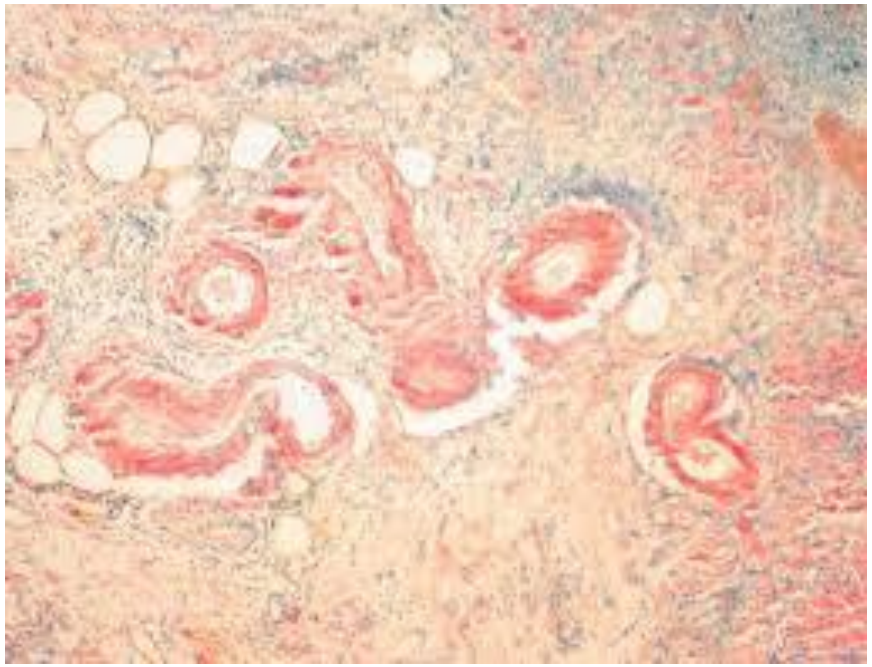


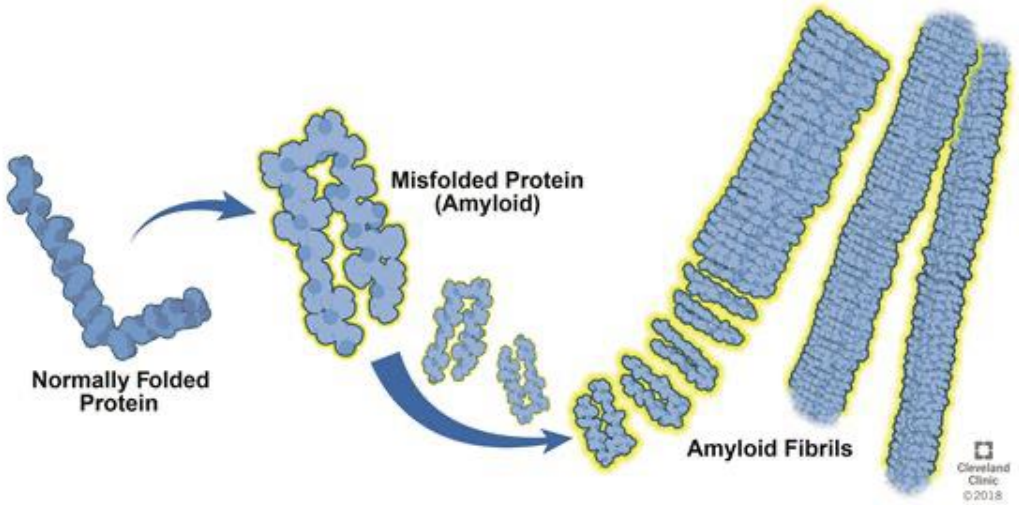
Amyloidosis

Isabelle Vande Broek

VITAZ
STERK IN ZORG

Defining Systemic Amyloidosis

- Protein misfolding disorder
- Amyloid = highly organized protein fibrils, insoluble and degradation-resistant
- Extracellular deposition of amyloid leads to organ dysfunction
- To date, 36 different proteins have been identified as amyloidogenic; at least 14 of them can cause systemic disease



Benson et al. Amyloid 2021

Dogan et al. Annu Rev Pathol 2017

PATHOGENESIS

Normal proteins, when produced in **abnormal numbers**

Acquired mutation

↓

Monoclonal B lymphocyte proliferation

↓

Increased plasma cells

↓

Immunoglobulin light chains

↓ **Incomplete proteolysis**

AL protein

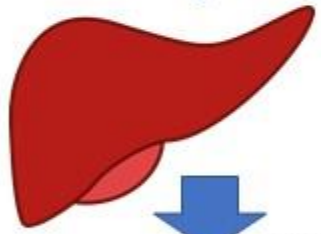
Chronic Inflammation

↓

Macrophages activation

↓

IL1 &IL6



↓

Increased **SAA protein**

↓ **Incomplete proteolysis**

AA protein

Production of normal amounts of **mutant proteins**

Eg : Transthyretin (TTR)

Mutation

↓

Mutant TTR

↓ **Aggregation**

ATTR protein

AMYLOIDOSIS

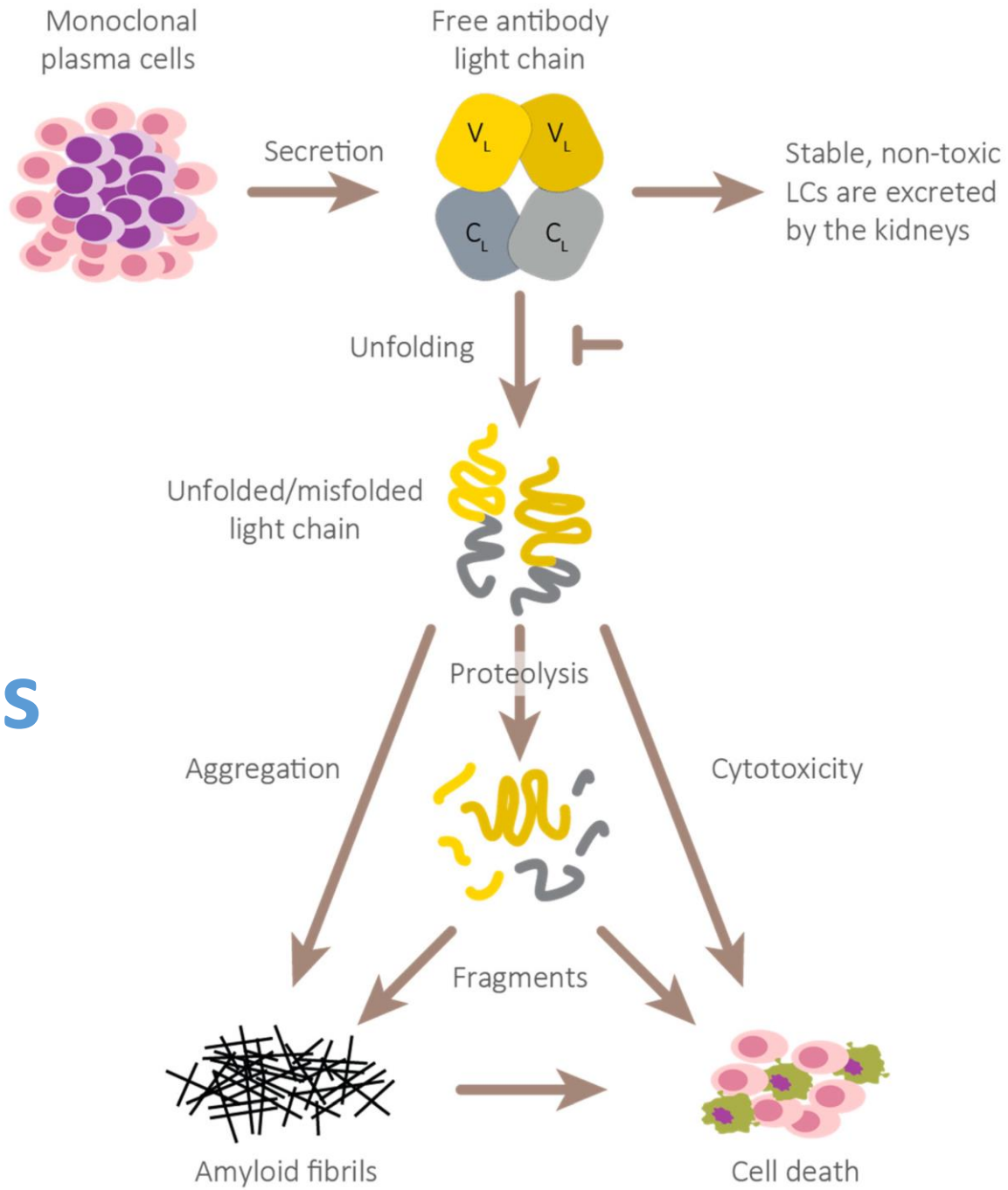
TABLE 1. Classification of the Most Common Amyloidoses

Type of amyloidosis	Precursor protein component	Clinical presentation
AL[a] (previously referred to as primary amyloidosis)	κ or λ immunoglobulin light chain	Systemic or localized; see text
AH	γ, μ, α, δ, ε immunoglobulin heavy chain	Systemic or localized; see text
ATTR		
Wild-type ATTR[b] (age-related amyloidosis)	Normal transthyretin	Restrictive cardiomyopathy; carpal tunnel syndrome Lumbar spinal stenosis Biceps tendon rupture
Variant ATTR[b] (also referred to as hereditary ATTR)	Mutant transthyretin	Polyneuropathy phenotype, cardiomyopathy phenotype, and mixed phenotype; leptomeningeal involvement; vitreous opacities
AA (previously referred to as secondary amyloidosis)	Serum amyloid A	Renal presentation most common; associated with chronic inflammatory conditions; underlying disease is typically acquired, but hereditary in case of familial periodic fever syndromes
ALECT2	Leukocyte chemotactic factor 2	Acquired; renal or liver presentation
Aβ2M	β_2-microglobulin	Acquired in patients on long-term dialysis; carpal tunnel syndrome, large joint arthropathy
AApoA-IV	Apolipoprotein A-IV	Acquired; renal or cardiac amyloidosis
Rare hereditary amyloidosis types		
AGel; also known as familial amyloidosis, Finnish type	Gelsolin	Triad of corneal lattice dystrophy, facial nerve paralysis, and cutis laxa
AFib	Fibrinogen α-chain	Usually renal presentation
ALys	Lysozyme	Sicca syndrome, renal dysfunction, liver or spleen rupture, gastrointestinal ulcers
AApoA-I	Apolipoprotein A-I	Mutation-dependent, can affect various organs
AApoA-II	Apolipoprotein A-II	Renal amyloidosis
AApoC-II	Apolipoprotein C-II	Renal amyloidosis
AApoC-III	Apolipoprotein C-III	Renal amyloidosis, sicca syndrome

[a]AL/AH amyloidosis is the only form of amyloidosis that is secondary to a clonal plasma cell disorder. AL amyloidosis can be associated with multiple myeloma or more rarely with other B-cell–secreting disorders.

[b]TTR refers to transthyretin, previously known as prealbumin.

AL amyloidosis

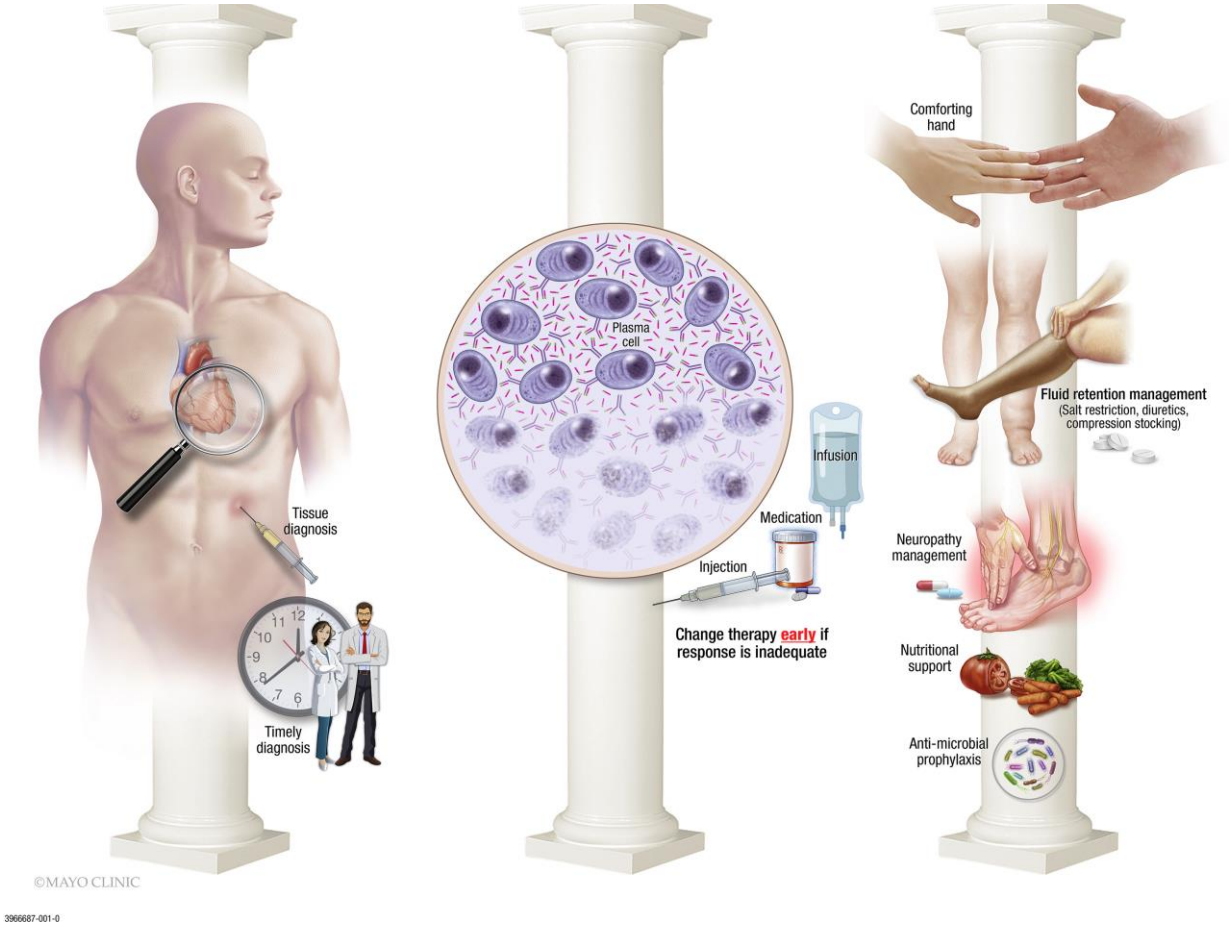


How we diagnose & manage AL amyloidosis : 3 fundamental pillars to improve outcome

EARLY RECOGNITION

ANTI-PLASMA CELL THERAPY

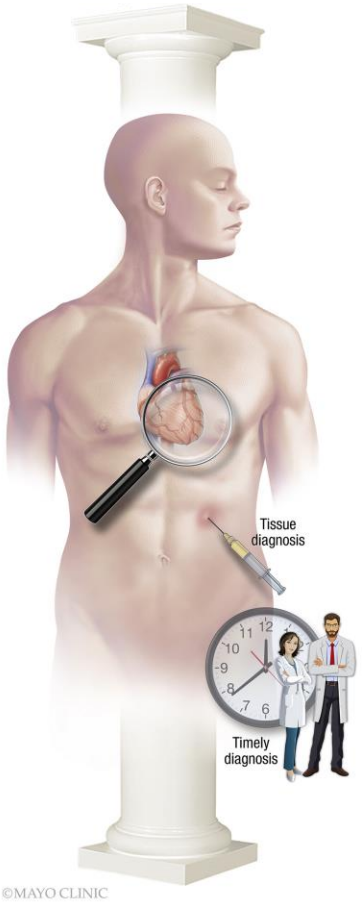
SUPPORTIVE CARE



Cibeira et al. Blood 2011
Muchtar et al. Br J Haematol 2019
Sidana et al. Am J Hematol 2019

Management of amyloidosis

Pillar 1 : Early recognition



Early recognition is important to avoid further organ damage

Recognition of amyloidosis = CHALLENGE

< non – specific symptoms

< heterogeneity in presentation

Many specialists can be involved

FACTS :

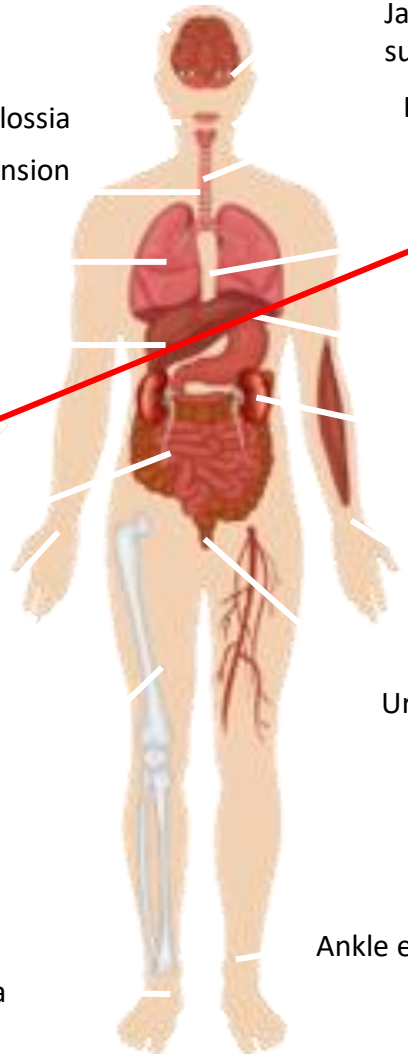
- Median time from symptom onset to diagnosis = 6-12 m
- 3-4 physicians visited before diagnosis is established
- Misdiagnosis = not uncommon.
  Further contributes to diagnosis delay !

Lousada et al. Adv Ther 2015

Kourelis et al. Am J Haematol 2014

McCausland et al. Patient 2018

Presentation and Organ involvement



Cerebral hemorrhage, stroke, dementia

Periorbital purpura
Impaired vision

Jaw claudication, xerostomia, submandibular swelling

Most common symptom (80%)

Macroglossia

Dysphagia, hoarseness

Orthostatic hypotension

Heart failure, arrhythmias, conduction abnormalities, syncope, hypotension, chest pain

Dyspnea, cough

Hepatomegaly, hepatic failure

Hyposplenism

Fatigue, anorexia, weight loss

Proteinuria, nephrotic syndrome, renal failure

GI dysmotility, malabsorption, ulceration, GI bleeding

Carpal tunnel syndrome

Easy bruising

Urinary retention, erectile dysfunction

Nail dystrophy

Muscle weakness

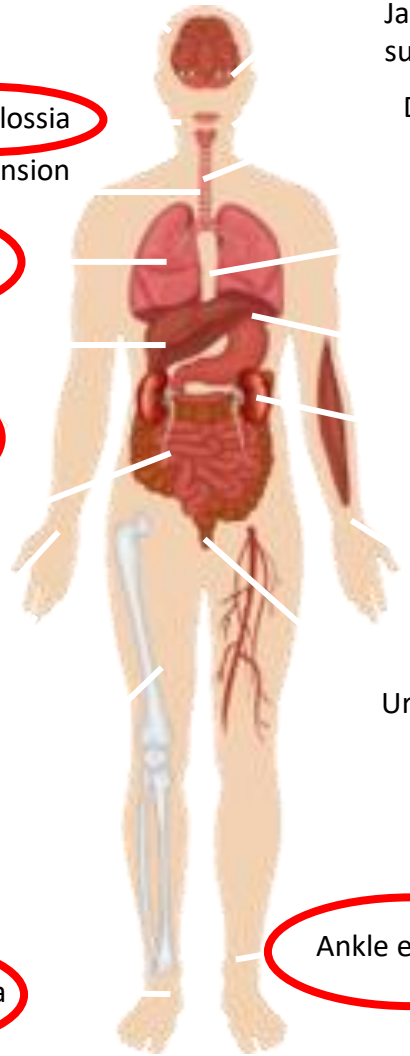
Ankle edema

Painful paresthesia

EM-93892

Gertz et al. JAMA 2020

Presentation and Organ involvement



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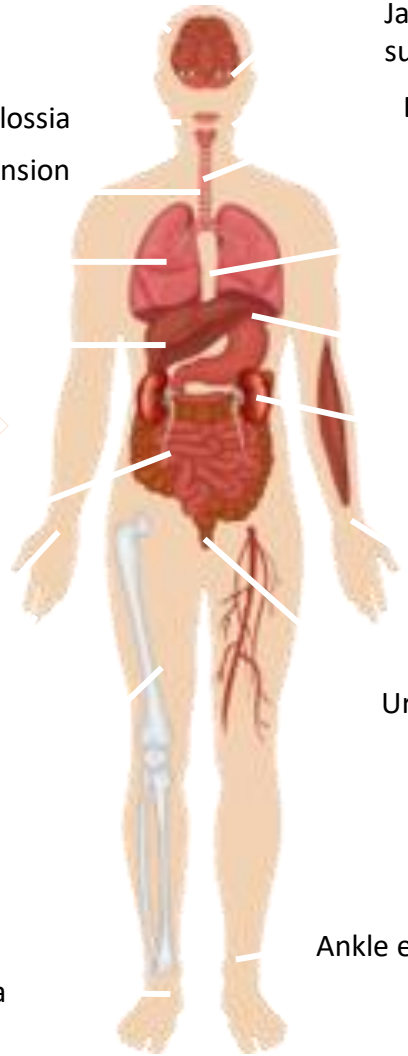

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Painful paresthesia

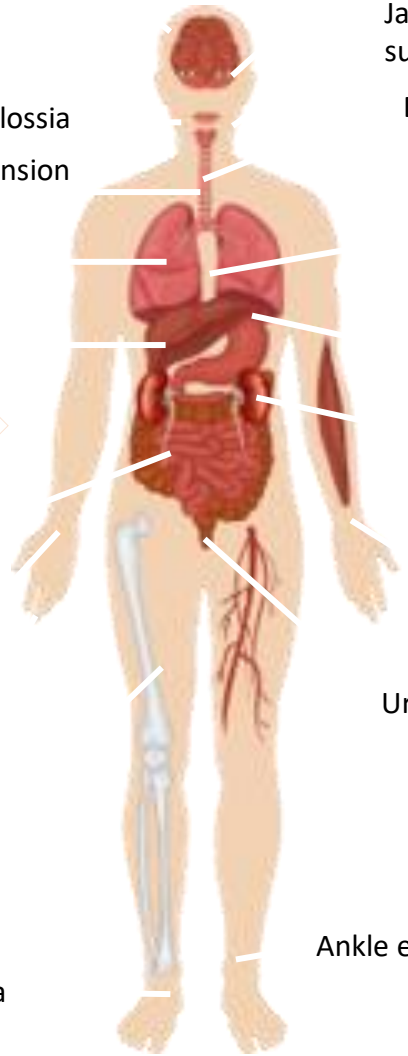
Most common involved organs (60-80% of patients):

- Heart
- Kidneys

EM-93892

Gertz et al. JAMA 2020

Presentation and Organ involvement



Most common involved organs (60-80% of patients):

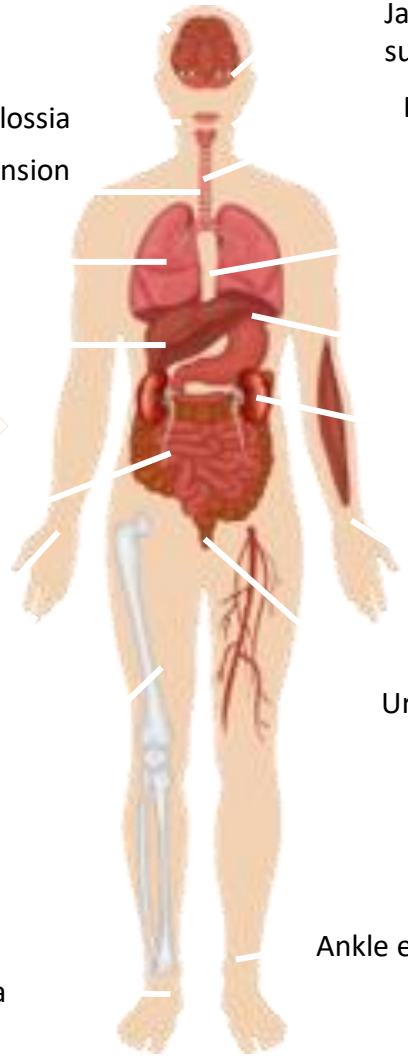
<u>Heart</u>

- Typical echocardiographic findings
  - ✓ Thickened heart walls
  - ✓ Rectrictive filling pattern
- Elevated soluble cardiac biomarkers (Troponin & NatriumProBNP)

EM-93892

Gertz et al. JAMA 2020

Presentation and Organ involvement



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Ankle edema

Painful paresthesia

Most common involved organs (60-80% of patients):

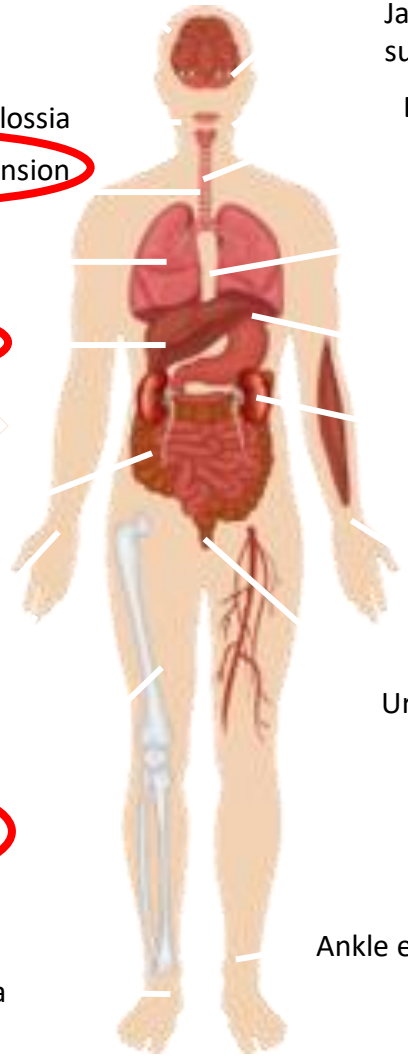
<u>Kidneys</u>

- Proteinuria
- With or without renal failure

EM-93892

Gertz et al. JAMA 2020

Presentation and Organ involvement



<u>Other organs involved :</u>

Nerve system (peripheral, autonomic)

Liver

Gastro intestinal tract

Muscles / Joints

Clotting factor deficiencies (ex fX)

Skin

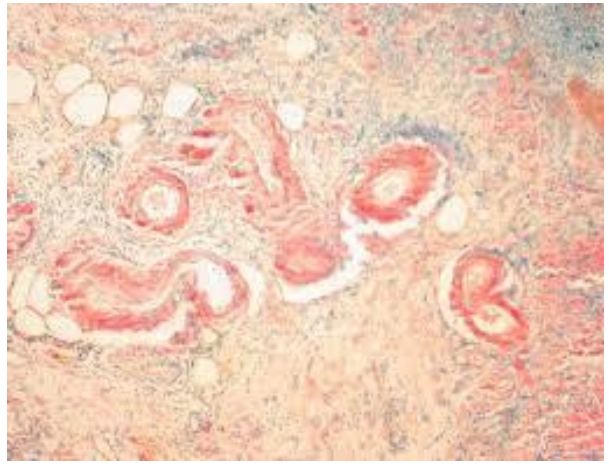
(spleen, lungs)

EM-93892

Gertz et al. JAMA 2020

Diagnosis of AL Amyloidosis

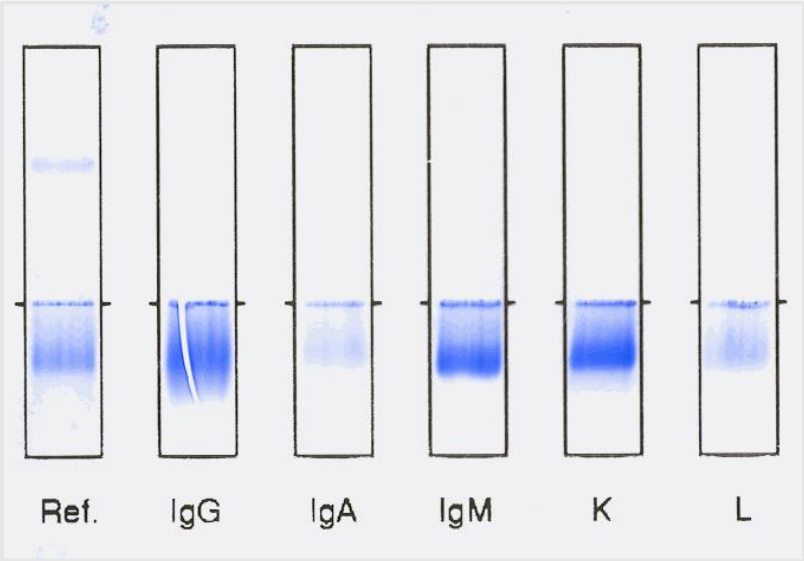
- Diagnosis relies on **demonstration of amyloid deposits** on a tissue sample
- **Tissue source**
  - Affected organ
  - Or a more accessible tissue :
    - ex subcutaneous fat
    - NOTE : Fat aspiration + BM biopsy : yields diagnosis in $\sim 90\% \, of \, patients$
  - CONGO Red staining = “gold standard”

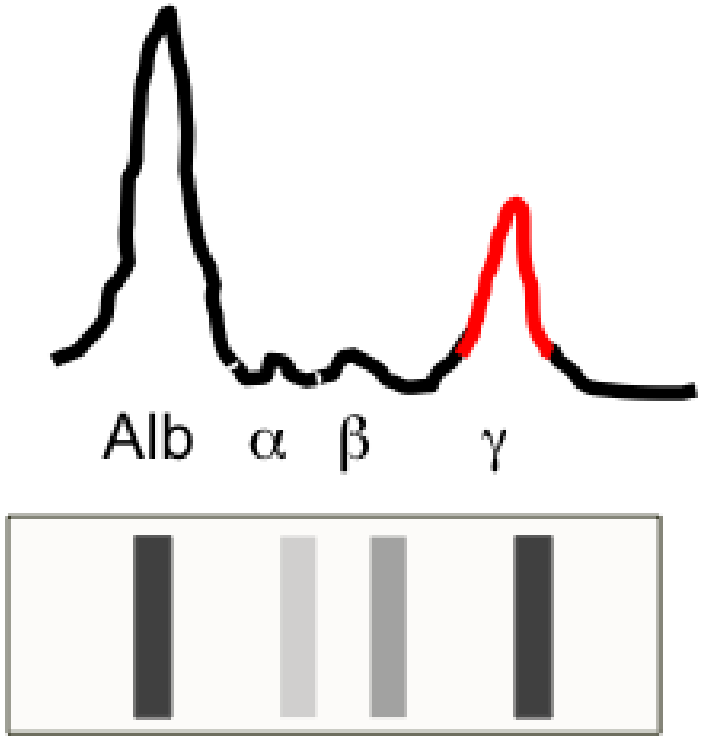


Muchtar et al. Ann Med 2017

Evaluation of patients with AL amyloidosis

- Screening for a **monoclonal protein**
  - Serum electropheresis
  - Immunofixation
  - Serum Free Light Chain (FLC) assay





- **Bone marrow biopsy**
  - BM plasmacytosis : associated MM ?
  - Exclude other B cell secretory diseases (Waldenstrom, NHL, CLL)
  - Demonstrate amyloid deposition

Prognosis of amyloidosis

- Prognosis depends on 2 compartments of the disease
  1. **Organ involvement**
     - ✓ Degree of heart involvement = most important predictor of short & long term survival
     - ✓ Number of involved organs and hepatic as well as autonomic involvement influence survival
  2. **Underlying plasma cell clone**
     - ✓ Predictor of long term survival
- Despite improvement in survival in recent years, proportion of patients dying within 6-12m of diagnosis remains fixed at 25%

Muchtar et al. Blood 2017

Muchtar et al. Br J Haematol 2017

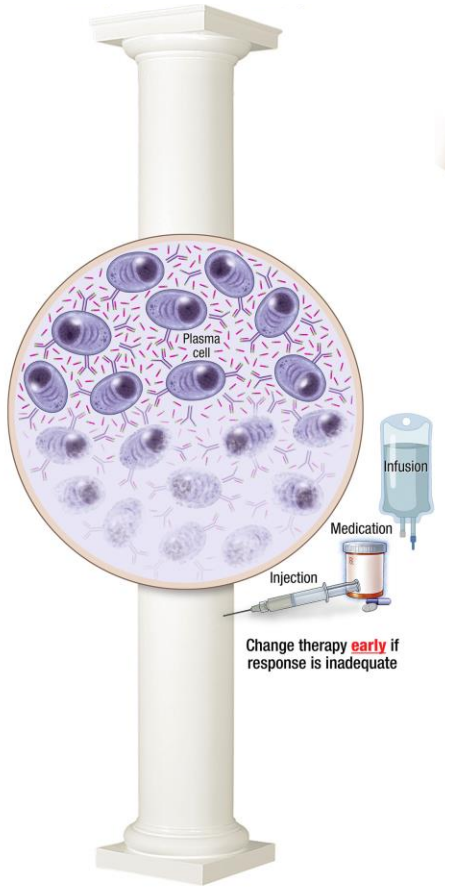
Staging & Prognostic impact of organ damage

Staging system	Markers and thresholds	Stages	Outcomes*
CARDIAC STAGING	NT-proBNP >332 ng/L cTnT >0.035 ng/mL (or cTnI > 0.01 ng/mL)	I. no markers above the cutoff II. one marker above the cutoff IIIa. both markers above the cutoff and NT-proBNP <8500 ng/L IIIb. both markers above the cutoff and NT-proBNP ≥8500 ng/L	I. median survival not reached, 60% surviving 10 years II. median survival 49 months IIIa. median survival 14 months IIIb. median survival 5 months
REVISED MAYO STAGING	NT-proBNP >1800 ng/L cTnT >0.025 ng/mL dFLC >180 mg/L	I. 0 markers above the cutoff II. 1 marker above the cutoff III. 2 markers above the cutoff IV. 3 markers above the cutoff	I. median survival not reached, 55% surviving 10 years II. median survival 57 months III. median survival 18 months IV. median survival 6 months
RENAL STAGING	eGFR <50 mL/min per 1.73 m^2 proteinuria >5 g/24h	I. both eGFR above and proteinuria below the cutoffs II. either eGFR below or proteinuria above the cutoffs III. both eGFR below and proteinuria above the cutoffs	I. 1% risk of dialysis at 2 years II. 12% risk of dialysis at 2 years III. 48% risk of dialysis at 2 years

Muchtar et al. Leukemia 2019

Management of amyloidosis

Pillar 2 : Plasma-cel directed therapy



Mainstay of treatment = targeting the underlying PC clone
→ decrease amyloid deposition as source of tissue injury
→ ↓ tissue injury & ↑ organ recovery

Another approach : targeting amyloid deposits using monoclonal antibodies : has been investigated – non has yet reached a regulatory approval stage

Treatment of amyloidosis : challenges

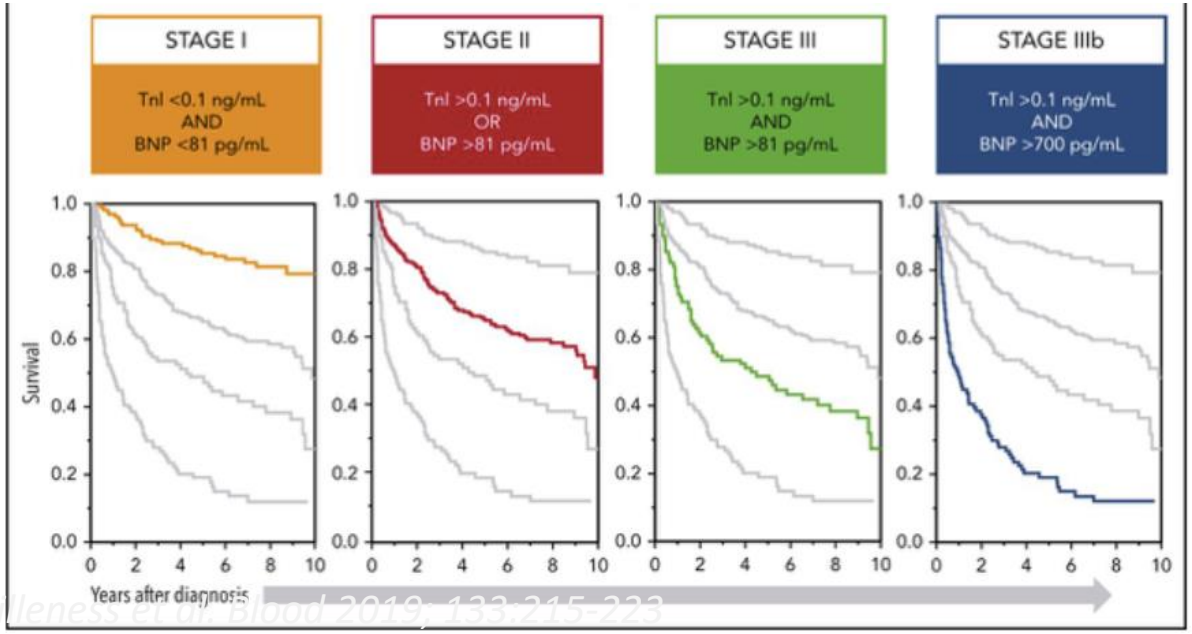
Early response is critical to maximize organ recovery and survival

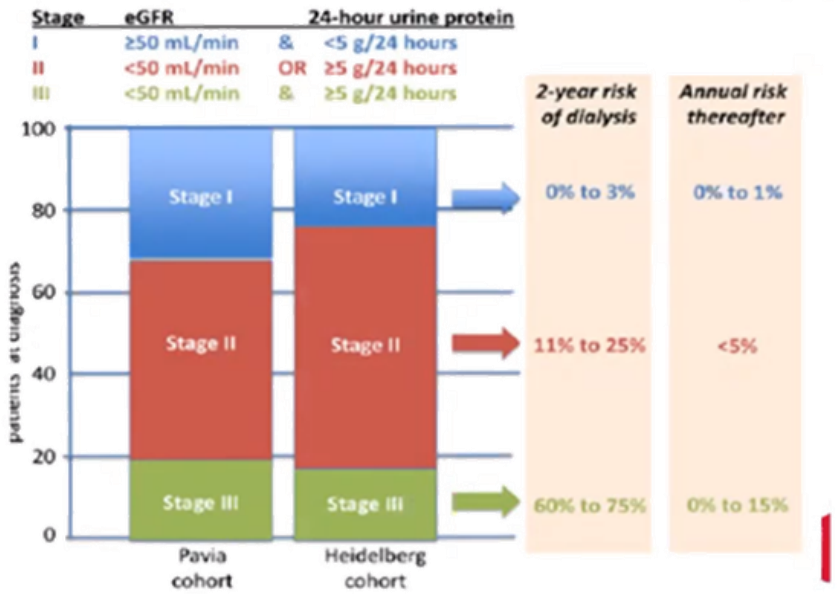
Deep responses are **difficult** to achieve

Organ responses are **slow**

Patients with cardiac Al die even when in a deep hematological response

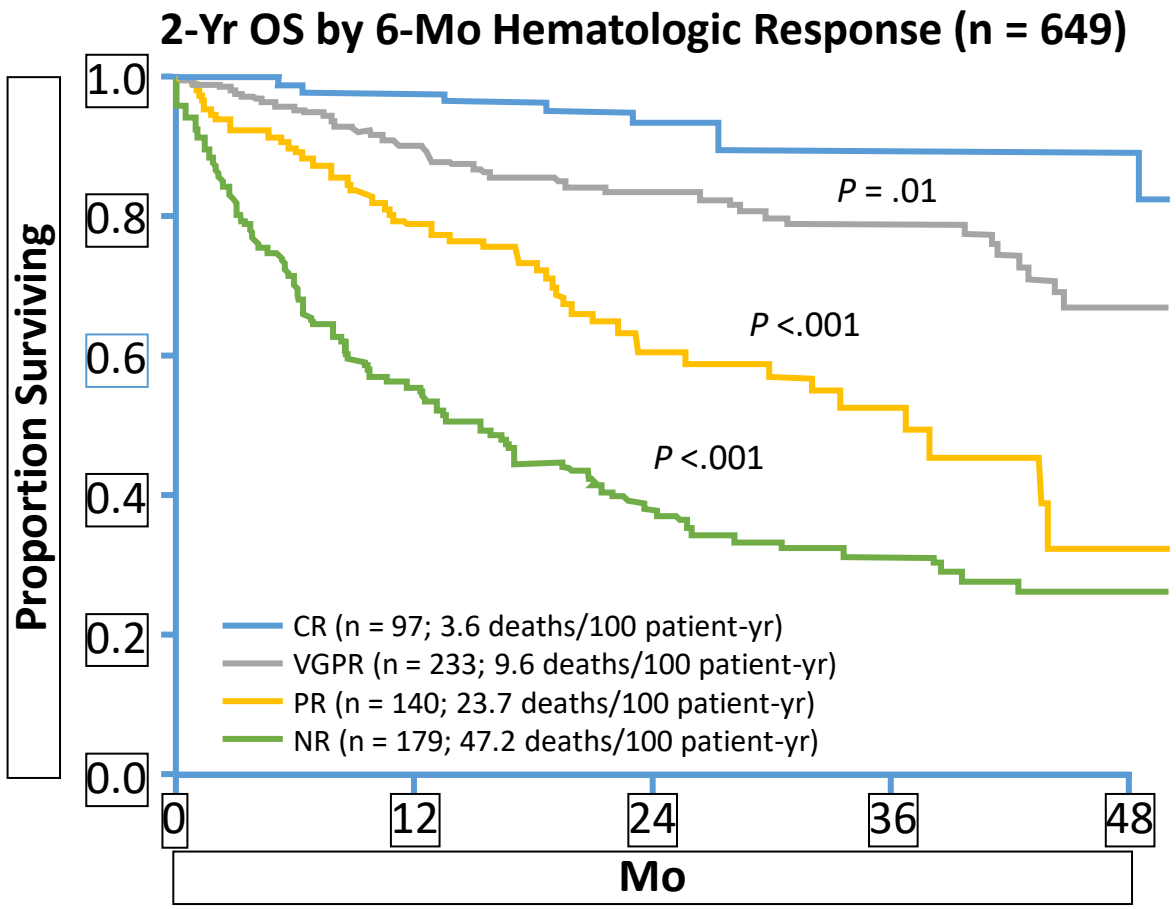
A high proportion of renal stage II & III patients still progress to dialyse

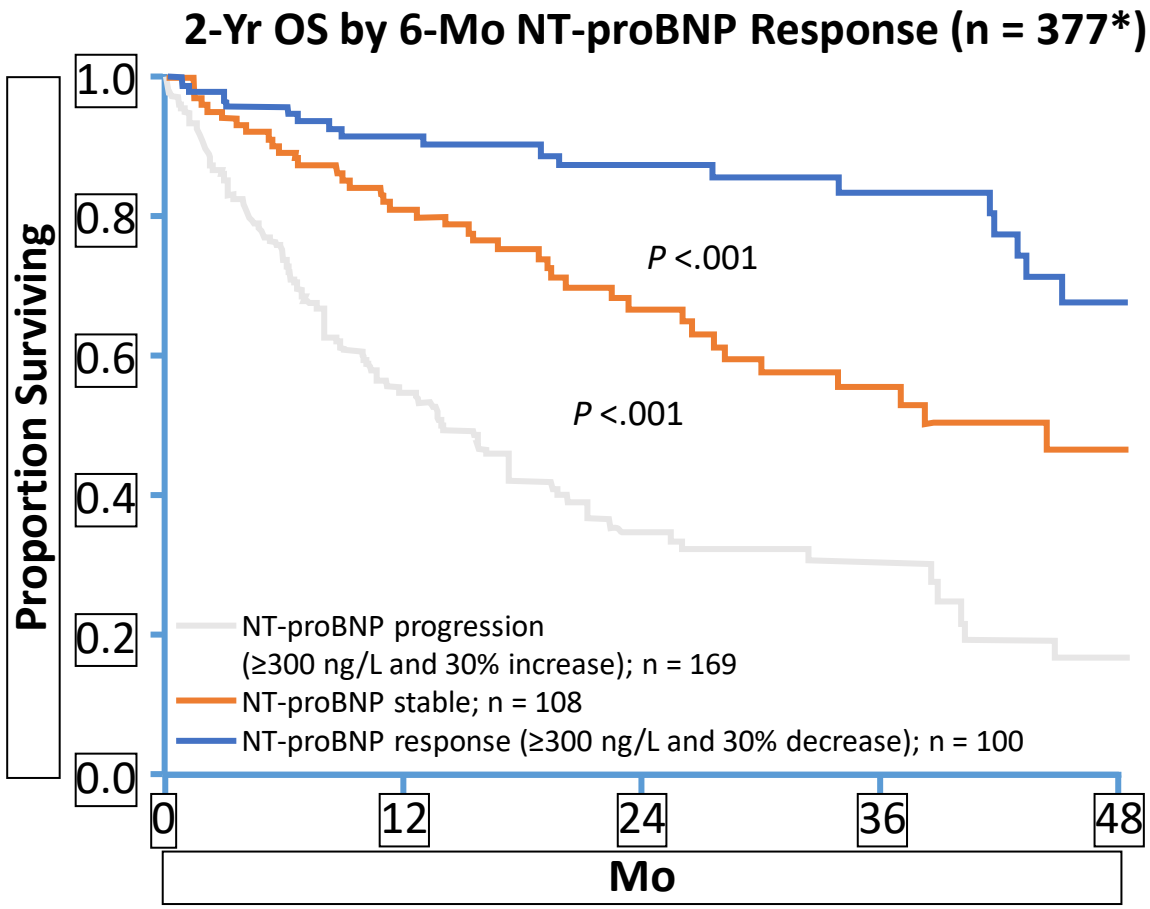




OS in Amyloidosis by Hematologic and Organ Response

- Multicenter analysis of 816 patients with AL amyloidosis





*Baseline NT-proBNP ≥650 ng/L.

Palladini 2020

Goals for Therapy : recommendations

- **HEMATOLOGICAL RESPONSE (HR)**
  - ✓ Goal of treatment = at least haematologic **very good partial response (VGPR)**
    = difference between involved aand unvolved light chains (dFLC)< 40 mg/L
  - ✓ **Optimal response = CR** : normalization of FLC ratio and negative immunofixation
    - But this has to be weighted against toxicity of therapy (so it can only be achieved in a limited number of pts)
    - So VGPR is a realistic treatment goal (can be achieved in 40-80% of pts with modern therapies)
  - ✓Patients who do not achieve at least PR after 2 cycles of VGPR after 4 cycles of therapy should be offered alternative therapy

- **ORGAN RESPONSE (OR)**
  - Prefered organ response = improvement of organ function to near normal value
  - OR criteria are binary = response versus no response
  - Lags behind HR with several months

Overview :
Hematologic and organ response criteria

Response type	Criteria
Hematologic response[63]	
Complete response	Negative serum and urine immunofixation and normal serum immunoglobulin κ/λ FLC ratio
Very good partial response	dFLC <40 mg/L
Partial response	dFLC decrease of >50%
No response	Less than a partial response
Organ response[19,63]	
Cardiac response	Decrease of NT-proBNP by >30% and 300 ng/L (if baseline NT-proBNP >650 ng/L)
Renal response	At least 30% decrease in proteinuria or drop below 0.5 g/24 h, in the absence of renal progression, defined as a >25% decrease in eGFR
Hepatic response	50% decrease in abnormal alkaline phosphatase value or decrease in radiographic liver size by at least 2 cm

dFLC, difference between involved and uninvolved serum immunoglobulin free light chains (a value adequate to measure response is deemed to be 50 mg/L); eGFR, estimated glomerular filtration rate; FLC, free light chain; NT-proBNP, N-terminal brain natriuretic peptide.

Muchtar Mayo Clin Proc 2021

Initial therapy

- Consider high dose + autoSCT in selected pts

- Risk adapted : select candidates for SCT

Mayo Eligibility Criteria for ASCT

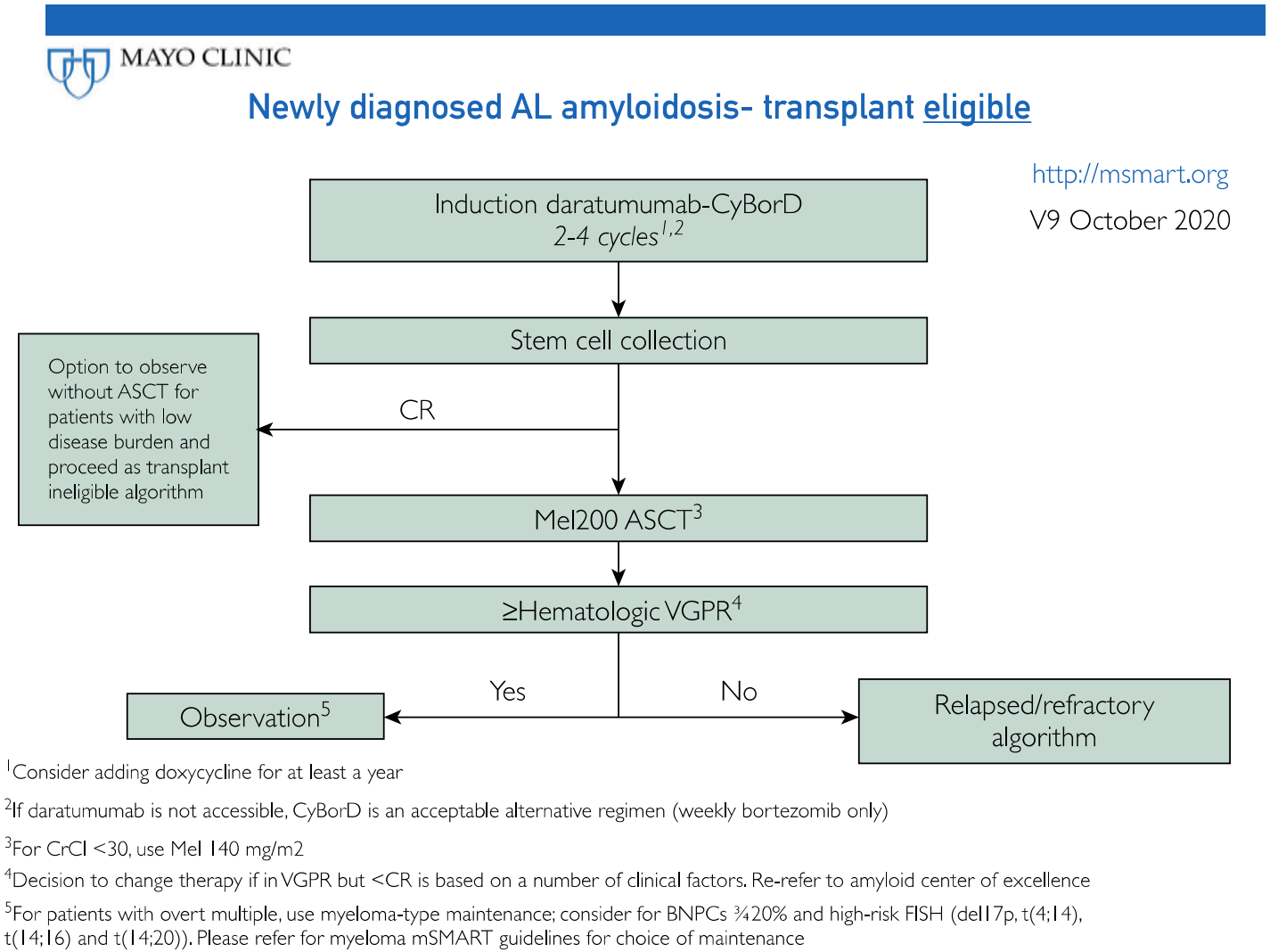
"Physiologic" age ≤70 years
Performance score ≤2
Systolic blood pressure ≥90 mm Hg[a]
Troponin T level <0.06 ng/mL (or high-sensitivity troponin T level <75 ng/mL)
Creatinine clearance ≥30 mL/min[b] (unless on long-term dialysis)
New York Heart Association class I/II

[a]Caution as well for patients with systolic blood pressure <100 mm Hg.

[b]Selected patients may become eligible for autologous stem cell transplant with cardiac and renal transplant.

Gertz et al. BMT 2013

Treatment algoritm for newly diagnosed transplant eligible AL amyloidosis patients



Muchtar Mayo Clin Proc 2021

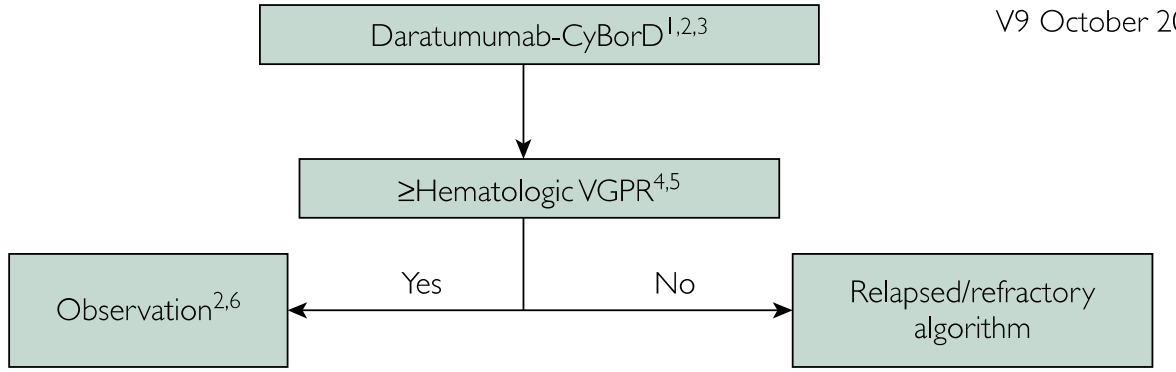
Treatment algoritm for newly diagnosed transplant non eligible AL amyloidosis patients

MAYO CLINIC

Newly diagnosed AL amyloidosis- transplant non eligible#

http://msmart.org

V9 October 2020



[1]Consider adding doxycycline for at least a year

[2]If daratumumab CyBorD, 6 cycles followed by daratumumab monotherapy, completing up to 24 cycles. If daratumumab is not accessible, CyBorD and BMDex are acceptable alternatives regimens (weekly bortezomib)

[3]If young, consider stem cell collection for eventual ASCT if eligibility for transplant is foreseeable

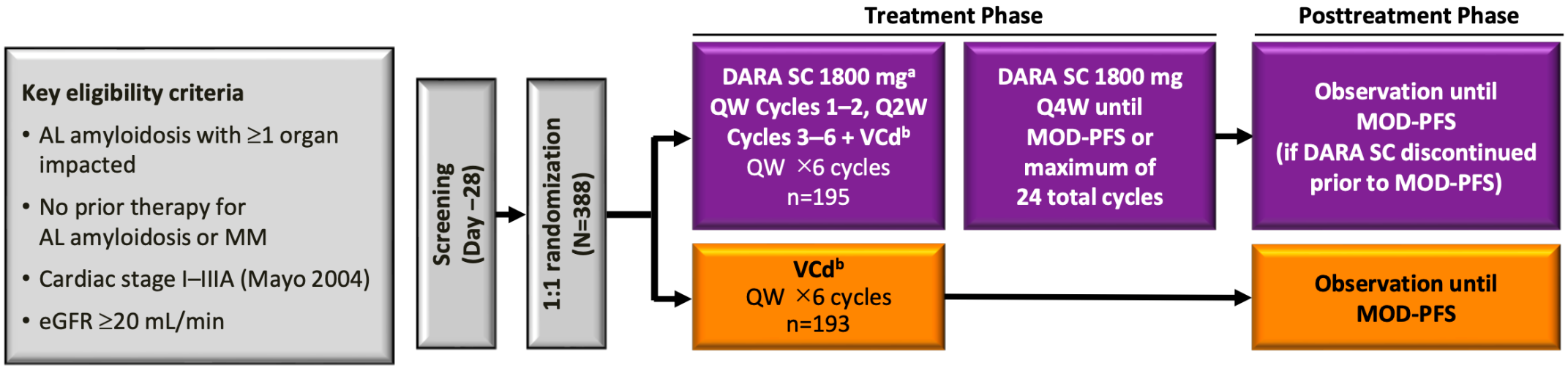
[4]If <PR at 2d months or <VGPR withi 4 cycles change therapy, unless signs of organ response are seen

[5]Decision to change therapy if in VGPR but <CR is based on a number of clinical factors Re-refer to amyloid center of excellence

[6]Only for patients with overt multiple myeloma, BMPCs ¾20% or high-risk FISH and who are not receiving extended duration daratumumab, consider maintenance. Lenalidomide should not be used in patients with advanced heart or autonomic nerve involvement

[#]For IgM AL amyloidosis consider referral to amyloidosis center due to a more challenging management

ANDROMEDA
Eligibility criteria & study design



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)

Primary endpoint: Overall hematologic CR rate

Secondary endpoints: MOD-PFS, organ response rate, time to hematologic response, overall survival, safety

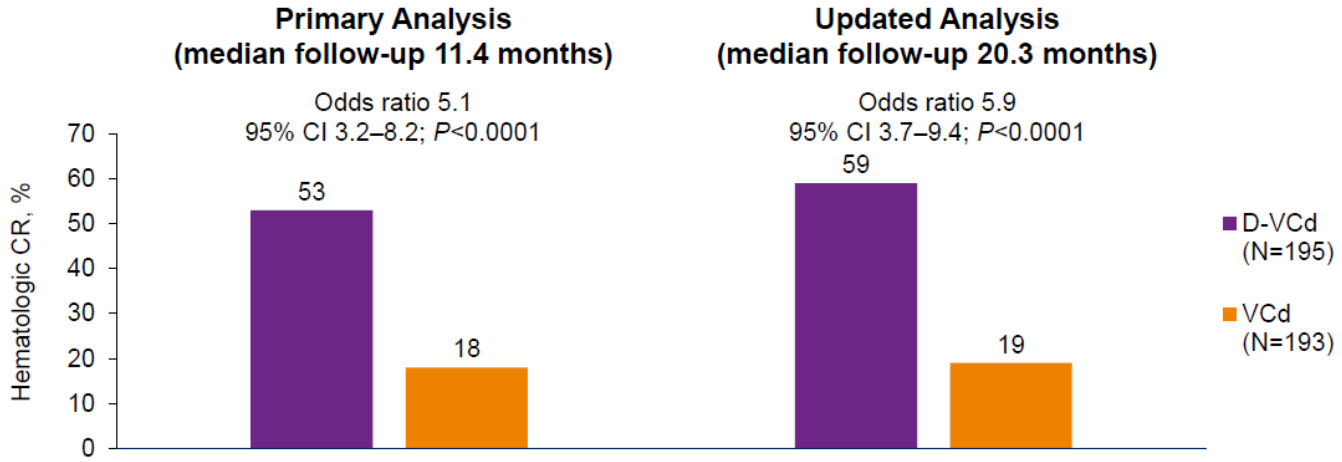
ANDROMEDA is a randomized, open-label, active-controlled, phase 3 study of DARA-VCd versus VCd alone in patients with newly diagnosed AL amyloidosis

AL, amyloid light chain; CR, complete response; DARA, daratumumab; eGFR, estimated glomerular filtration rate; IV, intravenous; MM, multiple myeloma; MOD-PFS, major organ deterioration progression-free survival; PO, oral; Q2W, every 2 weeks; Q4W, every 4 weeks; QW, weekly; SC, subcutaneous; VCd, bortezomib, cyclophosphamide, and dexamethasone.

VCd in amyloidosis: bortezomib 1.5 mg/m^2
VCd in multiple myeloma: bortezomib 1.3 mg/m^2

ANDROMEDA
Hematologic CR (primary endpoint)

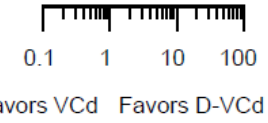
- **Hematologic CR was defined as normalization of FLC levels and FLC ratio and negative serum and urine immunofixation**
  - If iFLC < upper limit of normal, normalization of the uninvolved FLC and FLC ratio were not required
- **Rates of hematologic CR remained significantly higher with D-VCd than VCd**
- **Median time to hematologic CR[a] was 2.0 months with D-VCd vs 2.8 months with VCd**



[a]Among CR responders (D-VCd, n=115; VCd, n=37).
CI, confidence interval; CR, complete response; D-VCd, daratumumab/bortezomib/cyclophosphamide/dexamethasone; FLC, free light chain; iFLC, involved free light chain.

ANDROMEDA
Hematologic CR rates remained high across all prespecified subgroups

Subgroup	D-VCd n (% resp)	VCd n (% resp)	Odds ratio (95% CI)
Overall	115 (59.0)	37 (19.2)	5.0 (3.7–9.4)
Sex			
Male	64 (59.3)	17 (14.5)	8.7 (4.5–16.3)
Female	51 (58.6)	20 (26.3)	4.0 (2.0–7.7)
Age			
<65 years	68 (63.0)	20 (20.6)	6.6 (3.5–12.3)
≥65 years	47 (54.0)	17 (17.7)	5.5 (2.8–10.7)
Baseline weight			
≤65 kg	41 (66.1)	10 (13.5)	12.5 (5.4–29.2)
>65-85 kg	53 (55.2)	14 (18.9)	5.3 (2.6–10.7)
>85 kg	21 (56.8)	13 (28.9)	3.2 (1.3–8.1)
Race			
White	88 (58.3)	28 (19.6)	5.7 (3.4–9.7)
Asian	21 (70.0)	5 (14.7)	13.5 (4.0–46.3)
Others	6 (42.9)	4 (25.0)	2.3 (0.5–10.6)
Baseline cardiac stage			
I	24 (51.1)	13 (30.2)	2.4 (1.0–5.7)
II	46 (60.5)	17 (21.3)	5.7 (2.8–11.5)
III[a]	45 (62.5)	7 (10.0)	15.0 (6.0–37.5)
Cardiac involvement at baseline			
Yes	88 (55.8)	22 (16.1)	8.9 (5.0–15.7)
No	27 (49.1)	15 (26.8)	2.6 (1.2–5.8)
Baseline renal stage			
I	21 (53.8)	6 (16.7)	5.8 (2.0–17.2)
II	41 (73.2)	14 (23.3)	9.0 (3.9–20.8)
III	10 (52.6)	5 (27.8)	2.9 (0.7–11.4)
Baseline ECOG performance score			
0	51 (56.7)	16 (22.5)	4.5 (2.2–9.0)
1 or 2	64 (61.0)	21 (17.2)	7.5 (4.1–13.9)
FISH t(11;14)			
Present	30 (58.8)	7 (12.7)	9.8 (3.7–25.8)



[a]Cardiac stage III includes both IIIA patients and patients who were IIIA at randomization and progressed to IIIB at Cycle 1, Day 1.
CI, confidence interval; CR, complete response; D-VCd, daratumumab/bortezomib/cyclophosphamide/dexamethasone; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescent in situ hybridization; resp, response.

ANDROMEDA
Conclusions

Longer follow up supports the benefit of the addition of Daratumumab to VCD

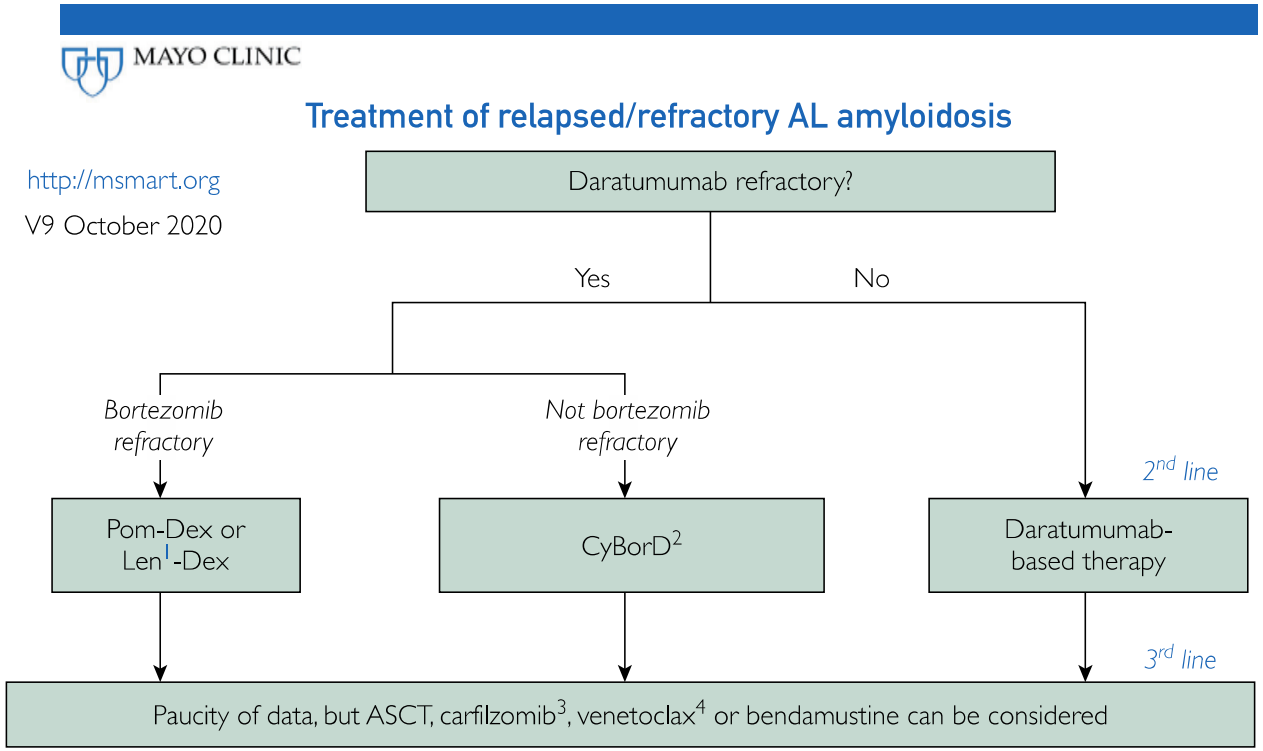
- ✓ Significantly improved hematological response
- ✓ Doubling rates of cardiac and renal response

Treatment is safe

These data support D-VCD as the new standard of care for patients with AL amyloidosis

Kasritis et al., Abstract 8003, ASCO 2021

Treatment algoritm for relapsed / refractory AL amyloidosis patients

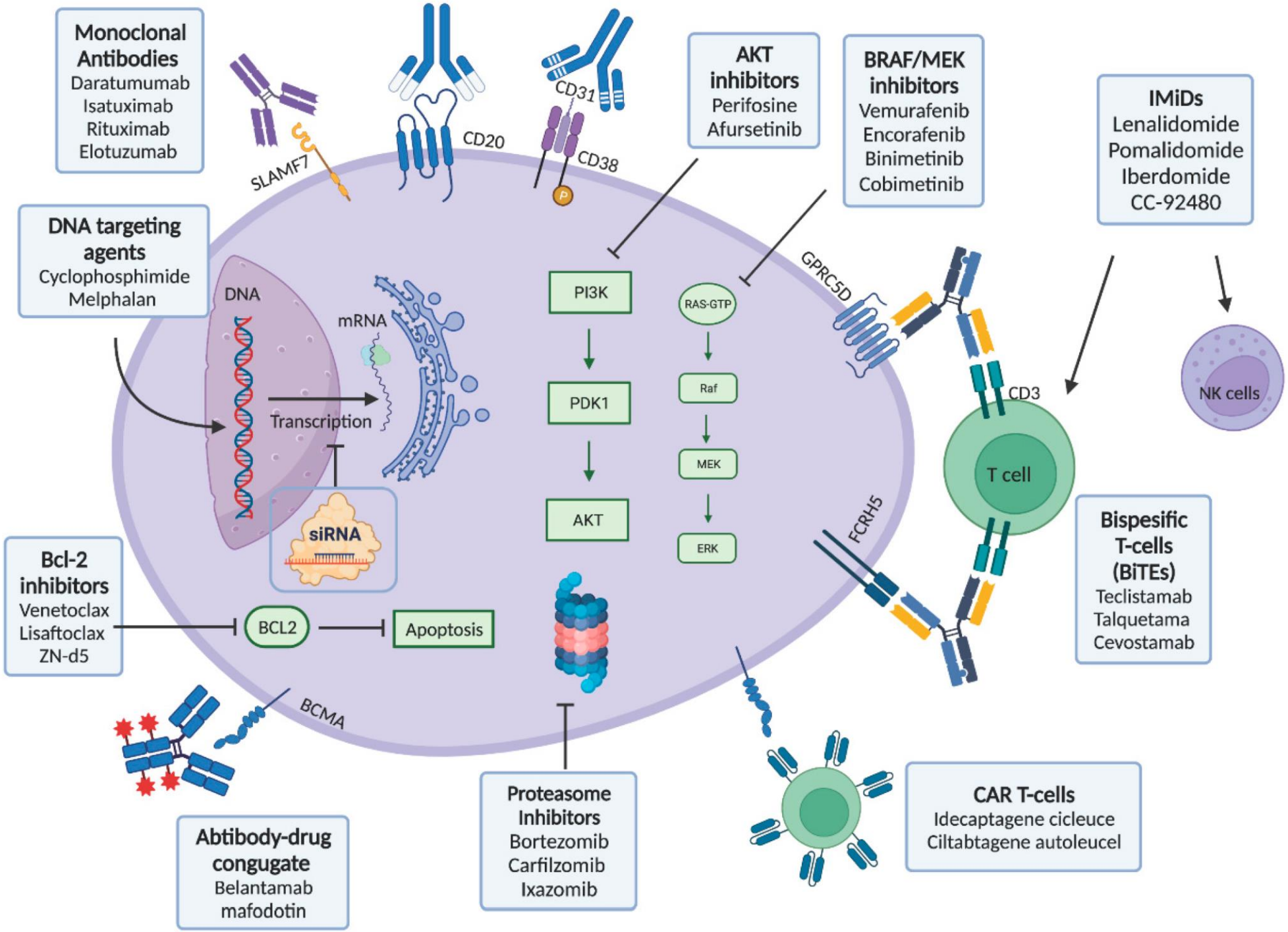


[1]Starting dose of lenalidomide should be no higher than 15 mg/d

[2]Melphalan-dexamethaone and ixazomib-dexamethasone are appropriate if patient has significant neuropathy

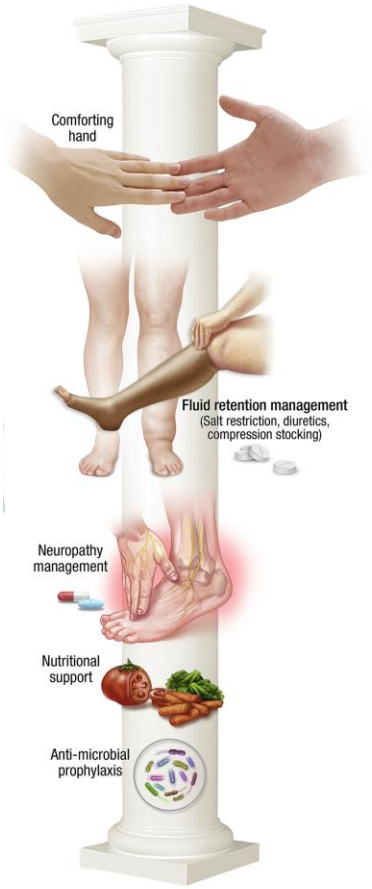
[3]Not recommended in patients with cardiac involvement

[4]For patients with(11;14). Be cautious of infection risk.


Monoclonal Antibodies
Daratumumab
Isatuximab
Rituximab
Elotuzumab
SLAMF7
CD20
CD31
CD38
AKT inhibitors
Perifosine
Afursetinib
BRAF/MEK inhibitors
Vemurafenib
Encorafenib
Binimetinib
Cobimetinib
IMiDs
Lenalidomide
Pomalidomide
Iberdomide
CC-92480
DNA targeting agents
Cyclophosphimide
Melphalan
DNA
mRNA
Transcription
siRNA
PI3K
PDK1
AKT
RAS-GTP
Raf
MEK
ERK
GPRC5D
CD3
T cell
NK cells
FCRH5
Bispesific T-cells (BiTEs)
Teclistamab
Talquetama
Cevostamab
Bcl-2 inhibitors
Venetoclax
Lisaftoclax
ZN-d5
BCL2
Apoptosis
BCMA
Abtibody-drug congugate
Belantamab mafodotin
Proteasome Inhibitors
Bortezomib
Carfilzomib
Ixazomib
CAR T-cells
Idecaptagene cicleuce
Ciltabtagene autoleucel

Management of amyloidosis

Pillar 3 : Supportive Care



A multidisciplinary approach

- Based on predominant involved organs and symptoms

Palliative care team

- Patients with advanced illness
- Counselling patients on symptom management
  - Psycho-social
  - Advanced care planning

AL Amyloidosis : Summary

- AL Amyloidosis = **rare** disease
- Management is **challenging**
  - Difficulties in diagnosis
  - Advanced disease at presentation
- Organ failures – heart especially make **treatment related toxicity very common**
- **Multidisplinary approach**
- **Deep and rapid response** is important (impact on survival)
- **Higher quality of response** with introduction of Daratumumab
- **Supportive care** is very important