Thursdays Webinars

EuroBloodNet

# Treatment of Amyloidosis

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**11. 02. 2020 17:00**

Co-funded by the Health Programme of the European Union

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Network Hematological Diseases (ERN EuroBloodNet)

- Advisory Boards

  Janssen, Prothena, Takeda

- Travel and congress participation grants

  Janssen, Prothena, Celgene, Binding Site, Jazz

- Honoria

  Janssen, Celgene, Pfizer

- Research support

  Sanofi, Celgene, Janssen

# Learning objectives of the webinar

1. Diagnosis and Staging of AL Amyloidosis
2. Choices of first-line treatment
3. Impact of clonal markers

# Amyloidoses are protein misfolding and deposition disorders

- local – systemic
- hereditary – acquired
- associated with „aging“
- All organs might be involved
- **Local amyloid deposition** in
  - Alzheimer, Parkinson, Huntington and Prion diseases
  - Diabetes mellitus
- **Underlying conditions in systemic amyloidosis** are
  - chronic inflammation
  - clonal bone marrow disease
  - genetic diseases
- **Causes of misfolding or deposition are not well understood**
  - Overproduction and
  - Mutations or other modifications of the precursor protein
  - Impairment of protein homeostasis

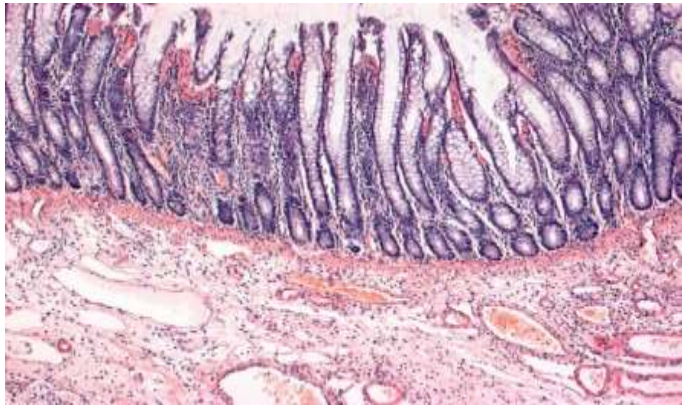
**Table 1.** Amyloid fibril proteins and their precursors in human[a].

| Fibril protein | Precursor protein | Systemic and/or localised | Acquired or hereditary | Target organs |
|---|---|---|---|---|
| AL | Immunoglobulin light chain | S, L | A, H | All organs, usually except CNS |
| AA | (Apo) serum amyloid A | S | A | All organs except CNS |
| ATTR | Transthyretin, wild type | S | A | Heart mainly in males, lung, ligaments, tenosynovium |
| | Transthyretin, variants | S | H | PNS, ANS, heart, eye, leptomeninges |
| AApoCIII | Apolipoprotein C III, variants | S | H | Kidney |
| AGel | Gelsolin, variants | S | H | Kidney<br>PNS, cornea |
| ALys | Lysozyme, variants | S | H | Kidney |
| ALECT2 | Leukocyte chemotactic factor-2 | S | A | Kidney, primarily |
| AFib | Fibrinogen α, variants | S | H | Kidney, primarily |
| ACys | Cystatin C, variants | S | H | CNS, PNS, skin |
| ABri | ABriPP, variants | S | H | CNS |
| ADan[b] | ADanPP, variants | L | H | CNS |
| Aβ | Aβ protein precursor, wild type | L | A | CNS |
| | Aβ protein precursor, variant | L | H | CNS |
| AαSyn | α-Synuclein | L | A | CNS |
| ATau | Tau | L | A | CNS |
| APrP | Prion protein, wild type | L | A | CJD, fatal insomnia |
| | Prion protein variants | L | H | CJD, GSS syndrome, fatal insomnia |
| | Prion protein variant | S | H | PNS |
| ACal | (Pro)calcitonin | L | A | C-cell thyroid tumours |
| | | S | A | Kidney |
| AIAPP | Islet amyloid polypeptide[c] | L | A | Islets of Langerhans, insulinomas |
| AANF | Atrial natriuretic factor | L | A | Cardiac atria |
| APro | Prolactin | L | A | Pituitary prolactinomas, aging pituitary |
| AIns | Insulin | L | A | Iatrogenic, local injection |
| ASPC[d] | Lung surfactant protein | L | A | Lung |
| ACor | Corneodesmosin | L | A | Cornified epithelia, hair follicles |
| AMed | Lactadherin | L | A | Senile aortic, media |
| AKer | Kerato-epithelin | L | A | Cornea, hereditary |
| ALac | Lactoferrin | L | A | Cornea |
| AOAAP | Odontogenic ameloblast-associated protein | L | A | Odontogenic tumours |
| ASem1 | Semenogelin 1 | L | A | Vesicula seminalis |
| AEnf | Enfurvitide | L | A | Iatrogenic |
| ACatK[e] | Cathepsin K | L | A | Tumour associated |
| AEFEMP1[e] | EGF-containing fibulin-like extracellular matrix protein 1 (EFEMP1 | L | A | Portal veins<br>Aging associated |

[a]Proteins are listed, when possible, according to relationship. Thus, apolipoproteins are grouped together, as are polypeptide hormones.
[b]ADan is the product of the same gene as ABri.
[c]Also called amylin.
[d]Not proven by amino acid sequence analysis.
[e]Full amino acid sequence to be established.

# Diagnosis of systemic amyloidosis

- **Biopsy is obligatory** (except ATTRwt)
  - Congo Red Staining
  - Amyloid typing
    - Immunhistochemistry
    - Immunogold electron microscopy (Italy)
    - MALDI (USA, Great Britain)
- **Exclusion of hereditary forms**
- **Screening biopsies**
  - Subcutanous fat — Sensitivity (AL) 80-90%
  - Deep rectal biopsy — 40-80%
  - Bone marrow biopsy — 60%



Inst. of. Pathology, Univ. HD

# Treatment principles for systemic amyloidosis

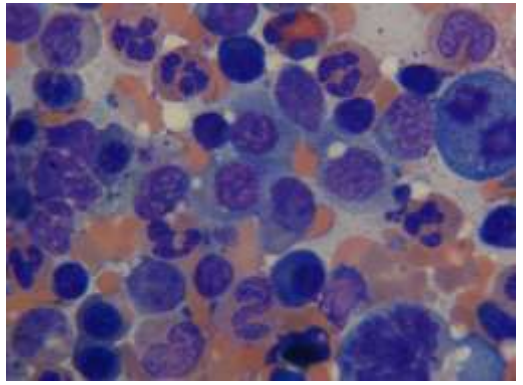
- **Reduce production of amyloidogenic proteins**
  - Chemotherapy / Antibodies / stem cell transplantation (AL)
  - Gene therapy (siRNA, anti-sense) and liver transplantation (ATTRmt)
  - Anti-inflammatory treatment (AA)
- **Prevent protein misfolding and deposition**
  - Tafamidis, Diflunisal (ATTR)
  - *EGCG (ATTR; AL)*
  - *Doxycycline (AL, B2MG)*
- **Reduce amyloid load**
  - *Antibodies against amyloid fibrils and precursor*
- **Symptomatic treatment**
  - Heart (AL, ATTR) and Kidney (AL, rare hereditary forms) transplantation
  - Diuretics / analgetics/ nutrition

# Systemic Light Chain (AL) Amyloidosis

- Rare disease
  - Incidence: about 10 first diagnoses / Mio. / year
- Median age at first diagnosis 65 years
- Male are at higher risk than females
- Involvement of heart and kidneys are to the fore

# Systemic AL amyloidosis

## Underlying disease, well characterized



Dept. Of Hematology, Univ. HD

**Clonal B cell disorder** producing free light chains (FLC)

- Plasma cell dyscrasia with monoclonal gammopathy
  - Symptomatic multiple myeloma in < 10%
  - Rarely other B cell lymphoma like M. Waldenström and MCL
- Clone is usually small (<20% of the bone marrow cells) and low proliferative

- **Most common form of MGCS** (monoclonal gammopathy of clinical significance)

# Cytogenetic aberration in the plasma cells of AL Amyloidosis

High Sensitivity of iFISH after CD138 enrichment (>95%)

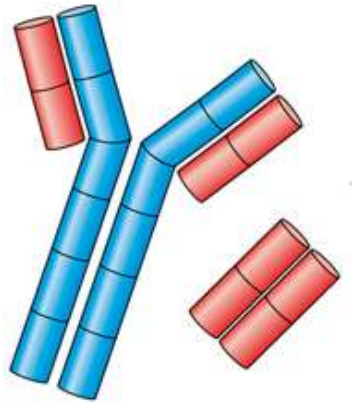
- **Translocation t(11;14)** in 50%
  - light chain only / Bence Jones type
  - Genetic stable, only few subclones, less proliferation
- High risk aberrations (t(4;14), deletion del17p) in < 10%
- **Gain of 1q21** in 20%
  - higher plasma cell infiltration of the bone marrow
  - lambda light chain restriction
- Hyperdiploidy (def. by Wuillame et al.), in 11%
  - kappa light chain restriction
  - higher plasma cell infiltration
  - Higher age at diagnosis and heavy chain type



Bochtler et al., *Blood* 2008 and 2011, *Blood advances* 2018

# Systemic AL amyloidosis

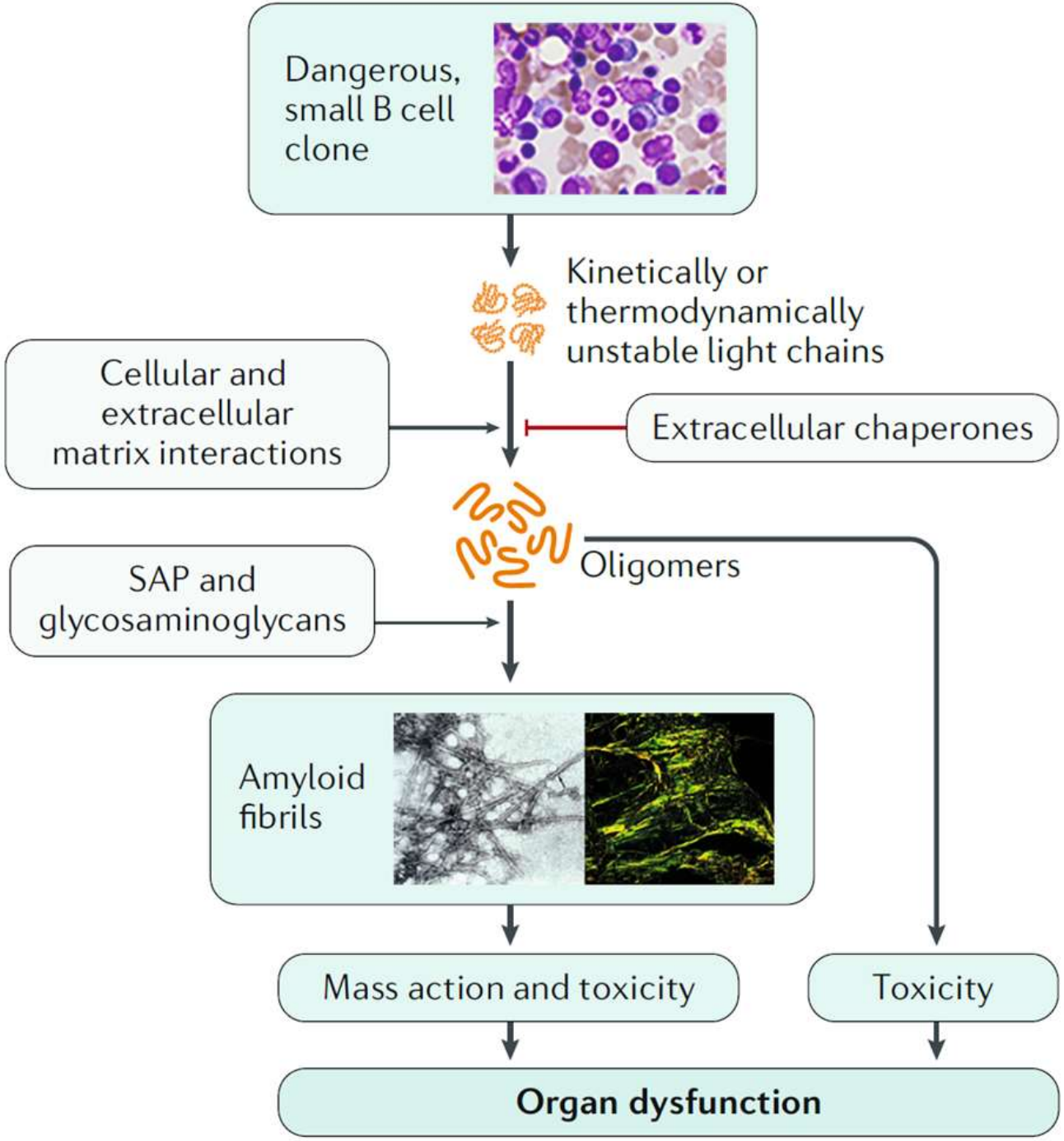
## Pathologic agents are not well characterized

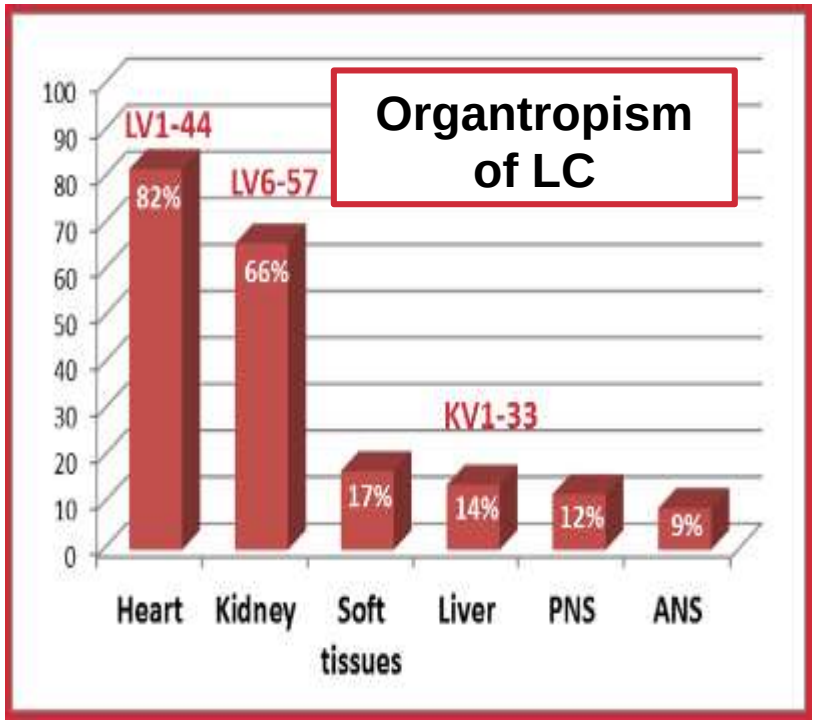


## Free light chain (FLC)

- Without heavy chain in 50% of patients
- Isotype more lambda than kappa (3:1)
- Can be reliably measured in the serum
  - Different amounts (<10 to > 1000 mg/l)
  - Lower levels associated with kidney involvement, higher with cardiac.
- Sequence patient specific

# Pathogenesis of systemic AL amyloidosis



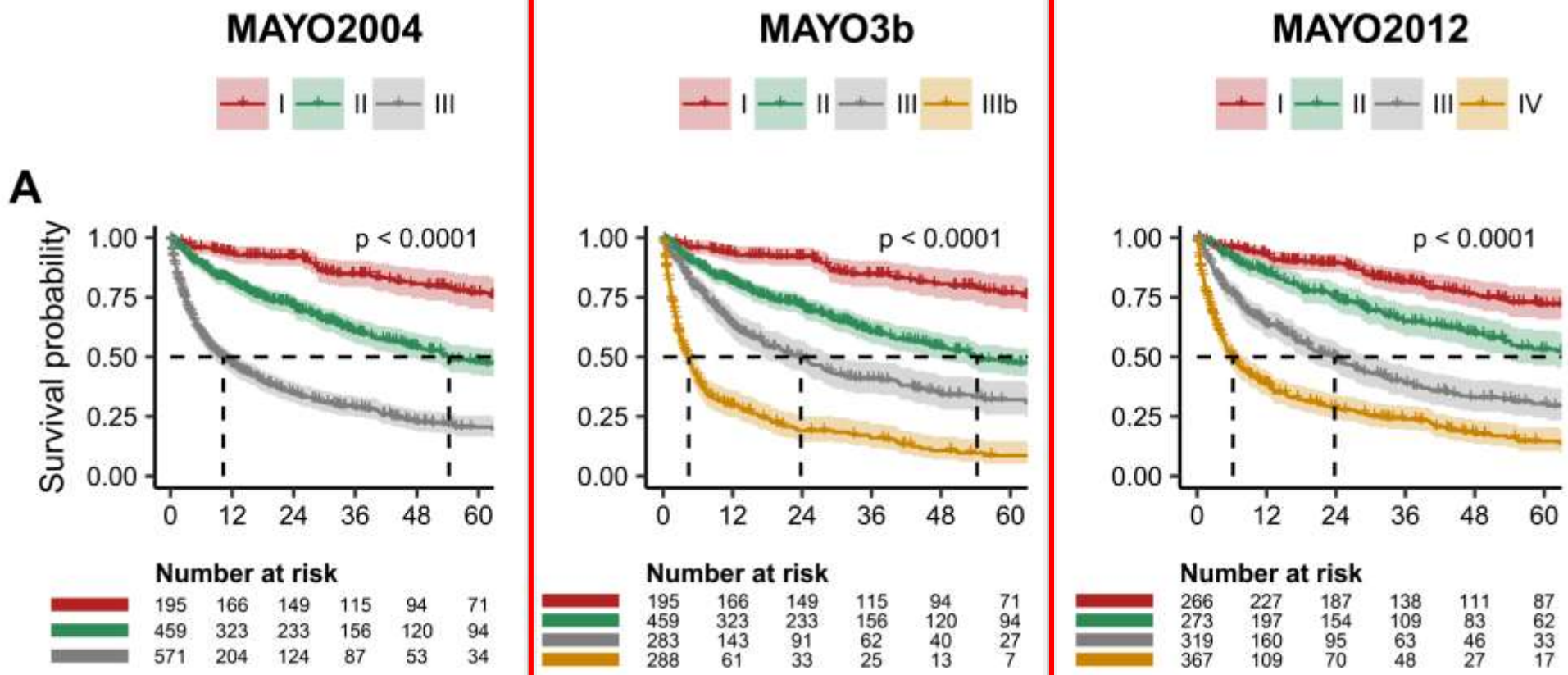

Merlini, G. et al. (2018) *Nat. Rev. Dis. Primers*

# Prognosis – Overall Survival

**NT-BNP** > 320
cTNT > 0.03

**NT-BNP** > 320 / **8500**
cTNT > 0.03

**dFLC** >180
**NT-BNP** > 1800
cTNT > 0.025




Dittrich et al., *Haem* 2019

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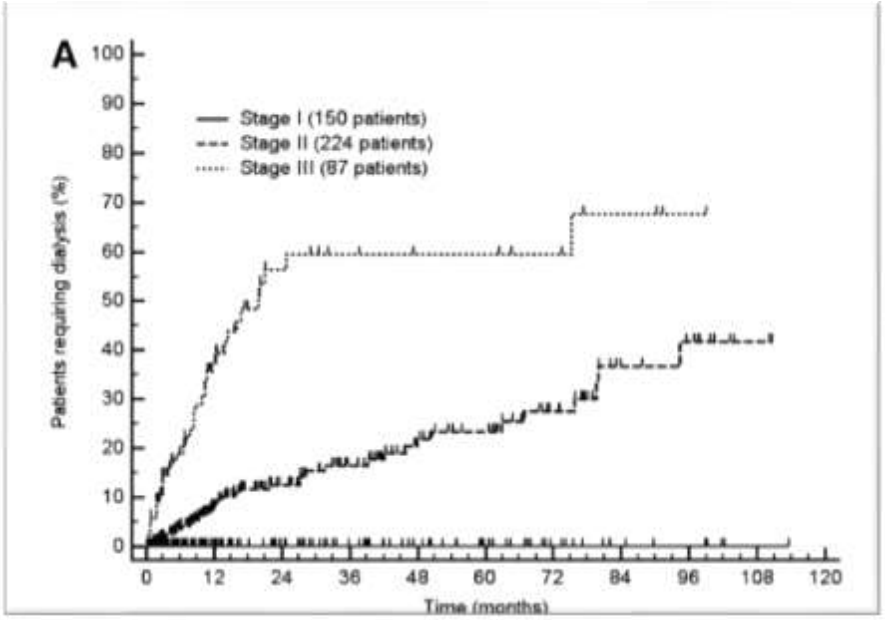
CLINICAL TRIALS AND OBSERVATIONS

*Blood 2014*

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

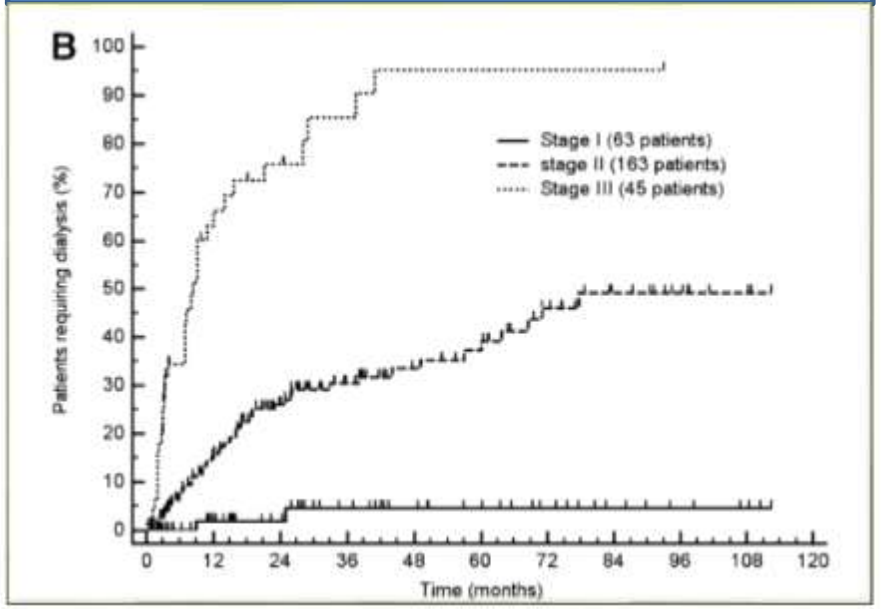
Giovanni Palladini,[1,2] Ute Hegenbart,[3] Paolo Milani,[1,2] Christoph Kimmich,[3] Andrea Foli,[1,2] Anthony D. Ho,[3] Marta Vidus Rosin,[1,2] Riccardo Albertini,[4] Remigio Moratti,[5] Giampaolo Merlini,[1,2,4] and Stefan Schönland[3]

## Testing cohort
## Pavia (N=461)




Stage I: both **proteinuria** ≤5g/24h and **eGFR** ≥50 mL/min
Stage II: either proteinuria >5g/24h or eGFR <50 mL/min
Stage III: both proteinuria >5g/24h and eGFR <50 mL/min

## Validation cohort
## Heidelberg (N=271)

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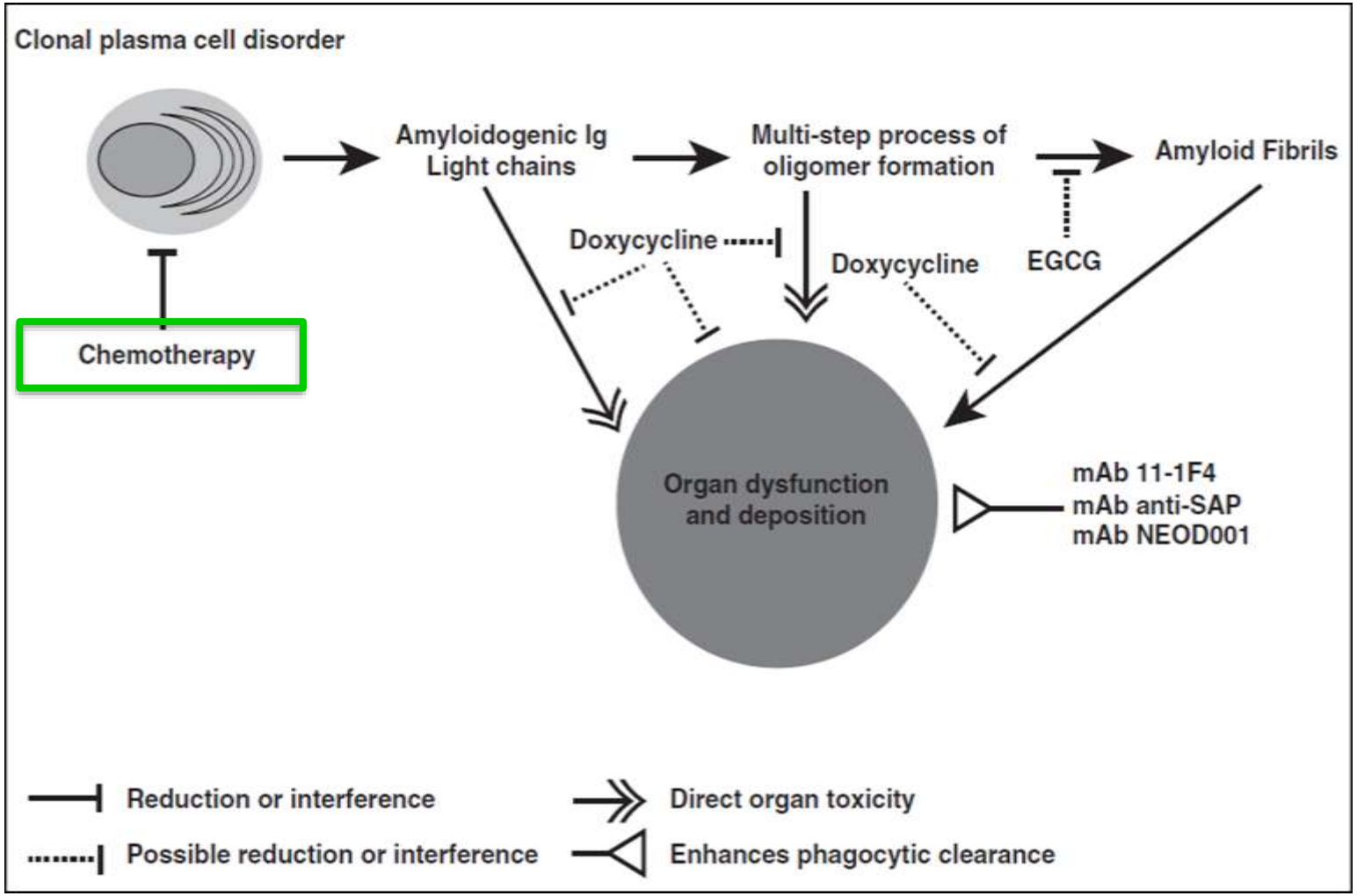
# Treatment strategies for systemic AL amyloidosis




Adapted from Weiss et al., *Blood* 2016

# Treatment regimen over the years

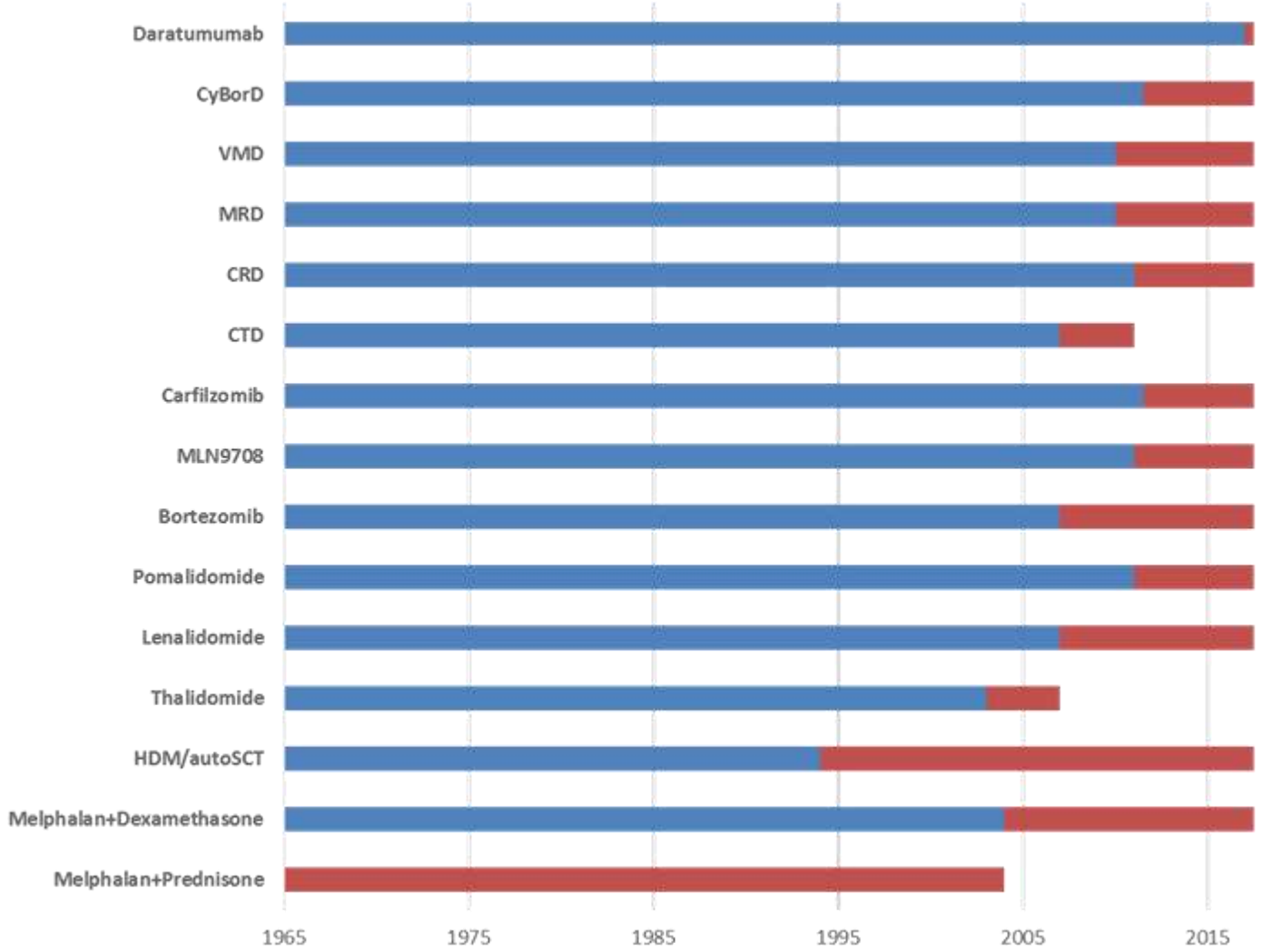
Antibodies

Combination Regimens

Proteasome Inhibitors

Immunomodulators (IMiDs)

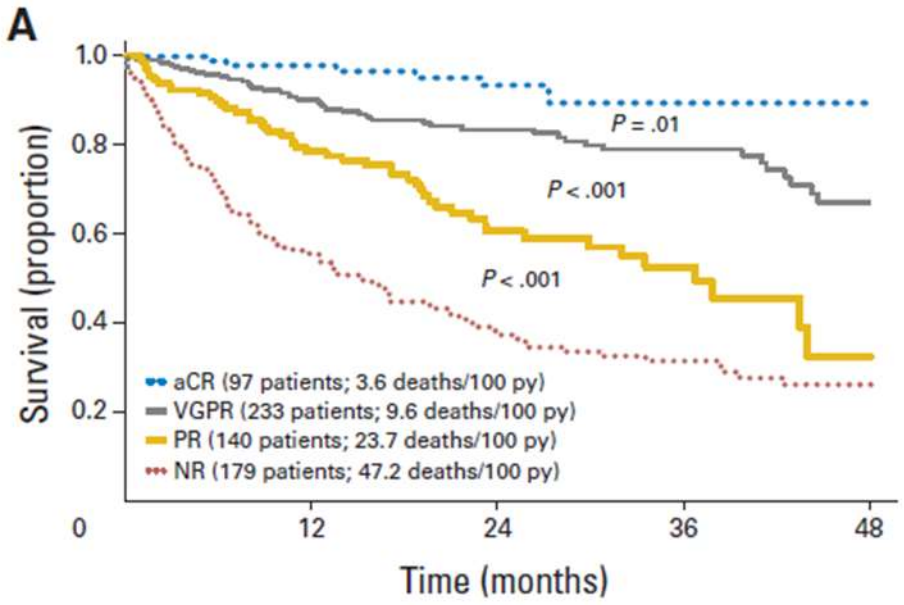
Oral Alkylators



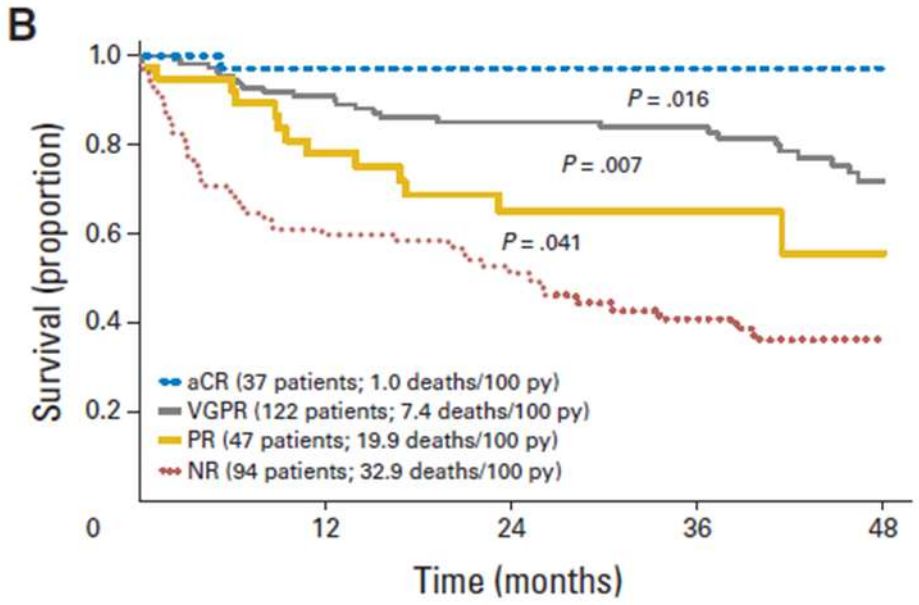
# Definition of hematologic remission

## Organ response criteria for heart and kidney have also been established

6 months landmark




3 months landmark




| | |
|---|---|
| **aCR** | IFE neg. and normal FLC ratio |
| **VGPR** | dFLC < 40 mg/L in patients with dFLC>50 mg/L |
| **PR** | More than 50% reduction of dFLC in patients with dFLC>50 mg/L |

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Palladini et al. *J Clin Onc* 2012

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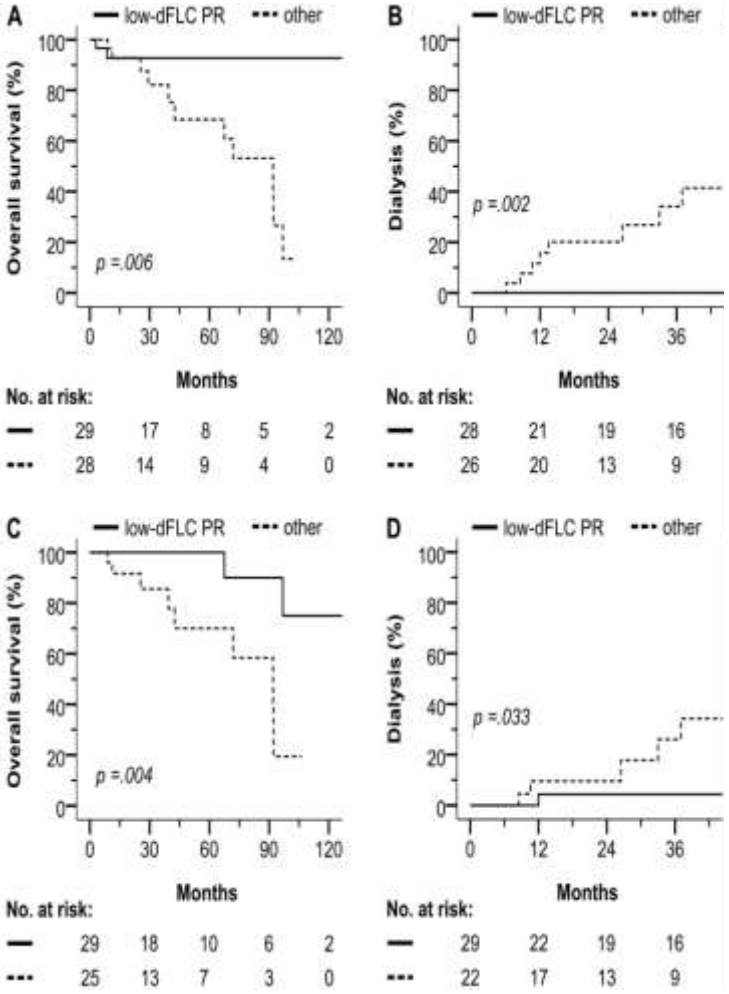
# New remission criterion in dFLC < 50 mg/l
# low-dFLC PR (<10 mg/l)

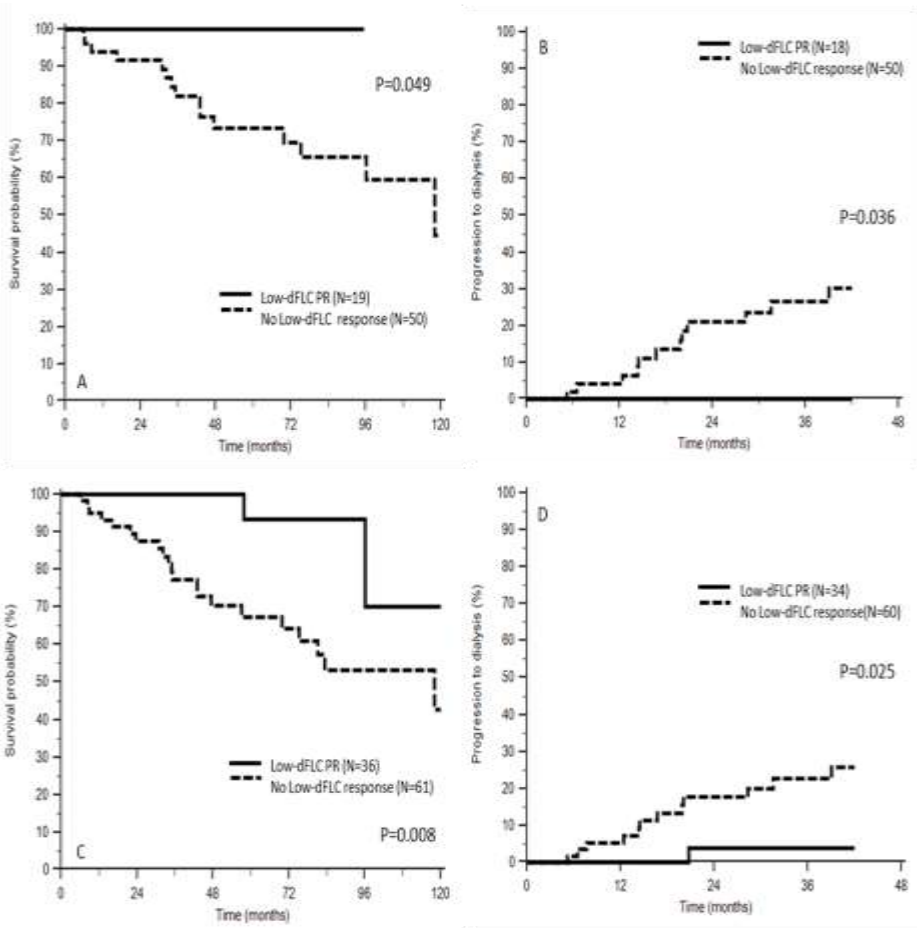
3 months landmark

6 months landmark

## Heidelberg




## Pavia




Dittrich et al. and Milani et al. *Blood* 2018

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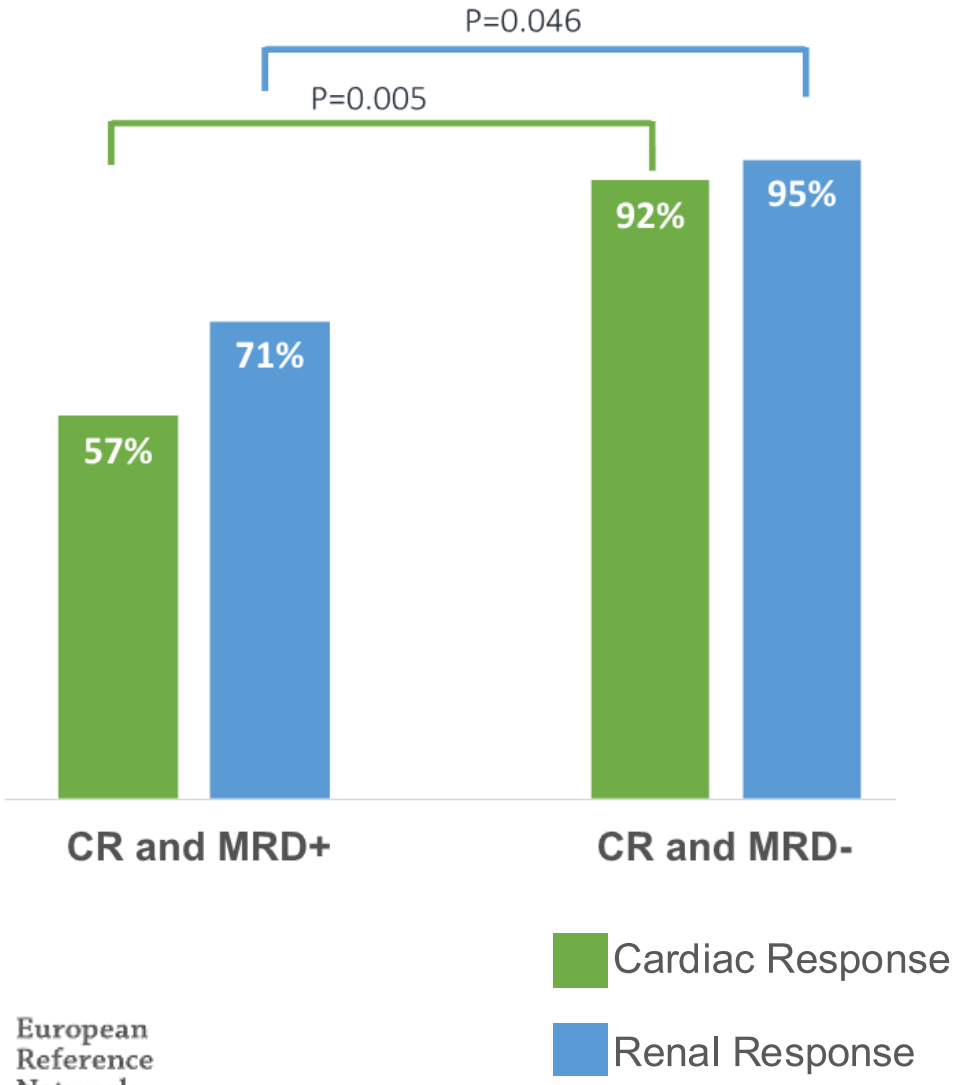
# MRD bone marrow assessment by NGF in AL amyloidosis




- Between 40% and 75% of patients in CR are reported to be MRD negative by NGF
- Patients without detectable MRD by NGF have higher probability of organ response

*Paiva, et al. Blood 2011*
*Lisenko, et al. Cancer Med. 2016*
*Muchtar, et al. Blood 2017*
*Staron, et al. Am J Hematol 2020*
*Kastritis, et al. Blood Cancer J 2018*
*Sidana, et al. Am J Hematol 2020*
*Muchtar, et al. Amyloid 2020*
*Staron, et al. Blood Adv 2020*
*Kastritis, et al. Amyloid 2020*

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*Palladini, et al. Blood Cancer J 2020*

*Courtesy of Giovanni Palladini, modified*

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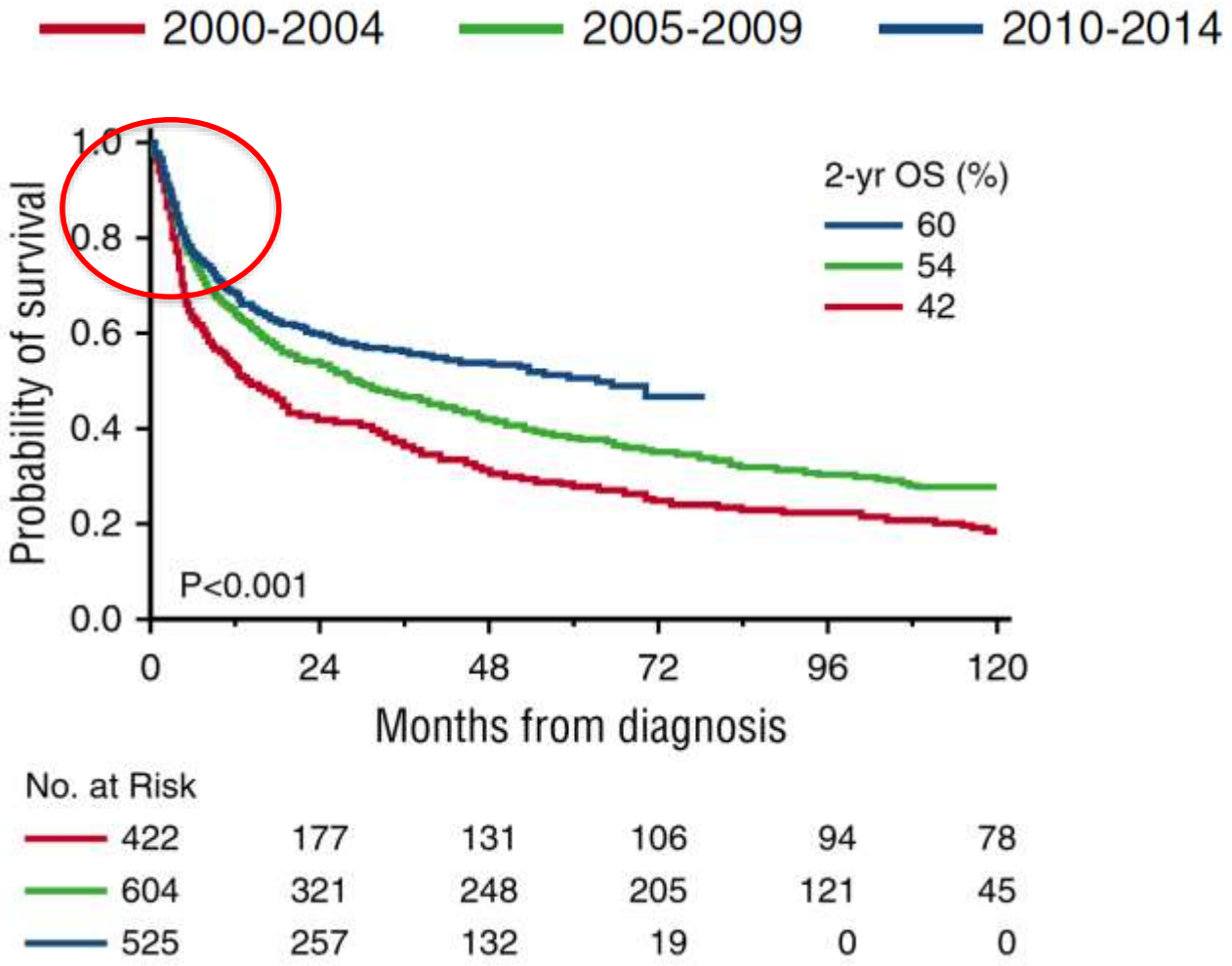
# Improvement of Prognosis since 2000

**Advanced cardiac pts**
**have a high early mortality**

**Early diagnosis still a problem**




Muchtar et al., *Blood* 2017

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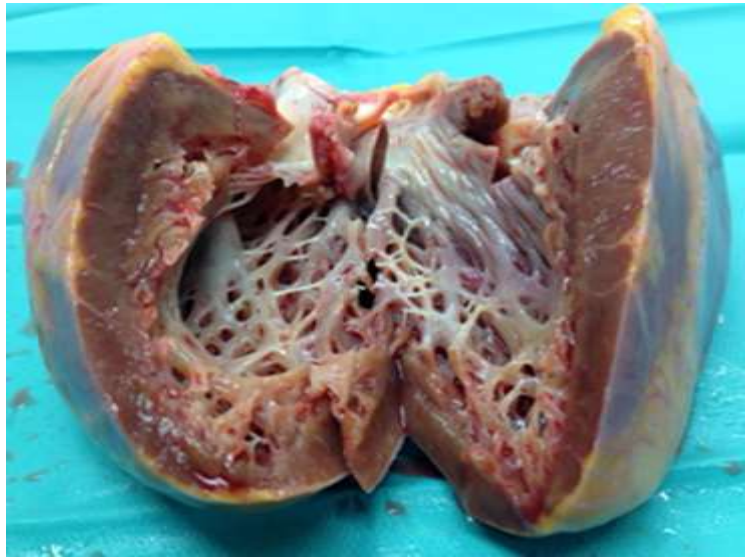
# Early diagnosis can be made by hematologists

Patients with monoclonal gammopathy or smoldering Myeloma (who are only under observation)

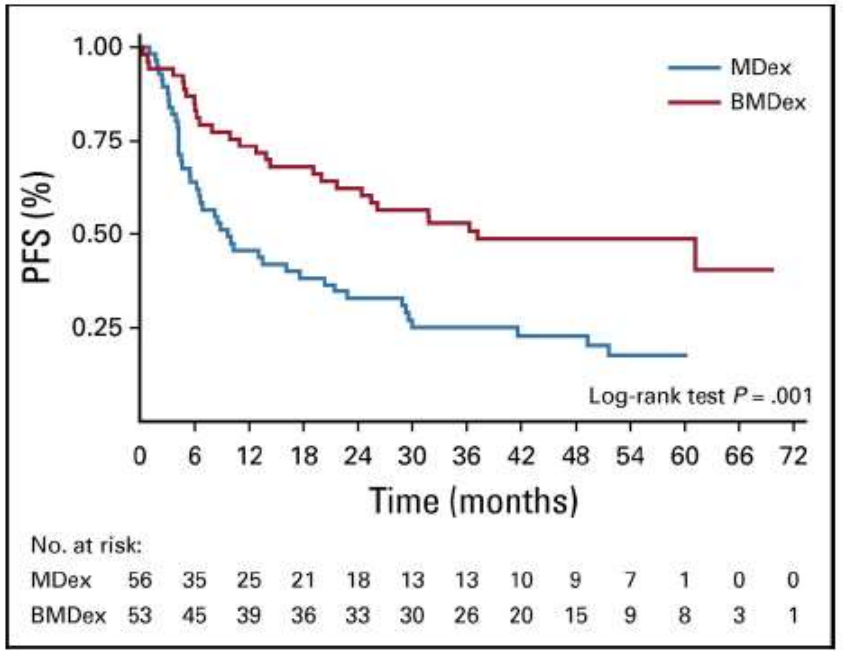
- Albumine in urine
- NT-BNP in plasma

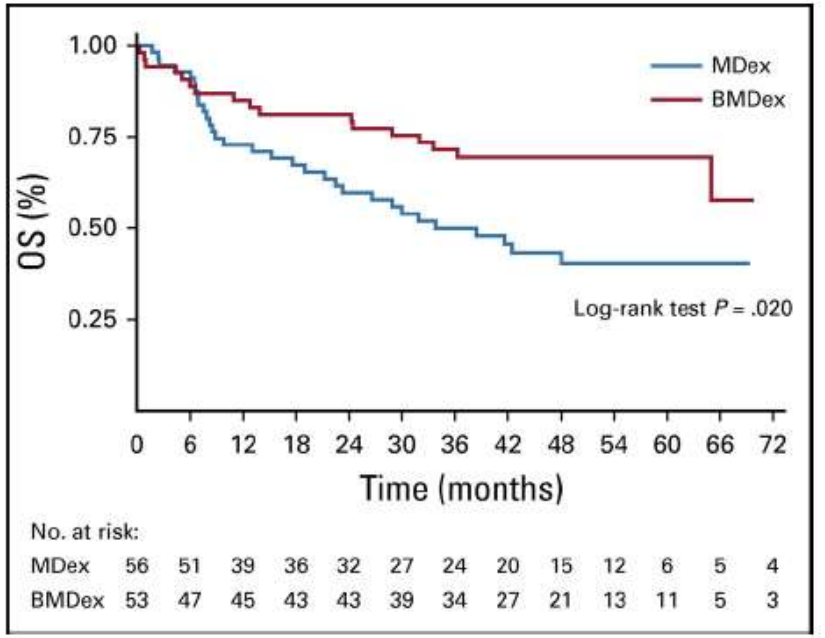
- FLC in serum



Amyloidosis Center HD

# A phase III EMN trial of BMDex vs. Mdex (non-transplant patients)




| Variable | MDex (n=56 pts.) | BMDex (n=53 pts.) | P |
|---|---|---|---|
| Any HR at 3 months | 29 (52%) | 42 (79%) | 0.002 |
| CR | 2 (4%) | 4 (8%) | |
| VGPR | 14 (25%) | 25 (47%) | |
| PR | 13 (23%) | 13 (24%) | |
| NR | 27 (48%) | 11 (21%) | |

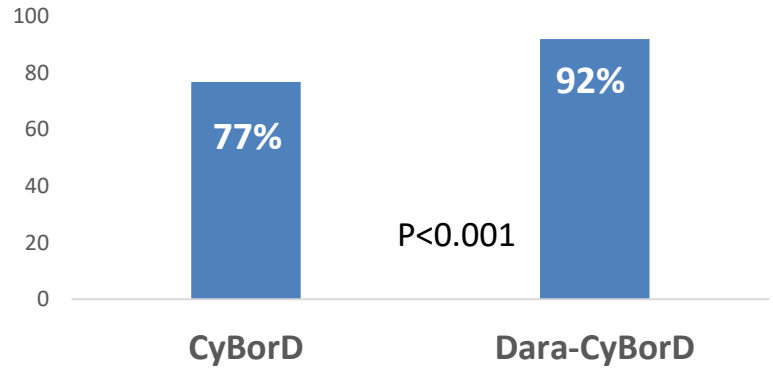
| Variable | MDex | BMDex | P |
|---|---|---|---|
| Cardiac response 3 months | 8/36 (22%) | 8/26 (31%) | 0.834 |
| Cardiac response 6 months | 8/36 (22%) | 10/26 (38%) | 0.207 |
| Renal response 3 months | 13/35 (37%) | 13/36 (36%) | 0.969 |
| Renal response 6 months | 15/35 (43%) | 14/36 (39%) | 0.768 |

Kastritis, et al. *JCO* 2020

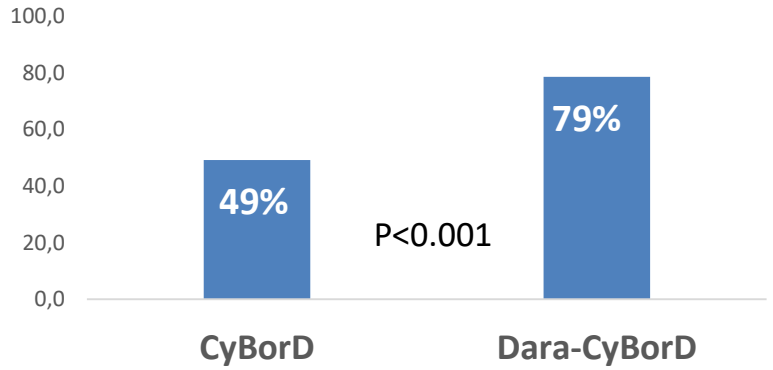
# Daratumumab plus CyBorD
# a new standard of care (non-transplant pts)

**ANDROMEDA: a randomized, open-label phase 3 study of DARA SC plus CyBorD vs CyBorD alone in newly diagnosed AL amyloidosis**

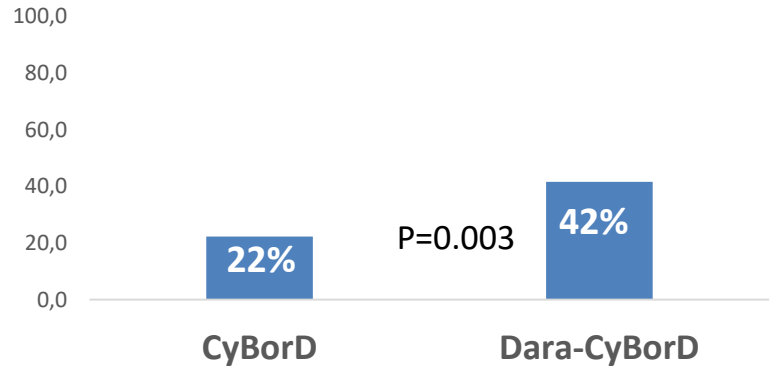
### Hematologic best response



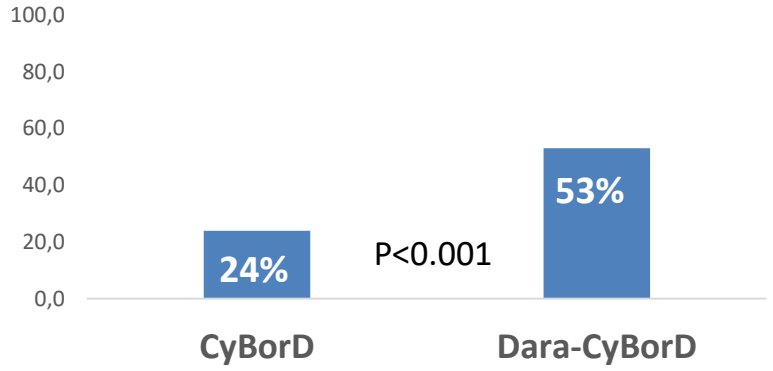

### CR/VGPR




### Cardiac response at 6 mo




### Renal response at 6 mo




Kastritis, et al. 2020 *EHA* abstract

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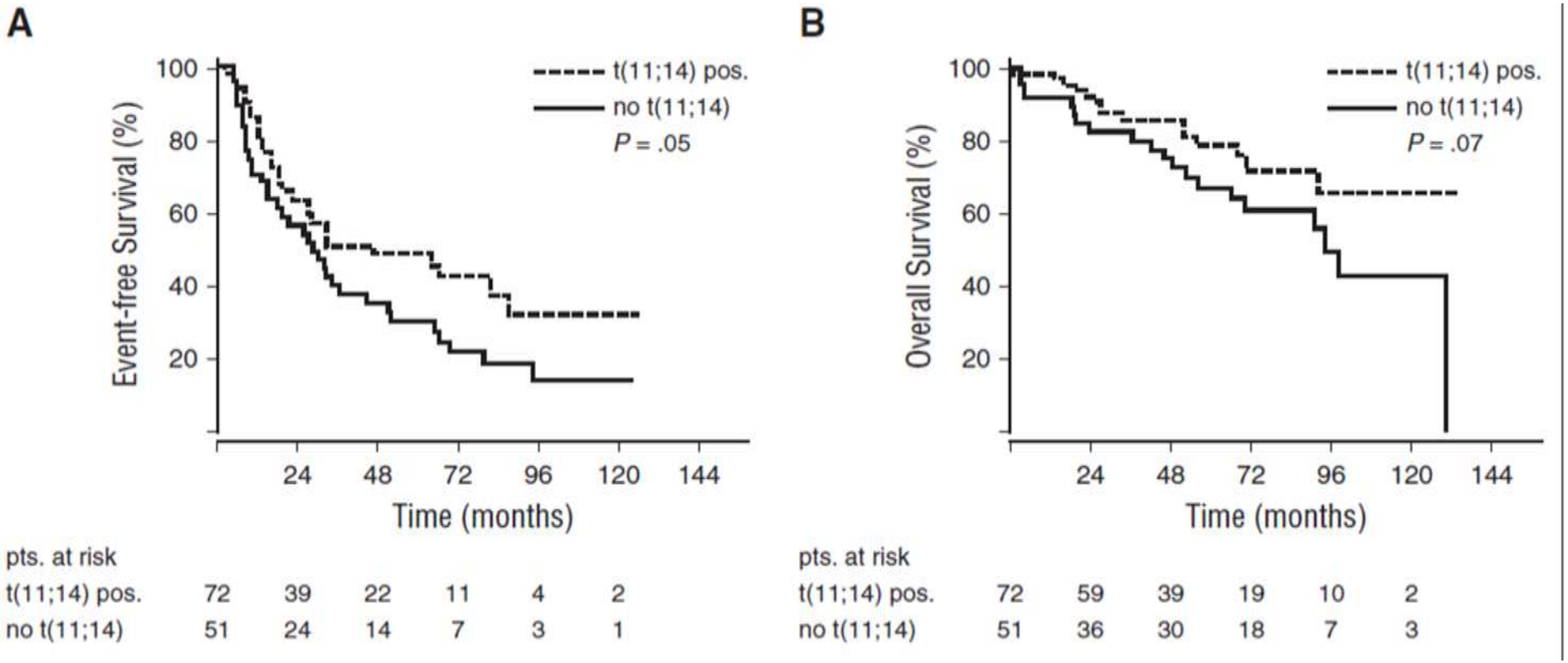
# High dose chemotherapy and autologous stem cell transplantation

t(11;14) associated with with more CR

44% versus 25%, p = 0.05




Bochtler et al., *Blood* 2016

# High dose chemotherapy and autologous stem cell transplantation

t(11;14) is a favorable independent prognostic factor

| | Event-free Survival | | | Overall Survival | | |
|---|---|---|---|---|---|---|
| Parameter | HR | 95%- CI | p-value | HR | 95%- CI | p-value |
| Higher age | 1.01 | [0.71 - 1.42] | 0.97 | 0.74 | [0.43 - 1.27] | 0.27 |
| Translocation t(11;14) pos. | **0.49** | **[0.29 - 0.83]** | **0.008** | 0.55 | [0.26 - 1.16] | 0.12 |
| Gain of 1q21 pos. | 1.12 | [0.59 - 2.13] | 0.72 | 0.60 | [0.23 – 1.52] | 0.28 |
| Light chain (λ vs. κ) | 1.76 | [0.85 - 3.66] | 0.13 | **3.67** | **[1.12 - 12.06]** | **0.03** |
| Higher dFLC | **1.99** | **[1.29 - 3.06]** | **0.002** | **3.55** | **[1.62 – 7.76]** | **0.002** |
| Mayo Score (II/III vs. I) [1] | 0.86 | [0.50 - 1.48] | 0.59 | 1.63 | [0.69 – 3.86] | 0.27 |
| Lower MDRD | 1.08 | [0.78 - 1.49] | 0.65 | 0.92 | [0.64 - 1.33] | 0.65 |
| Reduced melphalan dosage | 1.35 | [0.98 - 1.87] | 0.07 | **1.50** | **[1.00 - 2.22]** | **0.05** |

Bochtler et al., *Blood* 2016

# Upfront risk-adapted anti-clonal treatment for PC-AL

**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%

**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/$m^2$), very effective in **t(11;14)**

**Consider consolidation therapy if**
- No organ response or MRD positivity

**Intermediate-risk patients, ineligible for ASCT, cardiac stage II-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

**Intensive monitoring during therapy**

Start with reduced doses
- and escalate if well tolerated or
- sequentially introduce therapeutic agents

**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 **t(11;14)**
- **BMDex.** Potentially overcomes the effects of t(11;14)
- MDex, LMDex, CLD. Useful in patients with contraindication to bortezomib

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Dittrich *et al., Acta Haem* 2020

*Courtesy of Giovanni Palladini, modified*

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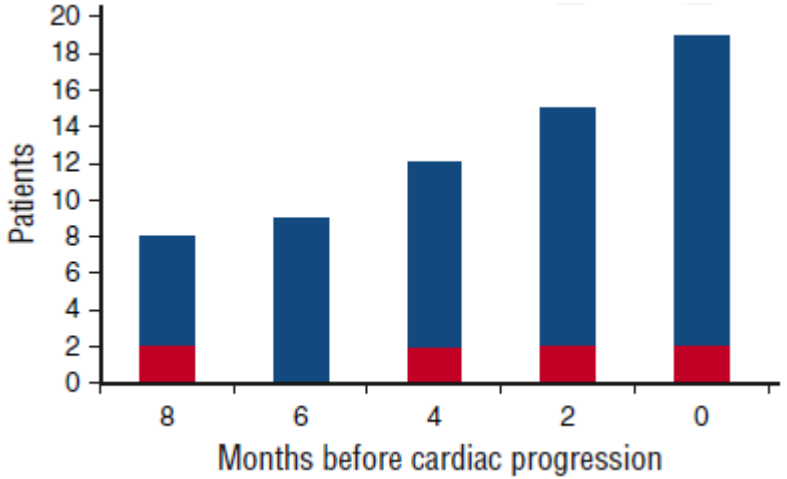
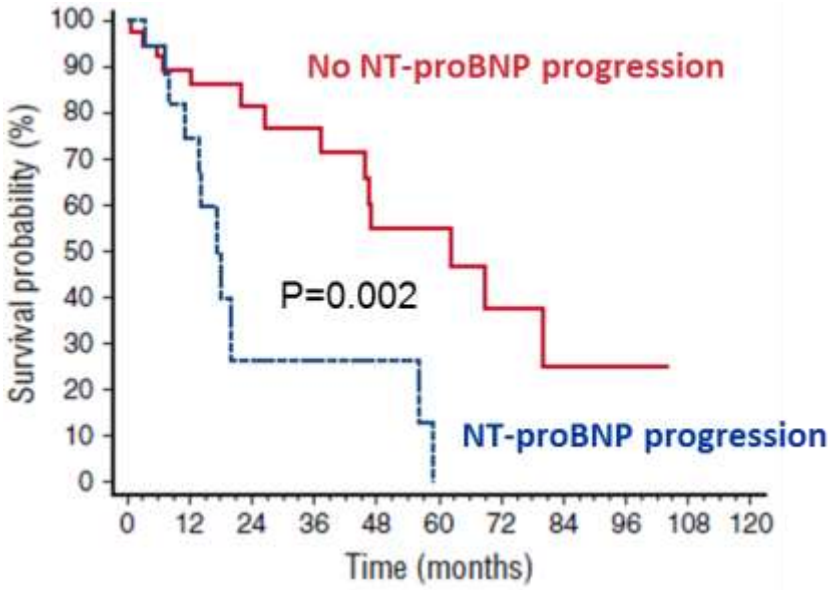
# Patterns of relapse/progression in AL amyloidosis




dFLC increase >10%

"**high-risk dFLC progression**," defined as an increase in dFLC that is:

- >20 mg/L,
- >20% of baseline value observed at diagnosis, and
- >50% of the value reached at best response




"High-risk dFLC progression" could be considered a trigger for rescue therapy initiation before cardiac progression, which is associated with poor survival.

Palladini et al., *Blood* 2017

# Lenalidomide can overcome resistance to alkylating agents and proteasome inhibitors

| Regimen | Time period | Previously treated patients (prior therapies) | HR | OR | Survival |
|---|---|---|---|---|---|
| **L(Dex)** *Dispenzieri 2007[1]* | 2004-2005 | 13 (ASCT 46%) | 38% | 15% | - |
| **L(Dex)** *Sanchorawala 2007[2]* | 2004-2006 | 31 (ASCT 61%, T 23%) | 52% | 51% (kidney) | - |
| **CLD** *Kumar 2012[3]* | 2007-2008 | 11 (ASCT 64%, T 9%) | 60% Including newly-diagnosed | 32% Including newly-diagnosed | Median 38 months |
| **CLD** *Kastritis 2012[4]* | 2008-2011 | 13 (ASCT 31%, T 31%, B 39%) | 58% (CR 8%) | 42% | Median 29 months |
| **LDex** *Palladini 2012[5]* | 2007-2009 | 24 (ASCT 29%, MDex 71%, T 37%, B 100%) | 41% | 6% (heart) | Median 14 months |
| **CLD** *Palladini 2013[6]* | 2008-2009 | 21 (ASCT 24%, MDex 81%, T 29%, B 19%) | 62% (CR 5%, VGPR 24%) | 19% (kidney) | Median 36 months |
| **LDex** *Mahmood 2014[7]* | 2007- 2013 | 84 (ASCT 15%, T 76%, B 68%) | 61% (CR 20%) | 55% (kidney) | 84% @ 2y |

**Recommended dose 15 mg**

1. Dispenzieri et al. Blood 2017; 2. Sanchorawala et al. Blood. 2007; 3. Kumar et al. Blood. 2012; 4. Kastritis et al. Blood 2012; 5. Palladini et al. Ann Hematol 2012; 6. Palladini et al. Haematologica. 2013; 7. Mahmood et al., Br J Haematol. 2014;



*Courtesy of Giovanni Palladini*

# Daratumumab in relapsed/refractory patients

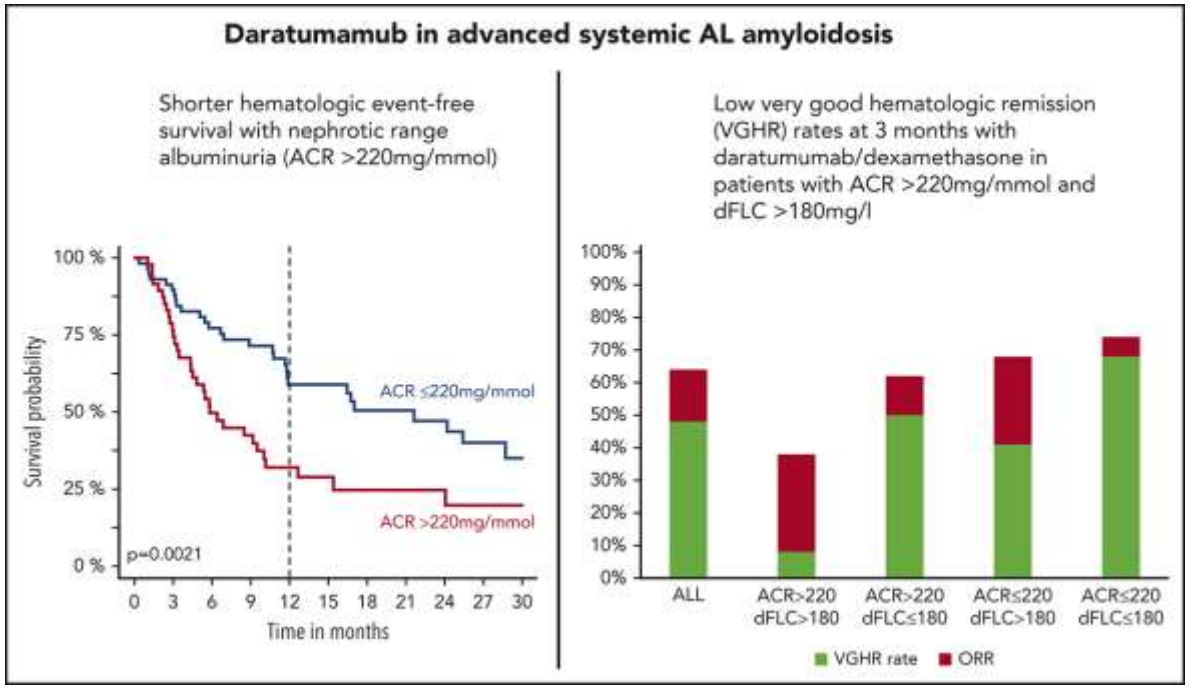
| Regimen (M/C) | Previously treated patients (prior therapies) | HR | OR | Median time to response (months) |
|---|---|---|---|---|
| *Mono*[1] | 25<br>(PI 100%, IMiDs 72%, ASCT 16%) | 76%<br>(CR 36%, VGPR 24%) | - | 1 |
| *Mono*[2] | 20<br>(ASCT 65%) | 86%<br>(CR 33%, VGPR 53%) | - | 1 |
| *Mono*<br>*Combo*[3] | 40<br>(B 91%, I 11%, Ca 16%, L 57%, P 20%, ASCT 52%) | 78% (CR 14%, VGPR 64%)<br>88% (CR 19%, VGPR 63%) | H 43%, K 18%<br>H 46%, K 36% | 3<br>2 |
| *Mono*<br>*Prospective trial*[4] | **22**<br>**(PI 73%, IMiDs 41%, ASCT 68%)** | **90% (CR 41%, VGPR 45%)** | **H 50%, K 67%** | **0.25** |
| *Mono*[5] | 72<br>(B 96%, L 44%, P 14%, ASCT 18%) | 77% (CR 40%, VGPR 23%) | H 55%, K 52% | 1 |
| *Mono*<br>*Combo*[6] | 38 (35 monotherapy)<br>(B 100%, IMiDs 47%, ASCT 40%) | 72% (CR 28%, VGPR 36%) | H 37%, K 59% | 0.5 |
| *Mono*<br>*Combo (+B)*[7] | 106 (PI 92%, IMiDs 73%, ASCT 23%)<br>62 (B 95%, IMiDs 5%, ASCT 8%) | 64% (CR/VGPR 48%)<br>66% (CR/VGPR 55%) | H 22%, K 20%<br>H 26%, K 24% | - |
| *Mono*<br>*Prospective trial*[8] | **40**<br>**(B 32%, IMiDs 59%)** | **55% (CR 8%, VGPR 40%)** | **H 25%, K 31%** | **0.25** |
| *Mono*<br>*Combo*[6] | 72<br>(B 94%, L 52%, P 25%, ASCT 24%) | 83% (CR 30%, VGPR 29%) | H 29%, K 60% | 2 |

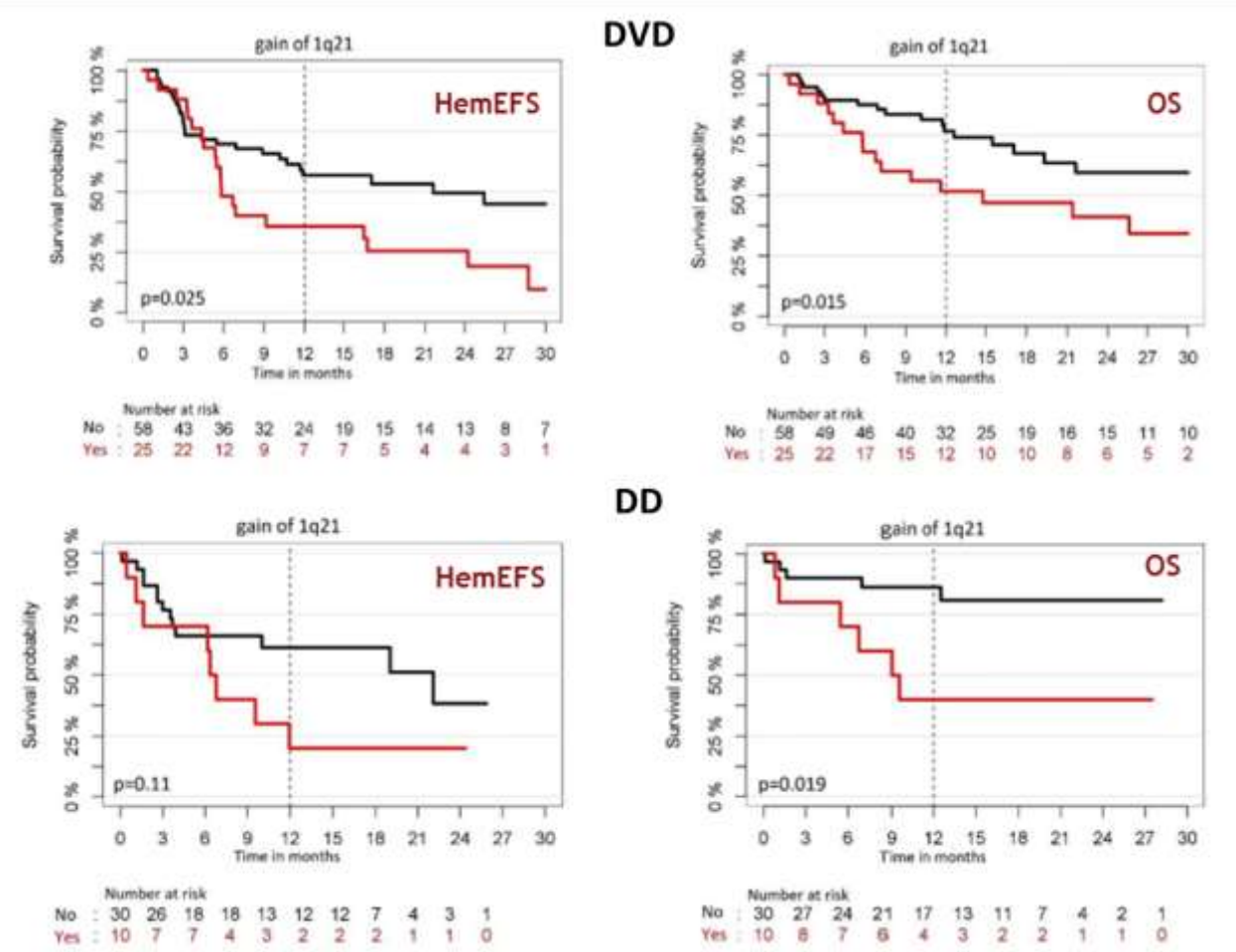
**Same dosages as for multiple myeloma**


1. Kaufman, et al. Blood. 2017
2. Khouri, et al. Br J Haematol. 2019
3. Abeykoon, et al. Leukemia. 2019
4. Sanchorawala, et al. Blood. 2020
5. Chung, et al. Blood Adv. 2020
6. Lecumberri, et al. Amyloid 2020
7. Kimmich, et al. Blood 2020
8. Roussel, et al. Blood 2020
9. Milani, et al. Am J Hematol. 2020

# Daratumumab in relapsed/refractory patients

## - Heidelberg -




**Gain 1q21 might be a neg. predictive marker for Daratumumab**

Kimmich, et al., *Blood* 2020

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Thursdays Webinars

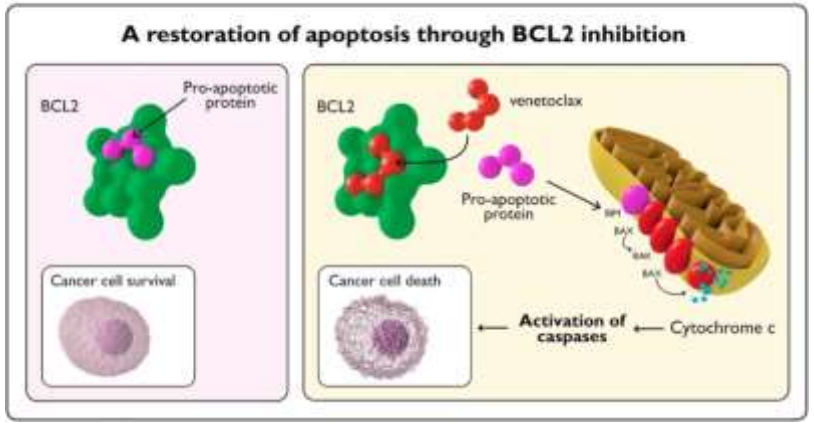
# Venetoclax – t(11;14) - predictive marker for therapy?!

## Mayo Clinic study

12 patients with relapsed/refractory AL amyloidosis treated with Venetoclax

| | |
|---|---|
| t(11;14) positive | 11 patients |
| t(11;14) negative | 1 patient |
| CR/VGPR | 88% |

**Venetoclax - a BCL2 specific inhibitor**




## Multicentric international study

44 patients with relapsed/refractory AL amyloidosis treated with Venetoclax

| | |
|---|---|
| t(11;14) positive | 31 patients |
| t(11;14) negative | 11 patients |
| CR/VGPR | |
| t(11;14) positive | 78% |
| t(11;14) negative | 30% |

Premkumar *et al. Blood Cancer J* 2021

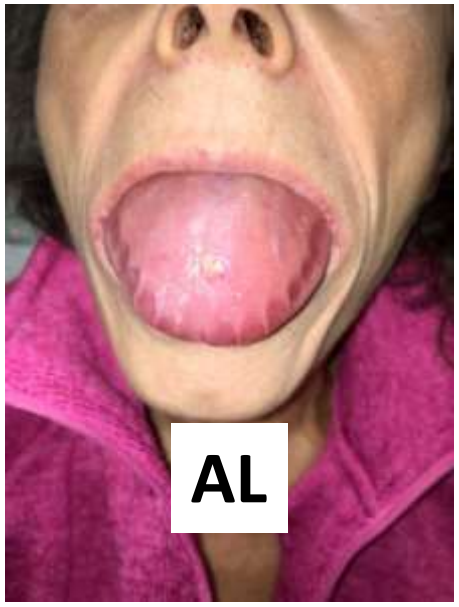
Sidiqi *et al. Blood Cancer J* 2020

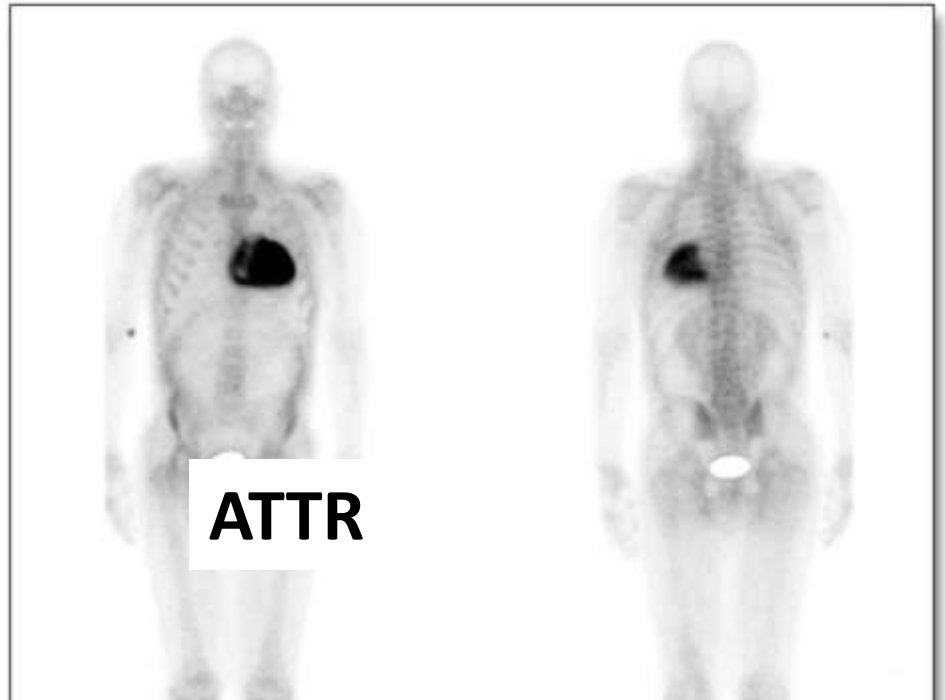
# Summary systemic AL Amyloidosis

Most common form of MGCS

**Diagnosis**

- Rigorous evaluation at presentation (clone and organ)
- Distinguish AL from ATTR cardiac amyloidosis

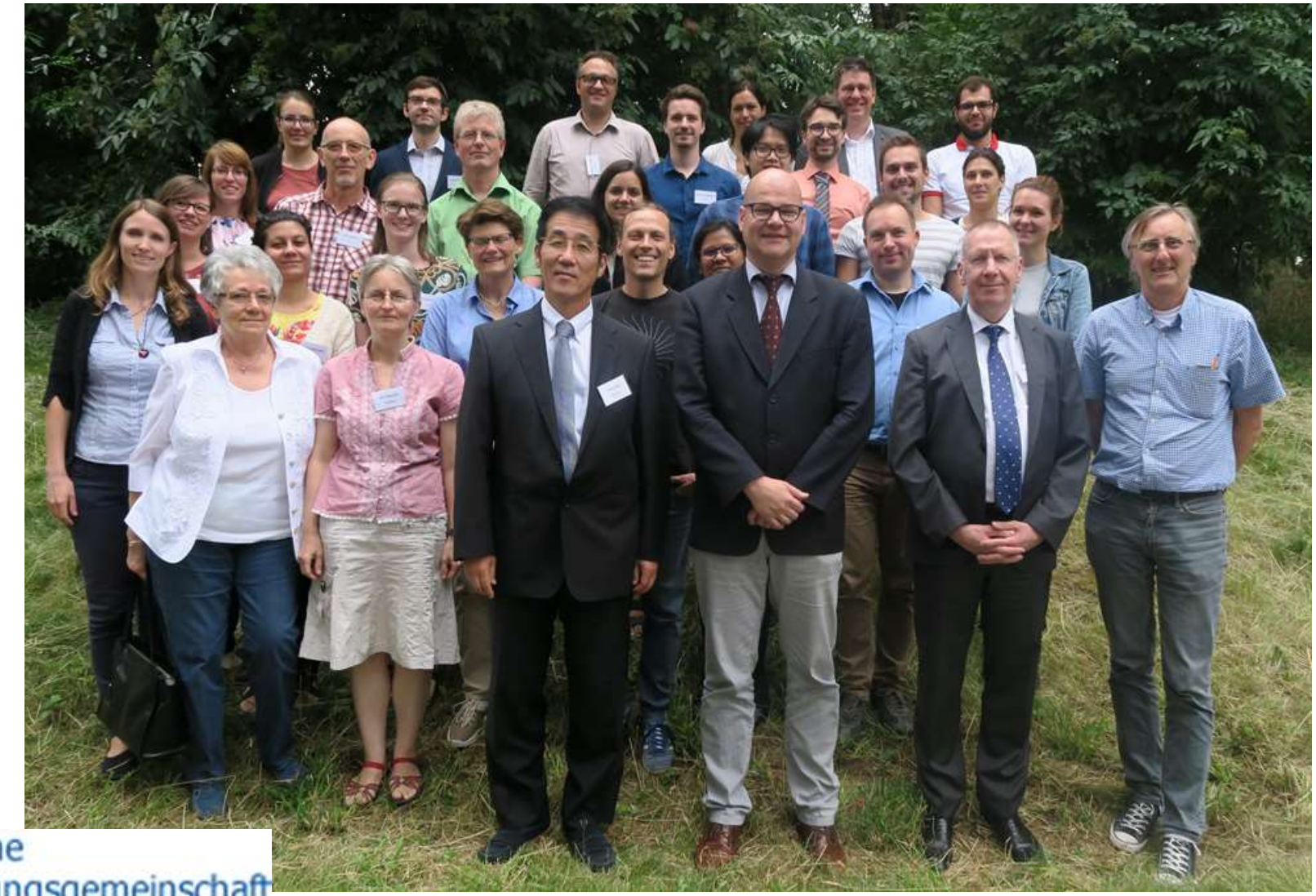


# Summary systemic AL Amyloidosis

- **Clonal and organ biomarkers**
  - established and validated for staging, prognosis and response, but NOT yet for hematologic progression
- **Major developments in anti-clonal treatment (in PC AL)**
  - Combination therapies are more powerful
  - Daratumumab is very effective
    - in non-nephrotic patients with low clonal burden
  - Cytogenetic results and other clonal markers are prognostic
- **No Anti-Fibril / Amyloid therapy yet**
  - Urgent need to better understand fibril formation

# Mechanisms of antibody light chain misfolding in systemic AL amyloidosis



FOR 2969

DFG Deutsche Forschungsgemeinschaft

1. AL amyloidosis as a rare and highly patient specific and complex disease

2. Anti-clonal treatment has to be risk adapted

3. Genetic factors can influence treatment decisions

4. *At least in difficult cases* – ask experienced centers

# Thanks to my colleagues and the funding sources


ZENTRUM FÜR SELTENE ERKRANKUNGEN
Universitätsmedizin Heidelberg

EuroBloodNet
European Reference Network in Rare Hematological Diseases

GEFÖRDERT VOM

Geramy
Nationales Netzwerk für Amyloidose Erkrankungen

Bundesministerium für Bildung und Forschung

DFG Deutsche Forschungsgemeinschaft

ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

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# XVIII International Symposium on Amyloidosis
## Heidelberg – Germany
## 4th - 8th September 2022