14TH International Myeloma Workshop

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Management of AL amyloidosis in 2013

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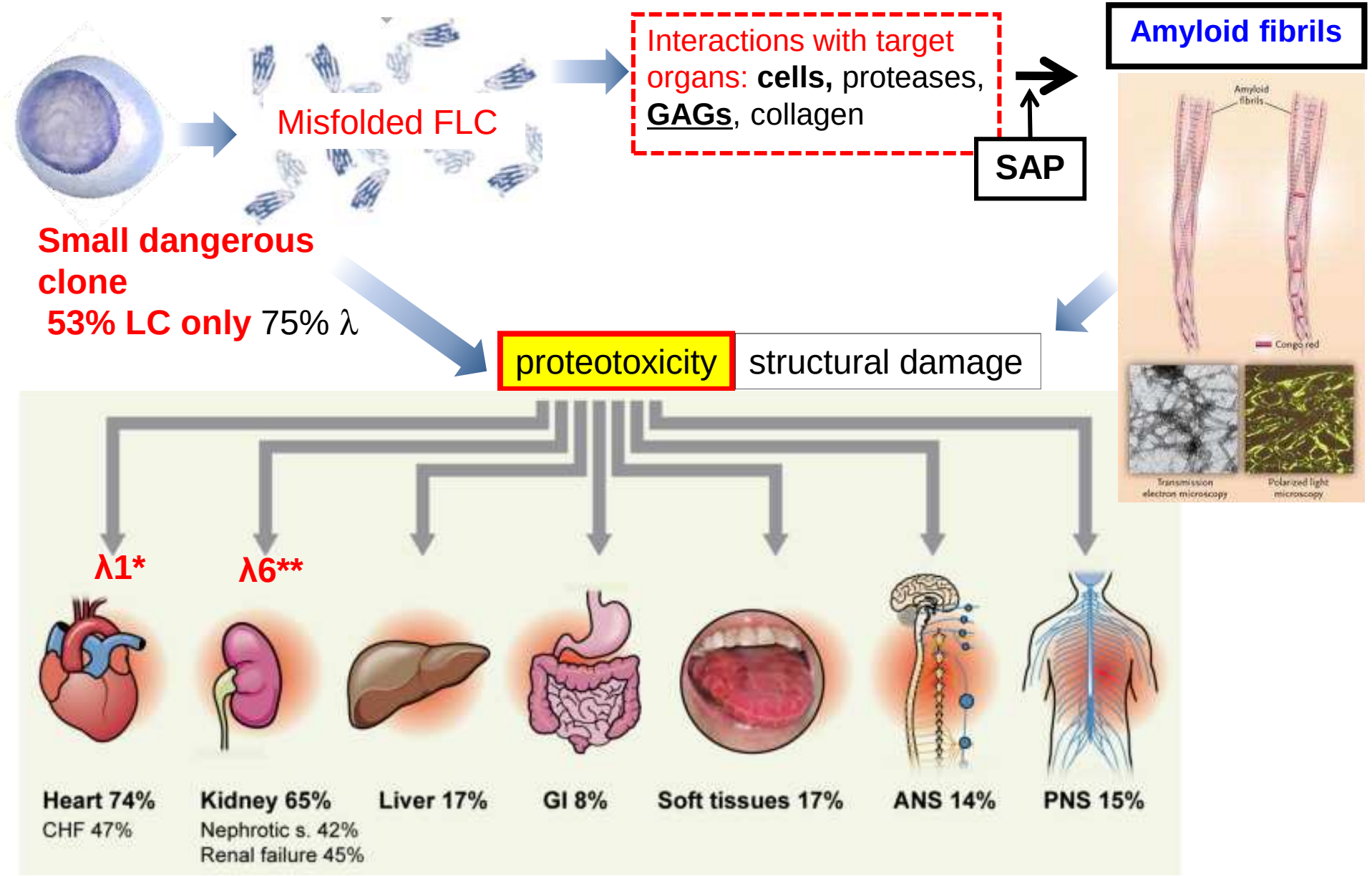
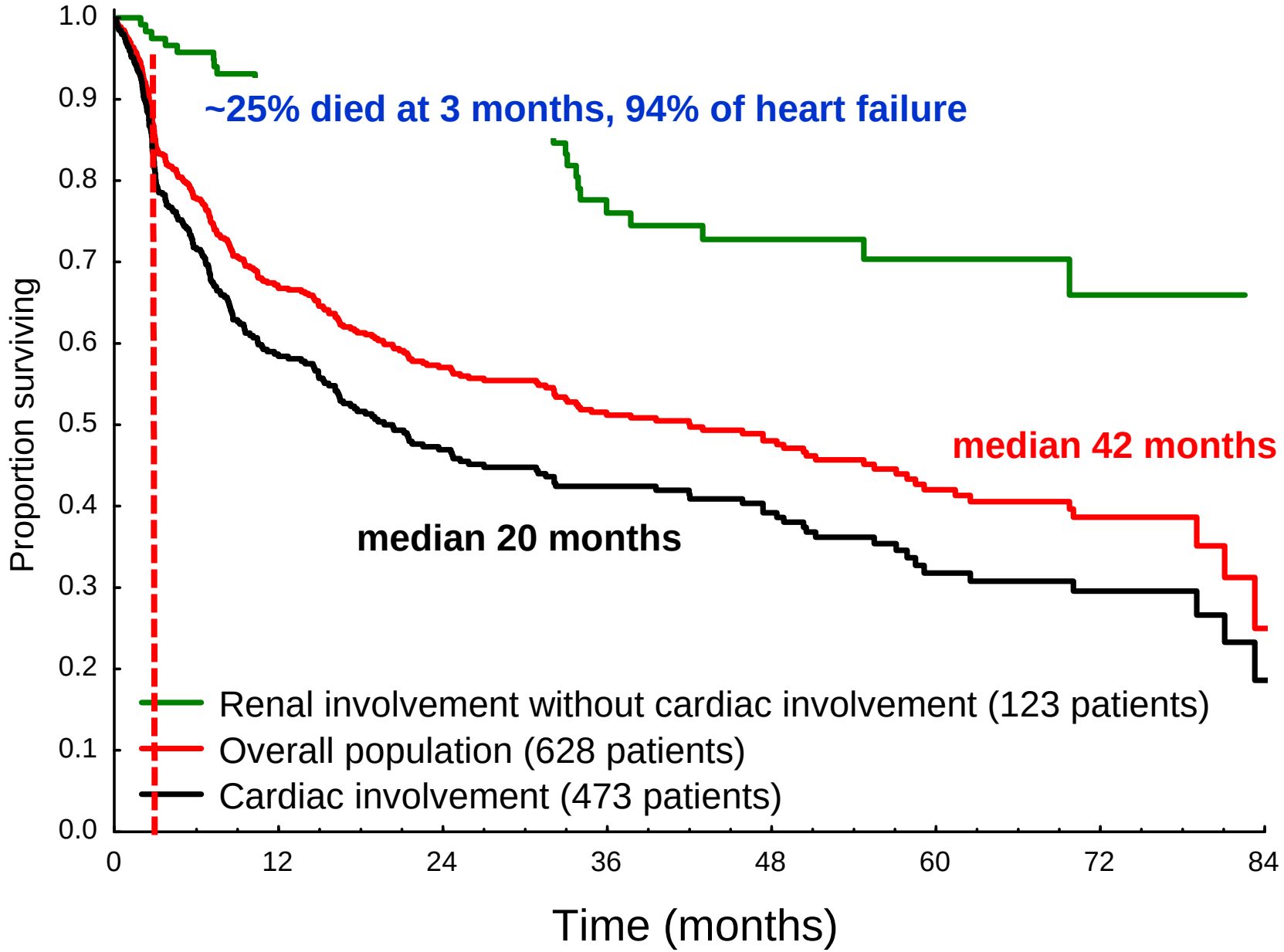
AL Amyloidosis: protein misfolding disease

Incidence 10 patients/million/year

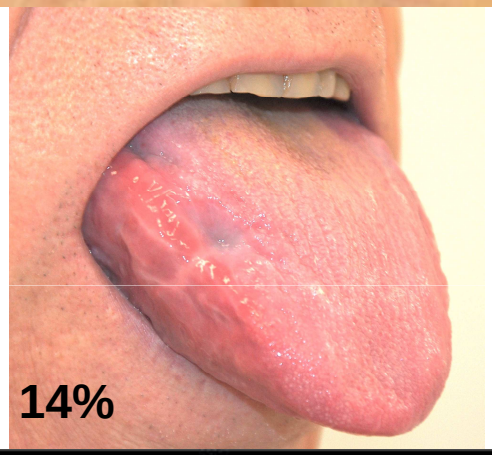


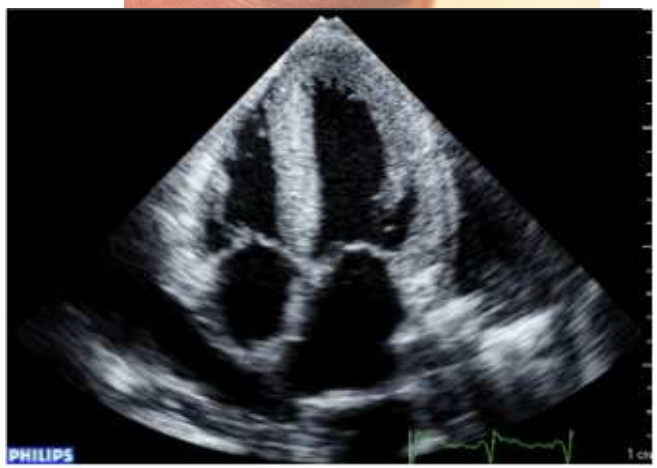
*Merlini & Stone, Blood. 2006; *Perfetti et al, Blood. 2012; **Comenzo et al, Br J Haematol. 1999*

Survival of 628 patients with AL amyloidosis diagnosed between 2004 and 2011 at the Pavia Amyloid Center



When to suspect amyloidosis





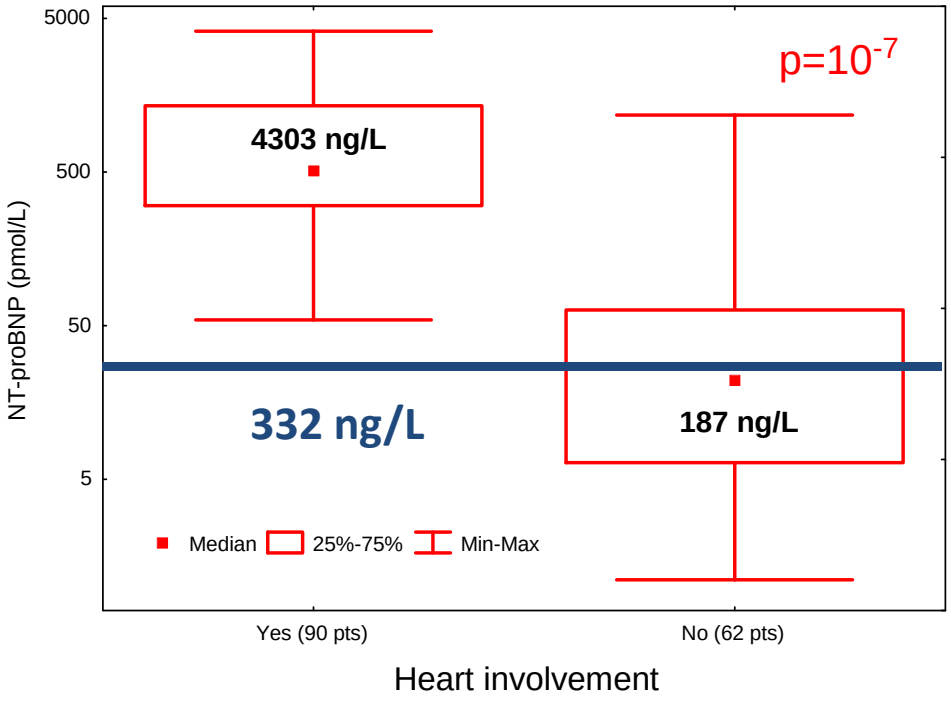
Concentric hypertrophy + low ECG voltage

Signs and Symptoms of AL

- Lethargy, fatigue
- Weight loss
- Peripheral edema
- Heart failure
- Diarrhea/constipation
- Peripheral &/or autonomic neuropathy
- Postural hypotension
- **Purpura, macroglossia**

Signs and symptoms usually reflect advanced organ damage

Serum N-terminal Pro-Natriuretic Peptide type B (NT-proBNP) is a sensitive marker of myocardial dysfunction in AL amyloidosis

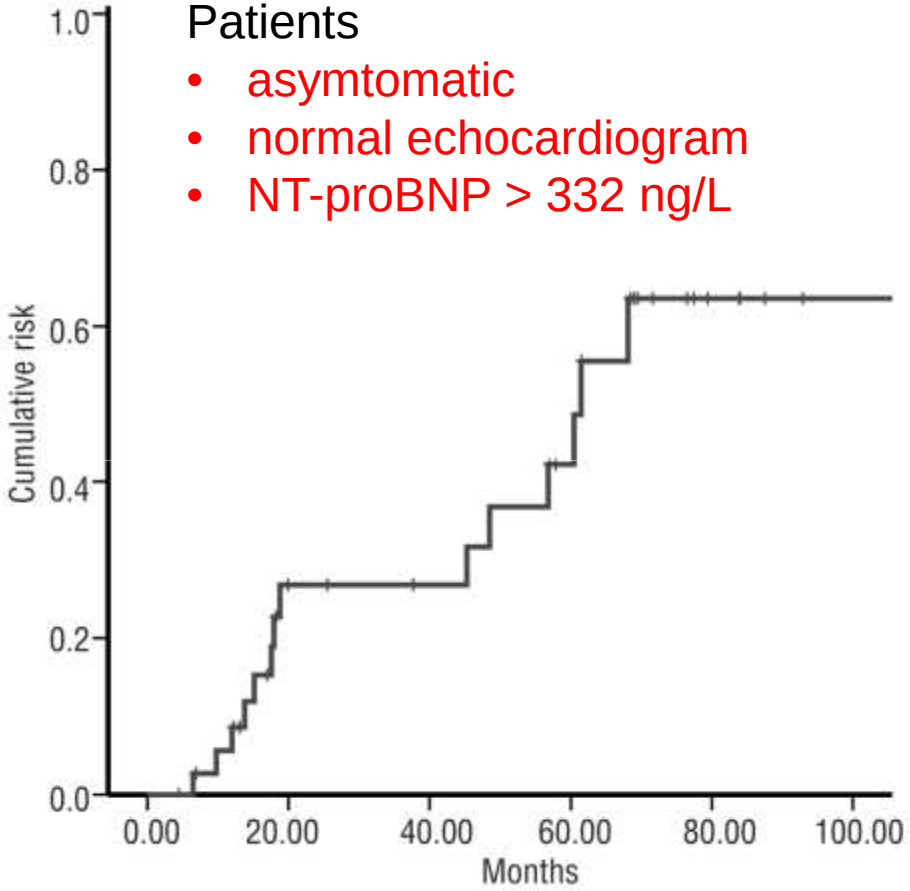


Diagnostic sensitivity: 100%

Palladini et al Circulation 2003;107:2440-5

Patients

- asymtomatic
- normal echocardiogram
- NT-proBNP > 332 ng/L



Risk for development of cardiac amyloidosis by International Consensus Criteria

Wechalekar et al Haematologica 2011;96:1079-80

Early detection of end-organ damage in AL amyloidosis

50% with complete Ig→70% preceded by MGUS with abnormal FLC ratio lasting a median of 4 years

Subjects with intermediate- and high-risk MGUS **with abnormal FLC ratio should be followed annually for life:**

- should be monitored to early detect cardiac and renal damage caused by **amyloid** light chain by measuring:
  - **NT-pro-BNP or BNP**
  - urine albumin at MGUS presentation and at each follow-up visit

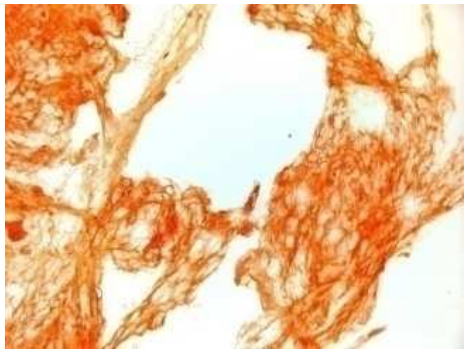
If these tests are positive a procedure to **diagnose AL amyloidosis**[1] should be promptly pursued including:

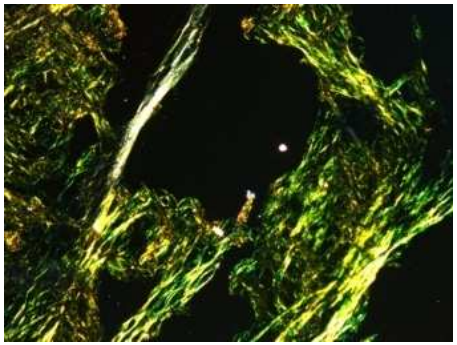
1. detecting and typing amyloid deposits
2. assessing the monoclonal disease
3. risk stratification/staging

[1]*Merlini G, Seldin DC, Gertz MA. J Clin Oncol 2011;29:1924-33*

Proving systemic amyloid deposition

Diagnosis of amyloidosis relies on Congo red staining of tissue biopsy





Luminescent conjugated polymers*

Tissue of choice: **abdominal fat**

sensitivity 88% + BM biopsy 95% specificity 97%

If negative

Biopsy of the labial minor **salivary glands** (sensitivity in patients with negative fat aspirate: 58%, NPV 91%)

If negative

Biopsy of the **involved organ** (kidney, liver, heart): beware of the hemorrhagic risk

Sipe et al, *Amyloid. 2012;19:167-170* – *Nilsson et al, *Am J Pathol*. *2010;176:563-574.*

Typing of amyloidosis is essential for the choice of therapy

Amyloid type	Organ involvement					
	Heart	Kidney	Liver	PNS	ANS	Soft tiss.
AL amyloidosis	++	++	+	+	+	+
Hereditary ATTR amyloidosis	++	±	-	++	+	(+)
Hereditary AApoAI amyloidosis	++	+	++	-	-	-
AA (reactive) amyloidosis	±	++	+	-	+	-
Senile systemic amyl. (wtTTR) median age 62, similar to MGUS	++	-	-	-	-	-

- Up to 10% of patients with hereditary amyloidosis have a monoclonal gammopathy
- 21% of patients with SSA have a monoclonal gammopathy

Palladini & Merlini, Eur J Int Med 2013; Comenzo et al, Blood. 2006;107:3489-91; Lachmann et al, N Engl J Med. 2002;346:1786-9

Typing of amyloidosis is essential for the choice of therapy

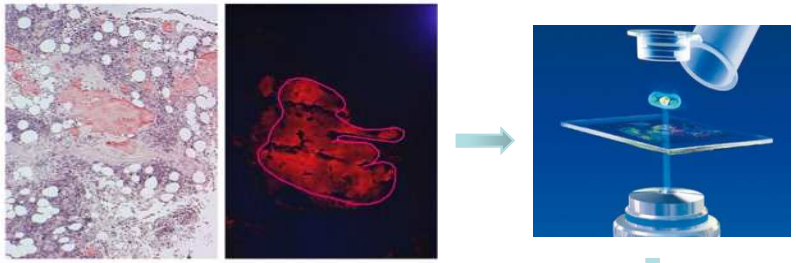
- mass spectrometry (the current gold standard)
- immuno-electronmicroscopy (99.5% specificity on 745 abdominal fat biopsies*)
- immunohistochemistry in specialized laboratories
- DNA analysis for hereditary amyloidosis

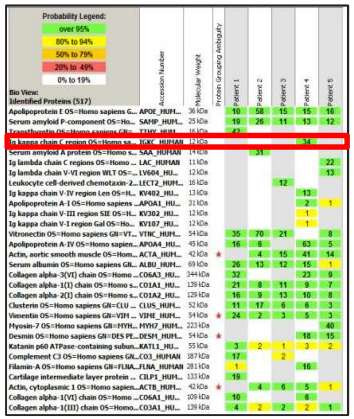
Vrana et al, *Blood 2009;114:4957-9*; Brambilla et al, *Blood 2012;119:1844-7;* Arbustini et al, *Amyloid 1997;4:157-70;* Schoenland et al, *Blood 2012;119:488-93;** Fernández de Larrea et al, *2013*

Amyloid typing by proteomics

Coupling proteomics with histology: analysis of laser-dissected amyloid

Vrana et al, *Blood 2009;114:4957-9*





Proteins contained in the amyloid deposits are specifically analyzed

Analysis of intact (abdominal fat) tissue: MudPIT approach

Brambilla et al, *Blood. 2012;119:1844-7*

Protein extraction and digestion

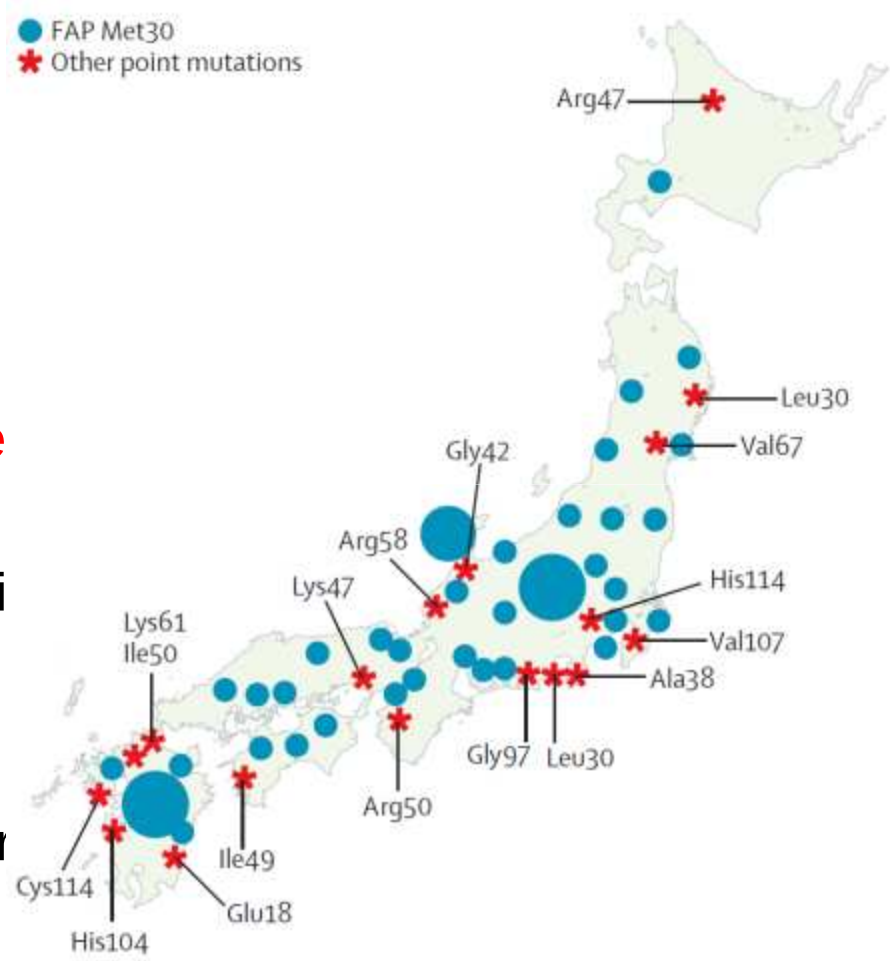
2D chromatography, LC-MS/MS

Identification of amyloid based on (semi)quantitative evaluation

Case	IEM-confirmed diagnosis	IgLCk*	IgLCλ*	TTR	SAA
P6	ALA	13	212	6	6
P11		6	165	4	0
P2		0	130	0	0
P1		0	88	0	0
P9		13	61	9	0
P12		8	50	0	0
P13		14	34	0	0
P8		7	33	0	0
P4		0	22	0	0
P3		0	21	0	0
P5		0	13	0	0
P10		0	6	0	0
P15	ALK	372	0	0	0
P14		176	0	0	0
P25		44	0	0	0
P26		14	0	0	0
P19	ATTR	4	0	1158	0
P20		0	0	185	0
P18		4	0	145	0
P16		0	0	89	0
P7		4	0	16	0
P22	SAA	0	0	0	638
P23		0	0	0	261
P17		10	0	0	166
P24		0	0	0	93
P21		0	0	0	71

Gene sequencing is needed when familial amyloidosis is a possibility

- isolated neuropathic or cardiac disease → transthyretin
- isolated renal involvement → fibrinoge
- renal/liver/cardiac involvement in relati →apolipoprotein-A1
- dry mouth/gastro-intestinal/kidney/liver
- corneal lattice dystrophy, progressive bilateral facial paralysis and cutis laxa →gelsolin



Araki & Ando *Proc Jpn Acad Ser B Phys Biol Sci* 2010; 86: 694–97.

RISK STRATIFICATION

VOLUME 22 · NUMBER 18 · SEPTEMBER 15 2004

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Serum Cardiac Troponins and N-Terminal Pro-Brain Natriuretic Peptide: A Staging System for Primary Systemic Amyloidosis

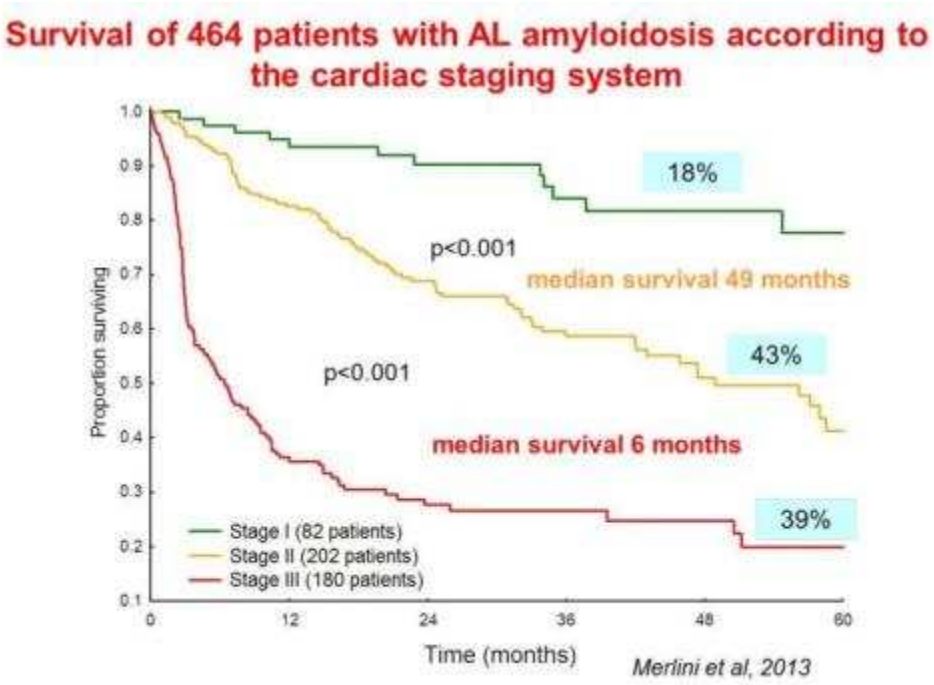
Angela Dispenzieri, Morie A. Gertz, Robert A. Kyle, Martha Q. Lacy, Mary F. Burritt, Terry M. Therneau, Philip R. Greipp, Thomas E. Witzig, John A. Lust, S. Vincent Rajkumar, Rafael Fonseca, Steven R. Zeldenrust, Christopher G.A. McGregor, and Allan S. Jaffe

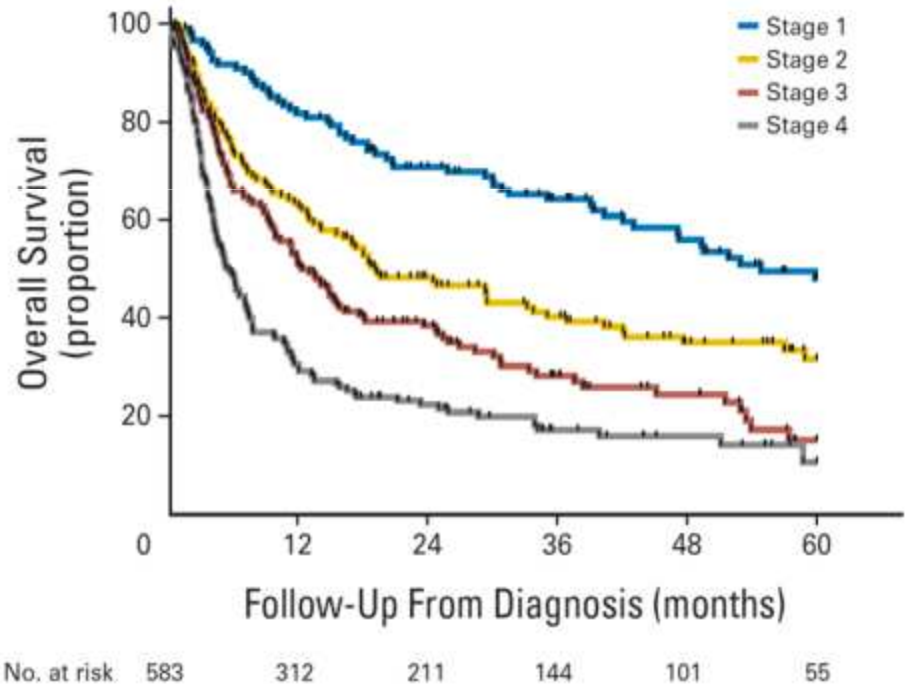
VOLUME 30 · NUMBER 9 · MARCH 20 2012

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Revised Prognostic Staging System for Light Chain Amyloidosis Incorporating Cardiac Biomarkers and Serum Free Light Chain Measurements

Shaji Kumar, Angela Dispenzieri, Martha Q. Lacy, Suzanne R. Hayman, Francis K. Buadi, Colin Colby, Kristina Laumann, Steve R. Zeldenrust, Nelson Leung, David Dingli, Philip R. Greipp, John A. Lust, Stephen J. Russell, Robert A. Kyle, S. Vincent Rajkumar, and Morie A. Gertz





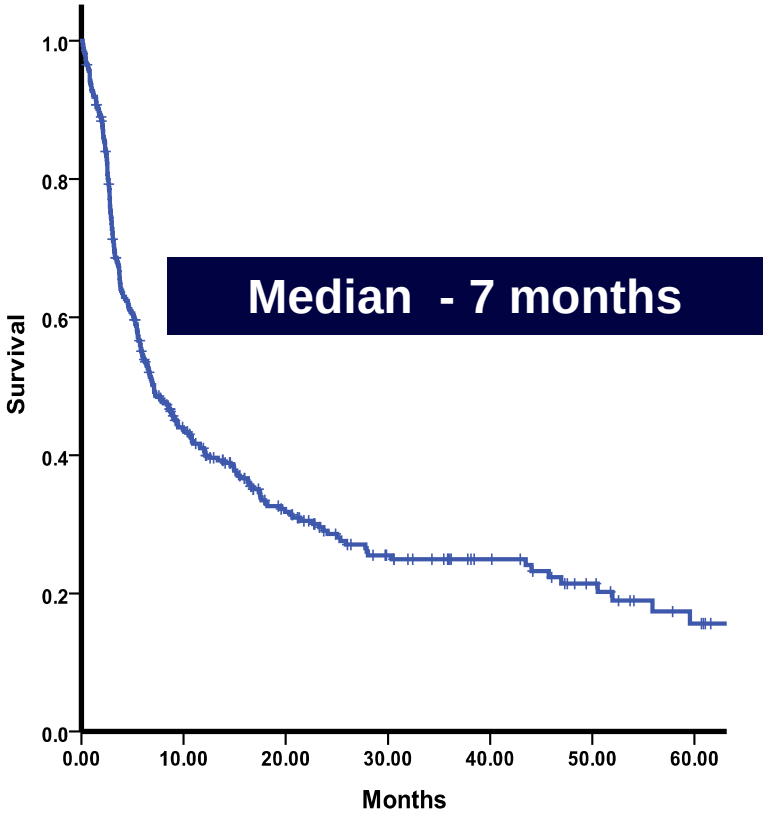
Two main prognostic determinants:

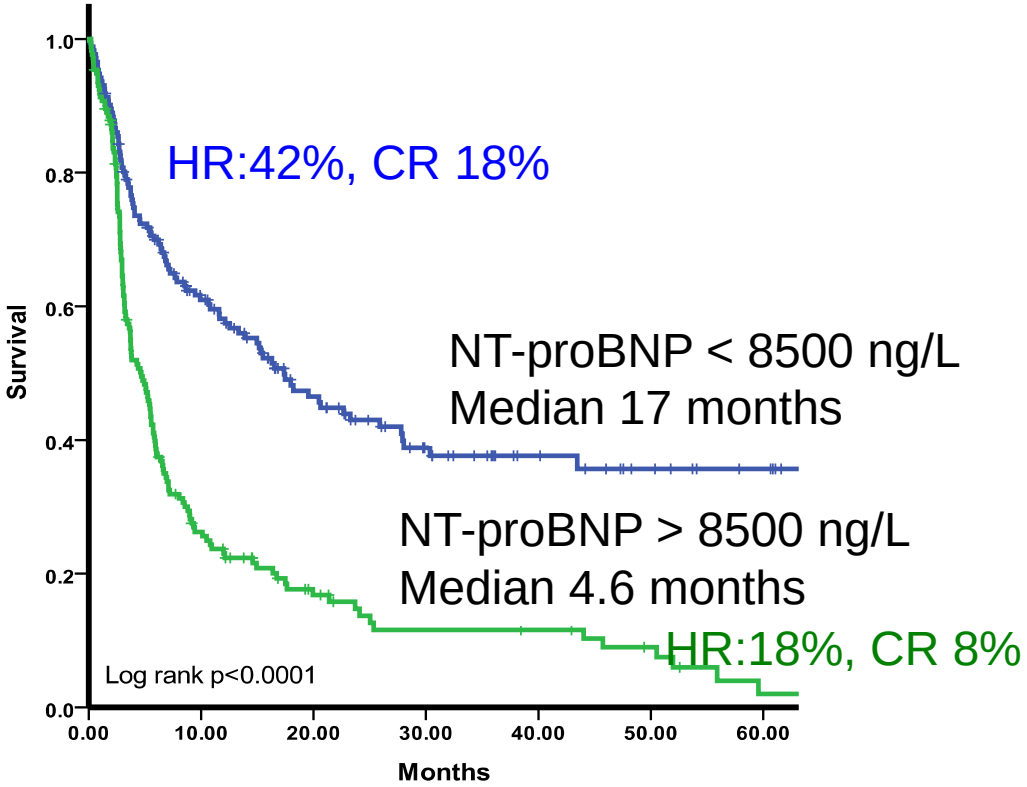
- FLC burden
- Severity of heart involvement

A European collaborative study of treatment outcomes in 346 Patients with Stage III AL amyloidosis

Wechalekar AD, Schonland SO Kastritis E, Gillmore JD, Dimopoulos M, Venner C, Lane T, Foli A, Foard D, Milani P, Rannigan L, Hegenbart U, Hawkins PN, Merlini G and Palladini G

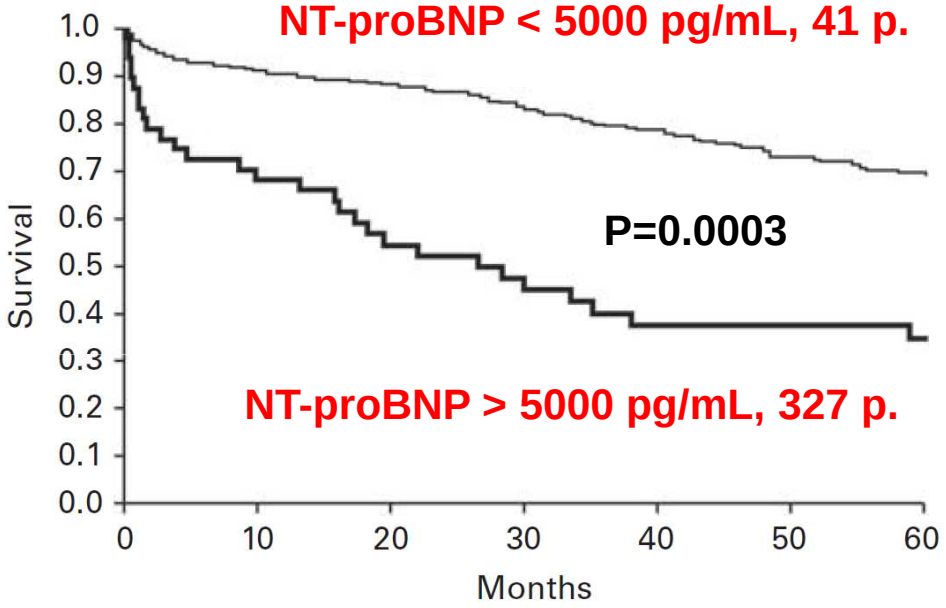
Blood, 2013

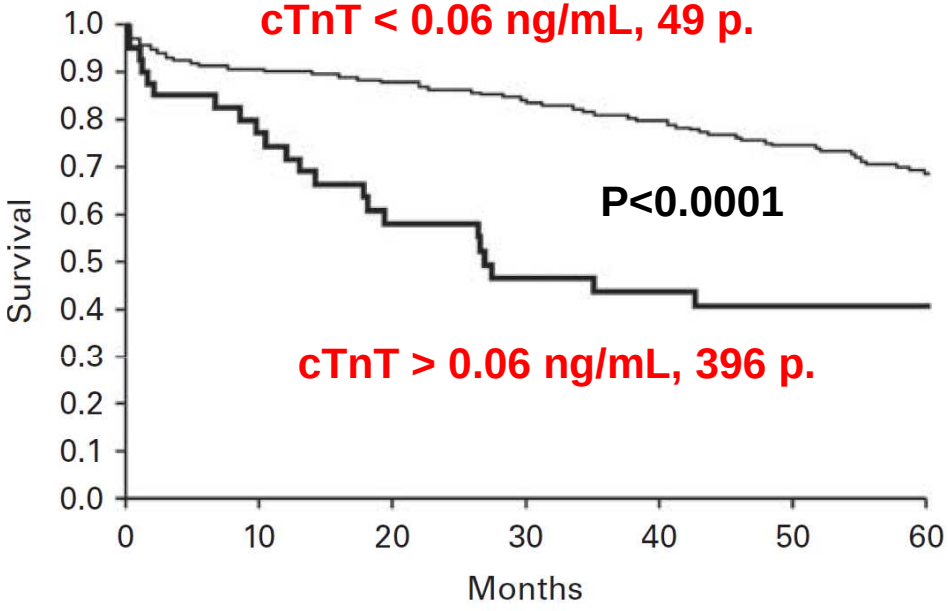




Refinement in patient selection to reduce treatment-related mortality from SCT in amyloidosis

Gertz et al, *Bone Marrow Transplant. 2012 Sep 10 [Epub ahead of print]*





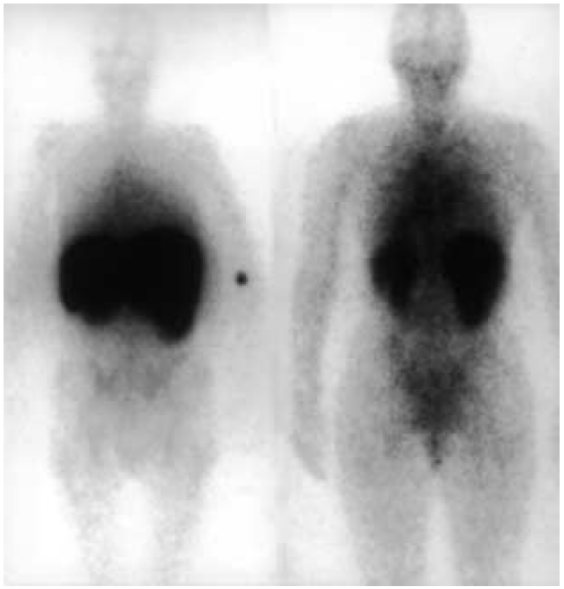
Patients with serum troponin T >0.06 ng/mL or NT-proBNP >5000 pg/mL (not on dialysis) **should not** be considered candidates for SCT because of early mortality.

IMAGING OF AL AMYLOIDOSIS

Monitoring amyloid load - SAP scan

Lachmann et al, Br. J. Haematol, 2003, 122:78–84

Amyloid load assessed by I^{123}-SAP labelled scintigraphy

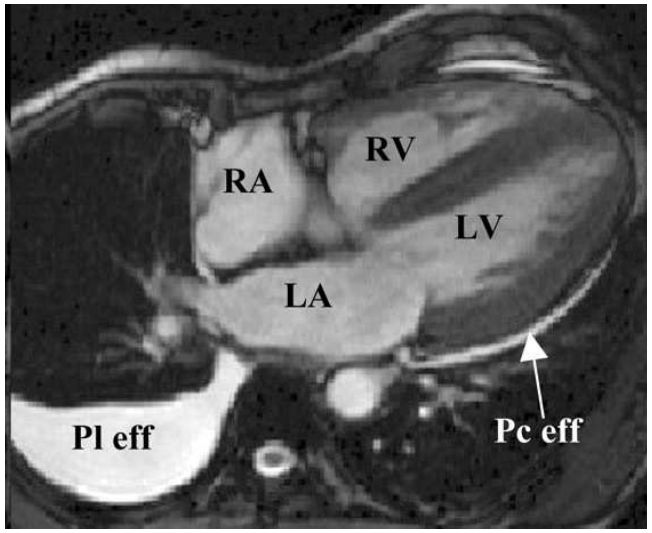


Limited availability outside UK,
cannot image the heart

Ecocardiografic evaluation of longitudinal left ventricular function

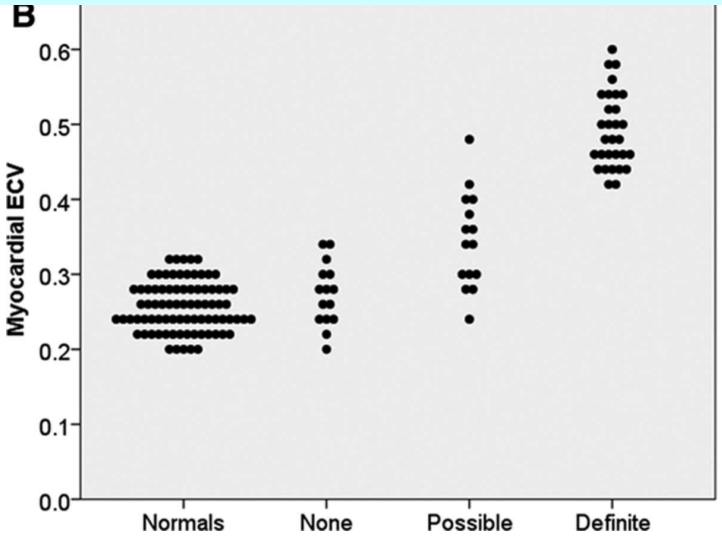
Buss et al, JACC 2012

Cardiac MR



Maceira et al, Circulation 2005

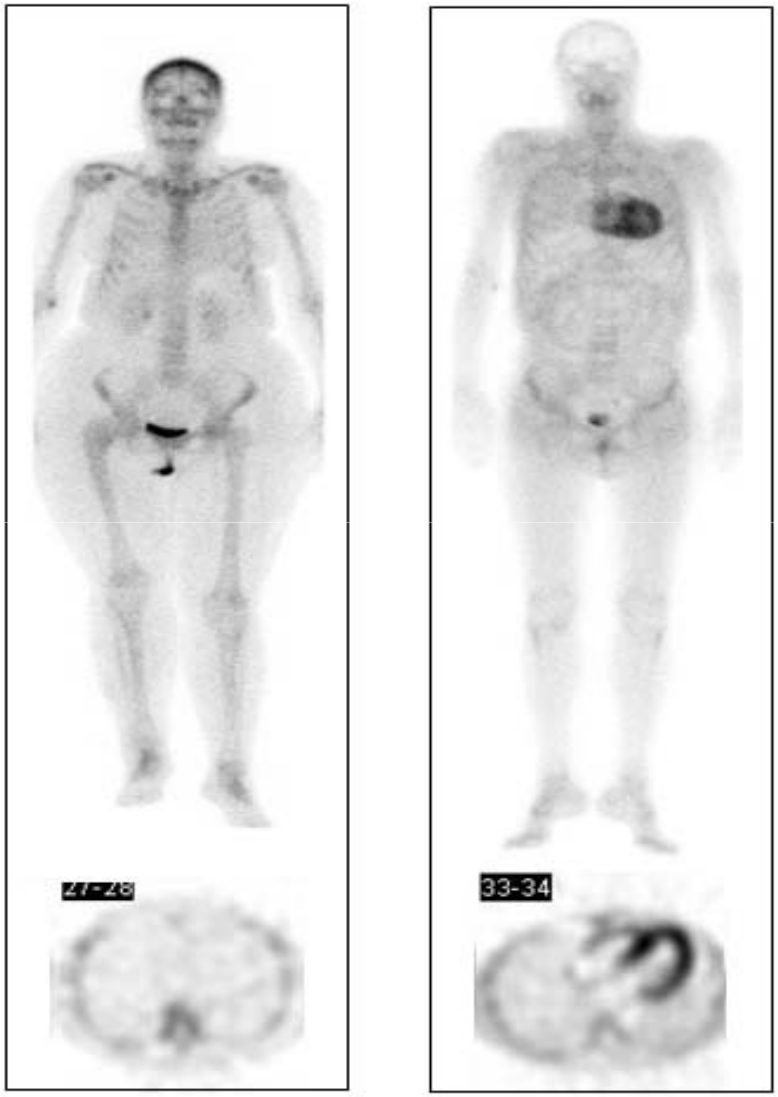
Quantification of **Myocardial Extracellular Volume** by Equilibrium Contrast CMR

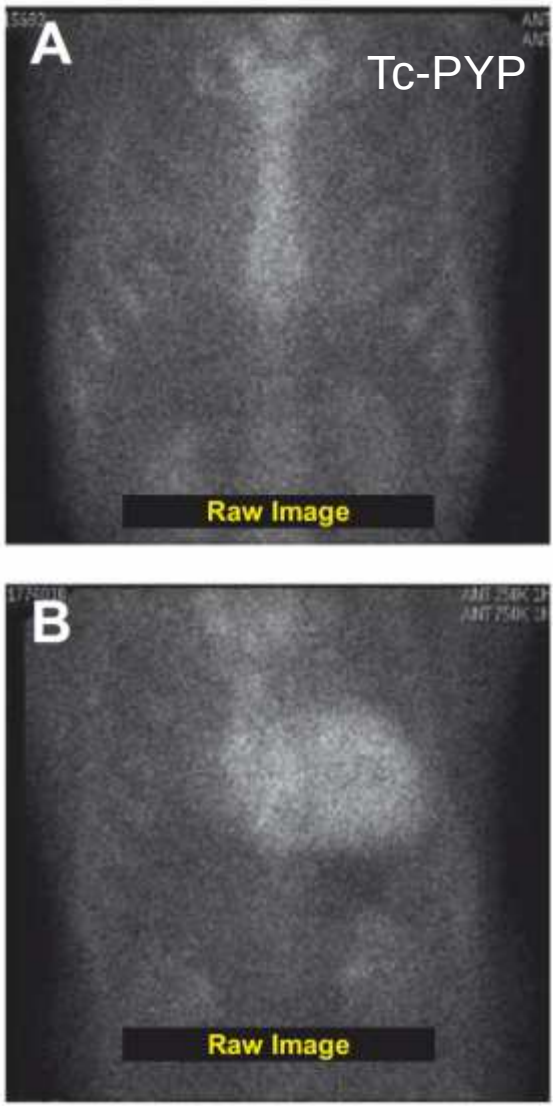


Banypersad et al. Circ Cardiovasc Img 2013

TcDPD and Tc-PYP scintigraphy

AL TcDPD ATTR



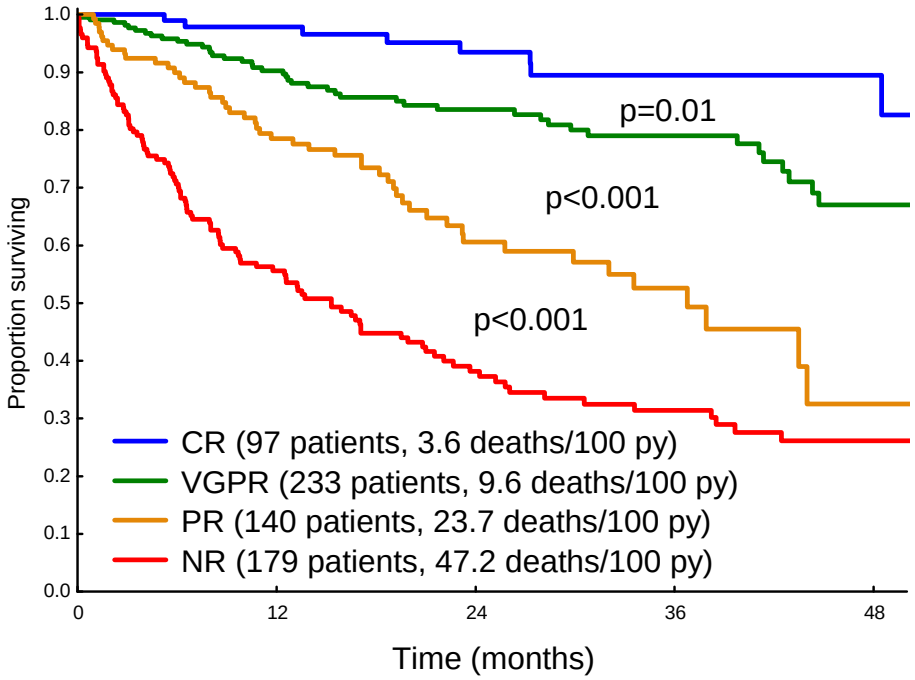


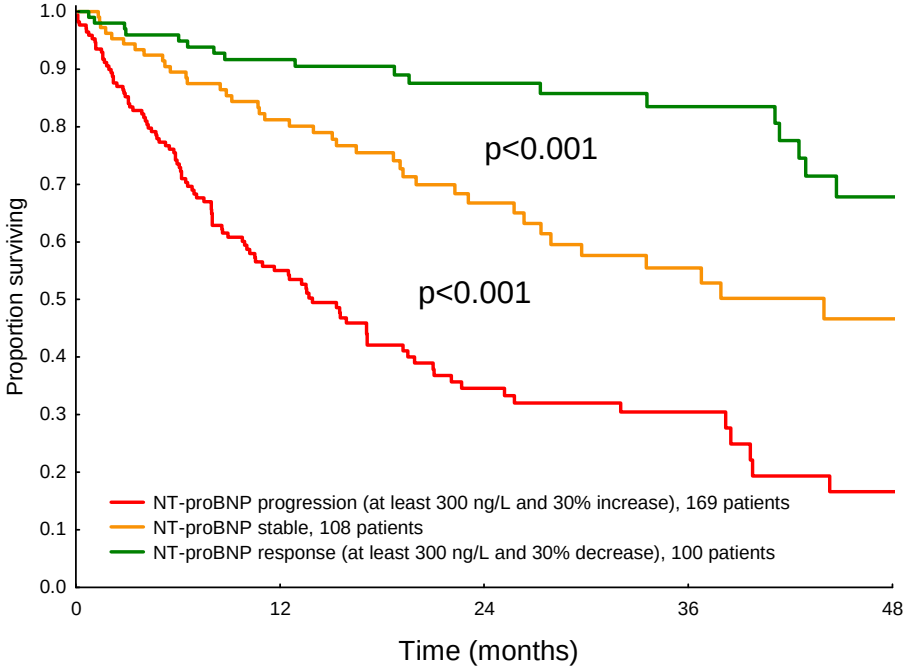
Rapezzi et al, J Am Coll Cardiol Img 2011;4:659 –70

Bokhari et al, Circ Cardiov Img 2013;6:195-201

New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes.

Palladini et al, J Clin Oncol. 2012;30:4541-9





aCR	Negative s. & u.IFE, normal FLR
VGPR	dFLC <40 mg/L
PR	dFLC decrease ≥50%
NR	other

Renal insufficiency and IMiDs may alter NT-proBNP metabolism

New cardiac response criteria

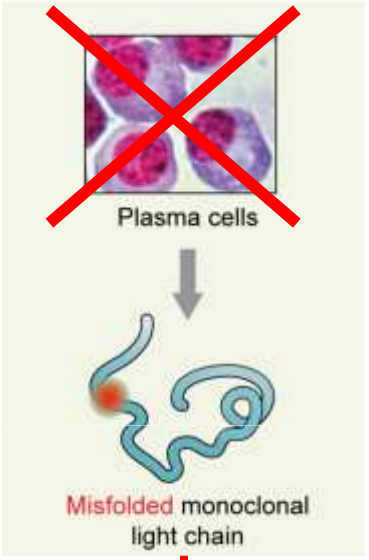
- reduction (>30% and >300 ng/L) of NT-proBNP

Organ response can be delayed

Depth of the response is the leading indicator of durability of treatment benefits

AL AMYLOIDOSIS: THERAPY

AL amyloidosis



Cardiac damage

Reduced survival

Clonal, hematologic response

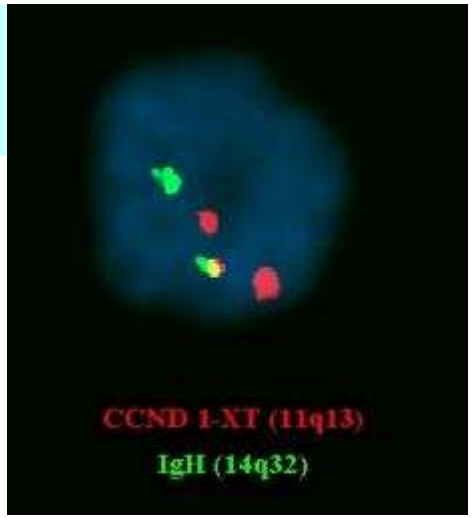
Organ (cardiac) response

Improved survival

Toxicity monitoring and management

Therapy is highly individualized and must be risk-adapted based on cardiac biomarkers and response-tailored

Amyloid plasma cell clone



- Low plasma cell burden (median 5-7%) and low proliferative rate
- High frequency of t(11;14) translocation (~40-50%)
  → Cyclin D1 upregulation
- Low frequency of *t(4;14)* (4%) and deletion of *17p13* (2%)
- Low frequency of hyperdiploidy (11%)

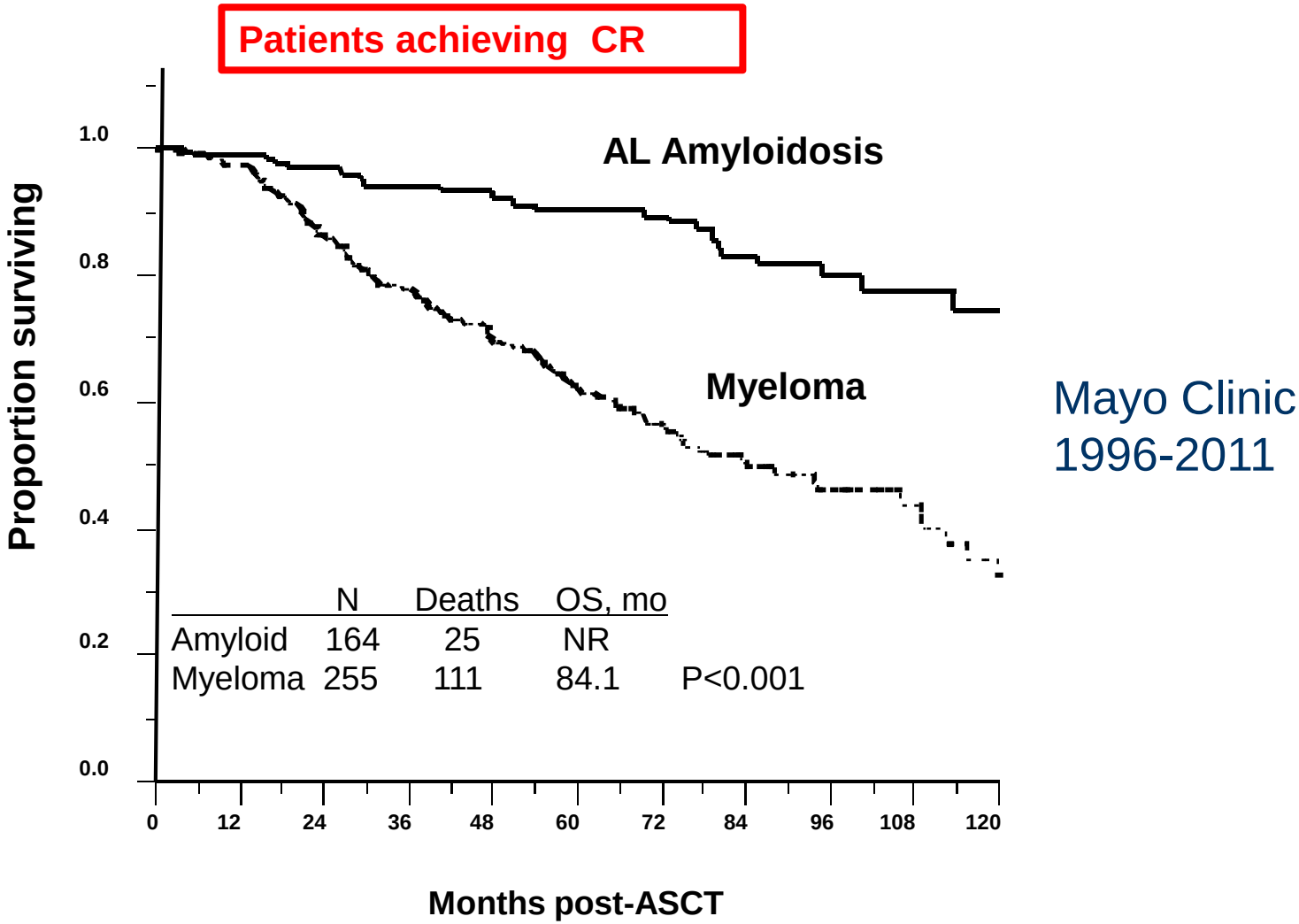
"AL represents a particular early stage of monoclonal gammopathy"
Bochtler et al, *Blood* 2011;117:3809-15

- Patients with AL have superior outcomes than patients with MM after ASCT

Gertz et al, Blood 1989;74:1108-11 - Fonseca et al, Br J Haematol 1998;103:704-10 - Hayman et al, Blood. 2001;98:2266-68 - Harrison et al, Br J Haematol 2002;117:427-35 - Abraham et al, Blood 2005;105:794-803 – Bochtler et al, Blood 2008;111:4700-5 - Bryce et al, Haematologica 2009;94:380-6 - Bochtler et al, Blood 2011;117:3809-15 – Zhou et al, Clin Lymph Myel Leuk 2012;12:49-58

Patients with immunoglobulin light chain amyloidosis (AL) undergoing high dose chemotherapy with autologous stem cell transplantation (ASCT) have superior outcomes as compared to patients with multiple myeloma

Seenithamby et al, ASH 2012 Abstr. 600



Mayo Clinic
1996-2011

Current treatment options for AL amyloidosis
Autologous stem cell transplantation

Regimen	N	HR (CR)	Org. Resp.	100-day mortality	PFS / OS (y)
ASCT *Cibeira et al 2011*	421	MEL200 (43%) MEL140 (24%)	53%	9% 14%	CR 8.3/13.2 3.4 / 8.4 1.8 / 3.8
ASCT *Gertz et al 2010*	434	76% (39%)	47%	10%	CR - / not r. PR - / 8.9 NR - / 2.7
Risk-adapted ASCT +adj. BDex *Landau et al 2012*	40	79% (58%)	70%	ASCT 10% BDex 4%	@2y 69% / 82%
MDex vs ASCT *Jaccard et al, 2007, 2010*	43 37	68% (32%) 67%(41%)	39% 45%	2% 24%	TTP 2.7/OS 4.7 TTP 2.7/OS 1.8

Current treatment options for AL amyloidosis
Conventional chemotherapy

Regimen	HR (CR)	Org. Resp.	Common SAEs	100-day mortality	PFS / OS (y)
MDex *Palladini 2004*	67% (33%)	48%	Overall 11%	4%	3.8 / 5.1

Current treatment options for AL amyloidosis
IMiDs-based therapy and other agents

Regimen	No (front-l)	HR (CR)	Org. Rsp	Common SAEs	100-d mortal.	PFS / OS (y)
CTD *Wechalekar 2007*	75 (41%)	74% (21%)	27%	Sedation 40% Fluid retent. 21%	4%	1.7 / 3.4
LDex[+] *Dispenzieri 2007*	22 (41%)	41%	23%	Overall 86% Neutropenia 45%	18%	1.6 / -
CLD[#] *Kumar 2012*	35 (11%)	60% (11%)	31%	Overall 74% Neutropenia 40%	9%	2.4 / 3.1
MLD *Moreau 2010*	26 (100%)	58% (23%)*	50%	Overall 81% Neutropenia 11%	-	@2y 54% / 81%
PomDex *Dispenzieri 2012*	33 (0)	48% (3%)	15%	Neutropenia 30%	3%	1.2 / 2.3
BendaDex *Palladini 2012 ASH*	36 (14%)	47% (3%)	17%	Overall 33% Neutropenia 17%	5%	@3y -/65%

[+]also Sanchorawala et al, Blood 2007;109:492-6; [#]also Kastritis et al, Blood. 2012;119: 5384-90
**(42% with full-dose L)*

Current treatment options for AL amyloidosis
Proteasome inhibitor-based therapy

Regimen	No (front-l)	HR (CR)	Org. Rsp	Common SAEs	100-d mortal	PFS / OS (y)
Bortez *Reece 2011*	70 (0)	68%§ (29%)	29% K 13% H	Fatigue, Thrombcytpn Vomiting Diarrhea	3%	@1y 74%/93%
BDex *Kastritis 2010*	94 (19%)	71% (25%)	30%	PN Edema Orthost. hyp.	3%	2/@1y 76%
CyBorD* *Venner 2012*	43 (47%)	81% (65% fl)	46%	19% discontinued (PN in 14%)	0	@2y 53% / 98%
Ixazomib *Merlini 2012***	20 (0)	55% (10%)	30% H	Diarrhea Fatigue Thrombcytpn	5%	-/ -

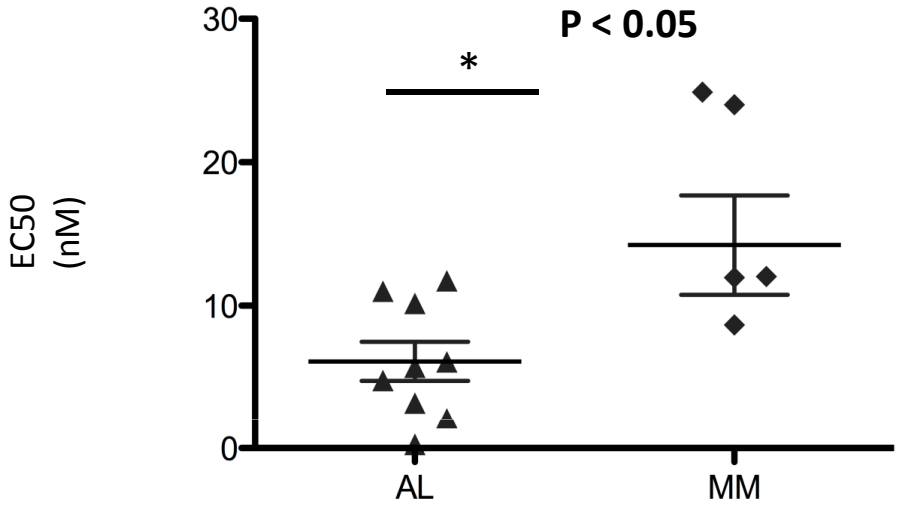
*also *Mikhael et al, Blood 2012; 119:4391-4 : ** also Sanchorawala IMW2013 P-229*

§Median times to first and best HR: 2.1 and 3.2 months in the 1.6 mg/m^2 QW group, and 0.7 and 1.2 months in the 1.3 mg/m^2 BW group

Electron microscopy and functional studies reveal cellular stress in amyloidogenic plasma cells

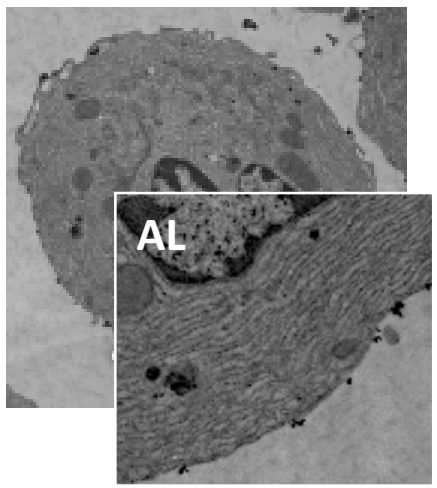
Oliva et al, IMW 2013 P-458

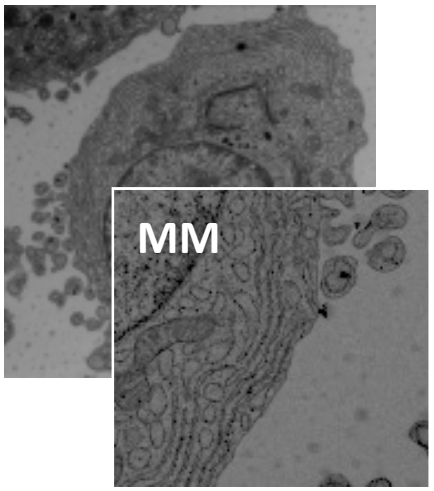
Apoptotic sensitivity to bortezomib

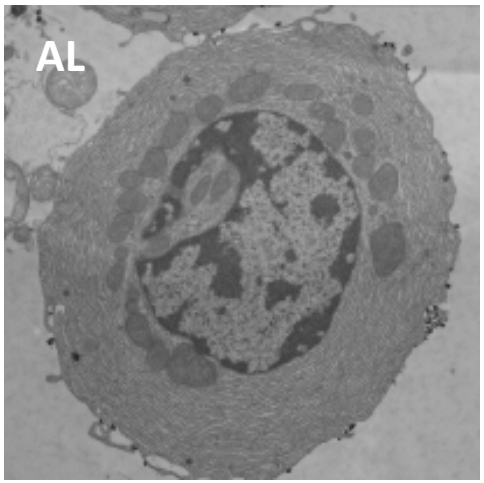


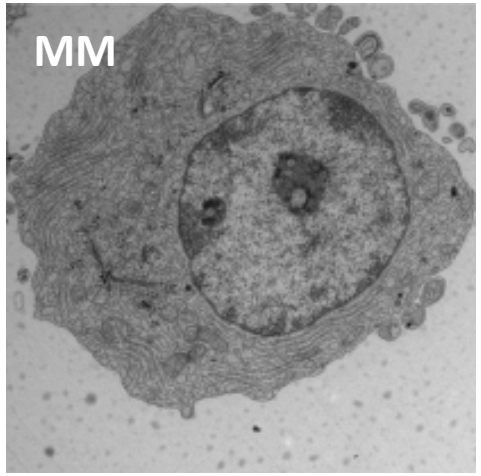
Primary AL cells are 2-3 times more sensitive to bortezomib than myeloma cells

AL PCs are more stressed than MM PCs, with more expanded ER ($p<0.0001$) and more perinuclear mitochondria ($p = 0.0007$)









Risk-adapted front line treatment of AL

Excellent PS,
Limited organ involvement,
Good renal function,
Troponin-T <0.06 ng/ml and
NTproBNP <5000 ng/L
15-20% of patients

↓

"Low Risk"
Consider ASCT with HDM (Mel 200 mg/m^2) or dose attenuated HDM-ASCT with bortezomib consolidation

Reasonable PS,
NT-proBNP <8500 ng/L
~60% of patients

↓

"Intermediate Risk"
Combination, response-tailored chemotherapy
MDex
or CTD
(CyBorD, BMDex)*

NT-proBNP >8500 ng/L
15-20% of patients

↓

"High Risk"
Cautious chemotherapy with dose-attenuated combinations of Bor with synergistic mechanisms and close monitoring

Patients should be treated within controlled clinical trials

** Milani et al, IMW2013 P-459*

Management of AL amyloidosis in 2013

- Treatment endpoint: at least VGPR
- Hematologic and cardiac response should be assessed frequently, every 1-2 cycles (or three months after ASCT)
- **Rapid switch if no response**
- Therapy can be continued for 1-2 cycles beyond best response for consolidation

Management of AL amyloidosis in 2013

Supportive therapy

- multidisciplinary (nephrologist, cardiologist) monitoring

  - kidney transplantation
    - age < 65 yrs, no heart or liver involvement,
    - complete response usually required

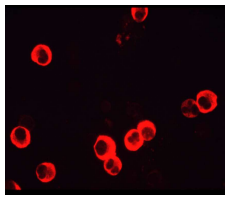
  - heart transplantation
    - age < 65 yrs
    - at high cardiac risk
    - without significant extra-cardiac amyloidosis

Best tolerated treatment should start immediately at diagnosis and after OHT while waiting for possible ASCT

- left ventricular assist device, experience in 9 patients: it is technically feasible, but poor outcomes and high morbidity*

*Casserly et al, Kidney Int 2003;63:1051–7; Dey et al, Transplantation 2010; 90:905-11; Sattianayagam et al, Am J Transplant 2010;10:2124-31; Herrmann et al, Nephrol Dial Transplant 2011;26:2032–6; Pinney et al, Am J Transplant. 2013;13:433-41; Kristen et al, Eur J Heart Fail 2009; 11:1014-20; Lacy et al,; J Heart Lung Transplant 2008; 27:823-9; Mignot et al. Arch Cardiovasc Dis. 2008;101:523-32.; * Swiecicki et al, J Heart Lung Transplant. 2013 Mar 5.*

Treatment of cardiac AL amyloidosis: Perspectives

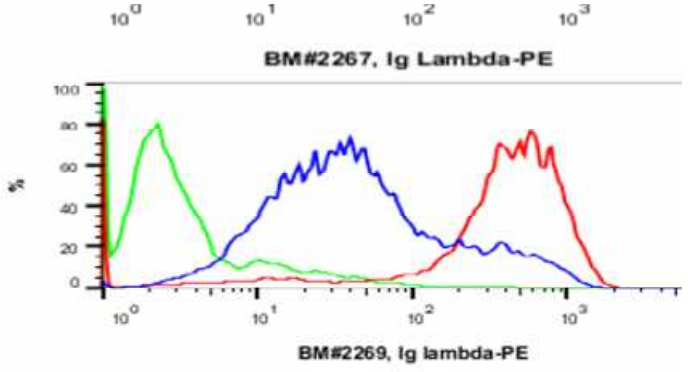


Novel agents and combinations with synergistic mechanisms of action

Drug targeting the amyloid deposits in combination with cytotoxic therapy may accelerate recovery of cardiac function

Bone marrow PC

siRNA inhibiting LC synthesis[1,2]



Cardiac fibroblasts

Cardiomyocytes toxicity

GAG mimetics[4]

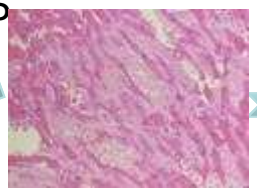
GAGs

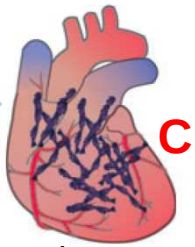
CPHPC[5]

SAP

Anti-SAP MoAb[6]
Anti-amyloid MoAb[7]
Doxycycline[8]

Inhibitors of proteotoxicity
EGCG[3], novel agents





CHF

[1]Hovey et al, Gene Ther. 2011;12: 1150-6; [2]Zhou et al, Personal comm.; [3]ClinicalTrials.gov NCT01511263; [4]Dember et al, N Engl J Med. 2007;356:2349-60;5 [5]Pepys et al, Nature 2002;417:254–259;[6]Bodin et al, Nature. 2010;468:93-7; [7]Wall et al, PLoS One. 2012;7:e52686. [8]Ward et al, Blood. 2011 ;118:6610-7

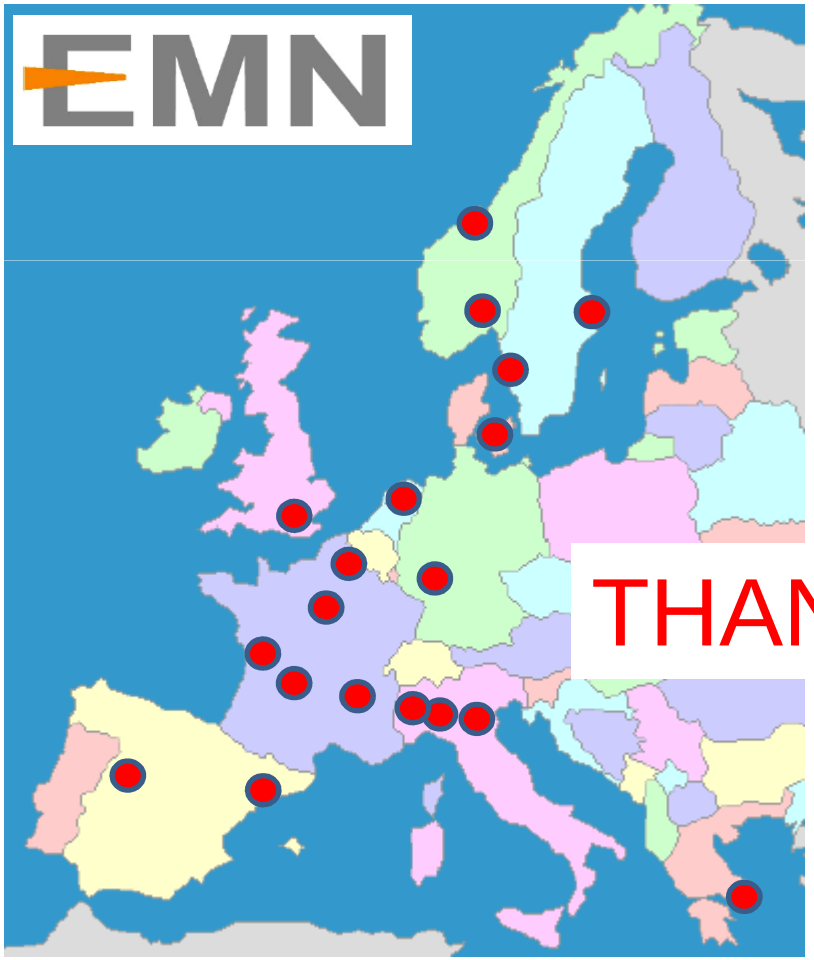
Conclusions

- Earlier diagnosis remains the keystone for improving the care of AL amyloidosis:
  - Routine adoption of checking NT-proBNP levels and urine albumin during monitoring of patients with MGUS may help early diagnosis
- Therapy is highly individualized and must be risk-adapted and response-tailored
- Novel therapeutic approaches are needed for patients with advanced amyloid cardiomyopathy

Phase III trials necessary through international collaboration:
EMN-03 European Network and Centers in Australia for Phase III trial comparing MDex vs BortezMDex

Acknowledgements

European Network - EMN-03 Phase III trial comparing MDex vs BortezMDex



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THANK YOU !

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