Agents ciblants BCMA, hors CAR-T

Pr Philippe Moreau

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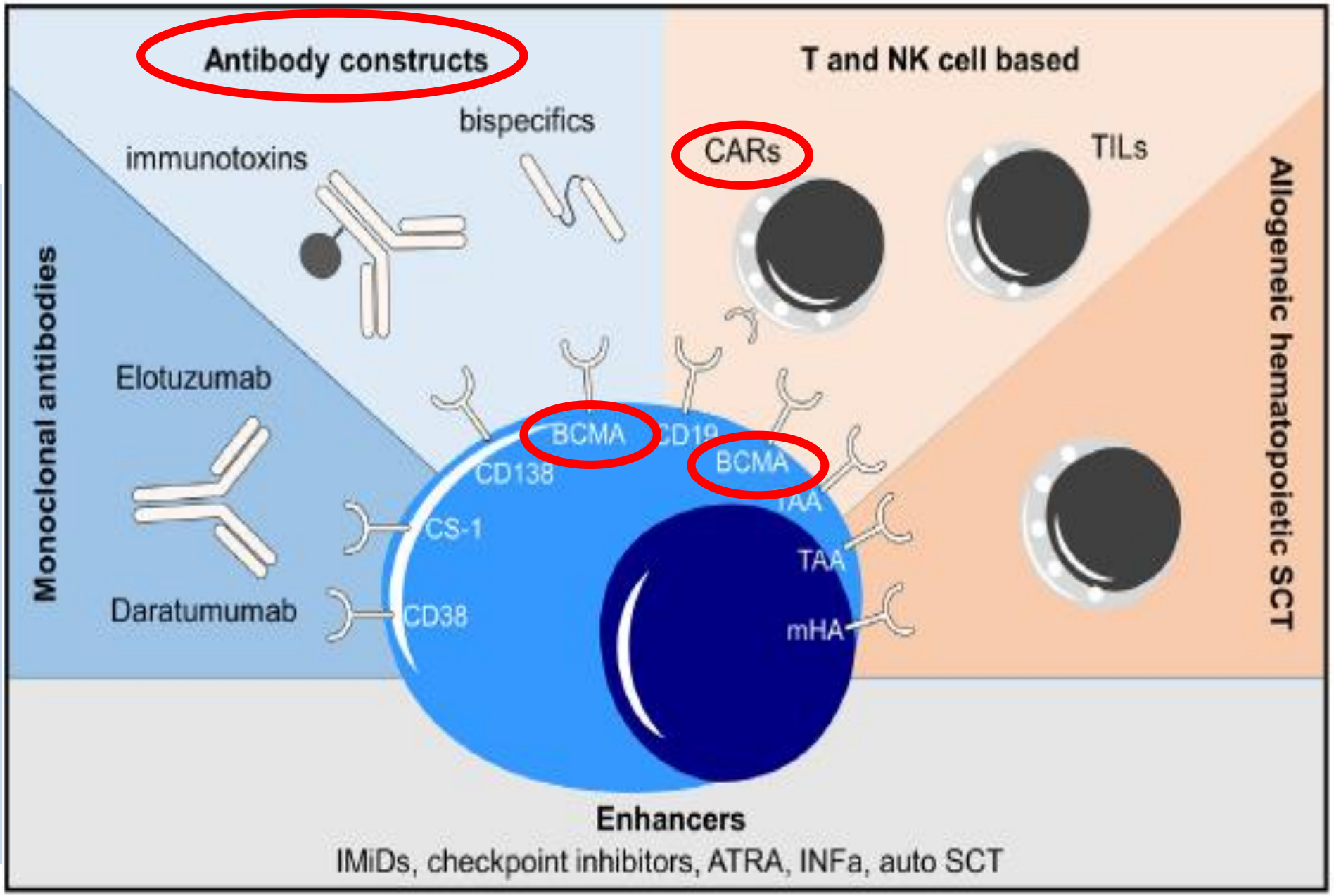
liens d'intérêt :

advisory boars et honoraires : janssen, abbvie, amgen, celgene, sanofi, GSK

stock options : non



Current strategies using immunologic components to treat MM

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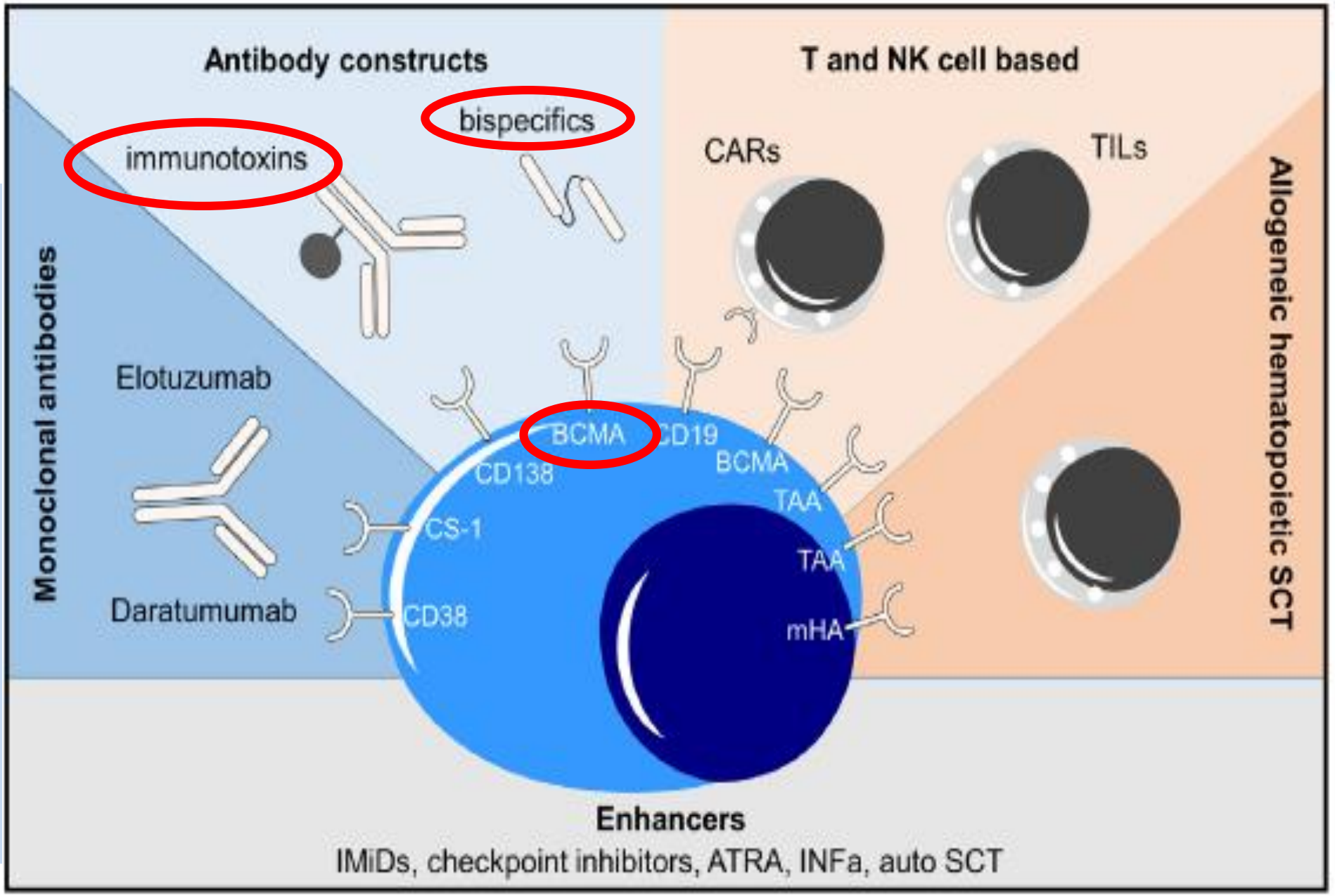

Current strategies using immunologic components to treat MM

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Current investigational approaches and select pipeline agents targeting BCMA

Antibody-drug conjugate		
Company	Asset	Phase
GSK	**belantamab mafodotin**	**III**
AZ/ MedImmune LLC	MEDI2228	I
Celgene/ BMS	CC-99712	I
Heidelberg	HDP-101	PC

CAR-T		
Company	Asset	Phase
BMS/ bluebird	**bb2121**	**III**
	bb21217	I
Janssen/ Legend Biotech	**LCAR-B38M (JNJ-68284528)**	**Ib/II**
BMS/Juno	JCARH125	I/II
Novartis/ Poseida	P-BCMA-101	I/II
Iaso Bio/ Innovent	CT-103A	I

Bispecific Antibodies		
Company	Asset	Phase
Amgen	**AMG-420***	**Ib/II**
	AMG-701†	I/II
Celgene/ BMS	**CC-93269**	**I**
Janssen/ Genmab	**JNJ-64007957**	**I**
Regeneron	REGN5458	I/II
Pfizer	PF-06863135	I

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Current investigational approaches and select pipeline agents targeting BCMA

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ABSTRACT 143

First Clinical Study of the B-Cell Maturation Antigen 2+1 T Cell Engager CC-93269 in Patients With Relapsed/Refractory Multiple Myeloma: Interim Results of a Phase 1 Multicenter Trial

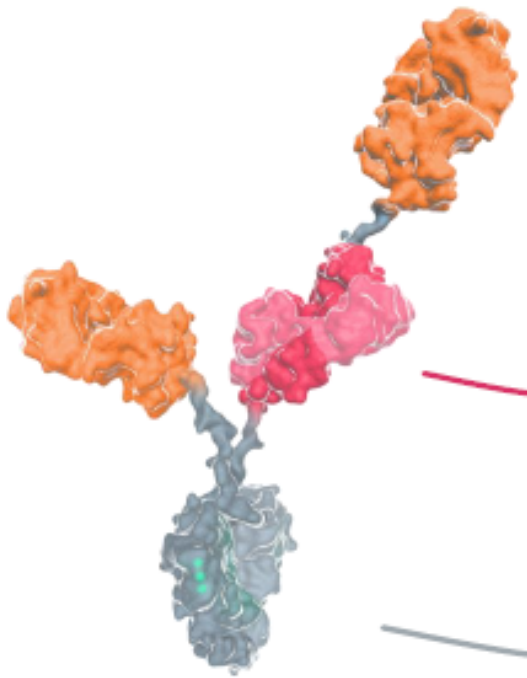
Luciano J. Costa[1], Sandy W. Wong[2], Arancha Bermúdez[3], Javier de la Rubia[4], María-Victoria Mateos[5], Enrique M. Ocio[3], Paula Rodríguez-Otero[6], Jesús San-Miguel[6], Shaoyi Li[7], Rafael Sarmiento[8], Pilar Lardelli[8], Allison Gaudy[7], Isaac Boss[7], Lisa M. Kelly[7], Michael R. Burgess[7], Kristen Hege[7] and William I. Bensinger[9]

[1]Division of Hematology and Oncology, University of Alabama at Birmingham, Birmingham, AL, USA; [2]Department of Medicine, University of California, San Francisco, CA, USA; [3]Hospital Universitario Marqués de Valdecilla (IDIVAL), Santander, Spain; [4]Hematology Service, University Hospital Doctor Peset, Valencia, Spain; [5]Institute of Cancer Molecular and Cellular Biology, University Hospital of Salamanca, Salamanca, Spain; [6]Department of Hematology, Clínica Universidad de Navarra, CIMA, Pamplona, Spain; [7]Bristol-Myers Squibb, Summit, NJ, USA; [8]Celgene, a Bristol-Myers Squibb Company, Summit, NJ; [9]Myeloma and Transplant Program, Swedish Cancer Institute, Seattle, WA, USA

Presented at the Annual Meeting of the American Society of Hematology (ASH); December 7–10, 2019; Orlando, FL, USA.

CC-93269 KEY ENGINEERING CHARACTERISTICS

- CC-93269 is a humanized 2+1 IgG1-based TCE that binds to BCMA on myeloma cells and to CD3ε on T cells, enabling specific and tight BCMA binding[1,2]



Anti-BCMA (bivalent)[1–5]

Bivalent binding to BCMA in a 2+1 format for superior potency, tumor targeting, and retention

Anti-CD3ε (monovalent)[1–5]

Head-to-tail geometry of BCMA- and CD3ε-binding Fab domains using a flexible linker

Heterodimeric FcγR-silent Fc[1–6]

No binding to FcγR and C1q to minimize infusion-related reactions and binding to FcRn retained for IgG-like PK

- CC-93269 induces tumor regression in animal models of myeloma and promotes myeloma cell death in primary patient bone marrow aspirates[1,2]

BCMA, B-cell maturation antigen; CD3, cluster of differentiation 3; Fab, antigen-binding fragment; FcγR, Fc gamma receptor, FcRn, neonatal Fc receptor; Ig, immunoglobulin; PK, pharmacokinetics; TCE, T cell engager.

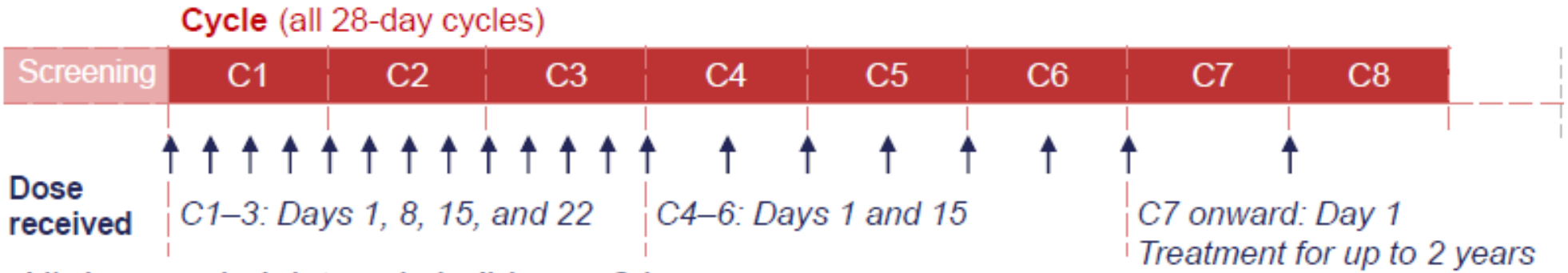
1. Seckinger A, et al. Cancer Cell. 2017;31:396-410. 2. Vu DM, et al. Blood 2015;128;abstract 2998. 3. Klein C, et al. Cancer Res. 2017;77:abstract 3629. 4. Bacac M, et al. Clin Cancer Res. 2016;22:3286-3297. 5. Lehmann S, et al. Clin Cancer Res. 2016;22:4417-4427. 6. Schlothauer T, et al. Prot Eng Des Sel. 2016;29:457-466.

CC-93269-MM-001 PHASE 1 TRIAL (NCT03486067): STUDY DESIGN

Key Eligibility Criteria

- RRMM after ≥ 3 prior regimens
- Progressive disease within 60 days of last regimen
- No prior BCMA-directed therapy

Dose Schedule



All doses administered via IV over 2 hours

Part A: Dose Escalation

- Stage 1: Fixed doses
- Stage 2: Step-up in dose on C1D8

Part B: Cohort Expansion

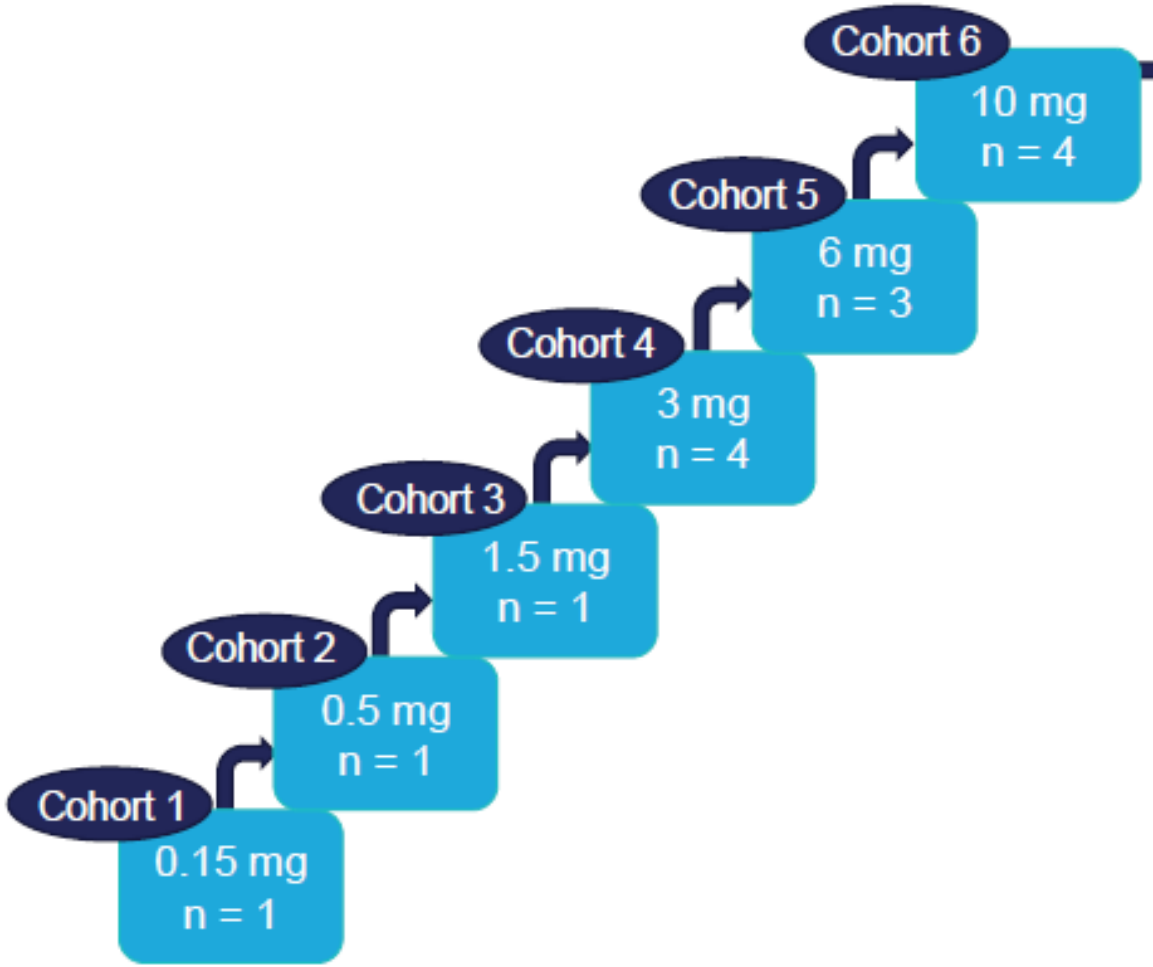
Endpoints

Primary: Safety including DLTs, AEs, NTD, and MTD
Secondary: Preliminary efficacy including MRD, PK, ADA, and PD endpoints

ADA, anti-drug antibody; AE, adverse event; C, Cycle; D, Day; DLT, dose-limiting toxicity; IV, intravenous; MRD, minimal residual disease; MTD, maximum tolerated dose; NTD, non-tolerated dose; PD, pharmacodynamics; RRMM relapsed/refractory multiple myeloma.

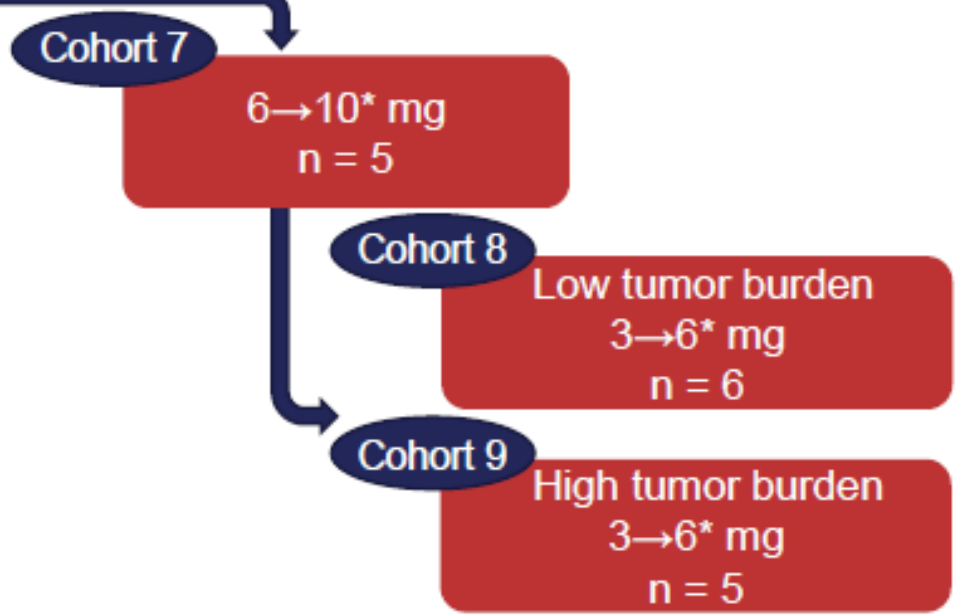
CC-93269-MM-001 PART A: DOSE ESCALATION

Stage 1: Fixed Doses



Stage 2: Intra-Patient Dose Escalation

*Step-up in dose on C1D8



Low tumor burden was defined as ≤ 50% bone marrow plasma cells and ≤ 5 extramedullary lesions

High tumor burden was defined as > 50% bone marrow plasma cells or > 5 extramedullary lesions

Data as of October 28, 2019.

BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Characteristics	All Patients (N = 30)
Age, median (range), years	64.0 (42–78)
Male, n (%)	21 (70.0)
Time since initial diagnosis, median (range), years	5.94 (1.4–16.6)
Presence of extramedullary lesions, n (%)	8 (26.7)
Eastern Cooperative Oncology Group performance status, n (%)	
0	8 (26.7)
1	22 (73.3)
Derived International Staging System stage, n (%)	
I	9 (30.0)
II	11 (36.7)
III	9 (30.0)
Unknown	1 (3.3)
High-risk cytogenetics, n (%)[a]	
del(17p) or t(4;14) or t(14;16)	9 (30.0)

Data as of October 28, 2019.
[a] At screening by central laboratory.

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.

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)

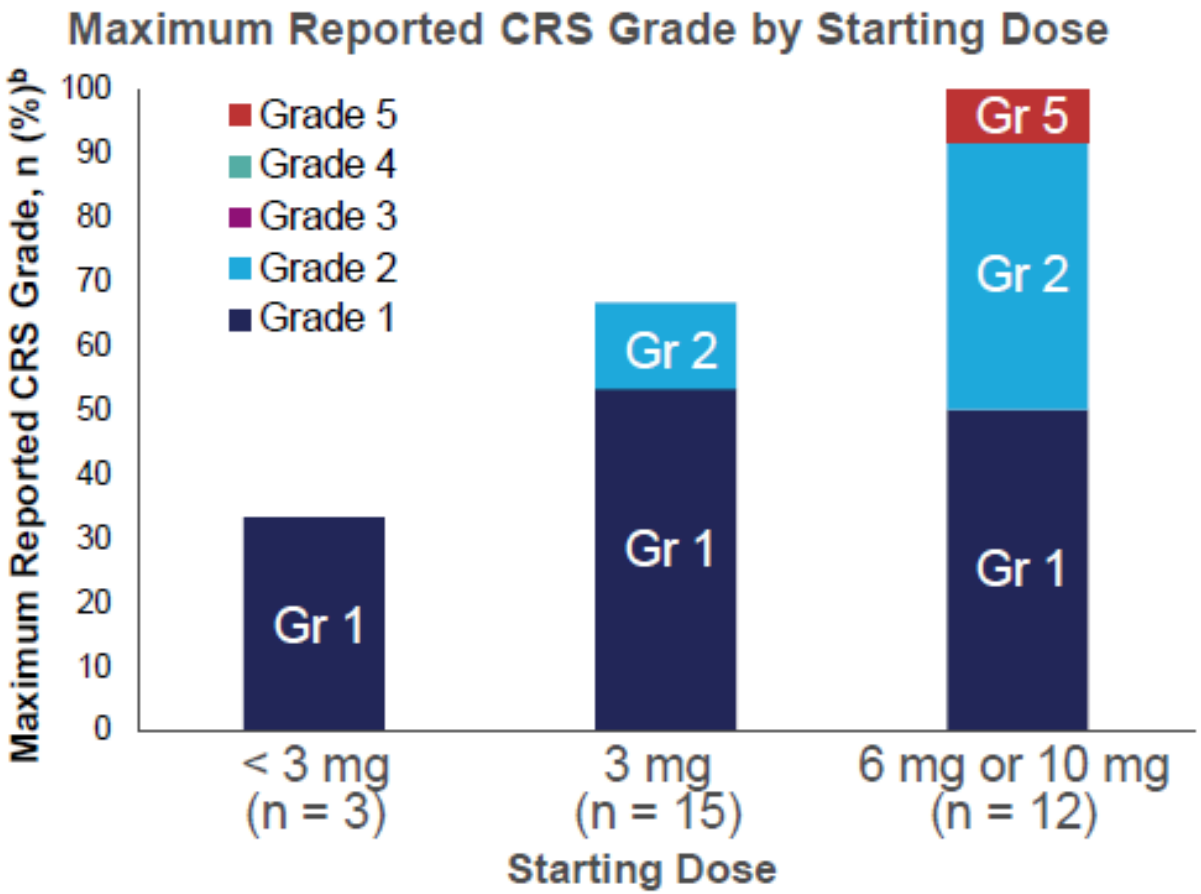
Data as of October 28, 2019.

[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.

CYTOKINE RELEASE SYNDROME

Parameter	All Patients (N = 30)
Patients with a CRS event, n (%)	**23 (76.7)**
After first dose	23 (76.7)
After second dose	7 (23.3)
After third dose	2 (7.4)[a]
Maximum CRS grade, n (%)	
1	15 (50.0)
2	7 (23.3)
≥ 3	1 (3.3)
Time to onset, median (range), d	1 (1–9)
Duration, median (range), d	2 (1–6)
Tocilizumab use, n (%)	13 (43.3)
Corticosteroid use, n (%)	22 (73.3)

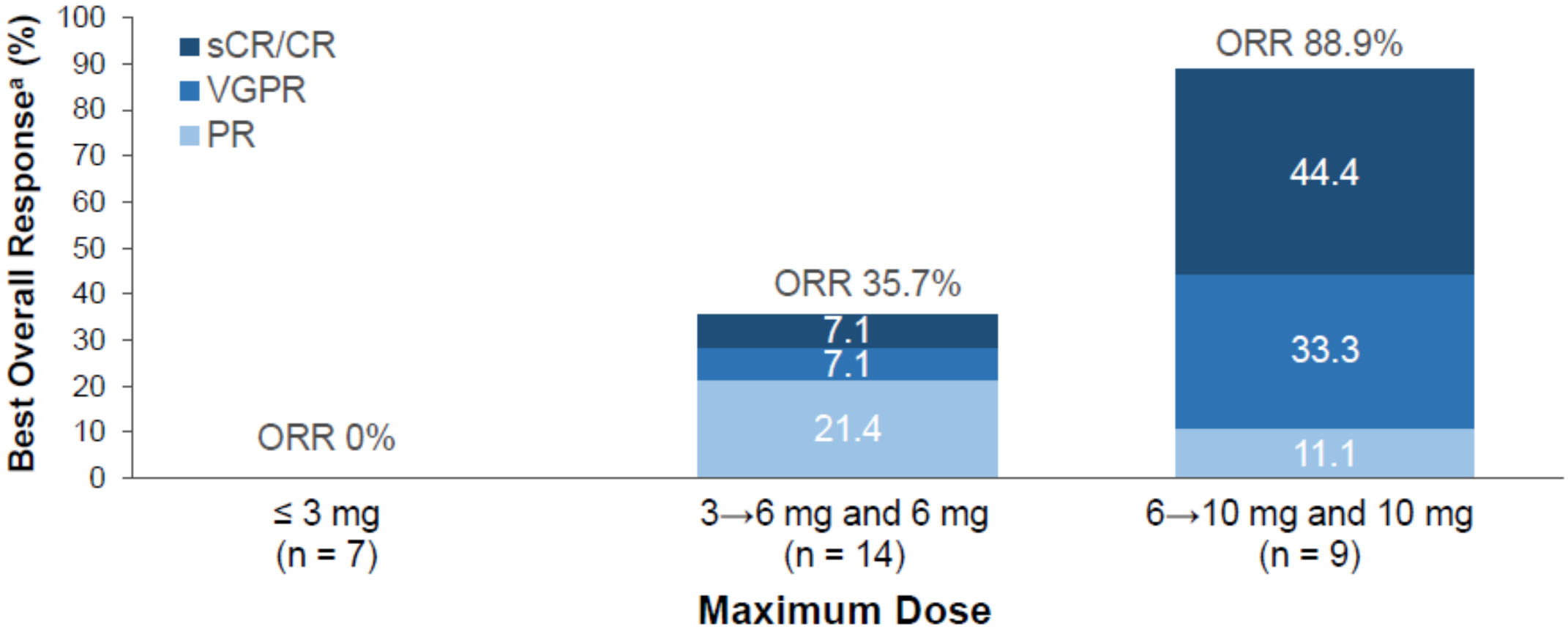


- Dexamethasone prophylaxis was administered to patients receiving ≥ 6 mg (Cohorts 5–9)
- In Cohort 7 (6→10 mg), 1 patient experienced grade 3 (6 mg) followed by grade 5 CRS (10 mg); contributing factors included myeloma progression with extensive extramedullary disease, and concomitant infection

Data as of October 28, 2019.
[a] 27 patients received a third dose; [b] Graded using the Lee criteria[1]
CRS, cytokine release syndrome; Gr, grade.

1. Lee DW, et al. Blood. 2014;124:188-195.

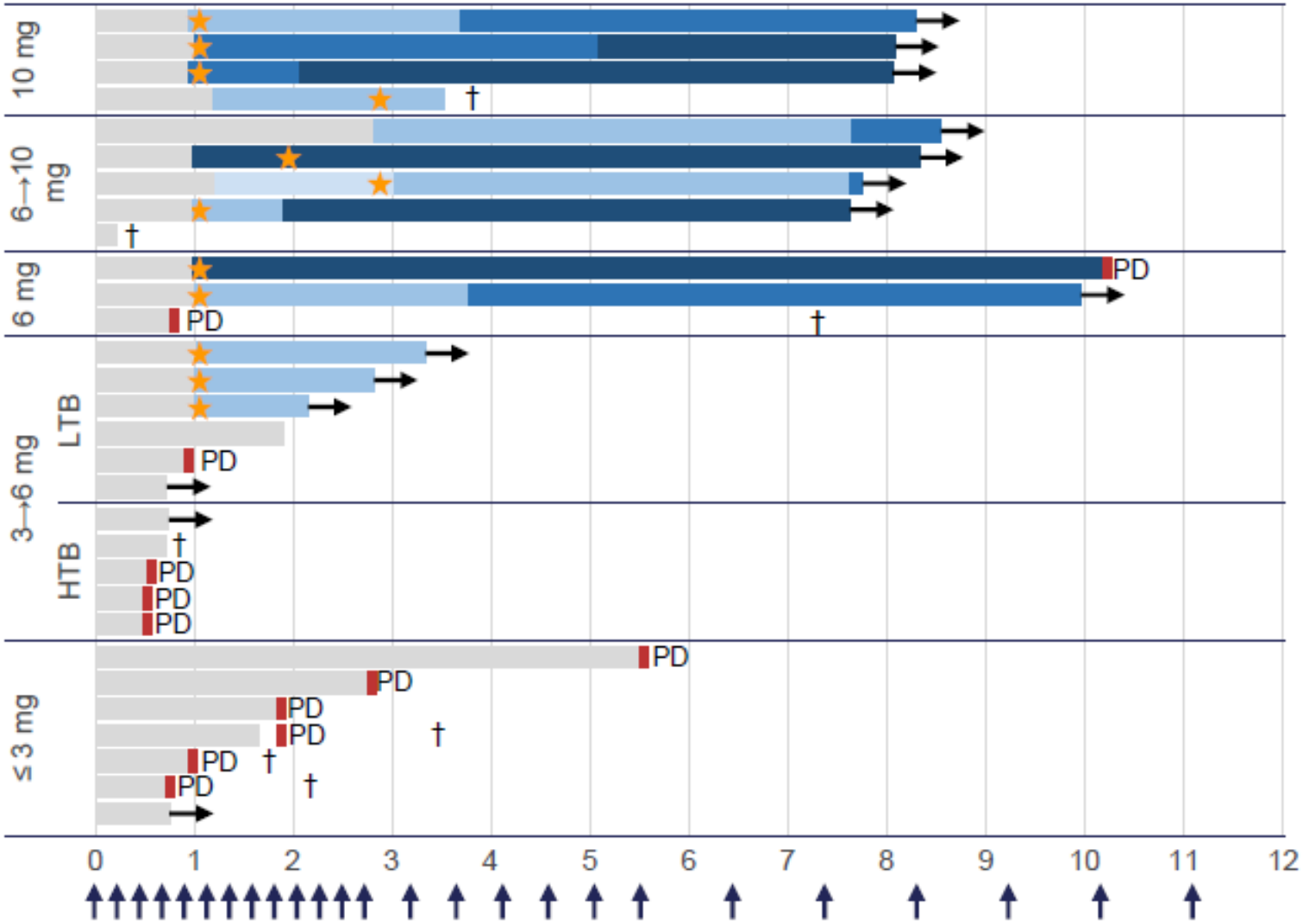
CC-93269 PRELIMINARY EFFICACY



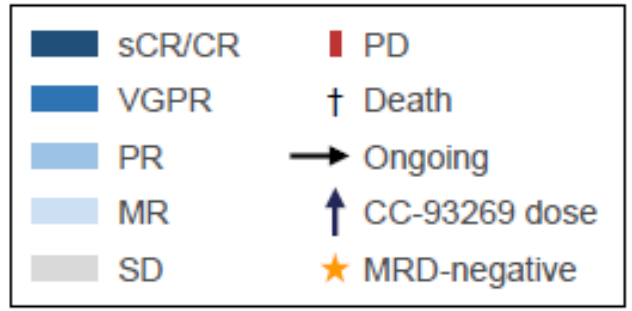
- In all patients (N = 30), the ORR was 43.3% with a sCR/CR of 16.7%
- Among patients receiving 10 mg (n = 9), the ORR was 88.9% with a sCR/CR of 44.4%

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.

RESPONSE OVER TIME



- Median time to first response was 4.1 weeks (range 4.0–13.1)
- 11 of 13 responses are ongoing
- 5 of 30 (16.7%) patients achieved an MRD-negative sCR/CR
  - Of 13 responding patients, 92.3% achieved MRD negativity (≤ $1/10^5$) in the bone marrow on or before C4D1 by Euroflow[a]



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.

Current investigational approaches and select pipeline agents targeting BCMA

Antibody-drug conjugate		
Company	Asset	Phase
GSK	**belantamab mafodotin**	**III**
AZ/ MedImmune LLC	MEDI2228	I
Celgene/ BMS	CC-99712	I
Heidelberg	HDP-101	PC

CAR-T		
Company	Asset	Phase
BMS/ bluebird	**bb2121**	**III**
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Celgene/ BMS	**CC-93269**	**I**
Janssen/ Genmab	**JNJ-64007957**	**I**
Regeneron	REGN5458	I/II
Pfizer	PF-06863135	I

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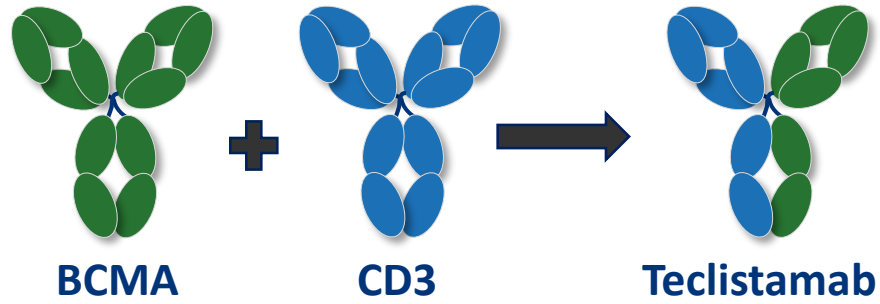
Phase 1 Study of Teclistamab, a Humanized B-Cell Maturation Antigen (BCMA) x CD3 Bispecific Antibody, in Relapsed or Refractory Multiple Myeloma

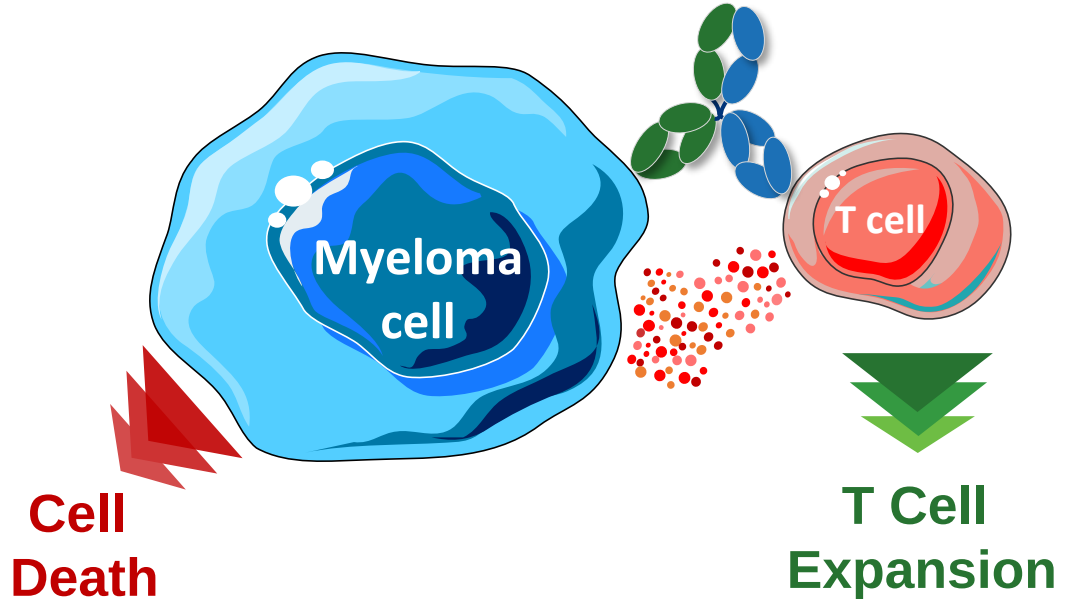
Saad Z. Usmani,[1] Maria-Victoria Mateos,[2] Hareth Nahi,[3] Amrita Y. Krishnan,[4] Niels W.C.J. van de Donk,[5] Jesus F. San-Miguel,[6] Albert Oriol Rocafiguera,[7] Laura Rosinol,[8] Ajai Chari,[9] Homer Adams III,[10] Suzette Girgis,[10] Shun Xin Wang Lin,[10] Tara Stephenson,[10] Kristy Kemmerer,[10] Jennifer Smit,[10] Yusri A. Elsayed,[10] Jeffrey R. Infante,[10] Jenna D. Goldberg,[11] Arnob Banerjee,[10] Alfred L. Garfall[12]

[1]Levine Cancer Institute-Atrium Health, Charlotte, NC, USA; [2]Hospital Clínico Universitario de Salamanca, Salamanca, Spain; [3]Karolinska University Hospital at Huddinge, Stockholm, Sweden; [4]City of Hope, Duarte, CA, USA; [5]Amsterdam University Medical Center, Location VU University Medical Center, Amsterdam, The Netherlands; [6]Clínica Universidad de Navarra, Navarra, Spain; [7]Institut Català d'Oncologia and Institut Josep Carreras. Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; [8]Hospital Clinic, Barcelona, Spain; [9]Mount Sinai School of Medicine, New York, NY, USA; [10]Janssen R&D, Spring House, PA, USA; [11]Janssen R&D, Raritan, NJ, USA; [12]Perelman School of Medicine and Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA

Teclistamab: BCMA x CD3 Bispecific DuoBody® Antibody

- Teclistamab (JNJ-64007957) is a humanized IgG-4 bispecific DuoBody® antibody that binds to BCMA and CD3
- Teclistamab redirects $CD3^+$ T cells to BCMA-expressing myeloma cells to induce cytotoxicity of the targeted cells in preclinical studies[1,2]
- Teclistamab potently kills myeloma cell lines and primary myeloma cells from heavily pretreated patients[2]
- A Phase 1 first-in-human study is underway to evaluate safety and antitumor activity of teclistamab in patients with RRMM (NCT03145181)





Teclistamab includes technology licensed from GenMab. [1]Labrijn AF et al. *Proc Natl Acad Sci USA*. 2013;110:5145. [2]Frerichs KA et al. *Clin Cancer Res*. 2020; doi: 10.1158/1078-0432.CCR-19-2299. BCMA=B-cell maturation antigen; MM=multiple myeloma; RR=relapsed or refractory

Teclistamab: Phase 1 Study Design

Key Objectives

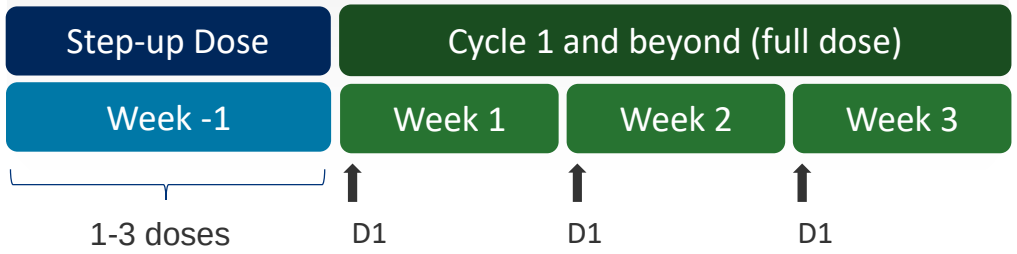
- Part 1: Identify RP2D
- Part 2: Safety and tolerability
- Antitumor activity, PK, PD

Key Eligibility Criteria

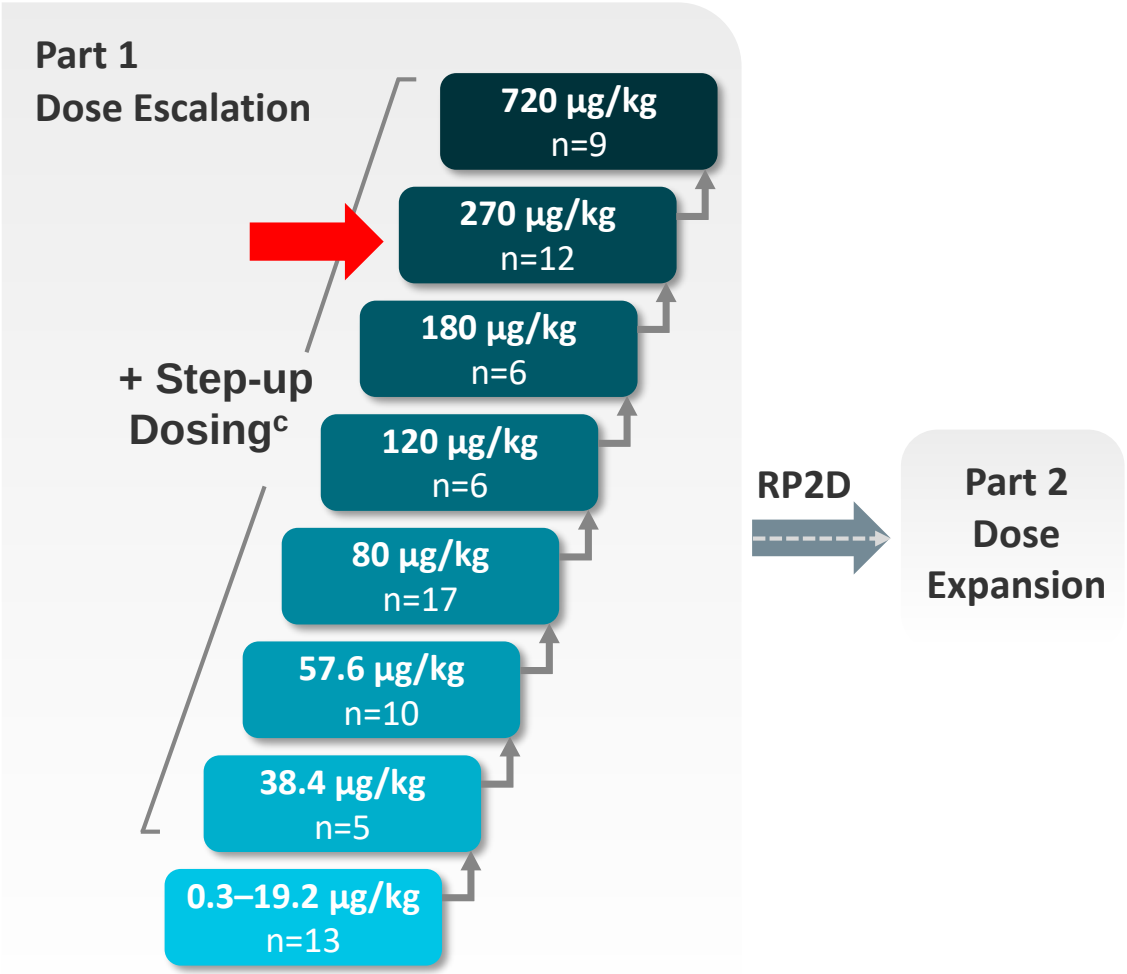
- Measurable MM
- RR or intolerant to established MM therapies
- Hb ≥8 g/dL, platelets[a] ≥75x10^9/L, ANC ≥1.0x10^9/L
- No prior BCMA-targeted therapy

Intravenous Dosing

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



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



Data cutoff: 30 Apr 2020. [a]≥50x10^9/L for patients with ≥50% bone marrow plasma cells, [b]Glucocorticoid, antihistamine, antipyretic, H_2-antagonist, and antiemetic, [c]1-3 step-up doses given within 1 week before full dose. ANC=absolute neutrophil count; Hb=hemoglobin; PD=pharmacodynamics; PK=pharmacokinetics; Q2W=every 2 weeks; RP2D=recommended phase 2 dose

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)

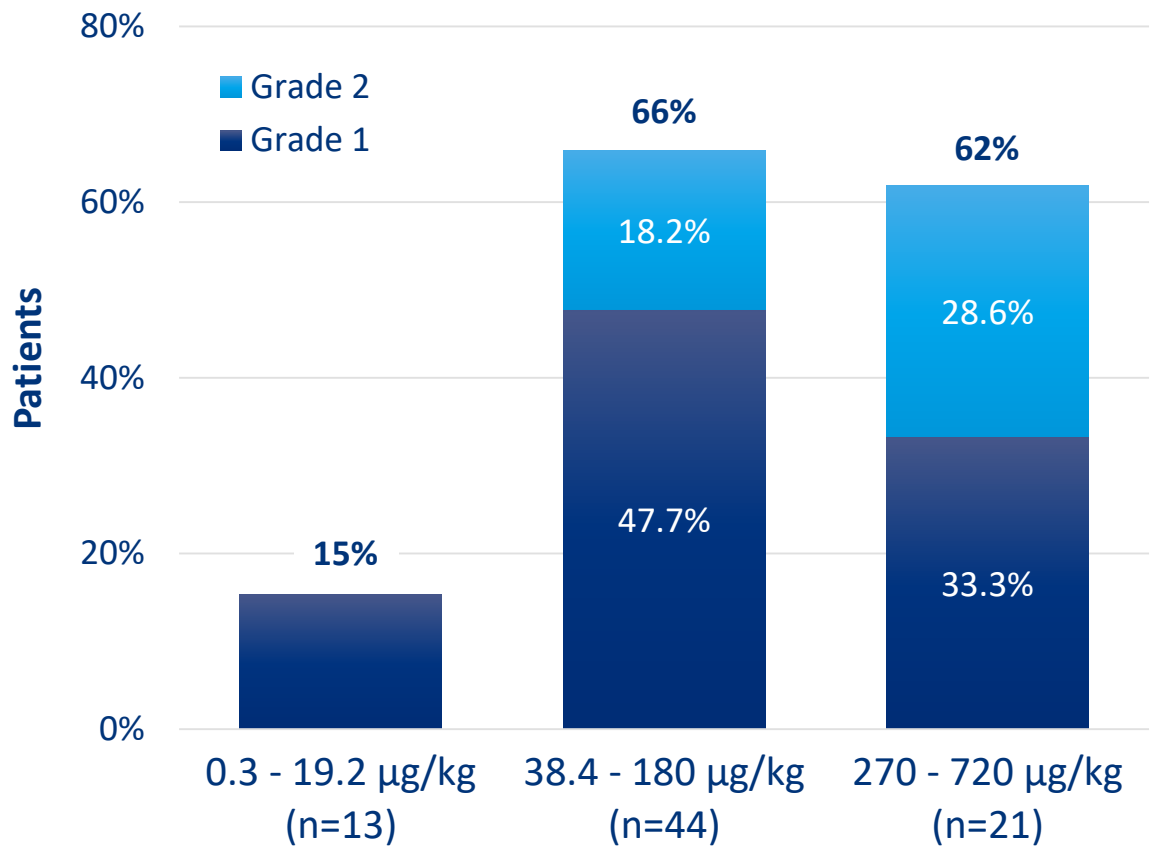
[a]N=75, [b]Based on FISH or karyotype testing and includes del(17p), t(4;14), t(14;16); N=61, [c]PI, IMiD, and anti-CD38, [d]≥2 PIs, ≥2 IMiDs, and an anti-CD38, [e]Includes isatuximab (n=1), [f]Progressive disease within 60 days of last regimen. ISS=International Staging System

Teclistamab: Cytokine Release Syndrome

Cytokine Release Syndrome	Total (N = 78)
Patients with CRS, n (%)	44 (56)
Median time to CRS onset (range), days	1 (1–3)
Median duration of CRS (range), days	1 (1–6)
Patients with supportive measures to treat CRS	42 (54)
Tocilizumab	20 (26)
Steroids	15 (19)
Low flow oxygen	5 (6)
Single low dose vasopressor	1 (1)

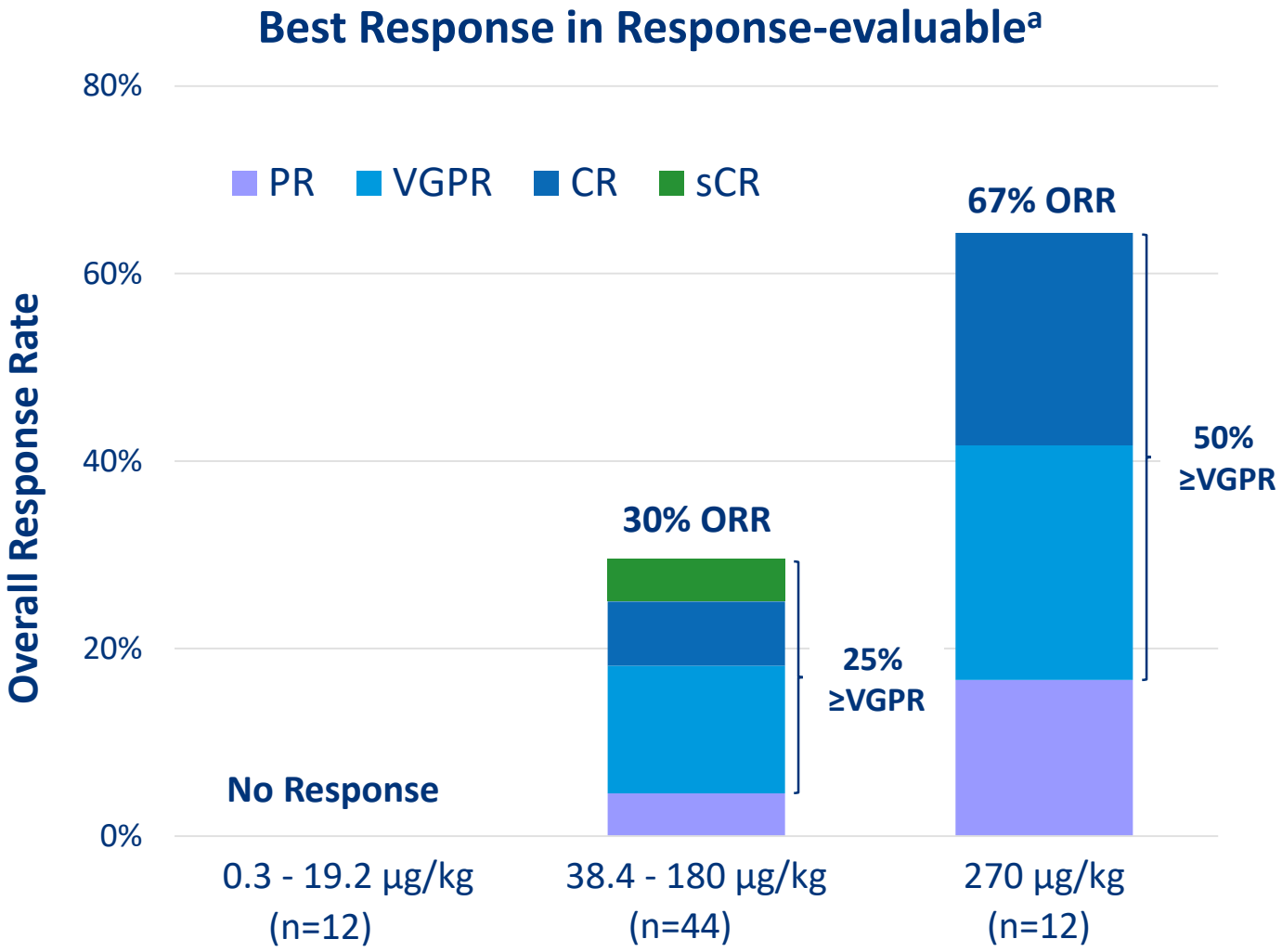
- No high-grade CRS events following step-up dosing
- No treatment discontinuations due to CRS

Maximum CRS Grade by Dose Groups[a]



[a]Graded according to Lee et al. *Blood* 2014;124:188. CRS=cytokine release syndrome

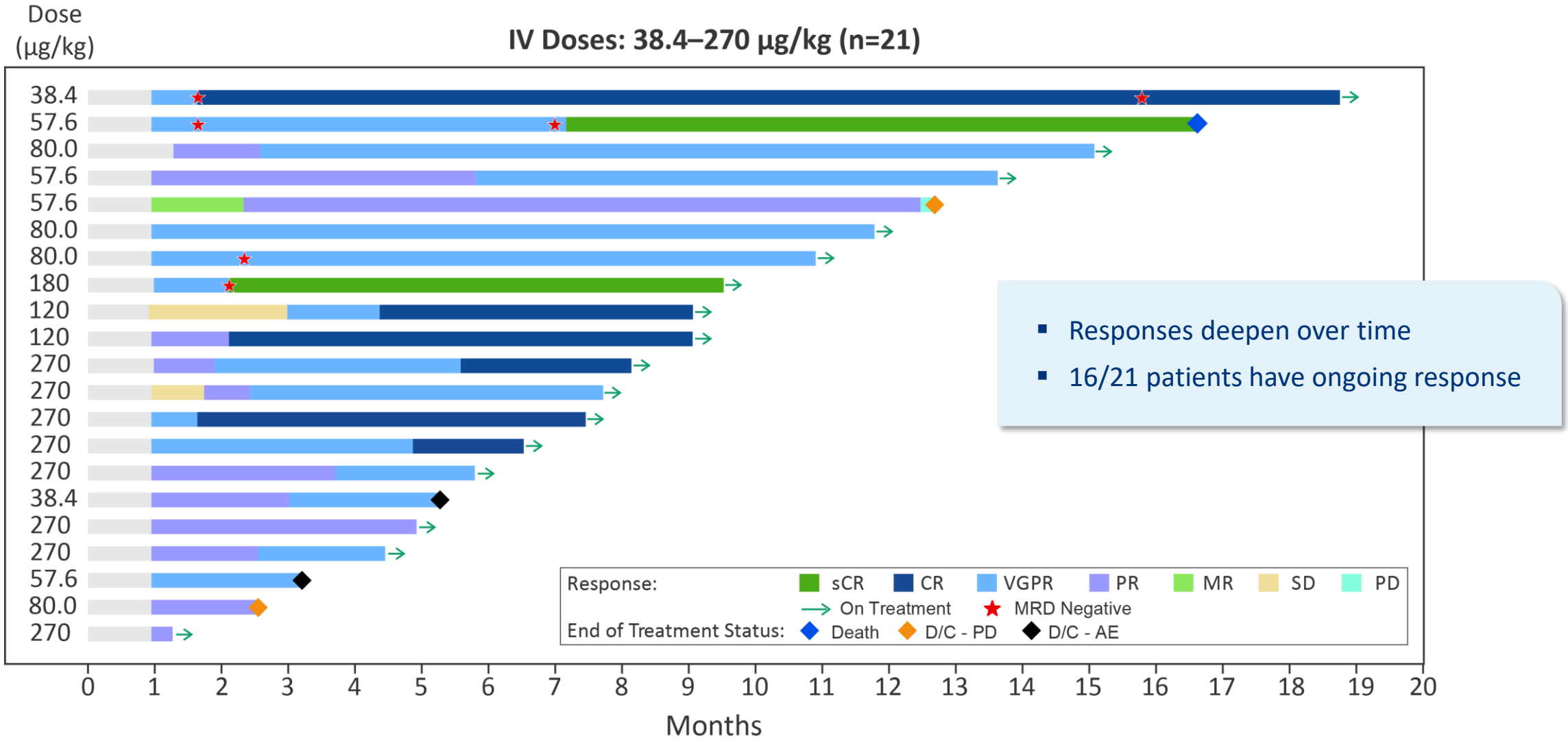
Teclistamab: Overall Response Rate



- 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

Teclistamab: Duration of Response



- Responses deepen over time
- 16/21 patients have ongoing response

D/C=discontinued; PD=progressive disease; MR=minimal response; SD=stable disease

Current investigational approaches and select pipeline agents targeting BCMA

Antibody-drug conjugate		
Company	Asset	Phase
GSK	**belantamab mafodotin**	**III**
AZ/ MedImmune LLC	MEDI2228	I
Celgene/ BMS	CC-99712	I
Heidelberg	HDP-101	PC

CAR-T		
Company	Asset	Phase
BMS/ bluebird	**bb2121**	**III**
	bb21217	I
Janssen/ Legend Biotech	**LCAR-B38M (JNJ-68284528)**	**Ib/II**
BMS/Juno	JCARH125	I/II
Novartis/ Poseida	P-BCMA-101	I/II
Iaso Bio/ Innovent	CT-103A	I

Bispecific Antibodies		
Company	Asset	Phase
Amgen	**AMG-420***	**Ib/II**
	AMG-701†	I/II
Celgene/ BMS	**CC-93269**	**I**
Janssen/ Genmab	**JNJ-64007957**	**I**
Regeneron	REGN5458	I/II
Pfizer	PF-06863135	I

P Moreau Personnal Communication

Belantamab mafodotin, the first off-the-shelf BCMA-targeted immunoconjugate, has a multimodal mechanism[1,2]

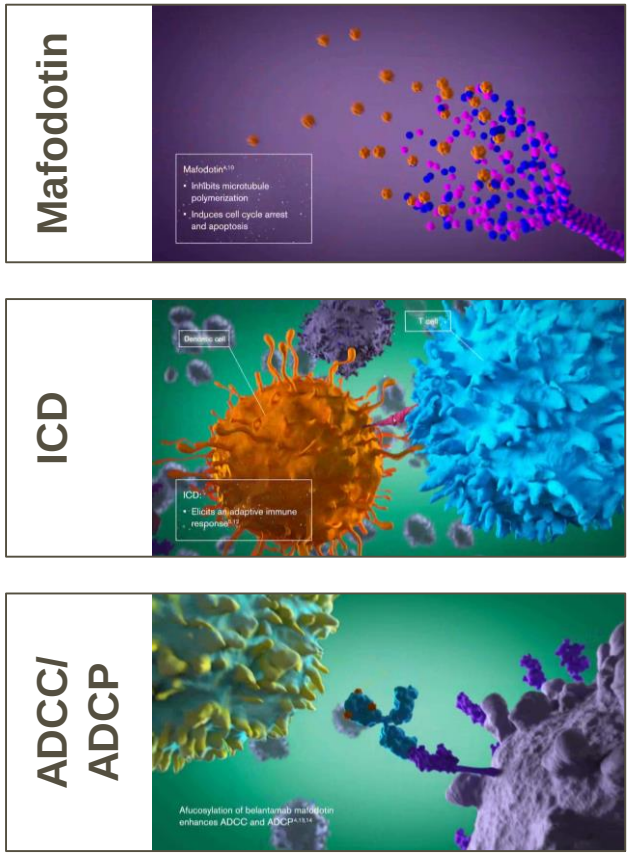
Belantamab mafodotin is an investigational humanized, afucosylated, anti-BCMA monoclonal antibody conjugated to the microtubule inhibitor, mafodotin[1]

It specifically binds to BCMA and eliminates myeloma cells by a multimodal mechanism[1,3]:

- Delivers mafodotin to BCMA-expressing malignant plasma cells and inhibits microtubule polymerization resulting in immune-independent apoptosis
- Induces immunogenic cell death (ICD)
- Enhances antibody-dependent cellular cytotoxicity and phagocytosis (ADCC/ADCP)

Immune-independent mechanism

Immune-dependent mechanisms



BCMA, B-cell maturation antigen.

1. Tai YT et al. *Blood*. 2014;123(20):3128-3138. **2.** Mullard A. *Nat Rev Drug Discov.* 2019;18:481-484. **3.** Montes de Oca R et al. Poster presented at: 24th Congress of the European Hematology Association; June 13-16, 2019; Amsterdam, Netherlands. Poster PF558.

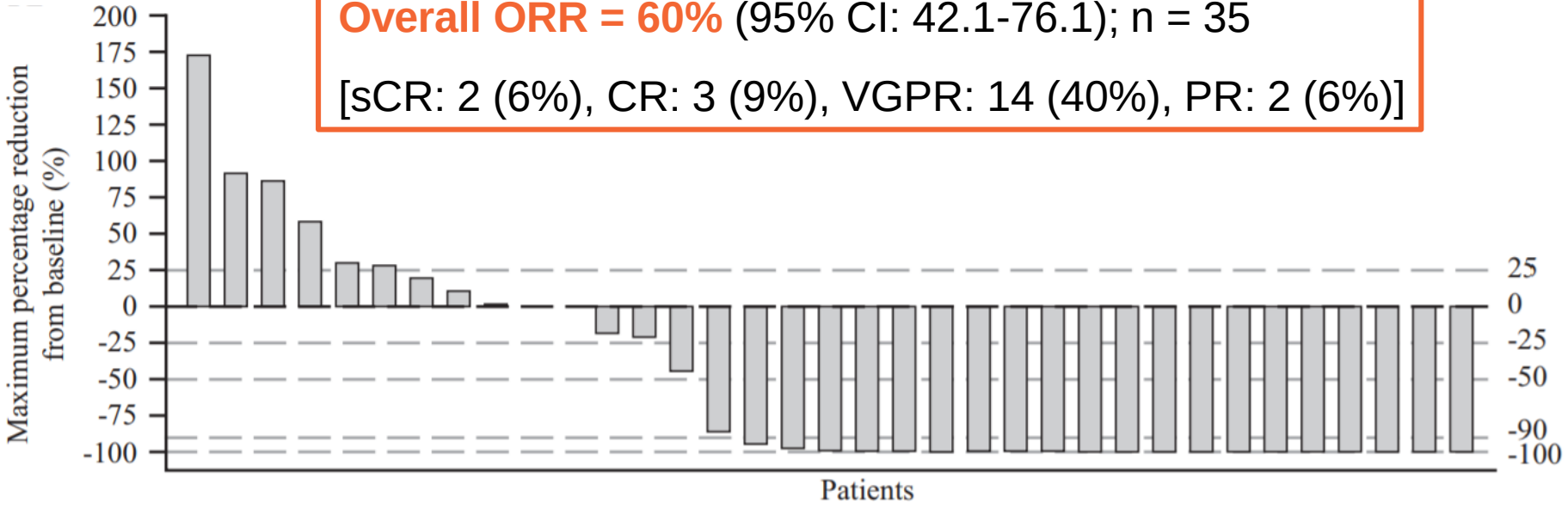
Belantamab Mafodotin: Efficacy in Multiple Myeloma

DREAMM – 1: single-agent dose expansion results

Dose 3.4 mg/kg every 3 weeks, 1hr infusion

Overall ORR = 60% (95% CI: 42.1-76.1); n = 35

[sCR: 2 (6%), CR: 3 (9%), VGPR: 14 (40%), PR: 2 (6%)]



Heavily pretreated - 89% double refractory;
- 34% double + dara refractory

29% with high-risk cytogenetics

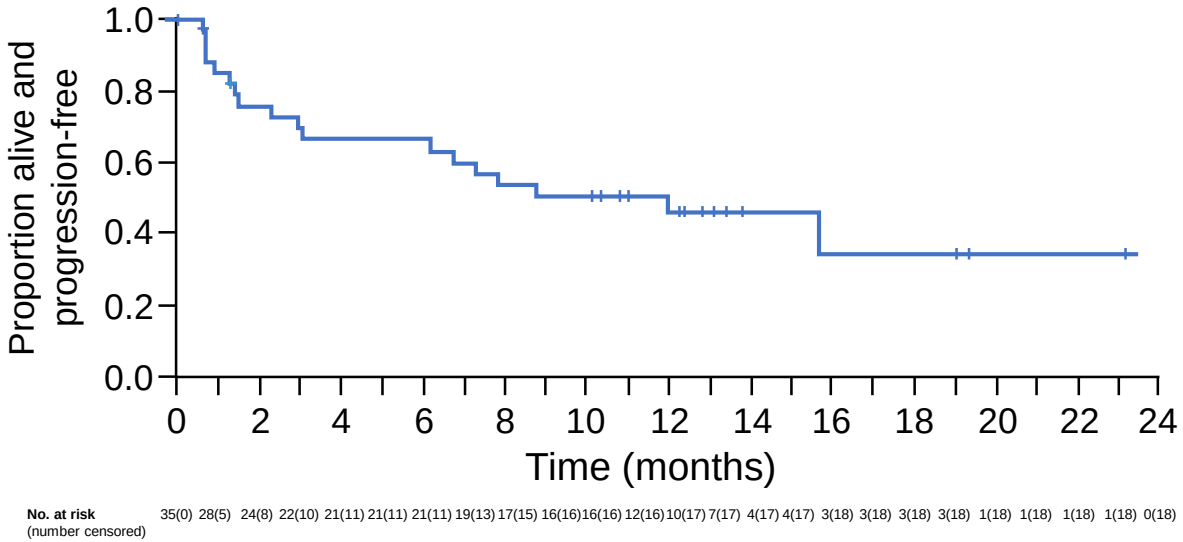
Efficacy in refractory populations

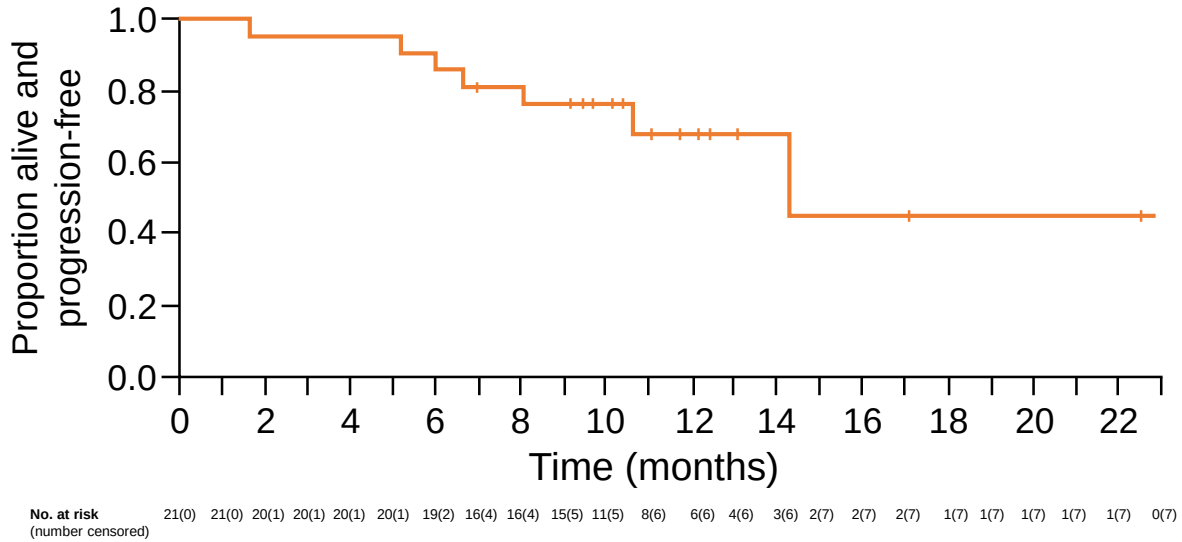
Patients refractory to IMID and PI (n = 32)
ORR: 56.3%
(95% CI: 37.7-73.6)

Patients previously treated with dara AND refractory to IMID and PI (n = 13)
ORR: 38.5%
(95% CI: 13.9-68.4)

Trudel. Blood Cancer J. 2019;9:37.

Belantamab Mafodotin DREAMM-1 Phase I Study (Part 2): PFS and DOR





Progression-free survival

Number of subjects	35
Censored	18 (51%)
Ongoing	17 (49%)
PFS, median (95% CI), months	**12.0 (3.1–NE)**

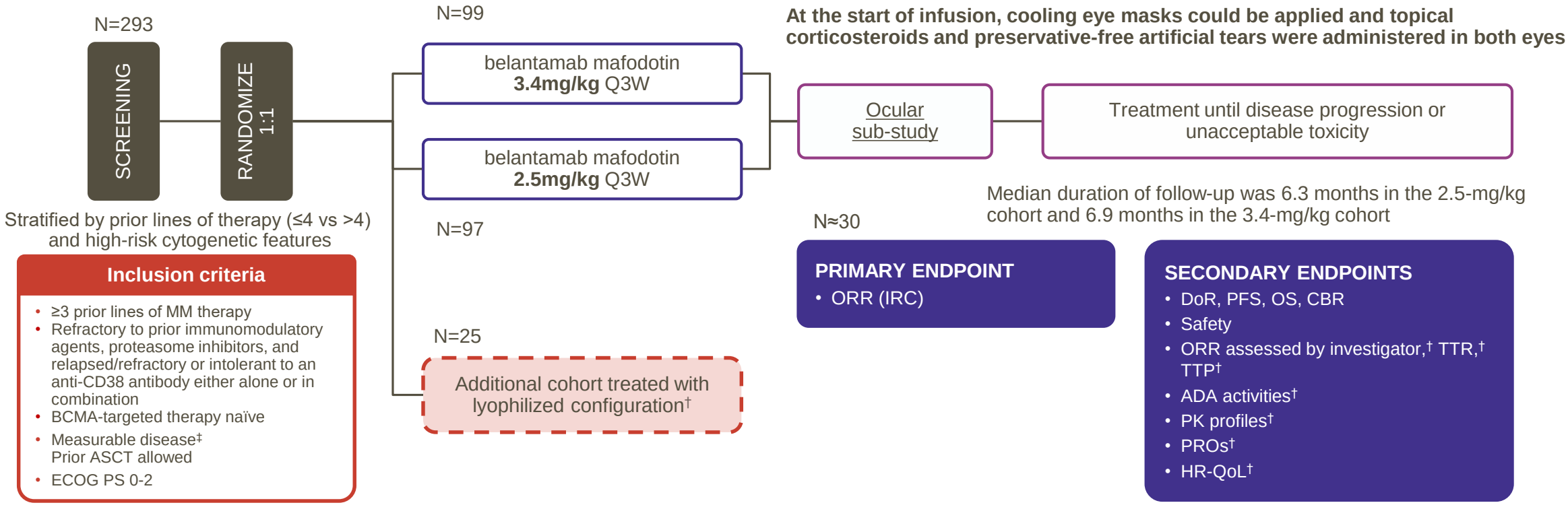
Duration of response

Number of subjects	21
Censored	4 (19%)
Ongoing	17 (81%)
DOR, median (95% CI), months	**14.3 (10.6–NE)**

Trudel. Blood Cancer J. 2019;9:37.

Study design

A phase II, open-label, randomized, 2-dose study in RRMM patients who were refractory to an immunomodulatory drug, proteasome inhibitor, and refractory/intolerant to an anti-CD38 monoclonal antibody



Screening occurred between June 18, 2018, and Jan 2, 2019. *Presence or absence of t(4;14), t(14;16) or 17p13del, or 1q21+. †Will be reported separately.
‡Measurable disease defined as serum myeloma protein (M-protein) ≥0.5 g/dL; urine M-protein ≥200 mg/24h; serum FLC assay: involved FLC level ≥10 mg/dL and an abnormal serum FLC ratio (<0.26 or >1.65).

ADA, anti-drug antibody; ASCT, autologous stem cell transplant; CBR, clinical benefit rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; FLC, free light chain; HR-QoL, health-related quality of life; IRC, independent review committee; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; PRO, patient-reported outcome; RRMM, relapsed/refractory multiple myeloma; TTP, time to progression; TTR, time to response.

1. Lonial S et al. *Lancet Oncol.* 2020;21(2):207-221. **2**. Lonial S 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 29-31, 2020; Virtual Format, USA. Poster 436.

Baseline Characteristics and Treatment Exposure

Similar baseline demographics and disease characteristics were observed in the two dose groups

Patients with ISS stage III disease, extramedullary disease, and high-risk cytogenetic features were well represented in both dose groups

Characteristic	Belamaf 2.5 mg/kg (N=97)	Belamaf 3.4 mg/kg (N=99)
Age, median (IQR), years	65 (60–70)	67 (61–72)
Male, n (%)	51 (53)	56 (57)
ISS stage at screening, n (%)*		
I	21 (22)	18 (18)
II	33 (34)	51 (52)
III	42 (43)	30 (30)
High-risk cytogenetics, n (%)†	41 (42)	47 (47)
Extramedullary disease, n (%)	22 (23)	18 (18)
Number of prior lines of therapy, median (range)	7 (3–21)	6 (3–21)
Refractory to prior immunomodulatory agents and PIs, n (%)	97 (100)	99 (100)

Both dose groups received a median of 3 treatment cycles (range 1–11 in the 2.5 mg/kg group and 1–10 in the 3.4 mg/kg group)

Median dose intensity was 2.47 mg/kg (IQR 1.56–2.50) for the 2.5 mg/kg group; due to the higher incidence of dose modifications, dose intensity was lower than the intended dose for the 3.4 mg/kg dose group (median 2.95 mg/kg; IQR 1.85–3.40)

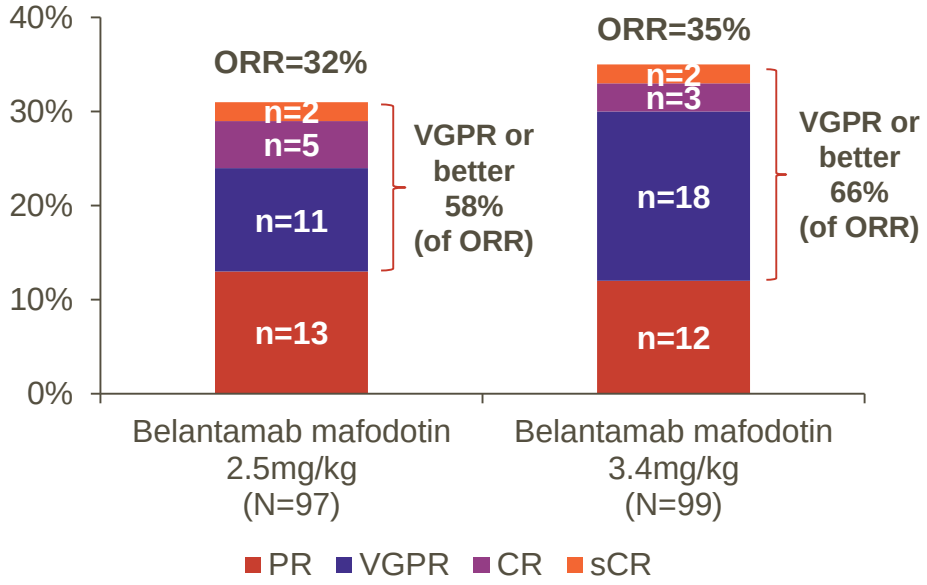
* 1 patient in the belamaf 2.5 mg/kg group had unknown disease stage at screening. †High-risk cytogenetics defined as having any of the following cytogenetic features: t(4;14), t(14;16), 17p13del, or 1q21+.
IQR, interquartile range; ISS, International Staging System; PI, proteasome inhibitor.
Lonial S et al. *Lancet Oncology* 2020;21:207.

Belantamab mafodotin demonstrated a mOS of 14.9 months and a mDOR of 11.0 months in the heavily pretreated 2.5-mg/kg cohort

	belantamab mafodotin 2.5mg/kg (n=97)	belantamab mafodotin 3.4mg/kg (n=99)
mOS	14.9 months (95% CI: 9.9-NR)	14.0 months (95% CI: 10-NR)
mDOR	11.0 months (95% CI: 4.2-NR)	6.2 months (95% CI: 4.8-NR)
mPFS	2.8 months (95% CI: 1.6-3.6)	3.9 months (95% CI: 2.0-5.8)
ORR*	32% (97.5% CI: 21.7-43.6)	35% (97.5% CI: 24.8-47.0)

Duration of follow-up was 13 months in the 2.5-mg/kg and 3.4-mg/kg cohorts

Belantamab mafodotin demonstrated a meaningful ORR



*Best response as assessed by independent review committee using 2016 IMWG criteria. Intent-to-treat population (all randomly assigned patients, regardless of treatment administration). All patients who received ≥2 doses of belantamab mafodotin and completed at ≥1 disease assessment after the second dose were evaluable for response. For response-rate analyses, patients with unknown or missing data were treated as non-responders.

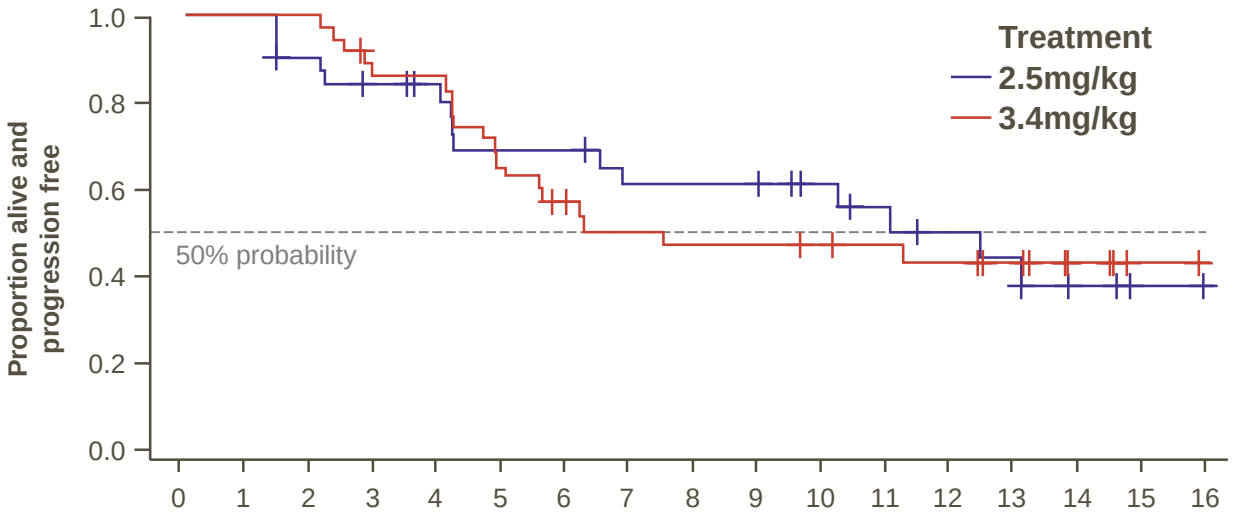
CI, confidence interval; CR, complete response; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; ORR, overall response rate; OS, overall survival; VGPR, very good partial response.

Lonial S 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 29-31, 2020; Virtual Format, USA. Poster 436.

DREAMM-2 13-month follow-up

Belantamab mafodotin demonstrated deep and durable responses in patients who achieved a response

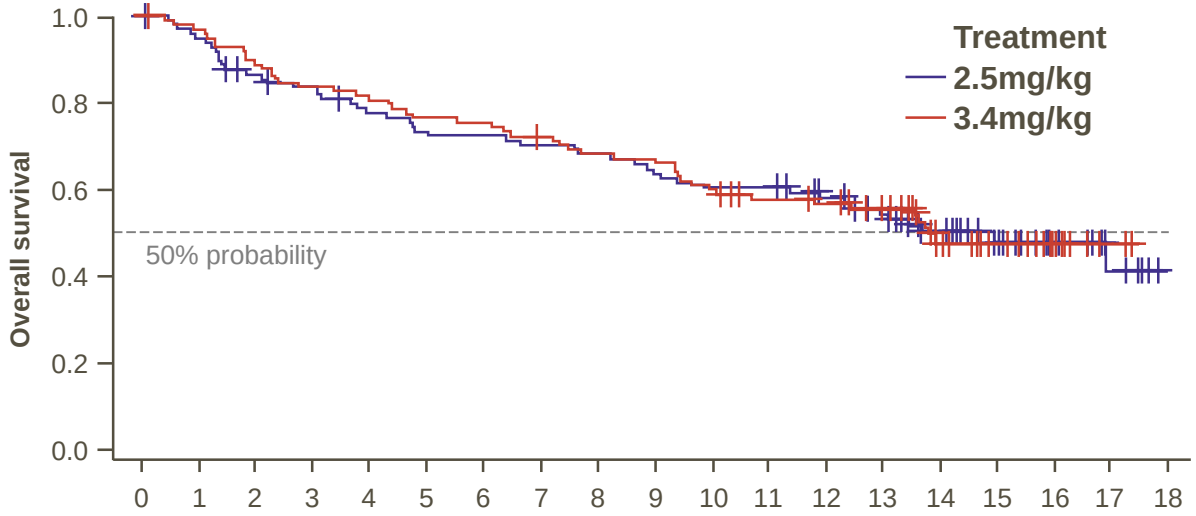
Duration of response



Number at risk (Number of events)

2.5mg/kg	31 (0)	31 (0)	27 (3)	24 (5)	21 (6)	18 (9)	18 (9)	15 (11)	15 (11)	15 (11)	12 (11)	10 (12)	8 (13)	7 (14)	3 (15)	1 (15)	0 (15)	
3.4mg/kg	35 (0)	35 (0)	35 (0)	29 (5)	29 (5)	22 (12)	18 (15)	15 (17)	14 (18)	14 (18)	13 (18)	12 (18)	11 (19)	9 (19)	4 (19)	1 (19)	0 (19)	

Overall survival



Number at risk (Number of events)

2.5mg/kg	97 (0)	91 (5)	81 (13)	77 (16)	71 (21)	67 (25)	66 (26)	64 (28)	62 (30)	59 (33)	55 (37)	55 (37)	49 (39)	43 (42)	31 (45)	22 (46)	13 (46)	6 (47)	0 (47)						
3.4mg/kg	99 (0)	95 (3)	88 (10)	82 (16)	80 (18)	75 (23)	74 (24)	70 (27)	66 (31)	65 (32)	58 (39)	53 (41)	51 (42)	46 (43)	32 (48)	20 (49)	10 (48)	2 (49)	0 (49)						

Lonial S 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 29-31, 2020; Virtual Format, USA. Poster 436.

Treatments and outcomes in trials supporting approved and investigational compounds in MM*

Treatment	Trial	Median # of previous lines of therapy (range)	PR or better response rate	VGPR or better response rate	Median duration of response	Overall survival	Progression-free survival
Pomalidomide/ dexamethasone[1]	MM-003	5 (2-14)	31.5%	5.6%	7.0 months	12.7 months	4.0 months
Carfilzomib[2]	PX-171-003-A1	5 (1-20)	23.7%	5.4%	7.8 months	15.6 months	3.7 months
Daratumumab[3]	GEN-501 SIRIUS	5 (2-14)	31.1%	13.5%	7.6 months	20.1 months	4.0 months
Selinexor/ dexamethasone†[4]	STORM	7 (3-18)	26.2%	6.6%	4.4 months	8.6 months	3.7 months
Belantamab mafodotin (2.5mg/kg)‡[5]	DREAMM-2	7 (3-21)	32.0%	18.6%	**11.0 months§**	**14.9 months§**	2.8 months

***Indirect comparisons should not be performed in the absence of true head-to-head trials. Cited data do not necessarily establish superior or comparable safety or efficacy. †Data as of 5/26/2020. ‡Belantamab mafodotin is an investigational agent. §Median duration of follow-up was 13 months.[5]**

MM, multiple myeloma; RRMM, relapsed/refractory multiple myeloma.

1. Miguel JS et al. *Lancet Oncol.* 2013;14(11):1055-1066. **2.** Siegel DS et al. *Blood.* 2012;120(14):2817-2825. **3.** Usmani SZ et al. *Blood.* 2016;128(1):37-44. **4.** Chari et al. *N Engl J Med.* 2019;381(8):727-728. **5.** Lonial S et al. Poster presented at: American Society of Clinical Oncology Annual Meeting; May 29-31, 2020; Virtual Format, USA. Poster 436.

Most common adverse events observed were keratopathy and thrombocytopenia

Adverse events*	Any grade, n (%)		Grades ≥ 3, n (%)	
	2.5mg/kg n=95	3.4mg/kg n=99	2.5mg/kg n=95	3.4mg/kg n=99
Any event	93 (98)	99 (100)	80 (84)	83 (84)
Keratopathy (MECs)†	68 (72)	76 (77)	44 (46)	42 (42)
Thrombocytopenia‡	36 (38)	56 (57)	21 (22)	32 (32)
Anemia	NR	NR	20 (21)	27 (27)
Lymphocyte count decreased	NR	NR	12 (13)	7 (7)
Neutropenia§	NR	NR	10 (11)	17 (17)
Pneumonia	NR	NR	6 (6)	11 (11)

Keratopathy (MECs) defined as changes to the superficial corneal epithelium[1]

Infusion-related reactions[1,2]

- 20 patients (21%) in the 2.5-mg/kg group
- 16 patients (16%) in the 3.4-mg/kg group
- Preinfusion prophylaxis not mandatory per protocol

*Events reported based on CTCAE v4.03 (with the exception of MECs) in the safety population (all patients who received ≥1 dose of study treatment). †Represents severe MECs based on corneal examination findings and changes in BCVA from baseline (does not include patient-reported symptoms). ‡Includes preferred terms thrombocytopenia, decreased platelet count, and cerebral hemorrhage (2 cases within the 3.4-mg/kg group only). §Includes preferred terms neutropenia, febrile neutropenia, and neutrophil count decreased.

MEC, microcyst-like epithelial change; NR, not reported.

1. Lonial S 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 29-31, 2020; Virtual Format, USA. Poster 436.
2. Lonial S et al. *Lancet Oncol.* 2020;21(2):207-221.

Summary of Adverse Events

Belamaf Demonstrated a Manageable Safety Profile With No New Safety Concerns Identified

Number of patients with event (safety population), n (%)*	Belamaf 2.5 mg/kg (N=95)				Belamaf 3.4 mg/kg (N=99)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Keratopathy or corneal epithelium changes†	41 (43)	26 (27)	0	0	53 (54)	20 (20)	1 (1)	0
Thrombocytopenia‡	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

The most common Grade 1-2 adverse event was keratopathy; the most common Grade 3–4 adverse events were keratopathy, thrombocytopenia, and anaemia

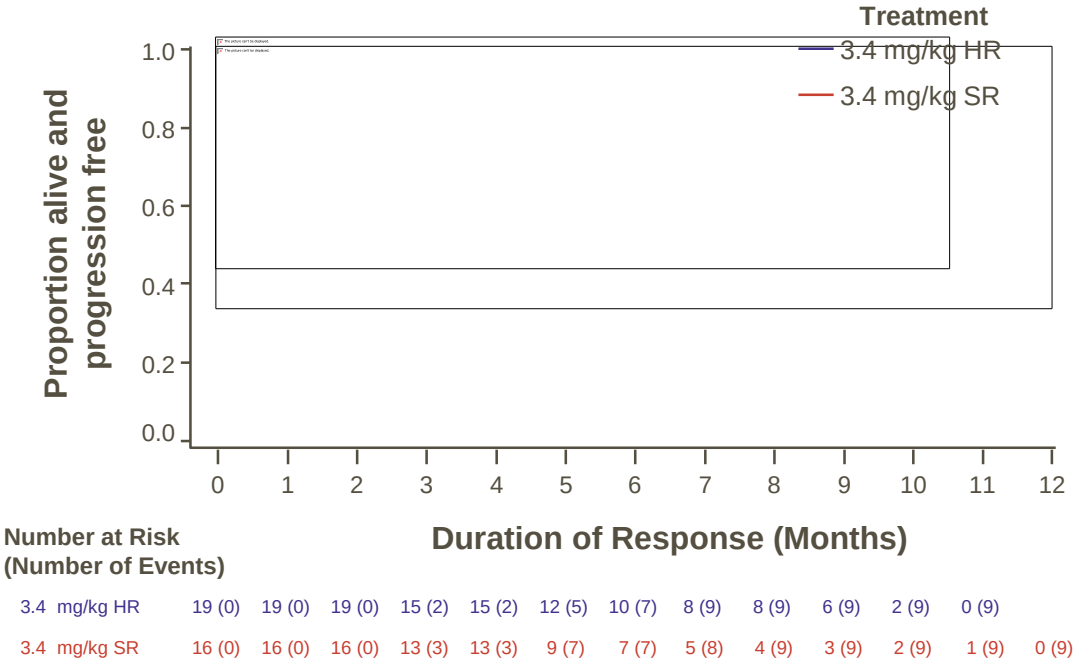
Listed in order of decreasing frequency of Any Grade events in the 2·5-mg/kg cohort. *Events reported based on Common Terminology Criteria for Adverse Events criteria v4.03 in the safety population (including all patients who received at least one dose of trial treatment). †Keratopathy or corneal epithelium changes (considered an adverse event of special interest [AESI]) were observed by ophthalmic examination. ‡Thrombocytopenia (considered an AESI) includes preferred terms thrombocytopenia, decreased platelet count, and cerebral haemorrhage. §Blurred vision includes preferred terms vision blurred, diplopia, visual acuity reduced and visual impairment. ¶Infusion-related reactions (considered an AESI) includes preferred terms infusion-related reaction, pyrexia, chills, diarrhoea, nausea, asthenia, hypertension, lethargy, tachycardia, vomiting, cough and hypotension occurring within 24 hours of infusion. **Dry eye includes preferred terms dry eye, ocular discomfort, eye pruritus and foreign body sensation in eye. ††Neutropenia includes neutropenia, febrile neutropenia and neutrophil count decreased. Lonial S et al. *Lancet Oncology* 2020;21:207.

Patients with HR cytogenetics maintained deep and durable responses comparable to those with standard risk cytogenetics

High risk (HR) cytogenetics are comprised of patients with any of **t(4;14), t(14;16), 17p13del,** or **1q21+** features and have a **poor prognosis**

	belantamab mafodotin			
	2.5mg/kg (n=97)		3.4mg/kg (n=99)	
	HR	SR	HR	SR
ORR, %	27	34	40	31
mDOR, %	NR	NR	6.2	6.2
mOS, mo	9.4	NR	13.8	9.7

DOR in HR and SR cytogenetics receiving 3.4mg/kg belantamab mafodotin[1]

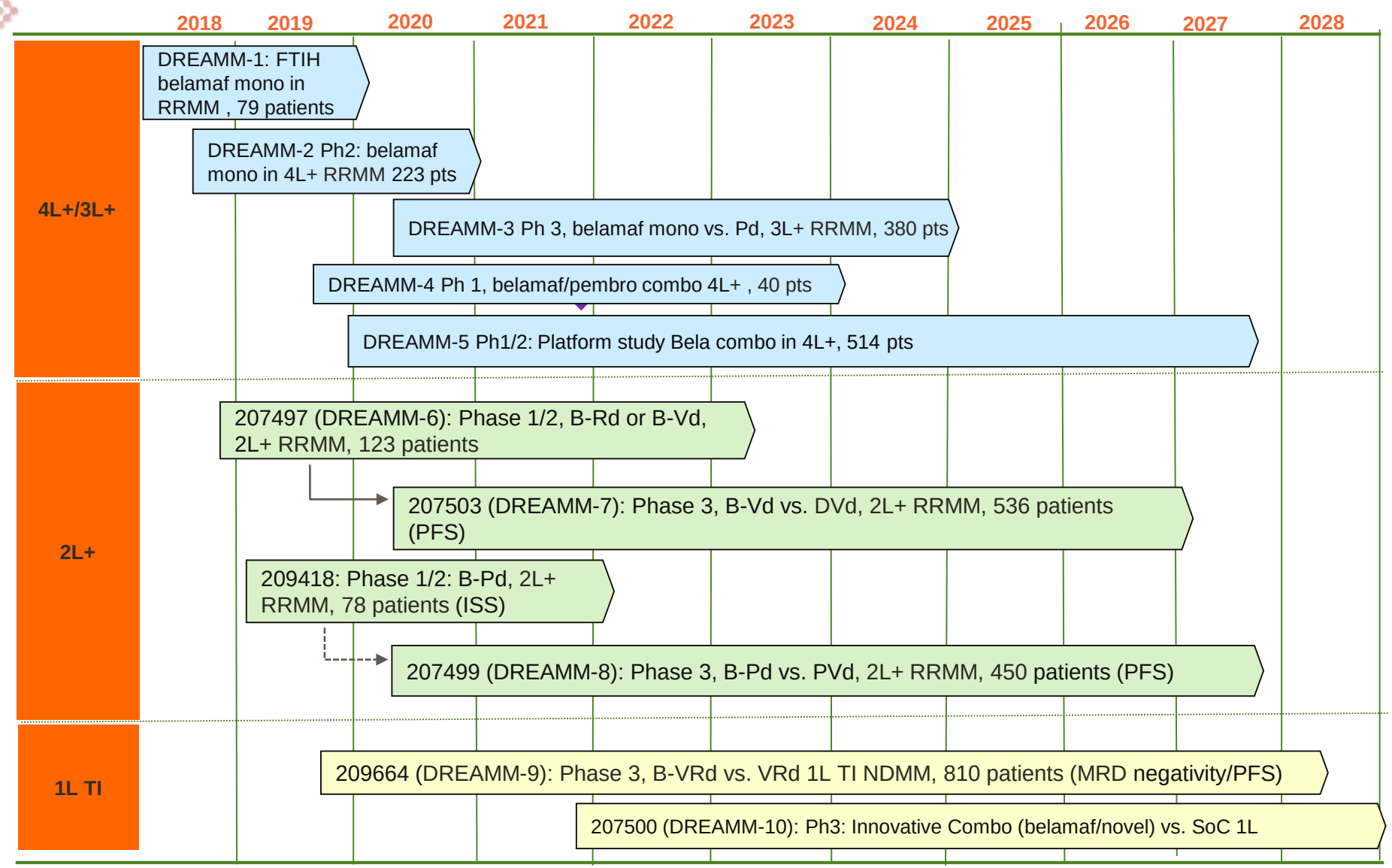


Belantamab mafodotin may represent an important new treatment in patients with RRMM and HR cytogenetics

DOR, duration of response; HR, high risk; mDOR; median duration of response; SR, standard risk; ORR, overall response rate; mo, months; mOS, median overall survival.

Cohen AD et al. Poster presented at: American Society of Clinical Oncology Annual Meeting; May 29-31, 2020; Virtual Format, USA. Poster 441.

Belantamab mafodotin development programme (selected studies)



B=belantamab mafodotin
P=Pomalidomide
R=Lenalidomide
V=Bortezomib
D=Daratumumab
d=Dexamethasone

Timelines may be subject to change

This information is intended for healthcare providers only. Compounds may be investigational. Inclusion in this presentation does not imply regulatory approval for these compounds or indications.

Belamaf = belantamab mafodotin; FTIH= First time in human; ISS= Investigator-sponsored study; 1L= First line; 2L= Second Line; 3L= Third Line; 4L= Fourth Line; Mono= Monotherapy; MRD= Minimal residual disease; NDMM= Newly diagnosed multiple myeloma; PFS= Progression-free survival; RRMM= Relapsed/refractory multiple myeloma; TI= Transplant ineligible

Belantamab mafodotin, Blenrep*

est approuvé par FDA & EMA

Sur la base de l’essai DREAMM-2

Conclusions

- BCMA : cible idéale

- Bispécifiques : prometteurs en ph1; développement sous-cutané; phase 2 en cours; rôle dans maintenance ? Consolidation ?

- Blenrep* : approuvé par EMA pour maladie avancée; développement en phase 3 dans des stades plus précoces

Electronic Certificate

Version: 1 . 0

Document Number: SE-FR-BLM-PPTX-200003

Document Name: Agents ciblants BCMA, hors CAR-T

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: 11-Sep-2020 08:55:12 GMT+0000