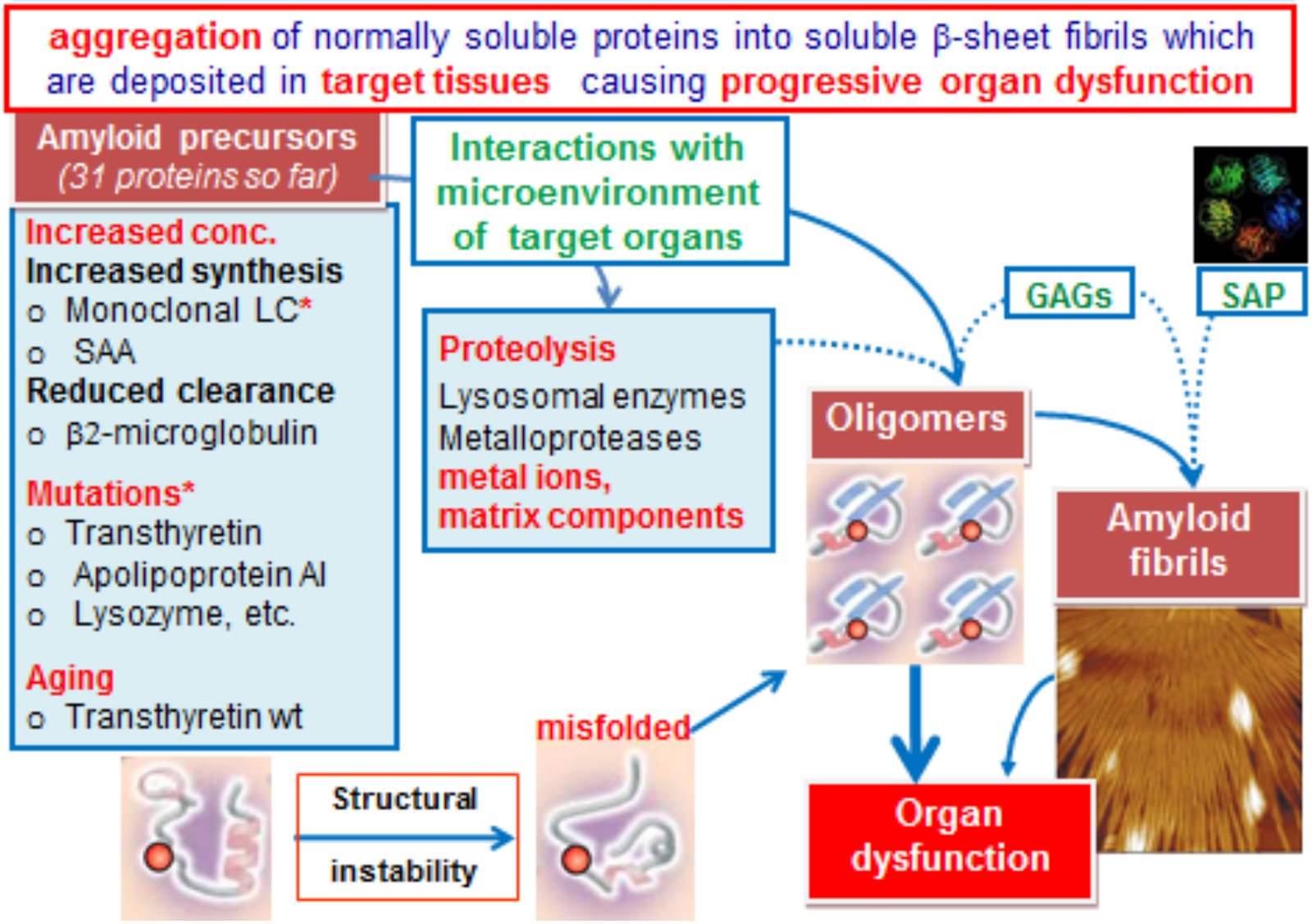
2017

Progetto
Ematologia
Romagna

Amiloidosi AL: clinica, esami diagnostici e prognosi

Giovanni Palladini

Amyloidosis: protein misfolding disease



Clinical presentation of the most common forms of systemic amyloidosis

Amyloid type	Organ involvement					
	Heart	Kidney	Liver	PNS	ANS	ST
AL amyloidosis (>75%)	++	++	+	+	+	+
Hereditary ATTR amyloidosis	++	±	-	++	+	-
AA (reactive) amyloidosis	±	++	+	-	+	-
Wild-type ATTR amyloidosis (10%) (Senile systemic amyloidosis)	++	-	-	-	-	-
Hereditary AApoAI amyloidosis	+	+	+	-	-	-
ALECT2 Amyloidosis (Leukocyte chemotactic factor 2)	-	+	+	-	-	-

Palladini & Merlini Blood 2016

Diagnosis of AL amyloidosis

Signs or symptoms of systemic amyloidosis

- Heart failure; myocardial wall thickening on echocardiography with normal or low limb lead voltages on ECG; late gadolinium enhancement, ECV, pre-contrast T1 on MRI
- Nephrotic syndrome
- Fatigue, weight loss
- Peripheral (ascending, symmetric, small fibers / axonal) neuropathy in non-diabetic patients
- Autonomic neuropathy (postural hypotension, "resolution" of pre-existing hypertension, erectile / bladder / bowel dysfunction)
- Hepatomegaly with normal imaging
- Purpura, macroglossia, carpal tunnel syndrome, claudication of the jaw, articular deposits

Positive biomarker-based screening in patients at risk (MGUS with abnormal FLC ratio)

- Elevated NT-proBNP in the absence of other causes
- Albuminuria

Tissue biopsy

- **Abdominal fat aspirate**, and if negative
- **Salivary gland biopsy**, or
- **Organ biopsy** (beware of hemorrhagic risk, transjugular approach preferred for liver biopsy)

Identification of the plasma cell clone by serum and urine immunofixation electrophoresis and FLC measurement
Bone marrow studies including iFISH of plasma cells and skeletal survey

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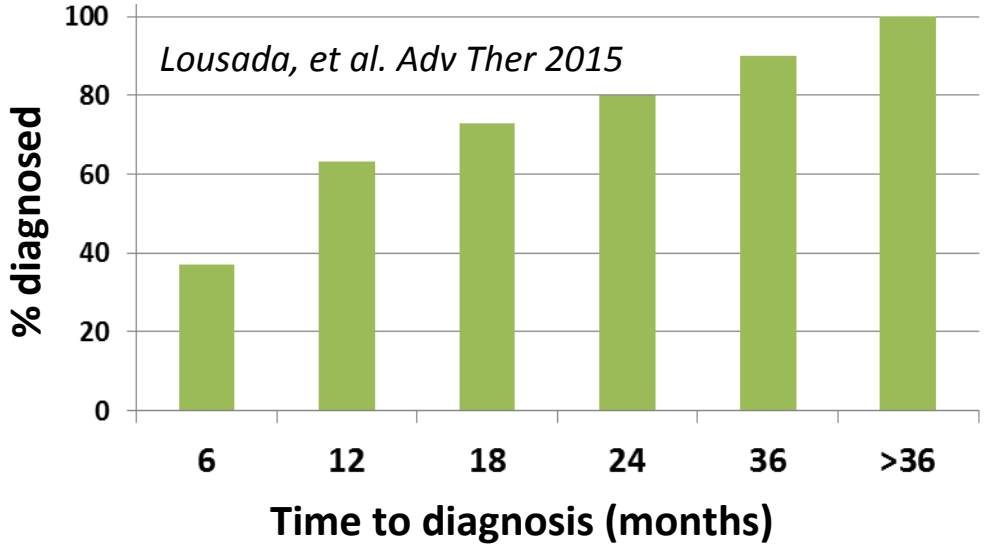
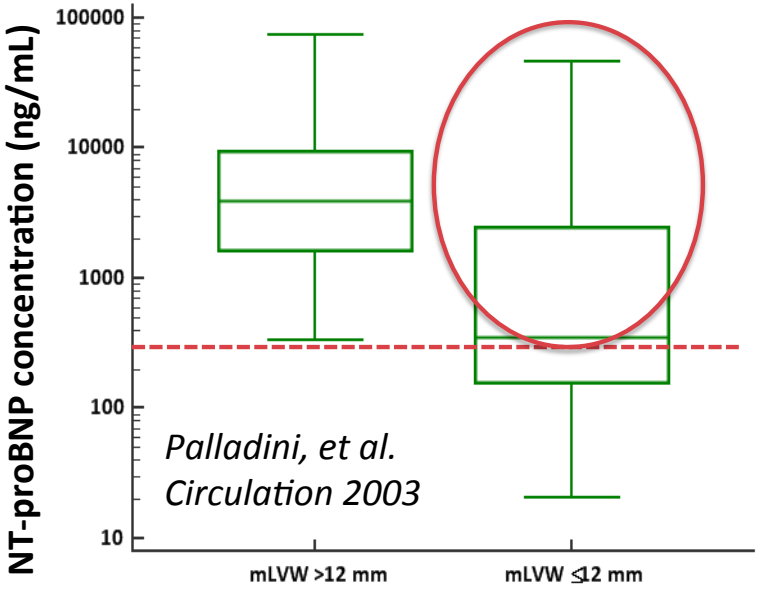
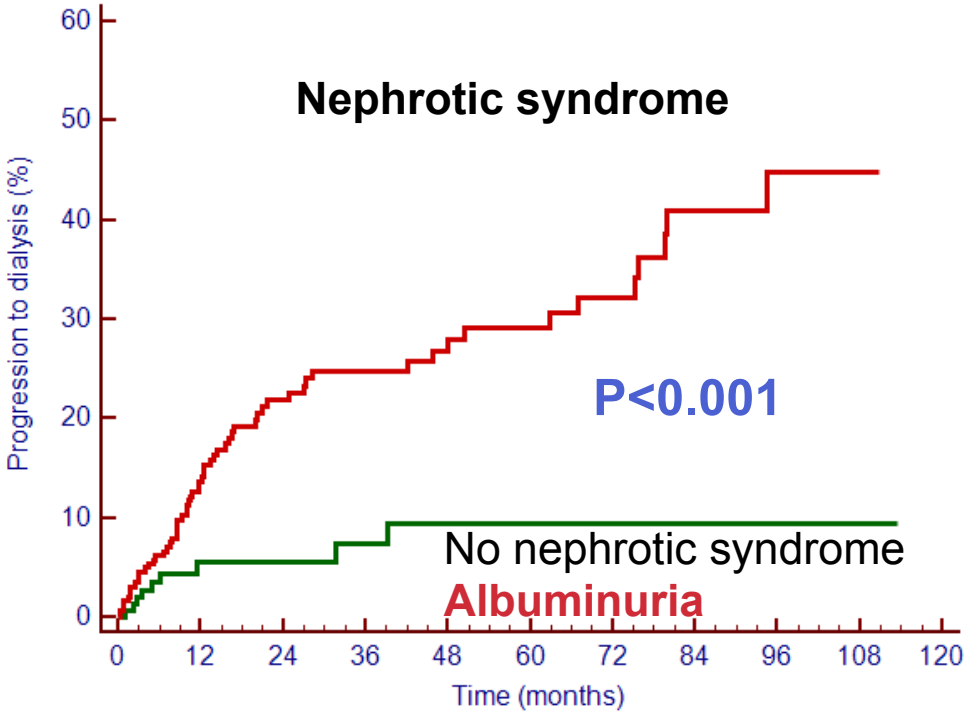
AL amyloidosis is often diagnosed late

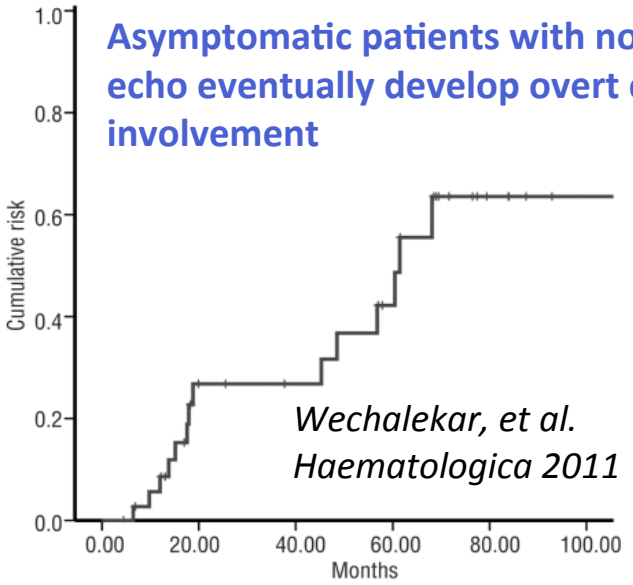


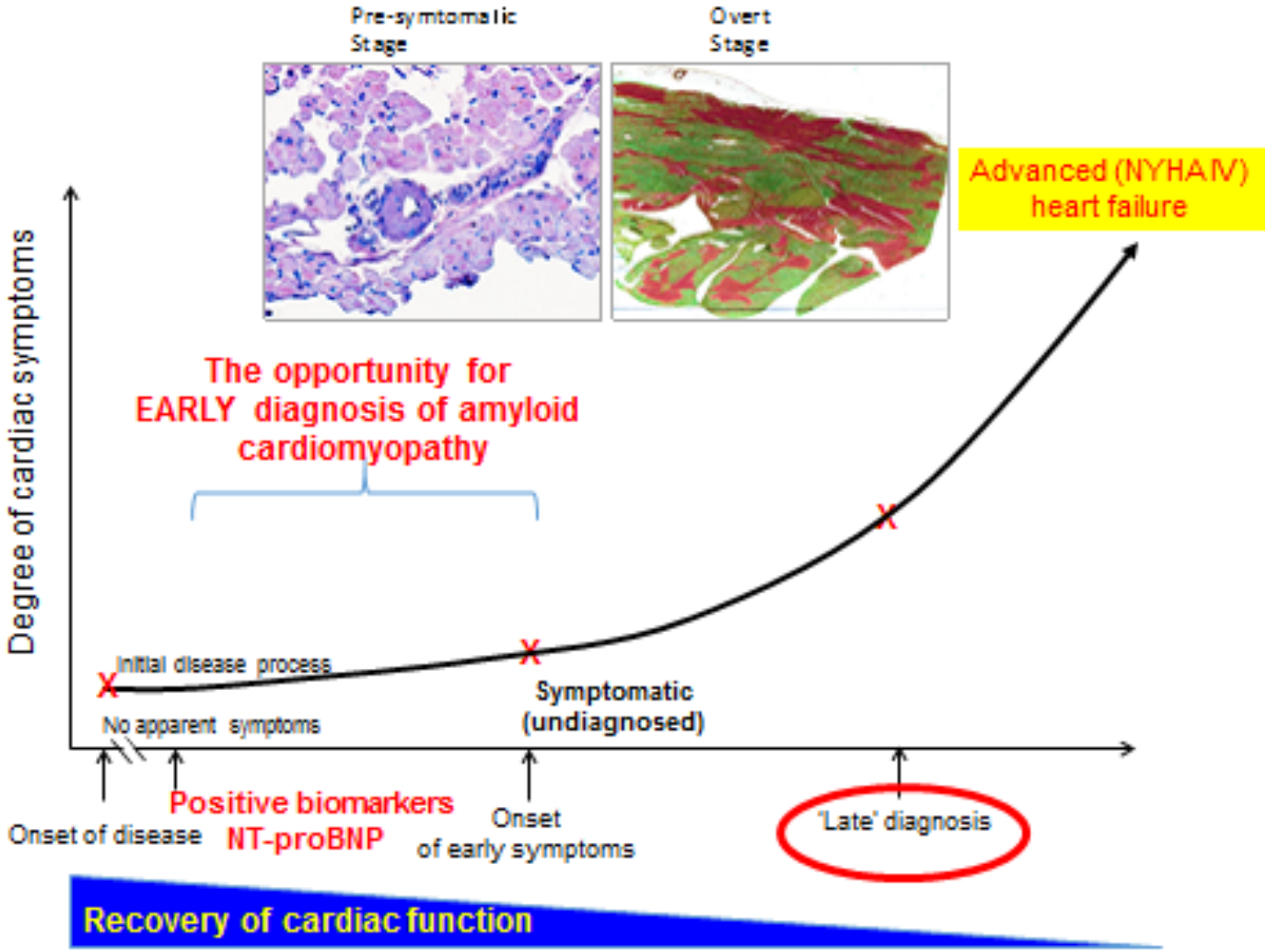
NT-proBNP has 100% diagnostic sensitivity





Asymptomatic patients with normal echo eventually develop overt cardiac involvement

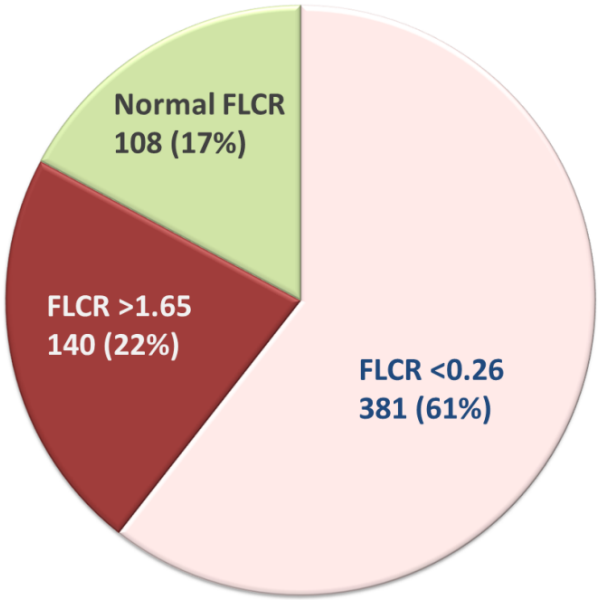



Pre-symtomatic Stage
Overt Stage
Advanced (NYHA IV) heart failure
The opportunity for EARLY diagnosis of amyloid cardiomyopathy
Degree of cardiac symptoms
Initial disease process
No apparent symptoms
Symptomatic (undiagnosed)
Onset of disease
Positive biomarkers NT-proBNP
Onset of early symptoms
"Late" diagnosis
Recovery of cardiac function

Can we screen for AL amyloidosis ?

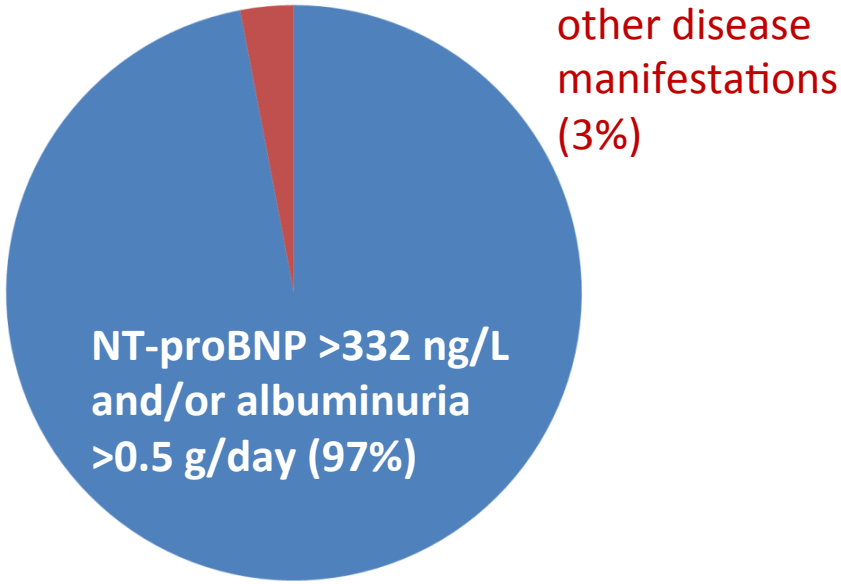
- Nine percent of patients with MGUS who progress develop AL amyloidosis (Kyle, et al. NEJM 2002)
- Patients with MGUS and abnormal FLCR should undergo life-long monitoring

- ~85% of patients with AL amyloidosis have abnormal FLCR at diagnosis



Merlini & Palladini. Hematology 2012
Merlini, et al. Blood 2013

- >95% of patients with AL amyloidosis have NT-proBNP >332 ng/L and/or albuminuria >0.5 g/day



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- Nine percent of patients with MGUS who progress develop AL amyloidosis (Kyle, et al. NEJM 2002)
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- ~85% of patients with AL amyloidosis have abnormal FLCR at diagnosis
- >95% of patients with AL amyloidosis have NT-proBNP >332 ng/L and/or albuminuria >0.5 g/day

- Patients with MGUS and abnormal FLCR should have biomarkers of early amyloid organ involvement (**NT-proBNP and albuminuria**) included in their periodic workup

Merlini & Palladini. Hematology 2012
Merlini, et al. Blood 2013

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Palladini & Merlini Blood 2016

Amyloid typing by immunohistochemistry

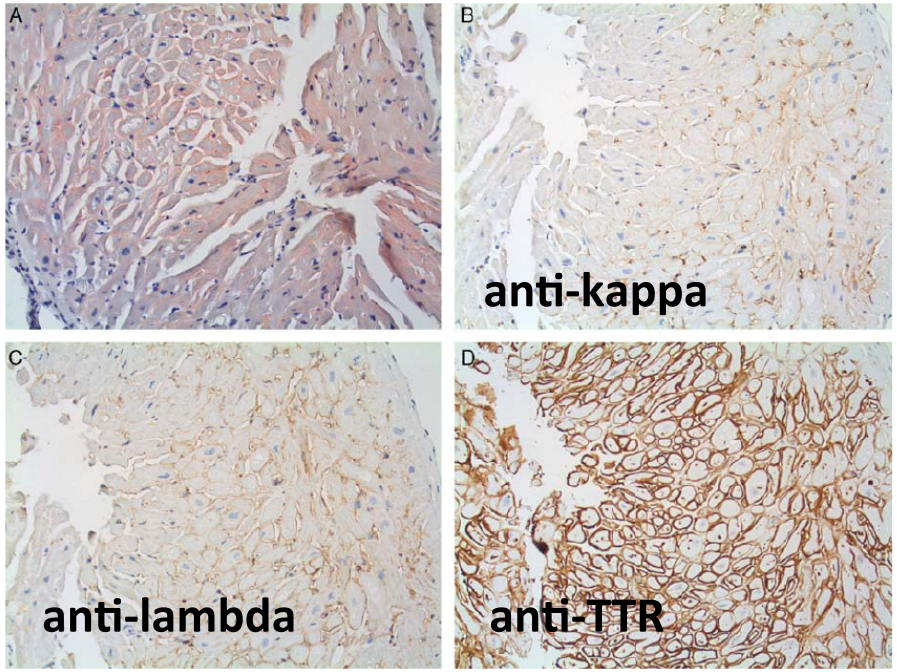
Strong Transthyretin Immunostaining: Potential Pitfall in Cardiac Amyloid Typing

Anjali A. Satoskar, MD, Yvonne Efebera, MD,† Ayesha Hasan, MD,‡ Sergey Brodsky, MD, PhD,* Gyongyi Nadasdy, MD,* Ahmet Dogan, MD,§ and Tibor Nadasdy, MD, PhD**

TABLE 4. Sensitivity and Specificity of Transthyretin and Light Chain Immunostaining

	Transthyretin	Light Chains
Sensitivity	7/8 (87.5%)	7/15 (46.6%)
Specificity	6/14 (42.8%)	6/9 (66.6%)
PPV	7/15 (46.6%)	7/10 (70%)
NPV	6/7 (85.7%)	6/14 (42.8%)

NPV indicates negative predictive value; PPV, positive predictive value.



Patient with AL lambda

Strong, false-positive immunostaining for transthyretin in cardiac amyloid is a potential pitfall, augmented by the frequent lack of staining for immunoglobulin light chains

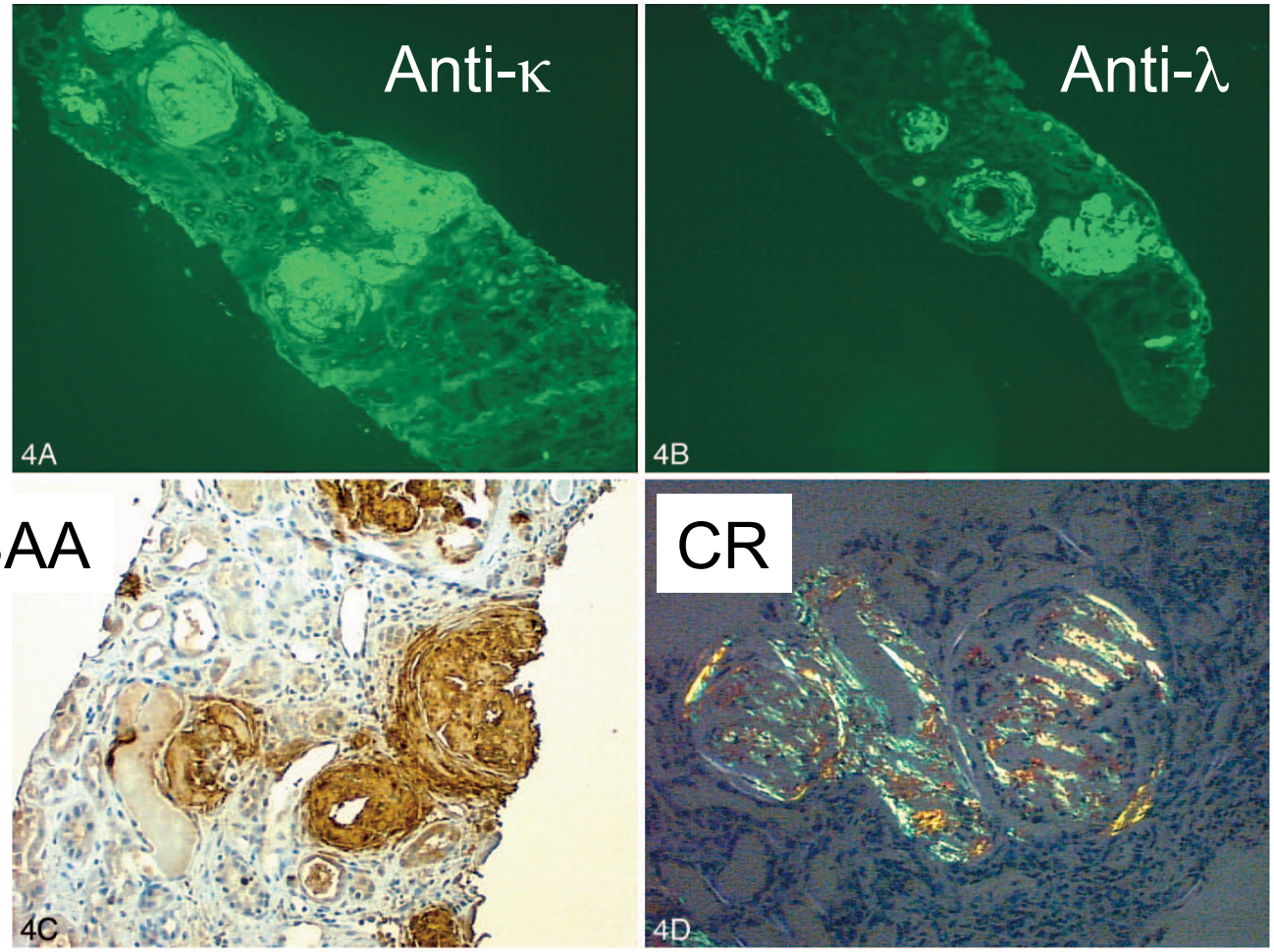
Am J Surg Pathol • Volume 35, Number 11, November 2011

Typing of Amyloidosis in Renal Biopsies

Diagnostic Pitfalls

Arch Pathol Lab Med. 2007;131:917–922

Anjali A. Satoskar, MD; Kelly Burdge, MD; Daniel J. Cowden, MD; Gyongyi M. Nadasdy, MD; Lee A. Hebert, MD; Tibor Nadasdy, MD



Patient with AA amyloidosis

Unequivocal amyloid typing is vital to avoid catastrophic therapeutic mistakes

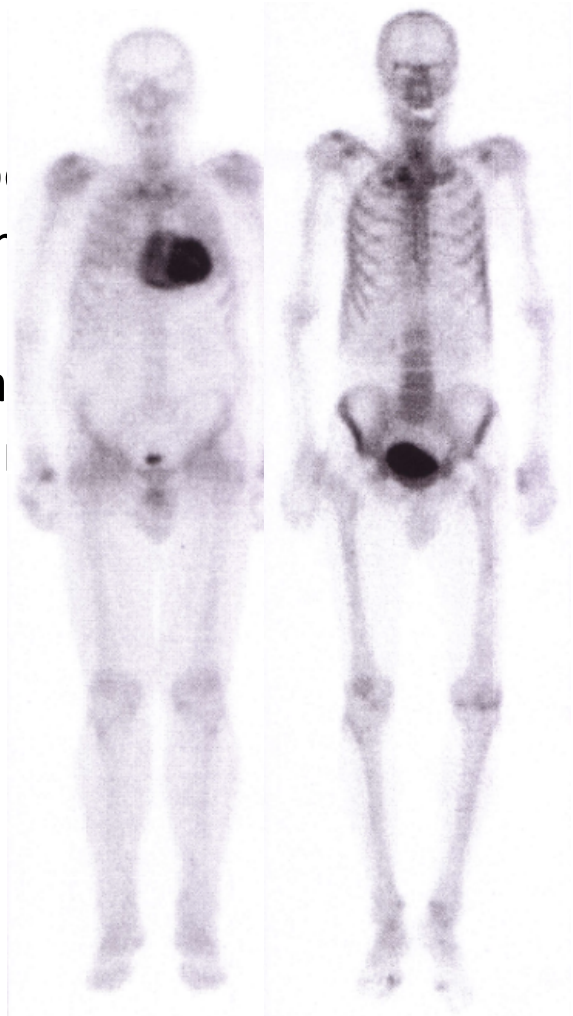
Tissue typing

- **Light microscopy immunohistochemistry**
  - reliable in AA amyloidosis with commercial antib
  - correctly classifies 94% of patients with custom-r
- **Immuno-electron microscopy**
  - sensitivity 76%, specificity 100% on abdominal fa
  - correctly classifies >99% of patients with comme
- **MS-based proteomics**[3, 4]
  - laser capture microdissection, MudPIT
  - not antibody dependant

DNA analysis

Cardiac scintigraphy with bone tracers[5]

- cardiac uptake in ATTR but not in AL amyloidosis



1. *Schönland, et al. Blood 2012*
2. *Férnandez de Larrea, et al. Blood 2014*
3. *Vrana, et al. Blood 2009*
4. *Brambilla, et al. Blood 2012*
5. *Perugini, et al. J Am Coll Cardiol 2005*

Identification (and measurement) of the amyloidogenic precursor

The BM PC clone is usually small (median 10%, <5% in 20% of patients)

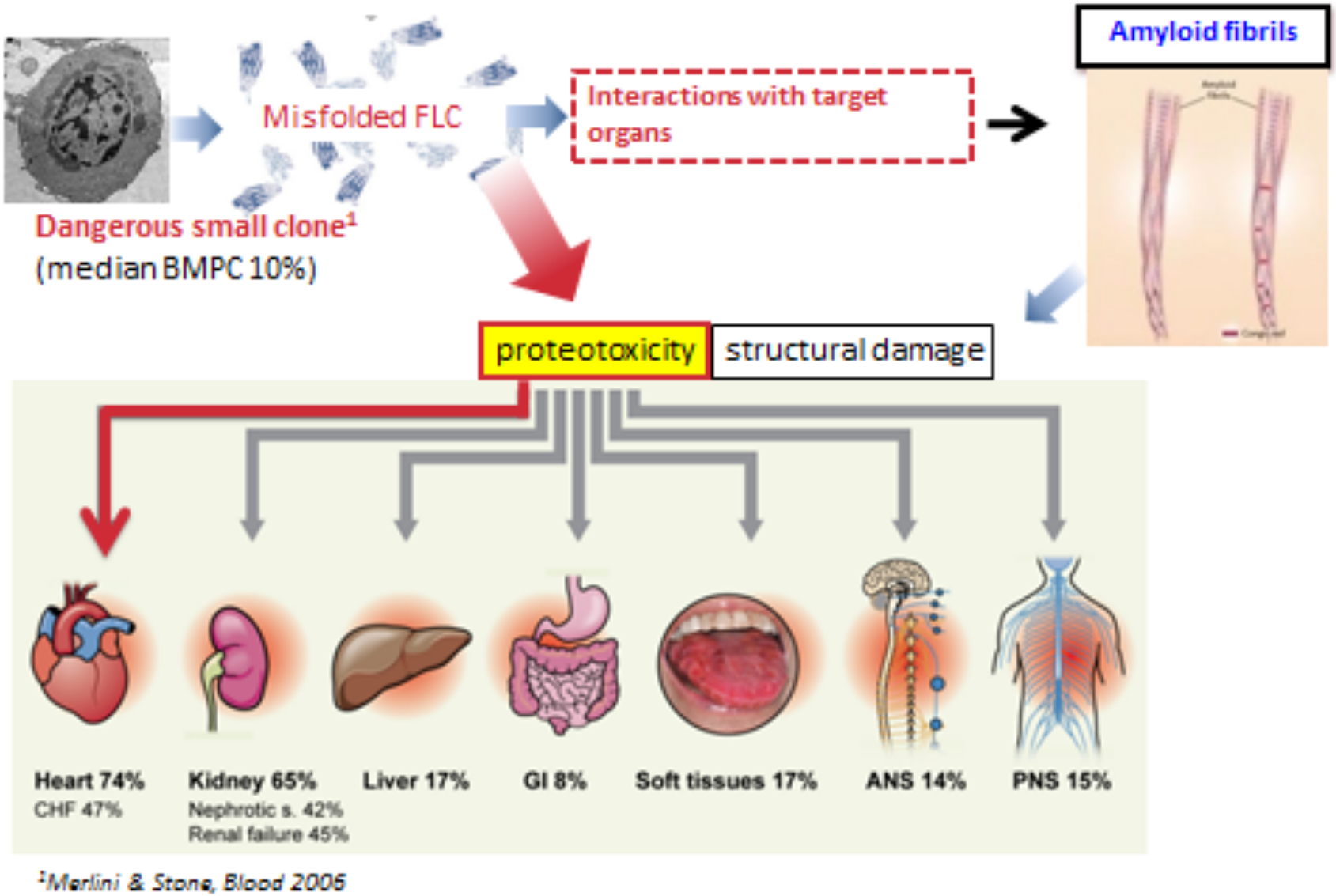
Method	Diagnostic sensitivity in AL amyloidosis		
	Palladini et al. Clin Chem 2009	Katzmann et al. Clin Chem 2009	Bochtler et al. Haematologica 2008
sEP	-	66%	-
sIFE	80%	87%	69%
uIFE	67%	-	86%
sEP + sIFE + uIFE	96%	94%	92%
FLCR	76%	88%	89%
sEP + sIFE + FLCR	96%	97%	-
sEP + sIFE + uIFE + FLCR	100%	98%	98%

The N-latex FLC assay, based on monoclonal antibodies, has similar diagnostic sensitivity alone (84%) and in combination with s and u IFE (98%).

However the Freelite and N-latex FLC assays are not interchangeable and either one should be used in the follow-up.

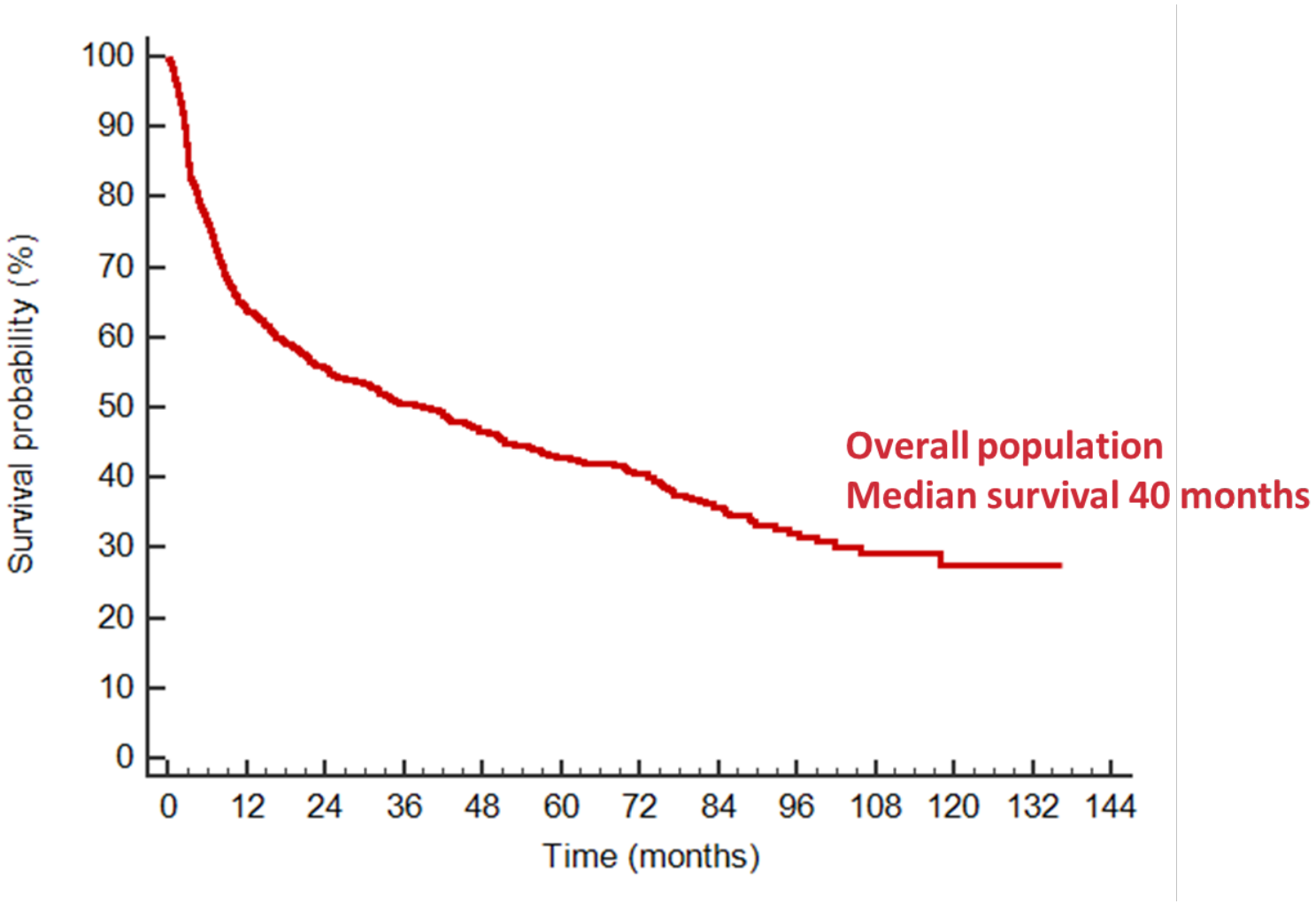
Palladini, et al. Clin Chem Lab Med 2017 in press

AL amyloidosis



[1]*Merlini & Stone, Blood 2006*

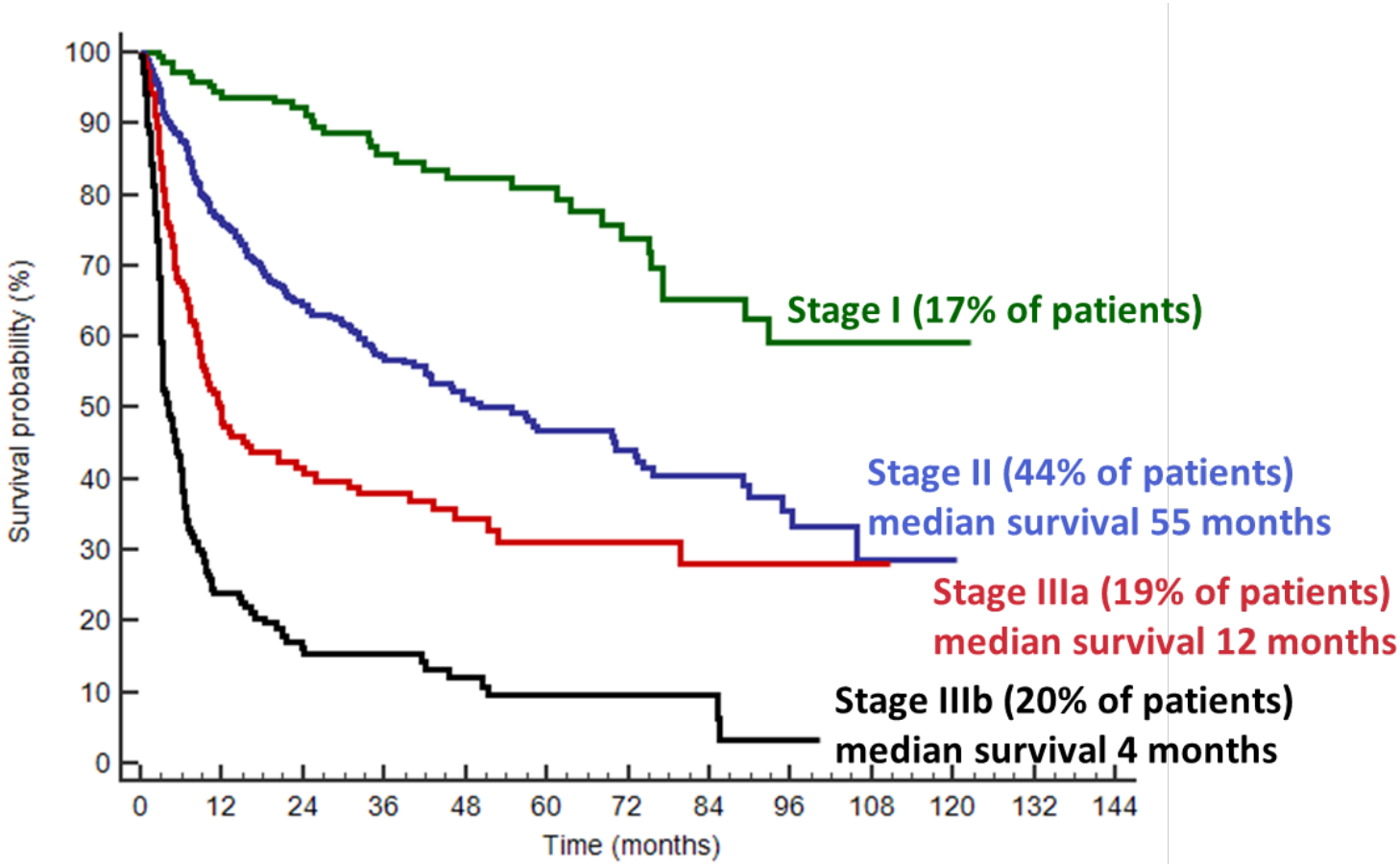
Survival of 984 patients with AL amyloidosis



Staging of AL amyloidosis

Dispenzieri, et al JCO 2004

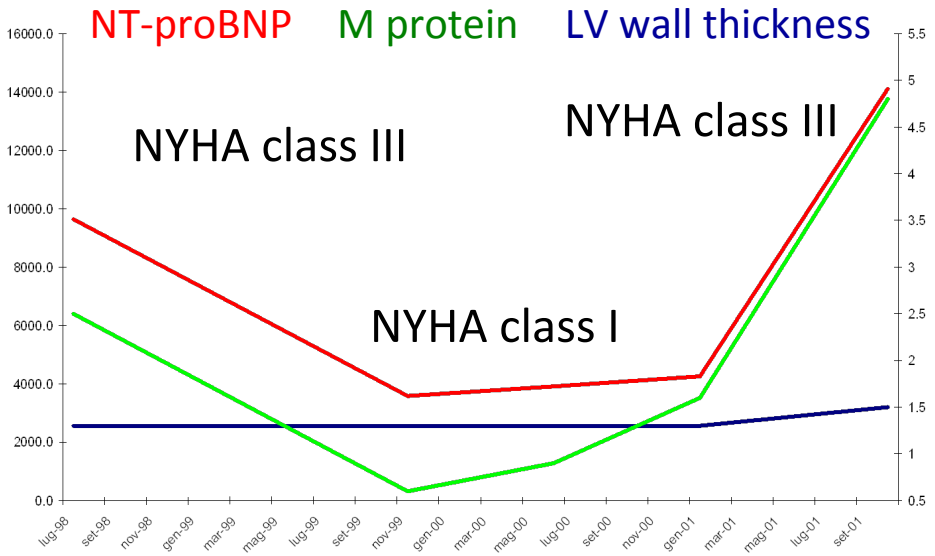
Wechalekar, et al Blood 2013



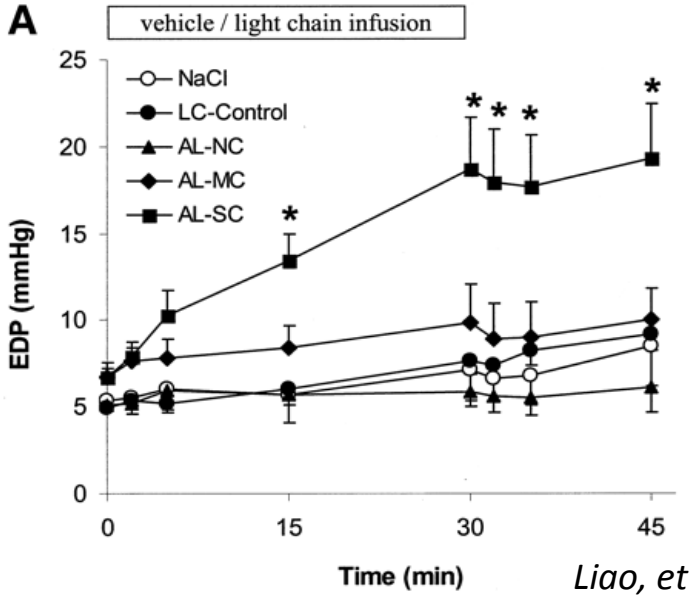
Staging is based on **NT-proBNP** (cutoff 332 ng/L) and **troponin I** (cutoff 0.1 ng/mL) with stage I, II, and III patients having 0, 1, or 2 both markers above the cutoffs

Very high (>8500 ng/L) NT-proBNP identifies patients with advanced cardiac dysfunction

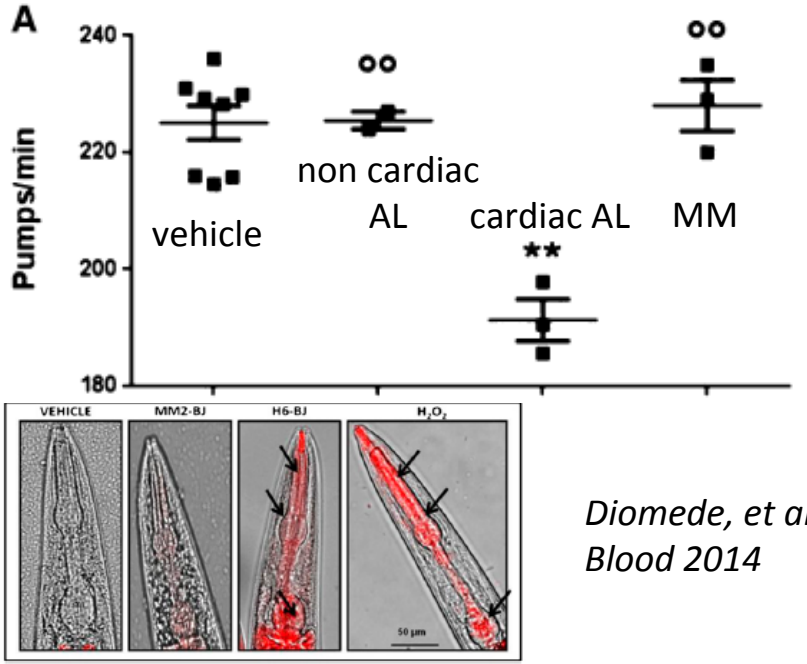
Amyloidogenic light chains are cardiotoxic



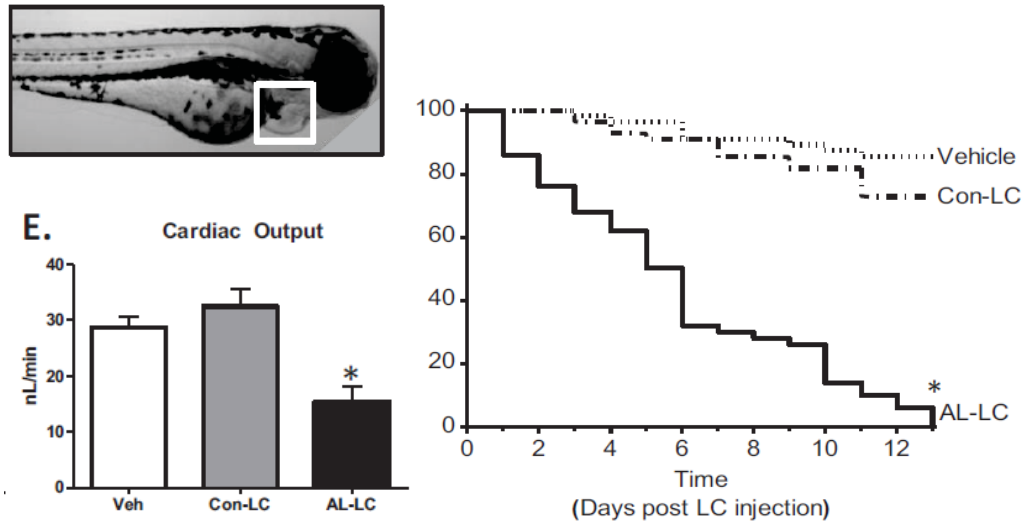
Palladini, et al. Circulation 2003; Palladini, et al. Blood 2006



Liao, et al. Circulation 2001



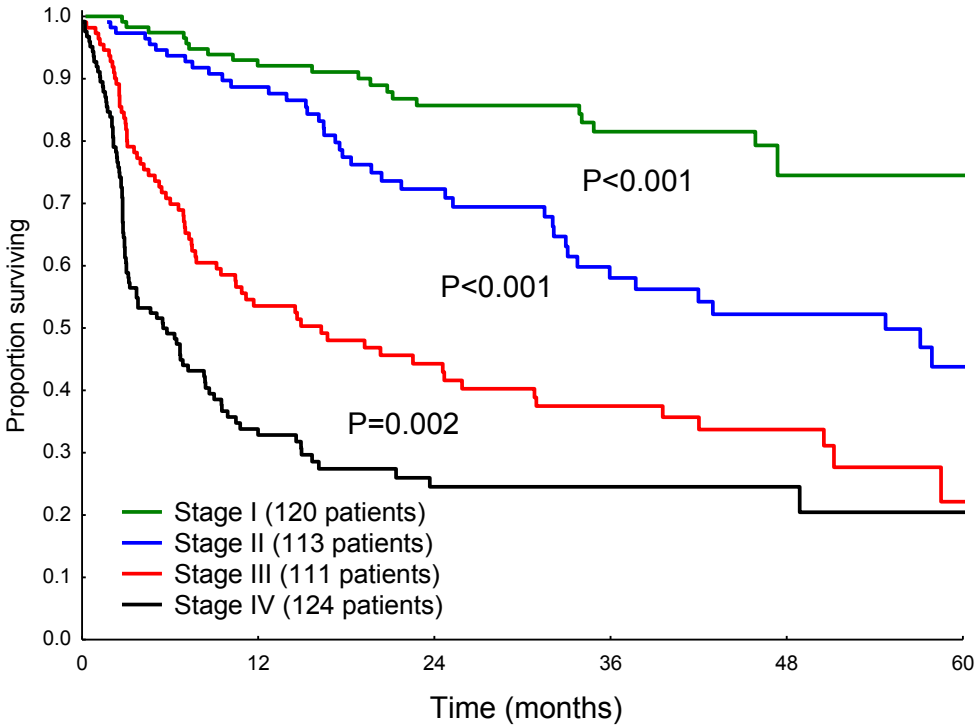
Diomede, et al. Blood 2014



Mishra, et al. Am J Physiol Heart Circ Physiol 2014

Clonal markers predict survival in AL amyloidosis

Survival according to the revised Mayo Clinic staging system including FLC in the Pavia series

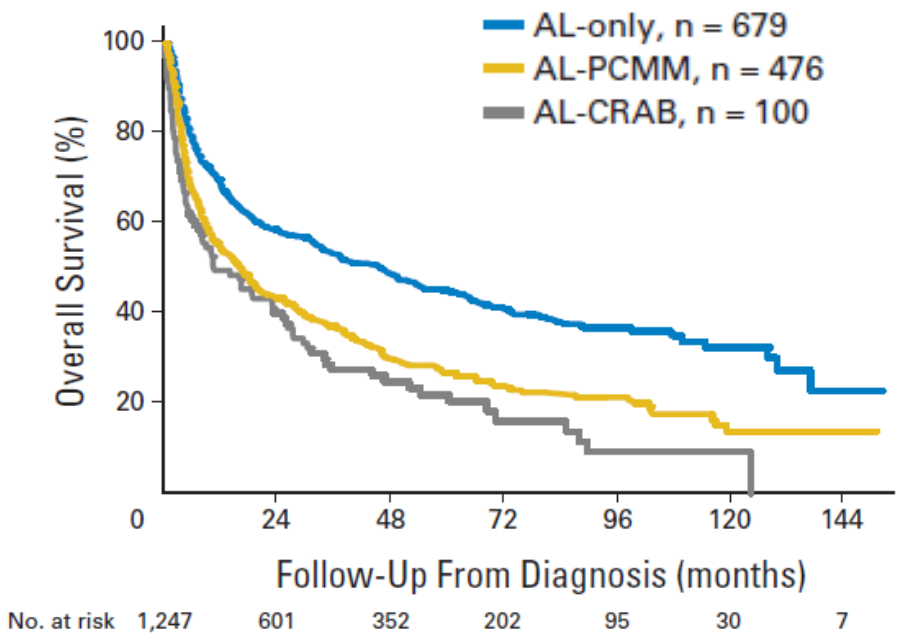


Revised staging system

NT-proBNP >1800 ng/L, cTnI >0.07 ng/L, dFLC >180 mg/L

Kumar, et al. JCO 2012
Kourelis, et al. JCO 2013

Survival according to BMPC infiltrate



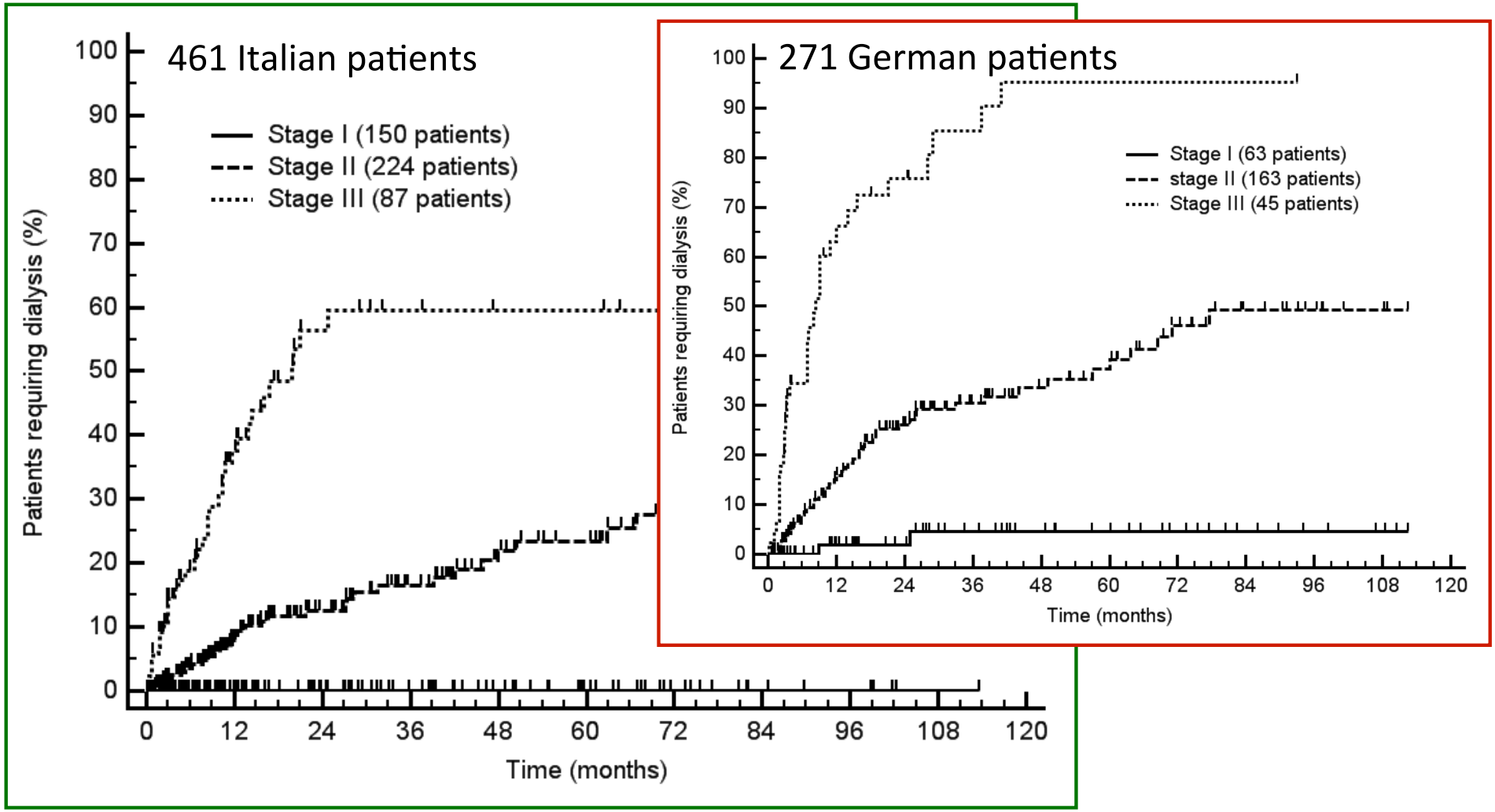
High frequency of t(11;14) translocation (~40-60%): lower benefit from bortezomib, greater benefit from melphalan

Patients with higher tumor burden benefit most from induction therapy pre-ASCT

Bochtler, et al. JCO 2015
Bochtler, et al. Blood 2016

Muchtar, et al. Leukemia 2016

A staging system for renal involvement



Palladini, et al. Blood 2014

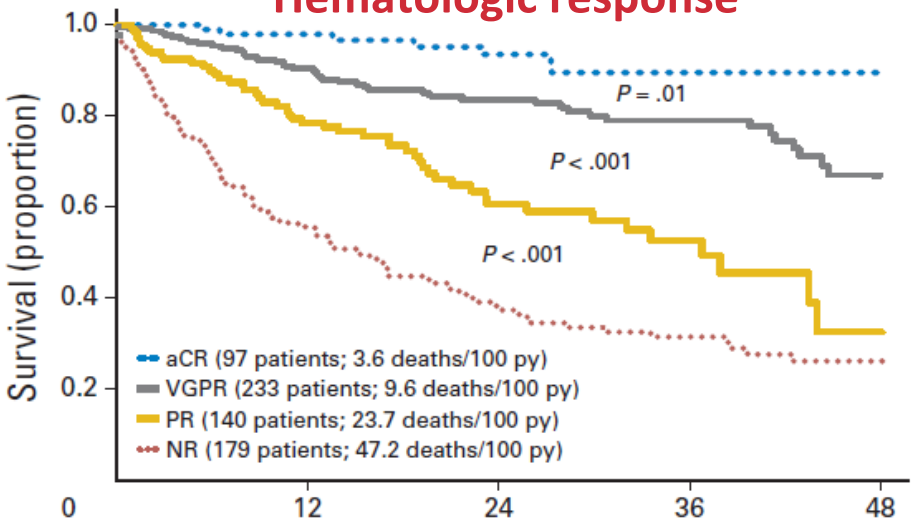
Stage I: both proteinuria ≤5g/24h and eGFR ≥50 mL/min per 1.73 m^2
Stage II: either proteinuria >5g/24h or eGFR <50 mL/min per 1.73 m^2
Stage III: both proteinuria >5g/24h and eGFR <50 mL/min per 1.73 m^2

Validated criteria for early assessment of response to chemotherapy in AL amyloidosis based on biomarkers

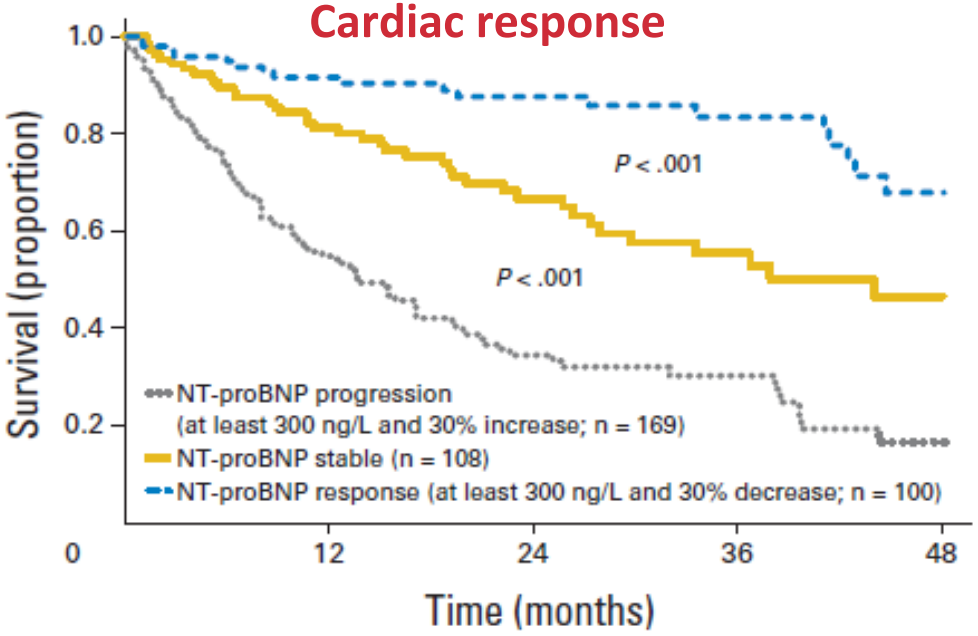
Response	Definition
Hematologic	**CR:** negative s&u IFE + normal FLCR **VGPR:** dFLC <40 mg/L **PR:** dFLC decrease >50%
Cardiac	NT-proBNP decrease >30% & >300 ng/L
Renal	Proteinuria decrease >30%

Response criteria were validate at 3 and 6 months after treatment initiation

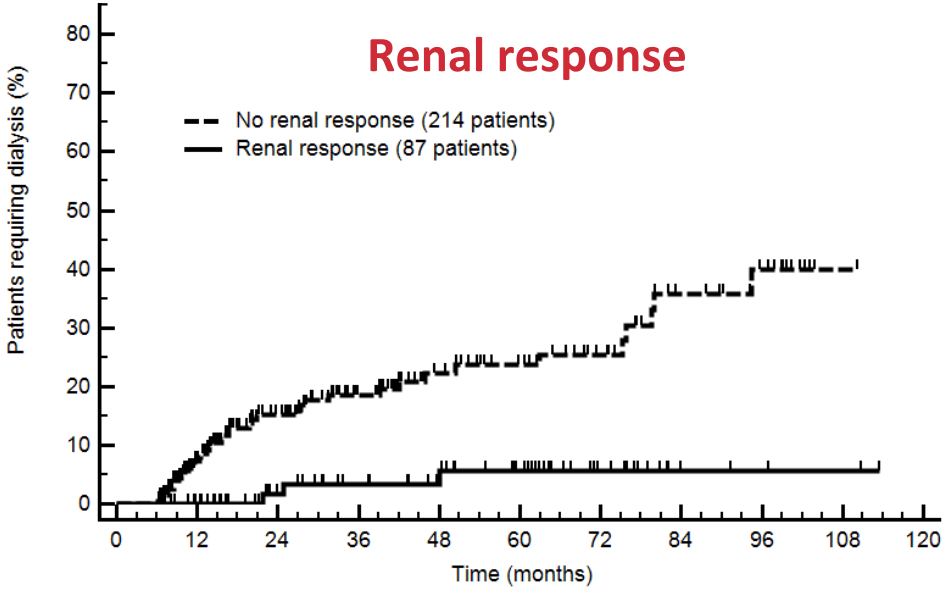
Hematologic response



Cardiac response



Renal response



Palladini, et al. JCO 2012
Palladini, et al. Blood 2014

Conclusion

- Management of AL amyloidosis is based on:
  - early diagnosis
  - unequivocal typing
  - assessment of organ dysfunction and staging
  - risk-adapted treatment design
  - close follow-up (every 2 months during chemotherapy, 3 months post-ASCT)

- **Biomarkers** of clonal and organ disease are crucial in these steps

- Overall, **clinical research** and **standard practice** still need to be coupled in AL amyloidosis

- Patients should be routinely referred to specialized centers / networks for diagnosis and evaluation of response

Acknowledgements

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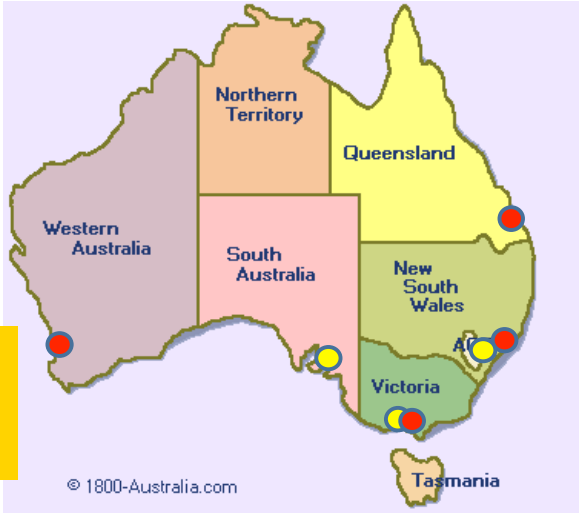
In order to make progress national and international collaboration is vital

EMN

Rotterdam and Torino

ALL G

Australasian Leukaemia & Lymphoma Group



Thank you !

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