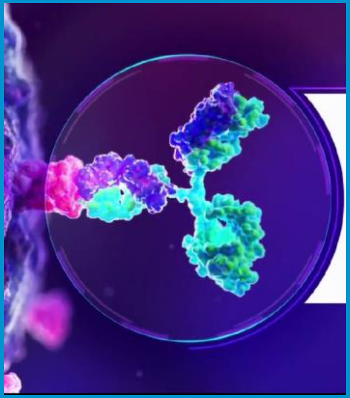


Thema middag Bloedtransfusie: Nieuwe Ontwikellingen

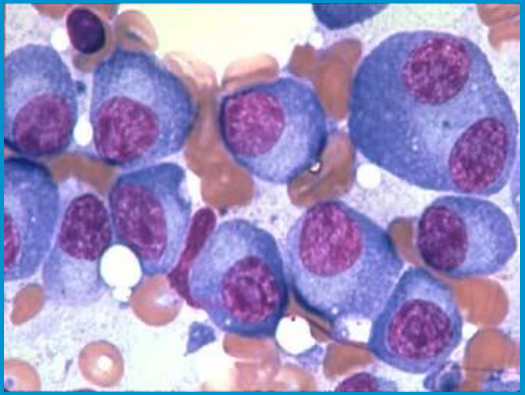
22 maart 2018

Daratumumab: doelgerichte therapie?

Dr. Erik Beckers,
internist-hematoloog/transfusiespecialist

Maastricht UMC+

academisch ziekenhuis Maastricht azM | Maastricht University



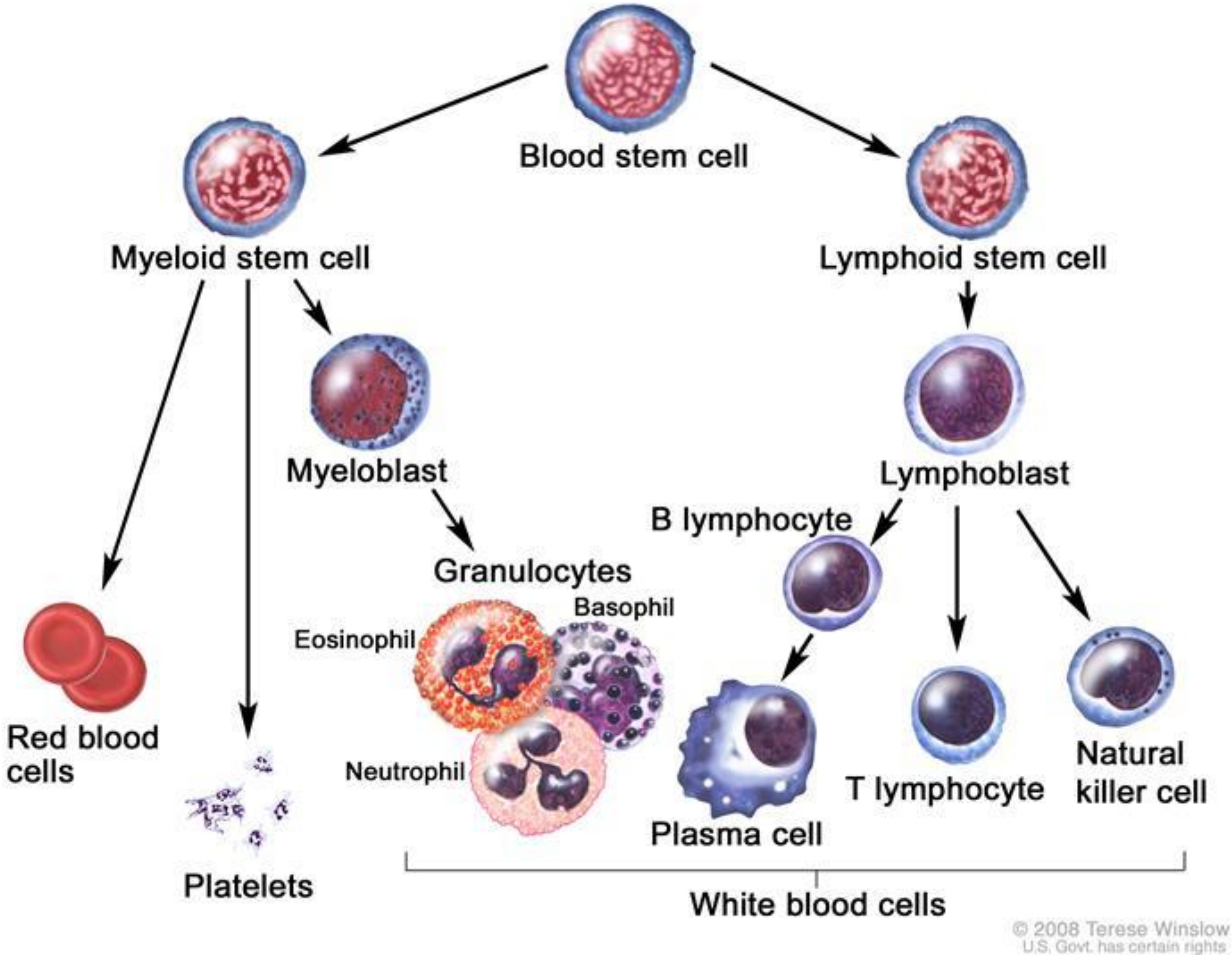
Disclosure belangen spreker bijeenkomst Kennisplatform 22 maart 2018	
Naam: dr. Erik AM Beckers, internist-hematoloog/transfusiespecialist	
Voor bijeenkomst mogelijk relevante relaties	**Bedrijfsnamen**
• Sponsoring of onderzoeksgeld	• Bayer
• Honorarium of andere (financiële) vergoeding	• Roche, Pfizer, Bayer, Sanquin, CSL Behring. (Transparantieregister)

Daratumumab: doelgerichte therapie?

Leerdoelen:

- Wat is de ziekte van Kahler, multiple myeloom?
- Ontwikkelingen in de behandelingen van MM
- Wat is daratumumab?
- Wat is het werkingsmechanismem?
- Wanneer wordt daratumumab toegepast?
- Uitdaging voor het compatibiliteitsonderzoek

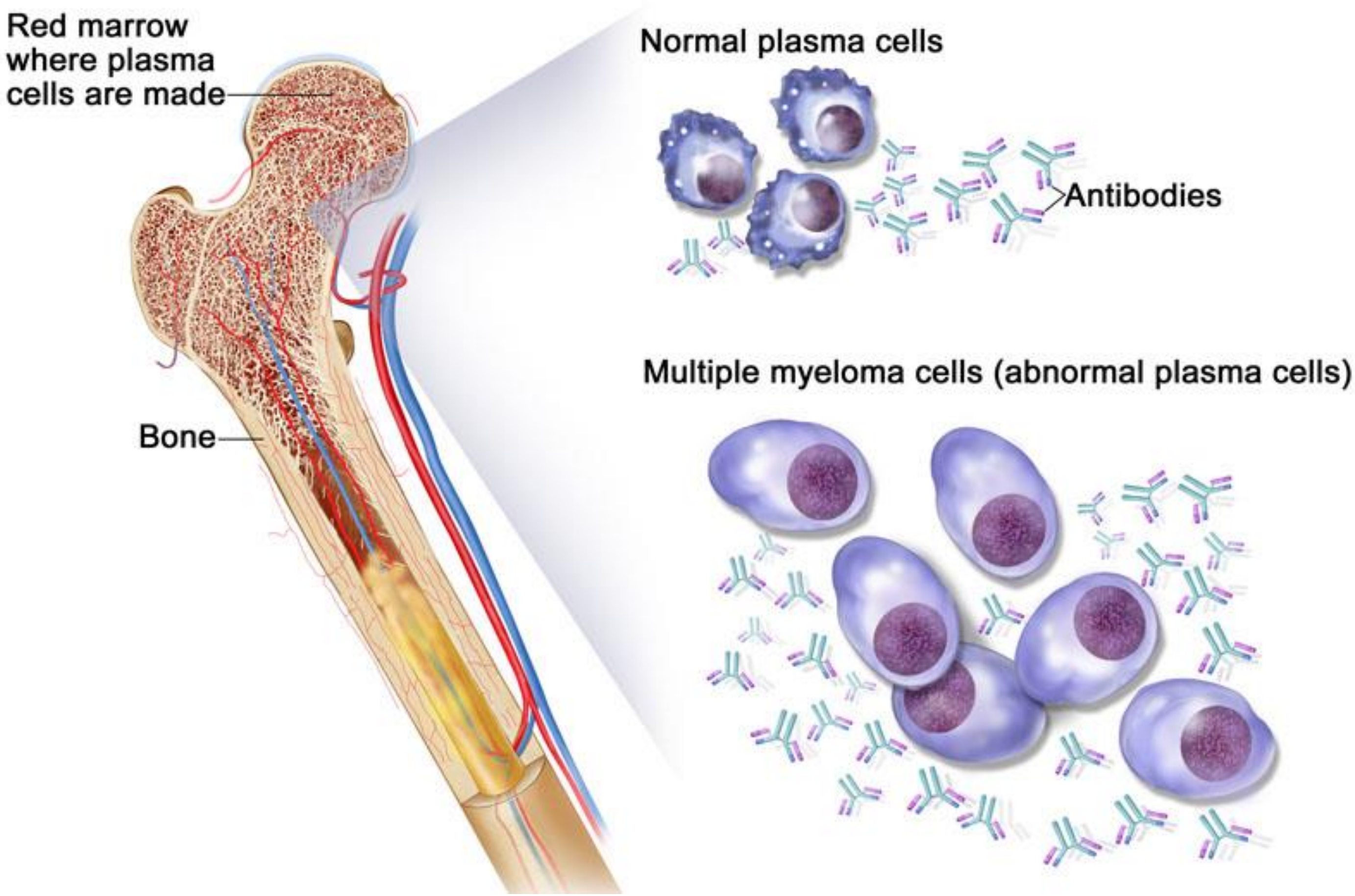
Normale hematopoeise



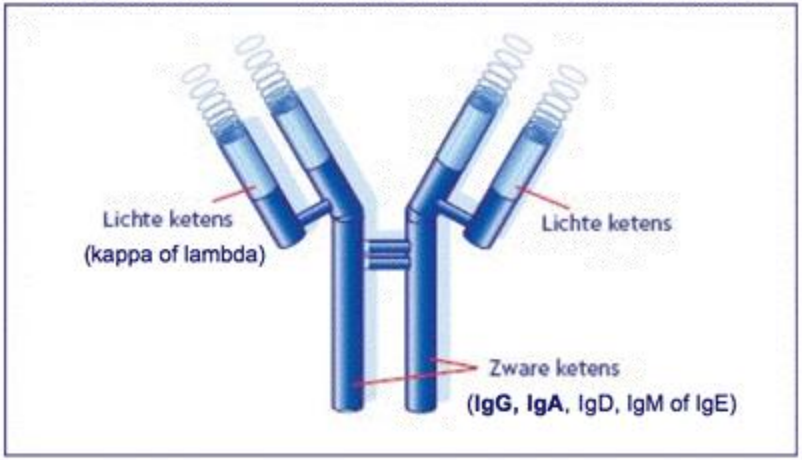
Ziekte van Kahler (multiple myeloom)

=

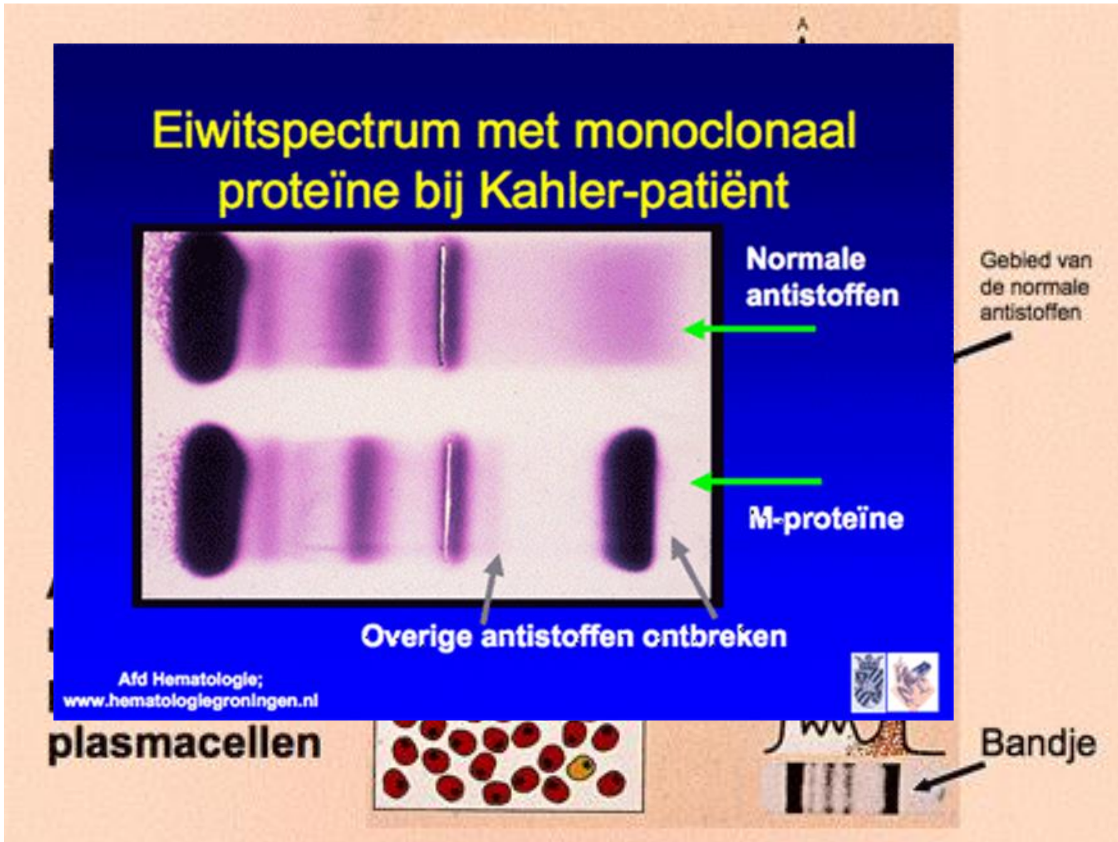
Proliferatie van monoclonale plasmacellen


Red marrow where plasma cells are made
Bone
Normal plasma cells
Antibodies
Multiple myeloma cells (abnormal plasma cells)

Antistoffen (immuunglobulinen)



Uit: Contactgroep Multipel Myeloom Patiënten, Vlaanderen


Eiwitspectrum met monoclonaal proteïne bij Kahler-patiënt
Normale antistoffen
M-proteïne
Overige antistoffen ontbreken
Afd Hematologie;
www.hematologiegroningen.nl
Gebied van de normale antistoffen
plasmacellen
Bandje

Ziekte van Kahler (multiple myeloom)

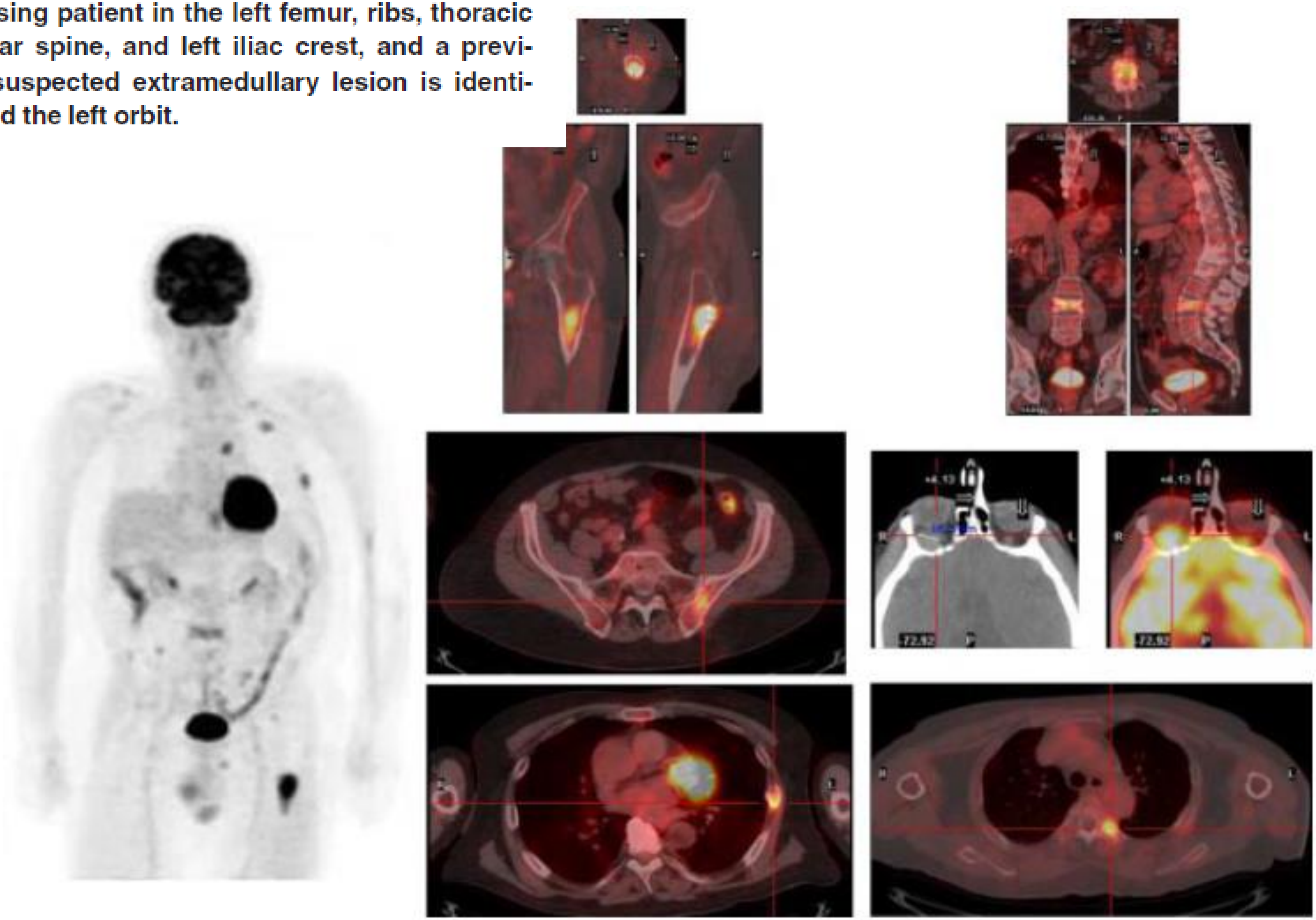
Klachten:

Toevalsbevinding: ontdekking van M-proteine in serum

Botfracturen, wervelinzakkingen
Osteoporose
Anemie
Nierfunctie stoornissen
Hypercalciemie

>>>>> CRAB criteria

Figure 1. Myeloma deposits are identified by PET-CT in a relapsing patient in the left femur, ribs, thoracic and lumbar spine, and left iliac crest, and a previously unsuspected extramedullary lesion is identified behind the left orbit.



BLOOD, 24 DECEMBER 2009 • VOLUME 114, NUMBER 27

Ziekte van Kahler (multiple myeloom)

Ontwikkelingen in de behandeling

	Alkyleer-ders	Cortico-steroiden	Immuno-Moduleer-ders	Proteosoom remmers	HDAC remmers	Monocl. antistoffen
Voor 2000	Melfalan Cyclofosfamide	Prednison Dexamethason				
2000			Thalidomide			
2005-2010			Lenalidomide	Bortezomib		
2010-2015			Pomalidomide	Carfilzomib		
Na 2015				Ixazomib	Panobinostat	Elotuzumab (anti-CD317 =SLAMF7) **Daratumumab (anti-CD38)**

Maastricht UMC+

Ziekte van Kahler (multiple myeloom)

Ontwikkelingen in de behandeling

Autologe stamceltransplantatie

Tandem autologe stamceltransplantaties

Allogene stamceltransplantatie: HLA-identiek

Allogene stamceltransplantatie: Haplo-identiek,
NK alloreactief

Leeftijdsgrens? Tot 70 jaar

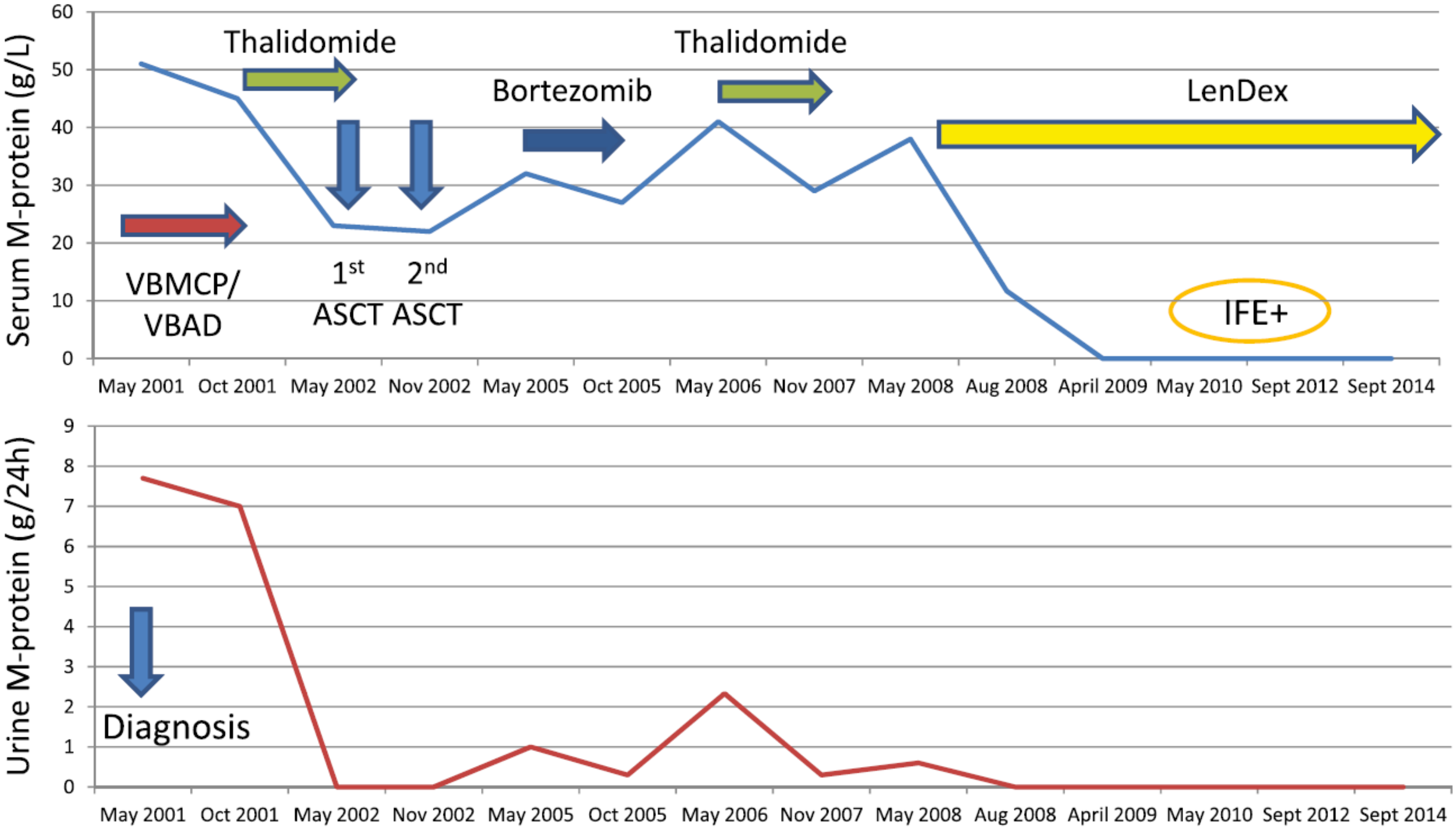


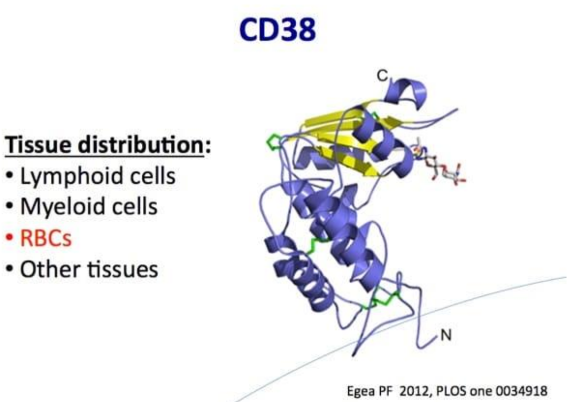
Figure 2. A patient with primary resistance to alkylating agents and to bortezomib. VBMCP/VBAD, vincristine, carmustine, cyclophosphamide, melphalan, prednisone alternated with vincristine, carmustine, doxorubicin, dexamethasone.

BLOOD, 5 MARCH 2015 • VOLUME 125, NUMBER 10

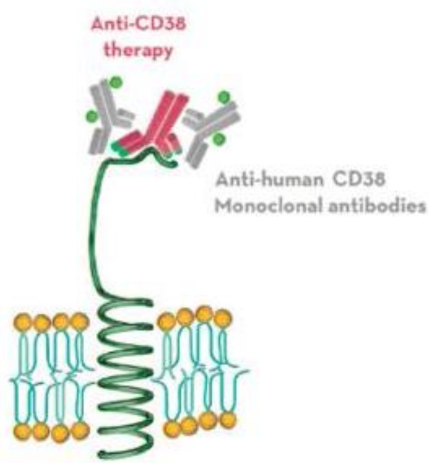
Ziekte van Kahler (multiple myeloom)

Wat is daratumumab?

Anti-CD38



Merker van cel activatie
Rol in de regulatie van intracellulair calcium



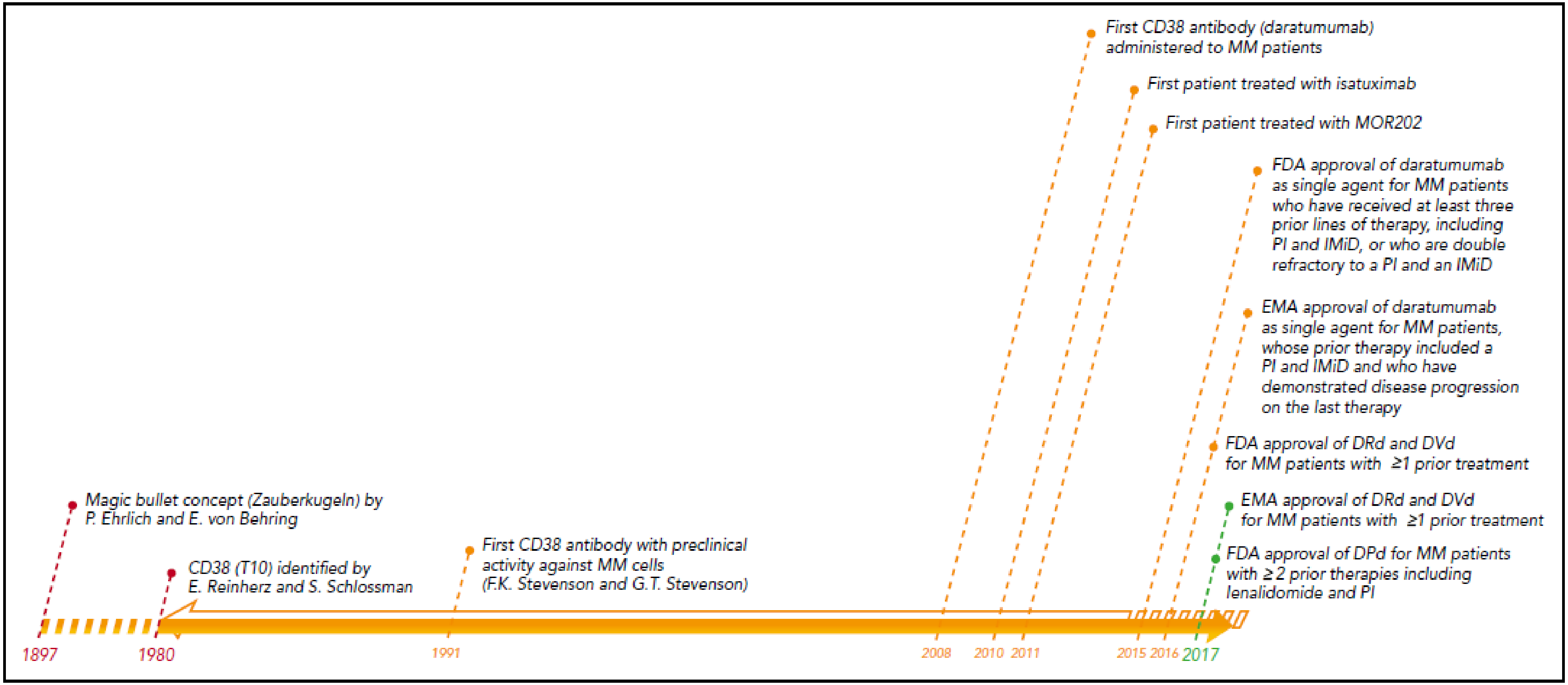
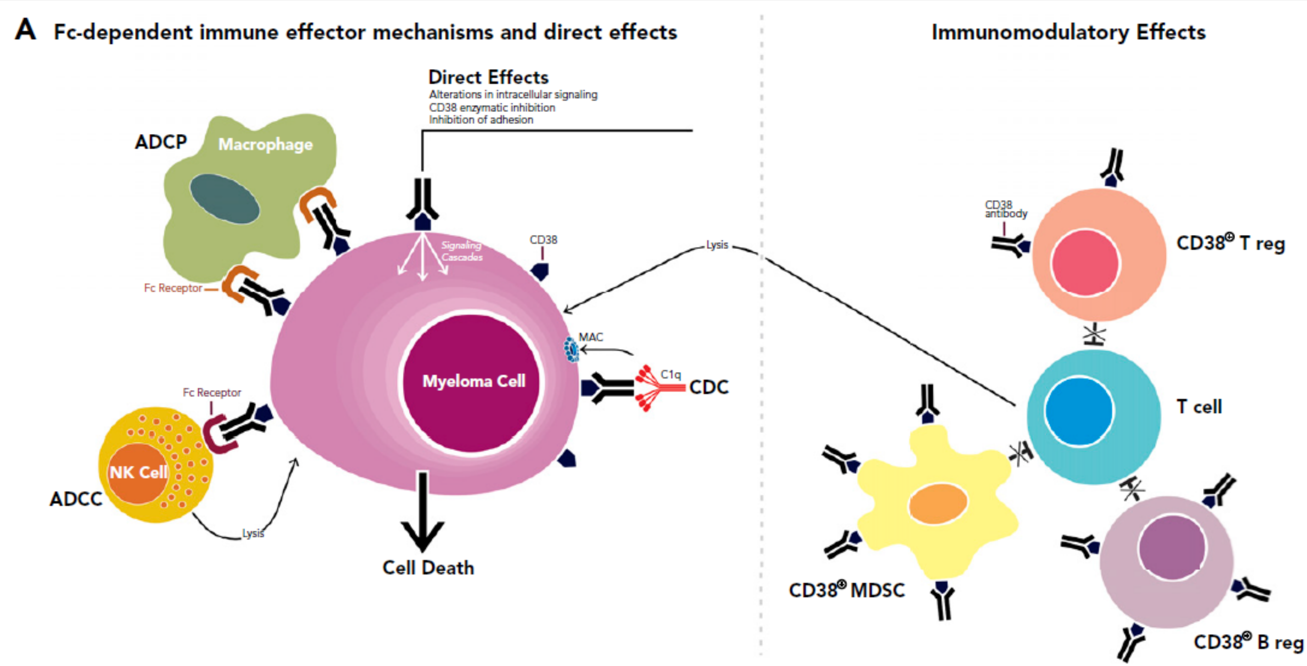


Figure 1. History of CD38 antibodies.

***Blood*. 2018;131(1):13-29**



B

MoA	DARATUMUMAB	ISATUXIMAB	MOR202
Origin, isotype	Human IgG-kappa	Chimeric IgG1-kappa	Human IgG1-lambda
CDC	+++	+	+
ADCC	++	++	++
ADCP	+++	nd	++
PCD direct	-	++	-
PCD cross linking	+++	+++	+++
Modulation ectoenzyme function	+	+++	-

Blood. 2018;131(1):13-29

Figure 2. Mechanism of action of CD38 antibodies.

Blood. 2018;131(1):13-29

	NCT02076009 (POLLUX)[59,62]	
Phase	Phase 3	
Regimen	Rd	DRd
Treatments	Lenalidomide: 25 mg on days 1-21 per 28-d cycle (10 mg if CrCl 30-60 mL/min) Dexamethasone: 40 mg weekly (20 mg if age >75 y) Treatment until progression	Daratumumab (16 mg/kg): weekly for 8 wk, then Q2W for 16 wk, thereafter Q4W Lenalidomide: 25 mg on days 1-21 per 28-d cycle (10 mg if CrCl 30-60 mL/min) Dexamethasone: 40 mg weekly (20 mg if age >75 y) Treatment until progression
No. of patients	283	286
Median age, y	65	65
Median no. of prior therapies	1	1
Len-refractory, %	Len-refractory patients were excluded	Len-refractory patients were excluded
Bort-refractory, %	16.3	19.9
IRR, %	Not applicable	47.7
≥PR, %	76.4	92.9
≥VGPR, %	44.2	75.8
≥CR, %	19.2	43.1
MRD^{-} disease (10^{-5}), %	5.7	24.8
PFS	12-mo: 60.1%	12 mo: 83.2%
OS	12 mo: 86.8%	12 mo: 91.2%

Table 1. CD38 antibodies plus lenalidomide-dexamethasone in relapsed/refractory MM

	NCT02136134 (CASTOR)[48,61]	
Phase	Phase 3	
Regimen	Vd	DVd
Treatments	Bortezomib 1.3 mg/m^2: days 1, 4, 8, 11 of 21-d cycle; 8 cycles Dexamethasone 20 mg: days 1, 2, 4, 5, 8, 9, 11,12; 8 cycles (20 mg once weekly if age >75 y)	Daratumumab (16 mg/kg): weekly ×10, Q3W until end of Vd, then Q4W until progression Bortezomib 1.3 mg/m^2: days 1, 4, 8, 11 of 21-d cycle; 8 cycles Dexamethasone 20 mg: days 1, 2, 4, 5, 8, 9, 11,12; 8 cycles (20 mg once weekly if age >75 y)
No. of patients	247	251
Median age, y	64	64
Median no. of prior therapies	2	2
Previous IMiD therapy, %	80.2	71.3
Previous PI therapy, %	69.6	67.3
IRR, %	Not applicable	45.3
≥PR, %	63.2	82.9
≥VGPR, %	29.1	59.2
≥CR, %	9.0	19.2
MRD$^-$ disease (10^{-5}), %	2.4	10.4
12-mo PFS, %	26.9	60.7
OS	Median OS, not evaluable; HR, 077	Median OS, not evaluable; HR, 0.77

Table 3. Bortezomib-dexamethasone with or without daratumumab in MM patients with at least 1 prior line of therapy (Castor study)

Blood. 2018;131(1):13-29

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma

M.-V. Mateos, M.A. Dimopoulos, M. Cavo, K. Suzuki, A. Jakubowiak, S. Knop, C. Doyen, P. Lucio, Z. Nagy, P. Kaplan, L. Pour, M. Cook, S. Grosicki, A. Crepaldi, A.M. Liberati, P. Campbell, T. Shelekhova, S.-S. Yoon, G. Iosava, T. Fujisaki, M. Garg, C. Chiu, J. Wang, R. Carson, W. Crist, W. Deraedt, H. Nguyen, M. Qi, and J. San-Miguel, for the ALCYONE Trial Investigators*

N Engl J Med 2018;378:518-28.

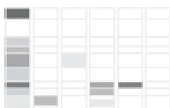
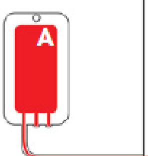
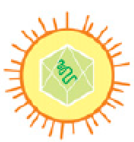
	Management Aspect	Applicable to	Management and Developments
	Administration -Duration of infusion -Infusion-related reactions	All antibodies	Appropriate pre- and post-infusion medication; subcutaneous administration of daratumumab
	Interference of therapeutic antibody with SPEP/IFE assays	All antibodies but dependent on plasma concentrations	Shift assays; mass spectrometry
	Auto-immune adverse events	PD-1/PD-L1 neutralizing antibodies (not observed with CD38 antibodies)	Institution of appropriate treatment (including prompt treatment with prednisone)
	Interference with blood transfusion tests	CD38-targeting antibodies (and CD44-targeting antibodies)	DTT, anti-idiotype, serotyping/genotyping before start therapy; provide patients with blood transfusion card
	Infections	Dependent on antibody type and other drugs in combination regiments	Herpes zoster prophylaxis is recommended for CD38 antibodies

Figure 3. Practical aspects of management of CD38 antibody therapy.

Table 4. Selected ongoing or planned studies with CD38-targeting antibody-containing regimens in other conditions

Study	Phase	Patients	Treatment
NCT02841033	1/2	Relapsed or refractory AL amyloidosis	Daratumumab as single agent
NCT02816476 (AMYDARA)	2	Patients with AL amyloidosis not in VGPR or better after previous treatment	Daratumumab as single agent
NCT03067571	2	AML or high-risk myelodysplastic syndrome (relapsed or refractory)	Daratumumab as single agent
NCT03011034	2	Transfusion-dependent patients with low or intermediate-1 risk myelodysplastic syndrome who are relapsed or refractory to erythropoiesis-stimulating agents	Daratumumab as single agent
NCT03095118	2	PGNMID and C3GN	Daratumumab as single agent
NCT03098550	1/2	Advanced or metastatic solid tumors	Daratumumab plus nivolumab
NCT02488759 (CheckMate358)	1/2	Virus-associated tumors such as squamous cell carcinoma of the head and neck, cervix, and anal canal	Nivolumab or nivolumab combinations, including nivolumab plus daratumumab
NCT02060188 (CheckMate142)	2	Recurrent and metastatic colon cancer	Nivolumab or nivolumab combinations, including nivolumab plus daratumumab
NCT03023423	1/2	Previously treated advanced or metastatic non–small cell lung cancer	Daratumumab plus atezolizumab vs atezolizumab
NCT02413489 (Carina)	2	Relapsed/refractory $CD38^+$ mantle cell lymphoma, diffuse large B-cell lymphoma, and follicular lymphoma	Daratumumab as single agent
NCT02927925	2	Relapsed/refractory NKTCL, nasal type	Daratumumab as single agent
NCT01084252	1/2	Relapsed/refractory $CD38^+$ hematological malignancies such as B-cell non-Hodgkin lymphoma, MM, AML, B-ALL, and CLL	Isatuximab as single agent
NCT02999633	2	Relapsed or refractory T-ALL and T-LBL	Isatuximab as single agent

AL amyloidosis
AML
MDS
NHL
ALL

PGNMID

Metastatic solid Tumours

Plaveiselcelcarcinoom

Coloncarcinoom

Longcarcinoom

Mantelcellymfoom

Daratumumab: doelgerichte therapie?

JA is gericht tegen CD38

NEE niet alleen tegen maligne plasmacellen

Uitdaging voor het compatibiliteitsonderzoek

Panreactieve reacties bij compatibiliteitsonderzoek

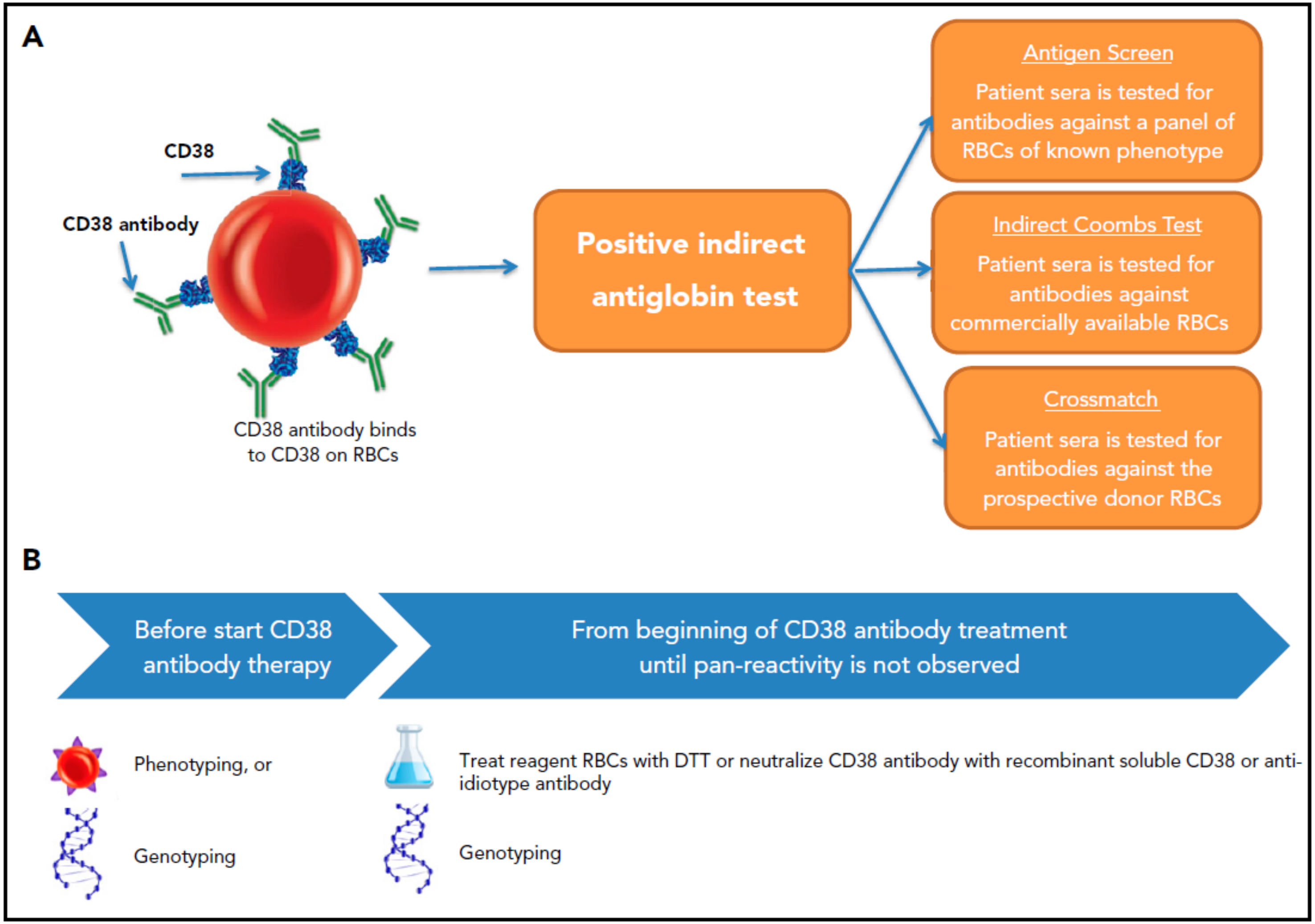


Figure 5. CD38 antibodies interfere with blood group compatibility testing.

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