Resultados de la inmunoterapia avanzada en Mieloma

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Conflict of interest disclosure

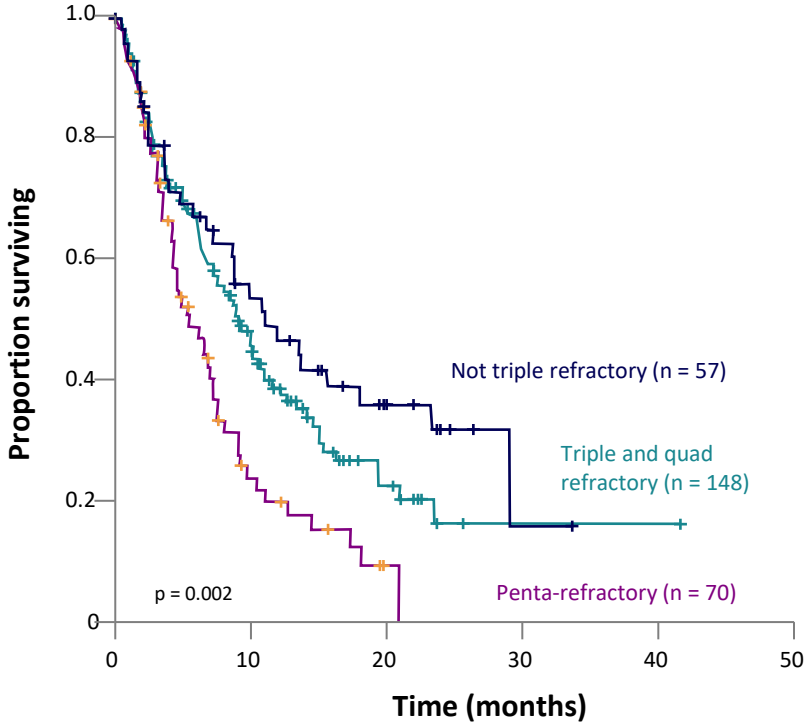
I have received honoraria from lectures and participation in advisory boards from: BMS, Janssen, Sanofi, Kite Pharma, Abbvie, Oncopeptides, Amgen, Takeda and GSK.

Do we need new therapies for MM patients
MAMMOTH study

- 275 MM patients refractory to anti-CD38 mAbs
- mOS from refractoriness to CD38:
  - all patients: 8.6 months
  - “non-triple-refractory”: 11.2 months
  - “triple- and quad-refractory”: 9.2 months
  - “penta-refractory”: 5.6 months

- 249 patients received further treatment:
  - mPFS: 3.4 months
  - mOS: 9.3 months

OS according to refractoriness



- Non-triple-refractory: refractory to 1 CD38 mAb, and not both PI and IMiD compound
- Triple- and quad-refractory: refractory to 1 CD38 mAb + 1 IMiD compound + 1 PI; or 1 CD38 mAb + 1 PI + 1 or 2 IMiD compounds; or 1 CD38 mAb + 1 or 2 PIs + 1 IMiD compound
- Penta-refractory: refractory to 1 CD38 mAb + 2 PIs + 2 IMiD compounds

mOS, median overall survival; mPFS, median progression-free survival.

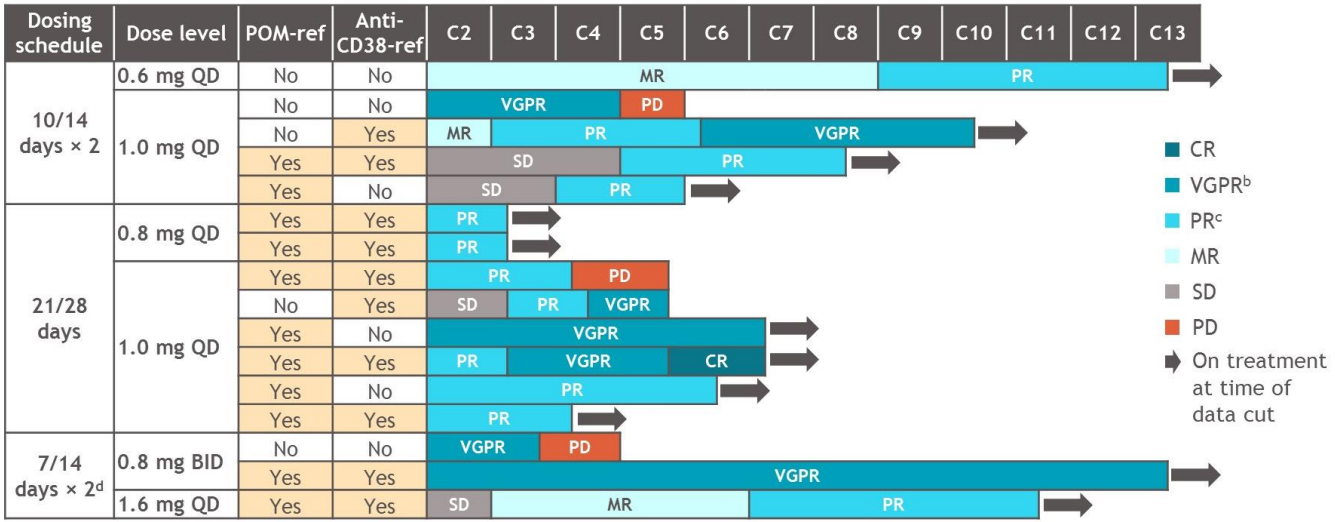
Gandhi UH, et al. Leukemia. 2019;Mar 11 [Epub ahead of print].

CC-92480 (CELMoD) in combination with Dex in RRMM
Phase I dose escalation study in RRMM (n=76) – Efficacy

- **ORR all evaluable (n=76): 21.1 %. CBR 26.3%**
- **MTD (10/14 days x 2 1.0 mg QD): 40.0% (CBR 50%)**
- **RP2D (21/28 days 1mg QD) (n=11): 54.5% (CBR 63.6%)**

Median nº of prior lines: 6
36.8% EMD
Triple-Refractory: 50%

- Majority of responders were dual-IMiD-refractory[a] (10 out of 16 patients [63%])



[a] Refractory to both LEN and POM; [b]1 patient in the 21/28 1.0 mg QD cohort had an unconfirmed VGPR as of the data cutoff date; [c]2 patients in the 21/28 0.8 mg QD cohort had an unconfirmed PR as of the data cutoff date; [d]No response at 2.0 mg QD 7/14 days × 2.

C, cycle; CR, complete response; IMiD, immunomodulatory drug; MR, minimal response; PD, progressive disease; PR, partial response; QD, once daily; ref, refractory; SD, stable disease; VGPR, very good partial response.

Safety ➔ Main TEAEs (myelosupression)
- Neutropenia all grade 73.3% (G3 30.3%/G4 34%)
- Febrile neutropenia all grade 7.9% (G3 5.3%)

Richardson P et al, ASCO 2020. Abstract 8500.

Iberdomide (CC-220) in combination with Dex in RRMM
Phase 1/2 study design – Cohort B (Iber + Dex) n=76

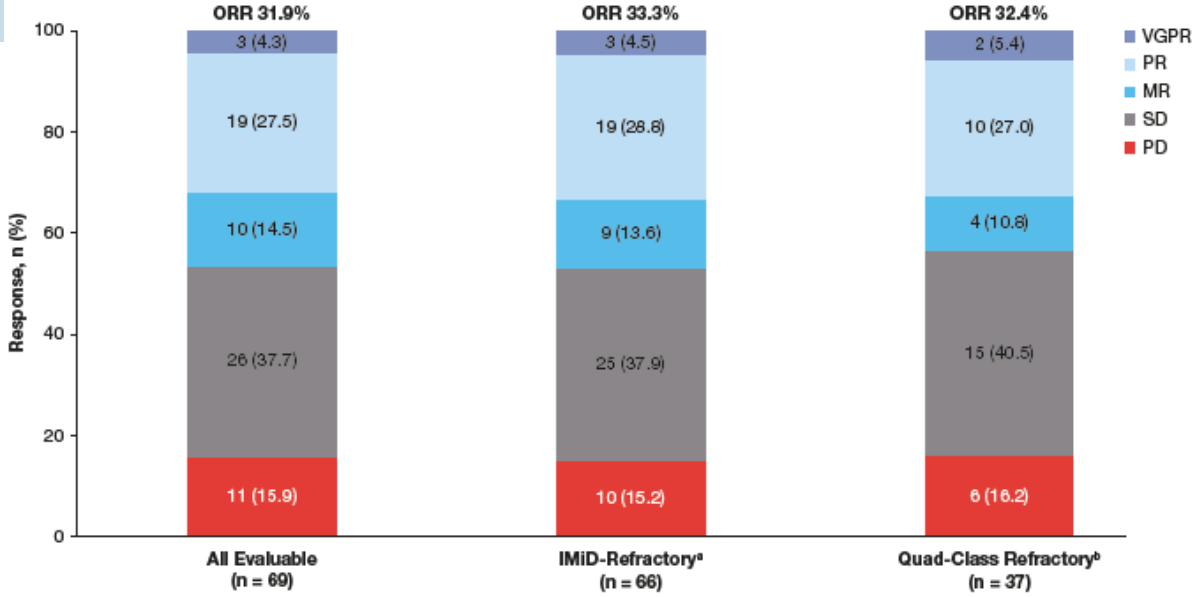
Key inclusión criteria:

- **RRMM**
- **≥2 prior lines, exposed to IMID and PI and refractory to the last line.**

Median nº of prior lines: 6

Prior therapies: ASCT (79%), LEN (100%), POM (71%), PI (100%), Dara (74%), BCMA (8%).

RP2D: 1.6mg QD 21/28 days

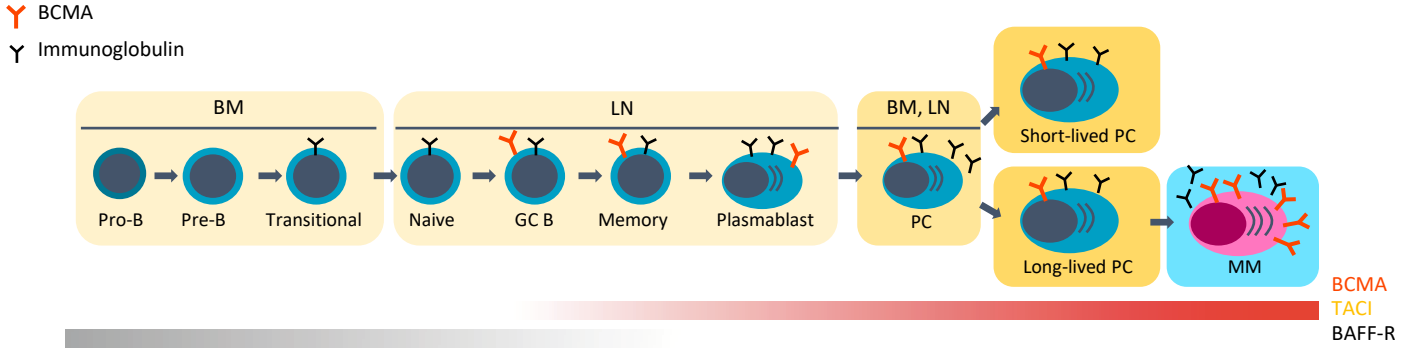


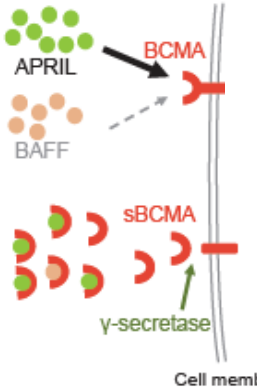
Safety ➔ Overall excelent safety profile

- Neutropenia all grade 40% (G3 17.3%/G4 16%)
- Thrmbocytopenia 17.3% (G3 4%/ G4 6.7%)

Lonial S et al, ASH 2019 poster Abstract 3119.

B-cell maturation antigen (BCMA)





- BCMA is an antigen expressed specifically on PCs and myeloma cells[1]
  - higher expression in myeloma cells than normal PCs[1]
  - key role in B-cell maturation and differentiation[1]
  - promotes myeloma cell growth, chemoresistance and immunosuppression in the BM microenvironment[1,2]
- Expression of BCMA increases as the disease progresses from MGUS to advanced myeloma[3]

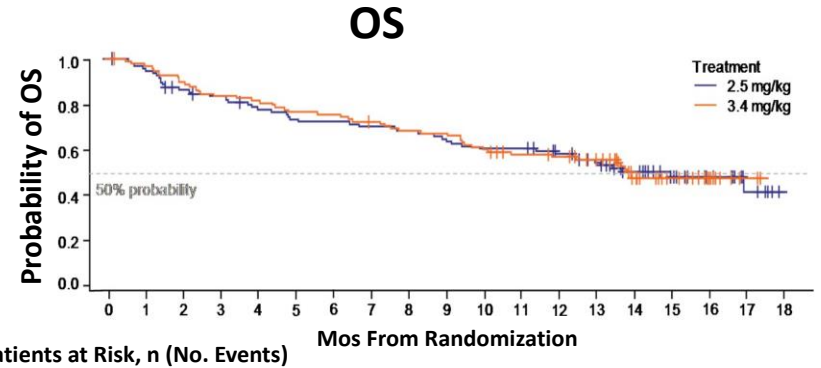
APRIL, a proliferation-inducing ligand; BAFF-R, B-cell activating factor receptor; BM, bone marrow; GC, germinal center; LN, lymph node; MGUS, monoclonal gammopathy of unknown significance; sBCMA, soluble BCMA; TACI, transmembrane activator and CAML interactor.

1. Cho SF, et al. Front Immunol. 2018;9:1821. 2. Moreaux J, et al. Blood. 2004;103:3148-57.
3. Sanchez E, et al. Br J Haematol. 2012;158:727-38.

Belantamab-Mafodotin (BCMA-ADC)
DREAMM-2 phase 2 pivotal study (n=196, 1:1 randomization)

Key inclusion: > 3 PL, refractory to PI and IMIDs and refractory/Intolerant to Dara.
Median nº prior lines: 7 (2.5 mg/kg) and 6 (3.4 mg/kg). 45% HR CA.

Response by IRC	Belamaf 2.5 mg/kg (n = 97)	Belamaf 3.4 mg/kg (n = 99)
ORR, % (95% CI)	**32 (21.7-43.6)**	**35 (24.8-47.0)**
▪ sCR, %	2	2
▪ CR, %	5	3
▪ VGPR, %	11	18
▪ PR, %	13	12
MR, %	4	5
SD, %	28	22
CBR, % (95% CI)	36 (26.6-46.5)	40 (30.7-50.7)
Median DoR, mos (95% CI)	11.0 (4.2-NR)	6.2 (4.8-NR)
Median PFS, mos (95% CI)	2.8 (1.6-3.6)	3.9 (2.0-5.8)



	Belantamab Mafodotin 2.5 mg/kg (N = 97)	Belantamab Mafodotin 3.4 mg/kg (N = 99)
Median DoR, months (95% CI)[1]	11 (4.2-NR)	6.2 (4.8-NR)
Median PFS, months (95% CI)[1]	2.8 (1.6-3.6)	3.9 (2.0-5.8)
Median OS, months (95% CI)[1]	13.7 (9.9-NR)	13.8 (10.0-NR)

- Safety profile also comparable and slightly better for 2.5 mg/Kg cohort
- G3-4:
  - Thrombocytopenia: 20% vs 33%
  - Keratopathy: 27% vs 21%
  - SAEs: 40% vs 47%

Lonial S et al. The Lancet Oncology 2019, Lonial S, et al. EHA 2020; abstract EP937. Lonial S et al ASCO 2020 Abstract 8536

Bela-Maf _ DREAMM-2 phase 2 pivotal study
Adverse events of Special Interest (13-month Follow-up)

Adverse Events of Special Interest*	Belantamab Mafodotin 2.5 mg/kg (N = 95)	Belantamab Mafodotin 3.4 mg/kg (N = 99)
Thrombocytopenia	36 (38)	56 (57)**
IRRs	20 (21)	16 (16)
Keratopathy (MECs)	68 (72)	76 (77)
Median time to onset of first MEC, days	37.0	22.5
Percent recovered from first event	77	73
Percent recovered from last event	48	47
Other Corneal Events		
Blurred vision†	24 (25)	33 (33)
Dry eye†	14 (15)	25 (25)
BCVA decline to 20/50 or worse in better-seeing eye	17 (18)	20 (20)

*Values expressed as n (%) unless otherwise noted
**Events include 2 Grade 5 events in the 3.4 mg/kg cohort only
†For events of any grade

Grade 3/4 symptoms were less common: dry eye (1% and 0% in the 2.5 and 3.4-mg/kg groups) and blurred vision (4% in both groups).

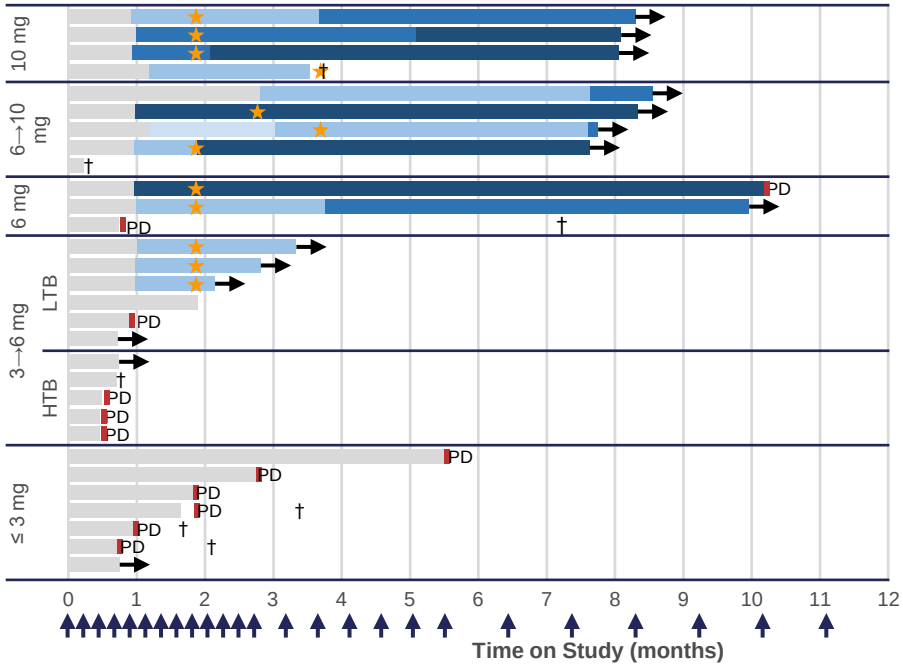
AE = adverse event; BCVA = best-corrected visual acuity; IRR = infusion-related reaction; MEC = microcyst-like epithelial change.

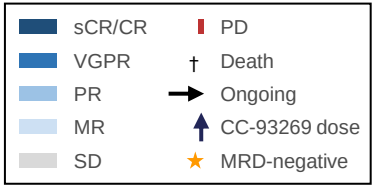
Lonial S, Lee HC, Badros A, et al. Pivotal DREAMM-2 study: single-agent belantamab mafodotin (GSK2857916) in patients with relapsed/refractory multiple myeloma (RRMM) refractory to proteasome inhibitors (PIs), immunomodulatory agents, and refractory and/or intolerant to anti-CD38 monoclonal antibodies (mAbs). Poster presented at: American Society of Clinical Oncology Annual Meeting; May 29-June 2, 2020; Virtual.

CC-93269 (2+1 IgG_1 TCE) Phase 1 dose escalation trial
Summary of efficacy data

Key inclusion: RRMM, 3 or more prior lines. Refractory to last line. No prior BCMA.
Median nº prior lines: 5 (3 – 13)
80% IMID refractory. 80% antiCD38 refr. 76.7% PI-refractory. **66.7% Triple-class refractory**

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%





AEs	All grade	G ≥3
Anemia, n(%)	13 (43.3)	11 (36.7)
Neutropenia, n(%)	35 (46.7)	30 (43.3)
Thrombocyt, n(%)	9 (30%)	5 (16.7%)
CRS, n(%)	**23 (76.7%)**	1 (3.3%)
Infections, n(%)	**17 (56.7%)**	9 (30%)

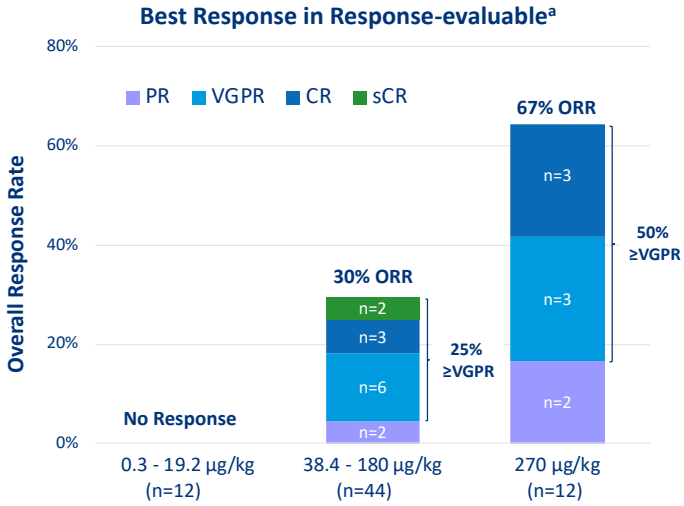
Data as of October 28, 2019.
[a] MRD negativity by Euroflow analysis was reported only if a minimum sensitivity of ≤ 1 tumor cell in 10^5 nucleated cells was achieved and in patients who had ≥ 1 baseline and ≥ 1 post-baseline MRD assessment. HTB, high tumor burden (defined as > 50% bone marrow plasma cells or > 5 extramedullary lesions); LTB, low tumor burden (defined as ≤ 50% bone marrow plasma cells and ≤ 5 extramedullary lesions); MR, minimal response.

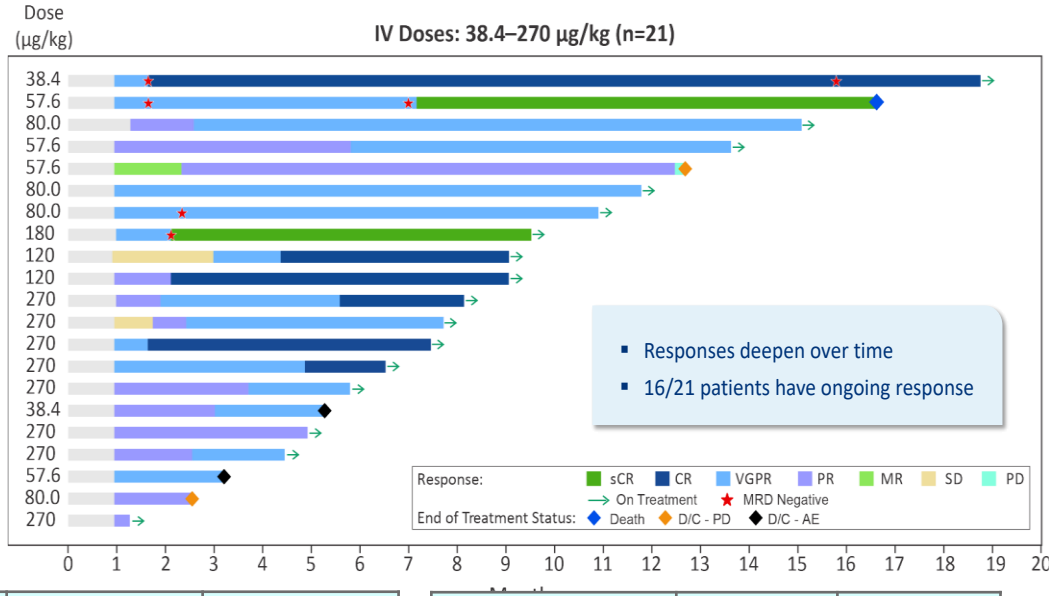
Costa L. et al. ASH 2019. Abstract 143. Oral presentation
Costa L et al. EHA 2020. Oral presentation. S206

Teclistamab: BCMA x CD3 Bispecific DuoBody® Antibody

Phase 1 dose escalation: Outline Efficacy and safety data (n=66)

- Key elegibility criteria: RR or intolerant to established MM therapies
- Median nº prior lines: 6 (2 – 14)
- Triple class R 86%.





Teclistamab safety profile was manageable across all doses

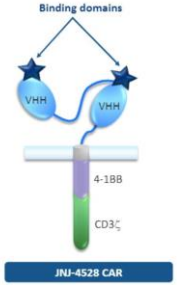
AEs	All grade	Grade ≥3
Anemia, n(%)	45 (58)	28 (36)
Neutropenia, n(%)	35 (45)	30 (38)

AEs	All grade	Grade ≥3
Infections, n(%)	51 (65)	16 (21)
CRS, n(%)	44 (56)	0

Usmani S, ASCO 2020 roal presentation (abstract #100); Mateos MV et al. EHA 2020 Oral presentation, abstract S206

Phase 1b/2 CARTITUDE-1 Study of JNJ-4528 in RRMM: Efficacy

mFUP: 11.5 m



- **JNJ-68284528 (JNJ-4528) is a structurally differentiated chimeric antigen receptor T (CAR-T) cell therapy**
  - Contains a CD3ζ signaling domain and 4-1BB costimulatory domain
  - 2 BCMA-targeting single domain antibodies designed to confer avidity
  - Identical to the CAR construct used in the LEGEND-2 study

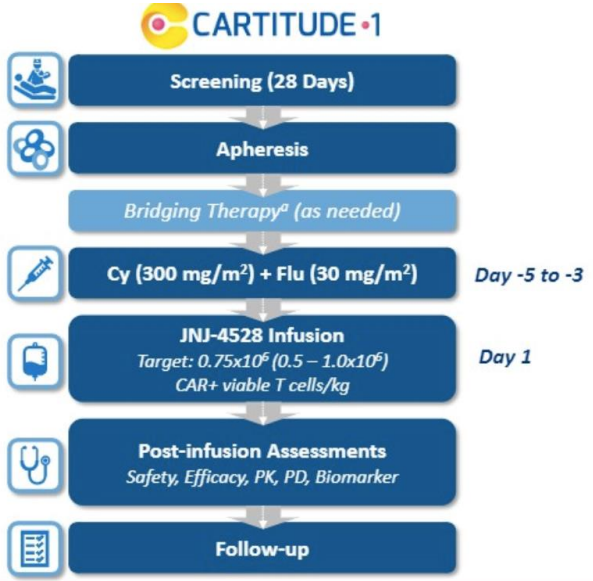
Primary Objectives

- **Phase 1b**: Characterize safety and confirm phase 2 dose as informed by the LEGEND-2 study
- **Phase 2**: Evaluate efficacy of JNJ-4528

Key Eligibility Criteria

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

- Median administered dose = 0.73×10^6 ($0.52 – 0.89 \times 10^6$) CAR+ viable T cells/kg
- Median follow-up at data cut-off = 6 mo (3 – 14)



Berdeja et al., ASCO 2020; abstract 8505. Usmani S et al. EHA 2020. EP927

Phase 1b/2 CARTITUDE-1 Study of JNJ-4528 in RRMM: Patient's characteristics mFUP: 11.5 m

- Of the 35 patients who were enrolled/apheresed, 30 underwent lymphodepletion (1 patient withdrew and 4 died before lymphodepletion), and 29 received an infusion of JNJ-4528 (1 patient withdrew before dosing; **Table 1**).
- Patients were heavily-pretreated: 5 (range, 3 – 18) median prior lines of therapy, 86% triple-refractory, and 97% refractory to last line of therapy (**Table 1**).

Table 1. Demographics and Disease Characteristics

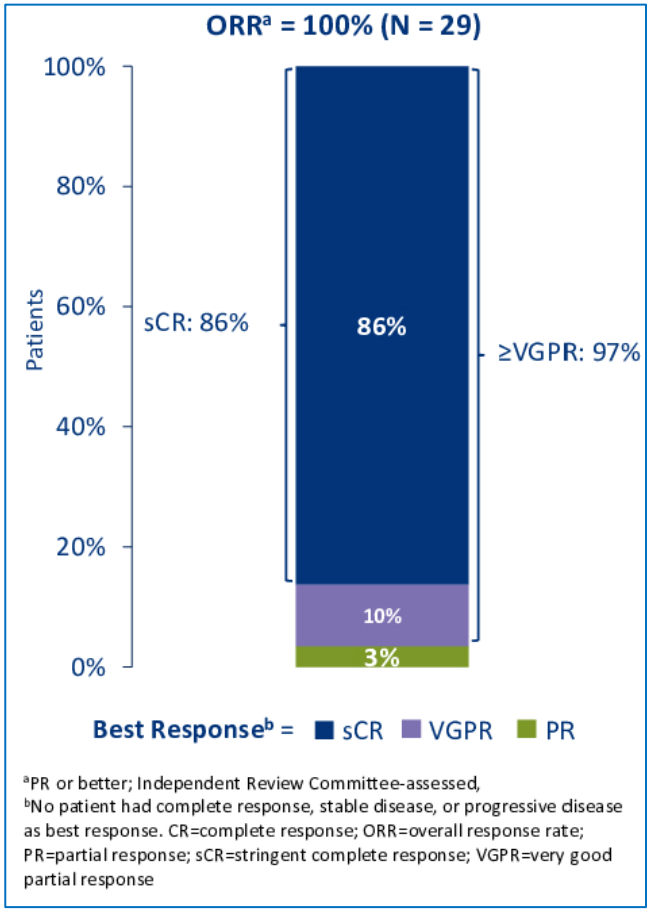
	Total (N = 29)
Median age, (range)	60 (50 – 75)
Female, n (%)	15 (52)
Extramedullary plasmacytomas ≥1, n (%)	3 (10)
Bone marrow plasma cells ≥60%, n (%)	7 (24)
Median years since diagnosis (range)	5 (2 – 16)
High-risk cytogenetic profile,[a] n (%)	7 (27)
del17p	4 (15)
t(14;16)	2 (8)
t(4;14)	1 (4)
Received bridging therapy, n (%)	23 (79)

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

[a]By central FISH; out of 26 patients, [b]PI, IMiD, and anti-CD38, [c]≥2 PIs, ≥2 IMiDs, and anti-CD38, [d]Progressive disease within 60 days (measured from last dose) of last regimen

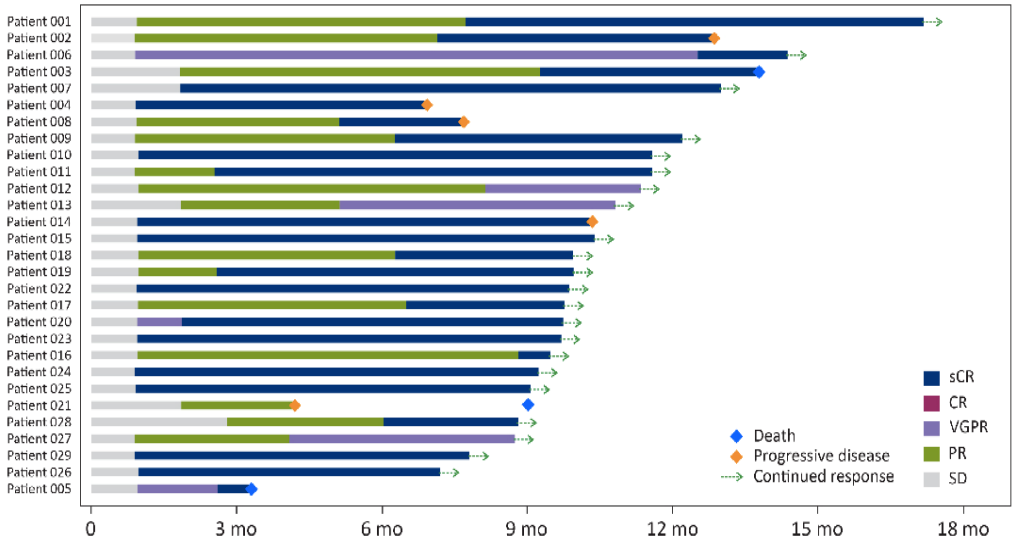
Usmani S et al. EHA 2020. EP927

Phase 1b/2 CARTITUDE-1 Study of JNJ-4528 in RRMM: Efficacy (mFUP: 11.5 m)



[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

Duration of response



- 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)

- Of 16 patients in CR who were evaluable for MRD at the time CR*
  - 81% (n=13) MRD negative at 10^{-5} or 10^{-6}
  - 69% (n=11) MRD negative at 10^{-6}

Berdeja et al., ASCO 2020; abstract 8505. Usmani S et al. EHA 2020. EP927

Phase 1b/2 CARTITUDE-1 Study of JNJ-4528 in RRMM: Safety

Hematologic AEs (≥25% All Grade)	N = 29	
	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 AEs (≥25% All Grade)		
Increased AST	9 (31)	2 (7)
Increased ALT	9 (31)	2 (7)
Diarrhea	10 (35)	0
Upper respiratory tract infection	8 (28)	0

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

- **Median (range) time to onset of CRS: 7 days (2 – 12)**
- Median (range) duration of CRS: 4 days (2 – 64)

- Prolonged severe cytopenias >day 60 were infrequent
  - Most Grade 3–4 cytopenias were resolved after 60 days
  - Median time to G3-4 neutropenia recovery: 1.6 week (95% CI 1.3 -1.9)
  - Median time to G3-4 thrombocytopenia recovery: 5.3 weeks (95% CI 2.4 - 8.1)

- Low incidence of infectious complications

[a]Graded according to Lee et al. Blood 2014;124:188, [b]Graded using Common Terminology Criteria for Adverse Events v.5.0 and American Society for Transplantation and Cellular Therapy grading system. [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; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome

Usmani SZ, et al. EHA 2020; abstract 926

LCAR-B38M: Legend-2 single center (n=57)

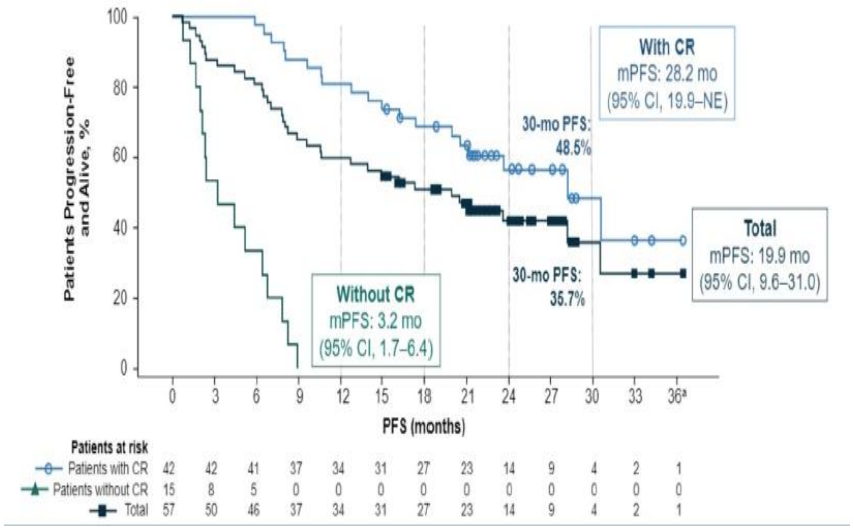
Updated Efficacy (ORR and PFS). Median FUP 25.0 m

Key inclusion: Resistant to > 3 prior lines, BCMA expression in >10% clonal PCs
Median number of prior lines: 3 (1–9)
Prior bort: 68%; prior len: 44%; prior PI + IMiD: 60%; prior SCT: 18%

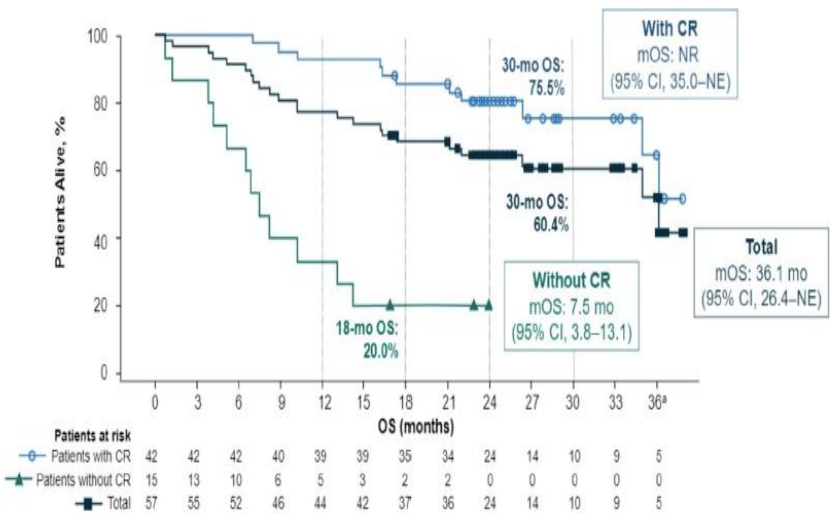
- **Conditioning**: Cyclophosphamide 300mg/m^2
- **CAR-T cells**/kg: 0.07 – 2.1 x 10^6. Median dose: 0.5 x10^6 cells/kg
- **Split infusion** (Day 1 20%, Day 3 30%, Day 7 50%)

ORR 88%. CR rate 74%. 68% MRD negative CR (8-color flow; 10^{-5})

Progression-free survival

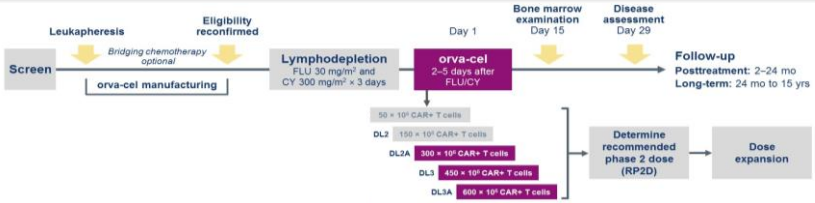


Overall survival

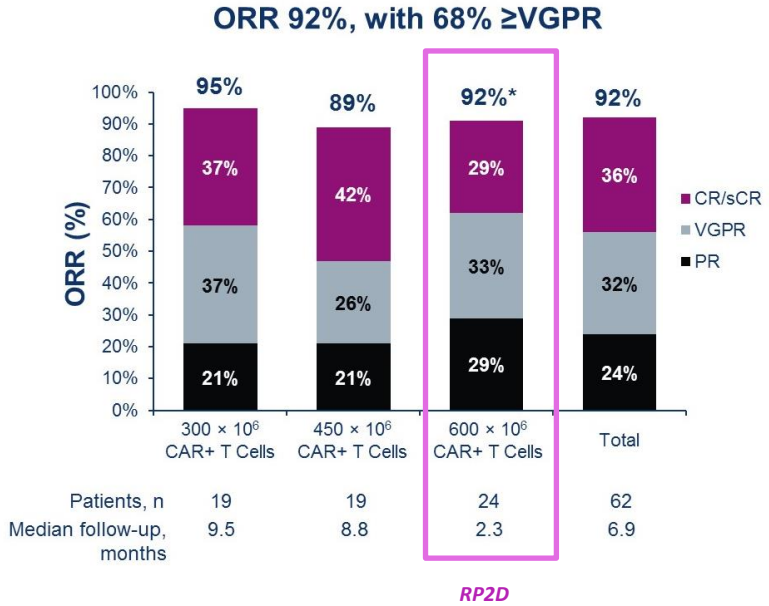


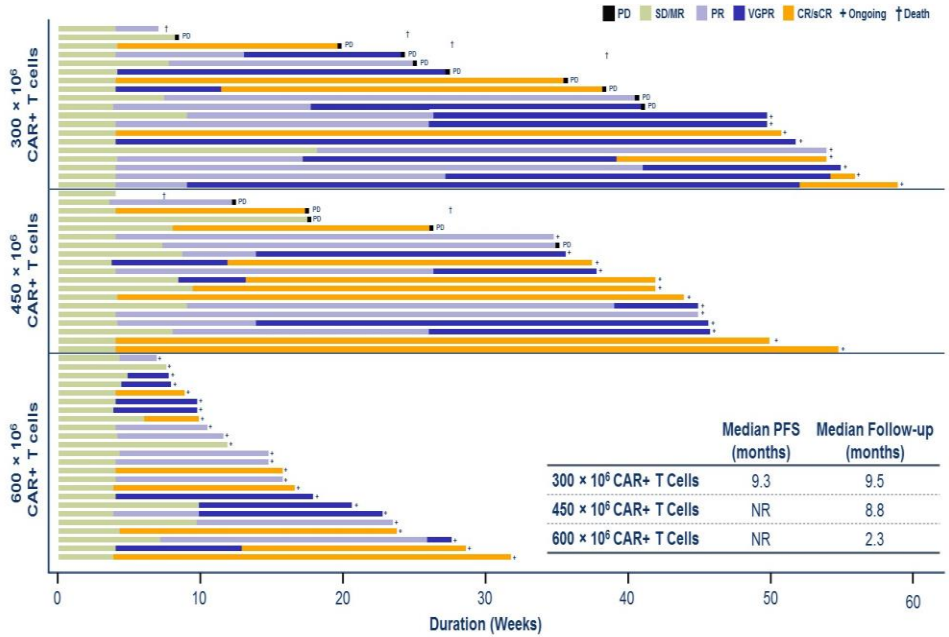
Wang et al. ASH 2019. Abstract #579

Orvacabtagene-autoleucel (orva-cel) for patients with RRMM: update of the phase 1/2 EVOLVE study (n=62)



- Fully-human binder. Manufactured in a 1:1 CD4:CD8 ratio.
- Key inclusión: ≥3 PL (PI, IMID and anti-CD38 exposure)
- Median age 61 y. 23% had EMD and 41% HR CA
- **Median nº of prior lines 6 (3 – 18).**
- **94% triple-class refr. 48% penta-refr.**





PD, progressive disease; SD, stable disease; MR, minimal response; PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response; NR, not reached.

Mailankody S et al. J Clin Oncol 38:2020 (suppl; abst 8504)

Orvacabtagene-autoleucel (orva-cel) for patients with RRMM: update of the phase 1/2 EVOLVE study (n=62)

Hematologic AEs (≥25% All Grade)	N = 62	
	All Grade	Grade ≥3
Neutropenia	56 (90)	56 (90)
Thrombocytopenia	32 (52)	29 (47)
Anemia	31 (50)	30 (48)
Leukopenia	21 (34)	20 (32)
Non-Hematologic AEs (≥25% All Grade)		
Infections	25 (40)	8 (13)
Upper respiratory tract infection	4 (7)	0

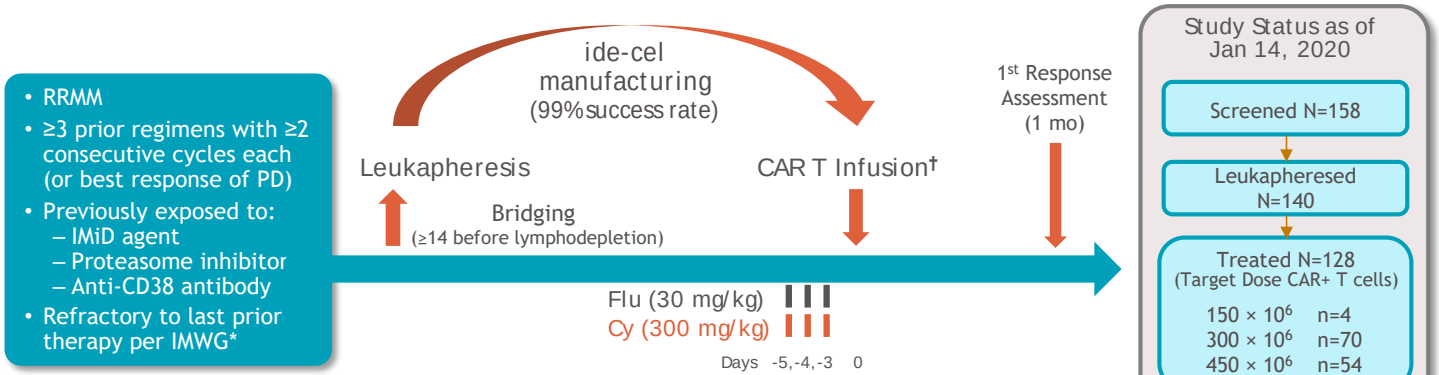
- CRS and cytopenias were the most common AE.
- Prolongued cytopenias were common, with 67% of patients having grade ≥ 3 cytopenias at day 29, and 35% having these at Month 2.
- For patients with Grade ≥ 3 cytopenias at Day 29, median time to resolution to grade ≤ 2 was ≤ 2.3 months from infusion.

	300 × 10^6 CAR+ T Cells (n=19)	450 × 10^6 CAR+ T Cells (n=19)	600 × 10^6 CAR+ T Cells (n=24)	Total (N=62)
CRS, n (%)	**17 (89)**	**17 (89)**	**21 (88)**	**55 (89)**
Grade ≥3 CRS	0	1 (5)	1 (4)	2 (3)
Median time to onset, days (range)	2 (1–4)	2 (1–4)	2 (1–4)	2 (1–4)
Median time to resolution, days (range)	3 (1–6)	5 (2–10)	3 (1–7)	4 (1–10)
NE, n (%)	**3 (16)**	**2 (11)**	**3 (13)**	**8 (13)**
Grade ≥3 NE	1 (5)	1 (5)	0	2 (3)
Median time to onset, days (range)	6 (3–6)	4 (1–6)	1 (1–4)	4 (1–6)
Median time to resolution, days (range)	3 (2–4)[a]	7 (5–8)	2 (2–10)	4 (1–10)

- Tocilizumab 76%
- Steroids 52%
- Anakinra 23%
- Siltuximab 3%
- Toci + Steroids 50%

Mailankody S et al. J Clin Oncol 38:2020 (suppl; abst 8504)

KarMMa
Ide-cel pivotal phase 2 single-arm study



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

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

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

Munshi et al. Idecabtagene vicleucel (ide-cel; bb2121), a BCMA-targeted CAR T cell therapy, in patients with relapsed and refractory multiple myeloma (RRMM): Initial KarMMa results. Presentation at American Society of Clinical Oncology (ASCO) meeting, 2020; May 29-31, 2020. Abs. 8503.

Ide-cel pivotal phase 2 single-arm study: Patient's characteristics

Characteristics		Ide-cel Treated (N=128)
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, %	IMiD agent-refractory	98
	PI-refractory	91
	Anti-CD38 Ab-refractory	94
	Triple-refractory	84
	Penta-refractory	26

- All were refractory to their last line per IMWG criteria
- Most were refractory to all 3 major MM drug classes (IMiD agents, PIs, and anti-CD38 antibodies)
- Most patients (88%) received bridging therapy during CAR T cell manufacturing
  - Only 4% of patients responded (4 PR, 1 VGPR) to bridging therapy

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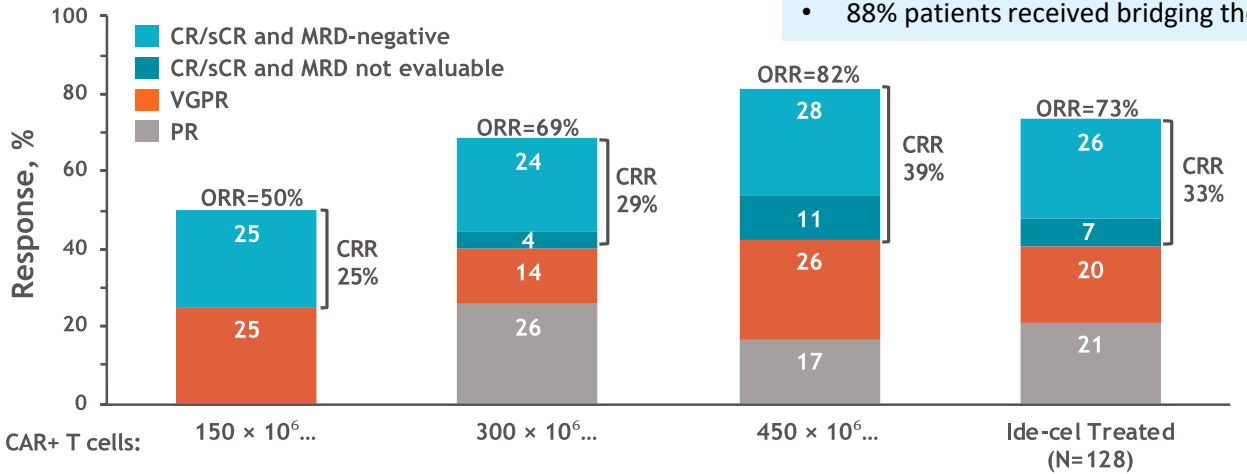
Ide-cel pivotal phase 2 single-arm study: Overall response

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



- Primary (ORR >50%) and key secondary (CRR >10%) endpoints were met in the ide-cel treated population
  - *ORR of 73% (95% CI, 65.8–81.1; P<0.0001*) and CRR (CR/sCR) of 33% (95% CI, 24.7–40.9; P<0.0001)*
  - ***Both ORR and CRR increased with higher target dose***
- **Median time to first response of 1.0 mo** (range, 0.5–8.8); median time to CR of 2.8 mo (range, 1.0–11.8)
- Median follow-up of 13.3 mo across target dose levels

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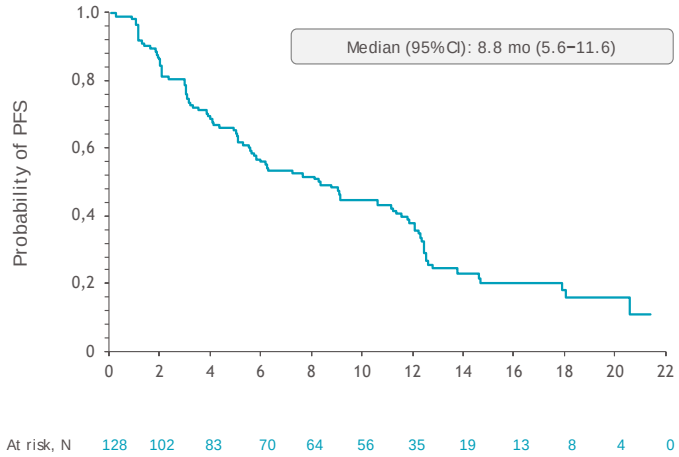
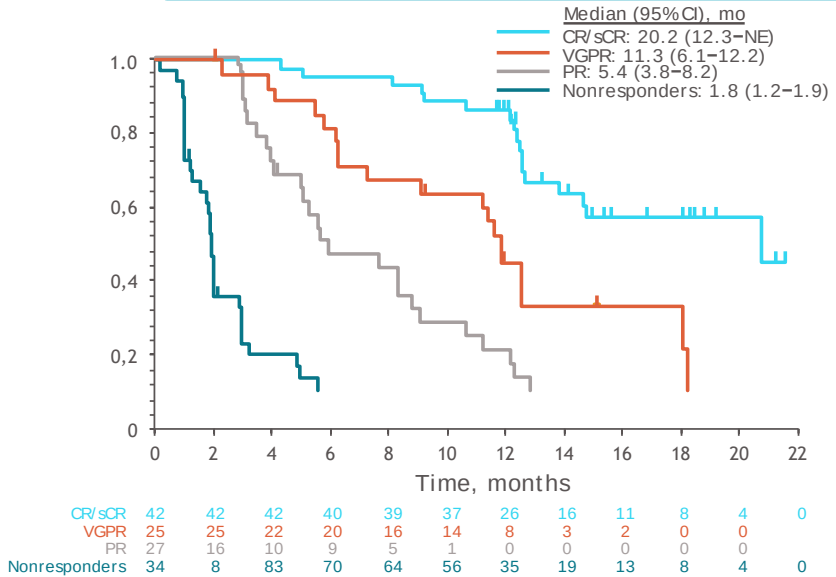
Ide-cel pivotal phase 2 single-arm study: PFS

PFS in all treated patients (mITT)



PFS by Best Response



- Median PFS was 8.8 months across all dose ranges in all treated patients.
- PFS increased with higher target dose; median PFS was 12 mo at 450 × 10^6 CAR+ T cells
- PFS increase by depth of response; median PFS was 20 mo in patients with CR/sCR

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Ide-cel pivotal phase 2 single-arm study: Safety

Cytokine-release syndrome

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 3 4 5	 2 (50) 0 0 0	 49 (70) 2 (3) 1 (1) 1 (1)	 49 (91) 3 (6) 0 0	 100 (78) 5 (4) 1 (<1) 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)

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 2 3	 0 0 0	 7 (10) 4 (6) 1 (1)	 5 (9) 3 (6) 3 (6)	 12 (9) 7 (5) 4 (3)

Other AEs:

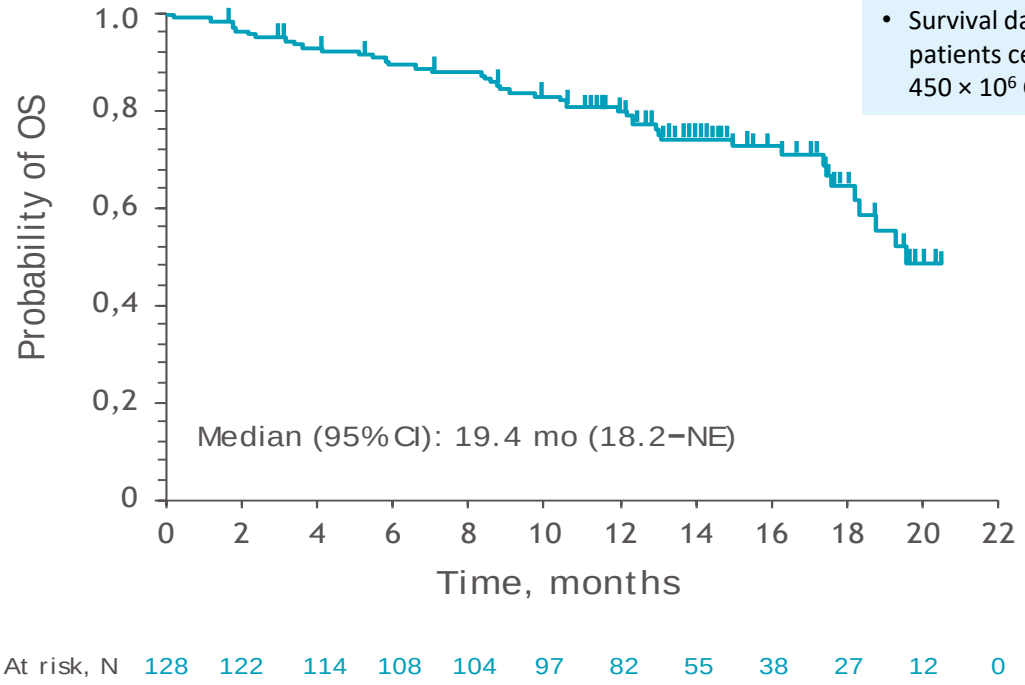
- Cytopenias were common; not dose related
- Median time to recovery of grade ≥3 neutropenia and thrombocytopenia was 2 mo (95% CI, 1.9–2.1) and 3 mo (95% CI, 2.1–5.5), respectively
- Delayed recovery (>1 mo) of grade ≥3 neutropenia in 41% of patients and thrombocytopenia in 48%‡
- Infections (including bacterial, viral, fungal) were common (69%); not dose-related
- 5 deaths (4%) within 8 wk of ide-cel infusion
  - 2 following MM progression
  - 3 from AEs (CRS, aspergillus pneumonia, GI hemorrhage)
- 1 additional death from AE (CMV pneumonia) within 6 mo, in the absence of MM progression

Munshi et al. Idecabtagene vicleucel (ide-cel; bb2121), a BCMA-targeted CAR T cell therapy, in patients with relapsed and refractory multiple myeloma (RRMM): Initial KarMMa results. Presentation at American Society of Clinical Oncology (ASCO) meeting, 2020; May 29-31, 2020. Abs. 8503. San Miguel J et al. Oral presentation EHA 2020, abstract number S209

KarMMa-1

Ide-cel pivotal phase 2 single-arm study: 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



Data cutoff: 14 Jan 2020. NE, not estimable; OS, overall survival.

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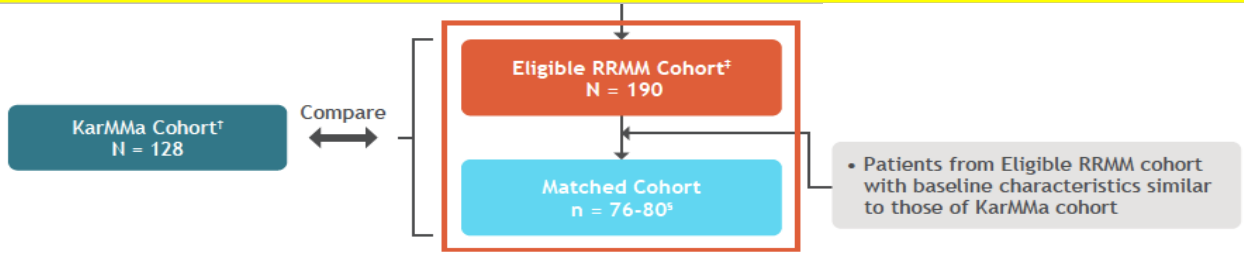
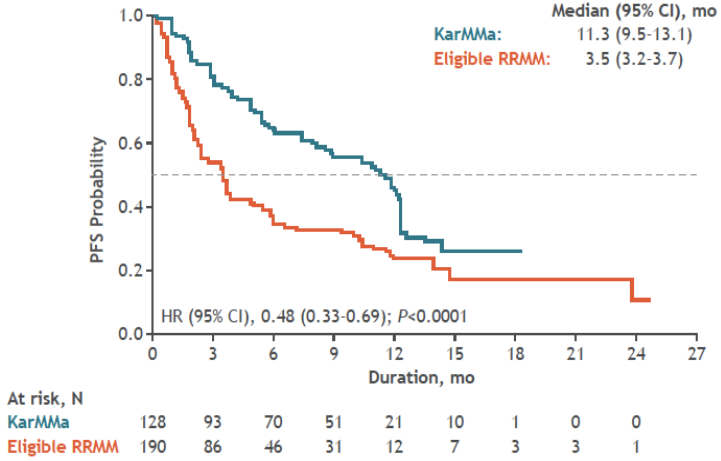
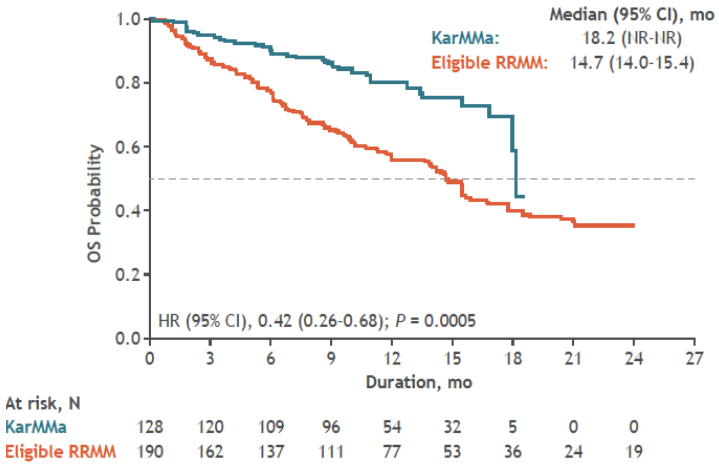
KarMMa-RW: a study of real-world treatment patterns in heavily pretreated RRMM and comparison of outcome with KarMMa



ORR: KarMMa 76% (67.8 – 86.1) vs Eligible RRMM 32% (24.4 – 42.3)





Significant improved outcomes were demonstrated with ide-cel treatment in the KarMMa cohort vs similar real-world popularion

Jagganath S et al. Poster presentation. ASCO 2020, abstract #8525

Closing remarks

- Triple-class refractory patients remain an unmet medical need. New therapies are being developed to target this difficult-to-treat population.
- BCMA is a promising therapeutic target and clinical results with the new BCMA-directed treatments are encouraging among patients with RRMM. Other targets are under evaluation (GPRC5d, FcRH5) but clinical data is still scanty.
- **Belantamab-Mafodotin, is a first-in-class antibody drug conjugate and 1st anti-BCMA agent approved:**
  - 32% ORR with deep and durable responses (mDOR 11.0 months).
  - Manageable safety profile. Thrombocytopenia and corneal toxicity are the most frequent TRAEs. AEs are reversible and managed with dose reductions and dose delays.
- **Biespecific TCE has shown remarkable clinical efficacy (ORR ≈ 60-90% at the higher doses) with apparently long duration of responses and adequate safety profile but we need longer follow-up.**
- **Several CAR-T cells have been presented with impressive clinical activity in triple class refractory patients but relapses still occur and no-plateau is yet seen in the survival curves.**
  - Ide-Cel will be likely the first CAR-T approved with ORR 73% in all idel-cel treated patients, 33% CR and mPFS 8.8 m (12 months among patients treated at the higher dose level).
  - JNJ 4528 has also shown impressive clinical results with 100% ORR (sCR 86%), 9-m PFS 86% with a mFUP of 11.5 m These results are still inmature and further follow-up is needed.
- **Future development in all these treatment modalities is granted to further improve the outcome in myeloma patientes, specially in those with triple-class refractory disease.**