Organizado por:

Clínica Universidad de Navarra

PUESTA AL DÍA

HEMATOLOGÍA EN 48H [LO QUE DEBES CONOCER PARA TU PRÁCTICA CLÍNICA]

X EDICIÓN

ACTUALÍZATE 48 HORAS

# Amiloidosis AL: una visión contemporánea

**Ramón Lecumberri**

*Clínica Universidad de Navarra, Pamplona*

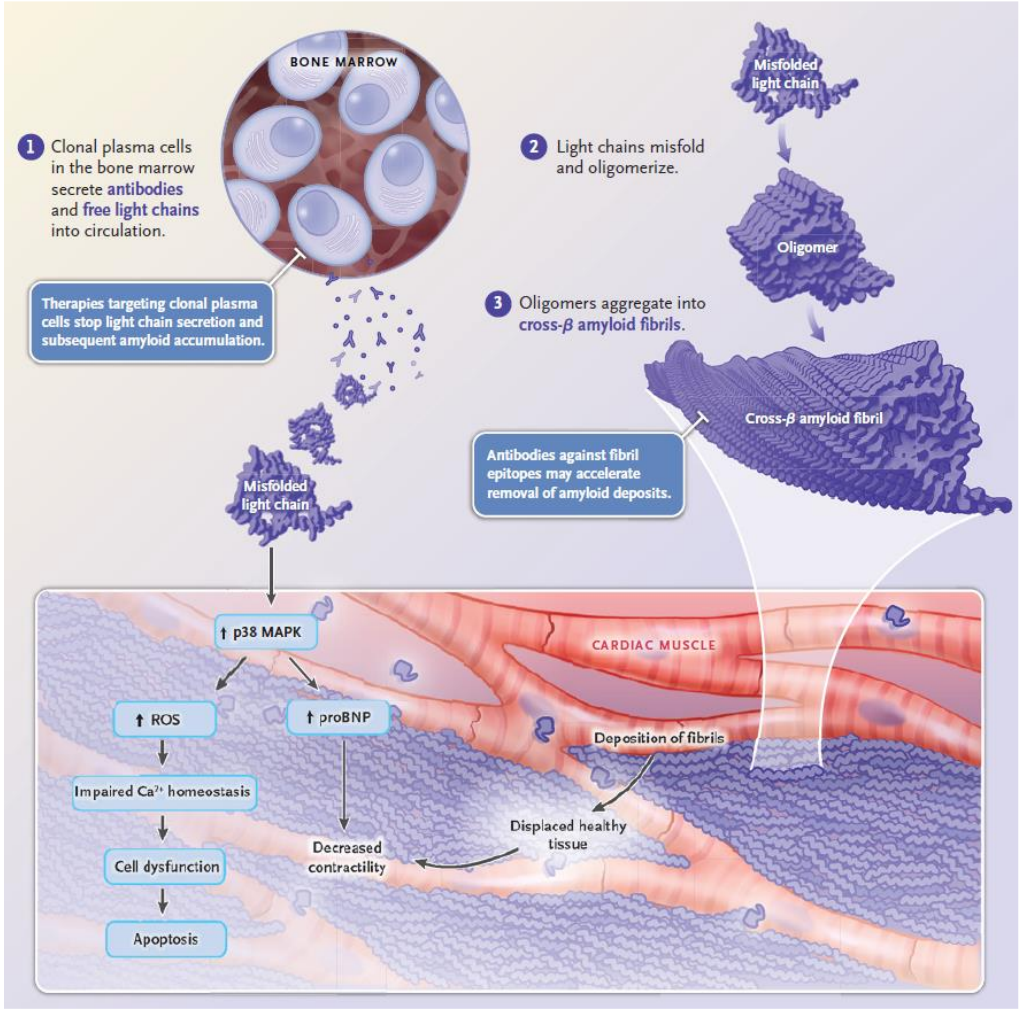
# Conflictos de interés

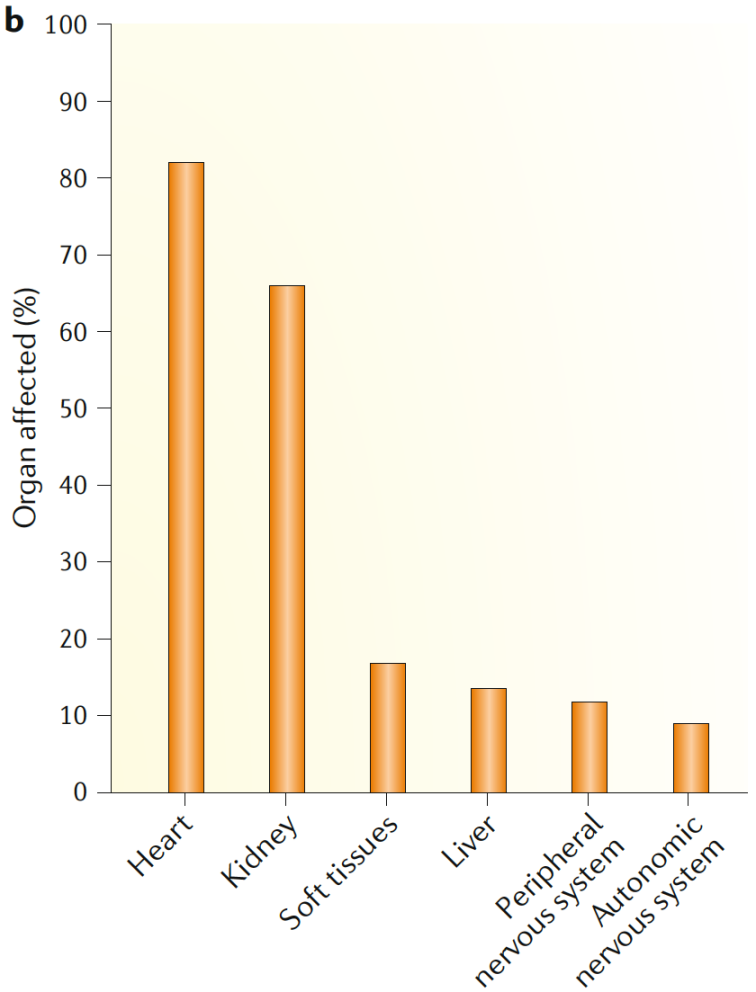
| | |
|---|---|
| Ayudas a la investigación | Haemalogix |
| Empleado | N/A |
| Consultor | N/A |
| Acciones | N/A |
| Ponente | Janssen |
| Honorarios | N/A |
| Advisory Board | Janssen, Regeneron, Prothena |

# Amiloidosis AL

Incidencia: 10-15 casos por millón de personas-año

10% de los pacientes con mieloma múltiple pueden asociar depósitos de amiloide AL



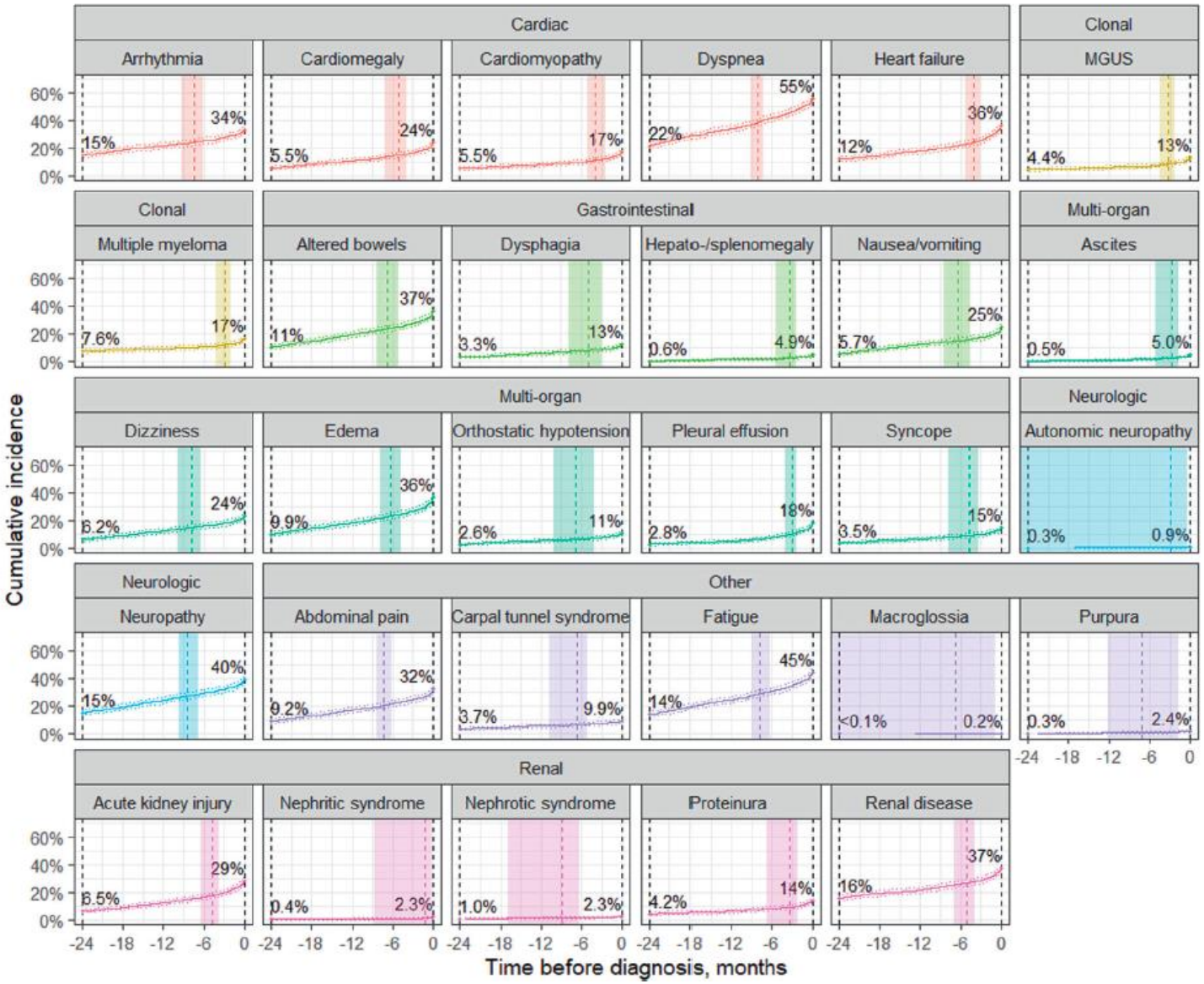




Merlini G et al. Nat Rev Dis Primers, 2018

Sanchorawala V. N Engl J Med, 2024

# Agenda

- Diagnóstico precoz
- Tratamiento de primera línea
  - Objetivos de respuesta
  - Enfermedad mínima residual
  - Papel del mantenimiento
  - Rol del auto-TPH
- Tratamiento de la recaída
- Perspectivas de futuro



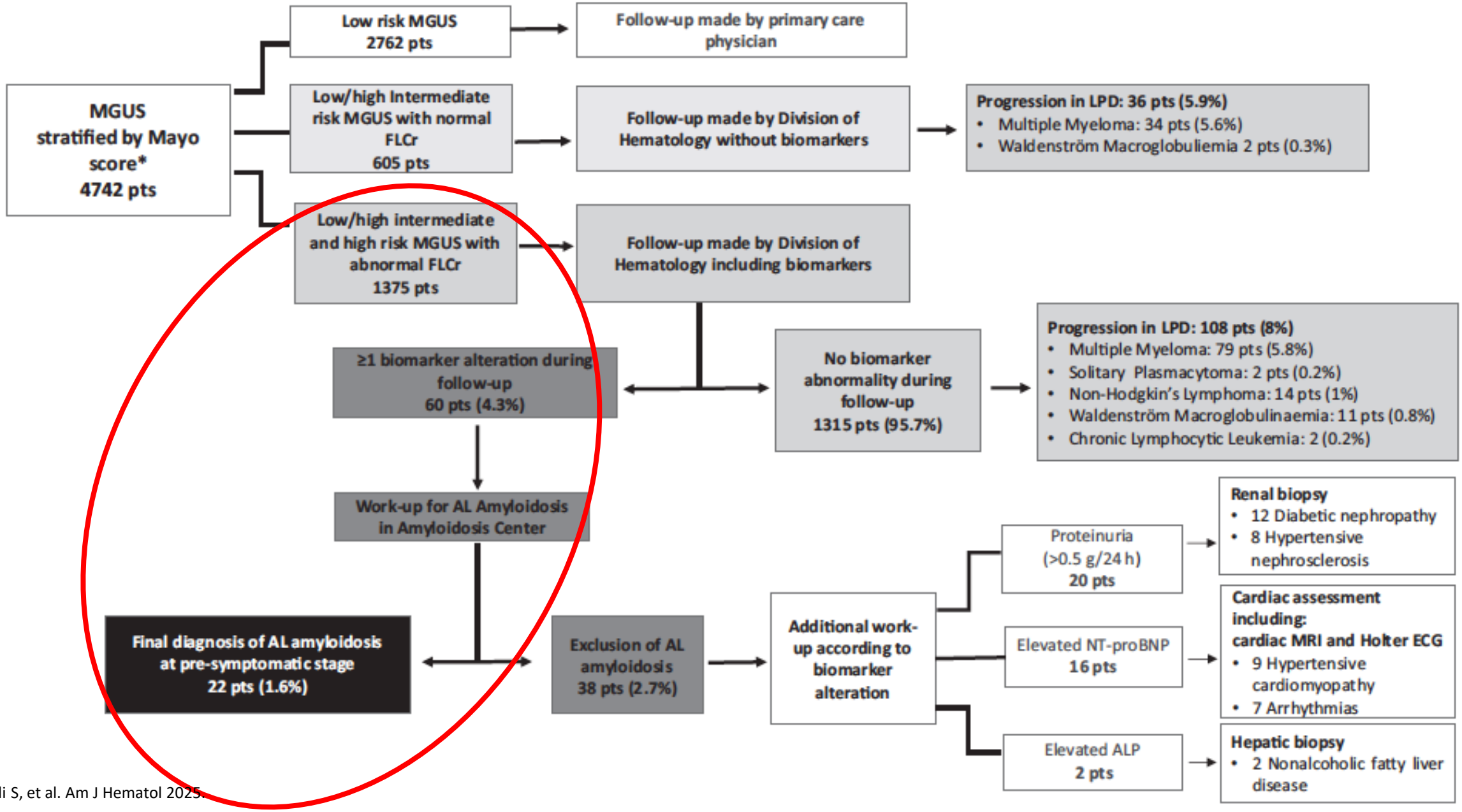

- **Median time between symptoms and diagnosis > 1 year**
- **Median number of specialists visited: 4-5**
- **Monoclonal Gammopathy already known in 30% before diagnosis**


Louzada I, et al. Adv Ther 2015.
Hester LL, et al. Eur J Haematol 2021.
Palladini G, et al. Blood 2021.
Singh A, et al. Blood Cancer J 2024.

- MGUS with FLC impairment
  - Pro-BNP
  - 24h proteinuria (albuminuria)
  - Alkaline phosphatase

- MGUS/Multiple Myeloma with:
  - Atypical symptoms
  - Carpal tunnel syndrome (bilateral)
  - Low-voltage ECG

Palladini G, et al. Blood Cancer J 2023.




Mangiacavalli S, et al. Am J Hematol 2025.

**En un futuro próximo**:

- Propiedades de la cadena ligera monoclonal circulante
- Caracterización del clon de células plasmáticas
- Pruebas de imagen de órganos afectados

**Algoritmos de IA/Machine learning**

# Caso clínico

Mujer de 79 años

ANTECEDENTES PERSONALES

- Dislipemia
- Fibrilación auricular
- ERC 4 A2 no filiada
- Proteína monoclonal desde hace 20 años
- Ingesta de AINES de forma crónica

No antecedentes familiares de interés

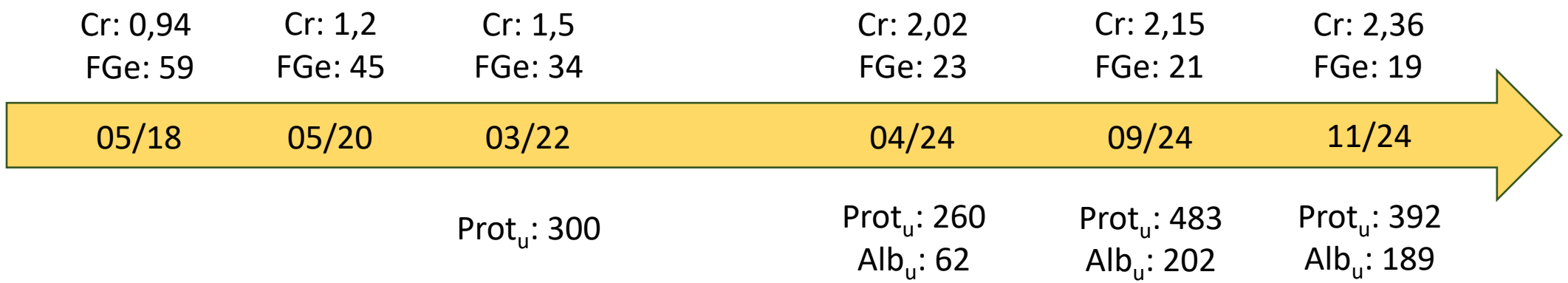
Medicación habitual:

- Apixabán 2.5 mg: 1-0-1
- Pravastatina 20 mg: 0-0-1
- Clonazepam 1mg: 0-0-1
- Calcio y omega 3

# Caso clínico

## HISTORIA ACTUAL

En seguimiento por Medicina interna y Nefrología en otro centro.




Desestimada biopsia renal por edad

Cr (creatinina): mg/dL .FGe (filtrado glomerular estimado): ml/min/1.73m$^2$. Prot$_u$(proteinuria): mg/g .Alb$_u$(Albuminuria): mg/g

# Caso clínico

## Estudios complementarios

- C3 y C4 normales
- Proteinuria mixta, con presencia de albúmina e inmunoglobulinas policlonales
- sCM IgG-lambda de 0,97g/dL
- Cadenas ligeras libres kappa: 57 mg/L
- Cadenas ligeras libres lambda: 98 mg/L
- Cociente kappa/lambda: 0,64
- No hipercalcemia, anemia ni lesiones esqueléticas
- BMO: 5% CP (97% con fenotipo patológico)
- Sin alteraciones citogenéticas/FISH

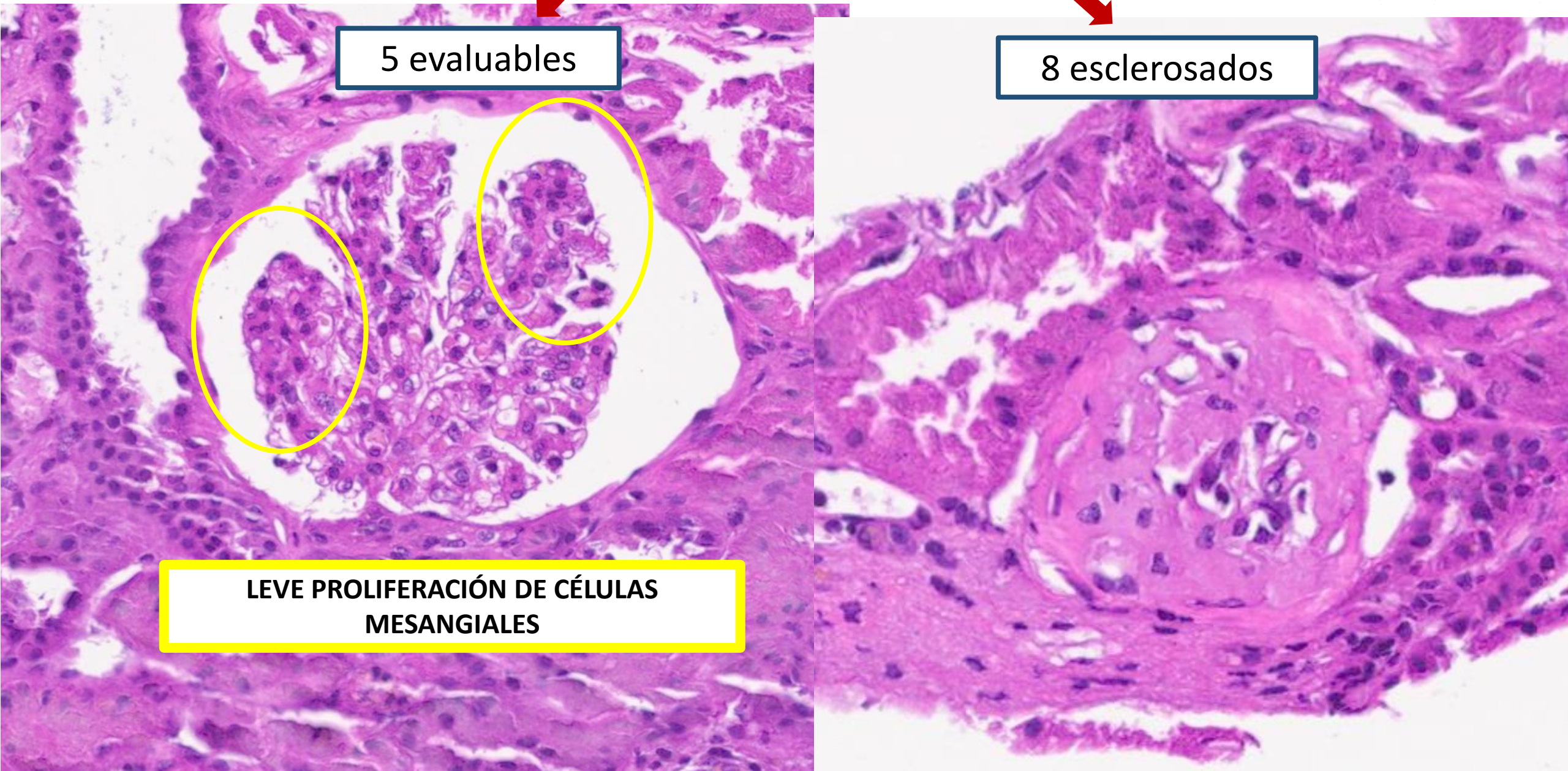
**Biopsia renal**

# Biopsia renal

13 GLOMÉRULOS

5 evaluables

8 esclerosados



**LEVE PROLIFERACIÓN DE CÉLULAS MESANGIALES**

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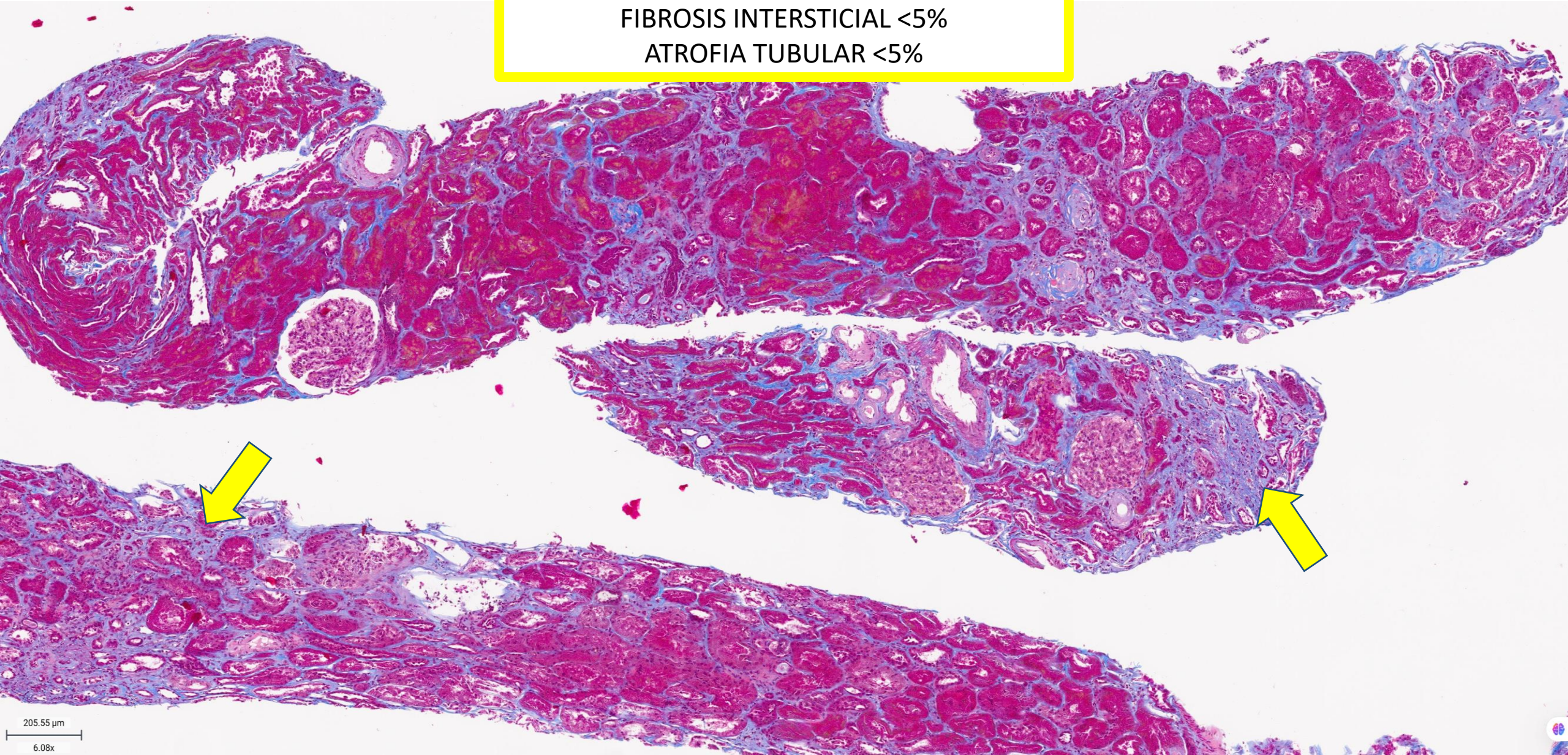
# Biopsia renal

INTERSTICIO

FIBROSIS INTERSTICIAL <5%
ATROFIA TUBULAR <5%

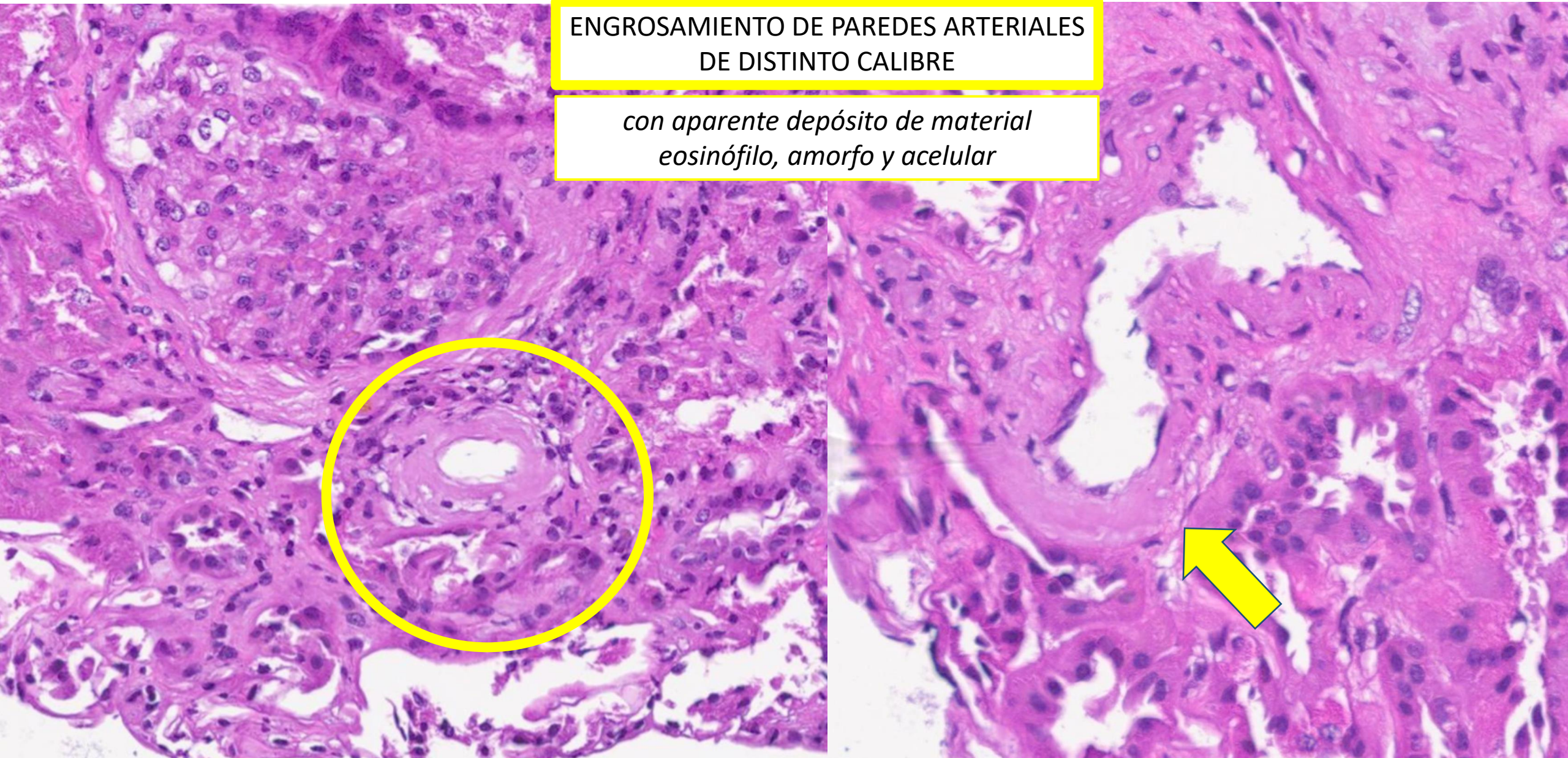


# Biopsia renal

VASOS

ENGROSAMIENTO DE PAREDES ARTERIALES DE DISTINTO CALIBRE

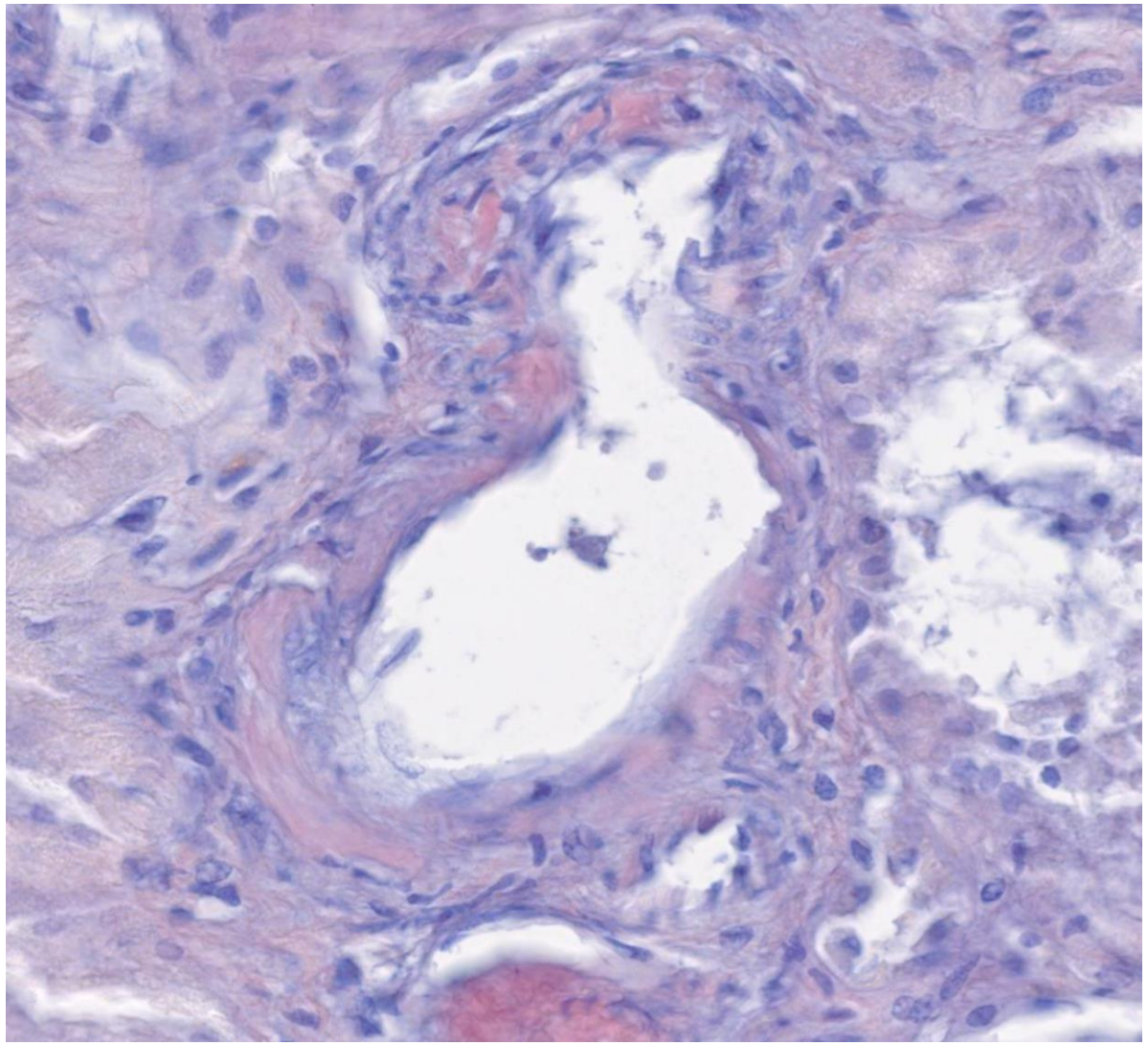
*con aparente depósito de material eosinófilo, amorfo y acelular*

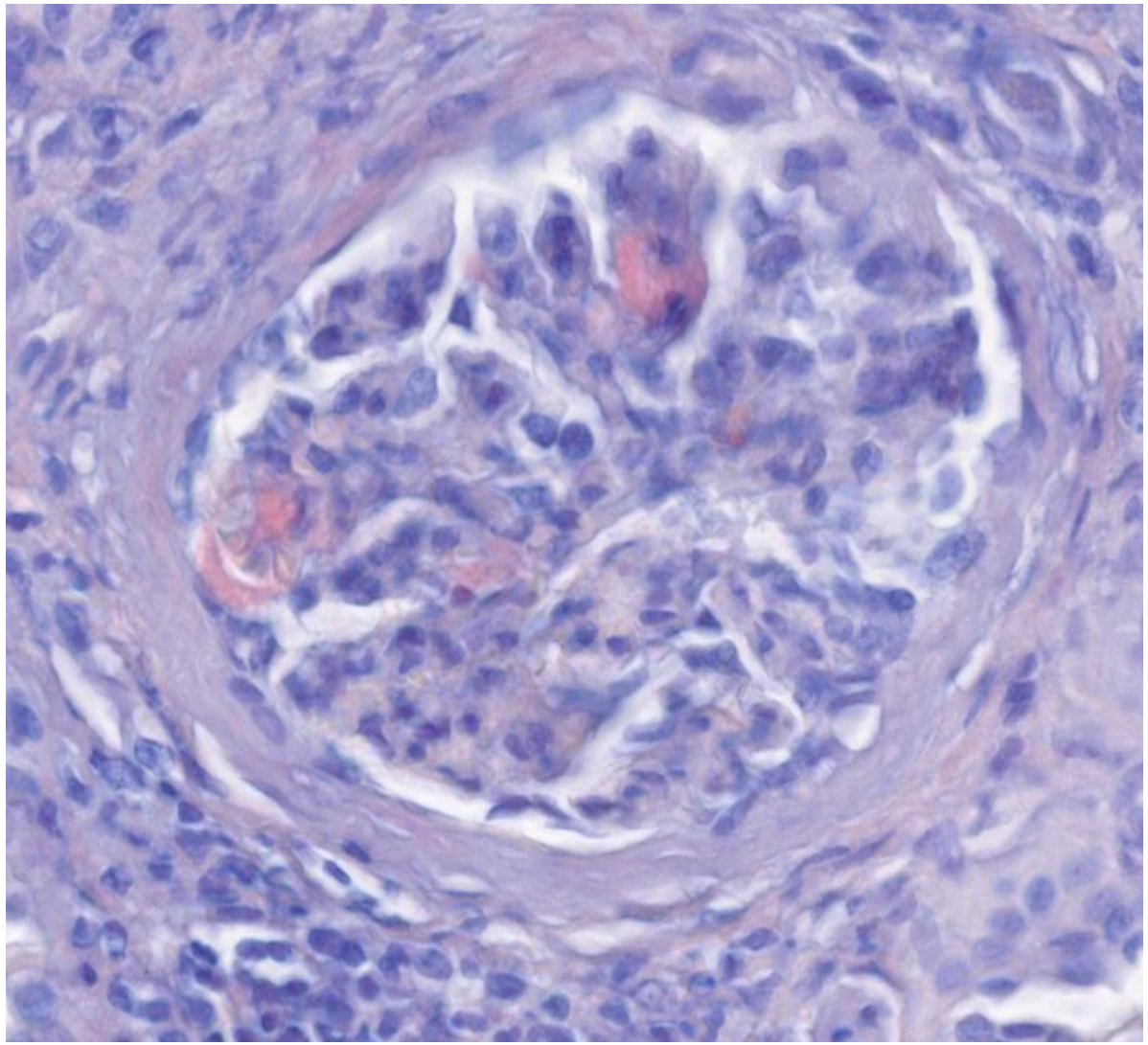


# Biopsia renal

ROJO CONGO +

Clínica Universidad de Navarra





# Biopsia renal

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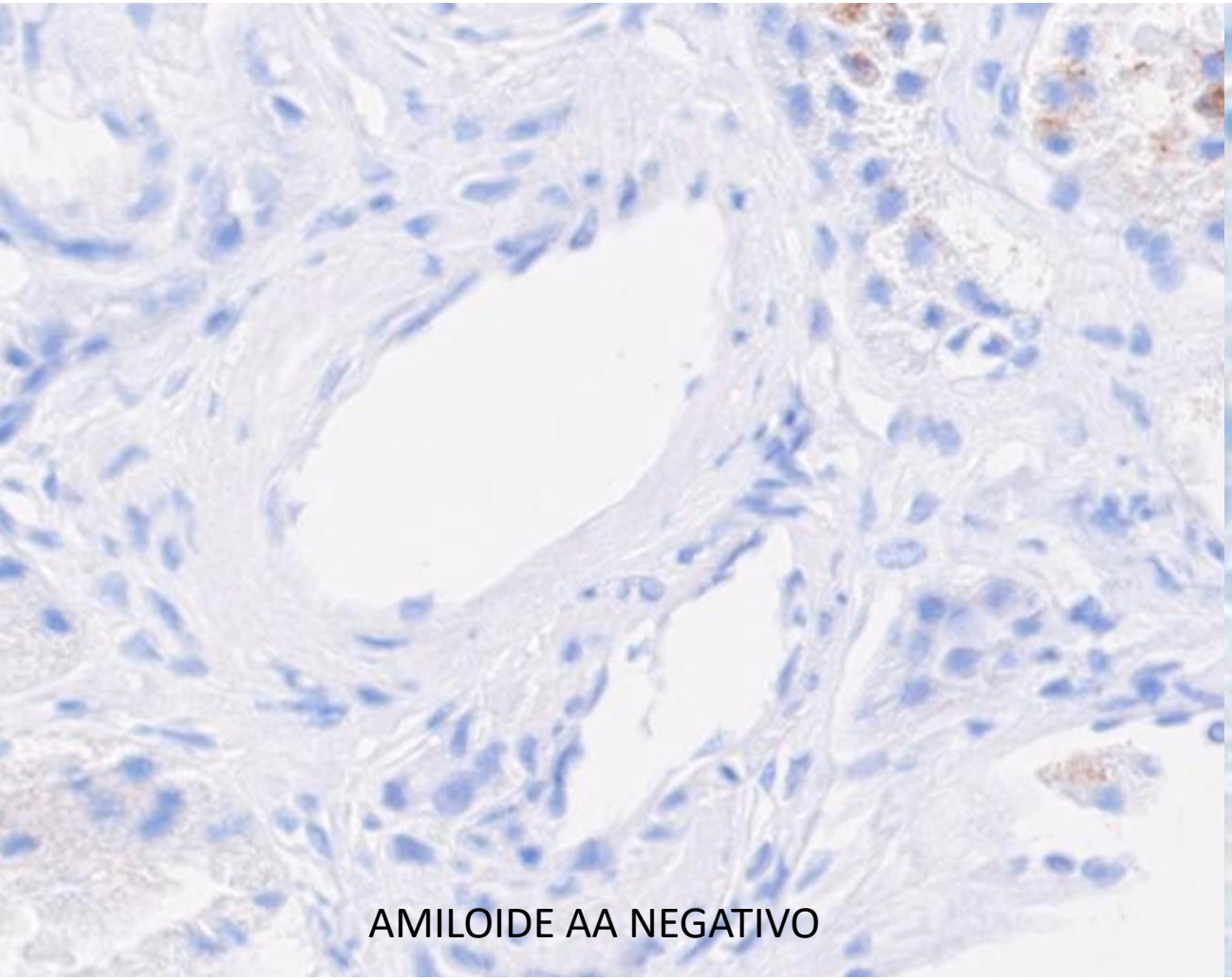
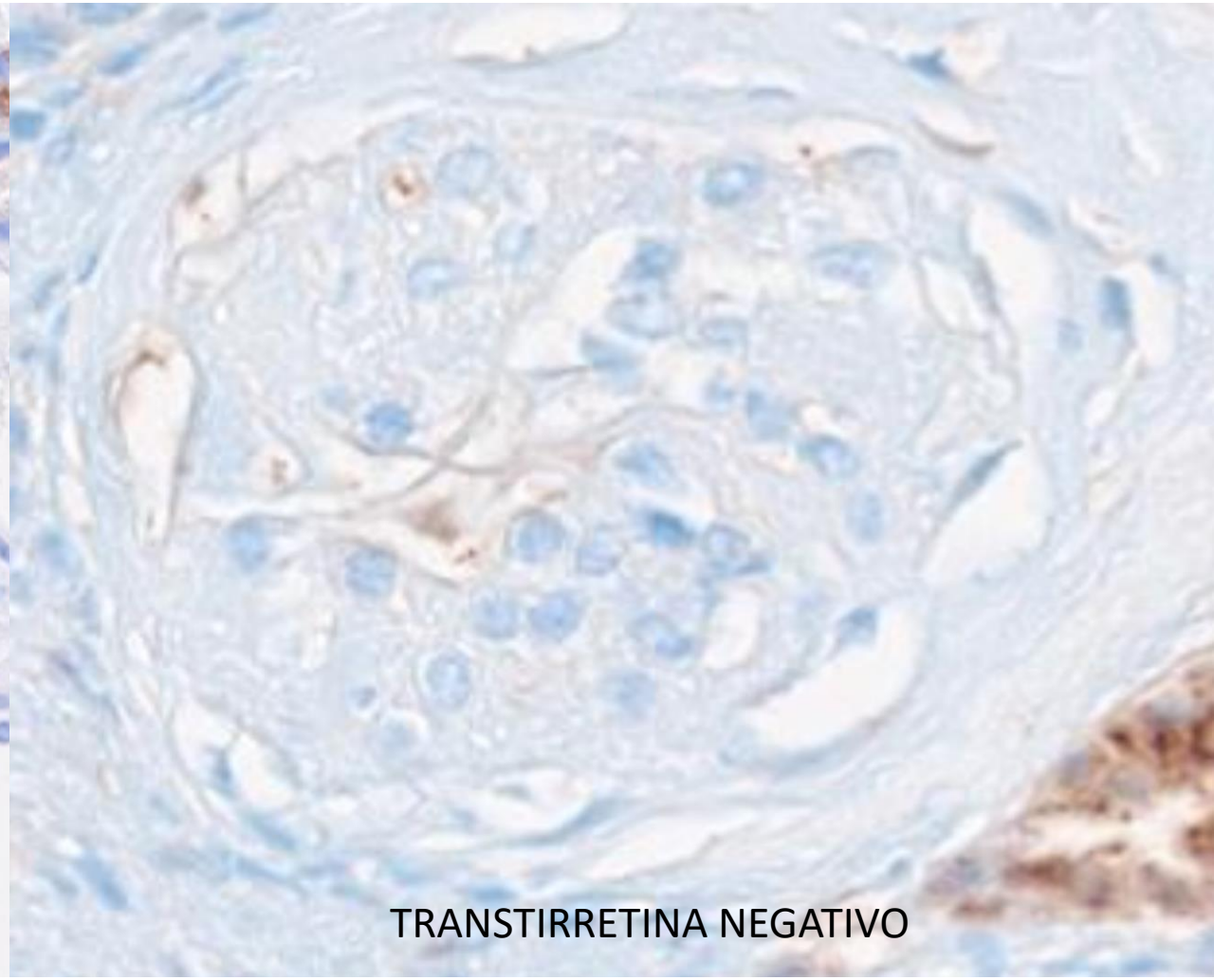
IHQ TIPIFICACIÓN AMILOIDE



AMILOIDE AA NEGATIVO

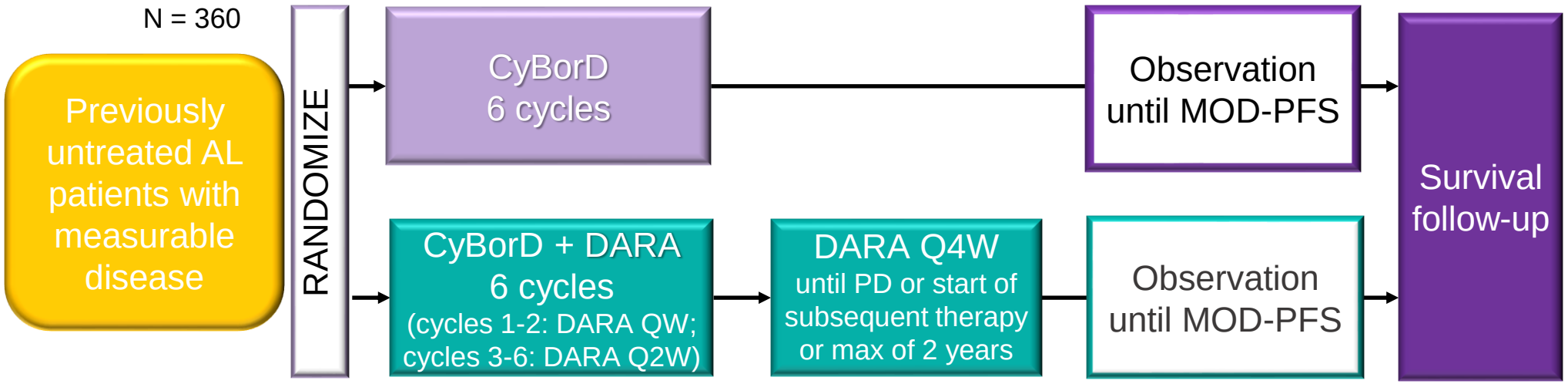


TRANSTIRRETINA NEGATIVO

Kappa y Lambda no valorable

| 1 | Accession | Score | Mass | Num. of significant matches | Num. of significant sequences | emPAI | Description |
|---|---|---|---|---|---|---|---|
| 2 | P35527 | 37679 | 62255 | 1063 | 37 | 231,36 | Keratin, type I cytoskeletal 9 OS=Homo sapiens OX=9606 GN=KRT9 PE=1 SV=3 |
| 3 | P04264 | 54490 | 66170 | 1310 | 39 | 100,92 | Keratin, type II cytoskeletal 1 OS=Homo sapiens OX=9606 GN=KRT1 PE=1 SV=6 |
| 4 | P02533 | 15609 | 51872 | 480 | 31 | 98,89 | Keratin, type I cytoskeletal 14 OS=Homo sapiens OX=9606 GN=KRT14 PE=1 SV=4 |
| 5 | P13645 | 27050 | 59020 | 738 | 29 | 77,91 | Keratin, type I cytoskeletal 10 OS=Homo sapiens OX=9606 GN=KRT10 PE=1 SV=6 |
| 6 | P02649 | 9935 | 36246 | 272 | 20 | 65,44 | Apolipoprotein E OS=Homo sapiens OX=9606 GN=APOE PE=1 SV=1 |
| 7 | P08670 | 9673 | 53676 | 285 | 32 | 58,61 | Vimentin OS=Homo sapiens OX=9606 GN=VIM PE=1 SV=4 |
| 8 | P13647 | 11469 | 62568 | 344 | 27 | 18,63 | Keratin, type II cytoskeletal 5 OS=Homo sapiens OX=9606 GN=KRT5 PE=1 SV=3 |
| 9 | P06727 | 5532 | 45344 | 204 | 21 | 17,94 | Apolipoprotein A-IV OS=Homo sapiens OX=9606 GN=APOA4 PE=1 SV=4 |
| 10 | P68871 | 2213 | 16102 | 58 | 9 | 17,6 | Hemoglobin subunit beta OS=Homo sapiens OX=9606 GN=HBB PE=1 SV=2 |
| 11 | P02768 | 8267 | 71317 | 272 | 35 | 16,91 | Albumin OS=Homo sapiens OX=9606 GN=ALB PE=1 SV=2 |
| 12 | P0DOY2 | 1461 | 11458 | 50 | 4 | 6,69 | Immunoglobulin lambda constant 2 OS=Homo sapiens OX=9606 GN=IGLC2 PE=1 SV=1 |
| 13 | P07355 | 2229 | 38808 | 64 | 15 | 6,11 | Annexin A2 OS=Homo sapiens OX=9606 GN=ANXA2 PE=1 SV=2 |
| 14 | P0DP23 | 293 | 16827 | 23 | 5 | 6,06 | Calmodulin-1 OS=Homo sapiens OX=9606 GN=CALM1 PE=1 SV=1 |
| 15 | P08727 | 3991 | 44079 | 145 | 14 | 6,01 | Keratin, type I cytoskeletal 19 OS=Homo sapiens OX=9606 GN=KRT19 PE=1 SV=4 |
| 16 | P06703 | 316 | 10230 | 15 | 2 | 2,92 | Protein S100-A6 OS=Homo sapiens OX=9606 GN=S100A6 PE=1 SV=1 |
| 17 | P63104 | 1259 | 27899 | 35 | 7 | 2,91 | 14-3-3 protein zeta/delta OS=Homo sapiens OX=9606 GN=YWHAZ PE=1 SV=1 |
| 18 | P35625 | 793 | 24813 | 26 | 6 | 2,8 | Metalloproteinase inhibitor 3 OS=Homo sapiens OX=9606 GN=TIMP3 PE=1 SV=2 |
| 19 | P67936 | 1234 | 28619 | 46 | 8 | 2,77 | Tropomyosin alpha-4 chain OS=Homo sapiens OX=9606 GN=TPM4 PE=1 SV=3 |
| 20 | P08758 | 773 | 35971 | 28 | 9 | 2,76 | Annexin A5 OS=Homo sapiens OX=9606 GN=ANXA5 PE=1 SV=2 |
| 21 | P02743 | 1603 | 25485 | 47 | 6 | 2,67 | Serum amyloid P-component OS=Homo sapiens OX=9606 GN=APCS PE=1 SV=2 |
| 22 | P15924 | 7454 | 334021 | 272 | 88 | 2,65 | Desmoplakin OS=Homo sapiens OX=9606 GN=DSP PE=1 SV=3 |
| 23 | P05109 | 382 | 10885 | 12 | 3 | 2,61 | Protein S100-A8 OS=Homo sapiens OX=9606 GN=S100A8 PE=1 SV=1 |

# Daratumumab in AL amyloidosis: ANDROMEDA
# Phase 3 study in newly diagnosed AL (stage 1-3A)




Primary outcome: Overall complete hematologic response

Secondary outcomes : Major organ deterioration progression-free survival (MOD-PFS), progression-free survival (PFS), organ response rate (OrRR), overall survival (OS), QOL measurements, time to next treatment (TNT), hematologic VGPR, time to CR and time to hematologic VGPR or better, duration of CR and duration of hematologic VGPR or better, time to organ response, duration of organ response

U.S. FOOD & DRUG ADMINISTRATION

Home / Drugs / Development & Approval Process | Drugs / Drug Approvals and Databases / Resources for Information | Approved Drugs / FDA grants accelerated approval to Darzalex Faspro for newly diagnosed light chain amyloidosis

# FDA grants accelerated approval to Darzalex Faspro for newly diagnosed light chain amyloidosis

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Resources for Information | Approved Drugs

Oncology (Cancer) / Hematologic Malignancies Approval Notifications

On January 15, 2021, the Food and Drug Administration granted accelerated approval to daratumumab plus hyaluronidase (Darzalex Faspro, Janssen Biotech Inc.) in combination with bortezomib, cyclophosphamide and dexamethasone for newly diagnosed light chain (AL) amyloidosis.

Efficacy was evaluated in ANDROMEDA (NCT03201965), an open-label, randomized, active-controlled trial in 388 patients with newly diagnosed AL amyloidosis with

Content current as of: 01/15/2021

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Darzalex

*daratumumab*

Medicine | Human

Share | RSS

Authorised
This medicine is authorised for use in the European Union

Page contents

Overview

Product information

## Overview

Darzalex is a medicine used to treat adults with multiple myeloma (a cancer of the bone marrow) and light chain (AL) amyloidosis (a blood disease in which deposits of abnormal proteins, called amyloids, accumulate and cause damage in tissues and organs).

SEHH Sociedad Española de Hematología y Hemoterapia

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**Informe de Posición de la SEHH**

**Daratumumab, ciclofosfamida, bortezomib y dexametasona para el tratamiento de los pacientes con amiloidosis AL de nuevo diagnóstico**

MINISTERIO DE SANIDAD | DIRECCIÓN GENERAL DE CARTERA COMÚN DE SERVICIOS DEL SNS Y FARMACIA | agencia española de medicamentos y productos sanitarios

**REvalMed SNS**
Comisión Permanente de Farmacia

**INFORME DE POSICIONAMIENTO TERAPÉUTICO**
**PT 95-2023/V1/12012023**

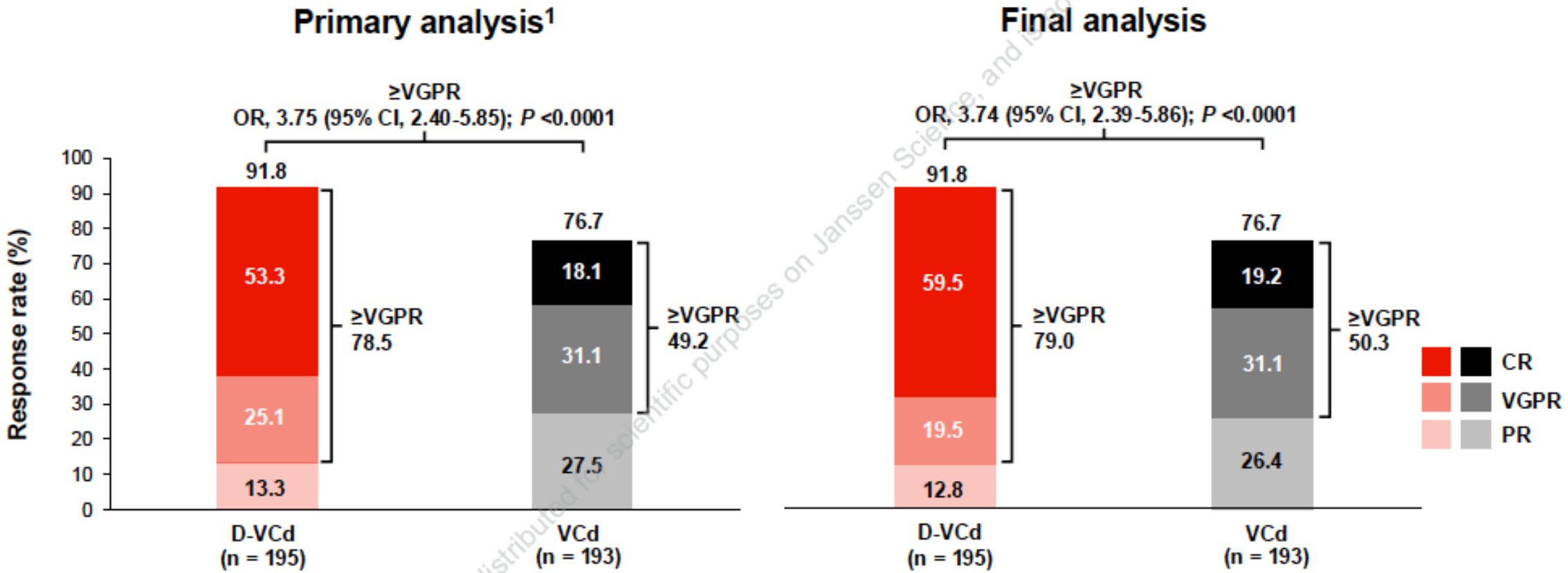
# Informe de Posicionamiento Terapéutico de Daratumumab (Darzalex®) en combinación con ciclosfosfamida, bortezomib y dexametasona en pacientes con Amiloidosis Sistémica de Cadenas Ligeras

**Fecha de publicación: 12/01/2023**

## CONSIDERACIONES FINALES DEL GC REVALMED SNS

*La Dirección General de Cartera Común de Servicios del SNS y Farmacia (DGCCSSNSYF) ha emitido resolución de no financiación para la indicación de **DARZALEX®** (daratumumab) en combinación con ciclofosfamida, bortezomib y dexametasona para el tratamiento de pacientes adultos con amiloidosis sistémica de cadenas ligeras de nuevo diagnóstico.*

# ANDROMEDA: Overall Hematologic Response at the Final Analysis



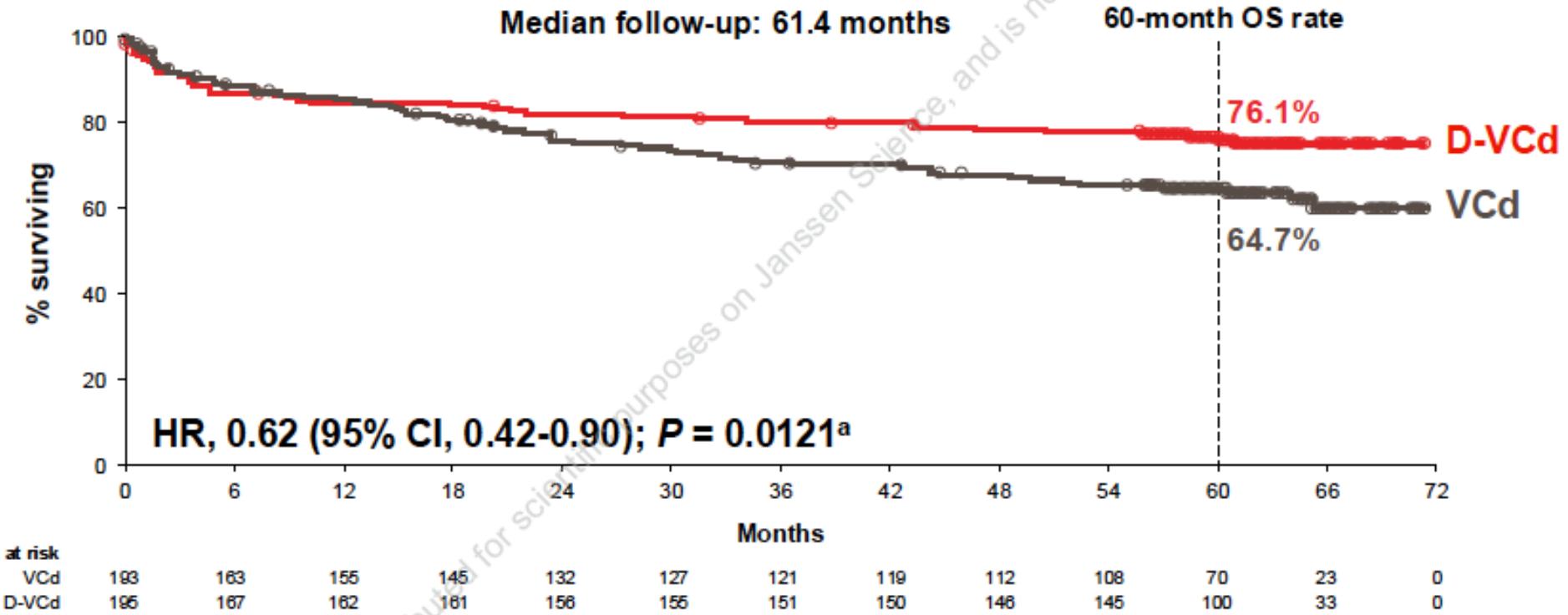

**The addition of DARA to VCd consistently led to higher rates of hematologic response**

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**

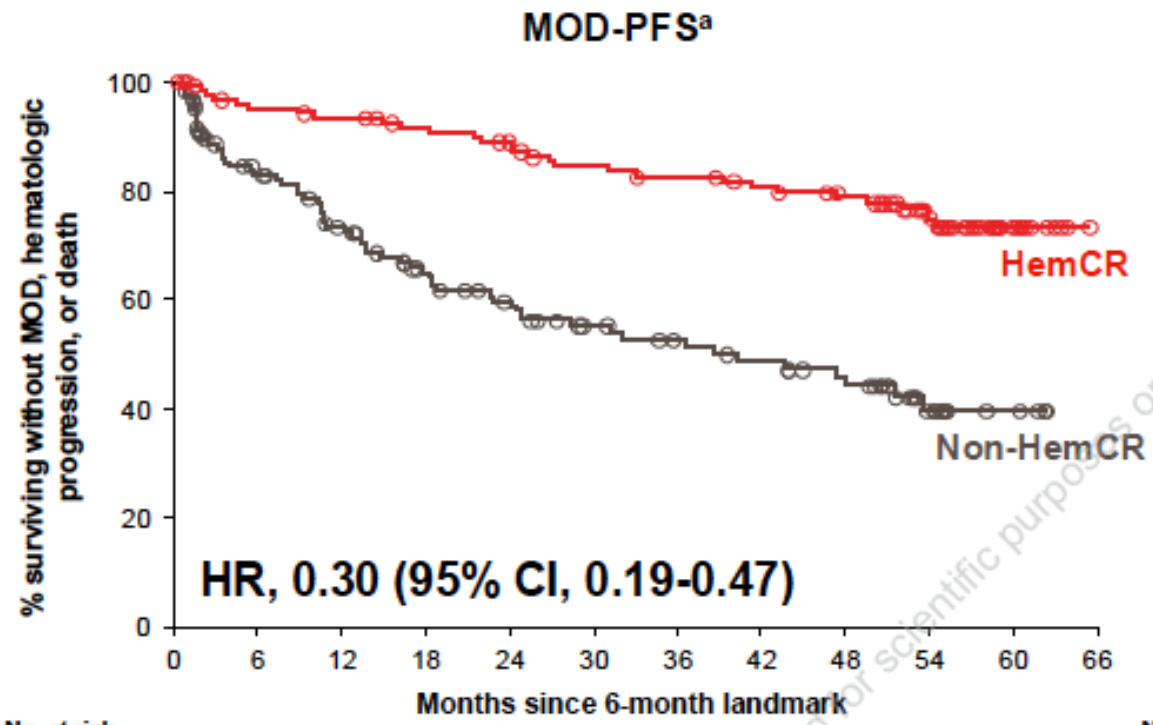
aCrossing the prespecified stopping boundary of 0.0163.

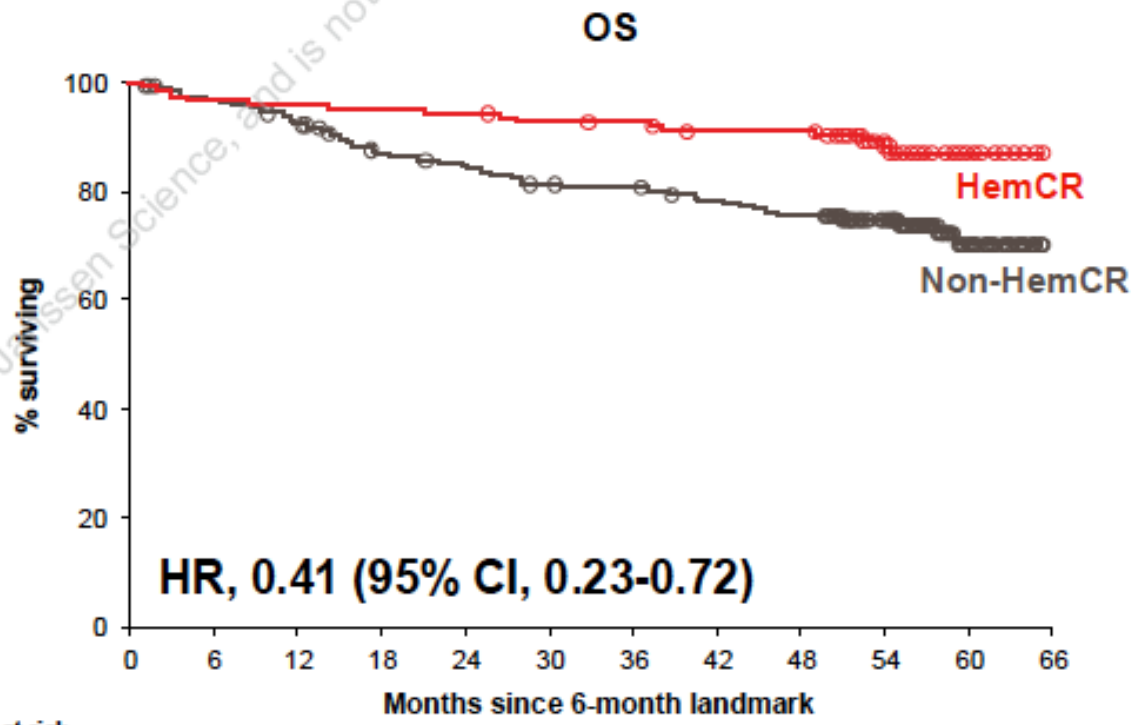




Presented by E Kastritis at the 66th American Society of Hematology (ASH) Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA, USA

# ANDROMEDA: Major Organ Deterioration (MOD)–PFS and Overall Survival by Hematologic Complete Response




**Achieving HemCR was associated with improved MOD-PFS and OS from the 6-month landmark analysis and beyond**

[a]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. Kaplan–Meier estimates in those patients who achieved HemCR versus those who did not achieve HemCR.





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

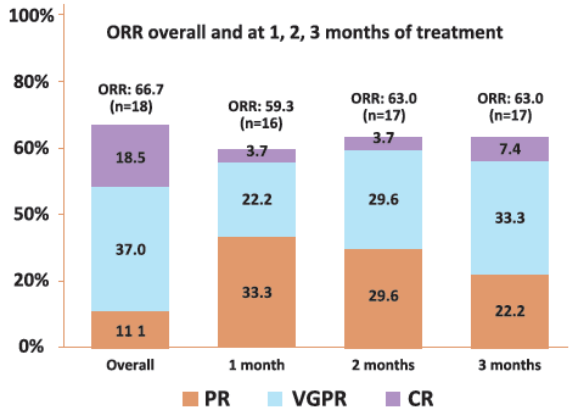
# Efficacy And Safety of Daratumumab Monotherapy in Newly Diagnosed Patients with Stage 3B Light Chain Amyloidosis: A Phase 2 Study by the European Myeloma Network

## Patient Characteristics At Screening (N=27)

**Besides the heart, the median number of organs involved was 2 (range 0–5), most commonly kidneys (14 pts, 52%) and peripheral nerves (11 pts, 41%).**

| Intention-To-Treat patients (N=27) | |
|---|---|
| **Age**, median (Min-Max) | 68.0 (45.0-84.0) |
| **Gender**<br>Male<br>Female | <br>16 (59.3%)<br>11 (40.7%) |
| **NYHA classification screening**, n(%)<br>**II**<br>**IIIA**, n (%) | <br>10 (37%)<br>17 (63%) |
| **NT-proBNP (pg/mL)**, median (Min-Max) | 15,512 (8,816–72,522) |
| **HS Troponin T (pg/mL)**, median (Min-Max) | 133 (60–692) |
| **dFLC (mg/dL)**, median (Min-Max) | 40.6 (2.4-337.7) |
| **Patients with Organ involvement apart from heart**, n (%) | 24 (88.9%) |

## Response Evaluation (N=27)

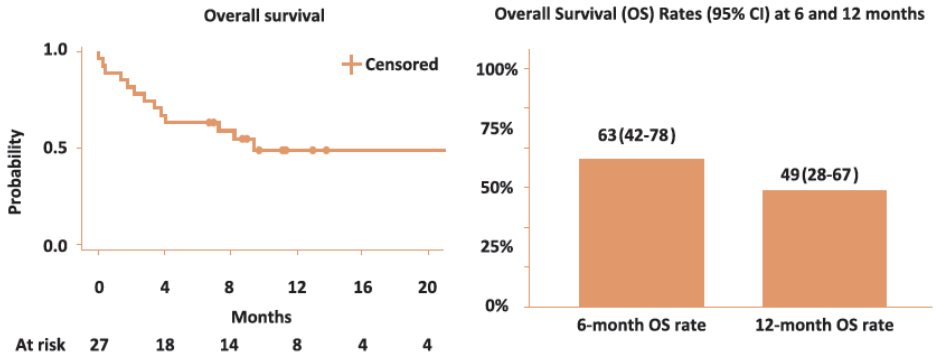



**The median duration of DARA therapy was 7 months (range <1–24); seven (26%) pts received additional Vd. At a median observation time of 8 months (range <1–11).**

**Median time to first response was 7 days (range 6–114), and to VGPR or better 54 days (range 6–219)**

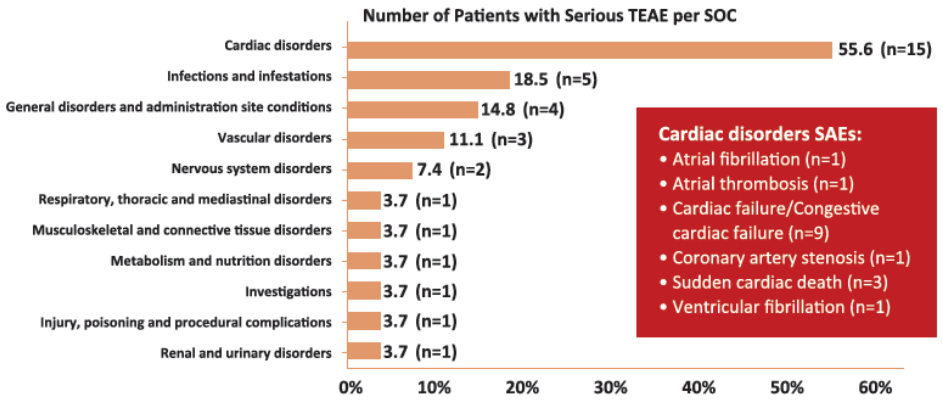
## Overall Survival

Median OS was 9 months (95% CI, 3–not reached).




*The median (95% confidence interval [CI]) OS and the respective 6- and 12-month rates was obtained by Kaplan-Meier analysis*

## Patients with serious TEAEs by SOC term

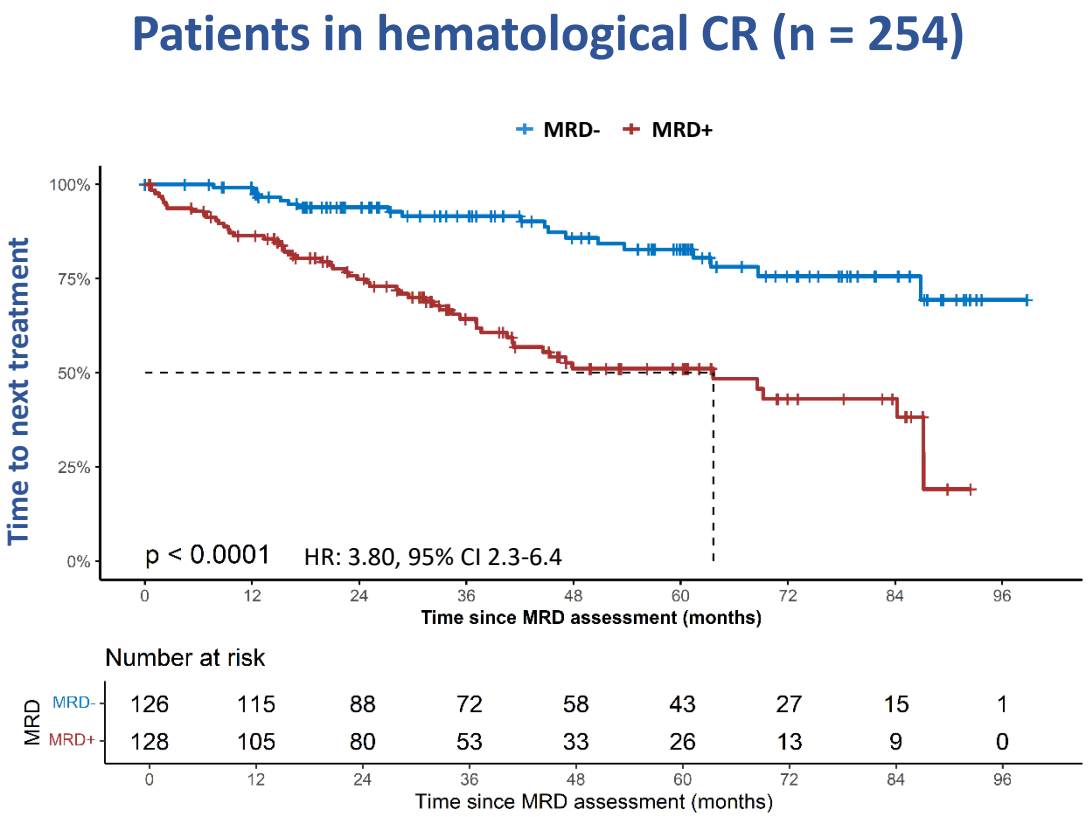



**Cardiac disorders SAEs:**
- Atrial fibrillation (n=1)
- Atrial thrombosis (n=1)
- Cardiac failure/Congestive cardiac failure (n=9)
- Coronary artery stenosis (n=1)
- Sudden cardiac death (n=3)
- Ventricular fibrillation (n=1)

**20 patients (74.1%) with at least one SAE,**
4 patients with at least one treatment-related SAE and in total 6 treatment-related SAEs overall

Kastritis E, et al. ISA 2022.

# Detectable MRD redefines the prognosis of patients in hematological CR

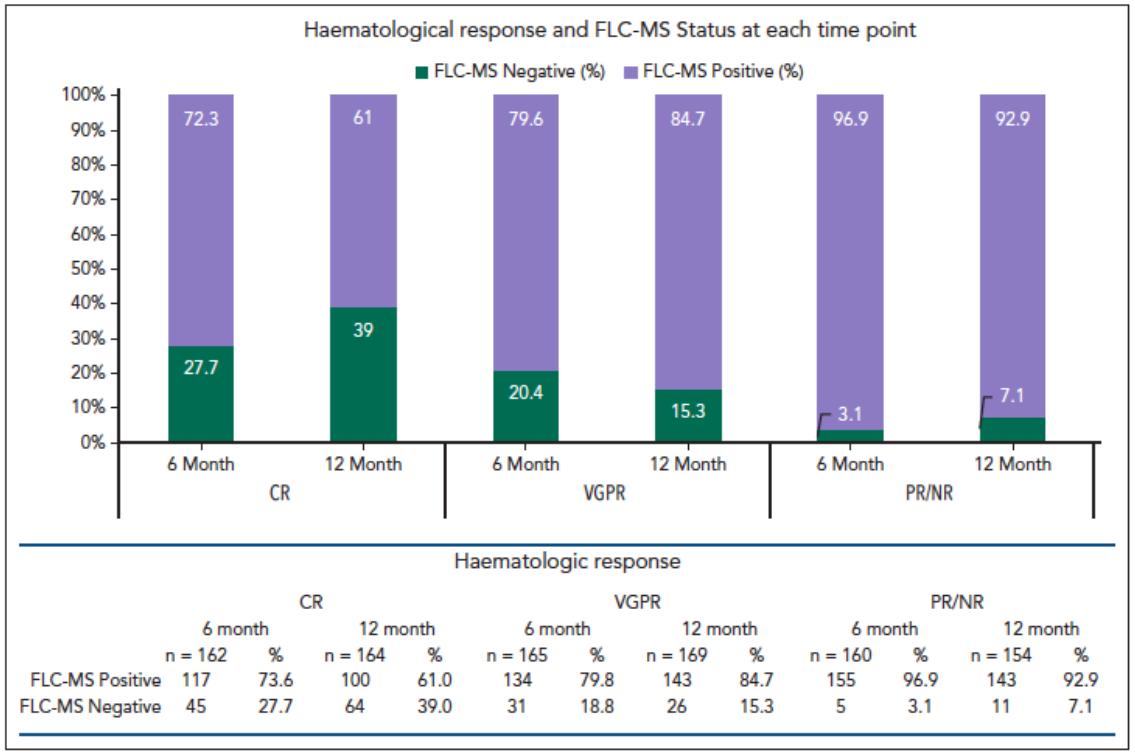



Lasa M et al. ASH 2024.

# MRD status by serum FLC-MS

**KEY POINTS**

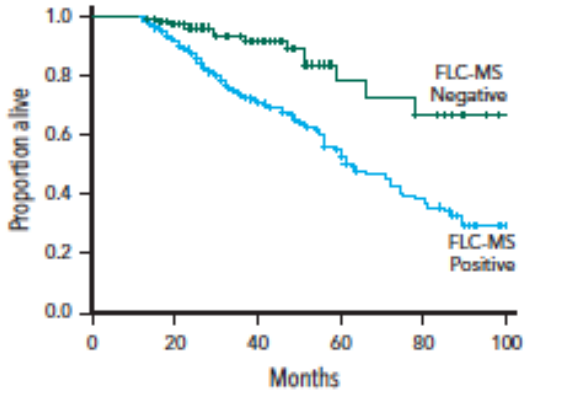
- **FLC-MS can detect persistent light chains in a significant proportion of patients in a conventional hematologic CR.**
- **Patients with no detectable FLC by FLC-MS have significantly better OS and organ response irrespective of conventional hematologic response.**




Haematologic response

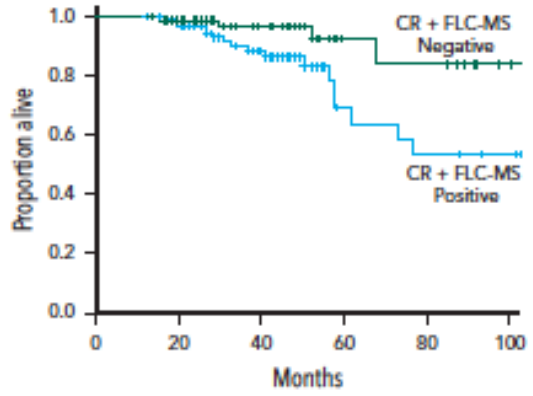
| | CR | | | | VGPR | | | | PR/NR | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 6 month | | 12 month | | 6 month | | 12 month | | 6 month | | 12 month | |
| | n = 162 | % | n = 164 | % | n = 165 | % | n = 169 | % | n = 160 | % | n = 154 | % |
| FLC-MS Positive | 117 | 73.6 | 100 | 61.0 | 134 | 79.8 | 143 | 84.7 | 155 | 96.9 | 143 | 92.9 |
| FLC-MS Negative | 45 | 27.7 | 64 | 39.0 | 31 | 18.8 | 26 | 15.3 | 5 | 3.1 | 11 | 7.1 |

A




| At risk | 0 | 20 | 40 | 60 | 80 | 100 |
|---|---|---|---|---|---|---|
| FLC-MS Positive | 386 | 333 | 155 | 50 | 30 | 11 |
| FLC-MS Negative | 101 | 90 | 52 | 13 | 11 | 1 |

B

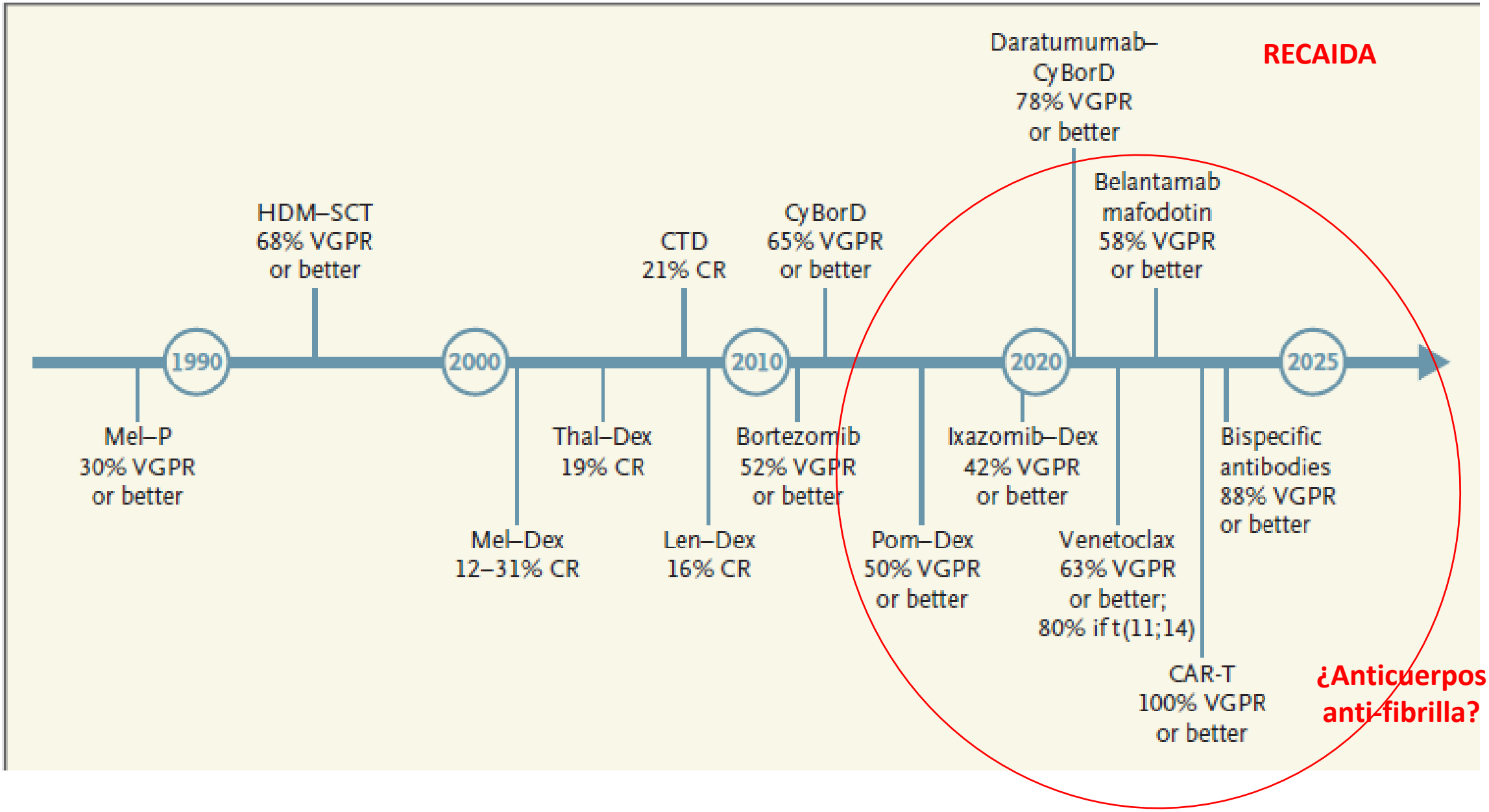



| At risk | 0 | 20 | 40 | 60 | 80 | 100 |
|---|---|---|---|---|---|---|
| CR + FLC-MS Positive | 100 | 87 | 47 | 13 | 10 | 7 |
| CR + FLC-MS Negative | 64 | 58 | 35 | 11 | 10 | 1 |

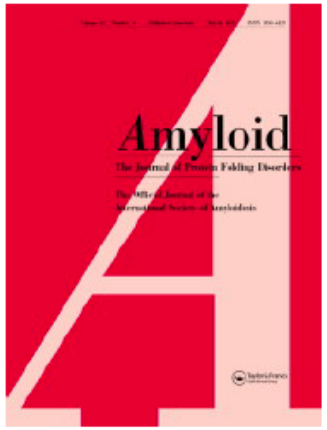
Bomsztyk et al. Blood 2024.

# Objetivos de respuesta (opinión personal):

- Mínimo: hVGPR + RO (o estabilidad si afectación muy leve)
- Pacientes jóvenes: hRC + RO
- ¿EMR?
  - Info pronóstico en pacientes con hRC
  - Si no RO a pesar de hRC → ¿consolidación?
- AutoTPH:
  - Consolidación si respuesta subóptima (y candidato)
  - Recaída
- ¿Mantenimiento con daratumumab? ¿No si RC y EMR-?

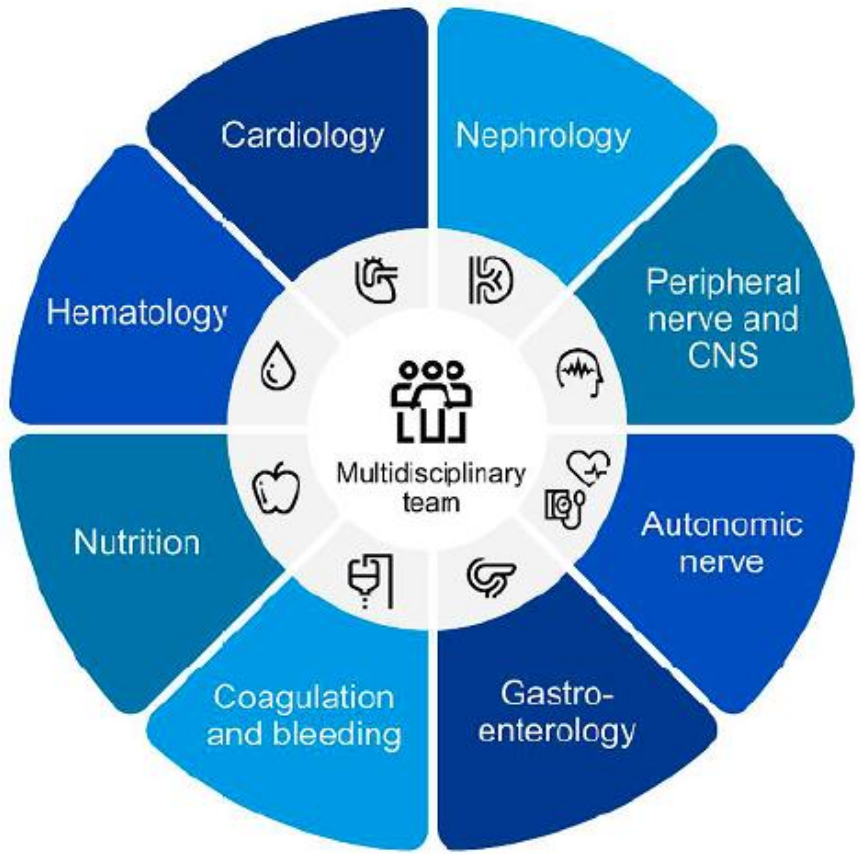



Sanchorawala V. N Engl J Med, 2024.




# Supportive care for systemic amyloidosis: International Society of Amyloidosis (ISA) expert panel guidelines

Eli Muchtar, Martha Grogan, Fabian aus dem Siepen, Marcia Waddington-Cruz, Yohei Misumi, Antonia S. Carroll, John O. Clarke, Vaishali Sanchorawala, Paolo Milani, Riccardo Caccialanza, Valentina Da Prat, Rajiv Pruthi, Luis F. Quintana & Frank Bridoux



World Amyloidosis Day

October 26th