Athens Conference on PLASMA CELL DYSCRASIAS

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ATHENS - GREECE, Athens Hilton Hotel

Diagnosis, prognosis and management of systemic light chain amyloidosis

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Fare clic per modificare lo stile del sottotitolo dello schema

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Amyloidosis: protein misfolding disease

aggregation of normally soluble proteins into soluble β-sheet fibrils which are deposited in **target tissues** causing **progressive organ dysfunction**

Amyloid precursor

Increased conc.

Increased synthesis

- Monoclonal LC*
- SAA

Reduced clearance

- β2-microglobulin

Mutations*

- Transthyretin
- Apolipoprotein AI
- Lysozyme, etc.

Aging

- Transthyretin wt

Interactions with microenvironment of target organs

Proteolysis

Lysosomal enzymes

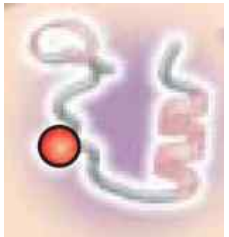
Metalloproteases

metal ions,

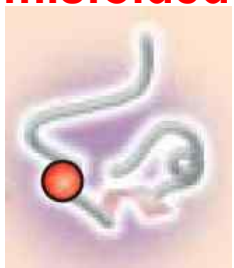
matrix components

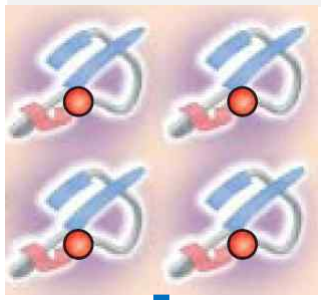
GAGs

SAP



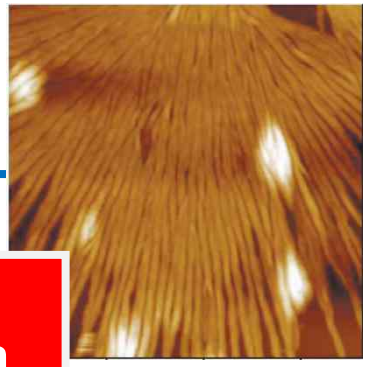
misfolded





Oligomers

Amyloid fibrils



Organ dysfunction

Most common systemic amyloidoses

Acquired amyloidoses

Type	Precursor (site of synthesis)	Syndrome
Immunoglobulin LC amyloidosis (AL)	Monoclonal LC (BM plasma cells)	Primary amyloidosis, myeloma-associated: 10%
Reactive amyloidosis (AA)	Serum amyloid A (liver)	Chronic diseases (rheumatoid arthritis, infections, cancer)
Senile systemic amyloidosis	**wt** transthyretin (liver > 90%)	Heart in elderly men

Hereditary amyloidoses

Type	Precursor (site of synthesis)	Syndrome/involved tissue
Familial transthyretin amyloidosis (ATTR)	Variant transthyretin (liver > 90%)	Peripheral and autonomous neuropathy, heart
Familial apolipoprotein AI amyloidosis (AApoA-1)	Variant apolipoprotein A-I (liver, intestine)	Heart, liver, kidney, testis

1702 patients referred to the Pavia Center for Amyloidosis

1208 patients with AL amyloidosis

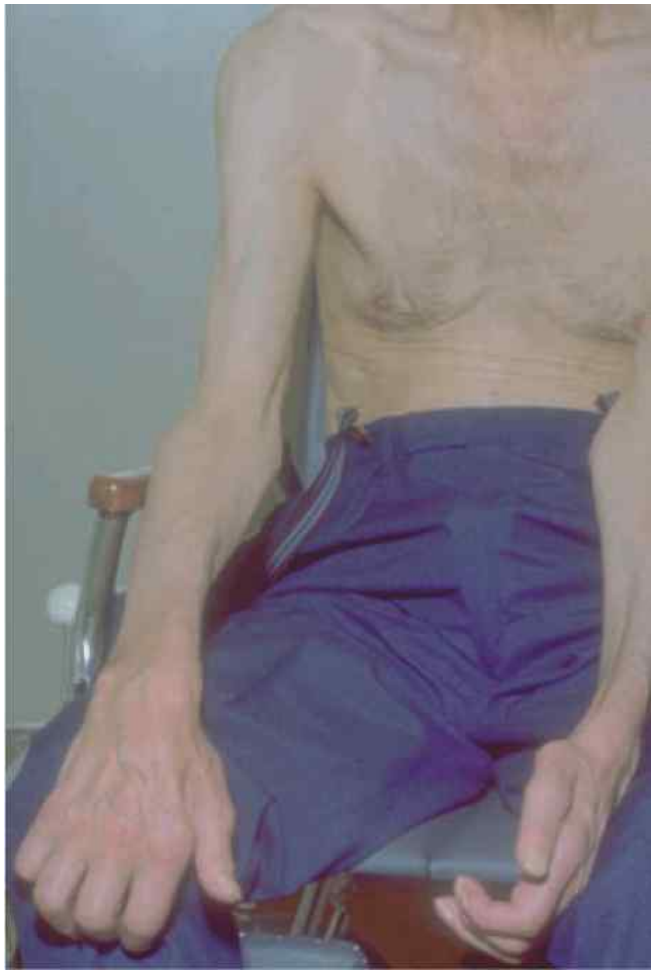
182 patients diagnosed in 2008

457 patients in follow-up

Apolipoprotein AI amyloidosis
N-terminal 83-93 residues in amyloid deposits

Mutation	Clinical Features	Geographic Kindreds
Gly26Arg	PN, Nephropathy	United States
Trp50Arg	Nephropathy	United Kingdom
Leu60Arg	Nephropathy	United Kingdom
Leu64Pro	Nephropathy	United States, Italy
del 60-71 ins Val/Thr	Hepatic	Spain
Del 70-72	Nephropathy	South Africa
Leu75Pro	Primary hypogonadism, liver dysfunction Tubulo-interstitial nephropathy	Italy (70 families)
Leu90Pro	Cardiomyopathy, cutaneous, laryngeal	France
Arg173Pro	Cardiomyopathy, cutaneous, laryngeal	United States
Leu174Ser	Cardiomyopathy	Italy
Ala175Pro	Laryngeal	United Kingdom
Leu178His	Cardiomyopathy, Laryngeal	France

Transthyretin amyloidosis



Patient with familial amyloidotic polyneuropathy with peripheral muscle wasting

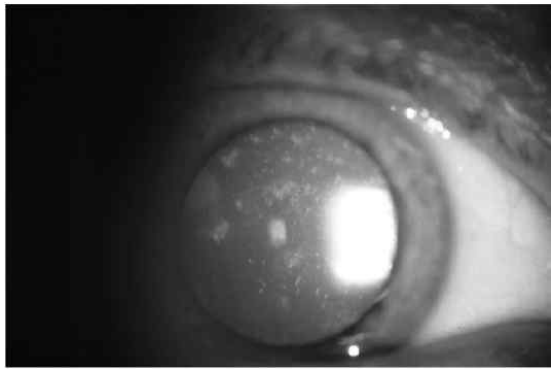
Approximately 100 mutations: incomplete penetrance and frequent late-onset

sensorimotor peripheral neuropathy

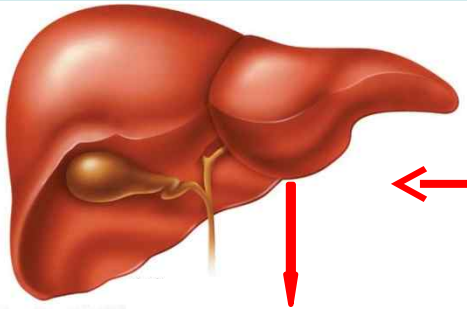
autonomic nervous system: orthostatic hypotension, altered GI motility (diarrhea alternating with constipation), impotence, and urinary disturbances

cardiac (arrhythmias, CHF)

some associated with renal, vitreous, or leptomeningeal amyloid



Reactive (AA) amyloidosis



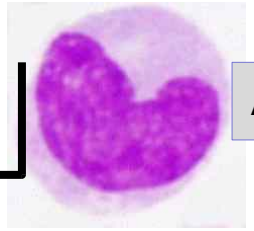
Sustained, marked increase of SAA (SAA1)

IL-1, IL-6, TNFα

Persistent Inflammation

- **Rheumatic Diseases**
- **Hereditary autoinflammatory dis.(FMF)**
- **Chronic infections**
- **Neoplasia**

Castleman dis.
Waldenström M.
Schnitzler s.
Hairy cell leuk.
Hodgkin lymph.



Abnormal processing of SAA by mononuclear phagocytes

Matrix metalloproteases proteolytic processing

Interaction with tissue glycosaminoglycans

SAP

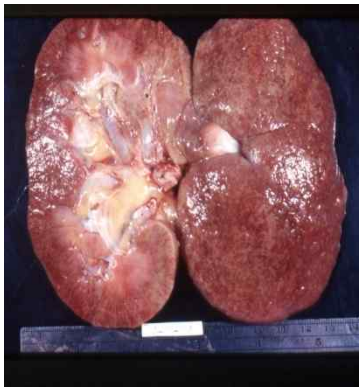
Amyloid Deposits

Kidney
GI tract
Spleen
Liver

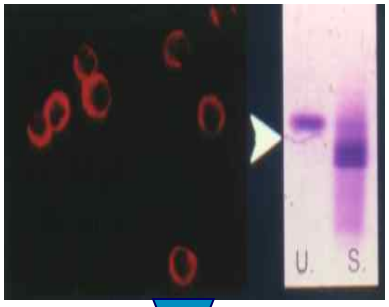
Systemic AL Amyloidosis

10/million person-year

1208 AL patients (620 males; median age 62, range 23-91)



kidney (72%)
Nephrotic s. 52%
Renal fail. 18%



λ6a

λ1c

λ 75%
k 25%

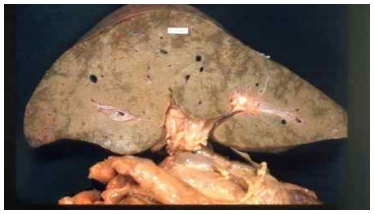
κ

PNS (19%)

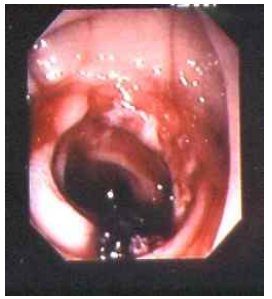
ANS (16%)

soft tissues (12%)

heart (63%)
CHF 20%

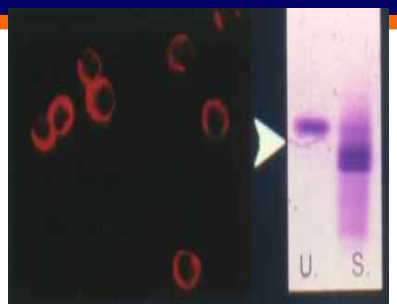


liver (26%)

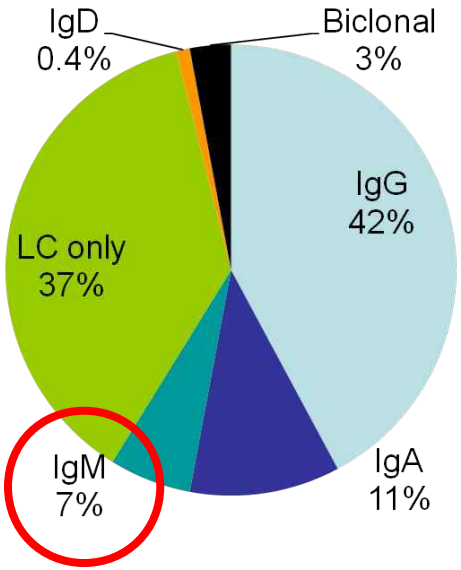


GI (8%)

AL Amyloidosis: characteristics of the amyloidogenic clone

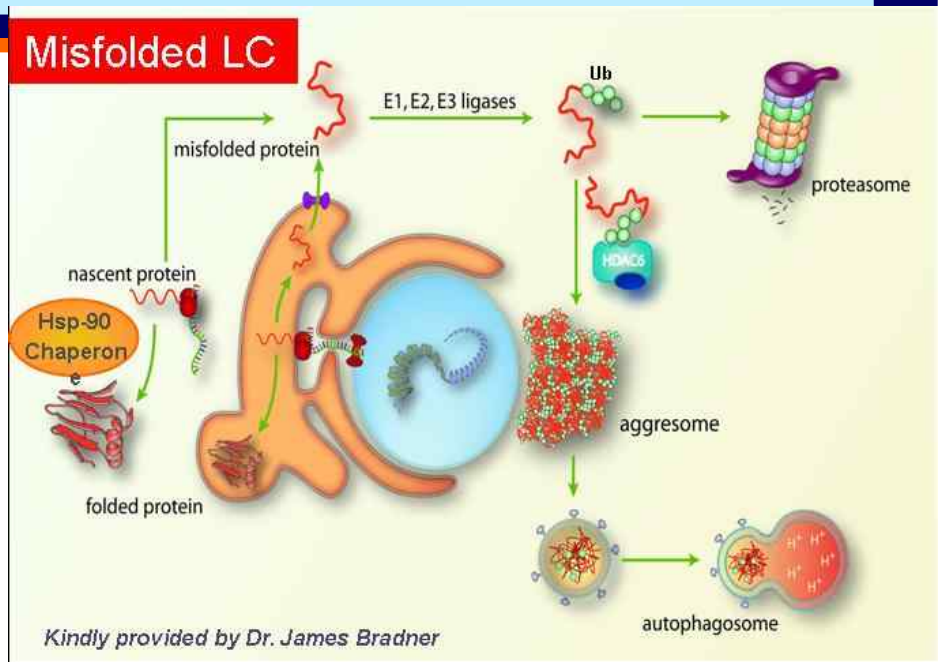


Small clone (median BMPC 7%)



t(11;14) in 39%, adverse prognosis
Bryce et al, Haematologica, 2009

About 40% express CD20
Deshmukh et al, J Clin Pathol 2009



proteasome capacity decreases during plasma cell differentiation
Sitia et al, 2007-2009

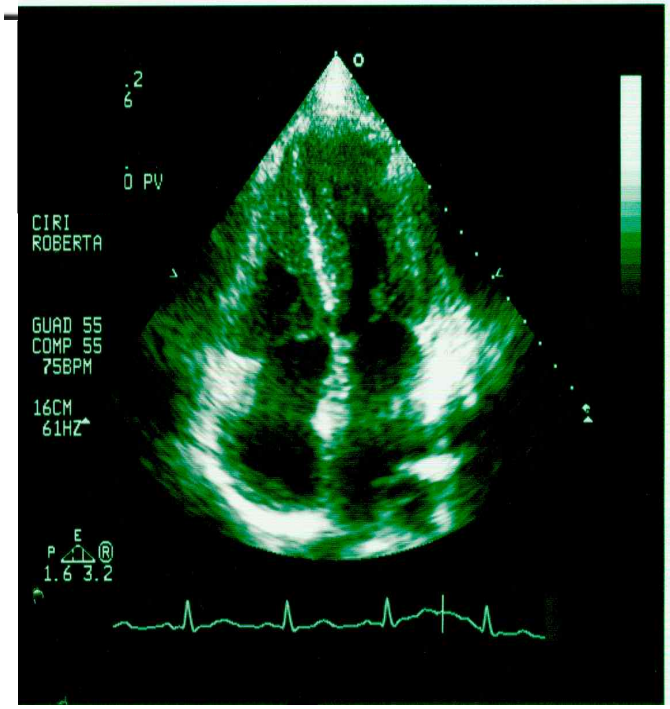
the production of misfolded light chains further increases the proteasome load and sensitizes the plasma cells to proteasome inhibitors

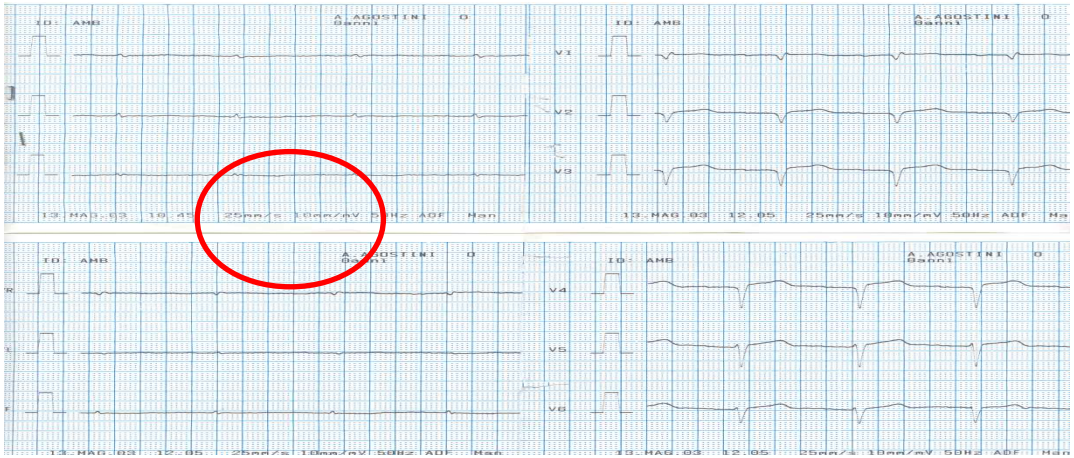
AL amyloidosis associated with monoclonal IgM protein: a distinct entity

Main characteristics

- Patients are older (median age 68 vs 61 yrs in non-IgM AL)
- The IgM spike is usually small
- The LC type is more frequently kappa and at low conc.
- Less frequent and less severe heart involvement (lower cardiac biomarkers) and kidney involvement (lower urinary protein conc.)

CARDIAC INVOLVEMENT IN AL AMYLOIDOSIS





Cardiac involvement is causing the death of ~ 80% of AL patients

It is the most important prognostic factor

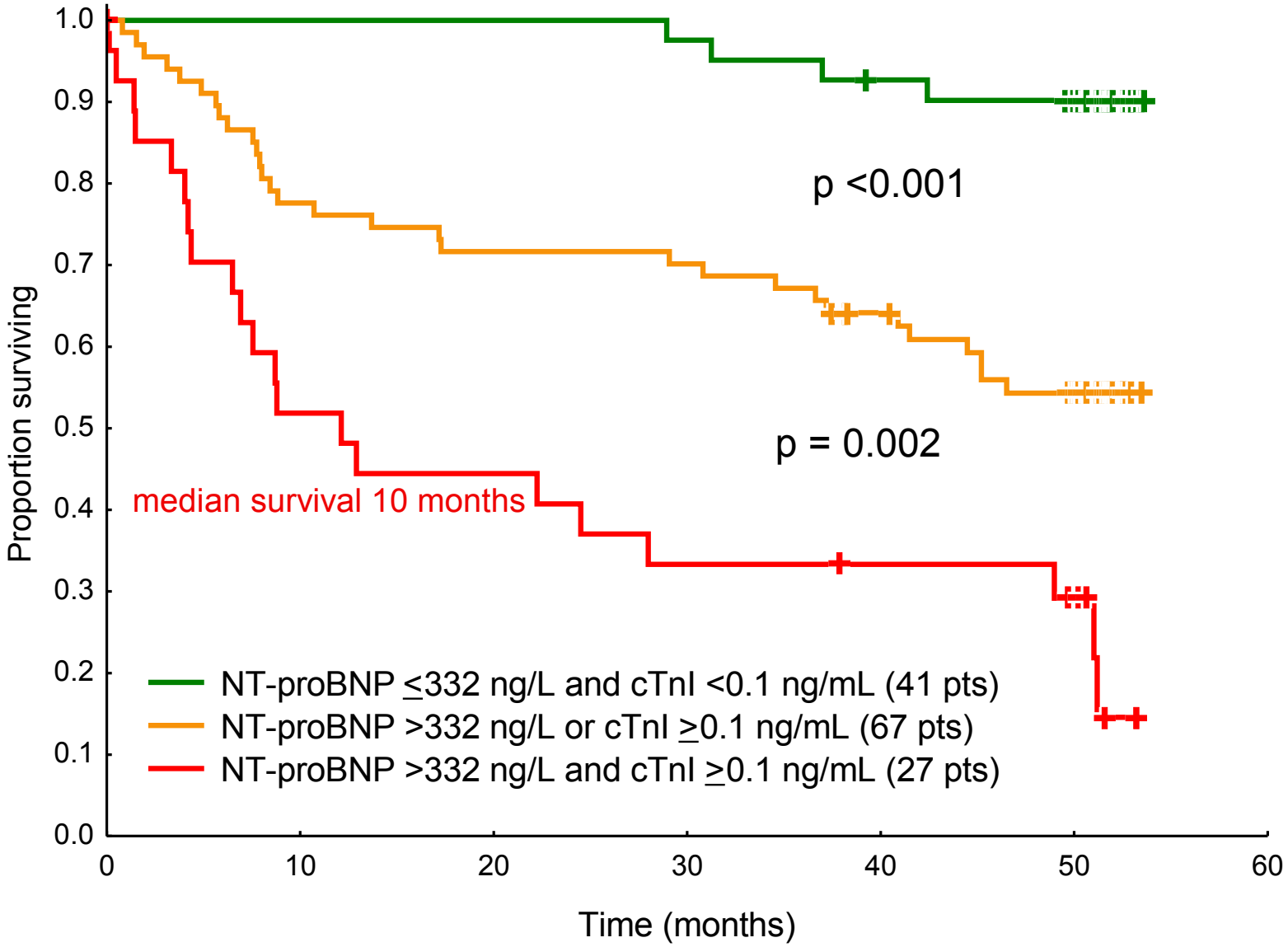
Cardiac biomarkers:

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

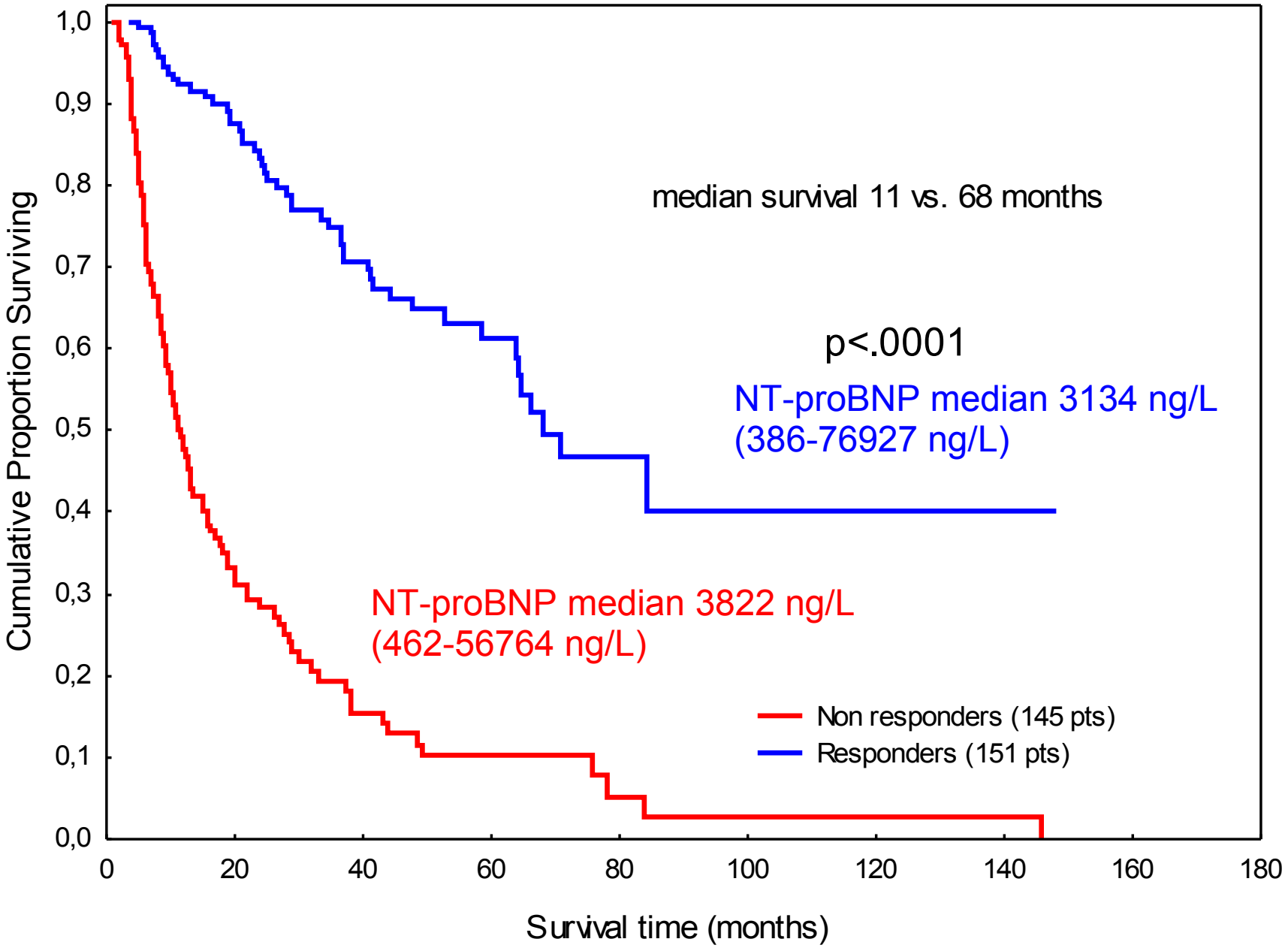
  Palladini et al, Circulation 2003; 107:2440-45
  Dispenzieri et al, Lancet 2003;361:1787-9

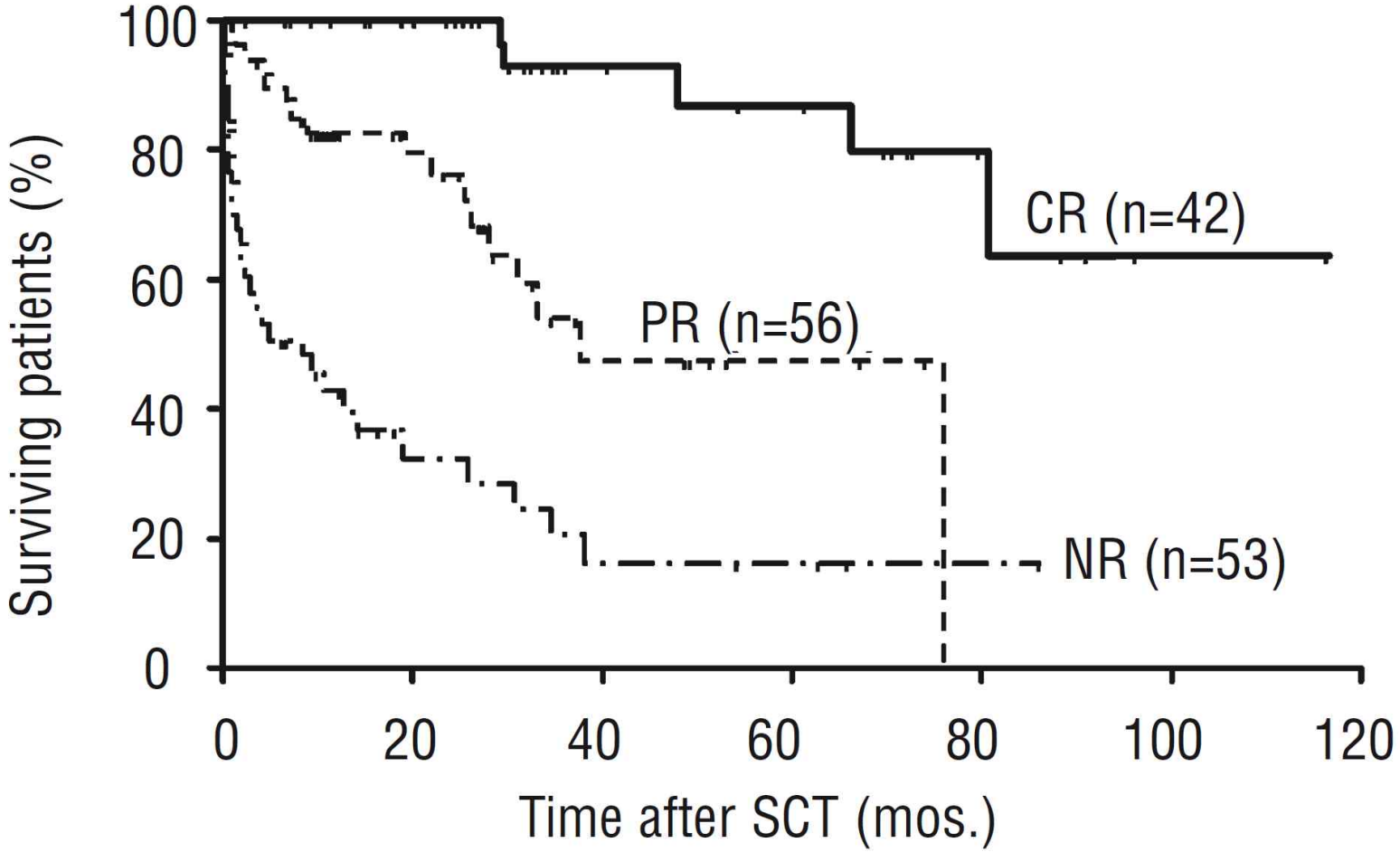
Staging system for AL amyloidosis
Dispenzieri et al, *J Clin Oncol 2004; 22:3751-3757*

Survival of 135 patients with AL amyloidosis according to NT-proBNP and cTnI (Dispenzieri's staging system)



Survival of 296 patients with AL amyloidosis with **cardiac involvement according to hematologic response to no-HD-chemotherapy**





Overall survival after transplantation of patients with **cardiac amyloidosis** (n=151). Patients were stratified according to hematologic response ($p<0.001$)

Gertz et al, Haematologica 2007; 92:1415-18

Cox multivariate analysis of survival

1208 patients

- hematologic response: p= 9.1□10-28 (protective)
- heart involvement: p= 1.8□10-12

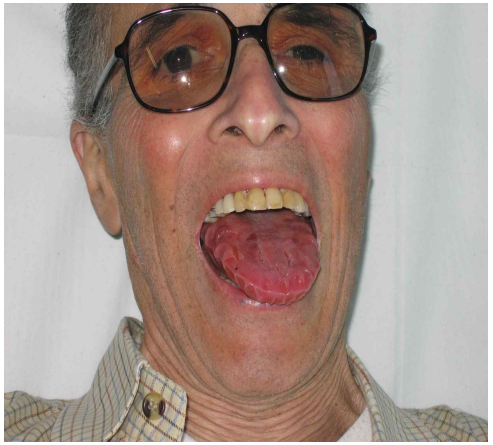
DIAGNOSING AMYLOIDOSIS

A clinician should suspect amyloidosis whenever a patient presents with:

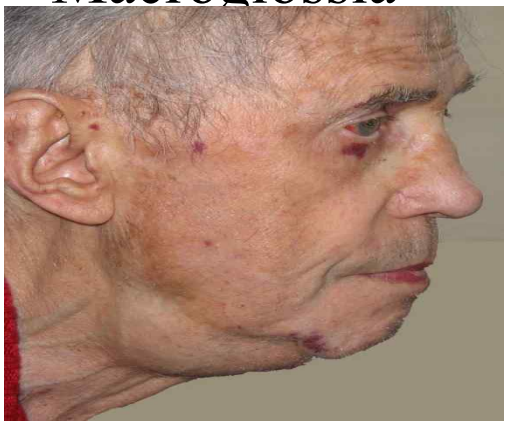
- non-diabetic proteinuria
- non-ischemic cardiomyopathy
- hepatomegaly with no scan defects
- progressive peripheral neuropathy
- orthostatic hypotension, autonomic neuropathy (diarrhea, impotence)
- unexplained weight loss (> 8 kg/6 mos)

Clinical presentation in patients with AL

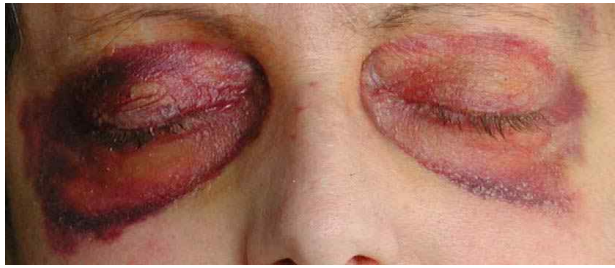
	%
Fatigue	68
Peripheral edema	62
Weight loss (kg) median 8 (2-30)	43
Exertional dyspnea	40
Orthostatic hypotension	27
Dysesthesias, Paresthesias	23
Dysgeusia	18
Macroglossia	14
Purpura	11
Diarrhea	9



Macroglossia



Submandibular swelling (15%)

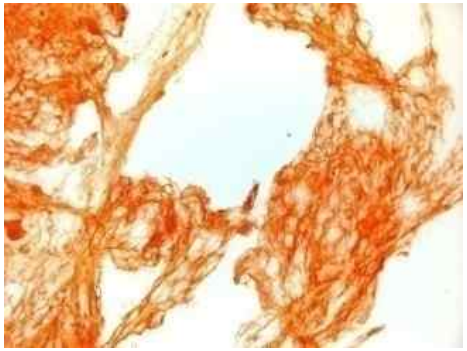


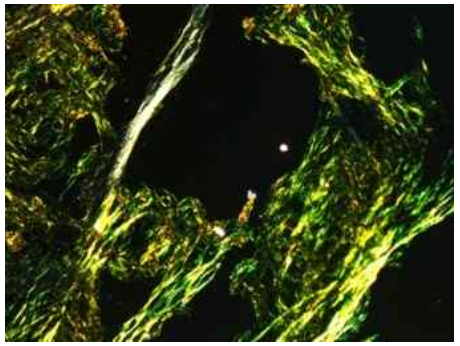
Periorbital purpura

Diagnosis of amyloidosis relies on tissue biopsy

· Tissue of choice: abdominal fat

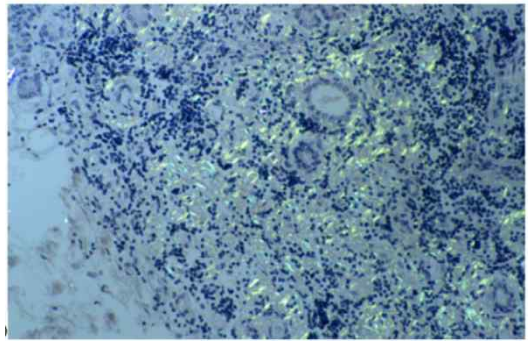
· Available from virtually all patients, innocuous, fast, inexpensive: **sensitivity 88%, specificity 97%**



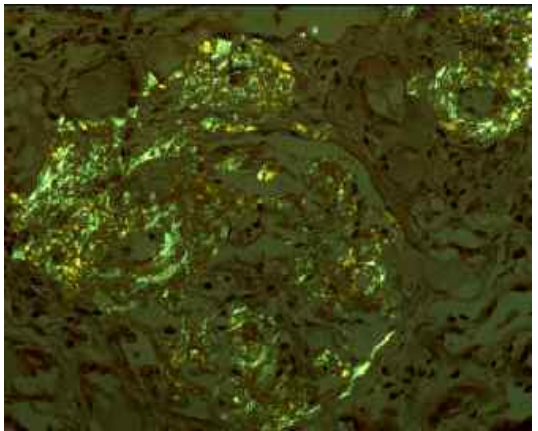


Congo red stain

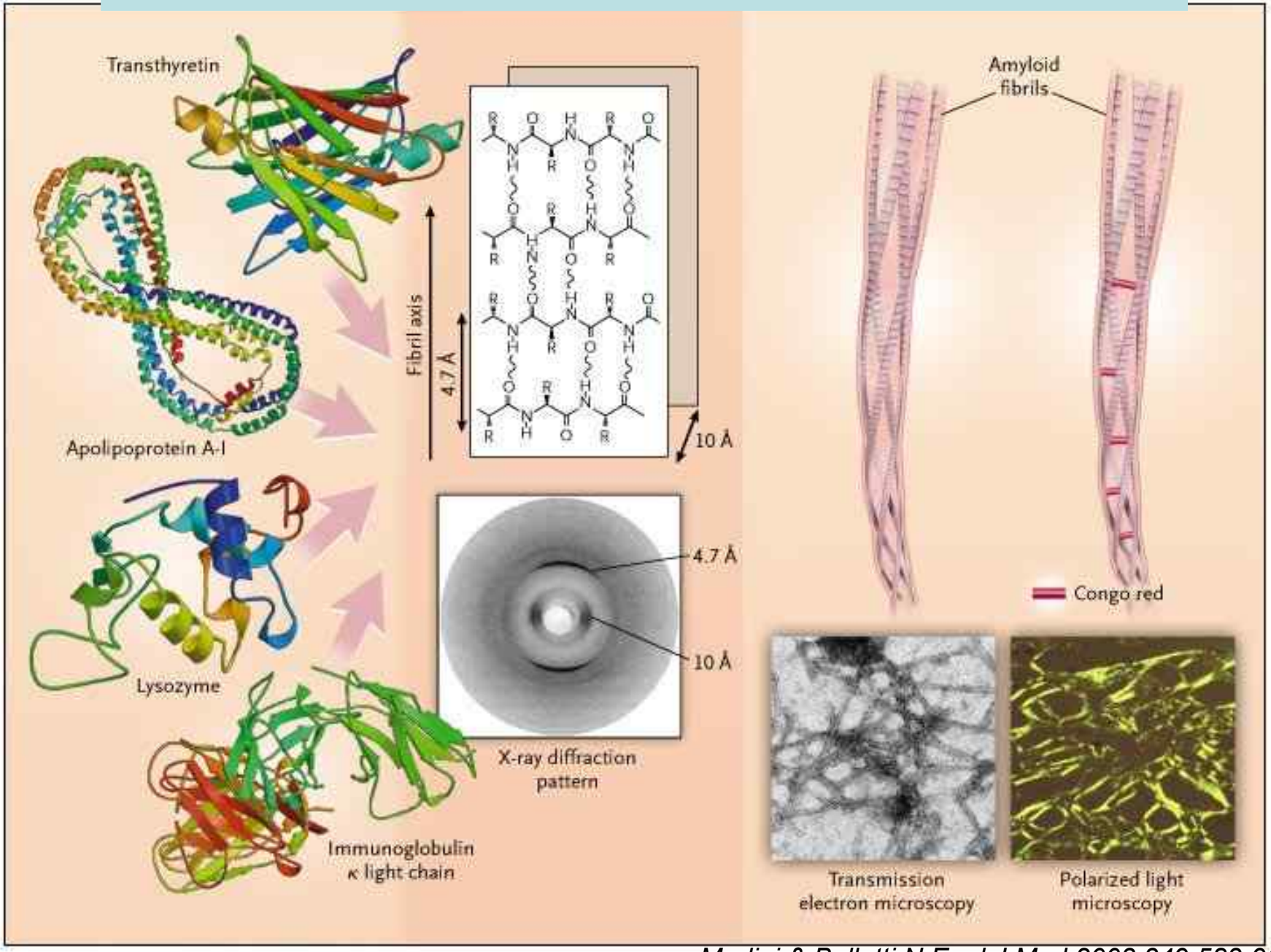
Biopsy of the labial minor salivary glands



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



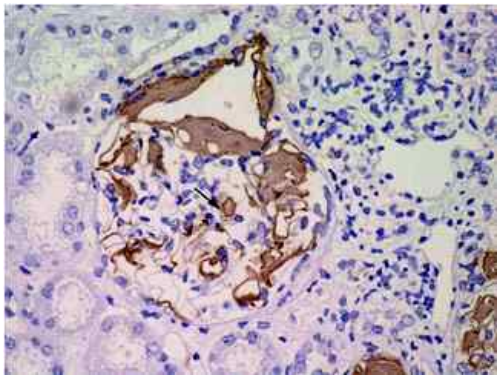
Amyloidosis: protein misfolding disease

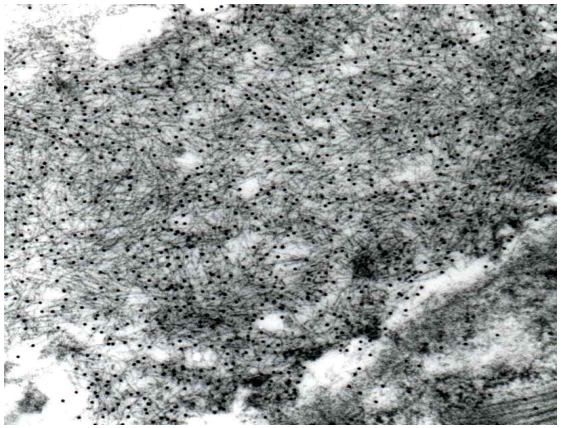


Merlini & Bellotti N Engl J Med 2003;349:583-96

Typing of amyloidosis is essential for the choice of therapy

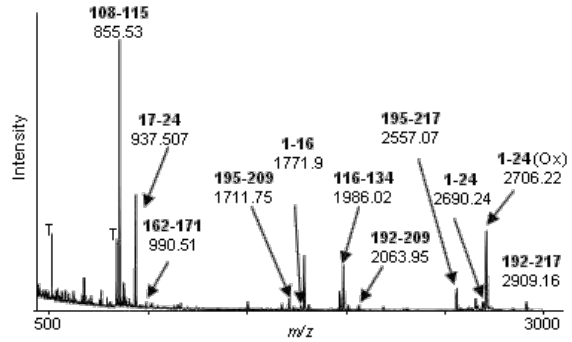
Immunohistochemistry
effective for AA, unreliable in AL



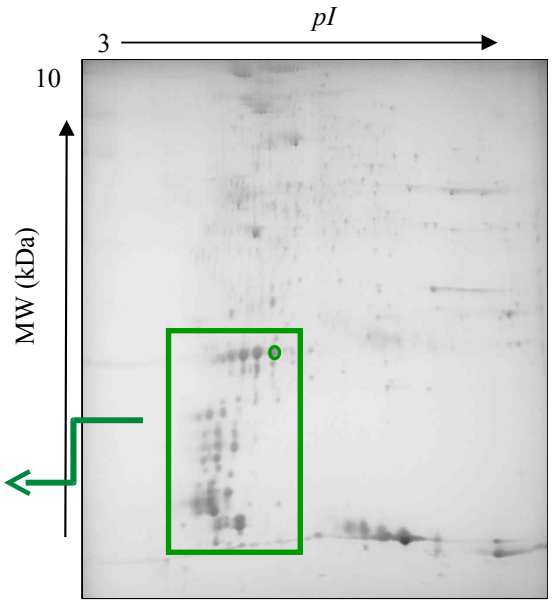


Ultrastructural (EM) immunohistochemistry
sensitivity 93%, specificity 99%

Protein identification by MS

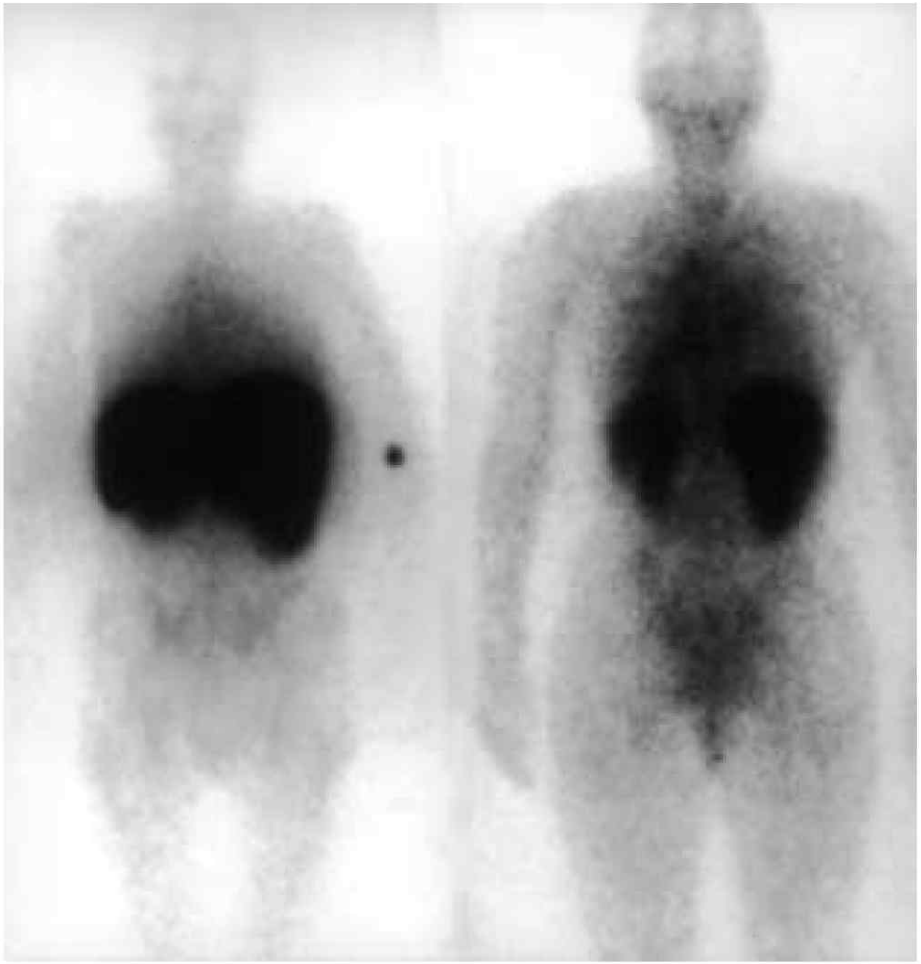


DNA analysis



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

AL Amyloidosis: diagnostic investigations

1. Immunofixation electrophoresis of serum **and urine** and FLC assay

Diagnostic sensitivity of IFE and FLC □/□ ratio in 115 patients with systemic AL amyloidosis

Palladini et al, Clin Chem. 2009;55:499-504.

Technique	Overall (n. 115)	κ clones (n. 30)	λ clones (n. 85)
	% positive (95% CI)		
IFE serum	80 (72-87)	60 (42-76)	87 (79-93)
urine	67 (58-75)	70 (52-84)	65 (55-75)
serum+urine	96 (91-98)	90 (75-97)	98 (92-100)
FLC κ/λ ratio	88 (68-94)	97 (85-100)	82 (69-89)
IFE serum + FLC κ/λ	96 (91-98)	100 (90-100)	94 (97-98)
IFE serum+urine+FLC κ/λ	100 (97-100)	100 (90-100)	100 (96-100)

In patients with AL amyloidosis urine immunofixation should be performed to ensure best diagnostic sensitivity

Screening Panels for Detection of Monoclonal Gammopathies

Katzmann et al, Clin Chem. 2009;55:1517-22

Table 3. Screening panels for different plasma cell disorders.

	Serum PEL	Serum FLC	Serum IFE	Urine PEL/IFE
MM	Yes	Yes		
WM	Yes	Yes		
SMM	Yes	Yes		
MGUS	Yes	Yes		
Plasmacytoma	Yes	Yes	Yes	
POEMS	Yes	Yes	Yes	
AL	Yes	Yes	Yes	Yes
LCDD	Yes	Yes	Yes	Yes

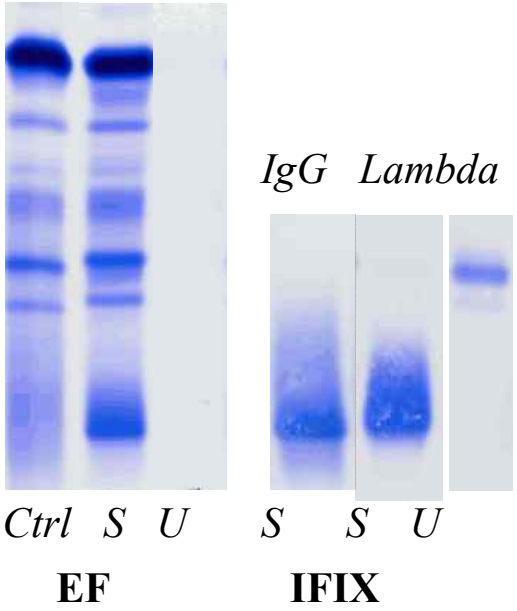
Data on 581 patients with AL amyloidosis

AL Amyloidosis: diagnostic investigations

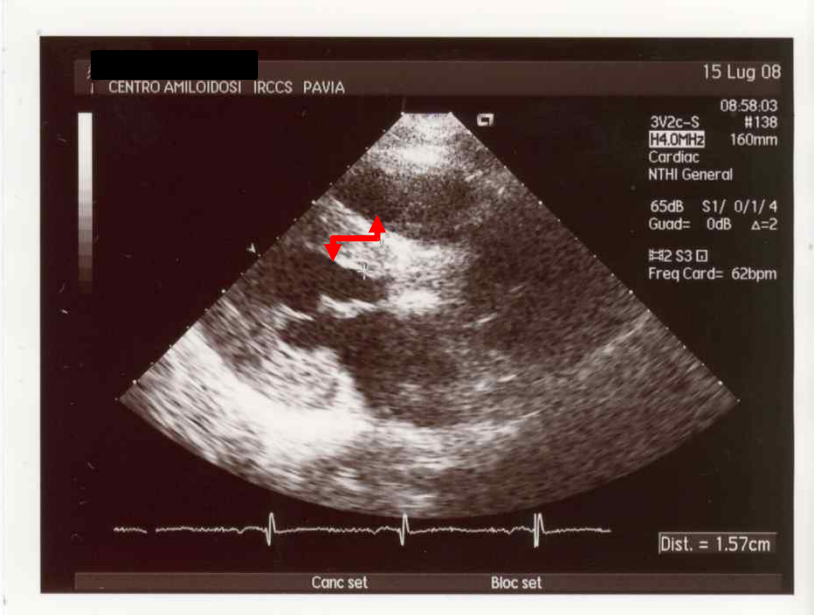
1. Immunofixation electrophoresis of **serum and urine** and FLC assay
1. Bone marrow aspiration, median bone marrow plasma-cell: 7% (1-30%), 6% of patients having >20%, □/□ ratio by immunofluorescence
1. Bone x-ray
1. Beware: up to 10% of patients with hereditary amyloidosis have a monoclonal gammapathy
1. Clinically, it is difficult to distinguish between the various types of amyloidosis
1. In old male patients consider systemic senile amyloidosis (wt TTR): 8-25% older than 80

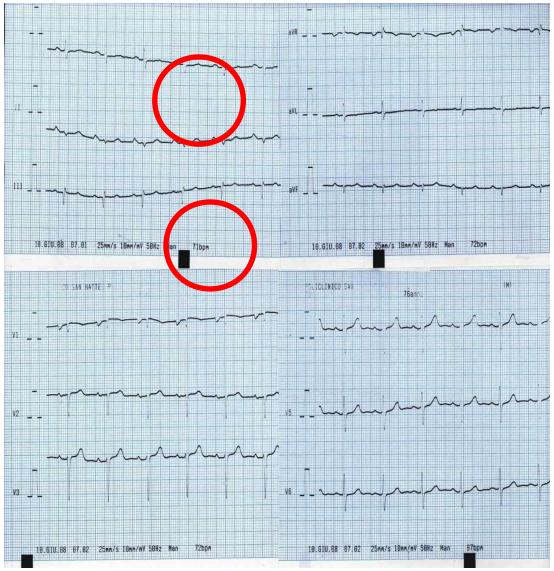
Man, 65-years old

- February 2006 Occasional identification of a monoclonal protein
  - Family history and past personal medical history: silent
  - Serum and urine immunofixation: IgG□ (1.48 g/dL) + BJP□
  - FLC: κ 9.97 mg/L, λ 59 mg/L (rif. <26.3), κ/λ ratio 0.17 (range 0.26-1.65)
  - Proteinuria 0.04 g/24h, serum creatinine 1.1 mg/dL
  - Normal Hb and calcemia
  - NT-proBNP 199 pg/mL (rif < 227); TnI 0.01 ng/mL



- January 2008 **Man, 65-years old**
  - IgG□ (1.3 g/dl) + BJP□
  - FLC λ 52.3 mg/L (rif. <26.3), κ/λ 0.15 ratio
  - NT-proBNP 577 pg/mL; TnI 0.05 ng/mL (rif. <0.06)
  - Infiltrative cardiomiopathy on echocardiography (IVS: 15.7 mm; PW: 15 mm; EF:50%), ECG: Q wave in V1 and V2
  - Heart MRI: myocardial hypertrophy, late enhancement
  - ECG Holter: unsustained ventricular tachycardia
  - **Genetic tests for TTR and Apo-AI: negative**



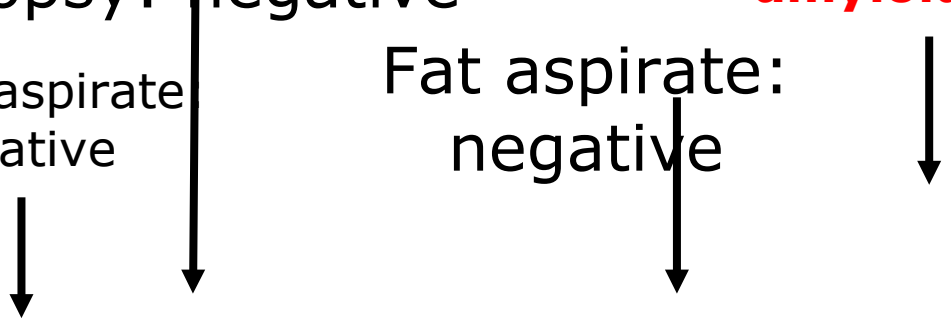


Minor labial salivary glands biopsy: negative

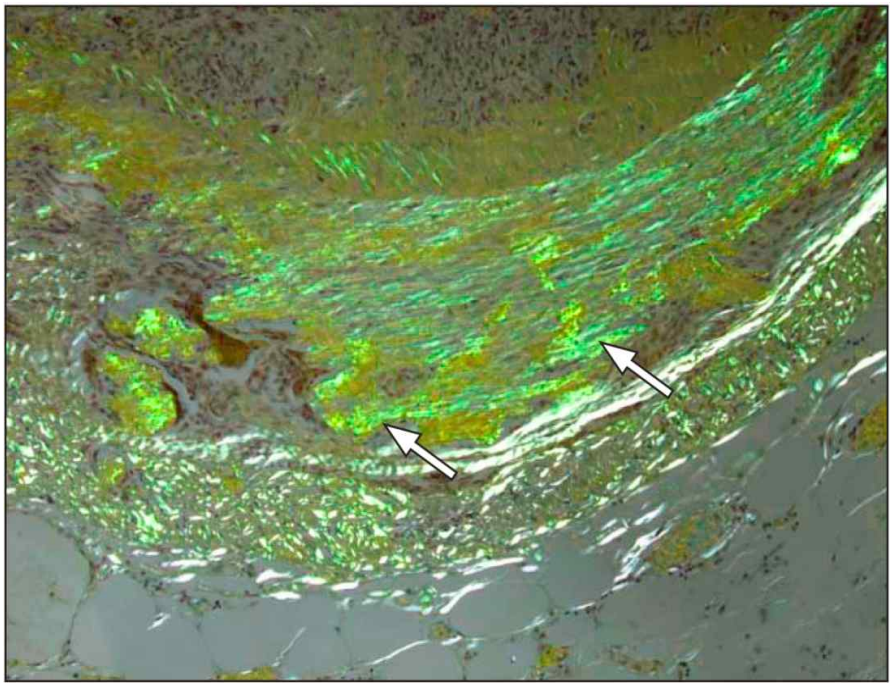
1st fat aspirate negative

Fat aspirate: negative

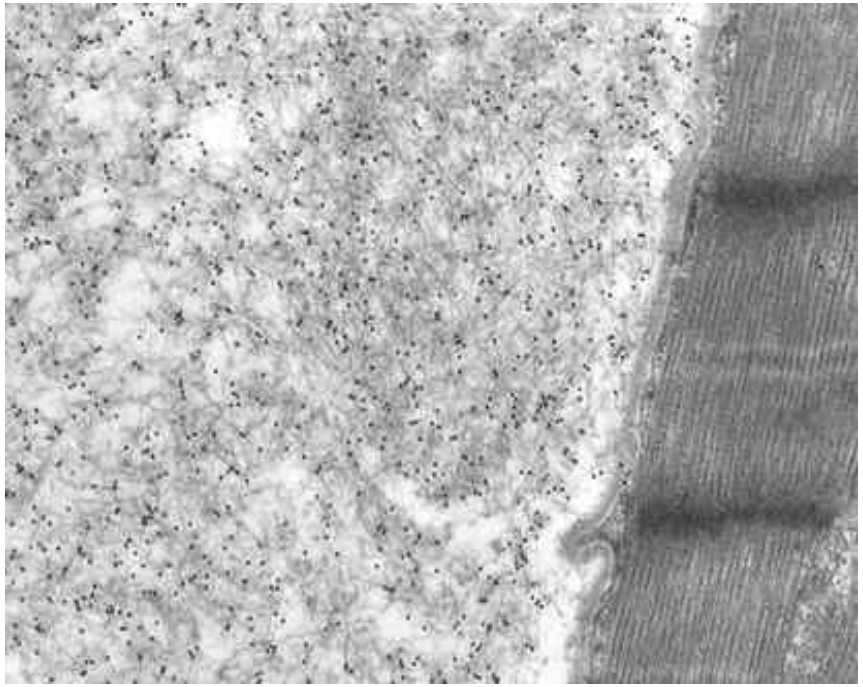
endomyocardial biopsy: amyloidosis



Endomyocardial biopsy



Green birefringence under polarized light after Congo red staining



EM-immunohistochemistry anti-TTR antibody

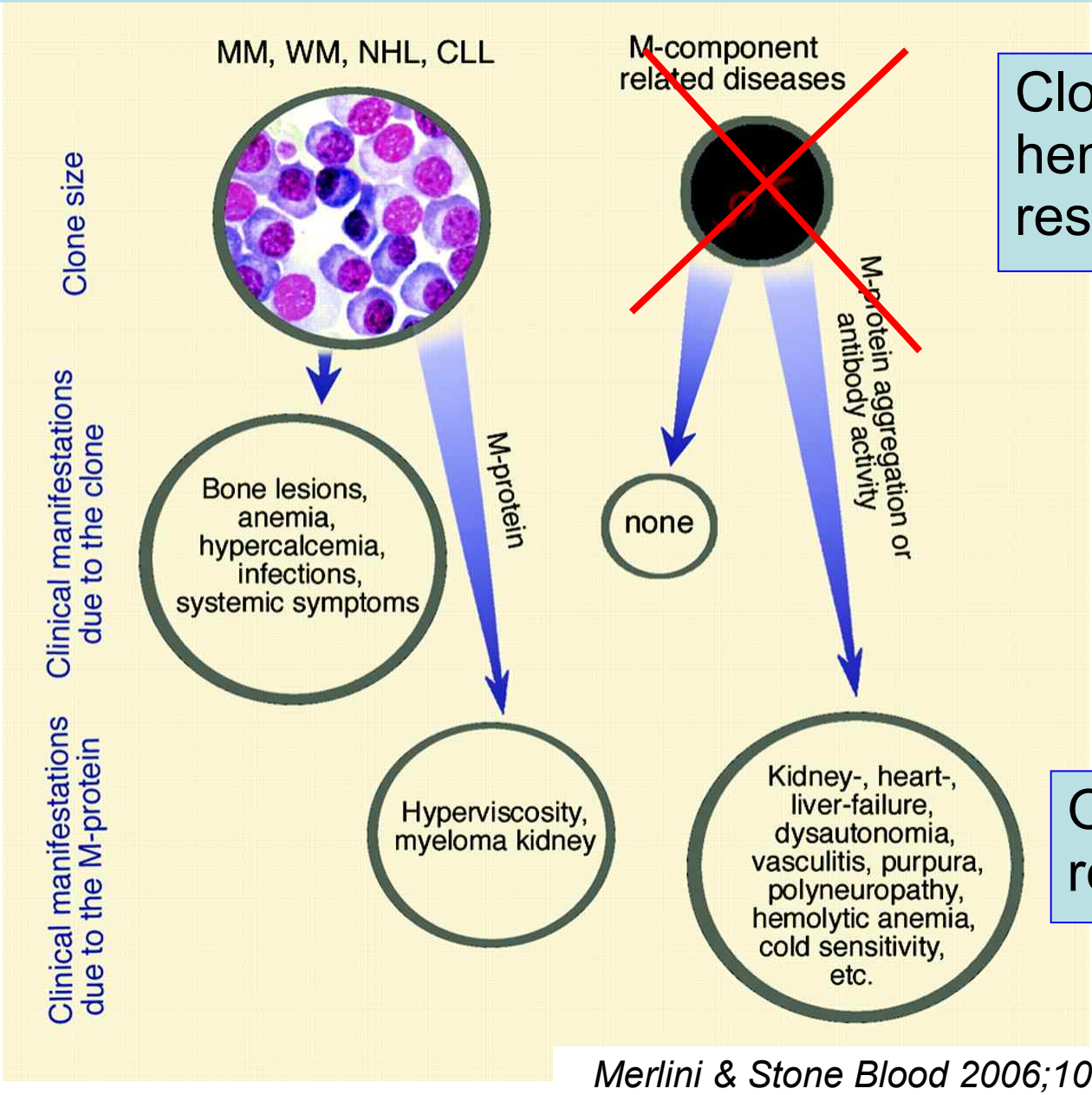
Diagnosis: AL amyloidosis with heart involvement

Therapy: VMDex

Diagnosis: Senile systemic amyloidosis

Therapy: Transthyretin stabilizer

TREATMENT OF AL AMYLOIDOSIS



Clonal, hematologic response

Organ response

Merlini & Stone Blood 2006;108:2520-2530

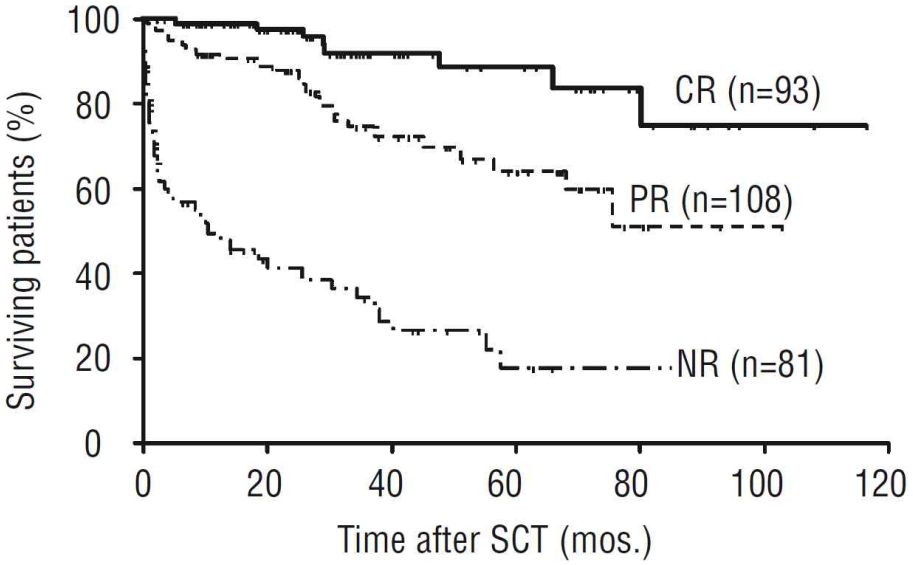
Definition of Organ Involvement and Treatment Response in Immunoglobulin Light Chain Amyloidosis (AL):A Consensus Opinion From the 10th International Symposium on Amyloid and Amyloidosis

Criteria for organ response

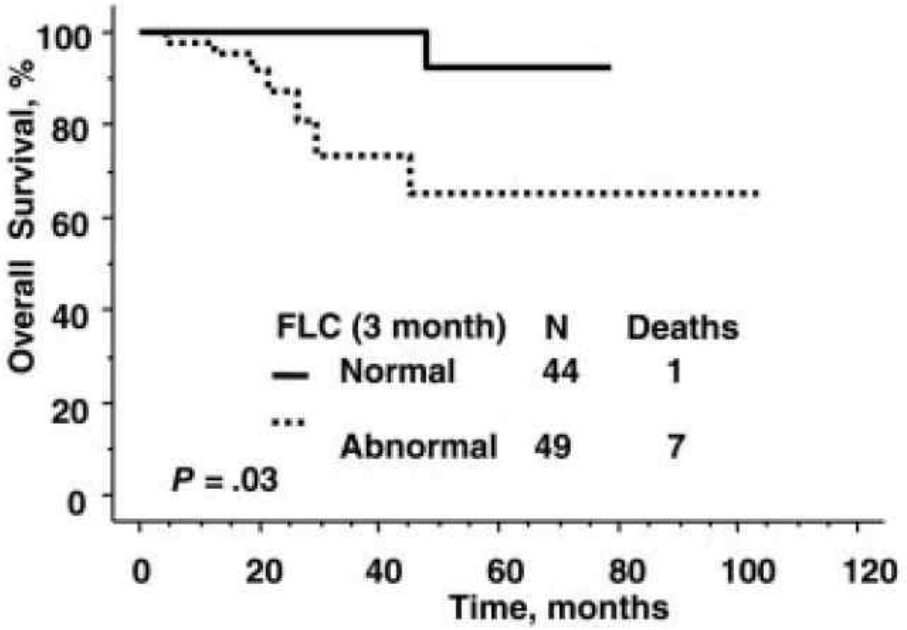
Heart	Mean interventricular septal thickness decreased by 2 mm, 20% improvement in ejection fraction, improvement by 2 NYHA classes **(NT-proBNP reduction >30% (>300 ng/L))**
Kidney	50% decrease (at least 0.5 g/day) of 24-hr urine protein (urine protein must be>0.5 g/day pretreatment) Creatinine and creatinine clearance must not worsen by 25% over baseline
Liver	50% decrease in abnormal alkaline phosphatase value Decrease in liver size radiographically at least 2 cm
Nerve	Improvement in electromyogram nerve conduction velocity (rare)

Gertz et al, Am. J. Hematol. 2005; 79:319–328

Effect of response on survival



Gertz et al, Haematologica 2007; 92:1415-18



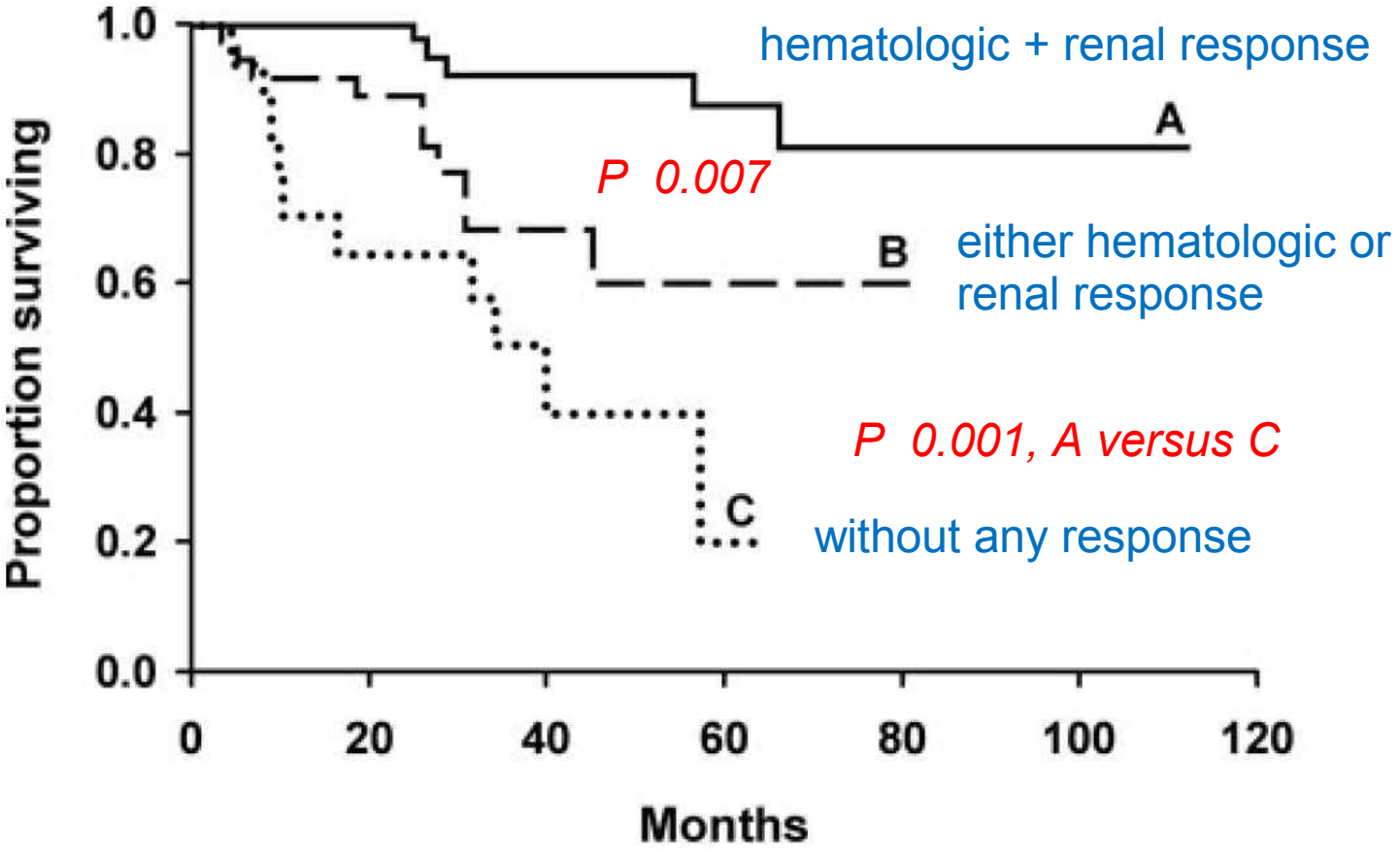
Dispenzieri et al, Blood. 2006;107:3378-3383)

The hematologic response of patients after transplantation is a valid study end point because it is associated directly with improved survival

The percent FLC reduction did not predict for survival, but the absolute level of FLC achieved after therapy did

Severity of Baseline Proteinuria Predicts Renal Response in Immunoglobulin Light Chain–Associated Amyloidosis after Autologous Stem Cell Transplantation

Leung et al, Clin J Am Soc Nephrol 2: 440-444, 2007



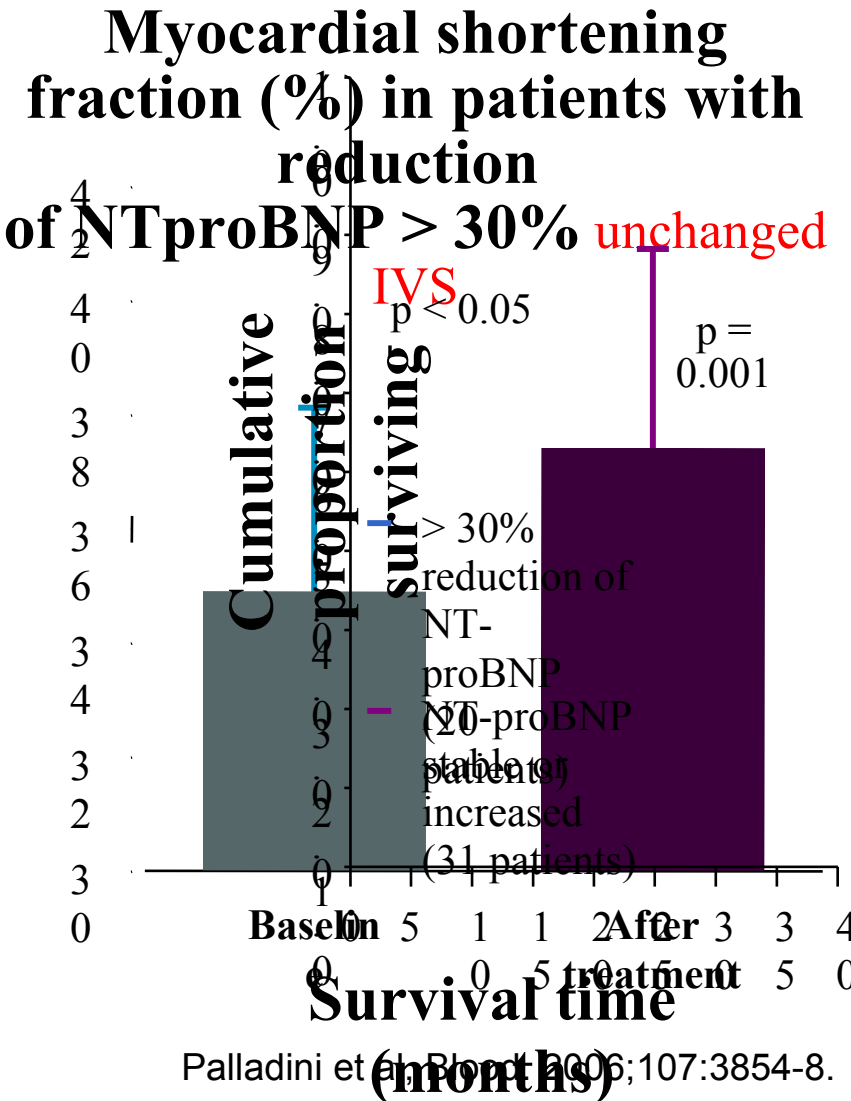
Landmark survival of 122 patients who were assessed from day 100 of autologous stem cell transplantation.

The beneficial effect of renal response was cumulative to the benefits of hematologic response

FLC and NT-proBNP response in 115 AL patients with cardiac amyloidosis

Haematological response	NT-proBNP decreased ≥ 30%
Complete response (elimination of the amyloidogenic light chain)	18/21 pts (86%)
Partial response (reduction to < 50% of the amyloidogenic light chain)	29/50 pts (58%)
No response	1/44 pts (2%)

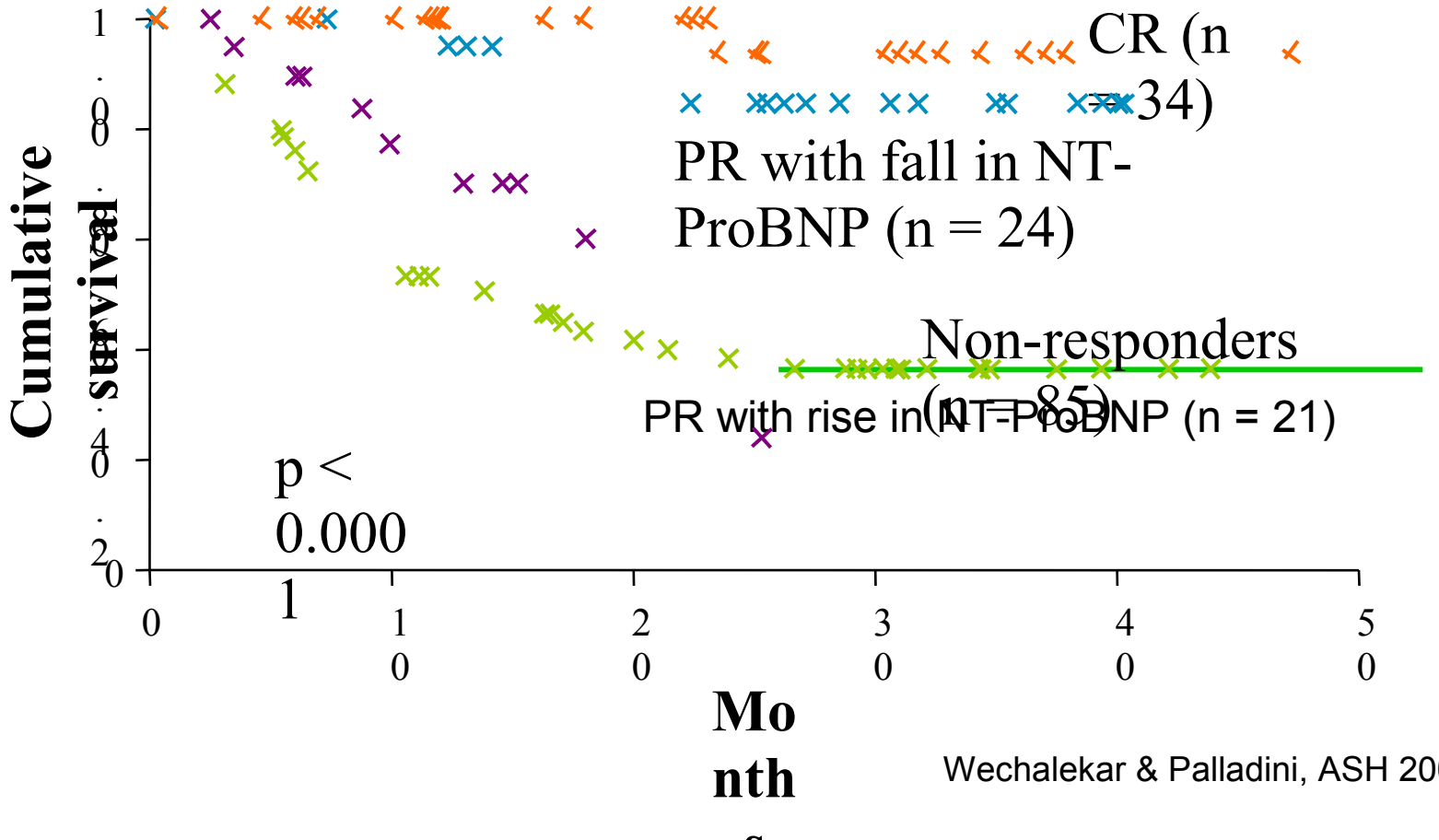
Palladini et al, 2008.



Palladini et al, Blood 2006;107:3854-8.

Survival according to haematological and cardiac response

Overall survival stratified by rise or fall in NT-ProBNP (n = 164) (UK National Amyloid Centre and Italian Amyloid Centre, Pavia)



Wechalekar & Palladini, ASH 2008.

A new paradigm for treatment strategies

Aim of therapy

- obtain **durable improvement** of AL amyloidosis-related organ function extend survival

Monitoring response to therapy

- Chemotherapy guided by frequent assessment of FLC and cardiac biomarkers (every 2 cycles)

- Organ response:
  - NT-proBNP, troponins, *rapid*
  - Kidney markers (proteinuria, s. creatinine) *median time to response: 10 mo (1 to 40 mo)*

Early intervention with aggressive therapy is recommended to achieve optimal response

Available treatments for AL amyloidosis

year

70s

90s

2000

2004

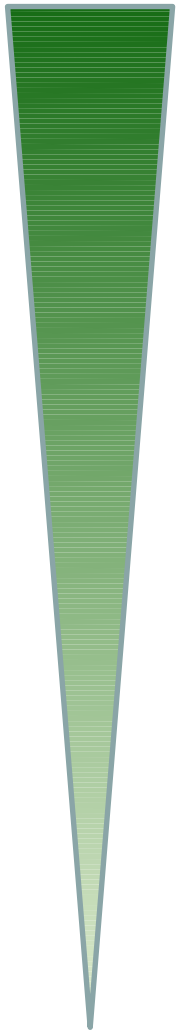
2005

2006

2007

2008

2009

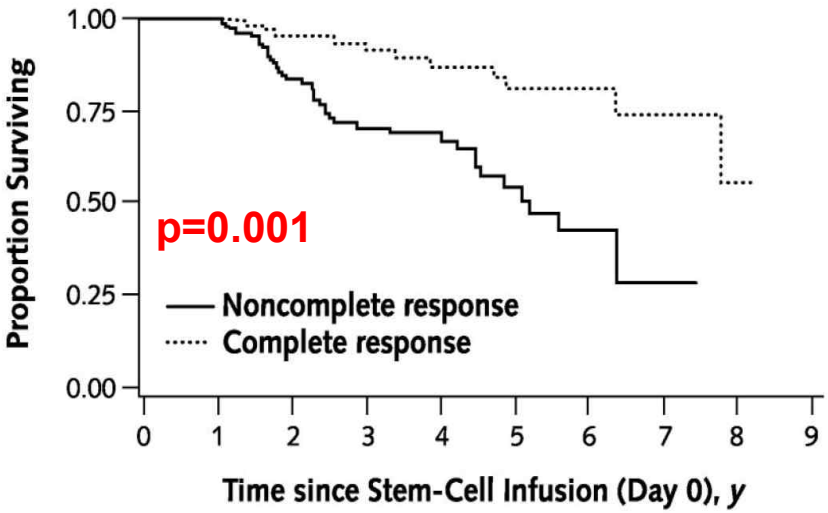


New drugs
antibodies

Regimen	Clonal response (PR + CR)	CR	Treatment Related Mortality
Melphalan-Pred.	28%	rare	0%
ASCT (MEL 200)	76%	33%	10-12%
(MEL 140-100)	53%	18%	16%
Dexamethasone	53%	24%	7% (SAE 59%)
MDex	65-68%	27-33%	2-4% (SAE 11-18%)
TDex	48%	19%	0% (SAE 48-65%)
CTDex	74%	15%	4% (SAE 32%)
Bortezomib ± Dex	50-83%	20-39%	3% (SAE 52%)
Lenalidomide ± Dex.	45-53%	22%	3-18% (SAE 86%, 9%TE)
CLenDex	39%	6%	0% (SAE 56%)

Autologous stem cell transplantation in AL amyloidosis

Skinner et al. Ann Intern Med 2004;140:85-93



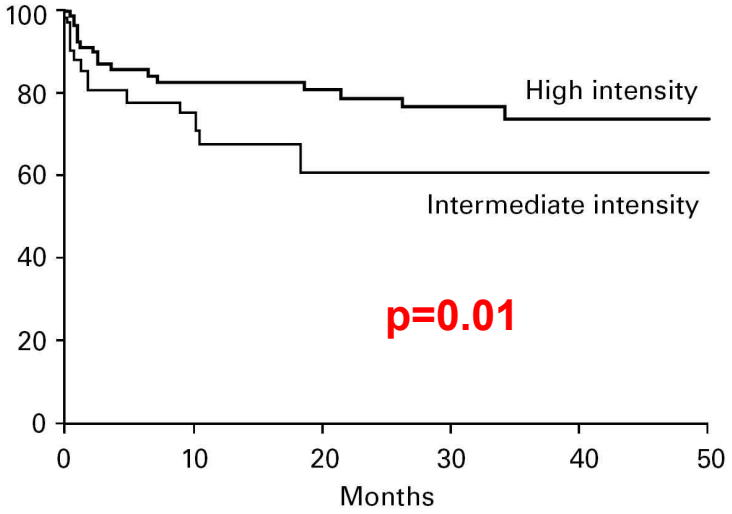
MEL 200: 155 pts;
MEL 140/100: 122 pts

complete remission (intent-to-treat):
MEL 200: 33%,
MEL 140/100: 18%

median survival:
MEL 200: 7.9 y,
MEL 140/100 2.9 y

TRM: 13%

Gertz et al. Bone Marrow Transplant 2004;34:1025-31



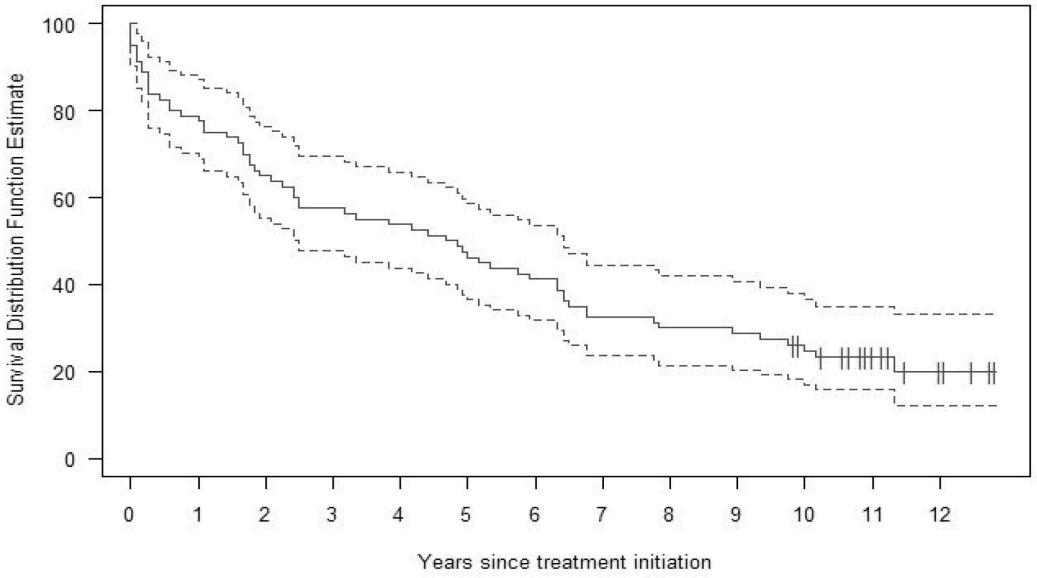
MEL 200: 103 pts;
MEL 140/100: 51 pts

hematologic response (intent-to-treat):
MEL 200: 76%,
MEL 140/100: 53%

TRM: 12%

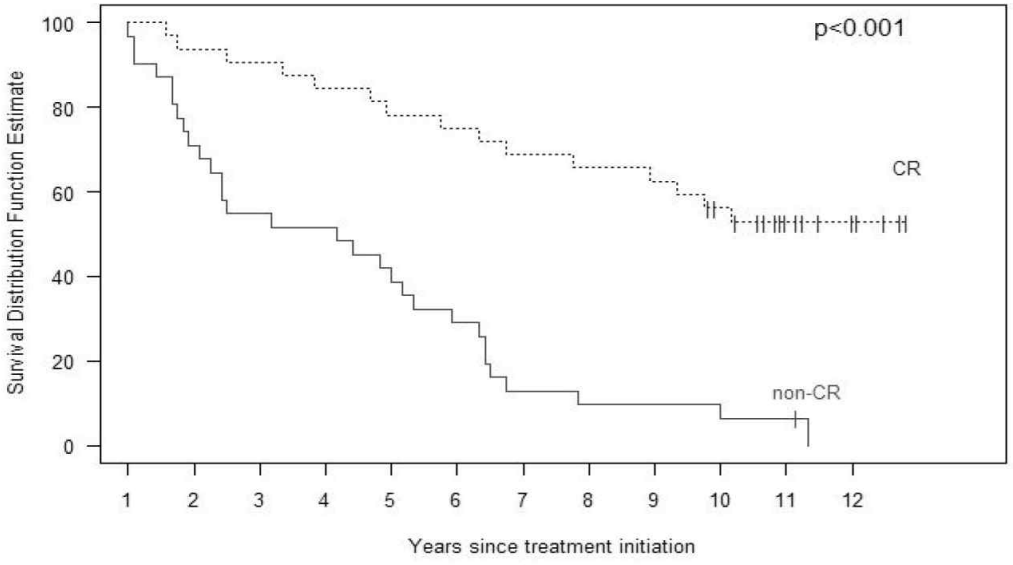
Long-Term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem cell transplantation

Sanchorawala et al, Blood. 2007;110:3561-3563



OS for all 80 patients treated with HDM/SCT more than 10 years ago (1994-1997). Median: 57 mos

OS according to hematologic response, comparing those patients who achieved a hematologic complete response at one year (dashed upper plot) to those who did not (solid lower plot).



Outcomes with SCT in large patient series

Author	N	TRM (%)	RR/CR	Organ Resp. (%)	Median Surv (yrs)	MEL200/ Red. dose
Goodman et al, 2006	92	23	37/20	NA	5.3	69/31
Vesole et al, 2006	107	27	32/16	26	3.9	46/54

Risk-adapted SCT with adjuvant thal/dex is feasible and results in low TRM (4.4%) and high haematological and organ response rates in AL patients.

Comenzo et al, British Journal of Haematology, 2007; 139, 224–233

Troponin T level as an exclusion criterion for stem cell transplantation in light-chain amyloidosis

Gertz et al, Leukemia & Lymphoma, 2008; 49: 36 – 41

Day 100 survival rate

	Troponin T level ≥0.06 µg/L (*n* = 40)		Troponin T level <0.06 µg/L (*n* = 231)		Total patients (*N* = 271)	
Patients	No.	%	No.	%	No.	%
Died before day 100*	11	28	16	7	27	10
Alive on or after day 100	29	72	215	93	244	90

*$P < 0.001$.

Patients with BNP levels less than 150 ng/L and troponin T levels less than 0.06 µg/L had an extremely low risk (1%) of early death.

Association of melphalan and high-dose dexamethasone is effective and well tolerated in patients with AL (primary) amyloidosis who are ineligible for stem cell transplantation *Palladini et al, Blood 2004;103:2936-8*

46 patients ineligible for ASCT: 70% heart involv. 76%> 2 organs involv.

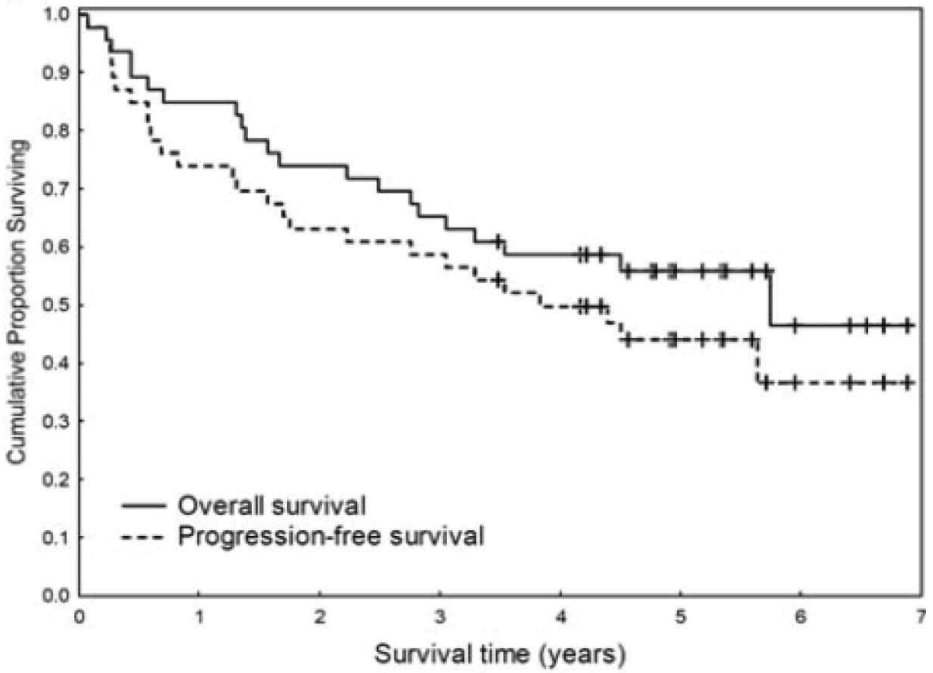
Treatment schedule:
M 0.22 mg/kg + Dex 40 mg on days 1-4 q28 days for up to 9 cycles

Outcome:
Hematologic response (intent-to-treat): **67% (CR 33%)**
Organ response: **48%**
(including 20% heart response)

Deaths on treatment: 4%

Grade □3 AE: 11%
(respiratory infections 9%)

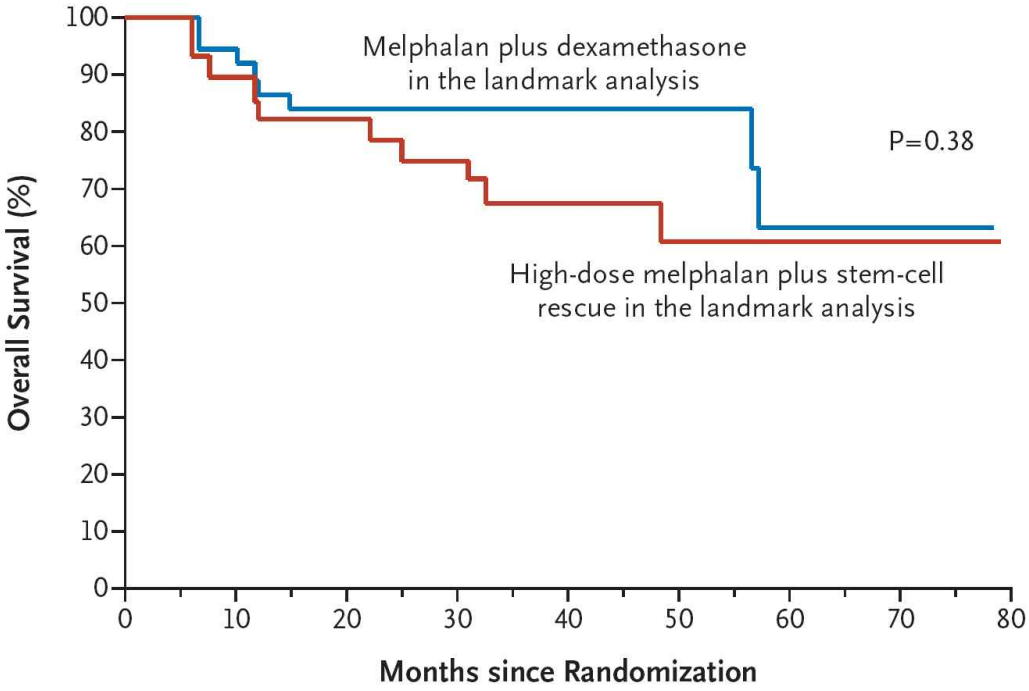
Progression-free (median, 46 mos) and overall (median, 61 mos) survival
Palladini et al, Blood 2007;110:787-8



High-dose i.v. melphalan and ASCT vs. oral M-Dex

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

Outcome	M-Dex N=38	ASCT N=27
CR	12 (32%)	11 (41%)
CR + PR	26 (68%)	18 (67%)
Organ R	39%	45%
TRM	1/43 (2%)	9/37 (24%)



Safety and efficacy of risk-adapted cyclophosphamide, thalidomide, and dexamethasone in systemic AL amyloidosis

Wechalekar et al, Blood 2007;109:457-64

75 patients (44 relapsed)

Treatment schedules:
CTD: C 500 mg on d 1, 8, 15 + T 100-200 mg/day + Dex 40 mg on d 1-4, 9-12 q21d
CTDa: C 500 mg on d 1, 8, 15 + T 50-200 mg/day + Dex 40 mg on d 1-4, 15-18 q28d

- Hematologic response: 74% (immunofixation-negative CR 15%)
- Organ response 26% (no heart response)
- TRM 4%, SAE 32%
- median OS 3.4 years
- spares stem cells

The activity of lenalidomide with or without dexamethasone in patients with primary systemic amyloidosis

	Dispenzieri et al, Blood 2007;109:465-70	Sanchorawala et al, Blood 2007;109:492-6
No patients (prev. treat.)	22 (13, 6 ASCT)	34 (31, 19 ASCT)
Schedule*	25 mg d1-21 q 28 days - if no resp. after cycle 3: + Dex 40 mg d 1-4, 15-18	The same but: Dex 10-20 mg d 1-4, 9-12, 17-20 every other cycle
Hematol. Resp.**	41%	47% (CR 21%)
To Lenalid. alone	4%	21%
Organ response	23%	21%
Toxicity (grade 3-4)	86%	
Neutropenia	45%	Myelosuppression 35%
Fatigue	18%	35%
Skin rash	18%	18%
Infection	18%	12%
Thromboembolism	9%	9%

* Dose reduction to 5-15 mg **Intention to treat

An open-label, phase II study of cyclophosphamide, lenalidomide and dexamethasone (CLD) for previously treated patients with AL amyloidosis

20 patients enrolled so far

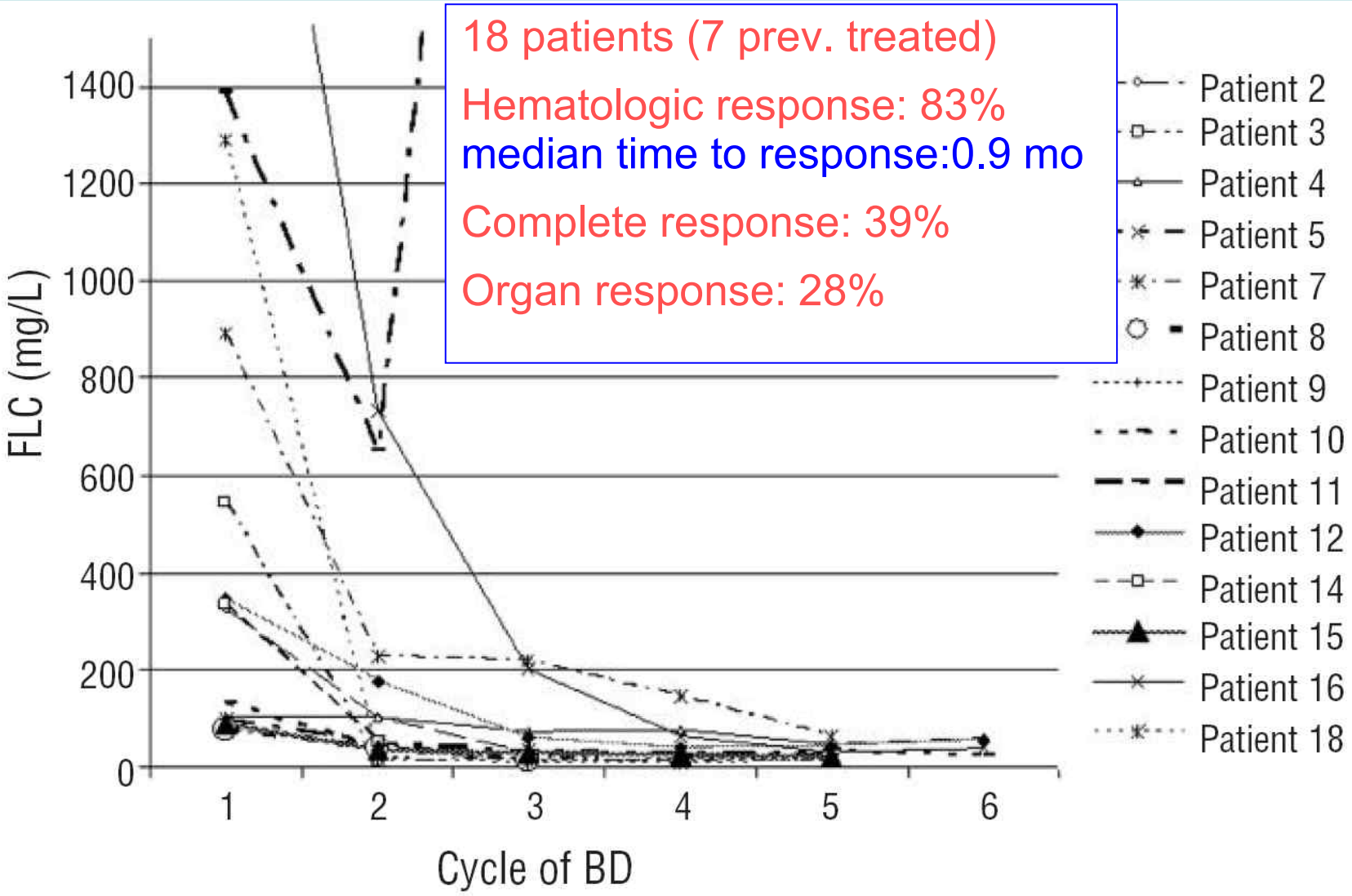
Treatment schedule: C 500 mg d 1, 8, 15
L 15 mg d 1-21 (adjusted according to Creat.clear)
D 40 mg d 1, 8, 15, 22
q28 days

Previous treatment (12 refractory / 8 relapsed):
melphalan 20 pts (100%)
thalidomide 5 pts (25%)
bortezomib 3 pts (15%)

Cardiac Stage (NT-proBNP + cTnI): I 30%
II 70%
III exclusion criterion

Treatment of light chain (AL) amyloidosis with the combination of bortezomib and dexamethasone

Kastritis et al, Haematologica 2007;92:1351-8
Wechalekar et al, Haematologica 2008; 93:295-8



Weekly and twice-weekly bortezomib in patients with systemic AL amyloidosis: results of a phase 1 dose-escalation study

Reece, et al Blood 2009;114:1489-1497

- **31 patients previously treated** enrolled in the phase I part of the trial
- bortezomib **once weekly** (0.7-1.6 mg/m2; days 1, 8, 15, and 22; 35-day cycles) and **twice weekly** (0.7-1.3 mg/m2; days 1, 4, 8, and 11; 21-day cycles) up to 8 cy

- Hematologic response: 50% - Median time to first response: 1.2 months
  - Complete: 20%
  - Partial: 30%

- Organ response:
  - Renal: 26%
  - Cardiac: 16%
  - Nerve: 11%

- Grade 3/4 treatment-related adverse events: 52%
  - Fatigue: 23%
  - Thrombocytopenia 6%
  - **CHF: 6%**

Significant activity of bortezomib-based therapy in patients with primary systemic (AL) amyloidosis

Kastritis et al, JCO 2009 in press

- 94 patients from 3 Centers: Athens, London, Pavia
- 19% received the combination upfront, 81% had a median of 2 previous therapies; 69% had refractory disease; 73% had heart involvement

- Hematologic response: 71% within a median of 1.7 months
  - Complete: 25% (in previously untreated: 47%)
  - Median time to clonal progression: 25 months

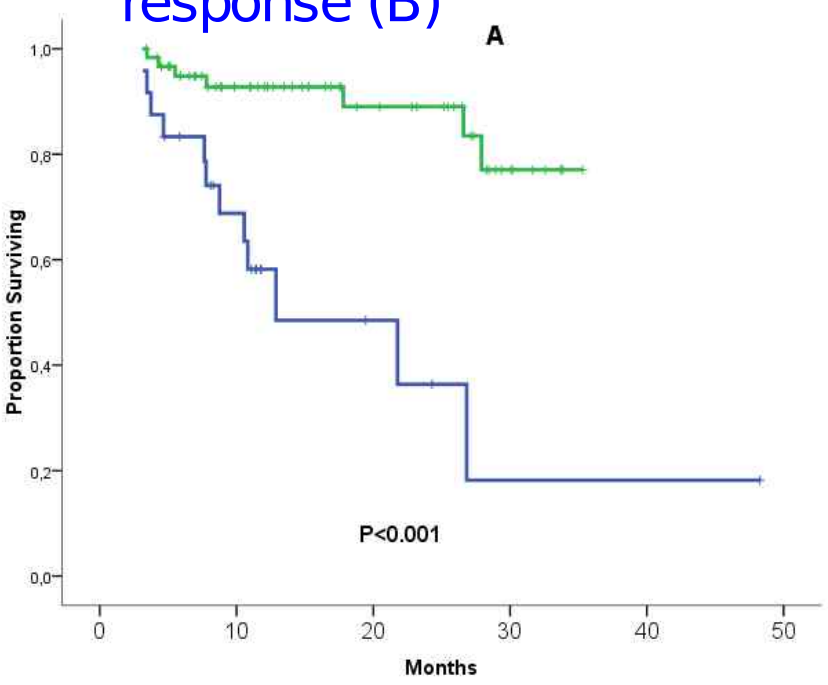
- Organ response (30%):
  - Cardiac: 29%
  - Liver: 22%
  - Renal: 19%

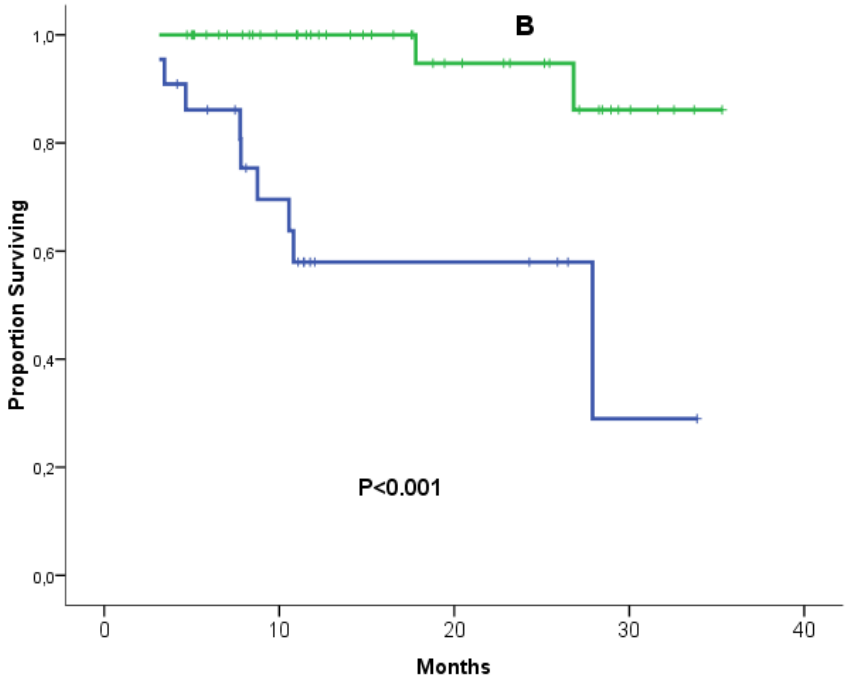
- Grade 2/4 peripheral neuropathy: 30%
- Grade 3/4 toxicities: 29%
  - Edema: 23%
  - Orthostatic hypothension: 13%%

Significant activity of bortezomib-based therapy in patients with primary systemic (AL) amyloidosis

Kastritis et al, JCO 2009 in press

Survival according to hematologic (A) and NT-proBNP response (B)





Multivariate analysis of survival

- baseline NT-proBNP: p=0.001
- ECOG performance status >1: p=0.028

Strategy for AL treatment

Good risk 15%
< 60 yr, 1 or 2 organs involved
Creatinine clear. ≥ 60 ml/min
normal NT-proBNP and troponins

→ Novel agents + MEL 200

Intermediate risk 65%

→ MDex (VMDex) CTD

Poor risk 20%
High NT-proBNP and cTn
severe comorbidity

→ MDex20 VMDex20

Isolated Heart
< 60 yr

→ Heart Transpl.

→ ASCT

Relapsing patients

→ Repeat 1st line treatment

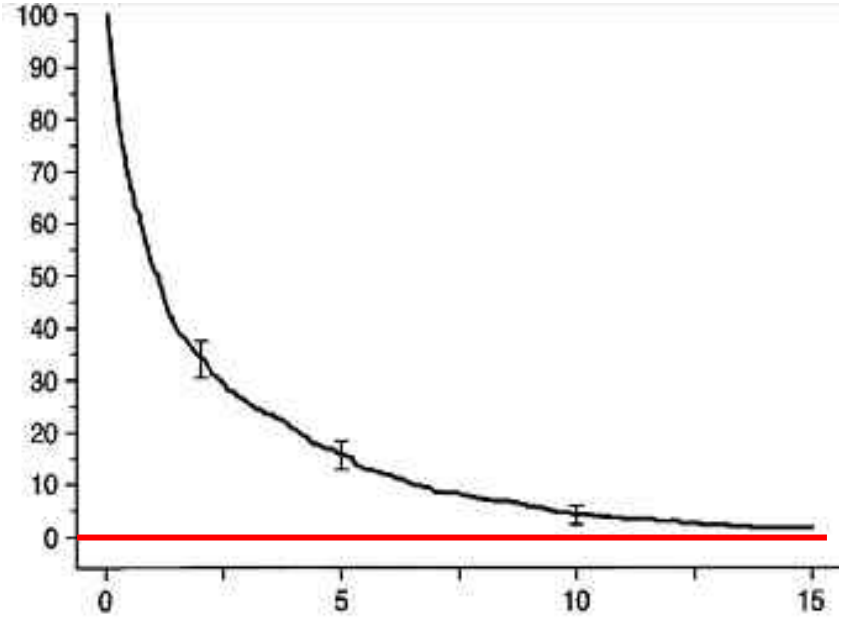
→ TDex RDex CRDex VDex

Refractory patients

→ CRDex (VRDex)

SUPPORTIVE THERAPY
Sequential solid organ (heart) □ stem cell transplantation

Are we making in progress with treating AL amyloidosis ?



Kyle et al. Blood; 93(3);1999

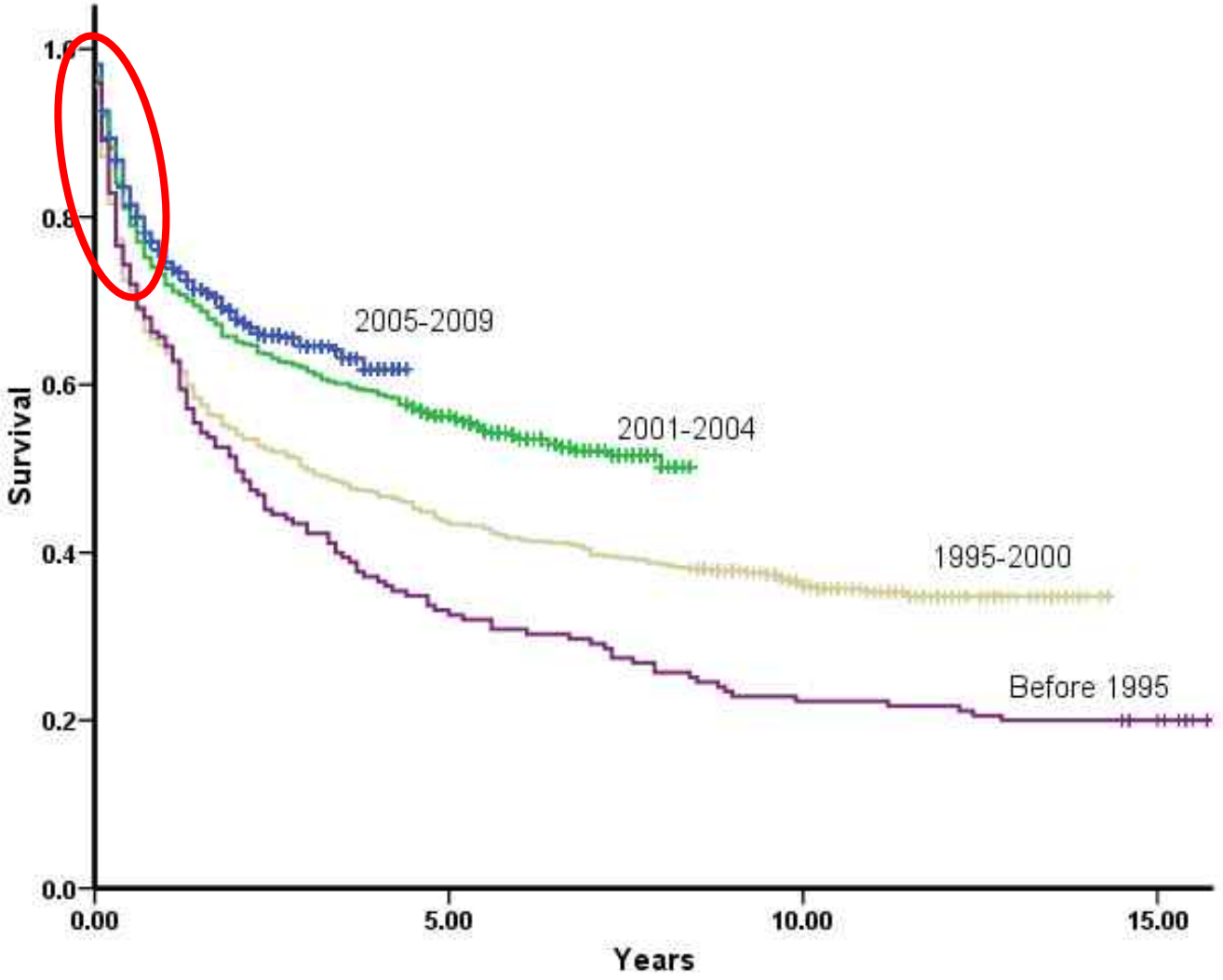
Cohort 1966 -1988

Median survival – 1 year

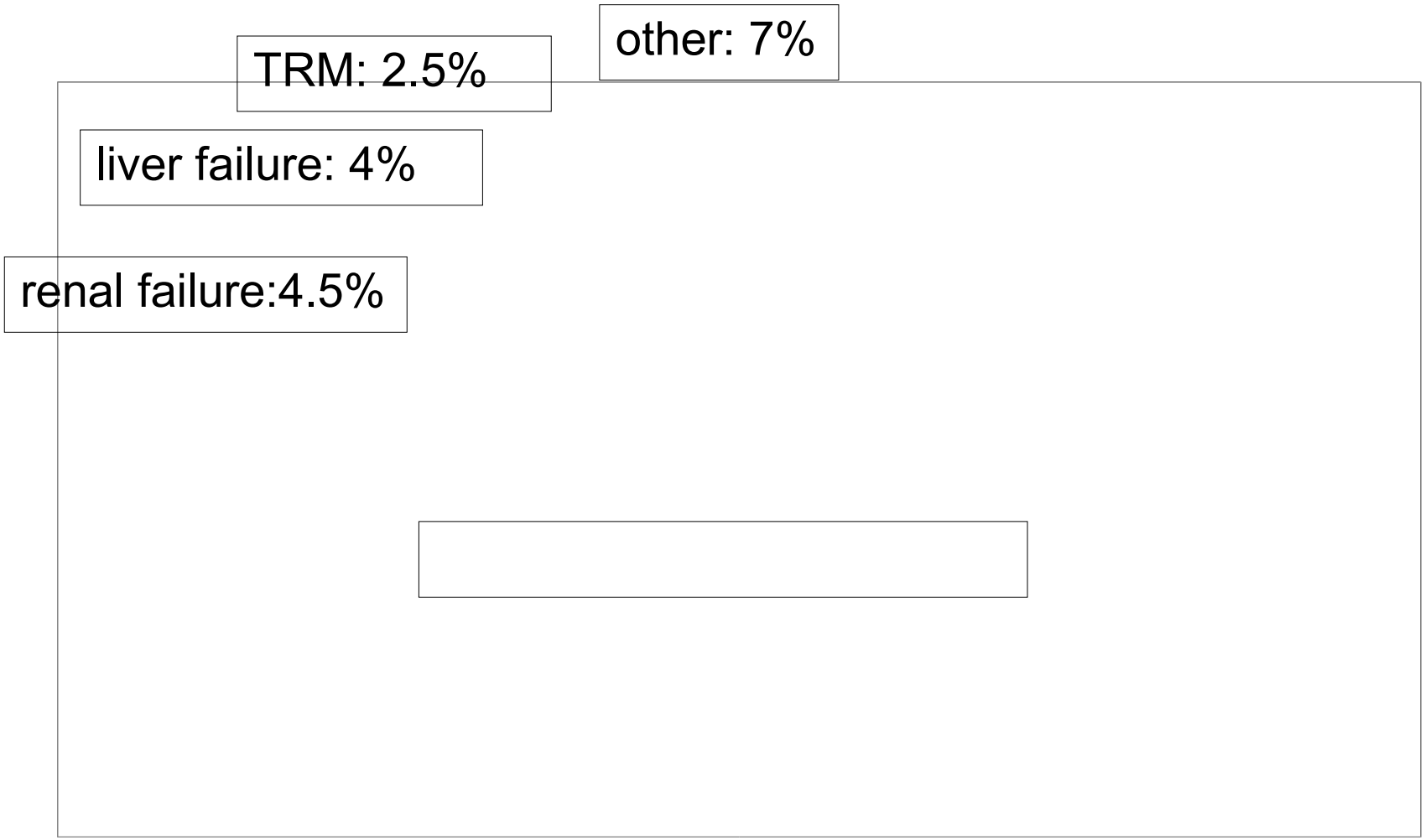
Cohort 1986 -2006

Median survival – 3.8 years

Are we making in progress with treating AL?



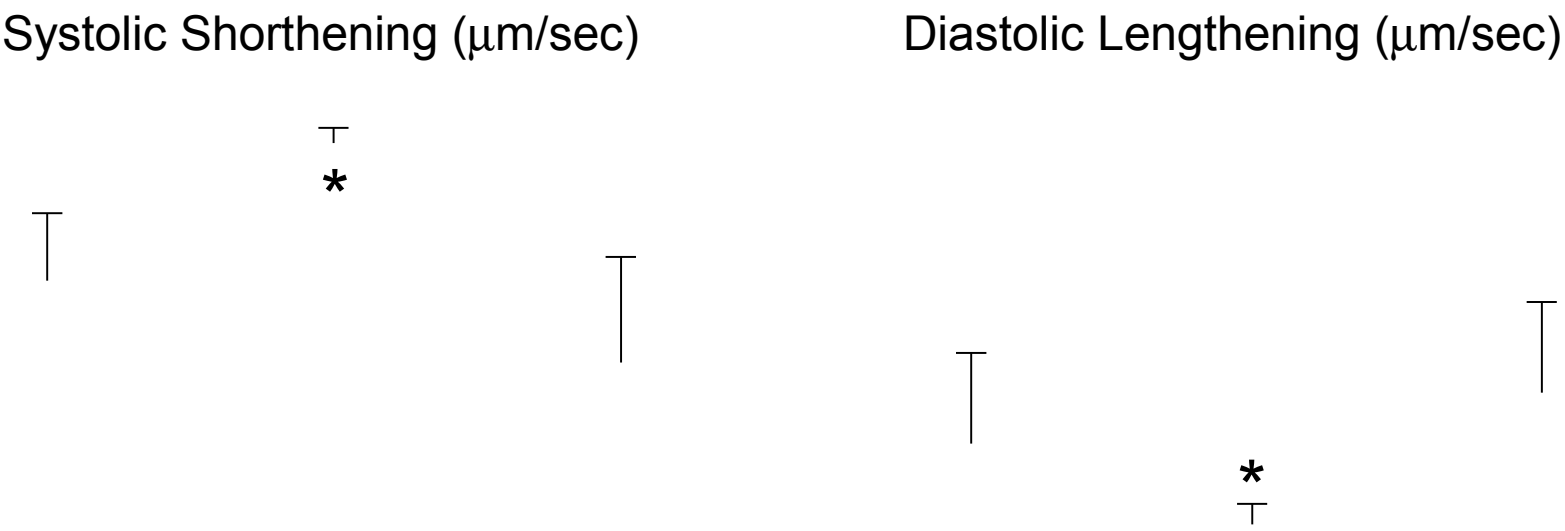
Cause of death in 210 patients with AL amyloidosis who died **in the first year after diagnosis**



Cardiotoxicity of amyloidogenic light chains

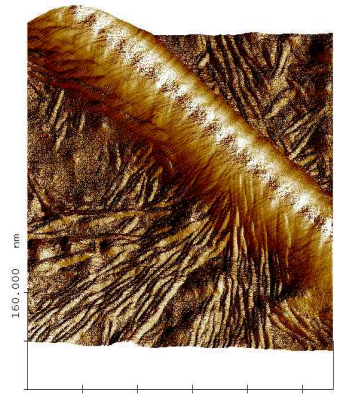
· **Production of recombinant amyloidogenic complete light chains**

· **Purification of light chains from patients with severe cardiac involvement**

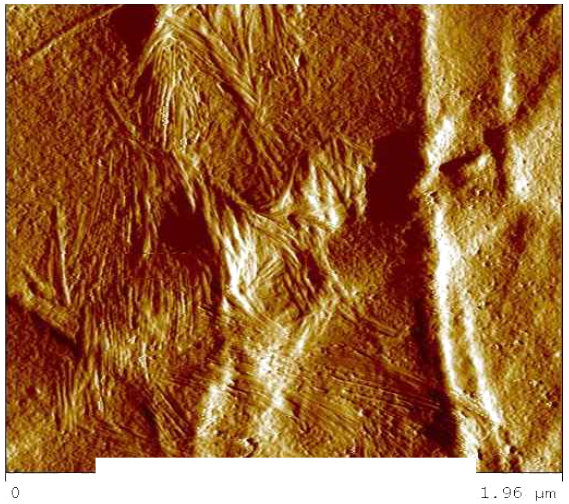


Isolated adult rat cardiomyocytes, n=14 per group, 24-hour exposure in **collagen-coated** wells

From molecular mechanism to therapy: investigating the interaction with the microenvironment



Atomic force microscopy of ***ex-vivo* amyloid material**



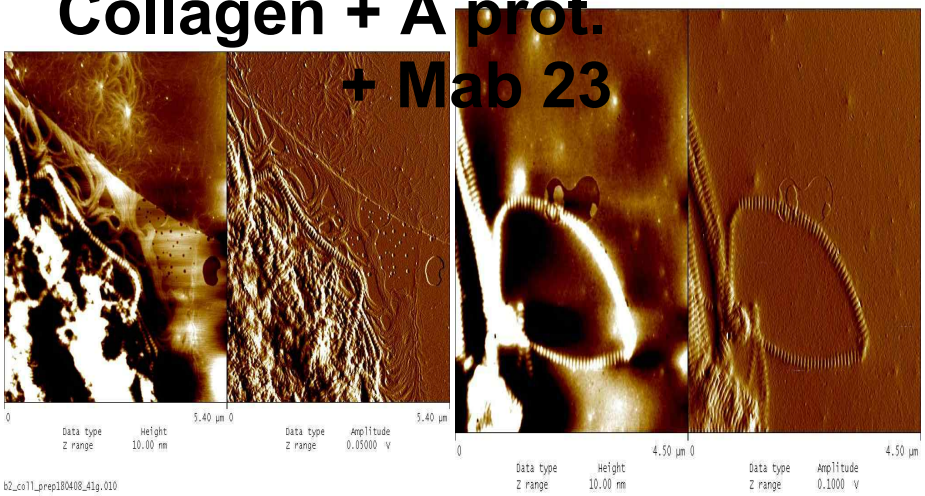
-

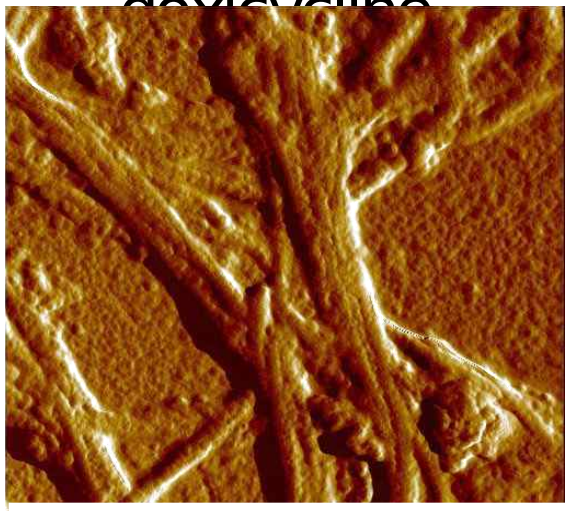
doxicycline

Collagen + A prot

Collagen + A prot.

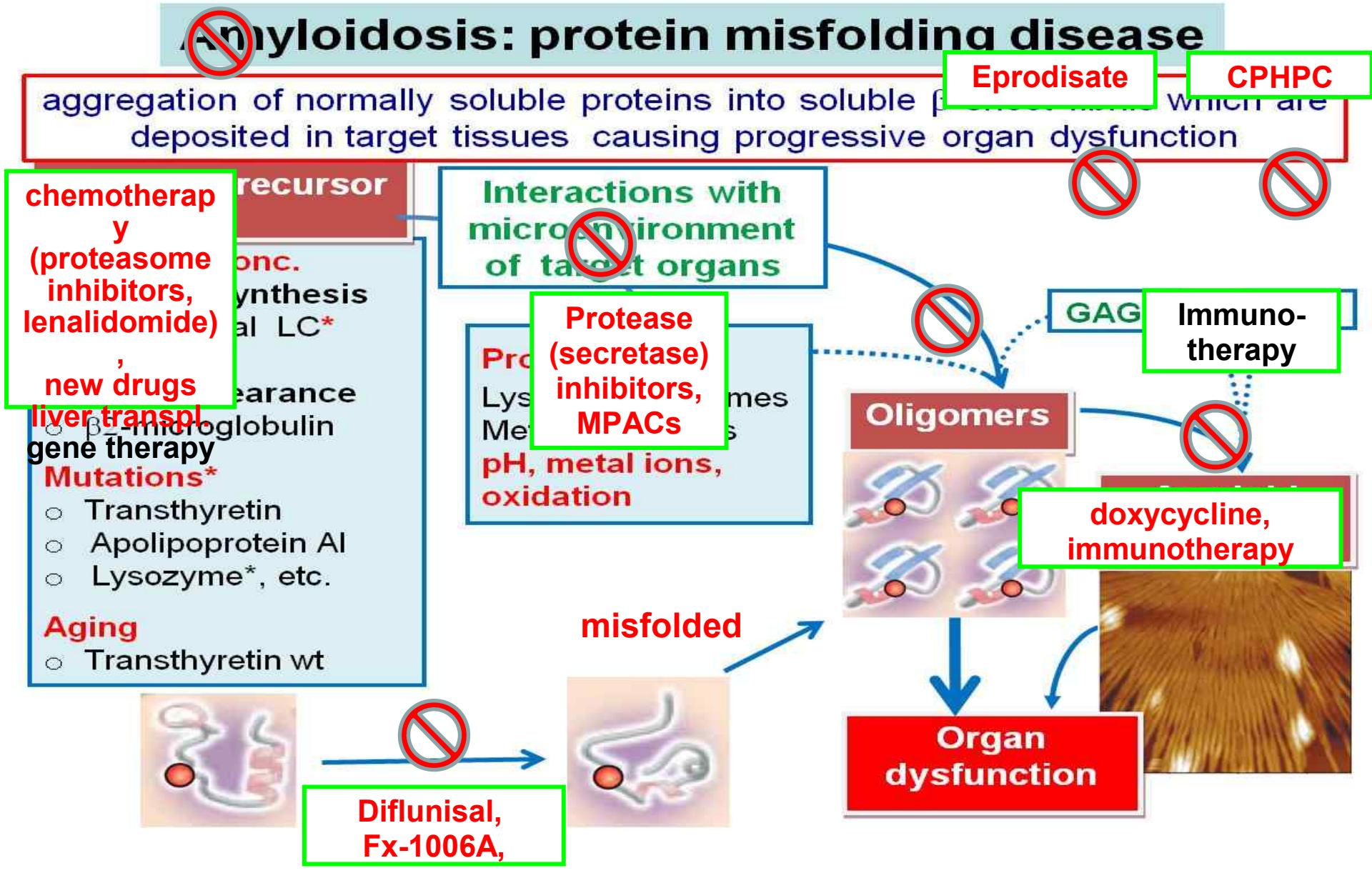
+ Mab 23





+100µM doxicycline

Amyloidosis: from molecular mechanisms to therapy



The future of the treatment of AL amyloidosis

- Improved patient selection based on cardiac biomarkers
- Frequent assessment of FLC and BNP response to improve the risk/benefit ratio
- Introduction of new agents in combination chemotherapy regimens
- Target critical steps of the amyloidogenic cascade using innovative drugs

Fare clic per modificare lo stile del sottotitolo dello schema

At present, one third of patients is projected to survive longer than 10 years and this figure is going to improve once we will see the long-term effect of new treatments

University of Pavia and University Hospital San Matteo

Amyloid Research and Treatment Center

Vittorio Bellotti
Vittorio Perfetti
Laura Obici
Giovanni Palladini
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Simona Casarini
Simona Donadei
Valentina Navazza
Gabriele Sarais

Ministero della Salute

EURAMY
Systemic Amyloidoses in Europe

fondazione cariplo

progetto NOBEL

Fondazione
IRCCS Policlinico
San Matteo
Pavia

XII INTERNATIONAL SYMPOSIUM ON AMYLOIDOSIS

From molecular mechanisms toward the cure of systemic amyloidoses

ISA
INTERNATIONAL SOCIETY OF AMYLOIDOSIS

April 18-21, 2010
Rome, Crowne Plaza Rome - St. Peter's

FIRST ANNOUNCEMENT

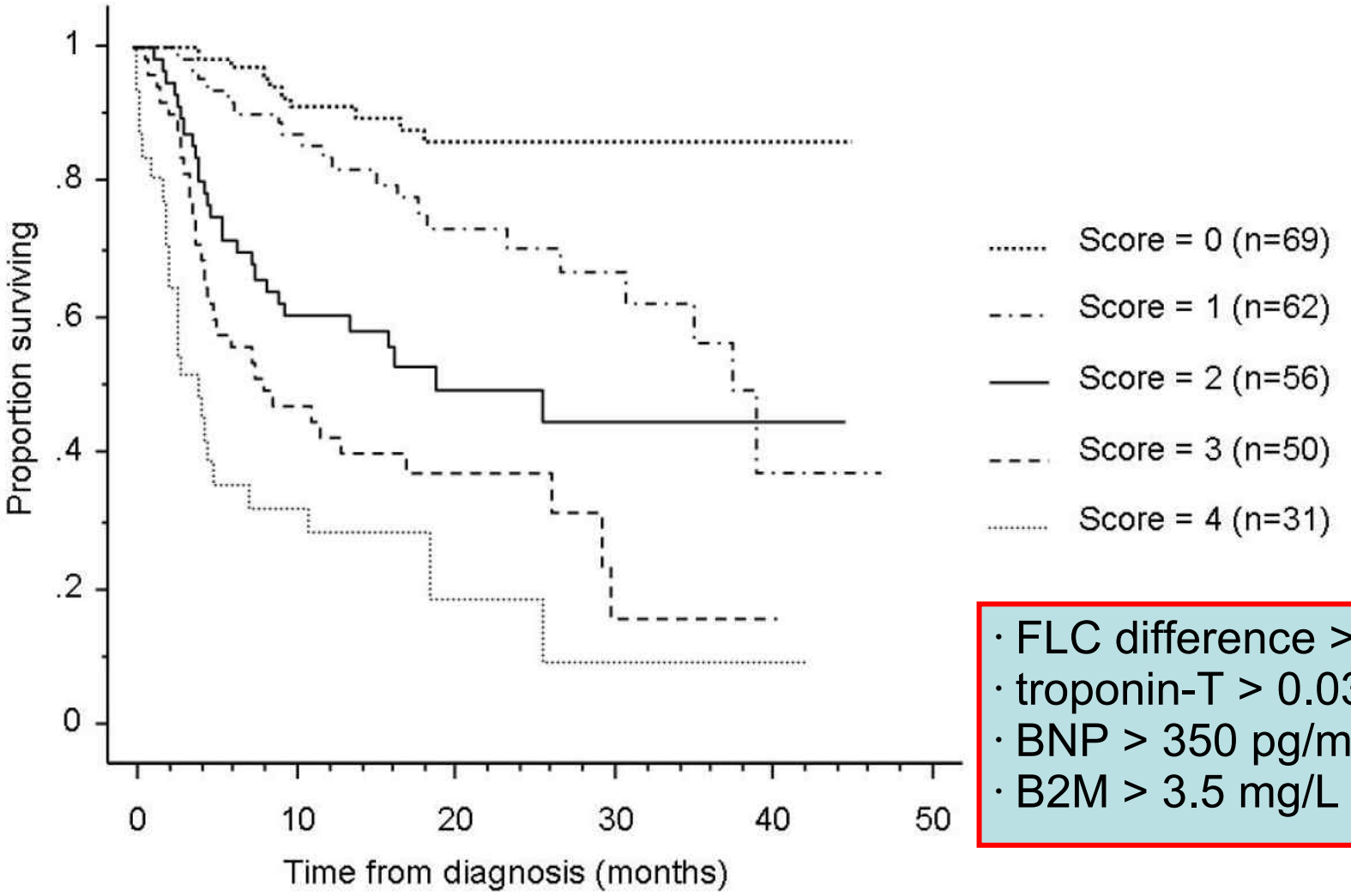
SEE YOU IN ROME APRIL 18-21, 2010

courtesy of Marco Di Girolamo

SIA
SOCIETÀ ITALIANA PER L'AMILOIDOSI

A novel staging system for light chain amyloidosis incorporating free light chain levels

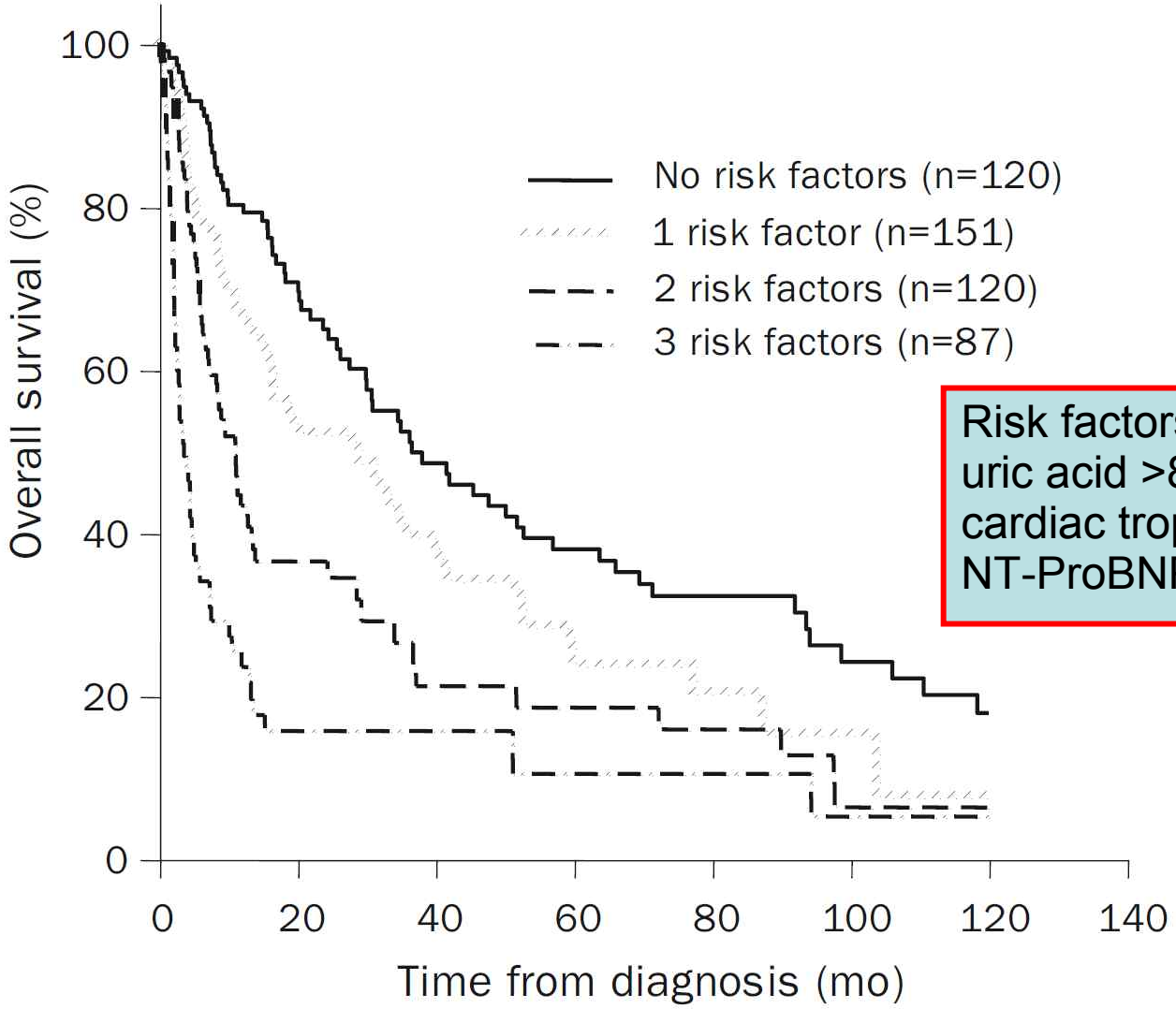
Kumar et al, EHA 13 Congress, 2008 Abstract 917



- FLC difference > 35 mg/dL
- troponin-T > 0.035 ng/mL
- BNP > 350 pg/mL
- B2M > 3.5 mg/L

Serum uric acid: novel prognostic factor in primary systemic amyloidosis

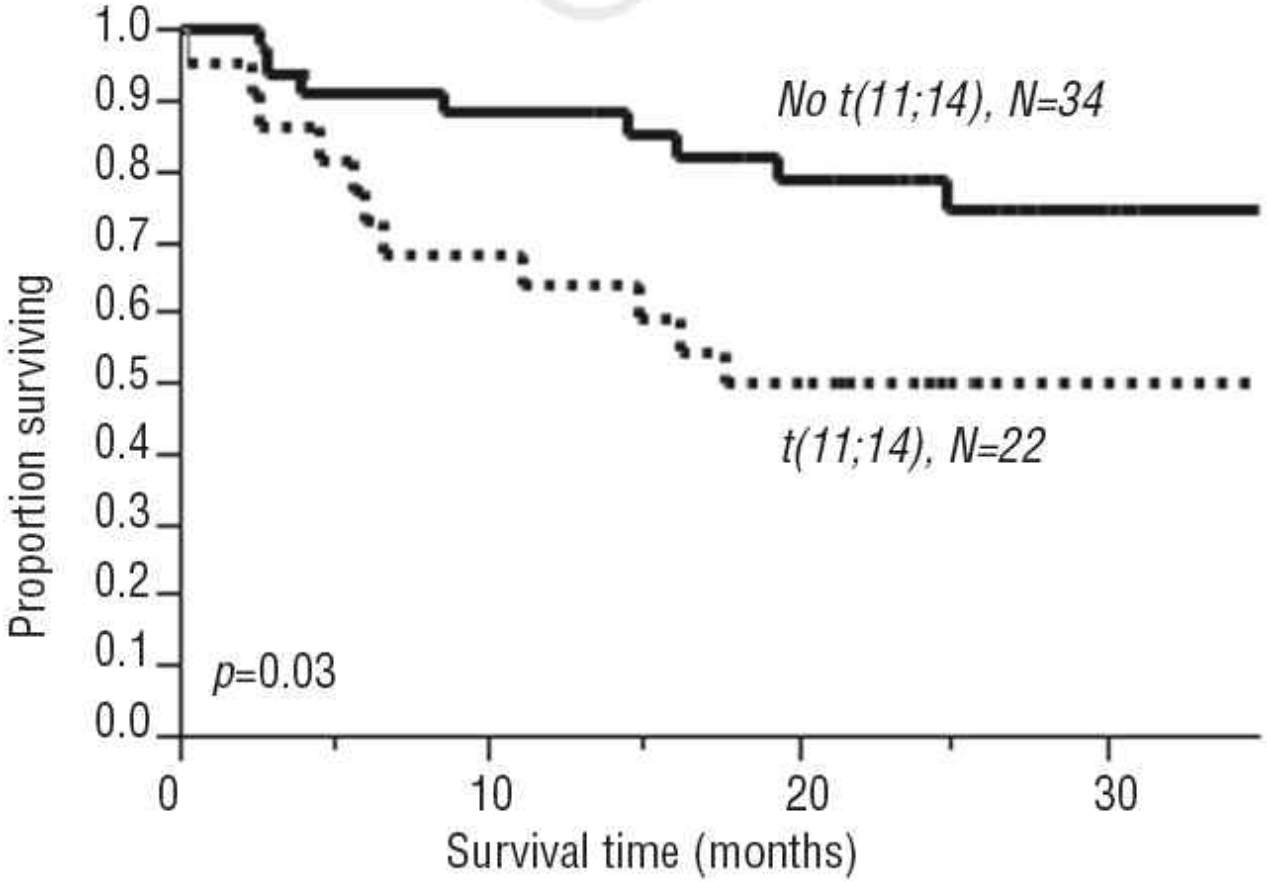
Kumar et al, Mayo Clin Proc. 2008; 83:297-303



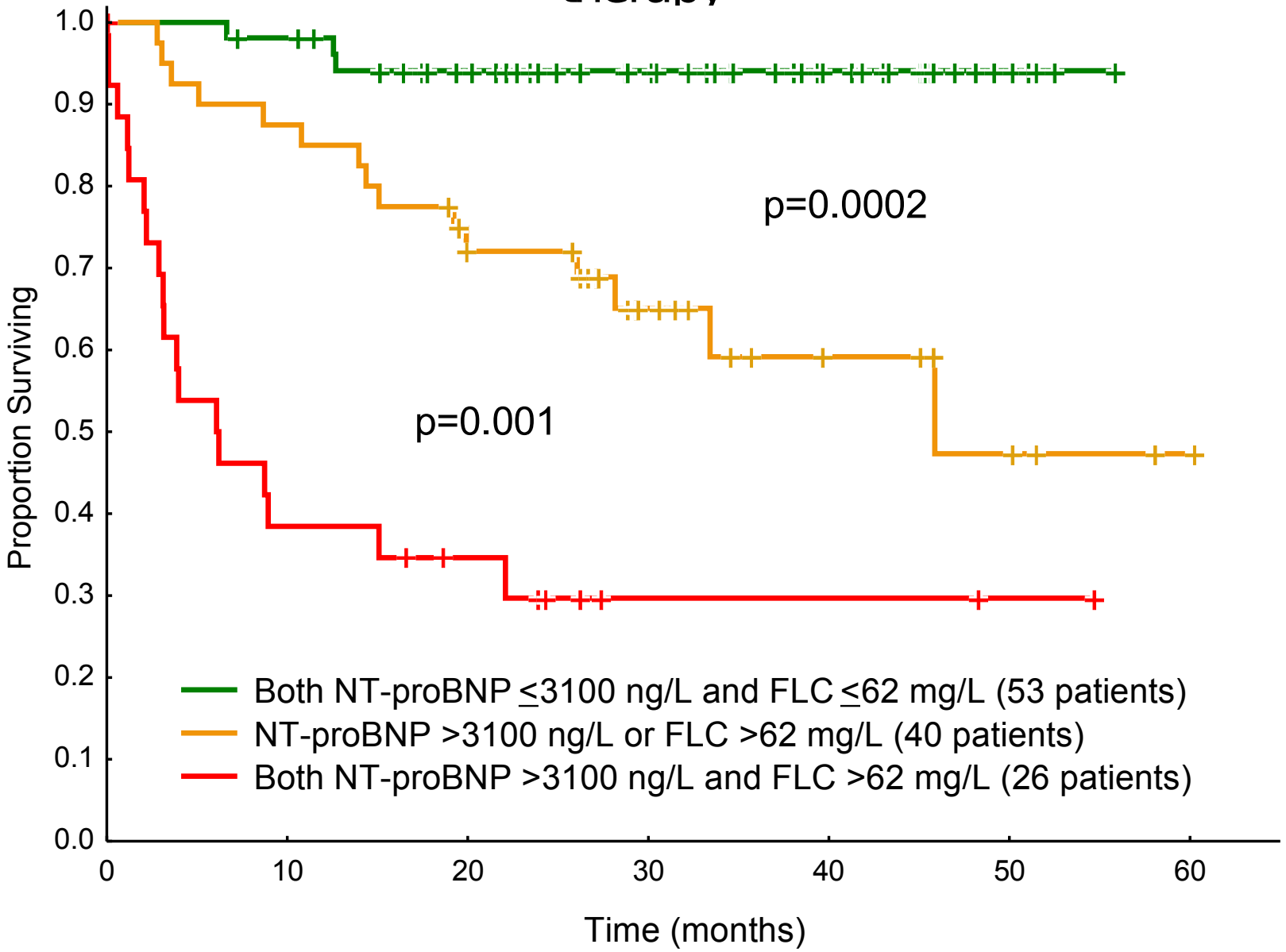
Risk factors:
uric acid >8 mg/dL,
cardiac troponin T >0.035 ng/mL
NT-ProBNP>332 pg/mL

Translocation t(11;14) and survival of patients with light chain (AL) amyloidosis

Bryce et al, Haematologica 2009; 94:380-386.



Survival of 119 patients with AL amyloidosis treated with MDex according to NT-proBNP and iFLC concentration remaining after therapy



Cox multivariate analysis of survival in 109 patients with AL amyloidosis according to hs-cTnT

	HR	95% CI	P
ln(hs-cTnT)	1.576	1.048 - 2.371	0.030
ln(NT-proBNP)	1.304	0.997 - 1.706	0.054

The following variables were tested and excluded from the final model:

age, gender, heart involvement by echo, mLVW thickness, ejection fraction, heart failure, cTnI, iFLC, BMPC, eGFR.

MELPHALAN-DEXAMETHASONE IN PATIENTS WITH AL AMYLOIDOSIS NOT ELIGIBLE FOR HIGH-DOSE MELPHALAN THERAPY

S.O. Schönland,[1] S. Dietrich,[2] U. Hegenbart,[2] T. Bochtler,[2] A.V. Kristen,[3] H. Goldschmidt,[4] A.D. Ho,[5] S.O. Schönland[2]

61 patients ineligible for ASCT due to high-risk disease (any of the following criteria) age >70y, advanced cardiac desease (NYHA class III, 59%), Karnowsky PS <70%, symptomatic pleural effusion.

Melphalan **16 mg/m2 i.v.** + Dex 40 mg, d1-4 q28d
Dex 20 mg if >70y or NYHA class III

Hematologic response: **71%** (intent-to-treat: 47%)
Complete remission: **17%** (intent-to-treat: 11%)
Median time to response: **3 cycles** (range: 2-6 cycles)

Deaths on treatment: **34%**
Median survival: **16.5 months**

Haematologica 2008;93 (S1):260

Patients with high NT-proBNP and poor performance status were at

Oral MDex treatment in AL amyloidosis: the Pavia experience in 126 newly diagnosed AL patients

Hematologic response: **62%**
Complete remission: **26%**
Median time to response: 3.5 months (range: 1-13 months)

Overall organ response: **33%**
NYHA and NT-proBNP resp.: 35%
echocardiography resp.: 6%
renal response: 23%
liver response: 23%

SAE: **19%**
fluid retention: 12%
Deaths on treatment: **3%** (disease progression)

Survival of 119 patients with AL amyloidosis treated with MDex according to hematologic response