Optimizing Therapy of Relapsed/Refractory Multiple Myeloma

Noopur Raje, MD
Director, Center for Multiple Myeloma
MGH Cancer Center
Professor of Medicine
Harvard Medical School

MASSACHUSETTS GENERAL HOSPITAL

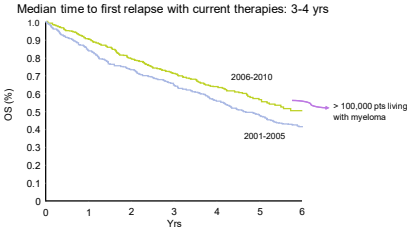
MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

Disclosures

- Consultant /Advisory Board: Celgene, Millenium Takeda, Amgen-Onyx, Novartis, Janssen, BMS, Merck, Bluebird
- Research Funding: Astra Zeneca
- Steering Committee: Amgen, Roche

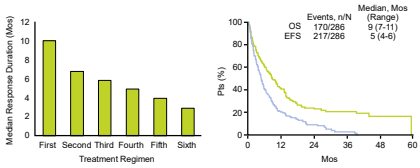
Myeloma: Scope of the Problem

Median time to first relapse with current therapies: 3-4 yrs



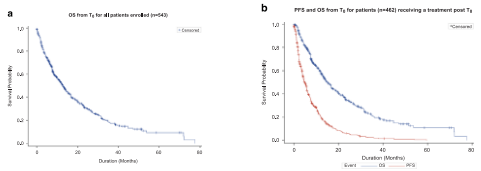
Kumar SK, et al. Leukemia. 2014;28:1122-1128.

Confronting Disease Relapse in Myeloma



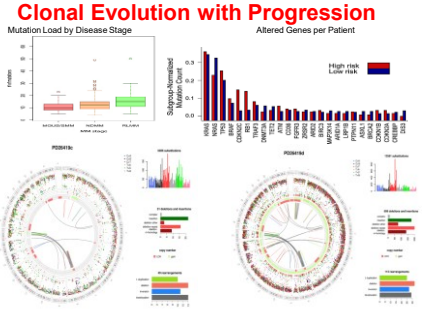
Kumar SK, et al. Mayo Clin Proc. 2004;79:867-874.
Kumar SK, et al. Leukemia. 2012;26:149-157.

Current estimates for patients refractory to both IMiDs and PIs

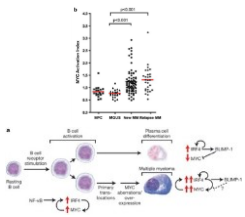


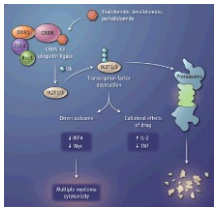
Kumar et al, Leukemia 2017

Clonal Evolution with Progression



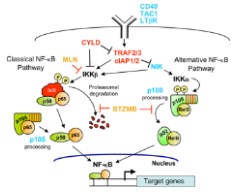
Targeting the drivers- Myc: IMiDs

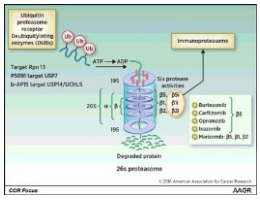




Schaffer et al, Nature. 454. 226-31 Stewart. Science 2014;343:256-257; Lu et al Science 2014;343:305-309; Kronke et al. Science 2014;343:301-305

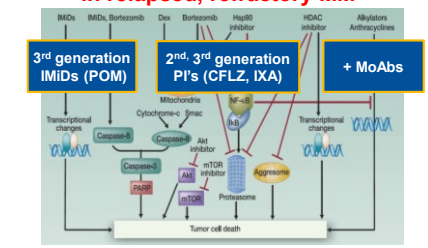
Targeting the Proteasome





Gillmore, Cancer Cell, 12(2), p95–97, 14 August 2007; Anderson Clin Cancer Res 2016;22:5419-5427

Rational combination strategies in relapsed, refractory MM



Lonial S, Mitsiades CS, Richardson PG. *Clin Cancer Res* 2011;17:1264-77.

Selected phase III trials in relapsed disease

Name of trial	No. prior lines	Arm	N	PFS (months)	ORR	≥VGPR	≥CR
ENDEAVOR	1-3	Kd	464	18.7	77%	54%	13%
		Vd	465	9.4	63%	29%	6%
TOURMALINE-MM1	1-3	IRd	360	20.6	78%	48%	12%
		Rd	362	14.7	72%	39%	7%
ELOQUENT-2	1-3	Elo-Rd	321	19.4	79%	33%	4%
		Rd	325	14.9	66%	28%	7%
ASPIRE	1-3	KRd	396	26.3	87%	70%	32%
		Rd	396	17.6	67%	40%	9%
PANORAMA 1	1-3	Pano-Vd	387	11.99	61%		11%
		Vd	381	8.08	55%		6%
NIMBUS (MM-003)	≥2§	Pd	302	4.0	31%	6%	1%
		D	153	1.9	10%	1%	0%
CASTOR	≥1	Vd-dara	251	NE	82.9%	59.2%	19.2%
		Vd	247	7.2	63.2%	29.1%	9%
POLLUX	≥1	Rd-dara	286	NE	93%	76%	43%
		Rd	283	18.4	76%	44%	19%

A.R.R.O.W. Study Design

1:1 Randomization
N = 478

- Relapsed and Refractory MM
- 2-3 prior lines
- Prior exposure to IMID & PI
- PS 0-1

Stratification:

- ISS stage
- Refractory to bortezomib
- Age (<65 vs. ≥65)

Arm A: Once-weekly carfilzomib + dex
(30 min infusion of K)
Carfilzomib 20 mg/m² IV D1 (Cycle 1)
Carfilzomib 70 mg/m² IV D8, 15 (Cycle 1), D1, 8, 15 (Cycle 2+)
Dexamethasone 40 mg IV/PO D1, 8, 15 (All cycles)
Dexamethasone 40 mg IV/PO D22 (Cycles 1-9 only)

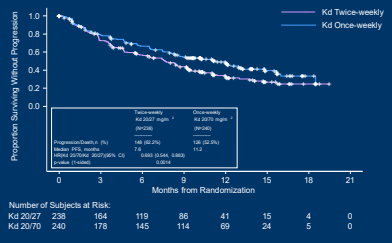
28-day cycles

Arm B: Twice-weekly carfilzomib + dex
(10 min infusion of K)
Carfilzomib 20 mg/m² IV D1, 2 (Cycle 1)
Carfilzomib 27 mg/m² IV D8, 9, 15, 16 (Cycle 1), D1, 2, 8, 9, 15, 16 (Cycle 2+)
Dexamethasone 40 mg IV/PO D1, 8, 15 (All cycles)
Dexamethasone 40 mg IV/PO D22 (Cycles 1-9 only)

Follow-up for Disease Status until Confirmed PD

Long-term Follow-up for Survival

Primary Endpoint: Progression-Free Survival Assessed by Computational Algorithm Based on IMWG-URC



What about Len refractory patients?

Len-refractory RRMM

Available Efficacy Data on Len-refractory RRMM Patients

Trial/Regimen	Analysis set	N	PFS	ORR	MRD neg. rate at 10^{-5}
CASTOR[2] D-Vd vs Vd	Len-refractory at last prior line of therapy	D-Vd: n = 45 Vd: n = 60	Median: **9.3 mo vs 4.4 mo** HR: 0.36; 95% CI, 0.21-0.63; *P* = 0.0002 18-mo PFS rate: 34% vs 2%	**81% vs 50%** *P* = 0.0021	**9% vs 0%** *P* = 0.0082
MMY1001[4] D-Pd	All treated (89% len-refractory)	n = 103	Median: **9.9 mo** **24-mo PFS rate: 31%**	**66%**	**7%**
ENDEAVOR[5,6] Kd vs Vd	Len-refractory	Kd: n = 113 Vd: n = 122	Median: **8.8 mo vs 6.6 mo**[5] HR: 0.80; 95% CI, 0.57-1.11[6]	N/R	N/R
MM-003[7] P-low d vs high d	Len-refractory	P-low d: n = 286 High d: n = 141	Median: **3.9 mo vs 1.9 mo** HR: 0.50; 95% CI, 0.40-0.62	**30% vs 9%** *P* <0.0001	N/R

Addition of DARA to SOC is effective in len-refractory RRMM

1. Harousseau JL and Attal M. *Blood* 2017;130:963-973. 2. Sengsayadeth S, et al. Blood Cancer J 2017;7(3):e545. 3. Lentzsch S, et al. Oral presentation at JSH, Oct 20-22, 2017; Tokyo, Japan; Abstract OS3-12D-2. 4. Facon T, et al. Poster presented at ASH, Dec 9-12, 2017; Atlanta, GA; Abstract 1824. 5. Moreau P, et al. *Leukemia* 2017;31:115-122. 6. Dimopoulos MA, et al. *Lancet Oncol* 2016;17(1):27-38. 7. San-Miguel J, et al. Lancet Oncol 2013;14(11):1055-1066.

Ajai Chari, MD

Len, lenalidomide; Vd, bortezomib/dexamethasone; PFS, progression-free survival; ORR, overall response rate; MRD, minimal residual disease; HR, hazard ratio; Pd, pomalidomide/dexamethasone; Kd, carfilzomib/dexamethasone; N/R, not reported; SOC, standard of care.

Study Design: D-Kd Arm of MMY1001

- Open-label, nonrandomized, multicenter, phase 1b study in RRMM patients
- Per protocol, DARA was administered as a **single first dose (n = 10)** or as a **split first dose (n = 75)**

Eligibility/treatment

- Relapsed MM
  - 1-3 prior lines of therapy, including bortezomib and an IMiD
  - Len-refractory pts allowed
- Carfilzomib-naïve
- ECOG status ≤2
- LVEF ≥40%
- ANC ≥1 × 10^9/L
- Platelet count ≥75 × 10^9/L

Dosing schedule (28-day cycles)

DARA:

- Split first dose*: 8 mg/kg Days 1-2 of Cycle 1
- Single first dose: 16 mg/kg on C1D1
- 16 mg/kg IV QW on Cycles 1-2, Q2W on Cycles 3-6, and Q4W thereafter until PD

Carfilzomib[b]:

- 20 mg/m^2 IV Cycle 1 Day 1
- Escalated to 70 mg/m^2 Cycle 1 Day 8+; weekly (Days 1, 8, 15) until PD

Dexamethasone: 40 mg/week (Days 1, 8, 15, 22) IV or PO until PD

Endpoints

Primary

- Safety, tolerability

Secondary

- ORR and duration of response
- OS

Exploratory

- PFS
- MRD (NGS)[c]
- PK

*In 500-mL dilution volume.
[b]Both 20 mg/m^2 and 70 mg/m^2 were administered as 30-min IV infusions.
[c]Among patients evaluated for MRD, MRD was assessed using NGS at time of suspected CR and at 12 and 18 mo after initial dose. In cases where daratumumab is suspected of interfering with IFE and preventing clinical CR response calls, subjects with VGPR may also be evaluated for MRD.

Ajai Chari, MD

ECOG, Eastern Cooperative Oncology Group; LVEF, left ventricular ejection fraction; ANC, absolute neutrophil count; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; IV, intravenous; PO, oral; OS, overall survival; MRD, minimal residual disease; NGS, next generation sequencing; PK, pharmacokinetic; IFE, immunofixation; IRR, infusion-related reaction

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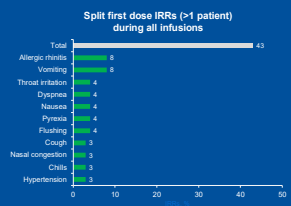
Infusion Rates and IRRs: Split First Dose DARA (All Treated)

	IRR, n (%)	Median (range) infusion time
Single first infusion (n = 10)		
Cycle 1 Day 1	5 (50.0%)	7.1 (6.5-8.9) h
Split first infusion (n = 75)		
Cycle 1 Day 1	27 (36.0%)	4.3 (3.9-10.6) h
Cycle 1 Day 2	2 (2.7%)	4.2 (3.8-4.8) h

- IRR % and infusion times were consistent between single and split first dose for subsequent infusions



Split first dose of DARA is feasible and improves patient convenience

IRR, infusion-related reaction.

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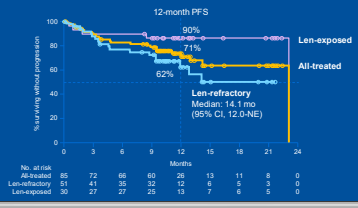
PFS

- Median follow up: 12.0 months



PFS benefit observed in len-refractory patients

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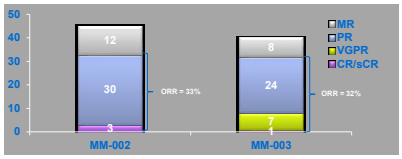
What about Pomalidomide ?

Efficacy Results of Pomalidomide + LoDEX in advanced RR MM (Phase II/III Studies MM002 & MM003)

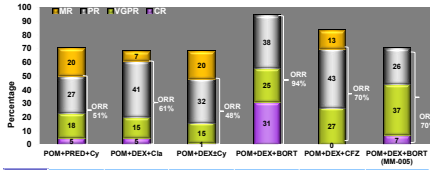


	MM-002[1]	MM-003[2,3]
Median follow-up, months	14.2	15.4
Median DoR, months	8.3	7.5
Median PFS, months	4.2	4.0
Median OS, months	16.5	13.1

response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; POM, pomalidomide; PR, partial response; sCR, stringent

1.Richardson PG, et al. *Blood* 2014;123:1826-32.2. San Miguel J, et al. *LancetOncology* 2013;14:1055-1066. 3. San Miguel et al: ASH 2013;Oral Presentation and Abstract 686.

Efficacy Results of POM-based Triple Therapy Combinations in Advanced RRMM

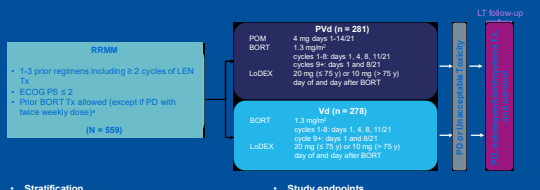


Study	Larocca[1]	Mark[2]	Baz[3]	Mikhael[4]	Shah[5]	Richardson[6]
Phase	1/2	2	1/2	2	1/2	1/2
N	55*	114	70	16	79	27
Population	1–3 prior therapies; LEN-relapsed or refractory	≥ 3 prior therapies including LEN (not all refractory)	≥ 2 prior therapies; LEN-refractory	1–4 prior therapies, resistant or refractory to LEN	Relapsed and/or refractory; LEN-refractory	1–4 prior therapies; LEN-refractory, prior BORT

BORT, bortezomib; CFZ, carfilzomib; Cla, clarithromycin; CR, complete response; Cy, cyclophosphamide; DEX, dexamethasone; LEN, lenalidomide; LoDEX, low-dose dexamethasone; MR, minimal response; ORR, overall response rate; POM, pomalidomide; PR, partial response; PRED, prednisone; VGPR, very good partial response.

1. Larocca A, et al. *Blood* 2013;122:2798a2806.
2. Mark et al: ASH 2013; Poster Presentation and Abstract 1866.
3. Baz et al: ASH 2013; Poster Presentation and Abstract 3200.
4. Mikhael J et al: ASH 2013; Poster Presentation and Abstract 1940.
5. Shah et al: ASH 2013; Oral Presentation and Abstract 688.
6. Richardson et al: ASH 2013; Oral Presentation and Abstract 8589.

OPTIMISMM Study Design and methods



- **Stratification**
  - age (≤ 75 y vs > 75 y)
  - number of prior antimyeloma regimens (1 vs > 1)
  - β2-microglobulin levels at screening (< 3.5 mg/L vs ≥ 3.5 to ≤ 5.5 mg/L vs > 5.5 mg/L)
- **Study endpoints**
  - Primary: PFS
  - Secondary: OS, ORR by IMWG criteria, DOR, safety
  - Key exploratory: TTR, PFS2, efficacy analysis in subgroups
- **Data cutoff:** October 26, 2017

aPatients with PD during therapy or within 60 days of the last dose of a BORT-containing therapy under the approved dosing schedule of 1.3 mg/m² twice weekly were excluded.
BORT, bortezomib; DOR, duration of response; IMWG, International Myeloma Working Group; LT, long-term; PFS2, progression-free survival after next line of therapy; TTR, time to response.

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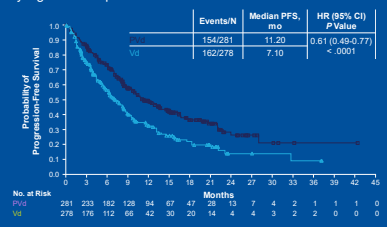
Progression-Free Survival (ITT Population)

- OPTIMISMM met its primary endpoint, demonstrating a clinically meaningful and statistically significant improvement in PFS with PVd vs Vd



Abstract 8001 - OPTIMISMM—Paul Richardson, MD

What is New in MM

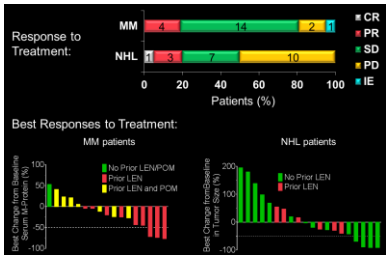
Oral proteasome inhibitors	New IMiDs	HDACi	Kinase inhibitors	Monoclonal antibodies	Novel mechanisms	Immuno-therapies
• Ixazomib	• CC-122	• Panobinostat	• Vermurafenib	• Elotuzumab	• Venetoclax	• PDL-1/PD-1
• Oprozomib	• CC-220	• Ricolinostat	• Afuresertib	• Daratumumab	• Selinexor	• CAR-T
• Marizomib		• ACY 241	• Dinaciclib	• Isatuximab		• BITE
			• PIM (LGH447)			
			• Trametinib			

HDACi histone deacetylase inhibitor

Oprozomib in Myeloma: still in development

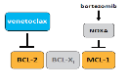
- The most common grade ≥3 nonhematologic AEs were diarrhea, nausea, and vomiting; rates of treatment-emergent PN and rash were low.
- Recommended phase 2 dose and schedule: 240/300 mg/day in the 2/7 step-up schedule and 150/180 mg/day in the 5/14 step-up schedule.
- Preliminary data suggest that step-up dosing is associated with improved tolerability.
- Enrollment of patients with MM continues both schedules in the phase 2 study with a target of 94 patients; all patients are now receiving a new (extended-release) formulation of oprozomib.
- Single-agent oprozomib has promising antitumor activity, with responses observed in patients who had carfilzomib-refractory MM.

CC-122: New IMiD



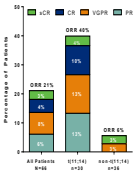
Venetoclax Background

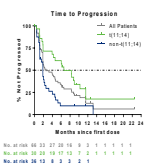
- BCL-2 and MCL-1 promote multiple myeloma (MM) cell survival
- Venetoclax is a selective, orally available small molecule BCL-2 inhibitor[1] and bortezomib can indirectly inhibit MCL-1
- Venetoclax enhanced bortezomib



Punnoose E et al. Mol Cancer Ther 2016

Phase 1 Venetoclax for RRMM: response and TTP in all patients and by t(11;14) status





Ph 1: Venetoclax in combination with Btz+Dex

Ven (50-500mg po daily); Btz (1.3mg/msq days 1,4,8,11); Dex (20mg days 1-2, 4-5, 8-9, 11-12) x8 cycles N=32

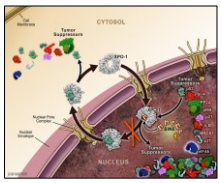
Criteria	Response % (36 pts)
CR	9% (3)
VGPR	11% (4)
PR	25% (10)

Cytogenetics	ORR % (36 pts)
t(11;14) (n=4)	75%
t(4;14) (n=3)	33%
del17p (n=8)	25%
Hyperdiploid (n=14)	64%

A Phase 3, multicenter, randomized, double blind, placebo-controlled study of venetoclax plus bortezomib and dexamethasone in subjects with relapsed or refractory myeloma in 1-3 prior lines of therapy and are sensitive or naïve to proteasome inhibitors

Chanan-Khan Lugano 2015

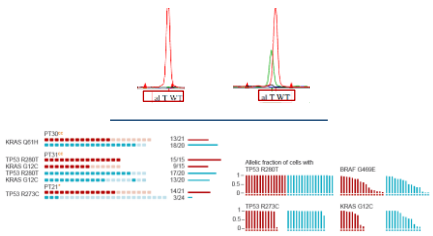
Selinexor Mechanism of Action



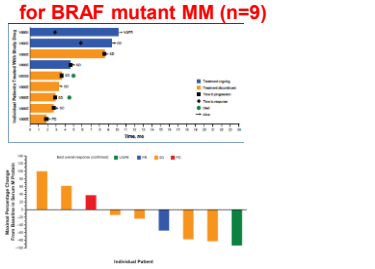
Exportin 1 (XPO1) is the only nuclear exporter for the majority of tumor suppressor proteins (TSPs), the glucocorticoid receptor (GR), and eIF4E-bound oncoprotein mRNAs

Selinexor is a first-in-class XPO1 inhibitor that induces nuclear retention and activation of TSPs and the GR in the presence of steroids and suppresses oncoprotein expression

Tracking Genetic Hetrogeneity



BASKET STUDY: VEMURAFENIB for BRAF mutant MM (n=9)



Raje et al, ASH 2015

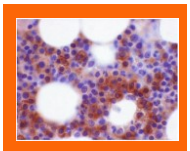
An open-label, pilot study of dabrafenib and/or trametinib in patients with relapsed and/or refractory multiple myeloma

Jens Lohr, MD PhD
Noopur Raje, MD

BCMA: A Promising Target in Multiple Myeloma (MM)

B cell maturation antigen (BCMA)

- A member of the TNF receptor superfamily
- Expression is largely restricted to plasma cells and mature B cells
- Not detectable in any other normal tissues
- Expressed nearly universally on multiple myeloma cells
- Anti-MM efficacy validated in initial studies[1]



Multiple myeloma cells expressing BCMA

(brown color = BCMA protein)

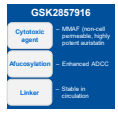
GSK 2857916:Background

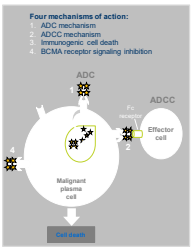
requisite for long-lived plasma cells' survival

BCMA is broadly expressed on malignant plasma cells

GSK2857916: humanized, afucosylated IgG1 **anti-BCMA antibody;** neutralization of soluble BCMA

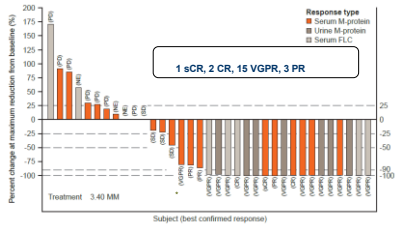
Preclinical studies demonstrate its selective and potent activity[1]





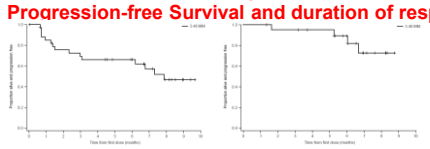
[1]Tai YT, et al. Blood 2014;123(20):3128-38.

DREAMM-1 Part 2: Maximum % Reduction in M-Protein or Free Light Chain from Baseline



One patient with a VGPR had a <90% reduction in serum M-protein due to missing laboratory data, which was confirmed by investigators as too small to quantify after the data cut-off

DREAMM-1 Part 2: Efficacy – Progression-free Survival and duration of response

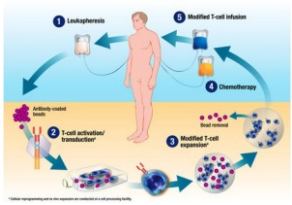


Number of subjects	**35**
Progressed or died	15 (43%)
Censored, f/u ended	3 (9%)
Censored, f/u ongoing	17 (49%)
Progression-free survival (months)	
Q1 (95% CI)	2.3 (0.7, 6.8)
Median (95% CI)	**7.9 (3.1, -)**
Q3 (95% CI)	N/A

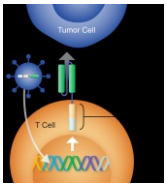
Number of subjects	**21**
Progressed or died	4 (19%)
Censored, f/u ended	0
Censored, f/u ongoing	17 (81%)
Duration of response (months)	
Q1 (95% CI)	6.7 (1.6, -)
Median (95% CI)	**N/A (6.7, -)**
Q3 (95% CI)	N/A

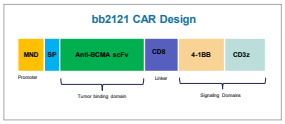
CI, confidence interval; f/u, follow-up; N/A, not available; Q, quartile

Chimeric Antigen Receptor (CAR) T cells



bb2121: AN OPTIMAL BCMA CAR T CELL DESIGN



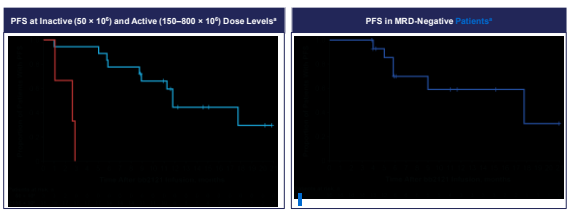


- Autologous T cells transduced with a lentiviral vector encoding a CAR specific for human BCMA
- State of the art lentiviral vector system
- Optimal 4-1BB costimulatory signaling domain: associated with less acute toxicity and more durable CAR T cell persistence than CD28 costimulatory domain[1]

1. Ali SI, et al. *Blood* 2016;128(13):1688-700.

PROGRESSION-FREE SURVIVAL

- mPFS of 11.8 months at active doses (≥150 × 10^6 CAR+ T cells) in 18 subjects in dose escalation phase
- mPFS of 17.7 months in 16 responding subjects who are MRD-negative



Data cutoff: March 29, 2018. Median and 95% CI from Kaplan-Meier estimate. NE, not estimable. *PFS in dose escalation cohort.

Current Understanding

Combinations will allow us to improve responses and cure a higher fraction of patients.

Drugs with different MOA will overcome genetic heterogeneity

High risk disease can be identified and specifically targeted

Future Directions in Myeloma Post ASCO: Clinical Trials

Krina Patel MD MSc
Assistant Professor
Department of Lymphoma/Myeloma
University of Texas MD Anderson Cancer Center

Optimizing Dosing Schedule

Once-weekly Versus Twice-weekly Carfilzomib Dosing in Patients with Relapsed and Refractory Multiple Myeloma: Results of the Randomized Phase 3 Study A.R.R.O.W.

María-Victoria Mateos,[1] Philippe Moreau,[2] James R. Berenson,[3] Katja Weisel,[4] Antonio Lazzaro,[5] Kevin Song,[6] Meletios A. Dimopoulos,[7] Mei Huang,[8] Anita Zahlten-Kumeli,[8] and A. Keith Stewart[9]

[1]Hematology, Hospital Clínico Universitario de Salamanca-IBSAL, Salamanca, Spain; [2]Hematology Department, University of Nantes, Nantes, France; [3]Institute for Myeloma and Bone Cancer Research, West Hollywood, CA, USA; [4]Universitatsklinikum Tübingen, Tübingen, Germany; [5]Department of Clinical Oncology and Hematology, Division of Hematology and Bone Marrow Transplant Center, Hospital Guilelmo da Saliceto, Piacenza, Italy; [6]Leukemia/Bone Marrow Transplant Program of British Columbia, Vancouver, British Columbia, Canada; [7]National and Kapodistrian University of Athens, Athens, Greece; [8]Amgen Inc., [9]Thousand Oaks, CA, USA; [9]Division of Hematology/Oncology, Mayo Clinic, Scottsdale, AZ, USA

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A.R.R.O.W. Study Rationale

- To develop a more convenient carfilzomib regimen, once-weekly Kd was assessed in the phase 1/2 CHAMPION-1 study in RRMM patients who had 1-3 prior lines of therapy[1]
  - Established the maximum tolerated dose (MTD) of carfilzomib at 70 mg/m^2
  - ORR was 77% and median PFS was 12.6 months; grade ≥3 AEs occurred in 62% of patients at MTD
- Based on promising results of the CHAMPION-1 study and to further explore the once-weekly regimen, the A.R.R.O.W. study was initiated to compare once-weekly Kd at 70 mg/m^2 with twice-weekly Kd at 27 mg/m^2 in patients with relapsed and refractory multiple myeloma

[1]Berenson JR, et al. Blood. 2016;127:2360-2368; [2]EMEA. Kyprolis: Product Information. EMEA: London, UK, 2016.
ORR, overall response rate

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A.R.R.O.W. Study Design

1:1 Randomization
N = 478

- Relapsed and Refractory MM
- 2-3 prior lines
- Prior exposure to IMiD & PI (except carfilzomib or oprozomib)
- PS 0-1
- CrCl of ≥30 mL/min

Stratification:

- ISS stage
- Refractory to bortezomib
- Age (<65 vs. ≥65)

Arm A: Once-weekly carfilzomib + dex
(30 min infusion of K)
Carfilzomib 20 mg/m^2 IV D1 (Cycle 1)
Carfilzomib 70 mg/m^2 IV D8, 15 (Cycle 1), D1, 8, 15 (Cycle 2+)
Dexamethasone 40 mg IV/PO D1, 8, 15 (All cycles)
Dexamethasone 40 mg IV/PO D22 (Cycles 1-9 only)

28-day cycles

Arm B: Twice-weekly carfilzomib + dex
(10 min infusion of K)
Carfilzomib 20 mg/m^2 IV D1, 2 (Cycle 1)
Carfilzomib 27 mg/m^2 IV D8, 9, 15, 16 (Cycle 1), D1, 2, 8, 9, 15, 16 (Cycle 2+)
Dexamethasone 40 mg IV/PO D1, 8, 15 (All cycles)
Dexamethasone 40 mg IV/PO D22 (Cycles 1-9 only)

Follow-up for Disease Status until Confirmed PD → Long-term Follow-up for Survival

Primary end point: PFS

CrCl, creatinine clearance; D, day; IMiD, immunomodulator; ISS, international staging system; IV, intravenous; K, carfilzomib; PD, progressive disease; PI, proteasome inhibitor; PO, by mouth

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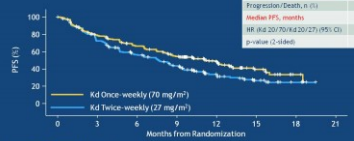
Primary Endpoint: PFS

	Once-weekly Kd 20/70 mg/m^2 (n=240)	Twice-weekly Kd 20/27 mg/m^2 (n=238)
Progression/Death, n (%)	126 (53%)	148 (62%)
Median PFS, months	11.2	7.6
HR (Kd 20/70/Kd 20/27) (95% CI)	0.693 (0.544, 0.883)	
p-value (2-sided)	0.0029	



Number of Patients at Risk:

Kd 20/70	240	178	145	114	69	24	5	0
Kd 20/27	238	164	119	86	41	15	4	0

Data cutoff date: June 15, 2017; Median follow-up: 12.6 (once-weekly) and 12.0 (twice-weekly) months
CI, confidence interval; HR, hazard ratio

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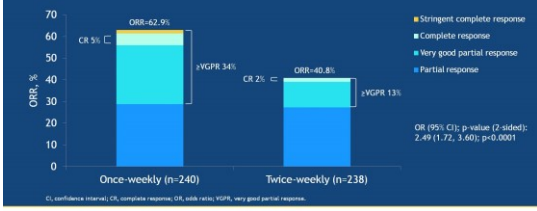
Overall Response Rates



CI, confidence interval; CR, complete response; OR, odds ratio; VGPR, very good partial response.

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Adverse Events Summary

Category	Once-weekly Kd (n=238)	Twice-weekly Kd (n=235)
Median duration of treatment, weeks		
Carfilzomib	38.0	29.1
Dexamethasone	37.1	29.1
TEAEs, %		
Any grade AE	95	97
Grade ≥3 AE	68	62
Serious AE	43	41
Leading to carfilzomib discontinuation	13	12
Leading to carfilzomib dose reduction	11	5
Deaths on study, %	9	8
Treatment-related deaths n (%)	5 (2%)*	1 (<1%)**

* sepsis (1), acute respiratory distress syndrome (1), acute lung injury (1), tumor lysis syndrome (1), unknown (1)

** congestive heart failure (1)

- Exposure-adjusted incidence of grade ≥3 AEs was slightly higher in once-weekly vs twice-weekly group, but the exposure-adjusted for SAEs, AEs leading to carfilzomib discontinuation, or death were similar between the treatment groups

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Adverse Events of Interest

AE, % (SMQN)	Once-weekly Kd (n=238)		Twice-weekly Kd (n=235)	
	All grades	Grade ≥3	All grades	Grade ≥3
Peripheral neuropathy	4	0	7	<1
Acute renal failure	7	4	7	6
Cardiac failure	4	3	5	4
Ischemic heart disease	2	1	1	1
Pulmonary hypertension	2	0	1	<1

- Safety findings were consistent with the known safety profile of carfilzomib, and no new risks were identified.

AE, adverse event; SMQN, standardized MedDRA Query, narrow scope

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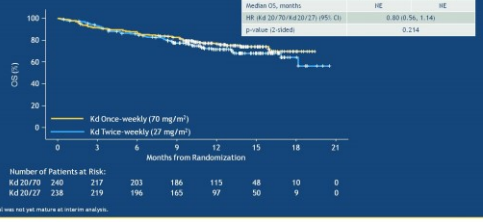
Overall Survival (OS)



	Once-weekly Kd 20/70 mg/m² (n=240)	Twice-weekly Kd 20/27 mg/m² (n=238)
Death, n (%)	58 (24.2)	68 (28.6)
Median OS, months	NE	NE
HR (Kd 20/70/Kd20/27) (95% CI)	0.80 (0.56, 1.14)	
p-value (2-sided)	0.214	

Number of Patients at Risk:

Kd 20/70	240	217	203	186	115	48	10	0
Kd 20/27	238	219	196	165	97	50	9	0

Overall survival was not yet mature at interim analysis.

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Conclusions

- Once-weekly Kd at 70 mg/m² significantly improved PFS by 3.6 months and reduced the risk of progression or death by 30.7% compared with twice-weekly Kd at 27 mg/m²
- Patients who received once-weekly Kd achieved a statistically significant higher overall response rate than patients who received twice-weekly Kd
- The overall safety profile was comparable between the 2 treatment groups and no new safety risks were identified
- Thus, in comparison with twice-weekly Kd at the 27 mg/m² schedule, once-weekly Kd at 70 mg/m²
  - Showed a favorable benefit-risk profile for patients with RRMM
  - Provides a more convenient schedule and can improve access to an efficacious therapy for patients unable to make twice-weekly visits to the clinic

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Maintenance Revlimid

Does dose matter?

Abstract 8016 (226971)

Maintenance Therapy with 25 versus 5 mg Lenalidomide after Prolonged Lenalidomide Consolidation Therapy in Newly-Diagnosed, Transplant-Eligible Patients with Multiple Myeloma

Fenk R[1], Giagounidis A[2], Goldschmidt H[3], Heinsch M[4], Rummel M[5], Kroeger N[6], Boquoi A[1], Lopez D[1], Gerrlich C[1], Baier J[1], Liesenjohann S[1], Hauck K[1], Savickaite I[1], Mai E[3], Aul C[1], Stragiotas J[1], Dienst A[1], Kondakci M[1], Haas R[1], Kobbe G[1]

[1]University Hospital Duesseldorf, Dept. of Hematology, Oncology and clin. Immunology, Germany; [2]Marien Hospital Duesseldorf, Germany; [3]University Hospital Heidelberg and National Center for Tumor Diseases, Dept. of Medicine V, Germany; [4]Helios St. Johannis-Hospital Duisburg, Germany; [5]University Hospital Giessen, Dept. of Hematology and Oncology, Germany; [6]University Cancer Center Hamburg, Dept. of Stem Cell Transplantation, Germany

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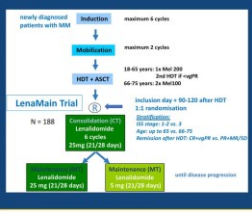
Study Design



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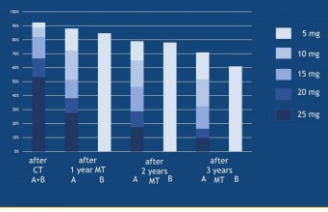
Dosage



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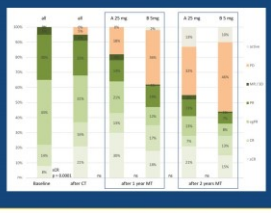
Response

- Remission category improved in 26% of pts during CT and 16% (5%) and 7% (3%) during first (second) year of MT in Arm A 25 mg and Arm B 5 mg
- Looking at best response at any time during MT, 36 % and 23 % of pts in arm A and B achieved sCR (p = 0.08)



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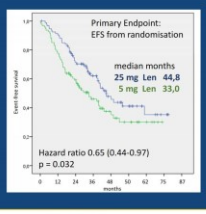
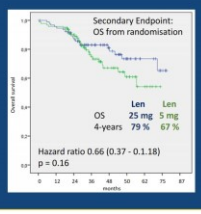
EFS and OS





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Safety

	Arm A 25 mg	Arm B 5mg
Discontinuation	61 (65%)	74 (78%)
due to disease progression	27 (29%)	42 (45%)
due to AE	27 (29%)	26 (28%)
due to death *	3 (3%)	1 (1%)
due to refusal	4 (4%)	5 (5%)
Median time until EOT (median, range; months)	26.8 (0.5 – 87)	22.9 (0.3 – 69)
AEs		
any AE	100 %	100 %
any AE ≥ grade 3	87.5 %	64.6 %
any AE ≥ grade 4	27. 1 %	12.5 %
any SAE	61.7 %	56.3 %
SAE	97	53
SUSAR	1	1

* Cause of deaths: 2x Infection (1x refusal of ICU treatment, 1x untreated Infection), 1x LAE, 1x sudden death

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Conclusions

- Low-dose lenalidomide is associated with significantly shorter EFS compared to the concept of upholding high-dose lenalidomide.
- The rate of toxicity observed and the need for dose reductions in most patients requires reconsideration of the high-dose schedule and awaits outcomes of long-term OS analyses

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Targeted therapy

Phase 2 Study of Venetoclax Plus Carfilzomib and Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma

Luciano J. Costa,[1] Edward Stadtmauer,[2] Gareth Morgan,[3] Gregory Monohan,[4] Tibor Kovacsovics,[5] Nicholas Burwick,[6] Andrzej Jakubowiak,[7] Mehrdad Mobasher,[8] Kevin Freise,[9] Jeremy A. Ross,[9] John Pesko,[9] Wijith Munasinghe,[9] Jaclyn Cordero,[9] Lura Morris,[9] Paulo Maciag,[9] Orlando F. Bueno,[9] Shaji Kumar[10]

[1]University of Alabama at Birmingham, Birmingham, AL; [2]University of Pennsylvania, Philadelphia, PA; [3]University of Arkansas for Medical Sciences, Little Rock, AR; [4]University of Kentucky, Lexington, KY; [5]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; [6]VA Puget Sound Health Care System, University of Washington, Seattle, WA; [7]The University of Chicago Medicine, Chicago, IL; [8]Genentech Inc., South San Francisco, CA; [9]AbbVie Inc., North Chicago, IL, [10]Mayo Clinic, Rochester, MN

American Society of Clinical Oncology (ASCO) – 54th Annual Meeting
Chicago, IL USA ● June 1, 2018

Presented By Luciano Costa at 2018 ASCO Annual Meeting

Study Overview

- Phase 2, dose-escalation study of venetoclax combined with K and dexamethasone (VenKd) for relapsed/refractory MM (NCT02899052)
  - Part 1: Dose escalation; Part 2: Expansion with selected dose
  - Primary study objectives: Safety and tolerability
  - Secondary and exploratory objectives: PK, ORR, TTP, DoR, MRD sub-study by FDG-PET scan imaging

Key Inclusion criteria:
- Previously treated MM (1-3 prior therapy)
  - PI refractory (besides K) were allowed
- Measurable Disease
  - M-protein ≥0.5 g/dL (serum)/≥200 mg/24h (urine)
  - sFLC ≥10 mg/dL
- ECOG Score ≤2
- Adequate Organ Function
  - ANC ≥1000/µL - Hb ≥8 g/dL
  - Platelets ≥50,000/mm³ - CrCl ≥30 mL/min

Key Exclusion criteria:
- Prior treatment with K
- Grade 3 or 4 peripheral neuropathy
- Significant cardiovascular disease, including uncontrolled angina, hypertension, arrhythmia, and LVEF ≤ 40%

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Dosing

- Patients received treatment in 28-day cycles:

Dosing regimens:	Day 1 2	8 9	15 16	22 23	28
Ven 400 mg QD + K 27 mg/m² + d 40 mg	●●	●●	●●	○	
Ven 800 mg QD + K 27 mg/m² + d 40 mg	●●	●●	●●	○	
Ven 800 mg QD + K 70 mg/m² + d 40 mg	●	●	●	○	
Ven 800 mg QD + K 56 mg/m² + d 20 mg	●●	●●	●●	○○	

● K (carfilzomib) dose ○ d (dexamethasone) dose

- Carfilzomib was administered at 20mg/m² on cycle 1 days 1 and 2
- The 27mg/m² and 56mg/m² carfilzomib twice weekly dosing were based on the USPI
- Patients stay on combination therapy for up to 18 cycles with the option to continue on venetoclax monotherapy

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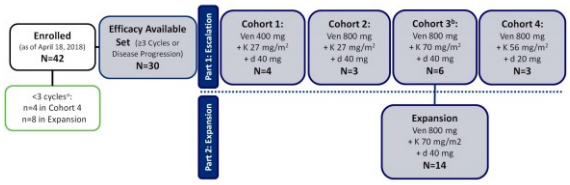
Enrollment and Patient Disposition



a. 1 discontinued by withdrawing consent, and 2 people who did not complete 1 cycle discontinued due to an AE (shortness of breath) or death (influenza and pneumonia)
b. This dose combination was selected for the expansion based on patient convenience and the CHAMPION-1 study results (Berenson et al Blood 2016)

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Summary of Safety (N=42)

Adverse event, n (%)	Any Grade	Grade 3/4
Any adverse event	**40 (95)**	**29 (69)**
AEs for ≥20% of patients for any grade or for ≥10% with grade 3/4		
Diarrhea	24 (57)	0
Fatigue	17 (41)	3 (7)
Platelet count decreased	15 (36)	3 (7)
Nausea	14 (33)	1 (2)
Lymphocyte count decreased	13 (31)	10 (24)
Dyspnea	10 (24)	2 (5)
Insomnia	10 (24)	1 (2)
WBC count decreased	9 (21)	4 (10)
Other AEs of interest		
Hypertension	4 (10)	3 (7)

Serious adverse event	n (%)
Any serious event	**12 (29)**
Serious adverse events in ≥2 patients	
Acute kidney injury	2 (5)
Congestive heart failure	2 (5)
Influenza	2 (5)
Pneumonia	2 (5)
Other SAEs of interest	
TLS	1 (2)[a]

By MedDRA preferred terms

a. patient was t(11;14) positive with >80% BM infiltration at screening; was hospitalized, received hydration and allopurinol. TLS labs resolved and treatment resumed

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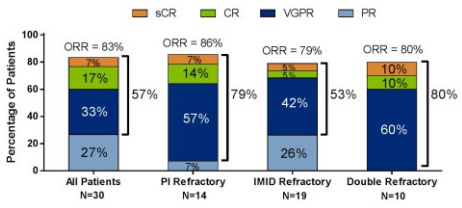
Objective Responses in All Patients and Those Refractory to PIs and IMiDs



1 PR was unconfirmed as of 18Apr2018 11

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Conclusions

- To date, the combination of VenKd appears tolerable with no additional safety concerns
  - Once weekly dose of carfilzomib (70mg/m^2) was selected based on patient convenience and the CHAMPION-1 study results[1]
- VenKd has shown promising preliminary efficacy (ORR of 83%, and ≥VGPR of 57%) that supports the investigation of this combination in patients with relapsed/refractory multiple myeloma
  - While responses in the small subset of t(11;14) patients were highest, high-risk and standard-risk patients had comparable responses with VenKd
- Venetoclax exposures when co-administered with carfilzomib appear comparable to those observed when venetoclax was co-administered with bortezomib
- The study continues with 42 patients enrolled to date

1. Berenson et al *Blood* 2016 14

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New combinations with “old”drugs

ABSTRACT 8001

Pomalidomide, Bortezomib, and Low-Dose Dexamethasone (PVd) vs Bortezomib and Low-Dose Dexamethasone (Vd) in Lenalidomide-Exposed Patients With Relapsed or Refractory Multiple Myeloma: Phase 3 OPTIMISMM Trial

Paul Richardson,[1] Albert Oriol,[2] Meral Beksac,[3] Anna Marina Liberati,[4] Monica Galli,[5] Fredrik Schjesvold,[6] Jindriska Lindsay,[7] Katja Weisel,[8] Darrell White,[9] Thierry Facon,[10] Jesus San Miguel,[11] Kazutaka Sunami,[12] Peter O'Gorman,[13] Pieter Sonneveld,[14] Xin Yu,[15] Thomas Doerr,[15] Amine Bensmaine,[15] Mohamed Zaki,[15] Kenneth Anderson,[1] Meletios Dimopoulos[16] *on behalf of the OPTIMISMM trial investigators*

[1]Jerome Lipper Multiple Myeloma Center, Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [2]Institut Català d'Oncologia and Institut Josep Carreras, Hospital Germans Trias i Pujol, Badalona, Spain; [3]Ankara University, Cebeci Yerleskesi, Dikimevi, Ankara, Turkey; [4]University of Perugia, Terni, Perugia, Italy; [5]A.O. Papa Giovanni XXIII, U.O. di Ematologia, Bergamo, Italy; [6]Oslo University Hospital, Oslo, Norway; [7]East Kent Hospitals University NHS Foundation Trust, Canterbury, United Kingdom; [8]University Hospital of Tuebingen, Tuebingen, Germany; [9]Dalhousie University and Queen Elizabeth II Health Sciences Centre, Halifax, Canada; [10]Service des Maladies du Sang, Hôpital Claude Huriez, Lille, France; [11]Clínica Universidad de Navarra, CIMA, IDISNA, Pamplona, Spain; [12]National Hospital Organization Okayama Medical Center, Kitaku, Okayama, Japan; [13]Mater Misericordiae University Hospital, University College Dublin, Dublin, Ireland; [14]Erasmus MC Cancer Institute, Rotterdam, the Netherlands; [15]Celgene Corporation, Summit, NJ, USA; [16]National and Kapodistrian University of Athens, Athens, Greece

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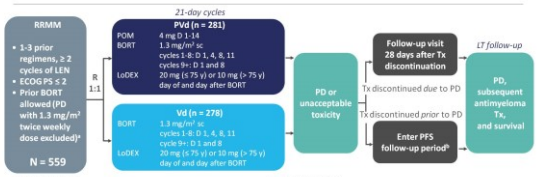
PHASE 3 OPTIMISMM STUDY DESIGN



- **Stratification**
  - Age (≤ 75 y vs > 75 y)
  - Prior regimens (1 vs > 1)
  - β2-microglobulin at screening (< 3.5 mg/L vs ≥ 3.5 to ≤ 5.5 mg/L vs > 5.5 mg/L)
- **Study endpoints**
  - Primary: PFS
  - Secondary: OS, ORR by IMWG criteria, DOR, safety
  - Key exploratory: TTR, PFS2, efficacy analysis in subgroups
- **Data cutoff:** October 26, 2017

NCT01734928

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PATIENT DISPOSITION (ITT)

- Median treatment duration: 8.8 months with PVd vs 4.9 months with Vd
- Median follow-up: 15.9 months
- Most common reason for treatment discontinuation was PD

Characteristic	PVd (n = 281)[a]	Vd (n = 278)[b]
Median duration of treatment, months[c]	8.8	4.9
Ongoing treatment, n (%)	93 (33.1)	45 (16.2)
Discontinued treatment, n (%)	185 (65.8)	225 (80.9)
PD	110 (39.1)	131 (47.1)
AE	30 (10.7)	49 (17.6)
Withdrawal of consent	21 (7.5)	21 (7.6)
Death (all cause)	18 (6.4)	9 (3.2)
Other[d]	6 (2.1)	15 (5.4)

[a]3 patients did not receive treatment in the PVd arm. [b]8 patients did not receive treatment in the Vd arm. [c]Calculated in the safety population: PVd, n = 279; Vd, n = 270. [d]Other included other reasons, lost to follow-up, and pregnancy.

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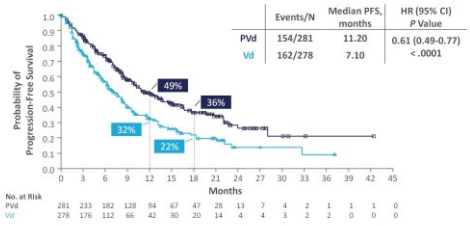
PROGRESSION-FREE SURVIVAL (ITT)

- PVd reduced the risk of progression and death by 39% compared with Vd



	Events/N	Median PFS, months	HR (95% CI) *P* Value
PVd	154/281	11.20	0.61 (0.49-0.77)
Vd	162/278	7.10	< .0001

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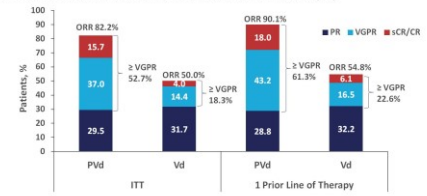
RESPONSE

- ORR was significantly higher with PVd vs Vd in the ITT population (*P* < .001) and in patients with 1 prior line of therapy (*P* < .001)
  - PVd led to deeper responses with higher sCR/CR and ≥ VGPR rates vs Vd
- Median TTR was 0.9 vs 1.4 months and median DOR was 13.7 vs 10.9 months (ITT)



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CONCLUSIONS AND FUTURE DIRECTIONS

- Phase 3 OPTIMISMM trial: significantly improved PFS and ORR with PVd in RRMM (100% LEN exposed and 70% LEN refractory)
  - This study investigated a clinically relevant and growing patient population who received upfront LEN but for whom LEN is no longer a treatment option
- PVd significantly reduced the risk of disease progression or death by 39% vs Vd
  - PFS benefit generally consistent among subgroups, including LEN-refractory patients, prior PI exposure, and high-risk cytogenetics
  - PFS advantage accompanied by earlier, deeper, and more durable responses
  - PFS and ORR improvements were more pronounced in patients with 1 prior line of therapy
- Safety profile consistent with known toxicities associated with POM + LoDEX and BORT therapy
  - Longer treatment duration and exposure reported with PVd vs Vd
- These results support the use of PVd in first relapse in patients with RRMM and prior exposure to LEN
- Future directions include analysis of correlatives, MRD, and QoL

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Improving Monoclonal Antibodies

A phase II study of elotuzumab in combination with pomalidomide, bortezomib and dexamethasone (Elo-PVD) in relapsed and refractory myeloma (abstract 8012)

- Elotuzumab is a monoclonal antibody targeting SLAMF7
  - Elotuzumab doesn't have single agent activity in RRMM; however does increase the activity of Rd and to some extent Vd [1,2]
  - Is not expected to have overlapping toxicity with PVD (caution: Elo-RVD in NDMM was associated with 2 infectious death) [3]
- Experience with PVD in RRMM
  - PVD with weekly bortezomib (28 day cycle) : ORR 86% [4]
  - PVD with a twice weekly bortezomib (21 day cycle) : ORR 65% [5]
  - OPTIMISM 1 study (PVD versus VD) is reported at this meeting #8001
    - ORR 82% for PVD and mPFS 11.2 months

Yee et al. ASCO 2018 abstract 8012 ; 1- Lonial et al. N Engl J Med. 2015;373(7):621 ;
2- Jakubowiak et al. Blood 2016 127:2833; 3- Laubach et al. ASCO 2017 abstract 8002;
4- Paludo et al. Blood (2017) 130 (10):1198; 5-Richardson et al. Leukemia (2017) 31: 2695

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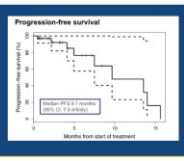
Elo-PVD Results

Age, median	64 (range 52-79)
Sex (male)	76%
Prior lines of therapy	
Median (range)	3 (1-9)
1	13 (39%)
2	2 (6%)
3	5 (15%)
4+	13 (39%)
Prior aSCT	15 (45%)
Prior IMiD	33 (100%)
Lenalidomide	33 (100%)
Pomalidomide	12 (33%)
Prior proteasome inhibitor	33 (100%)
Bortezomib	31 (94%)
Carfilzomib	8 (24%)
Ixazomib	2 (6%)
CD38 mAb	8 (24%)
Daratumumab	7 (21%)
Isatuximab	1 (3%)
FISH	
Normal risk	25 (75%)
High risk	9 (27%)
Del17p	5 (15%)
t(4;14)	3 (9%)
t(14;16)	1 (3%)
Unknown	7 (21%)

Overall response

	overall (N=31)	Prior anti CD38 (N=7)	Prior pom (N=10)	Prior carfilzomib (N=7)	1-2 prior lines (N=15)	3+ prior lines (N=16)
CR	1 (3)	0	0	0	1 (7)	0
VGPR	4 (13)	1 (14)	0	1 (14)	3 (20)	1 (6)
PR	11 (35)	2 (29)	4 (40)	2 (29)	5 (33)	6 (38)
SD	15 (48)	4 (57)	6 (60)	4 (29)	6 (40)	9 (56)
ORR	52%	43%	40%	43%	60%	44%

Progression-free survival



3- Yee et al. ASCO 2018 abstract 8012

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Subcutaneous daratumumab in patients with relapsed or refractory multiple myeloma (RRMM): Part 2 update of the open label, multicenter, dose escalation Phase Ib study (PAVO) (abstract 8013)

- IV Dara is safe but
  - IRR occur in about 40-50% of patients / mostly first infusions
  - First infusion duration of about 7 hours
- Dara SC : pre-mixed co-formulation of daratumumab and recombinant human hyaluronidase with a higher daratumumab concentration, lower injection volume, and shorter injection time with manual SC injection in the abdomen
- Dara SC: IRR 4% and ORR 42% (ASH 2017) [1]
- Dara SC + CyBorD (ANDROMEDA): IRR 2/15 pts (13%) [2]

Chari et al. ASCO 2018 abstract 8013
1- Chari et al ASH 2017 abstract 838
2- Comenzo et al ASCO 2018 abstract 8011

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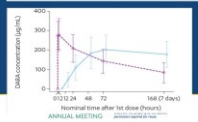
Dara IV or SC?

	Dara IV [1]	Dara SC [2] N=25
Median number of prior therapies Refractoriness	5 (2-14) 86% double refractory	3 (2-9) 56% double refractory
ORR	31%	52%
Administration time	First infusion - 7h Second infusion - 4.3h Third infusion - 3.5h	3-5 min
IRR	40-50%	16%



1- Usmani SZ., et al. *Blood*. 2016;128(1):37-44
2- Chari A et al., ASCO 2018 abstract 8013

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Phase 1b Study of Isatuximab and Carfilzomib for the Treatment of Relapsed and/or Refractory Multiple Myeloma (abstract 8014)

- Isatuximab (Isa)
  - ORR 32% as a single agent [1]
  - ORR 52% in combination with Len/ Dex in lenalidomide refractory patients [2]
  - ORR 56% in combination with Pom / Dex [3]
  - Ongoing phase III trial comparing Isa Pom Dex versus Pom Dex
- Phase Ib combination study CFZ + Isa
  - Study population: at least 2 prior lines, IMID and PI. CFZ refractory allowed but no prior CD38 mab
  - Kd given 20/27 mg/m² D1,2,8,9,15,16
- 3 cohorts: Isa 10 mg/Kg Q2W; Isa 10 mg/kg QW x 4, then Q2W and Isa 20 mg/kg QW x 4, then Q2W.
- Note that Dara KD data presented at this meeting #8002

Charl et al. ASCO 2018 abstract 8014
1- Martin T. et al. Blood 2015 126:509
2- Martin T et a.. Blood. 2017 129(25):3294-3305
3- Richardson P et al. Blood 2017 130:1887

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KD with Isa or Dara?

	Dara KD [1] N=85	Isa KD [2] N=33
KD dose and schedule	20 / 70 mg/m² D1,8,15[3]	20/27 mg/m² D1,2,8,9,15,16
Median prior therapy (range)	2 (1-3)	3 (2-8)
Prior Carfilzomib	No	Yes, 30% refractory to CFZ
ORR	86%	61% 50% in CFZ refractory pts (5/10)
Thrombocytopenia Gr3+	27%	3%
Heutropenia Gr 3+	18%	3%
Hypertension Gr 3+	12%	9%
IRR	42%	48%

Isa 10 mg/kg QW x4 then Q2W dose was selected as the optimal dose for the expansion cohort based on ORR, safety and PK modeling.
3- ARROW study (abstract 8000) suggest this weekly KD is better than std schedule

1- Lonial S et al. ASH 2017 130:186+, Charl ASCO 2018; 8002
2- Charl, A et al. ASCO 2018 abstract 8014
3- Mateos et al ASCO 2018 abstract 8000

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Conclusions

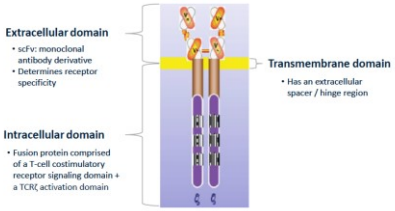
- Available myeloma treatments are increasing at a rate higher than ever before.
- Trials are aimed at continuing to improve efficacy as well as quality of life.
- Optimal combinations of the varying categories of treatments and sequence of these combinations needs continued evaluation.

Thank you!

Slides from ASCO meeting library

kpatel1@mdanderson.org

Generic Chimeric Antigen Receptor (CAR)



B cell maturation antigen (BCMA)

- Consistently expressed on plasma cells/MM cells[1]
- Possibly protects MM cells in BM niche[2]
- BMCA expression increases with disease progression[3]
- Limited expression on normal, non-hematopoietic cells[1]

1. Carpenter et al, *Clinical Cancer Research*, 2013
2. Novak et al, Blood 2004
3. Sanchez, 2012

Summary of ongoing BCMA CAR-T Trials for MM

Name	Anti-BCMA CAR	Bb2121	LCAR-B38M	CART-BCMA
Group	NCI	Bluebird/Celgene	Nanjing/Legend Biotech	Novartis/Penn
Binder/co-stimulatory signal	Murine/CD3ζ, CD28	Murine/CD3ζ, 4-1BB	Murine/CD3ζ, 4-1BB	Fully human/CD3ζ, 4-1BB
Transfection	γ-retroviral	Lentiviral	Lentiviral	Lentiviral
BCMA expression required?	Yes	Yes	Yes	No

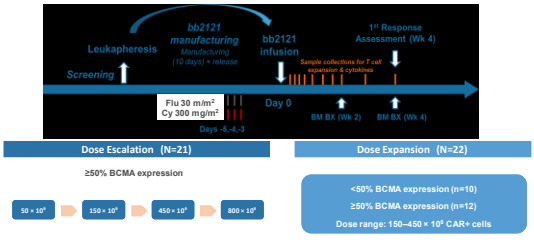
ABSTRACT 8007

bb2121 Anti-BCMA CAR T Cell Therapy in Patients With Relapsed/Refractory Multiple Myeloma: Updated Results From a Multicenter Phase I Study

Noopur Raje, MD,[1] Jesus Berdeja, MD,[2] Yi Lin, MD, PhD,[3] Nikhil Munshi, MD,[4] David Siegel, MD, PhD,[5] Michaela Liedtke, MD,[6] Sundar Jagannath, MD,[7] Deepu Madduri, MD,[7] Jacalyn Rosenblatt, MD,[8] Marcela Maus, MD, PhD,[1] Ashley Turka,[9] Lyh Ping Lam, PharmD,[9] Richard A. Morgan, PhD,[9] M. Travis Quigley,[9] Monica Massaro, MPH,[9] Kristen Hege, MD,[10] Fabio Petrocca, MD,[9] and James N. Kochenderfer, MD[11]

[1]Massachusetts General Hospital Cancer Center, Boston, MA; [2]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN; [3]Mayo Clinic, Rochester, MN; [4]Dana-Farber Cancer Institute, Boston, MA; [5]Hackensack University Medical Center, Hackensack, NJ; [6]Stanford University Medical Center, Palo Alto, CA; [7]Mount Sinai Medical Center, New York, NY; [8]Beth Israel Deaconess Medical Center, Boston, MA; [9]bluebird bio, Inc, Cambridge, MA; [10]Celgene Corporation, San Francisco, CA; [11]Experimental Transplantation and Immunology Branch, National Cancer Institute/National Institutes of Health, Bethesda, MD

CRB-401 PHASE 1 STUDY DESIGN



Manufacturing success rate of 100%

TREATMENT HISTORY

	Escalation (N=21)	Expansion (N=22)
Median (min, max) prior regimens	7 (3, 14)	8 (3, 23)
Prior autologous SCT, n (%)	21 (100)	19 (86)
0	0	3 (14)
1	15 (71)	14 (64)
>1	6 (29)	5 (23)

	Escalation (N=21)		Expansion (N=22)	
	Exposed	Refractory	Exposed	Refractory
Prior therapies, n (%)				
Bortezomib	21 (100)	14 (67)	22 (100)	16 (73)
Carfilzomib	19 (91)	12 (57)	21 (96)	14 (64)
Lenalidomide	21 (100)	19 (91)	22 (100)	18 (82)
Pomalidomide	19 (91)	15 (71)	22 (100)	21 (96)
Daratumumab	15 (71)	10 (48)	22 (100)	19 (86)
Exposed/Refractory, n (%)				
Bort/Len	21 (100)	14 (67)	22 (100)	14 (64)
Bort/Len/Car/Pom/Dara	15 (71)	6 (29)	21 (96)	7 (32)

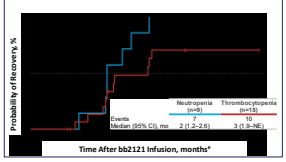
Data cutoff: March 29, 2018. SCT, stem cell transplant.

ADVERSE EVENTS OF SPECIAL INTEREST

CAR T Treatment-Emergent Adverse Events All Infused Patients (N=43)

TEAE, n (%)	Overall	Grade ≥3
Cytokine release syndrome[a]	27 (63)	2 (5)
Neurotoxicity[b]	14 (33)	1 (2)
Neutropenia	35 (81)	34 (79)
Thrombocytopenia	26 (61)	22 (51)
Anemia	24 (56)	19 (44)
Infection[c]		
Overall	26 (61)	9 (21)
First Month	10 (23)	2 (5)

Time to Recovery of Grade 3/4 Cytopenias in Patients Without Recovery by Month 1[d]



- No grade 4 CRS events
- No fatal CRS or neurotoxicity events
- 31/40 (78%) recovered ANC to ≥1000/μL by Day 32
- 22/40 (55%) recovered PLT to ≥50,000/μL by Day 32

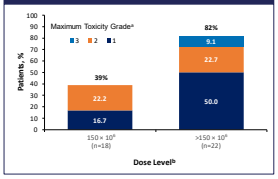
Data cutoff: March 29, 2018. NE, not estimable. [a]CRS uniformly graded per Lee DW, et al. *Blood*. 2014;124(2):188-195. [b]Events occurring in first 28 d and including dizziness, bradyphrenia, somnolence, confusional state, nystagmus, insomnia, memory impairment, depressed level of consciousness, neurotoxicity, lethargy, tremor and hallucination. [c]Includes the SOC Infections and Infestations. Events observed in >10% include upper respiratory tract infection and pneumonia. [d]Includes patients treated with active doses (150–800 × 10^6 CAR+ T cells; N=40). Median and 95% CI from Kaplan-Meier estimate. [e]Time from first bb2121 infusion to the first grade ≥2 event after day 32.

CYTOKINE RELEASE SYNDROME: MOSTLY LOW GRADE AND MANAGEABLE

Cytokine Release Syndrome Parameters

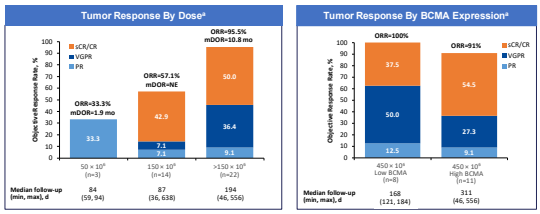
Parameter	Dosed Patients (N=43)
Patients with a CRS event, n (%)	27 (63)
Maximum CRS grade[a]	
None	16 (37)
1	16 (37)
2	9 (21)
3	2 (5)
4	0
Median (min, max) time to onset, d	2 (1, 25)
Median (min, max) duration, d	6 (1, 32)
Tocilizumab use, n (%)	9 (21)
Corticosteroid use, n (%)	4 (9)

Cytokine Release Syndrome By Dose Level



Data cutoff: March 29, 2018. [a]CRS uniformly graded according to Lee DW, et al. *Blood*. 2014;124(2):188-195. [b]3 patients were treated at the 50 x 10^6 dose level for a total of 43 patients.

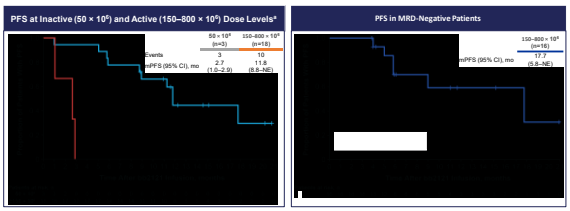
TUMOR RESPONSE: DOSE-RELATED; INDEPENDENT OF TUMOR BCMA EXPRESSION



Data cutoff: March 29, 2018. CR, complete response; mDOR, median duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; sCR, stringent CR; VGPR, very good partial response. [a]Patients with ≥2 months of response data or PD/death within <2 months. ORR is defined as attaining sCR, CR, VGPR, or PR, including confirmed and unconfirmed responses. Low BCMA is <50% bone marrow plasma cells expression of BCMA; high BCMA is defined as ≥50%.

PROGRESSION-FREE SURVIVAL

- mPFS of 11.8 months at active doses (≥150 × 10^6 CAR+ T cells) in 18 subjects in dose escalation phase
- mPFS of 17.7 months in 16 responding subjects who are MRD-negative



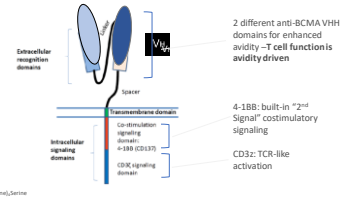
Data cutoff: March 29, 2018. Median and 95% CI from Kaplan-Meier estimate. NE, not estimable. *PFS in dose escalation cohort.

Summary of ongoing BCMA CAR-T Trials for MM

Name	Anti-BCMA CAR	Bb2121	LCAR-B38M	CART-BCMA
Group	NCI	Bluebird/Celgene	Nanjing/Legend Biotech	Novartis/Penn
Binder/co-stimulatory signal	Murine/CD3ζ, CD28	Murine/CD3ζ, 4-1BB	Murine/CD3ζ, 4-1BB	Fully human/CD3ζ, 4-1BB
Transfection	γ-retroviral	Lentiviral	Lentiviral	Lentiviral
BCMA expression required?	Yes	Yes	Yes	No
Median prior lines of tx	7, 11	7	3	9
Efficacy	1 sCR (relapsed), 1 VGPR, 2 PR, 8 SD Responses in highest cell dose; **9/11 in top dose**	10 CRs, 6 VGPR, 1 PRs (4 eventual PD), n=18 at >5 e7 : **94% RR** 9 MRD neg	**33 CR or VGPR**, n=35, 1 relapse; 5 MRD neg > 1 yr	**6/9, 2/5, 5/6** responses in 3 cohorts
Safety	Toxicity substantial (Gr3-4CRS) but reversible esp in highest doses (9 e6/kg); protocol modified to pts with lower tumor burden	CRS in 71%; transient Gr3 10%; 5 deaths (cardio-pulm arrest, unrelated, 1 MDS, 3 PD at lowest dose) Early report of 1 Gr 4 neurotoxicity	Transient CRS 29/35, no neurotox	CRS in 17/21 pts (6 with Gr2), with neurotox in 3 pts 1 death – candidemia/PD

JNJ-68284528 (LCAR-B38M CAR-T cells)

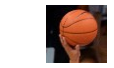
Genetically modified autologous T-cell immunotherapy directed at B-cell maturation antigen (BCMA) which is being developed for the treatment of Multiple Myeloma



JNJ-528 is a unique bispecific CAR that binds with high affinity to 2 different epitopes on BCMA, enabling tight binding of the CAR to the BCMA-expressing cells

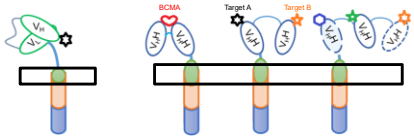
Courtesy of Janssen

JNJ-68284528 (LCAR-B38M) CAR T cell: designed for high affinity interaction with BCMA-expressing tumor cells



Conventional CAR-T

LCAR-B38M VHH multi-specific CAR



scFv-Conventional CAR | VHH-Bi-epitope CAR | VHH-multi-specific CAR

Courtesy of Janssen

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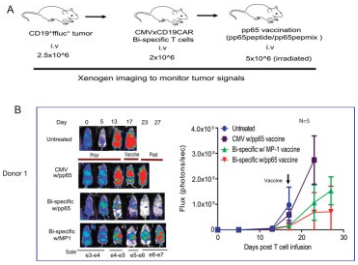
Name	Anti-BCMA CAR	Bb2121	LCAR-B38M	CART-BCMA
Group	NCI	Bluebird/Celgene	Nanjing/Legend Biotech	Novartis/Penn
Binder/co-stimulatory signal	Murine/CD3ζ, CD28	Murine/CD3ζ, 4-1BB	Murine/CD3ζ, 4-1BB	Fully human/CD3ζ, 4-1BB
Transfection	γ-retroviral	Lentiviral	Lentiviral	Lentiviral
BCMA expression required?	Yes	Yes	Yes	No
Median prior lines of tx	7, 11	7	3	9
Efficacy	1 sCR (relapsed), 1 VGPR, 2 PR, 8 SD Responses in highest cell dose; **9/11 in top dose**	**ORR= 57% , 96% in pts @>150 e6**; mPFS 11.8 mo, 17.7 mo in MRD neg pts	**33 CR or VGPR**, n=35, 1 relapse; 5 MRD neg > 1 yr	**6/9, 2/5, 5/6** responses in 3 cohorts
Safety	Toxicity substantial (Gr3-4CRS) but reversible esp in highest doses (9 e6/kg); protocol modified to pts with lower tumor burden	CRS in 71%; transient Gr3 10%; 5 deaths (cardio-pulm arrest, unrelated, 1 MDS, 3 PD at lowest dose) Early report of 1 Gr 4 neurotoxicity	Transient CRS 29/35, no neurotox	CRS in 17/21 pts (6 with Gr2), with neurotox in 3 pts 1 death – candidemia/PD

Challenges in CAR T therapy for MM

- CRS (hopefully not as much of an issue as with ALL)
- Persistence
  - Lymphodepletion
  - Cytokine-based T-reg elimination
  - Virus-specific T cells as primary CAR-T population

Virus-specific T cells as primary CAR-T population

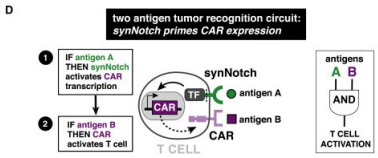


1. Maus et al, *CCR* 2016

Challenges in CAR T therapy for MM

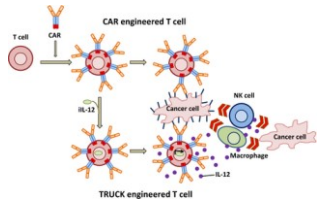
- CRS (hopefully not as much of an issue as with ALL)
- Persistence
  - Lymphodepletion
  - Cytokine-based T-reg elimination
  - Virus-specific T cells as primary CAR-T population
- Optimizing co-stimulatory signaling
  - 41BB>CD28
- Nature of MM is waxing and waning, should the cells be that way as well?
  - "ON-switch" CARs
  - Targeting multiple antigens
  - T cells redirected for universal cytokine-mediated killing (TRUCKs)

"On" switch CAR T cells



1. Roybal et al, *Cell* 2016

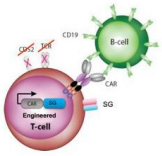
T cells redirected for universal cytokine-mediated killing (TRUCKs)



1. Chiemelewski et al, *Immunological Reviews*, 2013

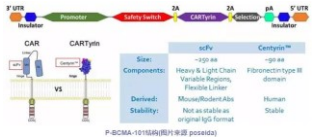
Cellectis Universal SLAMF7-Specific CAR T (abs 502)

- "Off-the-shelf"
- Normal healthy PB donors
- Inactivation of the *TCRα constant* (*TRAC*) gene using TALEN® gene-editing technology to prevent GVHD and expression of T cell SLAMF7.



Poseida: CARTyrin (abs 3068)

- DNA transposon system
- iCasp9-based safety switch
- Anti-BCMA CARTyrin
- Selection gene (~ 100% pure CAR$^+$ product)
- Enrich stem cell memory T cell subset

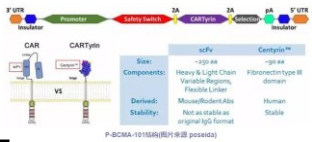


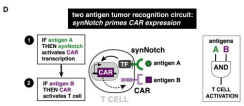
But where are we really going…?

- Timing of CART
- Disease burden
- Position relative to autologous transplant
- Cost
- Time and financial cost of proving superiority
  - Clinical trial design
  - MRD as endpoint

"It's my CAR-T and I'll cry if I want to…"

- Persistence
- Inducibility





Case

- 65 YO M without significant PMH presents with new back pain and incidentally found abnormal protein level
- Further work-up shows IgG kappa M-spike 3.8 g/dL
- Additional labs: normal Cr, Ca; Hb=11.8 g/dL
- MRI shows new L4 compression fracture
- BM biopsy: 60% kappa-restricted plasma cells, normal cytogenetics, FISH positive for t(11;14)

Treatment course

- VRD induction→ achieves VGPR after 6 cycles
- Mel 200 ASCT→ sCR at day 100 with MRD negativity
- Len maintenance x 2.5 y--> biochemical progression
- KRD with PR; Goes 18 months but then presents with new bone lesions
- Starts DRD→ Stable x 12 months but then presents wit new anemia. BM with 70% plasma cells and clonal evolution (-16)

Now what??

Thank you!
nina.shah@ucsf.edu

Smoldering Myeloma

Irene Ghobrial, MD
Associate Professor of Medicine
Harvard Medical School
Dana Farber Cancer Institute
Boston, MA

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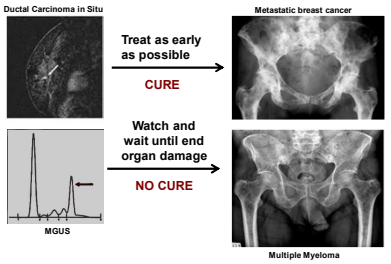
Is it time to treat patients with Smoldering MM



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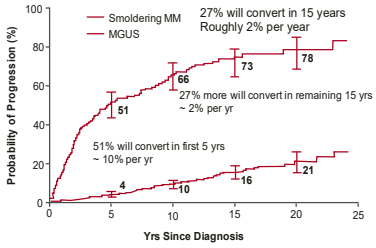
Which patient population to consider for SMM?



Kyle R. N Engl J Med 2007; 356:2582-90; Greipp RR, et al. J Clin Oncol 2005;23:3412–3420

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What is the definition of MM or SMM?

Panel: Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smouldering multiple myeloma

Definition of multiple myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL)
    - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
- Any one or more of the following biomarkers of malignancy:
  - Clonal bone marrow plasma cell percentage* ≥60%
  - Involved:uninvolved serum free light chain ratio§ ≥100
  - >1 focal lesions on MRI studies¶

Rajkumar et al. Lancet Oncology 2014; 15: e538-48

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What is high risk SMM?

Identification of high-risk SMM→ 50% of progression risk at 2y

- ***Mayo Clinic:*** ≥10% clonal plasma cell bone marrow infiltration, and ≥30g/L of serum M-protein, and serum-free light ratio >0.125 or <8
- ***Spanish:*** ≥95% of aberrant plasma cells measured by flow plus >25% decrease in one or both uninvolved immunoglobulins
- ***Heidelberg:*** Tumor mass defined by Mayo risk model plus t(4;14)/del17p/gains of 1q/
- ***Japanese:*** Beta 2-microglobulin ≥ 2.5 mg/L plus M-protein increment rate > 1 mg/dL/day
- ***SWOG:*** serum M-protein ≥2 g/dL plus involved free light chain >25 and GEP >-0.26 (71% of risk progression at 2 yrs)
- ***PENN:*** ≥ 40% clonal PCBM infiltration plus sFLC ratio ≥ 50 plus Albumin □ 3.5 mg/dL (81% of risk at 2 yrs
- ***Czech & Heidelberg:*** immunoparesis plus serum M-protein ≥ 2.3 g/dL plus involved/uninvolved sFLC > 30 **(81% of risk at 2 yrs)**
- ***Barcelona:*** evolving pattern plus serum M-protein ≥ 3 g/dL plus immunoparesis **(80% of risk at 2 yrs)**

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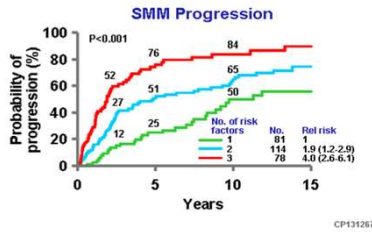
Mayo Clinic model: serum immunoglobulin free-light chain (FLC) ratio (n:273)



PCsBM Infiltration ≥ 10%
Serum M protein ≥ 3 g/dL
Serum FLC ratio <1/8 or >8

Dispenzieri A. Blood 2008; 111:785-9

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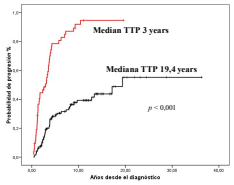
Evolution pattern of the M-spike: evolving vs nonevolving (n:207)

Evolving SMM (52 (25%)): at least 10% increase within the first 6 months from diagnosis when M-Protein was ≥30 g/L or progressive increase in M-Protein in each of the annual consecutive measurements during a period of 3 years in patients with an initial MP < 30 g/L

Non-evolving (75%): **Stable serum M-protein until progression occurs**



Evolving SMM

- Risk progression at 2 years: 45%
- Risk progression at 5 years: 78%
- IgA isotype: (41,2% frente a 23,8%, p=0,02)

Fernández Larrea C et al. ASH 2014

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Which patient population to consider for high risk SMM?

Each model appears to identify patients at high risk, with some but not complete overlap

Bone marrow clonal plasma cells ≥10% and any one or more of the following:

- Serum M protein ≥3.0gm/dL
- IgA SMM
- Immunoparesis with reduction of two uninvolved immunoglobulin isotypes
- Serum involved/uninvolved free light chain ratio ≥8 (but less than 100)
- Progressive increase in M protein level (Evolving type of SMM)[†]
- Bone marrow clonal plasma cells 50-60%
- Abnormal plasma cell immunophenotype (≥95% of bone marrow plasma cells are clonal) and reduction of one or more uninvolved immunoglobulin isotypes
- t (4;14) or del 17p or 1q gain
- Increased circulating plasma cells
- MRI with diffuse abnormalities or 1 focal lesion (≥5mm)
- PET-CT with one focal lesion (≥5mm) with increased uptake without underlying osteolytic bone destruction
- Monoclonal light chain excretion of 500mg/24 hours or higher

Rajkumar et al, Blood 2015

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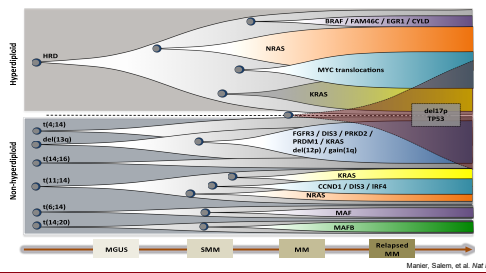
Should we consider therapeutic interventions in SMM



Manier, Salem, et al. *Nat Rev Clin Oncol*, 2016

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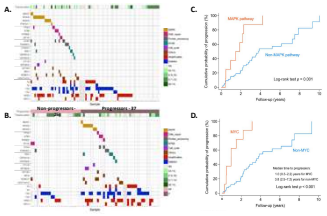
Should we use single agents or combination therapy to treat high-risk SMM

Whole-exome and targeted sequencing of SMM BM samples

Genomic profile of high risk SMM indicates that it is similar to overt MM



Bustoros et al, Unpublished data

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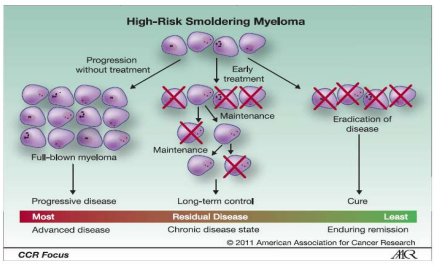
Treatment goals for high-risk smouldering myeloma



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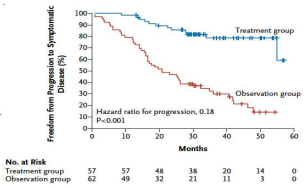
Early Therapeutic Intervention

Lenalidomide plus Dexamethasone for High-Risk Smoldering Multiple Myeloma

María-Victoria Mateos, M.D., Ph.D., Miguel-Teodoro Hernández, M.D., Pilar Giraldo, M.D., Javier de la Rubia, M.D., Felipe de Arriba, M.D., Ph.D., Lucía López Corral, M.D., Ph.D., Laura Rosiñol, M.D., Ph.D., Bruno Paiva, Ph.D., Luis Palomera, M.D., Ph.D., Joan Bargay, M.D., Albert Oriol, M.D., Felipe Prosper, M.D., Ph.D., Javier López, M.D., Ph.D., Eduardo Olavarría, M.D., Ph.D., Nuria Quintana, M.D., José-Luis García, M.D., Joan Bladé, M.D., Ph.D., Juan-José Lahuerta, M.D., Ph.D., and Jesús-F. San Miguel, M.D., Ph.D.



Mateos MV, et al. NEJM 2013
Mateos MV, et al. Lancet Oncology 2016

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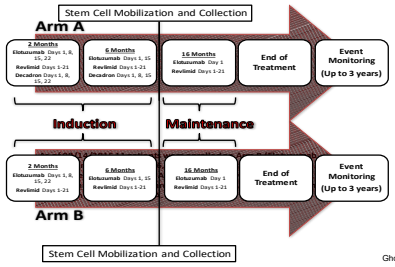
Phase II trial of Elotuzumab/Len/Dex in high risk SMM



Ghobrial I, et al. ASH 2016. Abstract 976

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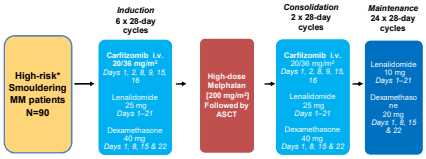
GEM-CESAR: Study Design

- Multicenter, open-label, phase II trial



High-risk was defined according to the Mayo and/or Spanish models

- Patients with any one or more of the biomarkers predicting imminent risk of progression to MM were allowed to be included but…
- New imaging assessments were mandatory at screening and if bone disease was detected by CT or PET-CT, patients were excluded

Mateos MV, et al. ASH 2017, abstract 402

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Current Studies in High-Risk Smoldering MM

- Lenalidomide or observation (phase III)[1]
- **Ixazomib + lenalidomide + dexamethasone (phase II)[2]**
- Isatuximab (phase II)[3]
- Daratumumab single agent at different doses (Centaurus trial)[4]
- **Dara ph II for high-risk MGUS and low-risk smoldering[5]**
- **Randomized Ph III AQUILA (sc)[6]**

A Study of Subcutaneous Daratumumab Versus Active Monitoring in Participants With High-Risk Smoldering Multiple Myeloma
Recruitment status: Recruiting
Start date: November 2017
Estimated completion date: December 2025

1. ClinicalTrials.gov. NCT01169337.
2. ClinicalTrials.gov. NCT02916771.
3. ClinicalTrials.gov. NCT02960555.
4. Hofmeister CC, et al. Blood 2017 130:510
5. ClinicalTrials.gov. NCT03236428.
6. ClinicalTrials.gov. NCT03301220.

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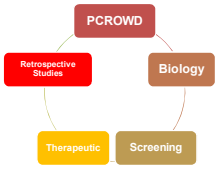
Center for Prevention of Progression of Blood Cancers

www.dana-farber.org/cpop



CPOP
Center for Prevention of Progression of Blood Cancers

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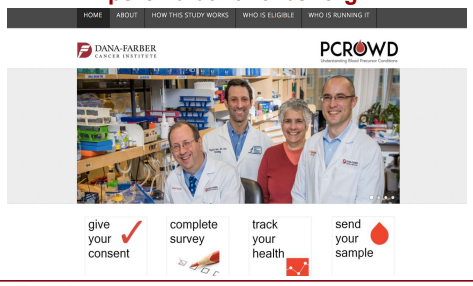
pcrowd.dana-farber.org/



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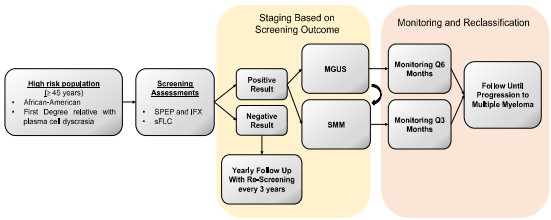
Predicting progression of developing Myeloma in a High-Risk screened population (PROMISE)



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http://ghobrialab.danafarber.org/

Aldo Roccaro, Salomon Manier, Jihye Park, Antonio Sacco, Yujia Shi, Yuji Mishima, Oksana Zavidij, Marzia Capelletti, Daisy Huynh, Karma Salem, Yosuke Kawano, Sridan Glavey , Jiantao Shi, Michele Moschetta, Adriana Perilla-Glen, Patrick Henrick, Kim Nooren, Kaitlen Reyes, Joe Cappuccio, Aaron Casla.

Gad Getz, Viktor Adalsteinsson, Ken Anderson, Rob Soiffer, Nikhil Munshi, Paul Richardson, Ben Ebert.
Other collaborators: David Scadden, Shaji Kumar, Ola Landgren, Antonio Palumbo, Herve Ave L'oiseau, Xavier Leleu, Leif Bergsagel, Marta Chesi, Bruno Paiva, Jesus San-Miguel, Richard Hynes, George Daley, Jon Licht, Gad Getz, David Rizzi, Viktor Adalsteinsson