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Welcome & Introductions

Dr. Chari's slides are available for download at www.LLS.org/programs

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers
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Emerging Therapies for Multiple Myeloma

Including Updates from the ASCO® 2017 Annual Meeting

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Disclosures

Nature of Relevant Financial Relationship	Commercial Interest
Grant or research support	Amgen, Array Biopharma, Celgene, Millennium/Takeda, Novartis Pharmaceuticals, Janssen, Pharmacyclics
Paid consultant	Celgene, Millennium/Takeda, Novartis Pharmaceuticals, Janssen

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Overview

ASCO 2017 Updates

- Hottest new thing: BCMA CAR-T
- Smoldering MM: Risk Stratification & to Treat or Not to Treat
- Newly Diagnosed MM:
  - Beyond RVD: Quadruplets?
  - Denosumab vs Zolendronic Acid
- Relapsed MM: pembrolizumab

ASH 2016 Updates:

- Dara SubQ
- Venetoclax
- Nelfinavir
- Selinexor

So Many Choices: Choosing the Right Treatment for Each Patient

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Available Anti- Myeloma Agents

Steroids	Conventional Chemo	ImIDs	Proteasome Inhibitors	HDAC inhibitors	Monoclonal antibodies
Prednisone	Melphalan	Thalidomide	Bortezomib	Panobinostat	Daratumumab: anti CD38
Dexamethasone	Cyclophosphamide	Lenalidomide	Carfilzomib (low/high dose)		Elotuzumab : anti CS1/SLAMF7
	Doxil	Pomalidomide	Ixazomib		
	DCEP/D-PACE				
	BCNU				
	Bendamustine				

9 drugs approved in last 15 years – including 4 in 2015!

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  - DaraKRD
  - EloRVD
- Newly Diagnosed MM Bone Health: Denosumab vs Zolendronic Acid
- Relapsed MM: Pembrolizumab

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First-in-human multicenter study of bb2121 anti-BCMA CAR T-cell therapy for relapsed/refractory multiple myeloma: Updated results

Berdeja JG, et al. ASCO 2017. Abstr 3010

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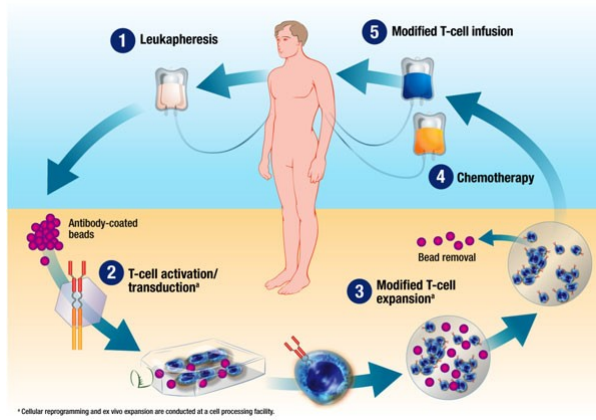
Chimeric Antigen Receptor –T cell Immunotherapy (CAR-T)



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First-in-human multicenter study of bb2121 anti-BCMA CAR T cell therapy for relapsed/refractory multiple myeloma: Updated results

Jesus G. Berdeja, MD1, Yi Lin, MD, PhD2, Noopur Raje, MD3, Nikhil Munshi, MD4, David Siegel, MD, PhD5, Michaela Liedtke, MD6, SundarJagannath, MD7, Marcela Maus, M.D., PhD3, Ashley Turka8, LyhPing Lam8,Kristen Hege, M.D9., Richard Morgan, PhD8, M. Travis Quigley8, and James N. Kochenderfer, MD10

1-Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN; 2-Mayo Clinic, Rochester, MN; 3-Massachusetts General Hospital Cancer Center, Boston, MA; 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-bluebird bio, Inc., Cambridge, MA; 9-Celgene, San Francisco, CA; 10-Experimental Transplantation and Immunology Branch, National Cancer Institute/National Institutes of Health, Bethesda, MD

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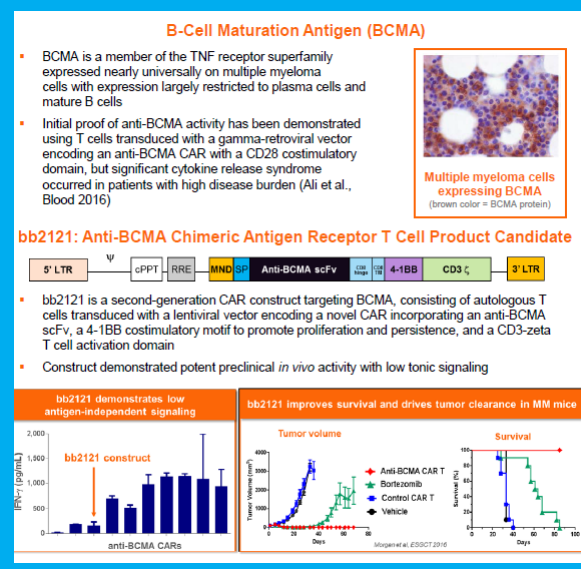
Introduction



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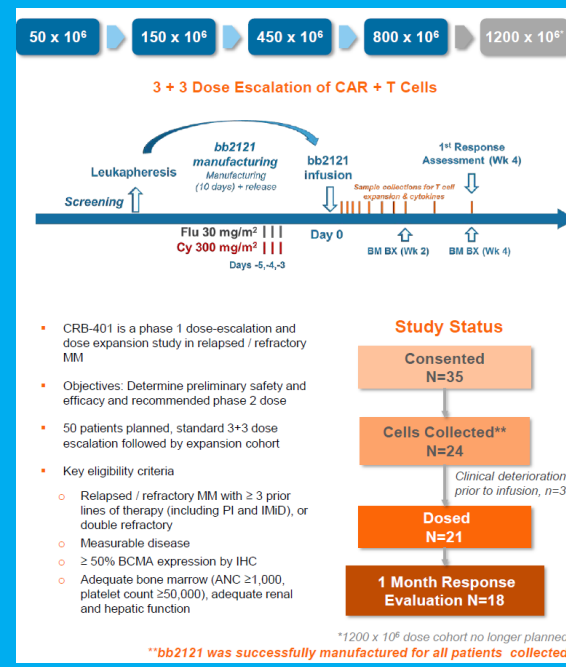
Study Design



- CRB-401 is a phase 1 dose-escalation and dose expansion study in relapsed / refractory MM
- Objectives: Determine preliminary safety and efficacy and recommended phase 2 dose
- 50 patients planned, standard 3+3 dose escalation followed by expansion cohort
- Key eligibility criteria
  - Relapsed / refractory MM with ≥ 3 prior lines of therapy (including PI and IMiD), or double refractory
  - Measurable disease
  - ≥ 50% BCMA expression by IHC
  - Adequate bone marrow (ANC ≥1,000, platelet count ≥50,000), adequate renal and hepatic function

Study Status

Consented N=35

Cells Collected** N=24

Clinical deterioration prior to infusion, n=3

Dosed N=21

1 Month Response Evaluation N=18

**1200 x 10⁶ dose cohort no longer planned*

bb2121 was successfully manufactured for all patients collected

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Baseline Demographics, Clinical Characteristics and Treatment History

- 21 patients have received bb2121 as of the data cut-off of May 4, 2017. Median follow-up is 15.4 weeks (range 1.4 to 54.4).

Demographics and Clinical Characteristics

Parameter	Statistic	N=21 Dosed Patients
Age years	Median (range)	58 (37-74)
Male gender	n (%)	13 (62%)
Time since diagnosis (years)	Median (range)	5 (1-16)
ECOG = 0	n (%)	10 (48%)
ISS Stage I II III	n (%)	 6 (29%) 11 (52%) 4 (19%)
High-risk cytogenetics (del17p, t(4;14), t(14;16), 1q, del 13)	N\n (%)	14 (67%)

MM Treatment History

Parameter	Statistic	N=21 Dosed Patients
Prior lines of therapy	Median (range)	7 (3-14)
Prior autologous SCT	n (%)	21 (100%)
Prior therapies	**Exposed**	**Refractory**
Bortezomib	100%	67%
Carfilzomib	91%	57%
Lenalidomide	100%	86%
Pomalidomide	91%	71%
Daratumumab	71%	48%
Cumulative Exposure	**Exposed**	**Refractory**
Bort / Len	100%	67%
Bort / Len / Car	91%	48%
Bort / Len / Pom	91%	57%
Bort / Len / Car / Pom	86%	43%
Bort / Len / Car / Pom / Dara	71%	29%

ECOG: Eastern Cooperative Oncology Group Performance Score
ISS: International Staging System
SCT: stem cell transplant

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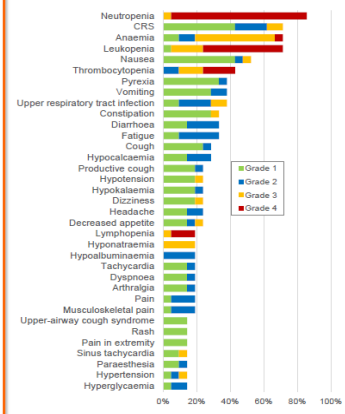
Safety Results & Adverse Events

Treatment Emergent Adverse Events in >2 Patients (N = 21 Dosed with bb2121)



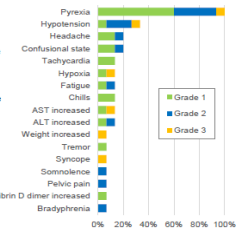
*CRS uniformly graded according to Lee et al., Blood 2014;124:188-195

- No dose-limiting toxicities (DLTs) observed as of data cut-off.
- Cytopenias related to Cy/Flu lymphodepletion.
- 1 unrelated death due to cardio pulmonary arrest in a patient with an extensive cardiac history. The event occurred more than 4 months after bb2121 infusion. The patient had achieved a stringent CR at 1 month and remained in remission at time of event.
- 11 patients experienced 1 or more SAEs. SAEs occurring in more than 1 patient were CRS Grade 1-2 that required hospitalization per protocol (N=4) and pyrexia (N=2).

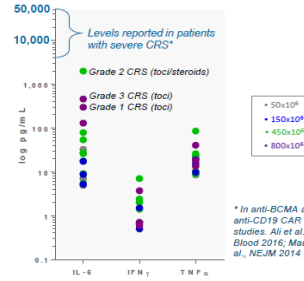
Reported CRS-Related Symptoms

In 15/21 treated patients with CRS

- 15/21 (71%) with cytokine release syndrome (CRS)
  - 2 patients with Grade 3 CRS that resolved in 24 hours
  - 4 patients received tocilizumab, 1 (Grade 2 CRS) with steroids
  - CRS grade does not appear related to tumor burden
- CRS-related symptoms mostly Grade 1-2
- No Grade 3/4 neurotoxicity



Peak Cytokine Levels



*In anti-BCMA and anti-CD19 CAR T studies. Ali et al., Blood 2016; Maude et al., NEJM 2014

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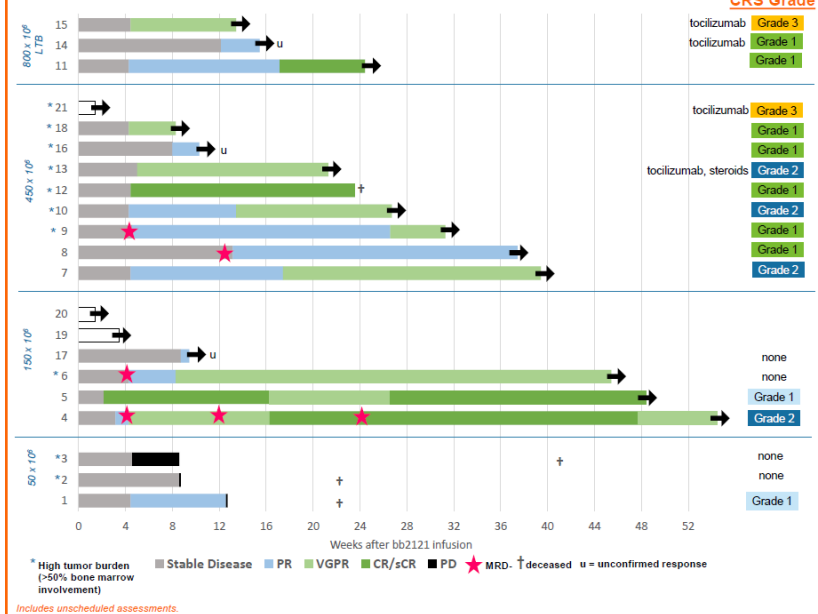
Clinical Response Over Time



* High tumor burden (>50% bone marrow involvement)

Stable Disease PR VGPR CR/sCR PD MRD- †deceased u = unconfirmed response

Includes unscheduled assessments.

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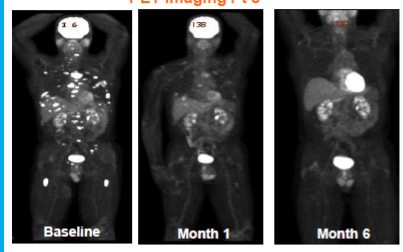
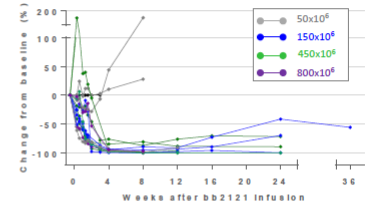
Tumor Response Kinetics: Rapid clearance of PET uptake, sBCMA and sFLC; slower clearance of M-protein

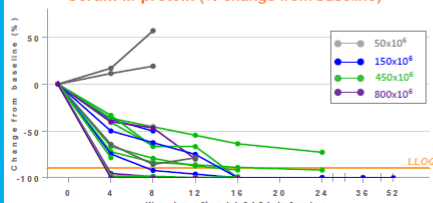
PET imaging Pt 8



Serum BCMA (% change from baseline)

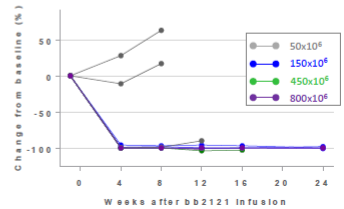


Serum M-protein (% change from baseline)



calculated only in patients with a baseline M protein > 0.5 g/dL (n=17)

dFLC (% change from baseline)*



ratio=involved LC-uninvolved LC, calculated only in patients with a baseline LC > 10 mg/dL (N=13)

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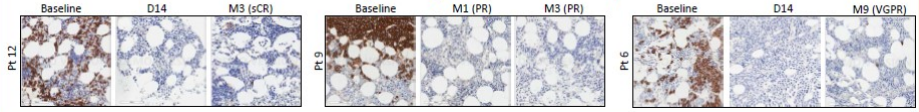
Response Rates and Timing

Efficacy Parameter	Rate (95% CI)
ORR all doses	89% (65-99)
ORR (> 50 x 10^6 CAR+ cells)	100% (78.2-100)
≥VGPR (> 50 x 10^6 CAR+ cells)	73%
CR rate (> 50 x 10^6 CAR+ cells)	27%
	Median (range)
Time to First Response (days)	31 (15-92)
Time to Best Response (days)	59.5 (15-186)
Duration of Response (days, as of data cut-off)	134+ (7-361)

ORR: overall response rate among patients evaluable for clinical response

Clearance of Myeloma in the Bone Marrow by IHC as Early as Day 14 (CD138+ cells)



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Conclusions

1. To date, the safety profile of bb2121 has been manageable through doses as high as 800 x 106CAR + cells in this Phase 1 study of bb2121
   - −The 2 reported events of grade 3 CRS resolved within 24 hours
   - −No grade 3/4 neurotoxicity reported
2. No dose-limiting toxicities have yet been observed, and no maximum tolerated dose has been identified
3. bb2121 has induced durable and deepening responses in a heavily pre-treated population with relapsed/refractory MM, including:−100% ORR, 73% VGPR or better, 27% CR (at doses > 50 x 106CAR+ cells)
   - −MRD negative results in all evaluable patients (N=4)
   - −No disease progression in patients treated with doses higher than 50 x 106, with 1 patient past 1 year and 8 past 6 months
4. These results will inform identification of the dose(s) to bring forward into the expansion phase of the study and future development

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Durable remissions with BCMA-specific chimeric antigen receptor (CAR)-modified T cells in patients with refractory/relapsed multiple myeloma

- Fan F, et al. ASCO 2017. Abstr LBA3001

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Nanjing Legend Biotech: BCMA Targeted CAR-T

- N = 35 relapsed or refractory MM
- 3 split doses (20%, 30% and 50% respectively) of cells over a week, and first signs of efficacy appeared as early as 10 days after the initial injection.
- 33/35 (94%) had a remission within 2 months of receiving the CAR T cells; 1 had progression after 3 month PR
- Of 19 more than 4 months: 14 Complete remission + 5 Partial remission
- Of 5 followed 12 to 14 months so far, and all have no detectable cancer cells in their bone marrow.
- CRS occurred in 85% of the patients, but it was temporary and most patients had mild and manageable symptoms. Two patients had severe CRS but recovered. No patients had neurologic side effects.
- The researchers plan to keep adding patients to this study until they reach 100 total patients.

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- Relapsed MM: Pembrolizumab

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Smoldering Multiple Myeloma (SMM): Predictive Value of Free Light Chains and Group Based Trajectory Modeling (GBTM)

Vernon Wu, Erin Moshier, Ajai Chari
Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

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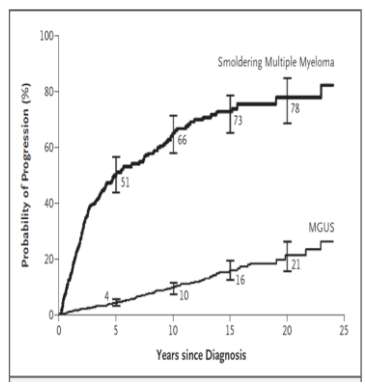
Mayo and Pethema Risk Stratification of SMM



Risk factor	Progression at 5 years
Mayo Risk Factors (> 10% PC, m > 3/gl, FLCR < 0.125 or > 8)	
0	25%
1	51%
2	76%
Pethema Risk Factors (≥95% abn PC, immunoparesis)	
0	4%
1	46%
2	72%

Kyle RA, et al. *N Engl J Med.* 2007;356:2582-2590; . Perez-Persona E, et al. Blood. 2007;110:2586-92

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Risk Factors for Non-CRAB SMM Progression at 2 Years

Risk group	Probability of progression to myeloma or related disorder in first 2 years from initial diagnosis of SMM (%)
Bone marrow clonal plasma cells ≥60%	90
Serum involved/uninvolved free light chain ratio ≥100	80
Abnormalities on MRI (>1 focal lesion)	70
Abnormal plasma cell immunophenotype ≥95%	50
Evolving type of SMM*	65
t(4;14) or del 17p	50
M protein ≥30 g/l and bone marrow clonal plasma cells ≥10%	50
Serum involved/uninvolved free light chain ratio ≥8 and <100	40
No high-risk factors	10–20

*Increase in serum monoclonal protein by ≥10% on each of two successive evaluations within a 6-month period. ‡Further efforts to refine cut-off values are ongoing to identify a patient population with ≥80% risk of progression in the first 2 years. Abbreviation: SMM, smoldering multiple myeloma.

Rajkumar, S. V. & Kyle, R. A. (2013) *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2013.160

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Current Definitions of MGUS, SMM and MM

	MGUS	SMM	MM
(1) Serum M-protein	< 3 g/dL	≥ 3 g/dL or BJP > 500 mg/d	Any paraprotein
(2) Bone marrow plasma cell %	< 10%	10-60%	≥ 10% or biopsy-proven plasmacytoma
(3) CRAB*	None	None	At least one
(4) Myeloma Defining Events**	None	None	Possible
For diagnosis	All 4 criteria must be met	Either (1) OR (2), WITHOUT (3) OR (4)	Either (2) + (3), OR (2) + (4)

***CRAB criteria:**
(1) Serum calcium > 11 mg/dL or > 1 mg/dL above ULN,
(2) renal insufficiency (serum Cr > 2 mg/dL or Cr Cl < 40 mL/min),
(3) anemia (hemoglobin > 2 g/dL below the LLN, or < 10 g/dL), and
(4) bone lesions (one or more osteolytic lesions revealed by skeletal radiography, CT, or PET)

**** Myeloma defining events:**
(1) clonal bone marrow plasma cell % ≥60
(2) involved to uninvolved serum free light chain ratio ≥ 100
(3) > 1 focal lesions (each ≥ 5 mm in size) on MRI

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Comparison of high risk SMM at various institutions

	Mayo Clinic	University of Athens	University of Pennsylvania	Denmark	MM GIMEMA-Latium Working Group	Mount Sinai
Years of investigation	1970-2010 (FLCR), 1996-2010 (BMPC)	-	2008-2012	2005-2013	1980-2010	2010-2015
Number of Centers	single	-	single	multi	multi	single
Inclusion Criteria†	yes	-	-	yes	yes	yes
FLCR						
n	586	96	118	209	-	185
FLCR ≥ 100 (n/%)	90(15%)	-	11(9%)	23(11%)	-	27(15%)
median TTP (mo)	15mo	13mo	20mo	-***	-	23mo
2 year progression (%)	72%	98%*	64%	30%	-	52%
Overall progression†† (%)	98%	100%	-	-	-	67%
BMPC						
n	655	96	121	-	397	273
BMPC ≥ 60 (n/%)	21(3.2%)	8(8%)	6(5%)	-	10(2.5%)****	22(8%)
median TTP (mo)	7mo	15mo	-	-	-	25mo
2 year progression (%)	95%	95.5%**	100%	-	100%	45%
Overall Progression†† (%)	-	100%	100%	-	100%	77%

Abbreviations: † stipulation that lab data be obtained within 3mo of diagnosis. †† progression during study follow up period which is median of 77mo for N=273 and median of 60mo for N=185. - data not available. *data at 14mo. ** data at 18mo. *** not enough patients progressed to calculate median TTP. **** N= 7 by bone marrow biopsy core, N=10 by bone marrow aspirate

Predictive Value of Group-Based Trajectory Modeling Factors

	n (%)	median TTP (mo)	Log-Rank P-value	2y PD %	overall PD %	Specificity %	Sensitivity %	Diagnostic Accuracy
GBTM Factors								
eHB								
No eHb	188 (69%)	77.3	0.0010	16%	43%	91%	72%	79%
eHb	27 (10%)	36.1		45%	59%			
Not Evaluable	58 (21%)							
eMP								
No eMP	87 (32%)	159.8	0.0003	13%	34%	66%	63%	66%
eMP	58 (21%)	39.8		35%	66%			
Not Evaluable	128 (47%)							
eFLCr								
No eFLCr	108 (40%)	Not Reached	0.0053	16%	37%	88%	28%	76%
eFLCr	19 (7%)	35.1		41%	68%			
Not Evaluable	146 (53%)							
edFLC								
No edFLC	104 (38%)	115.2	0.0367	16%	38%	85%	32%	75%
edFLC	23 (9%)	35.1		35%	57%			
Not Evaluable	146 (53%)							

Over 1 year

- eHb patients decrease of 1.27g/dL [95% CI: 0.86, 1.68] or maintained a Hb of 11g/dL
- eMP patients experienced either a 64% [95% CI: 44%, 83%] increase in M-protein or maintained a M-protein of at least 3g/dL.
- eFLCr patients on average experienced either a 188% [95% CI: 183%, 193%] increase in FLCr
- edFLC patients on average experienced a 169% [95%CI: 143%, 195%] increase in dFLC

Multivariable Modeling to predict 2y PD

n=90	Univariable		Multivariable	
	HR [95% CI]	P-value	HR [95% CI]	P-value
Age	1.004 [0.98-1.03]	0.7890		
Male Sex	0.95 [0.52-1.75]	0.8788		
BMPC ≥ 20%	3.19 [1.47-6.90]	0.0033	**2.15 [0.96-4.86]**	**0.0644**
BMPC ≥ 60%	1.22 [0.43-3.46]	0.7087		
M-Protein ≥ 3g/dl	3.12 [1.59-6.13]	0.0010		
IgA SMM	0.64 [0.27-1.53]	0.3192		
Immunoparesis	2.68 [1.41-5.12]	0.0028		
FLCr ≥ 100 and dFLC≥100	1.72 [0.71-4.15]	0.2294		
LDH>333	0.44 [0.06-3.27]	0.4214		
B2mg > 3.5 ug/ml	0.49 [0.12-2.05]	0.3289		
dFLC≥100	1.59 [0.86-2.96]	0.1415		
eMP	4.38 [2.29-8.39]	<0.0001	**4.32 [2.22-8.42]**	**<0.0001**
eHb	1.86 [0.78-4.43]	0.1629		
eFLCr	1.84 [0.93-3.67]	0.0817		
edFLC	3.40 [1.73-6.71]	0.0004	**2.89 [1.41-5.94]**	**0.0039**

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Early SMM Treatment vs Symptomatic Treatment - Considerations for Future Therapeutic Studies

	Early treatment	Treatment @ Symptoms
Clinical	- Deep responses in SMM possible now - Prevention/reduction of end-organ damage and infections - Potential for increased OS and ? cure	- Insufficient data re improved OS and PFS - Treatment toxicity- Grade 3 /4 or chronic Grade 1/2; QOL impairment/PROs - # needed to treat vs harm
Patho-physiologic	- Potential for increased curability due to presence of less genomic complexity - Ability to target significant mutations	- Unclear impact on PFS2 - Driver mutations have yet to be identified - Disease heterogeneity
Risk stratification	- Truly high-risk SMM very high probability of early progression - Kinetic risk stratification may mitigate some biases	- Lack of global concordance, consensus regarding high-risk status - Need to incorporate additional phenotypic and genomics features
Trial design	- Randomized early vs late treatment using same regimen ethical & feasible - Stratify by time from diagnosis - Standardized sensitive osseous screening (WBLDCT, PET-CT, or MRI) - Fix duration of treatment	- Inability to specifically target significant/driver mutations - Lead & length time biases can make benefits difficult to discern
Economic	- Less end-organ damage costs - Potential for increased OS - ? Cure	- Likely prolonged therapy if not fixed duration - Need for stem cell harvest if IMIDs used

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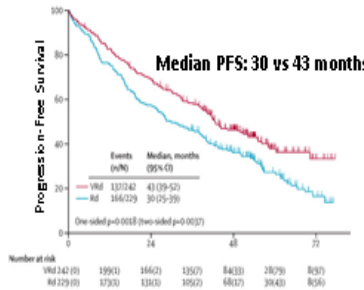
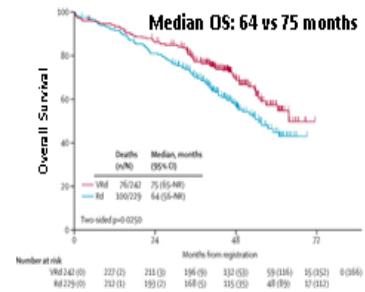
RVD without Transplantation for Myeloma: SWOG S0777

RVD Arm
Eight, 21-day induction cycles. Len 25 mg D1 –14; Bort 1.3 mg/m2 IV D1, 4, 8 and 11; Dex 20 mg D1, 2, 4, 5, 8, 9, 11 and 12
RD Arm
Six, 28-day cycles. Len 25 mg D1 –21; Dex 40 mg on D1, 8, 15 and 22
Maintenance (Both Arms)
28-day cycles. Len 25 mg D1 –21; Dex 40 mg D1, 8, 15 and 22

Response	RVD	RD
ORR	81.5%	71.5%
PR	38%	39.7%
VGPR	27.8%	23.4%
CR	15.7%	8.4%
≥VGPR	43.5%	31.8%





Durie B et al. Lancet 2017;389:519-27.

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RVD with Transplantation for Myeloma

Phase III study of upfront vs deferred ASCT in the context of RVD-based therapy for newly-diagnosed multiple myeloma

Upfront ASCT Arm

3 cycles of RVD induction → Cyclophosphamide + G-CSF mobilization → high-dose MEL ASCT → 2 cycles of RVD consolidation → Len maintenance x 1 year

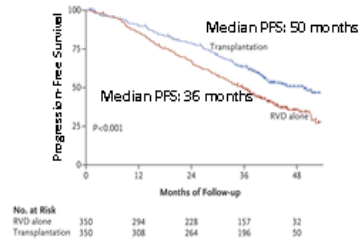
Deferred ASCT Arm

3 cycles of RVD induction → Cyclophosphamide + G-CSF mobilization → 5 cycles of RVD consolidation → Len maintenance x 1 year

Best Response	Deferred ASCT	Upfront ASCT	P Value
ORR	97%	99%	
PR	20%	11%	
VGPR	29%	29%	
CR	48%	59%	0.03
≥VGPR	77%	88%	0.001
MRD-[1]	65%	79%	<0.001

[1]MRD tested by flow cytometry in VGPR/CR pts

Median Follow-Up: 44 months for the deferred ASCT group, 43 months for the upfront ASCT group



4-Year OS: 82% vs 81% for deferred and upfront ASCT, respectively

Attal M et al. NEJM 2017;376:1311-20.

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Carfilzomib Lenalidomide and Dexamethasone (KRD)

Outcome (%)	Post-Induction		
	MMRC SCT N= 76	MMRC Non-SCT N = 49	IFM SCT N = 46
Flow MRD	NR	NR	63%
NGS MRD			
CR/sCR	16%	18%	25.5%
≥VGPR	73%	69%	83.5%

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Daratumumab (DARA) in Combination with Carfilzomib, Lenalidomide, and Dexamethasone (KRd) in Patients (pts) With Newly Diagnosed Multiple Myeloma (MMY1001): an Open-label, Phase 1b Study

Andrzej Jakubowiak,[1] Ajai Chari,[2] Sagar Lonial,[3] Brendan Weiss,[4] Raymond L. Comenzo,[5] Kaida Wu,[6] Nushmia Z. Khokhar,[6] Jianping Wang,[7] Parul Doshi,[6] Saad Z. Usmani[8]

[1]University of Chicago Medical Center, Chicago, IL; [2]Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA; [3]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, USA; [4]Abramson Cancer Center and Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [5]Division of Hematology/Oncology, John C. Davis Myeloma and Amyloid Program, Tufts Medical Center, Boston, MA; [6]Janssen Research & Development, LLC, Spring House, PA, USA; [7]Janssen Research & Development, LLC, Raritan, NJ, USA; [8]Levine Cancer Institute/Carolinas HealthCare System, Charlotte, NC, USA.

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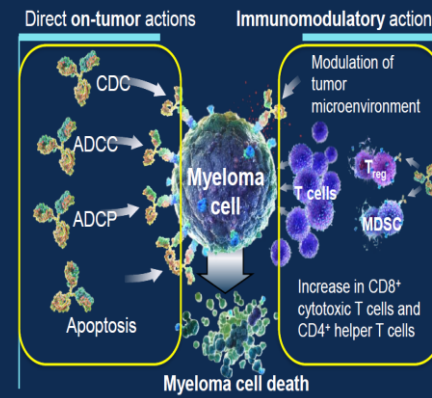
Daratumumab (DARA)

- Human IgGκ monoclonal antibody targeting CD38 with a direct on-tumor and immunomodulatory MoA[1]
- Approved as monotherapy in many countries for heavily pretreated RRMM
- Approved in combination with standard of care regimens in RRMM after ≥1 prior therapy in the USA, EU, and Brazil
- DARA induces rapid, deep and durable responses in combination with a PI (bortezomib) or an IMiD (lenalidomide) in RRMM[2,3]



RRMM, relapsed/refractory multiple myeloma; PI, proteasome inhibitor; IMiD, immunomodulatory drug.

1. Touzeau, C and Moreau, P. *Expert Opin Biol Ther.* 2017; Epub ahead of print.
2. Mateos MV, et al. Oral presentation at the 59th American Society of Hematology Annual Meeting and Exposition, December 9-12, 2016; Abstract: 1150.
3. Usmani SZ, et al. Oral presentation at the 59th American Society of Hematology Annual Meeting and Exposition, December 9-12, 2016; Abstract: 1151.

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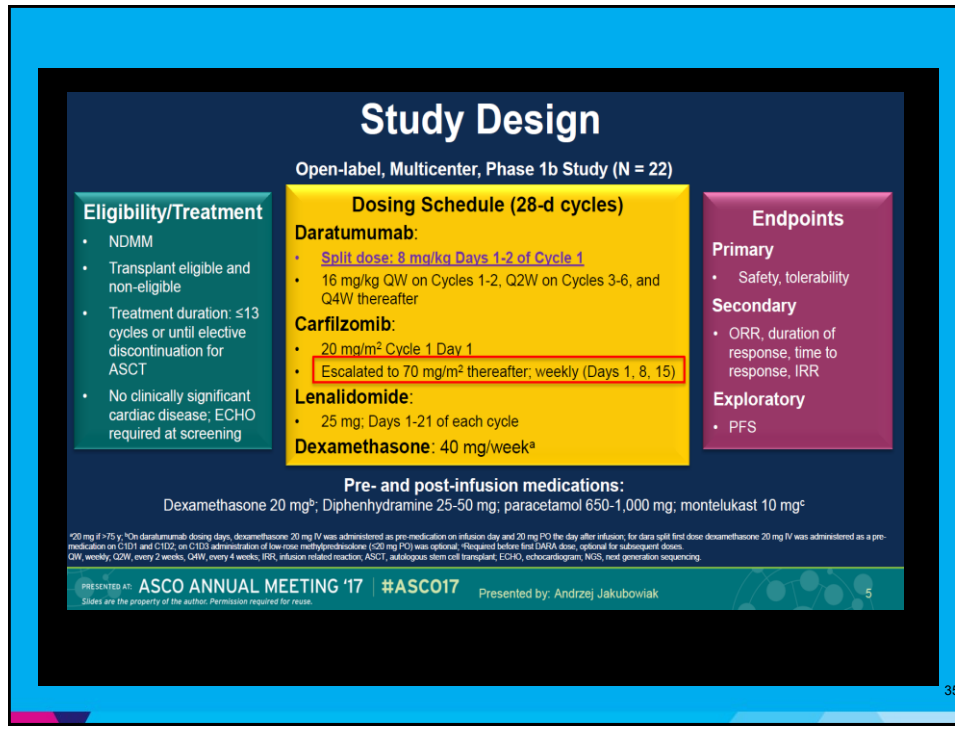
Study Design
Open-label, Multicenter, Phase 1b Study (N = 22)
Eligibility/Treatment
NDMM
Transplant eligible and non-eligible
Treatment duration: ≤13 cycles or until elective discontinuation for ASCT
No clinically significant cardiac disease; ECHO required at screening
Dosing Schedule (28-d cycles)
Daratumumab:
Split dose: 8 mg/kg Days 1-2 of Cycle 1
16 mg/kg QW on Cycles 1-2, Q2W on Cycles 3-6, and Q4W thereafter
Carfilzomib:
20 mg/m² Cycle 1 Day 1
Escalated to 70 mg/m² thereafter; weekly (Days 1, 8, 15)
Lenalidomide:
25 mg; Days 1-21 of each cycle
Dexamethasone: 40 mg/week[a]
Endpoints
Primary
Safety, tolerability
Secondary
ORR, duration of response, time to response, IRR
Exploratory
PFS
Pre- and post-infusion medications:
Dexamethasone 20 mg[b]; Diphenhydramine 25-50 mg; paracetamol 650-1,000 mg; montelukast 10 mg[c]
[a]20 mg if >75 y; [b]On daratumumab dosing days, dexamethasone 20 mg IV was administered as pre-medication on infusion day and 20 mg PO the day after infusion; for dara split first dose dexamethasone 20 mg IV was administered as a pre-medication on C1D1 and C1D2; on C1D3 administration of low-rose methylprednisolone (≤20 mg PO) was optional. [c]Required before first DARA dose, optional for subsequent doses.
QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; IRR, infusion related reaction; ASCT, autologous stem cell transplant; ECHO, echocardiogram; NGS, next generation sequencing.
PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17
Presented by: Andrzej Jakubowiak
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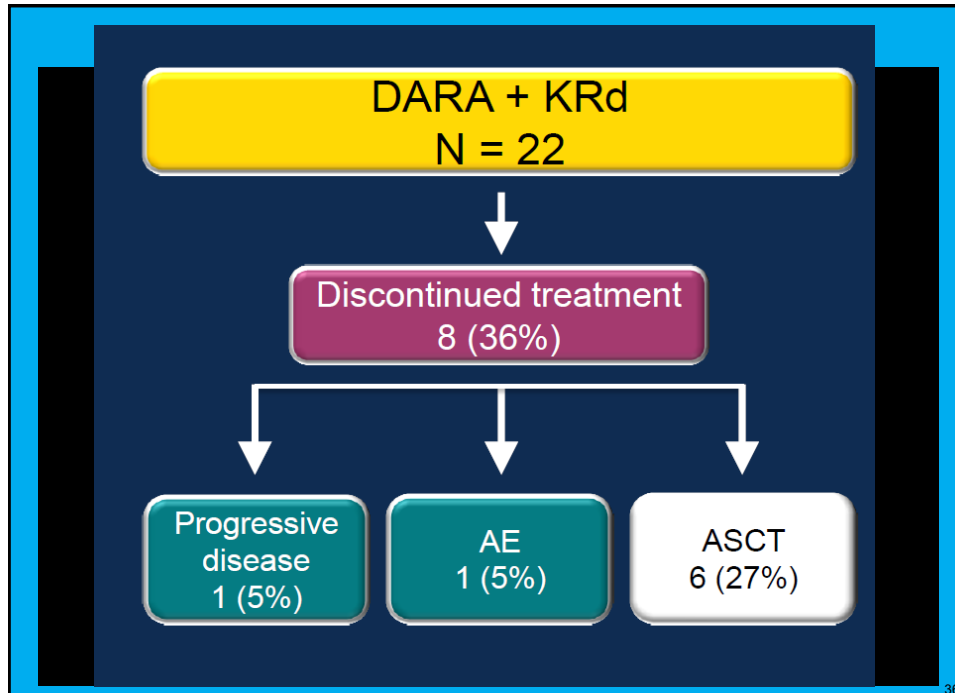
DARA + KRd
N = 22
Discontinued treatment
8 (36%)
Progressive disease
1 (5%)
AE
1 (5%)
ASCT
6 (27%)

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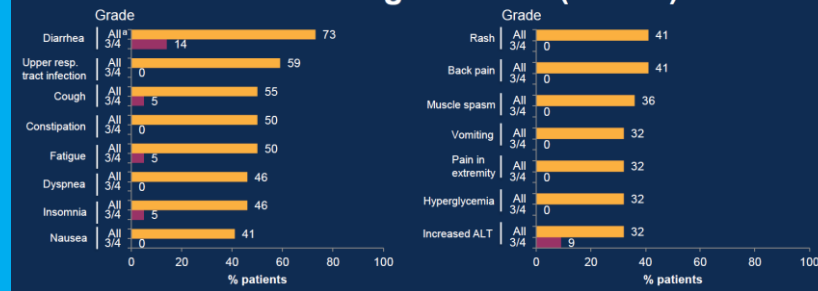
Nonhematologic TEAEs (N = 22)



- 1 (5%) treatment discontinuation due to pulmonary embolism; unrelated to daratumumab or carfilzomib
- 2 (9%) grade 3/4 pulmonary embolisms; both patients were on aspirin prophylaxis
- No deaths

Safety profile is consistent with previous reports for DARA and KRd

[a]≥30%
TEAE, treatment emergent adverse event

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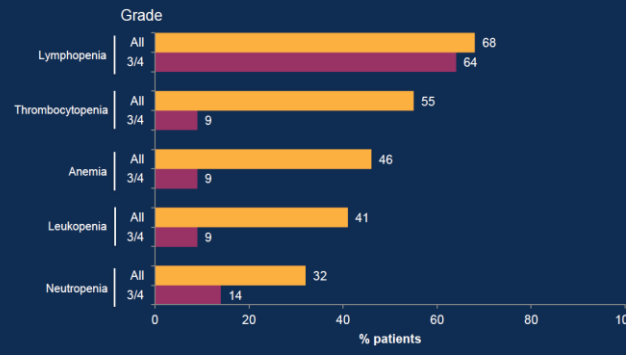
Hematologic TEAEs (N = 22)



Lymphopenia rate is consistent with previous KRd studies[1]

1. Korde N et al. *JAMA Oncol*. 2015;1(6):746-754.

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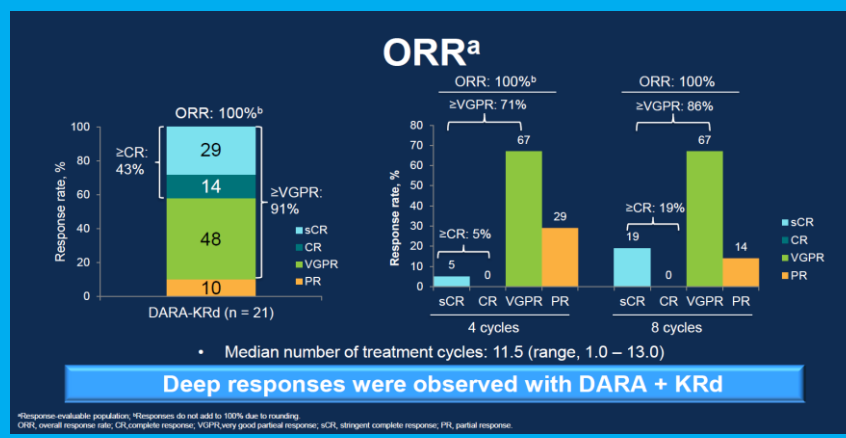
ORR[a]
ORR: 100%[b]
≥CR: 43%
≥VGPR: 91%
29
14
48
10
sCR
CR
VGPR
PR
Response rate, %
DARA-KRd (n = 21)
ORR: 100%[b]
≥VGPR: 71%
≥CR: 5%
5
0
67
29
4 cycles
ORR: 100%
≥VGPR: 86%
≥CR: 19%
19
0
67
14
8 cycles
• Median number of treatment cycles: 11.5 (range, 1.0 – 13.0)
Deep responses were observed with DARA + KRd
[a]Response-evaluable population; [b]Responses do not add to 100% due to rounding.
ORR, overall response rate; CR,complete response; VGPR,very good partial response; sCR, stringent complete response; PR, partial response.

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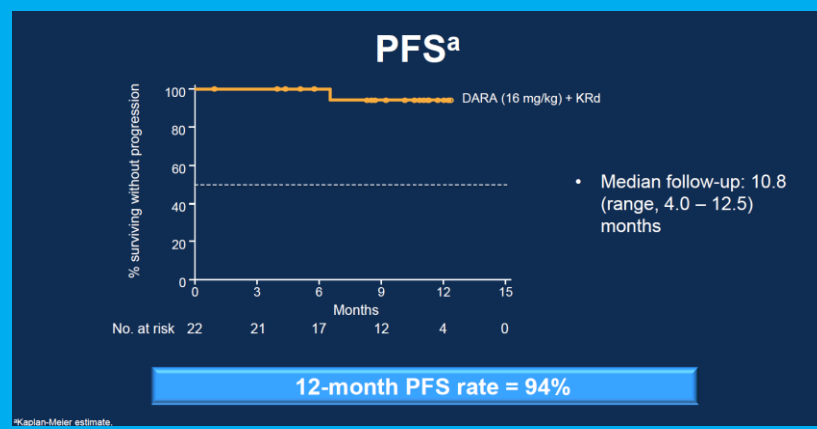
PFS[a]
% surviving without progression
DARA (16 mg/kg) + KRd
Months
No. at risk 22 21 17 12 4 0
• Median follow-up: 10.8 (range, 4.0 – 12.5) months
12-month PFS rate = 94%
[a]Kaplan-Meier estimate.

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Conclusions

- DARA + KRd was well tolerated
  - Safety is consistent with previous reports of DARA and KRd
  - Low IRR rates associated with split first dose; no grade 3/4
- 100% response rate
  - Deep responses despite short follow up
- Stem cell yield was sufficient for ASCT
- CANDOR (DARA + Kd) phase 3 study in RRMM
- ALCYONE (DARA + VMP), MAIA (DARA + Rd), and CASSIOPEIA (DARA + VTd) are ongoing phase 3 studies in NDMM

These data support further investigation of DARA-KRd in NDMM

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KRD-Dara vs KRD

Outcome (%)	After 4 Cycles		After 8 Cycles	
	DaraKRD N = 21	KRD Non-SCT N = 49	DaraKRD N = 15	KRD Non-SCT N = 44
CR/sCR	5%	18%	27%	34%
≥VGPR	71%	69%	87%	89%

Jakubowiak A et al. ASCO 2017, Abstract 8000.
Jakubowiak, A et al. Blood 2012;120:1801-9.

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An open-label, single arm, phase IIa study of bortezomib, lenalidomide, dexamethasone, and elotuzumab in newly diagnosed multiple myeloma

Jacob Laubach, Ajay K. Nooka, Craig Cole, Elizabeth O'Donnell, Ravi Vij, Saad Z. Usmani, Gregory Joshua Orloff, Joshua Ryan Richter, Robert Redd, Heidi Dipietro, Kristen Cummings, Joshua Hansen, Patrick M. Henrick, Paul Bassett, Haley Schachter, Paul G. Richardson, Sagar Lonial

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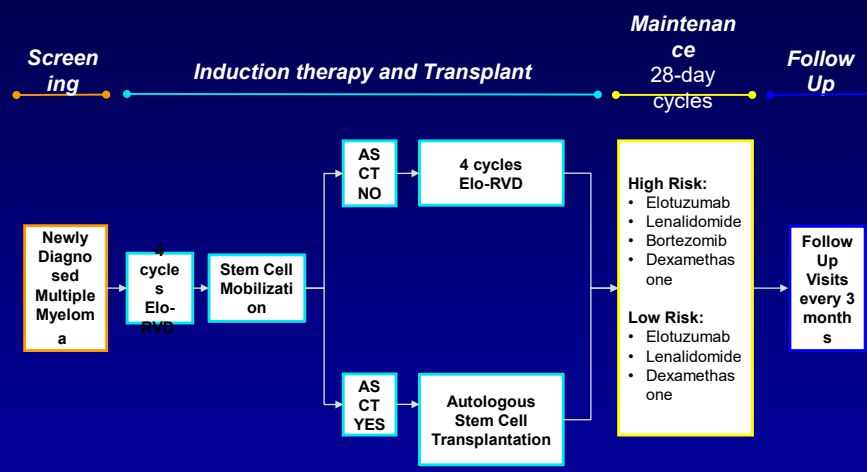
Treatment Schema



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Baseline Characteristics

	Total n = 40 (%)
Age at registration	
Median (range)	60 (34 - 75)
≤ 60	20 (50)
61+	20 (50)
Sex	
Female	17 (42)
Male	23 (57)
Race	
Black or African American	7 (18)
Other	3 (8)
White	30 (75)
ISS Stage	
I	24 (60)
II	10 (25)
III	6 (15)

Cytogenetics

Unfavorable cytogenetics, n/N(%)	6/39 (15)
Unfavorable abnormalities, n(%)	
t(4:14)	4 (10)
t(14:16)	1 (3)
del 17p	1 (3)

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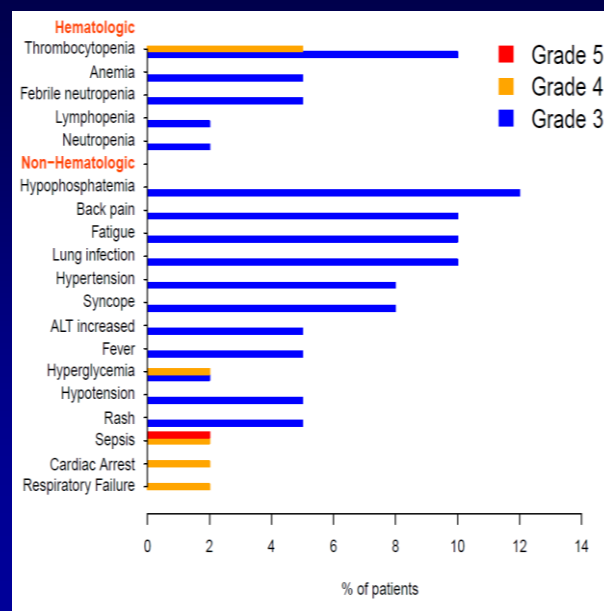
Grade ≥ 3 Adverse Events



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Response Data Among Pts who Completed at least 4 Cycles of Therapy

	After 4 Cycles	Best response
	n = 34	n = 34
ORR (≥ PR)	33 (97)	33 (97)
VGPR (≥ VGPR)	22 (65)	29 (88)
CR + sCR	6 (15)	14 (41)

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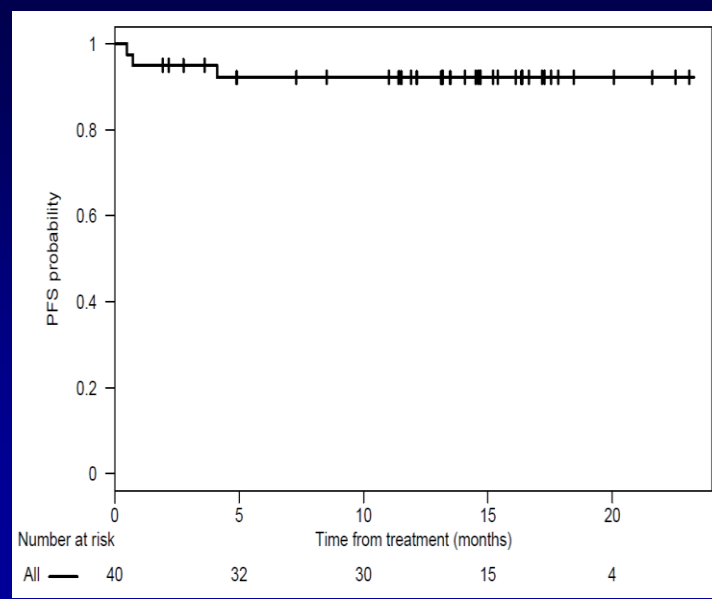
Progression-free Survival



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Conclusions

- The combination of Elo plus RVD was associated with a level of overall response similar to prior studies of RVD in newly diagnosed MM
- A higher than expected number of patients (6/40, 15%) discontinued therapy within the first four cycles of treatment due to adverse events
- Infection occurred in 50% of patients overall, including one grade 5 sepsis, one grade 4 sepsis, and four patients with grade ≥ 3 lung infection
- The high rate of overall response, VGPR or better, and CR + nCR among pts who received at least 4 cycles of therapy is promising
- Dose or schedule modifications of Elo plus RVD may improve toxicity profile and augment clinical benefit

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RVD-Elo

Response	RVD-Elo Ph II After 4 Cycles N = 33	RVD Ph I/II After 4 Cycles N = 35	VRD Ph II After 4 cycles N = 42	RVD Ph III After 3 cycles N = 350
ORR	82%	75%	73%	94%
≥VGPR	55%	11%	32%	45%
CR/sCR	15%	6% (+nCR)	9%	NR

- Based on ELOQUENT-2, time dependent variables will likely be more informative than response data
  - Preliminary data suggest that responses are durable, with or without SCT
- Data on risk adapted maintenance will be of interest
  - Definition of high risk disease in this protocol liberal
    - Are Del(13q) and t(11;14) high risk?
- Stem cell mobilization does not appear to be adversely impacted
  - Median # of CD34 cells / kg: 10.48 x 10^6/kg (range 1.88–27.4 x 10^6/L)
- **18% of pts discontinued therapy within the first 4 cycles of treatment due to toxicity**
- **Infection seen in 50% of patients, including 1 grade 5 infection, 1 grade 4 sepsis and 4 grade 3 pneumonias**

Kumar S et al. Blood 2012;110:4375-82.
Attal M et al. NEJM 2017;376:1311-20.
Richardson PG et al. Blood 2010;116:279-86.
Laubach J et al. ASCO 2017, Abstract 8002.

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Beyond RVD: but at what cost?

Regimen	Cycle Length (Days)	Cost / Cycle Cycle 1 and 2	Cost / Cycle Cycles 3 – 6	Cost / Cycle Cycle 7 and Beyond	Cost of 12 Weeks of Therapy
RVD	21	$14,792	$14,792	$14,792	$59,168
RAD*	28	$18,211	$18,211	$18,211	$54,633
RVD-Elo	21	$29,213	$24,406	$24,406	$107,238
KRD-Dara	28	$47,611	$36,231	$30,541	$167,684

Estimates based on Wholesale Acquisition Costs (WAC). *Cost of pegfilgrastim included in RAD calculation

Other considerations:
- Supportive care costs not included in the above calculations (infusion time, nursing care, IVFs etc)
- Bortezomib poised to go generic

What magnitude of clinical benefit is required to utilize RVD-Elo or KRD-Dara over RVD or KRD?

WAC data obtained with the help of Issam Hamadeh and Justin Arnall

Levine Cancer Institute

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Conclusions

- **RVD remains the standard of care**
  - …for now
- **IMID / PI-containing triplets outperform triplets containing an IMID or PI with a conventional agent**
  - Increased high quality response rates
  - Impact on PFS and OS to be determined
- **RVD-Elo and KRD-Dara appear promising**
  - More mature clinical efficacy data from ongoing and planned randomized studies needed
  - The addition of mAbs to IMID / PI – based therapy is well tolerated but not without risk
    - Infection risk appears increased with the use of elo and dara in combination therapy
- **Financial toxicity / healthcare economics are important endpoints**
  - Must weigh short-and long-term costs of care
    - Does adding dara to induction allow a shorter duration of induction, omission of consolidation or discontinuation of lenalidomide maintenance?
    - What is the impact of the mAbs on treatment- and myeloma-related morbidity?

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Overview

ASCO Updates

- The hottest new thing: BCMA CAR-T
- Smoldering Myeloma: Risk Stratification and to Treat or Not to Treat
- Newly Diagnosed MM: Beyond RVD Quadruplets?
  - DaraKRD
  - EloRVD
- Newly Diagnosed MM Bone Health: Denosumab vs Zolendronic Acid
- Relapsed MM: Pembrolizumab

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Impact of Denosumab Compared With Zoledronic Acid on Renal Function in the Treatment of Myeloma Bone Disease

[1]Noopur Raje, [2]G. David Roodman, [3]Wolfgang Willenbacher,[4]Kazuyuki Shimizu, [5]Ramón García-Sanz, [6]Brian Durie, [7]Li Zhu, [8]Paul Cheng, [7]Sumita Bhatta, [9]Evangelos Terpos

Massachusetts General Hospital Cancer Center, Boston, MA, USA[1]; Indiana University Simon Cancer Center, Indianapolis, Indiana, USA[2] Center for Multiple Myeloma, Medical University of Innsbruck, Innsbruck, Austria[3]; National Hospital Organization Higashi Nagoya National Hospital, Nagoya, Japan[4]; Hospital Universitario de Salamanca, Salamanca, Spain[5]; Cedars-Sinai Medical Center, Los Angeles, CA, USA[6]; Amgen Inc., Thousand Oaks, CA, USA[7]; Kite Pharma, Santa Monica, CA, USA[8]; University of Athens School of Medicine, Alexandra General Hospital, Athens, Greece[9]

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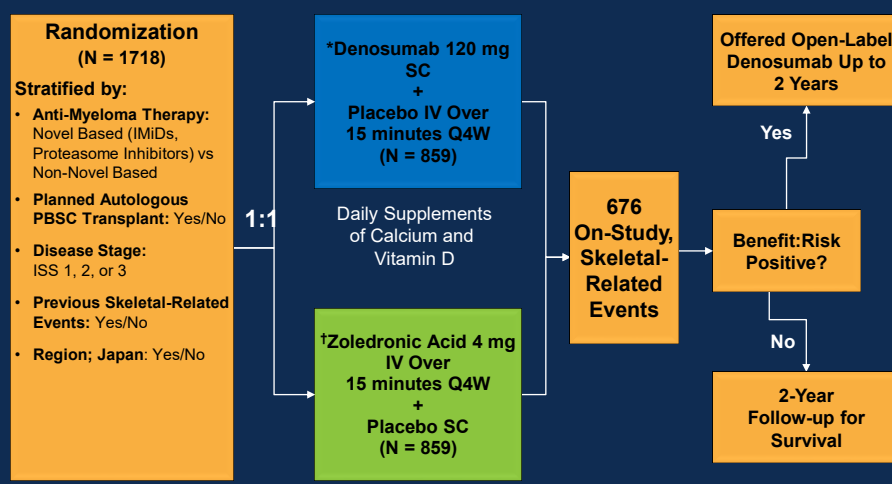
Introduction

- Osteolytic bone disease and renal dysfunction are the most frequent complications of multiple myeloma, presenting in up to 90% and 60% patients respectively.
- Denosumab is a human monoclonal antibody that targets RANKL, a key driver of osteoclast-mediated osteolysis, which in turn increases the risk of skeletal-related events (SREs), morbidity, and mortality.
- Denosumab can be administered regardless of renal function and does not need to be dose adjusted, unlike bisphosphonates.
- This international, phase 3, randomized, double-blind study evaluates the efficacy and safety of denosumab compared with zoledronic acid in newly diagnosed multiple myeloma patients and represents the largest international phase 3 trial ever conducted in multiple myeloma, with 1718 patients enrolled from 259 sites and 29 countries.

Study Design



*No SC dose adjustments were required. † Per protocol and Zometa® label, IV product was dose adjusted for baseline creatinine clearance and subsequent dose intervals were determined by serum creatinine levels.

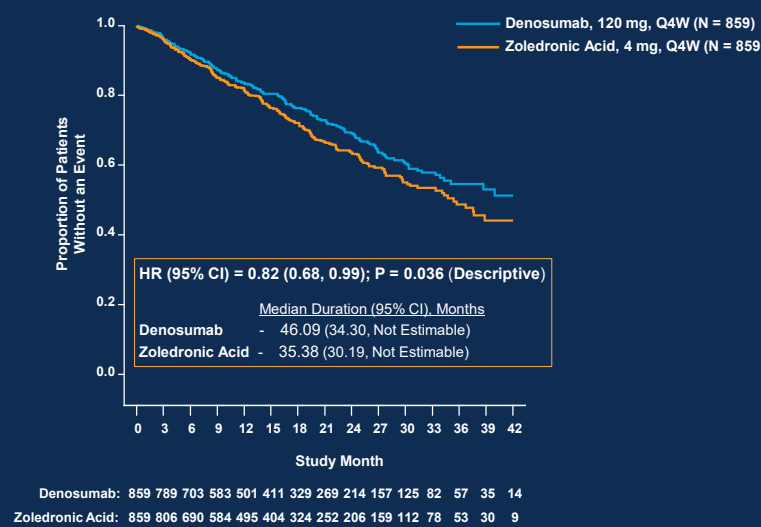
IMiDs Immunomodulatory drugs; ISS International staging system; IV intravenous; PBSC peripheral blood stem cell; SC subcutaneous; Q4W every four weeks

Results

- This study successfully demonstrated that denosumab met the primary endpoint of noninferiority to zoledronic for time to first skeletal-related events (HR [95% CI] = 0.98 [0.85, 1.14], P = 0.01); superiority was not significant.
- The difference in overall survival (HR [95% CI] = 0.90 [0.70, 1.16], P = 0.41) was not significant. However, there were limited numbers of deaths on the study.
- Progression-free survival for denosumab was numerically longer (10.7 months) compared to zoledronic acid, with a HR (95% CI) = 0.82 (0.68, 0.99), descriptive P = 0.036.

Results: Exploratory Endpoint

Progression-Free Survival



Results: Safety Events of Interest

- There were significantly lower incidences of adverse events potentially related to renal toxicity with denosumab therapy compared to zoledronic acid, particularly in those patients with baseline CrCl ≤60mL/minute
- The incidence of hypocalcemia, with the majority of events either grade 1 or 2, was greater for denosumab compared to zoledronic acid; there were no grade 5 events

	All Patients			Patients With Baseline CrCl ≤60mL/minute		
	Denosumab N = 850	Zoledronic Acid N = 852		Denosumab N = 233	Zoledronic Acid N = 220	
TEAEs Potentially Associated With Renal Toxicity; n (%)	85 (10.0)	146 (17.1)	P<0.001	30 (12.9)	58 (26.4)	P<0.001
Creatinine >2mg/dL; n/N1 (%)	31/824 (3.8)	54/823 (6.6)	P=0.010	20/216 (9.3)	32/203 (15.8)	P=0.054
Creatinine Doubled From Baseline; n/N2 (%)	28/841 (3.3)	55/840 (6.5)	P=0.002	6/233 (2.6)	16/220 (7.3)	P=0.027
TEAEs Potentially Associated With Hypocalcemia; n (%)	144 (16.9)	106 (12.4)	P=0.009	46 (19.7)	28 (12.7)	P=0.056
Osteonecrosis of the Jaw, Positively Adjudicated; n (%)	35 (4.1)	24 (2.8)	P=0.147	10 (4.3)	4 (1.8)	P=0.175

CrCl Creatinine clearance; N = Number of patients who received ≥1 active dose of investigational product; N1 = Number of patients with baseline serum creatinine ≤2 mg/dL; N2 = Number of patients with non-missing baseline value of serum creatinine; TEAE Treatment-emergent adverse event

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  - DaraKRD
  - EloRVD
- Newly Diagnosed MM Bone Health: Denosumab vs Zolendronic Acid
- Relapsed MM: Pembrolizumab

Pembrolizumab (Pembro) plus lenalidomide (Len) and low-dose dexamethasone (Dex) for relapsed/refractory multiple myeloma (RRMM): Efficacy and biomarker analyses

Ocio EM, et al. ASCO 2017. Abstr 8015

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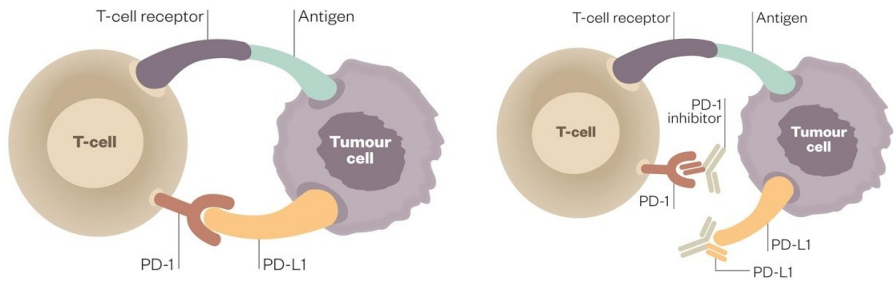
Checkpoint Inhibitors with: Transplant or Pom or Dara or Elotuzumab/Pom/Dex



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Pembro+Rd

Design: Phase 1, open label

Study Population: RRMM, ≥2 prior therapies

Methods: 28-day cycles
- Pembro: 200 mg IV Q2W
- Len: 25 mg PO on d1-21
- Dex: 40 mg PO weekly

- Exploratory biomarker analyses included flow cytometry (FC) at screening or predose cycle 1, d 1 BM aspirate.
- Absolute and/or relative numbers of circulating immune cells (by FC) and gene expression profile (GEP) were evaluated in predose cycle 1, d1 and cycle 2, d1 blood.

- Median age:61 y
- Median (range) prior lines: 4 (1-10);
- 38 (75%) pts were len-refractory
- 27 (53%) pts were double refractory

Efficacy	Pembro+Rd
ORR	50% (20/40) (1 sCR, 14 PR, 5 VGPR)
ORR-Len refractory	38% (11/29)

Safety	Pembro+Rd
Common grade ≥3 TRAEs	
Neutropenia	33%
Thrombocytopenia	18%
Anemia	12%
Deaths due to TRAEs	2 (4%) hepatic failure, ischemic stroke
Immune-related AEs	5 (10%)

- In 16/32 pts with FC-evaluable BM aspirate, all were PD-L1+, while PD-L2 expression was variable.
- At cycle 2, d1, frequency of circulating HLA-DR+, central, and effector memory CD8+ T cells significantly increased and naive CD8+ T cells significantly decreased; all with multiplicity adjusted P values ≤ 0.01.

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  - Denosumab vs Zolendronic Acid
- Relapsed MM: pembrolizumab

ASH 2016 Updates:

- Dara SubQ
- Venetoclax
- Nelfinavir
- Selinexor

Personalized Medicine: Choosing the Right Treatment for Each Patient

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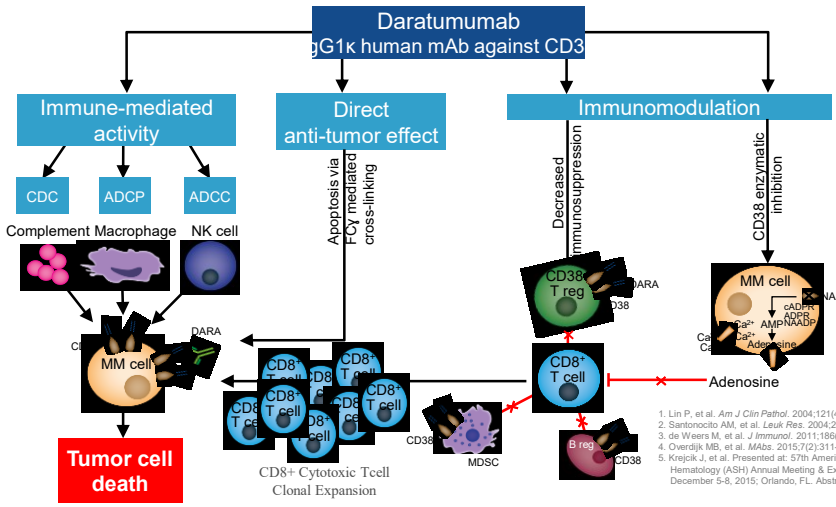
DARA: Mechanisms of Action



CD38 - transmembrane glycoprotein and ectoenzyme with high receptor density on MM cells[1] (80-100%) vs NHL[2,3] (30-80%) vs AML[4] 58% vs B-CLL[5] 20-25%

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Daratumumab Background

- **Daratumumab (DARA)**
  - Human monoclonal antibody targeting CD38
  - Direct on-tumor and immunomodulatory MoA[1-5]
- **Early studies demonstrated efficacy of DARA**
  - Rapid, deep, and durable responses
  - Well tolerated with manageable adverse events
- **Approved**
  - As monotherapy for heavily pretreated RRMM by the FDA, EMA, Health Canada, Mexico, India, and Singapore
  - In combination with standard of care regimens in RRMM after ≥1 prior therapy (POLLUX and CASTOR) by the FDA
    - CHMP positive opinion received in Europe on Feb 2017

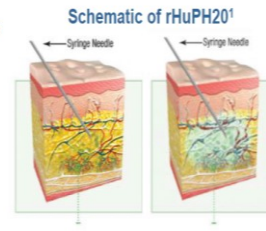
MoA, mechanism of action; RRMM, relapsed or refractory multiple myeloma ; FDA, US Food and Drug Administration; EMA, European Medicines Agency; CHMP, committee for medicinal products for human use; CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody-dependent cellular phagocytosis

1. Lammerts van Bueren J, et al. *Blood*. 2014;124. Abstract 3474.
2. Overdijk MB, et al. *J Immunol*. 2016;197(3):807-813.
3. de Weers M, et al. *J Immunol*. 2011;186(3):1840-1848.
4. Overdijk MB, et al. *MAbs*. 2015;7(2):311-321.
5. Krejcik J, et al. *Blood*. 2016;128(3):384-394.

66

Recombinant Human Hyaluronidase

- ENHANZE™ platform of recombinant human hyaluronidase (rHuPH20) temporarily breaks down the hyaluronan barrier, allowing rapid absorption of injected drugs[1]
- Herceptin SC® and MabThera SC® are approved in Europe as co-formulate products with rHuPH20[2,3]
  - Dosing time is 5 to 8 minutes with SC versus 0.5 to 6 hours with IV[4-6]



Aim: To determine the safety, pharmacokinetics, and efficacy of DARA as SC administration

1. Halozyme Therapeutics. Mechanism of action for Hylenex recombinant (hyaluronidase human injection). www.hylenex.com/mechanism-of-action. Accessed 11/8/2016.
2. European Medicines Agency. Herceptin: EPAR – product information. 2016
3. European Medicines Agency. MabThera: EPAR – product information. 2016.
4. Ismael G, et al. *Lancet Oncology*. 2012;13(9):869-878.
5. Shpilberg O, et al. *Br J Cancer*. 2013;109(6):1556-1561.
6. De Cock E, et al. *Plos One*. 2016;11(6):e0157957.

Usmani S, et al. ASH 2016. Abstract 1149.

PAVO: Subcutaneous Daratumumab

Design: Ph Ib, open label, multicenter, dose-escalation study of SC Dara with rHuPH20 (Dara-PH20)

Study Population: N=41
- ≥2 prior lines of therapy
- Prior therapy included an IMiD and a PI

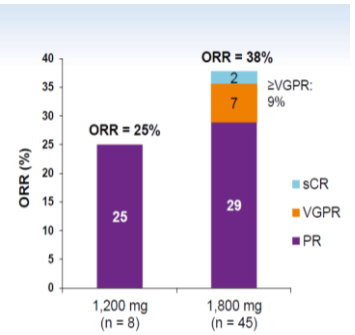
Dose & Schedule:
D (cohort 1): 1200 mg in 60 mL over 20 min (n=8)
D (cohort 2): 1800 mg in 90 mL over 30 min (n=33)

Dara-PH20 was infused via a syringe pump in rotating areas on the abdomen in 4-week treatment cycles: QW for 8 weeks, Q2W for 16 weeks, and Q4W thereafter

Usmani S, et al. ASH 2016. Abstract 1149.

Subcutaneous Daratumumab

	1,200 mg n = 8	1,800 mg n = 45
IRR, % (n)	13 (1)	24 (11)
Chills	13 (1)	9 (4)
Pyrexia	0 (0)	9 (4)
Pruritus	0 (0)	4 (2)
Dyspnea	13 (1)	0 (0)
Flushing	0 (0)	2 (1)
Hypertension	0 (0)	2 (1)
Hypotension	0 (0)	2 (1)
Nausea	0 (0)	2 (1)
Non-cardiac chest pain	13 (1)	0 (0)
Oropharyngeal pain	0 (0)	2 (1)
Paresthesia	0 (0)	2 (1)
Rash	0 (0)	2 (1)
Sinus headache	0 (0)	2 (1)
Tongue edema	0 (0)	2 (1)
Vomiting	0 (0)	2 (1)
Wheezing	0 (0)	2 (1)



- IRRs: all were Grade 1-2 in 1800 mg group, occurred within 1st 4 hours, and all in 1st infusion
- PK profile of 1800 mg SQ comparable to dara 16 mg/kg IV

Usmani S, et al. ASH 2016. Abstract 1149.

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ASH 2016 Multiple Myeloma Abstracts

- Dara SubQ
- Venetoclax Monotherapy and
  Venetoclax + Bortezomib Dexamethasone
- Nelfinavir + Bortezomib Dexamethasone
- Selinexor

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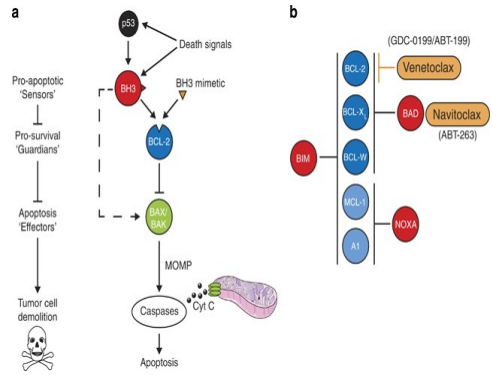
Venetoclax Background

- Bcl-2 is an important anti-apoptotic protein in MM
- Venetoclax is a potent oral Bcl-2 inhibitor approved for use in CLL
- Bcl-2 expression is higher in t(11;14)



Merrino D et al. *Oncogene* (2016) **35,** 1877–1887

Venetoclax Monotherapy for Relapsed/Refractory Multiple Myeloma: Safety and Efficacy Results from a Phase I Study

Design: Phase I, open label, study of venetoclax monotherapy

Study Population: RRMM (N=66)
- Median age: 63 yrs
- ISS stage II/III: 62%
- Median prior therapies: 5 (1-5)
- Prior BTZ: 94% (70% ref)
- Prior REV: 94% (77% ref)

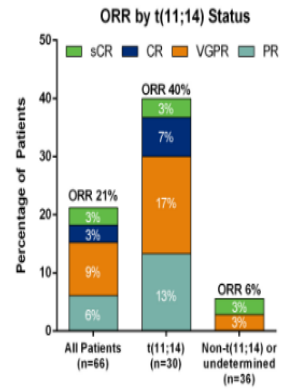
Dosing & Schedule:
VEN: initial 2 week lead in period with weekly dose-escalation
- Final doses: daily at 300 mg, 600 mg, 900 mg, or 1200 mg
- Patients who progressed could receive VEN + dex and remain on study

- **Median time on VEN: 2.5 mo (0.2-23);**
- **26% received VEN + dex for a median of 1.4 mo (0.1-11)**

Kumar S, et al. ASH 2016. Abstract 488.

Venetoclax Monotherapy for Relapsed/Refractory Multiple Myeloma: Safety and Efficacy Results from a Phase I Study

Safety, n (%)	Venetoclax
Gr 3/4 (≥10%)	Thrombocytopenia (26%), neutropenia (20%), lymphopenia (15%), anemia (14%), and decreased white blood cells (12%)
SAEs ≥2 pts	Pneumonia (n=5), sepsis (3), pain, pyrexia, cough, and hypotension (2 each)
Deaths	8 (all considered unrelated to VEN)



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Kumar S, et al. ASH 2016. Abstract 488.

Venetoclax Combined with Bortezomib and Dexamethasone for Patients with Relapsed/Refractory Multiple Myeloma

Design: Phase Ib, open label, dose escalation study of venetoclax + Vd

Study Population: RRMM (N=66)
- Median age: 64 yrs
- ISS stage II/III: 59%
- Median prior therapies: 3 (1-13)
- Prior BTZ: 32% ref
- Prior REV: 56% ref

Dosing & Schedule:
VEN: daily, 50 mg – 1200 mg dose escalation
- RP2D: 800 mg qd

Vd: Dose and schedule not reported

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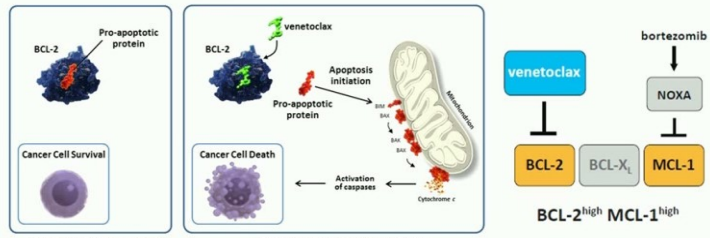
Moreau P, et al. ASH 2016. Abstract 975.

Background

- Venetoclax is a potent, selective, orally available small molecule BCL-2 inhibitor[1]
- Bortezomib can inhibit MCL-1, a potential resistance factor for venetoclax, by stabilizing the MCL-1 neutralizing protein NOXA[2]
- The addition of venetoclax enhances the activity of bortezomib in multiple myeloma (MM) cell lines and xenograft models[2]



1. Roberts AW et al. NEJM 2015; 2. Punnoose E et al. Mol Cancer Ther 2016.

75

Venetoclax Combined with Bortezomib and Dexamethasone for Patients with Relapsed/Refractory Multiple Myeloma

Safety, n (%)	Venetoclax + Bortezomib + Dexamethasone
Gr 3/4 (≥10%)	Thrombocytopenia (29%), anemia (15%) and neutropenia (14%)
SAEs ≥2 pts	Febrile neutropenia, thrombocytopenia, cardiac failure, pyrexia, influenza, lower respiratory tract infection, pneumonia, sepsis, acute kidney injury, respiratory failure, embolism, and hypotension 1 DLT: lower abdominal pain (1200 mg Ven)
Deaths	5 (4=PD, 1=RSV infection)

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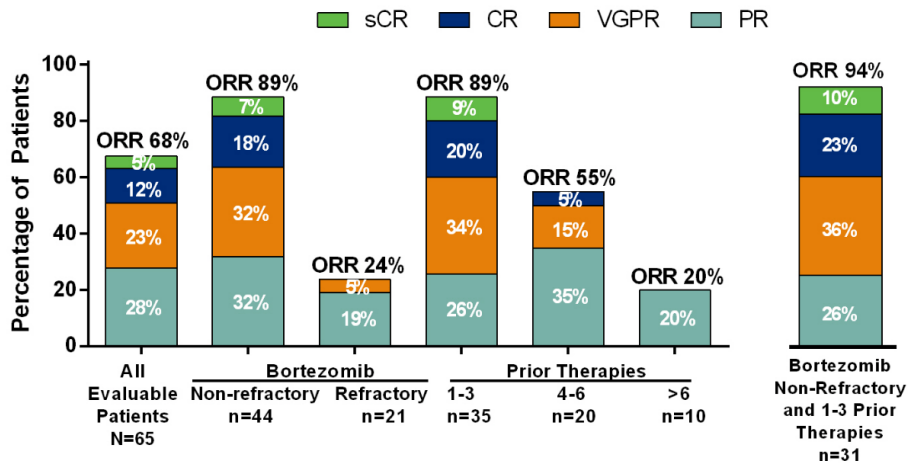
Moreau P, et al. ASH 2016. Abstract 975.

Venetoclax, bortezomib, and dexamethasone

Objective Responses Rates for Patients with R/R MM



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Moreau P, et al. ASH 2016. Abstract 975.

Venetoclax Combined with Bortezomib and Dexamethasone for Patients with Relapsed/Refractory Multiple Myeloma

Efficacy	All	1-3 Priors
DOR	8.8 mo	V non-ref: 10.6 mo V naïve: 15.8 mo
TTP	8.6 mo	V non-ref: 11.3 mo V naïve: 17.1 mo

Efficacy	With t(11;14)	Without t(11;14)
ORR	78%	66%

- **Discontinuations:** 43 (65%), PD (33), AE (5), withdrawn consent (2), not specified (3)

Moreau P, et al. ASH 2016. Abstract 975.

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ASH 2016 Multiple Myeloma Abstracts

- Dara SubQ
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- Nelfinavir + Bortezomib Dexamethasone
- Selinexor

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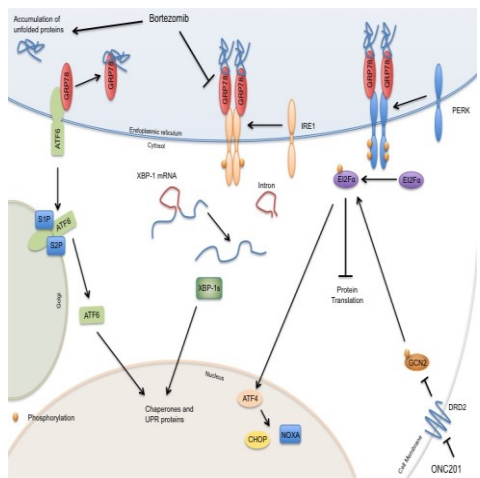
Nelfinavir background



Driessen, C, et al. ASH 2016.

IRE1/XBP1 downregulation provides proteasome inhibitor resistance and upregulation re-sensitizes

Nelfinavir, an HIV protease inhibitor, induces UPR activation and IRE1/XBP1 expression and overcomes proteasome inhibitor resistance in vitro (Kraus et al., Blood Cancer J. 2013 Mar 1;3)

when unfolded proteins bound by complex of HSP70 chaperone GRP78 + transcription factor ATF6, ATF6 is released

- subsequently ATF6 cleaved into active form in the Golgi by S1P and S2P phosphatases
- active ATF6 translocates to the nucleus and activates transcription of chaperones and other proteins to reduce the ER stress
- nelfinavir, activates the UPR and also selectively inhibits S1P and S2P

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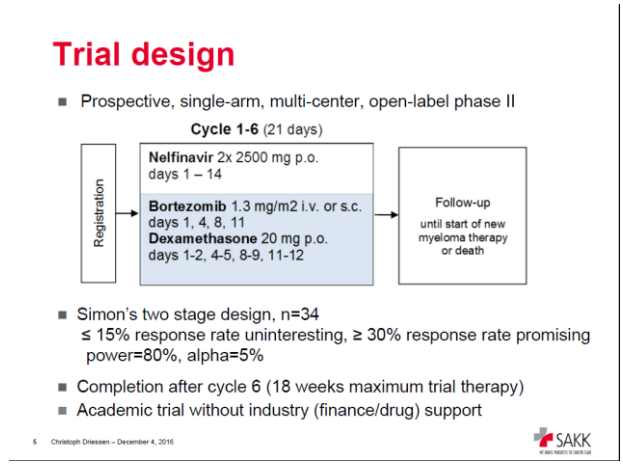
Nelfinavir + Bortezomib Dex



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Driessen, C, et al. ASH 2016.

Nelfinavir, bortezomib, dexamethasone

	Total - 34 patients n (%)	
	Exposed	**Refractory**
Bortezomib (BTZ) Number of lines, median (min-max)	34 (100%) 2 (1-5)	34 (100%)
Lenalidomide (LEN)	34 (100%)	27 (79%)
Pomalidomide (POM)	16 (47%)	15 (44%)
Carfilzomib (CFZ)	2 (6%)	2 (6%)
BTZ + LEN + POM + CFZ	1 (3%)	1 (3%)

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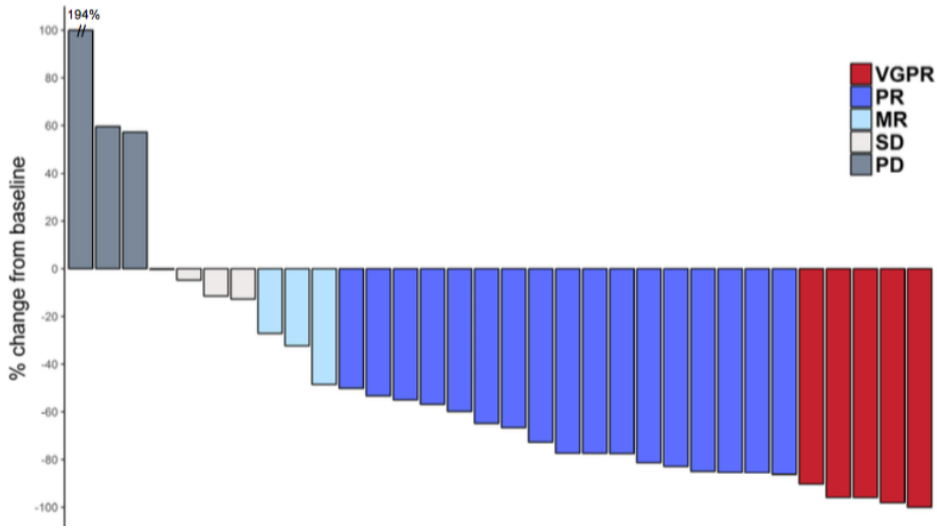
Driessen, C, et al. ASH 2016.

Nelfinavir, bortezomib, dexamethasone



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Driessen, C, et al. ASH 2016.

Efficacy outcomes

	Total - 34 patients Median (min-max) or n (%)
Therapy cycles delivered within the trial	4.5 (1-6)
Best response ≥ PR (90% CI)	**22 (65%)** **(49%-76%)**
Best response categories – VGPR – PR – MR – SD – **CBR (VGPR+PR+MR)**	 5 (15%) 17 (50%) 3 (9%) 4 (12%) 25 (74%)
Poor risk CG patients (n=13) **Best response ≥ PR**	 10 (77%)
Time to new anti-myeloma therapy or death (weeks), median (95% CI)	 16 (13-24)
PD under trial therapy (confirmed / unconfirmed)	13 (38%) / 18 (53%)

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Driessen, C, et al. ASH 2016.

ASH 2016 Multiple Myeloma Abstracts

- Dara SubQ
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- Nelfinavir + Bortezomib Dexamethasone
- Selinexor

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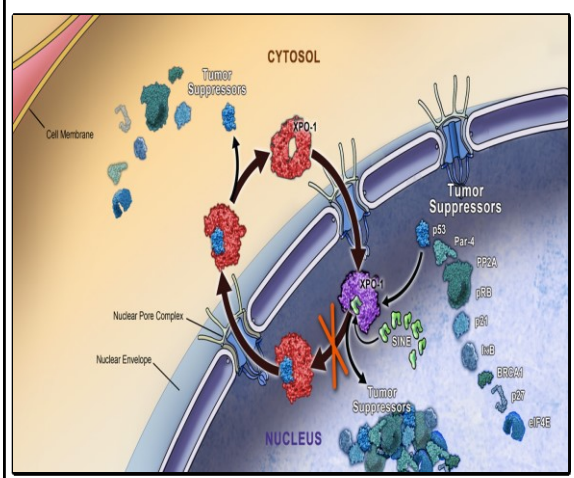
Selinexor Mechanism of Action



- Exportin 1 (XPO1) is the 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
- In a first-in-human Phase I study, selinexor in combination with dexamethasone showed a 27% ORR in heavily pretreated MM patients

86

Vogl DT, et al. ASH 2016. Abstract 491.

Selinexor and Low Dose Dexamethasone (Sd) in Patients with Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib and Anti-CD38 Ab Refractory Multiple Myeloma (MM): STORM Study

Design: Phase II study of Sd

Study Population: RRMM (N=79(
- 48 pts refractory to REV, POM, V, K (Quad)
- 33 pts refractory to above + anti-CD38 mAbs (Penta)

Dosing & Schedule:
S: 80 mg BIW for 6 or 8 doses of a 28 d cycle
D: 20 mg BIW

Median age: 68 yrs

Safety, n (%) Gr 3/4 (≥10%)	All patients
Thrombocytopenia	58
Neutropenia	21
Anemia	25
Fatigue	14
Hyponatremia	20

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Vogl DT, et al. ASH 2016. Abstract 491.

Independent Review Committee (IRC) Assessed Efficacy

Category	N*	ORR (%)	CBR (%)	VGPR (%)	PR (%)
Overall	78	**16 (21%)**	26 (33%)	4 (5%)	12 (15%)
Quad Refractory	48	**10 (21%)**	14 (29%)	2 (4%)	8 (17%)
Penta Refractory	30	**6 (20%)**	12 (40%)	2 (7%)	4 (13%)
6 Doses / Month	51	**10 (20%)**	15 (29%)	3 (6%)	7 (14%)
8 Doses / Month	27	**6 (22%)**	11 (41%)	1 (4%)	5 (19%)

Efficacy	ORR, n (%)
Standard Risk	4 (17)
High Risk	6 (33)
(17p13)	3 (38)
t(14;16)	1 (100)
t(4;14)	2 (50)

Efficacy	All	Responders	Non-responders
mOS	9.3 mo	NR (>11 mo)	5.7 mo
PFS	2.1 mo		
DOR		5 mo	

*1 patient did not have measurable disease at baseline

- **Most quad patients (83%) received 6 doses/cycle; penta patients (65%) received 8 doses/cycle**

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Vogl DT, et al. ASH 2016. Abstract 491.

Available Anti- Myeloma Agents

Steroids	Conventional Chemo	ImIDs	Proteasome Inhibitors	HDAC inhibitors	Immunologic approaches
Prednisone	Melphalan	Thalidomide	Bortezomib	Panobinostat	Daratumumab: anti CD38
Dexamethasone	Cyclophosphamide	Lenalidomide	Carfilzomib (low/high dose)		Elotuzumab : anti CS1/SLAMF7
	Doxil	Pomalidomide	Ixazomib		Anti-BCMA (CAR-T)
	DCEP/D-PACE				
	BCNU				
	Bendamustine				

Overcome resistance: pembrolizumab nelfinavir venetoclax

XPO-1 inhibitor
Selinexor

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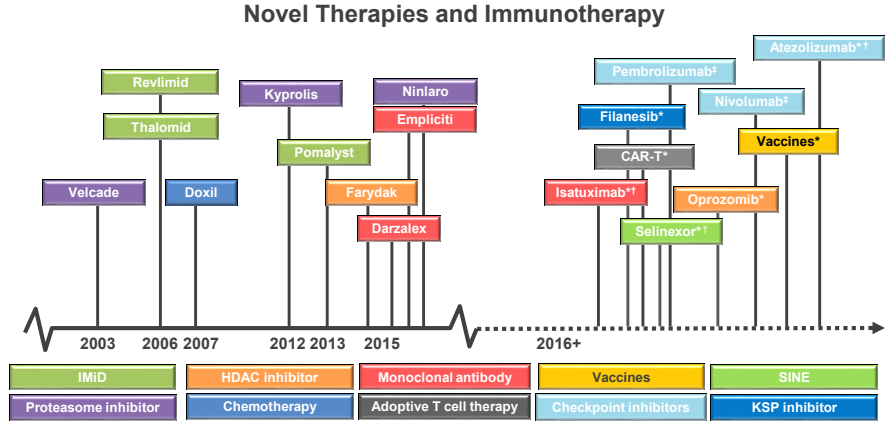
Continuing Evolution of Multiple Myeloma Treatment: New Classes and Targets



PLD, peglylated liposomal doxorubicin; IMiD, immunomodulatory drug; HDAC, histone deacetylase; KSP, kinesin spindle protein, SINE, selective inhibitor of nuclear export
*Not yet FDA-approved; only available in clinical trials
†Treatments studied in MMRC trials
‡FDA-approved for a non-MM indication

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Overview

ASCO 2017 Updates

- Hottest new thing: BCMA CAR-T
- Smoldering MM: Risk Stratification & to Treat or Not to Treat
- Newly Diagnosed MM:
  - Beyond RVD: Quadruplets?
  - Denosumab vs Zolendronic Acid
- Relapsed MM: pembrolizumab

ASH 2016 Updates:

- Dara SubQ
- Venetoclax
- Nelfinavir
- Selinexor

So Many Choices: Choosing the Right Treatment for Each Patient

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Factors in Selecting MM Therapy

PATIENT	DISEASE	TREATMENT
Age/Frailty **Performance Status** **Lifestyle/Pt preferences** **Renal Insufficiency** **Comorbidities** - **Neuropathy** - **Cardiac** - **Diabetes** - **Low blood counts**	**Burden** - **Rate of rise** - **Marrow burden** - **CRAB symptoms** - **Extramedullary** **Biology** - **Molecular** **- del[17p], t(4;14)**	**If Previously Treated** - **Depth/duration** - **Relapse > 60d vs progression** **Toxicity** - **Lower counts** - **Neuropathy** - **Clots** - **Risk of other cancers** **Administration Route** **Single or Combination** **Cost**

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Making Anti- Myeloma Agents Patient Friendly

Steroids	Conventional Chemo	ImIDs	Proteasome Inhibitors	HDAC inhibitors	Monoclonal antibodies
Prednisone	Melphalan Oral or IV In or Outpt SCT	Thalidomide Bedtime	Bortezomib Skin or IV Weekly	Panobinostat Every other week	Daratumumab: anti CD38 Skin formulation
Dexamethasone Oral or IV	Cyclophosphamide Oral or IV	Lenalidomide Welchol or Prednisone	Carfilzomib (low/high dose) Weekly		Elotuzumab : anti CS1/SLAMF7 Monthly
	Doxil	Pomalidomide 2 or 4 mg	Ixazomib		
	DCEP/D-PACE In or Outpt	Take aspirin			
	BCNU		Take shingle prevention medication		
	Bendamustine Day 1,2 or 1,4				

Keep a chemo calendar and write down any symptoms you experience
Ask about co-pay assistance and travel assistance programs!

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Emerging Therapies for Multiple Myeloma
Including Updates from the ASCO® 2017 Annual Meeting

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers
someday is today®

Q&A Session

Ask a question by phone:
- Press star (*) then the number 1 on your keypad.

Ask a question by web:
- Click “Ask a question”
- Type your question
- Click “Submit”

Due to time constraints, we can only take one question per person.

Thursday, June 22, 2017

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Emerging Therapies for Multiple Myeloma
Including Updates from the ASCO® 2017 Annual Meeting

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SUPPORT RESOURCES

- **Online chats:** Online moderated chat forums: **www.LLS.org/chat**
- **What to ask:** Questions to ask your treatment team: **www.LLS.org/whattoask**
- **Myeloma link: www.LLS.org/myelomalink**
- **Free publications: www.LLS.org/booklets**
- **Past education programs: www.LLS.org/programs**
- **Additional information on myeloma: www.LLS.org/myeloma**
- **Information Resource Center:** Speak one-on-one with an Information Specialist who can assist you through cancer treatment, financial, and social challenges.
  - **EMAIL: infocenter@LLS.org**
  - **TOLL-FREE PHONE: (800) 955-4572**