GESTIONE DEGLI ANTICORPI MONOCLONALI NELLA PRATICA CLINICA

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Il Mieloma Multiplo

Viareggio – 29 marzo 2017

Monoclonal antibodies in MM

Target	mAb		Stage of development
Surface molecules			
SLAMF7 (CS1)	Elotuzumab	Humanized	Phase 1/2/3
CD38	Daratumumab	Fully human	Phase 1/2/3/4
	Isatuximab (SAR650984)	Chimeric	Phase 1/2
	MOR202	Fully human	Phase 1/2
CD138	Indatuximab ravtansine (BT062)		Phase 1/2
BCMA	J6M0-mcMMAF (GSK2857916)		Phase 1
Signaling molecules			
IL-6	Siltuximab		Phase 2
RANKL	Denosumab		Phase 3
VEGF	Bevacizumab		Phase 2
DKK1	BHQ880		Phase 2
Immune checkpoint inhibitors			
PD-1	Pembrolizumab		Phase 1/2/3
	Nivolumab		Phase 1/2
	Pidilizumab		Phase 1/2
PD-L1	Durvalumab		Phase 1
CTLA4	Ipilimumab		Phase 1/2
KIR	Lirilumab		Phase 1

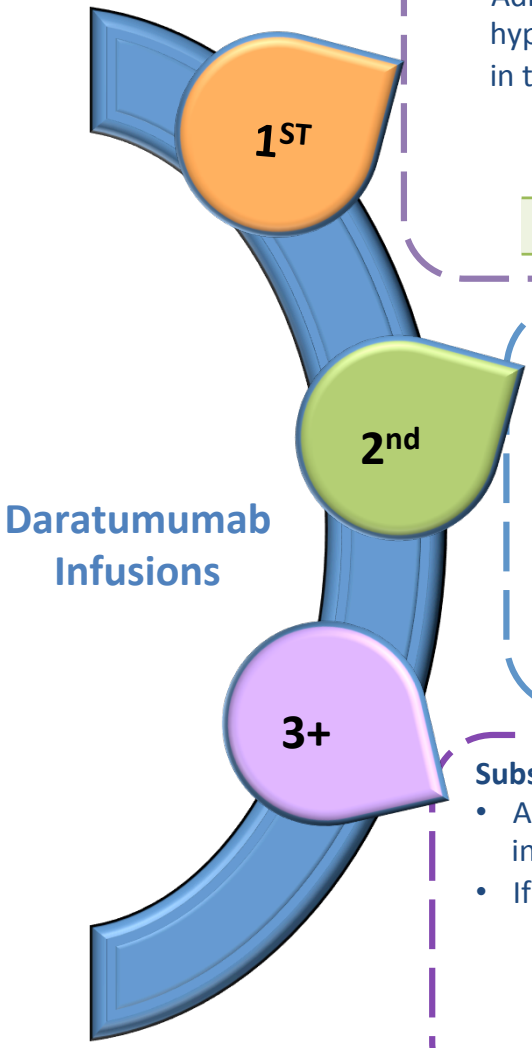
Bianchi G et al. Blood 2015;126:300–310; van de Donk NW et al. Blood 2016;127:681-95

PAZIENTI TRATTATI CON DARATUMUMAB (Clinica Ematologica Università di Genova)

N° PAZIENTI		6
M/F		5/1
V/M		5/1
ND/Rel-Ref		2/4
DARA in associazione (VMP)/Dara SINGLE AGENT		2/4
Precedenti linee di terapia		4 (2-6)
	IMIDs	4
	PI	4
	autoBMT	1
MEDIA CICLI DI TERAPIA		3 (1-8)
RISPOSTA ALLA TERAPIA	PD/SD/PR	1/2/2
REAZIONI INFUSIONALI (max gr.2 = stop infusione e steroide)		2
TOSSICITA' EMATOLOGICA		0*

Administration and Infusion management

Dosage and Administration



Daratumumab Infusions

First infusion – diluted in 1,000 mL of 0.9% NaCl

- Administered at an initial rate of 50 mL/hr. In the absence of infusion-related reactions/ hypersensitivity, the rate of the infusion will be escalated in increments of 50 mL/hr every 60 minutes in the first 3 hours to a maximum rate of 200 mL/hr.

	Hour 1	Hour 2	Hour 3	Hour 4	Hour 5	Hour 6	Hour 6.5
Infusion Rate, mL/hr	50	100	150	200	200	200	200

Second Infusion – diluted in 500 mL of 0.9% NaCl*

- Administered at an initial rate of 50 mL/hr and increased by 50 mL/hr increments at 60-minute intervals to a maximum rate of 200 mL/hr
- If the previous infusion was not well tolerated, then instructions for the first infusion will be used

	Hour 1	Hour 2	Hour 3	Hour 4
Infusion Rate, mL/hr	50	100	150	200

Subsequent Infusions- diluted in 500 mL of 0.9% NaCl*

- Administered at an initial rate of 100 mL/hr and increased by 50-mL/hr increments at 60-minute intervals, as tolerated, to a maximum rate of 200 mL/hr
- If the previous infusion was not well tolerated, then instructions for the second infusion will be used

	Hour 1	Hour 2	Hour 3	Hour 3.5
Infusion Rate, mL/hr	100	150	200	200

***If the patients previous infusion (second infusion) or first two infusions (subsequent infusions) were well tolerated** (defined by an absence of ≥Grade 1 infusion-related reactions during the first 3 hours)

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

Infusion time

- The median duration of the first infusion is 7 hours, and it decreases for subsequent infusions

	1st infusion	2nd infusion	Subsequent infusions
Median duration of infusion	7.0	4.6	3.4

Darzalex US Prescribing Information, last accessed April 2016.

Infusion related reactions

management and supportive measures for daratumumab IRR

For IRRs of any grade/severity, immediately interrupt the daratumumab infusion and manage symptoms

Institute additional supportive measures according to local guidelines and best clinical practice immediately, comprising but not limited to:

- IV saline solution
- IV antihistamines and IV corticosteroids
- Oxygen
- Bronchodilators

Upon abatement of symptoms, depending on the severity of the IRR, infusion with daratumumab can be continued in the majority of cases

Voorhees P *et al.* Abstract #60. Presented at the 2015 ASH Meeting on Hematologic Malignancies; September 19, 2015; Chicago, IL. Darzalex US Prescribing Information, last accessed April 2016.

Infusion related reactions management

- **In case of restarting daratumumab infusion, a reduction of infusion rates is required as indicated below:**

Severity of IRR	Action Daratumumab infusion management
Grade 1/2 (mild to moderate)	Once reaction symptoms resolve, resume the infusion at **no more than half the rate at which the IRR occurred**. If the patient does not experience any further IRR symptoms, infusion rate escalation may resume at increments and intervals as appropriate.
Grade 3 (severe)	If the intensity of the IRR decreases to Grade 2 or lower, consider restarting the infusion at **no more than half the rate at which the reaction occurred**. If the patient does not experience additional symptoms, resume infusion rate escalation at increments and intervals as appropriate. Repeat the procedure above in the event of recurrence of Grade 3 symptoms. ***Permanently discontinue Daratumumab upon the third occurrence of a Grade 3 or greater infusion reaction.***
Grade 4 (life threatening)	***Permanently discontinue Daratumumab treatment***

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

Treatment Modifications Due to DARA-related IRRs

- Treatment modifications, including infusion interruptions and infusion rate decreases, were implemented in most patients who experienced IRRs
- Three patient 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

Action taken during infusion, n (%)[a]	16 mg/kg (n = 106)	8 mg/kg (n = 18)
Infusion interrupted[b]	30 (28.3)	6 (33.3)
Infusion rate decreased	10 (9.4)	3 (16.7)
Infusion aborted	2 (1.9)	1 (5.6)

DARA, daratumumab; IRR, infusion-related reaction.
[a]Percentages were calculated using the number of patients in each group as the denominator.
[b]Includes per-protocol infusion rate reductions.

Voorhees PM, et al. Poster presented at: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2015; Orlando, FL. Abstract 1829.

Summary of IRR management

- 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 or a third occurrence of a Grade 3 or greater infusion reaction permanently discontinue treatment

Darzalex US Prescribing Information, last accessed April 2016.
Voorhees P, et al. Poster presented at: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2015; Orlando, FL. Abstract 1829.

USE OF MONTELUKAST TO REDUCE INFUSION REACTIONS IN AN EAP OF DARATUMUMAB IN US PATIENTS WITH REL REF MM

Chari et al., poster 2142, ASH 2016

- **Anecdotal reports indicated that premedication with montelukast, a leukotriene receptor antagonist, may reduce the IRR rate associated with daratumumab therapy**

- ■ The findings of the EAP study in US patients with MM who had received >3 prior therapies including a PI and IMID or were double-refractory observed an IRR rate and median infusion times that were similar to what were observed in the pivotal registration study MMY2002 in this patient population
- ■ **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 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 can not be determined from these uncontrolled observations
- ■ Additional studies to determine if montelukast mitigates the IRRs associated with the first infusion of daratumumab are indicated

Blood transfusion compatibility testing

Understanding CD38 Antibodies Interference with Blood Typing

Objectives

1. Be familiar with the mechanism of interference
2. Understand the clinical impact of the interference with blood compatibility testing
3. Be aware of the protocols that exist to mitigate daratumumab interference
4. Know what information to provide to the blood bank
5. Communicate the implications of daratumumab interference to your patients

How Do CD38 Monoclonal Antibodies Interfere With Blood Compatibility Testing?

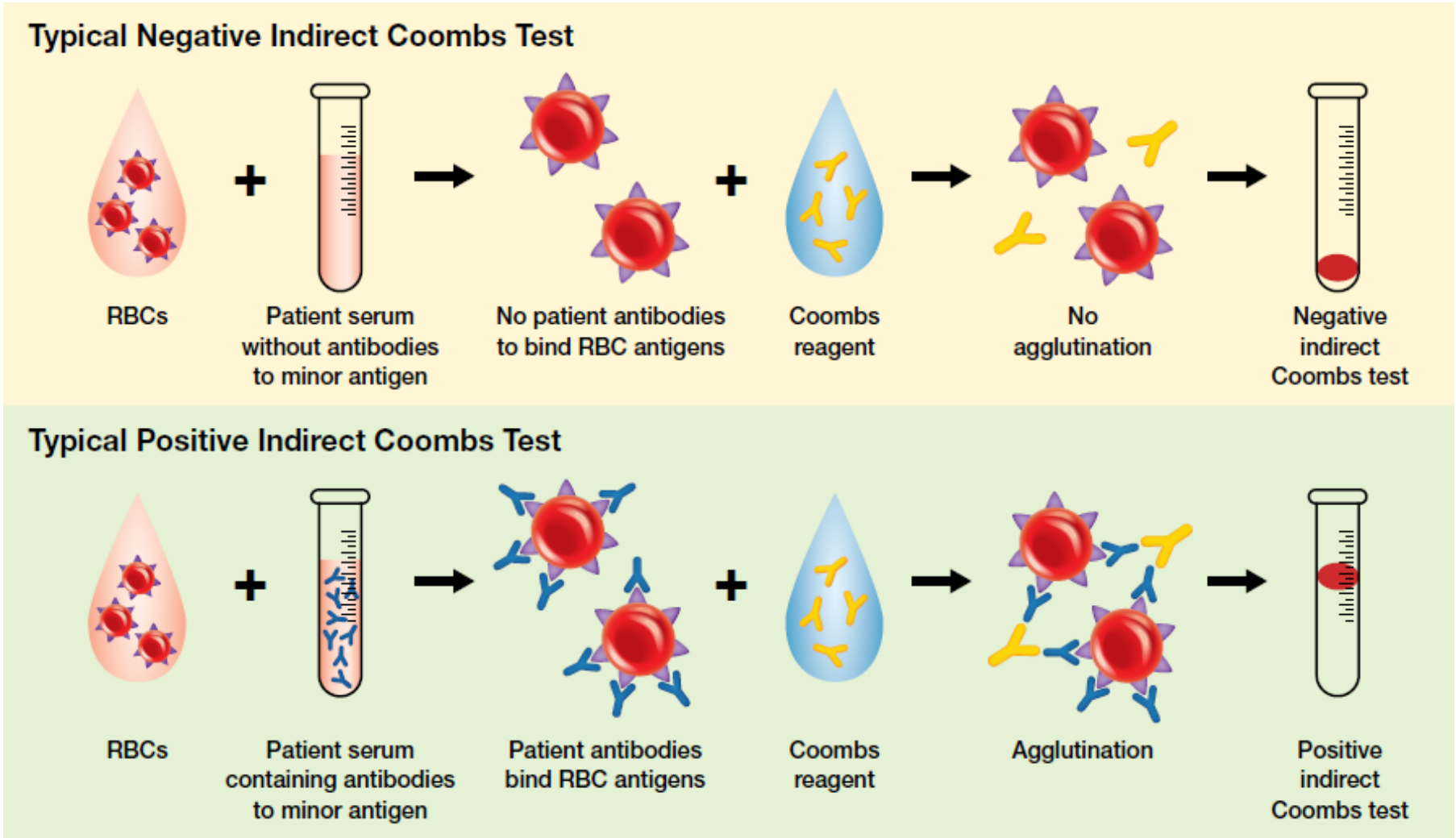
Blood transfusion compatibility testing for patients receiving CD38 mAbs

- 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
- Effect is class specific for CD38 monoclonal antibodies
- This may complicate timely release of blood products

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, a patient's antibodies to minor antigens on reagent RBCs are detected by agglutination



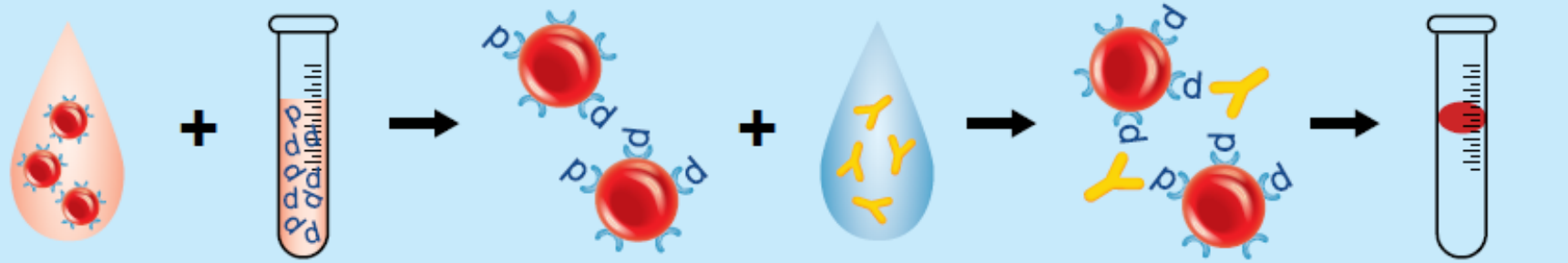
RBCs, red blood cells

Chari A, et al. Poster presented at: 2015 American Society of Hamatology (ASH); December 5-8, 2015; Orlando, FL, USA (Abstract 3571).

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[1,2]
- Daratumumab interference was identified when 100% of daratumumab-treated patients were panreactive during RBC panel testing[1,2]

Typical Indirect Coombs Test From a daratumumab-treated Patient[3]

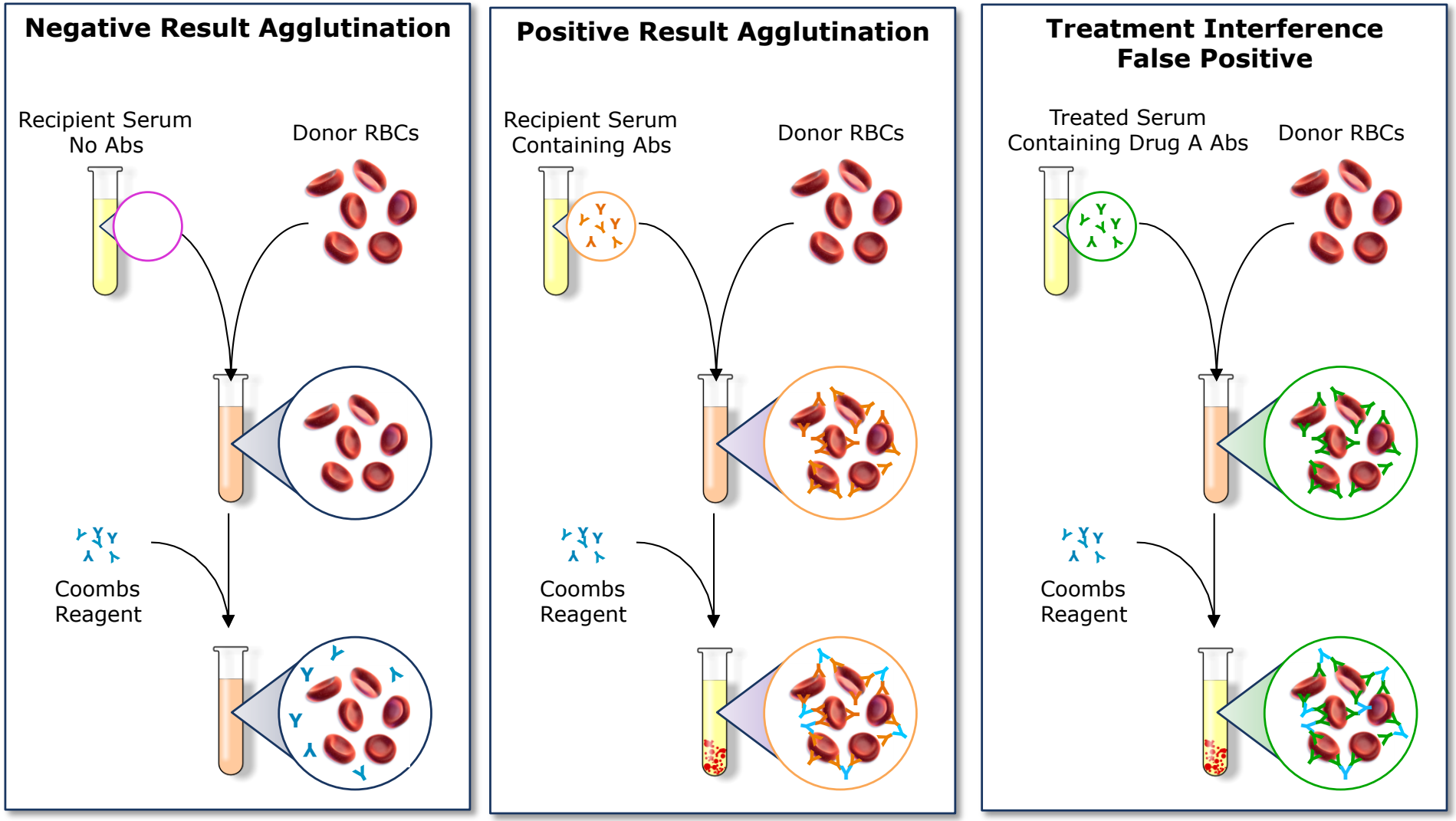


RBCs, red blood cells.

1. Chapuy et al. Transfusion. 2015;55(6 Pt 2):1545-54
2. Oostendorp et al. Transfusion. 2015;55(6 Pt 2):1555-62
3. Chari A, et al. Poster presented at: 2015 American Society of Hematology (ASH); December 5-8, 2015; Orlando, FL, USA (Abstract 3571).

RBCs, red blood cells

Treatment Interference With The Indirect Coombs Assay



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

What is the Clinical Impact of Daratumumab Interference?

Daratumumab Interference Is Clinically Manageable

- To date, **no clinically significant hemolysis** has been observed in patients receiving daratumumab, and **no transfusion reactions** have occurred in patients requiring RBC and whole blood transfusions (data on file)
- Chari et al (2015) conducted an analysis of RBC transfusions and transfusion-related adverse events in the SIRIUS study[1]
  - Forty-seven (38%) patients received a total of 147 transfusions of packed RBCs (PRBCs) and these transfusions were not associated with complications
- To **avoid unnecessary delays**, it is essential that **the blood bank** is **informed** that a patient will start a CD38 monoclonal antibody or that they will receive a sample from a CD38mAb-treated patient, so th'at appropriate protocols can be applied

RBC, red blood cell

Chari A et al. ASH 2015 (Abstract 3571) Poster presentation

Can daratumumab interference be mitigated?

Compatibility Testing Can Be Performed on Daratumumab-treated Patients (1)

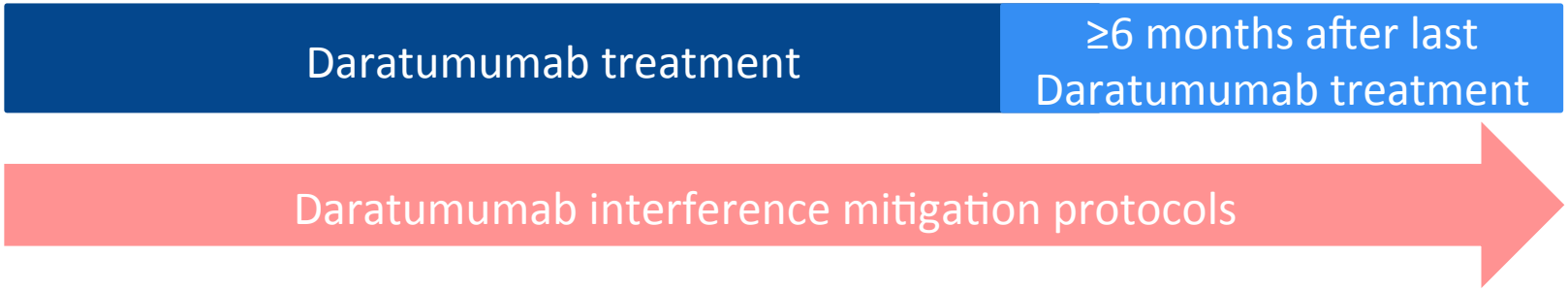
- Immunohematology labs and blood banks need to be made aware when patients are receiving CD38 mAbs
- Blood banks have been advised to use a variety of methods to help mitigate daratumumab interference
- If an emergency transfusion is required, non-crossmatched, ABO/RhD–compatible RBCs can be given, per local blood bank practices[2]

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

RBCs, red blood cells

Compatibility Testing Can Be Performed on Daratumumab-treated Patients (2)

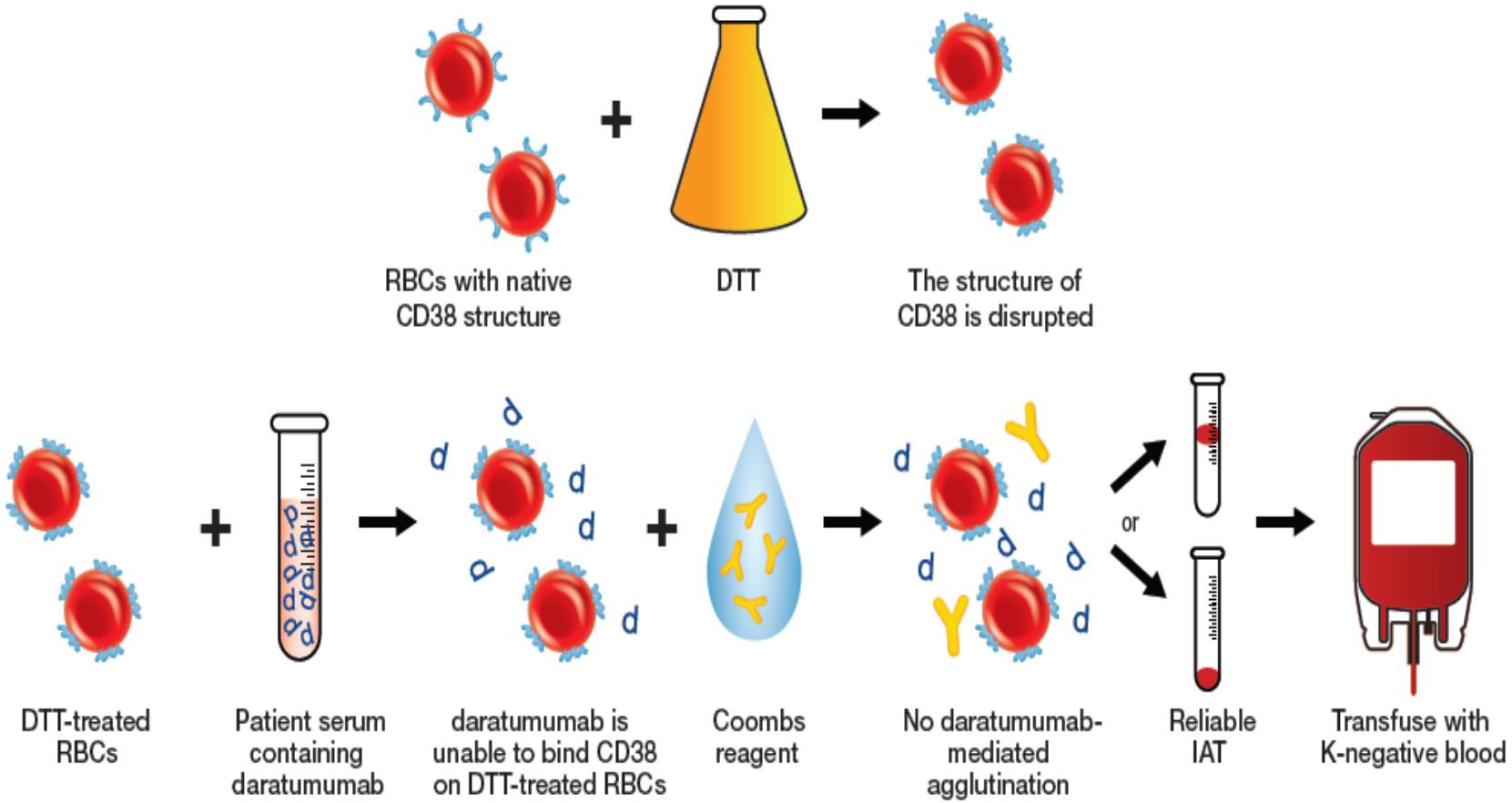
- If a patient's history of receiving daratumumab is not clearly communicated to the blood bank, delays in the release of blood products for transfusion may occur
  - Once treatment with daratumumab is discontinued, pan-agglutination may persist; the duration of this effect varies from patient to patient but may persist for up to 6 months after the last daratumumab infusion[1]. Therefore, patients should carry their Patient ID Card for 6 months after the treatment has ended
  - Mitigation methods should be used until pan-agglutination is no longer observed



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

Mitigating Daratumumab Interference:
Treat Reagent RBCs with DTT or Locally Validated Methods

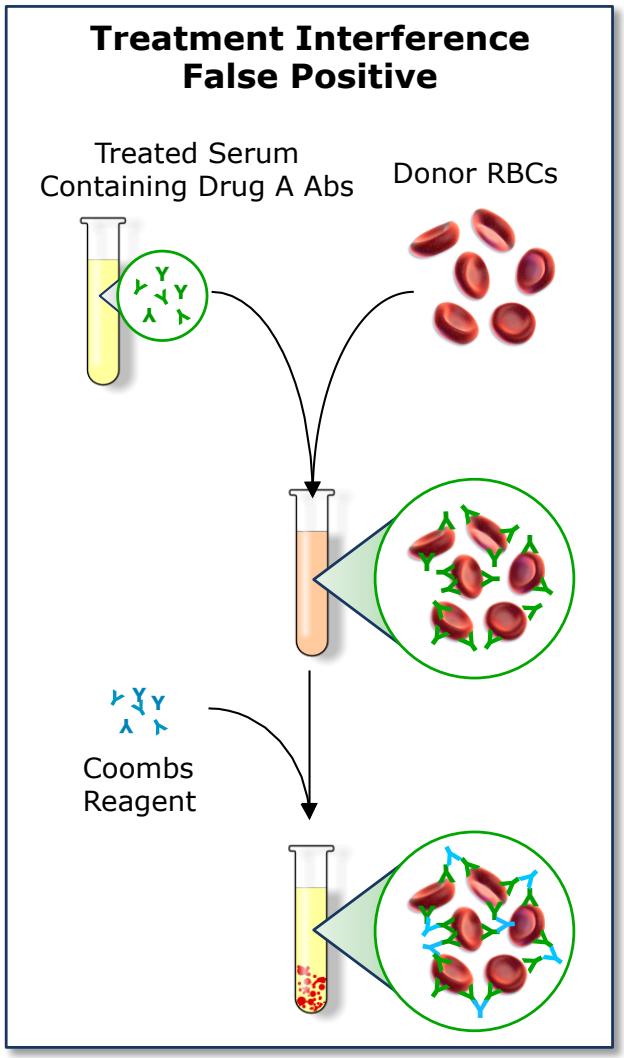
- Since the Kell blood group system is also sensitive to DTT treatment[2], K-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs

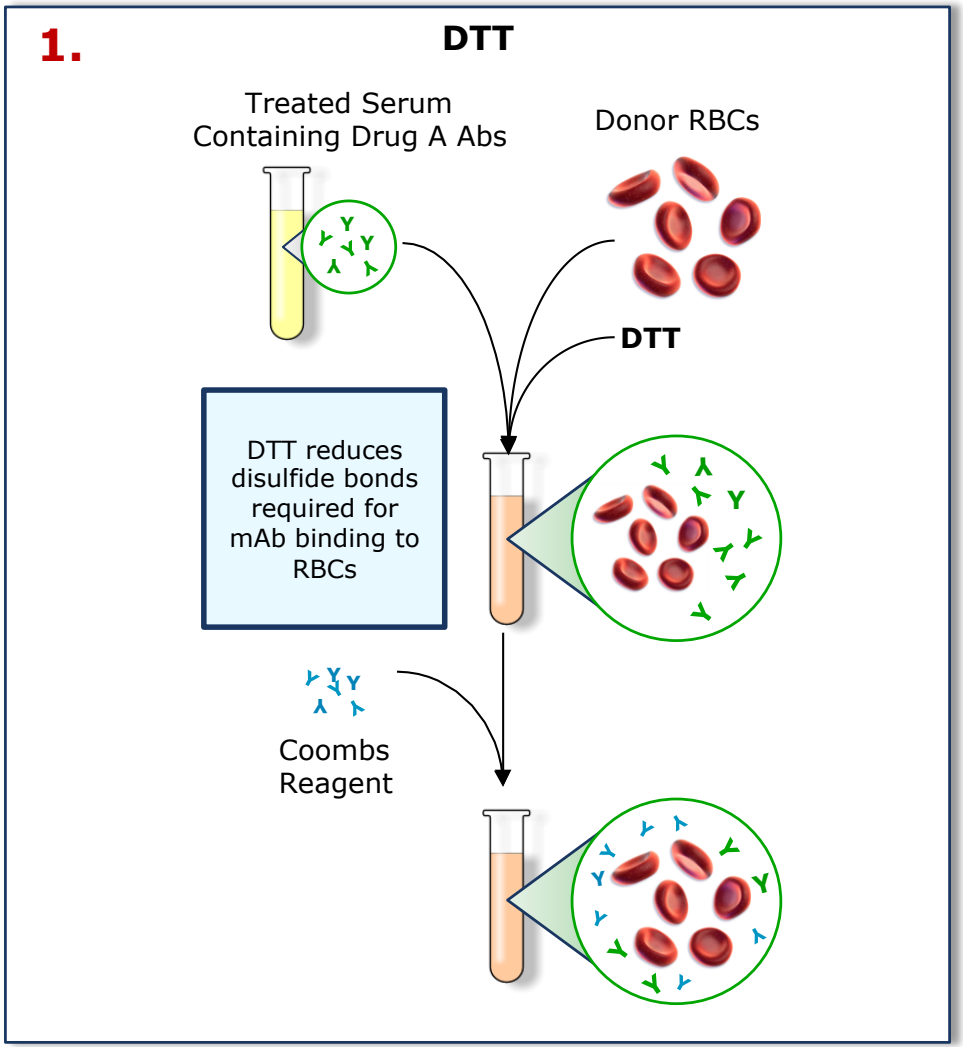


1. Chapuy et al. Transfusion. 2015;55(6 Pt 2):1545-54
2. Westhoff CM, Reid ME. Immunohematology. 2004;20(1):37-49

Potential Solution To Assay Interference

Methods for Mitigating Monoclonal Antibody Therapy Assay Interference

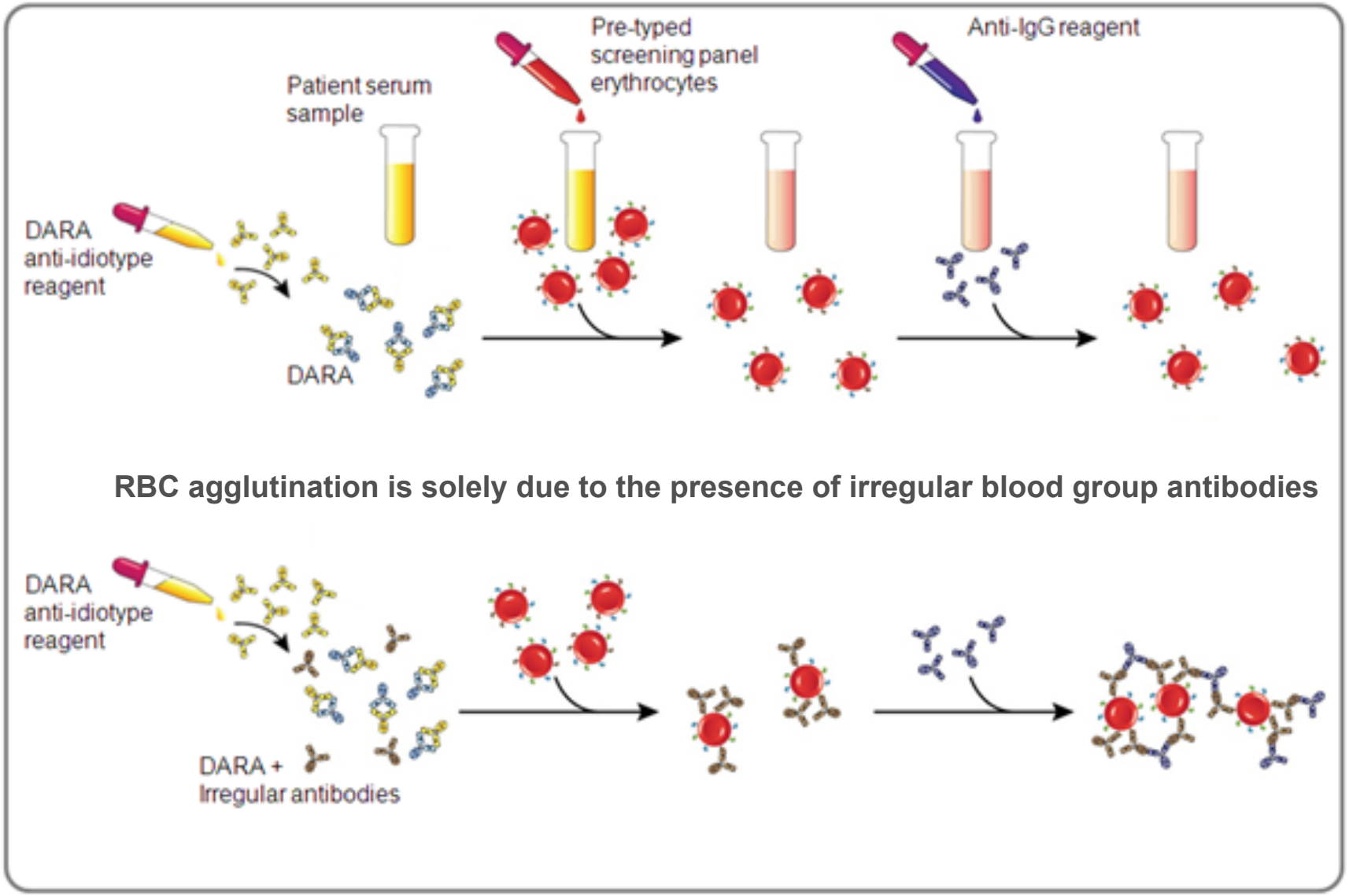




1. van de Donk Blood 2016;27(6):681–695; 2. van de Donk Immunol Rev 2016;270: 95–112

Potential Solution To Assay Interference: anti-idiotype

No RBC agglutination



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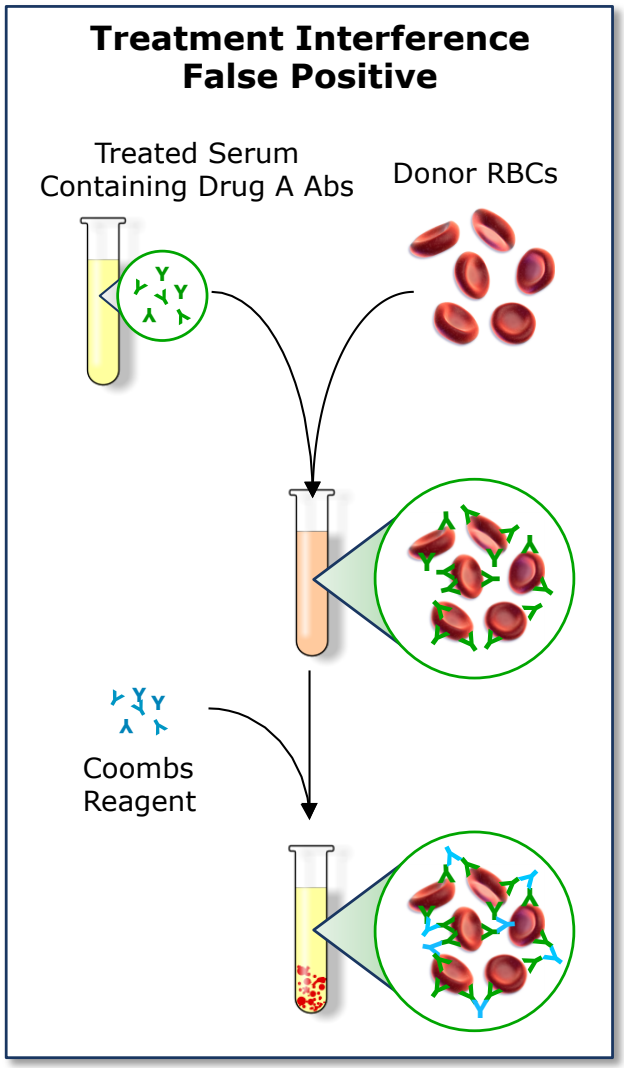

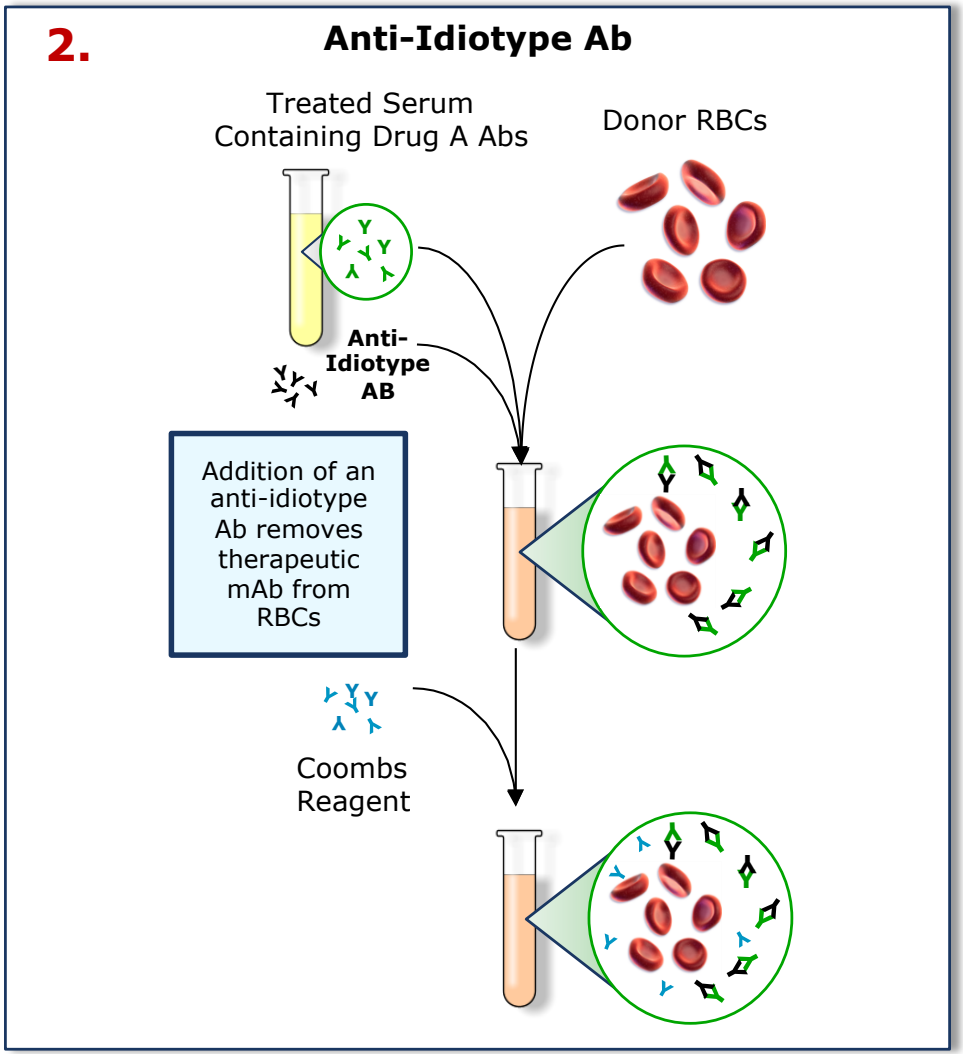

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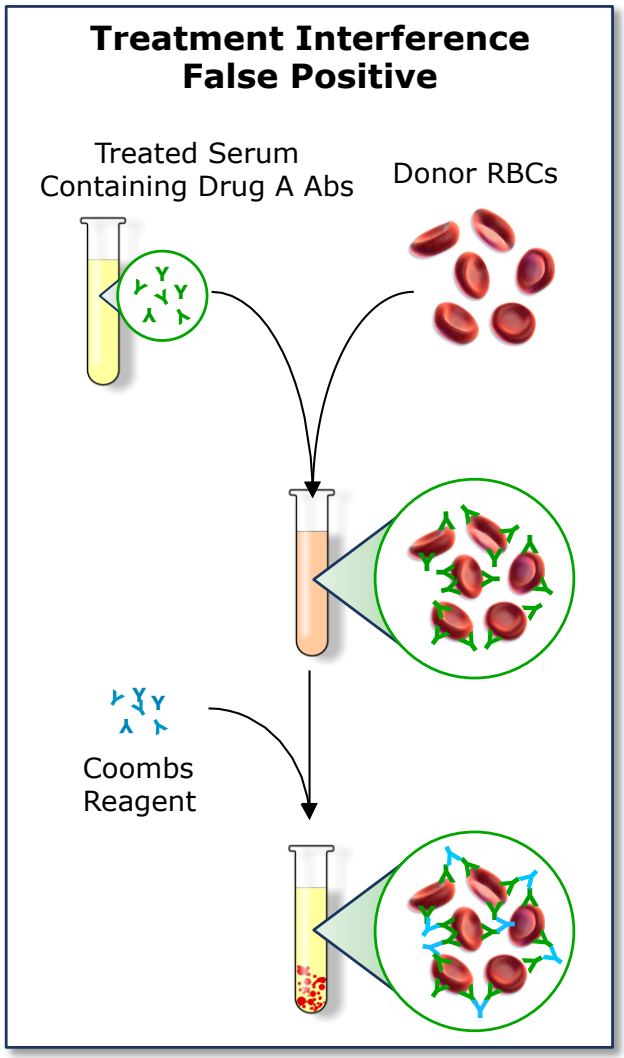
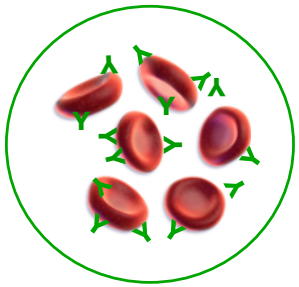


3. Phenotyping

(Phenotyping is a direct serological method for identifying expressed antigens that uses specific antibodies directed against known antigens.)



Phenotyping can be used as an alternative to antibody screening prior to the first infusion of CD38-targeting mAb

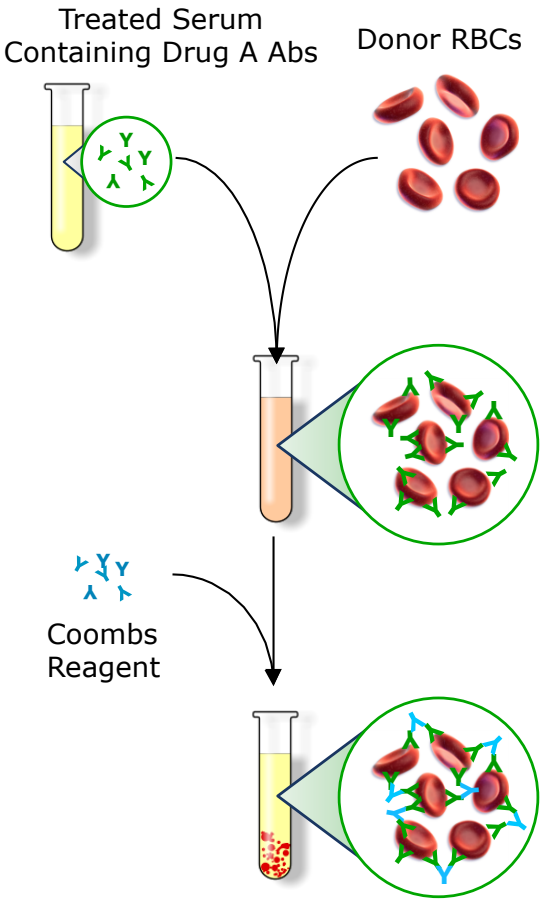
Phenotype after positive Indirect Coombs Assay/IAT to assess compatibility

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

Potential Solution To Assay Interference

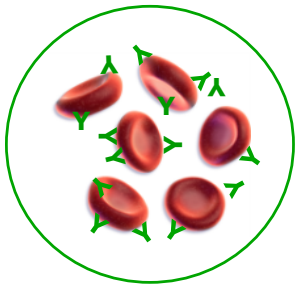
Methods for Mitigating Monoclonal Antibody Therapy Assay Interference

Treatment Interference False Positive



4. Genotyping

(Genotyping is an indirect method for identifying the antigens that an individual expresses (their phenotype) by assessing the genes that encode those antigens.)



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

Interference in the blood bank Conclusion: Methods to negate DARA

1. Serotyping / genotyping before first DARA infusion

2. Treating reagent RBCs with DTT→ panreactivity with the samples is eliminated
   - Disruption of limited number of blood group antigens including Kell

3. Adding anti-DARA idiotype (DARA neutralizing antibody) to the plasma of DARA-treated patients eliminates positive antibody screen reactions
   - Simple but not available

What Should I Communicate to My Daratumumab-treated Patients?

Conclusions

- Daratumumab is a human monoclonal antibody for the treatment of MM[1]*
- Daratumumab binds to RBCs and interferes with blood bank compatibility tests, including the antibody screening and crossmatching[2] (both indirect Coombs tests) that are part of a routine pretransfusion work up
- To date, no clinically significant hemolysis has been observed in patients receiving daratumumab and no transfusion reactions have occurred in patients requiring red blood cell or whole blood transfusions (data on file)
- If a patient's history of receiving daratumumab is not clearly communicated to the blood bank, delays in the release of blood products for transfusion may occur
- To ensure that your patient receives a timely transfusion, type and screen patients prior to starting daratumumab and inform the blood bank that they will receive a sample from a daratumumab-treated patient. Phenotyping may be considered prior to starting daratumumab treatment as per local practice

*Currently only approved by FDA in the US and under regulatory review in Europe and other countries

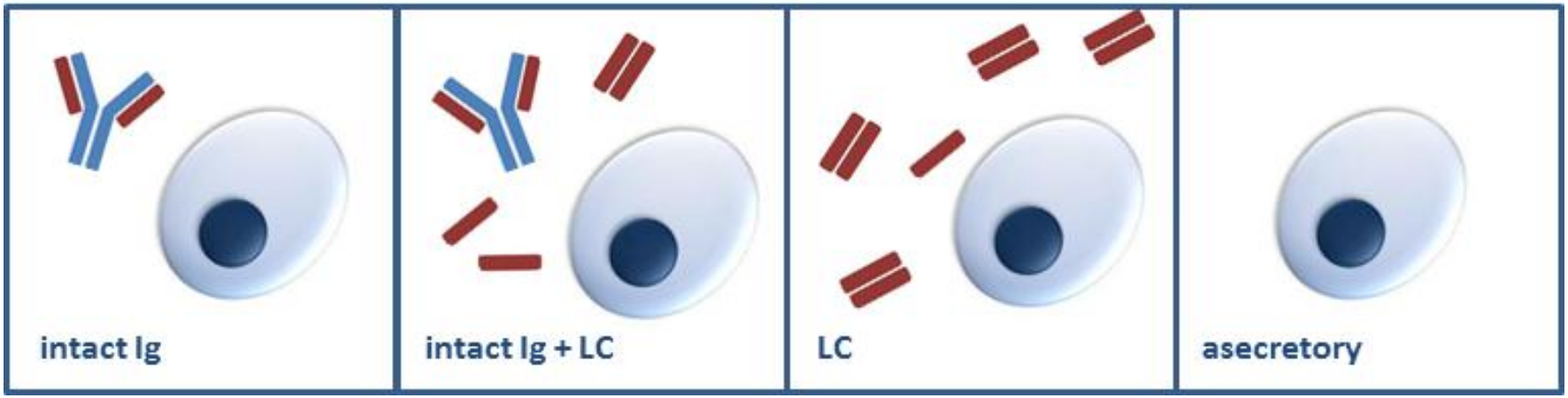
1. de Weers M et al. J Immunol. 2011;186:1840-8.
2. Chapuy CI et al. Transfusion. 2015;55(6Pt2):1545-1554.

Assessment of response with IgG monoclonal antibodies

Assessing treatment response in multiple myeloma

- Multiple myeloma is characterized by the neoplastic proliferation of a single clone of plasma cells

- Majority of patients - monoclonal immunoglobulin (M-protein) can be detected in the serum and urine. Around 15-20% of myeloma cells secrete light chains only and a minority (3%) of patients suffer from so-called asecretory myeloma and have unremarkable serum/urine electrophoresis/ immunofixation as well as unremarkable light-chain findings.



1. Kyle R et al. Lancet Haematol 2014;1(1):e28-e36
2. Rajkumar V et al. Lancet Oncol 2014;15(12):e538-48.

Uniform response criteria

- Uniform response criteria by International Myeloma Working Group (IMWG) - used to measure the effect of treatment

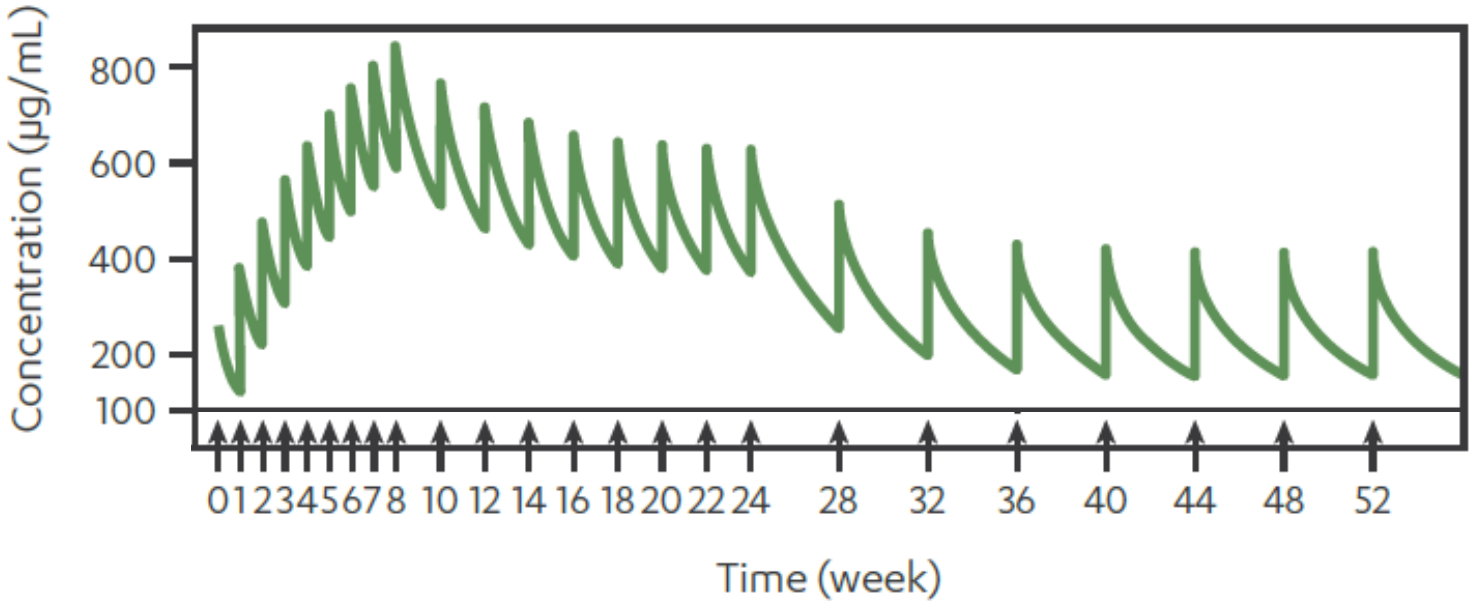
- Response to treatment can be measured via quantitative or semiquantitative changes in the amount of M-protein in serum or urine (preferred), the free-light chain ratio in the serum or by investigating plasma cell populations in the bone marrow by conventional light microscopy, flow cytometry or PCR techniques

- Patients should be evaluated before starting a new treatment and at the beginning of each new treatment cycle to determine how their disease is responding to therapy. Response/progression of disease should be confirmed in a 2nd evaluation before starting a new treatment

1. Durie BG et al. 2006 Sep;20(9):1467-73
2. Rajkumar SV et al. Blood. 2011 May 5;117(18):4691-5.

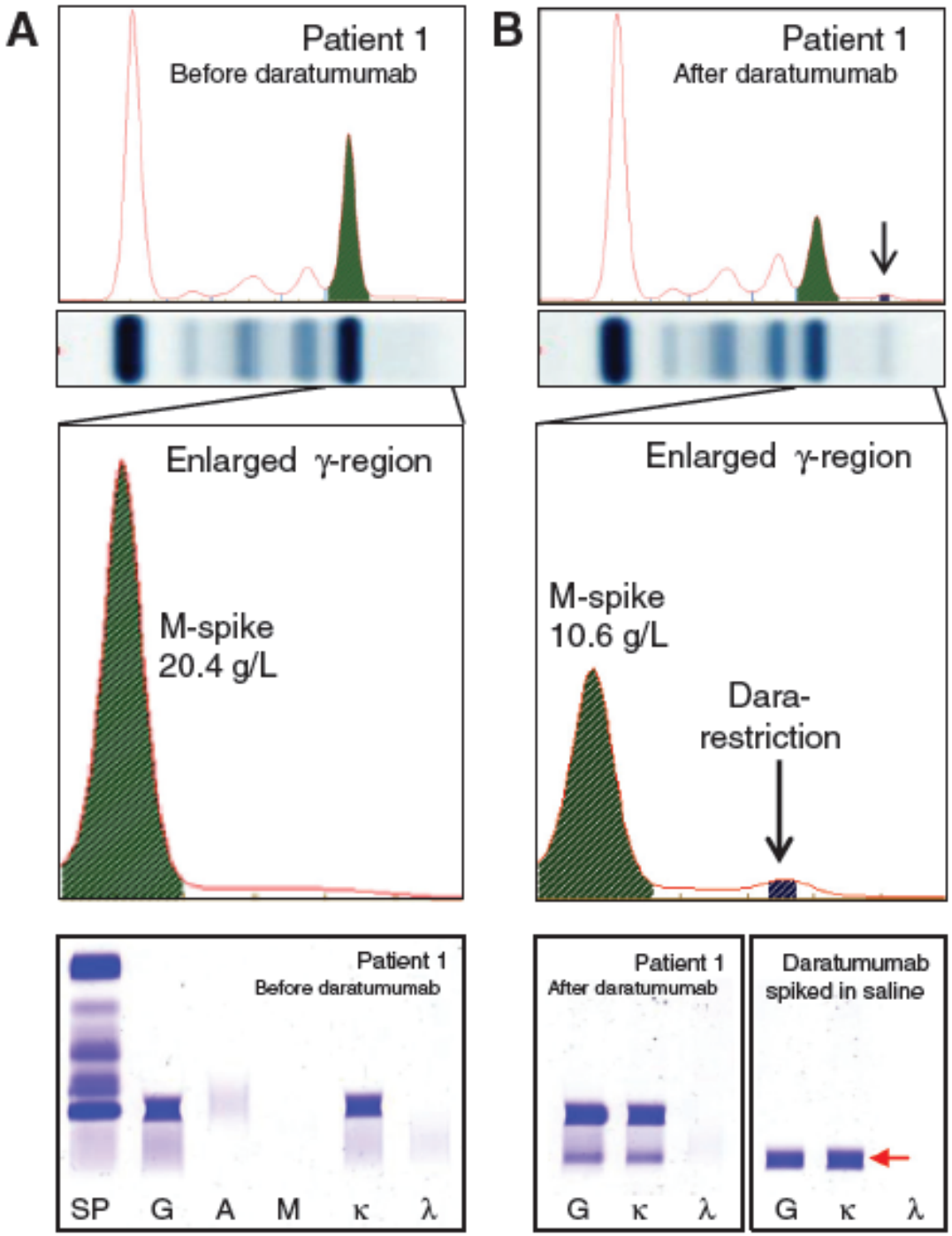
Daratumumab level

Representative PK profile of DARA for the recommended dose and schedule



Arrows indicate that a dose was administered.

1. Xu XS, et al. Poster presented at: 2015 American Society of Hematology (ASH); December 5-8, 2015; Orlando, FL, USA (Abstract 4254).



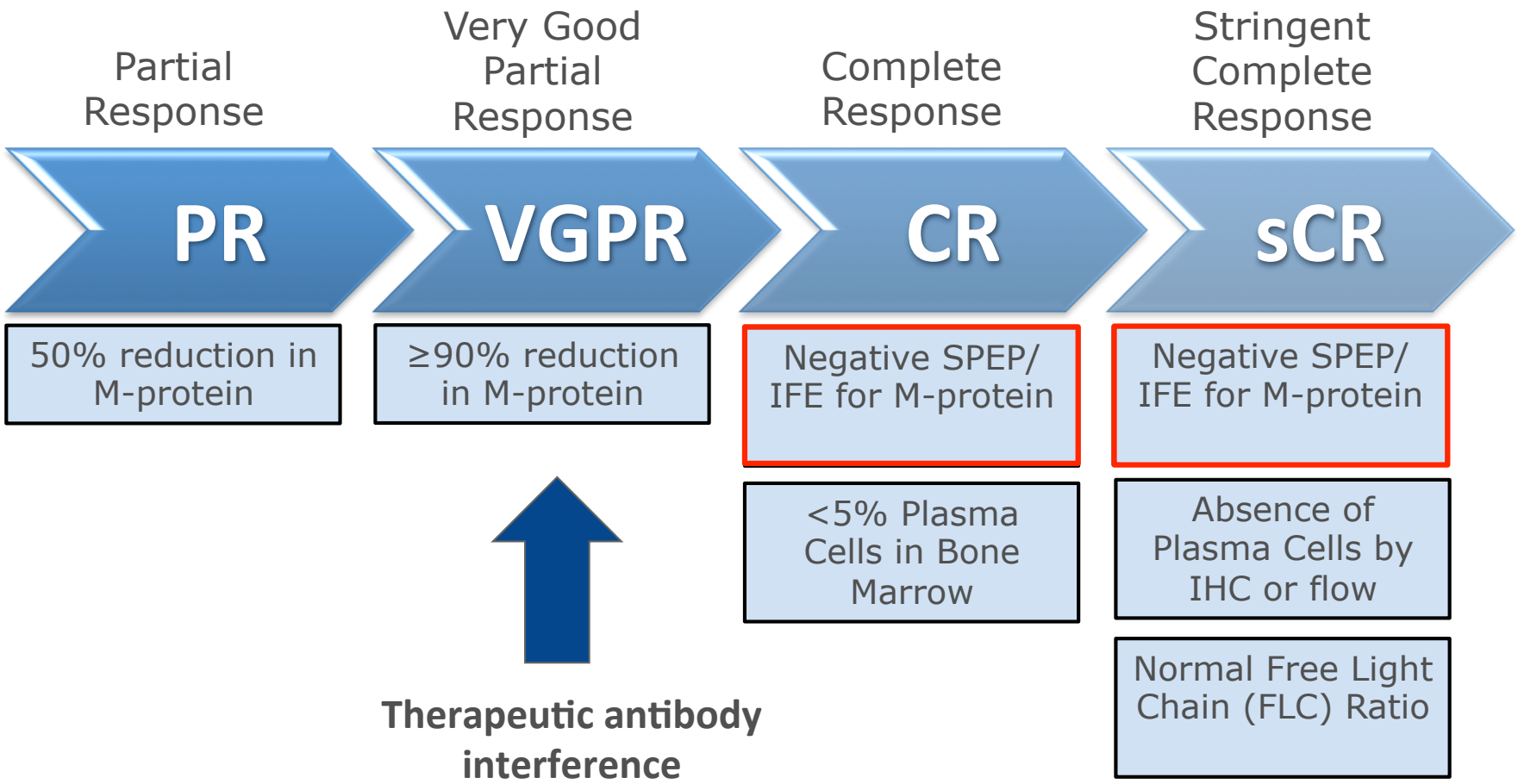
1. Van De Donk Clin Chem Lab Med 2016;54:1105-9.

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
- Interference depends on isotype of the patient
- Daratumumab, Elotuzumab, Isatuximab and MOR202 are IgG mAbs
- Daratumumab can be detected by serum IFE and SPEP and may interfere with endogenous M-protein detection in MM samples
  - At the recommended dosing schedule (16 mg/kg weekly for 8 weeks, then every 2 weeks for 16 weeks, and every 4 weeks thereafter), daratumumab reaches peak serum concentrations of approximately 915 µg/mL (0.915 g/L) at the end of the weekly dosing period, making it readily detectable on most SPE/IFE assays

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 2016 ;127(6):681-695;
McCudden C, et al. Clin Chem Lab Med 2016; aop; DOI 10.1515/cclm-2015-1031

IMWG response criteria requires a negative IFE to declare patients CR



McCudden C, et al. Poster presented at: 2015 American Society of Clinical Oncology (ASCO); May 29-June 2, 2015; Chicago, IL, USA.

Assessment strategies for serological responses during daratumumab therapy

- Daratumumab has demonstrated clinical responses that deepen over time, necessitating evaluation of CR/sCR by SPEP/IFE

- Approximately 50% of patients with MM produce an IgGκ M-protein. As an immunoglobulin, daratumumab may be detected by iFe and may co-migrate with endogenous M-protein in a subset of patients

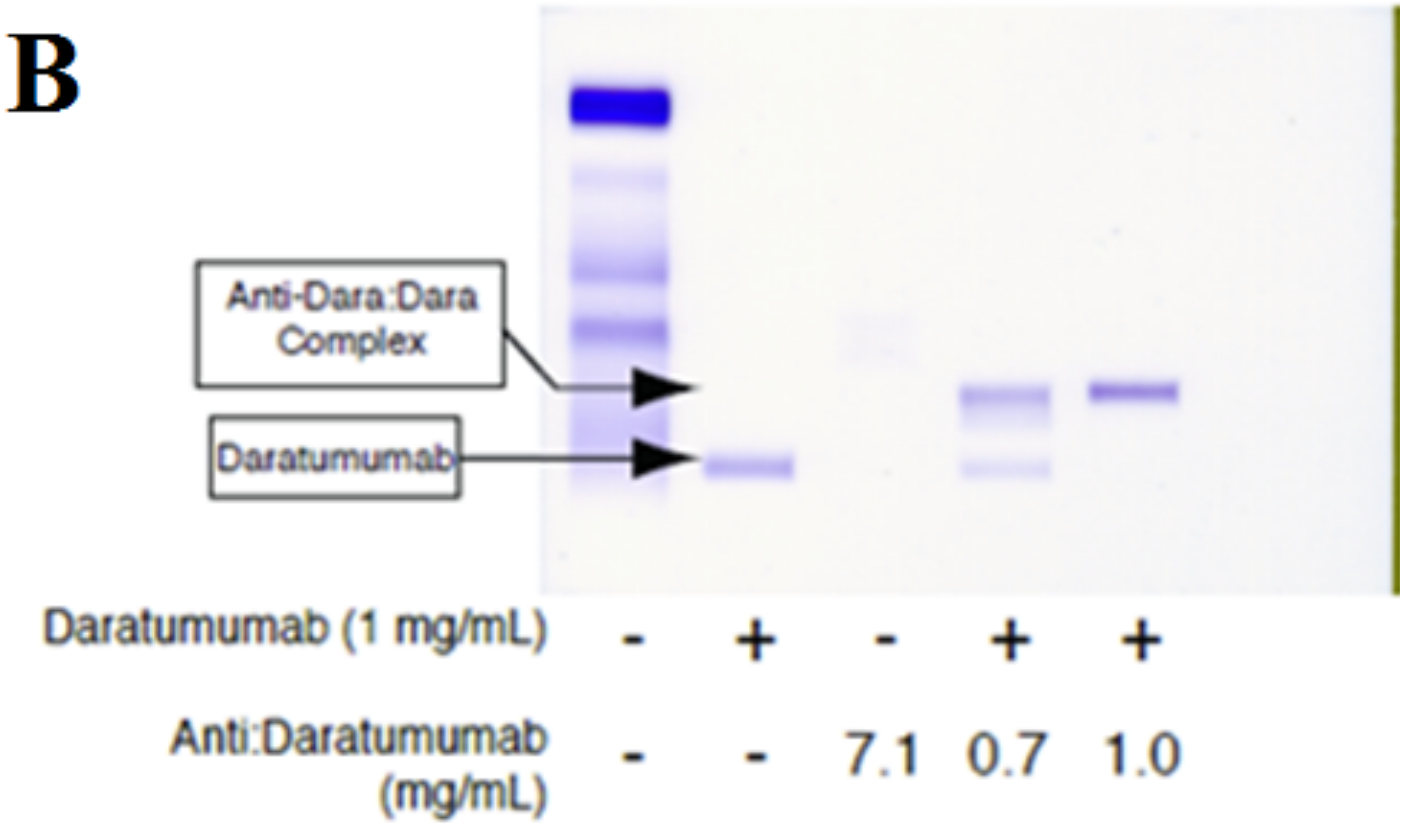
McCudden Clin Chem Lab Med 2016; aop; DOI 10.1515/cclm-2015-1031;
McCudden C, et al. Poster presented at: 2015 American Society of Clinical Oncology (ASCO); May 29-June 2, 2015; Chicago, IL, USA.

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

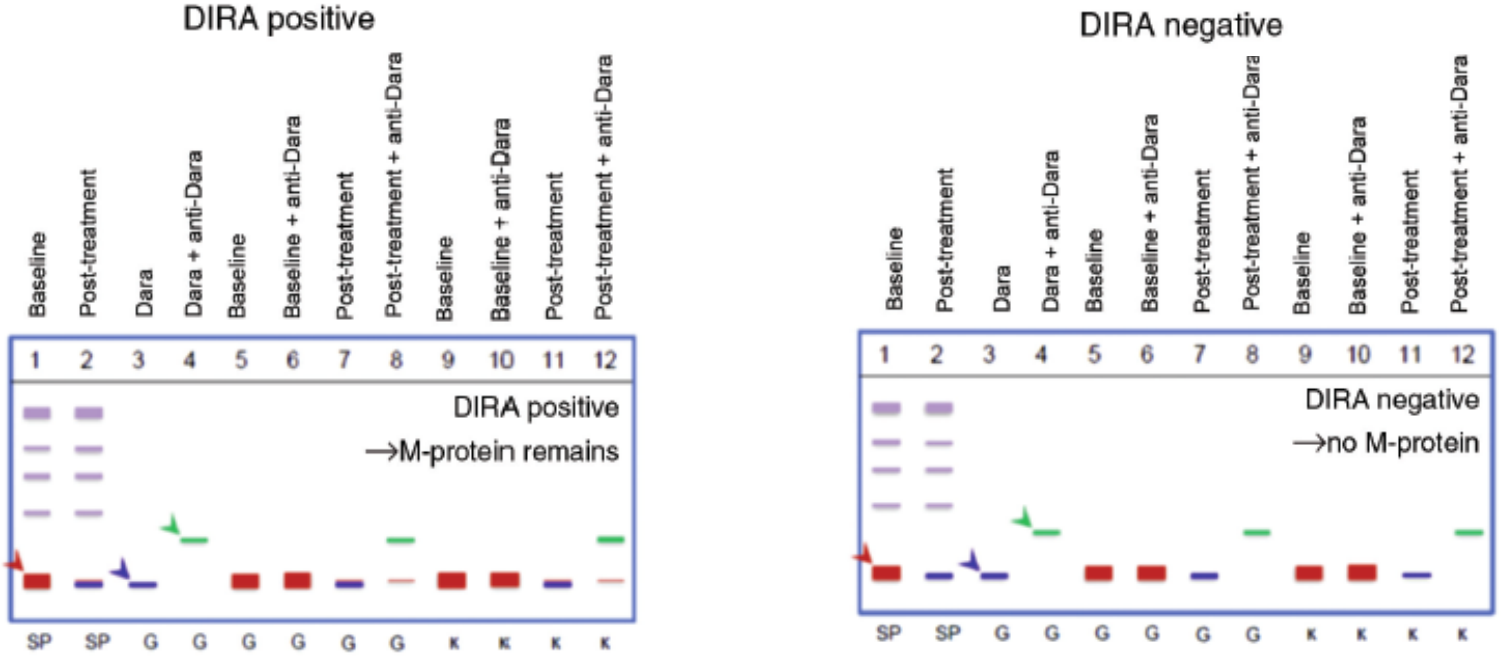
McCudden C, et al. Clin Chem Lab Med 2016; aop; DOI 10.1515/cclm-2015-1031

DIRA



McCudden C, et al. Clin Chem Lab Med 2016; aop; DOI 10.1515/cclm-2015-1031

Clinical Assay to Mitigate Daratumumab Interference (cont)



- Baseline (prior to treatment) serum samples are run ± anti-daratumumab next to serum samples from a post-treatment time point with suspected daratumumab interference, ± anti-daratumumab, to determine whether the remaining M-protein band shifts completely with antidaratumumab
- Lanes 5–8 use IgG antisera and lanes 9–12 use κ antisera for staining and fixation. DIRA positive, similar to IFE positive, indicates that endogenous M-protein (in red, and indicated by a red arrow in lane 1) remains. DIRA negative, similar to IFE negative, indicates that only daratumumab (in blue, and indicated by a blue arrow in lane 3) is remaining and endogenous M-protein is no longer detected. The daratumumab-anti-daratumumab shifted complexes are shown in green, and indicated by a green arrow in lane 4

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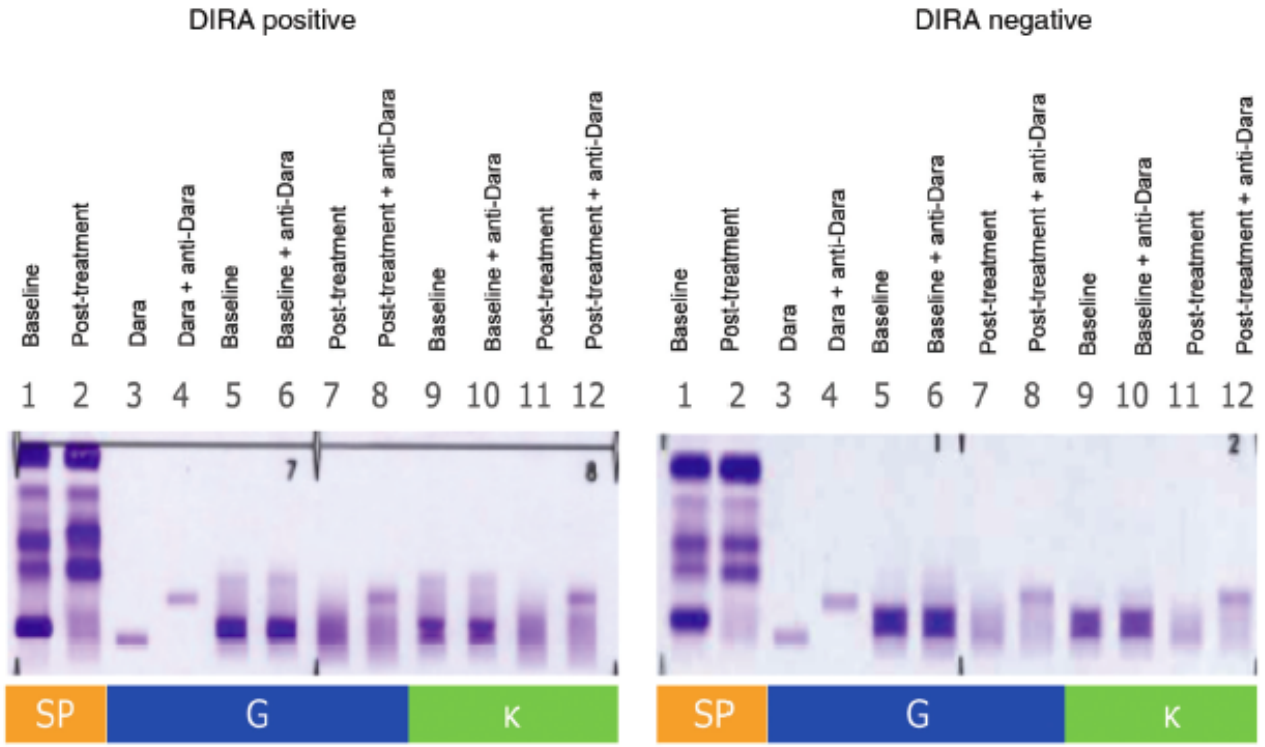
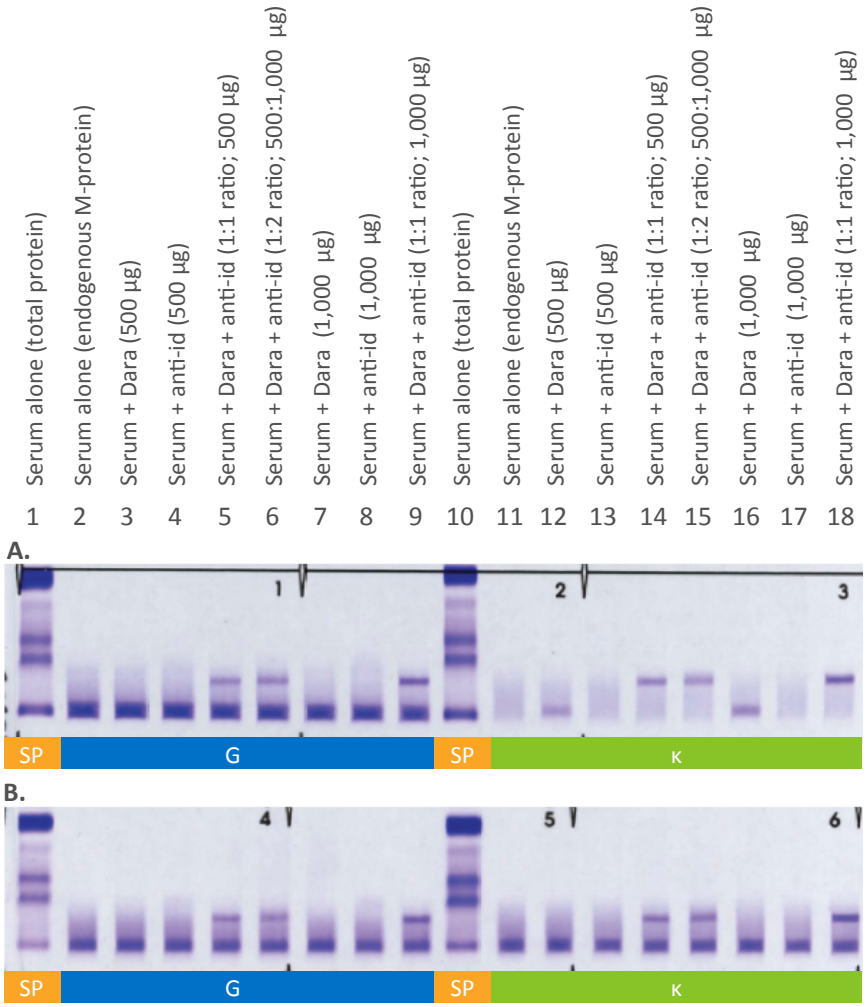
Daratumumab IFE Reflex Assay: DIRA



- The DIRA template used daratumumab ±anti-idiotype as controls for migration of the therapeutic antibody and the daratumumab–anti-idiotype shifted complexes.
- Baseline and post-treatment serum ±anti-idiotype were compared to determine whether M-protein remained after shifting daratumumab.
- DIRA-positive results showed M-protein, whereas DIRA-negative results showed only a shift in daratumumab but no remaining M-protein (lanes 8 and 12)

McCudden C, et al. Clin Chem Lab Med 2016; aop; DOI 10.1515/cclm-2015-1031

DIRA: Validation



- In all of the tested samples, DIRA distinguished between daratumumab and residual M-protein in commercial serum samples spiked with daratumumab and in daratumumab-treated patient samples. The DIRA limit of sensitivity was 0.2 g/L daratumumab, using spiking experiments.
- Results from DIRA were reproducible over multiple days, operators, and assays.
- The anti-daratumumab antibody was highly specific for daratumumab and did not shift endogenous M-protein.
- In conclusion, DIRA was highly specific, sensitive, and reproducible both in commercial samples spiked with daratumumab and in clinical samples from daratumumab-treated patients.

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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)

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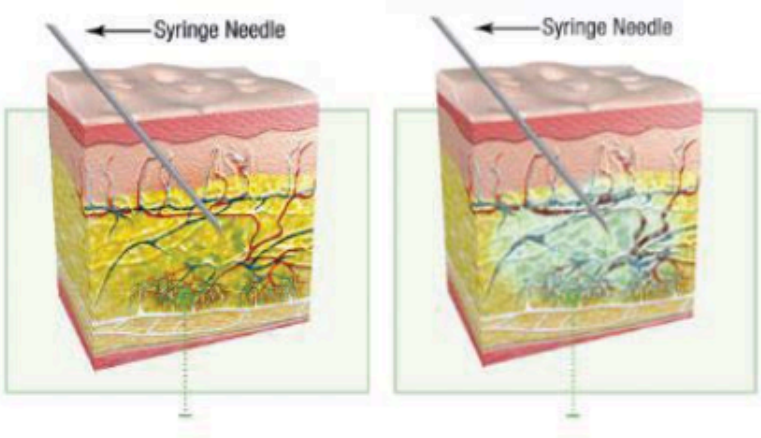
Recombinant Human Hyaluronidase

- 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 SC 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 11/8/2016.
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.

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)

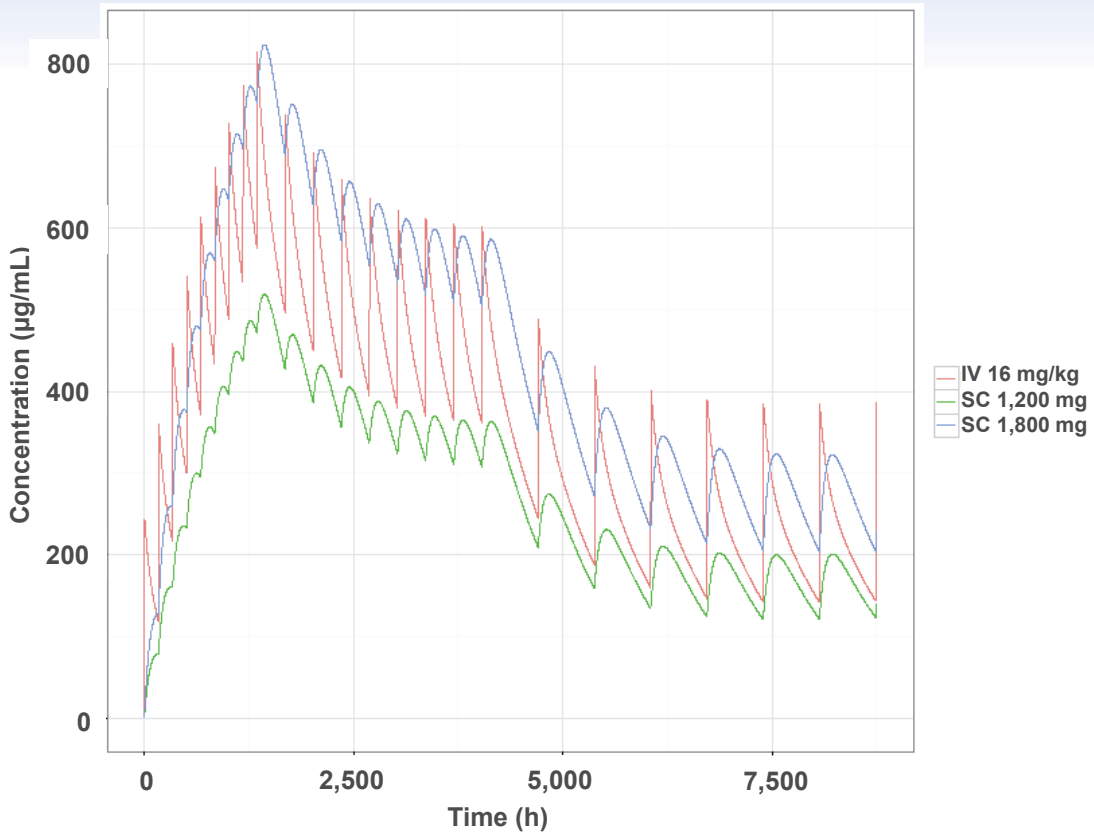
Pre-[b]/post-infusion medication
- Acetaminophen, diphenhydramine, montelukast, and methylprednisolone

RRMM, relapsed or refractory multiple myeloma; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; 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.

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 QW in Cycles 1 to 2, Q2W in Cycles 3 to 6, and Q4W thereafter.

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

Low IRR incidence and severity with DARA SC

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

GESTIONE DEGLI ANTICORPI MONOCLONALI NELLA PRATICA CLINICA

In qualità di Relatore al Convegno

«Il Mieloma Multiplo – Viareggio 29 marzo 2017»

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 18,19 del Reg. Applicativo dell'Accordo Stato-Regione del 12 aprile 2012, per conto dello Studio E.R. Congressi s.r.l., la Dr.ssa Letizia Canepa dichiara che negli ultimi due anni NON ha avuto alcun rapporto di finanziamento con soggetti portatori di interessi commerciali in campo sanitario