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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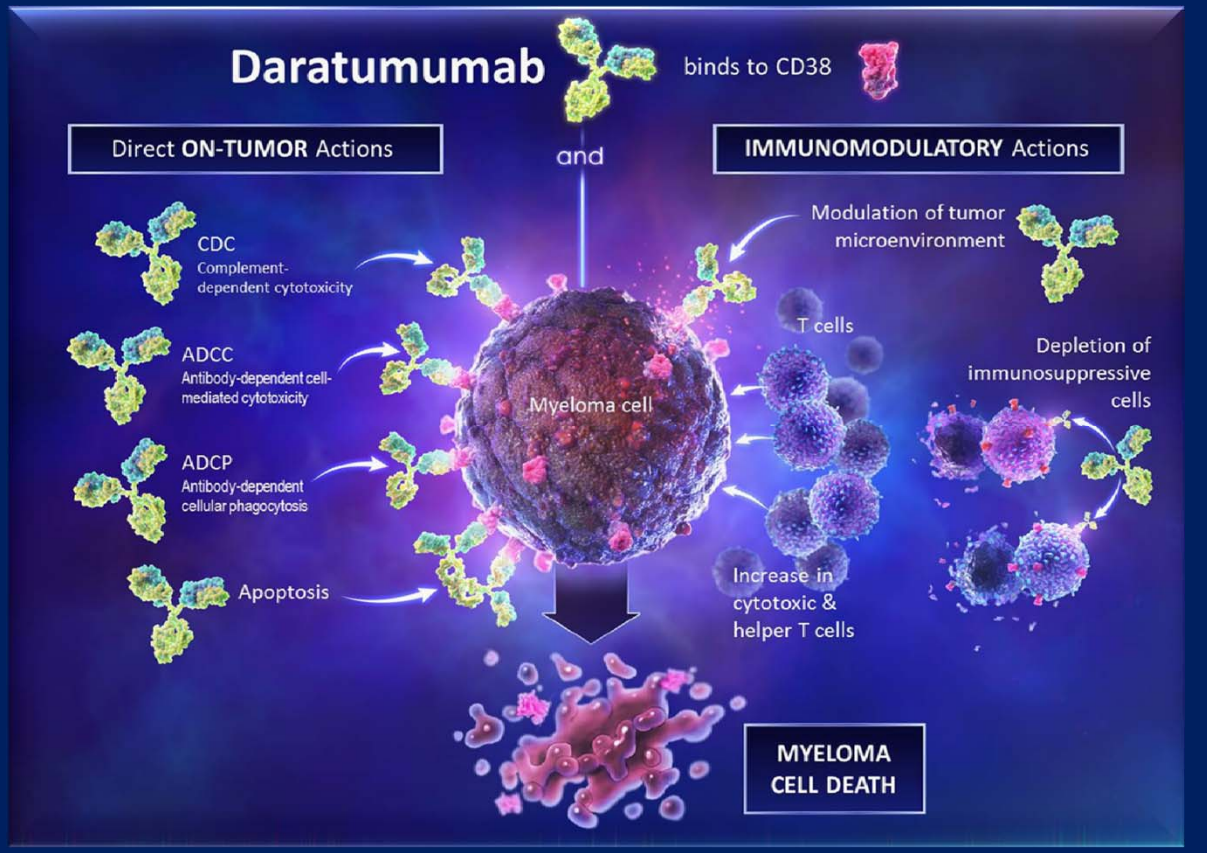
*NCT02136134

Daratumumab: Mechanism of Action

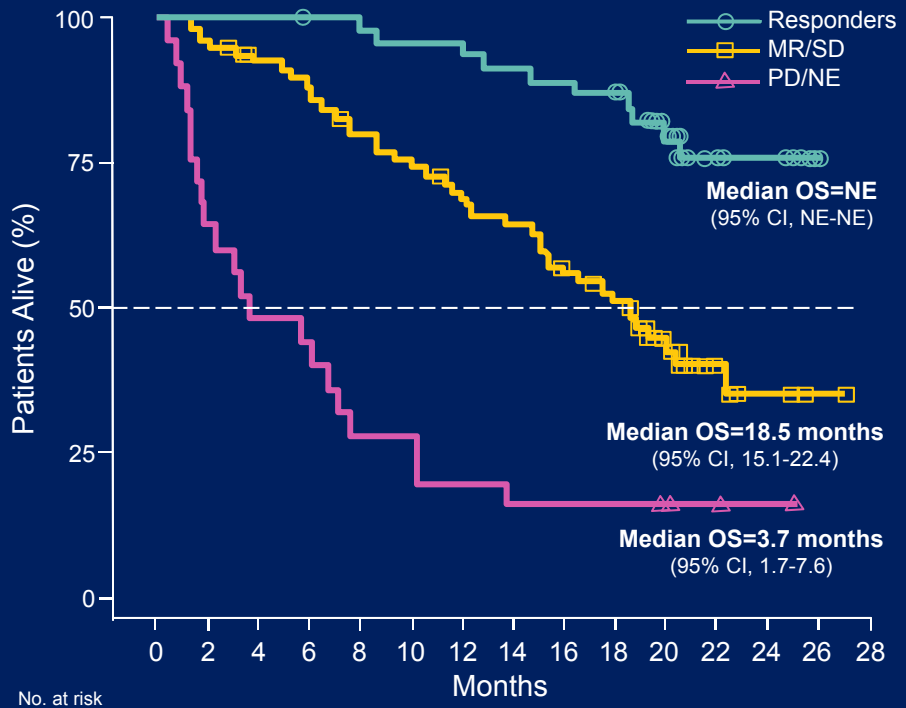
- Human CD38 IgGκ monoclonal antibody
- Direct and indirect anti-myeloma activity[1-5]
- Depletes CD38+ immunosuppressive regulatory cells[5]
- Promotes T-cell expansion and activation[5]



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 MR/SD patients



No. at risk

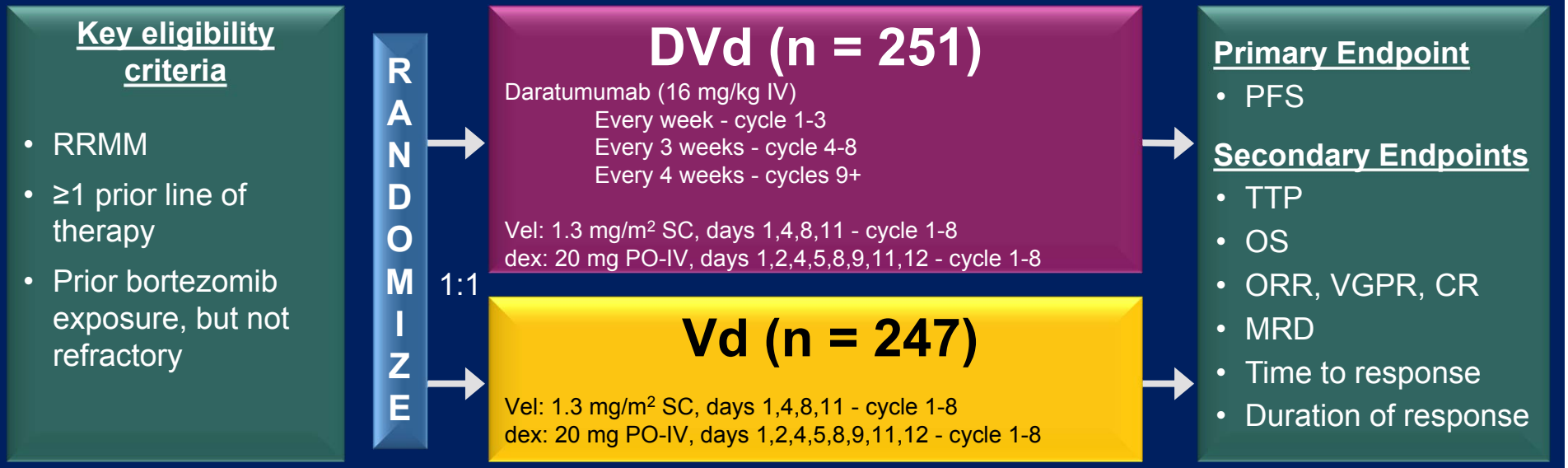
Responders	46	46	46	45	44	43	43	41	40	39	28	12	12	2	0
MR/SD	77	74	67	63	57	53	48	45	38	34	20	8	4	1	0
PD/NE	25	16	12	11	7	7	5	4	4	4	3	2	1	0	0

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

Daratumumab IV administered in 1000 mL to 500 mL; gradual escalation from 50 mL to 200 mL/min 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)

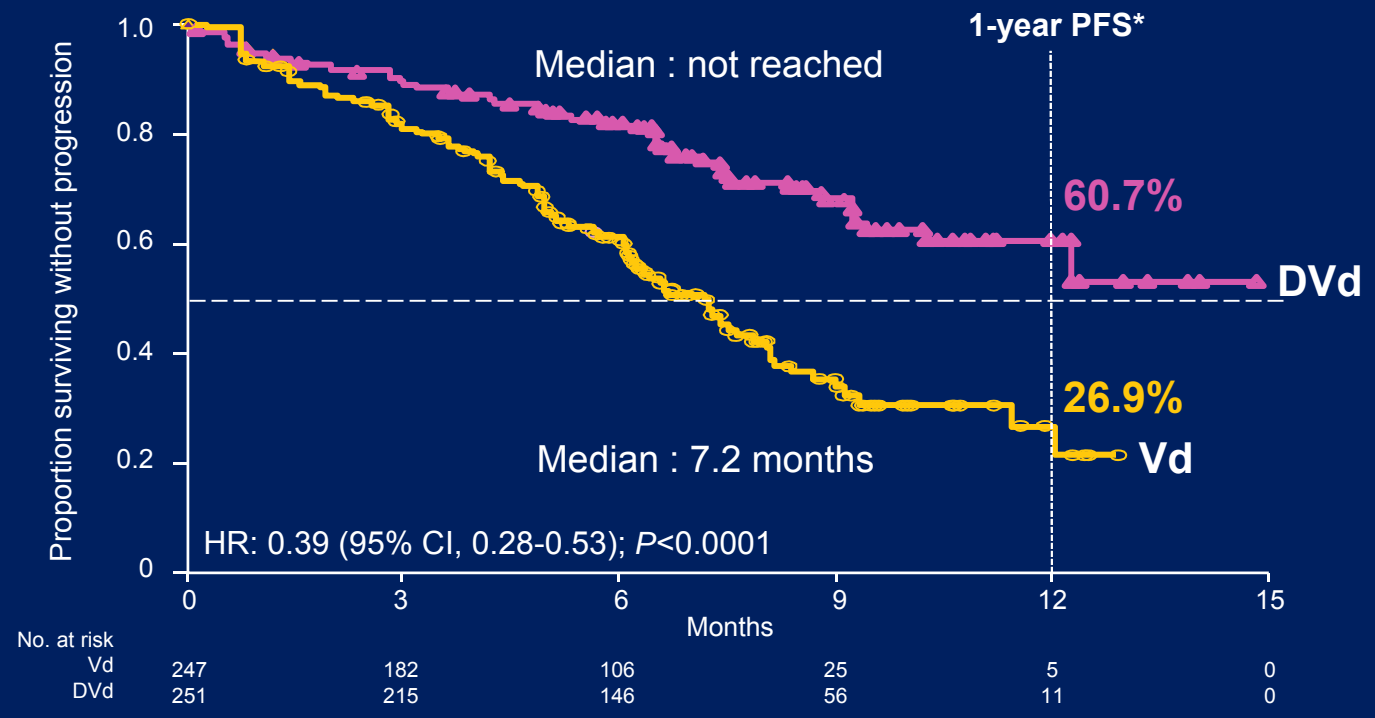
ISS, international staging system; ASCT, autologous stem cell transplant; [a]ISS staging is derived based on the combination of serum β2-microglobulin and albumin; [b]Investigator-reported.

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)

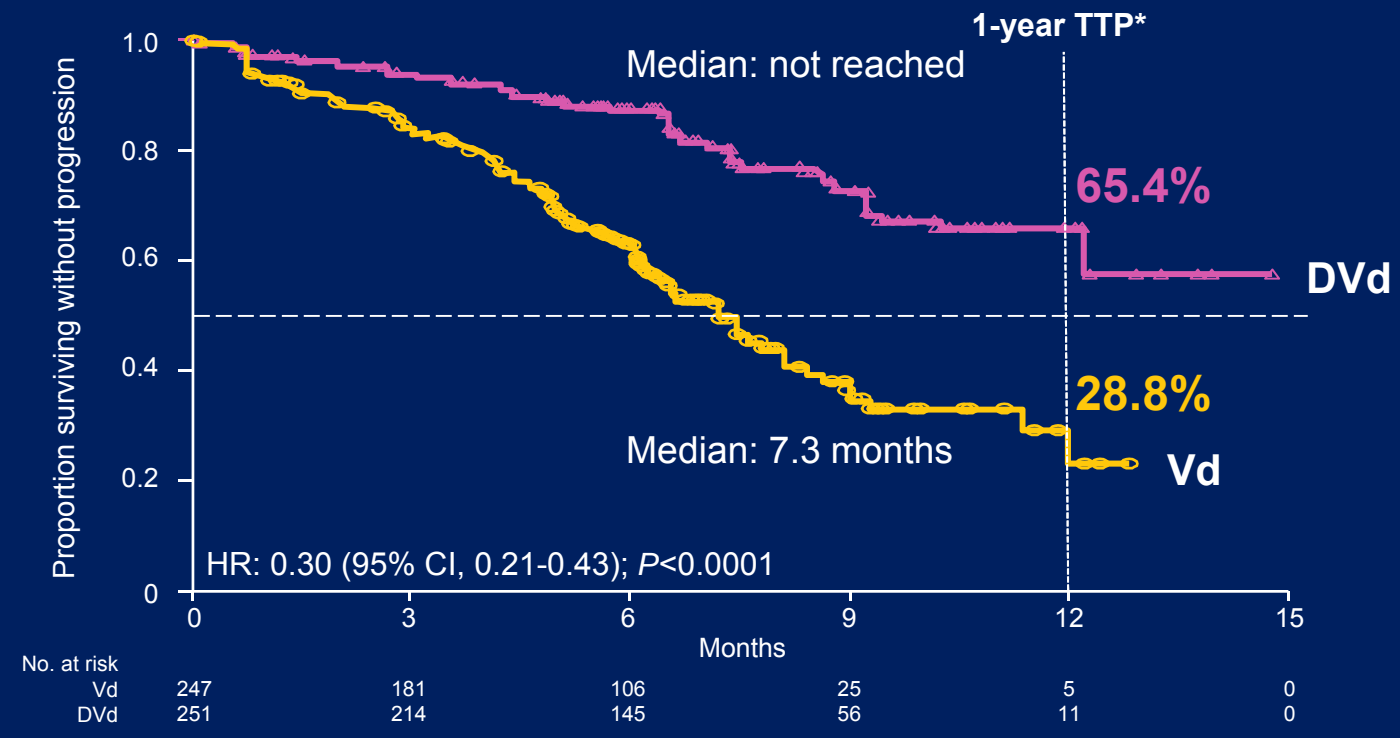
Progression-free Survival



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

*KM estimate; HR, hazard ratio.

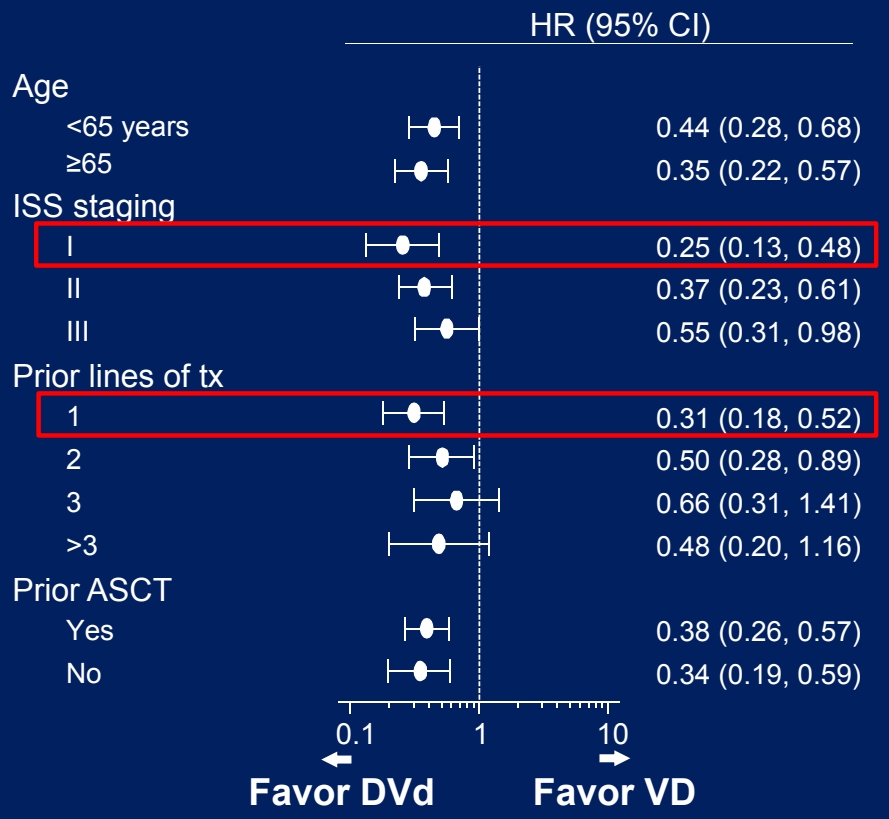
Time to Progression

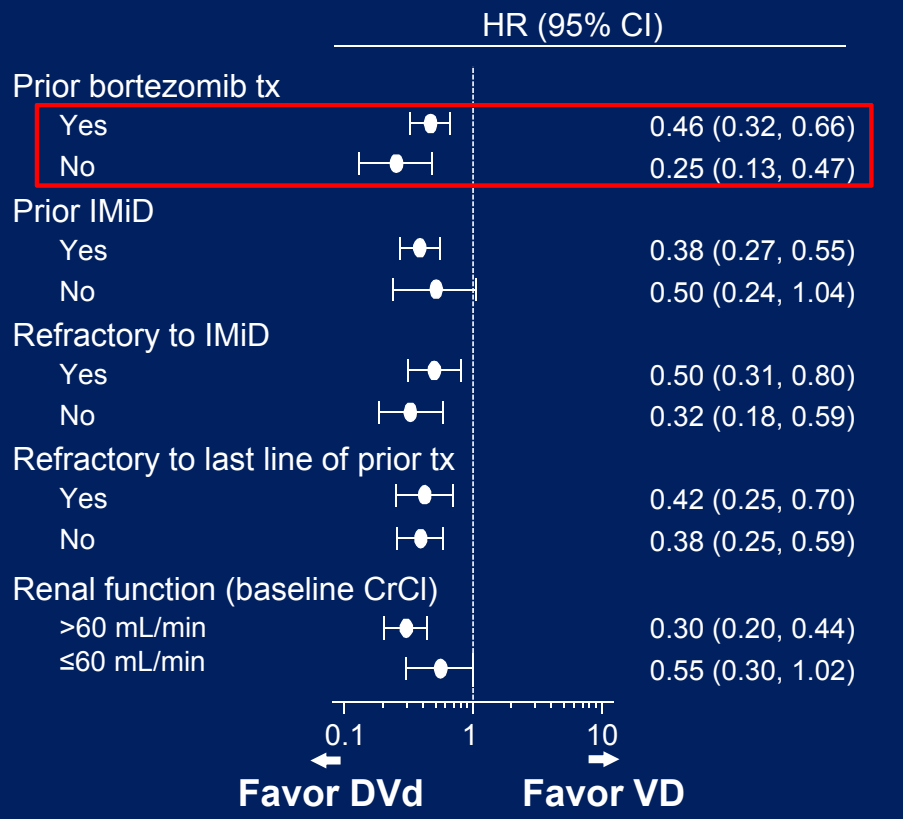


70% reduction in the risk of disease progression for DVd vs Vd

*KM estimate

PFS: Subgroup Analysis

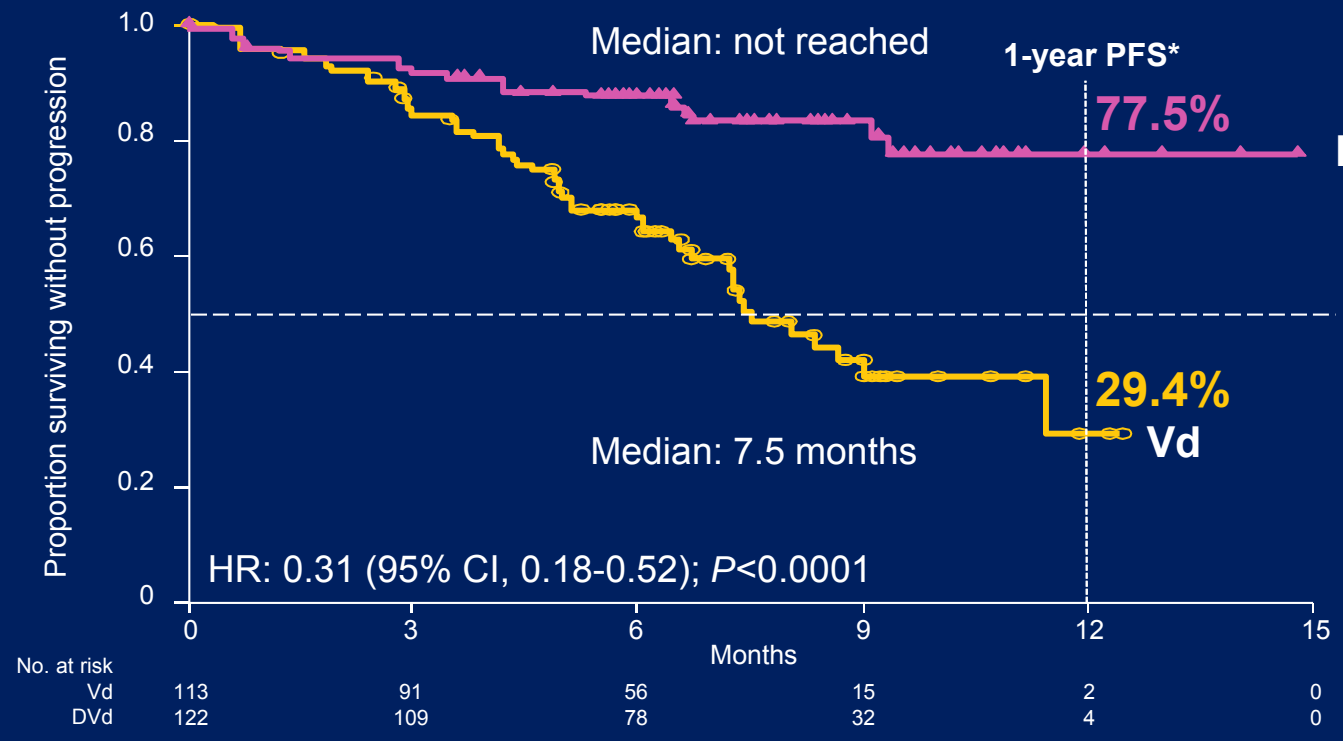




Tx, treatment; CrCl, creatinine clearance.

CrCl, creatinine clearance.

PFS: 1 Prior Line of Treatment



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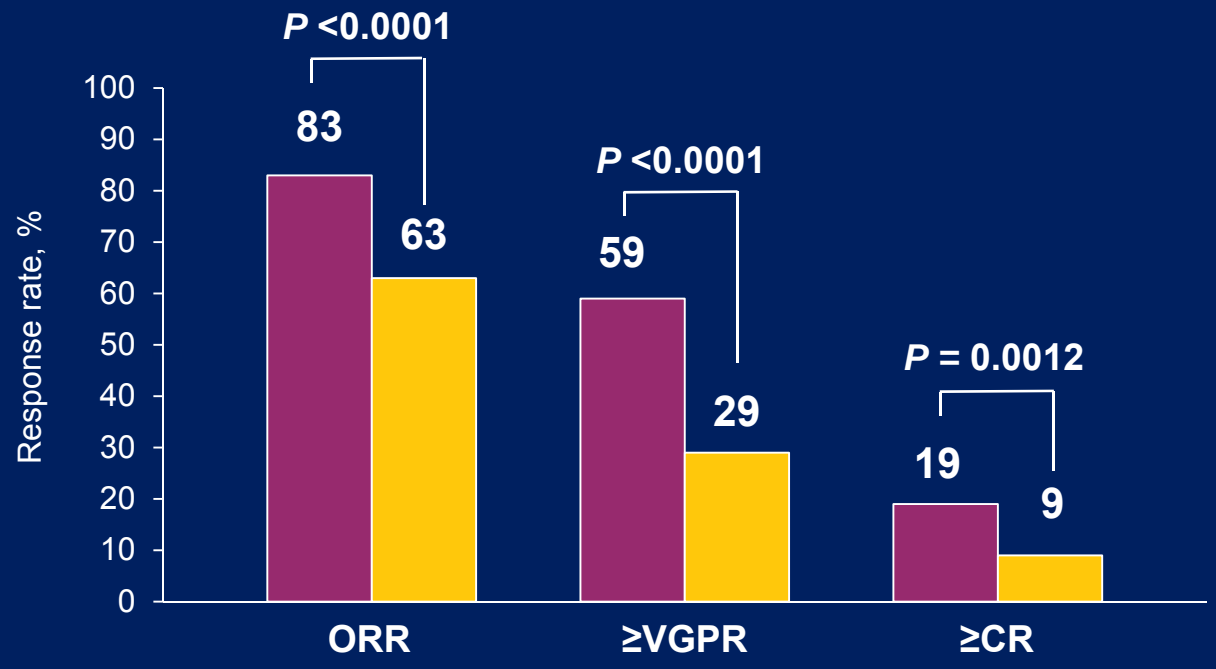
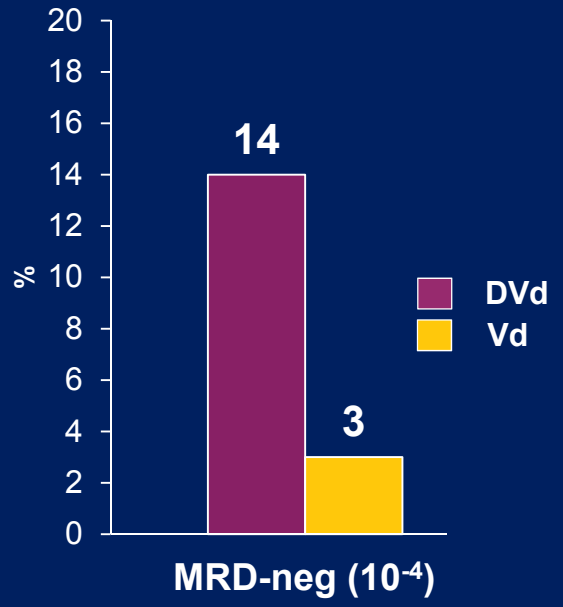
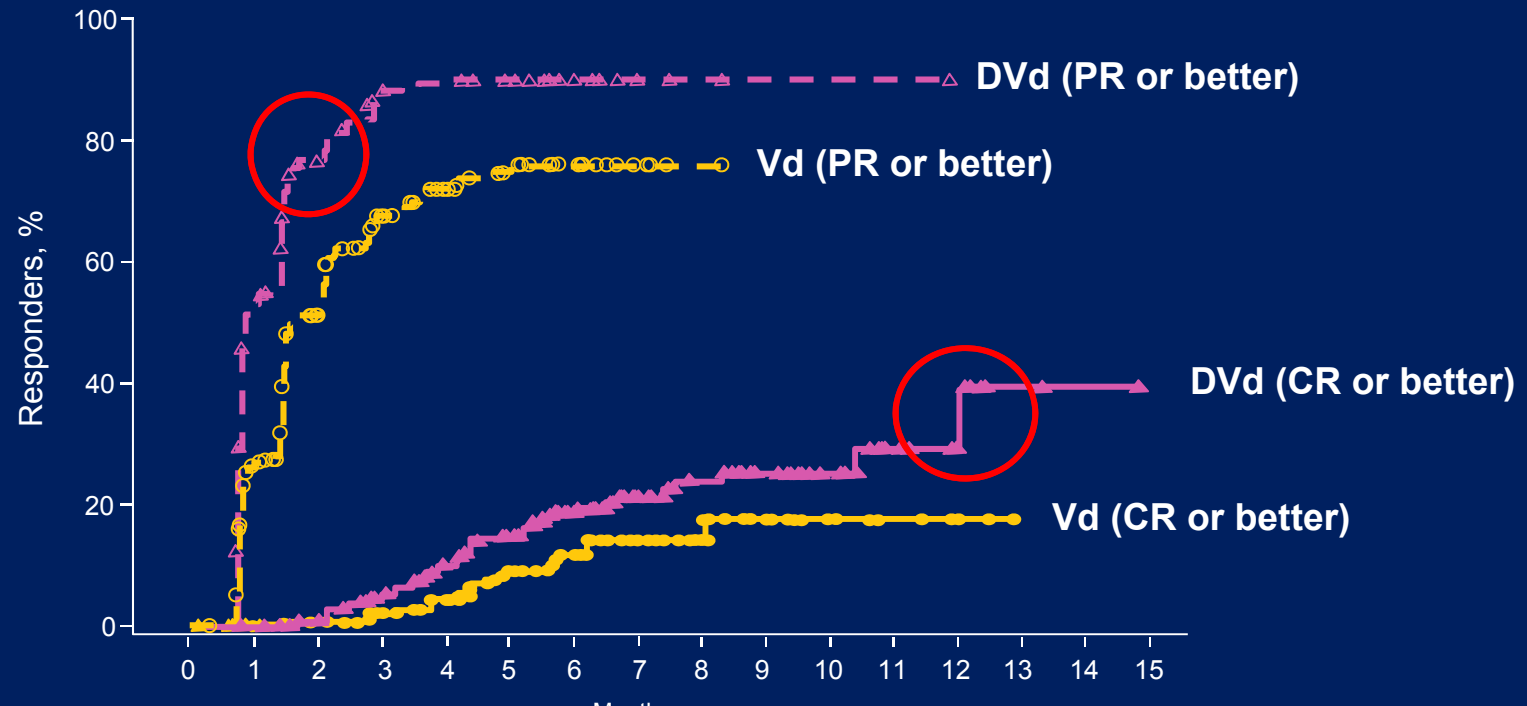
Overall Response Rate[a]





[a]Response-evaluable population.

Time to Response



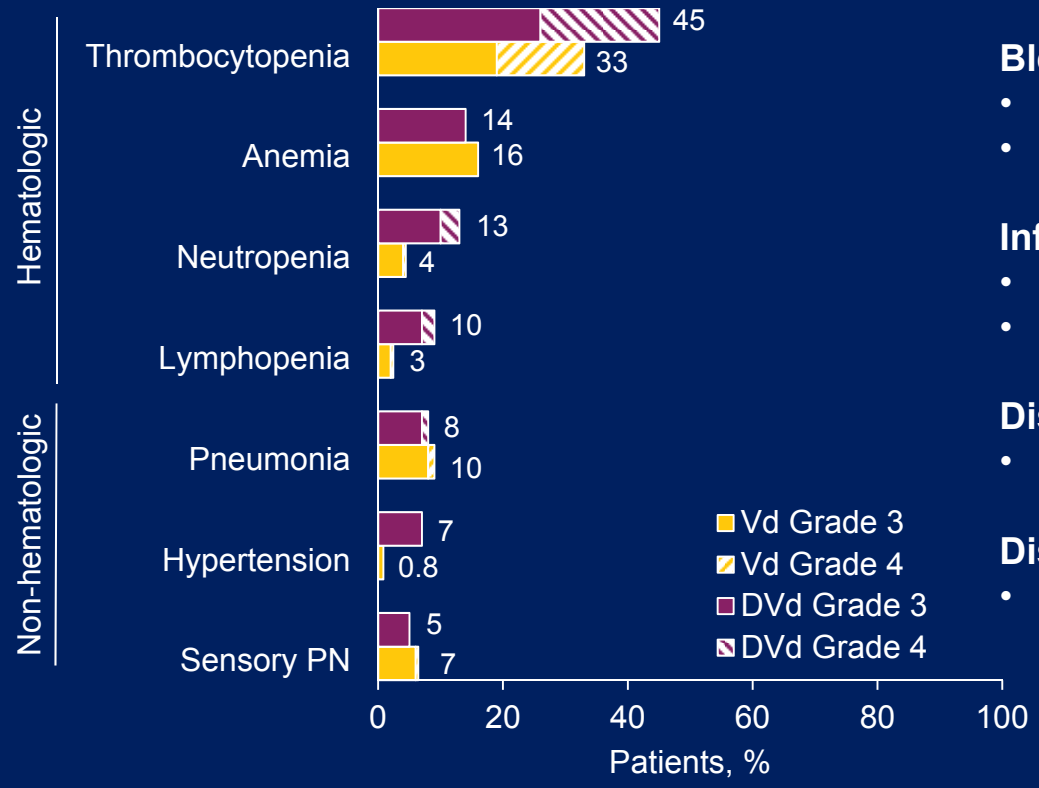
No. at risk

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)

1. Dimopoulos MA, et al. *Lancet Oncol*. 2016;17(1):27-38.
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
- Daratumumab-Vd was not associated with any cumulative toxicities

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- Daratumumab-Vd doubled VGPR and CR rates
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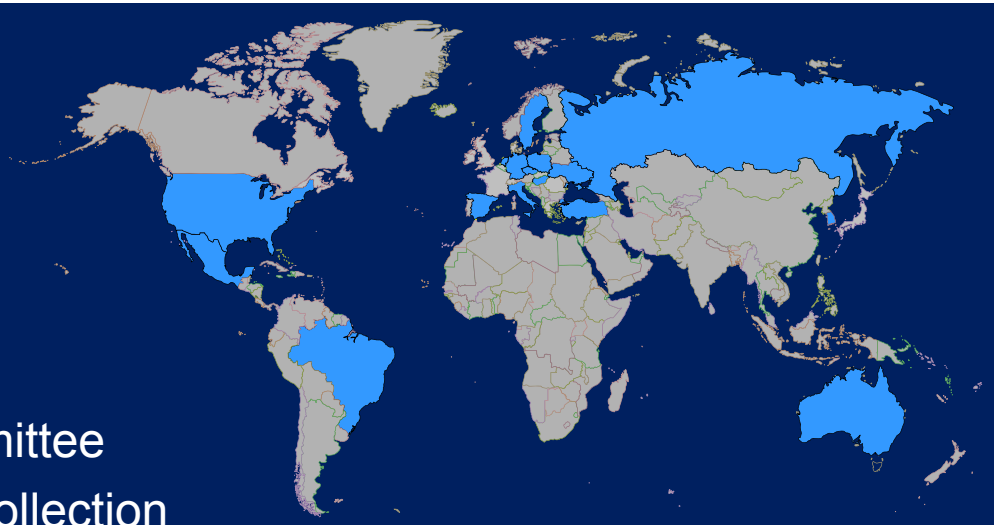
Daratumumab-Vd can potentially be considered a new standard of care for RRMM currently receiving Vd alone

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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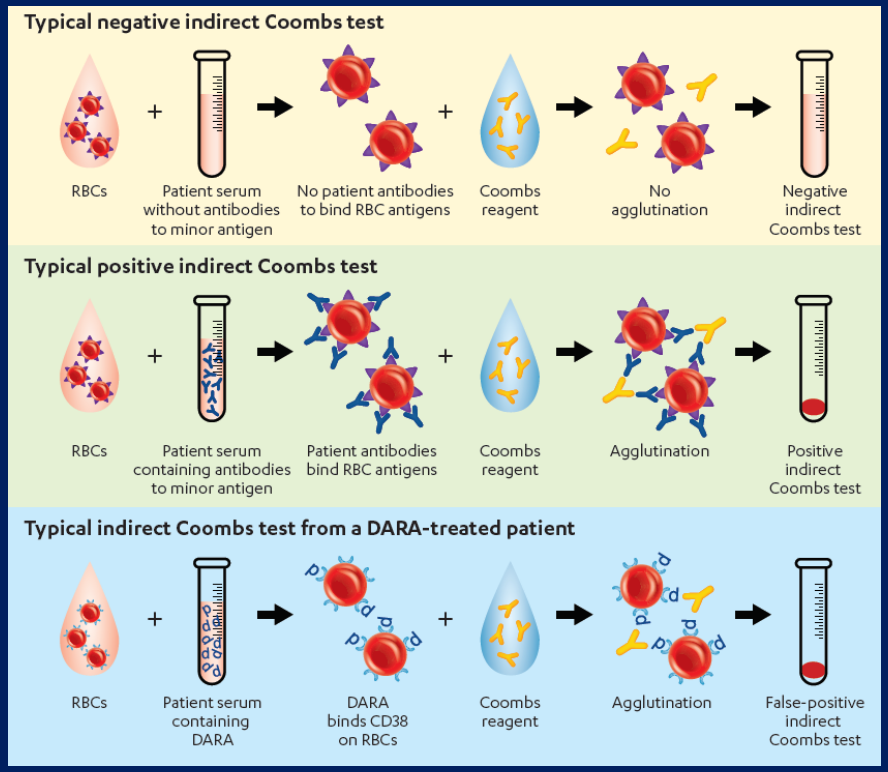
- Medical writing and editorial support was provided by Jason Jung, PhD (MedErgy) and was funded by Janssen Global Services, LLC

Back-up Slides: Management of IRRs in CASTOR

- Pre-infusion medication
  - Dexamethasone 20 mg IV (preferred) or PO (an equivalent of long-acting corticosteroid may substitute); this dose of dexamethasone will be the only steroid received on this day
  - Paracetamol (acetaminophen) 650 to 1,000 mg IV or PO
  - An antihistamine given IV or PO (diphenhydramine 25 to 50 mg, or equivalent)
- Post-infusion medication
  - For patients with a higher risk of respiratory complications (eg, patients with COPD who have an FEV1 <80%, or patients with asthma), the following post-infusion medications should be considered:
    - Antihistamine (diphenhydramine or equivalent) on the first and second days after all infusions
    - Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
    - Control medications for lung disease (eg, inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for patients with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for patients with COPD)
- If an IRR develops, then the infusion should be temporarily interrupted or slowed down
- Patients who experience adverse events during an infusion must be treated according to the investigator's judgement and best clinical practice

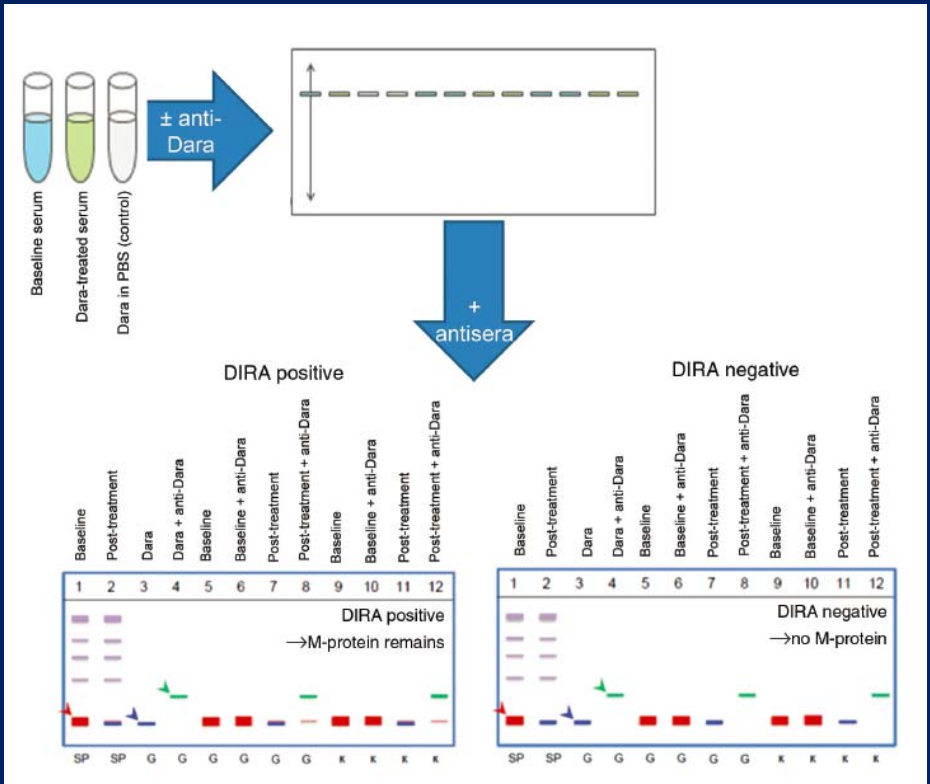
Back-up Slides: Blood Testing for Transfusions

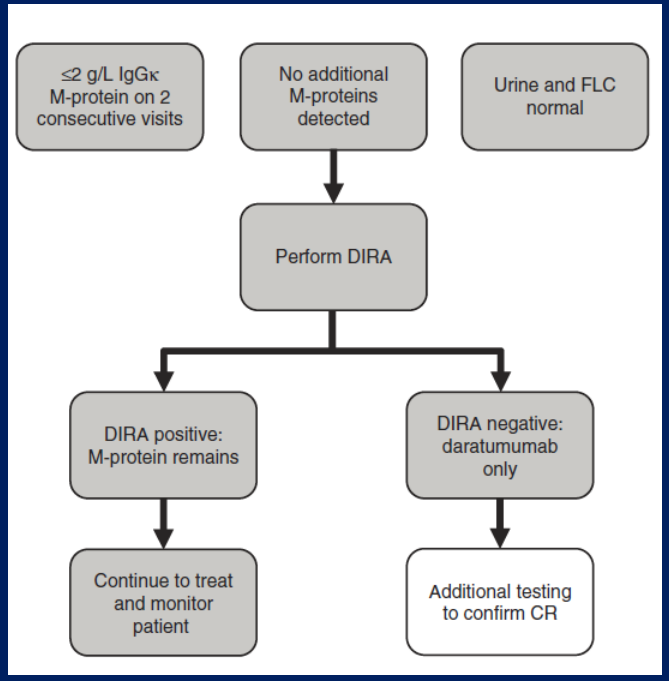


- Strategies to prevent transfusion delays due to assay interference with daratumumab:
- Treat RBCs with dithiothreitol (DTT) to denature CD38 so that daratumumab no longer binds to RBCs[1]
- RBC phenotyping prior to the first dose of daratumumab and providing phenotypically matched blood for up to 1 year after the patient's last daratumumab infusion[2]

1. Chapuy CI, et al. *Transfusion*. 2015;56(6 Pt 2):1545-54.
2. Chari A, et al. *Blood*. 2015;126:Abstract 3571.

Back-up Slides: Daratumumab Interference





Guidelines for daratumumab-specific immunofixation electrophoresis reflex assay (DIRA) recently published:

McCudden C, et al. Clin Chem Lab Med. 2016. 54;1095-1104.