Gli anticorpi monoclonali nel mieloma multiplo

Management degli anticorpi in pratica clinica

Elena Zamagni

Seràgnoli Institute of Hematology
Bologna University School of Medicine
Bologna

Managing Daratumumab in the clinic

- Special considerations with daratumumab therapy
  - Infusion-related reactions (IRRs)
  - Assessment of response
  - Blood typing

Infusion-related reactions (IRRs) with monoclonal antibodies for hem.malignancies

- IRRs can occur with mAbs
  - e.g. rituximab causes mild to moderate infusion reactions in most patients[1]

- Possible signs and symptoms of acute infusion reactions[2]
  - Allergic reactions/hypersensitivity
  - Skin reactions (itching , rash, urticaria)
  - Systemic reactions (fatigue, fever, sweating, dizziness, myalgia)
  - Respiratory reactions (bronchospam, dyspnea,
  - Cardiovascular symptoms (tachycardia, hypotension)

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

blood®
Prepublished online May 23, 2016;
doi:10.1182/blood-2016-03-705210

Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma

Saad Z. Usmani, Brendan M. Weiss, Torben Plesner, Nizar J. Bahlis, Andrew Belch, Sagar Lonial, Henk M. Lokhorst, Peter M. Voorhees, Paul G. Richardson, Ajai Chari, A. Kate Sasser, Amy Axel, Huaibao Feng, Clarissa M. Uhlar, Jianping Wang, Imran Khan, Tahamtan Ahmadi and Hareth Nahi

SIRIUS, Lonial et al, Lancet 2016
GEN501, Lokhorst et al, New England J Med 2015

Summary of Clinical Safety

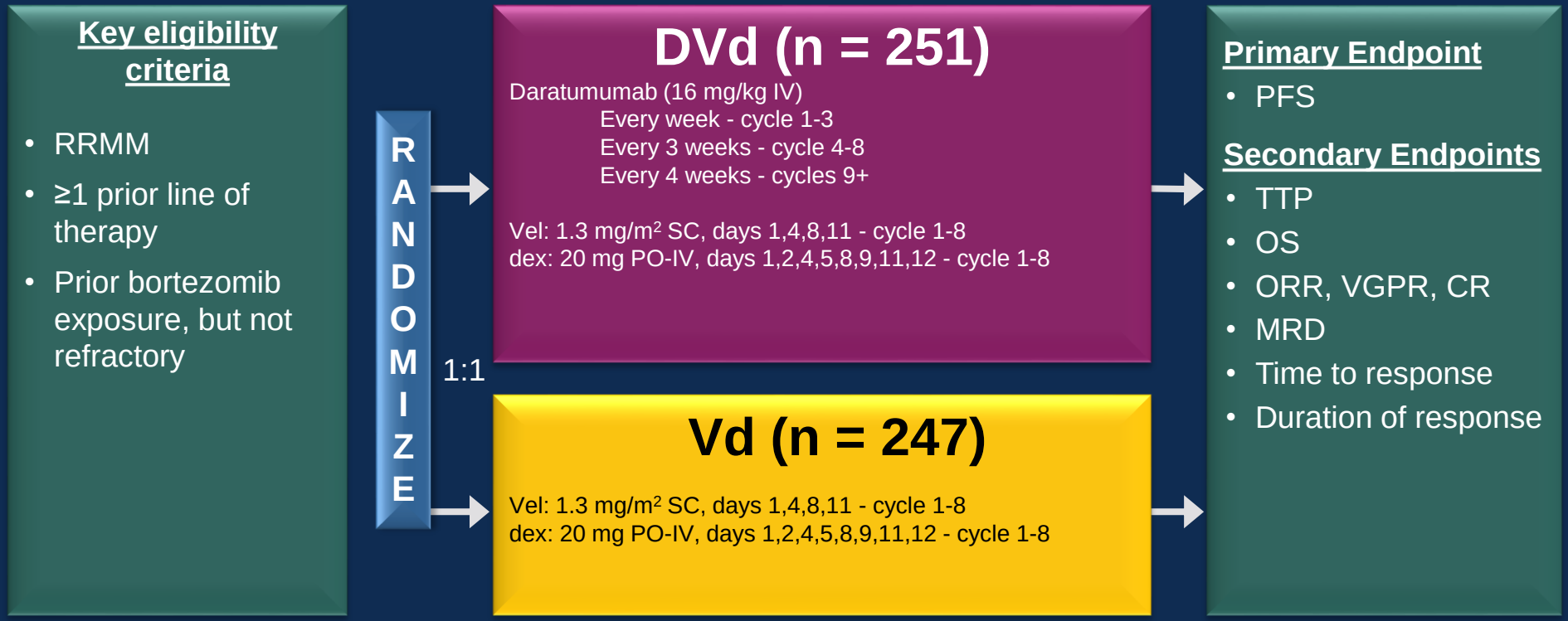
Treatment-emergent adverse event, n (%)	Any grade N = 148	Grade ≥3 N = 148
Fatigue	61 (41)	3 (2)
Nausea	42 (28)	0
Anemia	41 (28)	26 (18)
Back pain	36 (24)	3 (2)
Cough	33 (22)	0
Neutropenia	30 (20)	15 (10)
Thrombocytopenia	30 (20)	21 (14)
Upper respiratory tract infection	30 (20)	1 (<1)

48% of patients had infusion-related reactions

- 46%, 4%, and 3% occurred during the first, second, and subsequent infusions, respectively

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.

Infusion-related Reactions (IRRs)

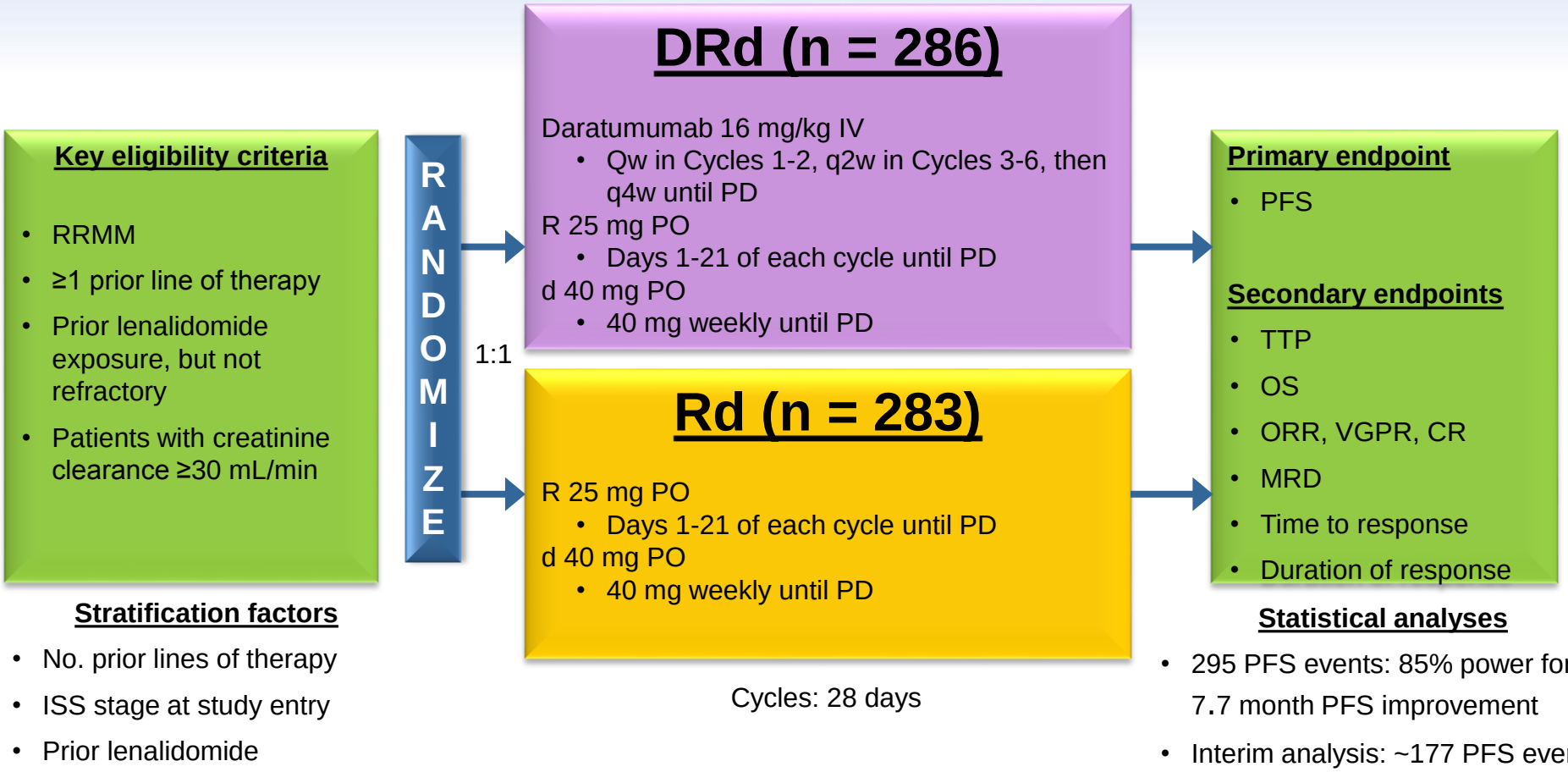
	Safety Analysis Set (n = 243)	
	All grades	Grade 3
Patients with IRRs, %	45	9
Most common (>5%) IRRs		
Dyspnea	11	2
Bronchospasm	9	3
Cough	7	0

- 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

POLLUX: Study Design

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



Pre-medication for the DRd treatment group consisted of dexamethasone 20 mg, paracetamol, and an antihistamine

Dimopoulos et al; EHA 2016, plenary session

Infusion-related Reactions (IRRs)

IRRs ≥2%	Safety Analysis Set (n = 283)	
	All grades (%)	Grade 3 (%)
Patients with IRRs	48	5
Cough	9	0
Dyspnea	9	0.7
Vomiting	6	0.4
Nausea	5	0
Chills	5	0.4
Bronchospasm	5	0.4
Pruritus	3	0.4
Throat irritation	3	0
Headache	3	0
Nasal congestion	3	0
Wheezing	2	0.7
Laryngeal edema	2	0.4
Rhinorrhea	2	0
Pyrexia	2	0

- No grade 4 or 5 IRRs were reported
- 92% of all IRRs occurred during the first infusion
- 1 patient discontinued daratumumab due to an IRR

Drugs
DOI 10.1007/s40265-016-0573-4

THERAPY IN PRACTICE

Practical Considerations for the Use of Daratumumab, a Novel CD38 Monoclonal Antibody, in Myeloma

Philippe Moreau[1] · Niels W. C. J. van de Donk[2] · Jesus San Miguel[3] · Henk Lokhorst[2] · Hareth Nahi[4] · Dina Ben-Yehuda[5] · Michele Cavo[6] · Gordon Cook[7] · Michel Delforge[8] · Hermann Einsele[9] · Sonja Zweegman[2] · Heinz Ludwig[10] · Christoph Driessen[11] · Antonio Palumbo[12] · Thierry Facon[13] · Torben Plesner[14] · Meletios Dimopoulos[15] · Pia Sondergeld[16] · Pieter Sonneveld[17] · María-Victoria Mateos[18]

25 April 2016

Prevention of IRRs

- Administer pre-medication to reduce the risk of IRRs (approximately 1 hour prior to every daratumumab infusion)
  - intravenous corticosteroid

    (methylprednisolone 100 mg or an equivalent long acting corticosteroid)
  - oral antipyretic

    (paracetamol at 650-1000 mg)
  - oral or intravenous antihistamine

    (diphenhydramide 25-50 mg or equivalent)

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

- Post-medication corticosteroids on 1st and 2nd day after all infusions

Adapted from: Protocol for: Lokhorst et al. N Engl J Med 2015 Aug 26 [Epub]

Practical Considerations for the Use of Daratumumab

Table 3 Infusion rates for daratumumab administration [31]

	Dilution volume (ml)	Initial infusion rate (first hour) (ml/h)	Increments of infusion rate	Maximum infusion rate (ml/h)
First infusion	1000	50	50 ml/h every hour	200
Second infusion[a]	500	50	50 ml/h every hour	200
Subsequent infusions[b]	500	100	50 ml/h every hour	200

[a] Escalate only if there were no grade 1 (mild) or higher infusion reactions during the first 3 h of the first infusion

[b] Escalate only if there were no grade 1 (mild) or higher infusion reactions during a final infusion rate of $\geq$100 ml/h in the first two infusions

Moreau et al. Drugs; 25 April 2016

Management of IRRs

- In case of occurrence of IRRs
  - React **early** to mild signs of symptoms and immediately stop the infusion
  - Manage symptoms appropriately, consider e.g. antihistamines, corticosteroids
  - Once symptoms have resolved, treatment may be resumed at half the infusion rate
  - In case of grade 4 IRRs permanently discontinue treatment

Adapted from: Protocol for: Lokhorst et al. N Engl J Med 2015 Aug 26 [Epub]

Table 5 Recommendations for the management of infusion-related reactions [64]

IRR	Action
Grade 1 or 2	The infusion should be paused and can be restarted when the patient's condition is stable When restarting, the infusion rate should be half of that used before the interruption The infusion rate can subsequently be increased

Moreau et al. Drugs; 25 April 2016

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

Moreau et al. Drugs; 25 April 2016

- **Use of Montelukast to Reduce Infusion Reactions in an Early Access Program (EAP) of Daratumumab in United States Patients With Relapsed or Refractory Multiple Myeloma**

- A. Chari,[1] T.M. Mark,[2] A. Krishnan,[3] K. Stockerl-Goldstein,[4] S.Z. Usmani,[5] A. Londhe,[6] D. Etheredge,[7] H. Parros,[7] S. Fleming,[7] B. Liu,[8] S. Freeman,[6] J. Ukropec,[6] T. Lin[6] A.K. Nooka[9]

ASH 2016

IRRs and Infusion Time

- Sixty patients received montelukast during therapy, including 50 patients who received montelukast 10 mg given >30 minutes prior to the first infusion
- **Median time for first infusion was 6.7 and 7.6 hours for patients who did and did not receive montelukast, respectively, while times for the second and all subsequent infusions were similar in both groups**
- A total of 24 patients experienced IRRs that were considered serious adverse events, but no patient discontinued the study due to an IRR

	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

ASH 2016

Conclusions

- In the EAP study of US patients with MM who had received >3 prior therapies, including a PI and IMID, or who were double refractory to a PI and an IMiD, IRR rates and median infusion times were similar to those observed in the pivotal registration study, MMY2002
- **The observed IRR rate during the first daratumumab infusion was one-third lower in patients who received 10 mg of montelukast >30 min prior to the first daratumumab infusion** than it was in patients who did not receive montelukast
- **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
- Because the use of montelukast was limited to a small number of centers, the role of montelukast in reducing IRRs cannot be determined from these uncontrolled observations
- Additional studies to determine if montelukast mitigates the IRRs associated with the first infusion of daratumumab are needed

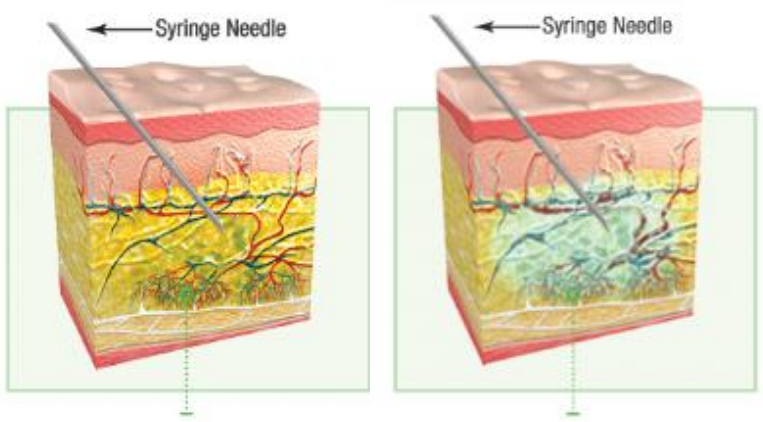
ASH 2016

Daratumumab IV vs SC – PAVO
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.

Daratumumab IV vs SC
PAVO: 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

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.

Daratumumab IV vs SC – PAVO
Grade 3/4 TEAEs

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

Usmani et al, Abs1149 ASH2016

Daratumumab IV vs SC – PAVO
IRRs

	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)

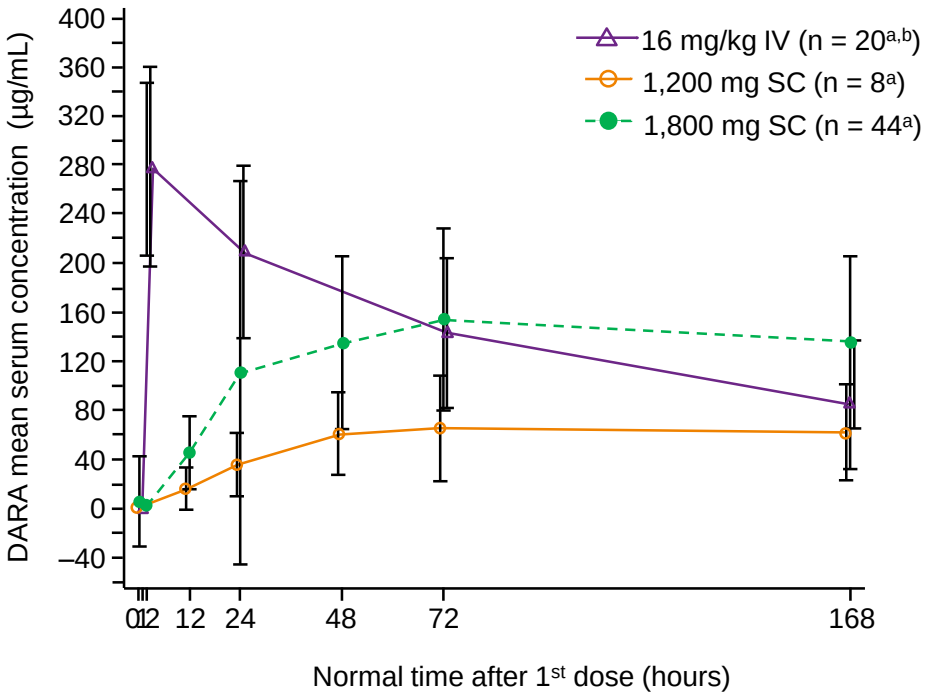
- All IRRs in the 1,800-mg group were grade 1 or 2
- One grade 3 IRR of dyspnea in the 1,200-mg group
- No grade 4 IRRs were observed
- All IRRs occurred during or within 4 hours of the first infusion
- No IRRs occurred during subsequent infusions in either group
- Abdominal wall SC injections were well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

Usmani et al, Abs1149 ASH2016

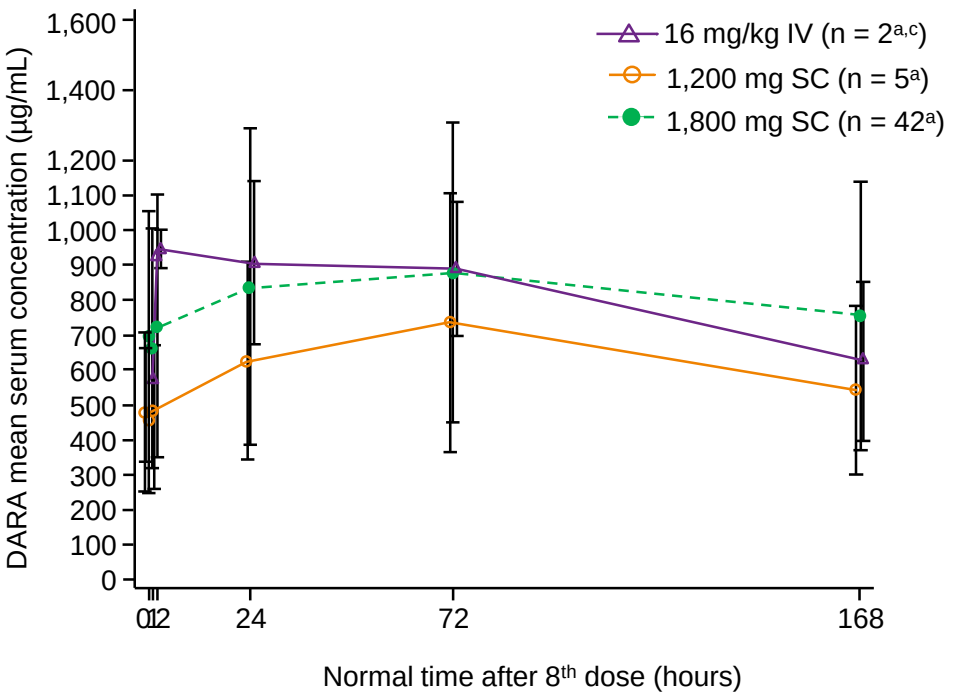
Low IRR incidence and severity with DARA SC

Daratumumab IV vs SC – PAVO
Dose Mean (SD) Profiles

1st dose mean



8th dose mean

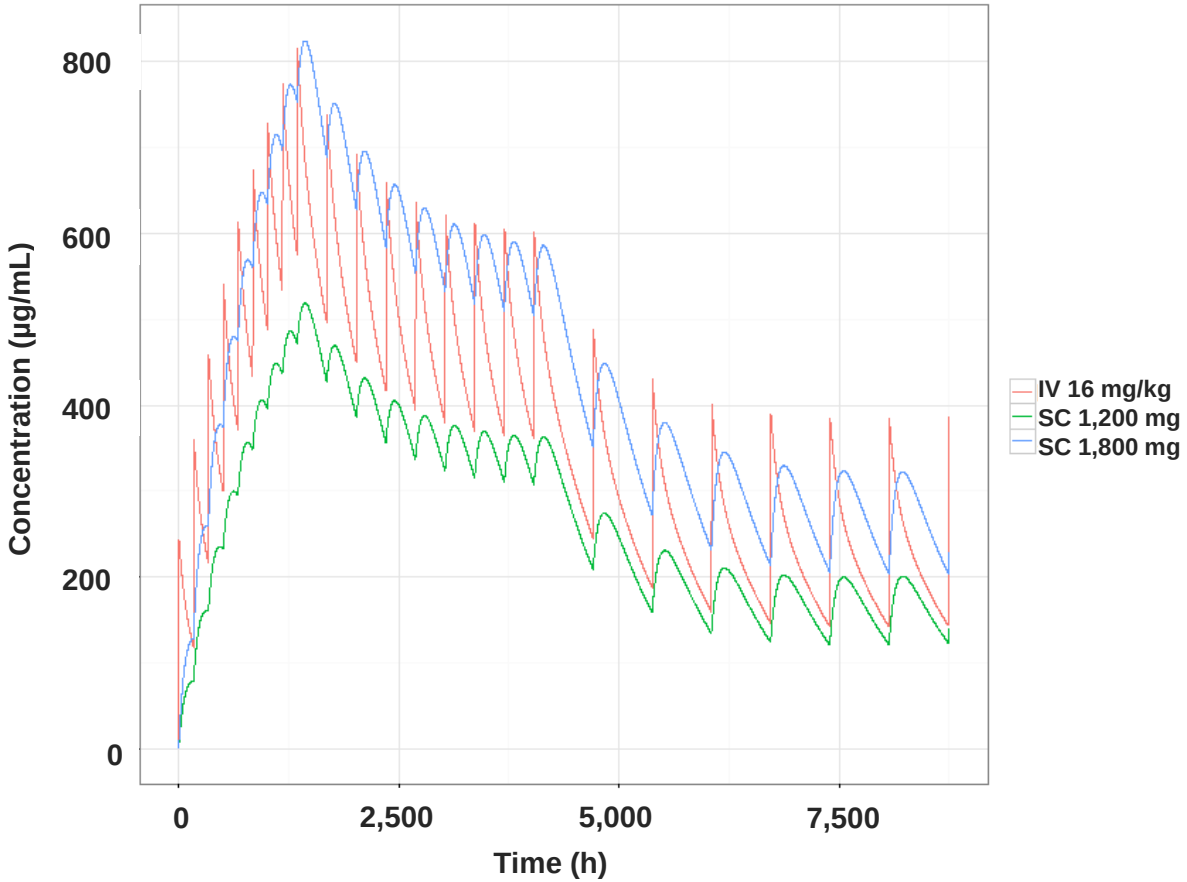


PK for the 1,800-mg SC dose is consistent with the 16-mg/kg IV dose, with comparable C_{trough} and variability

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.

Usmani et al, Abs1149 ASH2016

Daratumumab IV vs SC – PAVO
Simulation of Mean Concentration-Time Profiles of DARA Following SC and IV Dosing[a]



- Similar C_{max} for SC 1,800 mg versus IV 16 mg/kg overall
- Lower C_{max} for SC 1,800 mg during the initial weekly administration
- Higher C_{trough} for SC 1,800 mg versus SC 1,200 mg

C_{max}, peak plasma concentration.
[a]Dosing schedule is once weekly in Cycles 1 to 2, every 2 weeks in Cycles 3 to 6, and every 4 weeks thereafter.

Usmani et al, Abs1149 ASH2016

Daratumumab IV vs SC – PAVO
Conclusions

- DARA can be combined safely with rHuPH20
- SC DARA was well tolerated with low IRR rates
  - SC injections were well tolerated
- PK profile of the 1,800-mg dose was consistent with DARA 16 mg/kg IV
- Efficacy was consistent with IV DARA in a similar patient population
  - 38% ORR, including deep responses (1 sCR)

Tolerability, safety, and PK data support continued development of SC DARA in different settings

Usmani et al, Abs1149 ASH2016

Managing mAb therapy in the clinic

- Special considerations with anti-CD38 mAb therapy
  - Infusion-related reactions (IRRs)
  - Assessment of response
  - Blood typing

Clinical assessment of M-protein response in MM and interference through mAbs

- All therapeutic mAbs may interfere with serum electrophoresis and immunofixation

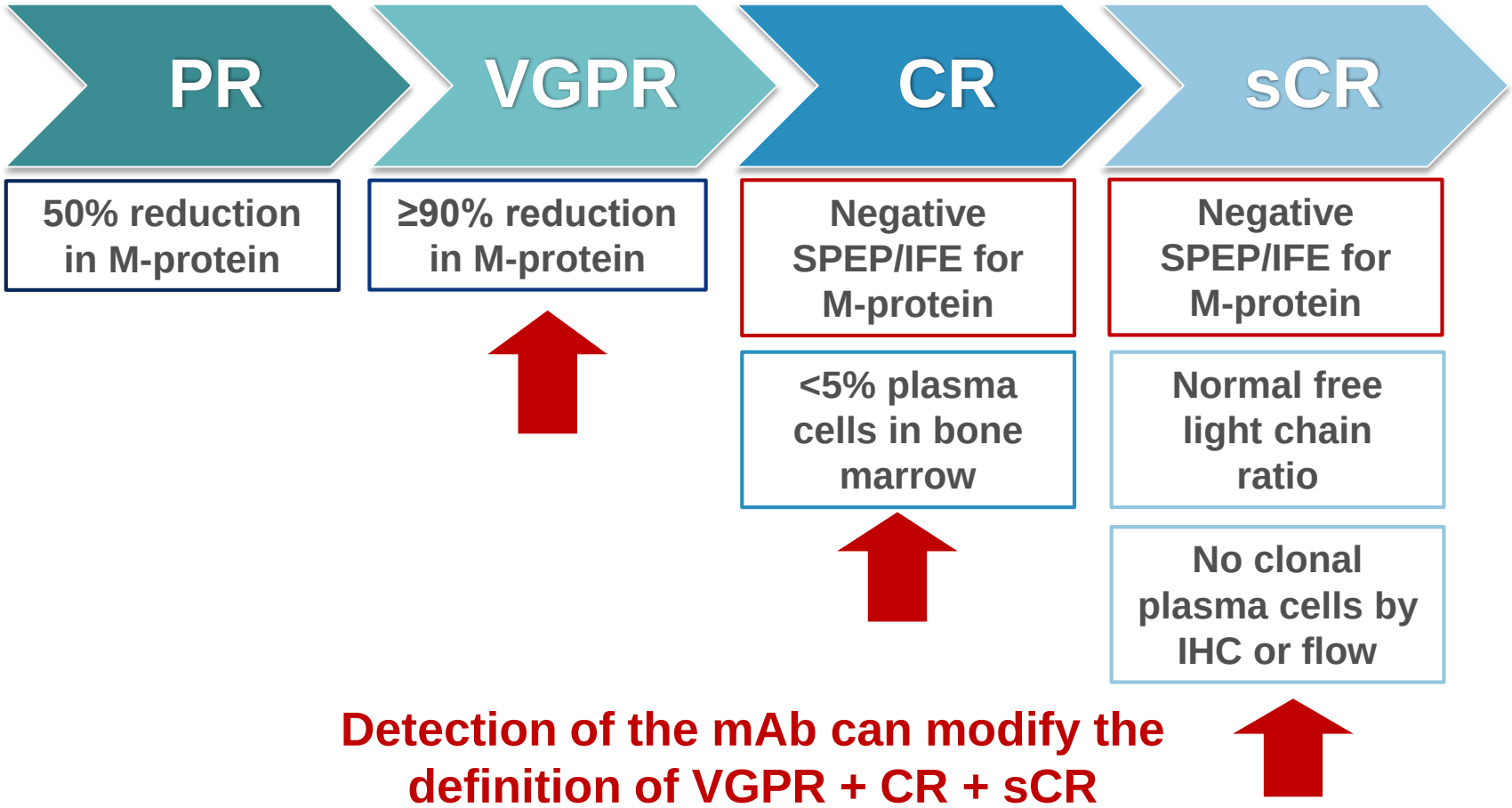
  → Difficult to discern between therapeutic antibody and the patient's clonal immunoglobulin

- Class effect of mAbs in myeloma
- Interference depends on isotype of the patient
- Daratumumab, Elotuzumab, Isatuximab and MOR202 are IgG mAb

Durie et al. Leukemia. 2006;20(9):1467-1473.
McCudden et al. Clin Chem. 2010;56(12):1897-1899.
Van de Donk et al. Blood. 2015 Dec 2. [Epub ahead of print]
Moreau et al. Drugs. 2016 Apr 25

Therapeutic antibody interference with response assessment

Progressive Clinical Response



Detection of the mAb can modify the definition of VGPR + CR + sCR

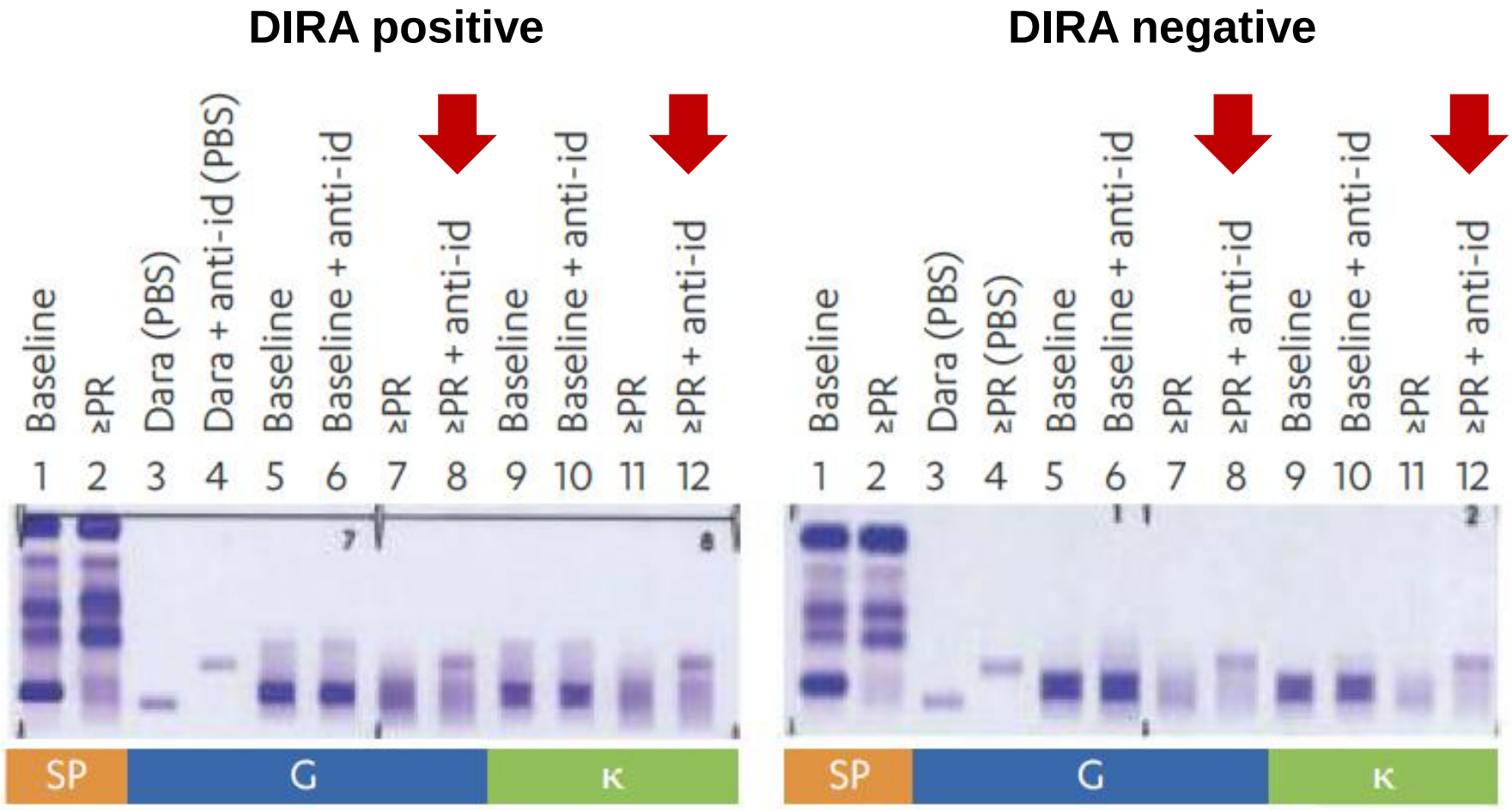
The daratumumab concentration used clinically is equivalent to 1g/L

Development of an assay to distinguish M-protein from therapeutic antibody

- Daratumumab IFE reflex assay (DIRA):
  - Incubation of serum samples of baseline and daratumumab-treated patients with or without an anti-idiotype mAb
  - IFE: Daratumumab migration is shifted from the gamma region by the anti-idiotype mAb

Van de Donk et al. Blood. 2015 Dec 2. [Epub ahead of print
Moreau et al. Drugs 2016 Apr 25

Development of an assay to distinguish M-protein from therapeutic antibody



BLOOD, 11 FEBRUARY 2016 • VOLUME 127, NUMBER 6

blood®

Clinical efficacy and management of monoclonal antibodies targeting CD38 and SLAMF7 in multiple myeloma

Niels W. C. J. van de Donk,[1] Philippe Moreau,[2] Torben Plesner,[3] Antonio Palumbo,[4] Francesca Gay,[4] Jacob P. Laubach,[5] Fabio Malavasi,[6] Hervé Avet-Loiseau,[7] Maria-Victoria Mateos,[8] Pieter Sonneveld,[9] Henk M. Lokhorst,[1] and Paul G. Richardson[5]

BLOOD, 11 FEBRUARY 2016 • VOLUME 127, NUMBER 6

Management

DIRA should be performed when daratumumab-treated patients with IgG-κ M-protein have achieved deep response (M-protein <2 g/L)

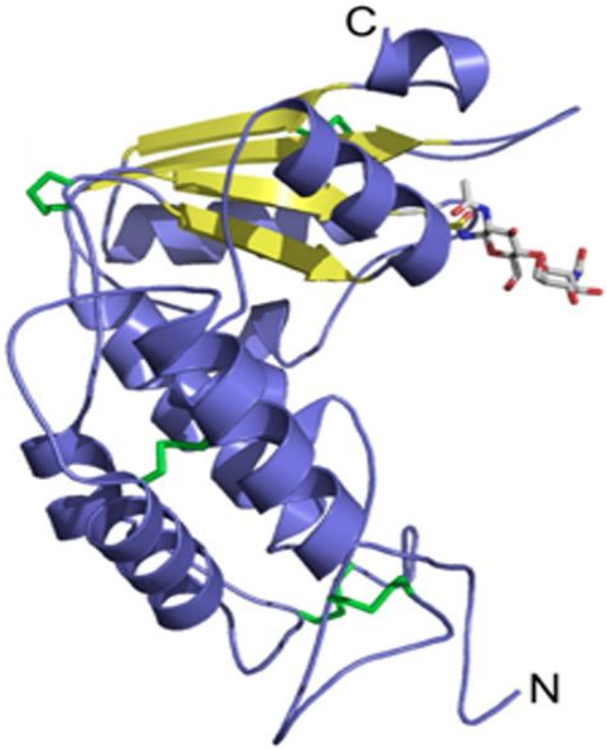
Managing mAb therapy in the clinic

- Special considerations with anti-CD38 mAb therapy
  - Infusion-related reactions (IRRs)
  - Assessment of response
  - Blood typing

Daratumumab Antibody to CD38
CD38 – A Surface Antigen

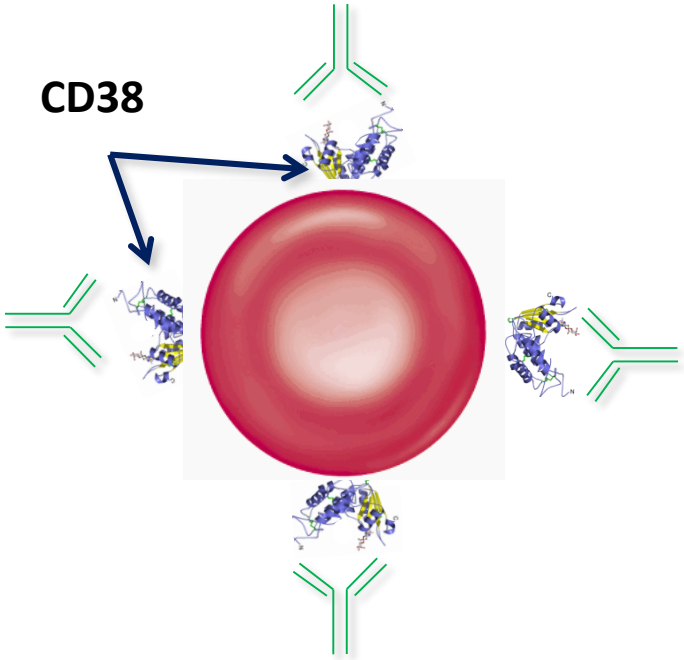
CD38 Normal Tissue distribution:

- Lymphoid cells
- Myeloid cells
- RBCs
- Other tissues



Egea PF 2012, PLOS one 0034918

Daratumumab binds to CD38 on RBCs



Daratumumab

- CD38 is expressed on RBCs at very low levels
- Daratumumab will bind to CD38 on RBCs
- **There have been no adverse events due to this binding**
- It is this binding that causes the blood transfusion testing interference in the IAT

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 does not interfere with the major antigens of ABO/RhD typing, but with the minor ones

Chapuy et al. Transfusion. 2015;55(6 Pt 2):1545-54
Oostendorp et al. Transfusion. 2015;55(6 Pt 2):1555-62
Van de Donk et al. Blood. 2015 Dec 2. [Epub ahead of print
Moreau et al. Drugs 2016, Apr 25

Establishing compatibility in patients receiving anti-CD38 mAbs
(Immunohematology labs and blood banks)

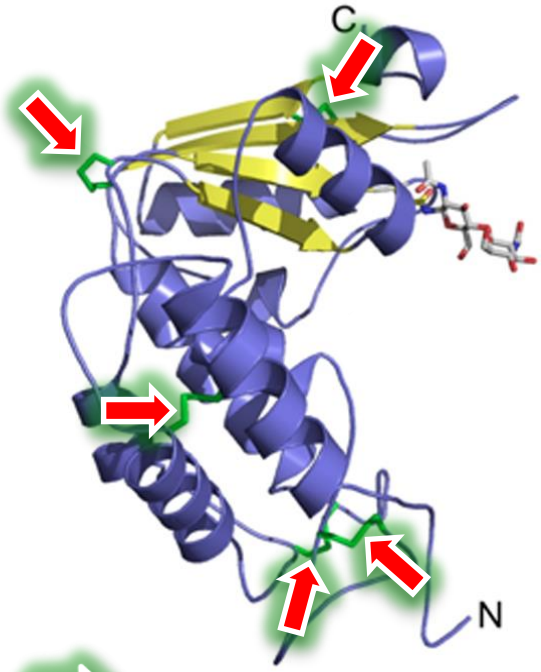
- Several options exist to circumvent the *in vitro* effect of interference with blood compatibility tests
  - Dithiothreitol (DTT): denaturation of RBC CD38 epitopes → prevention of Dara binding to RBCs
  - Anti-idiotype mAb and soluble CD38 → prevention of Dara binding to RBCs
  - Genotyping to establish compatibility

Chapuy et al. Transfusion. 2015;55(6 Pt 2):1545-54
Oostendorp et al. Transfusion. 2015;55(6 Pt 2):1555-62
Van de Donk et al. Blood. 2015 Dec 2. [Epub ahead of print
Moreau et al. Drugs 2016, Apr 25

RBC: red blood cell

DTT Treated Red Blood Cells

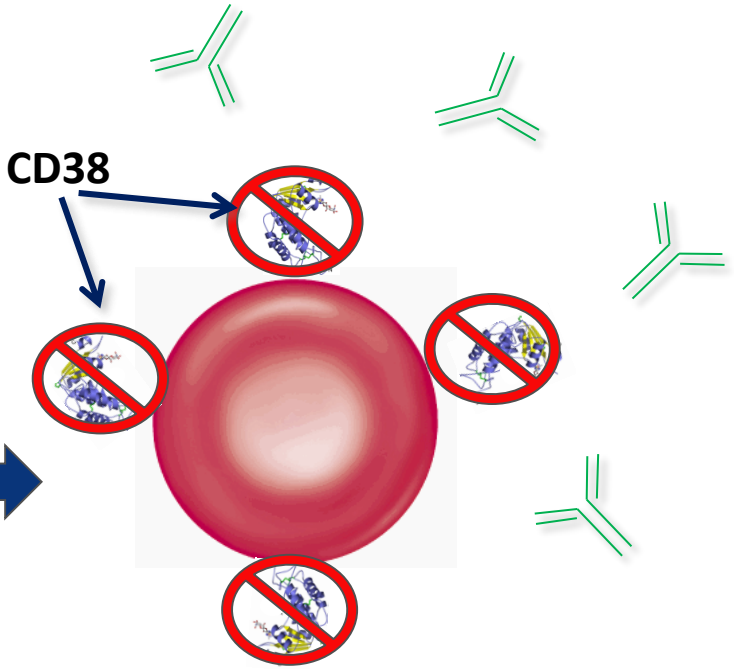
DTT denatures the CD38 on RBC's so that daratumumab cannot bind



S-S bonds

DTT

(dithiothreitol)



Daratumumab

Phenotyping and Genotyping

- **Phenotyping** is a process to determine the antigen expression on RBC
  - Antigen expression on RBC does not change over time
  - Daratumumab-treated patient serum will show interference with phenotyping
  - Phenotyping must be done prior to daratumumab administration
  - Phenotyping is not applicable after transfusion
- **Genotyping** is DNA analysis to determine the presence of minor antigen genes
  - Genotyping can be done before or after daratumumab administration

Blood compatibility testing for patients receiving anti-CD38 mAbs

- Effect only of relevance *in vitro*
  - To date, no hemolysis observed and no transfusions required due to interference
- Effect is class specific for anti-CD38 monoclonal antibodies
- Immunohematology labs and blood banks need to be made aware when patients are receiving anti-CD38 mAbs
- Patients may carry a blood transfusion card indicating that they receive anti-CD38 mAb therapy

Chapuy et al. Transfusion. 2015;55(6 Pt 2):1545-54
Oostendorp et al. Transfusion. 2015;55(6 Pt 2):1555-62
Van de Donk et al. Blood. 2015 Dec 2. [Epub ahead of print
Moreau et al. Drugs 2016, Apr 25

Summary: Managing mAb therapy in the clinic

- Infusion-related reactions may occur with Daratumumab

  → Use pre- and post-medication; infusion rate; inform nurses and patients

- mAbs interfere with response assessment in myeloma → need for specific assay to confirm responses > (VG)PR

- *In vitro* effect of anti-CD38 mAbs in blood compatibility testing → Immunohematology labs and blood banks need to be made aware that patient is receiving Daratumumab to circumvent interference