UMC Utrecht

Morbus Waldenström

diagnostiek/monitoring/behandeling

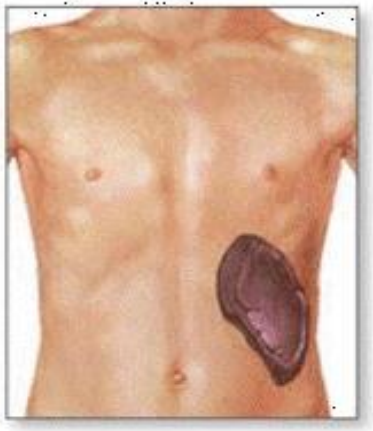
SKML 2017

Monique Minnema, internist-hematoloog

Morbus Waldenström; B cel NHL in beenmerg

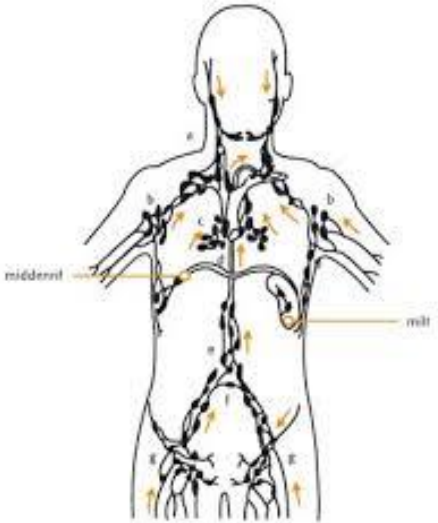
- PA diagnose; lymfoplasmacellulair lymfoom / LPL (vroeger immunocytoom)
  - bevat klonale B cellen *en* klonale plasmacellen
- Alleen indien serum IgM M proteine bevat = Morbus Waldenström
- > 95% ; LPL + IgM = MW
- Immunofenotypering toont dus 2 populaties aan
- FLC geen duidelijke rol in diagnostiek

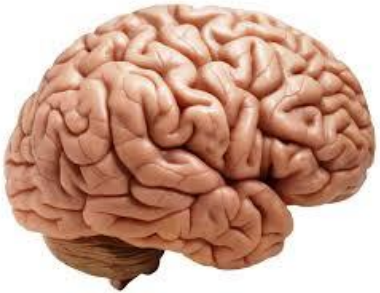
Overige lokalisaties Morbus Waldenstrom



Milt, 15-30%

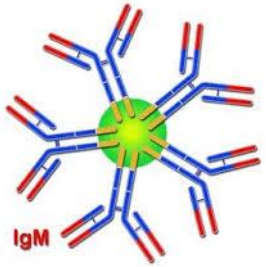
Lymfeklieren;
15-30%





Hersenen + hersenvocht
< 1% (Bing Neel)

Klachten



- Moeheid (70%)
- Nachtzweten, afvallen (B-symptomen) (25%)
- Anemie (40%)
- Hyperviscositeit (15%)
- Bloedingen (25%)
- Infecties (*immunoparese*)
- Auto reactiviteit:
  - Polyneuropathie, hemolyse, vasculitis

Getallen over Waldenström

- 150-200 nieuwe patiënten per jaar
- Prognose na stellen diagnose: 78% in leven na 5 jaar
- Gemiddelde leeftijd 63 jaar bij diagnose
- Ongeneeslijk, maar wel meerdere effectieve behandelingen mogelijk; **WAIT and SEE** indien geen tot milde klachten
- Behandeling steeds minder effectief bij 1ste recidief – 2de recidief etc

Familiair voorkomen

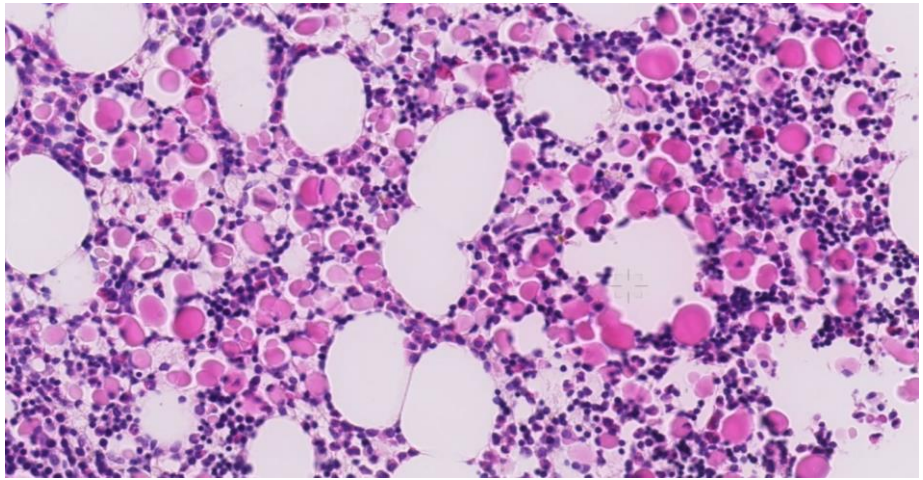
In familie meerdere patiënten met MW, B-cel lymfomen, CLL, multipel myeloom

- MW: 20% heeft familieleden met andere B-cel maligniteiten
- Geen 1 soortige erfelijke genafwijking vastgesteld
- Gedacht wordt aan associatie meerdere erfelijke en omgevings factoren
- Geen advies voor screening van familieleden: vroege diagnose geeft geen overlevingsvoordeel

Diagnostische valkuilen

- Marginale zone lymfoom; geen definieerde kenmerken
- CD20+ Multipel Myeloom
- IgM MGUS; "**toxisch** kleine kloon" kan soms ook al klachten geven!

??
Totaal IgM 3.2 gr/L

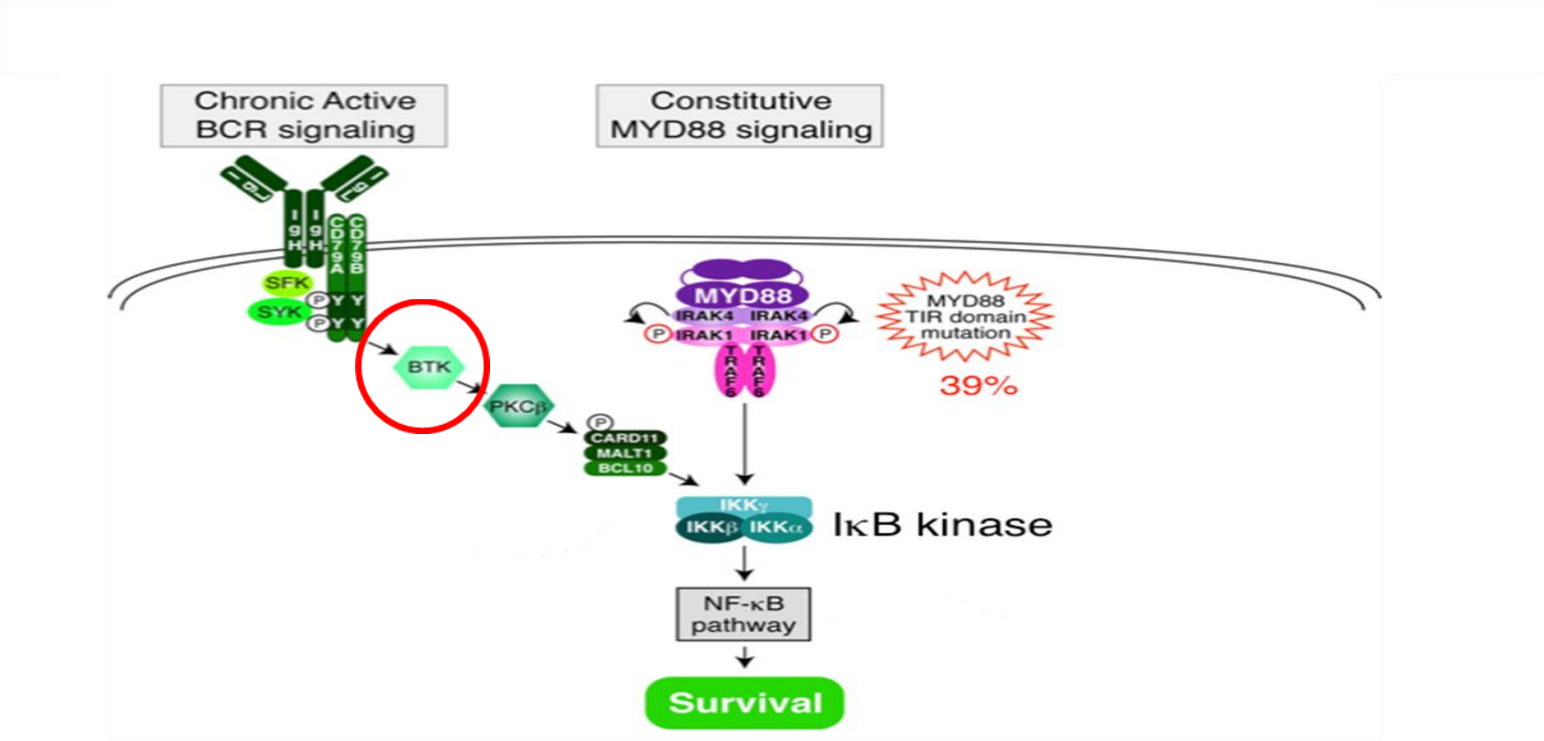


Classificatie WHO 2008; consensus IWWM

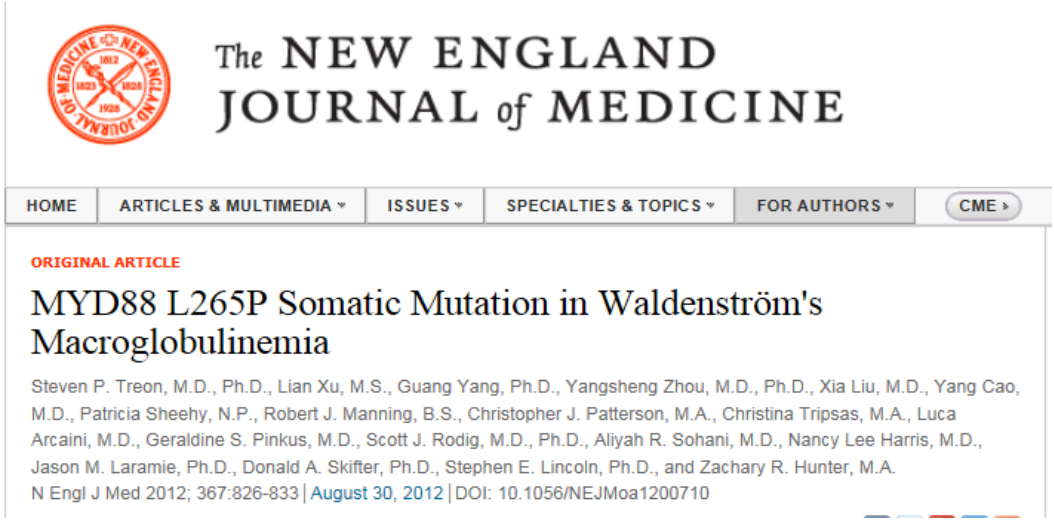
Tabel 3. Diagnostische indeling van M. Waldenström (MW).

	IgM-MGUS	asymptomatische MW	symptomatische MW	IgM-gerelateerde ziekte
IgM-M-proteïne (serum)	ja	ja	ja	ja
lymfoplasmocytair infiltraat (beenmerg)	nee	ja	ja	nee
MW-gerelateerde symptomatologie	nee	nee	ja	ja
beleid	vervolgen	'wait and see'	behandeling	afhankelijk van welke manifestatie, zie tekst
kans op progressie naar MW	1,5% per jaar	50-60% na 5 jaar	n.v.t.	onbekend

Nieuw; MYD88 mutatie; > 90% aanwezig bij Waldenström



MYD88L256P



The NEW ENGLAND JOURNAL of MEDICINE

HOME | ARTICLES & MULTIMEDIA | ISSUES | SPECIALTIES & TOPICS | FOR AUTHORS | CME

ORIGINAL ARTICLE

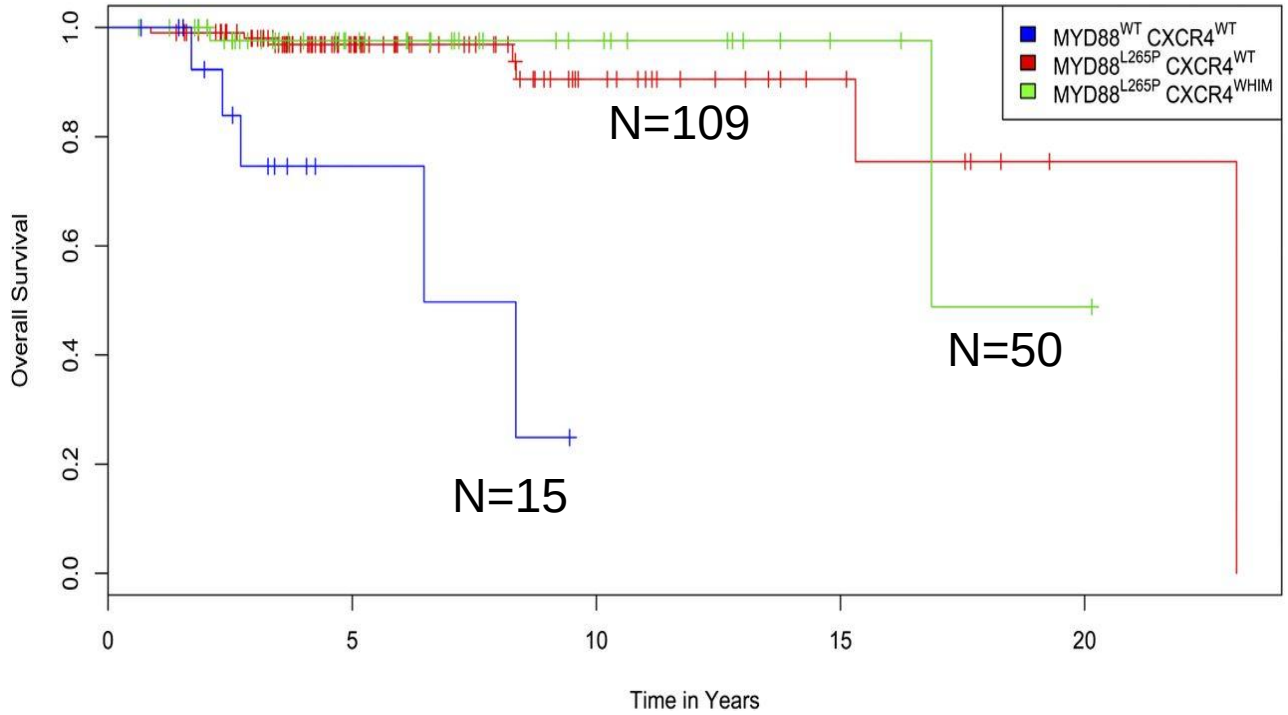
MYD88 L265P Somatic Mutation in Waldenström's Macroglobulinemia

Steven P. Treon, M.D., Ph.D., Lian Xu, M.S., Guang Yang, Ph.D., Yangsheng Zhou, M.D., Ph.D., Xia Liu, M.D., Yang Cao, M.D., Patricia Sheehy, N.P., Robert J. Manning, B.S., Christopher J. Patterson, M.A., Christina Tripsas, M.A., Luca Arcaini, M.D., Geraldine S. Pinkus, M.D., Scott J. Rodig, M.D., Ph.D., Aliyah R. Sohani, M.D., Nancy Lee Harris, M.D., Jason M. Laramie, Ph.D., Donald A. Skifter, Ph.D., Stephen E. Lincoln, Ph.D., and Zachary R. Hunter, M.A.

N Engl J Med 2012; 367:826-833 | August 30, 2012 | DOI: 10.1056/NEJMoa1200710

- Publikatie 2012
- Al bekende mutatie in andere lymfomen
- Ingevoerd als diagnostische test in Nederland
- Bijkomend; diverse CXCR4 mutaties (30%); prognose?

Kaplan-Meier plot for overall survival of 175 WM patients from time of diagnosis stratified by MYD88 and CXCR4 mutation status.



Steven P. Treon et al. Blood 2014;123:2791-2796

Refs.	Method	WM	LPL	MGUS	MZL/MALT	CLL/SLL	Other
Ngo et al. [8]	mRNA sequencing				9% (6/67)		29% ABC-DLBCL (55/192)
Treon et al. [9]	WGS Sanger	91% (49/54)	100% (3/3)				
Xu et al. [13]	Sanger AS-PCR	93% (97/104)		54% (13/24)	10% (2/20)	4% (1/26)	
Varettoni et al. [12]	Sanger AS-PCR	100% (58/58)		47% (36/77)	6% (5/84)		4% B-CLPD (3/52)
Poulain et al. [13]	Sanger	79% (53/67)	100% (1/1)	50% (1/2)	6% (1/16)		4% FCL (1/23)
Puente et al. [14]	WGS					3% (9/310)	
Fernandez-Rodriguez et al. [16]	AS-PCR						10% DLBCL (17/175)
Capaldi et al. [17]	Sanger AS-PCR	97% (31/32)	100% (1/1)	43% (9/21)			25% DLBCL (2/8)
Bohers et al. [19]	Sanger						29% DLBCL (18/61)
Ondrejka et al. [39]	AS-PCR		100% (13/13)				8% HCL (1/13)
Mori et al. [40]	Sanger Restriction-Enzyme Digest AS-PCR	76% (19/25)	50% (1/2)				
Jimenez et al. [41]	AS-PCR	86% (101/117)		87% (27/31)	21% (3/14)		19% DLBCL (9/48)
Willenbacher et al. [42]	Sanger	85% (6/7)					
Insuasti-Beltran et al. [46]	Pyro-sequencing		96% (43/45)		4% (2/53)	3% (6/220)	

Monitoring

- Respons criteria; *update BJH 2013, Owen et al*

- Vervolgen op IgM/M proteine
  - Bekend dat deze langzaam zakt, gaat door na stop therapie
- Beenmerg;
  - Wil patient niet altijd ondergaan
- Verbetering mogelijk?

Response category	Definition
Complete response (CR)	Absence of serum monoclonal IgM protein by immunofixation Normal serum IgM level Complete resolution of extramedullary disease, i.e., lymphadenopathy and splenomegaly if present at baseline Morphologically normal bone marrow aspirate and trephine biopsy
Very good partial response (VGPR)	Monoclonal IgM protein is detectable ≥90% reduction in serum IgM level from baseline [a] Complete resolution of extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
Partial response (PR)	Monoclonal IgM protein is detectable ≥50% but<90% reduction in serum IgM level from baseline [a] Reduction in extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
Minor response (MR)	Monoclonal IgM protein is detectable ≥25% but<50% reduction in serum IgM level from baseline [a] No new signs or symptoms of active disease

Stable disease (SD)	Monoclonal IgM protein is detectable <25% reduction and <25% increase in serum IgM level from baseline [a] No progression in extramedullary disease, i.e.,lymphadenopathy/splenomegaly No new signs or symptoms of active disease
Progressive disease (PD)	≥25% increase in serum IgM level [a] from lowest nadir (requires confirmation) and/or progression in clinical features attributable the disease

a Sequential changes in IgM levels may be determined either by M protein quantitation by densitometry or total serum IgM quantitation by nephelometry.

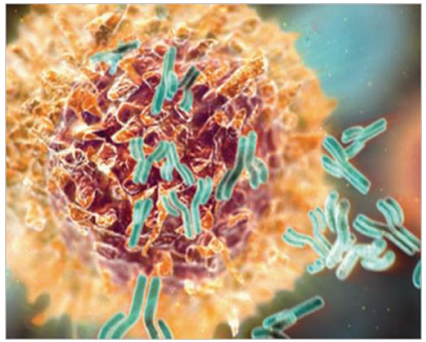
The biological variability for M protein quantitation by densitometry and immunoglobulin quantitation by nephelometry are 8% and 13%, respectively (Katzmann et al, 2011).

Toekomst: monitoring bloed/“liquid biopsy”

A				
Paired patients	N	MYD88 L265P positive		
		BM	PB	% Of patients positive by PB with positive BM
Untreated (all)	61	58 (95.1%)	57 (93.4%)	98.20%
Smoldering	13	12 (92.3%)	11 (84.6%)	91.60%
Symptomatic	48	46 (95.8%)	46 (95.8%)	100%
Previously treated (all)	66	61 (92.4%)	45 (68.2%)	73.70%
IgM MGUS	12	6 (50%)	5 (41.7%)	83.30%
B				

Xu et al, Leukemia (2014) **28,** 1698–1704

Behandeling

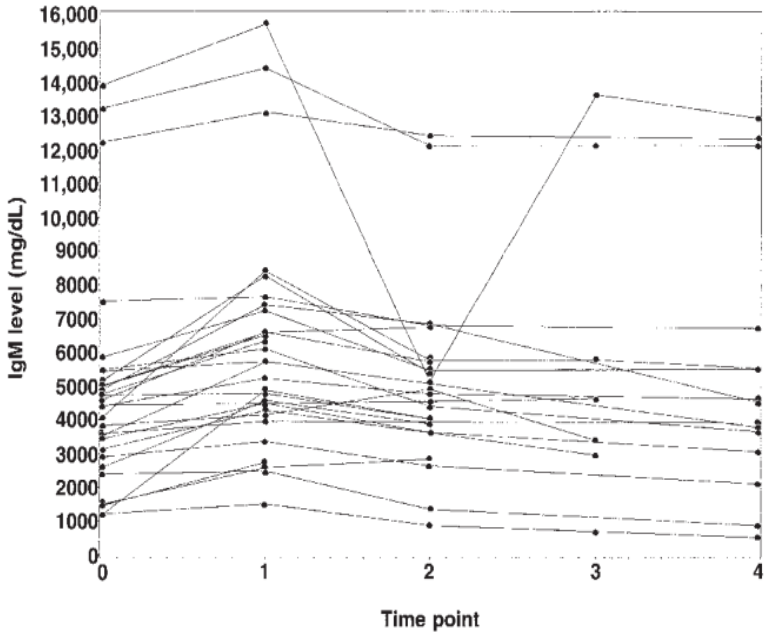


- Combinatie therapie meest effectief
  - Rituximab = monoklonale antistof
  - Chemotherapie =
    - cyclofosfamide, fludarabine, bendamustine
  - Prednison

- In specifieke gevallen : stamceltransplantatie
  - Leeftijd < 65 jaar
  - Autologe SCT; agressieve ziektebeloop
  - Allogene SCT; recidiverend en resistent ziektebeloop

IgM flare

Ghobrial et al, Cancer 2004



Gem duur 4 mnd

- Tot 54% van MW patienten
- Geen relatie met prognose
- Dus niet te snel concluderen dat er progressie is!
- Bij hoge begin IgM cave hyperviscositeit of exacerbatie bijv. IgM gerelateerde neuropathie,
- evt eerst chemotherapie alleen of plasmaferese

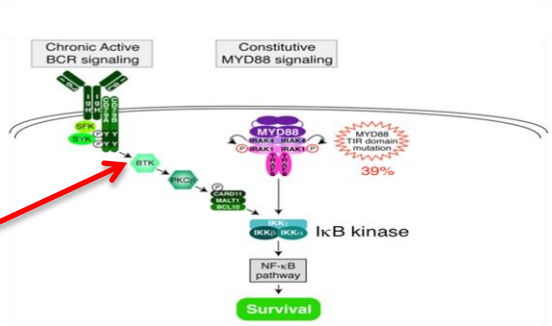
“Nieuwe” middelen; Proteasoom remmers

- Zeer effectieve medicijnen bij plasmacel kankers zoals Multipel Myeloom
  - Bortezomib; Polyneuropathie
  - Carfilzomib, infuus, effectiever, minder PNP
  - Ixazomib, pil, minder PNP
- Bortezomib voor Waldenström ; add on jan 2017
- **HOVON 124**

HOVON 124

- Voor patiënten met **recidief MW**
- 1 tot 3 eerdere behandelingen gehad
- Nieuwe proteasoomremmer **ixazomib** in combinatie met rituximab en dexamethason
- Gevolgd door 2 jaar rituximab onderhoud
- Mogelijke voordelen: oraal middel, **minder neurotoxisch**, wel mgl lage bloedplaatjes, moeheid en maag-darmklachten
- Start begin 2015, samenwerking HOVON + Athene

Ibrutinib



- Remt bruton tyrosine kinase / BTK
- BTK remmers zijn ook actief in meerdere types B cel lymfomen zoals mantelcel NHL en B-CLL (geen MYD88 mutatie)
- Slechts 1 Waldenström studie met resultaten bekend
- Fase 2 studie, 63 pt; 1 dd 420 mg, continue slikken
- Registratie voor recidief patienten of niet geschikt voor immuno-chemotherapie
- BTK mutaties, waardoor resistentie, inmiddels bekend

Progessie op Ibrutinib

Patient	*BTK* *Cys481Arg(T>C)*	*BTK* *Cys481Ser(T>A)*	*BTK* *Cys481Ser(G>C)*	*BTK* *Cys481Tyr(G>A)*	*PLCγ2* *Tyr495His(T>C)*	*CARD11* *Leu878Phe(C>T)*
WM1	ND	ND	ND	ND	ND	ND
WM2	**32.4%**	**6.6%**	**5.8%**	**1.0%**	ND	ND
WM3	**0.3%**	**34.4%**	**6.5%**	**0.3%**	ND	**0.2%**
WM4	ND	ND	ND	ND	ND	ND
WM5	ND	ND	ND	ND	ND	ND
WM6	ND	ND	**10.3%**	ND	**11.9%**	ND
WM7	ND	ND	**1.5%**	ND	ND	ND
WM8	ND	ND	**0.7%**	ND	ND	ND

Best Clinical Responses to Ibrutinib

Median of 9 (range 1-18) Cycles

	(N=)	(%)
VGPR	6	9.5
PR	34	54
MR	12	19
SD	10	16
Non-Responder	1	2

ORR: 83% Major RR (≥ PR): 64%

Response criteria adapted from 3rd International Workshop on WM (Treon et al, BJH 2011)

Ibrutinib Related Adverse Events

Adverse event	# Grade 2 Events	# Grade 3 Events	# Grade 4 Events	Total # of Events
Neutropenia	3	7	2	12
Thrombocytopenia	3	6	1	10
Bleeding	4	1		5
Pneumonic Infection	2	1		3
Anemia	2	1		3
Tachyarrhythmia	2	1		3
Syncope/Pre-syncope	1	1		2
Herpes Zoster	1	1		2
Endocarditis infective		1		1
Fever	1			1
Hypertension	1			1
Pruritus	1			1
Mucositis	1			1
Oral Pain	1			1
Diarrhea	1			1
Arthralgia	1			1

MYD88 /CXCR4 Status and Ibrutinib Major Responses

MYD88	N=	VGPR/PR	MR/SD/NR
L265P	48	31 (65%)	17 (35%)
Wild Type	5	2 (40%)	3 (60%)

p = 0.3536 Odds ratio = 2.68 95% CI 0.28-35.02

CXCR4	N=	VGPR/PR	MR/SD/NR
WHIM	10	3 (30%)	7 (70%)
Wild Type	30	24 (80%)	6 (20%)

p = 0.0065 Odds ratio = 0.115 95% CI 0.02-0.68

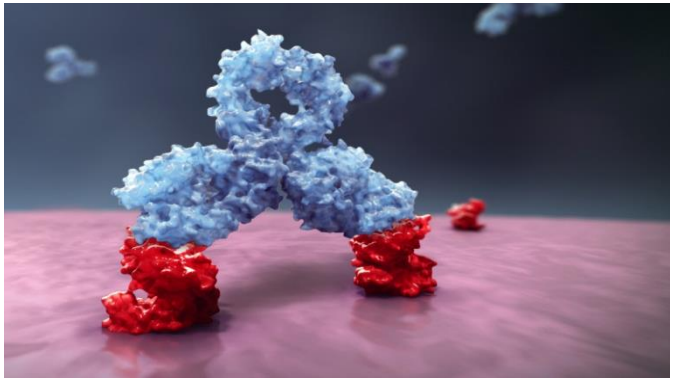
Ibrutinib look-a-likes

- Hetzelfde werkingsmechanisme
- **ACP-196 / acalabrutinib**
  - An Open-label, Phase 1b/2 Study
- **BGB-3111**
  - Fase III gerandomiseerde studie vs Ibrutinib start binnenkort in AMC & UMC Utrecht

Daratumumab Overview

Mechanism of Action and Key Attributes

- **First-in-class** human immunoglobulin G1 kappa (IgG1κ) mAb with high affinity to CD38
- **CD38 expressed at a high level** in a variety of **malignancies**, including:
  - Myeloma
  - Lymphoma
  - Leukemia
- Intended for administration by the IV route after dilution at 16mg/kg



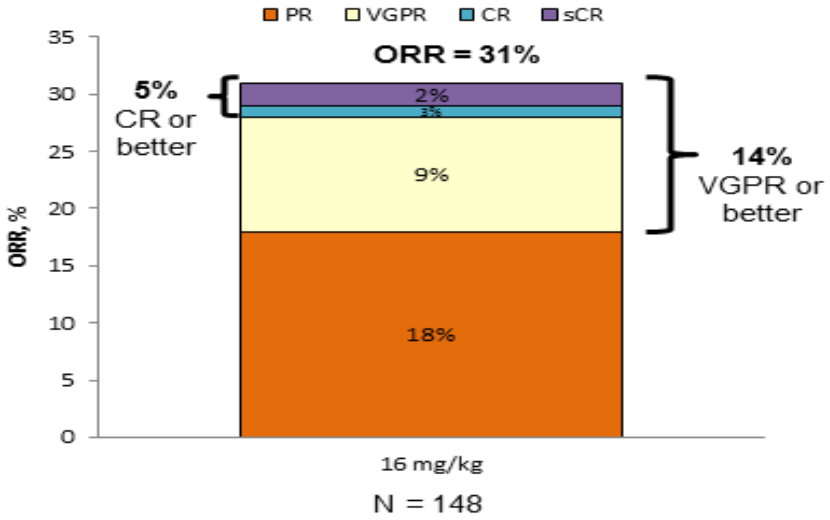
GEN501 and SIRIUS (MMY2002) Combined Analysis:
Baseline Characteristics

	16 mg/kg		
	GEN501, Part 2 n = 42	SIRIUS n = 106	Combined N = 148
Median (range) age, y	64.0 (44-76)	63.5 (31-84)	64 (31-84)
65 to <75 y, n (%)	16 (38)	36 (34)	52 (35)
≥75 y, n (%)	4 (10)	12 (11)	16 (11)
Female/male sex, %	36/64	51/49	47/53
ECOG score, n (%)			
0	12 (29)	29 (27)	41 (28)
1	28 (67)	69 (65)	97 (66)
2	2 (5)	8 (8)	10 (7)
Extramedullary plasmacytomas, n (%)			
0	38 (90)	92 (87)	130 (88)
≥1	4 (10)	14 (13)	18 (12)
Cytogenetic profile,* n (%)			
t(4;14)		9 (10)	
del17p		16 (17)	
del13q		30 (32)	
amp1q21		23 (24)	
Other		43 (45)	

Lokhorst HM, et al. *New Engl J Med*. 2015 373(13):1207-19.
Lonial S, et al. Lancet 2016;387(10027):1551-60.
Usmani S, et al. Blood 2016. May 23 [Epub ahead of print].

GEN501 and SIRIUS (MMY2002) Combined Analysis:
Efficacy

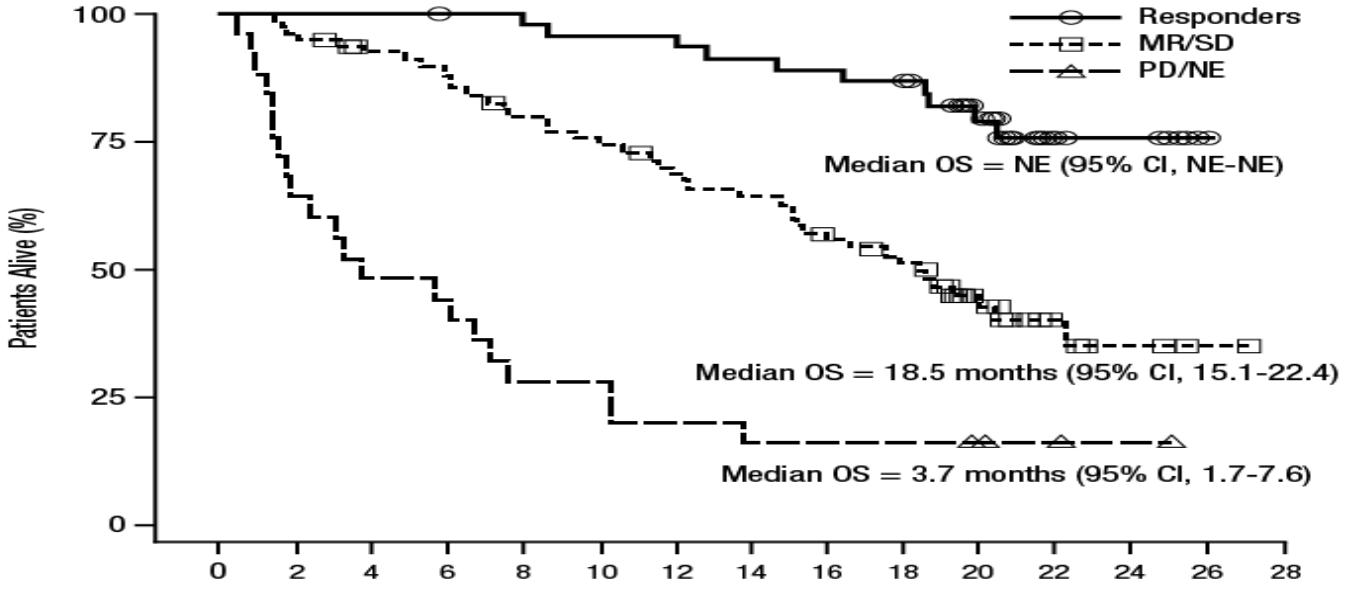
	16 mg/kg (N = 148)	
Response	n (%)	95% CI
ORR	46 (31.1)	23.7-39.2
Clinical benefit (ORR + MR)	55 (37.2)	29.4-45.5
VGPR or better (sCR+CR+VGPR)	20 (13.5)	8.5-20.1
CR or better (sCR+CR)	7 (4.7)	1.9-9.5
sCR	3 (2.0)	0.4-5.8
CR	4 (2.7)	0.7-6.8
VGPR	13 (8.8)	4.8-14.6
PR	26 (17.6)	11.8-24.7
MR	9 (6.1)	2.8-11.2
SD	68 (45.9)	37.7-54.3
PD	18 (12.2)	7.4-18.5
NE	7 (4.7)	1.9-9.5



- ORR = 31%
- ORR was consistent in subgroups including age, number of prior lines of therapy, refractory status, or renal function

GEN501 and SIRIUS (MMY2002) Combined Analysis:

OS by response category



Patients at risk															
Responders	46	46	46	45	44	43	43	41	40	39	28	12	11	2	0
MR/SD	77	74	67	63	57	53	48	45	38	34	20	8	4	1	0
PD/NE	25	16	12	11	7	7	5	4	4	4	3	2	1	0	0

Forced Expiratory Volume
during the 1st second of expiration (FEV_1)

- Volume of air expired in the first second during maximal expiratory effort.

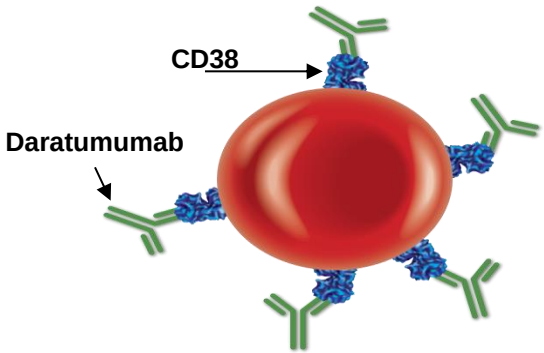
- The FEV1 is reduced in obstructive lung disease, such as COPD

Class[1]	FEV1	Symptoms
I	FEV1 ≥ 80% predicted	At this stage, the patient may not be aware that their lung function is abnormal
II	50% ≤ FEV1 < 80% predicted	Symptoms usually progress at this stage, with shortness of breath typically developing on exertion
III	30% ≤ FEV1 < 50% predicted	Shortness of breath typically worsens at this stage and often limits patients´daily activities. Exacerbations are especially seen beginning at this stage
IV	FEV1 < 30% predicted or FEV1 < 50% plus chronic respiratory failure	At this stage, quality of life is very appreciably impaired and exacerbations may be life-threatening

GOLD spirometric FEV1 criteria for COPD severity, available at http://www.goldcopd.org/uploads/users/files/GOLD_Spirometry_2010.pdf

Interference with Indirect Antiglobulin Tests (Coombs Test)

- CD38 is ubiquitously expressed on myeloma and lymphoma cells but expressed at low levels on normal lymphoid and myeloid cells
- CD38 is also expressed at low levels on red blood cells (RBCs)
- Daratumumab binding to RBCs interferes with blood bank compatibility tests, including the antibody screening and crossmatching (both indirect Coombs tests) that are part of a routine pretransfusion work up

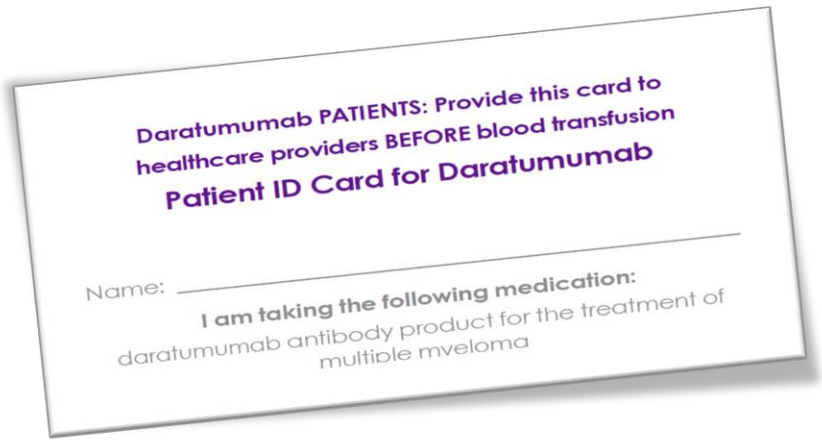


Daratumumab binds to CD38 on RBCs

Chapuy CI et al. *Transfusion.* 2015;55(6Pt2):1545-1554.

Interference with Indirect Antiglobulin Tests

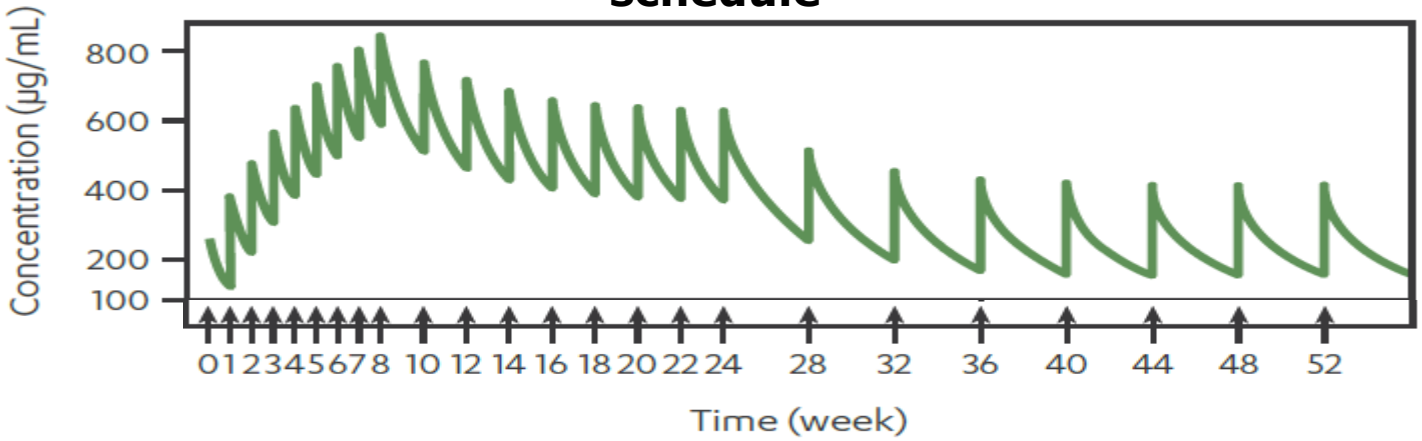
- <u>Ensure That Your Patients Take an Active Role in Their Treatment</u>
- Reassure your patient that compatible blood products for transfusion can still be identified
- **From start and for at least 6 months after their last Daratumumab treatment, patients should**
  - Carry their patient ID card, if applicable, and provide it to their HCPs



PHNL/DAR/1116/0001

Daratumumab level

Representative PK profile of DARA for the recommended dose and schedule



Arrows indicate that a dose was administered.

Concentratie wisselt tussen 0,1 en 0.8 gr/L

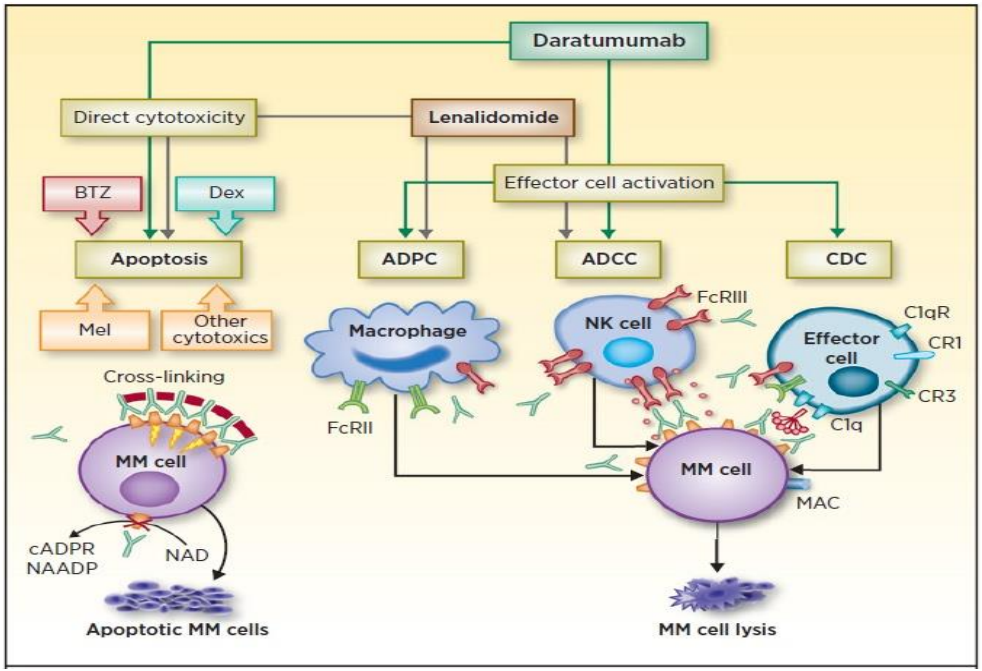
Xu XS, et al. Poster presented at: 2015 American Society of Hematology (ASH); December 5-8, 2015; Orlando, FL, USA (Abstract 4254).

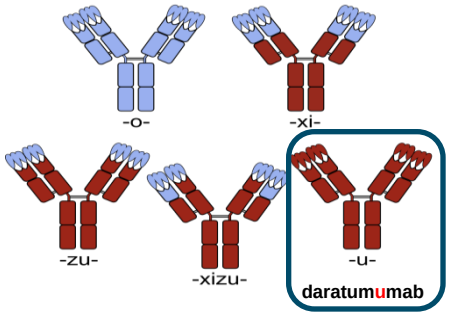
Daratumumab in clinical practice

The NEW ENGLAND JOURNAL of MEDICINE

Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma

H.M. Lokhorst, T. Plesner, J.P. Laubach, H. Nahi, P. Gimsing, M. Hansson, M.C. Minnema, U. Lassen, J. Krejcik, A. Palumbo, N.W.C.J. van de Donk, T. Ahmadi, I. Khan, C.M. Uhlar, J. Wang, A.K. Sasser, N. Losic, S. Lisby, L. Basse, N. Brun, and P.G. Richardson





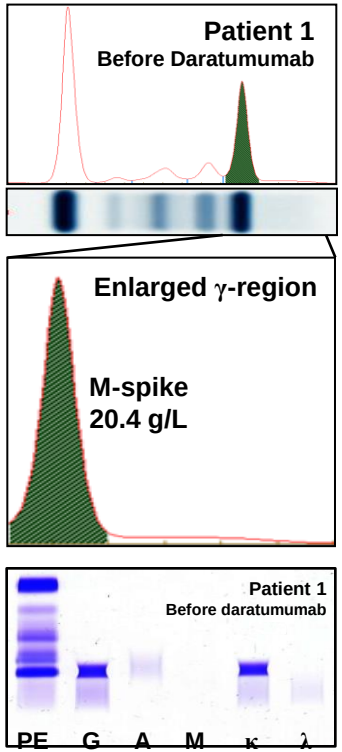
Lokhorst et al. NEJM 2015

Laubach et al. Clin Cancer Research 2015

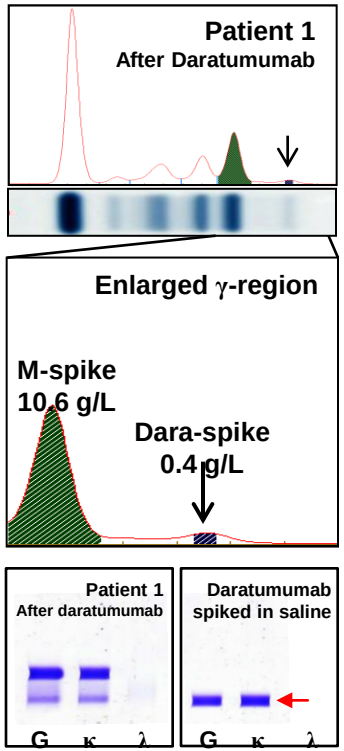
Radboudumc

Daratumumab and M-protein interference

1A

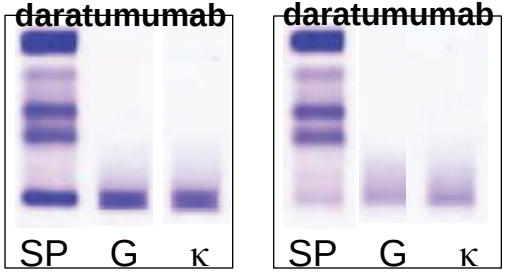


B

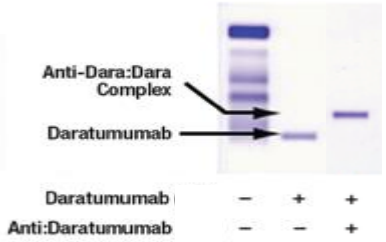


IMWG response criteria (Durie et al. 2006)

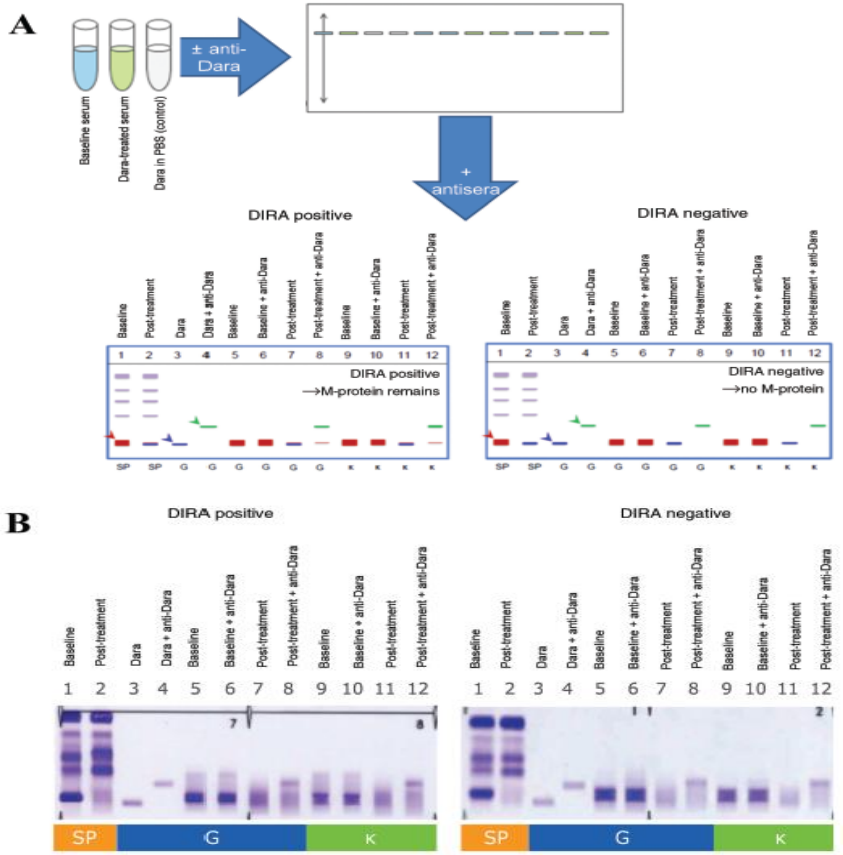
a.o. IFE negative…



Abrogate interference using mAb against biological



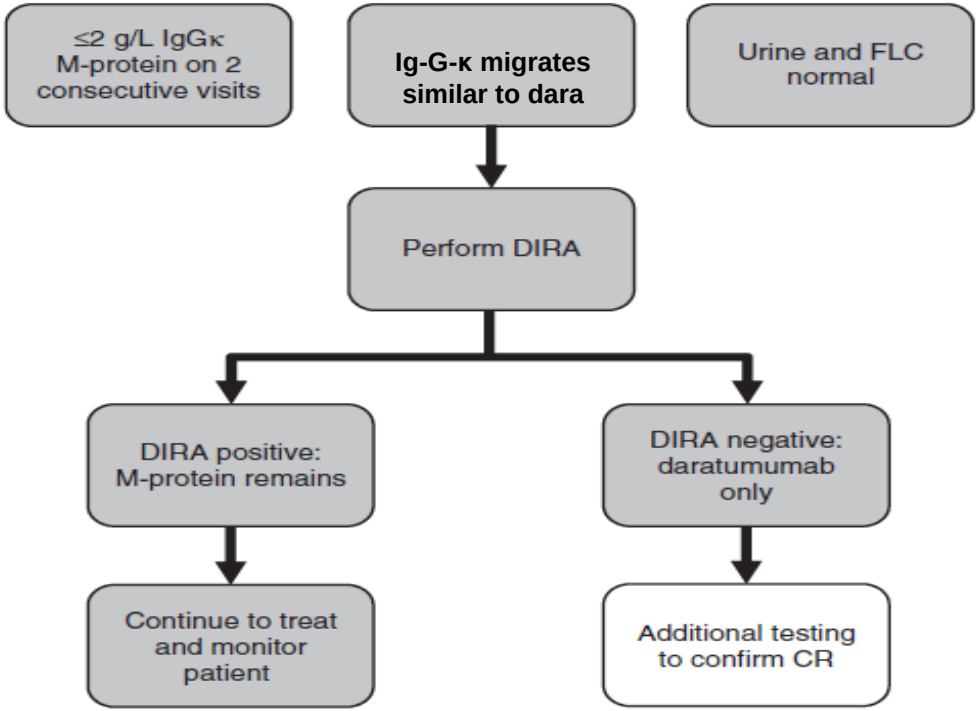
‘DARA shift-assay’

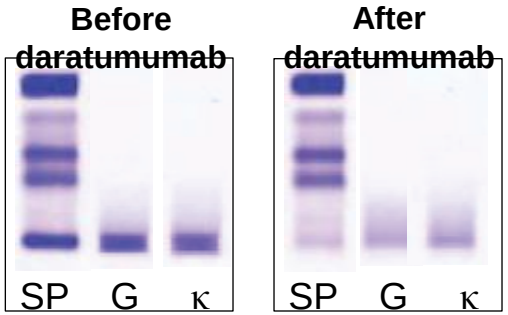


McCudden et al. Clin Chem Lab Med 2016

Radboudumc

Indication to use DIRA





McCudden et al. Clin Chem Lab Med 2016

Dank voor uw aandacht