Phase 3 Randomized Controlled Study of Daratumumab, Bortezomib and Dexamethasone (DVd) vs Bortezomib and Dexamethasone (Vd) in Patients with Relapsed or Refractory Multiple Myeloma (RRMM): CASTOR*

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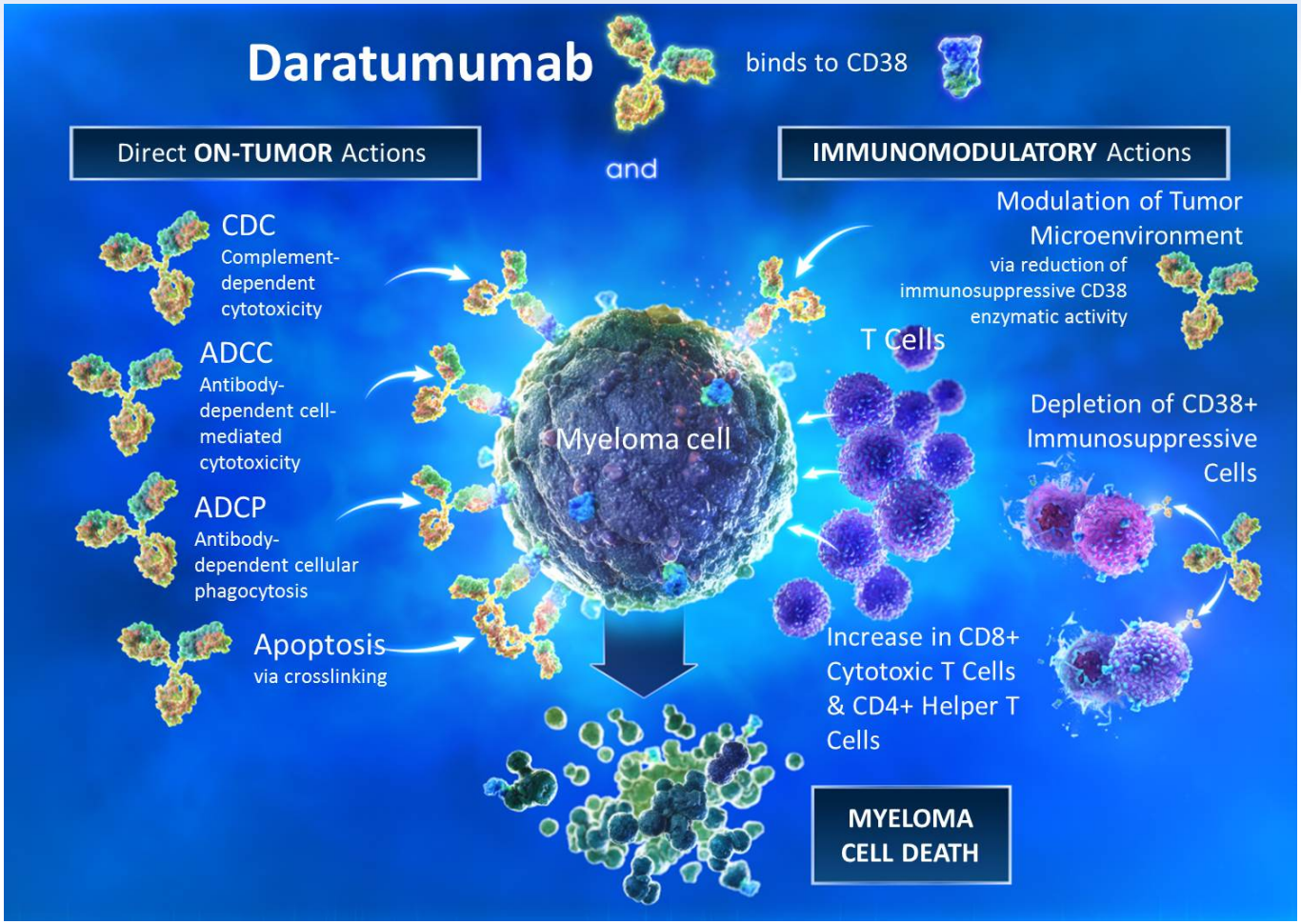
Daratumumab: Mechanism of Action

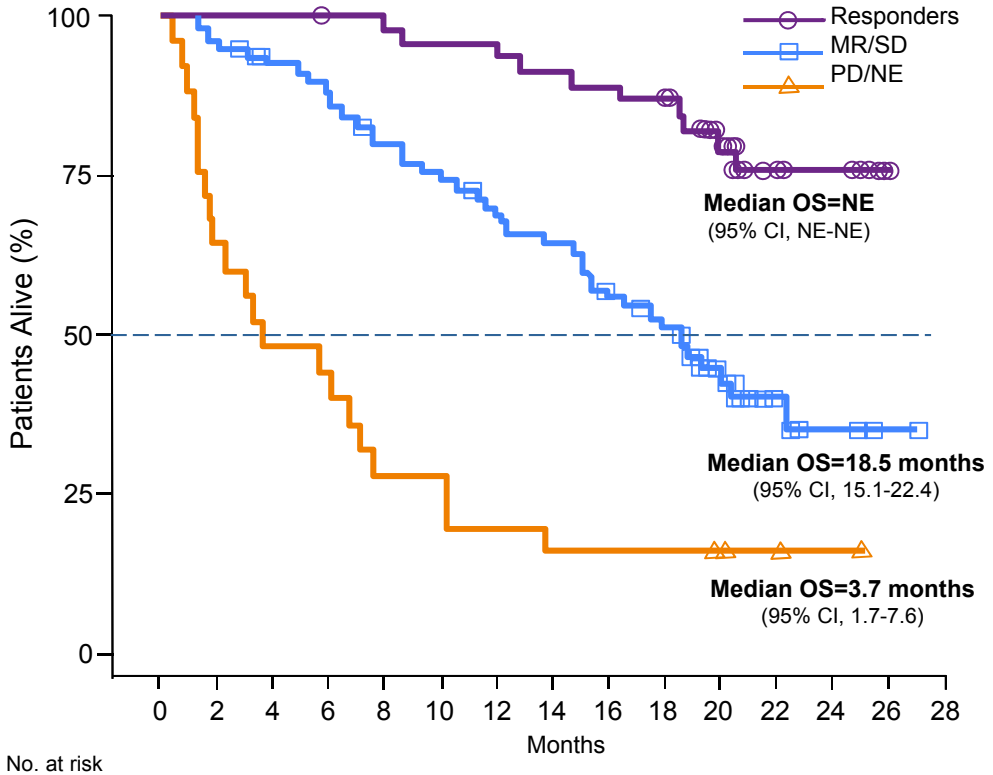
- Human CD38 IgGκ monoclonal antibody
- Direct and indirect anti-myeloma activity[1-5]
- Depletes CD38+ immunosuppressive regulatory cells[5]
- Promotes T-cell expansion and activation[5]



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.

Daratumumab: Single-agent Activity

- **Daratumumab as a single agent**
  - Approved by FDA and conditionally approved by EMA in relapsed/refractory multiple myeloma[1,2]
- **Patients received a median of 5 prior lines of therapy**
  - 86.5% of patients were double refractory to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD)[3]
- **Combined overall response rate (ORR): 31%[3]**
- **Median overall survival (OS): 20.1 months[3]**
  - 2-year OS was ~75% in responders
  - Median OS was 18.5 months in patients with MR/SD

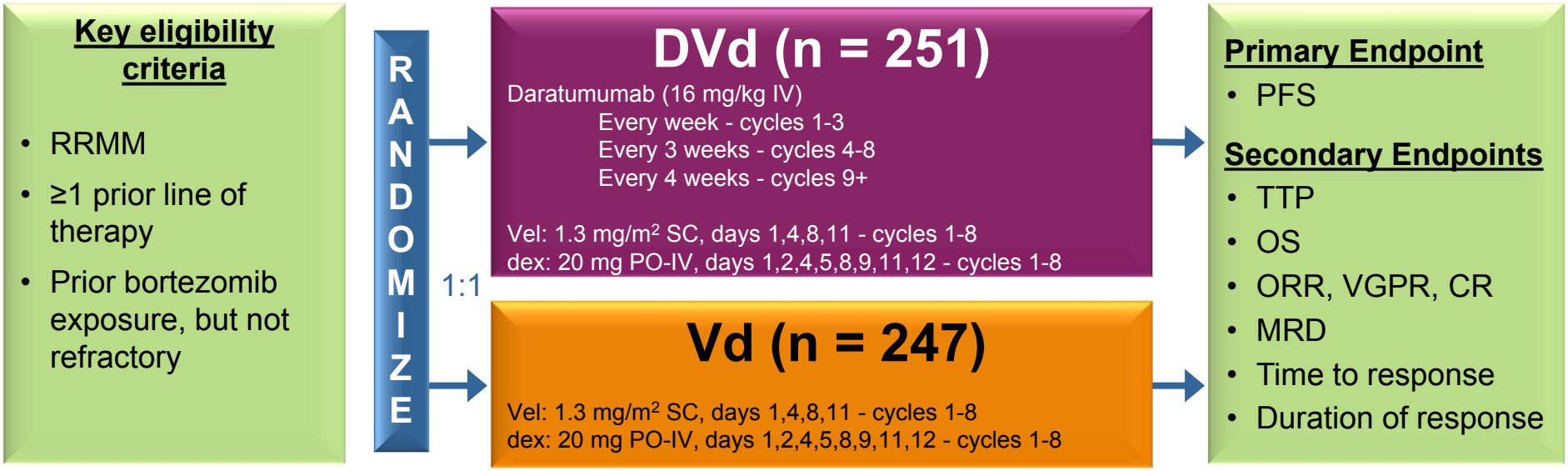


MR, minimal response; SD, stable disease; PD, progressive disease; OS, overall survival; CI, confidence interval; NE, not evaluable.

1. Lokhorst HM, et al. *N Engl J Med*. 2015;373:1207-19.
2. Lonial S, et al. *Lancet*. 2016;387:1551-60.
3. Usmani SZ, et al. *Blood*. 2016. Epub ahead of print.

CASTOR: Study Design

Multicenter, randomized, open-label, active-controlled phase 3 study



- Cycles 1-8: repeat every 21 days
- Cycles 9+: repeat every 28 days

Statistical analyses

- 295 PFS events: 85% power for 4.3 month PFS improvement
- Interim analysis: ~177 PFS events

Daratumumab IV administered in 1000 mL to 500 mL; gradual escalation from 50 mL to 200 mL/hour permitted

RRMM, relapsed or refractory multiple myeloma; DVd, daratumumab/bortezomib/dexamethasone; IV, intravenous; Vel, bortezomib; SC, subcutaneous; dex, dexamethasone; PO, oral; Vd, bortezomib/dexamethasone; PFS, progression-free survival; TTP, time to progression; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease.

Baseline Demographics and Clinical Characteristics

Characteristic	DVd (n = 251)	Vd (n = 247)
Age, years		
Median (range)	64 (30-88)	64 (33-85)
≥75, n (%)	23 (9)	35 (14)
ISS staging, n (%)[a]		
I	98 (39)	96 (39)
II	94 (38)	100 (41)
III	59 (24)	51 (21)
Cytogenetic profile, n (%)[b]		
Del17p	28 (16)	21 (12)
t(4;14)	14 (8)	15 (9)
Time from diagnosis, years	3.87	3.72
Median (range)	(0.7-20.7)	(0.6-18.6)

Characteristic	DVd (n = 251)	Vd (n = 247)
Prior lines of therapy, n (%)		
1	122 (49)	113 (46)
2	70 (28)	74 (30)
3	37 (15)	32 (13)
>3	22 (9)	28 (11)
Prior ASCT, n (%)	156 (62)	149 (60)
Prior PI, n (%)	169 (67)	172 (70)
Prior IMiD, n (%)	179 (71)	198 (80)
Prior PI + IMiD, n (%)	112 (45)	129 (52)
Refractory to IMiD, n (%)	74 (30)	90 (36)
Refractory to last line of therapy, n (%)	76 (30)	85 (34)

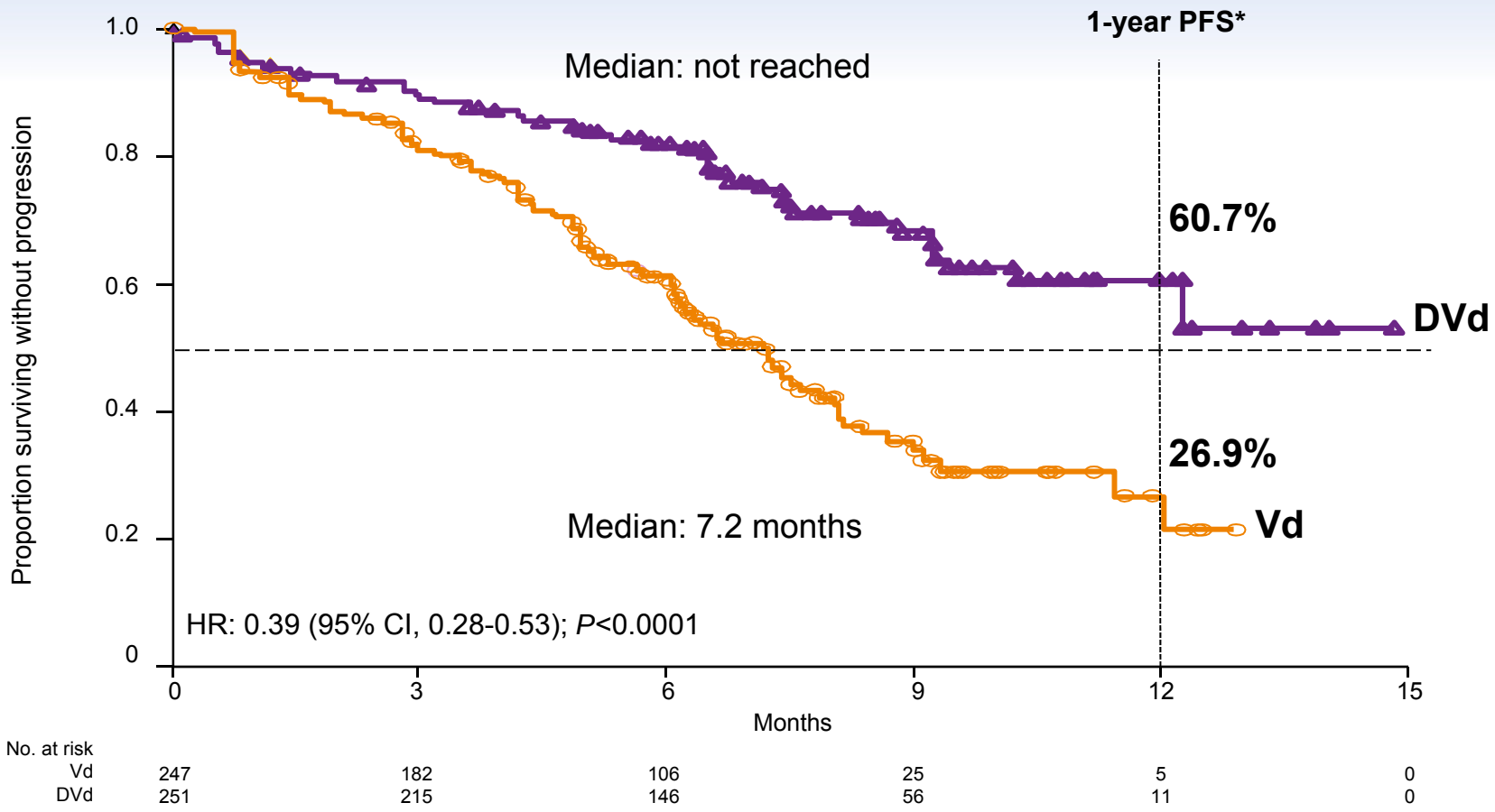
ISS, international staging system; ASCT, autologous stem cell transplant; [a]ISS staging is derived based on the combination of serum β2-microglobulin and albumin; [b]Investigator-reported.

Patient Disposition

- Accrual: September 2014 – September 2015
- Clinical cut-off date: January 11, 2016
- Median follow-up: 7.4 (range, 0-14.9) months

Patients	DVd (n = 251)	Vd (n = 247)
Randomized, n	251	247
Treated, n (%)	243 (97)	237 (96)
Discontinued treatment, n (%)	74 (31)	104 (44)
Reasons for discontinuation		
Progressive disease	47 (19)	60 (25)
Adverse event	19 (8)	23 (10)
Non-compliance with study drug	3 (1)	8 (3)
Withdrawal by patient	1 (0.4)	9 (4)
Death	4 (2)	4 (2)

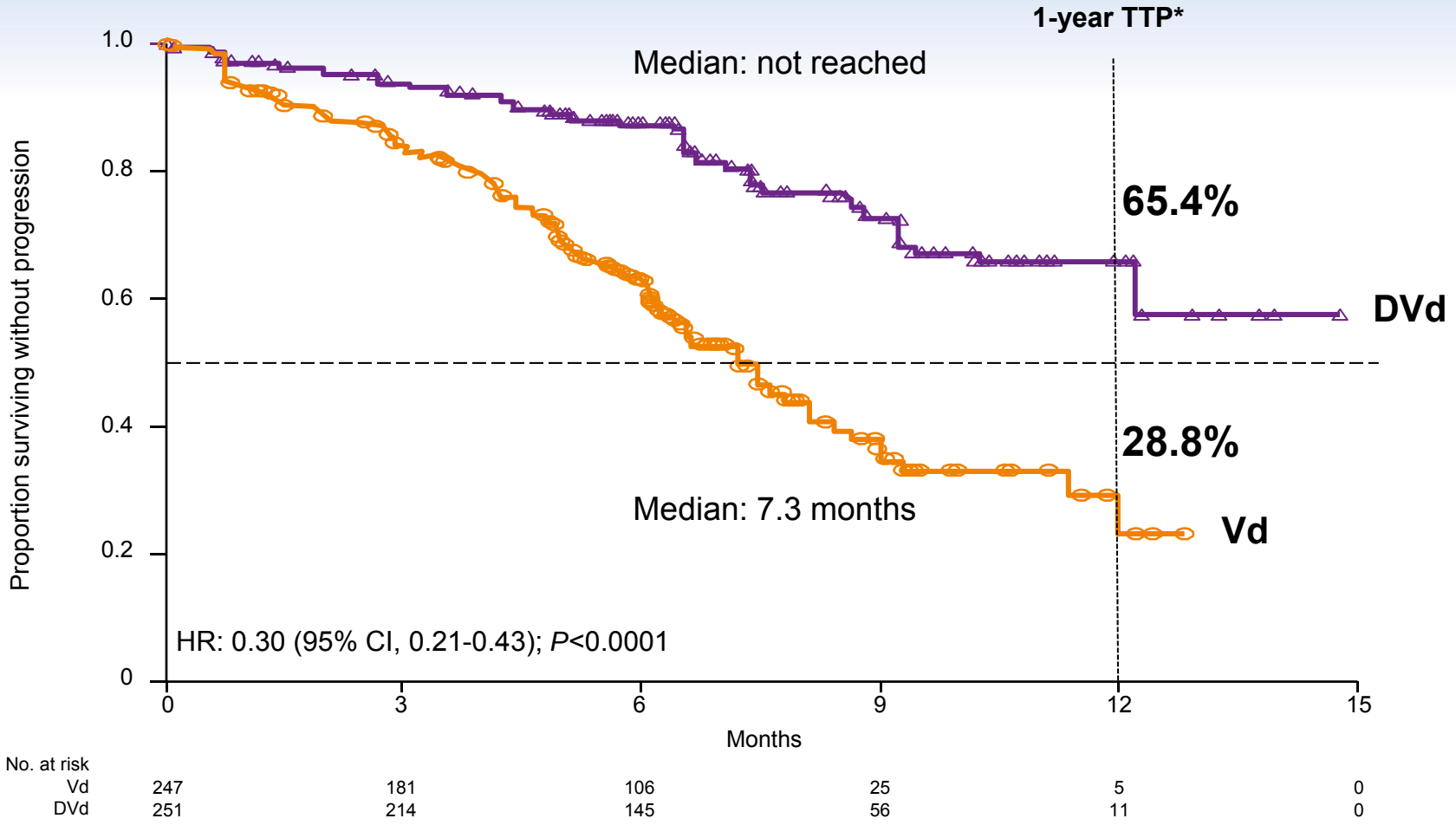
Progression-free Survival



61% reduction in the risk of disease progression or death for DVd vs Vd

*KM estimate; HR, hazard ratio.

Time to Progression



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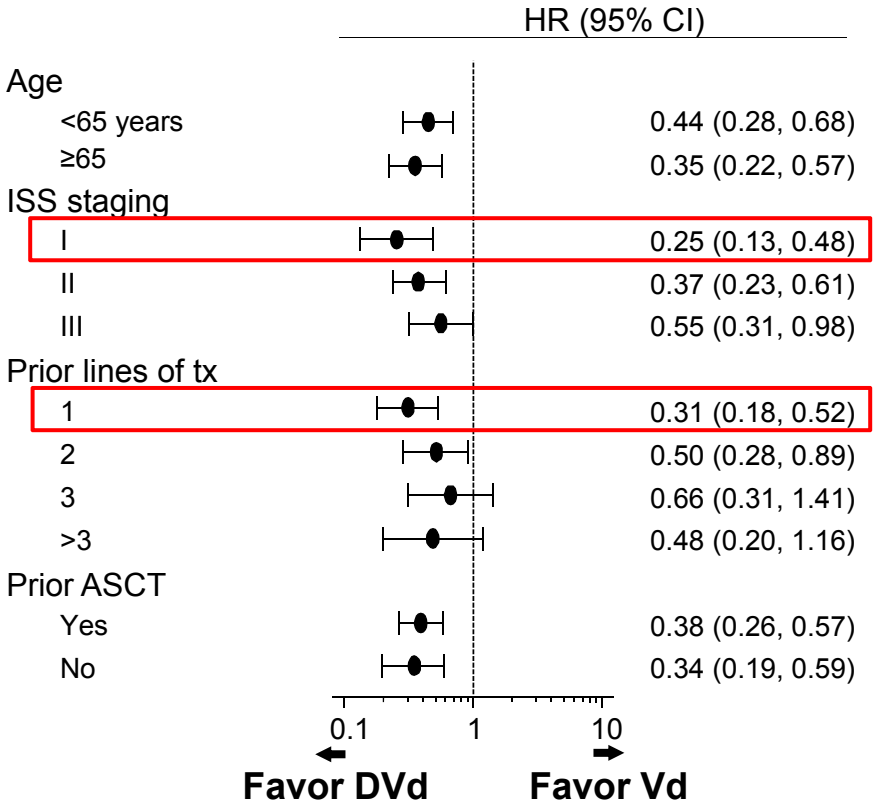
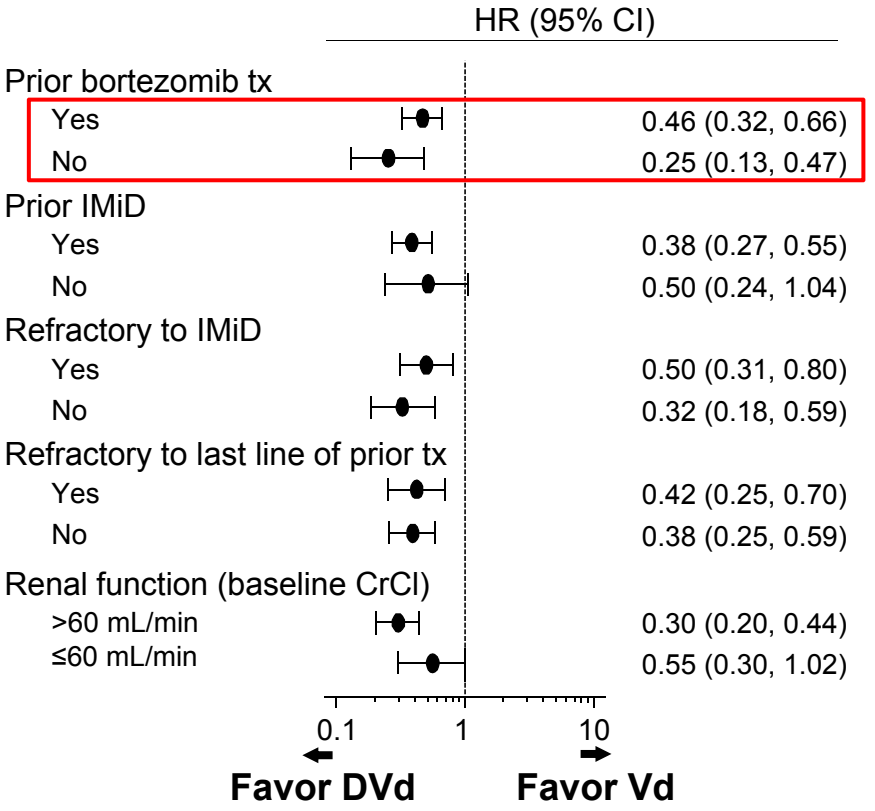
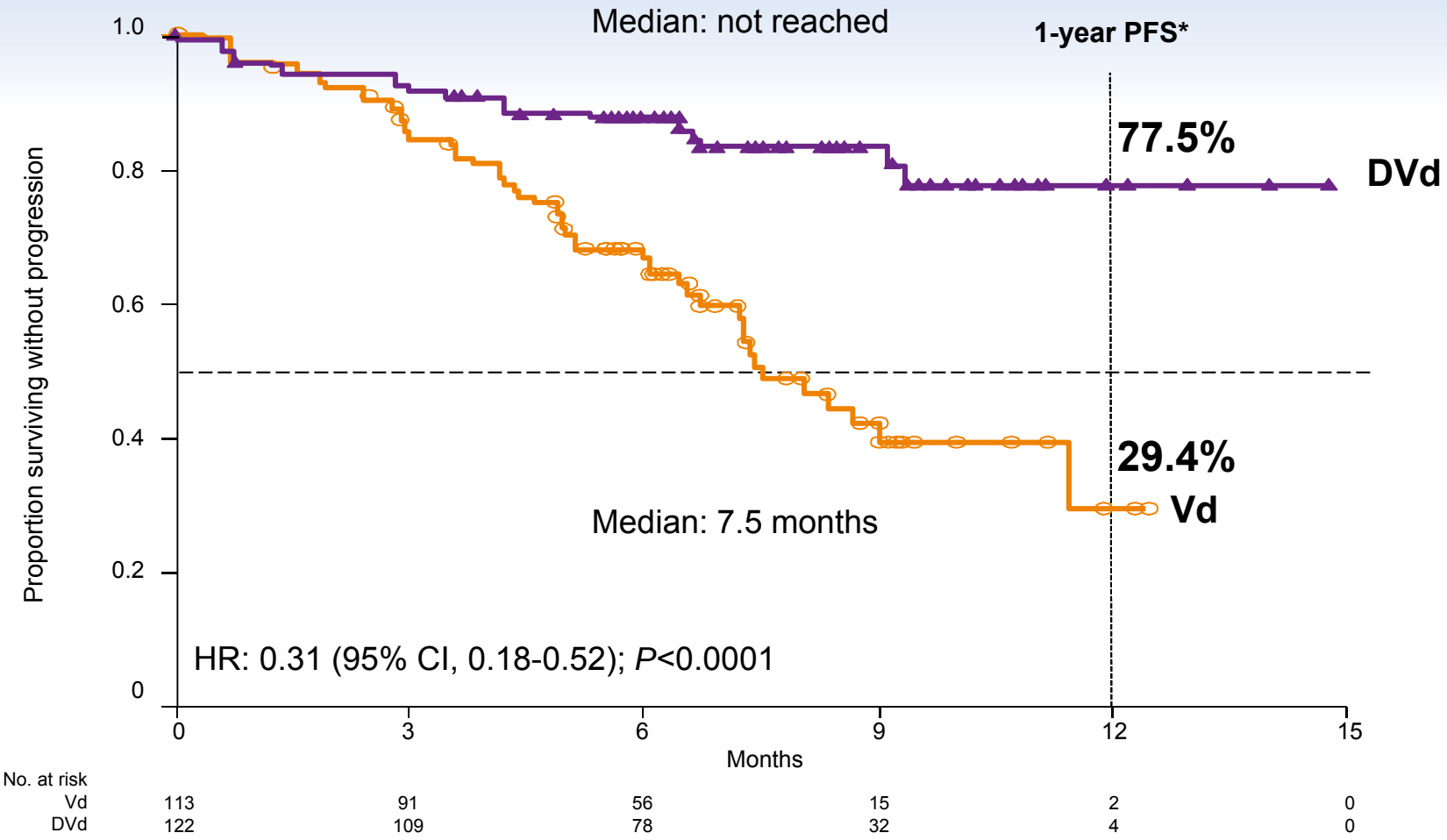
PFS: Subgroup Analysis





Tx, treatment; CrCl, creatinine clearance.

PFS: 1 Prior Line of Treatment



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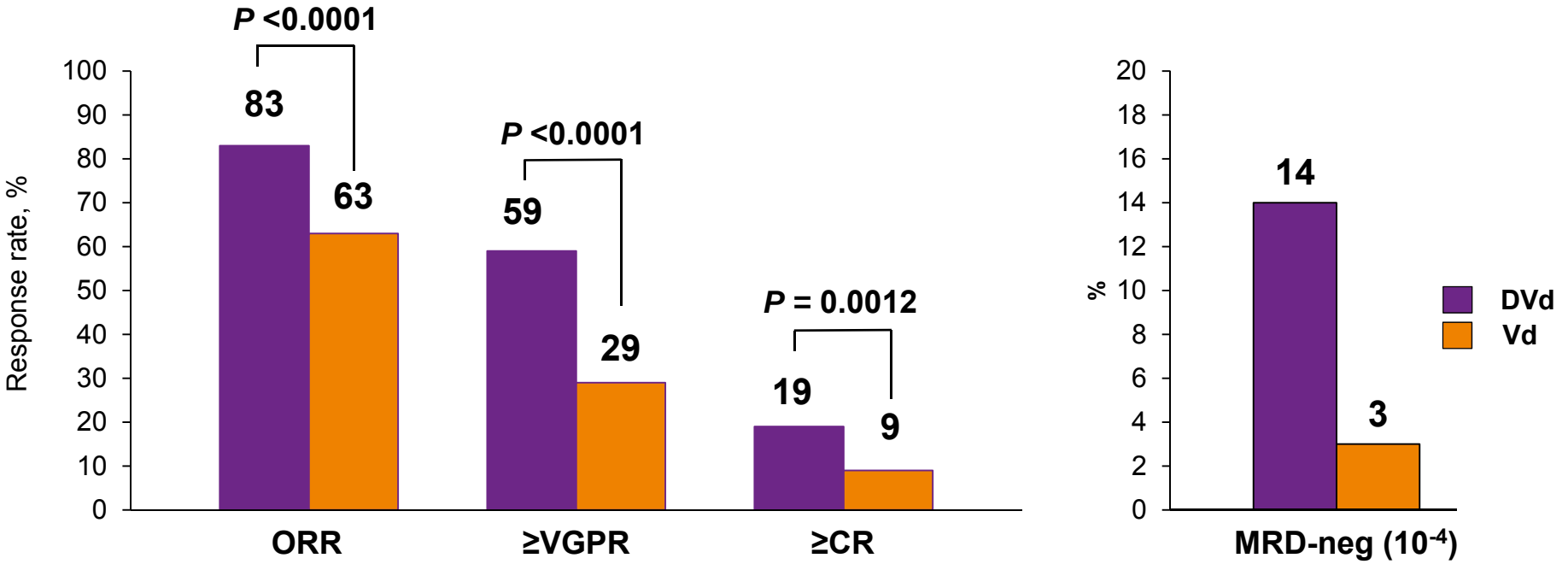
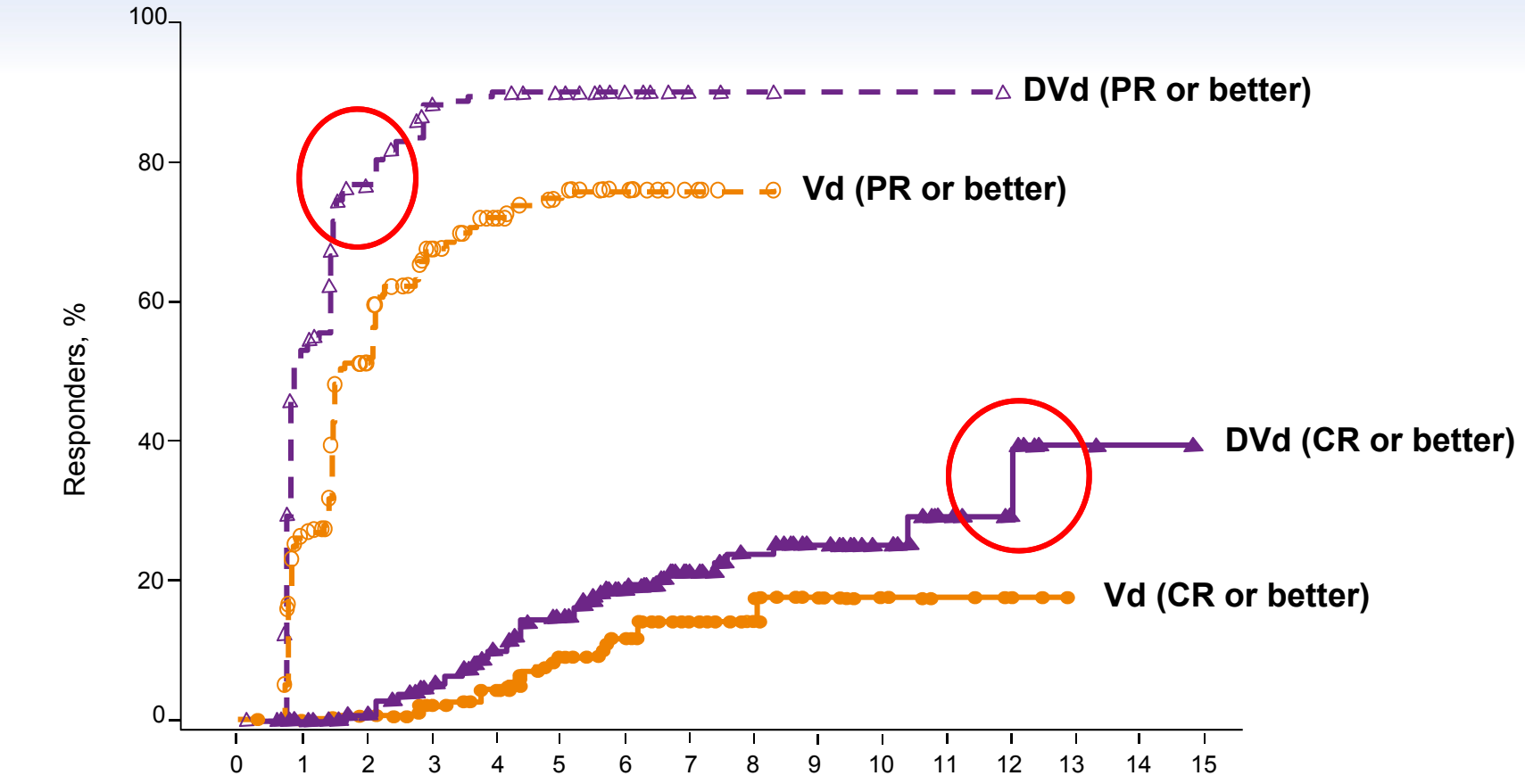
Overall Response Rate[a]



[a]Response-evaluable population.

Time to Response



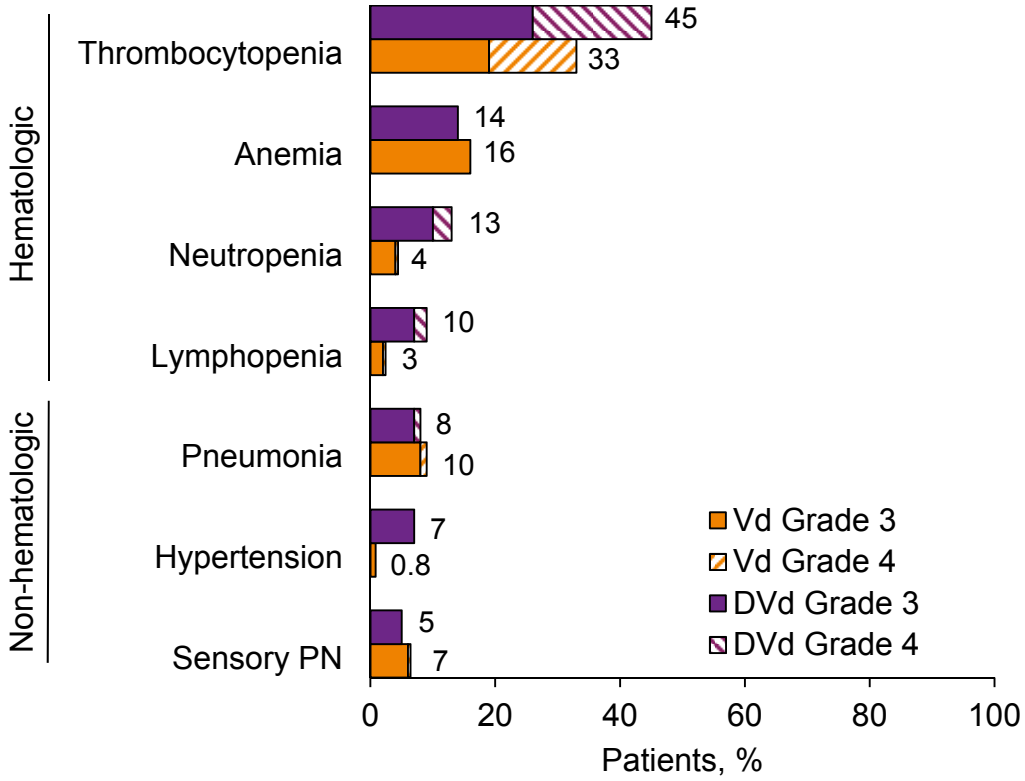
No. at risk

Vd (PR or better)	234	155	89	49	35	21	14	4	1	0	0	0	0	0	0	0
DVd (PR or better)	240	108	48	22	17	14	9	4	2	1	1	1	0	0	0	0
Vd (CR or better)	234	215	197	177	161	121	91	48	27	17	8	5	3	0	0	0
DVd (CR or better)	240	229	220	203	185	163	116	76	55	40	27	13	7	2	1	0

Most Common (≥20%) Treatment-emergent Adverse Events (TEAE)

Patients	DVd	Vd
Number treated	243	237
Patients with TEAE, %		
Thrombocytopenia	59	44
Sensory peripheral neuropathy (PN)	47	38
Diarrhea	32	22
Anemia	26	31
Upper respiratory tract infection	25	18
Cough	24	13
Fatigue	21	25
Constipation	20	16

Most Common (>5%) Grade 3-4 TEAE



Bleeding:

- All grades: 7% in DVd vs 4% in Vd
- Grade 3-4: 3 pts in DVd vs 2 pts in Vd

Infections:

- Grade 3-4 AEs: 21% in DVd vs 19% in Vd
- Serious AEs: 20% in DVd vs 18% in Vd

Discontinued for sensory peripheral neuropathy:

- All grades: 0.4% in DVd vs 3% in Vd

Discontinued for TEAE:

- 7% in DVd vs 9% in Vd

Infusion-related Reactions (IRRs)

	Safety Analysis Set (n = 243)	
	All grades	Grade 3
Patients with IRRs, %	45	9
Most common (>5%) IRRs		
Dyspnea	11	2
Bronchospasm	9	3
Cough	7	0

- No grade 4 or 5 IRRs observed
- 98% of patients with IRRs experienced the event on the first infusion
- 2 patients discontinued due to IRRs
  - Bronchospasm in the first patient
  - Bronchospasm, laryngeal edema, and skin rash in the second patient

Preinfusion: dexamethasone 20 mg, paracetamol 650-1000 mg, diphenhydramine 25-50 mg
Stop infusion immediately for mild symptoms; once resolved, resume at half the infusion rate

PI-based Studies

	Daratumumab DVd vs Vd	Carfilzomib Kd vs Vd[1]	Panobinostat PVd vs Vd[2,3]	Elotuzumab EVd vs Vd[4]
PFS HR (95% CI)	0.39 (0.28-0.53)	0.53 (0.44-0.65)	0.63 (0.52-0.76)	0.72 (0.59-0.88)
PFS, median mo	NE	18.7	12.0	9.7
≥VGPR	59%	54%	28%	36%
≥CR	19%	13%	11%	4%
Duration of response, mo	NE	21.3	13.1	11.4
OS HR (95% CI)	0.77 (0.47, 1.26)	0.79 (0.58-1.08)	0.94 (0.78-1.14)	0.61 (0.32-1.15)

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2. San-Miguel JF, et al. *Lancet Oncol*. 2014;15(11):1195-1206.
3. San-Miguel JF, et al. *Blood*. 2015;126(23):Abstract 3026.
4. Jakubowiak A, et al. *Blood*. 2016. Epub ahead of print.

Conclusions

- Daratumumab-Vd significantly improved PFS, TTP, and ORR in comparison with Vd alone
  - DVd was associated with a 61% reduction in the risk of progression/death
- Treatment benefit of DVd vs Vd was consistent across subgroups
  - Earlier treatment with DVd may be the most beneficial
- Daratumumab-Vd doubled VGPR and CR rates
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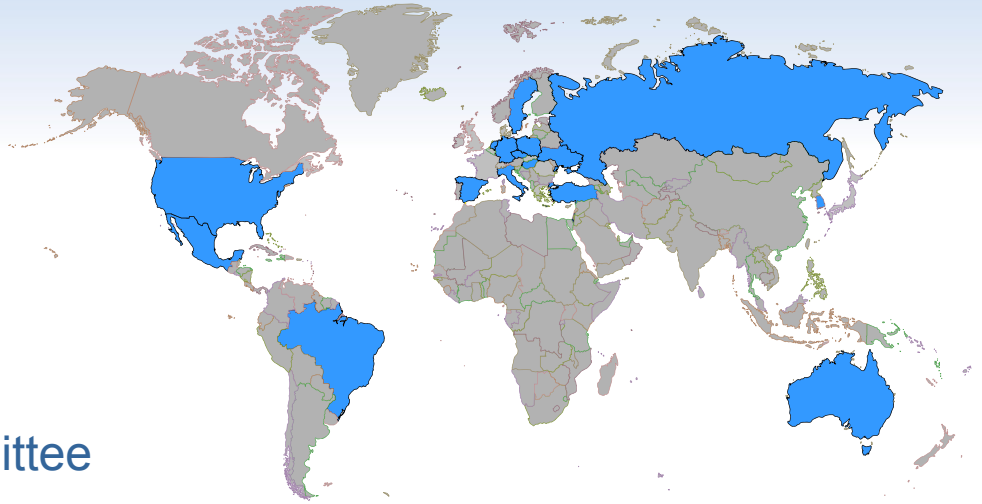
Daratumumab-Vd can potentially be considered a new standard of care for RRMM currently receiving Vd alone

Acknowledgments

- Patients who participated in this study
  - Staff members at the study sites
  - Data and safety monitoring committee
  - Staff members involved in data collection and analyses



16 countries

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