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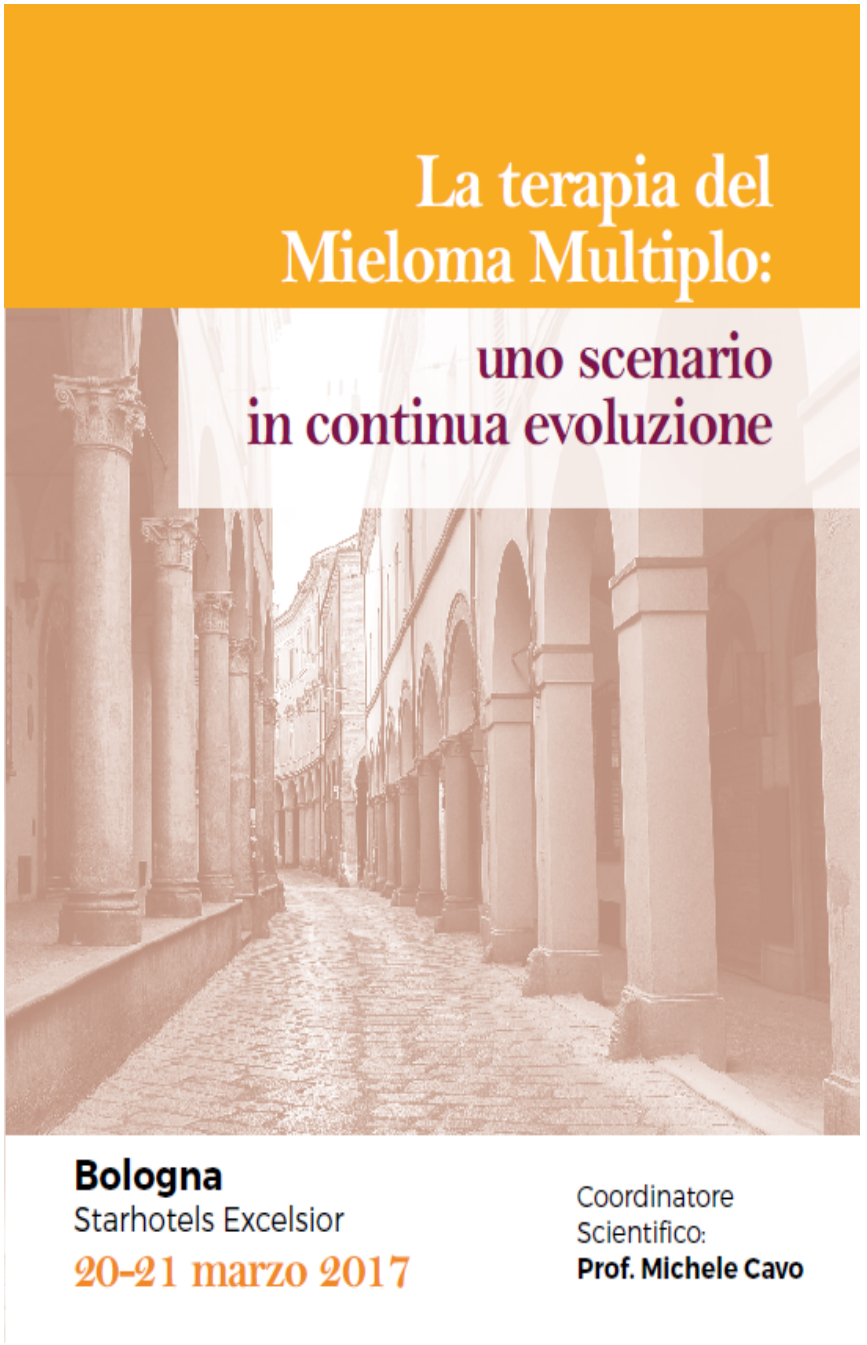
Gestione degli Eventi Avversi Correlati alla Terapia con Anticorpi Monoclonali



My Agenda

- Adverse events of MoAbs in major clinical studies (single agent/combinations approved or close to be approved)
- Management of infusion-related reactions (IRRs)
- Interference with response assessment (all MoAbs)
- Interference with blood typing (anti-CD38)

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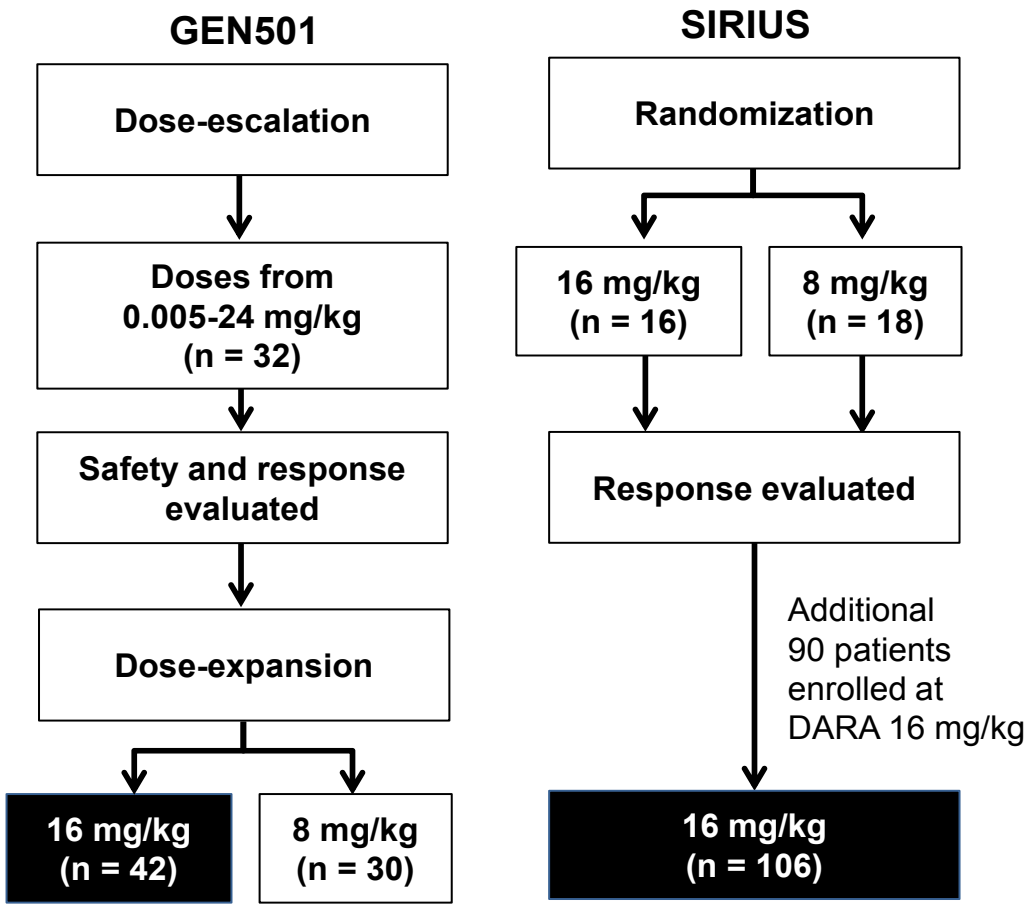
Clinical Efficacy of Daratumumab Monotherapy in Patients with Heavily Pretreated Relapsed or Refractory Multiple Myeloma

Pooled analysis Studies GEN501 and MMY2002 (Sirius)



16 mg/kg
N = 148

1. Lokhorst HM, *N Engl J Med*. 2015;373(13):1207-1219
2. Lonial S. *Lancet*. 2016;387(10027):1551-1560.

Usmani, SZ. Blood. 2016. http://dx.doi.org/10.1182/blood-2016-03-705210.

Patient Disposition

	16 mg/kg Combined N = 148
Discontinued from treatment, n (%)	136 (91.9)
Progressive Disease	123 (83.1)
Adverse event	**6 (4.1)**
Physician decision	4 (2.7)
Withdrawal of consent	3 (2.0)

- In the combined dataset
  - Median (range) duration of follow-up = **20.7 (1-27) months**
  - Median (range) duration of treatment = **3.4 (0-26) months**
  - Median (range) number of infusions = **12 (1-40)**

- There were **3 deaths** that were recorded as being **due to AEs**
  - **Not related to study treatment**
  - Consisted of viral H1N1 infection, pneumonia, and aspiration pneumonia

Usmani, SZ. Blood. 2016. http://dx.doi.org/10.1182/blood-2016-03-705210.

Incidence and Severity of Most Common (≥20%) Treatment-emergent Adverse Events (TEAEs)

	16 mg/kg N = 148		
Event, n (%)	**All grades**	**Grade ≥3**	**Grade 4**
Fatigue	62 (41.9)	3 (2.0)	0
Nausea	44 (29.7)	0	0
Anemia	42 (28.4)	**26 (17.6)**	0
Back pain	40 (27.0)	4 (2.7)	0
Cough	38 (25.7)	0	0
Thrombocytopenia	32 (21.6)	**13 (8.8)**	**8 (5.4)**
Upper respiratory tract infection	32 (21.6)	1 (0.7)	0
Neutropenia	31 (20.9)	**11 (7.4)**	**4 (2.7)**

TEAE, treatment-emergent adverse event.

AEs were consistent with the individual GEN501 and SIRIUS studies; no new safety signals were identified

Usmani, SZ. Blood. 2016. http://dx.doi.org/10.1182/blood-2016-03-705210.

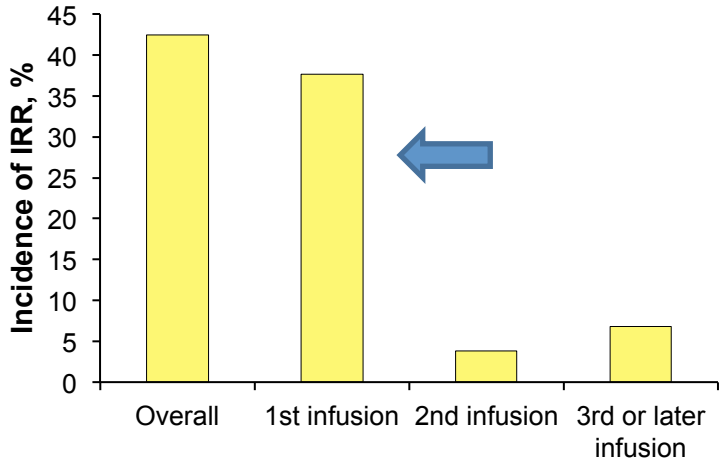
Infusion related reactions (IRRs) ≥ 5%

	16 mg/kg N = 148	
Event, n (%)	**All grades**	**Grade ≥3**
Nasal congestion	17 (11.5)	0
Cough	12 (8.1)	0
Rhinitis allergic	10 (6.8)	0
Chills	10 (6.8)	0
Throat irritation	9 (6.1)	0
Dyspnea	8 (5.4)	1 (0.7)
Nausea	8 (5.4)	0

IRR, infusion-related reaction.

IRRs were observed in 48% of patients and those observed in ≥ 5% of patients were mainly respiratory conditions

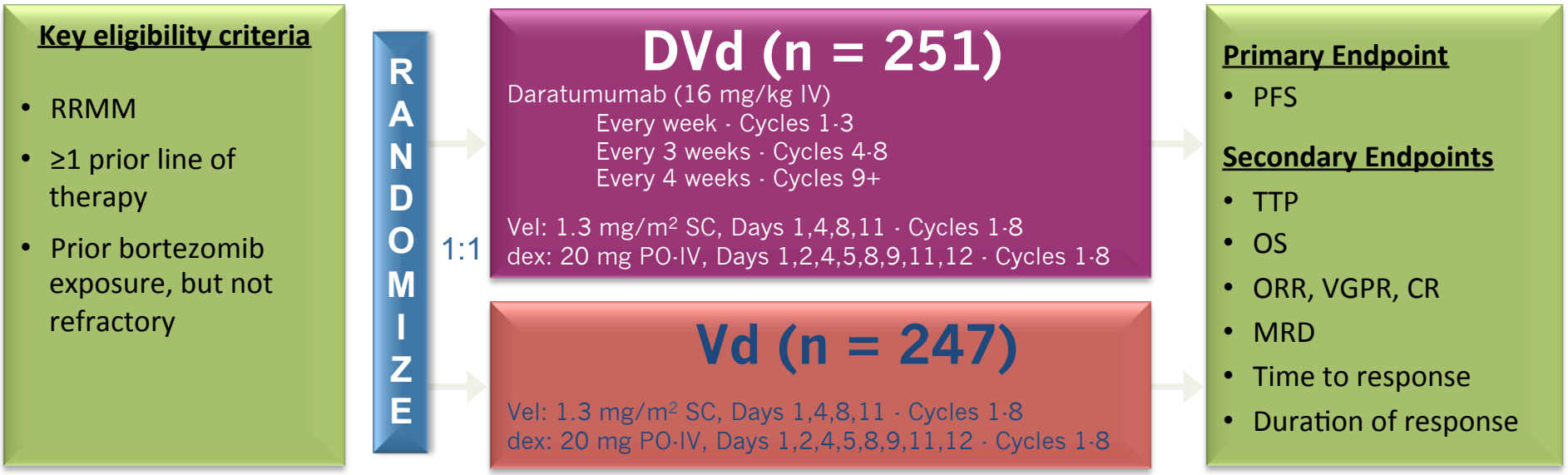
- **4 (2.7%) patients had grade ≥3 IRRs** (bronchospasm [n = 2]; dyspnea, hypoxia, and hypertension [n = 1 each])
- **95.8% of IRRs were observed during the first infusion** and the incidence of IRRs decreased during the second (7.0%) and subsequent (7.0%) infusions
- **IRRs were managed** with pre- and post-infusion medications, (antihistamines, corticosteroids, and paracetamol/acetaminophen)
- Supportive care treatment with **G-CSF** was required by 12 patients **(8.1%)**
- **46 (31.1%) patients received transfusions** during the study: red blood cell and platelet transfusions received by 44 (29.7%) and 14 (9.5%) of patients, respectively, **without any AE related to hemolysis**.
- **No patients discontinued** treatment due to IRRs (in MMY2002 SIRIUS study)



Usmani, SZ. Blood. 2016. http://dx.doi.org/10.1182/blood-2016-03-705210.

CASTOR MMY3004 DaraVd vs Vd

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.

Palumbo et al. N Engl J Med 2016;375:754-66

Most Common (≥20%) Treatment-emergent Adverse Events (TEAEs): CASTOR

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

Palumbo et al. N Engl J Med 2016;375:754-66

Infusion-related Reactions (IRRs): CASTOR

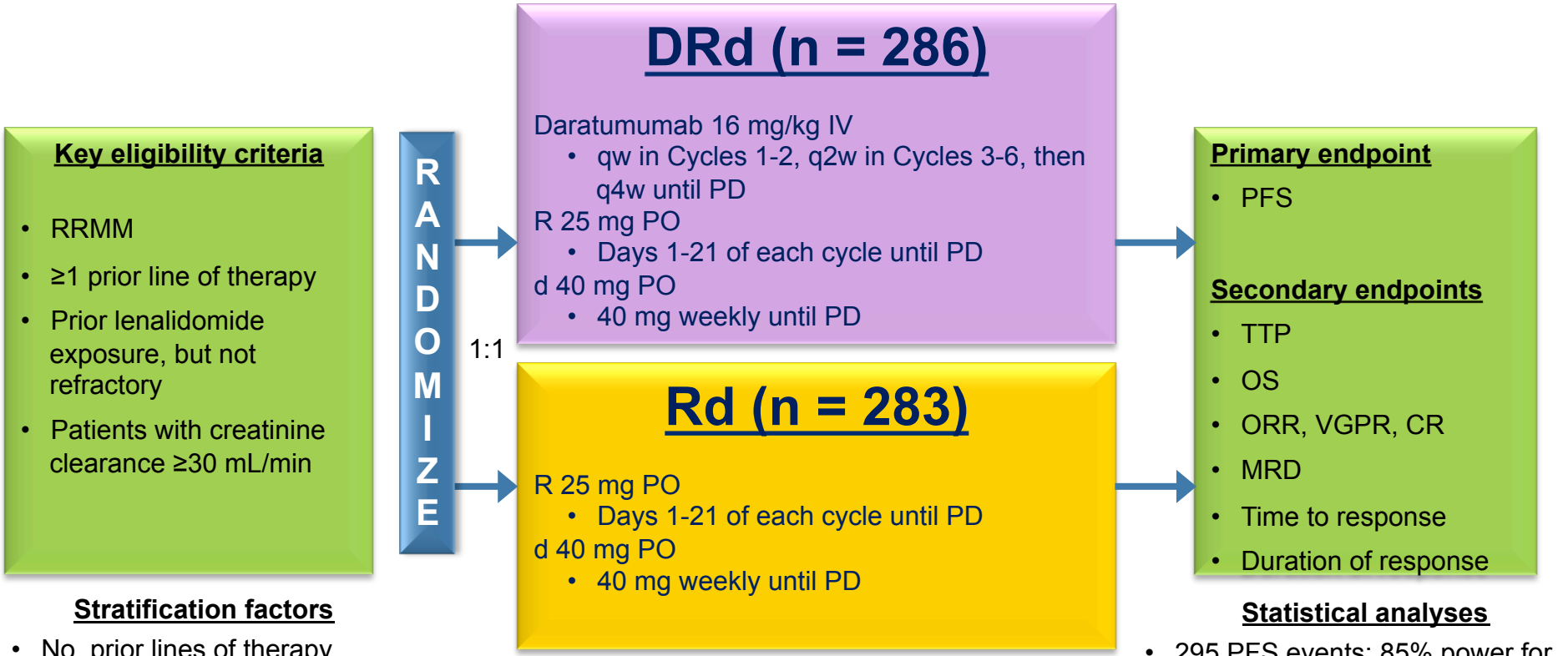
	Safety Analysis Set DVd (n = 243)	
	All grades	Grade 3
Patients with IRRs, %	**45**	**9**
Most common (>5%) IRRs		
Dyspnea	11	2
Bronchospasm	9	3
Cough	7	0

- **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

Palumbo et al. N Engl J Med 2016;375:754-66

POLLUX MMY3003 Dara-Rd vs Rd

Multicenter, randomized (1:1), open-label, active-controlled, phase 3 study



Premedication for the DRd treatment group consisted of dexamethasone 20 mg,[a] paracetamol, and an antihistamine

[a]On daratumumab dosing days, dexamethasone was administered 20 mg premedication on Day 1 and 20 mg on Day 2.
ISS, International Staging System; R, lenalidomide; IV, intravenous; qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; PO, oral; d, dexamethasone; TTP, time to progression; MRD, minimal residual disease.

Dimopoulos er al. N Engl J Med 2016;375:1319-31

Most Common AEs: POLLUX

	DRd (n = 283)		Rd (n = 281)	
Hematologic AEs	All-grade (%) ≥25%	Grade 3/4 (%) ≥5%	All-grade (%) ≥25%	Grade 3/4 (%) ≥5%
Neutropenia	**59**	**52**	**43**	**37**
Febrile neutropenia	**6**	**6**	**3**	**3**
Anemia	31	12	35	20
Thrombocytopenia	27	13	27	14
Lymphopenia	6	5	5	4
Nonhematologic AEs				
Diarrhea	**43**	**5**	25	3
Fatigue	**35**	**6**	28	3
Upper respiratory tract infection	**32**	1	21	1
Constipation	**29**	1	25	0.7
Cough	**29**	0	13	0
Muscle spasms	26	0.7	19	2
Pneumonia	14	8	13	8

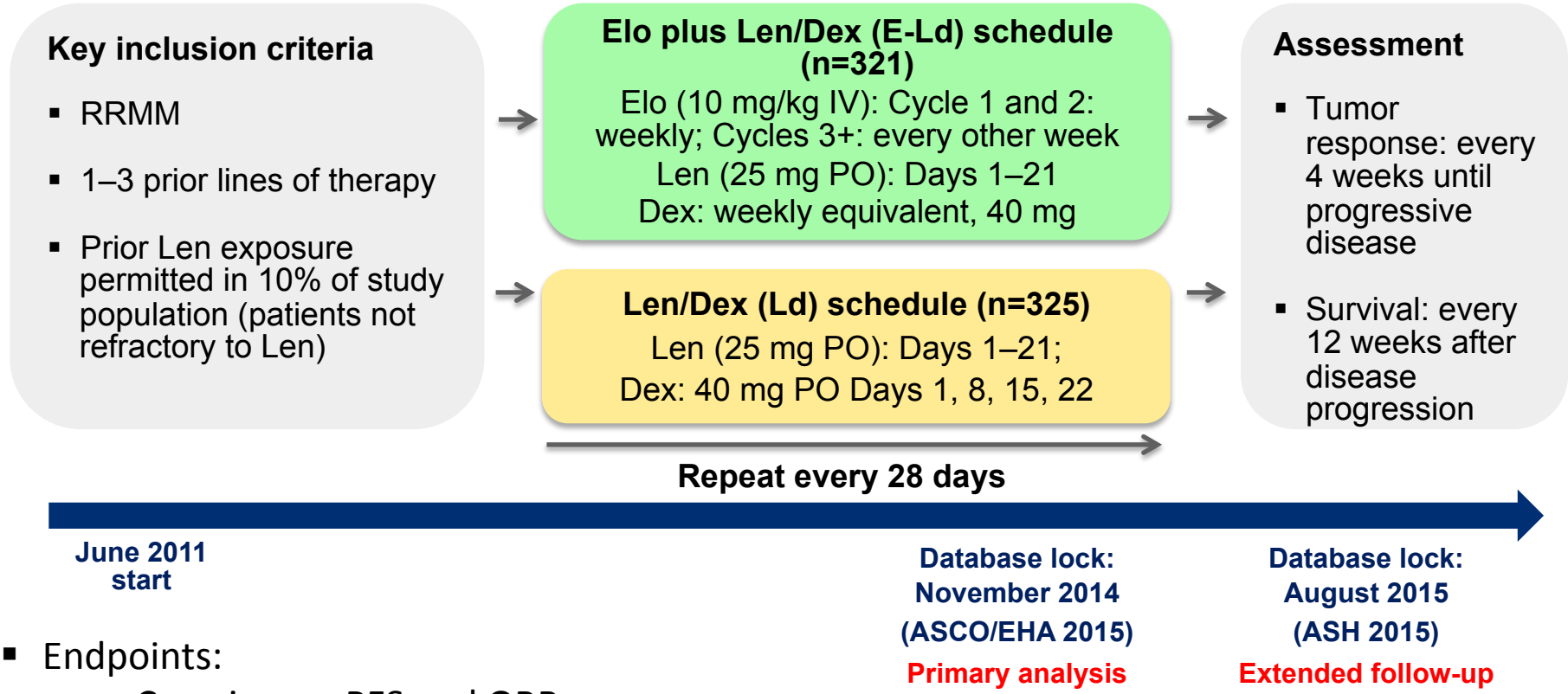
Infections and infestations:

- **Grade 3 or 4: 28%** patients in DRd vs **23%** patients in Rd
- The most common **grade 3 or 4** infections/infestations AE was **pneumonia (8% vs 8%)**

Dimopoulos et al. N Engl J Med 2016;375:1319-31

ELOQUENT-2 Study Design

- Open-label, international, randomized, multicenter, phase 3 trial (168 global sites)



- Endpoints:
  - Co-primary: PFS and ORR
  - Other: OS, DOR, quality of life, safety
- All patients received premedication to mitigate infusion reactions prior to elotuzumab administration; Elotuzumab IV infusion administered ~ 2–3 hours

Adverse Events Reported in ≥ 30% of Patients: ELOQUENT-2

Adverse event, n (%)	E-Ld (n=318)		Ld (n=317)	
	Any grade	Grade 3 to 4	Any grade	Grade 3 to 4
Common non-hematologic adverse events				
Fatigue	149 (47)	27 (9)	123 (39)	26 (8)
Pyrexia	119 (37)	8 (3)	78 (25)	9 (3)
Diarrhea	149 (47)	16 (5)	114 (36)	13 (4)
Constipation	113 (36)	4 (1)	86 (27)	1 (0.3)
Muscle spasms	95 (30)	1 (0.3)	84 (27)	3 (1)
Cough	100 (31)	1 (0.3)	57 (18)	0
Common hematologic toxicities				
Lymphopenia	316 (99)	244 (77)	311 (98)	154 (49)
Anemia	306 (96)	60 (19)	301 (95)	67 (21)
Thrombocytopenia	266 (84)	61 (19)	246 (78)	64 (20)
Neutropenia	260 (82)	107 (34)	281 (89)	138 (44)
Infections	259 (81)	89 (28)	236 (74)	77 (24)

- **The exposure-adjusted* infection rate** was 198 in the E-Ld arm and 192 in the Ld arm, respectively
- **Herpes zoster** rate was 4.1 vs 2.2 incidence per 100 patient-years for ERd vs Rd, respectively
- No other increase in the incidence of **opportunistic infection**
- Exposure-adjusted* **second primary malignancy** rate was 5 and 3 in the E-Ld and Ld arms, respectively
- There was no significant detriment to overall **HRQO**L with the addition of elotuzumab to Rd

* Incidence rate per 100 patient-years of exposure)

Dimopoulos MA et al , ASH 2015 (Abstract 28) *Oral presentation*

Safety and Efficacy of Elotuzumab With Lenalidomide/Dexamethasone for Multiple Myeloma in a Japanese Subpopulation Analysis of the Phase 3 ELOQUENT-2 Trial

Kazuteru Ohashi,[1] Kenshi Suzuki,[2] Kazutaka Sunami,[3] Shinsuke Iida,[4] Shinichiro Okamoto,[5] Hiroshi Handa,[6] Kosei Matsue,[7] Masafumi Miyoshi,[8] Eric Bleickardt,[9] Morio Matsumoto,[10] Masafumi Taniwaki[11]

Parameter	ELd (n=31)	Ld (n=29)
Infection, n (%)		
Any grade	25 (81)	23 (79)
Grade 3–4	12 (39)	5 (17)
Exposure-adjusted infections, per 100 person-years	172.6	183.4
Discontinuation due to infection, n (%)	2 (6)	0
Serious infections (any grade), n (%)	14 (45)	6 (21)
Pneumonia, n (%)	9 (29)	2 (7)
Exposure-adjusted pneumonia, per 100 person-years	16.7	4.5

The incidence of pneumonia tended to be **higher with ELd** versus Ld in the Japanese subanalysis. However, all cases were **manageable**, and none led to treatment discontinuation

Adapted from poster presented at the 58th ASH meeting December 3–6, 2016; San Diego, CA, USA

ELOQUENT-2: Infusion Reactions[1,2]

Event, n (%)[1]	ERd (n=318)		
	Grade 1/2	Grade 3	Grade 4/5
Infusion reaction	**29 (9)**	**4 (1)**	**0**
Pyrexia	10 (3)	0	0
Chills	4 (1)	0	0
Hypertension	3 (1)	1 (<1)	0

- **Infusion reactions occurred in 10% of patients (1% grade 3) [1,2]**
- **70% of infusion reactions occurred with the first dose[1,2]**
- **Elotuzumab infusion was interrupted in 15 (5%) patients due to an infusion reaction (median interruption duration 25 minutes)[1,2]**
- **2 (1%) patients discontinued the study due to an infusion reaction[1,2]**

ERd, elotuzumab, lenalidomide/dexamethasone.

1. Lonial S et al. Oral presentation at ASCO 2015. Abstract 8508. 2. Lonial S et al. *N Engl J Med*. 2015;373:621-631.

Randomized phase 2 study: elotuzumab plus bortezomib/dexamethasone vs bortezomib/dexamethasone for relapsed/refractory MM

Andrzej Jakubowiak,[1] Massimo Offidani,[2] Brigitte Pégourie,[3] Javier De La Rubia,[4] Laurent Garderet,[5] Kamel Laribi,[6] Alberto Bosi,[7] Roberto Marasca,[8] Jacob Laubach,[9] Ann Mohrbacher,[10] Angelo Michele Carella,[11] Anil K. Singhal,[12] L. Claire Tsao,[12] Mark Lynch,[13] Eric Bleickardt,[13] Ying-Ming Jou,[14] Michael Robbins,[15] and Antonio Palumbo[16]

[1]Myeloma Program, Section of Hematology/Oncology, University of Chicago Medical Center, Chicago, IL; [2]Clinica di Ematologia, Azienda Ospedaliero Universitaria Ospedali Riuniti di Ancona, Ancona, Italy; [3]Centre Hospitalier Universitaire de Grenoble–Hôpital Albert Michallon, Grenoble, France; [4]Hospital Universitario Doctor Peset and Universidad Católica "San Vicente Mártir," Valencia, Spain; [5]Service d'hématologie, Hôpital Saint Antoine, Paris, France; [6]Department of Hematology, Centre Hospitalier, Le Mans, France; [7]Department of Hematology, Azienda Ospedaliero Universitaria Careggi, Florence, Italy; [8]Department of Hematology, Azienda Ospedaliera Universitaria–Policlinico di Modena, Modena, Italy; [9]Department of Hematology/Oncology, Dana-Farber Cancer Institute, Boston, MA; [10]Division of Hematology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; [11]Hematology Unit, Istituto di Ricovero e Cura a Carattere Scientifico San Martino–Istituto Scientifico Tumori, Genoa, Italy; [12]Statistics, AbbVie Biotherapeutics Inc, Redwood City, CA; [13]Oncology Clinical Development, Bristol-Myers Squibb, Wallingford, CT; [14]Global Biometric Sciences, Bristol-Myers Squibb, Hopewell, NJ; [15]Exploratory Clinical and Translational Research–Oncology, Bristol-Myers Squibb, Princeton, NJ; and [16]Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy

Key Points

- Elotuzumab, an immunostimulatory antibody, prolongs PFS with no added clinical toxicity when combined with Bd vs Bd alone in RRMM.
- Based on results from this phase 2 study, further investigation of elotuzumab with a proteasome inhibitor in RRMM is warranted.

In this proof-of-concept, open-label, phase 2 study, patients with relapsed/refractory multiple myeloma (RRMM) received elotuzumab with bortezomib and dexamethasone (EBd) or bortezomib and dexamethasone (Bd) until disease progression/unacceptable toxicity. Primary endpoint was progression-free survival (PFS); secondary/exploratory endpoints included overall response rate (ORR) and overall survival (OS). Two-sided 0.30 significance level was specified (80% power, 103 events) to detect hazard ratio (HR) of 0.69. Efficacy and safety analyses were performed on all randomized patients and all treated patients, respectively. Of 152 randomized patients (77 EBd, 75 Bd), 150 were treated (75 EBd, 75 Bd). PFS was greater with EBd vs Bd (HR, 0.72; 70% confidence interval [CI], 0.59-0.88; stratified log-rank $P = .09$); median PFS was longer with EBd (9.7 months) vs Bd (6.9 months). In an updated analysis, EBd-treated patients homozygous for the high-affinity FcγRIIIa allele had median PFS of 22.3 months vs 9.8 months in EBd-treated patients homozygous for the low-affinity allele. ORR was 66% (EBd) vs 63% (Bd). Very good partial response or better occurred in 36% of patients (EBd) vs 27% (Bd). Early OS results, based on 40 deaths, revealed an HR of 0.61 (70% CI, 0.43-0.85). To date, 60 deaths have occurred (28 EBd, 32 Bd). No additional clinically significant adverse events occurred with EBd vs Bd. Grade 1/2 infusion reaction rate was low (5% EBd) and mitigated with premedication. In patients with RRMM, elotuzumab, an immunostimulatory antibody, appears to provide clinical benefit without added clinically significant toxicity when combined with Bd vs Bd alone. Registered to ClinicalTrials.gov as NCT01478048.
(*Blood.* 2016;127(23):2833-2840)

Table 3. Adverse events in at least 25% of patients

	EBd (n = 75)		Bd (n = 75)	
Events*	Any grade†	Grade 3-4	Any grade†	Grade 3-4
All AEs	75 (100)	53 (71)	72 (96)	45 (60)
Infections	50 (67)	16 (21)	40 (53)	10 (13)
Diarrhea	33 (44)	6 (8)	25 (33)	3 (4)
Constipation	30 (40)	1 (1)	22 (29)	0
Cough	33 (44)	1 (1)	18 (24)	0
Anemia	28 (37)	5 (7)	22 (29)	5 (7)
Peripheral neuropathy	27 (36)	7 (9)	27 (36)	9 (12)
Pyrexia	28 (37)	0	21 (28)	3 (4)
Peripheral edema	22 (29)	3 (4)	18 (24)	0
Insomnia	22 (29)	1 (1)	14 (19)	1 (1)
Asthenia	21 (28)	3 (4)	22 (29)	2 (3)
Fatigue	22 (29)	3 (4)	19 (25)	1 (1)
Paresthesia	20 (27)	0	14 (19)	4 (5)
Nausea	20 (27)	1 (1)	16 (21)	1 (1)
Thrombocytopenia	12 (16)	7 (9)	20 (27)	13 (17)

Data are n (%) of patients. Data cutoff: August 10, 2015.

*AEs were categorized using the Medical Dictionary for Regulatory Activities and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3).[12]

†Grade 5 AEs occurred in 4 patients in the EBd group and 6 patients in the Bd group.

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Infusion-related reactions (IRRs)

- **Possible signs and symptoms of acute infusion reactions[2]**
  - Allergic reactions/hypersensitivity
  - Skin reactions
  - Systemic reactions
  - Respiratory reactions
  - Cardiovascular symptoms

- **Most common IRRs with Dara:**
  - Nasal congestion, throat irritation, laryngeal edema, cough, dyspnea, chills, vomiting[2-3]
  - Look out for upper respiratory tract reactions as early signs

1. Chung CH. The Oncologist 2008;13: 725–732
2. Lenz HJ. The Oncologist 2007;12:601–609

MMY2002: Onset of IRRs and Duration of Infusions for Each Treatment Cycle

	16 mg/kg		
	1st Infusion n = 106	2nd Infusion n = 104	Subsequent Infusions n = 103
Total number of patients with IRRs*	40 **(37.7%)**	3 **(2.9%)**	8 **(7.8%)**
Total number of IRRs†	**80**	**4**	**8**
Time to onset of IRRs, min			
Number of IRRs	76	3	2
Median	90.0	93.0	53.5
Range	1-470	93-363	38-69
Duration of infusion, h			
Number of infusions	106	103	1,105
Median	**7.0**	**4.2**	**3.4**
Range	1.5-14.3	2.7-8.5	1.1-6.7

* There were 45 and 8 patients with IRRs in the 16-mg/kg and 8-mg/kg groups, respectively; it was possible for patients to have IRRs during >1 infusion.
† Some patients had >1 IRR during an infusion.

- Most IRRs occurred **during the first infusion**
- Median **duration of infusion decreased with each cycle**

Voorhees P, et al. Poster presented at: 2015 ASH Meeting on Hematologic Malignancies; September 17-19, 2015; Chicago, IL, USA.

MMY2002: Treatment Modifications Due to DARA related IRRs

Action taken during infusion, n (%)*	16 mg/kg n = 106
Infusion interrupted	28 (26.4)
Infusion rate decreased	10 (9.4)
Infusion aborted	2 (1.9)

*Percentages were calculated with the number of patients in each group as the denominator.

- **Treatment modifications were implemented in most patients** experiencing IRRs
- **Three patients were unable to finish an infusion** due to an IRR but received subsequent DARA infusions
- **All remaining patients** who experienced an IRR continued the infusion and **received the full-dose of DARA** with supportive treatment
- **No IRRs led to treatment discontinuation**

Voorhees P, et al. Poster presented at: 2015 ASH Meeting on Hematologic Malignancies; September 17-19, 2015; Chicago, IL, USA.

Table 2. Comparison of AE Rates Between Predicted DARA Exposure Quartiles From the Combined Analysis

AE	Exposure quartiles,[a] % (95% CI)			
	1st	2nd	3rd	4th
IRRs	63 (50-75)	56 (43-69)	51 (38-64)	47 (35-60)
Grade ≥3	9 (3-18)	4 (1-10)	2 (<1-8)	4 (1-11)
Thrombocytopenia	18 (11-31)	23 (13-35)	18 (9-29)	14 (7-25)
Grade ≥3	16 (8-27)	14 (7-25)	12 (6-22)	11 (4-20)
Neutropenia	7 (2-16)	16 (8-27)	19 (11-31)	12 (6-22)
Grade ≥3	7 (2-16)	9 (3-18)	11 (4-20)	4 (1-10)
Anaemia	25 (15-37)	37 (25-50)	16 (8-27)	16 (8-27)
Grade ≥3	16 (8-27)	25 (15-37)	7 (2-16)	9 (3-18)
Lymphopenia	9 (3-18)	–	4 (1-10)	4 (1-10)
Grade ≥3	5 (1-13)	–	4 (1-10)	4 (1-11)
Infections	40 (28-53)	54 (42-67)	56 (43-69)	61 (49-73)
Grade ≥3	5 (1-13)	12 (6-22)	12 (6-22)	5 (1-13)

AE, adverse event; DARA, daratumumab; CI, confidence interval; IRR, infusion-related reaction; $C_{max,1st}$, maximal concentration after the first infusion; $C_{post\text{-}infusion,max}$, maximal end-of-infusion concentration.

[a]End-of-infusion concentration after $C_{max,1st}$ was used as the exposure measure for analyses on IRRs, while $C_{post\text{-}infusion,max}$ was used as the exposure measure for analyses on other AEs.

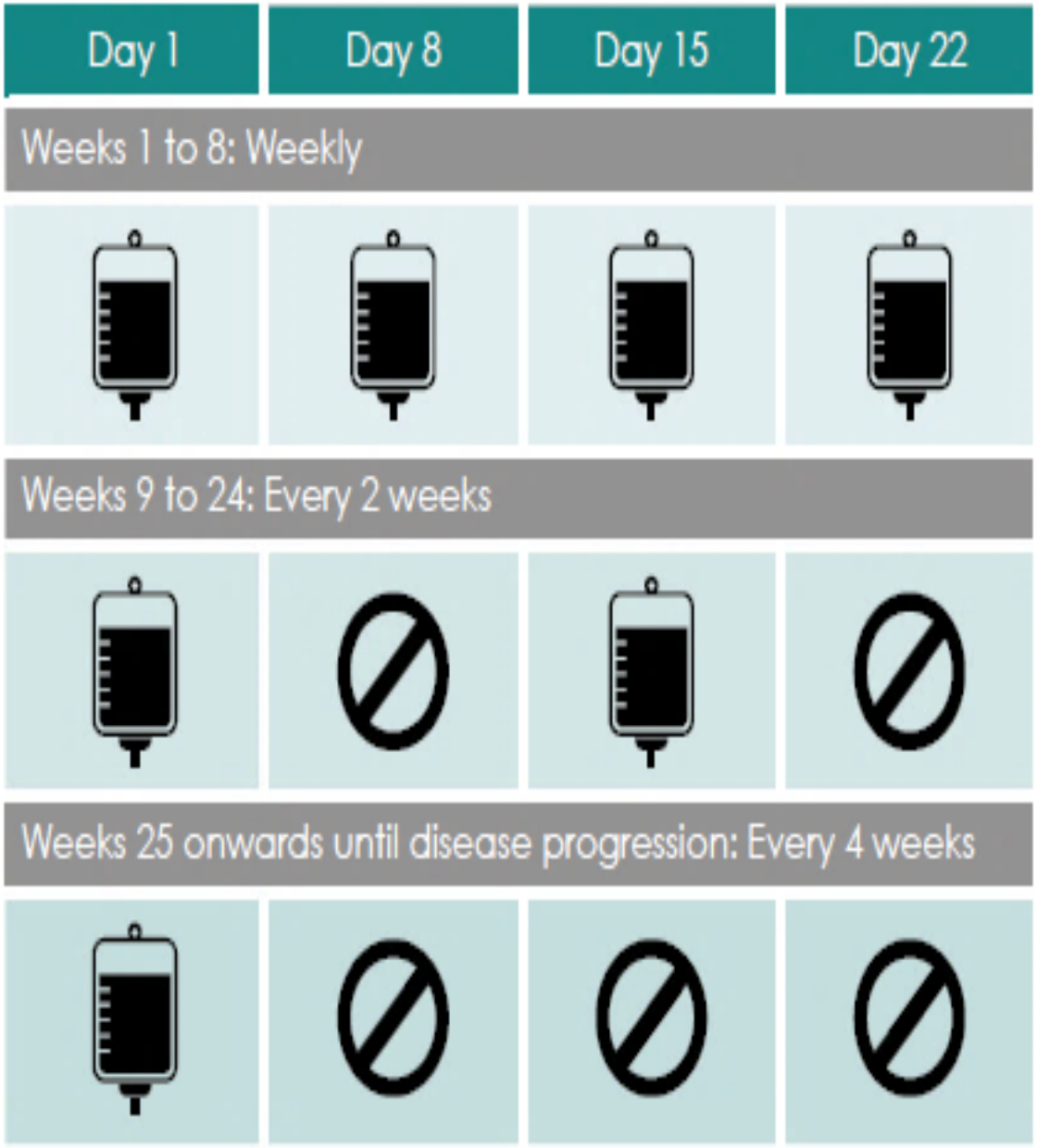
The quartiles for $C_{max,1st}$ are: Quartile 1 (≤134 µg/mL), Quartile 2 (>134-245 µg/mL), Quartile 3 (>245-310 µg/mL), and Quartile 4 (>310-470 µg/mL).

The quartiles for $C_{post\text{-}infusion,max}$ are: Quartile 1 (≤270 µg/mL), Quartile 2 (>270-511 µg/mL), Quartile 3 (>511-907 µg/mL), and Quartile 4 (>907-1,840 µg/mL).

- **No apparent relationship was identified between drug exposure and adverse events** of interest: infusion-related reaction (IRR), thrombocytopenia, anemia, neutropenia, lymphopenia
- Overall event rate of **infection appeared to numerically increase with drug exposure**, however this **trend was not observed for infections Grade 3 or higher.**

Xu et al Poster BP057 IMW 2015 Rome

Daratumumab schedule

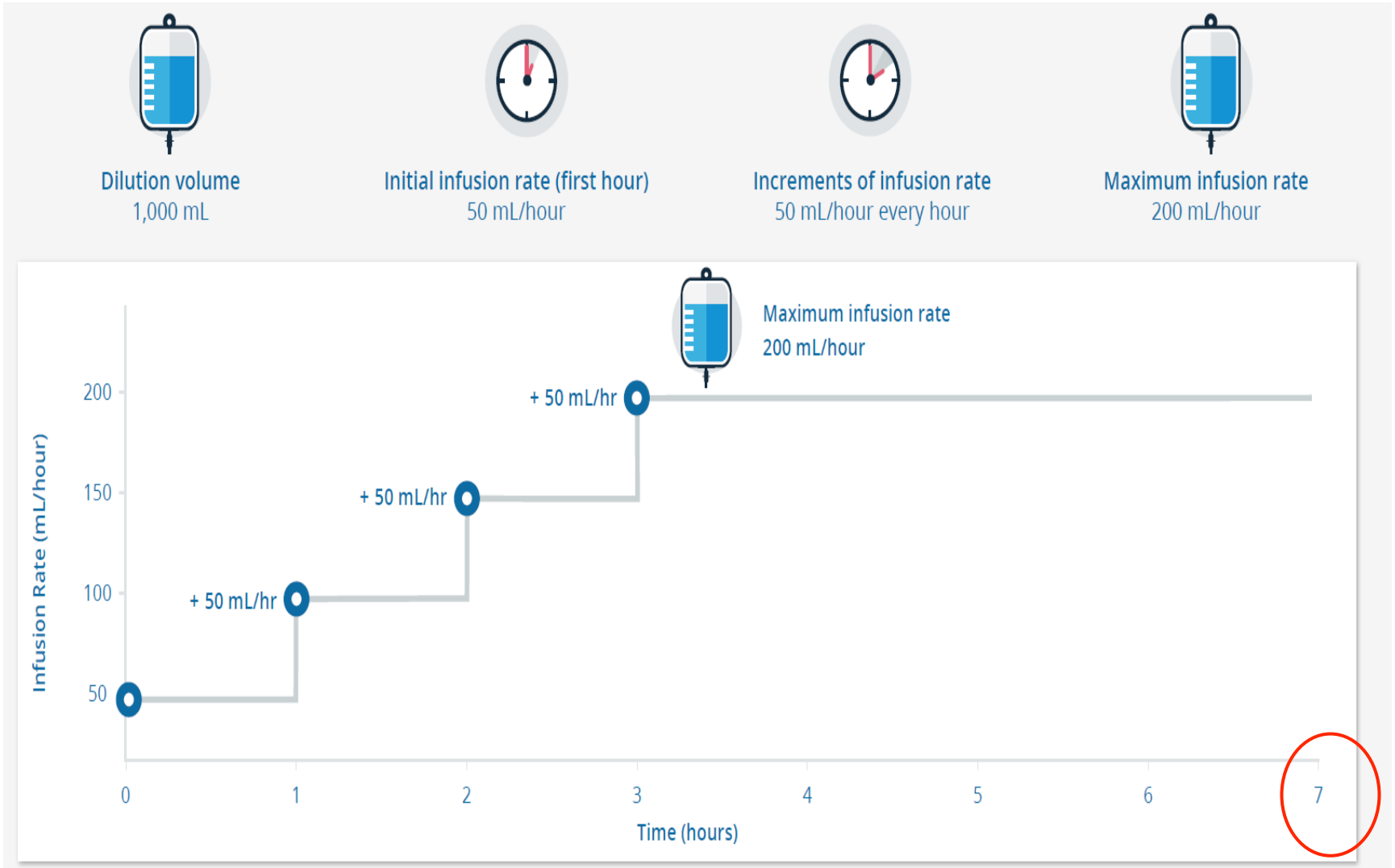


Infusion flow control
Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator

Pre-medications
1 hour prior to every daratumumab infusion

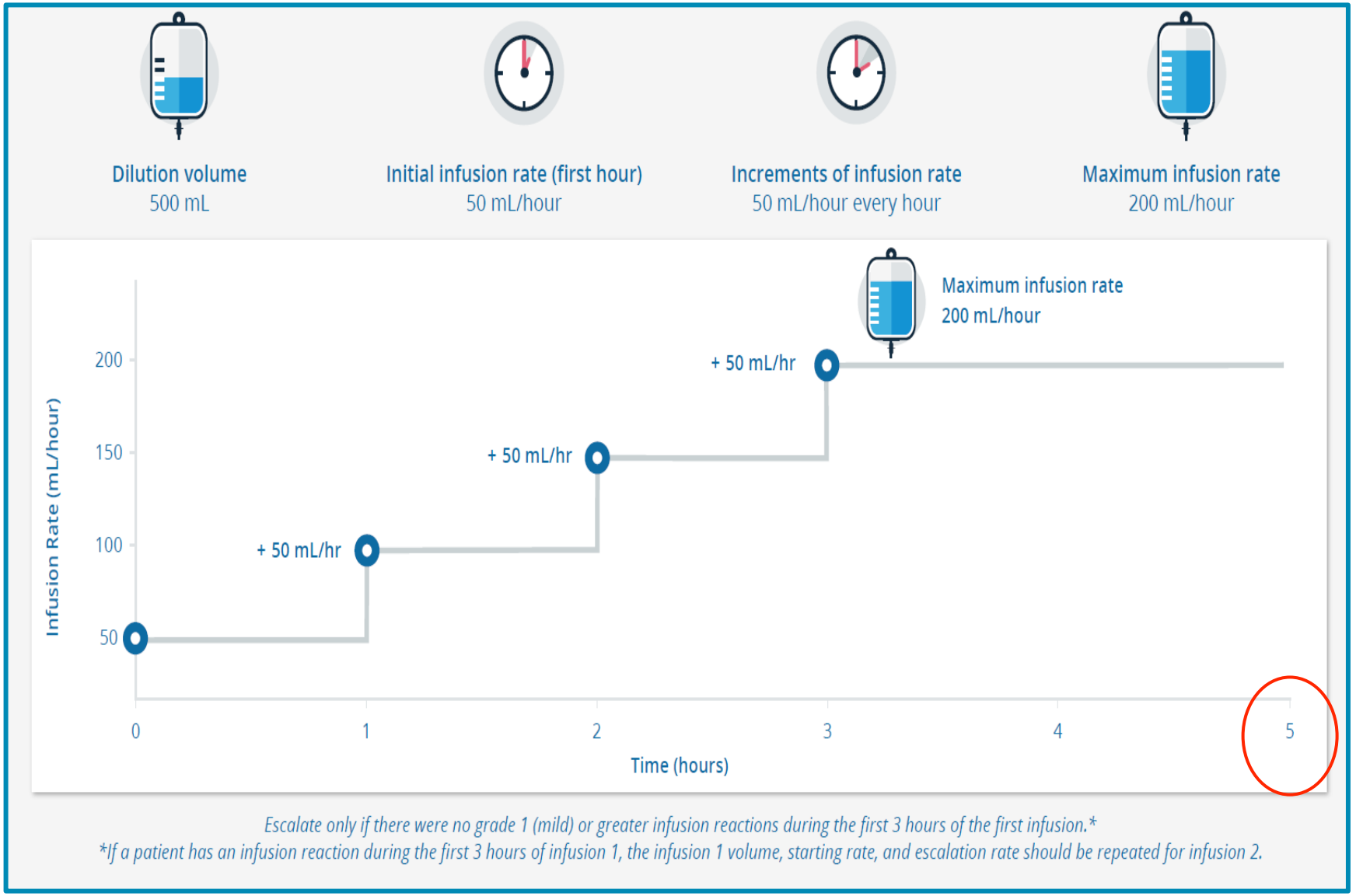
Post-medications
On each of the two days following all infusions (beginning the day after the infusion)

First infusion



**If a patient has an infusion reaction during the first 3 hours of infusion 1, the infusion 1 volume, starting rate, and escalation rate should be repeated for infusion[2].*

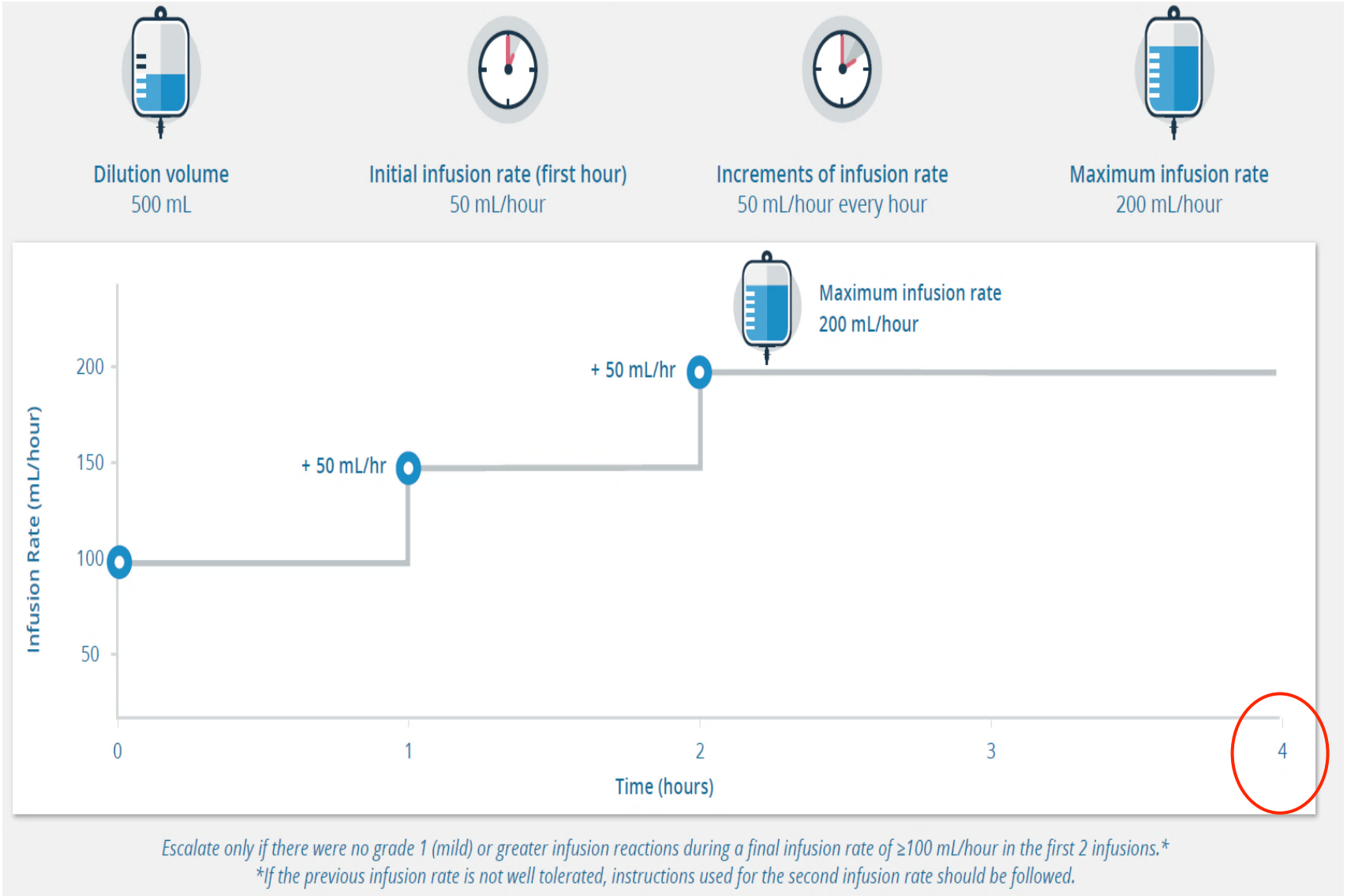
Second infusion



*Escalate only if there were no grade 1 (mild) or greater infusion reactions during the first 3 hours of the first infusion.**

**If a patient has an infusion reaction during the first 3 hours of infusion 1, the infusion 1 volume, starting rate, and escalation rate should be repeated for infusion 2.*

Subsequent infusions



*Escalate only if there were no grade 1 (mild) or greater infusion reactions during a final infusion rate of ≥100 mL/hour in the first 2 infusions.**
**If the previous infusion rate is not well tolerated, instructions used for the second infusion rate should be followed.*

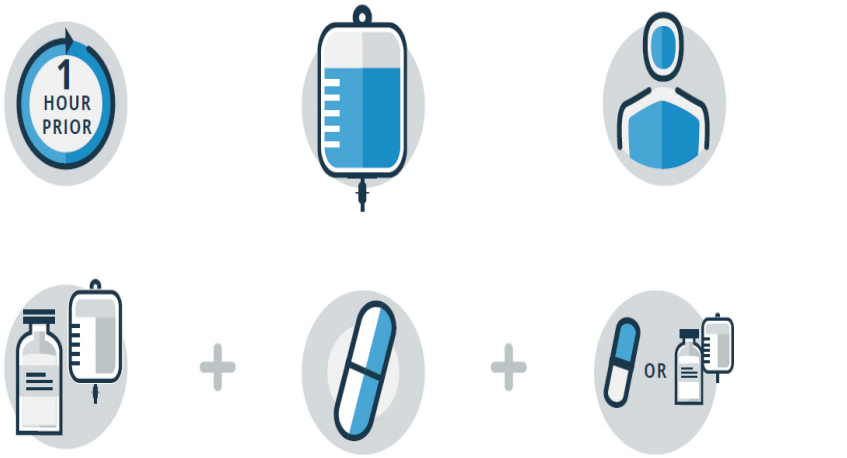
I pazienti devono ricevere una adeguata pre-medicazione per ridurre il rischio di IRRs

Medicazione pre-infusione

Durante i giorni di infusione di datatumumab, i pazienti riceveranno la seguente pre-medicazione prima dell'infusione:

- Acetaminofene (paracetamolo) 650-1000 mg orale (PO) circa 1 ora prima dell'infusione
- Un antistaminico (difenidramina 25-50 mg IV o PO,o equivalente)
- Metilprednisolone 100 mg IV per la prima e seconda infusione di daratumumab; a partire dalla terza infusione il metilprednisolone può essere ridotto a 60 mg IV

Approssimativamente 1 ora prima di ogni infusione di Daratumumab la pre-medicazione dovrebbe essere somministrata a tutti i pazienti



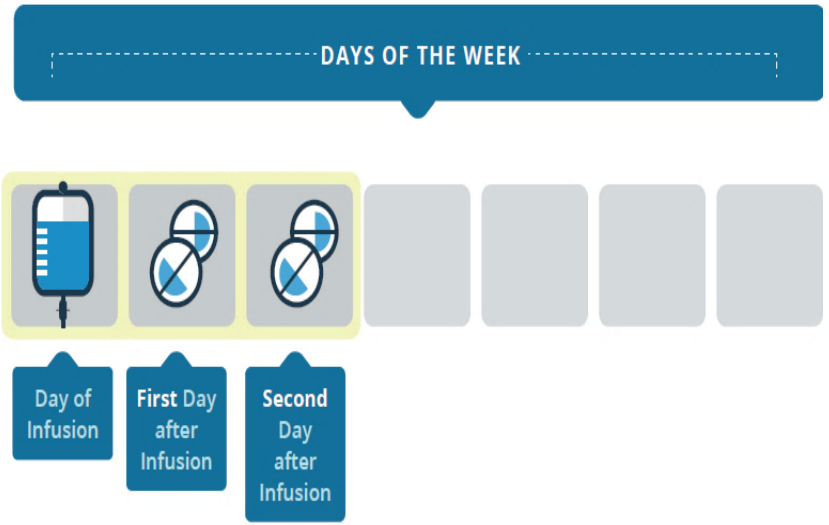
Corticosteroide per via intravenosa + **Antipiretico orale** + **Antistaminico orale o per via intravenosa**

EMEA SmPc: Daratumumab US Prescribing Information, last accessed April 2016.

I pazienti devono ricevere anche una adeguata medicazione post trattamento per ridurre il rischio di IRRs

Medicazione post-infusione

- Durante ciascuno dei due giorni seguenti tutte le infusioni di Daratumumab (iniziando il giorno dopo l'infusione) i pazienti riceveranno Metilprednisolone 20 mg PO
- In pazienti con una storia di malattia polmonare ostruttiva dovrebbero essere considerate medicazioni aggiuntive post-infusione comprendenti broncodilatatori e corticosteroidi inalatori.
- Dopo le prime quattro infusioni, se il paziente non ha IRR serie, questi farmaci inalatori post-infusione possono essere interrotti a discrezione del medico.
- Iniziare la profilassi antivirale per prevenire la riattivazione di herpes zoster entro 1 settimana dall'inizio del daratumumab e proseguire per 3 mesi dopo il trattamento



US PI: Daratumumab US Prescribing Information, last accessed April 2016.

Montelukast as Prevention of IRRs

- Use of Montelukast (an Inhibitor of Leucotriene Receptors) to Reduce Infusion Reactions in an Early Access Program (EAP) of Daratumumab in United States Patients With Relapsed or Refractory Multiple Myeloma:
- 10 mg of montelukast >30 min prior to the first daratumumab infusion

Table 5. Observed IRRs in Patients With and Without Montelukast Therapy

	Montelukast 10 mg as Pre-Infusion (n=50)	No Montelukast Given as Pre-Infusion (n=298)
IRR rate at first infusion	38.0%	58.5%
Respiratory symptoms	20%	32%
Gastrointestinal symptoms	4%	11%
Chills	14%	14%
Median time for first infusion (hours)	6.7	7.6

- A total of 24 subjects experienced infusion related reactions that were considered SAEs but no subject discontinued the study due to an infusion related reaction

- The observed IRR rate during the first daratumumab infusion **was one-third lower** in patients who received montelukast than in patients who did not receive it
- **Respiratory and gastrointestinal symptoms were lower** in patients who received montelukast, whereas chills were observed at a similar rate in both groups
- The **median time for the first infusion was 0.9 hours shorter** in patients who received montelukast

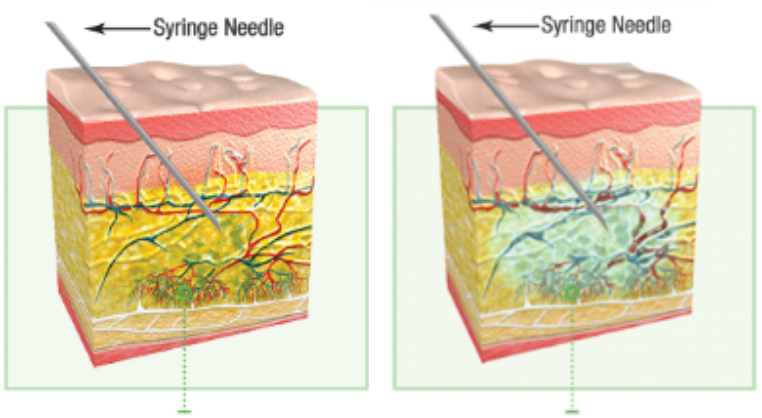
Adapted from: Chari et al, Abs n.2142 ASH 2016

Recombinant Human Hyaluronidase

- The ENHANZE™ platform of recombinant human hyaluronidase (rHuPH20) temporarily breaks down the hyaluronan barrier, allowing rapid absorption of injected drugs[1]

- Herceptin SC® and MabThera SC® are approved in Europe as co-formulate products with rHuPH20[2,3]
  - Dosing time is 5 to 8 minutes with subcutaneous (SC) administration versus 0.5 to 6 hours with IV[4-6]

Schematic of rHuPH20[1]



Aim: To determine the safety, pharmacokinetics, and efficacy of DARA as SC administration

1. Halozyme Therapeutics. Mechanism of action for Hylenex recombinant (hyaluronidase human injection). www.hylenex.com/mechanism-of-action. Accessed November 8, 2016.
2. European Medicines Agency. Herceptin: EPAR – product information. 2016.
3. European Medicines Agency. MabThera: EPAR – product information. 2016.
4. Ismael G, et al. *Lancet Oncology*. 2012;13(9):869-878.
5. Shpilberg O, et al. *Br J Cancer*. 2013;109(6):1556-1561.
6. De Cock E, et al. *PLoS One*. 2016;11(6):e0157957.

Open-label, Multicenter, Dose-escalation Phase 1b Study to Assess the Subcutaneous Delivery of Daratumumab in Patients (Pts) With Relapsed or Refractory Multiple Myeloma (PAVO)

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

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

→

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

Primary endpoints

- C_{trough} of DARA at Cycle 3/Day 1
- Safety

Secondary endpoints

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

Dosing schedule

- Approved schedule for IV
  - 1 Cycle = 28 days

Infusion time

- 1,200 mg: 20-min infusion (60 mL)
- 1,800 mg: 30-min infusion (90 mL)

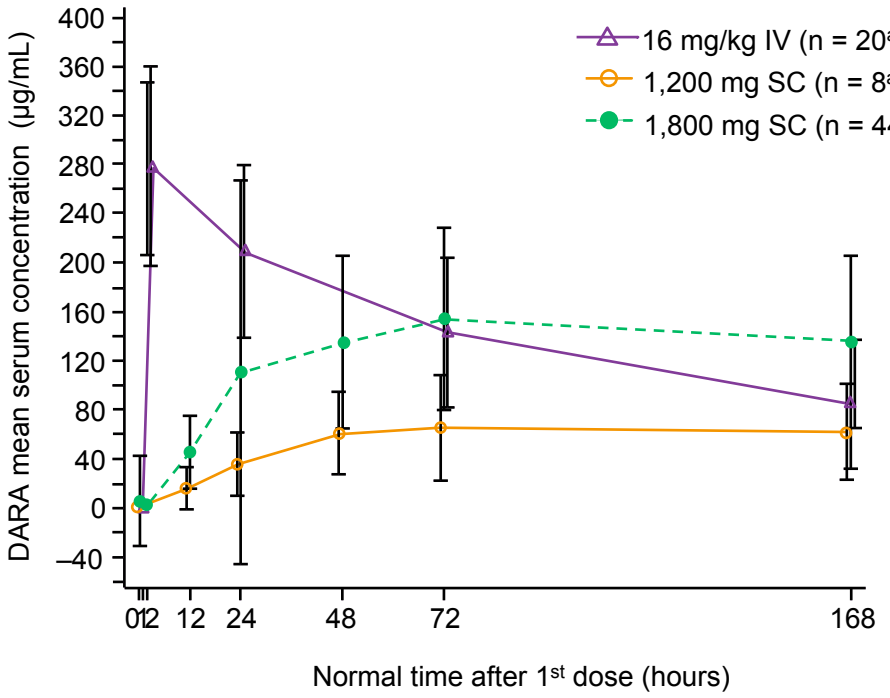
Pre-[b]/post-infusion medication
Acetaminophen, diphenhydramine, montelukast, and methylprednisolone

RRMM, relapsed or refractory multiple myeloma; C_{trough}, trough concentration; ORR, overall response rate; CR, complete response; PK, pharmacokinetic.
[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 hour prior to infusion.

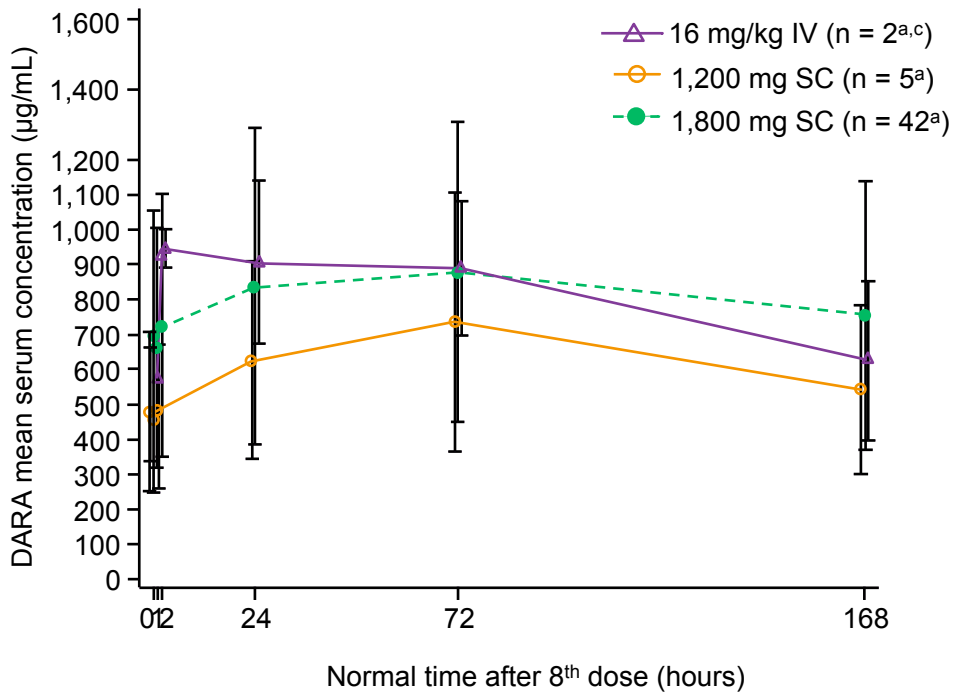
Usmani,et al. ASH Meeting 2016, abs. 1149

Dose Mean (SD) Profiles

1st dose mean



8th dose mean



PK for the 1,800-mg SC dose is consistent with the 16-mg/kg IV dose, with comparable C_{trough} and variability

SD, standard deviation.
[a]Number of patients with full PK profile at pre-dose.
[b]From study GEN501 Part 2.
[c]From study GEN501 Part 1.

Grade 3/4 TEAEs: PAVO (Dara s.c.)

Grade 3/4 TEAEs (>1 patient), % (n)	1,200 mg n = 8	1,800 mg n = 45
Hematologic		
Anemia	**13** (1)	**13** (6)
Thrombocytopenia	**13** (1)	**7** (3)
Neutropenia	**13** (1)	**7** (3)
Lymphopenia	**0** (0)	**7** (3)
Nonhematologic		
Hypertension	**25** (2)	**4** (2)
Fatigue	**25** (2)	**2** (1)
Device-related infection	**0** (0)	**4** (2)
Hyponatremia	**0** (0)	**4** (2)

AE profile of DARA-PH20 was consistent with IV DARA

IRRs: PAVO (Dara s.c.)

	1,200 mg n = 8	1,800 mg n = 45
IRR, % (n)	**13** (1)	**24 (11)**
Chills	**13** (1)	**9** (4)
Pyrexia	**0** (0)	**9** (4)
Pruritus	**0** (0)	**4** (2)
Dyspnea	**13** (1)	**0** (0)
Flushing	**0** (0)	**2** (1)
Hypertension	**0** (0)	**2** (1)
Hypotension	**0** (0)	**2** (1)
Nausea	**0** (0)	**2** (1)
Non-cardiac chest pain	**13** (1)	**0** (0)
Oropharyngeal pain	**0** (0)	**2** (1)
Paresthesia	**0** (0)	**2** (1)
Rash	**0** (0)	**2** (1)
Sinus headache	**0** (0)	**2** (1)
Tongue edema	**0** (0)	**2** (1)
Vomiting	**0** (0)	**2** (1)
Wheezing	**0** (0)	**2** (1)

- All IRRs in the 1,800-mg group were grade 1 or 2
- One grade 3 IRR of dyspnea in the 1,200-mg group
- No grade 4 IRRs were observed
- All IRRs occurred during or within 4 hours of the first infusion
- No IRRs occurred during subsequent infusions in either group
- Abdominal wall SC injections were well tolerated

Low IRR incidence and severity with DARA SC

Am J Hematol. 2017 Feb 18. doi: 10.1002/ajh.24687. [Epub ahead of print]

A phase 2 safety study of accelerated elotuzumab infusion, over less than 1 hour, in combination with lenalidomide and dexamethasone, in patients with multiple myeloma.

Berenson J1, Manges R, Badarinath S, Cartmell A, McIntyre K, Lyons R, Harb W, Mohamed H, Nourbakhsh A, Rifkin R.

Elotuzumab, an immunostimulatory SLAMF7-targeting monoclonal antibody, induces myeloma cell death with minimal effects on normal tissue. **In a previous phase 3 study in patients with relapsed/refractory multiple myeloma (RRMM), elotuzumab (10 mg/kg, ~3-hour infusion),** combined with lenalidomide and dexamethasone, demonstrated durable efficacy and acceptable safety; 10% (33/321) of patients had infusion reactions (IRs; Grade 1/2: 29; Grade 3: 4). This phase 2 study NCT02159365) investigated an accelerated infusion schedule in 70 patients with newly diagnosed multiple myeloma or RRMM. The primary endpoint was cumulative incidence of Grade 3/4 IRs by completion of treatment Cycle 2. Dosing comprised elotuzumab 10 mg/kg intravenously (weekly, Cycles 1-2; biweekly, Cycles 3+), lenalidomide 25 mg (daily, Days 1-21) and dexamethasone (28 mg orally and 8 mg intravenously, weekly, Cycles 1-2; 40 mg orally, weekly, Cycles 3+), in 28-day cycles. Premedication with diphenhydramine, acetaminophen, and ranitidine (or their equivalents) was given as in previous studies**. If no IRs occurred, infusion rate was increased in Cycle 1 from 0.5 to 2 mL/min during dose 1 (~2 hours 50 min duration) to 5 mL/min for the entire infusion by dose 3 and also during all subsequent infusions (~1-hour duration).** Median number of treatment cycles was six. No Grade 3/4 IRs occurred; only one Grade 1 and one Grade 2 IR occurred, both during the first infusion. These data support the safety of a faster infusion of elotuzumab administered over ~1 hour by the third dose, providing a more convenient alternative dosing option for patients.

MMY2002: Recommendations for the Management of Grade 1 or 2 IRRs

IRR	Action
Grade 1 or 2	• IV saline, antihistamine, oxygen, corticosteroids, and/or bronchodilators can be used per investigator discretion • The infusion should be paused. When patient's condition is stable, infusion may be restarted at the investigator's discretion • Upon restart, the infusion rate should be half of that employed before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion
Grade 2 or higher event of laryngeal edema	• Patient must be withdrawn from treatment
Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from onset	• Patient must be withdrawn from treatment

IRR, infusion-related reaction; IV, intravenous.

Voorhees P, et al. Poster presented at: 2015 ASH Meeting on Hematologic Malignancies; September 17-19, 2015; Chicago, IL, USA.

MMY2002: Recommendations for the Management of Grade ≥3 IRRs

IRR	Action
Grade 3 or higher	• Infusion must be stopped and the patient must be observed carefully until resolution of the IRR
If the intensity of the IRR remains at grade 3 or 4 after 2 hours	• Patient must be withdrawn from treatment
If the intensity of the IRR decreases to grade 1 or 2 within 2 hours	• Infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that employed before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion
If the intensity of the IRR returns to grade 3 or 4 after restart of the infusion	• The procedure described above may be repeated at the investigator's discretion
If the intensity of the IRR increases to grade 3 or 4 for a third time	• Patient must be withdrawn from treatment

Voorhees P, et al. Poster presented at: 2015 ASH Meeting on Hematologic Malignancies; September 17-19, 2015; Chicago, IL, USA.

My Agenda

- Adverse events of MoAbs in major clinical studies (single agent/combinations approved or close to be approved)
- Management of infusion-related reactions (IRRs)
- Interference with response assessment (all MoAbs)
- Interference with blood typing (anti-CD38)

Overview

- **MoAbs** currently employed for the treatment of MM comigrate with other serum proteins; therefore, they **are also detected by SPEP/IFE tests, thus interfering with response evaluation** and making it challenging to differentiate therapeutic antibody and the endogenous patient's clonal immunoglobulin

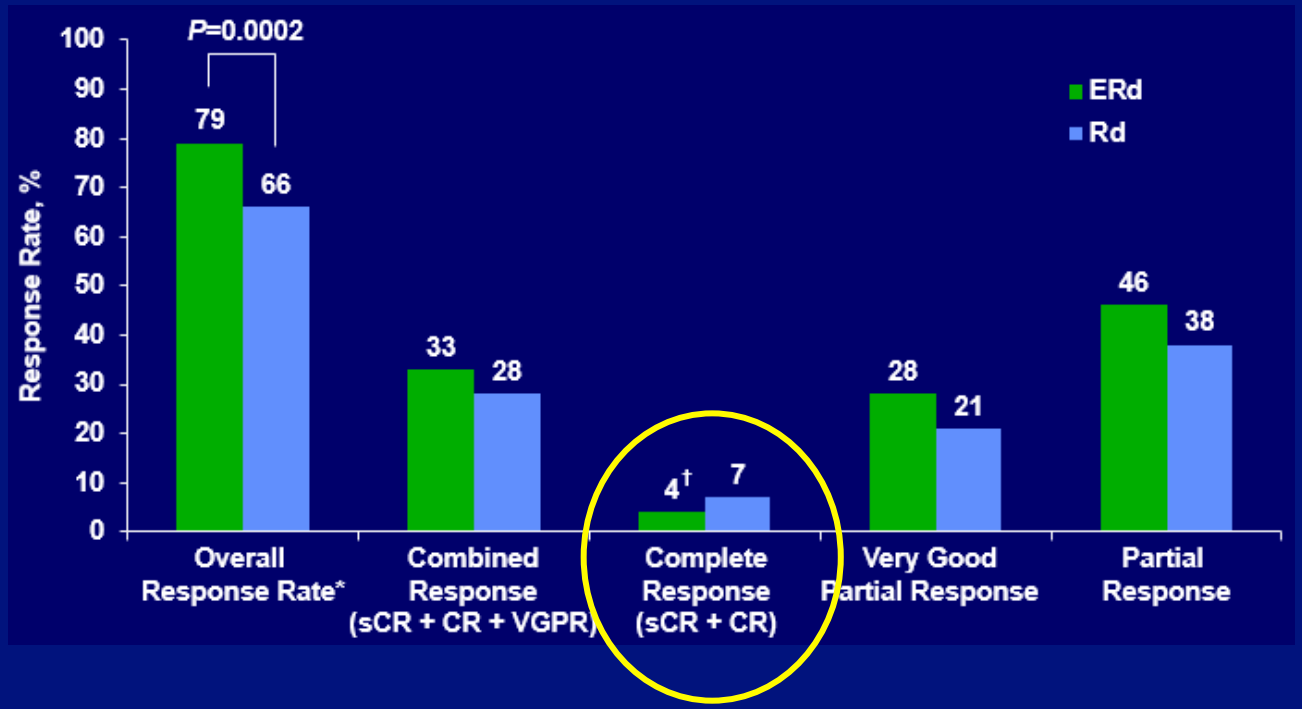
- Particularly, this interference increases the possibility of **false-positive SPEP and IFE** results in patients receiving therapeutic MoAbs and could result: a) in the **underestimation of CR,** and b) **a possible misdiagnosis of relapse** in patients that initially achieved a CR

- This is a **class effect of MoAbs** in myeloma and interference depends on isotype of the patient: Daratumumab, Elotuzumab, Isatuximab (SAR650984) and MOR202, and other molecules not employed in MM (Adalimumab, Bevacizumab, Cetuximab, Infliximab, Ofatumumab, Rituximab, Siltuximab, and Trastuzumab) are all IgG MoAbs

CR, complete response; IFE, immunofixation electrophoresis; mAb, monoclonal antibody; MM, multiple myeloma; SPEP, serum protein electrophoresis.

Dimopoulos M et al. Poster presentation at IMW 2015. Abstract PO-330. McCudden CR et al. *Clin Chem.* 2010;56:1897–1899. Genzen JR et al. *Br J Haematol.* 2011;155:123–125. McCudden CR et al. Poster présentation at ASCO 2015. Abstract 8590.

Elotuzumab: ELOQUENT-2 (Erd vs RD in patients with RRMM (1-3 prior therapies)



- Higher ORR favoring elotuzumab arm: 79% vs 66% (*P*<0.001)
- Deeper combined response (sCR + CR + VGPR) favoring elotuzumab: 33% vs 28%
- **CR rate appears to be superior in the control arm (4% for elotuzumab vs 7% for Rd)**

*Overall response rate was defined as partial response or better, per European Group for Blood and Marrow Transplantation criteria .
†Complete response rates in the elotuzumab group may be underestimated because of interference from the presence of therapeutic antibody in results on immunofixation and serum protein electrophoresis assays.
CR, complete response; ERd, elotuzumab, lenalidomide/dexamethasone; ORR, overall response rate; PFS, progression-free survival; Rd, lenalidomide/dexamethasone; sCR, stringent complete response; VGPR, very good partial response.
1. Lonial S et al. *N Engl J Med*. 2015;373:621-631.

Elotuzumab-Specific SIFE

- One of the anti-Ig antibodies (anti-IgM or anti-IgA) used to precipitate the Igs was replaced by an anti-elotuzumab antibody (2 mg/mL) with anti-reactivity to an elotuzumab epitope
- If elotuzumab is present in patient sera, the anti-idiotypic antibody-elotuzumab complex precipitates and a band is detected
- Typically, myeloma protein does not run in the early gamma position, thus it is less likely for MM M-protein to overlap with the elotuzumab band

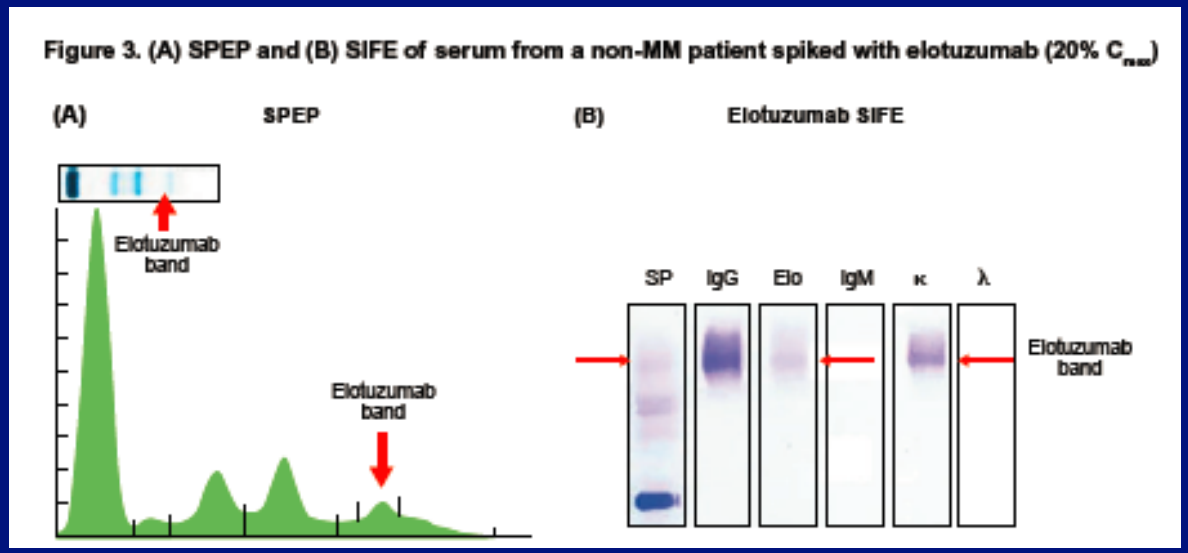


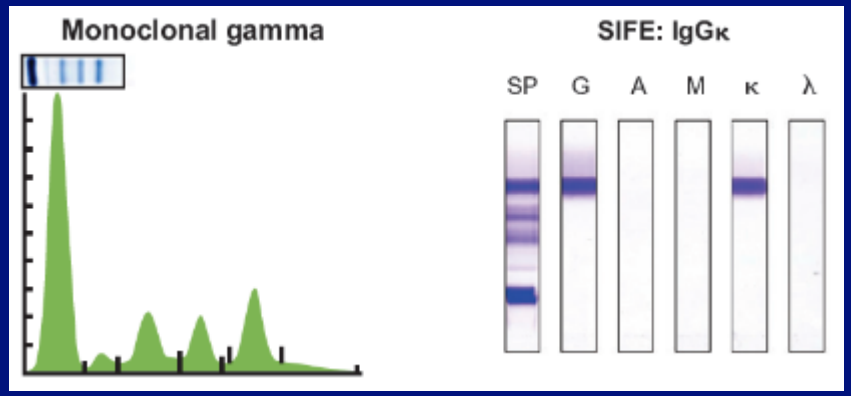
Image from Dimopoulos M et al. 2015.[1]

Ig, immunoglobulin; MM, multiple myeloma; SIFE, serum immunofixation; SPEP, serum protein eletrophoresis.

1. Dimopoulos M et al. Poster presentation at IMW 2015. Abstract PO-330.

ELOQUENT-2: Detection of Elotuzumab (IgGκ) in a Patient With IgGκ M-protein by SPEP and SIFE

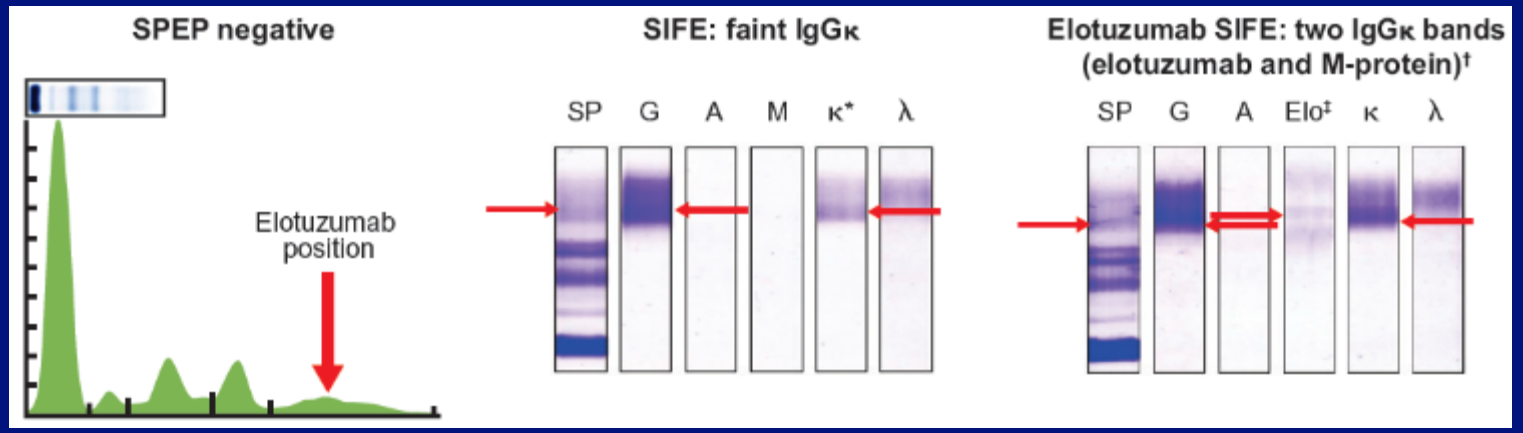
- **Baseline**



IRC response assessment: **PR**

- **Cycle 34 (2.6 years of treatment)**

Images from Dimopoulos M et al. 2015.[1]



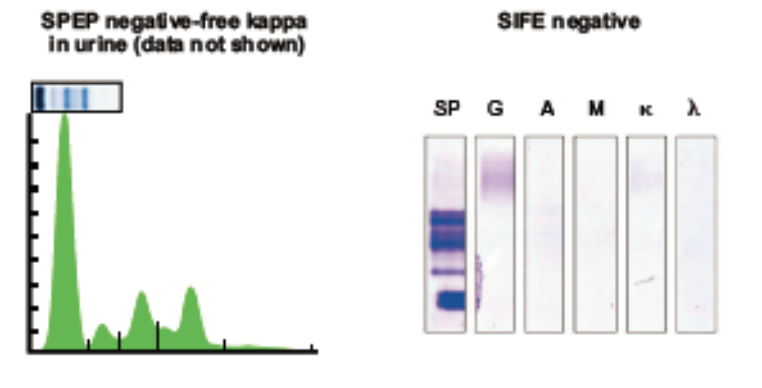
The perceived depth of response may be impacted by the presence of elotuzumab

IFE, immunofixation electrophoresis; IgG, immunoglobulin G; IRC, independent review committee; PR, partial response.SIFE, serum Immunofixation electrophoresis; SPEP, serum protein electrophoresis.

1. Dimopoulos M et al. Poster presentation at IMW 2015. Abstract PO-330.

ELOQUENT-2: Early Relapse Detected Due to Presence of Elotuzumab (IgGκ)

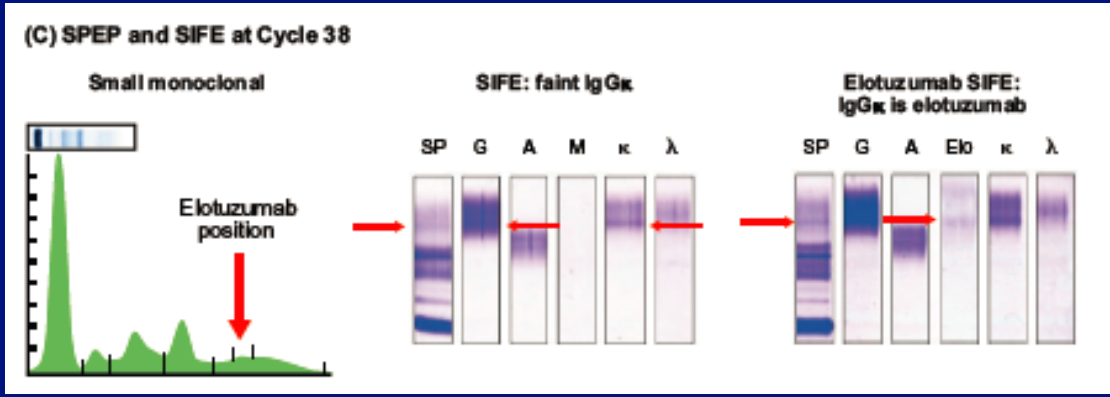
- **Baseline**



IRC response assessment based on SIFE positivity: **CR**

- **Cycle 38**

Images from Dimopoulos M et al. 2015.[1]

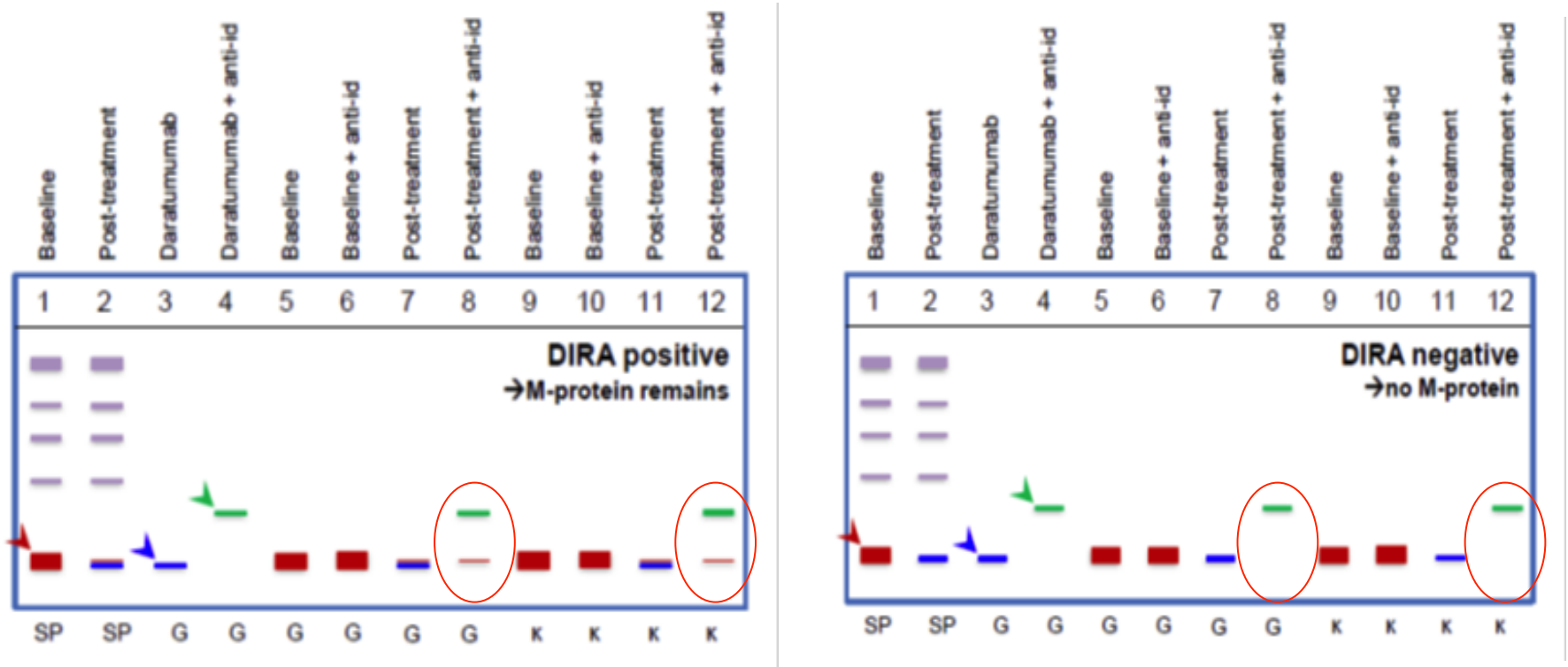


Elotuzumab was detected in the SIFE after CR, leading to a possible premature determination of relapse by the IRC

CR, complete response; IFE, immunofixation electrophoresis; IgG, immunoglobulin G; IRC, independent review committee; SIFE, serum immunofixation electrophoresis; SPEP, serum protein electrophoresis.

1. Dimopoulos M et al. Poster presentation at IMW 2015. Abstract PO-330.

Daratumumab specific IFE Reflex Assay (DIRA) is based on a anti-idiotype MoAb assay and separates therapeutic antibody from M-protein



SP = total serum protein fix
G = anti-IgG antisera
K = kappa antisera

Daratumumab
Dara + anti-id complex
M-protein

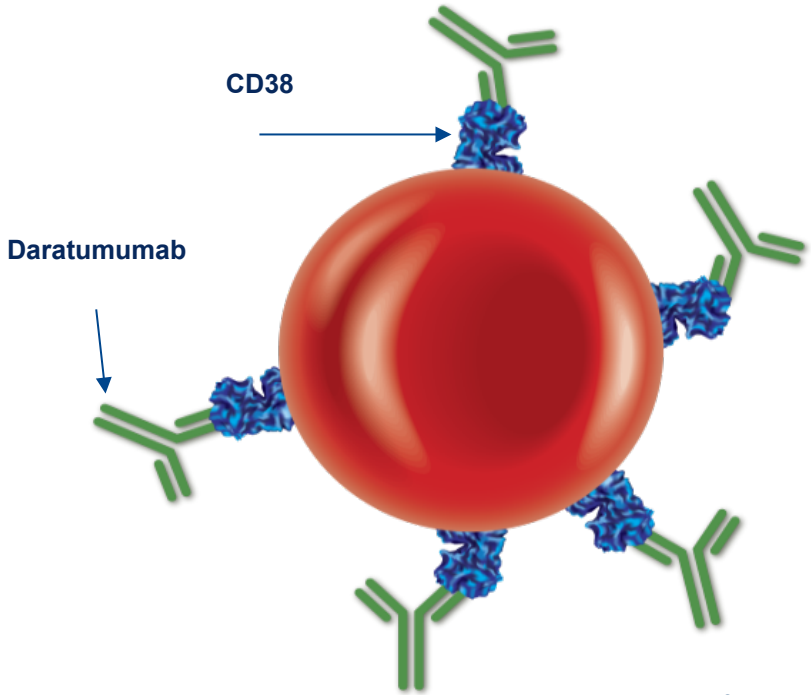
McCudden C, et al. ASCO 2015 (abstract 8590); poster presentation

My Agenda

- Adverse events of MoAbs in major clinical studies (single agent/combinations approved or close to be approved)
- Management of infusion-related reactions (IRRs)
- Interference with response assessment (all MoAbs)
- Interference with blood typing (anti-CD38)

Blood compatibility testing for patients receiving anti-CD38 mAbs

- CD38 is weakly expressed on human red blood cells (RBCs)
- Daratumumab binds to CD38 on RBCs → false positive results in the Indirect Antiglobulin Test (indirect Coombs test)

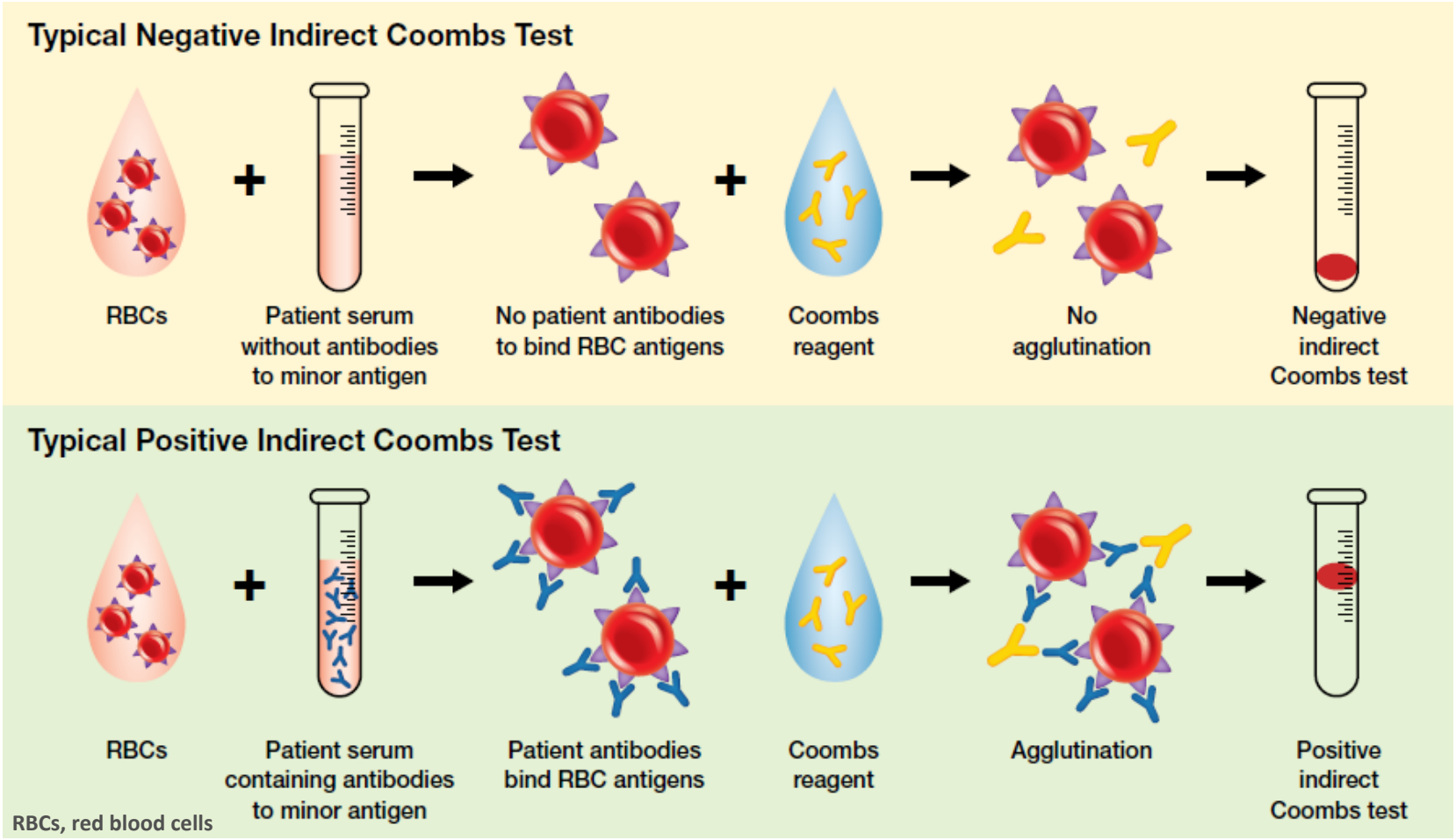


Daratumumab binds to CD38 on RBCs[2]

Chapuy et al. Transfusion. 2015;55(6 Pt 2):1545-54
Oostendorp et al. Transfusion. 2015;55(6 Pt 2):1555-62

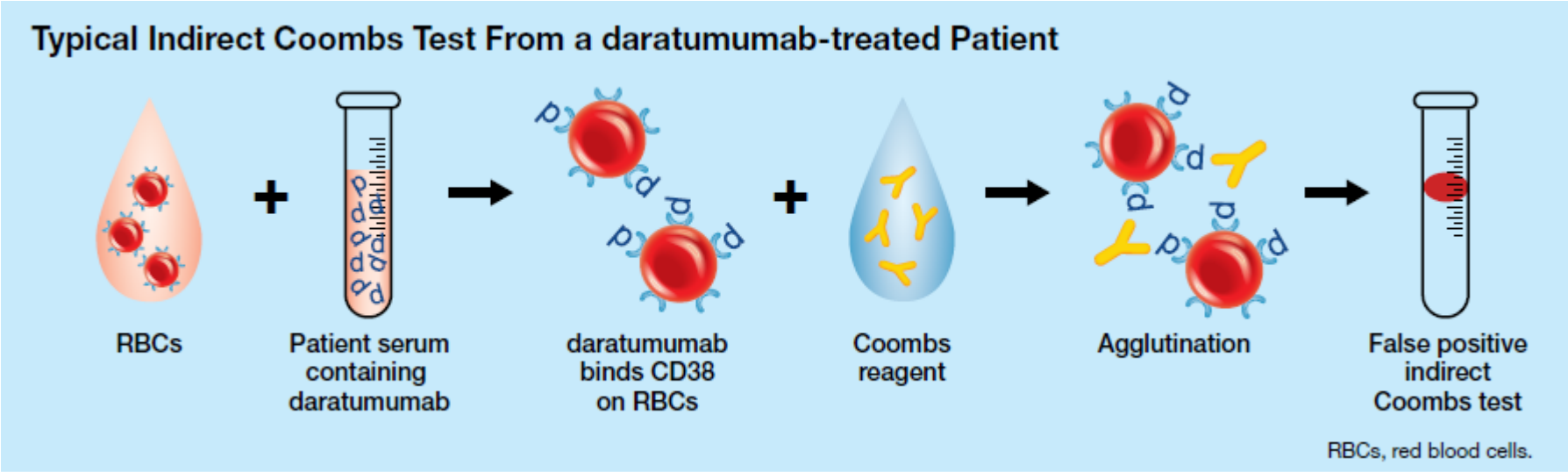
Mechanism of a Typical Indirect Coombs Test

- In an indirect Coombs test, patient's antibodies to minor antigens on reagent RBCs are detected by agglutination

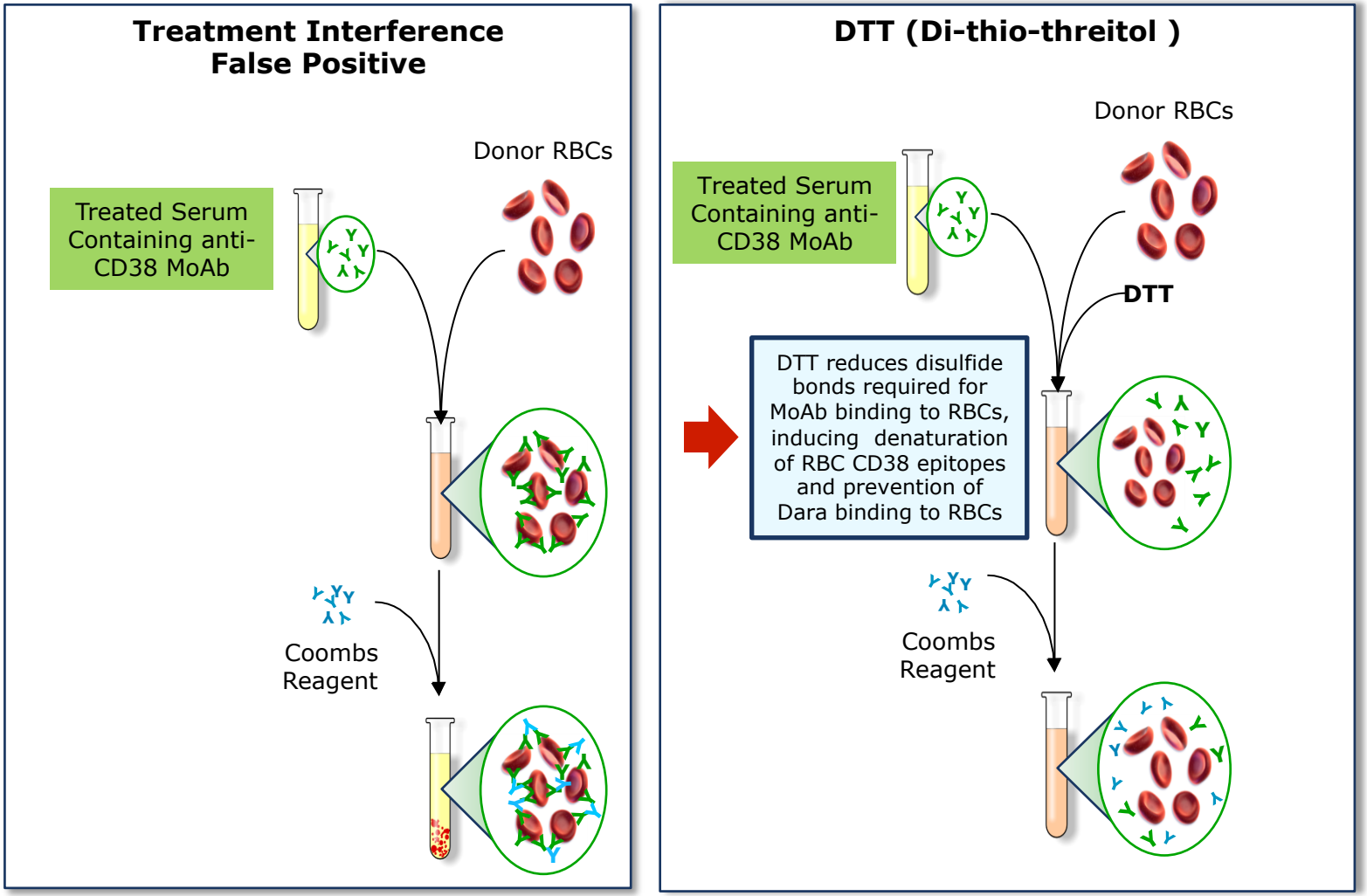


Sera Containing Daratumumab Mimic a Positive Indirect Coombs Test

- In an indirect Coombs test, Daratumumab binds to reagent or donor RBCs, resulting in agglutination and giving **a false positive result**
- Daratumumab interference was identified when **almost 100%** of Daratumumab-treated patients were panreactive during RBC panel testing
- "False" positive indirect Coombs's may variably persist **until 6 months** after last infusion of Daratumumab



Methods for Mitigating Monoclonal Antibody Therapy Assay Interference



DTT treatment of CD38+ cells reduced Daratumumab binding by 92%.

van de Donk Blood 2016;27(6):681–695; 2. van de Donk Immunol Rev 2016;270: 95–112

TABLE 2. Advantages and disadvantages of current anti-CD38 interference mitigation methods

Method	Mitigation mechanism	Advantages	Disadvantages
DTT[6]	Denatures CD38 on reagent cells	Inexpensive Fairly easy DTT commonly used in many blood banks	Must give K– units Always fails to detect antibodies to: KEL, DO, IN, JMH, KN, LW Often fails to detect antibodies to: YT, LU, MER2, CROM[12]
Trypsin[6]	Cleaves CD38 from reagent cells	Inexpensive Fairly easy Antibodies to KEL group antigens detected.	Less commonly used than DTT Always fails to detect antibodies to: Bp^a, Ch/Rg, XG, IN, JMH, M, N, En^aTS, Ge2, Ge4, LU, MER2, KN, DO[12]
Cord cell antibody screen[8]	Decreased CD38 expression on cord cells	Inexpensive Fairly easy No chemical or enzyme treatment needed.	Not commercially available Not practical for antibody identification Always fails to detect antibodies to: Le^a, Ch/Rg, AnWj, Sd^a Often fails to detect antibodies to: Le^b, P1, Lu^a, Lu^b, Yt^a, JMH, Xg^a, Vel, Bg, KN, DO, Fy3[12]
Soluble CD38[6,7,13]	Anti-CD38 neutralization	Easy No antibodies missed Commercially available Would work with any anti-CD38	Expensive Short shelf life Additional validation required
Anti-CD38 idiotype[6,7]	Anti-CD38 neutralization	Easy No antibodies missed	Not commercially available Additional validation required Would need a different anti-idiotype for each manufacturer's anti-CD38
Phenotype matching	Nonserologic method	Commonly performed in blood banks	Rarely, clinically significant antibodies could be missed depending on extent of matching Initial phenotyping should be done before starting anti-CD38 Rarely, even with extended matching, additional clinically significant antibody may be produced Availability of matched units and possible extended time to obtain
Genotype matching[9]	Nonserologic method	Allows identification of individuals lacking high-frequency antigens (e.g., Yt^a) May be performed after anti-CD38 treatment has begun	Expensive Rarely, genotype results fail to correctly predict phenotype Rarely, clinically significant antibodies could be missed depending on extent of matching Rarely even with extended matching, additional clinically significant antibody may be produced Availability of matched units and possible extended time to obtain

DARA interference with blood typing: What impact in the clinical practice?

- To date, **neither clinically significant hemolysis, nor transfusion reactions** after RBC and whole blood transfusions have occurred in patients receiving 16 mg/kg Daratumumab
- Daratumumab **does not interfere with ABO/RhD typing** but with minor ones; therefore blood products for transfusion can be identified for Daratumumab-treated patients by blood banks performing routine compatibility tests or by using genotyping
- If an emergency transfusion is required, **non-crossmatched, ABO/RhD–compatible RBCs can be given,** per local blood bank practices
- To avoid unnecessary delays, **blood bank should be informed,** preferably before MoAb is started, that they will receive a sample from a Daratumumab-treated patient, so that appropriate protocols for typing and screening procedures can be applied
- Patients should carry a **blood transfusion card** indicating that they receive anti-CD38 MoAb therapy

SUMMARY (1)

- Overall, safety profile of MoAbs is acceptable and manageable
- Addition of MoAbs to back-bone therapies (i.e. VD or RD) does not substantially modify expected toxicities (possible caveat for infections?)
- IRRs are the most frequent AE (Dare > Elo) and are often characterized by respiratory symptoms
- They occur mainly during the first infusion, are rarely of grade 3/4 and may be adequately prevented and managed with appropriate medical procedures
- IRRs very rarely result in definitive interruption of MoAbs infusion

SUMMARY (2)

- MoAbs currently employed for the treatment of MM are detected by SPEP/IFE tests, making it challenging to differentiate therapeutic antibody and the endogenous patient's clonal immunoglobulin
- This interference could result in an underestimation of CR rate, as well as a possible misdiagnosis of relapse in patients that initially achieved a CR
- Daratumumab may induce false positive results in the Indirect Antiglobulin Test (indirect Coombs test)
- This interference has no clinical impact in terms of clinically significant hemolysis, as well as of transfusion reactions
- Blood bank should be informed about patients planned to receive or under daratumumab (patient blood transfusion card)

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ORIGINAL REPORT

Systematic Literature Review and Network Meta-Analysis of Treatment Outcomes in Relapsed and/or Refractory Multiple Myeloma

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ABSTRACT

Purpose

Since 2000, many new treatment options have become available for relapsed and/or refractory multiple myeloma (R/R MM) after a long period in which dexamethasone and melphalan had been the standard treatment. Direct comparisons of these novel treatments, however, are lacking. This makes it extremely difficult to evaluate the relative added value of each new treatment. Our aim was to synthesize all efficacy evidence, enabling a comparison of all current treatments for R/R MM.

Methods

We performed a systematic literature review to identify all publicly available phase III randomized controlled trial evidence. We searched Embase, MEDLINE, MEDLINE In-Process, Cochrane Central Register of Controlled Clinical Trials, and the Web site www.ClinicalTrials.gov. In addition, two trials presented at two international hematology congresses (ie, ASCO 2016 and European Hematology Association 2016) were added to include the most recent evidence. In total, 17 randomized controlled trials were identified, including 18 treatment options. The evidence was synthesized using a conventional network meta-analysis. To include all treatments within one network, two treatment options were combined: (1) bortezomib monotherapy and bortezomib plus dexamethasone, and (2) thalidomide monotherapy and thalidomide plus dexamethasone.

Results

The combination of daratumumab, lenalidomide, and dexamethasone was identified as the best treatment. It was most favorable in terms of (1) hazard ratio for progression-free survival (0.13; 95% credible interval, 0.09 to 0.19), and (2) probability of being best (99% of the simulations). This treatment combination reduced the risk of progression or death by 87% versus dexamethasone, 81% versus bortezomib plus dexamethasone, and 63% versus lenalidomide plus dexamethasone.

Conclusion

Our network meta-analysis provides a complete overview of the relative efficacy of all available treatments for R/R MM. Until additional data from randomized studies are available, on the basis of this analysis, the combination of daratumumab, lenalidomide, and dexamethasone seems to be the best treatment option.

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Treatment	% Being Best Treatment	Hazard Ratio *v* Dexamethasone (95% CrI), PFS
DaraLenDex	99	0.13 (0.09 to 0.19)
CarLenDex	0	0.24 (0.18 to 0.32)
EloLenDex	0	0.25 (0.19 to 0.33)
DaraBorDex	1	0.27 (0.18 to 0.38)
IxaLenDex	0	0.26 (0.19 to 0.35)
CarDex	0	0.36 (0.26 to 0.48)
LenDex	0	0.35 (0.29 to 0.43)
PegDoxBor	0	0.37 (0.26 to 0.52)
PanoBorDex	0	0.43 (0.31 to 0.56)
BorThalDex	0	0.47 (0.33 to 0.65)
PomDex	0	0.48 (0.39 to 0.6)
VorinoBor	0	0.52 (0.38 to 0.69)
BorDex	0	0.67 (0.53 to 0.84)
ThalDex	0	0.76 (0.64 to 0.9)
Dex	0	1
ObIDex	0	1.08 (0.79 to 1.45)