Approccio diagnostico e terapia dell'Amiloidosi nel 2023

Paolo Milani

Amyloidosis Research and Treatment Center - Foundation «IRCCS Policlinico San Matteo»
Department of Molecular Medicine - University of Pavia - Pavia, Italy

UNIVERSITÀ DI PAVIA

Fondazione IRCCS Policlinico San Matteo

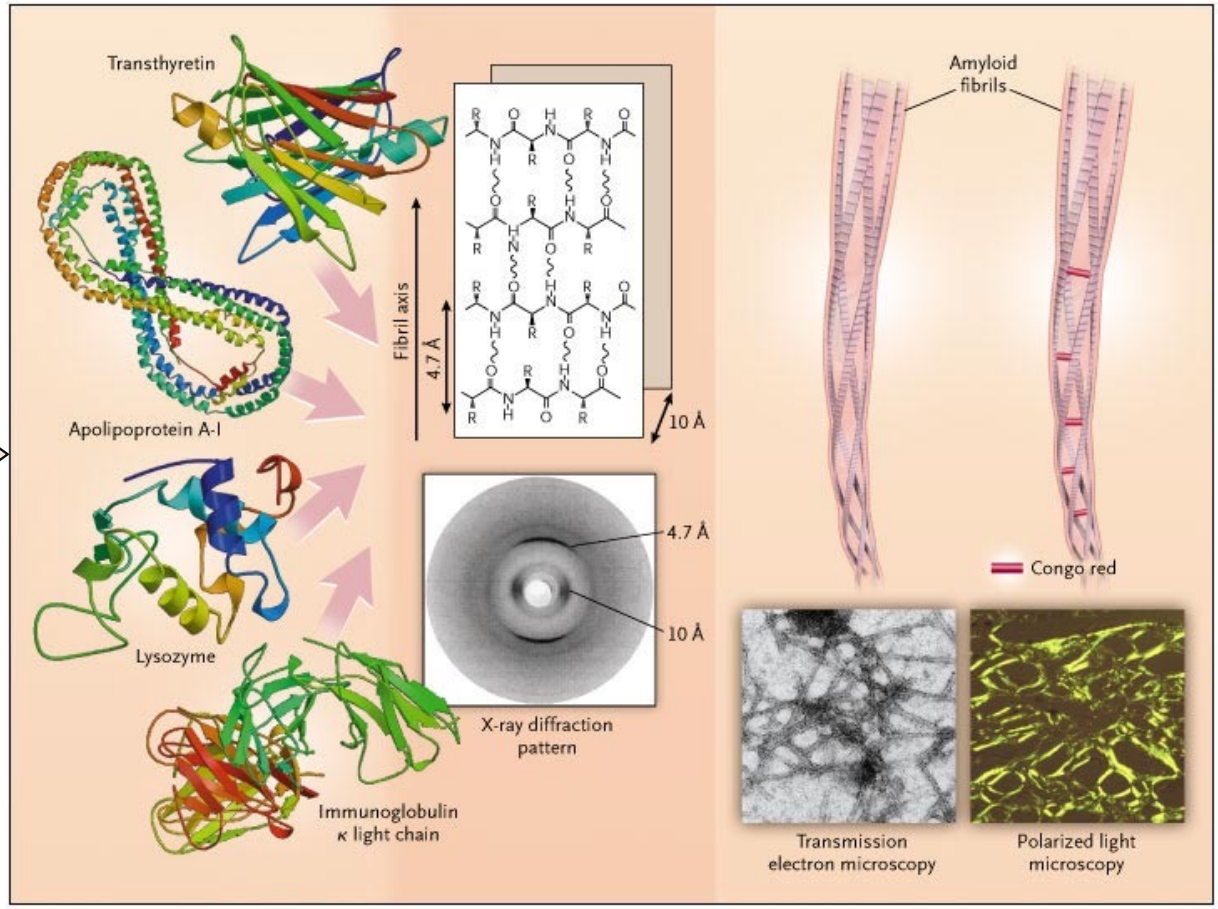
Sistema Socio Sanitario Regione Lombardia

Disclosures

- Jannsen-Cilag (Honoraria and Advisory Board)
- Siemens (Advisory Board)
- Pfizer (Honoraria)
- Sebia (Honoraria)

Systemic amyloidoses: protein misfolding diseases

- Mutations
- Increased concentration (increased synthesis or reduced clearance)
- Intrinsic propensity (ageing)



Merlini & Bellotti NEJM 2003

The main types of systemic amyloidosis have overlapping clinical presentations

Amyloid Type	Precursor protein	Major organ involvement					
		Heart (bone tracers 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	-	+++	+	-	-	-

Palladini, et al. Blood 2020

The main types of systemic amyloidosis have overlapping clinical presentations

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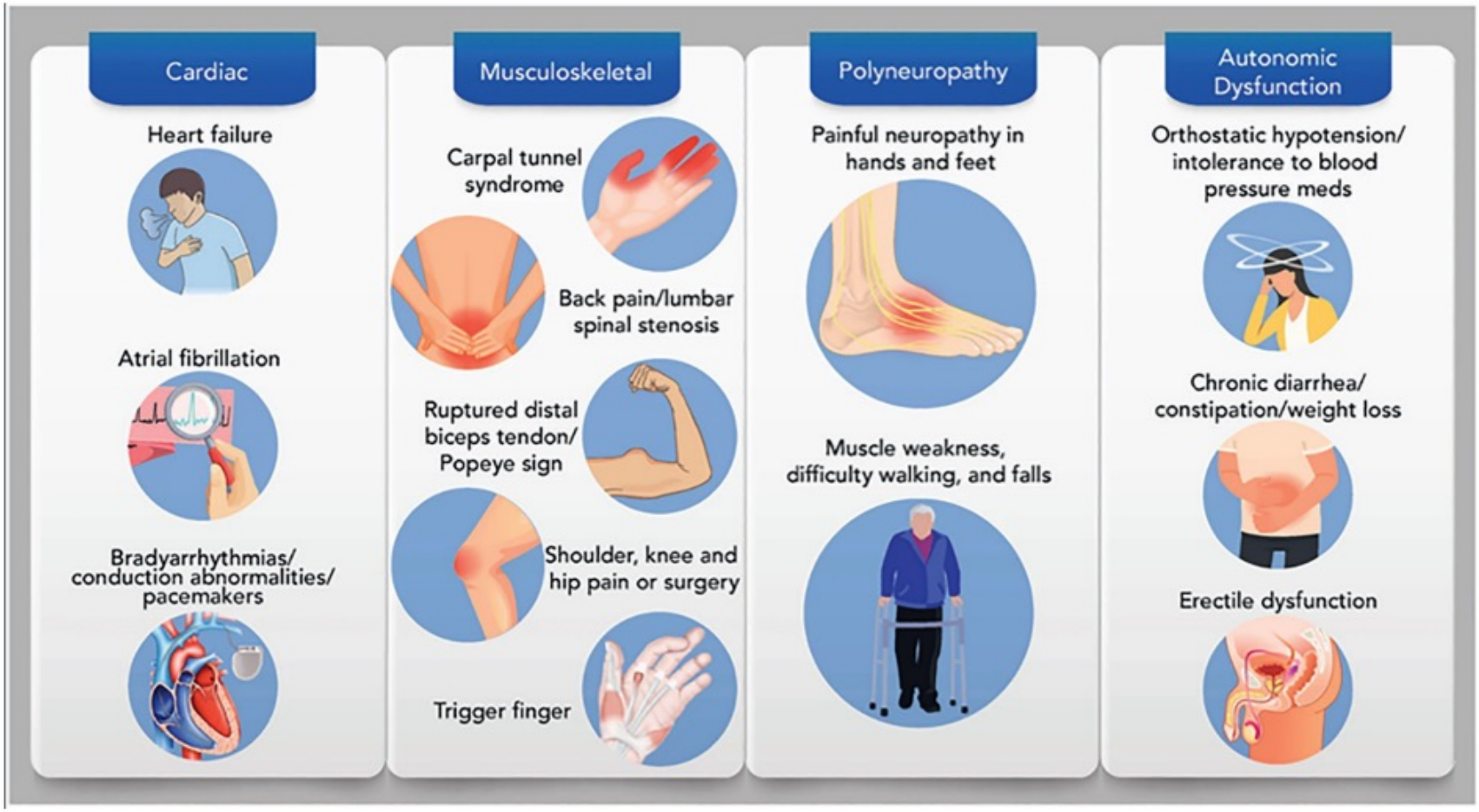
AA amyloidosis (acquired)	Serum amyloid A protein	+	+++	+	-	+	-
ALECT2 (acquired)	Leukocyte chemotactic factor 2	-	+++	+	-	-	-

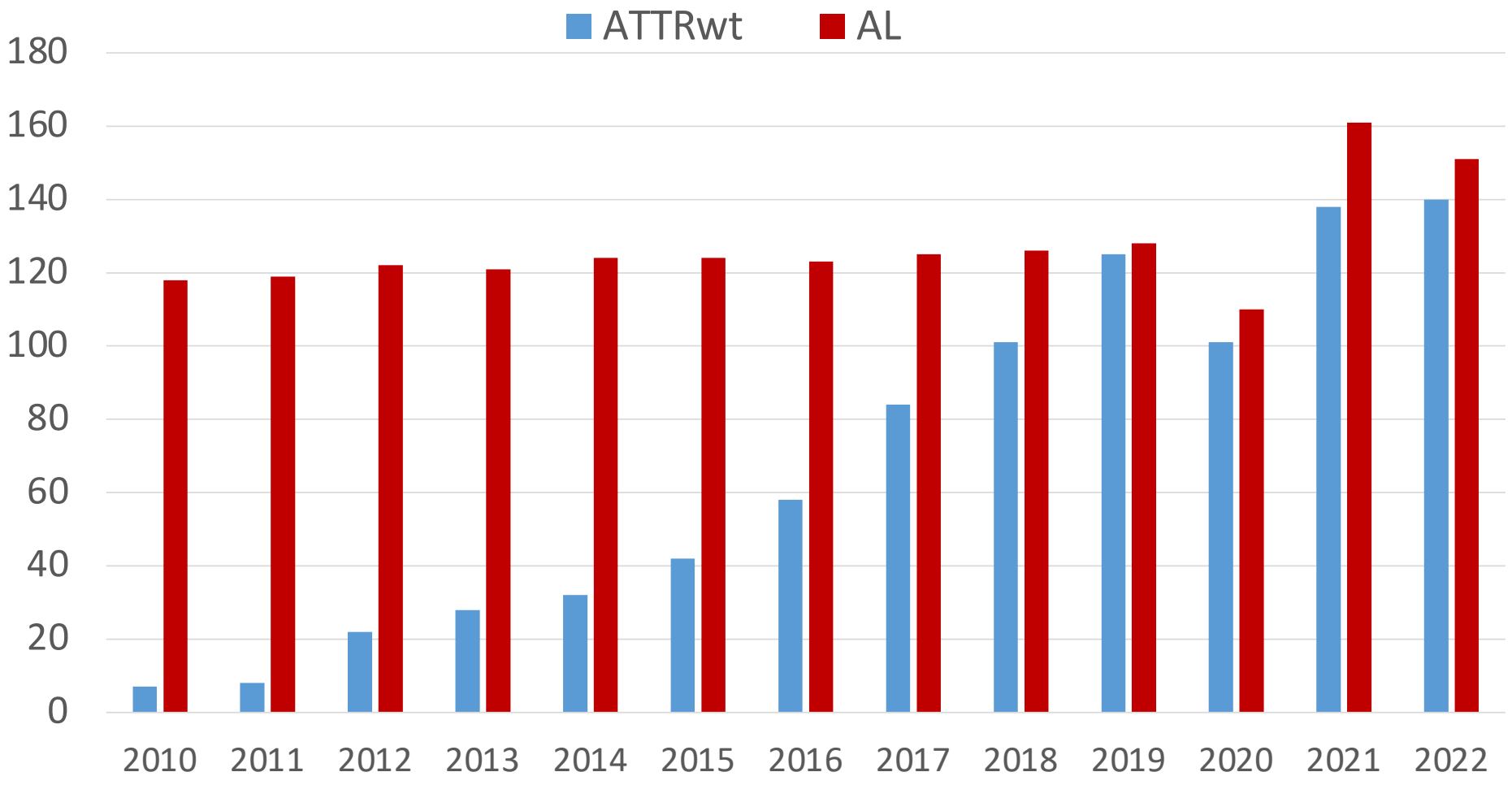
Palladini, et al. Blood 2020

AL amyloidosis manifests with signs and symptoms of organ involvement …

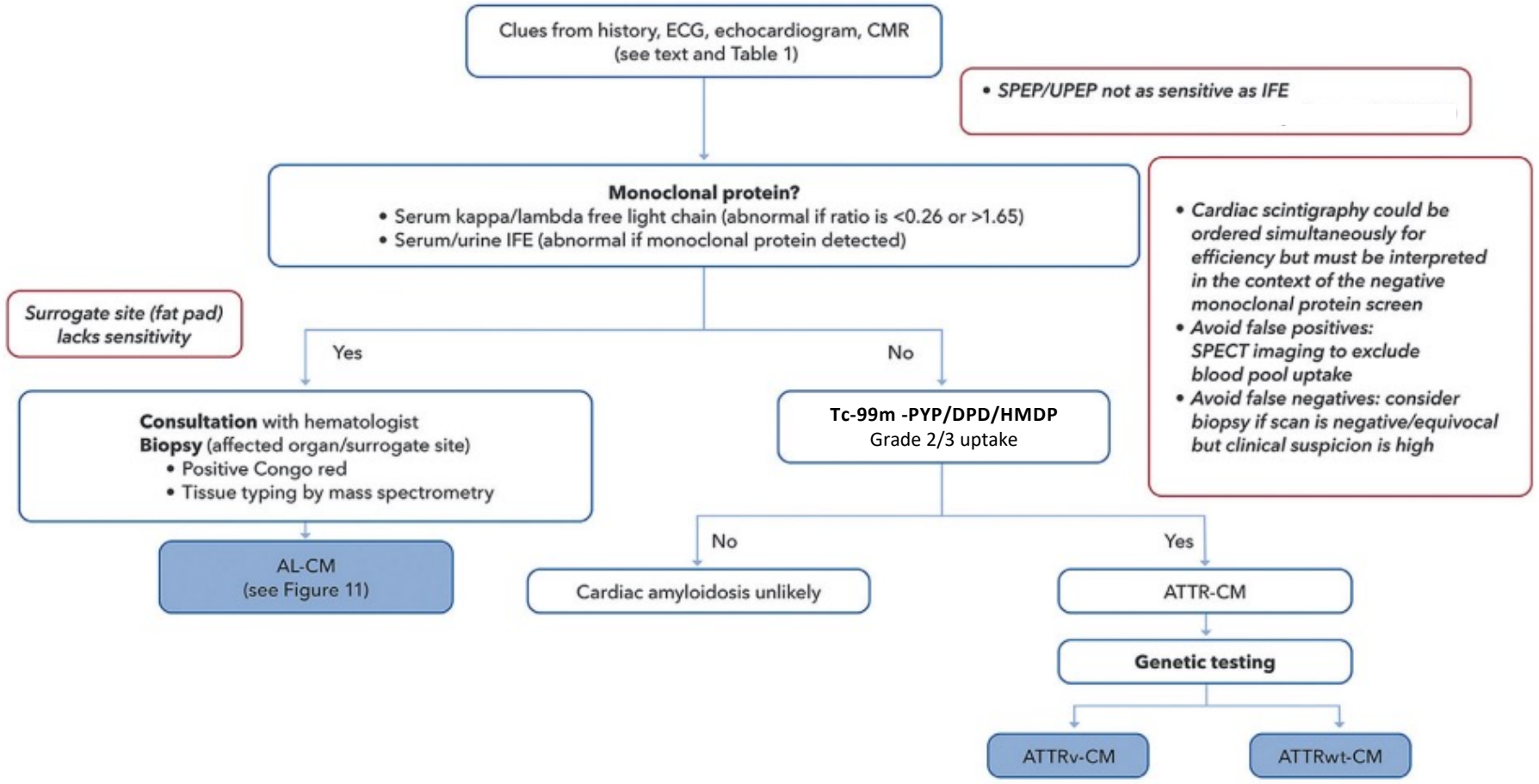


Nativi-nicolau et al. Heart Failure Rev 2022

Systemic amyloidosis in Pavia



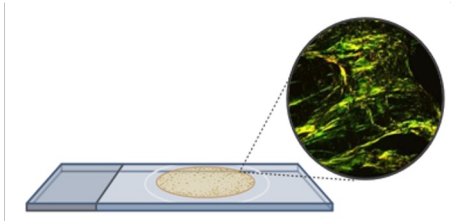
A Diagnostic Algorithm for Cardiac Amyloidosis



Modified from Kittleson et al. JACC 2023

The Italian Amyloid Referral Center of Pavia approach

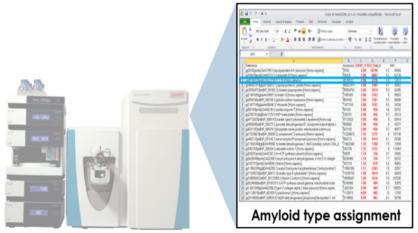
Congo red staining



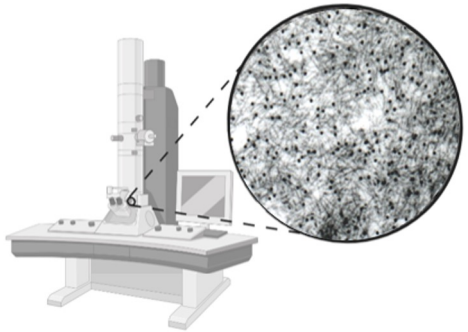
Characteristic green birefringence
when viewed under cross polarized light

Amyloid typing

Mass spectrometry



Immuno-electron microscopy



AMYLOID
2022, VOL. 29, NO. 1, 8–13
https://doi.org/10.1080/13506129.2021.1994386

Taylor & Francis
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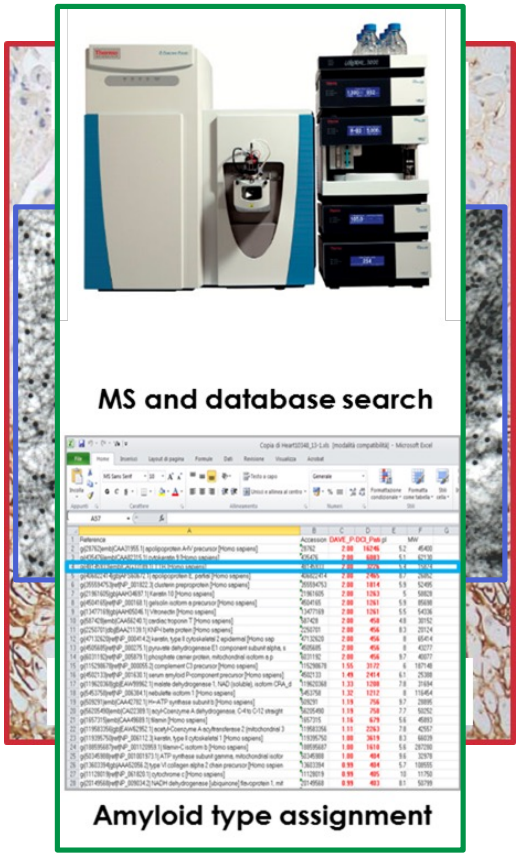
ARTICLE

OPEN ACCESS Check for updates

Tissue biopsy for the diagnosis of amyloidosis: experience from some centres

Merrill D. Benson[a], John L. Berk[b], Angela Dispenzieri[c], Thibaud Damy[d], Julian D. Gillmore[e], Bouke P. Hazenberg[f], Francesca Lavatelli[g], Maria M. Picken[h], Christoph Röcken[i], Stefan Schönland[j], Mitsuharu Ueda[k] and Per Westermark[l]

Amyloid typing



Typing – light microscopy immunohistochemistry

- X unreliable with commercial antibodies
- X correctly classifies 94% of patients with custom-made antibodies
- X **not allowed by Italian Medicines Agency (AIFA) for prescriptions**

Typing – electron microscopy immunohistochemistry

- ✓ correctly classifies >99% of patients with commercial antibodies

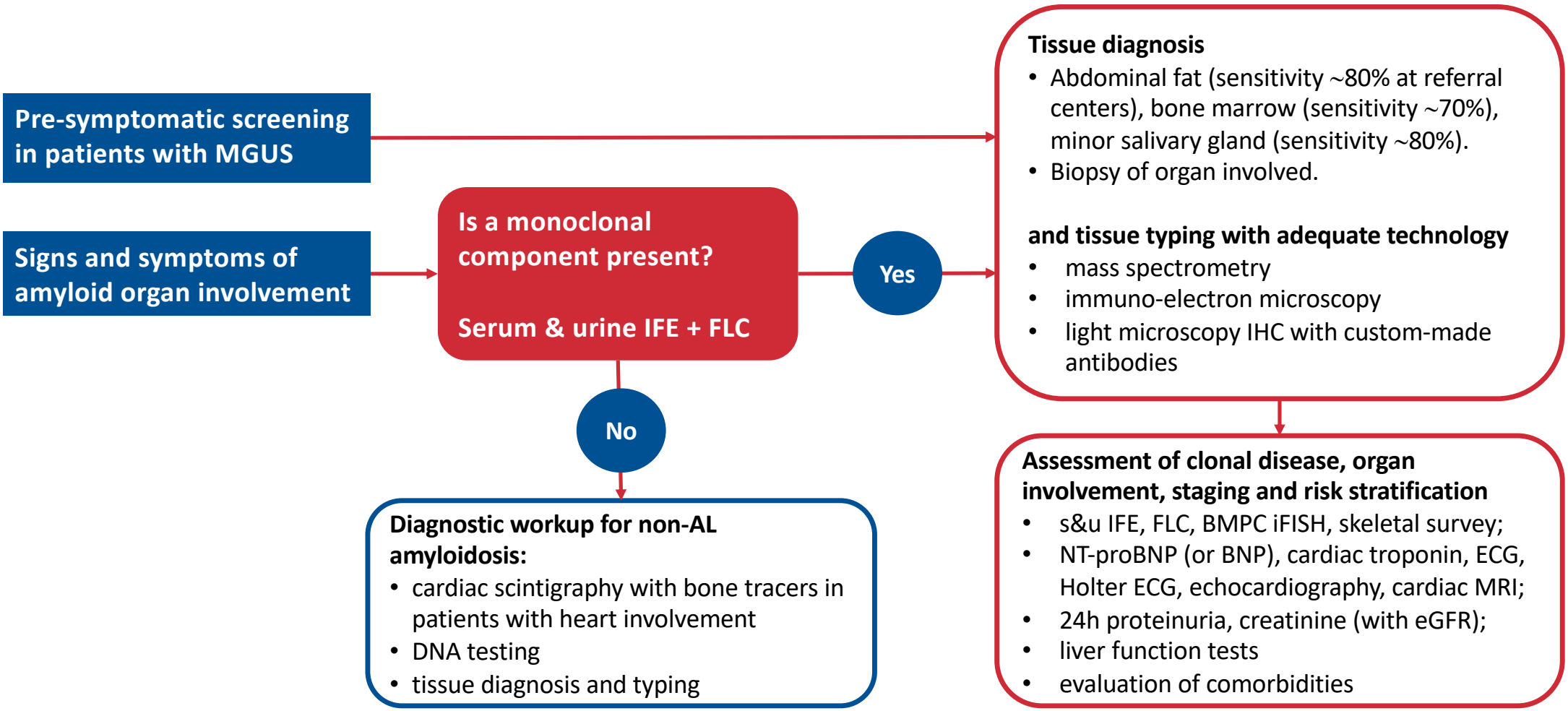
Typing – mass spectrometry

- ✓ laser capture microdissection, MudPIT
- ✓ not antibody dependent

Adequate technology and experience (high number of samples examined) are mandatory

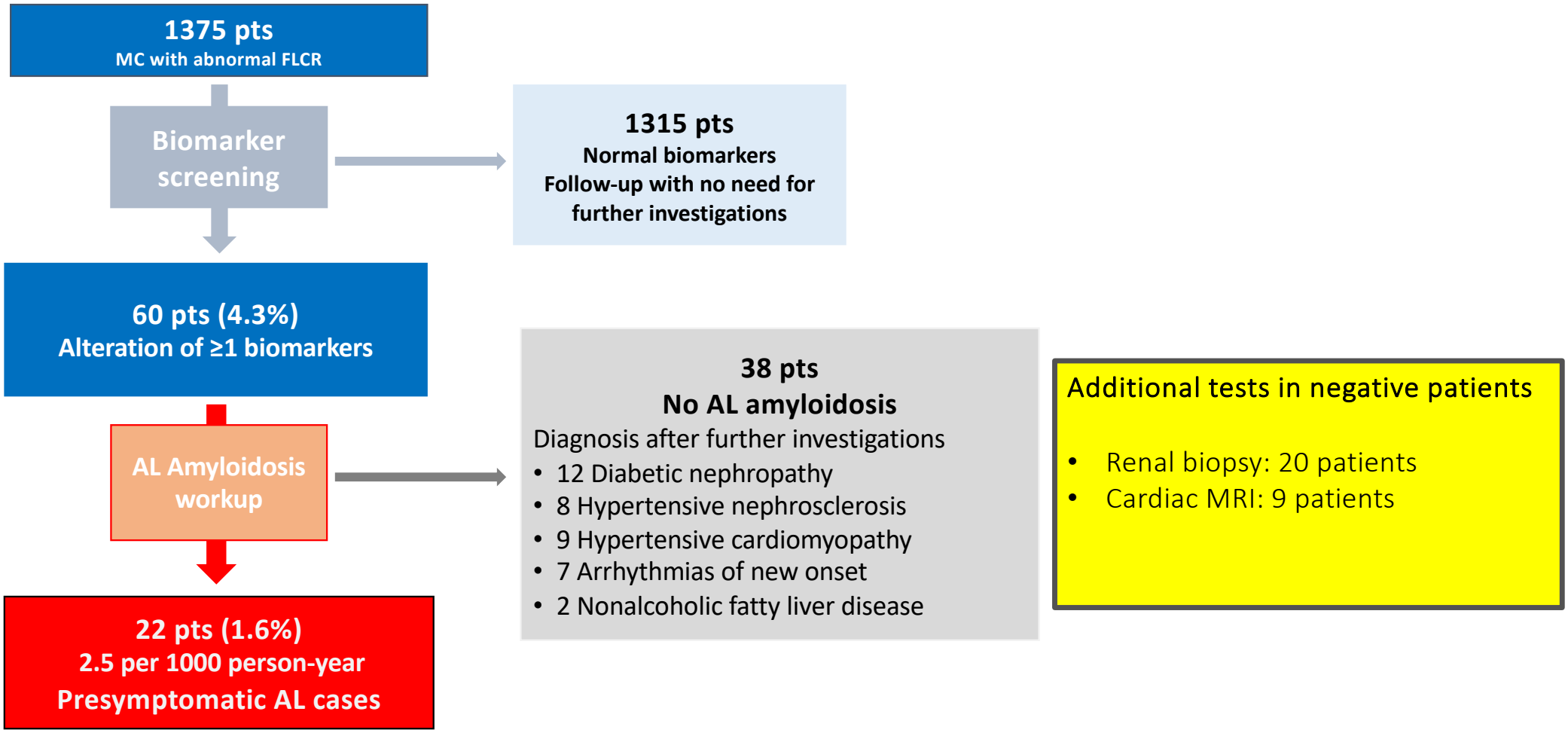
Satoskar, et al. Am J Surgical Pathol 2011
Schönland, et al. Blood 2012
Fernandez de Larrea, et al. Blood 2015
Vrana, et al. Blood 2009
Brambilla, et al. Blood 2012
Benson, et al. Amyloid 2021

Diagnosis of systemic amyloidosis



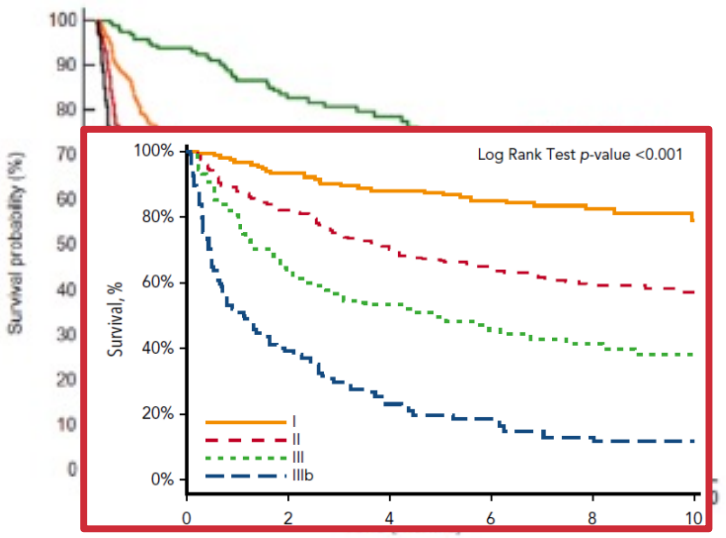
Pre-symptomatic diagnosis of systemic AL amyloidosis by biomarker based screening in patients with MGUS

Mangiacavalli et al. ISA2022



Biomarkers in cardiac staging

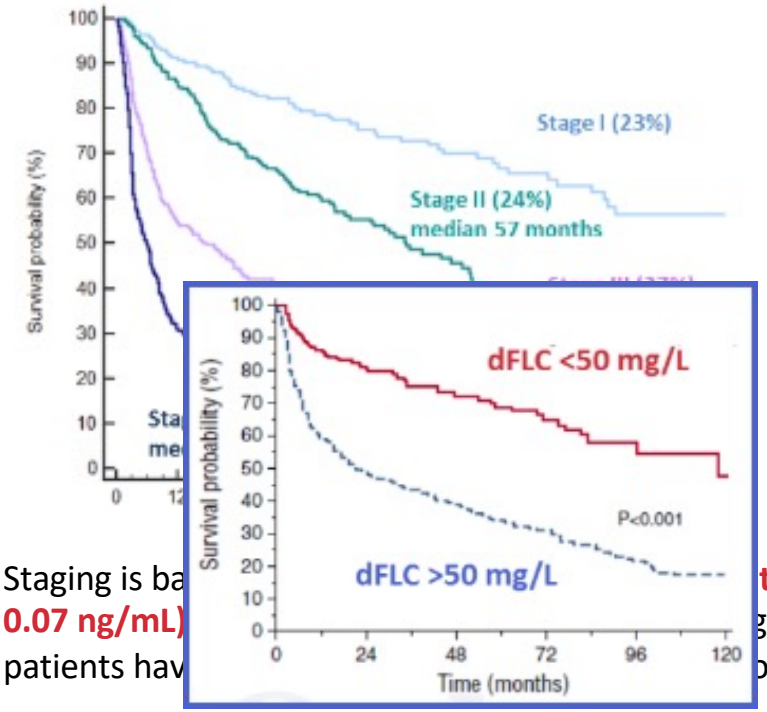
Mayo Clinic / European staging system



Staging is based on **BNP (cutoff 81 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 (>700 ng/L) BNP identifies patients with advanced cardiac dysfunction (Stage IIIb)

Dispenzieri, et al. JCO 2004
Wechalekar, et al. Blood 2013
Palladini, et al. Blood 2015

Revised Mayo Clinic staging system

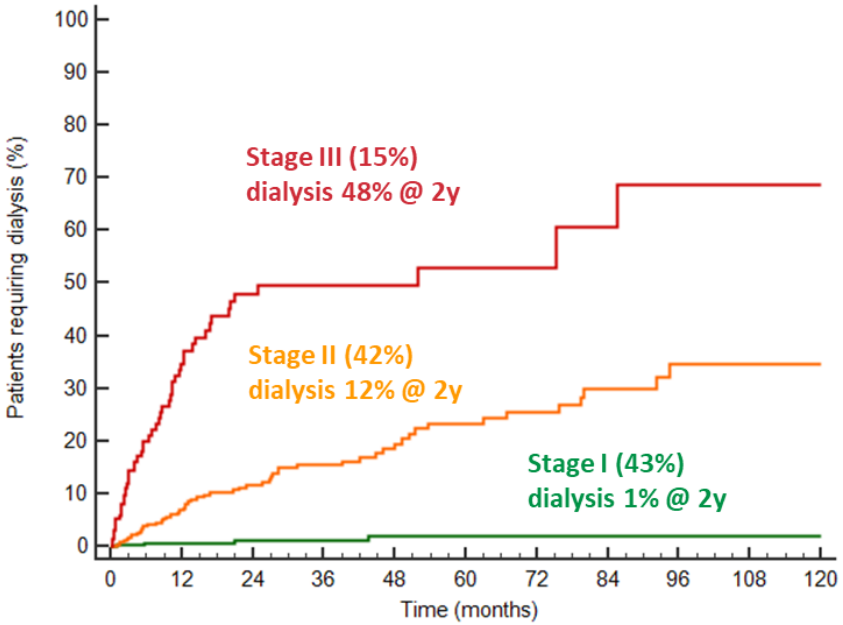


Staging is ba troponin I (cutoff 0.07 ng/mL) ge I, II, III, and IV patients hav offs.

Lilleness, et al. Blood 2019
Kumar, et al. JCO 2012
Palladini, et al. Haematologica 2014

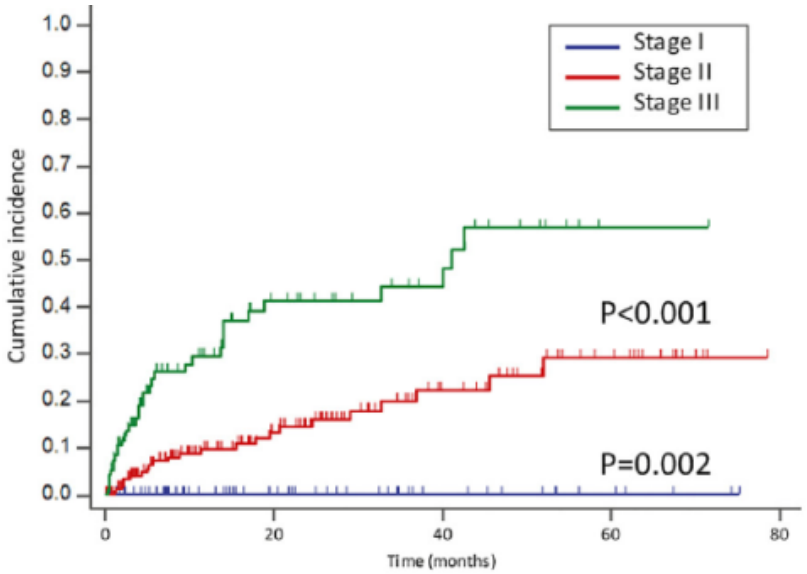
Milani, et al. Blood 2017
Dittrich, et al. Blood 2017
Sidana, et al. Leukemia. 2018

Biomarkers in renal staging



- 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, et al. Blood 2014



- Stage I: both **UACR** ≤3600 mg/g and **eGFR** ≥50 mL/min per 1.73 m^2
- Stage II: either **UACR** >3600 mg/g or **eGFR** <50 mL/min per 1.73 m^2
- Stage III: both **UACR** >3600 mg/g and **eGFR** <50 mL/min per 1.73 m^2

Basset et al. CCLM 2022

iFISH cytogenetics in AL amyloidosis

Associations with clinical characteristics

Heidelberg data

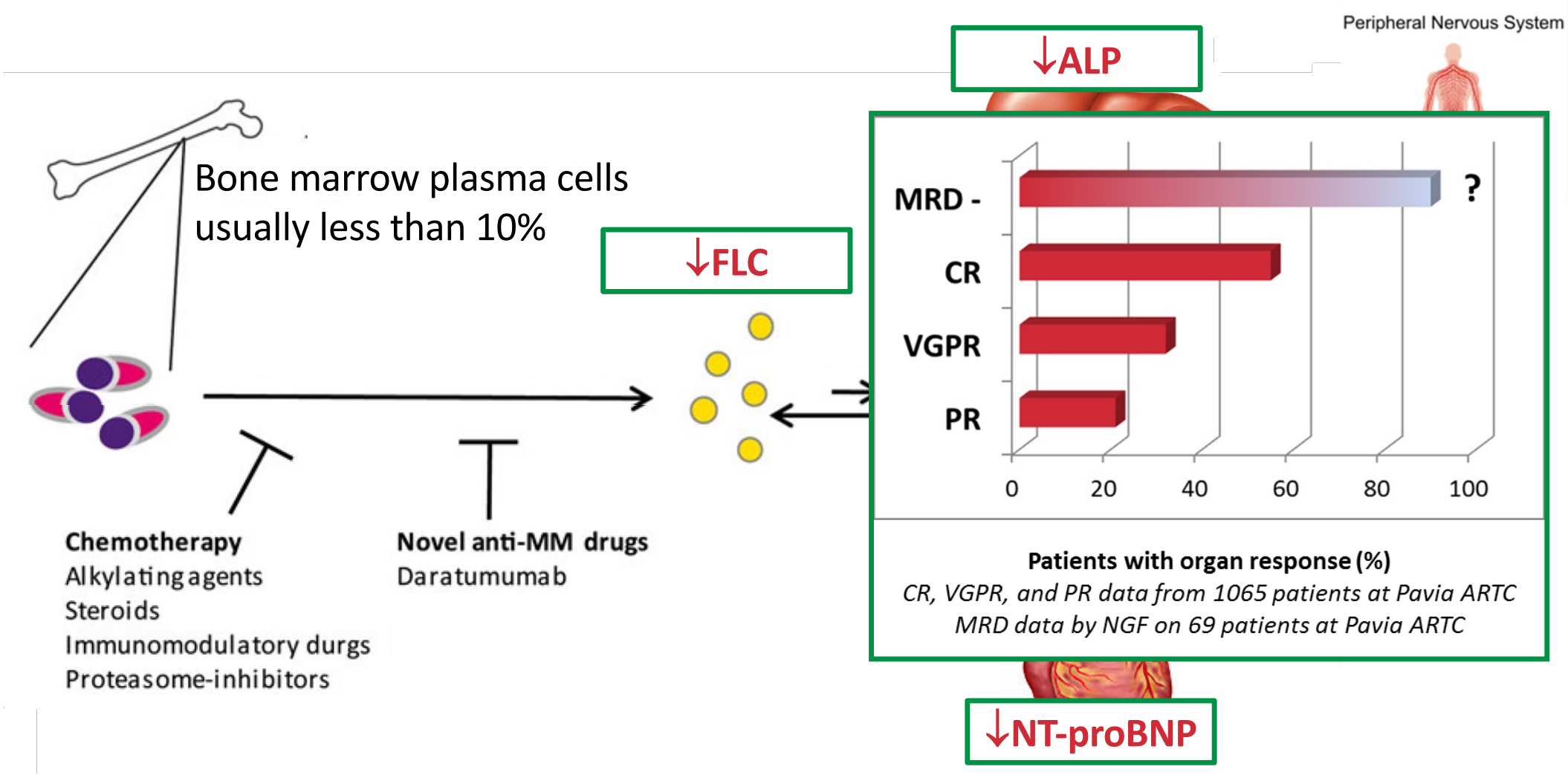
- **Translocation t(11;14) in 50%**
  - Light chain only / Bence Jones type
- **Hyperdiploidy in 11%**
  - Kappa light chain restriction
  - Higher plasma cell infiltration of the bone marrow
  - Higher age at diagnosis and heavy chain type
- **Overlap between t(11;14) and hyperdiploidy (2%)**
- **Gain of 1q21 in 20%**
  - Higher plasma cell infiltration of the bone marrow
  - Lambda light chain restriction

Mayo Clinic data

- **Translocation t(11;14) 39%**
- **Any Trisomy in 26%**
  - Kappa isotype more frequent
  - Highest dFLC and BMPC at diagnosis
  - Higher age at diagnosis
- **Overlap between t(11;14) and trisomies in (4%)**

Bochtler, *et al. Blood* 2008
Bochtler, *et al. Blood* 2011
Muchtar, *et al. Leukemia* 2017
Bryce, *et al. Haematologica* 2009
Warsame, *et al. Blood Cancer J* 2015

AL amyloidosis: hematologic disease + organ damage



AL, amyloid light-chain; ALP, alkaline phosphatase; ARTC, Amyloidosis Research and Treatment Centre; CR, complete response; FLC, free-light chains; MRD, minimal residual disease; NGF, next-generation flow; NT-proBNP, N-terminal-pro-hormone brain natriuretic peptide; PR, partial response; VGPR, very good partial response

Adapted from Nuvolone & Merlini. NDT 2016;32(5):770-80

AMYLOID
2022, VOL. 29, NO. 1, 1–7
https://doi.org/10.1080/13506129.2021.2002841

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GUIDELINE ARTICLE

Guidelines for high dose chemotherapy and stem cell transplantation for systemic AL amyloidosis: EHA-ISA working group guidelines

Vaishali Sanchorawala[a], Mario Boccadoro[b], Morie Gertz[c], Ute Hegenbart[d], Efstathios Kastritis[e], Heather Landau[f], Peter Mollee[g], Ashutosh Wechalekar[h] and Giovanni Palladini[i]

AMYLOID
https://doi.org/10.1080/13506129.2022.2093635

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GUIDELINE ARTICLE

Guidelines for non-transplant chemotherapy for treatment of systemic AL amyloidosis: EHA-ISA working group

Ashutosh D. Wechalekar[a], M. Teresa Cibeira[b], Simon D. Gibbs[c], Arnaud Jaccard[d], Shaji Kumar[e], Giampaolo Merlini[f], Giovanni Palladini[f], Vaishali Sanchorawala[g], Stefan Schönland[h], Christopher Venner[i], Mario Boccadoro[j] and Efstathios Kastritis[k]

Treatment selection in AL amyloidosis

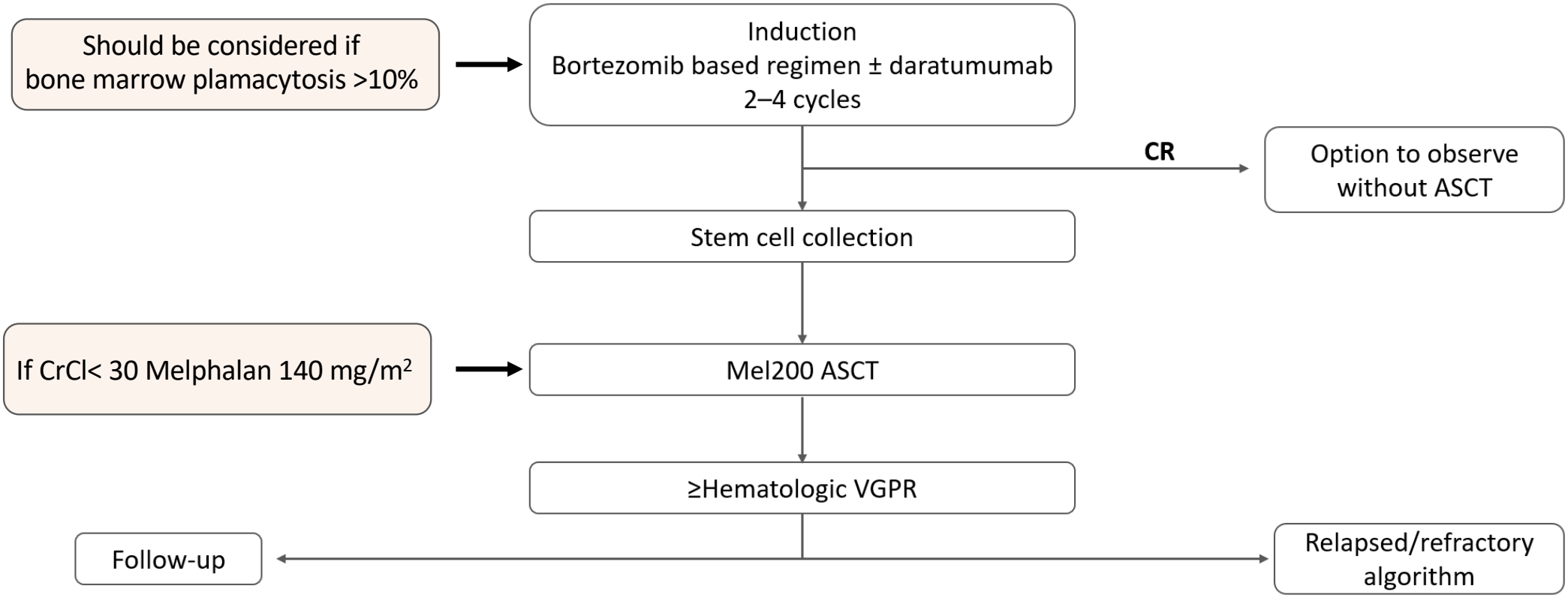
1. Assess eligibility for ASCT

ISA/EHA guidelines for ASCT eligible patients: eligibility criteria

Clinical evaluation	Inclusion criteria	Exclusion criteria
Age	• ≤65 years (patients aged 66-69 years can be considered at referral centers after careful multidisciplinary discussion).	-
Performance status	• Performance status (ECOG) 0-2 (unless caused by peripheral neuropathy).	-
Blood pressure	• Supine systolic blood pressure ≥90 mmHg	• Orthostatic hypotension refractory to medical therapy.
Heart assessment	• NYHA class I or II (if heart involvement is present). • Ejection fraction by echocardiography ≥40%. • Cardiac stage I or II (cardiac stage III patients can be considered at referral centers after careful multidisciplinary discussion). • NT-proBNP <5000 ng/L. • Troponin I <100 ng/L or troponin T <60 ng/L or hs-troponin T <75 ng/L	• Symptomatic and/or medically refractory ventricular and atrial arrhythmias. • Uncompensated heart failure.
Liver assessment	• Direct bilirubin <2 mg/dL	-
Kidney assessment	• eGFR >50 mL/min per 1.73 m^2 (patients whose eGFR is between 50 and 30 mL/min can be considered at referral centers after careful multidisciplinary discussion). • Patients on chronic and stable schedule of dialysis should not be excluded.	-
Respiratory function	• Oxygen saturation ≥95% on room air. • DLCO >50%.	• Symptomatic and/or medically refractory pleural effusions.
Hemorrhagic risk assessment	-	• Factor X deficiency with factor X level of <25% or/and evidence of active bleeding. • Extensive GI involvement with evidence of active GI bleeding or risk of bleeding.

Sanchorawala, et al. Amyloid 2022

ISA/EHA guidelines for ASCT eligible patients



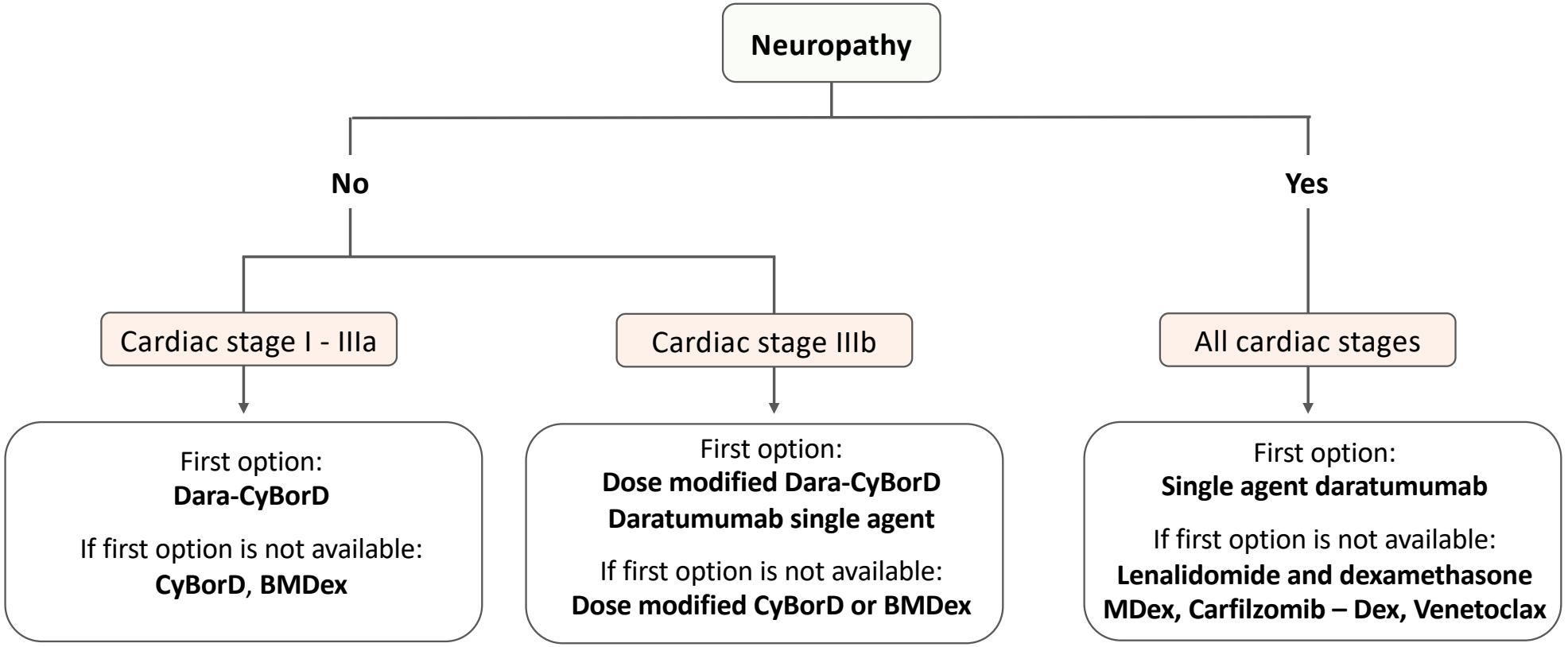
Sanchorawala, et al. Amyloid 2022

Treatment selection in AL amyloidosis

1. Assess eligibility for ASCT

2. Assess specific comorbidities in subjects who are not transplant candidates

ISA/EHA guidelines for non-transplant chemotherapy

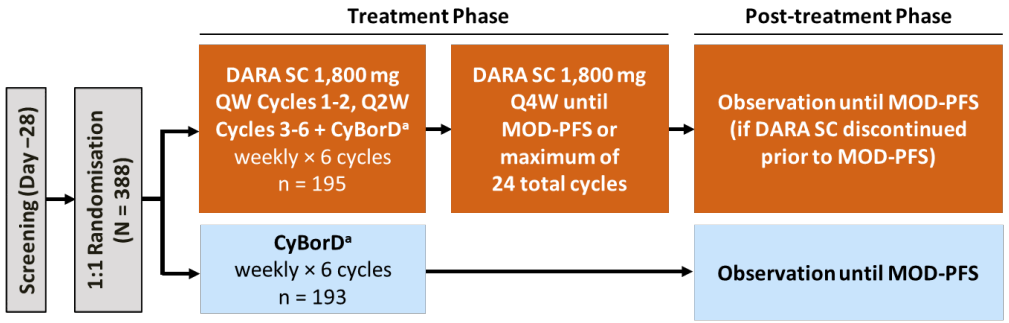


Wechalekar, et al. Amyloid 2022

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

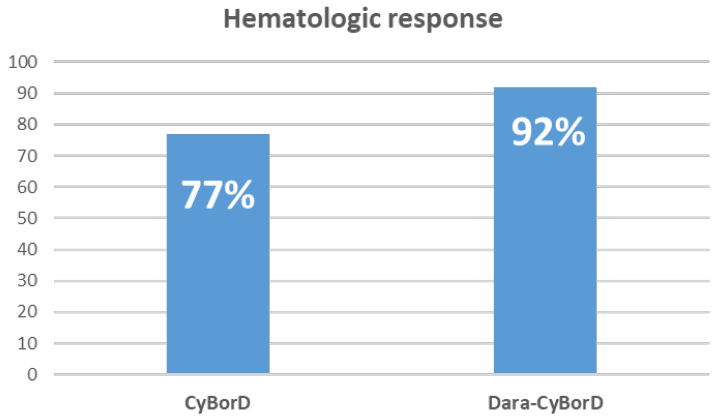
Key eligibility criteria:

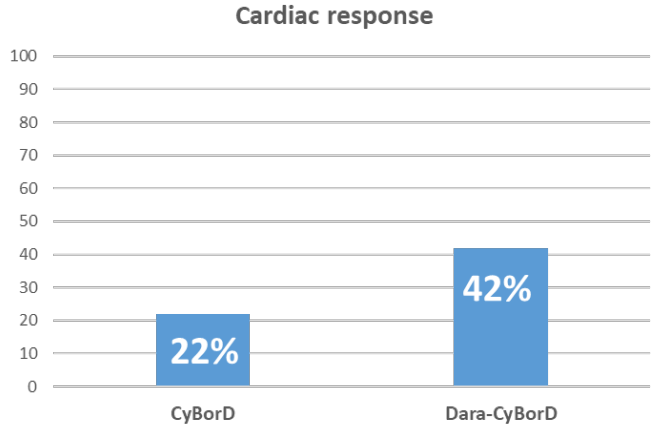
- AL amyloidosis with ≥1 organ impacted
- No prior therapy for AL amyloidosis or MM
- Cardiac stage I-IIIA (Mayo 2004)
- eGFR ≥20 mL/min

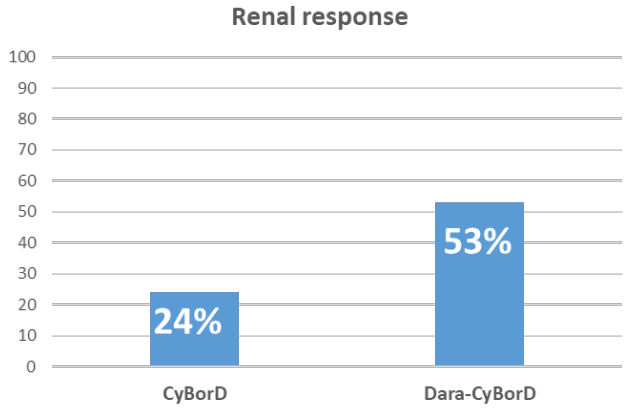


Stratification criteria:

- Cardiac stage (I vs II vs IIIA)
- Transplant typically offered in local country (yes vs no)
- Creatinine clearance (≥60 mL/min vs <60 mL/min)



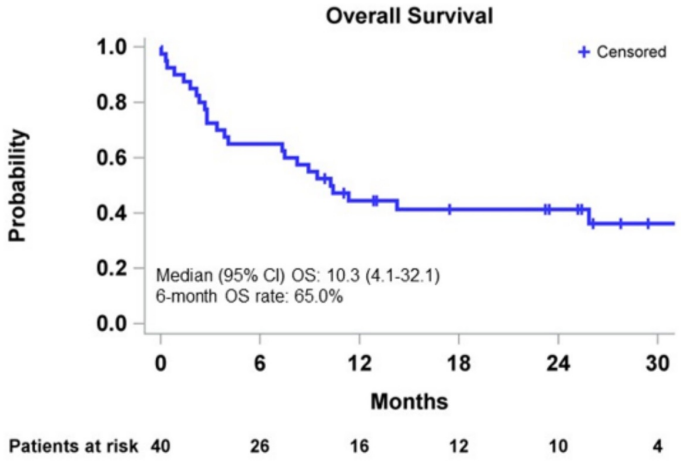


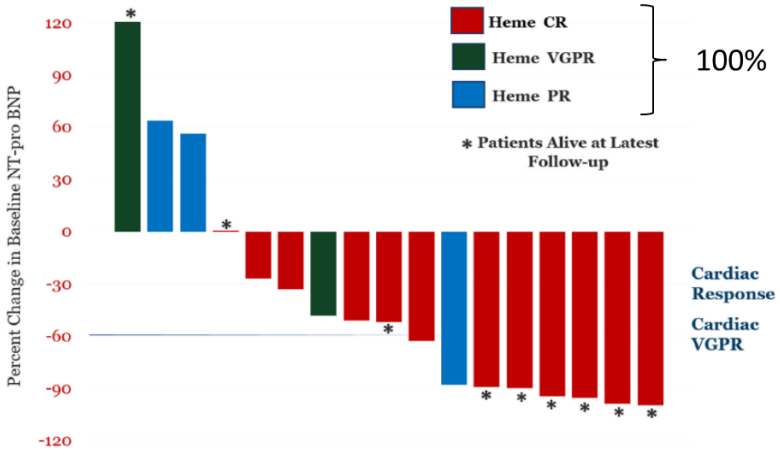


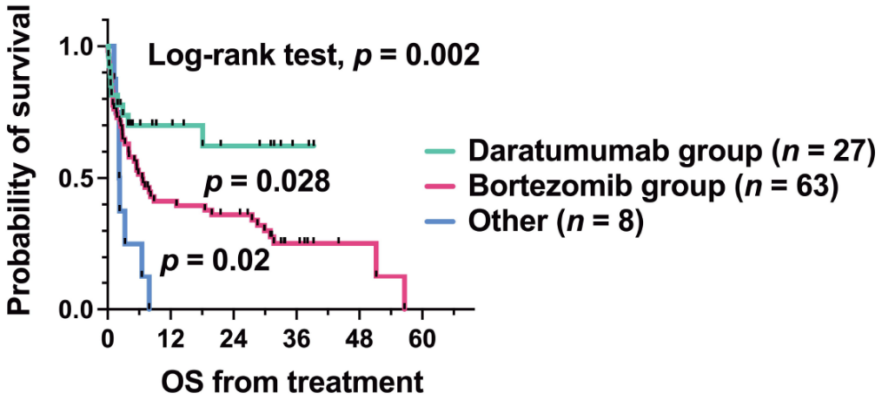
Kastritis, et al. NEJM 2021

Daratumumab combinations in stage IIIb patients

Figure. Overall Survival





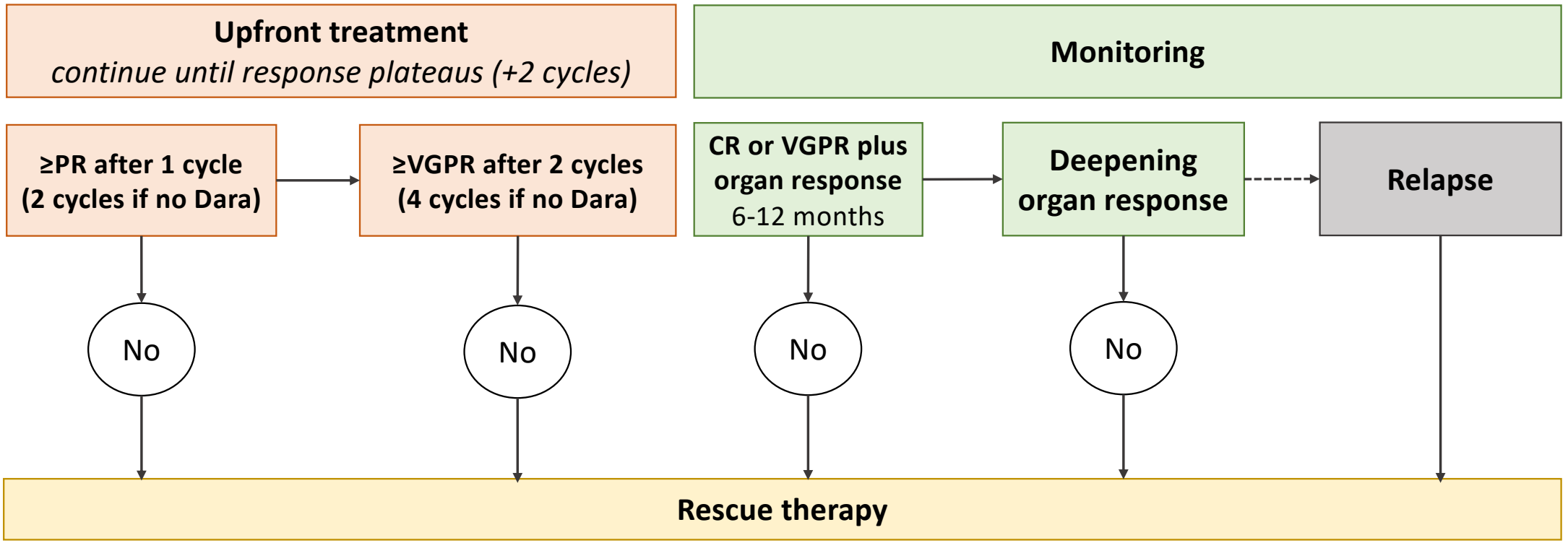


In high-risk (stage 3B) AL amyloidosis pts, dara monotherapy induced early and profound hematologic responses over 6 months with 77.5% of pts achieving more than PR and 50% VGPR/CR, and cardiac responses were seen in 27.5% of pts.

Kastritis, et al. ASH 2023 – oral abstract

Chakraborty Br J Haematol 2023
Oubari, et al. Haematologica 2023

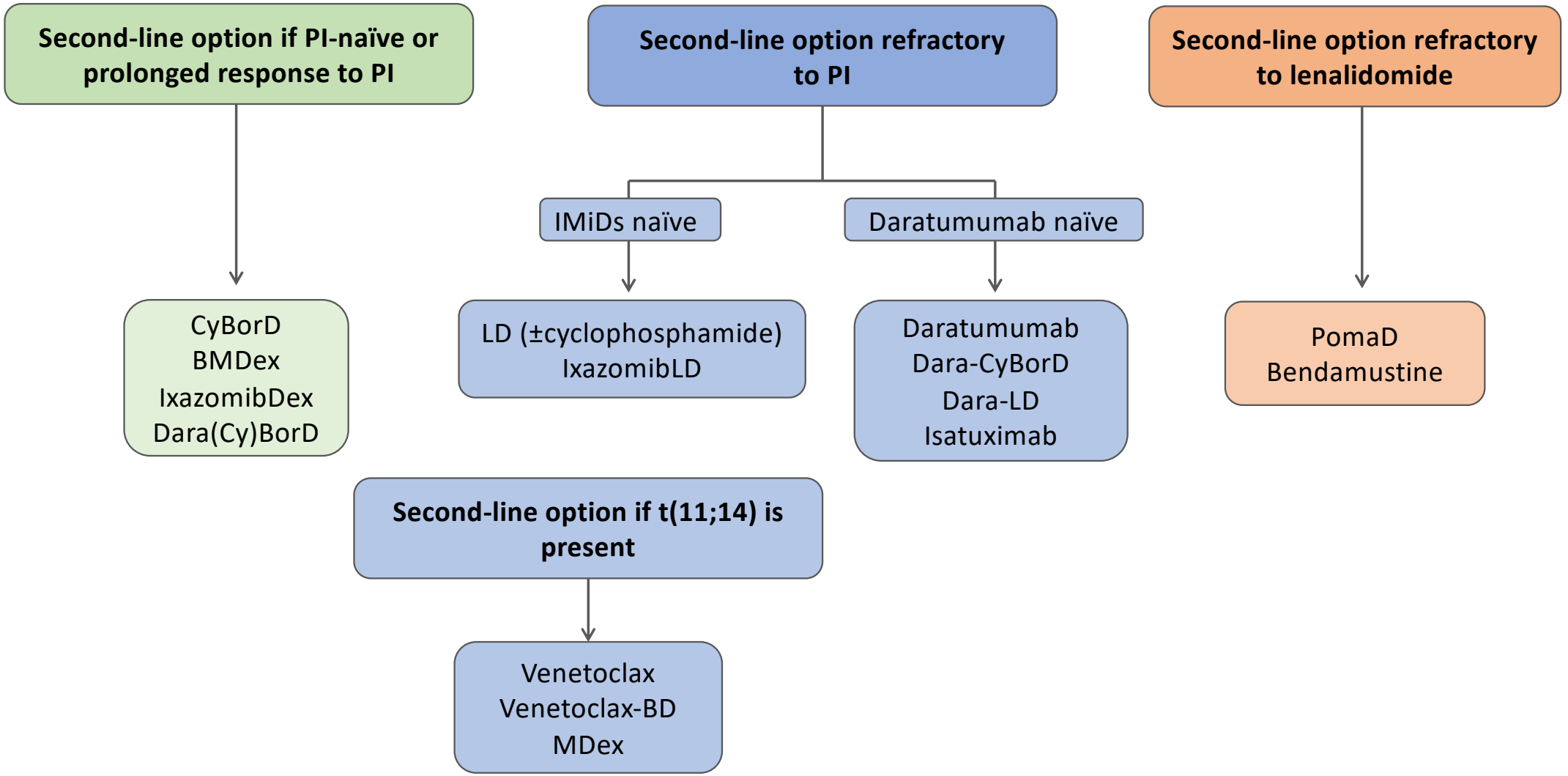
Tentative monitoring schedule during (and after) treatment



CR, complete response; dara, daratumumab; PR, partial response; VGPR, very good response

Adapted from Palladini & Milani. Curr Opinion Oncol 2022

ISA/EHA guidelines for non-transplant chemotherapy



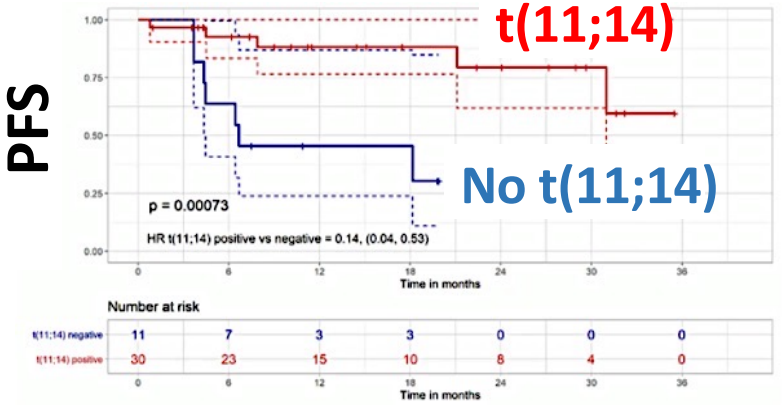
BD, bortezomib, dexamethasone; BMDex, bortezomib, melphalan, dexamethasone; CyBorD, cyclophosphamide, bortezomib, dexamethasone; Dara, daratumumab; IMiDs, immunomodulatory drug; PI, proteasome inhibitor; PomaD, pomalidomide, dexamethasone

Wechalekar et al. Amyloid 2022;1-15

Novel anti plasma cell agents in AL

Venetoclax in patients with t(11;14)

- VGPR/CR: 78%
- Effective after daratumumab

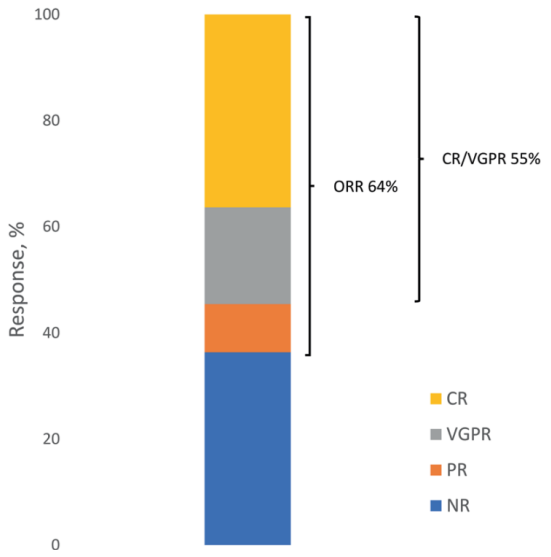


Premkumar, et al. Blood Cancer J 2021

- The overall hematologic response rate was 88%, 35% achieved a CR, and 35% achieved VGPR.

Lebel et al. Cancer 2023

Belantamab mafodotin



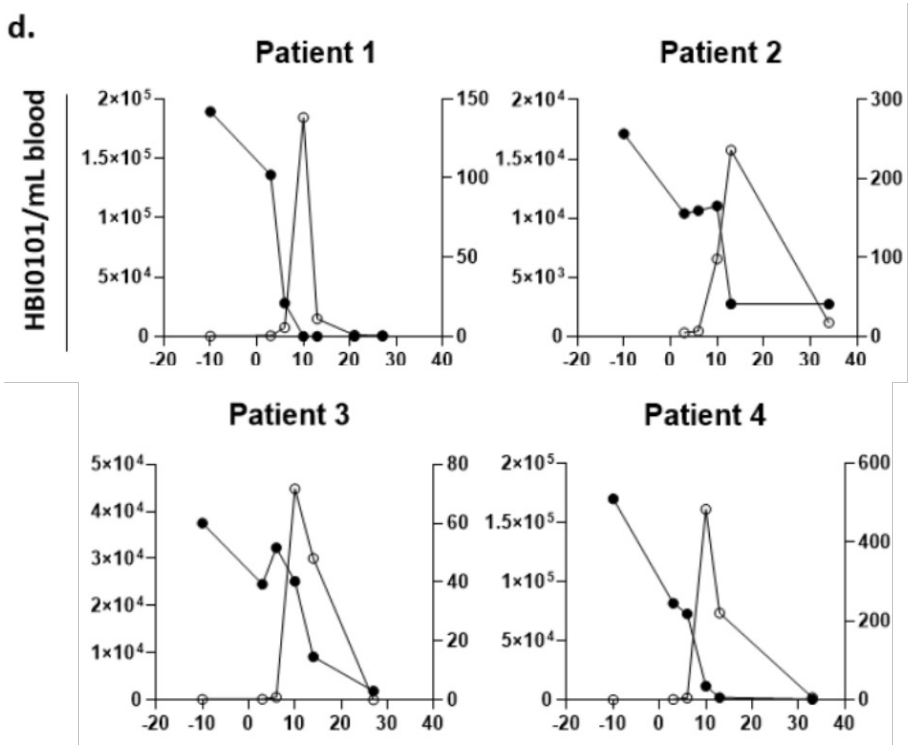
Khwaja et al. Blood Cancer J 2022

- The overall response rate was 72.7% (8 pts; VGPR: 3 pts and PR: 5 pts).
- Four (36.4%) pts had ≥1 SAE, including 2 (18.2%) pts with a belamaf-related grade 2 and 4 visual impairment (1 [9.1%] pt each).

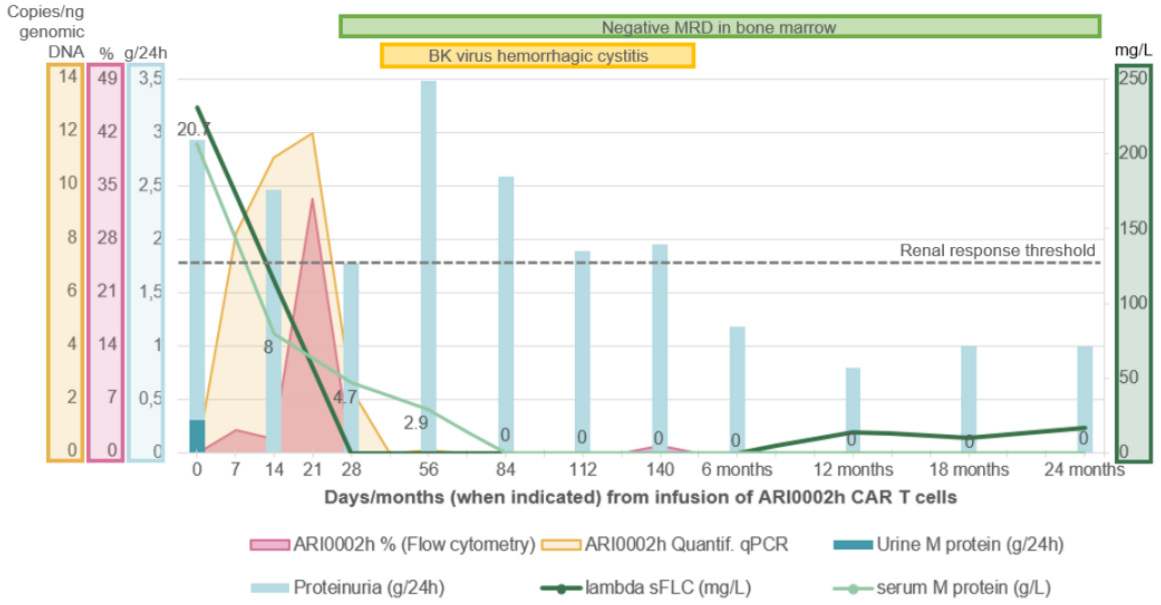
Kastritis et al. EHA2023 abstract

Novel anti plasma cell agents in AL

A novel academic BCMA-CART (HBI0101)



4/4 patients attained CR + organ response



Responses to CAR-T are long-lasting

538 Feasibility of a Novel Academic Anti-BCMA Chimeric Antigen Receptor T-Cell (CART) (HBI0101) for the Treatment of Relapsed and Refractory AL Amyloidosis *Gatt et al. ASH23 – oral abstract*

Kfir-Erenfeld, Asherie, et al. Clin Cancer Res 2022

Oliver-Caldes, et al. ISA 2022

Anti-Fibrillar Antibodies: CAEL-101

- **CAEL-101**
  - **Phase 1a/b: 27 pts, 63% had evidence of organ response**
  - **Phase 2: CAEL-101 dose 1000 mg/m² with CyBorD (+/- Dara)**
    - No obvious impact on rate of hematologic responses
    - Organ responses in 2-7 months (heart 15/19, renal 9/9)

540 Safety and Tolerability of Cael-101, an Anti-Amyloid Monoclonal Antibody, Combined with Anti-Plasma Cell Dyscrasia Therapy in Patients with Light-Chain Amyloidosis: 24-Month Results of a Phase 2 Study.

Valent et al. ASH2023 – oral abstract

A Study to Evaluate the Effectiveness and Safety of CAEL-101 in Patients With Mayo Stage IIIa AL Amyloidosis (NCT04512235) → closed

A Study to Evaluate the Effectiveness and Safety of CAEL-101 in Patients With Mayo Stage IIIb AL Amyloidosis (NCT04504825) → closed

Valent et al. ASH2021 abstracts 468 & 482
Solomon, et al. Clin Cancer Res 2003
Edwards, et al. Blood 2021

Survival Benefit of Birtamimab in Mayo Stage IV AL Amyloidosis in the Phase 3 VITAL Study

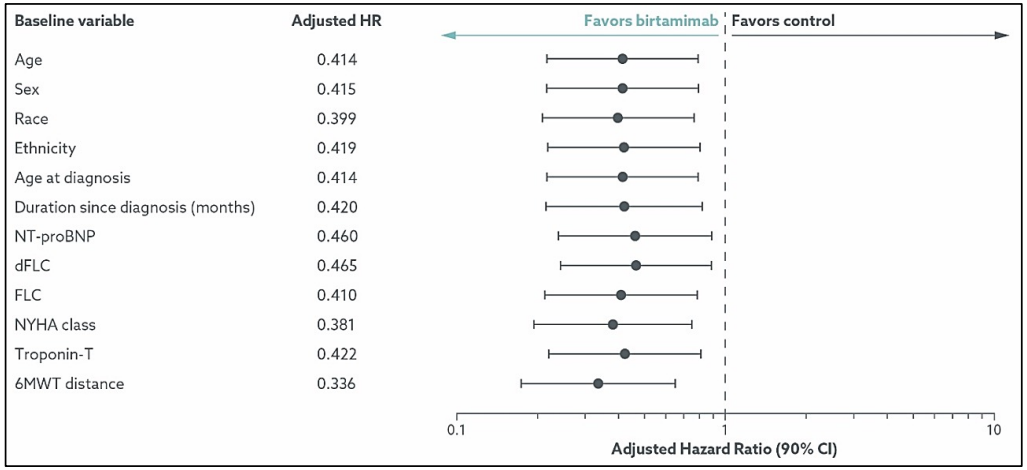
Results

- Of the 260 patients enrolled in the VITAL study,
  77 (29.6%) were characterized as Mayo Stage IV at baseline,
  38 randomized to birtamimab + SOC, and
  39 to placebo + SOC
  - Patients had a median age of 64 years and were primarily white (93.5%) and male (68.8%)
  - Baseline demographic and clinical characteristics were generally balanced between the 2 treatment groups among these patients

Conclusions

- Birtamimab is the only investigational therapy that has shown a significant survival benefit in Mayo Stage IV AL amyloidosis patients
- The survival benefit of birtamimab was consistent across all key baseline variables, including demographic factors, clinical characteristics, and laboratory parameters

Forest Plot of Birtamimab Survival Benefit Adjusted for Key Baseline Variables for Patients With Mayo Stage IV AL Amyloidosis (ITT population [9 months])



A Study to Evaluate the Efficacy and Safety of Birtamimab in Mayo Stage IV Patients With AL Amyloidosis (AFFIRM-AL) (NCT04973137)

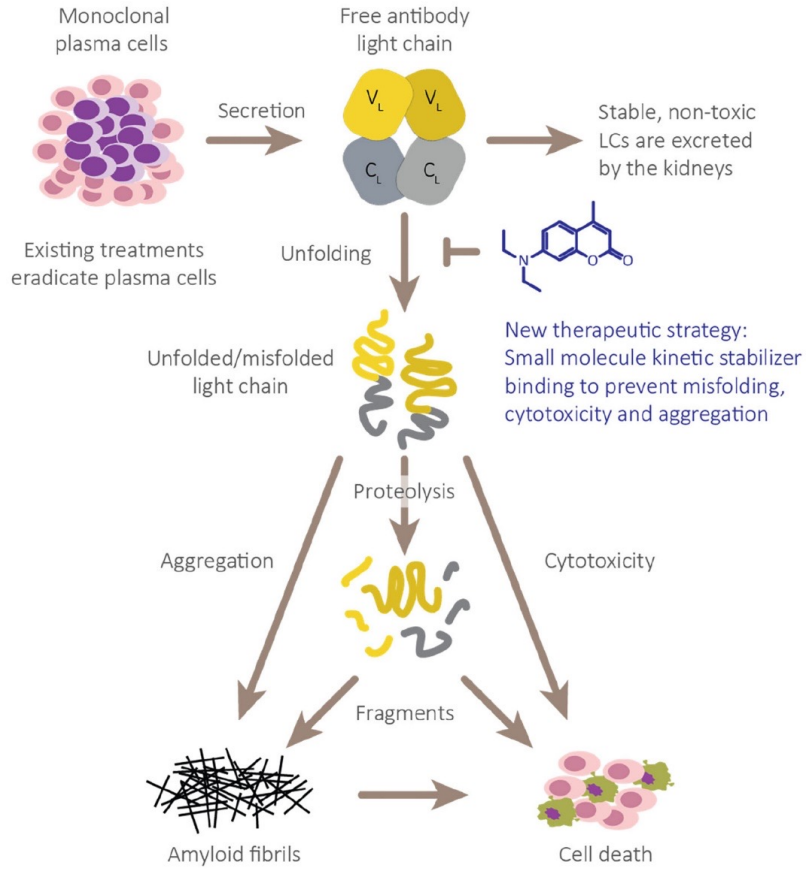
Gertz MA, et al. Blood 2023.

Other therapies

Light chain stabilizers

- Pharmacologic stabilization of native LCs could stop LC aggregation, potentially stopping disease progression

- Several classes of molecules have been identified as potential stabilizers



Morgan, et al. Proc Natl Acad Sci USA. 2019.
Yan, et al. Bioorganic & Medicinal Chemistry Letters. 2020
Morgan et al Hemato 2021.

Conclusions

- Management of systemic amyloidosis – where do we stand:
  - ✓ biomarkers allow early diagnosis, risk-adapted treatment design, and reliable assessment of response with validated criteria
  - ✓ daratumumab-CyBorD is a new standard of care in the majority of patients

- Much is left to do:
  - ✓ improve early diagnosis (education, screening programs)
  - ✓ define a standard-of-care for high-risk patients with AL amyloidosis
  - ✓ validate a definition of hematologic progression
  - ✓ validate new sensitive technologies (MS, MRD) to assess response
  - ✓ newer anti-PC approaches
  - ✓ alternative treatment targets (LC stabilizers, doxycycline, anti-amyloid Abs)

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Laura Obici
Paola Rognoni
Maria Antonietta Sesta
Study Coordinators and data managers

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Stefano Perlini
Francesco Salinaro

Nuclear Medicine Department
Giorgio Cavenaghi
Gianluce De Matteis
Lorenzo Lodola
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