VCC VIRTUAL Challenging Case Clinic

Multiple Myeloma SERIES

New Approvals and Advanced Targets in MM

September 21, 2022

University of Nebraska Medical Center

Bio Ascend™

Introductions

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Disclosures

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Consulting Fees: Amgen Inc., Bristol-Myers Squibb Company, Celgene Corporation, GlaxoSmithKline LLC, Janssen Oncology, Karyopharm Therapeutics, Merck & Co., Novartis

Joshua Richter, MD

Speakers' Bureau: Bristol-Myers Squibb, Janssen, Sanofi
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Consulting: Bristol-Myers Squibb, GlaxoSmithKline, Oncopeptides, Secura Bio

Planning Committee

The following planning committee members have nothing to disclose:
UNMC: Brenda Ram, CMP, CHCP
Bio Ascend: Chloe Dunnam; Danielle Kashou; Tisheeka Graham-Steed, PhD; Kraig Steubing

Learning Objectives

- ✓ Evaluate best available evidence regarding the treatment of newly diagnosed and relapsed/refractory MM
- ✓ Assess the implications of emerging clinical trial data regarding therapeutic approaches for patients with MM
- ✓ Develop strategies to optimize the outcomes of complicated MM cases

Reminders!

- ✓ Visit www.OncologyCaseClinic.com to register for upcoming webinars

VCC VIRTUAL Challenging Case Clinic

Multiple Myeloma SERIES

New Approvals and Advanced Targets in Multiple Myeloma

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Bio Ascend™

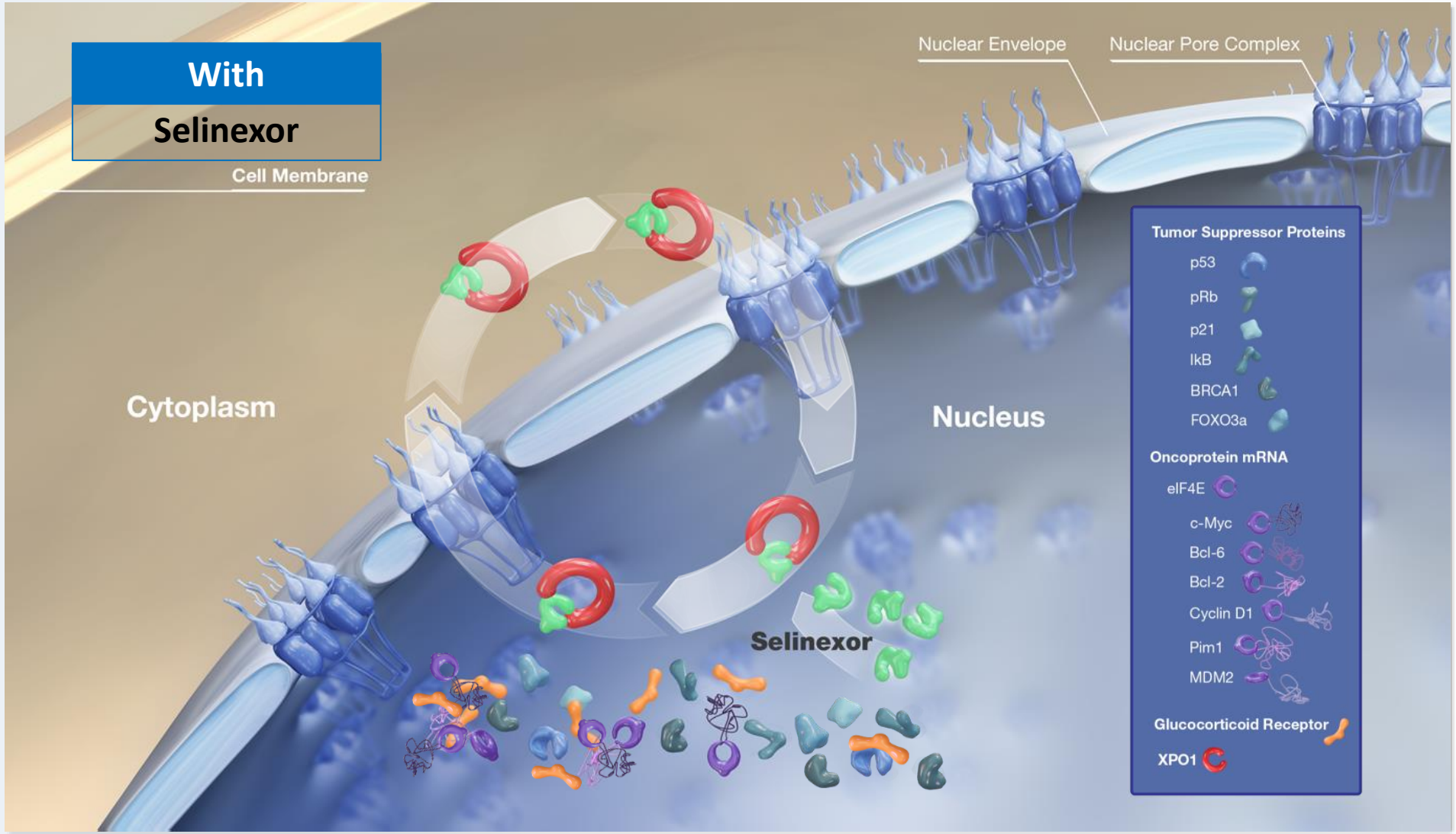
Choosing Therapies for Myeloma

IMiDs	Proteasome Inhibitors	Anthracyclines	Alkylators	Steroids	Antibodies	SINE	ADC	CAR-T	*Bispecific Ab*
Thalidomide	**Bortezomib**	**Liposomal doxorubicin**	**Melphalan**	**Dexamethasone**	**Elotuzumab**	**Selinexor**	**Belantamab**	**Ide-cel**	***Teclistamab***
Lenalidomide	**Carfilzomib**	**Doxorubicin**	**Cyclo-phosphamide**	**Prednisone**	**Daratumumab**			**Cilta-cel**	
Pomalidomide	**Ixazomib**		**Bendamustine**	**Methyl-prednisolone sodium succinate**	**Isatuximab**				

Selinexor Mechanism of Action

First in Class, Oral Selective Inhibitor of Nuclear Export (SINE)

FDA Approved 7/3/19



XPO1 in MM

- Transports >200 proteins from the nucleus to cytoplasm
- Expression increased in MM vs normal PC/MGUS/SMM
- Correlates with shorter survival and increased bone disease

Selinexor

- Inhibits XPO1 through reversible covalent modification
- Currently FDA approved in combination with dexamethasone based on the **STORM** study
- Selinexor in combinations with bortezomib and dexamethasone was recently filed with FDA based on the **BOSTON** study
- Ongoing **STOMP** study looking into combinations of Selinexor with other anti-myeloma agents

Tai et al *Leukemia* 2014.
Schmidt et al *Leukemia* 2013.

Pivotal STORM Part II: Study Design

Oral Selinexor 80 mg + **Dexamethasone** 20 mg

Selinexor / dexamethasone twice weekly (Days 1 and 3) until Disease Progression

Patient Population:

- MM previously treated with bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, an alkylator, and glucocorticoids.
- Disease documented to be refractory to ≥1 PI, ≥1 IMiD, daratumumab, glucocorticoid and last line of therapy

Primary Endpoint:

- Overall Response Rate (ORR)

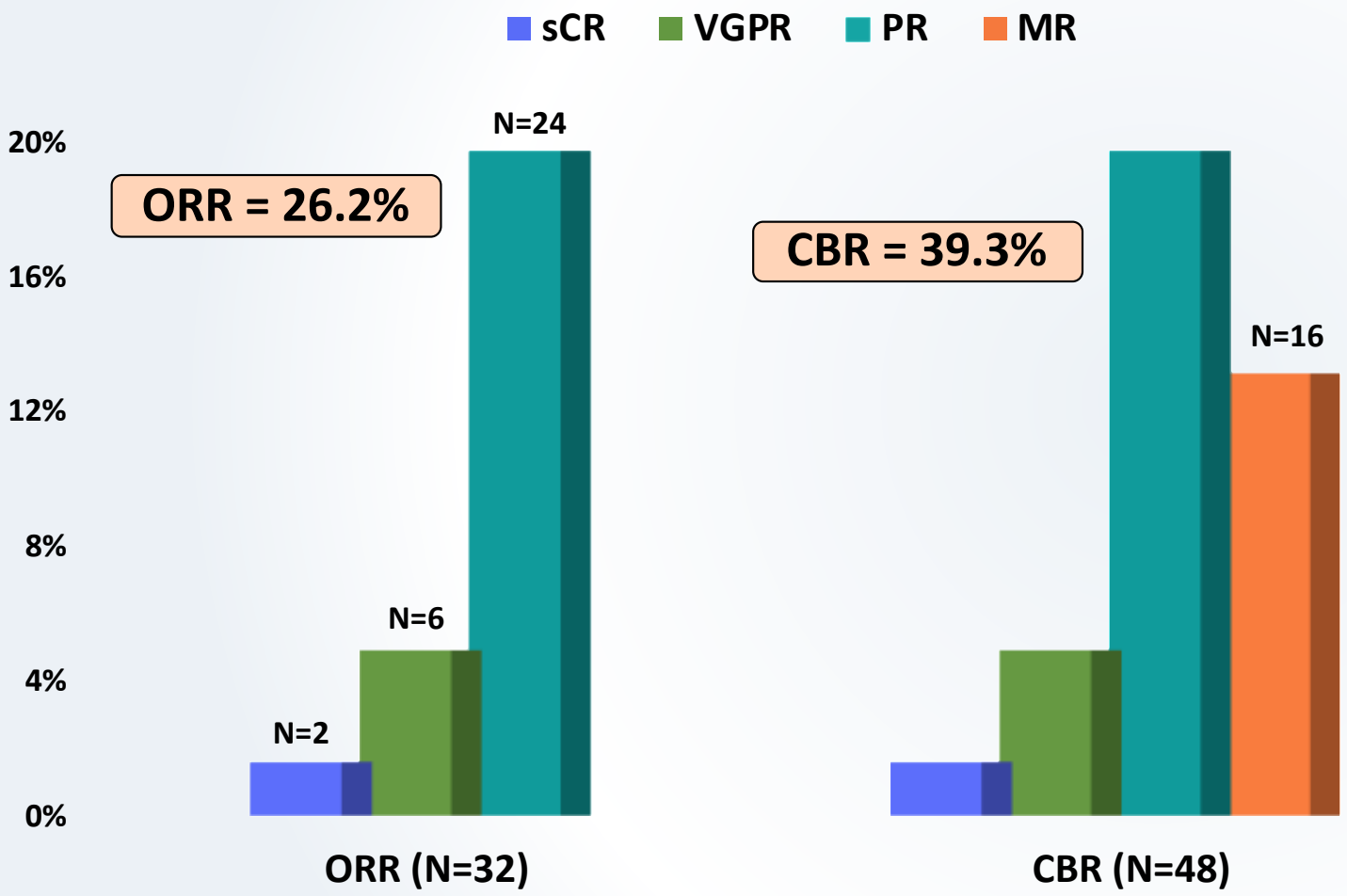
Secondary Endpoints:

- Duration of Response (DOR)
- Clinical benefit rate (CBR)
- Overall survival (OS)
- Progression free survival (PFS)
- Safety

Key Inclusion/Exclusion:

- Creatinine clearance ≥ 20 mL/min
- ANC ≥ 1,000/mm^3
- Platelets ≥ 75,000/mm^3
- (if bone marrow plasma cell > 50%; plt > 50,000/mm^3)
- Hemoglobin ≥ 8.5 g/dL

Efficacy

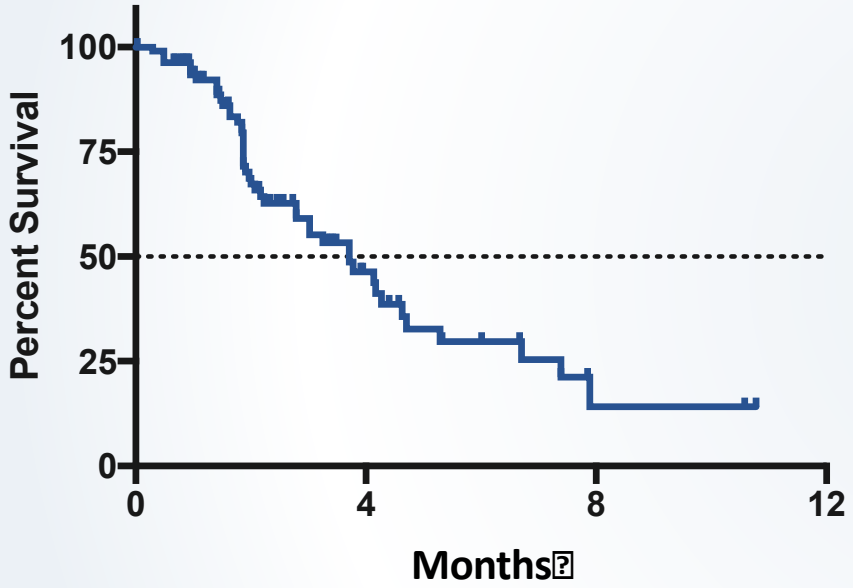


- In penta-refractory MM patients with a median of 7 prior treatment regimens, **ORR of 26.2%,** including **2 stringent CRs**
  - **sCRs were MRD negative** at 10^{-6} and 10^{-4}
- Median time to response was 1 month (range 1 to 14 weeks) and duration of response was 4.4 months
- 16 patients (13.1%) progressed (PD) on therapy and 10 patients (8.2%) were not evaluable for response

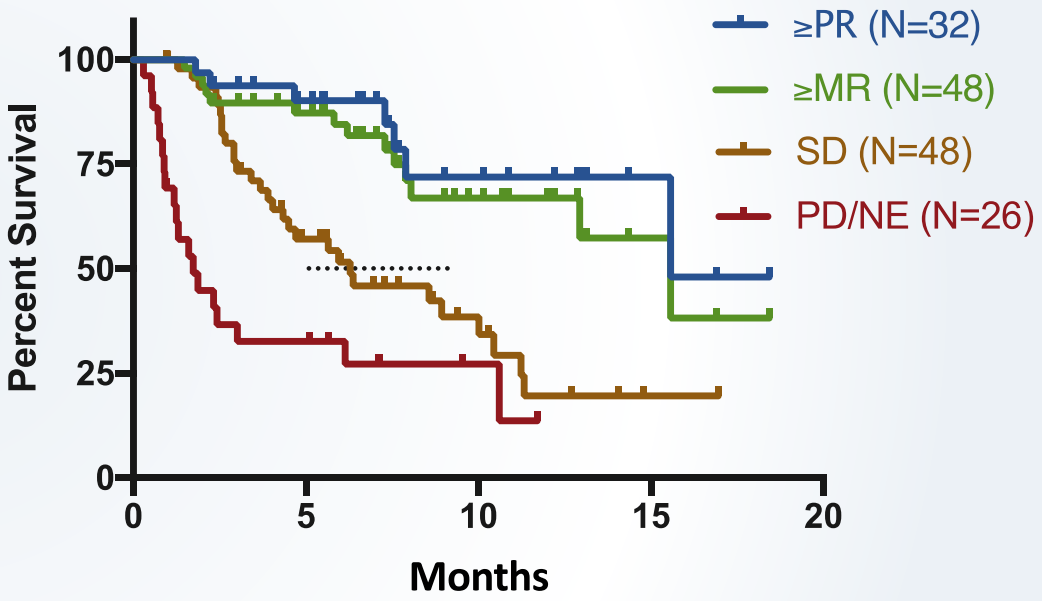
Responses as of August 17, 2018 were adjudicated according to the IMWG criteria *(Kumar, 2016)* by an independent review committee (IRC)

Progression Free and Overall Survival

Progression Free Survival – All

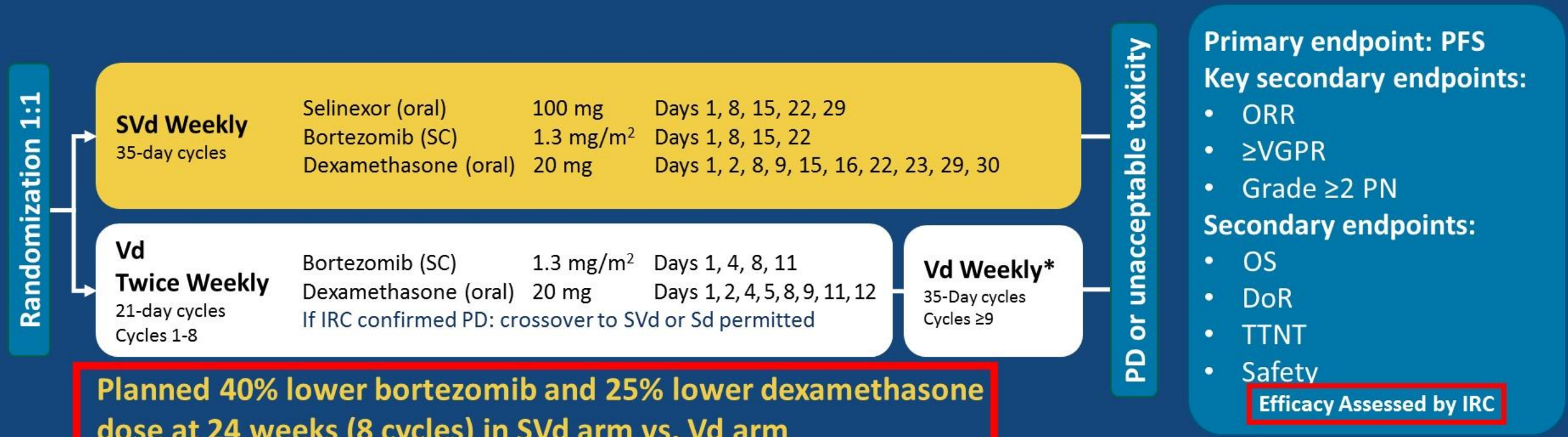


Overall Survival – Groups



Category	All Patients (N=122)	≥ PR (N=32)	≥ MR (N=48)	SD (N=48)	PD/NE (N=26)
Median PFS	3.7 Months	5.3 Months	4.6 Months	2.2 Months	1.1 Months
Median OS	8.6 Months	15.6 Months	15.6 Months	6.3 Months	1.7 Months

BOSTON Trial: Phase 3, Global, Randomized, Open Label, Controlled Study in Patients With MM who Had Received 1–3 Prior Therapies



Planned 40% lower bortezomib and 25% lower dexamethasone dose at 24 weeks (8 cycles) in SVd arm vs. Vd arm

Stratification:
- Prior PI therapies (Yes vs No)
- Number of prior anti-MM regimens (1 vs >1)
- R-ISS stage at study entry (Stage III vs Stage I/II)

5HT-3 prophylactic recommended in SVd arm

CR= complete response, DoR = duration of response, IMWG = International Myeloma Working Group, IRC = Independent Review Committee, OS = overall survival, PD = progressive disease, PFS = progression free survival, PR = partial response, PN = peripheral neuropathy, sCR = stringent complete response, TTNT = time to next therapy, VGPR = very good partial response. PFS defined as: Time from date of randomization until the first date of progressive disease, per IMWG response criteria, or death due to any cause, whichever occurred first, as assessed by IRC. ORR: Any response ≥PR (ie, PR, VGPR, CR, or sCR) based on the IRC's response outcome assessments, according to IMWG response criteria (Kumar et al. Lancet oncology 2016). All changes in MM disease assessments were based on baseline MM disease assessments.
*Vd weekly dosing and schedule for cycles≥ 9 as per SVd arm description.

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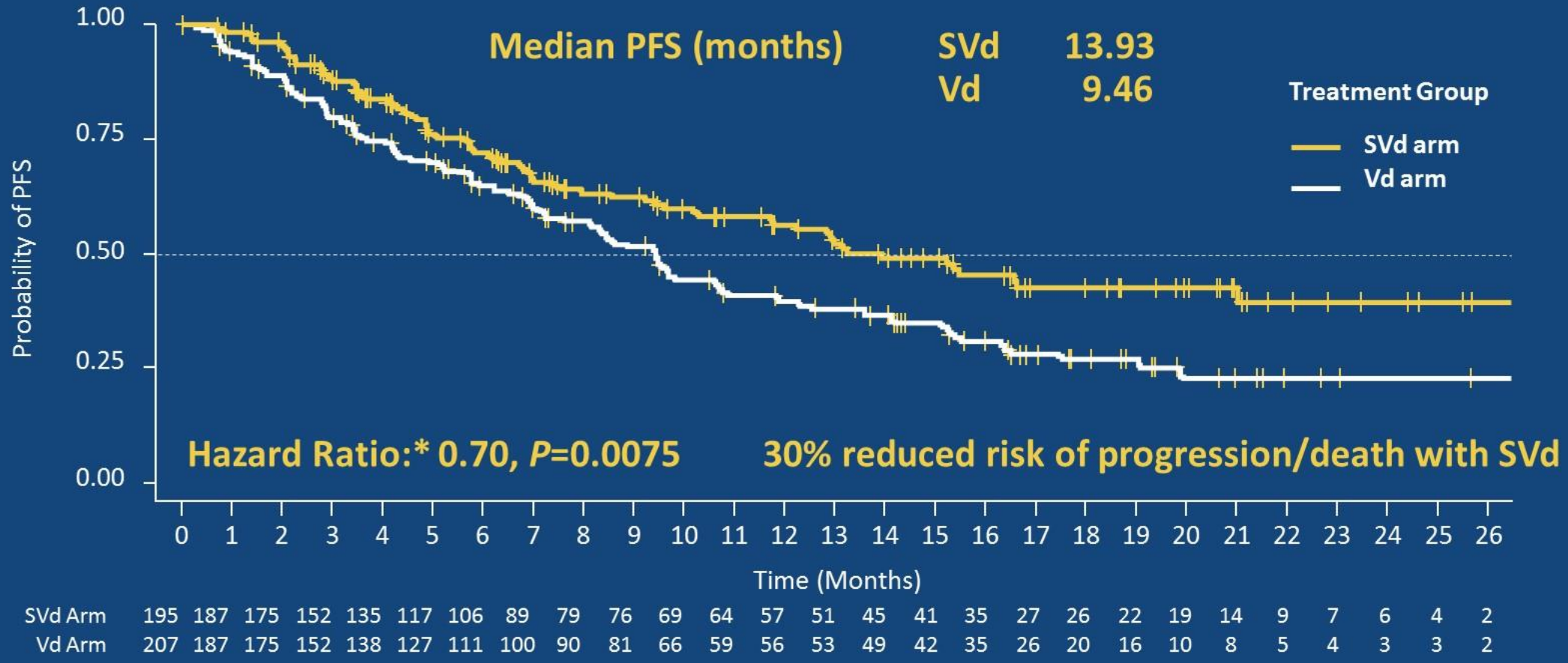
BOSTON Trial: PFS Significantly Longer With SVd Compared to Vd

Early and Sustained PFS Benefit (Assessed by IRC)



SVd Arm	195	187	175	152	135	117	106	89	79	76	69	64	57	51	45	41	35	27	26	22	19	14	9	7	6	4	2
Vd Arm	207	187	175	152	138	127	111	100	90	81	66	59	56	53	49	42	35	26	20	16	10	8	5	4	3	3	2

Intention-to-treat (ITT) population N=402, Data cut-off February 18, 2020
*Hazard Ratio 95% CI=0.53–0.93 one-sided *P* value.

Median follow-up: 13.2 and 16.5 months in SVd and Vd arms, respectively.

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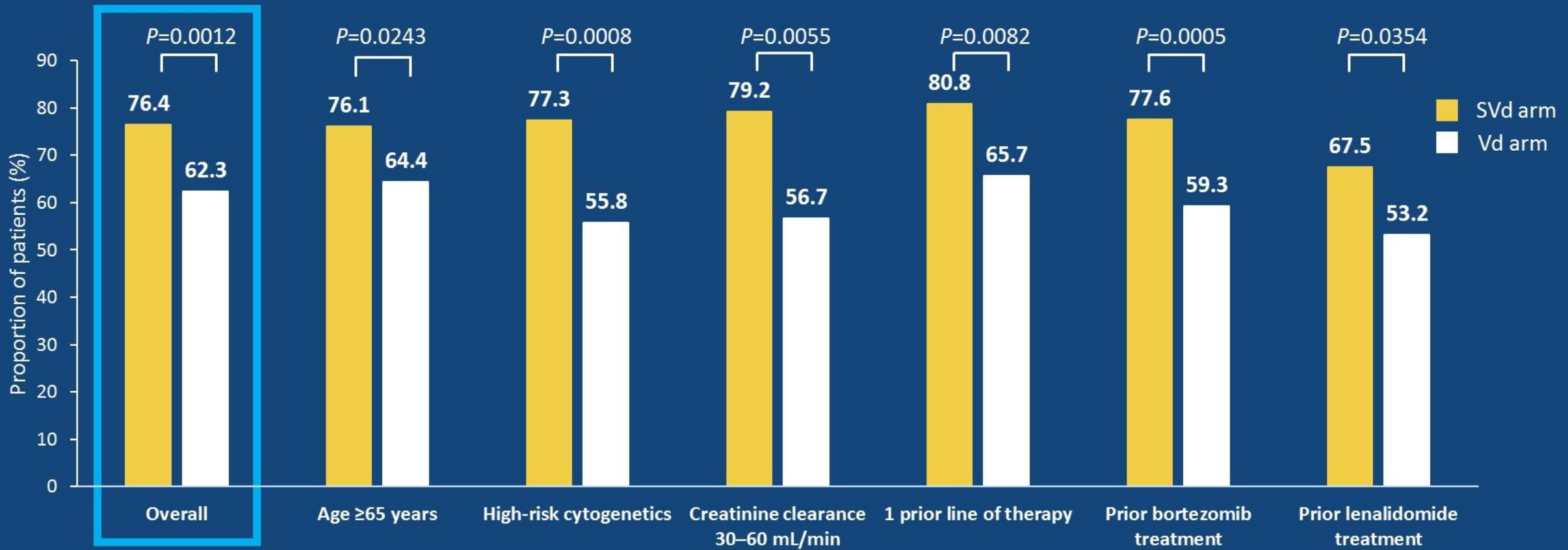
SVd Was Associated With a Significantly Higher ORR Overall and Across Subgroups



One-sided *P* values for the Cochran-Mantel-Haenszel Test based on unstratified model. Data cut-off February 18, 2020.
Overall response, based on Independent Review Committee's response outcome assessments, according to IMWG response criteria (Kumar et al. Lancet Oncology 2016).
All changes in MM disease assessments were based on baseline MM disease assessments.

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STOMP: Study Overview & Objectives

Selinexor and backbone Treatments Of multiple Myeloma Patients (STOMP): multi-center, open-label, randomized dose escalation (Phase 1) and expansion (Phase 2) study to assess the MTD, efficacy, and safety of selinexor in patients with RRMM

Phase 1 (Dose Escalation) Objectives

Primary: to determine the MTD for selinexor QW or BIW when combined with SOC MM therapies

Secondary: to determine the RP2D schedule for each arm independently

XPd
Pomalidomide + Dexamethasone

XVd
Bortezomib + Dexamethasone

XKd
Cohort 1 & 2
Carfilzomib + Dexamethasone

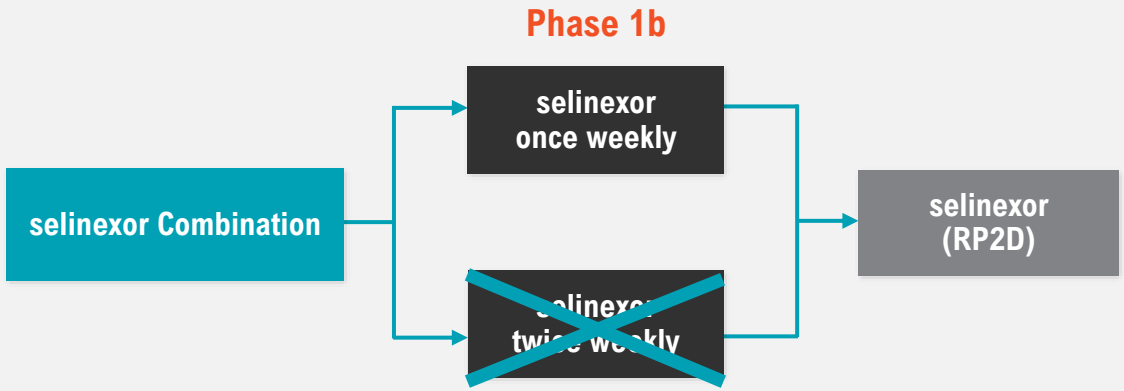
XNd
Ixazomib + Dexamethasone

XRd RRMM and NDMM
Lenalidomide + Dexamethasone

XDd
Daratumumab + Dexamethasone

XPVd
Pomalidomide + Bortezomib + Dexamethasone

XPEd
Pomalidomide + Elotuzumab + Dexamethasone



BIW, twice weekly; MTD, maximum tolerated dose; QW, once weekly; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma; SOC, standard of care.

1. Bahlis N, et al. Blood Dec 2018 132(24):2546-2554. 2. Gasparetto C, et al. XDd Presented at EHA annual meeting, 2019. 3. Chen C, et al. XPd Presented EHA annual meeting, 2019 4. Gasparetto C, et al. XKd Presented at EHA annual meeting, 2019 5. White D, et al. XRd Presented at ASH Annual Meeting, December 2017 6. Data on file. Karyopharm Therapeutics, Inc.

Selinexor, Daratumumab and Dexamethasone (XDd) in Patients with R/R Multiple Myeloma

RP2D: selinexor 100mg QW, dara 16mg/kg QW, dex 40mg QW – 4 week cycles
ORR: 73%, mPFS 12.5 mos

FINDINGS:

Safety Results:

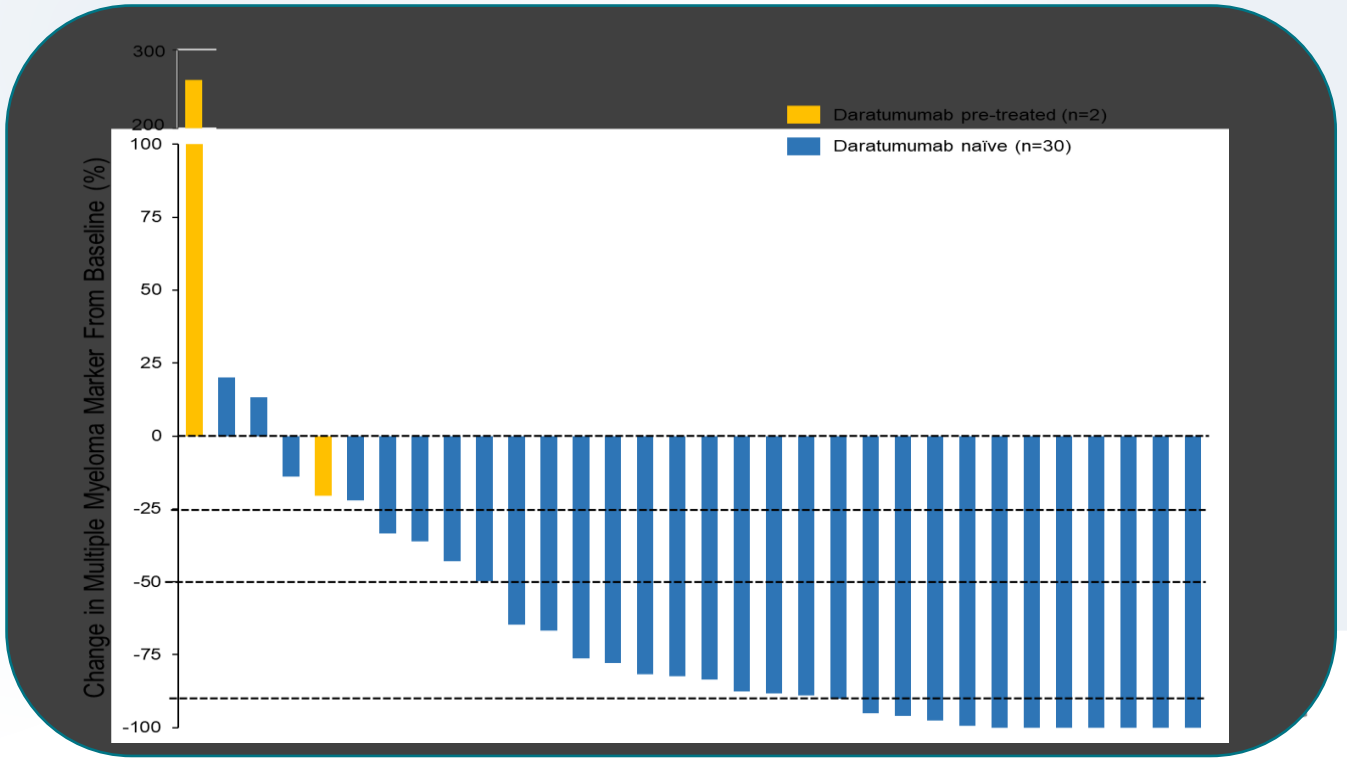
- Common TRAEs in RP2D patients [All Grades, Grade 3 / 4]: thrombocytopenia (70.6%, 47%), fatigue (61.8%, 17.6%), nausea (70.6%,8.8%), anemia (61.8%, 32.4%), and neutropenia (50%, 26.5%).
- 2 DLTs were reported in the 60 mg BIW cohort:
  - Grade 3 thrombocytopenia and Grade 2 fatigue requiring dose reduction in selinexor to 100 mg QW

Efficacy Results (based on 32 evaluable patients)**:**

- **ORR:** 69% (11, **VGPR;** 11**, PR**)
- **mPFS**: 12.5 months at both dose schedules

- ORR and CBR were 73% and 87% respectively in daratumumab-naïve patients
- Median progression-free survival was 12.5 months in all patients who had median of 3 prior therapies

Category	N*	ORR (%)	VGPR (%)	PR‡ (%)	CBR (%)	MR‡ (%)	SD (%)	PD (%)
All	32	22 (69%)	11 (34%)	11 (34%)	26 (81%)	4 (13%)	5 (16%)	1 (3%)
Daratumumab Naïve	30	22 (73%)	11 (37%)	11 (37%)	26 (87%)	4 (13%)	4 (13%)	--
RP2D	29	20 (69%)	9 (31%)	11 (38%)	24 (83%)	4 (14%)	4 (14%)	1 (3%)



Gasparetto et al., *STOMP XDd*; ASCO POSTER #8510, 2020

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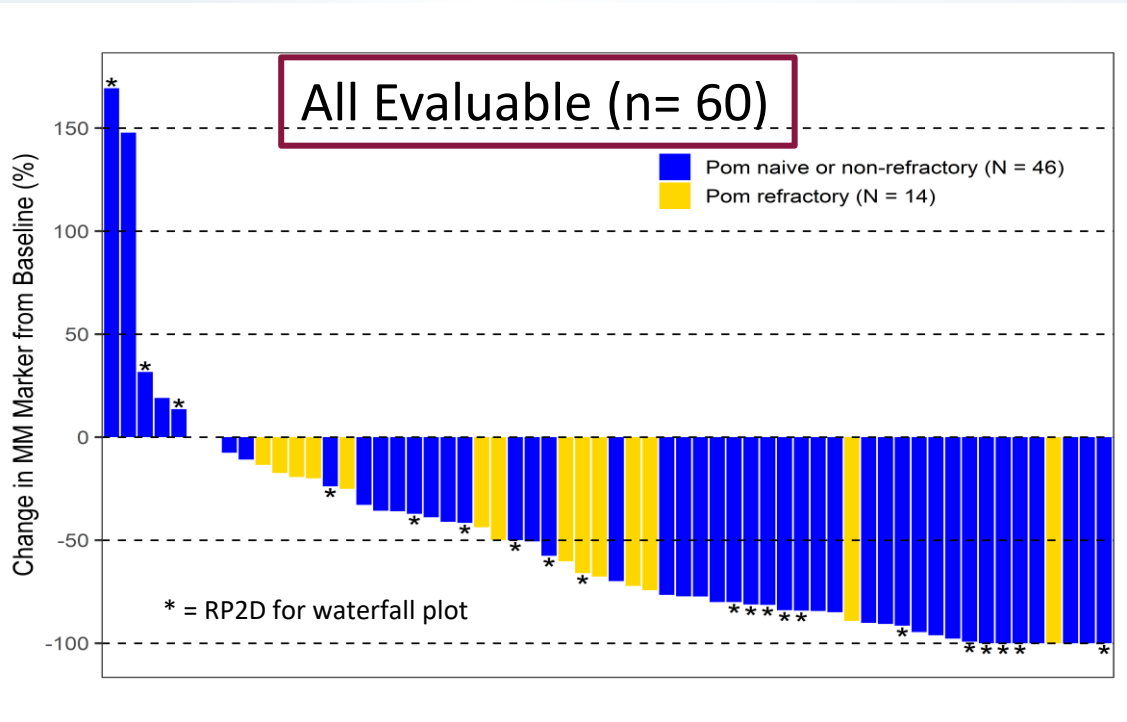
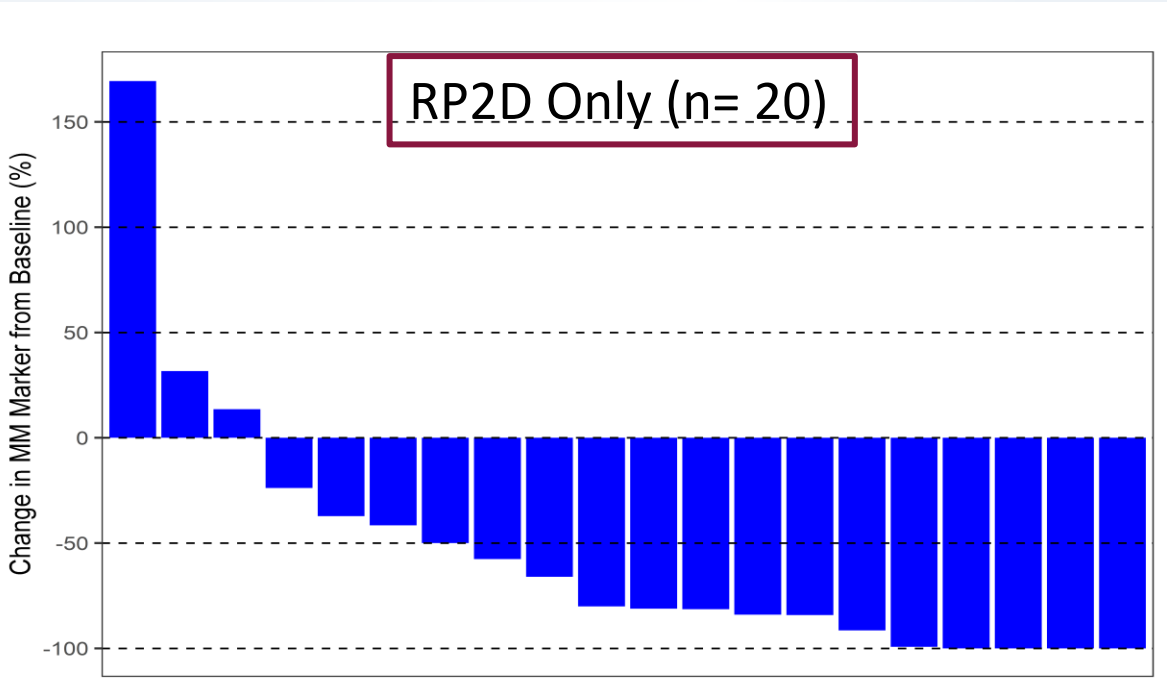
XPd Efficacy

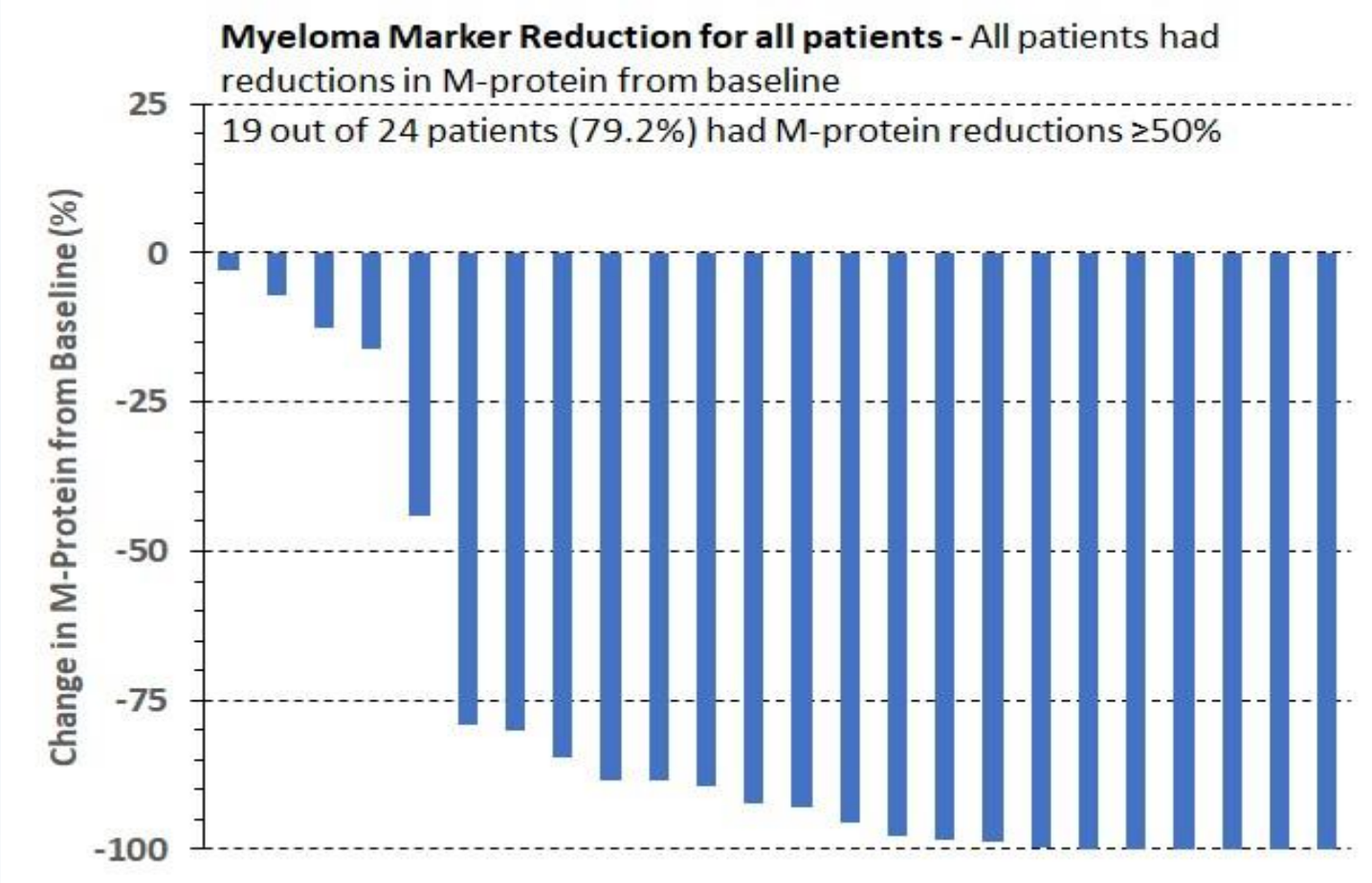
Best Responses in Evaluable SPd Patients									
	N	ORR (%)	CBR (%)	CR (%)	VGPR (%)	PR (%)	MR (%)	SD (%)	PD (%)
Pom naïve or non-refractory	46	25 (54.3)	33 (71.7)	1 (2.2)	†9 (19.6)	‡15 (32.6)	*8 (17.4)	10 (21.7)	3 (6.5)
Pom Refractory	14	5 (35.7)	9 (64.3)	--	1 (7.1)	4 (28.6)	4 (28.6)	5 (35.7)	-
RP2D: Selinexor 60 mg QW + Pom 4 mg	20	12 (60.0)	15 (75.0)	0	†6 (30.0)	‡6 (30.0)	*3 (15.0)	3 (15.0)	2 (10.0)





XKd Results in Deep Responses in heavily pretreated patients: (100% Velcade Exposed; 95% prior Len; 67% prior Pom; 63% prior Dara)

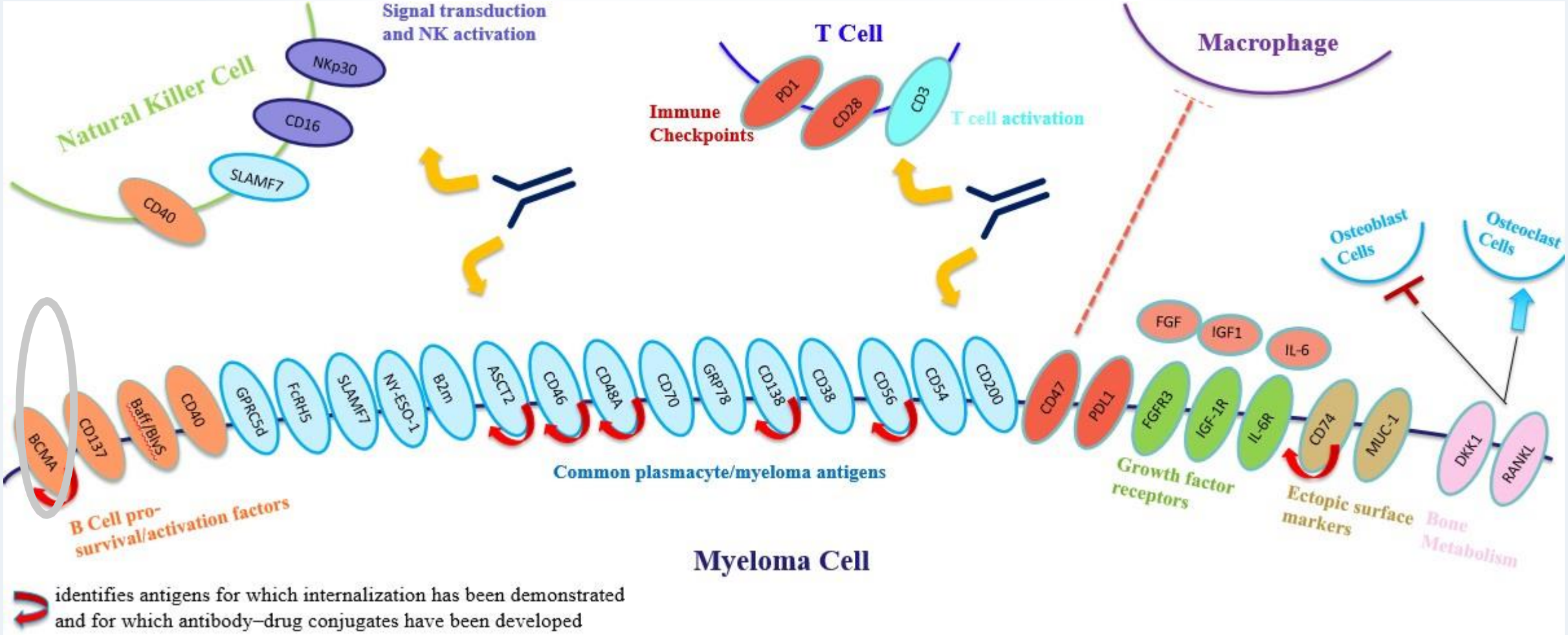
	Best Response (%) n=24
CR (%)	5 (20.8%)
VGPR (%)	8 (33.3%)
PR (%)	5 (20.8%)
MR (%)	1 (4.2%)
SD (%)	5 (20.8%)
ORR	18 (75%)
CBR	19 (79.2%)



(as of October 1, 2020)

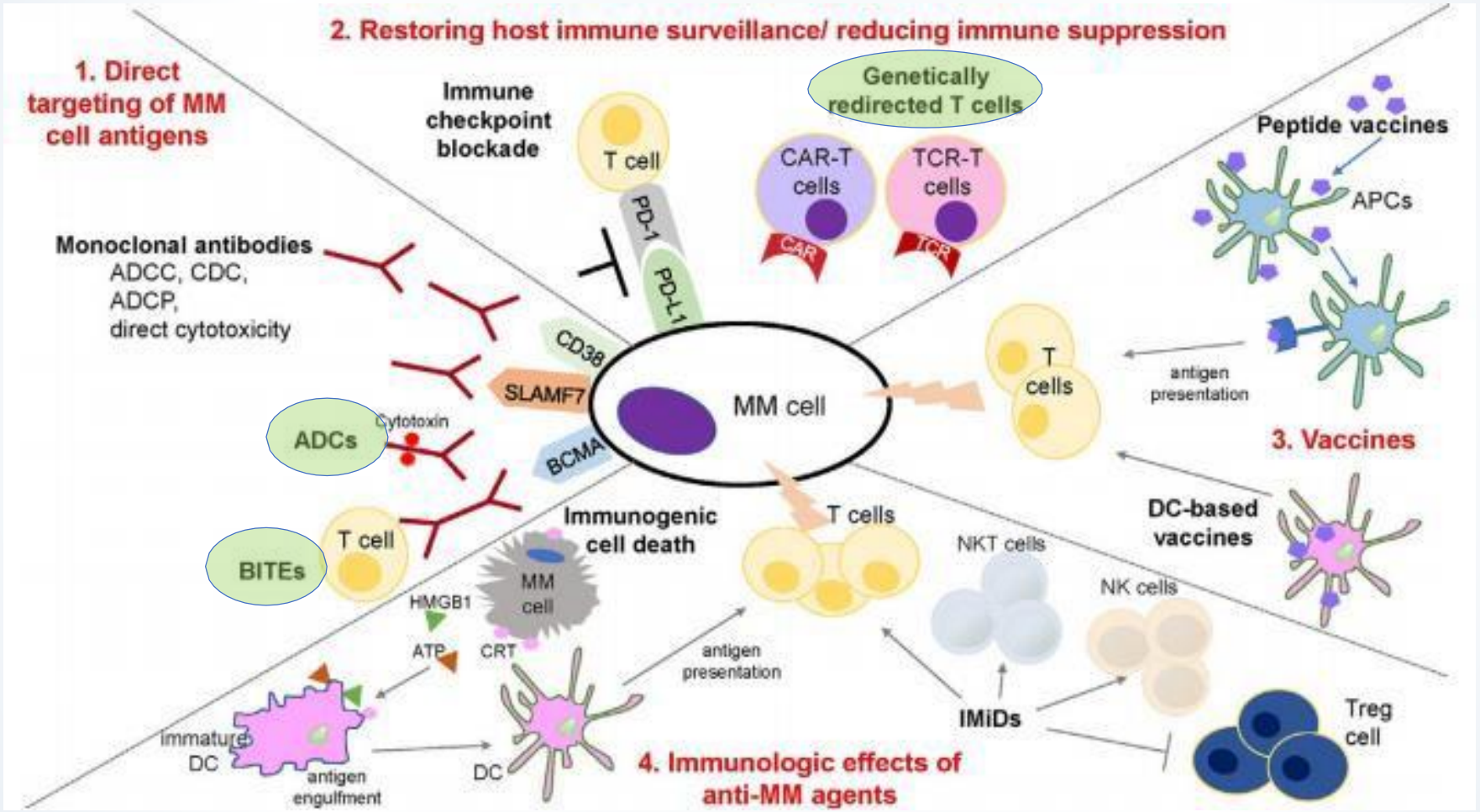
Responses were determined according to the International Myeloma Working Group (IMWG) criteria. ORR=Overall Response Rate (CR+VGPR+PR), CBR=Clinical Benefit Rate (ORR+MR), CR=Complete Response, VGPR=Very Good Partial Response, PR=Partial Response, MR=Minimal Response, SD=Stable Disease, PD=Progressive Disease. Responses as of October 1, 2020 based on interim unaudited data.

Immunotherapeutic Targets in Multiple Myeloma



Lancman et al. Hematology ASH Educ Program (2020) 2020 (1): 264–271.

Overview of Immune Therapies in Multiple Myeloma
Targeting approaches



Yamamoto et al. Front Oncol. 2021 Jan 27;10:606368.

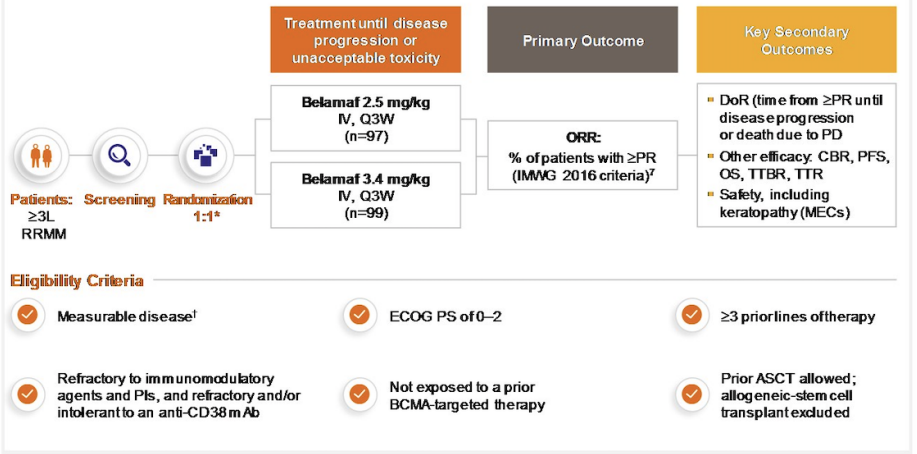
Pivotal DREAMM-2 Study: Single-agent Belantamab Mafodotin (GSK2857916) in Patients With Relapsed/Refractory Multiple Myeloma (RRMM) Refractory to Proteasome Inhibitors (PIs), Immunomodulatory Agents, and Refractory and/or Intolerant to Anti-CD38 Monoclonal Antibodies (mAbs)

Poster No. 436

Sagar Lonial[1], Hans C Lee[2], Ashraf Badros[3], Suzanne Trudel[4], Ajay K Nooka[1], Ajai Chari[5], Al-Ola Abdallah[6], Natalie Callander[7], Douglas Sborov[8], Attaya Suvannasankha[9], Katja Weisel[10], Peter M. Voorhees[11], Axel Hoos[12], Eric Zhi[12], January Baron[12], Trisha Piontek[12], Roxanne C Jewell[13], Joanna Opalinska[12], Ira Gupta[12], Adam D Cohen[14]

[1]Emory University, Winship Cancer Institute, Atlanta, GA, USA; [2]MD Anderson Cancer Center, Houston, TX, USA; [3]University of Maryland at Baltimore, Baltimore, MD, USA; [4]Princess Margaret Cancer Centre, Toronto, ON, Canada; [5]Icahn School of Medicine at Mount Sinai, NY, USA; [6]University of Kansas Cancer Center, Fairway, KS, USA; [7]University of Wisconsin, Carbone Cancer Center, Madison, WI, USA; [8]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [9]Indiana University Cancer Center, Indianapolis, IN, USA; [10]Medical Center of Hamburg-Eppendorf, Hamburg, Germany; [11]Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; [12]GlaxoSmithKline, Philadelphia, PA, USA; [13]GlaxoSmithKline, Research Triangle Park, NC, USA; [14]Abramson Cancer Center, Philadelphia, PA, USA

Figure 1: Study design[6]



*Patients stratified based on number of previous lines of therapy (≤4 vs >4) and presence or absence of high-risk cytogenetic features; †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).

Table 1. Clinical response

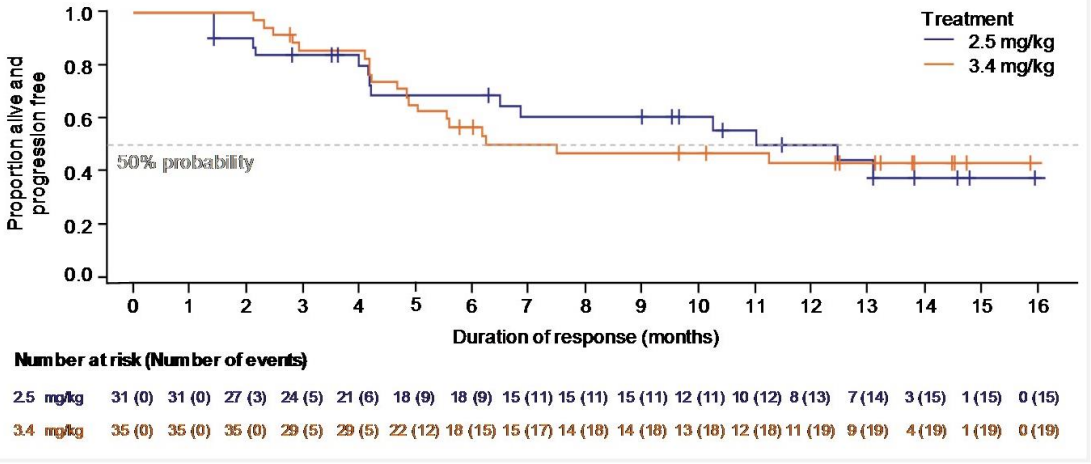
Independent Review Committee-Assessed Response*	Belamaf 2.5 mg/kg (N=97)	Belamaf 3.4 mg/kg (N=99)
ORR, n (%) (97.5% CI)	31 (32) (21.7–43.6)	35 (35) (24.8–47.0)
sCR, n (%)	2 (2)	2 (2)
CR, n (%)	5 (5)	3 (3)
VGPR, n (%)	11 (11)	18 (18)
PR, n (%)	13 (13)	12 (12)
MR, n (%)	4 (4)	5 (5)
SD, n (%)	27 (28)	22 (22)
CBR, n (%) (95% CI)	35 (36) (26.6–46.5)	40 (40) (30.7–50.7)

*Best response as assessed by independent review committee using IMWG 2016 criteria.[8] Intention-to-treat population (all randomly assigned patients, regardless of treatment administration). All patients who received ≥2 doses of belamaf and completed ≥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. CBR: sCR+CR+VGPR+PR+MR; ORR: sCR+CR+VGPR+PR.

The median DoR estimate was 11.0 months (95% CI, 4.2–NR) in the 2.5-mg/kg group and 6.2 months (95% CI, 4.8–NR) in the 3.4-mg/kg group (**Figure 2**).

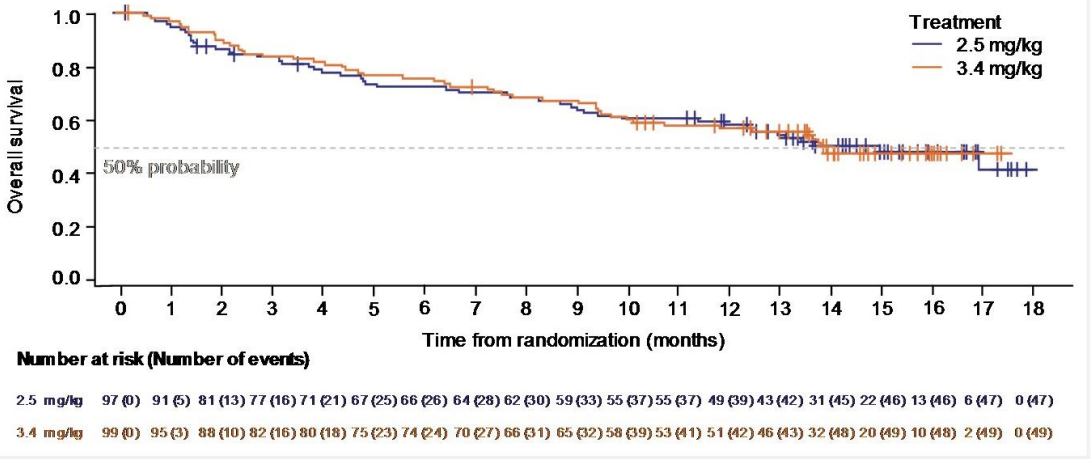
Median PFS was 2.8 months (95% CI, 1.6–3.6) in the 2.5-mg/kg group and 3.9 months (95% CI, 2.0–5.8) in the 3.4-mg/kg group.

Figure 2. Duration of response in either group



Median OS estimate was 14.9 months (95% CI, 9.9–NR) in the 2.5-mg/kg group and 14.0 months (95% CI, 10.0–NR) in the 3.4-mg/kg group (**Figure 3**)

Figure 3. Overall survival in either group



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Poster No. 436

Sagar Lonial[1], Hans C Lee[2], Ashraf Badros[3], Suzanne Trudel[4], Ajay K Nooka[1], Ajai Chari[5], Al-Ola Abdallah[6], Natalie Callander[7], Douglas Sborov[8], Attaya Suvannasankha[9], Katja Weisel[10], Peter M. Voorhees[11], Axel Hoos[12], Eric Zhi[12], January Baron[12], Trisha Piontek[12], Roxanne C Jewell[13], Joanna Opalinska[12], Ira Gupta[12], Adam D Cohen[14]

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Table 2. AEs ≥Grade 3 occurring in ≥5% of patients in either group

Patients with AE, n (%)*	Belamaf 2.5 mg/kg (N=95)	Belamaf 3.4 mg/kg (N=99)
Any event	80 (84)	83 (84)
Keratopathy (MECs)†	44 (46)	42 (42)
Anemia	20 (21)	27 (27)
Thrombocytopenia‡	21 (22)	32 (32)
Lymphocyte count decreased	12 (13)	7 (7)
Neutropenia§	10 (11)	17 (17)
Hypercalcemia	7 (7)	3 (3)
Pneumonia	7 (7)	13 (13)
GGT increased	3 (3)	9 (9)
Hypertension	4 (4)	7 (7)
AST increased	2 (2)	8 (8)
Fatigue	2 (2)	5 (5)

Events shown in decreasing order of incidence in the 2.5-mg/kg group. *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,

Table 3. Dose delays, reductions and discontinuations due to AEs

n (%)	Belamaf 2.5 mg/kg (N=95)	Belamaf 3.4 mg/kg (N=99)
AEs leading to dose delays	51 (54)	61 (62)
Dose delays due to keratopathy (MECs), n (%)	45 (47)	52 (53)
AEs leading to dose reductions	33 (35)	44 (44)
Dose reductions due to keratopathy (MECs), n (%)	24 (25)	30 (30)
AEs leading to permanent treatment discontinuation	9 (9)	12 (12)
Discontinuations due to keratopathy (MECs), n (%)	1 (1)	3 (3)
Discontinuations due to patient-reported AEs/symptoms, n (%)	2 (2)*	0

*Blurred vision or change in BCVA (n=1 each).

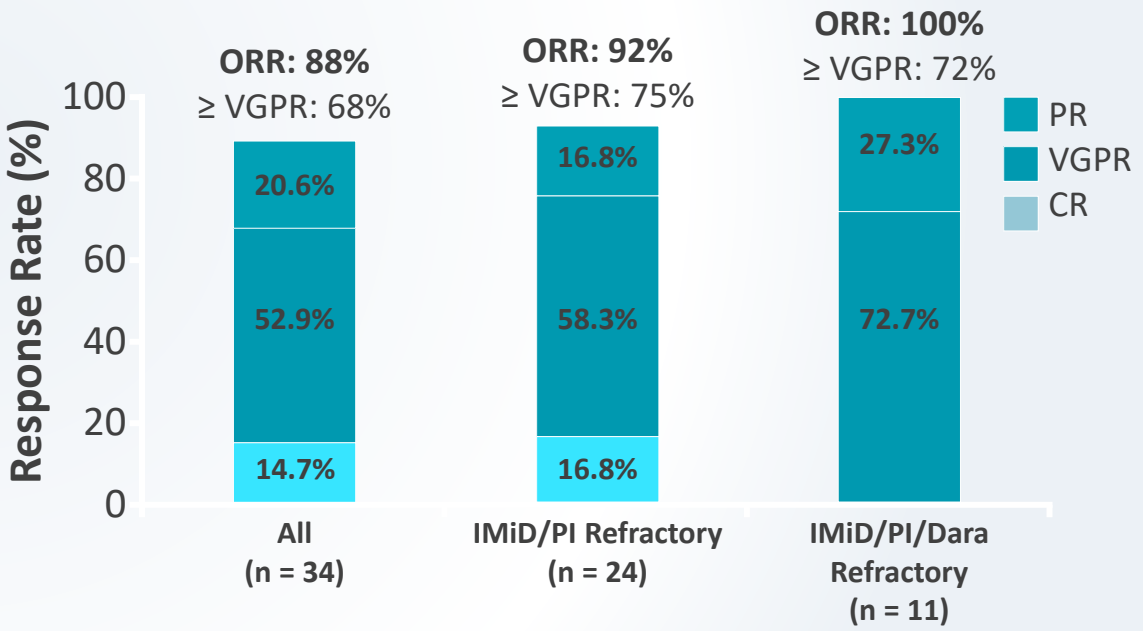
In a post-hoc analysis (**Figure 4**), approximately half of responders (16/31) in 2.5-mg/kg group had a treatment hold for ≥3 cycles and were able to re-start. Most (88%) maintained or improved their response category during the dose delay.

Preliminary Results of Combination Treatment with Belantamab Mafodotin

Phase II DREAMM-6 trial Arm B: belantamab mafodotin + bortezomib/dexamethasone[1]

Outcome	All Patients (N = 18)	Prior Bortezomib (n = 16)	Prior Dara (n = 9)
ORR, n (%)	14 (78)	12 (75)	6 (67)
Clinical benefit rate,* %	83	81	67
≥ VGPR, n (%)	12 (67)	10 (63)	4 (44)

Phase I ALGONQUIN Part 1: belantamab mafodotin + pomalidomide/dexamethasone[2]



- 75.7% of patients experienced keratopathy (MEC) events, 51.4% (19/28) were grade 3

1. Popat. ASH 2020. Abstr 1419. 2. Trudel. ASH 2020. Abstr 725.

VCC VIRTUAL Challenging Case Clinic

University of Nebraska Medical Center

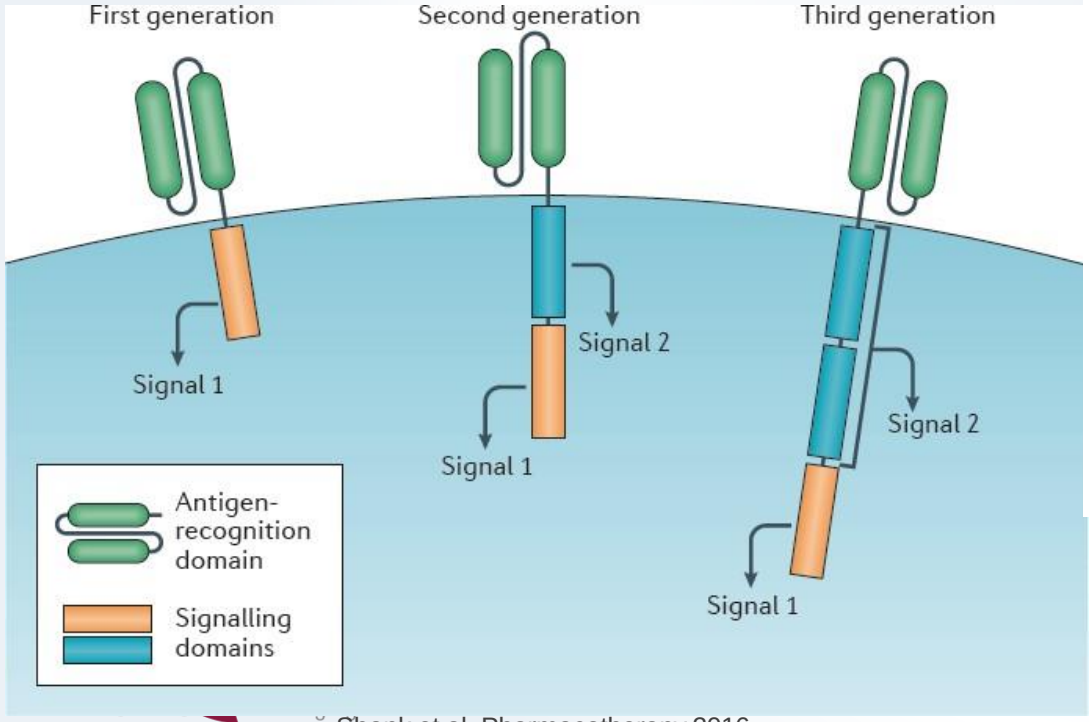
Bio Ascend

Chimeric Antigen Receptor (CAR) T-cells are Genetically Engineered to Target Antigens on Cancer Cells

CARs: Chimeric Antigen Receptor engineered to be expressed on the surface of T-cells

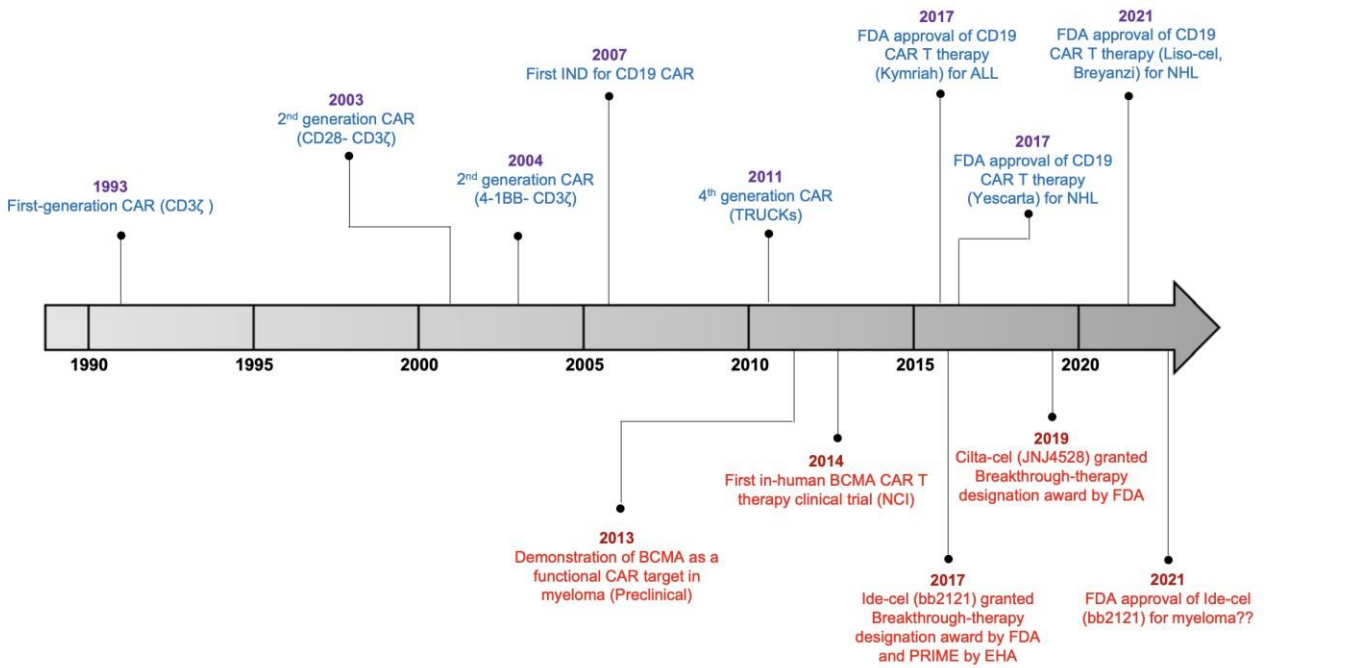
Chimeric: an antibody single chain variable fragment (scFv) linked to T-cell signaling domain – CD3ζ

CARs permit recognition of specific antigen by the T cell independent of MHC and the signaling domain stimulate T-cell proliferation, cytolysis and cytokine secretion to eliminate the tumor cells.



Shank et al. Pharmacotherapy 2016

CAR-T Timeline



Teoh and Chng Blood Cancer Journal (2021) 11:84

University of Nebraska Medical Center

Bio Ascend™

List of currently ongoing registered CAR-T cell clinical trials

Developer	Name (NCT)	Target antigen	Tools, technology, vectorization, or other notes	Status	Country
Single-target CAR-T cells					
Janssen	CARTITUDE-1 (NCT03548207)	BCMA	JNJ-68284528 (former LCAR-B38M)	Phase 1b/2, active and not recruiting	USA, Japan
Janssen	CARTITUDE-4 (NCT04181827)	BCMA	Compare efficacy of JNJ-68284528 (former LCAR-B38M) with either pomalidomide, bortezomib and dexamethasone or daratumumab, pomalidomide and dexamethasone	Phase 3, not yet recruiting	USA, Australia, UK, EU
Juno (Celgene)	JCARH125 (NCT03430011)	BCMA	LVV, 4-1BB, human	Phase 1/2, recruiting	USA
Juno (MSKCC)	MSKCC huBCMA-CAR (NCT03070327)	BCMA	RVV, human, BCMA + > 1%, EGFRt/ BCMA-41BB, with or without lenalidomide	Phase 1, recruiting	USA
Juno (NCI, FHCRC)	JSMD194 (NCT03502577)	BCMA + gamma-secretase inhibition	LVV, 4-1BB, human	Phase 1, recruiting	USA
Juno (NCI, FHCRC)	FCARH143 (NCT03338972)	BCMA	LVV, 4-1BB, human	Phase 1, recruiting	USA
NCI	NCT03602612	BCMA	Human	Phase 1, recruiting	USA
Bluebird (Celgene)	CRB-401 (NCT02658929)	BCMA	LVV, 4-1BB, murine (bb2121)	Phase 1, active and not recruiting	USA
Bluebird (Celgene)	CRB-402 (NCT03274219)	BCMA	LVV, 4-1BB, murine, bb21217 (uses the same design as bb2121, but adds the phosphoinositide 3-kinase inhibitor bb007 during ex vivo culture to enrich the drug product for memory-like T cells)	Phase 1, recruiting	USA
Celgene	KarMMa (NCT03361748)	BCMA	LVV, 4-1BB, murine (bb2121)	Phase 2, active and not recruiting	USA, Canada, EU, Japan
Celgene	KarMMa-2 (NCT03601078)	BCMA	In patients with RRMM (cohort 1), progressed <18 months of initial treatment including ASCT (Cohort 2a), and without ASCT (Cohort 2b) or, in subjects with inadequate response post ASCT	Phase 2, recruiting	USA, EU, UK
Celgene	KarMMa-3 (NCT03651128)	BCMA	Compared with daratumumab, pomalidomide and low-dose dexamethasone, or daratumumab, bortezomib and low-dose dexamethasone, or ixazomib, lenalidomide and low-dose dexamethasone	Phase 3, recruiting	USA, Canada, EU, Japan
Novartis (UPenn)	CART-BCMA	BCMA	LVV, 4-1BB, human	Active, closed	USA
Poseida	P-BCMA-101 (NCT03288493)	BCMA	PiggyBac, 4-1BB, human	Phase 1/2, recruiting	USA
			other notes		
KITE (Gilead)	KITE-585 (NCT03318861)	BCMA	NR	Phase 1, active and not recruiting	USA
Cartesian	Descartes-11 (NCT03994705, NCT03448978)	BCMA	Autologous CD8 + T-cells	Phase 1/2, recruiting	USA
Arcellx	ARM 1 (NCT04155749)	BCMA	non-scFv binding domain	Phase 1, recruiting	USA
Nanjing Legend Biotech (Janssen)	CARTIFAN-1 (NCT03758417)	BCMA	LCAR-B38M, LVV, 4-1BB, non-scFv	Phase 2	China
Allife Medical Science and Technology	NCT03559764	BCMA	NR	Phase 1, not yet recruiting	China
The Pregene Biotechnology (Henan Cancer Hospital)	NCT03664661	BCMA	LVV, 4-1BB, and CD3ζ	Phase 1, recruiting	China
The Pregene Biotechnology (Henan Cancer Hospital)	NCT03661554	BCMA	Humanized alpaca-derived single-domain antibody, 4-1BB and CD3ζ	Phase 1, recruiting	China
PersonGen BioTherapeutics	NCT04186052	BCMA	NR	Early phase 1, recruiting	China
The Pregene Biotechnology (Henan Cancer Hospital)	NCT03322735	BCMA	NR	Unknown	China
Hrain Biotechnology	NCT03943472	BCMA	NR	Early phase 1, recruiting	China
Hrain Biotechnology	NCT03093168	BCMA	RVV-mediated transduction of activated T cells to express a second-generation CAR with the 4-1BB costimulatory domain along with a EGFRt as a safety switch	Phase 1, recruiting	China
Hebei Yanda Ludaopei Hospital	C-CAR088 (NCT03751293)	BCMA	NR	Phase 1, recruiting	China
Shanghai Bioray Laboratory	NCT03492268	BCMA	NR	Phase 1, recruiting	China
Carsgen Therapeutics	CT053 (NCT03716856, NCT03302403, NCT03380039, NCT03975907, NCT03302403)	BCMA	fully human single chain fragment variant, a 4-1BB co-stimulatory domain and a CD3ζ signaling domain	Phase 1, Fast Track and Breakthrough (FDA), PRIME (EMA), recruiting	China
Beijing Immunochina Medical Science & Technology	IM21 (NCT03711864)	BCMA	Inclusion criteria: e.g., focal lesions of >1 found by functional imaging examination including PET/CT and/or whole-body MRI	Phase 1, recruiting	China
Nanjing Legend Biotech	NCT03672253	BCMA	After CAR T relapse	Phase 1, active and not recruiting	China

Developer	Name (NCT)	Target antigen	Tools, technology, vectorization, or other notes	Status	Country
Southwest Hospital	NCT02954445	BCMA	For CD19- B cell malignancies including MM	Phase 1, recruiting	China
Sorrento Therapeutics	CAR2 Anti-CD38 A2 (NCT03464916)	CD38	NR	IND filing, Phase 1, recruiting	USA
UNC Lineberger Comprehensive Cancer Center	CAR138 (NCT03672318)	CD138	NR	Phase 1, recruiting	USA
Chinese PLA General Hospital	CART-138 (NCT01886976)	CD138	NR	Phase 1, unknown	China
EU (University Hospital Würzburg)	CARAMBA	SLAMF7 or CS1	Humanized targeting domain, CARs equipped with an EGFRt safety switch triggered with anti-EGFR antibodies, "Sleeping Beauty" transposition	Phase 1, recruiting	EU
NCI	NCT03958656	SLAMF7 or CS1	Suicide gene incorporated	Preclinical	USA
City of Hope Medical Center (NCI)	CS1-CAR (NCT03710421)	SLAMF7 or CS1	LVV, hinge-optimized, 4-1BB costimulatory CAR and a truncated EGFR	Phase 1, recruiting	USA
Celyad	CYAD-01 (NCT03018405)	NKG2-D	full-length native human NKG2D gene fused with CD3ζ, NKG2D associates with DAP10 for membrane stabilization and function	Dose escalation phase I, recruiting	USA/EU
Asclepius Technology	CAR-NK 92 (NCT03940833)	BCMA	CAR NK cell therapy	Dose escalation phase I, recruiting	China
Allogeneic CAR–T cells					
Allogene Therapeutics	ALLO-715 (NCT04093596)	BCMA	TRAC and CD52 KO, TALEN mRNA	Single-arm, open-label, phase 1, recruiting	USA
CRISPR Therapeutics	CTX-120 (NCT04244656)	BCMA	TRAC and PD1 KO, CRISPR/Cas9	IND enabling, phase 1, recruiting	USA
Cellectis	UCART-CS1 (NCT04142619)	SLAMF7 or CS1	TRAC and CS1 KO, TALEN mRNA	FDA approved IND application to initiate MELANI-01, phase 1	MDACC, USA
Celyad	CYAD-211	BCMA	Expression of a TRAC- inhibitory molecule peptide consisting of a truncated form of CD3ζ, RVV (co-expression of TRAC-inhibitory molecule with CAR)	IND submission	USA/EU
Precision BioSciences	PBCAR269A (NCT04171843)	BCMA	ARCUS genome editing	IND cleared, phase 1/2a, not yet recruiting	No sites documented yet
Shanghai Bioray Laboratory	UCART (NCT03752541)	BCMA	NR	NA, recruiting	China
Multi-target CAR-T cells					
Autolus Limited	AUTO2 (NCT0328780)	BCMA-TACI	NR	Terminated (Preliminary efficacy seen to date following treatment with AUTO2 has been determined not sufficient to warrant further development)	UK, Netherlands
University of Pennsylvania	CART-BCMA + huCART19 (NCT03549442)	BCMA-CD19	LVV, 4-1BB/CD3ζ-based CARs transduced	Phase 1, recruiting	USA
iCell Gene Therapeutics	Compound CAR (NCT04156269)	BCMA-CS1	LVV, an anti-BCMA CAR comprised of a CD8-derived hinge and transmembrane regions, and 4-1BB co-activation domains linked to the CD3ζ signaling domain is fused to a complete anti-CS1 CAR by a self-cleaving P2A peptide; a strong spleen focus forming virus promoter and a CD8 leader sequence were used for efficient expression of the BC1cCAR molecule on the T-cell surface	Phase 1, recruiting	China
Chinese PLA General Hospital	(NCT03767751, CHN-PLAGH-BT-037)	CD38-BCMA	NR	Phase ½, recruiting	China
Huazhong University of Science and Technology (Cellyan Therapeutics)	ChiCTR1800018143	CD38-BCMA	4-1BB signaling and CD3ζ domain	Phase 1, dose-climbing, recruiting	China
Chinese PLA General Hospital	BCMA-PD1-CART (NCT04162119)	BCMA-PD1	BCMA CAR T cells which secrete the mutant PD-1Fc fusion protein	Phase 2, recruiting	China
Gracell Biotechnology	GC012F (NCT04236011, NCT04182581)	BCMA-CD19	NR	Newly posted 22 January 2020, phase 1, recruiting	China
Hrain Biotechnology (Shanghai Zhongshan Hospital)	NCT03706547	BCMA-CD19	RVV	Phase 1, not yet recruiting	China
Other					
The First Affiliated Hospital of Soochow University	NCT03196414	BCMA-CD38-CD19 (or more)	NR	Phase 1, recruiting	China
The First Affiliated Hospital of Soochow University	NCT03455972	BCMA-CD19	CD19 + or BCMA + high-risk MM after ASCT	Phase 1, recruiting	China
Shenzhen Second People's Hospital	NCT03767725	BCMA and/or CD19	NR	Phase 1, recruiting	China

Developer	Name (NCT)	Target antigen	Tools, technology, vectorization, or other notes	Status	Country
The First Affiliated Hospital of Nanchang University	NCT04194931	BCMA-CD19	Humanized, BCMA + and CD19 + patients	Phase 1, recruiting	China
The Sixth Affiliated Hospital of Wenzhou Medical University	NCT03778346	CD138, integrin β7, CS1, CD38 and BCMA	NR	Phase 1, recruiting	China
Zhujiang Hospital	NCT03473496		single CAR-T or double CAR-T cells with BCMA, CD138, CD56, or CD38	NR, recruiting	China

2020 ASCO ANNUAL MEETING
UNITE AND CONQUER: ACCELERATING PROGRESS TOGETHER

KarMMa™

Idecabtagene vicleucel (ide-cel, bb2121), a BCMA-targeted CAR T cell therapy, in patients with relapsed and refractory multiple myeloma (RRMM): initial KarMMa results

Nikhil C. Munshi, MD[1]; Larry D. Anderson, Jr, MD, PhD[2]; Nina Shah, MD[3]; Sundar Jagannath, MD[4]; Jesus Berdeja, MD[5]; Sagar Lonial, MD[6]; Noopur Raje, MD[7]; David S. Siegel, MD, PhD[8]; Yi Lin, MD, PhD[9]; Albert Oriol, MD[10]; Philippe Moreau, MD[11]; Ibrahim Yakoub-Agha, MD, PhD[12]; Michel Delforge, MD[13]; Fabio Petrocca, MD[14]; Jamie N. Connarn, PhD[15]; Payal Patel[15]; Liping Huang, PhD[15]; Timothy B. Campbell, MD, PhD[15]; Kristen Hege, MD[15]; and Jesus San Miguel, MD, PhD[16] *on behalf of the KarMMa study investigators*

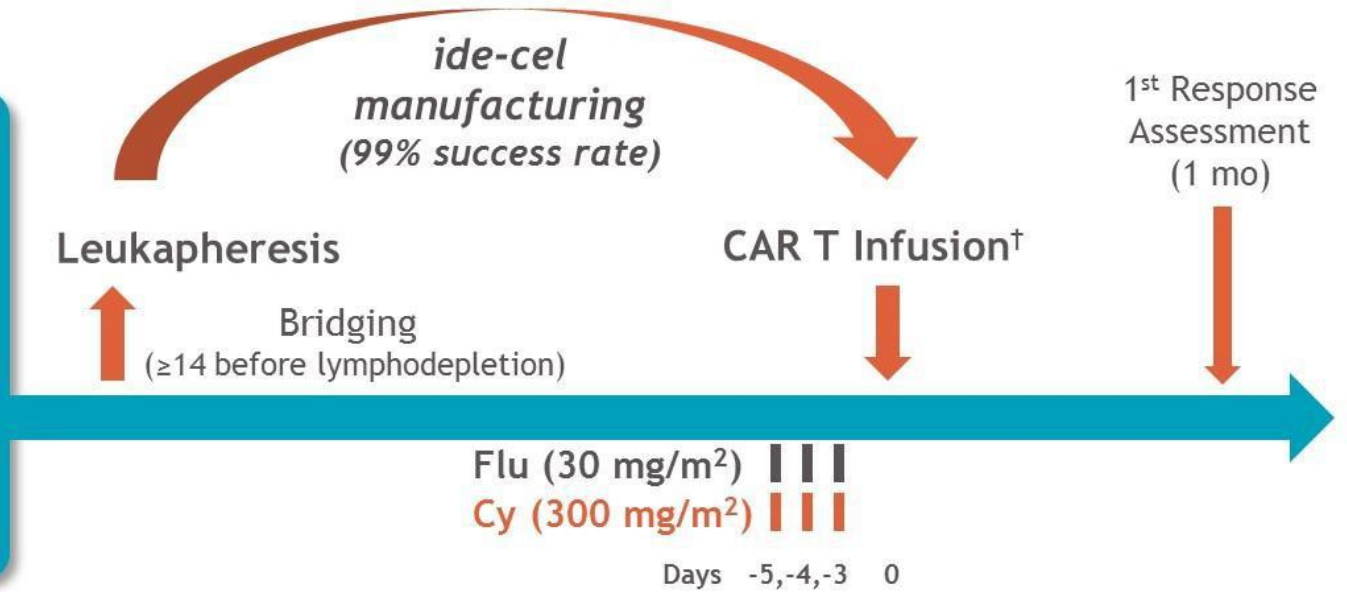
[1]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [2]Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, USA; [3]University of California San Francisco, San Francisco, CA, USA; [4]Mount Sinai Hospital, New York, NY, USA; [5]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN, USA; [6]Emory School of Medicine, Atlanta, GA, USA; [7]Massachusetts General Hospital, Boston, MA, USA; [8]Hackensack University Medical Center, Hackensack, NJ, USA; [9]Mayo Clinic, Rochester, MN, USA; [10]Institut Josep Carreras and Institut Catala d'Oncologia, Hospital Germans Trias i Pujol, Badalona, Spain; [11]Centre Hospitalier Universitaire de Nantes, Nantes, France; [12]Centre Hospitalier Regional Universitaire de Lille, Lille, France; [13]University Hospital Leuven, Leuven, Belgium; [14]bluebird bio, Cambridge, MA, USA; [15]Bristol Myers Squibb, Princeton, NJ, USA; and [16]Clinical Universidad de Navarra, Navarra, Spain

Presentation Number 8503

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*



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

Study Status as of Jan 14, 2020

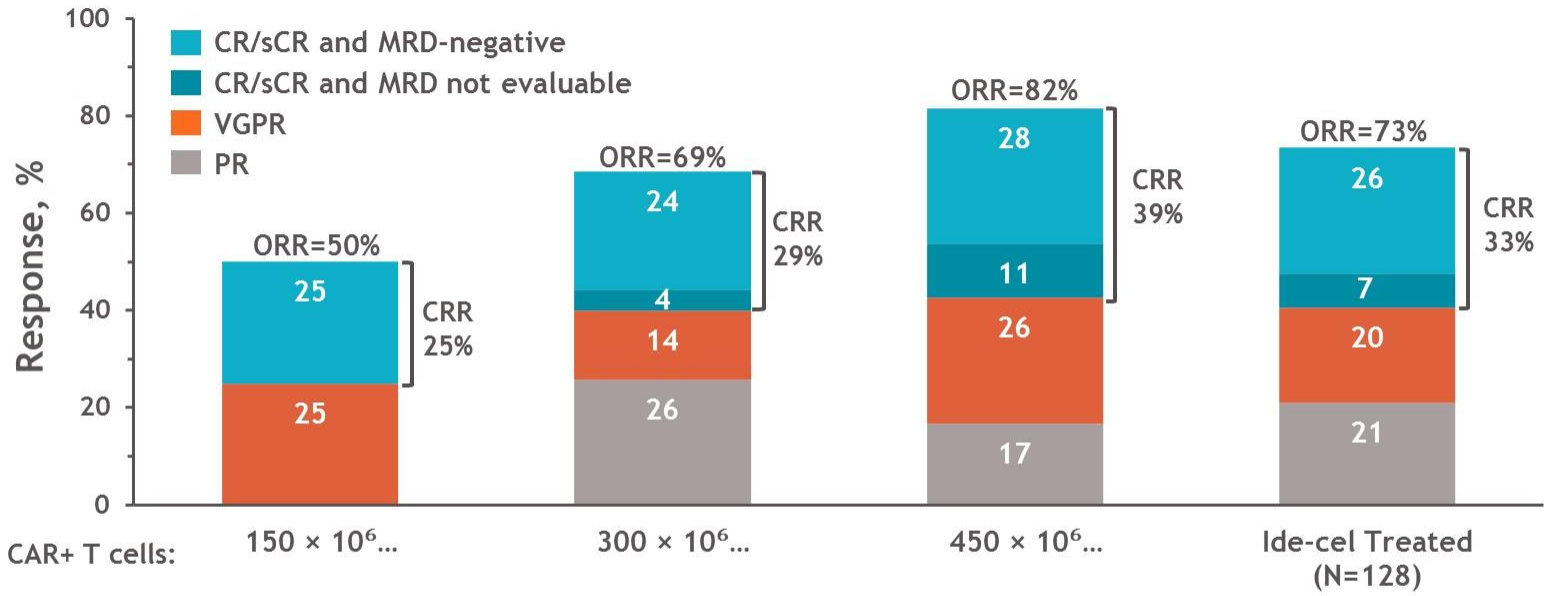
Screened N=158	
Leukapheresed N=140	
Treated N=128 (Target Dose CAR+ T cells)	
150 × 10^6	n=4
300 × 10^6	n=70
450 × 10^6	n=54

Median Follow-up (mo)	
150 × 10^6	18.0
300 × 10^6	15.8
450 × 10^6	12.4
Total	13.3

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.

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

Best Overall Response

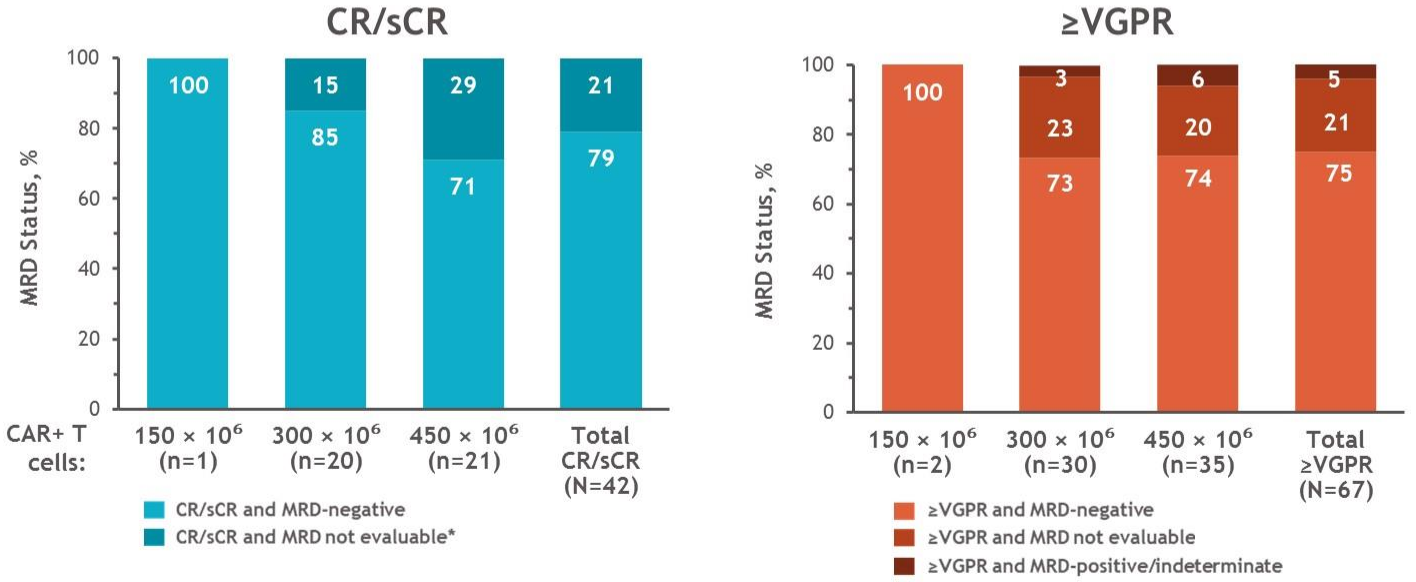


- Primary (ORR >50%) and key secondary (CRR >10%) endpoints met in the ide-cel treated population
  - *ORR of 73% (95% CI, 65.8–81.1; P<0.0001*)*
  - *CRR (CR/sCR) of 33% (95% CI, 24.7–40.9; P<0.0001)*
- Median time to first response of 1.0 mo (range, 0.5–8.8); median time to CR of 2.8 mo (range, 1.0–11.8)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

Data cutoff: 14 Jan 2020. MRD-negative defined as $<10^{-5}$ nucleated cells by next generation sequencing. Only MRD values within 3 mo of achieving CR/sCR until progression/death (exclusive) were considered.
Values may not add up due to rounding.
CR/sCR, complete response/stringent CR; CRR, CR rate; MRD, minimal residual disease; ORR, overall response rate (≥PR); PR, partial response; VGPR, very good PR. **P* value at the primary data cutoff with same ORR and 95% CI.

MRD Negativity

Target Dose, CAR+ T cells	150 × 10^6	300 × 10^6	450 × 10^6	Total
All ide-cel treated	n=4	n=70	n=54	n=128
MRD-negative and ≥CR, n (%) [95% CI]	1 (25) [0.6–80.6]	17 (24) [14.8–36.0]	15 (28) [16.5–41.6]	33 (26) [18.5–34.3]
MRD-negative and ≥VGPR, n (%) [95% CI]	2 (50) [6.8–93.2]	22 (31) [20.9–43.6]	26 (48) [34.4–62.2]	50 (39) [30.6–48.1]

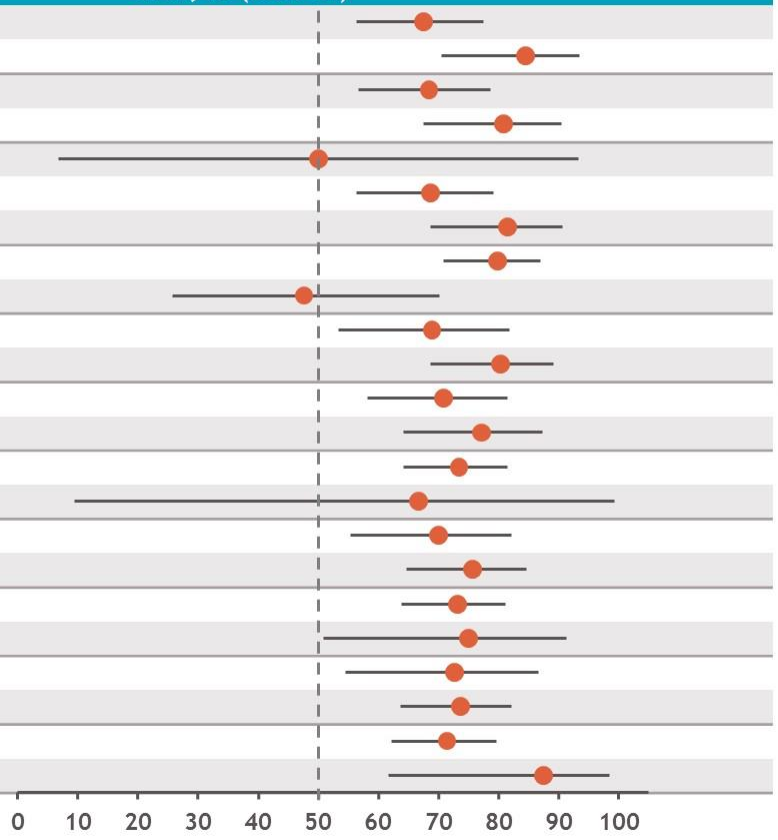


Data cutoff: 14 Jan 2020. MRD-negative defined as <10^{-5} nucleated cells by next generation sequencing. Only MRD values within 3 mo of achieving CR/sCR until progression/death (exclusive) were considered. Values may not add up due to rounding. CR/sCR, complete response/stringent CR; MRD, minimal residual disease; VGPR, very good partial response. *Of 42 patients with ≥CR, 8 were not evaluable for MRD and 1 had values outside the 3-mo window prior to CR/sCR.

Clinically Meaningful Efficacy (ORR) Observed Across Subgroups

KarMMa™

Subgroup		N	ORR, % (95% CI)
Age group, years	<65	83	
	≥65	45	
Sex	Male	76	
	Female	52	
Ide-cel target dose level, CAR+ T cells	150 × 10^6	4	
	300 × 10^6	70	
	450 × 10^6	54	
R-ISS stage at enrollment	I or II	104	
	III	21	
High-risk cytogenetics del(17p), t(4;14), t(14;16)	Yes	45	
	No	66	
Tumor burden at baseline, % BMPCs	≥50%	65	
	<50%	57	
Tumor BCMA expression	≥50%	109	
	<50%	3	
Extramedullary disease	Yes	50	
	No	78	
Triple-refractory*	Yes	108	
	No	20	
Penta-refractory†	Yes	33	
	No	95	
Bridging therapy	Yes	112	
	No	16	



Data cutoff: 14 Jan 2020. *Defined as refractory to an IMiD agent, PI, and CD-38 antibody. †Defined as refractory to 2 IMiD agents, 2 PIs, and 1 anti-CD38 antibody. BCMA, B-cell maturation antigen; BMPC, bone marrow plasma cell; R-ISS, revised International Staging System.

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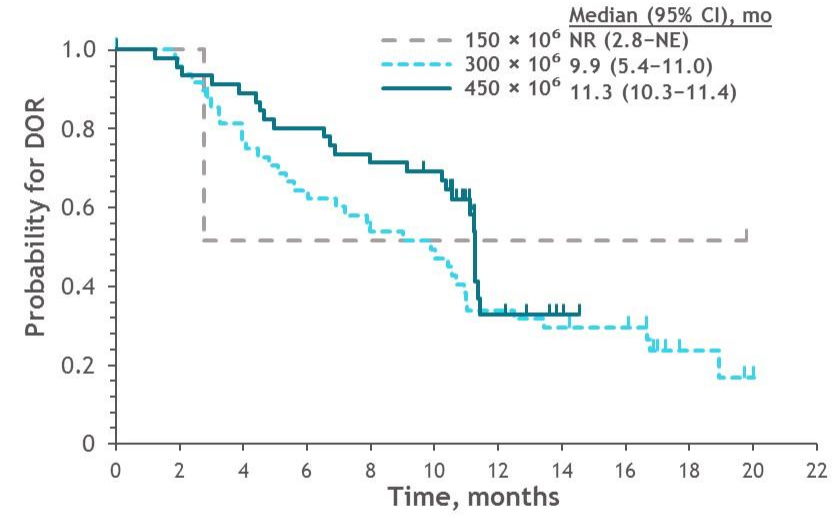
Duration of Response By Target Dose and Best Response

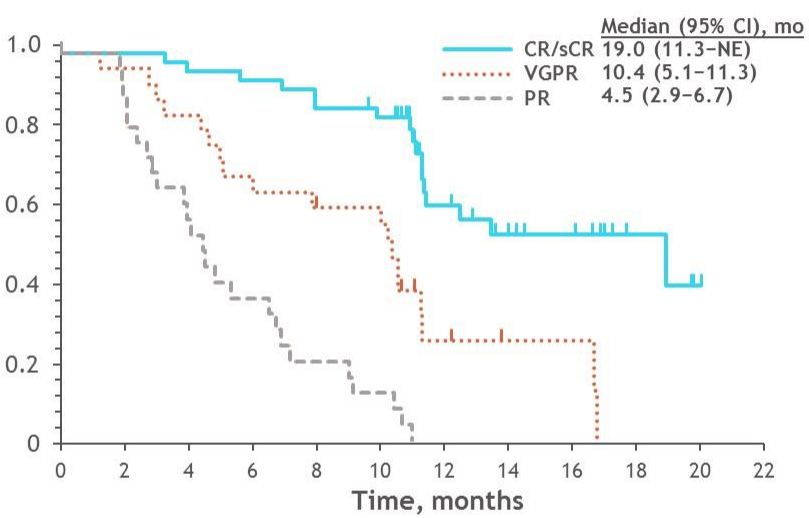
DOR by Target Dose



At risk, N

150 × 10⁶	2	2	1	1	1	1	1	1	1	1	0	
300 × 10⁶	48	45	35	29	24	21	14	12	11	3	1	0
450 × 10⁶	44	42	39	35	31	29	7	2	0	0	0	

DOR by Best Response



At risk, n

CR/sCR	42	42	40	39	36	34	18	13	10	4	1	0
VGPR	25	24	21	17	15	14	4	2	2	0	0	
PR	27	23	14	9	5	3	0	0	0	0	0	

- Durable responses were observed across all target doses; median DOR of 11.3 mo at 450 × 10^6 CAR+ T cells
- DOR increased with depth of response; median DOR of 19 mo in patients achieving CR/sCR

Data cutoff: 14 Jan 2020. CR/sCR, complete response/stringent CR; DOR, duration of response; NE, not estimable; NR, not reached; PR, partial response; VGPR, very good PR.

Incidence and Management of CRS

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

Data cutoff: 14 Jan 2020. Siltuximab was used to manage CRS in 1 patient who was treated with 300 x 10^6 CAR+ T cells. Anakinra was used to manage CRS in 1 patient who was treated with 300 x 10^6 CAR+ T cells.
*CRS graded according to Lee criteria [Lee et al., *Blood* 2014;10;124(2):188-195].
CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; NA, not applicable; NCI, National Cancer Institute.

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

Data cutoff: 14 Jan 2020. CTCAE, Common Terminology Criteria for Adverse Events; NA, not applicable; NCI, National Cancer Institute; NT, neurotoxicity (investigator-identified).
*Investigator-identified NT events were graded according to the NCI CTCAE v4.03.

Update of CARTITUDE-1: A phase 1b/2 study of JNJ-4528, a B-cell maturation antigen (BCMA)-directed CAR-T cell therapy, in relapsed/refractory multiple myeloma

Jesus G. Berdeja,[1] Deepu Madduri,[2] Saad Z. Usmani,[3] Indrajeet Singh,[4] Enrique Zudaire,[4] Tzu-Min Yeh,[5] Alicia J. Allred,[4] Yunsi Olyslager,[6] Arnob Banerjee,[4] Jenna D. Goldberg,[5] Jordan M. Schecter,[5] Dong Geng,[7] Xiaoling Wu,[7] Marlene J. Carrasco-Alfonso,[7] Syed Rizvi,[7] Frank Fan,[8] Andrzej Jakubowiak,[9] Sundar Jagannath[2]

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CARTITUDE-1: Phase 1b/2 Study Design

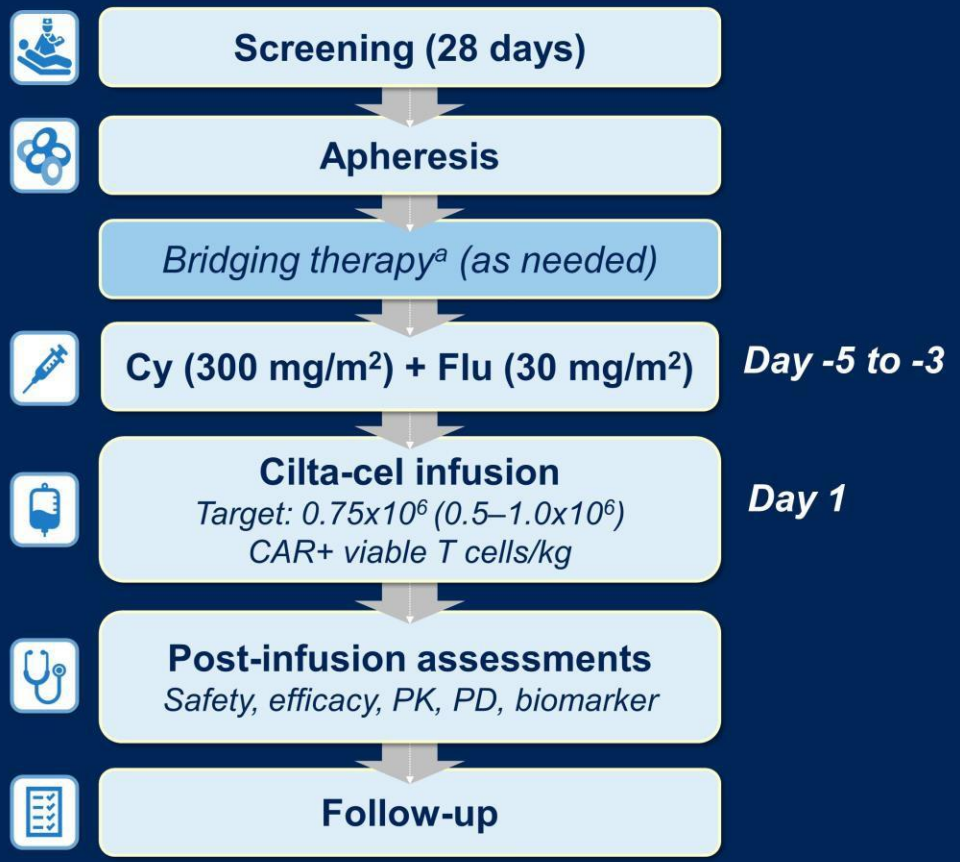
Primary Objectives

- Phase 1b: Characterize cilta-cel safety and confirm the recommended phase 2 dose
- Phase 2: Evaluate cilta-cel efficacy

Key Eligibility Criteria

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

Median administered dose:
$0.71x10^6$ ($0.51–0.95x10^6$) CAR+ viable T cells/kg



CAR, chimeric antigen receptor; Cy, cyclophosphamide; ECOG PS, Eastern Cooperative Oncology Group performance status; Flu, fludarabine; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MM, multiple myeloma; PD, pharmacodynamics; PI, proteasome inhibitor; PK, pharmacokinetics. Feb 11, 2021 data cut-off. [a]Treatment with previously used agent resulting in at least stable disease.

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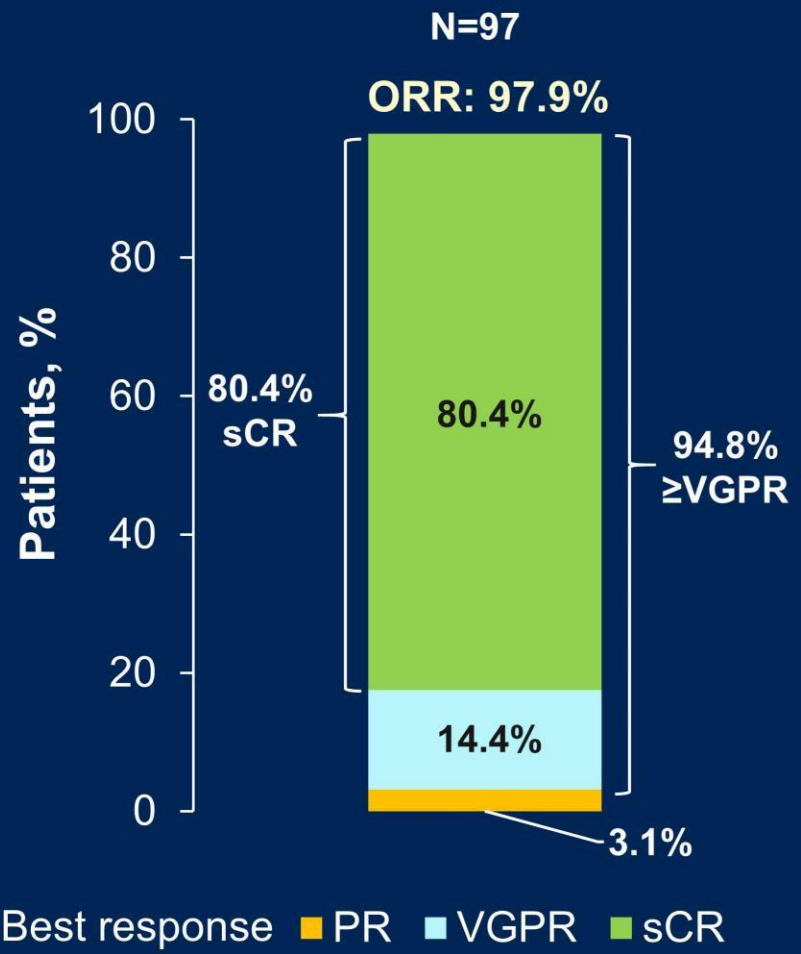
CARTITUDE-1: Overall Response Rate



With longer follow-up, responses deepened with increasing rate of sCR

- Median time to first response: 1 month (range, 0.9–10.7)
- Median time to best response: 2.6 months (range, 0.9–15.2)
- Median time to ≥CR: 2.6 months (range, 0.9–15.2)
- Median duration of response: 21.8 months (95% CI, 21.8–NE)
  - Estimated 73% of responders have not progressed or died at 12 months
  - Median duration of response not reached in patients with sCR
- Response rates were comparable (range, 95–100%) across different subgroups (eg, number of prior lines of therapy, refractoriness, extramedullary plasmacytomas, and cytogenetic risk)[a]

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

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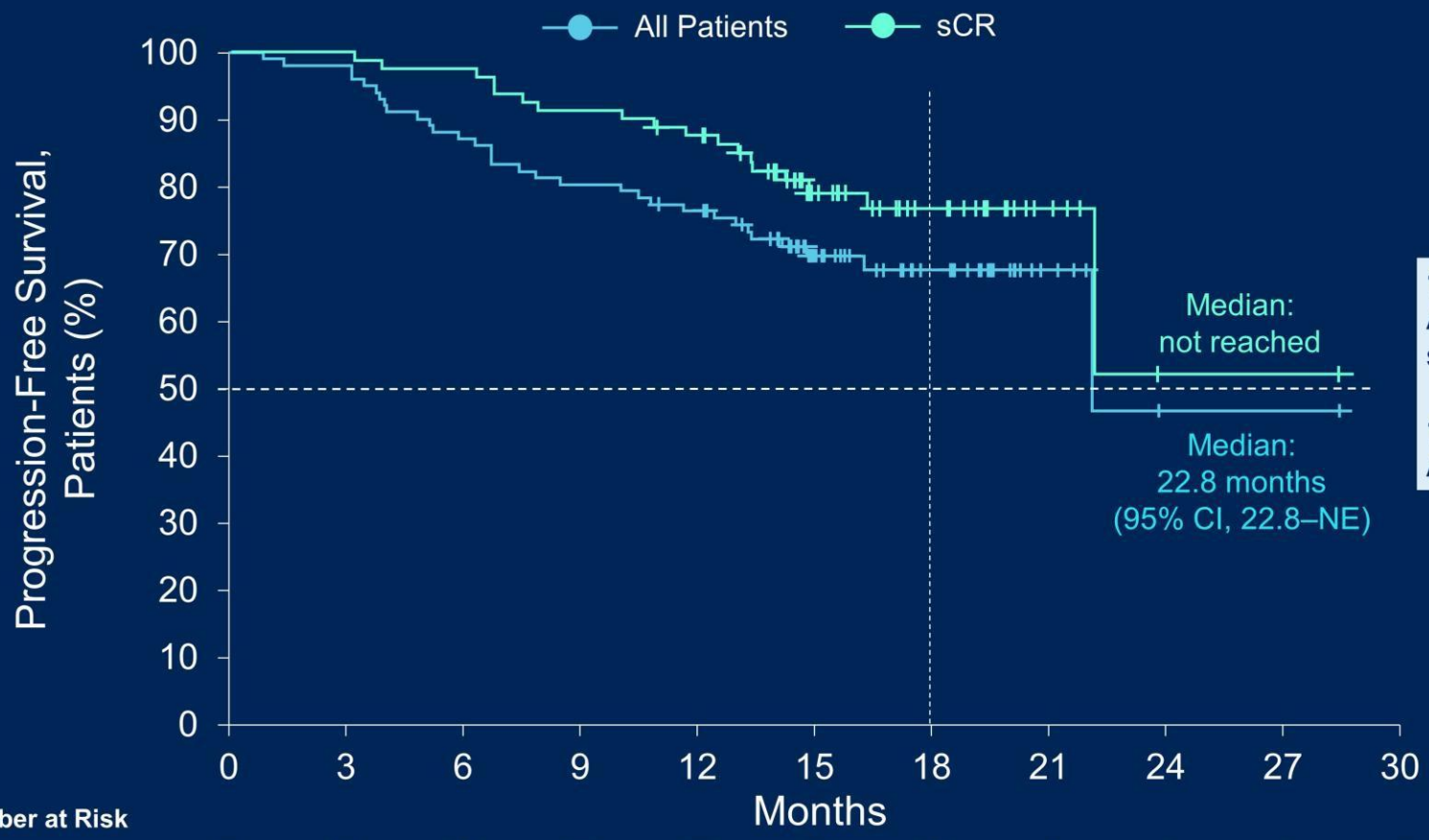
CARTITUDE-1: Progression-Free Survival



Number at Risk

All Patients	97	95	85	77	73	55	26	9	1	1	0
Responders With sCR	78	78	76	71	68	51	26	9	1	1	0

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

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

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

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

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CARTITUDE-1: Safety

No new safety signals with longer follow-up

	N=97	
	Any grade	**Grade 3/4**
Hematologic AEs ≥25%, n (%)		
Neutropenia	93 (95.9)	92 (94.8)
Anemia	79 (81.4)	66 (68.0)
Thrombocytopenia	77 (79.4)	58 (59.8)
Leukopenia	60 (61.9)	59 (60.8)
Lymphopenia	51 (52.6)	48 (49.5)
Nonhematologic AEs ≥25%, n (%)		
Metabolism and nutrition disorders		
Hypocalcemia	31 (32.0)	3 (3.1)
Hypophosphatemia	30 (30.9)	7 (7.2)
Decreased appetite	28 (28.9)	1 (1.0)
Hypoalbuminemia	27 (27.8)	1 (1.0)
Gastrointestinal		
Diarrhea	29 (29.9)	1 (1.0)
Nausea	27 (27.8)	1 (1.0)
Other		
Fatigue	36 (37.1)	5 (5.2)
Cough	34 (35.1)	0
AST increased	28 (28.9)	5 (5.2)
ALT increased	24 (24.7)	3 (3.1)

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

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

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

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis.
[a]CRS was graded using Lee et al. (*Blood* 2014) in the phase 1b portion of the study and ASTCT in phase 2; in this combined analysis, Lee et al. criteria were mapped to ASTCT criteria for patients in the phase 1b portion.
[b]The patient with 97-day duration died due to CRS/HLH. [c]Events not reported as ICANS (ie, onset after a period of recovery from CRS and/or ICANS).

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KarMMa-Rw: A study of real world treatment patterns in heavily pretreated RRMM and comparison of outcomes to KarMMa

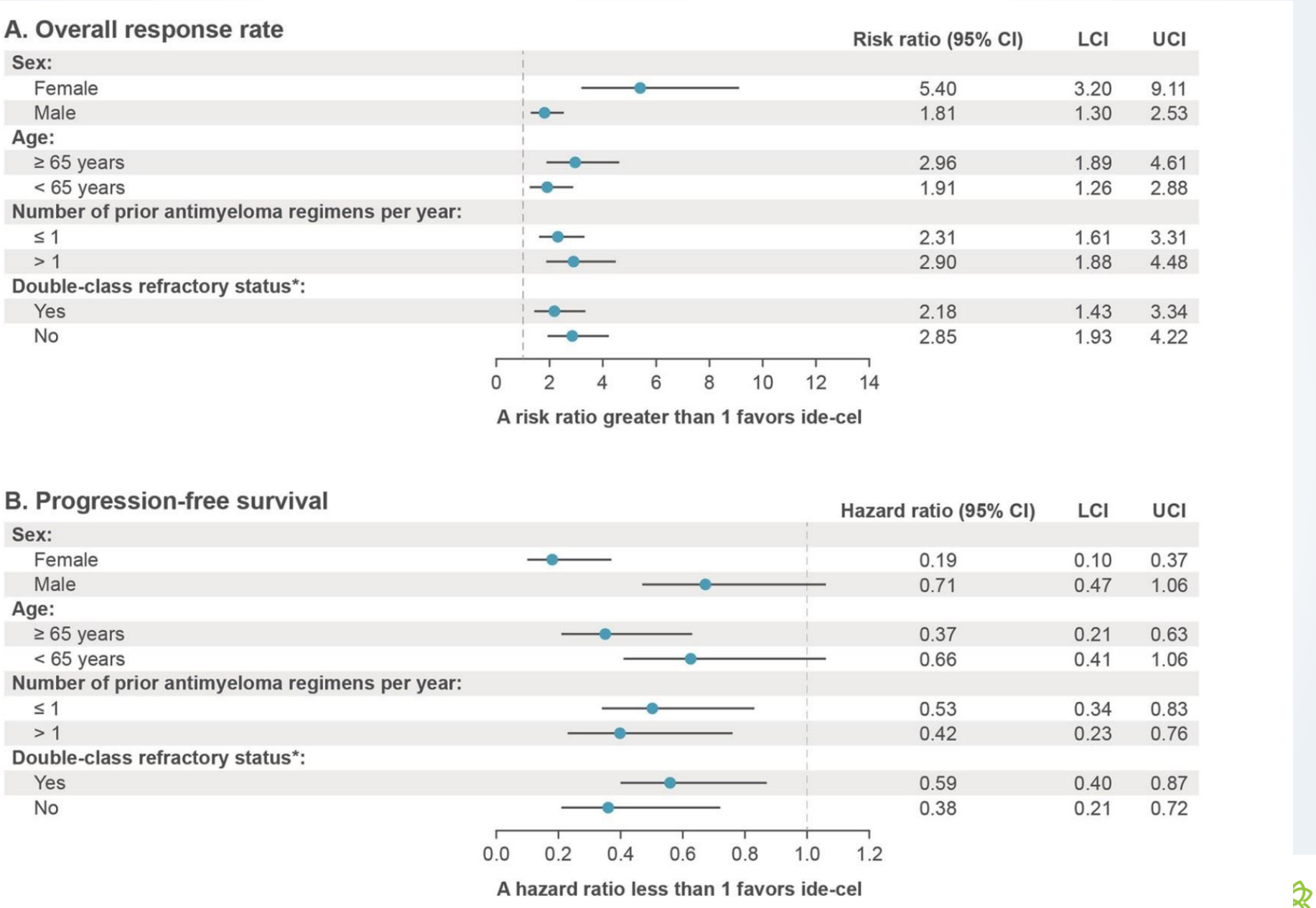
Eligible Cohort

Baseline Characteristic	EC (N = 190)	KarMMa* (N = 128)
Median age, y	64	61
R-ISS disease stage III, %	4	16
High-risk cytogenetics, %	30	35
Median no. prior regimens	5	6
Triple-class refractory/plasmacytoma, %	43/11	84/39
Effectiveness†		
ORR, % (95% CI)	32 (24-42) RR, 2.4 (1.7-3.3);	76 (69-86) *P*< 0.0001
≥VGPR‡, % (95% CI)	14 (9-22) RR, 4.2 (2.4-7.2);	57 (47-70) *P*< 0.0001
Median PFS, mo	3.5 (3.2-3.7) HR, 0.48 (0.33-0.69);	11.3 (9.5-13.1) *P*< 0.0001

* Across all target doses

Jagannath S et al. J Clin Oncol. 2020;38:(Supplement 15)8525-8525

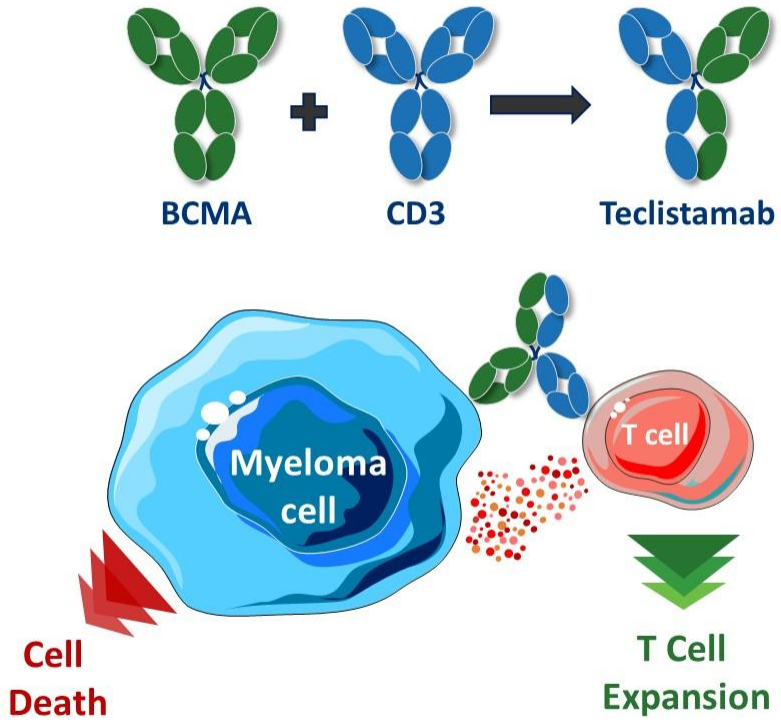
Comparison of idecabtagene vicleucel with real-world outcomes in relapsed and refractory multiple myeloma



Jagannath, et al. Blood Cancer Journal (2021) 11:116

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

56th ASCO Annual Meeting 2020, Usmani SZ, et al. Abstract #100

MajesTEC-1: Baseline Characteristics

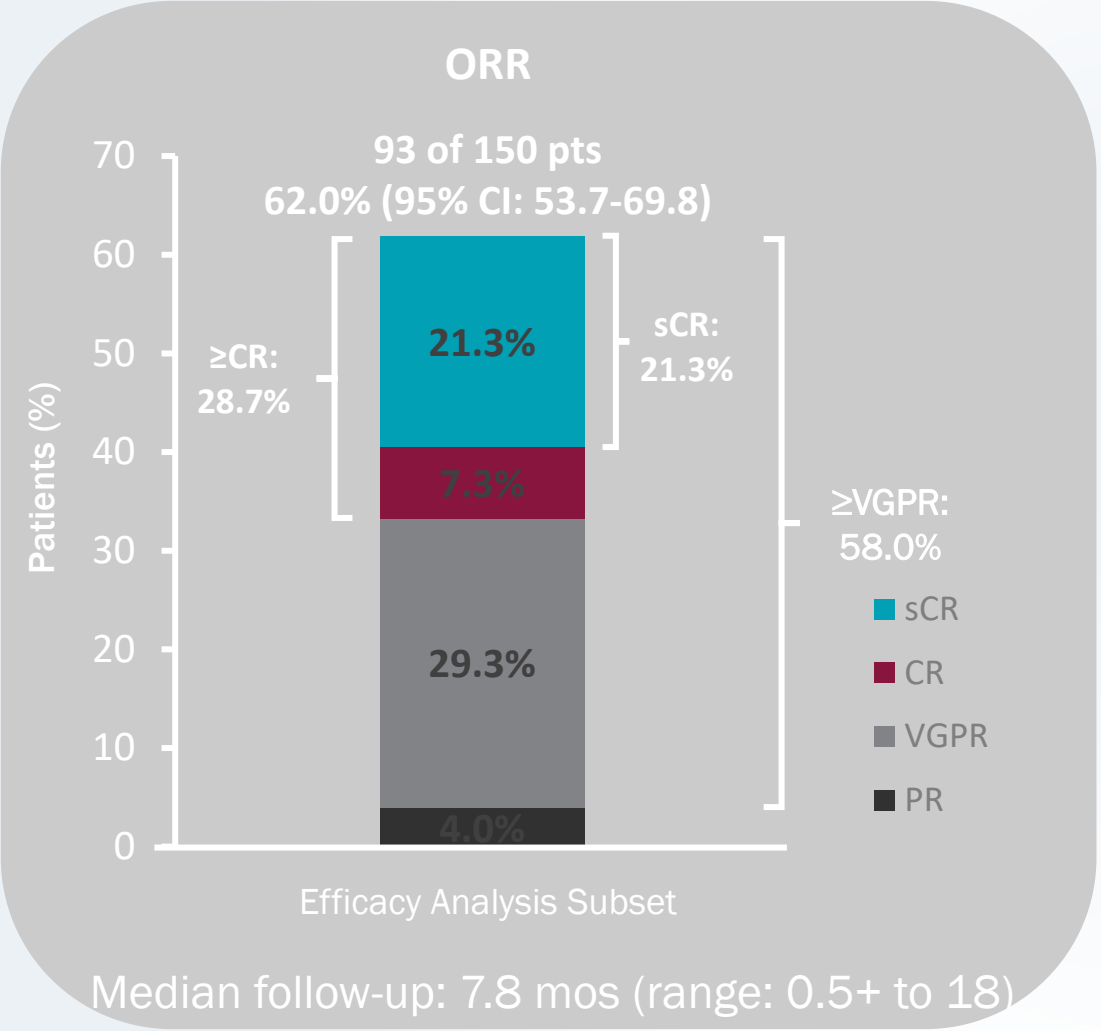
Characteristic	All Patients (N = 165)
Median age, yr (range) ▪ Age ≥75 yr, n (%)	64.0 (33-84) 24 (14.5)
Male, n (%)	96 (58.2)
Race, n (%) ▪ White ▪ Black ▪ Other	 134 (81.2) 21 (12.7) 10 (6.1)
BM plasma cells ≥60%, n (%)*	18 (11.3)
Extramedullary plasmacytomas ≥ 1, n (%)[†]	28 (17.0)
High-risk cytogenetics, n (%)[‡]	38 (25.9)
ISS stage at BL, n (%)[§] ▪ I ▪ II ▪ III	 85 (52.5) 57 (35.2) 20 (12.3)

Characteristic	All Patients (N = 165)
eGFR < 60 mL/min/1.73 m^2, n (%)	44 (26.7)
Median time since dx, yr (range)	6.0 (0.8-22.7)
Median prior lines of therapy, n (range)	5 (2-14)
Prior SCT, n (%)	135 (81.8)
Exposure status, n (%) ▪ Triple class exposed[‖] ▪ Penta drug exposed[¶] ▪ Selinexor	 165 (100) 116 (70.3) 6 (3.6)
Refractory status, n (%) ▪ Triple class refractory[‖] ▪ Penta drug refractory[¶] ▪ Refractory to last line of therapy	 128 (77.6) 50 (30.3) 148 (89.7)

*n = 160; includes bone marrow biopsy and aspirate. [†]Included soft-tissue plasmacytomas not associated with bone. [‡]n = 147; del(17p), t(4:14), and/or t(14;16). [§]n = 162. [‖]≥1 PI, ≥1 IMiD, ≥1 anti-CD38 mAb. [¶]≥2 PI, ≥2 IMiD, ≥1 anti-CD38 mAb.

Moreau. ASH 2021. Abstr 896.

MajesTEC-1: Efficacy Outcomes



Event	All Patients (N = 165)
MRD negativity, n (%, 95% CI) ▪ At 10^{-5} ▪ At 10^{-6}	(n = 150) 37 (24.7; 18.0-32.4) 25 (16.7; 11.1-23.6)
MRD negativity with ≥CR, %	41.9
Median TTR, mo (range)	1.2 (0.2-5.5)
Median DoR, mo	Not yet reached
EFS rates, % (95% CI) ▪ 6-Mos ▪ 9-Mos	 92.5 (80.6-97.2) 85.9 (70.0-93.7)
PFS rates, % (95% CI) ▪ 6-Mos ▪ 9-Mos	 64.4 (56.0–71.7) 58.5 (48.8–67.0)
Median OS	Not yet reached

Moreau. ASH 2021. Abstr 896.

MajesTEC-1: Safety

AEs in ≥20% of Patients, n (%)	All Patients (N =165)	
	Any Grade	Grade 3/4
Hematologic		
▪ Neutropenia	108 (65.5)	94 (57.0)
▪ Anemia	82 (49.7)	57 (34.5)
▪ Thrombocytopenia	63 (38.2)	35 (21.2)
▪ Lymphopenia	56 (33.9)	53 (32.1)
Nonhematologic		
▪ CRS	118 (71.5)	1 (0.6)
▪ Injection site erythema	42 (25.5)	0
▪ Fatigue	41 (24.8)	3 (1.8)
▪ Nausea	40 (24.2)	1 (0.6)
▪ Headache	36 (21.8)	1 (0.6)
▪ Diarrhea	34 (20.6)	4 (2.4)

No patients required teclistamab dose reduction; only
1 patient discontinued due to AE (adenoviral pneumonia)

Serious AEs: 88 (53.3%)

Teclistamab-related per investigator: 33 (20.0%)

Injection-site reactions (all grade 1/2): 58 (35.2%)

Infections: any grade, 104 (63.0%); grade 3/4: 35.2%

Opportunistic infections: 9 (5.5%)

Hypogammaglobulinemia: 119 (72.1%)

41 patients received IVIG at any time during the study (at physician discretion)

9 deaths due to AEs; none related to teclistamab

7 COVID-19, 1 pneumonia, 1 hemoperitoneum

Moreau. ASH 2021. Abstr 896.

MajesTEC-1: CRS

CRS Parameter	All Patients (n = 165)
CRS, n (%)	118 (71.5)
≥2 CRS events, n (%)	54 (32.7)
Median time to onset, days (range)	2 (1-6)
Median duration, days (range)	2 (1-9)
Supportive measures, n (%)*	109 (66.1)
▪ Tocilizumab	60 (36.4)
▪ Low-flow oxygen by nasal cannula†	21 (12.7)
▪ Steroids	13 (7.9)
▪ Single vasopressor	1 (0.6)

*Patients could receive >1 supp[illegible] †≤6 L/min

All CRS events grade 1 (49.7%) or grade 2 (21.2%), except for 1 transient grade 3 CRS event (0.6%) that fully resolved

97% of events confined to step-up and cycle 1

All CRS events resolved without the need for treatment discontinuation

2.4% of patients received >1 dose of tocilizumab for a single CRS event

Moreau. ASH 2021. Abstr 896.

MajesTEC-1: Neurotoxicity

Neurotoxicity Parameter	All Patients (n = 165)
Neurotoxicity, n (%)	21 (12.7)
▪ Grade ≥3	0
Specific event, n (%)	
▪ Headache	14 (8.5)
▪ ICANS	5 (3.0)
▪ Encephalopathy	2 (1.2)
▪ Tremor	2 (1.2)
Median time to onset, days (range)	2.5 (1-7)
Median duration, days (range)	3 (1-37)
Supportive measures, n (%)	12 (7.3)
▪ Tocilizumab	3 (1.8)
▪ Dexamethasone	3 (1.8)
▪ Levetiracetam	1 (0.6)

No treatment discontinuations or dose reductions due to neurotoxicity

5 patients had ICANS events at RP2D, all grade 1/2

Most (7/9) ICANS events occurred concurrently with CRS

All resolved

Moreau. ASH 2021. Abstr 896.

Comparison of BCMA-Targeted agents in RRMM

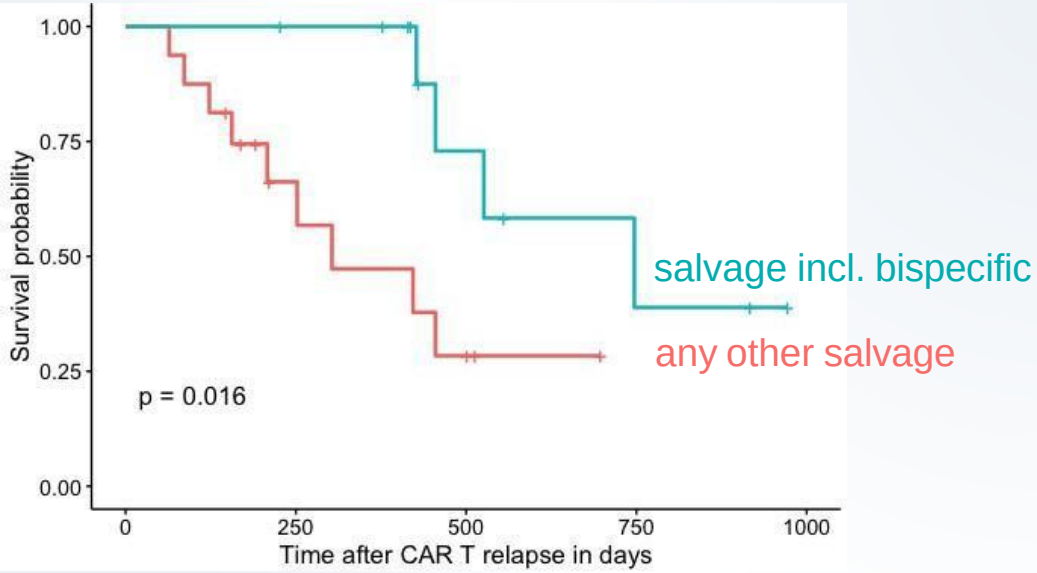
Perspective	CAR-T cell therapy	BiTE/Bispecific Antibodies	Antibody-Drug Conjugate
Strength	1. Most clinical data support clinical efficacy 2. High response/MTD- rate in RRMM patients received multiple lines of prior treatment 3. May be effective for extramedullary disease 4. Development of long-term anti-tumor immunity	1. "Off-the shell" products, no delay in treatment 2. Clinical benefit observed in RRMM patients 3. No lymphodepletion treatment required	1. "Off-the shell" products, no delay in treatment 2. Clinical benefit observed in RRMM patients 3. Potent anti-tumor activity of payload 4. Clinical efficacy doesn't rely on host immune function status
Challenges	1. Long and labor-intensive manufacturing process 2. Require treatment at a specialized center 3. High CRS and neurotoxicity rate 4. Toxicity of lymphodepletion therapy 5. Clinical activity relies on adequate number and function of collected patients T cells 6. High treatment cost	1. Less data in heavily pretreated patients, may be less effective in this subgroup 2. CRS and neurotoxicity 3. Short half-life, need continuous infusion 4. Clinical activity relies on adequate number and function of collected patient's effector cells 5. Hight treatment cost	1. High serum level of sBCMA may affect clinical efficacy 2. Payload related toxicity 3. Multiple treatment leads to increased cost.

https://www.readcube.com/library/98e11646-1046-44cc-acc5-a2924251bdc4:c0eb9663-88ff-4f0b-9963-e788c0b4f6e5

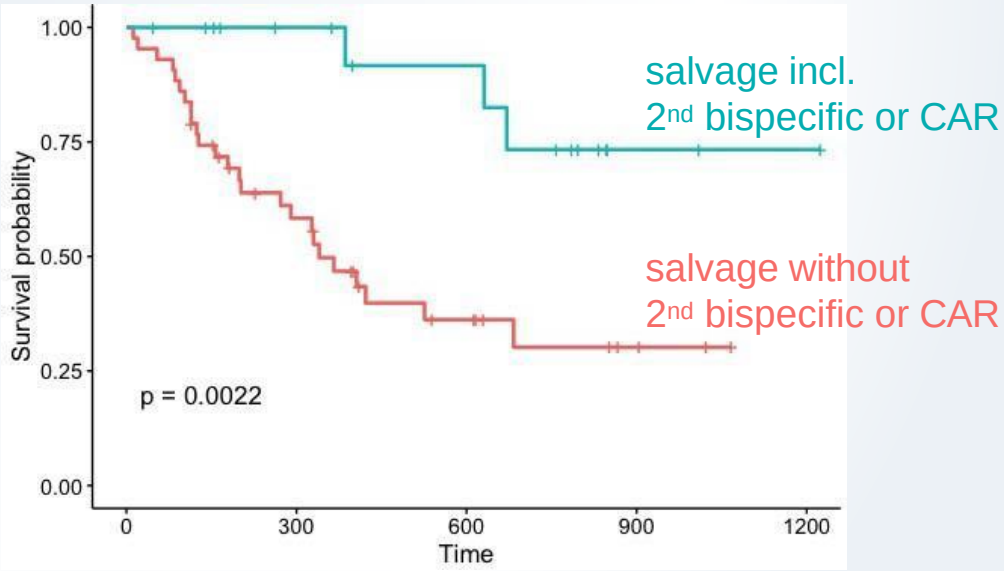
CAR T – bispecific antibody sequence: does it matter?

- Both approaches have resulted in **durable responses and are tolerable** anecdotally
- Important unanswered question as products go into market
- More data needed to interpret role **switch/sequencing of target antigen**

OS after CAR T relapse

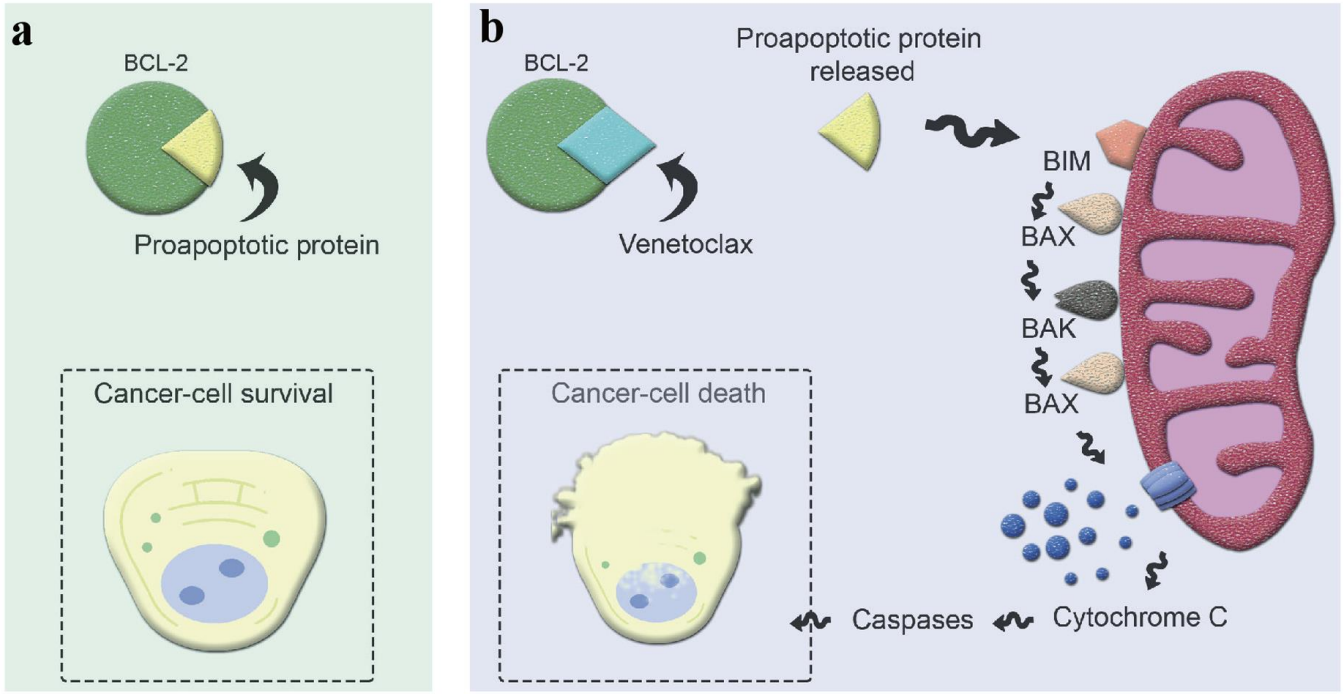


OS after bispecific relapse

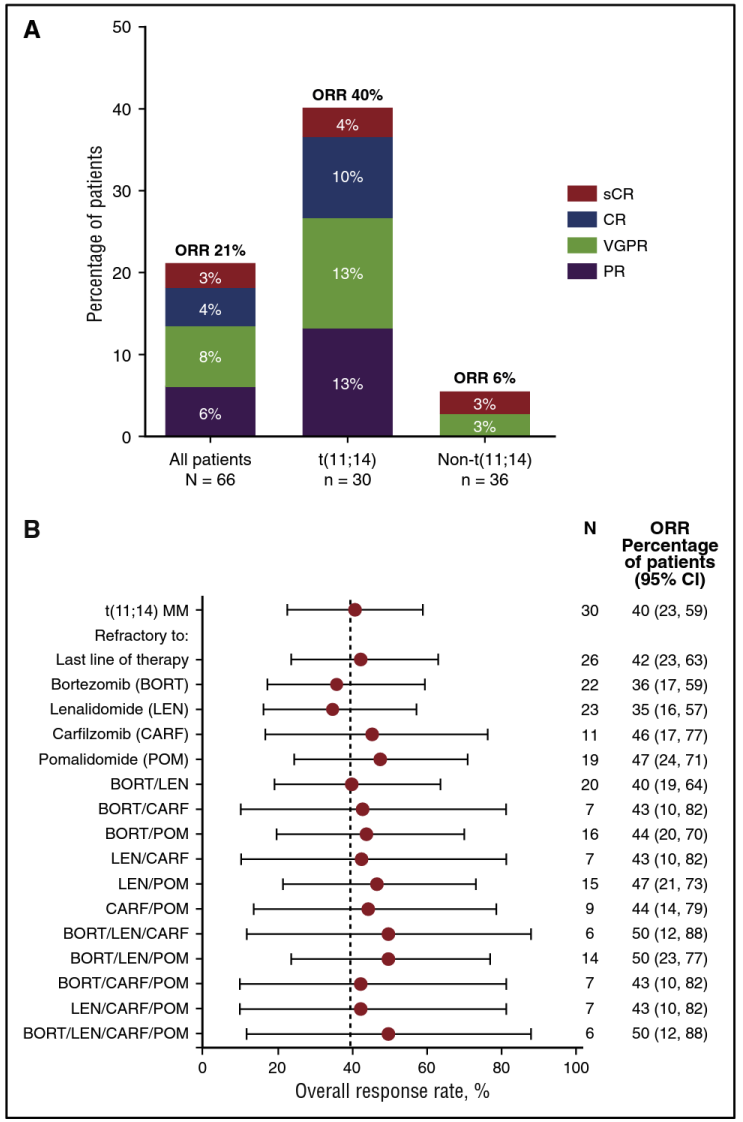


Van Oekelen, et al. IMW 2021

Venetoclax



Ehsan, et al. J Hematol. 2021 Jun;10(3):89-97.



Kumar, et al. Blood. 2017 Nov 30;130(22):2401-2409

Selective BCL-2 Inhibitor Venetoclax in RRMM
Phase III BELLINI

N= 291
- RRMM
- 1-3 prior lines of tx
- PI non-refractory

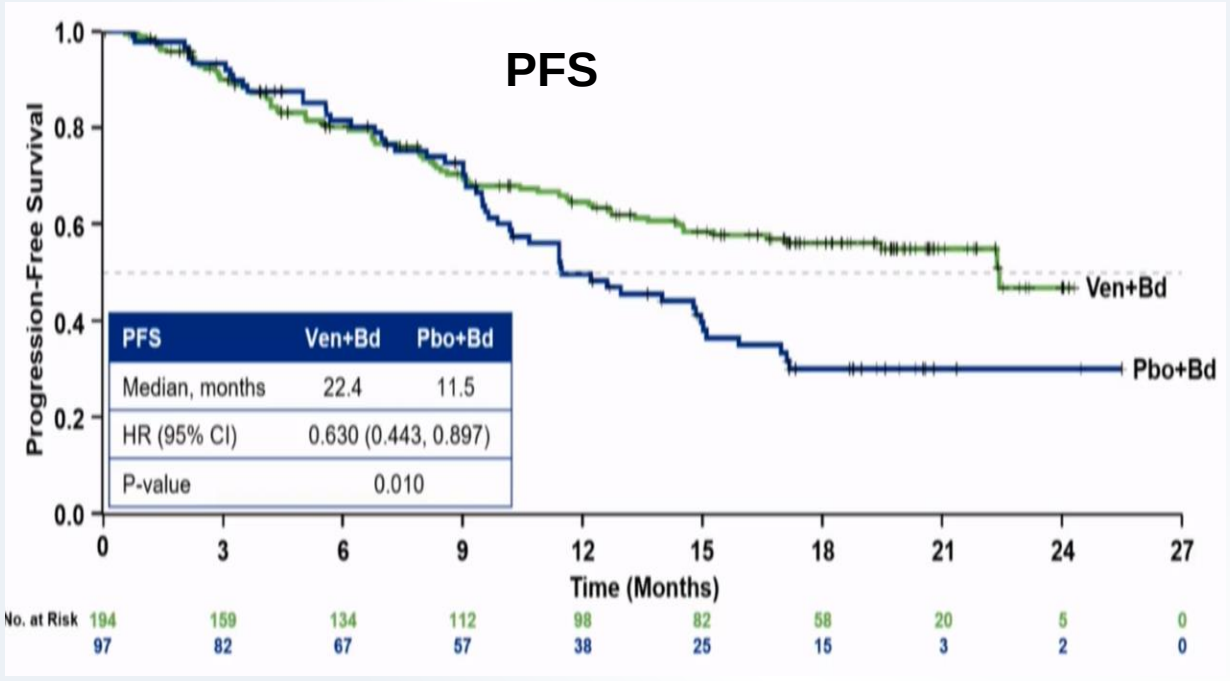
R 2:1

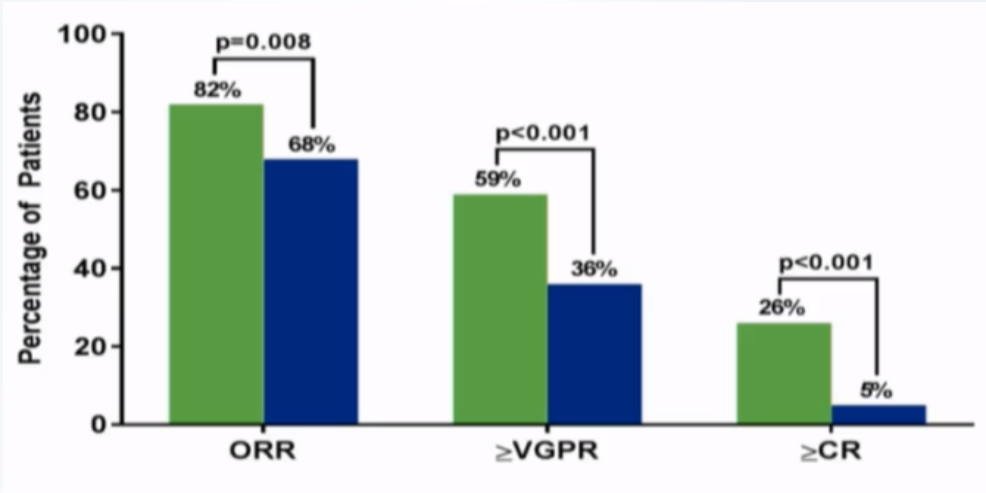
Venetoclax 800 mg QD + **Bortezomib + dex**

Placebo+ Bortezomib + dex

Until PD

- **Primary endpoint: PFS**
- **Secondary endpoints: ORR, ≥ VGPR, OS, QoL**



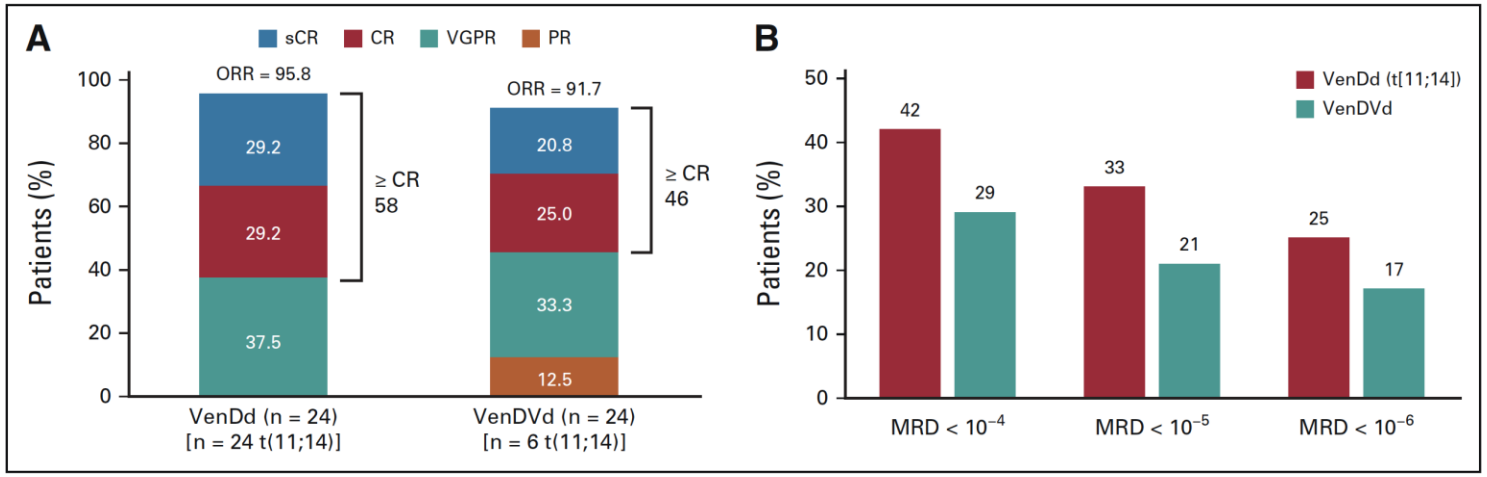


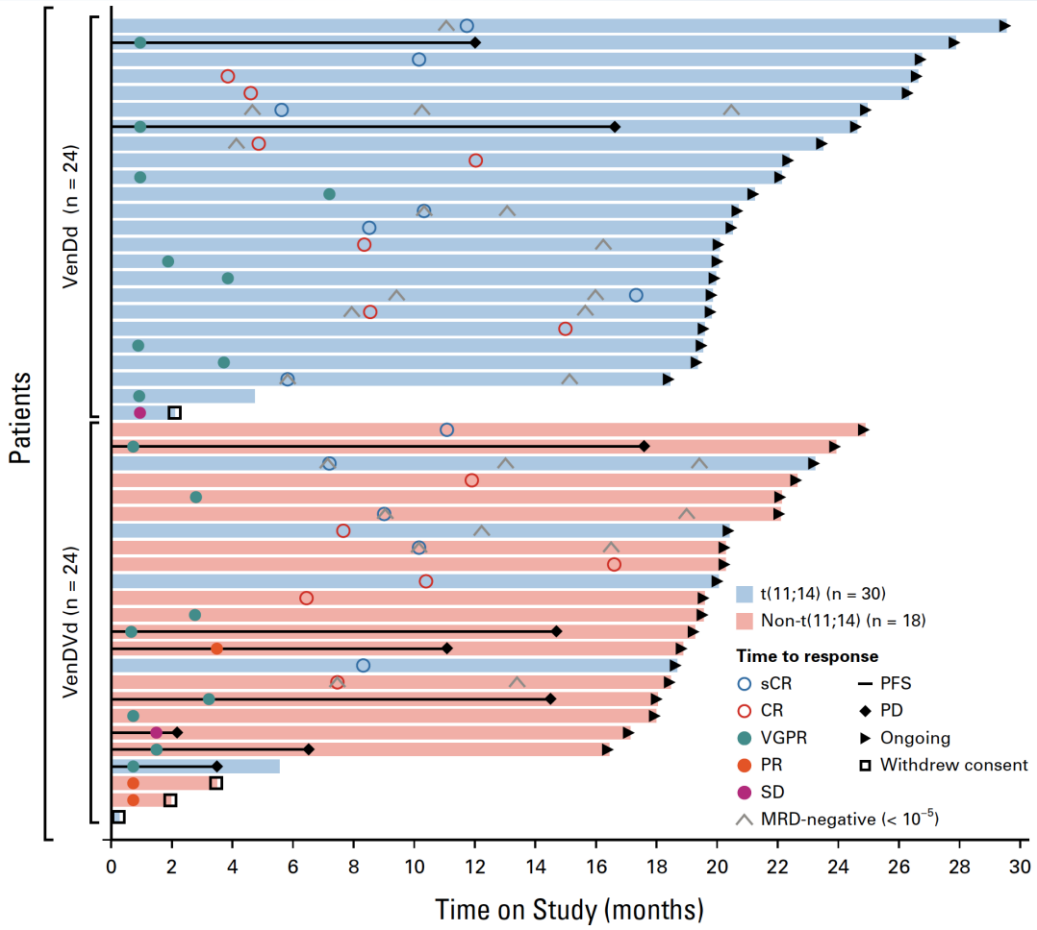
- **Low BCL-2 expression, high-risk cytogenetics**, or **ISS III** disease were associated with **decreased PFS and OS** in the Ven+Vd arm
- Patients with **t(11:14)** had **consistent clinical benefit** when treated with Ven + Vd; benefit-risk profile appears to be favorable in this MM subset

VCC VIRTUAL Challenging Case Clinic

Figures from Kumar S, et al. 2019 EHA: Abstract LB2601.

VenDd and VenDVd in RRMM





Bahlis, et al. J Clin Oncol 39:3602-3612.

VCC VIRTUAL Challenging Case Clinic

University of Nebraska Medical Center

Bio Ascend™

Antimicrobial prophylaxis with venetoclax-based regimens in plasma cell disorders

Antibacterial prophylaxis	Antiviral prophylaxis	Antifungal prophylaxis
Oral levofloxacin or amoxicillin clavulanate during the following time-periods: • First 90 days of treatment initiation • If ANC < 500/cc • 30 days following disease progression on venetoclax-based regimen	Oral acyclovir or valacylovir for the duration of therapy for prophylaxis against herpes simplex virus or varicella zoster virus reactivation	Typically not used. However, can consider mold-active prophylaxis (voriconazole or posaconazole) if prolonged neutropenia (ANC < 500/cc for more than 7 days) on venetoclax-based regimen or high-dose dexamethasone is being used

Abbreviations: ANC, absolute neutrophil count.

Chakraborty, et al. Br J Haematol 2022 May 20. doi: 10.1111/bjh.18243. Online ahead of print.

Patient Case #1

- ✓ 85 y/o patient with triple-class refractory IgG Kappa Myeloma (ISS stage III; FISH del 17p) presents to you with progressive disease. Her prior regimens include: VRD → DPd → KCyD. Her medical history is notable for HTN, DM2, history of corneal transplant. She is an ECOG 2.

Based on current FDA approvals how would you treat this patient?

1. Venetoclax + Dexamethasone
2. Belantamab Mafodotin
3. Selinexor + Dexamethasone
4. Ide-cel
5. Cilta-cel

Patient Case #2

- ✓ 64 y/o male with a history of IgA Lambda Multiple Myeloma, Durie Salmon stage IIa, FISH t(11;14) is initially treated with RVD (lenalidomide, bortezomib, dexamethasone) followed by ASCT. He develops persistent grade 1 neuropathy from his treatment with bortezomib. He opts for no maintenance therapy. 3 years after stem cell transplant he develops a biochemical relapse. He is then treated with KPd (Carfilzomib, pomalidomide, dexamethasone). He had a very troubling experience during his transplant and does not want to be admitted to the hospital for treatment

How would you treat this patient?

1. Belantamab mafodotin
2. Selinexor, bortezomib, dexamethasone (XVd)
3. Venetoclax, daratumumab, dexamethasone (VenDd)
4. Cilta-cel
5. Teclistamab

Patient Case #3

- ✓ 45 y/o male with triple-class refractory IgG Lambda Multiple Myeloma is progressing s/p 3 lines of prior therapy. He states that he is interested in receiving whatever treatment has demonstrated the highest efficacy for his disease.

How would you treat this patient?

1. Belantamab Mafodotin
2. Cilta-cel
3. Ide-cel
4. Teclistamab
5. Selinexor, Carfilzomib, Dexamethasone (XKd)

Conclusions

- ✓ The early phases of myeloma therapy are commonly treated with IMIds, PIs and Mabs. There are a number of new targets that utilize novel MOAs to treat more advanced disease.
- ✓ For patients who have relapsed beyond these initial three classes consider the following therapies
  - ✓ Selinexor
  - ✓ Venetoclax [for t(11;14)]
  - ✓ BCMA targeted therapy
- ✓ BCMA is an exciting new target with three modalities currently being utilized
  - ✓ Antibody-drug conjugate
  - ✓ Bispecific antibody
  - ✓ CAR-T
- ✓ There are a number of ongoing trials combining these novel MOAs with more traditional myeloma therapies to optimize patient outcomes

Thank You!

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Next presentation: Wednesday, November 16, 2022
Optimal Induction and Maintenance Therapies
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