ONCOEMATOLOGIA TRA SOSTENIBILITA' E ADERENZA

Padova, 22 Marzo 2019

SAFETY DEI TRATTAMENTI NEI PAZIENTI AD ALTO RISCHIO CITOGENETICO

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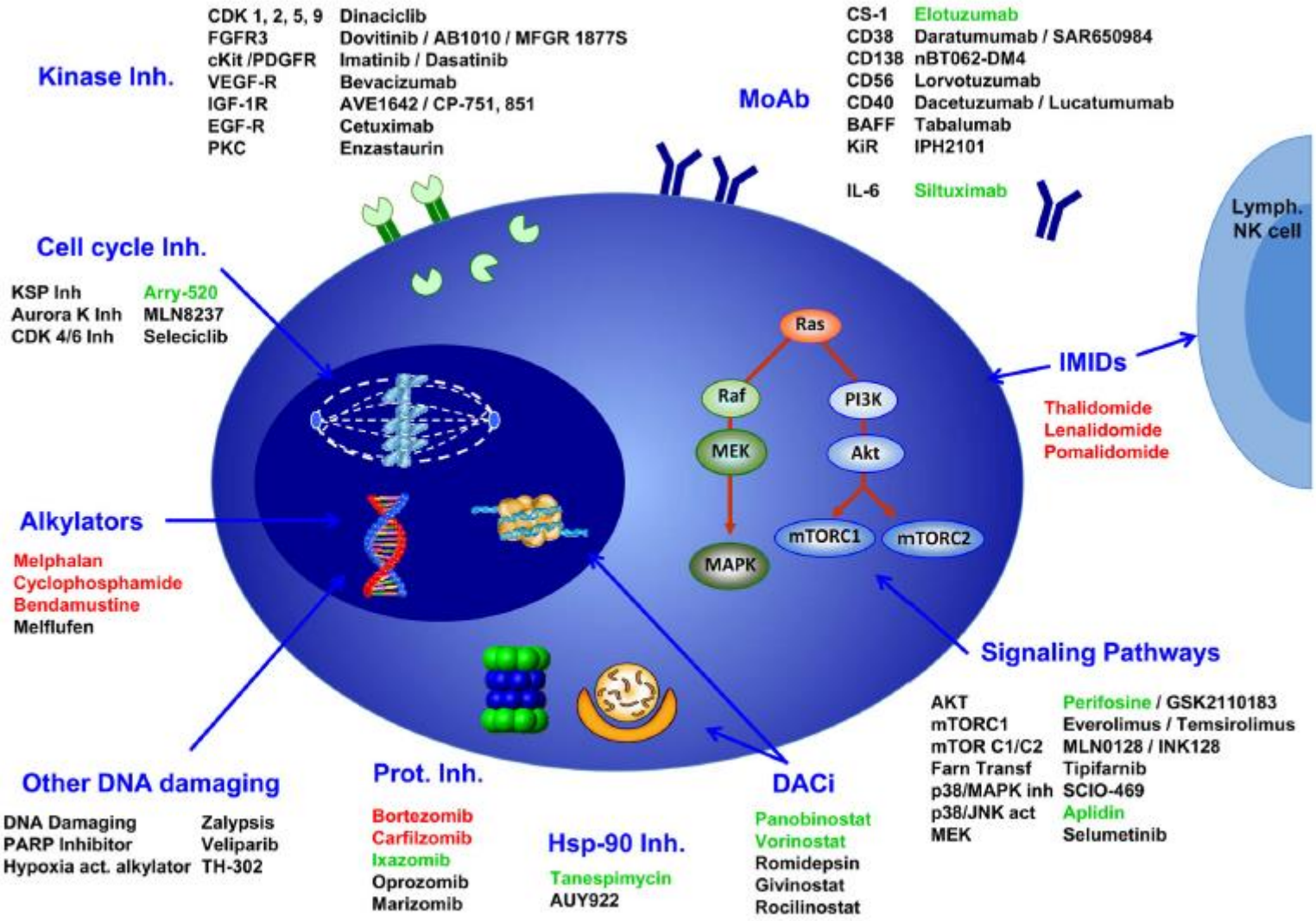


Figure 1. Schematic representation of the main targets in MM plasma cells and the drugs tested against them

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 1/2/3
	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

DARATUMUMAB

INDICAZIONI:

- IN MONOTERAPIA PER IL TRATTAMENTO DI PAZIENTI ADULTI CON MM RECIDIVATO O REFRATTARIO, LE CUI TERAPIE PRECEDENTI ABBIANO INCLUSO UN INIBITORE DEL PROTEASOMA E UN IMMUNOMODULANTE, E CHE ABBIANO MOSTRATO PROGRESSIONE DELLA MALATTIA DURANTE L'ULTIMA TERAPIA

- IN ASSOCIAZIONE CON LENALIDOMIDE E DESAMETASONE, O BORTEZOMIB E DESAMETASONE, PER IL TRATTAMENTO DI PAZIENTI ADULTI CON MM CHE ABBIANO RICEVUTO ALMENO UNA PRECEDENTE TERAPIA

- IN ASSOCIAZIONE CON BORTEZOMIB, MELPHALAN, PREDNISONE PER IL TRATTAMENTO DI PAZIENTI ADULTI CON MM DI NUOVA DIAGNOSI NON ELEGGIBILI AL TRAPIANTO AUTOLOGO DI CELLULE STAMINALI

Monoclonal Antibodies for Multiple Myeloma: 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

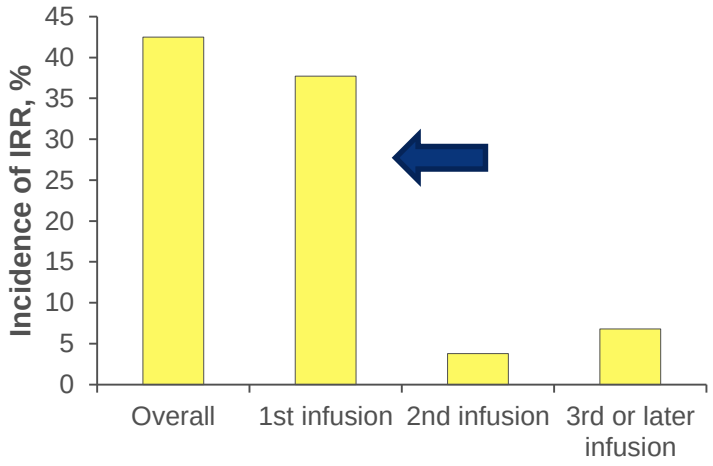
Infusion related reactions (IRRs) ≥ 5%

	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.

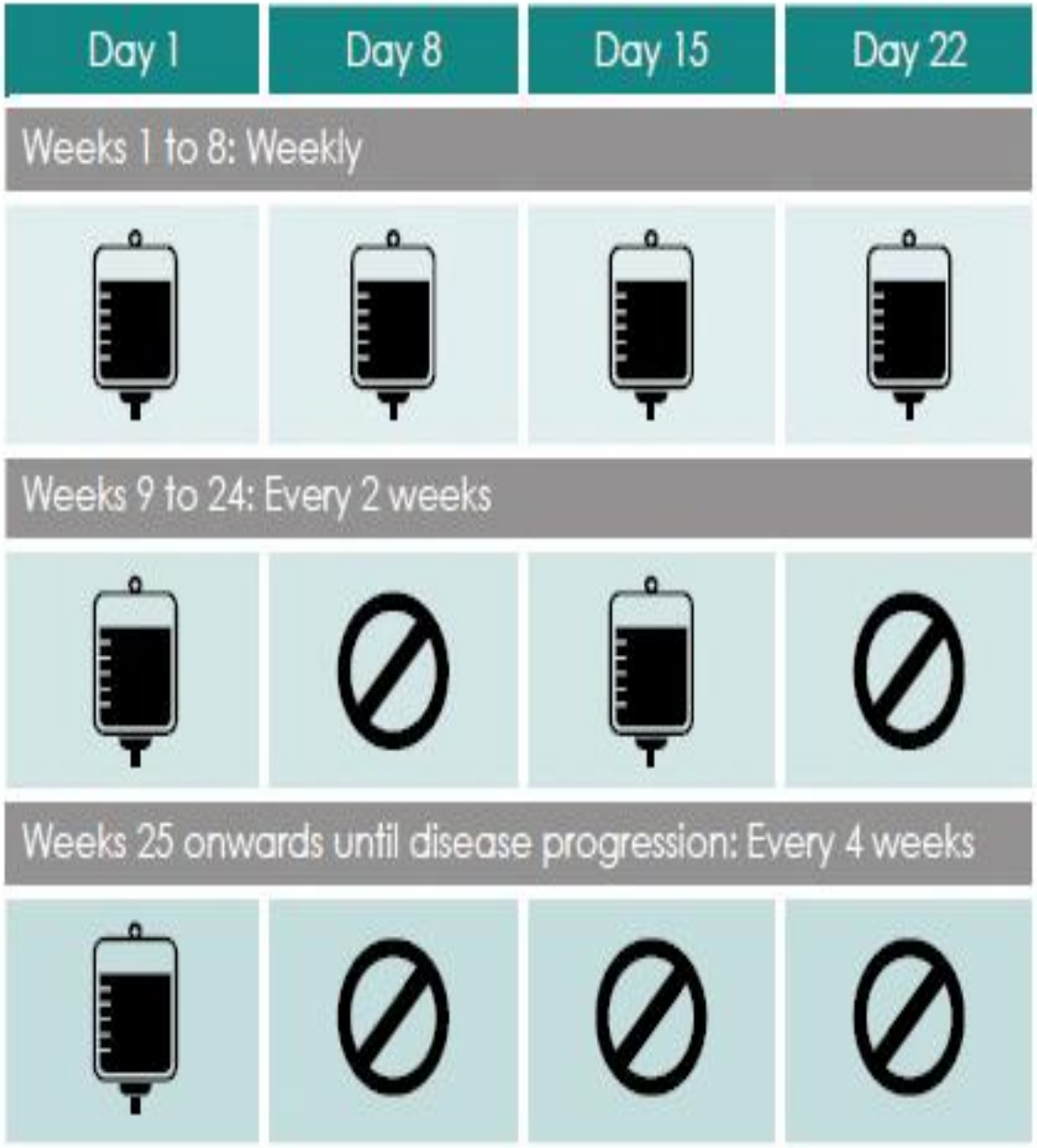
IRRs were observed in 48% of patients and those observed in ≥ 5% of patients were mainly respiratory conditions

- **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.

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)

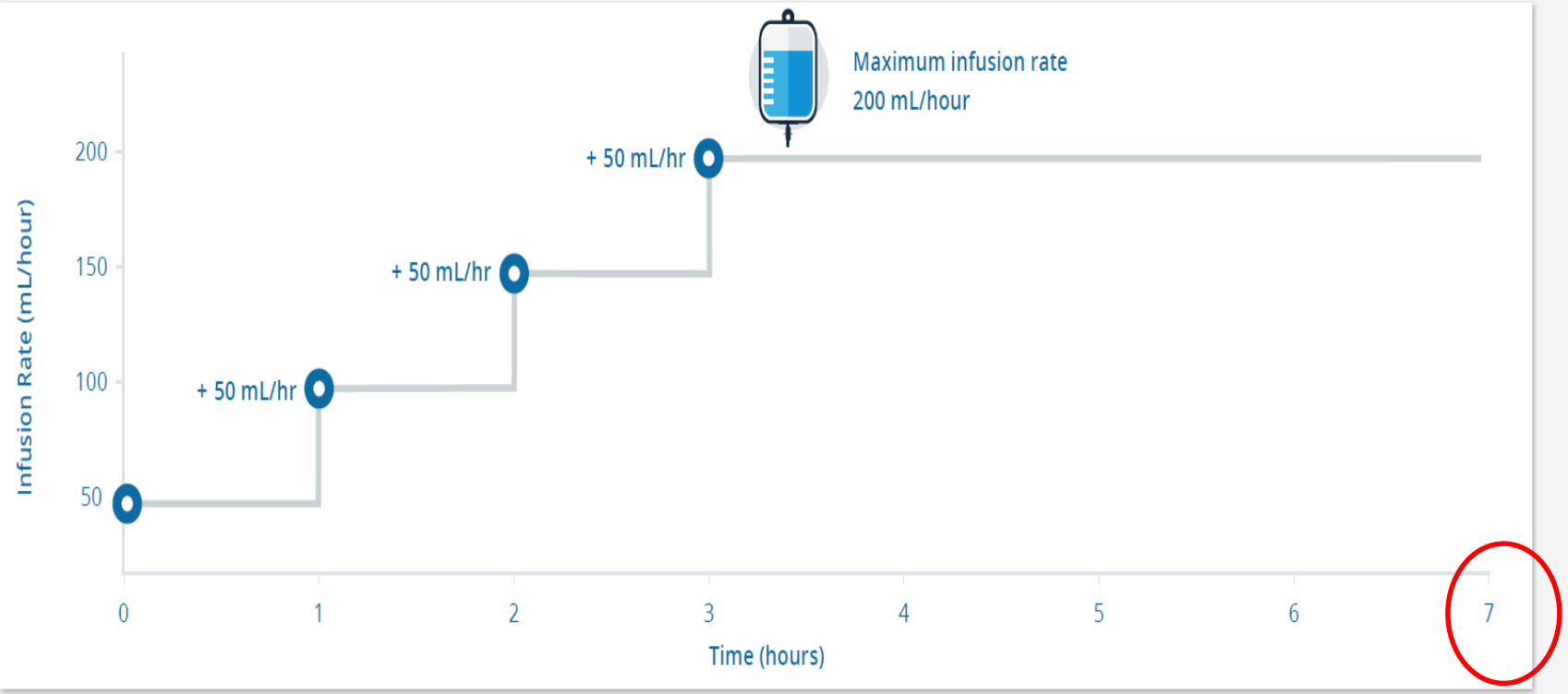
First infusion

Dilution volume
1,000 mL

Initial infusion rate (first hour)
50 mL/hour

Increments of infusion rate
50 mL/hour every hour

Maximum infusion rate
200 mL/hour



**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].*

First infusion

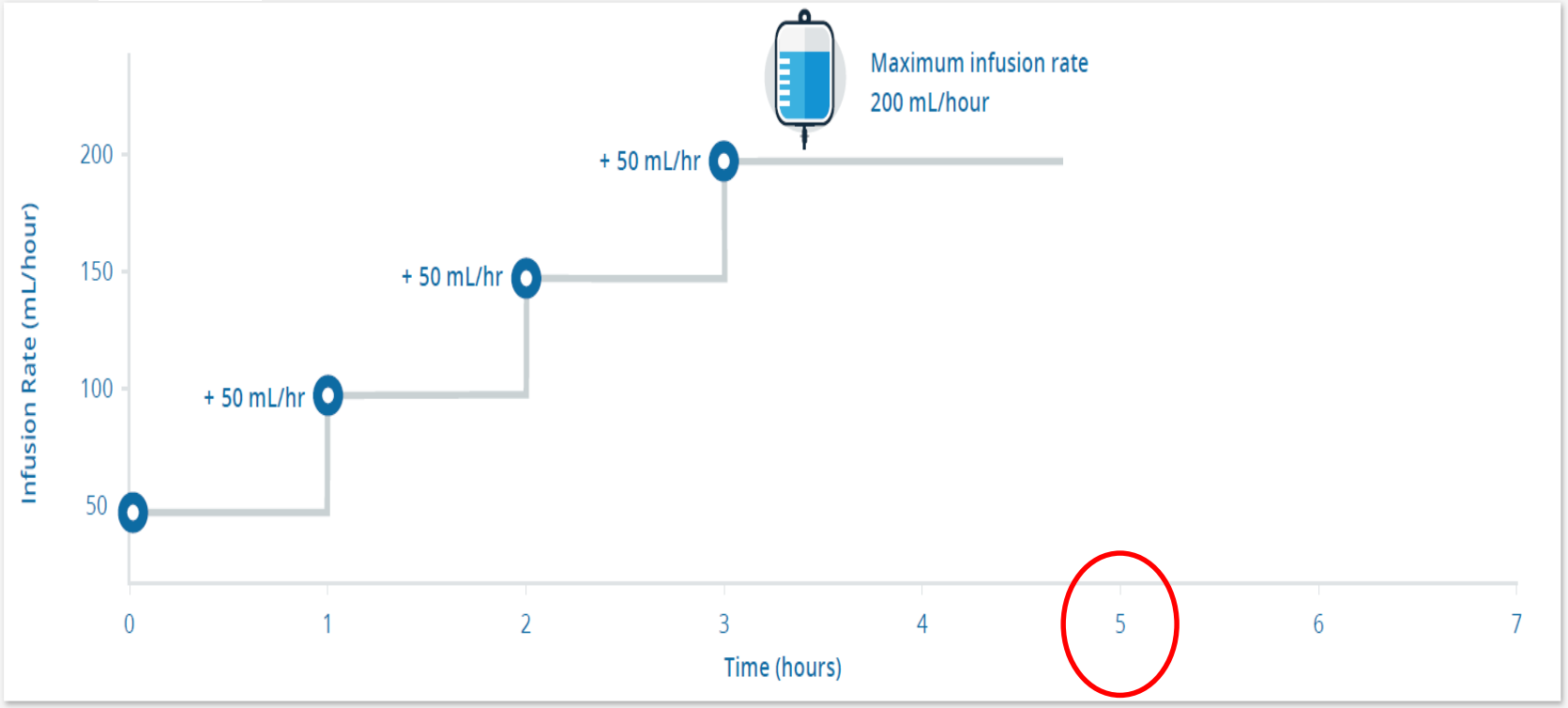
In fractionated dose (8 mg/Kg/die per due giorni consecutivi)

Dilution volume
500 ml

Initial infusion rate (first hour)
50 mL/hour

Increments of infusion rate
50 mL/hour every hour

Maximum infusion rate
200 mL/hour



**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].*

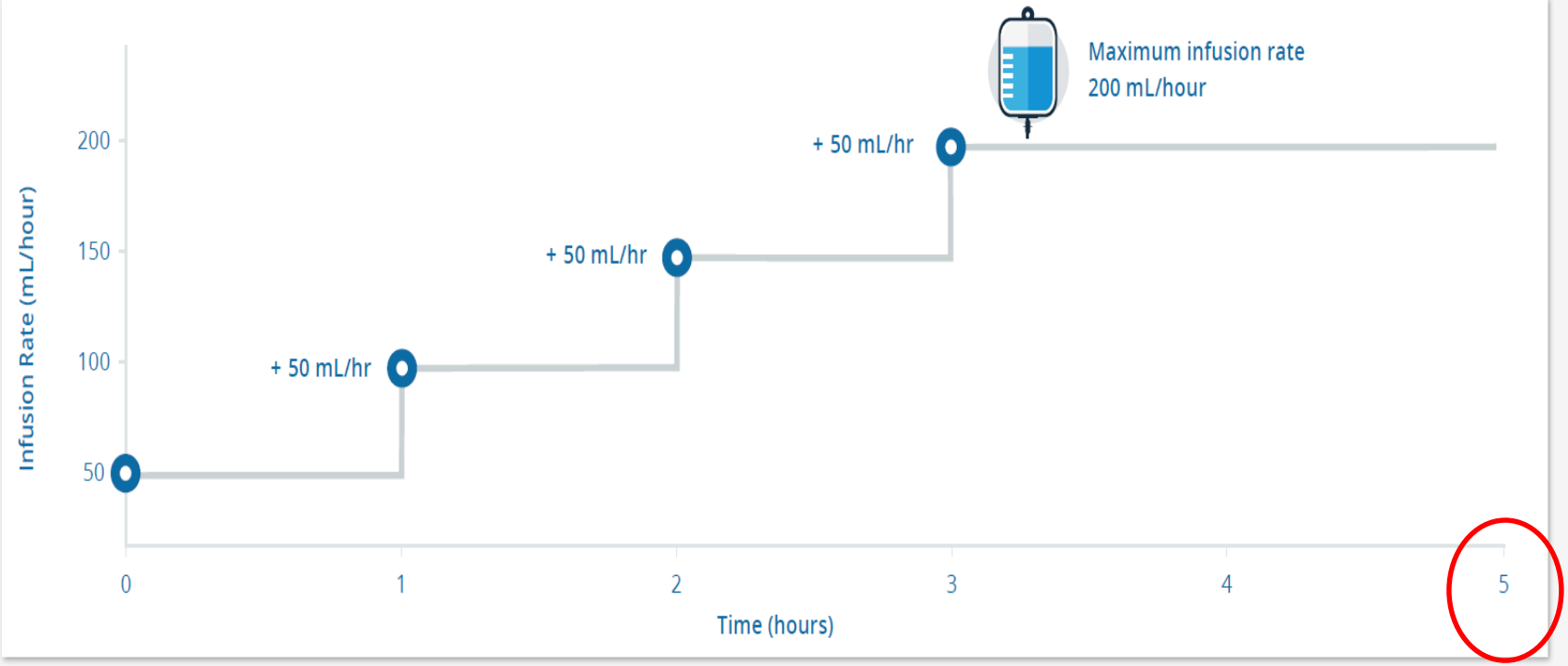
Second infusion

Dilution volume
500 mL

Initial infusion rate (first hour)
50 mL/hour

Increments of infusion rate
50 mL/hour every hour

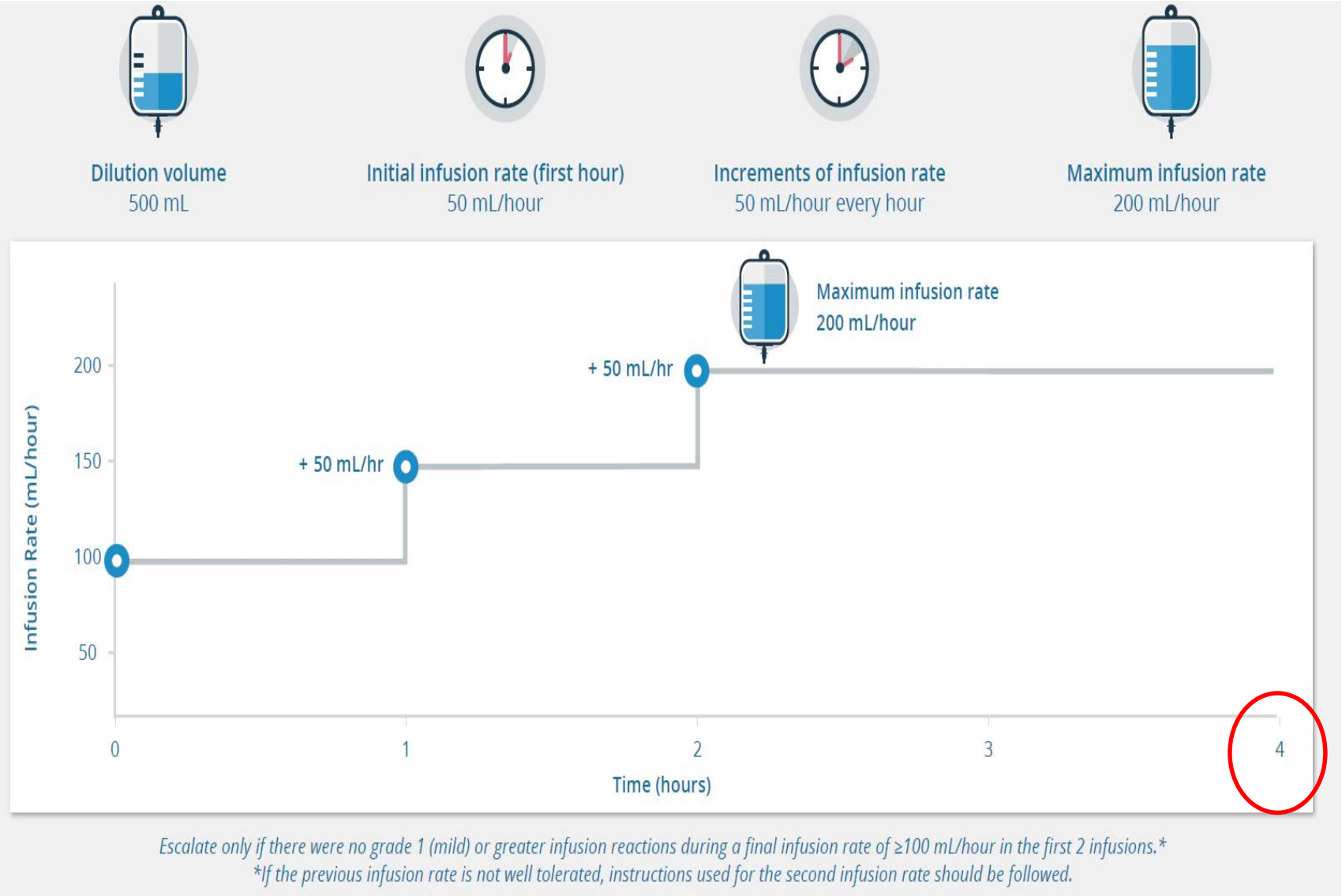
Maximum infusion rate
200 mL/hour



*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.*

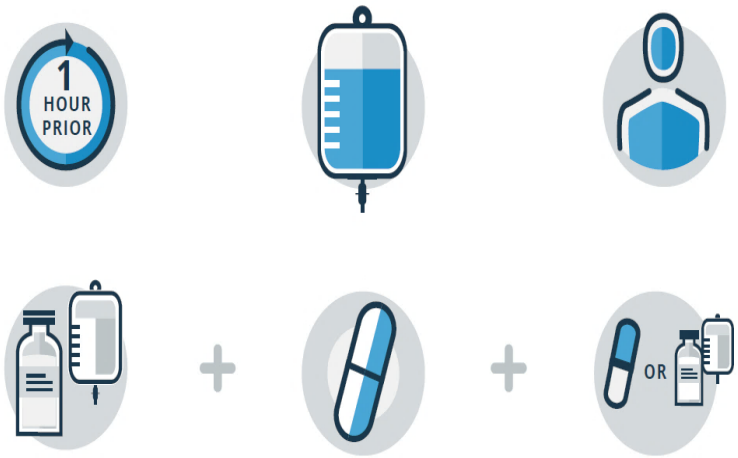
I pazienti devono ricevere una adeguata pre-medicazione per ridurre il rischio di IRRs

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



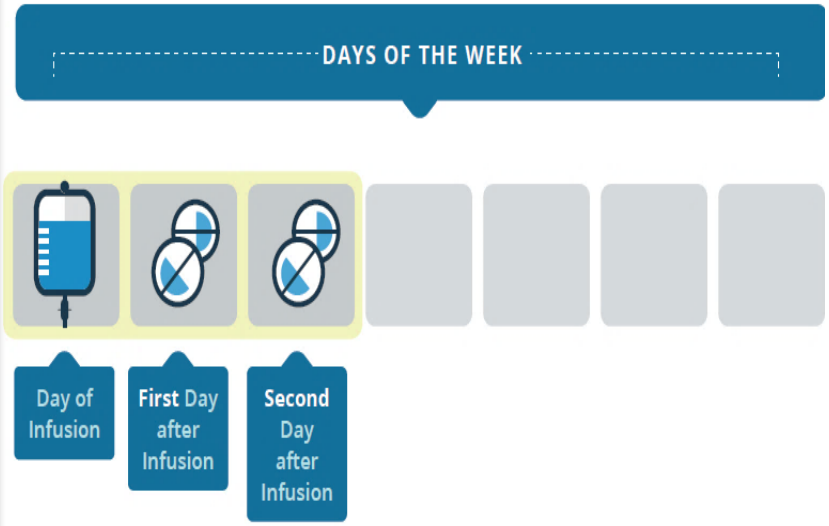
Corticosteroide per via intravenosa + **Antipiretico orale** + **Antistaminico orale o per via intravenosa**

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

Interferences of monoclonal antibodies in MM: with response evaluation

- **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

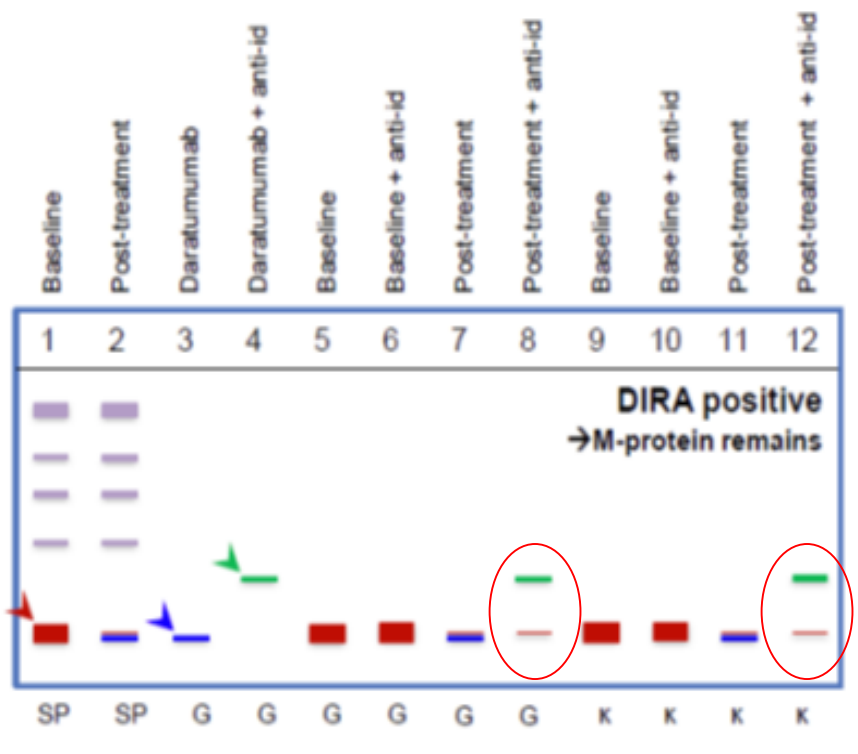
- Particularly, this interference increases the possibility of **false-positive SPEP and IFE** results in patients receiving therapeutic MoAbs and could result: a) in the **underestimation of CR,** and b) **a possible misdiagnosis of relapse** in patients that initially achieved a CR

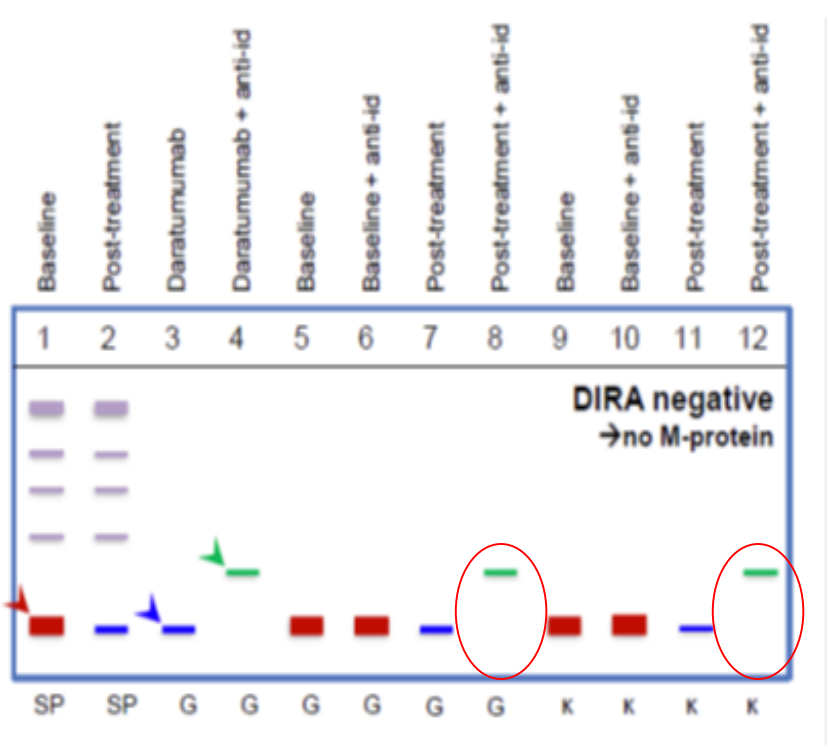
- This is a **class effect of MoAbs** in myeloma and interference depends on isotype of the patient: Daratumumab, Elotuzumab, Isatuximab (SAR650984) and MOR202, and other molecules not employed in MM (Adalimumab, Bevacizumab, Cetuximab, Infliximab, Ofatumumab, Rituximab, Siltuximab, and Trastuzumab)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

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

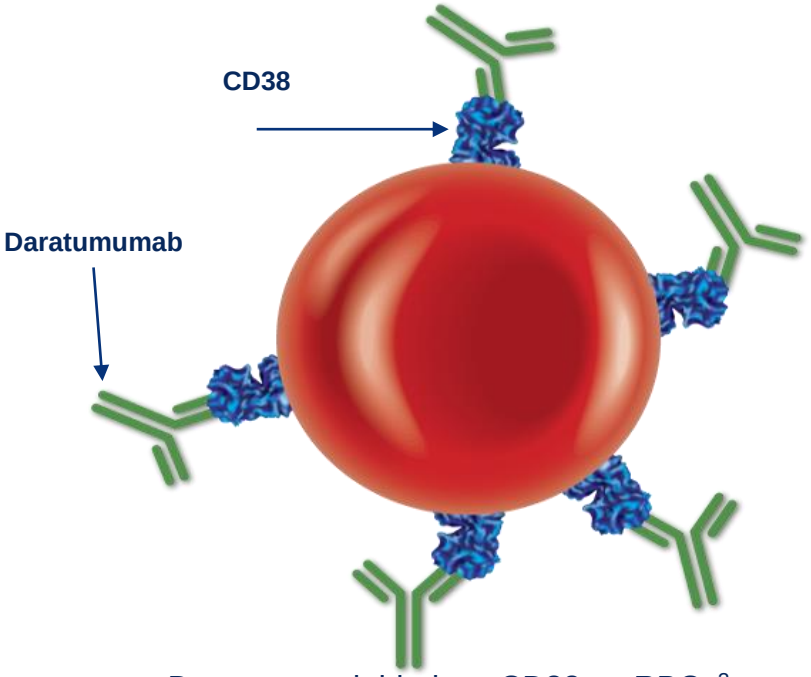
→ Daratumumab
→ Dara + anti-id complex
→ M-protein

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

Interferences of monoclonal antibodies in MM: with blood compatibility testing

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)



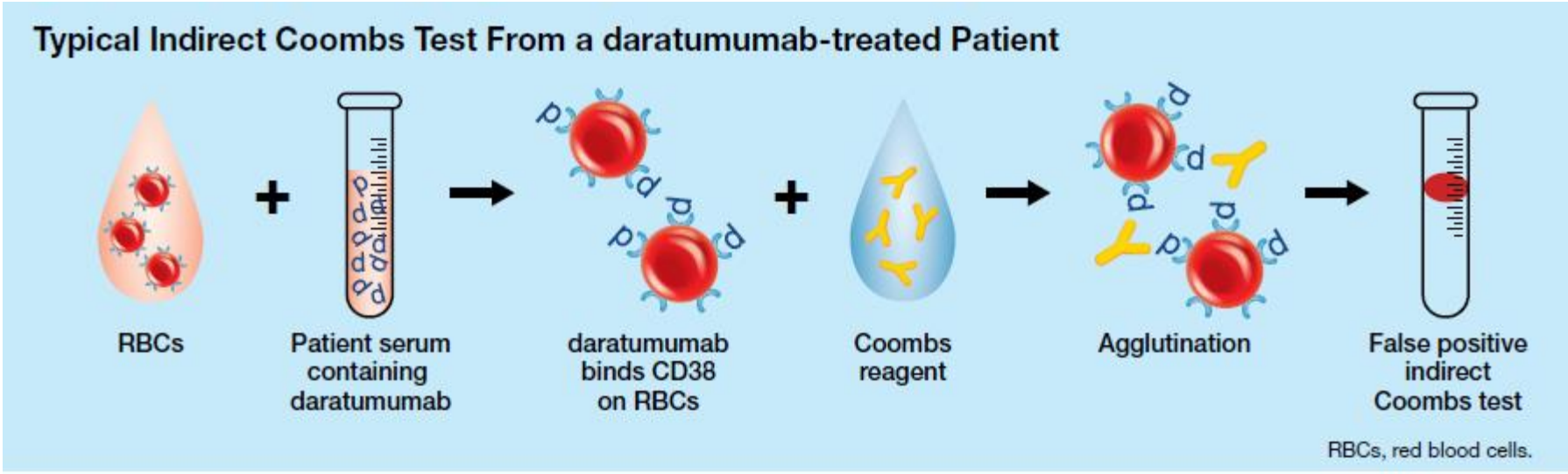
Daratumumab binds to CD38 on RBCs[2]

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

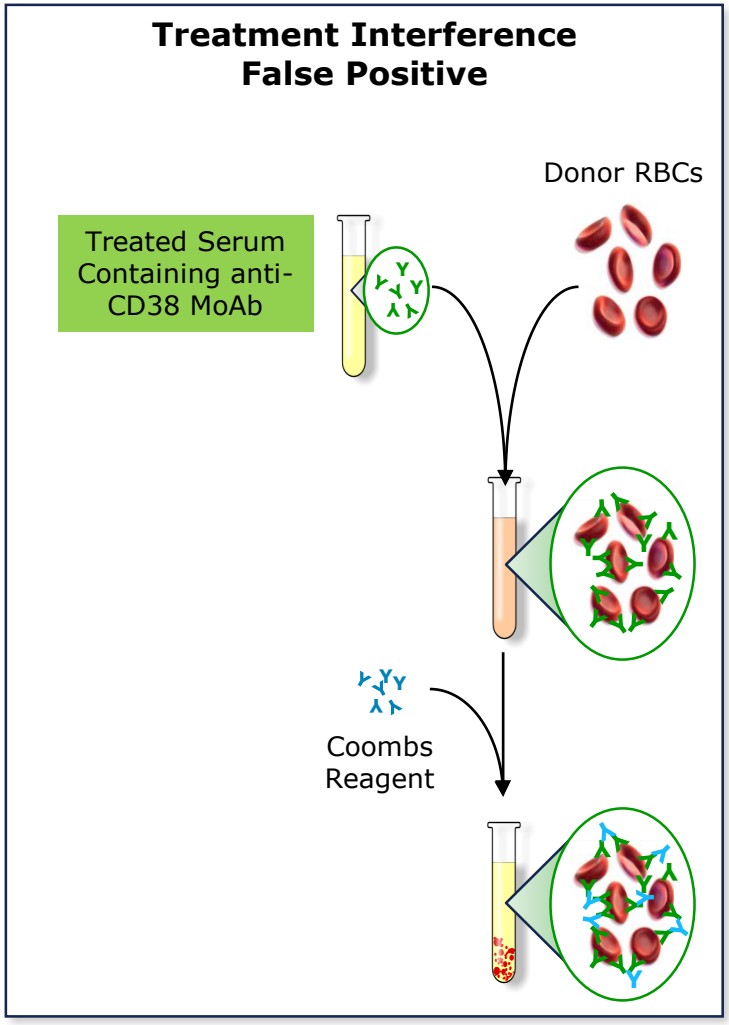
Sera Containing Daratumumab Mimic a Positive Indirect Coombs Test

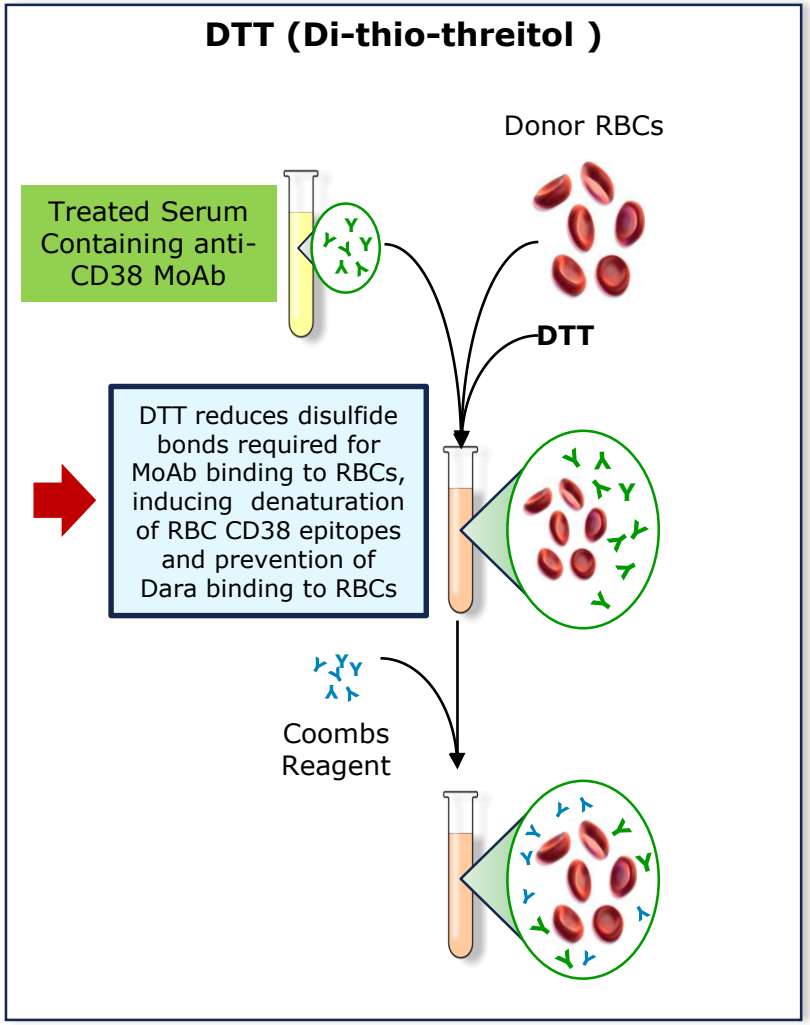
- In an indirect Coombs test, Daratumumab binds to reagent or donor RBCs, resulting in agglutination and giving **a false positive result**
- Daratumumab interference was identified when **almost 100%** of Daratumumab-treated patients were panreactive during RBC panel testing

until 6 months



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

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

PAVO: Study Design (Dara s.c.)

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

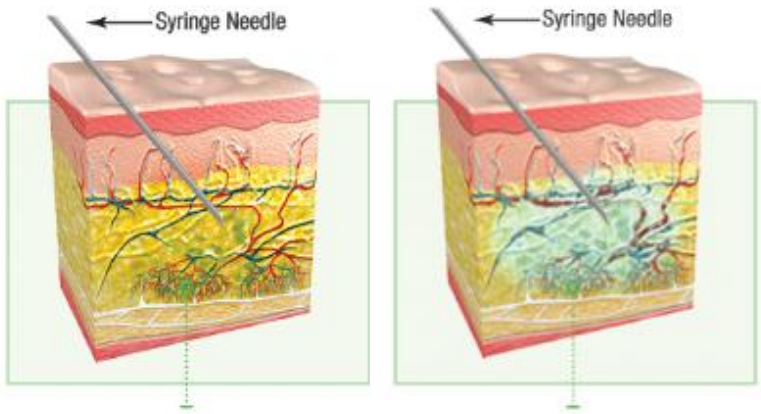
Moreau P et al. IMW 2017; Industry Symposium

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.

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.

PAVO (Dara s.c.) 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

Moreau P et al. IMW 2017; Industry Symposium

PAVO (Dara s.c.) 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

Moreau P et al. IMW 2017; Industry Symposium

PAVO (Dara s.c.) IRRs

ANALISI FARMACOCINETICA

Tmax = 72 h

C trough at cycle 3/day 1 = sovrapponibile a Dara ev

ORR 44%

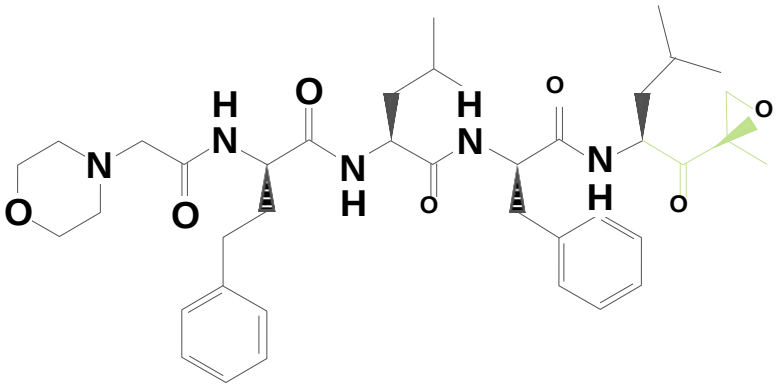
VGPR 28%

Follow Up medio = 4.6 mesi

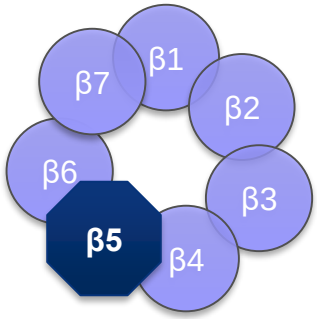
Carfilzomib

PROFILE

- **Epoxyketone**
- **Second-generation irreversible inhibitor of the constitutive 26S proteasome[1]**
  - Primarily inhibits β5 subunit (chymotrypsin-like) of 20S proteolytic core[1,2]
  - Compared with bortezomib[1]
    - Greater selectivity for β5
    - Lower affinity for β2 (trypsin-like) and β1 (caspase-like) proteases
  - Extensive penetration of tissues excluding brain[1]
- Administered intravenously[1]



Carfilzomib (**primarily** and irreversibly inhibits β5)



1. Kortuem KM, Stewart AK. Blood 2013;121:893–7;
2. Moreau P. Blood 2014;124:986–7.

CARFILZOMIB

INDICAZIONI:

- IN ASSOCIAZIONE O CON LENALIDOMIDE E DESAMETASONE O CON SOLO DESAMETASONE E' INDICATO PER IL TRATTAMENTO DI PAZIENTI ADULTI CON MM GIA' SOTTOPOSTI AD ALMENO UNA PRECEDENTE TERAPIA

Table 3 Summary of the adverse events (AEs) reported in carfilzomib trials in the relpsed/refractory setting

	Single-egent carfilzomib Integrated safety profile (36) ($n = 526$)		ENDEAVOR trial (5)				ASPIRE trial (6)			
			Carfilzomib–dexamethasone arm ($N = 463$)		Bortezomib–dexamethasone arm ($N = 456$)		CRd arm ($N = 392$)		Rd arm ($N = 389$)	
	All grades	≥Grade 3	All grades	≥Grade 3	All grades	≥Grade 3	All grades	≥Grade 3	All grades	≥Grade 3
Hematological										
Anemia	46.8%	22.4%	39%	14%	27%	10%	42.6%	17.9%	39.8%	17.2%
Thrombocytopenia	36.3%	23.4%	21%	9%	17%	9%	29.1%	16.6%	22.2%	16.3%
Non-hematological										
Fatigue	55.5%	7.6%	29%	5%	28%	7%	32.9%	7.7%	30.6%	6.4%
Nausea	44.9%	1.3%	19%	1%	18%	<1%	Not provided	Not provided	Not provided	Not provided
Diarrhea	32.7%	1%	30%	3%	38%	7%	42.3%	3.8%	33.7%	4.1%
Constipation	20.9%	0.2%	14%	<1%	27%	2%	20.2%	0.3%	17.2%	0.5%
Dyspnea	34.6%	4.9%	28%	5%	11%	2%	19.4%	2.8%	14.9%	1.8%
Cough	26%	0.2%	25%	0	14%	<1%	28.8%	0.3%	17.2%	0
Pyrexia	30.4%	1.7%	28%	2%	14%	<1%	28.6%	1.8%	20.8%	0.5%
Any renal AE[1]	9.1%	5.5%	8%	4%	4%	2%	8.4%	3.3%	7.2%	3.1%
Any cardiac AE[2]	12.3%	7.6%	18%	7%	5%	3.5%	12.3%	7.1%	8.7%	3.9%
Arrhythmias	13.3	2.3%	Not provided	Not provided	Not provided	Not provided	Not provided	Not provided	Not provided	Not provided
Headache	27.6%	1.3%	17%	<1%	19%	<1%	Not provided	Not provided	Not provided	Not provided
Systemic hypertension	14.3%		25%	9%	9%	3%	14.3%	4.3%	6.9%	1.8%
Pneumonia	12.7%	10.5%	9%	7%	10.5%	8%	Not provided	Not provided	Not provided	Not provided
Upper respiratory tract infection	28.3%	3.2%	20%	2%	15%	<1%	28.6%	1.8%	19.3%	1%
Peripheral neuropathy	13.9%	1.3%	19%	2.2%	51%	8.3%	17.1%	2.6%	17%	3.1%
Muscle spasms	Not provided	Not provided	18%	<1%	6%	<1%	26.5%	1%	21.1%	0.8%

[1]Renal AEs include: acute renal failure, renal failure, renal impairment, azotemia, oliguria, anuria, toxic nephropathy, and prerenal failure.

[2]cardiac AEs include: congestive heart failure, pulmonary edema, hepatic congestion, cardiopulmonary failure, right ventricular failure, angina pectoris, myocardial infarction or ischemia, coronary artery occlusion, increased troponin, abnormal cardiac stress test, abnormal electrocardiogram ST-T segment, and/or T wave (cardiac arrhythmia were not reported for the ENDEAVOR and ASPIRE trial and are not included in this table).

Muchtar E. et al European Journal of Haematology, Feb 2016

Analysis of carfilzomib cardiovascular safety profile across relapsed and/or refractory multiple myeloma clinical trials

Ajai Chari,[1] A. Keith Stewart,[2] Stuart D. Russell,[3] Philippe Moreau,[4] Joerg Herrmann,[5] Jose Banchs,[6] Roman Hajek,[7] John Groarke,[8] Alexander R. Lyon,[9,10] George N. Batty,[11] Sunhee Ro,[11] Mei Huang,[11] Karim S. Iskander,[11] and Daniel Lenihan[12]

[1]Hematology/Oncology, Mount Sinai School of Medicine, New York, NY; [2]Division of Hematology/Oncology, Department of Internal Medicine, Mayo Clinic, Scottsdale, AZ; [3]Department of Medicine, Duke University Medical Center, Durham, NC; [4]Department of Hematology, University Hospital Hotel-Dieu, Nantes, France; [5]Department of Cardiovascular Medicine, Mayo Clinic College of Medicine, Phoenix, AZ; [6]Department of Cardiology, Division of Internal Medicine, MD Anderson Cancer Center, Houston, TX; [7]Department of Haematooncology, Faculty of Medicine, University of Ostrava and University Hospital Ostrava, Ostrava, Czech Republic; [8]Department of Cardiology, Division of Internal Medicine, Partners/Brigham and Women's Hospital, Boston, MA; [9]Department of Cardiology, Imperial College London, London, United Kingdom; [10]Cardiology, Royal Brompton Hospital, London, United Kingdom; [11]Amgen Inc., Thousand Oaks, CA; and [12]Cardiovascular Division, Washington University in St. Louis, St. Louis, MO

Key Points

- Despite increased incidence of CV events, relative risk of CV AEs with carfilzomib is low and manageable; risk of fatal AEs is not elevated.
- Carfilzomib-based regimens have a favorable benefit-risk profile in RRMM; monitoring/management of CV risk is recommended.

Carfilzomib is a selective proteasome inhibitor approved for the treatment of relapsed and/or refractory multiple myeloma (RRMM). It has significantly improved outcomes, including overall survival (OS), and shown superiority vs standard treatment with lenalidomide plus dexamethasone and bortezomib plus dexamethasone. The incidence rate of cardiovascular (CV) events with carfilzomib treatment has varied across trials. This analysis evaluated phase 1-3 trials with >2000 RRMM patients exposed to carfilzomib to describe the incidence of CV adverse events (AEs). In addition, the individual CV safety data of >1000 patients enrolled in the carfilzomib arm of phase 3 studies were compared with the control arms to assess the benefit-risk profile of carfilzomib. Pooling data across carfilzomib trials, the CV AEs (grade ≥3) noted included hypertension (5.9%), dyspnea (4.5%), and cardiac failure (4.4%). Although patients receiving carfilzomib had a numeric increase in the rates of any-grade and grade ≥3 cardiac failure, dyspnea, and hypertension, the frequency of discontinuation or death due to these cardiac events was low and comparable between the carfilzomib and control arms. Serial echocardiography in a blinded cardiac substudy showed no objective evidence of cardiac dysfunction in the carfilzomib and control arms. Moreover, carfilzomib had no significant effect on cardiac repolarization. Our results, including the OS benefit, showed that the benefit of carfilzomib treatment in terms of reducing progression or death outweighed the risk for developing cardiac failure or hypertension in most patients. Appropriate carfilzomib administration and risk factor management are recommended for elderly patients and patients with underlying risk factors.

Chari A. et al Blood Advances 2018,

TOSSICITA' CARDIOVASCOLARE E CARFILZOMIB

- INCIDENZA PIU' ELEVATA DI INSUFFICIENZA CARDIACA ≥ 3 NELLA FASE PRECOCE DELLA TERAPIA CON CARFILZOMIB.

- UN UNICO STUDIO HA RIPORTATO UNA CORRELAZIONE TRA LIVELLI BASALI DI PEPTIDE NATRIURETICO (NT-proBNP) E RISCHIO AUMENTATO DI EVENTI CARDIACI.

TOSSICITA' CARDIOVASCOLARE E CARFILZOMIB

- NON CHIARA EVIDENZA DI RAPPORTO DIRETTO TRA LA DOSE DI CARFILZOMIB (27 mg/mq o 56 mg/mq 2 VOLTE ALLA SETTIMANA, 70 mg/mq UNA VOLTA ALLA SETTIMANA) E L'INCIDENZA DI EVENTI CARDIACI.

- NON CHIARA EVIDENZA TRA LA DOSE CUMULATIVA DI CARFILZOMIB E L'INCIDENZA DI EVENTI CARDIACI.

TOSSICITA' CARDIOVASCOLARE E CARFILZOMIB

- ETA' AVANZATA E PRE-ESISTENTI PATOLOGIE CARDIACHE POSSONO RAPPRESENTARE FATTORI DI RISCHIO PER SVILUPPARE EVENTI CARDIOVASCOLARI IN CORSO DI CARFILZOMIB.

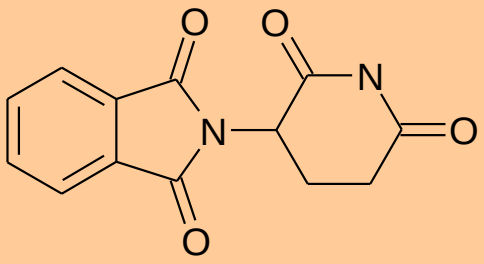
- UN TEMPO DI SOMMINISTRAZIONE PIU' LUNGO (> 30 minuti) E' SUGGERITO NEI PAZIENTI A MAGGIOR RISCHIO.

- IL TRATTAMENTO "AGGRESSIVO" DEI FATTORI DI RISCHIO CARDIO-VASCOLARE DEVE ESSERE CONSIDERATO PARTE INTEGRANTE DELLA GESTIONE DEL PAZIENTE IN TRATTAMENTO CON CARFILZOMIB.

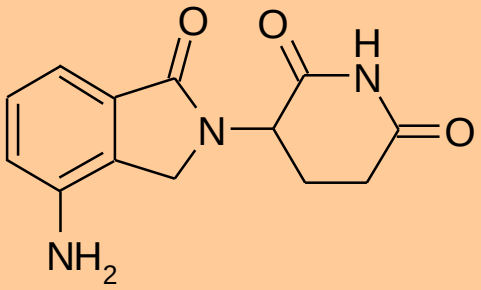
- COMPLESSIVAMENTE L'ANALISI COSTO-BENEFICIO SUGGERISCE CHE IL VANTAGGIO DELL'USO DEL CARFILZOMIB IN TERMINI DI RIDUZIONE DELLA PROGRESSIONE DEL MIELOMA NEI PAZIENTI RICADUTI/RESISTENTI SORPASSA CONSIDEREVOLMENTE IL RISCHIO POTENZIALE DI SVILUPPARE UN EVENTO CARDIOVASCOLARE.

IMIDs IMMUNOMODULATORY DRUGS

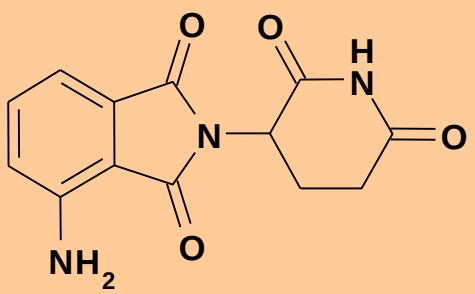
Molecular and preclinical profile of thalidomide, pomalidomide & lenalidomide



Thalidomide



Lenalidomide (Revlimid®; CC-5013)



Pomalidomide (CC-4047)

IMiDs are structurally similar, but functionally different both qualitatively and quantitatively

POMALIDOMIDE

INDICAZIONI:

- IN ASSOCIAZIONE CON DESAMETASONE NEI PAZIENTI ADULTI CON MM RECIDIVATO O REFRATTARIO, SOTTOPOSTI AD ALMENO DUE PRECEDENTI TERAPIE, COMPRENDENTI SIA LENALIDOMIDE CHE BORTEZOIMB, E CON DIMOSTRATA PROGRESSIONE DELLA MALATTIA DURANTE L'ULTIMA TERAPIA.

POM + LoDEX in RRMM: Pooled AE Analysis (MM-002, MM-003, MM-010) - *Safety*

- The most common grade 3/4 AEs were **neutropenia and infections**

Grade 3/4 AEs ≥5% Overall and AEs of Interest	MM-002 (n = 112)	MM-003 (n = 300)	MM-010 (n = 676)	Overall (N = 1088)
Hematologic AEs, %				
Neutropenia[a]	**50**	**57**	**57**	**56**
Febrile neutropenia	3	9	5	6
Leukopenia	10	9	8	8
Anemia[a]	24	33	33	32
Thrombocytopenia[a]	21	24	27	26
Non-hematologic AEs, %				
Infections[a]	**45**	**30**	**34**	**34**
Pneumonia	23	13	13	14
Fatigue	14	5	6	7
AEs of special interest, %				
Peripheral neuropathy[a]	0	2	1	1
DVT/PE	3	1	2	2

[a] Grouped AE term.
AE, adverse events; DVT, deep vein thrombosis; LoDEX, low-dose dexamethasone; PE, pulmonary embolism; POM, pomalidomide; RRMM, relapsed and refractory multiple myeloma.
Moreau P, et al. ASCO 2016 [abstract 8031].

POM + LoDEX in RRMM: Pooled Age Analysis (MM-002, MM-003, MM-010) - *Safety*

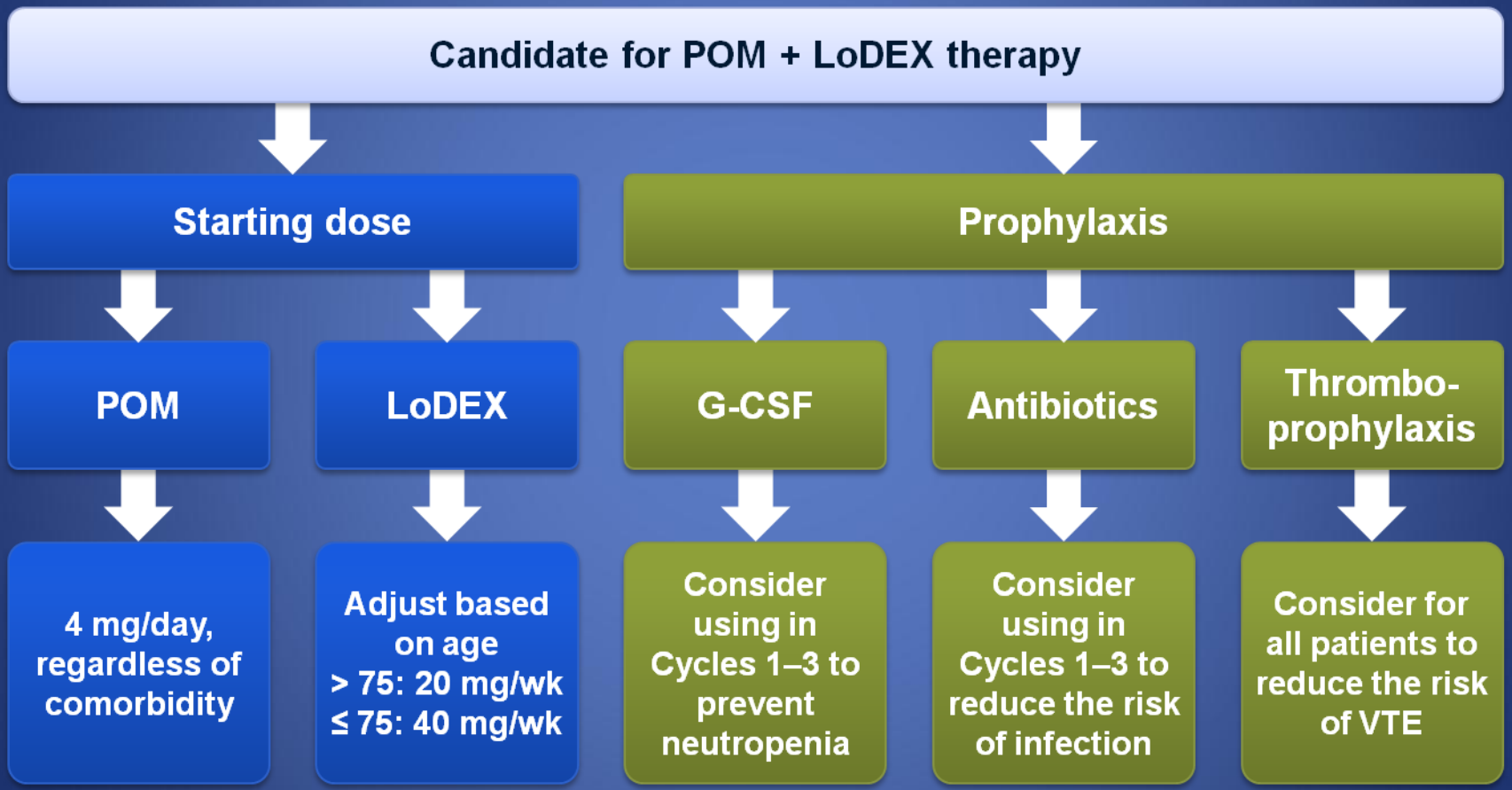
Grade 3/4 TEAEs[a]	≤ 65 Years (n = 537)	> 65 Years (n = 551)	≤ 75 Years (n = 962)	> 75 Years (n = 126)
Hematologic TEAEs, %				
Neutropenia	**50**	**47**	**48**	**50**
Anemia	32	31	32	29
Thrombocytopenia	25	21	24	17
Leukopenia	8	9	8	10
Non-hematologic TEAEs, %				
Infections	**35**	**32**	**34**	**33**
Pneumonia	13	15	14	11
Tx duration, median (range), months	**4.8 (0.1-47.6)**	**4.8 (0.1-47.8)**	**4.8 (0.1-47.8)**	**4.8 (0.4-25.1)**
Relative dose intensity, median[a]	**0.9**	**0.9**	**0.9**	**0.9**
≥ 1 AE leading to dose reduction, %	23	24	23	26
≥ 1 AE leading to dose interruption, %	64	69	66	68
≥ 1 AE leading to dose discontinuation,%	5	8	7	8

[a] Reported in ≥ 10% of pts; [b] Includes preferred terms: deep vein thrombosis and pulmonary embolism; [c] Includes preferred terms: peripheral sensory neuropathy, polyneuropathy, hypoesthesia, and paresthesia.
DVT, deep vein thrombosis; LoDEX, low-dose dexamethasone; PE, pulmonary embolism; POM, pomalidomide; pt, patient; RRMM, relapsed and refractory multiple myeloma; TEAE, treatment-emergent adverse event.

Palumbo A. A Pooled Analysis of the Impact of Age on Outcomes in Patients With Refractory or Relapsed and Refractory Multiple Myeloma Treated With Pomalidomide + Low-Dose Dexamethasone. *EHA 2016, abstract E1295.*

Summary of considerations for initiating POM + LoDEX therapy

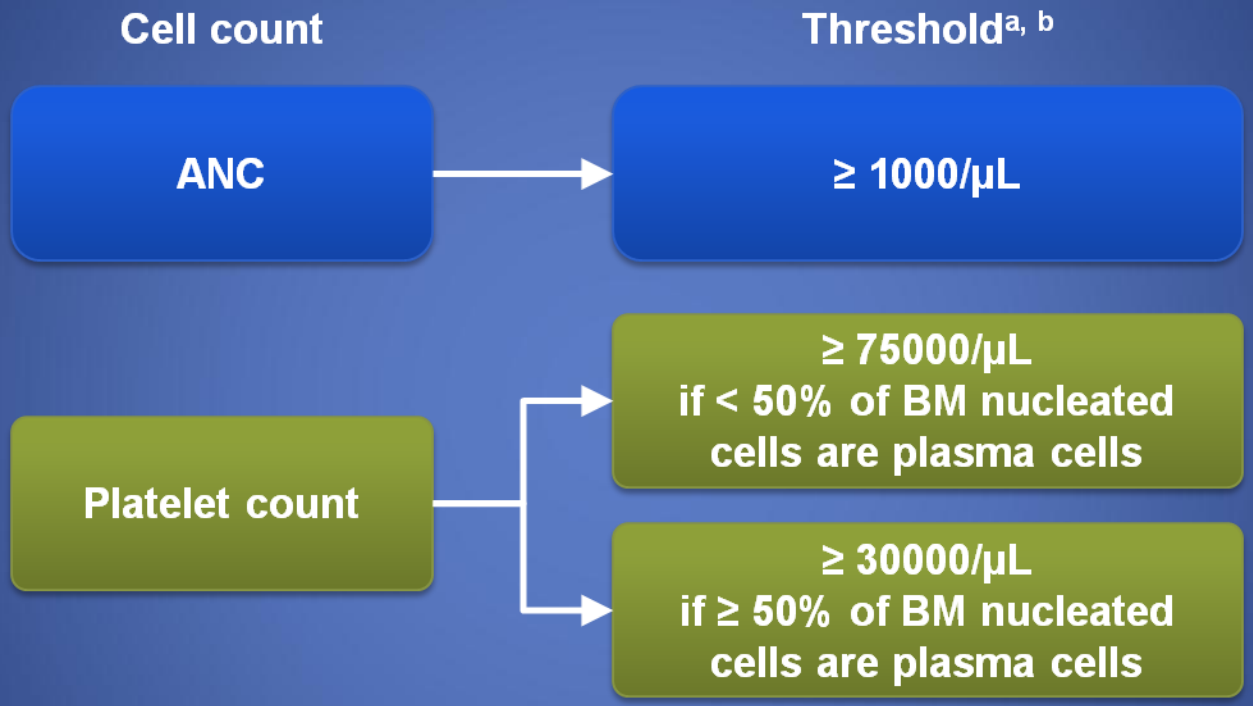
Expert panel opinion



G-CSF, granulocyte colony-stimulating factor; LoDEX, low-dose dexamethasone; POM, pomalidomide; wk, week; VTE, venous thromboembolism.

Dimopoulos MA, et al. *Leukemia*. 2014; Feb 5 [Epub].

Minimum blood counts for starting POM + LoDEX based on clinical trial experience



[a] If ANC and platelet counts are below these thresholds, POM + LoDEX may be considered if adequate growth factor support and platelet transfusion is provided

[b] Thresholds as per MM-003 study design

ANC, absolute neutrophil count; BM, bone marrow; LoDEX, low-dose dexamethasone; POM, pomalidomide.

Dimopoulos MA, et al. *Leukemia*. 2014; Feb 5 [Epub].
San Miguel J, et al. *Lancet Oncol.* 2013;14:1055–1066.

Managing myelosuppression with POM + LoDEX

Expert panel opinion

- Perform a complete blood count
  - At baseline
  - Every 1–2 weeks (depending on patient condition) for the first 8 weeks of therapy
  - Every month thereafter
- Follow the recommended dose-modification scheme for POM-related neutropenia and thrombocytopenia
- Prophylactic use of G-CSF at the physician's discretion during the first few treatment cycles may reduce the risk of neutropenia
- Consider growth factor use for cases of neutropenia with the goal of maintaining patients on therapy

G-CSF, granulocyte colony-stimulating factor; LoDEX, low-dose dexamethasone; POM, pomalidomide

Dimopoulos MA, et al. *Leukemia*. 2014; Feb 5 [Epub].

Managing infection with POM + LoDEX

Expert panel opinion

- Antibiotic prophylaxis should be considered for all patients during the first 3 cycles of POM due to the high risk of infection in this period
- For patients with a very high risk of infection (low blood counts, prior history of infection, or both), consider antibiotic prophylaxis for the duration of POM therapy
- Caution is warranted when POM is administered concurrently with strong CYP1A2 inhibitors, such as ciprofloxacin and enoxacin, because these agents may increase exposure to POM and therefore increase the risk of AEs
- Early intervention is warranted for patients who develop infection, including treatment interruption and immediate initiation of empirical antibiotic treatment

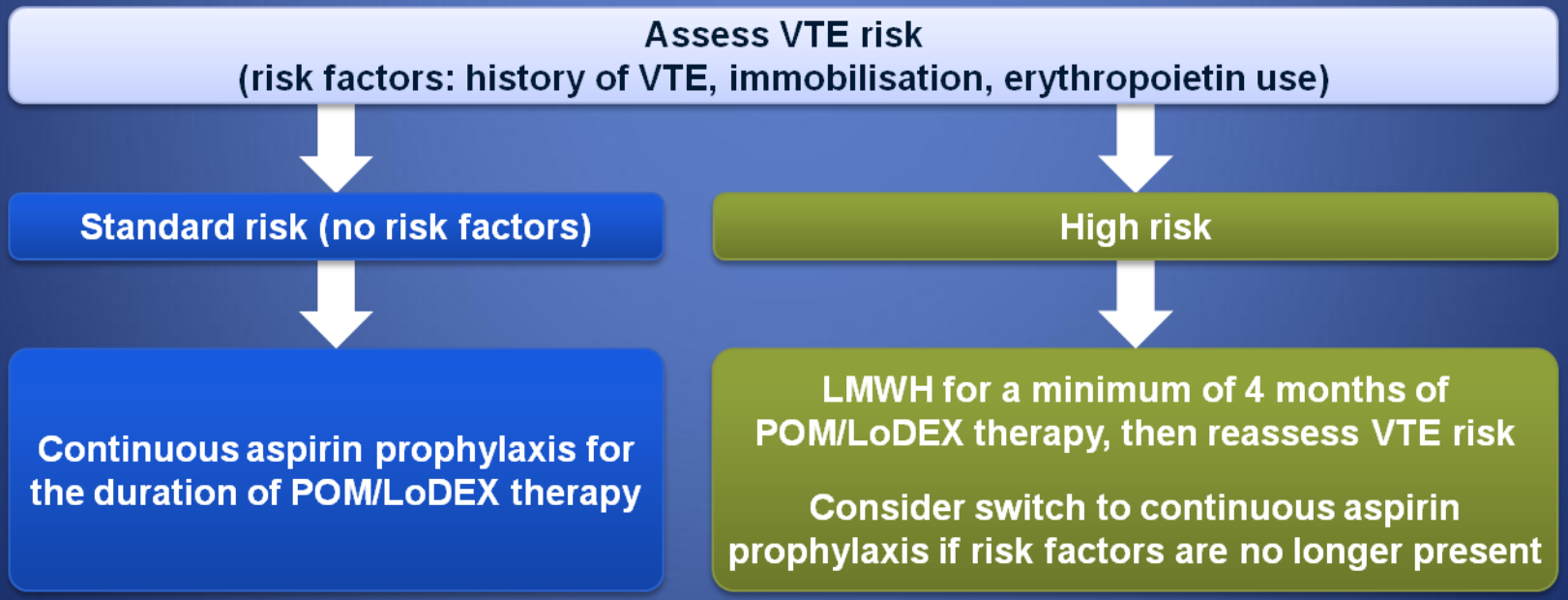
AE, adverse event; LoDEX, low-dose dexamethasone; POM, pomalidomide.

Dimopoulos MA, et al. *Leukemia*. 2014; Feb 5 [Epub].

Managing VTE with POM + LoDEX

Expert panel opinion

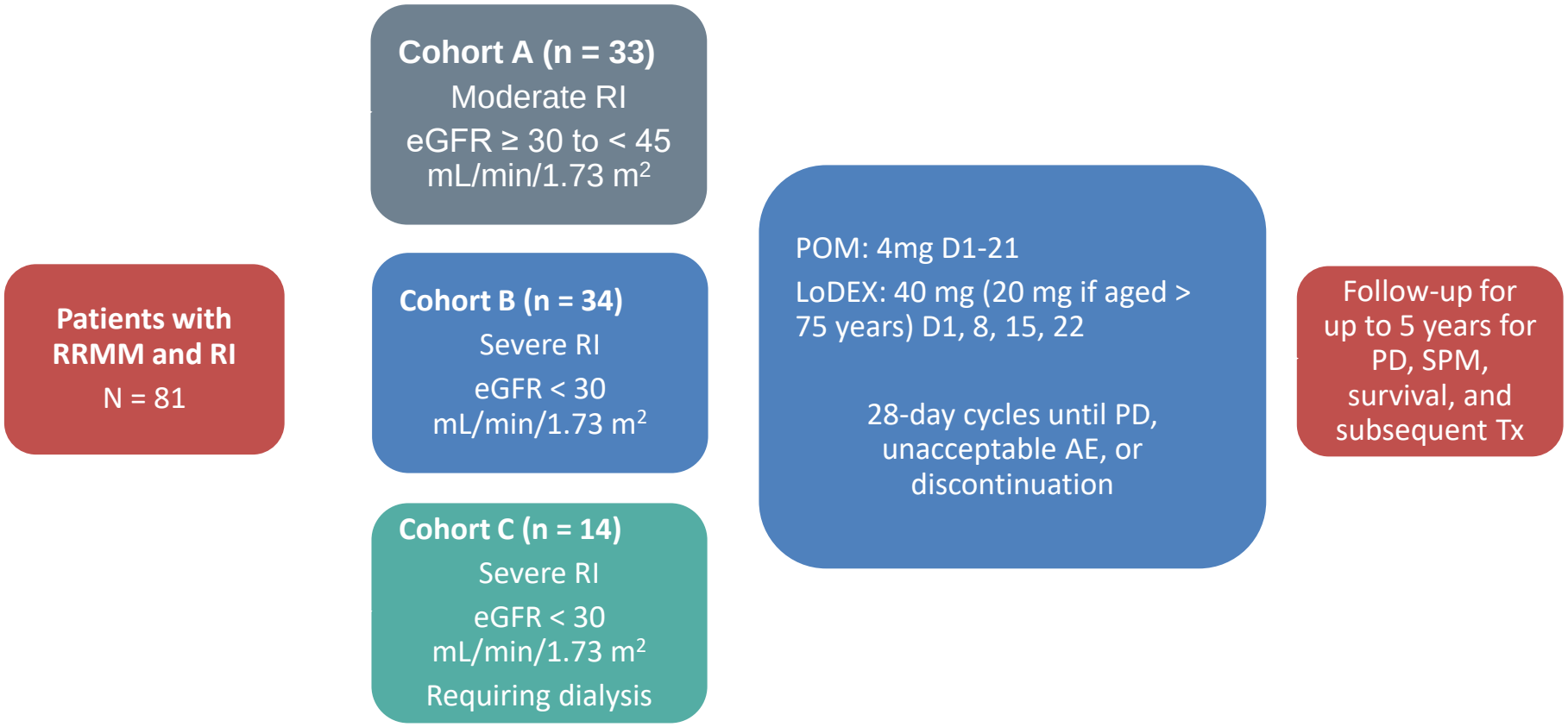
- Follow existing guidelines on thromboprophylaxis during IMiD® therapy, i.e. aspirin if standard risk and LMWH for those with ≥ 1 risk factor, to reduce the VTE incidence to < 5%
- Patients at high risk for VTE due to a concomitant medical condition should continue to receive anticoagulation as prescribed
- For patients with high risk for reasons other than comorbidity, VTE risk can be reassessed after 4 months and those with standard risk can switch to aspirin



DVT, deep vein thrombosis; IMiD, immunomodulatory drug; LMWH, low-molecular-weight heparin; LoDEX, low-dose dexamethasone; POM, pomalidomide; VTE, venous thromboembolism.

Dimopoulos MA, et al. *Leukemia*. 2014; Feb 5 [Epub].

MM-013: pom + lodex In rrMM and ri



- **Primary endpoint:** ORR
- **Key secondary endpoints:** PFS, TTP, TTR, DOR in responders (≥ PR), OS, renal response, TTRR, safety (including SPMs), PK
- Data cutoff date: January 28, 2017

Dimopoulos M, et al. *J Clin Oncol*. 2018. [Epub ahead of print].

MM-013: pom + lodex In rrMM and ri

summary of authors conclusions[1]

- **The MM-013 trial is the first prospective trial to demonstrate that POM + LoDEX can provide benefit in patients with severe RI, including those requiring hemodialysis and with high disease burden**

- **Median POM dose was 4.0 mg/day (range, 2.4-4.0) among all patients**

- After administration of multiple oral doses of POM 4 mg, the PK of POM was comparable among the 3 renal cohorts
  - It is recommended that POM be administered after patients undergo hemodialysis because the procedure removed POM from the blood

- **POM dosed at 4 mg can be safely administered with LoDEX in patients with moderate or severe RI, including those on hemodialysis**[a]

[a] Please refer to the US and EU package inserts for full dosing and prescribing information for POM.[4,5]

1. Dimopoulos M, et al. *J Clin Oncol*. 2018. [Epub ahead of print]. 2. Richardson PG, et al. *Blood.* 2014;123:1826-1832. 3. San Miguel J, et al. *Lancet Oncol.* 2013;14:1055-1066. 4. Pomalyst (pomalidomide) [package insert]. Summit, NJ: Celgene corporation; 2016. 5. Imnovid (pomalidomide) [summary of product characteristics]. Uxbridge, UK: Celgene Europe; 2016.

POMALIDOMIDE: SICUREZZA E TOLLERABILITA'

- LA TOSSICITA' PIU' FREQUENTE E' LA CITOPENIA (CIRCA 50% DI NEUTROPENIA G3-G4).
- LE INFEZIONI RAPPRESENTANO UN EVENTO AVVERSO FREQUENTE (POLMONITI)
- IL RISCHIO DI TVP RICHIEDE UNA SISTEMATICA TROMBOPROFILASSI
- NESSUN AGGIUSTAMENTO DELLE DOSI IN CASO DI INSUFFICIENZA RENALE
- ATTENZIONE AD EVENTI AVVERSI MOLTO RARI A LIVELLO POLMONARE, EPATICO O CARDIACO

POMALIDOMIDE: SICUREZZA E TOLLERABILITA'

COME TUTTI I FARMACI ASSUNTI PER VIA ORALE, VANNO TENUTI IN CONSIDERAZIONE I SEGUENTI FATTORI:

✓**INTERAZIONI FARMACOLOGICHE**

•POMALIDOMIDE E' PREVALENTEMENTE METABOLIZZATA DAI CITOCROMI CYP3A4 E CYP1A2

✓**RAPPORTO CON I PASTI**

•POMALIDOMIDE DEVE ESSERE ASSUNTA LONTANO DAI PASTI

✓**ADERENZA AL TRATTAMENTO**

•EDUCAZIONE DEL PAZIENTE E DEL CARE-GIVER

IXAZOMIB

INDICAZIONI:

- INDICATO IN COMBINAZIONE CON LENALIDOMIDE E DESAMETASONE PER IL TRATTAMENTO DI PAZIENTI ADULTI CON MM SOTTOPOSTI AD ALMENO UNA PRECEDENTE TERAPIA

- RIMBORSATO IN ITALIA IN CLASSE H NEI PAZIENTI CHE ABBIANO RICEVUTO ≥ 2 LINEE DI TERAPIA OPPURE CON UNA PRECEDENTE LINEA DI TERAPIA CON CITOGENETICA SFAVOREVOLE

Table I. AEs of clinical importance occurring in at least 20% of patients in either arm.

	Placebo-Rd (n = 359)				IRd (n = 361)			
AE category, n (%)	AE	Gr ≥3	SAE	D/C	AE	Gr ≥3	SAE	D/C
Haematological events*								
Thrombocytopenia†	57 (16)	32 (9)	6 (2)	7 (2)	112 (31)	69 (19)	7 (2)	5 (1)
Neutropenia	111 (31)	85 (24)	2 (<1)	5 (1)	118 (33)	81 (22)	2 (<1)	3 (<1)
Non-haematological events*								
Nausea	79 (22)	0	0	0	104 (29)	6 (2)	2 (<1)	0
Vomiting	42 (12)	2 (<1)	0	0	84 (23)	4 (1)	2 (<1)	0
Diarrhoea	139 (39)	9 (3)	2 (<1)	3 (<1)	164 (45)	23 (6)	9 (2)	6 (2)
Constipation	94 (26)	1 (<1)	1 (<1)	1 (<1)	126 (35)	1 (<1)	1 (<1)	0
Rash†	82 (23)	6 (2)	1 (<1)	1 (<1)	131 (36)	18 (5)	1 (<1)	3 (<1)
PN†	78 (22)	6 (2)	0	2 (<1)	97 (27)	9 (2)	0	9 (2)
Peripheral oedema‡	73 (20)	4 (1)	1 (<1)	0	101 (28)	8 (2)	1 (<1)	0
Back pain	62 (17)	9 (3)	7 (2)	1 (<1)	87 (24)	3 (<1)	2 (<1)	0

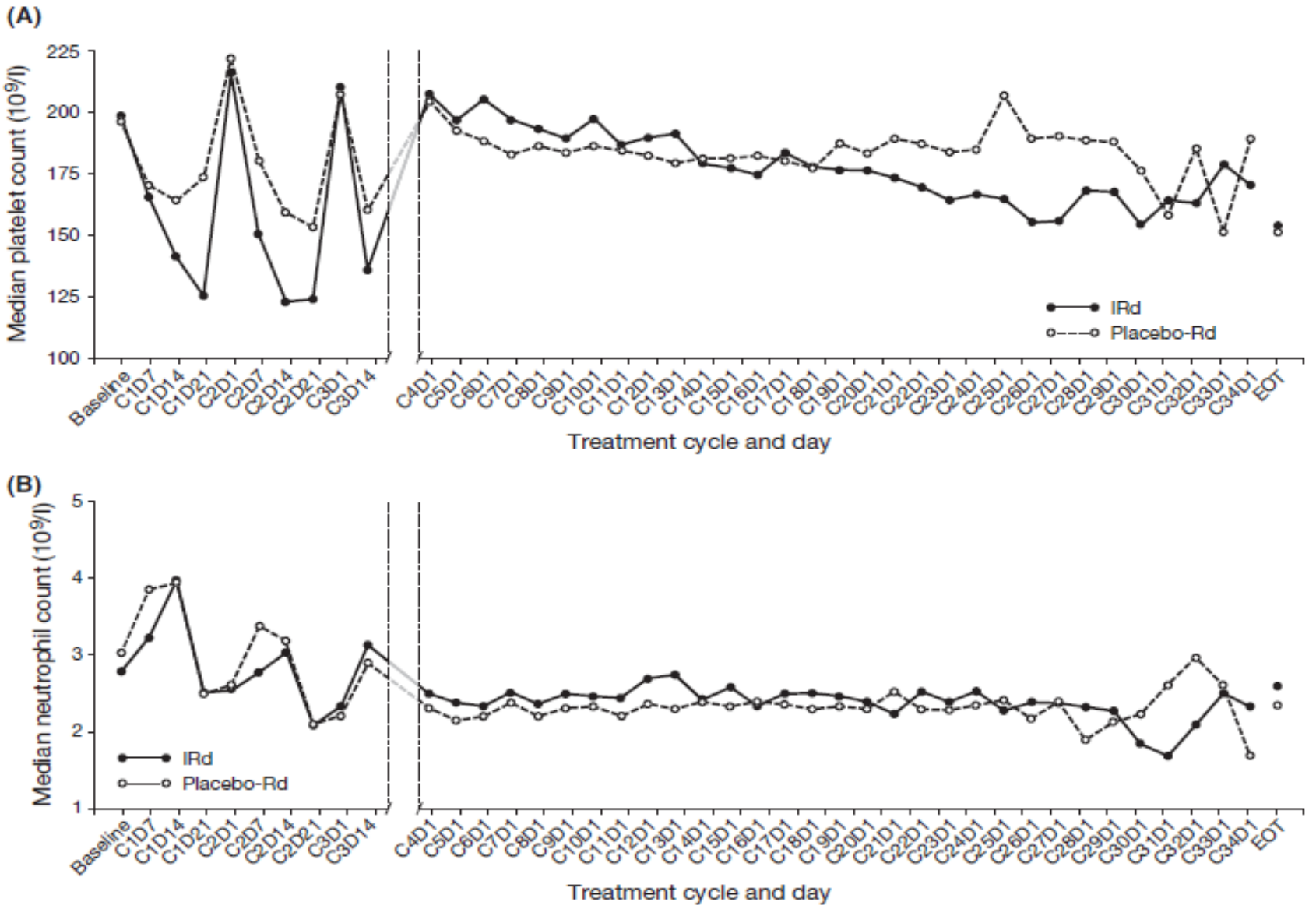
AE, adverse event; D/C, discontinued; Gr, grade; IRd, ixazomib, lenalidomide and dexamethasone; Placebo-Rd, placebo plus lenalidomide and dexamethasone; PN, peripheral neuropathy; SAE, serious adverse event.

*Grade 4 thrombocytopenia reported in 13 (4%) and 26 (7%) patients in the placebo-Rd and IRd groups, respectively; grade 4 neutropenia reported in 22 (6%) and 17 (5%) patients, respectively. No grade 4 events reported for the non-haematological AEs listed here.

†Pooled preferred terms (broad pooling of standardized Medical Dictionary for Regulatory Activities query [SMQ] preferred terms).

‡An association between oedema and cardiac failure was similar between the two regimens (IRd: 1%; placebo-Rd: <1%).

Kumar S. et al BJH 2017



Kumar S. et al BJH 2017

IXAZOMIB = MODIFICAZIONI DELLA DOSE

Tabella 1: Livelli di riduzione della dose di ixazomib

Dose iniziale raccomandata*	Prima riduzione a	Seconda riduzione a	Interruzione
4 mg	3 mg	2,3 mg	

*La dose ridotta di 3 mg è raccomandata in presenza di compromissione epatica moderata o severa, compromissione renale severa o insufficienza renale terminale (ESRD) con necessità di dialisi.

IXAZOMIB = MODIFICAZIONI DELLA DOSE

Tabella 2: Linee guida per la modifica della dose di ixazomib in associazione con lenalidomide e desametasone

Tossicità ematologiche	Azioni raccomandate
Trombocitopenia (conta piastrinica)	
Conta piastrinica <30.000/mm³	• Sospendere la somministrazione di ixazomib e lenalidomide fino a quando la conta piastrinica non torna a un valore ≥30.000/mm³. • Dopo il recupero, riprendere la somministrazione di lenalidomide alla dose immediatamente inferiore, secondo le indicazioni contenute nell'RCP di lenalidomide, e riprendere la somministrazione di ixazomib all'ultima dose assunta. • Se la conta piastrinica scende nuovamente a un valore <30.000/mm³, sospendere la somministrazione di ixazomib e lenalidomide fino a quando la conta piastrinica non torna a un valore ≥30.000/mm³. • Dopo il recupero, riprendere la somministrazione di ixazomib alla dose immediatamente inferiore e la somministrazione di lenalidomide all'ultima dose assunta.*
Neutropenia (conta assoluta dei neutrofili)	
Conta assoluta dei neutrofili <500/mm³	• Sospendere la somministrazione di ixazomib e lenalidomide fino a quando la conta assoluta dei neutrofili non è ≥500/mm³. Valutare la possibilità di somministrare in aggiunta G-CSF, secondo le linee guida cliniche. • Dopo il recupero, riprendere la somministrazione di lenalidomide alla dose immediatamente inferiore, secondo le indicazioni di prescrizione di lenalidomide, e riprendere la somministrazione di ixazomib all'ultima dose assunta. • Se la conta assoluta dei neutrofili scende nuovamente a un valore <500/mm³, sospendere la somministrazione di ixazomib e lenalidomide fino a quando la conta assoluta dei neutrofili non torna a un valore ≥500/mm³. • Dopo il recupero, riprendere la somministrazione di ixazomib alla dose immediatamente inferiore e la somministrazione di lenalidomide all'ultima dose assunta.*

IXAZOMIB : EVVENTI AVVERSI

- NON AUMENTATO RISCHIO DI TROMBOEMBOLISMO
- CONSIGLIATA PROFILASSI PER HERPES ZOSTER VIRUS
- NON AUMENTO DI EVENTI CARDIACI (ANCHE NEI PAZIENTI CON PRE-ESISTENTI CARDIOPATIE O CON FATTORI DI RISCHIO CARDIOVASCOLARE)
- NON NECESSITA' DI ALCUN AGGIUSTAMENTO DELLA DOSE NEI PAZIENTI CON COMPROMISSIONE RENALE LIEVE O MODERATA (CLEARANCE CREATININA > 30 ML/MIN). IN CASO DI CLEARANCE DELLA CREATININA < 30 ML/MIN O INSUFFICIENZA RENALE TERMINALE, LA DOSE RACCOMANDATA E' DI 3 MG. IXAZOMIB NON E' DIALIZZABILE, PERTANTO PUO' ESSERE SOMMINISTRATO INDIPENDENTEMENTE DALLE TEMPISTICHE DELLA DIALISI
- A TUTT'OGGI NON RISCHIO AUMENTATO DI SECONDE NEOPLASIE
- SODDISFACENTE QoL, VALUTATA ATTRAVERSO I QUESTIONARI EORTC QLQ-C30 E MY-20.

Table 4. Overall safety profile with IRd and placebo-Rd among high-risk and standard-risk patients

	High risk		Standard risk	
	IRd, n = 74	Placebo-Rd, n = 62	IRd, n = 200	Placebo-Rd, n = 214
Median treatment duration, mo	16.3	9.9	16.1	14.7
Any adverse event	73 (99)	61 (98)	197 (99)	214 (100)
Any grade ≥3 adverse event	49 (66)	45 (73)	149 (75)	140 (65)
Any serious adverse event	31 (42)	32 (52)	90 (45)	101 (47)
Adverse event resulting in dose reduction of any drug	30 (41)	26 (42)	119 (60)	110 (51)
Adverse event resulting in discontinuation of any drug	13 (18)	16 (26)	55 (28)	42 (20)
Adverse event resulting in discontinuation of regimen	6 (8)	8 (13)	42 (21)	31 (14)
On-study death	0	6 (10)	9 (5)	13 (6)

Per the primary report from the study, exposure and safety data are reported from a prespecified analysis at a median follow up of ~23 months. One patient with high-risk cytogenetics who was randomized to the ixazomib arm did not receive ixazomib and was not included in the ixazomib group safety population. Among patients with standard-risk cytogenetics, 1 patient randomized to the ixazomib arm did not receive ixazomib, and 2 patients randomized to the placebo arm accidentally received ixazomib and were conservatively included in the ixazomib group for analyses of exposure and safety.

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SAFETY CONSIDERATIONS FOR THE TREATMENT OF RR MM

	POMA/DEXA	KRD	DARA RD	DARA VD	IXA RD
INFUSION REACTIONS			++	++	
NEUROPATHY				+	
CARDIAC EVENTS		+			
NEUTROPENIA	+	+/-	+/-	+/-	
THROMBOCYTOPENIA	+/-	+/-	+/-	+/-	+
THROMBOSIS					
MODERATE RENAL FAILURE		+/-	+/-		+/-
SEVERE RENAL FAILURE		+	+		+