

## Highlights from EHA

Novità dall'EHA >> [ Amiloidosi ]

Relatore: **M.T. PETRUCCI**

27-28 ottobre 2008

Borgo S. Luigi – Monteriggioni (Siena)

# CLINICAL STUDY OF 35 CASES OF PRIMARY SYSTEMIC AMYLOIDOSIS

*Coriu et al, EHA 13 Congress, 2008 Abstract 1301 (publication only)*

2

We wished to study patients with a premortem diagnosis of primary systemic amyloidosis to determine what clinical and laboratory features might assist in recognizing the disease and assessing prognosis

**Retrospective study** of 35 cases of AL amyloidosis diagnosed in a university hospital center between 2002 – 2007

The average age at diagnosis was 56 years (between 29 years and 80 years), 21 males and 14 females.

Organ involvement:

- heart; congestive heart failure – 31,4%; arrhythmias – 17,1%;
- echographic signs 57,1%;
- kidney (nephrotic range proteinuria or renal failure – 54,2%);
- peripheral nerves 37,2%;
- liver 11,4%;
- gastrointestinal tract 20%;
- spleen 11,4 %.

23 patients (65,7%) had one or two organ systems involved, 12 (34,2 %) had three or more organs involved.

# CLINICAL STUDY OF 35 CASES OF PRIMARY SYSTEMIC AMYLOIDOSIS

*Coriu et al, EHA 13 Congress, 2008 Abstract 1301 (publication only)*

3

Diagnosis was formulated on biopsy of the involved organ (kidney 14,2%, liver 2,8%), on rectal biopsy (5,7%) and on abdominal fat aspiration (60%).

60% had less than 5% plasma cell in the marrow; 14,2% of the patients had between 6-10%; 17,1% of the patients had between 11-20%; 8,5 % of the patients had more than 21% plasma cells.

Serum free light chains (FLC) assays and serum / urine immunofixation showed a monoclonal protein in 87,5% of the patients. 31,3% of these patients had a monoclonal intact immunoglobulin (IgG 22,8%, IgA 8,5%) and 68,7% of these patients had only a free monoclonal light chain in the serum. Lambda light chains were noted in the serum of 71,4% of the patients with a monoclonal protein.

For few patients these techniques fail to demonstrate a monoclonal protein. In these cases, definitive identification of amyloid deposits was done by mass spectrometry (MS/MS) using material extracted from formalin – fixed, amyloid – containing tissue biopsy or subcutaneous fat aspirate. In two cases systemic hereditary amyloidosis: lysozyme type and transthyretin type.

# CLINICAL STUDY OF 35 CASES OF PRIMARY SYSTEMIC AMYLOIDOSIS

*Coriu et al, EHA 13 Congress, 2008 Abstract 1301 (publication only)*

4

All the patients with AL amyloidosis received treatment with melphalan – dexamethasone or VAD. Presently, 23 patients (65,7%) are still alive with a median follow-up 24,3 of months ( ranging from 1 to 174 months).

12 patients died after a median survival of 10 months ( ranging from 1 to 36 months).

## Conclusions

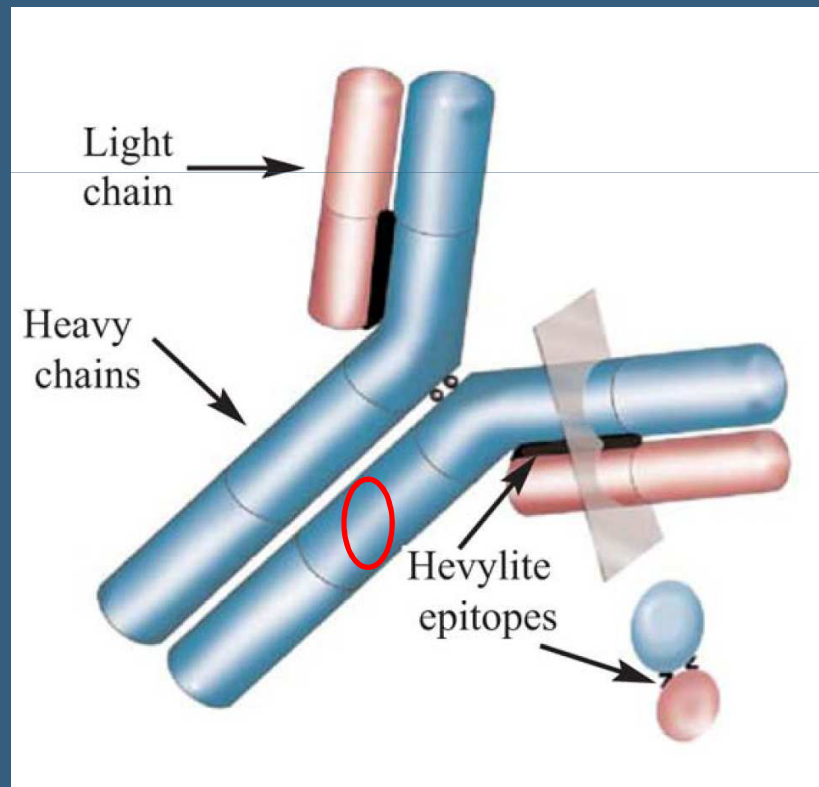
Accurate diagnosis and classification are essential for the prognosis and treatment of the disease. The diagnosis of amyloidosis must be supported by bioptic examination, serum and urine immunofixation, serum FLC assays and in special cases by amino acid sequencing and mass spectrometry of fibrillar material.

## NOVEL NEPHELOMETRIC IMMUNOASSAYS FOR THE SENSITIVE DETECTION OF IGA MONOCLONAL GAMMOPATHIES IN MULTIPLE MYELOMA AND AL AMYLOIDOSIS

*Harding et al, EHA 13 Congress, 2008 Abstract 668 (poster)*

5

Specific polyclonal antibodies have been produced which recognise conformational epitopes spanning the junction of the heavy and light chains of the immunoglobulin molecule.



# NOVEL NEPHELOMETRIC IMMUNOASSAYS FOR THE SENSITIVE DETECTION OF IGA MONOCLONAL GAMMOPATHIES IN MULTIPLE MYELOMA AND AL AMYLOIDOSIS

*Harding et al, EHA 13 Congress, 2008 Abstract 668 (poster)*

6

## Methods

IgA $\kappa$ /IgA $\lambda$  ratios were measured in 118 normal (blood donor) sera to generate a normal range.

The MM sera: 20 IgA (10 IgA $\kappa$  / 10 IgA $\lambda$ ) patient sera were analysed at presentation

17 IgA immunofixation (IFE) positive presentation sera from patients with AL amyloidosis

IgA $\kappa$ +IgA $\lambda$  summation correlated well with total IgA in normal (Pearsons Correlation 0.9 p<0.01) and monoclonal disease sera (Pearsons Correlation 0.96 p<0.01)

In the multiple myeloma patients, all 26 presentation sera had elevated concentrations of the relevant IgA immunoglobulins and abnormal IgA $\kappa$  / IgA $\lambda$  ratios

## NOVEL NEPHELOMETRIC IMMUNOASSAYS FOR THE SENSITIVE DETECTION OF IGA MONOCLONAL GAMMOPATHIES IN MULTIPLE MYELOMA AND AL AMYLOIDOSIS

*Harding et al, EHA 13 Congress, 2008 Abstract 668 (poster)*

7

### Results

In the 17 IgA IFE positive amyloid patients it was possible to quantify monoclonal bands in 8/17 by SPE.

All of the 8 patients with quantifiable M protein and 7/9 with non quantifiable M protein had abnormal IgA $\kappa$ /IgA $\lambda$  ratios

Normal serum free light chain measurements were recorded for 3 out of the 17 patients, but in all 3 cases the IgA $\kappa$  / IgA $\lambda$  ratios were abnormal.

### Conclusions

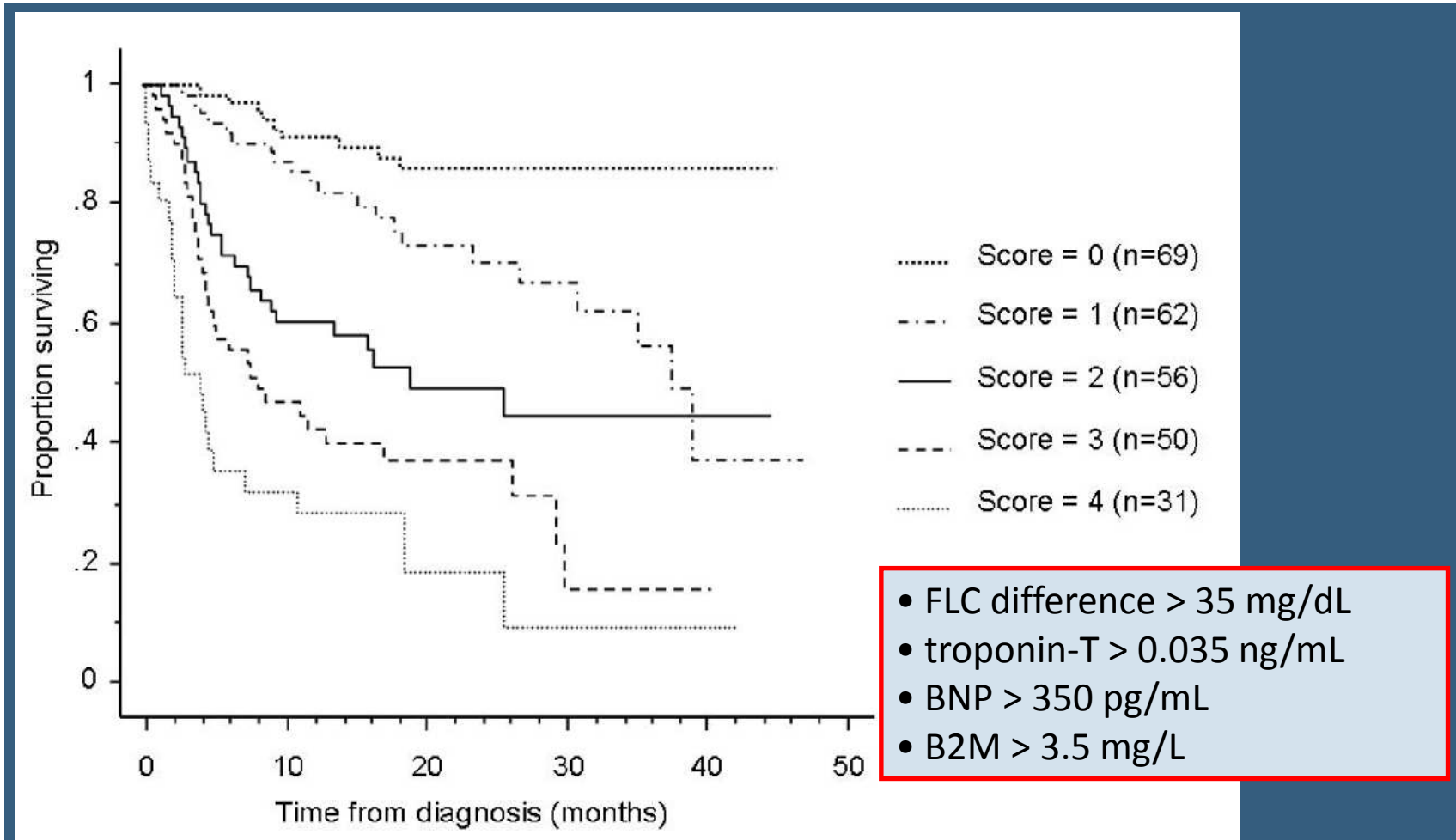
Measurement of IgA $\kappa$  / IgA $\lambda$  ratios allowed accurate quantification of monoclonal IgA immunoglobulins even when the immunoglobulin was obscured by other proteins on SPE.

The assays provided data concerning the monoclonal protein concentration when the SPE gels were negative and in some instances, a more sensitive indication of residual disease than IFE.

Finally, in AL amyloidosis patients with normal FLC ratios, measurement of involved and uninvolved intact immunoglobulins might offer a sensitive, quantitative alternative for disease monitoring.

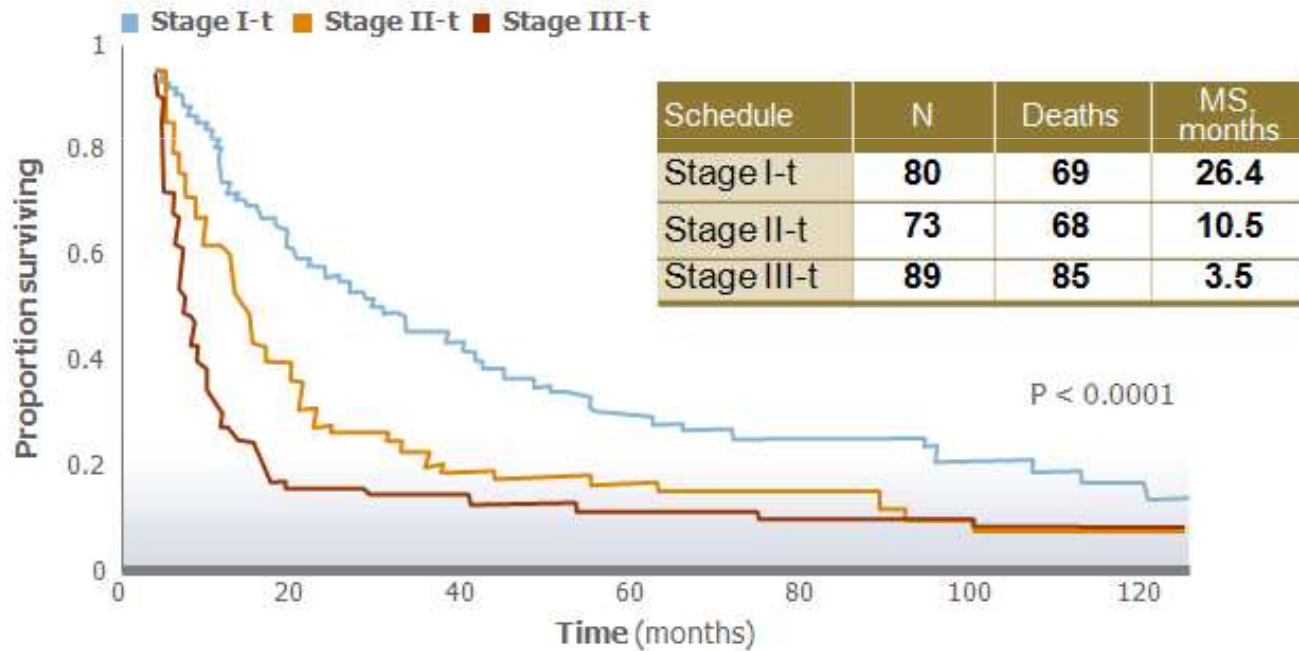
# A novel staging system for light chain amyloidosis incorporating free light chain levels *Kumar et al, EHA 13 Congress, 2008 Abstract 917 (oral)*

8



### 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. Lucy, Mary F. Burritt, Terry M. Therneau, Philip R. Greipp, Thomas E. Witzig, John A. Lust, S. Vincent Rajkumar, Rafael Fonseca, Steven R. Zeldenzust, Christopher G.A. McGregor, and Allan S. Jaffe*



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

*Schönland et al, EHA 13 Congress, 2008 Abstract 647 (poster)*

10

61 pts with AL amyloidosis

Median age: 67 (range 45-78) years

Median number of involved organs: 3 (range 1-6)

Advanced cardiac disease (NYHA stage III) n=36

Age > 70 years n=20

Symptomatic pleural effusion n=8

Melphalan 16 mg/m<sup>2</sup>/day 1 intravenously

Dexamethasone orally 40 mg day 1-4, every 28 days.

Pts over the age of 70 years or with cardiac disease NYHA III received 20mg of Dex.

Median of 4 cycles (range, 1-12), 20 pts < 3 cycles

Response assessed every 3 cycles

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

*Schönland et al, EHA 13 Congress, 2008 Abstract 647 (poster)*

11

### Results

Twenty-one patients (34%) died under therapy mostly due to advanced dis. Overall, 41 pts were evaluable for haematological remission (HR).

CR= 7 (17%)

PR= 22 (54%)

NR=12 (29%)

In 13 pts (32%) HR was followed by organ response (OR)

A median of three cycles (range 2-6) had to be given to achieve HR; it took a median of 5 months (range 2-15) to observe OR.

Multivariate analysis: patients with elevated NT-ProBNP ( $p=0.001$ ) and reduced KI ( $p=0.02$ ) were at high risk to die under therapy

### Conclusions

We could confirm that patients with haematological remission after M-Dex have a prolonged survival. However, the rate of death under therapy is remarkably high in our study. **We ascribe this to the inclusion of patients with very advanced disease.** For these patients less toxic therapies which induce a rapid HR are warranted.

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

Schönland et al, EHA 13 Congress, 2008 Abstract 647 (poster)

12

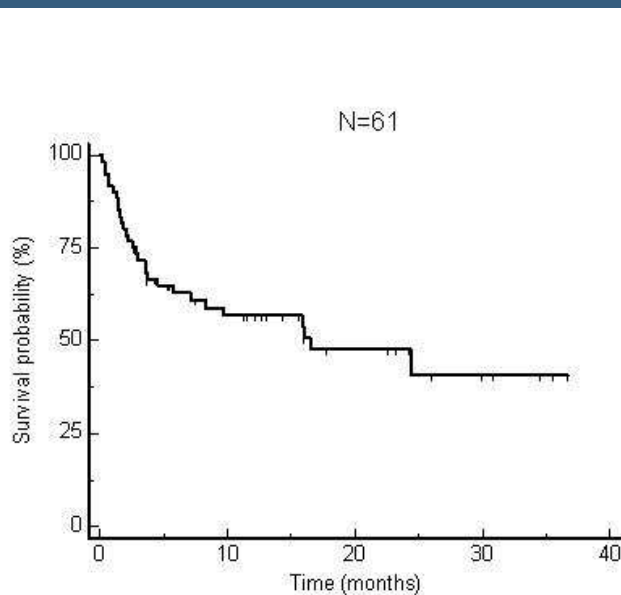


Figure 1a: Overall Survival of patients receiving M-dex

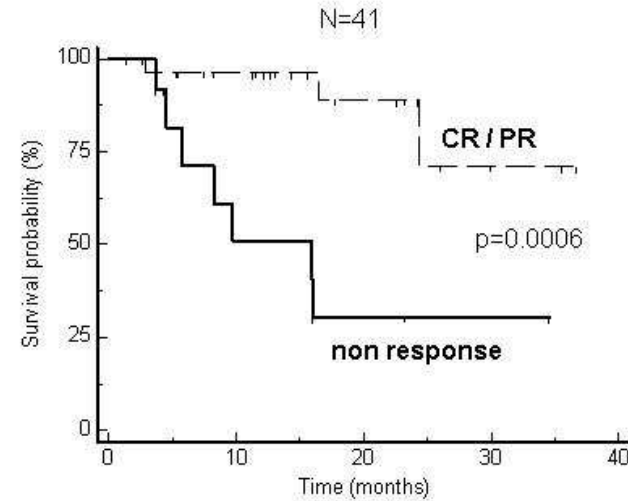


Figure 1b: Overall Survival according to haematological response

## HIGH-DOSE MELPHALAN AND AUTOLOGOUS STEM CELL TRANSPLANTATION FOR AL AMYLOIDOSIS PATIENTS

*Michael et al, EHA 13 Congress, 2008 Abstract 1207 (publication only)*

13

The aim of this retrospective analysis was to clarify the clinical characteristics, toxicity and long-term survival of AL patients treated with HDM/ASCT in 3 Greek centers

### Results

Between 1999 and 2006 **12 patients** underwent HDM/SCT for AL amyloid. 6 patients received HDM as first-line treatment and another 6 at relapse. Median age was 51 years; four patients had been previously diagnosed with multiple myeloma.

One organ was involved in 6, two in 4 and three or more in 2 patients respectively. Heart was involved in three (25%) cases, kidneys in 11 and liver in one. Four patients had symptoms of peripheral neuropathy and another 4 patients presented with soft tissue involvement.

All patients received peripheral stem cell graft and were mobilized with G-CSF alone while conditioning regimen delivered was melphalan 140 mg/m<sup>2</sup>.

## HIGH-DOSE MELPHALAN AND AUTOLOGOUS STEM CELL TRANSPLANTATION FOR AL AMYLOIDOSIS PATIENTS

*Michael et al, EHA 13 Congress, 2008 Abstract 1207 (publication only)*

14

All patients engrafted (median time, 12 days) and toxicity was mainly hematologic (grade IV) and mucositis (grade II), both manageable, while transplant related mortality **(TRM) reached 25%** (3/12).

9 patients who survived longer than day 100:

- 4 achieved complete hematologic response,
- 4 partial responses and 1 did not respond.

Organ response was achieved in 7 patients-including two patients with heart involvement. Two patients who achieved an organ response relapsed after 4 and 10 months respectively. With a median follow-up of 29 months overall survival has not been reached while the estimated 5-year survival rate is 75%.

### Conclusion

HDM/SCT proves an effective treatment option for AL patients with almost 2/3 showing durable hematologic and organ responses which is translated to prolonged survival. **Strict selection criteria for patients suitable for transplantation can significantly decrease TRM to less than 25%.**

## TREATMENT OF LIGHT CHAIN (AL) AMYLOIDOSIS WITH BORTEZOMIB AND DEXAMETASONE

*Canovas et al EHA 13 Congress, 2008 Abstract 1108 (publication only)*

15

To assess the effectiveness of bortezomib and dexametasone (BD) in patients with relapsed or refractory AL amyloidosis (AL-A) following at least one prior therapy.

**3 patients** with primary systemic amyloidosis and **1** with IgG lambda MM with AL-A (intestinal involvement and polyneuropathy) received treatment (Bortezomib 1,3mg/m<sup>2</sup> d 1, 4, 8 and 11 together with 20 mg of Dex each day and the following)

Mean age: 57 years (range 43-74), median performance status (ECOG): 2 (range 1-3) and mean number of organs involved: 2 (range 1-4), with 2 symptomatic cardiac disease, 1 end stage renal failure in dialysis and 1 gastrointestinal amyloidosis with malabsorption and bleeding.

Mean number of previous treatment schedules: 2 (one patient had undergone 2 ASCT). An average of 5 courses were administered (range 2-8).

Complete hematologic and partial organ response in three patients with involvement of the heart (2), liver (1) and gastrointestinal tract (1)

## TREATMENT OF LIGHT CHAIN (AL) AMYLOIDOSIS WITH BORTEZOMIB AND DEXAMETASONE

*Canovas et al EHA 13 Congress, 2008 Abstract 1108 (publication only)*

16

### Toxicity:

2 cases of grade 2 and 3 polyneuropathy,  
1 case of grade 2 mucositis and 1 case of grade 2 nausea and vomiting  
1 case of uncomplicated herpes zoster occurred.

### Conclusions

The experience with Bortezomib in AL-A remains limited. In our AL-A patients, BD has been feasible and three of them have achieved haematologic and organ responses with manageable toxicity. Further research is required to optimize the application of BD in this setting.

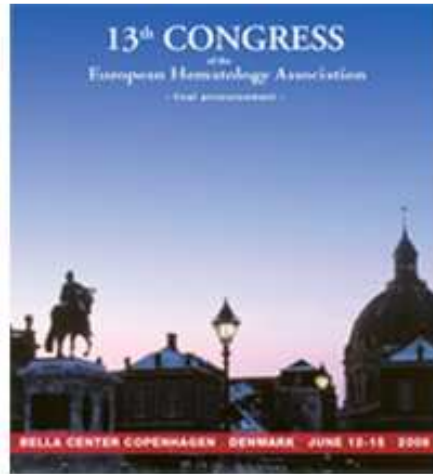
## OFF-LABEL USE OF ACTIVATED RECOMBINANT FACTOR VII. A SPANISH THREE LEVEL HOSPITAL'S EXPERIENCE

*Perez-Montes et al EHA 13 Congress, 2008 Abstract 994 (publication only)*

17

To evaluate efficacy and safety of rFVIIa in a wide variety of pathologies with critical bleeding refractory to standard treatment.

Two patients with massive abdominal hemorrhage in amyloidosis and after liver biopsy were treated: efficacy 2/2, 100%



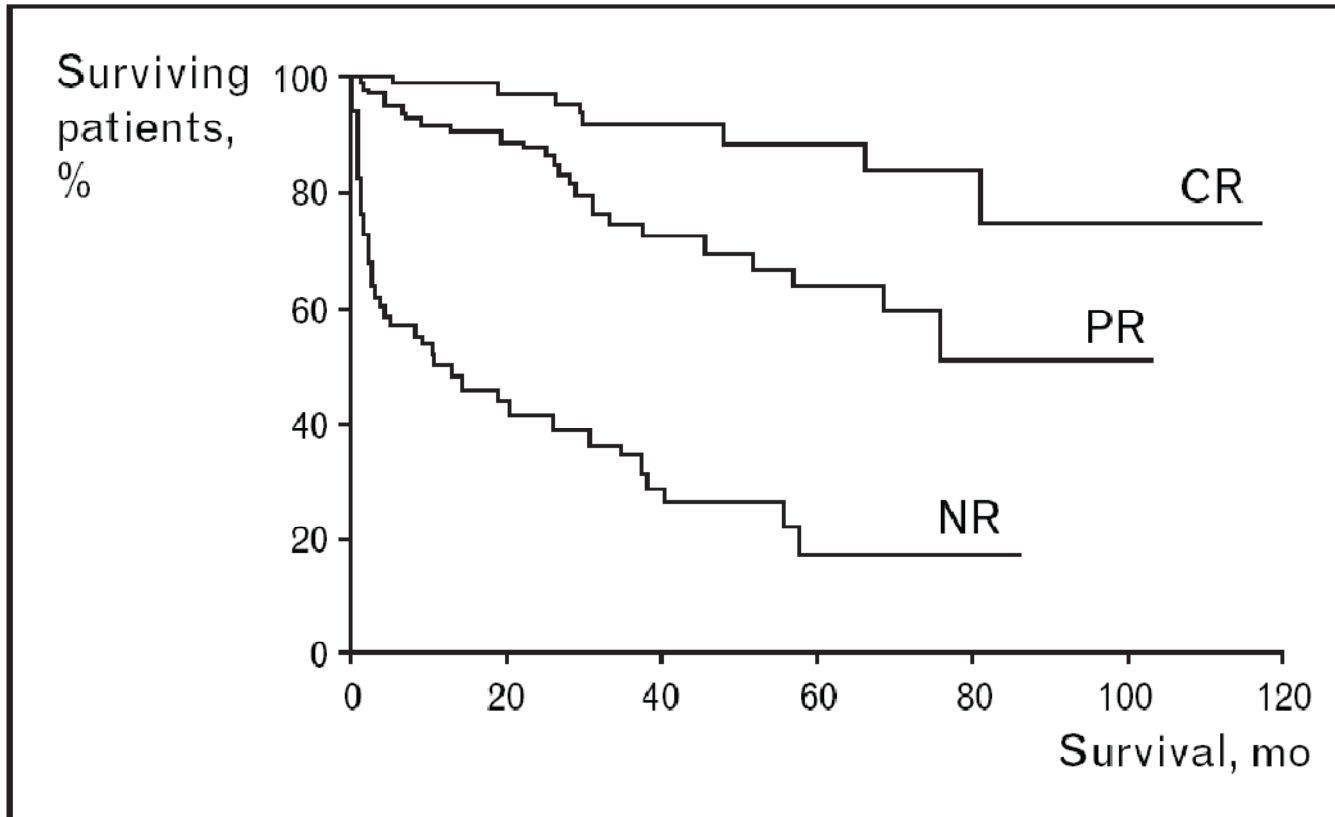
## Advances in AL amyloidosis

Giampaolo Merlini  
[gmerlini@unipv.it](mailto:gmerlini@unipv.it)

Amyloid Research and Treatment Center  
Fondazione IRCCS Policlinico San Matteo  
University of Pavia, Italy



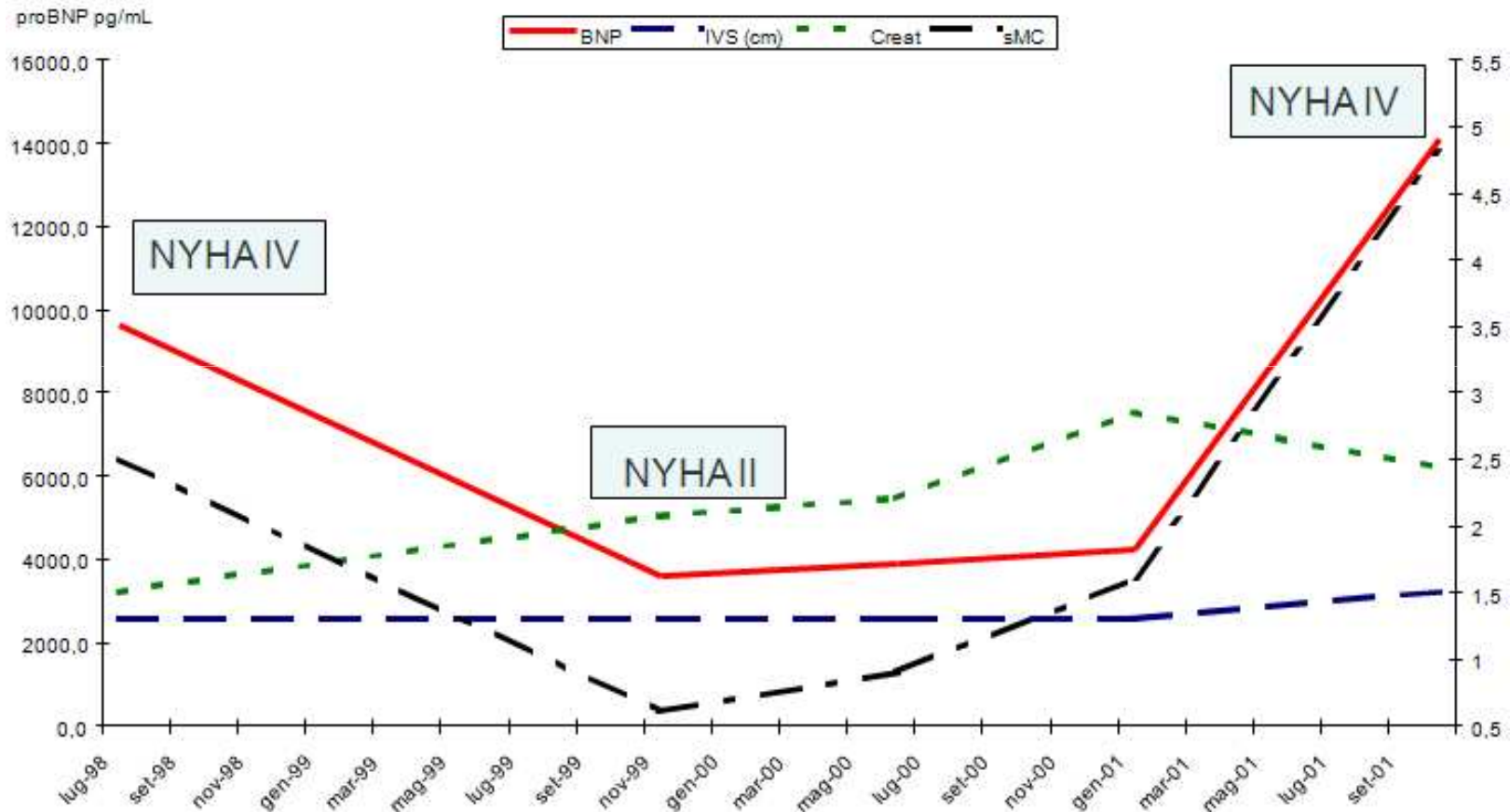
## Effect of response on survival



CR, complete response ( $n = 94$ ); NR, no response ( $n = 71$ ); PR, partial response ( $n = 105$ ). Tick marks indicate censored patients (alive).

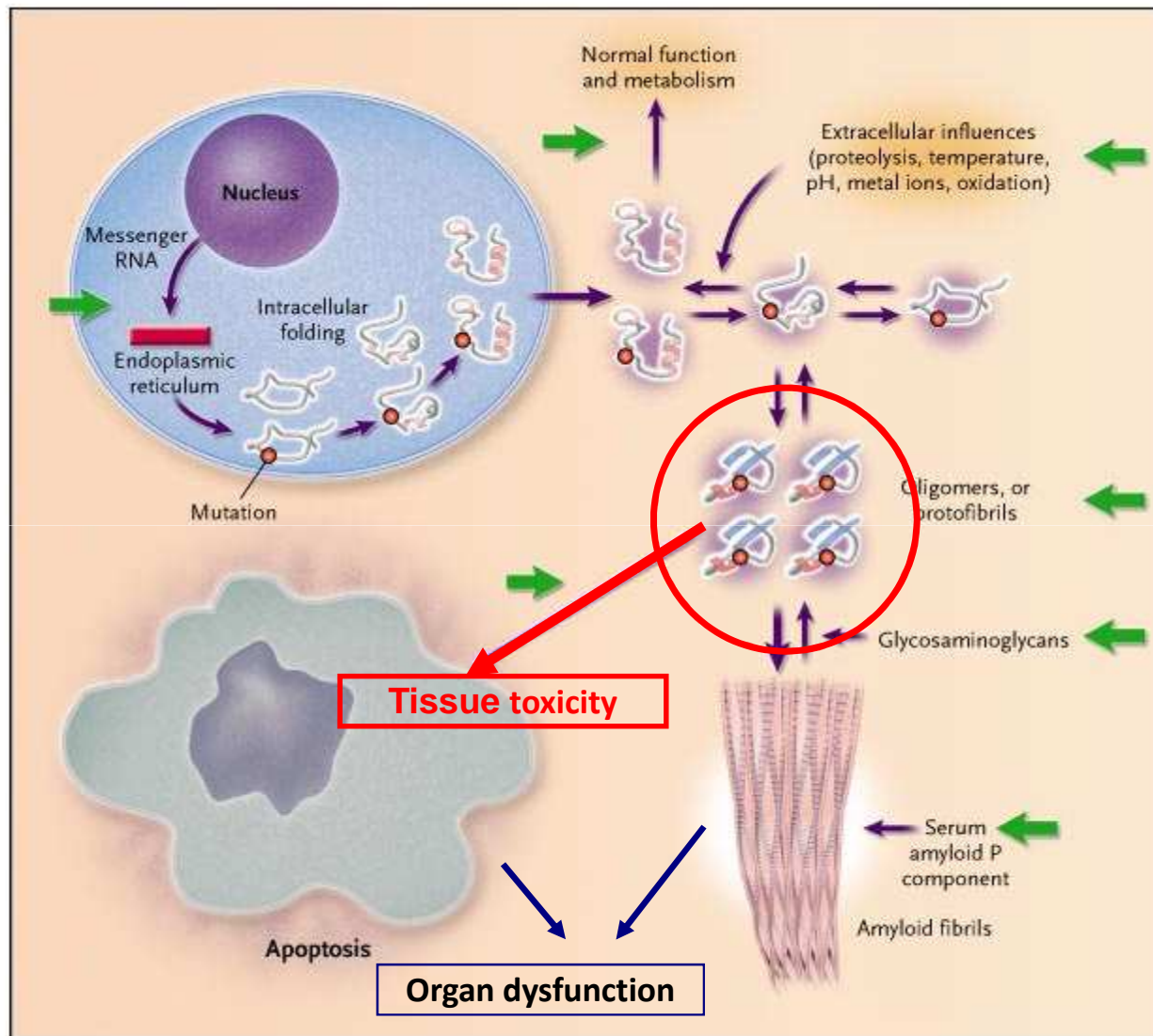
*Gertz et al, Curr Opin Oncol 2007;19:136–141*

## Serum N-Terminal Pro-Brain Natriuretic Peptide Is a Sensitive Marker of Myocardial Dysfunction in AL Amyloidosis



(Circulation. 2003;107:2440-2445.)

# AMYLOIDOSIS: PROTEIN MISFOLDING DISEASE



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

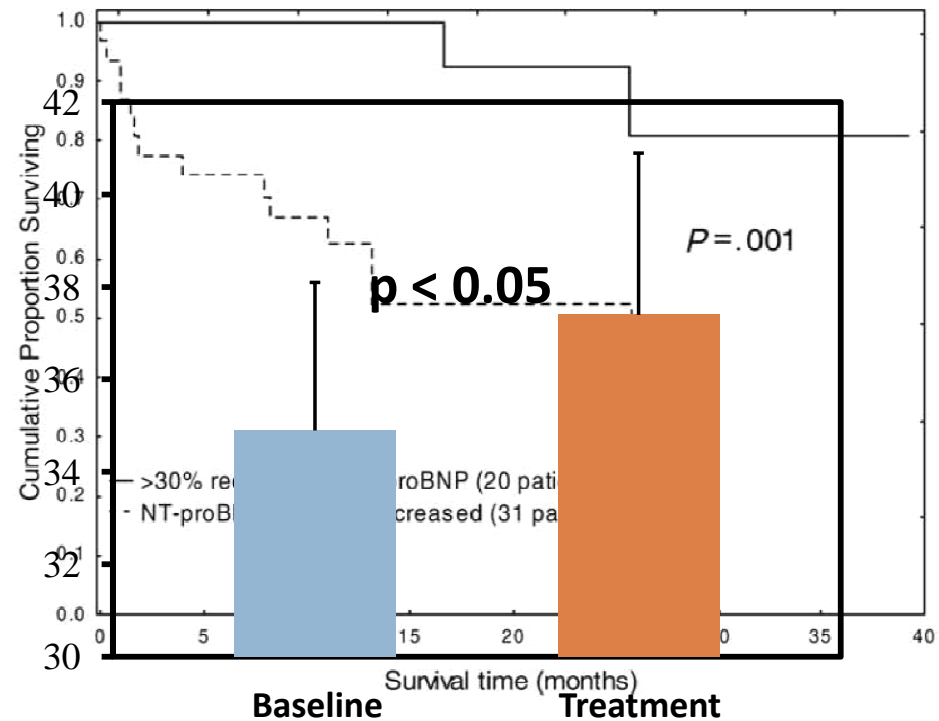
# FLC and NT-proBNP response in 115 AL patients with cardiac amyloidosis

22

<b>Hematologic response</b>	<b>NT-proBNP decreased <math>\geq 30\%</math></b>
<b>Complete Response</b> (elimination of the amyloidogenic light chain)	18/21 pts (86%)
<b>Partial Response</b> (reduction to $< 50\%$ of the amyloidogenic light chain)	29/50 pts (58%)
<b>No Response</b>	1/44 pts (2%)

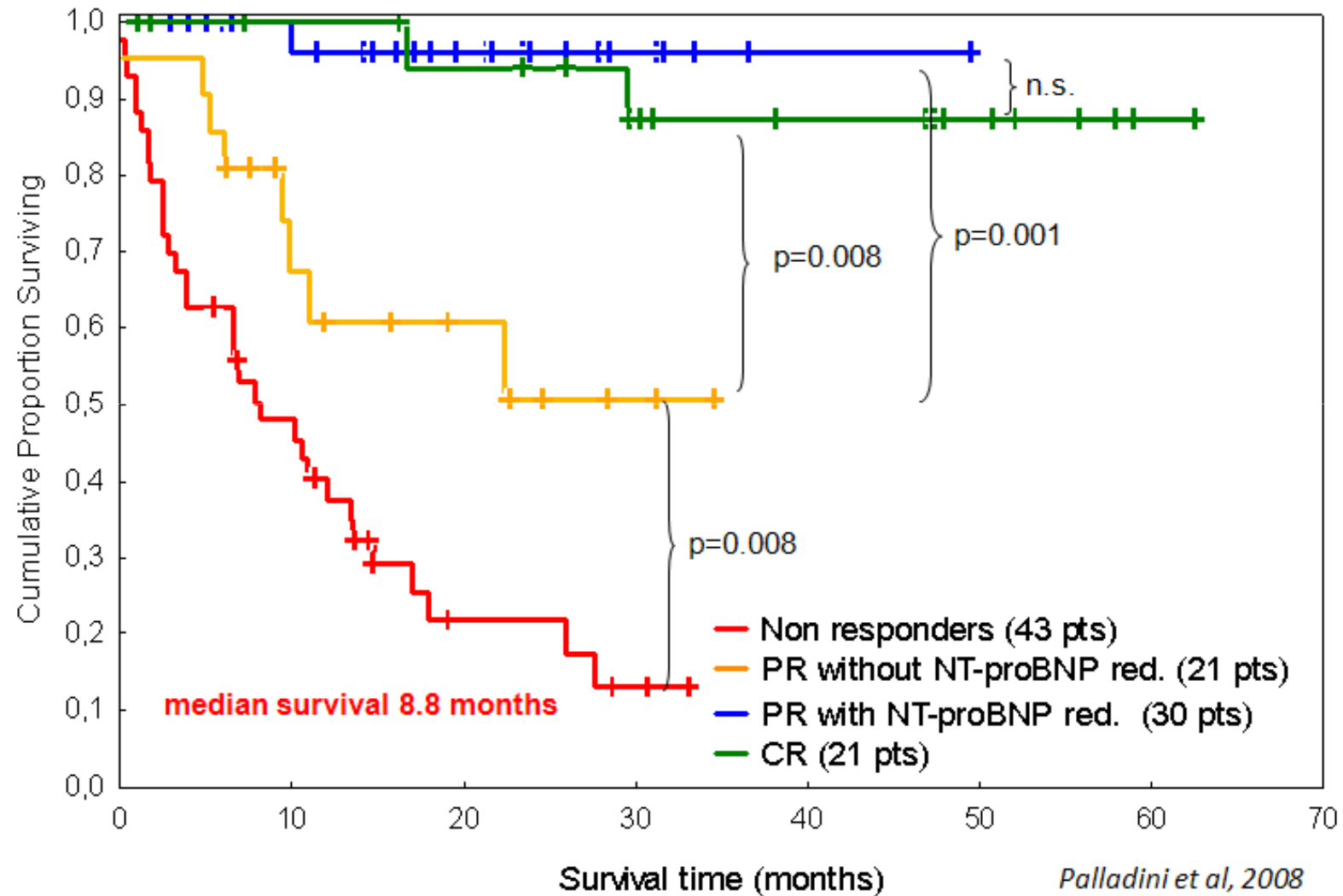
Palladini et al, 2008

## Shortening fraction (%)

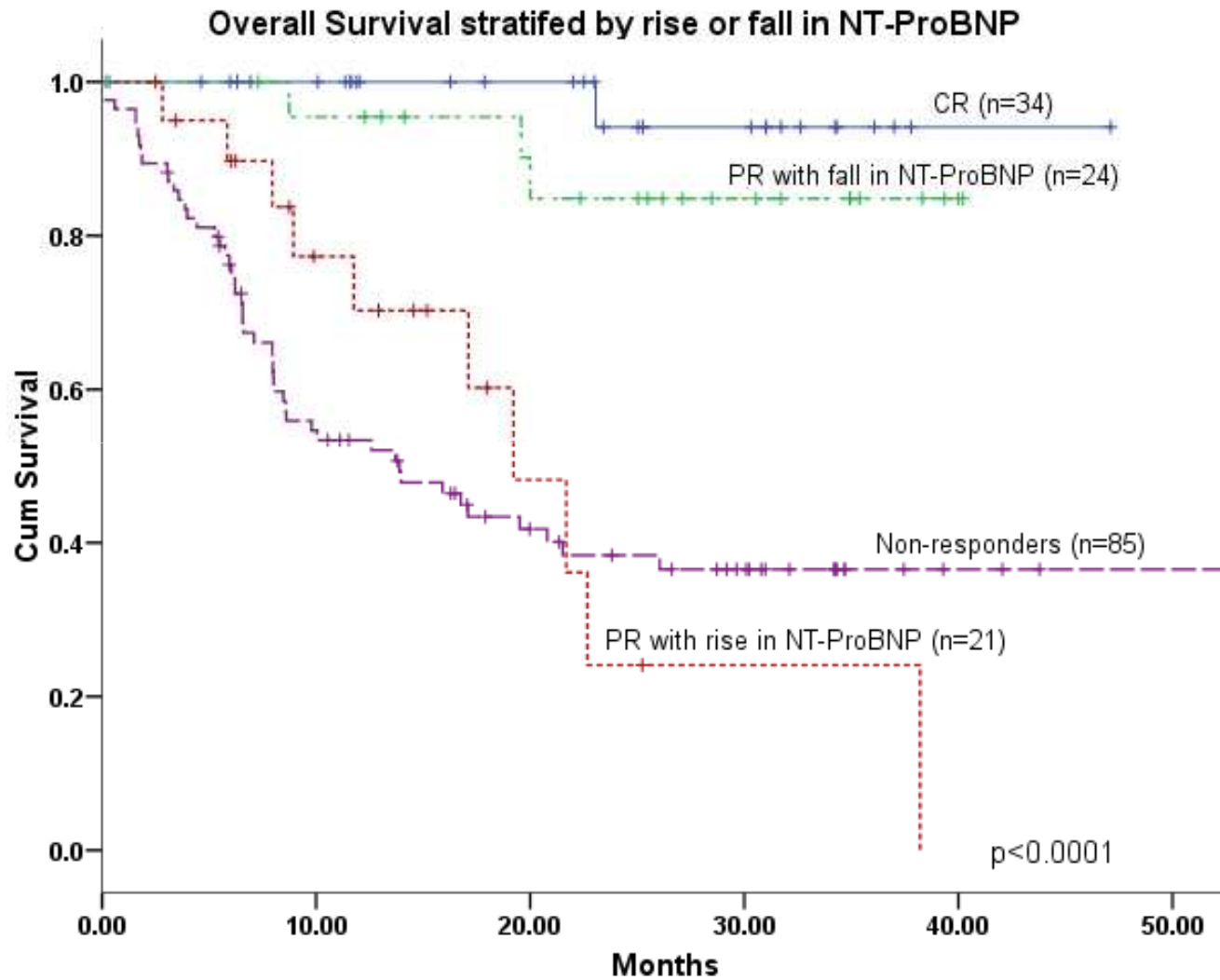


Palladini et al, Blood. 2006;107:3854-8

**Survival of 115 patients with cardiac AL amyloidosis according to response to therapy (FLC and NT-proBNP)**



Survival according to hematologic and cardiac response in 164 patients followed at UK National Amyloid Center, and at Italian Amyloid Center, Pavia



Wechalekar and Palladini, ASH 2008

# A NEW PARADIGM FOR TREATMENT STRATEGIES

25

## 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**:  
During therapy: every 2 cycles or every 3 mos after SCT
  - F.u.: every 3 mos x 1 yr, every 6 mos 2-3 yrs, then yearly if clinical conditions are stable
- Organ response:
  - NT-proBNP, troponins, **rapid**
  - Kidney markers (proteinuria, s. creatinine) **may be delayed by > 3 mos up to 1 yr**