Management of AL amyloidosis in 2011

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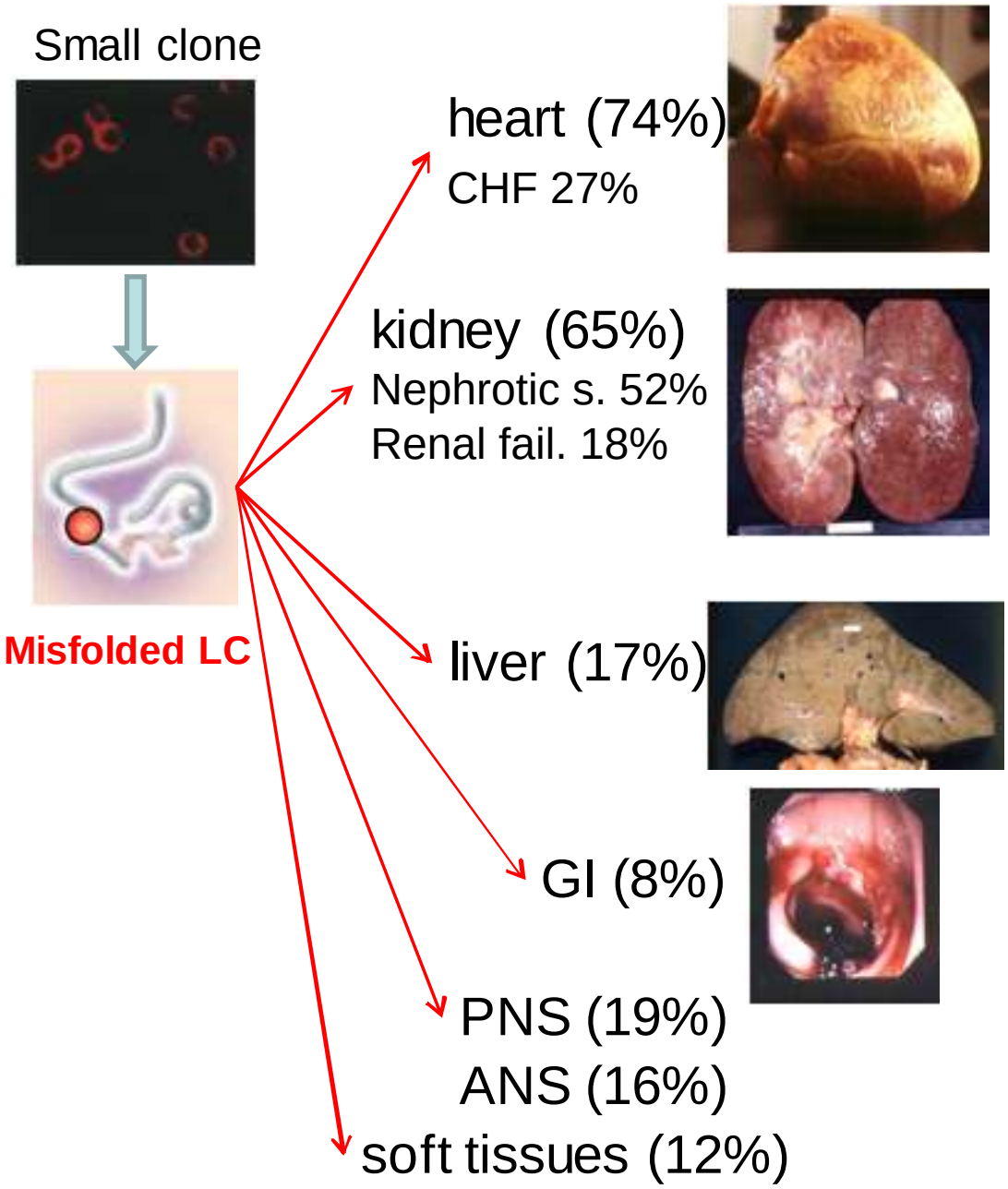
Disclosures

Honoraria:

Millennium, Novartis Diagnostics, Janssen

Systemic AL Amyloidosis: 8.9/million person-year



Management of AL amyloidosis in 2011

- AL amyloidosis is characterized by progressive damage of vital organs
- Patients are fragile and particularly sensitive to the toxic effects of chemotherapy
- Survival is determined by cardiac dysfunction and reduction of the FLC burden

Management of AL amyloidosis in 2011

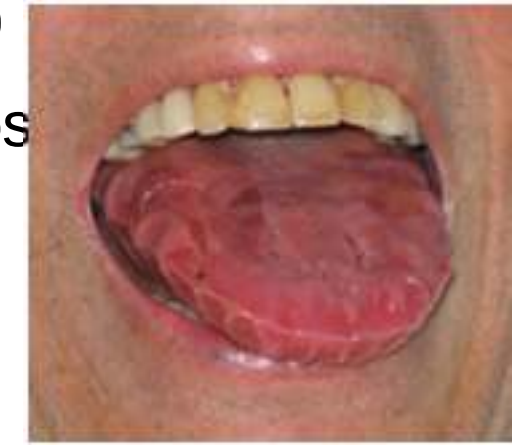
Early diagnosis: anticipate irreversible organ damage

DIAGNOSING AMYLOIDOSIS

Early red flags:

- increased levels of cardiac biomarkers (NT-proBNP) (monitor NT-proBNP in patients with MGUS)
- urinary albumin > 300 mg/g creatinine
- hepatomegaly or alkaline phosphatase elevation
- progressive peripheral neuropathy
- orthostatic hypotension, autonomic neuropathy (persistent diarrhea/constipation, impotence)
- profound fatigue and unexplained weight los

Periorbital purpura 11%



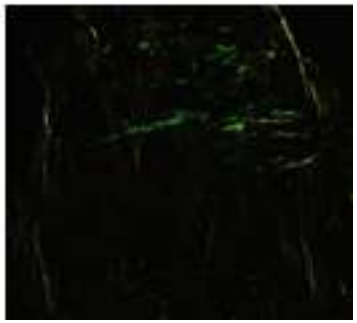
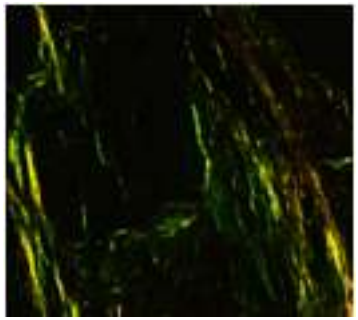
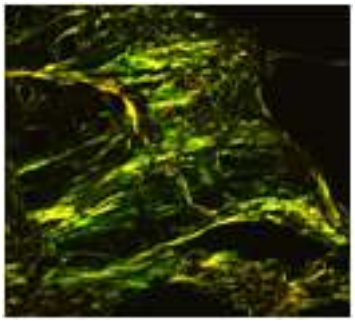
Macroglossia 14%

Diagnosis of amyloidosis relies on tissue biopsy

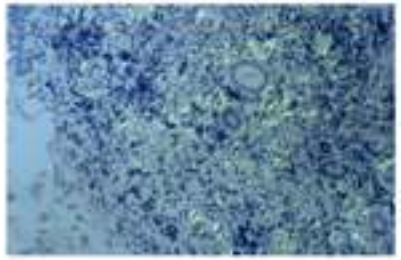
IFix of serum and urine + serum FLC

Obtain fat and bone marrow specimens for Congo red staining
Sensitivity ~ 90%

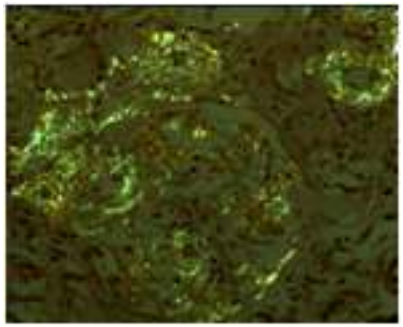


Biopsy of the labial minor salivary glands



Biopsy of the organ involved
(beware of the hemorrhagic risk)



The most common types of systemic amyloidoses

Type (abbreviation)	Precursor (site of synthesis)	Organs involved				
		Heart	Kidney	Liver/ GI	PNS/ ANS	Soft Tissue
Immunoglobulin LC amyloidosis (AL)	Monoclonal LC (BM plasma cells)	X	X	X	X	X
Reactive amyloidosis (AA)	SAA1 (liver)	(X)	X	X	X_{ANS}	
Senile systemic amyloidosis (SSA)	Transthyretin wild type (liver >90%)	X				
Transthyretin amyloidosis (ATTR)	Variant transthyretin, (liver >90%)	X	(X)		X	(X)
Fibrinogen amyloidosis (AFib)	Variant fibrinogen α-chain (liver)		X			
Apolipoprotein AI amyloidosis (AApoA-1)	Variant Apo A-1 (liver, intestine)	X	X	X	(X)	

Clinically, it is difficult to distinguish between the various types of amyloidosis:
MGUS coincidental with hereditary and senile amyloidosis in the elderly

The most common types of systemic amyloidoses

Type (abbreviation)	Precursor (site of synthesis)	Established Therapy
Immunoglobulin LC amyloidosis (AL)	Monoclonal LC (BM plasma cells)	**Chemotherapy** **ASCT** **novel agents**
Reactive amyloidosis (AA)	SAA1 (liver)	**Treat underlying diseases** **new drug**
amyloidosis (ATTR)	>100 amyloidogenic mutations (liver >90%)	**new drugs**
Fibrinogen amyloidosis (AFib)	Variant fibrinogen α-chain (liver)	**Organ transplantation**
Apolipoprotein AI amyloidosis (AApoA-1)	Variant Apo A-1 (liver, intestine)	**Organ transplantation** **Supportive**

Typing of amyloidosis is essential for the choice of therapy

Typing of amyloidosis

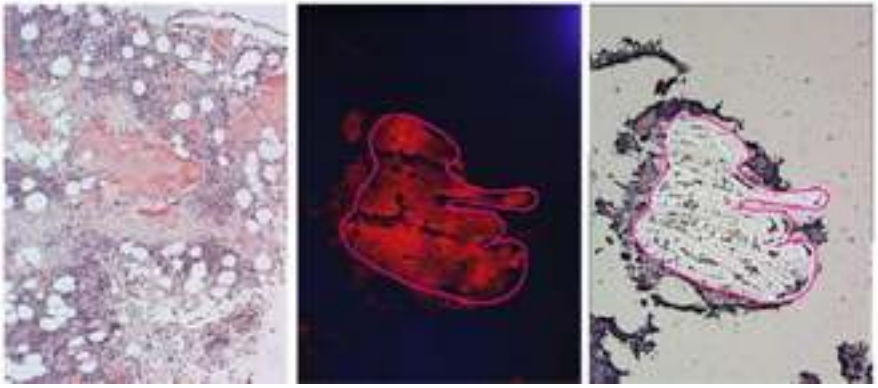
- Immunohistochemistry: unreliable in AL amyloidosis
- Electron microscopy + immunogold: reliable, limited by Ab availability

- MS based proteomics will become (is, Rome Symposium on Amyloidosis, 2010) the gold standard for classification of amyloidosis
  - When compared to immunohistochemistry, MS is
    - Objective-data driven
    - More specific
    - Reproducible
    - Open to further analysis: increase in disease knowledge

DNA analysis for hereditary amyloidosis

Classification of amyloidosis by laser microdissection and mass spectrometry–based proteomic analysis in clinical biopsy specimens

Vrana et al, Blood. 2009;114:4957-4959



#	Accession	MW	Control	1	2	3	4
1	ALBU_HUMAN	69 kDa		100% (36)	100% (35)	100% (36)	100% (35)
2	APOE_HUMAN	36 kDa		100% (19)	100% (17)	100% (18)	100% (17)
3	VTNC_HUMAN	54 kDa		100% (13)	100% (13)	100% (17)	100% (14)
4	KAC_HUMAN	12 kDa		100% (7)	100% (8)	100% (7)	100% (8)
5	APOA4_HUMAN	45 kDa		100% (15)	100% (19)	100% (17)	100% (13)
6	SAMP_HUMAN	25 kDa		100% (8)	100% (9)	100% (9)	100% (9)
7	C4BP_HUMAN	67 kDa		100% (11)	100% (10)	100% (12)	100% (10)
8	HBB_HUMAN	16 kDa		100% (4)	100% (8)	100% (9)	100% (7)
9	CLUS_HUMAN	52 kDa		100% (10)	100% (7)	100% (8)	100% (8)
10	CO6A3_HUMAN	344 kDa		100% (6)	100% (13)	100% (17)	100% (10)
11	APOA1_HUMAN	31 kDa		100% (7)	100% (5)	100% (9)	100% (7)
12	CO9_HUMAN	63 kDa		100% (5)	100% (5)	100% (5)	100% (7)
13	TRFE_HUMAN	77 kDa		100% (7)	100% (6)	100% (9)	100% (4)
14	HBA_HUMAN	15 kDa			100% (4)	100% (4)	100% (4)
15	CO3_HUMAN	187 kDa		100% (3)	100% (4)	100% (8)	100% (5)

Table 1. The results of MS-based proteomic analysis compared with th original gold standard diagnosis

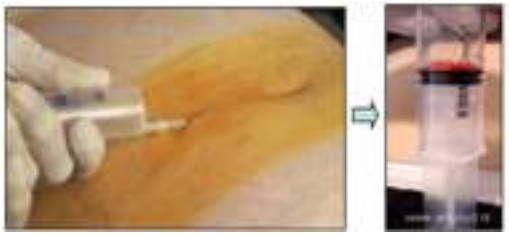
Case	Tissue	Original Diagnosis	MS Diagnosis	MS Analysis TTR	SAA	IGL	IGK
1	BM	AL-IGK	AL-IGK				
2	Lung		AL-IGK				
3	BM		AL-IGK				
4	Brain		AL-IGK				
5	Breast		AL-IGK				
6	Liver	AL-IGL	AL-IGL				
7	Heart		AL-IGL				
8	Intestine		AL-IGL				
9	Liver		AL-IGL				
10	Heart		AL-IGL				
11	BM		AL-IGL				
12	Brain		AL-IGL				
13	Brain		AL-IGL				
14	Heart		AL-IGL				
15	Lung		AL-IGL				
16	BM		AL-IGL				
17	Omentum		AL-IGL				
18	Lymph node		AL-IGL				
19	Lung		AL-IGL				
20	Lung		AL-IGL				
21	Liver		AL-IGL				
22	Bone		AL-IGL				
23	Lung		AL-IGL				
24	Omentum		AL-IGL				
25	Lymph node		AL-IGL				
26	BM	AA	AA				
27	Intestine		AA				
28	BM		AA				
29	BM		AA				
30	Heart		AA				
31	Kidney		AA				
32	Kidney		AA				
33	Kidney		AA				
34	Heart		AA				
35	Heart	ATTR	ATTR				
36	Heart		ATTR				
37	Heart		ATTR				
38	Heart		ATTR				
39	Heart		ATTR				
40	Heart		ATTR				
41	Heart		ATTR				
42	Heart		ATTR				
43	Intestine		ATTR				
44	Intestine		ATTR				
45	Lung		ATTR				
46	Heart		ATTR				
47	Heart		ATTR				
48	Intestine		ATTR				
49	Heart		ATTR				
50	Heart		ATTR				

Heat map for average number of total number of peptide spectra identified for each microdissection.

0	1	2-4	5-7	8-10	11-13	>13

Novel approach for proteomic analysis of whole subcutaneous adipose tissue allows reliable typing of systemic amyloidoses

Brambilla, Lavatelli et al, 2011



Congo red + **Congo red -**

10-30 mg

- washing
- protein extraction
- delipidation (centrifugation)

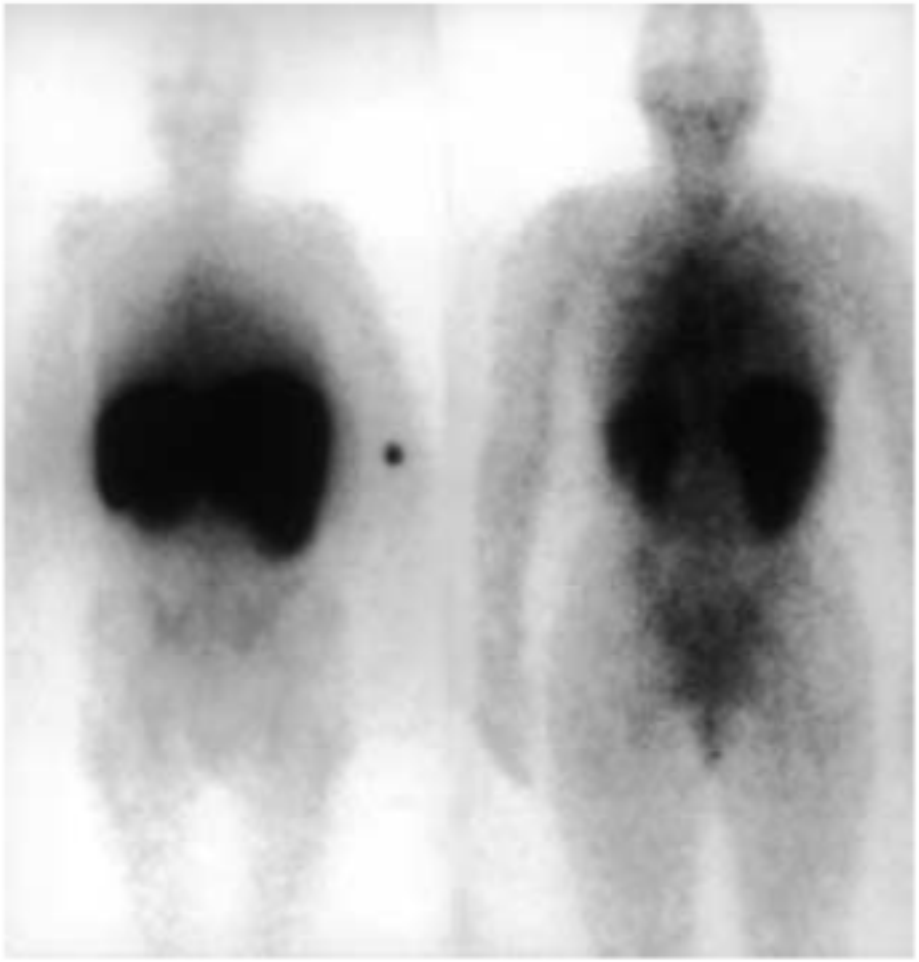
Digestion of the protein mixture

MudPIT
Multidimensional Protein Identification Technology

Case	IEM-confirmed diagnosis	IgLCk*	IgLCλ*	TTR	SAA
P6	ALλ	13	212	6	6
P11		6	165	4	0
P2		0	130	0	0
P1		0	88	6	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
P16		4	0	145	0
P18		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

Monitoring amyloid load - SAP scan

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



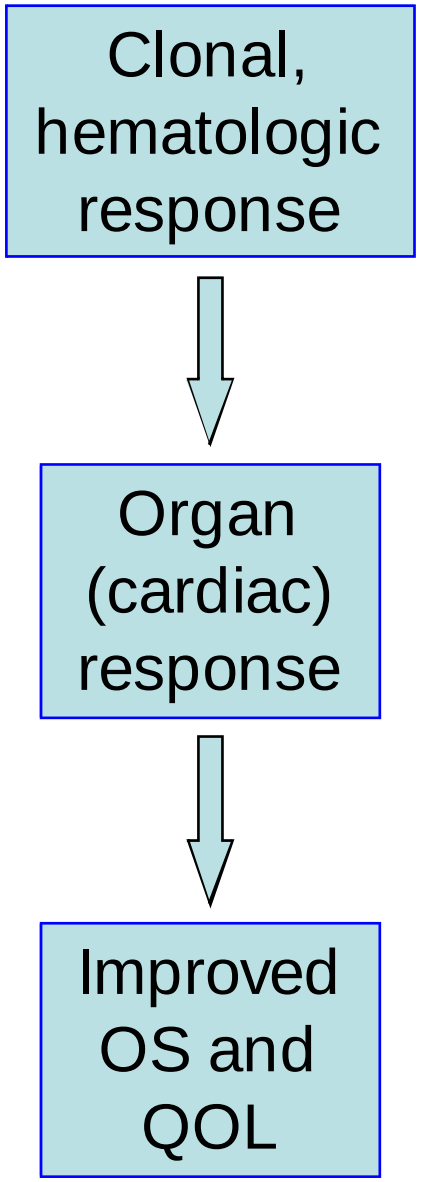
Radiolabelled SAP scintigraphy: posterior images of a 52-year-old woman with systemic AL kappa amyloidosis, before (left) and 1 year after (right) HDM chemotherapy. The serum concentration of free kappa light chains had fallen from 551 mg/l to 52 mg/l.

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

Treatment of AL amyloidosis

Aim of therapy:

- prompt elimination of the misfolded light chains
- stabilization or reduction of cardiac biomarkers
- minimization of treatment toxicity
- support of the function of target organs



Chemotherapy for AL amyloidosis is highly individualized and **risk-adapted**

Assessing the risk

Disease-related

Characteristics of the clone

- PC number, cyclin D1, miRNA, ploidy, karyotypic aberrations……

Characteristics of the LC

- **FLC burden**, germline genes usage, instability, cytotoxicity…

Patient-related

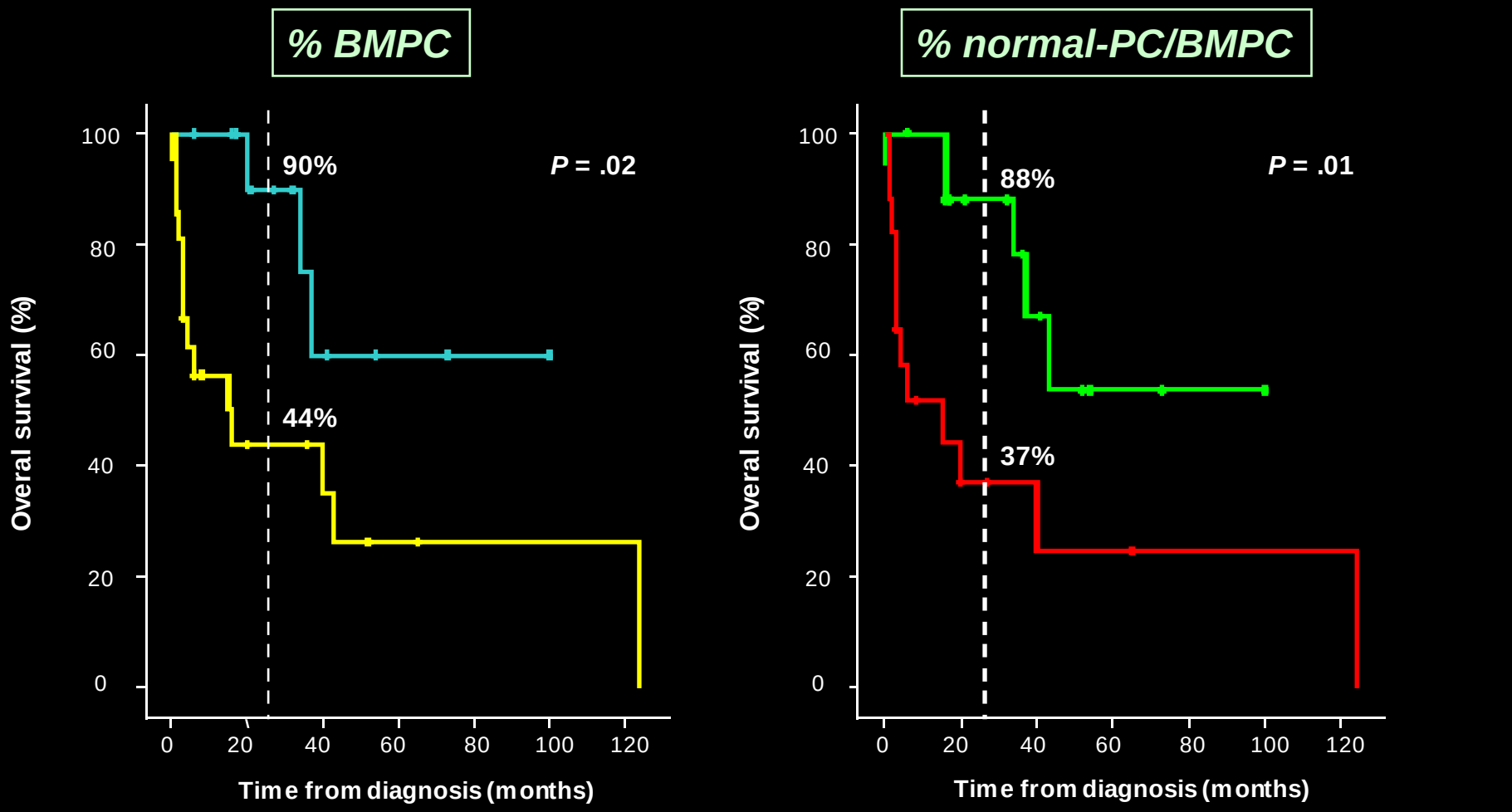
Severity of heart involvement

- **Cardiac biomarkers**, imaging

Other patient characteristics

- Age, renal function, other biomarkers (uric acid, β_2m…)

Overall survival according to the MFC immunophenotypic evaluation of the BMPC compartment

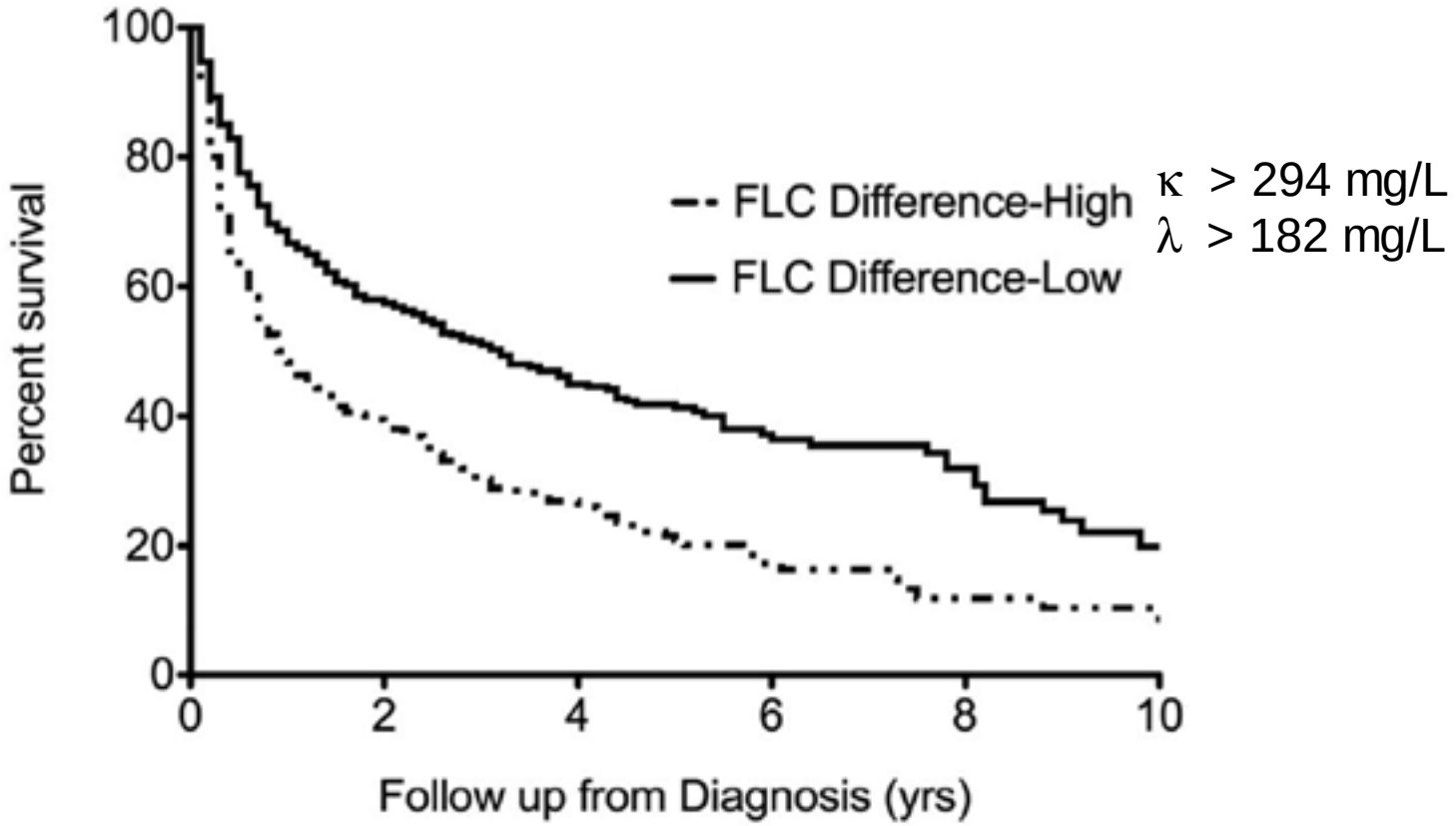


Paiva et al. Blood 2011 117: 3613-3616

Serum immunoglobulin free light-chain measurement in primary amyloidosis: prognostic value and correlations with clinical features

Kumar et al, Blood. 2010;116:5126-9

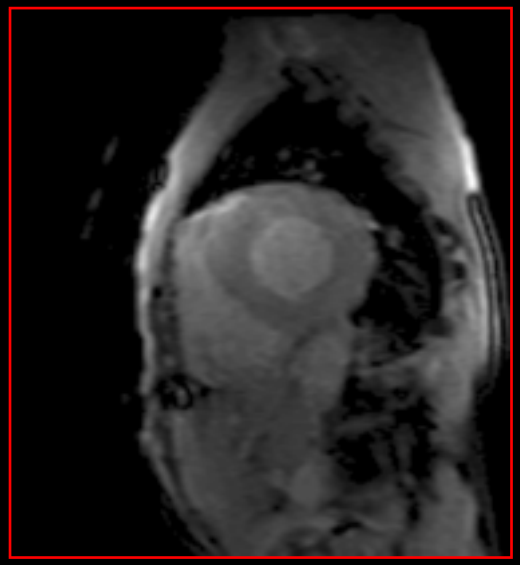
730 patients with newly diagnosed AL



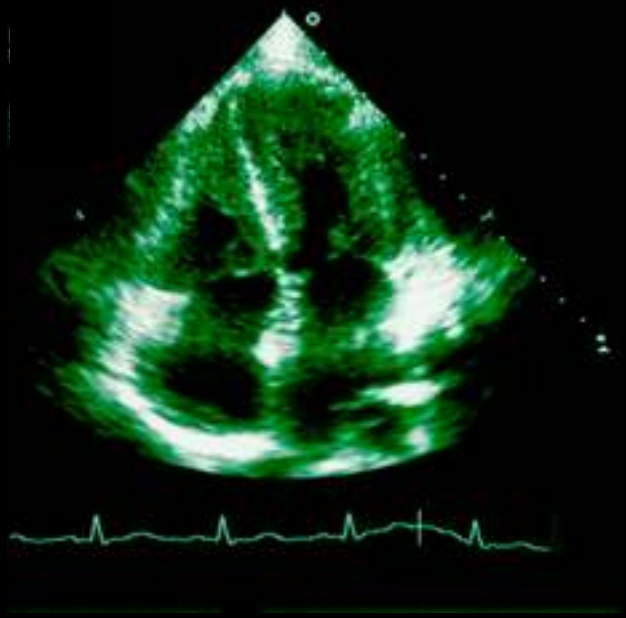
In multivariate analysis, dFLC was independent of other prognostic factors

HEART INVOLVEMENT IN AL AND PROGNOSIS

85% of patients die a cardiac death



Amyloid GAD kinetic on MRI
C. Rapezzi



- ventricular thickening
- diastolic (systolic) dysfunction
- pericardial effusion
- strain Doppler imaging
- low peripheral voltages at ECG

Cardiac biomarkers:

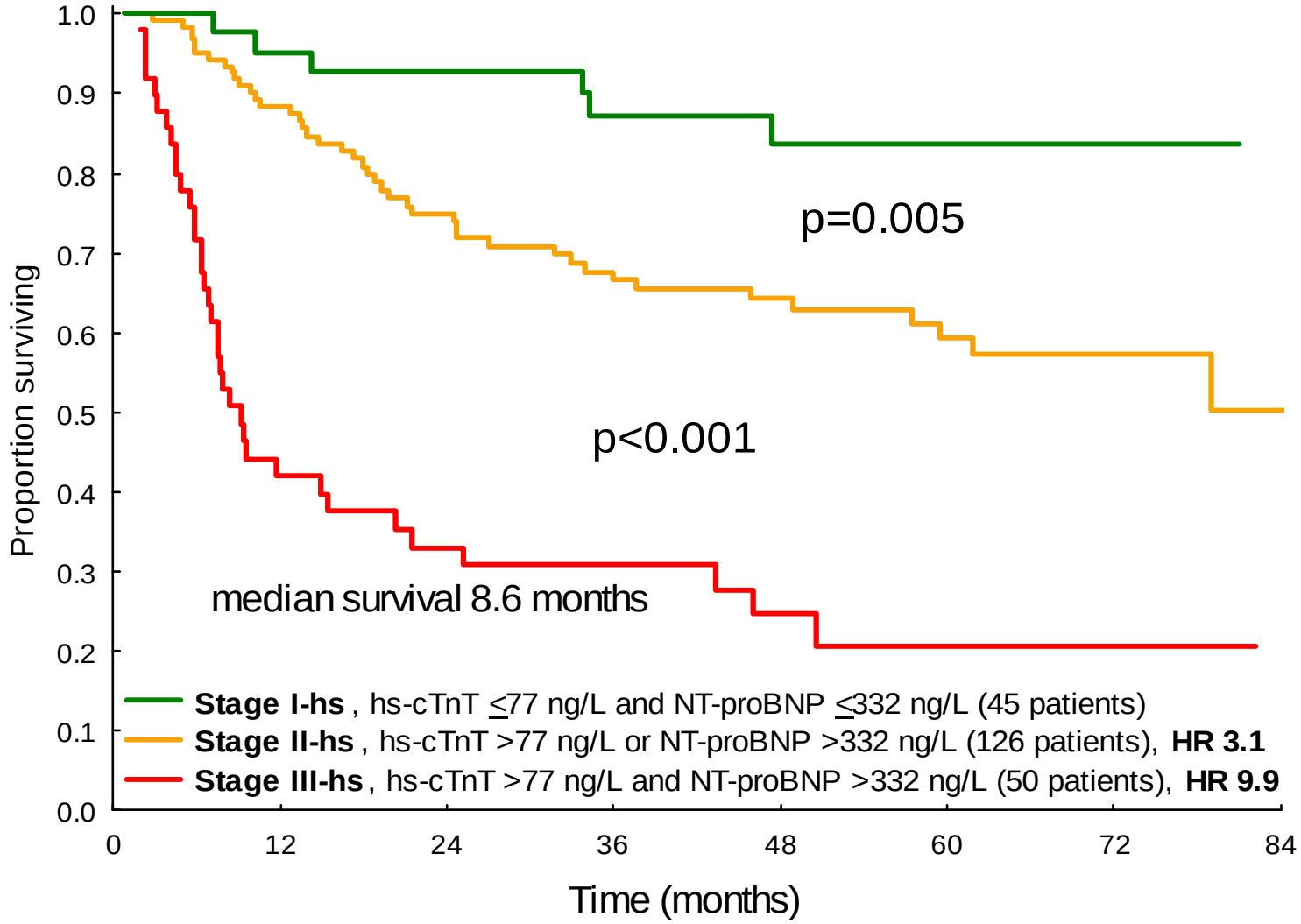
- Natriuretic peptide type B (NT-proBNP - BNP)
- Troponins (cTnI or cTnT)
- High-sensitivity troponins

Staging system for AL amyloidosis
Dispenzieri et al, *J Clin Oncol 2004; 22:3751-3757*

The new high-sensitivity assay for cardiac troponin T (hs-cTnT) can be used for cardiac staging in patients with AL amyloidosis.

Palladini G…Schönland S, 13th IMW Paris 2011, P-439

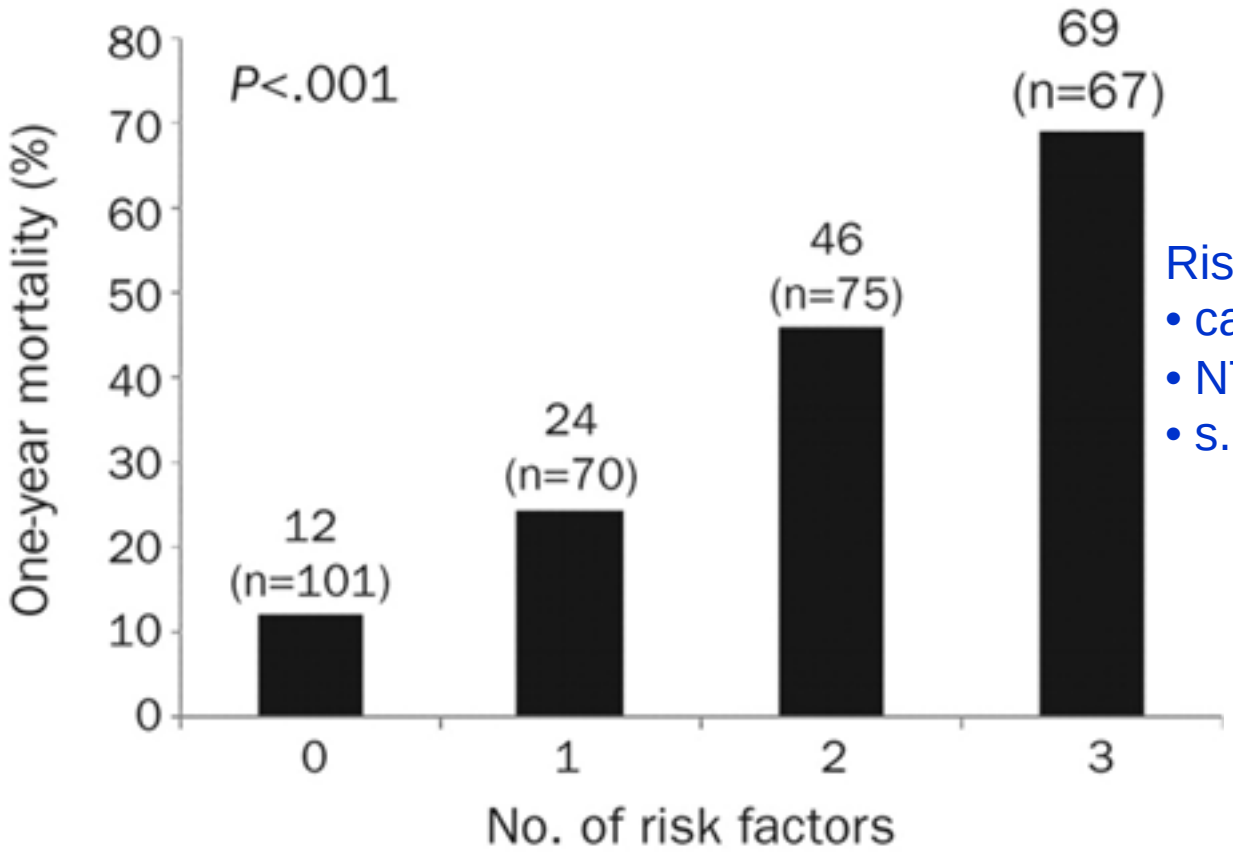
Survival of 221 patients with AL amyloidosis according to hs-cTnT and NT-proBNP concentrations



Recent improvements in survival in primary systemic amyloidosis and the importance of an early mortality risk score

Kumar et al, Mayo Clin Proc. 2011;86:12-8 used with Permission

313 patients seen during 2006-2009



Risk factors:

- cardiac troponin T >0.01 µg/L
- NT-proBNP >4200 ng/L
- s.uric acid >8.0 mg/dL

Management of AL amyloidosis in 2011

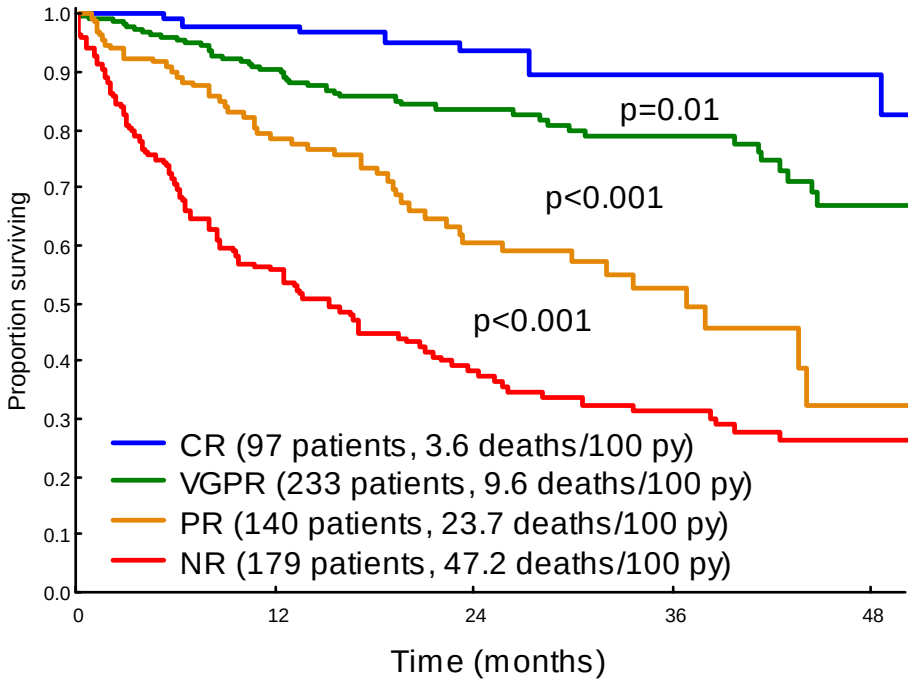
Survival determinants:
cardiac involvement and response to therapy

Validation of the criteria of response to treatment in AL amyloidosis

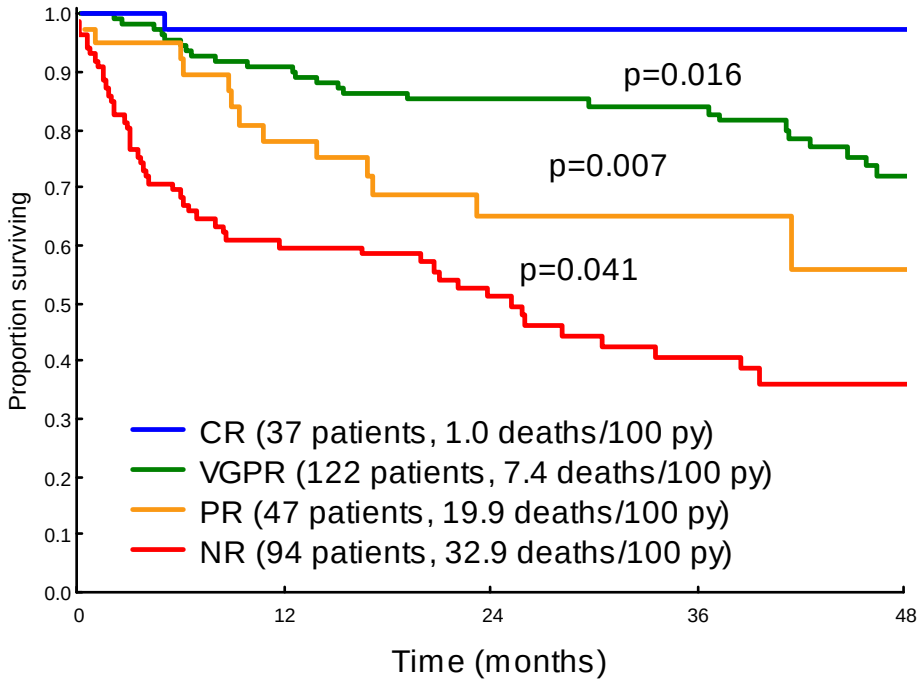
Palladini G, Dispenzieri A, Gertz MA, Wechalekar A, Hawkins PN, Schönland S, Hegenbart U, Comenzo R, Kastritis E, Dimopoulos MA, Jaccard A, Klersy C, Merlini G

XII Intl. Symposium on Amyloidosis, Rome 18-21 April, 2010 *ASH 2010 Abstr. # 1364*

816 patients from 7 centers (enrolled between 1995-2010)
649 (80%) with response data at 6 months.



Survival of 649 patients based on hematologic response at 6 months



Survival of 300 patients based on hematologic response at 3 months

Validation of the criteria of response to treatment in AL amyloidosis

Palladini G, Dispenzieri A, Gertz MA, Wechalekar A, Hawkins PN, Schönland S, Hegenbart U, Comenzo R, Kastritis E, Dimopoulos MA, Jaccard A, Klersy C, Merlini G

XII Intl. Symposium on Amyloidosis, Rome 18-21 April, 2010 *ASH 2010 Abstr. # 1364*

	New Response Criteria
aCR	negative serum and urine IFE normal κ/λ ratio
VGPR	dFLC <40 mg/L
PR	dFLC decrease ≥50%
NR	other

The use of dFLC (involved FLC-uninvolved) FLC compensates for altered FLC metabolism in patients with renal failure

Pinney et al, JCO 2011; 29:674-681

See also Poster 431 by Gibbs et al

Validation of the criteria of response to treatment in AL amyloidosis

Palladini G, Dispenzieri A, Gertz MA, Wechalekar A, Hawkins PN, Schönland S, Hegenbart U, Comenzo R, Kastritis E, Dimopoulos MA, Jaccard A, Klersy C, Merlini G

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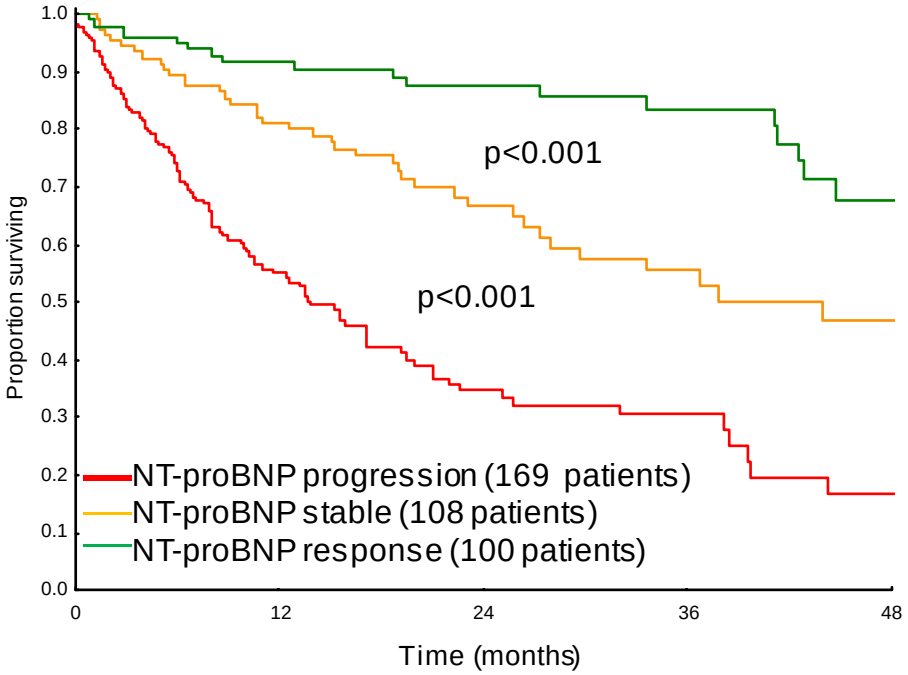
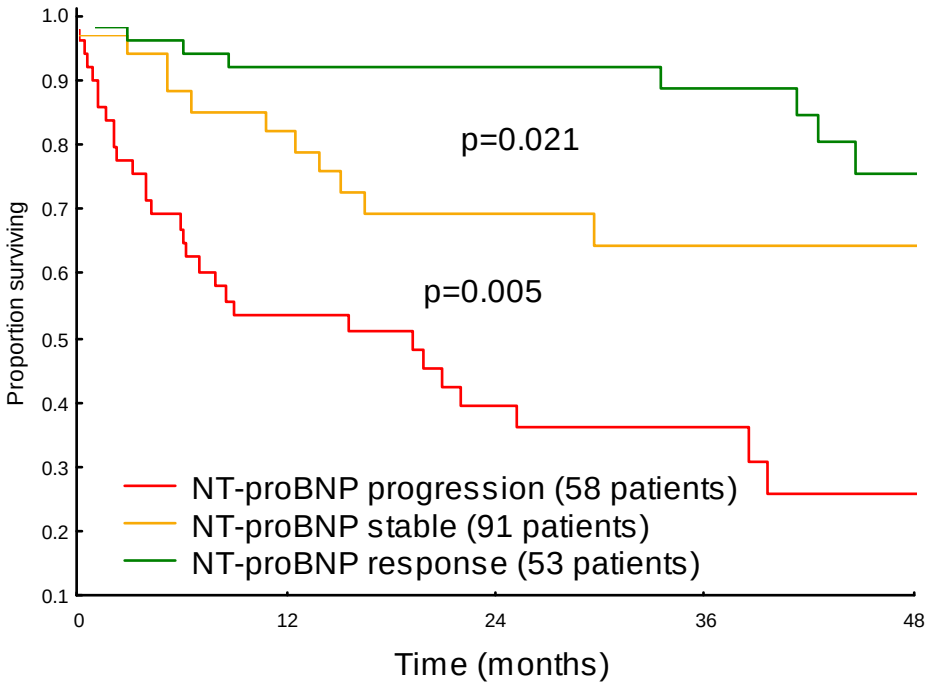


Survival of 377 patients with baseline NT-proBNP ≥650 ng/L according to NT-proBNP response and progression at 6 months



Survival of 202 patients with baseline NT-proBNP ≥650 ng/L according to NT-proBNP response and progression at 3 months

Caution using NT-proBNP in patients treated with IMiDs

Tapan et al, Blood 2010; 116: 5071-2

Dispenzieri et al, Am. J. Hematol 2010; 85:757–9

Management of AL amyloidosis in 2011

Chemotherapy guided by frequent assessment of FLC **and** cardiac biomarkers

Early intervention with rapidly-acting agents is necessary to achieve optimal response

Available treatments for AL amyloidosis (ITT)

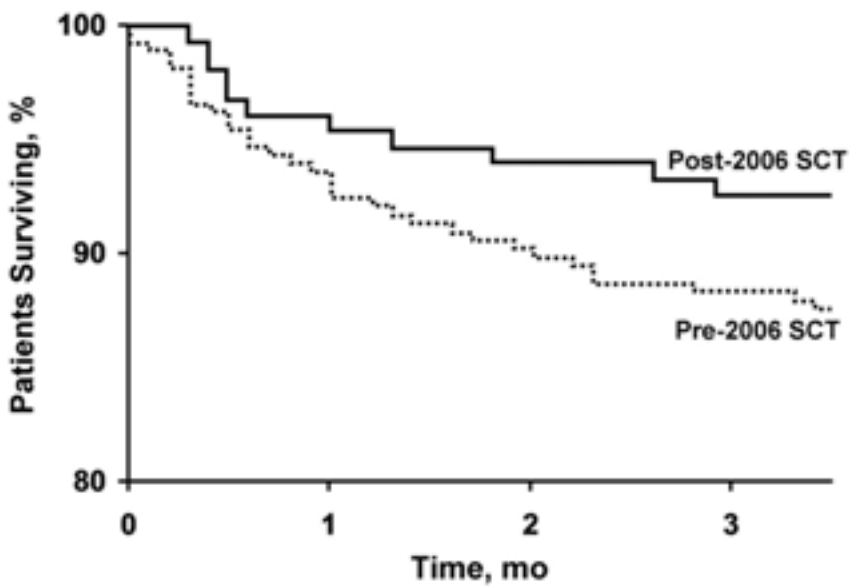
Melphalan and Dexamethasone

	Patient/ prev.tx	HR/CR %	Organ Resp %	TRM% (SAE%)	Author
Melph-predn-colch Melph-prednisone	50 148	NR 28	20 18	NR (8) NR (5)	Skinner 1996 Kyle 1997
Dexamethasone Dexa+maint. IFNα	44/19 87/14	40-53/10-16 33/15	12-16 45	5-8 (NR) 7 (67)	Gertz 1999 Dhodapkar 2004
HDM/SCT (single center) HDM/SCT (single center) HDM/SCT (multicenter)	312 171 37	58/23 68/NR 67/41	26 NR 45	13 (NR) 12 (NR) 24 (NR)	Skinner 2004 Gertz 2004 Jaccard 2007
Melphalan-Dex	46 43	67/33 68/32	48 39	4 (11) 2 (16)	Palladini 2004 Jaccard 2007

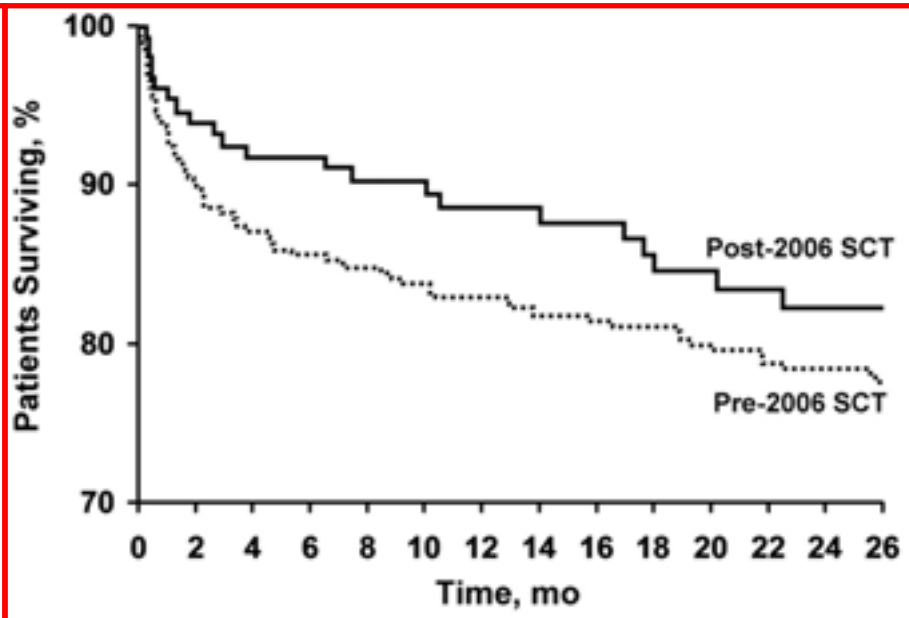
Trends in day 100 and 2-year survival after auto-SCT for AL amyloidosis: outcomes before and after 2006

Gertz et al, Bone Marrow Transplant. 2010 Oct 11.

265 patients pre Jan 2006 - 157 patients post Jan 2006



Survival through d 100 in patients with AL who underwent SCT before and after 2006 (*P*=.09)



Survival through 24 mo. in patients with AL who underwent SCT before and after 2006 (*P*=.09)

On multivariate survival analysis, higher levels of serum troponin T and NT-proBNP were the only predictors of early mortality after SCT.

Short-term mortality reduced more than 40% after 2005.

Outcome of AL amyloidosis after high-dose melphalan and autologous stem cell transplantation: long-term results in a series of 421 patients

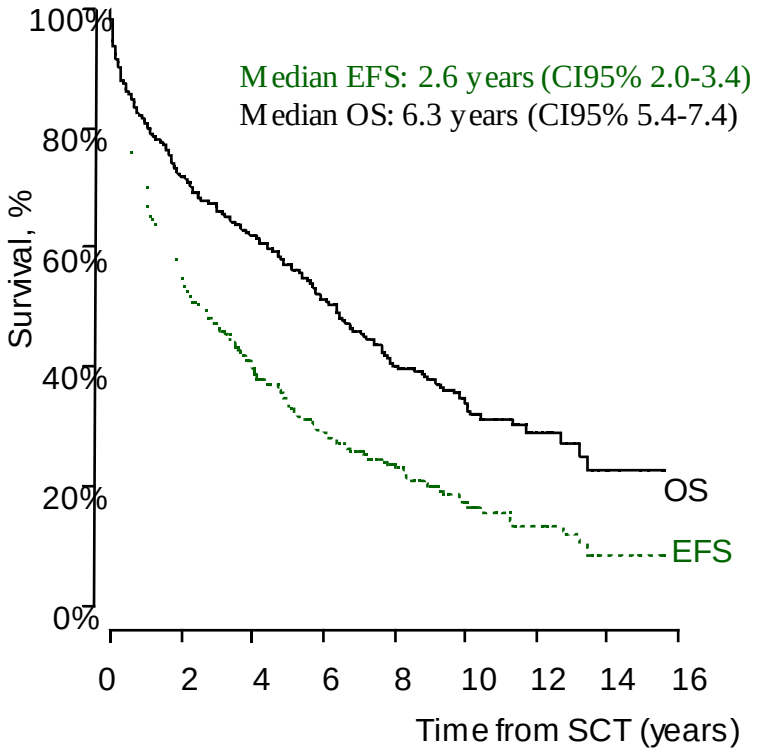
Cibeira et al, 13th IMW Paris, 2011 P-434

TRM: 11.4% overall, decreased to 5.6% in the last 5 years

340 (80%) evaluable at 1 year:
43% CR and 78% organ resp.

CR patients: median EFS 8.3 yrs and OS 13.2 yrs

ITT Analysis (N=421)



An Italian prospective study of outcomes in AL amyloidosis

Treatment of intermediate-risk patients with MDex

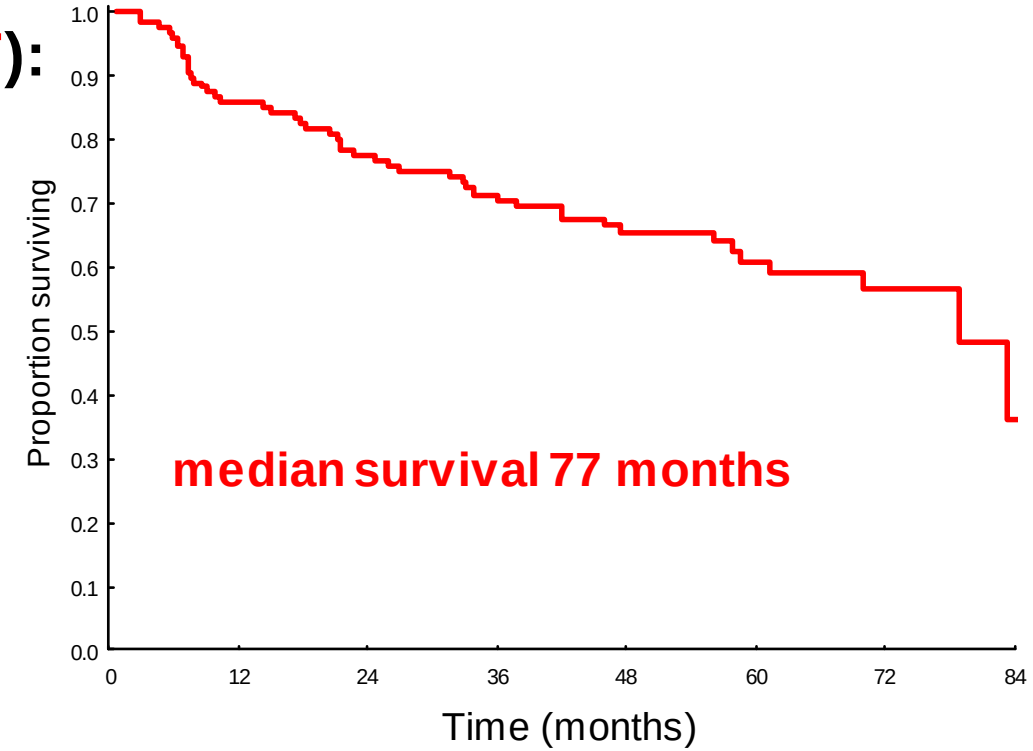
- 131 patients, median age 64y
- Mayo Stage I 29%, Mayo Stage II 71%
- Deaths at 3 months 2%, SAE 19%

- **Hematologic Response (ITT):**

CR:	26%	64%
VGPR:	24%	
PR:	14%	
NR:	36%	

- **Organ response**

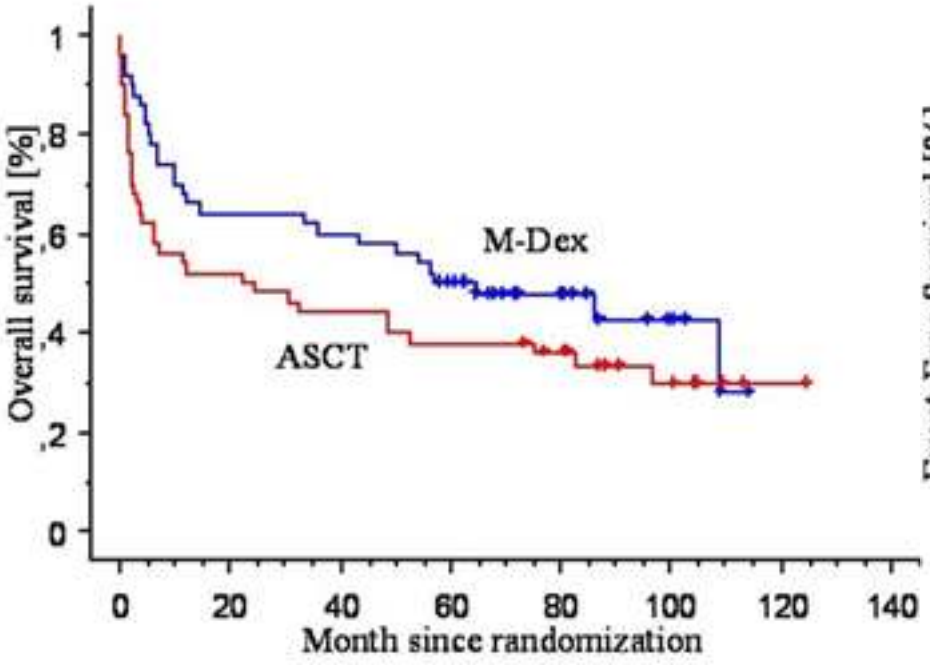
heart:	33%
kidney:	34%



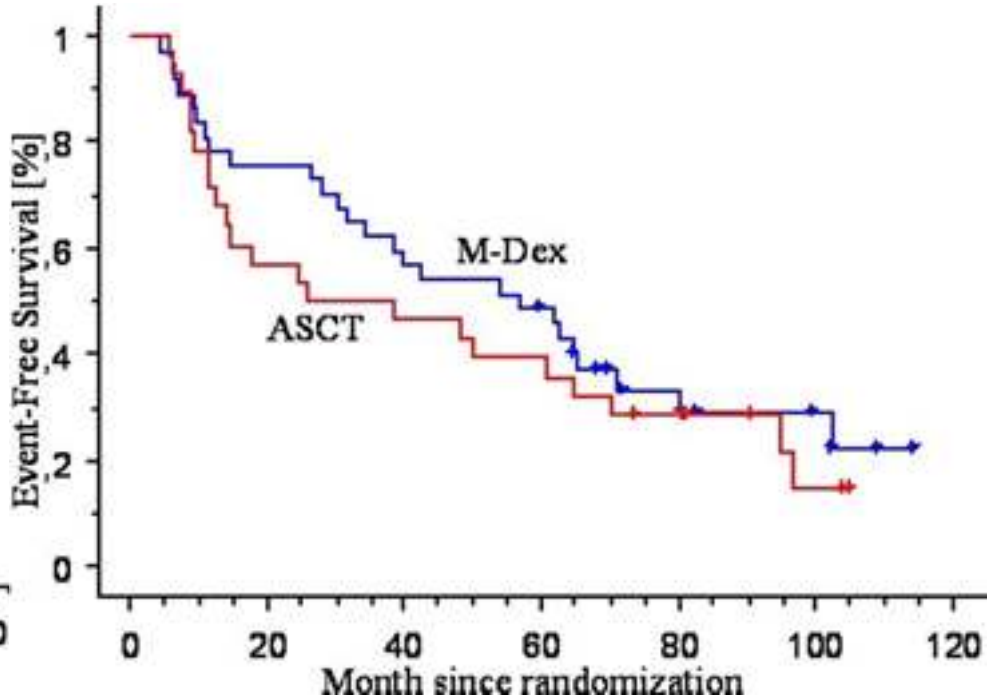
Autologous stem cell transplantation (ASCT) versus oral melphalan and high-dose dexamethasone in patients with AL (primary) amyloidosis: long term follow-up of the French multicentric randomized trial

Jaccard et al, N Engl J Med. 2007;357:1083-93

Jaccard et al, ASH 2010, Abstr. # 1344



Survival according to treatment



Event-free survival according to treatment group in the landmark analysis

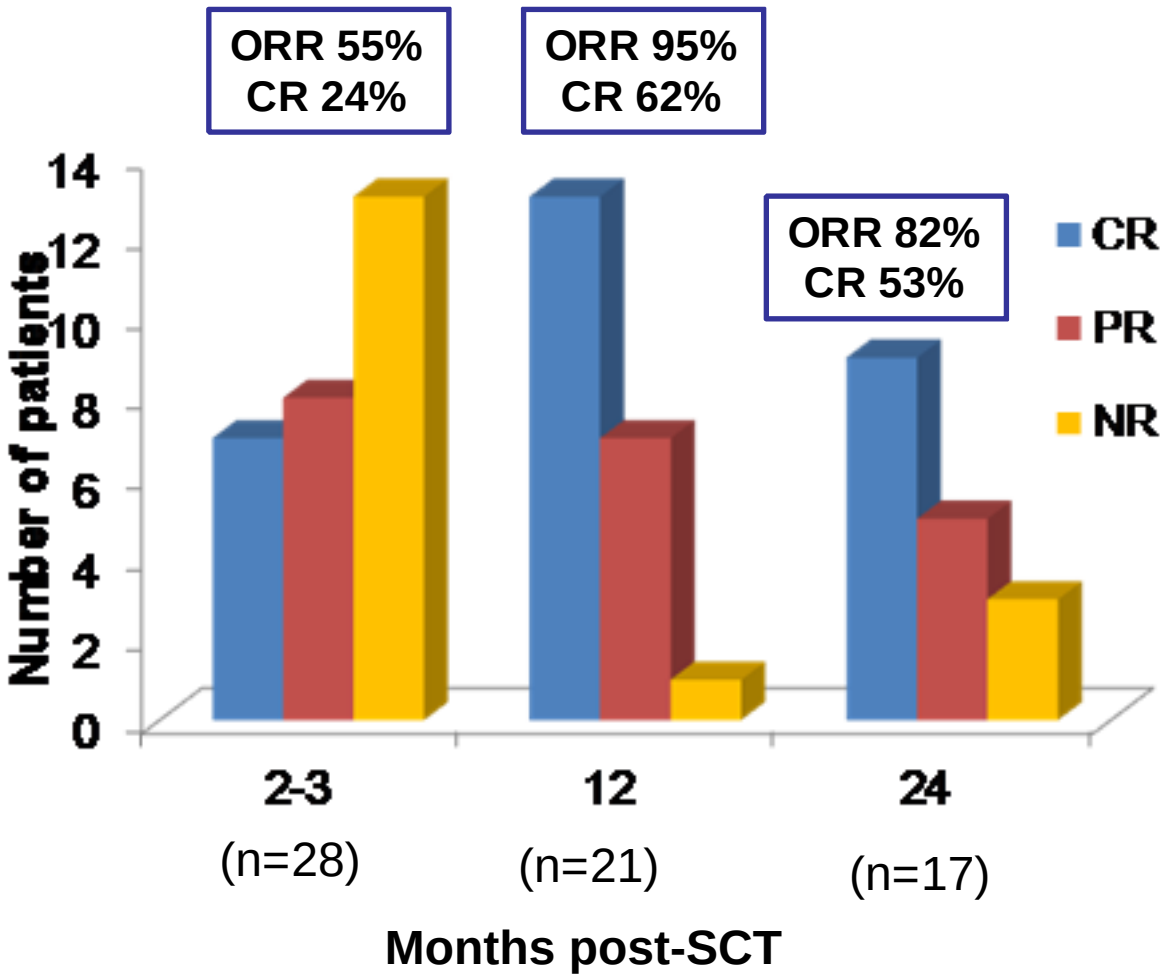
Available treatments for AL amyloidosis (ITT)

Novel agents

	Patient/ prev.tx	HR/CR %	Organ Resp %	TRM% (SAE%)	Author
Thalidomide-Dex	31/31	48/19	26	0 (65)	Palladini 2005
Cycl-Thal-Dex	75/44	74/21	27	4 (32%)	Wechalekar 2007
Lenalidomide±Dex	22/13 34/31	41/NR 47/21	23 21	18 (86) 3 (35)	Dispenzieri 2007 Sanchorawala 2007
Lenalidomide-MDex	26/0	58/23-42^{15mg}	50	0 (81)	Moreau 2010
Pomalidomide-Dex	32/32	41/9^{VGPR}	H 11, K 17	NR (65)	Dispenzieri 2010^{abs}
Bortezomib Bortezomib-Dex	54/54 94/76	67/29 71/25	28 30	0 (50-79) 0 (29)	Reece 2011 Kastritis 2010
Bortezomib-MDex	33/19	84/29	H 14, K 27	NR (60)	Gasparetto 2010^{abs}
Cycl-Bortez-Dex	15/7	93/73	K 40	NR	Mikhael 2010^{abs}

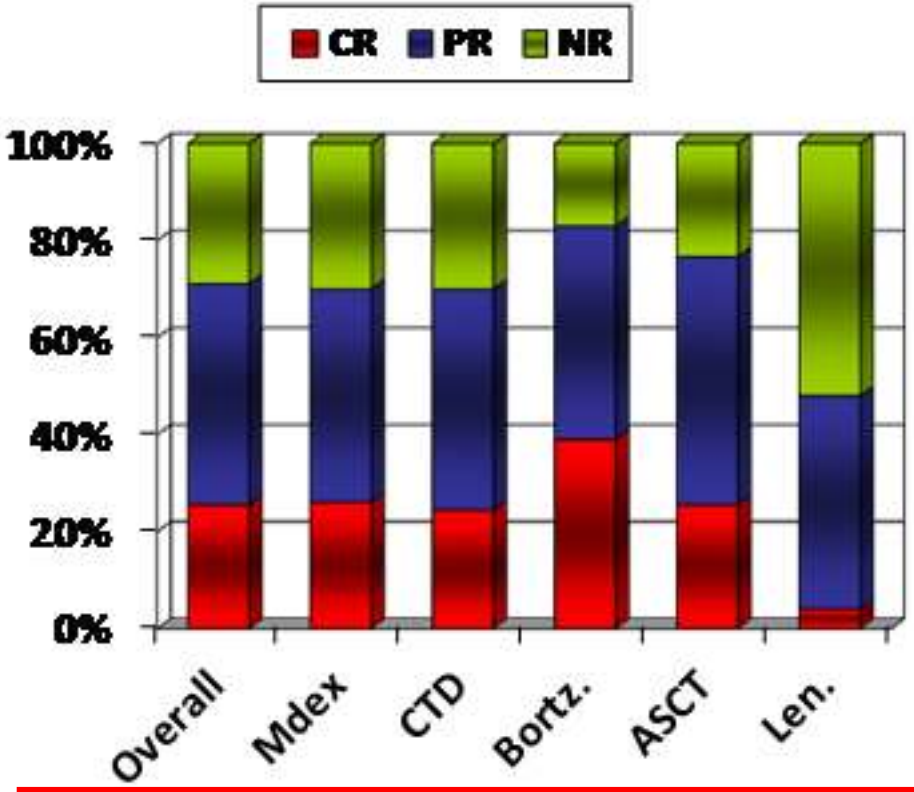
Adjuvant bortezomib and dexamethasone following risk-adapted melphalan and stem cell transplant in systemic light-chain amyloidosis (AL): A phase II study

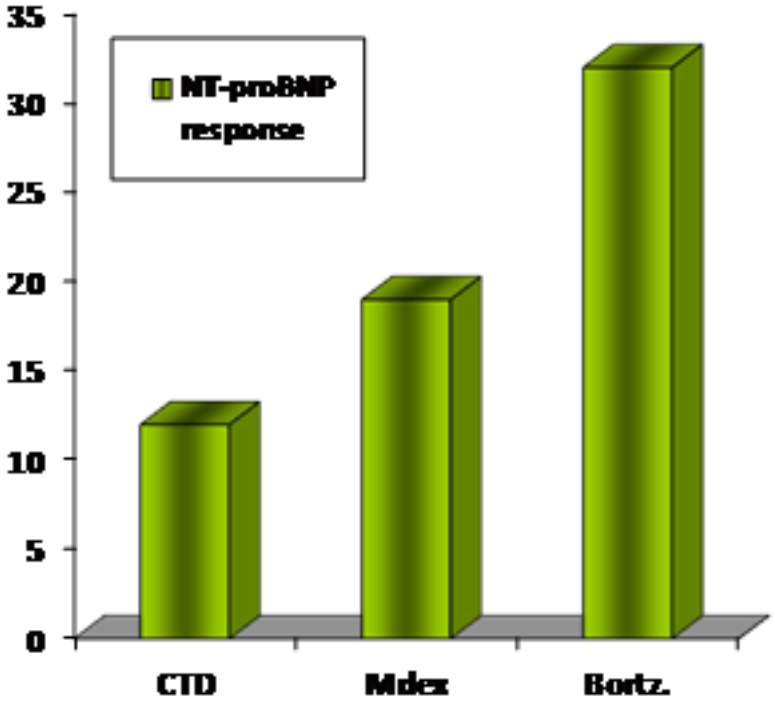
Landau et al, ASH 2010– Abstr. #2391



A European collaborative study of treatment outcomes in 428 patients with systemic AL amyloidosis

Wechalekar AD, Kastritis E, Merlini G, Hawkins PN, Dimopoulos MA, Gillmore J, Gibbs S, Palladini G. *ASH 2010, Abstr. #988*





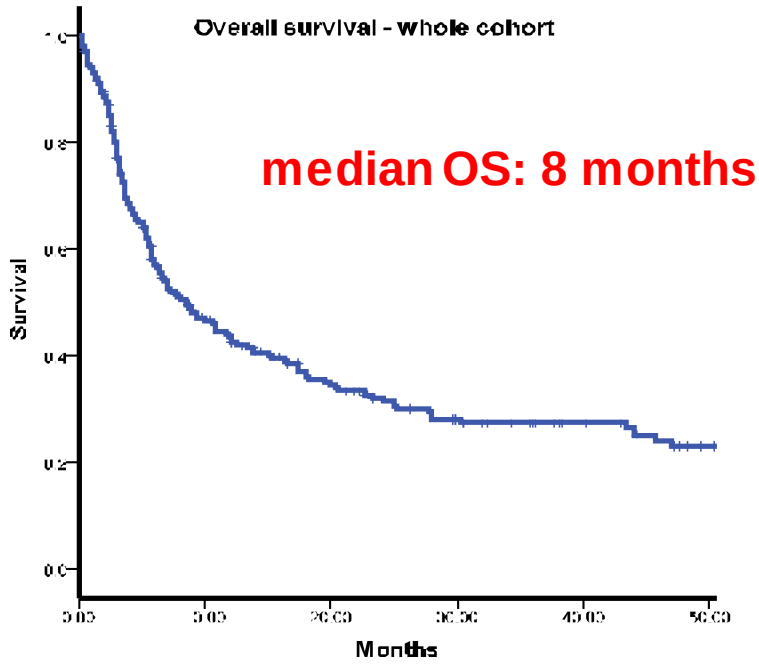
- Bortezomib is associated 80% haematological responses with 50% achieving at least dFLC-VGPR
- It is rapidly acting (hematologic responses in 4-6 weeks)
- Translates in high organ response rates even in advanced risk patients

European collaborative study of 242 patients with systemic AL amyloidosis with Mayo Stage III disease *Wechalekar AD, Schoenland S, Kastritis E, Merlini G, Hawkins PN, Dimopoulos MA, Russo P, Lane T, Foli A, Foard D, Milani P, Rannigan L, Hegenbart U, Gillmore JD, Palladini G.* *13th IMW Paris, 2011 P-438*

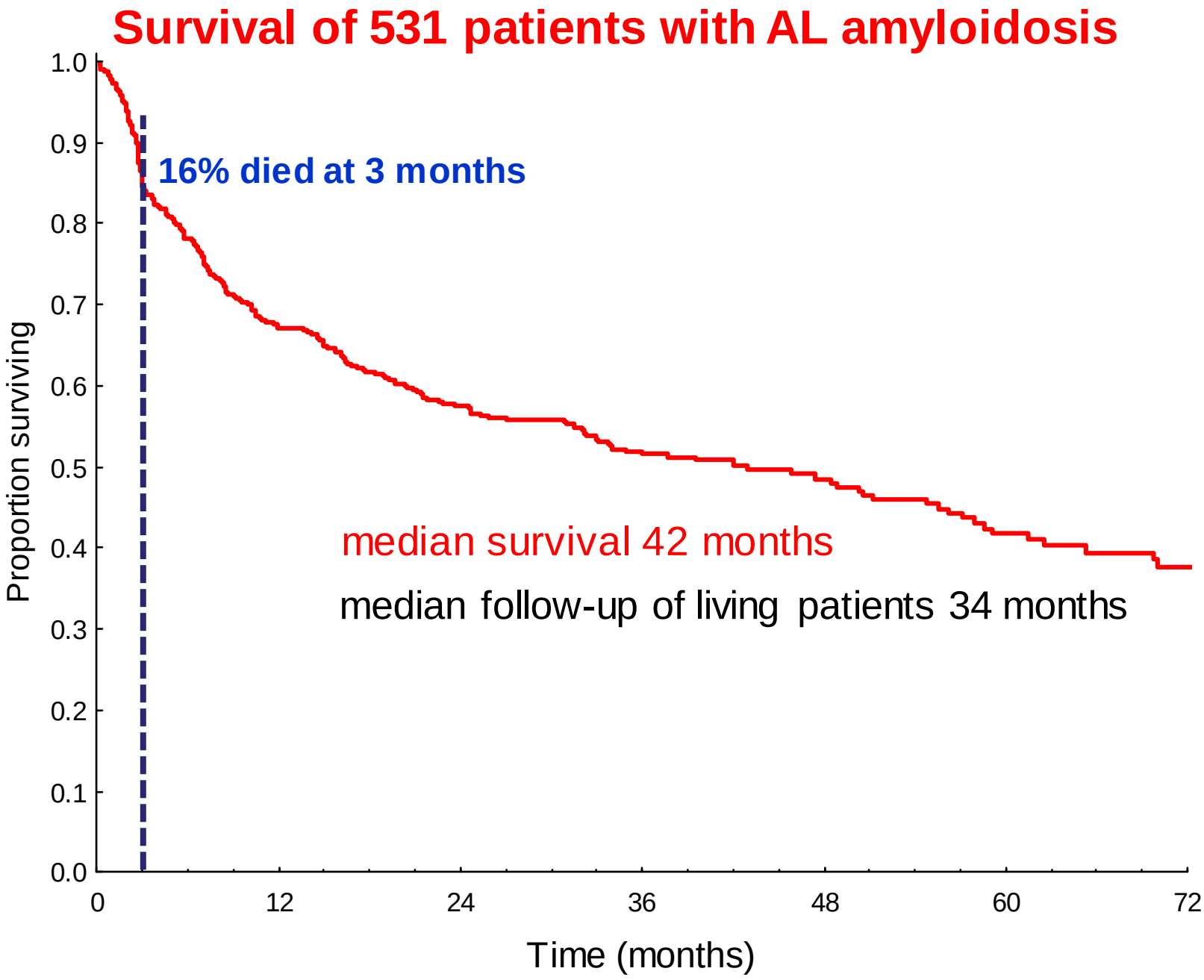
Response	dFLC response
CR/dFLC-VGPR	50 (21%)
PR	34 (14%)
NR	29 (12%)
Response (ITT)	84 (34%)

ECOG performance status	
≤1	112 (47%)
2	71 (29%)
≥3	59 (24%)
NYHA status	
≤1	41 (17%)
2	57 (23%)
≥3	114 (54%)

37% of patients completed the planned treatment

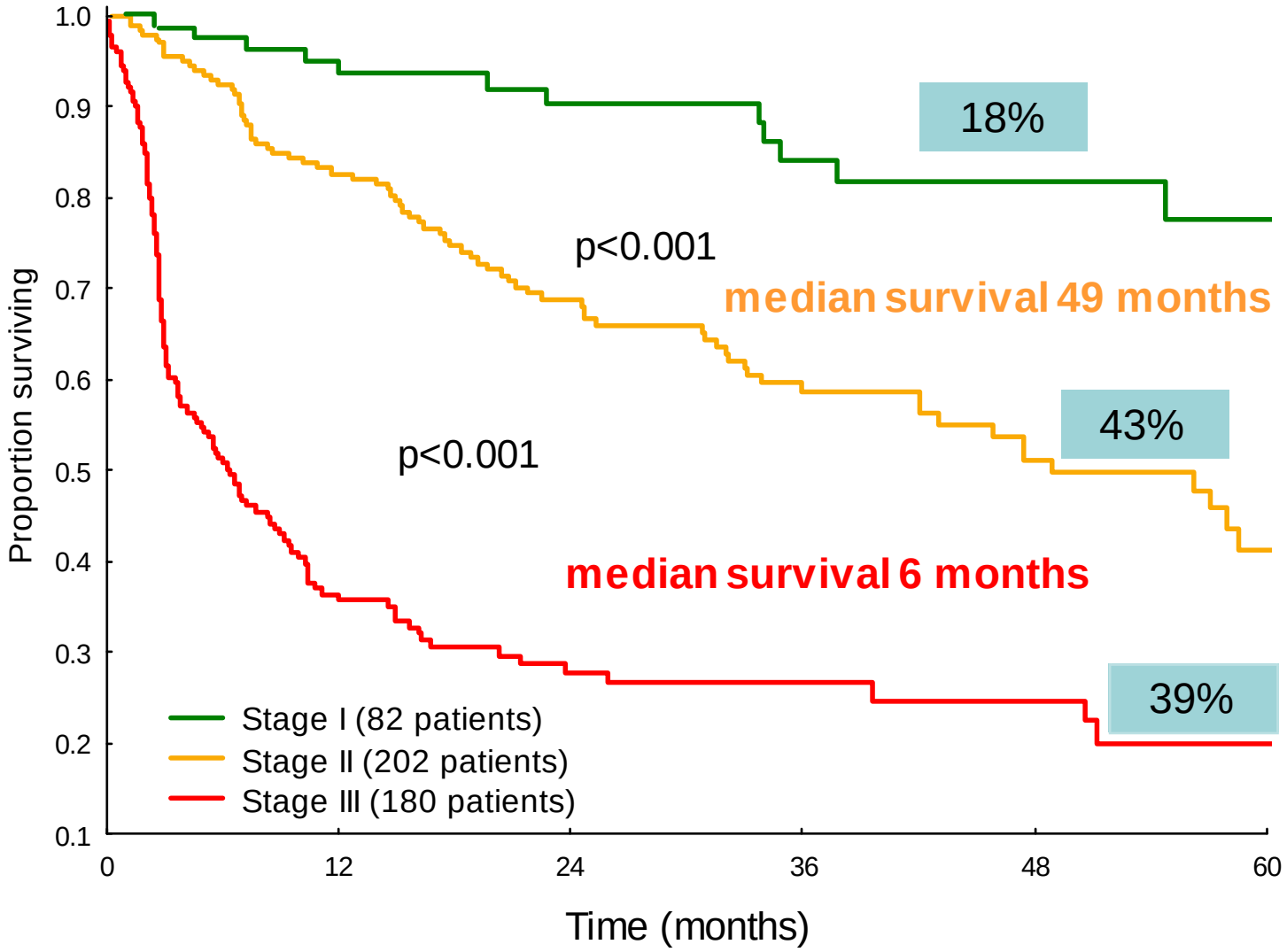


An Italian prospective study of outcomes in AL amyloidosis



An Italian prospective study of outcomes in AL amyloidosis

Survival of 464 patients with AL amyloidosis according to the Mayo Clinic staging system

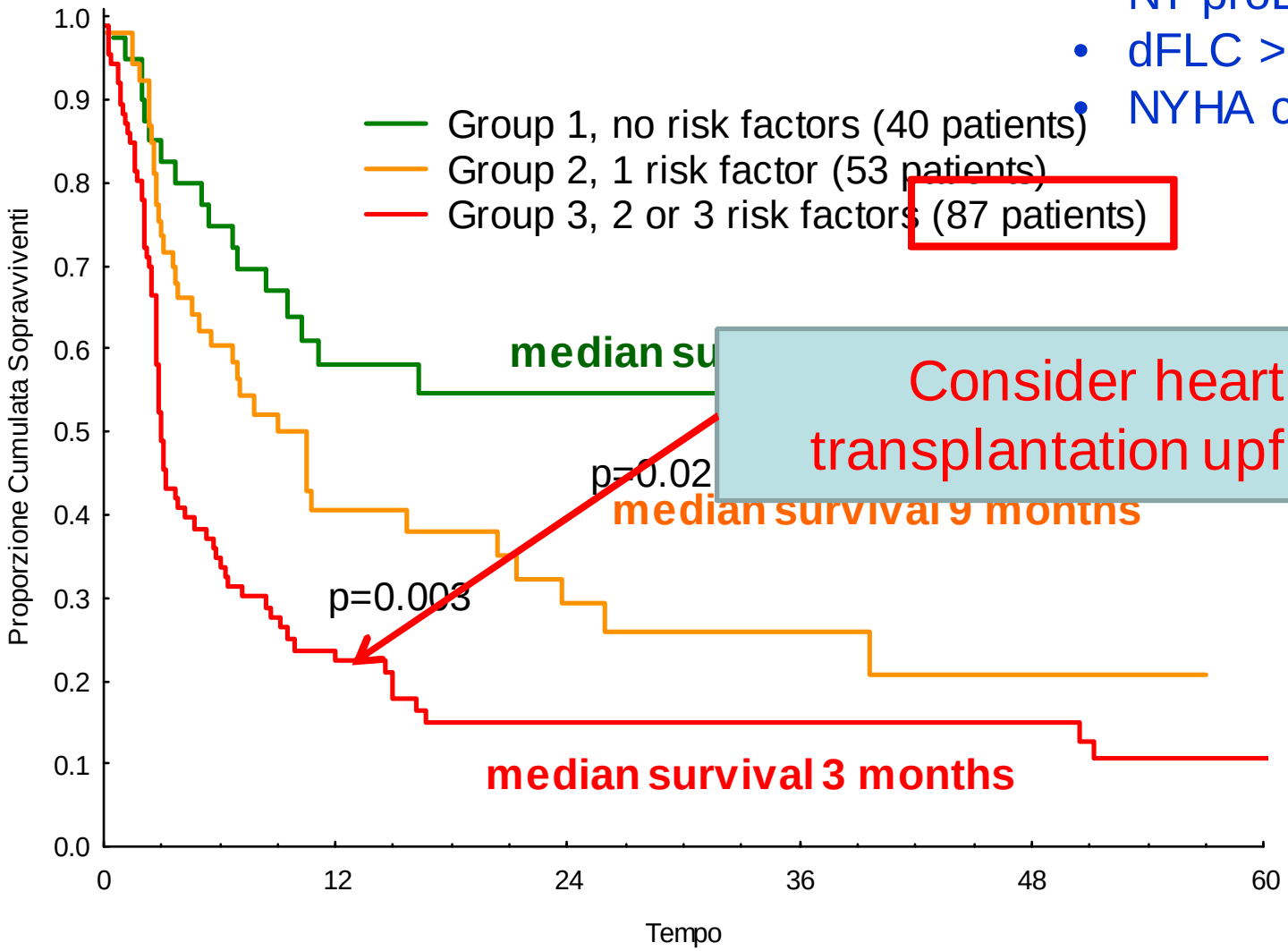


An Italian prospective study of outcomes in AL amyloidosis

Survival of 180 patients with Mayo Clinic stage III AL amyloidosis according to NYHA class, NT-proBNP and dFLC

Risk factors

- NT-proBNP >10,000 ng/L
- dFLC >500 mg/L
- NYHA class 3 or 4



Consider heart transplantation upfront

Management of AL amyloidosis in 2011

Transplanting the irreversibly damaged organs

Orthotopic heart transplantation (+ASCT)

in selected patients:

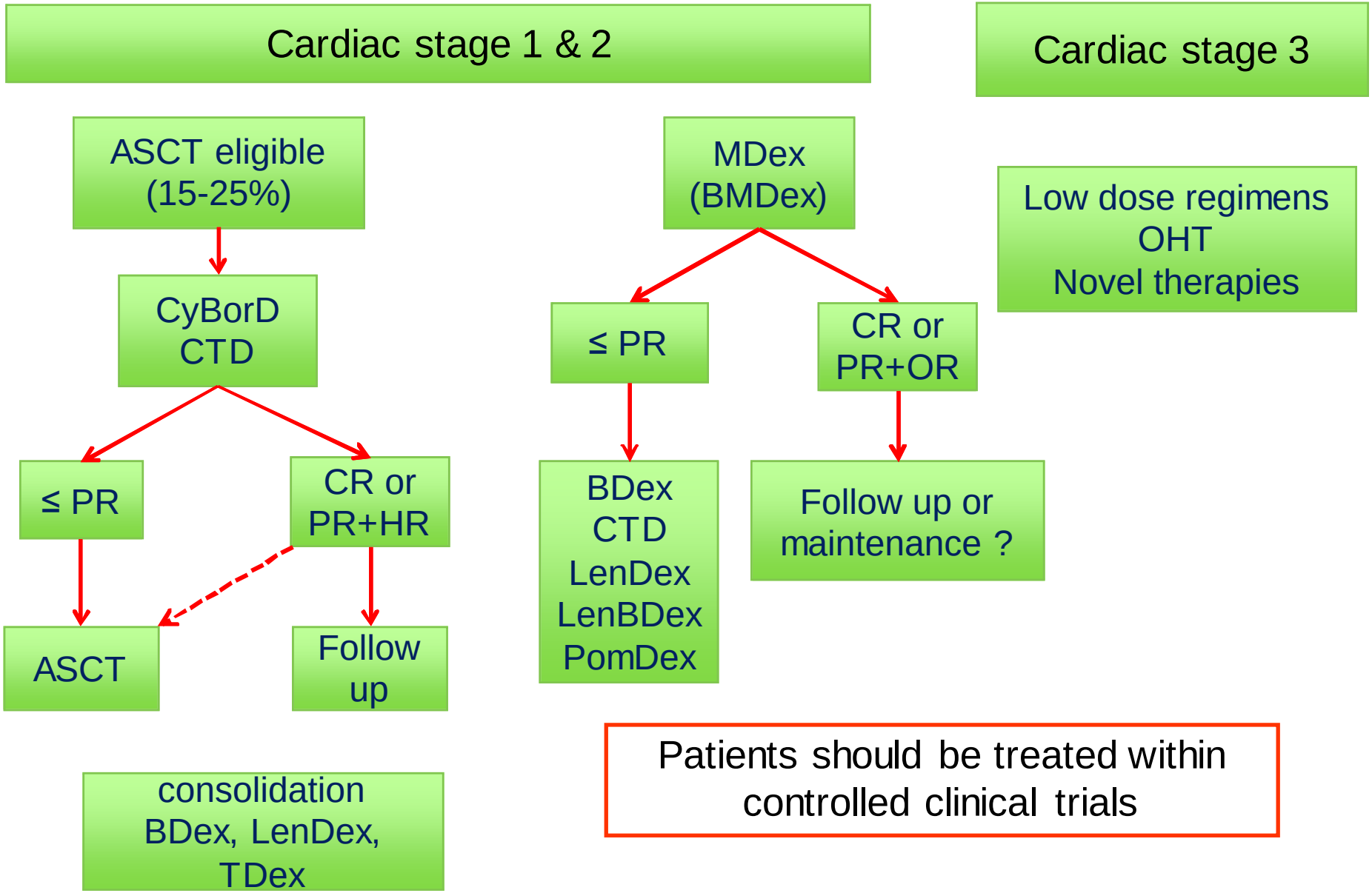
- younger
- at high cardiac risk
- without significant extra-cardiac amyloidosis

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

Criteria for eligibility remain to be defined
International prospective studies needed to establish guidelines

Dey et al, Transplantation 2010; 90:905-11
Sattianayagam et al, Am J Transplant 2010;10:2124-31
Kristen et al, Eur J Heart Fail 2009; 11:1014-20
Lacy et al, J Heart Lung Transplant 2008; 27:823
Mignot et al. Arch Cardiovasc Dis. 2008;101:523-32.

Management of AL amyloidosis in 2011



Conclusions

- Early and correct diagnosis is vital
- Use cardiac biomarkers for risk assessment
- Prompt therapy and frequent monitoring with FLC and cardiac biomarkers
- Novel therapeutic approaches needed for patients with advanced cardiac involvement
- Phase III trials necessary to define optimal therapy: international collaboration needed

AL amyloidosis is a rare disease. In order to make progress national and international collaborations are needed

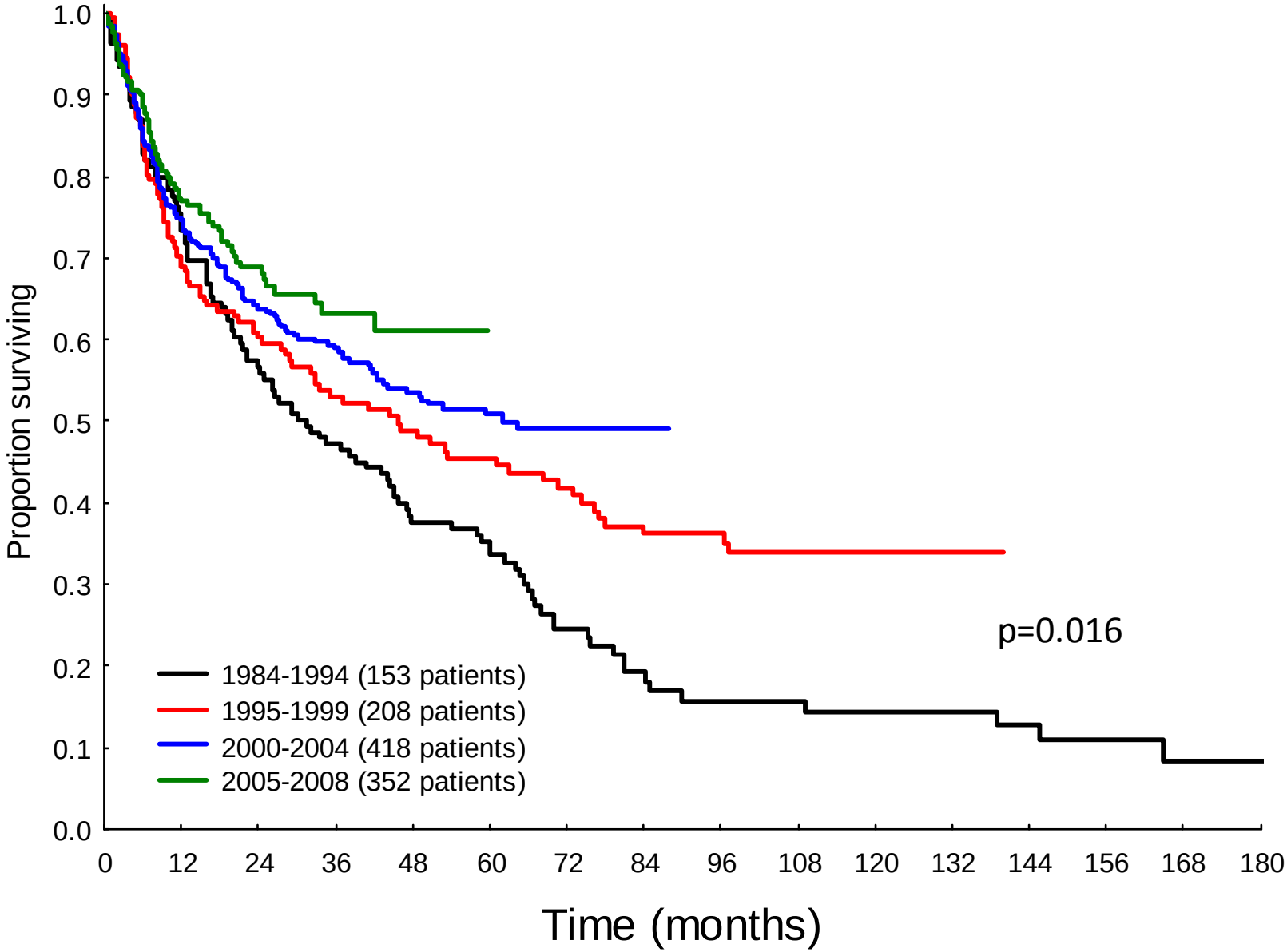
Italian Amyloidosis Network

A common diagnostic and therapeutic protocol is periodically discussed and updated: in Brescia on April 2, 2011

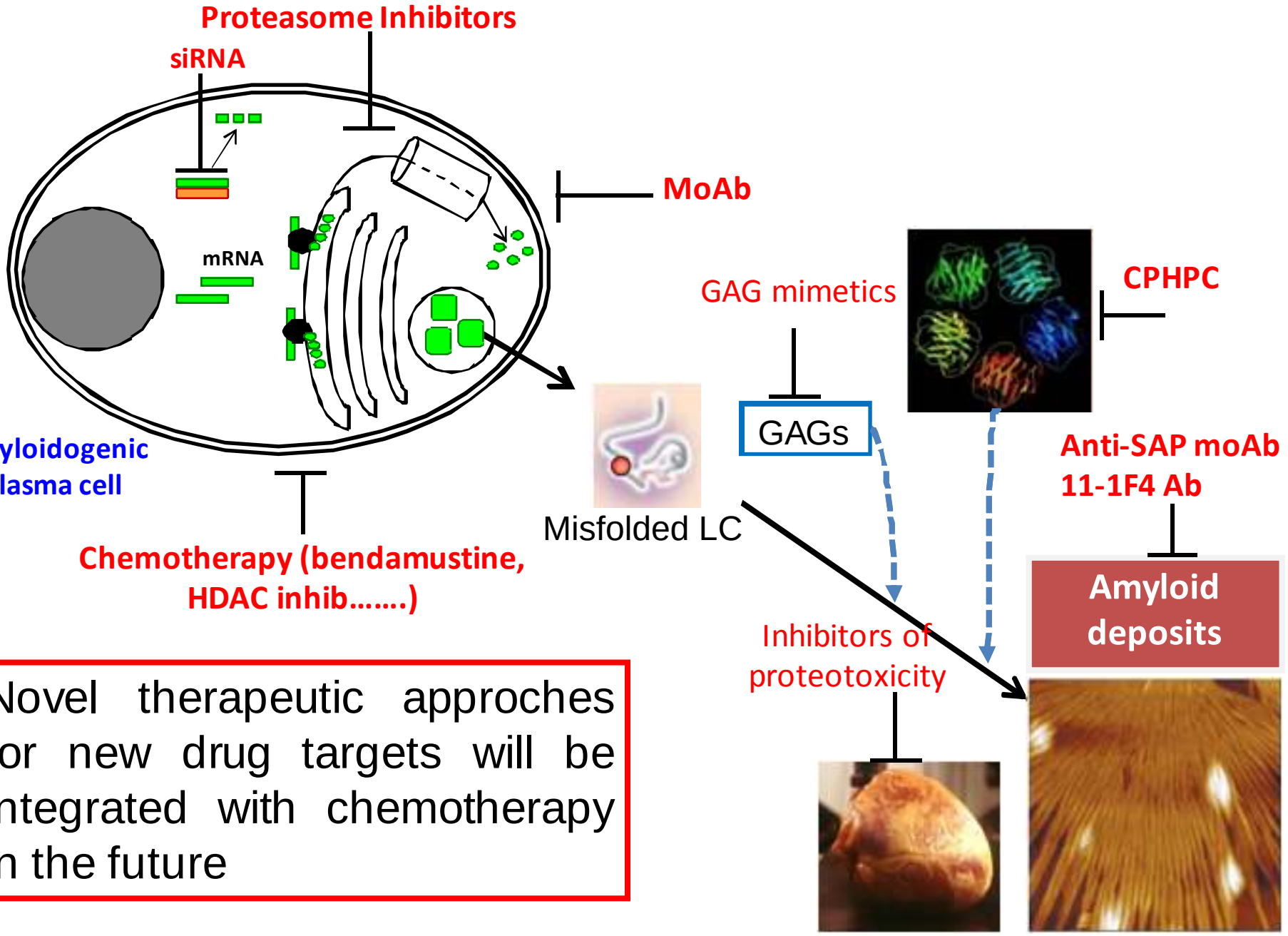
ISA
INTERNATIONAL SOCIETY OF AMYLOIDOSIS

European Network for Phase III trial comparing MDex vs BortezMDex

Survival of 1131 patients with AL amyloidosis according to the year of diagnosis followed at the Pavia Amyloid Research and Treatment Center



Perspectives in the treatment of AL amyloidosis



Novel therapeutic approches for new drug targets will be integrated with chemotherapy in the future

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Ministero della Salute

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