Efficacy of Daratumumab, Lenalidomide, and Dexamethasone Versus Lenalidomide and Dexamethasone in Relapsed or Refractory Multiple Myeloma Patients With 1 to 3 Prior Lines of Therapy: Updated Analysis of POLLUX

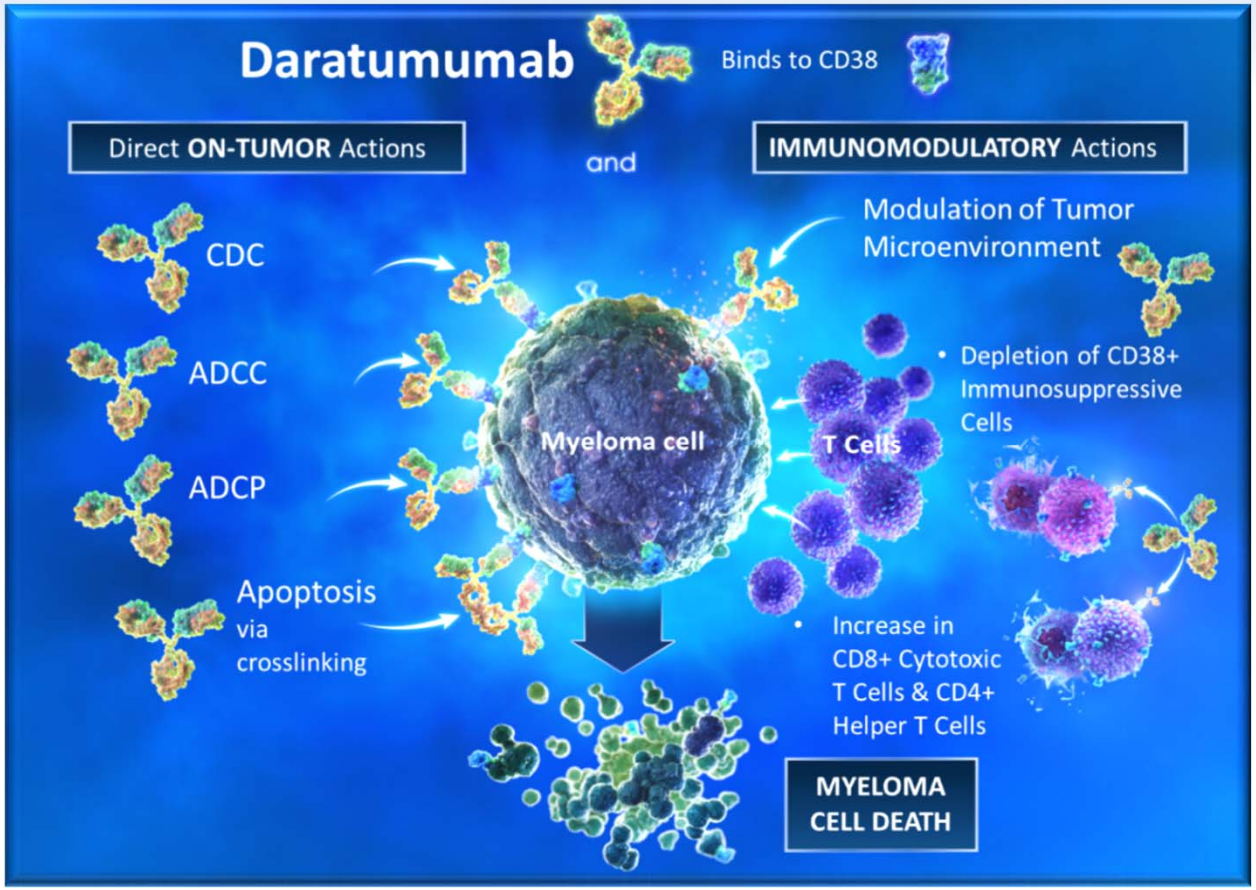
Saad Z. Usmani,[1] Meletios A. Dimopoulos,[2] Andrew Belch,[3] Darrell White,[4] Lotfi Benboubker,[5] Gordon Cook,[6] Merav Leiba,[7] James Morton,[8] P. Joy Ho,[9] Kihyun Kim,[10] Naoki Takezako,[11] Nushmia Z. Khokhar,[12] Mary Guckert,[12] Kaida Wu,[12] Xiang Qin,[12] Tineke Casneuf,[13] Christopher Chiu,[12] A. Kate Sasser,[12] Jesus San-Miguel[14]

[1]Levine Cancer Institute/Carolinas HealthCare System, Charlotte, NC, USA; [2]National and Kapodistrian University of Athens, Athens, Greece; [3]Department of Oncology, University of Alberta Cross Cancer Institute, Edmonton, Alberta, Canada; [4]QEII Health Sciences Center, Dalhousie University, Halifax, Nova Scotia, Canada; [5]Service d'Hématologie et Thérapie Cellulaire, Hôpital Bretonneau, Centre Hospitalier Régional Universitaire (CHRU), Tours, France; [6]St James's Institute of Oncology, Leeds Teaching Hospitals NHS Trust and University of Leeds, Leeds, UK; [7]Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel; [8]Icon Cancer Care, South Brisbane, QLD, Australia; [9]Institute of Haematology, Royal Prince Alfred Hospital, Camperdown, NSW, Australia; [10]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [11]Department of Hematology, National Hospital Organization Disaster Medical Center of Japan, Tachikawa, Japan; [12]Janssen Research & Development, LLC, Spring House, PA, USA; [13]Janssen Research & Development, Beerse, Belgium; [14]Clínica Universidad de Navarra-CIMA, IDISNA, Pamplona, Spain.

ClinicalTrials.gov Identifier: NCT02076009

Background

- Daratumumab
  - Human monoclonal antibody targeting CD38
  - Direct on-tumor and immunomodulatory MoA[1-5]
- Approved
  - As monotherapy for heavily pretreated RRMM by the FDA, EMA, Health Canada, Mexico, and Singapore
  - Combo with standard of care regimens for RRMM after ≥1 prior therapy (POLLUX and CASTOR) by the FDA
- Early studies demonstrated efficacy of daratumumab
  - Rapid, deep, and durable responses
  - Well tolerated with manageable adverse events

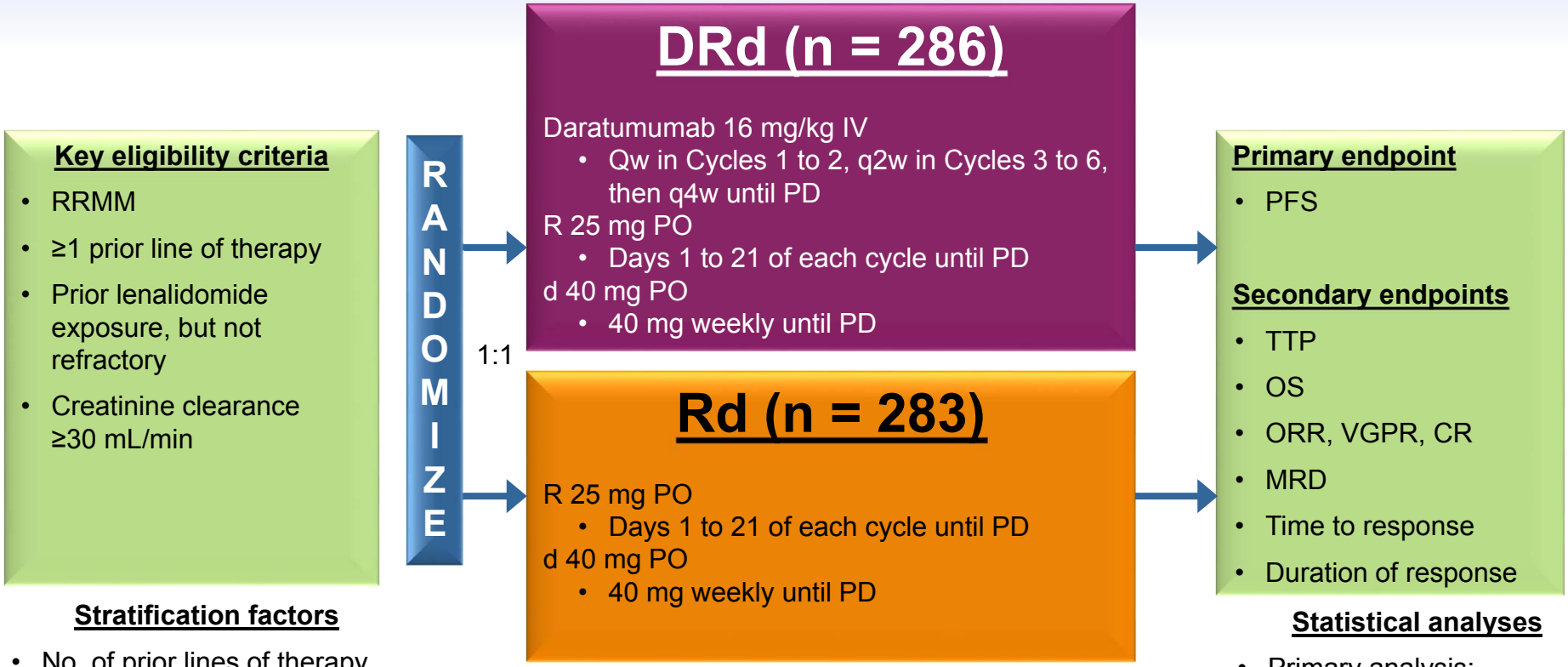


MoA, mechanism of action; RRMM, relapsed or refractory multiple myeloma ; FDA, Food and Drug Administration; EMA, European Medicines Agency; CDC, complement-mediated cytotoxicity; ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody-dependent cellular phagocytosis.

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.

Study Design

Multicenter, randomized (1:1), open-label, active-controlled, phase 3 study



Stratification factors

- No. of prior lines of therapy
- ISS stage at study entry
- Prior lenalidomide

Cycles: 28 days

Statistical analyses

- Primary analysis: ~177 PFS events

Pre-medication for the DRd treatment group consisted of dexamethasone 20 mg,[a] acetaminophen, and an antihistamine

ISS, international staging system; DRd, daratumumab/lenalidomide/dexamethasone; IV, intravenous; qw, weekly; q2w, every 2 weeks; q4w, every 4 weeks; PD, progressive disease; R, lenalidomide; PO, oral; d, dexamethasone; Rd, lenalidomide/dexamethasone; 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.

[a]On daratumumab dosing days, dexamethasone 20 mg was administered as pre-medication on Day 1 and Day 2.

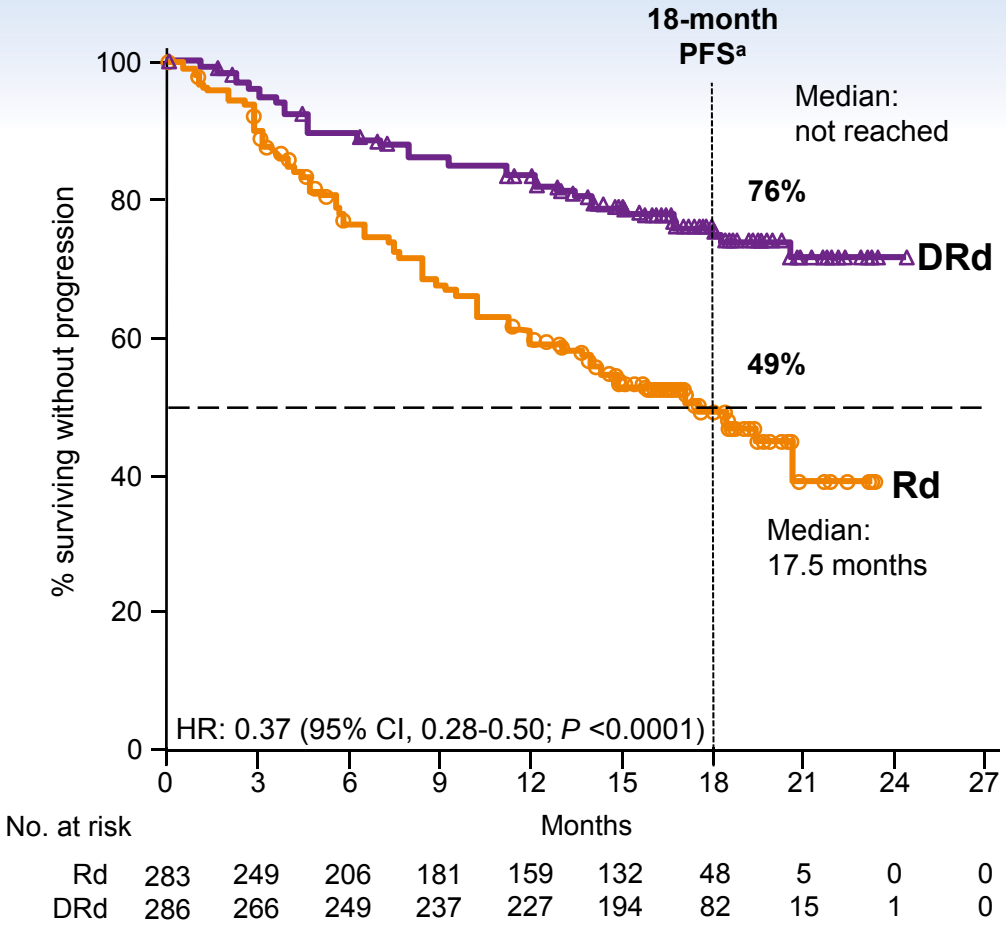
Baseline Demographic and Clinical Characteristics

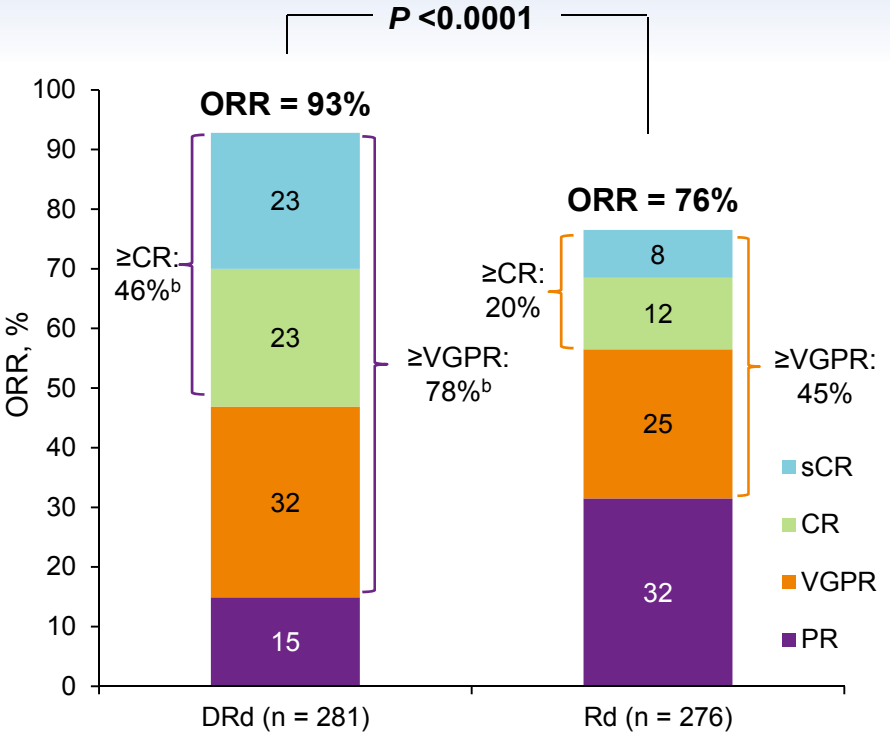
Characteristic	DRd (n = 286)	Rd (n = 283)
Age, y		
Median (range)	65 (34-89)	65 (42-87)
≥75, %	10	12
ISS stage, %[a]		
I	48	50
II	33	30
III	20	20
Median (range) time from diagnosis, y	3.48 (0.4-27.0)	3.95 (0.4-21.7)
Creatinine clearance (mL/min), %		
N	279	281
>30-60	28	23
>60	71	77
Cytogenetic profile, (%)[b]		
N	161	150
Standard risk	83	75
High risk	17	25

Characteristic	DRd (n = 286)	Rd (n = 283)
Prior lines of therapy, %		
Median (range)	1 (1-11)	1 (1-8)
1	52	52
2	30	28
3	13	13
>3	5	7
1-3[c]	95	93
Prior ASCT, %	63	64
Prior PI, %	86	86
Prior bortezomib, %	84	84
Prior IMiD, %	55	55
Prior lenalidomide, %	18	18
Prior PI + IMiD, %	44	44
Refractory to bortezomib, %	21	21
Refractory to last line of therapy, %	28	27

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]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.
[c]Exploratory.

Updated Efficacy



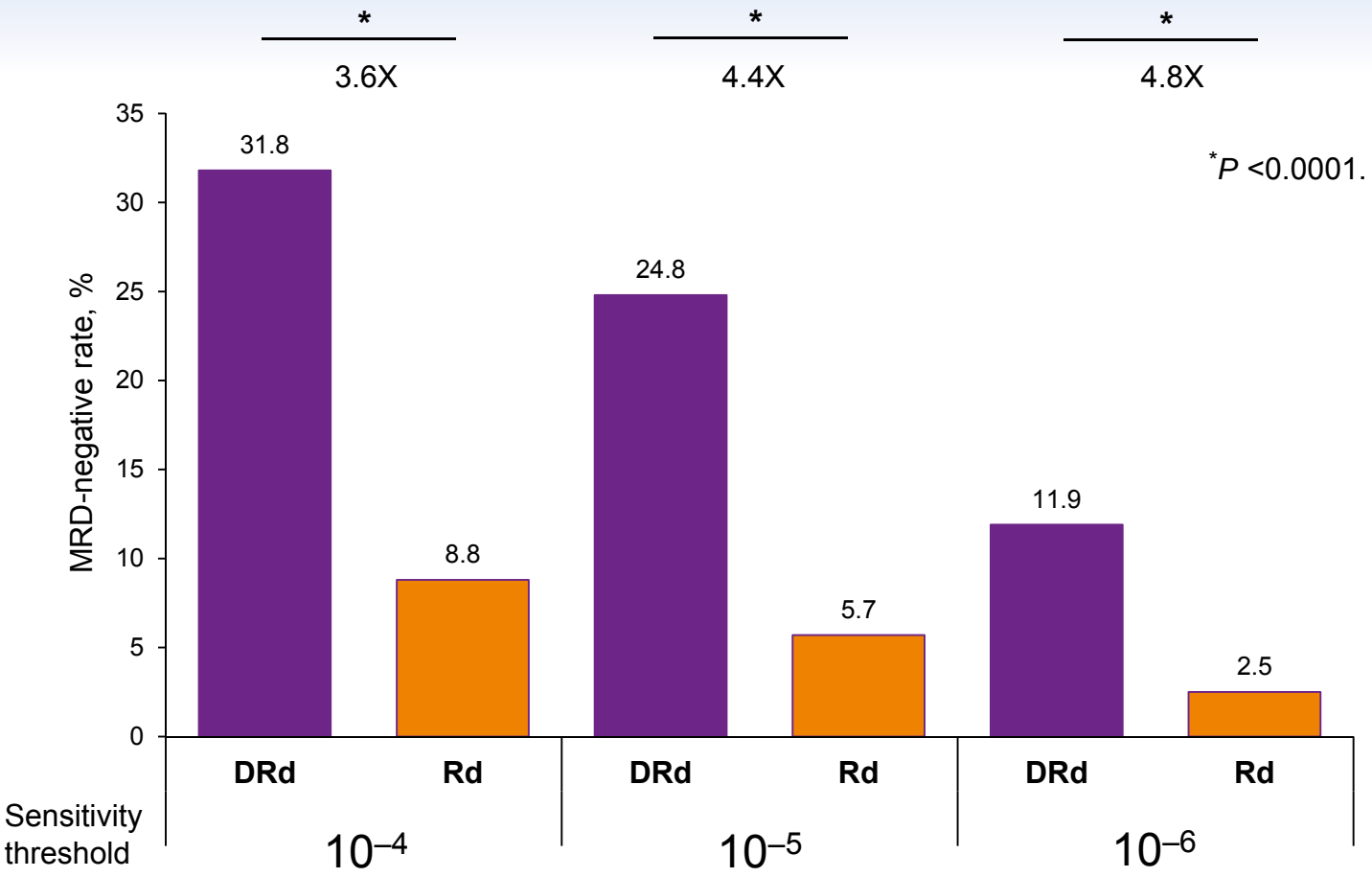


- **Median (range) follow-up: 17.3 (0-24.5) months**

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

HR, hazard ratio; CI, confidence interval; sCR, stringent complete response; PR, partial response.
Note: PFS = ITT population; ORR = response-evaluable population.
[a]Kaplan-Meier estimate;
[b]*P* <0.0001 for DRd vs Rd.

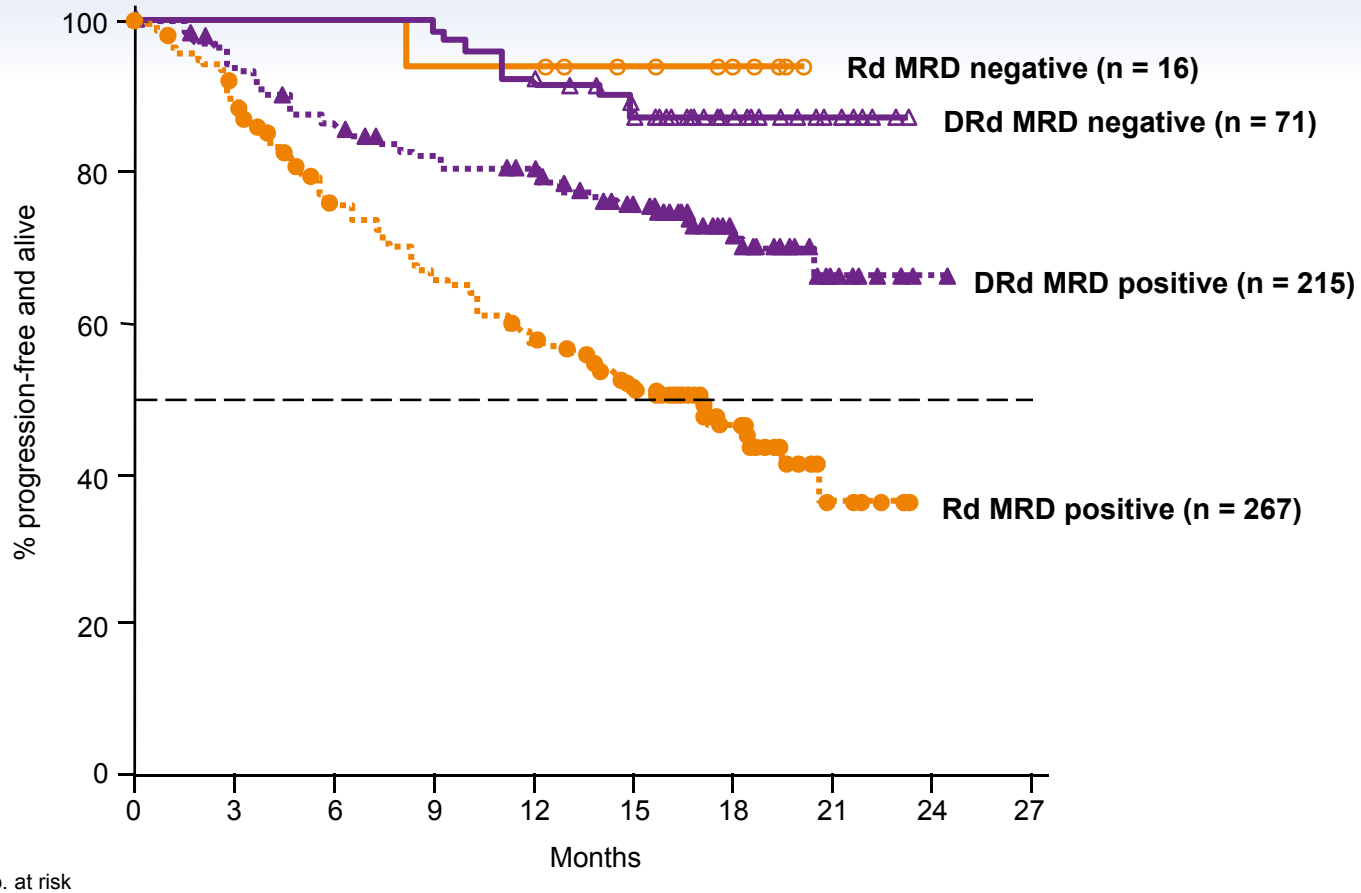
MRD-negative Rate



MRD-negative rates were >3-fold higher at all thresholds

Intent-to-treat population.
P values are calculated using likelihood-ratio chi-square test.

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



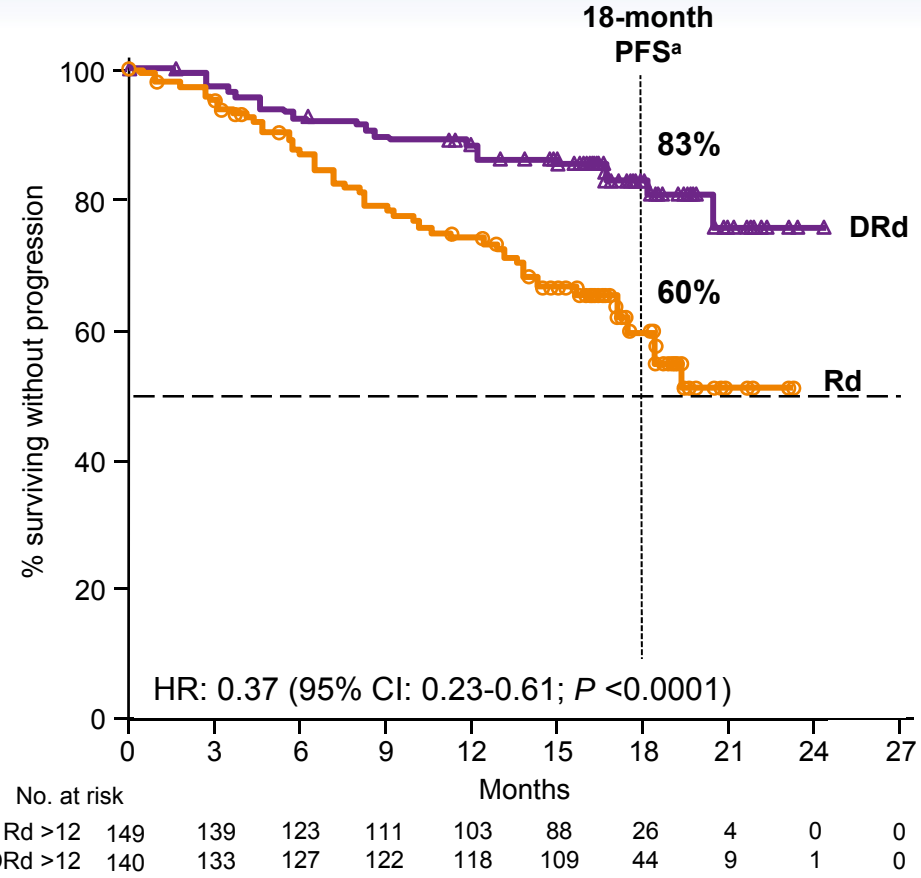
No. at risk										
Rd MRD negative	16	16	16	15	15	12	10	0	0	0
DRd MRD negative	71	71	71	70	66	57	28	6	0	0
Rd MRD positive	267	233	190	166	144	120	38	5	0	0
DRd MRD positive	215	195	178	167	161	137	54	9	1	0

MRD negativity is associated with better outcomes

Intent to treat population.

Time From Last Line of Therapy to Study Treatment of > or ≤12 Months

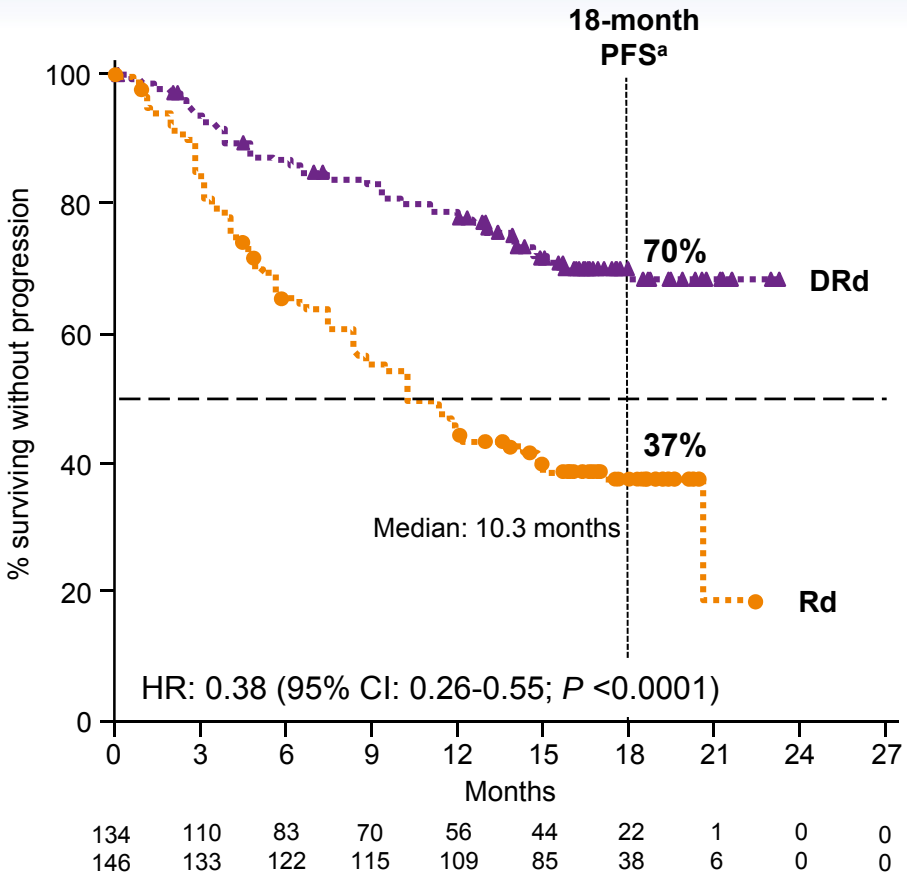
>12 Months



No. at risk

Rd >12	149	139	123	111	103	88	26	4	0	0
DRd >12	140	133	127	122	118	109	44	9	1	0

≤12 Months

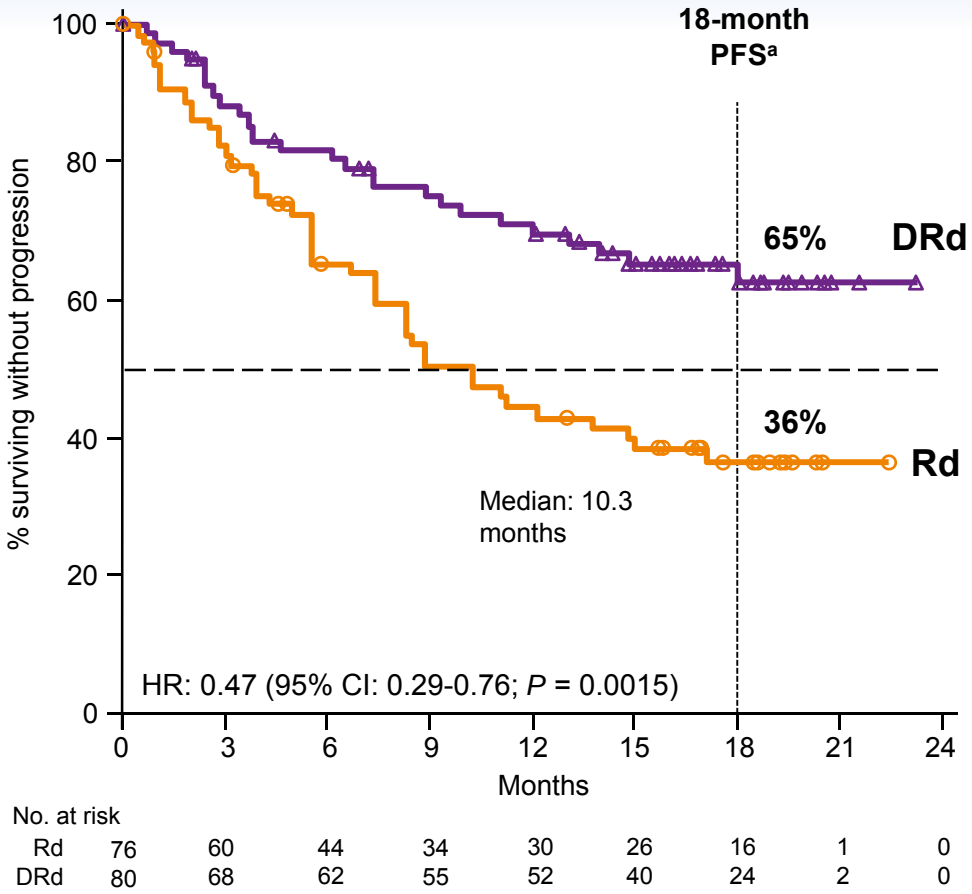


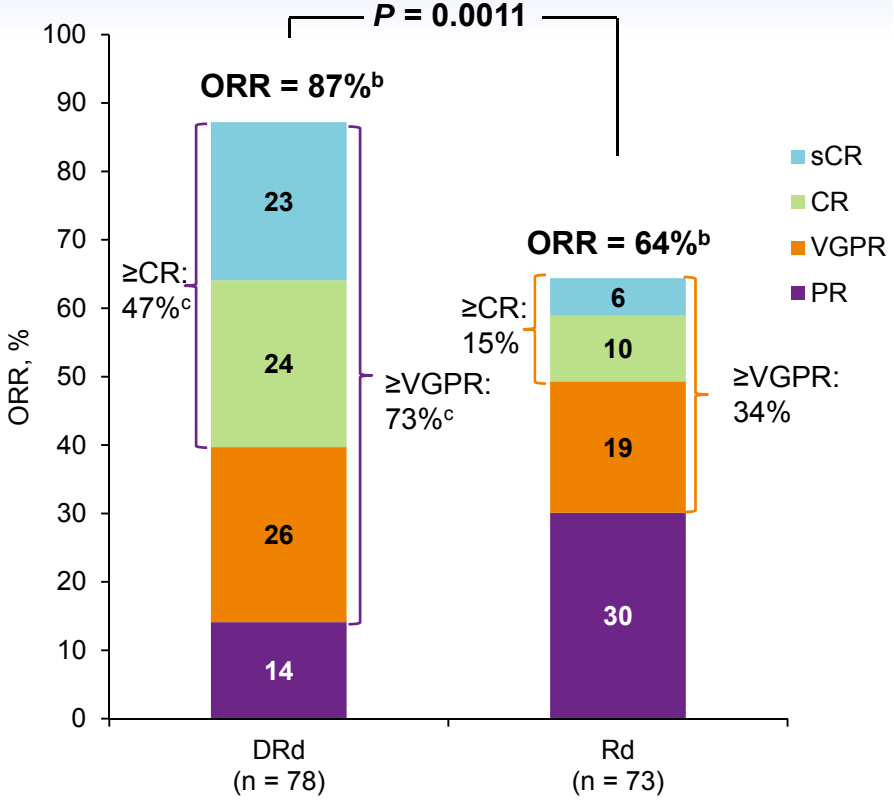
	134	110	83	70	56	44	22	1	0	0
	146	133	122	115	109	85	38	6	0	0

DRd is superior to Rd regardless of time since last therapy

[a]Kaplan-Meier estimate.
[b]Response-evaluable population.

Refractory to Last Line of Therapy



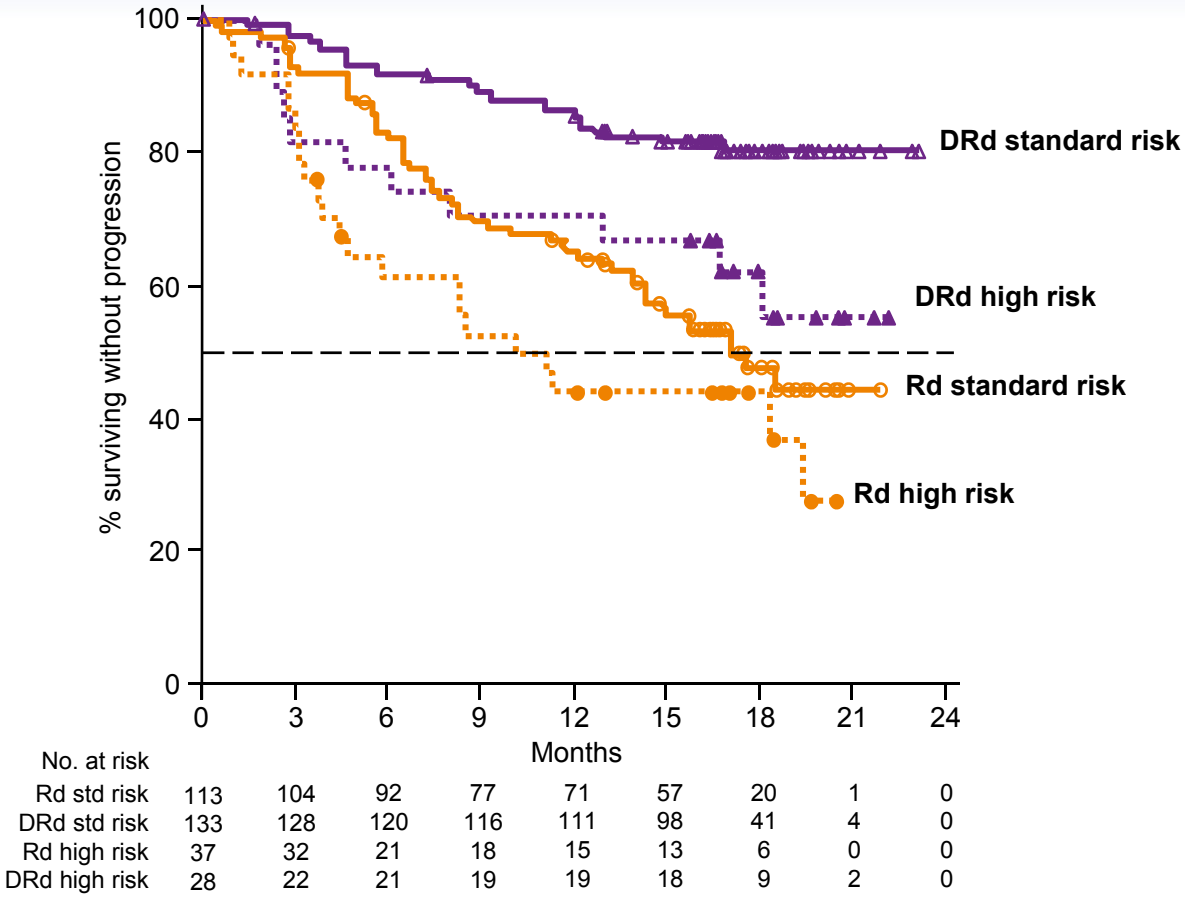


DRd benefits patients refractory to last line of therapy

[a]Kaplan-Meier estimate.
[b]Response-evaluable population.
[c]*P* <0.0001 for DRd vs Rd.

PFS: Cytogenetic Risk in All Evaluable Patients[a]

- **Comparable results in 1 to 3 prior lines population**



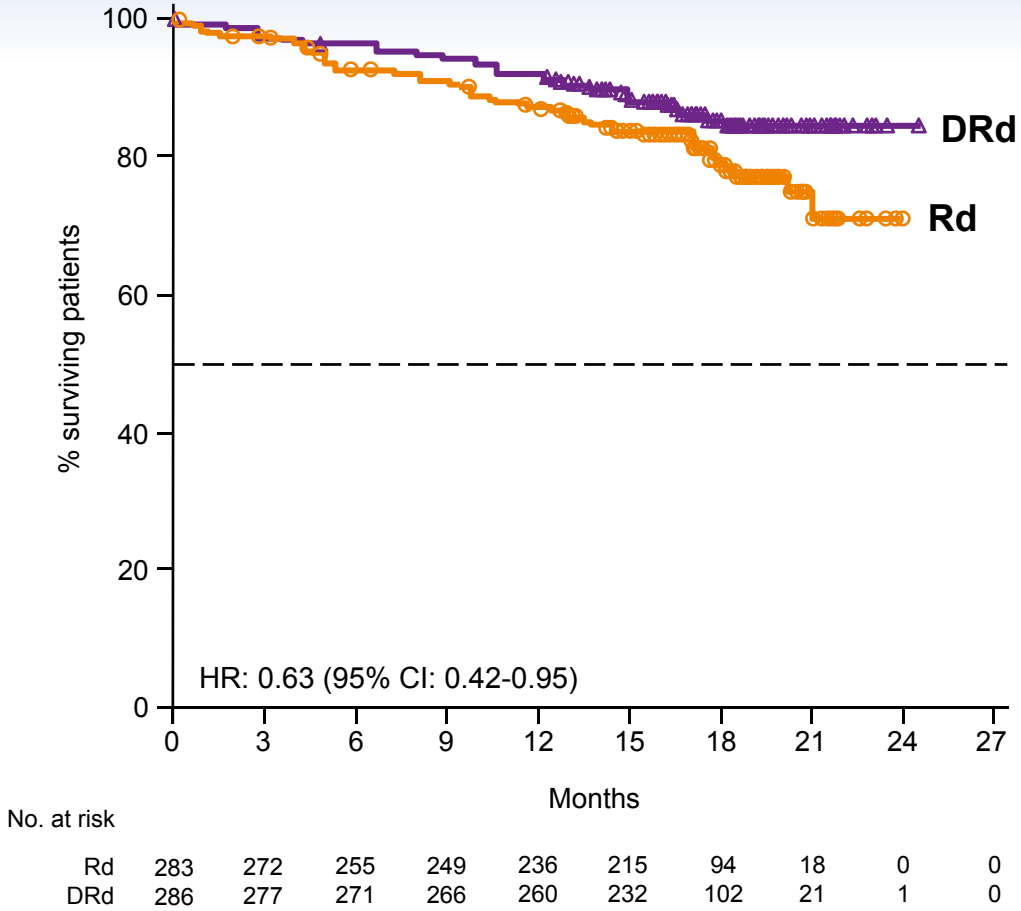
High risk	**DRd** n = 28	**Rd** n = 37
Median PFS, mo	**NR**	**10.2**
HR (95% CI)	0.44 (0.19-1.03)	
P value	0.0475	
	n = 27	n = 36
ORR, %	**85**	**67**
P value	NS	

Standard risk	**DRd** n = 133	**Rd** n = 113
Median PFS, mo	**NR**	**17.1**
HR (95% CI)	0.30 (0.18-0.49)	
P value	<0.0001	
	n = 132	n = 111
ORR, %	**95**	**82**
P value	0.0020	

DRd improves outcomes regardless of cytogenetic risk

NR, not reached; NS, not significant.
[a]ITT/Biomarker risk–evaluable analysis set. High-risk patients had any of t(4;14), t(14;16), or del17p. Standard-risk patients had an absence of high-risk abnormalities.

OS



- **OS events[a]**
  - 40 (14%) in DRd
  - 56 (20%) in Rd

Curves are beginning to separate, but OS data are immature

Intent-to-treat population.
Median OS was not reached; results did not cross the prespecified stopping boundary.

Summary of Efficacy Results: 1 to 3 Prior Lines Subgroup

	DRd	Rd
PFS		
Median, mo	NR[a]	18.4
HR (95% CI)	0.36 (0.26-0.49)	–
ORR, %	94[a]	78
≥CR, %	47[a]	20
≥VGPR, %	78[a]	46
MRD-negative rates, %		
10^{-4}	32[a]	9
10^{-5}	25[a]	6
10^{-6}	12[a]	3
Time from last line of tx to study tx: >12 months		
Median, mo	NR	NR
PFS HR (95% CI)	0.38 (0.23-0.63)[a]	–
ORR, %	94[b]	84
Time from last line of tx to study tx: ≤12 months		
Median, mo	NR	10.3
PFS HR (95% CI)	0.35 (0.23-0.53)[a]	–
ORR, %	90[a]	66
Refractory to last line of therapy		
Median, mo	NR	8.8
PFS HR (95% CI)	0.45 (0.27-0.74)[b]	–
ORR, %	89[b]	63
OS HR (95% CI)	0.69 (0.46-1.05)	–

NR, not reached; tx, treatment.
[a]*P* <0.0001 for DRd vs Rd.
[b]*P* <0.01 for DRd vs Rd.

Most Common AEs (All Patients): Updated Analysis

	DRd (n = 283)		Rd (n = 281)	
Hematologic, %	**All grade ≥25%[a]**	**Grade 3/4 ≥5%[a]**	**All grade ≥25%[a]**	**Grade 3/4 ≥5%[a]**
Neutropenia	60	53	44	38
Febrile neutropenia	6	6	3	3
Anemia	34	14	36	21
Thrombocytopenia	28	13	30	15
Lymphopenia	6	5	5	4
Nonhematologic, %				
Diarrhea	47	6	28	3
Fatigue	35	6	29	3
Upper respiratory tract infection	33	1	23	1
Cough	30	0	13	0
Constipation	30	1	26	0.7
Muscle spasms	27	0.7	20	2
Nasopharyngitis	26	0	17	0
Nausea	25	1	16	0.4
Pneumonia	16	9	13	8

No new safety signals reported

[a]Common treatment-emergent AEs listed are either ≥25% all grade OR ≥5% grade 3/4.

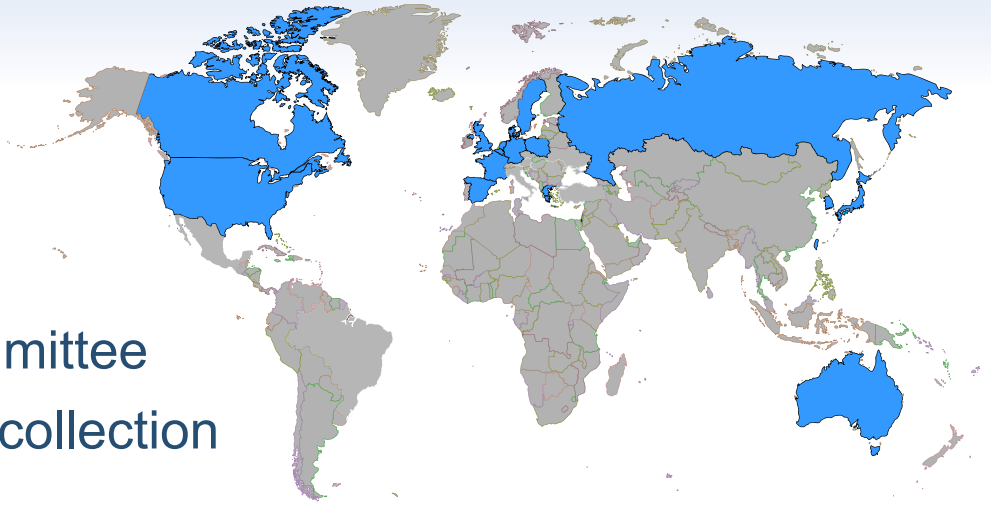
Conclusions

- DRd significantly improved outcomes for patients with myeloma
  - 63% reduction in risk of progression or death for DRd versus Rd
  - Similar findings observed across all analyses in the 1 to 3 prior lines population
- More patients achieve deeper responses including MRD negativity with DRd
- DRd is superior to Rd regardless of time since last therapy, refractoriness to last line of therapy, or cytogenetic risk
- Safety profile remains unchanged

These data support the use of DRd for patients who received ≥1 prior therapy regardless of risk status or refractoriness to prior treatment

Acknowledgments

- **Patients who participated in this study**
- Investigators
- Data and safety monitoring committee
- Staff members involved in data collection and analyses
  - David Soong and Christopher Velas



18 countries

- This study was funded by Janssen Research & Development, LLC
- Medical writing and editorial support were provided by Jason Jung, PhD, of MedErgy, and were funded by Janssen Global Services, LLC