Relapsed and Refractory Multiple Myeloma and Light Chain Amyloidosis

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- Sebia, Janssen, BMS, Sanofi, HopeAI, Adaptive Biotechnologies, Abbvie

Agenda

- Relapsed and refractory multiple myeloma
  - 1-3 prior lines of therapy
  - >3 prior lines of therapy
  - CAR T cell therapy
  - Bispecific antibodies
- Light chain (AL) Amyloidosis
  - Diagnosis, evaluation
  - Management

What is relapse in multiple myeloma and when do we treat?

- **Clinical relapse** **Always!**
  - Progression of new end organ damage:
    - Hypercalcemia
    - Anemia
    - Renal failure
    - Osteolytic bone disease
    - Plasmacytoma
    - Plasma cell leukemia

- **Biochemical relapse** **Usually…**
  - Increase in monoclonal protein or involved free light chains (> 0.5 g/dl or > 10 mg/dl)
  - Increase in bone marrow plasmacytosis (>10%)

Factors to consider

- Disease progression/relapse within 2 years of initial therapy when transplant and maintenance are used
- Relapse within 18 months in absence of transplant
- Acquisition of 1q gain/duplication, or Del 17p / TP53 mutation
- Extramedullary disease (EMD) at relapse

General principles of treating relapsed MM

- Preferable to use drug classes/agents that the patient has not previously been exposed to, typically in triplet combinations
- However… OK to repeat previously used regimen if not used recently (i.e., > 6 months)
- Intravenous immunoglobulin (IVIG) should be considered for patients with an IgG < 400 mg/dl, especially in the context of BsAb treatment
- Always use the best next therapy! Don’t save the best for last… there is attrition with each line of therapy in multiple myeloma

Management of Relapsed Multiple Myeloma in 1+ line of therapy in 2024

Most patients:

Dara RVD → autologous HCT → Lenalidomide (+/- Dara) maintenance

OR

Dara/Isa RD / RVD → lenalidomide maintenance

Progression of Disease

1-3 Lines of therapy

- CD38 + IMID: Carfilzomib, pomalidomide, dexamethasone
- CD38 + PI:Carfilzomib + either Daratumumab/Isatuximab and dexamethasone
- BCMA CAR T cells: Cilta-cel (1 LOT) or ide-cel (2 LOT)
- Selinexor regimens
- Clinical trial

4+ Lines of therapy

- BCMA CAR T cells:Cilta-cel, or Ide-cel
- BCMA Bispecific: Teclistamab, elrantabamab
- GPRC5D Bispecific: Talquetamab
- Clinical trial

Post-BCMA relapse

- Clinical trials
- GPRC5D bispecific: Talquetamab (if not already given)
- Selinexor based regimens

Sample board question

- 54 year old man diagnosed with multiple myeloma, with 1q gain. He was treated initially with Dara RVD, followed by autologous stem cell transplant, to which he achieved a complete response. He was on lenalidomide maintenance for 3 years and has recently had evidence of an increasing monoclonal protein up to 0.5 g/dl, with appearance of new FDG-avid osteolytic bone disease on PET-CT.

- Question 1: Should I treat this patient?
  - 1. Yes
  - 2. No

What are category 1 recommendations for treatment of this patient's disease?

- 1. Daratumumab, bortezomib and dexamethasone
- 2. Selinexor, bortezomib, and dexamethasone
- 3. Carfilzomib, pomalidomide, and dexamethasone
- 4. Elotuzumab, pomalidomide, and dexamethasone
- 5. Cilta-cel (Carvykti)
- 6. All of the above

Common non-immunotherapy based regimens for 1-3L MM

- CD38 + immunomodulatory agent (All Category 1)
  - Daratumumab, lenalidomide, dexamethasone (POLLUX)
  - Daratumumab + pomalidomide, dexamethasone (APOLLO)
  - Isatuximab + pomalidomide, dexamethasone (ICARIA)
- CD38 + proteasome inhibitor (All category 1)
  - Daratumumab, bortezomib, and dexamethasone (CASTOR)
  - Daratumumab, carfilzomib, and dexamethasone (CANDOR)
  - Isatuximab, carfilzomib, and dexamethasone (IKEMA)
- Selective inhibitors of nuclear export (Category 1)
  - Selinexor, bortezomib, and dexamethasone
- SLAMF7 antibody (Category 1)
  - Elotuzumab, pomalidomide, dexamethasone
- Cytoxan based regimens
  - Pomalidomide, Cytoxan, and dexamethasone

Dosing and administration

- Always prefer subcutaneous bortezomib; either weekly or twice weekly may be appropriate depending, but weekly usually preferable and has less neuropathy
- Carfilzomib – ok to give weekly; I usually prefer 56 mg/m2 IV weekly when giving in combination with CD38 mAbs or immunomodulatory agents
- Always try to reduce your dexamethasone dose after the first 1-2 cycles if the patient is responding! Consider 20 mg weekly for elderly/frail
- Pomalidomide – usually better to start with 2 mg daily; 4 mg can be tough for most patients
- Selinexor – we usually start with 60 or 80 mg weekly, especially in combination with proteasome inhibitors

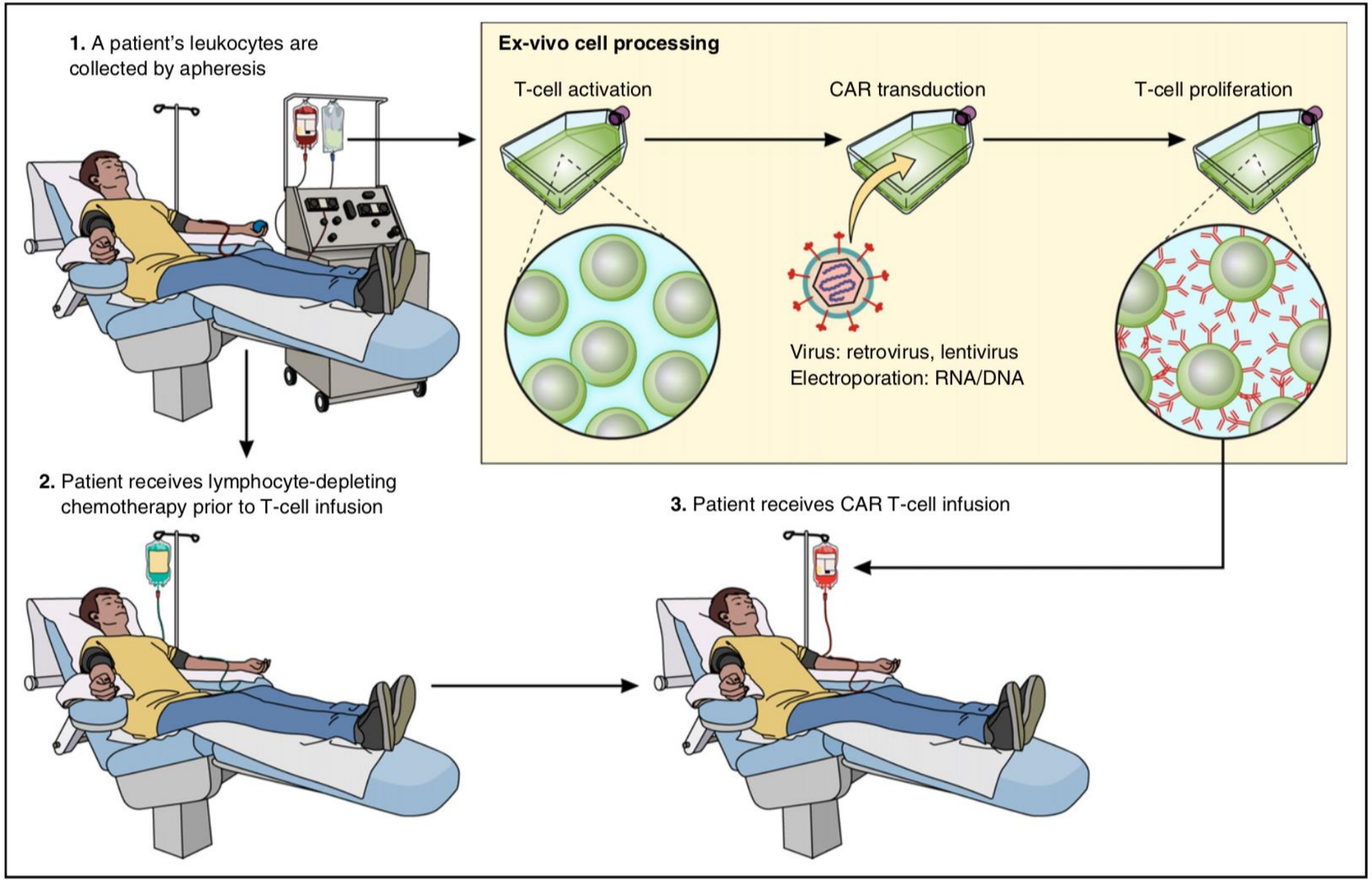
Common toxicities to be aware of

- Carfilzomib can cause both cardiac (5-10%) and renal toxicities (5-10%); be wary that both can occur at any time (early vs late)

- Selinexor – hyponatremia, anorexia, fatigue, moderate to severe nausea. Use 5HT3 antagonist + olanzapine

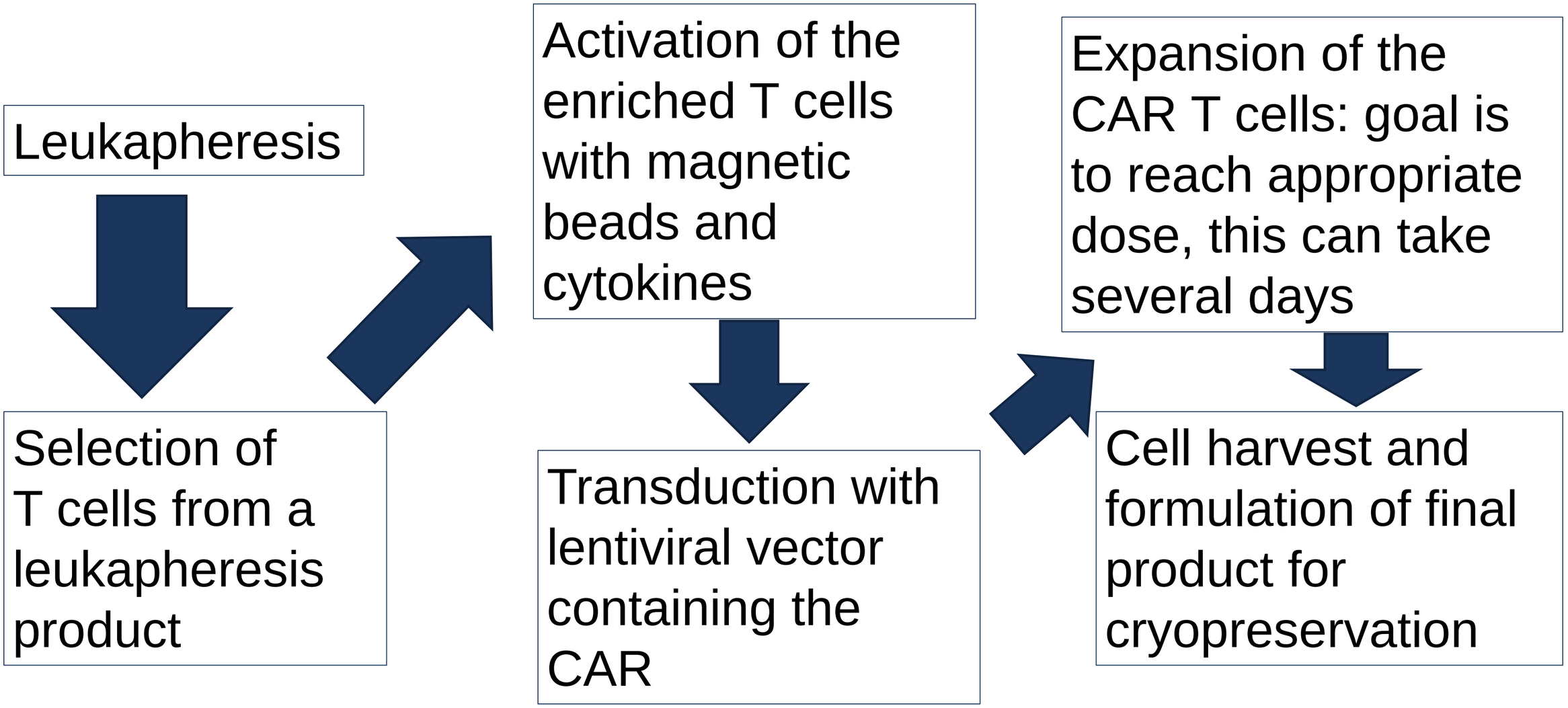
- Bendamustine – can impair ability to manufacture CAR T cells

CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY (CAR T CELLS)



Mikkilineni L, Kochenderfer J, *Blood* 2017.

CAR T-CELL MANUFACTURING

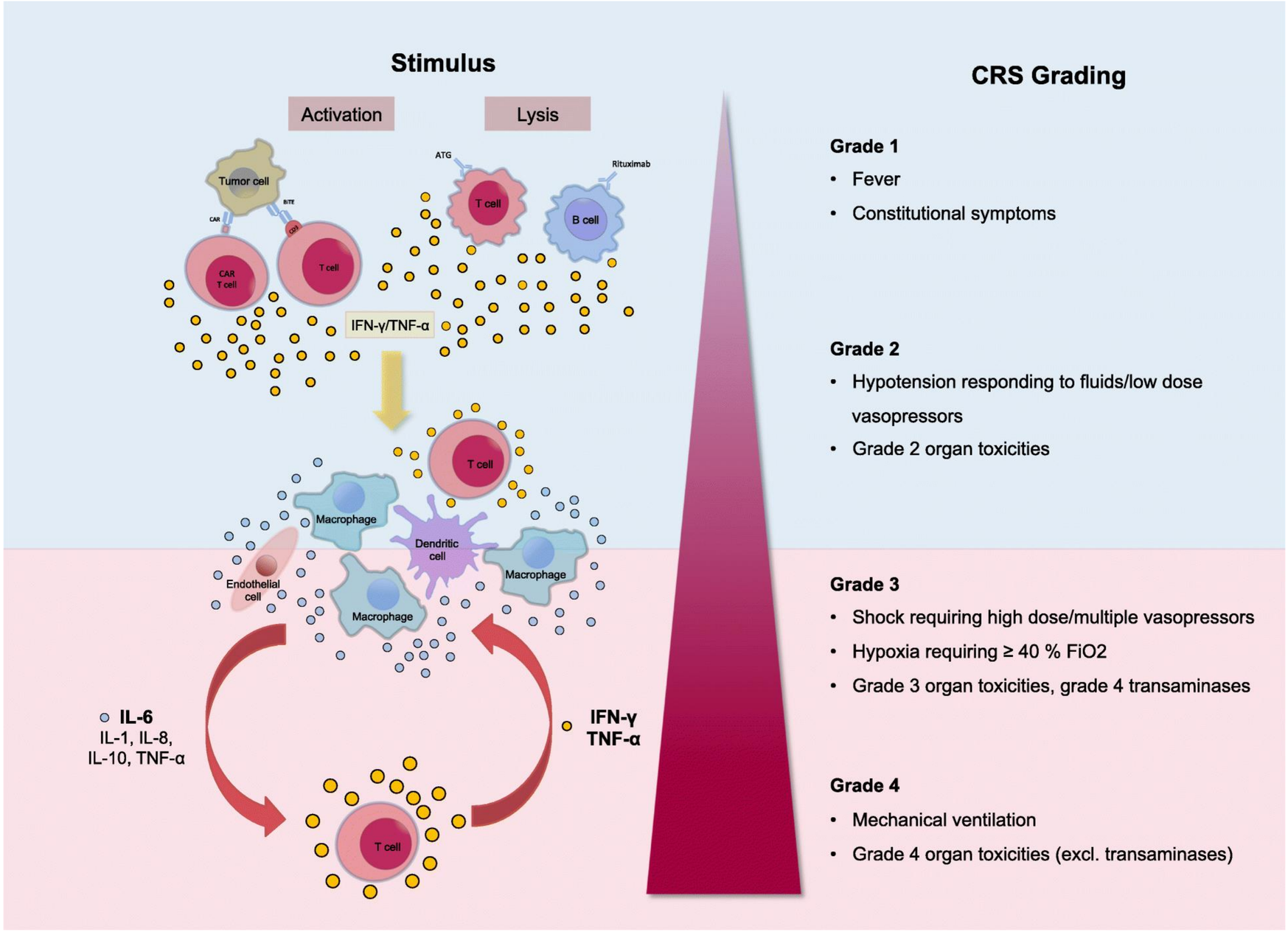


Toxicities from CAR T-cell therapy

- Cytokine release syndrome
- ICANS – aka neurotoxicity
- Prolonged cytopenias
- B-cell aplasia and hypogammaglobulinemia
- Secondary malignancy

What is cytokine release syndrome (CRS)?

- Pro-inflammatory syndrome caused by excessive immune activation from CAR T cell therapy
- If not recognized and treated early, results in substantial morbidity and mortality
- Hallmark of this syndrome is fever, hypotension, hypoxia



Shimabukuro-Vornhagen, et al. *Journal for Immunotherapy of Cancer*; 2018;6:56.

What is neurotoxicity associated with CAR T-cell therapy?

- Neurotoxicity – also more recently known as “Immune Effectory Cell-Associated Neurotoxicity Syndrome” – ICANS
- Predominant symptoms: Ranges from mild confusion, lethargy, word finding difficulties, to more severe states such involving global encelphalopathy such as coma, persistent vegetative states
- Important – has resulted in deaths in some patients receiving CAR T-cell therapy
- Dexamethasone – mainstay of treatment – treat early, don’t delay!

EARLIER USE OF BCMA CAR T

KarMMA-3 – Otero P et al, *NEJM* 2023

Ide-cel/Abecma: BCMA targeted chimeric antigen receptor T-cell therapy, approved by FDA in 2020

Multiple myeloma

2-4 prior lines of therapy

Triple class exposed

2:1 Randomization

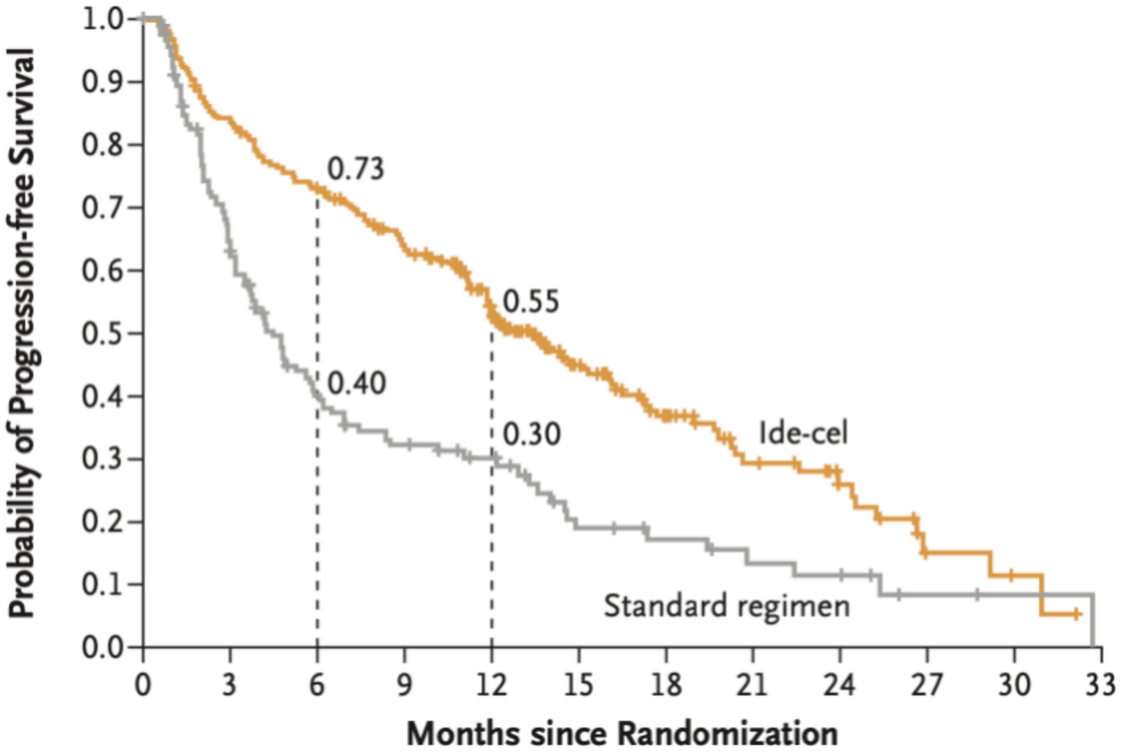
Ide-cel, N=254

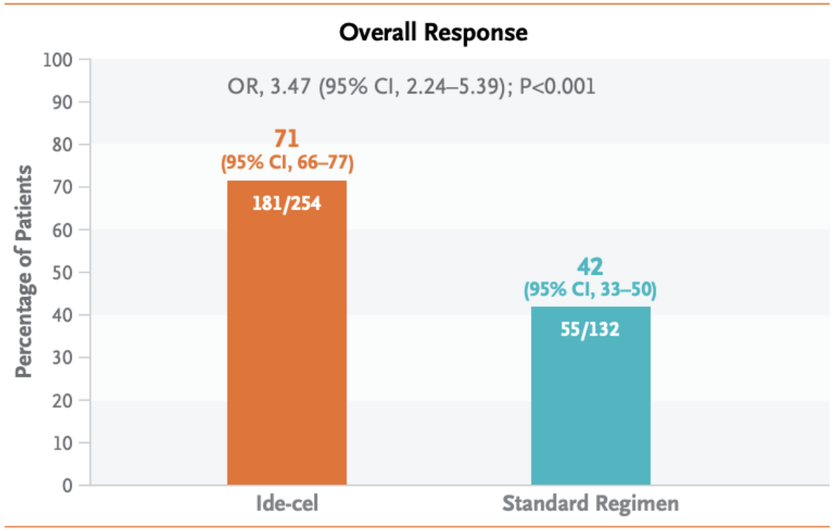
SOC therapy, n=132

n.b. KdDara or IsaKD not permitted as SOC; 5 approved regimens

Primary endpoint: PFS

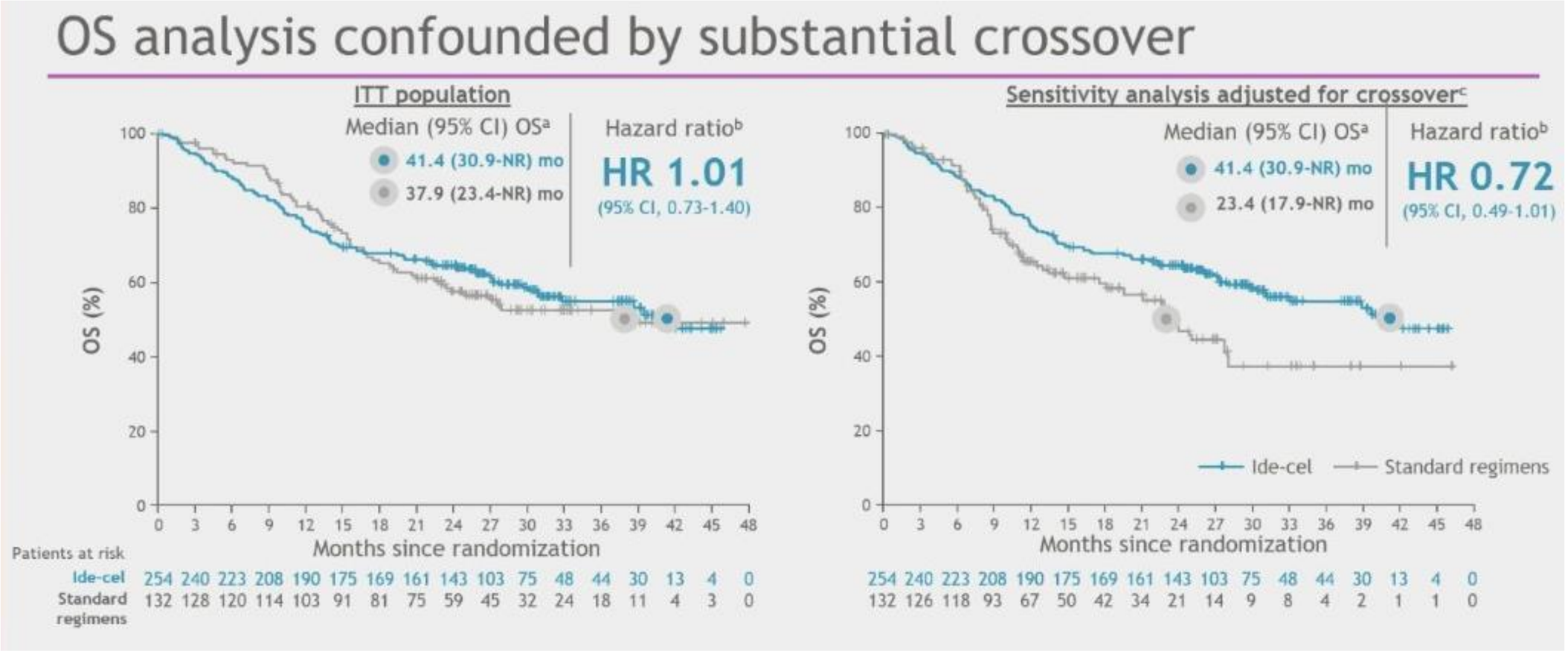
Crossover ALLOWED





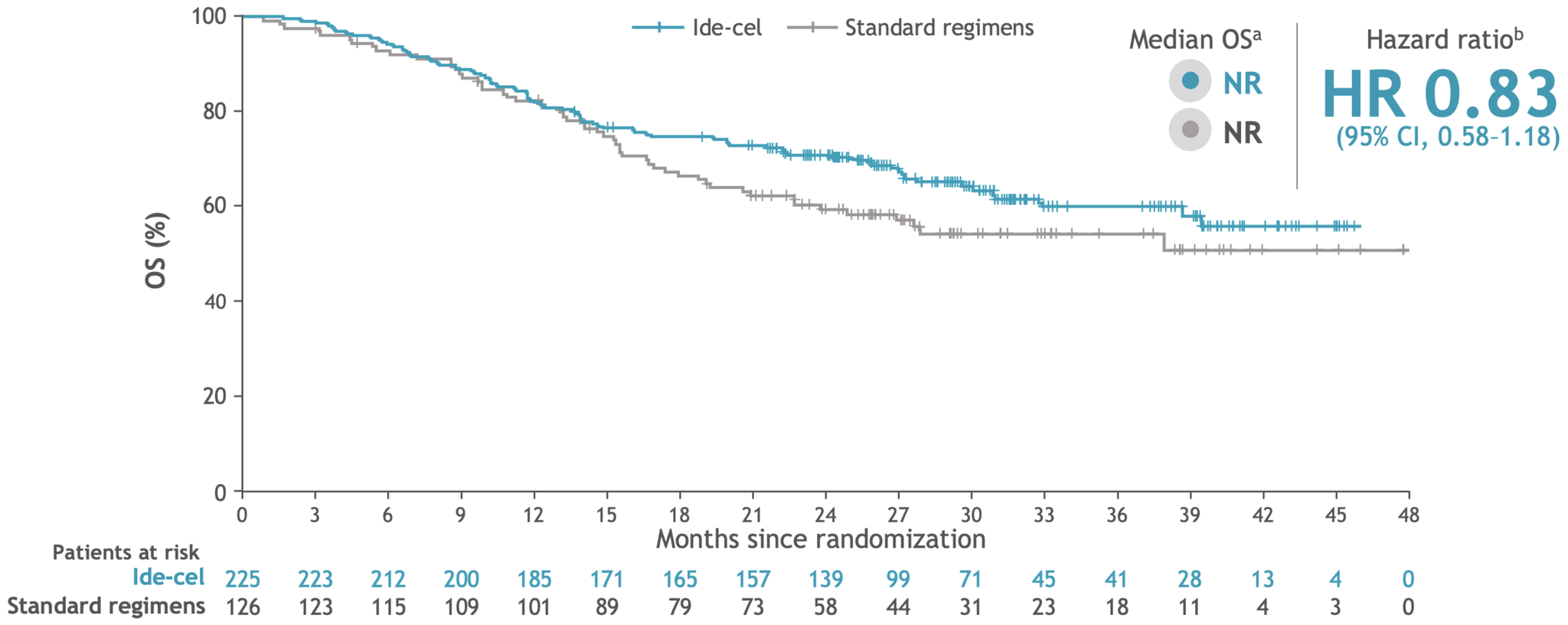
KARMMA-3: UPDATED ANALYSIS

Otero P et al, ASH 2023



a. Based on Kaplan-Meier approach. b. Stratified HR is based on the univariate Cox proportional hazards model. CI is two sided and calculated by bootstrap method; c. Two-stage Weibull model without recensoring (prespecified analysis)

TREND OF OS BENEFIT WITH IDE-CEL AMONG TREATED PATIENTS



- This is an exploratory analysis of the treated population without adjusting for crossover

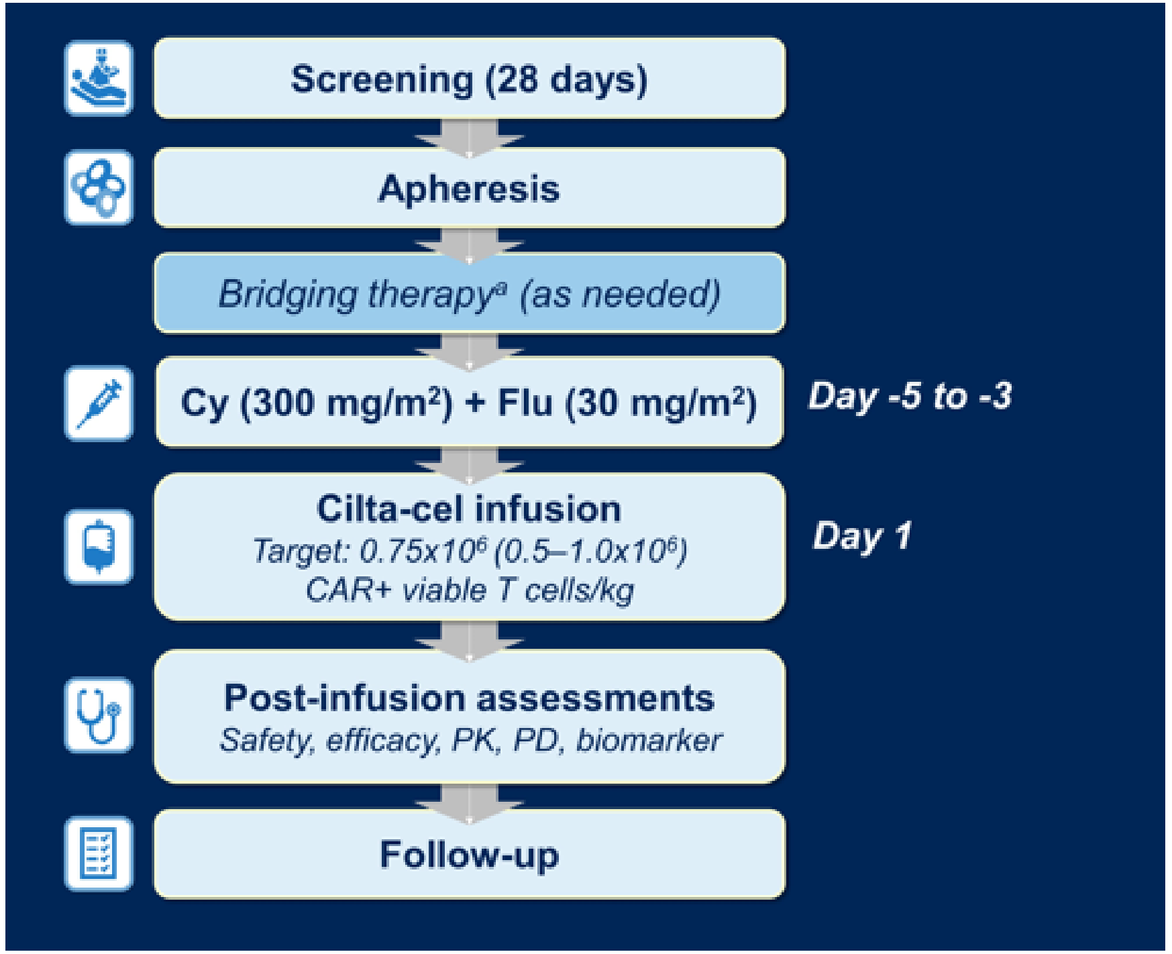
a. Based on Kaplan–Meier approach; b. Stratified HR based on the univariate Cox proportional hazards model. CI is 2-sided.

OS, overall survival.
Otero P et al, ASH 2023.

CARTITUDE 1 Study Design

- Primary Objectives
  - Phase 1b: Determine safety and RP2D
  - Phase 2: Efficacy

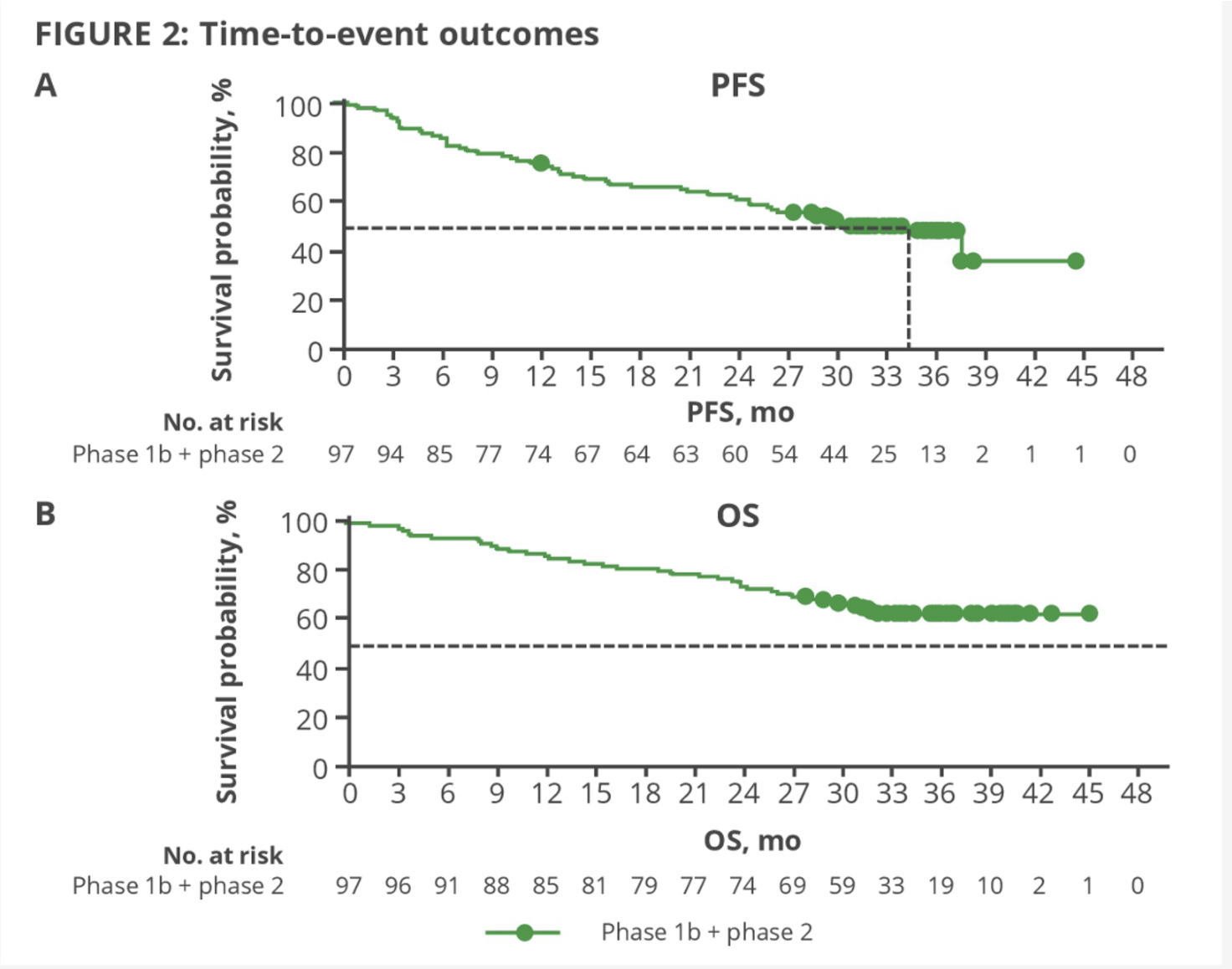
- Eligibility criteria, in brief
  - PD per IMWG
  - 3 or more prior therapies
  - Prior exposure to IMiD, PI, CD38
  - Measurable disease



[a]Treatment with previously used agent resulting in at least stable disease.

Usmani Z et al, ASCO Annual Meeting 2021.

CARTITUDE-1: FINAL RESULTS



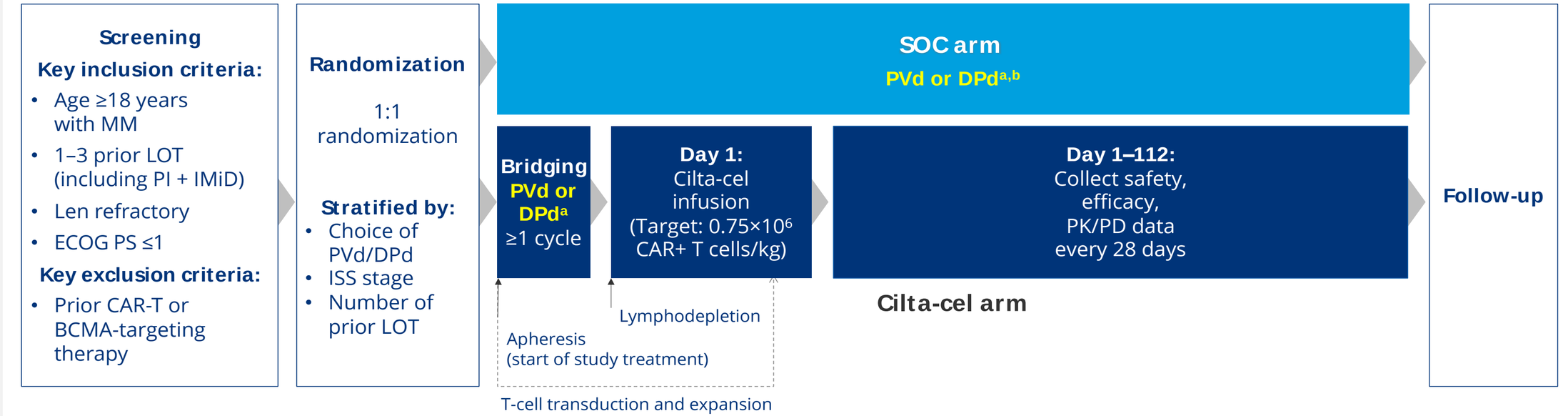
CR, complete remission; MRD, minimal residual disease; PFS, progression-free survival.

PFS by CR and sustained MRD neg:

- All pts: median PFS 34.9 months
- > CR, median PFS 38.2 months
- 12 mo sustained MRD neg: 30 mo PFS 74.9%
- 12 mo sustained MRD neg, > CR: 30 mo PFS 78.5%

Lin Y et al, ASCO 2023

CARTITUDE-4: STUDY DESIGN AND ENDPOINTS



Primary endpoint

- PFS[c]

Secondary endpoints

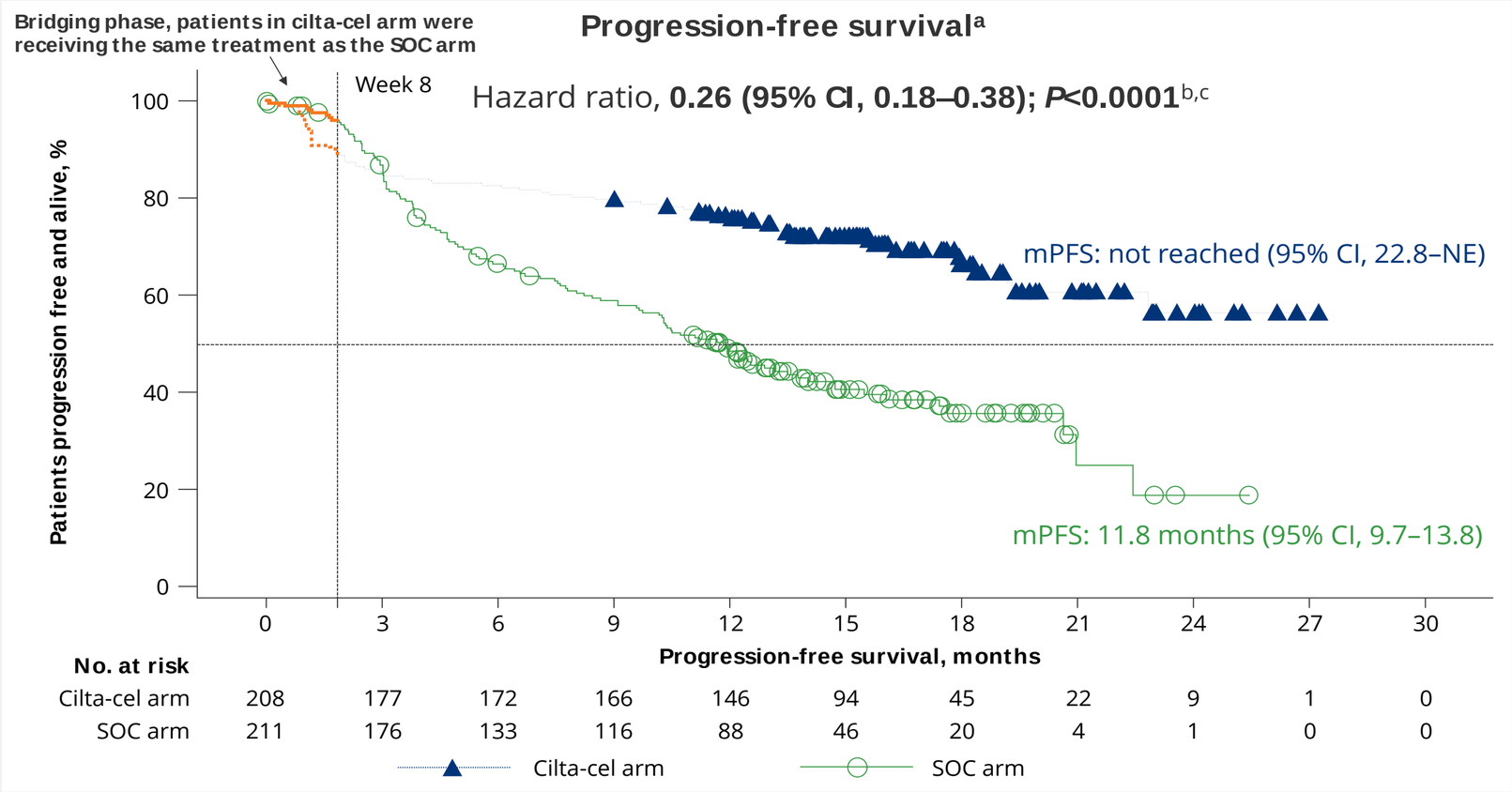
- Efficacy: ≥CR, ORR, MRD negativity, OS
- Safety
- PROs

[a]Physicians' choice. [b]Administered until disease progression. [c]Time from randomization to disease progression/death.
BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; cilta-cel, ciltacabtagene autoleucel; CR, complete response; DPd, daratumumab, pomalidomide, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory drug; ISS, International Staging System; Len, lenalidomide; LOT, line of therapy; MM, multiple myeloma; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PI, proteasome inhibitor; PK, pharmacokinetics; PRO, patient-reported outcome; PVd, pomalidomide, bortezomib, and dexamethasone; SOC, standard of care.

CARTITUDE-4:
PRIMARY ENDPOINT – PFS (ITT POPULATION)

Cilta-cel vs SOC

- 12-month PFS rate: 76% vs 49%
- SOC performed as expected



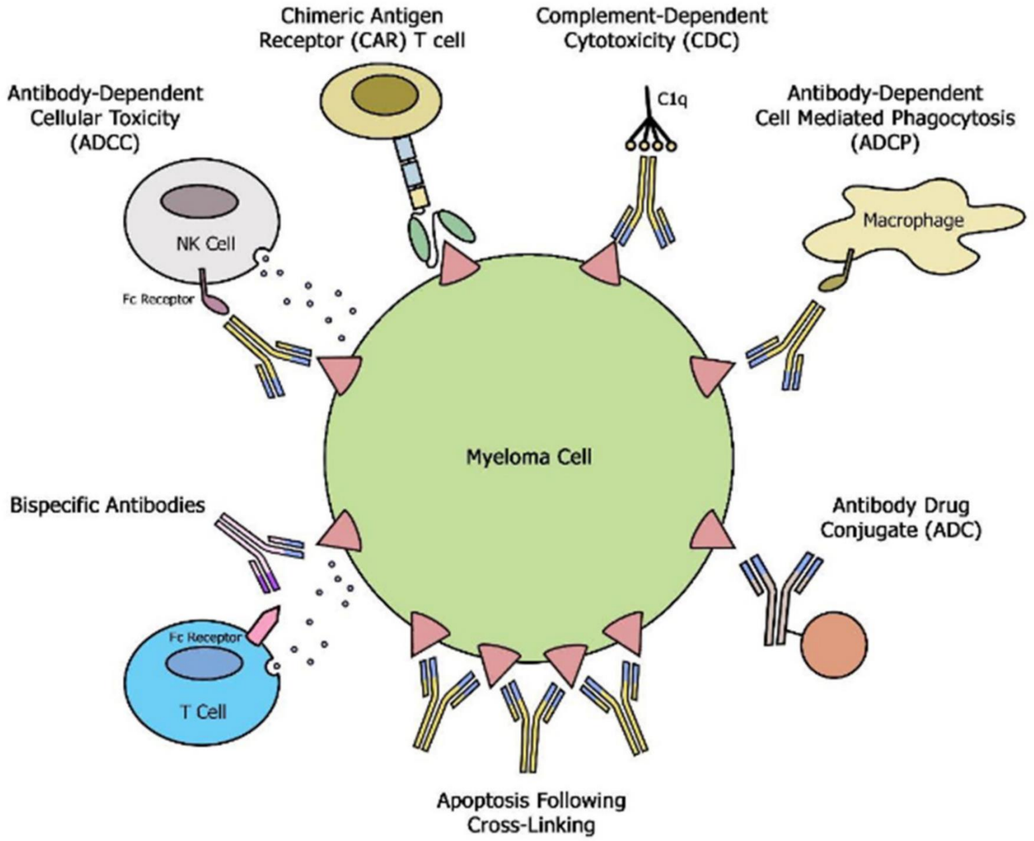
[a]Median follow-up, 15.9 months. [b]Constant piecewise weighted log-rank test. [c]Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable, including only progression-free survival events that occurred >8 weeks post randomization.
cilta-cel, ciltacabtagene autoleucel; HR, hazard ratio; ITT, intent-to-treat; mPFS, median progression-free survival; NE, not estimable; SOC, standard of care.

What is a bispecific antibody?

- An antibody with 2 unique binding sites that target different antigens or epitopes, typically CD3 on T cells, and a tumor antigen (BCMA or GPRC5D)

- **MM: Teclistamab, talquetamab, elranatamab, linvoseltamab, *et al***

- NHL: Glofitamab, epcoritamab, mosunetuzumab (*et al*)



BSABS FOR MM: APPROVED AND IN DEVELOPMENT

BCMAxCD3						
Agent name	**ORR**	**MRD (-)****	**PFS**	**CRS**	**Infections**	**Hospitalization**
Teclistamab[1]*	63%	26.7%	mPFS 11.3 mos	72%	G3-4, 44%	Y – 7 days
Elranatamab[2]*	61%	90%	12 mos PFS 58%	57%	G3-4 35%	Y – 3 days
ABBV-383b[3]	57%	73%	mPFS 10.4 mos	57%	41% all G	Y – 48 hrs D1
Linvoseltamab (REGN5458)[4]	51%	4/10 pts	NA	38%	Not reported	Y
Alnuctamab	43%	Not reported	NA	77%	Not reported	Y
GPRC5DxCD3						
Talquetamab[5]*	68%	69%	mDOR 10.2 mos	80% at 800 ug	G3-4 7%	Y, 7 days
FcRH5xCD3						
Cevostamab[6]	56.7%	7/10 pts	mDOR 11.5 mos	80%	~20%	Y

*FDA Approvals 10/2022, 8/23.
** In Evaluable patients.

1. Moreau P et al, *NEJM* 2022; 2. Bahlis N et al ASH 2022; 3. D Souza A et al, *JCO* 2022; 4. Zonder JA ASH 2021; 5. Chari A et al *NEJM* 2022; 6. Trudel S et al ASH 2021.

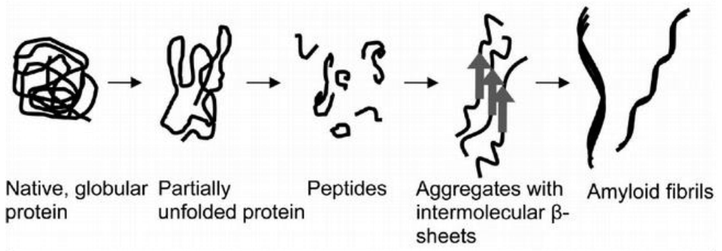
Key takeaways: Relapsed Multiple Myeloma

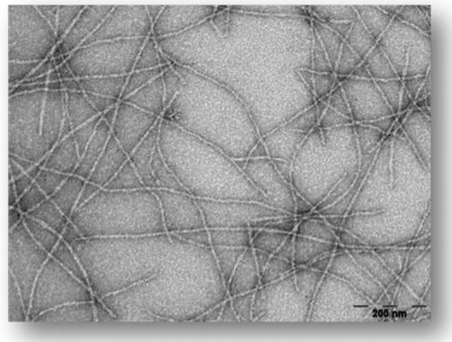
- Treatment approach based on prior lines of therapy, prior response to agents
- CD38 mAbs + IMiDs or PIs remain key options in early relapse
- CAR T-cell therapy (e.g., ide-cel, cilta-cel) shows promise in all lines (late/early)
- Bispecific antibodies (e.g., teclistamab) emerging as effective options
- Consider clinical trials at all stages of relapse

What is Amyloidosis?

- Definition: a group of diseases characterized by:
  - Normally soluble proteins deposit, leading to formation of insoluble extracellular amyloid fibrils

- Classification:
  - Systemic: amyloidogenic protein produced at site distant from site of deposition
  - Localized: amyloid deposition at same site as production of amyloidogenic protein





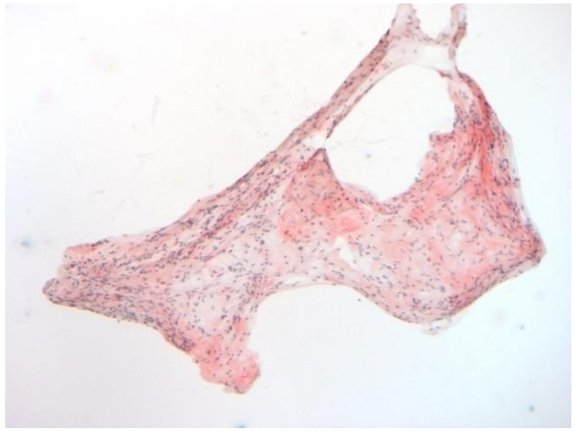
Clinical presentations that should raise concern for amyloidosis

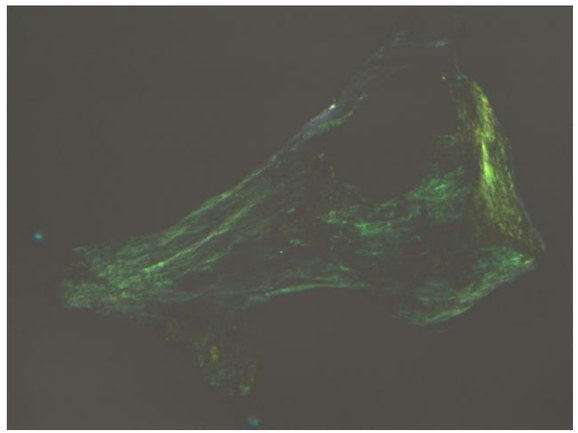
- Heart failure with preserved ejection fraction (HFPEF)
- Nephrotic range proteinuria
- Gastroparesis, isolated hepatomegaly
- Peripheral neuropathy with autonomic features, carpal tunnel syndrome
- Any patient with MGUS (esp λ clonality), or Multiple Myeloma (12-20% of patients)

How does a pathologist find amyloidosis?

- Congo Red: stain used in histology for documenting the presence of amyloidosis in tissue
- Congo red initially began as a textile dye; in 1922, was found to bind avidly to amyloid protein[1]
- “Amyloid” initially termed by German botanist Matthias Schleiden to describe starch material in plants that stained blue with iodine[1]

Specimen from abdominal fat aspirate; note intense congophilic staining

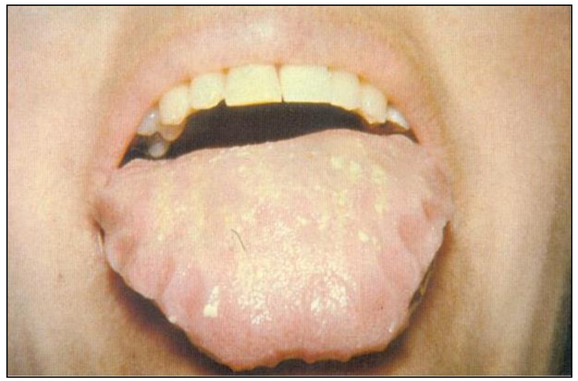


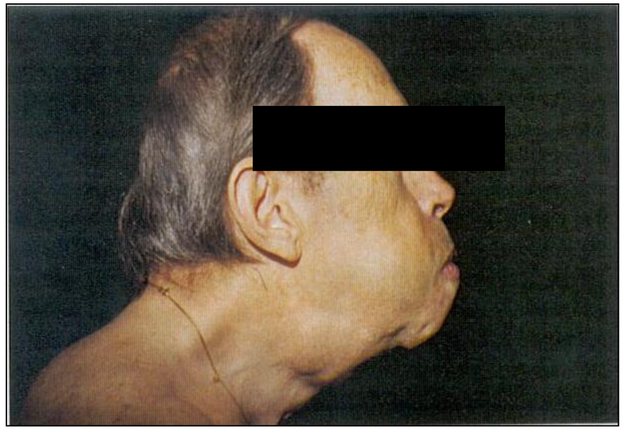


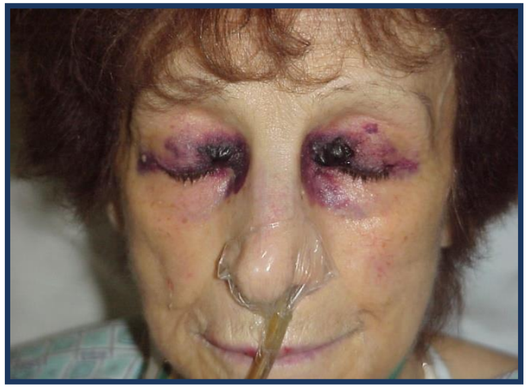
Characteristic “apple green birefringence” under polarized light microscopy

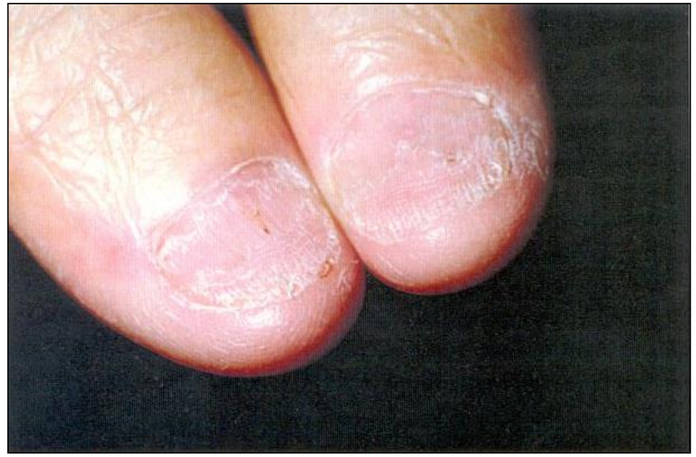
[1]David P. Steensma (*2001*) “Congo” Red. Archives of Pathology & Laboratory Medicine: February 2001, Vol. 125, No. 2, pp. 250-252.

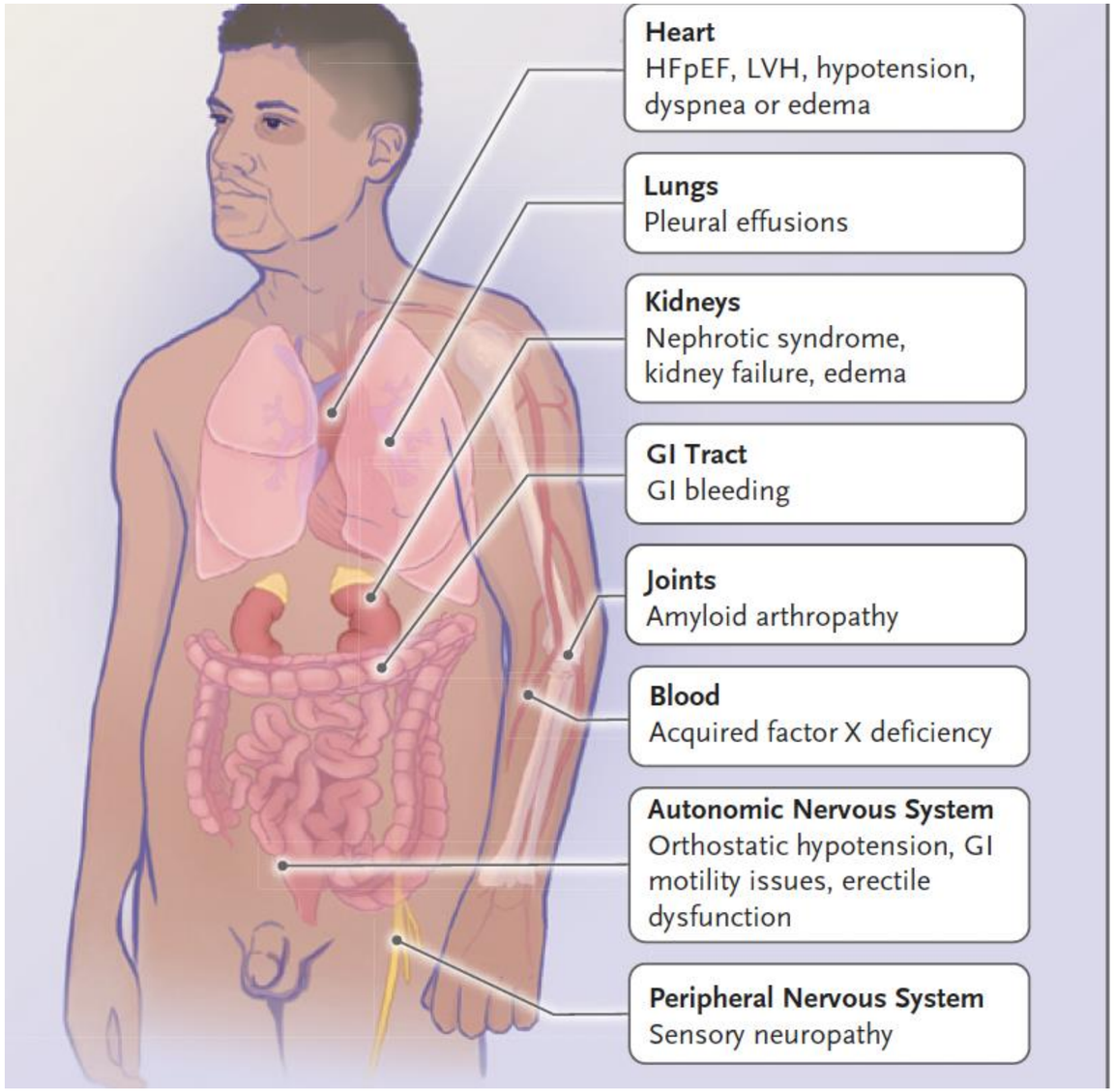
Classic Physical Examination Findings and Organ Involvement in AL Amyloidosis











Sanchorawala V et al NEJM 2024

Sample board question

You are seeing a 66 year old female in clinic with a new diagnosis of Light-chain Amyloidosis. At the time of diagnosis, her involved free light chain was 15 mg/dl, and she had NYHA class 3 heart failure with an Nt pro BNP of 1500 ng/mL and Troponin T of 6. Her creatinine was 0.8 mg/dl, but she had 2400 mg/24 hours of proteinuria, predominantly albumin. She also has some gastrointestinal symptoms with nausea and early satiety. On examination, she has profound macroglossia. Which organs are involved by amyloidosis?

- 1. GI
- 2. Cardiac
- 3. Renal
- 4. Soft tissue
- 5. 1 and 2
- 6. 1-4

Diagnostic Algorithm for Amyloidosis

Suspicion for Amyloidosis

Concern for ATTR?

PYP/DPD scan (for ATTR-CM) *

Other testing for assessment of vital organ involvement:

- Orthostatic vital signs
- nt-pro BNP, troponin T (or BNP, Tn-I)
- LFTs
- Transthoracic echocardiogram
- Cardiac MRI

Biopsy of surrogate site:

- Fat pad aspirate
- Minor labial salivary gland biopsy

If negative:

- Biopsy of involved organ

Typing:

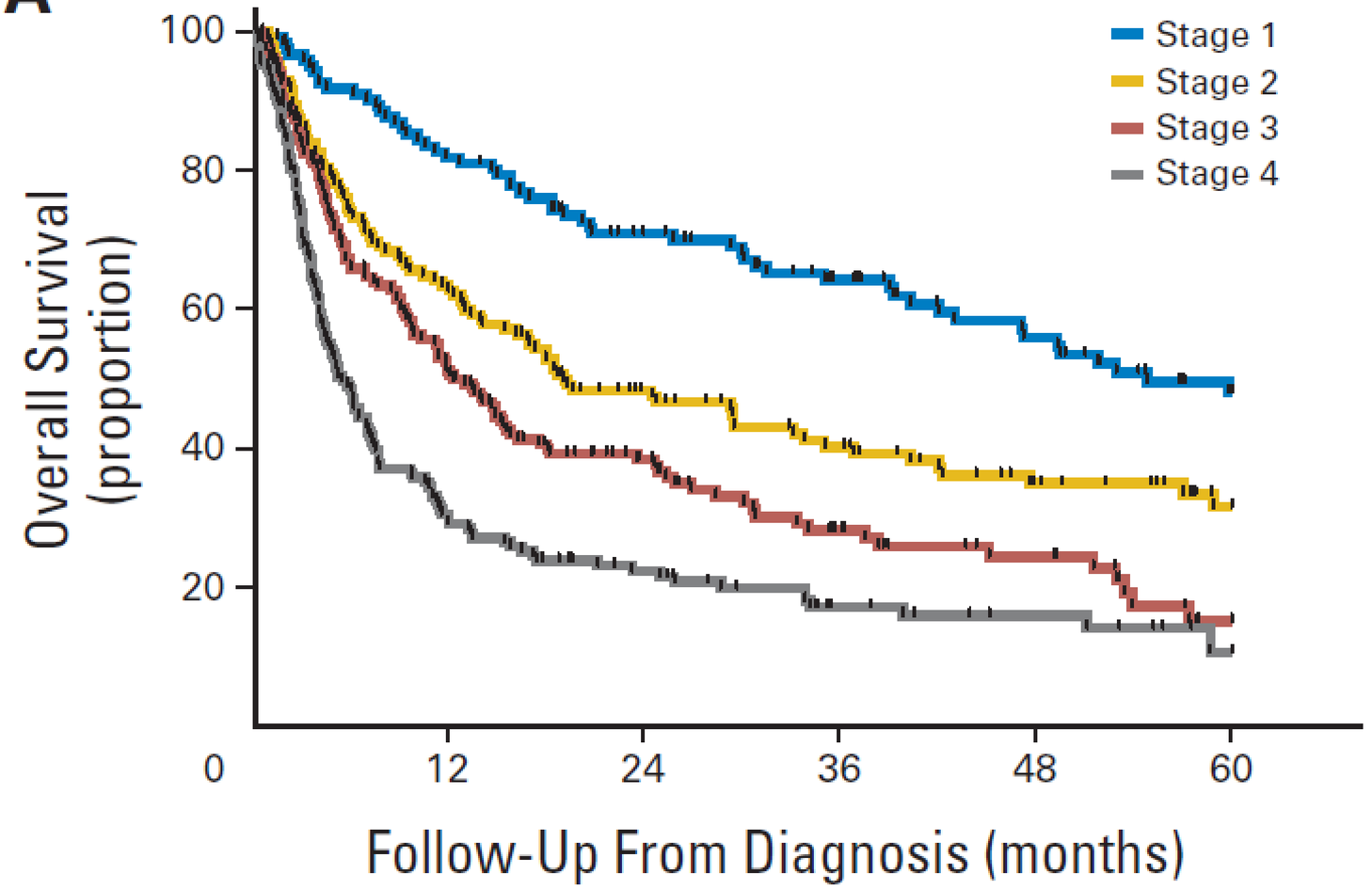
- Gold standard: Laser capture / Mass spectrometry
- Also: IHC; Immunogold electron microscopy

Plasma cell dyscrasia work-up:

- Serum free light chain assay
- Bone marrow aspirate and biopsy with flow cytometry, FISH, and conventional cytogenetics
- SPEP with immunofixation
- 24 hour urine protein with UPEP

Revised Prognostic Staging System for AL Amyloidosis

A



Factors
dFLC ≥ 18 mg/dL
Cardiac troponin-T ≥ 0.025 ng/ml
NT-ProBNP ≥ 1,800 pg/mL

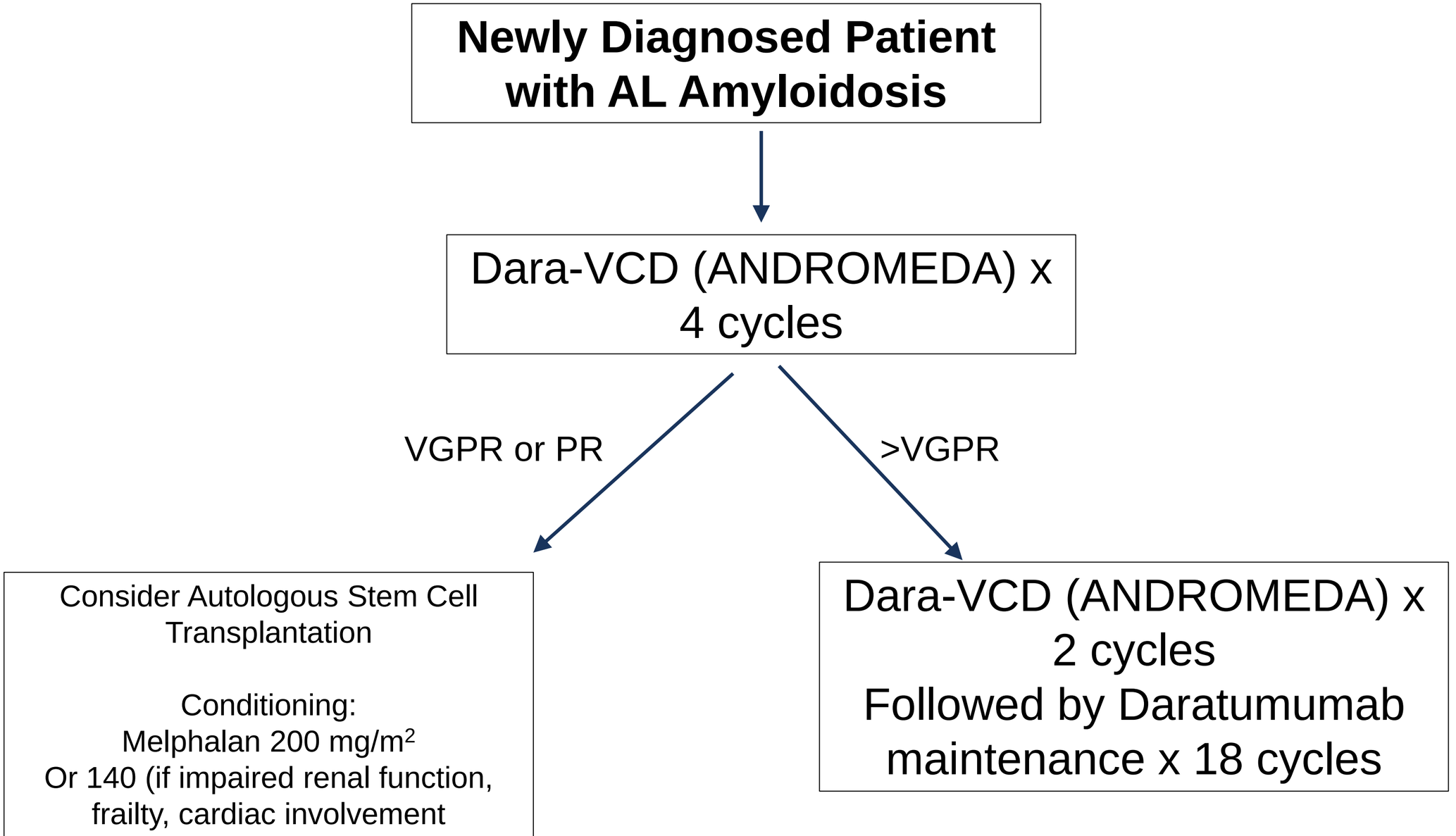
Each gets 1 point; score from 0, 1, 2, and 3 points denoting stages I, II, III and IV

Kumar S et al. J Clin Oncol. 2012 Mar 20;30(9):989-95

Board question, continued

- Which of the following treatments would you recommend, based on the results of a randomized phase 3 trial?
- 1. CyBorD
- 2. Dara-CyBorD
- 3. Dara-Vd
- 4. Autologous stem cell transplant
- 5. None of the above

Treatment of Newly Diagnosed AL Amyloidosis and LCDD



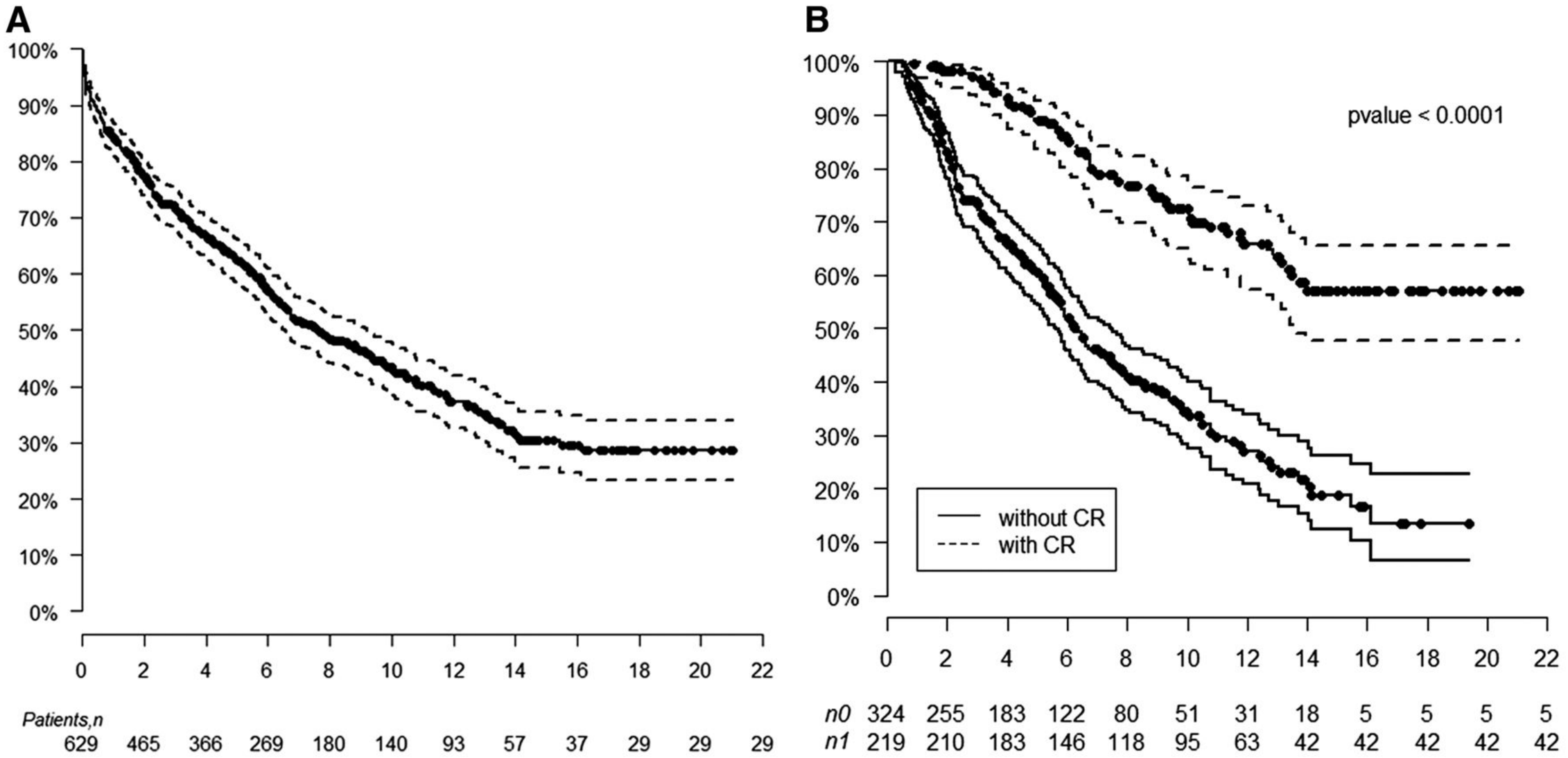
Clinical Pearls for Treating Patients with AL Amyloidosis

- Watch the dexamethasone dose… 10-20 mg is usually enough
- Manage fluid retention carefully
- Bortezomib can unmask neuropathy (peripheral and autonomic)
- Spironolactone can be helpful for amyloid cardiomyopathy
- Midodrine very useful for orthostatic hypotension
- **Key Point: Treating this like Multiple Myeloma (same doses, regimens, etc) is often too much for these frail patients**

Eligibility Criteria for ASCT – Key Concerns

- Due to risks of transplant-related mortality (TRM), eligibility criteria have evolved over time to select optimal patients
- Typical Criteria:
  - Cardiac ejection fraction > 40%
  - DLCO > 50% predicted
  - Supine systolic blood pressure > 90 mmHg
  - NT pro BNP < 5,000 / Troponin T < 0.06
- Common challenges:
  - Cardiac involvement – increased TRM (16%) seen in cardiac involvement with ASCT
  - Determining extent of organ involvement

Autologous Stem Cell Transplantation (ASCT) for AL Amyloidosis



Sanchorawala V, et al. Blood (2015) 126 (20): 2345-2347

Study Design

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

- 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
- CyBorD[a] weekly × 6 cycles n = 193

Post-treatment Phase

- Observation until MOD-PFS (if DARA SC discontinued prior to MOD-PFS)
- 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)

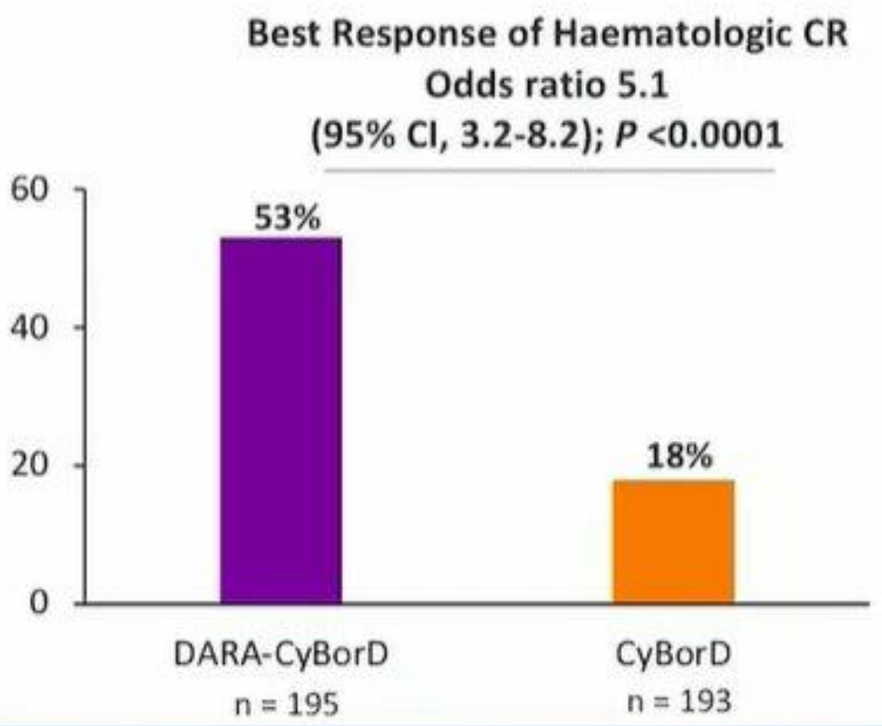
Primary endpoint: Overall haematologic CR rate

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

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

MM, multiple myeloma; eGFR, estimated glomerular filtration rate; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; MOD-PFS, major organ deterioration progression-free survival; CR, complete response; IV, intravenous; PO, oral.
[a]Dexamethasone 40 mg IV or PO, followed by cyclophosphamide 300 mg/m² IV or PO, followed by bortezomib 1.3 mg/m² SC on Days 1, 8, 15, and 22 in every 28-day cycle for a maximum of 6 cycles. Patients will receive dexamethasone 20 mg on the day of DARA SC dosing and 20 mg on the day after DARA SC dosing.

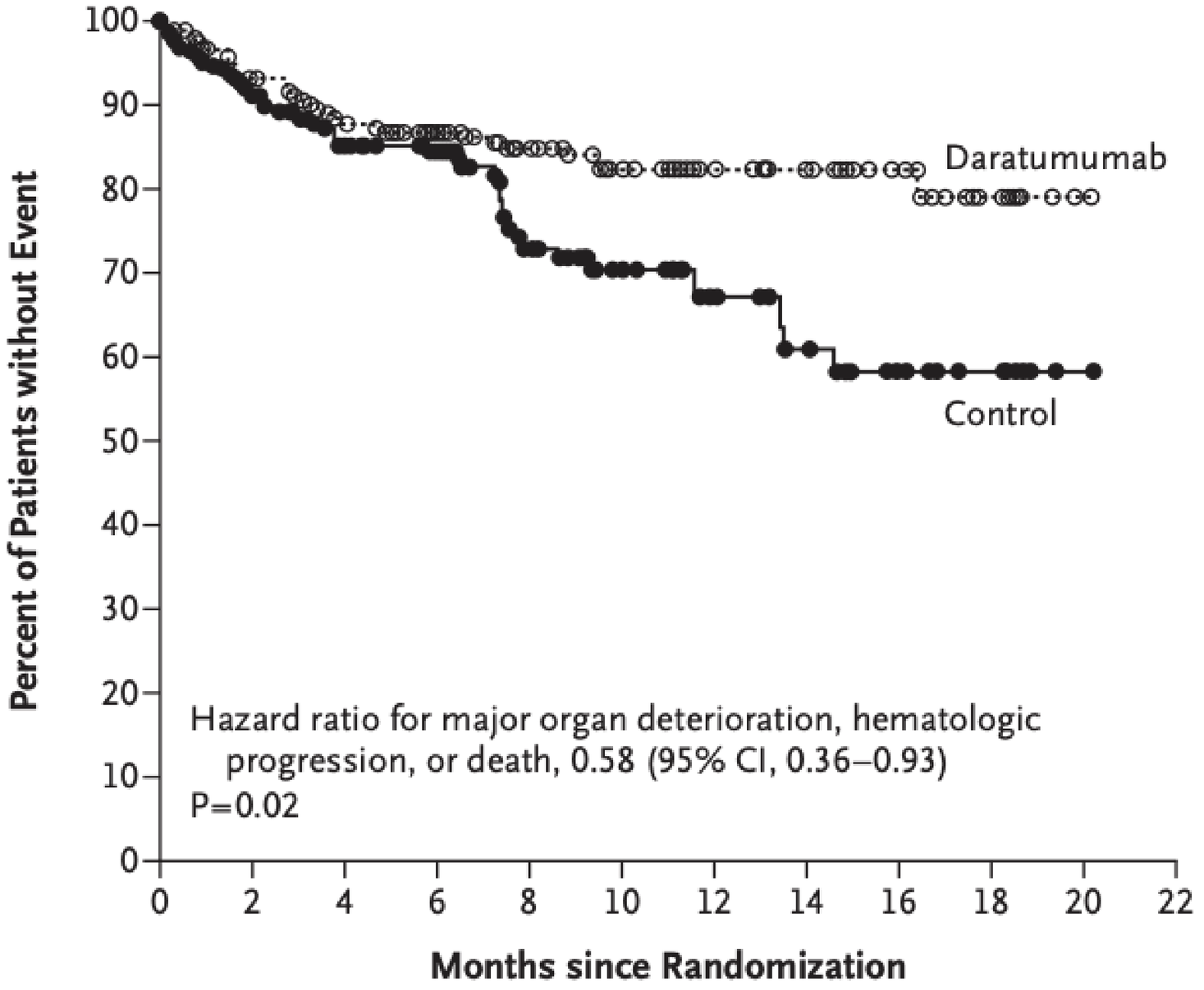
Haematologic CR: Primary Endpoint



- Assessed by blinded Independent Review Committee
- CR per Comenzo criteria[1] with clarifications:
  - Abnormal FLC ratio does not preclude CR[2]
  - CR requires confirmation
- The CR rate at 6 months was consistent with overall CR rate
  - 50% DARA-CyBorD vs 14% CyBorD (odds ratio 6.1; *P* <0.0001)
- Median time to CR[a]:
  - DARA-CyBorD: 60 days
  - CyBorD: 85 days

Responses with DARA-CyBorD were deeper and achieved more rapidly

CI, confidence interval; FLC, free light chain.
[a]Among CR responders (DARA-CyBorD, n = 104; CyBorD, n = 35).
1. Comenzo RL, et al. *Leukemia*. 2012;26(11):2317-2325. 2. Sidana S, et al. *Leukemia*. 2019;34(5):1472-1475.



Kastritis et al NEJM 2021

Immunomodulatory agents for Relapsed AL Amyloidosis

- Lenalidomide and dexamethasone:
  - Overall Response Rates: 41-67%, median time to response ~6 months[1,2]
  - Tox profile: Myelosuppression, dermatologic, fatigue
- Pomalidomide:
  - Overall Response Rates: 48-50 %, median time to response, 1.9 months[3,4]
  - Tox: Myelosuppression, fatigue

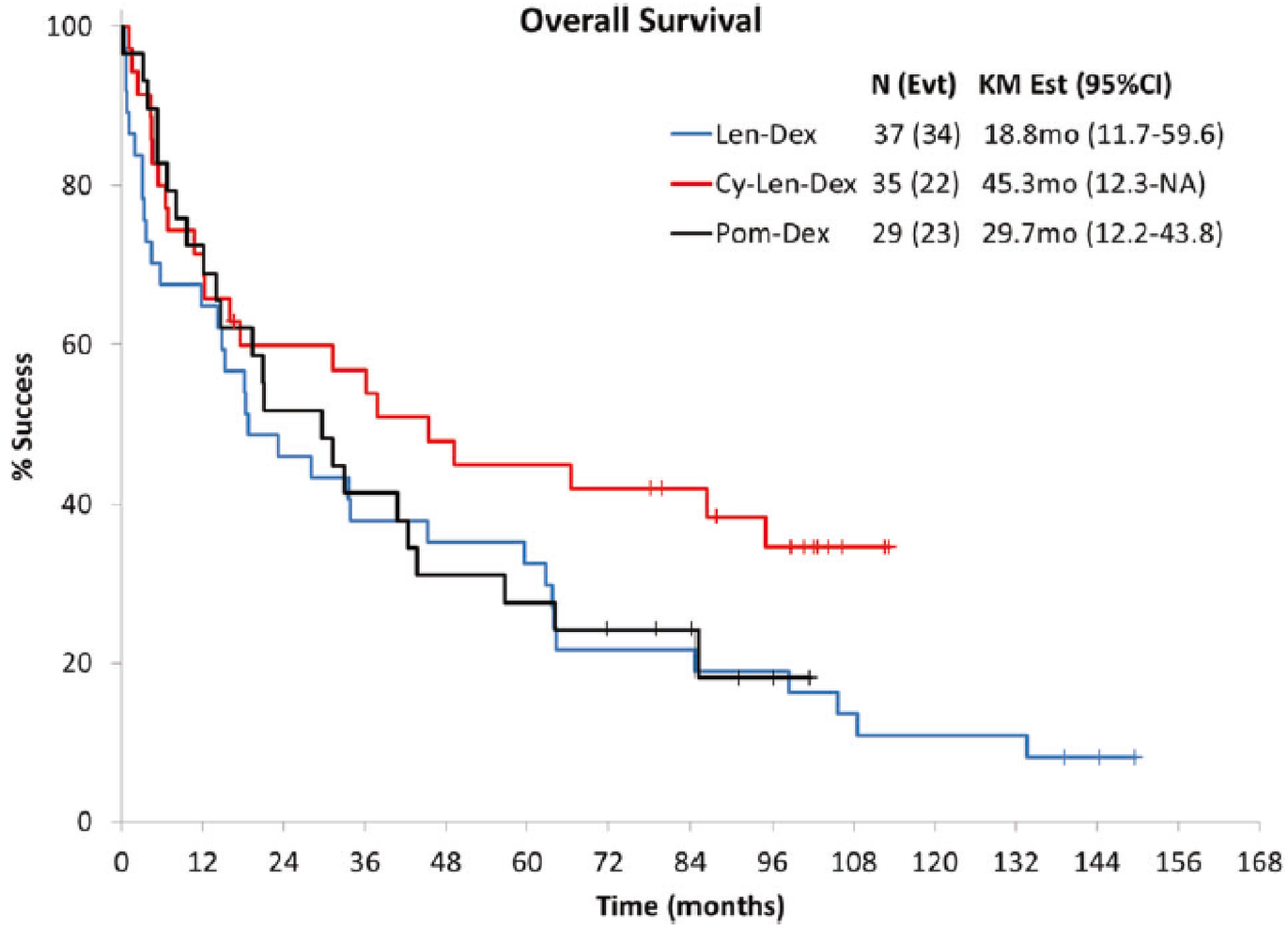


Fig. 3 Overall survival by trial.

[1]Dispenzieri A et al. Blood 2007 Jan 15;109(2):465-70; [2]Sanchorawala V et al. Blood. Blood. 2007 Jan 15;109(2):492-6
[3]Sanchorawala V et al. Blood. 2016 Aug 25;128(8):1059-62; [4]Dispenzieri A et al Blood 2012 Jun 7;119(23):5397-404
[5]Warsame R et al. Blood Cancer j. 2020 Jan 8;10(1):4

Key Takeaways: AL Amyloidosis

- Early diagnosis crucial - consider in unexplained organ dysfunction
- Typing essential for appropriate management
- Treatment aims to reduce amyloidogenic light chains
- Daratumumab-based regimens show high efficacy in newly diagnosed patients
- ASCT remains an option for eligible patients
- Careful management of organ dysfunction is critical

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Thank you!

Questions?

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