Evaluation of Minimal Residual Disease (MRD) in Relapsed/Refractory Multiple Myeloma (RRMM) Patients Treated With Daratumumab in Combination With Lenalidomide Plus Dexamethasone or Bortezomib Plus Dexamethasone

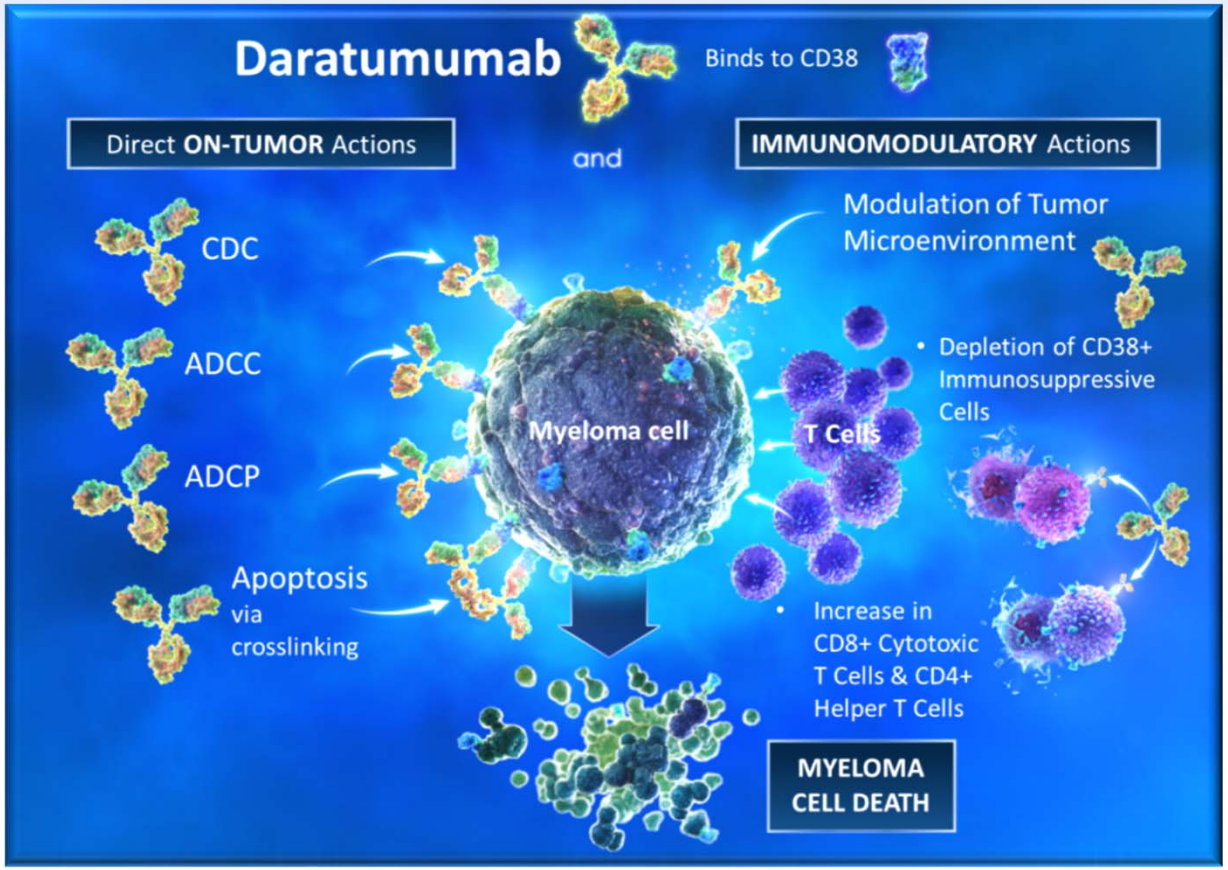
Hervé Avet-Loiseau,[1] Tineke Casneuf,[2] Christopher Chiu,[3] Jacob Laubach,[4] Je-Jung Lee,[5] Philippe Moreau,[6] Torben Plesner,[7] Hareth Nahi,[8] Nushmia Z. Khokhar,[3] Ming Qi,[3] Jordan Schecter,[9] Victoria Carlton,[10] Xiang Qin,[3] Kevin Liu,[9] Kaida Wu,[3] Sen Hong Zhuang,[9] Tahamtan Ahmadi,[3] A. Kate Sasser,[3] Jesus San-Miguel[11]

[1]Unite de Genomique du Myelome, CHU Rangueil, Toulouse, France; [2]Oncology Heme Translational Research Group, Janssen Research & Development, Beerse, Belgium; [3]Janssen Research & Development, LLC, Spring House, PA, USA; [4]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [5]Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, Hwasun, Jeollanamdo, South Korea; [6]Hematology, University Hospital Hôtel-Dieu, Nantes, France; [7]Vejle Hospital and University of Southern Denmark, Vejle, Denmark; [8]Karolinska Institute and the Department of Medicine, Division of Hematology, Karolinska University Hospital at Huddinge, Stockholm, Sweden; [9]Janssen Research & Development, LLC, Raritan, NJ, USA; [10]Adaptive Biotechnologies, Seattle, WA, USA; [11]Clínica Universidad de Navarra-CIMA, IDISNA, Pamplona, Spain.

ClinicalTrials.gov Identifiers: NCT02136134 and NCT02076009

Daratumumab

- Daratumumab
  - Human monoclonal antibody that targets CD38
  - Direct on-tumor and immunomodulatory mechanisms of action[1-5]
- Daratumumab is approved by the FDA as monotherapy and in combination with standard of care regimens for patients with multiple myeloma (MM) with ≥1 prior line of treatment
- Daratumumab + standard of care regimens
  - Resulted in a >60% reduction in the risk of disease progression or death[6,7]
  - The immunomodulatory effects of daratumumab may drive deep responses



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.
6. Dimopoulos MA, et al. *New Engl J Med*. 2016;375(14):1319-1331.
7. Palumbo A, et al. *New Engl J Med*. 2016;375(8):754-766.

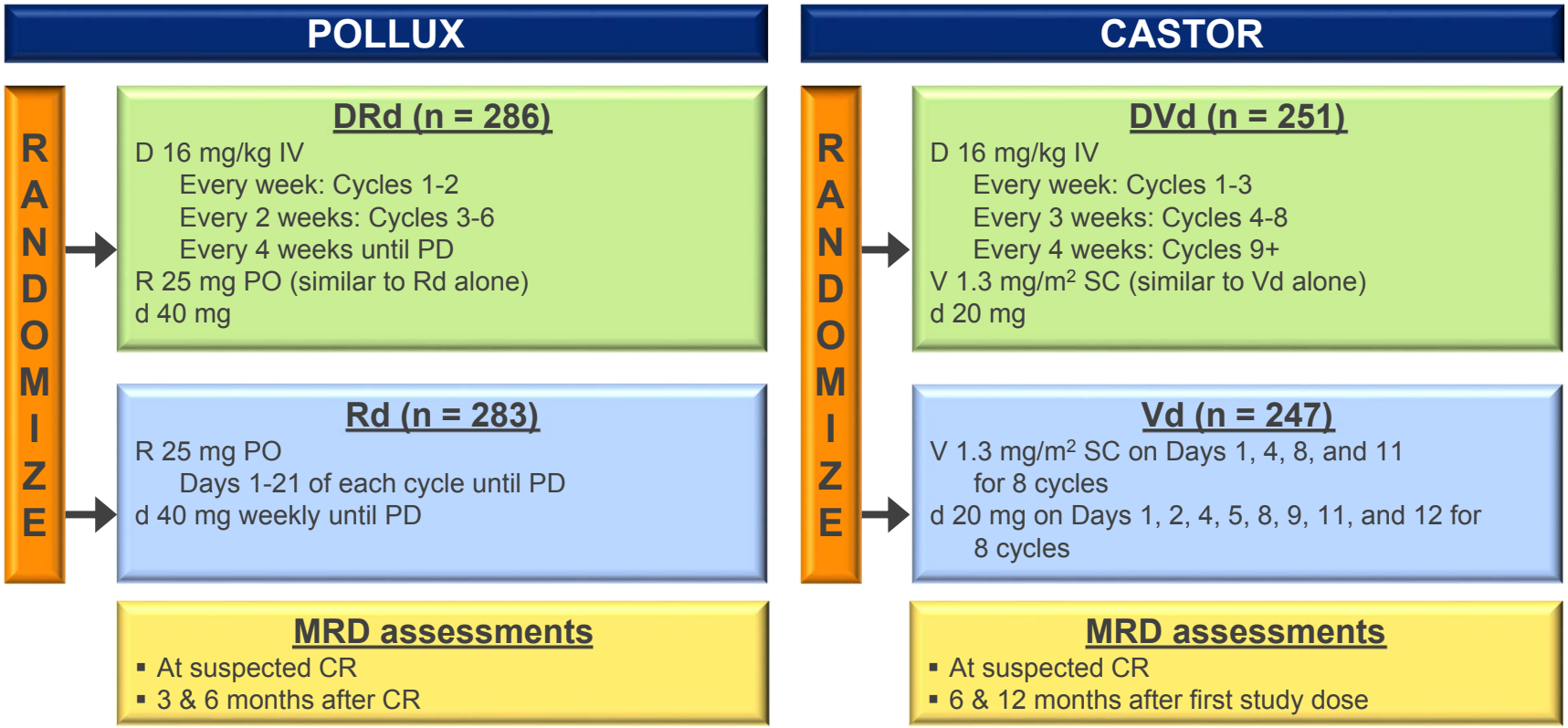
Minimal Residual Disease

- Minimal residual disease (MRD) is a more sensitive measure of disease burden than traditional definitions of clinical response[1,2]
- MRD-negative status is associated with prolonged progression-free survival (PFS) and overall survival (OS) in newly diagnosed MM patients[1,2]
  - In the future, MRD may be a primary endpoint for clinical studies
- International Myeloma Working Group guidelines recommend an MRD-sensitivity threshold of at least 10^{-5} using next-generation sequencing (NGS) or next-generation flow cytometry[3]
- This study is the first evaluation of MRD in relapsed and refractory (RR) MM using a randomized, controlled, and prospective analysis

1. Munshi NC, et al. *JAMA Oncol.* 2016. [Epub ahead of print.]
2. Landgren O, et al. *Bone Marrow Transplant*. 2016. [Epub ahead of print.]
3. Kumar S, et al. *Lancet Oncol.* 2016;17(8):e328-e346.

POLLUX and CASTOR

- Multicenter, randomized (1:1), open-label, active-controlled, phase 3 studies in ≥1 prior line of therapy for MM



Patient characteristics

- Median (range) prior lines: 1 (1-11)
- Prior V: 84%
- Prior R: 18%

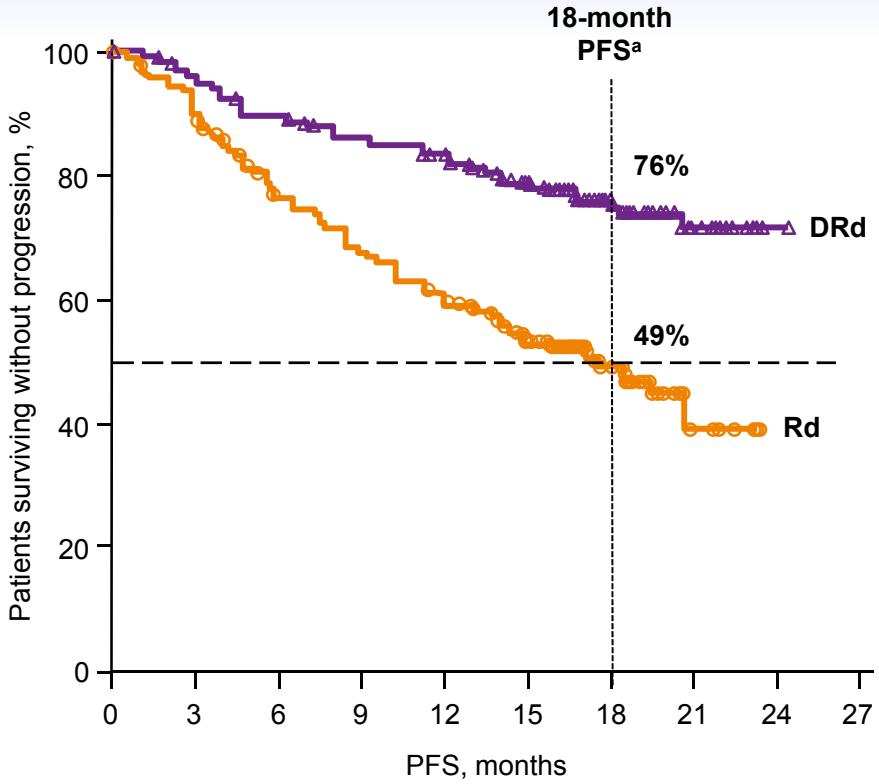
Patient characteristics

- Median (range) prior lines: 2 (1-10)
- Prior V: 66%
- Prior R: 42%

DRd, daratumumab, lenalidomide, and dexamethasone; D, daratumumab; IV, intravenous; PD, progressive disease; R, lenalidomide; PO, orally; Rd, lenalidomide and dexamethasone; d, dexamethasone; CR, complete response; DVd, daratumumab, bortezomib, and dexamethasone; V, bortezomib; SC, subcutaneously; Vd, bortezomib and dexamethasone.

Updated PFS: POLLUX and CASTOR

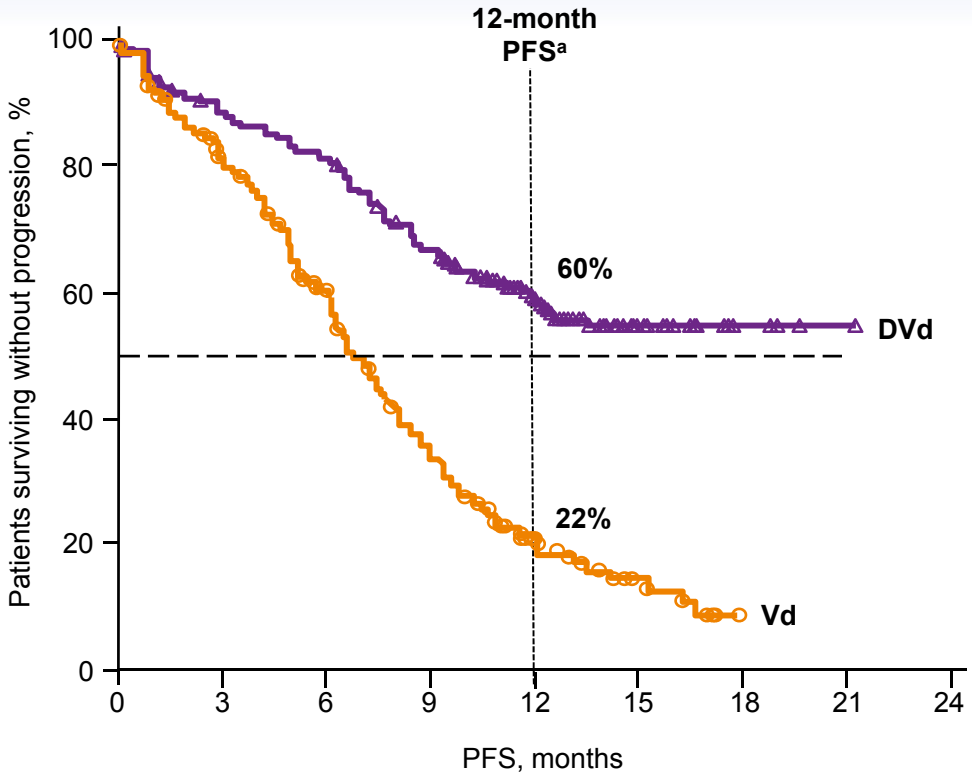
POLLUX



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

- **Median PFS**
  - DRd: not reached; Rd: 17.5 months
  - HR: 0.37 (95% CI, 0.28-0.50; *P* <0.0001)

CASTOR

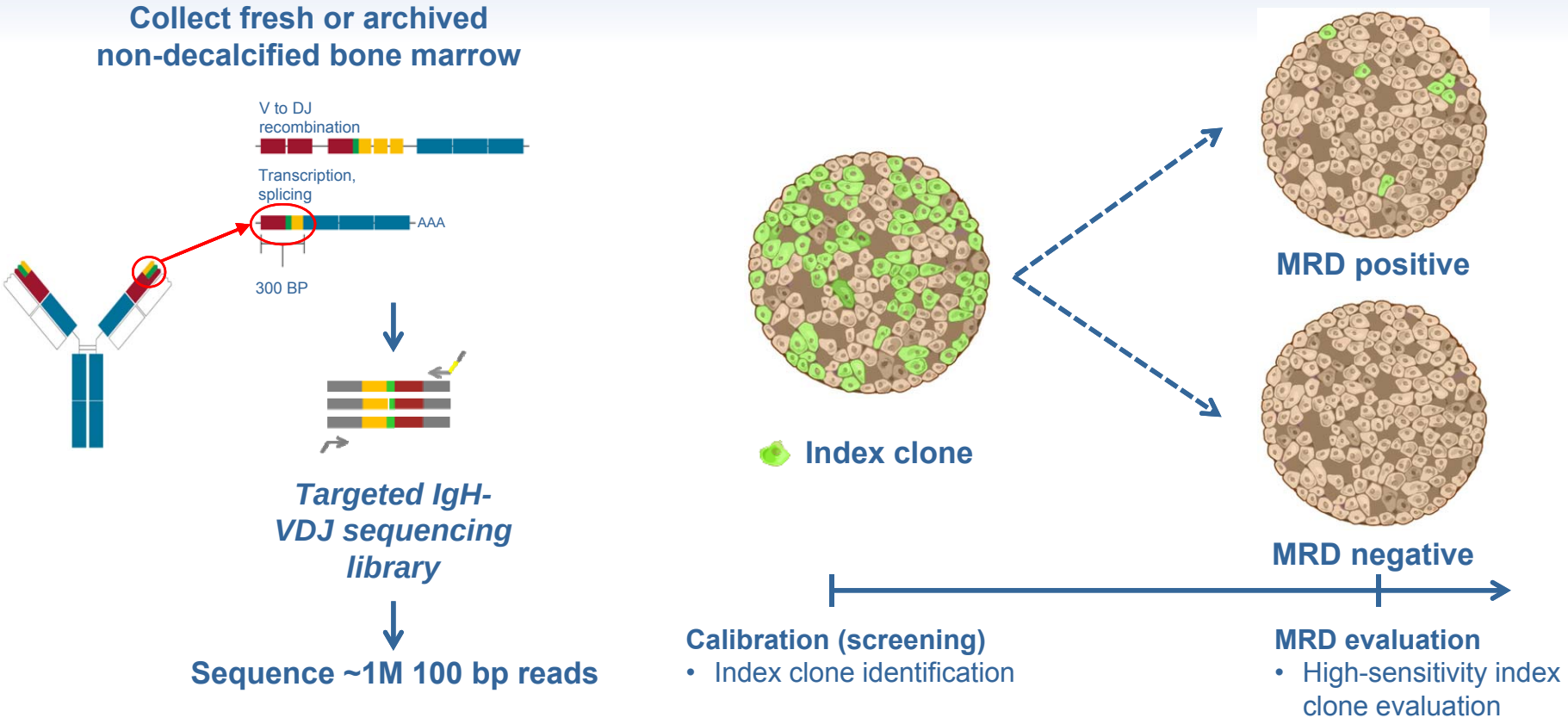


Median (range) follow-up:
13.0 (0-21.3) months

- **Median PFS**
  - DVd: not reached; Vd: 7.1 months
  - HR: 0.33 (95% CI, 0.26-0.43; *P* <0.0001)

HR, hazard ratio; CI, confidence interval.
[a]Kaplan-Meier estimates.
Clinical cut-off: June 30, 2016.

ClonoSEQ™ MRD Assay



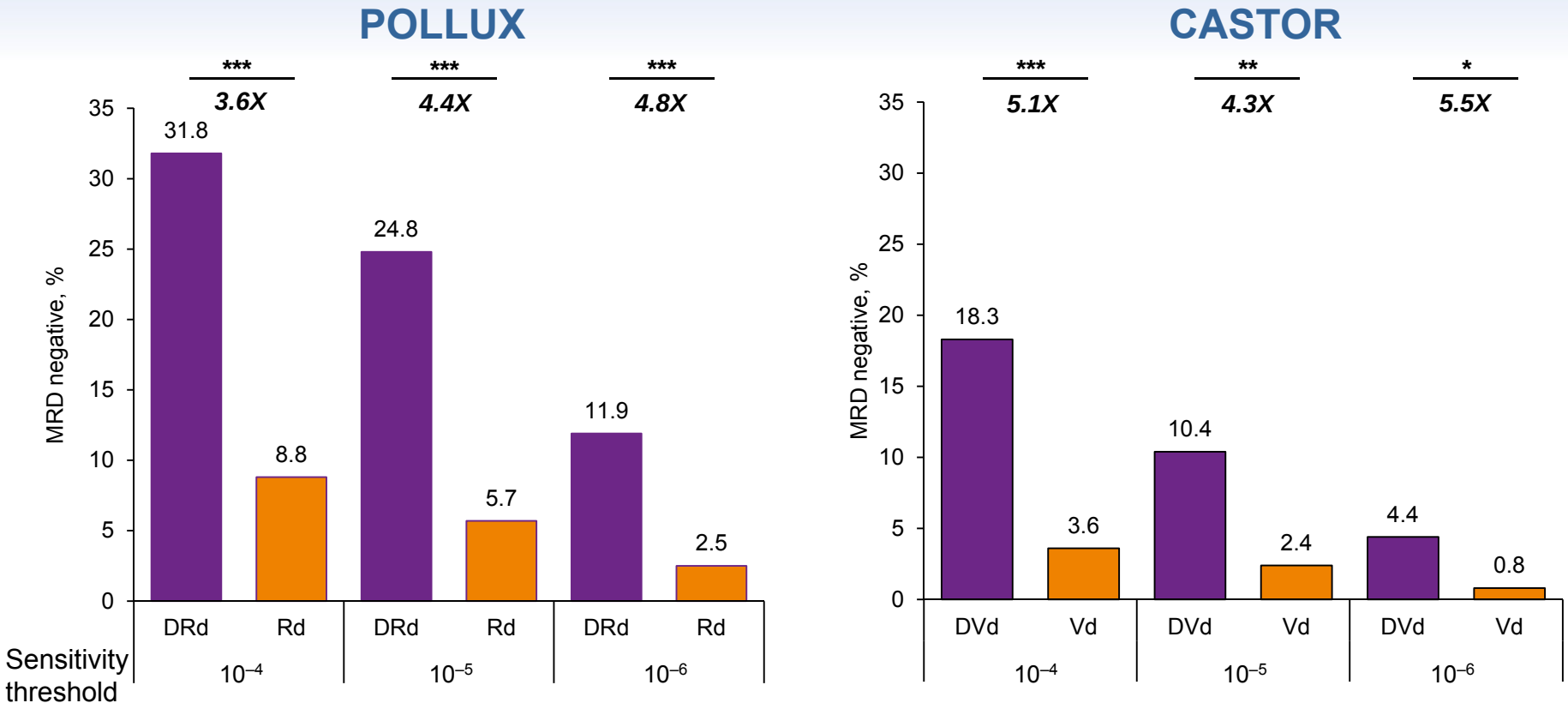
- MRD was assessed at suspected CR using bone marrow aspirate samples and evaluated by ClonoSEQ™ NGS-based assay[a]

MRD, minimal residual disease; BP, base pair; IgH, immunoglobulin H; 1M, 1 million.
[a]Version 1.3; Adaptive Biotechnologies.

Criteria for MRD Negativity

- MRD was evaluated at 3 sensitivity thresholds: 10^{-4}, 10^{-5}, and 10^{-6}
- MRD-negativity rate = proportion of patients with negative MRD test results at any time during treatment
- A stringent, unbiased MRD evaluation was applied
  - MRD-negativity counts were evaluated against the intent-to-treat (ITT) population
  - Any patient in the ITT population not determined to be MRD negative was scored as MRD positive
  - A minimum cell input equivalent to the given sensitivity threshold was required to determine MRD negativity
    - i.e., MRD at 10^{-6} required that ≥1 million cells were evaluated

Proportion of MRD-negative Patients at 10^{-4}, 10^{-5}, and 10^{-6} Thresholds



- Daratumumab in combination with standard of care significantly improved MRD-negative rates at all thresholds

*** *P* <0.0001
** *P* <0.005
* *P* <0.05

P values calculated using likelihood-ratio chi-square test.

MRD Negativity Among Patients With ≥CR

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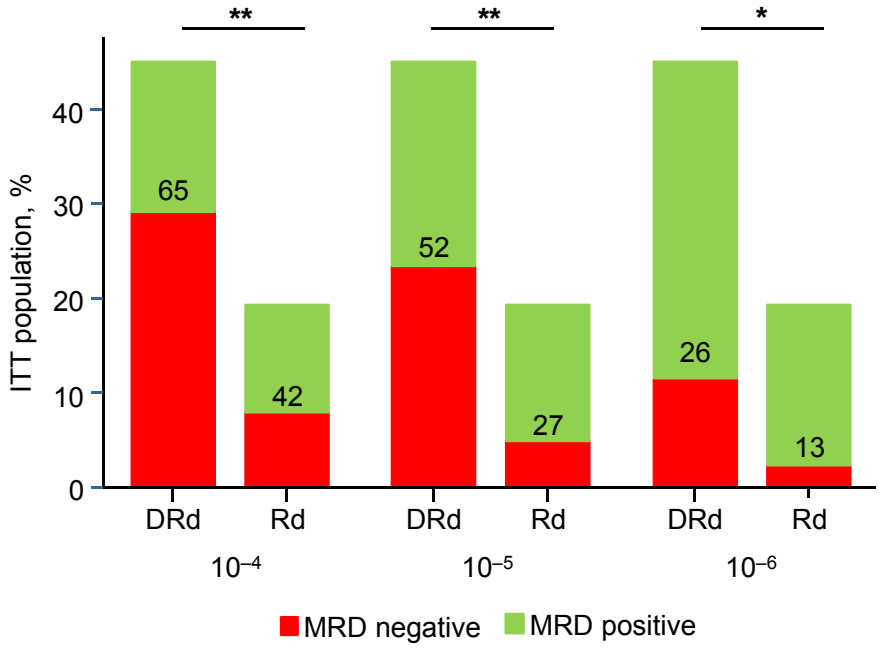

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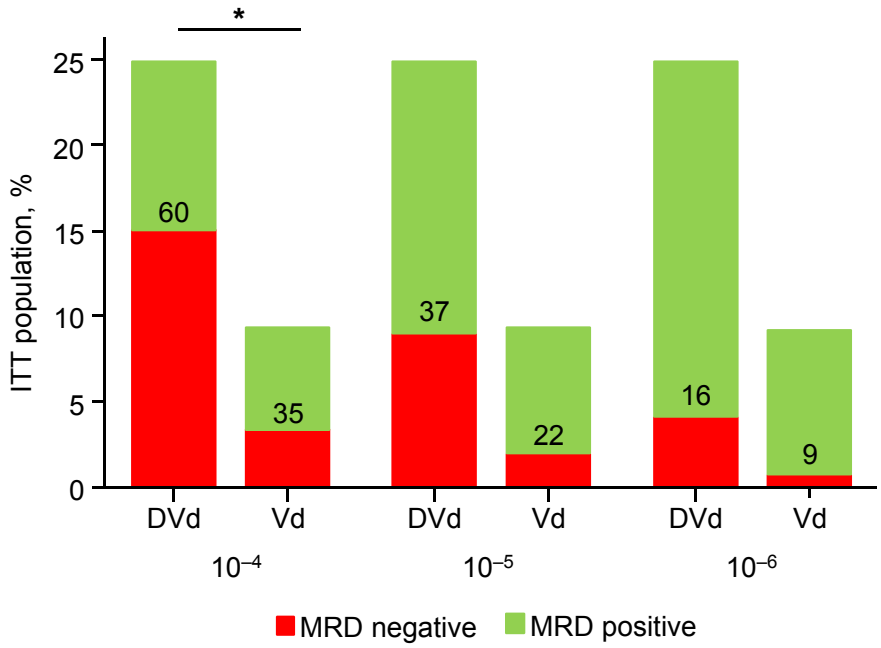


- Values refer to the percentage of MRD-negative patients among those who achieved ≥CR in a given treatment arm

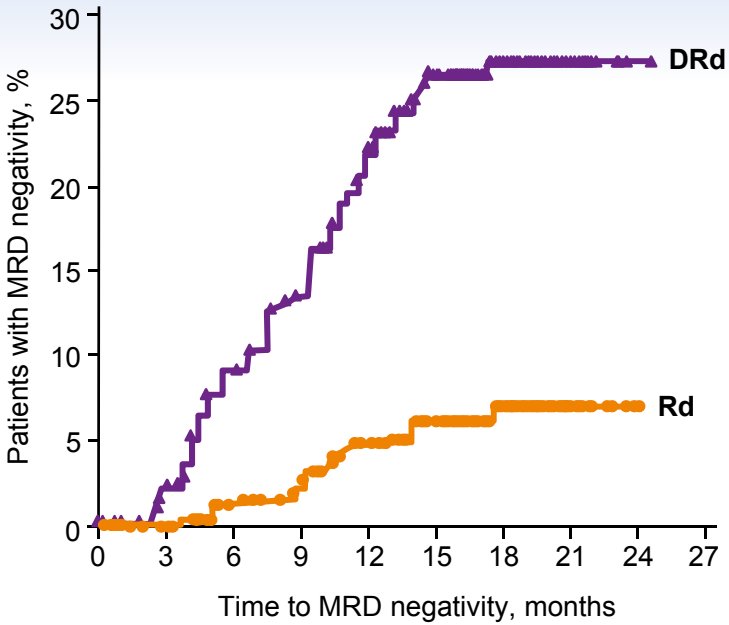
** *P* <0.005
* *P* <0.05

Consistently higher MRD-negative rates in patients with ≥CR treated with a daratumumab-containing regimen

P values calculated using likelihood-ratio chi-square test.

Time to MRD (10^{-5})

POLLUX



Patients at risk

Rd	283	272	252	243	225	202	83	18	0	0
DRd	286	271	247	229	202	169	71	15	1	0

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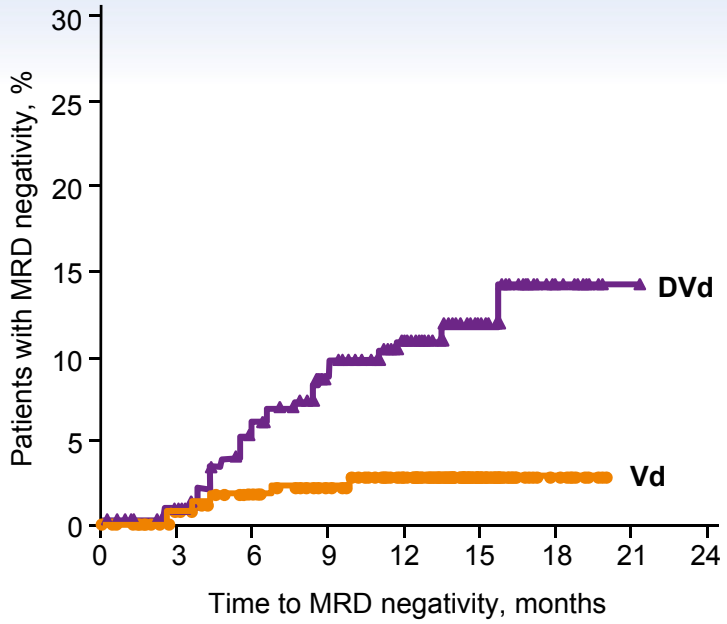


Patients at risk

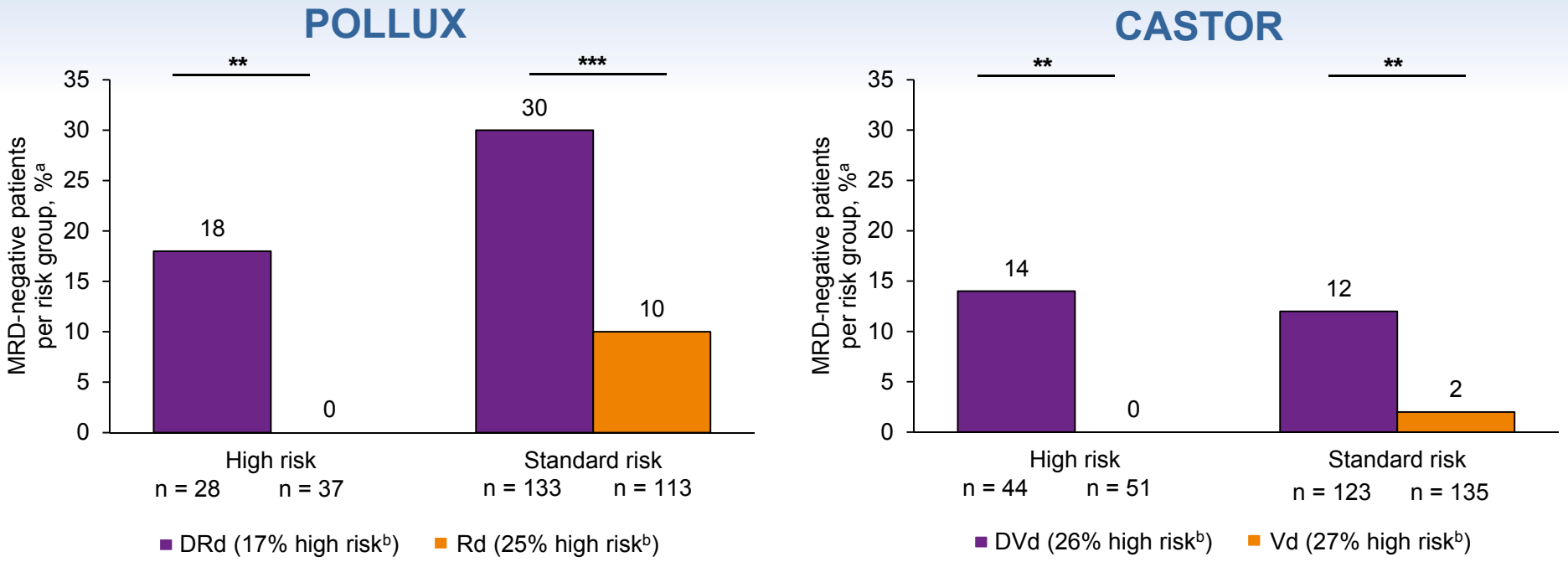
Vd	247	217	202	187	130	55	13	0	0
DVd	251	229	212	190	137	58	12	1	0

- Rapid accumulation of MRD-negative events in patients treated with daratumumab-containing regimens versus standard of care
- MRD-negative patients continued to accumulate over time in both studies

Majority of patients maintain MRD negativity; patients will continue to be followed annually

Only 1 MRD-negative sample counted per patient.

MRD at 10^{-5} by Cytogenetic Risk by NGS



- No high-risk MRD negative patients have progressed or converted to MRD positive
  - High risk = any of t(4;14), t(14;16), del17p
  - Standard risk = conclusive absence of all 3 markers

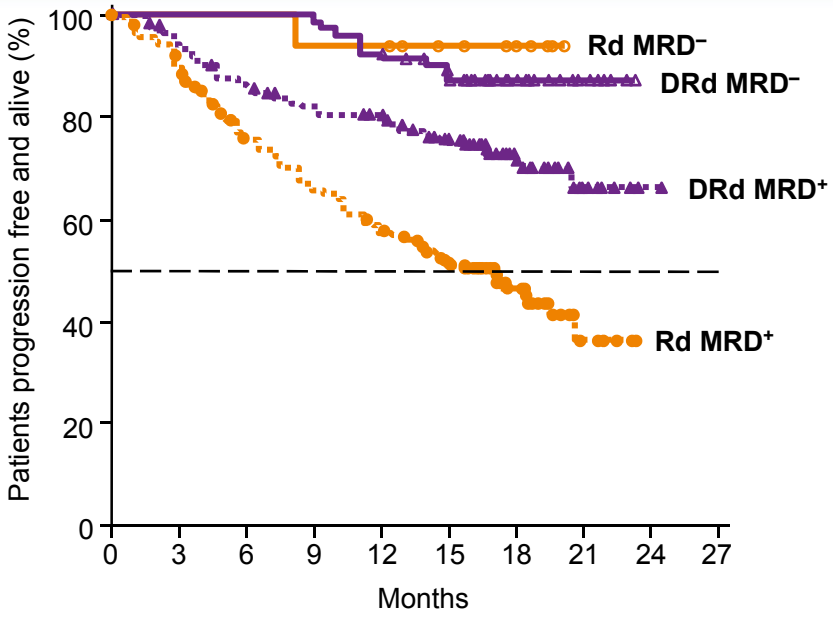
In high-risk patients, MRD-negative status was achieved only in those treated with daratumumab-containing regimens

P values calculated using likelihood-ratio chi-square test.
[a]Percentage of patients within a given risk group and treatment arm.
[b]Percentage of patients within a given treatment arm within the biomarker-evaluable population.

*** ***P* <0.0001**
** ***P* <0.005**

PFS According to MRD Status at 10^{-5}

POLLUX



Patients 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

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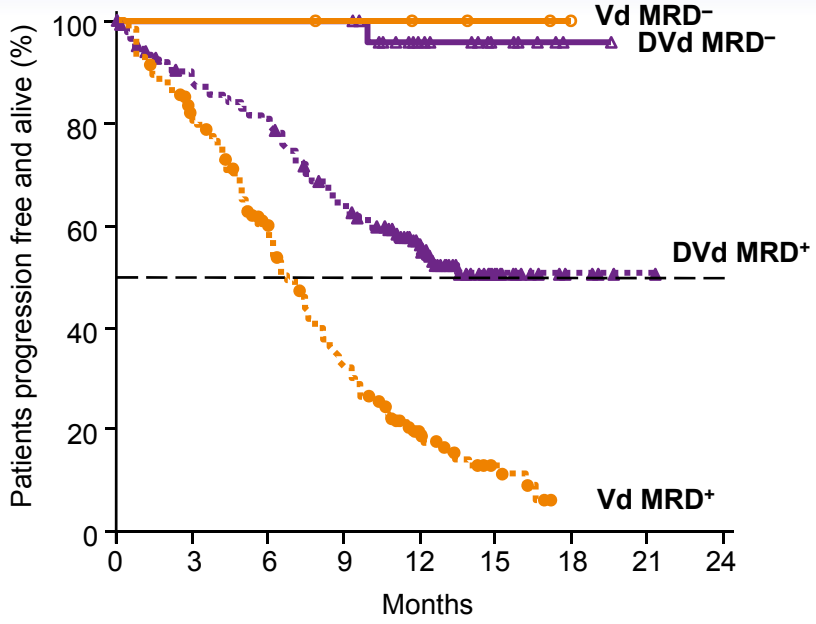


Patients at risk									
Vd MRD negative	6	6	6	5	3	2	0	0	0
DVd MRD negative	26	26	26	26	15	7	1	0	0
Vd MRD positive	241	176	123	68	20	7	0	0	0
DVd MRD positive	225	189	172	134	76	26	4	1	0

- Lower risk of progression in MRD-negative patients
- PFS benefit in MRD-positive patients who received daratumumab-containing regimens versus standard of care

Conclusions

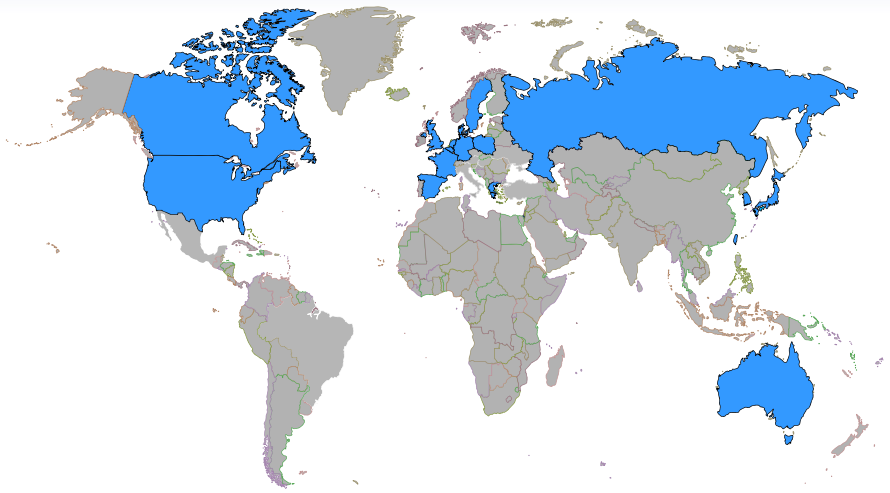
- Daratumumab induced MRD negativity in over 3 times as many patients as standard of care regimens
- Daratumumab led to rapid and durable achievement of MRD negativity
  - Patients continued to achieve MRD negativity over time
- Daratumumab allowed high-risk patients to achieve MRD-negative status
- MRD-negative status was associated with a lower risk of progression
- The high rate of MRD negativity and deep clinical responses induced by daratumumab may lead to improved long-term clinical benefit

The magnitude of daratumumab-induced MRD negativity in the RRMM setting is unprecedented

The potential benefit of MRD-negative status induced by daratumumab in newly diagnosed MM is being explored in ongoing studies

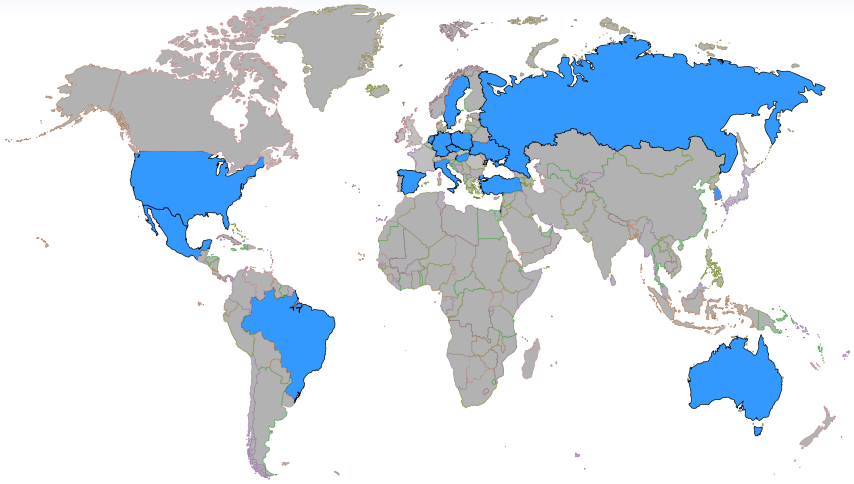
Acknowledgments

POLLUX



18 countries

CASTOR



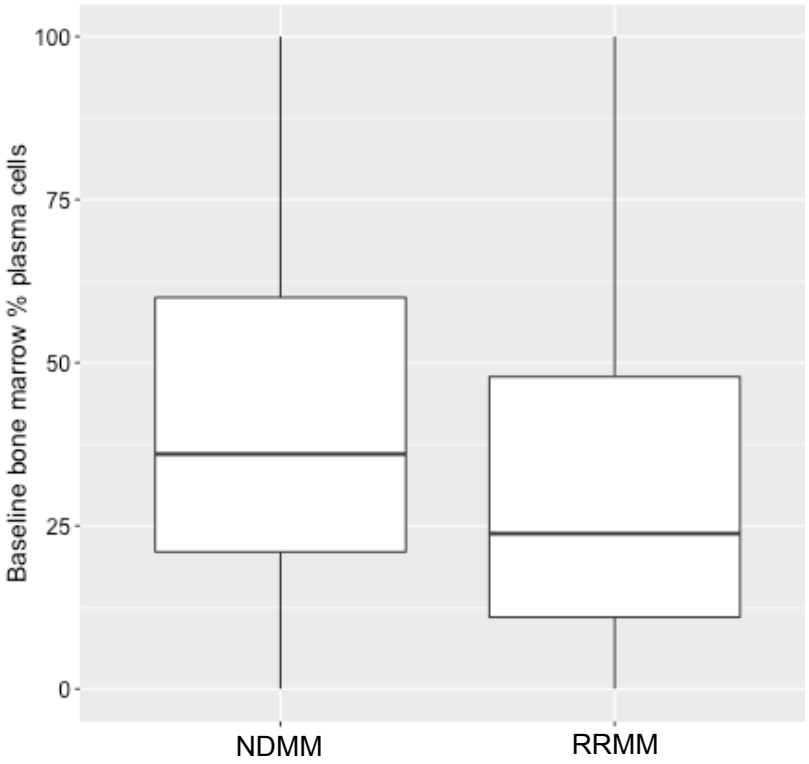
16 countries

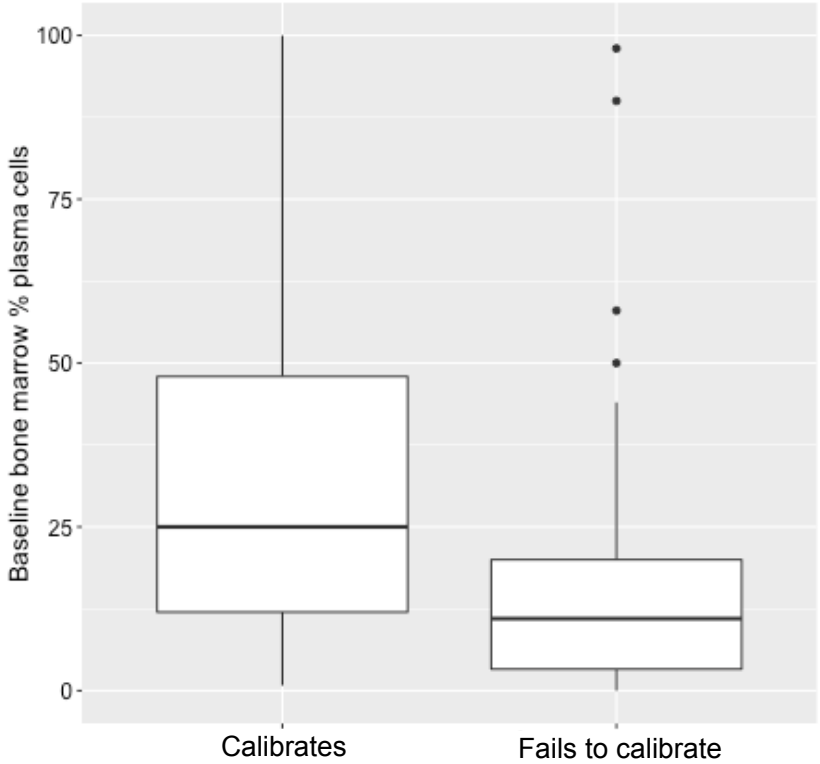
- **Patients who participated in these studies**
- Investigators
- Data and safety monitoring committee
- Staff members involved in data collection and analyses
- David Soong, PhD for his work on the NGS cytogenetic analyses

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

Backup

Baseline Bone Marrow Plasma Cell Percentages From Daratumumab Phase 3 Trials



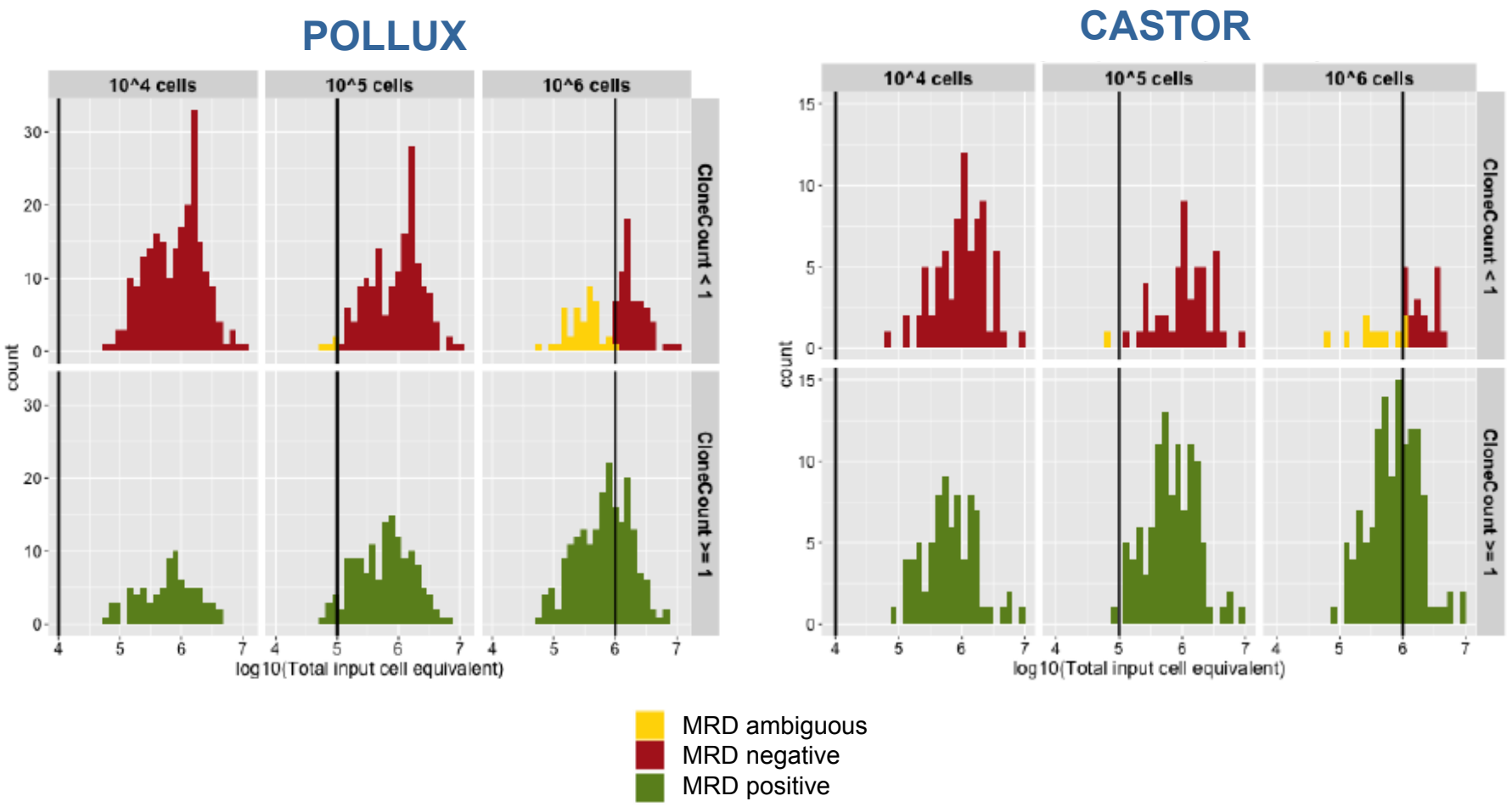


- Baseline bone marrow plasma cell percentages of the 238 samples that successfully calibrated were significantly higher than the 75 samples that failed to calibrate (median of 25% vs 11%, respectively; *P* <0.0001)

NDMM, newly diagnosed multiple myeloma.
Calibration using ClonoSEQ™ Version 1.3

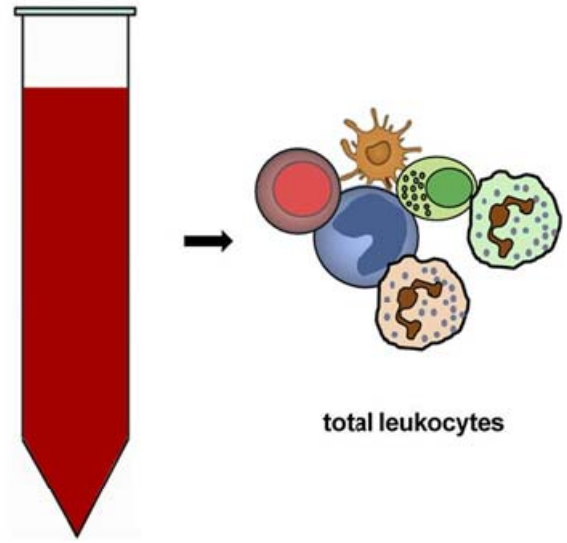
MRD Threshold

- Samples with input cell equivalents below the MRD-sensitivity level were considered MRD positive in the analysis of MRD-negativity rate



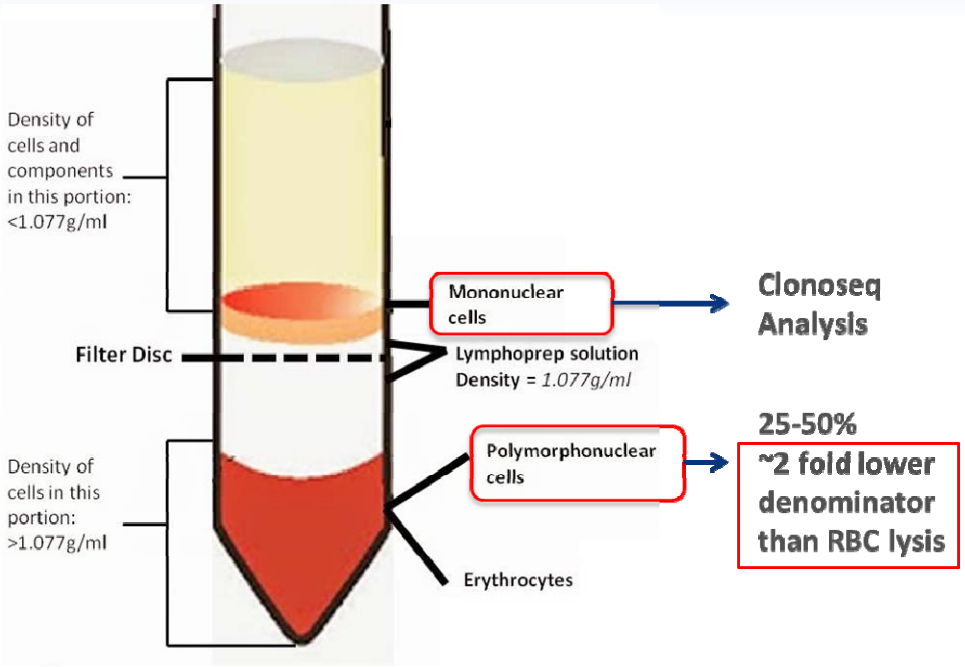
Bone Marrow Processing Considerations

RBC hypotonic lysis



ClonoSEQ™ analysis

Ficoll enrichment

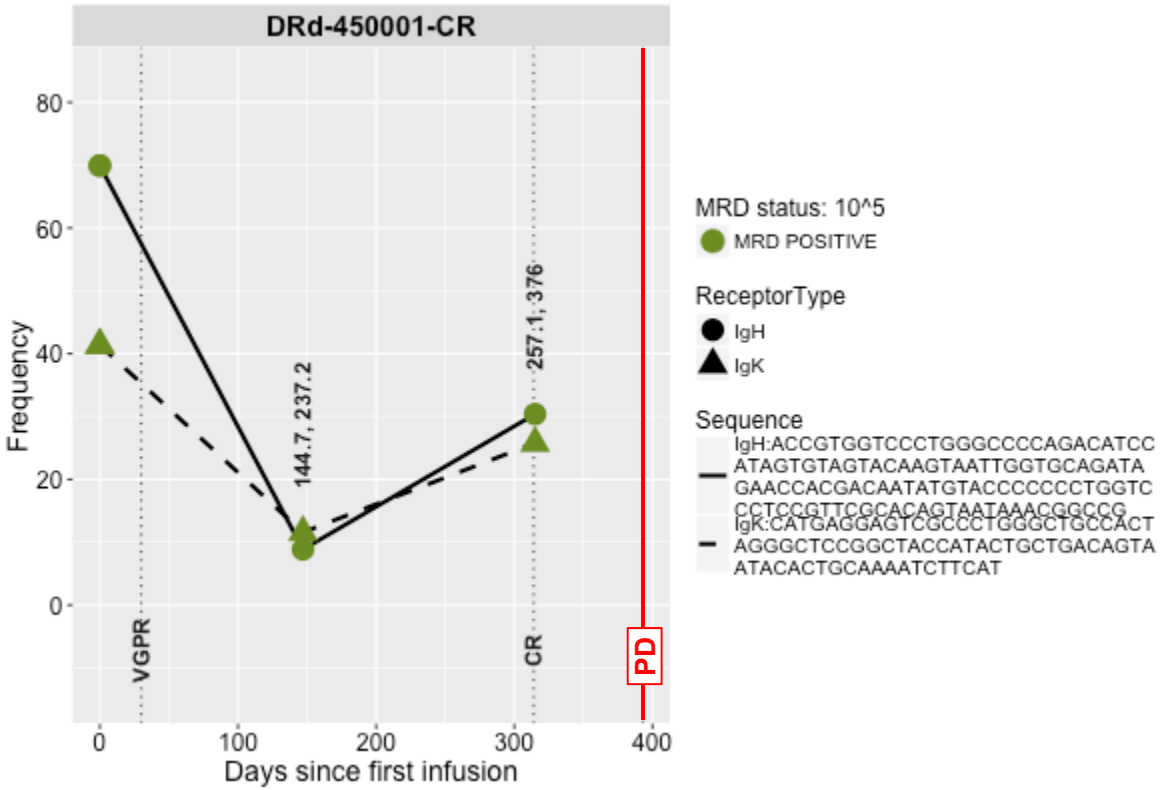


- Ficoll enrichment removes the granulocytic cell population that makes up 25-50% of nucleated cells in the sample
  - Calculations of MRD-negative rate in Ficoll-enriched samples are more stringent than those using RBC lysates, which would include all of the leukocytes in the sample

RBC, red blood cell.

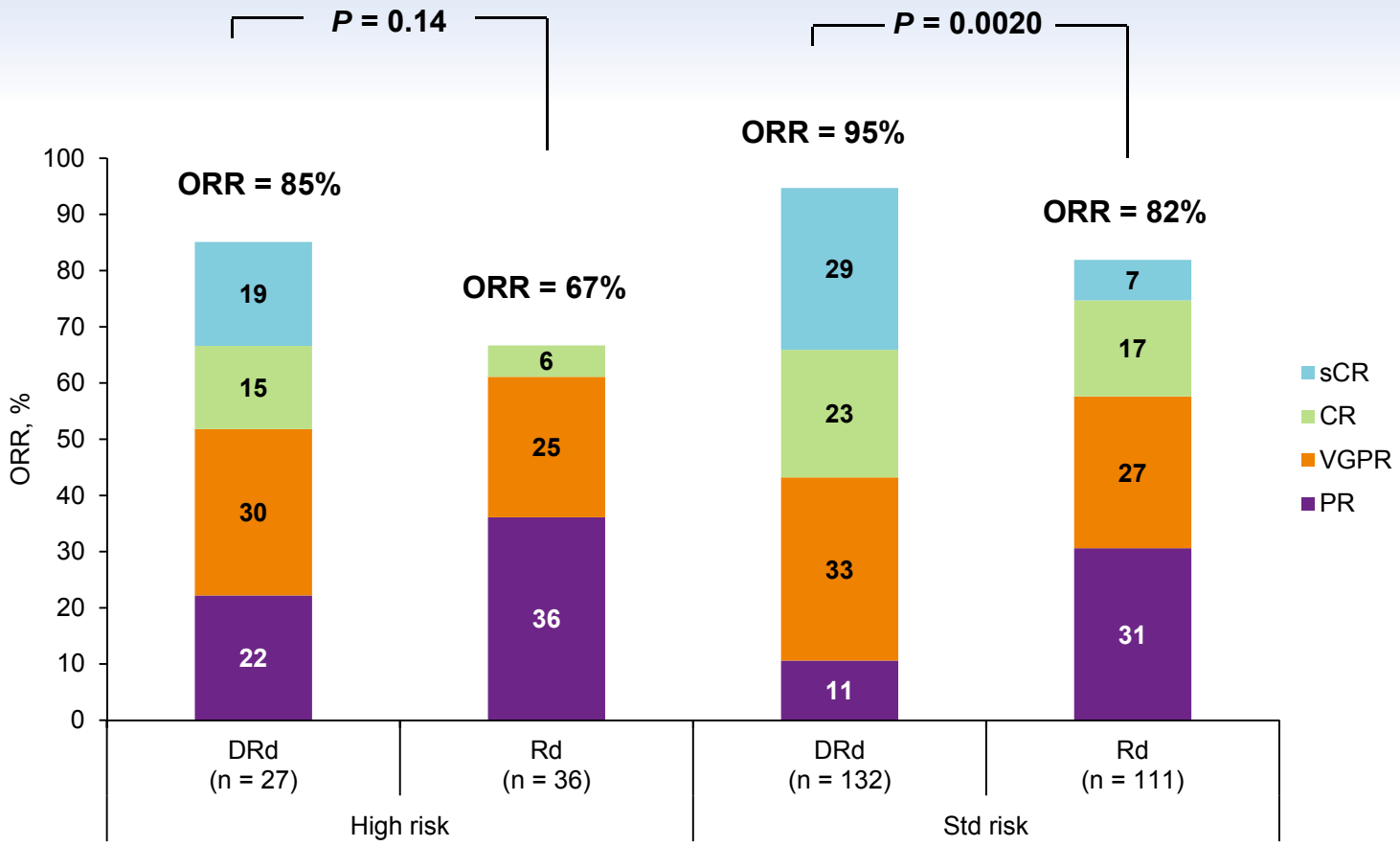
Assessment by MRD

- MRD assessment is a more sensitive measure of disease burden than traditional definitions of clinical response[1,2]



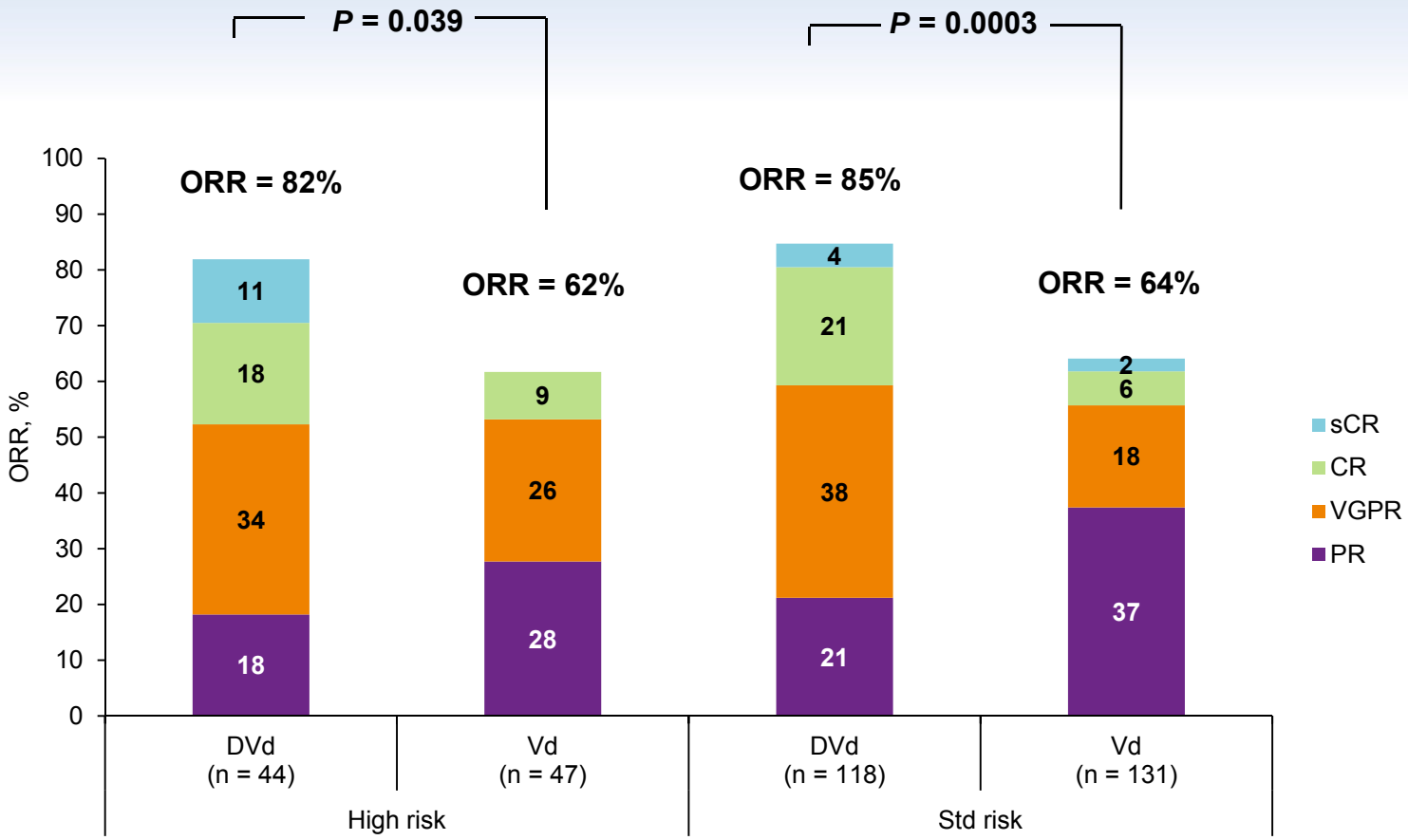
1. Munshi NC, et al. *JAMA Oncol.* 2016. [Epub ahead of print.]
2. Landgren O, et al. *Bone Marrow Transplant*. 2016. [Epub ahead of print.]

ORR by Cytogenetic Risk[a]: POLLUX



P values calculated using Mantel-Haenszel estimate of common odds ratios.
[a]Central NGS. High-risk patients had any of t(4;14), t(14;16), del17p. Standard-risk patients had an absence of high-risk abnormalities.

ORR by Cytogenetic Risk[a]: CASTOR



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[a]Central NGS. High-risk patients had any of t(4;14), t(14;16), del17p. Standard-risk patients had an absence of high-risk abnormalities.