Daratumumab plus lenalidomide and dexamethasone *versus* lenalidomide and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of POLLUX

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APPENDIX

Daratumumab plus lenalidomide and dexamethasone versus lenalidomide and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of POLLUX

METHODS

Safety

Safety assessments included evaluation of adverse events, vital signs, electrocardiograms, physical examinations, and clinical laboratory tests. Patients who discontinued treatment were assessed for safety at follow-up.

Minimal Residual Disease

Minimal residual disease (MRD) was evaluated on bone marrow aspirates that were prepared with Ficoll using the clonoSEQ™ V1.3 assay (Adaptive Biotechnologies, Seattle, WA, USA) at sensitivities of 0.001% (1 cancer cell per 100,000 nucleated cells or 10^{-5}) and 0.0001% (10^{-6}). To allow for stringent, unbiased MRD evaluation, the entire intent-to-treat population was evaluated, and patients were considered MRD positive if they had MRD-positive test results or no MRD assessment.

Cytogenetic Risk

For t(4;14), translocations were detected via RNA-seq reads fused between immunoglobulin heavy locus and *WHSC1* or *FGFR3*. For t(14;16), translocations involved immunoglobulin heavy locus and *WWOX*. Tophat-Fusion[1] and deFuse[2] were used for translocation detection. For del17p detection using exome-seq, a >50% deletion cut-off of the 17p region was utilized with CNVkit[3] and CNV Radar (manuscript in preparation).

Health-related Quality of Life Measures

Changes from baseline with the EuroQol 5-Dimension Questionnaire Utility and Visual Analog Scale Scores and the European Organization for Research and Treatment of Cancer Quality of

Life Questionnaire Core-30 Global Health Status Score were assessed every 4 weeks up to Week 116 using a Mixed Model for Repeated Measures (missing at random).

Statistical Analyses

Progression-free survival was compared between treatment groups based on a stratified log-rank test. Hazard ratios and 95% confidence intervals were estimated using a Cox regression model with treatment as the sole explanatory variable, and the Kaplan-Meier method was used to estimate the distributions. Stratified Cochran-Mantel-Haenszel tests were used to test treatment differences in overall response rate and rates of very good partial response or better and complete response or better.

Appendix Table 1. Best Confirmed Response in the Response-evaluable Population

	D-Rd (n = 281)	Rd (n = 276)
ORR, n (%)[a]	261 (92.9)	211 (76.4)
≥CR[a]	144 (51.2)	58 (21.0)
sCR	73 (26.0)	24 (8.7)
CR	71 (25.3)	34 (12.3)
≥VGPR[a]	221 (78.6)	132 (47.8)
VGPR	77 (27.4)	74 (26.8)
PR	40 (14.2)	79 (28.6)
MR	5 (1.8)	26 (9.4)
SD	13 (4.6)	33 (12.0)
PD	0 (0.0)	4 (1.4)
NE	2 (0.7)	2 (0.7)

D-Rd, daratumumab/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; ORR, overall response rate; CR, complete response; sCR, stringent complete response; VGPR, very good partial response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease; NE, not evaluable.

[a]*P* <0.0001 for D-Rd versus Rd.

Appendix Table 2. Progression-free Survival of Other Immunomodulatory Drug-containing Regimens by Subgroup

ASPIRE[4-6]

	1PL		2-3PL		Prior lenalidomide		Nonresponsive to bortezomib		Early disease relapse[a]	
Median PFS, mo	KRd 29.6	Rd 17.6	KRd 25.8	Rd 16.7	KRd N/A	Rd N/A	KRd N/A	Rd N/A	KRd 24.1	Rd 12.5
HR	0.69		0.69		0.80		0.80		0.75	
95% CI	N/A		N/A		0.52-1.22		0.49-1.30		0.50-1.13	
***P* value**	0.0083		0.0017		N/A		N/A		N/A	

ELOQUENT-2[7,8]

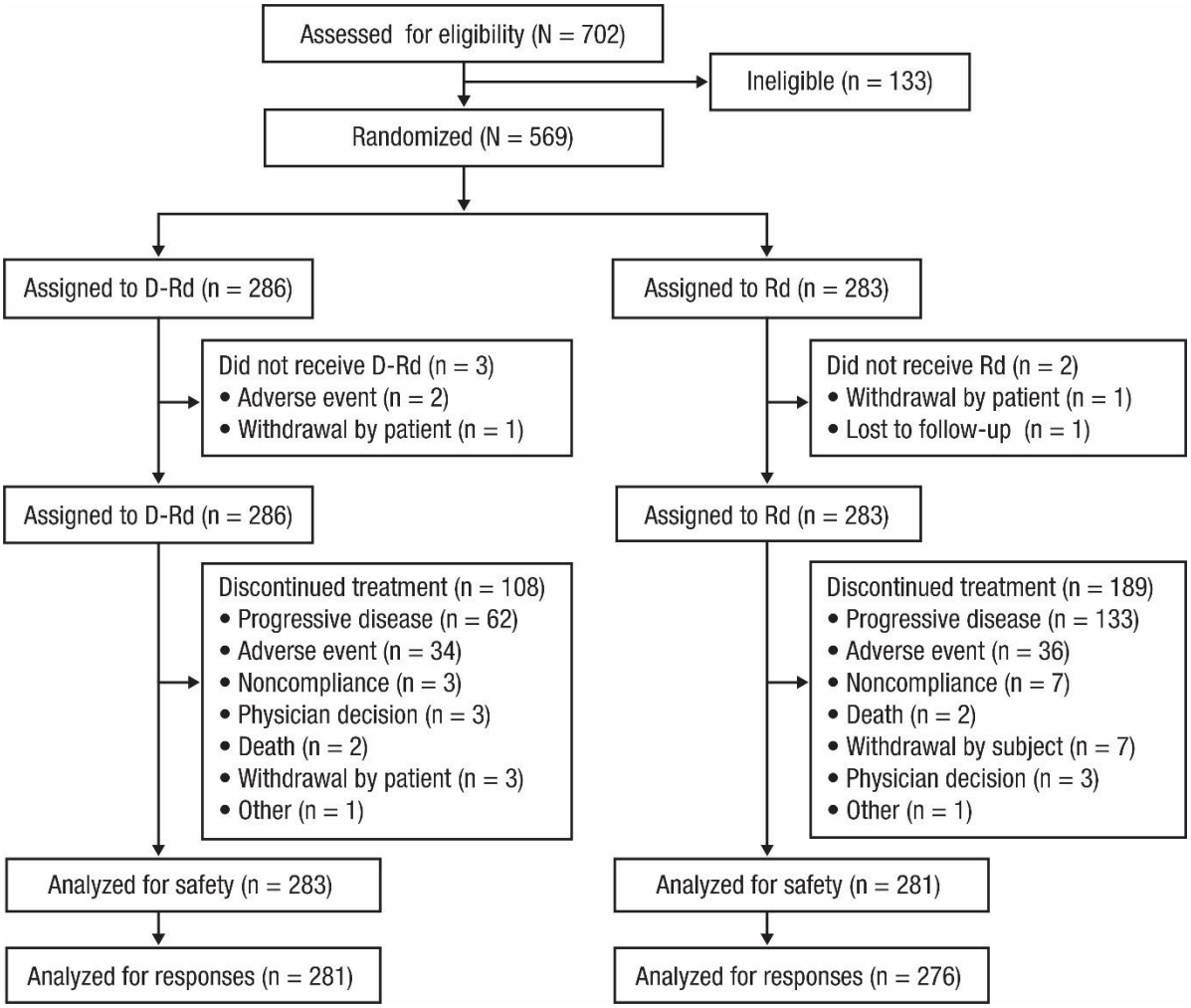
	1PL		2-3PL		Prior lenalidomide		Prior bortezomib	
Median PFS, mo	ERd N/A	Rd N/A	ERd N/A	Rd N/A	ERd 24.9	Rd 7.4	ERd 18.5	Rd 12.9
HR	0.75		0.65		0.55		0.68	
95% CI	0.56-1.00		0.49-0.87		0.24-1.25		0.55-0.85	
***P* value**	N/A		N/A		N/A		N/A	

TOURMALINE-MM1[9]

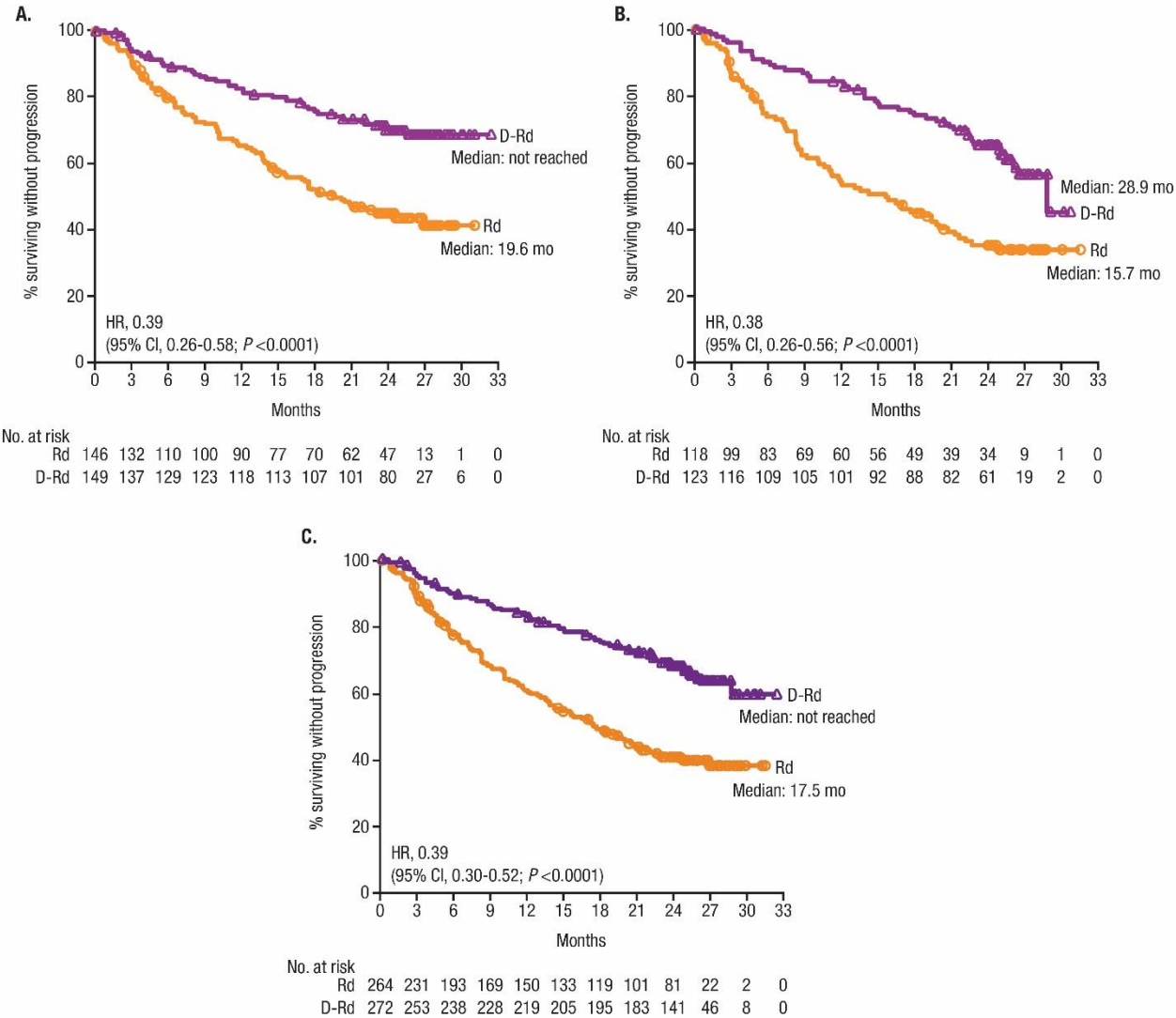
	1PL		2PL		3PL		Prior IMiD		Prior PI		Refractory to last line of therapy	
Median PFS, mo	NRd 20.6	Rd 15.9	NRd 17.5	Rd 14.1	NRd NE	Rd 10.2	NRd NE	Rd 17.5	NRd 18.4	Rd 13.6	NRd NE	Rd NE
HR	0.83		0.75		0.37		0.74		0.74		0.71	
95% CI	N/A		N/A		N/A		N/A		N/A		N/A	
***P* value**	N/A		N/A		N/A		N/A		N/A		N/A	

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; PL, prior line; KRd, carfilzomib/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; N/A, not available; ERd, elotuzumab/lenalidomide/dexamethasone; IMiD, immunomodulatory drug; PI, proteasome inhibitor; NRd, ixazomib/lenalidomide/dexamethasone; NE, not evaluable.

[a]≤12 months from starting the first prior regimen.



Appendix Figure 1. CONSORT diagram for POLLUX. Flow diagram of patients in POLLUX who were randomized to treatment, analyzed, and discontinued treatment. D-Rd, daratumumab/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone.



Appendix Figure 2. Progression-free survival in patients who received (A) 1 prior line of therapy, (B) 2 to 3 prior lines of therapy, and (C) 1 to 3 prior lines of therapy. Kaplan-Meier estimates of progression-free survival among patients in the intent-to-treat population. D-Rd, daratumumab/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval.

References

1. Kim D, Salzberg SL. TopHat-Fusion: An algorithm for discovery of novel fusion transcripts. Genome Biol. 2011;12(8):R72.

2. McPherson A, Hormozdiari F, Zayed A, et al. deFuse: An algorithm for gene fusion discovery in tumor RNA-Seq data. PLoS Comput Biol. 2011;7(5):e1001138.

3. Talevich E, Shain AH, Botton T, Bastian BC. CNVkit: Genome-wide copy number detection and visualization from targeted DNA sequencing. PLoS Comput Biol. 2016;12(4):e1004873.

4. Dimopoulos A, Stewart AK, Rajkumar SV, et al. Effect of carfilzomib, lenalidomide, and dexamethasone (KRd) vs lenalidomide and dexamethasone (Rd) in patients with relapsed multiple myeloma (RMM) by line of therapy: secondary analysis from an interim analysis of the phase III study ASPIRE (NCT01080391). J Clin Oncol. 2015;33(15_suppl):8525.

5. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med. 2015;372(2):142–152.

6. Ludwig H, Dimopoulos MA, Masszi T, et al. Carfilzomib, lenalidomide, and dexamethasone (KRd) vs lenalidomide and dexamethasone (Rd) in patients with relapsed multiple myeloma (RMM) and early progression during prior therapy: Secondary analysis from the phase 3 study ASPIRE (NCT01080391). J Clin Oncol. 2016;34(15_suppl):8045.

7. Lonial S, Richardson PG, Mateos MV, et al. ELOQUENT-2 update: Phase III study of elotuzumab plus lenalidomide/dexamethasone (ELd) vs Ld in relapsed/refractory multiple myeloma (RRMM)—identifying responders by subset analysis. J Clin Oncol. 2016;34(15_suppl):8037.

8. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. N Engl J Med. 2015;373(7):621–631.

9. Moreau P, Masszi T, Grzasko N, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2016;374(17):1621–1634.