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Daratumumab, Lenalidomide, and Dexamethasone (DRd) Versus Lenalidomide and Dexamethasone (Rd) in Relapsed or Refractory Multiple Myeloma (RRMM) Based on Prior Treatment History, Renal Function, and Cytogenetic Risk: Subgroup Analyses of POLLUX

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INTRODUCTION

- Daratumumab is a human, anti-CD38 monoclonal antibody with on-tumor and immunomodulatory mechanisms of action[1-4]
- A pooled analysis of daratumumab monotherapy studies (GEN501 and SIRIUS) demonstrated that daratumumab achieved deep and durable responses in patients with relapsed or refractory (RR) multiple myeloma (MM) with a manageable safety profile[5]
- In 2 randomized, open-label, active-controlled, phase 3 studies of daratumumab in combination with standard of care regimens (lenalidomide and dexamethasone [Rd] in POLLUX[6] or bortezomib and dexamethasone [Vd] in CASTOR[7]), daratumumab-based regimens demonstrated superior clinical benefit in patients with MM who had received ≥1 prior line of therapy
  - Daratumumab plus Rd or Vd significantly improved minimal residual disease (MRD)-negative rates[8]
    - At a sensitivity threshold of 10^{-5}, MRD-negative rates were >4-fold higher
    - MRD-negative status prolonged progression-free survival (PFS)
- More recently, a phase 1b study revealed daratumumab's efficacy in combination with pomalidomide and dexamethasone in patients with MM who had received ≥2 prior lines of therapy[11]
- Based on the findings from these pivotal studies, the US Food and Drug Administration (FDA) and European Commission approved daratumumab in combination with Rd (DRd) or Vd (DVd) for the treatment of patients with MM who had received ≥1 prior therapy[12]
- The FDA also recently approved daratumumab in combination with pomalidomide and dexamethasone for the treatment of patients with MM who had received ≥2 prior therapies, including lenalidomide and a proteasome inhibitor[12]
- The analysis presented here assessed the efficacy of DRd versus Rd in clinically relevant subgroups of patients treated in POLLUX

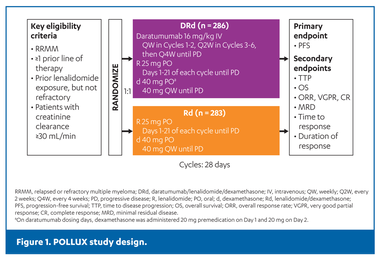
METHODS

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 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
- Patients with prior lenalidomide exposure or who were refractory to bortezomib were allowed in the study
- Key exclusion criteria were as follows:
  - Neutrophil count ≤1.0 × 10^9/L
  - Hemoglobin ≤7.5 g/dL
  - Platelet count <75 × 10^9/L
  - Creatinine clearance <30 mL/min/1.73 m^2
  - Alanine aminotransferase or aspartate aminotransferase ≥2.5 times the upper limit of normal (ULN)
  - Alkaline phosphatase ≥2.5 times the ULN
  - Bilirubin ≥1.5 times the ULN
  - Patients refractory or intolerant to lenalidomide

Study Design and Treatment

- This was a multicenter, randomized (1:1), open-label, active-controlled, phase 3 study of patients with RRMM (**Figure 1**)



RRMM, relapsed or refractory multiple myeloma; 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 disease progression; OS, overall survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease.
*On daratumumab dosing days, dexamethasone was administered 20 mg premedication on Day 1 and 20 mg on Day 2.

Figure 1. POLLUX study design.

- Randomization was stratified by the International Staging System (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 lenalidomide (no vs yes)
- All patients received cycles of Rd (28 days/cycle) until disease progression, withdrawal of consent, or unacceptable toxicity
  - Lenalidomide was administered orally (PO) at a dose of 25 mg on Days 1 through 21 of each cycle
  - Dexamethasone was administered at a dose of 40 mg PO per week
    - During weeks when daratumumab was administered, half of the dexamethasone dose was given on the day of infusion via intravenous (IV) or PO administration and half was given PO the day after the daratumumab infusion
    - Patients ≥75 years of age received a dose of 20 mg PO per week
      - During weeks when daratumumab was administered, patients received the entire 20-mg dose prior to the daratumumab infusion
  - For patients assigned to DRd, daratumumab 16 mg/kg IV was administered weekly (QW; Days 1, 8, 15, and 22) during Cycles 1 and 2, every 2 weeks (Q2W; Days 1 and 15) during Cycles 3 through 6, and every 4 weeks thereafter
- The primary endpoint was PFS
- Secondary endpoints included time to disease progression, overall response rate (ORR), proportion of patients achieving very good partial response (VGPR) or better, MRD, duration of and time to response, and overall survival
- Exploratory analyses were conducted within patient subgroups defined by number of prior lines of therapy (1, 2, 3, and 1-3), prior lenalidomide exposure, refractoriness to bortezomib, moderately impaired renal function (glomerular filtration rate >30-60 mL/min), prior autologous stem cell transplantation (ASCT), and cytogenetic risk status

Cytogenetic Risk Evaluation

- Bone marrow aspirates were collected at screening visits, and cytogenetic abnormalities were detected via next-generation sequencing
- Patients were considered to be of high cytogenetic risk status if they had ≥1 of the following abnormalities: t(4;14), t(14;16), or del17p
  - >50% cut-off was used for del17p
- Patients were considered to be of standard cytogenetic risk if they underwent cytogenetic testing and did not meet the high-risk criteria

MRD Evaluation

- MRD was assessed at the time of suspected complete response (CR; blinded to treatment group) and at 3,6, and every 12 months after achievement of CR
- MRD was assessed on bone marrow aspirate samples that were ficolled and evaluated using the clonoSEQ® assay V2.0 (Adaptive Biotechnologies, Seattle, WA, USA) at sensitivity thresholds of 10^{-6} (1 cancer cell per 10,000 nucleated cells), 10^{-5}, and 10^{-6}
  - clonoSEQ® assay V2.0 demonstrates increased calibration rates compared to V1.3 (85% vs 72%, respectively) in patients with a confirmed response of ≥CR with an available sample
- 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 assessments were considered MRD positive

Statistical Analyses

- Efficacy analyses were based on the intent-to-treat (ITT) population
- The safety analysis set included all patients who received ≥1 administration of study treatment
- 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 proportions of MRD-negative patients between treatment arms were compared using the likelihood-ratio test
- MRD-negative rates were based on the ITT population

RESULTS

Patients and Treatments

- A total of 569 patients were enrolled (DRd, n = 286; Rd, n = 283)
- Demographic, baseline disease, and clinical characteristics were well balanced (**Table 1**)
- Patients received a median (range) of 1 (1-11) prior line of therapy; 52% of patients received 1 prior line of therapy and 6% of patients received >3 prior lines of therapy
- In the ITT population, 18% of patients were pretreated with lenalidomide and 21% were refractory to bortezomib

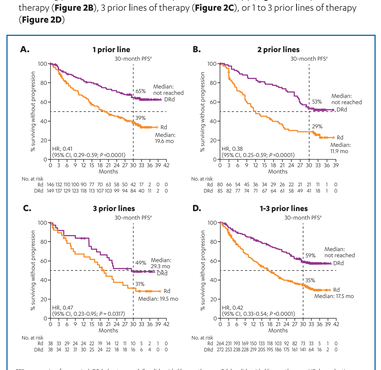
Table 1. Patient Demographic, Baseline Disease, and Clinical Characteristics (ITT)

Characteristic	DRd (n = 286)	Rd (n = 283)
Age, y		
Median (range)	65 (34-89)	65 (42-87)
≥75, %	10	12
ISS,[a] %		
I	48	50
II	33	30
III	20	20
Time from diagnosis, y		
Median (range)	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
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 to 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

ITT, intent-to-treat; DRd, daratumumab/lenalidomide/dexamethasone; Rd, lenalidomide/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]Cytogenetic risk was established by centralized analysis using next-generation sequencing. Patients with high-risk cytogenetics had t(4;14), t(14;16), or del17p abnormalities. Patients with standard-risk cytogenetics had an absence of high-risk abnormalities.
[c]Exploratory.

PFS With DRd Versus Rd by Number of Prior Lines of Therapy

- After a median follow-up of 32.9 months, DRd significantly prolonged PFS compared with Rd among patients who had received 1 prior line of therapy (**Figure 2A**), 2 prior lines of therapy (**Figure 2B**), 3 prior lines of therapy (**Figure 2C**), or 1 to 3 prior lines of therapy (**Figure 2D**)

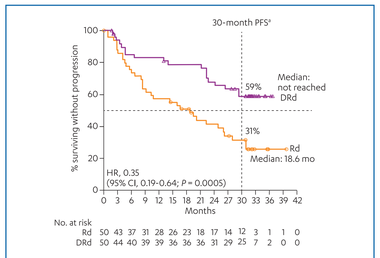


PFS, progression-free survival; DRd, daratumumab/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval.
*Kaplan-Meier estimate.

Figure 2. PFS with DRd versus Rd in patients who had received (A) 1 prior line of therapy, (B) 2 prior lines of therapy, (C) 3 prior lines of therapy, or (D) 1 to 3 prior lines of therapy.

Efficacy of DRd Versus Rd Among Patients With Prior Lenalidomide Exposure

- DRd significantly prolonged PFS compared with Rd among patients with prior lenalidomide exposure (**Figure 3**)

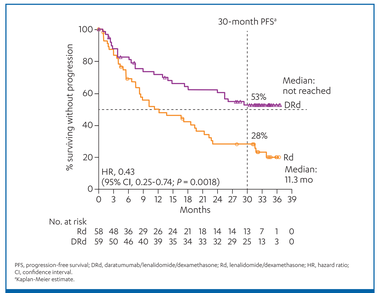


PFS, progression-free survival; DRd, daratumumab/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval.
*Kaplan-Meier estimate.

Figure 3. PFS with DRd versus Rd in patients with prior lenalidomide exposure.

Efficacy of DRd Versus Rd Among Patients Refractory to Bortezomib

- DRd significantly prolonged PFS compared with Rd among patients refractory to bortezomib (**Figure 4**)

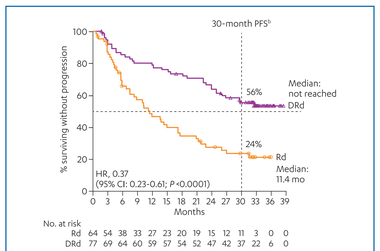


PFS, progression-free survival; DRd, daratumumab/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval.
*Kaplan-Meier estimate.

Figure 4. PFS with DRd versus Rd in patients refractory to bortezomib.

Efficacy of DRd Versus Rd Among Patients With Moderately Impaired Renal Function

- DRd significantly prolonged PFS compared with Rd among patients with moderately impaired renal function (**Figure 5**)



PFS, progression-free survival; DRd, daratumumab/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval.
[a]Baseline glomerular filtration rate >30-60 mL/min.
*Kaplan-Meier estimate.

Figure 5. PFS with DRd versus Rd in patients with moderately impaired renal function.[a]

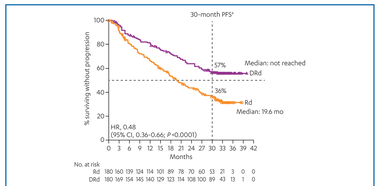
Table 2. Response Rates With DRd Versus Rd in Patient Subgroups

	Study population		1 prior line		2 prior lines		3 prior lines		1 to 3 prior lines		Prior lenalidomide		Bortezomib refractory		Moderately impaired renal function[b]		Prior ASCT		High risk		Standard risk	
Response, %	DRd	Rd	DRd	Rd	DRd	Rd	DRd	Rd	DRd	Rd	DRd	Rd	DRd	Rd	DRd	Rd	DRd	Rd	DRd	Rd	DRd	Rd
ORR[a]																						
N	281	276	147	142	84	79	36	36	267	257	50	47	57	56	77	63	178	177	27	36	132	111
%	93	76	93	80	95	73	94	75	94	77	84	64	88	68	91	68	92	79	85	67	95	82
P	<0.0001		0.0003		0.0002		0.0180		<0.0001		0.0233		0.0113		0.0008		0.0004		0.0435		0.0004	
≥VGPR,%[a]	80	49	78	56	82	42	89	36	81	49	80	36	75	41	73	43	78	50	67	31	86	56
P	<0.0001		<0.0001		<0.0001		<0.0001		<0.0001		<0.0001		0.0002		0.0002		<0.0001		0.0065		<0.0001	
≥CR, %[a]	55	23	57	27	56	19	53	11	56	22	54	12	51	16	55	18	51	24	41	6	63	29
P	<0.0001		<0.0001		<0.0001		<0.0001		<0.0001		<0.0001		<0.0001		<0.0001		<0.0001		NR		NR	
sCR, %[a]	28	9	29	11	27	8	22	3	28	9	26	2	26	4	29	8	24	10	19	0	38	9
MRD-negative rate (10^{-5})[c]																						
N	286	283	149	146	85	80	38	38	272	264	50	50	59	58	77	64	180	180	28	37	133	113
%	27	5	26	7	29	5	26	0	27	5	26	6	22	5	29	6	26	4	11	0	13	1
P	<0.000001		0.000008		0.000016		0.000088		<0.0001		0.0049		0.0061		0.000359		<0.000001		0.0220		<0.0001	

DRd, daratumumab/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; ASCT, autologous stem cell transplantation; ORR, overall response rate; VGPR, very good partial response; NR, not reported; CR, complete response; sCR, stringent complete response; MRD, minimal residual disease; ITT, intent-to-treat.
[a]Based on the response-evaluable population (response/biomarker risk–evaluable analysis set for patients with high- and standard-risk cytogenetic status).
[b]Baseline glomerular filtration rate <30-60 mL/min.
[c]Based on the ITT population (ITT/biomarker risk–evaluable analysis set for patients with high- and standard-risk cytogenetic status).

Efficacy of DRd Versus Rd Among Patients With Prior ASCT

- DRd significantly prolonged PFS compared with Rd among patients with prior ASCT (**Figure 6**)

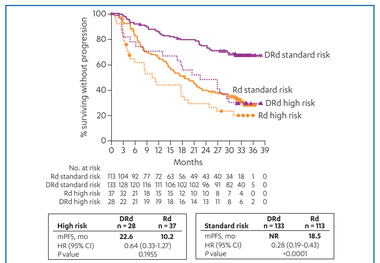


PFS, progression-free survival; DRd, daratumumab/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval.
*Kaplan-Meier estimate.

Figure 6. PFS with DRd versus Rd in patients with prior ASCT.

Efficacy of DRd Versus Rd by Cytogenetic Risk Status

- DRd prolonged PFS compared with Rd among patients with either high-risk or standard-risk cytogenetics (**Figure 7**)



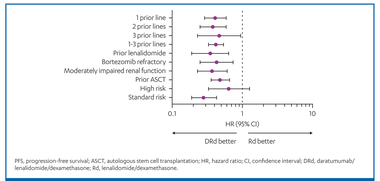
High risk	DRd n = 28	Rd n = 37
mPFS, mo	22.6	10.2
HR (95% CI)	0.64 (0.33-1.27)	
P value	0.1955	

Standard risk	DRd n = 133	Rd n = 113
mPFS, mo	NR	18.5
HR (95% CI)	0.28 (0.19-0.43)	
P value	<0.0001	

PFS, progression-free survival; DRd, daratumumab/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; mPFS, median progression-free survival; HR, hazard ratio; CI, confidence interval; NR, not reached; ITT, intent-to-treat.
*ITT/biomarker risk–evaluable analysis set: patients in the ITT population with both RNA and DNA results available.

Figure 7. PFS with DRd versus Rd in patients with high-risk and standard-risk cytogenetics.*

- A forest plot summarizing the PFS subgroup analyses of DRd versus Rd is shown in **Figure 8**



PFS, progression-free survival; ASCT, autologous stem cell transplantation; HR, hazard ratio; CI, confidence interval; DRd, daratumumab/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone.

Figure 8. PFS subgroup analyses.

Response Rates and MRD Negativity at 10^{-5} in Patient Subgroups

- ORRs, rates of deeper responses (≥CR), and MRD-negative rates were higher with DRd versus Rd in all patient subgroups (**Table 2**)

CONCLUSIONS

- **With a median follow-up of 32.9 months, DRd improved PFS, ORR, ≥CR, and MRD-negative rates at 10^{-5} versus Rd in patients with RRMM, regardless of prior treatment history, cytogenetic risk, or moderate renal impairment**
- **Results from the POLLUX study suggest that DRd should be considered for patients with RRMM who relapse after lenalidomide-based therapies and for those refractory to bortezomib**

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DISCLOSURES

PM consulted for and received honoraria from Celgene, Takeda, Janssen, Novartis, and Amgen. AO received honoraria from and consulted for Takeda, Janssen, and Amgen; and served on speakers bureaus for Janssen and Amgen. JLK consulted for Amgen, Roche, BMS, Seattle Genetics, Sutro Biopharma, and Pharmacyclics; and received research funding from Amgen and Novartis. HS received honoraria from and consulted for Janssen, Celgene, and Amgen. ML received honoraria from Bristol-Myers Squibb and Celgene. SI received honoraria from Ono Pharmaceutical, Bristol-Myers Squibb, Celgene, Novartis, and Janssen; and served as a consultant for Ono Pharmaceutical, Takeda, Bristol-Myers Squibb, Sanofi, Chugai Pharma, Kyowa Hakko Kirin, Toyama Chemical Co, Astellas, Celgene, Novartis, and Janssen. MP received honoraria from Janssen, Celgene, Amgen, Novartis, and Takeda. TC received travel expenses from Bristol-Myers Squibb, Novartis, Celgene, and Takeda. LO and JS are employees of Janssen. JS holds equity in Johnson & Johnson. KW is a former employee of Janssen. NB consulted for and received honoraria and compensation for travel expenses from Celgene, Takeda, Janssen, and Amgen; served on advisory boards for Celgene, Takeda, Janssen, and Amgen; served on speakers bureaus for Celgene, Janssen, and Amgen; and received research funding from and provided expert testimony for Celgene and Janssen. HM and JSK have no conflicts of interest to disclose.

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