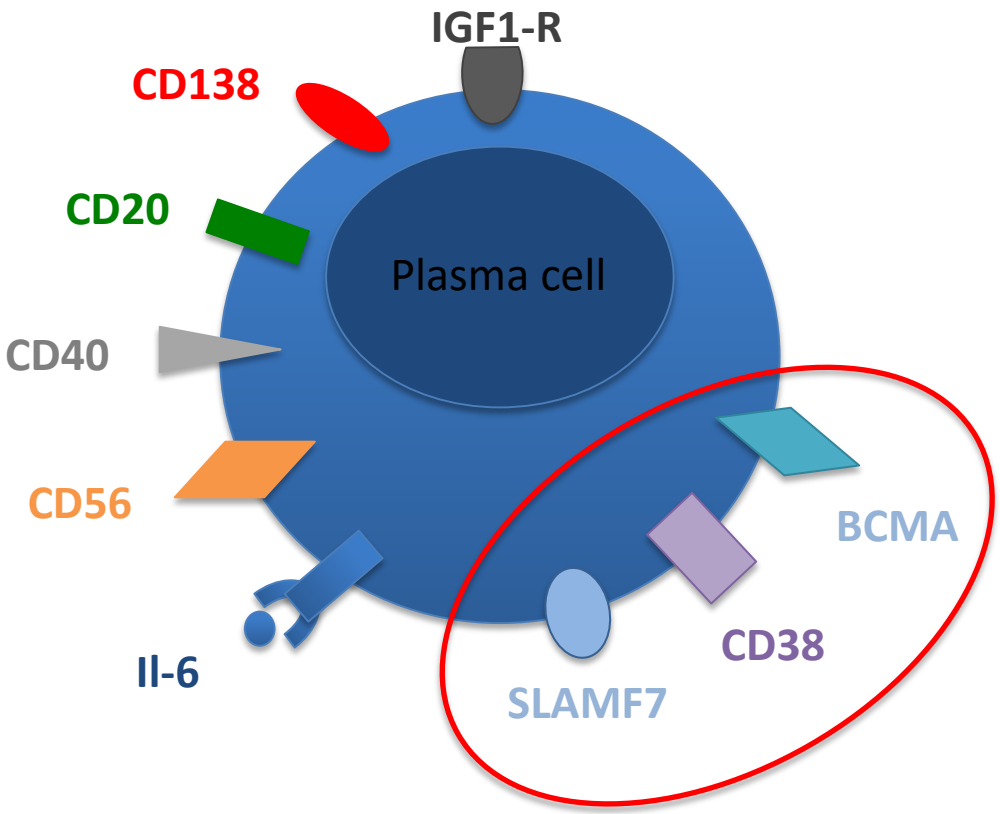
Siltuximab



Absence de résultats positifs

Touzeau et al, Leukemia 2017. Review

Les cibles antigéniques plasmocytaires



Immunothérapie du myélome multiple

Anticorps monoclonaux

CD38:
- daratumumab
- isatuximab

SLAMF7:
- elotuzumab

PD-1/L1:
- pembolizumab
- nivolumab

Anticorps monoclonaux conjugués

BCMA:
- Belantamab mafodotin

CAR-T cells

BCMA:
- bb2121 (ide-cell)
- JNJ4528 – Legend

GPRC5D

Anticorps monoclonaux bispécifiques

BCMA:
- AMG 420
- AMG 701
- CC93269
- Teclistamab

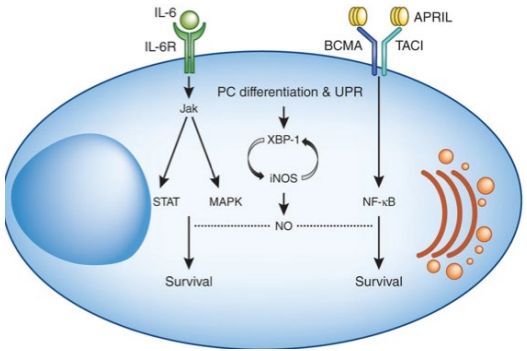
GPRC5D :
JNJ-64407564

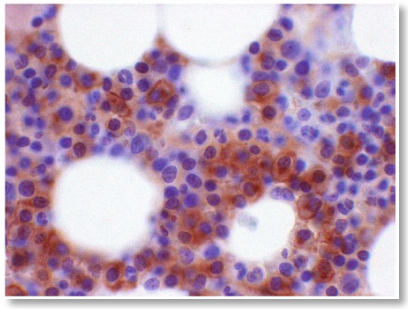
BCMA – B-Cell Maturation Antigen

- **BCMA : membre de la super famille des récepteurs du TNF**
  - Constamment exprimé par les plasmocytes tumoraux
  - Expression restreinte aux plasmocytes et certaines cellules B matures

- **Ligand d'APRIL -> induction de voies de survie /prolifération**

MEK/ERK , PI3K/AKT, NFkB





BCMA Expression on myeloma cells
(brown color = BCMA protein)

Njau & Jacob. Nat Immunol 2014;15(3):219-21

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GPRC5D

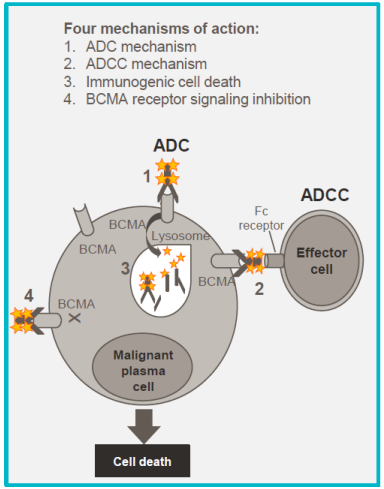
Belantamab Mafodotin

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,

GSK2857916

Cytotoxic agent	– MMAF (non-cell permeable, highly potent auristatin
Afucosylation	– Enhanced ADCC
Linker	– Stable in circulation



Lonial et al. Lancet Oncology 2019

Belantamab Mafodotin

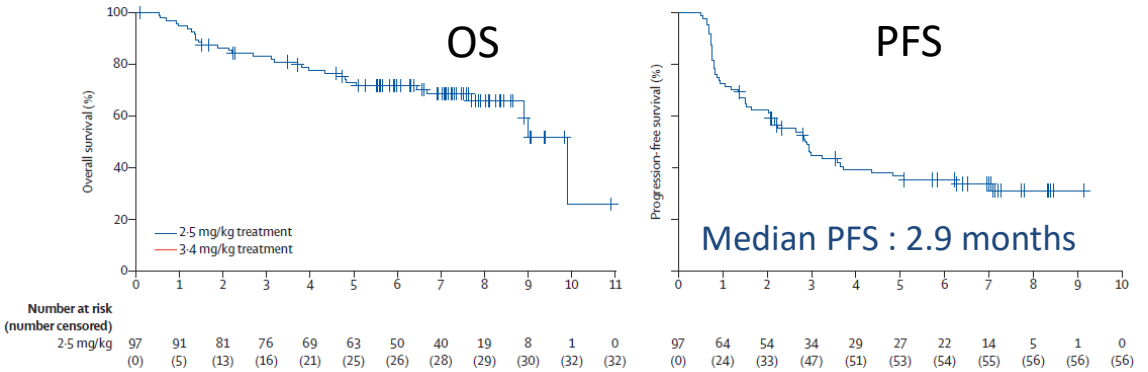
	Belantamab mafodotin 2·5 mg/kg group (n=97)	Belantamab mafodotin 3·4 mg/kg group (n=99)
(Continued from previous column)		
Previous therapies received		
Proteasome inhibitor		
Bortezomib	95 (98%)	97 (98%)
Carfilzomib	74 (76%)	64 (65%)
Immunomodulatory drug		
Lenalidomide	97 (100%)	99 (100%)
Pomalidomide	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%)

- Phase 2
- 2 doses: 2,5 et 3,4 mg/kg
- 196 patients traités
- 6 lignes antérieures en médiane,
  en majorité réfractaires IMIDS/IP/antiCD38

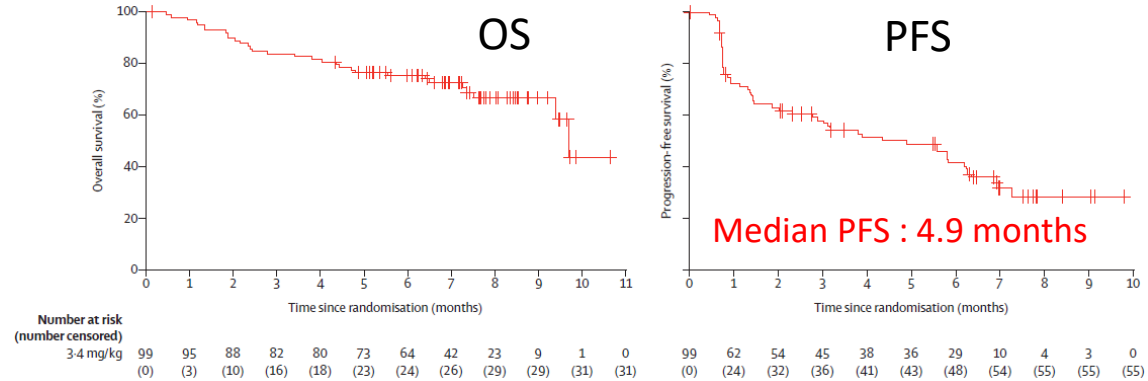
Lonial et al. Lancet Oncology 2019

Belantamab Mafodotin

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
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
Arthralgia	10 (11%)	1 (1%)	0	0	7 (7%)	0	0	0

Lonial et al. Lancet Oncology 2019

Belantamab Mafodotin

- 30% de réponse, PFS = 3 mois chez des patients réfractaires IMIDs, IP et anti CD38
- La limite de la toxicité oculaire
- AMM récente (« Blenrep »), encore disponible via ATU de cohorte
- **Essais en cours chez des patients moins avançés:**
    - DREAMM 6: Phase 1-2, BM-Rd ou BM-Vd en rechute
    - DREAMM 9: Phase 3, VRD+-BM en L1 non éligible à la greffe

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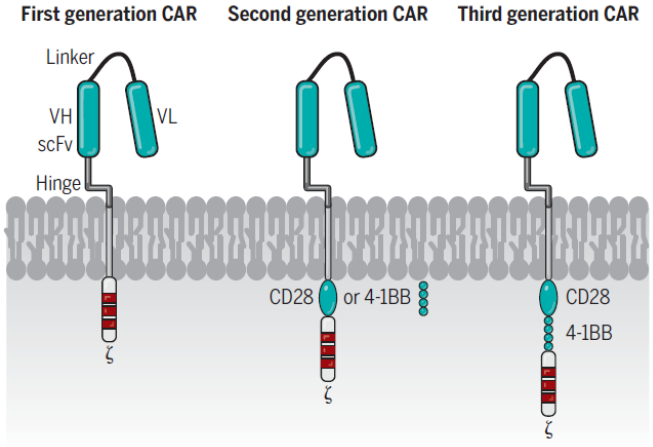
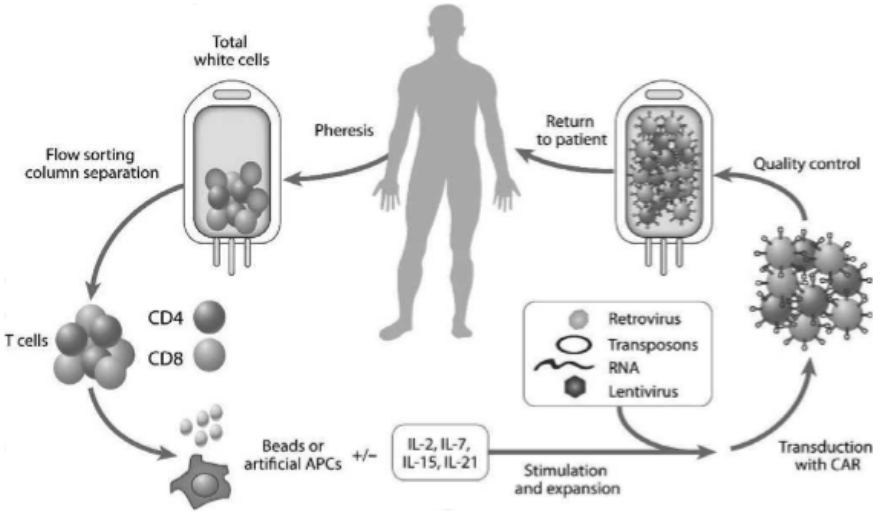




- Extracellular binding domain : BCR-derived, scFv
- Transmembrane domain
- Intracellular signalling domain : TCR-derived, CD3ζ

C June, Science 2018

bb2121 : étude de phase 1

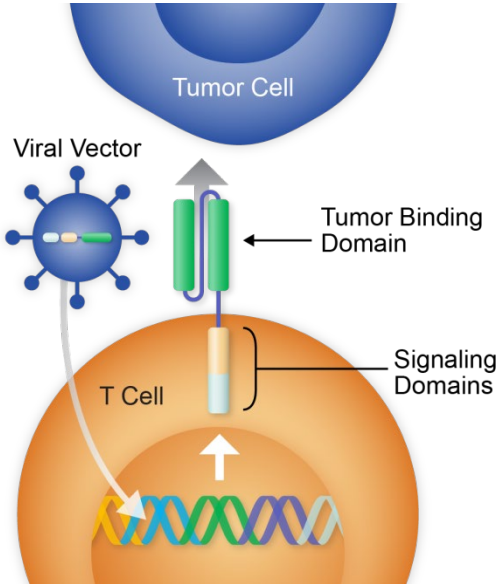
The NEW ENGLAND JOURNAL of MEDICINE

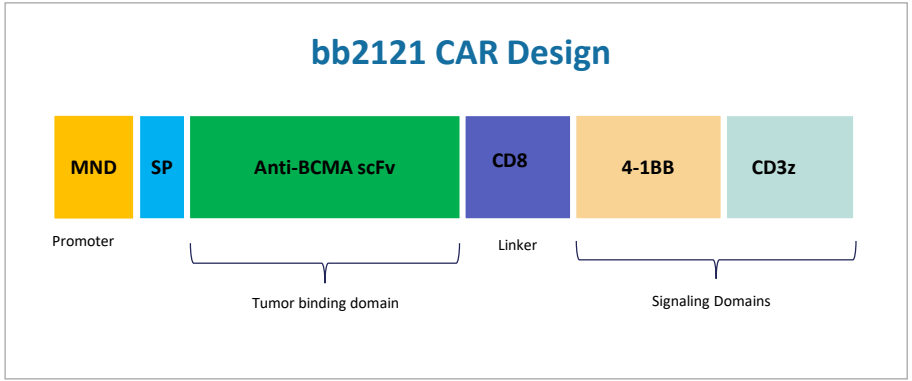
ORIGINAL ARTICLE

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

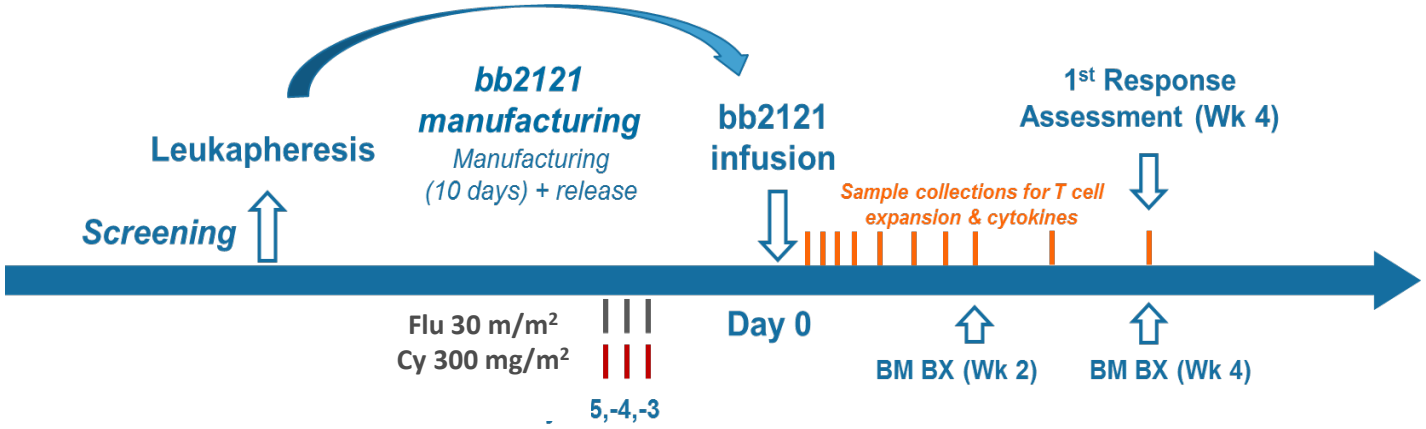
Noopur Raje, M.D., Jesus Berdeja, M.D., Yi Lin, M.D., Ph.D., David Siegel, M.D., Ph.D., Sundar Jagannath, M.D., Deepu Madduri, M.D., Michaela Liedtke, M.D., Jacalyn Rosenblatt, M.D., Marcela V. Maus, M.D., Ph.D., Ashley Turka, Lyh-Ping Lam, Pharm.D., Richard A. Morgan, Ph.D., Kevin Friedman, Ph.D., Monica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

bb2121 : étude de phase 1





Bb2121 : étude de phase 1



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)

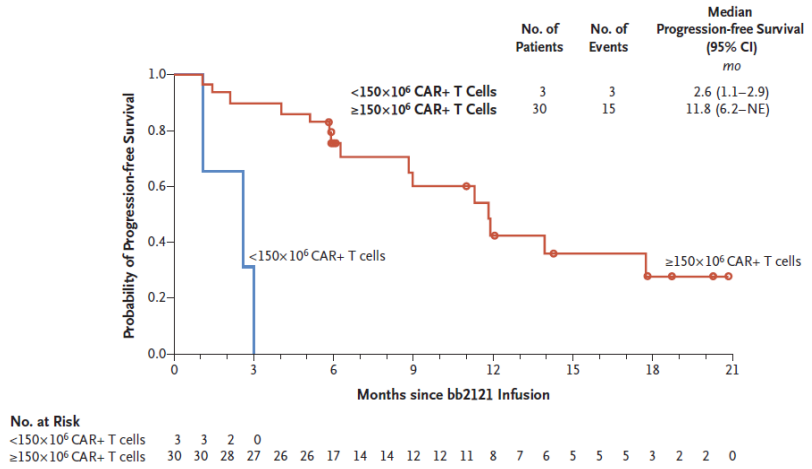
Dose range: 150–450 × 10^6 CAR+ cells

Raje et al. NEJM 2019

Bb2121 : étude de phase 1

Table 3. Tumor Response According to Dose of Chimeric Antigen Receptor–Positive (CAR+) T Cells.*

Variable	50×10^6 CAR+ T Cells (N=3)	150×10^6 CAR+ Tells (N=8)	450×10^6 CAR+ T Cells		800×10^6 CAR+ T Cells (N=3)	150×10^6–800×10^6 CAR+ T Cells (N=30)	50×10^6–800×10^6 CAR+ T Cells (N=33)
			<50% BCMA (N=8)†	≥50% BCMA (N=11)†			
Objective response‡							
No. of patients with a response	1	6	8	10	3	27	28
Rate — % (95% CI)	33 (1–91)	75 (35–97)	100 (63–100)	91 (59–100)	100 (29–100)	90 (74–98)	85 (68–95)
Best overall response — no. (%)							
Stringent complete response	0	5 (63)	3 (38)	4 (36)	0	12 (40)	12 (36)
Complete response	0	0	0	1 (9)	2 (67)	3 (10)	3 (9)
Very good partial response	0	0	4 (50)	4 (36)	1 (33)	[illegible]	9 (27)
Partial response	1 (33)	1 (12)	1 (12)	1 (9)	0	3 (10)	4 (12)
Stable disease	2 (67)	1 (12)	0	1 (9)	0	2 (7)	4 (12)
Progressive disease	0	1 (12)	0	0	0	1 (3)	1 (3)
Median duration of response (95% CI) — mo	1.9 (NE–NE)	NE	7.7 (5.3–14.8)		12.9 (10.9–12.9)	10.9 (7.2–NE)	10.9 (7.2–NE)
Negativity for MRD§							
No. of patients with a response who could be evaluated for MRD	0	4	11		1	16	16
Rate — %	0	100	100		100	100	100



Médiane de 7 lignes antérieures, réfractaires IP+Imid = 80%, ref. anti CD38 = 55%

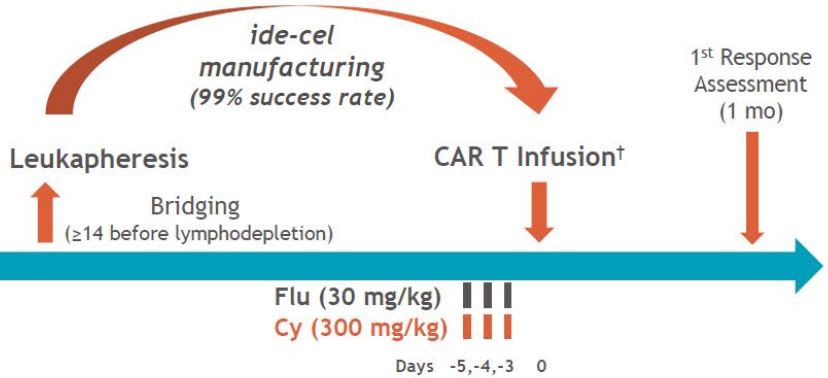
Raje et al. NEJM 2019

Ide-cell (bb2121)

Phase II Pivotal KarMMa Study

KarMMa™

- 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 ratio; 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 imide drugs; 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

Munschi, ASCO 2020

Ide-cell (bb2121)

Baseline Demographics and Clinical Characteristics

Characteristics		Ide-Cel–Treated (N=128)
Age, median (range), y		61 (33–78)
Male, %		59
ECOG PS, %	0	45
	1	53
	2	2
R-ISS Stage,* %	I	11
	II	70
	III	16
High-risk cytogenetics [del(17p), t(4;14), t(14;16)],† %		35
High tumor burden (≥50% BMPCs), %		51
Tumor BCMA expression (≥50% BCMA+),‡ %		85
Extramedullary disease, %		39
Time since initial diagnosis, median (range), y		6 (1–18)
No. of prior anti-myeloma regimens, median (range)		6 (3–16)
Prior autologous SCT, %	1	94
	>1	34
Any bridging therapies for MM, %		88
Refractory status, %	Anti-CD38 Ab-refractory	94
	Triple-refractory	84

- Patients were heavily pretreated, refractory to last line per IMWG criteria, and mostly refractory to all 3 major MM drug classes
- The majority had high tumor burden and more than one third had extramedullary disease and high-risk cytogenetics
- Tumor BCMA expression identified by IHC in all patients
- Most patients (88%) received bridging therapy during CAR T cell manufacturing
  - Only 5% of patients responded (5 PR, 1 VGPR) to bridging therapy

Munschi, ASCO 2020

Ide-cell (bb2121)

Incidence and Management of CRS

KarMMa™

Target Dose, × 10^6 CAR+ T cells	150 (n=4)	300 (n=70)	450 (n=54)	Ide-cel Treated (N=128)
≥1 CRS event, n (%)	2 (50)	53 (76)	52 (96)	107 (84)
Max. grade (Lee Criteria)*				
1/2	2 (50)	49 (70)	49 (91)	100 (78)
3	0	2 (3)	3 (6)	5 (4)
4	0	1 (1)	0	1 (<1)
5	0	1 (1)	0	1 (<1)
Median onset, d (range)	7 (2–12)	2 (1–12)	1 (1–10)	1 (1–12)
Median duration, d (range)	5 (3–7)	4 (2–28)	7 (1–63)	5 (1–63)
Tocilizumab, n (%)	1 (25)	30 (43)	36 (67)	67 (52)
Corticosteroids, n (%)	0	7 (10)	12 (22)	19 (15)

- CRS frequency increased with dose, but mostly low grade
- ≤6% grade 3 or higher CRS events at all target doses, including one grade 5 event
- CRS treated with corticosteroids was infrequent (≤22%) at all target doses

Munschi, ASCO 2020

Ide-cell (bb2121)

Incidence and Management of Neurotoxicity

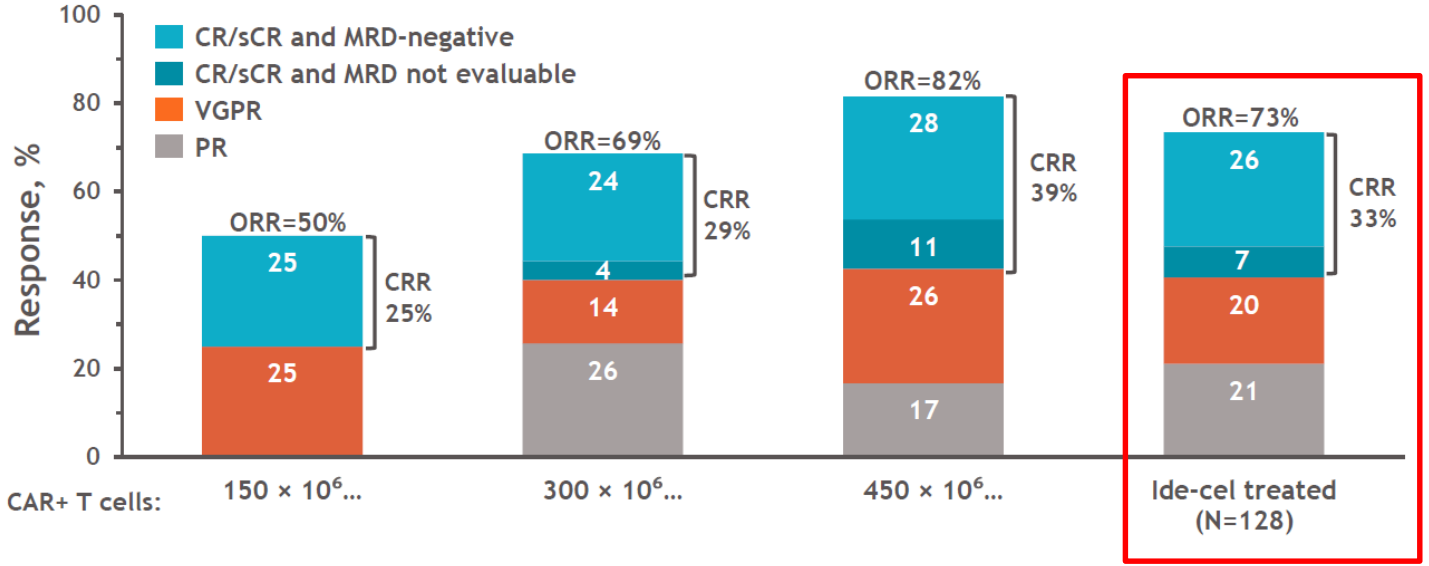
Target Dose, × 10^6 CAR+ T cells	150 (n=4)	300 (n=70)	450 (n=54)	Ide-cel Treated (N=128)
≥1 NT event, n (%)	0	12 (17)	11 (20)	23 (18)
Max. grade (CTCAE)*				
1	0	7 (10)	5 (9)	12 (9)
2	0	4 (6)	3 (6)	7 (5)
3	0	1 (1)	3 (6)	4 (3)
Median onset, d (range)	NA	3 (1–10)	2 (1–5)	2 (1–10)
Median duration, d (range)	NA	3 (2–26)	5 (1–22)	3 (1–26)
Tocilizumab, n (%)	NA	0	3 (6)	3 (2)
Corticosteroids, n (%)	NA	2 (3)	8 (15)	10 (8)

- NT mostly low grade and was similar across target doses
- Incidence of grade 3 NT events was uncommon (≤6%) at all target doses; no grade 4 or 5 events
- NT managed with corticosteroids was infrequent (≤15%) at all target doses

Munschi, ASCO 2020

Ide-cell (bb2121)

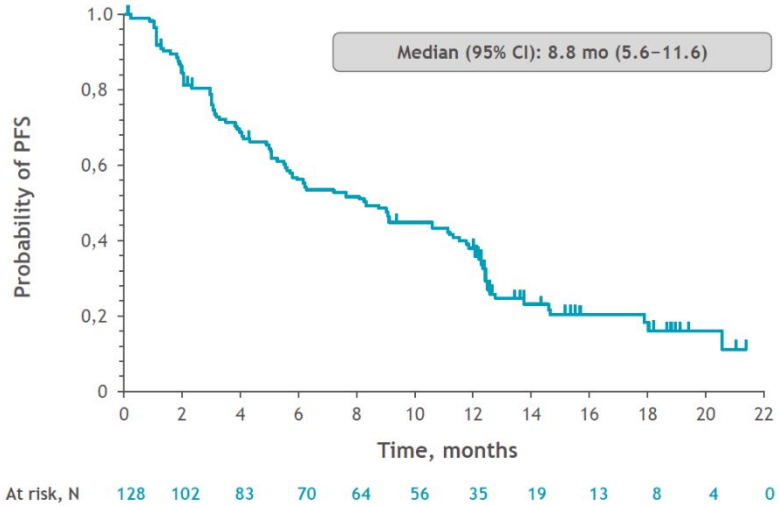
Best Overall Response



Munschi, ASCO 2020

Ide-cell (bb2121)

Progression-Free Survival



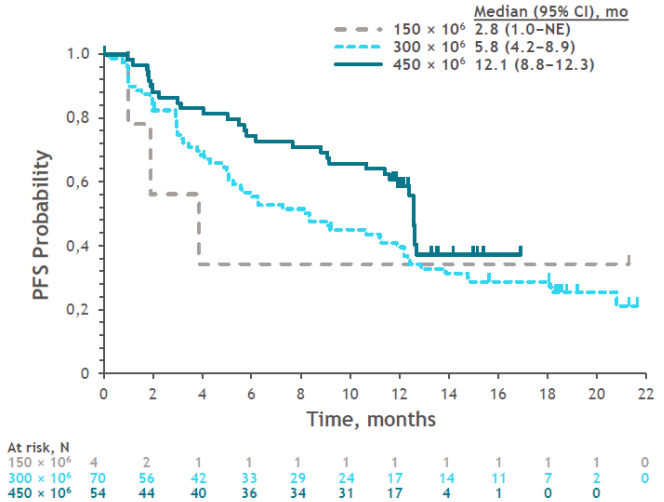
Munschi, ASCO 2020

Ide-cell (bb2121)

Progression-Free Survival

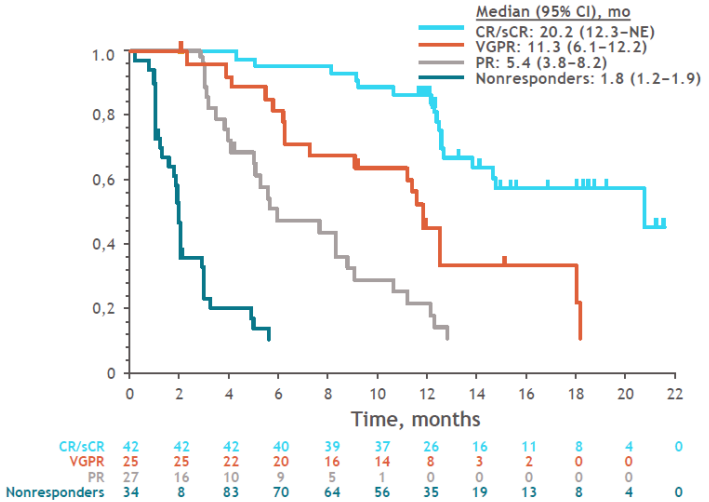
KarMMa™

PFS by Target Dose



- PFS increased with higher target dose; median PFS was 12 mo at 450 × 10⁶ CAR+ T cells

PFS by Best Response

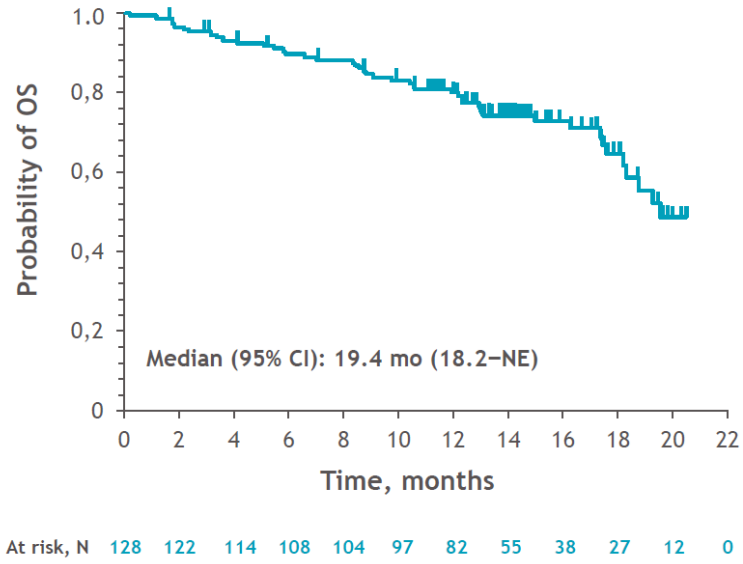


- PFS increased by depth of response; median PFS was 20 mo in patients with CR/sCR

Munschi, ASCO 2020

Ide-cell (bb2121)

Overall Survival

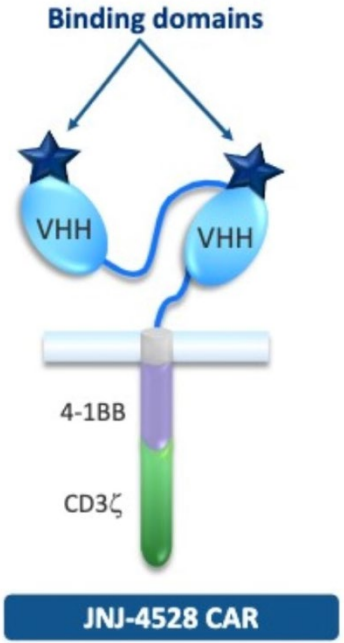


- 78% of all ide-cel–treated patients were event-free at 12 mo
- Survival data are immature with 66% of patients censored overall; 72% at target dose of 450 × 10^6 CAR+ T cells

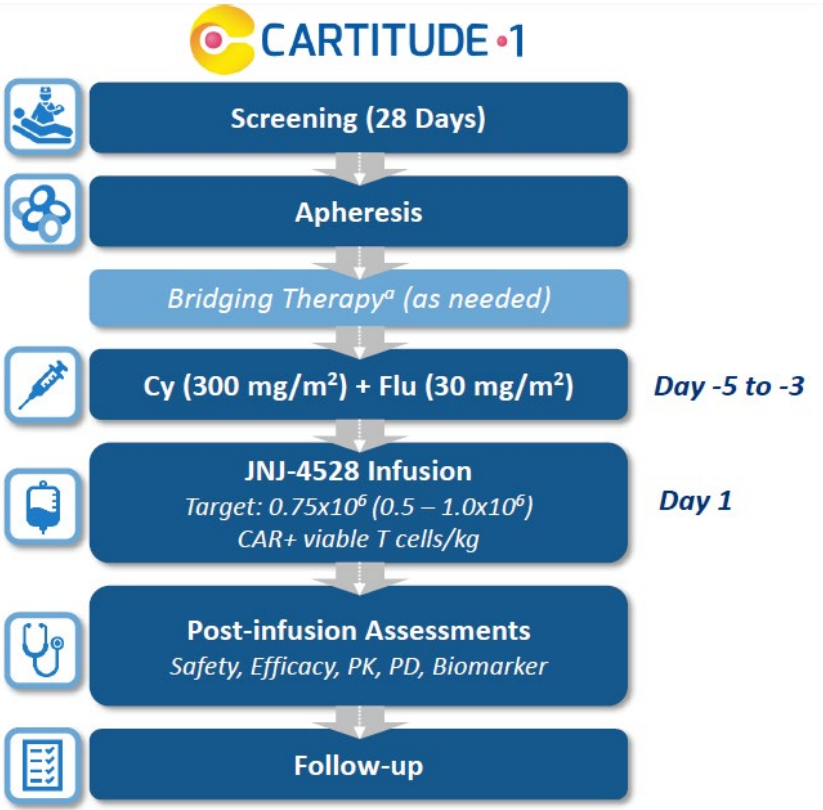
Munschi, ASCO 2020

CARTITUDE-1

JNJ-4528

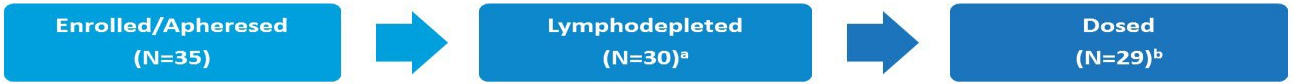


- JNJ-4528 is a structurally differentiated BCMA-targeted CAR-T cell therapy
- 2 BCMA-targeting single domain antibodies designed to confer avidity
- Contains a CD3ζ signaling domain and 4-1BB costimulatory domain



Berdega, ASCO 2020

CARTITUDE-1



	N = 29
Median age, (range)	60 (50 – 75)
Female, n (%)	15 (52)
Extramedullary plasmacytomas ≥1, n (%)	3 (10)
Bone marrow plasma cells ≥60%, n (%)	7 (24)
Median years since diagnosis (range)	5 (2 – 16)
High-risk cytogenetic profile,[c] n (%)	7 (27)
del17p	4 (15)
t(14;16)	2 (8)
t(4;14)	1 (4)

	N = 29
Median prior lines of therapy, n (range)	5 (3 – 18)
Prior autologous transplantation, n (%)	25 (86)
Triple-exposed,[d] n (%)	29 (100)
Penta-exposed,[e] n (%)	22 (76)
Refractory status, n (%)	
Carfilzomib	20 (69)
Pomalidomide	22 (76)
Daratumumab	27 (93)
Triple-refractory[d]	25 (86)
Penta-refractory[e]	8 (28)
Refractory to last line of therapy,[f] n (%)	28 (97)

[a]One patient withdrew and 4 died before lymphodepletion, [b]One patient withdrew before dosing, [c]By central FISH; out of 26 patients, [d]PI, IMiD, and anti-CD38, [e]≥2 PIs, ≥2 IMiDs, and anti-CD38, [f]Progressive disease within 60 days (measured from last dose) of last regimen

Berdega, ASCO 2020

CARTITUDE-1

	N = 29	
CAR-T-associated AEs, n (%)	**All Grade**	**Grade ≥3**
Cytokine release syndrome (CRS)[a]	27 (93)	2 (7)
Neurotoxicity consistent with ICANS[b]	3 (10)[c]	1 (3)

Timing and management of CRS

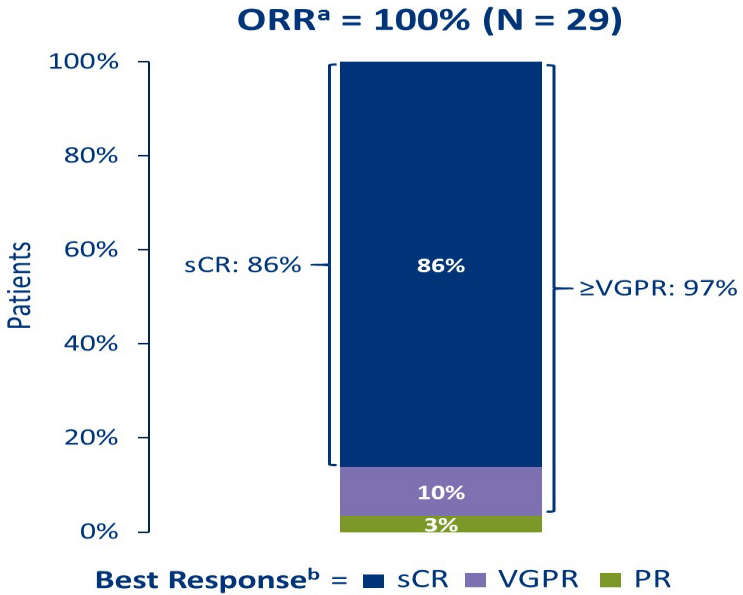
- Median time to onset of CRS = 7 days (2 – 12)
- Median duration of CRS = 4 days (2 – 64)
- 23 (79%) patients were given tocilizumab
- 6 (21%) patients each were given anakinra or corticosteroids

AE (≥25% All Grade), n (%)	N = 29	
Hematologic	**All Grade**	**Grade ≥3**
Neutropenia	29 (100)	29 (100)
Thrombocytopenia	25 (86)	20 (69)
Anemia	22 (76)	14 (48)
Leukopenia	20 (69)	19 (66)
Lymphopenia	15 (52)	14 (48)
Non-hematologic		
Increased AST	9 (31)	2 (7)
Increased ALT	9 (31)	2 (7)
Diarrhea	10 (35)	0
Headache	8 (28)	0

[a]Graded according to Lee *et al. Blood* 2014;124:188, [b]Graded using Common Terminology Criteria for Adverse Events, v.5.0, [c]One event of facial nerve disorder not included as it is not consistent with ICANS. AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ICANS=immune effector cell-associated neurotoxicity syndrome; SOC=system organ class

Berdega, ASCO 2020

CARTITUDE-1



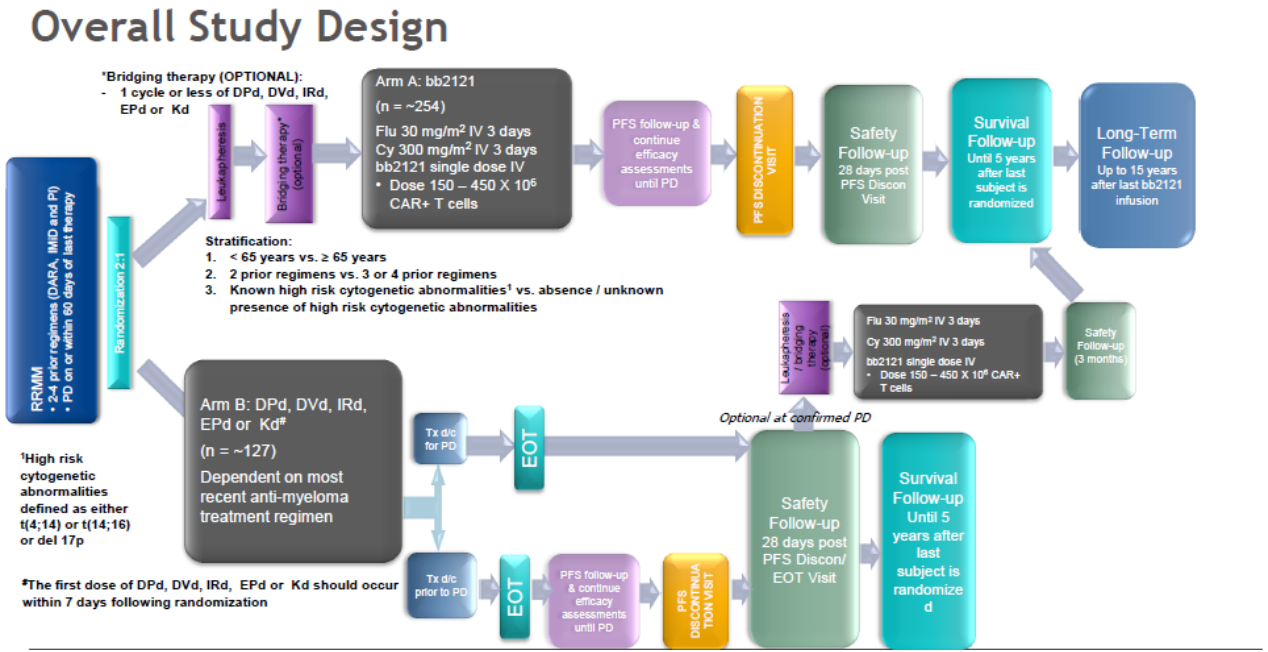
- 25 of 29 (86%) patients achieved sCR
- ORR and depth of response were independent of BCMA expression on myeloma cells at baseline
- Median time to first response = 1 mo (1 – 3)
- Median time to CR = 3 mo (1 – 13)

[a]PR or better; Independent Review Committee-assessed, [b]No patient had complete response, stable disease, or progressive disease as best response. CR=complete response; ORR=overall response rate; PR=partial response; sCR=stringent complete response; VGPR=very good partial response

Berdega, ASCO 2020

Perspectives ide-cel

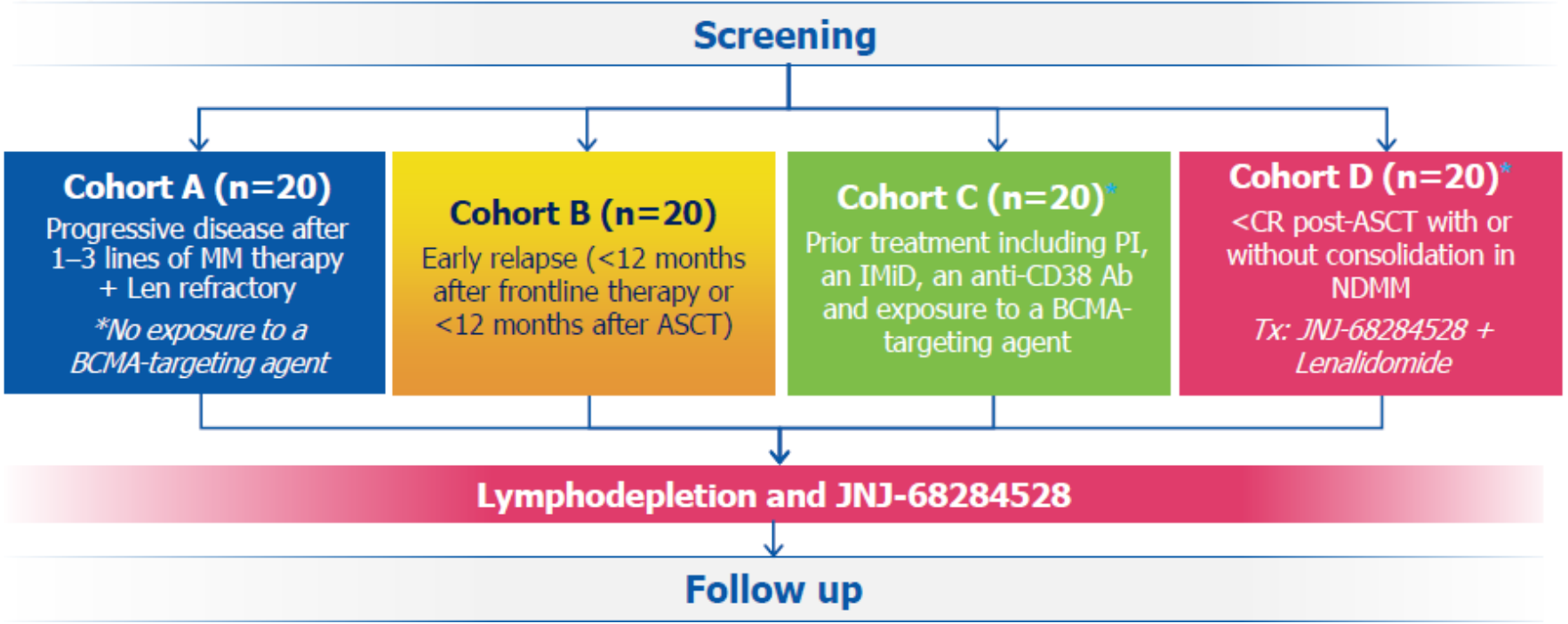
Essai phase 3 KARMMA-3



ATU-AMM attendue fin 2020

Perspectives JNJ4528

Essai phase 2 CARTITUDE-2



Vers de nouveaux CAR?

- **Améliorer la persistance des CAR / possibilité de retraitement?**
  - **CAR « fully human » :** CT103A (Li ASH 2019) ; Orva cell (Mailankody ASCO 2020)
  - **Favoriser l'expansion de CAR CD8 mémoire :** + PI3K (bb21217, Berdega ASH 2019)
- **Limiter la résistance** :
  - **CAR bi-spécifiques** : BCMA+GPRC5D (De larrea et al. ASH 2019)
- **Autres cibles :**
  - SLAMF7, GPRC5D

Immunothérapie du myélome multiple

Anticorps monoclonaux

CD38:
- daratumumab
- isatuximab

SLAMF7:
- elotuzumab

PD-1/L1:
- pembolizumab
- nivolumab

Anticorps monoclonaux conjugués

BCMA:
- Belantamab mafodotin

CAR-T cells

BCMA:
- bb2121 (ide-cell)
- JNJ4528 – Legend

GPRC5D

Anticorps monoclonaux bispécifiques

BCMA:
- AMG 420
- AMG 701
- CC93269
- Teclistamab

GPRC5D :
JNJ-64407564

AMG 420

Journal of Clinical Oncology®

rapid communications

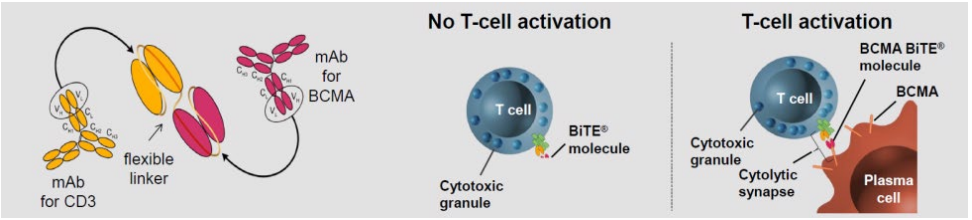
Anti–B-Cell Maturation Antigen BiTE Molecule AMG 420 Induces Responses in Multiple Myeloma

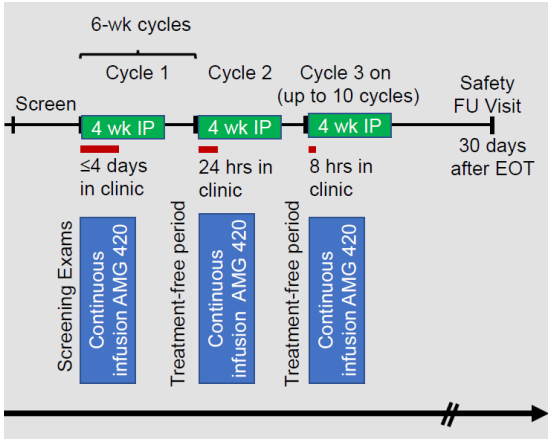
Max S. Topp, MD[1]; Johannes Duell, MD[1]; Gerhard Zugmaier, MD[2]; Michel Attal, MD[3]; Philippe Moreau, MD[4]; Christian Langer, MD[5]; Jan Krönke, MD[6]; Thierry Facon, MD[7]; Alexey V. Salnikov, MD, PhD[8]; Robin Lesley, PhD[9]; Karl Beutner, MS[10]; James Kalabus, PhD[9]; Erik Rasmussen, MS[10]; Kathrin Riemann, PhD[8]; Alex C. Minella, MD[10]; Gerd Munzert, MD[8]; and Hermann Einsele, MD[1]

Topp et al. J Clin Oncol 2020

AMG 420

Phase 1, n=42
5 lignes antérieures
Ref IP+IMID = 36% Ref dara : 21%





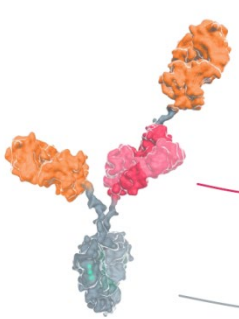
Pt	# Prior lines*	BL BM PC%†	Dose µg/d × # cycles	Discontinued due to	Best response (cycle)
1	4 incl SCT×2	10	6.5 × 10	NA (10 cycles)	CR (C8)
2	3 incl SCT×2	2	50 × 10	NA (10 cycles)	PR (C2-C5)
3	3 incl SCT	2	100 × 8	PD	CR (C4-C5)
4	6 incl Dara	6	200 × 4	Port infection	MRD- CR (C3-C4 to ~11 months post EOT)
5	3 incl SCT×2	8	400 × 7	NA (ongoing)	MRD- CR (C3-C7)
6	4 incl SCT×2	25	400 × 10	NA (10 cycles)	MRD- CR (C3-C10)
7	6 incl SCT×2	60	400 × 8	PD	MRD- CR (C1-C7)
8	2 incl SCT×2	80	400 × 10	NA (completing C10)	MRD- CR (C1-C10)
9	5 incl SCT, Dara	5	400 × 5	PD	MRD- CR (C3-C4)
10	4 incl SCT	80	400 × 1	Polyneuropathy	VGPR (EOT to ~7 months post EOT)
11	4 incl SCT, Dara	12	400 × 1	Death‡	PR (C1)**
12	5 incl SCT×3	28	800 × 2, then 400 × 1	Withdrew consent	VGPR (C2-C3)
13	5 incl SCT×2, Dara	90	800 × 0.5	Polyneuropathy	PR (C1), CR (~9 months post EOT)

2 décès d'infection : adénovirus, aspergillose

Topp MS *et al. J Clin Oncol* 2020;38:775-83

CC93269

Structure du CC93269



Anti-BCMA (bivalent)

Anti-CD3ε (monovalent)

Heterodimeric FcγR-silent Fc

Pas de liaison au FcγR ni C1q pour minimiser les réactions à l'injection

Schéma de dose

Critères d'inclusion

- ≥ 3 lignes antérieures
- Maladie progresssive dans les 60 jours suivant la derière ligne
- Pas de traitement anterieur ciblant BCMA

Cycle (28 jours)

Screening	C1	C2	C3	C4	C5	C6	C7	C8

C1-3 : J1, 8, 15, 22

C4-6 : J1 et J15

C7 et plus : J 1 Jusqu'à 2 ans de traitement

Administration sur 2 heures

Partie A : Escalade de dose
Etape 1 : dose fixe
Etape 2 : augmentation de dose au C1D8

Partie B : Cohorte d'expansion

Objectifs
Principal : tolérance dont DLT, SAE et MTD
Secondaires : Efficacité dont MRD, PK, ADA et PD

Costa et al. ASH 2019
Adapté de Le Cancer.fr

CC93269

CC-93269-MM-001

Treatment history

	All patients (N = 30)	
	Exposed	Refractory
Prior regimens, median (range), n	**5 (3-13)**	
PIs, n (%)	**30 (100)**	**23 (76.7)[a]**
Bortezomib	30 (100)	13 (43.3)
Carfilzomib	23 (76.7)	17 (56.7)
Ixazomib	5 (16.7)	3 (10.0)
IMiDs, n (%)	**30 (100)**	**24 (80.0)[a]**
Lenalidomide	30 (100)	14 (46.7)
Pomalidomide	26 (86.7)	22 (73.3)
Anti-CD38 monoclonal antibodies, n (%)	**29 (96.7)**	**24 (80.0)[a]**
Daratumumab	28 (93.3)	23 (76.7)
Isatuximab	4 (13.3)	2 (6.7)
PI, IMiD, and anti-CD38 antibody, n (%)	**29 (96.7)**	**20 (66.7)[a]**
Stem cell transplantation, n (%)		
Autologous	23 (76.7)	
Allogeneic	3 (10.0)	

Data as of October 28, 2019.
[a]Refractory to most recent PI, IMiD, anti-CD38, or triple-class refractory.
IMiD, immunomodulatory drug; PI, proteasome inhibitor.

Costa, EHA 2020

CC93269

CC-93269-MM-001

Safety summary

Common (≥ 20% all grade) TEAEs[a], n (%)	All patients (N = 30)	
	All grade	Grade ≥ 3
Patients with ≥ 1 TEAE	29 (96.7)	22 (73.3)
Hematologic TEAEs		
Neutropenia	14 (46.7)	13 (43.3)
Anemia	13 (43.3)	11 (36.7)
Thrombocytopenia	9 (30.0)	5 (16.7)
Nonhematologic TEAEs		
Cytokine release syndrome	23 (76.7)	1 (3.3)
Infections and infestations	17 (56.7)	9 (30.0)
Diarrhea	8 (26.7)	1 (3.3)
Vomiting	8 (26.7)	0
Back pain	7 (23.3)	0
Fatigue	6 (20.0)	0
Infusion-related reaction	6 (20.0)	0
Nausea	6 (20.0)	0

- Deaths (grade 5 TEAEs) were reported in 4 patients during the treatment period:
  - Suspected to be related to CC-93269: cytokine release syndrome (n = 1)
  - Not suspected to be related to CC-93269: sepsis in the setting of advanced prostate cancer, sudden cardiac death, and general health deterioration due to progressive myeloma (n = 1 each)

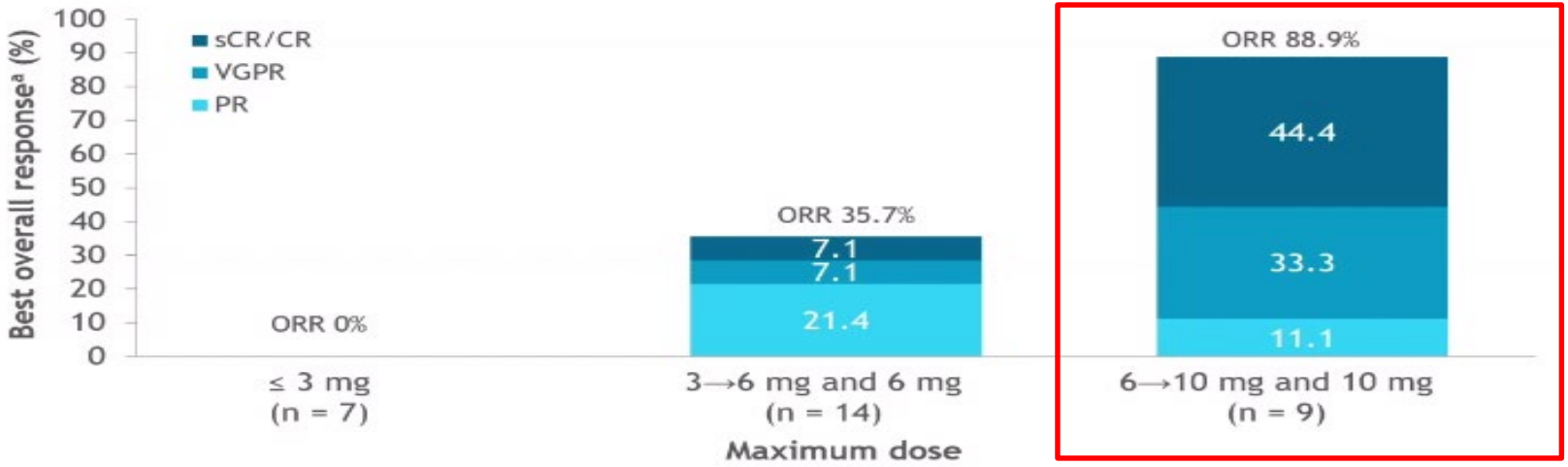
Data as of October 28, 2019.
[a]TEAEs include any AEs with onset or worsening between the date of first dose of CC-93269 and 37 days after the date of last dose of study treatment.
TEAE, treatment-emergent adverse event.

Costa, EHA 2020

CC93269

CC-93269-MM-001

CC-93269 preliminary efficacy



- In all patients (N = 30), the ORR was 43.3% with a sCR/CR of 16.7%
- Among patients receiving 10 mg (n = 9), the ORR was 88.9% with a sCR/CR of 44.4%

Data as of October 28, 2019.
[a]Response as assessed by the investigator.
CR, complete response; ORR, overall response rate (PR or better); PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

12

Costa, EHA 2020

Teclistamab

Teclistamab: BCMA x CD3 Bispecific DuoBody® Antibody

Key Objectives

- Part 1: Identify RP2D
- Part 2: Safety and tolerability
- Antitumor activity, PK, PD

Key Eligibility Criteria

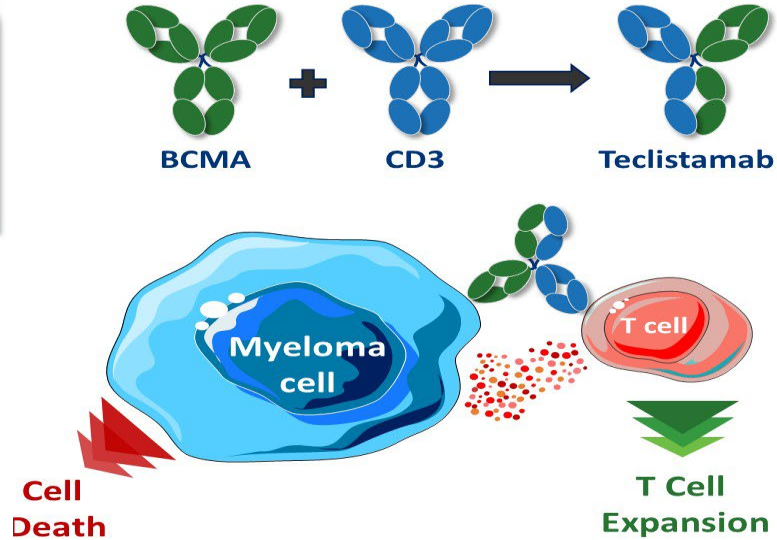
- Measurable MM
- RR or intolerant to established MM therapies
- Hb ≥8 g/dL, platelets[a] ≥75x10^9/L, ANC ≥1.0x10^9/L
- No prior BCMA-targeted therapy

Intravenous Dosing

- Initial Q2W dosing switched to weekly ± step-up dosing
- Pre-medications[b] limited to step-up doses and 1st full dose

Step-up Dose	Cycle 1 and beyond (full dose)		
Week -1	Week 1	Week 2	Week 3
1-3 doses	D1	D1	D1

- **Results from Part 1 intravenous dose escalation are presented**



Usmani, ASCO 2020

Teclistamab: Demographic and Disease Characteristics

Characteristic	Total (N = 78)
Median age (range), years	62 (24–82)
≥70 years, n (%)	16 (21)
Female, n (%)	41 (53)
ISS stage III, n (%)	21 (27)
≥1 Extramedullary plasmacytomas, n (%)	7 (9)
Bone marrow plasma cells ≥ 60%, n (%)	22 (30)
Median years from diagnosis (range)[a]	7 (1–26)
High-risk cytogenetics, n (%)[b]	19 (31)
Prior transplantation, n (%)	62 (80)

Characteristic	Total (N = 78)
Prior lines of therapy, median (range)	6 (2–14)
Triple-class exposed, n (%)[c]	72 (92)
Penta-drug exposed, n (%)[d]	51 (65)
Refractory status, n (%)	
Carfilzomib	48 (62)
Pomalidomide	56 (72)
Anti-CD38[e]	68 (87)
Triple-class refractory[c]	62 (80)
Penta-drug refractory[d]	32 (41)
Refractory to last line of therapy,[f] n (%)	67 (86)

[a]N=75, [b]Based on FISH or karyotype testing and includes del(17p), t(4;14), t(14;16); N=61, [c]PI, IMiD, and anti-CD38, [d]≥2 PIs, ≥2 IMiDs, and an anti-CD38, [e]Includes isatuximab (n=1), [f]Progressive disease within 60 days of last regimen. ISS=International Staging System

Usmani, ASCO 2020

Teclistamab: Safety Profile

AEs (≥20%), n (%)	N = 78	
	All Grade	Grade ≥3
Hematologic		
Anemia	45 (58)	28 (36)
Neutropenia	35 (45)	30 (38)
Thrombocytopenia	31 (40)	19 (24)
Leukopenia	22 (28)	10 (13)
Nonhematologic		
Cytokine release syndrome	44 (56)	0
Pyrexia	24 (31)	0
Cough	20 (26)	2 (3)
Diarrhea	18 (23)	1 (1)
Back pain	17 (22)	1 (1)
Headache	17 (22)	0
Fatigue	16 (21)	1 (1)

- 2 DLTs: Grade 4 delirium (n=1 at 20 µg/kg step-up dose) and grade 4 thrombocytopenia (n=1 at 180 µg/kg full dose)

SOC/AEs (≥10%), n (%)	N = 78	
	All Grade	Grade ≥3
Infections[a]	**51 (65)**	**16 (21)**
Upper respiratory tract infection	18 (23)	0
Respiratory tract infection	10 (13)	2 (3)
Urinary tract infections	10 (13)	2 (3)
Pneumonia	9 (12)	5 (6)

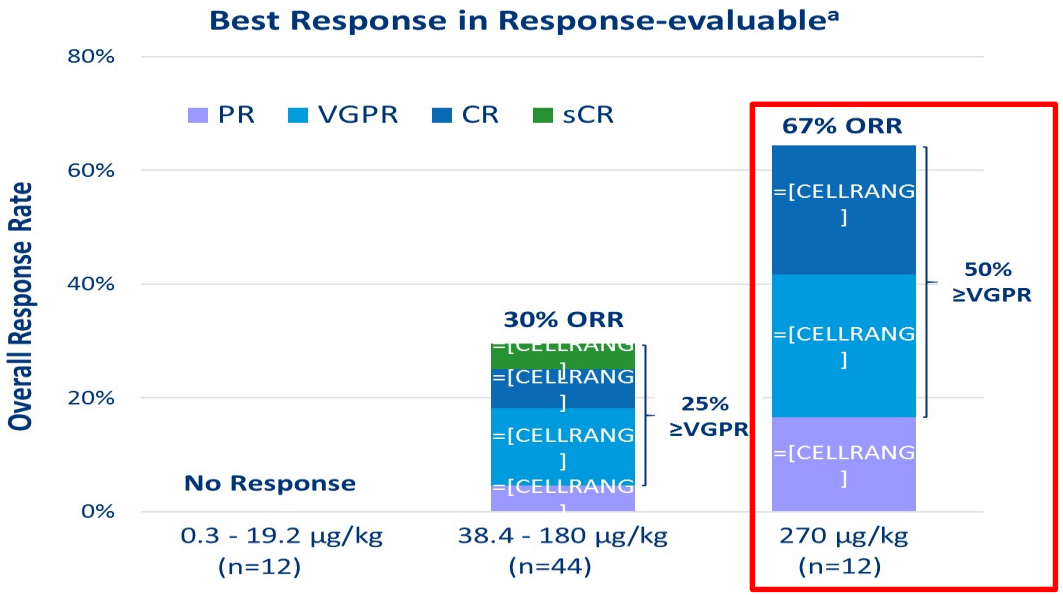
- 19% had infections considered treatment-related by the investigator; (3% of patients grade ≥3)

- Neurotoxic events were reported in 6 patients; 4 had grade 1-2 events
  - 1 DLT of grade 4 delirium, started the day after clinical signs of CRS resolved
  - 1 grade 3 mental status change, occurred in the setting of radiation therapy for new orbital plasmacytoma

[a]Values for system organ class grouping. AE=adverse event; DLT=dose-limiting toxicity; PD=progressive disease; SOC=system organ class

Usmani, ASCO 2020

Teclistamab: Overall Response Rate



- Efficacy data at 720 µg/kg dose are not mature
- At the 270 µg/kg dose, 7/8 responders were triple-class refractory; 5/8 were penta-drug refractory
- 4/5 evaluable-patients[b] were MRD-negative at 10^{-6}; 2 had MRD-negative CR
- 2/2 evaluable patients maintained MRD-negativity for 5 months (VGPR) and 14 months (CR)

[a]Response-evaluable patients received at least one study treatment with at least 1-month follow-up or at least one response evaluation, [b]MRD-evaluable patients have suspected CR and identified baseline clone for assessment.
CR=complete response; MRD=minimal residual disease; ORR=overall response rate; PR=partial response; sCR=stringent complete response; VGPR=very good partial response

Usmani, ASCO 2020

CONCLUSION

Anticorps monoclonaux

CD38:
- daratumumab
- isatuximab

SLAMF7:
- elotuzumab

PD-1/L1:
- pembolizumab
- nivolumab

Anticorps monoclonaux conjugués

BCMA:
- Belantamab mafodotin

CAR-T cells

BCMA:
- bb2121 (ide-cell)
- JNJ4528 – Legend

GPRC5D

Anticorps monoclonaux bispécifiques

BCMA:
- AMG 420
- AMG 701
- CC93269
- Teclistamab

GPRC5D :
JNJ-64407564

CONCLUSION

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Anticorps monoclonaux conjugués

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- Belantamab mafodotin

AMM
Option dispo pour nos patients réfractaires IP, IMID et anti CD38

CAR-T cells

BCMA:
- bb2121 (ide-cell)
- JNJ4528 – Legend

GPRC5D

Anticorps monoclonaux bispécifiques

BCMA:
- AMG 420
- AMG 701
- CC93269
- Teclistamab

GPRC5D :
JNJ-64407564

CONCLUSION

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CAR-T cells

BCMA:
- bb2121 (ide-cell)
- JNJ4528 – Legend

GPRC5D

Anticorps monoclonaux bispécifiques

BCMA:
- AMG 420
- AMG 701
- CC93269
- Teclistamab

GPRC5D :
JNJ-64407564

Stratégie la plus prometteuse à l'heure actuelle

CONCLUSION

Options thérapeutiques pour nos patients triple réfractaires

	Selinexor[1]	Melflufen[2]	Belamaf[3]	Ide-Cell[4]	Teclistamab[5]
n	123	157	196	128	78
Nb lignes antérieures	7	5	6	6	6
Réfractaires IP/Imid/Anti CD38	100%	76%	100%	84%	80%
ORR / CR	26% / 2%	29% / 1%	31% / 3%	73% / 33%	67% / 20% (dose=270µg/kg)
mPFS	3,7 mois	4,2 mois	2,9 mois	8,8 mois	ND

1 Chari NEJM 2019; 2 Richardson EHA 2020; 3 Lonial Lancet Oncol 2019; 4 Munshi ASCO 2020 ; Usmani ASCO 2020

CONCLUSION

CAR-T cells

Efficacité confirmée
(Phase 2 NEJM, phase 3 en cours)
ATU/AMM attendue 2021

Complexité du processus de fabrication (délai, bridge)
Accessibilité

Traitement « court »

Possibilité de retraitement?
(CAR humains, T-CE)

versus

T-Cell Engager

Développement mois avancé
Phase 1 - 2

« Off the shelf »
Soins courant

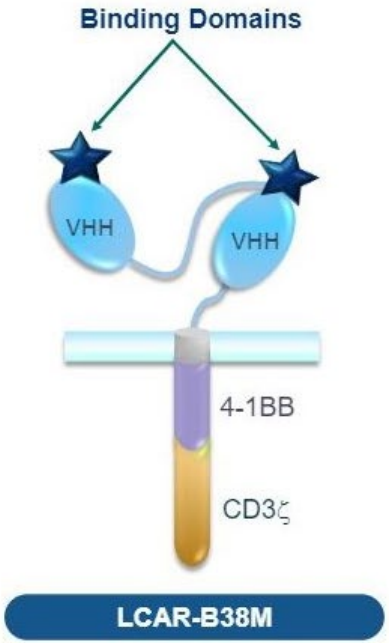
Traitement jusqu'à progression

Possibilité de combinaisons?

Merci pour votre attention

LEGEND-2

- LCAR-B38M is a structurally differentiated CAR-T cell therapy
  - Contains a CD3ζ signaling domain and a 4-1BB co-stimulatory domain
  - 2 BCMA-targeting single-domain antibodies designed to confer avidity
- LEGEND-2* (N=74): Phase 1 investigator-initiated study in RRMM conducted at 4 sites in China
  - Variable preconditioning regimens (Cy-Flu vs. Cy)
  - Variable CAR-T infusion methods (split vs. single infusion)
  - Median number of CAR+ viable T cells: 0.5×10^6 cells/kg ($0.07–2.1 \times 10^6$ cells/kg)
- 57-patient experience at Xi'an site as of July 31, 2019 is presented here, with a median follow-up of 25 months
- 17-patient experience at Ruijin, Changzheng, and Jiangsu sites presented as a poster (Abstract #1858; median follow-up of 26 months)



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LEGEND-2

Demographics and Disease Characteristics

	Total (N=57)
Median age, years (range)	54 (27–72)
Male, n (%)	34 (60)
ECOG PS, n (%)	
0	21 (37)
1	27 (47)
2	9 (16)
Durie-Salmon stage III, n (%)	42 (74)
ISS stage III, n (%)	21 (37)
Median time from initial diagnosis, years (range)	4 (1–9)

	Total (N=57)
Median prior lines of therapy, n (range)	3 (1–9)
Prior auto-SCT, n (%)	10 (18)
Prior PI, n (%)	39 (68)
Bortezomib	39 (68)
Carfilzomib	1 (2)
Prior IMiD, n (%)	49 (86)
Thalidomide	39 (68)
Lenalidomide	25 (44)
Pomalidomide	2 (4)
Prior PI + IMiD, n (%)	34 (60)

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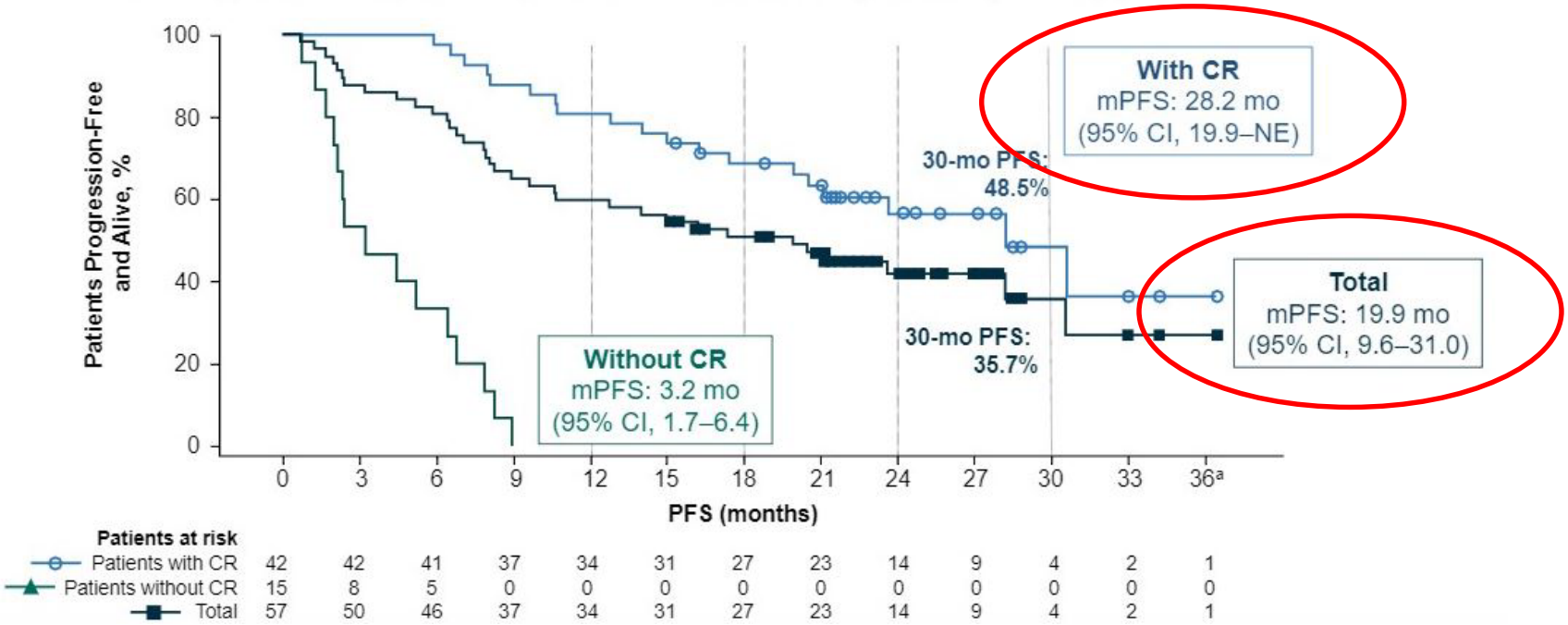
LEGEND-2

Progression-Free Survival

- PFS prolonged over 2 years for patients achieving CR (median follow-up, 25 mo)



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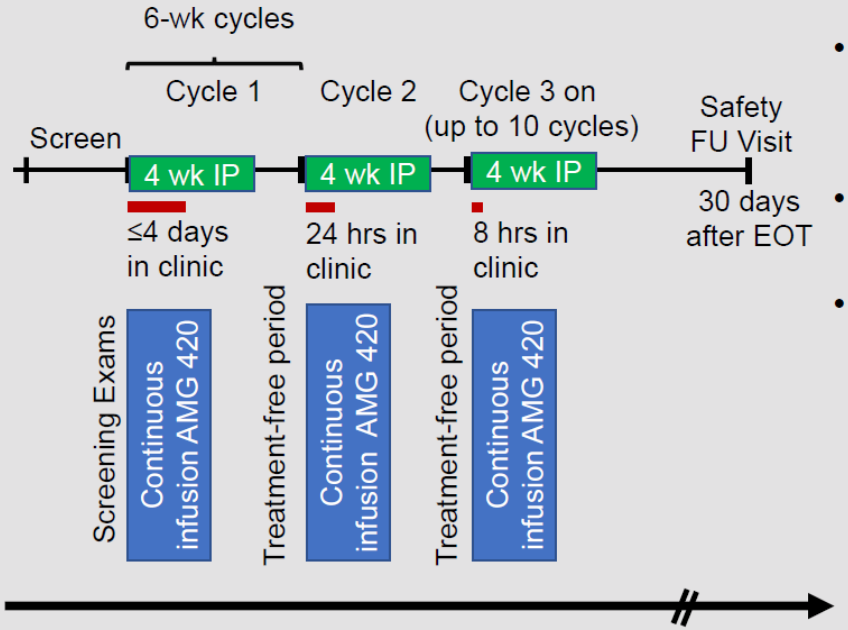
AMG 420

Study Schematic / Objectives



- First-in-human (FIH) phase 1 dose escalation study* of AMG 420 for up to 10 cycles, depending on response.
- Single-patient cohorts [0.2-1.6 µg/day (d)] were followed by cohorts of 3-6 patients (3.2-800 µg/d).
- Objectives of this phase 1 study of AMG 420 in patients with relapsed and/or refractory (R/R) MM included:
  - Assessing safety and tolerability per CTCAE 4.03
  - Determining the maximum tolerated dose (MTD)
  - Assessing anti-tumor activity

* NCT02514239. EOT, end of treatment; FU, follow-up; IP, investigational product.

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AMG 420 – Anti BCMA CD3 BiTE

TABLE 1. Baseline Characteristics

Characteristic	Value
No. of patients	42
Male, No. (%)	27 (64)
Median age, years (range)	65 (39-79)
ECOG performance status, %	
0	57
1	40
2	2
Median disease duration, years (range)	5.2 (1.3-20.0)
Cytogenetics per IMWG 2016 guidelines,[24] %	
Standard	67
High	33
Cytogenetics per Rajkumar[25] 2012 guidelines, %	
Standard	60
Intermediate	29
High	12
Median plasma cells at baseline, % (range)	18 (0-95)

TABLE 1. Baseline Characteristics

Characteristic	Value
Prior lines of therapy as assessed at study entry per investigator, median (range)	5 (2-14)
Prior lines of therapy as assessed post hoc per Rajkumar[26] 2015 guidelines, median (range)	3.5 (1.0-10.0)
Prior therapies, median (range)[a]	7 (3-14)
Prior daratumumab,[b] No. (%)	12 (29)
Prior elotuzumab, No. (%)	4 (10)
Prior autologous stem-cell transplant, No. (%)	36 (86)
Refractory to past therapies, median (range)	1 (0-10)
Refractory to which drug type, %	
Immunomodulatory drug	48
Proteasome inhibitor	38
Immunomodulatory drug and proteasome inhibitor	36
Refractory to daratumumab, %	21
Refractory to elotuzumab, %	7

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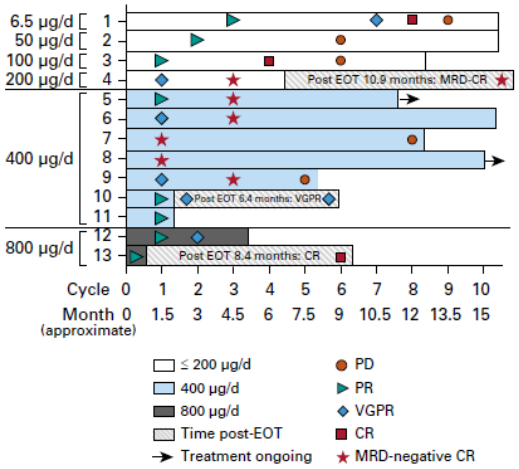
AMG 420 – Anti BCMA CD3 BiTE



Pt	# Prior lines*	BL BM PC%†	Dose µg/d × # cycles	Discontinued due to	Best response (cycle)
1	4 incl SCT×2	10	6.5 × 10	NA (10 cycles)	CR (C8)
2	3 incl SCT×2	2	50 × 10	NA (10 cycles)	PR (C2-C5)
3	3 incl SCT	2	100 × 8	PD	CR (C4-C5)
4	6 incl Dara	6	200 × 4	Port infection	MRD- CR (C3-C4 to ~11 months post EOT)
5	3 incl SCT×2	8	400 × 7	NA (ongoing)	MRD- CR (C3-C7)
6	4 incl SCT×2	25	400 × 10	NA (10 cycles)	MRD- CR (C3-C10)
7	6 incl SCT×2	60	400 × 8	PD	MRD- CR (C1-C7)
8	2 incl SCT×2	80	400 × 10	NA (completing C10)	MRD- CR (C1-C10)
9	5 incl SCT, Dara	5	400 × 5	PD	MRD- CR (C3-C4)
10	4 incl SCT	80	400 × 1	Polyneuropathy	VGPR (EOT to ~7 months post EOT)
11	4 incl SCT, Dara	12	400 × 1	Death‡	PR (C1)**
12	5 incl SCT×3	28	800 × 2, then 400 × 1	Withdrew consent	VGPR (C2-C3)
13	5 incl SCT×2, Dara	90	800 × 0.5	Polyneuropathy	PR (C1), CR (~9 months post EOT)

There were 13/42 responders (6 CRs, 3 CRs, 2 VGPRs, 2 PRs). Median time to any response was 1 month, with 11 of 13 patients responding in the first cycle. Responses lasted for a median of 8.4 months (range: 2.5-15.5 months).

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AMG 420 – Anti BCMA CD3 BiTE

TABLE 3. Cytokine Release Syndrome and Serious AEs

Variable	No. (%)	No. of Patients With AEs at Each Grade				
		1	2	3	4	5
No. of patients	42					
Infections serious AEs						
All	14 (33)	—	4	8	—	2[b]
Pulmonary[a]	6 (14)	—	3	3	—	—
Central line/port infections	5 (12)	—	—	5	—	—
Adenovirus[b,c]	1 (2)	—	—	—	—	1
Aspergillosis/influenza[b]	1 (2)	—	—	—	—	1
Infection of unknown origin (fever)[d]	1 (2)	—	1	—	—	—
Treatment-related serious AEs						
Peripheral polyneuropathy	2 (5)	—	—	2	—	—
Edema	1 (2)	—	—	1	—	—
Cytokine release syndrome						
All treatment related, maximum grade	16 (38)	13	2	1	—	—

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Perspectives JNJ4528

Essai phase 3

CARTITUDE-4