Convegno interregionale SIE

Delegazioni Emilia Romagna e Toscana

Gli ematologi insieme contro le malattie rare

21 Aprile 2026

Bologna, Aula Prodi

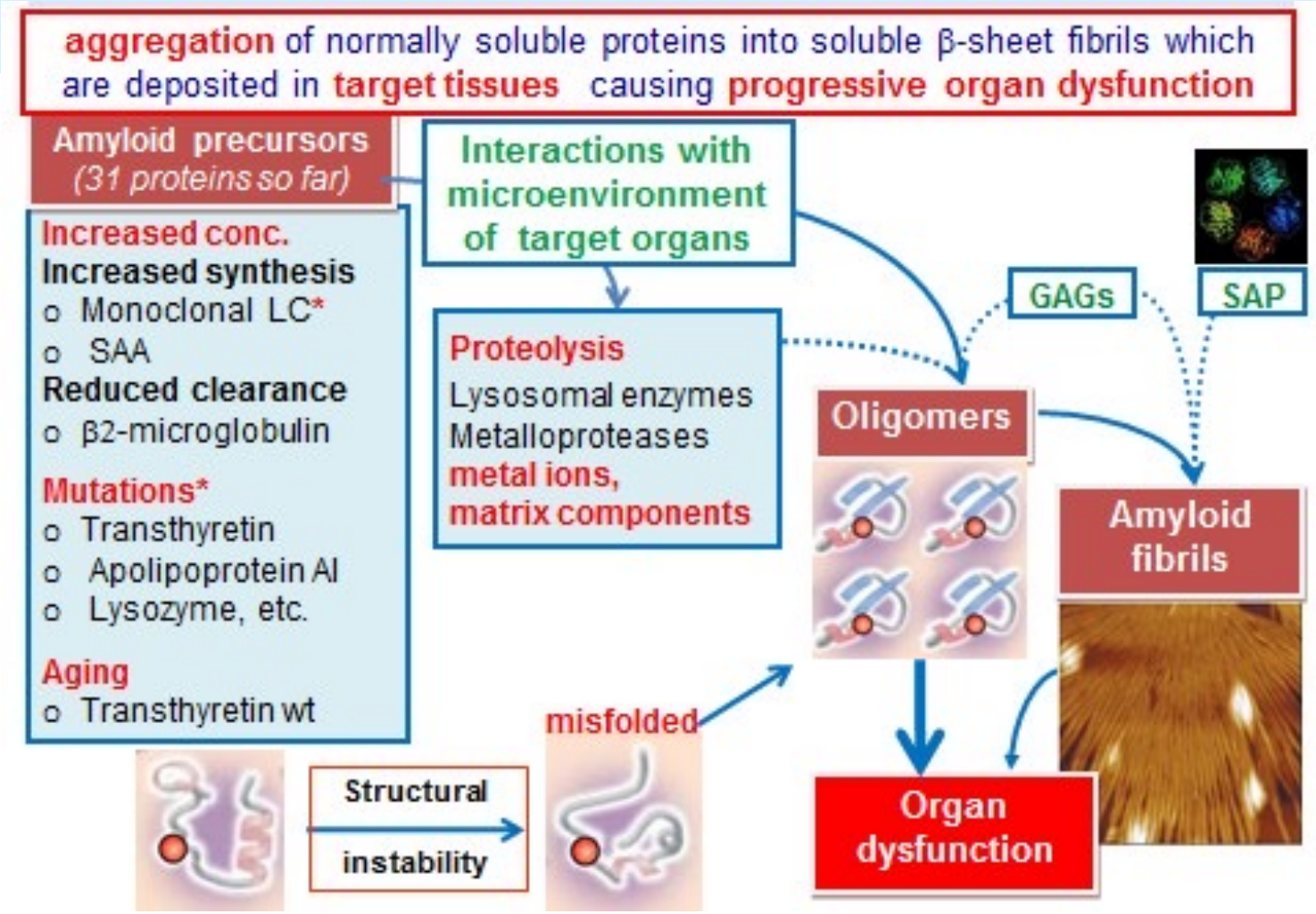
Amiloidosi
Cosa puo' fare l'ematologo

Gabriele Buda
Universita' di Pisa

Disclosures of Gabriele Buda

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Honoraria
GSK						x	x
JANSSEN						x	x
BMS						x	x
TAKEDA						x	x
SANOFI						x	x
PFIZER						x	x
AMGEN						x	x
MENARINI						x	x

Amyloidosis: protein misfolding disease



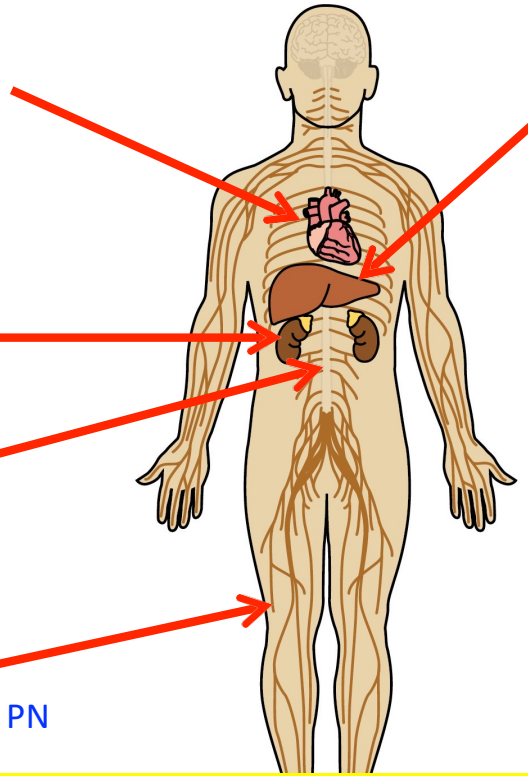
Amyloidosis is a great imitator

Heart
Heart failure with preserved ejection fraction
Thickened ventricular walls, low voltages at ECG
Dyspnea at rest or exertion, fatigue
Hypotension or syncope
Peripheral edema

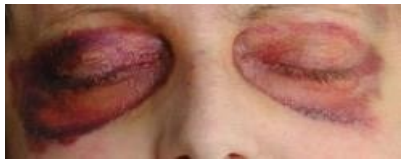
Kidney
Nephrotic range proteinuria
Renal failure
Peripheral edema

GI tract
Malabsorption, weight loss
Bleeding (Factor X def.)

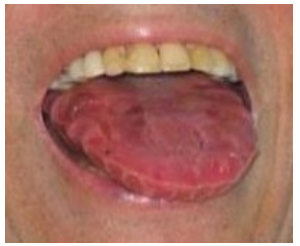
Nervous system
Peripheral: symmetric lower extremity sensorimotor PN
Carpal tunnel syndrome (bilateral)
Autonomic: postural hypotension,
erectile dysfunction (males), GI motility alte



Liver
Increased alkaline phosph
Hepatomegaly



Periorbital purpura 11%



Macroglossia 14%

→ **advanced stage of the disease!**

→ **need for more sensitive markers of organ involvement**

Tissue diagnosis of AL amyloidosis

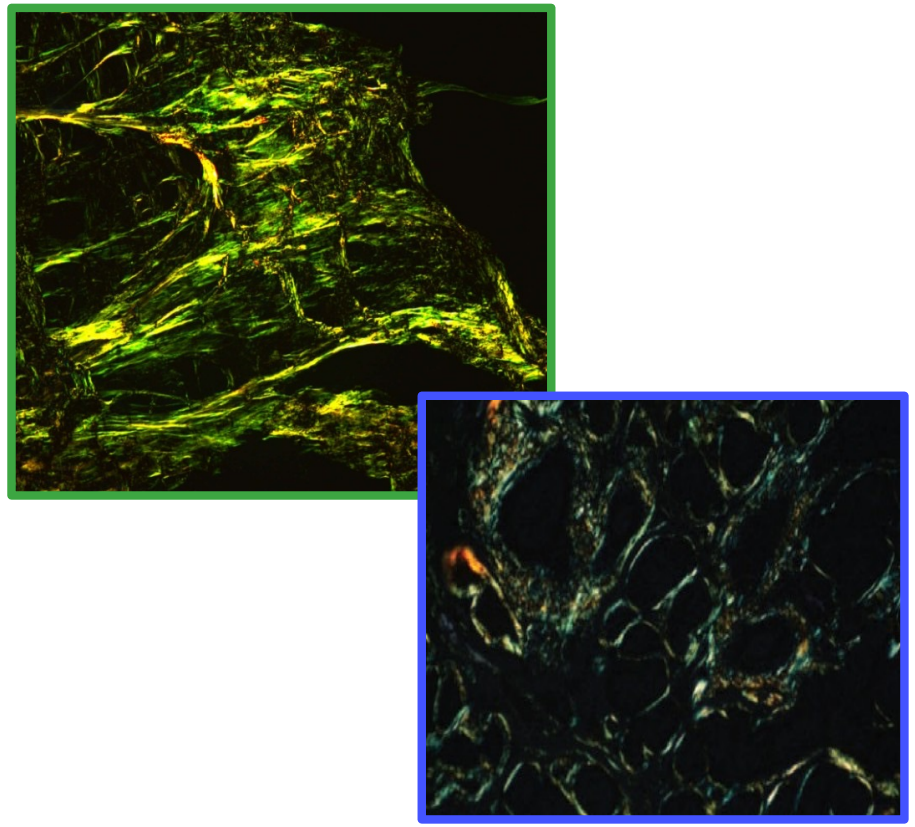
Abdominal fat aspirate
sensitivity 79%

↓

Minor salivary gland biopsy
sensitivity 58% in patients with negative fat aspirate

↓

Biopsy of the organ involved
beware of hemorrhagic risk, transjugular approach preferred for liver biopsy

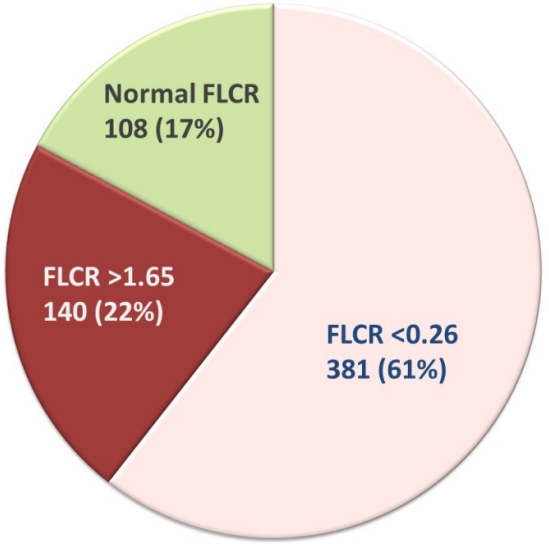


1. *Fernandez de Larrea, et al. Blood 2015*
2. *Foli, et al. Amyloid 2011*

Can we screen for AL amyloidosis ?

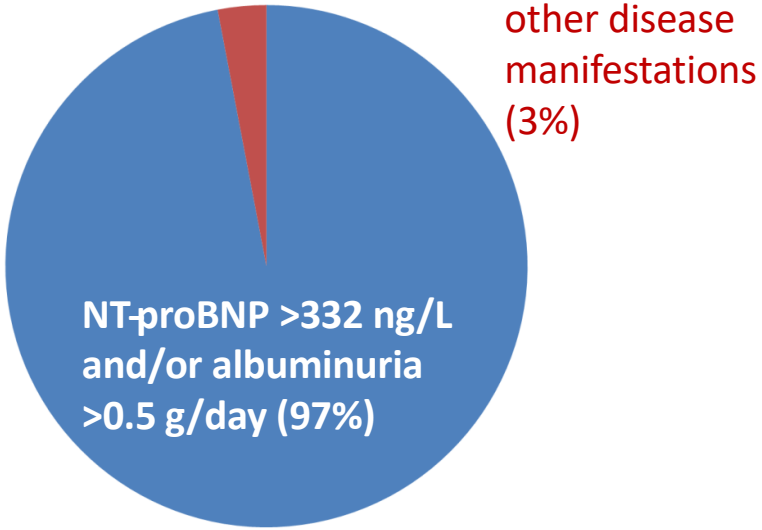
- Nine percent of patients with MGUS who progress develop AL amyloidosis (Kyle, et al. NEJM 2002)
- Patients with MGUS and abnormal FLCR should undergo life--long monitoring

- ~85% of patients with AL amyloidosis have abnormal FLCR at diagnosis



Merlini & Palladini. Hematology 2012
Merlini, et al. Blood 2013

- >95% of patients with AL amyloidosis have NT--proBNP >332 ng/L and/or albuminuria >0.5 g/day



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- >95% of patients with AL amyloidosis have NT–proBNP >332 ng/L and/or albuminuria >0.5 g/day

- Patients with MGUS and abnormal FLCR should have biomarkers of early amyloid organ involvement (**NT–proBNP and albuminuria**) included in their periodic workup

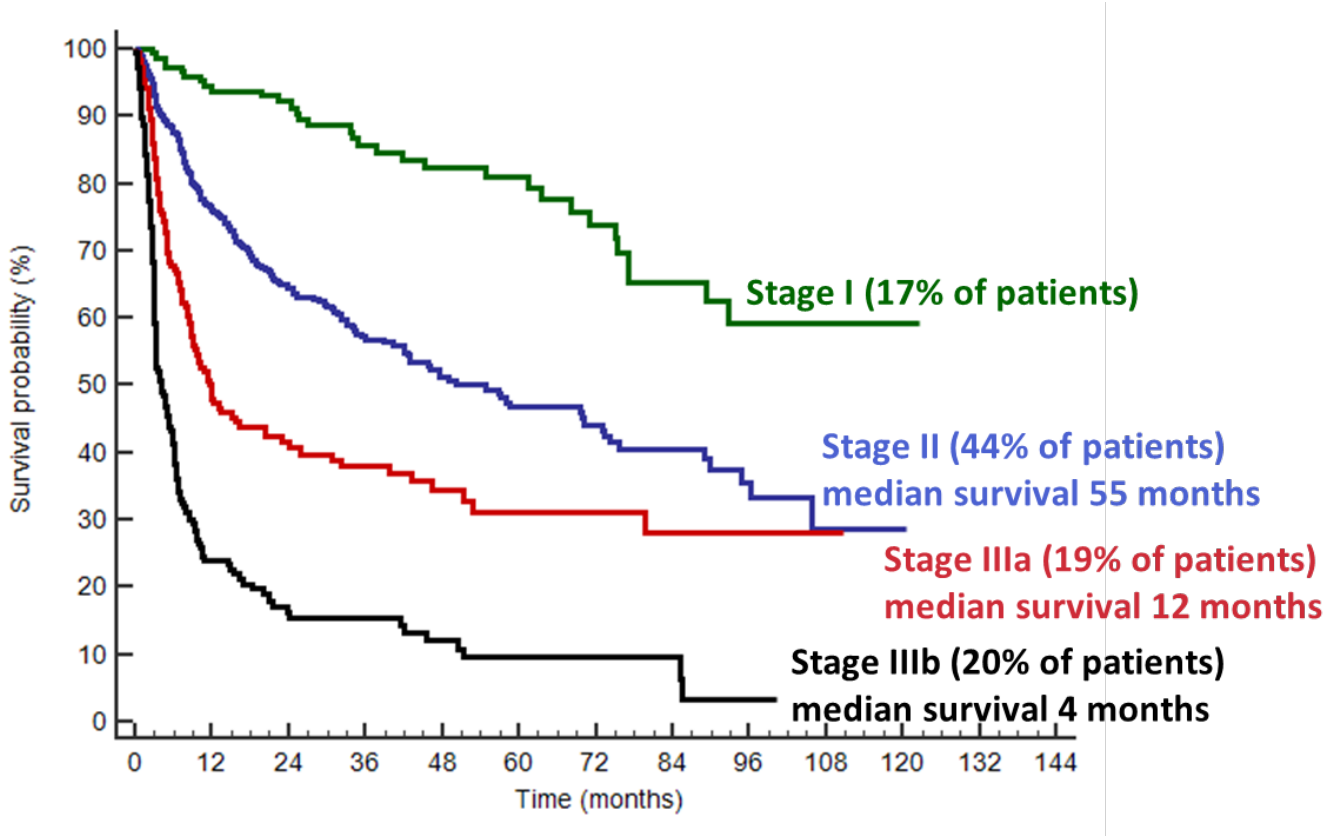
Merlini & Palladini. Hematology 2012
Merlini, et al. Blood 2013

Mayo Clinic / European staging system

Staging of AL amyloidosis

Dispenzieri, et al JCO 2004

Wechalekar, et al Blood 2013

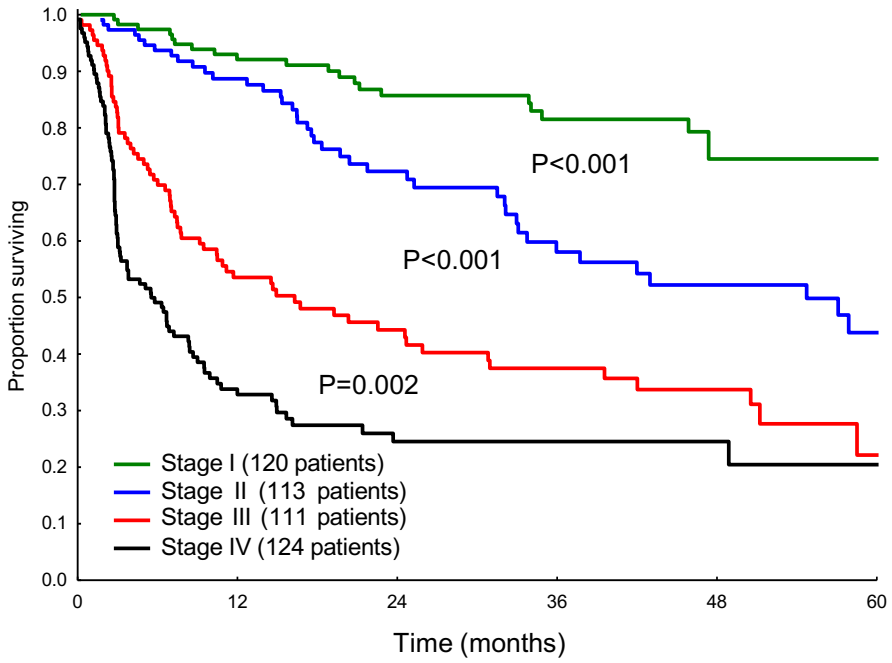


Staging is based on **NT–proBNP** (cutoff 332 ng/L) and **troponin I** (cutoff 0.1 ng/mL) with stage I, II, and III patients having 0, 1, or 2 both markers above the cutoffs

Very high (>8500 ng/L) NT–proBNP identifies patients with advanced cardiac dysfunction

Clonal markers predict survival in AL amyloidosis

Survival according to the revised Mayo Clinic staging system including FLC in the Pavia series

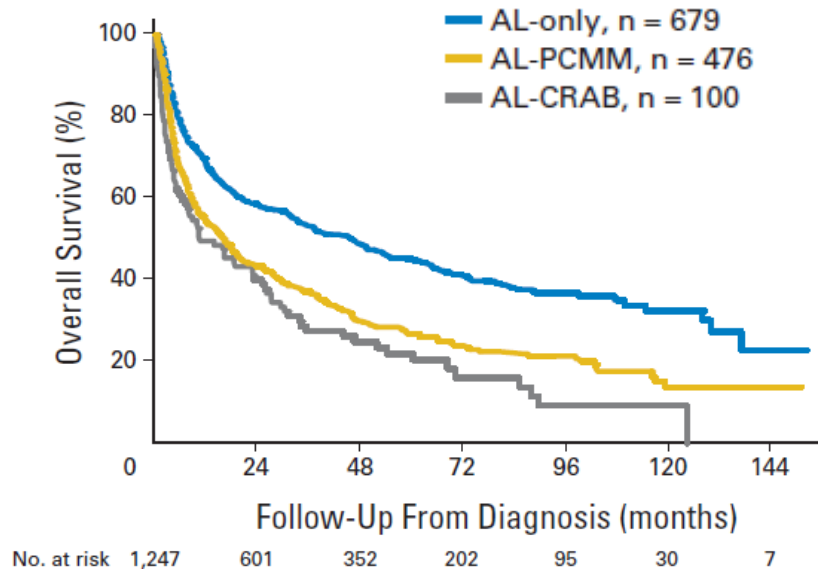


Revised staging system

NT-proBNP >1800 ng/L, cTnI >0.07 ng/L, dFLC >180 mg/L

Kumar, et al. JCO 2012
Kourelis, et al. JCO 2013

Survival according to BMPC infiltrate



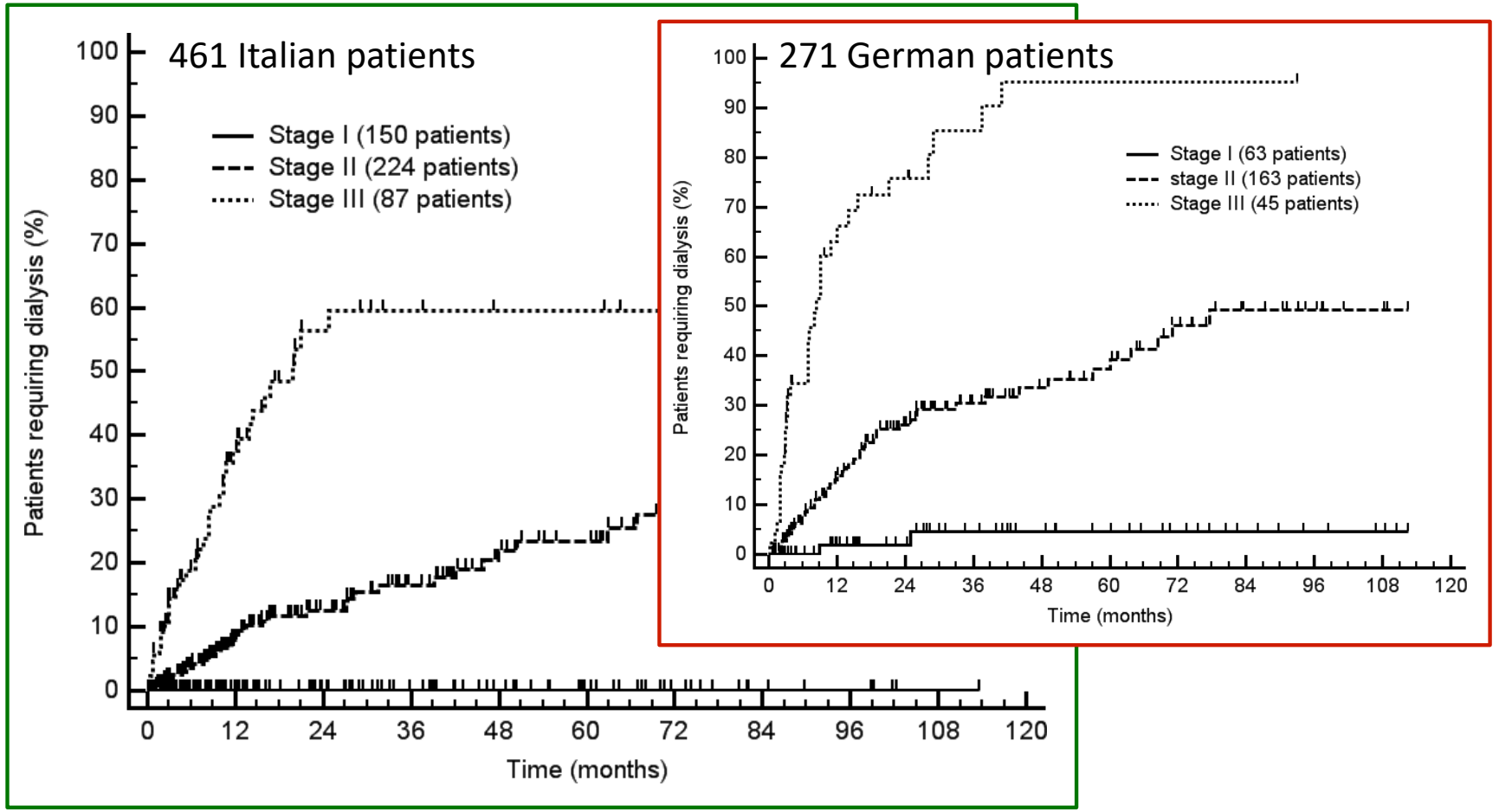
High frequency of t(11;14) translocation (~40–60%): lower benefit from bortezomib, greater benefit from melphalan

Patients with higher tumor burden benefit most from induction therapy pre–ASCT

Bochtler, et al. JCO 2015
Bochtler, et al. Blood 2016

Muchtar, et al. Leukemia 2016

A staging system for renal involvement



Palladini, et al. Blood 2014

Stage I: both proteinuria ≤5g/24h and eGFR ≥50 mL/min per 1.73 m^2
Stage II: either proteinuria >5g/24h or eGFR <50 mL/min per 1.73 m^2
Stage III: both proteinuria >5g/24h and eGFR <50 mL/min per 1.73 m^2

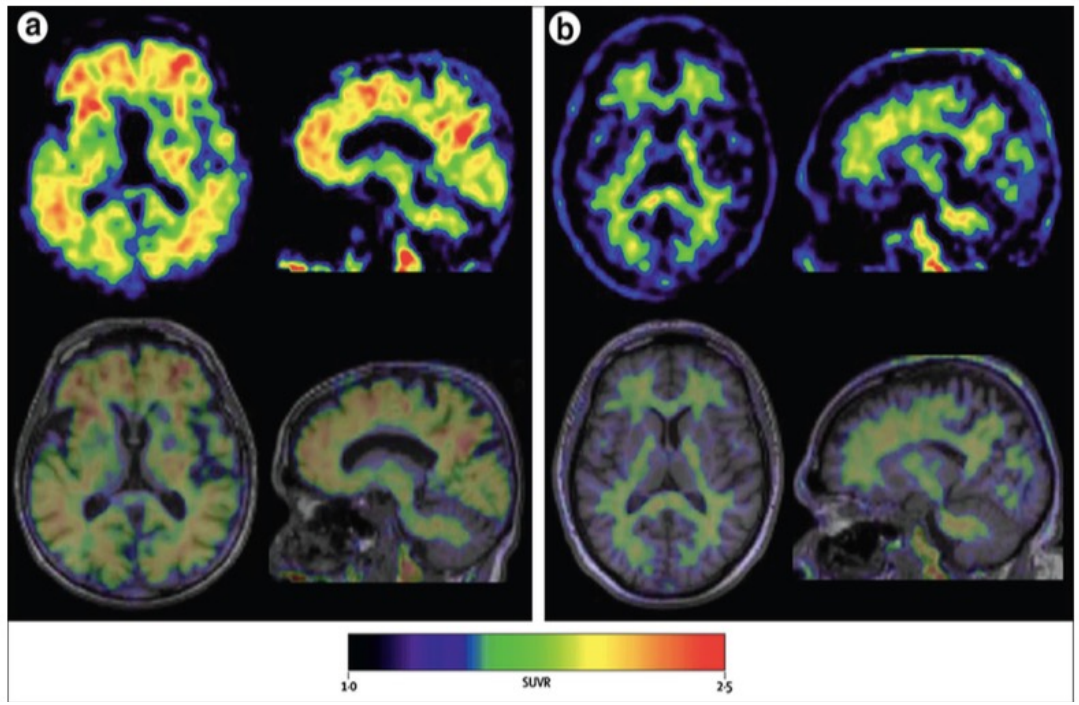
[18F]-FLORBETABEN PET/CT

- **18F-labeled polyethylene glycol** derivative with high affinity and specificity for beta-amyloid plaques.
- Tracer for routine clinical application to detect beta-amyloid plaques in the Alzheimer's disease (AD) brain

ALZHEIMER'S DISEASE DEMENTIA HEALTY CONTROL

PET

PET/MRI OVERLAY



- Healthy control only unspecific uptake in the white matter
- In Alzheimer's disease dementia patient extended to the outer gray matter.

Sabri O et al. "Beta-amyloid imaging with florbetaben". Clin Transl Imaging. 2015

	AL patients (n 33)
Age, years	65.2 (41-85)
Multiple Myeloma associated to AL amyloidosis, n	20 (33)
creatinine, mg/dL	1.49 (0.54-7.13)
NT-proBNP, ng/L	7944 (537-70000)
hs-Troponin T, ng/L	111,76 (25-203)
FLC ratio	443.89 (1.18-11700)
dFLC, ng/L	958,34 (1,22-19698)
24h proteinuria, mg/dL	2595 (119-9696)
Patients underwent to Cardiac Biopsy, n Patients positive to cardiac biopsy	17 (33) 17/17 100%
AL positive in Periombelical Fat, n	18 (33)
AL positive Bone Marrow Biopsy, n	10 (33)
AL positive Other Tissues Biopsy, n	8 (33)
[18F]-Florbetaben PET positive, n	33 (33)
Cardiac MRI performed, n	33(33)

RESULTS

- 29 patients (87,8 %) of study cohort presented elevated NT-pro BNP levels, as a cardiac damage sign
- Even though the high percentage of patients enrolled with renal impairement, creatinine levels in 60,6% of patients with renal involvement were normal
- Concerning the most relevant parameter of higher production of immunoglobulin light chains, FLC ratio and dFLC were normal in 3 patients

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[18F]-Florbetaben PET positive, n	33 (33)
Cardiac MRI performed, n	33(33)

RESULTS

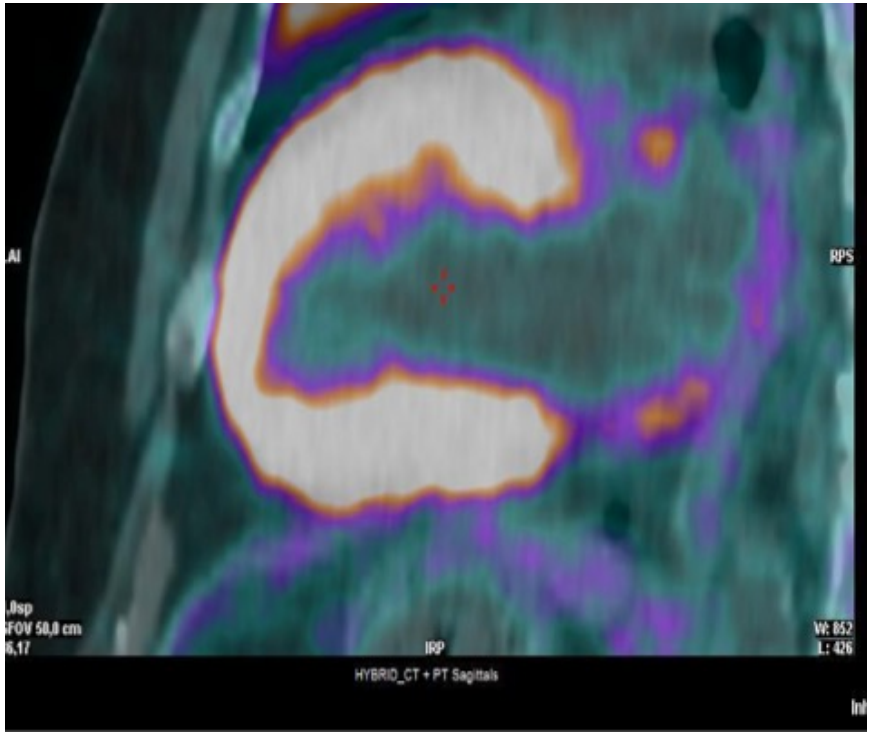
33/33 (100%) of AL patients demostrated cardiac uptake

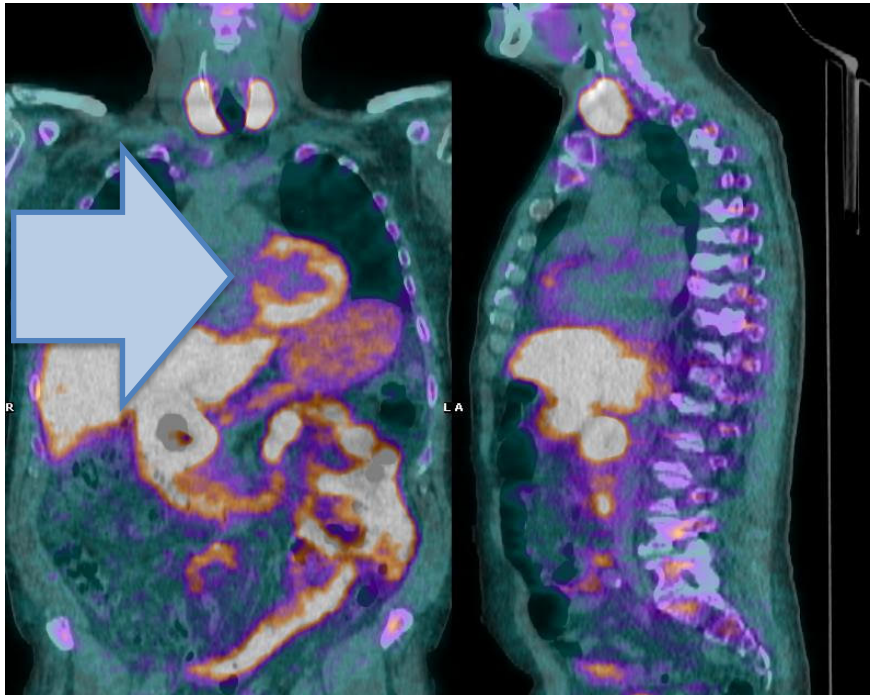
And

14/33 (42%) of AL patients demonstrated renal uptake

RESULTS

Cardiac uptake





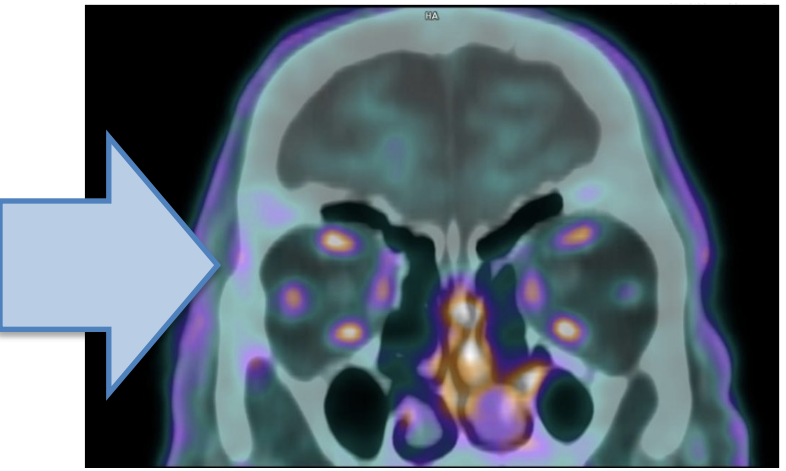
Schindler TH, et al 18F-Florbetaben and PET/CT Holds Promise for the Identification and Differentiation Among Cardiac Amyloidosis Entities. JACC Cardiovasc Imaging. 2021

RESULTS

In 8 patients who presented a demostrated histological diagnosis of AL amyloid in extra cardiac tissues, [18F]-florbetaben PET/CT uptake was also consistent

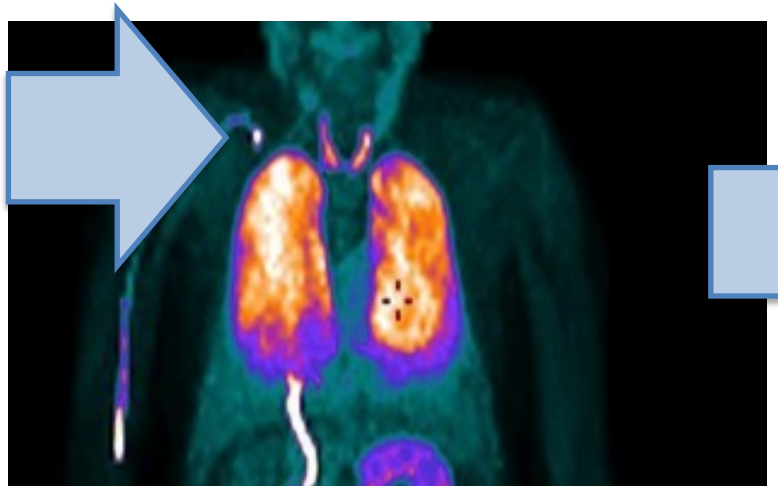
Extra cardiac uptake

Periorbital muscle



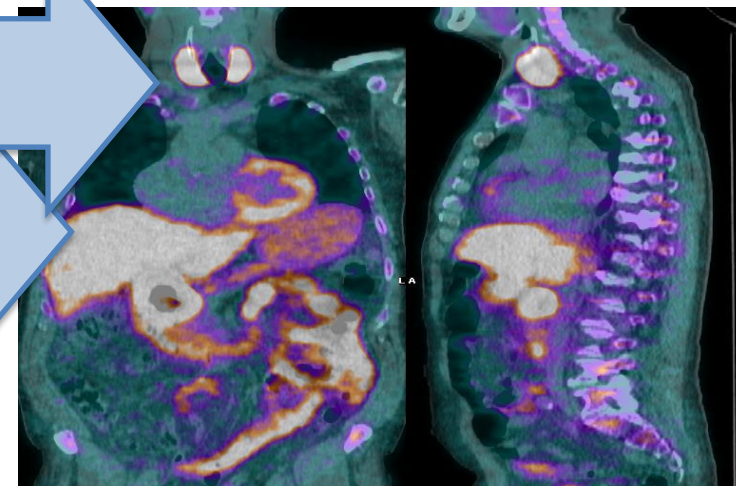
Patient 1

Thyroid



Patient 2

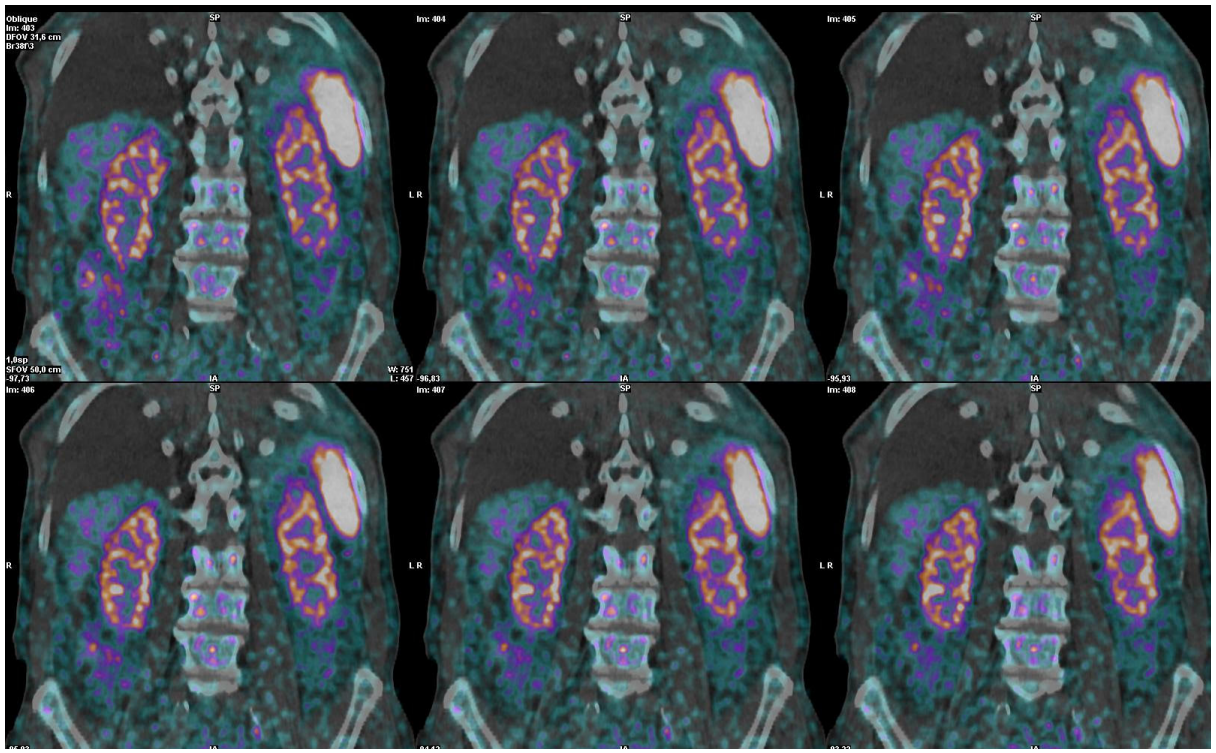
Thyroid and Liver



Patient 3

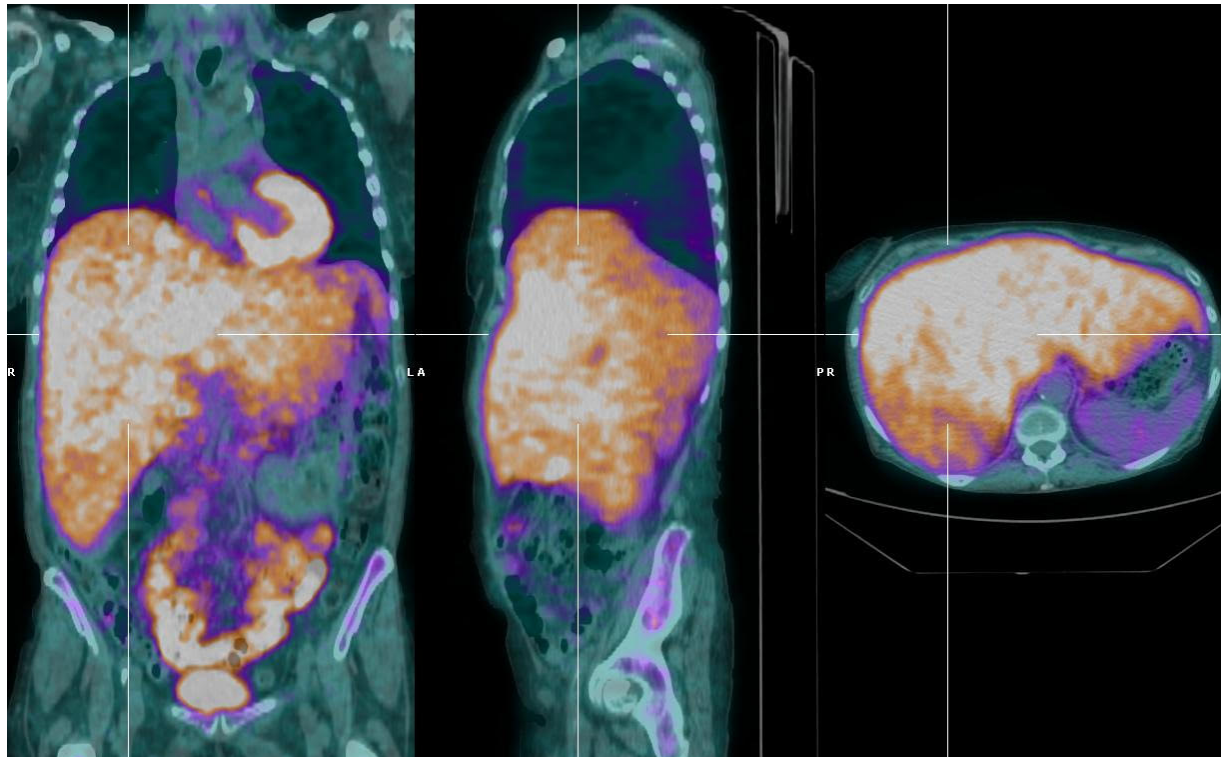
Extra cardiac uptake

Kidney



Patient 4

Liver



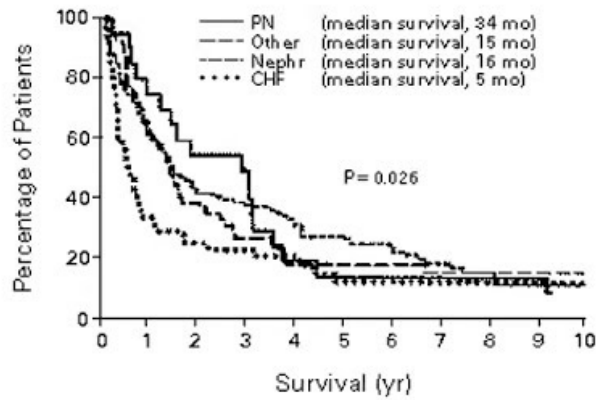
Patient 5

AMILOIDOSI AL

Terapia e prospettive

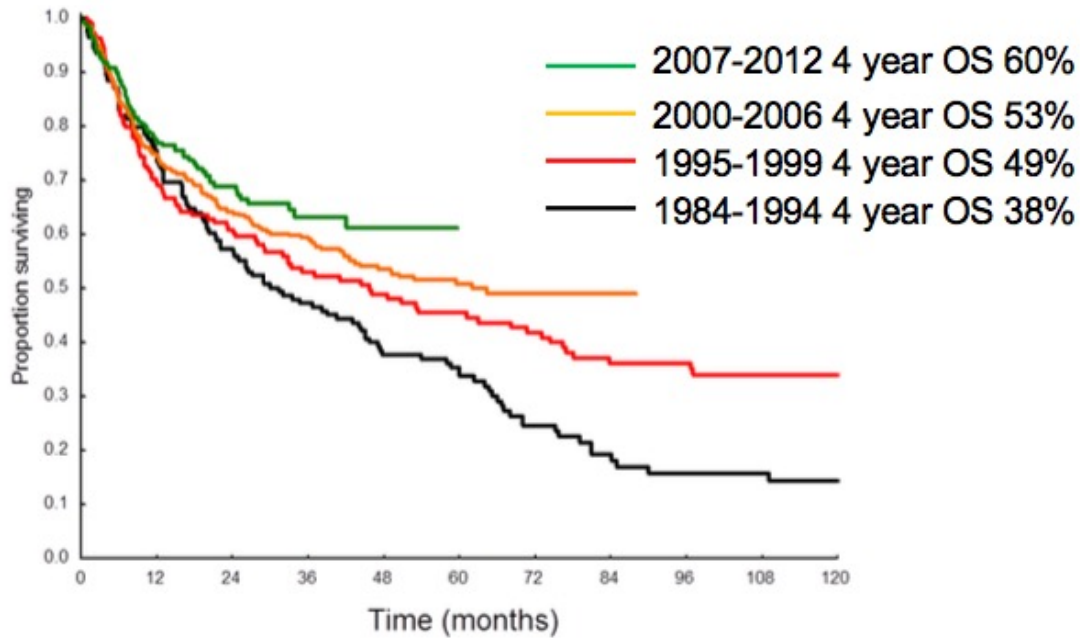
Treatment of AL amyloidosis

- **Historically**
  - **Melphalan-prednisone (MP) mainstay of treatment**
  - **Overall response rate: 25%**
  - **Overall survival: 12-13 month**
    - **Cardiac involvement: 5 months**



Skinner M et al. Am J Med. 1996.
Kyle R et al. NEJM 1997.

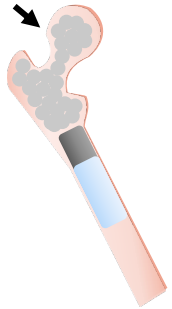
Improved outcomes in AL amyloidosis over the years



Merlini G 2012 Blood

Reduction in Light Chain Production

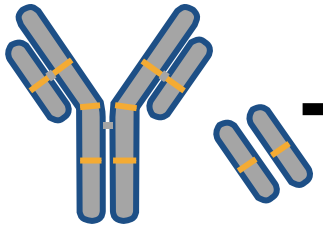
- Bortezomib
- Carfilzomib
- Daratumumab
- Elotuzumab
- Isatuximab
- Ixazomib
- Lenalidomide
- Pomalidomide
- Venetoclax



Abnormal plasma cells

Light Chain Overproduction

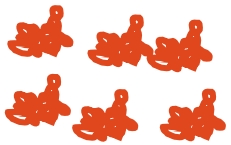
Immunoglobulin



Removal of Light Chain Amyloid Deposits

- Anselamimab (CAEL-101)
- Dezamizumab
- Birtamimab

Anti-fibril antibodies



Misfolded Light Chains

Light chain stabilizers likely to be in trials

Deposition Into Organs

Heart, kidney, liver, GI tract, soft tissue, peripheral/autonomic nervous system

Amyloid Fibrils

Inhibition of Amyloid Fibril Formation

- Doxycycline

Zhang. JACC Basic Transl Sci. 2019;24:4:438.

ISA/EHA guidelines for ASCT eligible patients: eligibility criteria

Clinical evaluation	Inclusion criteria	Exclusion criteria
Age	• ≤65 years (patients aged 66-69 years can be considered at referral centers after careful multidisciplinary discussion).	-
Performance status	• Performance status (ECOG) 0-2 (unless caused by peripheral neuropathy).	-
Blood pressure	• Supine systolic blood pressure ≥90 mmHg	• Orthostatic hypotension refractory to medical therapy.
Heart assessment	• NYHA class I or II (if heart involvement is present). • Ejection fraction by echocardiography ≥40%. • Cardiac stage I or II (cardiac stage III patients can be considered at referral centers after careful multidisciplinary discussion). • NT-proBNP <5000 ng/L. • Troponin I <100 ng/L or troponin T <60 ng/L or hs-troponin T <75 ng/L	• Symptomatic and/or medically refractory ventricular and atrial arrhythmias. • Uncompensated heart failure.
Liver assessment	• Direct bilirubin <2 mg/dL	-
Kidney assessment	• eGFR >50 mL/min per 1.73 m^2 (patients whose eGFR is between 50 and 30 mL/min can be considered at referral centers after careful multidisciplinary discussion). • Patients on chronic and stable schedule of dialysis should not be excluded.	-
Respiratory function	• Oxygen saturation ≥95% on room air. • DLCO >50%.	• Symptomatic and/or medically refractory pleural effusions.
Hemorrhagic risk assessment	-	• Factor X deficiency with factor X level of <25% or/and evidence of active bleeding. • Extensive GI involvement with evidence of active GI bleeding or risk of bleeding.

Sanchorawala, et al. Amyloid 2022

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

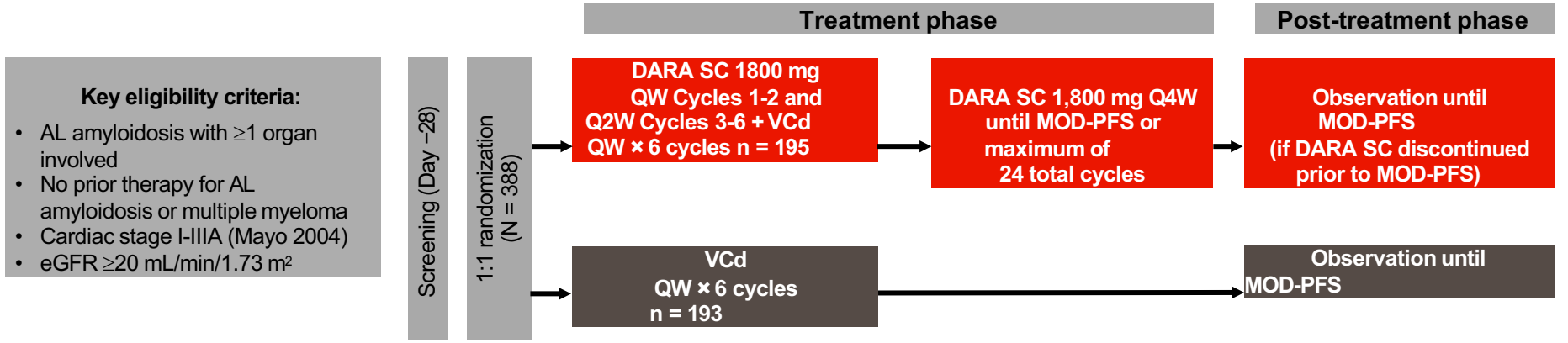
Efstathios Kastritis[1], Giovanni Palladini[2,3], Monique C Minnema[4], Ashutosh D Wechalekar[5], Arnaud Jaccard[6], Hans C Lee[7], Vaishali Sanchorawala[8], Peter Mollee[9], Jin Lu[10], Stefan Schönland[11], Moshe E Gatt[12], Kenshi Suzuki[13], Kihyun Kim[14], M Teresa Cibeira[15], Manisha Bhutani[16], 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; , LLC, Spring House, PA, USA; [26] LLC, Leiden, The Netherlands; [29]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

ANDROMEDA: Study Design

- ANDROMEDA is a randomized, open-label, phase 3 study of DARA plus VCd (D-VCd) versus VCd alone in patients with newly diagnosed AL amyloidosis



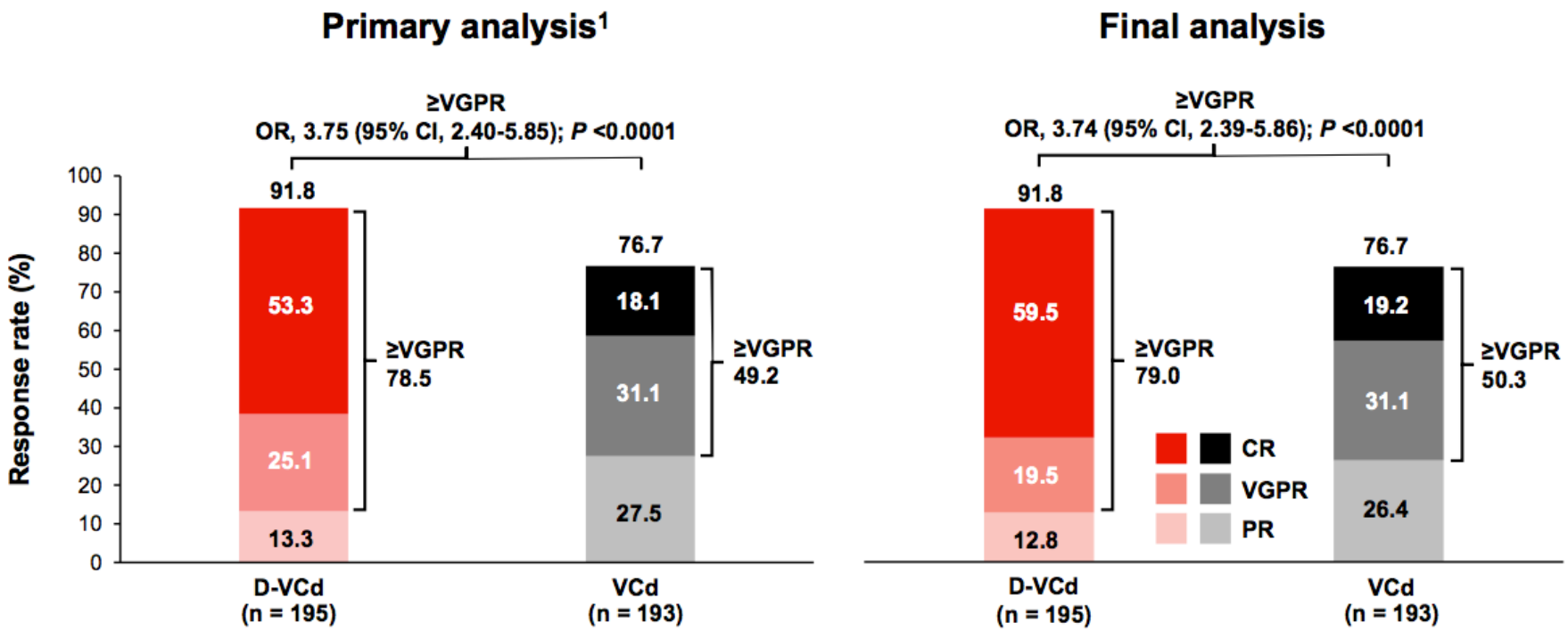
Stratification criteria:
- Cardiac stage (I vs II vs IIIA)
- Transplant typically offered in local country (yes vs no)
- Creatinine clearance (≥60 mL/min vs <60 mL/min)

Primary endpoint: Overall HemCR rate[a]

Secondary endpoints: MOD-PFS (end-stage cardiac or renal disease, hematologic progression, or death),[b] OS, organ response rate, time to hematologic response, safety

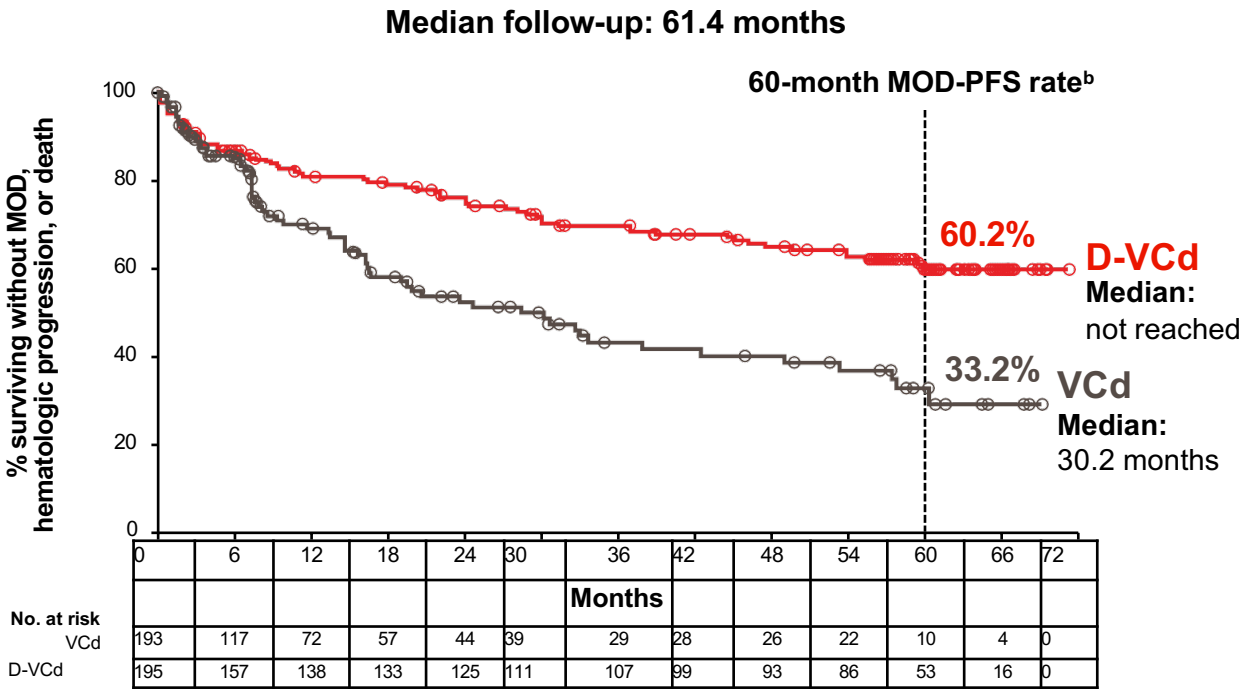
D-VCd, daratumumab 1,800 mg co-formulated with recombinant human hyaluronidase PH20 [rHuPH20; 2,000 U/mL; ENHANZE® drug delivery technology; Halozyme, Inc., San Diego, CA, USA)] plus VCd; eGFR, estimated glomerular filtration rate; SC, subcutaneous; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks. [a]Defined here as normalization of free light-chain (FLC) levels and ratio (FLCr) and negative serum and urine immunofixation, confirmed at a subsequent visit; normalization of uninvolved FLC level and FLCr were not required if involved FLC was lower than the upper limit of normal; [b]A composite endpoint defined as end-stage cardiac disease (requiring cardiac transplant, left ventricular assist device, or intra-aortic balloon pump), end-stage renal disease (requiring hemodialysis or renal transplant), hematologic progression per consensus guidelines,[1] or death. 1. Comenzo RL,

ANDROMEDA: Overall Hematologic Response at the Final Analysis



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

ANDROMEDA: Major Organ Deterioration (MOD)–PFS[a]



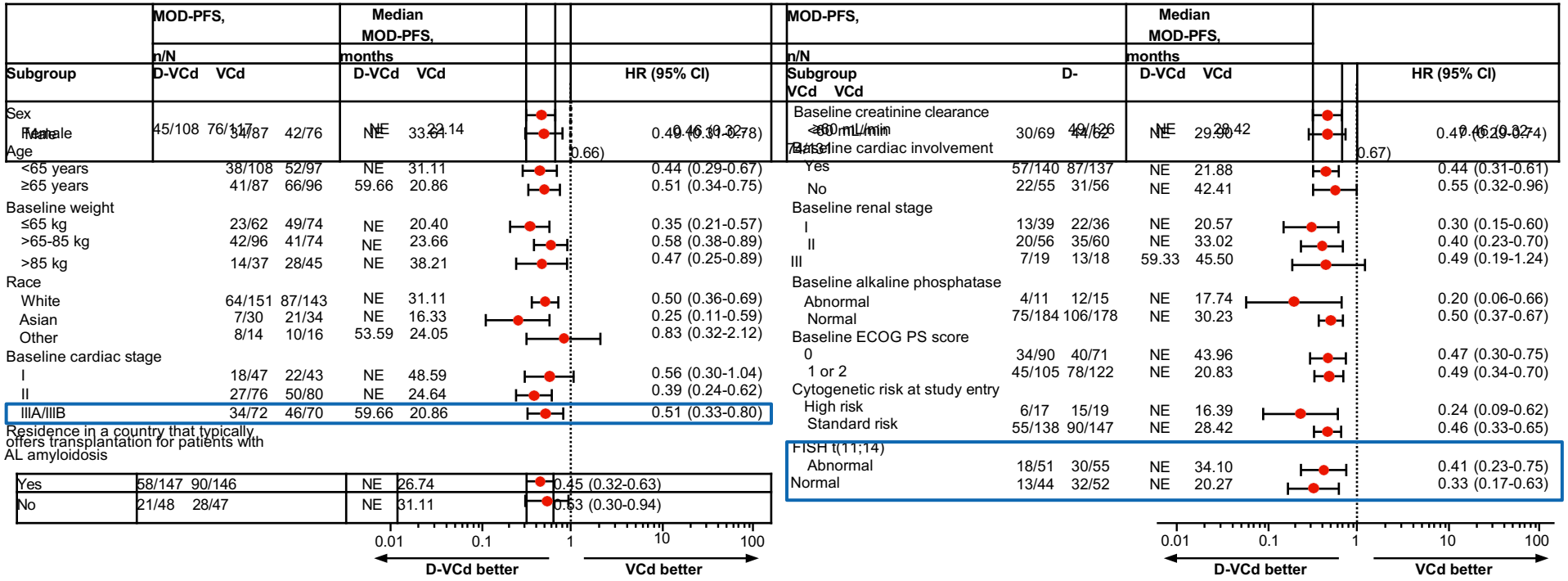
- **HR, 0.44 (95% CI, 0.31-0.63);**
  P <0.0001[c,d]

	D-VCd (n = 195)	VCd (n = 193)
MOD-PFS event, n	79	118
Hematologic progression	41	63
MOD	3	11
Death	35	44

The addition of DARA to VCd significantly improved MOD-PFS versus VCd

aMOD-PFS is a composite endpoint defined as end-stage cardiac disease (requiring cardiac transplant, left ventricular assist device, or intra-aortic balloon pump), end-stage renal disease (requiring hemodialysis or renal transplant), hematologic progression per consensus guidelines, or death. bKaplan–Meier estimates. cMOD-PFS was analyzed by employing the inverse probability of censoring weight method. dCrossing the prespecified

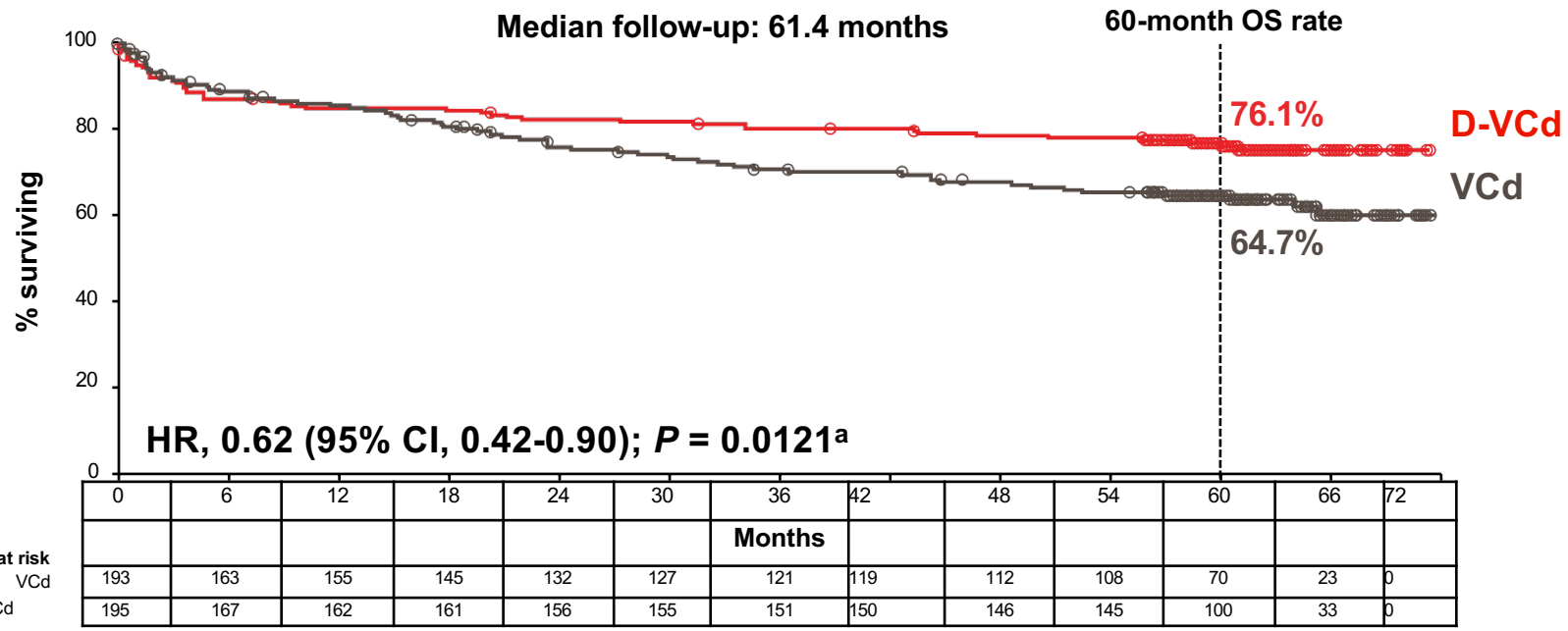
ANDROMEDA: Prespecified Subgroup Analysis of Major Organ Deterioration (MOD)–PFS



The addition of DARA to VCd provided MOD-PFS benefit across preplanned relevant subgroups

NE, not estimable; FISH, fluorescence in situ hybridization. MOD-PFS is a composite endpoint defined as end-stage cardiac disease (requiring cardiac transplant, left ventricular assist device, or intra-aortic balloon pump), end-stage renal disease (requiring hemodialysis or renal transplant), hematologic progression per consensus guidelines, or death.

ANDROMEDA: Overall Survival

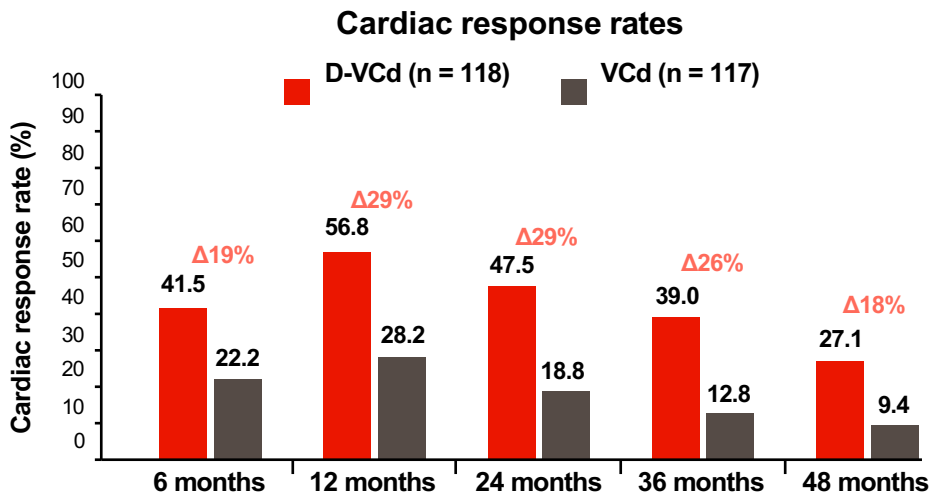


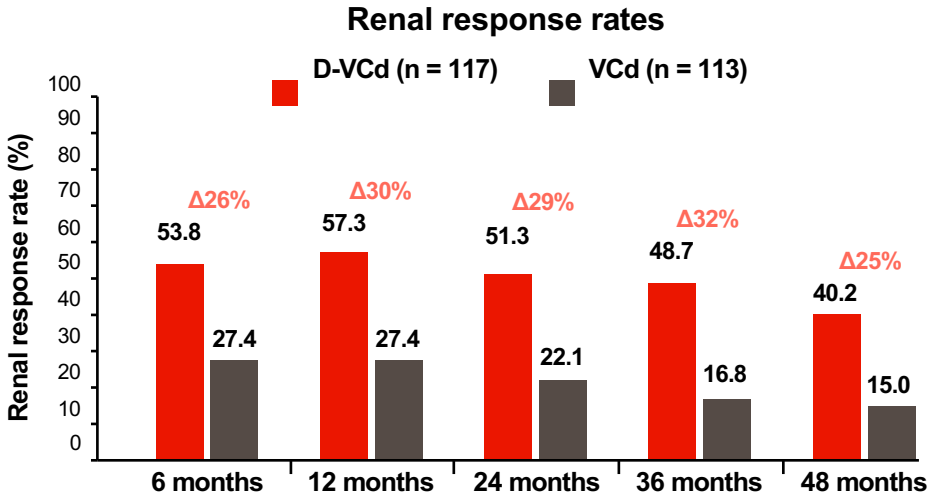
No. at risk	0	6	12	18	24	30	36	42	48	54	60	66	72
							Months						
VCd	193	163	155	145	132	127	121	119	112	108	70	23	0
D-VCd	195	167	162	161	156	155	151	150	146	145	100	33	0

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

aCrossing the prespecified stopping boundary of 0.0163.

ANDROMEDA: Cardiac and Renal Response Rates

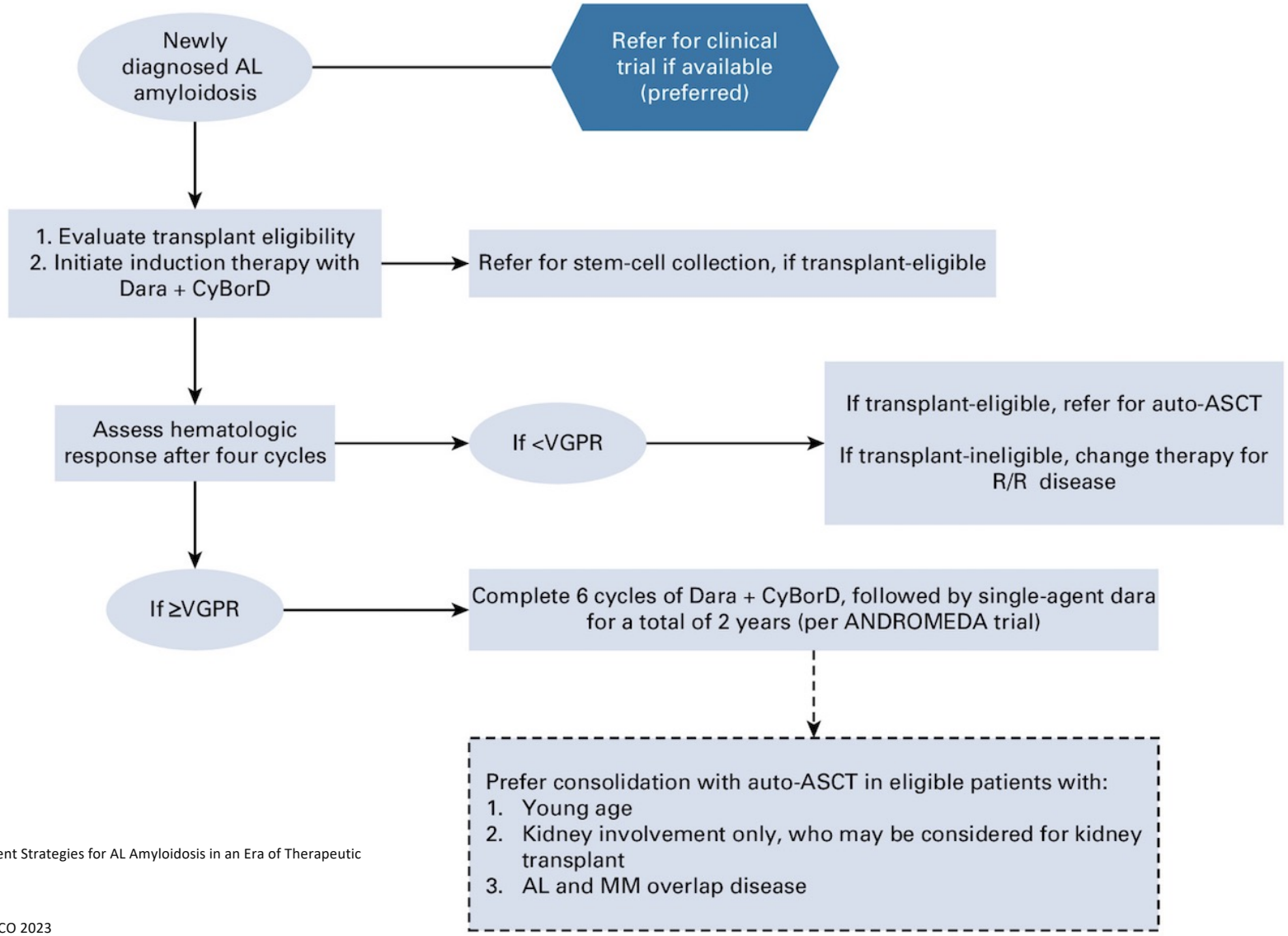




Graded response, %	D-VCd	VCd
Cardiac CR	40.7	13.7
Cardiac ≥VGPR	64.4	31.6

The addition of DARA to VCd led to 2 to 3 times higher cardiac and renal response rates versus VCd across study time points

CarCR, cardiac complete response. Both cardiac and renal response rates were determined by independent review committee assessment. Cardiac and renal response rates at a specific time point were calculated as the number of patients who had cardiac/renal response at the specific time point within a 1-month window; the denominator remained unchanged at each time point and represents the response-evaluable population. The cardiac/renal response rates displayed here are results without censoring non–cross-resistant anti–plasma therapy.



Diagnostic and Treatment Strategies for AL Amyloidosis in an Era of Therapeutic

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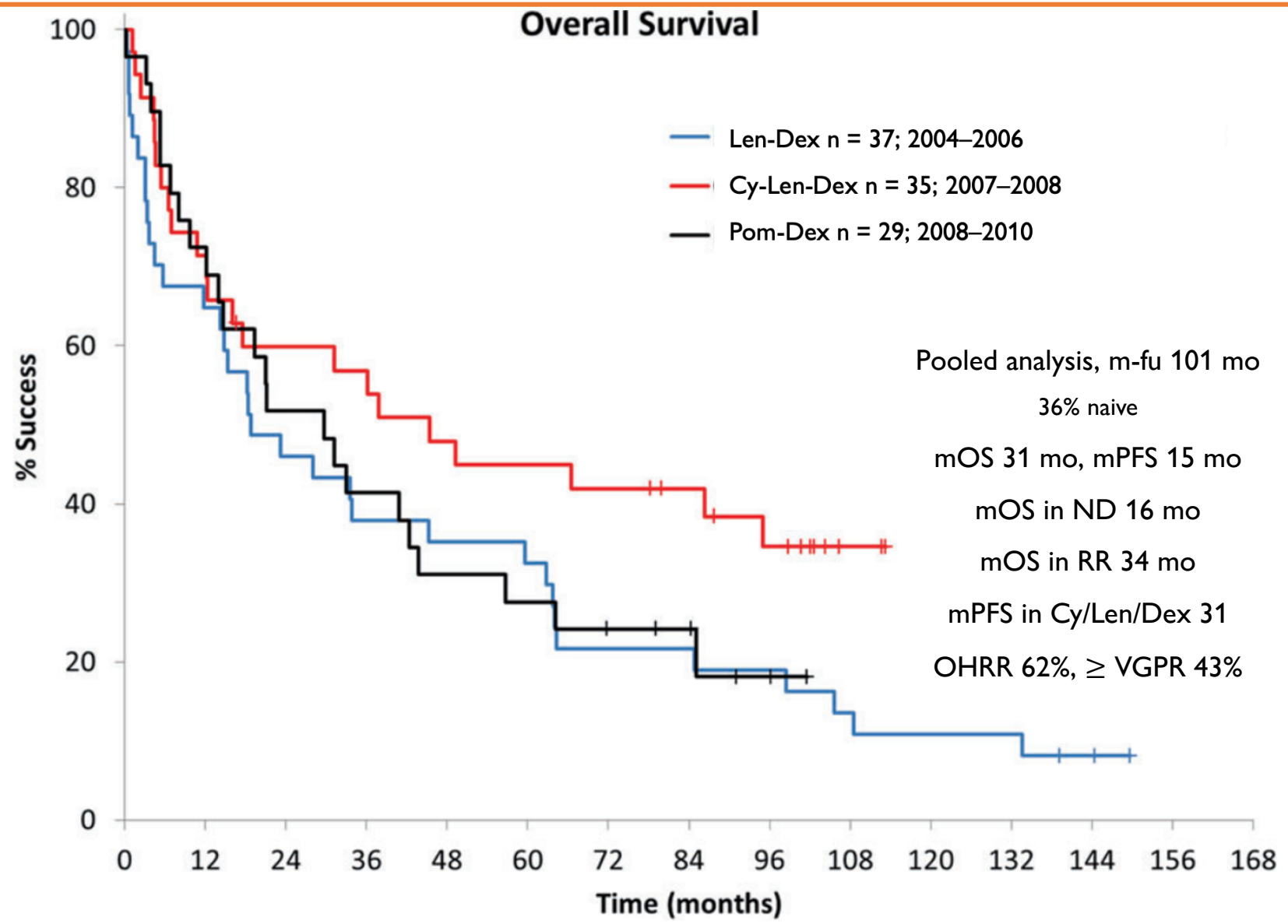


Pooled analysis, m-fu 101 mo

36% naive

mOS 31 mo, mPFS 15 mo

mOS in ND 16 mo

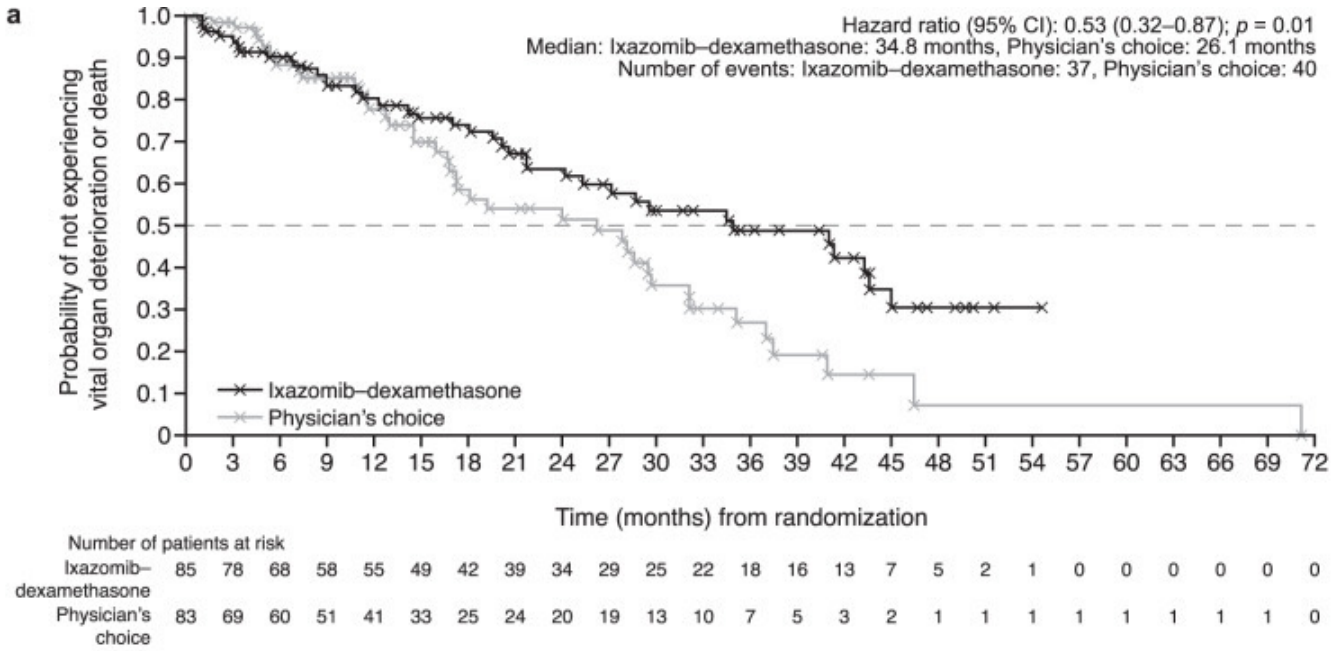
mOS in RR 34 mo

mPFS in Cy/Len/Dex 31

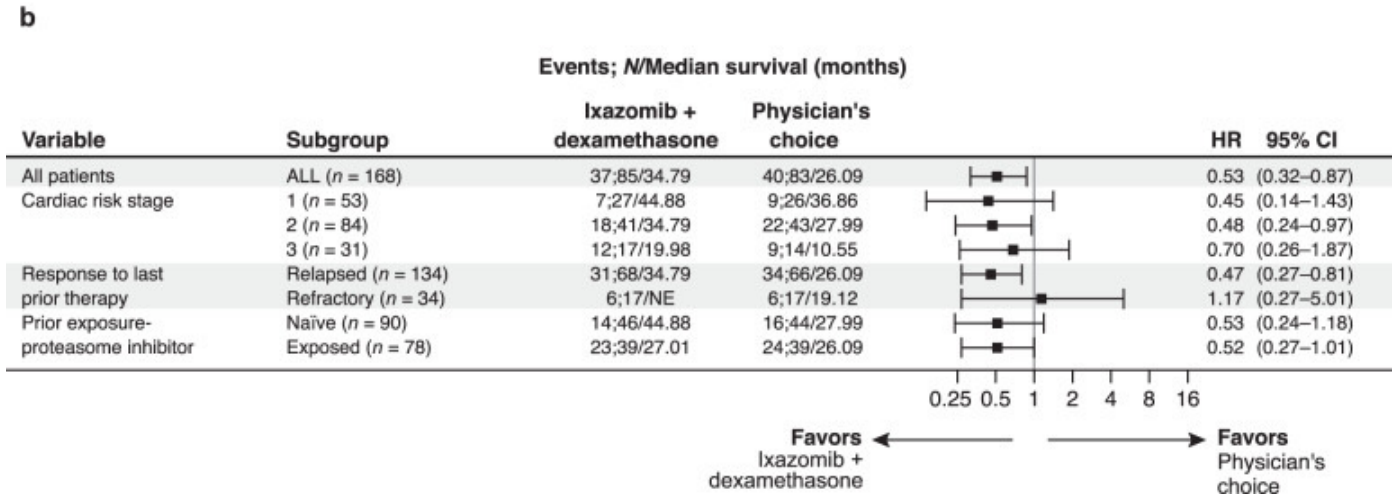
OHRR 62%, ≥ VGPR 43%

Time to vital organ deterioration or mortality in the intent-to-treat population

a



b

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Delegazioni Emilia Romagna e Toscana
Gli ematologi insieme contro le malattie rare
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Bologna, Aula Prodi