Nye behandlinger
Dansk Myelomatoseforening
Kolding
11. marts 2017

torben.plesner@rsyd.dk

Hvorfor er der brug for nye behandlinger af myelomatose?

Antistoffer som nyt behandlingsprincip ved myelomatose.

Immunterapi med antistoffer ved myelomatose.

Ny viden fra behandling af lungecancer.

Daratumumab i kombinationsbehandlinger.

Elotuzumab.

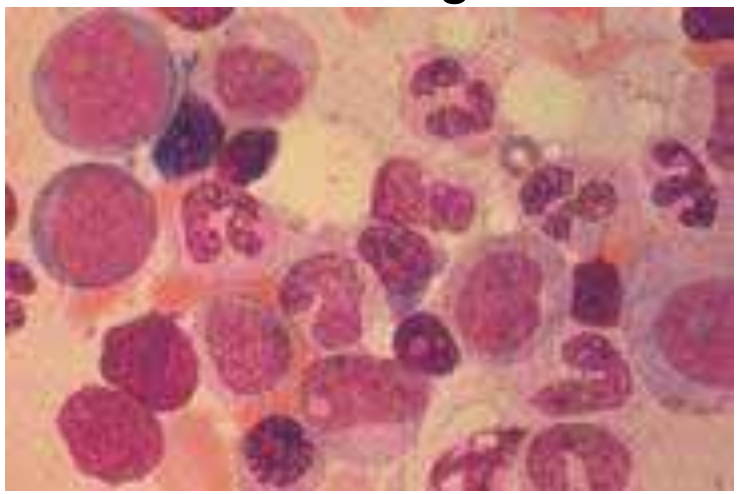
Resistensudvikling mod Daratumumab.

Nye behandlinger paa vej.

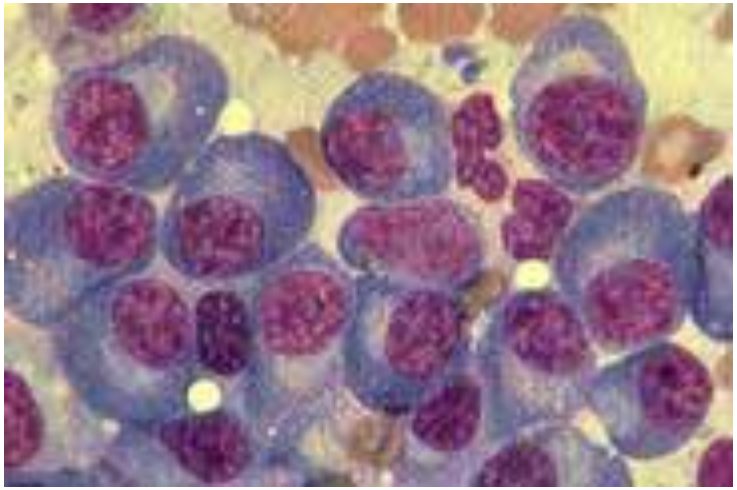
Praktiske forhold omkring behandling med Daratumumab.

Myelomatose: En kræftsygdom i knoglemarven

Normal knoglemarv

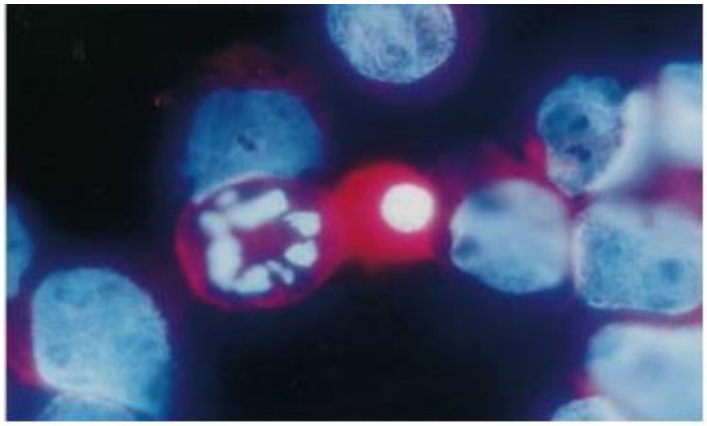


Myelomatose

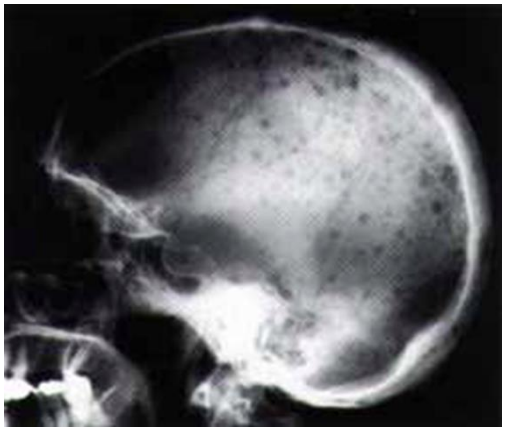


Vigtige fund ved myelomatose

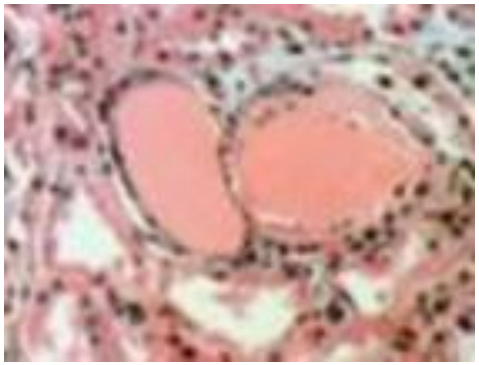
Anemia



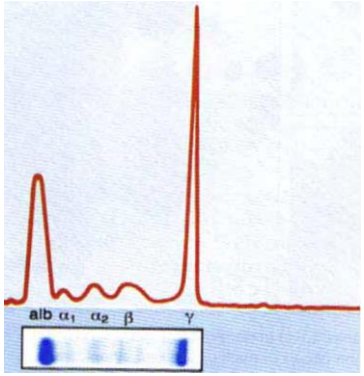
Bone lesions



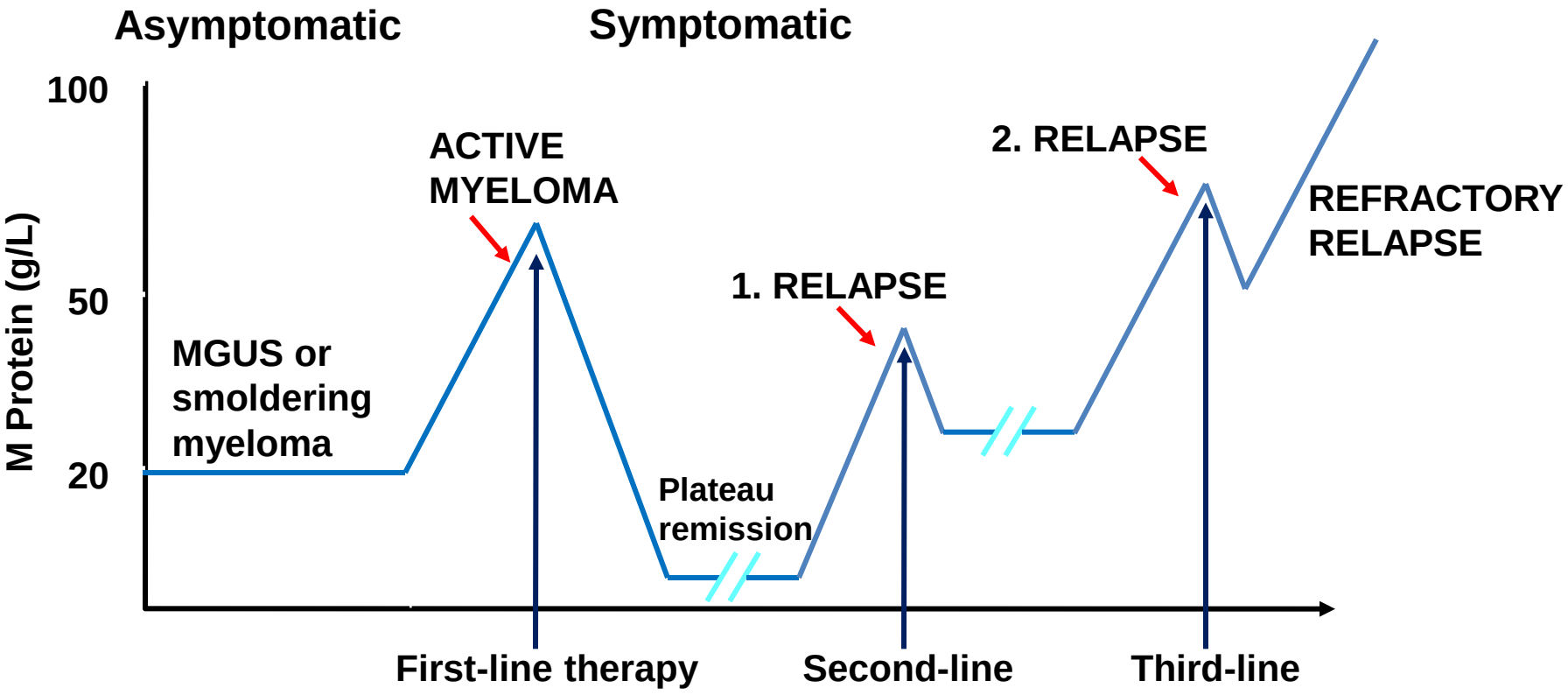
Cast nephropathy



M-protein



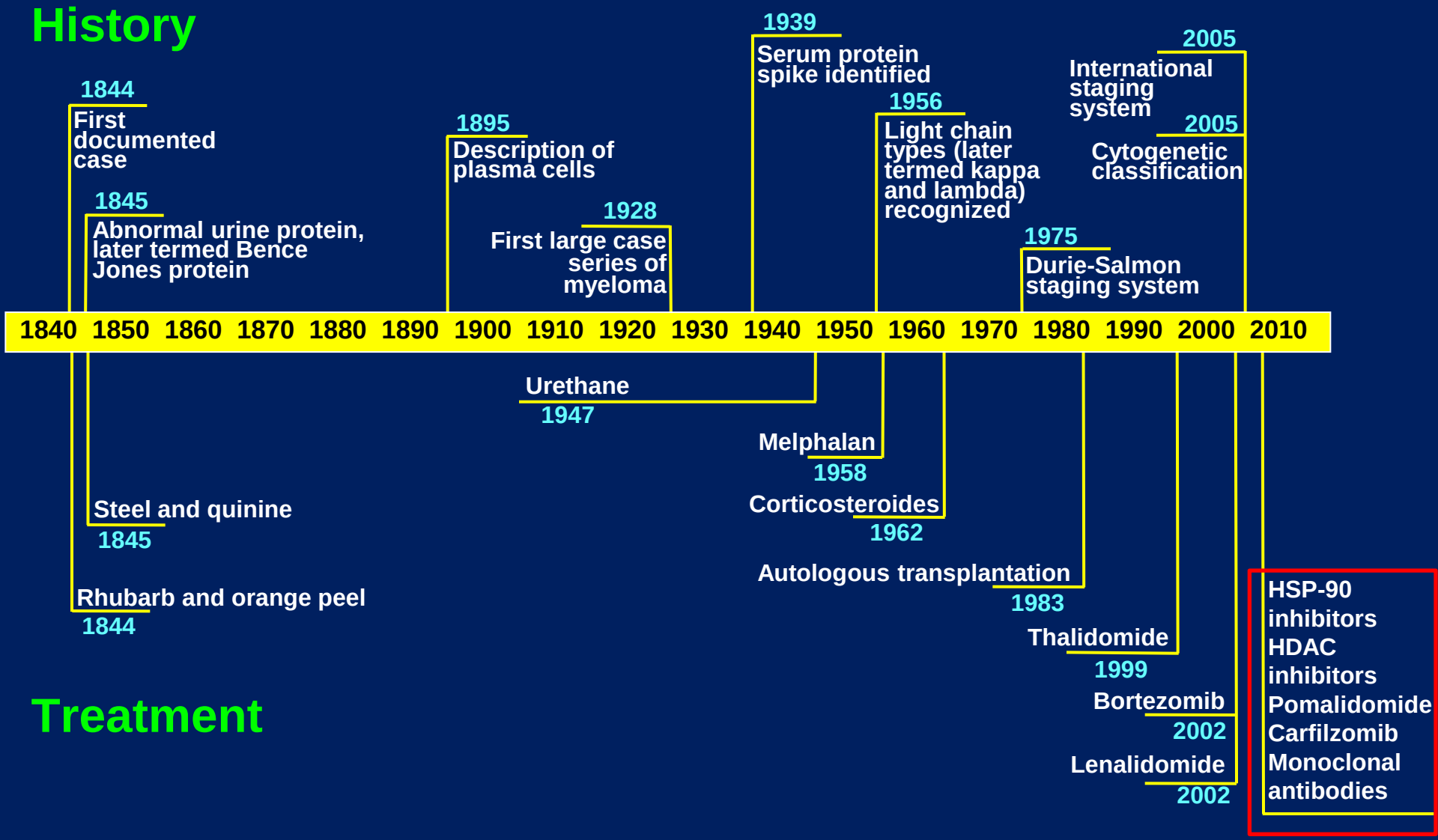
Natural history of multiple myeloma



Relapsed myeloma: Disease recurring after response to therapy
Refractory myeloma: Disease resistant to therapy

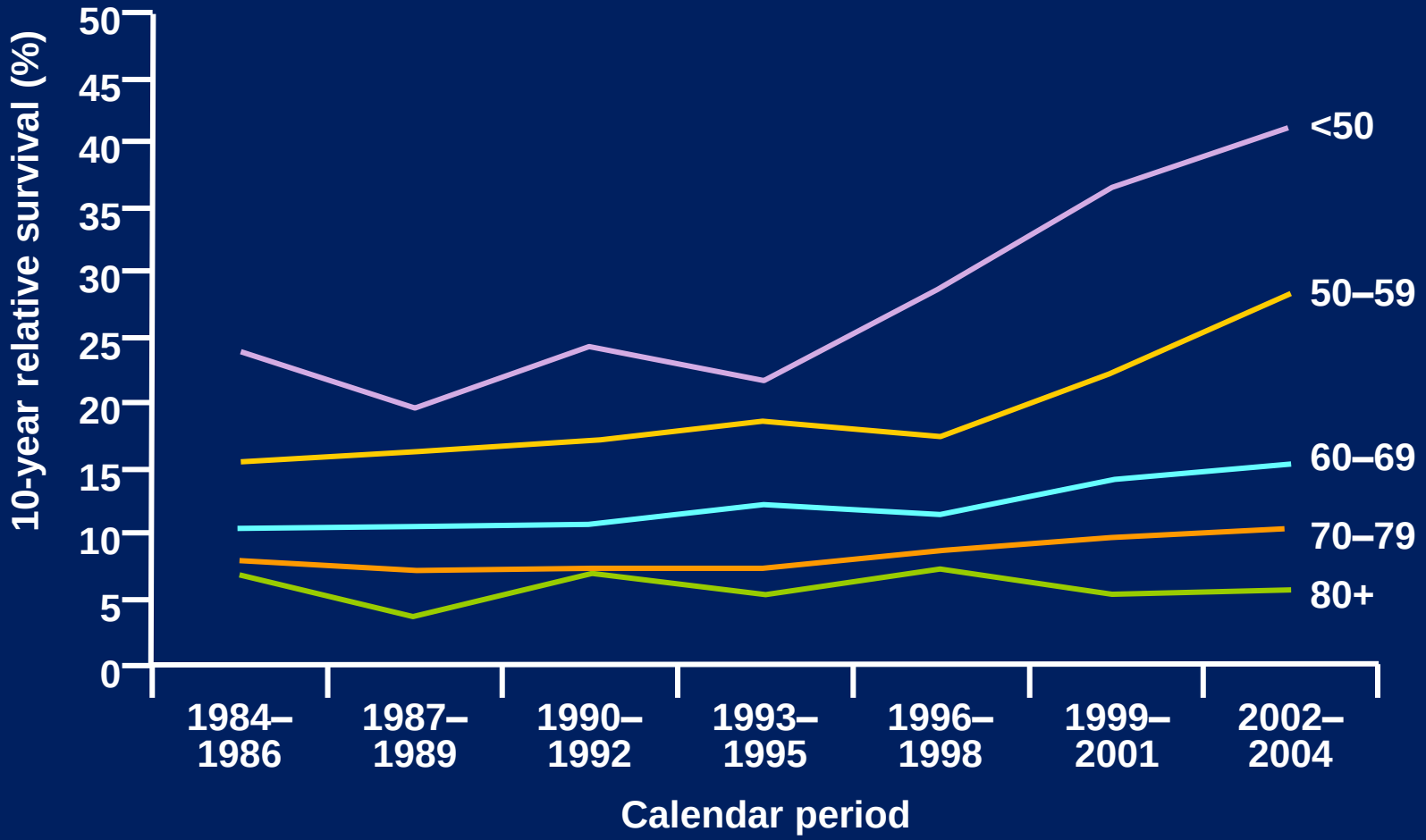
MGUS: monoclonal gammopathy of undetermined significance

History and treatment of multiple myeloma from 1844 to the present



Adapted from: Kyle and Rajkumar. Blood 2008;111:2962-2972

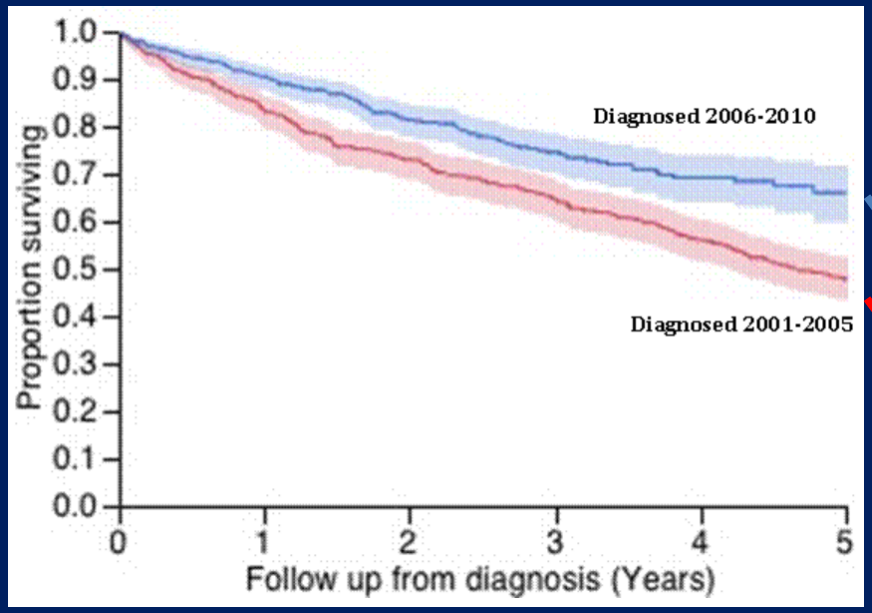
Period estimates of 10-year survival of patients with MM by major age groups in defined calendar periods from 1984–1986 to 2002–2004



Brenner *et al. Blood* 2008;111:2521–26

Progress in the treatment of MM
Impact of Novel Therapy on Survival

Median 7.3 years



5-year survival by age

	≤ 65 years	> 65 years
2006-2010	73%	56%
2001-2005	63%	31%

Kumar et al. ASH 2012 (Abstract #3972)

Kumar et al. Leukemia 2013 Oct 25. doi: 10.1038/leu.2013.313. [Epub ahead of print]

Thus the prognosis for myeloma patients has improved very much in recent years due to the introduction of two new classes of drugs:

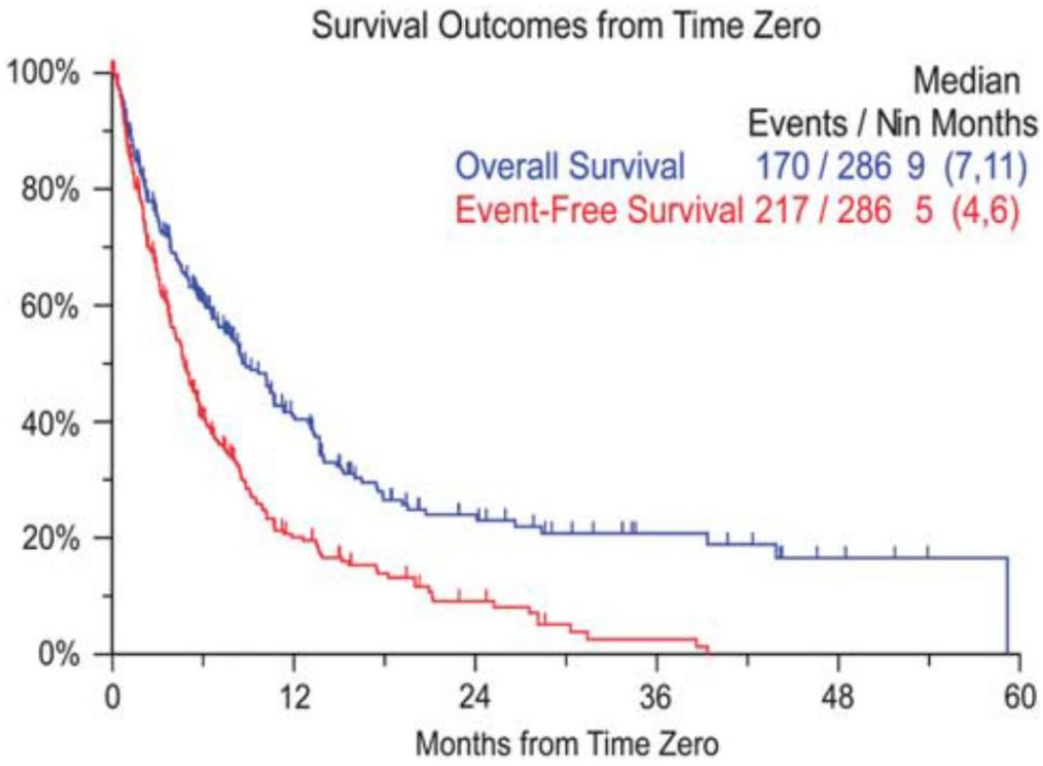
- **Proteasome Inhibitors (PIs):**
  Bortezomib, Carfilzomib, Ixazomib

and

- **Immunomodulatory Drugs (IMIDS):**
  Thalidomide, Lenalidomide, Pomalidomide

However patients may become refractory to both classes of new drugs (PIs and IMIDs)

Patients that are refractory to both PIs and IMIDs are called **“double refractory”** and they have a very poor prognosis (median OS: 9 months)



Leukemia 26 149 2012

Definition of “double refractory”

- **Double refractory (classical definition)**
  - **Refractory to bortezomib**
  - **Refractory to lenalidomide**

- **Refractory Myeloma:**
  - **Failure to achieve at least MR**
  - **Progression on current therapy**
  - **Progression on 60 days of last therapy**

Rajkumar, Blood 2011

Dynamic definition of “double refractory”

- **Double refractory (classical definition)**
  - **Refractory to bortezomib**
  - **Refractory to lenalidomide**

- **Double refractory (new definition)**
  - **Refractory to Proteasome Inhibitors: bortezomib / carfilzomib**
  - **Refractory to IMiDs: lenalidomide / pomalidomide**

Hvorfor er der brug for nye behandlinger af myelomatose?

Antistoffer som nyt behandlingsprincip ved myelomatose.

Immunterapi med antistoffer ved myelomatose.

Ny viden fra behandling af lungecancer.

Daratumumab i kombinationsbehandlinger.

Elotuzumab.

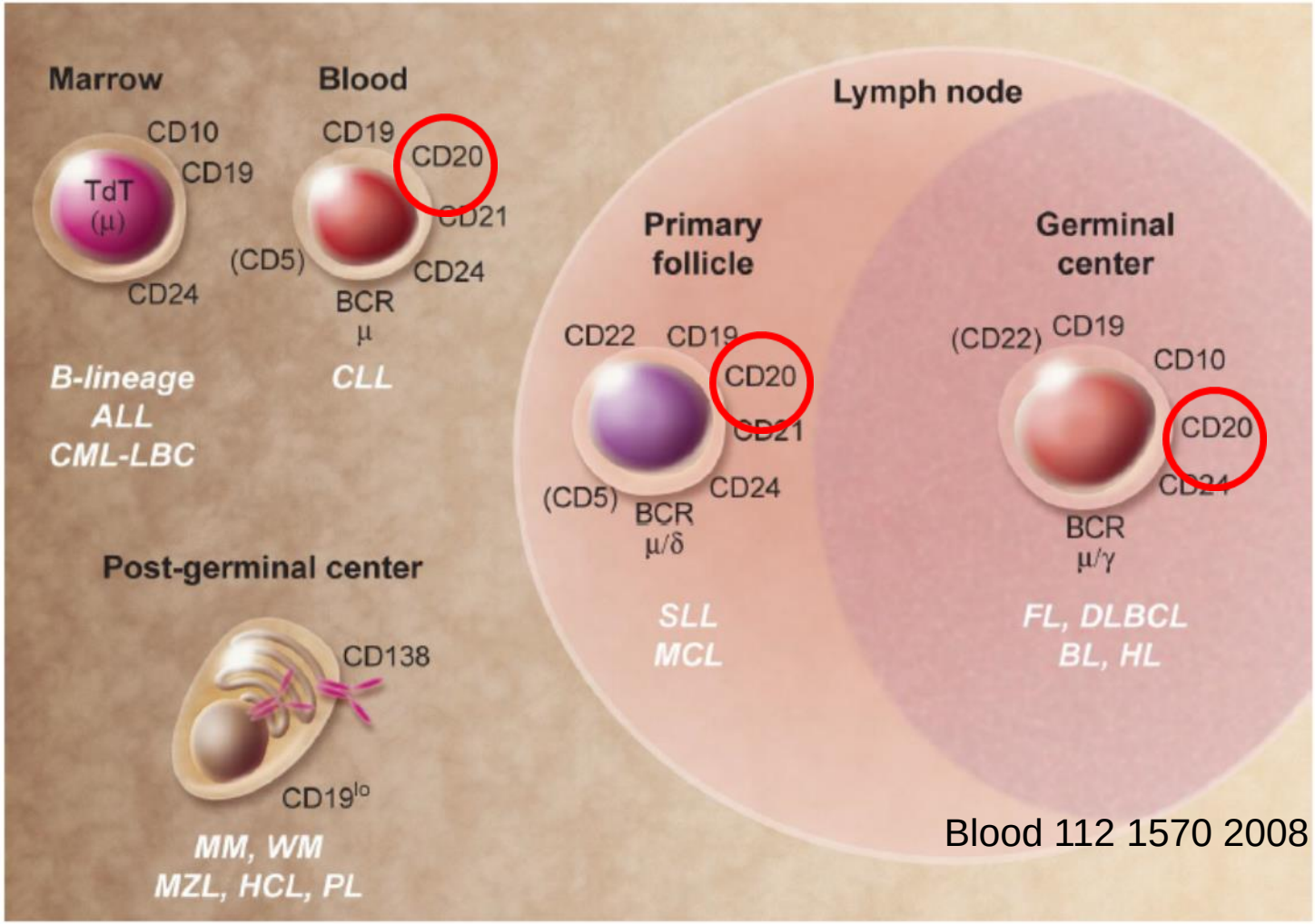
Resistensudvikling mod Daratumumab.

Nye behandlinger paa vej.

Praktiske forhold omkring behandling med Daratumumab.

Can we introduce a totally new way of treating multiple myeloma?

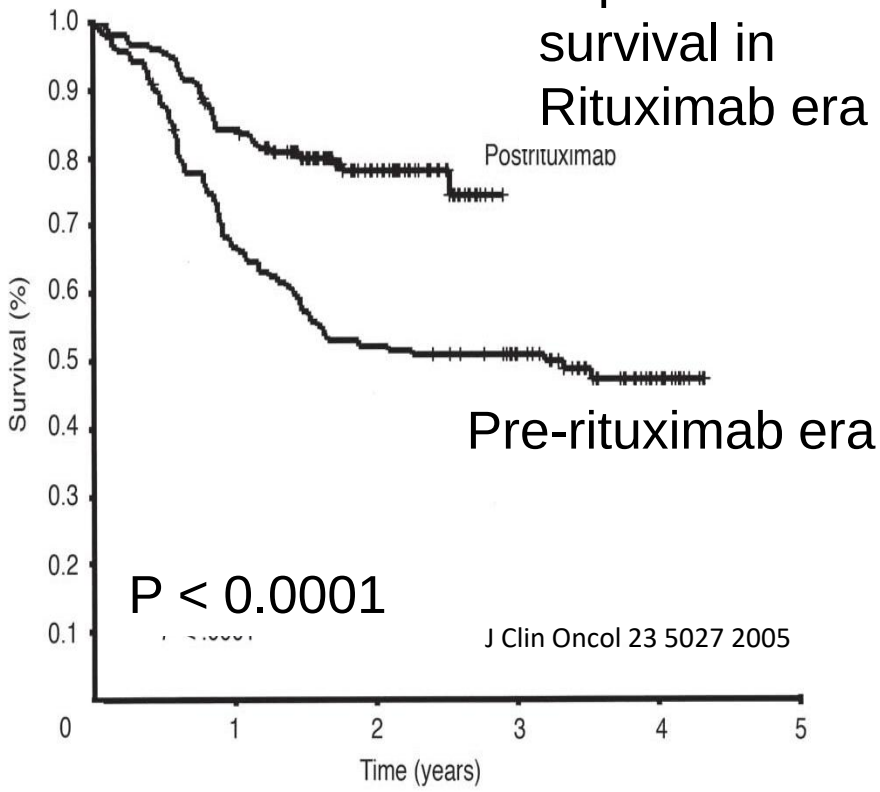
Can we learn from immunotherapy of malignant lymphomas?



CD20 is an appropriate target for antibody therapy of many B-cell malignancies

Addition of Rituximab (a CD20 antibody) to standard chemotherapy (CHOP) in diffuse large B-cell lymphoma has dramatically changed the outcome

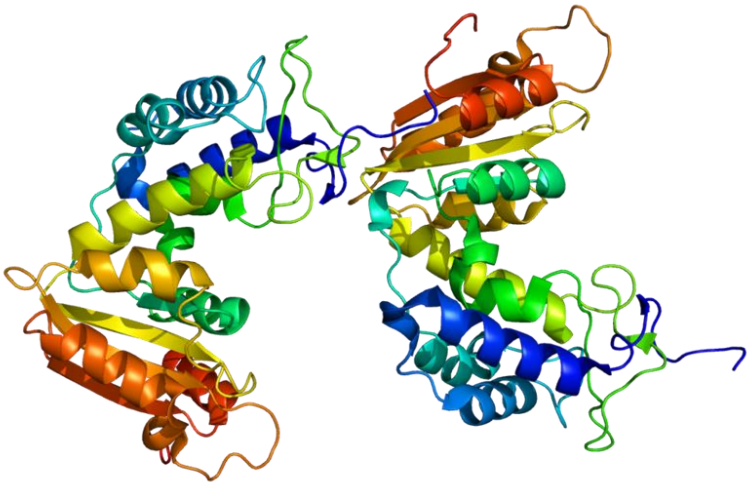
Overall survival by treatment era



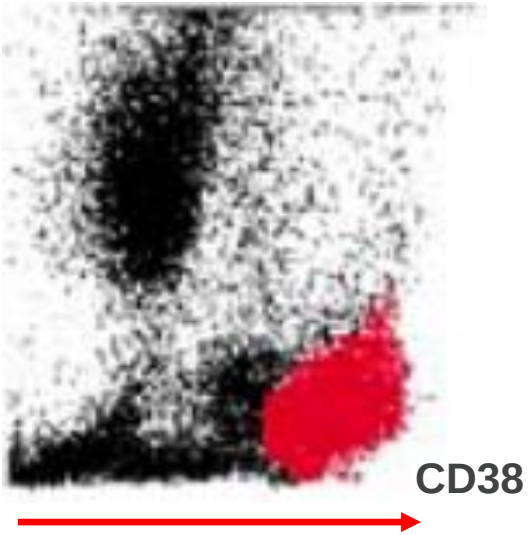
Can we find a monoclonal antibody that will change the course of myeloma in a similar way?

CD38 is strongly expressed by myeloma cells

Structure of CD38



Flow cytometry of CD38 on myeloma cells



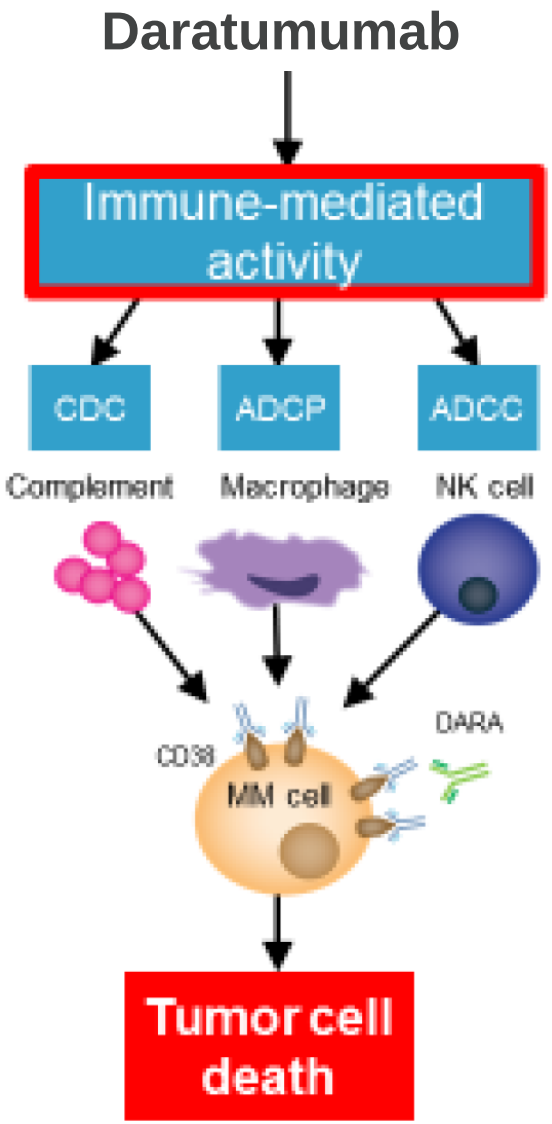
Am J Clin Pathol 121 482 2004

Glycoprotein with widespread expression in cells and tissues

Functions related to

- **cell adhesion**
- **signal transduction**
- **calcium homeostasis**
- **generation of adenosine (immunosuppression)**

Preclinical studies showed that Daratumumab (CD38 antibody) can kill myeloma cells with ***complement***, with ***phagocytes*** and with ***natural killer cells***



From pre-clinical studies to clinical trials showing activity of Daratumumab ***monotherapy***

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

NEJM 373 1207 2015

Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial

Sagar Lonial, Brendan M Weiss, Saad Z Usmani, Seema Singhal, Ajai Chari, Nizar J Bahlis, Andrew Belch, Amrita Krishnan, Robert A Vescio, Maria Victoria Mateos, Amitabha Mazumder, Robert Z Orlowski, Heather J Sutherland, Joan Bladé, Emma C Scott, Albert Oriol, Jesus Berdeja, Mecide Gharibo, Don A Stevens, Richard LeBlanc, Michael Sebag, Natalie Callander, Andrzej Jakubowiak, Darrell White, Javier de la Rubia, Paul G Richardson, Steen Lisby, Huaibao Feng, Clarissa M Uhlar, Imran Khan, Tahamtan Ahmadi, Peter M Voorhees

The Lancet 387 1551 2016

CLINICAL TRIALS AND OBSERVATIONS

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

Saad Z. Usmani,[1] Brendan M. Weiss,[2] Torben Plesner,[3] Nizar J. Bahlis,[4] Andrew Belch,[5] Sagar Lonial,[6] Henk M. Lokhorst,[7] Peter M. Voorhees,[8] Paul G. Richardson,[9] Ajai Chari,[10] A. Kate Sasser,[11] Amy Axel,[11] Huaibao Feng,[12] Clarissa M. Uhlar,[11] Jianping Wang,[11] Imran Khan,[12] Tahamtan Ahmadi,[11] and Hareth Nahi[13]

Blood 128 37 2016

Combined results of Daratumumab monotherapy from two trials: GEN501 and Sirius

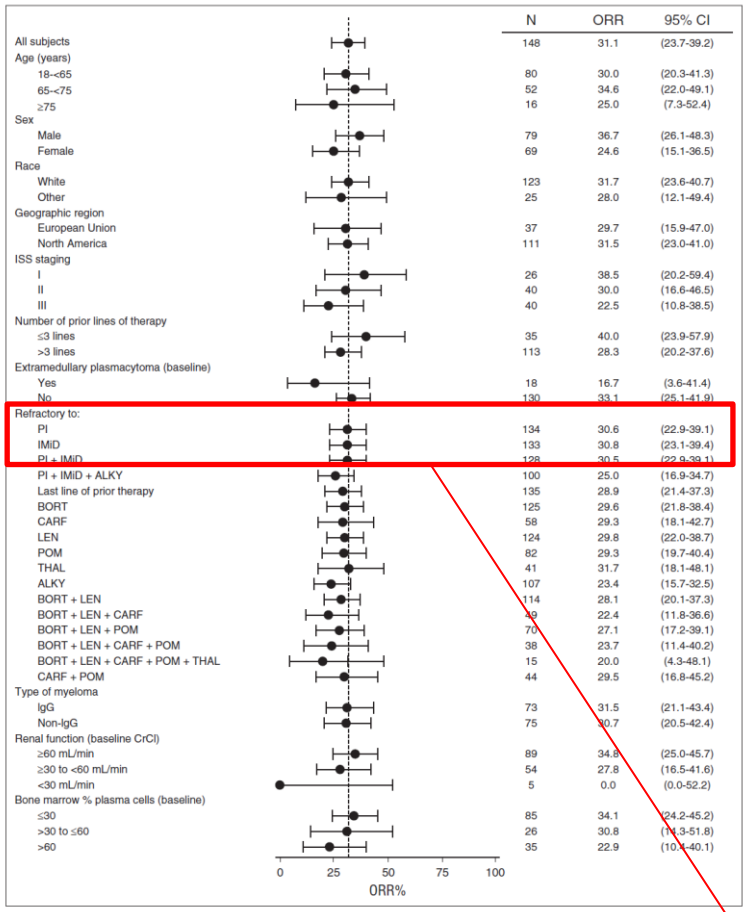


Figure 2. ORR in patient subgroups in the combined daratumumab 16 mg/kg group. Subgroup analysis of the overall best response in the 148 patients treated with daratumumab at a dose of 16 mg /kg. The dashed vertical line indicates 31.1%, which was the ORR in the total patient cohort. Exact 95% CIs are provided. International Staging System data are not available in GEN501 part 2. ALKY, alkylating agents, including autologous stem cell transplant; BORT, bortezomib; CARF, carfilzomib; CrCl, creatinine clearance; LEN, lenalidomide; POM, pomalidomide; THAL, thalidomide.

CLINICAL TRIALS AND OBSERVATIONS

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

Saad Z. Usmani,[1] Brendan M. Weiss,[2] Torben Plesner,[3] Nizar J. Bahlis,[4] Andrew Belch,[5] Sagar Lonial,[6] Henk M. Lokhorst,[7] Peter M. Voorhees,[8] Paul G. Richardson,[9] Ajai Chari,[10] A. Kate Sasser,[11] Amy Axel,[11] Huaibao Feng,[12] Clarissa M. Uhlar,[11] Jianping Wang,[11] Imran Khan,[12] Tahamtan Ahmadi,[11] and Hareth Nahi[13]

Blood 128 37 2016

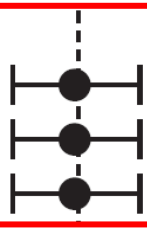
Also patients that are “double refractory” to PI and IMID respond to Daratumumab

Refractory to:

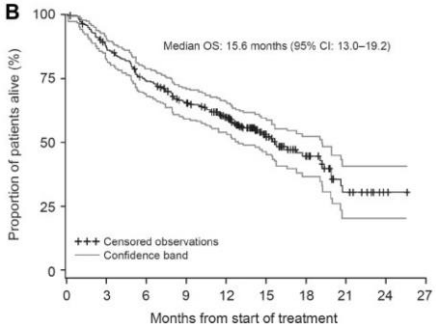
PI

IMiD

PI + IMiD



A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma

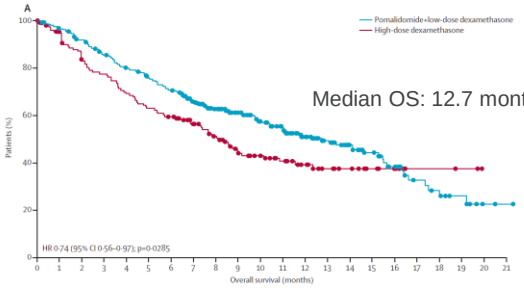


Median OS 15,6 mdr

Prior lines of therapy, median (range)	5 (1-20)
≥ 4, n (%)	217 (82)
Refractory to last regimen	
Progressive disease on therapy	198 (74)
Progressive disease within 60 d	38 (14)
≤ 25% response	16 (6)
Prior agents, median (range)	13 (3-45)
Bortezomib, n (%)‡	265 (99.6)
In most recent prior regimen, n (%)	132 (50)
Immunomodulatory agent, n (%)	266 (100)
Lenalidomide, n (%)	249 (94)
Thalidomide, n (%)	199 (75)
Pomalidomide, n (%)	9 (3)

Blood 120 2817 2012

Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial

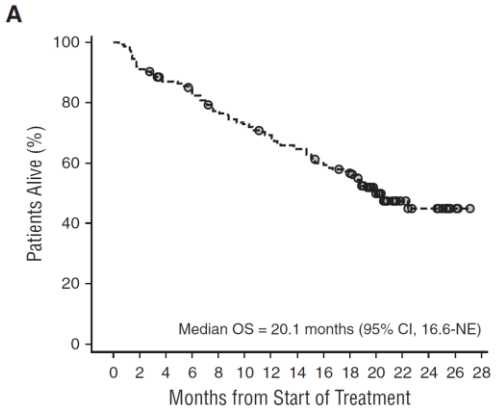


Median OS 12,7 mdr

Number of previous treatments	5 (2–14)	5 (2–17)
More than two	285 (94%)	145 (95%)
Previous treatments		
Dexamethasone	295 (98%)	152 (99%)
Thalidomide	173 (57%)	93 (61%)
Autologous stem-cell transplantation	214 (71%)	105 (69%)
Lenalidomide	302 (100%)	153 (100%)
Bortezomib	302 (100%)	153 (100%)
Refractory multiple myeloma	249 (82%)	125 (82%)
Intolerant to bortezomib	45 (15%)	23 (15%)
Refractory to lenalidomide	286 (95%)	141 (92%)
Refractory to bortezomib	238 (79%)	121 (79%)
Refractory to both bortezomib and lenalidomide	225 (75%)	113 (74%)

The Lancet Oncology 14 1055 2013

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



Median OS: 20,1 mdr

No. of prior lines of therapy						
Median (range)	4 (2-12)		5 (2-14)		5 (2-14)	
>3	26	62	87	82	113	76
Prior ASCT	31	74	85	80	116	78
Prior PI	42	100	106	100	148	100
Bortezomib	42	100	105	99	147	99
Carfilzomib	8	19	53	50	61	41
Prior IMiD	40	95	106	100	146	99
Lenalidomide	40	95	105	99	145	98
Pomalidomide	15	36	67	63	82	55
Thalidomide	19	45	47	44	66	45
Refractory to:						
Last line of therapy	32	76	103	97	135	91
Both a PI and an IMiD	27	64	101	95	128	87
PI only	3	7	3	3	6	4
IMiD only	4	10	1	1	5	3
PI + IMiD + alkylating agent	21	50	79	75	100	68

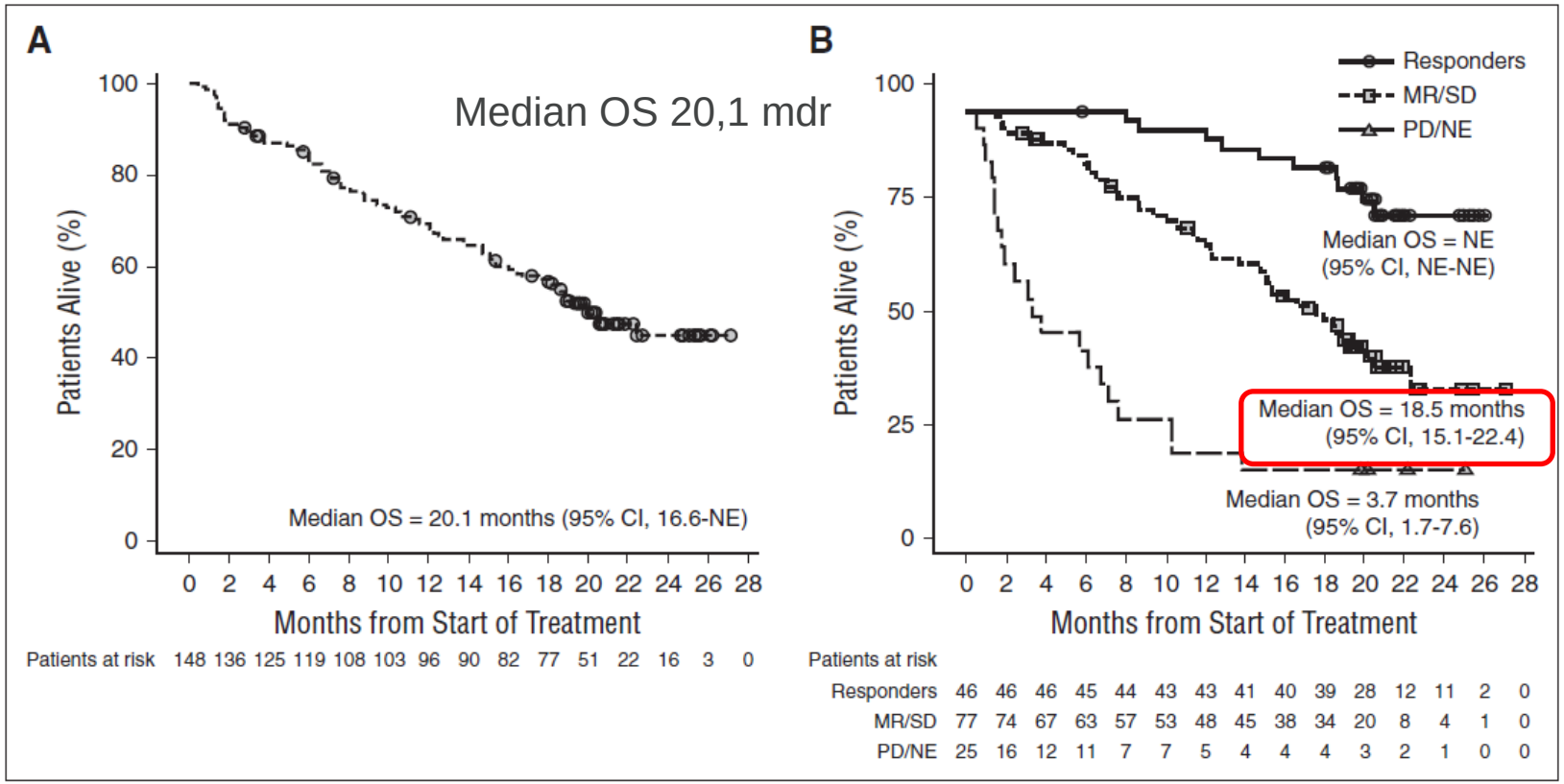
Blood 128 37 2016

Daratumumab prolonged survival in responders but also in patients with minimal response (Minor Response/Stable Disease)

Responders: Reduktion i M-komponent >/= 50%

All patients

Patients stratified according to response



>20 mdr

18,5 mdr

3,7 mdr

Blood 128 37 2016

Hvorfor er der brug for nye behandlinger af myelomatose?

Antistoffer som nyt behandlingsprincip ved myelomatose.

Immunterapi med antistoffer ved myelomatose.

Ny viden fra behandling af lungecancer.

Daratumumab i kombinationsbehandlinger.

Elotuzumab.

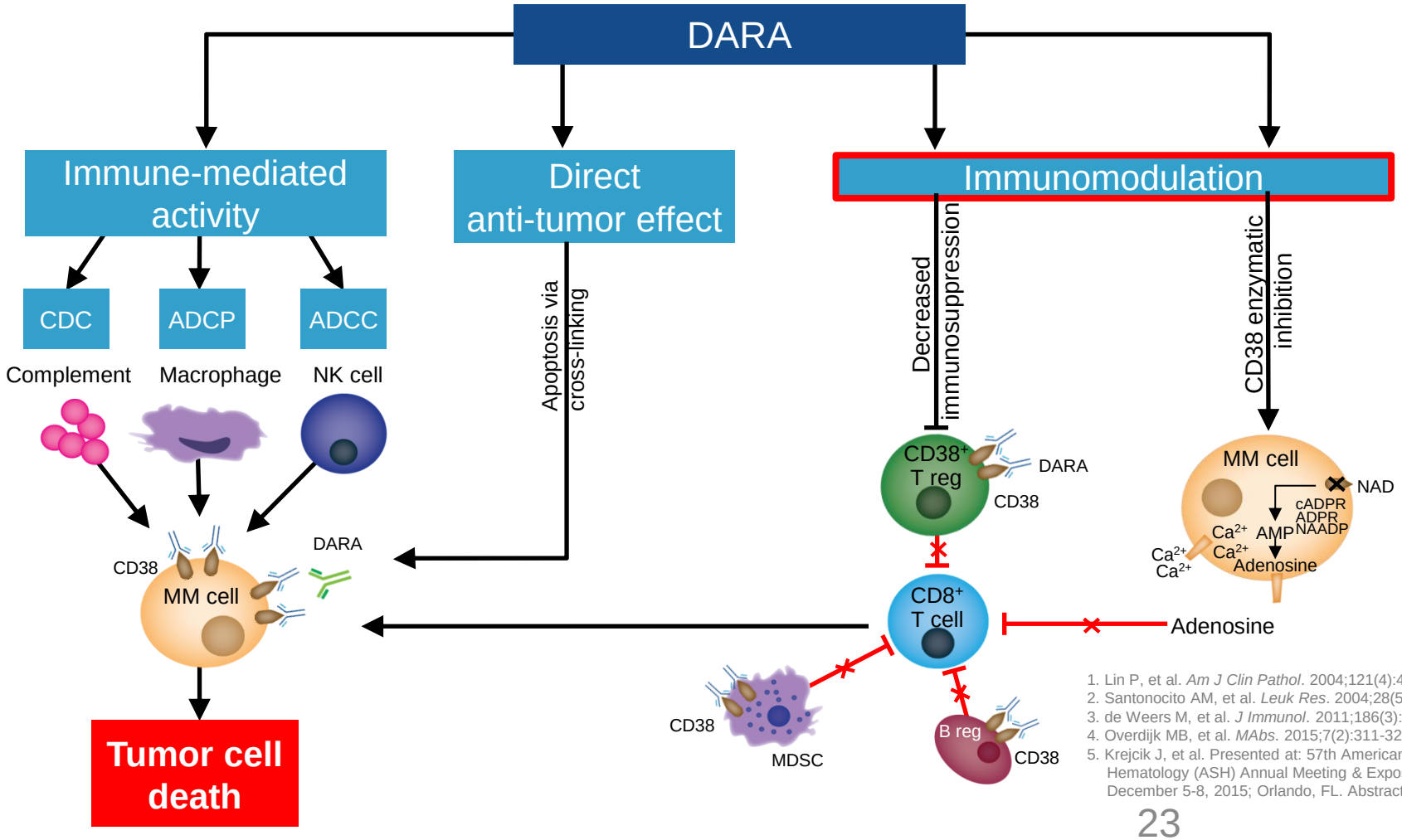
Resistensudvikling mod Daratumumab.

Nye behandlinger paa vej.

Praktiske forhold omkring behandling med Daratumumab.

DARA: Mechanisms of Action

- CD38 is highly and ubiquitously expressed on myeloma cells[1,2]
- DARA is a human IgG1 monoclonal antibody that binds CD38-expressing cells
- DARA binding to CD38 induces tumor cell death through direct and indirect mechanisms[3-5]

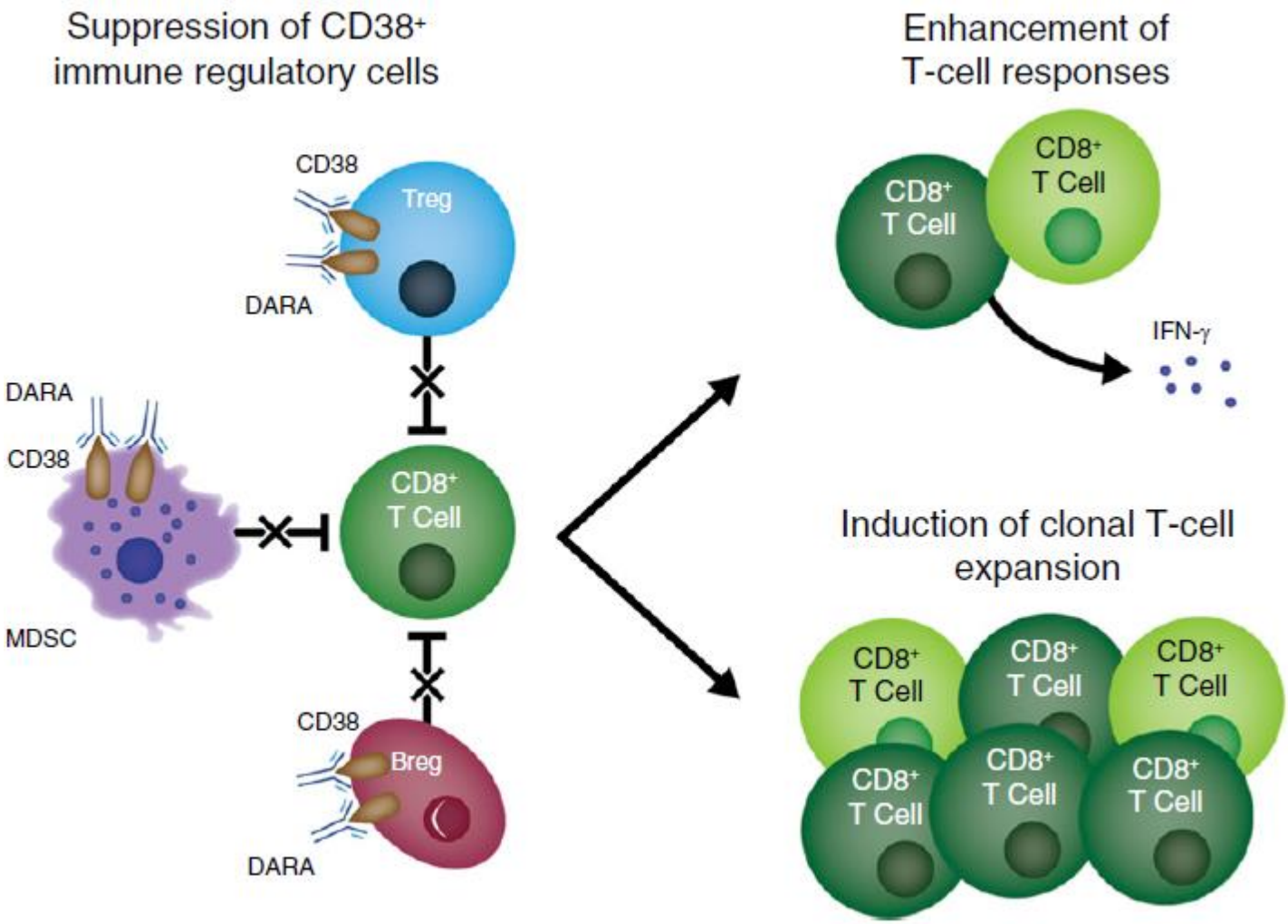


1. Lin P, et al. *Am J Clin Pathol*. 2004;121(4):482-488.
2. Santonocito AM, et al. *Leuk Res*. 2004;28(5):469-477.
3. de Weers M, et al. *J Immunol*. 2011;186(3):1840-1848.
4. Overdijk MB, et al. *MAbs*. 2015;7(2):311-321.
5. Krejcik J, et al. Presented at: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2015; Orlando, FL. Abstract 3037.

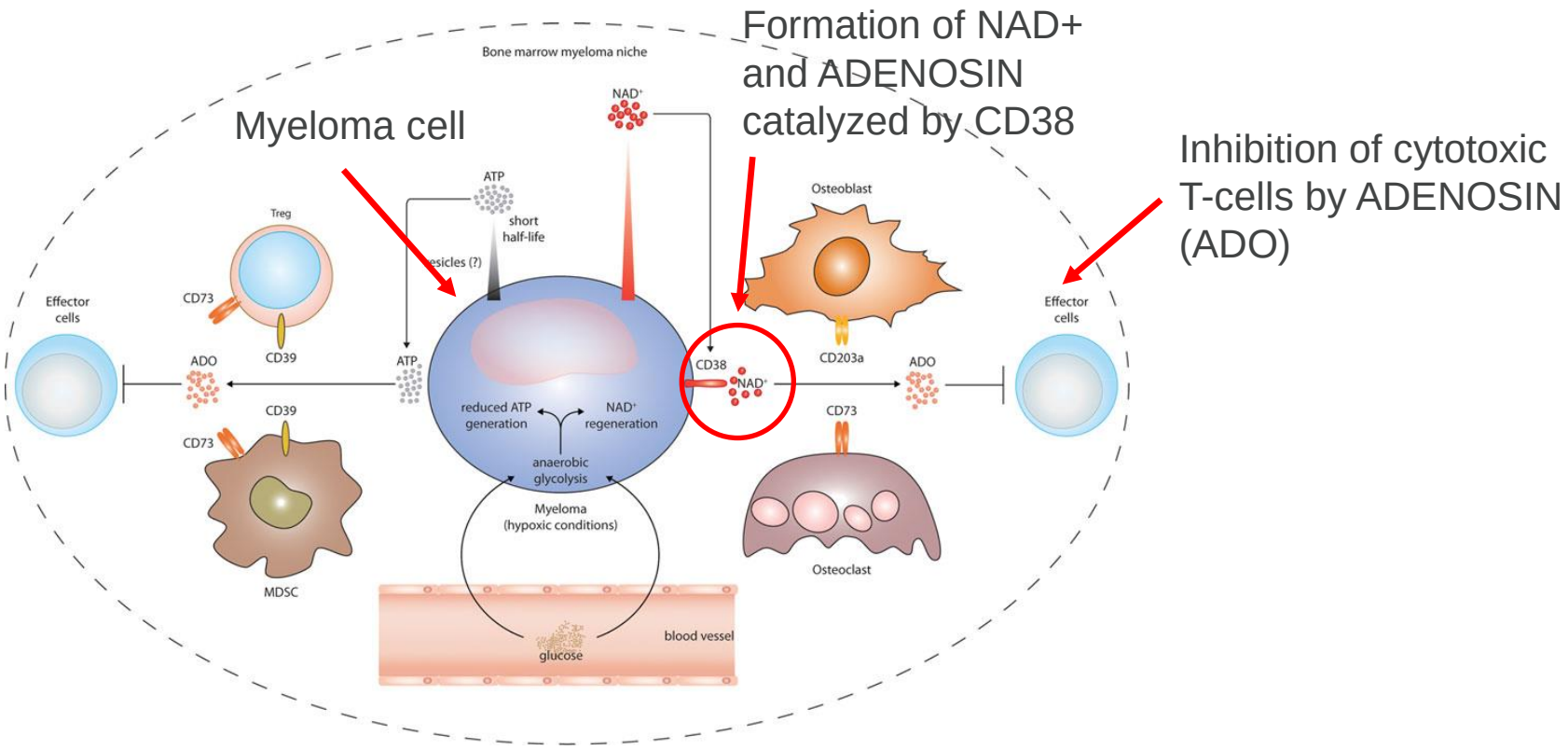
Daratumumab depletes CD38$^+$ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma

Jakub Krejcik,[1,2,*] Tineke Casneuf,[3,*] Inger S. Nijhof,[1] Bie Verbist,[3] Jaime Bald,[4] Torben Plesner,[2] Khaja Syed,[4] Kevin Liu,[5] Niels W. C. J. van de Donk,[1] Brendan M. Weiss,[6] Tahamtan Ahmadi,[4] Henk M. Lokhorst,[1] Tuna Mutis,[1,†] and A. Kate Sasser[4,†]

Blood 128 384 2016



Schematic model summarizing key events controlled by ectoenzymes in the myeloma niche that lead to the local production of adenosine (ADO).



Hypoxic conditions trigger anaerobic glycolysis, with reduced production of ATP and simultaneous increase in NAD+ generation.

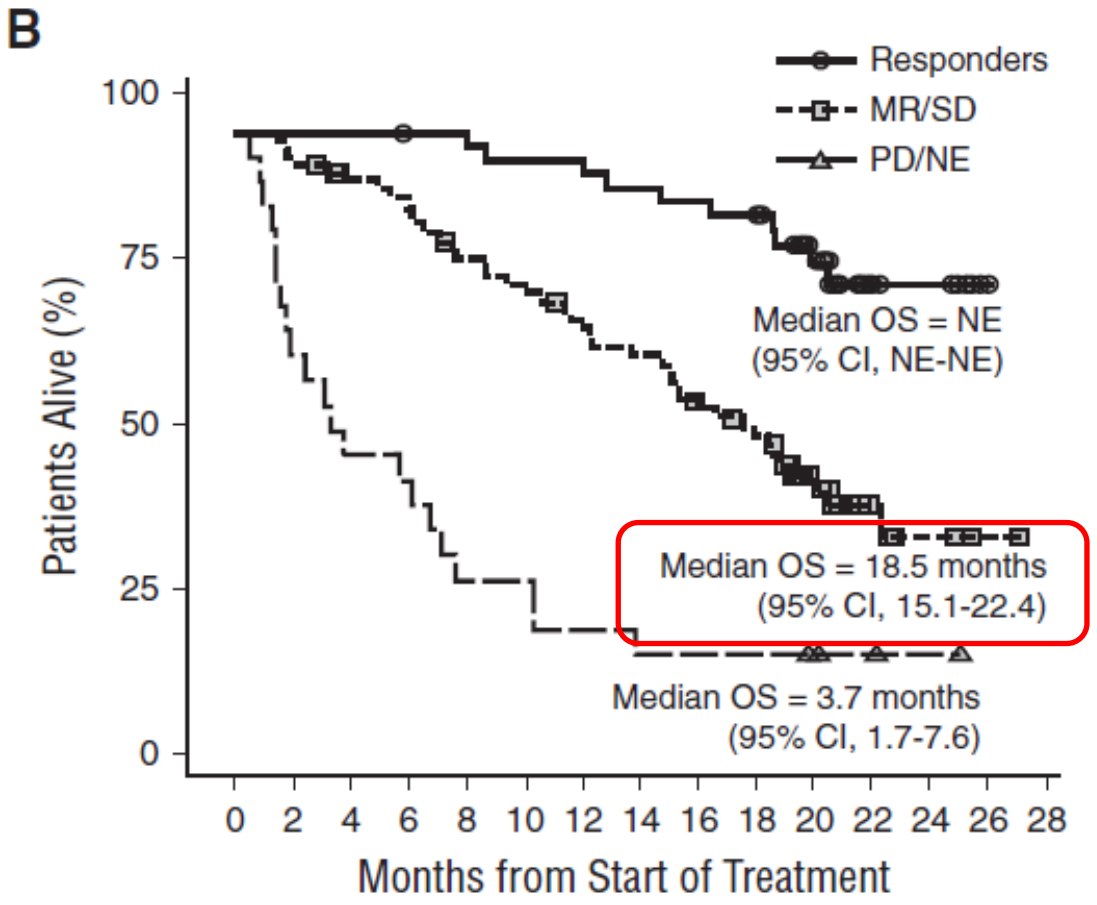
ATP is the substrate for the canonical CD39/CD73 pathway.

NAD+ is the substrate activating the alternative pathway, where the CD38 substrate is converted to the final product, ADO, via PC-1/CD203a and CD73.

Adenosin causes suppression of immune-effector cells.

Ann. N.Y. Acad. Sci. 1335 (2015) 10–22 © 2014 New York Academy of Sciences

The immunomodulatory activity of Daratumumab may explain the prolonged effect even in patients with Minor Response/Stable Disease



>20 mdr

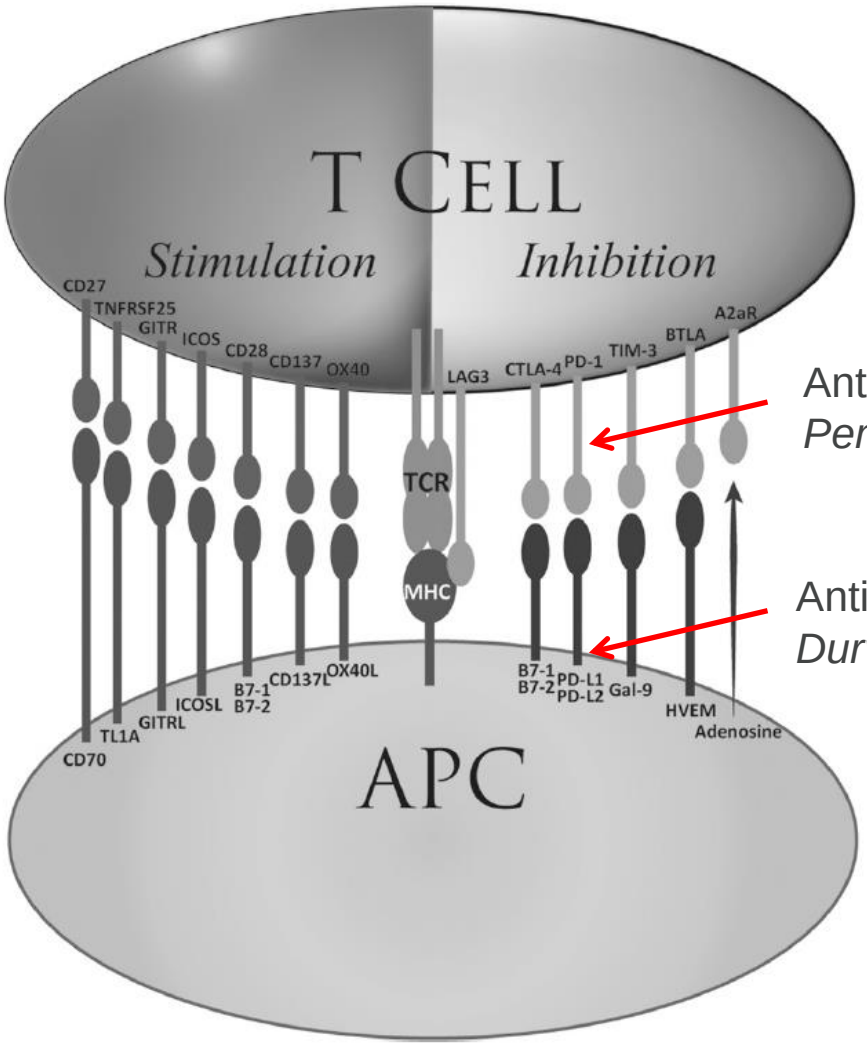
18,5 mdr

3,7 mdr

The immunomodulatory effect of Daratumumab is completely diffent from the effect of Immune Checkpoint Inhibitors

Daratumumab is releasing an abnormal break imposed on the immune system by myeloma

Immune Checkpoint Inhibitors are neutralizing a “protective shield” used by cancer cells but also by normal cells (i.e. risk of autoimmune reactions)



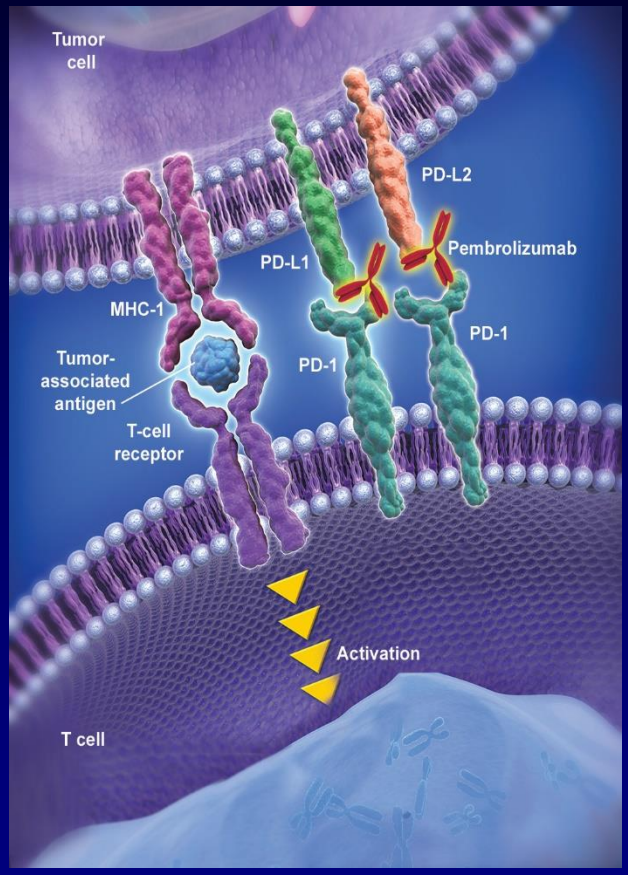
Anti-PD-1
Pembrolizumab

Anti-PD-L1
Durvalumab

Blood 125 3393 2015

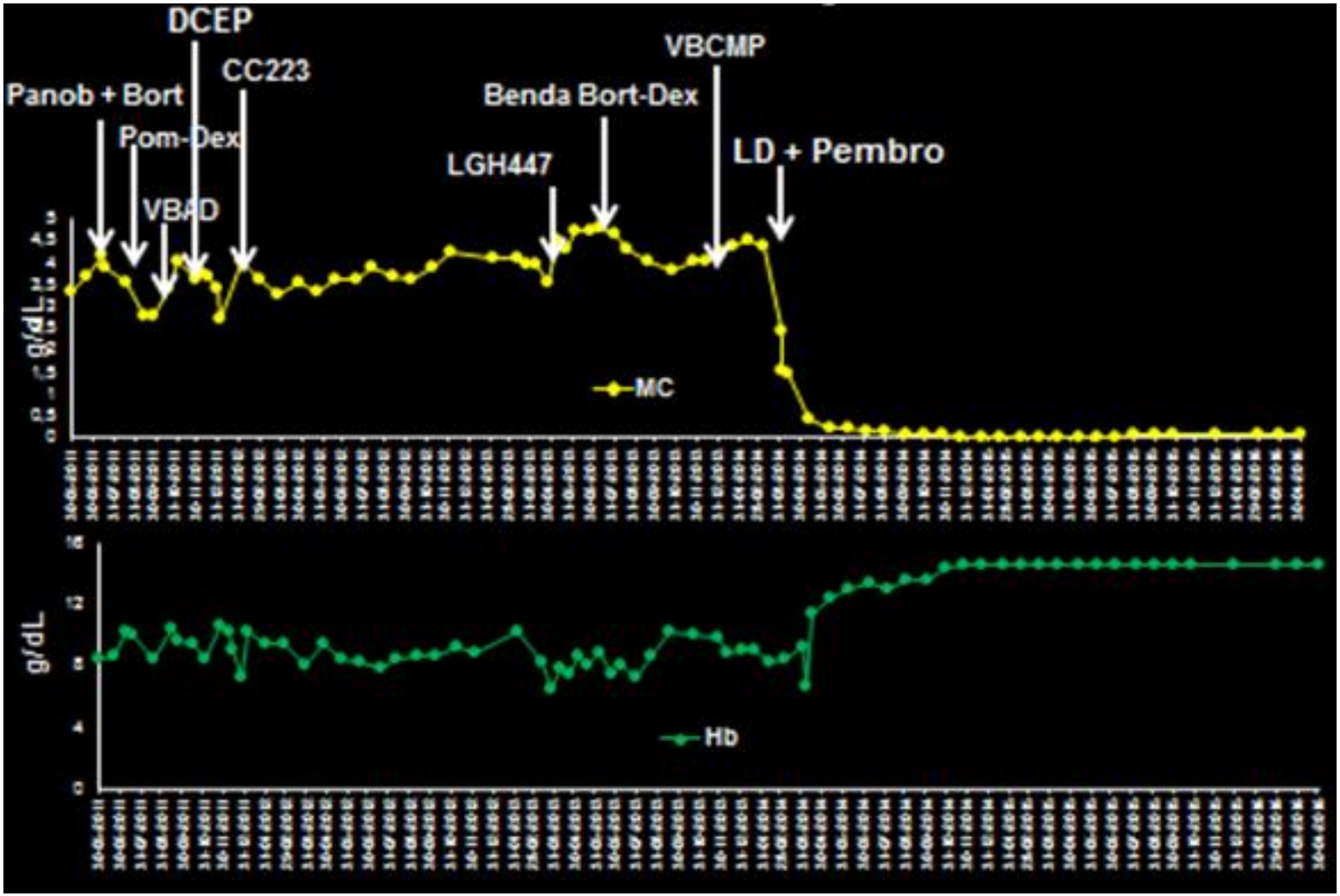
Pembrolizumab and the PD-1 Pathway

- The PD-1 pathway is often exploited by tumors to evade immune surveillance:[1-3]
  - PD1 is upregulated on activated T-cells
  - Binding of the PD-1 receptor to its ligands, PD-L1 and PD-L2 (expressed on the surface of APC & Tumor cells) inhibits T-cell activation
- Role of PD-1 inhibitors in multiple myeloma[1-2]
  - PD-1 is increased among T-cells of patients with MRD/RR disease
  - PD-1 blockade prolonged survival in mice with 5TGM-1 PD-L1–positive MM cells
- Pembrolizumab blocks interaction between PD-1 and PD-L1/PD-L2[4-6]
  - Robust antitumor activity and



1. Liu J et al. Blood. 2007;110:296-304; 2. Tamura H, et al. Leukemia. 2013;27:464-72; 3. Paiva B, et al. Leukemia. 2015;29:2110-3; 4. Keir ME et al. Annu Rev Immunol. 2008;26:677-704; 5. Hallett WH et al. Biol Blood Marrow Transplant. 2011;17:1133-1145;
6. Homet Moreno B, Ribas A. Br J Cancer. 2015;112:1421-1427; 7. Görgün G. et al. Clin Cancer Res. 2015;21:4607-18.

Myeloma patient treated at the University Hospital of Salamanca with the combination of Pembrolizumab (anti-PD-1), Lenalidomide and Dexamethasone



Courtesy to Professor Maria Victoria Mateos

Pembrolizumab + Len-dex in RRMM

Best Overall Response n (%)	Efficacy Population† (n = 40)	Len-Refractory (n = 29)
Overall response rate	**20 (50)**	**11 (38)**
Stringent complete response (sCR)	1 (3)	1 (3)
Very good partial response (VGPR)	5 (13)	3 (10)
Partial response (PR)	14 (35)	7 (24)
Stable disease (SD)	19 (48)	17 (59)
Disease control rate (CR+PR+SD)	39 (98)	28 (97)
Progressive disease (PD)	1 (3)	1 (3)

- Median follow-up: 9 months (range, 1-25)
- Median DOR: 11.3 months
- Median time to achieve first objective response: 1.5 months (range, 1.0-6.6)
- 4 patients who responded (20%) upgraded the quality of response
- 75% of patients were still alive

†11 patients NE by central review
3 discontinued within cycle 1 for reasons other than PD (2 no treatment assessments and 1 SD by investigator)
8 inadequate myeloma data for response assessment (5 PD and 3 SD by investigator)

Mateos MV- ASCO 2016: oral presentation

Pembrolizumab-Pom-dex in RR Myeloma patients:

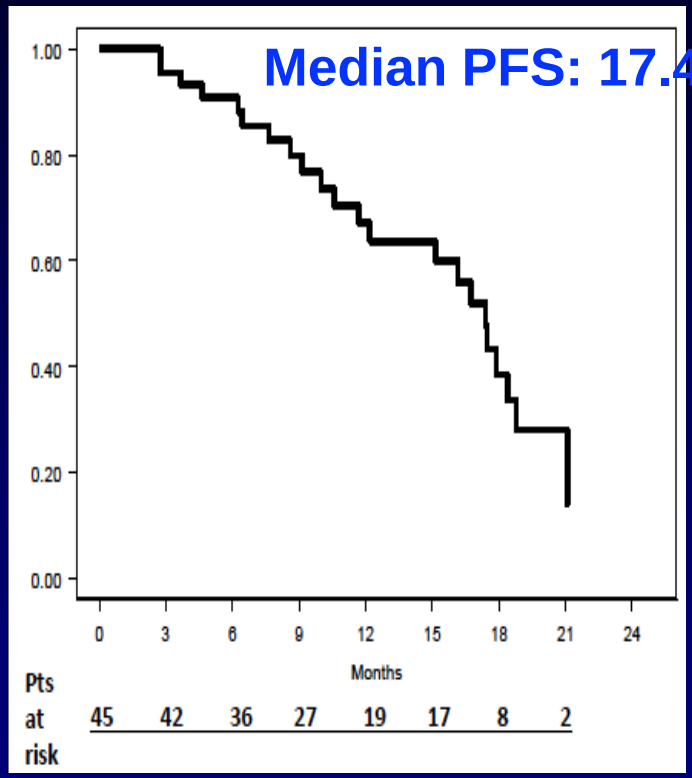
200 mg Q2W 4 mg (1-21) 40 mg QW

45pts refractoy a median of 3 prior lines; double refractory to PI&IMiD's 73%

Response category	Evaluable Patients (N=45)	Double refractory (N=32)
Overall response, n (%)	**29 (65)**	**22 (68)**
Best response, n (%)		
sCR	3 (7)	1 (3)
CR	1 (2)	1 (3)
VGPR	9 (20)	6 (18)
PR	16 (36)	14 (44)
MR	3 (7)	1 (3)
SD	11 (23)	7 (22)
PD	2 (5)	2 (4)

29%

24%



- **6 pts (12%) had G3-4 pneumonitis and 4 required discontinuation**
- **Correlation between PD-L1 expression in PCs and ORR but no between PD-1&CD3 and ORR**

Badros A, et al. Presented at ASH 2016 (Abstract 490), oral presentation

Important differences of immunotherapy with:

(A) CD38 antibody (Daratumumab) or

(B) "Checkpoint inhibitor" antibodies (anti-PD-1 or anti-PD-L1)

(A) An abnormal suppression of normal immune responses is relieved by Daratumumab ("hyperactive" Tregs, Bregs and Mregs are eliminated).
The "traffic rules" of the immune system are still respected.
No autoimmunity.

(B) A control mechanism of cytotoxic T-lymphocytes is neutralized.
The "traffic rules" of the immune system are not working.
Autoimmune disease may appear

Innocent bystander?

Hvorfor er der brug for nye behandlinger af myelomatose?

Antistoffer som nyt behandlingsprincip ved myelomatose.

Immunterapi med antistoffer ved myelomatose.

Ny viden fra behandling af lungecancer.

Daratumumab i kombinationsbehandlinger.

Elotuzumab.

Resistensudvikling mod Daratumumab.

Nye behandlinger paa vej.

Praktiske forhold omkring behandling med Daratumumab.

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

CD38 as a novel immune checkpoint and mechanism of resistance to the blockade of the PD-1/PD-L1 axis

Limo Chen, PhD

(Gibbons Lab)

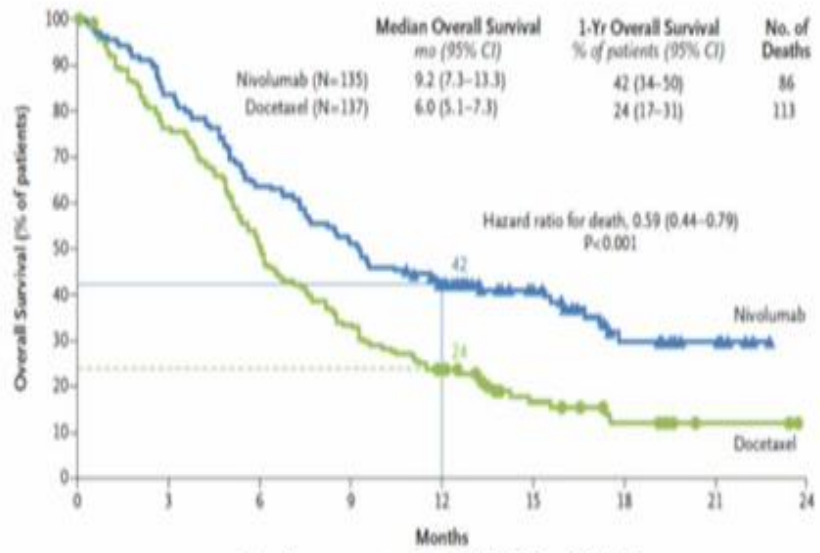
(Department of Thoracic/Head and Neck Medical Oncology)

ASCO-SITC Clinical Immuno-Oncology Symposium

February 23-25, 2017, Orlando, FL

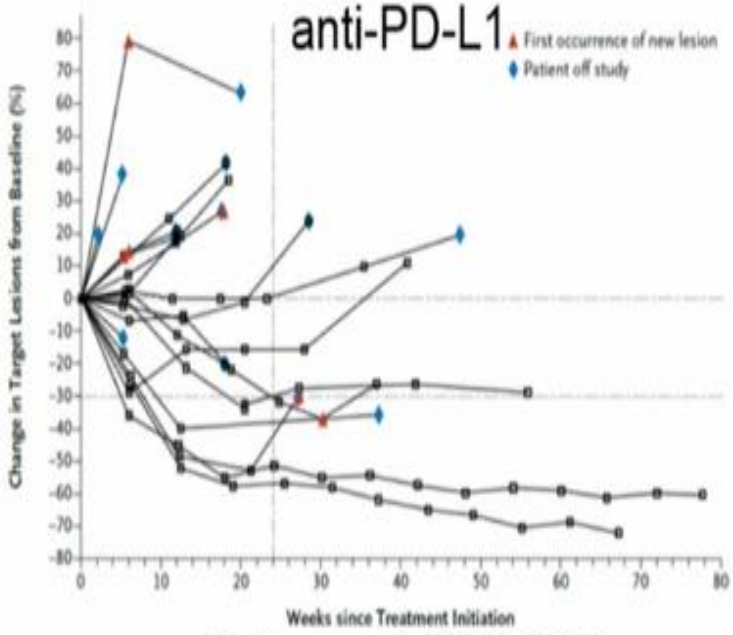
The fact of clinical outcome for PD-1/PD-L1 blockade in NSCLC

A



Brahmer et al., NEJM, 2015

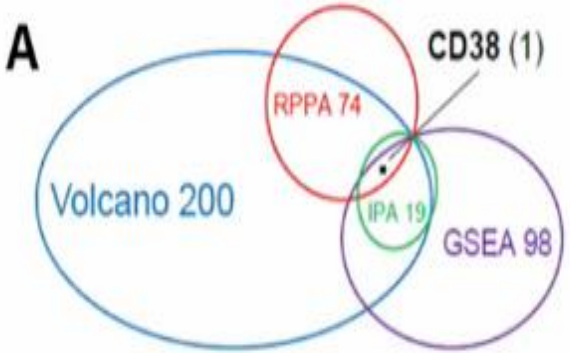
B

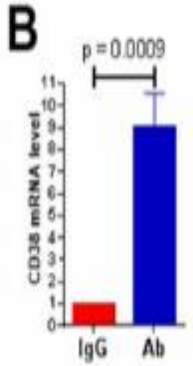


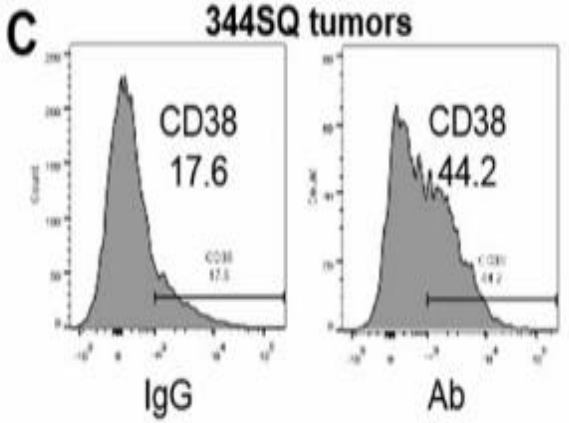
Brahmer et al., NEJM, 2012

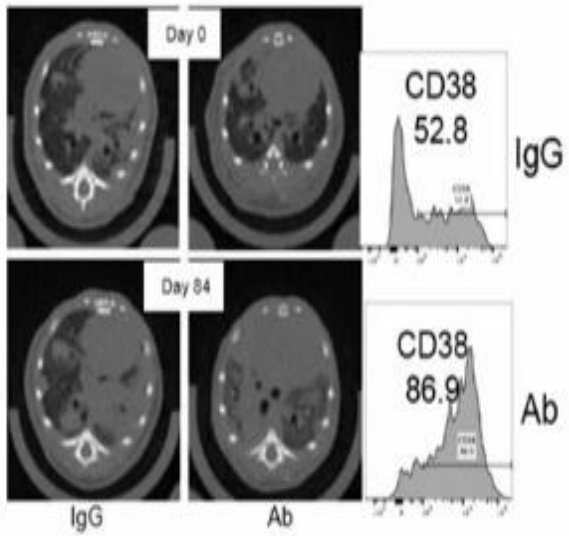
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

CD38 is upregulated after anti-PD-L1 antibody treatment, with an immune suppressive feature in resistant tumors

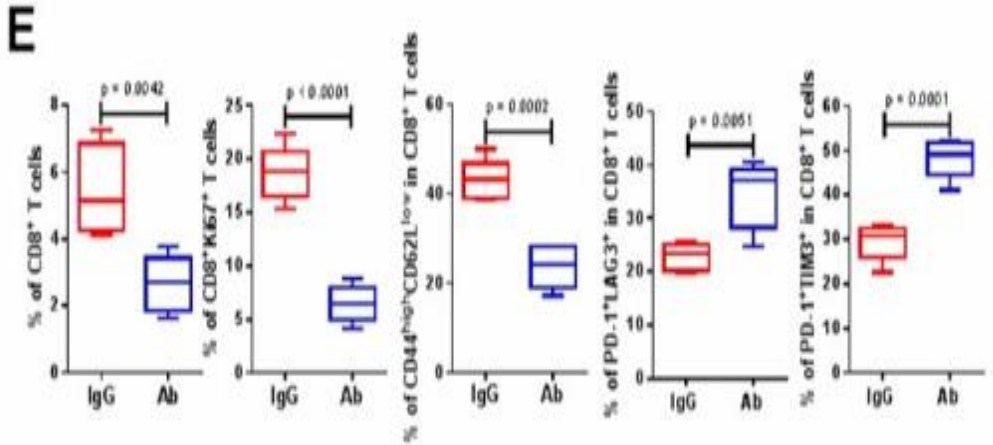




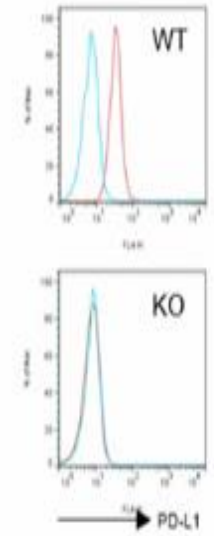


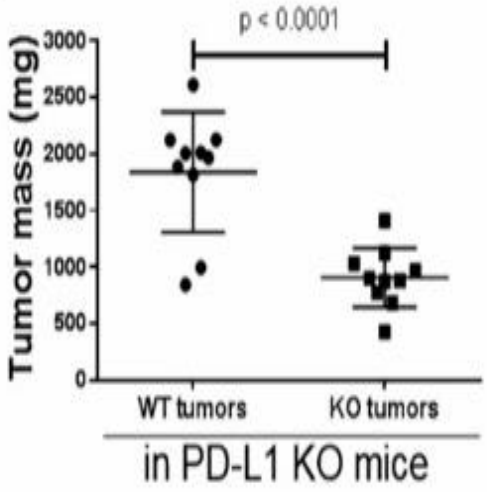


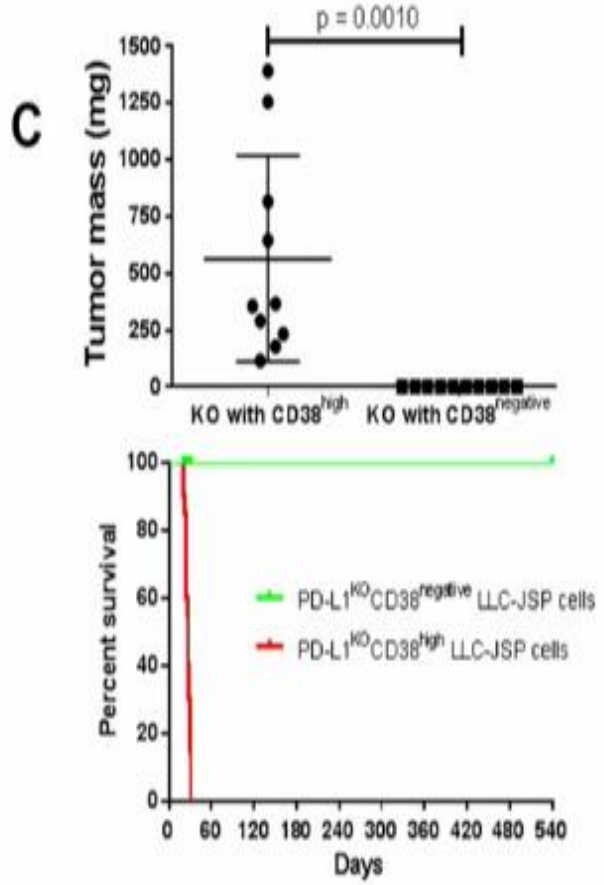
(in $Kras^{G12D/+};Trp53^{R172H/+}$ model)



Tumors still grow even after a complete blocking PD-L1 signaling, but the signaling loss of CD38 and PD-L1 causes a durable antitumor effect

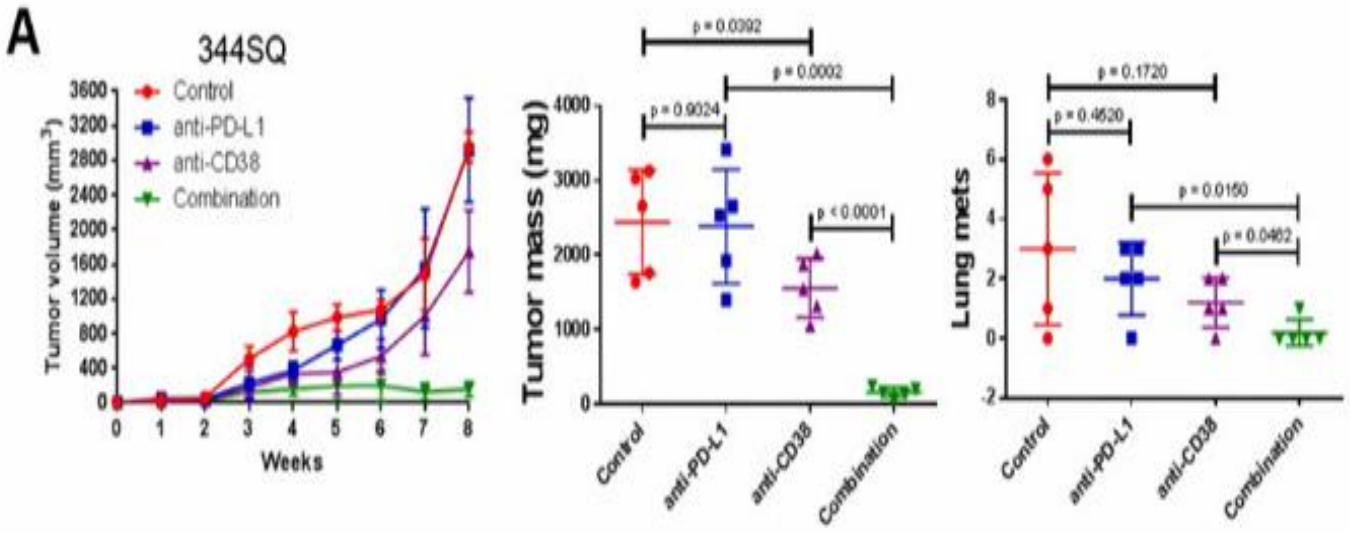


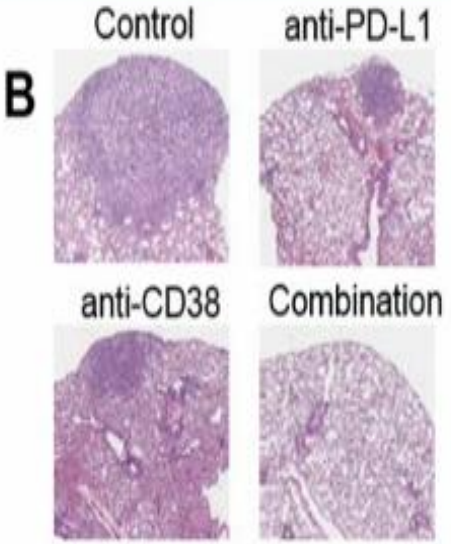


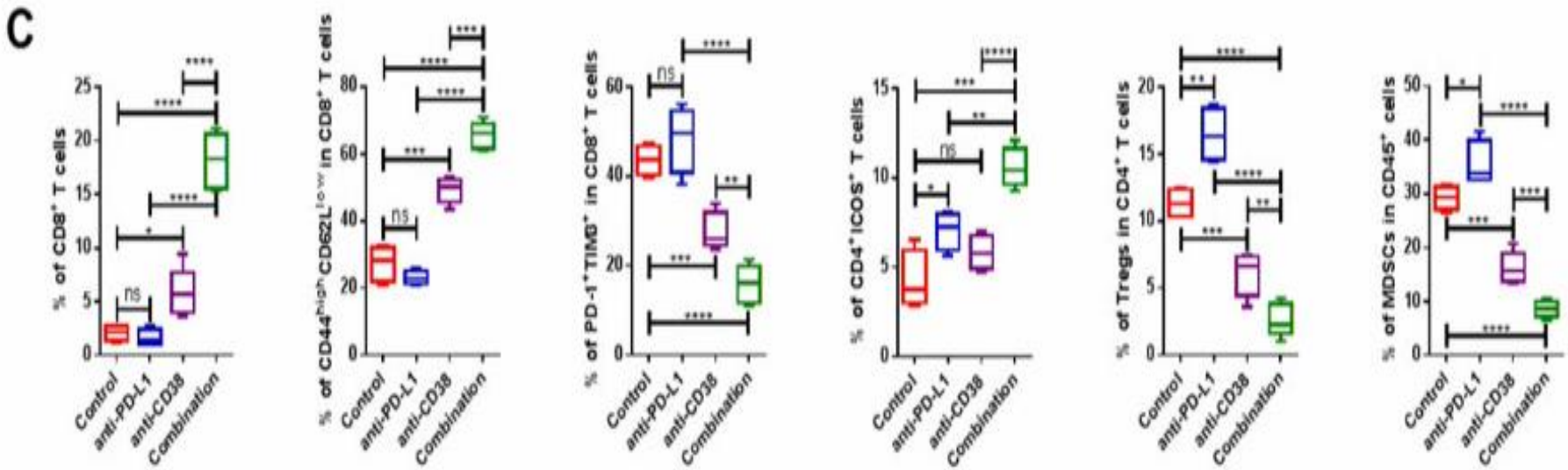


THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Co-inhibition of PD-L1 and CD38 improves antitumor immune responses







We also have the consistent results in other tumor models.

Conclusion

1) CD38 acts as a novel immune checkpoint by inhibiting $CD8^+$ T cell function.

2) CD38 is a major mechanism of resistance to PD-L1 blockade.

3) Co-inhibition of CD38 and PD-L1 causes the improved antitumor effect.

A PHASE 2, MULTICENTER, OPEN-LABEL, STUDY TO DETERMINE THE SAFETY AND EFFICACY FOR THE COMBINATION OF DURVALUMAB (DURVA) AND DARATUMUMAB (DARA) (D^2) IN SUBJECTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA (RRMM) (FUSION MM-003)

PROTOCOL NUMBER:	**MEDI4736-MM-003**
DATE FINAL:	**01 Apr 2016**
EudraCT NUMBER:	**2016-001209-17**
IND NUMBER:	**127058**
SPONSOR NAME/ ADDRESS:	**Celgene International II Sàrl Rue des Moulins 4 2108 Couvet Switzerland**

Anti-PD-L1

Hvorfor er der brug for nye behandlinger af myelomatose?

Antistoffer som nyt behandlingsprincip ved myelomatose.

Immunterapi med antistoffer ved myelomatose.

Ny viden fra behandling af lungecancer.

Daratumumab i kombinationsbehandlinger.

Elotuzumab.

Resistensudvikling mod Daratumumab.

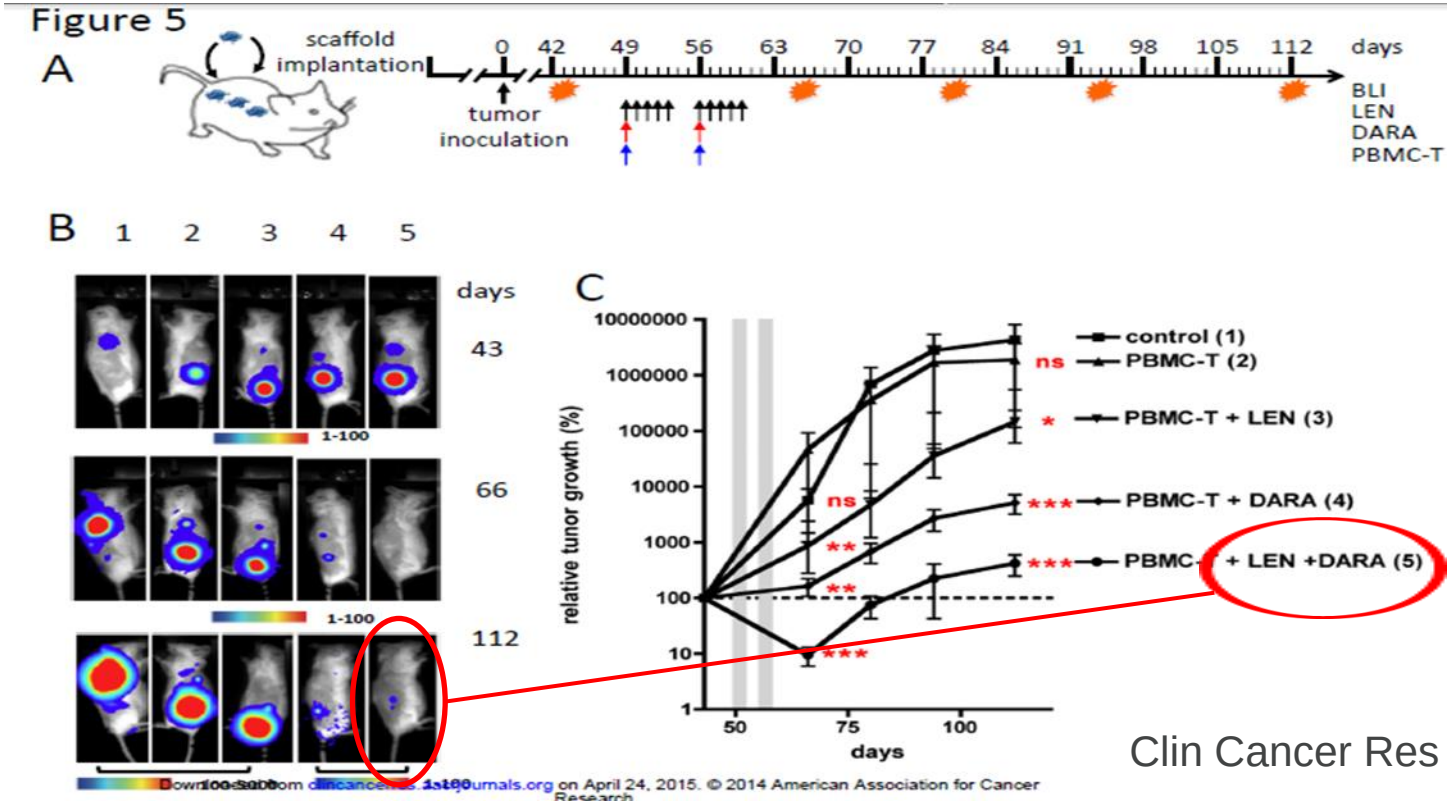
Nye behandlinger paa vej.

Praktiske forhold omkring behandling med Daratumumab.

Preclinical studies show enhanced anti-myeloma effect of Daratumumab by combination with other anti-myeloma drugs.

- Bortezomib: Additive effect
- Lenalidomide: Synergistic effect

Mouse model with human myeloma cells treated with LEN, DARA or the combination

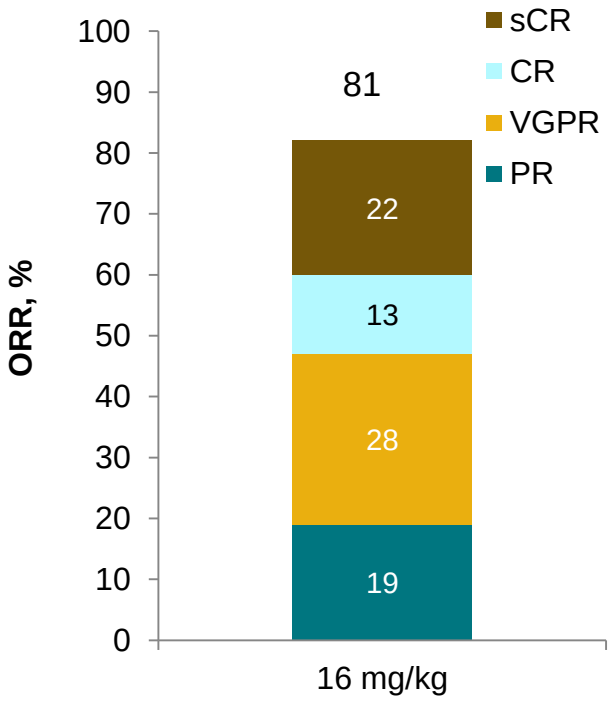


Clin Cancer Res 21 2802 2015

Phase 1/2 study of daratumumab, lenalidomide, and dexamethasone for relapsed multiple myeloma

Torben Plesner,[1] Hendrik-Tobias Arkenau,[2] Peter Gimsing,[3] Jakub Krejcik,[1] Charlotte Lemech,[2] Monique C. Minnema,[4] Ulrik Lassen,[3] Jacob P. Laubach,[5] Antonio Palumbo,[6] Steen Lisby,[7] Linda Basse,[7] Jianping Wang,[8] A. Kate Sasser,[9] Mary E. Guckert,[9] Carla de Boer,[10] Nushmia Z. Khokhar,[9] Howard Yeh,[9] Pamela L. Clemens,[9] Tahamtan Ahmadi,[9] Henk M. Lokhorst,[11] and Paul G. Richardson[5]

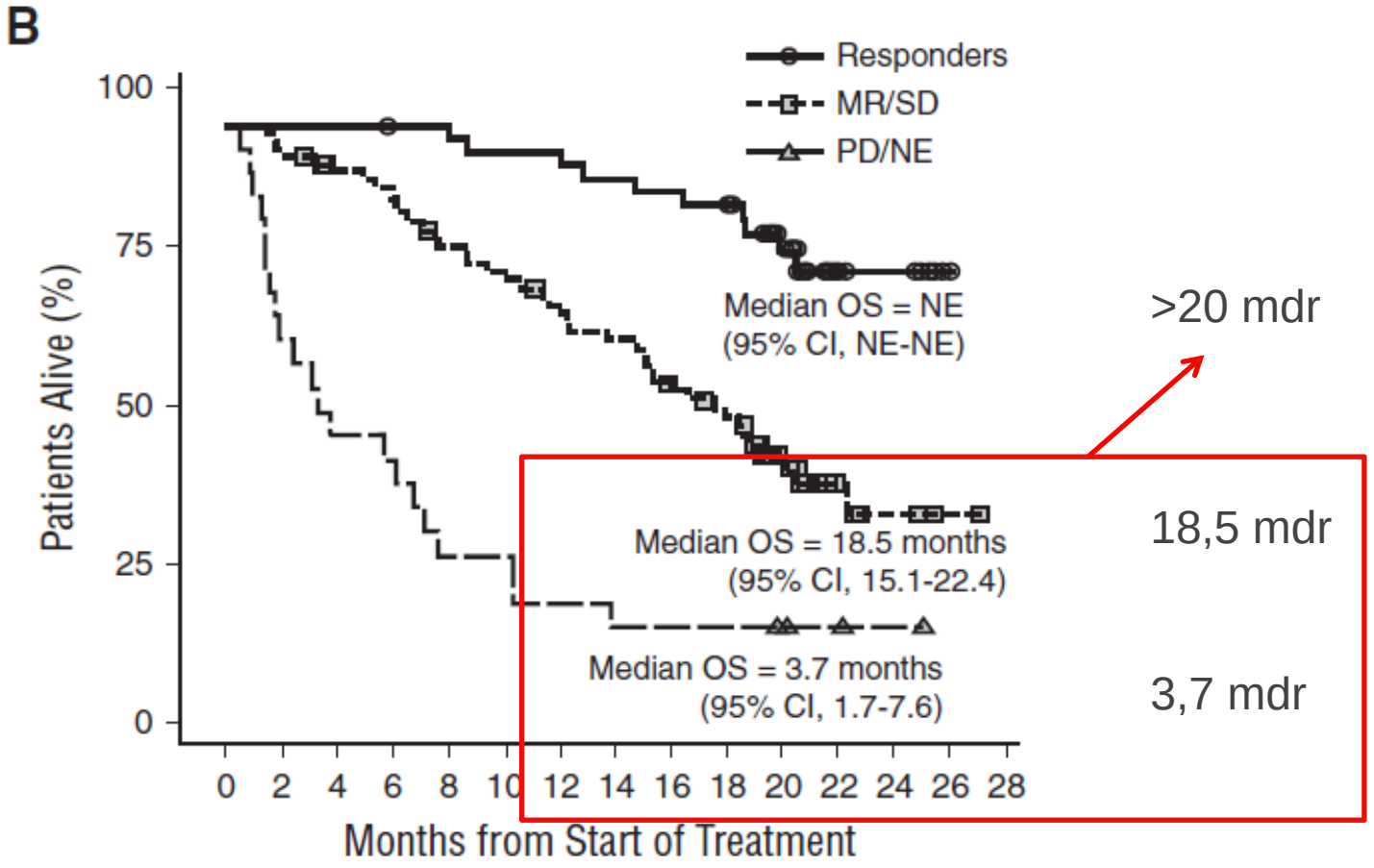
	16 mg/kg (n = 32)	
	n (%)	95% CI
Best response*		
sCR	7 (22)	9.3-40.0
CR	4 (13)	3.5-29.0
VGPR	9 (28)	13.7-46.7
PR	6 (19)	7.2-36.4
Overall response rate (ORR) (sCR+CR+VGPR+PR)	26 (81)	63.6-92.8
VGPR or better (sCR+CR+VGPR)	20 (63)	43.7-78.9
CR or better (sCR+CR)	11 (34)	18.6-53.2



Blood 128, 1821,2016

Tillæg af Lenalidomid eller Pomalidomid til Daratumumab øger muligheden for respons meget væsentligt også selvom man ikke har effekt af Len/Pom:

Immunstimulerende effekt



Randomized phase 3 trials of Daratumumab in combination with Bortezomib or Lenalidomide

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma

Antonio Palumbo, M.D., Asher Chanan-Khan, M.D., Katja Weisel, M.D., Ajay K. Nooka, M.D., Tamas Masszi, M.D., Meral Beksac, M.D., Ivan Spicka, M.D., Vania Hungria, M.D., Markus Munder, M.D., Maria V. Mateos, M.D., Tomer M. Mark, M.D., Ming Qi, M.D., Jordan Schecter, M.D., Himal Amin, B.S., Xiang Qin, M.S., William Deraedt, Ph.D., Tahamtan Ahmadi, M.D., Andrew Spencer, M.D., and Pieter Sonneveld, M.D., for the CASTOR Investigators*

NEJM 375 754 2016

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 6, 2016 VOL. 375 NO. 14

Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma

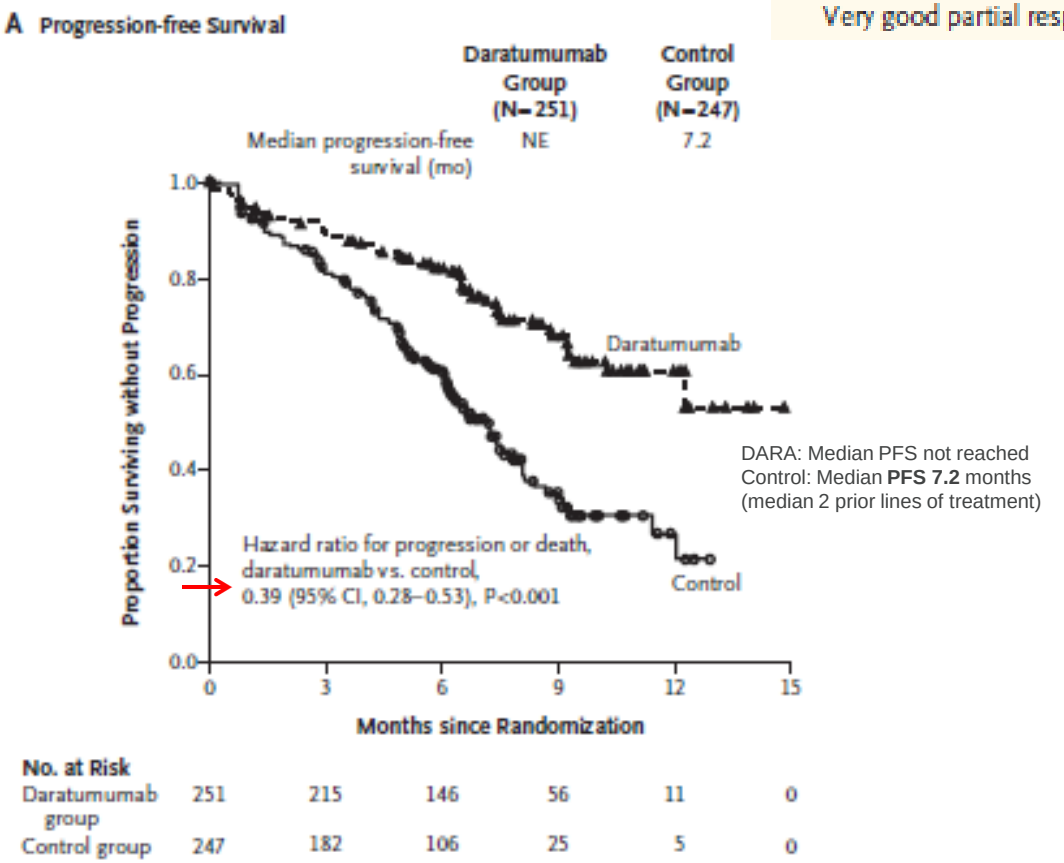
M.A. Dimopoulos, A. Oriol, H. Nahi, J. San-Miguel, N.J. Bahlis, S.Z. Usmani, N. Rabin, R.Z. Orlowski, M. Komarnicki, K. Suzuki, T. Plesner, S.-S. Yoon, D. Ben Yehuda, P.G. Richardson, H. Goldschmidt, D. Reece, S. Lisby, N.Z. Khokhar, L. O'Rourke, C. Chiu, X. Qin, M. Guckert, T. Ahmadi, and P. Moreau, for the POLLUX Investigators*

NEJM 375 1319 2016

Results of randomized trials with Daratumumab
CASTOR: BORTEZOMIB/DEX =/- DARA

CASTOR: VEL/DEX +/- DARA

	Daratumumab Group (N=240)	Control Group (N=234)
Complete response or better	46 (19.2)	21 (9.0)
Complete response	35 (14.6)	16 (6.8)
Stringent complete response‡	11 (4.6)	5 (2.1)
Very good partial response or better	142 (59.2)	68 (29.1)
Very good partial response	96 (40.0)	47 (20.1)



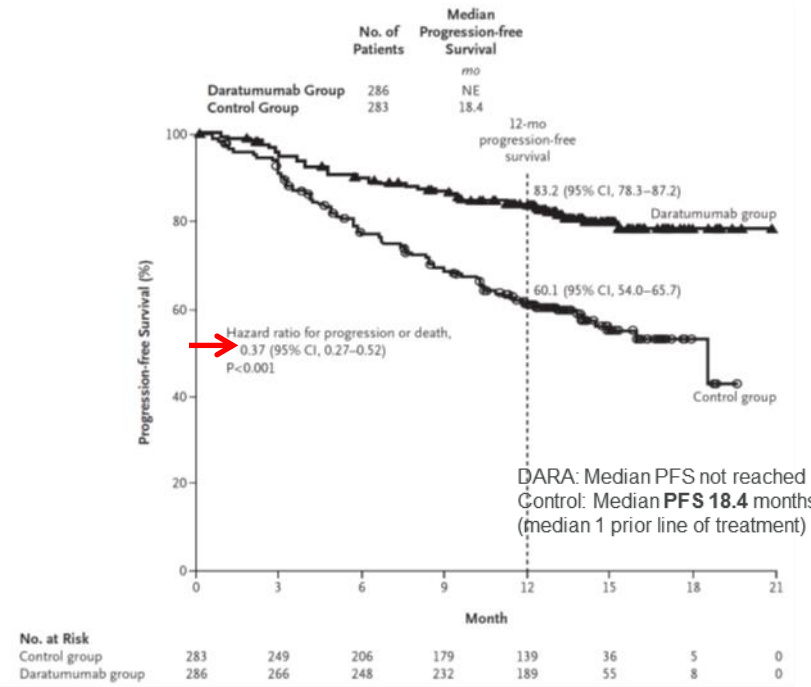
DARA: Median PFS not reached
Control: Median **PFS 7.2** months
(median 2 prior lines of treatment)

61 % reduktion af risikoen for sygdomsudvikling ved tillæg af Daratumumab til Velcade og Dexamethason

Kontrolarm: Median PFS 7,2 mdr

NEJM 375 754 2016

Results of randomized trials with Daratumumab
POLLUX: LEN/DEX +/- DARA



DARA: Median PFS not reached
Control: Median **PFS 18.4** months
(median 1 prior line of treatment)

	Daratumumab Group (N = 281)	Control Group (N = 276)
Best overall response — no. (%)		
Complete response or better	121 (43.1)	53 (19.2)
Stringent complete response§	51 (18.1)	20 (7.2)
Complete response	70 (24.9)	33 (12.0)
Very good partial response or better	213 (75.8)	122 (44.2)
Very good partial response	92 (32.7)	69 (25.0)
Partial response	48 (17.1)	89 (32.2)
Minimal response	5 (1.8)	26 (9.4)
Stable disease	13 (4.6)	33 (12.0)
Progressive disease	0	4 (1.4)

63 % reduktion af risikoen for sygdomsudvikling ved tillæg af Daratumumab til Lenalidomid og Dexamethason

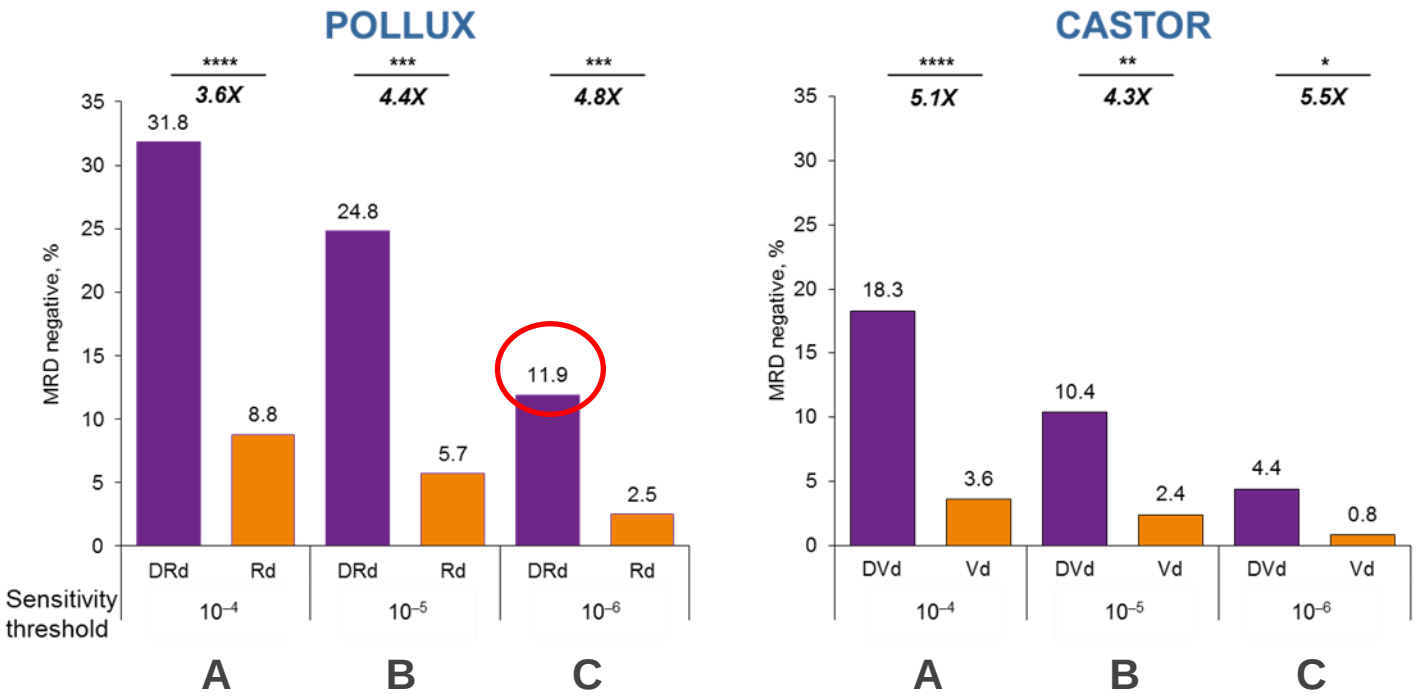
Kontrolarm: Median PFS 18,4 mdr

NEJM 375 1319 2016

Undersøgelse for minimal restsygdom efter behandling i ”Pollux” eller ”Castor” med ”Next Generation Sequencing” (”NGS”), - en meget følsom metode til specifikt at spore myelomcellernes DNA

Der testes på 3 følsomheds niveauer:

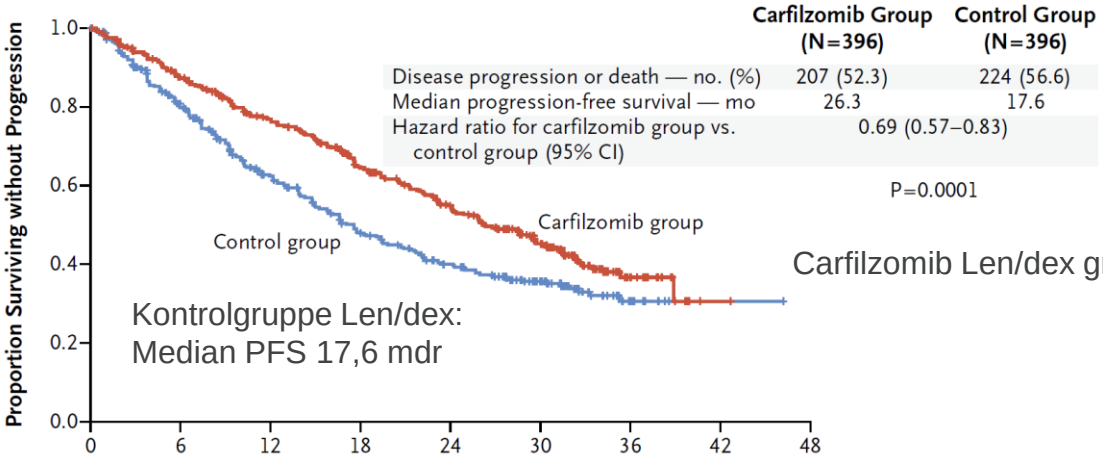
En myelomatosecelle ud af 10.000 knoglemarvsceller (**A**)
En myelomatosecelle ud af 100.000 knoglemarvsceller (**B**)
En myelomatosecelle ud af 1.000.000 knoglemarvsceller (**C**)



Eksempel: Hos 11,9 % af patienterne kan man ***ikke*** påvise 1 tumorcelle ud af 1 million celler fra knoglemarven efter behandling i Pollux med DARA/Len/dex

Carfilzomib, en ny proteasominhibitor, eller Daratumumab begge i kombination med Lenalidomid og dexamethason.

ASPIRE trial: Lenalidomide and dexamethasone with or without Carfilzomib



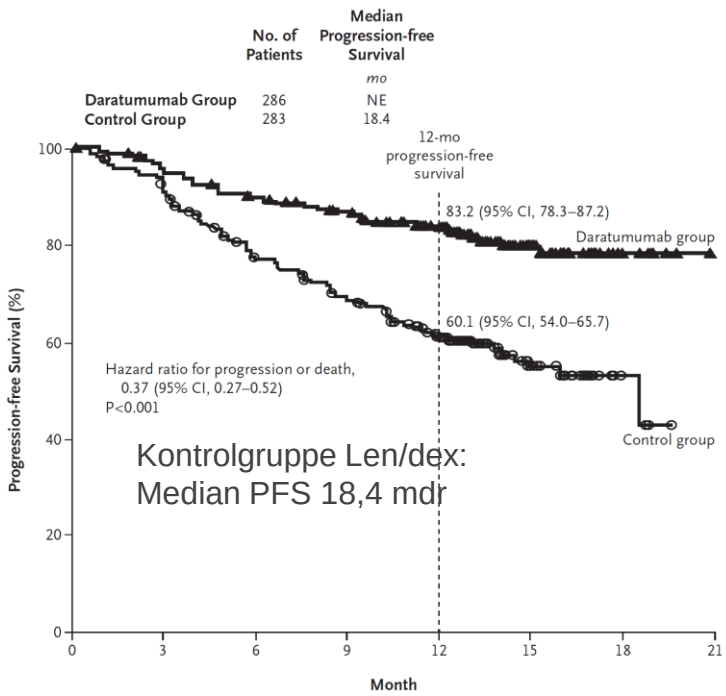
	Carfilzomib Group (N=396)	Control Group (N=396)
Disease progression or death — no. (%)	207 (52.3)	224 (56.6)
Median progression-free survival — mo	26.3	17.6
Hazard ratio for carfilzomib group vs. control group (95% CI)	0.69 (0.57–0.83)	

Kontrolgruppe Len/dex:
Median PFS 17,6 mdr

Carfilzomib Len/dex gruppe: Median PFS 26,3 mdr

NEJM 372 142 2015

POLLUX trial: Lenalidomide and dexamethasone with or without Daratumumab



Kontrolgruppe Len/dex:
Median PFS 18,4 mdr

Daratumumab Len/dex gruppe: Median PFS ?

NEJM 375 1319 2016

Hvorfor er der brug for nye behandlinger af myelomatose?

Antistoffer som nyt behandlingsprincip ved myelomatose.

Immunterapi med antistoffer ved myelomatose.

Ny viden fra behandling af lungecancer.

Daratumumab i kombinationsbehandlinger.

Elotuzumab.

Resistensudvikling mod Daratumumab.

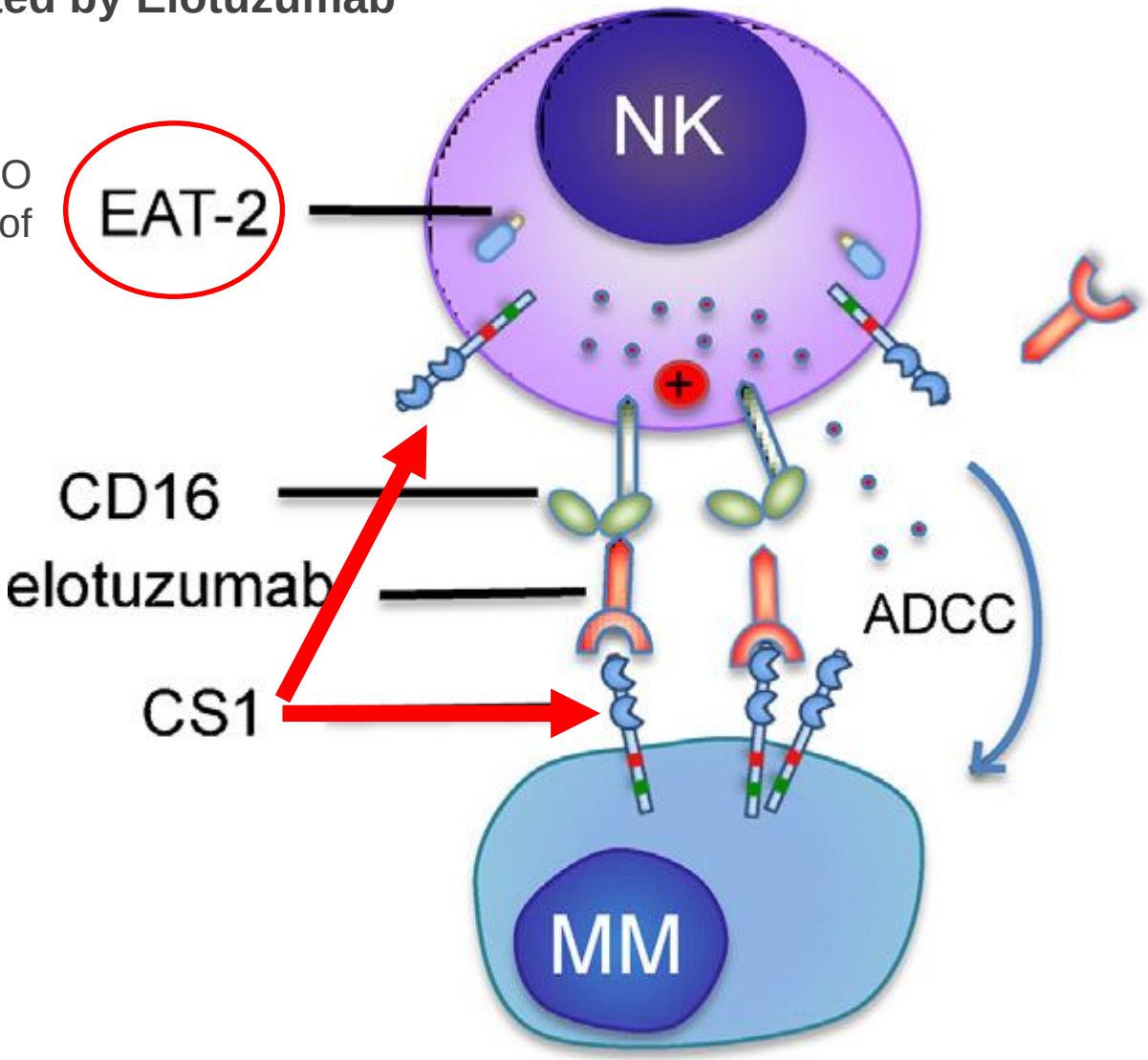
Nye behandlinger paa vej.

Praktiske forhold omkring behandling med Daratumumab.

Elotuzumab for treatment of Multiple Myeloma

CS1 or SLAMF7 is expressed by myeloma cells and NK-cells and may be targeted by Elotuzumab

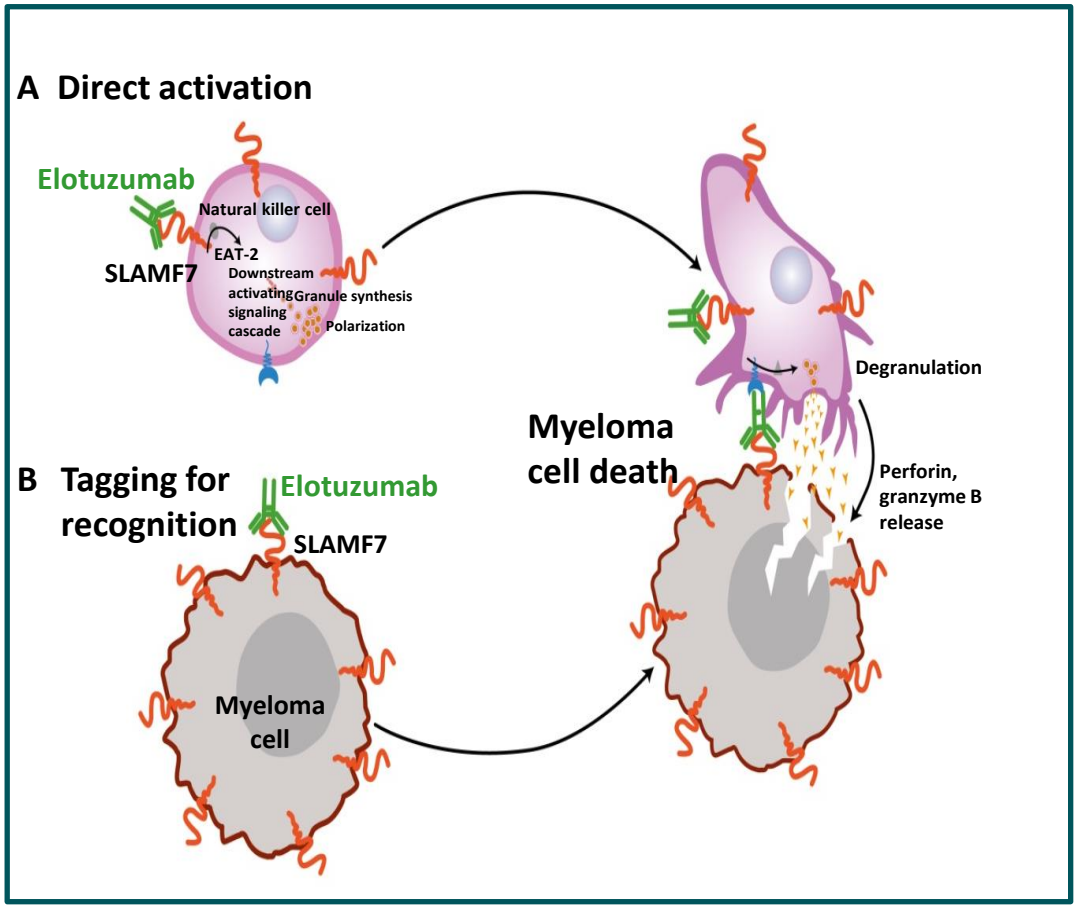
Activation by ELO in the presence of EAT-2



Elotuzumab: SLAMF7-targeted mAb therapy

- Humanized mAb targeted against SLAMF7; highly expressed on myeloma and NK cells but not on normal tissues[1]

- Dual mechanism of action:
  - Direct activation: Binding to SLAMF7 directly activates NK cells, but not myeloma cells[2,3]
  - Tagging for recognition: Activation of NK cells via CD16 → killing of myeloma cells via ADCC[2]



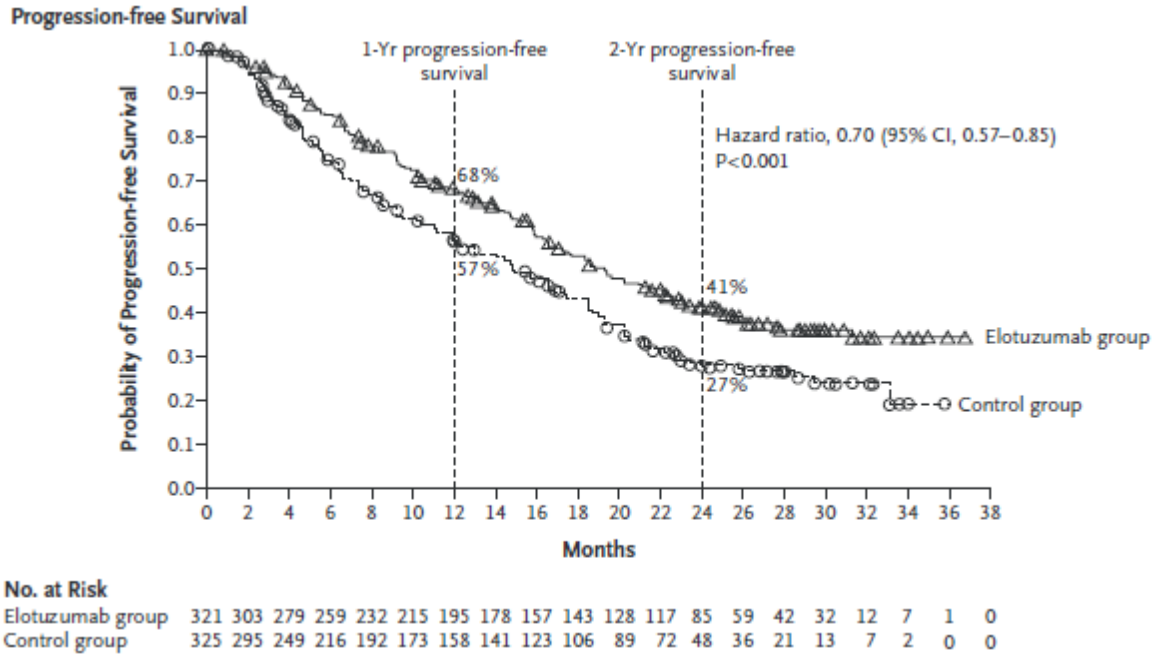
SLAMF7 = Signaling Lymphocyte Activation Molecule-F7

1. Hsi ED et al. *Clin Cancer Res* 2008;14:2775–84; 2. Collins SM et al. *Cancer Immunol Immunother* 2013;62:1841–9; 3.Guo H et al. *Mol Cell Biol* 2015;35:41–51

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma



Median PFS:
Elo 19.4 months
Control 14.9 months

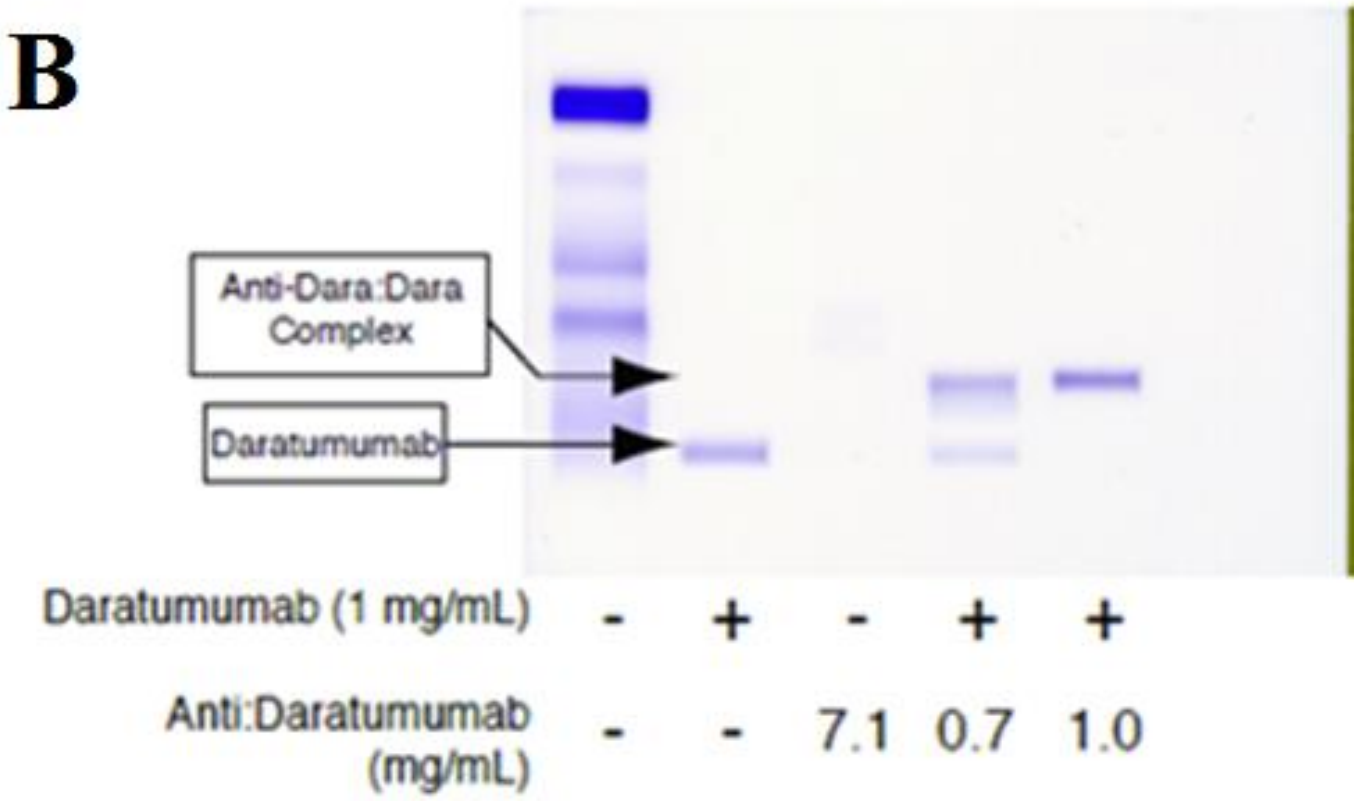
VGPR or better:
Elo 33 %
Control 28 %

Median prior lines of therapy: 2

In the analysis by the independent review committee, there were fewer complete responses in the elotuzumab group than in the control group.

NEJM 373 621 2015

DIRA

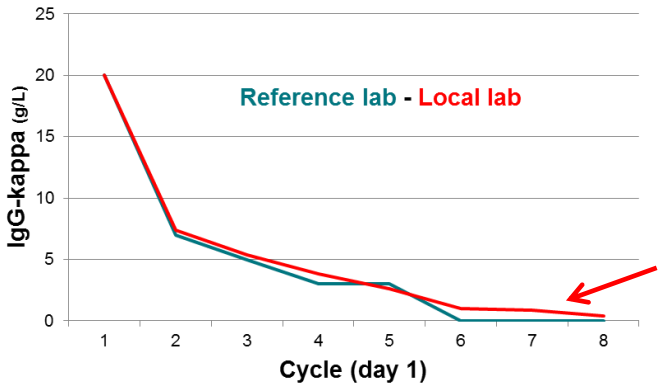


McCudden C, et al. Clin Chem Lab Med 2016; aop; DOI 10.1515/cclm-2015-1031

Case story: Respons paa Daratumumab

Patient (female 54 years) diagnosed with myeloma NOV 2011
Multiple small osteolytic lesions; ISS stage 1

Line, type and time of treatment	Response
1. CVD x 4/HD-melphalan/ASCT.	PR
2. Thalidomide/HD-melphalan/”Tandem”-ASCT.	VGPR
3. Lenalidomide/dexamethasone JAN 2014-JAN 2015	PR
4. Lenalidomide/dexamethasone MAR-AUG 2015	PD
5. Bortezomib/Len/Dex AUG-NOV 2015	PD
6. Bortezomib/Len/Dex/oral Cyclophosphamide NOV-DEC 2015	PD
7. Pomalidomide/dexamethasone DEC 2015-MAR 2016	MR/PD
8. Carfilzomib/dexamethasone/oral Cyclophosphamide MAR-MAY 2016	PD
9. Daratumumab JUN 2016-ongoing	**CR**



Residual IgG kappa M-component 0.4-0.7 g/l = Daratumumab

Monoclonal Antibodies in Multiple Myeloma Come of Age

Noopur Raje, M.D., and Dan L. Longo, M.D.

NEJM 373 1264 2015

A new era of immune therapy in multiple myeloma

Blood 128 316 2016

Yu-Tzu Tai and Kenneth C. Anderson DANA-FARBER CANCER INSTITUTE

Daratumumab in multiple myeloma

The Lancet 387 1490 2016

It is easy to be overwhelmed by hype in cancer research, with promising new discoveries often portrayed as so-called game changers.[1] Most new treatments for cancer are far from being transformative, but daratumumab is possibly a rare exception. It targets CD38, an antigen

single-age
profile is
enthusias
with curre
myeloma,

Progress in Myeloma — A Monoclonal Breakthrough

S. Vincent Rajkumar, M.D., and Robert A. Kyle, M.D.

NEJM 375 1390 2016

Hvorfor er der brug for nye behandlinger af myelomatose?

Antistoffer som nyt behandlingsprincip ved myelomatose.

Immunterapi med antistoffer ved myelomatose.

Ny viden fra behandling af lungecancer.

Daratumumab i kombinationsbehandlinger.

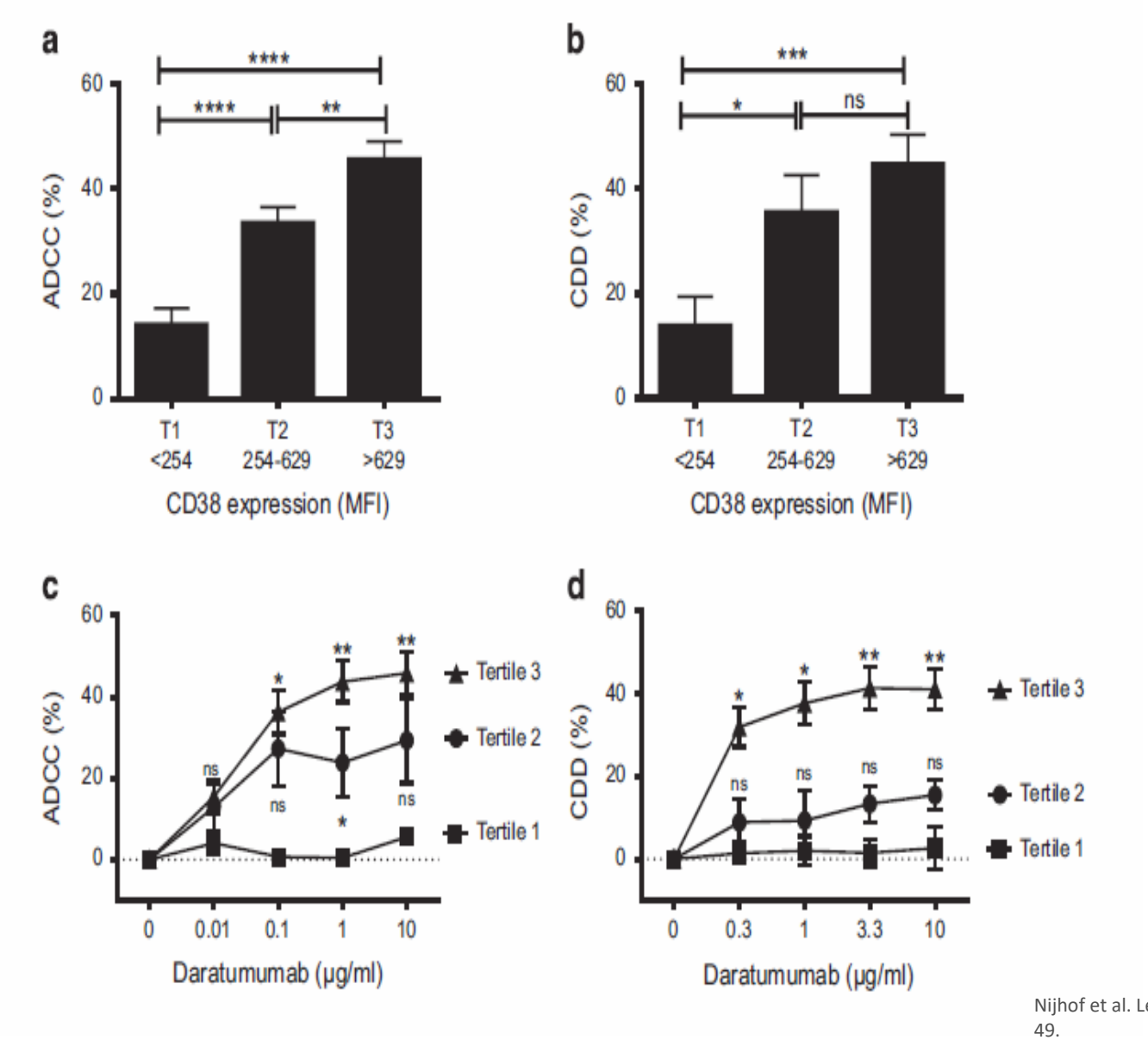
Elotuzumab.

Resistensudvikling mod Daratumumab.

Nye behandlinger paa vej.

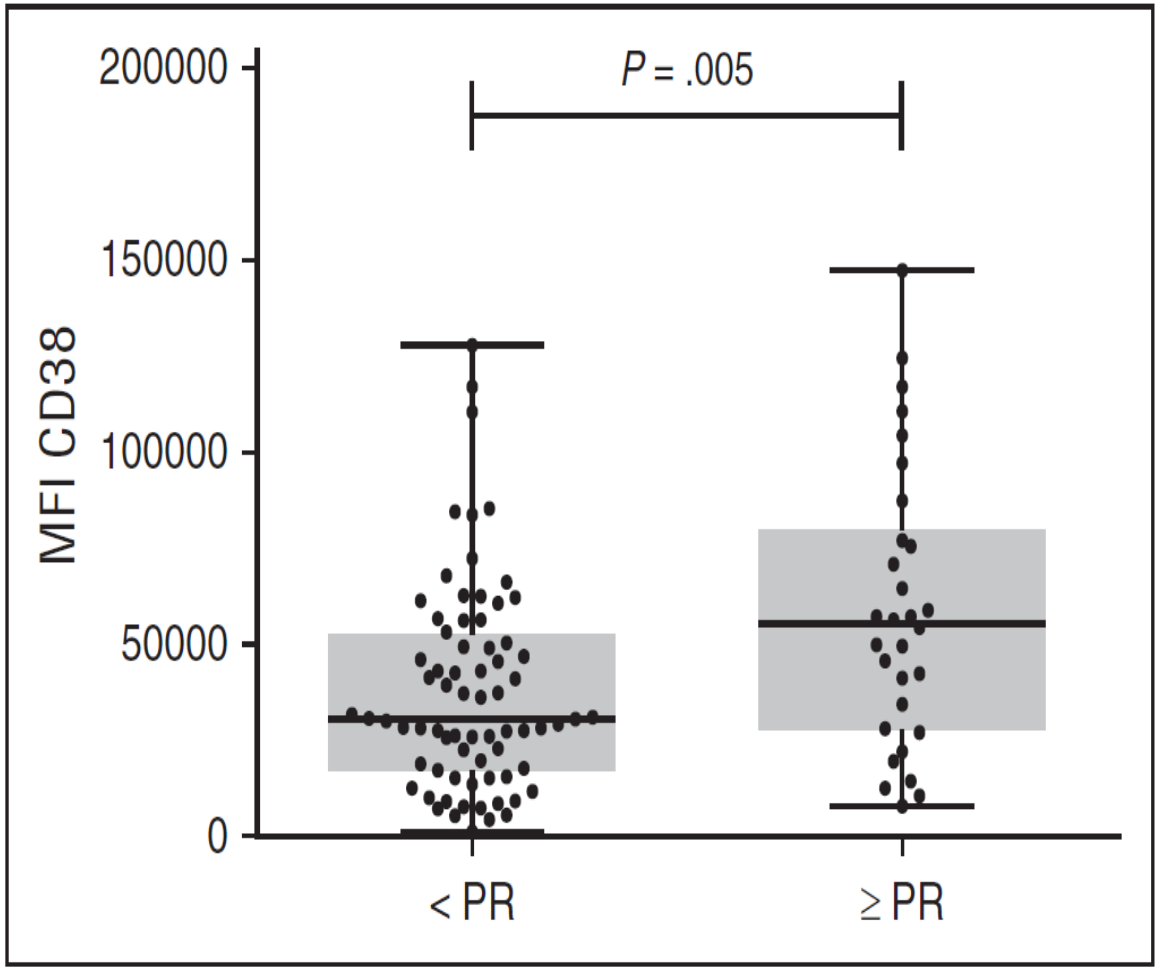
Praktiske forhold omkring behandling med Daratumumab.

Daratumumab: CD38 expression correlates with cell death (patient samples)



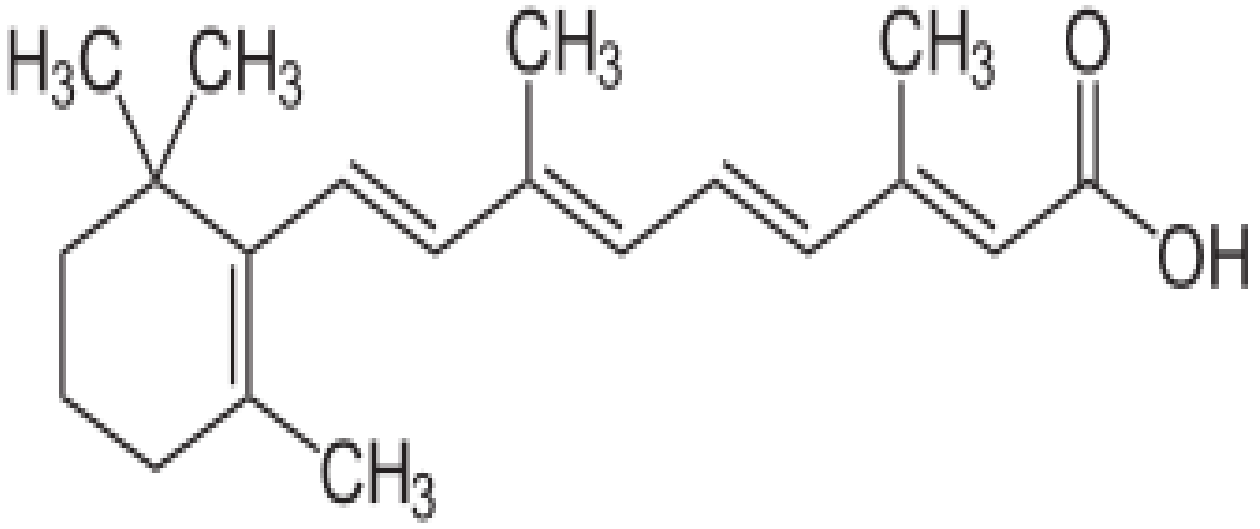
Nijhof et al. Leukemia 2015;29(10):2039-49.

Correlation of CD38 expression by myeloma cells with response to DARA monotherapy



Blood 128 959 2016

All-trans-retinoic acid (ATRA) increases expression of CD38



http://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:15367

ATRA and CD38

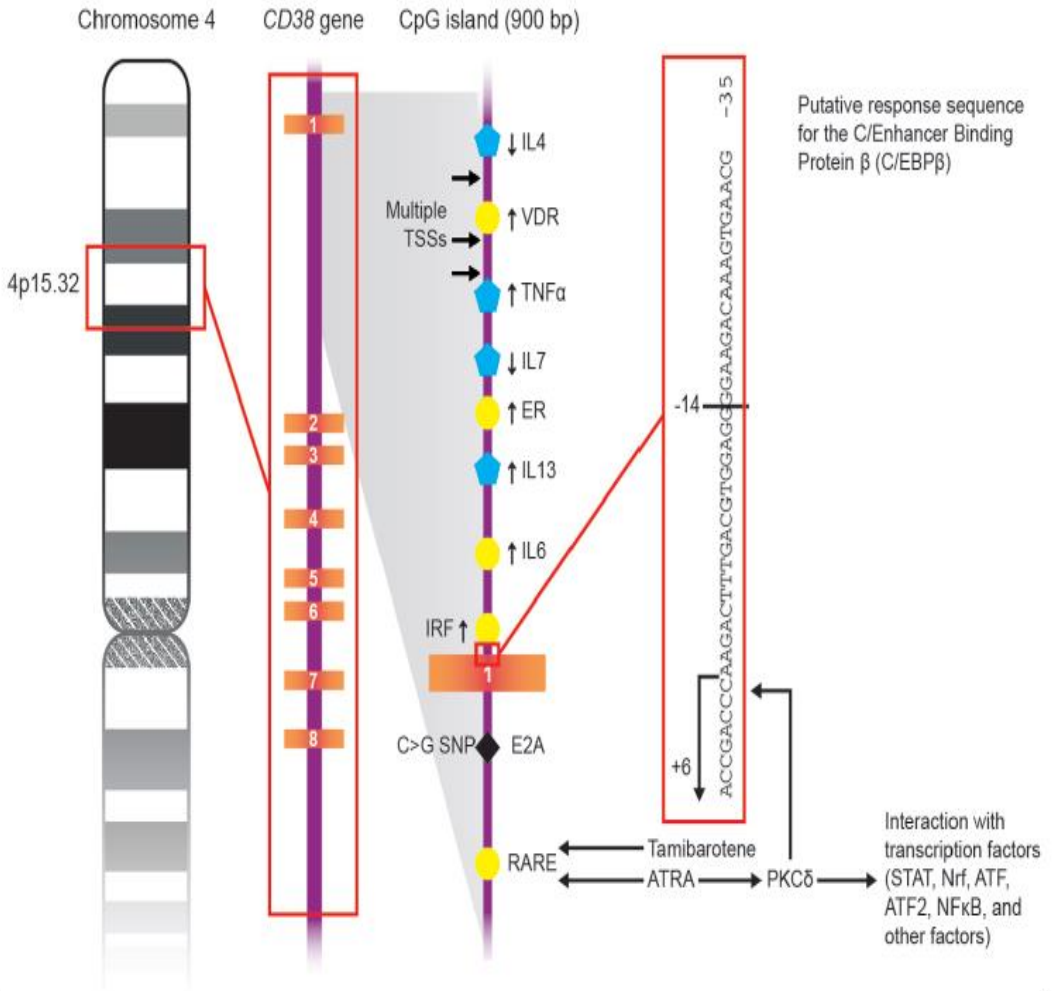
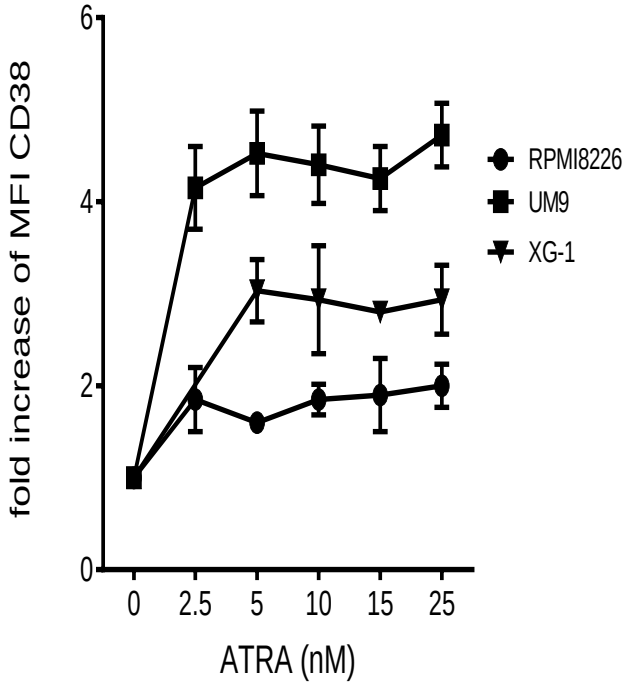
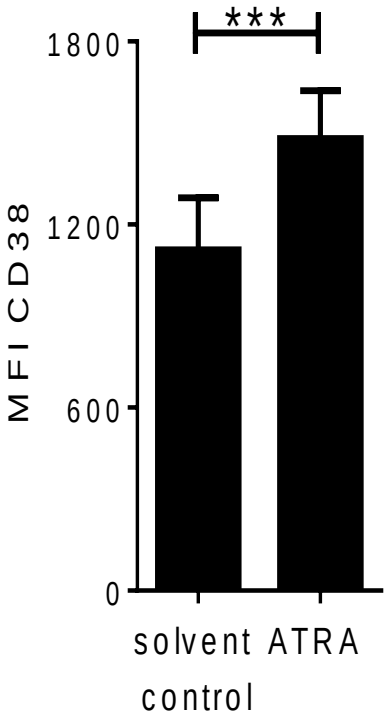


Figure 4. Schematic representation of the mechanisms of action of ATRA and tamibarotene on *CD38* gene.

Chillemi et al. Mol Med 2013; 19:99–108.

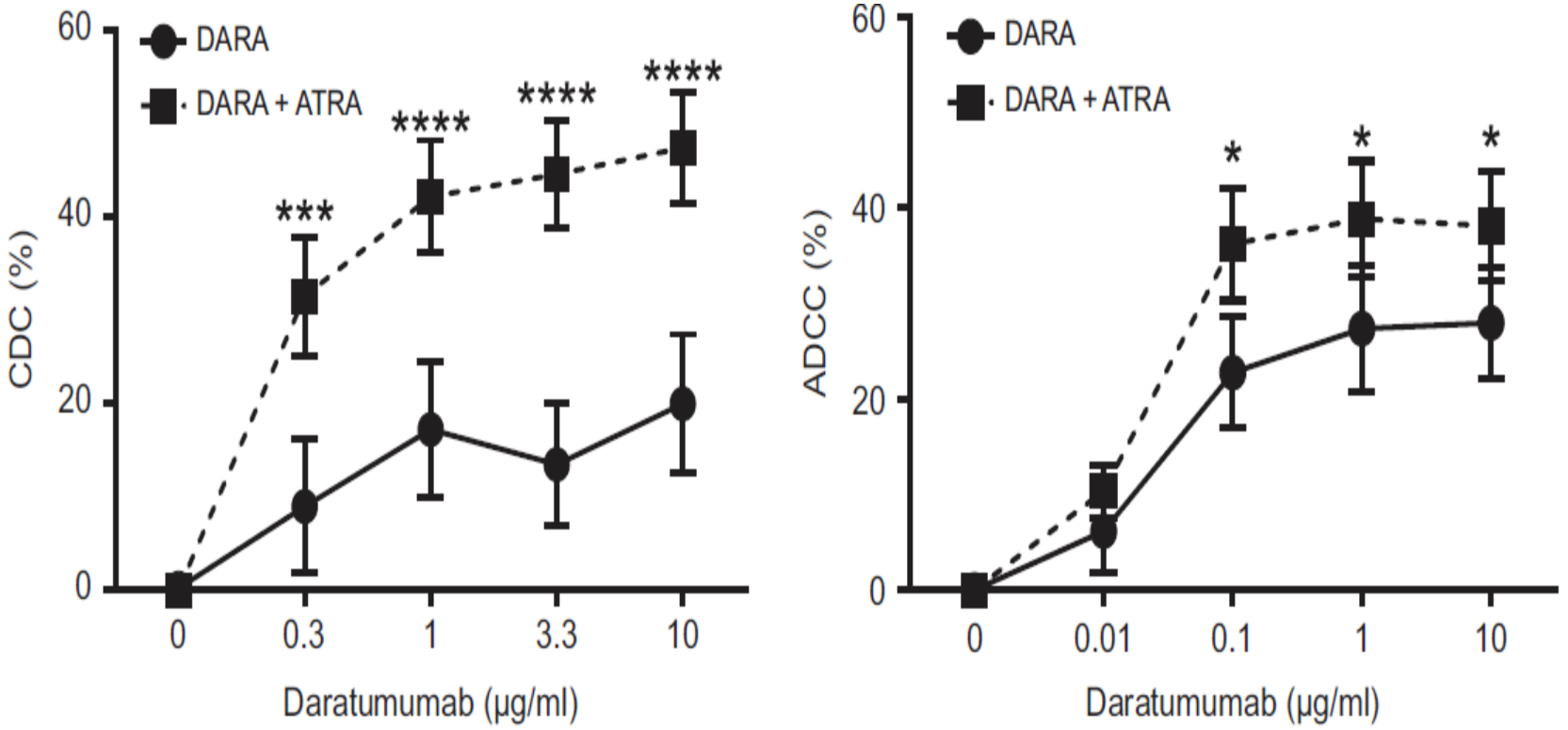
ATRA





Nijhof et al. Leukemia 2015;29(10):2039-49.

Efficacy of daratumumab +/– ATRA in patient-derived BM-MNC

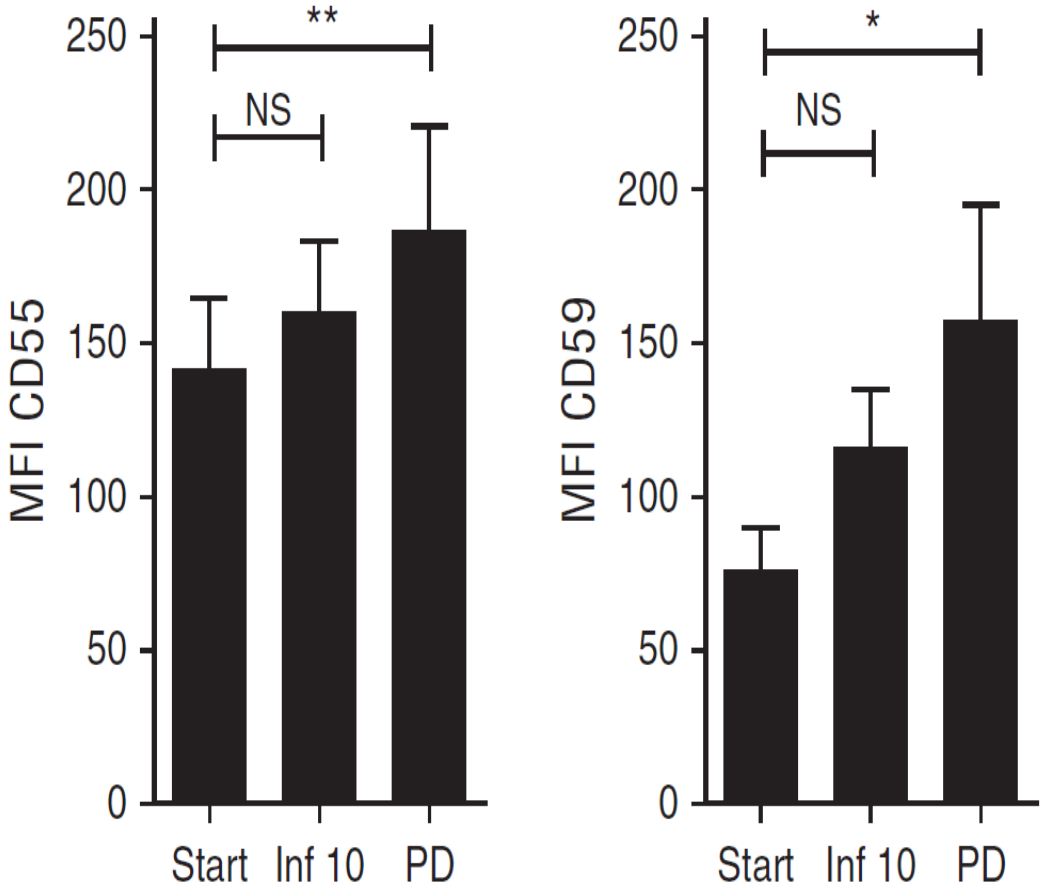


- Pretreatment of patients' BM-MNC (n = 16) with ATRA significantly enhanced daratumumab-mediated CDC and ADCC ex vivo

*P <0.05; ***P <0.001; ****P <0.0001. Paired Student's t test.

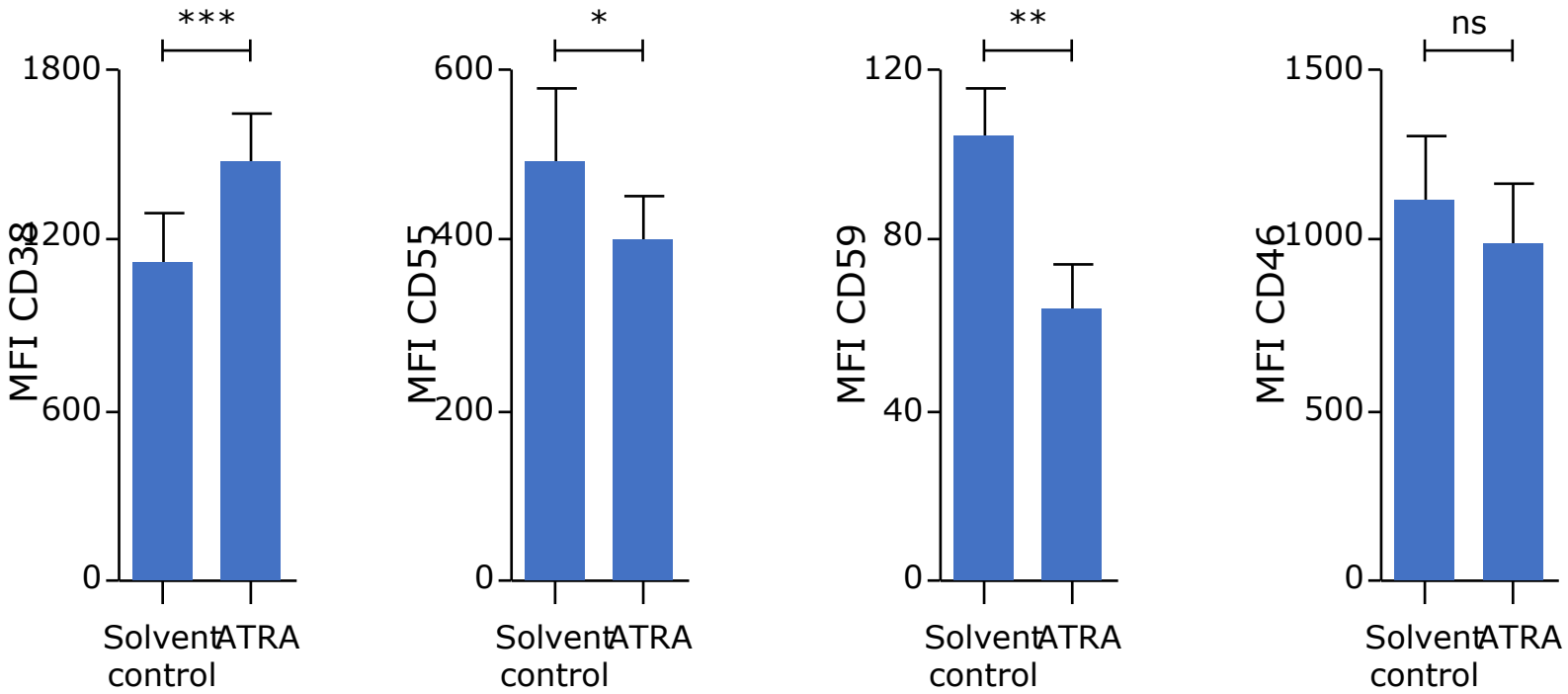
Nijhof et al. Leukemia 2015;29(10):2039-49.

The expression of complement-inhibitory proteins CD55 and CD59 increase at the time of progression (PD).



Blood 128 959 2016

ATRA increases CD38 expression and decreases CD55, CD59 and CD46 expression

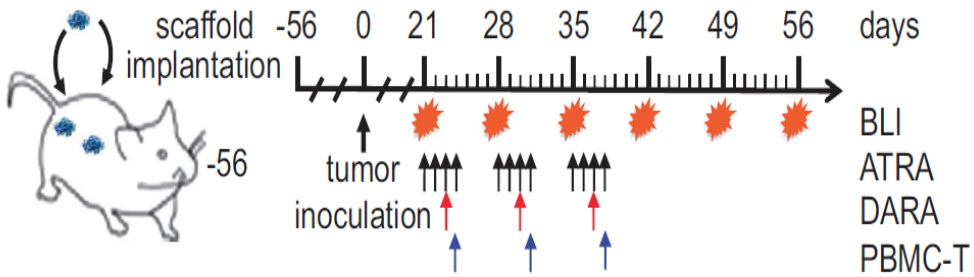


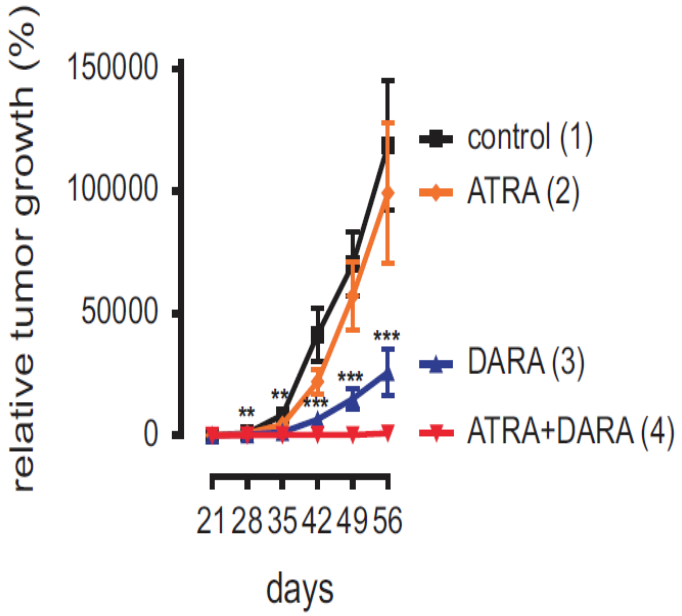
- In patient-derived BM-MNCs, ATRA pretreatment (10 nM for 48 hours) caused a significant increase in CD38 expression
- In primary MM cells, *ex vivo* ATRA treatment significantly reduced expression of complement-inhibitory proteins CD55 and CD59, but not CD46

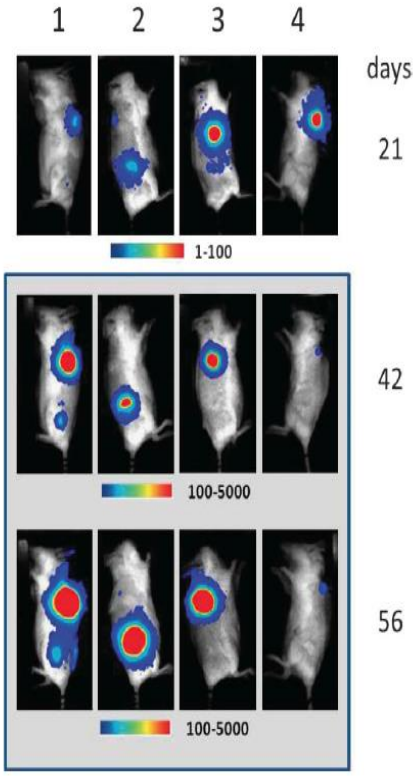
ATRA, all-*trans* retinoic acid; MFI, median fluorescence intensity; BM-MNC, bone marrow mononuclear cells; ns, not significant; MM, multiple myeloma.
**P* <0.05, ***P* <0.01, ****P* <0.001, *****P* <0.0001. Student's *t* test.
Nijhof IS, et al. *Leukemia*. 2015;29(10):2039-49.

ATRA improves response to daratumumab *in vivo*

- ATRA enhances the anti-MM activity of daratumumab in a humanized mouse model







**P <0.01; ***P <0.001; Paired Student's t test.
BLI, bioluminescent imaging.
Nijhof et al. Leukemia 2015;29(10):2039-49.

A phase 1 and phase 2 study of daratumumab in combination with all-trans retinoic acid in relapsed/refractory multiple myeloma

Principal Investigator	Niels W.C.J. van de Donk (VUmc) Henk M. Lokhorst (VUmc)
Sponsor	VU University Medical Center, Amsterdam
Financial support:	Janssen Pharmaceuticals
Data management: Central data management:	Local Hospital VUmc, Amsterdam
EudraCT number:	2015-003862-10

Hvorfor er der brug for nye behandlinger af myelomatose?

Antistoffer som nyt behandlingsprincip ved myelomatose.

Immunterapi med antistoffer ved myelomatose.

Ny viden fra behandling af lungecancer.

Daratumumab i kombinationsbehandlinger.

Elotuzumab.

Resistensudvikling mod Daratumumab.

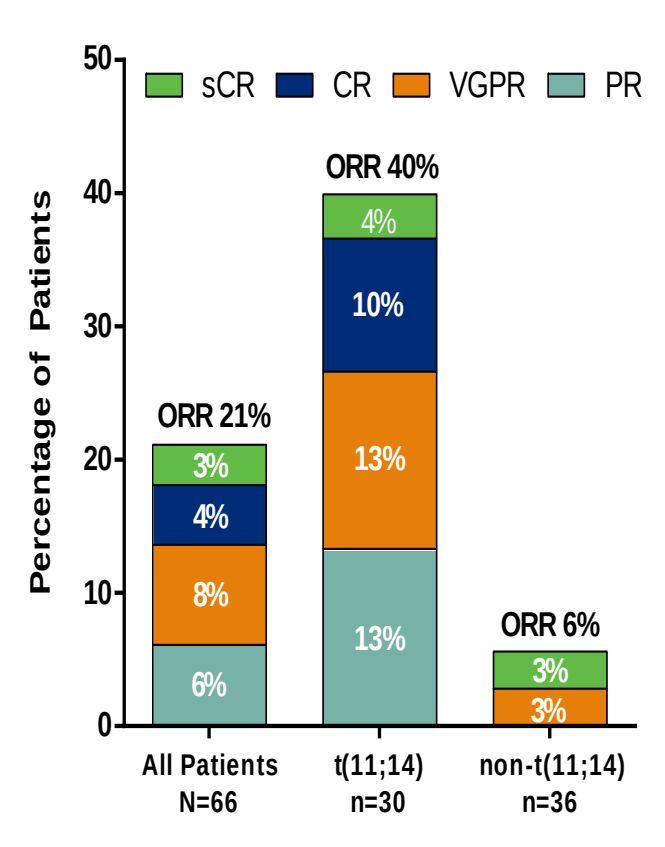
Nye behandlinger paa vej.

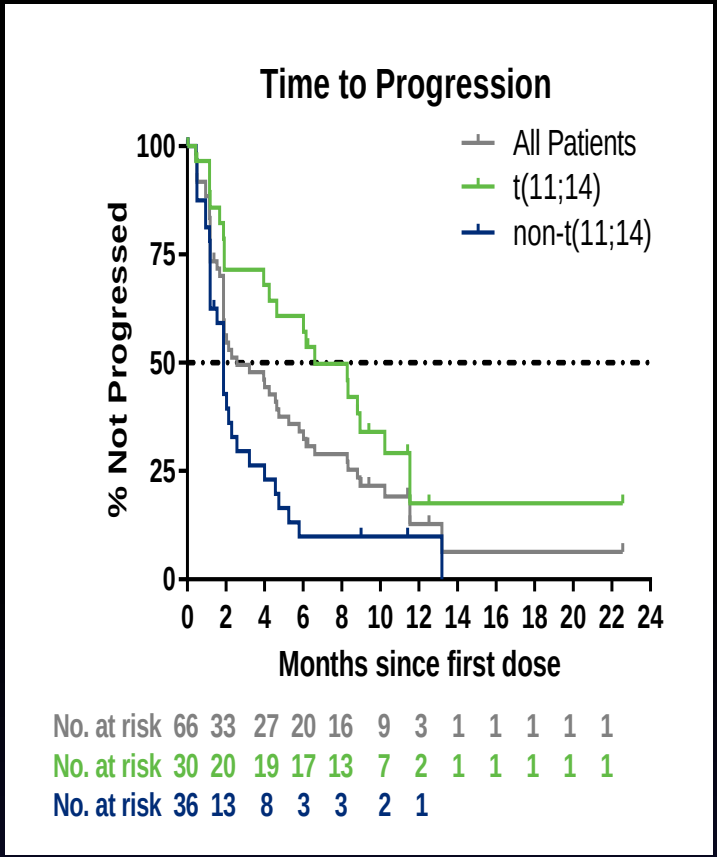
Praktiske forhold omkring behandling med Daratumumab.

Venetoclax monotherapy: Ph1 in RRMM patients

30-1200 mg oral administration (MTD: 1200 mg)

66 pts after a median of 5 prior lines of therapy: 79% refractory to last line of therapy; 61% double refractory to bortezomib and lenalidomide





Higher ORR (88% vs 20%) were seen in t(11;14) with a high BCL2:BCL2L1 ratio

Main toxicities are thrombocytopenia (26% G3-4) and neutropenia (21% G3-4)

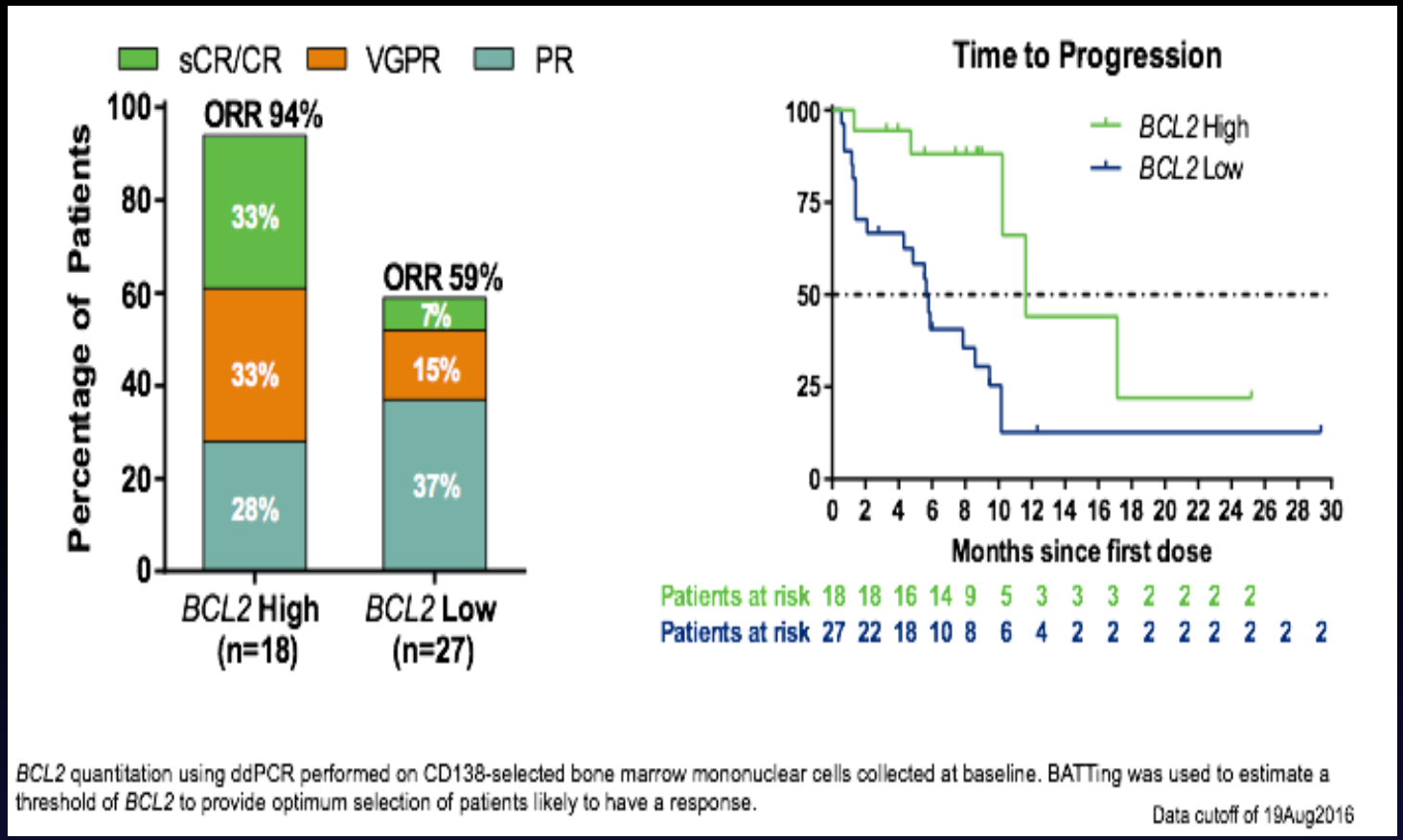
Serious AEs: pneumoniae (8%) and sepsis (5%)

Kumar, et al. Presented at ASH 2016 (Abstract 977), oral presentation

Venetoclax plus bortezomib and dexamethasone

50-1200 mg oral daily + 1.3 mg/m^2 SC TW x cycles1-8, QW 9-11 +
20-20 mg x cycles 1-8

BCL2 Gene Expression and Clinical Response

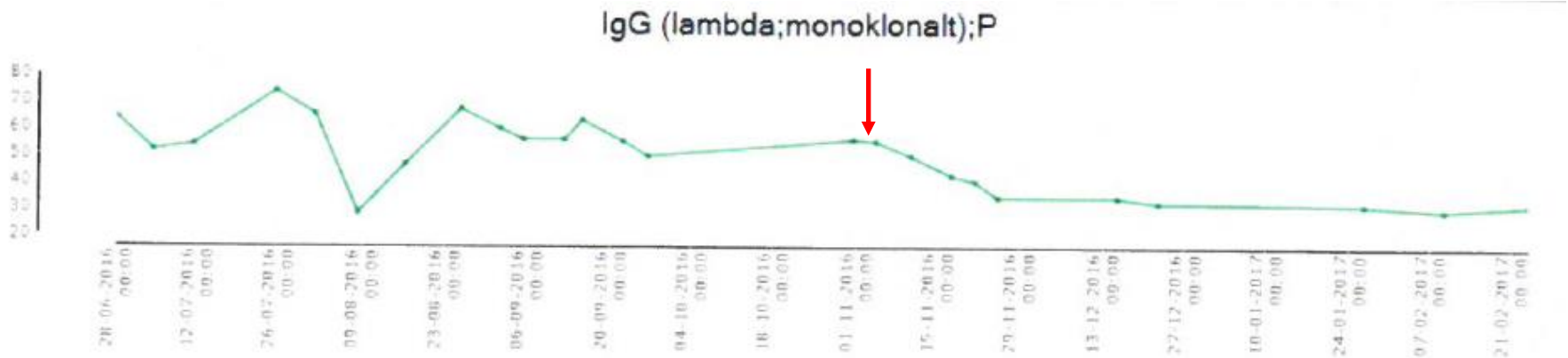


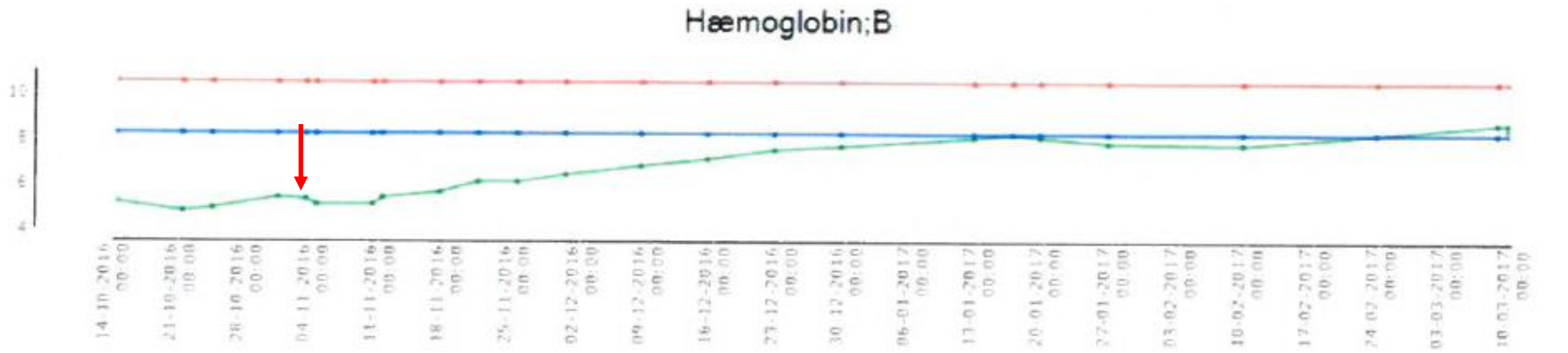
BCL2 quantitation using ddPCR performed on CD138-selected bone marrow mononuclear cells collected at baseline. BATTing was used to estimate a threshold of *BCL2* to provide optimum selection of patients likely to have a response.

Data cutoff of 19Aug2016

Moreau P, et al. Presented at ASH 2016 (Abstract), oral presentation

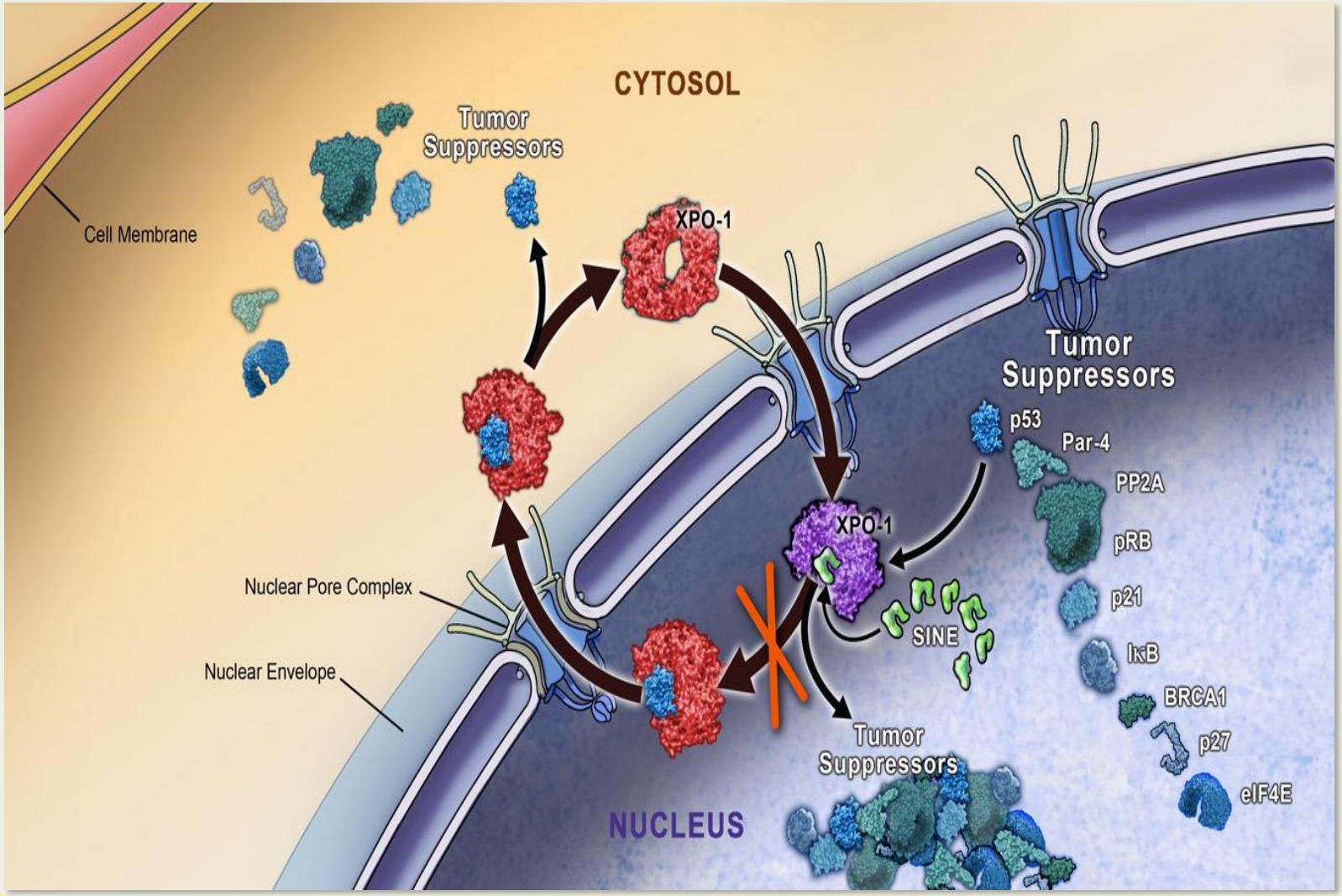
Behandlingsrefraktaer myelomatosepatient med t(11;14) ved FISH behandlet med Venetoclax





Start paa Venetoclax 400 mg/dag

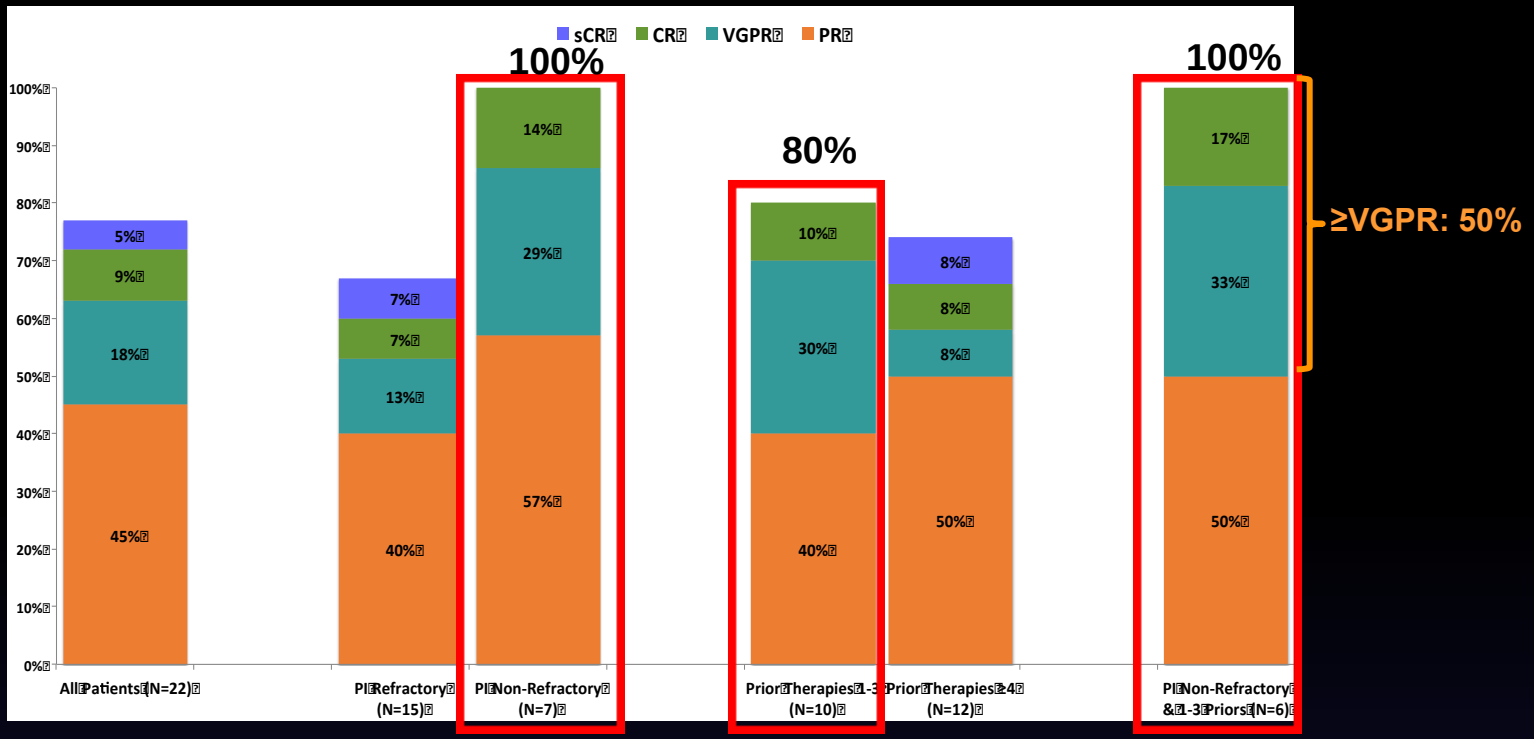
Selinexor: Novel Oral Anti-Cancer Agent Restores Tumor Suppressors & Reduces Oncoproteins



“Stomp”: Ph1 study of Selinexor + bortezomib + Dex

100 mg oral QW + 1.3 mg/m² SC QW x 4 / 5 + 40 mg QW

22 patients after >=1 prior lines of therapy (median=4), prior therapy could include bortezomib as long as not refractory to bortezomib in last line



Adverse events were manageable (mostly grade 1/2) and included nausea, fatigue, anorexia and thrombocytopenia

G3-4 AEs: Thrombocytopenia (18%), diarrea (6%), fatigue (6%), abdominal pain (6%)

Rationale for the BOSTON, phase 3 trial: Vd +/- Selinexor

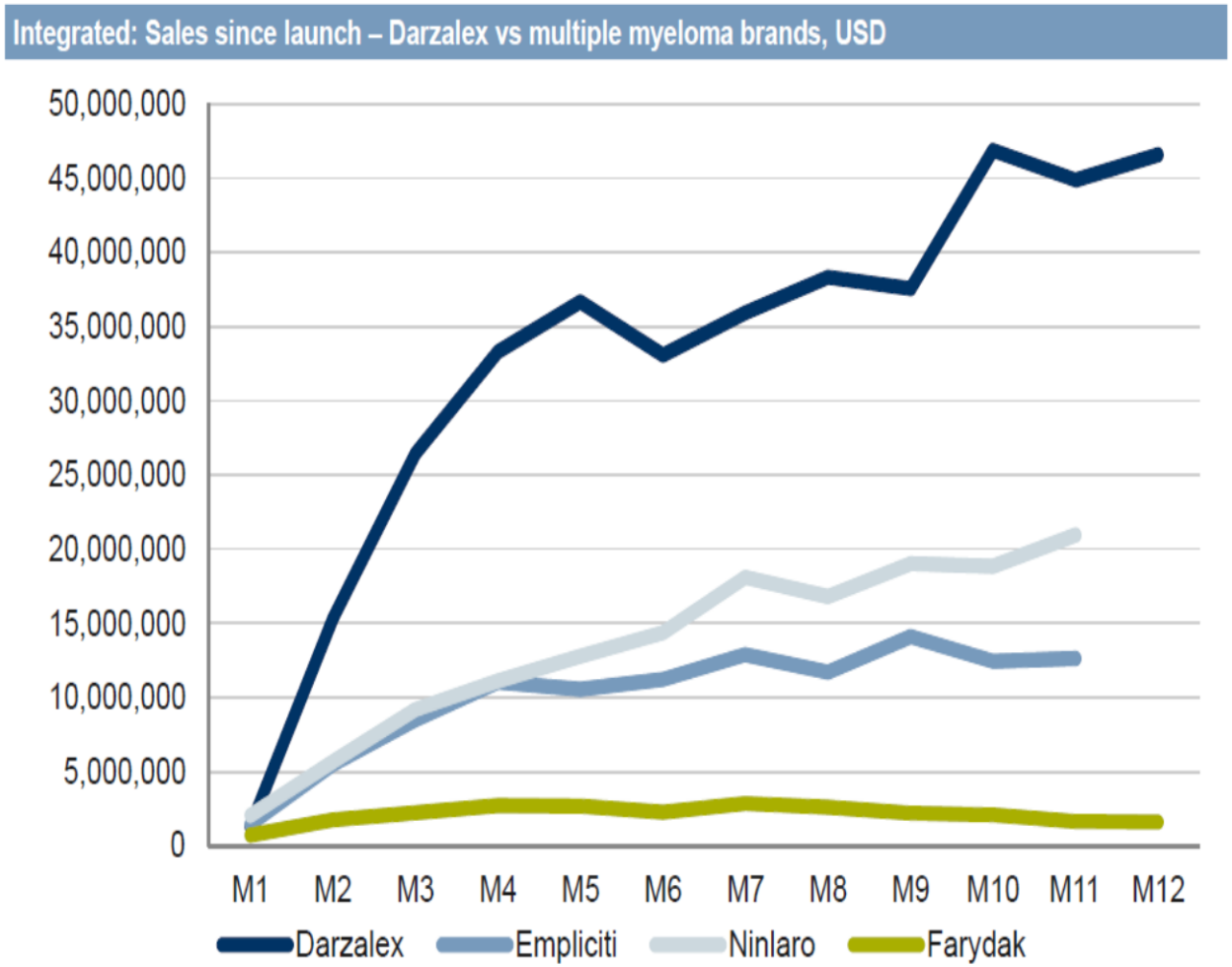
Bahlis NJ, et al. Presented at ASH 2016 (Abstract 977), oral presentation

CLINICAL STUDY PROTOCOL

KCP-330-023

A PHASE 3 RANDOMIZED, CONTROLLED, OPEN-LABEL STUDY OF SELINEXOR, BORTEZOMIB, AND DEXAMETHASONE (SVd) VERSUS BORTEZOMIB AND DEXAMETHASONE (Vd) IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA (RRMM)

Hvordan er de nye godkendte lægemidler til myelomatose slået an i USA?



Daratumumab

Elotuzumab

Ixazomib

Panobinostat

Hvorfor er der brug for nye behandlinger af myelomatose?

Antistoffer som nyt behandlingsprincip ved myelomatose.

Immunterapi med antistoffer ved myelomatose.

Ny viden fra behandling af lungecancer.

Daratumumab i kombinationsbehandlinger.

Elotuzumab.

Resistensudvikling mod Daratumumab.

Nye behandlinger paa vej.

Praktiske forhold omkring behandling med Daratumumab.

Praktiske forhold som skal tages i betragtning ved behandling med Daratumumab:

Blodtransfusioner (Daratumumab findes i blodplasmaet og binder til de røde blodlegemer uden at nedbryde dem, men det kan komplicere blodbankens arbejde med at finde forligeligt blod).

Infusion af Daratumumab kan fremkalde reaktioner (høfeber, astma-lignende eller andre), så der skal gives medicin forebyggende mod disse reaktioner. Det er fortringsvis den første infusion, som kan give reaktion og kun hos halvdelen af patienterne).

Vurdering af behandlingseffekt (Daratumumab ligner en lille IgG kappa type M-component i blodet).

How Do CD38 Monoclonal Antibodies Interfere With Blood Compatibility Testing?

Praktiske forhold omkring behandling med Daratumumab

Forebyggelse af reaktioner på infusionen af antistoffet

Forholdsregler vedrørende blodtransfusioner

Vurdering af behandlingeffekt

Infusion related reactions

- IRRs can occur with mAbs (e.g. rituximab causes mild to moderate infusion reactions in most patients)

- With Daratumumab, Infusion related reactions in MMY2002 study:
  - Occurred in 42% of patients
  - Predominantly Grade 1 or 2 Grade 3: 5%; no Grade 4
  - 87% of IRRs occurred during the first infusion
  - No patients discontinued treatment due to IRRs

Chung CH. The Oncologist 2008;13:725–732; Lonial S et al. *Lancet* 2016;387(10027):1551–1560;
8. Hsi ED et al. *Clin Cancer Res* 2008;14:2775–84; Darzalex US Prescribing

Infusion related reactions

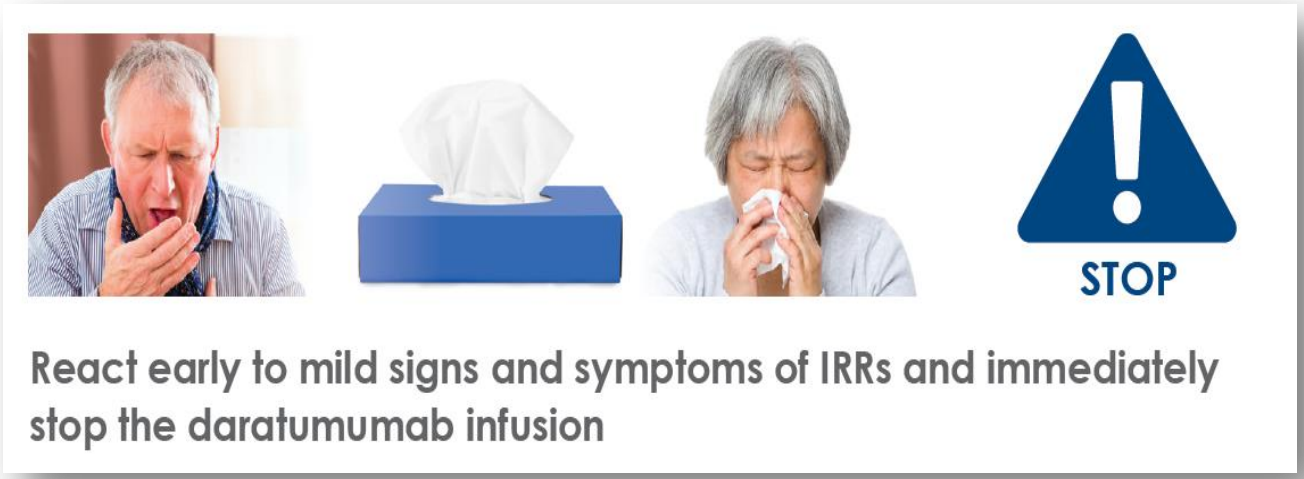
- Early recognition and temporary interruption is important for management of IRRs
- Most common IRRs in MMY 2002 study:
  - nasal congestion (12%),
  - throat irritation (7%),
  - cough, dyspnea, chills, vomiting (6% each);
- Patients with underlying pulmonary disease such as COPD or asthma are at increased risk for bronchospasms

Lonial S et al. *Lancet* 2016; 387(10027): 1551–1560.
Darzalex US Prescribing Information, last accessed April 2016.

Warnings and Precautions: IRRs

Management and supportive measures for daratumumab IRR[1-3]

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



”Kleenex testen”

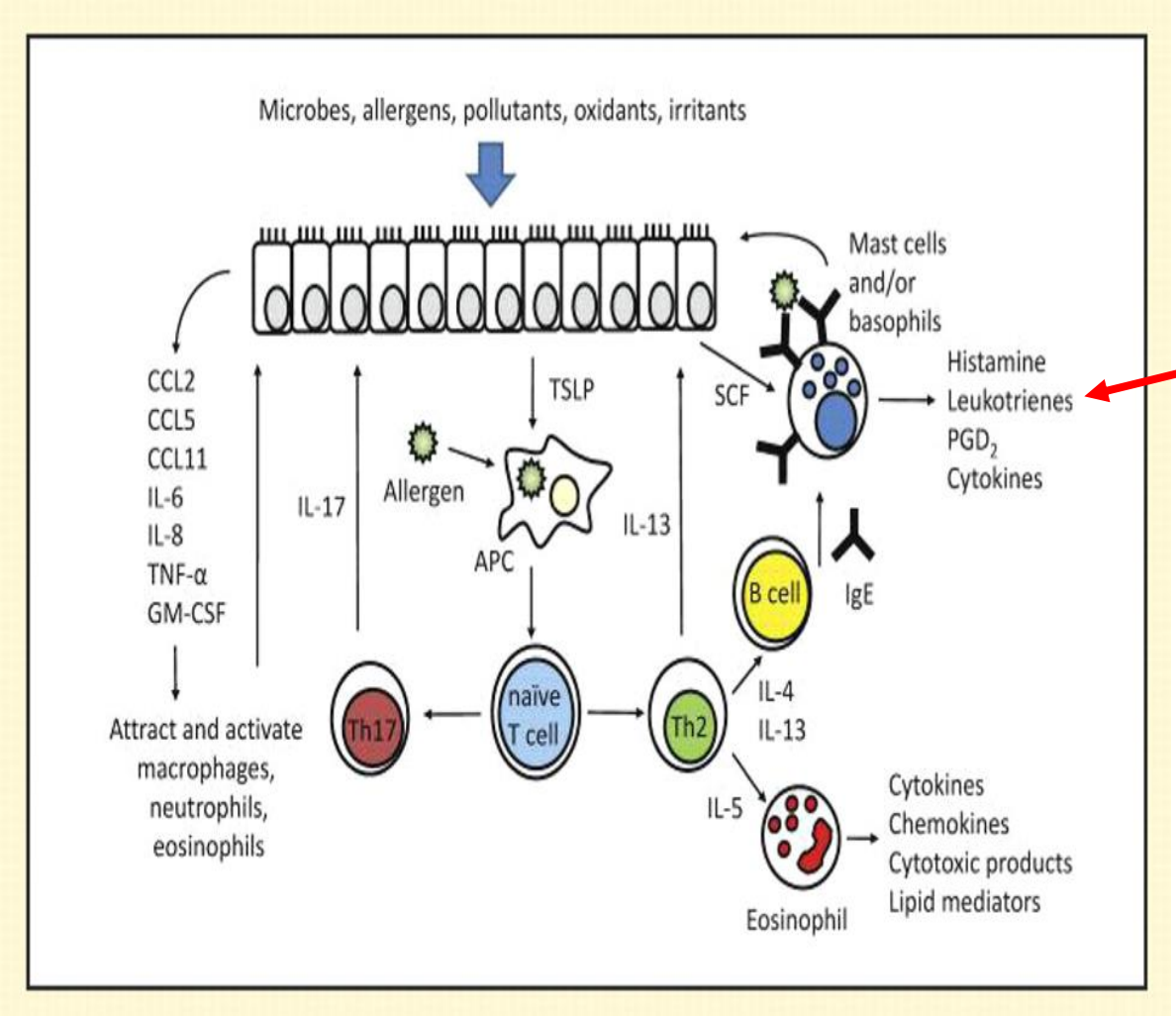
Institute additional supportive measures according to local guidelines and best clinical practice immediately, comprising but not limited to:

- 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 11-12, 2015; Chicago, IL. Janssen Prescribing Information, last accessed April 2016.

Rationale for adding *Montelukast* to the premedication to avoid air-way reactions



JAOA • Supplement 7 (The Whole Patient) • Vol 111 • No 11 • November 2011

Use of montelukast to reduce infusion-related reactions with daratumumab

- US multi-center, open-label Early Access Treatment Protocol opened in June 2015
- Daratumumab 16 mg/kg IV weekly for 8 weeks, then Q2W for 16 weeks, and then Q4W until PD, unacceptable toxicity, or 60 days after US approval
- Montelukast was not recommended but allowed at investigator's discretion

- **The observed IRR rate during the first daratumumab infusion was one third lower in patients who received montelukast 10 mg >30 min *) prior to first daratumumab infusion than in patients who did not receive montelukast**
- **Median time for the first infusion was 0.9 hours shorter in patients who received montelukast**

	Montelukast 10 mg as Pre-infusion (n=10)	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	7.5

*) NB: Dosing MONTELUKAST earlier may further improve the benefit (peak serum concentration at 3 hours after oral administration).

Chari A, et al. Presented at ASH 2016 (Abstract 2142), poster presentation

Pre- and Post-medication

- Patients must receive pre- and post-medications to reduce risk for IRRs

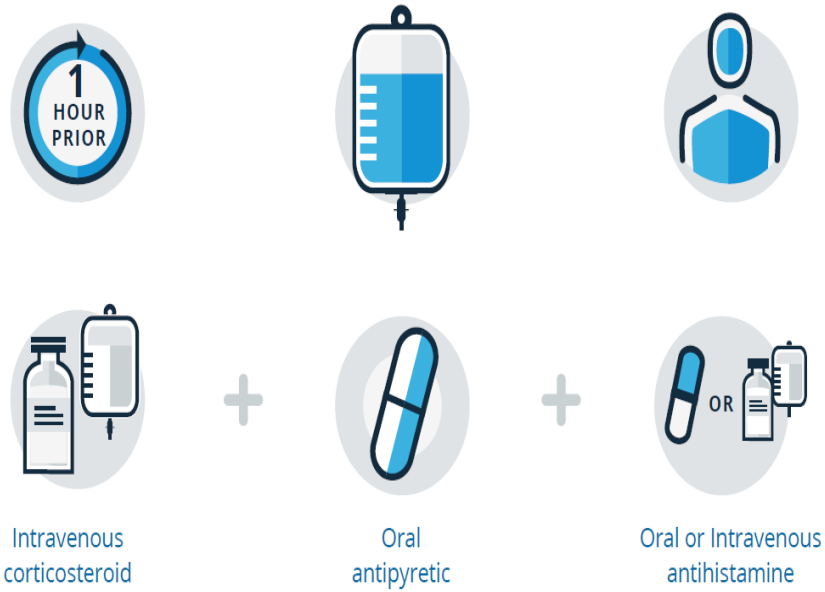
Pre-Infusion Medication

On datatumumab infusion days, patients will receive the following medications prior to infusion:

- Acetaminophen (paracetamol) 650-1000 mg orally (PO) approximately 1 hour prior to infusion
- An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent)
- Methylprednisolone 100 mg IV for the 1st and 2nd infusions of daratumumab; beginning with the 3rd dose of daratumumab methylprednisolone may be reduced to 60 mg IV

Approximately 1 hour prior to every DARZALEX® infusion pre-medications should be administered to all patients

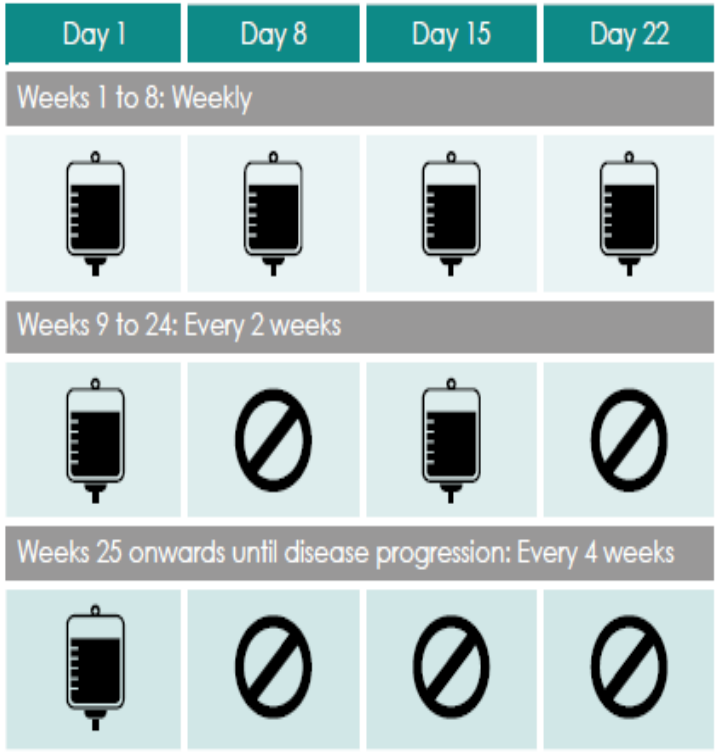
*) Plus Montelukast 10 mg oral the day before and on the morning of infusion (note added)



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

Dosing and scheduling

- Recommended dose is daratumumab 16 mg/kg administered as an intravenous infusion according to the following dosing schedule (as monotherapy):



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

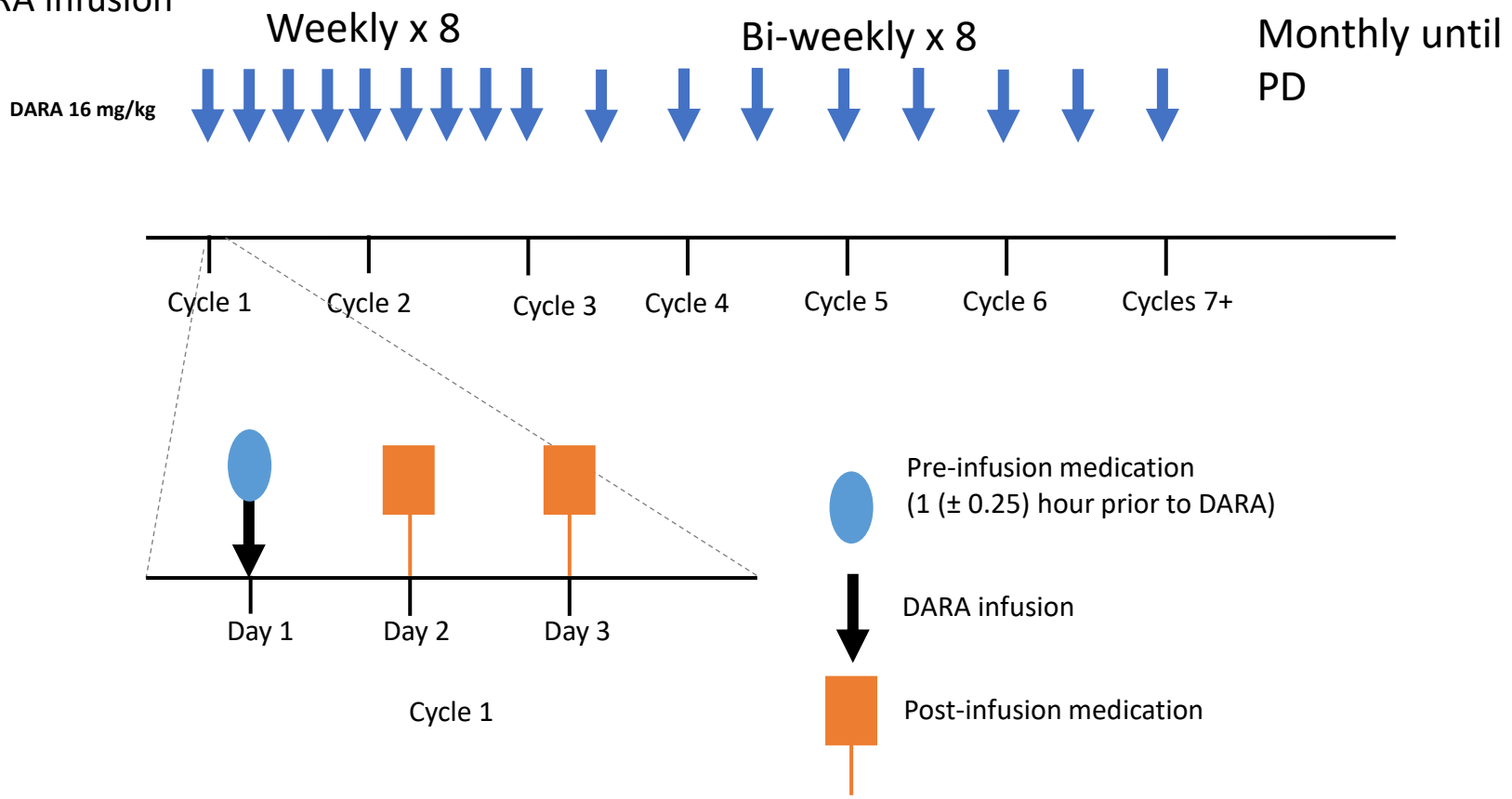
Post-medications
On each of the two days following all infusions (beginning the day after the infusion)

Subjects will continue to receive datatumumab until disease progression, occurrence of unacceptable toxicity, the subject is no longer receiving clinical benefit, or the end of study

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

Management of IRRs: Dosing Schedule

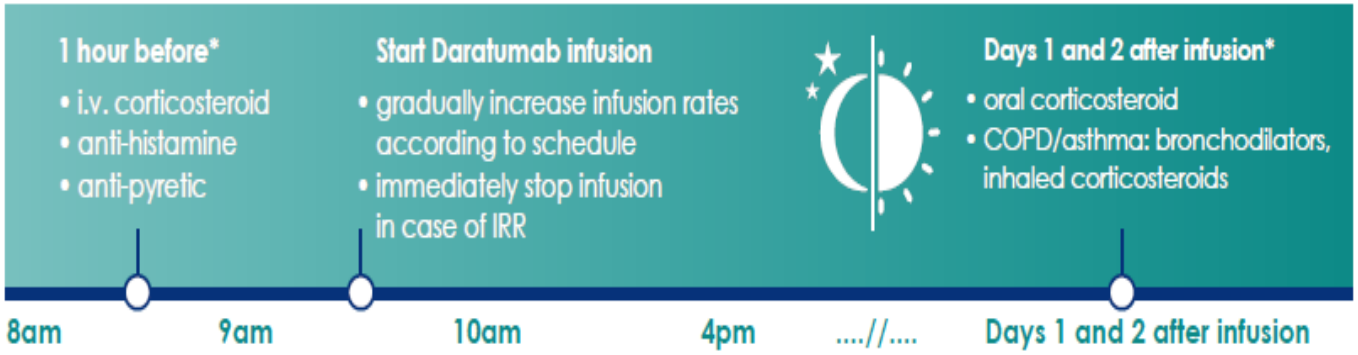
- Pre-infusion medication for the management of IRRs was administered 1 hour (±15 minutes) prior to DARA infusion and consisted of methylprednisolone, paracetamol, diphenhydramine or non-sedating anti-histamin and montelukast
- Post-infusion medication consisted of corticosteroid given on the 2 consecutive days following DARA infusion



Modified from Voorhees P, et al. Poster presented at: 2015 ASH Meeting on Hematologic Malignancies; September 17-19, 2015; Chicago, IL, USA.

Infusion rate

- Slow infusion rate important to limit IRRs especially in first infusion



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

[a] **Dilution volumes should only be decreased if the first infusion was well tolerated** as defined by an absence of ≥ Grade 1 IRRs during the first 3 hours. If the previous infusion was not well tolerated, then instructions for the first infusion will be used.

[b] **Modified rates should only be used if the first 2 infusions of daratumumab were well tolerated** as defined by an absence of ≥ Grade 1 IRRs during a final infusion rate of ≥ 100 mL/hr.

Prophylaxis for herpes zoster reactivation.
Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week of starting daratumumab and continue for 3 months following treatment.

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[7]

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

Lonial S et al. *Lancet* 2016;387(10027):1551–1560; 8. Hsi ED et al. *Clin Cancer Res* 2008;14:2775–84; 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.

Janssen Research & Development *

Clinical Protocol

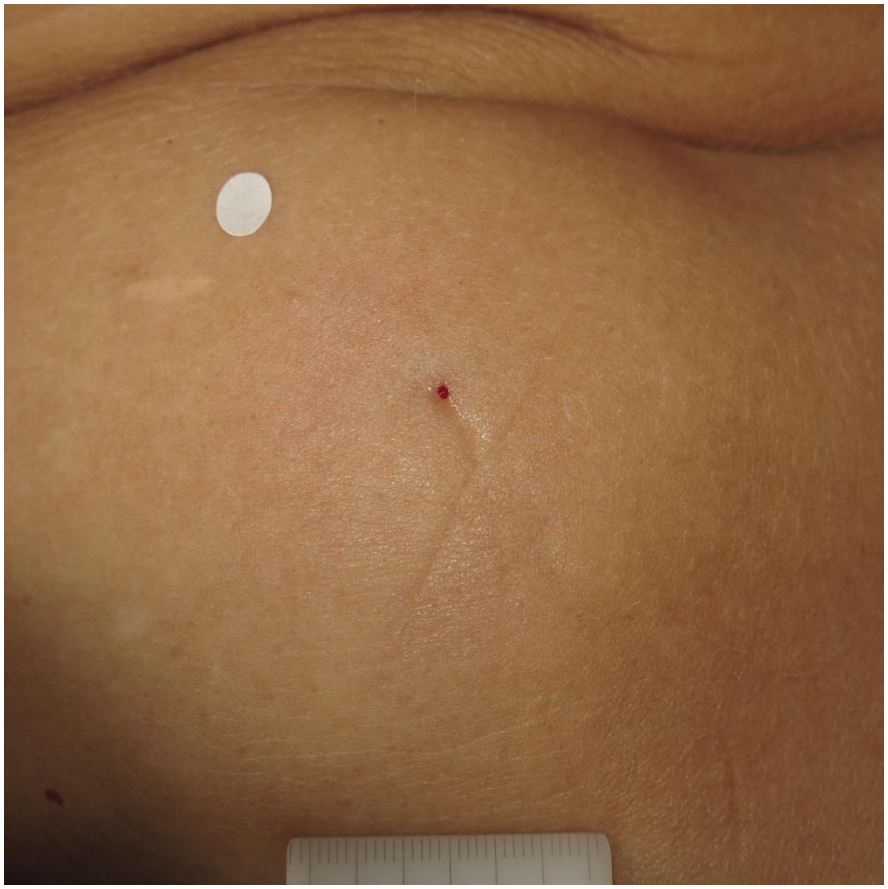
An Open-label, Multicenter, Dose Escalation Phase 1b Study to Assess the Safety and Pharmacokinetics of Subcutaneous Delivery of Daratumumab with the Addition of Recombinant Human Hyaluronidase (rHuPH20) for the Treatment of Subjects with Relapsed or Refractory Multiple Myeloma

---

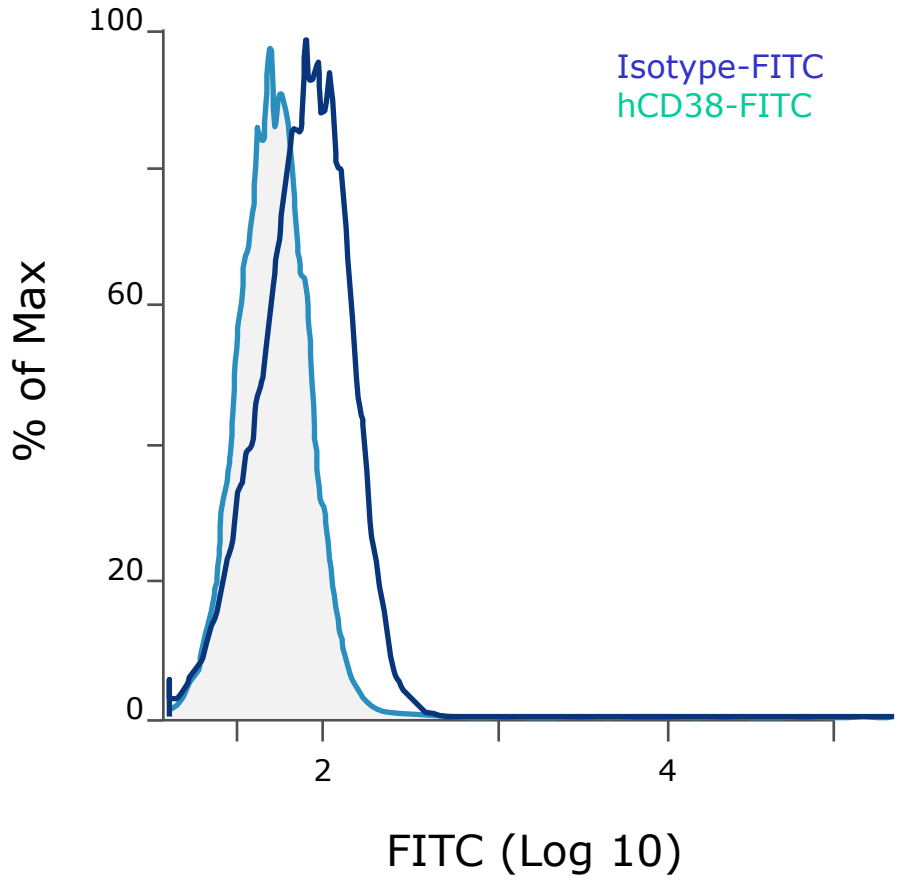
Protocol 54767414MMY1004; Phase 1b

JNJ-54767414 (daratumumab)

Daratumumab1600 mg in 90 ml/30 min by subcutaneous administration



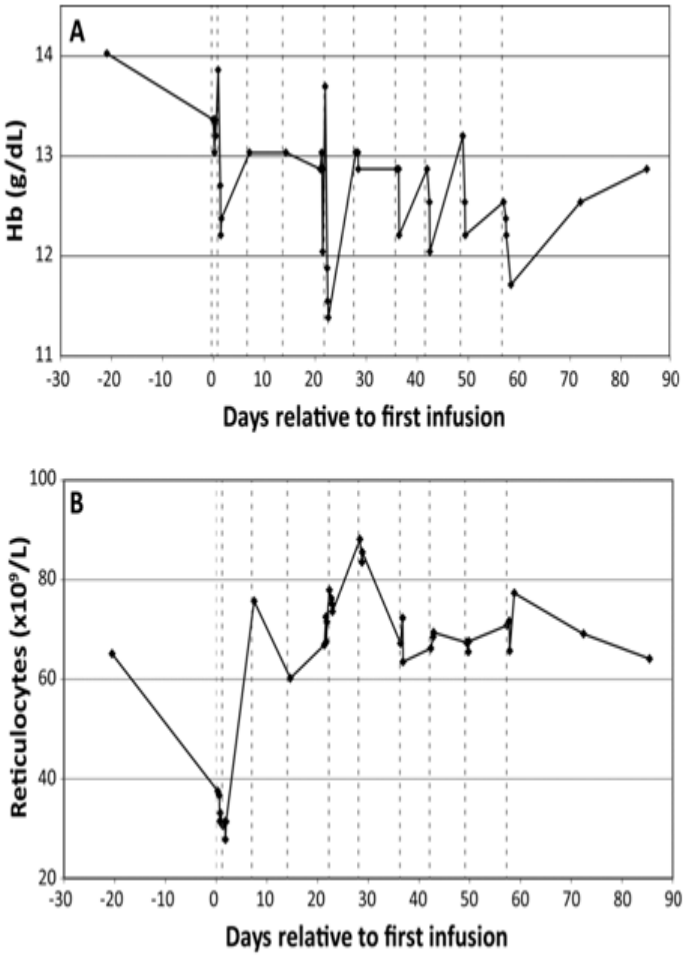
CD38 is weakly expressed on human RBCs



- CD38 expression on patient red blood cells (RBCs) assessed by flow cytometry after gating on Gly-A+ RBCs using anti-CD38 FITC conjugated antibody or an isotype control

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

Effect of Daratumumab Infusion on Hemoglobin



- In vivo mild hemoglobin decrease after daratumumab infusion
  - Rapid clearance of a subpopulation of daratumumab-coated erythrocytes presumably via the spleen

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

Consequences ???

A search of the global safety database for daratumumab identified no transfusion-related cases of hemolysis to date in the more than 76,000 treatment courses that have been administered since marketing approval.

NEJM 375 2497 2016

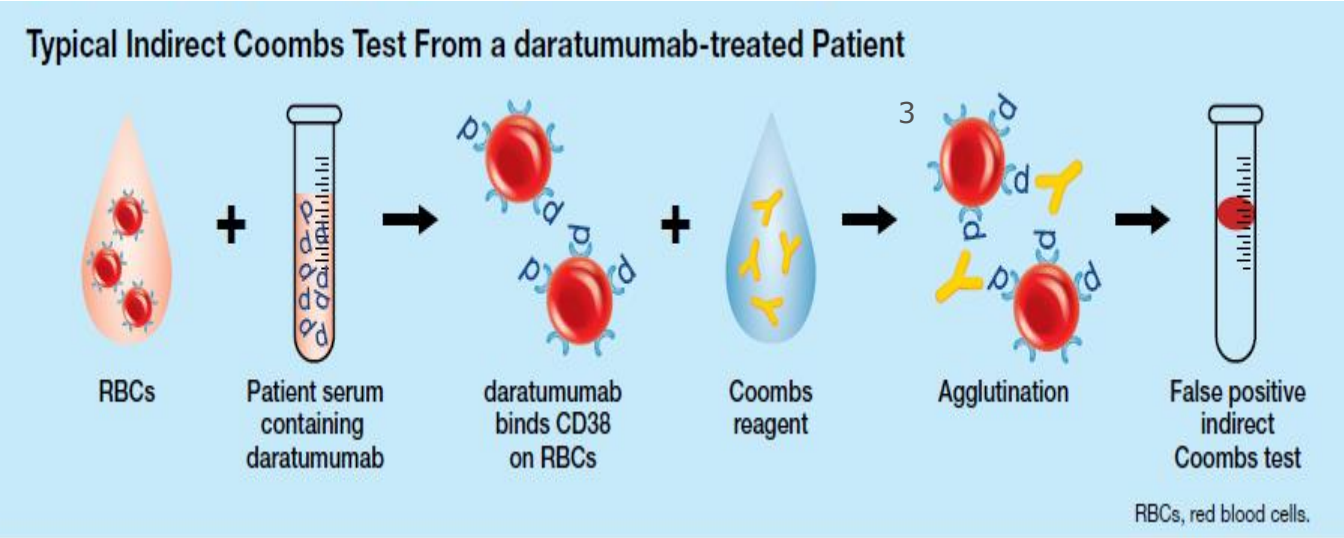
Blood transfusion compatibility testing for patients receiving CD38 mAbs

- CD38 is weakly expressed on human red blood cells (RBCs)
- Daratumumab binds to CD38 on RBCs → false positive results in the Direct Antiglobulin Test (Direct 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

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

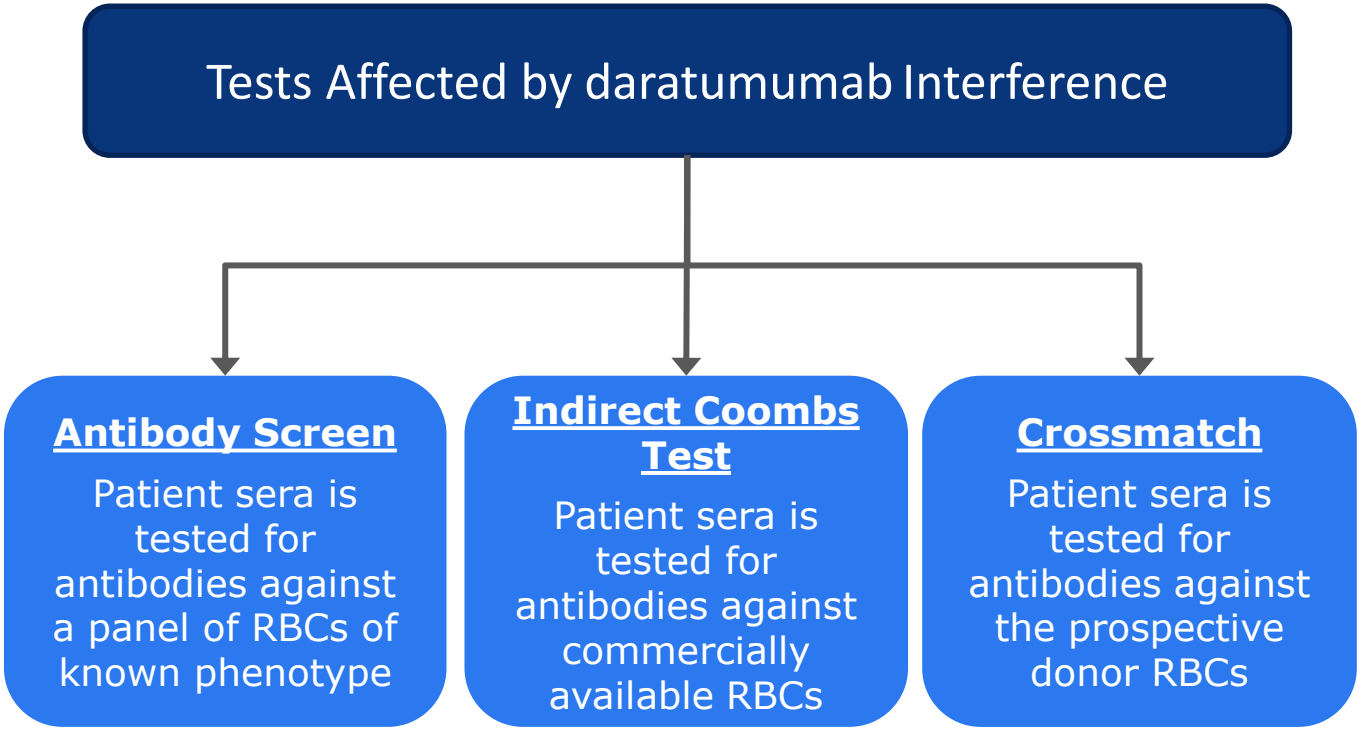


1. Chapuy et al. Transfusion. 2015;55(6 Pt 2):1545-54
2. Oostendorp et al. Transfusion. 2015;55(6 Pt 2):1555-62
3. Chari A, et al. Poster presented at: 2015 American Society of Hematology (ASH); December 5-8, 2015; Orlando, FL, USA (Abstract 3571).

RBCs, red blood cells

Blood Compatibility Tests

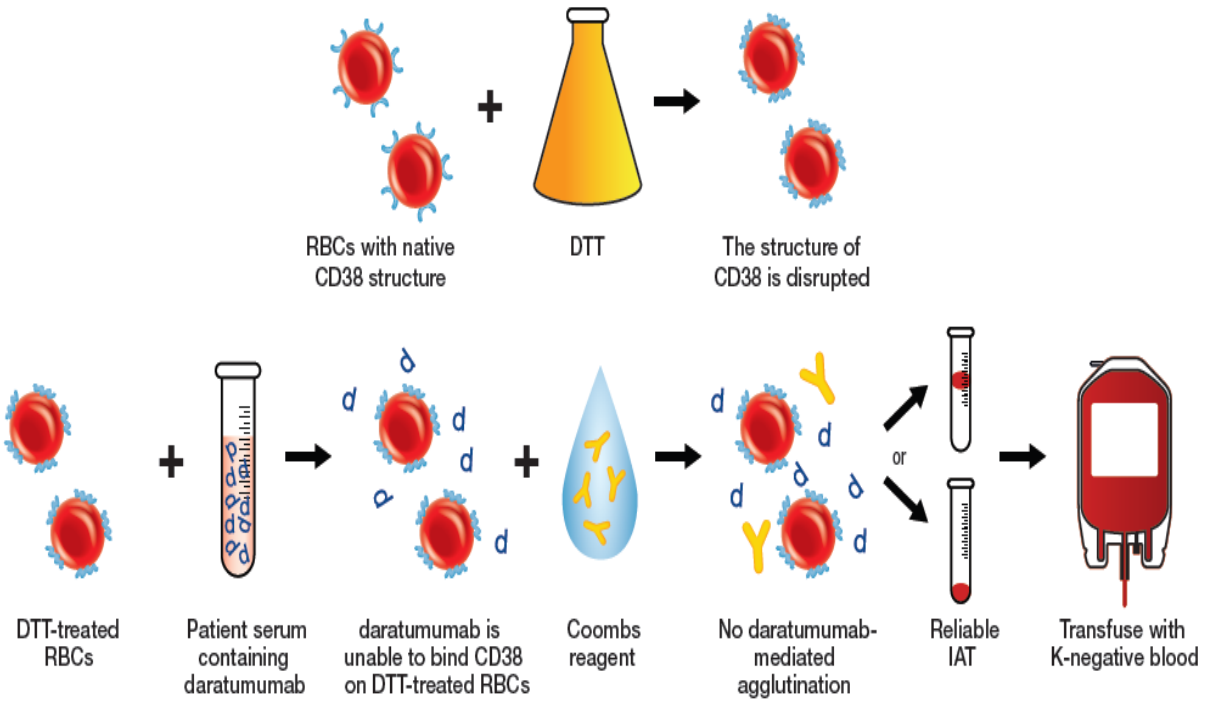
- Daratumumab **does not interfere** with identification of ABO/RhD antigens



Chapuy et al. Transfusion. 2015;55(6 Pt 2):1545-54;
Chapuy et al. Transfusion 2016;56:2964-2972.

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

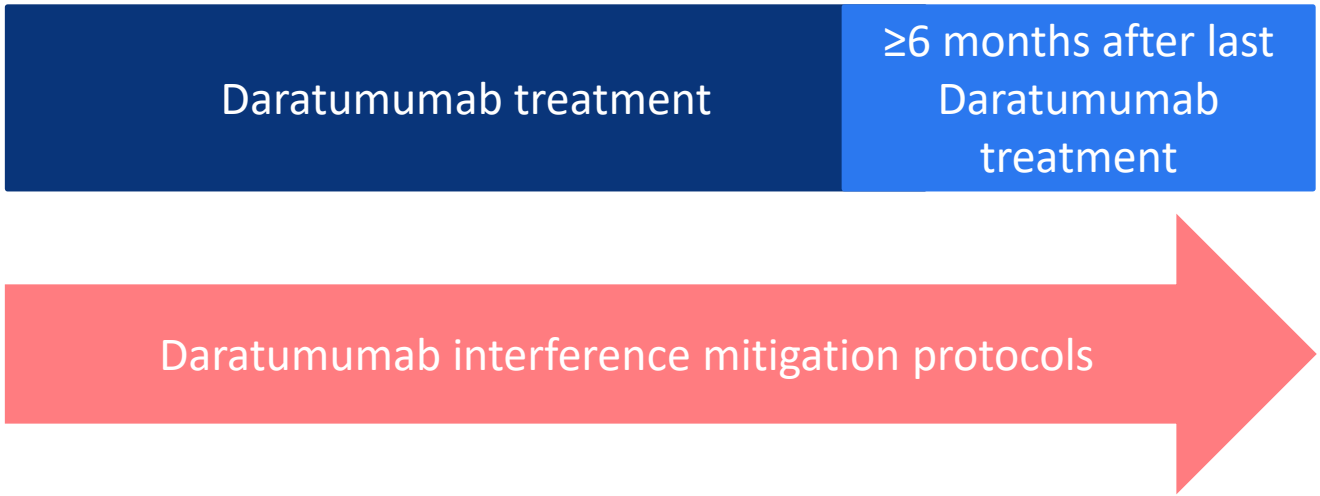
- Treating reagent or donor RBCs with dithiothreitol (DTT) disrupts daratumumab binding, thus allowing antibody screening and crossmatch to be performed[1]; the protocol can be found in Chapuy *et al*. Alternative locally validated methods can also be used
- Blood products for transfusion were identified for daratumumab-treated patients, after using DTT-treated reagent RBCs for antibody screening[1]
- Since the Kell blood group system is also sensitive to DTT treatment[2], K-negative units sh DTT-treated



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

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

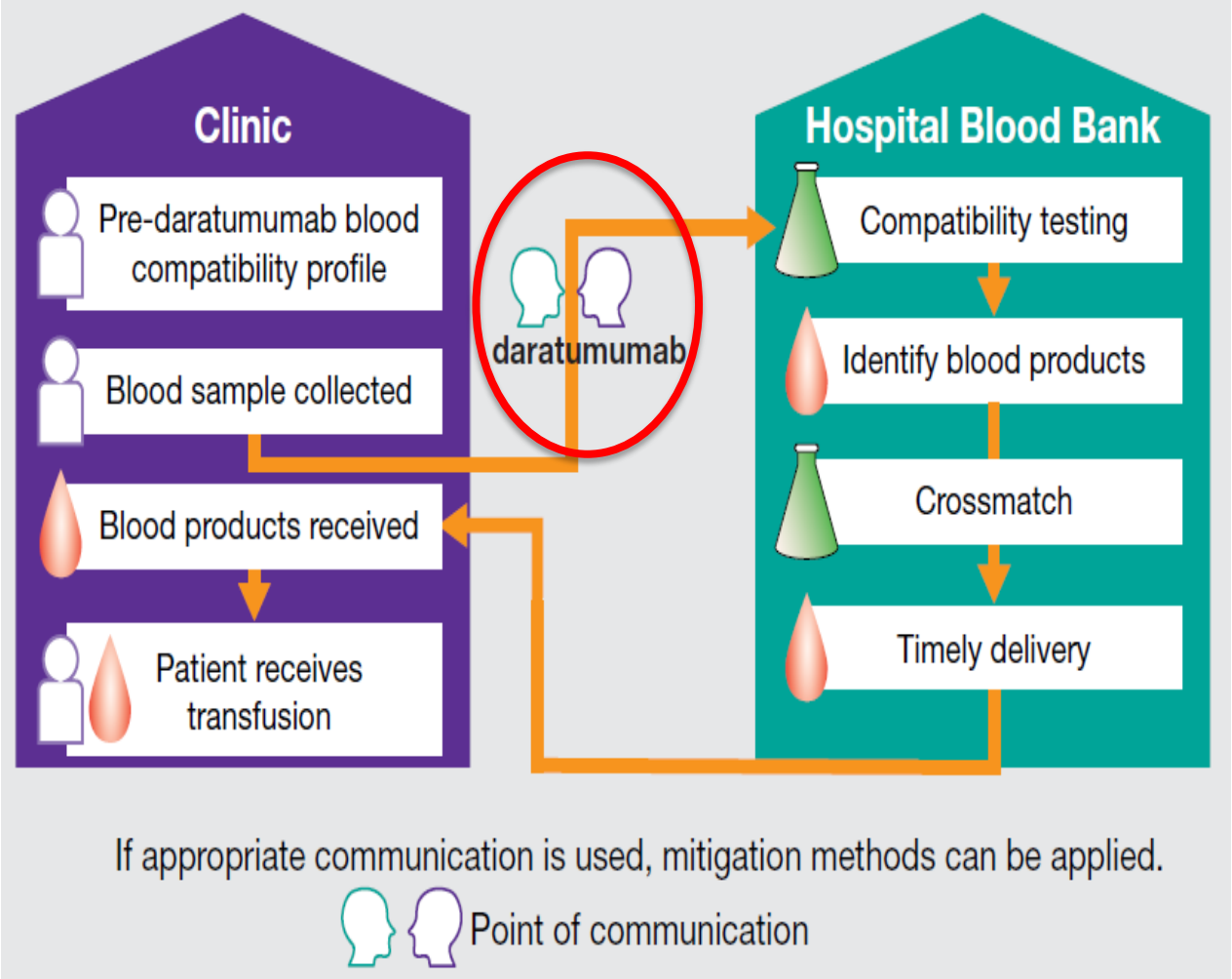
Daratumumab Interference Is Clinically Manageable

- 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 they will receive a sample from a daratumumab-treated patient, so that appropriate protocols can be applied

RBC, red blood cell

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

Communication Is Critical



- 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

Conclusions

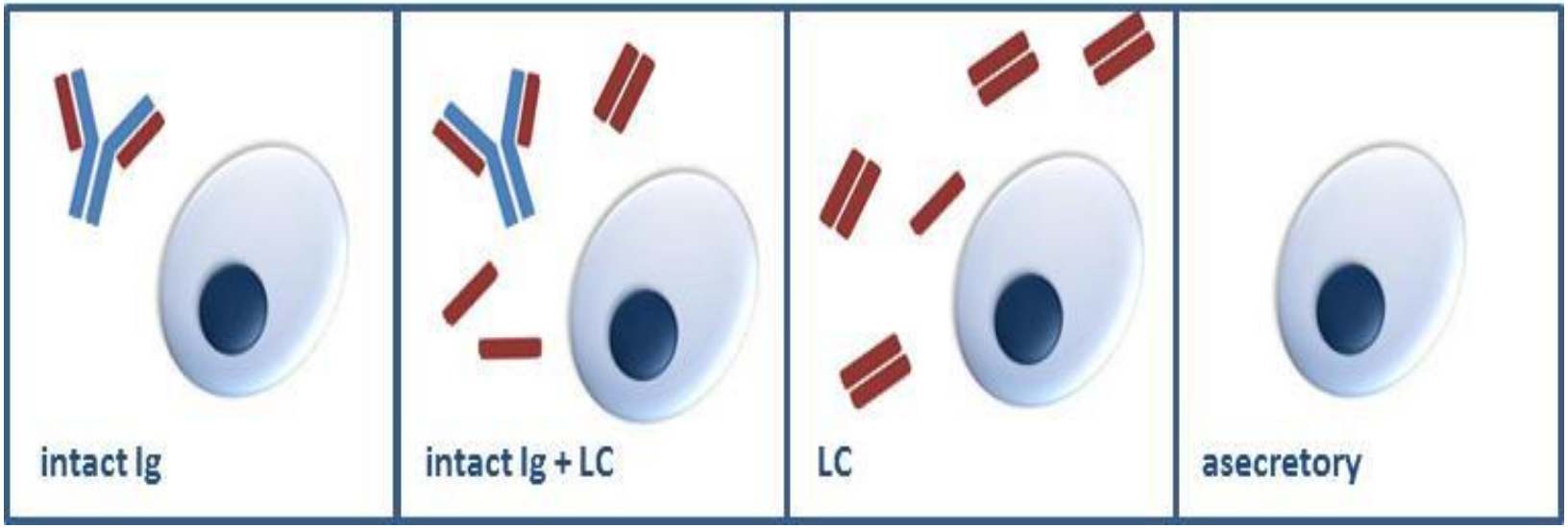
- Daratumumab is a human monoclonal antibody for the treatment of MM[1]
- Daratumumab binds to RBCs and interferes with blood bank compatibility tests, including the antibody screening and crossmatching[2] (both indirect Coombs tests) that are part of a routine pretransfusion work up
- To date, no clinically 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

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

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.



Kyle R et al. Lancet Haematol 2014;1(1):e28-e36
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

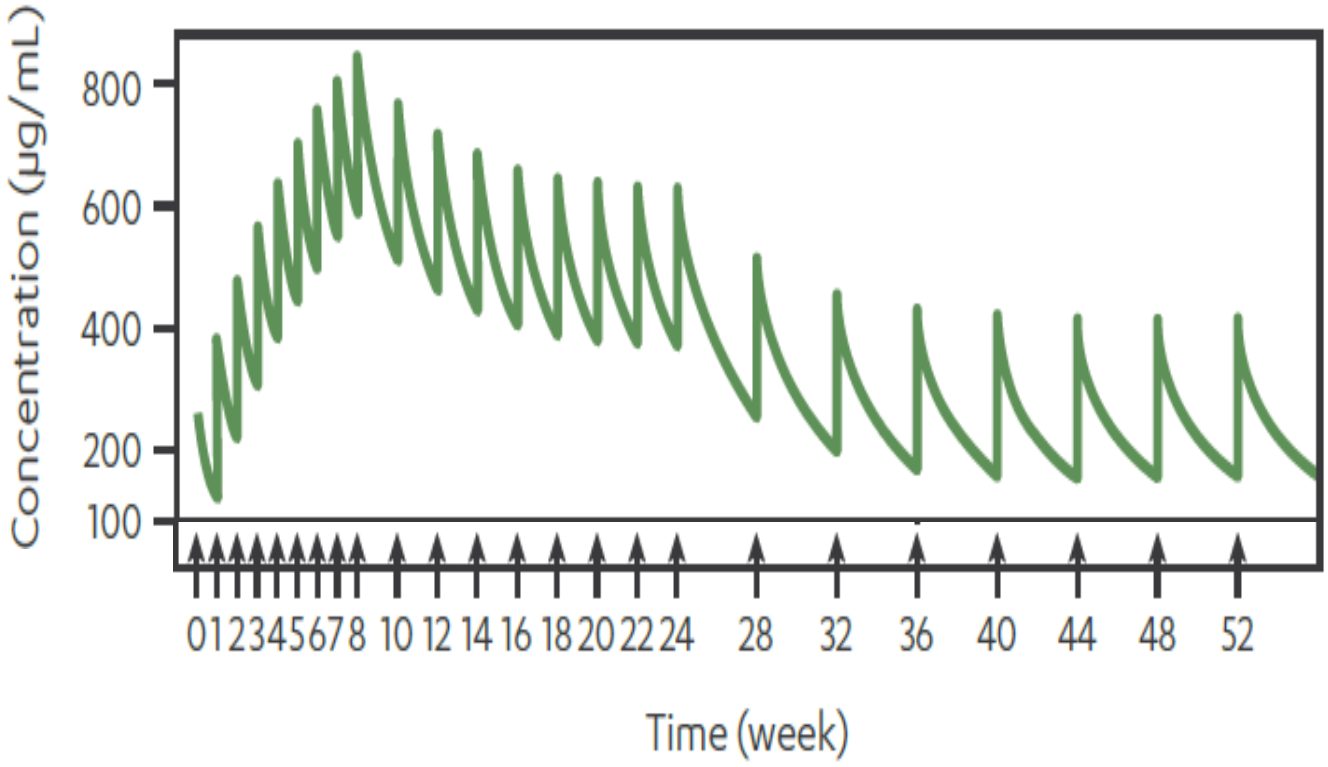
- Response to treatment can be measured via **quantitative** or **semiquantitative** changes in the amount of M-protein in **serum or urine (preferred)**, the **free-light chain ratio** in the **serum** or by investigating **plasma cell** populations in the **bone marrow** by conventional **light microscopy,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

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

Daratumumab level

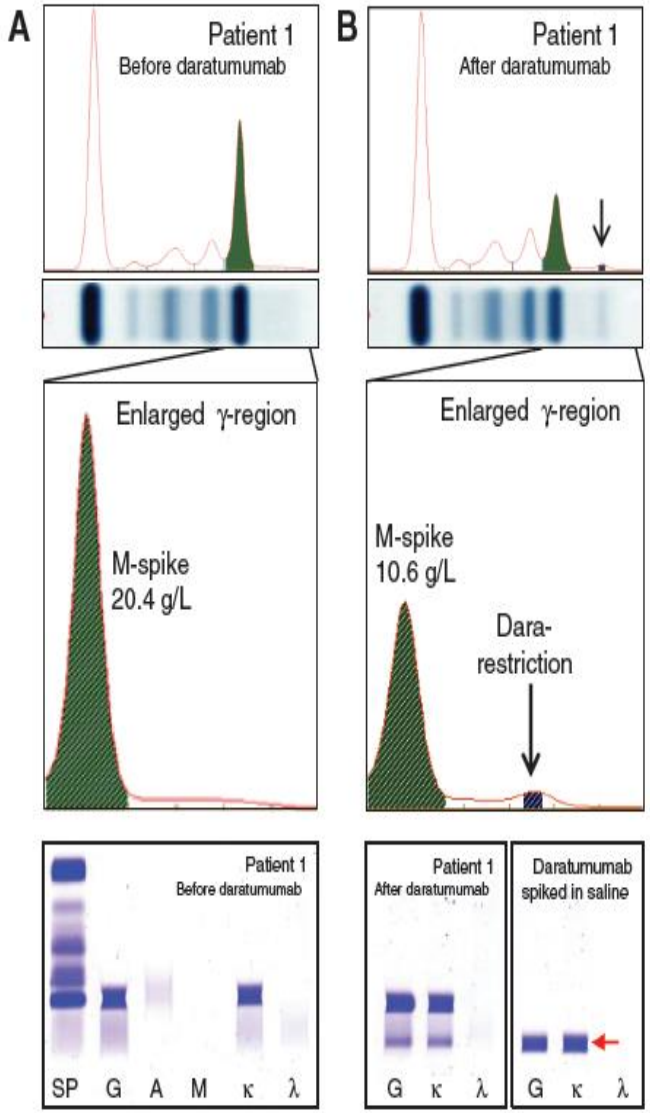
Representative PK profile of DARA for the recommended dose and schedule



Arrows indicate that a dose was administered.

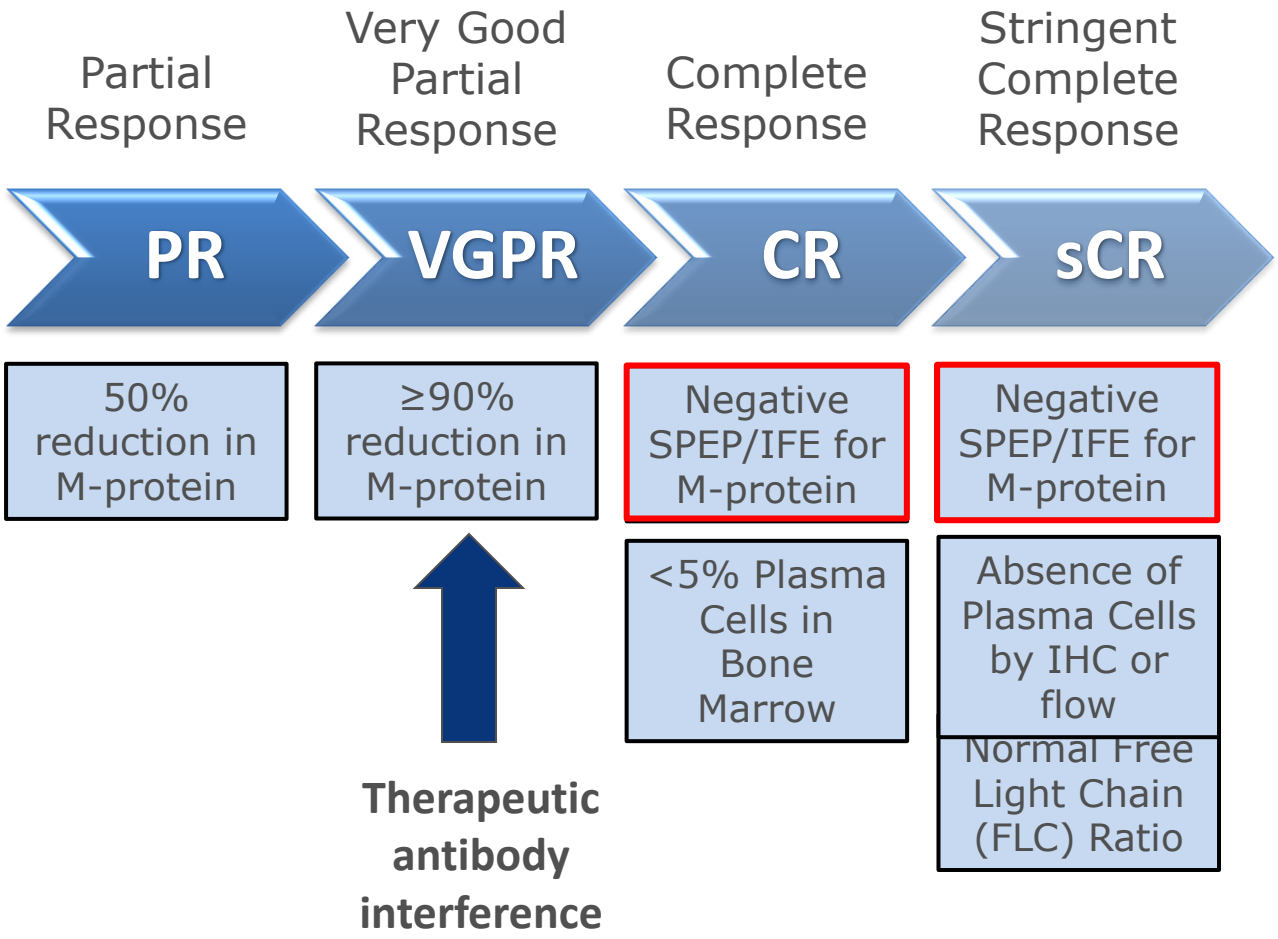
Xu XS, et al. Poster presented at: 2015 American Society of Hematology (ASH); December 5-8, 2015; Orlando, FL, USA (Abstract 4254).

Detection of daratumumab by serum protein electrophoresis (SPEP) and serum immunofixation electrophoresis (IFE)



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

IMWG response criteria requires a negative IFE to declare patients CR



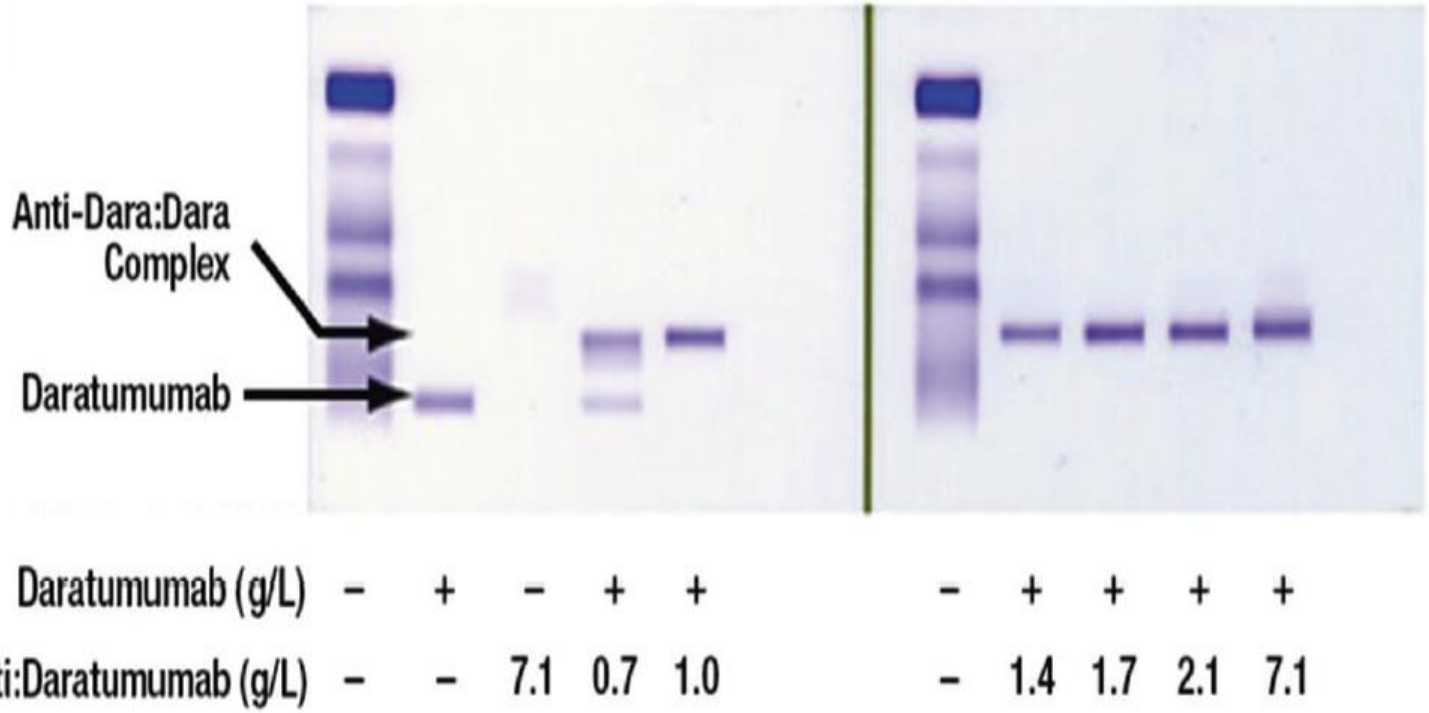
McCudden C, et al. Poster presented at: 2015 American Society of Clinical Oncology (ASCO); May 29-June 2, 2015; Chicago, IL, USA.

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

Conclusions regarding the assessment of M-protein response in MM and interference through mAbs

- All therapeutic mAbs may interfere with serum electrophoresis and immunofixation
  - Difficult to discern between therapeutic antibody and the patient's clonal immunoglobulin
- Class effect of mAbs in myeloma
- Interference depends on isotype of the patient
- Daratumumab, Elotuzumab, Isatuximab and MOR202 are IgG 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

Hvorfor er der brug for nye behandlinger af myelomatose?

Antistoffer som nyt behandlingsprincip ved myelomatose.

Immunterapi med antistoffer ved myelomatose.

Ny viden fra behandling af lungecancer.

Daratumumab i kombinationsbehandlinger.

Elotuzumab.

Resistensudvikling mod Daratumumab.

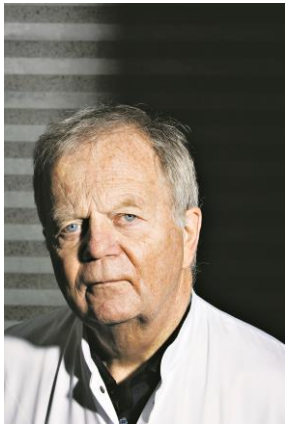
Nye behandlinger paa vej.

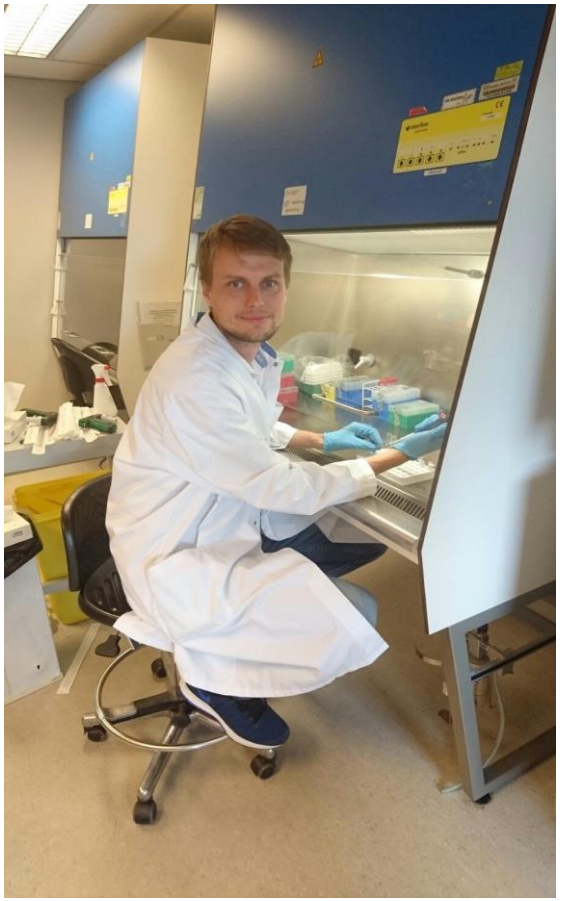
Praktiske forhold omkring behandling med Daratumumab.

Kristian

Brian

Maja





Jakub

Agoston