"Amyloidosis, update

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Disclosure

Advisory Board

BTG

Aduro

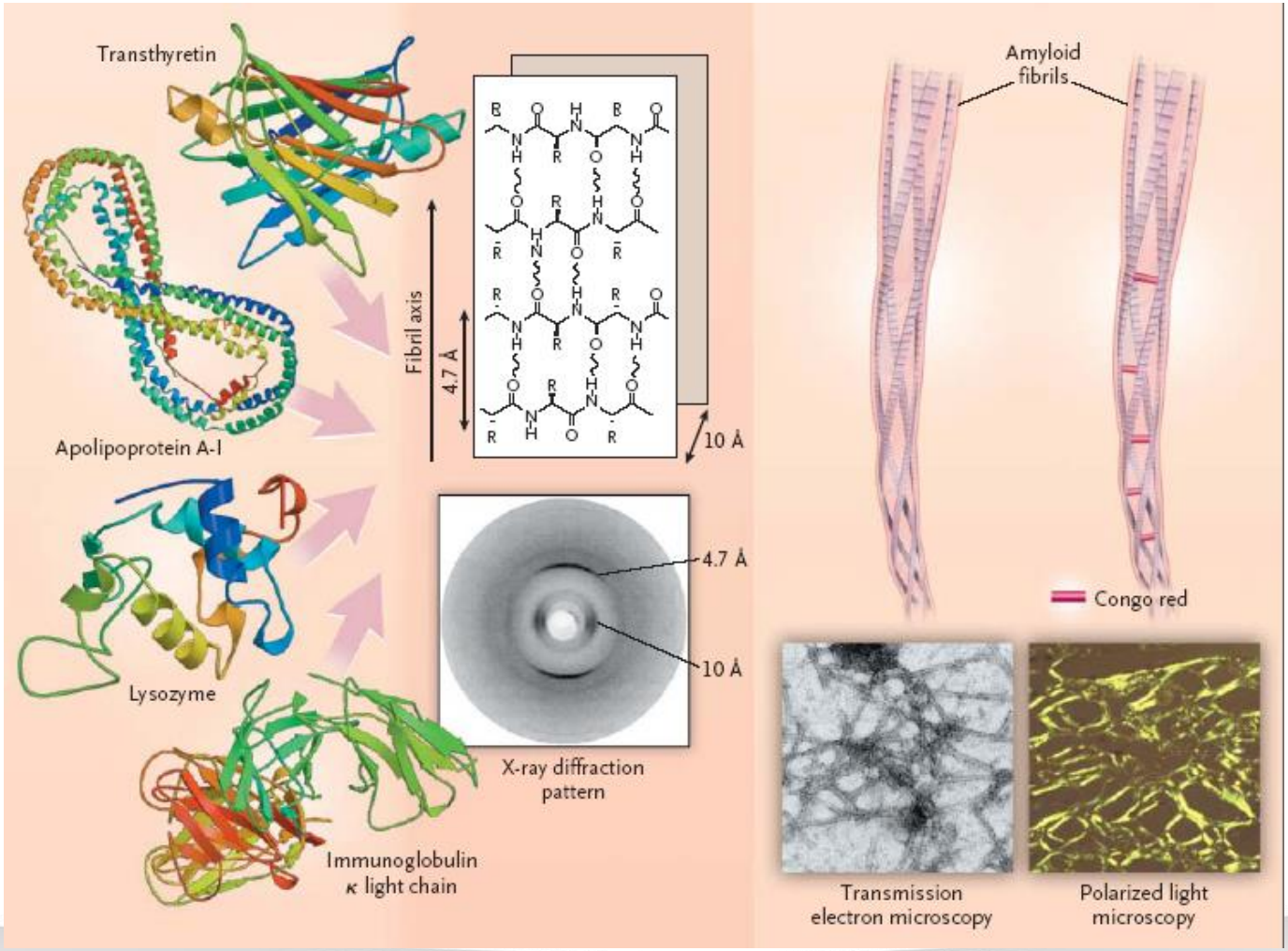
Takeda

Research Grant

Omeros

Alnylam

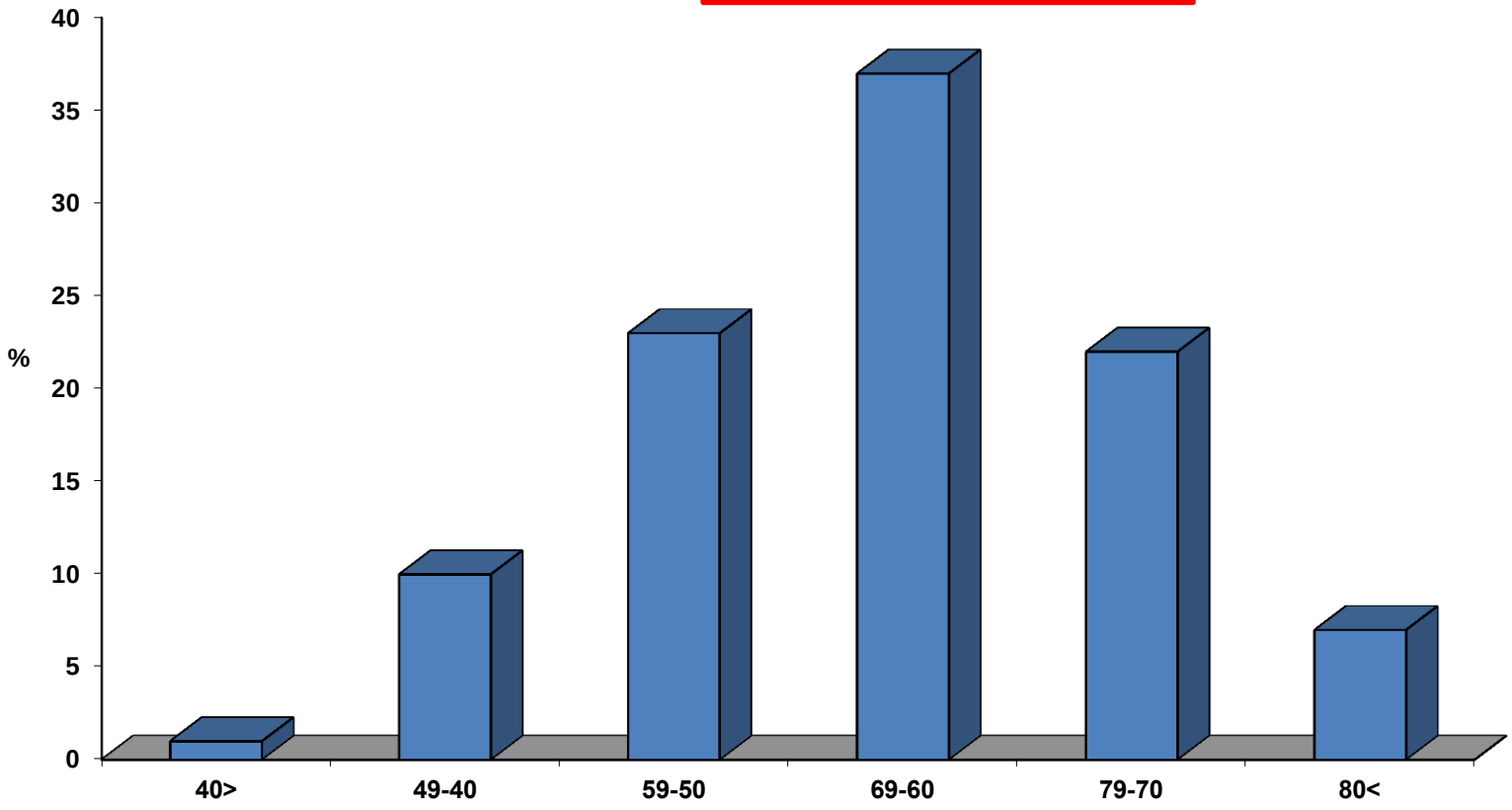
Amyloidosis



Merlini and Bellotti. NEJM 2003; 349: 583- 96

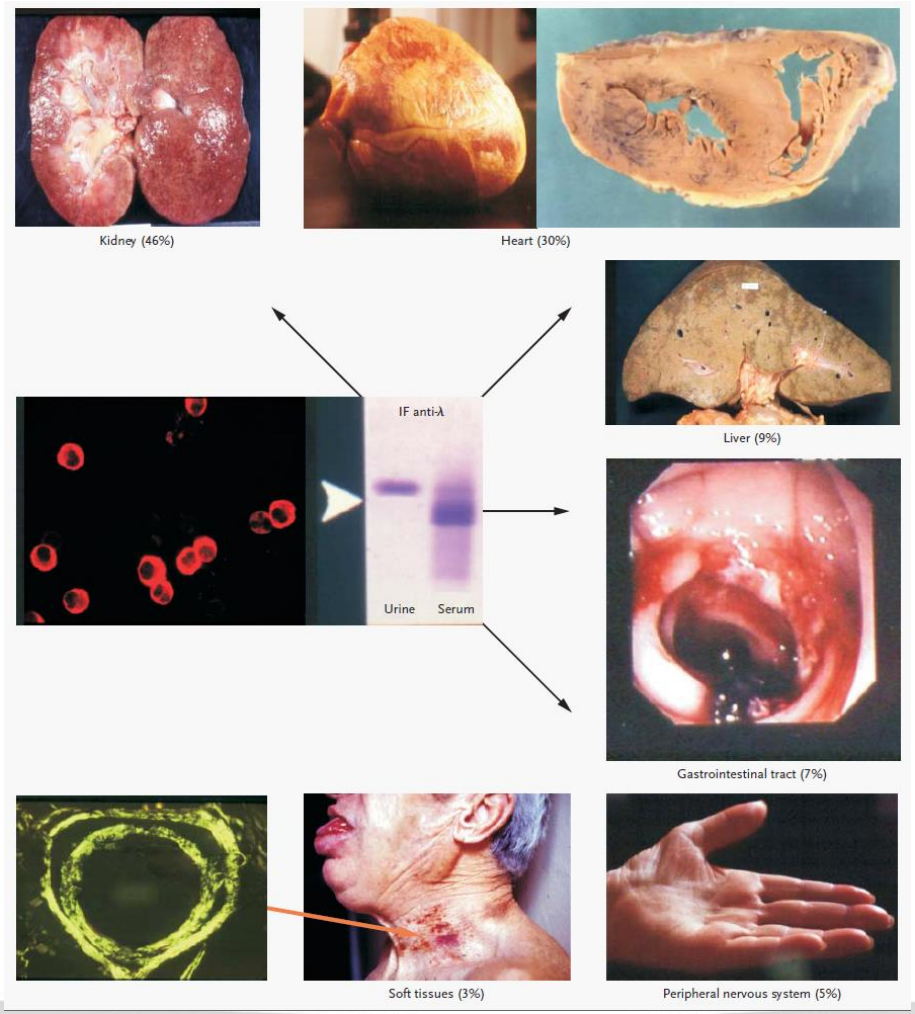
Age Distribution of AL Patients

Median = 64 years



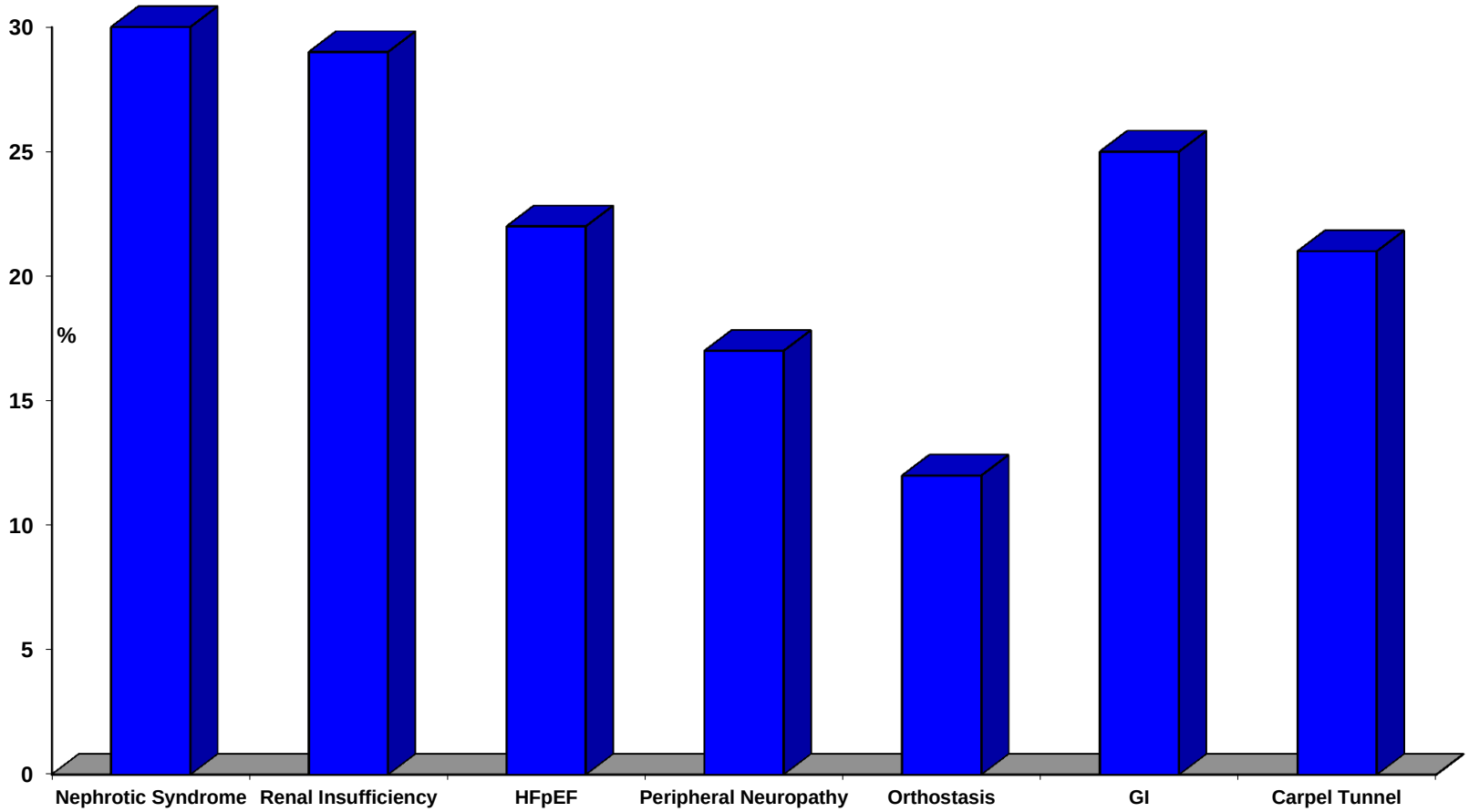
Kyle & Gertz. Sem in Hematol 1995

AL amyloidosis is a systemic disease



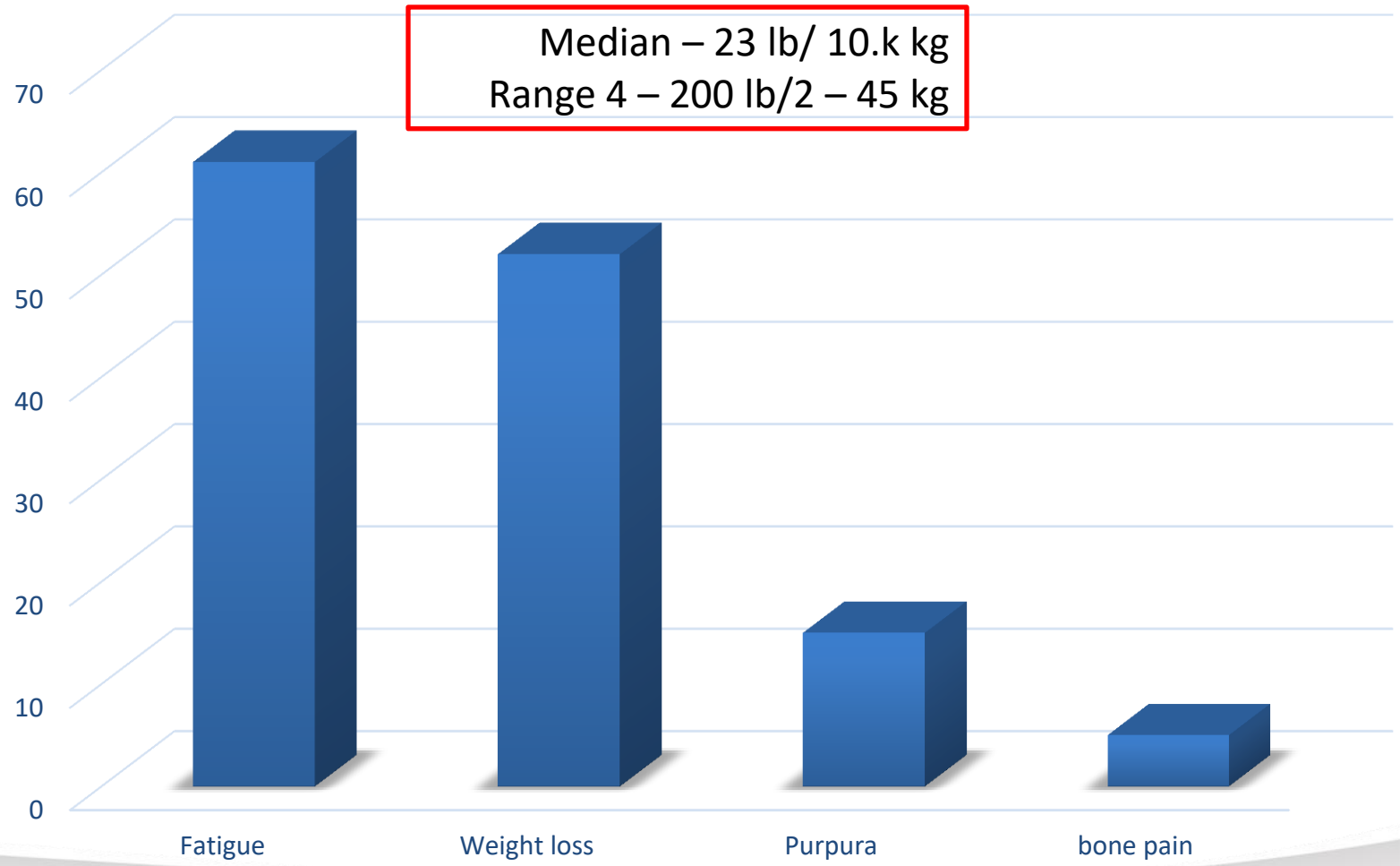
Merlini and Bellotti. NEJM 2003; 349: 583- 96

Syndromes at Diagnosis



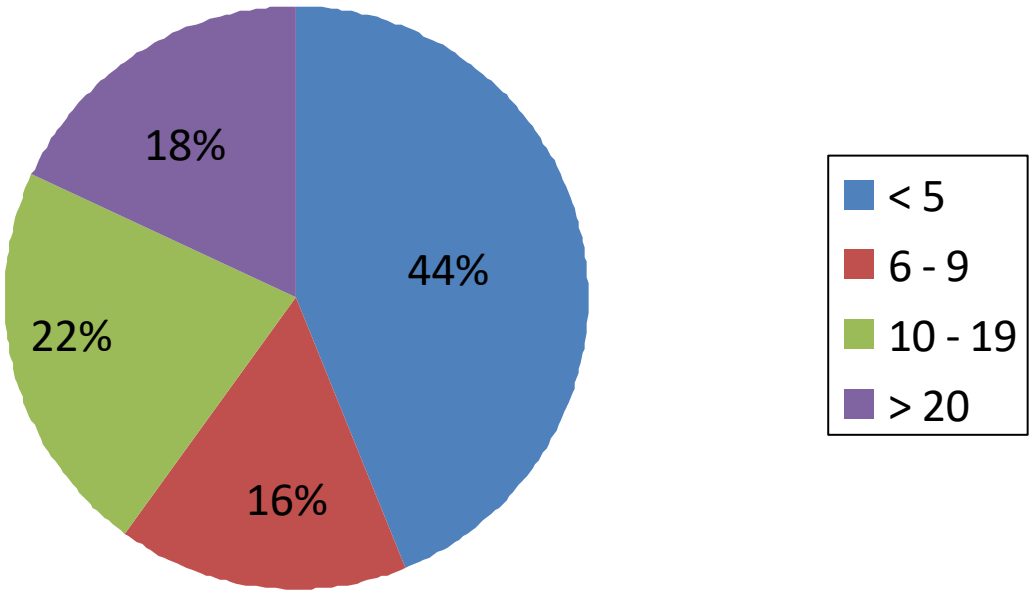
Kyle & Gertz. Sem in Hematol 1995

Most common presenting symptoms



Kyle & Gertz. Sem in Hematol 1995

Percentage of Bone Marrow Plasma Cells at Diagnosis

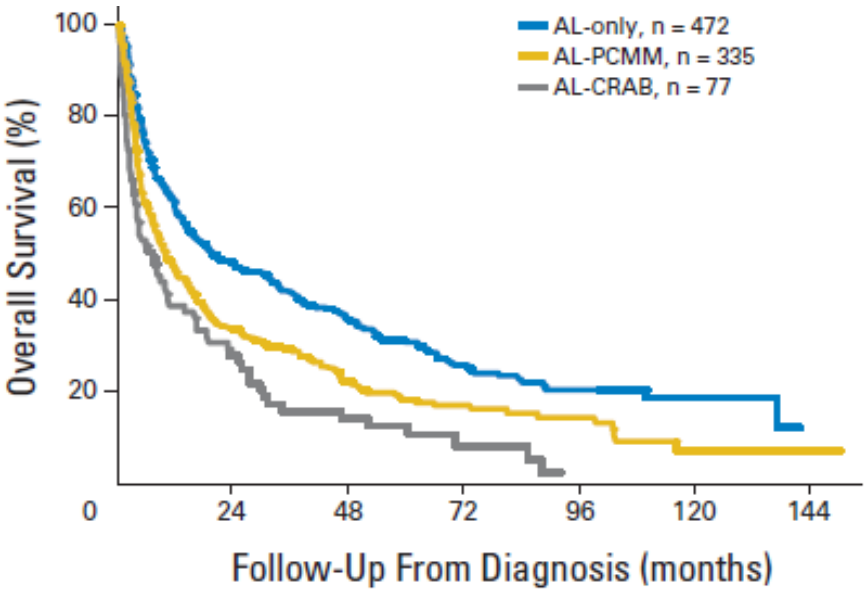


Only 10 -15% meet criteria for multiple myeloma

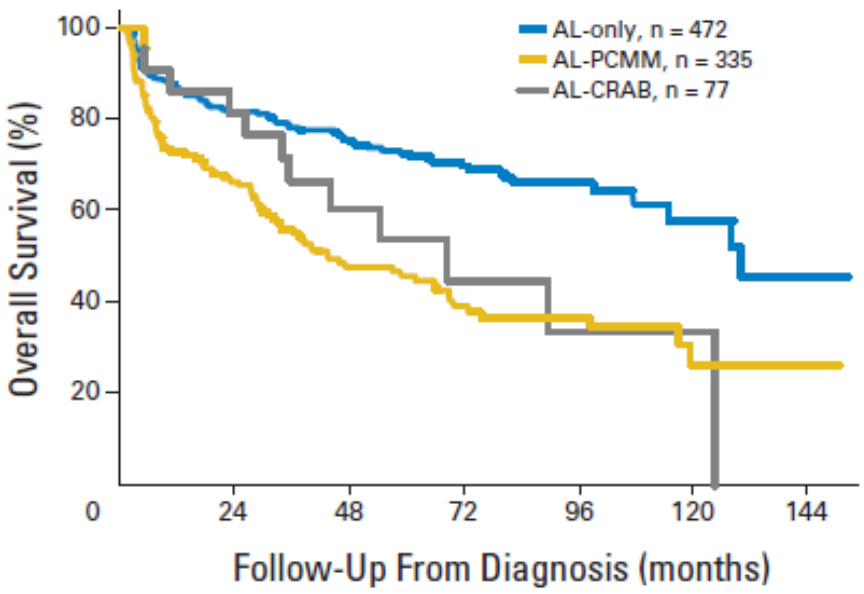
Kyle & Gertz. Sem in Hematol 1995

Overall Survival based on PC percentages and CRAB with or without ASCT

Non-transplanted



Transplanted

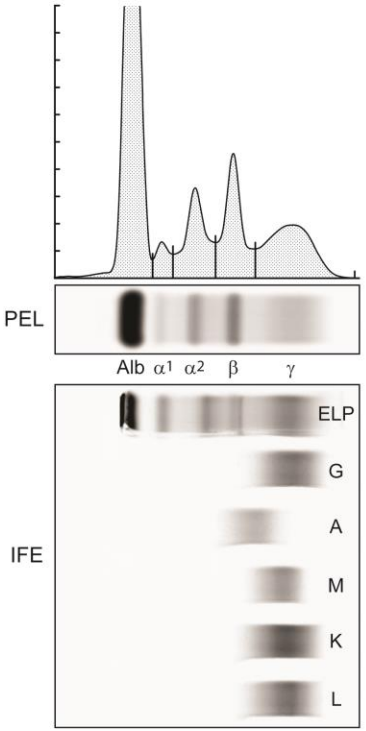


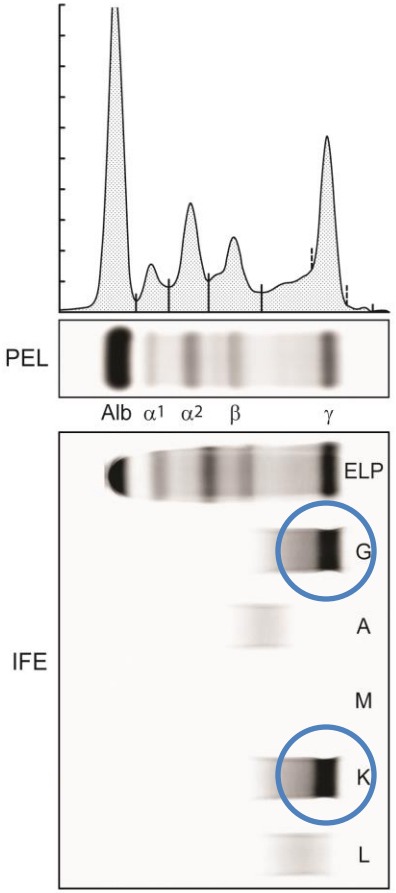
Kourelis et al. JCO 2013

Diagnostics

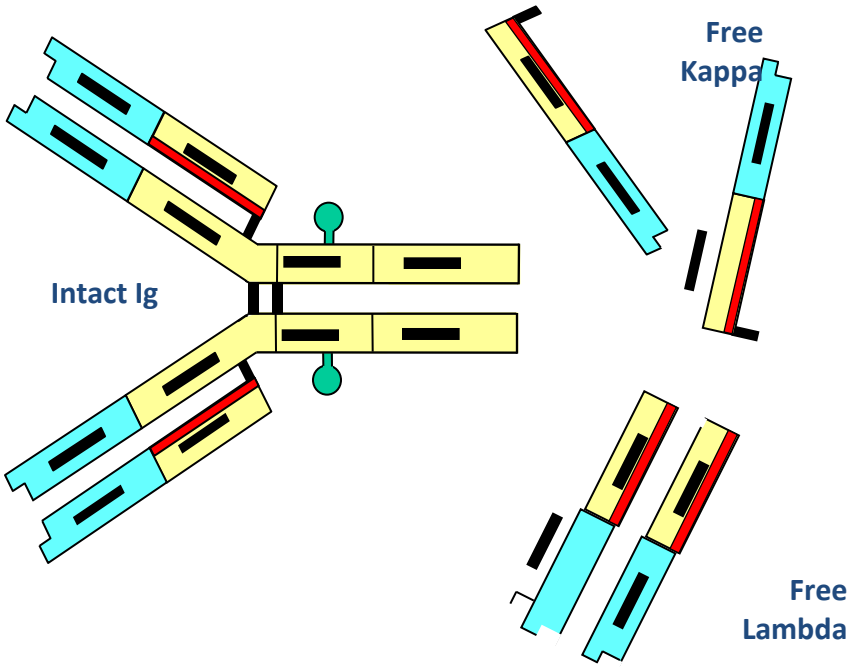
1. Serum free light chain test
2. Amyloid typing by mass spectrometry
3. Imaging studies
4. Monoclonal protein testing by mass spectrometry

Immunofixation





Free Light Chain Assay



- Targets unexposed domains of light chains
- Immunonephelometry
- Automated
- Does not distinguish clonality

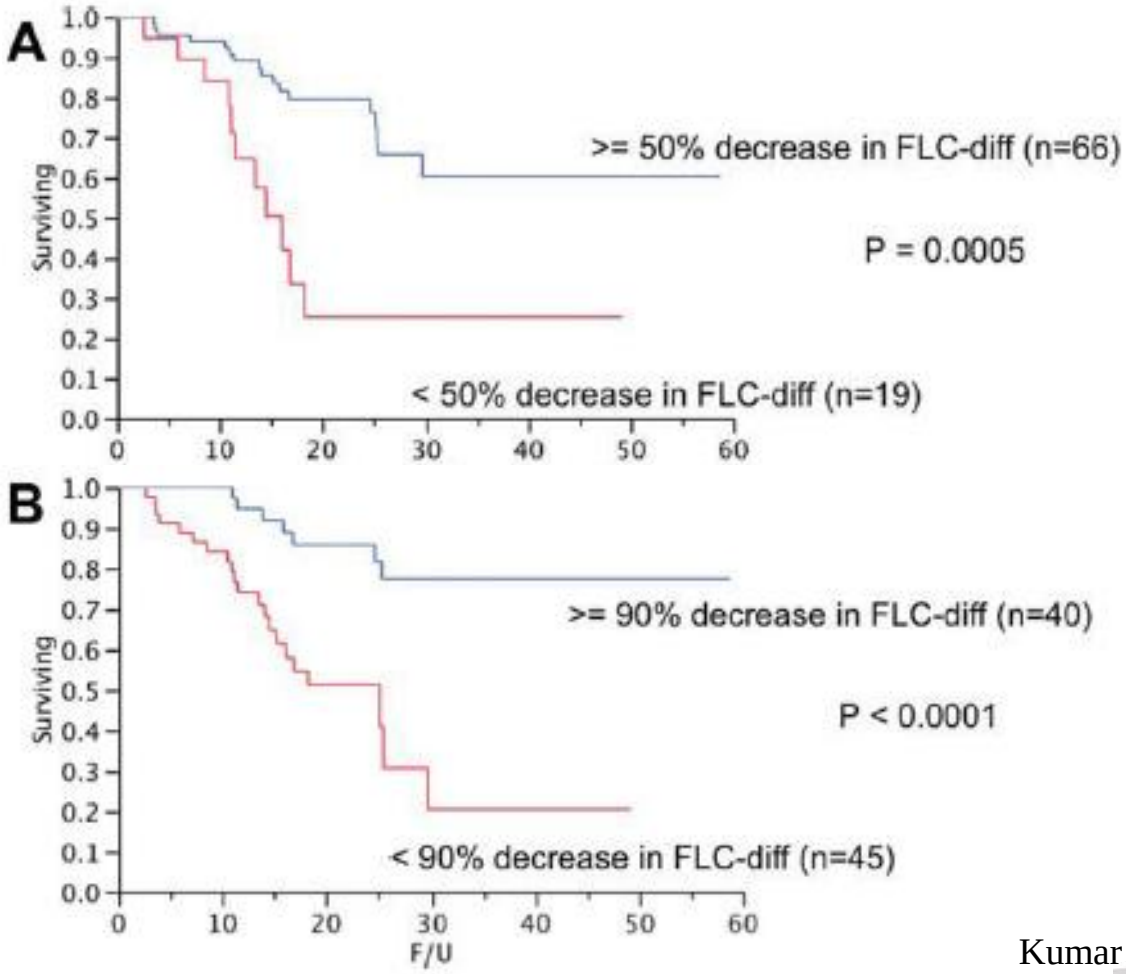
Katzmann et al. *Clin Chem.* 2002;48:1436-44

Comparison of sFLC assay to Serum and Urine IFE

	n	All 5 tests	Serum PEL and IFE; urine IFE	Serum PEL, IFE, and FLC	Serum PEL and FLC	Serum IFE	Serum PEL	Serum FLC
Diagnosis, %								
All		98.6	97.0	97.4	94.3	87.0	79.0	74.3
MM		100.0	98.7	100.0	100.0	94.4	87.6	96.8
Macroglobulinemia		100.0	100.0	100.0	100.0	100.0	100.0	73.1
SMM		100.0	100.0	100.0	99.5	98.4	94.2	81.2
MGUS		100.0	100.0	97.1	88.7	92.8	81.9	42.4
Plasmacytoma		89.7	89.7	89.7	86.2	72.4	72.4	55.2
POEMS		96.8	96.8	96.8	74.2	96.8	74.2	9.7
Extramedullary plasmacytoma		20.0	20.0	10.0	10.0	10.0	10.0	10.0
Primary AL		98.1	94.2	97.1	96.2	73.8	65.9	88.3
LCDD		83.3	77.8	77.8	77.8	55.6	55.6	77.8

Katzman et al. Clin Chem 2005

Changes in serum-free light chain rather than intact monoclonal immunoglobulin levels predicts outcome following therapy in primary amyloidosis

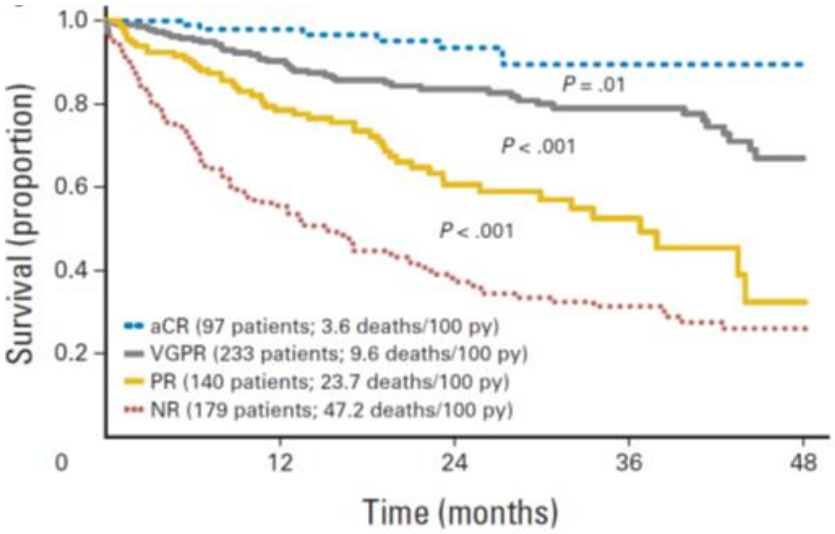


Kumar et al. Am J Hematol 2011

New Criteria for Response to Treatment in Immunoglobulin Light Chain Amyloidosis Based on Free Light Chain Measurement and Cardiac Biomarkers: Impact on Survival Outcomes

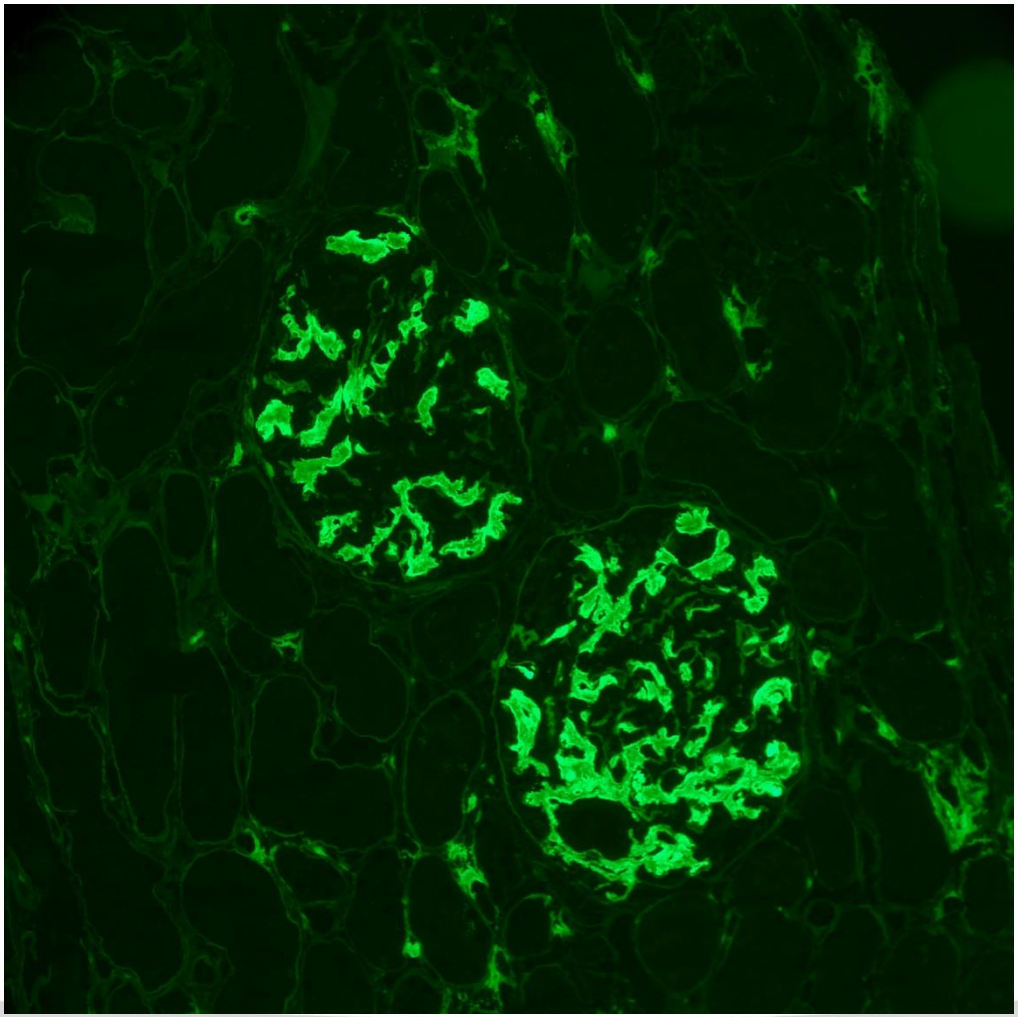
Giovanni Palladini, Angela Dispenzieri, Morie A. Gertz, Shaji Kumar, Ashutosh Wechalekar, Philip N. Hawkins, Stefan Schönland, Ute Hegenbart, Raymond Comenzo, Efstathios Kastritis, Meletios A. Dimopoulos, Arnaud Jaccard, Catherine Klersy, and Giampaolo Merlini

Criteria
Hematologic response†
aCR (negative serum and urine immunofixation and normal FLC ratio)
VGPR (dFLC < 40 mg/L)
PR (dFLC decrease > 50%)
NR



Palladini et al . J Clin Oncol. 2012

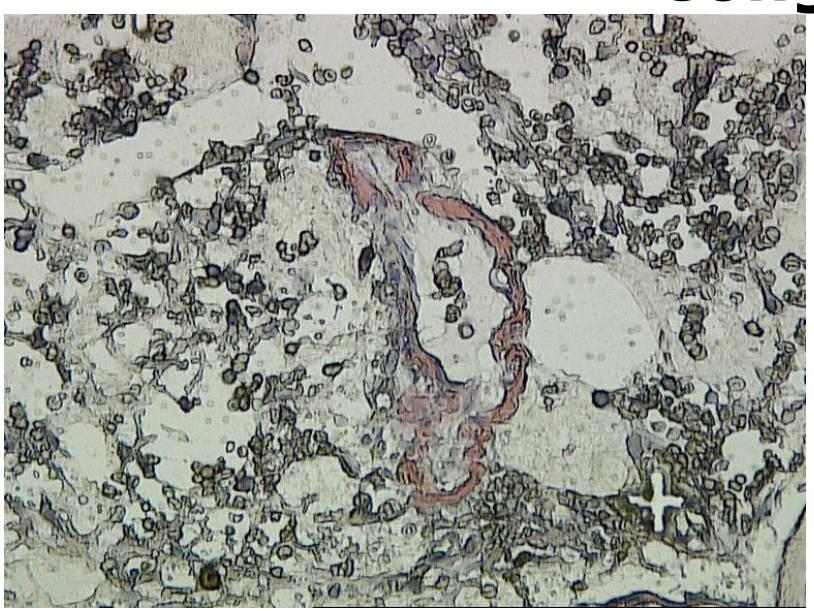
immunofluorescence



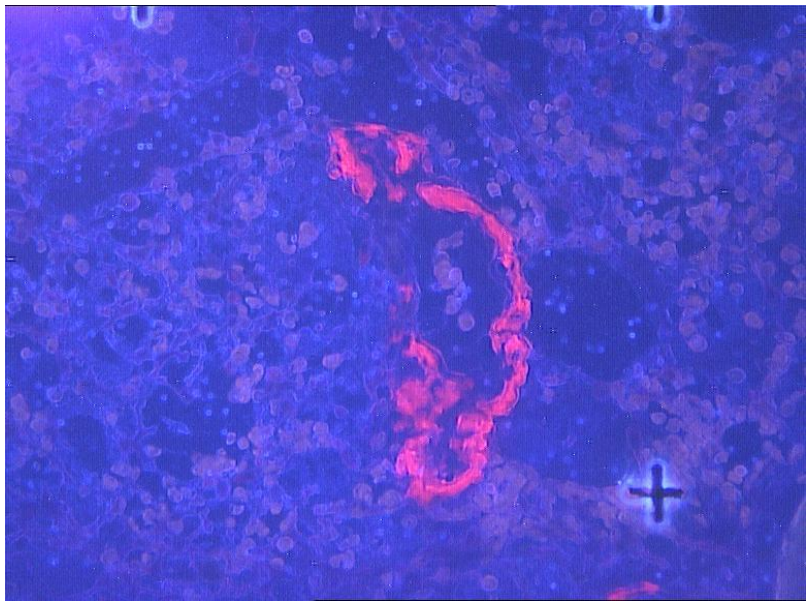
lambda

Step 1: Histological examination on FFPE tissues identifies amyloid deposits

Congo Red



Bright field

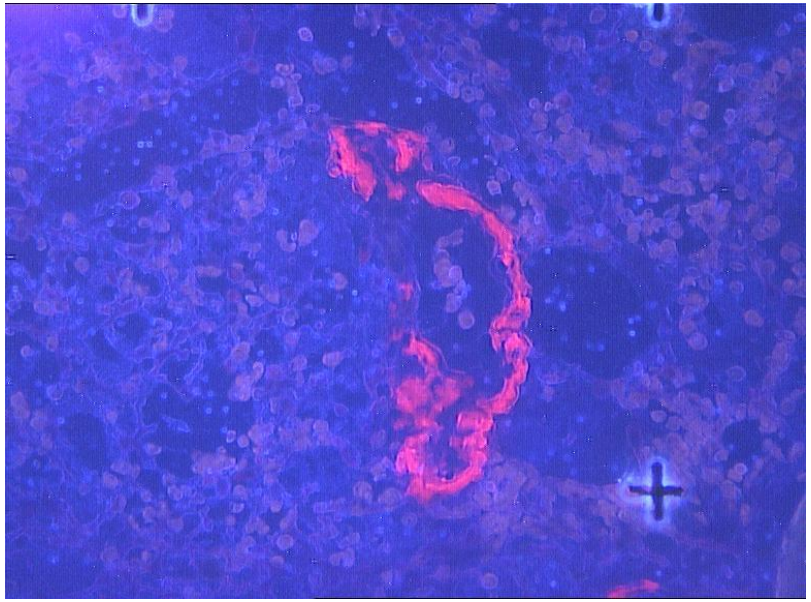


Fluoro

Step 2a: Trace around amyloid deposits

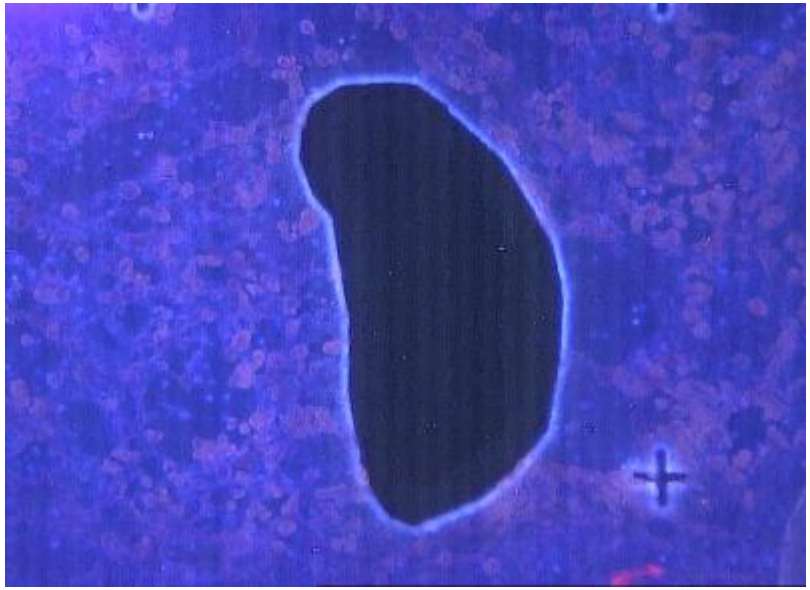
Congo Red

Bright field

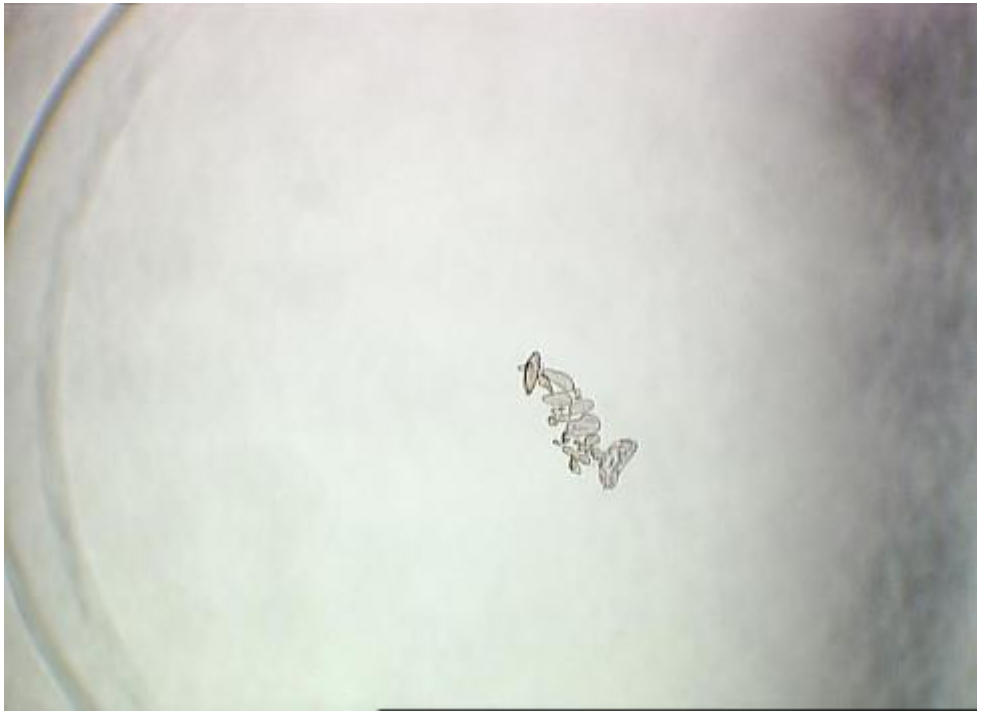


Fluoro

Step 2b: Laser cuts out amyloid deposits



Step 2c: Tissue drops into microfuge cap for trypsin digestion



Proteomics detection of the Ig variable region

Probability Legend:

Probability
over 95%
80% to 94%
50% to 79%
20% to 49%
0% to 19%

#	Starred	Bio View: Identified Proteins (402/406)	Blank	Sample 1	Sample 2	Sample 3
1	★	Serum amyloid P-component		2	6	23
2	★	Ig lambda chain C regions		9	12	5
3	★	Apolipoprotein E precursor		7	4	10
4	★	Ig lambda chain V-VI region EB4		2	3	5
5	☆	Hemoglobin subunit beta		33	63	42

Probability Legend:

Probability
over 95%
80% to 94%
50% to 79%
20% to 49%
0% to 19%

#	Starred	Bio View: Identified Proteins (401/403)	Blank	Sample 1	Sample 2	Sample 3
1	★	Ig Lambda Variable Region VI Locus 16a		22	27	51
2	★	Serum amyloid P-component		2	4	23
3	★	Ig Lambda Constant Region 2 J00253		7	11	8
4	★	Apolipoprotein E		6	4	10
5	☆	Hemoglobin subunit beta		30	54	43

Variable region

Brief report

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

Julie A. Vrana,[1] Jeffrey D. Gamez,[1] Benjamin J. Madden,[2] Jason D. Theis,[1] H. Robert Bergen III,[2] and Ahmet Dogan[1]

[1]Department of Laboratory Medicine and Pathology, and [2]Mayo Proteomics Research Center, Mayo Clinic, Rochester, MN

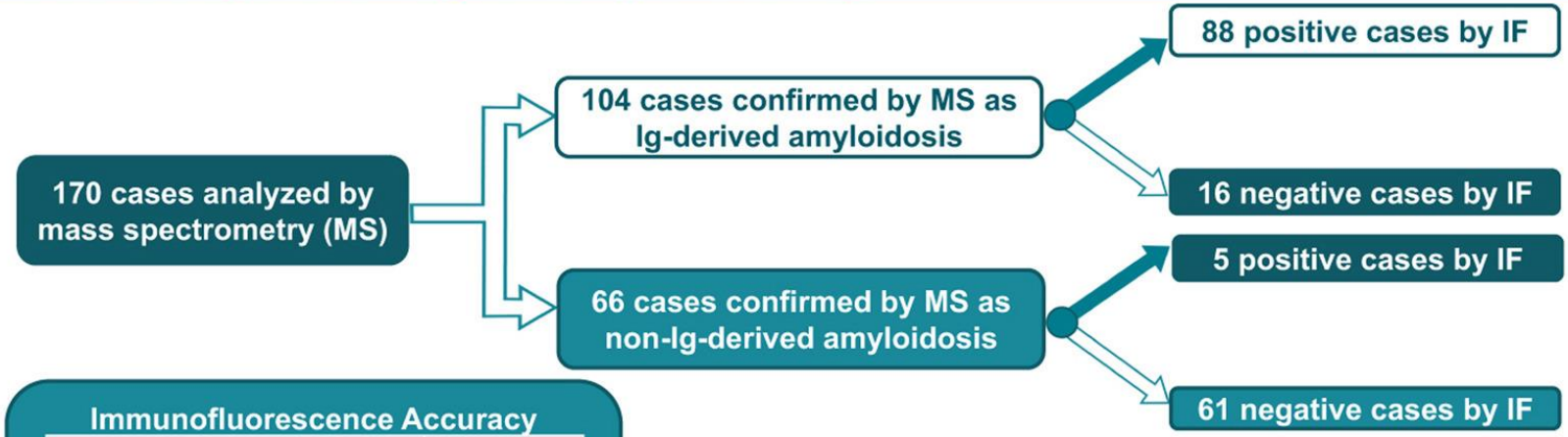
Case	Tissue	Original Diagnosis	MS Diagnosis	MS Analysis TTR	SAA	IGL	IGK
1	BM	AL-IGK	AL-IGK				
2	Lung		AL-IGK				
3	BM		AL-IGK				
4	Brain		AL-IGK				
5	Breast		AL-IGK				
6	Liver	AL-IGL	AL-IGL				
7	Heart		AL-IGL				
8	Intestine		AL-IGL				
9	Liver		AL-IGL				
10	Heart		AL-IGL				
11	BM		AL-IGL				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

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

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

The sensitivity and specificity of the routine kidney biopsy immunofluorescence panel are inferior to diagnosing renal immunoglobulin-derived amyloidosis by mass spectrometry

The sensitivity and specificity of the routine kidney biopsy immunofluorescence panel is inferior to diagnosing renal immunoglobulin-derived amyloidosis by mass spectrometry.



Immunofluorescence Accuracy	
Sensitivity	84.6 %
Specificity	92.4 %
Positive Predictive Value	91.1 %
Negative Predictive Value	79.4 %

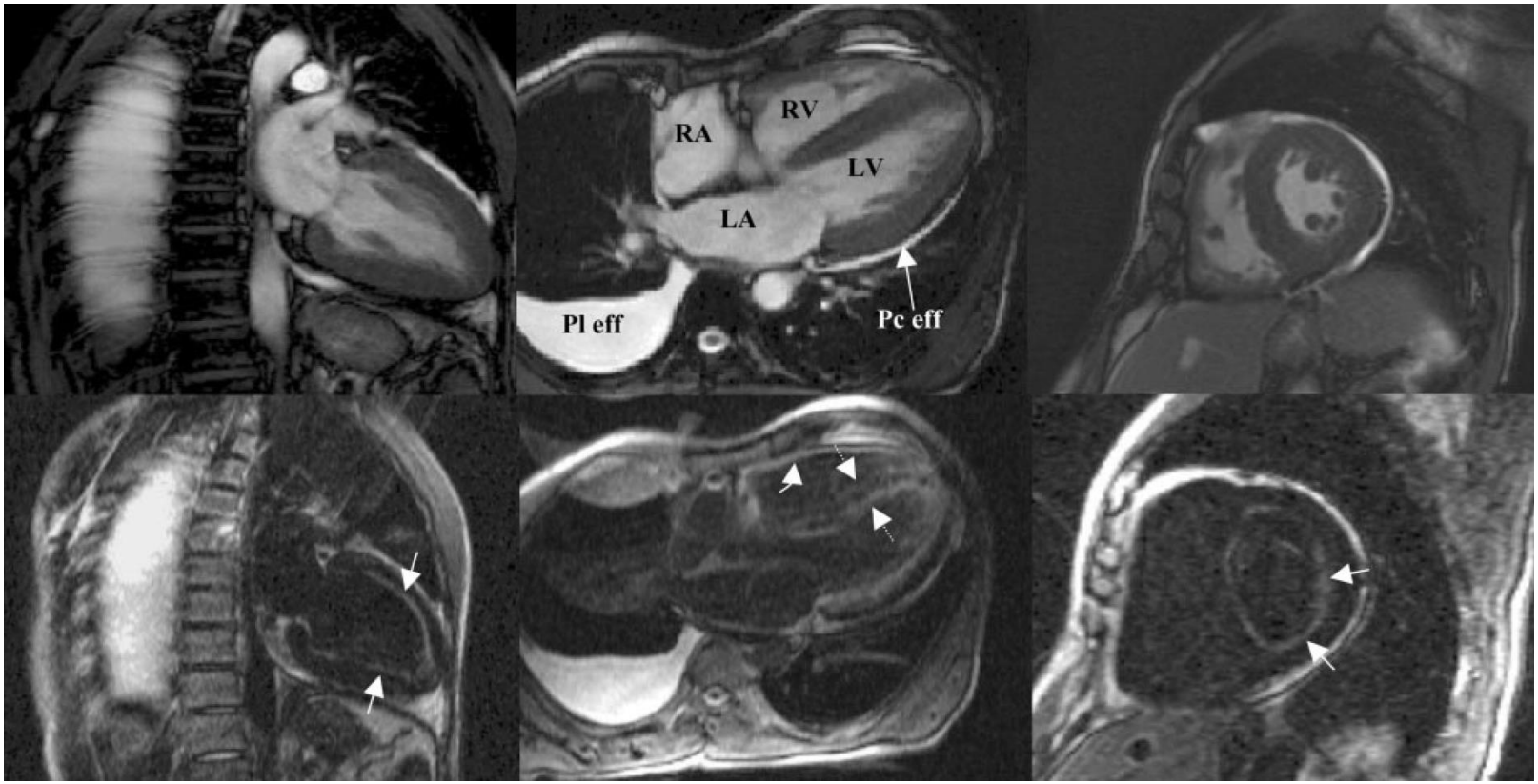
CONCLUSION:
Relying on IF alone for determining AIg-derived vs. non-AIg-derived amyloidosis may lead to misdiagnosis. IF had inferior sensitivity and specificity as compared with MS in the typing of AIg-derived amyloidosis in our study.

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Gonzalez Suarez, 2019

Gonzalez Suarez et al. Kidney Int 2019

Cardiac MRI in AL amyloidosis



enhencement

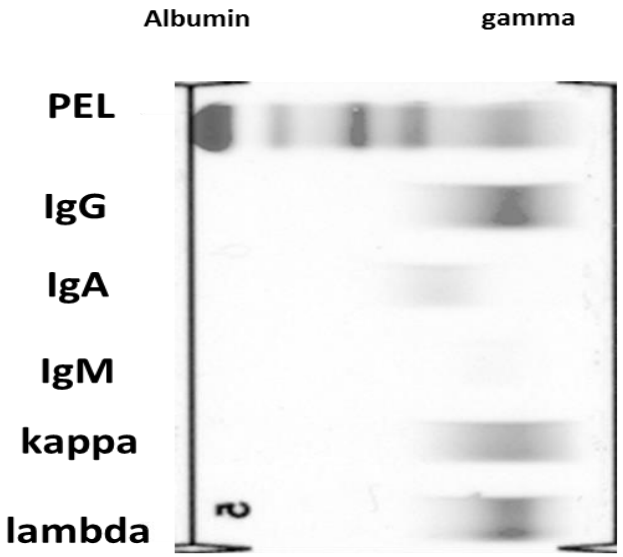
nulling

Marceira et al. Circulation 2005

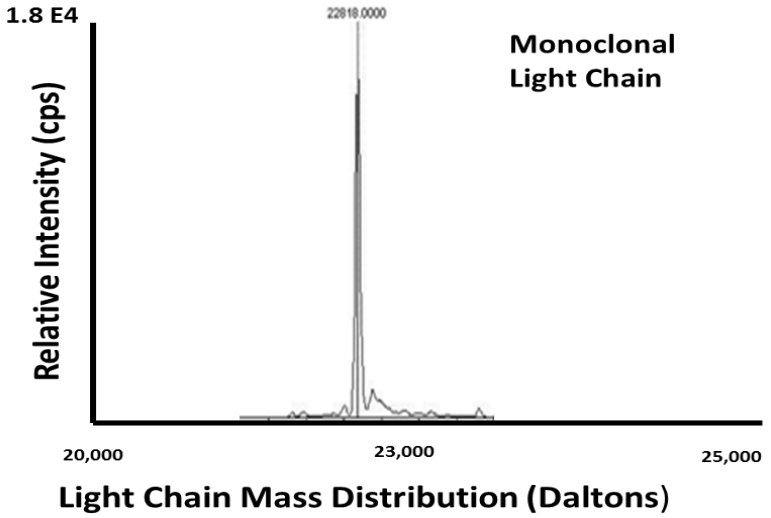
SAP scintigraphy for AL amyloidosis

Wechalekar et al. Blood 2007

Mass Spectrometry Protein Electrophoresis



Immunofixation Electrophoresis



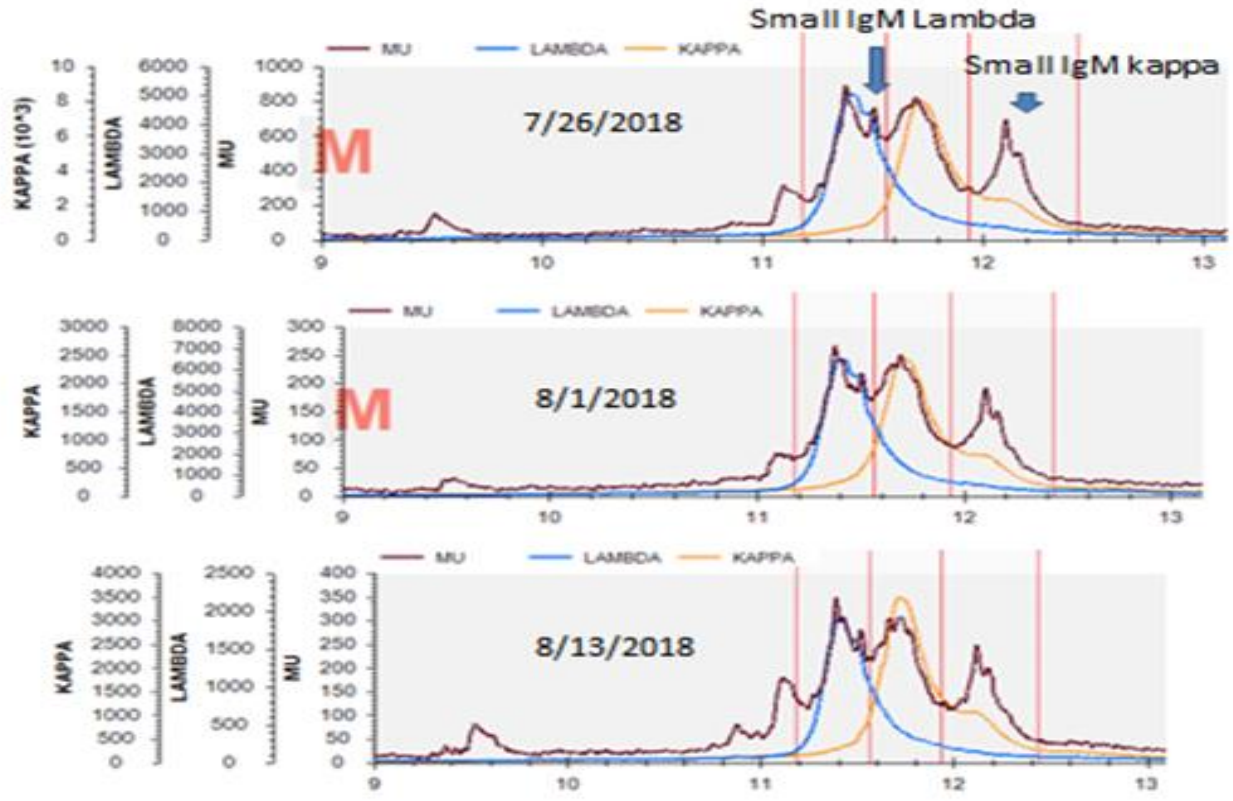
Murray et al. The XIVth International Symposium on Amyloidosis 2014

Single IgG kappa Patient over 7 years

Sample Date	M-spike (g/dL)	IFE	FLC ratio	miRAMM	Mass (Da)	miRAMM Peak Area
2/23/2005	4.8	Pos	Inc.	Pos	23453	3,010,900
3/292006	0.26	Pos	Inc.	Pos	23452	34,839
4/26/2007	0	Neg	Nml	Pos	23452	9,300
10/11/2007	0	Neg	Nml	Pos	23452	11,500
4/23/2008	0.54	Pos	Inc	Pos	23452	152,021
5/7/2009	0.43	Pos	Inc.	Pos	23452	322,400
7/27/2010	3.24	Pos	Inc.	Pos	23452	2,875,100
8/22/2011	0	Neg	Nml	Pos	23452	2100
3/5/2012	0.79	Pos	Inc.	Pos	23452	600,300

Murray et al. The XIVth International Symposium on Amyloidosis 2014

Detecting very small monoclonal proteins negative on immunofixation



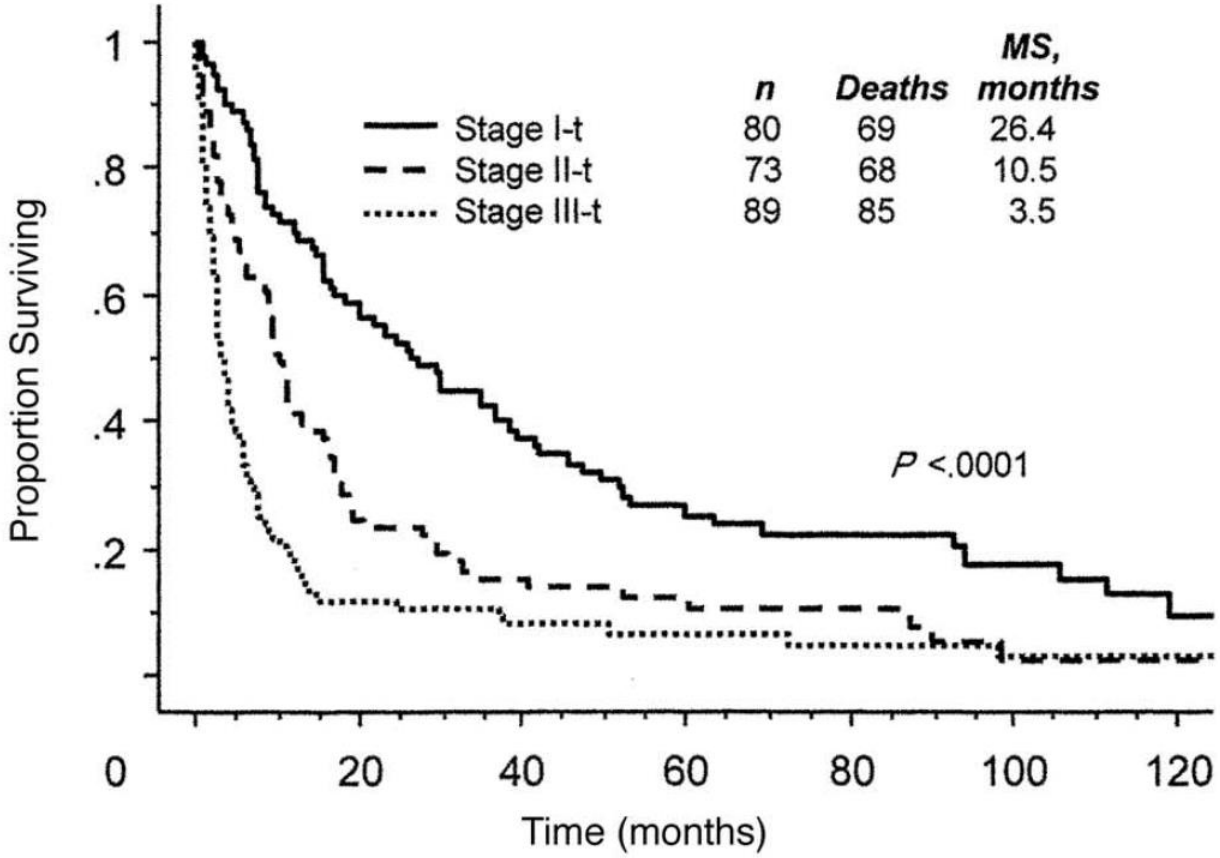
Prognosis

Staging systems

- Amyloid staging system
- Renal staging system

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

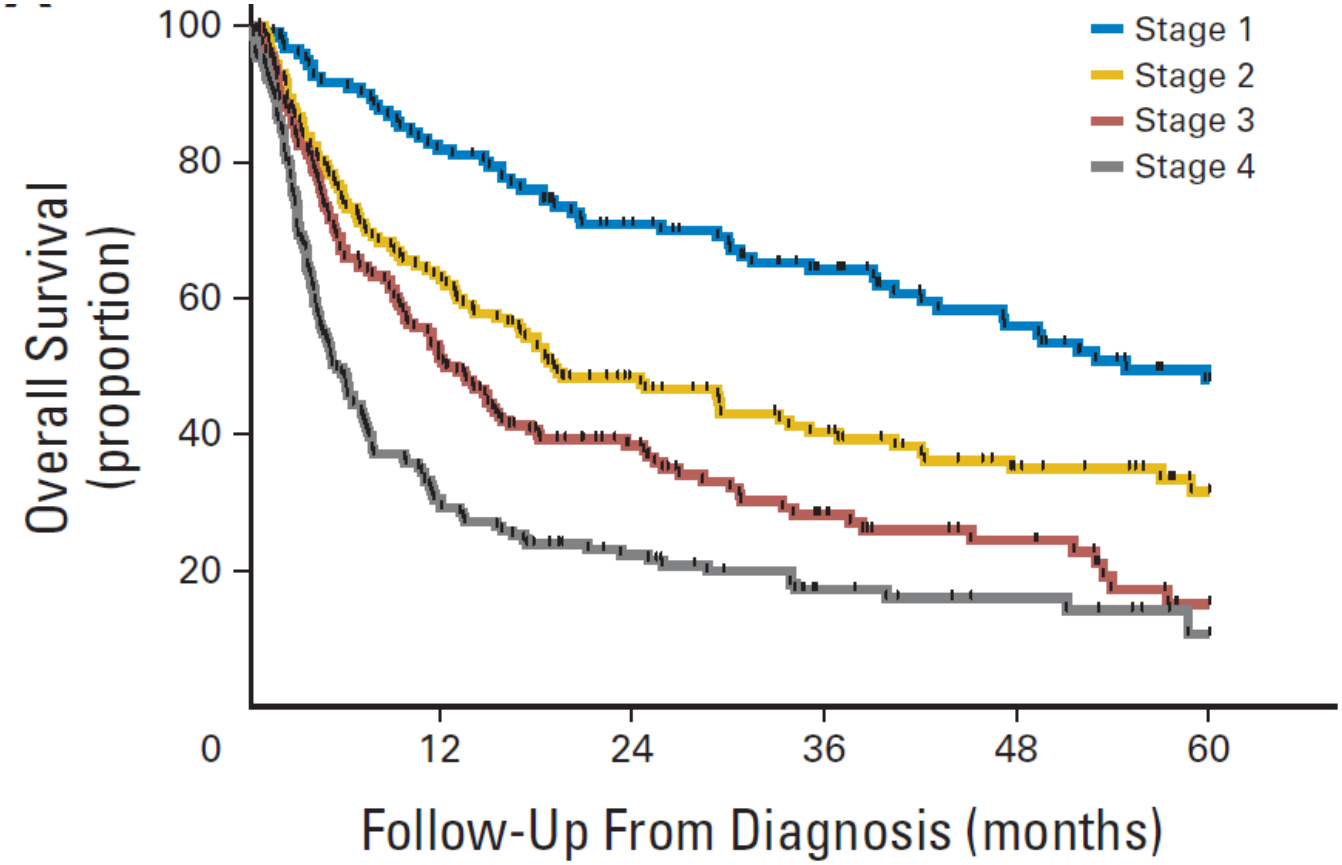


cTnT < 0.035 and NTproBNP < 332

Dispenzieri et al. JCO 2004

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

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



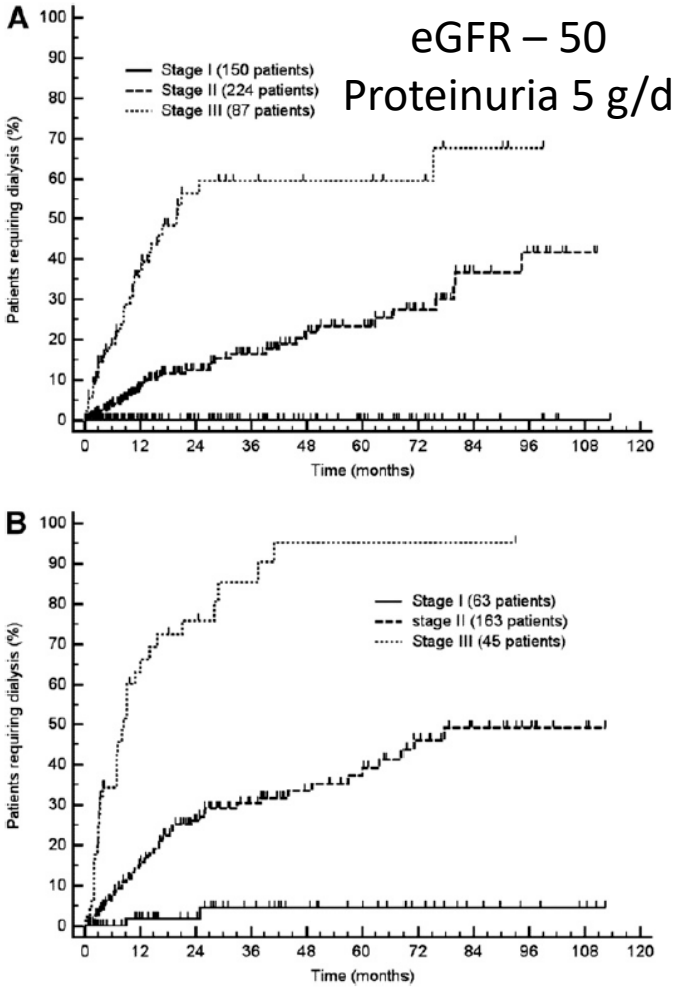
cTnT < 0.025, NTproBNP < 1800, dFLC < 18 mg/dL

Kumar et al. JCO 2012

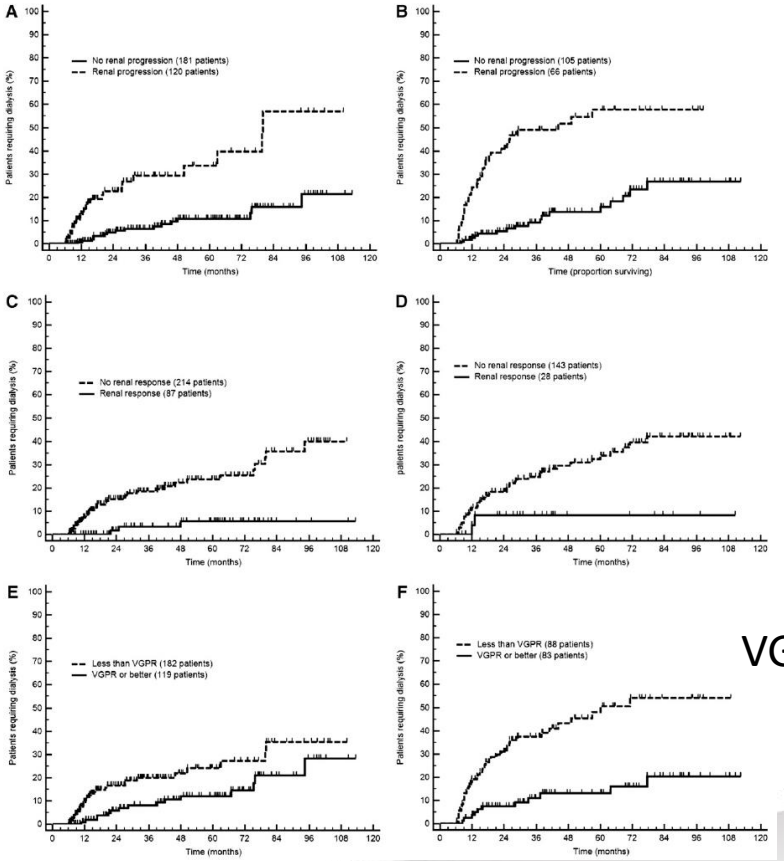
A staging system for renal outcome and early markers of renal response to chemotherapy in AL amyloidosis

Giovanni Palladini, Ute Hegenbart, Paolo Milani, Christoph Kimmich, Andrea Foli, Anthony D. Ho, Marta Vidus Rosin, Riccardo Albertini, Remigio Moratti, Giampaolo Merlini and Stefan Schönland

eGFR – 50
Proteinuria 5 g/d



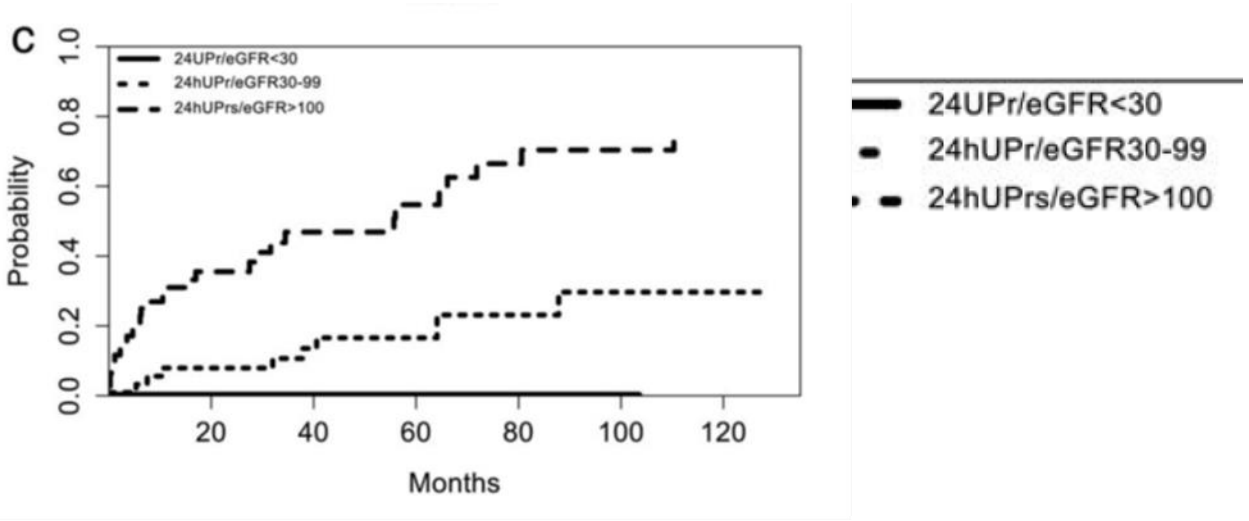
Proteinuria – >↓30%
eGFR – <↓25%

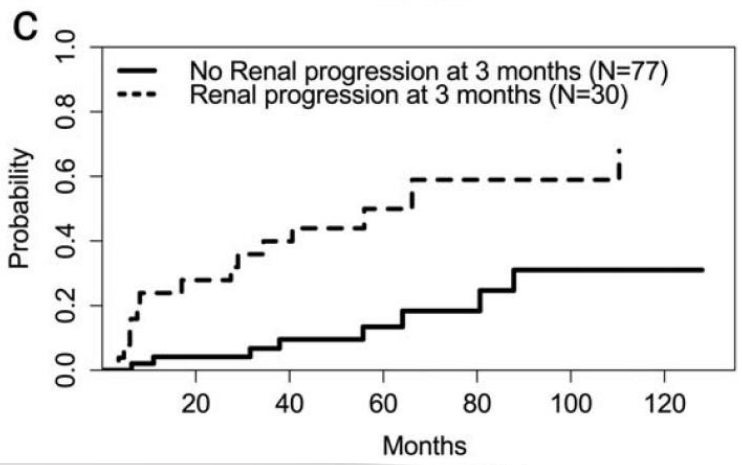


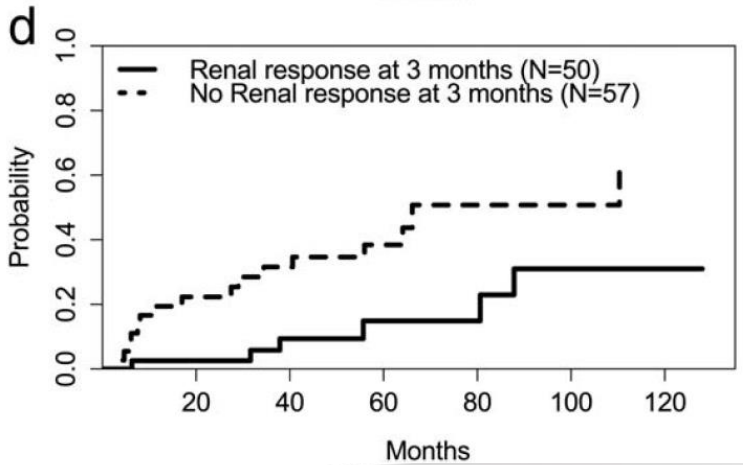
blood
2014 124: 2325-2332
doi:10.1182/blood-2014-04-570010 originally published online August 12, 2014

WILEY AJH

Renal outcomes in patients with AL amyloidosis: Prognostic factors, renal response and the impact of therapy







Kastritis et al . Am J Hematol. 2017

Treatment

Stem cell transplantation

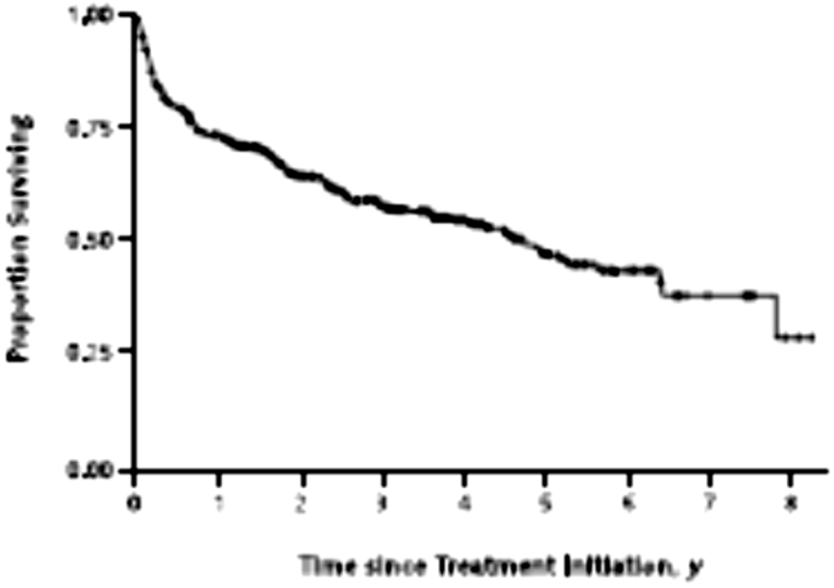
Melphalan dexamethasone

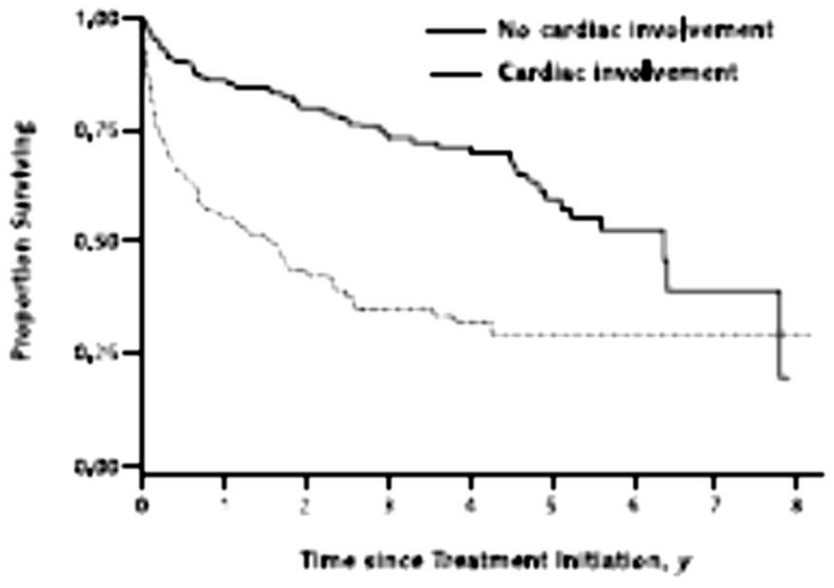
Bortezomib

Immunomodulatory drugs

Daratumumab

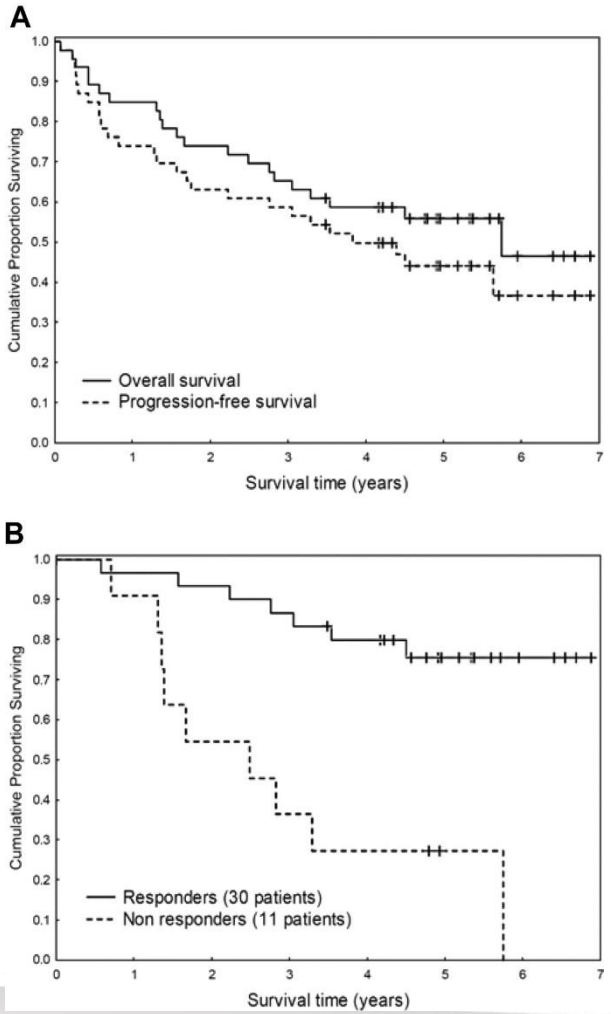
Patient Survival after SCT





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

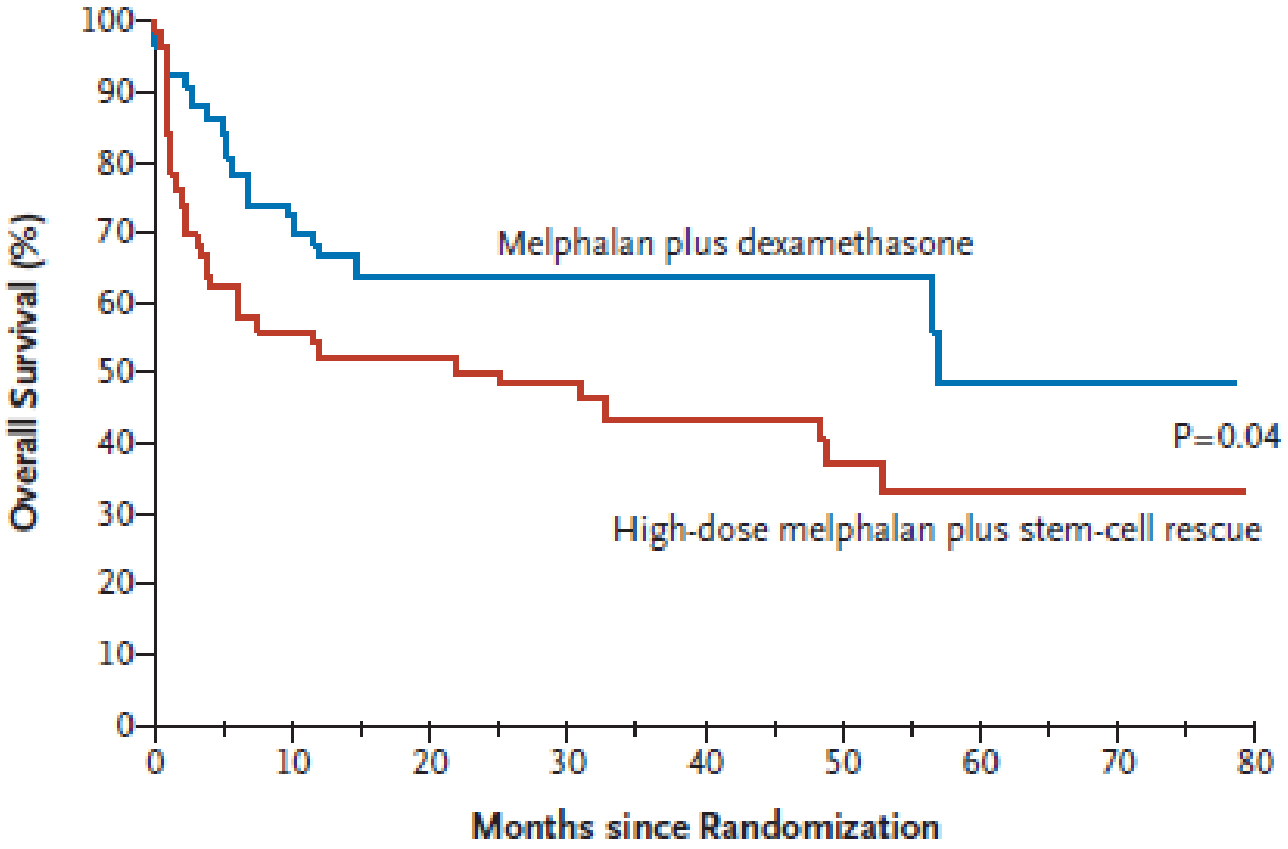
Long Term Follow-up of M-Dex Treated Patients



- Two died in CR
- 4 patients relapsed
- Progression free survival (PFS) = 3.8 years
- Median overall survival (OS) = 5.1 years

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

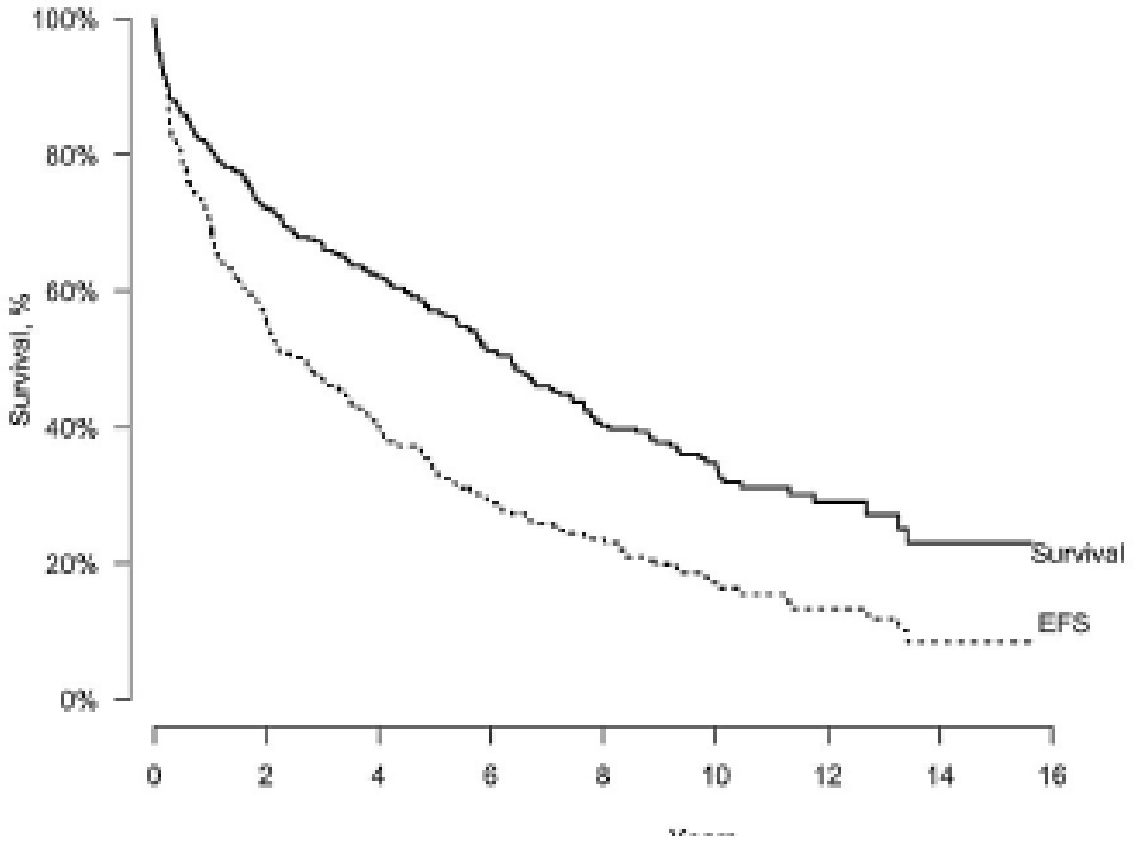
High-Dose Melphalan versus Melphalan plus Dexamethasone for AL Amyloidosis



Jaccard et al. NEJM 2007

Jaccard et al. NEJM 2007

Long term outcomes after ASCT



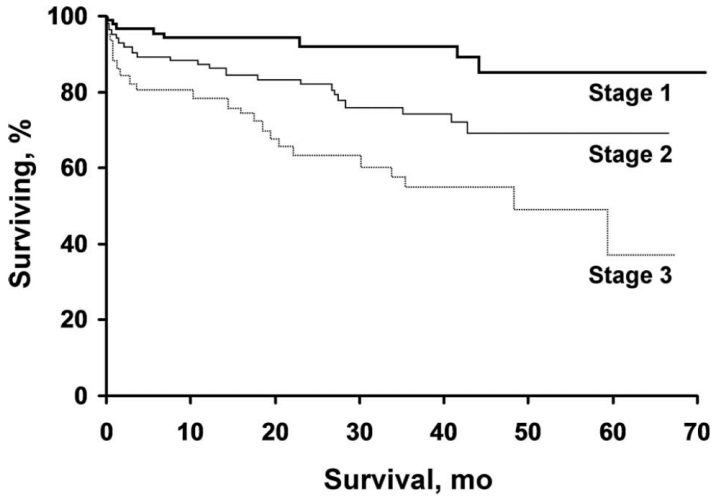
Ciberia et al. Blood 2014

Impact of cTnT and NTproBNP on survival of patients undergoing SCT

Table I. Day-100 survival rate.

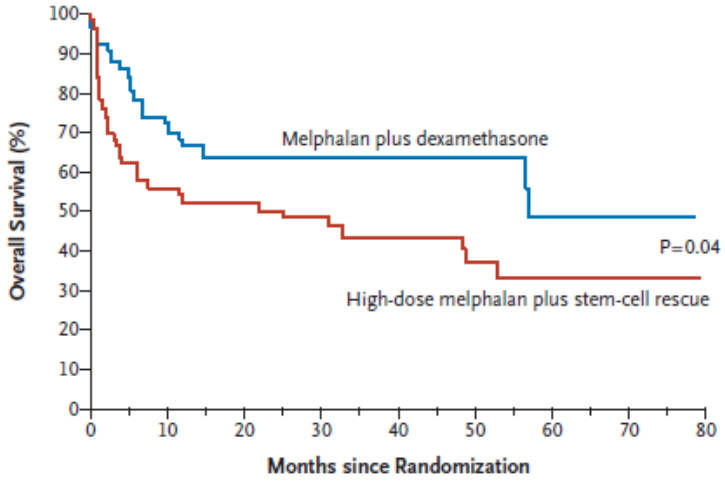
	Troponin T level ≥0.06 µg/L ($n=40$)		Troponin T level <0.06 µg/L ($n=231$)		Total patients ($N=271$)	
Patients	No.	%	No.	%	No.	%
Died before day 100*	11	28	16	7	27	10
Alive on or after day 100	29	72	215	93	244	90

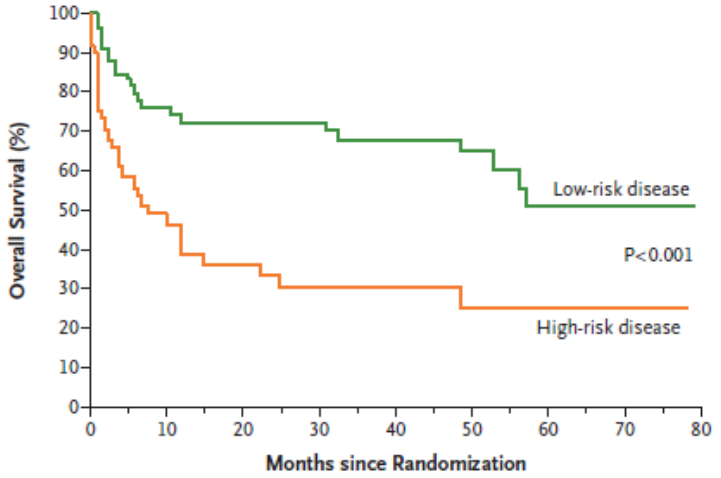
*$P < 0.001$.

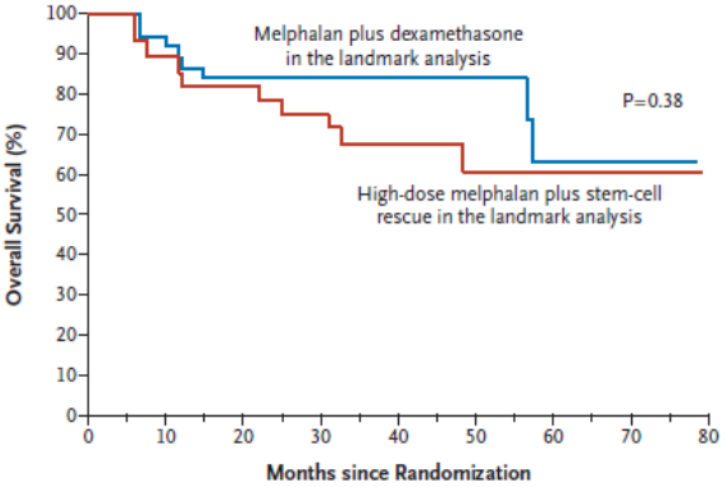


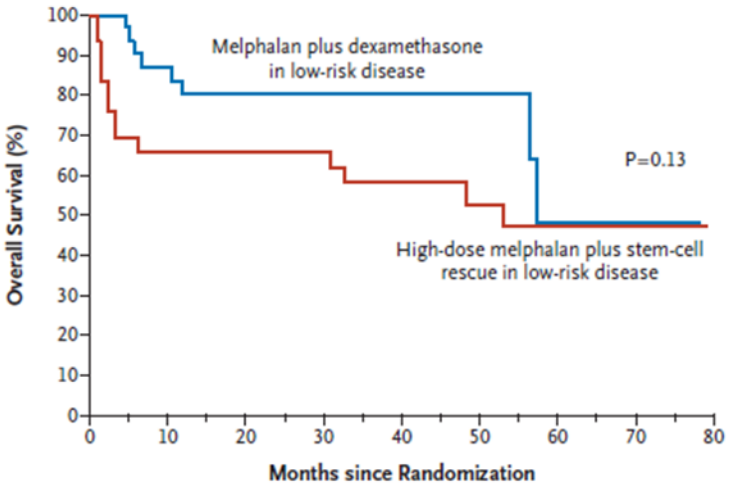
Gertz et al. Leukemia & Lymphoma 2008
Gertz et al. Leukemia & Lymphoma 2010

High-Dose Melphalan versus Melphalan plus Dexamethasone for AL Amyloidosis







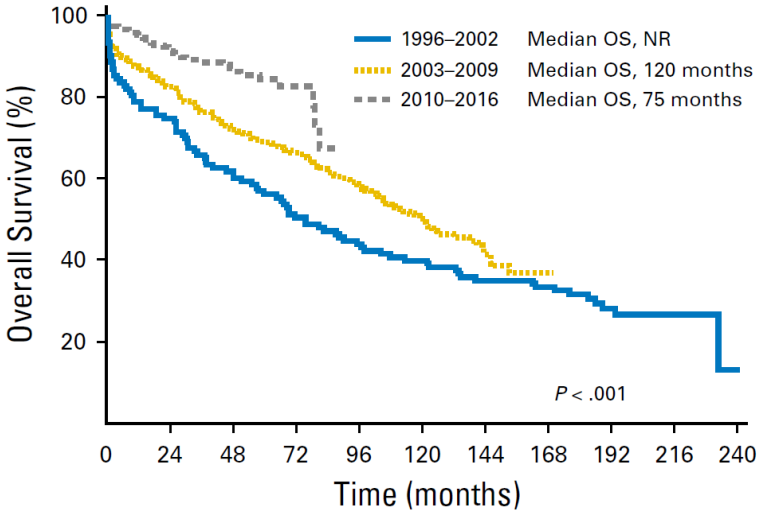


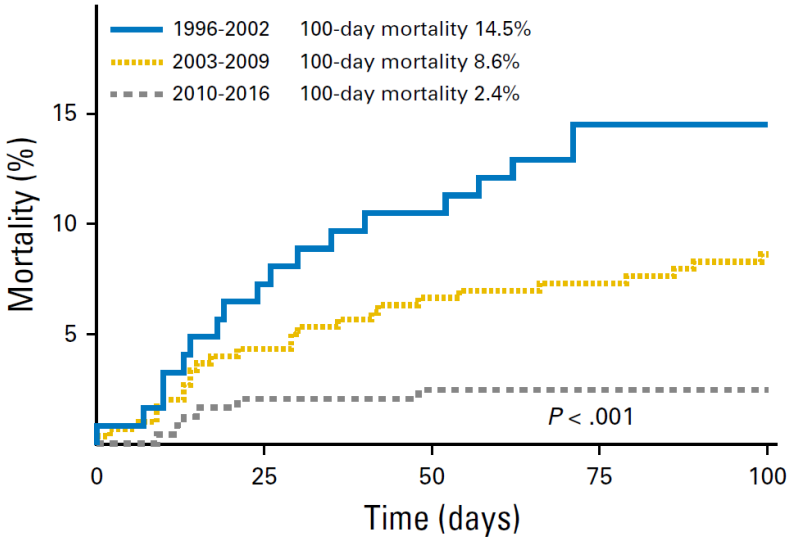
Jaccard et al. NEJM 2007

Jaccard et al. NEJM 2007

Stem Cell Transplantation for Light Chain Amyloidosis: Decreased Early Mortality Over Time

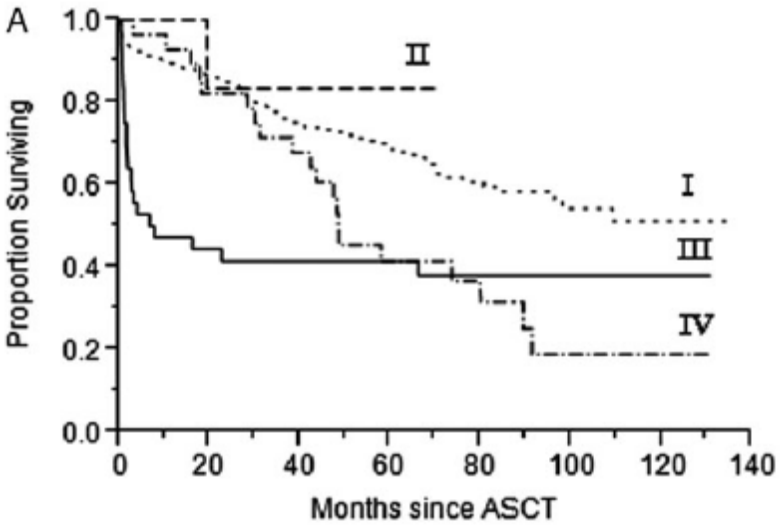
M Hasib Sidiqi, Mohammed A. Aljama, Francis K. Buadi, Rahma M. Warsame, Martha Q. Lacy, Angela Dispenzieri, David Dingli, Wilson I. Gonsalves, Shaji Kumar, Prashant Kapoor, Taxiarchis Kourelis, William J. Hogan, and Morie A. Gertz



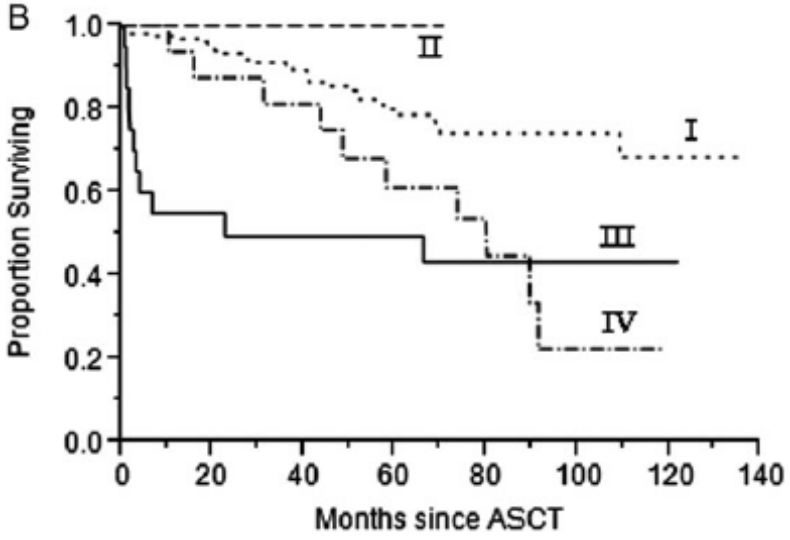


Sidiqi et al. JCO 2018

Timing of dialysis and its impact on overall survival



All patients



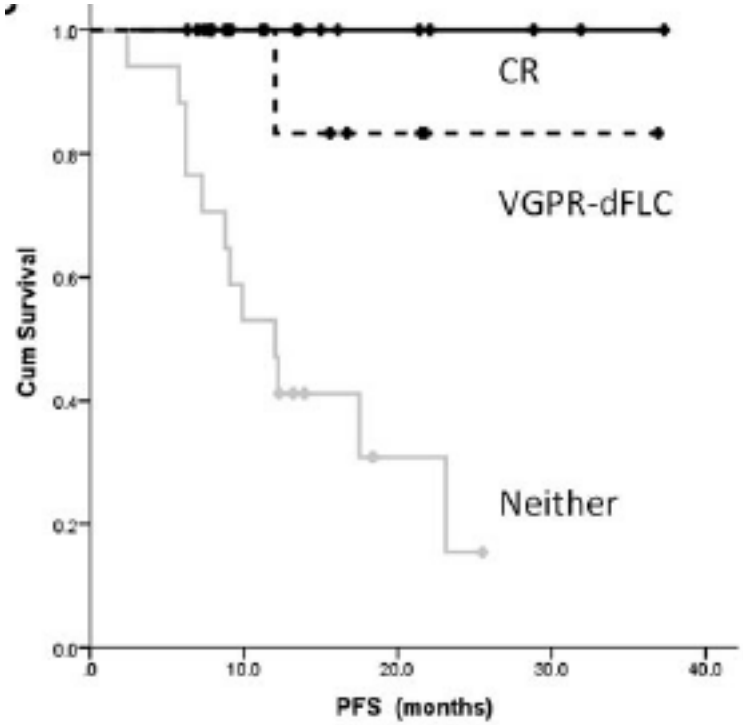
Patients with cardiac involvement

Leung et al. NDT 2015

blood
2012 119: 4387-4390
Prepublished online February 13, 2012;
doi:10.1182/blood-2011-10-388462

Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression-free survival

Christopher P. Venner, Thirusha Lane, Darren Foard, Lisa Rannigan, Simon D. J. Gibbs, Jennifer H. Pinney, Carol J. Whelan, Helen J. Lachmann, Julian D. Gillmore, Philip N. Hawkins and Ashutosh D. Wechalekar



- Responses
  - Hem Res –
    - 81.4%/CR – 41.9%
    - 82.9% by dFLC/VGPR 51.4%
  - Organ responses –
    - Cardiac – 11%
    - Liver – 40%
    - Renal – 29%
- 2 year OS - 97.7%
- Neuropathy – 30%

Venner et al. Blood 2012

A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis

Giovanni Palladini,[1] Sajitha Sachchithanantham,[2] Paolo Milani,[1] Julian Gillmore,[2] Andrea Foli,[1] Helen Lachmann,[2] Marco Basset,[1] Philip Hawkins,[2] Giampaolo Merlini,[1] and Ashutosh D. Wechalekar[2]

Response category	Stage I (30 patients)	Stage II (67 patients)	Stage IIIa (61 patients)	Stage IIIb (43 patients)
Overall response	23 (77%)	43 (64%)	42 (69%)	18 (42%)*
CR	10 (33%)	12 (18%)	14 (23%)	6 (14%)
VGPR	7 (23%)	18 (27%)	16 (26%)	4 (9%)
PR	6 (20%)	13 (19%)	12 (20%)	8 (19%)

Response category	Full bortezomib dose (35 patients)	Intermediate bortezomib dose (82 patients)	Low bortezomib dose (79 patients)
Overall response	29 (83%)	57 (69%)	42 (53%)†
CR	12 (34%)	20 (24%)	11 (14%)†
VGPR	7 (20%)	21 (26%)	17 (21%)
PR	10 (29%)	16 (19%)	14 (18%)

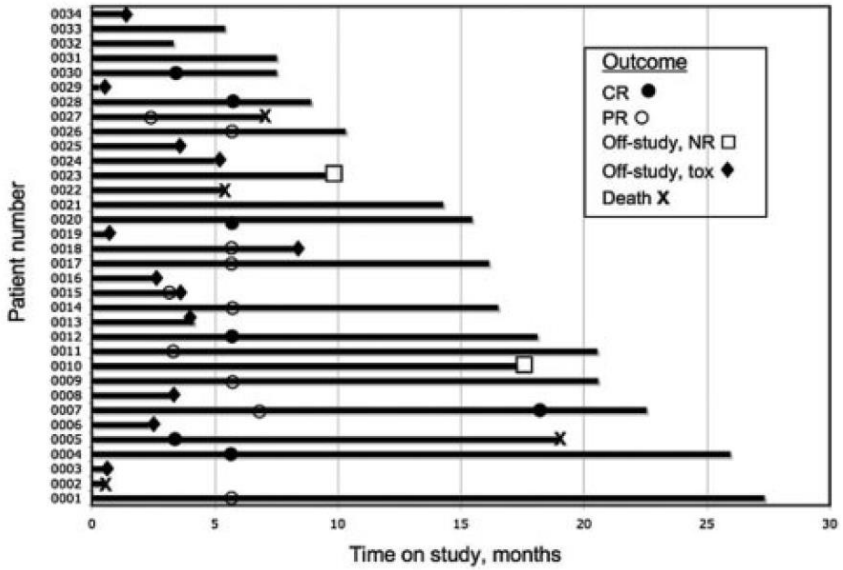
Response category	Full dexamethasone dose (58 patients)	Intermediate dexamethasone dose (102 patients)	Low dexamethasone dos (41 patients)
Overall response	45 (78%)	62 (61%)	20 (49%)†
CR	15 (26%)	21 (21%)	6 (15%)†
VGPR	17 (29%)	23 (22%)	5 (12%)†
PR	12 (21%)	18 (18%)	9 (22%)

Palladini et al. Blood 2015

blood

2007 109: 492-496
Prepublished online Sep 7, 2006;
doi:10.1182/blood-2006-07-030544

Lenalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 2 trial



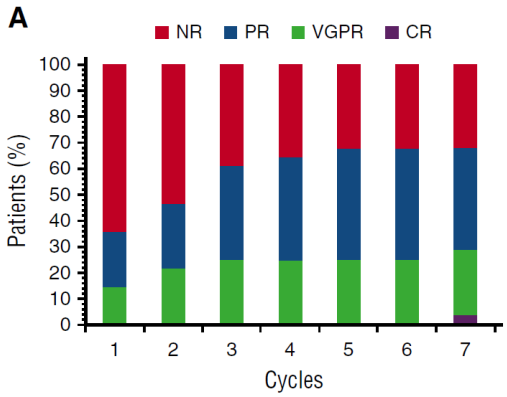
Adverse event	Grades 1 and 2, no. (%)	Grades 3 and 4, no. (%)
Fatigue	15 (44)	12 (35)
Dizziness	20 (59)	4 (12)
Edema	17 (50)	0 (0)
Skin rash	14 (41)	6 (18)
Respiratory infection	13 (38)	4 (12)
Hypoalbuminemia	8 (24)	10 (29)
Increased creatinine	17 (50)	3 (9)
Myelosuppression	20 (59)	12 (35)
Thromboembolic events	0 (0)	3 (9)
Muscle cramps	22 (65)	1 (3)
Worsening of PS*	7 (21)	9 (26)

Sanchorawala et al. Blood 2007

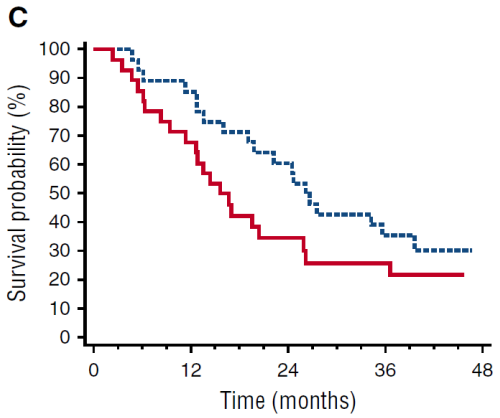
A phase 2 trial of pomalidomide and dexamethasone rescue treatment in patients with AL amyloidosis

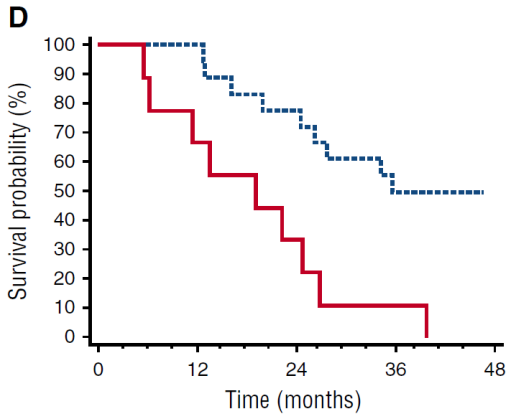
Giovanni Palladini,[1,2] Paolo Milani,[1,2] Andrea Foli,[1,2] Marco Basset,[1,2] Francesca Russo,[1,2] Stefano Perlini,[3,4] and Giampaolo Merlini[1,2]

[1]Amyloidosis Research and Treatment Center, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [2]Department of Molecular Medicine, University of Pavia, Pavia, Italy; [3]Internal Medicine, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; and [4]Department of Internal Medicine, University of Pavia, Pavia, Italy



Overall Response rate – 68%
VGPR or better – 29%
PFS – 16m
OS – 26m
Renal response – 17%





Palladini et al. Blood 2017

Daratumumab-based therapy in patients with heavily-pretreated AL amyloidosis

Jithma P. Abeykoon[1,2] · Saurabh Zanwar[1,2] · Angela Dispenzieri[1,2] · Morie A. Gertz[1,2] · Nelson Leung[1,2,3] · Taxiarchis Kourelis[1,2] · Wilson Gonsalves[1,2] · Eli Muchtar[1,2] · David Dingli[1,2] · Martha Q. Lacy[1,2] · Suzanne R. Hayman[1,2] · Francis Buadi[1,2] · Rahma Warsame[1,2] · Robert A. Kyle[1,2] · Vincent Rajkumar[1,2] · Shaji Kumar[1,2] · Prashant Kapoor[1,2]

Treatment before DMT/DCT	Patients exposed (%)	% refractory	Refractory patients receiving DMT (*n*)	Refractory patients receiving DCT (*n*)
Bortezomib	91	45	10	10
Lenalidomide	57	29	5	8
Carfilzomib	16	7	0	3
Pomalidomide	20	7	0	3
Ixazomib	11	7	1	2
Melphalan (outside of ASCT)	23	7	3	0
High-dose Melphalan (ASCT)	52	0	–	–
Cyclophosphamide	75	32	8	6

Abeykoon et al. Leukemia 2019

Daratumumab-based therapy in patients with heavily-pretreated AL amyloidosis

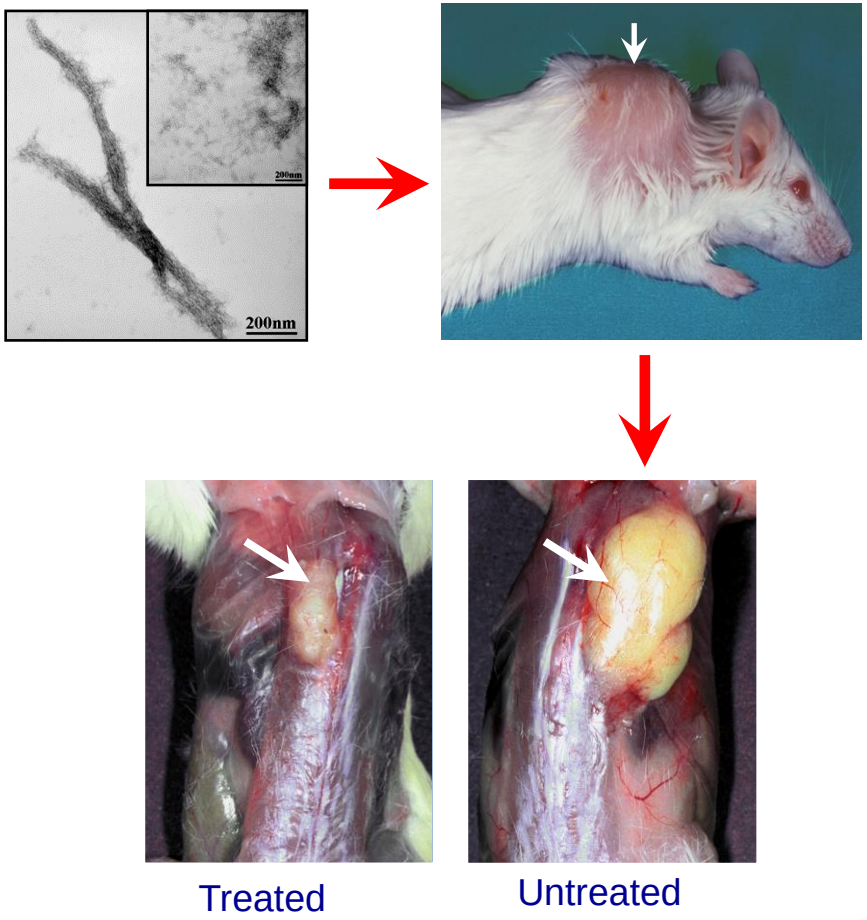
Jithma P. Abeykoon[1,2] · Saurabh Zanwar[1,2] · Angela Dispenzieri[1,2] · Morie A. Gertz[1,2] · Nelson Leung[1,2,3] · Taxiarchis Kourelis[1,2] · Wilson Gonsalves[1,2] · Eli Muchtar[1,2] · David Dingli[1,2] · Martha Q. Lacy[1,2] · Suzanne R. Hayman[1,2] · Francis Buadi[1,2] · Rahma Warsame[1,2] · Robert A. Kyle[1,2] · Vincent Rajkumar[1,2] · Shaji Kumar[1,2] · Prashant Kapoor[1,2]

	Entire cohort, $n = 44$[a]	DMT, $n = 22$[b]	DCT, $n = 22$[c,d,e]
Prior lines of therapy, *n* (range)	3 (1–8)	3 (1–5)	3 (1–8)
ORR[a], *n* (%)	25 (83)	11 (78)	14 (88)
CR[a], *n* (%)	5 (17)	2 (14)	3 (19)
VGPR[a], *n* (%)	19 (63)	9 (64)	10 (63)
PR[a], *n* (%)	1 (3)	0	1 (6)
Time to 1st/ best response, months (95% CI)[a]	2.2 (1.7–4.8) / 5.7 (3.4–7.7)	2.6 (1.7–6.2) / 6.2 (2.2–8.9)	1.9 (0.9–3.4)/ 5.7 (2.3–12.2)
Median follow-up, months (95% CI)	10.2 (8.0–13.1)	7.7 (5.6–10.4)	13.1 (9.1–17.8)
PFS, months (95% CI)	NR (15.5-NR)	NR (13.2-NR)	NR (15.5-NR)
PFS for 6 and 10 months (% of patients)	97% and 89%	100%,100%	100%, 83%
OS, months (95% CI)	NR (NR-NR)	NR (13-NR)	NR (15.5-NR)
OS for 10 months (% of patients)	94%	100%	89%
EFS, months (95% CI)	15.5 (12-NR)	13.2 (8.1–15.0)	NR (11.3-NR)
EFS for 6 and 10 months (% of patients)	86% and 76%	80% and 56%	90% and 81%

Abeykoon et al. Leukemia 2019

Immunotherapy Using the 11-1F4 mAb

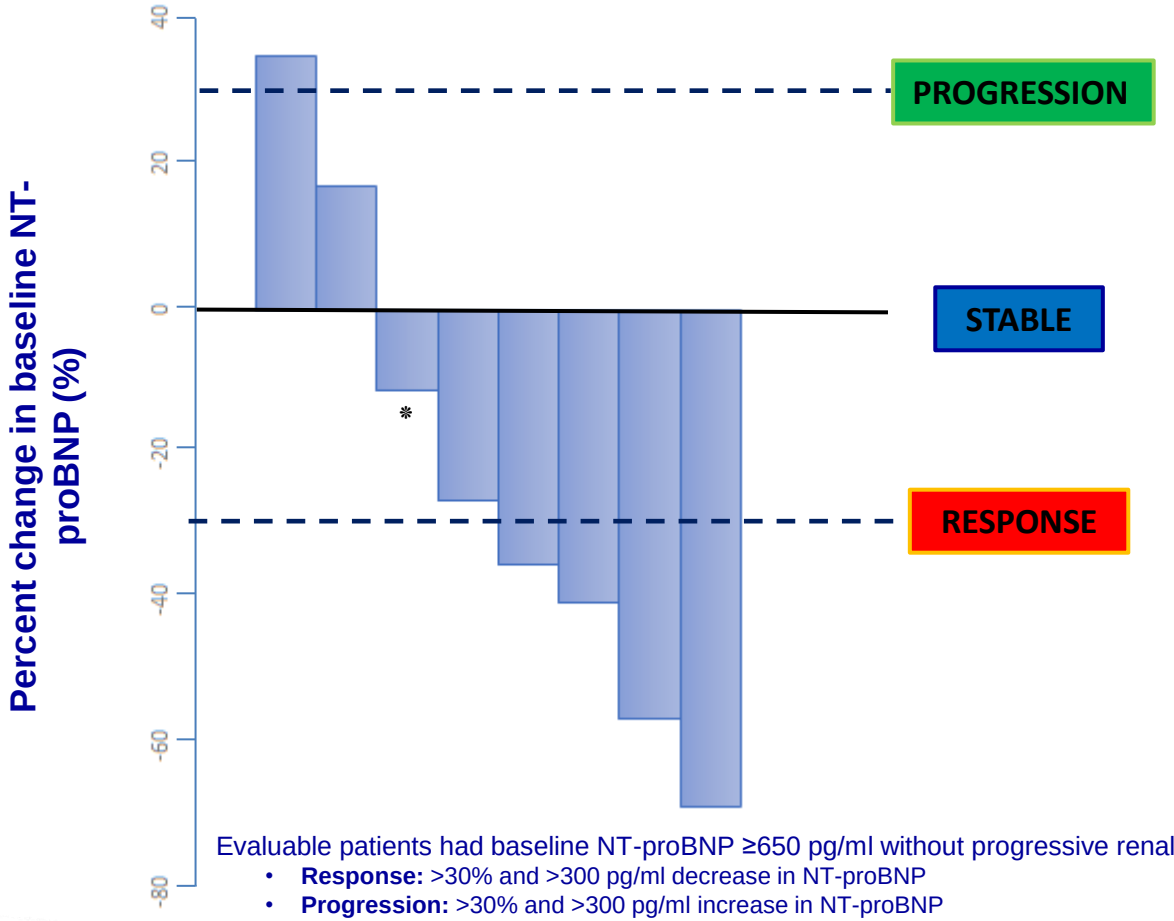
The 11-1F4 mAb expedites the dissolution of human AL λ and κ amyloidomas in mice



Wall, JS et al, Tijdschr Nucl Geneeskd. 2011Dec;33(4):807-814

Wall JS et al. Blood 2010;116:2241-2244.

Best Cardiac Response After Treatment with mAb 11-1F4 in Phase 1a and 1b



Response Criteria: Comenzo R et al, 2012; Palladini et al, 2012.

8 patients evaluable for response

5 responders (63%)

**Patient responded via NYHA Class criteria – NYHA Class III to I*

2 stable (25%)

1 patient with progression

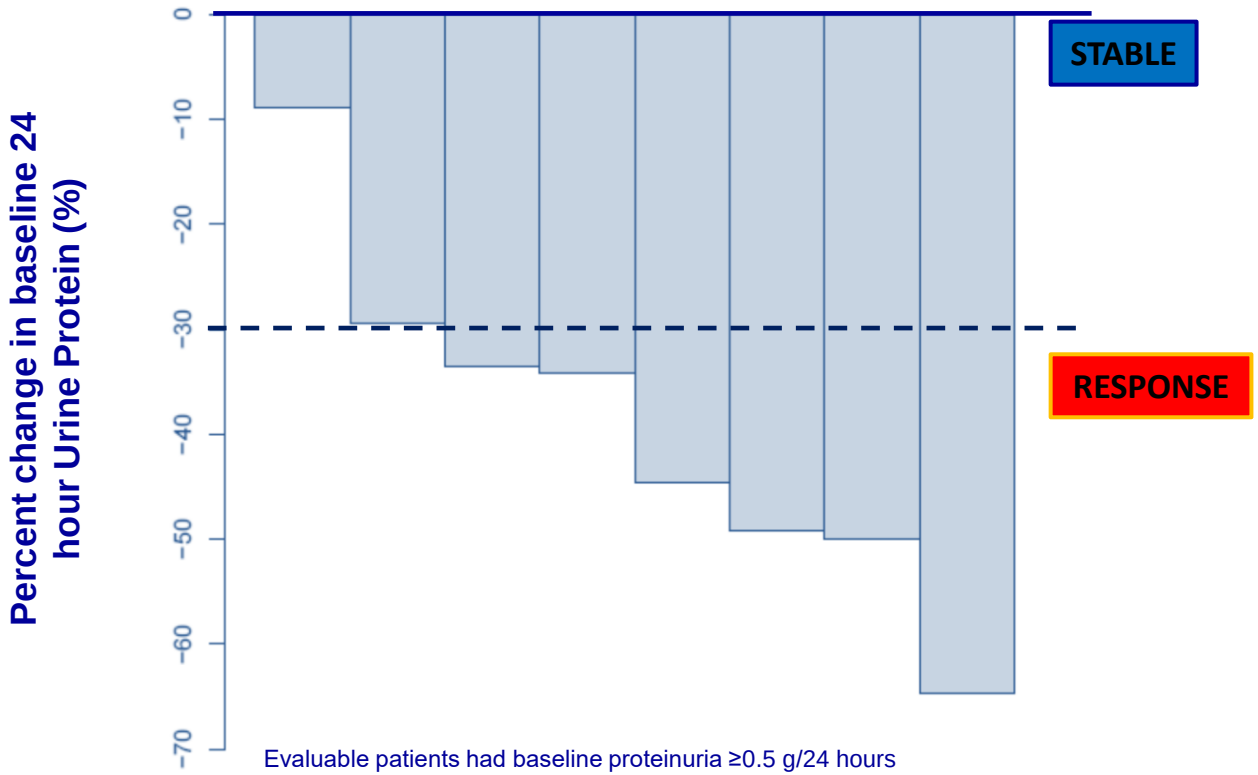
Evaluable patients had baseline NT-proBNP ≥650 pg/ml without progressive renal dysfunction

- **Response:** >30% and >300 pg/ml decrease in NT-proBNP
- **Progression:** >30% and >300 pg/ml increase in NT-proBNP
- **Stable disease:** neither response nor progression

Lentzsch et al, ASH 2016

https://clinicaltrials.gov/ct2/show/NCT02245867

Best Renal Response After Treatment with mAb 11-1F4 in Phase 1a and 1b



Renal Response Criteria: Palladini et al, Blood, 2014

8 patients evaluable for response

6 responders (75%)

2 stable (25%)

No patients with progression

Evaluable patients had baseline proteinuria ≥0.5 g/24 hours

- **Response:** >30% decrease in proteinuria or a decrease to <0.5 g/24 hours in the absence of renal progression
- **Progression:** >25% worsening in eGFR
- **Stable disease:** neither response nor progression

Lentzsch et al, ASH 2016

https://clinicaltrials.gov/ct2/show/NCT02245867

Questions

Scottsdale, Arizona

Rochester, Minnesota

Jacksonville, Florida