Efficacy of Daratumumab in Combination With Lenalidomide Plus Dexamethasone (DRd) or Bortezomib Plus Dexamethasone (DVd) in Relapsed or Refractory Multiple Myeloma (RRMM) Based on Cytogenetic Risk Status

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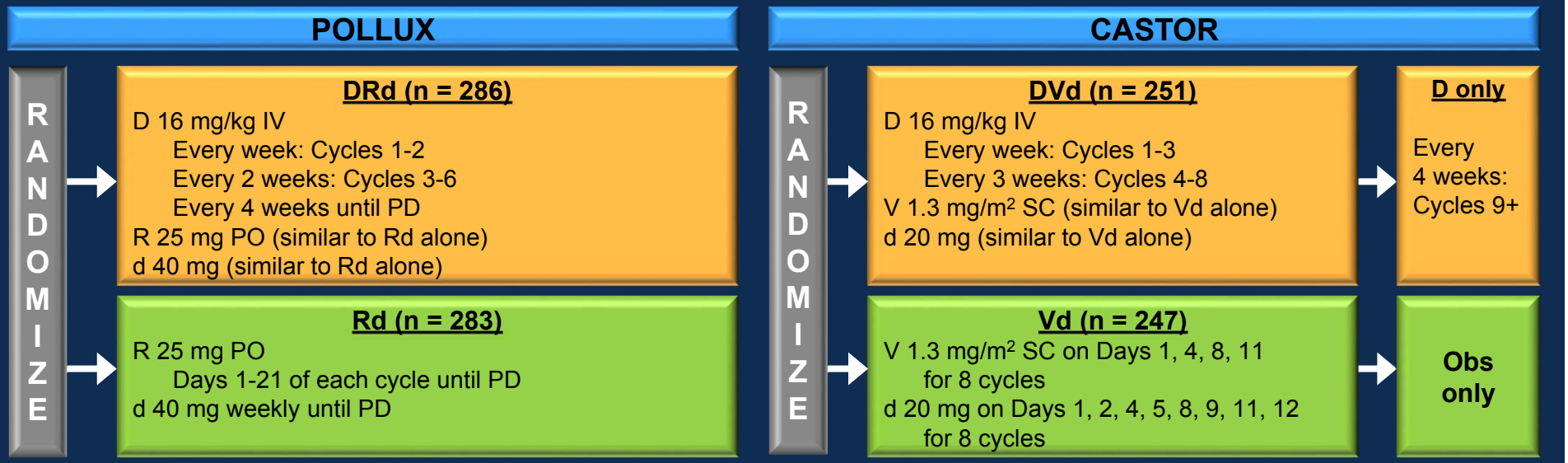
ClinicalTrials.gov Identifiers: NCT02136134 and NCT02076009.

POLLUX and CASTOR Study Designs[1,2]

Open-label, multicenter, randomized (1:1), active-controlled, phase 3 studies in RRMM patients with ≥1 prior line of therapy

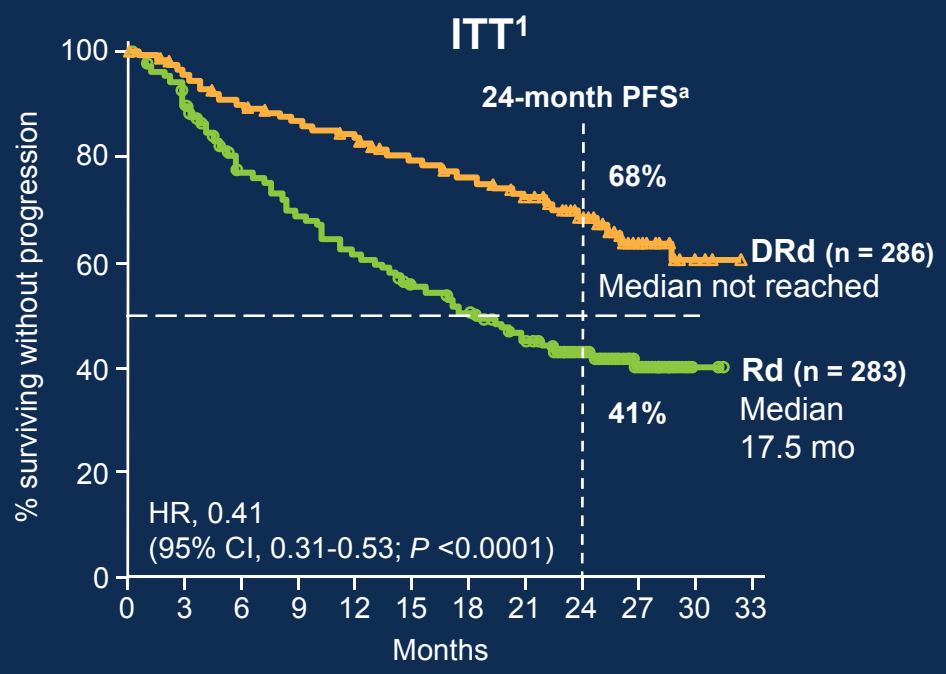


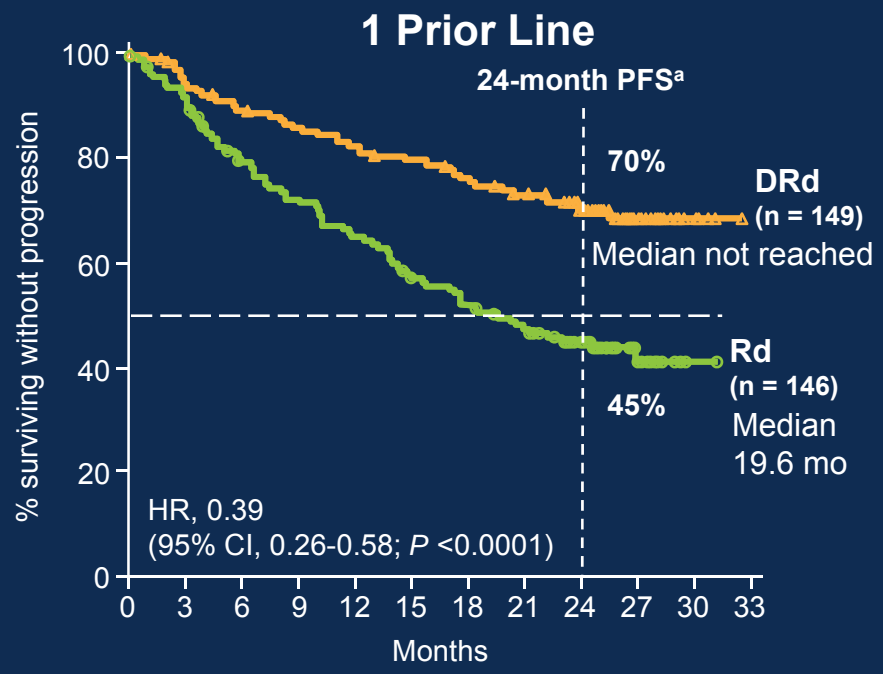
RRMM, relapsed or refractory multiple myeloma; DRd, daratumumab, lenalidomide, and dexamethasone; D, daratumumab; IV, intravenous; PD, progressive disease; R, lenalidomide; PO, orally; Rd, lenalidomide and dexamethasone; d, dexamethasone; DVd, daratumumab, bortezomib, and dexamethasone; V, bortezomib; SC, subcutaneous; Vd, bortezomib and dexamethasone; Obs, observation.

1. Dimopoulos MA, et al. *N Engl J Med*. 2016;375(14):1319-1331. 2. Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-766.

POLLUX: 1-Year Update[a]

- Median follow-up of 25.4 months

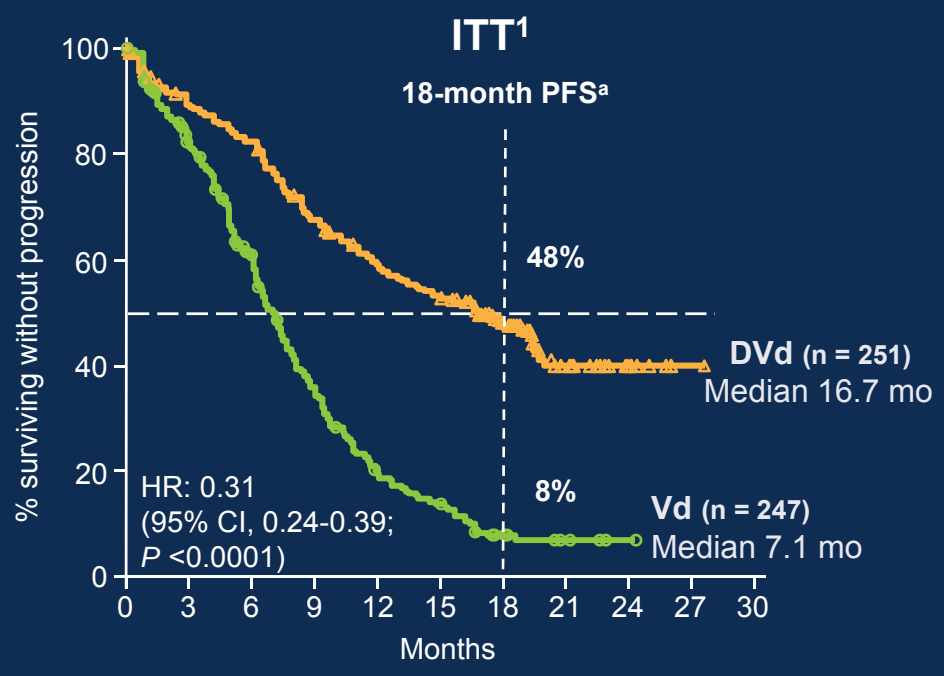


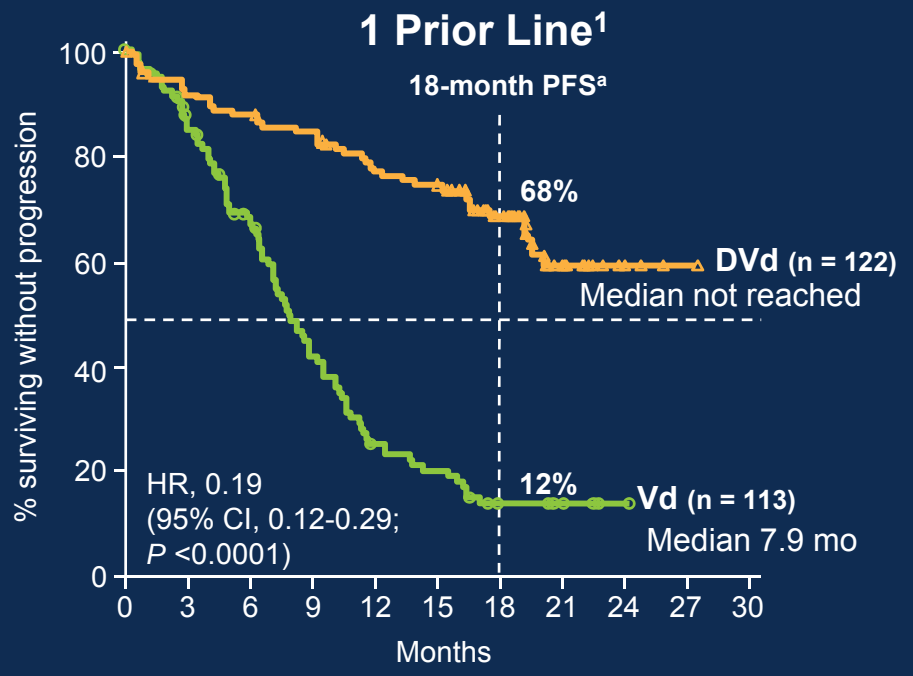


ITT, intent-to-treat; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.
[a]Kaplan-Meier estimates; exploratory analyses based on 1-year update: clinical cut-off date of March 7, 2017.
1. Bahlis NZ, et al. Poster presentation at ASCO 2017. Abstract 8025.

CASTOR: 1-Year Update[a]

- Median follow-up of 19.4 months





Adding daratumumab to SOC regimens significantly prolongs PFS

SOC, standard of care.
[a]Kaplan-Meier estimates; exploratory analyses based on 1-year update: clinical cut-off date of January 11, 2017. 1. Lentzsch S, et al. Poster presentation at ASCO 2017. Abstract 8036.

NGS Methodology

- NGS is a sensitive method for analyzing biomarkers, including cytogenetic abnormalities
- Prespecified local FISH and central NGS analyses, per CASTOR and POLLUX protocols
  - $CD138^{+}$-enriched bone marrow cells were collected at screening by local laboratories and assessed via conventional karyotyping or FISH
  - A portion of bone marrow aspirate was analyzed by central NGS
- High-risk patients had a t(4;14), t(14;16), or del17p cytogenetic abnormalities, as detected by central NGS
  - >50% cut-off was used for del17p
  - Standard-risk patients lacked a high-risk cytogenetic abnormality
- A subset of patients with NGS assessment also received local FISH assessment, allowing for direct comparison of NGS and FISH

First prospective analysis to utilize NGS in determining cytogenetic risk in phase 3 studies

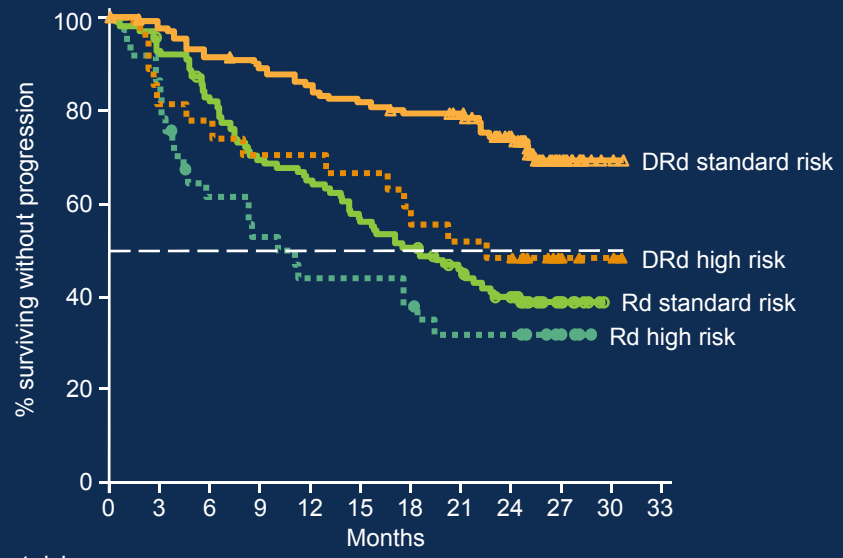
NGS, next-generation sequencing; FISH, fluorescence in situ hybridization.

Distribution of Genetic Abnormalities

NGS	POLLUX		CASTOR	
	DRd	Rd	DVd	Vd
Cytogenetic profile, N[a]	161	150	167	186
Standard risk, %	83	75	74	73
High risk, %[b]	17	25	26	27
Del17p, %	8	9	8	10
t(4;14), %	10	14	16	17
t(14;16), %	1	2	4	1

[a]Based on ITT/biomarker-risk evaluable analysis set.
[b]High-risk patients could have more than 1 abnormality.

POLLUX: PFS by Cytogenetic Risk Status[a]



Patients at risk												
Rd standard risk	113	104	92	77	72	63	56	47	36	10	0	0
DRd standard risk	133	128	120	116	111	106	102	99	76	19	2	0
Rd high risk	37	32	21	18	15	15	13	10	10	4	0	0
DRd high risk	28	22	21	19	19	18	16	14	13	4	2	0

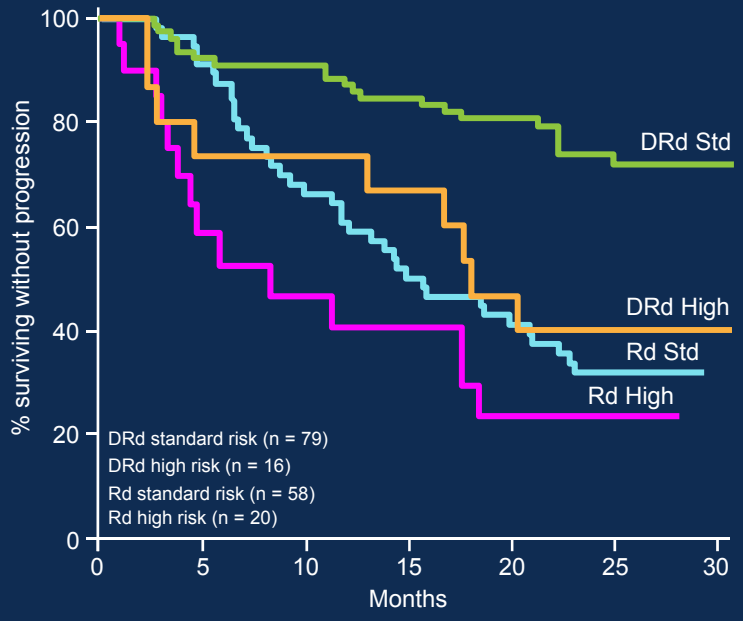
High risk	**DRd** n = 28	**Rd** n = 37
mPFS, mo	**22.6**	**10.2**
HR (95% CI)	0.53 (0.25-1.13)	
P value	0.0921	

Standard risk	**DRd** n = 133	**Rd** n = 113
mPFS, mo	**NR**	**18.5**
HR (95% CI)	0.30 (0.20-0.47)	
P value	<0.0001	

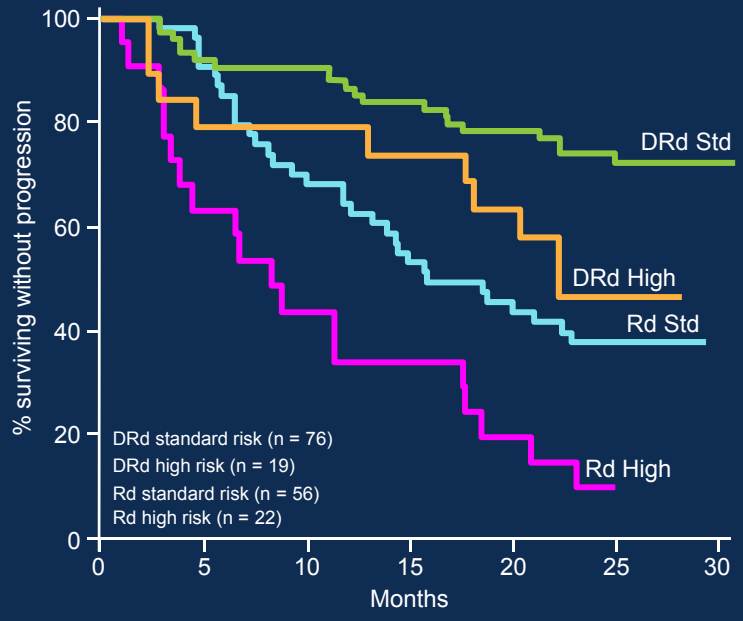
mPFS, median progression-free survival; NR, not reached.
[a]ITT/biomarker risk–evaluable analysis set: patients in the ITT population with both RNA and DNA results available.

POLLUX PFS: NGS Versus FISH

Central NGS[a]



Local FISH[a]

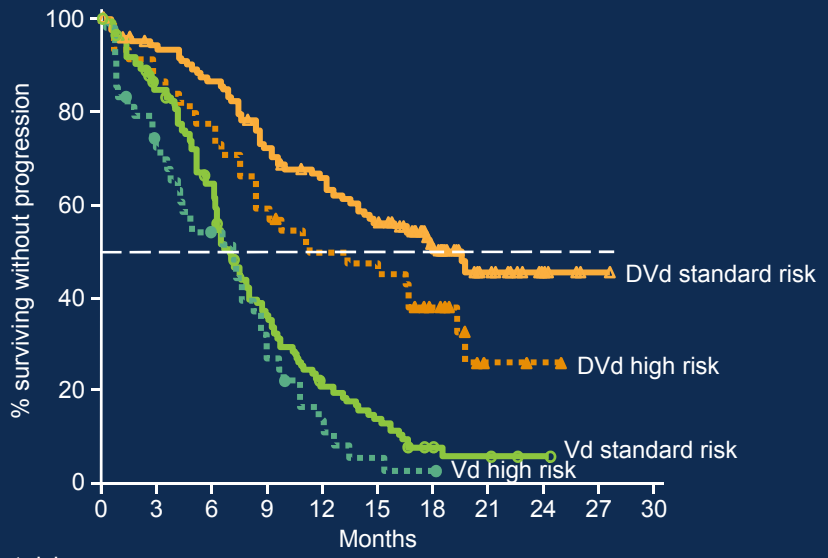


Concordance rates: NGS and FISH	
t(4;14)	96%
t(14;16)	98%
t(14;20)	99%
del17p	88%

High concordance between NGS and FISH

Std, standard.
[a]Prespecified analysis; analysis based on patients who received both NGS and FISH assessments.

CASTOR: PFS by Cytogenetic Risk Status[a]



Patients at risk											
Vd standard risk	135	106	79	44	25	16	5	3	1	0	0
DVd standard risk	123	110	101	83	74	63	36	15	5	1	0
Vd high risk	51	32	23	13	4	2	1	0	0	0	0
DVd high risk	44	38	34	26	21	20	11	2	1	0	0

High risk	**DVd** n = 44	**Vd** n = 51
mPFS, mo	**11.2**	**7.2**
HR (95% CI)	0.45 (0.25-0.80)	
P value	0.0053	

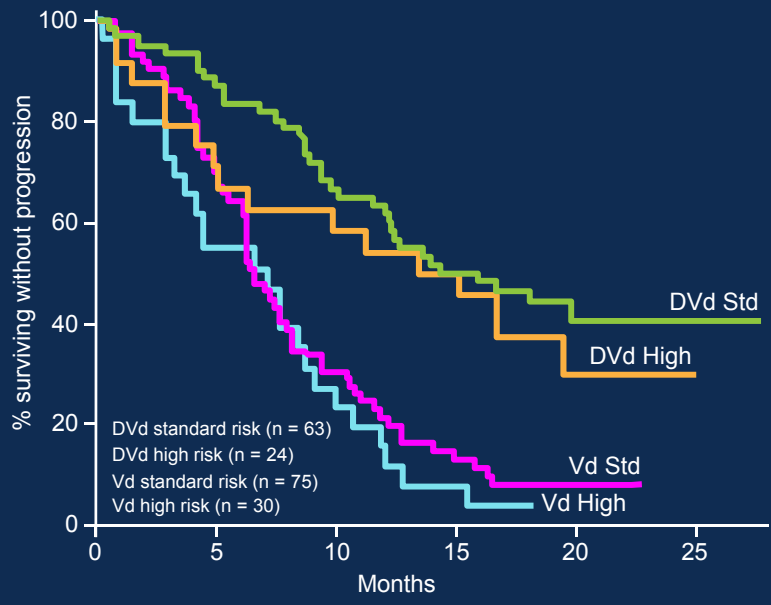
Standard risk	**DVd** n = 123	**Vd** n = 135
mPFS, mo	**19.6**	**7.0**
HR (95% CI)	0.26 (0.18-0.37)	
P value	<0.0001	

Addition of daratumumab to SOC prolongs PFS regardless of cytogenetic risk

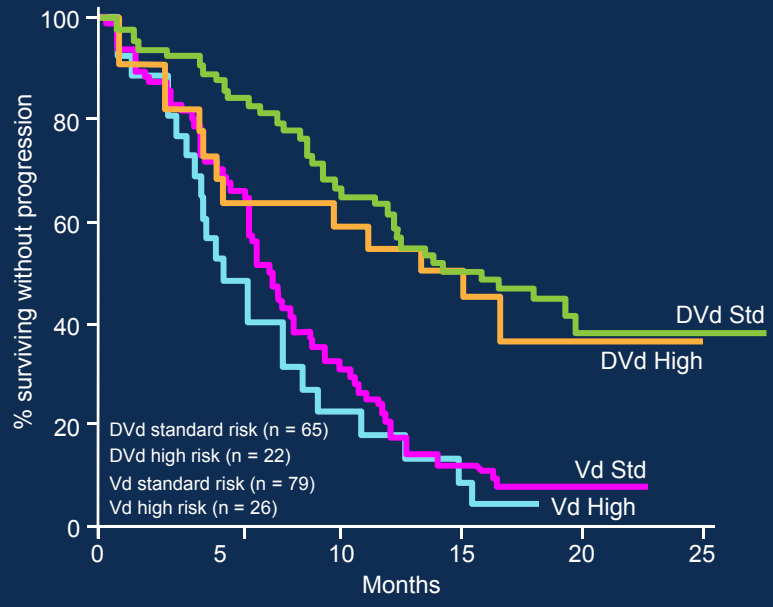
[a]ITT/biomarker risk–evaluable analysis set: patients in the ITT population with both RNA and DNA results available.

CASTOR PFS: NGS Versus FISH

Central NGS[a]



Local FISH[a]

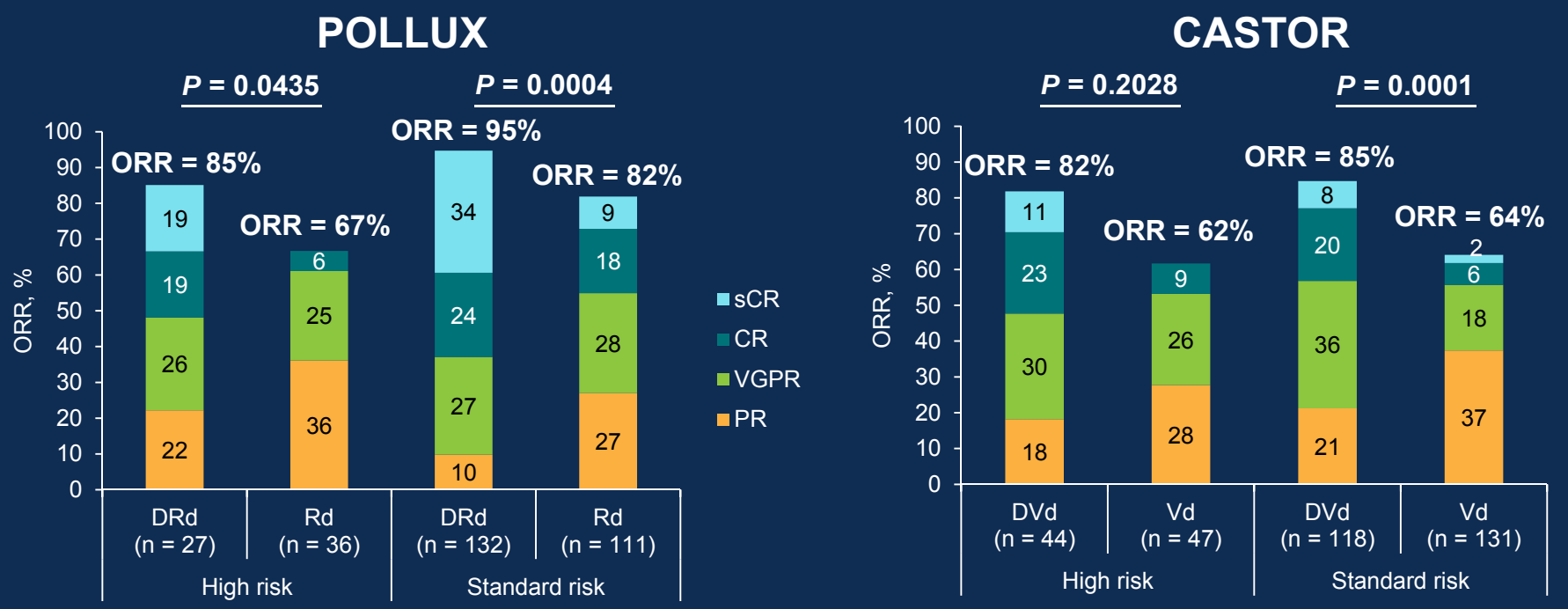


Concordance rates: NGS and FISH	
t(4;14)	92%
t(14;16)	97%
t(14;20)	100%
del17p	90%

High concordance between NGS and FISH

[a]Prespecified analysis; analysis based on patients who received both NGS and FISH assessments.

ORR by Cytogenetic Risk



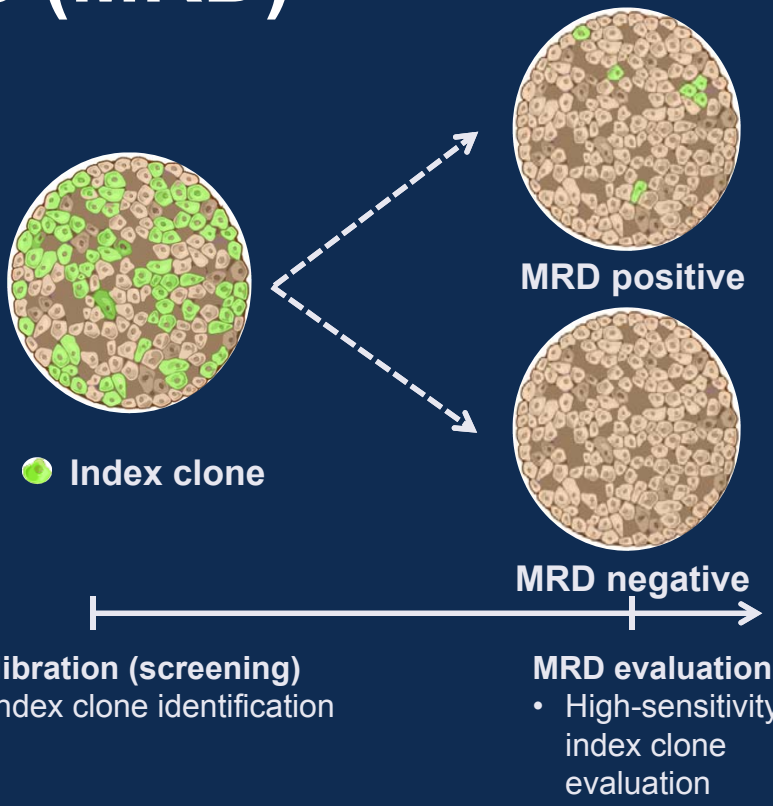
Daratumumab plus SOC improves depth of response regardless of cytogenetic risk

ORR, overall response rate; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response.

Minimal Residual Disease (MRD)

- MRD is a more sensitive measure of disease burden[1,2]
- MRD-negative status is associated with prolonged PFS and OS in multiple myeloma[1,2]

- In POLLUX and CASTOR, bone marrow was assessed at suspected CR using a ClonoSEQ™ NGS-based assay[3]
- Daratumumab plus SOC significantly improved MRD-negative rates[3]
  - At 10^{-5}, MRD-negative rates were >4-fold higher
  - MRD-negative status prolonged PFS versus MRD-positive status

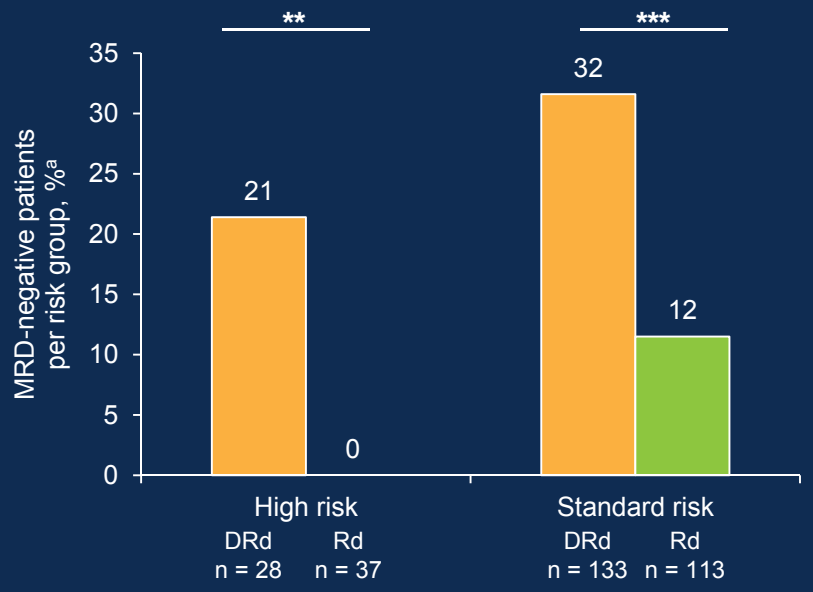


OS, overall survival.

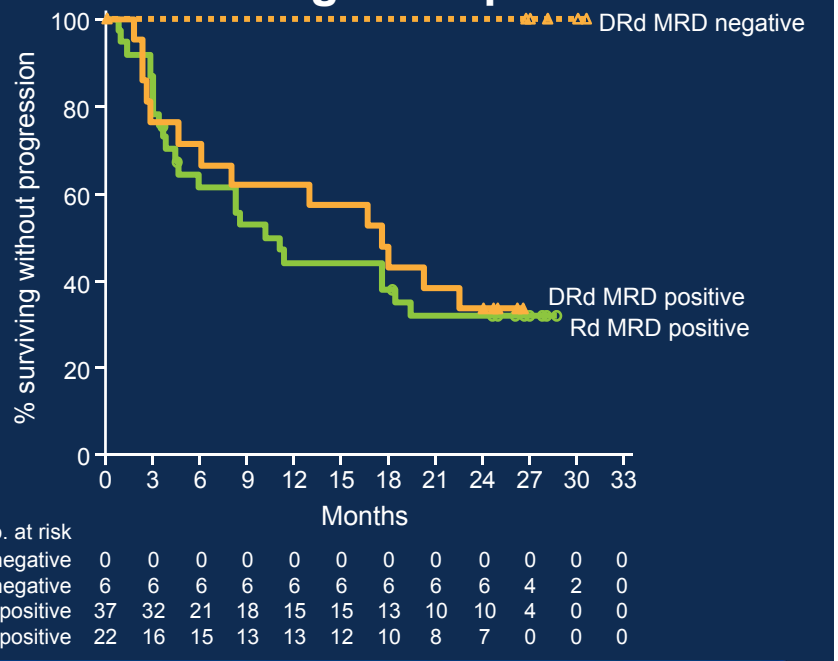
1. Munshi NC, et al. *JAMA Oncol*. 2016;3(1):28-35. 2. Landgren O, et al. *Bone Marrow Transplant*. 2016;51(12):1565-1568. 3. Avet-Loiseau H, et al. Oral presentation at ASH 2016. Abstract 246.

POLLUX: MRD by Cytogenetic Risk Status (10^{-5})

MRD-negative rates



PFS in high-risk patients



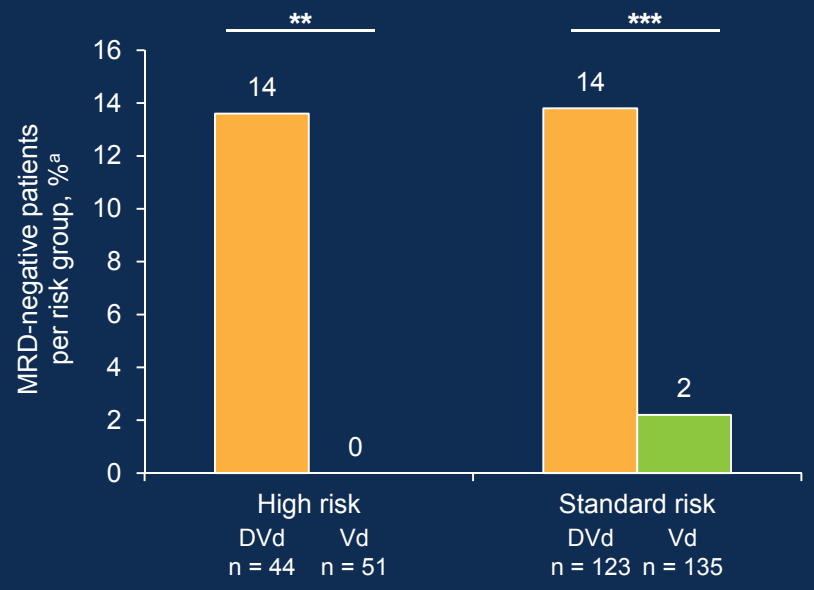
No. at risk												
Rd MRD negative	0	0	0	0	0	0	0	0	0	0	0	0
DRd MRD negative	6	6	6	6	6	6	6	6	6	4	2	0
Rd MRD positive	37	32	21	18	15	15	13	10	10	4	0	0
DRd MRD positive	22	16	15	13	13	12	10	8	7	0	0	0

In POLLUX, high-risk patients treated with daratumumab achieve MRD negativity and remain progression free

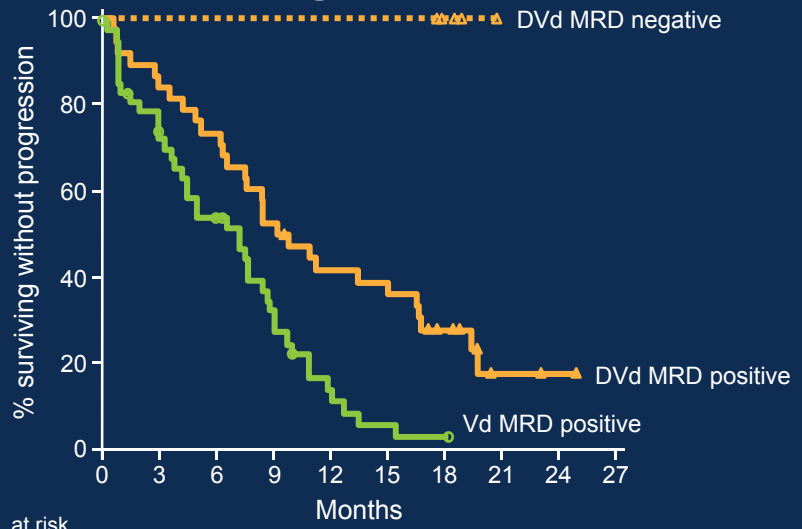
**P = 0.0009. ***P = 0.0001.
[a]Percentage of patients within a given risk group and treatment arm.

CASTOR: MRD by Cytogenetic Risk Status (10^{-5})

MRD-negative rates



PFS in high-risk patients



No. at risk										
Vd MRD negative	0	0	0	0	0	0	0	0	0	0
DVd MRD negative	6	6	6	6	6	6	3	0	0	0
Vd MRD positive	51	32	23	13	4	2	1	0	0	0
DVd MRD positive	38	32	28	20	15	14	8	2	1	0

In CASTOR, high-risk patients treated with daratumumab achieve MRD negativity and remain progression free

***P* = 0.0018. ****P* = 0.0003.
[a]Percentage of patients within a given risk group and treatment arm.

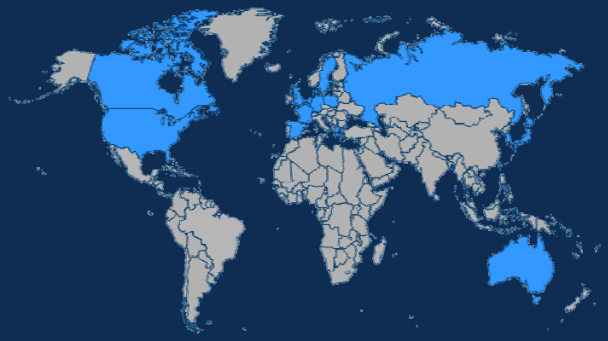
Conclusions

- Daratumumab plus SOC prolongs PFS and improves depth of response regardless of cytogenetic risk
- Although based on small sample sizes, in high-risk patients, MRD negativity was only achieved with daratumumab
  - No MRD-negative, high-risk patients progressed with extended follow-up
- Survival outcomes by cytogenetic risk in POLLUX and CASTOR are awaited
- First prospective analysis of cytogenetic status using NGS in phase 3 studies
  - High (≥88%) concordance rates between FISH and NGS in CASTOR and POLLUX

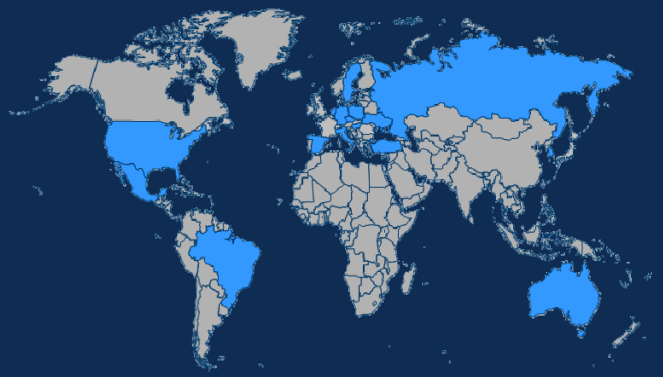
Deep responses achieved by daratumumab-treated, high-risk patients may lead to improved long-term clinical benefit

Acknowledgments

POLLUX



CASTOR



- Patients who participated in these studies
- Investigators
- Data and safety monitoring committee
- Staff members involved in data collection and analyses
  - Sonali Trivedi, Himal Amin, Tineke Casneuf, Chris Velas, Michael Schaffer and Phyllis Wolf

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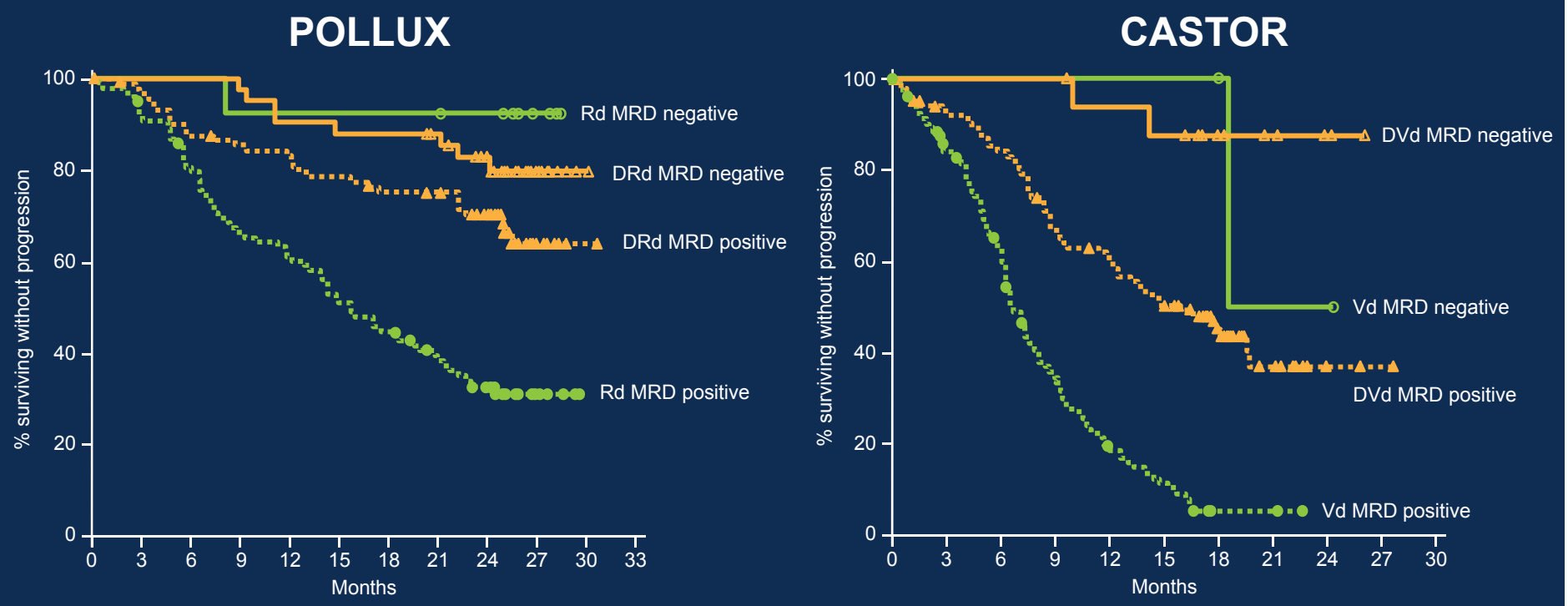
Back-up

PFS by MRD Status in Standard-risk Patients



NGS Methodology

- Bone marrow CD138^{+}-enriched cells
- Illumina HiSeq platform
- High confidence calls were identified with RNA-seq for t(4;14) and t(14;16) translocations
  - Total mRNA with ribo depletion
  - Fusions detected by Tophat-Fusion or deFuse
  - Validated using MMSET/FGFR3 expression and known break points
- Whole exome data was generated, and del13 and del17p analysis was performed
  - High confidence calls made by CNVkit and CNV Radar
  - Validated using B-allele frequency and manually reviewed by independent experts
  - >50% cut-off used for del17p