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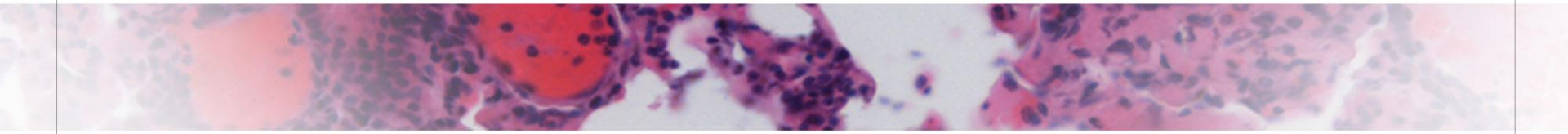

Daratumumab, Lenalidomide, and Dexamethasone (DRd) Versus Lenalidomide and Dexamethasone (Rd) in Relapsed or Refractory Multiple Myeloma (RRMM): Updated Efficacy and Safety Analysis of POLLUX*

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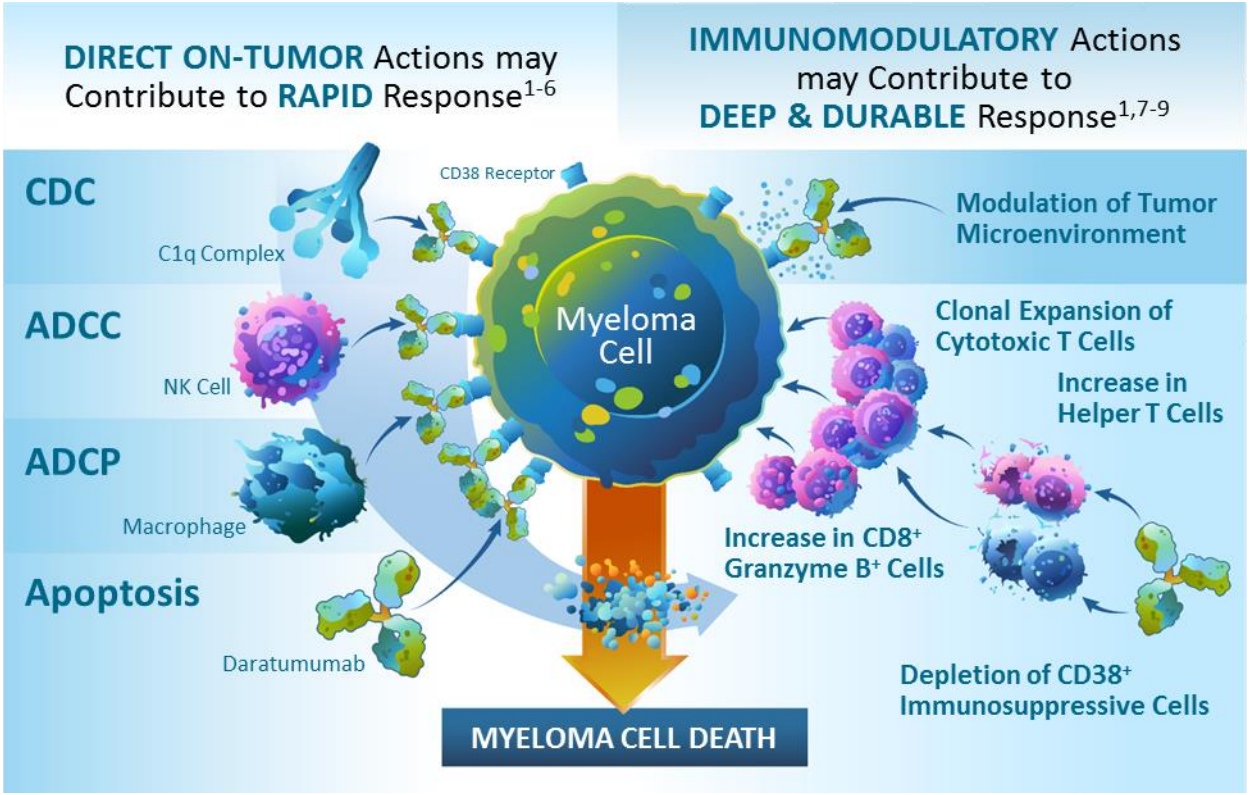
Background



- Daratumumab
  - Human IgGκ monoclonal antibody targeting CD38 with a direct on-tumor and immunomodulatory MoA[10]
- Approved
  - As **monotherapy** in many countries for heavily pretreated RRMM
  - In **combination** with standard of care regimens in RRMM after ≥1 prior therapy in many countries
- Efficacy
  - Daratumumab induces rapid, deep, and durable responses in combination with a PI (bortezomib) or an IMiD (lenalidomide) in RRMM[11,12]

1. DARZALEX [US PI], Horsham, PA: Janssen Biotech, Inc.; 2017. **2.** Liszewski MK, et al. *Adv Immunol*. 1996;61:201-283. **3.** Debets JM, et al. *J Immunol*. 1988;141(4):1197-1201. **4**. Overdijk MB, et al. *mABs*. 2015;7(2):311-321. **5.** Lokhorst HM, et al. *NEJM*. 2015;373(13):1207-1219. **6.** Plesner T, et al. Oral presentation at: ASH; December 8-11, 2012; Atlanta, GA **7**. Krejcik J, et al. *Blood*. 2016;128(3):384-394. **8.** Adams H, et al. Poster presented at: ASH; December 3-6, 2016; San Diego, CA. **9.** Chiu C, et al. Poster presented at: ASH; December 3-6, 2016; San Diego, CA. **10**. Blair H. *Drugs*. 2017; doi: 10.1007/s40265-017-0837-7 (Epub). **11.** Palumbo A, et al. *NEJM*. 2016;375(8):754-66. **12.** Dimopoulos, MA et al. *NEJM*. 2016;375(14):1319-1331.

CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; NK, natural killer; Ig, immunoglobulin; MoA, mechanism of action; RRMM, relapsed or refractory multiple myeloma; PI, proteasome inhibitor; IMiD, immunomodulatory drug.

POLLUX Study Design

Open-label, multicenter, randomized (1:1), active-controlled, phase 3 study

Key eligibility criteria

- RRMM
- ≥1 prior line of therapy
- Prior lenalidomide exposure allowed, but not if lenalidomide refractory
- Creatinine clearance ≥30 mL/min

Stratification factors

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

RANDOMIZE 1:1

DRd (n = 286)

Daratumumab 16 mg/kg IV
Every week in Cycles 1-2
Every 2 weeks in Cycles 3-6
Every 4 weeks
Lenalidomide 25 mg PO
Days 1-21 of each cycle
Dexamethasone 40 mg PO[a]
Every week
Treatment until PD

Rd (n = 283)

Lenalidomide 25 mg PO
Days 1-21 of each cycle
Dexamethasone 40 mg PO
Every week
Treatment until PD

Cycles: 28 days

Primary endpoint

- PFS

Secondary endpoints

- OS
- ORR, VGPR, CR
- MRD
- Time to response
- Duration of response

Statistical analyses

- Final OS analysis at 330 OS events

ISS, International Staging System; DRd, daratumumab/lenalidomide/dexamethasone; IV, intravenous; PO, oral; PD, progressive disease; Rd, lenalidomide/dexamethasone; PFS, progression-free survival; 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 on the day of the infusion and 20 mg was administered the day after the infusion.

Baseline Characteristics (ITT)

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

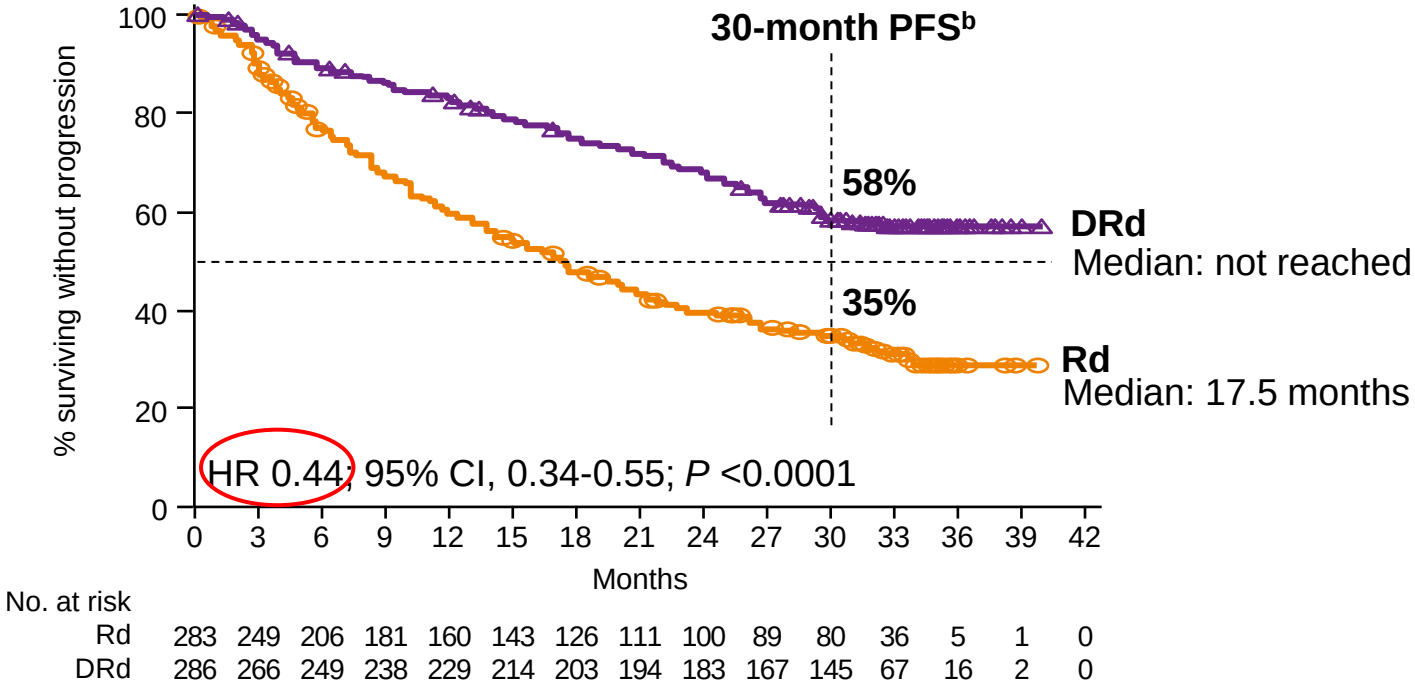
Characteristic	DRd (n = 286)	Rd (n = 283)
Prior lines of therapy, % Median (range) 1 2 3 >3	 1 (1-11) 52 30 13 5	 1 (1-8) 52 28 13 7
Prior ASCT, %	63	64
Prior PI, %	86	86
Prior IMiD, % Prior lenalidomide, %	55 18	55 18
Prior PI + IMiD, %	44	44
Refractory to bortezomib, %	21	21
Refractory to last line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

ITT, intent-to-treat; ASCT, autologous stem cell transplant.

[a]ISS stage was 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.

PFS[a]

- Median follow-up: 32.9 months (range, 0 - 40.0 months)

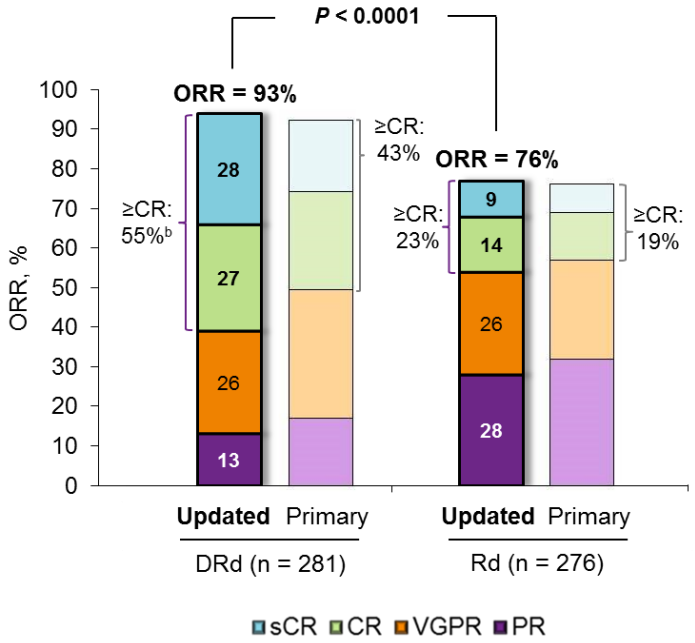


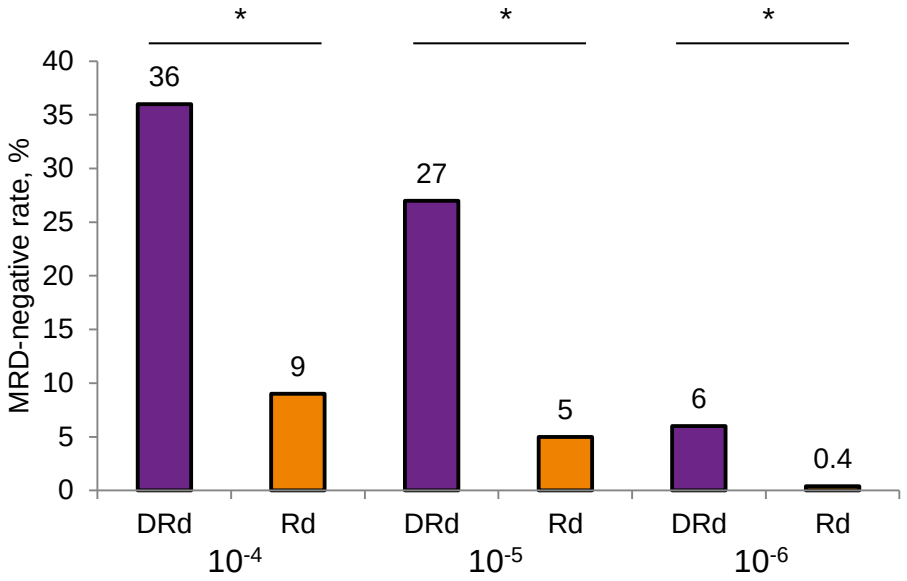
56% reduction in risk of progression/death for DRd versus Rd

HR, hazard ratio; CI, confidence interval.
[a]Exploratory analyses based on clinical cut-off date of October 23, 2017.
[b]Kaplan-Meier estimate.

ORR and MRD-negative Rates[a]

- Median follow-up: 32.9 months (range, 0 - 40.0 months)



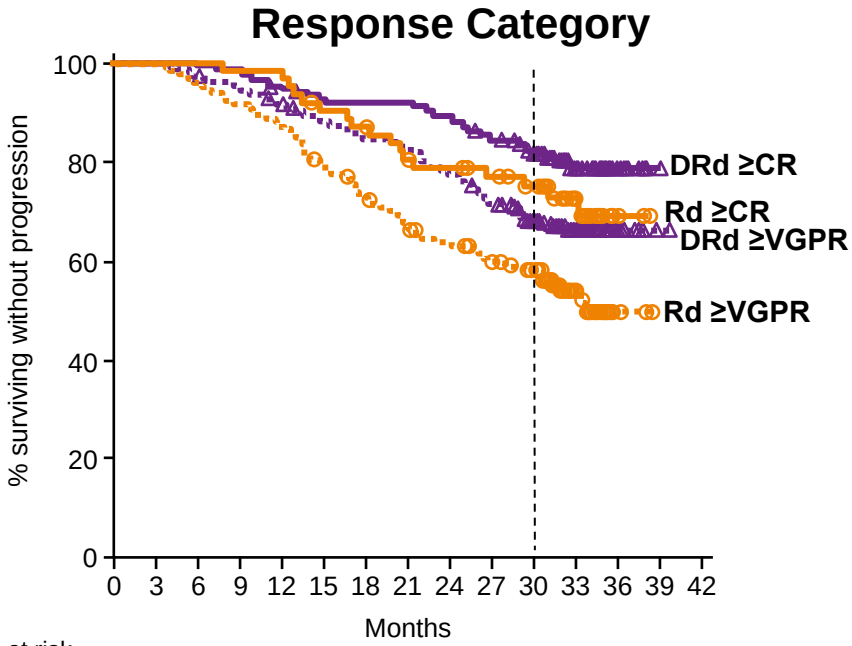


MRD assessed using clonoSEQ® assay V2.0

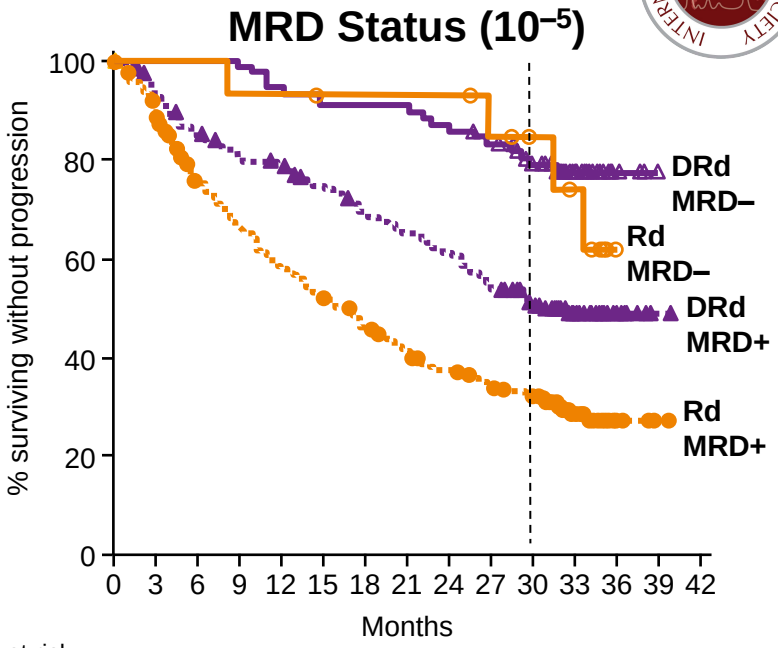
- **Responses continued to deepen in the DRd group**
- **Significantly higher (>3-fold) MRD-negative rates for DRd versus Rd**

sCR, stringent complete response; PR, partial response.
Primary analysis reported in Dimopoulos MA, et al. *N Engl J Med.* 2016;375(14):1319-1331.
[a]Exploratory analyses based on clinical cutoff date of October 23, 2017; [b]*P* <0.0001 for DRd versus Rd.

PFS by Depth of Response



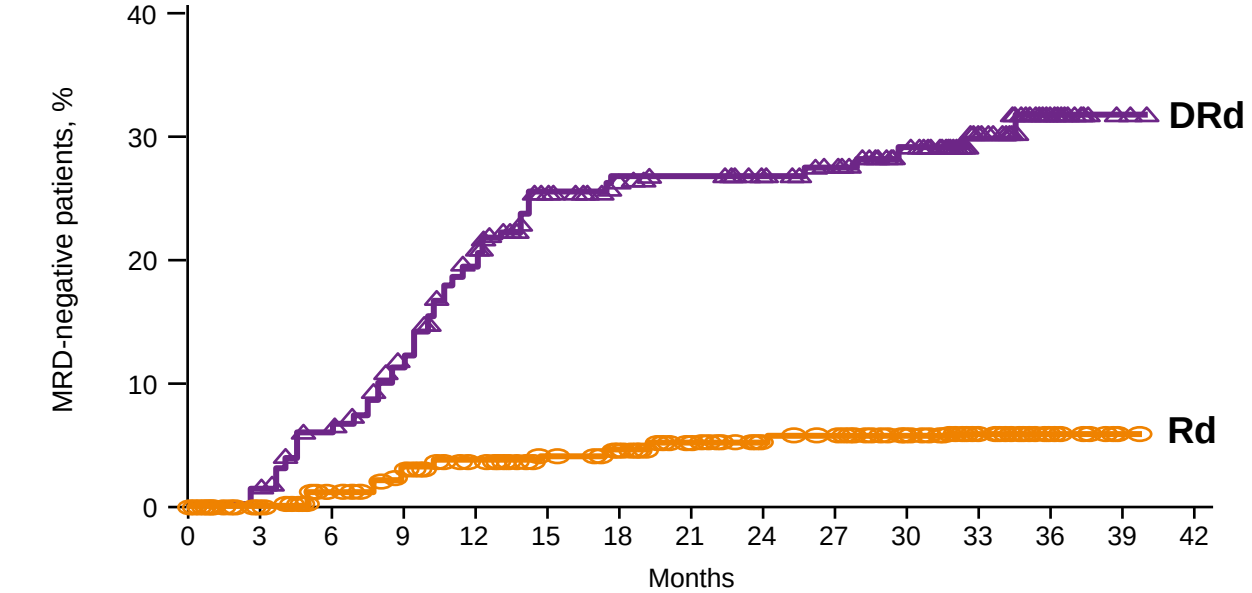
No. at risk															
DRd ≥CR	154	154	154	151	146	141	140	140	136	127	115	53	12	1	0
Rd ≥CR	62	62	62	61	61	56	53	48	46	43	39	22	3	0	0
DRd ≥VGPR	226	226	220	214	206	195	189	183	173	158	137	62	14	2	0
Rd ≥VGPR	134	134	129	123	117	106	96	87	80	73	66	31	4	0	0



No. at risk															
Rd MRD negative	14	14	14	13	13	12	12	12	12	10	8	6	0	0	0
DRd MRD negative	76	76	76	75	72	69	69	69	66	62	54	26	7	1	0
Rd MRD positive	269	235	192	168	147	131	114	99	88	79	72	30	5	1	0
DRd MRD positve	210	190	173	163	157	145	134	125	117	105	91	41	9	1	0

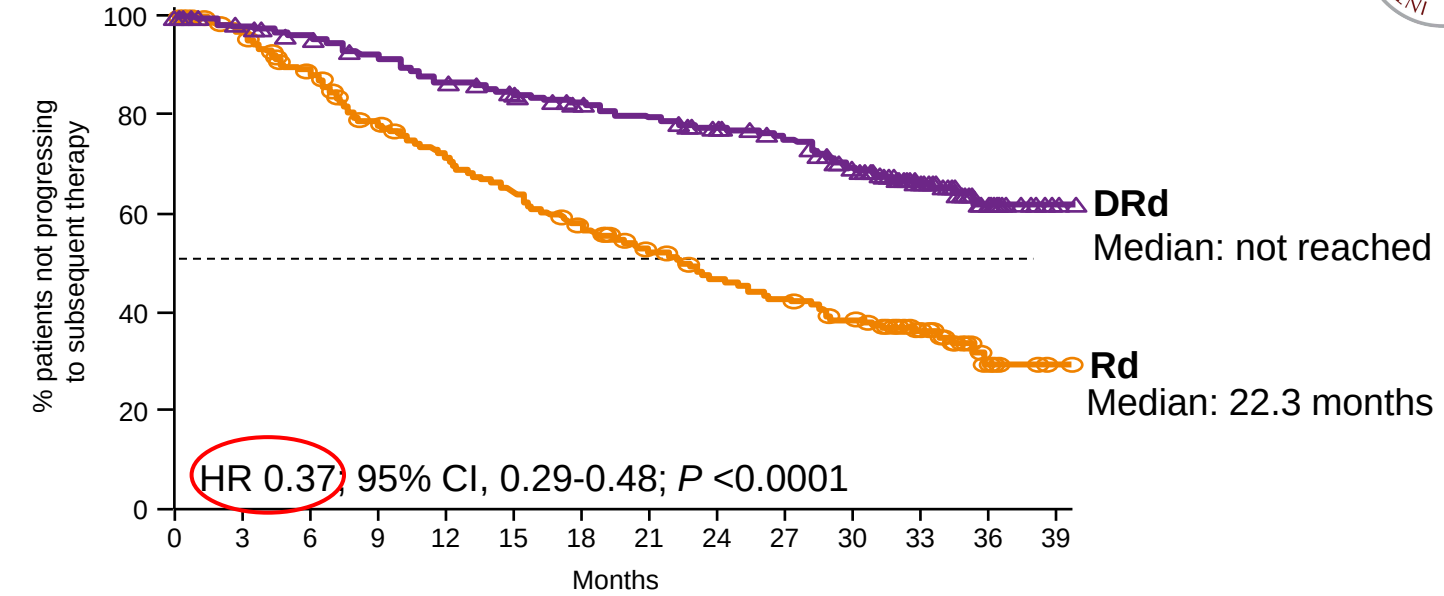
- **Deeper responses were more common on DRd and were associated with longer PFS**
- **MRD negativity was associated with longer PFS**

Time to MRD Negativity (10^{-5})



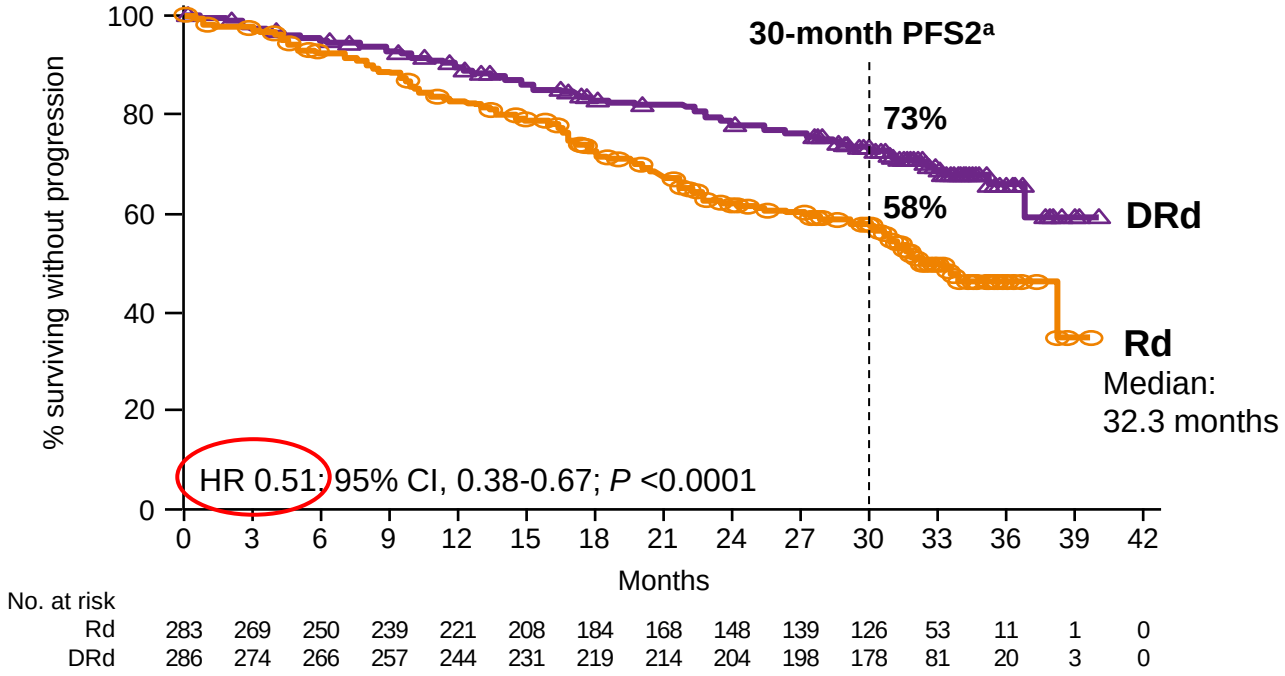
MRD negativity occurs more rapidly with DRd and increases over time

Time to Next Therapy



More than half of DRd patients have not yet started subsequent therapy

PFS With Subsequent Line of Therapy (PFS2)



DRd does not negatively impact outcomes of subsequent therapy

[a]Kaplan-Meier estimate.

Overview of Safety Profile

	All grades (≥25%)[a]		Grade 3/4 (≥5%)[a]	
TEAE, %	**DRd (n = 283)**	**Rd (n = 281)**	**DRd (n = 283)**	**Rd (n = 281)**
Hematologic				
Neutropenia	62	47	54	41
Febrile neutropenia	6	3	6	3
Anemia	38	41	16	22
Thrombocytopenia	29	31	14	16
Lymphopenia	7	6	6	4
Nonhematologic				
Diarrhea	56	34	7	4
Upper respiratory tract infection	41	27	1	1
Viral upper respiratory tract infection	31	19	0	0
Fatigue	38	31	6	4
Cough	34	15	0.4	0
Constipation	31	27	1	0.7
Muscle spasms	29	21	1	1
Nausea	27	18	2	0.7
Pneumonia	24	16	14	10
Hypokalemia	17	11	5	3

- Median duration of treatment: 30.4 months for DRd versus 16.0 months for Rd
- Discontinuations due to TEAEs were similar (13% in both arms)
- Rate of grade 3/4 infections: 39% for DRd versus 26% for Rd
- No differences in rates of SPMs between treatment groups (7% of patients in both groups)
  - Most common SPM in both arms was cutaneous, noninvasive SCC (2% each)

Safety profile remains unchanged with longer follow-up

TEAE, treatment-emergent adverse event; SPM, secondary primary malignancy; SCC, squamous cell carcinoma. [a]Common TEAEs listed are either ≥25% all grade OR ≥5% grade 3/4.

Conclusions

- DRd continues to significantly improve PFS with longer follow-up
- DRd induces deep and durable responses
- More patients receiving DRd achieved MRD negativity versus Rd
- MRD negativity occurs more rapidly with DRd and increases over time
- DRd does not negatively impact outcomes of subsequent therapy
- Safety profile remains unchanged with longer follow-up

Updated findings continue to support the use of DRd in patients with RRMM

Acknowledgments

POLLUX

18 countries

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