POST-SAN DIEGO 2024
Novità dal Meeting della Società Americana di Ematologia

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Bologna
Palazzo Re Enzo
13-15 Febbraio 2025

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Prothena							x
Pfizer	x						x
Sebia							x

AL amyloidosis

1. Diagnosis and pre-clinical studies

2. Prognosis & response assessment

3. Treatment

1. Diagnosis and pre-clinical studies

- **Session: ASH Clinical Practice Guidelines on Amyloidosis**
- **Anti-Amyloid 11-1F4 CAR-Phagocytres for the treatment of AL amyloidosis**
- **1921 Evaluating Diagnostic Performance of Light Chain Dimerization By Mass Spectrometry to Distinguish between AL Amyloidosis and Monoclonal Gammopathy of Undetermined Significance**
- **3305 Proteomic Determinants of Renal Organ Response in AL Amyloidosis**

Sensitivity of different biopsies for AL

Fat Pad	Bone Marrow	Peripheral Nerve Biopsy	Skin [1]	Liver	GI [2]	Kidney	Heart
76.6 (72.1-80.8)	55.1 (45.8 – 64.0)	66.3 (26.2 – 91.6)	60 (2-98)	86.8 (74-93.8)	66.6 (56-81)	95.5 (90.7-97.9)	93.5 (85.2 – 97.3)

FA +BM 89%

Surrogates

[1] For epidermal nerve fiber density [2] Can also serve as a surrogate

2. Prognosis & response assessment

- **Defining a New “Mayo Stage IIIc” Ultra Poor Risk Category in Systemic AL Amyloidosis: Incorporating Echocardiographic Global Longitudinal Strain to the European Modified Mayo Staging System**

- **Development of a Risk Prediction Model for 6-Month Early Mortality in Patients with Systemic Light Chain Amyloidosis Treated with Daratumumab-Based Frontline Therapy**

- **Clinical Significance of Measurable Residual Disease (MRD) in Light-Chain (AL) Amyloidosis**

- **3309 Gain or Amplification of 1q21 in Systemic Light Chain Amyloidosis Is Associated with Advanced Mayo Stage, Plasma Cell Disease and Worse Overall Survival**

Defining a new 'Mayo Stage IIIc' Ultra Poor Risk Category in Systemic AL amyloidosis

Incorporating echocardiographic global longitudinal strain to the European Modified Mayo Staging System

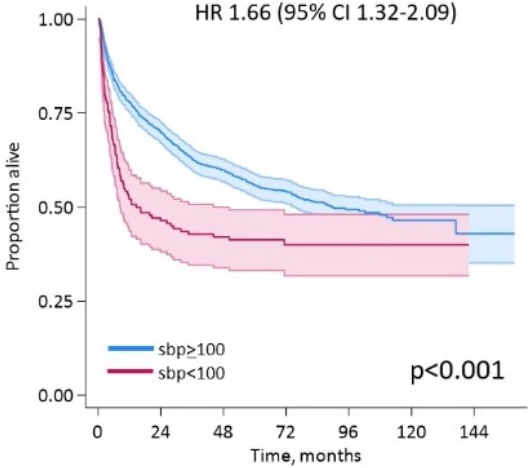
Jahanzaib Khwaja[1,2], Sriram Ravichandran[1], Joshua Bomsztyk[2], Oliver C Cohen[2], Darren Foard[2], Ana Martinez – Naharro[2], Lucia Venneri[2], Marianna Fontana[2], Carol Whelan[2], Philip N Hawkins[2], Julian Gillmore[2], Helen J Lachmann[2], Shameem Mahmood[2], Amy A Kirkwood[3], Ashutosh D Wechalekar[1,2]

[1]University College London Hospitals, UK. [2]National Amyloid Centre, Royal Free London Hospital, UK. [3]Cancer Research UK & UCL Cancer Trials Centre

65th ASH Annual Meeting
December 9th 2024

Stratification by GLS and blood pressure

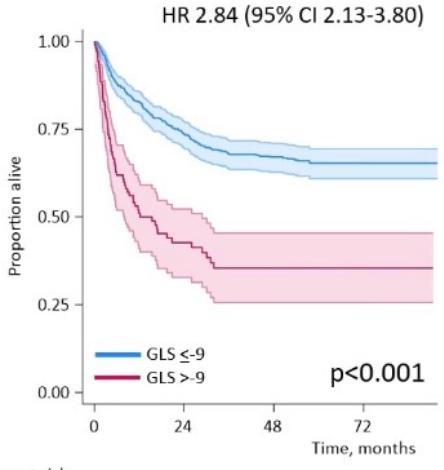
Stratified by systolic bp <100mmHg



Number at risk

sbp>100	1088	727	574	323	140	38	4
sbp<100	144	65	57	28	15	3	0

Stratified by GLS >-9%



Number at risk

GLS<-9%	550	348	272	96
GLS>-9%	105	31	21	4

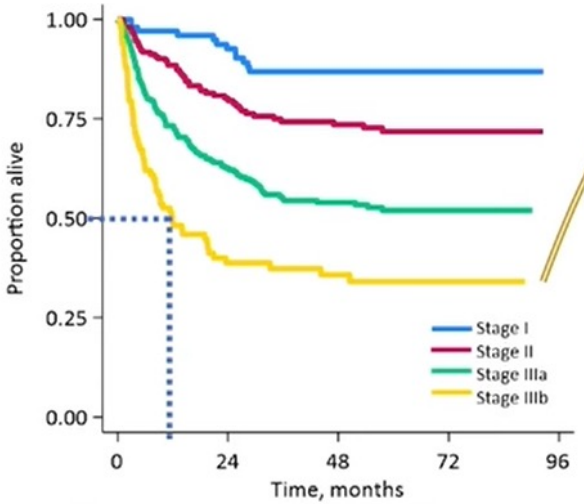
log-rank testing

Prognostic value of biomarkers as continuous variables

Risk factor	Univariable		Multivariable	
	HR (95% CI)	p value	HR (95% CI)	p value
dFLC, per log increase	1.01 (1.00-1.01)	0.001	0.99 (0.97-1.01)	0.33
NT-proBNP, per log increase	1.03 (1.02-1.04)	<0.001	**1.03 (1.01-1.05)**	**0.001**
Hs-TnT, per log increase	1.04 (1.03-1.04)	<0.001	**1.03 (1.02-1.04)**	**<0.001**
GLS, per %	1.11 (1.08-1.14)	<0.001	**1.07 (1.04-1.11)**	**<0.001**
Systolic bp, per 10mmHg	0.88 (0.84-0.92)	<0.001	0.96 (0.87-1.03)	0.22

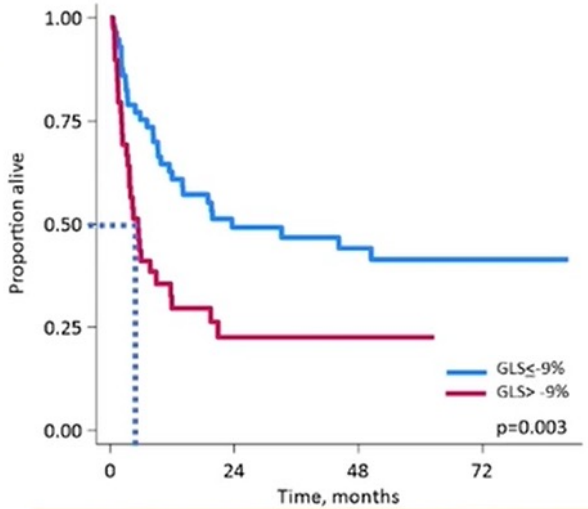
GLS >-9% sub-stratifies patients with IIIb

European staging



Stage IIIb: median OS 12 m

Stage IIIb stratified by GLS >-9%



GLS > -9% median OS 5 m
GLS ≤ -9%: median OS 24 m

Limitations

- Small numbers of daratumumab treated patients included in this cohort
- Inter-vendor and inter-operator variability may impact strain analysis
- This proposed staging system requires external validation

Summary

- Standard staging by Mayo 2012/European modification are no longer able to accurately discriminate the poorest outcomes
- dFLC is no longer prognostic for early survival
- We recommend that addition of GLS >-9% to IIIb to sub stratify the poorest survivors (stage IIIc)

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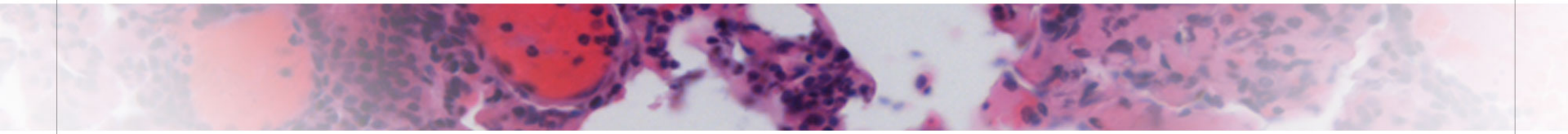
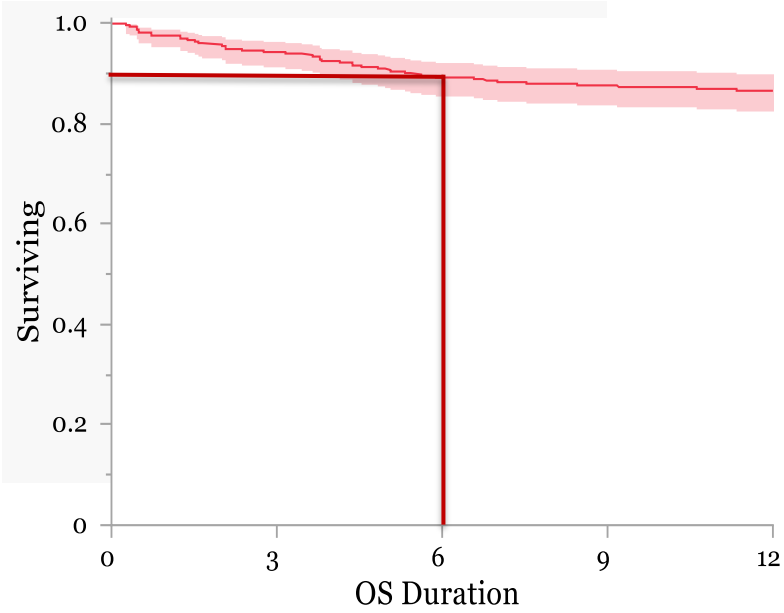


Development of a Risk Prediction Model for 6-Month Early Mortality In Patients with Systemic Light Chain Amyloidosis Treated with Daratumumab-Based Frontline Therapy

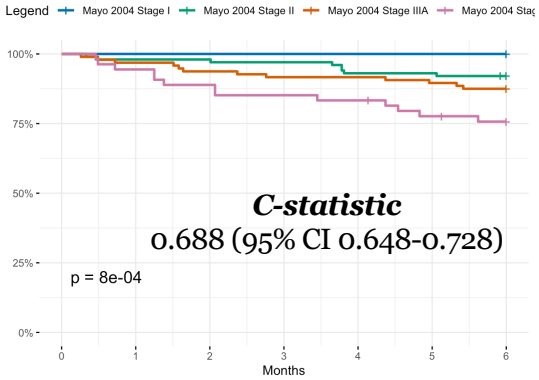
George Mellgard, Abdul-Hamid Bazarbachi, Saurabh Zanwar, MD, Ute Hegenbart, Geethika Bodanapu, Divaya Bhutani, Guizhen Chen, Anita D'Souza, Angela Dispenzieri, Morie A. Gertz, Shaji Kumar, Suzanne Lentzsch, Paolo Milani, Eli Muchtar, Giovanni O. Palladini, Anannya Patwari, Vaishali Sanchorawala, Shikun Wang, Stefan O. Schönland, Rajshekhar Chakraborty, and Andrew J. Cowan,

Early Mortality in Study Cohort

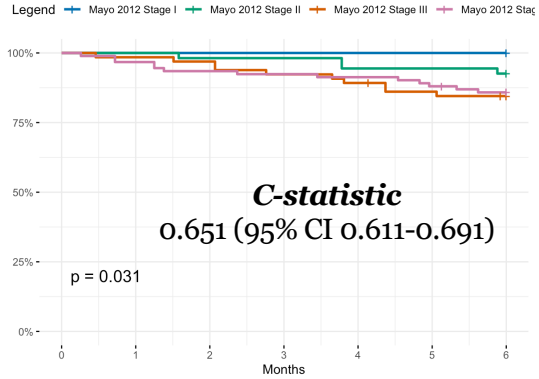


6-month EM ~11%

European Mod of Mayo 2004



Mayo 2012



Predictors of Early Mortality on Multivariate Analysis

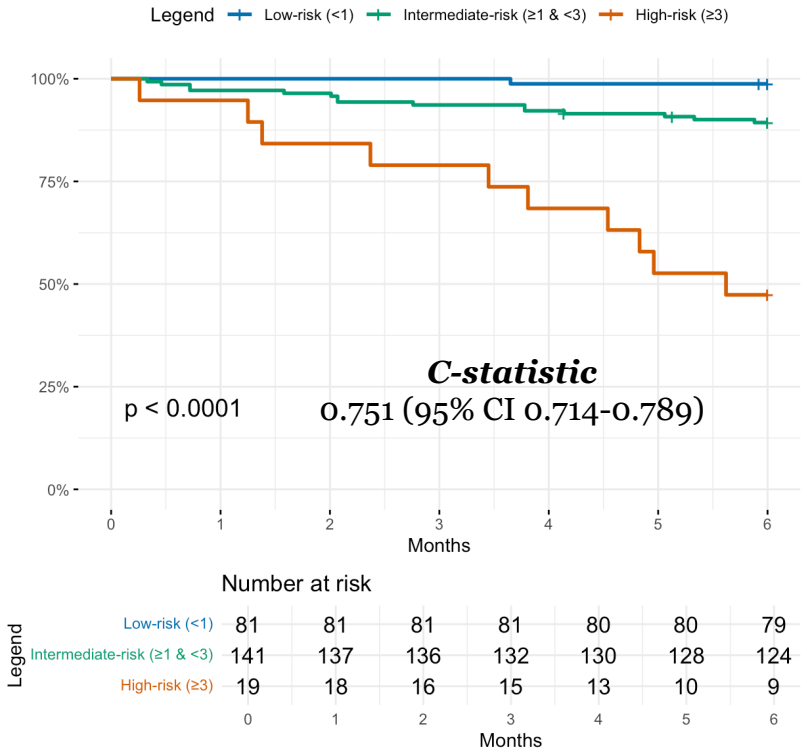
- Factors included in multivariate analysis: Age≥75 years, ECOG (0-4), NT-proBNP>5300 pg/mL, and t(11;14) status

Variable	Beta-coefficient	OR (SE)	*P*-value
Age ≥ 75 years (vs <75)	1.01	2.75 (0.568)	**0.038**
ECOG PS (*per 1 level increase*)	0.538	1.71 (0.27)	**0.046**
NT-proBNP>5,300 pg/mL (vs <5300)	1.37	4.0 (0.494)	**0.006**
Absence of t(11;14) [vs t(11;14)-positive]	1.16	3.19 (0.483)	**0.017**

Risk-Prediction Model for EM: PACE Score

Variable	Score
NT-proBN***P*** >5300	1
Age ≥75	1
Cytogenetics (t[11;14]-neg)	1
ECOG PS	0.5

Risk-Group	% EM (95% CI)
Low-Risk (<1) [34%]	1.2 (0-3.6)
Int.-Risk (≥1 & <3) [59%]	10.7 (5.4-15.6)
High-Risk (≥3) [8%]	52.6 (23.0-70.5)



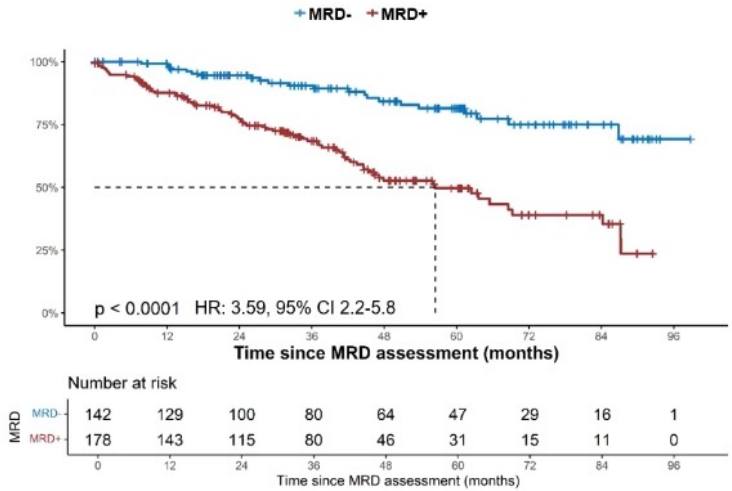
Clinical Significance of Measurable Residual Disease (MRD) in Light-Chain (AL) Amyloidosis

Marta Lasa[1], Mario Nuvolone[2], Ioannis V Kostopoulos[3], Tomas Jelinek[4], Marco Basset[2], Paolo Milani[2], Margherita Massa[2], Foteini Theodorakakou[3], Ashutosh Wechalekar[5], Anastasiia Zherniakova[1], Rafel Rios[6], Irene Romera[7], Maria-Teresa Cedena[8], Noemi Puig[9], Ramón Lecumberri[1], Jesús San Miguel[1], Roman Hajek[4], Giampaolo Merlini[2], Efstathios Kastritis[3], Bruno Paiva[1], Giovanni Palladini[2]

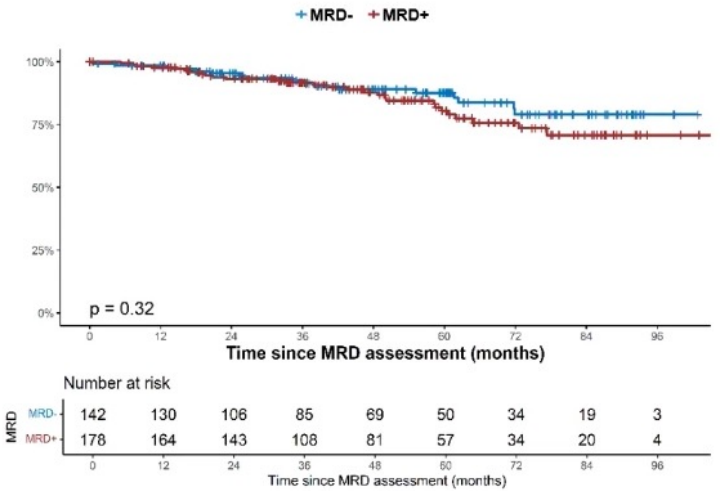
[1]Cancer Center Clinica Universidad de Navarra, Pamplona, Spain; [2]University of Pavia and Amyloidosis Research and Treatment Center, Pavia, Italy; [3]National and Kapodistrian University of Athens School of Medicine, Athens, Greece; [4]University Hospital Ostrava, Ostrava, Czech Republic; [5]National Amyloidosis Centre University College London, London, UK; [6]Hospital Virgen de las Nieves, Granada, Spain; [7]Hospital Universitario Puerta de Hierro, Hospital, Madrid, Spain; [8]Hospital Universitario 12 de Octubre, Madrid, Spain; [9]Hospital Universitario de Salamanca Salamanca, Spain.

Detectable MRD is associated with a 3.6-fold increased risk of requiring a new line of therapy

Time to next treatment



Overall survival



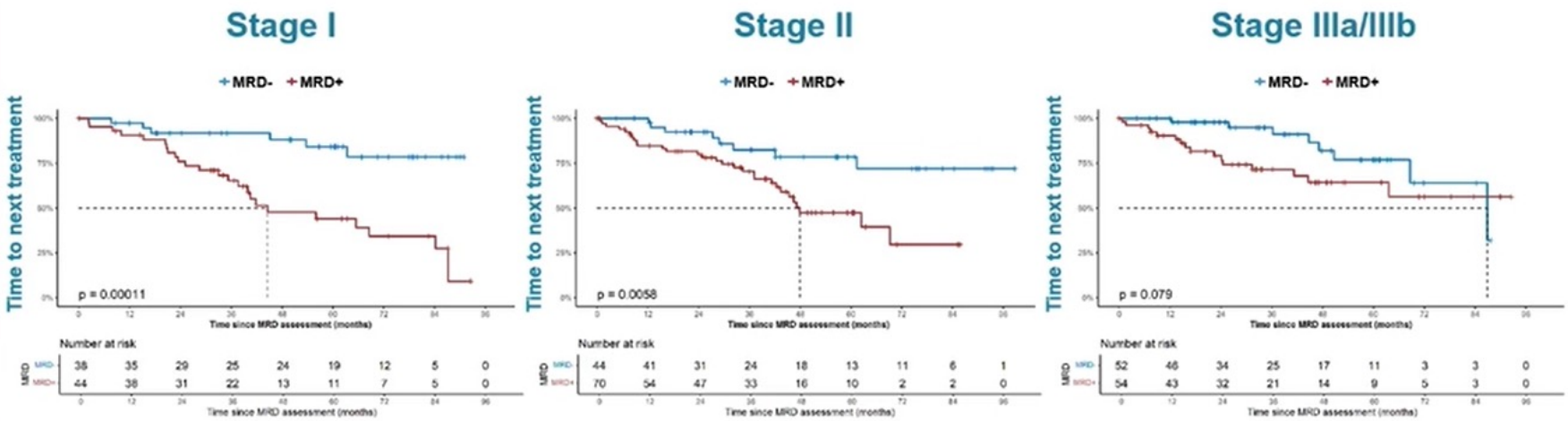
No correlation between MRD status and cardiac or renal response*

Cardiac response	At MRD		Progression	
	No	Yes	No	Yes
MRD -	22 (28%)	56 (72%)	85 (88%)	11 (12%)
MRD +	38 (37%)	64 (63%)	108 (86%)	17 (14%)
	P = .264		*P* = .687	

Renal response	At MRD		Progression	
	No	Yes	No	Yes
MRD -	25 (31%)	55 (69%)	87 (87%)	13 (13%)
MRD +	49 (46%)	58 (54%)	109 (82%)	23 (18%)
	P = .05		*P* = .464	

*Limited number of patients with liver involvement precluded statistical analysis

Impact of MRD status in risk subgroups defined at diagnosis by the 2013 European Staging System



Conclusions

- Detectable MRD – even at 10^{-6} – is associated with inferior outcome
- Patients in hematological CR with persistent MRD show inferior TTNT
- MRD status helps redefining patients risk determined at diagnosis
- MRD status was an independent prognostic factor
- MRD response was prognostic in different treatment scenarios
- **MRD should be assessed in patients with AL amyloidosis who attain hematological CR and MRD negativity could become a therapeutic endpoint**

3. Treatment 1/2

- **891. Subcutaneous Daratumumab (DARA) + Bortezomib, Cyclophosphamide, and Dexamethasone (VCd) in Patients with Newly Diagnosed Light Chain (AL) Amyloidosis: Overall Survival and Final Major Organ Deterioration Progression-Free Survival Results from the Phase 3 Andromeda Study**

- **893 Venetoclax Plus Dexamethasone As First-Line Treatment for t(11; 14) Light-Chain Amyloidosis: Preliminary Result of a Phase II Prospective, Multicenter, Single-Arm Study**

- **892 Efficacy and Safety of Isatuximab, Pomalidomide and Dexamethasone in Relapsed AL Amyloidosis: Interim Results of the Isamyp Phase 2 Joint Study from the IFM and ALLG**

- **894 Efficacy and Safety of Anti-BCMA Chimeric Antigen Receptor T-Cell (CART) for the Treatment of Relapsed and Refractory AL Amyloidosis**

3. Treatment 2/2

- **3304 Elranatamab in Patients with Daratumumab Relapsed and/or Refractory Light Chain Amyloidosis**
- **1927 Efficacy and Safety of Belantamab Mafodotin Monotherapy in Patients with Relapsed or Refractory Light Chain Amyloidosis: An Updated Analysis of a Phase 2 Study By the European Myeloma Network**
- **1911 Assessing the Efficacy and Safety of Reduced Dexamethasone Duration in Newly Diagnosed AL Amyloidosis Versus Standard Therapy**
- **3378 Isatuximab in Relapsed AL Amyloidosis: Results of a Prospective Phase II Trial (SWOG S1702)**

Subcutaneous Daratumumab (DARA) + Bortezomib, Cyclophosphamide, and Dexamethasone (VCd) in Patients With Newly Diagnosed Light-Chain (AL) Amyloidosis: Overall Survival and Final Major Organ Deterioration–Progression-free Survival Results from the Phase 3 ANDROMEDA Study

Efstathios Kastritis[1], Giovanni Palladini[2,3], Monique C Minnema[4], Ashutosh D Wechalekar[5], Arnaud Jaccard[6], Hans C Lee[7], Vaishali Sanchorawala[8], Peter Mollee[9], Jin Lu[10], Stefan Schönland[11], Moshe E Gatt[12], Kenshi Suzuki[13], Kihyun Kim[14], M Teresa Cibeira[15], Manisha Bhutani[16], Meral Beksac[17], Edward Libby[18], Jason Valent[19], Vania Hungria[20], Michael Rosenzweig[21], Naresh Bumma[22], Antoine Huart[23], NamPhuong Tran[24], Jianping Wang[25], Yuping Chen[26], Sandra Y Vasey[27], Jordan M Schecter[25], Jessica Vermeulen[28], Raymond L Comenzo[29], Giampaolo Merlini[2,3]

[1]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece; [2]Department of Molecular Medicine, University of Pavia, Pavia, Italy; [3]Amyloidosis Research and Treatment Center, Foundation IRCCS Policlinico San Matteo, Pavia, Italy; [4]Department of Hematology, University Medical Center Utrecht, University Utrecht, Utrecht, The Netherlands; [5]University College London, London, UK; [6]Reference Center for AL Amyloidosis, Limoges, France; [7]Department of Lymphoma and Myeloma, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [8]Amyloidosis Center, Boston University School of Medicine and Boston Medical Center, Boston, MA, USA; [9]Department of Haematology, Princess Alexandra Hospital and University of Queensland Medical School, Brisbane, Australia; [10]Peking University People's Hospital, Peking University Institute of Hematology, National Clinical Research Center for Hematologic Disease, Collaborative Innovation Center of Hematology, Beijing, China; [11]Universitaetsklinikum Heidelberg Medizinische Klinik V, Heidelberg, Germany; [12]Hadassah Medical Center, Jerusalem, Israel; [13]Japanese Red Cross Medical Center, Shibuya, Tokyo, Japan; [14]Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, South Korea; [15]Amyloidosis and Myeloma Unit, Hospital Clinic of Barcelona, IDIBAPS, Barcelona, Spain; [16]Department of Hematologic Oncology and Blood Disorders, Atrium Health Levine Cancer Institute, Wake Forest University School of Medicine, Charlotte, NC, USA; [17]Department of Hematology, Ankara University, Ankara, Turkey*; [18]Fred Hutchinson Cancer Center, Seattle, WA, USA; [19]Department of Hematology and Medical Oncology, Taussig Cancer Center, Cleveland Clinic, Cleveland, OH, USA; [20]Clínica São Germano, São Paulo, Brazil; [21]Department of Hematology and Hematopoietic Cell Transplantation, Judy and Bernard Briskin Center for Multiple Myeloma Research, City of Hope, Duarte, CA, USA; [22]Division of Hematology, Ohio State University Comprehensive Cancer Center, Columbus, OH, USA; [23]Département de Néphrologie et Transplantation d'Organes, Centre de Référence des Maladies Rénales Rares, Hôpital Rangueil, CHU de Toulouse, Toulouse, France.

[28]John C. Davis Myeloma and Amyloid Program, Tufts Medical Center, Boston, MA, USA. *At time work was performed.

Presented by E Kastritis at the 66th American Society of Hematology (ASH) Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA, USA

https://www.congresshub.com/ASH2024/Oncology/Daratumumab/Kastritis

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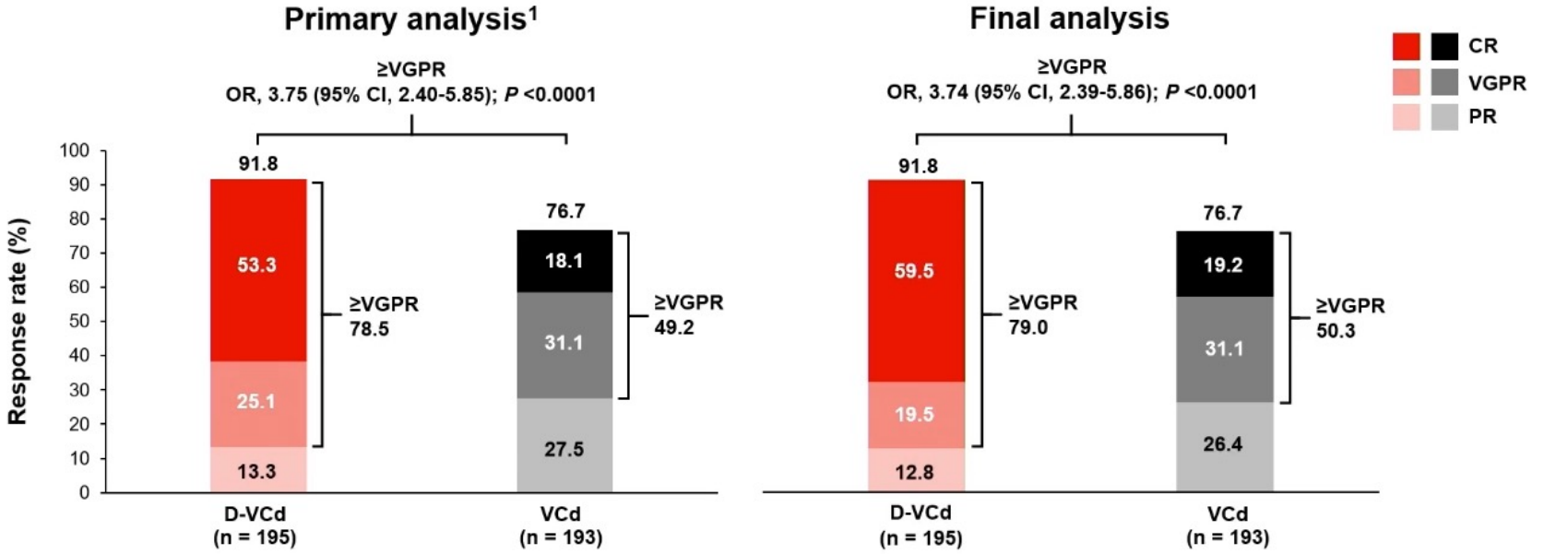
ANDROMEDA: Overall Hematologic Response at the Final Analysis

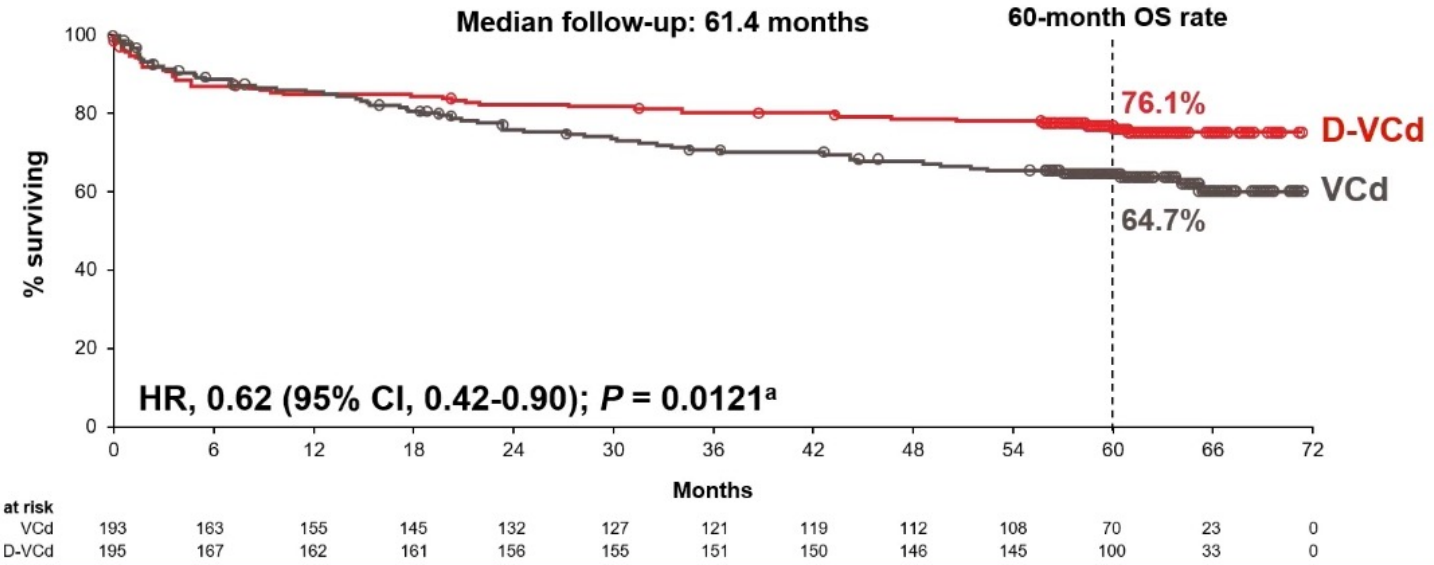


The addition of DARA to VCd consistently led to higher rates of hematologic response

VGPR, very good partial response; CR, complete response; PR, partial response. 1. Kastritis E, et al. *N Engl J Med*. 2021;385(1):46-58.

Presented by E Kastritis at the 66th American Society of Hematology (ASH) Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA, USA

ANDROMEDA: Overall Survival



No. at risk												
VCd	193	163	155	145	132	127	121	119	112	108	70	23	0
D-VCd	195	167	162	161	156	155	151	150	146	145	100	33	0

The addition of DARA to VCd significantly improved OS versus VCd despite cross-over in >70% of VCd patients who received DARA as subsequent therapy, highlighting the importance of DARA use in frontline treatment

[a]Crossing the prespecified stopping boundary of 0.0163.

Presented by E Kastritis at the 66th American Society of Hematology (ASH) Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA, USA

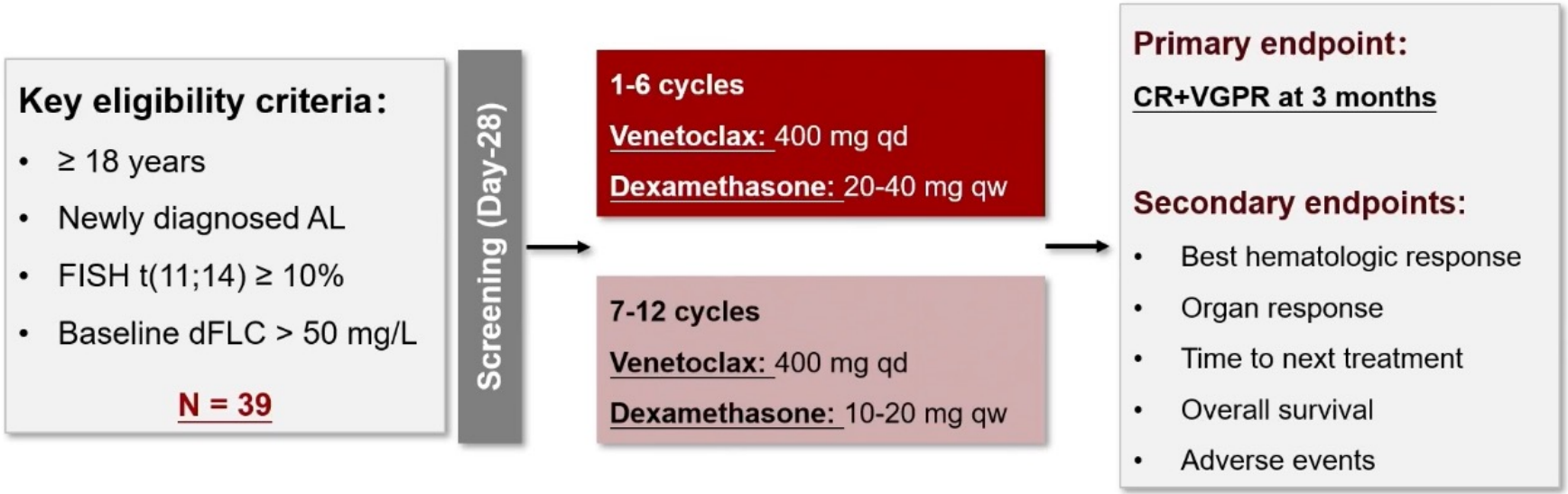
Venetoclax Plus Dexamethasone as First-line Treatment for t(11; 14) Light-chain Amyloidosis: Preliminary Result of a Phase II Prospective, Multicenter, Single-arm Study

Kai-ni Shen[1]*, Ai Guan[1]*, Yu Wu[2], Chun-yan Sun[3], Li-ye Zhong[4], Jun Luo[5], Jian Li[1#]

[1]Department of Hematology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College; [2]Department of Hematology and Hematology Research Laboratory, West China Hospital, Sichuan University; [3]Institute of Hematology, Union Hospital of Tongji Medical College, Huazhong University of Science and Technology; [4]Department of Hematology, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University; [5]Department of Hematology, The First Affiliated Hospital of Guangxi Medical University

Methods

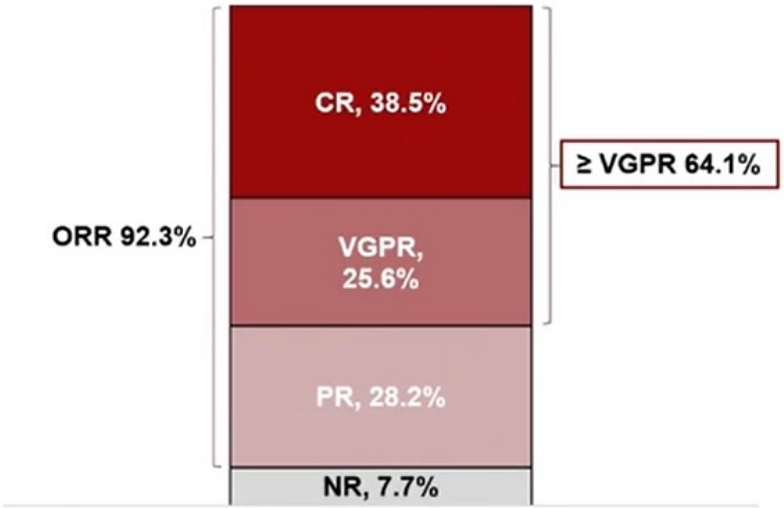
Phase II Prospective, Multicenter, Single-arm Study



Results

Hematologic CR + VGPR at 3 Months

- Median of 7 cycles (range, 1-12 cycles)
- Evaluable patients: 39



Time to response
- 31 (25-69) days

Time to best response
- 34 (25-371) days

Time to complete response
- 39 (26-371) days

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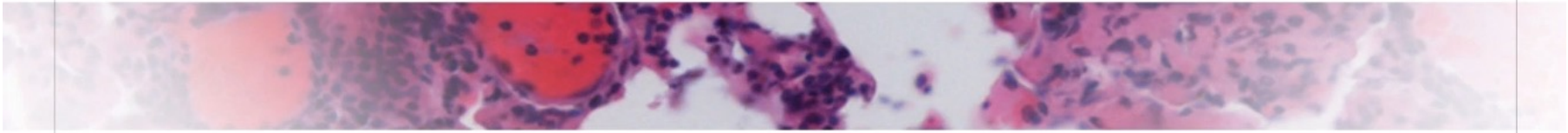


Efficacy and Safety of Isatuximab, Pomalidomide and Dexamethasone in Relapsed AL Amyloidosis: Interim Results of the IsAMYP Phase 2 Joint Study from the IFM and ALLG

Peter Mollee, Antoine Huart, Olga Mortona, Kentin Queru, Cecile Leyronnas, Stéphanie Harel, Hasib Sidiqi, Estelle Desport, Laure Vincent, Margaret Macro, Salomon Manier, Caroline Jacquet, Pierre Morel, Noemi Horvath, Sébastien Bender, Guillaume Olombel, Virginie Pascal, Jill Corre, Frank Bridoux, Arnaud Jaccard, and Murielle Roussel, on behalf the IFM and the ALLG

IFM 2020-01

MM24-IsAMYP

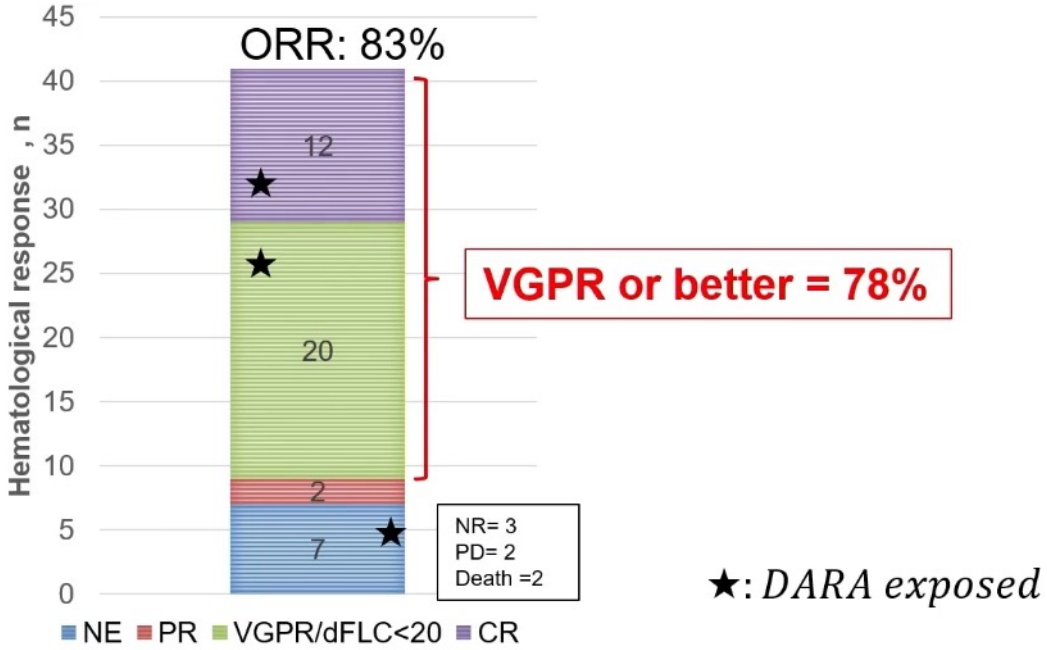
ifm

Centre national de référence Amylose AL & autres maladies par dépôt d'immunoglobulines monoclonales

CHU Limoges · CHU Poitiers · Hôpital Saint-Louis AP-HP

ALLG Australasian Leukaemia & Lymphoma Group

HEMATOLOGICAL RESPONSES AT THE COMPLETION OF 6 CYCLES OF ISATUXIMAB POMALIDOMIDE AND DEXAMETHASONE



HEMATOLOGICAL TOXICITIES

32 patients

	Anaemia	Neutropenia	Eosinophilia	Thrombocytopenia	Lymphopenia	Leucopenia	Thombocytosis	Total
Grade 1	1	7	2	2	3		2	17
Grade 2	7	4						11
Grade 3	3	**34**			**1**	**1**		**39**
Grade 4		**11**						**11**
Total	10	**56**	2	2	4	1	1	**78**

Neutropenia ≥ G3 : 43 (19 in France, 24 in Australia)

20 (46.5%) events were reported during cycle 1 and 8 during cycle 2

Delayed cycles: 12
Rx interruption: 9
Dose reduction: 4

pomalidomide
↓ 3 mg

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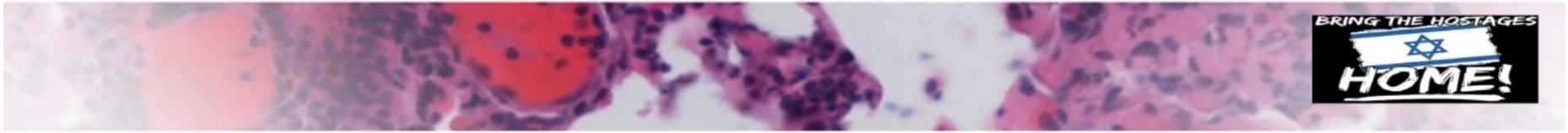

Efficacy and Safety of Anti-BCMA Chimeric Antigen Receptor T-Cell (CART) for the Treatment of Relapsed and Refractory AL amyloidosis

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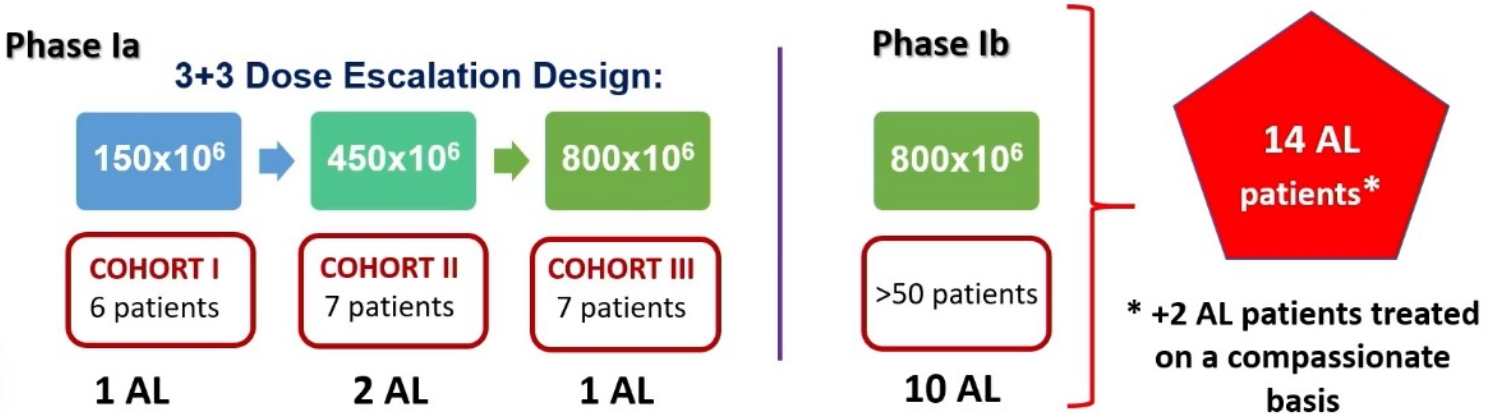
Clinical trial of HBI0101- NCT04720313

- A Phase Ia\Ib Study of HBI0101 anti-BCMA CART in R/R MM and AL amyloidosis
- Phase Ia was designed as a dose-escalation 3X3 protocol. (20 pts.)
- Phase Ib tested 800 $X10^6$ cart cells (phase 2 is ongoing)



Hadassah University Hospital

Results: Safety

TABLE 2. Adverse Events

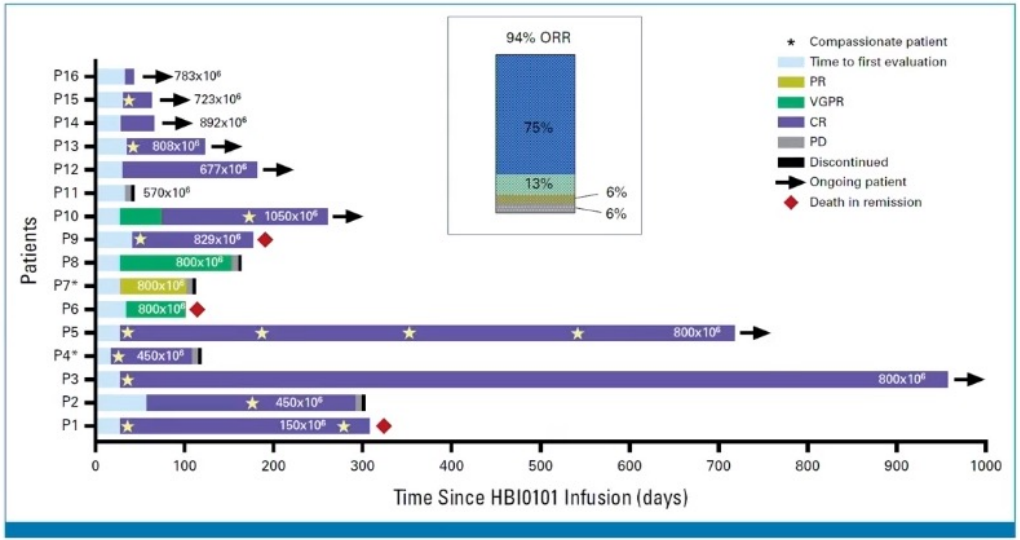
	Toxicity Results
CRS, n/N (%)	
No CRS	2/16 (12)
Grade 1	3/16 (19)
Grade 2	8/16 (50)
Grade 3	3/16 (19)
Grade 4/5	0/16 (0)
Time to onset of CRS, days, median (range)	1 (1-3)
Duration of CRS, days, median (range)	2 (1-5)
Tocilizumab use, n/N with CRS (%)	12/14 (86), median of one dose (range, 1-3)
Corticosteroid use, n/N with CRS (%)	3/14 (21)
Vasopressor use, n/N with CRS (%)	2/14 (14)
High-flow oxygen use, n/N with CRS (%)	2/14 (14)
ICANS and other neurotoxicity, n/N (%)	0/16 (0)

Abbreviations: CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome.

TABLE 2. Adverse Events

	Toxicity Results	
Variable	Total	Grade 3-4
Hematological toxicity, n/N		
Anemia	12/16	5/16
Thrombocytopenia	9/16	0/16
Neutropenia	12/16	10/16
Lymphopenia	16/16	16/16
Organ function toxicity, n/N		
Congestive heart failure exacerbation	3/16	3/16
Acute kidney injury	4/16	0/16
Hepatic injury	6/16	4/16
Infections, n/N		
Febrile neutropenia	5/16	5/16
Early infections (until day +28)	9/16	6/16
Late infections (after day +28)	7/16	5/16
Treatment-related mortality, n/N (%)	0/16 (0)	

Efficacy


94% ORR
75%
13%
6%
6%
Compassionate patient
Time to first evaluation
PR
VGPR
CR
PD
Discontinued
Ongoing patient
Death in remission
Patients
P16
P15
P14
P13
P12
P11
P10
P9
P8
P7*
P6
P5
P4*
P3
P2
P1
783x10⁶
723x10⁶
892x10⁶
808x10⁶
677x10⁶
570x10⁶
1050x10⁶
829x10⁶
800x10⁶
800x10⁶
800x10⁶
800x10⁶
450x10⁶
800x10⁶
450x10⁶
150x10⁶
0
100
200
300
400
500
600
700
800
900
1000
Time Since HBI0101 Infusion (days)

Conclusions

- ✓ This trial reports the first data of anti-BCMA CART treatment in AL amyloidosis, including frail cardiac patients.
- ✓ Due to the deep and quick reduction of light chain toxicity, *organ response is observed quickly*
- ✓ Organ Deconditioning was manageable. However cardiac related death in the first year were frequent, arguing for earlier usage in the course of disease.
- ✓ The high response rates and manageable toxicity profile are promising and provide the basis for future CART trials in AL amyloidosis.

Conclusions - AL amyloidosis

1. **Diagnosis and pre-clinical studies**
   - Upcoming diagnosis guidelines from ASH
   - New pre-clinical models and new terapeutic targets under investigation

2. **Prognosis & response assessment**
   - Stage IIIc disease
   - MRD assessment

3. **Treatment**
   - Dara-CyBorD confirmed as standard of care for newly diagnosis AL
   - Venetoclax, potential option first line
   - Isatuximab-pomalidomide, potential role in R/R setting
   - CAR-T cell is an option for AL amyloidosis