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Die vielen Facetten der Amyloidose

16.03.2022

Dr. Urs Odermatt
KD Dr. Axel Rüfer
PD Dr. Simon Stämpfli
Prof. Dr. Einar Wilder-Smith

Häufigste Formen der systemischen Amyloidose

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Amyloid type	Precursor protein	Major organ involvement					
		Heart (bone tracer uptake)*	Kidney	Liver	PNS	ANS	ST
AL amyloidosis (acquired)	Immunoglobulin light chain	+++ (usually absent, can be intense)	+++	++	+	+	++
ATTRv amyloidosis (hereditary)	Mutated transthyretin	+++ (usually intense, can be absent in some variants)	—	—	+++	+++	—
ATTRwt amyloidosis (acquired)	Wild-type transthyretin	+++ (usually intense)	—	—	—	—	+
ApoAI amyloidosis (hereditary)	Mutated apolipoprotein AI	+ (present)	+	+++	—	—	—
AA amyloidosis (acquired)	Serum amyloid A protein	+	+++	+	—	+	—
ALECT2 (acquired)	Leukocyte chemotactic factor 2	—	+++	+	—	—	—

*Bone tracers validated for the detection of cardiac amyloidosis are ^{99m}Tc-diphosphono-propanodicarboxylic acid, ^{99m}Tc-pyrophosphate, and ^{99m}Tc-hydroxymethylene diphosphonate

Palladini G et al. Blood. 2020;136:2620-2627

AL Amyloidose

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AL: Rüfer/Odermatt

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		Heart (bone tracer uptake)*	Kidney	Liver	PNS	ANS	ST
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Palladini G et al. Blood. 2020;136:2620-2627

ATTR Amyloidose

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ATTR: Stämpfli/Wilder-Smith

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		Heart (bone tracer uptake)*	Kidney	Liver	PNS	ANS	ST
AL amyloidosis (acquired)	Immunoglobulin light chain	+++ (usually absent, can be intense)	+++	++	+	+	++
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Palladini G et al. Blood. 2020;136:2620-2627

10-15 - Minuten - Roundtable der Referenten - Zeit für Q&A

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Zuweisung gemäss «Leitproblem»

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- **Monoklonale Gammopathie → Hämatologie**
- **Niereninsuffizienz ± Proteinurie → Nephrologie**
- **Herzinsuffizienz → Kardiologie**
- **Polyneuropathie → Neurologie**

Luzerner Amyloidose Netzwerk (LAN) –
Teil des Schweizer Amyloidose Netzwerkes (SAN)

Was ist wichtig für Internisten und Hausärzte (u.a.)?

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72-jähriger Mann, Zentralschweizer

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- **31.07.2020 Externe Kardiologie Kantonsspital:**
  - **Echo ohne regionale Kinetikstörungen, normale linksventrikuläre Funktion**
  - **Ergometrie: BD-Abfall bei leichter Belastung: 100/70mmHg → 70/60mmHg**
  - **Zuweisung Herzkatheter LUKS bei Verdacht auf KHK**

- **05.08.2020 Herzkatheter LUKS:**
  Keine relevanten Stenosen

- **08/2020 Hausarztpraxis Zentralschweiz:**
  Unauffällige Serum-Protein-Elektrophorese (SPEP)

- **08/2020 12-Kanal-EKG LUKS:**
  Vorhof-Flattern

72-jähriger Mann, Zentralschweizer

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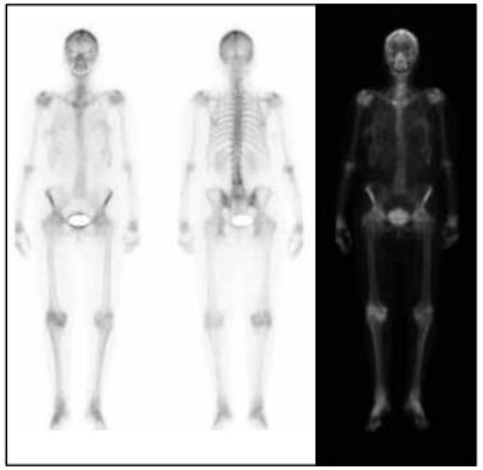
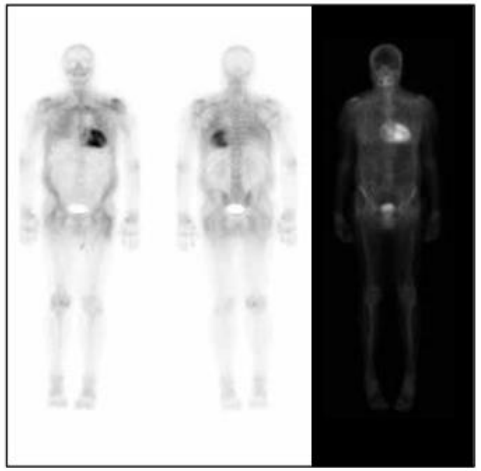
- **09/2020 MRI Herz LUKS:**
  Fortgeschrittene kardiale Amyloidose mit Beteiligung aller vier Herzhöhlen

- **09/2020 Technetium-Skelettszintigraphie (99mTc-HDP) LUKS:**
  Keine kardiale Anreicherung des Tracers

Normalbefund





TTR-Amyloidose

72-jähriger Mann, Zentralschweizer

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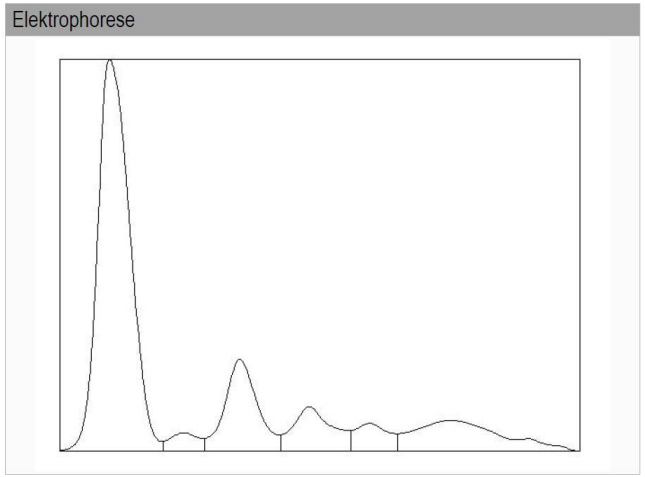
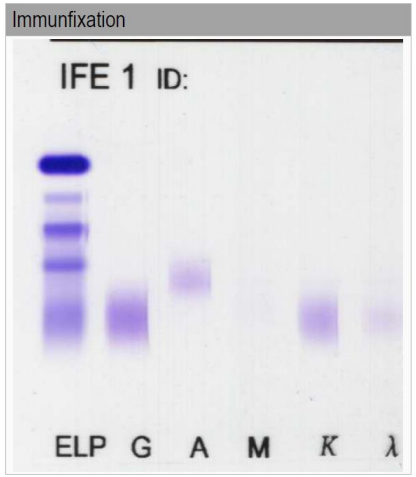
- **10/2020 LUKS:**
  - **SPEP mit Immunfixation (IF): Kein Hinweis auf monoklonale Banden**





  - **Freie Leichtketten: FLC lambda 103 mg/l (5.7-26.3), FLC kappa 20.5 (3.3-19.4)**

- **11/2020 Myokardbiopsie LUKS: Nachweis Amyloid - AL Amyloidose**

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- **23.12.2020 Hämatologie USZ auf Zuweisung Hausarzt:**
  - **FLC lambda 102.27 mg/l, dFLC 76 mg/l, NT-pro BNP 2458 ng/l**
  - **Organbefall: kardial, renal, gastrointestinal**

- **31.12.2020 Erstkonsultation Hämatologie LUKS auf Zuweisung Hämatologie USZ**

- **04.01.2021 Knochenmarkuntersuchung Hämatologie LUKS :**
  - **Aspirat / Biopsie: nicht vermehrte Plasmazellen, polyklonale Expression**
  - **Immunphänotypisierung: Lambda-klonale Plasmazell-Neoplasie (2% aller kernhaltigen Elemente im Plasmazell-Gate)**
  - **Zytogenetik: t(11;14)**

72-jähriger Mann, Zentralschweizer, mit systemischer AL Amyloidose

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- **Diagnosestellung mehr als 6 Monate nach ärztlichem Erstkontakt**

- **07.01.2021 Therapiebeginn mit Cyclophosphamid, Bortezomib, Dexamethason (CyBorD) – alles dosisreduziert**

- **13.01.2021 CyBorD kombiniert mit Daratumumab – analog ANDROMEDA-Studie**

- **14.01.2021 Patient verstorben – «Er ist am Morgen nicht mehr aufgewacht»**

Symptome und Zeichen bei AL Amyloidose

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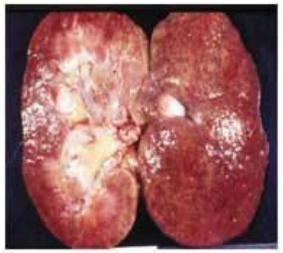
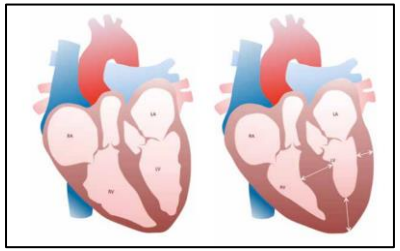
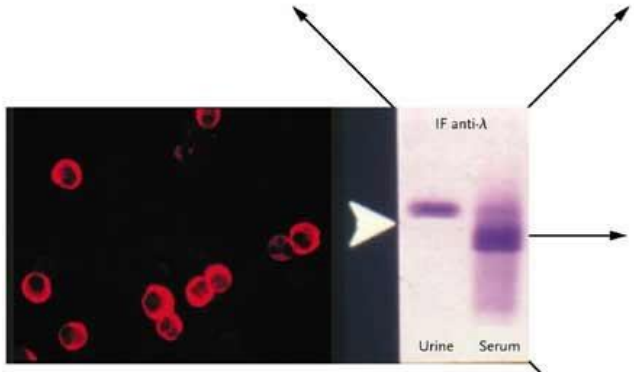
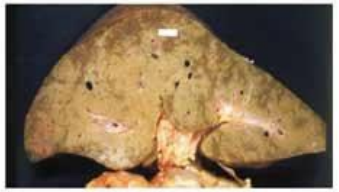


Kidney (46%)

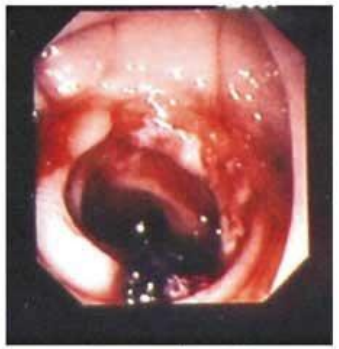
Heart (30%)



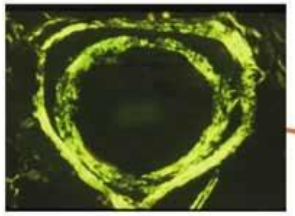


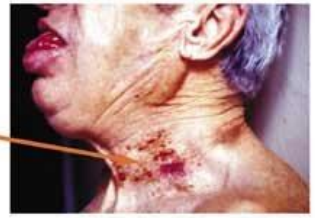


Liver (9%)



Gastrointestinal tract (7%)





Soft tissues (3%)

Peripheral nervous system (5%)

- **Nephrotisches Syndrom**

⇩

Renale Amyloidose? →

Dr. med. Urs Odermatt,
Chefarzt Nephrologie

Merlini G., Bellotti V. NEJM 2003;349:583-96

Typische Präsentation

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Klinik:	**Deutliche Ödeme**
	Blutdruck 132/71 mmHg
Urin:	**Mikrohämaturie meist diskret**
	Proteinurie 10 g/Tag
Blut:	**Kreatinin 74 µmol/l**
	Protein 52 g/l. Albumin 17 g/l
	Cholesterin 13.6 mmol/l
	Monoklonale Gammopathie IgA lambda

Renale Manifestation der Amyloidose

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Amyloid type	Kidney
AL amyloidosis (acquired)	+++
ATTRv amyloidosis (hereditary)	—
ATTRwt amyloidosis (acquired)	—
ApoAI amyloidosis (hereditary)	+
AA amyloidosis (acquired)	+++
ALECT2 (acquired)	+++

Palladini G et al. Blood. 2020;136:2620-2627

Pathophysiologie Proteinurie

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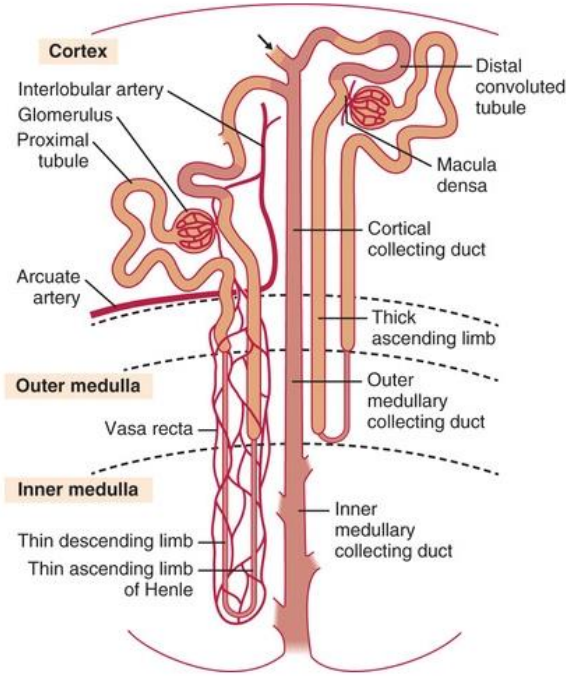
Nephron



Glomerulum

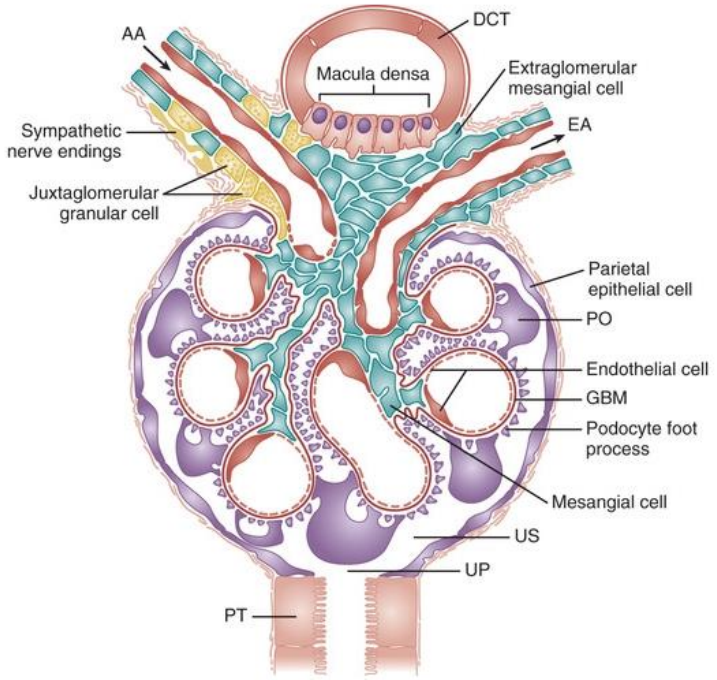


FIG. 1.4 Schematic diagram of a section of a glomerulus and its juxtaglomerular apparatus. *AA*, afferent arteriole; *DCT*, distal convoluted tubule; *EA*, efferent arteriole; *GBM*, glomerular basement membrane; *PT*, proximal tubule; *PO*, epithelial podocyte; *UP*, urinary pole; *US*, urinary space. (Previous edition, Fig. 1.3, Briggs J.)

PRIMER ON KIDNEY DISEASES, 7th Edition, National Kidney Foundation

Glomeruläre Proteinurie

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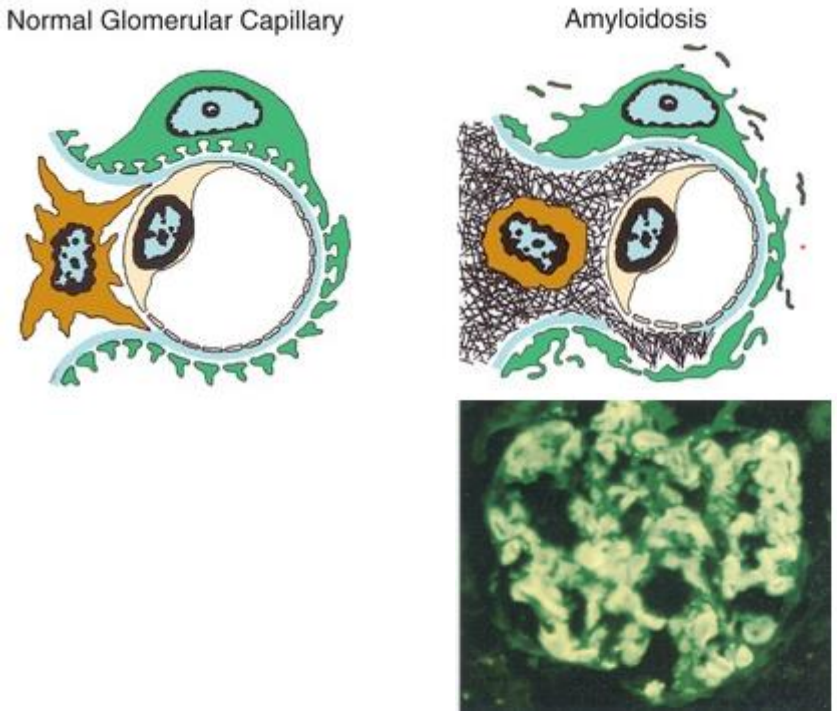
Die top 5

Tendencies of Glomerular Diseases to Manifest Nephrotic and Nephritic Features

Disease	Nephrotic Features	Nephritic Features
Minimal change disease	++++	–
Membranous nephropathy	++++	+
Diabetic glomerulosclerosis	++++	+
Amyloidosis	++++	+
FSGS	+++	++
Fibrillary glomerulonephritis	+++	++
Mesangioproliferative glomerulopathy[a]	++	++
Membranoproliferative glomerulonephritis[b]	++	+++
Proliferative glomerulonephritis[a]	++	+++
Acute postinfectious glomerulonephritis[c]	+	++++
Crescentic glomerulonephritis[d]	+	++++

Amyloidose



PRIMER ON KIDNEY DISEASES, 7th Edition, National Kidney Foundation

Histologie

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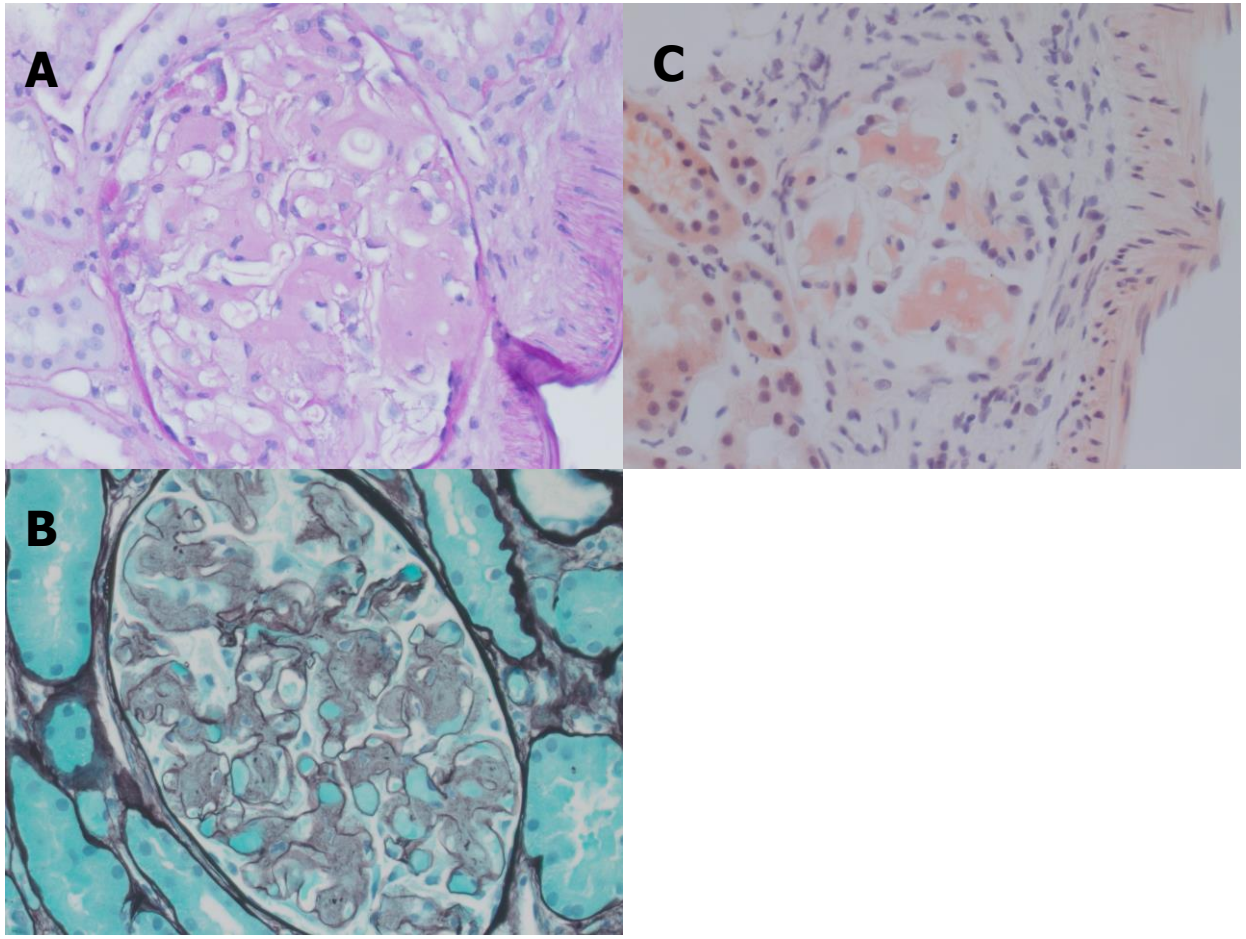

A: PAS

B: Silber Met.

C: Kongorot

D: Polarisation

In welchem Alter?

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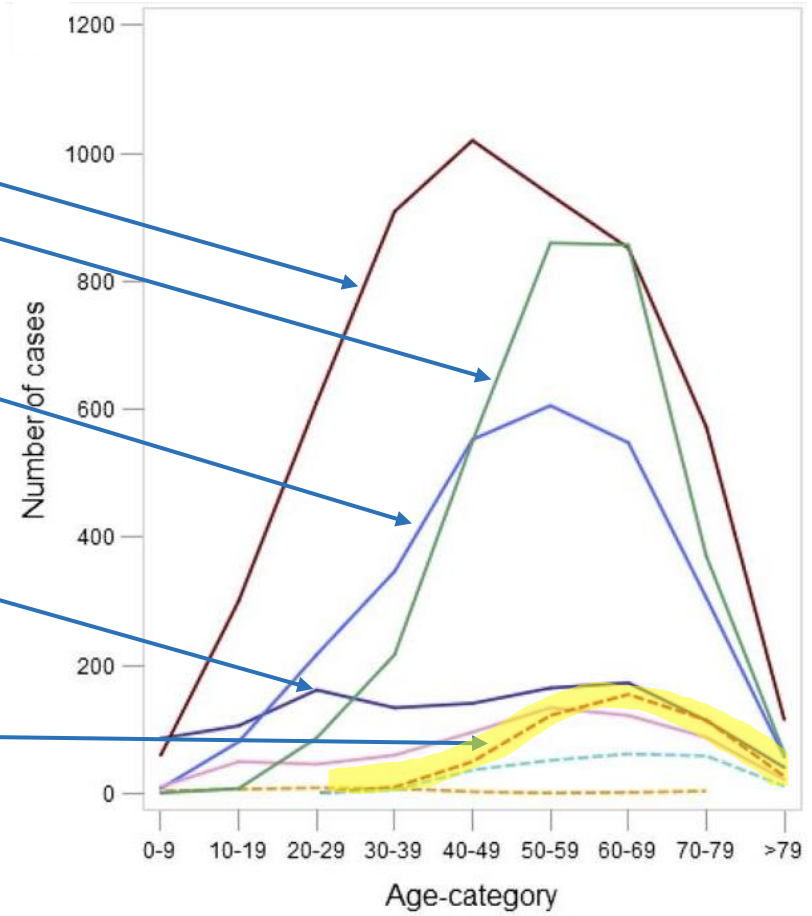
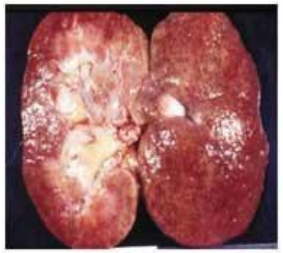
- **FSGS**
- **Diabetische Glomerulosklerose**
- **Membranöse Glomerulonephritis**
- **Minimal Change Disease (bei Kinder häufig, aber selten biopsiert)**
- **Amyloidose**



O'Shaughnessy MM, Hogan SL, Poulton CJ, et al. Temporal and demographic trends in glomerular disease epidemiology in the Southeastern United States, 1986–2015. Clin J Am Soc Nephrol. 2017;12:614-623

Symptome und Zeichen bei AL Amyloidose



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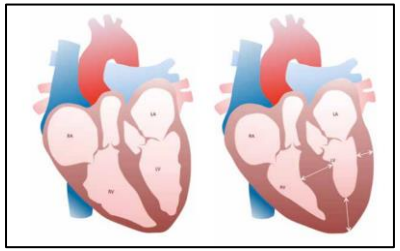

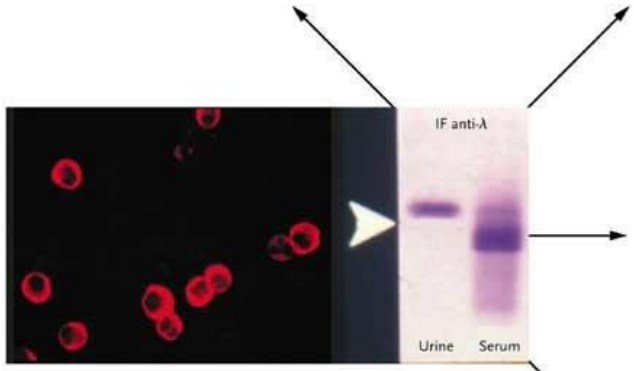

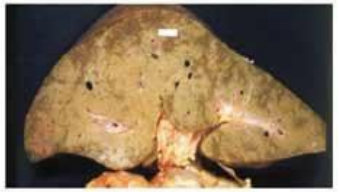

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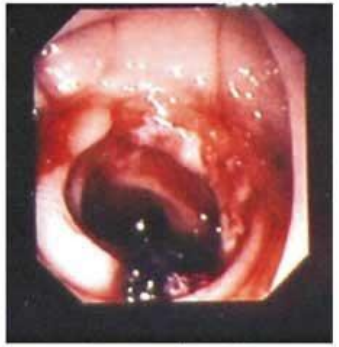

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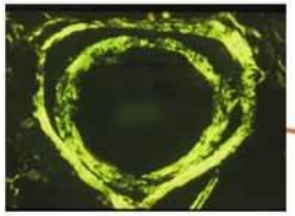

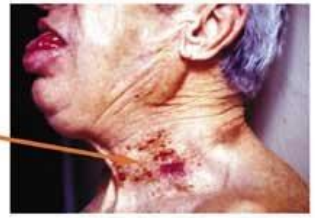

Soft tissues (3%)

Peripheral nervous system (5%)

- **Nephrotisches Syndrom**
- **Herzinsuffizienz mit erhaltener Ejektionsfraktion (HFpEF)**
- **Hepatomegalie mit Cholestase**
- **Mobilitätsstörungen GI-Trakt**
- **Periphere Neuropathie**
- **Orthostatische Hypotonie, Synkope**
- **Fatigue**
- **Gewichtsverlust**

Merlini G., Bellotti V. NEJM 2003;349:583-96

(Späte) Klinische Zeichen bei AL Amyloidose

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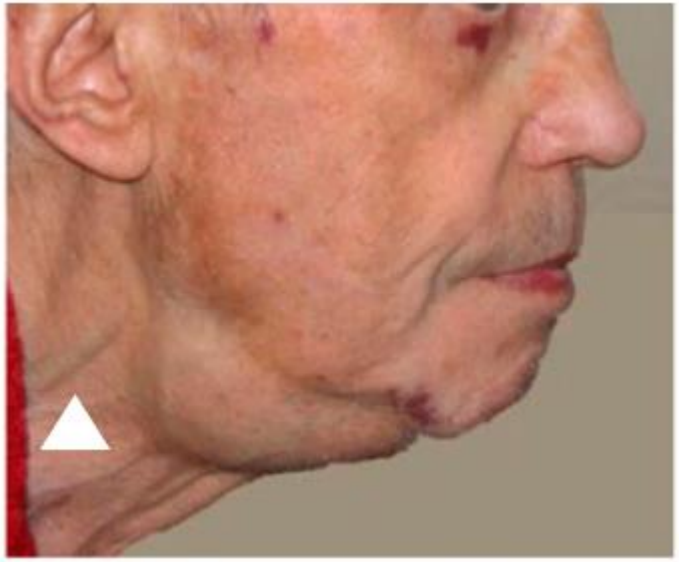
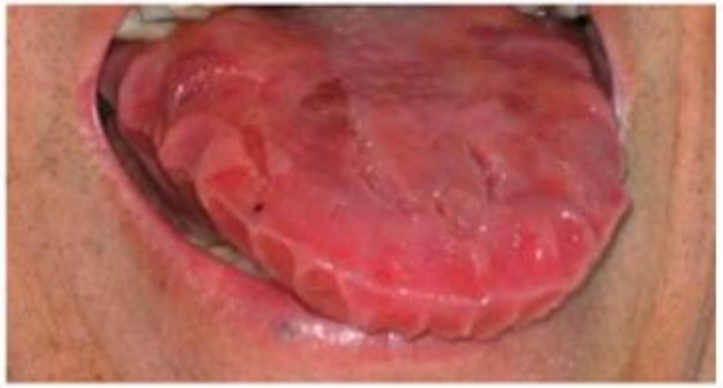
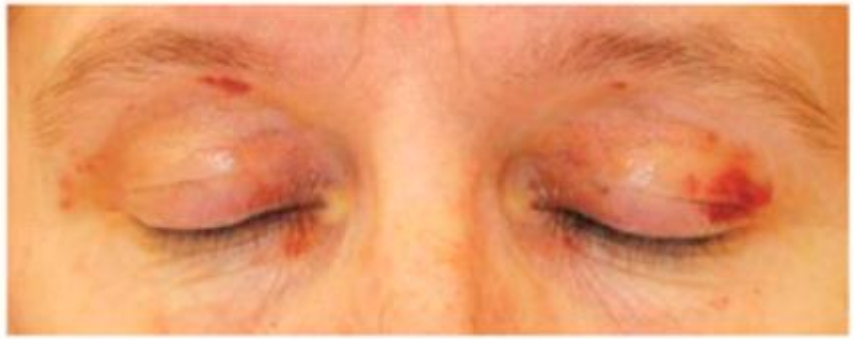


Jugular vein distention △
Submandibular gland swelling



Macroglossia



Periorbital purpura,
«Waschbärenaugen»

Merlini G. Blood. 2013;121:5124-30

Diagnostik – interdisziplinär und abhängig von klinischer Präsentation

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Evaluation	Hematology	Cardiology	Nephrology	Neurology	Gastro-enterology	General
Clinical examination	- Signs of hypercalcemia? - Signs of anemia? - Signs of bone disease?	- Signs of heart failure?	- Peripheral edema?	- Polyneuropathy? - Schellong test	- Hepato-/ Splenomegaly?	- Macroglossia? - Racoon eyes? - Shoulder pad sign?
Laboratory analysis	Full blood count + reticulocytes - Coagulation studies as clinically appropriate (e.g., factor X) - Type and screen	- NTproBNP - Troponin T	- Creatinine - Electrolytes - Albumin - Albumin/ creatinine ratio - Protein - Protein/ creatinine ratio - 24 h urine (optional)	- Anti-MAG-antibodies (especially in IgM monoclonal gammopathy)	- ALAT - ASAT - Alkaline phosphatase - GGT - Bilirubin	- SPEP+IF (serum and urine) - FLC - CRP - TSH, fT4 - Calcium - Albumin - Protein - Holotranscobalamin/ Vitamin B12 - Hepatitis B - HIV
Additional investigations	- Bone marrow aspirate with immunophenotyping and cytogenetic analysis (FISH) - Bone marrow biopsy with Congo red stain	- Blood pressure - Schellong test - ECG - Holter ECG - Echocardiography, transthoracic (- MRI) (- myocardial biopsy)	(- Ultrasound) (- Kidney biopsy)	- Nerve conduction studies (- Nerve biopsy)	(- Ultrasound) (- Colonoscopy with biopsy) (- Esophago-gastroduodenoscopy with biopsy)	

Rüfer A, Schwotzer R. healthbook TIMES Onco Hema 2021;(8):32-41

Biopsie- oder Szintigraphie-basierte Diagnostik?

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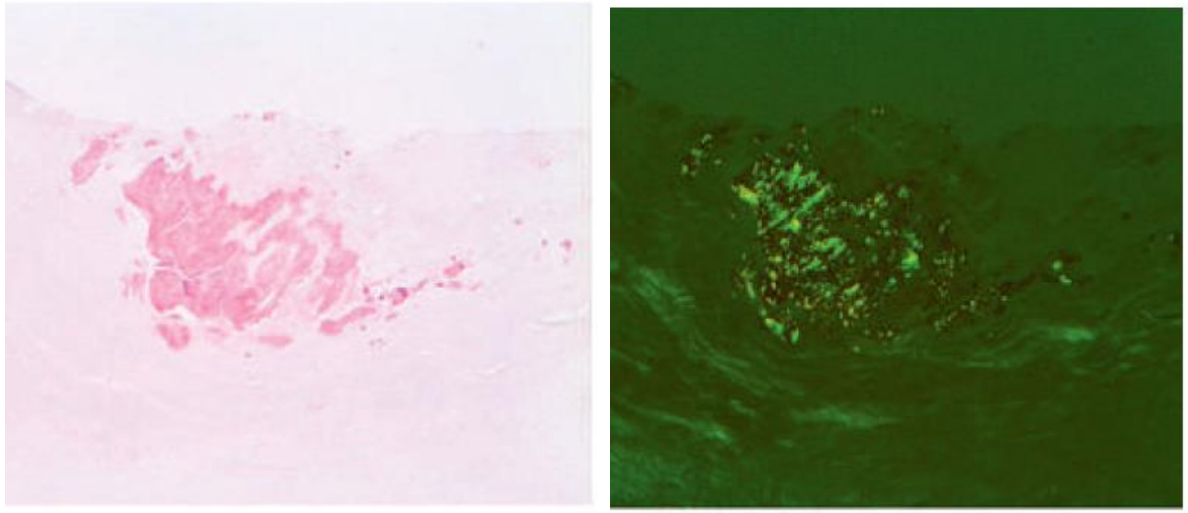
- **Symptomgeleitete Diagnose ist oft zu spät**
- **Präsymptomatische Diagnose ist möglich**
- **1. Schritt: Monoklonale Gammopathie?**

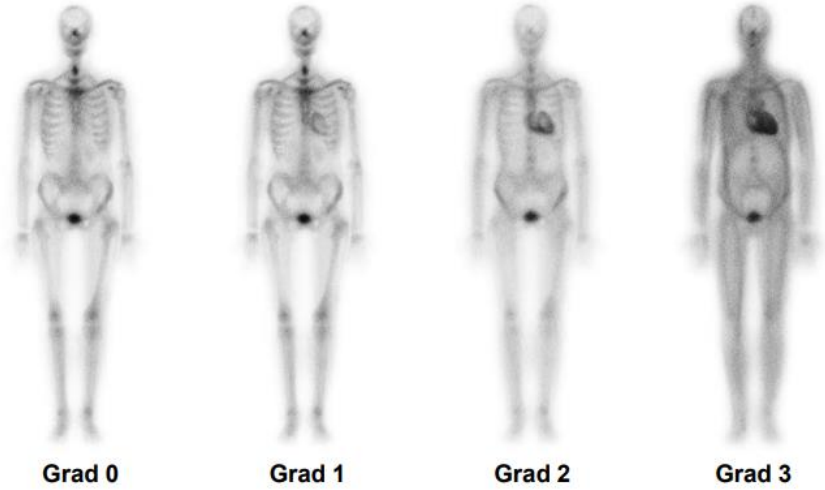
YES **NO**



Kongorot-Färbung

Amyloid färbt sich homogen rot

Polarisiertes Licht: Amyloid leuchtet grün



Perugini Score

Diagnostik

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- **Symptome und Zeichen: SPEP + IF + FLC**
- **Bekanntes Paraprotein («MGUS»): Biomarker**

- **NT-proBNP > 332 ng/l (100% sensitivity)**
- **Urinary albumin > 0.5 g/day**
- **Alkalische Phosphatase**

- **Biopsie: KM (diagnostische Sensitivität 70%, immer mit Zytogenetik), Bauchfett (80%), Speicheldrüsen (80%), involvierte Organe (Niere, Herz, Nerven)**
- **Typisierung: Immunhistochemie (Lichtmikroskop, Elektronenmikroskop), Massenspektrometrie**

4-Quadranten FNP Bauchfett Hämatologie LUKS

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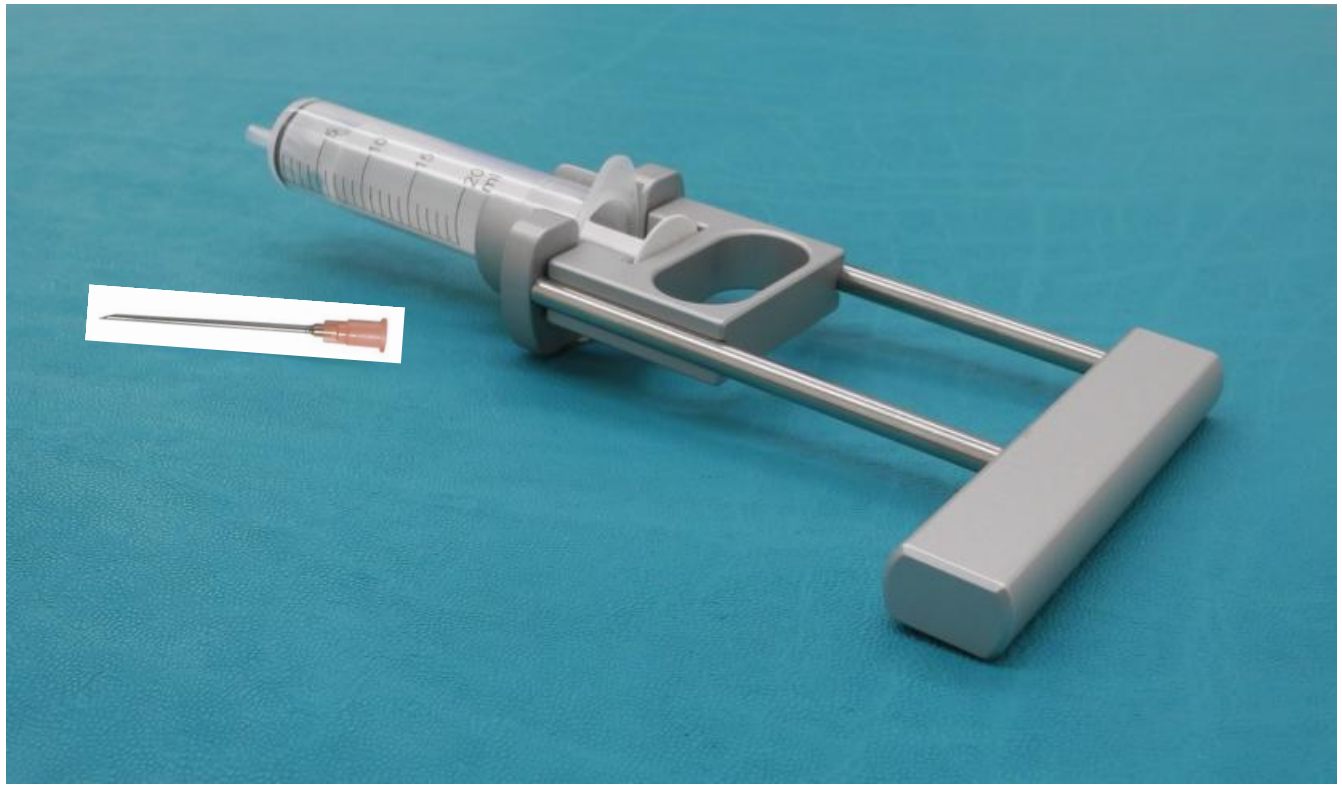
EUROPEAN CANCER CENTRES
JACIE joint accreditation committee isct emst



Staging

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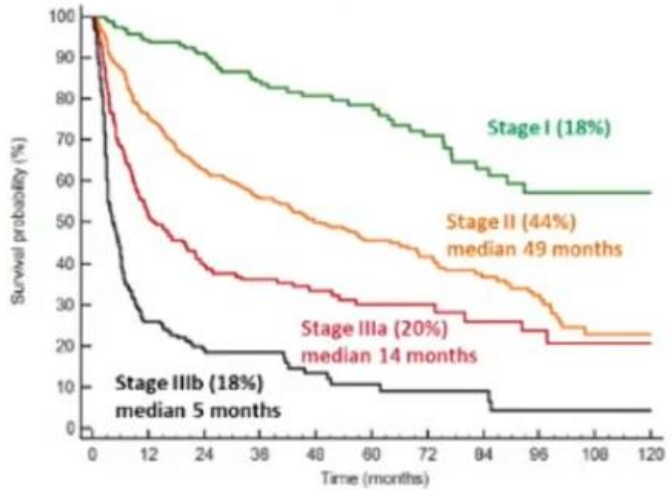
Entscheidend für Prognose:
Menge der freien Leichtketten + Schwere des Herzbefalls

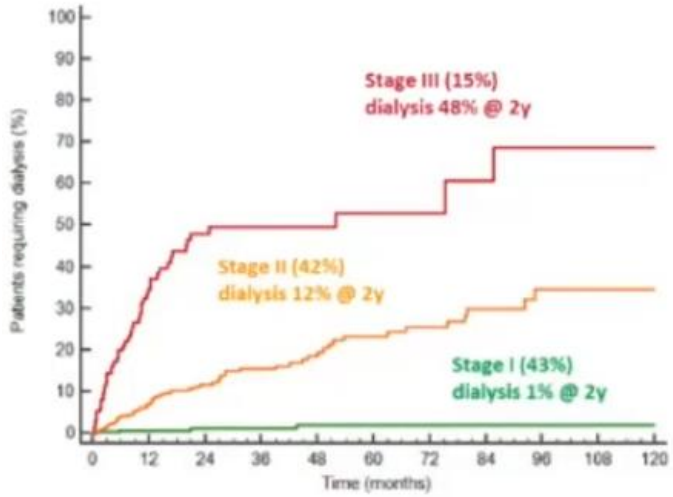
Mayo Clinic / European staging system



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 markers above the cutoffs.
Very high (>8500 ng/L) NT-proBNP identifies patients with advanced cardiac dysfunction (Stage IIIb)

Dispenzieri A et al. JCO 2004,
Wechalekar AD et al. Blood 2013

Renal staging system



- 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

Palladini G et al. Haematologica 2014,
Palladini G et al. Blood 2014

72-jähriger Mann, Zentralschweizer

- **Stadium IIIa**
- **Renales Stadium I**

Risikostratifizierung

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Low-risk patients, eligible for ASCT (~20% of patients)

- Age <70 years
- ECOG PS <2
- NT-proBNP <5000 ng/L
- cTnT <60 ng/L
- Left ventricular EF >45%
- NYHA class <III
- Systolic blood pressure ≥100 mmHg
- eGFR >50 mL/min per 1.73 m^2 unless on dialysis
- Bilirubin >2 mg/dL
- DLCO >50%

Assess relevant comorbidities

72-jähriger Mann, Zentralschweizer

Intermediate-risk patients, ineligible for ASCT, cardiac stage I-IIIa (~60% of patients)

Assess presence of potentially reversible contraindication to ASCT and relevant comorbidities

High-risk patients (~20% of patients)

- Cardiac stage IIIb
- NYHA class III of IV
- ECOG PS = 4

Assess relevant comorbidities

Palladini G et al. Blood. 2020;136:2620-2627

Low-risk patients, eligible for ASCT (~20% of patients)

Intermediate-risk patients, ineligible for ASCT, cardiac stage I-IIIa (~60% of patients)

High-risk patients (~20% of patients)

Consider bortezomib-based induction therapy if

- BMPC >10%
- or foreseeable delay before ASCT
- and no contraindications to bortezomib

High rates of deep and durable hematologic responses can be achieved with bortezomib-based therapy alone

ASCT (melphalan 200 mg/m^2)

Consider bortezomib-based "consolidation" therapy if

- <VGPR/CR
- and no contraindications to bortezomib

CyBorD + daratumumab if accessible

If daratumumab is not accessible, consider:

- **CyBorD**. Preferred in patients with potentially reversible contraindications to ASCT and in those with eGFR <30 mL/min per 1.73 m^2. Less effective in patients whose clonal PC harbor the t(11;14)
- **BMDex**. Potentially overcomes the effects of both t(11;14) and gain 1(q21)
- **MDex, LMDex, CLD.** Useful in patients with contraindication to bortezomib

Options currently being evaluated and awaiting more data:

- Carfilzomib in patients with peripheral neuropathy without relevant heart involvement
- Venetoclax in patients with t(11;14)

Palladini G et al. Blood. 2020;136:2620-2627

Es gibt gute Gründe, an die Amyloidose zu denken, weil …

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- … eine frühe Diagnose
  - das Gesamt-Überleben verbessert
  - die Organfunktionen schützt
  - zu mehr therapeutischen Optionen führt
  - eine bessere Lebensqualität bedeutet
- … validierte Biomarker (NT-pro BNP, Albuminurie) existieren, die eine
  - frühe Diagnose
  - risikoadaptierte Therapie
  - Beurteilung des Ansprechens ermöglichen
- … therapeutische Optionen bestehen
  - Standard bei AL Amyloidose: Daratumumab – CyBorD (Ausnahme: cardiac stage IIIb)