New Therapies for Systemic Light Chain (AL) Amyloidosis

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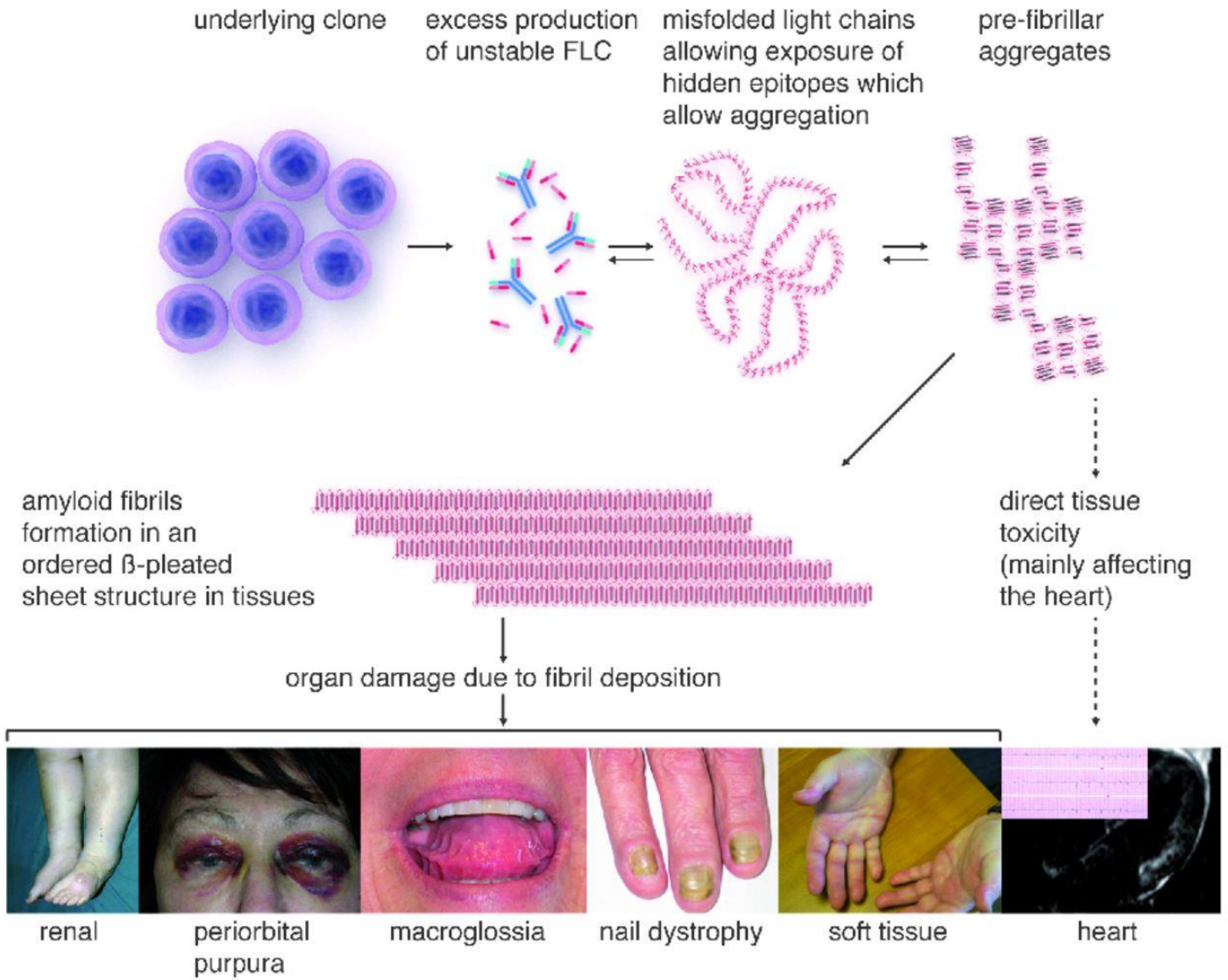
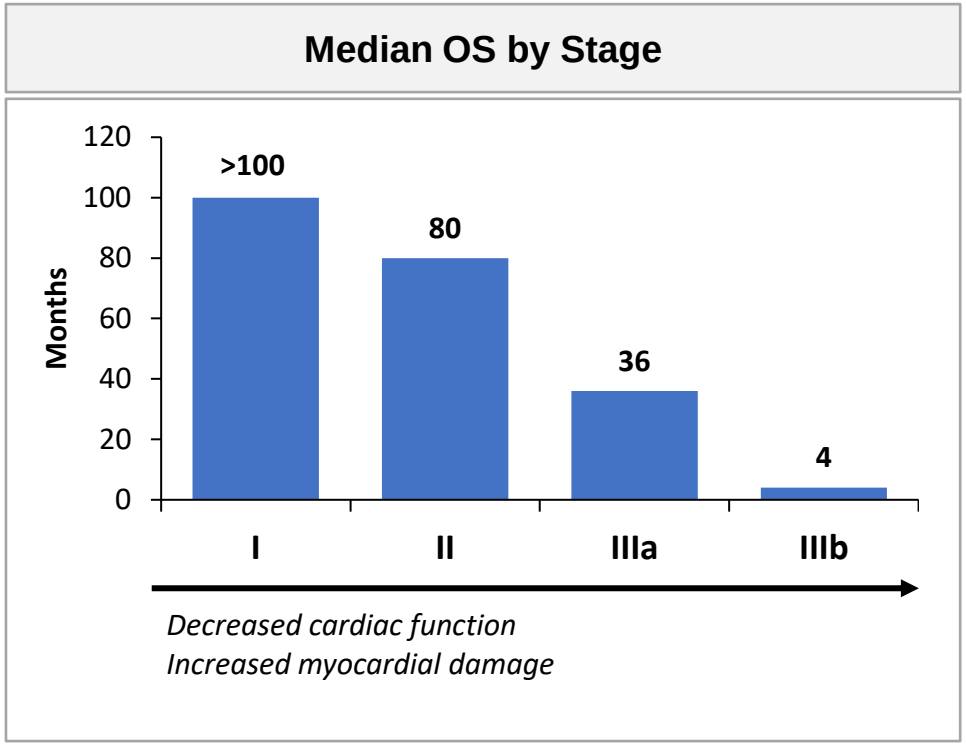
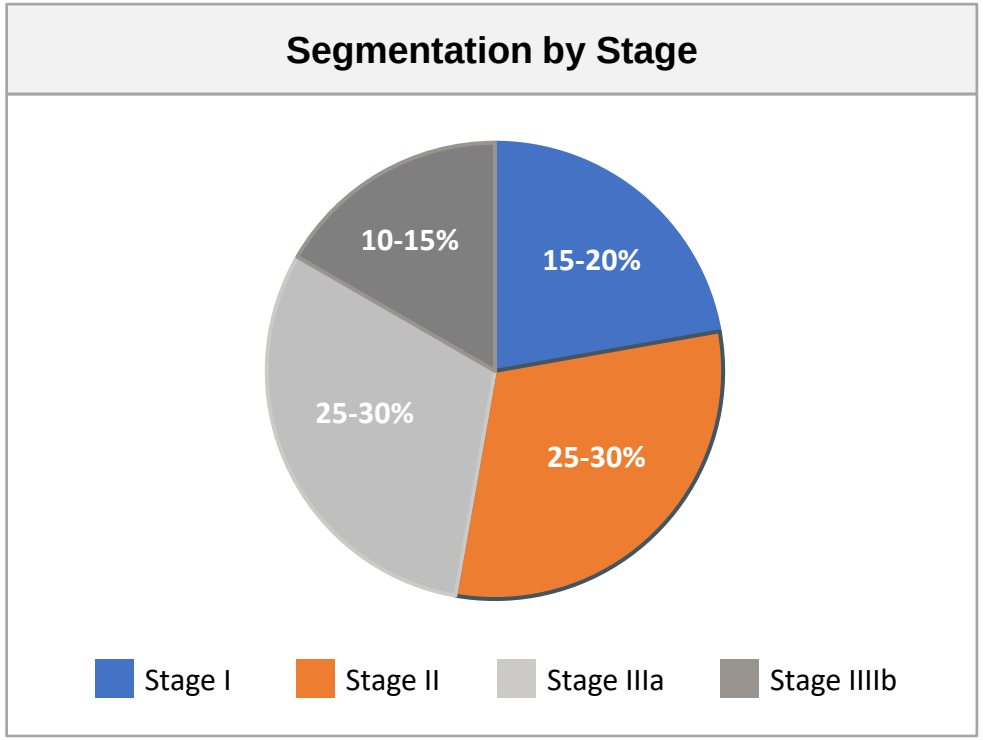
Mechanism of organs damage in AL Amyloidosis



Mahmood et. al, Haematologica Feb 2014

The prognosis of AL amyloidosis significantly worsens with increased cardiac involvement, as classified by the Mayo Staging System





- Increased cardiac involvement is strongly linked to higher morbidity and mortality, and various staging systems have been developed based on cardiac biomarkers

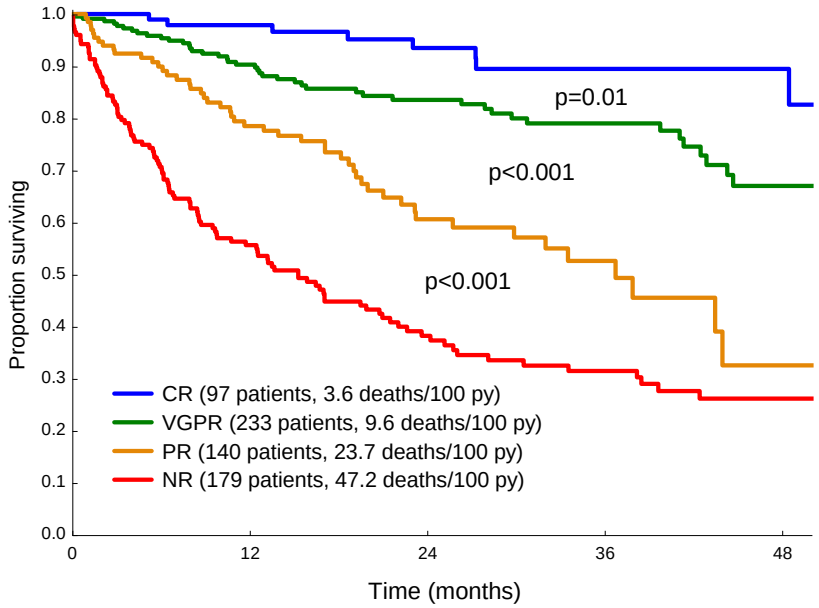
Dispenzieri et al, Mayo Clin Proc, 2015; Manwani et al, Blood, 2019; OS = overall survival

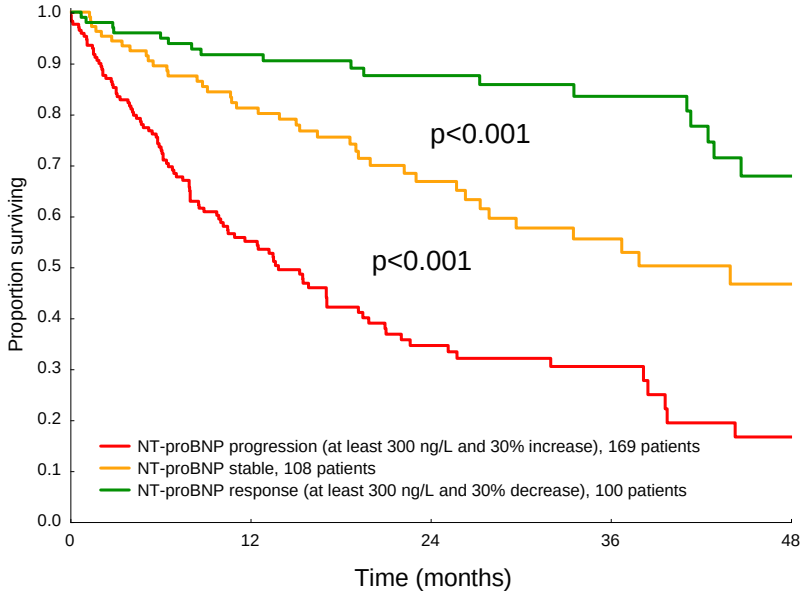
Revised Mayo Staging system is based on cardiac and clonal biomarkers, while European Mayo Staging system is based solely on cardiac biomarkers

	Prognostic biomarker cutoffs						
	NT-proBNP *(distension & stretching)*	**cTnT** *(myocardial damage)*	**dFLC** *(difference btw uninvolved vs. involved light chain)*				
Revised Mayo Clinic Staging (2012)	0.025 ng/mL	1800 pg/mL	18 mg/dL	**Stage I** All below cutoff >118 mo. mOS	**Stage II** One above cutoff >118 mo. mOS	**Stage III** Two above cutoff ~59 mo. mOS	**Stage IV** All above cutoff ~6 mo. mOS
European Modification of 2004 Mayo Staging (2015)	0.035 ng/mL	332 pg/mL	Not assessed	**Stage I** (15 – 20%) Both below cutoff >100 mo. mOS	**Stage II** (25 – 30%) One above cutoff ~80 mo. mOS	**Stage IIIa** (25 – 30%) Both above and NT-proBNP ≤ 8500 pg/mL ~36 mo. mOS	**Stage IIIb** (10 – 15%) Both above and NT-proBNP > 8500 pg/mL ~4 mo. mOS

Kumar et al, J Clin Oncol, 2012; Dispenzieri et al, Mayo Clin Proc, 2015; Barrett et al, JACC Heart Fail, 2019; Vaxman and Gertz, Acta Haematol, 2019; Wechalekar et al, Blood, 2013; Kastritis E and Dimopoulos MA, Brit J Haematol, 2016; Manwani et al, Blood, 2019; NT-proBNP = N-terminal-pro hormone BNP, BNP = B-type natriuretic peptide, cTnT = cardiac troponin T, dFLC = difference between involved and uninvolved free light chains

Hematologic & Organ Responses are Associated with Improved Survival in Systemic AL Amyloidosis

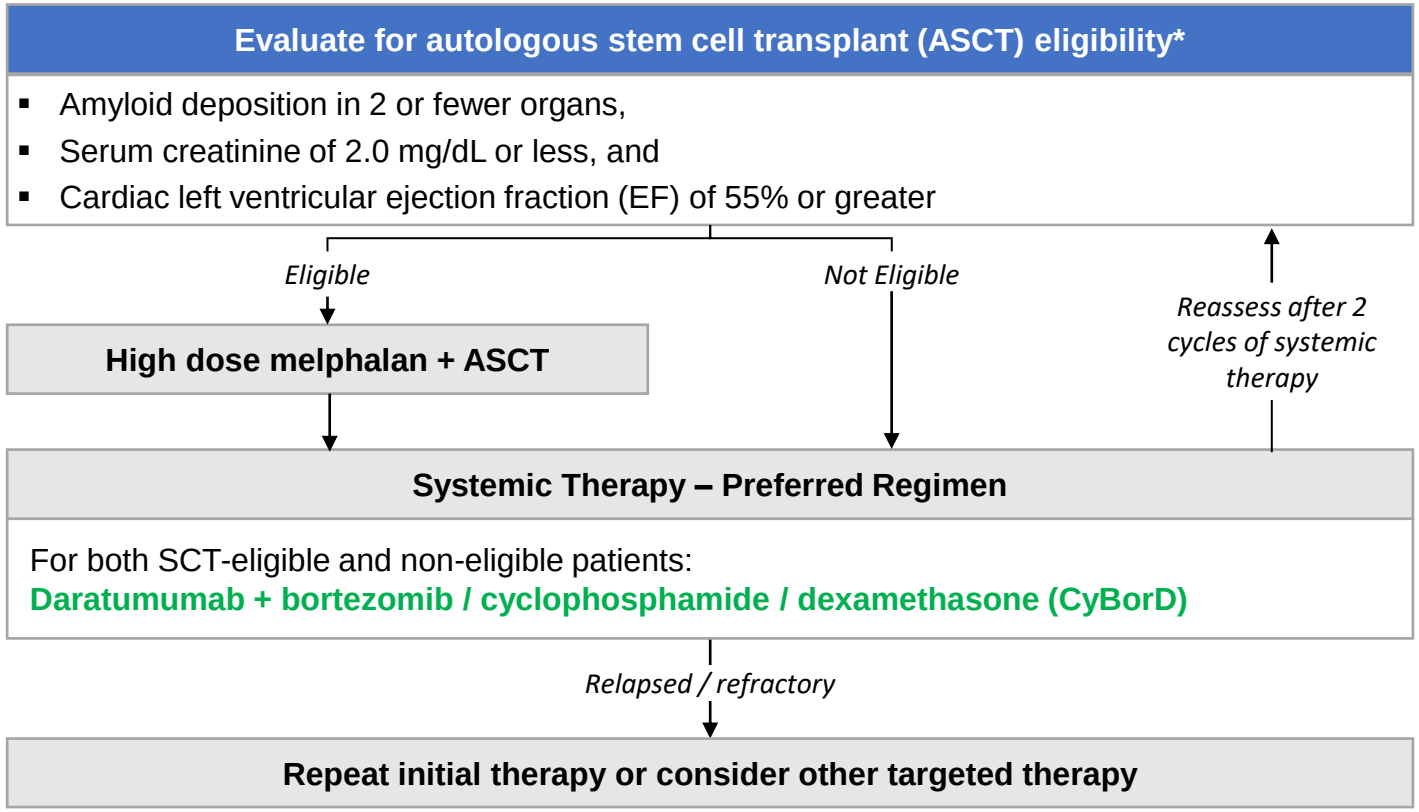




Am J Hematol 2005;79:319
J Clin Oncol 2012;30:4541
Leukemia 2012;26:2317

Current guidelines recommend stem cell transplant, but most patients are ineligible due to disease severity and are treated with chemoimmunotherapy / other targeted therapies

NCCN Treatment Guidelines for AL Amyloidosis



- For young patients with low-risk disease (25% of total), ASCT offers the potential for long, event-free survival
  - However, most patients are not eligible to receive ASCT due to age and advanced disease
- Systemic therapies are typically prescribed after ASCT (as consolidation), or for those who are not eligible
  - NCCN guidelines currently recommend combinations of chemotherapy
- For relapsed / refractory disease, immunomodulator-based treatments and monoclonal antibodies, including daratumumab, ixazomib, Lenalidomide or pomalidomide are recommended options

Guidelines currently do not make recommendations based on Mayo Staging

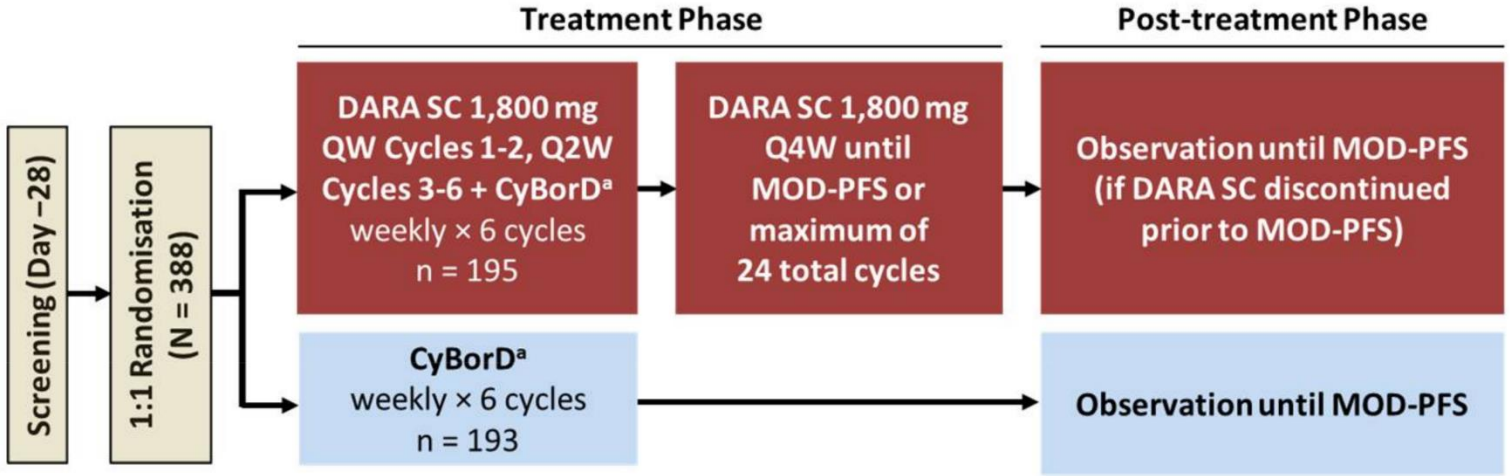
*Notes: *Eligibility criteria specified by The Centers for Medicare and Medicaid Services. Note that SCT eligibility varies by institution and is dependent on patient health and age; Source: NCCN Guidelines Version 1.2022 Systemic Light Chain Amyloidosis, Medicare Coverage Database, Gertz, Blood Cancer Journal, 2018, Palladini et al, Blood, 2016, Dispenzieri et al, Mayo Clin Proc, 2015; NCCN = National Comprehensive Cancer Network.*

ANDROMEDA study design

Phase III Randomized Controlled Trial (N=388)

Key eligibility criteria:

- AL amyloidosis with ≥1 organ impacted
- No prior therapy for AL amyloidosis or MM
- Cardiac stage I-IIIA (Mayo/European staging system 2015)
- eGFR ≥20 mL/min



Stratification criteria:

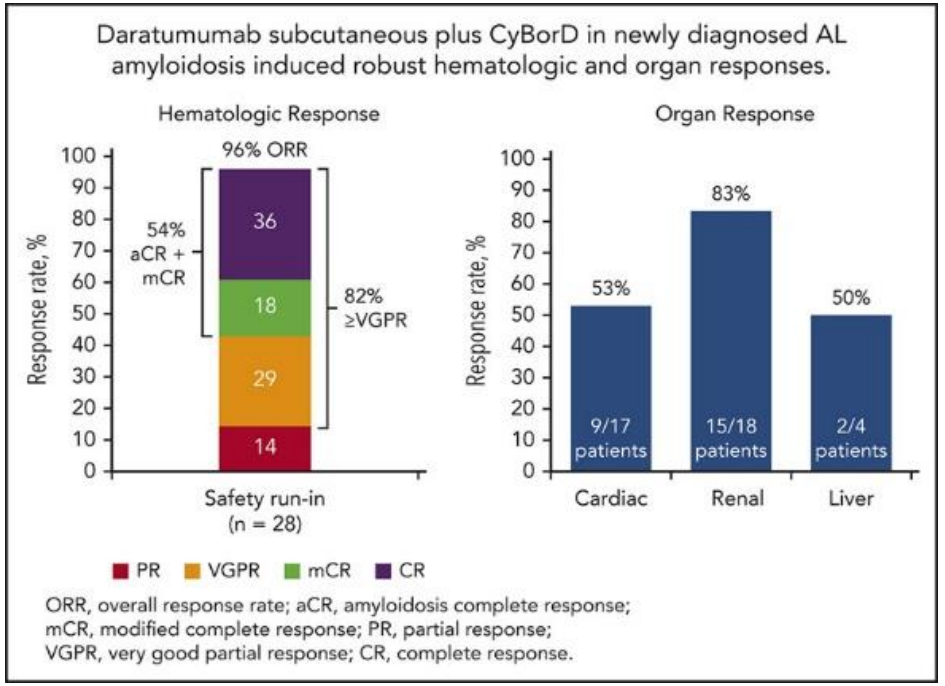
- Cardiac stage (I vs II vs IIIA)
- Transplant typically offered in local country (yes vs no)
- Creatinine clearance (≥60 mL/min vs <60 mL/min)

Primary End Points:

- hematologic complete Response

ANDROMEDA study-Findings

- **Complete Hematologic Response Rates** was higher with Dara+CyBorD (53.3%) vs 18.1% with CyBorD (P<0.001) at median follow up of 11.4 mo
  - **VGPR or better:** 78.5% in the daratumumab group and 49.2% in control
- **Cardiac response rates** was higher with Dara+CyBorD at 41.5% vs 22.2% at 6 mo.
- **Renal response rates** was higher with Dara+CyBorD 53% vs 23.9% at 6 mo.



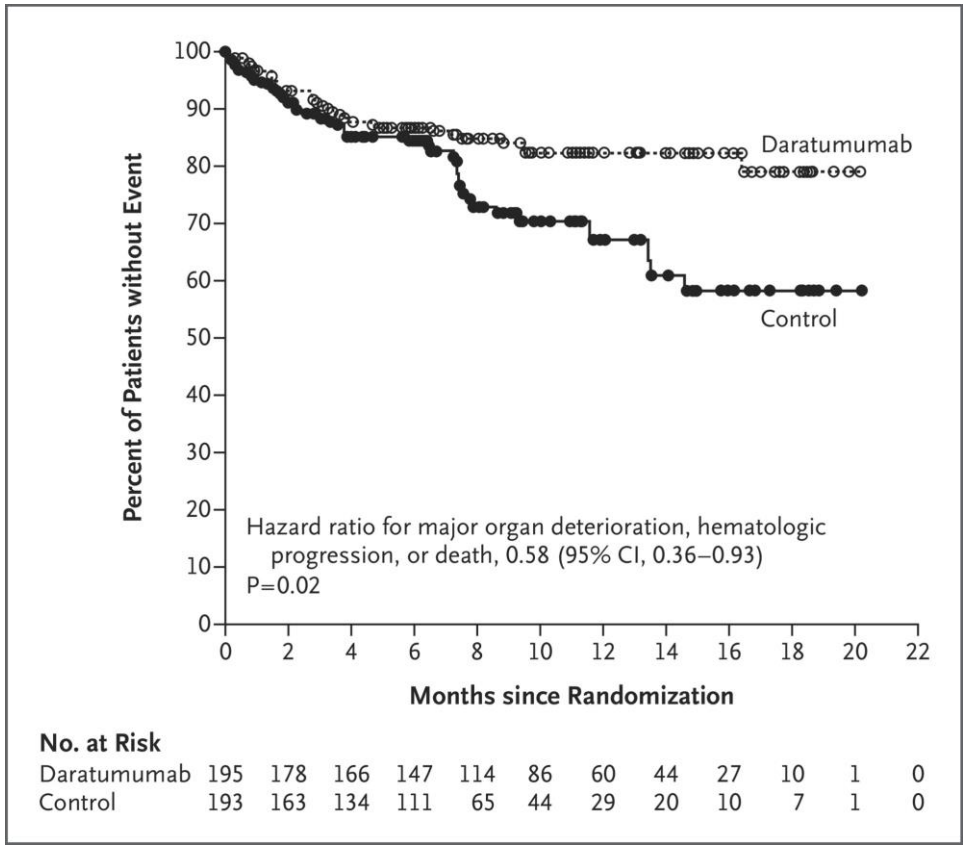
ANDROMEDA study-Findings

- **Safety:**

Events	Dara+ CyBorD	CyBorD
Lymphopenia	13%	10.1%
Pneumonia	7.8%	4.3%
Cardiac Failure	6.2%	4.8%
Diarrhea	5.7%	4.8%
Systemic reactions	7.3%	NA
Deaths	27	29

Dara=Daratumumab, CyBorD=cyclophosphamdide, bortezomib and dexamehtaosne

Survival:



Kastritis E et al. N Engl J Med 2021;385:46-58

ANDROMEDA study-Conclusions

- The addition of SC daratumumab to CyBorD was associated with higher frequencies of hematologic CR and survival free from major organ deterioration or hematologic progression
- This phase III RCT has established Dara+CyBorD as the standard of care for systemic AL amyloidosis
- Study did not include Stage IIIb cardiac patients and patients with GFR <20 and with ECOG >2, systolic BP <90, NYHA stage IIIB or IV at screening.
- We need agents to help remove pre-formed amyloid in vital organs such as heart and kidneys

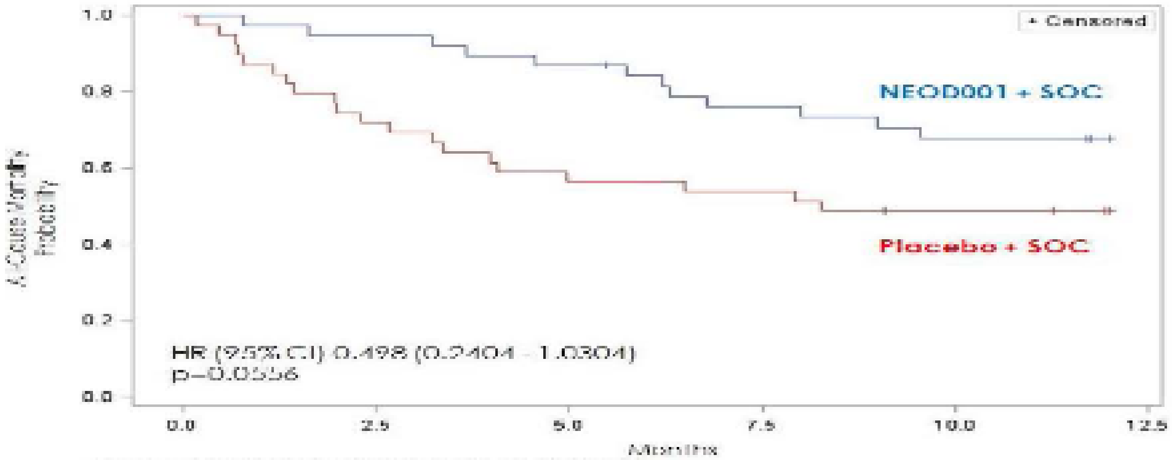
Results of the Phase 3 VITAL Study of NEOD001 (Birtamimab) Plus Standard of Care in Patients with Light Chain (AL) Amyloidosis Suggest Survival Benefit for Mayo Stage IV Patients

Table 1: ITT & mITT Results

Stage	Endpoint	N	ITT HR¹, 95% CI (p-value)	mITT (12-months) HR¹, 95% CI (p-value)
All	Composite primary endpoint	260	0.835 (0.5799–1.2011) p=0.3300	[illegible] p=0.2129
Stage I	All-cause mortality	21	0.364 (0.0637–2.0831) p=0.2554	0.364 (0.0637–2.0831) p=0.2554
Stage II	All-cause mortality	62	[illegible]	[illegible]
Stage III	All-cause mortality	100	[illegible]	[illegible]
Stage I-III	All-cause mortality	183	1.331 (0.7306–2.4107) p=0.3375	[illegible] p=0.5159
Stage IV	All-cause mortality	77	0.544 (0.2738–1.0826) p=0.0787	0.498 (0.2404–1.0304) p=0.0556

[illegible] hospitalization; ¹HR <1.0 in favor of NEOD001 + SOC; HR >1.0 in favor of placebo + SOC; All p-values other than for the composite primary endpoint for the ITT analysis are descriptive; p-value is a log rank test. mITT = initial 12-month time period.

Figure 1: Kaplan- Meier Estimate of All-Cause Mortality in Stage IV (mITT)



All-cause mortality regardless of cardiac hospitalization

Morie A Gertz, MD,Adam D. Cohen, …,Gene Kinney, PhD, Results of the Phase 3 VITAL Study of NEOD001 (Birtamimab) Plus Standard of Care in Patients with Light Chain (AL) Amyloidosis Suggest Survival Benefit for Mayo Stag[e IV Patients]

American Society *of* Hematology

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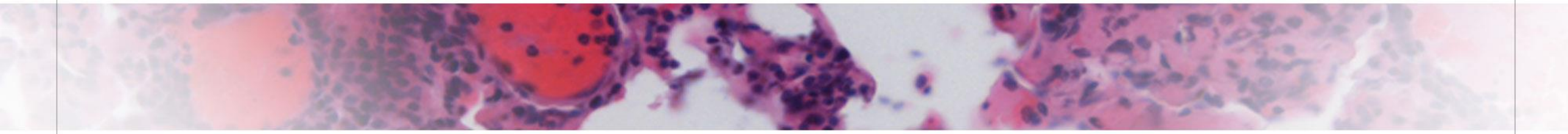

Safety, Tolerability and Efficacy of CAEL-101 in AL Amyloidosis Patients Treated on a Phase 2, Open-Label, Dose Selection Study to Evaluate the Safety and Tolerability of CAEL-101 in Patients with AL Amyloidosis (Abstract 729)

Jack Khouri, MD1, Faiz Anwer, MD2, Christy J. Samaras, DO2, Alex V. Mejia Garcia, MD1, Omer N. Koc, MD3, Beth M. Faiman, PhD, CNP2, Kimberly Hamilton, CNP2, Saveta Mathur, CNP2, Cynthia Scott, CNP2, Kathleen Stefunek, RN2, Josephine Sgobbo, RN2, Sherry Fada2, Brittany Lewis2, Kelly Shepherd2, Naqib Ahmad2, Madeleine Knebusch2, Susan B. Sobolov, PhD4, Janet Jobes4, Eileen Daniel4, Michael Spector, BS4 and Jason Valent, MD2

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Introduction

- **CAEL-101 is an investigational IgG1 monoclonal antibody that targets the mis-folded light chains of AL amyloid fibrils, a hallmark of AL amyloidosis**
- **CAEL-101 specifically binds to a conformational epitope present on both human kappa and lambda light-chain amyloid fibrils**
- **Phase 1 study established safety and tolerability of monotherapy CAEL-101 as a weekly treatment for 4 weeks up to an MTD of 500 mg/m2 in relapse/refractory patients**
  - **No dose limiting toxicity or drug related deaths were seen.**
- **Cardiac response was seen in 67% (8/12) and renal responses were seen in 33% (4/12) of evaluable patients** **(Edwards CV et al Blood (2016) 128 (22): 643)**

Patient and Disease Characteristics

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	CAEL-101 500 mg/m^2 + CyBorD N=4	CAEL-101 750 mg/m^2 + CyBorD N=3	CAEL-101 1000 mg/m^2 + CyBorD N=6	CAEL-101 1000 mg/m^2 + CyBorD + Dara (interim data) N=2	All Patients N=15
Median age, years (range)	55 (49 to 62)	70 (48 to 70)	75 (62 to 80)	63 (63 to 64)	64 (48 to 80)
Sex, n (% male)	4 (100%)	2 (66.7%)	4 (66.7%)	2 (100%)	12 (80%)
Number Previous PCD treatments range	3-4	0-4	0-4	Not yet available	0-4
Time since Diagnosis (months), median (range)	46 (19 to 163)	13 (3 to 23)	12 (3 to 23)	3 (2 to 3)	13 (2 to 163)
Mayo Stage n (%)					
I	1 (25.0)	0	0	0	1 (6.7)
II	2 (50.0)	2 (66.7)	5 (83.3)	2 (100.0)	11 (73.3)
IIIA	1 (25.0)	1 (33.3)	1 (16.7)	0	3 (20.0)
AL amyloidosis in Heart n (NTproBNP>650 pg/mL, %)	2 (50.0)	3 (100.0)	3 (50.0)	2 (100.0)	10 (66.7)
NT-ProBNP (pg/mL) median (range)	928 (50 to 3712)	752 (612 to 1002)	2926 (545 to 18696)	1799 (823 to 2774)	1002 (50 to 18696)
cTnT (ng/mL) median (range)	0.034 (0.010 to 0.041)	0.018 (0.010 to 0.047)	0.012 (0.010 to 0.106)	0.019 (0.013 to 0.024)	0.016 (0.010 to 0.106)
Baseline eGFR, median (range),	45 (34 to 54)	60 (44 to 60)	33 (22 to 60)	101 (84 to 118)	47 (22 to 118)

Accelerating Organ Response through Amyloid Clearance from Organs

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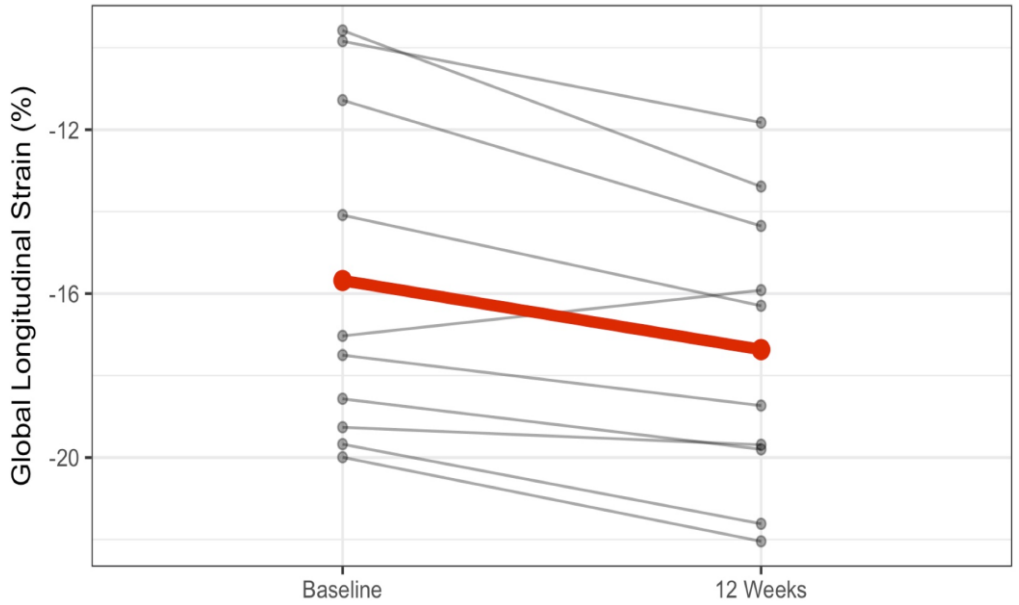
- **Novel anti-plasma cell therapies continue to emerge with improvements in hematologic responses**
- **Organ response even after hematologic response is established is still unpredictable**
- **Persistent organ dysfunction irrespective of hematologic response remains an issue**
- **There remains a need for therapies that target amyloid fibril removal to prevent and reverse organ damage**

Phase 1 CAEL-101 results: Improvement in GLS in Cardiac Patients at 12 weeks – irrespective of hematologic response



Organ Response

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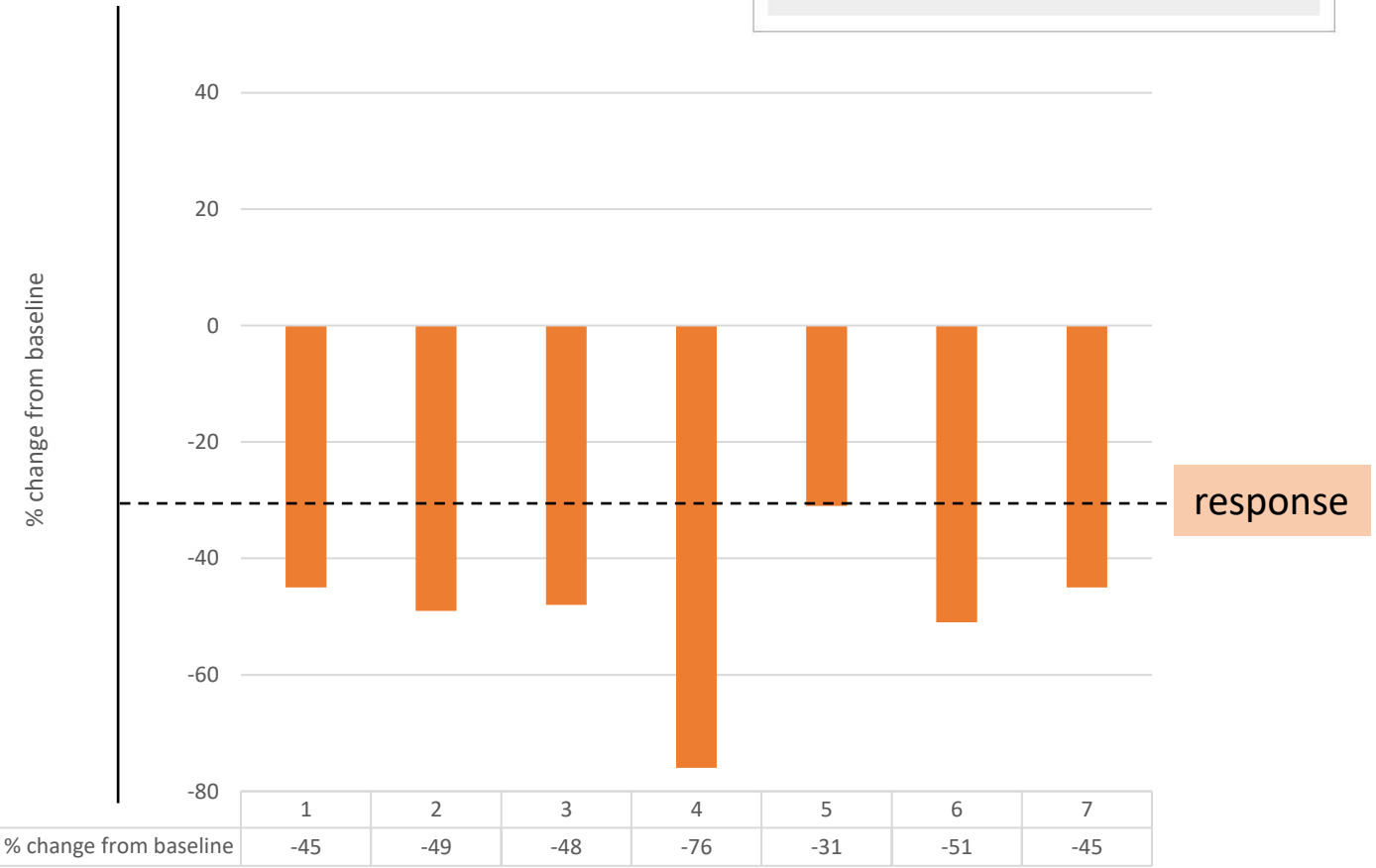
7 patients with kidney involvement: All had organ responses

(Palladini G et al Blood (2014) 124 (15): 2325–2332)

- **Of MOST INTEREST was 1 patient with PR subsequently progressed back to SD**
  - **Despite this, the patient has an ongoing deepening renal organ response currently showing a 76% reduction in 24 hour proteinuria without change in anti-plasma cell therapy**
  - **Median of 56 days to organ response**
- **One of 8 patients achieved cardiac organ response by NT pro BNP criteria**
  - **(Comenzo RL et al Leukemia (2012) 26, 2317-2325)**



Summary

- **CAEL-101 dosed at 1000 mg/m2 is the recommended dose in combination with CyBorD for the ongoing randomized, double blind, phase 3 trials**
- **Organ responses particularly in the kidney are common even in relapsed patients**
- **Only 1 patient is no longer on study due to need for change in anti-plasma cell therapy**
- **Most importantly, organ responses have been seen even without ongoing hematologic PR**

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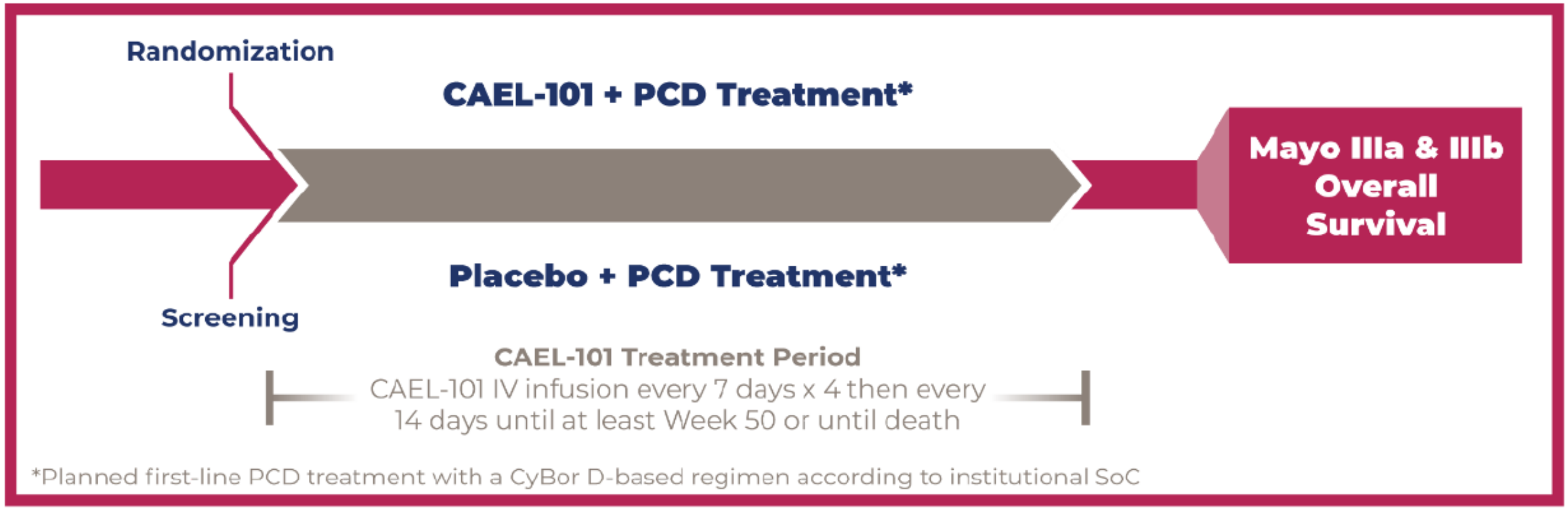
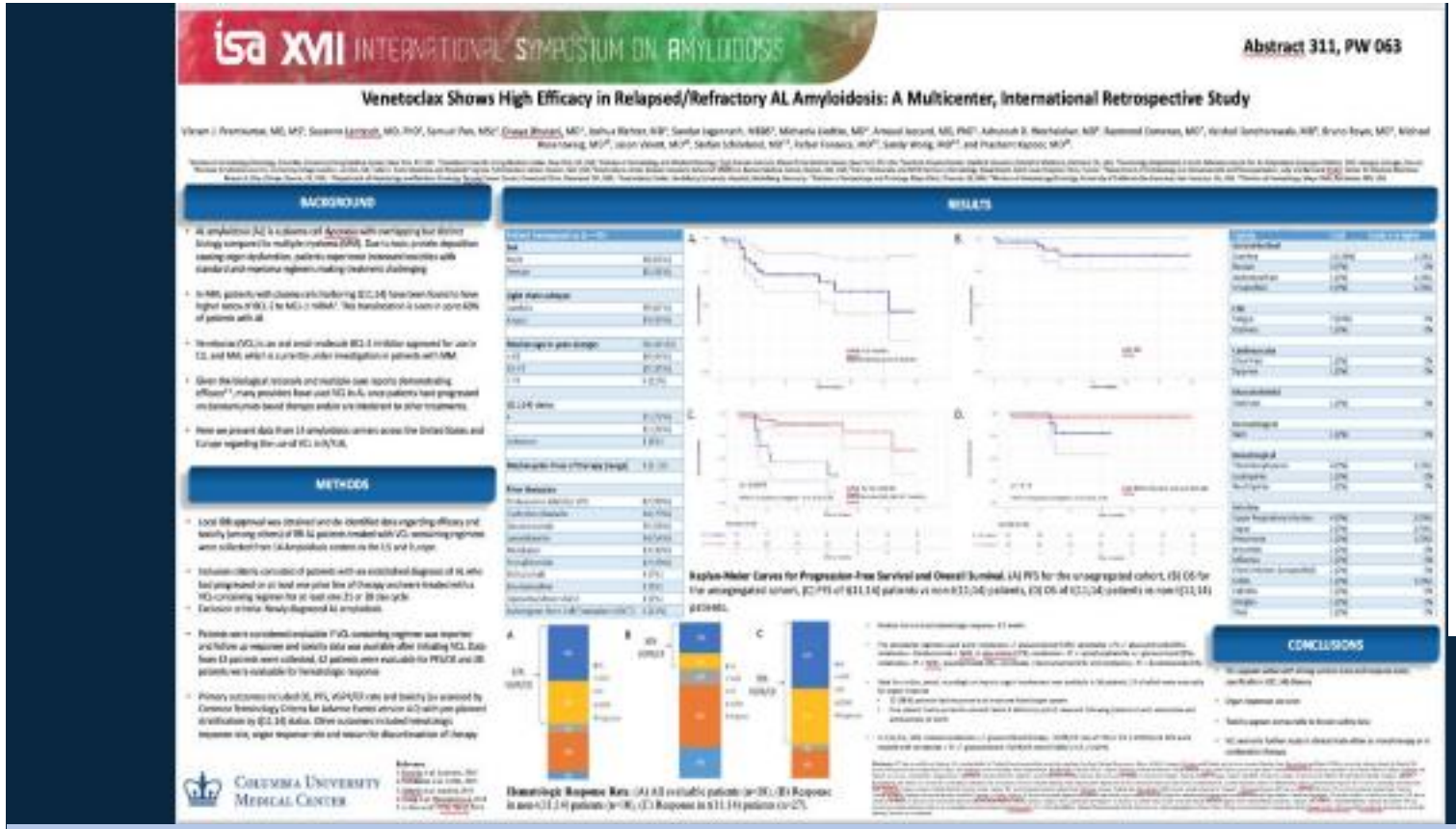
Caelum CARES 301 and 302 study design



PCD=Plasma Cell Disease
SoC=Standard of Care

Venetoclax for Amyloidosis?



isa XVI INTERNATIONAL SYMPOSIUM ON AMYLOIDOSIS

Abstract 311, PW 063

Venetoclax Shows High Efficacy in Relapsed/Refractory AL Amyloidosis: A Multicenter, International Retrospective Study

BACKGROUND

METHODS

RESULTS

CONCLUSIONS

Columbia University Medical Center

Sidiqi et al. *Blood Cancer Journal* (2020)10:55
https://doi.org/10.1038/s41408-020-0321-6

Blood Cancer Journal

CORRESPONDENCE Open Access

Venetoclax for the treatment of translocation (11;14) AL amyloidosis

M. Hasib Sidiqi[1,2], Abdullah S. Al Saleh[1], Nelson Leung[1,3], Dragan Jevremovic[4], Mohammed A. Aljama[5], Wilson I. Gonsalves[1], Francis K. Buadi[1], Taxiarchis V. Kourelis[1], Rahma Warsame[1], Eli Muchtar[1], Miriam A. Hobbs[1], Martha Q. Lacy[1], David Dingli[1], Ronald S. Go[1], Suzanne R. Hayman[1], S. Vincent Rajkumar[1], Angela Dispenzieri[1], Morie A. Gertz[1], Shaji K. Kumar[1], Rafael Fonseca[6] and Prashant Kapoor[1]

- Venetoclax: BCL2 inhibitor
- T(11;14) is present in 50% of amyloid patients
- Efficacy of venentoclax in amyloid w/ t(11;14) being studied

Birtamimab (NEOD001) is Back!

- **A Study to Evaluate the Efficacy and Safety of Birtamimab in Mayo Stage IV Patients With AL Amyloidosis (AFFIRM-AL)**
- A Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Clinical Trial
- NCT04973137

Final Thoughts, Future Directions

- **The phase III ANDROMEDA study results have established Dara+CyBorD as the standard of care for systemic AL amyloidosis**
- **Another anti-CD-38 MAB isatuximab is also being studied for Upfront Therapy for the Treatment of High Risk AL Amyloidosis (ClinicalTrials.gov Identifier: NCT04754945).**
- **Amyloid clearing antibodies (CAEL 1001 and Birtamimab (NEOD001) are currently in phase III clinical trials and may impact survival of patients with advanced AL cardiomyopathy (stage IIIa, IIIb, stage IV)**
- **Venetoclax has the potential to be an important agent for treatment of translocation t(11;14) AL amyloidosis**