Antonia Cagnetta, MD

Ospedale Policlnico San Martino
Università degli Studi di Genova

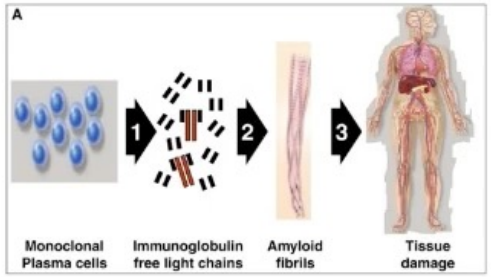
Amiloidosi: complessità diagnostiche e terapeutiche

DICHIARAZIONE AI SENSI DELLA LEGGE 24 Nov 2003, N. 326- ART 48 comma 25 AUTOCERTIFICAZIONE" - Ai sensi dell'art. 76.4 sul Conflitto di Interessi dell'Accordo Stato-Regione del 2 febbraio 2017

DICHIARO i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario avuti negli ultimi 2 anni:

- *Honoraria: Janssen, Amgen, Takeda*
- *Scientific Advisory Board: Amgen, Janssen, GSK*

Current challenges in the diagnosis of AL



Symptoms

Examination and tests

Diagnosis

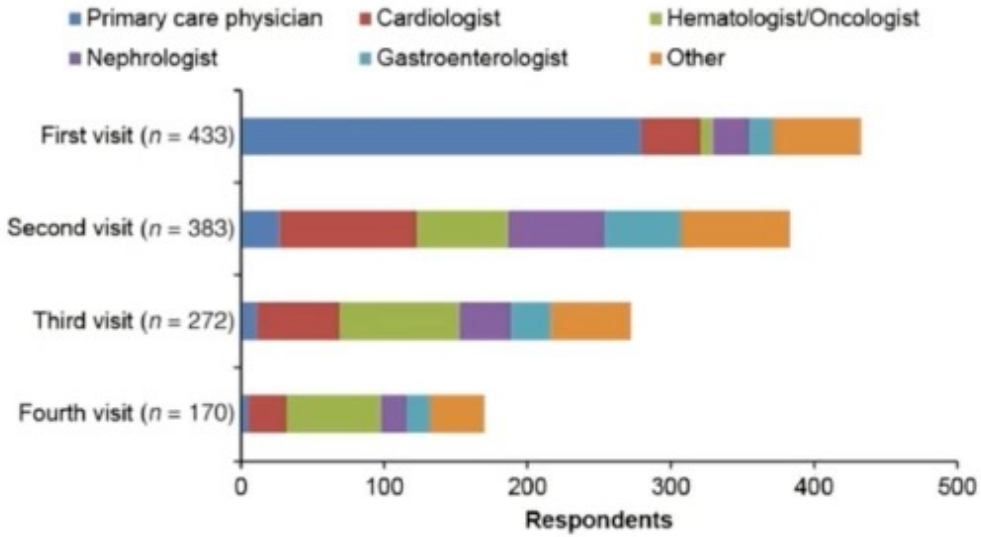
Months …..TIME ….. Years

A Dispenzieri, Bllod reviews 2012

From first symptoms to diagnosis

Table 2 Journey to diagnosis among survey participants ($n = 341$)

	Quantitative study: survey participants	
	n	%
Time between onset of symptoms and diagnosis		
<6 months	96	28.2
Between 6 months and 1 year	97	28.4
Between 1 and 2 years	76	22.3
Between 2 and 3 years	31	9.1
>3 years	41	12.0



Kristen L. Mc Causland; Patient 2018

I Lousada, Adv Ther 2015

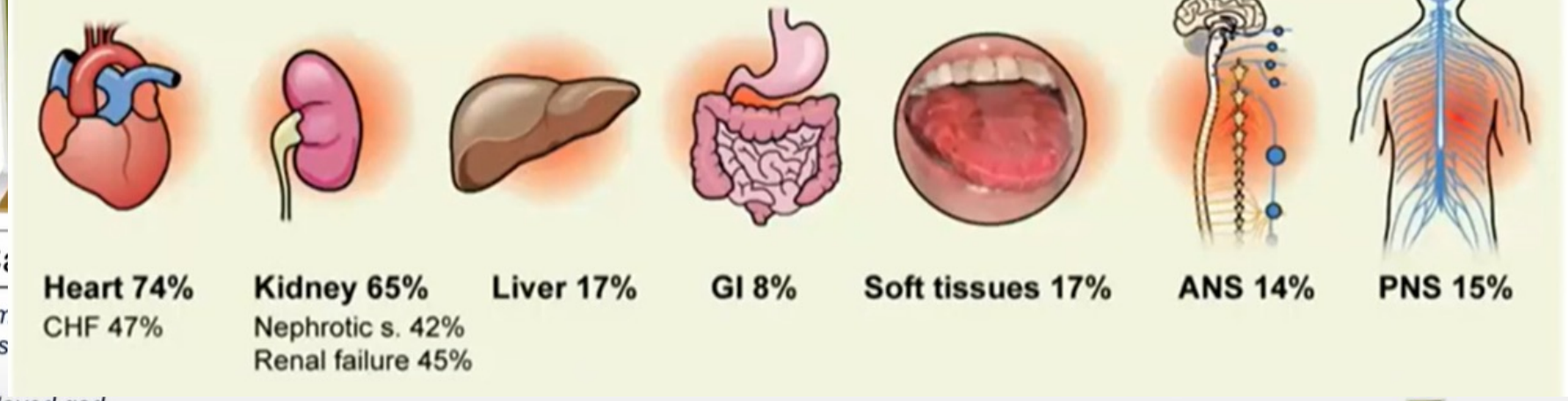
Top 3 reasons for misdiagnosis

1. Many different symptoms and presentations

2. If providers consider amyloidosis, they may get confused about HOW to screen appropriately

3. A provider makes a diagnosis of amyloidosis, but does not follow through on the typing

Doors to AL amyloidosis diagnosi



Ca

Sym
dias

n,

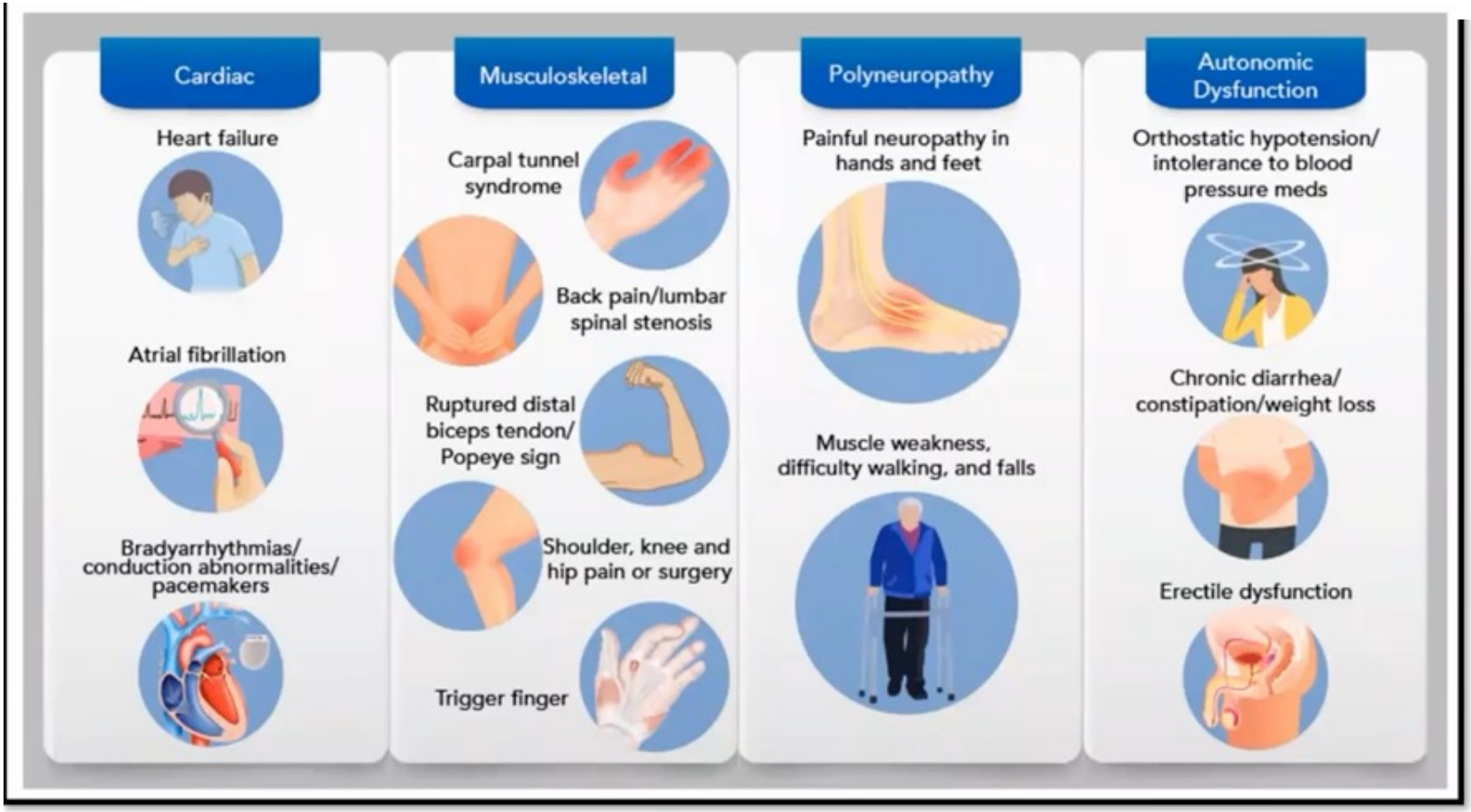
Delayed gad enhancement

Unexplained elevated troponin

Positive PYP

Orthopedics

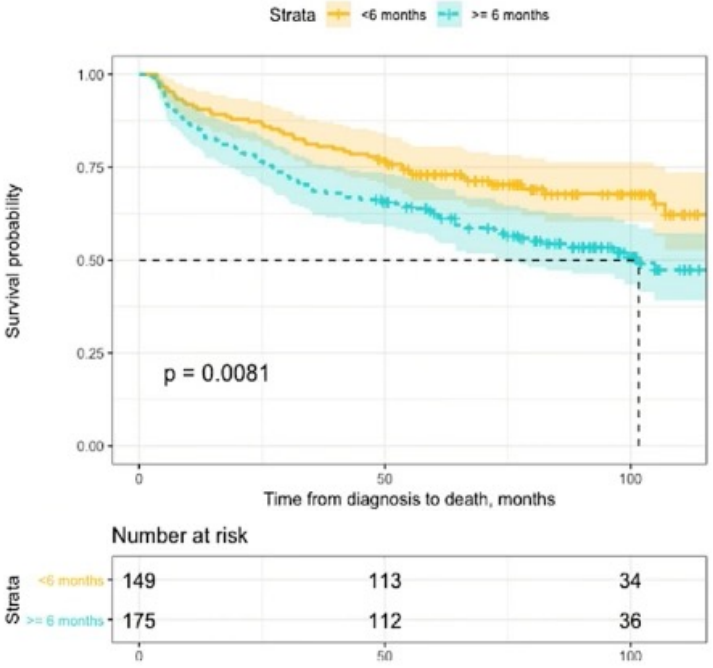
CTS, Spinal stenosis? pseudocladication



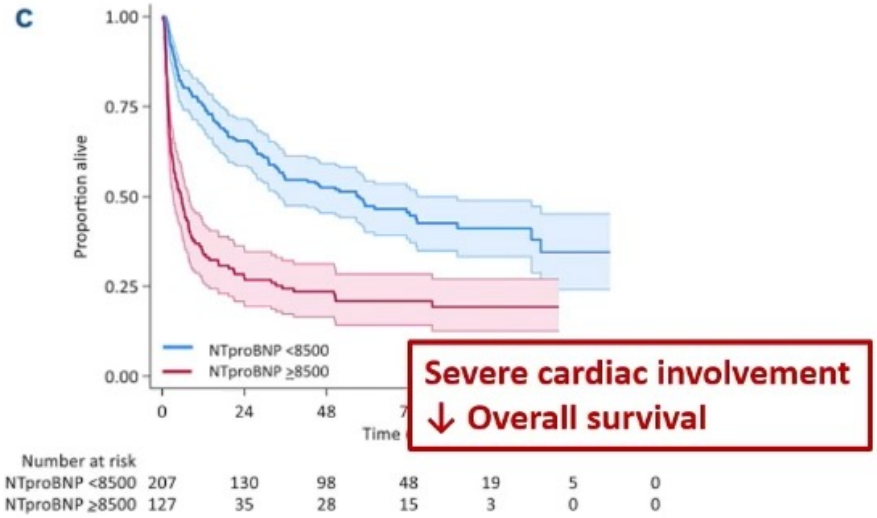
Nativi-Nicolau, Karam, Khella, Maurer. Heart Failure Reviews, 2021;Feb 20.

Why is it so important?

Tick Tock…



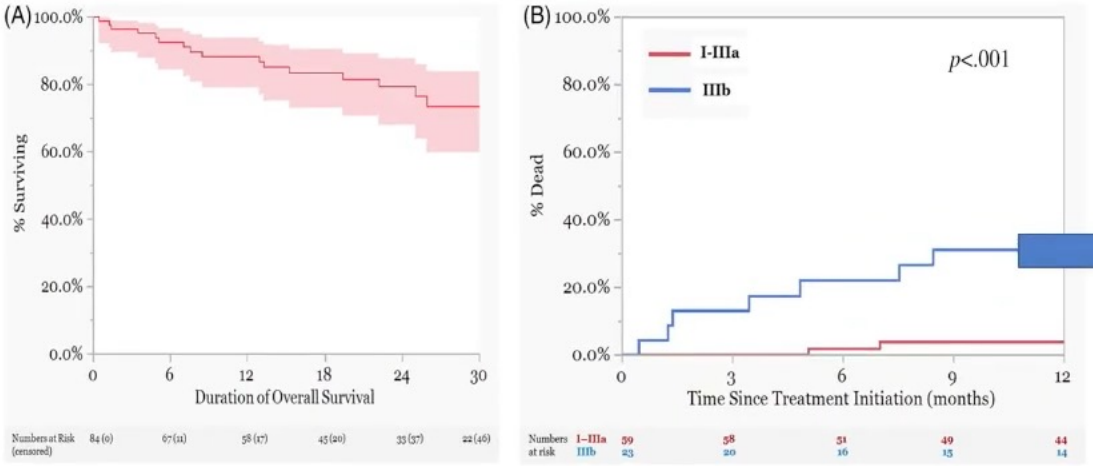
Schulman A; European Journal of Haematology. 2020



Severe cardiac involvement
↓ Overall survival

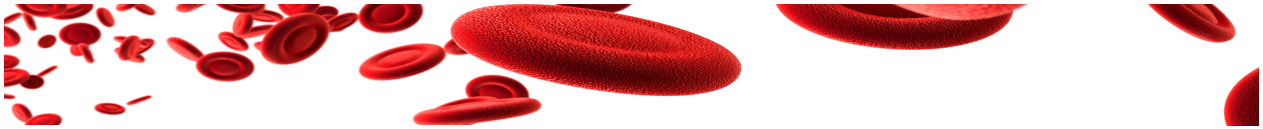
J Khwaja, Haematologica 2024

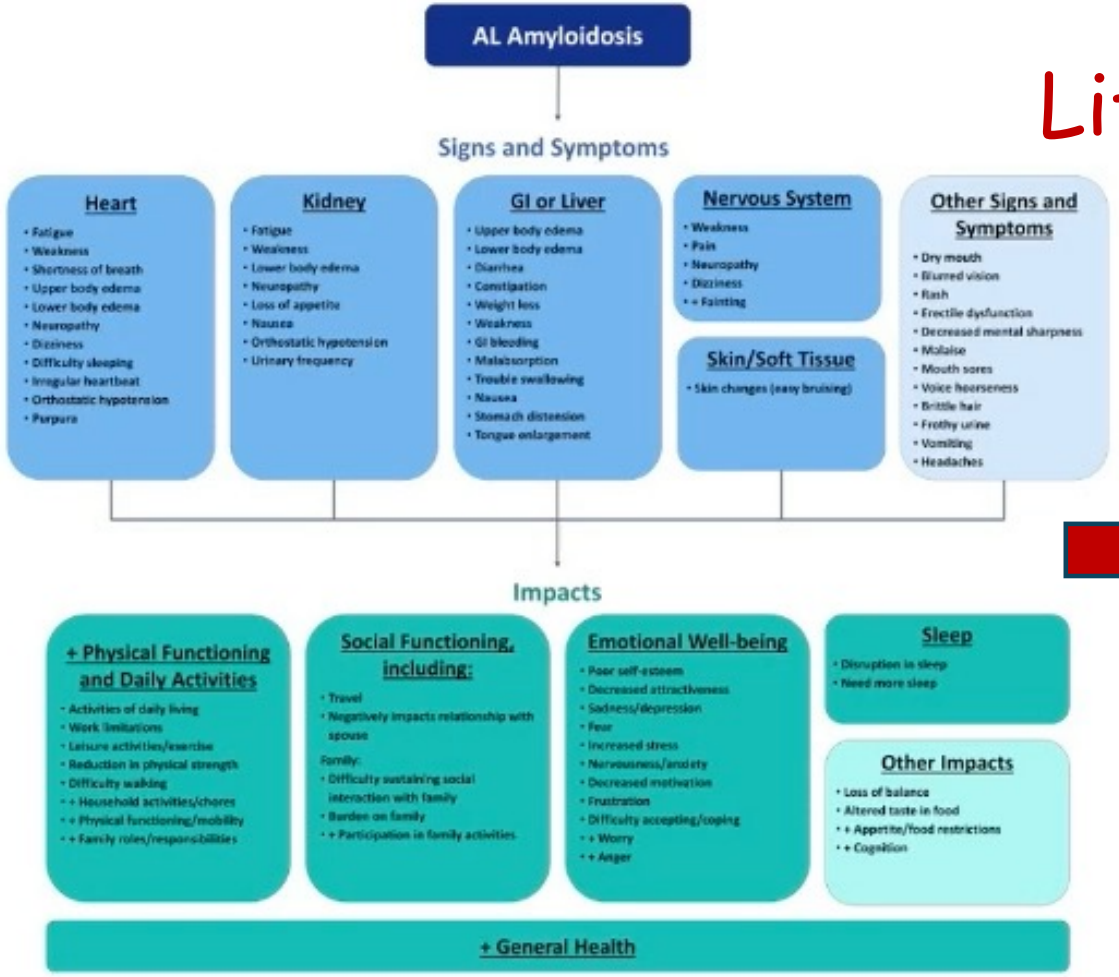
And in 2024 ?



Early cardiac mortality in in patients Severe cardiac diseases

With **daratumumab-based frontline therapy** comparing to historical data's there is an improve of prognostic **but** patients with advanced cardiac diseases (stage IIIb) experience still increase early mortality





Life is important but also QUALITY OF LIFE

SEGNI E SINTOMI DELL'AMILOIDOSI AL HANNO IMPATTO SULLA QUALITÀ DI VITA

NON TUTTI I SINTOMI SCOMPAIONO ANCHE SE LA MALATTIA VA INCONTRO A REMISSIONE CLINICA

UNA DIAGNOSI PRECOCE È ASSOCIATA A MENO EFFETTI AVVERSI SEVERI E AD UNA MAGGIORE PROBABILITÀ CHE MIGLIORINO CON IL CONTROLLO DELLA MALATTIA

SFIDE NELL'AMILOIDOSI

DIAGNOSI COMPLESSA → Processo multi step

COINVOLGIMENTO MULTIORGANO → Multipli specialisti

BARRIERE PER L'ACCESSO ALLE CURE → Disponibilità di farmaci nei diversi centri

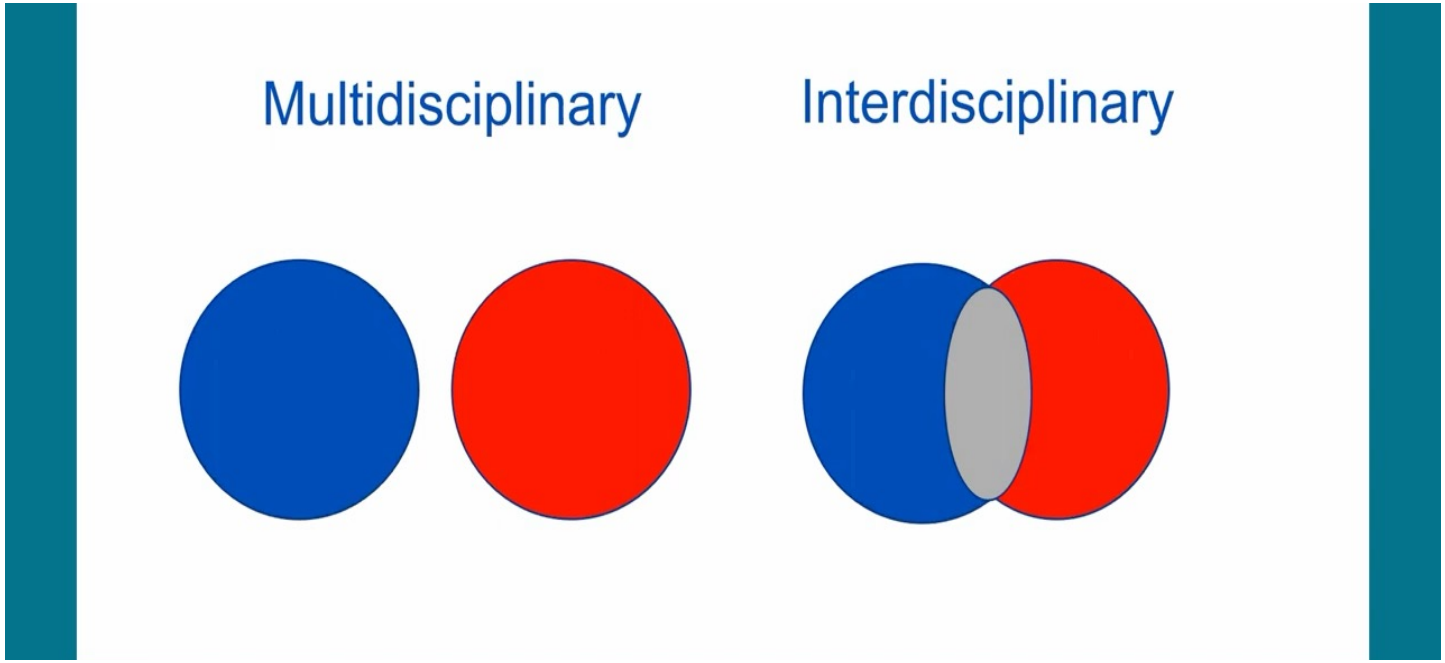
SFIDE NELL'AMILOIDOSI

DIAGNOSI COMPLESSA → Processo multi step

COINVOLGIMENTO MULTIORGANO → Multipli specialisti

BARRIERE PER L'ACCESSO ALLE CURE → Disponibilità di farmaci nei diversi centri

COLLABORATION ENSURES COMPREHENSIVE DIAGNOSIS AND TAILORED TREATMENT STRATEGIES FOR EACH ORGAN SYSTEM AFFECTED.



TEAM INTERDISCIPLINARE AMILOIDOSI-AL

EARLY REFERRAL

MMG

Cardiologi

Nefrologi

Ortopedici

EMATOLOGO

- DIAGNOSI
- TERAPIA
- COUNSELING TRAPIANTOLOGICO
- COORDINAMENTO CON ALTRI CENTRI DI RIFERIMENTO

If AL amyloidosis is suspected:

- STEP 1. Screen for monoclonal process
- STEP 2. Demonstrate tissue deposition of amyloid
- STEP 3. Confirm protein of origin

RUOLO DELL'EMATOLOGO

SEGNI CLINICI DI AMILOIDOSI SISTEMICA AL

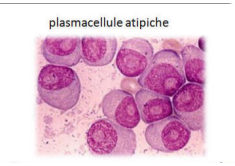
- Presenza di gammapatia monoclonale
- Aumento di NT-proBNP – TN Troponine in assenza di altre cause
- Proteinuria non selettiva
- Rialzo della fosfatasi alcalina

Screening I LIVELLO

- Immunofissazione sierica
- Immunofissazione urinaria
- Dosaggio proteinuria 24 h
- Dosaggio catene leggere sieriche

CON UN APPROPRIATO PROGRAMMA DI SCREENING
1 PAZIENTE CON MGUS CHE PROGREDISCE AD Amiloidosi AL
PER OGNI 7-10 CHE SVILUPPANO UN MULTIPLE MYELOMA.

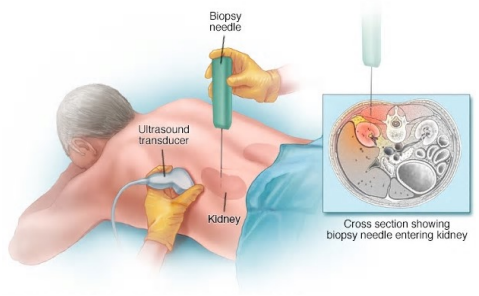
Diagnostica II livello



- VALUTAZIONE DEL BONE MARROW
- STUDIO DELLA MALATTIA OSSEA (LOW-DOSE CT, MRI, TC PET)

RUOLO DEL NEFROLOGO

RENAL BIOPSY



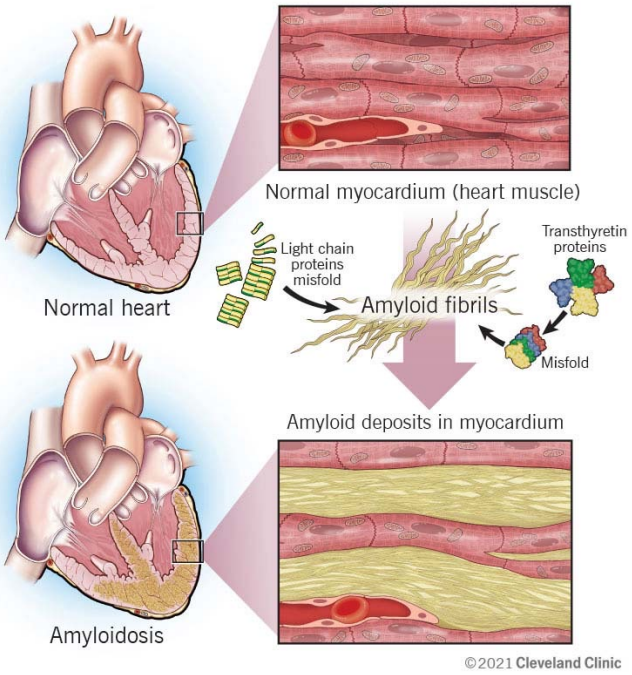
LIGHT MICROSCOPY

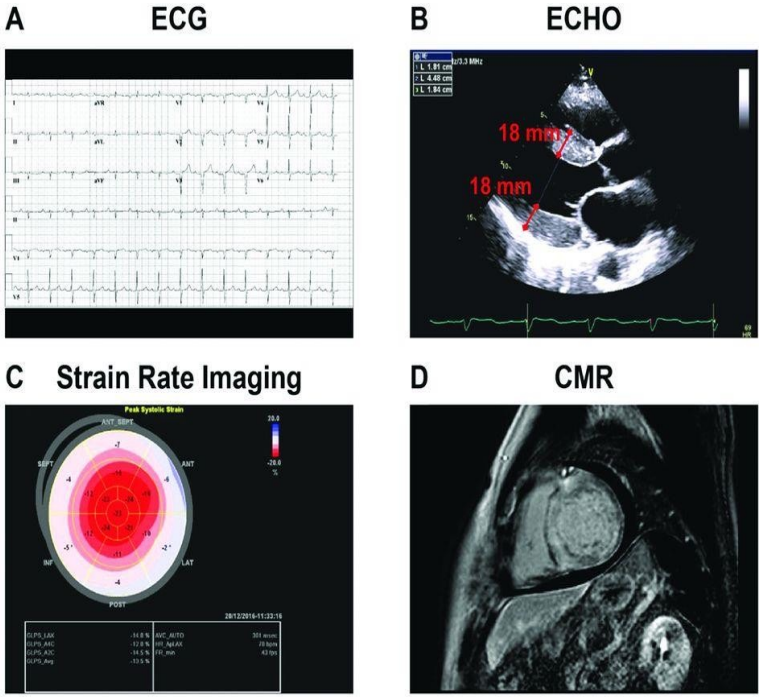
IMMUNOFLUORESCENCE
(Ab for light chains, heavy chains e intact Ig)

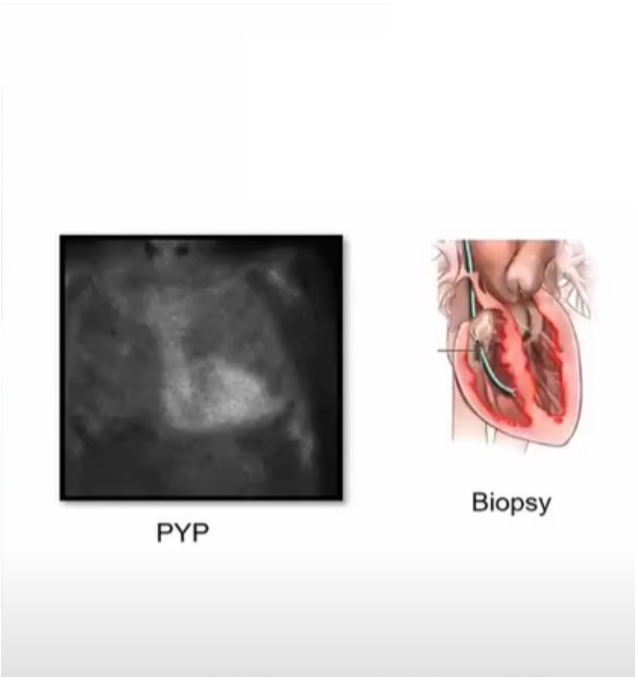
ELECTRONIC MICROSCOPY

- TRATTAMENTO DELLA DISFUNZIONE RENALE
- GESTIONE DELLA TERAPIA DI SUPPORTO ED EMODIALISI
- VALUTAZIONE DELLA RISPOSTA D'ORGANO

RUOLO DEL CARDIOLOGO







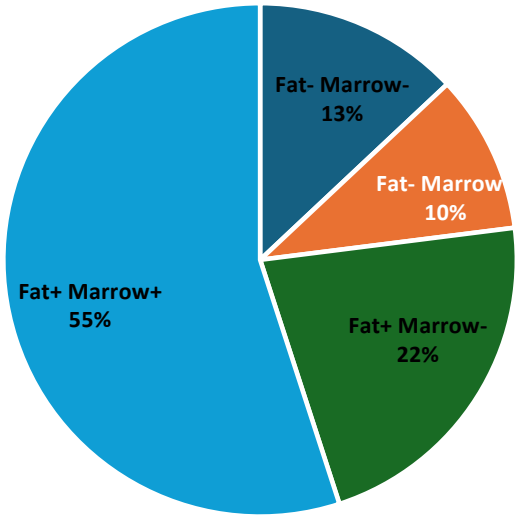
ALGORITMI DIAGNOSTICI

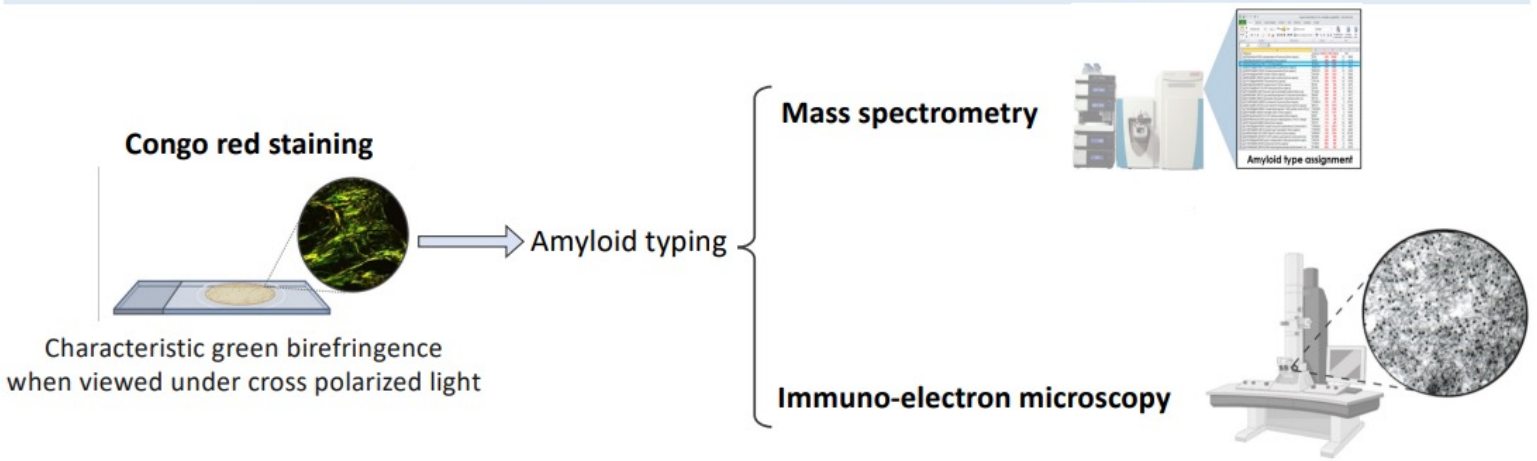
DIAGNOSI DIFFERENZIALE

Amyloid Type	Precursor Protein	Clinical
AL or AH	Immunoglobulin (light or heavy chain)	Immunoglobulin amyloidosis (formerly known as primary). Can be systemic or localized amyloidosis; associated with clonal plasma cell disorder
AA	SAA	Secondary or familial Mediterranean fever; familial periodic fever syndromes associated with mutated tumor necrosis factor receptor
$ATTR_{mut}$	Transthyretin, mutants	Familial amyloidosis; most often heart and/or nerve
$ATTR_{wt}$	Transthyretin	Age-related (formerly known as senile) amyloidosis
AFib	Fibrinogen A-α chain, mutants	Familial renal amyloidosis (Ostertag amyloidosis)
$A\beta_2M$	β_2-Microglobulin	Dialysis-associated carpal tunnel syndrome
Aβ	AβPP	Alzheimer disease; localized form of amyloid

Wintrobe's Clinical Hematology, 14° Ed., 2022

TIPIZZAZIONE AMILOIDOSI

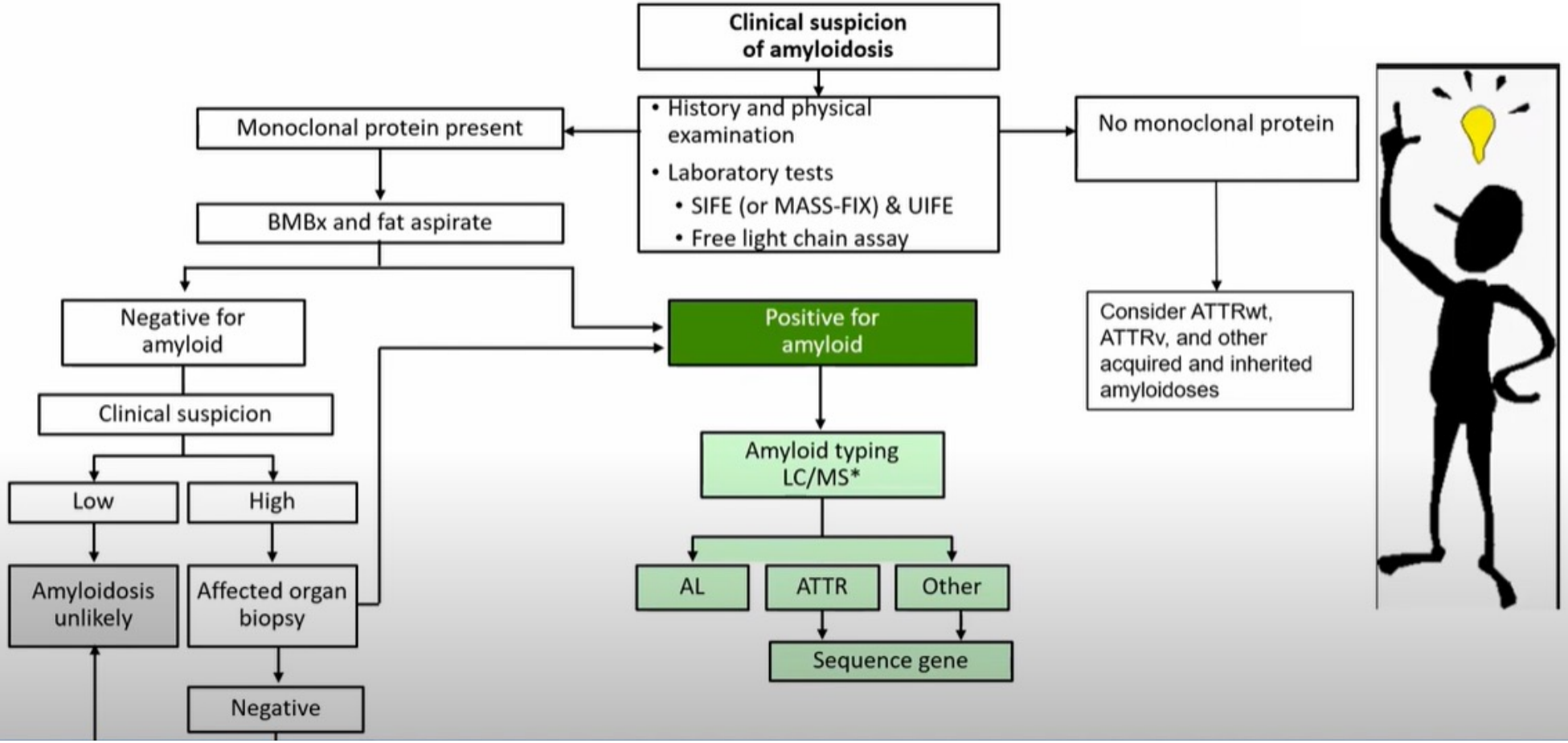


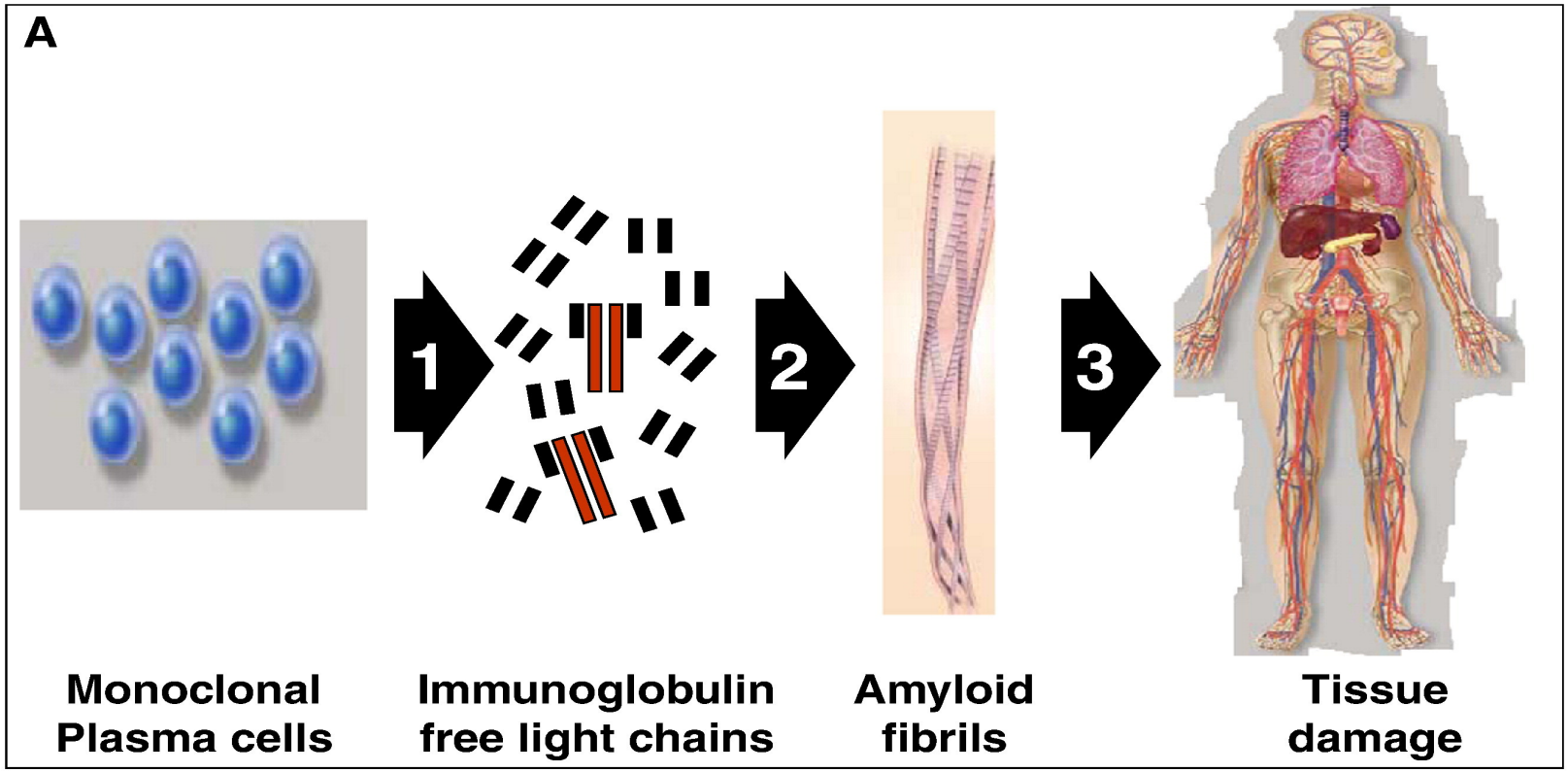


Fondazione IRCCS
Policlinico San Matteo

CENTRO AMILOIDOSI SISTEMICHE MALATTIE AD ALTA COMPLESSITA’

AMYLOIDOSIS DIAGNOSTIC ALGORITHM




A
1
2
3
Monoclonal
Plasma cells
Immunoglobulin
free light chains
Amyloid
fibrils
Tissue
damage
B
Hematologic response
Organ response
Toxicity monitoring and management

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

Taylor & Francis
Taylor & Francis Group

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

Taylor & Francis
Taylor & Francis Group

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]

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:

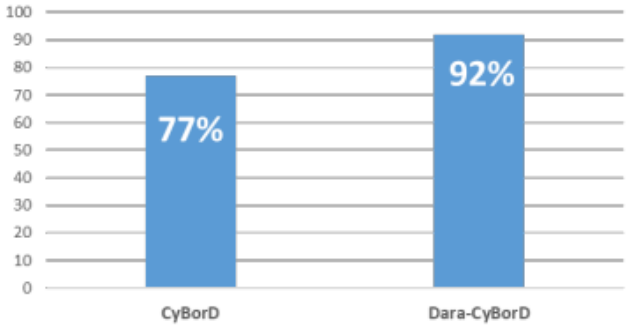
- AL amyloidosis with ≥1 organ impacted
- No prior therapy for AL amyloidosis or MM
- Cardiac stage I-IIIA (Mayo 2004)
- eGFR ≥20 mL/min

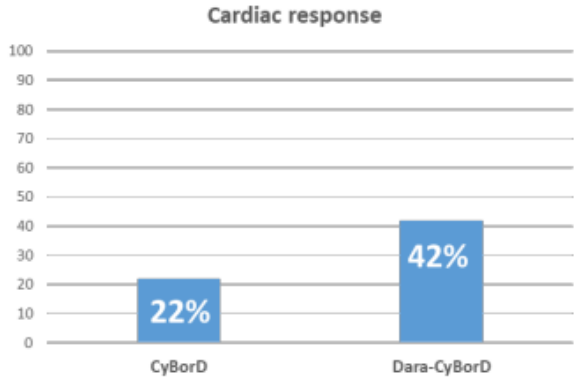
Screening (Day −28) → 1:1 Randomisation (N = 388)

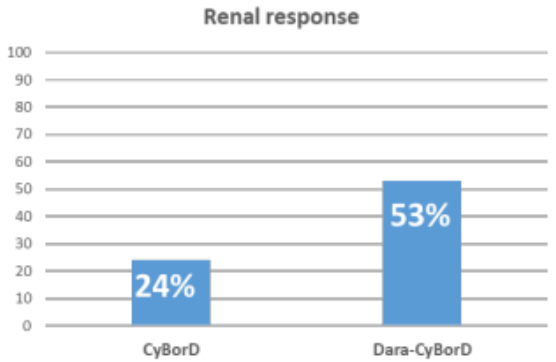
Treatment Phase		Post-treatment Phase
DARA SC 1,800 mg QW Cycles 1-2, Q2W Cycles 3-6 + CyBorD[a] weekly × 6 cycles n = 195	DARA SC 1,800 mg Q4W until MOD-PFS or maximum of 24 total cycles	Observation until MOD-PFS (if DARA SC discontinued prior to MOD-PFS)
CyBorD[a] weekly × 6 cycles n = 193		Observation until MOD-PFS

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

Treatment selection in AL amyloidosis

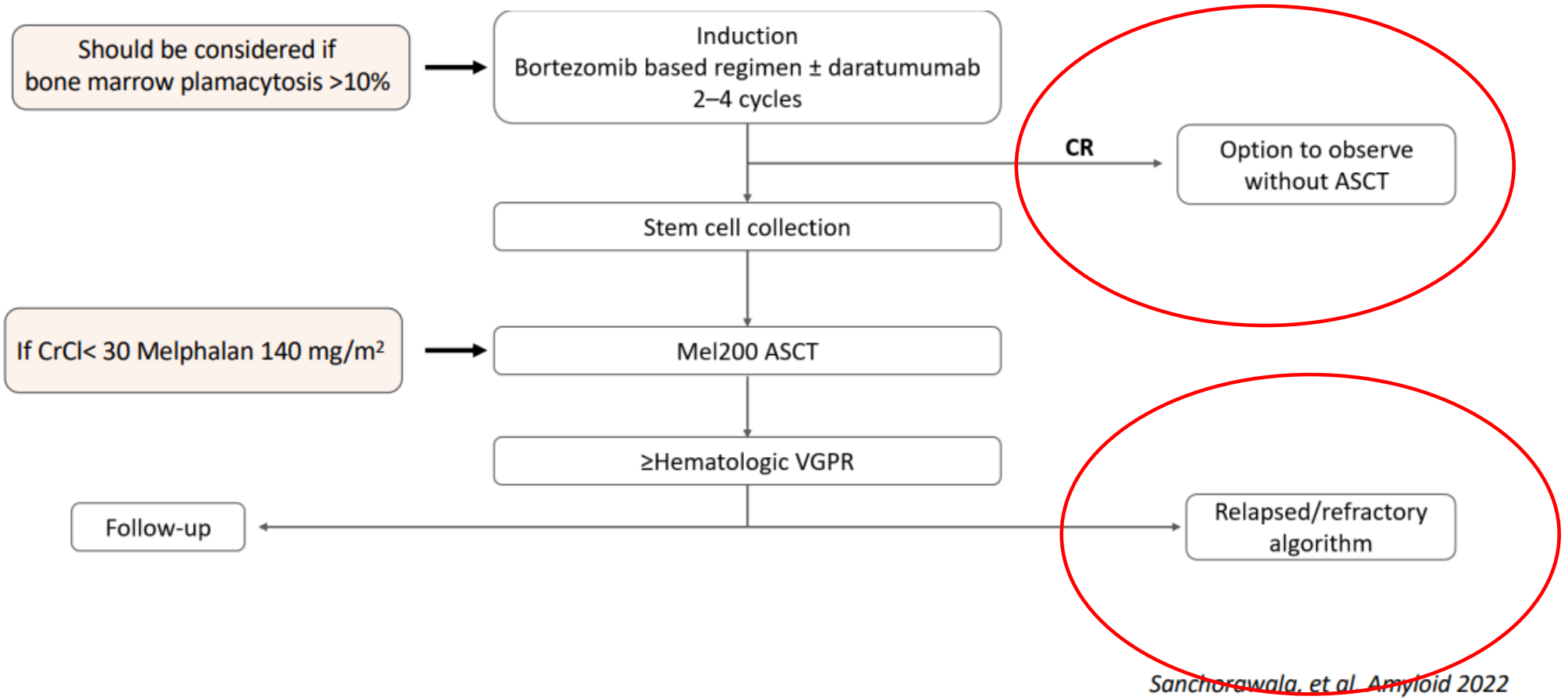
1. Assess eligibility for ASCT

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



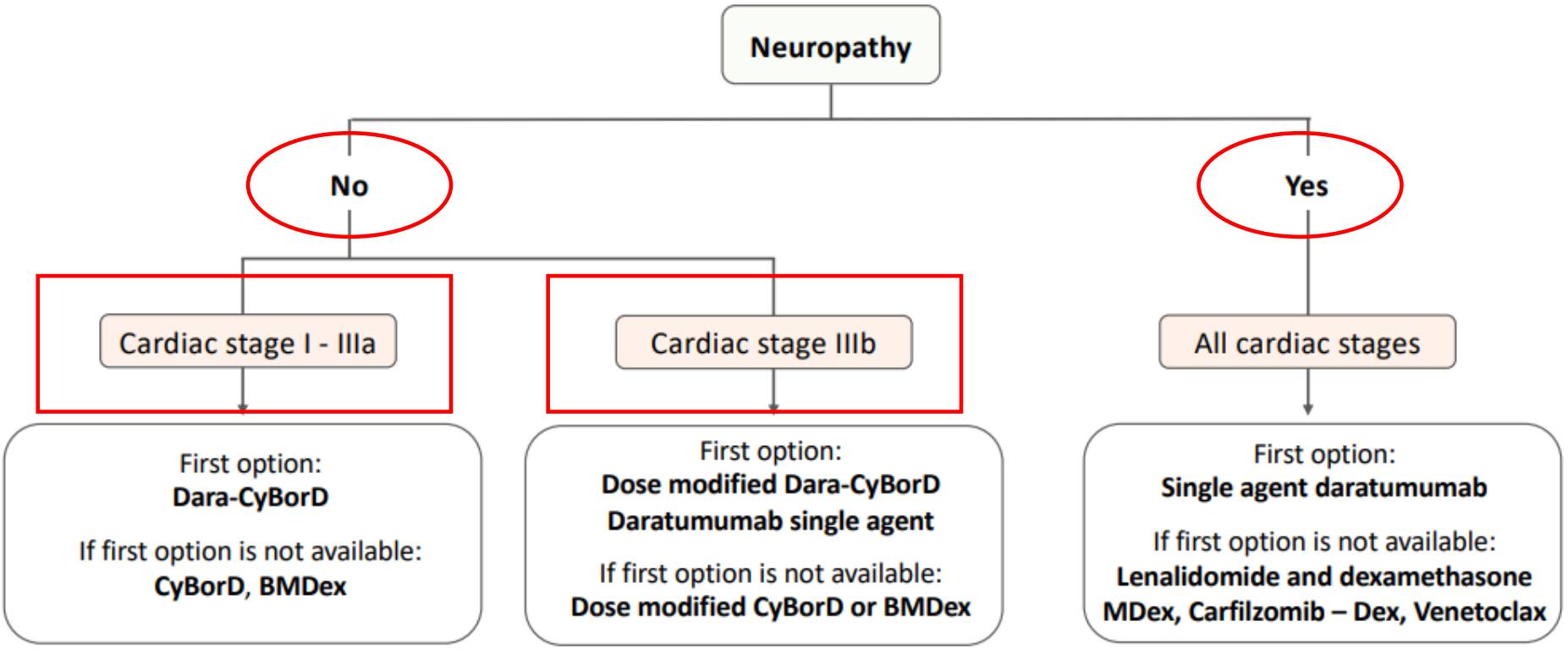
Sanchorawala, et al. Amyloid 2022

Treatment selection in AL amyloidosis

1. Assess eligibility for ASCT

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

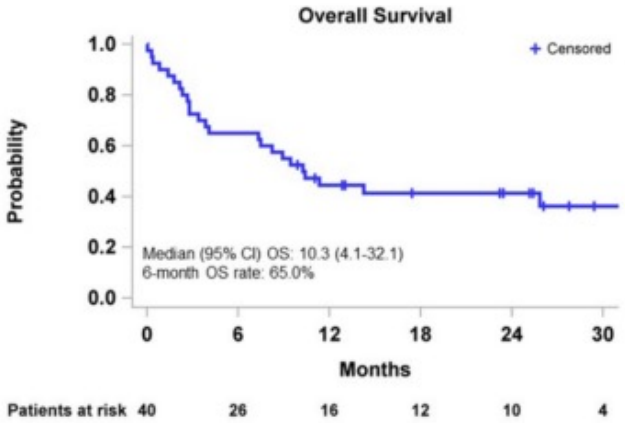
ISA/EHA guidelines for non-transplant chemotherapy



Wechalekar, et al. Amyloid 2022

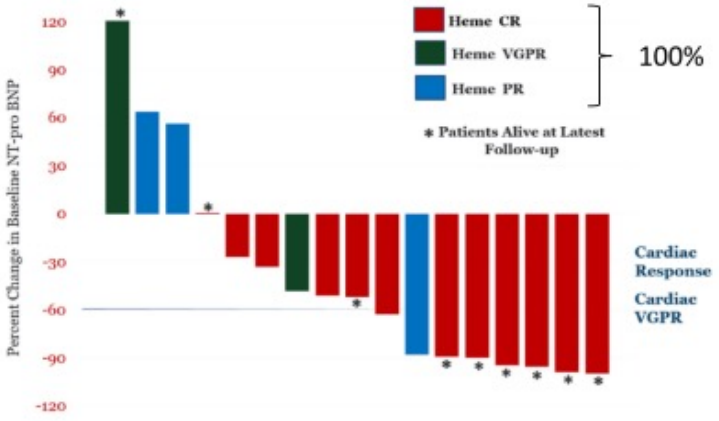
Daratumumab combinations in stage IIIb patients

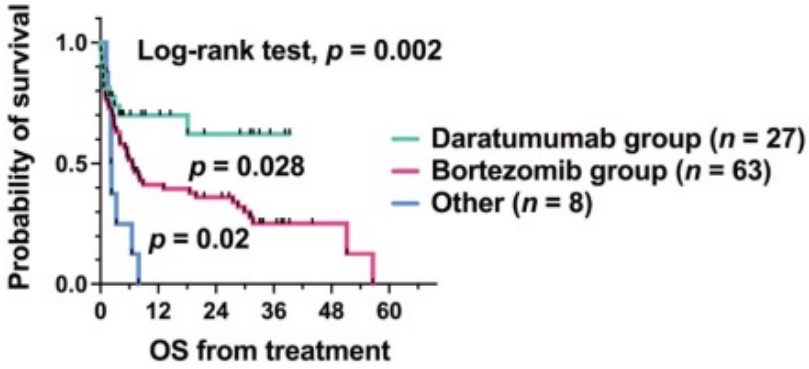
Figure. Overall Survival



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.

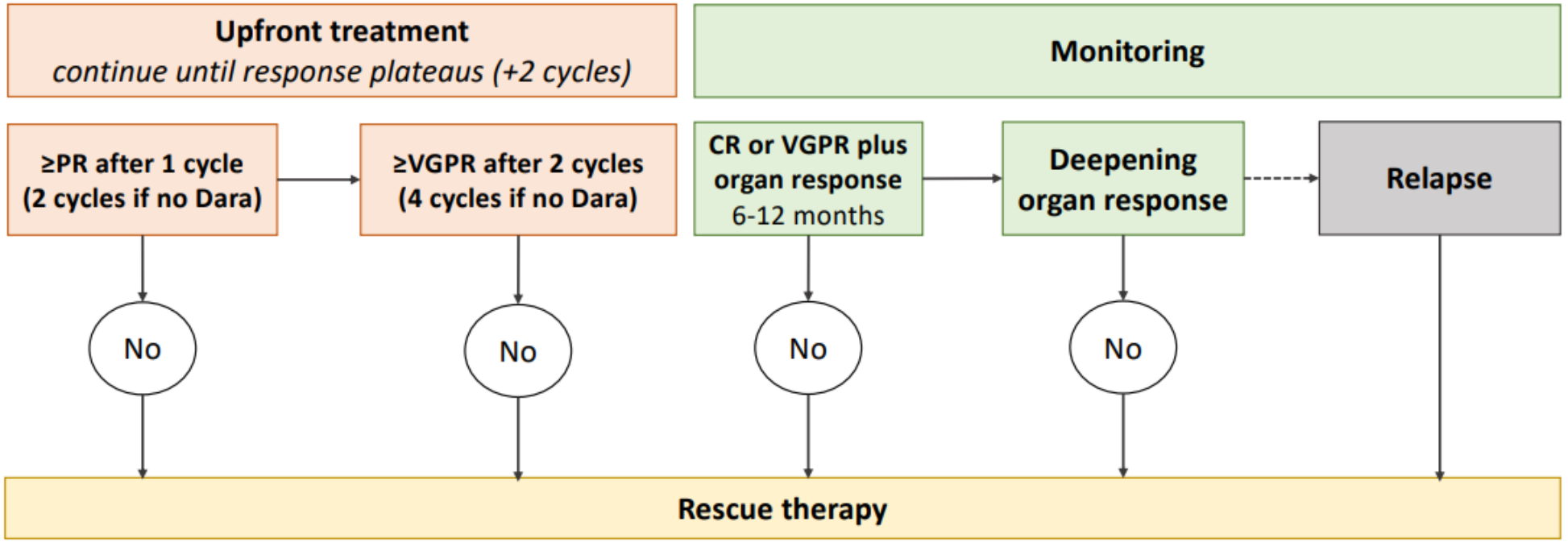
Kastritis, et al. ASH 2023 – oral abstract





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

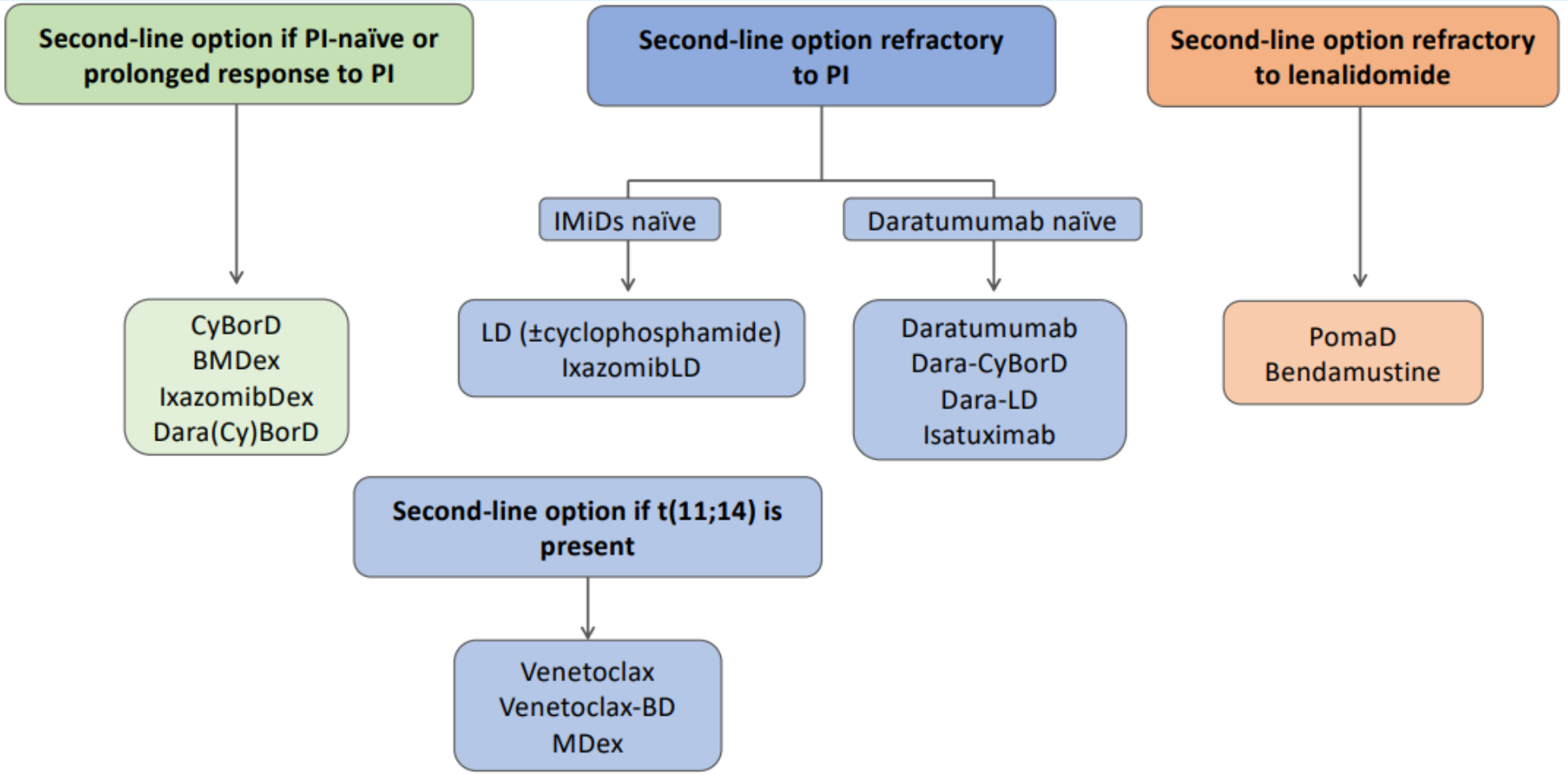
Tentative monitoring schedule during (and after) treatment



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

Adapted from Palladini & Milani. Curr Opinion Oncol 2022

ISA/EHA guidelines for RR treatment



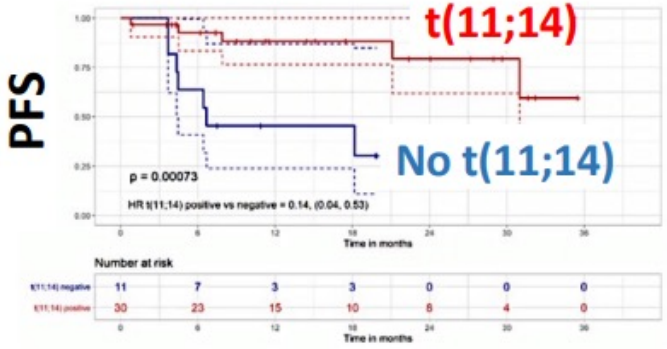
BD, bortezomib, dexamethasone; BMDex, bortezomib, melphalan, dexamethasone; CyBorD, cyclophosphamide, bortezomib, dexamethasone; Dara, daratumumab; IMiDs, immunomodulatory drug; PI, proteasome inhibitor; PomaD, pomalidomide, dexamethasone

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

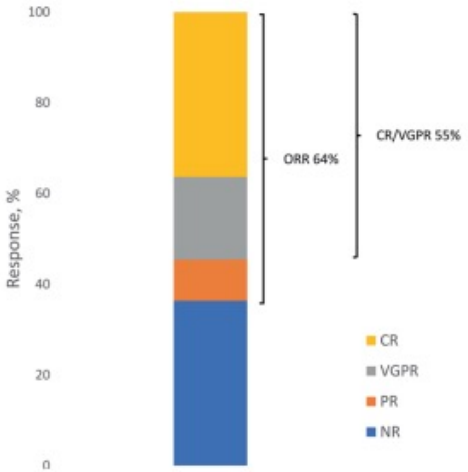


Premkumar, et al. Blood Cancer J 2021

- 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

Take home messages….

Management dell'Amiloidosi AL: dove siamo

Bio-marcatori sensibili che permettono una diagnosi precoce, una proposta terapeutica risk-adapted e un monitoraggio della risposta alla terapia

CY-Bor-D è il trattamento standard per la grande maggioranza dei pazienti

Molto rimane da fare…..

- Diagnosi precoce: programmi di screening-formazione-divulgazione
- Definire uno standard of care per i pazienti ad alto rischio
- Definire e validare criteri di progressione e recidiva di malattia
- Migliorare la tecnologia per la valutazione della risposta (MRD)
- Nuovi target terapeutici (Stabilizzatori delle fibrille, anticorpi anti

GRAZIE PER L'ATTENZIONE!

Clinica Ematologica

Direttore Roberto M. Lemoli

Staff medico
Maurizio Miglino
Antonia Cagnetta
Filippo Ballerini
Fabio Guolo
Paola Minetto
Andrea Todiere
Chiara Salvetti

Data manager
Mariagrazia Ciardo
Marianna Fava
Sabrina Sisinni

Scuola di specializzazione in Ematologia
Univerisità di Genova

Myeloma research members

Clinicians
Antonia Cagnetta
Matteo Garibotto
Marco Olivieri
Marco Gallo
Elisabetta Catini
Anna Elisa Laserra

Lab members
Soncini Debora
Pamela Becherini
Claudia Martinuzzi
Francesco Ladisa
Giulia Giorgetti
Isabella Traverso