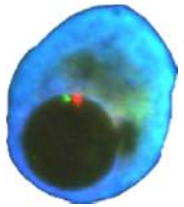
Morie Gertz
Chair Dept. of Medicine



Diagnostic Approach in Amyloidosis

Scottsdale, Arizona

Rochester, Minnesota

Jacksonville, Florida

Disclosures

- No drugs are FDA approved for Amyloidosis so thalidomide, bortezomib lenalidomide, melphalan, dexamethasone etc. are all off label uses.
- No influence on this presentation
- Honoraria Celgene Millenium Binding Site Alexion

Learning Objectives

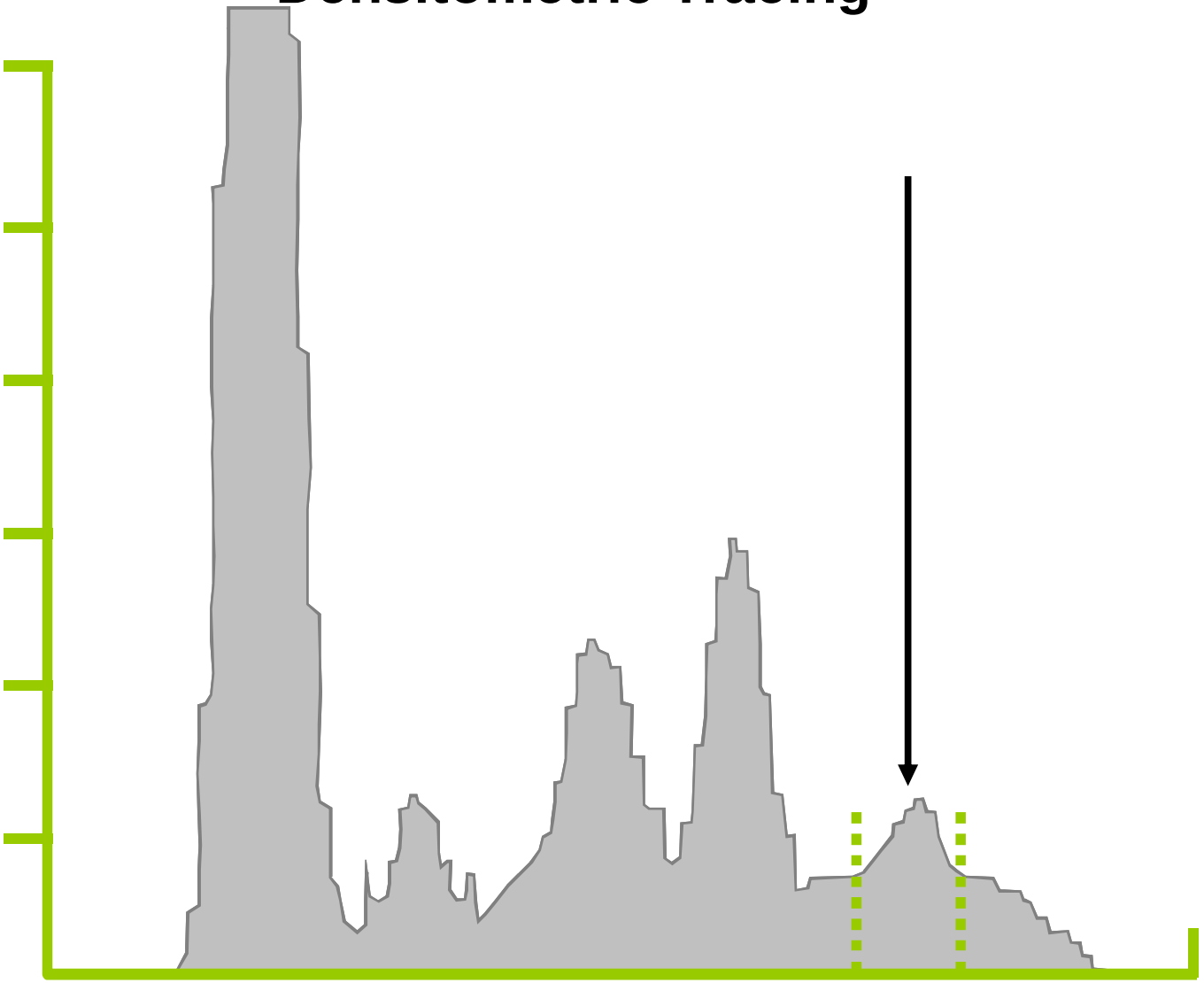
- Recognize clinical situations where amyloidosis should be seriously considered in differential
- Understand cost effective means of confirming diagnosis, staging & prognosis
- Weigh merits of conventional & high dose therapy as management

Patient

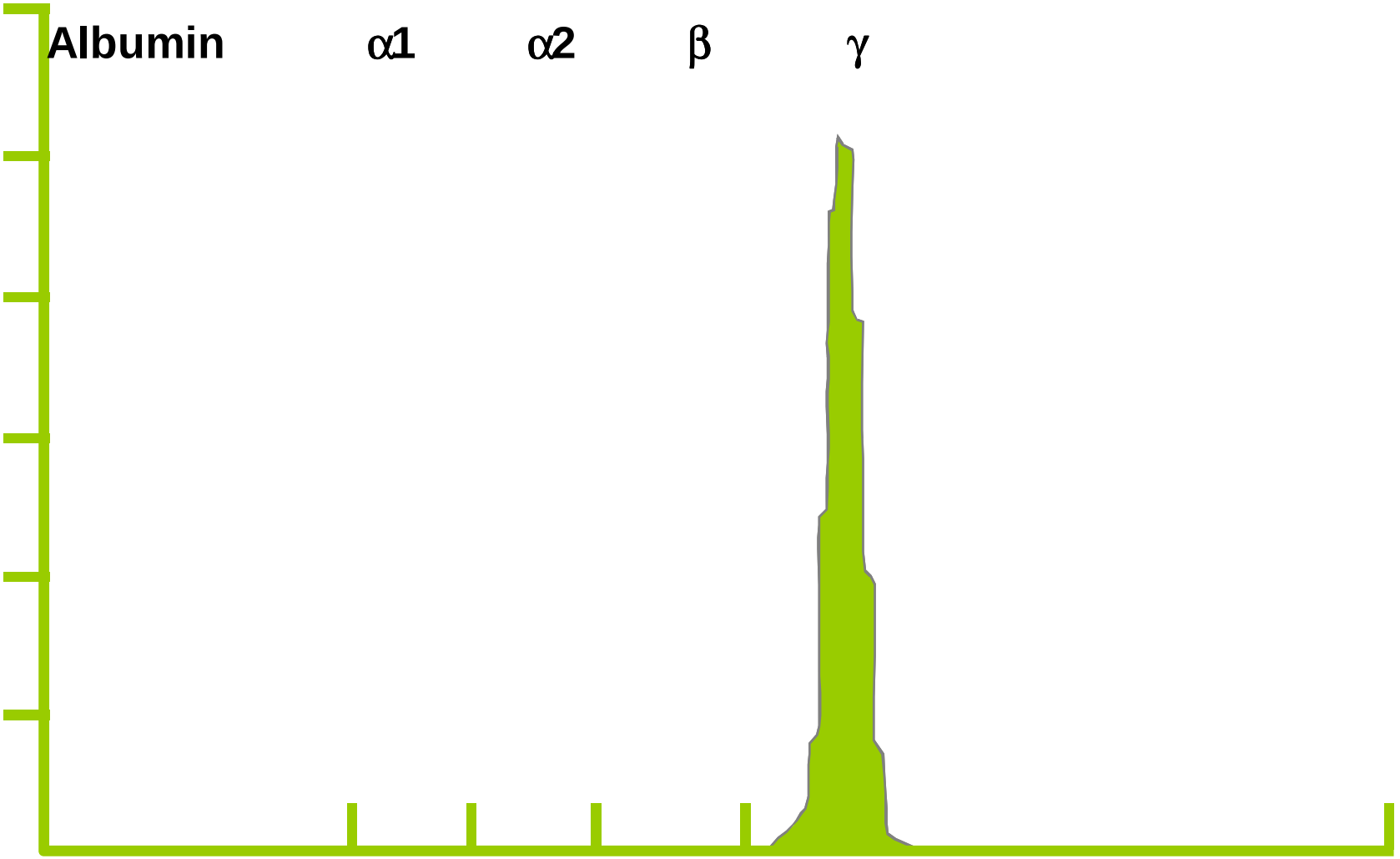
- 79 yo W M DOE 1 yr, LE edema
- Echo concentric LVH, EKG Anterior infarct
- Cath negative, normal coronaries
- Referred to Mayo for non cardiac dyspnea
- CT: adenopathy Laparoscopic Biopsy: Sinus Histiocytosis

SPEP

Densitometric Tracing

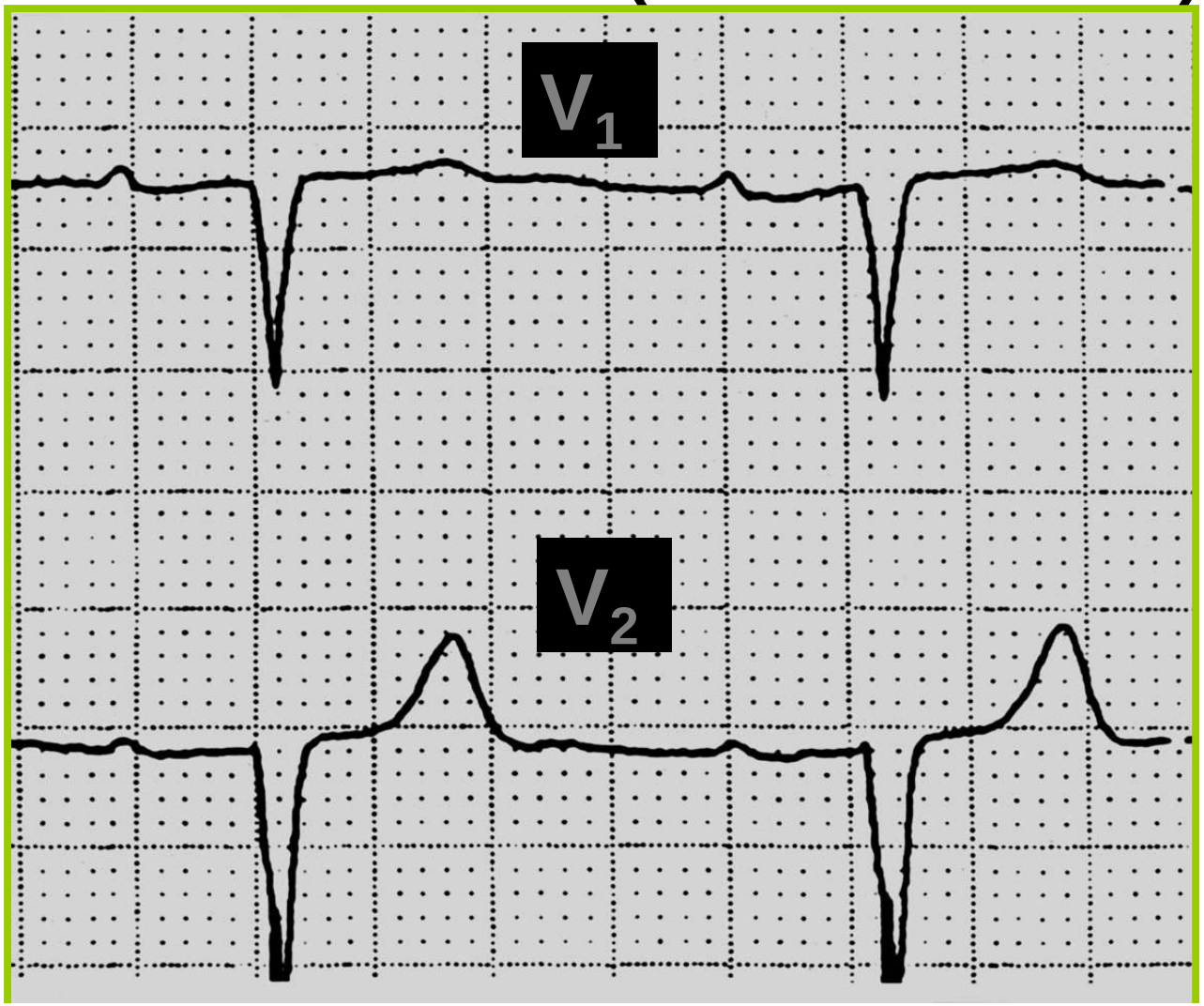


Urine Total Protein
0.22g/day



Patient EKG-Normal Coronary Angio

Anterior Infarction (“Pseudoinfarct”)



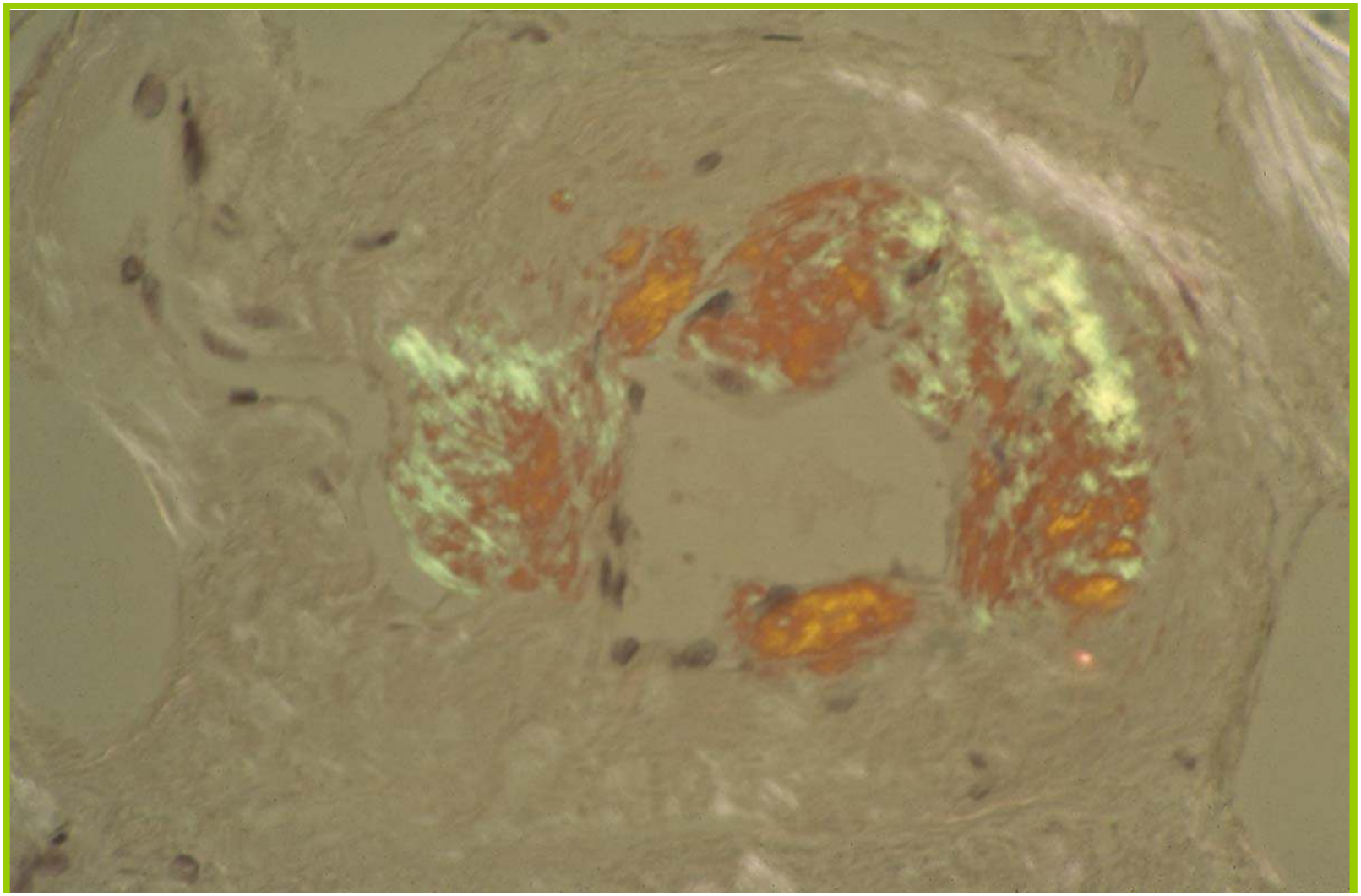
Patient

- Mayo Echo: Heart Walls & Valves Thickened Restrictive diastolic filling (stiff heart)
- Hypertrophy reinterpreted as infiltration
- Fat Aspirate +
- Lymph Node restained with Congo Red +
- Began Protocol Chemotherapy

Patient

- ‘Atypical Myeloma’ Aλ 0.8g/dL
- Marrow 8% PC’s Hb 14.4,
- Unexplained fatigue, can’t climb stairs, stops to rest 50 yards
- Depression about early myeloma
- Clues: EKG: low voltage & pseudo infarct, Neck veins distended due to restricted filling

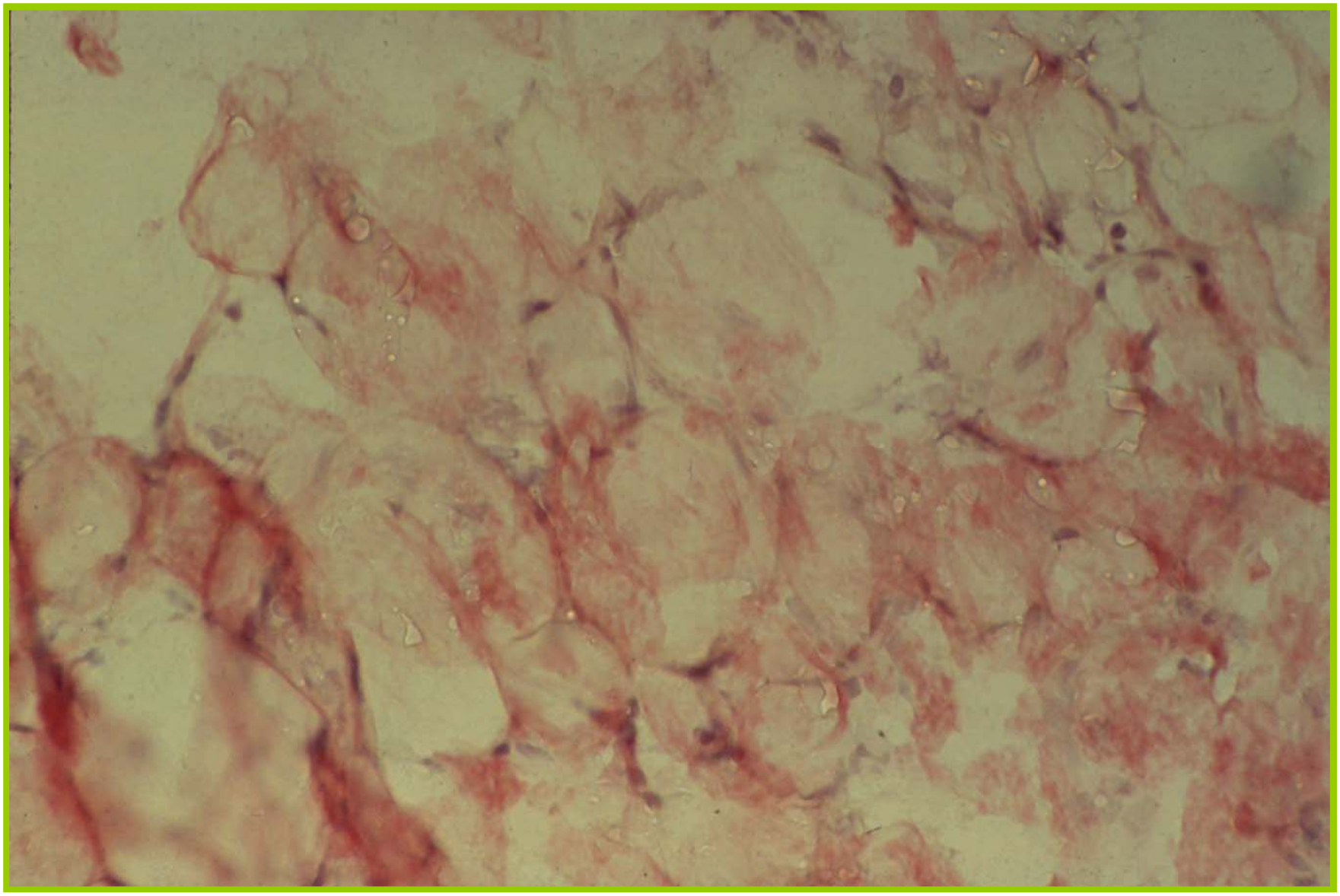
BONE MARROW BIOPSY CONGO RED X1000

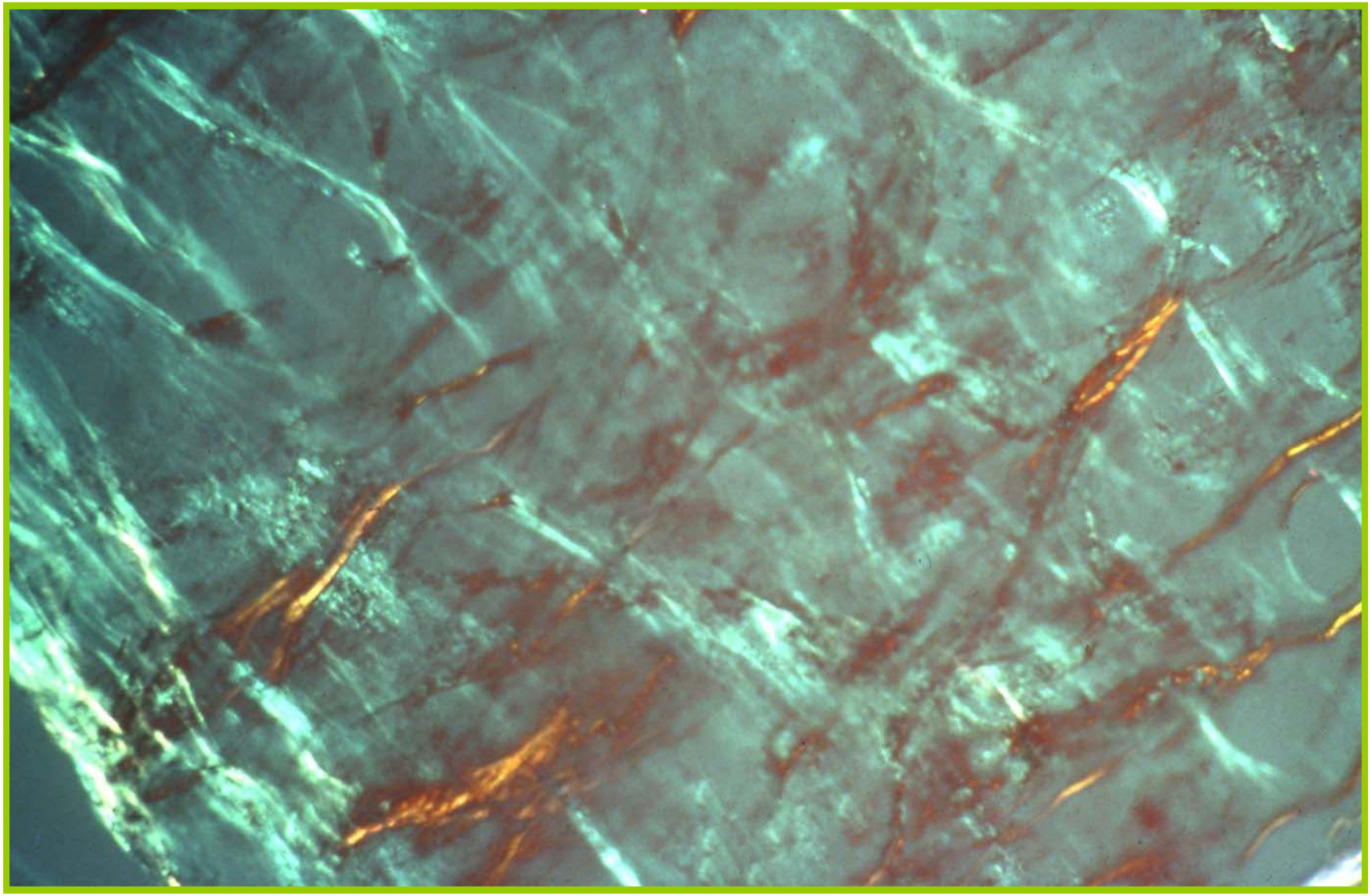


CP1106207-13

52 YO F 7194931

- Progressive sensory & motor neuropathy
- IgMλ 1.2g/dL Urine TP .879 M spike λ .029 g λ FLC 4.92 mg/dL
- Immunoglobulin infusions for dx of CIDP without benefit.
- bone marrow examination performed that showed 30% lymphocytes, 5% plasma cells diagnostic of Waldenstrom's.
- CRD 4 cycles

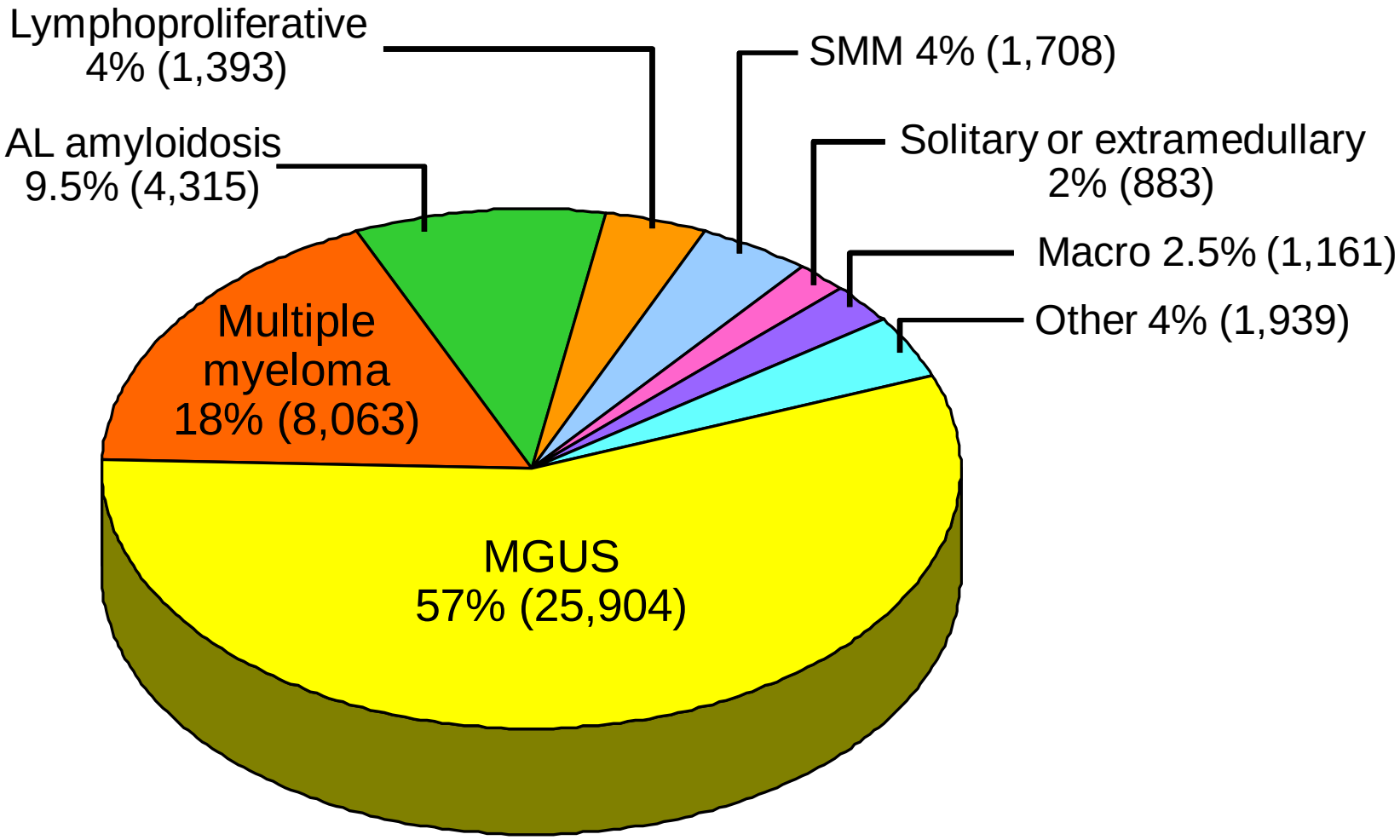




Monoclonal Gammopathies

Mayo Clinic 1960-2011

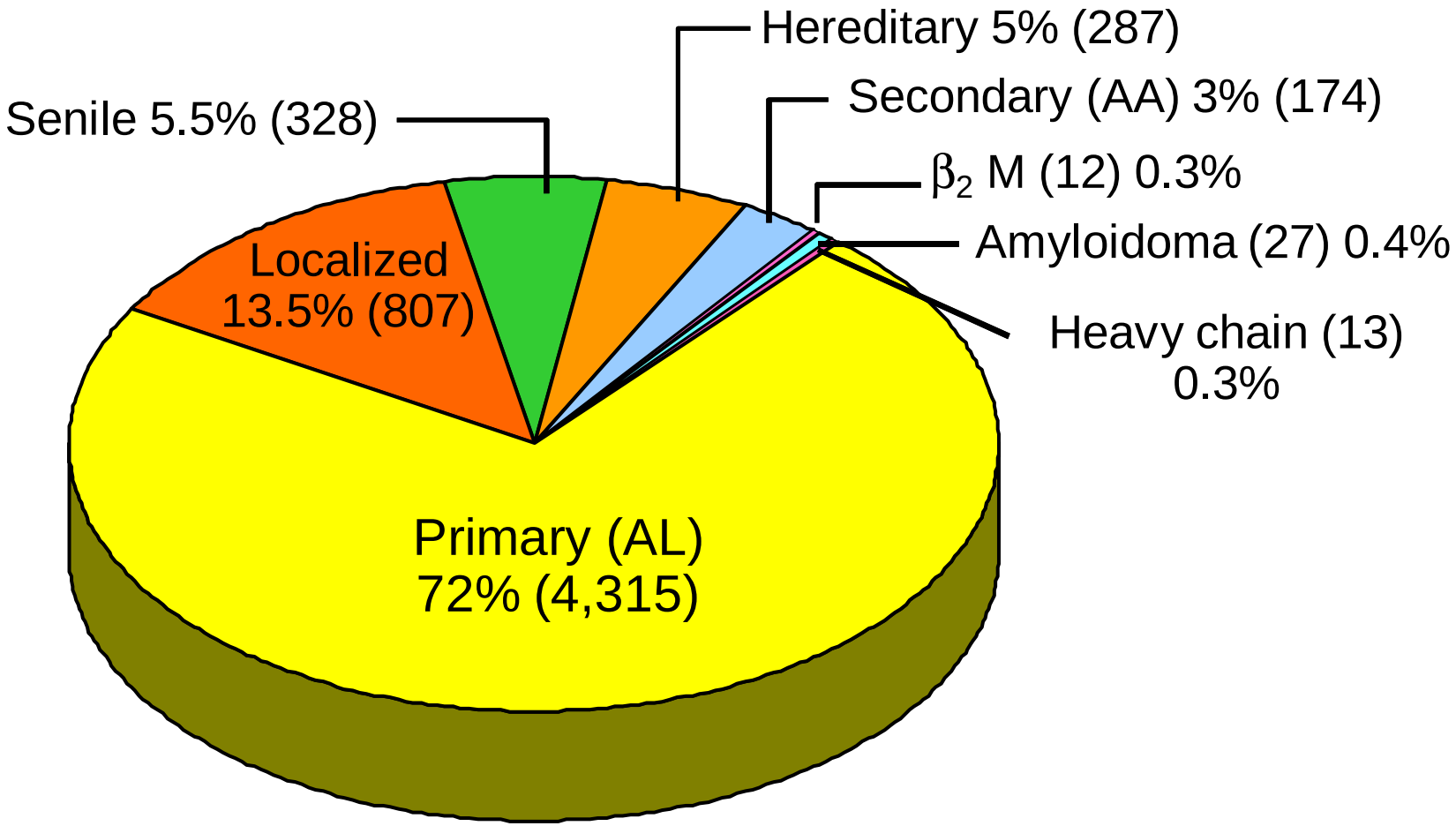
n=45,366



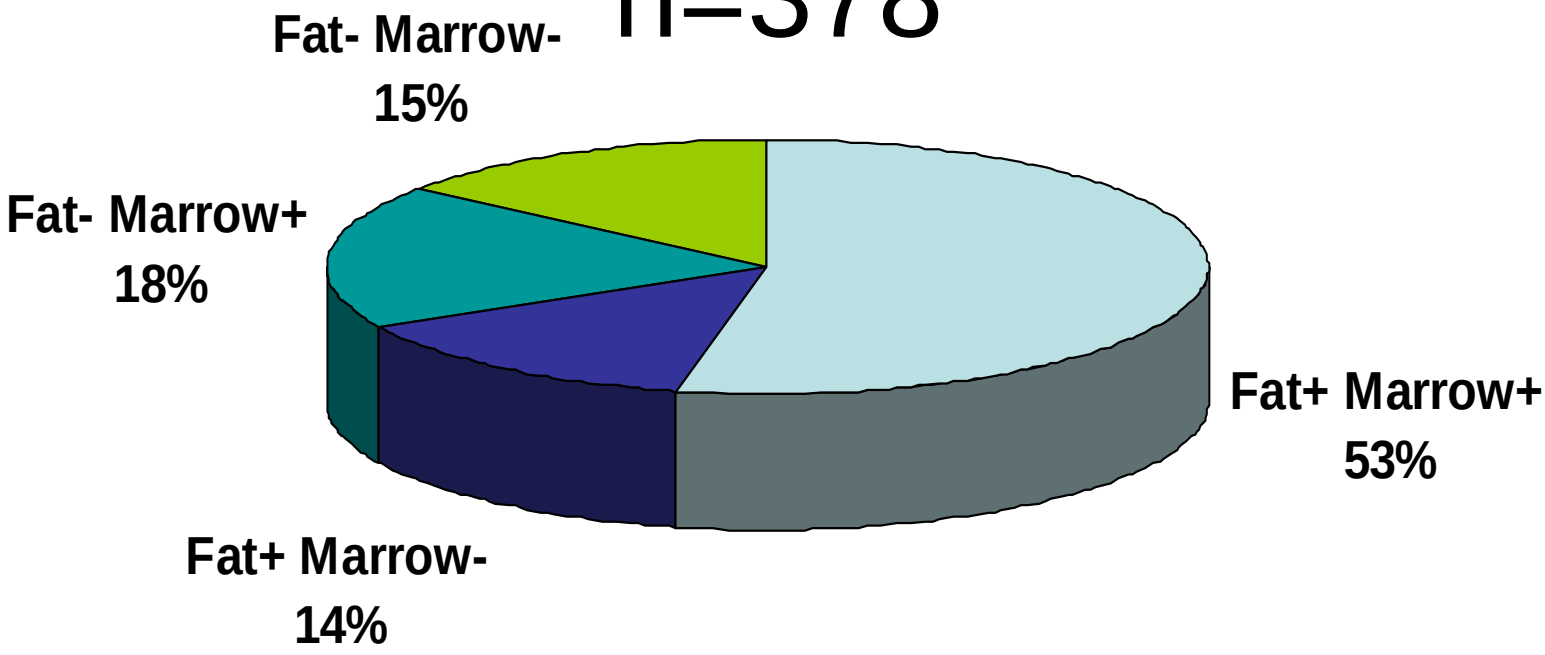
Amyloidosis

Mayo Clinic 1960-2011

n=5,963

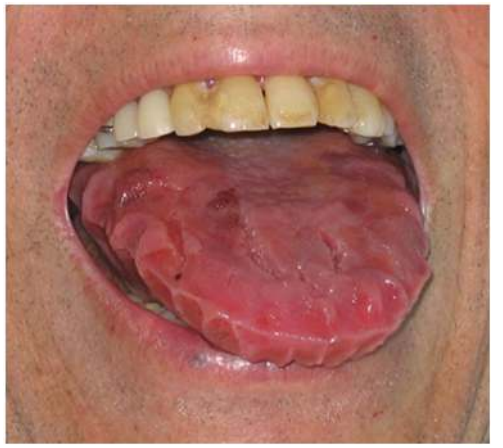


AMYLOIDOSIS
Making A Diagnosis Easily
n=378

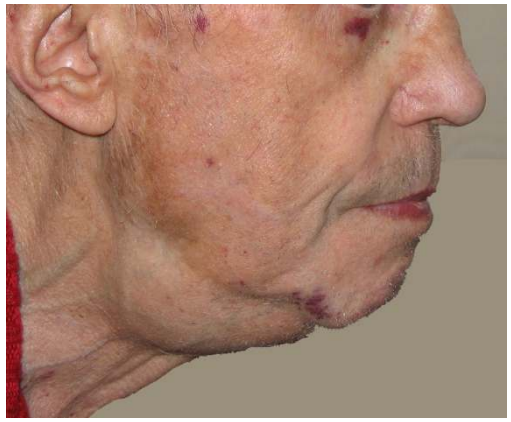


Clinical presentation in 868 patients with AL

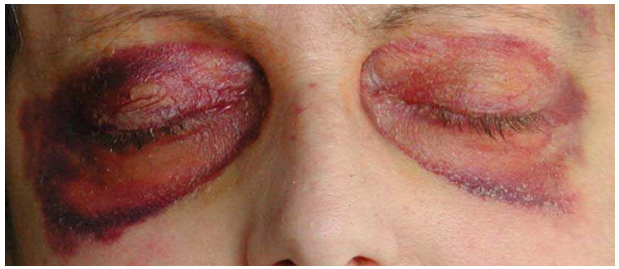
	%
Fatigue	68
Peripheral edema	62
Weight loss (kg) median 8 (2-30)	43
Exertional dyspnea	40
Orthostatic hypotension	27
Dysesthesias, Paresthesias	23
Dysgeusia	18
Macroglossia	14
Purpura	11
Diarrhea	9



Macroglossia 14%



Submandibular swelling (15%)



Periorbital purpura 11%

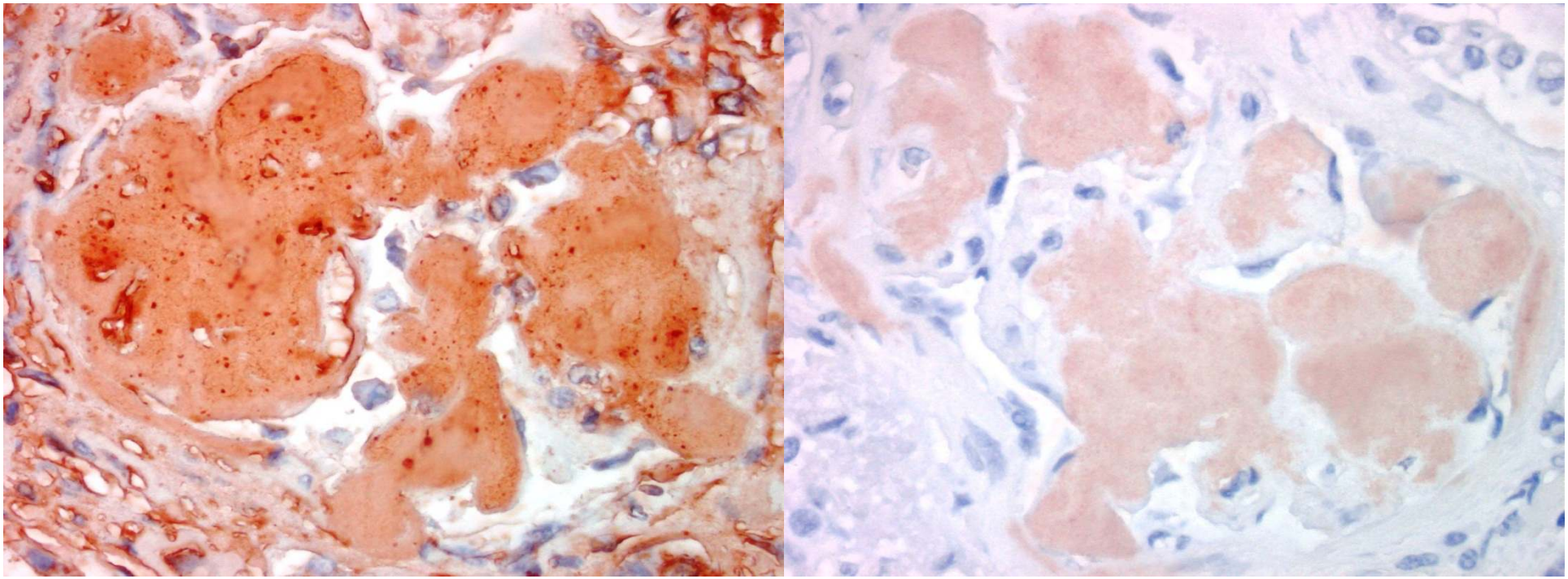
Amyloidosis 2012

- New Diagnostic Strategies
- New methods of monitoring
- New prognostic indicators
- New therapies

Amyloidosis 2012

- New Diagnostic Strategies
- New methods of monitoring
- New prognostic indicators
- New therapies

IMMUNOCHEMICAL CLASSIFICATION OF AMYLOID



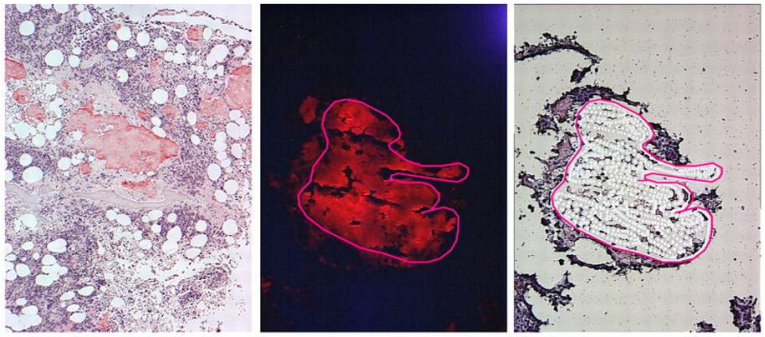
λ

Congo Red

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Figure 1. LMD/MS analysis of a case of AL-kappa amyloidosis (case 1)

A



(A) Bone marrow amyloid deposition (Left) CR (Middle) The area selected for microdissection is circled with a red line. (Right) Same area selected in the middle panel after microdissection of the amyloid plaque.

B

#	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)

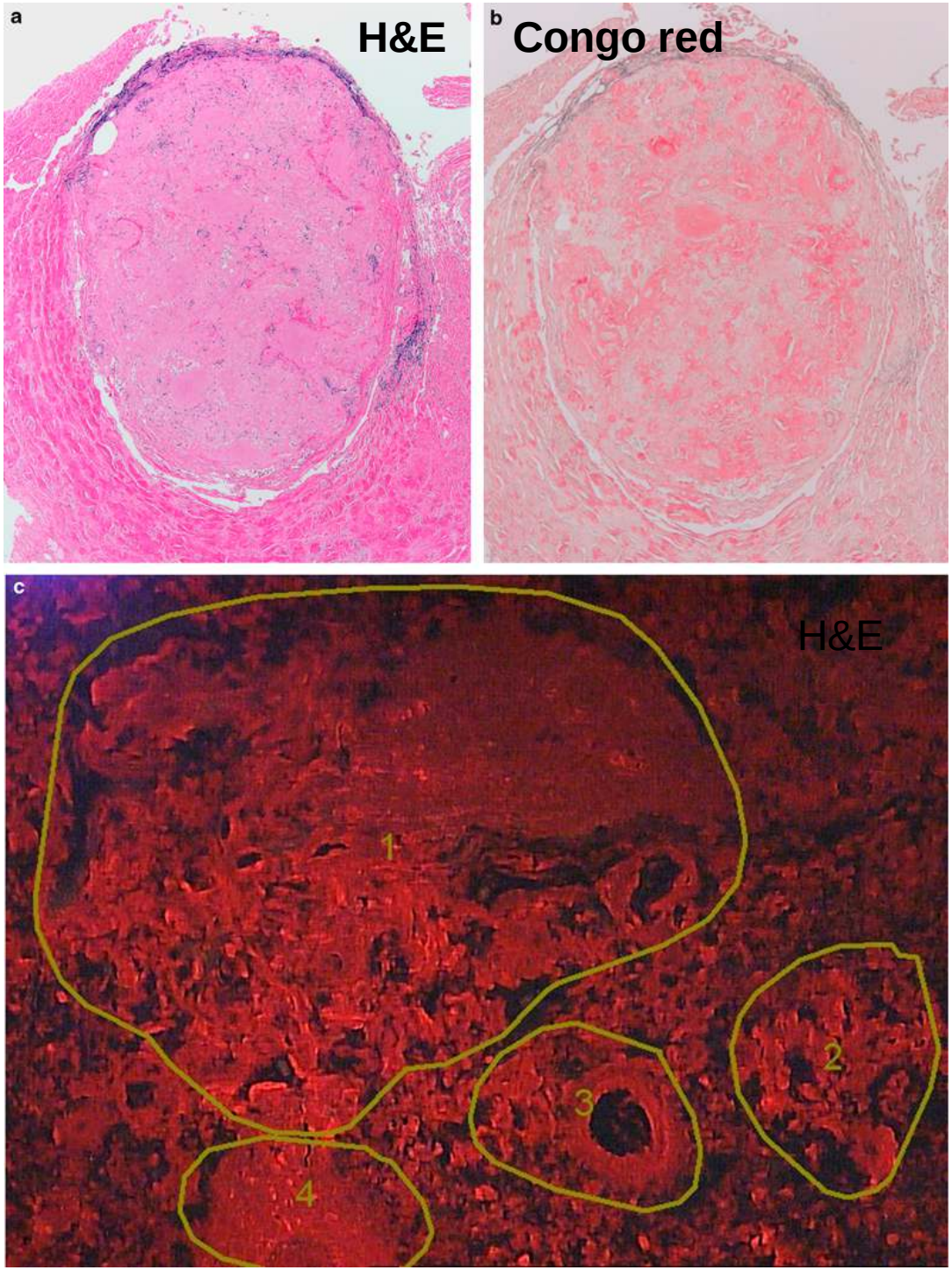
B) The list of proteins identified from the microdissected amyloid fragments are shown above in panel A. Of the 4 common types of systemic **amyloidosis** specifically studied (SAA, TTR, IGK, IGL), the samples contained peptides only belonging to IGK constant region

C

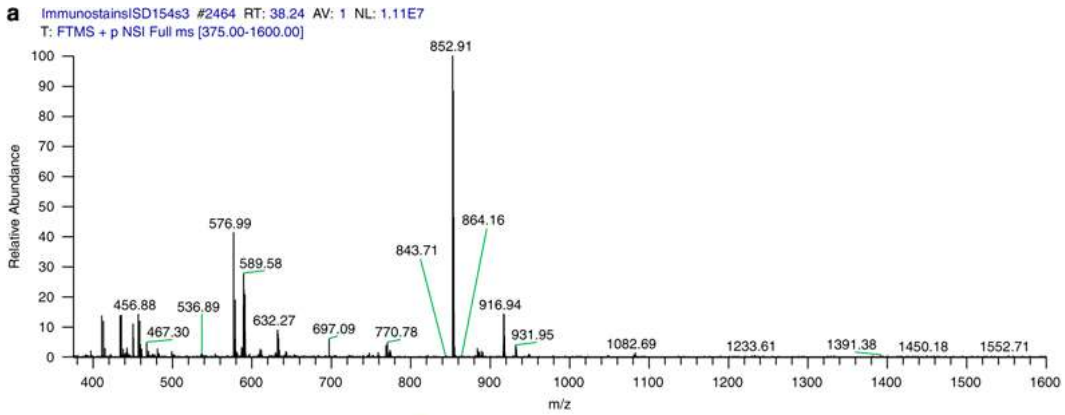
Protein	Sample	Probability	Unique Peptides	Unique Spectra	Total spectra	% Coverage
Ig kappa chain C region ·	Sample 1	100%	7	10	53	80%
Ig kappa chain C region ·	Sample 2	100%	8	11	53	67%
Ig kappa chain C region ·	Sample 3	100%	7	11	58	67%
Ig kappa chain C region ·	Sample 4	100%	8	12	61	80%

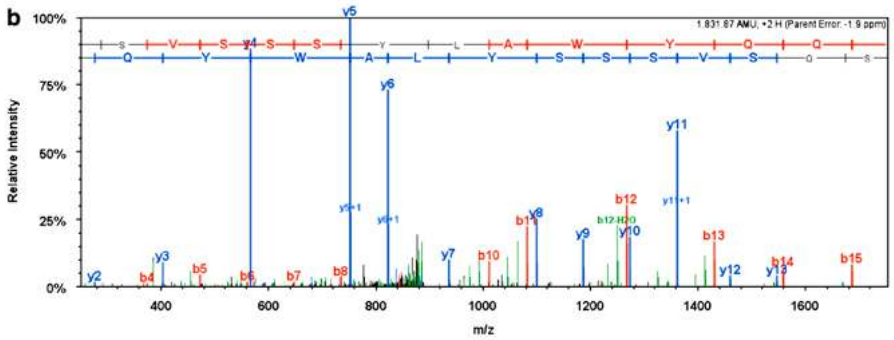
C) results of IGK constant region Probability of protein identification, the number of unique peptides

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



Several areas are traced in the computer screen, microdissected





B	B Ions	B+2H	B-NH3	B-H2O	AA	Y Ions	Y+2H	Y-NH3	Y-H2O	Y
1	72.0				A	1,832.9	916.9	1,815.9	1,814.9	16
2	159.1			141.1	S	1,761.8	881.4	1,744.8	1,743.8	15
3	287.1		270.1	269.1	Q	1,674.8	837.9	1,657.8	1,656.8	14
4	374.2		357.1	356.2	S	1,546.8	773.9	1,529.7	1,528.7	13
5	473.2		456.2	455.2	V	1,459.7	730.4	1,442.7	1,441.7	12
6	560.3	280.6	543.2	542.3	S	1,360.7	680.8	1,343.6	1,342.6	11
7	647.3	324.2	630.3	629.3	S	1,273.6	637.3	1,256.6	1,255.6	10
8	734.3	367.7	717.3	716.3	S	1,186.6	593.8	1,169.6	1,168.6	9
9	897.4	449.2	880.4	879.4	Y	1,099.6	550.3	1,082.5		8
10	1,010.5	505.7	993.5	992.5	L	936.5	468.8	919.5		7
11	1,081.5	541.3	1,064.5	1,063.5	A	823.4	412.2	806.4		6
12	1,267.6	634.3	1,250.6	1,249.6	W	752.4		735.3		5
13	1,430.7	715.8	1,413.6	1,412.6	Y	566.3		549.3		4
14	1,558.7	779.9	1,541.7	1,540.7	Q	403.2		386.2		3
15	1,686.8	843.9	1,669.7	1,668.8	Q	275.2		258.1		2
16	1,832.9	916.9	1,815.9	1,814.9	K	147.1		130.1		1

c **KV312_HUMAN (95%), 14,073.5 Da**
Ig kappa chain V-III region HAH precursor - Homo sapiens (Human) (P18135)

M E T P A Q L L F L L L L W L P D T T G E I V L T Q S P G T
L S L S P G E R A T L S C R **A S Q S V S** **S S Y L A W Y Q Q K**
P G Q A P R L L I Y G A S S R A T G I P D R F S G S G S G T
D F T L T I S R L E P E D F A V Y Y C Q Q Y G T S P R T F G
Q G T K V E I K R

Parent Mass +1831.8704, observed mass is 916.943 with Z=2,

κ-light chain V-III

Identifies amyloid in formalin fixed tissue as immunoglobulin - AL

Now done routinely on all amyloid deposits

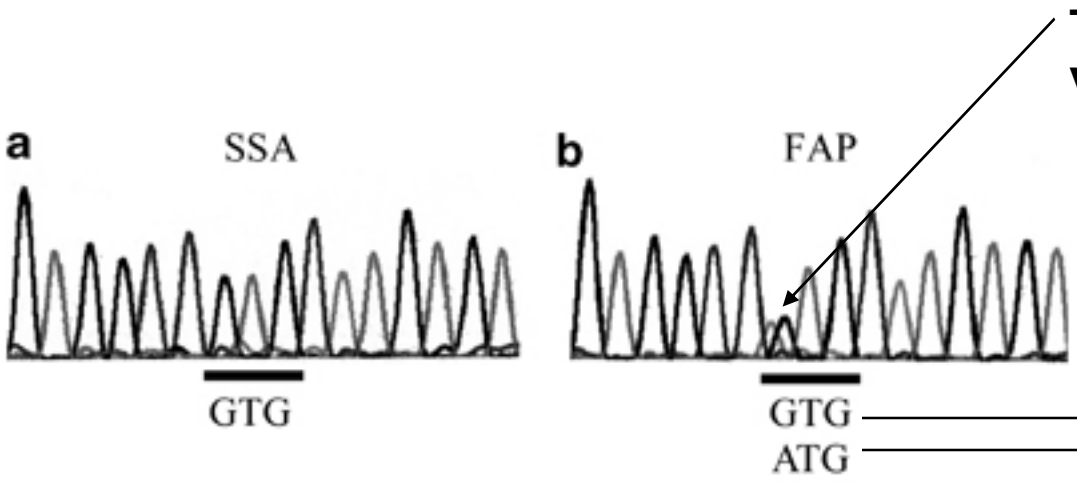
Laboratory Investigation (2008) **88,** 1024–1037

74 yo M CLL

- Fludarabine x 6 2001
- 4/05 + CTS Congo Red +
- CHF Oct. 2008 Echo: Infiltrative Cardiomyopathy
- Serum small Gλ, urine λ
- Light chains κ 1.84 λ 5.11
- BNP 393, Marrow CLL congo red +

- Mass Spec on Bone marrow + shows TTR
- Gene sequence of TTR shows no mutation
- Senile Systemic Amyloidosis formerly known as Senile Cardiac Amyloidosis
- Native TTR overwhelmingly men
- Exclusively heart; 50% CTS
- Prognosis much better than AL with heart
- Autopsy 12% > age 80 ? Tafamidis role

Modern Pathology 2011; 1533-44

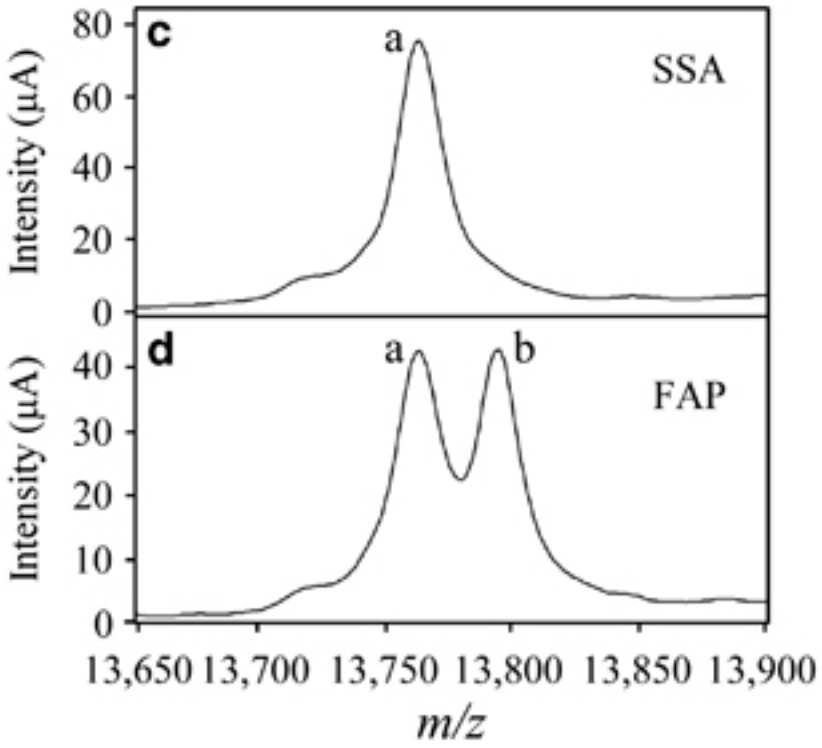


TTR
VAL30MET

Valine MW 117.15

Methionine MW 149.2

Δ 32



Mass Spec Native TTR 13761
Mutation TTR 13793 Δ 32

Amyloidosis 2012

- New Diagnostic Strategies
- New methods of monitoring
- New prognostic indicators
- New therapies

Free Light chain assays

- Prior to 2001 assessment of response was based on M protein measure which has poor reproducibility at low levels or by immunofixation which is qualitative
- Free light chain quantitatively measures by nephelometry only unbound Ig light chains & does not measure light chains as part of an intact Ig molecule

Clinical Suspicion Drives the Test Panel

Screening panels for different plasma cell disorders.

	SPEP	Serum FLC	Serum IFE	UPEP/Urine IFE
MM	✓	✓		
WM	✓	✓		
MGUS	✓	✓		
SMM	✓	✓		
Plasmacytoma	✓	✓	✓	
Extramedullary Plasmacytoma	✓	✓	✓	
POEMS	✓	✓	✓	
AL	✓	✓	✓	✓
LCDD	✓	✓	✓	✓

SPEP, serum protein electrophoresis; FLC, free light chains; IFE, immunofixation electrophoresis; UPEP, urine protein electrophoresis; M changes; AL, amyloidosis; LCDD, light chain deposition disease.

Katzmann JA. Clin Biochem Rev. 2009 Aug;30(3):105-11

Conclusions

- Serum FLC difference (Involved-uninvolved FLC) should be the primary marker for following hematological response:
  - More patients are evaluable for response using FLC compared to SPEP
  - It better predicts outcome (survival) compared to M-spike by SPEP

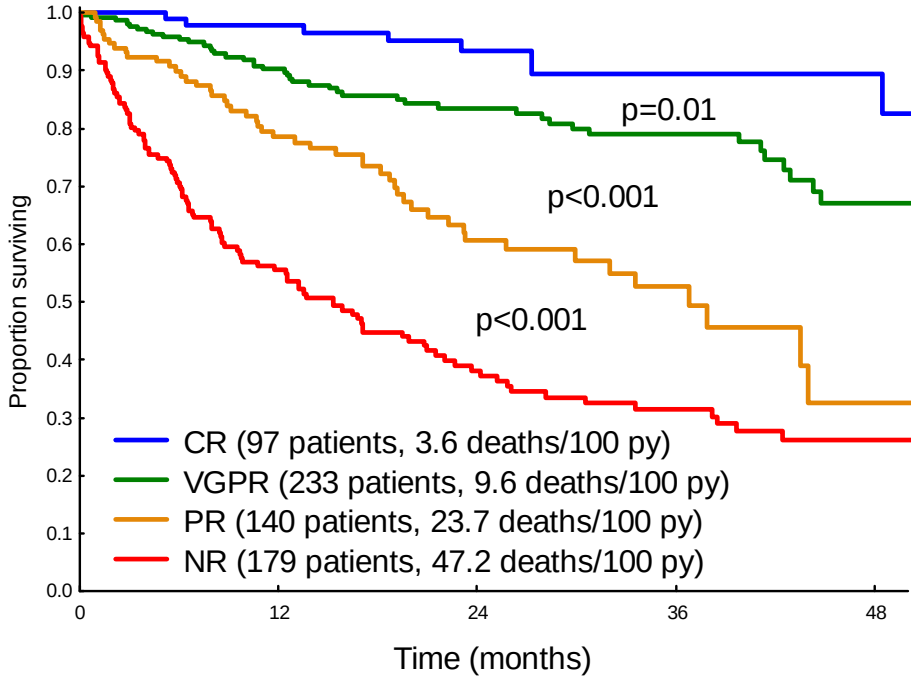
New criteria of response to treatment in AL amyloidosis

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

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

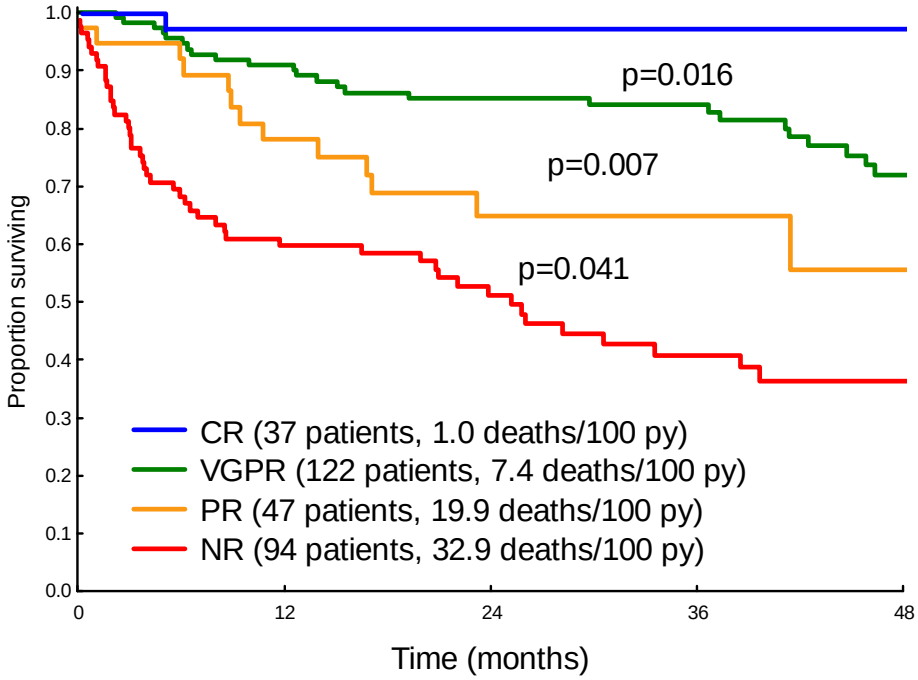
New criteria of response to treatment in AL amyloidosis

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



Survival of 649 patients based on hematologic response

6 month landmark



Survival of 300 patients based on hematologic response

3 month landmark

FROM:

Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis

R L Comenzo, D Reece, G Palladini, D Seldin, V Sanchorawala, H Landau, R Falk, K Wells, A Solomon, A Wechalekar, J Zonder, A Dispenzieri, M Gertz, H Streicher, M Skinner, R A Kyle and G Merlini

BACK TO ARTICLE

Table 2. Organ response and progression criteria

Previous table | Figures and tables index | Next table

Organ	*Response*	*Progression*
Heart	NT-proBNP response (>30% and >300 ng/l decrease in patients with baseline NT-proBNP ⩾650 ng/l) or NYHA class response (⩾2 class decrease in subjects with baseline NYHA class 3 or 4)	NT-proBNP progression (>30% and >300 ng/l increase) [a] or cTn progression (⩾33% increase) or Ejection fraction progression (⩾10% decrease)
Kidney	50% decrease (at least 0.5 g/day) of 24-h urine protein (urine protein must be >0.5 g/day pretreatment). Creatinine and creatinine clearance must not worsen by 25% over baseline	50% increase (at least 1 g/day) of 24-h urine protein to >1 g/day or 25% worsening of serum creatinine or creatinine clearance
Liver	50% decrease in abnormal alkaline phosphatase value Decrease in liver size radiographically at least 2 cm	50% increase of alkaline phosphatase above the lowest value
Peripheral nervous system	Improvement in electromyogram nerve conduction velocity (rare)	Progressive neuropathy by electromyography or nerve conduction velocity

Abbreviations: NT-proBNP, N-terminal prohormone of brain natriuretic peptide; cTn, cardiac troponin; NYHA, New York Heart Association.

[a] Patients with progressively worsening renal function cannot be scored for NT-proBNP progression.

Leukemia. 2012 Apr 5. doi: 10.1038/leu.2012.100. [Epub ahead of print]

Amyloidosis 2012

- New Diagnostic Strategies
- New methods of monitoring
- New prognostic indicators
- New therapies

Cardiac Status Drives Prognosis

- 1970- clinical CHF
- 1980-Echo Cardiography
- 1990-Doppler measures of inflow velocity
- 2000- MRI investigations begin
- 2005-Strain echo cardiography
- Currently Cardiac biomarkers

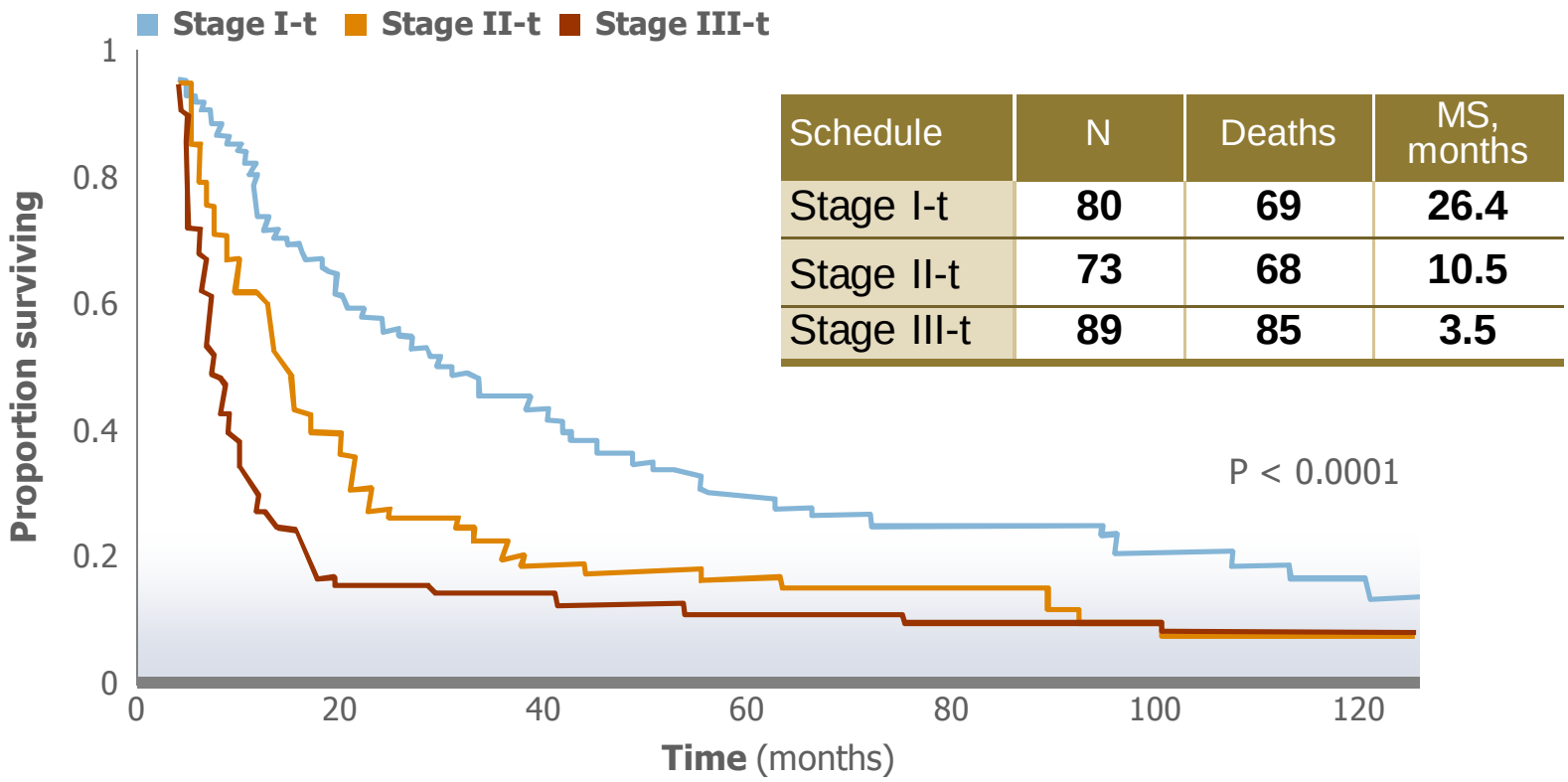
VOLUME 22 · NUMBER 18 · SEPTEMBER 15 2004

JOURNAL OF CLINICAL ONCOLOGY

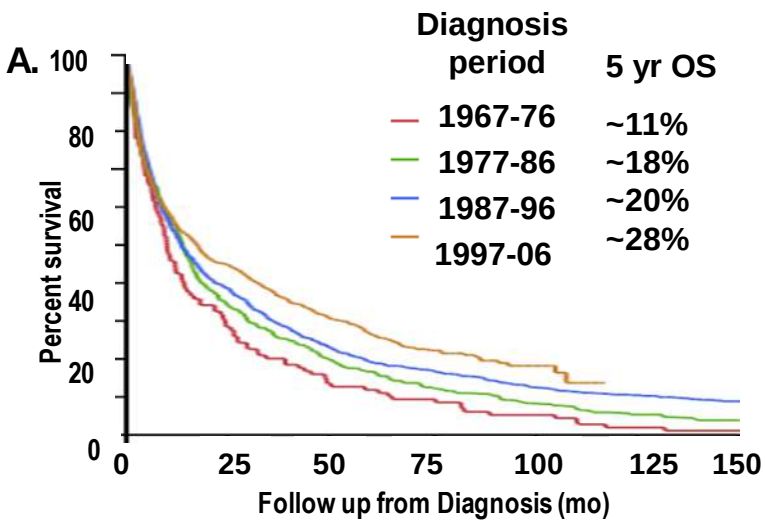
ORIGINAL REPORT

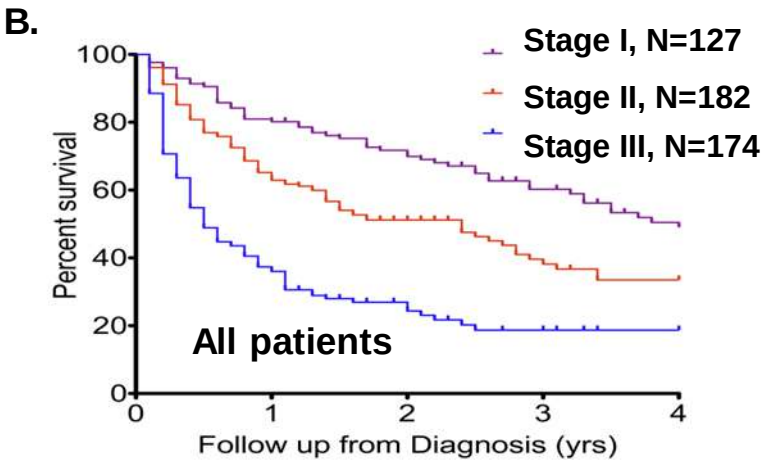
Serum Cardiac Troponins and N-Terminal Pro-Brain Natriuretic Peptide: A Staging System for Primary Systemic Amyloidosis

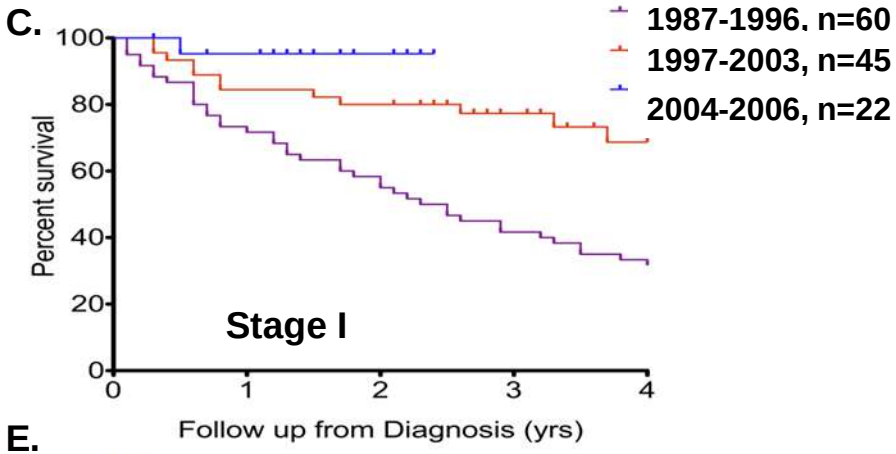
Angela Dispenzieri, Morie A. Gertz, Robert A. Kyle, Martha Q. Lacy, Mary F. Burritt, Terry M. Therneau, Philip R. Greipp, Thomas E. Witzig, John A. Lust, S. Vincent Rajkumar, Rafael Fonseca, Steven R. Zeldenrust, Christopher G.A. McGregor, and Allan S. Jaffe

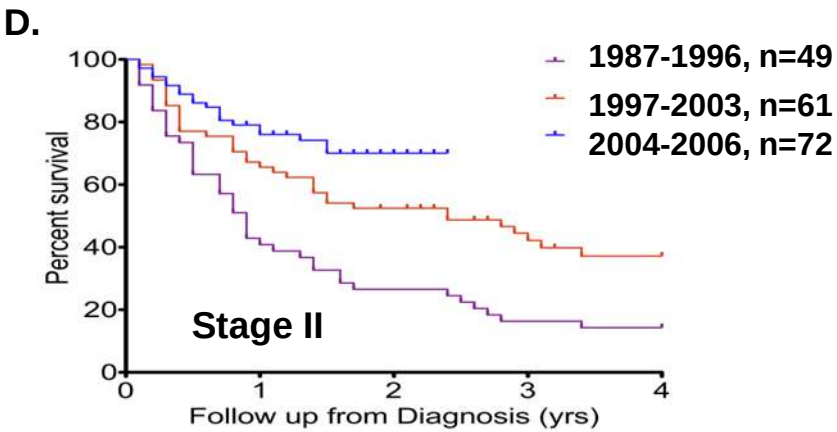


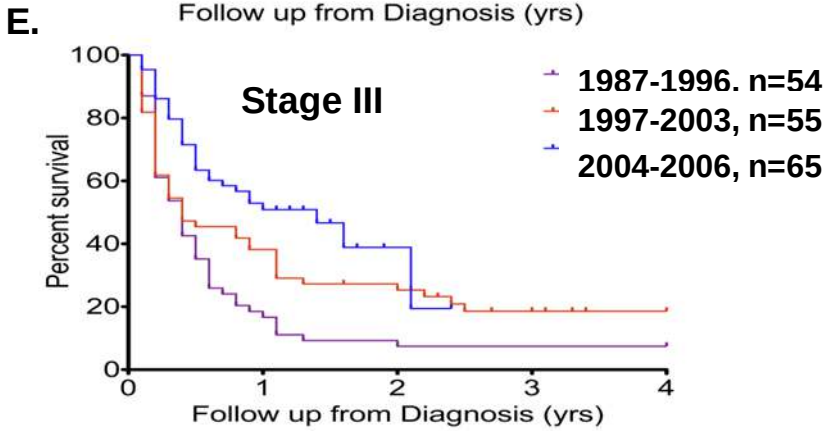
Schedule	N	Deaths	MS, months
Stage I-t	**80**	**69**	**26.4**
Stage II-t	**73**	**68**	**10.5**
Stage III-t	**89**	**85**	**3.5**

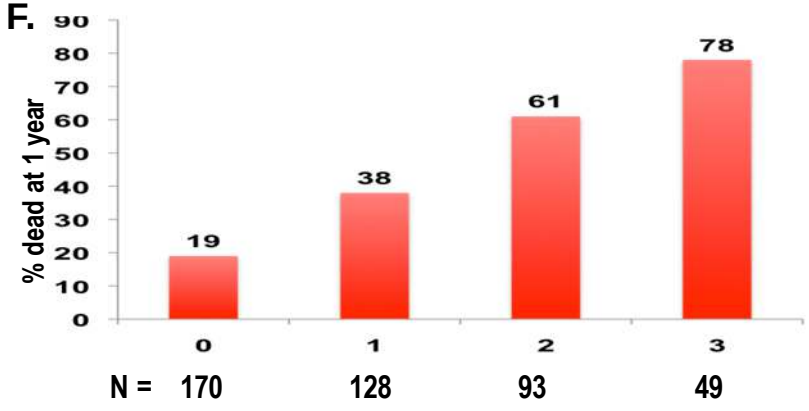

A.
Diagnosis period
5 yr OS
1967-76
~11%
1977-86
~18%
1987-96
~20%
1997-06
~28%
Percent survival
Follow up from Diagnosis (mo)


B.
Stage I, N=127
Stage II, N=182
Stage III, N=174
All patients
Percent survival
Follow up from Diagnosis (yrs)


C.
1987-1996. n=60
1997-2003, n=45
2004-2006, n=22
Stage I
Percent survival
Follow up from Diagnosis (yrs)


D.
1987-1996, n=49
1997-2003, n=61
2004-2006, n=72
Stage II
Percent survival
Follow up from Diagnosis (yrs)


E.
Stage III
1987-1996. n=54
1997-2003, n=55
2004-2006, n=65
Percent survival
Follow up from Diagnosis (yrs)


F.
% dead at 1 year
19
38
61
78
0
1
2
3
N = 170 128 93 49

Outcomes in 347 Patients with Systemic AL with Mayo Stage III

- stage III patients are heterogeneous and NT-proBNP and SBP can sub-classify patients.
- Patients with abnormal biomarkers just due to renal failure in absence of cardiac involvement should be excluded from the Mayo staging
- treatment responses of stage III patients, are poor with all regimes patients who achieve a CR have best outcomes.

Blood (ASH Annual Meeting Abstracts) 2011 118: Abstract **995**

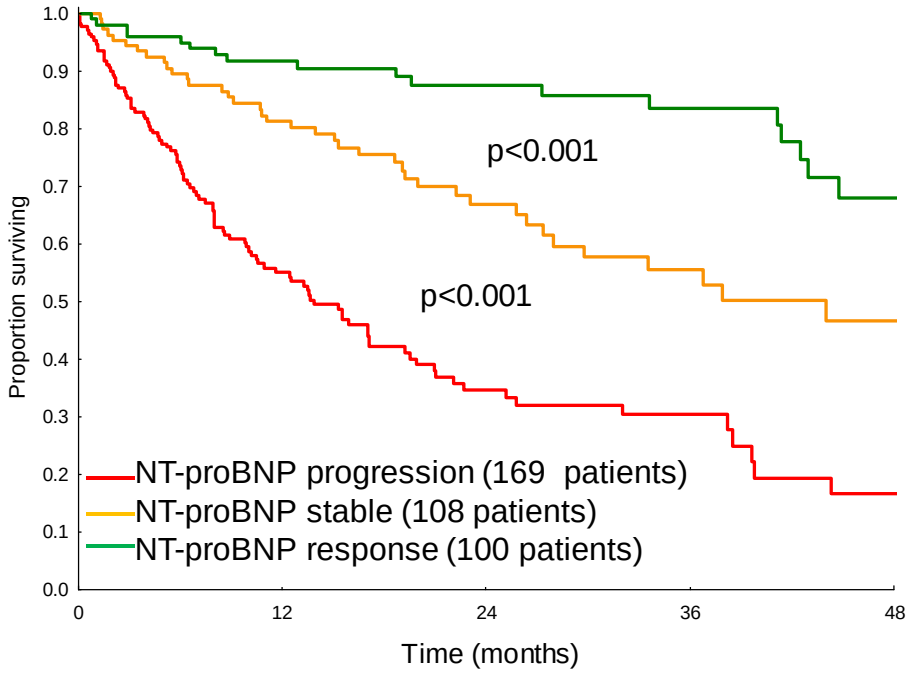
median overall survival (OS) was 7.1 mos.

- Stage III patients without echocardiographic evidence of cardiac involvement had excellent outcomes with 80% estimated 2 year OS
- Using NT-proBNP >8000 ng/L and SPB <100 as high risk criteria, stage III patients can be subdivided based on presence of 0,1 or 2 criteria with OS of 25 mo, 6 mo and 3 mo respectively

Blood (ASH Annual Meeting Abstracts) 2011 118: Abstract **995**

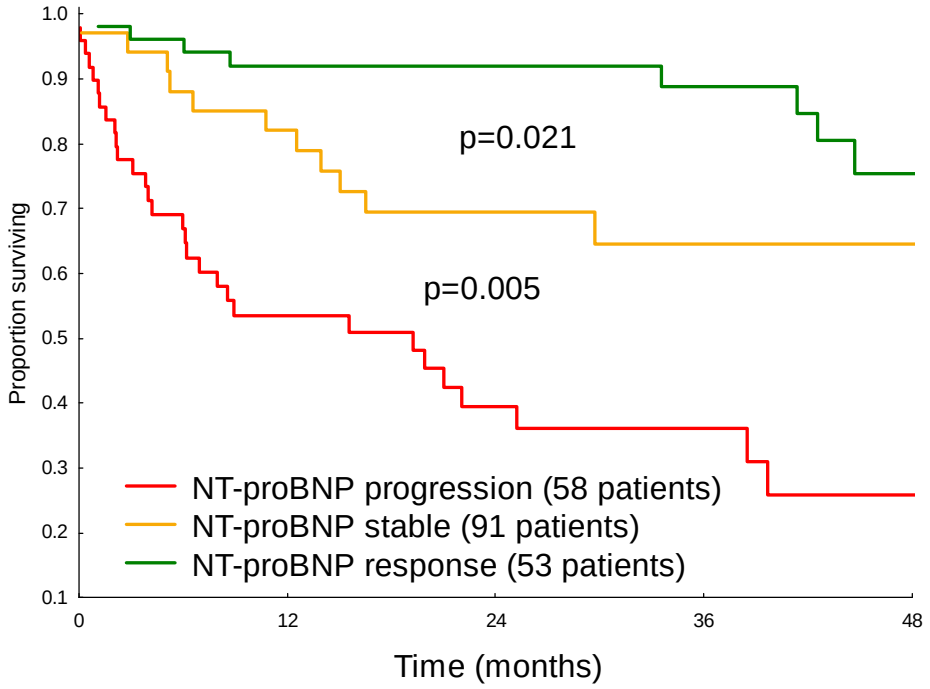
New criteria of response to treatment in AL amyloidosis

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



Survival of 377 patients based on NT-proBNP changes

6 month landmark



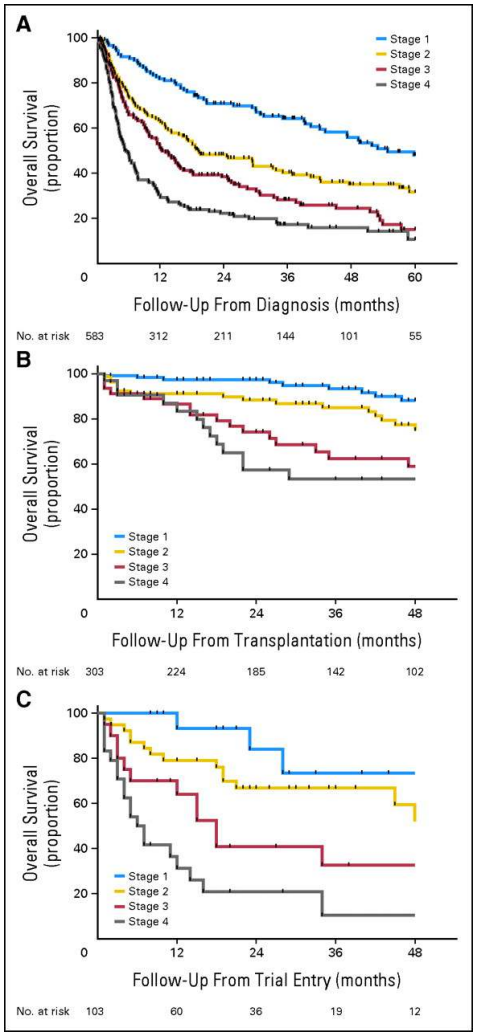
Survival of 202 patients based on NT-proBNP changes

3 month landmark

Caution using NT-proBNP in patients treated with IMiDs and changing eGFR

(A) Kaplan-Meier curves for overall survival (OS) from diagnosis among the subgroup of 583 patients based on the new staging system.

Patients were assigned a score of 1 for each of **FLC-diff** ≥ 18 mg/dL, cTnT ≥ 0.025 ng/mL, and NT-ProBNP ≥ 1,800 pg/mL, creating stages I to IV with scores of 0 to 3 points, respectively



OS from stem-cell transplantation among 303 patients based on the new staging system

103 patients enrolled onto different trials

Kumar S et al. JCO 2012;30:989-995

Proposed Staging Systems

Staging system	Stages	Median survival
Standard "Mayo" Staging (NT-proBNP >332 ng/L and TNT >0.035 ng/ml)	**Stage I (both < threshold)**	**26 months**
	Stage II (either > threshold)	**10 months**
	Stage III (both > threshold)	**3.5 months**
Revised Mayo Staging (dFLC 18mg/L, NT-proBNP >1800 pg/ml, TNT >0.025ng/ml)	**Stage I (all below threshold)**	**94 months**
	Stage II (any one > threshold)	**40 months**
	Stage III (any two > threshold)	**14 months**
	Stage IV (all three > threshold)	**5.8 months**
NT-proBNP and SBP in stage III (NTproBNP >8000 ng/L; SBP <100 mm of Hg)	**No risk factors**	**26 months**
	One risk factor	**6 months**
	Two risk factors	**3 months**
Hs-Troponin only (<14 ng/ml, >14 but <54ng/ml; >54 ng/ml)	**Stage I (hs-TNT low)**	**71 months**
	Stage II (hs- TNT intermediate)	**43 months**
	Stage III (Hs TNT high)	**6 months**
Chr 1q gain	**Present**	**12.5 months**
	Absent	**38 months**

Criteria for Cardiac Response and Progression

New criteria	Definition	Estimated 2-year survival (6-month landmark)	P
NT-proBNP response	>30% and >300 ng/L decrease if baseline NT-proBNP ≥650 ng/L	90%	<0.001
NT-proBNP progression	>30% and >300 ng/L increase	35%	<0.001
cTn progression	≥33% increase	60%	<0.001
NYHA class response	≥2 class decrease if baseline NYHA class 3 or 4	35%	0.001
EF progression	≥10% decrease	50%	0.007

Amyloidosis 2012

- New Diagnostic Strategies
- New methods of monitoring
- New prognostic indicators
- New therapies

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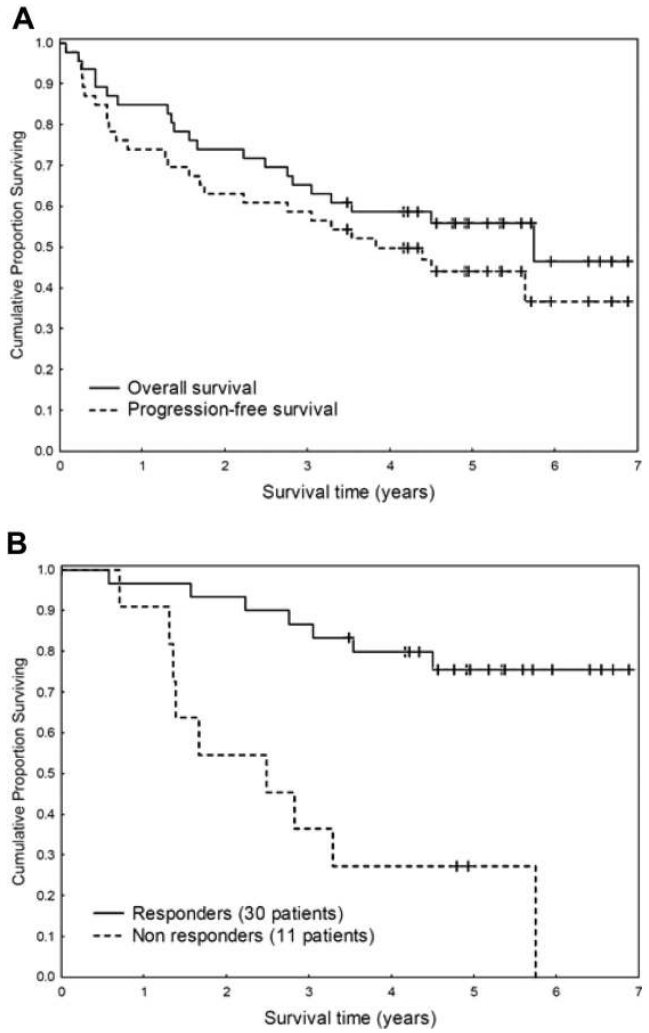
Mel Dex for Non SCT candidates AL; Long Term F/U



Palladini, G. et al. Blood 2007;110:787-788

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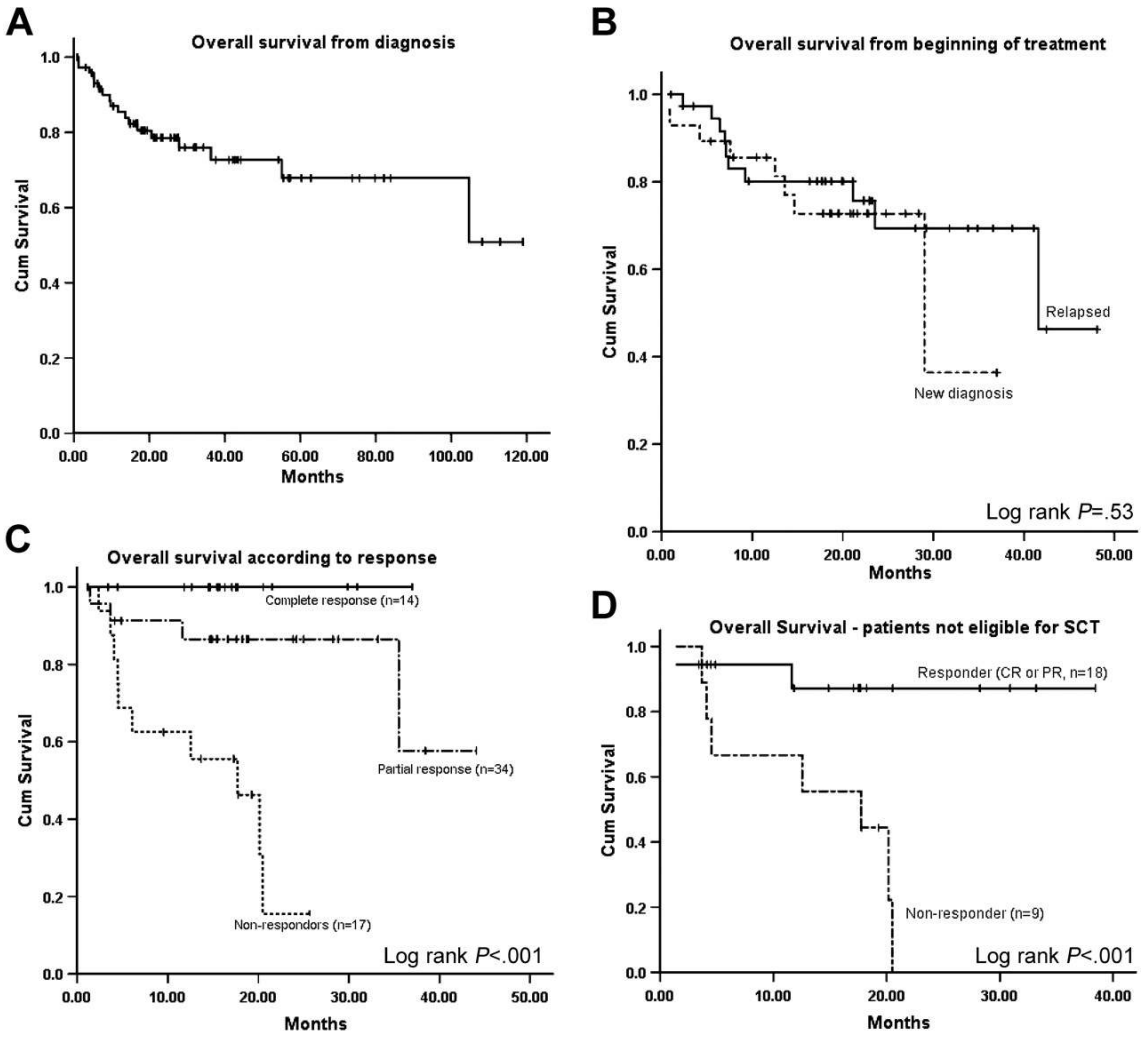
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Overall survival and effect of pretreatment status and hematologic response on survival using CTd.



Wechalekar A D et al. Blood 2007;109:457-464

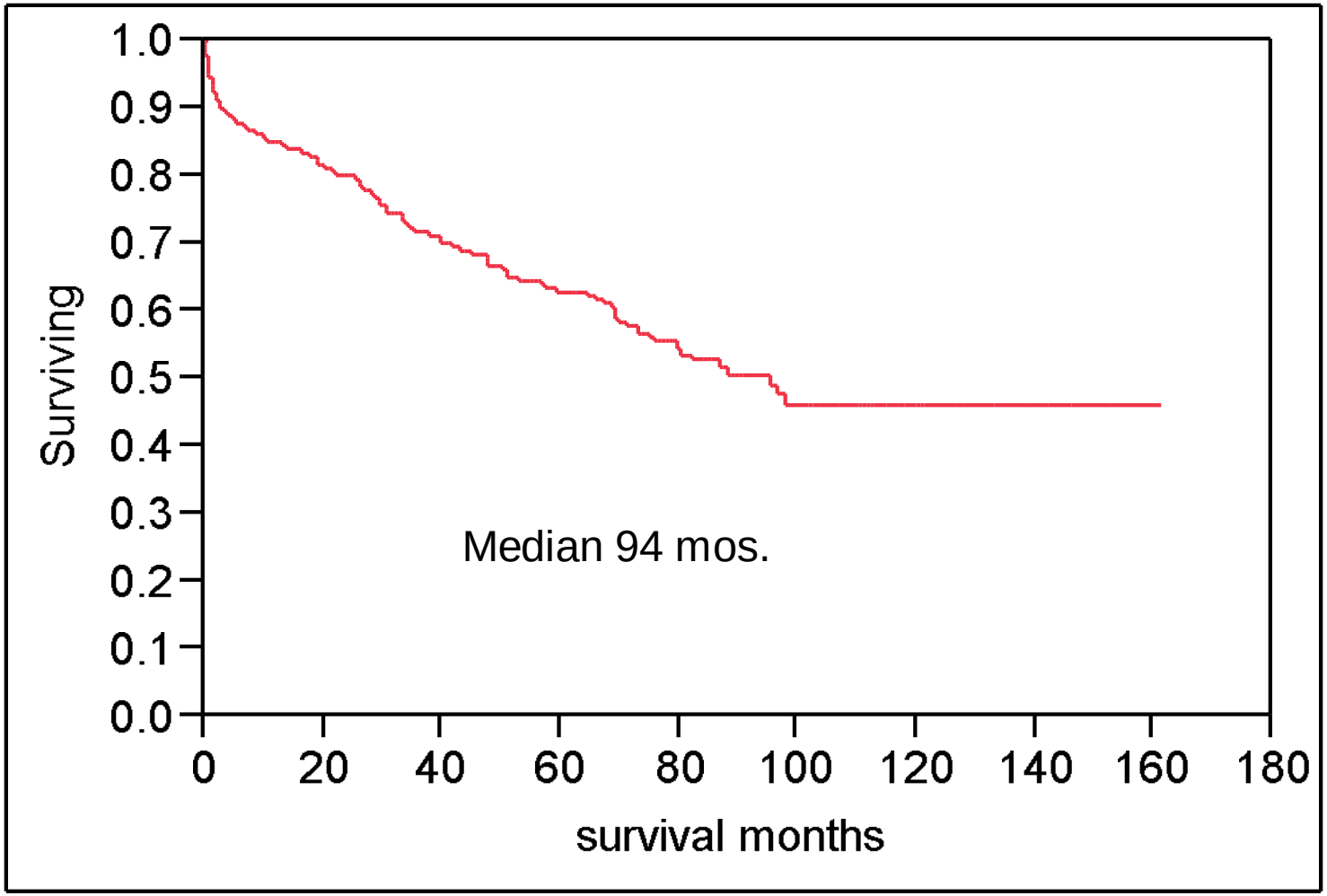
28-day cycle of cyclophosphamide 500 mg days 1, 8, and 15
; thalidomide 200 mg/day (starting dose, 50 mg/day, increased by 50 mg at 4-week intervals
and dexamethasone 20 mg days 1 to 4 and days 15 to 18

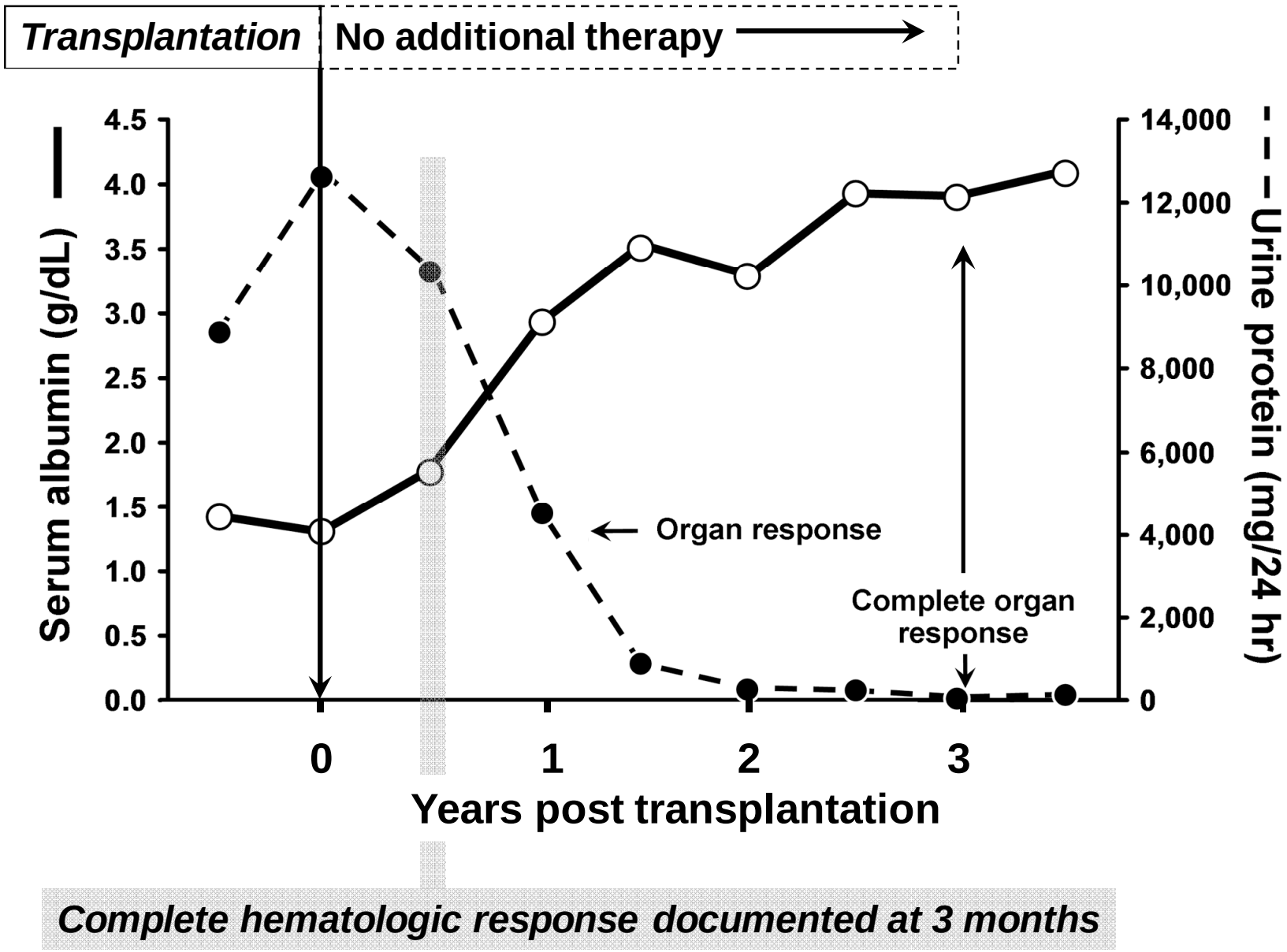
MDR for AL

- MDR AL
- Ph 1 dose escalation R 5→20 d1-21
- M .17 mg/kg/d 1-4; D40 1-4q28
- LMWH for DVT proph
- 26 evaluable , R 15 (DLT @20) 6 deaths
- CR 42%; PR 9/26 ORR 58% organ response 50% EFS 54%@2yr, OS 81%@2yr

Blood. 2010 Dec 2;116(23):4777-82.

Mayo Clinic survival post SCT




Transplantation
No additional therapy
Serum albumin (g/dL)
Urine protein (mg/24 hr)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
14,000
12,000
10,000
8,000
6,000
4,000
2,000
0
Organ response
Complete organ response
0
1
2
3
Years post transplantation
Complete hematologic response documented at 3 months

Bortezomib +/-Dex

- Untreated patients had a 47% CR rate. Twice weekly bortezomib (P = .041) higher response rates.
- Cardiac response 29%
- Hematologic responses were associated with a cardiac response and NT-proBNP reduction.
- The 1-year survival is 76%.
- NT-proBNP was independently associated with survival (P = .001)

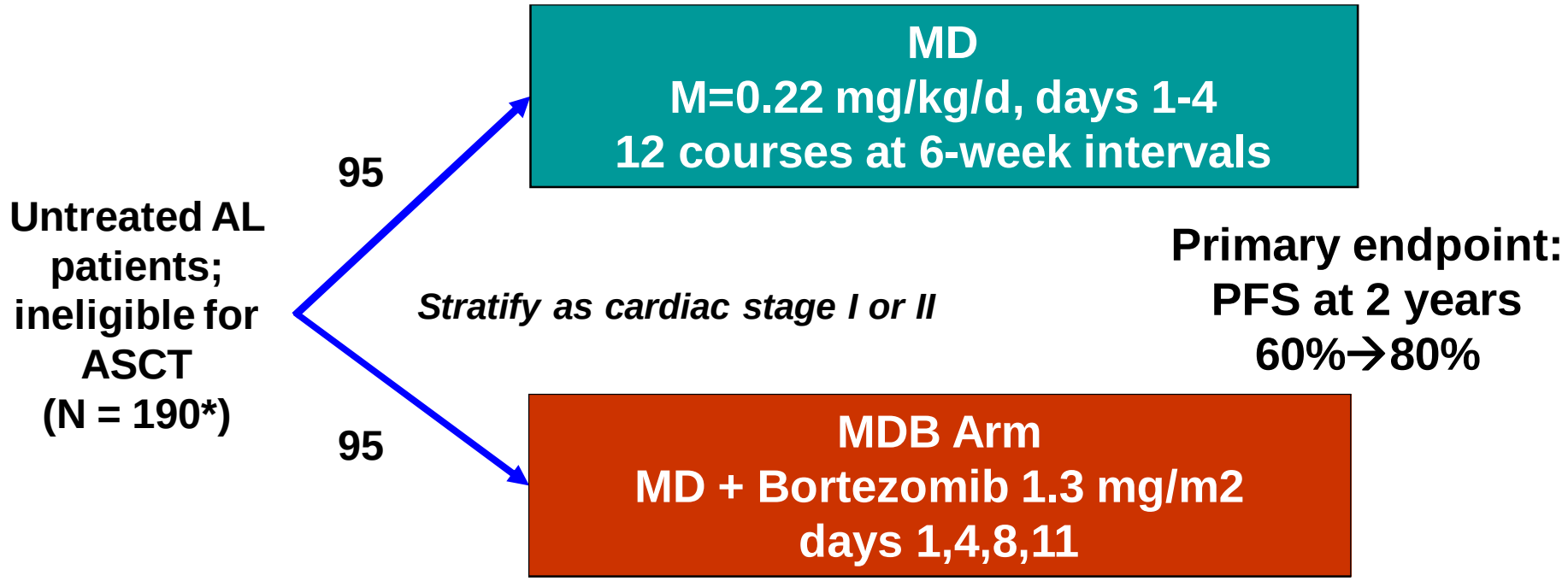
J Clin Oncol. 2010 Feb 20;28(6):1031-7.

CyBor-D amyloidosis

- **Bortezomib (1.5 mg/m2 weekly), ctx (300 mg/m2 po weekly) and dex (40 mg weekly)**
- **17 patients received 2-6 cycles of CyBorD. Ten (58%) had symptomatic cardiac involvement and 14 (82%) had >1 organ involved. Resp occurred in 16 (94%), with 71% CR and 24% a PR.**
- **Time to response was 2 mo. 3 patients not eligible for ASCT became eligible.**

Blood. 2012 Feb 13. [Epub ahead of print]

MD vs MDB in Newly Diagnosed Immunoglobulin Light Chain Amyloidosis (AL) Patients Who Are Not Candidates for ASCT



**Eighty-six required for each arm for α=0.05 (two-sided) and β=0.80. Additional 18 patients allowed for drops-outs and ineligibles*

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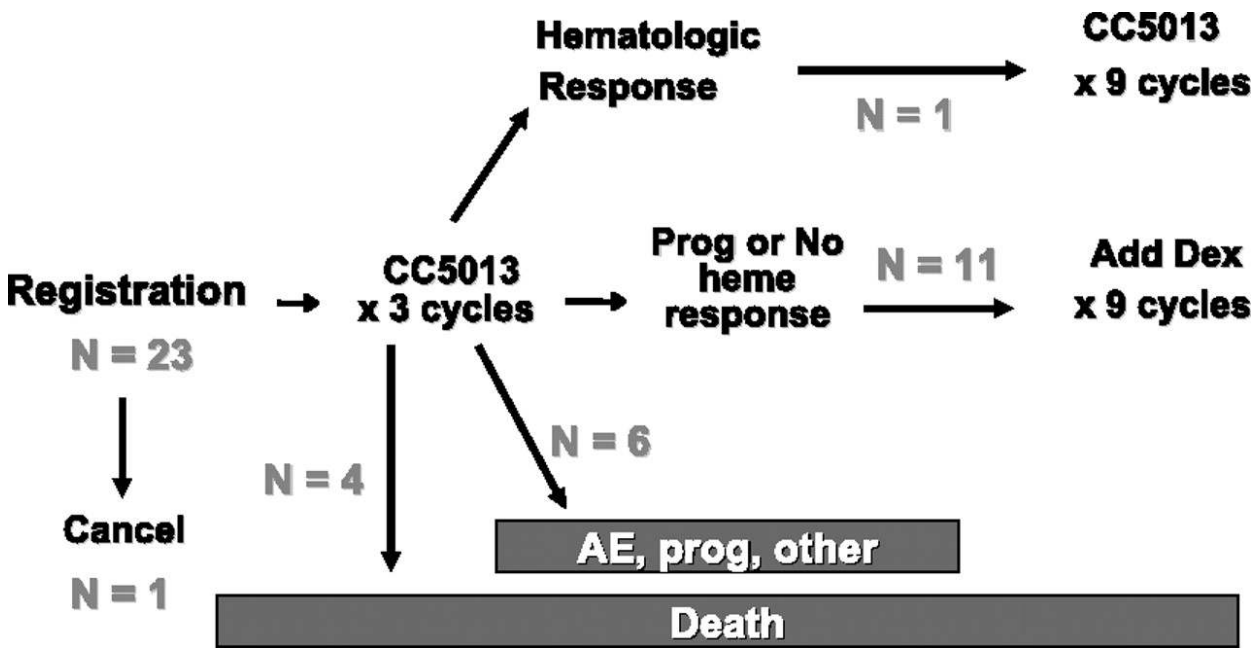
REV DEX for AL



Dispenzieri, A. et al. Blood 2007;109:465-470

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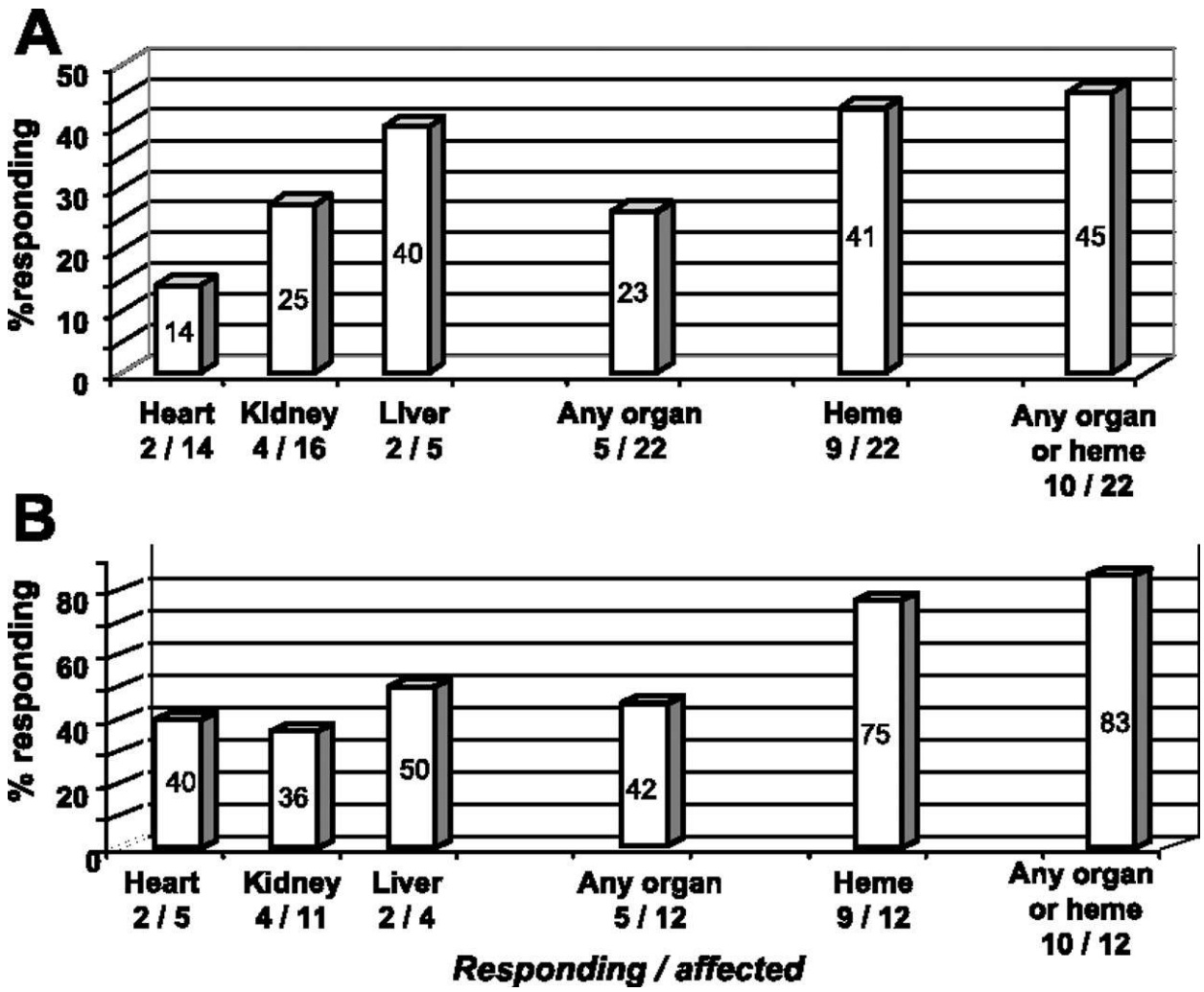
REV DEX RESPONSES



Dispenzieri, A. et al. Blood 2007;109:465-470

Rd amyloidosis

- **AL refractory to both melphalan and bortezomib Rx with lenalidomide and dexamethasone**
- **24 patients. 19 were also refractory to thal. Two died before evaluation of response, & 50% severe adverse events. Survival was significantly shorter in subjects with troponin I >0.1 ng/mL and in patients diagnosed <18 months before treatment initiation. HR was 41%; median OS 14 mo**

Ann Hematol (2012) 91:89–92

Pomalidomide

- Pom/dex combination in patients with previously treated AL
- 82% percent had cardiac involvement. Response rate was 48%, with a median time to response of 1.9 months. Organ improvement was documented in 5/33
- OS & PFS rates were 28 mo and 14 mo. The 1-year OS and PFS rates were 76% and 59%.

Blood First Edition Paper, prepublished online April 4, 2012;

Heart Transplantation for AL Amyloid
23 Patients Transplanted (05/31/1992 – 12/02/2011)

- 11 males 12 females
- Mean age 53 years (range 33 - 62 yrs)
- All NYHA Class IV and/or ventricular thickness >15 mm and/or EF <40%.
- Received standard quadruple therapy (including 1/2 dose OKT3)
- Mean waiting time 114 days (range 5 - 1160 days)

01/01/2012

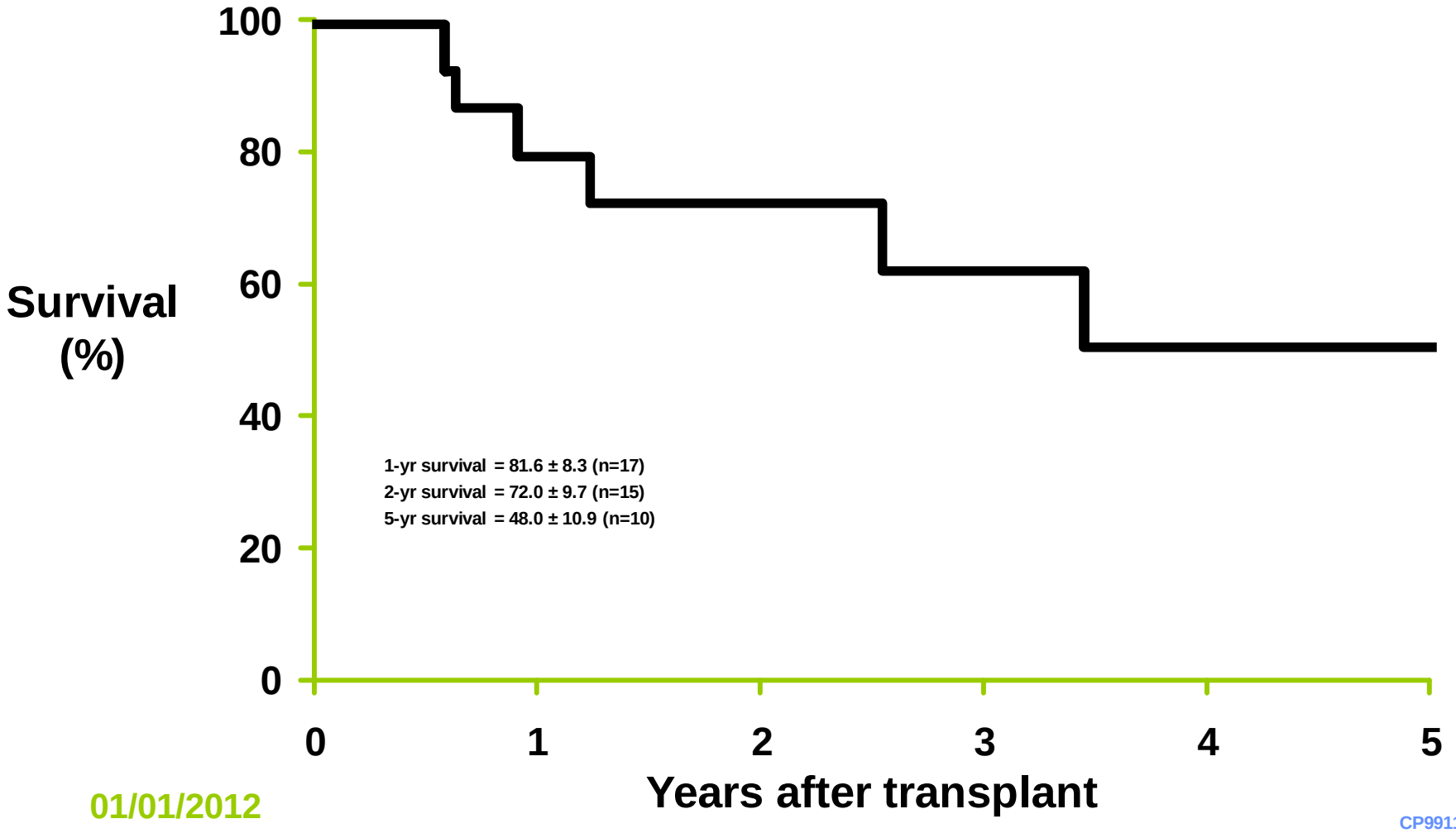
Heart Transplantation for AL Amyloid
Stem Cell Transplant

- 12 pts had stem cell transplants post cardiac transplant
    - 2 died early – complications of stem cell transplant
    - 10 survived
- 8 subsequently died from progressive amyloidosis at 94, 86, 66, 57, 55, 34, 22 and 10 months following stem cell transplant
- 2 alive and well at 93 and 148 months post stem cell transplant

01/01/2012

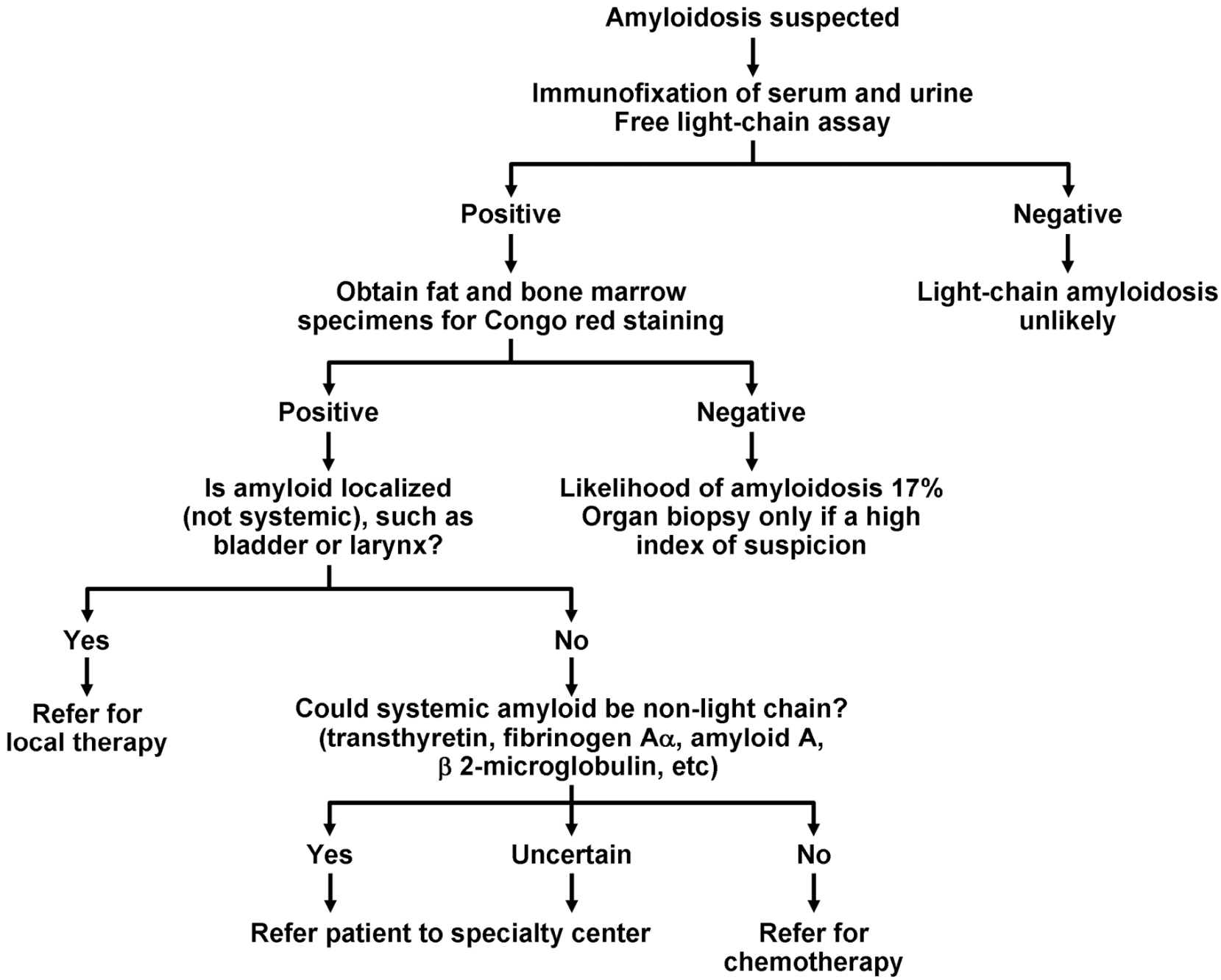
Heart Transplantation for AL Amyloid

Kaplan-Meier Survival for 23 Patients Transplanted 05/31/1992 – 12/01/2011

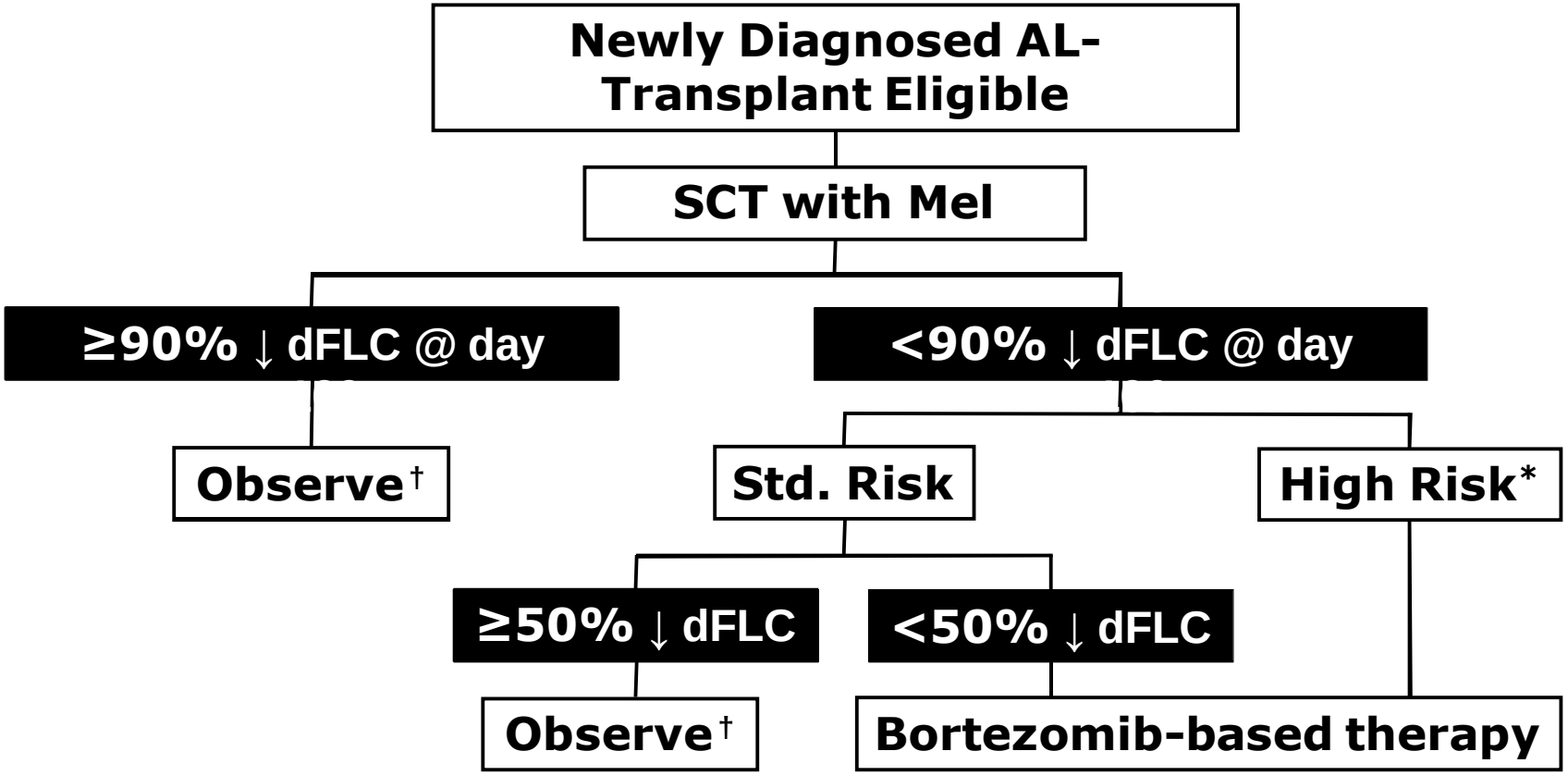


01/01/2012

CP991114-2


Amyloidosis suspected
Immunofixation of serum and urine
Free light-chain assay
Positive
Negative
Light-chain amyloidosis unlikely
Obtain fat and bone marrow specimens for Congo red staining
Positive
Negative
Is amyloid localized (not systemic), such as bladder or larynx?
Likelihood of amyloidosis 17%
Organ biopsy only if a high index of suspicion
Yes
No
Refer for local therapy
Could systemic amyloid be non-light chain? (transthyretin, fibrinogen Aα, amyloid A, β 2-microglobulin, etc)
Yes
Uncertain
No
Refer patient to specialty center
Refer for chemotherapy

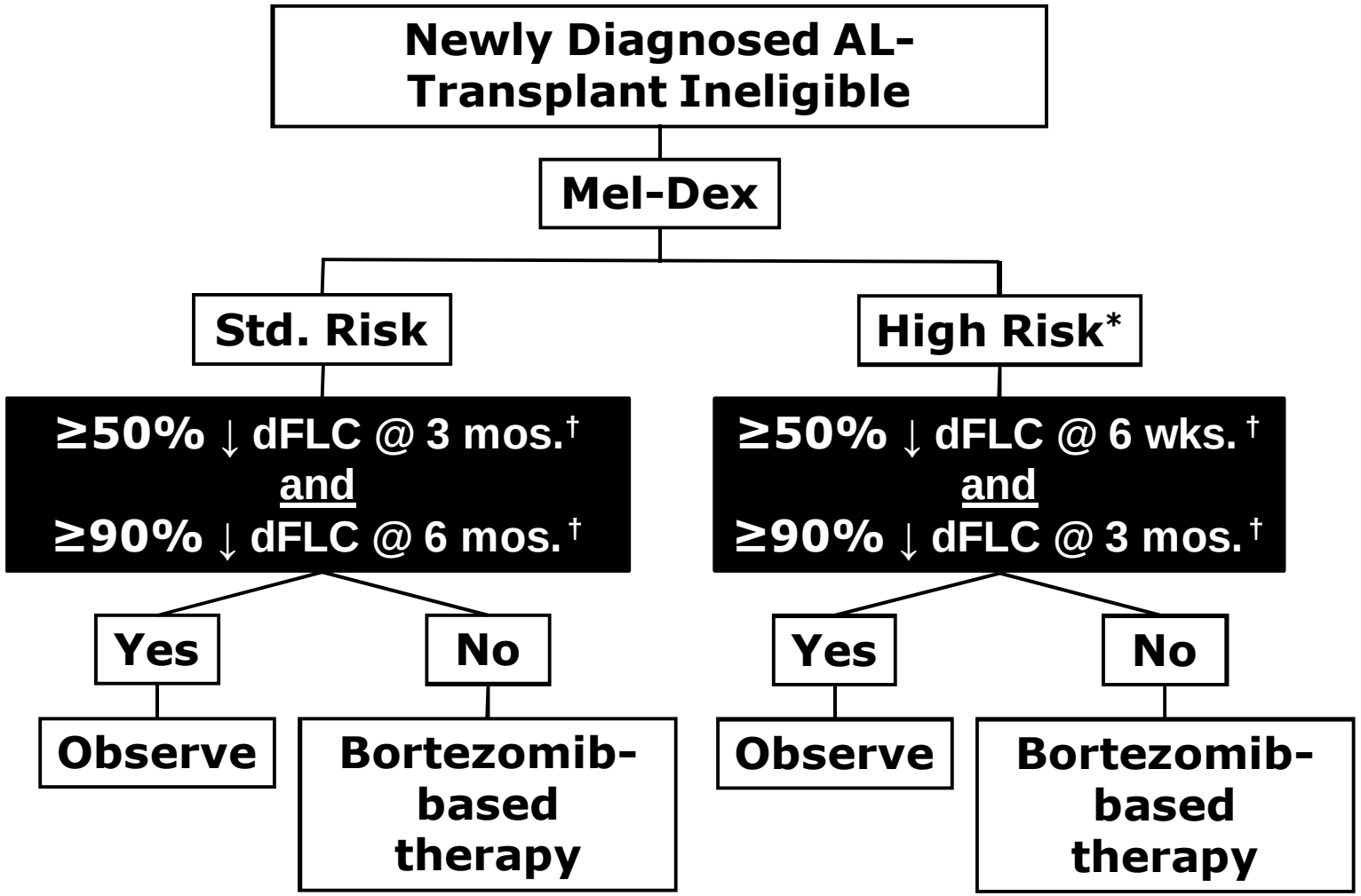
Treatment of AL – off-study



† Start alternate therapy if organ progression at any time

*High Risk = Mayo Stage III

Treatment of AL – off-study



† Start alternate therapy if organ progression at any time

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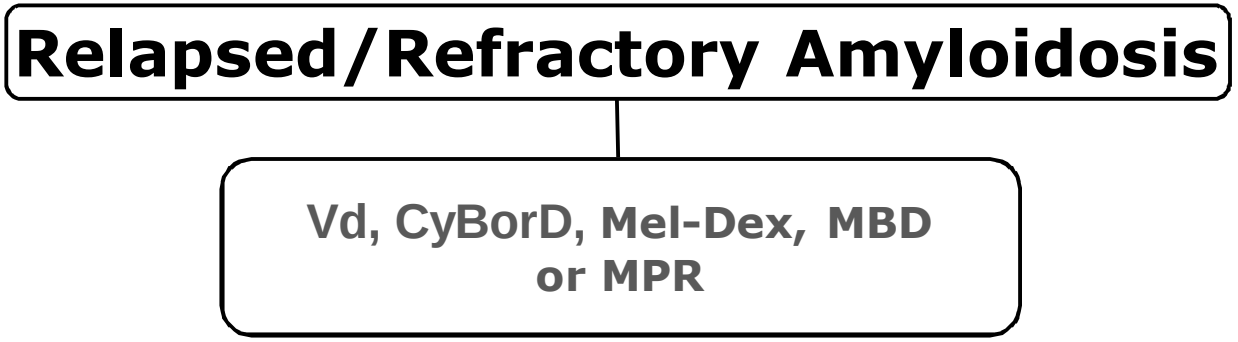
Treatment of AL – off study



Conclusions

- For patients who can be transplanted safely SCT remains a preferred option
- For non transplant candidates Mel Dex remains the default standard
- Bortezomib has clear activity but its integration into practice is not fully defined
- Imid therapy including CTd, MDR, Rd is being explored

CONCLUSION

- Think AL when:
  - Nephrotic, Cardiomyopathy, PN, ‘Atypical Myeloma’
- Do Immunofixation S&U +FLC
- Marrow, Fat, Congo Red + Immunochemistry, Mass Spectroscopy
- Prognosis: Cardiac involvement by echo, Troponin, BNP
- Rx Systemic Chemotherapy, SCT

- Questions: A urologist refers a patient to you who presented with gross hematuria, underwent cystoscopic biopsy that demonstrated amyloid deposits. Serum & urine immunofixation and free light chains are normal. After seeing you the most likely scenario would be?
  1. Renal biopsy to exclude that there is renal amyloidosis in addition to bladder amyloidosis.
  2. Echocardiogram preformed to assess suitability for high dose therapy.
  3. Referral to a transplant center.
  4. Initiation of oral chemotherapy.
  5. Referral back to the urologist for ongoing therapy.
  6. Cardiac biomarkers to determine the likelihood of cardiac amyloidosis.

- Answer: 5. Bladder amyloid is virtually always localized and is not associated with systemic amyloid deposits. After an appropriate evaluation the most likely outcome is that this will be limited to the bladder and this patient will need to be referred back to the urologist for cystoscopic therapy or intravesical DMSO installation.

- A 66 year old black male was seen by a cardiologist with dyspnea. The patient underwent a subcutaneous fat aspirate after an echo was thought to be consistent with infiltrative cardiomyopathy. The fat aspirate was positive for amyloid. Serum and urine immunofixation are negative, free light chain assay demonstrates a normal ratio. The following would be the most appropriate next step?

- Answer: b.A black male who has no light chain abnormality and evidence of systemic amyloidosis is far more likely to have an inherited cardiomyopathy related to amyloid from a mutation of TTR VAL122ILE. This has a prevalence in the Black population of 3% and is far more likely than light chain amyloidosis with negative marker studies.

- The most important studies to assess the prognosis of a newly diagnosed patient with AL would be?
- 1Troponin
- 2Serum albumin
- 3NTproBNP
- 4Beta2 Microglobulin
- a: 1 and 3; b: 2 and 4; c: 1, 2, and 3; d: 1, 2, 3, and 4; e: 4

- a: 1 and 3. Cardiac biomarkers are the most important prognostic features of amyloidosis and in a multi-variable analysis eliminates serum albumin and Beta2 Microglobulin which are both critically important to the prognosis of patients with multiple myeloma