

Highlights from IMW 2019

19-20 novembre 2019
Bologna
Royal Hotel Carlton

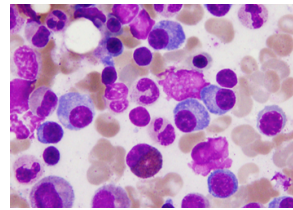
Giampaolo Merlini

Amiloidosi AL: nuovi approcci terapeutici

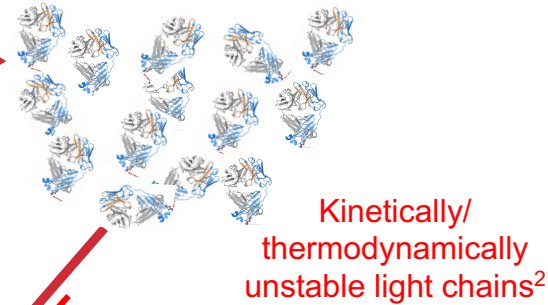
Coordinatore Scientifico
Michele CAVO

Comitato Scientifico
Mario BOCCADORO
Michele CAVO
Maria Teresa PETRUCCI

Pathways involved in AL systemic amyloidosis



Dangerous, small clone¹
t(11;14) in 50%
gain(1q21) in 20%



extracellular
chaperones

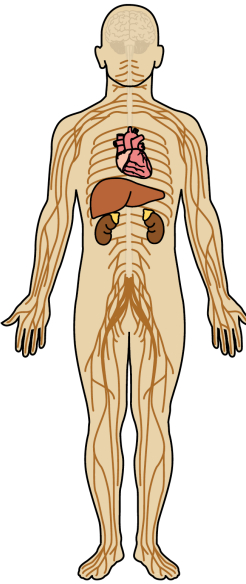
endoproteases, metal ions
shear forces, cell
interactions

Misfolding



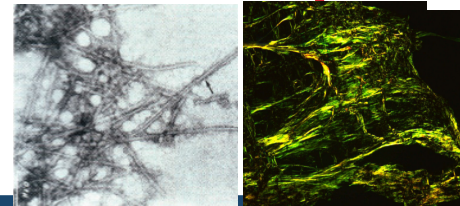
Oligomers

Toxicity³

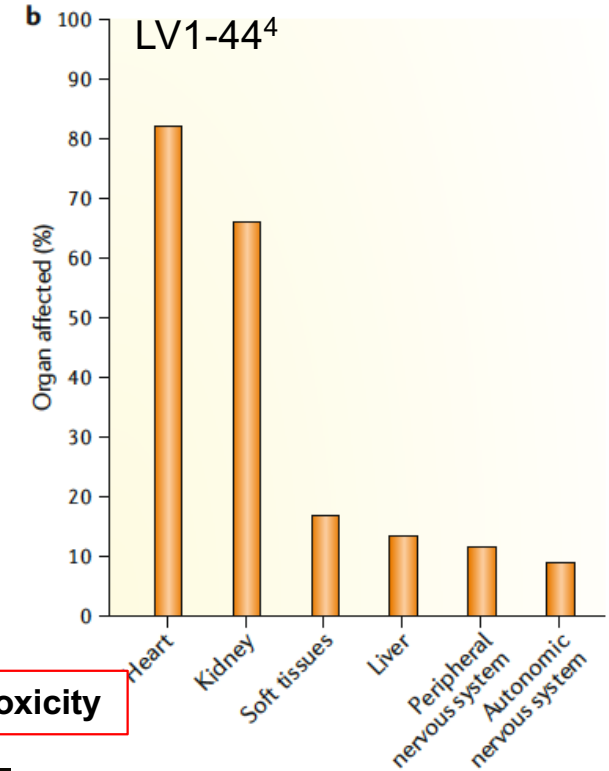


Mass action and toxicity

SAP,
GAGs



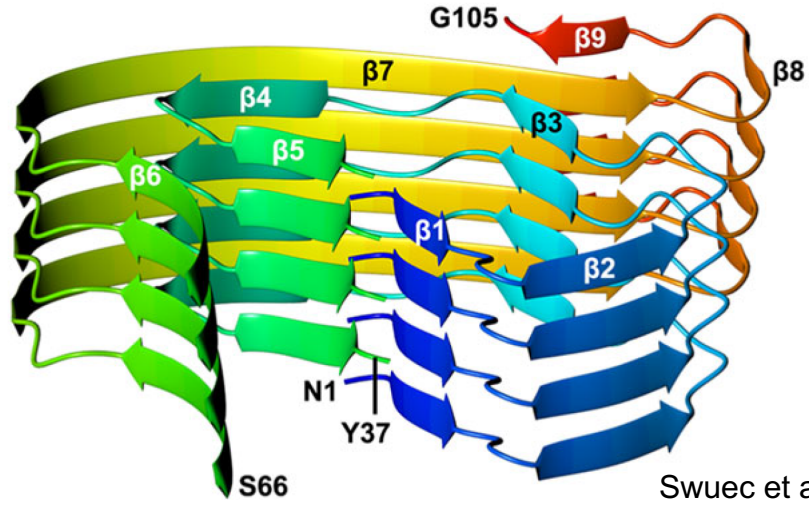
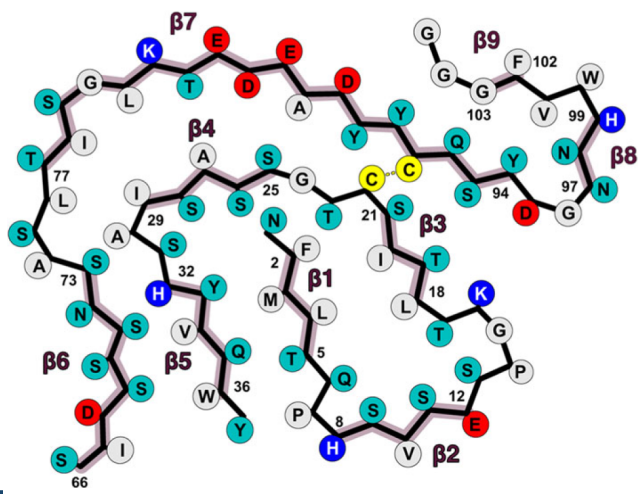
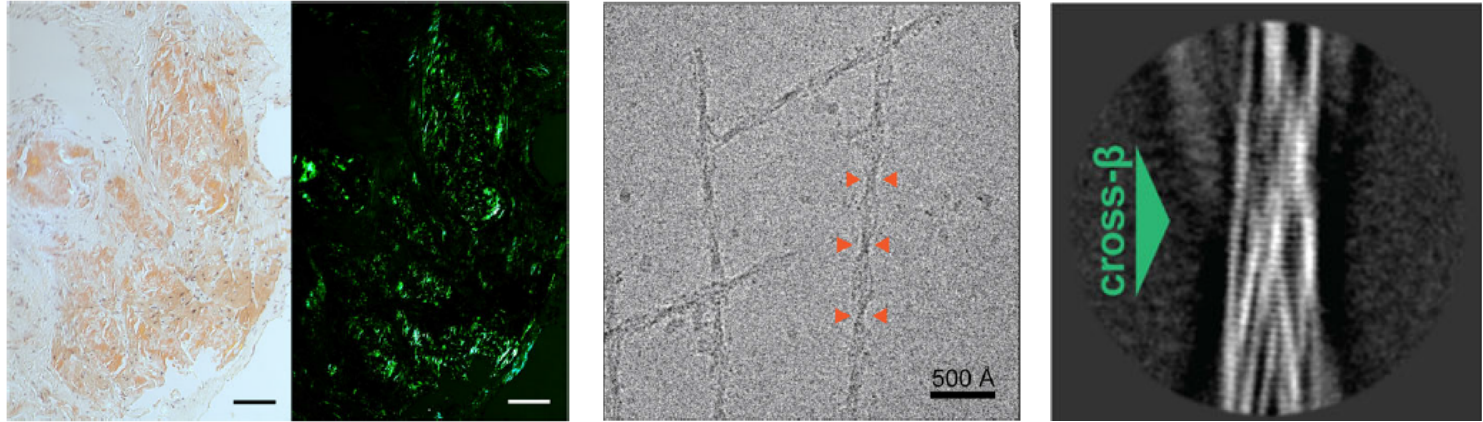
Amyloid fibrils



4. Perfetti et al, *Blood* 2012

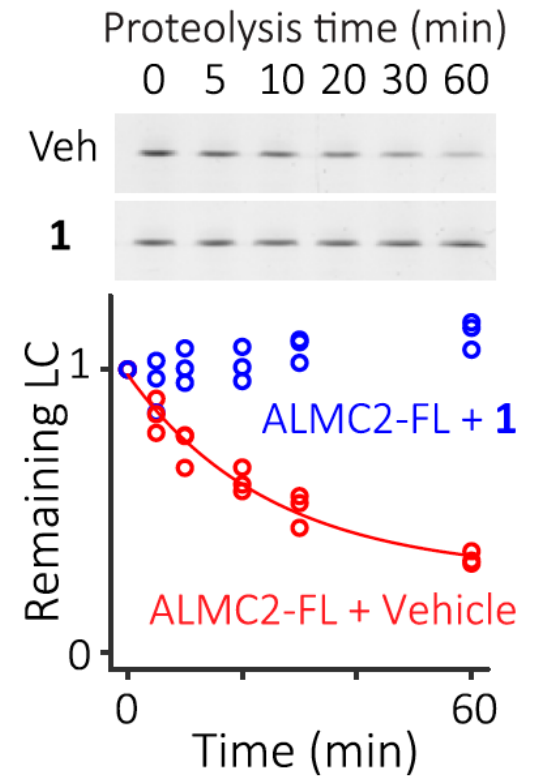
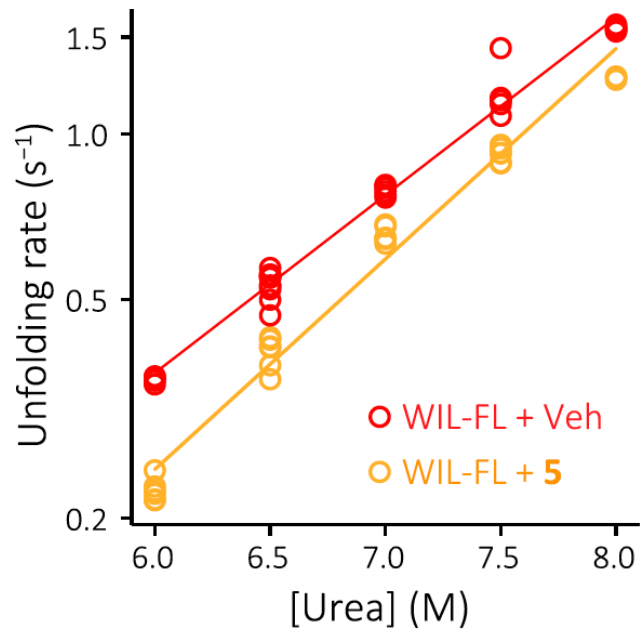
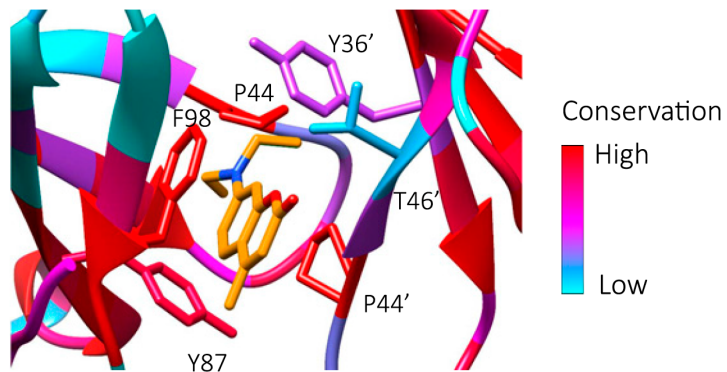
1. Merlini & Stone, *Blood* 2006
2. Oberti et al, *Sci Rep.* 2017
3. Imperlini et al, *Sci Rep.* 2017
- Merlini et al, *Nat Rev Dis Primers.* 2018

Cryo-EM structure of cardiac amyloid fibrils from a AL amyloidosis patient



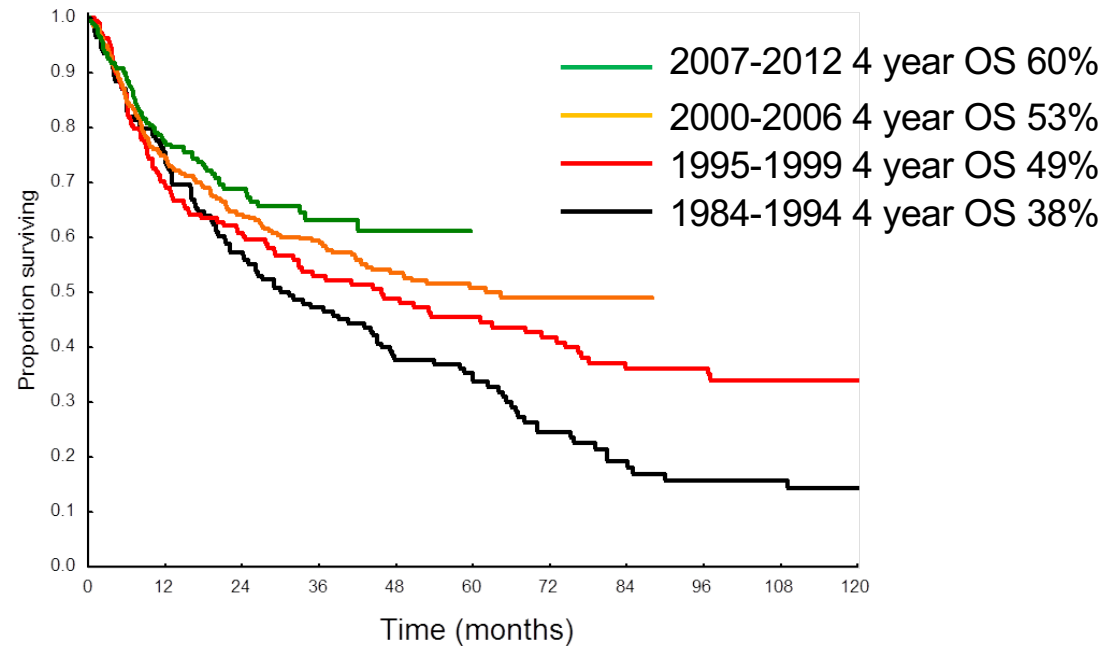
Swuec et al, *Nat Commun.* 2019

Stabilization of amyloidogenic LC by small molecules



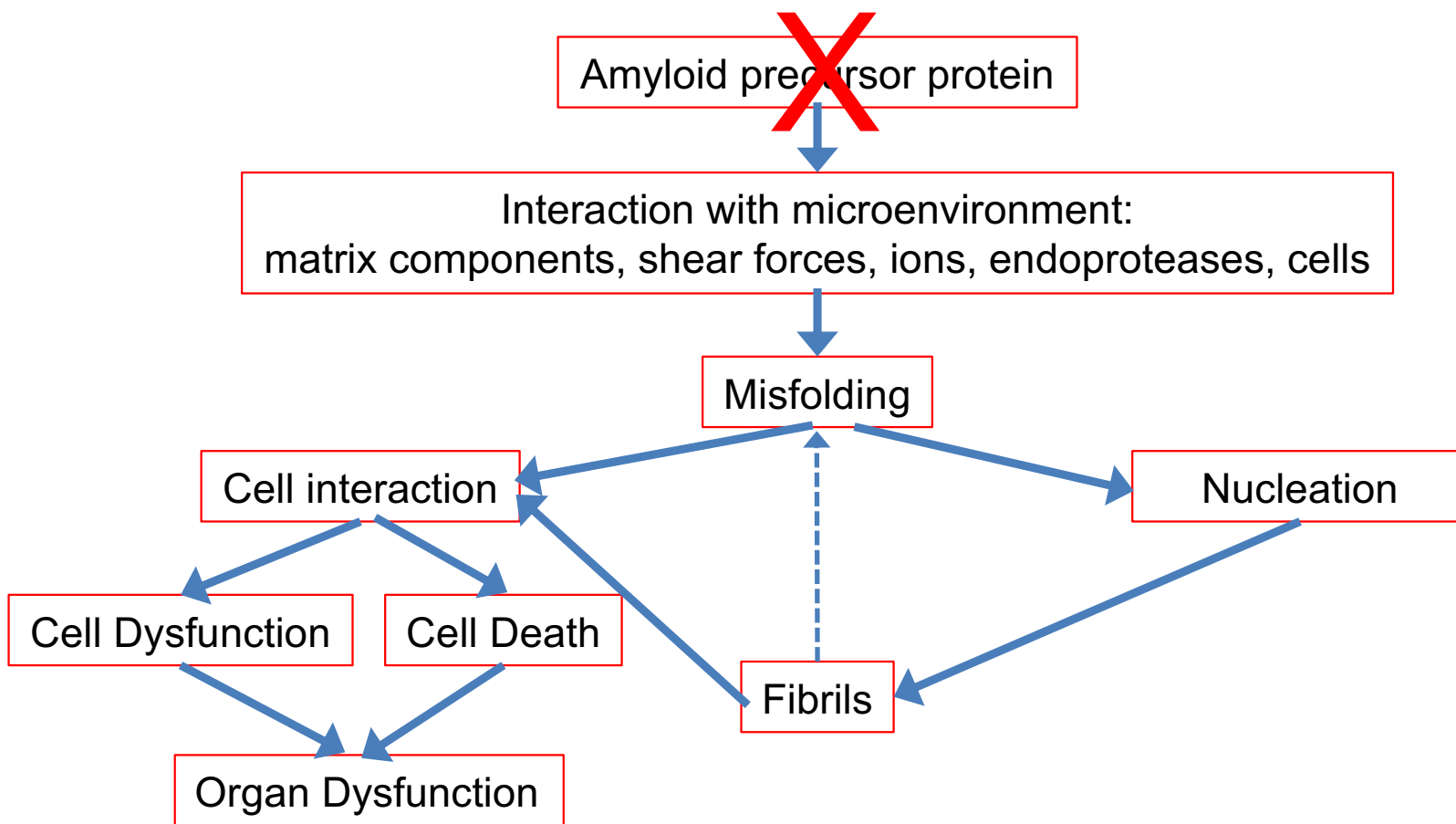
Morgan et al. *PNAS* 2019

Improved outcomes in AL amyloidosis over the years



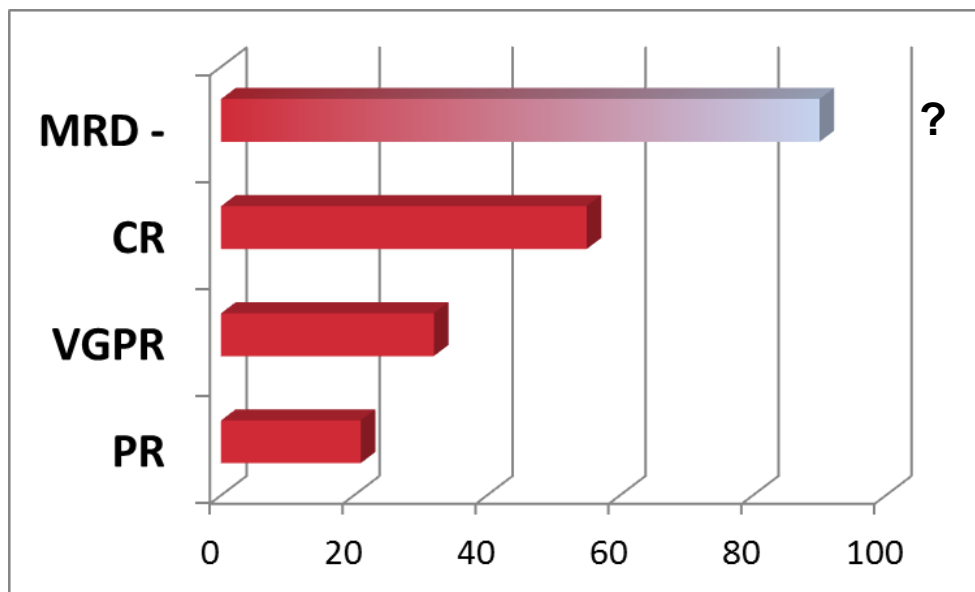
At present, AL amyloidosis represents the most successful example of effective treatment of all types of amyloidosis: Why?

Merlini, *Blood* 2012 updated



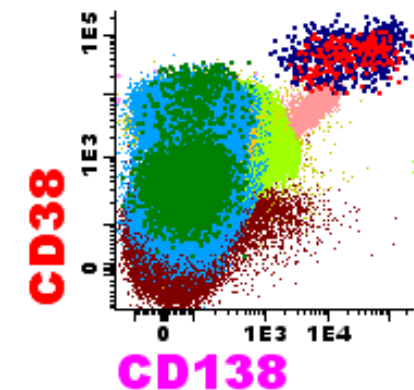
Targeting early steps of the amyloid cascade provides the highest therapeutic efficacy

Organ response strictly depends on the quality of hematologic response



Patients with organ response (%)
data from 1065 patients at Pavia ARTC

*MRD data by NGF on
69 patients at Pavia
ARTC*



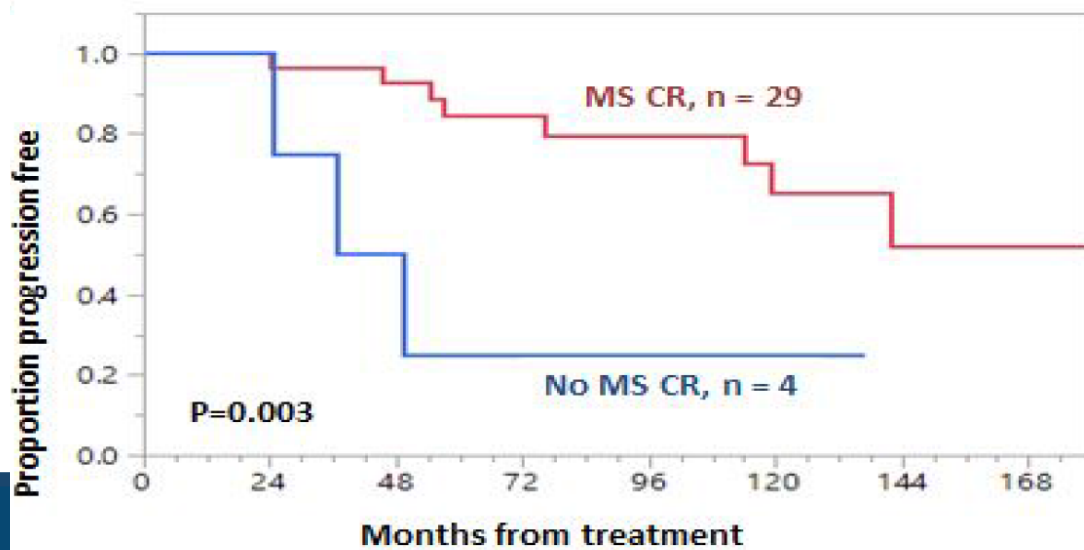
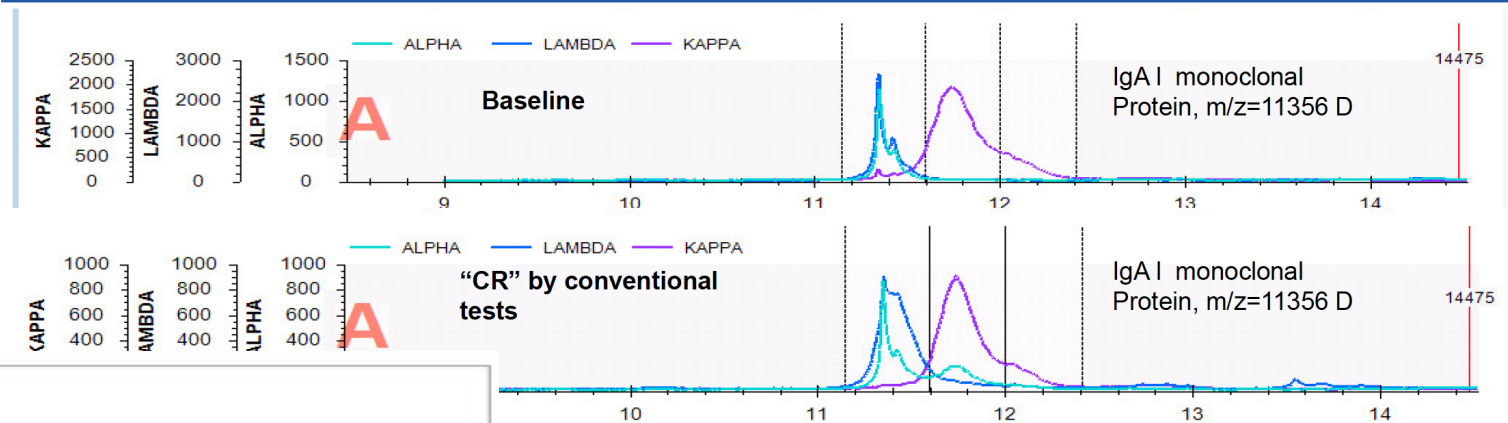
Orfao A. & Paiva B.
EuroFlow-based NGF

MS to Measure Response in AL Amyloidosis



33 patients in CR

FIGURE 3. Example of positive MASS-FIX



Dispenzieri et al, *IMW* 2019

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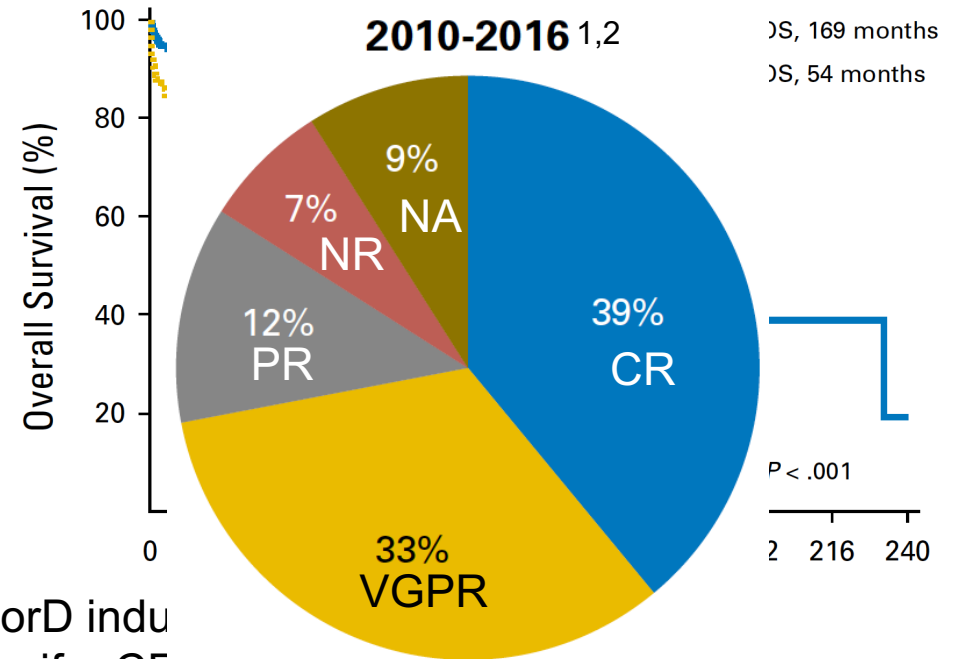
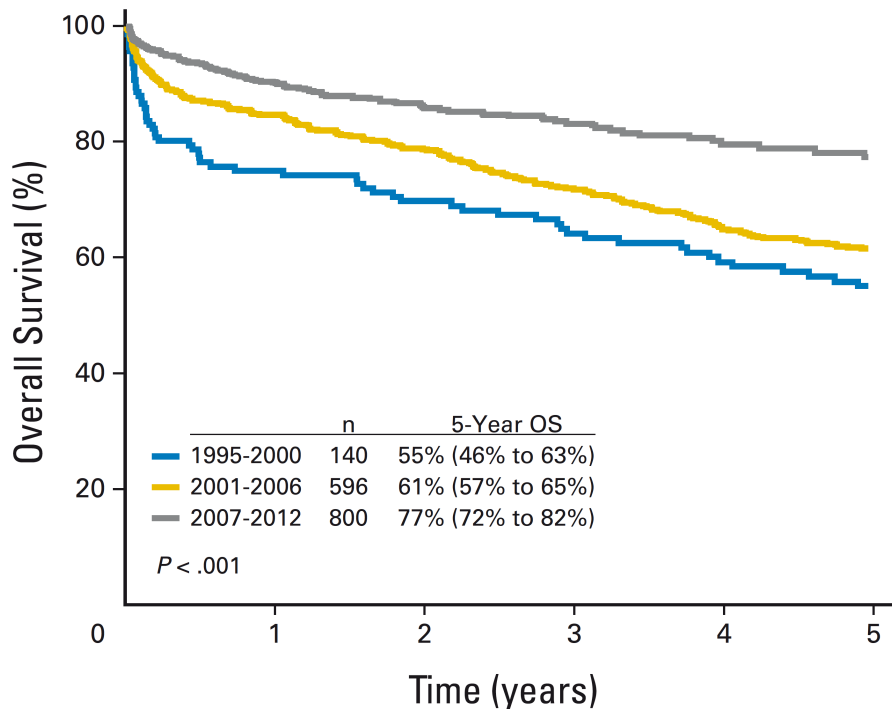
ASCT in AL amyloidosis

Sanchorawala V,
Educational IMW2019

- 1,536 patients at 134 centers from 1995 to 2012
- HR/CR 61/33%, TRM 4% (2007-2012)
- Renal response 30%

Fit patients: ~20%

age < 70 years, ECOG PS ≤ 2, BP > 90 mmHg,
cTnT < 0.06 ng/mL, Creatinine clear. > 30 mL/min,
NYHA I or II, ≤ 2 organs involved



- CyBorD indu
- BDex if < CR

1. Tandon et al, *BMT* 2017 - 2. Sidiqi et al, *JCO* 2018

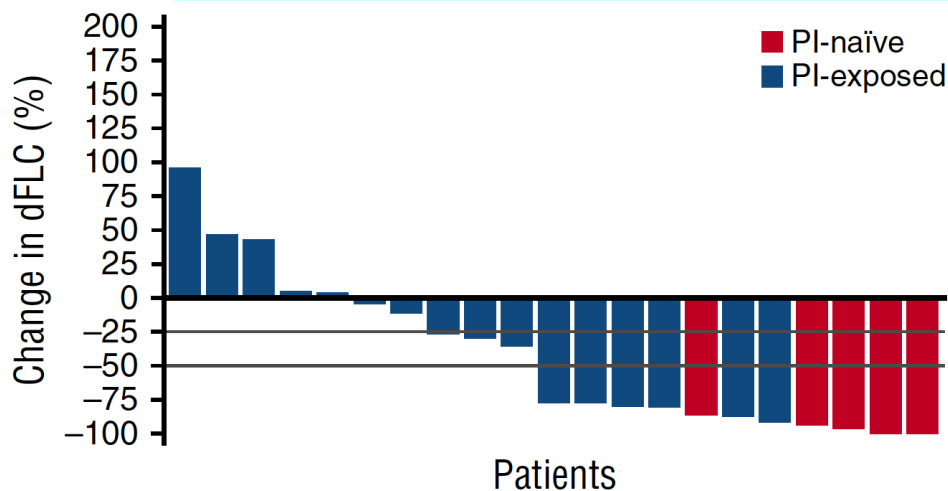
3. Hwa et al, *Am J Hematol*, 2016 - 4. Scharman et al, *ASH 2017 Abstr .4552* - 5. Landau et al, *Leukemia* 2017

Treatment of intermediate-risk patients (~60%) (ineligible for ASCT, stages I-IIIa)

Standard of care: Bortezomib-based regimens → VGPR/CR ~50%
(BDex, CyBorD, BMDex) → VGPR/CR ~40-20% in Stage IIIa/IIIb

Kastritis et al. *J Clin Oncol* 2010 - Reece et al. *Blood* 2014 - Palladini et al. *Leukemia* 2014 - Palladini et al. *Blood* 2015 –
Reece et al, *Blood* 2017

Phase I/II study of ixazomib in relapsed refractory AL amyloidosis



27 patients - Overall hematologic response rate: 52%, ≥VGPR 43%
Cardiac response 45%, renal response 45%

Sancharavala, et al. *Blood* 2017

A phase III trial of BMDex v. MDex in AL amyloidosis



BMDex (53 pts)	P
43 (81%)	0.005
12 (23%)	0.440
22 (42%)	0.007
9 (17%)	0.454
10/26 (38%)	0.195
16/36 (44%)	0.448

t(11;14) (~50% of patients)

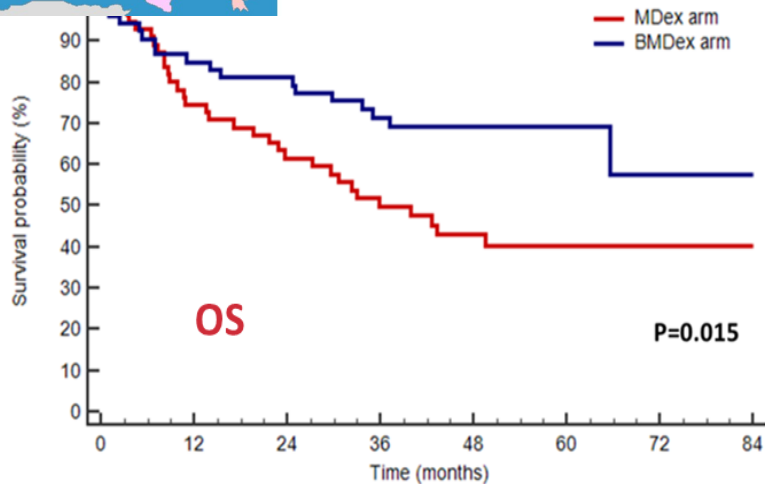
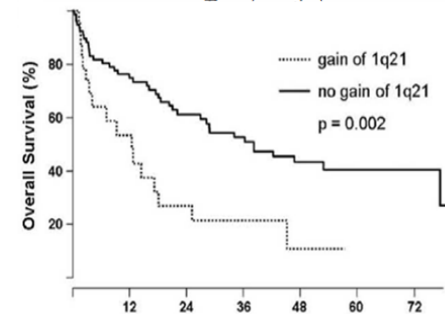
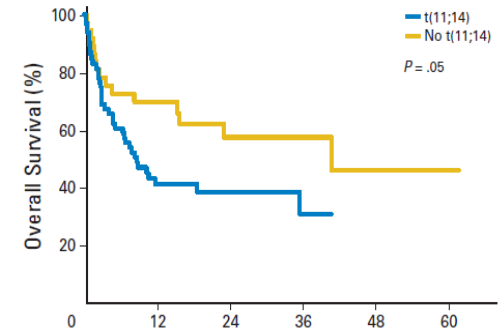
In patients treated with CyBorD and BDex

≥VGPR 23% vs. 47%

gain(1q21) (~20% of patients)

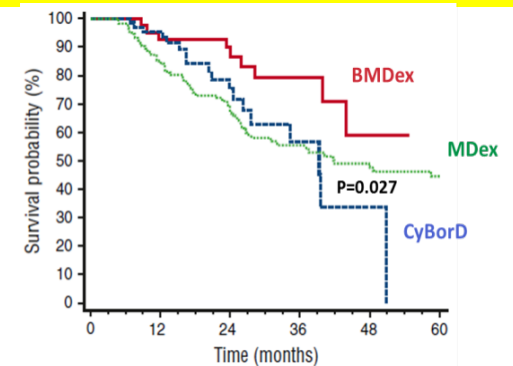
In patients treated with MDex

≥VGPR 5% vs. 25%



BMDex could overcome the effect of both gain(1q21) and t(11;14)

Exposure to both melphalan and bortezomib prolongs time to re-treatment

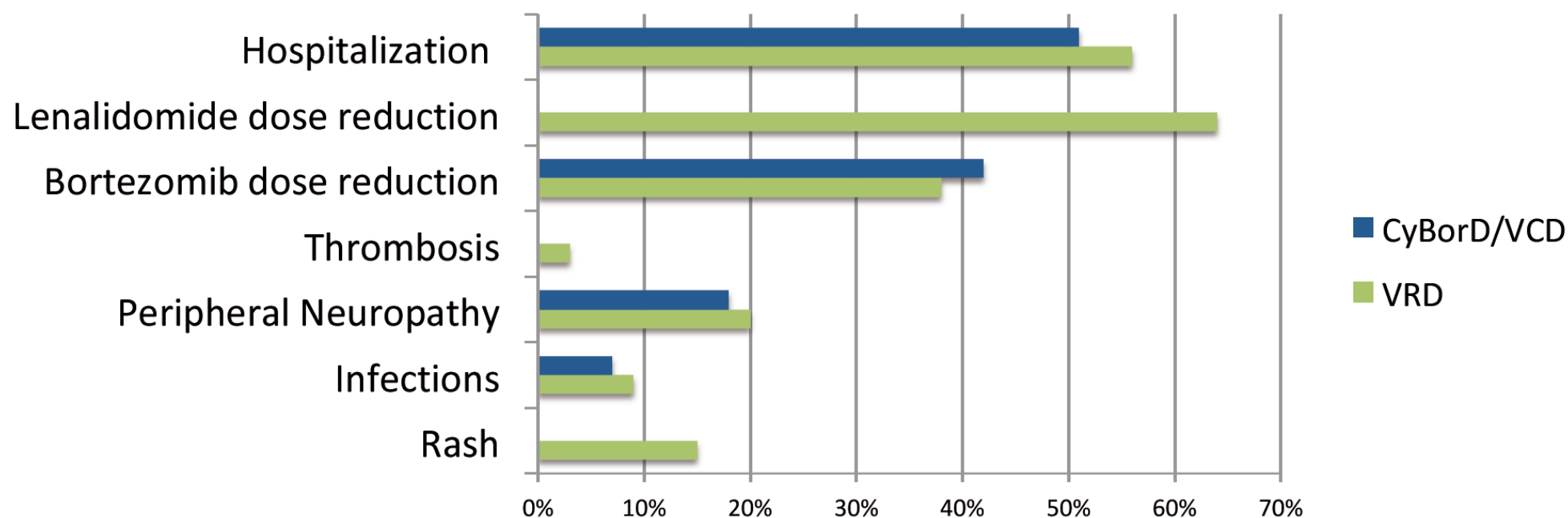


Kastritis, et al. *manuscript in preparation*
Bochtler, et al. *JCO* 2015

Bochtler, et al. *Amyloid* 2014
Palladini, et al. *Blood* 2017

Primary Treatment of Light Chain (AL) Amyloidosis With Bortezomib, Lenalidomide and Dexamethasone (VRD) or with Bortezomib, Cyclophosphamide and Dexamethasone (VCD/CyBorD): efficacy and toxicity

They compared the outcomes of 34 consecutive patients treated with VRD to a group of patients treated with CyBorD in their department, matched for Mayo stage, NTproBNP levels and baseline dFLC levels (1:2 matching, N=68 subjects treated with CyBorD).

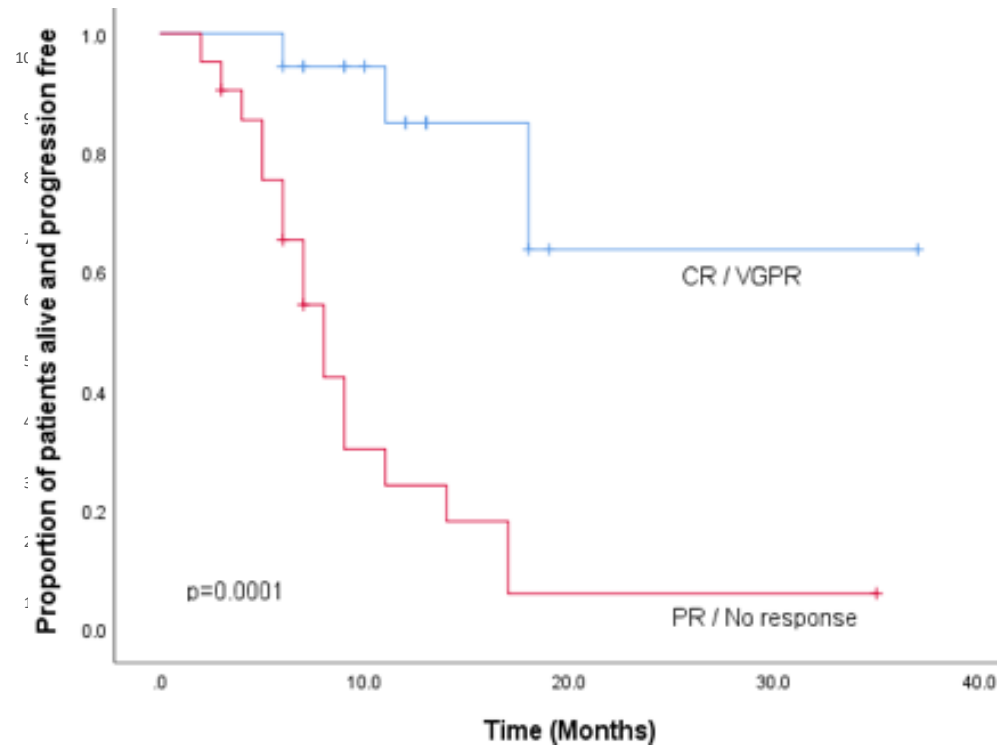


Kastritis et al, *IMW 2019* and *Blood Adv. 2019*

Ixazomib, lenalidomide and dexamethasone in relapsed AL amyloidosis – a first report

38 patients treated with IRd, between 2016 and 2019, were identified from the database at the UK National Amyloidosis Centre.

- Of 38 evaluable patients, 5 (13.2%) improved their response beyond 3 months
- 64.8% haematological response
- Median time to any response was 2 months (1-9 months)
- Cardiac and renal responses 5.9% and 14.3% respectively at 6 months



Wechalekar et al, *IMW* 2019

A Prospective Phase II study of Daratumumab in Previously Treated Systemic Light Chain (AL) Amyloidosis

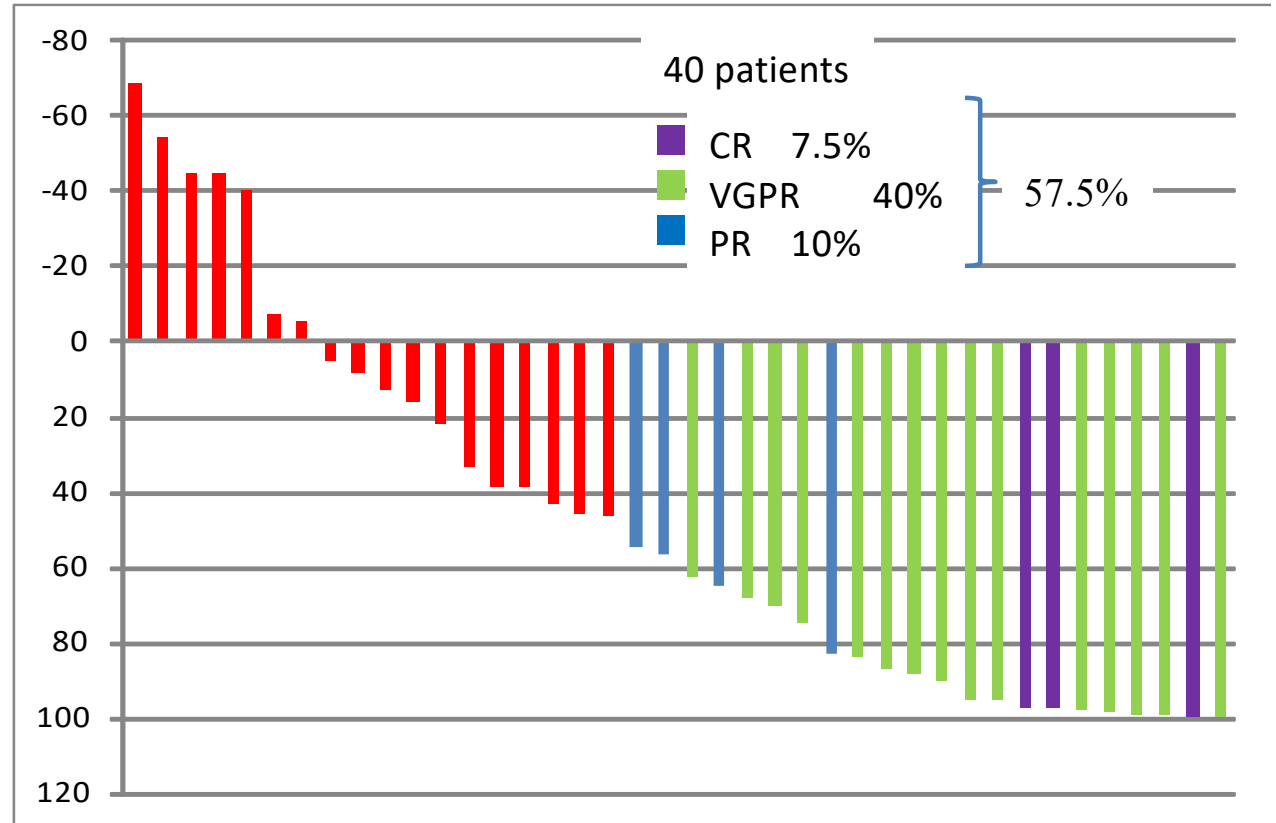
Best response	N (%)
≥VGPR	22 (55%)
PR	4 (10%)
NR	14 (35%)

Global response rate: 65%

Cardiac n=24 8 responses
 (30% decrease in NT-proBNP if baseline >650 ng/L)

Renal n=28 15 responses
 (30 % decrease in protU without 25% decrease in creat clearance)

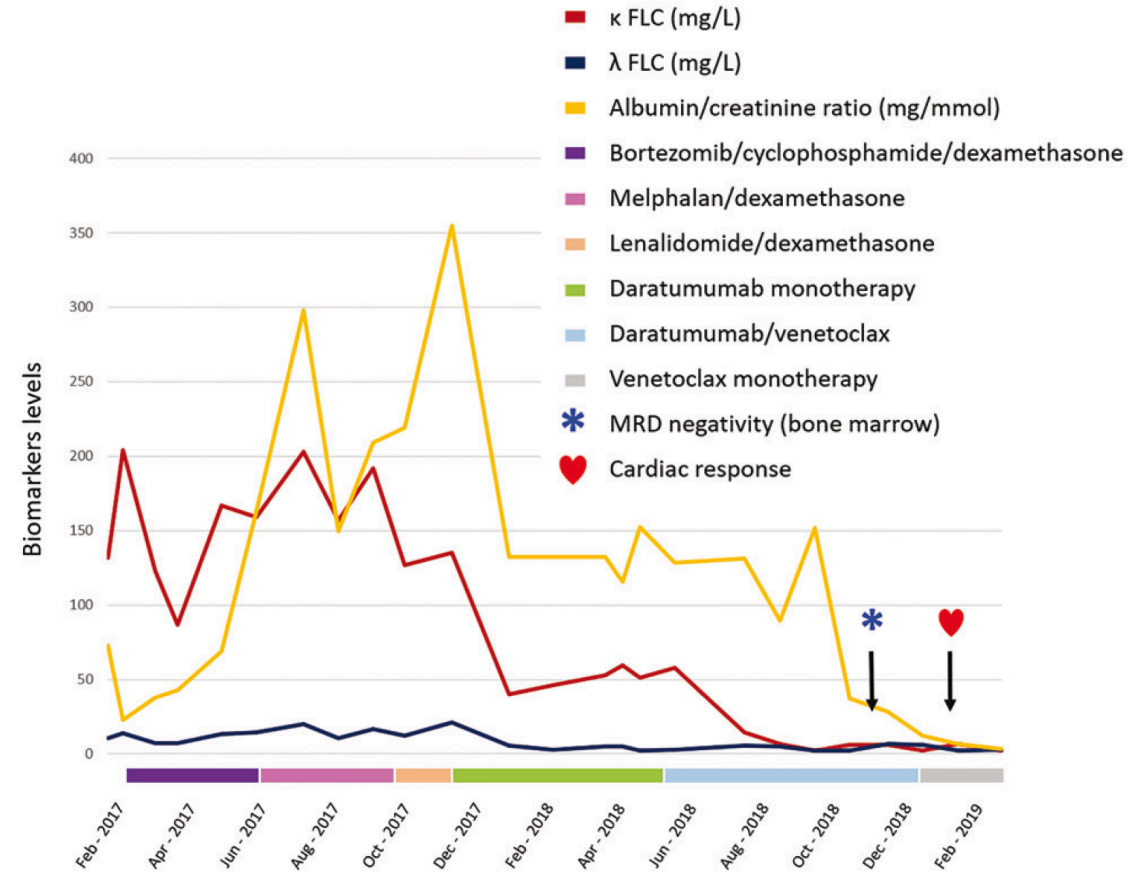
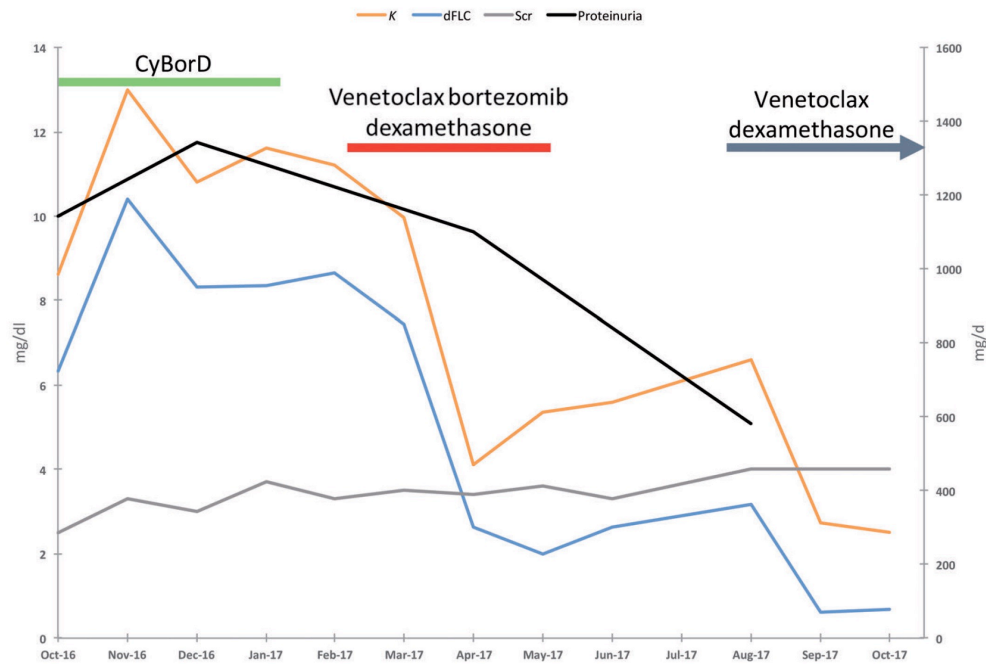
Deep and rapid clonal responses, even after the first injection



Phase III international study of CyBorD vs CyBorD+Dara upfront (ANDROMEDA) - Safety run-in results:
 Merlini et al, *EHA23 PS1318*

Roussel et al, *IMW2019 OAB-060*

Venetoclax in AL amyloidosis



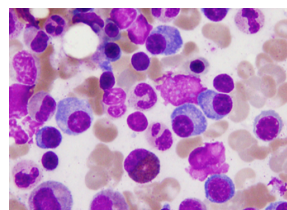
Leung et al, *Haematologica* 2018

Ghilardi et al, *Amyloid* 2019

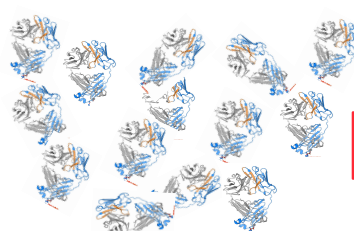
Pathways involved in AL systemic amyloidosis

Anti-plasma cell therapies

- ASCT
- Bortezomib-based
- MDex
- IMiDs
- Daratumumab
- Ixazomib
- Carfilzomib
- Bendamustine
- Venetoclax
- T-cell based therapy

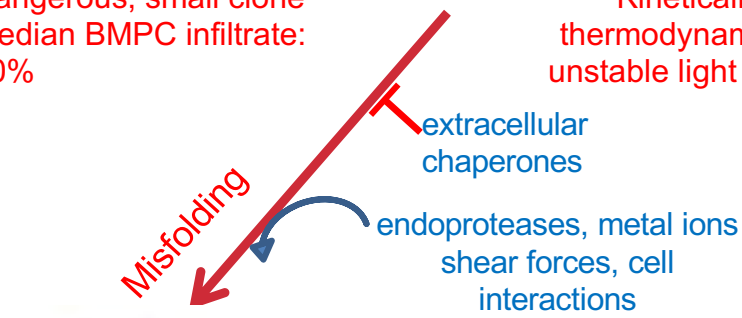
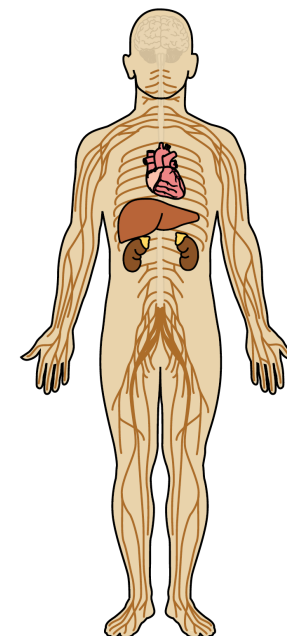


Dangerous, small clone
Median BMPC infiltrate:
10%



LC stabilizers

Kinetically/
thermodynamically
unstable light chains



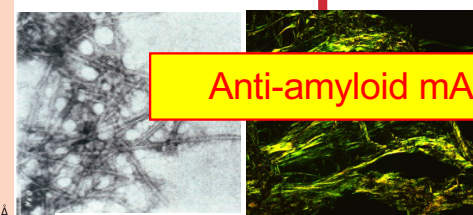
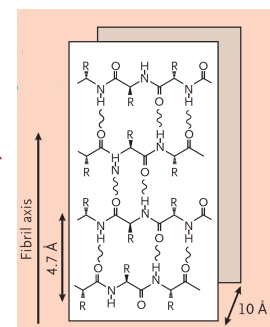
Oligomers

Doxycycline

Toxicity

Mass action and toxicity

SAP,
GAGs



Amyloid fibrils

Anti-amyloid mAbs

THANK YOU!