ALMA MATER STUDIORUM
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Three recent “impressive” stories:
Daratumumab

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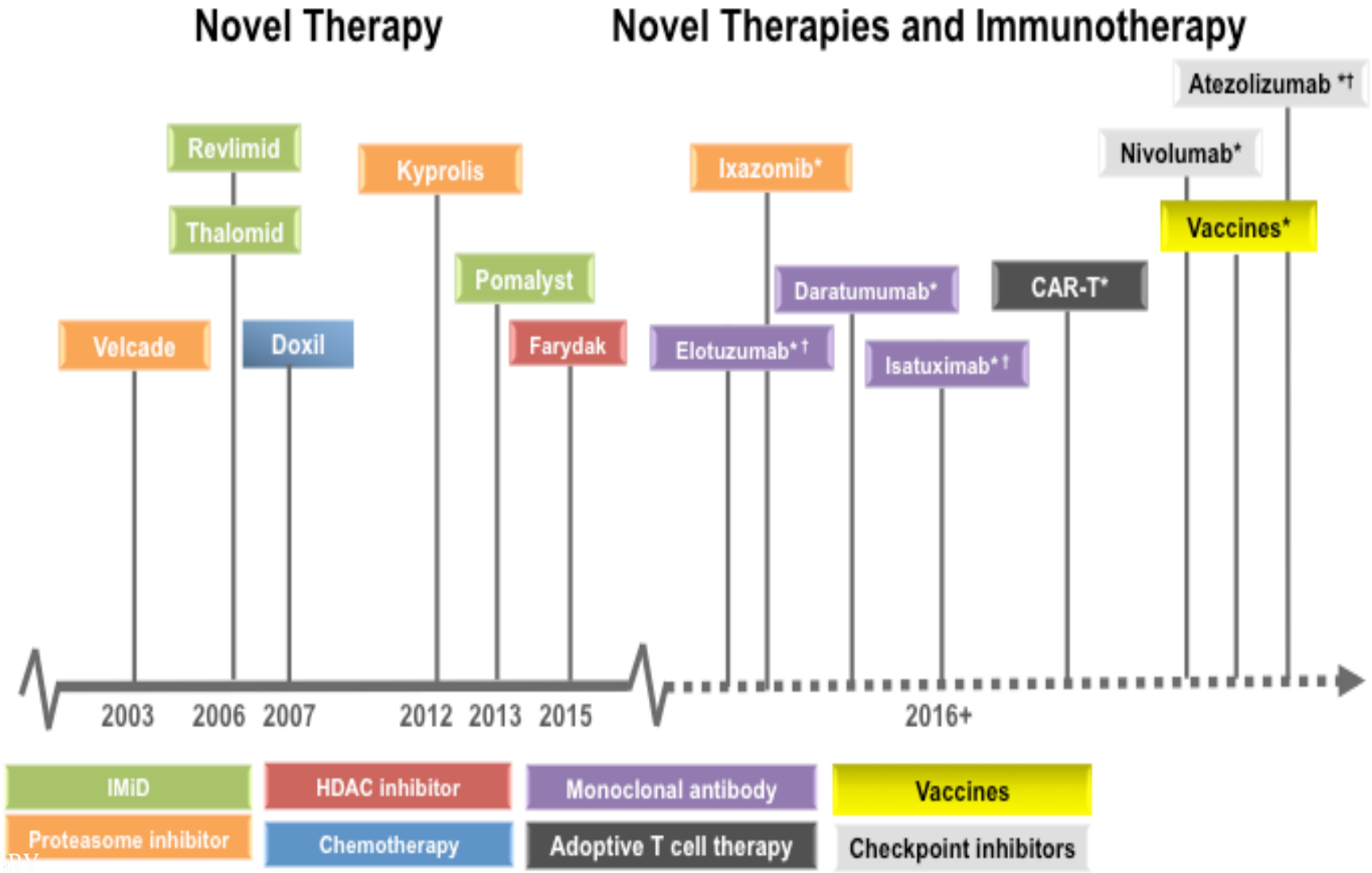
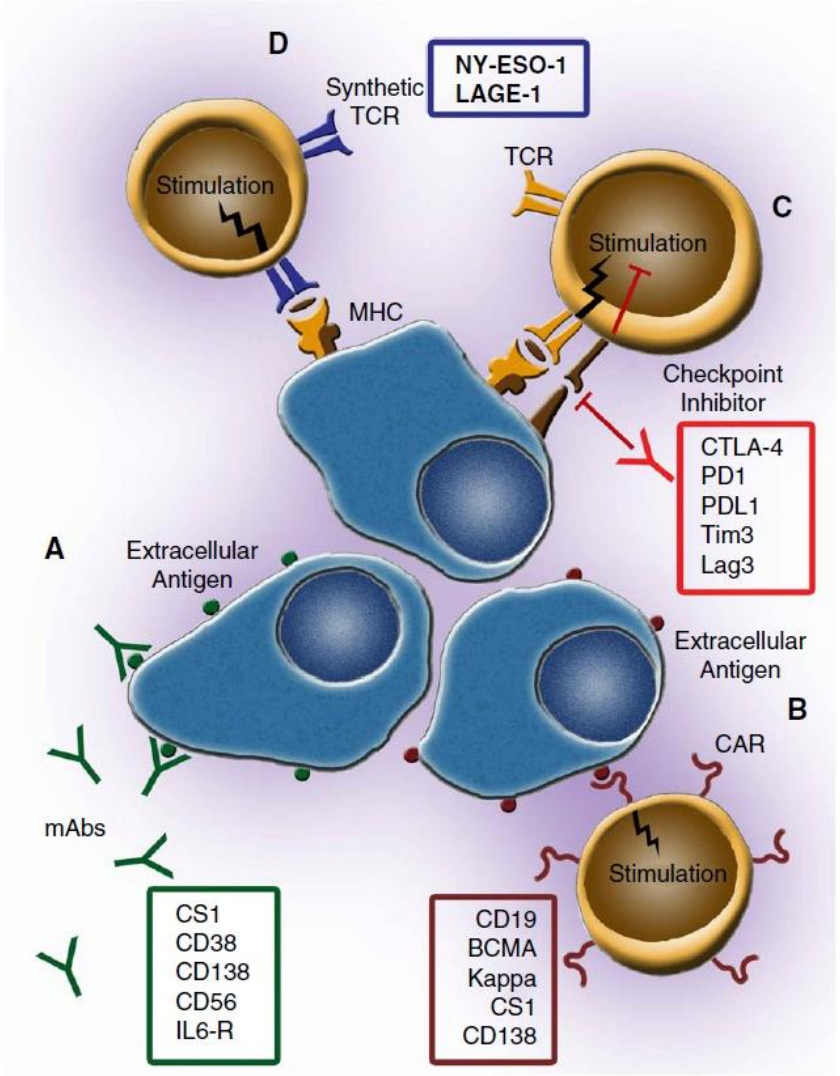
Myeloma Drug Development



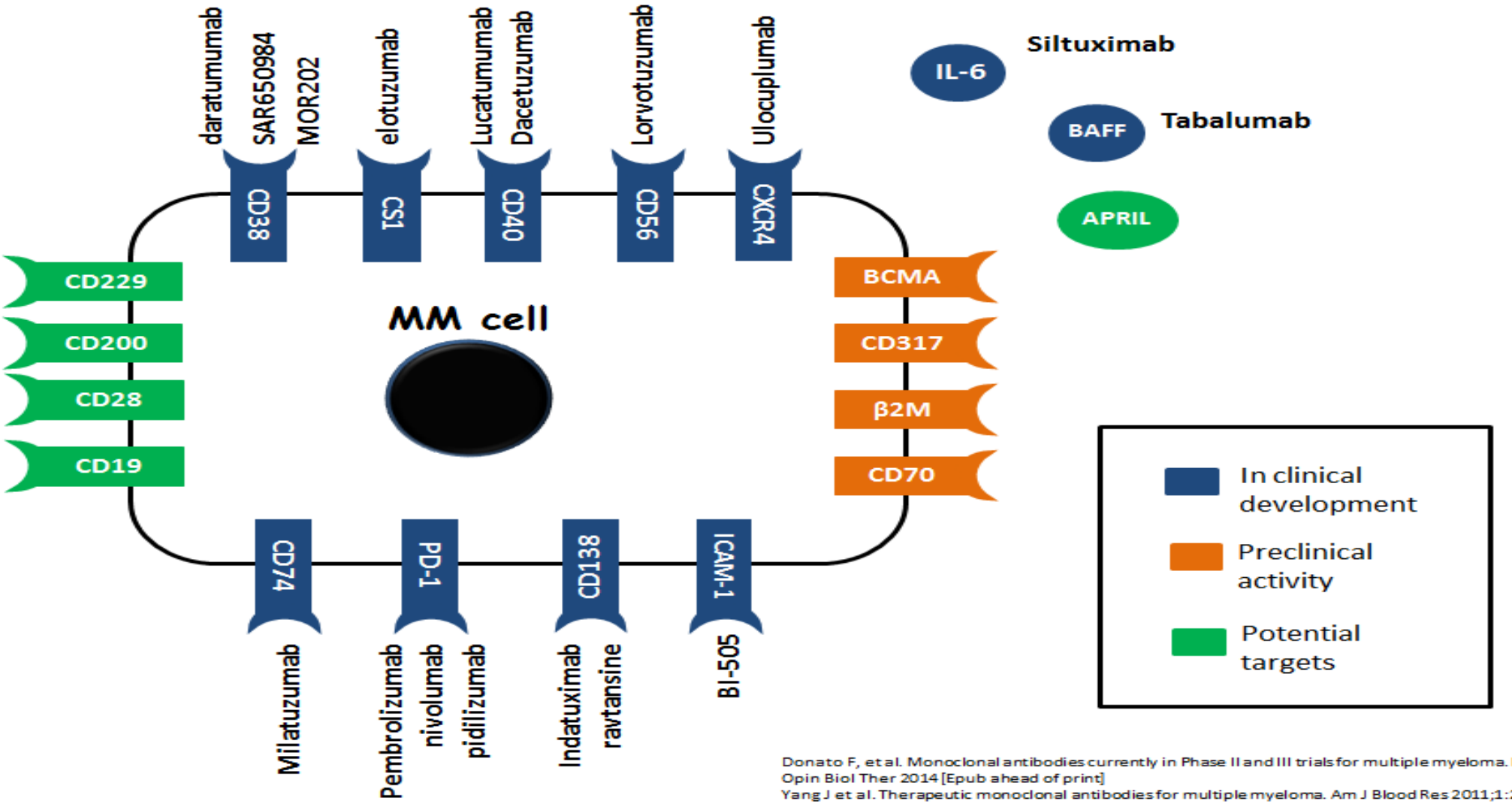
IMiD, immunomodulatory drug; HDAC, histone deacetylase; KSP, kinesin spindle protein, SINE, selective inhibitor of nuclear export
*Not yet FDA-approved for MM; only available in clinical trials
†Treatments studied in MMRC trials

Immunotherapy Targets in MM



Borrello et al. *Blood* 2016.

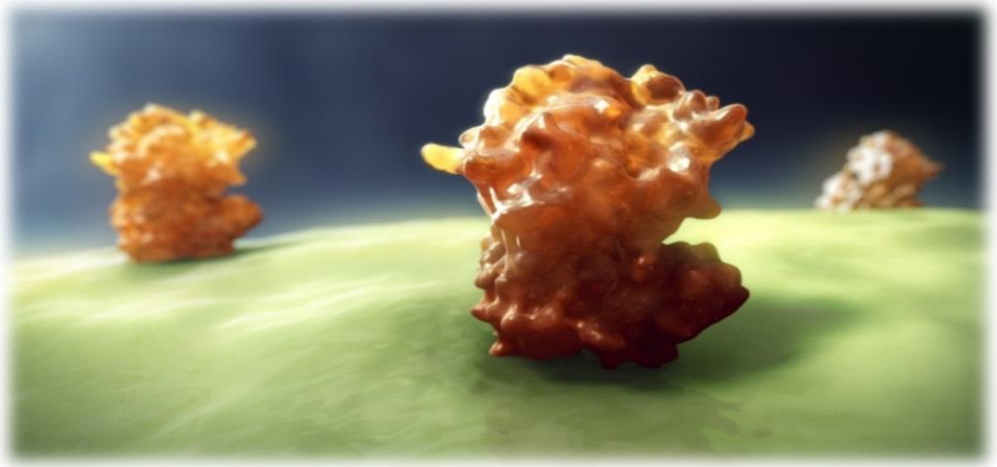
Targets for mAbs in MM



Donato F, et al. Monoclonal antibodies currently in Phase II and III trials for multiple myeloma. Expert Opin Biol Ther 2014 [Epub ahead of print]
Yang J et al. Therapeutic monoclonal antibodies for multiple myeloma. Am J Blood Res 2011;1:22–33
Mateo G, et al. Prognostic value of immunophenotyping in multiple myeloma: A study by the PETHEMA/GEM Coopereatvie study groups on patients uniformly treated with high-dose therapy
Atanackovic D, et al. Surface molecule CD229 as a novel target for the diagnosis and treatment of multiple myeloma. Haematologica 2014;96:1512–20.

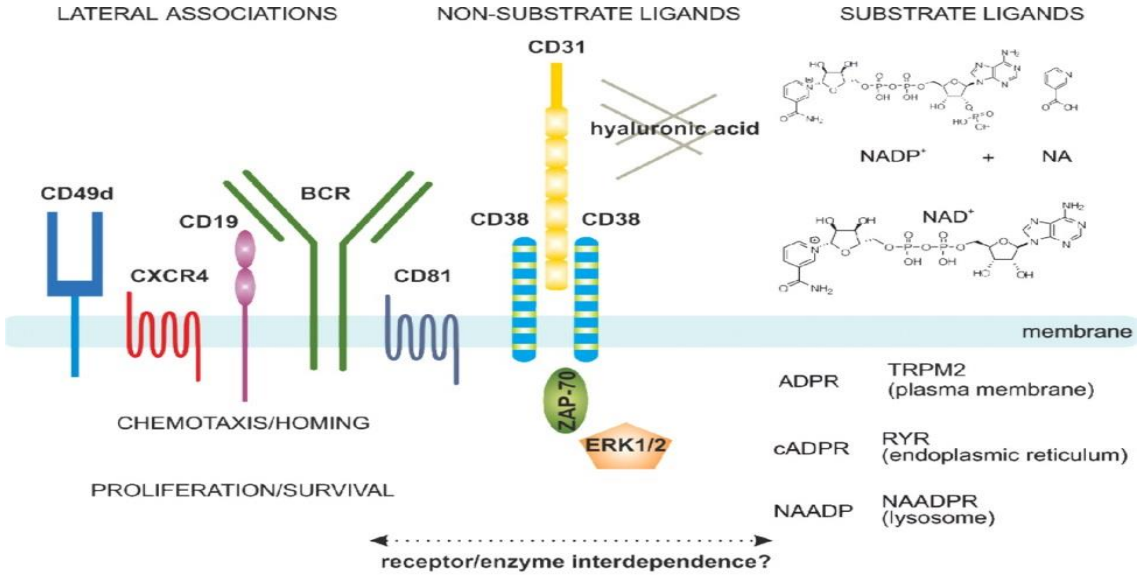
Lonial et al, Leukemia 2015

CD38 As an Ectoenzyme and Cell Surface Receptor



- Type II **transmembrane protein** (m.w. ≈45 kDa)
- **Highly and uniformly expressed on myeloma cells**
  - CD38 present on CD4, CD8, NK cells and B lymphocytes at relatively low levels
  - Also some CD38 expression on tissues of non-hematopoietic origin

- CD38 has several intracellular functions
  1. Regulates signaling, homing and adhesion in close contact with BCR complex and CXCR4
  2. Regulates activation and proliferation of human T lymphocytes
  3. As an ectoenzyme, CD38 interacts with NAD+ and NADP+, which are converted to cADPR, ADPR, and NAADP in intracellular Ca2+-mobilization



Malavasi F, et al. Blood 2011;118:3470-3478.

mAb(s) Targeting CD38 Under Clinical Development

Chimeric:

Isatuximab (IgG 1-k)

Fully human:

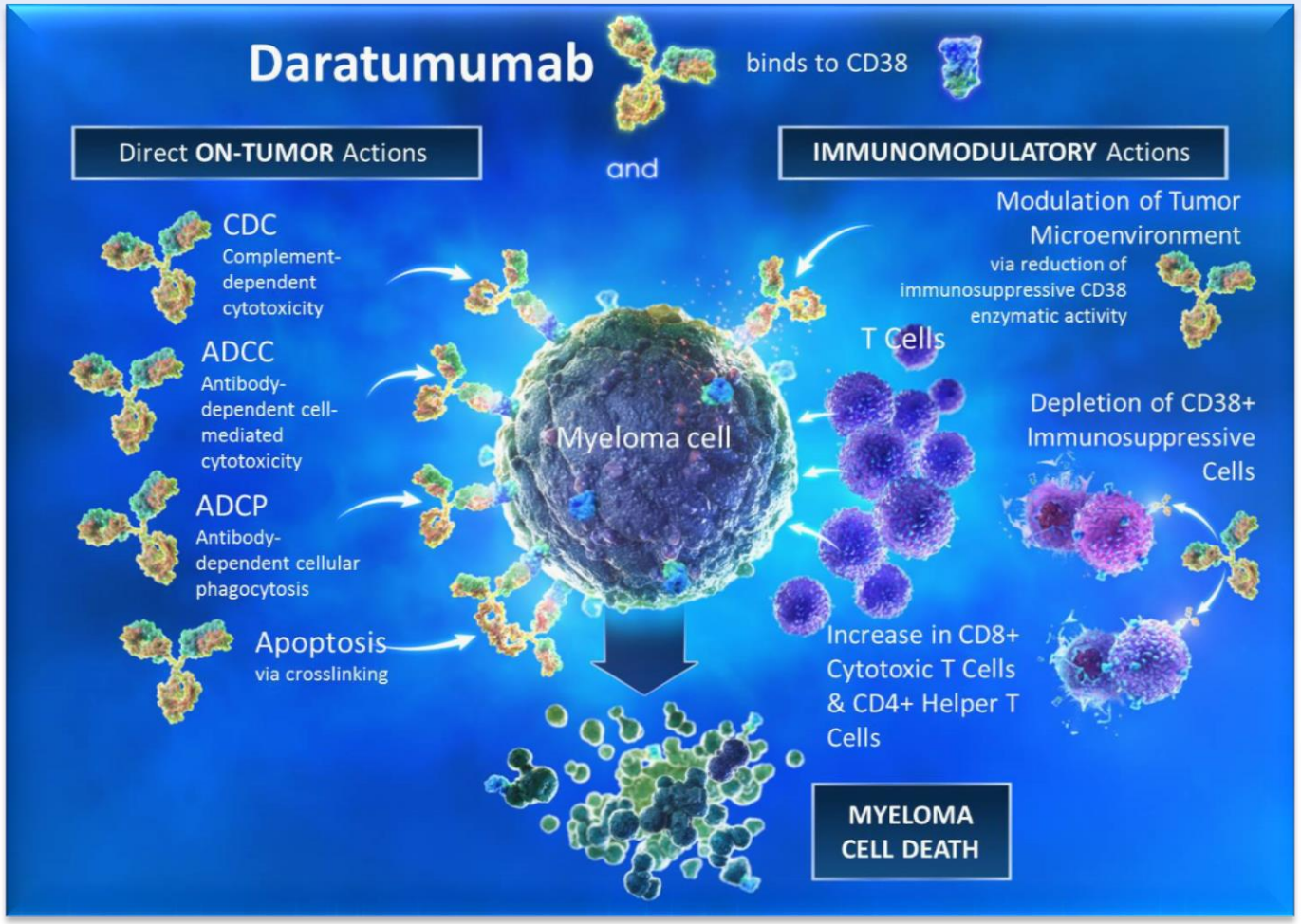
Daratumumab (IgG 1-k)

MOR202 (IgG 1-λ)

van de Donk et al. Blood 2016 ;127(6):681-695

Daratumumab: Mechanism of Action

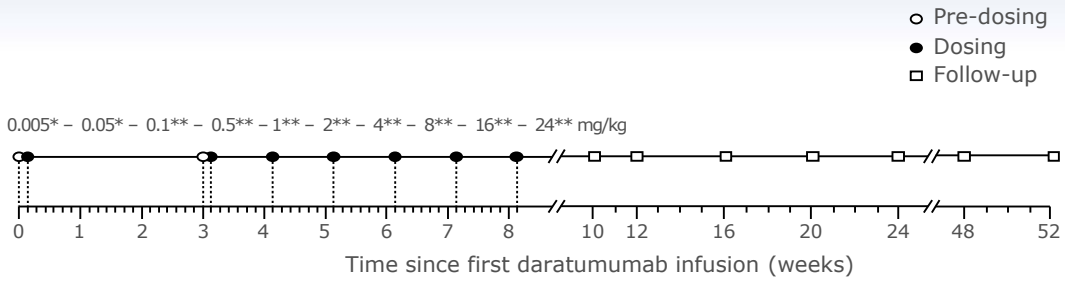
- **Direct anti-myeloma activity through Fc-dependent immune-effector mechanisms[1-4]**
- **Immunomodulatory effects through depletion of CD38^{+} immunosuppressive regulatory cells[5]**
- Promotes T-cell expansion and activation[5]



1. Lammerts van Bueren J, et al. *Blood*. 2014;124:Abstract 3474.
2. Jansen JMH, et al. *Blood*. 2012;120:Abstract 2974.
3. de Weers M, et al. *J Immunol*. 2011;186:1840-8.
4. Overdijk MB, et al. *MAbs*. 2015;7:311-21.
5. Krejcik J, et al. *Blood*. 2016. Epub ahead of print.

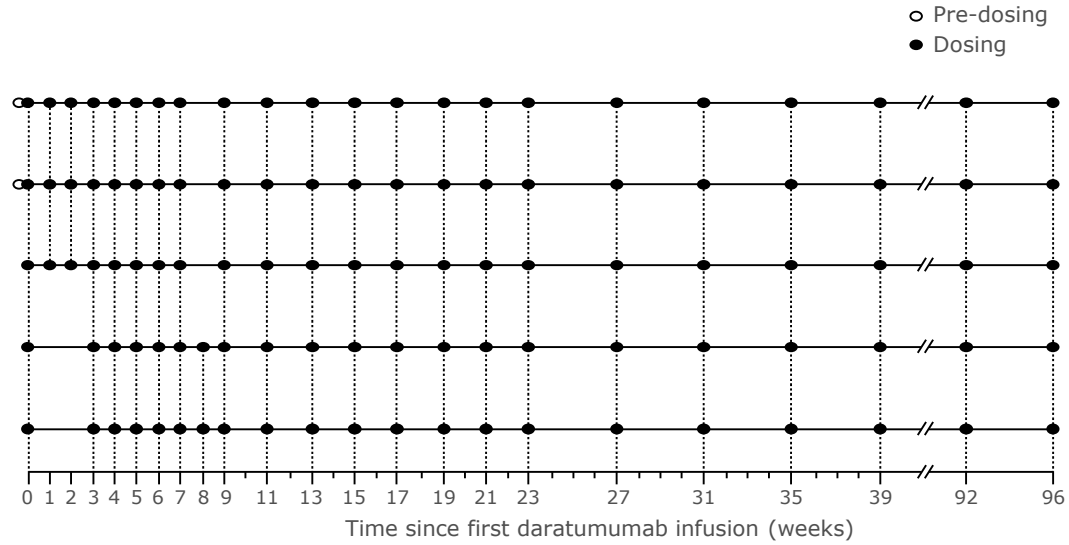
GEN501: First-in-Human Phase 1/2 Study

Part 1 – Open label, **dose-escalation**



*: 1 (+3)(+3) patients
*: 1 (+3) patients

Part 2 – Open label, single-arm, **dose-expansion**, sequential cohorts

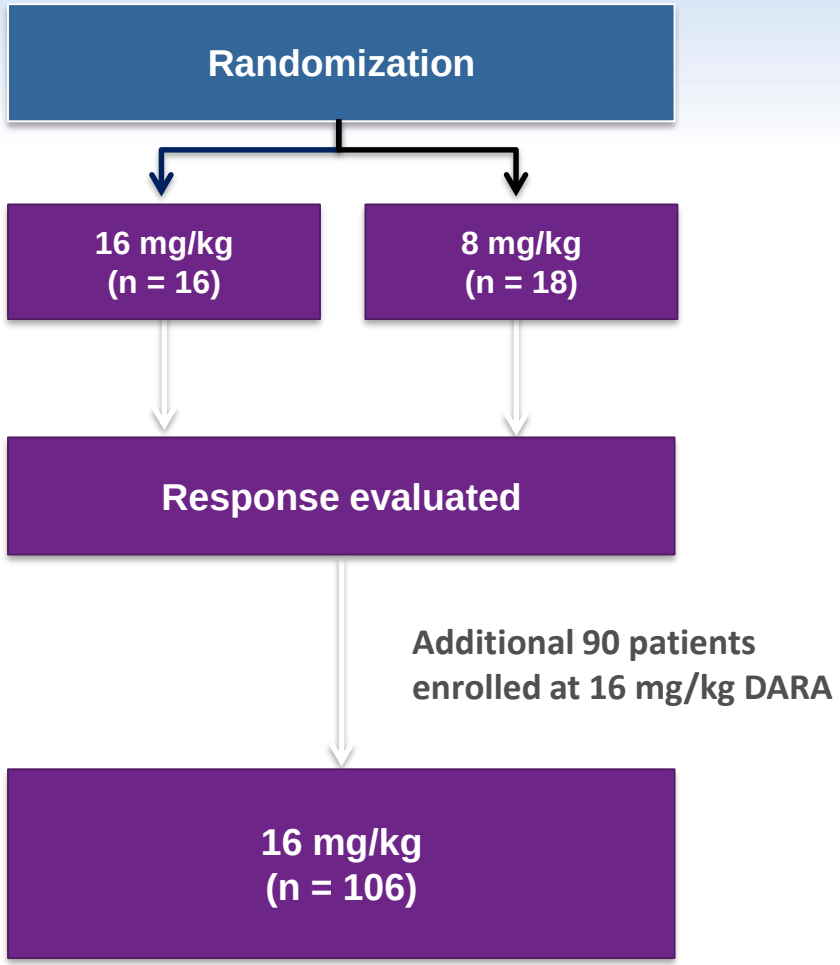


†: Schedules A-E were conducted consecutively

Lokhorst HM, et al. *New Engl J Med*. 2015 373(13):1207-19.

Phase 2 SIRIUS Randomized Study: Design

- **Open-label, international, multicenter study of Simon-2-stage design**
- **Initially, patients randomized 1:1 to receive DARA**
  - 8 mg/kg every 4 weeks (Q4W) or
  - 16 mg/kg every week (QW) for 8 weeks, every 2 weeks (Q2W) for 16 weeks, then Q4W thereafter
- **16 mg/kg DARA was established as the recommended dose for further study**
- **Results are reported for all patients who were treated with 16 mg/kg DARA (n = 106)**



Lonial S, et al. Presented at: 2015 American Society of Clinical Oncology (ASCO); May 29-June 2, 2015; Chicago, IL, USA.

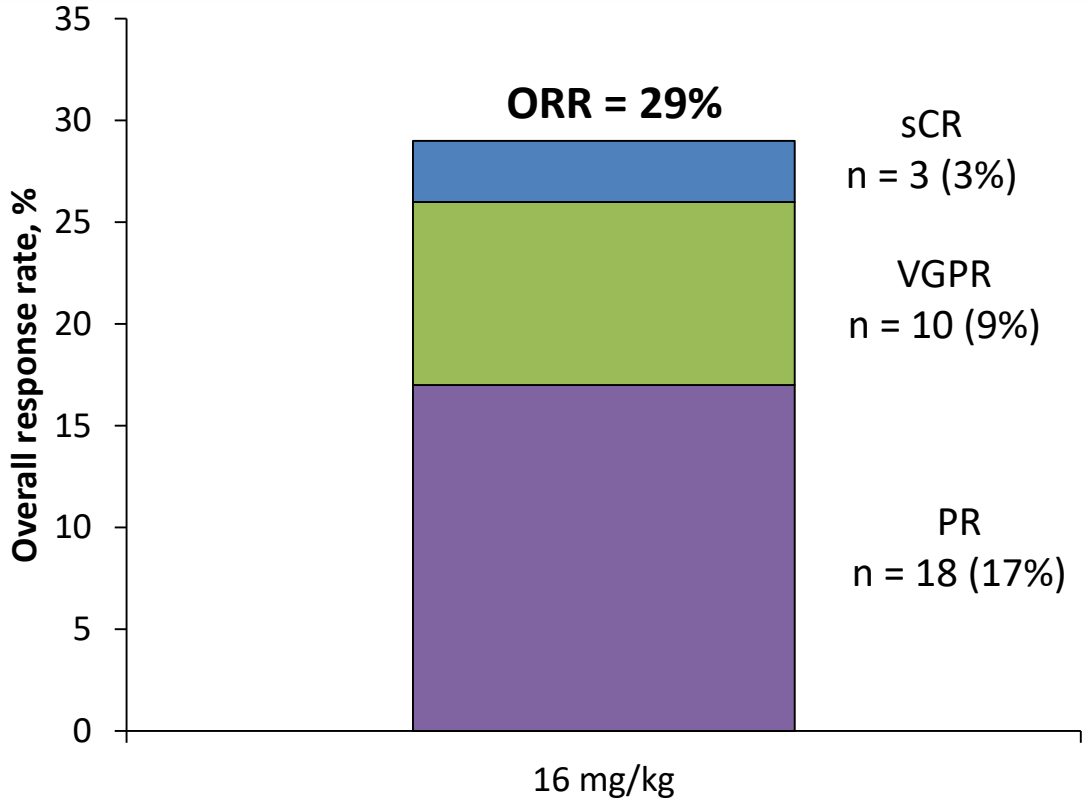
Phase 2 SIRIUS Study: Baseline Refractory Status

Refractory to, n (%)	n = 106
Last prior therapy	103 (97)
PI and IMiD	101 (95)
BORT	95 (90)
CARF	51 (48)
LEN	93 (88)
POM	67 (63)
Alkylating agent	82 (77)
BORT+LEN	87 (82)
BORT+LEN+CARF	42 (40)
BORT+LEN+POM	57 (54)
BORT+LEN+CARF+POM	33 (31)
BORT+LEN+CARF+POM+THAL	12 (11)

- Patients were heavily pretreated, and most patients were refractory to multiple lines of PI and IMiD treatment
  - **97% were refractory to their last line of therapy**
  - **95% were double refractory**
  - 66% were refractory to 3 of 4 therapies (BORT, LEN, CARF, and POM)
  - **63% were refractory to POM**
  - **48% were refractory to CARF**

Lonial S, et al. Presented at: 2015 American Society of Clinical Oncology (ASCO); May 29-June 2, 2015; Chicago, IL, USA.

Phase 2 SIRIUS Study: Overall Response Rate

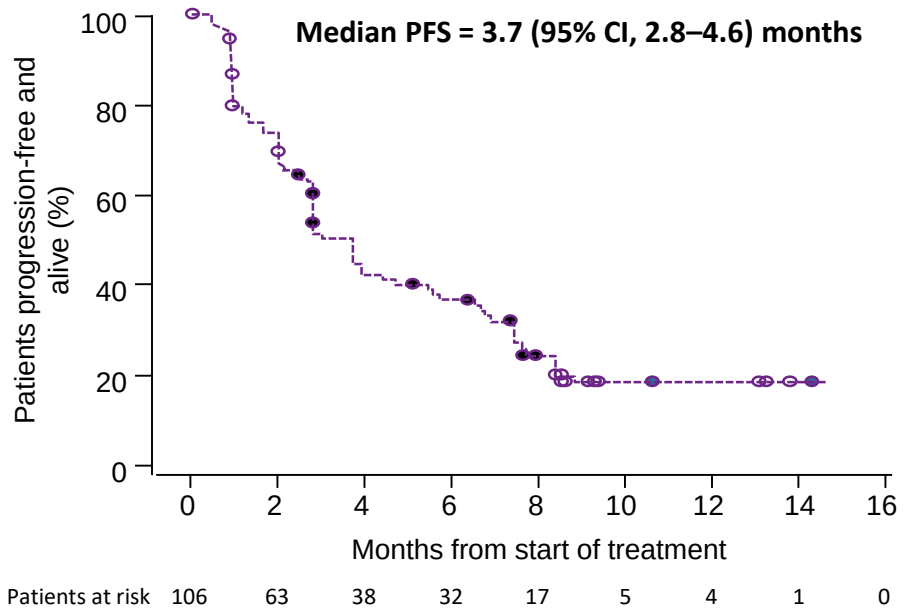


- **ORR was 29% (95% CI, 21–39) in patients receiving 16 mg/kg DARA**
- **The clinical benefit rate (ORR + MR) was 34% (95% CI, 25–44)**
- **VGPR or better was achieved in 12% (95% CI, 7–20) of patients, including stringent complete response (sCR) in 3% of patients (95% CI, 0.6–8.0)**

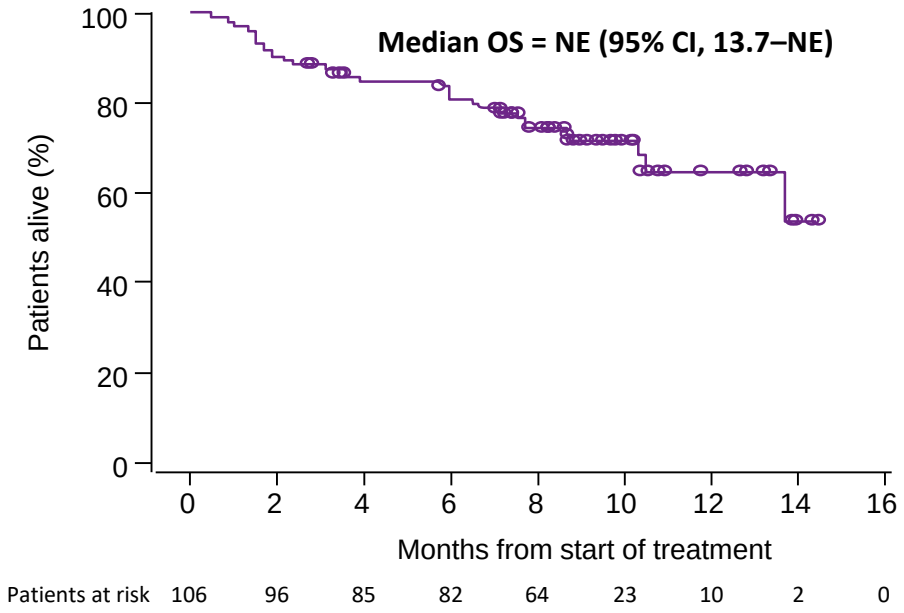
Lonial S, et al. Presented at: 2015 American Society of Clinical Oncology (ASCO); May 29-June 2, 2015; Chicago, IL, USA.

Phase 2 SIRIUS Study: PFS and OS

PFS



OS



- 29 of 31 responders are still alive
- The 1-year survival rate was 65% (95% CI, 51.2–75.5)

Lonial S, et al. Presented at: 2015 American Society of Clinical Oncology (ASCO); May 29-June 2, 2015; Chicago, IL, USA

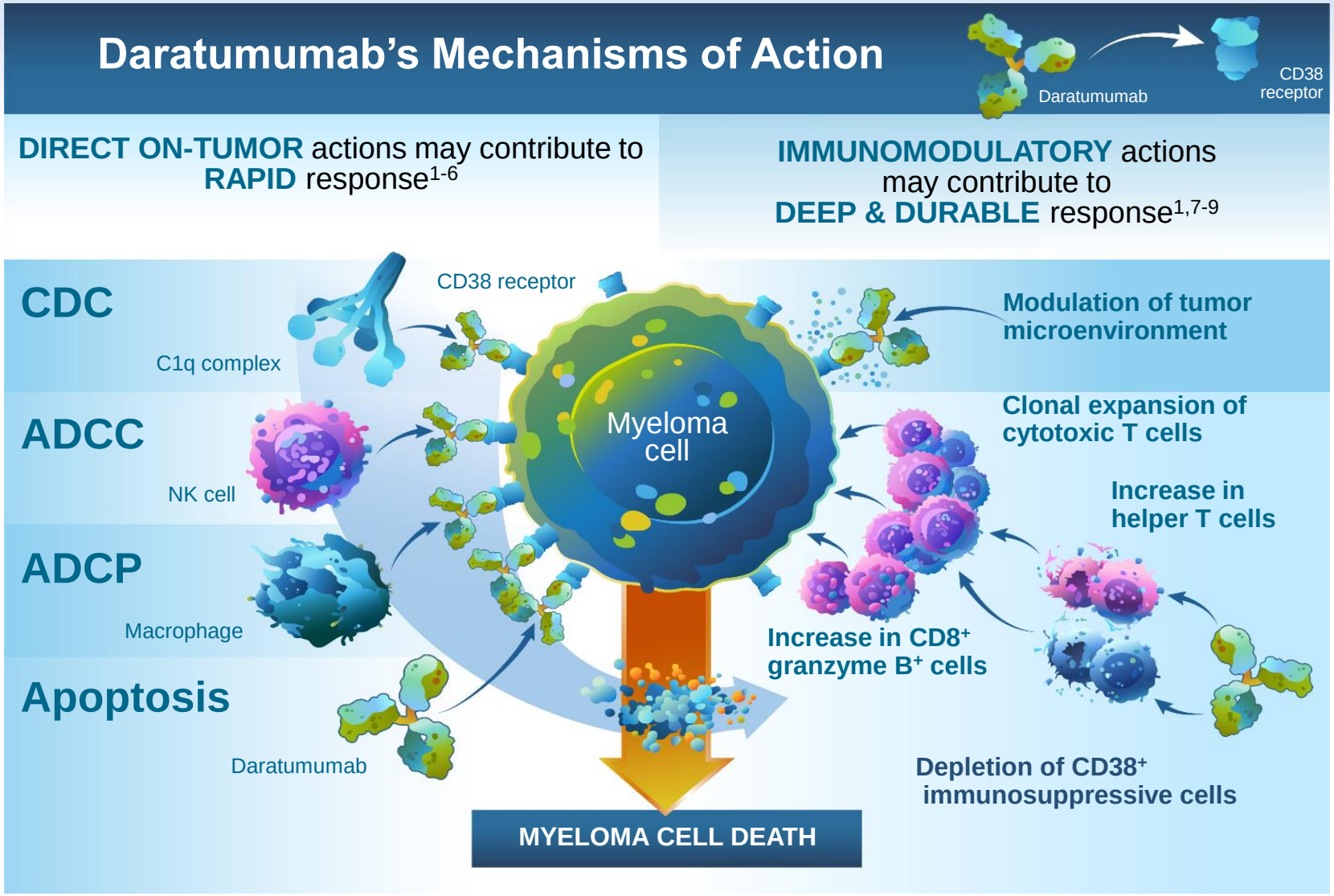
GEN501 and SIRIUS Studies: Clinical Safety

TEAE, n (%)	Any grade N = 148	Grade ≥3 N = 148
Fatigue	61 (41)	3 (2)
Nausea	42 (28)	0
Anemia	41 (28)	26 (18)
Back pain	36 (24)	3 (2)
Cough	33 (22)	0
Neutropenia	30 (20)	15 (10)
Thrombocytopenia	30 (20)	21 (14)
Upper respiratory tract infection	30 (20)	1 (<1)

- AEs were consistent with the individual GEN501 and SIRIUS studies; no new safety signals were identified
- **48% of patients had IRRs**
  - 46%, 4%, and 3% **occurred during the first**, second, and subsequent **infusions**, respectively

Usmani S, et al. Oral presentation: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2015; Orlando, FL. Abstract 29.

Anti-CD38 mAb Daratumumab



- Daratumumab
  - Human IgGκ monoclonal antibody targeting CD38 with a direct on-tumor and immunomodulatory mechanism of action
- Approved
  - **As monotherapy for RRMM patients after ≥3 prior lines of therapy including a PI and an IMiD or who are double refractory to a PI and an IMiD**
  - In combination with bortezomib, melphalan, and prednisone in non-transplant NDMM (United States, Brazil, etc.)
- Efficacy
  - Daratumumab-based combinations reduce risk of progression or death and induce rapid, deep, and durable responses in RRMM and NDMM[10-12]

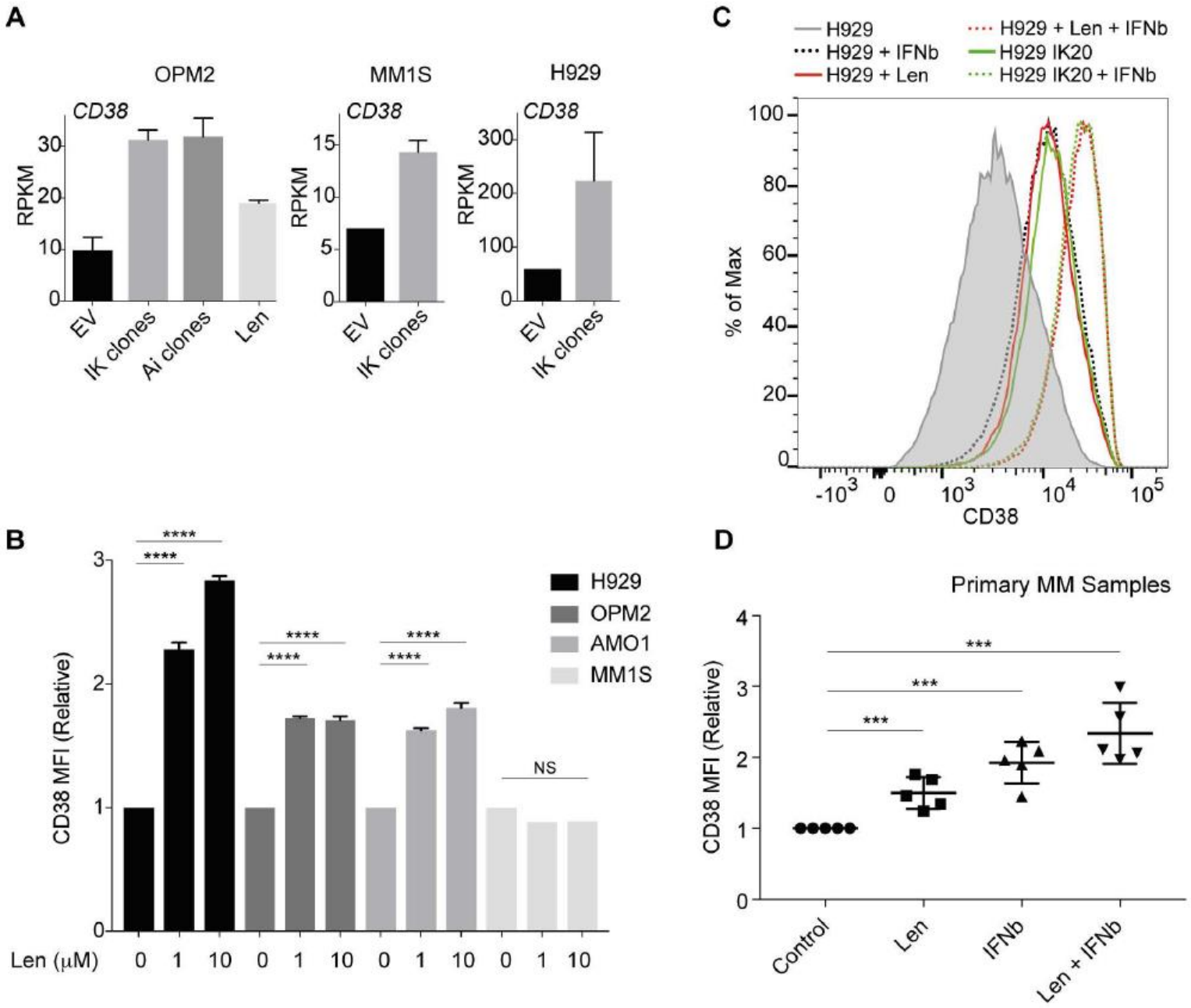
CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cellular cytotoxicity; NK, natural killer; ADCP, antibody-dependent cellular phagocytosis; RRMM, relapsed/refractory multiple myeloma.

1. DARZALEX US PI; 2018. 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. *N Engl J Med*. 2015;373(13):1207-1219. 6. Plesner T, et al. *Blood*. 2012;120:73. 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. Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-766. 11. Dimopoulos MA, et al. *N Engl J Med*. 2016;375(14):1319-1331. 12. Mateos MV, et al. *N Engl J Med*. 2018;378:518-528.

Preclinical Rationale Supporting the Combination of IMiDs with Daratumumab

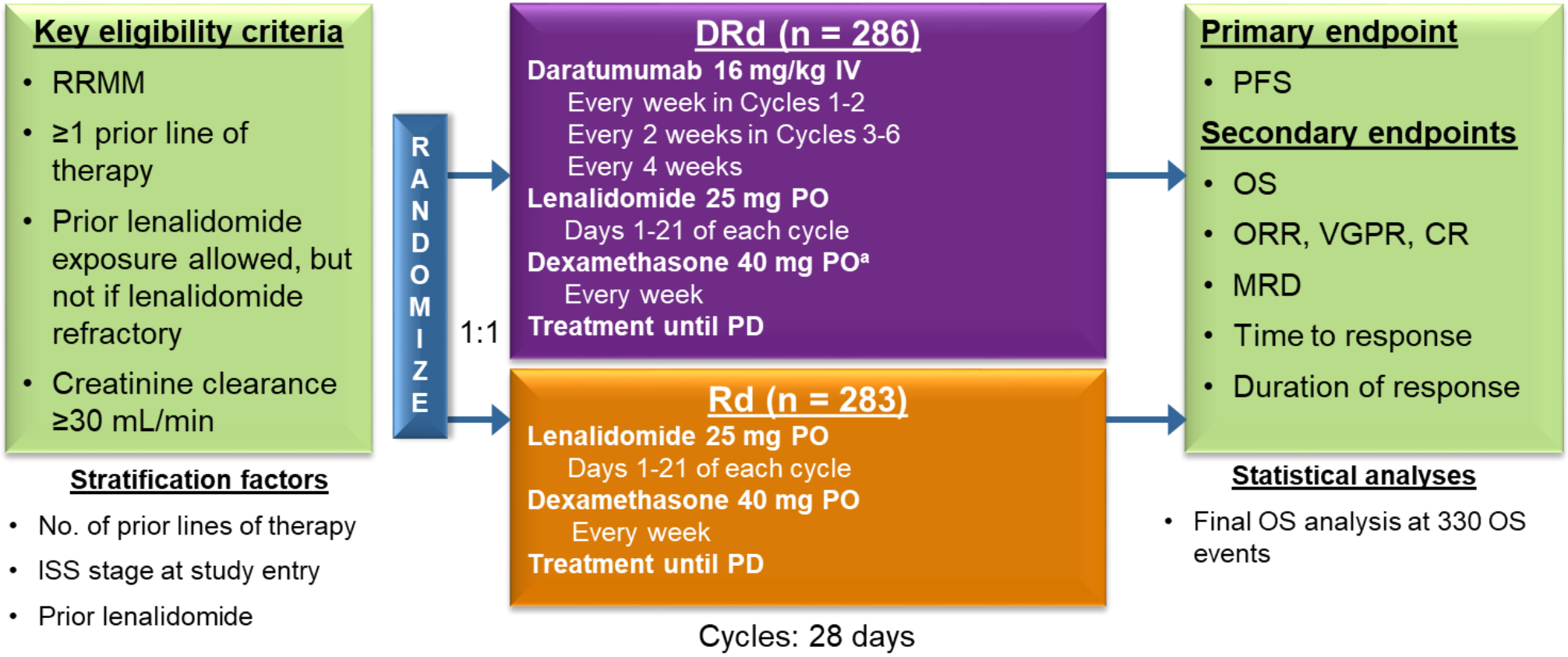
- IMiDs increase NK-cell number and activity, thus enhancing NK-cell mediated ADCC
- IMiDs promote tumoricidal activity of macrophages and enhance ADCP
- Mechanistic rationale: IMiDs bind to cereblon which acquires the ability to ubiquitinate and degrade the transcriptional factors Ikaros and Aiolos which repress the activity of interferon stimulated genes, including CD38
- ✓ **IMiD-induced loss of Ikaros and Aiolos results in the upregulation of CD38 surface expression on MM cells,** which are primed for Daratumumab induced NK-cell mediated ADCC

These data have supported the exploratory use of Daratumumab combined with IMiDs in both RRMM and NDMM



Fedele et al, *Blood First Edition, September 18 2018*

POLLUX Phase 3 Study Design



[a]On daratumumab dosing days, dexamethasone 20 mg was administered as pre-medication on Day 1 and Day 2.

Dimopoulos et al. Presented at EHA 2016 (Abstract LB2238), oral presentation.

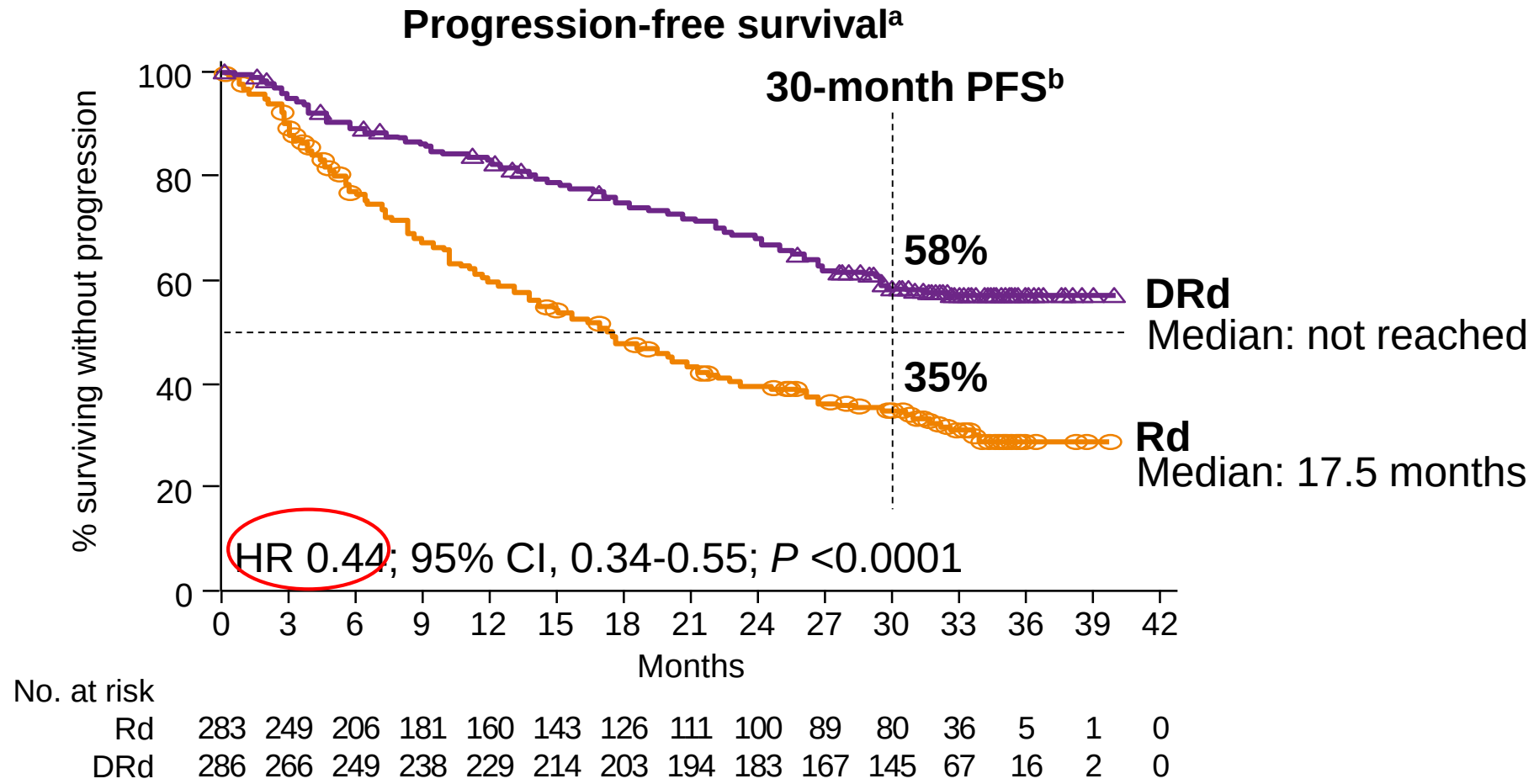
Baseline Demographics and Clinical Characteristics

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

Characteristic	DRd (n = 286)	Rd (n = 283)
Prior lines of therapy, %		
Median (range)	1 (1-11)	1 (1-8)
1	52	52
2	30	28
3	13	13
>3	5	7
1-3[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

DRd, daratumumab/lenadliomide/dexamethasone; Rd, lenalidomide/dexamethasone; ISS, international staging system; ASCT, autologous stem cell transplant; PI, proteasome inhibitor; IMiD, immunomodulatory drug.
[a]ISS staging is derived based on the combination of serum β2-microglobulin and albumin.
[b]Central next-generation sequencing. High risk patients had any of t(4;14), t(14;16), del17p. Standard risk had an absence of high risk abnormalities.
[c]Exploratory.

POLLUX updated analysis: PFS



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

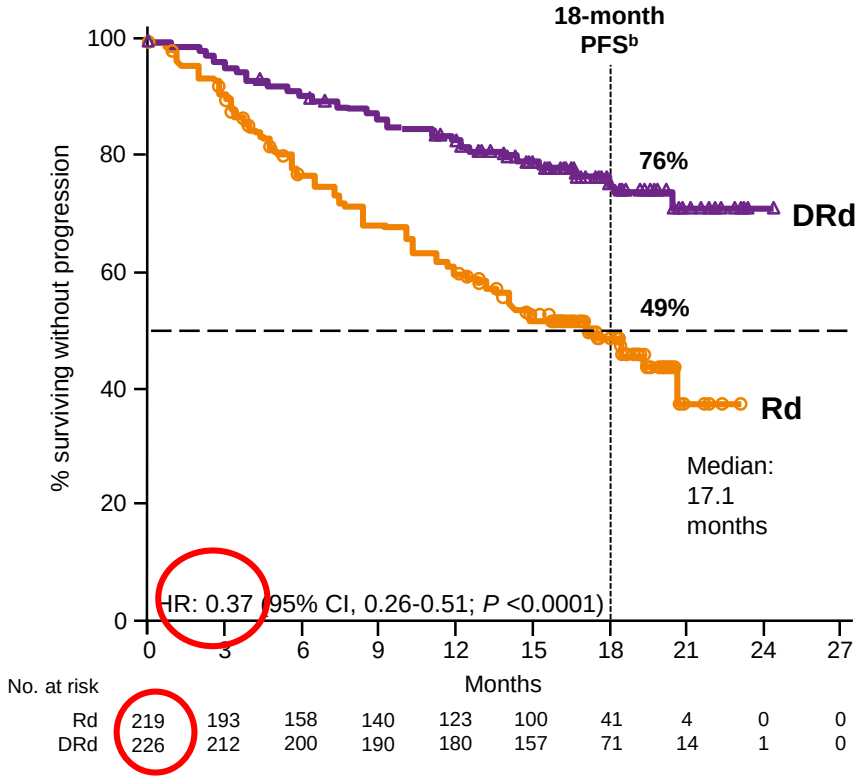
56% reduction in risk of progression/death for DRd versus Rd

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

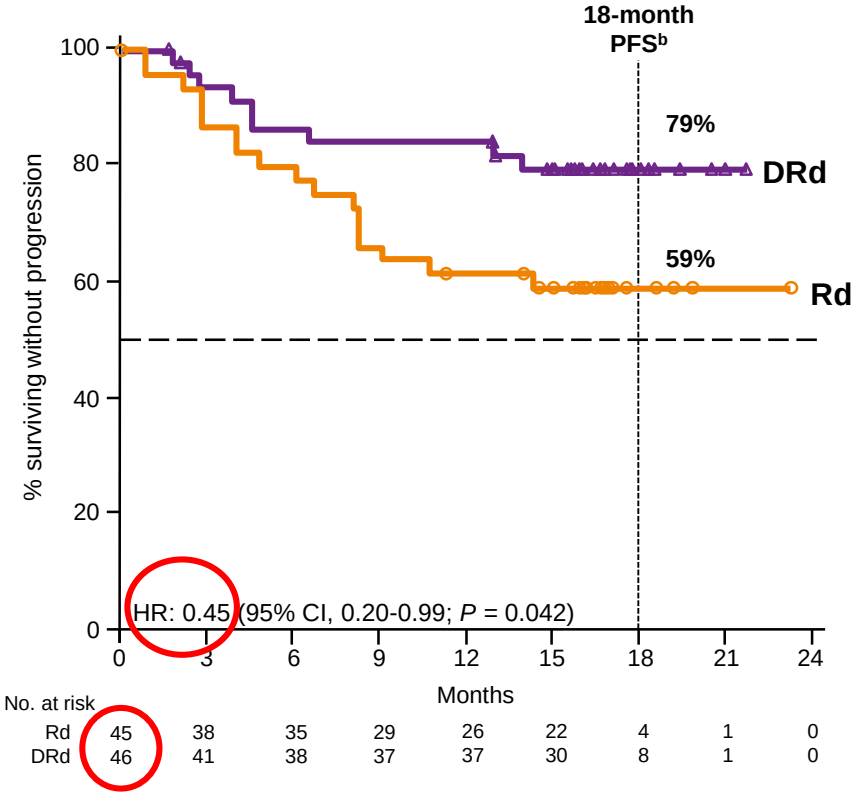
Dimopoulos MA, et al. Presented at ASH 2017 (Abstract 739), oral presentation.

POLLUX: PFS By Prior Lenalidomide Exposure

Lenalidomide-naïve [a]



Lenalidomide-exposed[a]



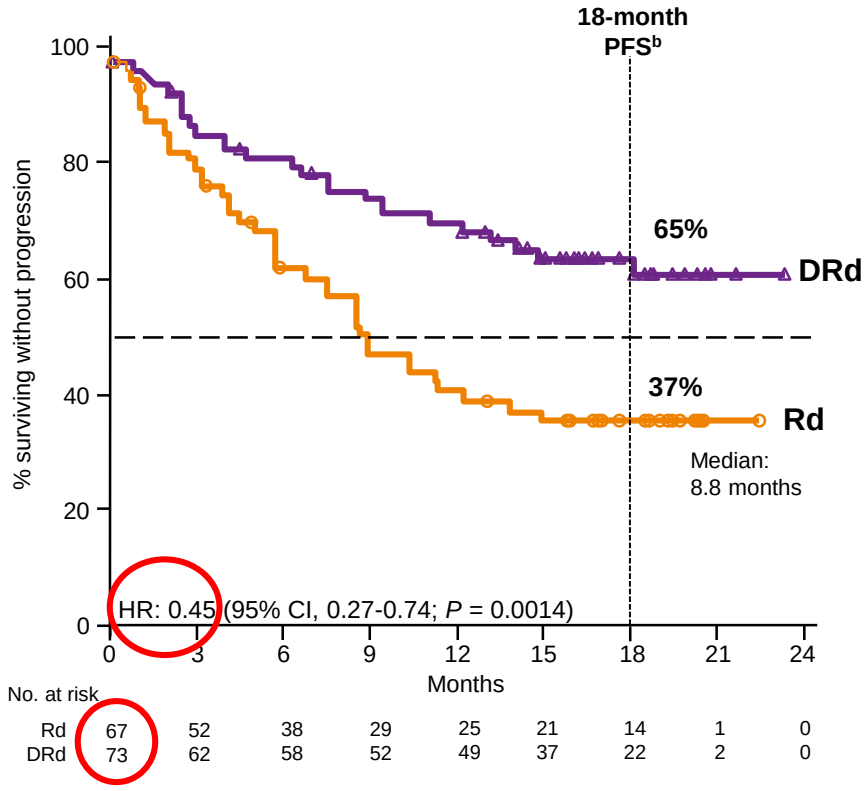
DaraRd maintains PFS benefit in lenalidomide-naïve and exposed patients

[a]in 1 to 3 prior lines
[b]Kaplan-Meier estimate.

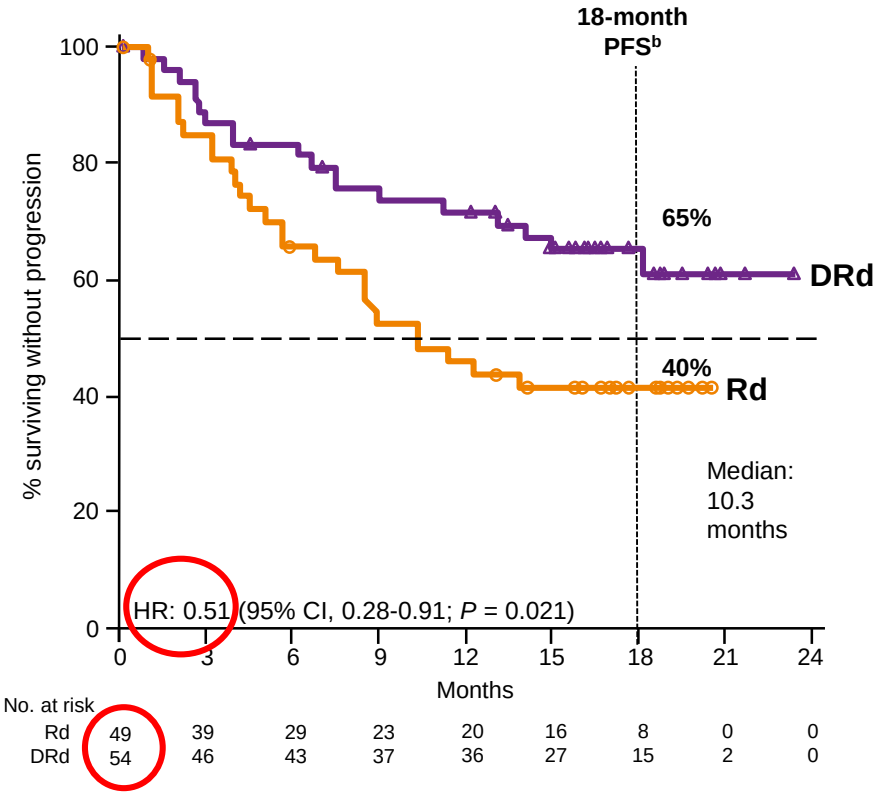
Moreau P, et al. Presented at ASH 2016 (Abstract 489), oral presentation

POLLUX: PFS According to Refractoriness to Last Line of Tx and to Bortezomib

Refractory to Last Line of Tx[a] (28% of patients in both arms)



Bortezomib-refractory[a]

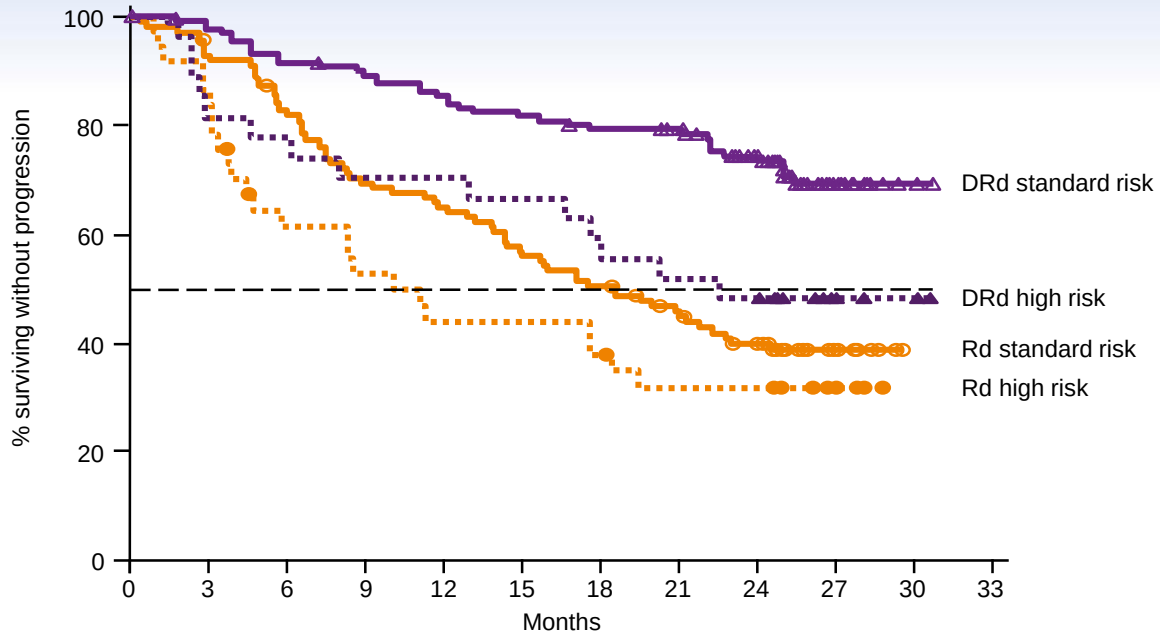


PFS benefit with DaraRd was retained in pts refractory to last line of therapy, including bortezomib-refractory pts

[a]in 1 to 3 prior lines
[b]Kaplan-Meier estimate.

Moreau P, et al. Presented at ASH 2016 (Abstract 489), oral presentation

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

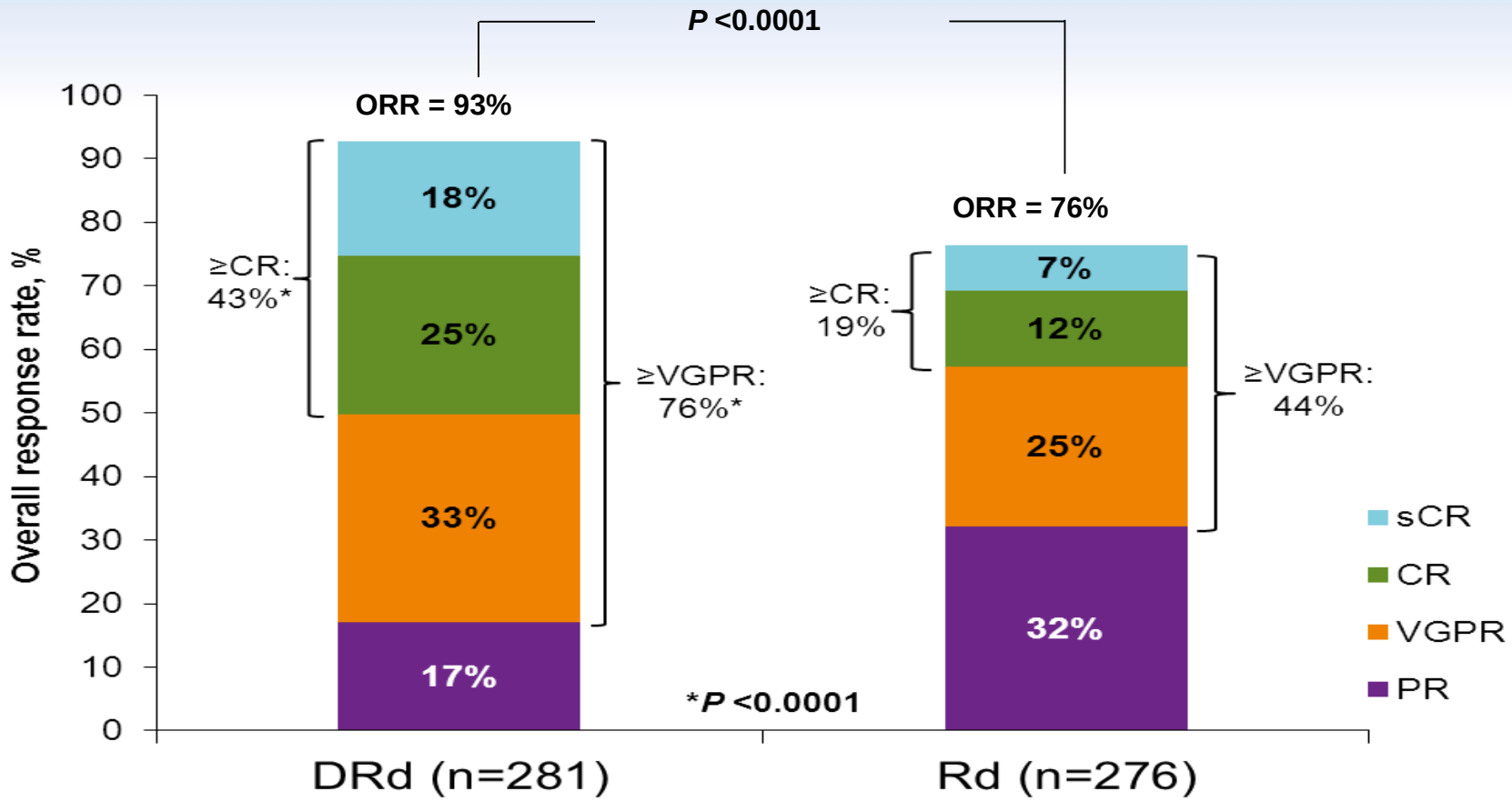
High risk	**DRd** n = 28	**Rd** n = 37
mPFS, mo	**22.6**	**10.2**
HR (95% CI)	0.53 (0.25-1.13)	
P value	0.0921	

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	

Adding DARA to Rd prolongs PFS regardless of cytogenetic risk

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

Overall Response Rate[a]

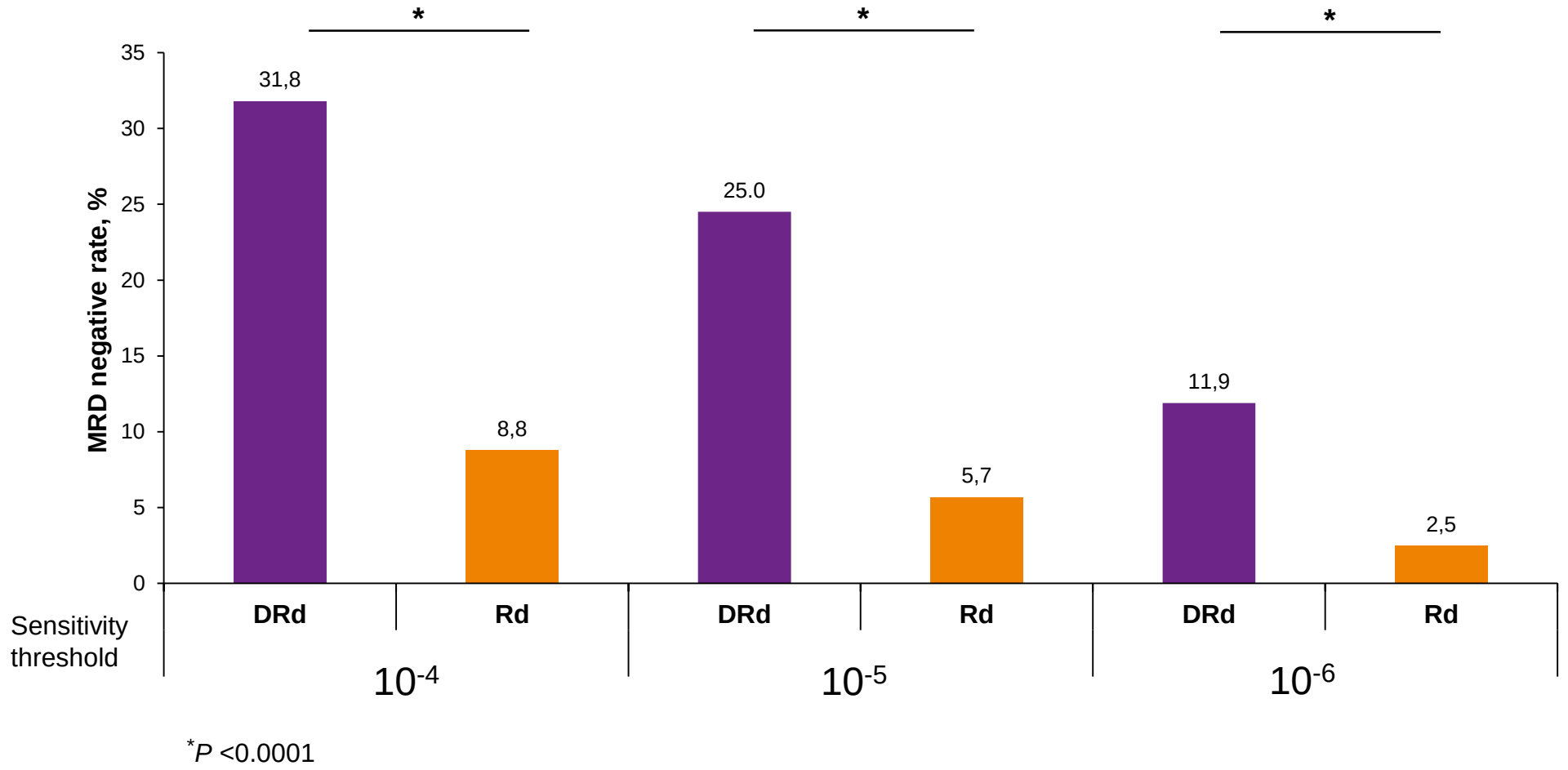


At the latest updated median follow-up of 32.9 months the rate of ≥CR in the DRd arm was 55% (>2-fold higher than with Rd) and that of ≥VGPR was 81%

[a]When serum interference was suspected, CR was confirmed using the daratumumab interference reflex assay.

MRD Negative Rate

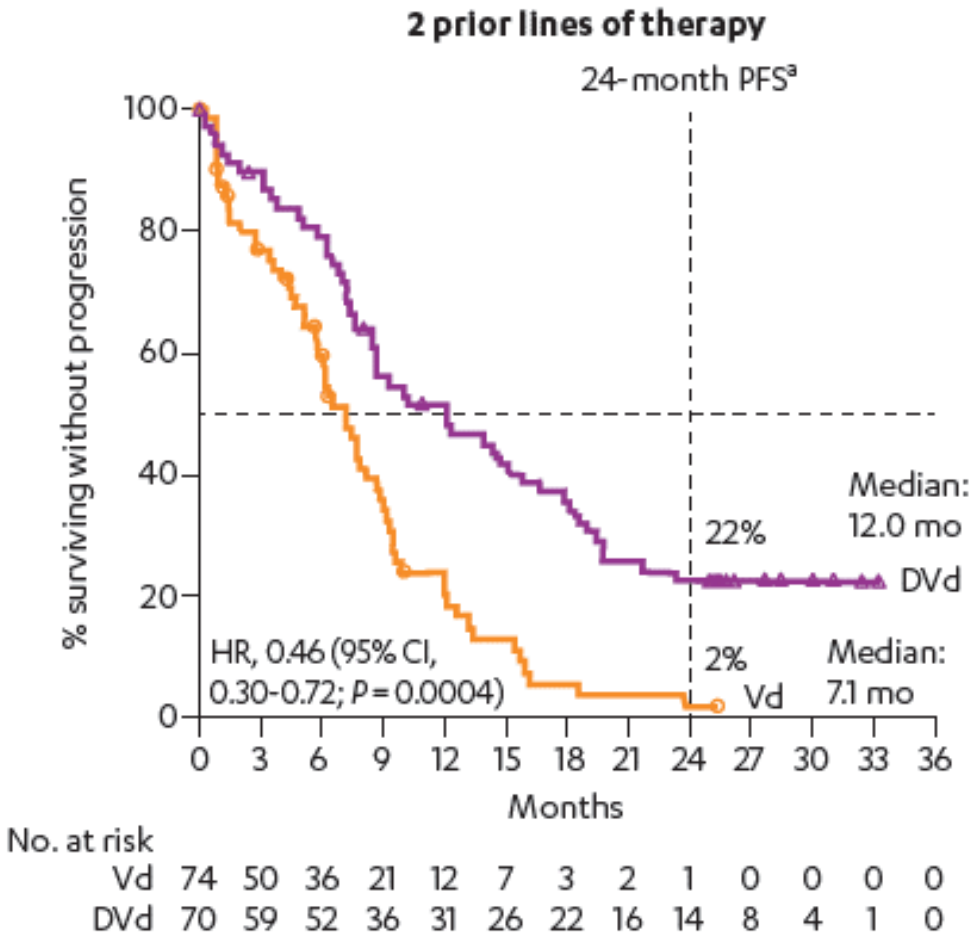
- MRD-negative rates were >3-fold higher across all sensitivity thresholds

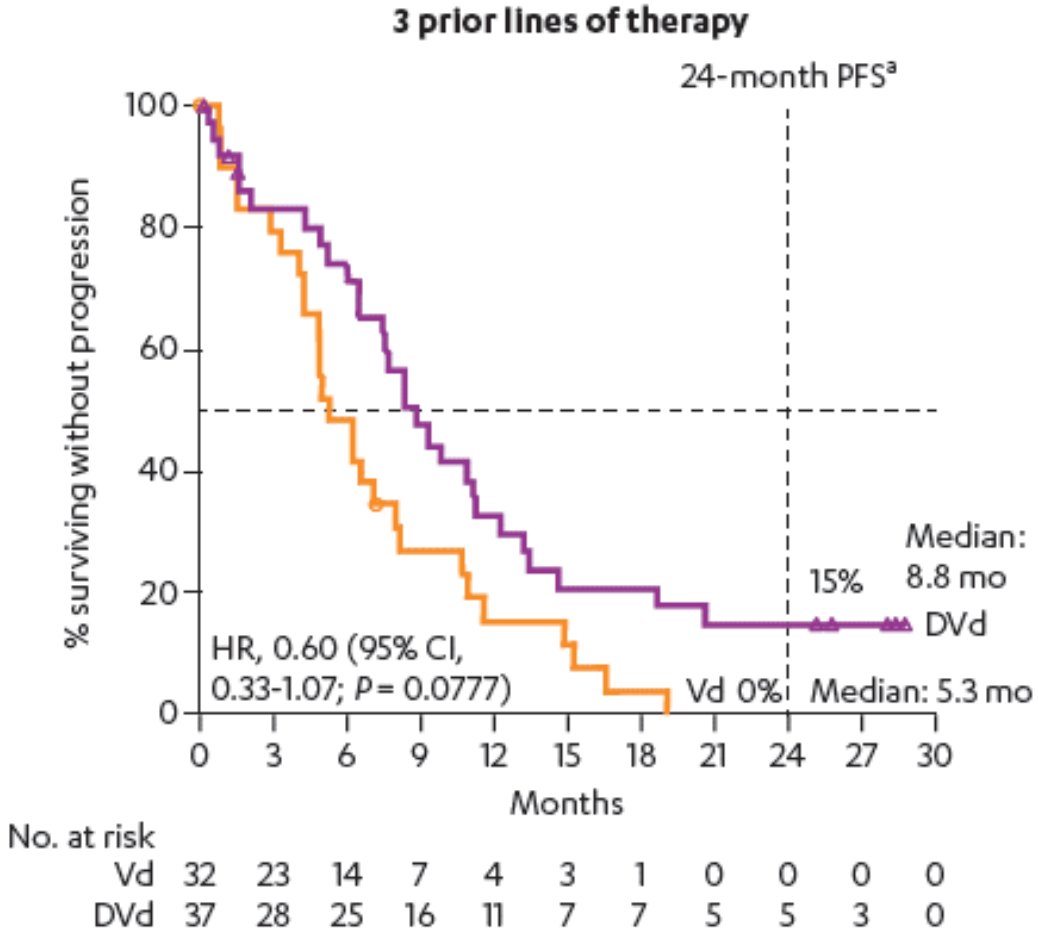


*P <0.0001

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

CASTOR updated analysis: PFS by prior lines of therapy

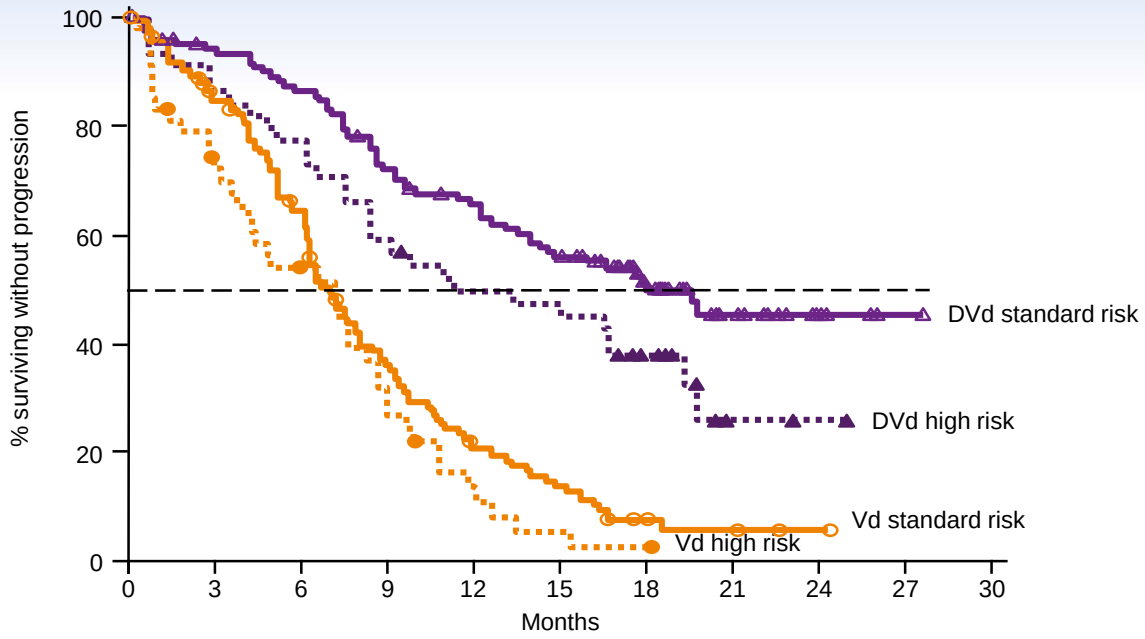




Median follow-up: 26.9 months

Spencer A, et al. Presented at ASH 2017 (Abstract 3145), poster presentation.

CASTOR: PFS by Cytogenetic Risk Status[a]



No. 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

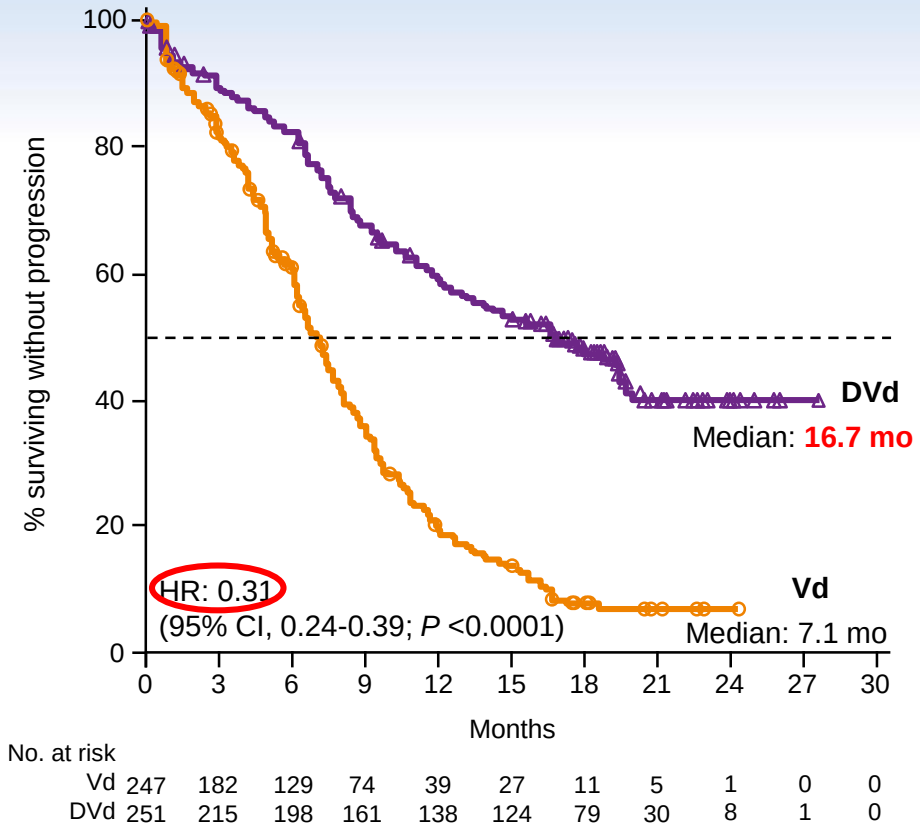
High risk	**DVd** n = 44	**Vd** n = 51
mPFS, mo	**11.2**	**7.2**
HR (95% CI)	0.45 (0.25-0.80)	
P value	0.0053	

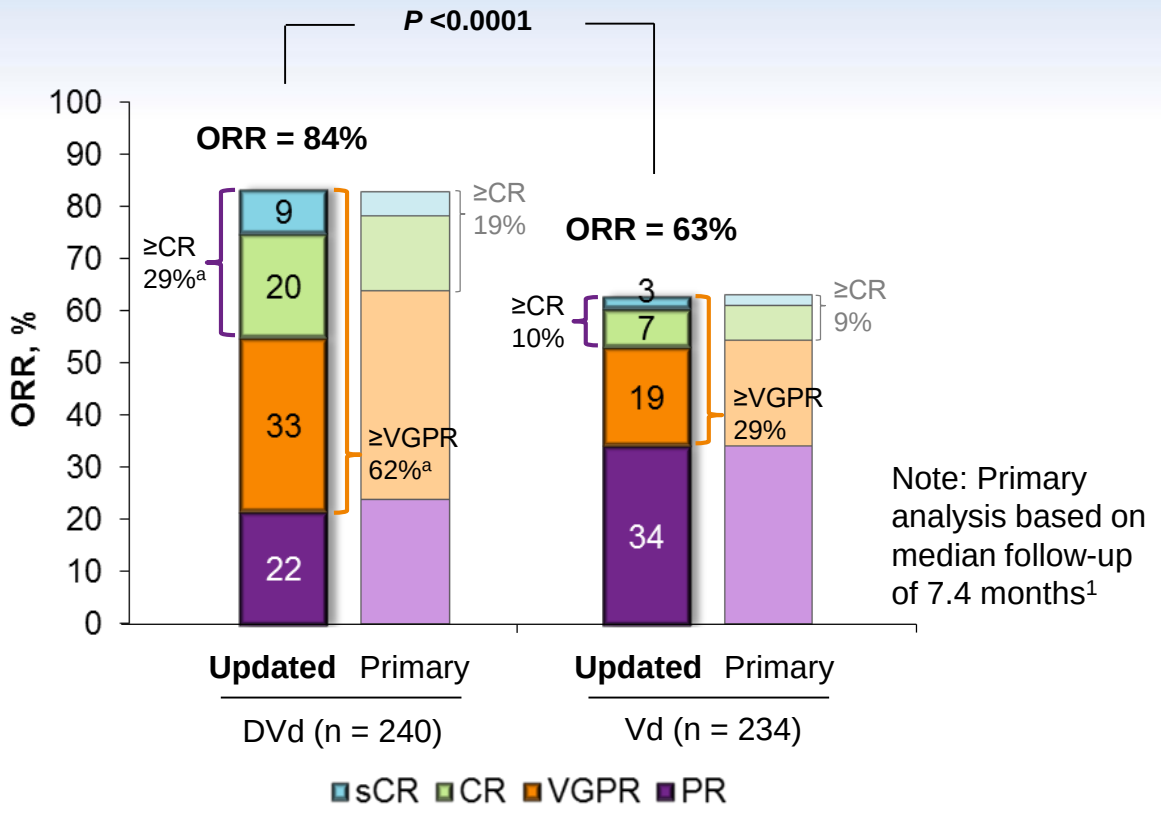
Standard risk	**DVd** n = 123	**Vd** n = 135
mPFS, mo	**19.6**	**7.0**
HR (95% CI)	0.26 (0.18-0.37)	
P value	<0.0001	

Adding DARA to standard of care 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: Overall Response Rate





Note: Primary analysis based on median follow-up of 7.4 months[1]

Duration of response: 18.9 months for DVd versus 7.6 months for Vd

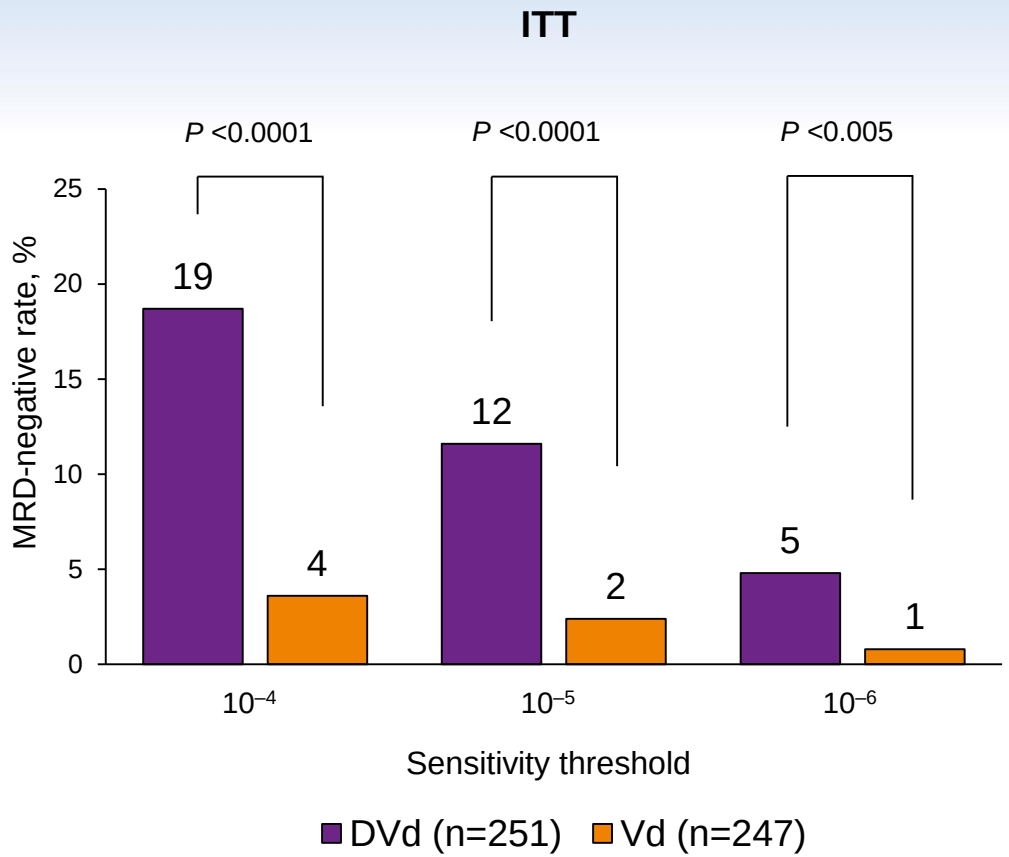
At the latest updated median follow-up of 26.9 months the rate of ≥CR in the DVd arm was 29% (3-fold higher than with Vd) and that of ≥VGPR was 62%

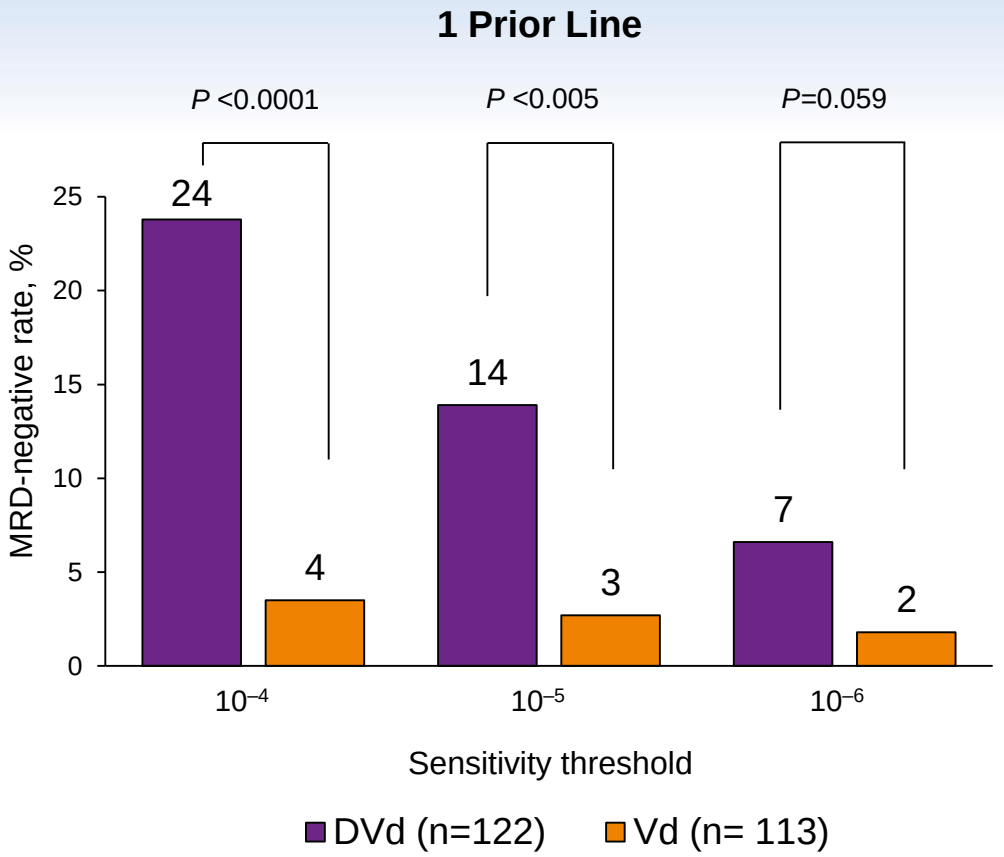
HR, hazard ratio; CI, confidence interval; PR, partial response; sCR, stringent complete response.

1. Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-766.

[a]*P* <0.0001 for DVd versus Vd.

Updated MRD-negative Rates



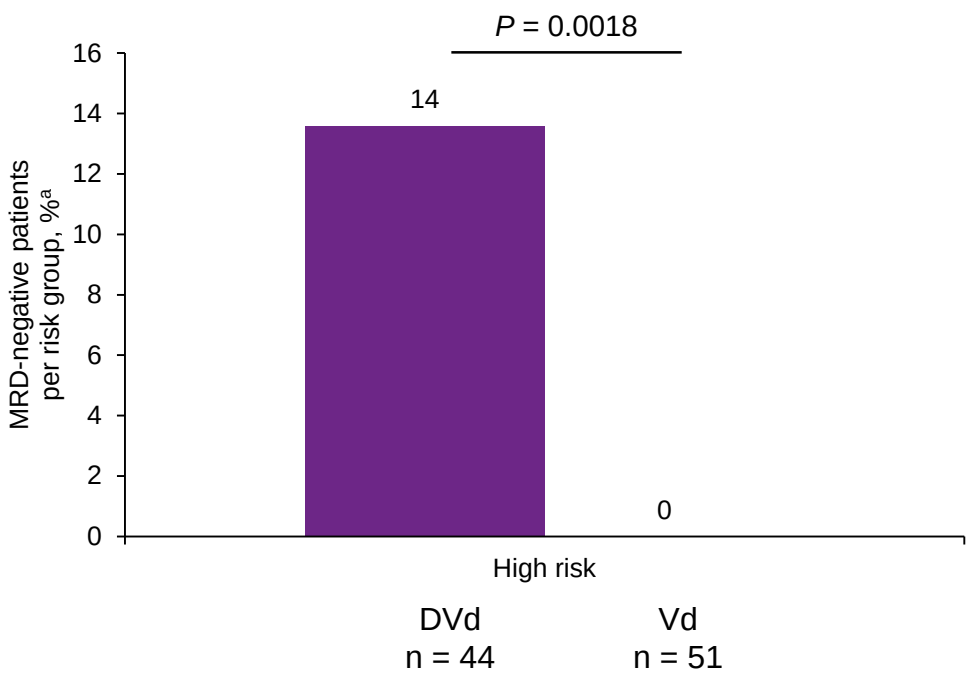


Significantly higher (>3-fold) MRD-negative rates for DVd versus Vd

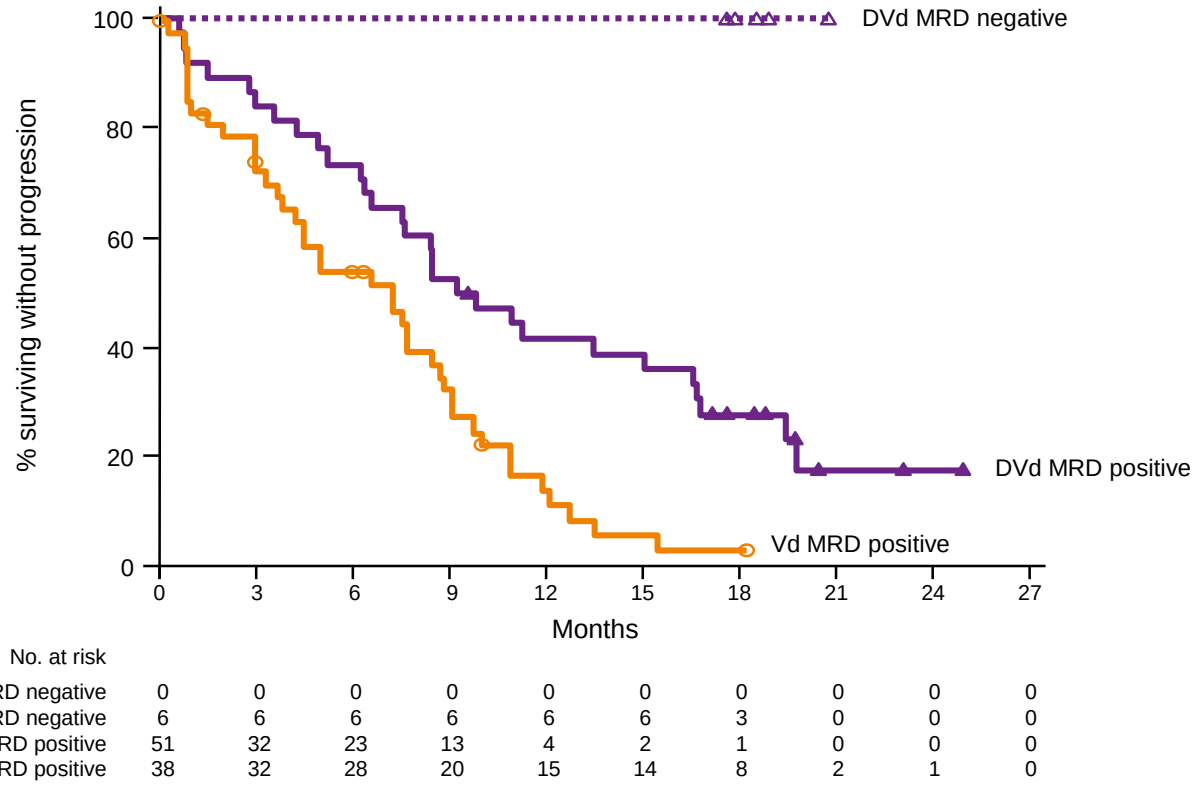
Assessed by next-generation sequencing in bone marrow.

MRD in Patients with High Cytogenetic Risk (10^{-5})

MRD-negative rates



PFS



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 DARA who were MRD negative remained progression free for up to 2 years

[a]Percentage of patients within a given risk group and treatment arm.

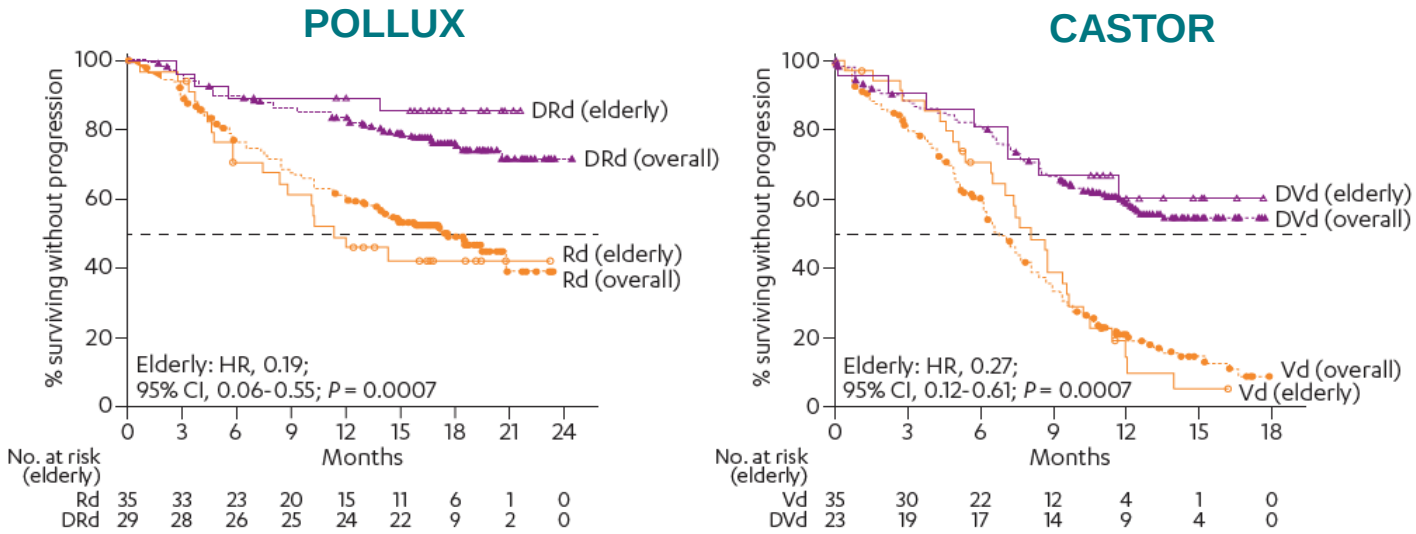
CASTOR: Overview of Safety Profile

	All grades ≥25%		Grades 3/4 ≥5%	
TEAE	**DVd**	**Vd**	**DVd**	**Vd**
Hematologic (%)				
Thrombocytopenia	59.7	44.3	**45.7**	**32.9**
Anemia	28.4	31.6	15.2	16.0
Neutropenia	18.9	9.7	13.6	4.6
Lymphopenia	13.2	3.8	9.9	2.5
Nonhematologic (%)				
Pneumonia	15.6	13.1	**10.3**	**10.1**
Peripheral sensory neuropathy	49.8	38.0	4.5	6.8
Hypertension	9.9	3.4	6.6	0.8
Upper respiratory tract infection	32.9	18.1	2.5	0.4
Diarrhea	35.4	22.4	3.7	1.3
Cough	28.0	12.7	0	0

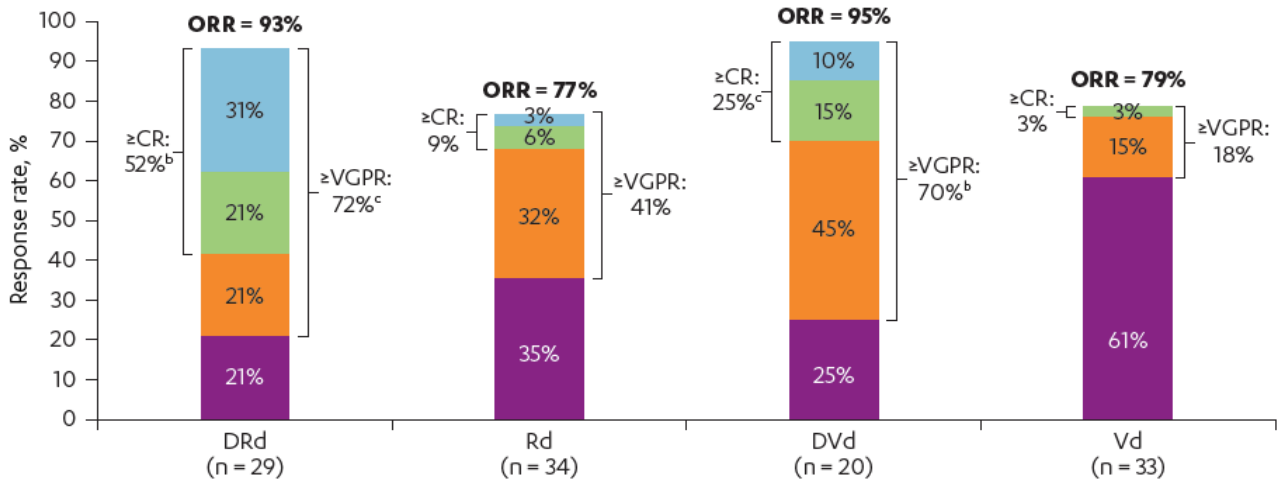
- The safety profile was consistent with previous analyses of CASTOR
- TEAE-related treatment discontinuations occurred in 9.5% and 9.3% of patients in the DVd and Vd arms, respectively
- With longer follow-up, secondary primary malignancies were reported in 10 (4.1%) and 3 (1.3%) patients who received DVd and Vd, respectively

Spencer A, et al. Presented at ASH 2017 (Abstract 3145), poster presentation.

CASTOR and POLLUX Phase 3 studies:
PFS and response in elderly patients (≥75 years)



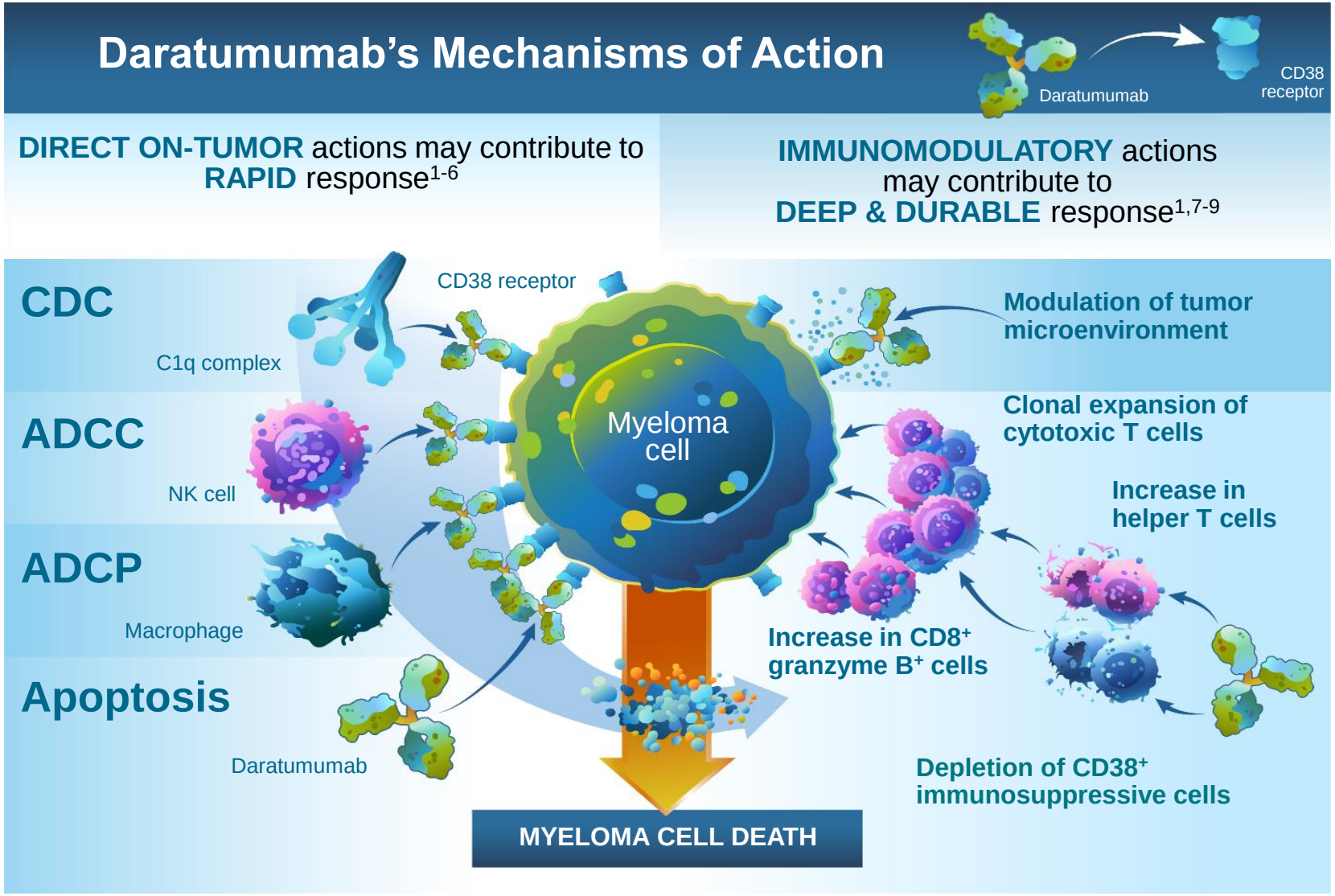
Response in elderly patients (≥75 years)



- Median follow-up
  - CASTOR: 13.0 months
  - POLLUX: 17.3 months

Mateos M-V, et al. Poster presentation at ASCO 2017. Abstract 8033.

Anti-CD38 mAb Daratumumab

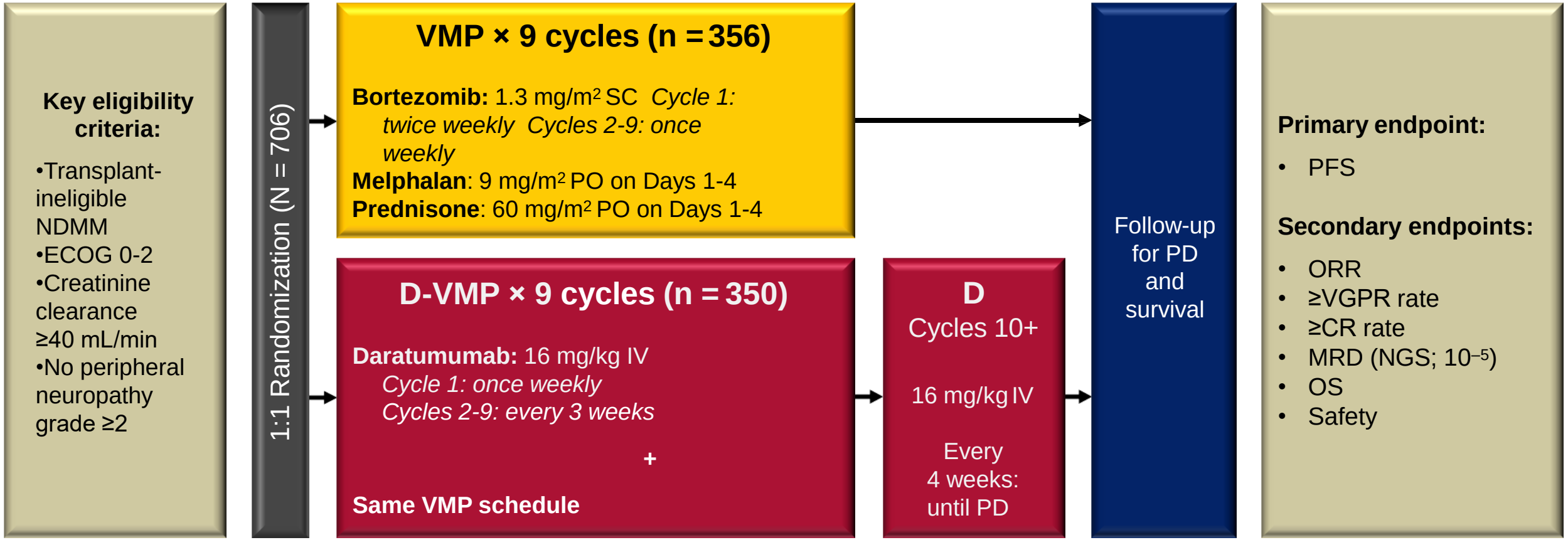


- Daratumumab
  - Human IgGκ monoclonal antibody targeting CD38 with a direct on-tumor and immunomodulatory mechanism of action
- Approved
  - **In combination with standard of care regimens in RRMM after ≥ 1 prior line of therapy**
  - In combination with bortezomib, melphalan, and prednisone in non-transplant NDMM (United States, Brazil, etc.)
- Efficacy
  - Daratumumab-based combinations reduce risk of progression or death and induce rapid, deep, and durable responses in RRMM and NDMM[10-12]

CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cellular cytotoxicity; NK, natural killer; ADCP, antibody-dependent cellular phagocytosis; RRMM, relapsed/refractory multiple myeloma.

1. DARZALEX US PI; 2018. 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. *N Engl J Med*. 2015;373(13):1207-1219. 6. Plesner T, et al. *Blood*. 2012;120:73. 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. Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-766. 11. Dimopoulos MA, et al. *N Engl J Med*. 2016;375(14):1319-1331. 12. Mateos MV, et al. *N Engl J Med*. 2018;378:518-528.

Phase 3 ALCYONE Study Design



Stratification factors

- ISS (I vs II vs III)
- Region (EU vs other)
- Age (<75 vs ≥75 years)

- Cycles 1-9: 6-week cycles
- Cycles 10+: 4-week cycles

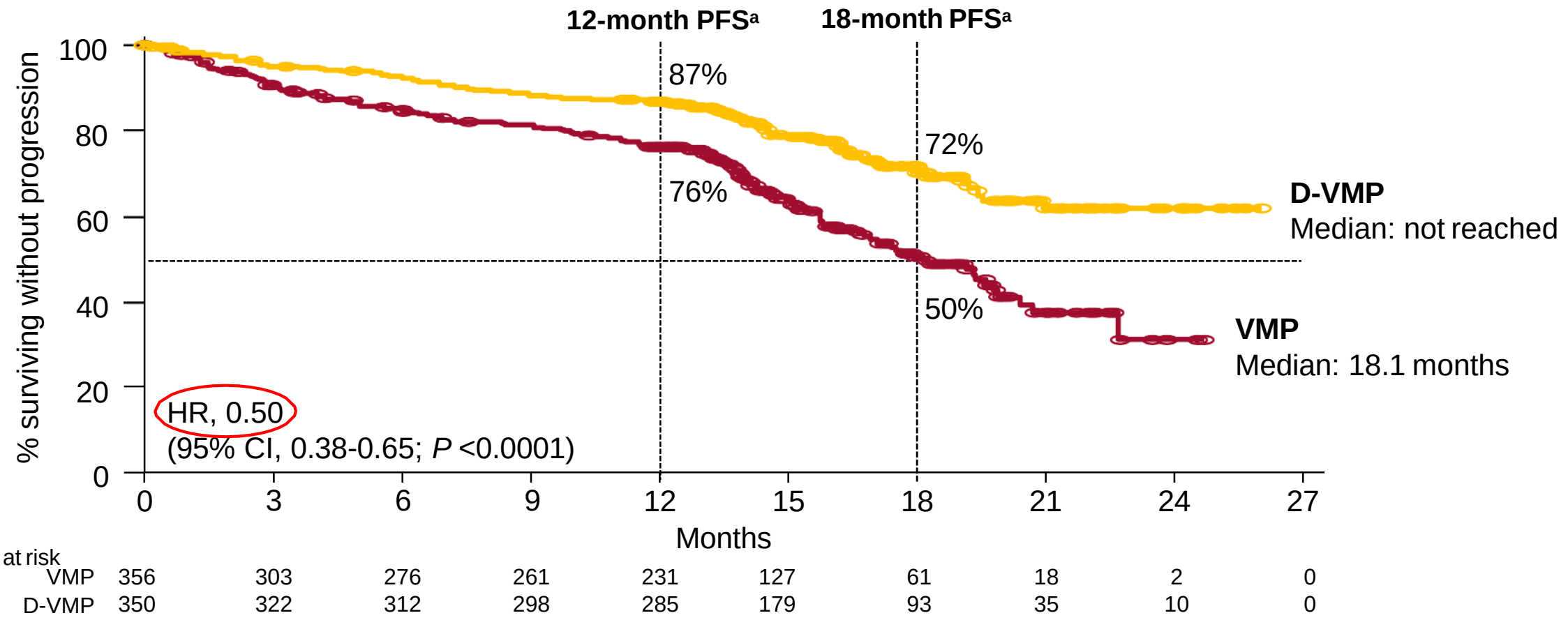
Statistical analyses

•360 PFS events: 85% power for 8-month PFS improvement[a]
•Interim analysis: ~216 PFS events

ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; EU, European Union; SC, subcutaneously; PO, oral ly; D, daratumumab; IV, intravenously; PD, progressive disease; PFS, progression-free survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease; NGS, next-generation sequencing; OS, overall survival.
[a]8-month PFS improvement over 21-month median PFS of VMP.

Efficacy: PFS

- Median (range) follow-up: 16.5 (0.1-28.1) months

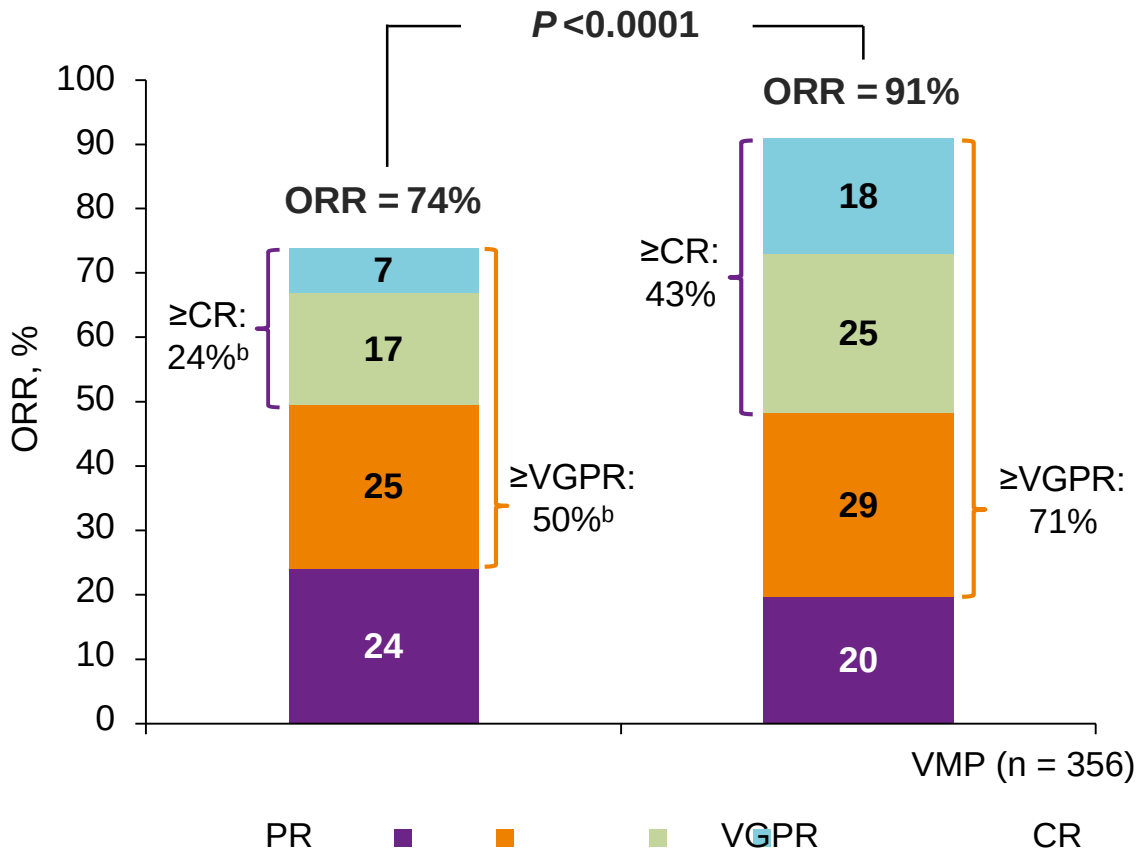


50% reduction in the risk of progression or death in patients receiving D-VMP

HR, hazard ratio; CI, confidence interval.
[a]Kaplan-Meier estimate.

Efficacy: ORR[a]

- Median duration of response: 21.3 months in VMP versus not reached in D-VMP



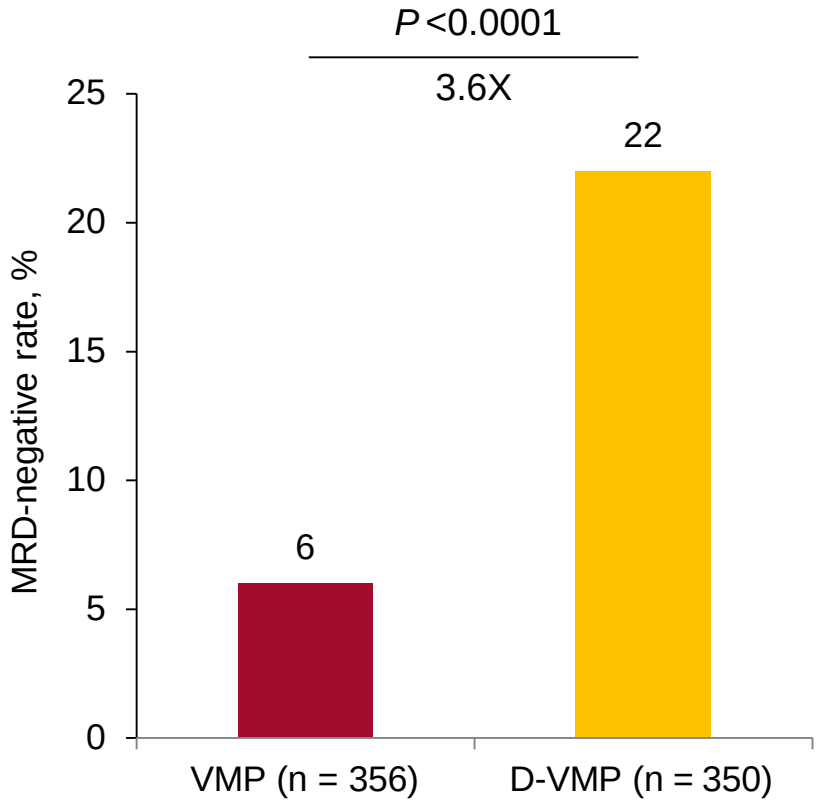
	VMP (n = 263)[c]	D-VMP (n = 318)[c]
Median (range) time to **first** response, months	0.82 (0.7-12.6)	0.79 (0.4-15.5)
Median (range) time to **best** response, months	4.11 (0.7-20.5)	4.93 (0.5-21.0)

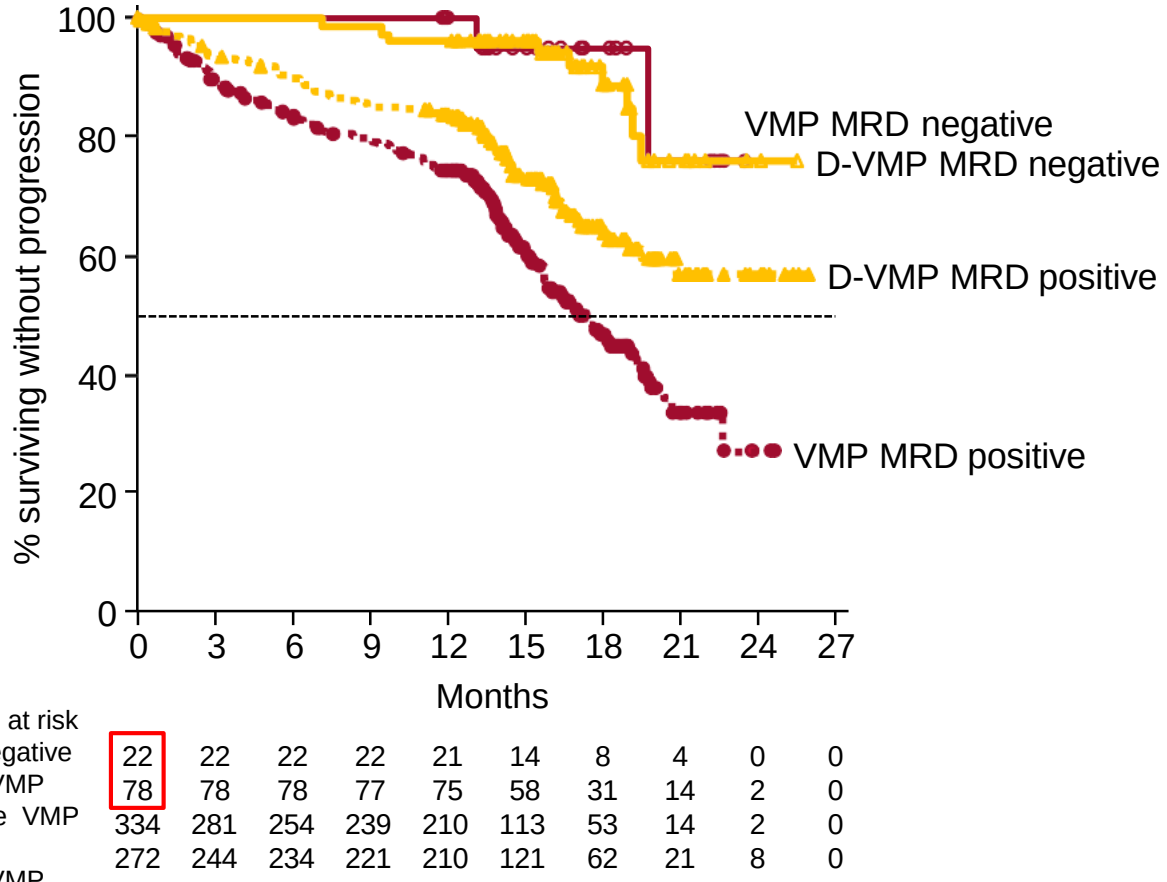
Significantly higher ORR, ≥VGPR rate, and ≥CR rate with D-VMP;
>2-fold increase in rate of sCR with D-VMP

PR, partial response; sCR, stringent complete response.
[a]ITT population. [b]*P* <0.0001; *P* value was calculated with the use of the Cochran–Mantel–Haenszel chi-square test.
[c]Responders in response-evaluable population.

MRD Negativity[a] (NGS; 10^{-5} Sensitivity)

- Median (range) follow-up: 16.5 (0.1-28.1) months

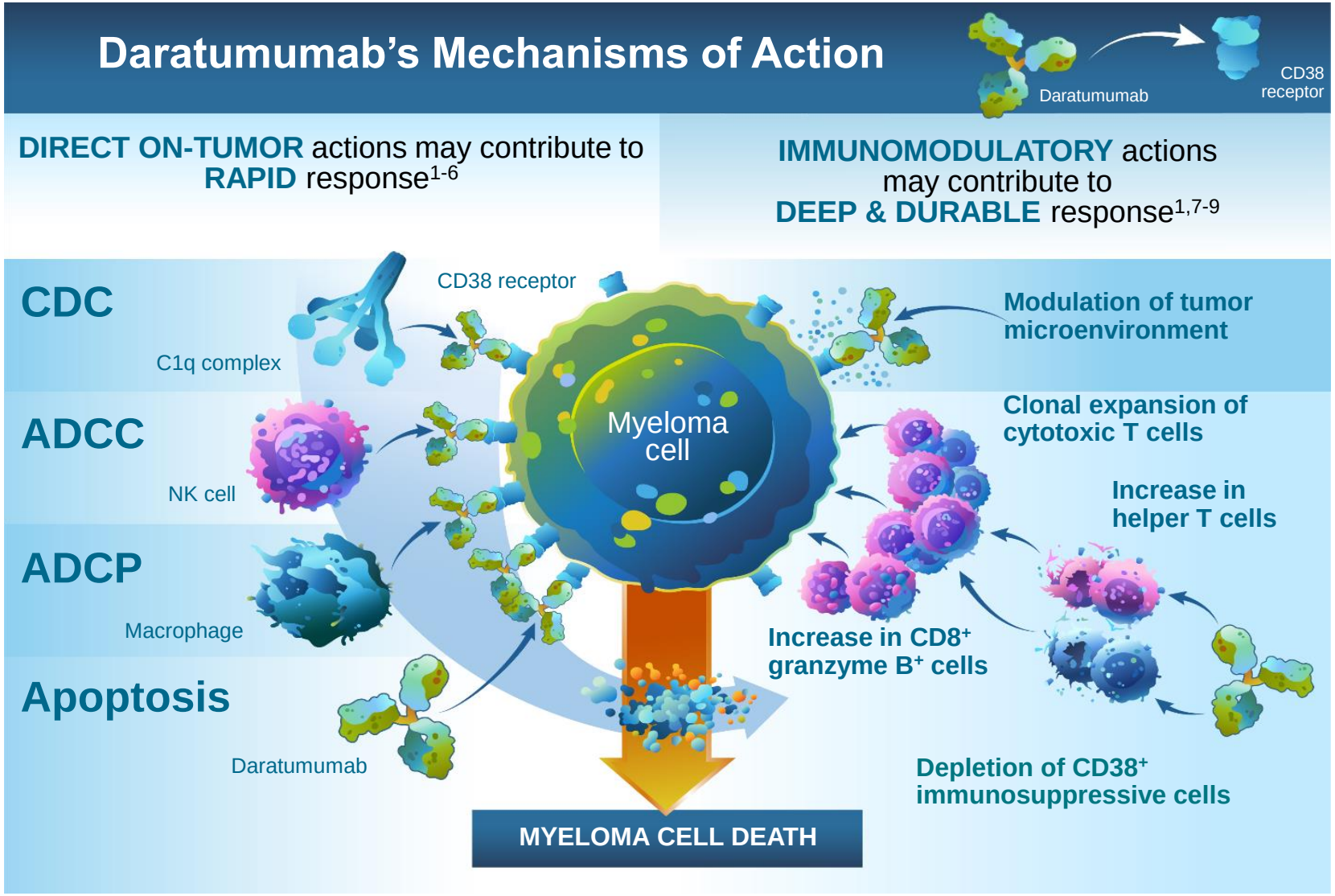




>3-fold higher MRD-negative rate with D-VMP;
Lower risk of progression or death in all MRD-negative patients

[a]Assessed at time of confirmation of CR/sCR and, if confirmed, at 12, 18, 24, and 30 months after first dose.

Anti-CD38 mAb Daratumumab



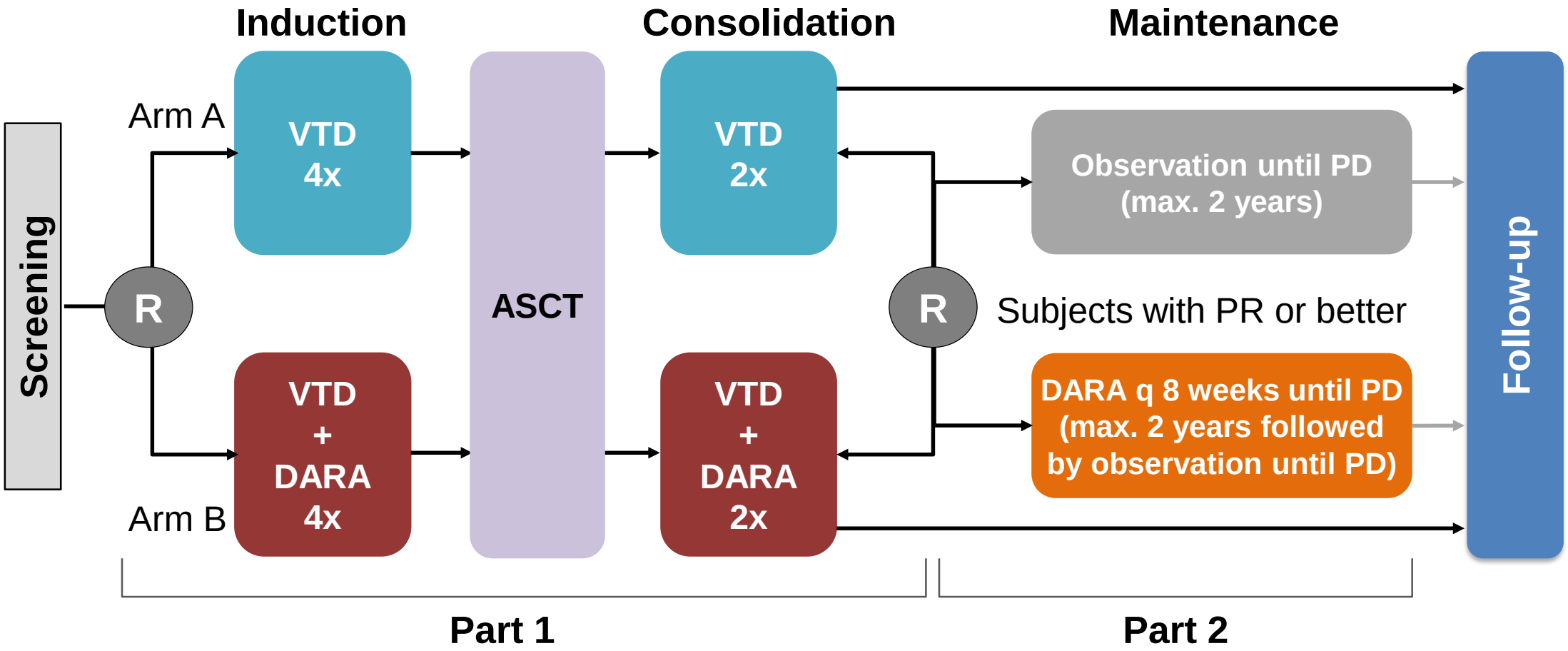
- Daratumumab
  - Human IgGκ monoclonal antibody targeting CD38 with a direct on-tumor and immunomodulatory mechanism of action
- Approved
  - **In combination with bortezomib, melphalan, and prednisone in non-transplant NDMM (United States, Europe)**
- Efficacy
  - Daratumumab-based combinations reduce risk of progression or death and induce rapid, deep, and durable responses in RRMM and NDMM[10-12]

CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cellular cytotoxicity; NK, natural killer; ADCP, antibody-dependent cellular phagocytosis; RRMM, relapsed/refractory multiple myeloma.

1. DARZALEX US PI; 2018. 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. *N Engl J Med*. 2015;373(13):1207-1219. 6. Plesner T, et al. *Blood*. 2012;120:73. 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. Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-766. 11. Dimopoulos MA, et al. *N Engl J Med*. 2016;375(14):1319-1331. 12. Mateos MV, et al. *N Engl J Med*. 2018;378:518-528.

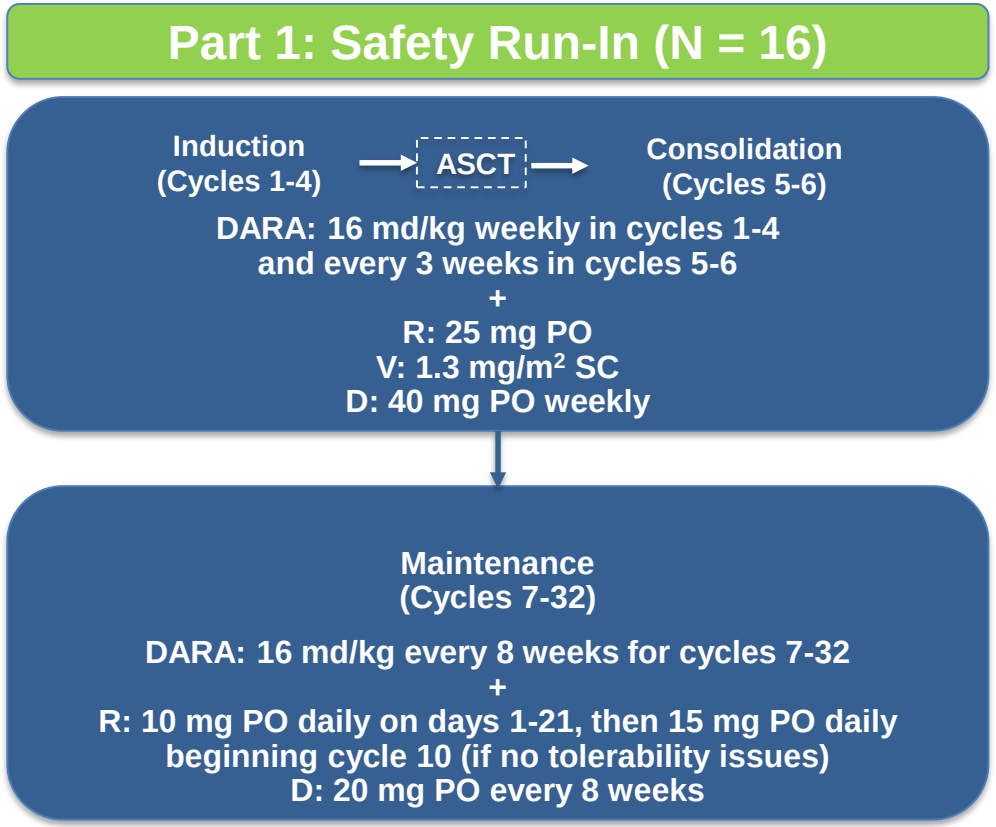
VTD vs Dara-VTD induction therapy

CASSIOPEIA phase III trial



https://clinicaltrials.gov/ct2/show/NCT02541383. Accessed 5 June 2018.

Daratumumab-VRd vs VRd Phase 2 Study



Safety Profile of Patients Treated During Cycles 1-4

	N = 16
At least 1 treatment-emergent adverse event TEAE), n (%)	16 (100)
Related to daratumumab	14 (88)
Most common TEAEs (all grades) occurring in ≥20% of patients, n (%)	
Neutropenia	8 (50)
Lymphopenia	7 (44)
Thrombocytopenia	7 (44)
Fatigue	6 (38)
Edema peripheral	6 (38)
Anemia	5 (31)
Constipation	5 (31)
Leukopenia	4 (25)
Hypoalbuminemia	4 (25)
Hypocalcemia	4 (25)
Insomnia	4 (25)

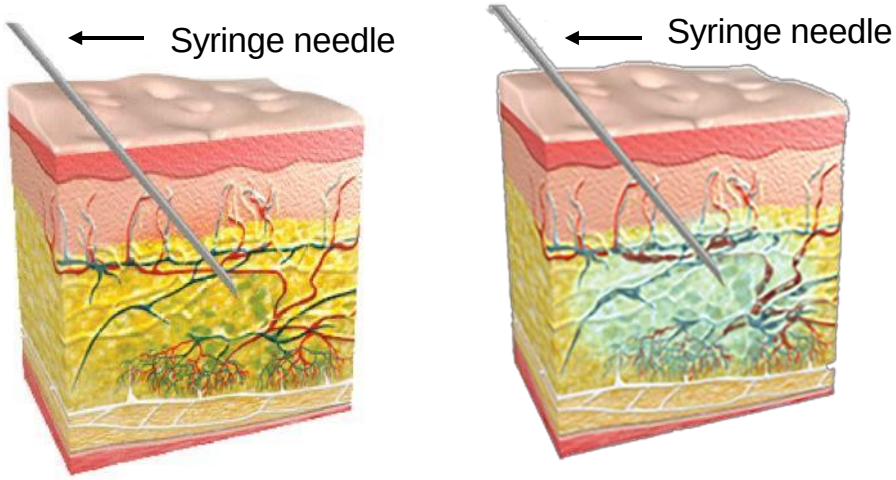
- 2 patients had SAE considered related to daratumumab (gastroenteritis, pneumonitis)
- 5 patients had a ≤grade 2 IRR

Voorhees PM, et al. *Blood.* 2017;130: Abstract 1879

Recombinant Human Hyaluronidase

- ENHANZE™ Drug Delivery Technology of recombinant human hyaluronidase (rHuPH20) temporarily breaks down the hyaluronan barrier, allowing rapid administration of larger volumes of injected drugs[1]
- Mixed formulation of DARA and rHuPH20 (DARA-MD) given subcutaneously by means of **syringe pump** was well tolerated with low rates of IRRs and similar efficacy to IV DARA[2]
- Pre-mixed co-formulation of DARA + rHuPH20 (DARA SC) with a higher DARA concentration, lower injection volume, and shorter injection time was developed, enabling **manual subcutaneous** injection in the abdomen

Schematic of rHuPH20[1]



Aim: To determine the safety, pharmacokinetics, and efficacy of subcutaneous DARA

1. Halozyme Therapeutics. Mechanism of action for Hylenex recombinant (hyaluronidase human injection). www.hylenex.com/mechanism-of-action. Accessed 11/8/2016.
2. Usmani SZ, et al. Presented at: ASH; December 3-6, 2016; San Diego, CA. Abstract 1149.

PAVO Phase 1b Study Design

Phase 1b, open-label, multicenter, dose-finding, proof-of-concept study

Key eligibility criteria
- RRMM with measurable disease
- ≥2 prior lines of treatment
- Not received anti-CD38 therapy

Part 1: mix and deliver

Group 1 (n = 8)
DARA-MD: 1,200 mg
rHuPH20: 30,000 U

→

Group 2[a] (n = 45)
DARA-MD: 1,800 mg
rHuPH20: 45,000 U

Part 2: concentrated co-formulation

Group 3 (n = 25)
DARA SC: 1,800 mg
rHuPH20: 30,000 U

Primary endpoints
- C_{trough} of DARA at Cycle 3/Day1
- Safety

Secondary endpoints
- ORR
- CR
- Duration of response
- Time to response

Infusion/injection time
- DARA-MD 1,200 mg: 20-min via pump (60 mL)
- DARA-MD 1,800 mg: 30-min via pump (90 mL)
- **DARA SC 1,800 mg: 3-5 min manually (15 mL)**

Dosing schedule
- Approved schedule for IV
- 1 Cycle = 28 days

Pre-[b]/post-administration medication
- Acetaminophen
- Diphenhydramine
- Montelukast
- Methylprednisolone[c]

[a]Group 2 comprises 4 distinct cohorts, each treated with DARA 1,800 mg and rHuPH20 45,000 U. C_{trough} on Cycle 3/Day 1 in Group 1 supported dose selection for Group 2. The study evaluation team reviewed safety after Cycle 1 and PK after Cycle 3/Day 1 for each group.
[b]Administered 1 to 3 hours prior to injection. [c]100 mg for the first and second injections; dose may be reduced to 60 mg thereafter; 20 mg for post-administration over 2 days. In the absence of infusion related AEs after the first 3 injections, postinjection corticosteroids should be administered per investigator discretion.

RRMM, relapsed or refractory multiple myeloma; C_{trough}, trough concentration; ORR, overall response rate; CR, complete response.

RATIONALE AND OBJECTIVE

- **LEN is an established therapy in NDMM; therefore, patients for whom LEN is no longer a treatment option represent a clinically relevant population with unmet need[1,2]**

Characteristics*	CASTOR DaraVd[3,4] (N = 251)	ENDEAVOR Kd[5,6] (N = 464)	PANORAMA-1 PANO-Vd[7] (N = 387)	ASPIRE KRd[8,9] (N = 396)	POLLUX DaraRd[10-12] (N = 286)	ELOQUENT-2 EloRd[13] (N = 321)	TOURMALINE-1 IRd[14] (N = 360)
Prior therapy, %[a]							
LEN	36	38	19	20	18	5	12
BORT	65	54	44	66	84	68	69
Refractory disease, %							
To last line of therapy	30	40	-	28	28	35	-
LEN	24	24	-	7	0	0	0
BORT	0.4	3	-	15	21	22[b]	-

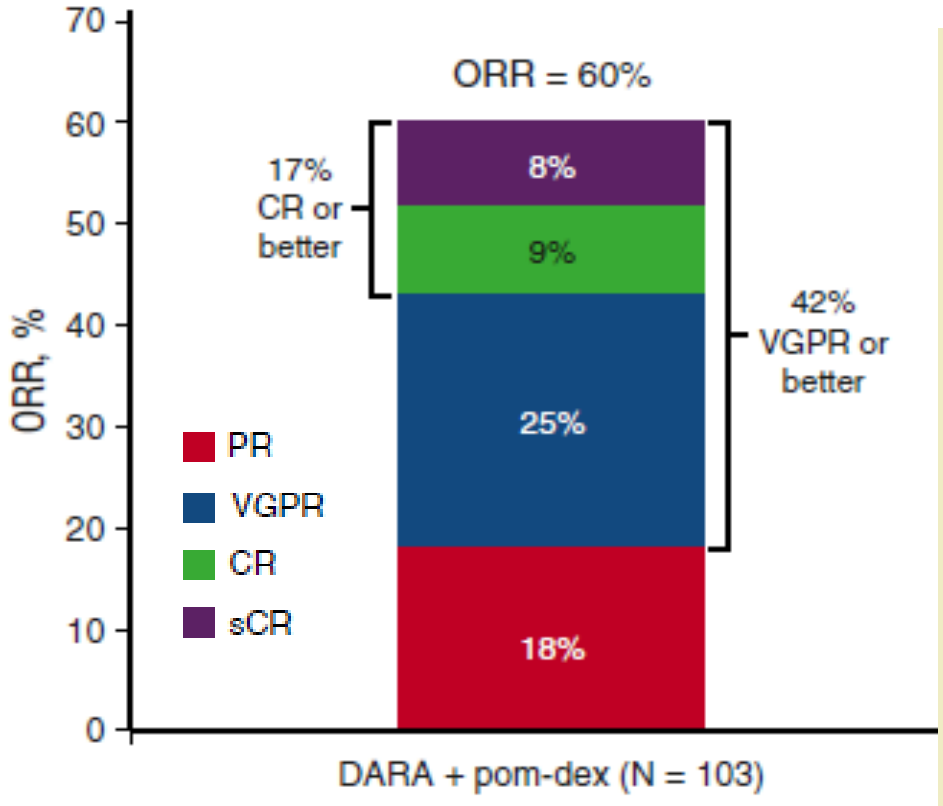
[a] **Median 1-2 prior regimens.** [b] **Refractory to BORT in last prior line of therapy**.

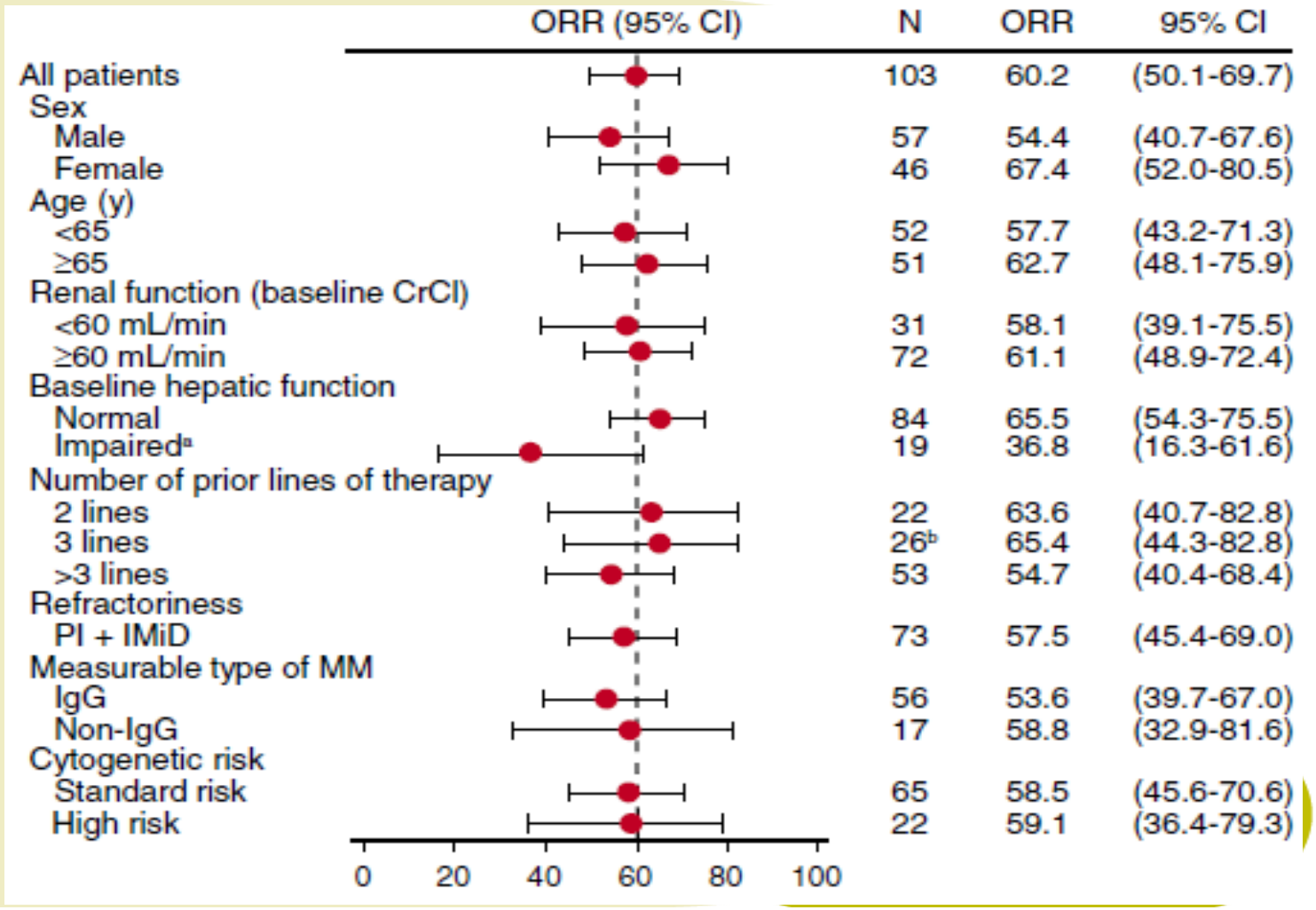
*The table is provided for ease of viewing information from multiple trials. Direct comparison across trials is not intended and should not be inferred.

1. NCCN: Multiple Myeloma. Version 4.2018. 2. Moreau P, et al. *Ann Oncol*. 2017;28:iv52-iv61. 3. Palumbo A, et al. *N Engl J Med*. 2016;375:754-766. 4. Darzalex European Public Assessment Report-CASTOR. Accessed April 2018. 5. Dimopoulos MA, et al. *Lancet Oncol.* 2016;17:27-38. 6. Kyprolis European Public Assessment Report-ENDEAVOR. Accessed April 2018. 7. San-Miguel JF et al. Lancet Oncol. 2014;15:1195-206. 8. Stewart KA, et al. *N Engl J Med*. 2015;372:142-52. 9. Kyprolis European Public Assessment Report-ASPIRE. Accesses April 2018. 10. Dimopoulos M, et al. *N Engl J Med.* 2016;375:1319-1331. 11. Moreau P, et al. ASH 2017 [abstract 1883]. 12. Darzalex European Public Assessment Report-POLLUX. Accessed April 2018. 13. Lonial S, et al. *N Engl J Med*. 2015;373:621-31. 14. Moreau P, et al. *N Engl J Med*. 2016;374:1621-1634.

Phase 1b study of DARA-POMALIDOMIDE + Dexamethasone:

RESPONSE RATE





≥CR pts: **29% MRD negativity at 10^{-5}**

Chari A, et al. *Blood.* 2017

Study Design: D-Kd Arm of MMY1001

- Open-label, non-randomized, multicenter, phase 1b study in RRMM patients
- Per protocol, DARA was administered as a **single first dose (n = 10)** or as a **split first dose (n = 75)**

Eligibility/treatment

- Relapsed MM
  - 1-3 prior lines of therapy, including bortezomib and an IMiD
  - Len-refractory patients allowed
- Carfilzomib-naïve
- ECOG status ≤2
- LVEF ≥40%
- ANC ≥1 × 10^9/L
- Platelet count ≥75 × 10^9/L

Dosing schedule (28-day cycles)

DARA:

- **Split first dose[a]: 8 mg/kg Days 1-2 of Cycle 1**
- Single first dose: 16 mg/kg on C1D1
- 16 mg/kg IV QW on Cycles 1-2, Q2W on Cycles 3-6, and Q4W thereafter until PD

Carfilzomib[b]:

- 20 mg/m^2 IV Cycle 1 Day 1
- Escalated to 70 mg/m^2 Cycle 1 Day 8+; **weekly (Days 1, 8, 15)** until PD

Dexamethasone:

- 40 mg/week (Days 1, 8, 15, 22) IV or PO until PD

Endpoints

Primary

- Safety, tolerability

Secondary

- ORR
- OS

Exploratory

- PFS
- MRD (NGS)[c]
- PK

[a]In 500-mL dilution volume.
[b]Both 20 mg/m^2 and 70 mg/m^2 were administered as 30-minute IV infusions.
[c]Among patients evaluated for MRD, MRD was assessed using NGS at time of suspected CR and at 12 and 18 months after initial dose. In cases where DARA is suspected of interfering with IFE and preventing clinical CR response calls, subjects with VGPR may also be evaluated for MRD.

D-Kd, daratumumab/carfilzomib/dexamethasone; IMiD, immunomodulatory drug; ECOG, Eastern Cooperative Oncology Group; LVEF, left ventricular ejection fraction; ANC, absolute neutrophil count; IV, intravenous; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; PD, progressive disease; PO, oral; OS, overall survival; NGS, next-generation sequencing; IFE, immunofixation; CR, complete response; VGPR, very good partial response.

Conclusions

- Dara is the first-in-class mAb targeting CD38 approved for treating RRMM and NDMM and is likely to be a game changer combined with PIs/IMiDs
- Addition of Dara to SOC (Vd or Rd) for RRMM continues to show improved clinical outcomes with longer follow-up in both standard-risk and high-risk pts in terms of
  - ✓longer PFS
  - ✓higher ORR and CR rates
  - ✓higher MRD negative rates (> 3-fold) that improve over time
- Addition of Dara to SCO for NDMM shows similar results than those seen in RRMM
- Safety profile remains consistent with longer follow up
- Dara s.c., once approved, is likely to substantially improve therapy convenience
- Mechanisms of Dara resistance and Dara re-treatment are currently under active investigation