2017

Progetto Ematologia Romagna

AMILOIDOSI AL
L'approccio terapeutico

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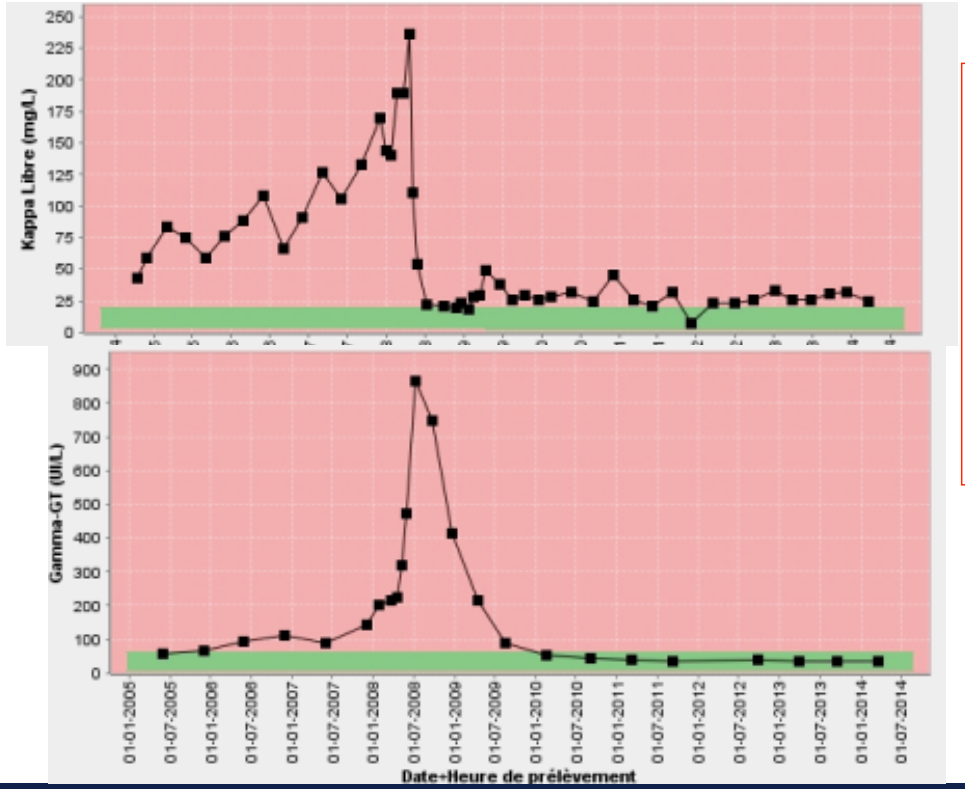
Treatment of AL amyloidosis

- If the serum level of the amyloidogenic protein decreases, involved organs are getting better, most of the time slowly, with different speed in different organs
- Liver > Kidney > heart > macroglossia

Kappa light chain

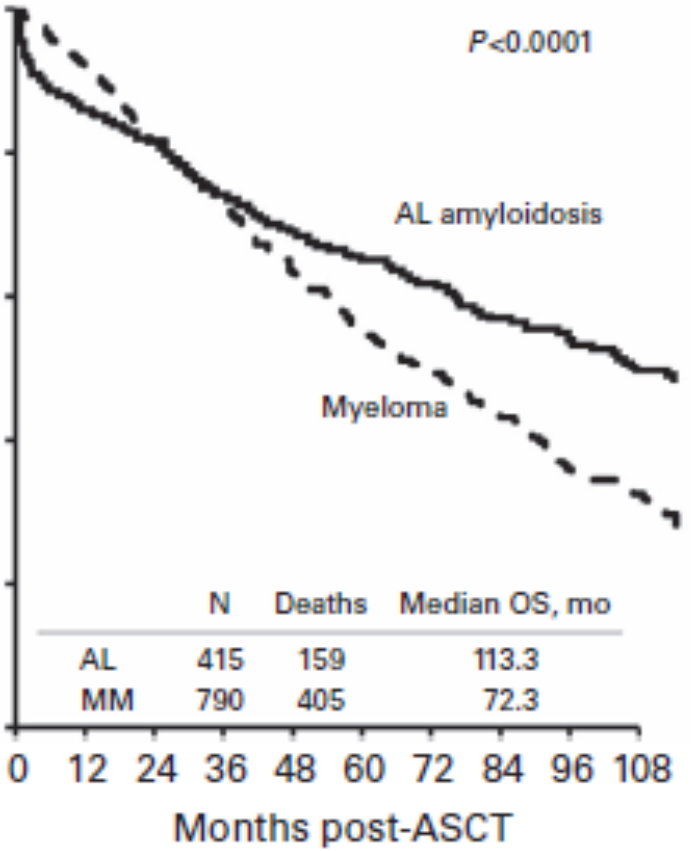
Gamma-GT

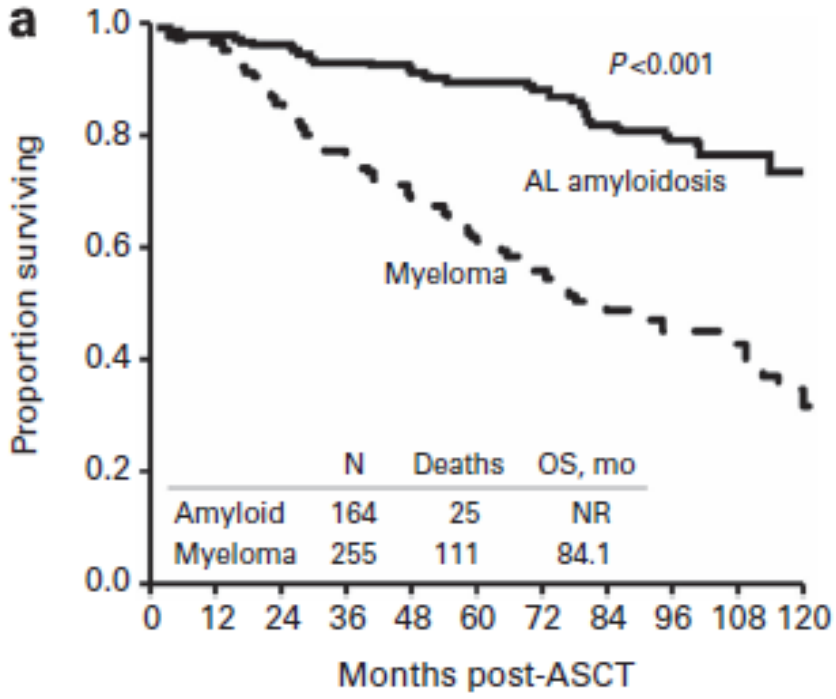


Chemotherapy is not directly active on amyloidosis deposits

Patients with immunoglobulin light chain amyloidosis undergoing autologous stem cell transplantation have superior outcomes compared with patients with multiple myeloma: a retrospective review from a tertiary referral center.

A Dispenzieri, K Seenithamby, MQ Lacy, SK Kumar, FK Buadi, SR Hayman, D Dingli, MR Litzow, DA Gastineau, DJ Inwards, IN Micallef, SM Ansell, PB Johnston, LF Porrata, MM Patnaik, WJ Hogan and MAA Gertz





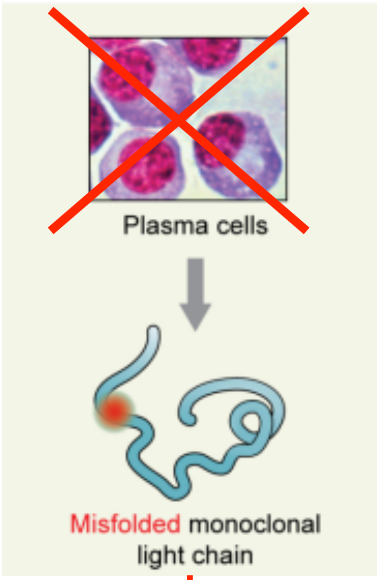
Patients in CR….fraction cured???

Bone Marrow Transplantation (2013), 1–6

www.nature.com/bmt

Therapy is guided by biomarkers

AL amyloidosis



Cardiac damage

Reduced survival

Clonal, hematologic response

Organ (cardiac) response

Improved survival

sFLC response

NT-proBNP response

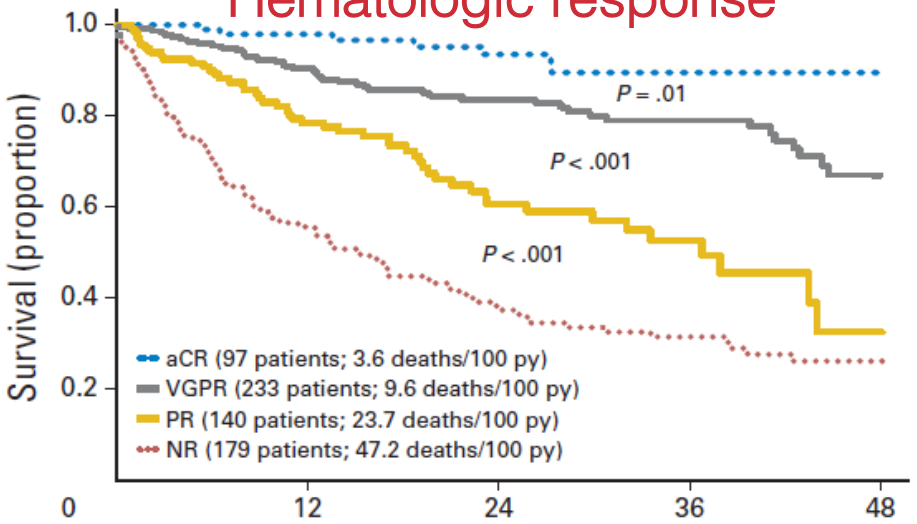
Improved survival

Validated criteria for early assessment of response to chemotherapy in AL amyloidosis based on biomarkers

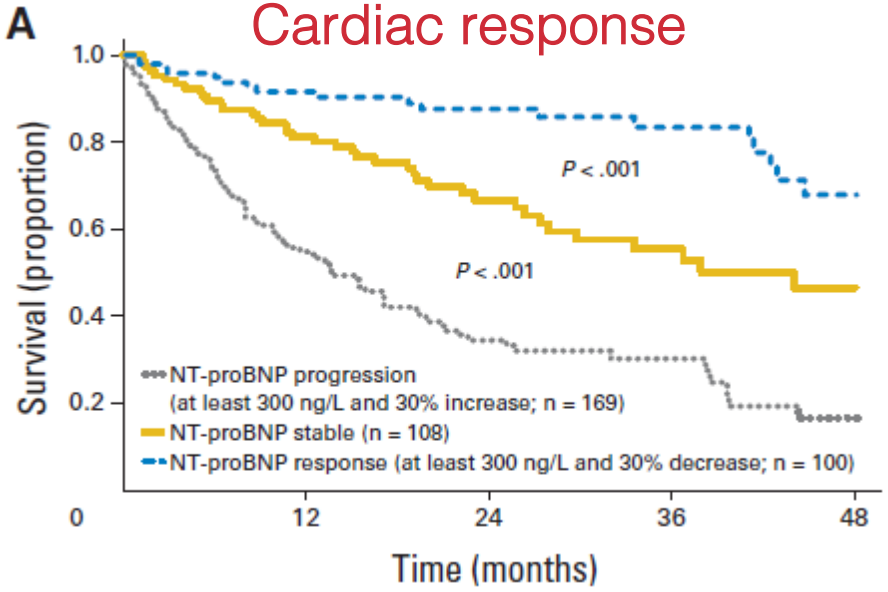
Response	Definition
Hematologic	CR: negative s&u IFE + normal FLCR VGPR: dFLC <40 mg/L PR: dFLC decrease >50%
Cardiac	NT-proBNP decrease >30% & >300 ng/L
Renal	Proteinuria decrease >30%

Response criteria were validate at 3 and 6 mos after treatment initiation

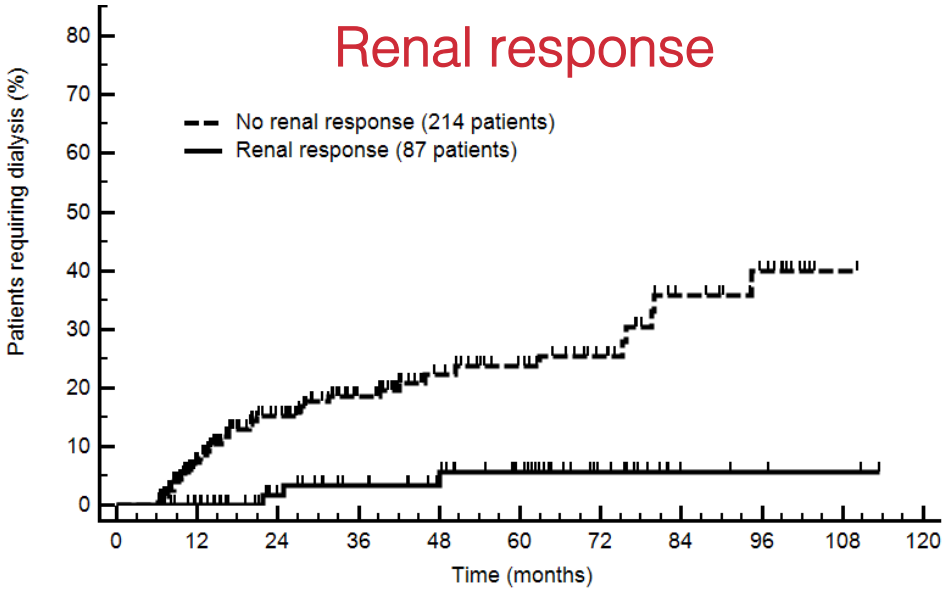
Hematologic response



Cardiac response

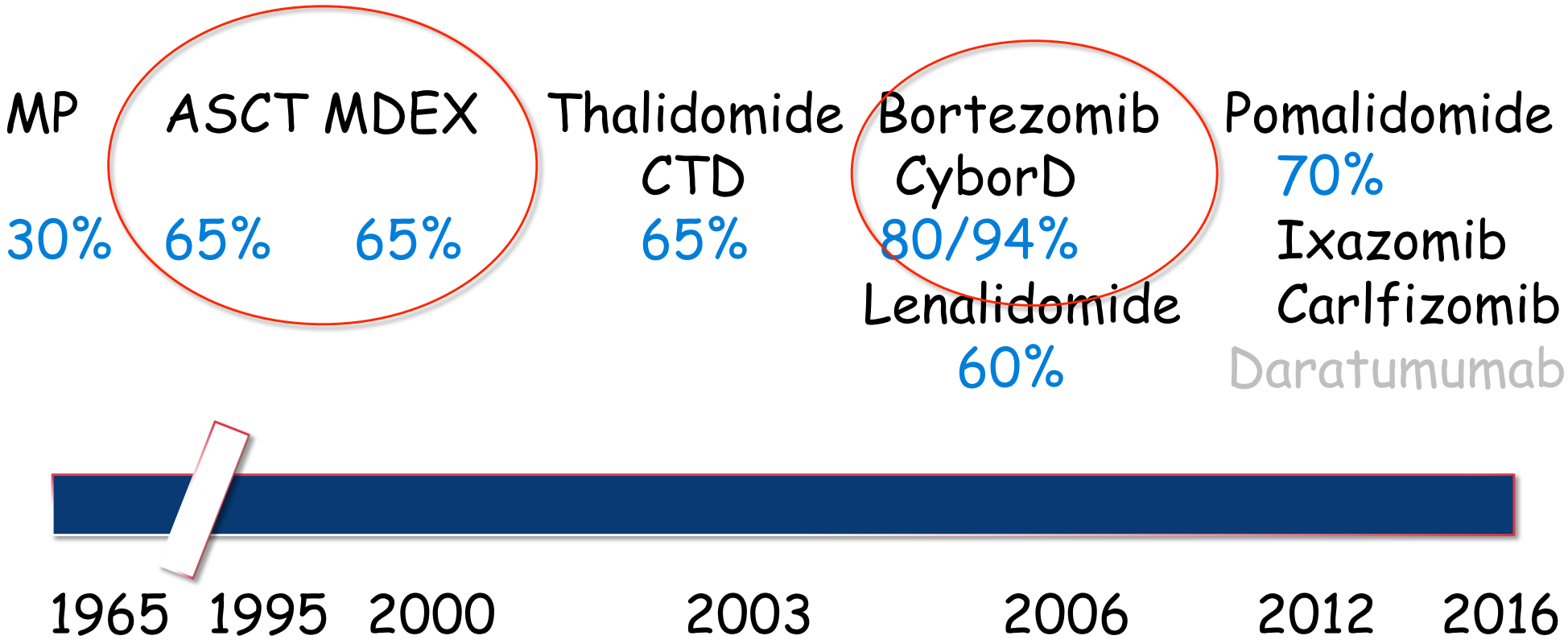


Renal response



Palladini, et al. JCO 2012
Palladini, et al. Blood 2014

Al amyloidosis therapies, time line and response rates (usually with dexamethasone)



ASCT in AL amyloidosis

July 1994 – December 2011: 522 pts received HDM/SCT

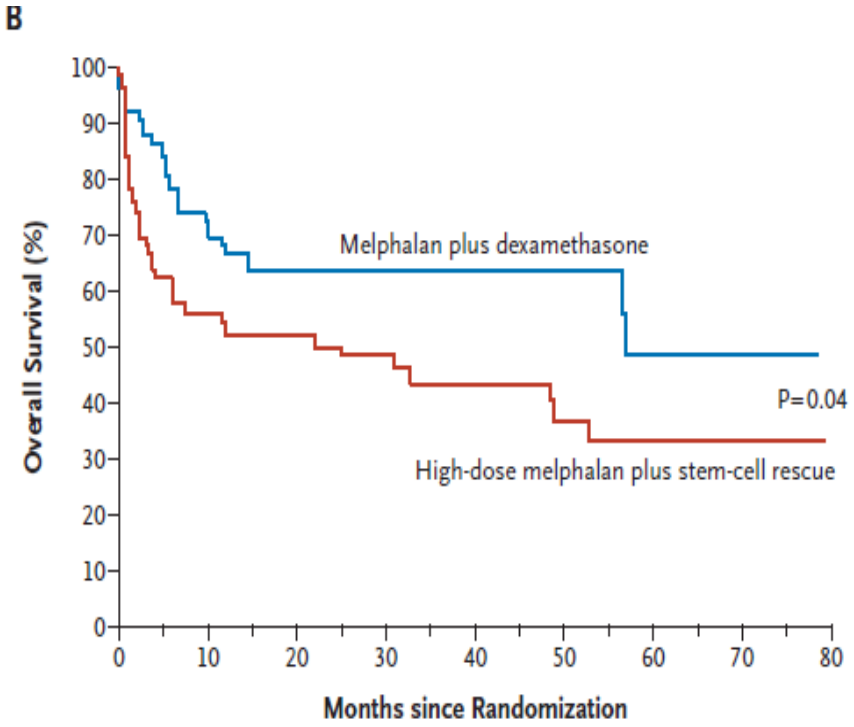
Table 1. Treatment-related mortality overall during 17 years, during the first decade and thereafter

	1994-2011 (n = 522)	1994-2003 (n = 310)	2004-2011 (n = 212)	*P* value (during 1st decade and thereafter)
TRM events (%)	61 (12%)	52 (17%)	9 (4%)	.000012
Median age (range)	56 (35-78)	55 (35-78)	62 (53-69)	
During SCMC	11 (2%)	10 (3%)	1 (0.5%)	.032
Cardiac events	8 (73%)	7 (70%)	1 (100%)	
Hemorrhagic events	2 (18%)	2 (20%)	0 (0%)	
Respiratory events	1 (9%)	1 (10%)	0 (0%)	
During SCT	4 (1%)	3 (1%)	1 (0.5%)	.65
Cardiac events	3 (75%)	2 (67%)	1 (100%)	
Pulmonary embolism	1 (25%)	1 (33%)	0 (0%)	
After SCT	46 (9%)	39 (13%)	7 (3%)	.0002
Infections	22 (48%)	18 (46%)	4 (57%)	
Bacterial	11	9	2	
Fungal	9	7	2	
Viral	2	2	0	
Cardiac events	17 (37%)	15 (39%)	2 (29%)	
Hemorrhagic events	5 (11%)	4 (10%)	1 (14%)	
Respiratory events	3 (7%)	3 (7%)	0 (0%)	
Other events	2 (4%)	2 (5%)	0 (0%)	
Disease pattern				
> 2 organ involvement	54 (89%)	49 (94%)	5 (56%)	.007
Cardiac involvement	53 (87%)	45 (87%)	8 (89%)	.99

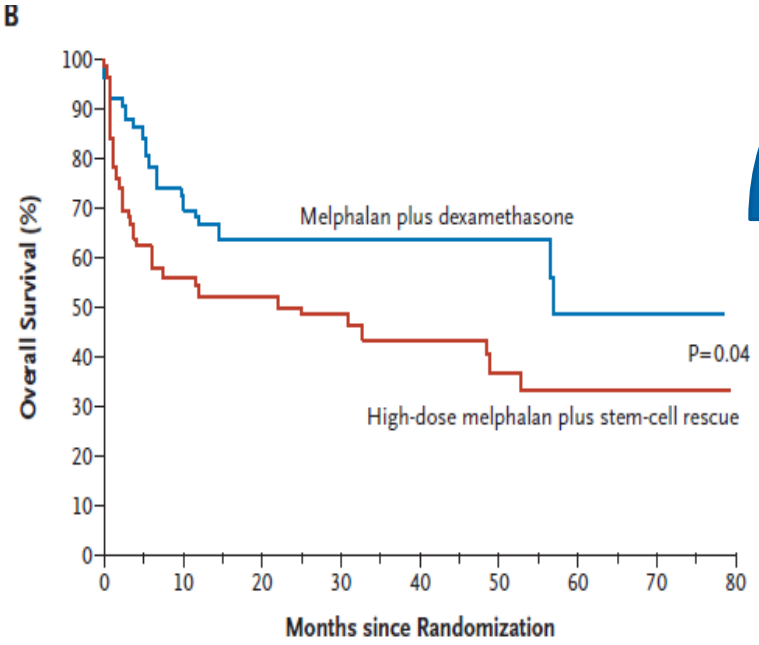
Tsai et al. Blood 2012

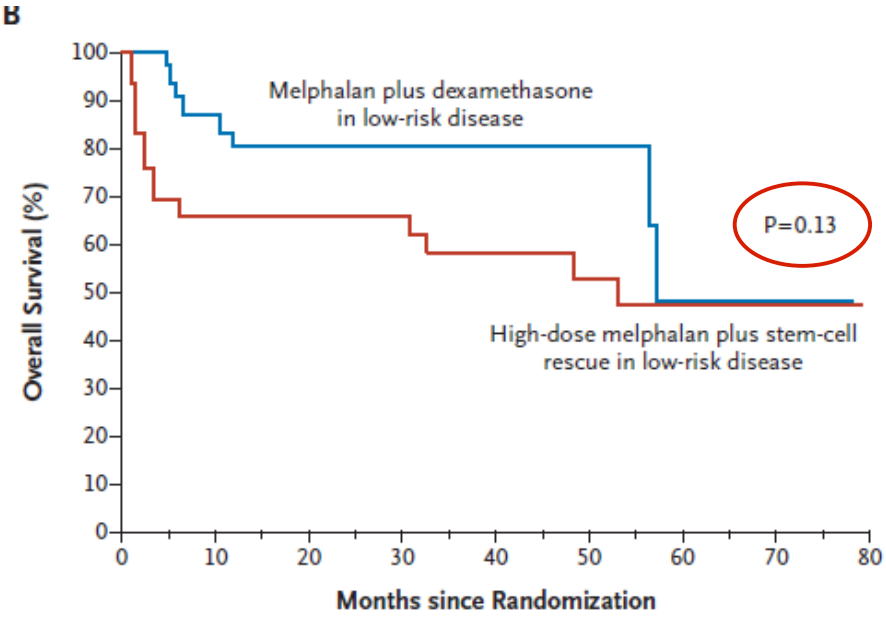
MDex vs. ASCT: a randomized trial

Regimen	HR (CR)	OR	Common SAEs	100-day mortality	PFS / OS (y)
MDex	68% (32%)	39%	Overall 16%	2%	2.7 / 4.7
vs.					
ASCT	67% (41%)	45%	Hemodialysis 22%	24%	2.7 / 1.8



Jaccard et al, *N Engl J Med 2007*

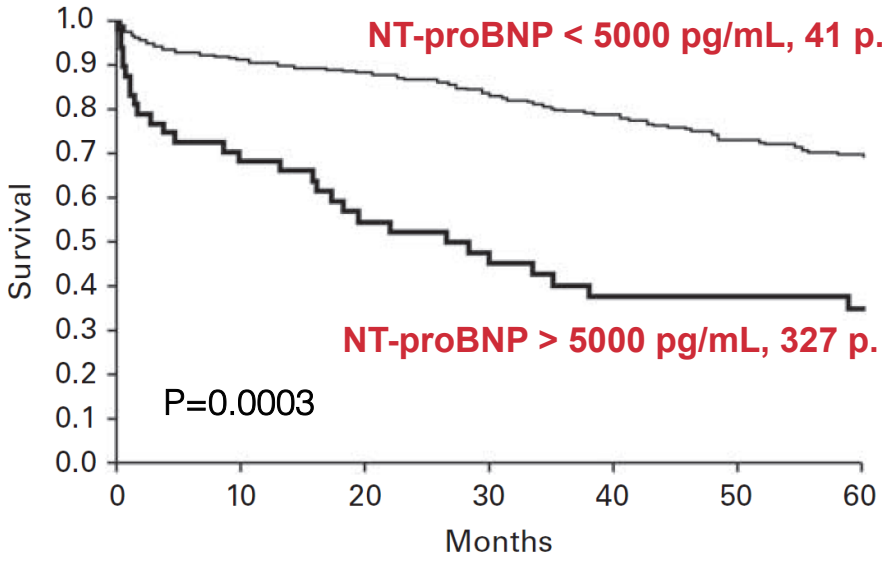


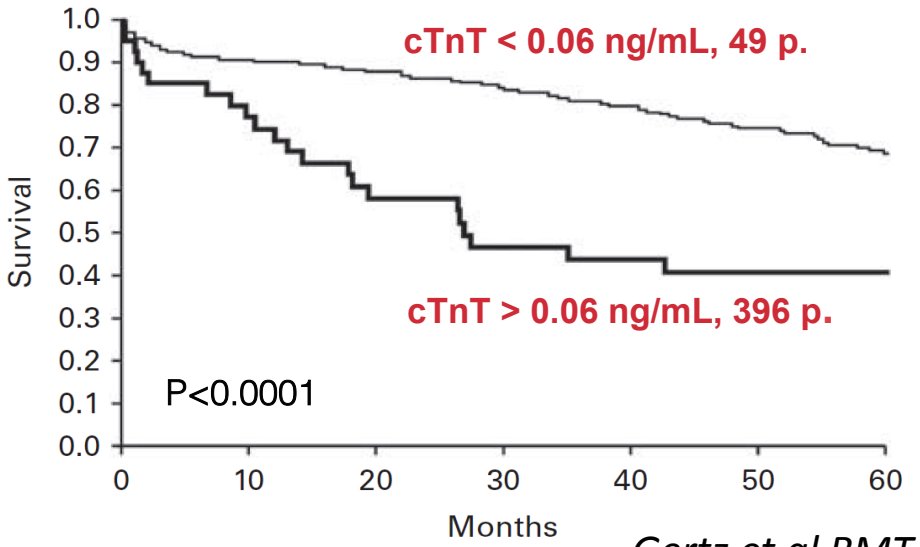


To reduce the influence of early treatment related deaths, a landmark analysis has been performed that included **only patients who survived for more than 6 months after randomization and who received their assigned treatment**

Jaccard et al, *N Engl J Med 2007*

Eligibility for ASCT in AL amyloidosis

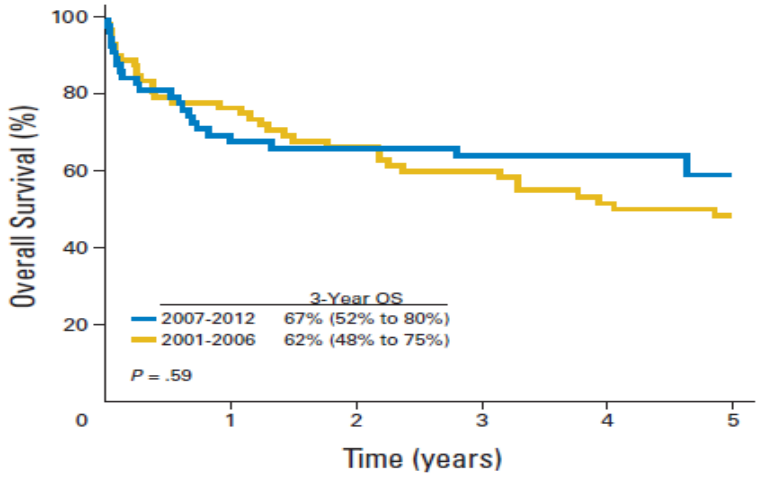


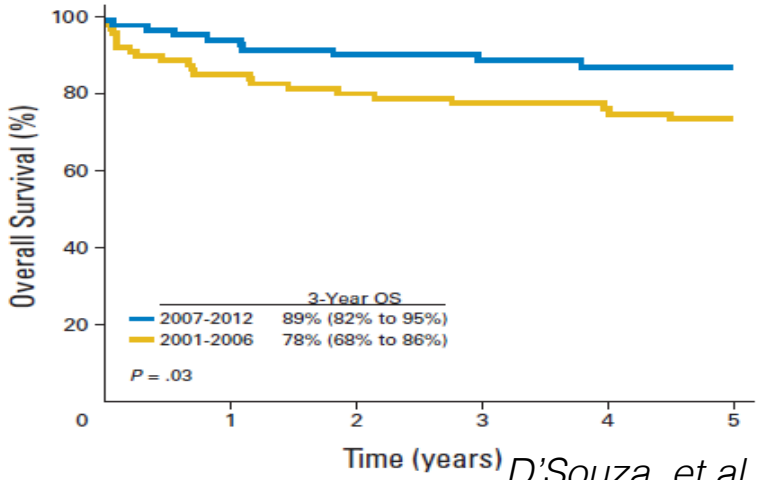


Gertz et al BMT 2013

Exclusion from ASCT: serum troponin T level > 0.06 ng/mL and NT-proBNP level > 5000 pg/mL.

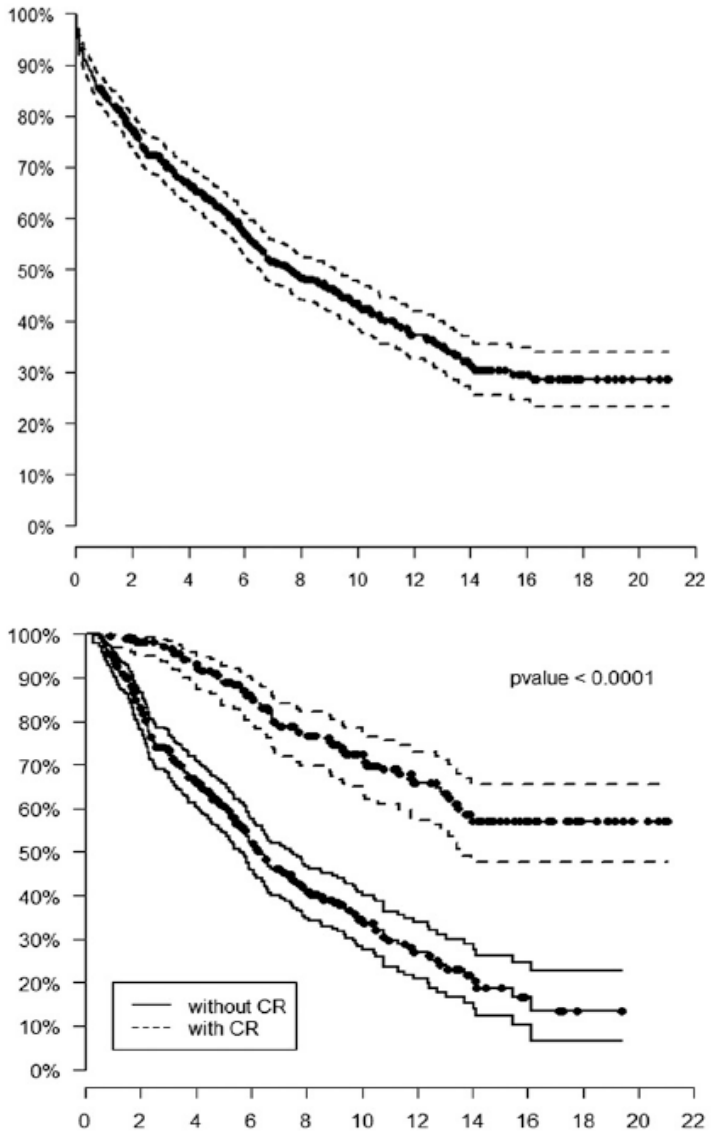
Application of these SELECTION CRITERIA is capable of reducing TRM to < 2%.





D'Souza, et al. JCO 2015

ASCT in AL amyloidosis



Overall hematologic response: 71%
Complete response: 35-37% (up to 60% with Bort)
Median survival:7.6 years

55% of patients in CR are projected to be alive at 14 years, with no deaths observed in patients with longer follow-up

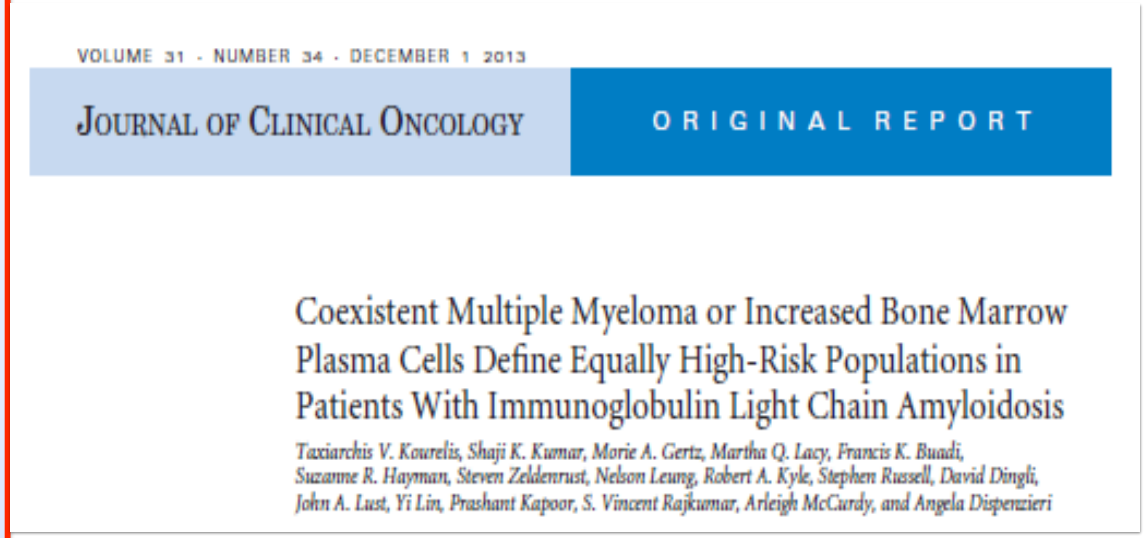
Feasible in 15-30% of the patients

Seldin, et al. Blood 2015
D'Souza, et al. JCO 2015
Landau, et al. Leukemia 2013
Gatt et al. BJH 2013

Treatment of AL amyloidosis should be risk-adapted

Low-risk, transplant eligible (~15%)
(NT-proBNP <5000 ng/L, cTnT <0.06 ng/mL, age <65 years, PS 0-2, eGFR >50 mL/min per 1.73 m^2 unless on dialysis, NYHA class <III, EF >45%, sBP >90 mmHg (standing), DLCO >50%)

- ASCT with MEL 200 mg/m^2
- Consider induction with CyBorD if BMPC >10% or if patient refuses upfront transplant
- Consider BDex if <CR after ASCT



adapted from Palladini & Merlini Blood 2016

Oral melphalan and dexamethasone grants extended survival with minimal toxicity in AL amyloidosis: long-term results of a risk-adapted approach

259 pts

119 pts M 0.22 mg/kg + D 40 mg D1-4/28

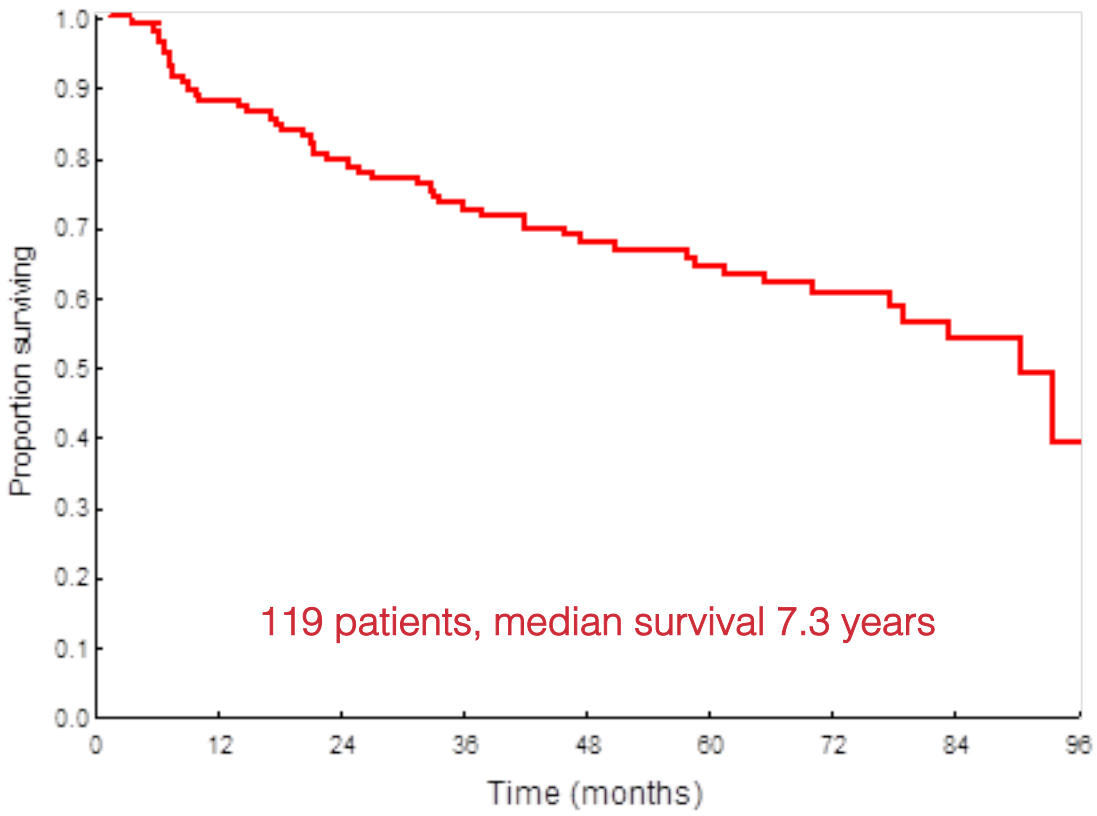
140 pts M 0.22 mg/kg + D 20 mg D1-4/28, 90% with cardiac amyloidosis, 60% NYHA III-IV

	Intent-to-treat analysis			3-month landmark analysis		
	Full-dose (N=119) N (%)	Attenuated (N=140) N (%)	P	Full-dose (N=119) N (%)	Attenuated (N=115) N (%)	P
CR	37 (31)	17 (12)	<0.001	37 (31)	17 (15)	0.003
VGPR	35 (29)	28 (20)	0.078	35 (29)	28 (24)	0.383
PR	19 (16)	26 (19)	0.581	19 (16)	26 (23)	0.200
Cardiac	25/67 (37)	24/122 (20)	0.008	25/67 (37)	24/97 (25)	0.084
Renal	20/82 (24)	15/87 (17)	0.252	20/82 (24)	15/71 (21)	0.599

- HR full-dose 76% vs attenuated-dose 51%, p < 0.0001, in landmark 76% vs 62%, p 0.03
- OrgR full-dose 36% vs attenuated-dose 21%, p 0.0009
- Severe AEs full-dose 16% vs attenuated-dose 20%, p 0.4

Palladini et al. Hematologica 2014

Melphalan / dexamethasone (MDex) in intermediate-risk patients



- Hematologic Response:

CR:	31%	**76%**
VGPR:	29%	
PR:	16%	
NR:	24%	

- Organ response

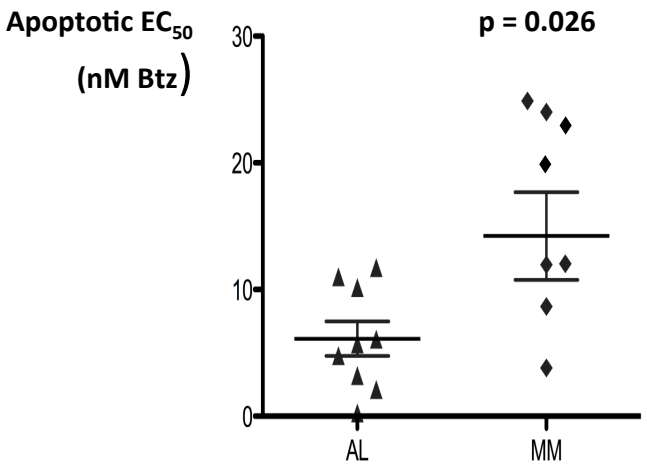
heart:	37%
kidney:	24%

Deaths at 3 months 0%, SAE 16%

The projected survival of patients in CR after MDex is >80% at 7 years

Palladini, et al. Haematologica 2014

Novel agents: Proteasome inhibitors



- Amyloidogenic plasma cells synthesize a misfolded light chain which causes proteasome overload and increased sensitivity to Bortezomib;
- Bone marrow purified plasma cells from amyloid patients were shown to be twice as vulnerable to Bortezomib inhibition than those of MM patients;
- **Thus Bortezomib may represent prototype for a targeted therapy in AL amyloidosis.**

Chemotherapy / Reference	Number of patients	Hematologic response % (CR %)	Overall survival (months) or 1-3 year OS (%)
		Bortezomib containing regimens	
Bortezomib (Reece *et al.*)[31]	70	OW: 68.8 (37.5) TW: 66.7 (24.2)	OW: 94% (1 yr OS) TW: 84% (1 yr OS)
Bor/Dex (Kastritis *et al.*)[32]	94	71 (25)	76% (1 yr OS)
Cyclo/Bor/Dex (Venner *et al.*)[33]	43	81.4 (41.9)	97.7% (2 yr OS)
Cyclo/Bor/Dex (Mikhael *et al.*)[34]	17	94 (71%)	Not specified
Bor/Mel/Dex – 33 Cyclo/Bor/Dex -17 (Palladini *et al.*)[35]	50	67 (27) stage I & II 40 (5) stage III	Not reached 58% (1 yr OS projected)

Gatt et al. BJH 2013; Mahmood et al. Hematologica 2014

BORTEZOMIB + DEXAMETHASONE: TOXICITY

Table 4. Common Toxicities Documented in Patients Treated With Bortezomib With or Without Dexamethasone (N = 94)

Toxicity	All Grades (%)	Grades 2-4 (%)	Grades 3-4 (%)
Peripheral neuropathy	40	30	
Neuropathic pain	14	9	
Hyponatremia	11		3
Constipation	18		4
Diarrhea	21		6
Fever/infection/NOS	8		8
Edema	33		15
Orthostatic hypotension	36		13
Overall toxicity	82		29

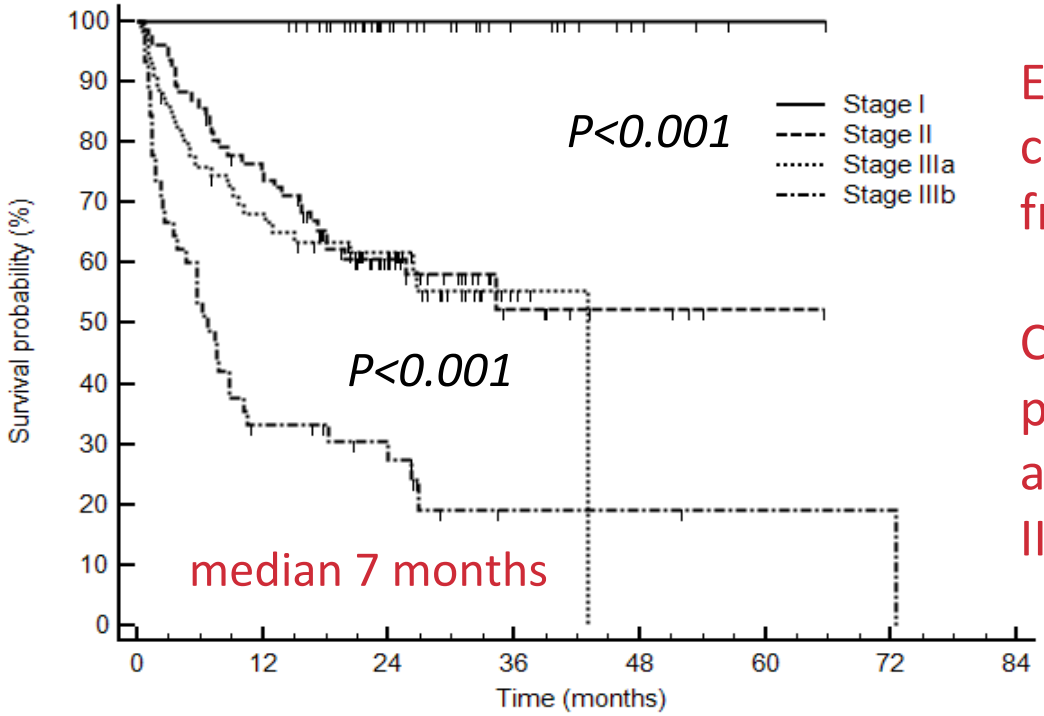
Abbreviation: NOS, not otherwise specified.

Table 3 Major toxicities of treatment with B/D

Toxicity	Grade 1+2	Grade 3+4
Anemia	70%	0%
Thrombopenia	27%	4%
Leukopenia	25%	4%
Akute renal failure	4%	0%
Hyponatremia	4%	4%
Hypokalemia	4%	0%
Fatigue	23%	0%
Diarrhea	12%	0%
Constipation	4%	0%
Nausea	8%	0%
Edema	27%	0%
Hypotension	23%	0%
Arrhythmia	4%	4%
Neurotoxicity	42%	0%
Herpes zoster	12%	0%
Other	27%	0%

Kastritis et al. JCO 2010; Lamm et al. Ann Hematol 2011

CyBorD in AL amyloidosis: a retrospective study of 230 patients



Early stage patients (stage I) without cardiac involvement, benefit most from CyBorD

CyBorD does not overcome the poor prognosis of patients with very advanced cardiac involvement (stage III with NT-proBNP >8500 ng/L)

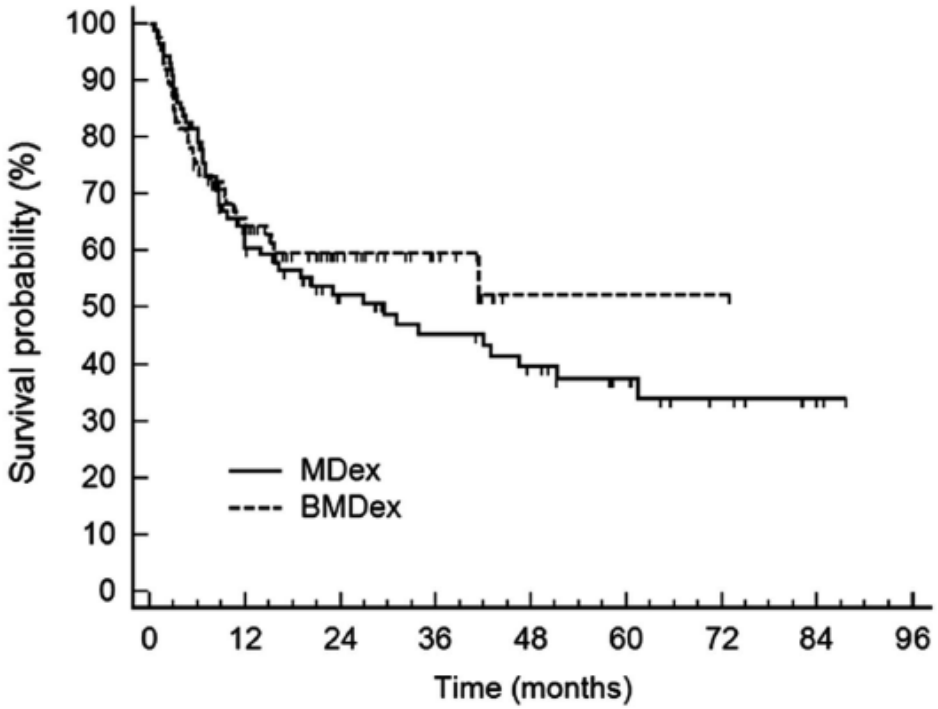
Response category	Stage I (30 patients)	Stage II (67 patients)	Stage IIIa (61 patients)	Stage IIIb (43 patients)
Overall hem.	77%	64%	69%	42%*
CR	33%	18%	23%	14%
VGPR	23%	27%	26%	9%
PR	20%	19%	20%	19%
Cardiac	-	29%	17%	4%*

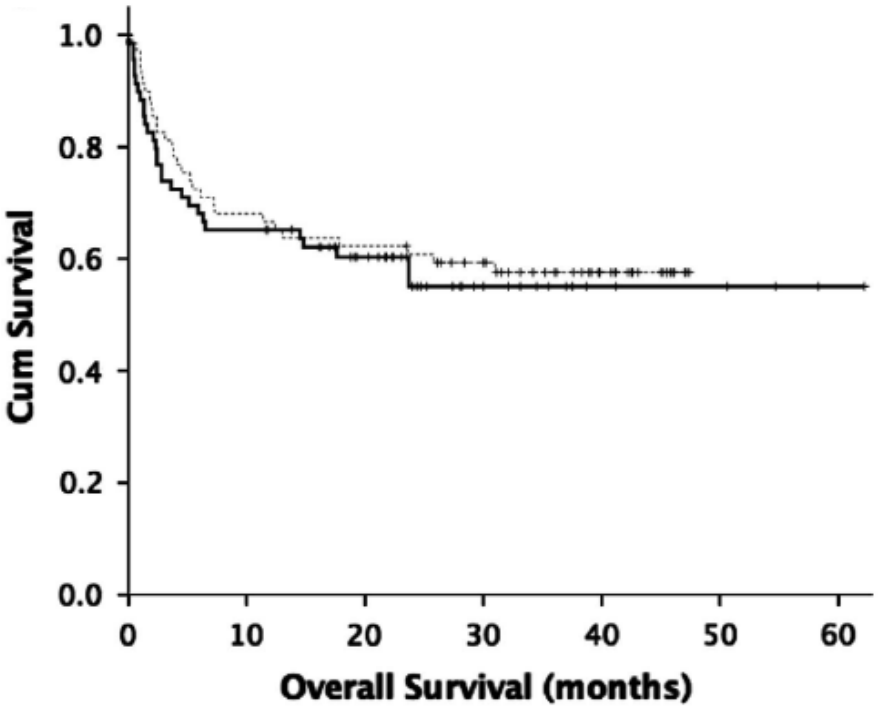
**P<0.05 compared to stages (I), II, and IIIa*

Palladini, et al. Blood 2015

Bortezomib-based and standard treatments

Matched comparisons





Hem Resp	MDex 87 pts	BMDex 87 pts
Overall	51%	69%
CR	19%	42%

Palladini, et al. Leukemia 2014

Hem Resp	CTD 69 pts	CyBorD 69 pts
Overall	71%	80%
CR	25%	41%

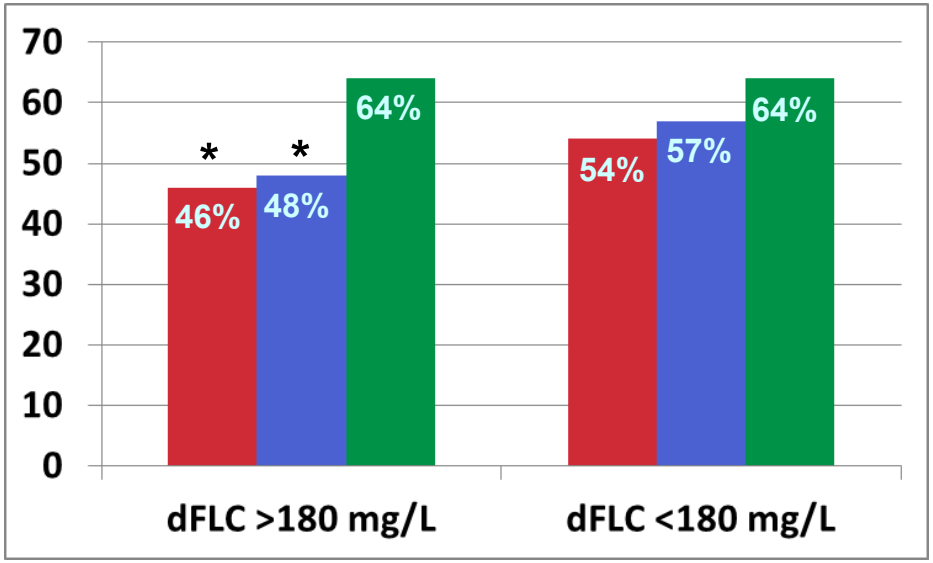
Wechalekar, et al. Leukemia 2014

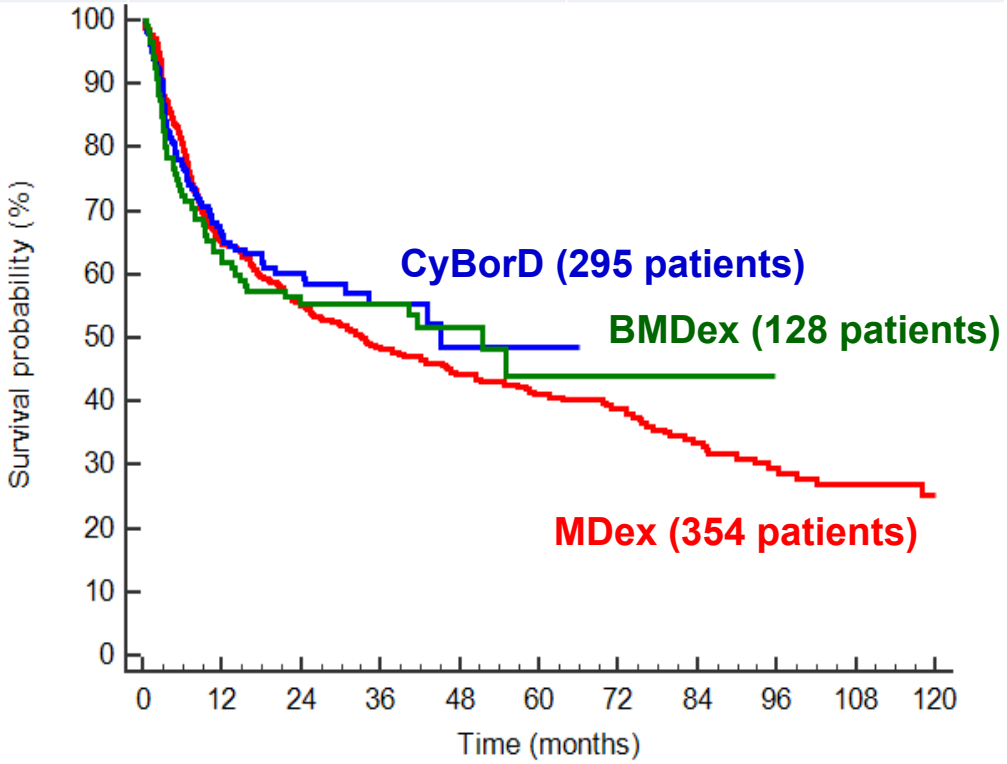
Most common upfront treatments in the Pavia series

Variable	MDex (N 354)	BMDex (N 128)	CyBorD (N 295)
Stages IIIa/IIIb	18% / 21%	19% / 20%	19% / 14%
Renal stage III	12%	8%	16%°
Overall hem. resp.	181 (51%)*	81 (64%)	156 (53%)*
CR/VGPR	131 (37%)°	66 (52%)	115 (39%)°
Cardiac response	18%	21%	17%
Renal response	29%	22%	21%

*P<0.05 compared to BMDex
°P=0.001 compared to BMDex

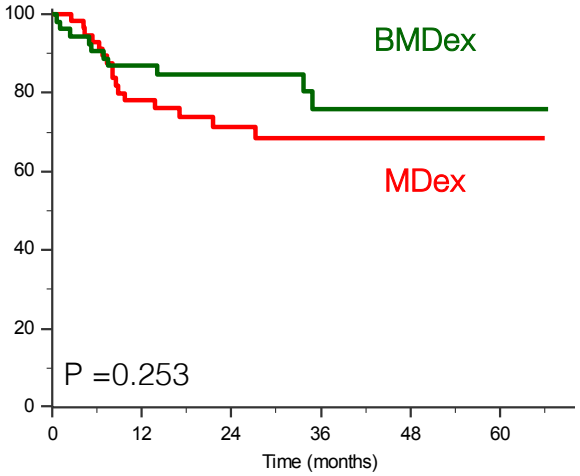
Response rates according to baseline dFLC

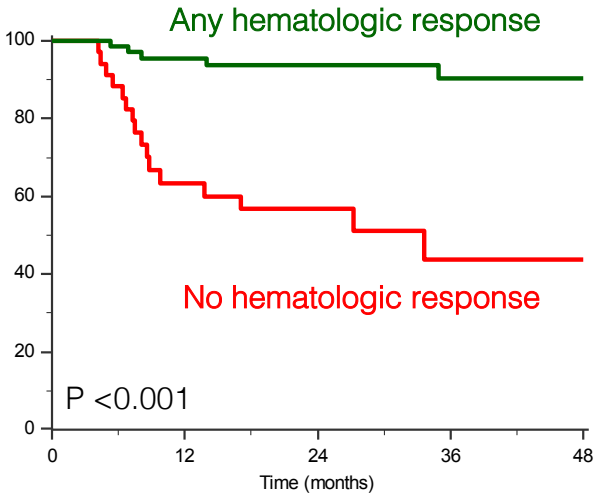


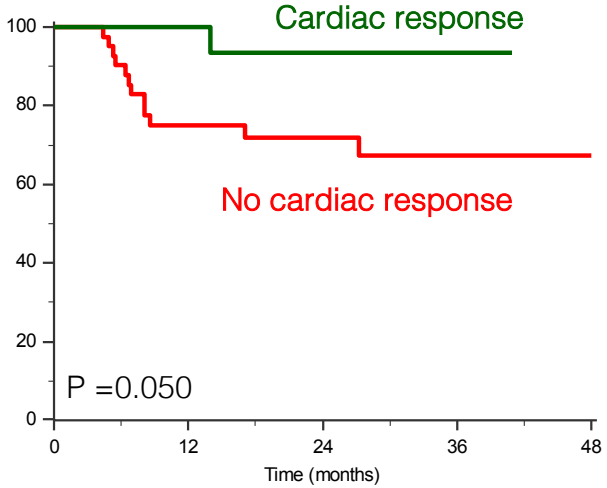


Palladini, et al. ASH 2015

Phase III MDex vs. BMDex trial







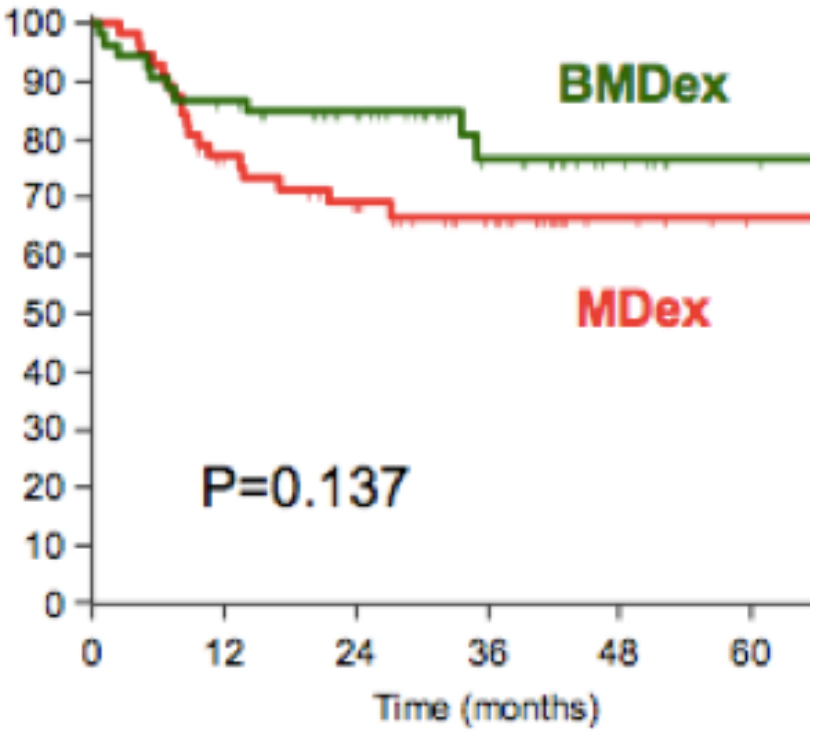
Best response (median 5 cycles)	MDex (55 pts)	BMDex (55 pts)	P
Overall Hem.	56%	**81%**	0.001
CR/VGPR	38%	64%	0.002
Heart	24%	38%	0.119
Kidney	48%	48%	-

Kastritis, et al. ASH 2016

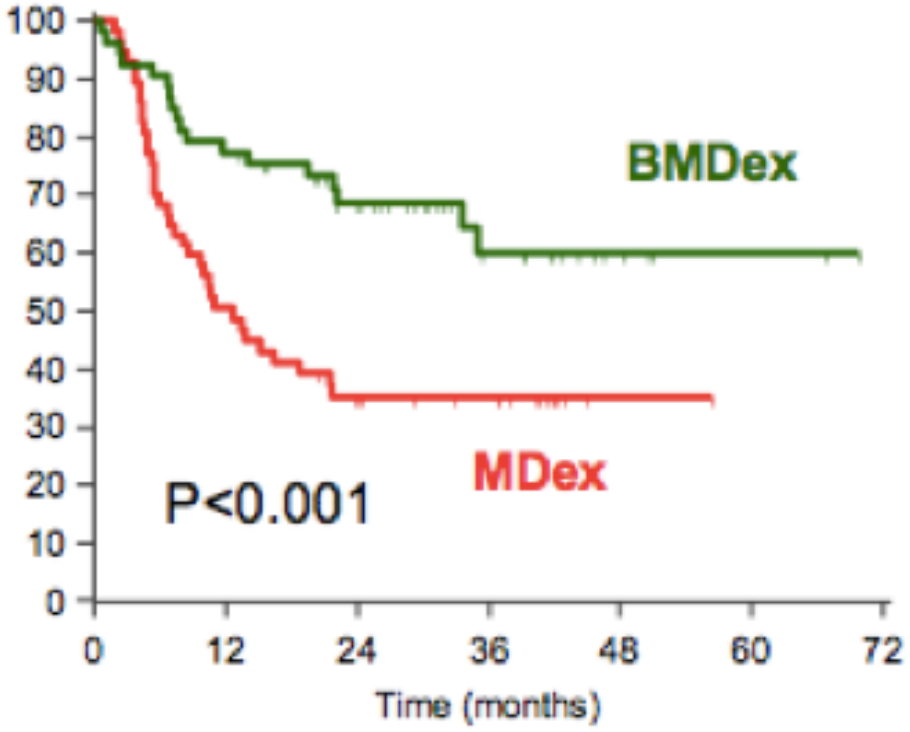
Survival

- 28 patients died, 18 (32%) in the MDex arm and 10 (19%) in the BMDex arm
- The median follow-up of living patients is 33 months

Overall survival



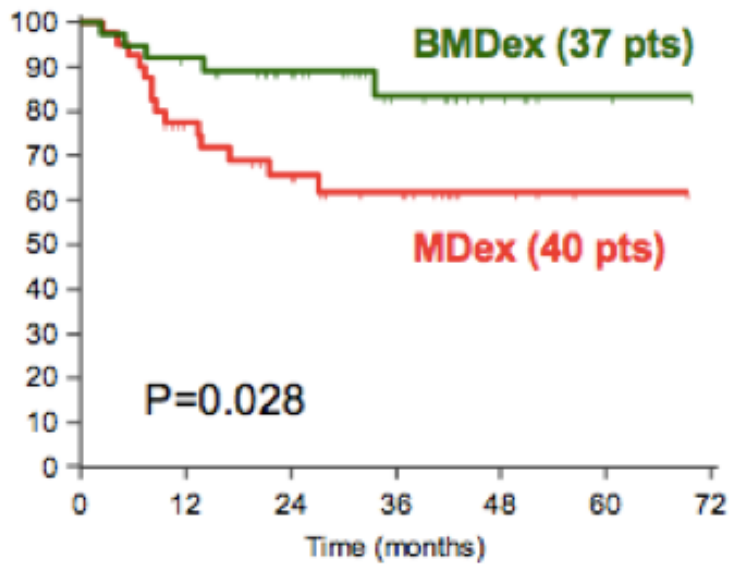
Time to second-line therapy or death



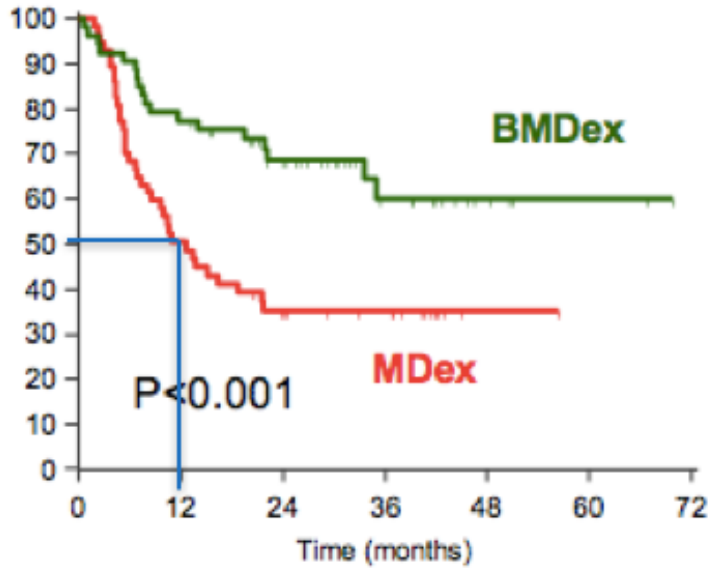
Survival

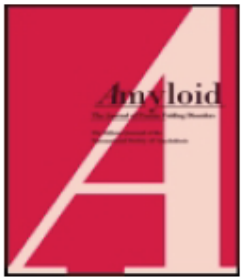
- 28 patients died, 18 (32%) in the MDex arm and 10 (19%) in the BMDex arm
- The median follow-up of living patients is 33 months

Overall survival in cardiac stage II patients



Time to second-line therapy or death





Amyloid
The Journal of Protein Folding Disorders

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Gain of chromosome 1q21 is an independent adverse prognostic factor in light chain amyloidosis patients treated with melphalan/ dexamethasone

Tilmann Bochtler, Ute Hegenbart, Christina Kunz, Axel Benner, Anja Seckinger, Sascha Dietrich, Martin Granzow, Kai Neben, Hartmut Goldschmidt, Anthony D. Ho, Dirk Hose, Anna Jauch & Stefan O. Schönland

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Translocation t(11;14) Is Associated With Adverse Outcome in Patients With Newly Diagnosed AL Amyloidosis When Treated With Bortezomib-Based Regimens

Tilmann Bochtler, Ute Hegenbart, Christina Kunz, Martin Granzow, Axel Benner, Anja Seckinger, Christoph Kimmich, Hartmut Goldschmidt, Anthony D. Ho, Dirk Hose, Anna Jauch, and Stefan O. Schönland

Treatment of AL amyloidosis should be risk-adapted

Low-risk, transplant eligible (~15%)
(NT-proBNP <5000 ng/L, cTnT <0.06 ng/mL, age <65 years, PS 0-2, eGFR >50 mL/min per 1.73 m^2 unless on dialysis, NYHA class <III, EF >45%, sBP >90 mmHg (standing), DLCO >50%)

- ASCT with MEL 200 mg/m^2
- Consider induction with CyBorD if BMPC >10% or if patient refuses upfront transplant
- Consider BDex if <CR after ASCT

Intermediate-risk (~45%)
(ineligible for ASCT, stages I-IIIa)

- MDex, preferred in case of neuropathy and in patients with t(11;14)
- CyBorD, stem cell sparing, preferred in renal failure and in patients with gain 1q21
- BMDex, preferred if high dFLC

adapted from Palladini & Merlini Blood 2016

Outcome of patients with very advanced cardiac involvement (stage III with NT-proBNP >8500 ng/L) treated with different regimens

Regimen	Number of patients	Median survival
mostly MDex and CTD[1]	182	5 months
MDex[2]	62	7 months
MDex[3]	12, NYHA class III heart failure	4 months
BMDex[3]	15, NYHA class III heart failure	3 months
CTD[4]	15	4 months
CyBorD[4]	18	3 months
CyBorD[5]	18, NT-proBNP >9500 ng/L	4 months
CyBorD[6]	45	7 months

1. *Wechalekar, et al. Blood 2013*
2. *Palladini, et al. Haematologica 2014*
3. *Palladini, et al. Leukemia 2014*
4. *Venner, et al. Leukemia 2014*
5. *Jaccard, et al. Haematologica 2014*
6. *Palladini, et al. Blood 2015*

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- **MDex**, preferred in case of neuropathy and in patients with t(11;14)
- **CyBorD**, stem cell sparing, preferred in renal failure and in patients with gain 1q21
- **BMDex,** preferred if high dFLC and patients with t(11;14)

High-risk
(Stage IIIb, NYHA class ≥III)

Low-dose combination regimens

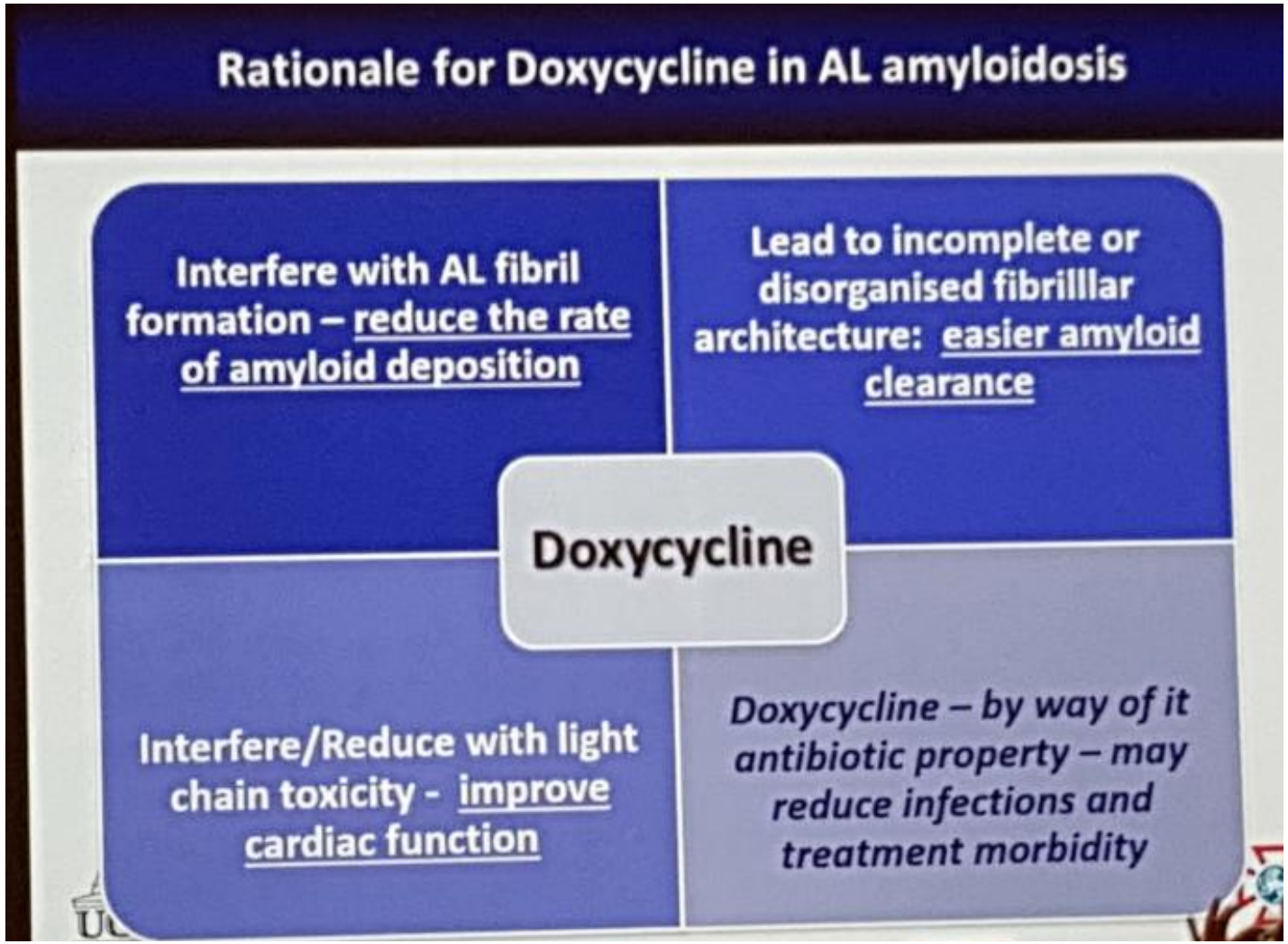
vs.

Non attenuated regimens with intensive care support

Cardiac transplant
Drugs to remove amyloid fibrils

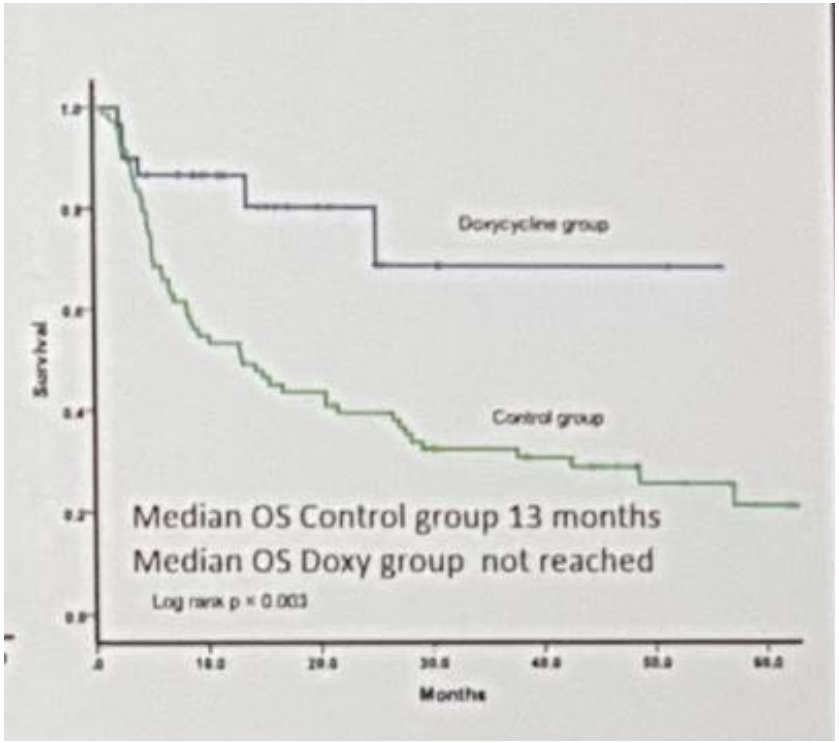
adapted from Palladini & Merlini Blood 2016

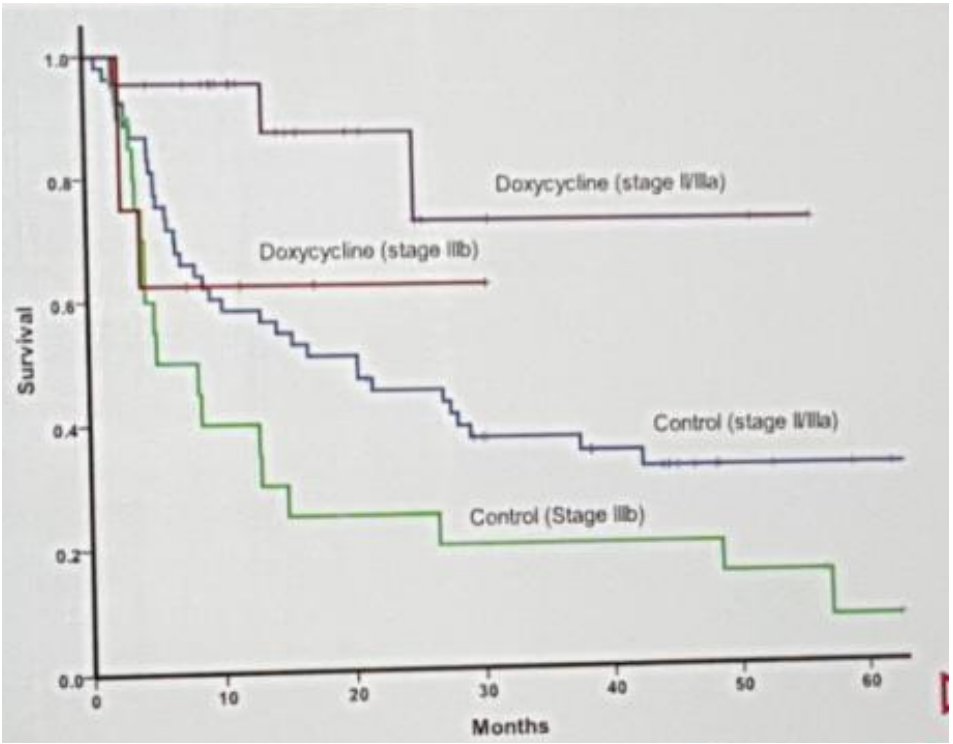
Tetracyclines ? A Wechalekar ASH 2015



Tetracyclines ? A. Wechalekar ASH 2015

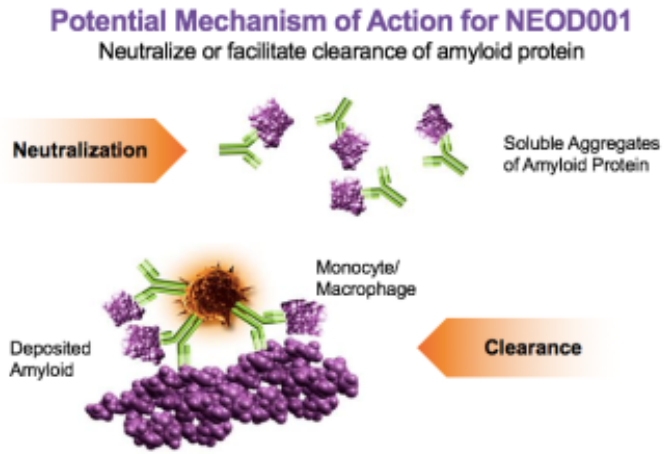
- 63 patients with cardiac involvement treated with VCD + tetracycline 100 mg Bid
- 67 control patients matched for disease characteristics (for treatment ?)





New strategies : to accelerate deposits elimination

- Monoclonal antibodies targeting amyloid



  - 2 anti conformartional antibodies
    - 11-1F4 (Phase I)
    - NEOD001 (2A4)
      - International Phase III for naive patients VCD + NEOD001 or placebo, 50 patients included
      - Phase II for patients already treated with a persistent cardiac dysfunction

  - Anti-SAP antibody after treatment with CPHPC (in vivo SAP KO)

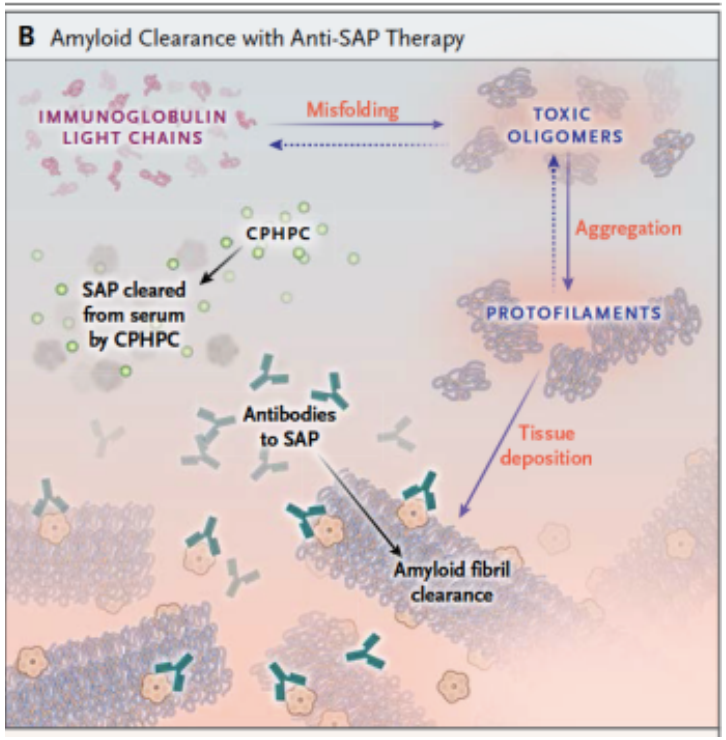
The NEW ENGLAND JOURNAL of MEDICINE July 15, 2015

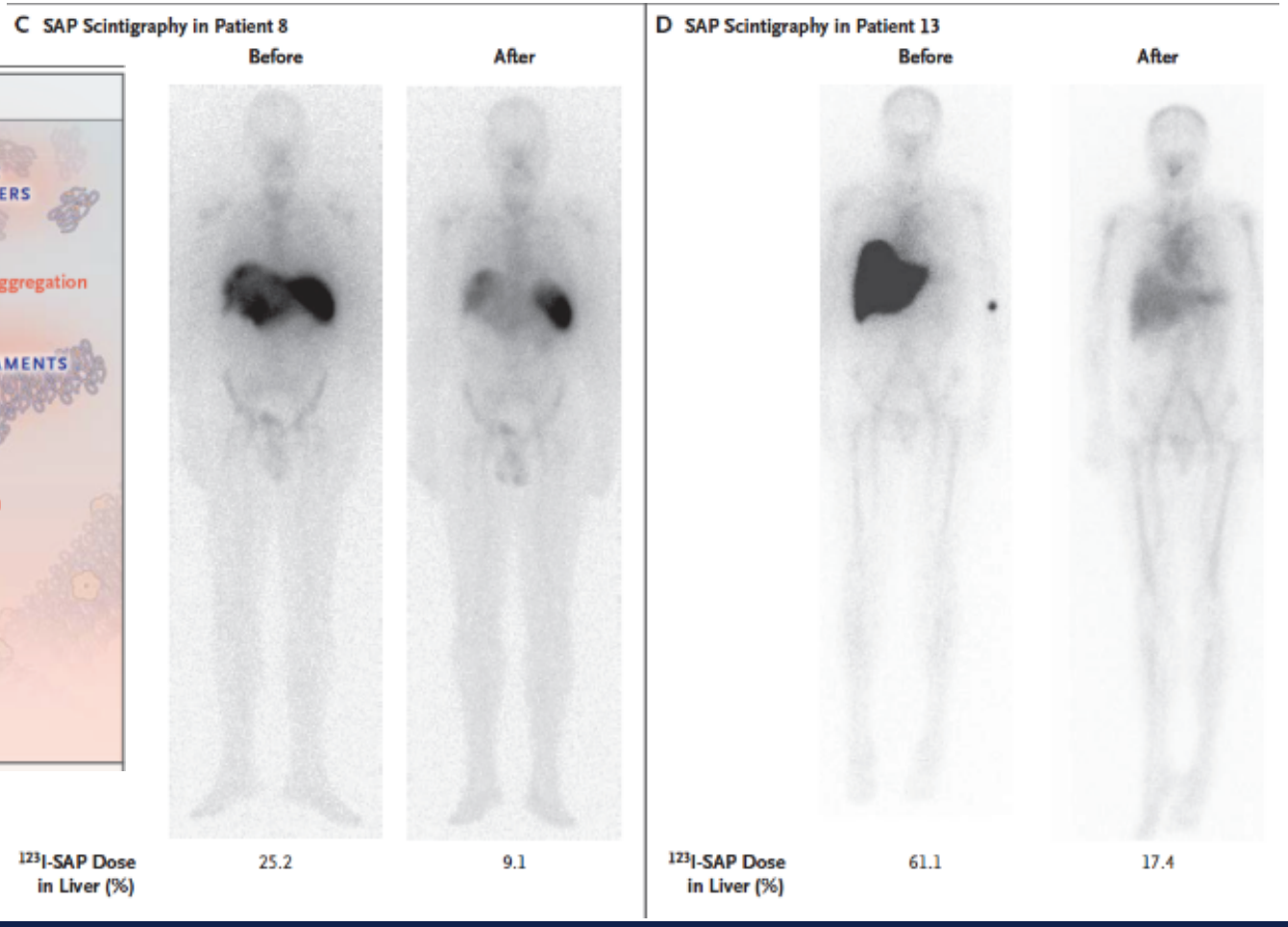
ORIGINAL ARTICLE

Therapeutic Clearance of Amyloid by Antibodies to Serum Amyloid P Component

Duncan B. Richards, D.M., Louise M. Cookson, B.Sc., Alienor C. Berges, Pharm.D., Sharon V. Barton, M.Sc., Thirusha Lane, R.N., M.Sc., James M. Ritter, D.Phil., F.Med.Sci., Marianna Fontana, M.D., James C. Moon, M.D., Massimo Pinzani, M.D., Ph.D., Julian D. Gillmore, M.D., Ph.D., Philip N. Hawkins, Ph.D., F.Med.Sci., and Mark B. Pepys, Ph.D., F.R.S.

15 patients
very rapid clearance of liver deposits :
Heart and kidney ?

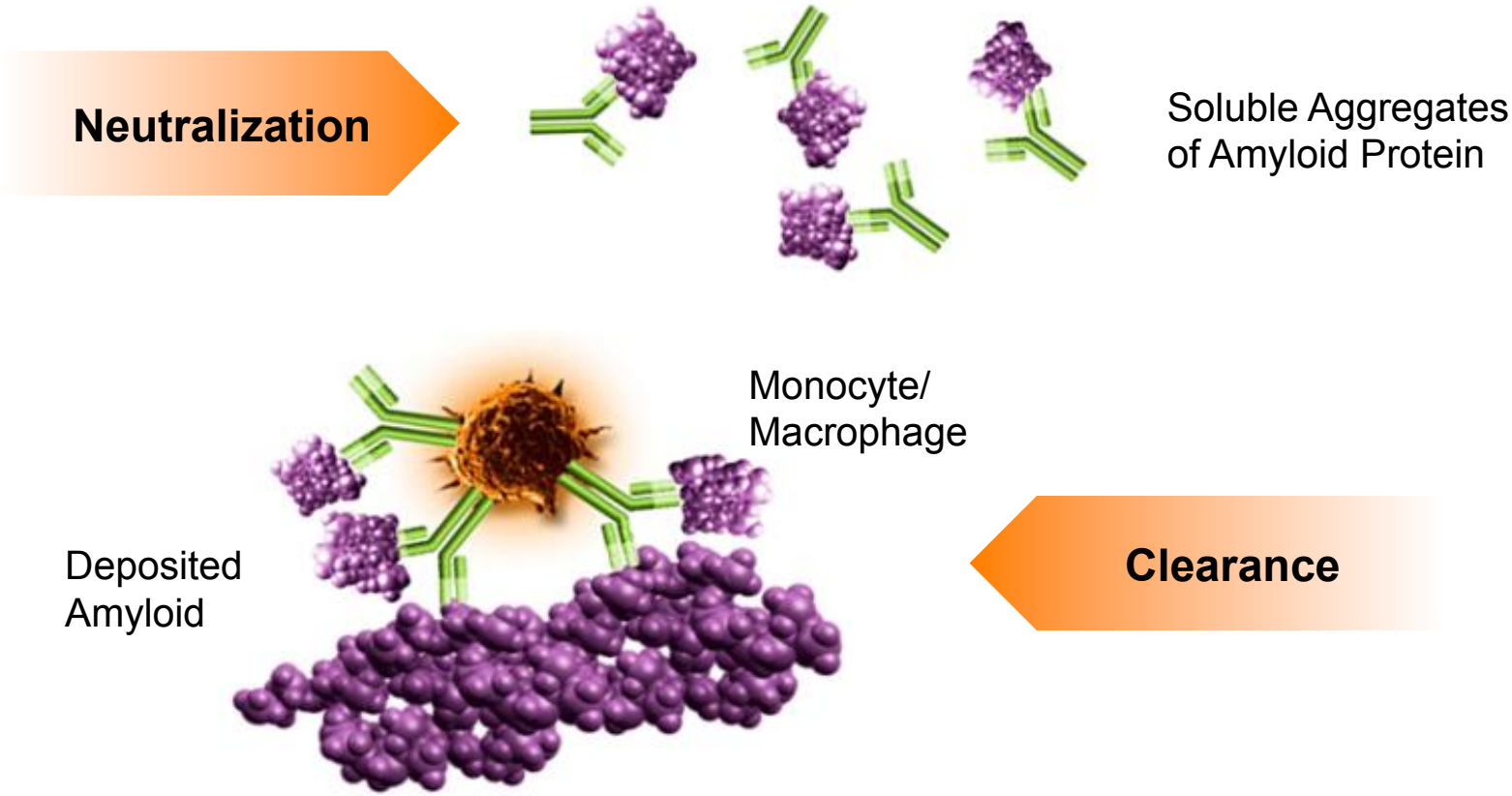




Potential NEOD001 MOA: Neutralizes Soluble Toxic Aggregates and Clears AL Amyloid Deposits

Potential Mechanism of Action for NEOD001

Neutralize or facilitate clearance of amyloid protein



NEOD001 Demonstrates Organ Biomarker Responses in Patients With Light Chain Amyloidosis and Persistent Organ Dysfunction: Final Results From a Phase 1/2 Study

Morie A. Gertz,[1] Raymond L. Comenzo,[2] Heather Landau,[3]
Vaishali Sanchorawala,[4] Brendan Weiss,[5] Jeffrey Zonder,[6] Jackie Walling,[7]
Gene G. Kinney,[8] Martin Koller,[8] Dale B. Schenk,[8] Spencer D. Guthrie,[8]
Enchi Liu,[8] Michaela Liedtke[9]

Organ Biomarker Responses in Patients With Light Chain Amyloidosis Treated With NEOD001 Are Independent of Previous Hematologic Responses

Michaela Liedtke,[1] Raymond L. Comenzo,[2] Heather Landau,[3]
Vaishali Sanchorawala,[4] Brendan Weiss,[5] Jeffrey Zonder,[6] Jackie Walling,[7]
Gene G. Kinney,[8] Martin Koller,[8] Dale B. Schenk,[8] Spencer D. Guthrie,[8]
Enchi Liu,[8] Morie A. Gertz[9]

ASH 2016

NEOD001 Organ Responses Not Related to Previous Plasma Cell–Directed Therapy

- Not related to ***depth*** of best or last hematologic response
- Not related to ***time*** since best or last hematologic response
- Not related to time since last plasma cell–directed therapy
- Not related to type of previous plasma cell–directed therapy

These data will be presented during session 647 (ASH2016, Dr. Michaela Liedtke, 8 AM)

Phase 2b:

THE PRONTO AMYLOIDOSIS STUDY

Patients must have previously received ≥1 therapy (≥6 months before study start) with partial hematologic response or better, confirmed AL amyloidosis diagnosis, and persistent cardiac dysfunction

Phase 3:

THE VITAL AMYLOIDOSIS STUDY

Patients must be treatment naive and have a confirmed diagnosis of AL amyloidosis with cardiac involvement

Treatment of refractory-relapsed patients

- **Bortezomib** if not yet exposed to this drug or **re-treatment**
- **Lenalidomide** or **Pomalidomide** grant 40-60% hematologic response rate in patients exposed to alkylators , bortezomib and other IMiDs.[1, 2, 3]
- **Bendamustine** grants 40-50% hematologic response rate, promising in IgM-AL amyloidosis.[4, 5]
- **Ixazomib** grants ~90% hematologic response rate in proteasome inhibitor-naïve patients; phase III study underway.[6]
- **Carfilzomib** was reported to grant high (~75%) rate of hematologic response; cardiac toxicity causes concern.[7]

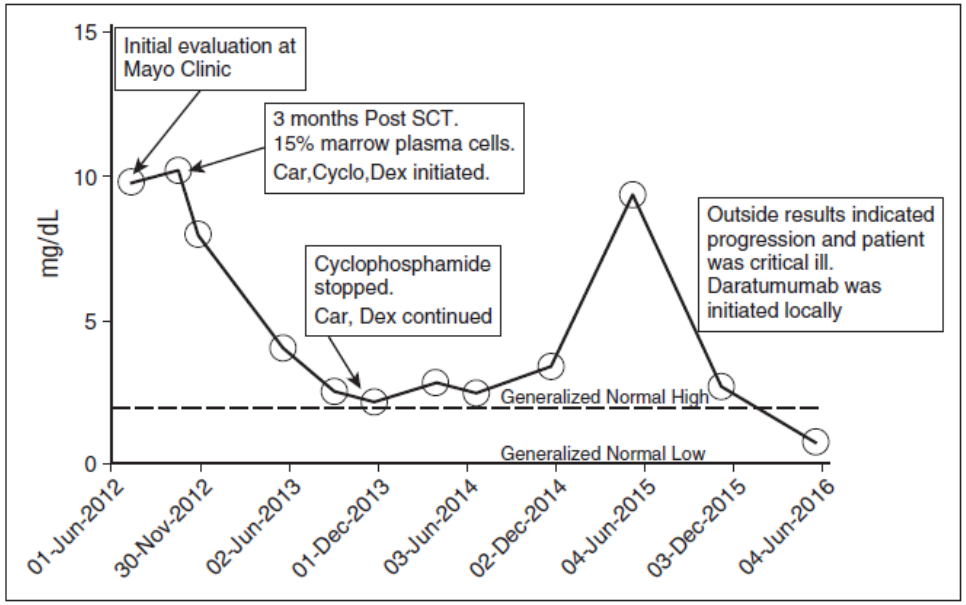
1. *Palladini, et al. Ann Hematol 2009*
2. *Dispenzieri, et al. Blood 2012*
3. *Palladini, et al. Blood 2017*
4. *Milani, et al. IWMW 2014 [abstract]*

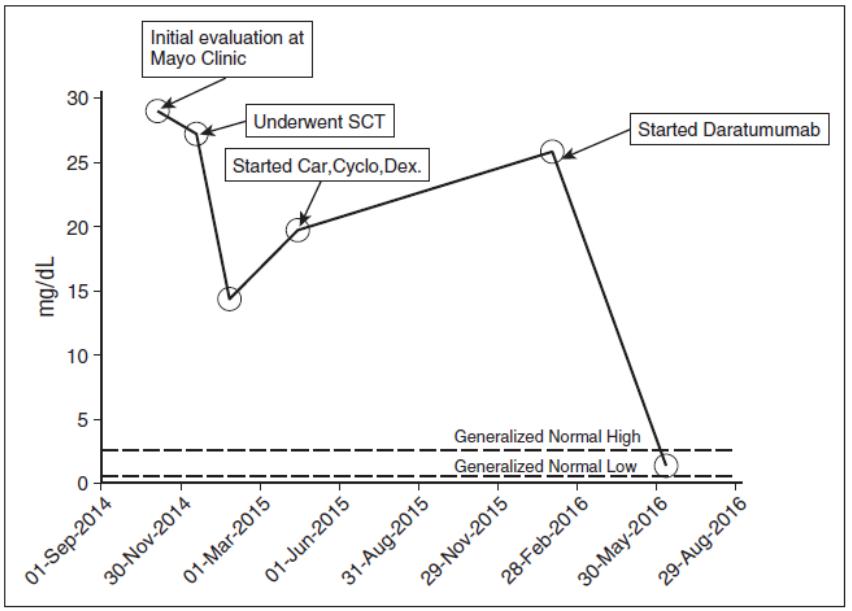
5 Lenztsch et al ASH 2015 [abstract]
6 Merlini, et al. ASH 2014 [abstract]
7 Cohen, et al. ASH 2014 [abstract]

To the editor:

First report of safety and efficacy of daratumumab in 2 cases of advanced immunoglobulin light chain amyloidosis

Taimur Sher,[1] Brooke Fenton,[1] Adnan Akhtar,[2] and Morie A. Gertz[1,3]



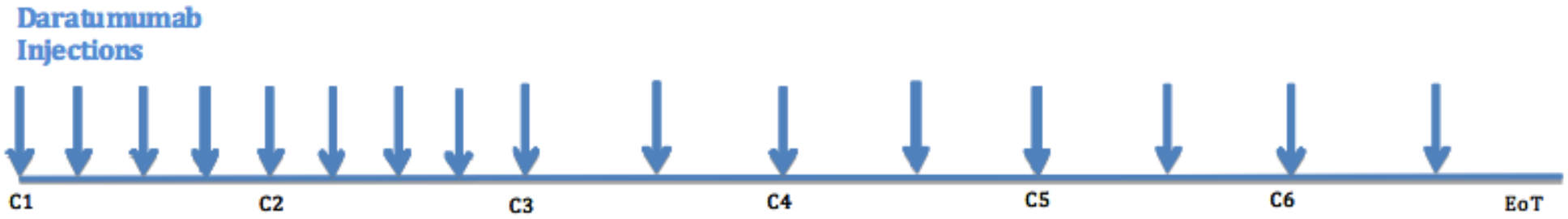


AmyDara (IFM 2016-02)

A Multicentre Open label Phase II study of Daratumumab in AL Amyloidosis Patients not in VGPR or Better (dFLC > 50mg, NT-pro BNP < 8500)

Daratumumab Phase II in AL AMYLOIDOSIS

Daratumumab 6 cycles, 28 days, 16 mg/kg IV ,

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LORENZO E ARIOSTO SERÀGNOLI