ANTICORPI MONOCLONALI + INIBITORI DEL PROTEASOMA

Giulia Benevolo

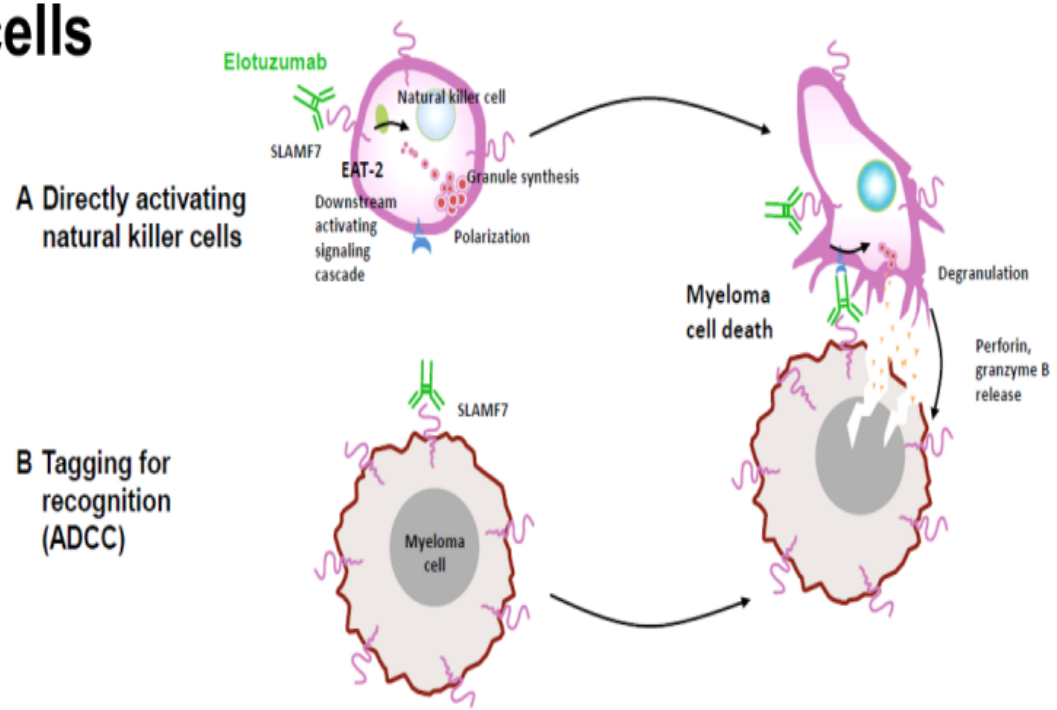
Monoclonal antibodies in MM

Target	mAb			Stage of development
Surface molecules				
SLAMF7 (CS1)	Elotuzumab	FDA & EMA approved	Humanized	Phase 1/2/3
CD38	Daratumumab	FDA & EMA approved	Fully human	Phase 1/2/3/4
	Isatuximab (SAR650984)		Chimeric	Phase 1/2/3
	MOR202		Fully human	Phase 1/2
CD138	Indatuximab ravtansine (BT062)			Phase 1/2
BCMA	J6M0-mcMMAF (GSK2857916)			Phase 1
Signaling molecules				
IL-6	Siltuximab			Phase 2
RANKL	Denosumab			Phase 3
VEGF	Bevacizumab			Phase 2
DKK1	BHQ880			Phase 2
Immune checkpoint inhibitors				
PD-1	Pembrolizumab			Phase 1/2/3
	Nivolumab			Phase 1/2
	Pidilizumab			Phase 1/2
PD-L1	Durvalumab			Phase 1
CTLA4	Ipilimumab			Phase 1/2
KIR	Lirilumab			Phase 1

www.clinicaltrials.gov. Accessed January 2017; Empliciti Prescribing information 2015, http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761035s000lbl.pdf; Empliciti SmPC 2016, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003967/WC500206673.pdf; Darzalex Prescribing information 2016, http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761036s004lbl.pdf; Darzalex SmPC 2016, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004077/WC500207296.pdf; Bianchi G et al. Blood 2015;126:300–310; van de Donk NW et al. Blood 2016;127:681-95.

Elotuzumab

- **A humanized IgG1 monoclonal Ab directed against SLAMF7 (CS1)[1-3]**
- **Proposed MOA:**
  - **Direct activation of NK cells**
  - **NK cell–mediated ADCC**

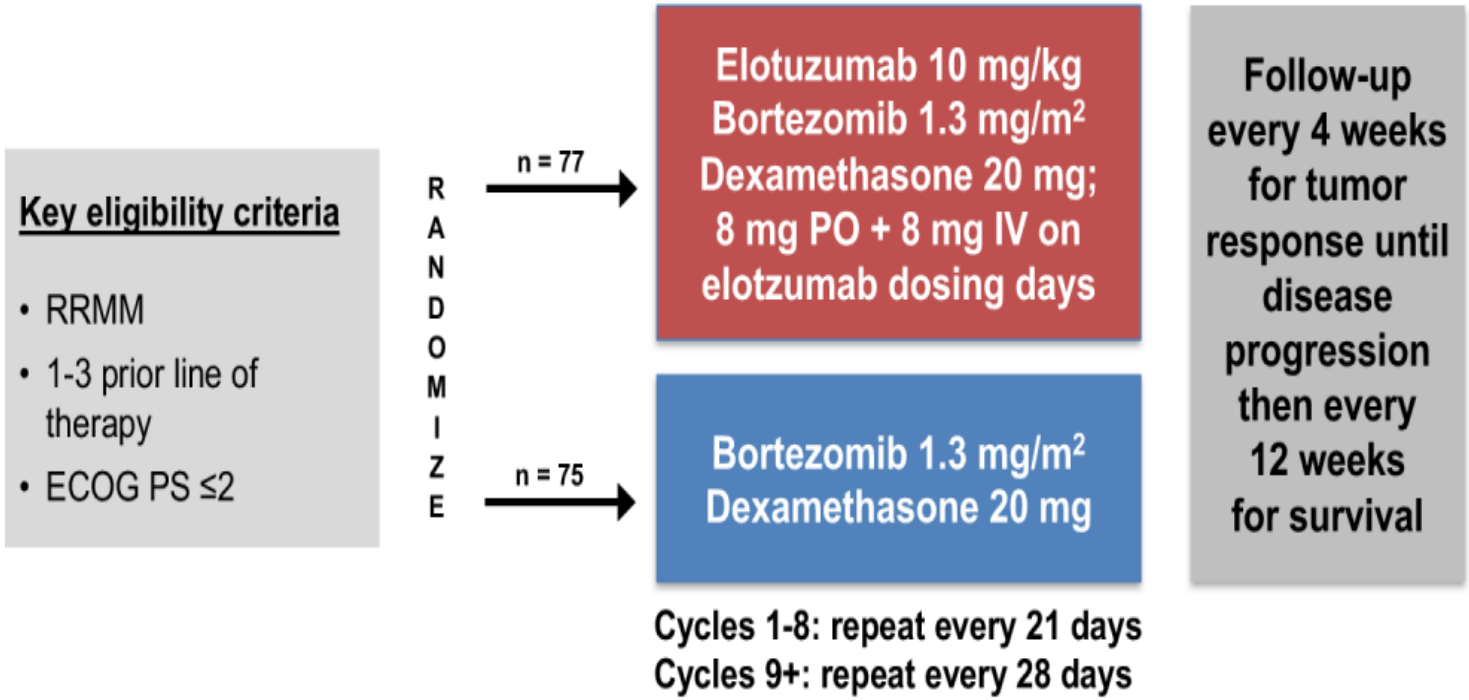


AB, antibody; ADCC, antibody-dependent cellular toxicity; MOA, mechanism of action; NK, natural killer

1. Sondergeld P, et al. *Clin Adv Hematol Oncol*. 2015;13(9):599-609. 2. Cottini F, et al. *Clin Adv Hematol Oncol*. 2015;13(4):236-248. 3. His ED, et al. *Clin Cancer Res*. 2008;14(9):2775-2784.

Elotuzumab + Bortezomib/Dexamethasone

- Multicenter, open-label, randomized phase II study



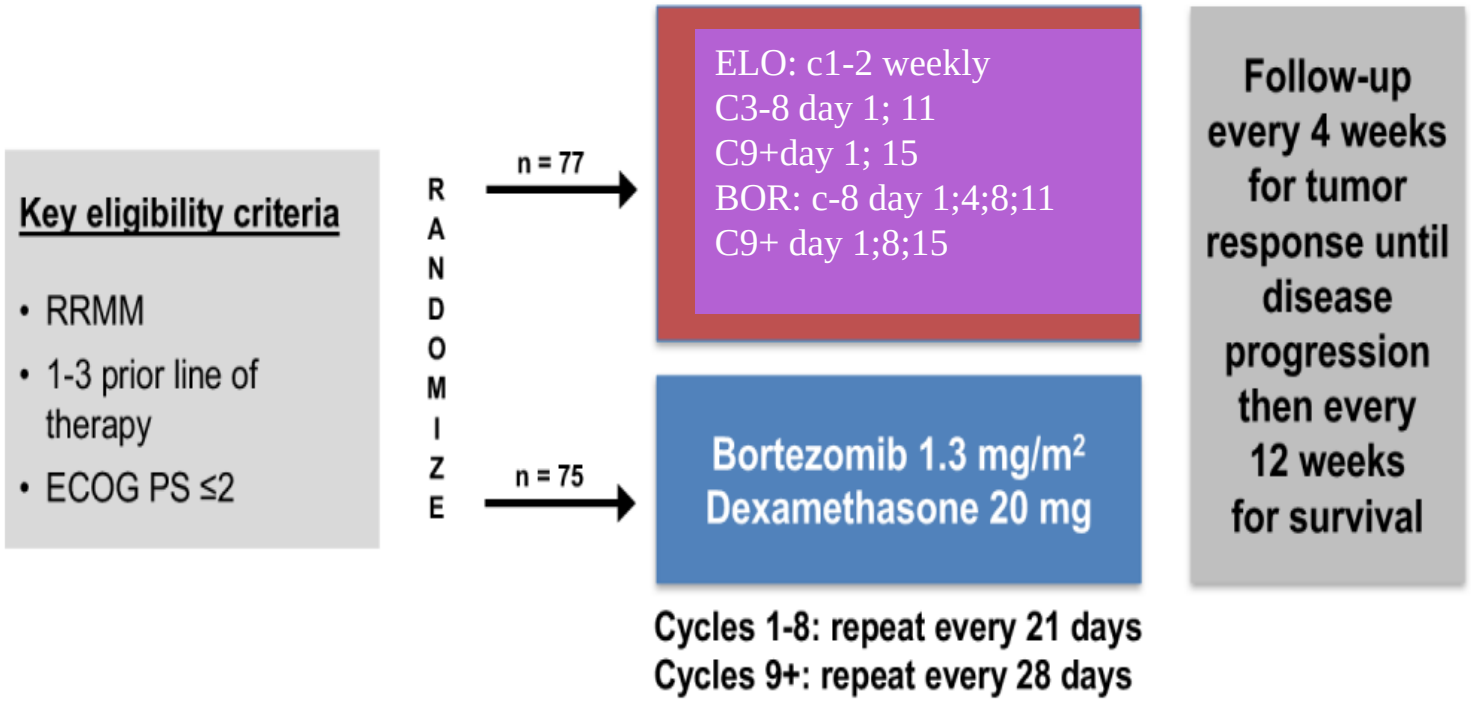
- Primary endpoint: PFS
- Secondary endpoints: ORR, time to response, duration of response, and OS

ECOG PS, Eastern Cooperative Oncology Group performance status

Jakubowiak A, et al. *Blood.* 2016;127(23): 2833-2840.

Elotuzumab + Bortezomib/Dexamethasone

- Multicenter, open-label, randomized phase II study



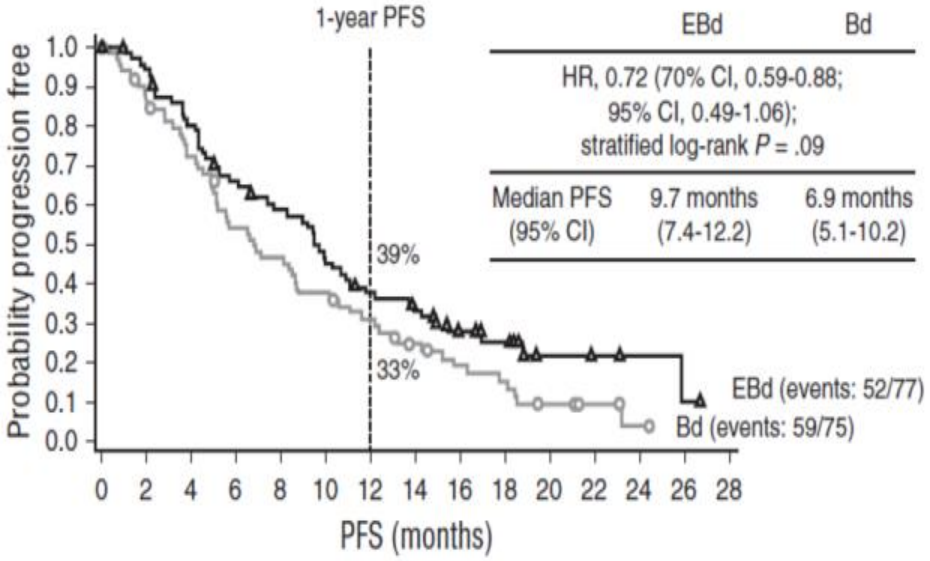
- Primary endpoint: PFS
- Secondary endpoints: ORR, time to response, duration of response, and OS

ECOG PS, Eastern Cooperative Oncology Group performance status

Jakubowiak A, et al. *Blood.* 2016;127(23): 2833-2840.

Elotuzumab + Bortezomib/Dexamethasone: Results

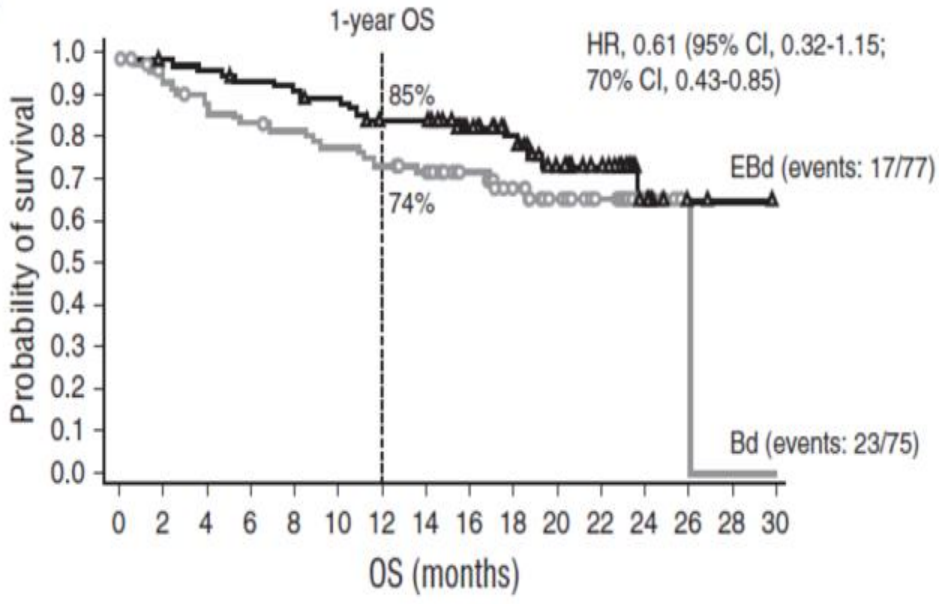
PFS



No. of patients at risk

EBd	77	69	58	47	41	32	26	22	14	11	5	3	2	1	0
Bd	75	61	50	37	32	26	21	15	11	9	5	3	1	0	0

OS



No. of patients at risk

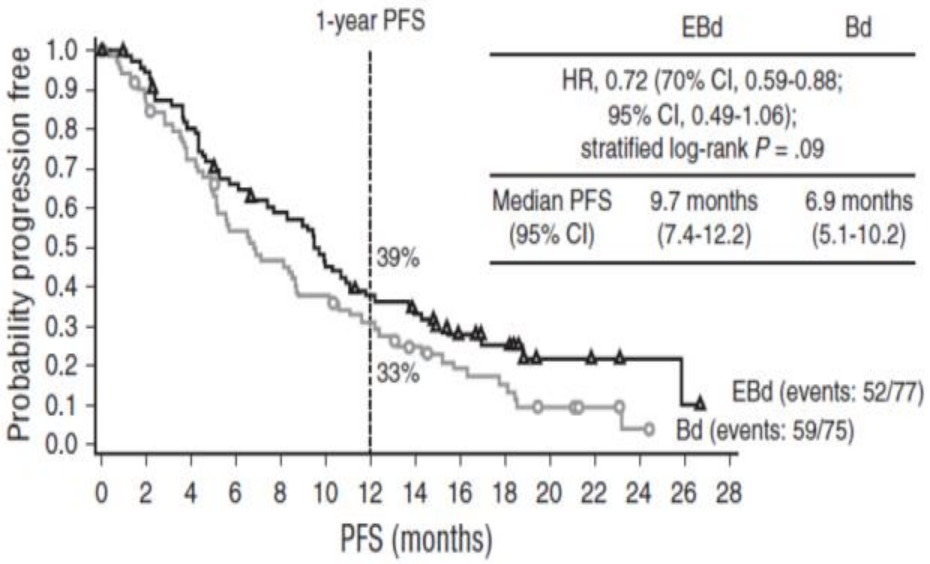
EBd	77	76	74	71	69	67	61	61	50	38	26	20	7	3	1	0
Bd	75	67	62	59	57	54	51	48	38	30	22	15	6	1	0	0

Jakubowiak A, et al. *Blood.* 2016;127(23): 2833-2840.

Elotuzumab + Bortezomib/Dexamethasone: Results

28% reduction in the risk of PD or death in EBd

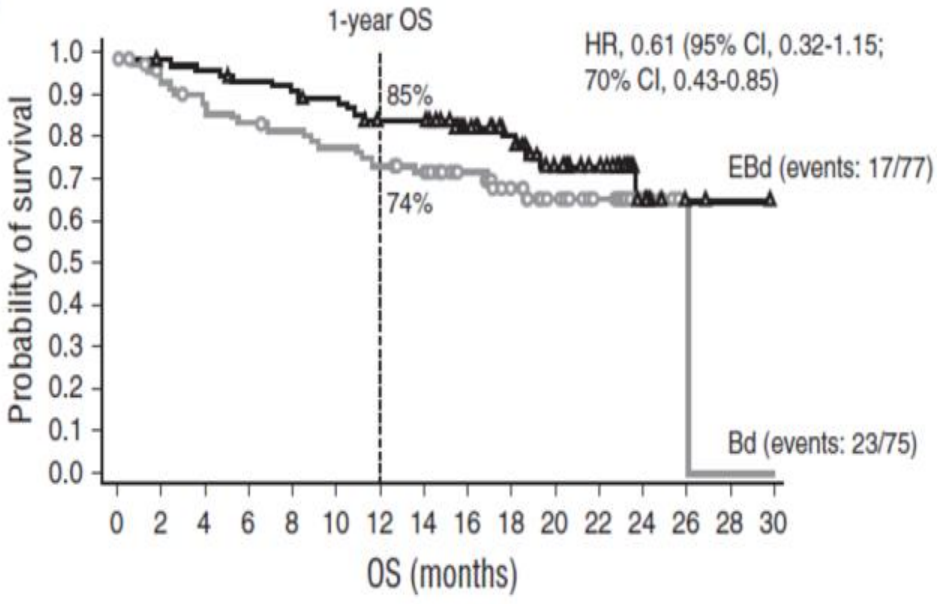
PFS



No. of patients at risk

EBd	77	69	58	47	41	32	26	22	14	11	5	3	2	1	0
Bd	75	61	50	37	32	26	21	15	11	9	5	3	1	0	0

OS



No. of patients at risk

EBd	77	76	74	71	69	67	61	61	50	38	26	20	7	3	1	0
Bd	75	67	62	59	57	54	51	48	38	30	22	15	6	1	0	0

Jakubowiak A, et al. *Blood.* 2016;127(23): 2833-2840.

Elotuzumab + Bortezomib/Dexamethasone: Safety

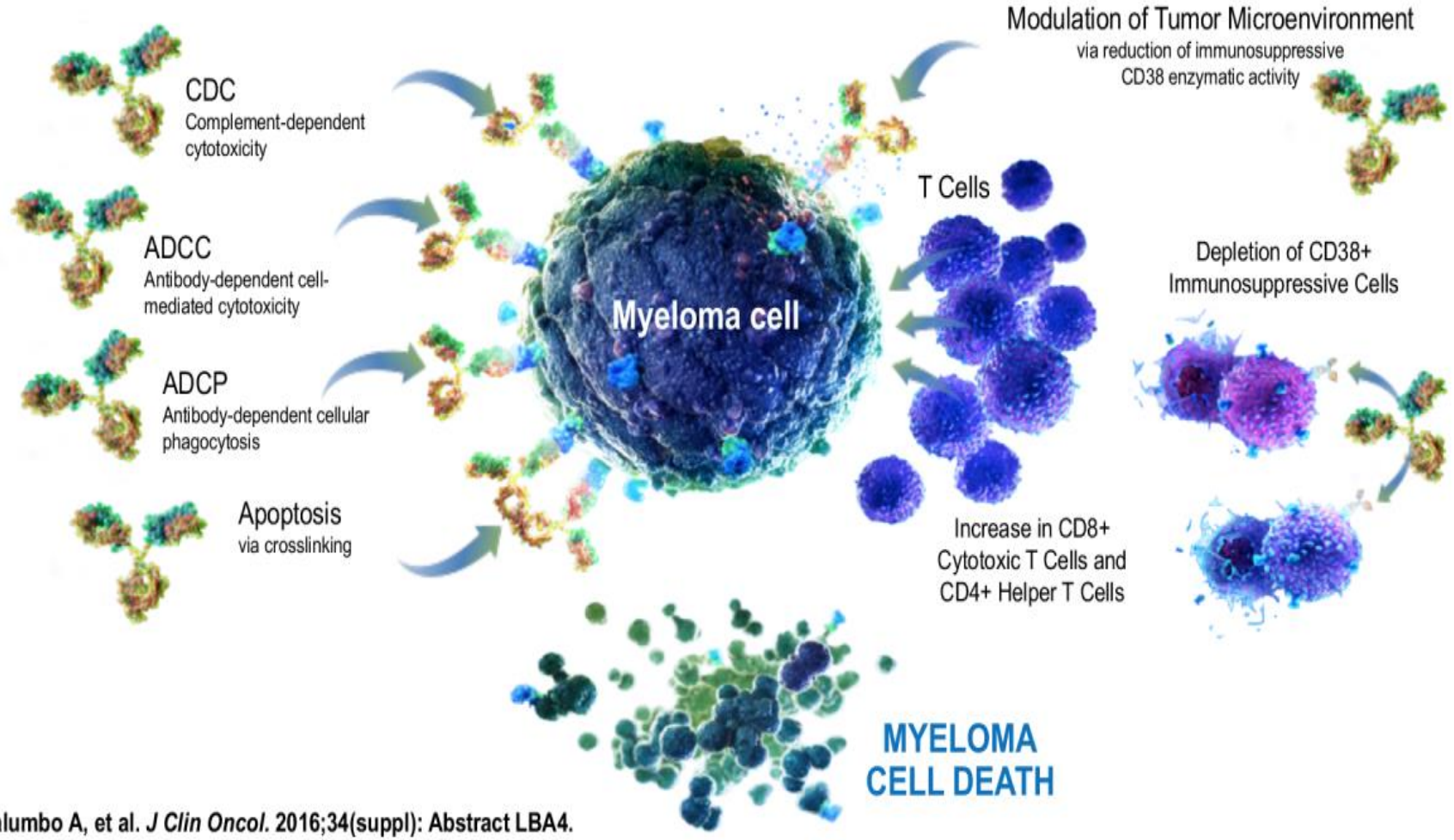
Events	EBd (n = 75)		Bd (n = 75)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All AEs	75 (100)	53 (71)	72 (96)	45 (60)
Infections	50 (67	16 (21)	40 (53)	10 (13)
Diarrhea	33 (44)	6 (8)	25 (33)	3 (4)
Constipation	30 (40)	1 (1)	22 (29)	0
Cough	33 (44)	1 (1)	18 (24)	0
Anemia	28 (37)	5 (7)	22 (29)	5 (7)
Peripheral neuropathy	27 (36)	7 (9)	27 (36)	9 (12)
Pyrexia	28 (37)	0	21 (28)	3 (4)
Peripheral edema	22 (29)	3 (4)	18 (24)	0
Insomnia	22 (29)	1 (1)	14 (19)	1 (1)
Asthenia	21 (28)	3 (4)	22 (29)	2 (3)
Fatigue	22 (29)	3 (4)	19 (25)	1 (1)
Paresthesia	20 (27)	0	14 (19)	4 (5)
Nausea	20 (27)	1 (1)	16 (21)	1 (1)
Thrombocytopenia	12 (16)	7 (9)	20 (27)	13 (17)

Jakubowiak A, et al. *Blood.* 2016;127(23): 2833-2840.

Daratumumab

Binds to CD38

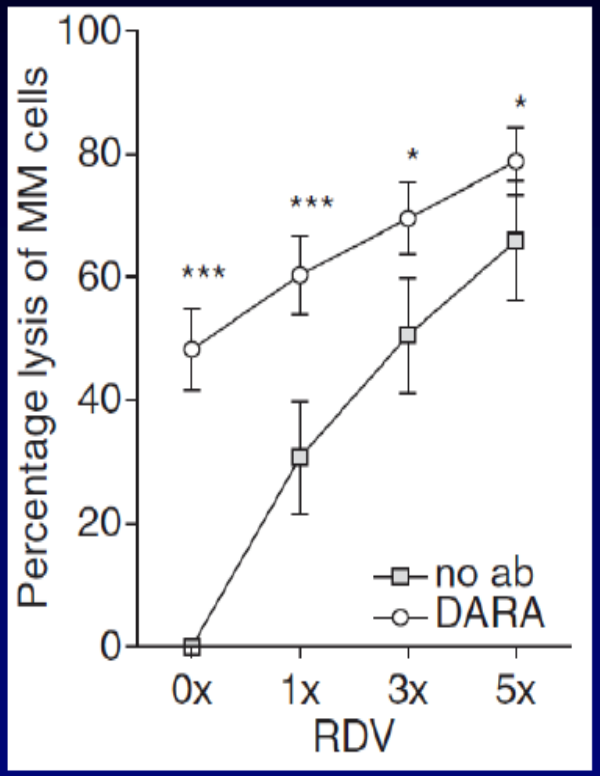
Direct **ON-TUMOR** Actions and **IMMUNOMODULATORY** Actions



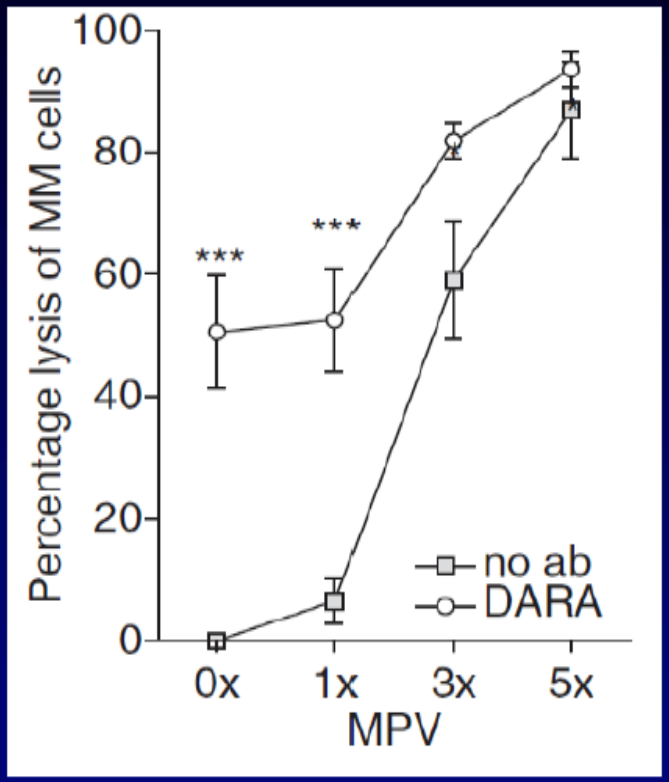
Palumbo A, et al. *J Clin Oncol.* 2016;34(suppl): Abstract LBA4.

What is the rationale for the trials combining Dara plus PI-based combinations?

DARA + RVD



DARA + VMP



- Samples of mononuclear cells from BM of 7 patients
- Addition of DARA to both RVD or MPV increased the treatment efficacy by almost doubling the dose-dependent lysis of MM cells
- Rationale for the clinical trials combining Dara with backbone regimens

*P < 0.05; ***P < 0.001

van der Veer. Blood Cancer J. 2011;1:e41.

Phase 3 Randomized Controlled Study of Daratumumab, Bortezomib and Dexamethasone (DVd) vs Bortezomib and Dexamethasone (Vd) in Patients with Relapsed or Refractory Multiple Myeloma (RRMM): CASTOR*

Palumbo, A. N Engl J Med 2016.375(8):754-766.

*NCT02136134

Study Design

- Multicenter, randomized, open-label, active-controlled, phase 3 study

N = 498

Key eligibility criteria

- RRMM
- ≥1 prior line of therapy
- Prior bortezomib exposure, but not refractory

RANDOMIZE 1:1

DVd (n = 251)
Daratumumab (16 mg/kg IV)
Every week: Cycles 1-3
Every 3 weeks: Cycles 4-8
V: 1.3 mg/m^2 SC on Days 1, 4, 8, and 11 of Cycles 1-8
d: 20 mg PO-IV on Days 1, 2, 4, 5, 8, 9, 11, and 12 of Cycles 1-8

D only
Every 4 weeks: Cycles 9+

Vd (n = 247)
V: 1.3 mg/m^2 SC on Days 1, 4, 8, and 11 of Cycles 1-8
d: 20 mg PO-IV on Days 1, 2, 4, 5, 8, 9, 11, and 12 of Cycles 1-8

Obs only

Primary endpoint
- PFS

Secondary endpoints
- TTP
- OS
- ORR, VGPR, CR
- MRD

Stratification factors
- ISS (I, II, and III)
- Number of prior lines (1 vs 2 or 3 vs >3)
- Prior bortezomib (no vs yes)

- Cycles 1-8: repeat every 21 days
- Cycles 9+: repeat every 28 days

Statistical analyses
- Planned to enroll 480 patients
- Primary analysis: ~177 PFS events

- Premedication for the DVd treatment group consisted of dexamethasone 20 mg, acetaminophen, and an antihistamine

DVd, daratumumab, bortezomib and dexamethasone; IV, intravenous; V, bortezomib; SC, subcutaneously; d, dexamethasone; PO, orally; VD, bortezomib and dexamethasone; D, daratumumab; Obs, observation; PFS, progression-free survival; TTP, time to progression; OS, overall survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response;
MRD, minimal residual disease; ISS, International Staging System.
Mateos M-V, et al. Oral presentation at: 58th American Society of Hematology (ASH) Annual Meeting and Exposition; December 3-6 2016; San Diego, CA, USA.

Baseline Demographic and Clinical Characteristics

Characteristic	DVd (n = 251)	Vd (n = 247)
Age, y		
Median (range)	64 (30-88)	64 (33-85)
≥75, n (%)	23 (9)	35 (14)
ISS staging, n (%)[a]		
I	98 (39)	96 (39)
II	94 (38)	100 (41)
III	59 (24)	51 (21)
Creatinine clearance (mL/min), n (%)		
N	243	233
>30-60	49 (20)	59 (25)
>60	186 (77)	163 (70)
Median time from diagnosis, y (range)	3.87 (0.7-20.7)	3.72 (0.6-18.6)
Cytogenetic profile, n (%)[b]		
N	167	186
Standard risk	123 (74)	135 (73)
High risk	44 (26)	51 (27)

Characteristic	DVd (n = 251)	Vd (n = 247)
Prior lines of therapy, n (%)		
Median	2 (1-9)	2 (1-10)
1	122 (49)	113 (46)
2	70 (28)	74 (30)
3	37 (15)	32 (13)
>3	22 (9)	28 (11)
1-3[c]	229 (91)	219 (89)
Prior ASCT, n (%)	156 (62)	149 (60)
Prior PI, n (%)	169 (67)	172 (70)
Prior IMiD, n (%)	179 (71)	198 (80)
Prior PI + IMiD, n (%)	112 (45)	129 (52)
Refractory to IMiD only, n (%)	74 (30)	90 (36)
Refractory to last line of therapy, n (%)	76 (30)	85 (34)

ASCT, autologous stem cell transplantation; PI, proteasome inhibitor; IMiD, immunomodulatory drug.

[a]ISS staging is derived based on the combination of serum β2-microglobulin and albumin.

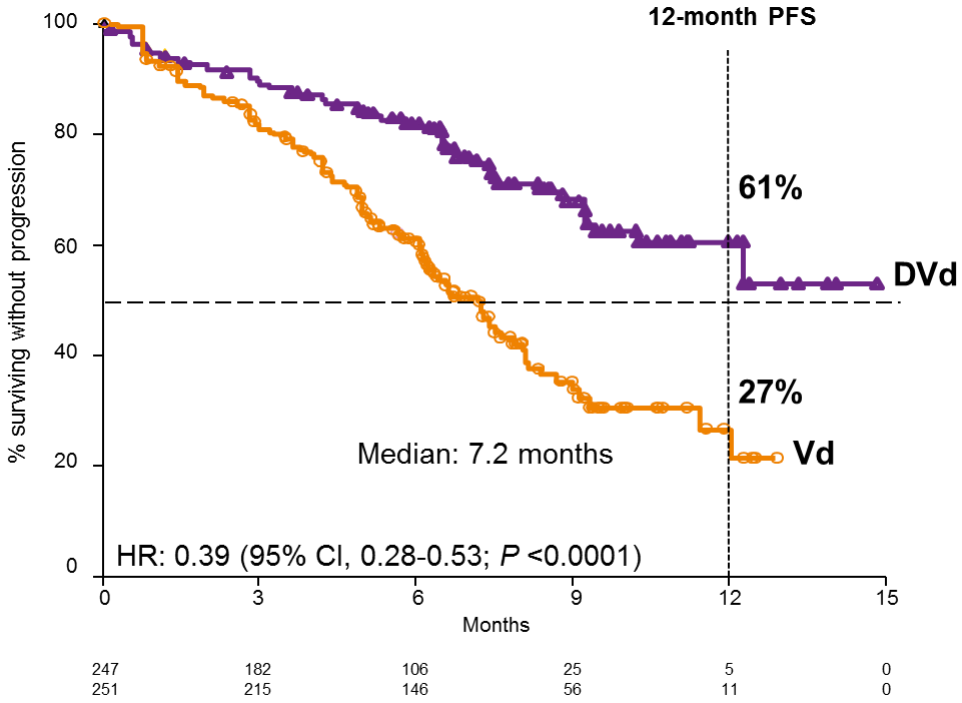
[b]Centralized analysis using next-generation sequencing. Patients with high risk had t(4;14), t(14;16), or del17p abnormalities.

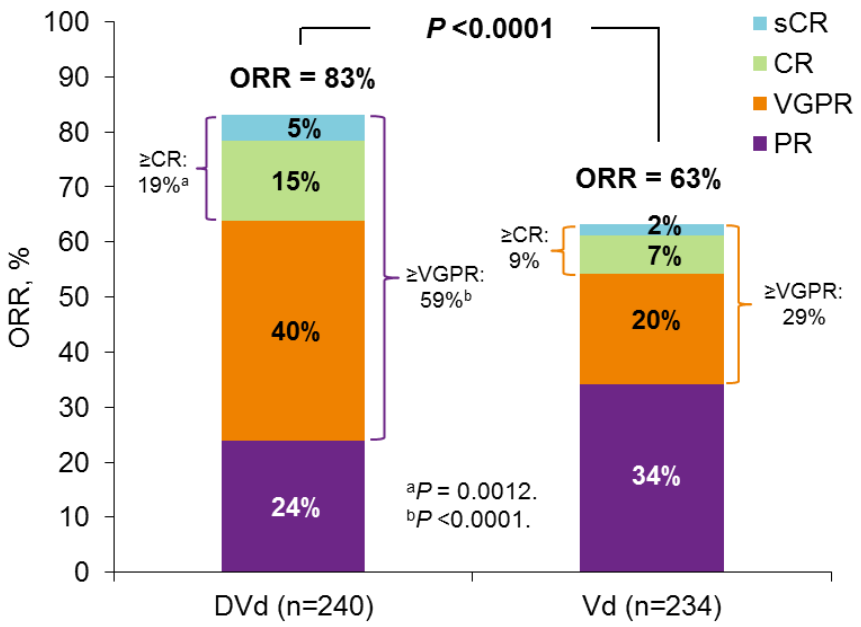
[c]Exploratory.

Mateos M-V, et al. Oral presentation at: 58th American Society of Hematology (ASH) Annual Meeting and Exposition; December 3-6 2016; San Diego, CA, USA.

Primary Analysis Results

- The primary endpoint was met at the primary analysis (7.4 months of median follow-up)
  - **Hazard ratio (HR): 0.39; 61% reduction in the risk of progression or death with DVd versus Vd**
- Significantly higher and deeper responses for DVd versus Vd
- At the primary analysis, the independent data and safety monitoring committee recommended that Vd patients with progressive disease receive daratumumab monotherapy

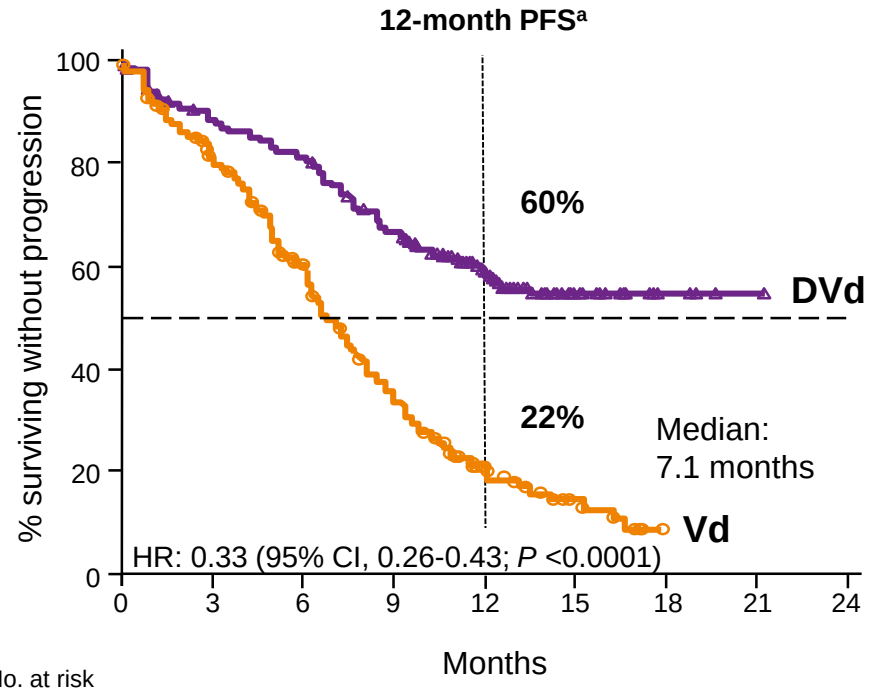


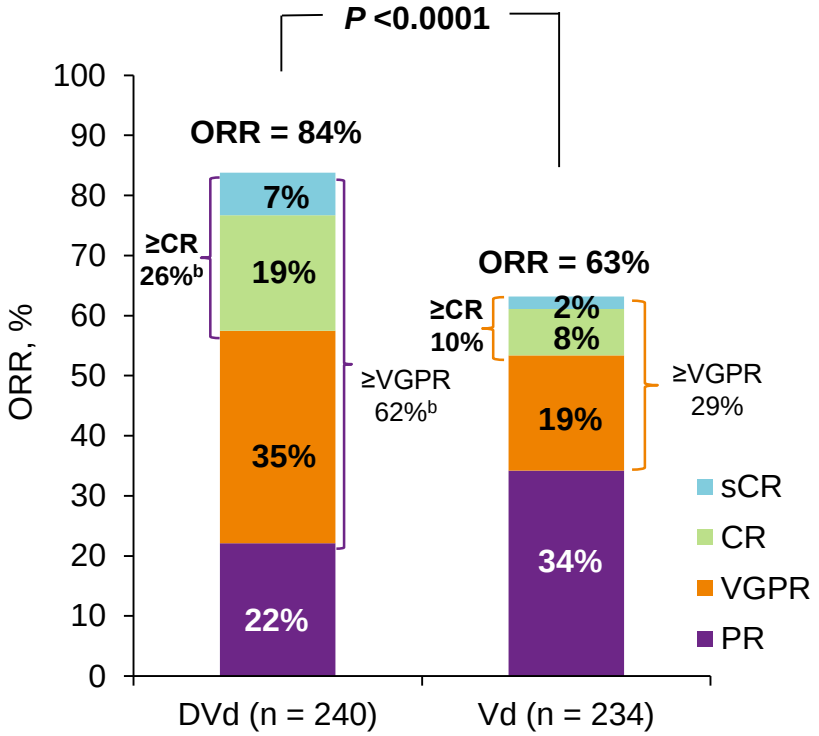


CI, confidence interval; sCR, stringent complete response; PR, partial response.

Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-766.

Updated Efficacy





- Median (range) follow-up: 13.0 (0-21.3) months
- An additional 7% of patients receiving DVd achieved ≥CR with longer follow up

Responses continue to deepen in the DVd group with longer follow-up

ITT, intent to treat.
Note: PFS: ITT population; ORR: response-evaluable population.
[a]Kaplan-Meier estimate.
[b]*P* <0.0001 for DVd versus Vd.
Mateos M-V, et al. Oral presentation at: 58th American Society of Hematology (ASH) Annual Meeting and Exposition; December 3-6 2016; San Diego, CA, USA.

F-238

Daratumumab, Bortezomib, and Dexamethasone (DVd) Versus Bortezomib and Dexamethasone (Vd) in Relapsed or Refractory Multiple Myeloma Based on Prior Lines and Treatment Exposure: CASTOR

Suzanne Lentzsch,[1,*] Ajay Nooka,[2] Hang Quach,[3] Cindy Lee,[4] Wolney Barreto,[5] Paolo Corradini,[6] Chang-Ki Min,[7] Emma Scott,[8] Asher A. Chanan-Khan,[9] Noemi Horvath,[4] Marcelo Capra,[10] Meral Beksac,[11] Roberto Ovilla,[12] Jae-Cheol Jo,[13] Ho-Jin Shin,[14] David Soong,[15] Tineke Casneuf,[16] Christopher Chiu,[15] Xiang Qin,[15] Himal Amin,[17] Pieter Sonneveld,[18] Jordan Schecter,[17] A. Kate Sasser,[15] Ming Qi,[15] Maria-Victoria Mateos[19]

[1]Division of Hematology/Oncology, Columbia University, New York, NY, USA; [2]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [3]St. Vincent's Hospital, University of Melbourne, Melbourne, Australia; [4]Royal Adelaide Hospital, North Terrace, Adelaide, Australia; [5]Hospital Santa Marcelina, São Paulo, Brazil; [6]Fondazione IRCCS Instituto Nazionale dei Tumori, Milan, Italy; [7]Seoul St. Mary's Hospital, Wonju, Korea; [8]Oregon Health & Science University, Portland, OR, USA; [9]Mayo Clinic Florida, Jacksonville, FL, USA; [10]Instituto do Cancer COR Hospital Mae de Deus, Porto Alegre, Brazil; [11]Ankara University, Ankara, Turkey; [12]Hospital Angeles Lomas, Naucalpan de Juárez y alrededores, México; [13]Ulsan University Hospital, Ulsan, South Korea; [14]Pusan National University Hospital, Busan, South Korea; [15]Janssen Research & Development, LLC, Spring House, PA, USA; [16]Janssen Research & Development, Beerse, Belgium; [17]Janssen Research & Development, LLC, Raritan, NJ, USA; [18]Erasmus Medical Center, Rotterdam, The Netherlands; [19]University Hospital of Salamanca/IBSAL, Salamanca, Spain.

*Presenting author.

INTRODUCTION

- Daratumumab is a human monoclonal antibody that targets CD38 and has direct on-tumor mechanisms of action, including complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, induction of apoptosis, and modulation of CD38 enzyme activities; daratumumab is also associated with immunomodulatory activity[1-5]
- In a pooled analysis, daratumumab 16 mg/kg monotherapy demonstrated an overall response rate (ORR) of 31% in heavily pretreated patients with relapsed/refractory multiple myeloma (RRMM) and induced rapid, deep, and durable responses[6]
- Daratumumab was added to standard of care regimens in 2 randomized phase 3 trials in RRMM, with both studies demonstrating significant improvements in progression-free survival (PFS) and ORR with the addition of daratumumab to these regimens[7,8]
- The majority of patients in the CASTOR study (66%) previously received a bortezomib-containing regimen, and 33% of patients were refractory to immunomodulatory drugs[8]
- Based on an updated analysis of CASTOR with longer follow-up data, this post hoc analysis compared the efficacy of DVd versus Vd according to the number of prior lines of therapy received and prior treatment exposure
  - This analysis was conducted to examine how patients' prior treatment history may impact the efficacy of DVd in RRMM and to identify patient subgroups that benefit most from this regimen

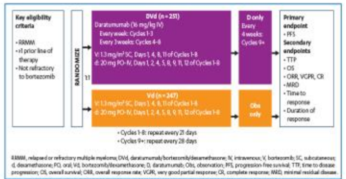
METHODS

Patients

- Patients received ≥1 prior line of therapy and achieved at least a partial response to ≥1 of their prior therapies for multiple myeloma, and had documented progressive disease according to International Myeloma Working Group (IMWG) criteria on or after their last regimen
- All patients were required to have measurable disease in the serum and/or urine or serum free light chain at screening, as defined by IMWG criteria
- Key exclusion criteria were as follows:
  - Patients refractory to or intolerant of bortezomib
  - Patients refractory to another proteasome inhibitor (after amendment 1)

Study Design and Treatment

- This was a multicenter, randomized (1:1), open-label, active-controlled, phase 3 study of patients with RRMM (**Figure 1**)
- Randomization was stratified by International Staging System (ISS; I, II, or III) at screening (based on central laboratory results), number of prior lines of therapy (1 vs 2 or 3 vs >3), and prior bortezomib (no vs yes)
- All patients received up to 8 cycles (21 days/cycle) of Vd
  - Bortezomib was administered subcutaneously at a dose of 1.3 mg/m² on Days 1, 4, 8, and 11 of Cycles 1 to 8
  - Dexamethasone was administered orally or intravenously (IV) at a dose of 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 for a total dose of 160 mg per cycle during Cycles 1 to 8
  - For patients assigned to DVd, daratumumab 16 mg/kg IV was administered weekly (Days 1, 8, and 15) during Cycles 1 to 3, every 3 weeks (Day 1) during Cycles 4 to 8, and every 4 weeks thereafter until withdrawal of consent, disease progression, or unacceptable toxicity
- For patients with suspected complete response (CR) and at 6 and 12 months after the first study dose, minimal residual disease (MRD) was assessed on bone marrow aspirate samples that were ficolled and subjected to next-generation sequencing using the ClonoSEQ™ assay (Adaptive Biotechnologies, Seattle, WA, USA)
  - Patients were considered to be MRD negative if they achieved an MRD-negative test result; patients with only MRD-positive test results or who had no MRD assessment were considered MRD positive
- High cytogenetic risk (determined using next-generation sequencing) was defined as having any t(4;14), t(14;16), or del17p abnormalities


Key eligibility criteria
• RRMM
• ≥1 prior line of therapy
• Not refractory to bortezomib
RANDOMIZE
1:1
DVd (n = 251)
Daratumumab (16 mg/kg IV)
Every week: Cycles 1-3
Every 3 weeks: Cycles 4-8
V: 1.3 mg/m² SC, Days 1, 4, 8, 11 of Cycles 1-8
d: 20 mg PO-IV, Days 1, 2, 4, 5, 8, 9, 11, 12 of Cycles 1-8
D only
Every 4 weeks: Cycles 9+
Vd (n = 247)
V: 1.3 mg/m² SC, Days 1, 4, 8, 11 of Cycles 1-8
d: 20 mg PO-IV, Days 1, 2, 4, 5, 8, 9, 11, 12 of Cycles 1-8
Obs only
Primary endpoint
• PFS
Secondary endpoints
• TTP
• OS
• ORR, VGPR, CR
• MRD
• Time to response
• Duration of response
• Cycles 1-8: repeat every 21 days
• Cycles 9+: repeat every 28 days

RRMM, relapsed or refractory multiple myeloma; DVd, daratumumab/bortezomib/dexamethasone; IV, intravenous; V, bortezomib; SC, subcutaneous; d, dexamethasone; PO, oral; Vd, bortezomib/dexamethasone; D, daratumumab; Obs, observation; PFS, progression-free survival; TTP, time to disease progression; OS, overall survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease.

Figure 1. CASTOR study design.

Statistical Analyses and Assessments

- Efficacy analyses were based on the intent-to-treat (ITT) population
- The response-evaluable analysis set included patients with measurable disease at the baseline or screening visit who received ≥1 study treatment and had ≥1 post-baseline disease assessment
- Exploratory efficacy analyses were conducted according to the number of prior lines of therapy and time since last line of therapy, and within bortezomib-pretreated and lenalidomide-refractory (in their last prior line of therapy) subgroups
- The proportions of MRD-negative patients between treatment arms were compared using the likelihood-ratio test
- MRD-negative rates were based on the ITT population
  - Patients were considered to be MRD negative if they achieved an MRD-negative test result; patients with only MRD-positive test results or who had no MRD assessment were considered MRD positive
- PFS by MRD status was based on the ITT/biomarker risk–evaluable population (patients who had confirmed cytogenetic risk status based on next-generation sequencing data)

RESULTS

Patients and Treatments

- The clinical cut-off date was June 30, 2016
- A total of 498 patients were enrolled (DVd, n = 251; Vd, n = 247)
- Demographic, baseline disease, and clinical characteristics were well balanced (**Table 1**)

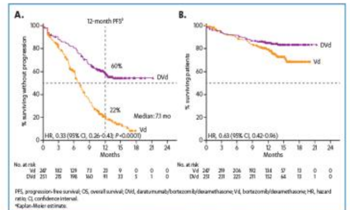
Updated Efficacy in the Overall Study Population

- After a median follow-up of 13.0 months, PFS was significantly prolonged with DVd versus Vd (median not reached [NR] vs 7.1 months; hazard ratio [HR], 0.33; 95% confidence interval [CI], 0.26-0.43; $P<0.0001$; **Figure 2A**)
- 37 (15%) deaths were observed with DVd versus 58 (24%) with Vd (**Figure 2B**); follow-up is ongoing
- ORR was significantly higher with DVd versus Vd (84% vs 63%; $P<0.0001$), with significantly higher rates of very good partial response (VGPR) or better (62% vs 29%; $P<0.0001$) and of CR or better (26% vs 10%; $P<0.0001$)
- Rates of MRD negativity (10^{-5} sensitivity threshold) for DVd and Vd were 10.4% versus 2.4% ($P = 0.000183$)

Table 1. Patient Demographic, Baseline Disease, and Clinical Characteristics (ITT)

Characteristic	DVd (n = 251)	Vd (n = 247)
Age, y		
Median (range)	64 (30-88)	64 (33-85)
≥75 y, n (%)	23 (9)	35 (14)
ISS staging, n (%)[a]		
I	98 (39)	96 (39)
II	94 (38)	100 (41)
III	59 (24)	51 (21)
Cytogenetic profile, n (%)[b]		
N	167	186
Standard risk	123 (74)	135 (73)
High risk	44 (26)	51 (27)
Time from diagnosis, y		
Median (range)	3.87 (0.7-20.7)	3.72 (0.6-18.6)
Prior lines of therapy, n (%)		
Median (range)	2 (1-9)	2 (1-10)
1	122 (49)	113 (46)
2	70 (28)	74 (30)
3	37 (15)	32 (13)
>3	22 (9)	28 (11)
Prior ASCT, n (%)	156 (62)	149 (60)
Prior PI, n (%)	169 (67)	172 (70)
Previous bortezomib-containing regimen, n (%)	162 (65)	164 (66)
Prior IMiD, n (%)	179 (71)	198 (80)
Prior PI + IMiD, n (%)	112 (45)	129 (52)
Refractory to IMiD, n (%)	74 (30)	90 (36)
Refractory to last line of therapy, n (%)	76 (30)	85 (34)
Refractory to lenalidomide at last prior line of therapy, n (%)	45 (18)	60 (24)

ITT, intent-to-treat; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; ISS, International Staging System; ASCT, autologous stem cell transplantation; PI, proteasome inhibitor; IMiD, immunomodulatory drug.
[a]ISS staging was derived based on the combination of serum β2-microglobulin and albumin.
[b]Determined using centralized next-generation sequencing. High-risk cytogenetics were defined as having ≥1 of the following abnormalities: t(4;14), t(14;16), or del17p.

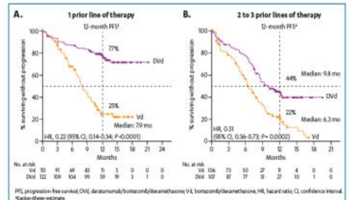


PFS, progression-free survival; OS, overall survival; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; HR, hazard ratio; CI, confidence interval.
[a]Kaplan-Meier estimate.

Figure 2. Updated (A) PFS and (B) OS in the overall population.

Efficacy by Prior Lines of Therapy

- In the 1 prior line of therapy subgroup of 235 patients, median PFS was NR for DVd versus 7.9 months for Vd (HR, 0.22; 95% CI, 0.14-0.34; $P<0.0001$; **Figure 3A**)
- In the 2 to 3 prior lines of therapy subgroup of 213 patients, median PFS was 9.8 months for DVd versus 6.3 months for Vd (HR, 0.51; 95% CI, 0.36-0.73; $P = 0.0002$; **Figure 3B**)



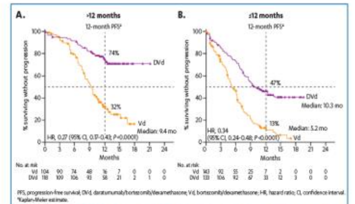
PFS, progression-free survival; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; HR, hazard ratio; CI, confidence interval.
[a]Kaplan-Meier estimate.

Figure 3. Overall PFS in patients with (A) 1 prior line of therapy and (B) 2 to 3 prior lines of therapy.

- In the 1 prior line of therapy subgroup, ORR (91% vs 74%; $P = 0.0014$) and rates of VGPR or better (75% vs 42%; $P<0.0001$) and CR or better (36% vs 15%; $P = 0.0006$) were significantly higher for DVd versus Vd in the response-evaluable population
- In the 2 to 3 prior lines of therapy subgroup, ORR (79% vs 58%; $P = 0.0022$) and rates of VGPR or better (52% vs 21%; $P<0.0001$) and CR or better (19% vs 7%; $P = 0.0133$) were significantly higher for DVd versus Vd in the response-evaluable population
- Rates of MRD negativity (10^{-5} sensitivity threshold) for DVd and Vd were 12.3% versus 2.7% in the 1 prior line of therapy subgroup ($P = 0.0037$) and 10.3% versus 2.8% in the 2 to 3 prior lines of therapy subgroup ($P = 0.0239$)

Efficacy by Time Since Last Prior Therapy

- In the >12 months since last prior therapy subgroup of 222 patients, median PFS was NR for DVd versus 9.4 months for Vd (HR, 0.27; 95% CI, 0.17-0.43; $P<0.0001$; **Figure 4A**)
- In the ≤12 months since last prior therapy subgroup of 276 patients, median PFS was 10.3 months for DVd versus 5.2 months for Vd (HR, 0.34; 95% CI, 0.24-0.48; $P<0.0001$; **Figure 4B**)
- ORR was numerically higher for DVd versus Vd in the >12 months subgroup (91% vs 83%; $P = 0.0632$) and significantly higher for DVd versus Vd in the ≤12 months subgroup (77% vs 49%; $P<0.0001$)

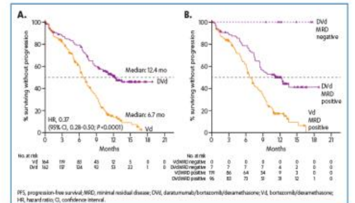


PFS, progression-free survival; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; HR, hazard ratio; CI, confidence interval.
[a]Kaplan-Meier estimate.

Figure 4. Overall PFS in patients with (A) >12 months since last prior therapy and (B) ≤12 months since last prior therapy.

Efficacy in Patients With Prior Bortezomib Exposure

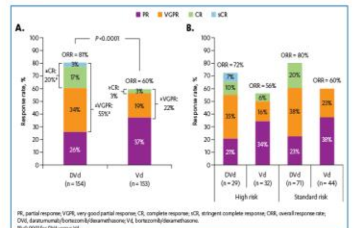
- In patients who previously received bortezomib, median PFS was 12.4 months for DVd versus 6.7 months for Vd (HR, 0.37; 95% CI, 0.28-0.50; $P<0.0001$; **Figure 5A**)
  - In patients who received 1 prior line of therapy that included bortezomib, median PFS was NR for DVd versus 8.0 months for Vd (HR, 0.23; 95% CI, 0.13-0.41; $P<0.0001$)
- Rates of MRD negativity (10^{-5} sensitivity threshold) for DVd and Vd in bortezomib-pretreated patients were 5.6% and 0.6%, respectively ($P = 0.0056$)
  - Patients who achieved MRD negativity demonstrated prolonged PFS (**Figure 5B**)



PFS, progression-free survival; MRD, minimal residual disease; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; HR, hazard ratio; CI, confidence interval.

Figure 5. (A) Overall PFS and (B) PFS by MRD status (10^{-5}) in patients previously exposed to bortezomib.

- The ORR was 81% for DVd versus 60% for Vd in the response-evaluable analysis set ($P<0.0001$; **Figure 6A**)
- High response rates were observed in high-risk and standard-risk patients treated with DVd (**Figure 6B**)

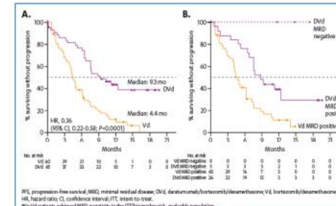


PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response; ORR, overall response rate; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone.
[a]$P<0.0001$ for DVd versus Vd.

Figure 6. Summary of (A) overall best confirmed response and (B) responses by cytogenetic status in patients previously exposed to bortezomib in CASTOR (response-evaluable analysis set).

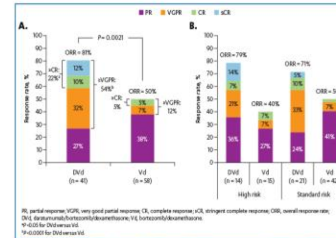
Efficacy in Patients Who Were Refractory to Lenalidomide at Last Prior Line of Therapy

- In patients who were refractory to lenalidomide at last prior line of therapy, median PFS was 9.3 months for DVd versus 4.4 months for Vd (HR, 0.36; 95% CI, 0.22-0.58; $P<0.0001$; **Figure 7A**)
- Rates of MRD negativity (10^{-5} sensitivity threshold) for DVd and Vd in patients who were refractory to lenalidomide at last prior line of therapy were 8.9% and 0%, respectively ($P = 0.0082$)
  - Patients who achieved MRD negativity demonstrated prolonged PFS (**Figure 7B**)
- The ORR was 81% for DVd versus 50% for Vd in the response-evaluable analysis set ($P = 0.0021$; **Figure 8A**)
- High response rates were observed in high-risk and standard-risk patients who were treated with DVd (**Figure 8B**)



PFS, progression-free survival; MRD, minimal residual disease; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; HR, hazard ratio; CI, confidence interval; ITT, intent-to-treat.
[a]No Vd patients achieved MRD negativity in the ITT/biomarker risk–evaluable population.

Figure 7. (A) Overall PFS and (B) PFS by MRD status (10^{-5})[a] in patients who were refractory to lenalidomide at last prior line of therapy.



PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response; ORR, overall response rate; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone.
[a]$P<0.05$ for DVd versus Vd.
[b]$P<0.0001$ for DVd versus Vd.

Figure 8. Summary of (A) overall best confirmed response and (B) responses by cytogenetic status in patients who were refractory to lenalidomide at last prior line of therapy in CASTOR (response-evaluable analysis set).

CONCLUSIONS

- **DVd is superior to Vd regardless of prior lines of therapy, time since last therapy, prior exposure to bortezomib, or refractoriness to lenalidomide**
- **The largest magnitude of benefit with DVd is observed in patients with 1 prior line of therapy**
  - **There was a 78% reduction in the risk of disease progression or death for DVd versus Vd**
- **DVd significantly improves outcomes for patients with RRMM, regardless of prior treatment with bortezomib**
- **Importantly, the treatment benefit of DVd versus Vd was maintained in patients who were refractory to lenalidomide at their last prior line of therapy**
  - **These results suggest that DVd treatment can be sequenced after patients become refractory to lenalidomide**
- **Patients who achieved MRD negativity demonstrated prolonged PFS regardless of prior exposure to bortezomib or lenalidomide**
- **High response rates were observed in high-risk and standard-risk patients treated with DVd across all subgroups examined**
- **These data support the use of DVd as a new standard of care regimen in RRMM regardless of prior treatment history, with the greatest benefit observed in patients with only 1 prior line of therapy**

REFERENCES

1. Lammerts van Bueren J, et al. Presented at: 56th ASH Annual Meeting & Exposition; December 6-9, 2014; San Francisco, CA, USA. Abstract 3474.
2. de Weers M, et al. J Immunol. 2011;186(3):1840-1848.
3. Overdijk MB, et al. MAbs. 2015;7(2):311-321.
4. Overdijk MB, et al. J Immunol. 2016;197(3):807-813.
5. Krejcik J, et al. Blood. 2016;128(3):384-394.
6. Usmani SZ, et al. Blood. 2016;128(1):37-44.
7. Dimopoulos MA, et al. N Engl J Med. 2016;375(14):1319-1331.
8. Palumbo A, et al. N Engl J Med. 2016;375(8):754-766.

ACKNOWLEDGEMENTS

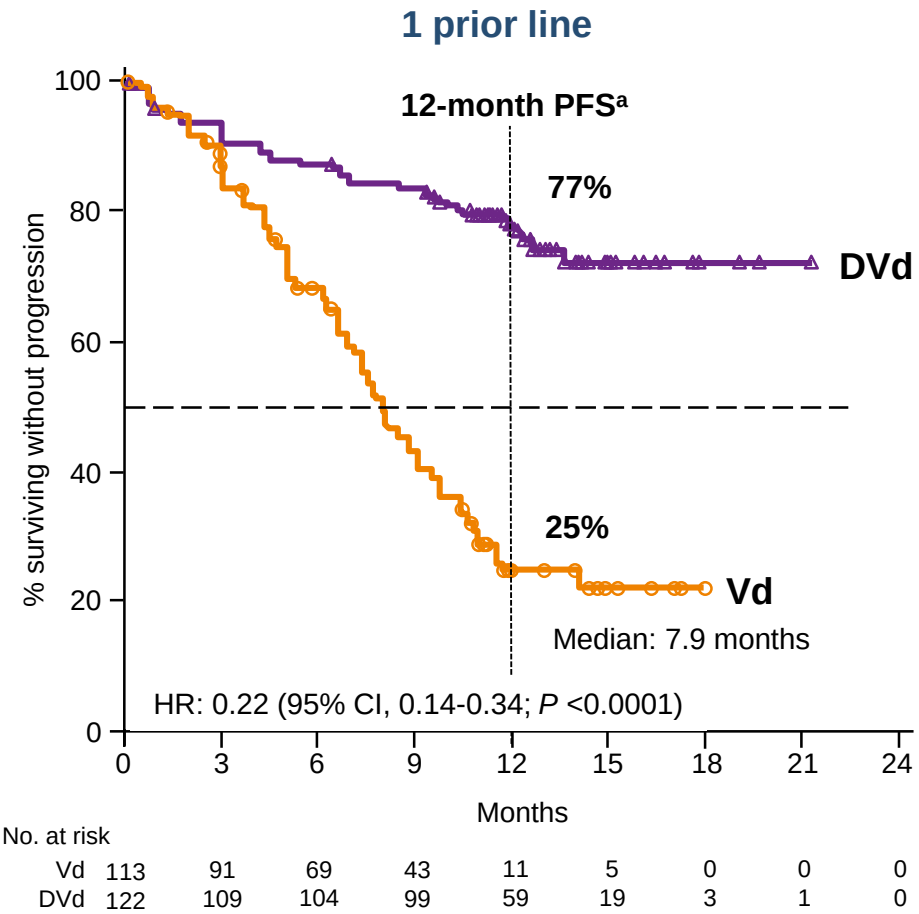
The authors thank the patients who participated in this study, the staff members at the study sites, the data and safety monitoring committee, and staff members who were involved in data collection and analyses.
This study (ClinicalTrials.gov Identifier: NCT02136134) is sponsored by Janssen Research & Development, LLC. Editorial and medical writing support was provided by Jason Jung, PhD, of MedErgy, and were funded by Janssen Global Services, LLC.

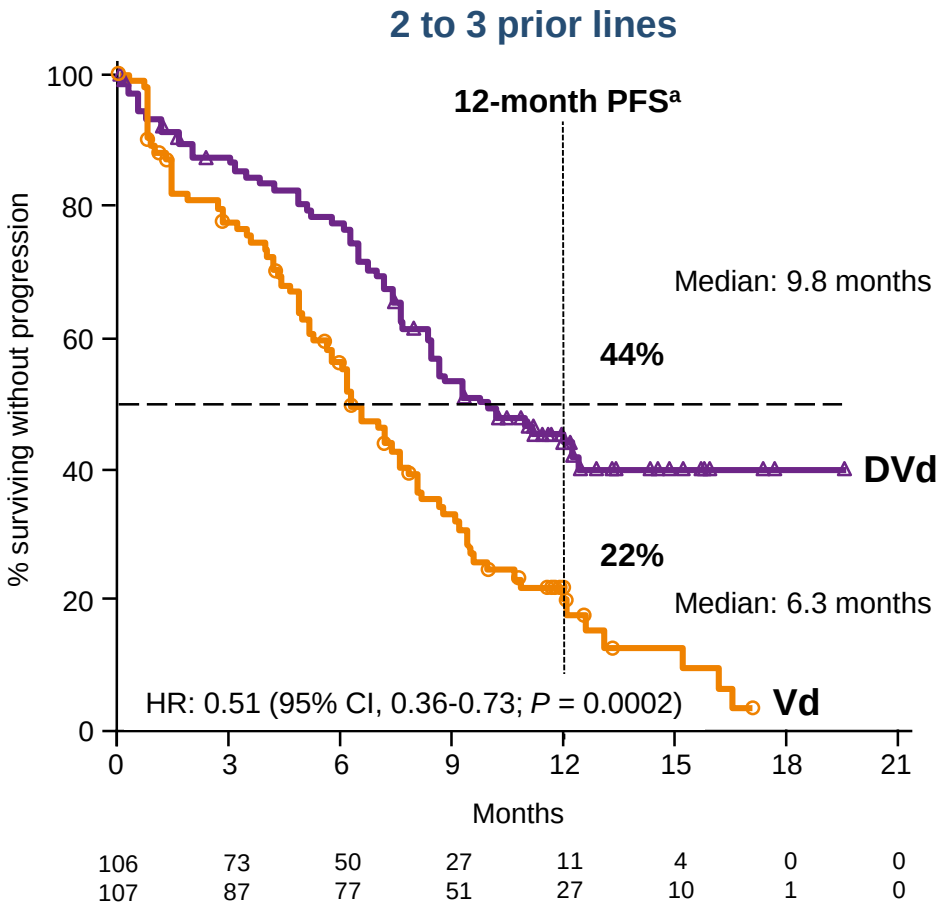
DISCLOSURES

[illegible]

An electronic version of the poster can be viewed by scanning the QR code. The QR code is intended to provide scientific information for individual reference. The PDF should not be altered or reproduced in any way.
http://jjd_imw.scientificpresentations.org/Lentzsch_JJD41608.pdf

PFS: Prior Lines of Treatment





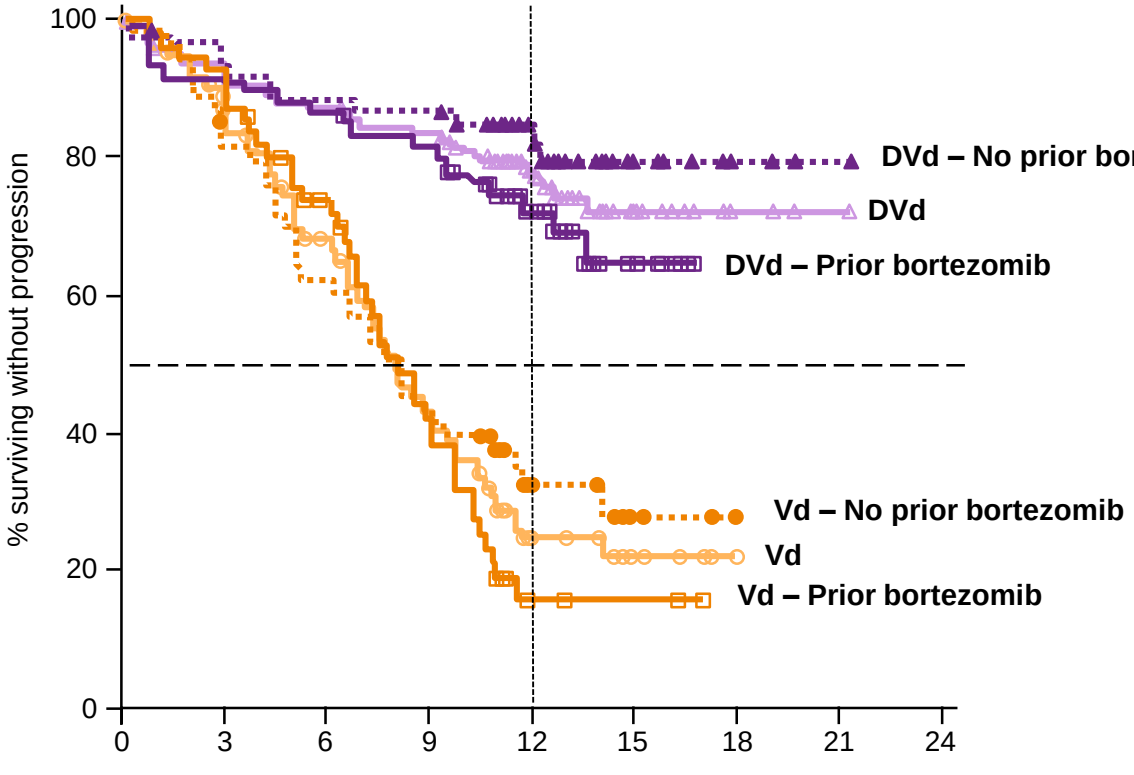
DVd is superior to Vd regardless of prior lines of therapy, with greatest benefit observed in 1 prior line

[a]Kaplan-Meier estimate

Mateos M-V, et al. Oral presentation at: 58th American Society of Hematology (ASH) Annual Meeting and Exposition; December 3-6 2016; San Diego, CA, USA.

.

PFS by Prior Bortezomib Exposure: 1 Prior Line Population

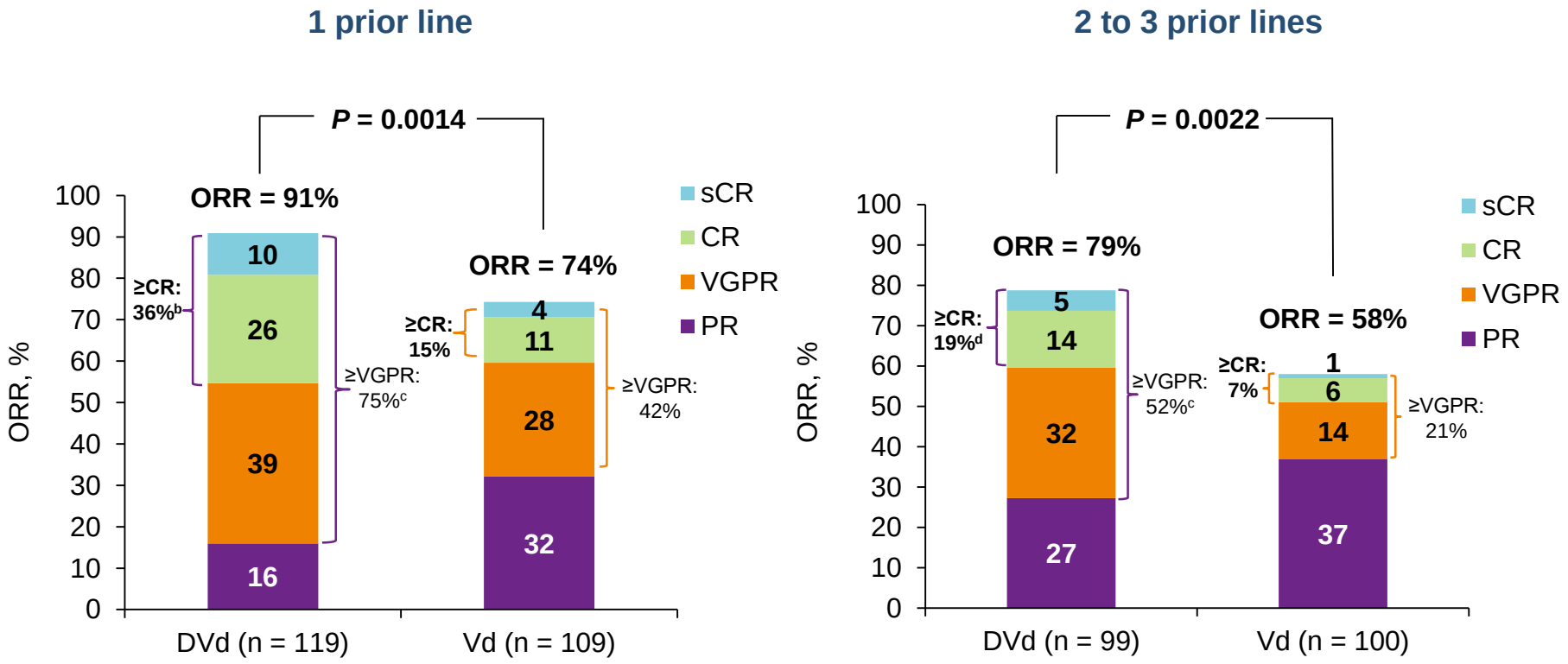


No. at risk									
Vd	113	91	69	43	11	5	0	0	0
DVd	122	109	104	99	59	19	3	1	0
Vd – No prior bortezomib	56	43	33	23	8	3	0	0	0
DVd - No prior bortezomib	60	54	52	51	30	10	3	1	0
Vd – Prior bortezomib	57	48	36	20	3	2	0	0	0
DVd - Prior bortezomib	62	55	52	48	29	9	0	0	0

DVd provides treatment benefit regardless of prior bortezomib exposure

Mateos M-V, et al. Oral presentation at: 58th American Society of Hematology (ASH) Annual Meeting and Exposition; December 3-6 2016; San Diego, CA, USA.

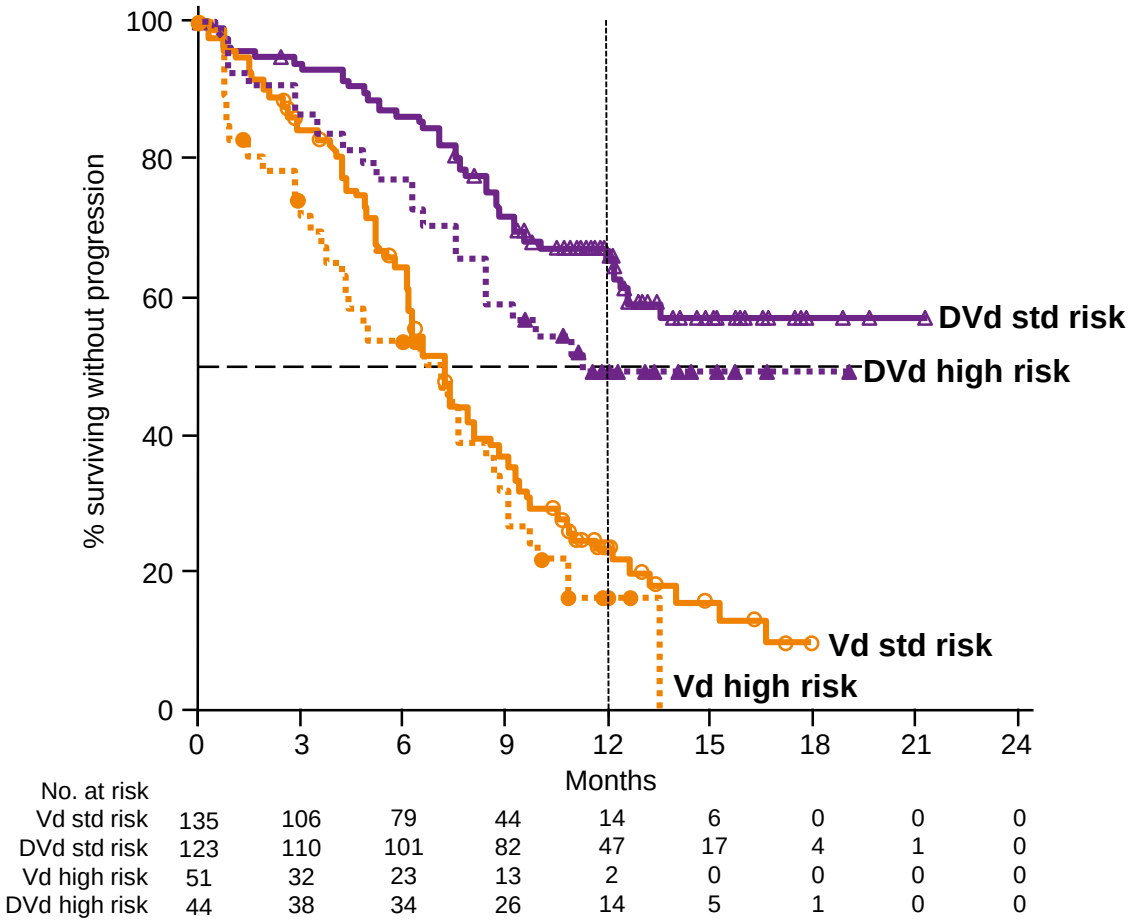
ORR by Prior Lines[a]



More patients achieve a deeper response with DVd after 1 prior line of treatment

[a]Response-evaluable population.
[b]*P* = 0.0006 for DVd vs Vd.
[c]*P* <0.0001 for DVd vs Vd.
[d]*P* = 0.0133 for DVd vs Vd.
Mateos M-V, et al. Oral presentation at: 58th American Society of Hematology (ASH) Annual Meeting and Exposition; December 3-6 2016; San Diego, CA, USA.

PFS: Cytogenetic Risk in All Evaluable Patients[a]



High risk[b]	DVd n = 44	Vd n = 51
Median PFS, mo	**11.2**	**7.2**
HR (95% CI)	0.49 (0.27-0.89)	
P value	0.0167	
	n = 44	n = 47
ORR, %	**82**	**62**
P value	0.039	

Standard risk	DVd n = 123	Vd n = 135
Median PFS, mo	**NR**	**7.0**
HR (95% CI)	0.29 (0.20-0.43)	
P value	<0.0001	
	n = 118	n = 131
ORR, %	**85**	**64**
P value	0.0003	

DVd improves outcomes regardless of cytogenetic risk

NR, not reached.

[a]ITT/Biomarker risk–evaluable analysis set.

[b]Central next-generation sequencing. High-risk patients had any of t(4;14), t(14;16), or del17p. Standard-risk patients had an absence of high-risk abnormalities.

Mateos M-V, et al. Oral presentation at: 58th American Society of Hematology (ASH) Annual Meeting and Exposition; December 3-6 2016; San Diego, CA, USA.

CONCLUSIONS

- DVd is superior to Vd regardless of prior lines of therapy, time since last therapy, prior exposure to bortezomib, or refractoriness to lenalidomide
- The largest magnitude of benefit with DVd is observed in patients with 1 prior line of therapy
  - There was a 78% reduction in the risk of disease progression or death for DVd versus Vd
- DVd significantly improves outcomes for patients with RRMM, regardless of prior treatment with bortezomib
- Importantly, the treatment benefit of DVd versus Vd was maintained in patients who were refractory to lenalidomide at their last prior line of therapy
  - These results suggest that DVd treatment can be sequenced after patients become refractory to lenalidomide
- Patients who achieved MRD negativity demonstrated prolonged PFS regardless of prior exposure to bortezomib or lenalidomide
- High response rates were observed in high-risk and standard-risk patients treated with DVd across all subgroups examined
- These data support the use of DVd as a new standard of care regimen in RRMM regardless of prior treatment history, with the greatest benefit observed in patients with only 1 prior line of therapy

T-151

Depth of Response and Minimal Residual Disease With Daratumumab Plus Bortezomib and Dexamethasone (DVd) Versus Bortezomib and Dexamethasone (Vd) in Relapsed or Refractory Multiple Myeloma: CASTOR

Andrew Spencer,[1,*] Tomer Mark,[2] Ivan Spicka,[3] Tamas Masszi,[4] Birgitta Lauri,[5] Mark-David Levin,[6] Alberto Bosi,[7] Vania Hungria,[8] Michele Cavo,[9] Je-Jung Lee,[10] David Soong,[11] Tineke Casneuf,[12] Christopher Chiu,[11] Xiang Qin,[11] William Deraedt,[12] Ming Qi,[11] A. Kate Sasser,[11] Jordan Schecter,[13] Katja Weisel[14]

[1]Malignant Haematology and Stem Cell Transplantation Service, Alfred Health–Monash University, Melbourne, Australia; [2]Weill Cornell Medical College, New York, NY, USA; [3]Clinical Department of Haematology, 1st Medical Department, Charles University in Prague, Prague, Czech Republic; [4]Department of Haematology and Stem Cell Transplantation, St László Hospital, Semmelweis University, Budapest, Hungary; [5]Department of Hematology, Sunderbyn Hospital, Luleå, Sweden; [6]Department of Internal Medicine, Albert Schweitzer Hospital, Dordrecht, The Netherlands; [7]Department of Hematology, Careggi Hospital and University of Florence, Firenze, Italy; [8]Irmandade Da Santa Casa De Misericordia De São Paulo, São Paulo, Brazil; [9]Institute of Hematology and Medical Oncology "Seràgnoli" DIMES, Department of Experimental, Diagnostic, and Specialty Medicine, Bologna University School of Medicine, S. Orsola's University Hospital, Bologna, Italy; [10]Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, Hwasun, Jeollanamdo, South Korea; [11]Janssen Research & Development, LLC, Spring House, PA, USA; [12]Janssen Research & Development, Beerse, Belgium; [13]Janssen Research & Development, LLC, Raritan, NJ, USA; [14]Universitaetsklinikum Tuebingen der Eberhard-Karls-Universitaet, Abteilung fuer Innere Medizin II, Tuebingen, Germany.

*Presenting author.

INTRODUCTION

- Daratumumab is a human CD38 IgGκ monoclonal antibody that has a direct on-tumor and immunomodulatory mechanism of action[1]
- The on-tumor activity of daratumumab occurs through several CD38 immune-mediated actions, including complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis, as well as apoptosis and the modulation of CD38 enzymatic activity[3-5]
- Daratumumab also induces an immunomodulatory effect that increases T-cell clonality and minimizes the immune-suppressive functions of CD38+ myeloid-derived suppressor cells, regulatory B cells, and regulatory T cells[6]
- In 2 randomized, open-label, active-controlled, phase 3 studies, daratumumab demonstrated superior clinical benefit when combined with standard of care regimens (bortezomib and dexamethasone [Vd; CASTOR[7]] or lenalidomide and dexamethasone [POLLUX[8]]) for the treatment of patients with multiple myeloma (MM) who have received ≥1 prior line of therapy
- At the time of the prespecified interim analysis of CASTOR (median follow-up of 7.4 months), median progression-free survival (PFS) was not reached in the DVd group versus 7.2 months in the Vd group (hazard ratio [HR], 0.39; 95% confidence interval [CI], 0.28-0.53; $P<0.0001$), conferring a 61% lower risk of disease progression or death[7]
- In that analysis, daratumumab significantly improved the overall response rate (ORR) compared with the control group (82.9% vs 63.2%; $P<0.001$), as well as the rates of complete response (CR) or better (19.2% vs 9.0%; $P=0.001$) and very good partial response (VGPR) or better (59.2% vs 29.1%; $P<0.001$)[7]
- Minimal residual disease (MRD) is a more sensitive measure of disease burden than traditional definitions of clinical response[9,10]
  - MRD-negative status is associated with prolonged PFS and overall survival (OS) in newly diagnosed patients with MM,[9,10] and may be a primary endpoint for clinical studies in the future
  - International Myeloma Working Group (IMWG) guidelines recommend an MRD sensitivity threshold of $\geq 10^{-5}$ using next-generation sequencing (NGS) or next-generation flow cytometry[11]
- This study reports long-term follow-up of patients in the CASTOR trial, focusing on the depth of response achieved using DVd versus Vd

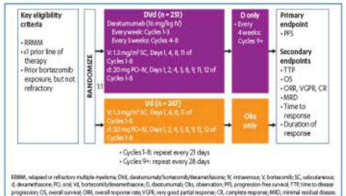
METHODS

Patients

- Patients were ≥18 years of age with an Eastern Cooperative Oncology Group performance status of ≤2
- Patients received ≥1 prior line of therapy and achieved at least a partial response (PR) to ≥1 of their prior therapies for MM, and had documented progressive disease according to IMWG criteria on or after their last regimen
- All patients were required to have measurable disease in the serum and/or urine or serum free light chain at screening, as defined by IMWG criteria
- Key exclusion criteria were as follows:
  - Patients refractory to or intolerant of bortezomib
  - Patients refractory to another proteasome inhibitor (after amendment 1)
  - Grade ≥2 peripheral neuropathy or neuropathic pain

Study Design and Treatment

- This was a multicenter, randomized (1:1), open-label, active-controlled, phase 3 study of patients with relapsed or refractory MM (**Figure 1**)
- Randomization was stratified by International Staging System (ISS; I, II, or III) at screening (based on central laboratory results), number of prior lines of therapy (1 vs 2 or 3 vs >3), and prior bortezomib (no vs yes)
- All patients received up to 8 cycles (21 days/cycle) of Vd
  - Bortezomib was administered subcutaneously at a dose of 1.3 mg/m² on Days 1, 4, 8, and 11 of Cycles 1 to 8
  - Dexamethasone was administered orally or intravenously (IV) at a dose of 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 for a total dose of 160 mg per cycle during Cycles 1 to 8
  - For patients assigned to DVd, daratumumab 16 mg/kg IV was administered weekly (Days 1, 8, and 15) during Cycles 1 to 3, every 3 weeks (Day 1) during Cycles 4 to 8, and every 4 weeks thereafter until withdrawal of consent, disease progression, or unacceptable toxicity



RRMM, relapsed or refractory multiple myeloma; DVd, daratumumab/bortezomib/dexamethasone; IV, intravenous; V, bortezomib; SC, subcutaneous; d, dexamethasone; PO, oral; Vd, bortezomib/dexamethasone; D, daratumumab; Obs, observation; PFS, progression-free survival; TTP, time to disease progression; OS, overall survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease.

Figure 1. CASTOR study design.

MRD Evaluation

- MRD was assessed at the time of suspected CR (blinded to treatment group) and at 6 and 12 months following the first treatment dose. The 6-month assessment occurred at the end of Vd background therapy, and the 12-month assessment occurred 6 months later
- MRD was assessed on bone marrow aspirate samples that were ficolled and evaluated by the ClonoSEQ™ assay (Adaptive Biotechnologies, Seattle, WA, USA) at sensitivity thresholds of 10^{-4} (1 cancer cell per 10,000 nucleated cells), 10^{-5}, and 10^{-6}
- Patients were considered to be MRD negative if they achieved an MRD-negative test result; patients with only MRD-positive test results or who had no MRD assessment were considered MRD positive

Evaluation of Cytogenetic Abnormalities

- Centralized NGS was used at the screening visit prior to randomization to determine cytogenetic abnormalities
- High-risk cytogenetic status was defined as patients having ≥1 of the following abnormalities: t(4;14), t(14;16), or del17p
- Standard-risk cytogenetic status was defined as patients who received cytogenetic testing and did not meet the high-risk criteria

Statistical Analyses and Assessments

- Efficacy analyses were based on the intent-to-treat (ITT) population
  - The response-evaluable analysis set included patients with measurable disease at the baseline or screening visit who received ≥1 study treatment and had ≥1 post-baseline disease assessment
  - The biomarker risk–evaluable analysis set included patients in the ITT population whose cytogenetic risk was determined using NGS
- A stratified log-rank test was used to compare PFS between the DVd and Vd treatment groups
  - HRs and 95% CIs were estimated by using a stratified Cox's regression model, with treatment as the sole explanatory variable
  - The Kaplan-Meier method was used to estimate the distributions
- A stratified Cochran-Mantel-Haenszel chi-square test was used to measure treatment differences in ORR, rate of VGPR or better, and rate of CR or better
- The entire ITT population was evaluated to allow for a stringent and unbiased evaluation of MRD
- The rate of MRD negativity per treatment arm was determined as the proportion of patients with MRD-negative status at any time point following the first treatment dose

RESULTS

Patients and Treatments

- The clinical cut-off date was June 30, 2016, with a median (range) follow-up of 13.0 (0-21.3) months
- A total of 498 patients were enrolled (DVd, n = 251; Vd, n = 247)
- Patient demographic, baseline disease, and clinical characteristics were well balanced (**Table 1**)
- The median (range) number of prior lines of therapy was 2 (1-10)

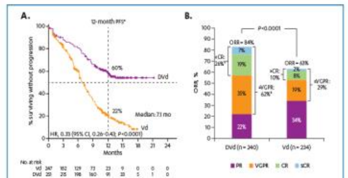
Table 1. Patient Demographic, Baseline Disease, and Clinical Characteristics (ITT)

Characteristic	DVd (n = 251)	Vd (n = 247)
Age, y		
Median (range)	64 (30-88)	64 (33-85)
≥75 y, n (%)	23 (9)	35 (14)
ISS staging, n (%)[a]		
I	98 (39)	96 (39)
II	94 (38)	100 (41)
III	59 (24)	51 (21)
Creatinine clearance, mL/min, n (%)		
N	243	233
>30-60	49 (20)	59 (25)
>60	186 (77)	163 (70)
Time from diagnosis, y		
Median (range)	3.87 (0.7-20.7)	3.72 (0.6-18.6)
Cytogenetic profile, n (%)[b]		
N	167	186
Standard risk	123 (74)	135 (73)
High risk	44 (26)	51 (27)
Prior lines of therapy, n (%)		
Median (range)	2 (1-9)	2 (1-10)
1	122 (49)	113 (46)
2	70 (28)	74 (30)
3	37 (15)	32 (13)
>3	22 (9)	28 (11)
Prior ASCT, n (%)	156 (62)	149 (60)
Prior PI, n (%)	169 (67)	172 (70)
Prior IMiD, n (%)	179 (71)	198 (80)
Prior PI + IMiD, n (%)	112 (45)	129 (52)
Refractory to IMiD only, n (%)	74 (30)	90 (36)
Refractory to last line of therapy, n (%)	76 (30)	85 (34)

ITT, intent-to-treat; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; ISS, International Staging System; ASCT, autologous stem cell transplantation; PI, proteasome inhibitor; IMiD, immunomodulatory drug; NGS, next-generation sequencing.
[a]ISS staging was derived based on the combination of serum β2-microglobulin and albumin.
[b]Cytogenetic risk was established by centralized analysis using NGS. Patients with high-risk cytogenetics were defined as having t(4;14), t(14;16), or del17p abnormalities.

Updated Efficacy Results

- Responses continued to deepen in the DVd group with longer follow-up
- After a median follow-up of 13.0 months, PFS was significantly prolonged with DVd compared with Vd (median not reached vs 7.1 months; HR, 0.33; 95% CI, 0.26-0.43; $P<0.0001$; **Figure 2A**)
- A higher ORR was observed with DVd vs Vd (84% vs 63%; $P<0.0001$), with significantly higher rates of VGPR or better (62% vs 29%; $P<0.0001$) and CR or better (26% vs 10%; $P<0.0001$), respectively (**Figure 2B**)
  - An additional 7% of patients receiving DVd achieved CR or better with longer follow-up

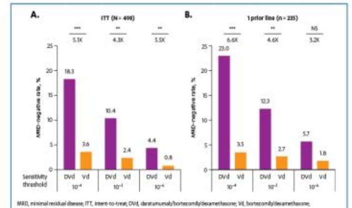


PFS, progression-free survival; ORR, overall response rate; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; HR, hazard ratio; CI, confidence interval; CR, complete response; VGPR, very good partial response; PR, partial response; sCR, stringent complete response.
[a]Kaplan-Meier estimate.
[b]P<0.0001 for DVd versus Vd.

Figure 2. (A) Median PFS and (B) ORR with DVd versus Vd in CASTOR.

MRD Negativity

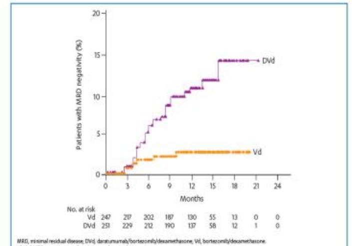
- Daratumumab in combination with standard of care significantly improved MRD-negative rates at all sensitivity thresholds
  - In the ITT population, a higher proportion of patients achieved deeper responses with DVd compared with Vd (**Figure 3**)
  - Similar MRD-negative rates were observed in the subgroup of patients (n = 235) who received 1 prior line of therapy (**Figure 3**)



MRD, minimal residual disease; ITT, intent-to-treat; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; NS, not significant.
**P<0.005.
***P<0.0001.

Figure 3. Proportion of MRD-negative patients at 10^{-4}, 10^{-5}, and 10^{-6} sensitivity thresholds in the entire ITT population and in the ITT subgroup with 1 prior line of therapy.

- MRD-negative status was durable within these patients (**Figure 4**)
  - MRD-negative patients continued to accumulate over time (even beyond 12 months) in the DVd arm
  - Patients in the DVd arm received daratumumab monotherapy after 8 cycles of Vd



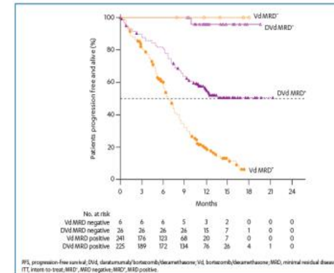
MRD, minimal residual disease; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone.
[a]Only 1 MRD-negative sample was counted per patient.

Figure 4. Time to MRD with DVd versus Vd at the 10^{-5} sensitivity threshold.[a]

- MRD-negative patients demonstrated prolonged PFS compared with MRD-positive patients across all sensitivity thresholds
  - PFS by MRD status at the 10^{-5} sensitivity threshold is represented in **Figure 5**
- In MRD-positive patients, a PFS benefit was observed in patients who received DVd compared with those who received Vd

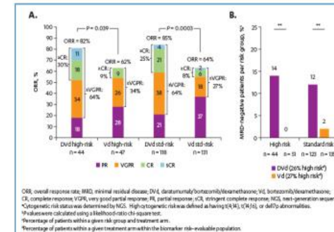
Patients at High Cytogenetic Risk

- The biomarker risk–evaluable analysis set included 167 patients who received DVd (standard risk, n = 123; high risk, n = 44) and 186 patients who received Vd (standard risk, n = 135; high risk, n = 51)
  - In high-risk patients, ORR (82% vs 62%; $P=0.039$; **Figure 6A**) and MRD-negative rates (14% vs 0% at 10^{-5}; $P=0.0018$; **Figure 6B**) were significantly higher with DVd compared with Vd, and no MRD-negative patients progressed
  - Notably, in high-risk patients, MRD-negative status was achieved only in those treated with daratumumab-containing regimens
- Similar findings were observed among standard-risk patients with respect to ORR (85% vs 64%; $P=0.0003$) and MRD-negative rates (12% vs 2% at 10^{-5}; $P=0.0011$; **Figure 6**)



PFS, progression-free survival; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; MRD, minimal residual disease; ITT, intent-to-treat; MRD−, MRD negative; MRD+, MRD positive.

Figure 5. PFS for DVd versus Vd according to MRD status at the 10^{-5} sensitivity threshold (ITT).



ORR, overall response rate; MRD, minimal residual disease; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; CR, complete response; VGPR, very good partial response; PR, partial response; sCR, stringent complete response; NGS, next-generation sequencing.
[a]Cytogenetic risk status was determined by NGS. High cytogenetic risk was defined as having t(4;14), t(14;16), or del17p abnormalities.
[b]P values were calculated using a likelihood-ratio chi-square test.
[c]Percentage of patients within a given risk group and treatment arm.
[d]Percentage of patients within a given treatment arm within the biomarker risk–evaluable population.
**P<0.005.

Figure 6. (A) ORR and (B) MRD-negative rates with DVd versus Vd at the 10^{-5} sensitivity threshold by cytogenetic risk.[a,b]

CONCLUSIONS

- **Long-term follow-up of patients in the CASTOR trial demonstrated that the PFS benefit continued to be maintained with DVd over time**
- **DVd induced MRD negativity in ≥3 times as many patients as Vd, with durable achievement of MRD negativity**
  - **Patients continued to achieve MRD negativity over time**
- **MRD negativity was achieved in high-risk patients receiving DVd but not Vd**
  - **No MRD-negative, high-risk patients progressed during the study**
- **MRD negativity was associated with prolonged PFS**
- **The deep clinical responses and higher rate of MRD negativity induced by daratumumab may lead to improved long-term clinical benefit**

REFERENCES

1. van de Donk NW, et al. Immunol Rev. 2016;270(1):95-112.
2. de Weers M, et al. J Immunol. 2011;186(3):1840-1848.
3. Lammerts van Bueren J, et al. Blood. 2014;124(21):3474.
4. Overdijk MB, et al. MAbs. 2015;7(2):311-321.
5. Overdijk MB, et al. J Immunol. 2016;197(3):807-813.
6. Krejcik J, et al. Blood. 2016;128(3):384-394.
7. Palumbo A, et al. N Engl J Med. 2016;375(8):754-766.
8. Dimopoulos MA, et al. N Engl J Med. 2016;375(14):1319-1331.
9. Munshi NC, et al. JAMA Oncol. 2017;3(1):28-35.
10. Landgren O, et al. Bone Marrow Transplant. 2016;51(12):1565-1568.
11. Kumar S, et al. Lancet Oncol. 2016;17(8):e328-e346.

ACKNOWLEDGEMENTS

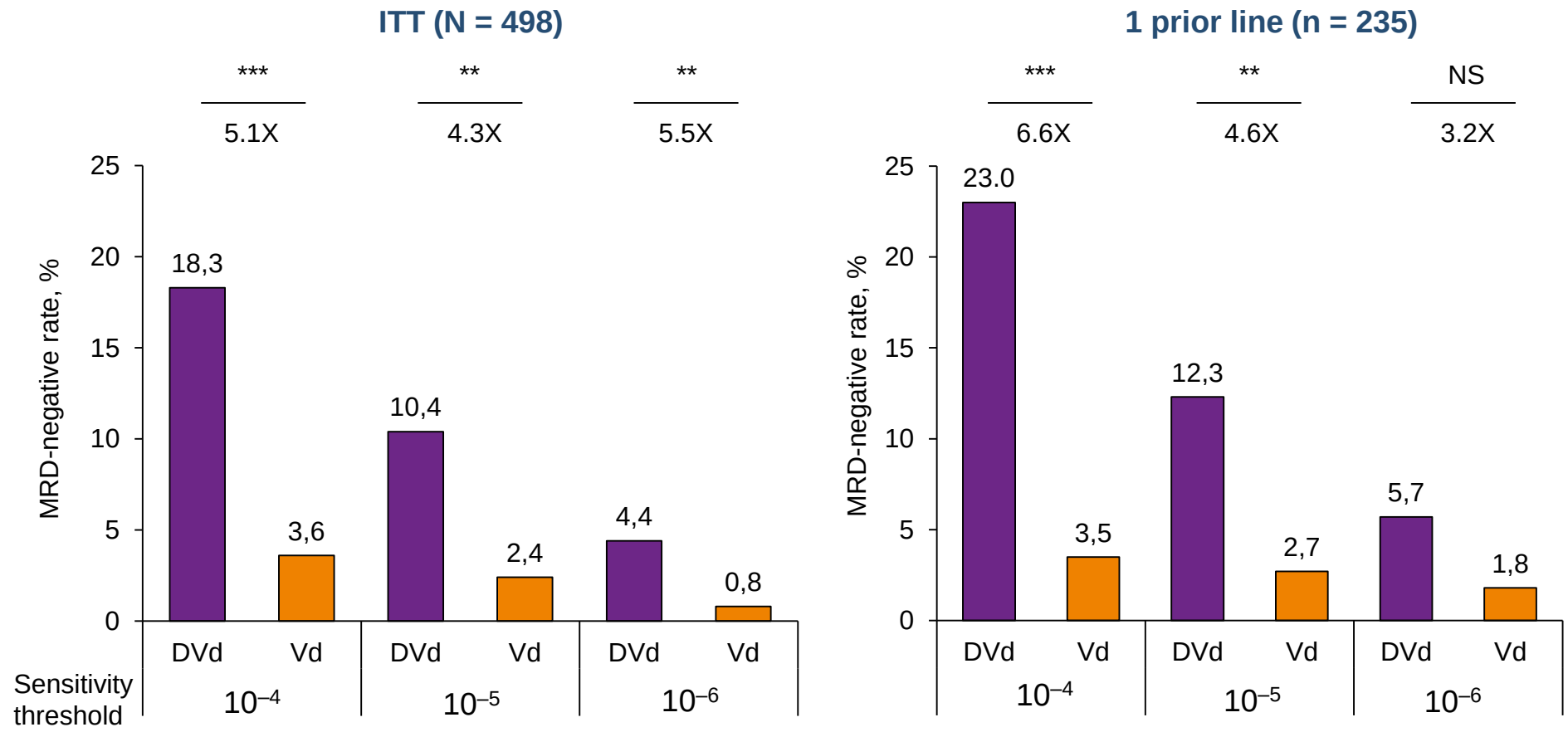
The authors thank the patients who participated in this study, the staff members at the study sites, the data and safety monitoring committee, and staff members who were involved in data collection and analyses.
This study (ClinicalTrials.gov Identifier: NCT02136134) was sponsored by Janssen Research & Development, LLC. Editorial and medical writing support were provided by Jason Jung, PhD, of MedErgy, and were funded by Janssen Global Services, LLC.

DISCLOSURES

AS received research funding and personal fees from Janssen Cilag. IS served as a consultant for Bristol-Myers Squibb, Celgene, Amgen, and Janssen Cilag; received research funding from Celgene; received honoraria from Bristol-Myers Squibb, Celgene, Amgen, Janssen Cilag, and Millennium; and served on the advisory committee for Bristol-Myers Squibb, Celgene, and Janssen Cilag. VH served as a consultant for Janssen and Takeda and received advisory fees from Janssen and Takeda. MC received honoraria from Bristol-Myers Squibb, Celgene, Amgen, Janssen, and Takeda. J-JL is an employee of Chonnam National University Hwasun Hospital. TC, CC, XQ, WD, MQ, AKS, and JS are employees of Janssen. TC, WD, AKS, and JS hold equity in Johnson & Johnson. T Mark, T Masszi, BL, M-DL, AB, DS, and KW have no conflicts of interest to disclose.

An electronic version of the poster can be viewed by scanning the QR code. The QR code is intended to provide scientific information for individual reference. The PDF should not be altered or reproduced in any way.
http://jjd_imw.scientificpresentations.org/Spencer_JJD61606.pdf

MRD rates by prior lines of therapy



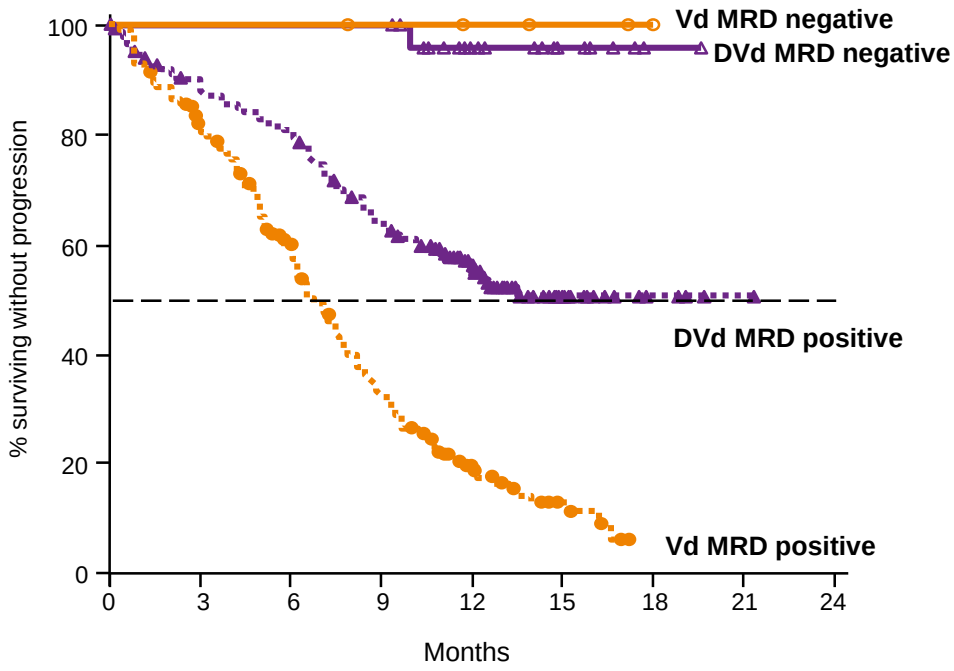
- MRD was evaluated by ClonoSEQ-NGS-based assay in a central lab at three sensitivity thresholds, for patients with suspected CR and also for patients who maintain CR at C9 and C15

MRD-negative rates for DVd were ≥3-fold higher across all thresholds

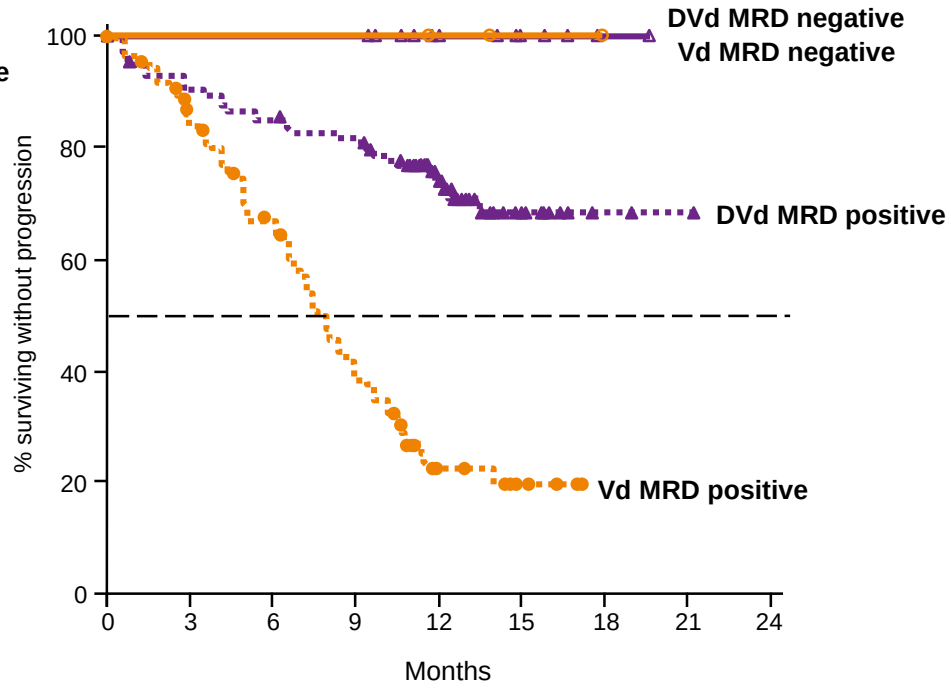
****P* <0.0001; ***P* <0.01; NS, not significant.
P values calculated using likelihood-ratio chi-square test.
MRD-negativity rate = proportion of patients with negative MRD test results at any time during treatment.
Mateos M-V, et al. Oral presentation at: 58th American Society of Hematology (ASH) Annual Meeting and Exposition; December 3-6 2016; San Diego, CA, USA.

PFS: MRD Status (10^{-5})

ITT



1 prior line



MRD negativity is associated with better outcomes

Mateos M-V, et al. Oral presentation at: 58th American Society of Hematology (ASH) Annual Meeting and Exposition; December 3-6 2016; San Diego, CA, USA.

T-151

Depth of Response and Minimal Residual Disease With Daratumumab Plus Bortezomib and Dexamethasone (DVd) Versus Bortezomib and Dexamethasone (Vd) in Relapsed or Refractory Multiple Myeloma: CASTOR

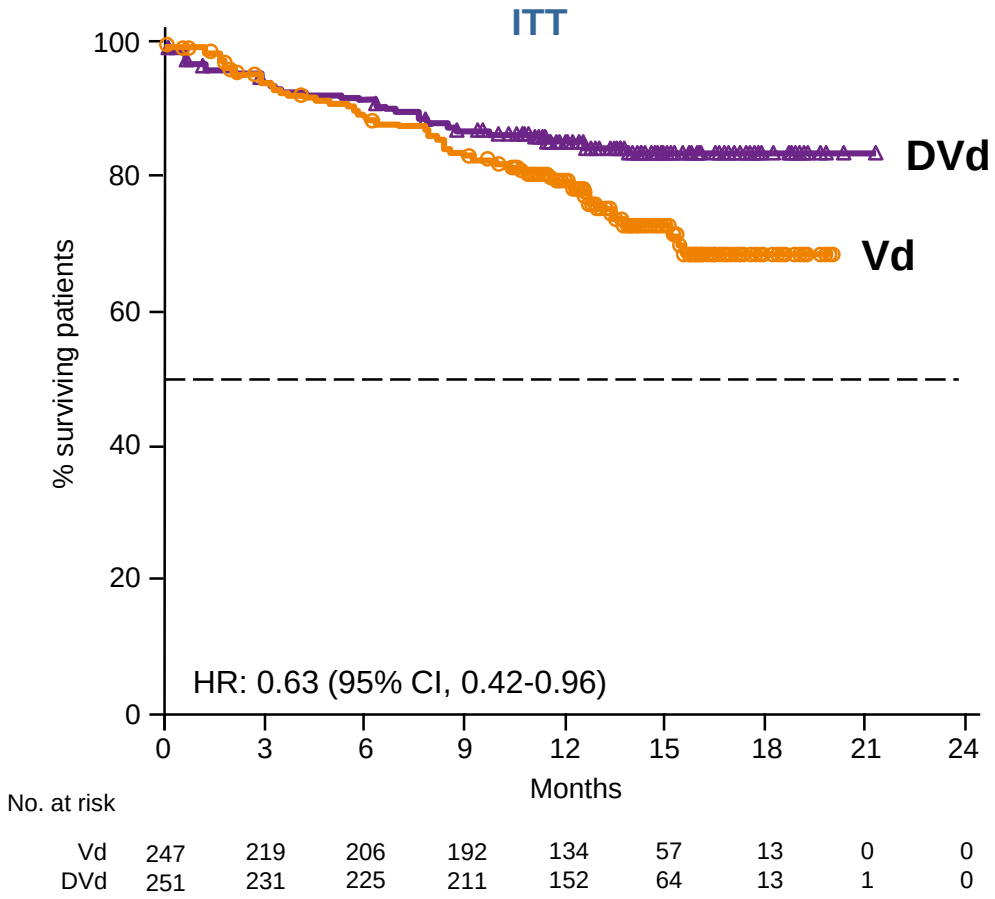
Andrew Spencer,[1,*] Tomer Mark,[2] Ivan Spicka,[3] Tamas Masszi,[4] Birgitta Lauri,[5] Mark-David Levin,[6] Alberto Bosi,[7] Vania Hungria,[8] Michele Cavo,[9] Je-Jung Lee,[10] David Soong,[11] Tineke Casneuf,[12] Christopher Chiu,[11] Xiang Qin,[11] William Deraedt,[12] Ming Qi,[11] A. Kate Sasser,[11] Jordan Schecter,[13] Katja Weisel[14]

[1]Malignant Haematology and Stem Cell Transplantation Service, Alfred Health–Monash University, Melbourne, Australia; [2]Weill Cornell Medical College, New York, NY, USA; [3]Clinical Department of Haematology, 1st Medical Department, Charles University in Prague, Prague, Czech Republic; [4]Department of Haematology and Stem Cell Transplantation

CONCLUSIONS

- Long-term follow-up of patients in the CASTOR trial demonstrated that the PFS benefit continued to be maintained with DVd over time
- DVd induced MRD negativity in ≥3 times as many patients as Vd, with durable achievement of MRD negativity
  - Patients continued to achieve MRD negativity over time
- MRD negativity was achieved in high-risk patients receiving DVd but not Vd
  - No MRD-negative, high-risk patients progressed during the study
- MRD negativity was associated with prolonged PFS
- The deep clinical responses and higher rate of MRD negativity induced by daratumumab may lead to improved long-term clinical benefit

OS



- OS events
  - 37 (15%) in DVd
  - 58 (24%) in Vd
- OS HR for DVd versus Vd by prior lines:
  - 1 prior line = HR: 0.42 (95% CI, 0.19-0.93)
  - 1-3 prior line = HR: 0.54 (95% CI, 0.34-0.84)

Curves are beginning to separate, but OS data are immature

Median OS was not reached; results did not cross the prespecified stopping boundary.

Mateos M-V, et al. Oral presentation at: 58th American Society of Hematology (ASH) Annual Meeting and Exposition; December 3-6 2016; San Diego, CA, USA.

Most Common TEAEs (All Patients): Updated Analysis

	DVd (n = 243)		Vd (n = 237)	
Hematologic, n (%)	All-grade ≥25%[a]	Grade 3/4 ≥5%[a]	All-grade ≥25%[a]	Grade 3/4 ≥5%[a]
Thrombocytopenia	145 (60)	110 (45)	105 (44)	78 (33)
Anemia	67 (28)	36 (15)	75 (32)	38 (16)
Neutropenia	45 (19)	32 (13)	23 (10)	11 (5)
Lymphopenia	32 (13)	24 (10)	9 (4)	6 (3)
Nonhematologic, n (%)				
Peripheral sensory neuropathy	120 (49)	11 (5)	90 (38)	16 (7)
Diarrhea	83 (34)	9 (4)	53 (22)	3 (1)
Upper respiratory tract infection	72 (30)	6 (3)	43 (18)	1 (0.4)
Cough	66 (27)	0	30 (13)	0
Fatigue	53 (22)	12 (5)	58 (25)	8 (3)
Pneumonia	33 (14)	22 (9)	28 (12)	23 (10)
Hypertension	22 (9)	16 (7)	8 (3)	2 (0.8)

- Grade 3/4 TEAEs: 79% of DVd patients versus 63% of Vd patients
- Discontinuations due to TEAEs: 9% of DVd patients versus 9% of Vd patients[b]
- No new IRRs; incidence remains stable with longer follow up (45%)

TEAE, treatment-emergent adverse event; IRR, infusion-related reaction.

[a]Common TEAEs listed are either ≥25% all grade OR ≥5% grade 3/4. [b]Vd arm treated for 8 cycles and DVd arm treated until progressive disease, per protocol.

Mateos M-V, et al. Oral presentation at: 58th American Society of Hematology (ASH) Annual Meeting and Exposition; December 3-6 2016; San Diego, CA, USA.

Infusion-Related Reactions (IRRs)

	Safety Analysis Set	
	All Grades	Grade 3
Patients with IRRs, %	45	9
Most common (>5%) IRRs, %		
Dyspnea	11	2
Bronchospasm	9	3
Cough	7	0

- No grade 4 or 5 IRRs observed
- 98% of patients with IRRs experienced the event on first infusion
- 2 patients discontinued due to IRRs
  - Bronchospasm in the first patient
  - Bronchospasm, laryngeal edema, and skin rash in the second patient

Preinfusion: Dexamethasone 20 mg, paracetamol (APAP) 650 mg to 1000 mg, diphenhydramine 25 mg to 50 mg
Stop infusion immediately for mild symptoms; once resolved, resume at half the infusion rate

Palumbo A, et al. *Haematologica.* 2016;101(Suppl): Abstract LB2236. Palumbo A, et al. *N Engl J Med.* 2016;375(8):754-766.

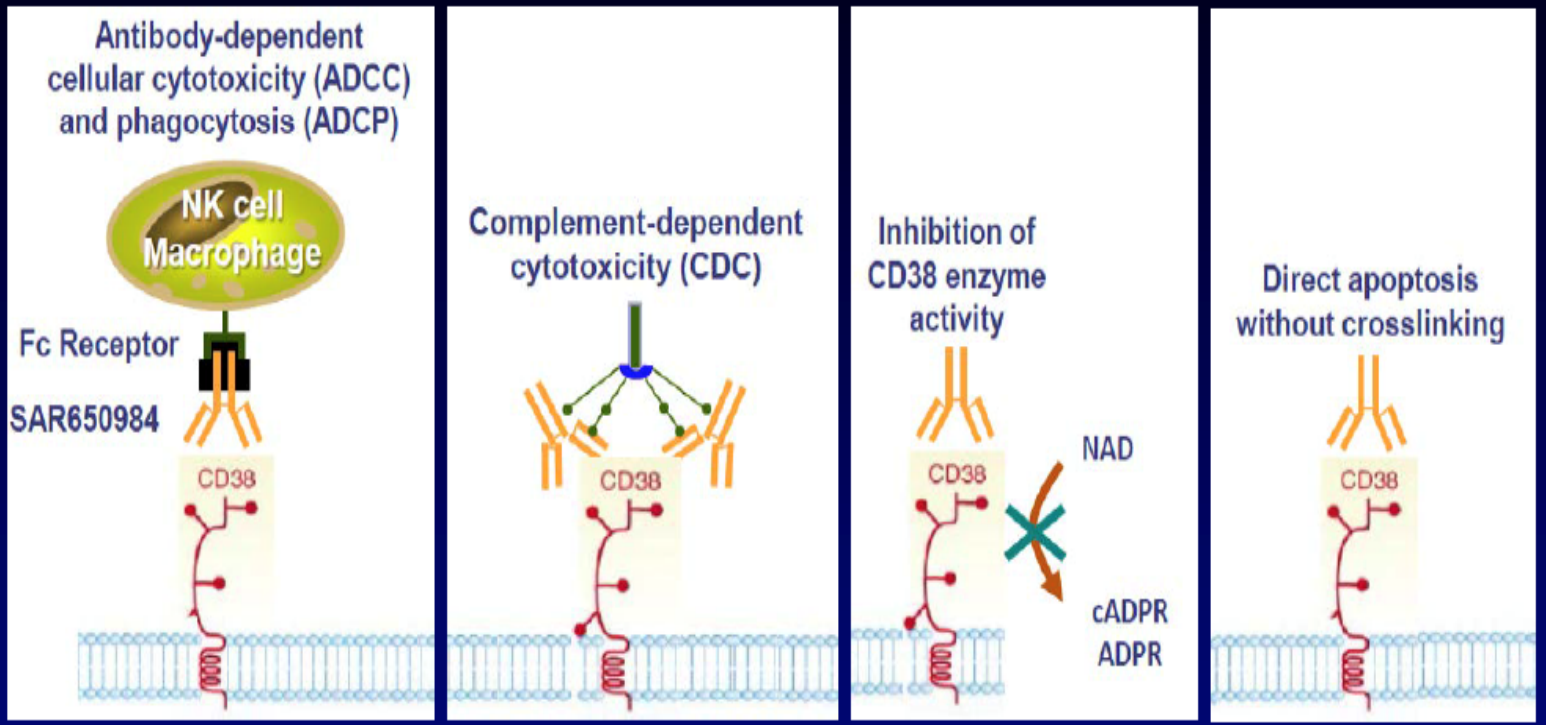
PI-based Studies: Efficacy outcome

	Daratumumab DVd vs Vd	Carfilzomib Kd vs Vd[1]	Panobinostat PVd vs Vd[2,3]	Elotuzumab EVd vs Vd[4]
PFS HR (95% CI)	0.39 (0.28-0.53)	0.53 (0.44-0.65)	0.63 (0.52-0.76)	0.72 (0.59-0.88)
PFS, median mo	NE	18.7	12.0	9.7
≥VGPR	59%	54%	28%	36%
≥CR	19%	13%	11%	4%
Duration of response, mo	NE	21.3	13.1	11.4
OS HR (95% CI)	0.77 (0.47, 1.26)	0.79 (0.58-1.08)	0.94 (0.78-1.14)	0.61 (0.32-1.15)

1. Dimopoulos MA, et al. *Lancet Oncol*. 2016;17(1):27-38.
2. San-Miguel JF, et al. *Lancet Oncol*. 2014;15(11):1195-1206.
3. San-Miguel JF, et al. *Blood*. 2015;126(23):Abstract 3026.
4. Jakubowiak A, et al. *Blood*. 2016. Epub ahead of print.

Palumbo, A. *Oral Presentation EHA* 2016

Isatuximab (SAR650984, anti-CD38) MoA



Canonical and lysosome-dependent cell death*

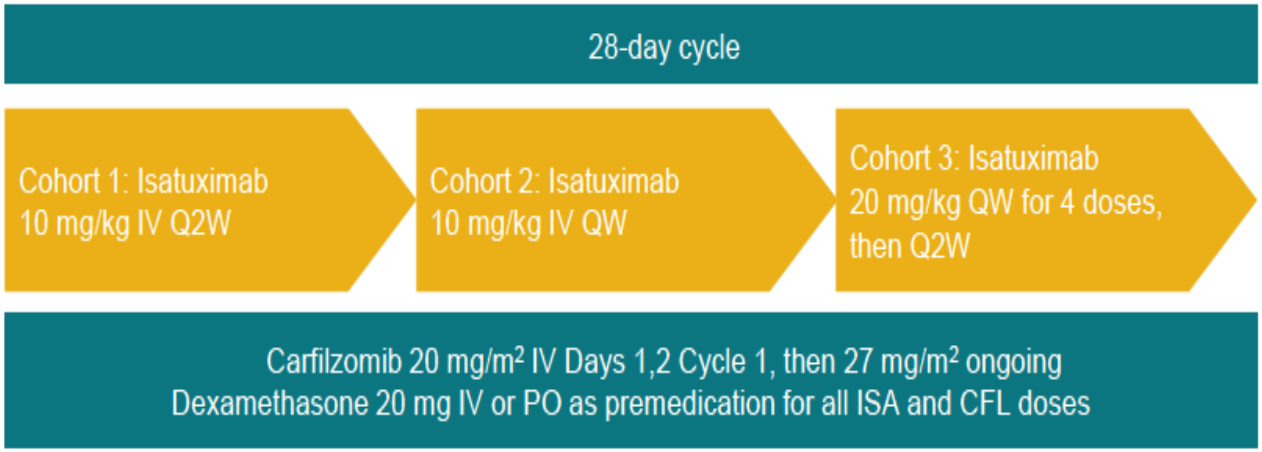
- ADCC was observed in all the CD38+ lines tested
- CDC activity was dependent on receptor density
- Crosslinking-independent apoptosis
- Inhibition of the CD38 ectoenzyme activity

Synergistic and/or additive effect in combination with Len, Bort, Car and Mel in animal models

Deckert et al. Clin Cancer Res 2014;20(17):4574-83; Martin et al. ASH 2014 (Abstract 83); oral presentation; *Jiang et al. Leukemia 2016;30(2):399-408.

Phase 1b study: isatuximab + carfilzomib-dex in RRMM

- 3 + 3 dose escalation + expansion study
- Adults with RRMM and 2 prior therapies including an IMiD and PI (prior carfilzomib allowed even if refractory)



- Patients: N=12
  - Median (range) prior lines: 3.5 (2-8); 75% refractory to IMiD and PI; 65% refractory to carfilzomib
- Response data (n=12):
  - ORR 66.7%: 2 with VGPR, 6 with PR, and 2 with MR
- No new safety signals
- MTD not reached; 21 patients to be enrolled into expansion phase

Interim analysis results. Data cut-off: November 20, 2016

Martin, T et al. Presented at ASH 2016 (Abstract 2111), poster presentation.

Introduction (1)

- **Elotuzumab in combination with lenalidomide-dex: Approved in RRMM**
- **Daratumumab single-agent: Approved in advanced patients**
- **Daratumumab in combination with lenalidomide-dex: Approved in the US + EMA CHMP positive opinion**
- **Daratumumab in combination with bortezomib-dex: Approved in the US + EMA CHMP positive opinion**

Empliciti Prescribing information 2015, http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761035s000lbl.pdf;
Empliciti SmPC 2016, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003967/WC500206673.pdf;
Darzalex Prescribing information 2016, http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761036s004lbl.pdf;
Darzalex SmPC 2016, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004077/WC500207296.pdf;
http://www.businesswire.com/news/home/20170224005351/en/DARZALEX%C2%AE%E2%96%BC-daratumumab-Receives-Positive-CHMP-Opinion-Treatment

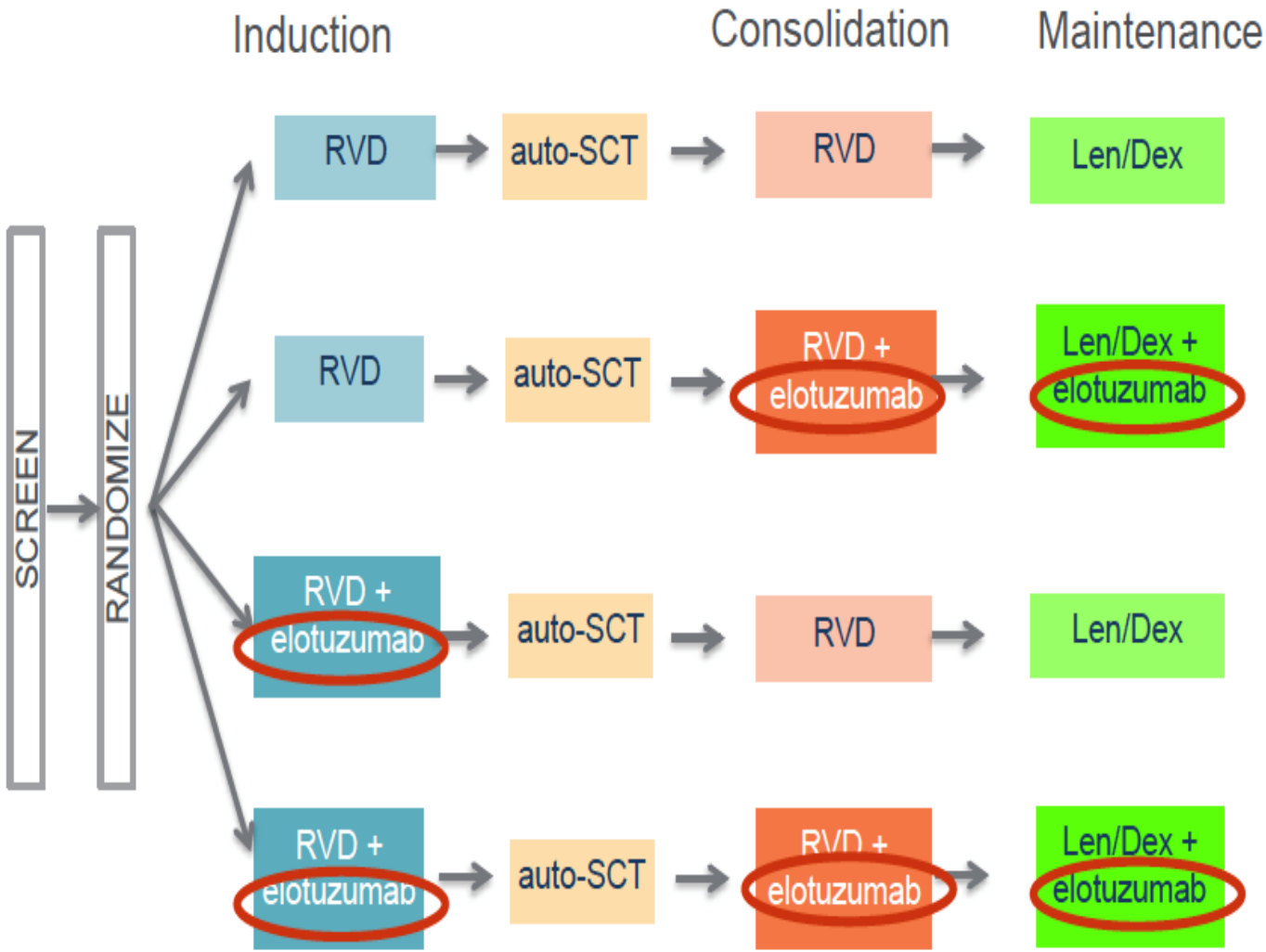
Introduction (2)

- **Phase 1/2 trials ongoing or completed combining:**
  - **Pom-dex Daratumumab**
  - **Pom-dex Elotuzumab**
  - **Pom-dex Isatuximab**
  - **Pom-dex MOR202**
  - **Len-dex Isatuximab**
  - **Carfil-dex Isatuximab**
  - **Len-dex MOR202**
- **Phase 3 pending or recruiting:**
  - **Pom-dex +/- Daratumumab**
  - **Pom-dex +/- Isatuximab**
  - **Carfil-dex +/- Isatuximab**
  - **Carfil-dex Daratumumab**

Clinicaltrials.gov identifiers: NCT01946477; NCT02654132; NCT02283775; NCT01421186; NCT01749969; NCT02990338; NCT02332850: Martin, T et al. Presented at ASH 2016 (Abstract 2111), poster presentation; Moreau, personal communication; http://www.amgen.com/media/news-releases/2016/11/amgen-announces-collaboration-with-janssen-to-cofund-studies-with-kyprolis-carfilzomib-and-darzalex-daratumumab-in-patients-with-multiple-myeloma/.

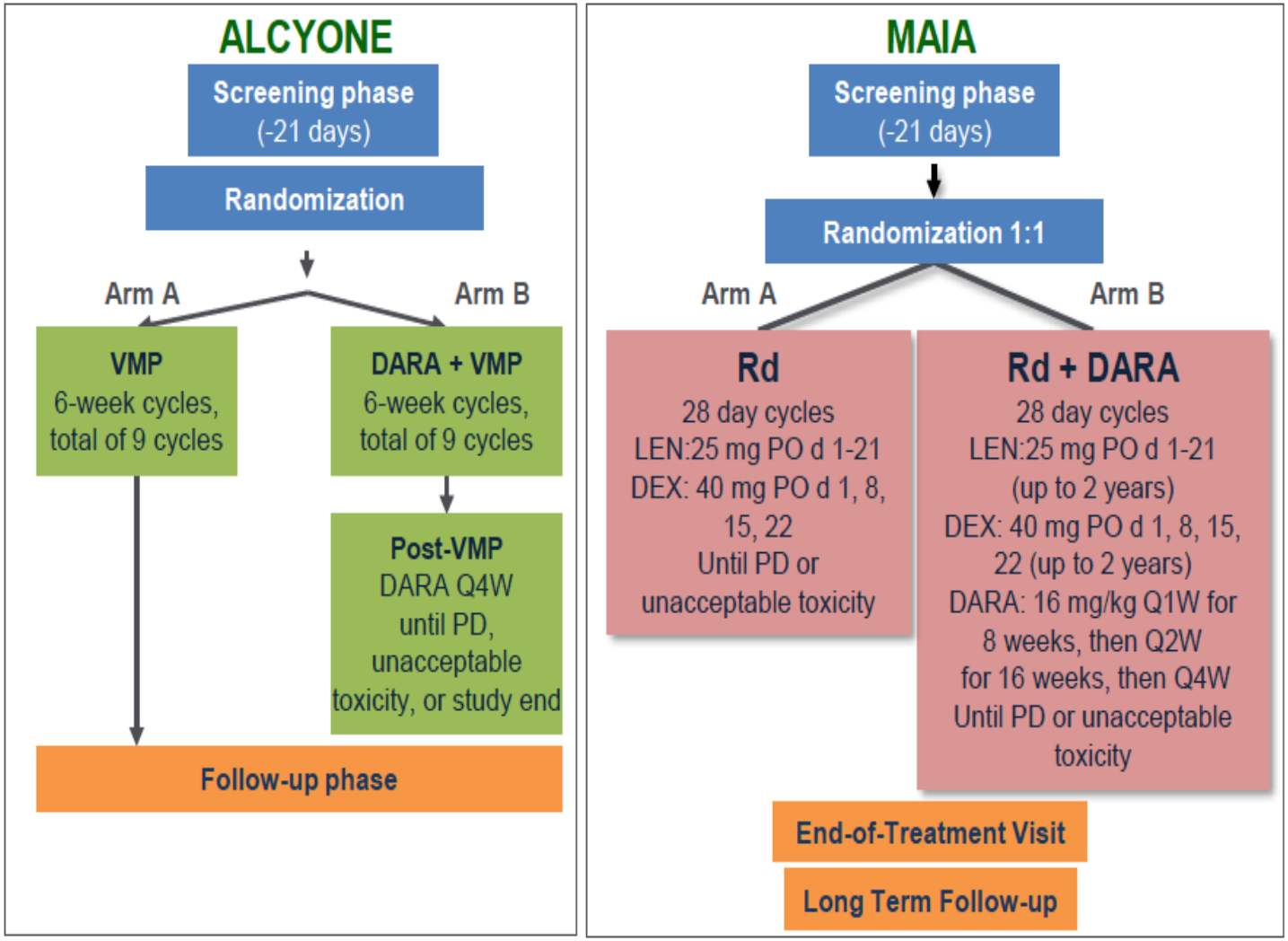
Ongoing or completed trials for future approvals ?

Phase 3: Elotuzumab + VRD induction/consolidation + Lenalidomide maintenance in newly diagnosed MM (GMMG-HD6)



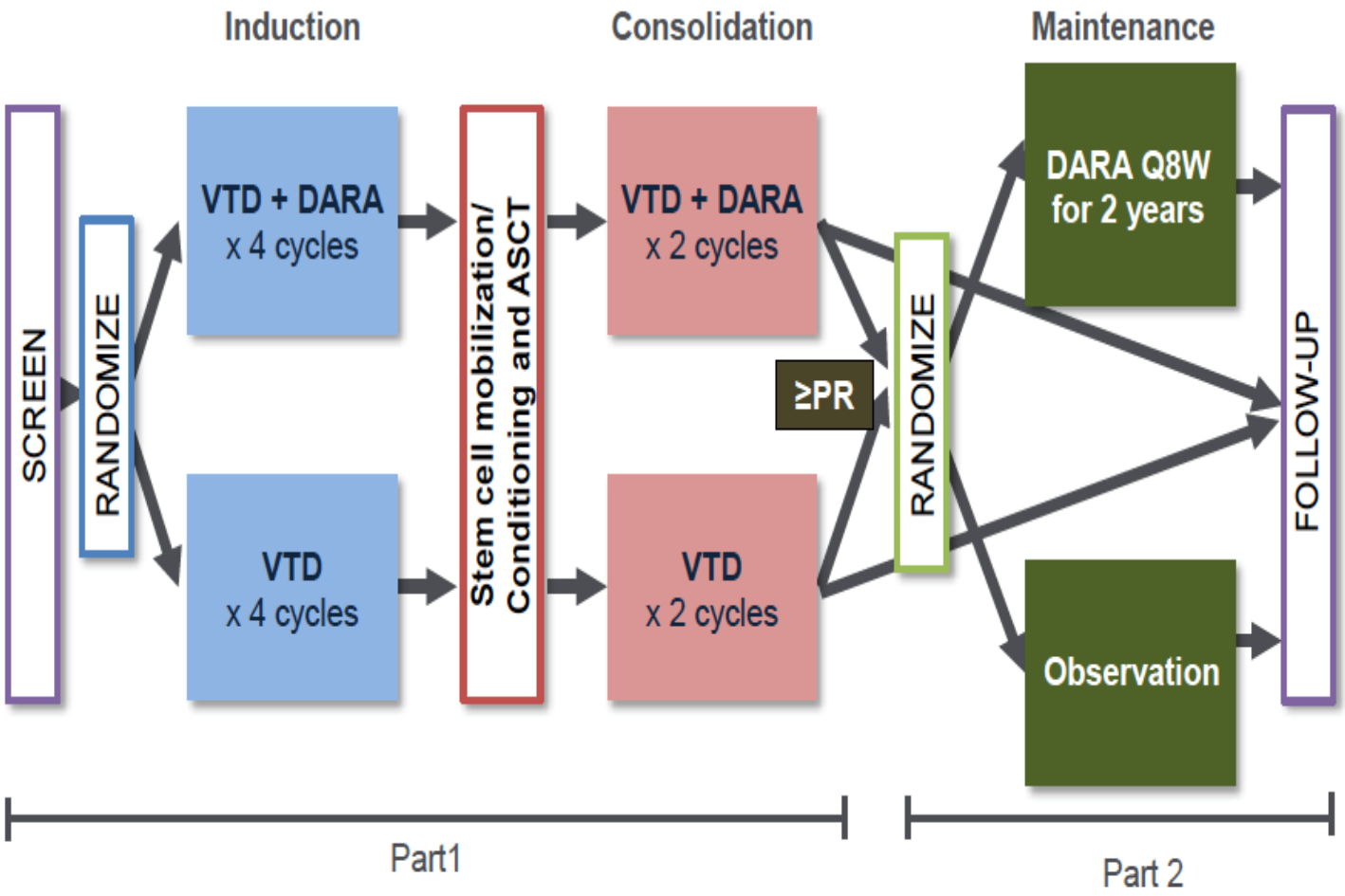
www.clinicaltrials.gov; NCT02495922

Ongoing daratumumab studies in the non-transplant setting



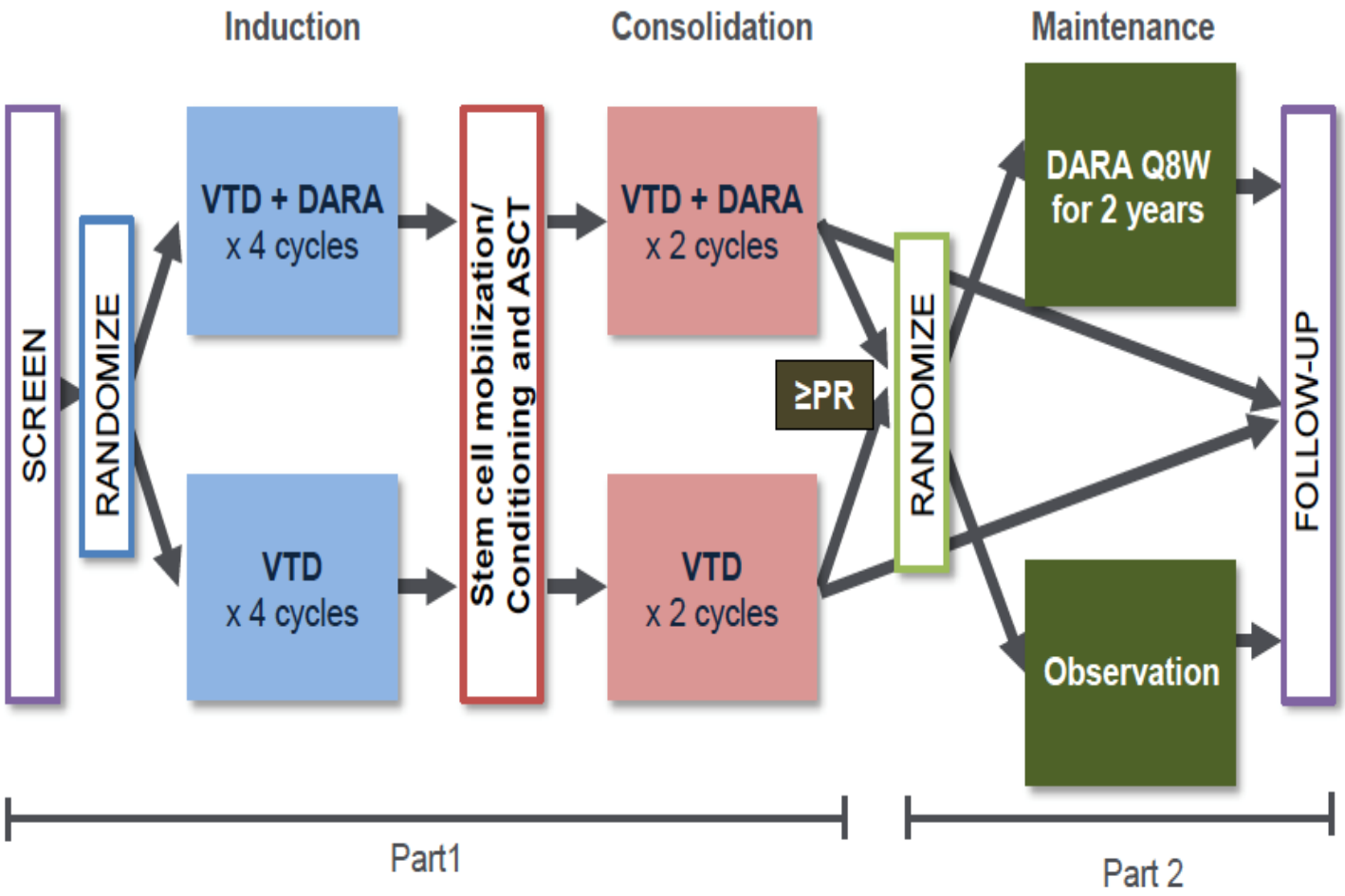
www.clinicaltrials.gov; NCT02195479, NCT02252172

CASSIOPEIA trial



ClinicalTrials.gov Identifier: NCT02541383. Available at: https://clinicaltrials.gov/ct2/show/NCT02541383?term=NCT02541383&rank=1.

CASSIOPEIA trial



ClinicalTrials.gov Identifier: NCT02541383. Available at: https://clinicaltrials.gov/ct2/show/NCT02541383?term=NCT02541383&rank=1.