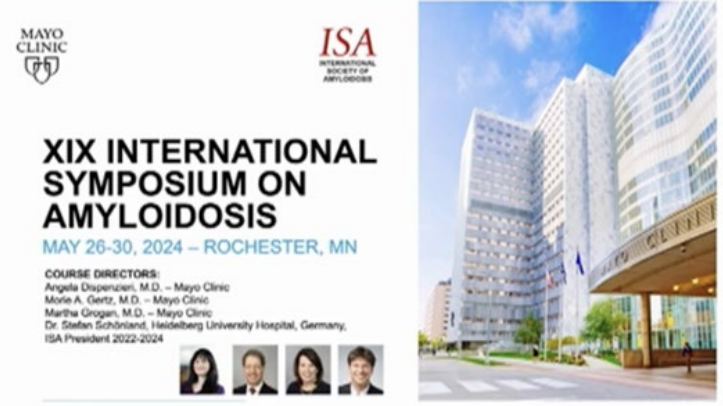

AL Amyloidosis post-congress

N Meuleman October 2024

H.U.B HÔPITAL UNIVERSITAIRE DE BRUXELLES ACADEMISCH ZIEKENHUIS BRUSSEL

INSTITUT JULES BORDET INSTITUUT
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EuroBloodNet

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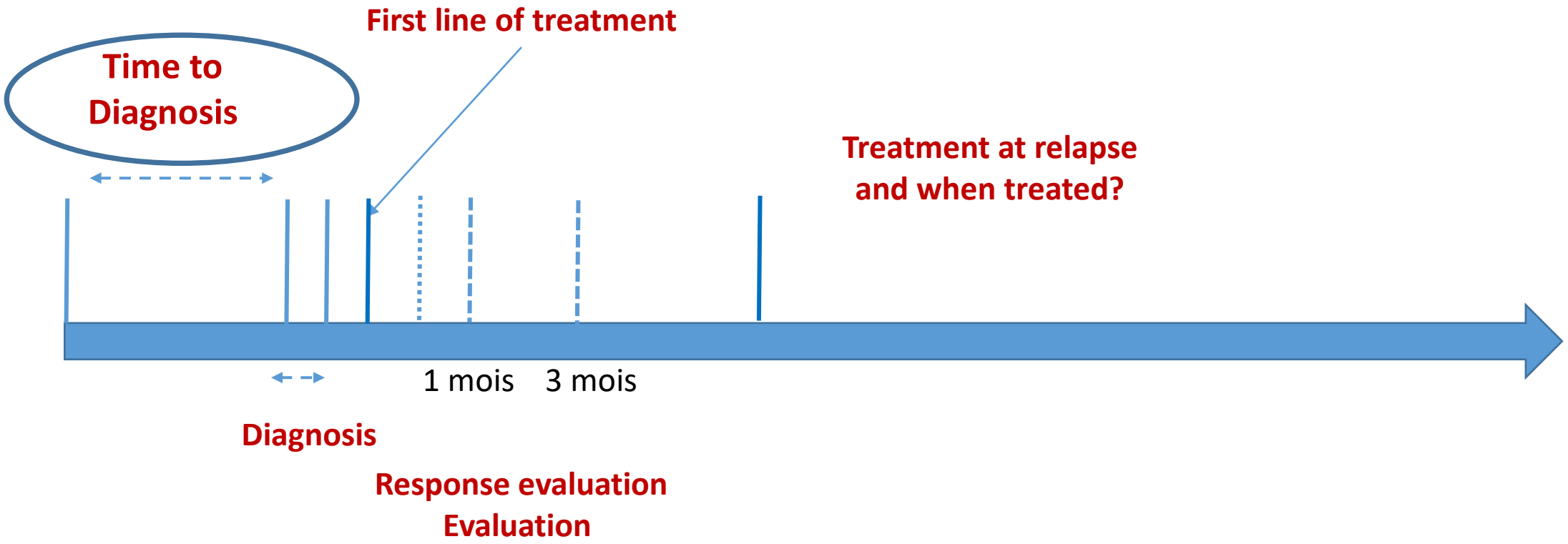
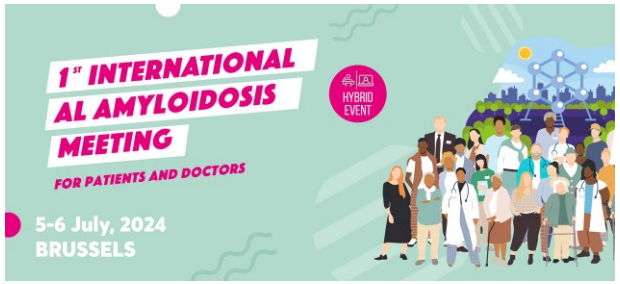
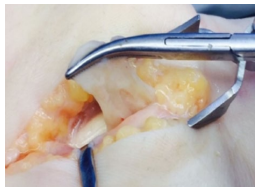
Management of AL Amyloidosis



Reduce the time between symptoms and diagnosis



Systematic screening for amyloidosis during carpal tunnel surgery.



Discussion
Interest in annual NT-ProBNP testing?

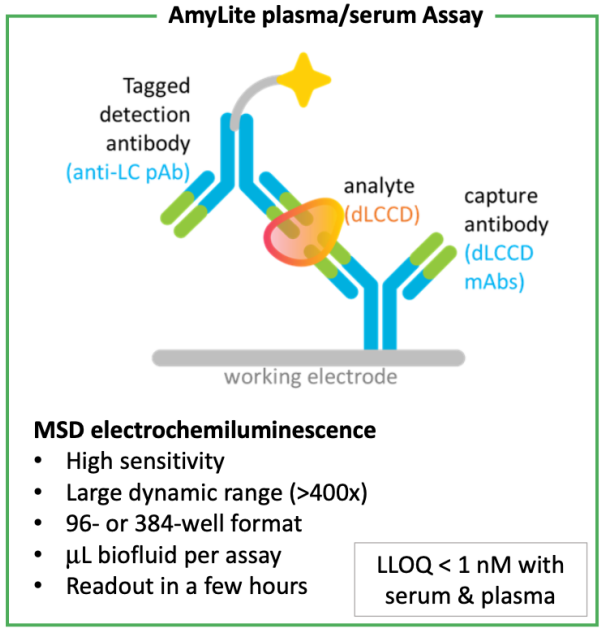
- 2 (3) centers /7

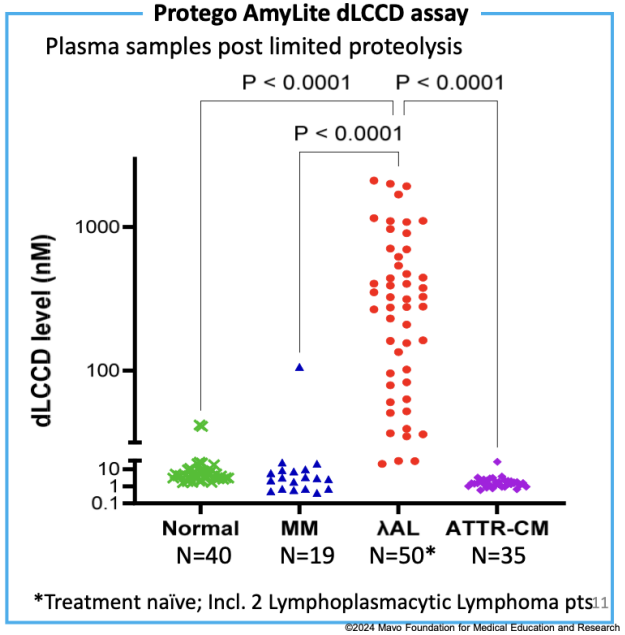
Rouge Congo + 16,7% (199/1196)

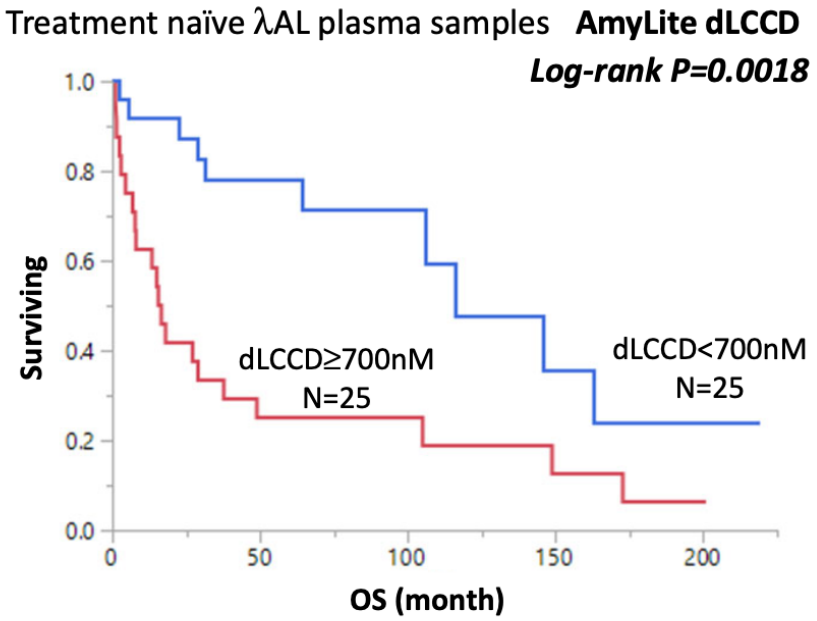
- 100 TTR
- 15 AL
- 2 AL+ ATTR
- 25 pts with cardiac involvement

Mazen H, ISA 2024

AmyLite Assay: Quantifies Kinetically Unstable Circulating Amyloidogenic **Lambda FLC:** Diagnosis and Prognostic Implications for **Lambda** AL





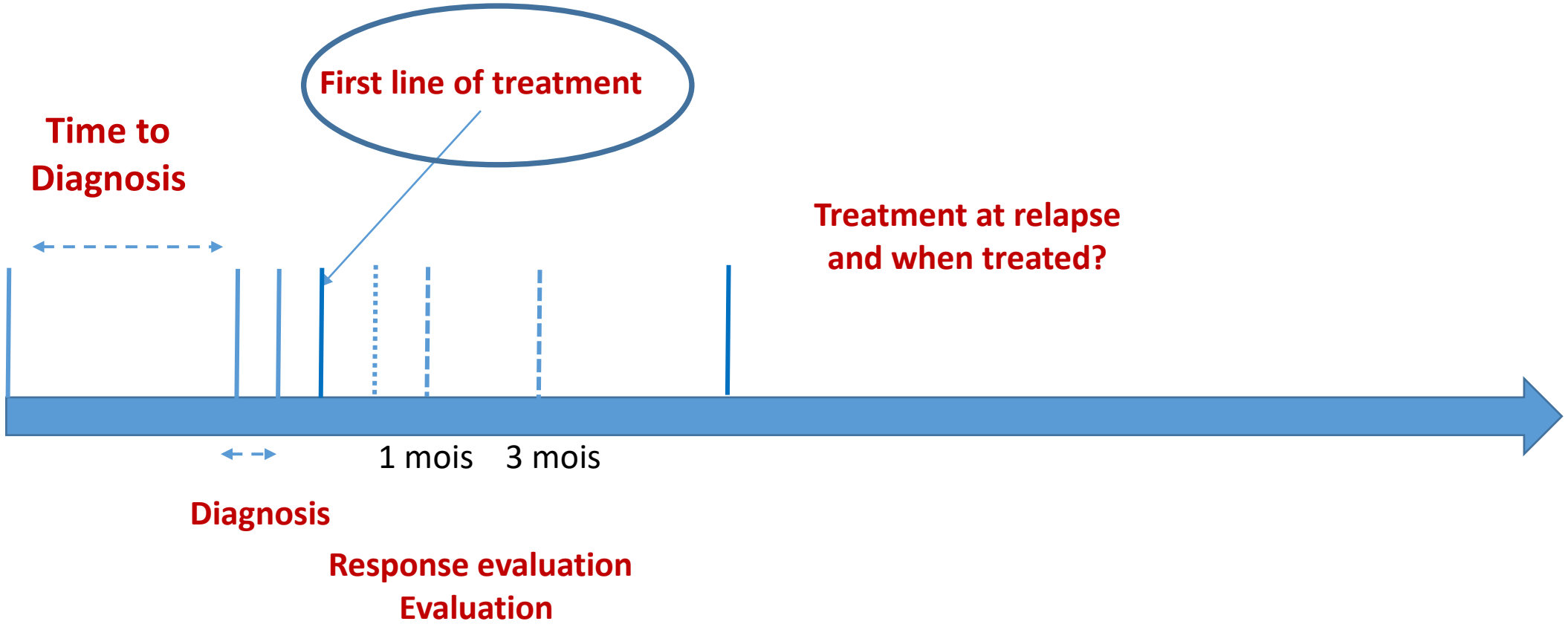


- Limited proteolysis + specific detection of the resulting dimeric LC constant domain (dLCCD)
- Specifically (p<0.0001) and sensitively detect dLCCD in ND **lambda** AL patients vs MM or ATTR

- Baseline dLCCD correlate with overall survival (log-rank p=0.0018).

Xin Jiang et al, ISA 2024,O99

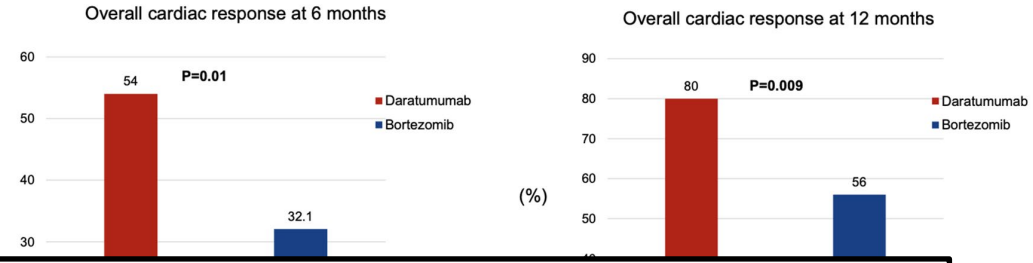
Management of AL Amyloidosis



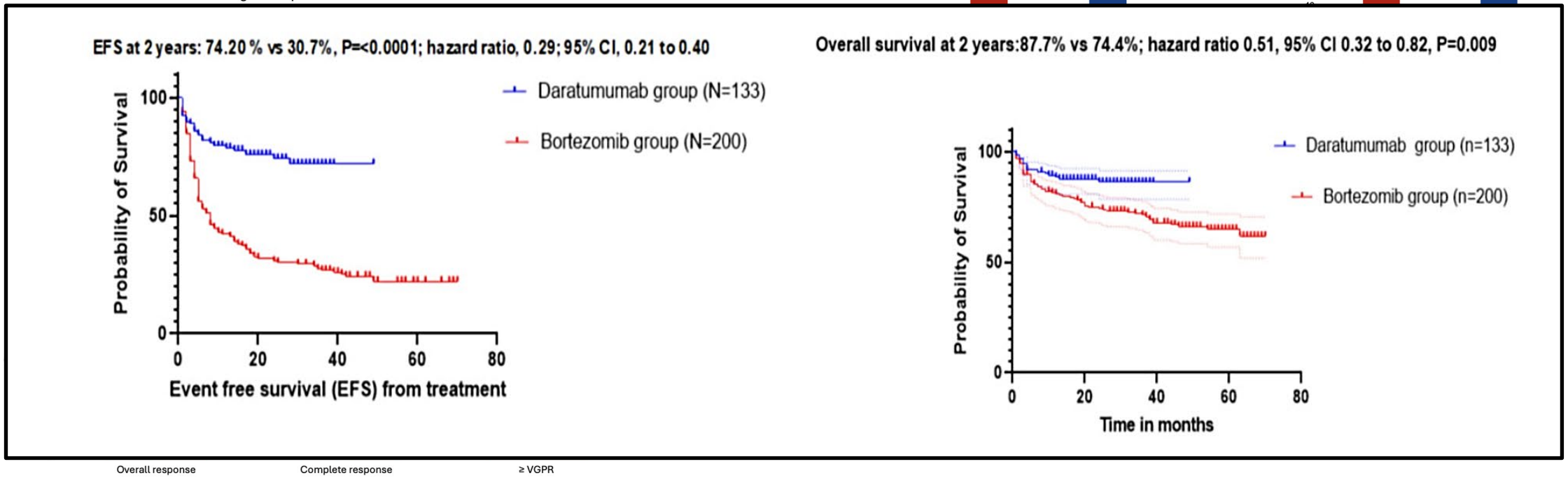
Dara-based front-line therapy improves treatment response and survival in AL amyloidosis: the mayo clinic experience

Single-center retrospective study

- 2018-2022: Dara-VCD (125)- DVD/D (8)
- 2018-2020 Bzb-based therapy: VCD (189)-VD (11)
- ASCT 14 (DaraBT) vs 29 (VBT)% p=0.001
- m-FU 24 vs 54 months



Hematological response rates at 2 months



Overall response Complete response ≥ VGPR

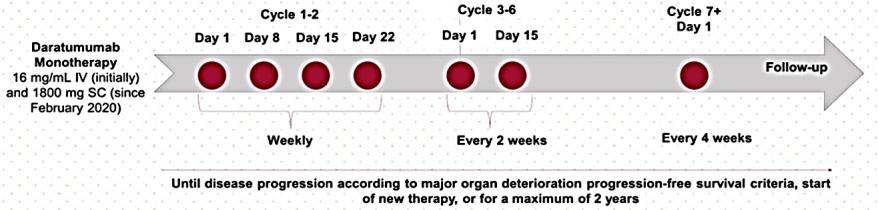
6 m ≥VGPR 47 vs 16,2%(p<0.001)

Early death 8.78% vs 17.3% (p=0,02)

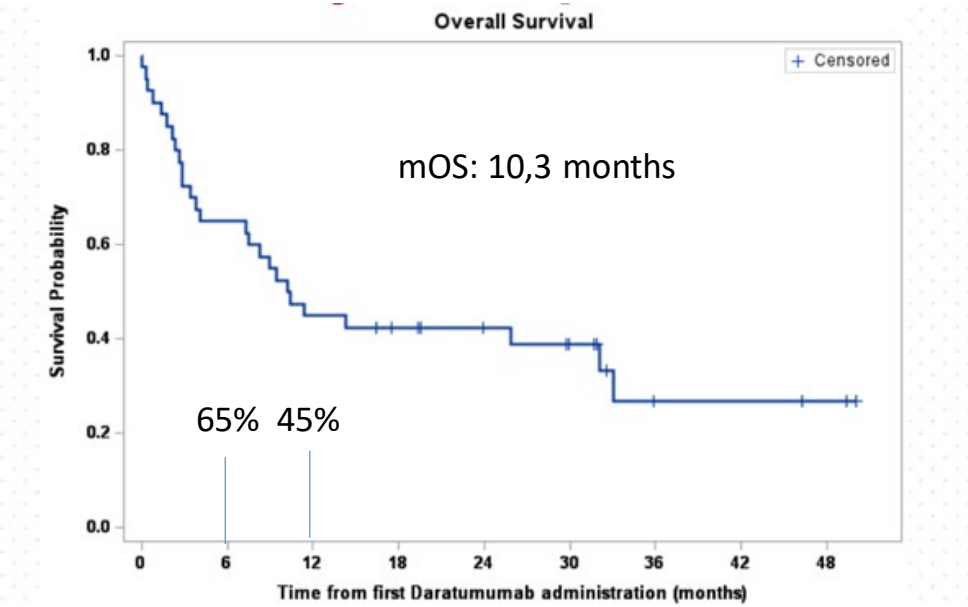
Binoy Y, ISA 2024

Efficacy and safety of daratumumab monotherapy in ND stage IIIB AL amyloidosis: a phase 2 study by the EMN

Stage IIIB?



- N= 40 (Greece, The Netherlands, Italy and France)
- Primary endpoint: Os at 6 months



Median OS: 10.3 months

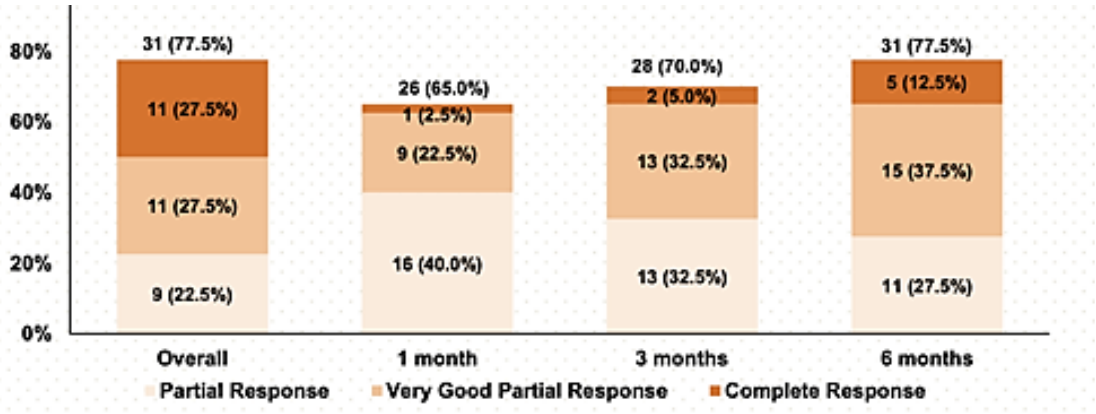
- Historical m-OS 4-6 months

Early mortality

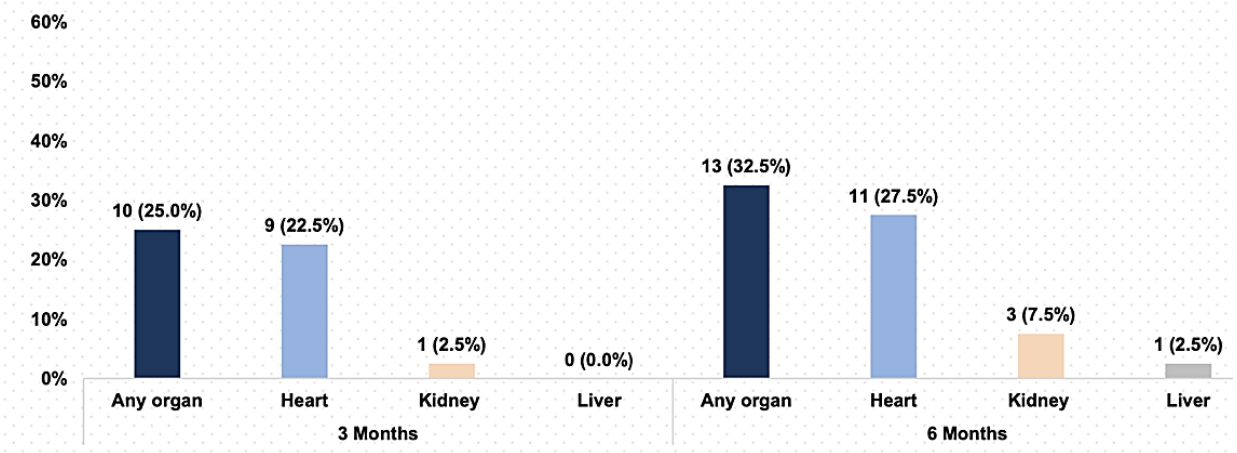
- 15 days: 7,5%
- 1 month: 10%
- 3 months: 27.5%

E Kastritis et al, ISA 2020

Efficacy and safety of daratumumab monotherapy in ND stage IIIB AL amyloidosis: a phase 2 study by the EMN



Secondary endpoint: HR



Organ responses at 3 and 6 months

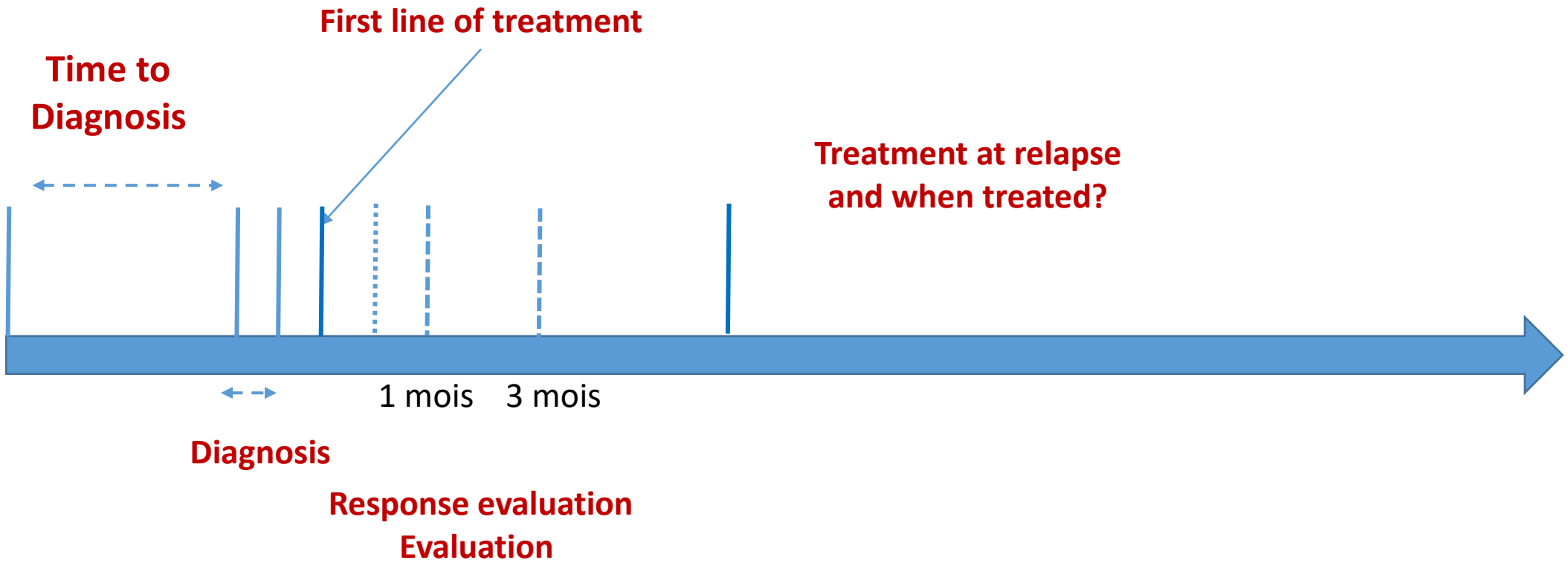
E Kastritis et al, ISA 2020

Evaluating the Efficacy and Safety of Limiting Dexamethasone in ND AL Amyloidosis Compared to Conventional Dosing

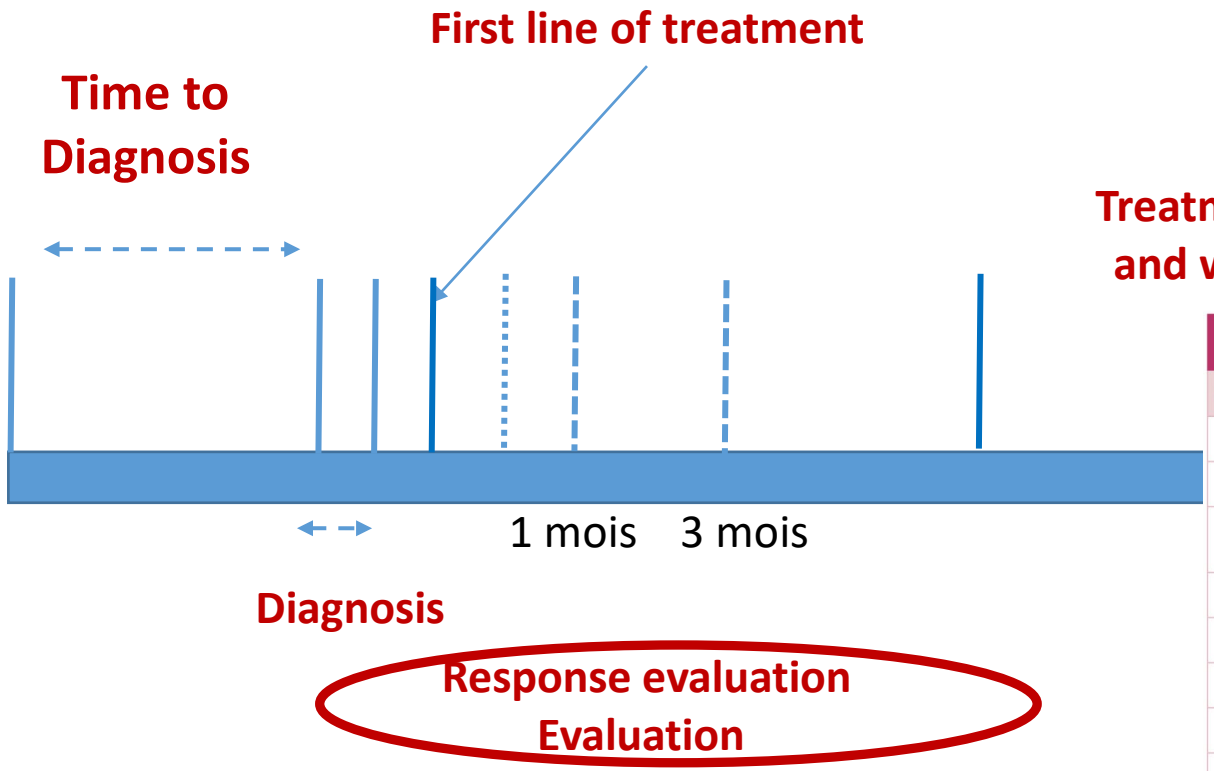
- Rretrospective study, 201 -2023, 216 ND AL
- Toxicities: hospitalization, heart failure exacerbations, increased diuretics, diabetic complications, and others
- Analysis on duration of DXM use : < 4.0 months (n=56), 4.0-5.4 months (n=52), 5.5-13.4 months (n=54), and ≥13.5 months (n=54)
- Early discontinuation of steroids (< 6 months, n=117) vs prolonged steroid exposure (≥6 months, n=99):
  - **Comparable CR/VGPR** rates at 24 months 82.3% vs. 80.8% (p=0.78)
  - **Decrease toxicities whe**n early discontinuation of DXM
    - Lower rates of hospitalizations (62.3% vs 75.5%. p=0.041), heart failure exacerbations (27.4% vs 41.4% p=0.029), and decreased diuretic use (62.4% vs 82.8%. p< 0.001).

J Hanna, IMS 2024, P-300

Management of AL Amyloidosis



Management of AL Amyloidosis



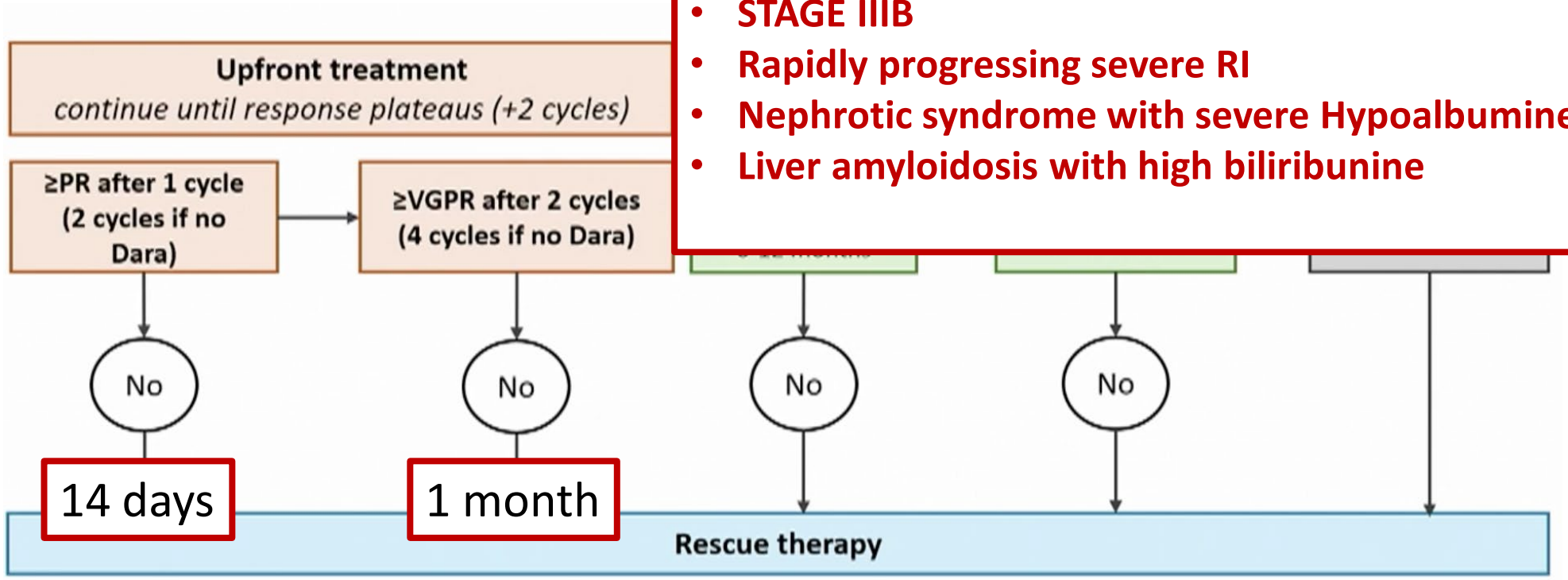
Treatment at relapse and when treated?

TABLE 6. Haematologic response criteria in AL.

Criterion	Definition
Stringent CR[1]/ MRD negative [38]	aCR + no evidence of clonal plasma cells in BM by multiparametric flow cytometry[2]
aCR	No evidence of involved M component by serum and urine IFE; FCL ratio normal
Perspective Stringent dFLV response [37]	If initial dFLC ≥ 20 mg/L : dFLC < 10 mg/L iFLC < 20 mg/L or dFLC < 10 mg/L
VGPR	If initial dFLC ≥ 50 mg/L: dFLC < 40 mg/L
PR	If initial dFLC ≥ 50 mg/L: 50% reduction
No response	Less than PR
Low dFLC PR	If initial dFLC 20 – 50 mg/L: dFLC < 10 mg/L
Progression / relapse [20]	From CR, any detectable monoclonal protein or abnormal FLC ratio (iFLC must double) From PR or stable response, 50% increase in serum M protein to > 0.5 g/dL or 50% increase in urine M protein to > 200 mg/day (visible peak) or dFLC increase of 50% to > 100 mg/L

Response evaluation: could we do better?

Adaptation of the treatment to the response

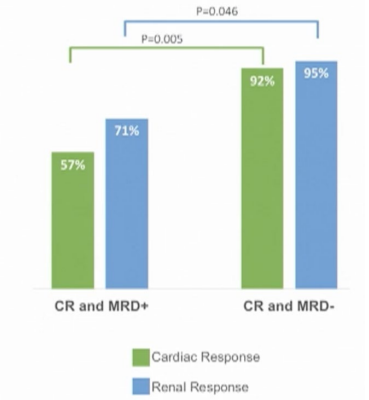


For Severe Disease?

- **STAGE IIIB**
- **Rapidly progressing severe RI**
- **Nephrotic syndrome with severe Hypoalbuminemia < 20g**
- **Liver amyloidosis with high biliribunine**

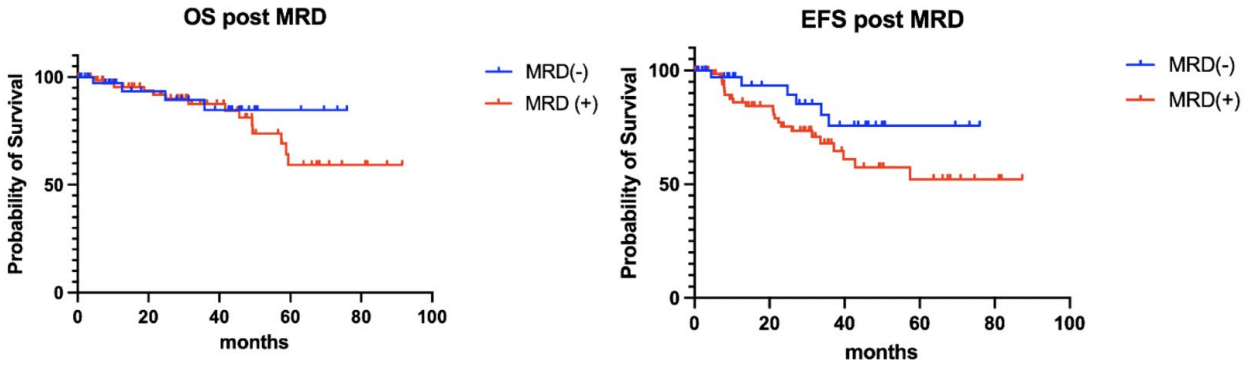
CR, complete response; dara, daratumumab; PR, partial response; VGPR, very good response

Palladini & Milani, JNCCN 2023



Minimal Residual Disease

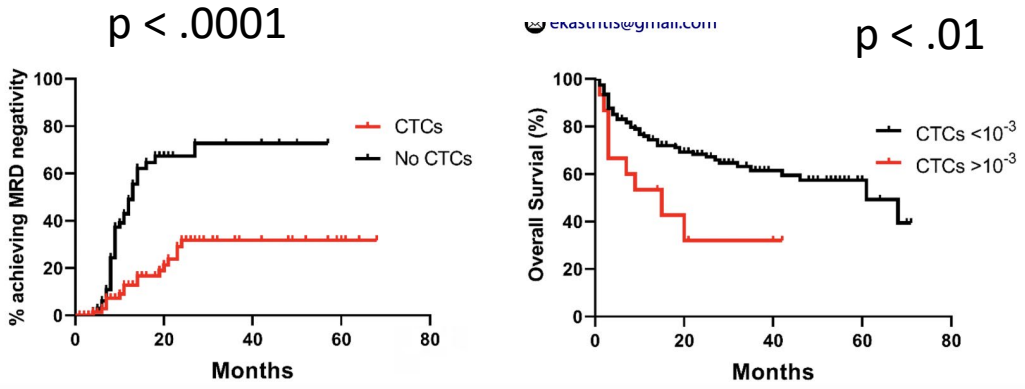
Evaluation of MRD using NG flowcytometry in patients with AL amyloidosis



- N=126
- No association MRD and dFLC <10 or iFLC <20

Kastritis S, ISA 2004 P156
Palladini G et all, Bloog Journal cancer 2020

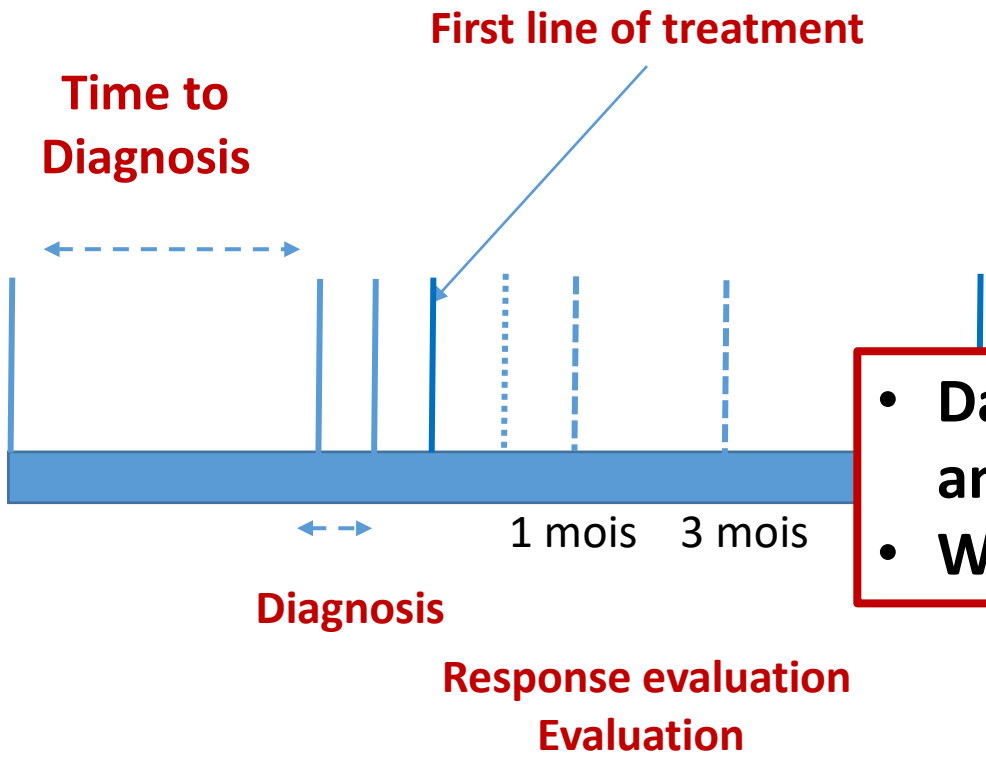
Prognostic significance of circulating tumor cells assessed with NGF in patients with AL amyloidosis



- + 59% (106/179)
- median 0.0015% of total nucleated cells

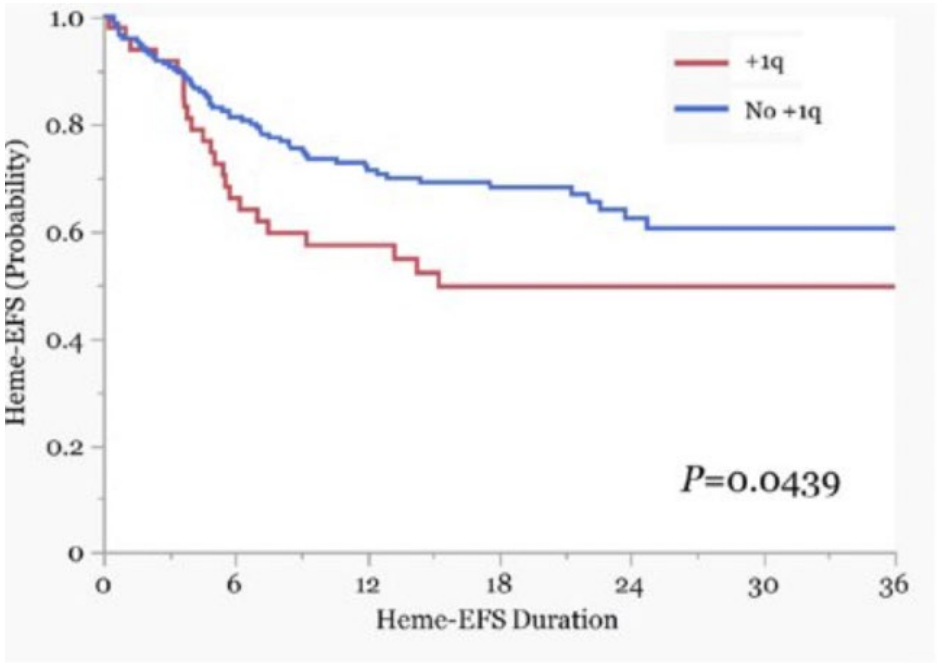
Kastritis S, ISA 2004 P550

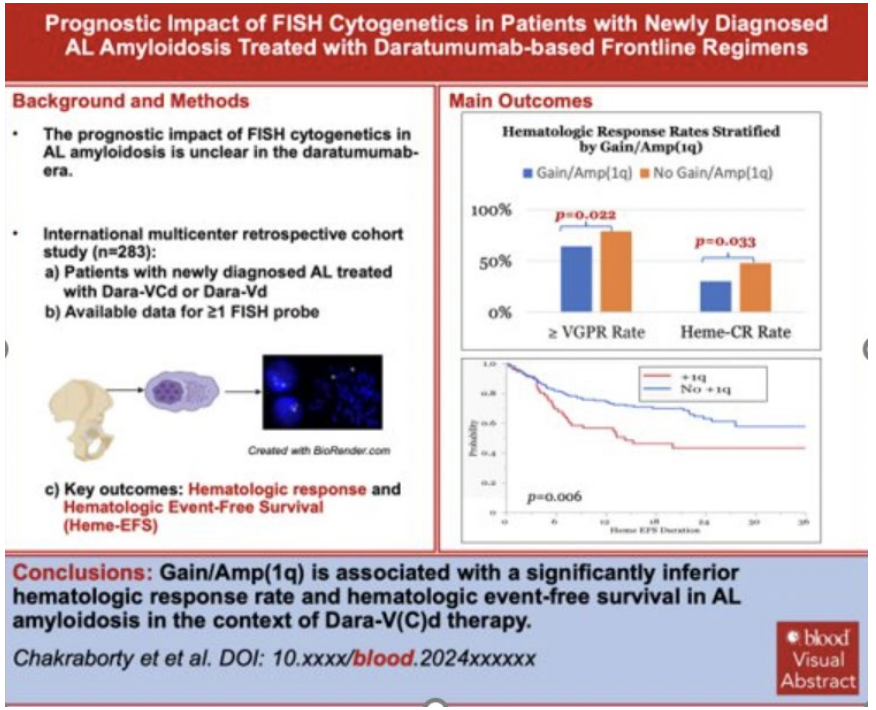
Management of AL amyloidosis



- **Dara-VCd : 20-30% will not achieve ≥VGPR and 40-50% CR**
- **What treatment if non optimal answer?**

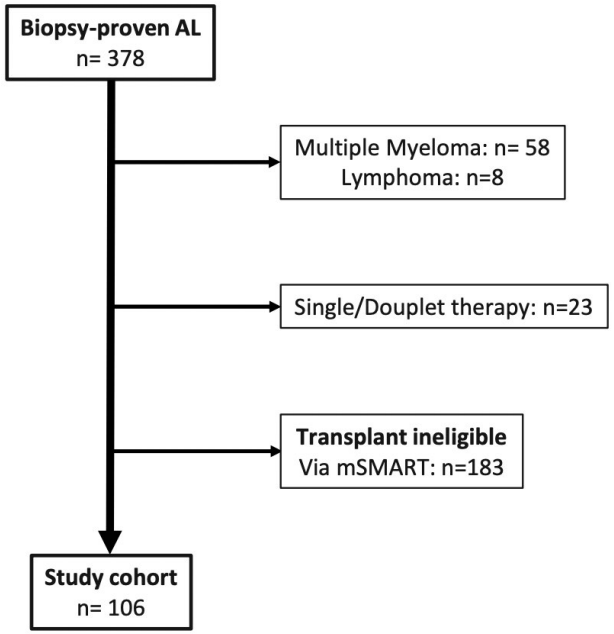
- **35. Prognostic impact of cytogenetic abnormalities by FISH in systemic AL amyloidosis in the era of daratumumab and bortezomib-based frontline combination regimens**
  - Rajshekhar Chakrabortya et al
- **Conclusion:** In the Dara-VCD/Dara-VD frontline therapy era, +1q presence is linked to lower deep hematologic response rates and poorer heme-EFS compared to its absence. On the other hand, t(11;14) is no longer linked to worse outcomes in the daratumumab-era.

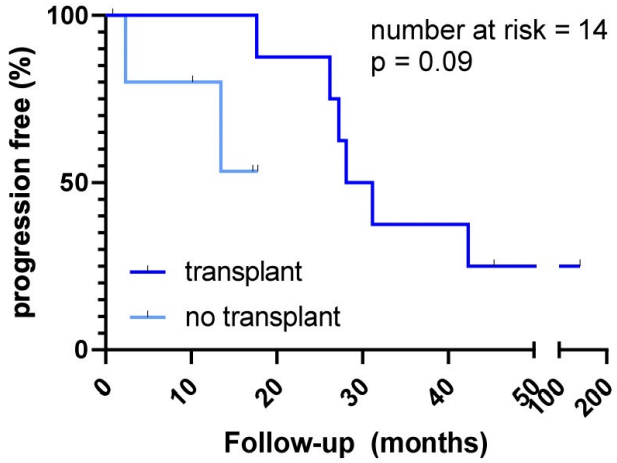




Is there still a place for ASCT?

PLASMA CELL CHARACTERISTICS PREDICT BENEFIT FROM INTENSIFIED THERAPY IN AL AMYLOIDOSIS





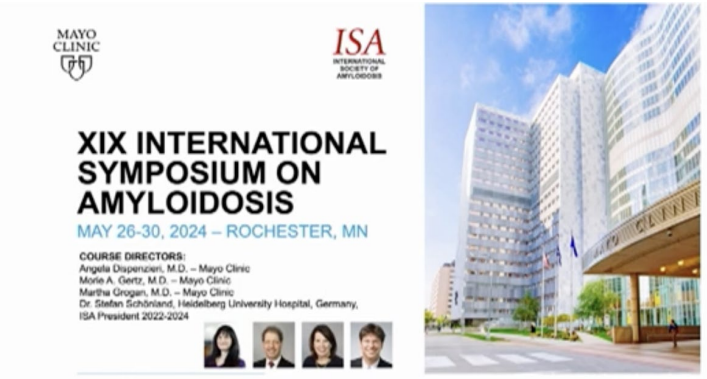
- R2-ISS derived high-risk FISH - del17p, t(4;14), t(14;16), t(14;20) and gain1q - is strongly associated with shorter PFS
- Only transplant had a trend to ameliorate the poor prognosis conveyed by high-risk FISH

Mj. Steinhardt, ISA 2024

ASCT FOR AL. STILL A ROLE?

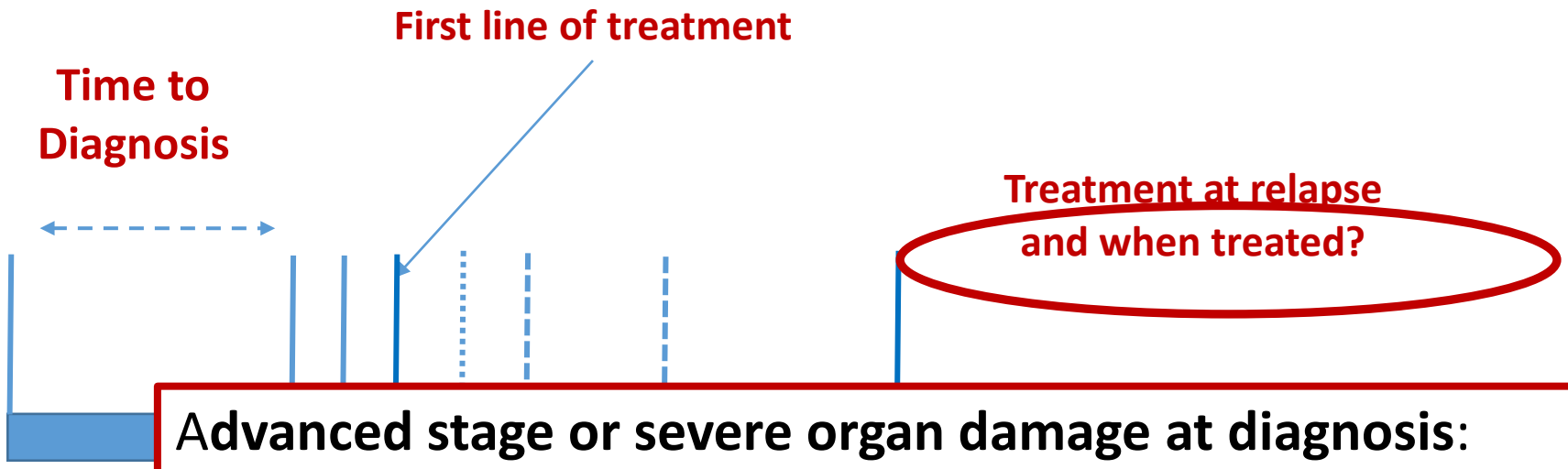
MURIELLE ROUSSEL

TRANSPLANT IN AL IS NO MORE A VALID OPTION



- TRANSPLANT IN AL CAN BE AN OPTION, IN SPECIFIC CONDITIONS
  - Non responding patients with an IgM AL patients
  - Symptomatic multiple myeloma and HR cytogenetics and no severe organ involvement
  - Refractory patients without severe organ involvement?
    - BUT venetoclax, BiTEs, CAR-T cells....

Management of AL amyloidosis



Advanced stage or severe organ damage at diagnosis:

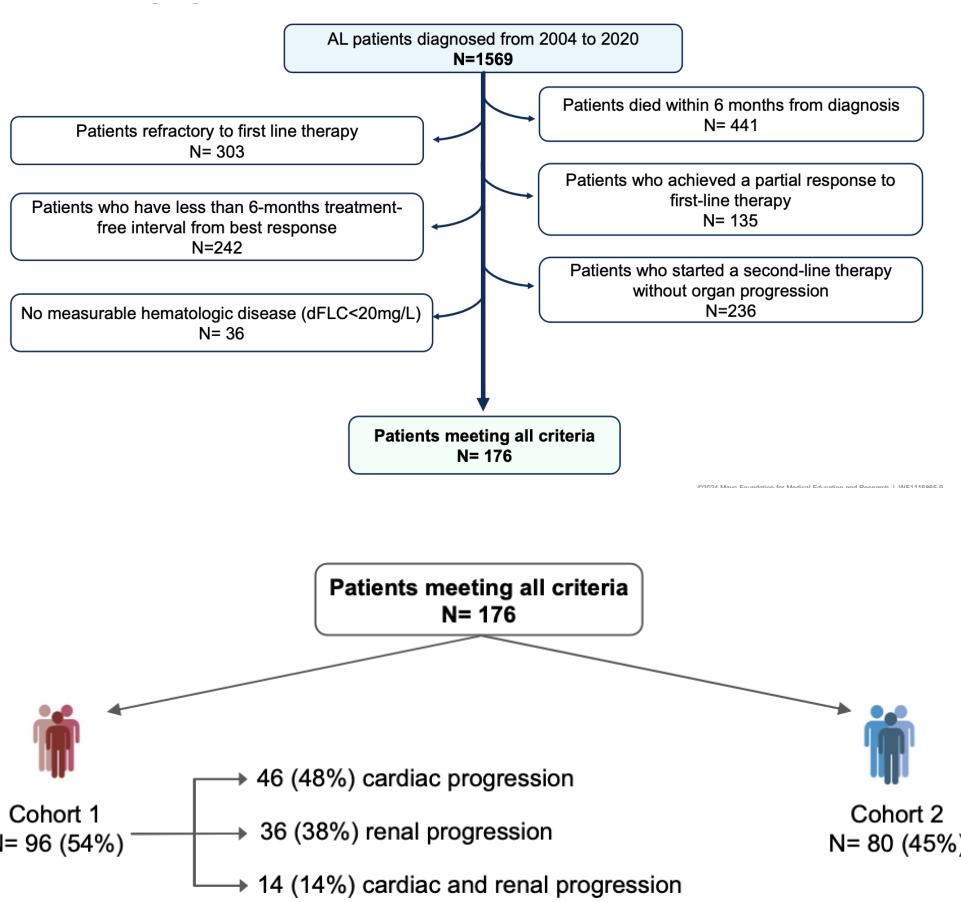
- Pavia group criteria: ↑dFLC >20 mg/L, level >20% of baseline value, and >50% increase from the value reached at best response

Patient with **low stage diseases and limited organ** involvement at diagnosis:

- Wait ↑ dFCL 50% of the diagnostic level could be an option

Particular attention for patients with low dFLC at diagnosis

Proposed hematologic progression criterion in AL amyloidosis

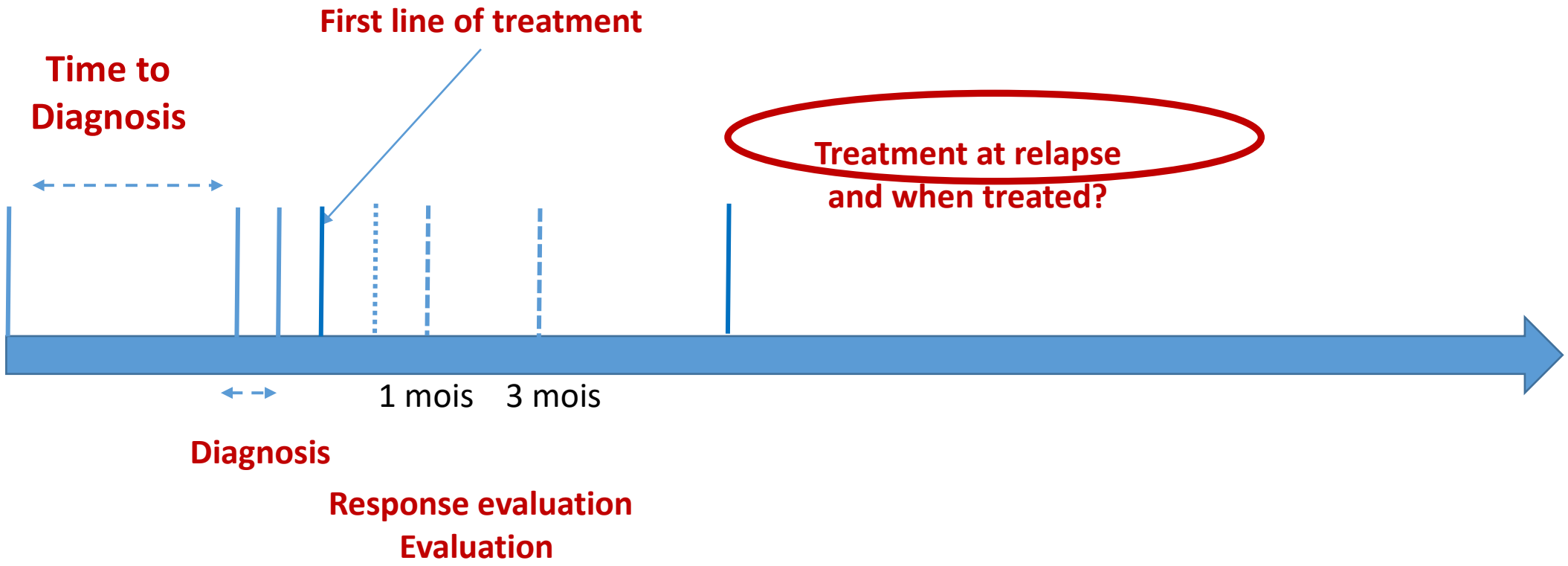


- Best dFLC cutoffs predicting organ progression:
  - **↑ > 10% from the value at diagnosis.**
  - **↑ >more than 15mg/L compared to best hematologic response value**
  - combined, both cutoffs predict organ progression with a specificity of 96%.

Median follow-up 10 years

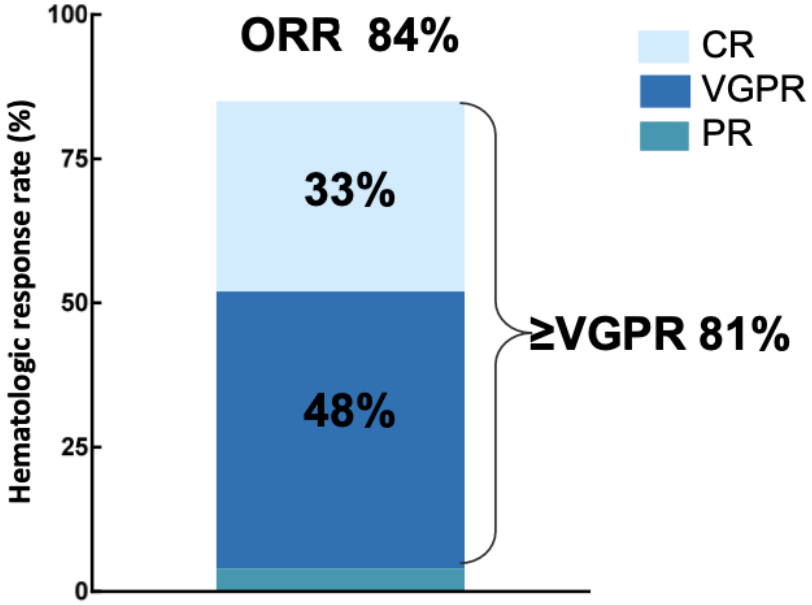
G Palladini, OA18 ISA 2024

Management of AL amyloidosis

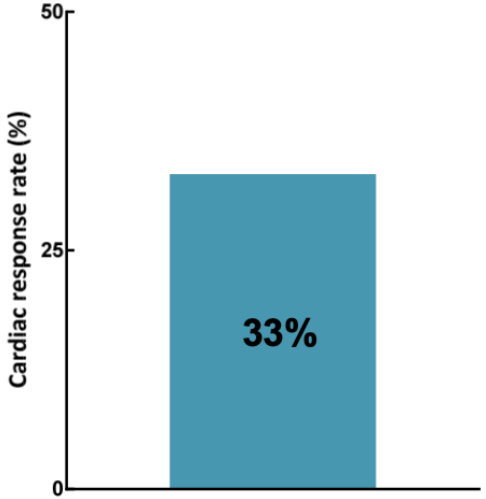


PHASE II STUDY: DARA-POMALIDOMIDE IN PREVIOUSLY TREATED AL AMYLOIDOSIS

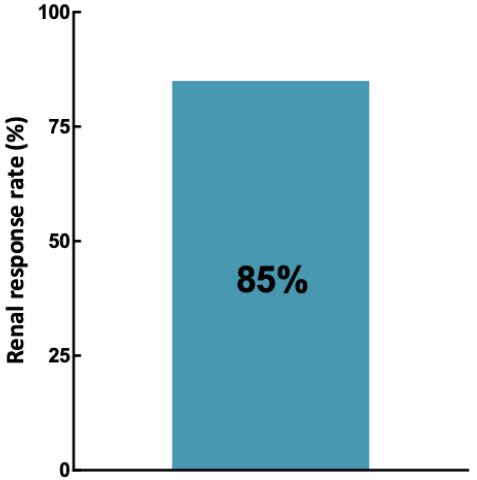
Hematological response



Cardiac response (cycle 6)



Renal response (cycle 6)

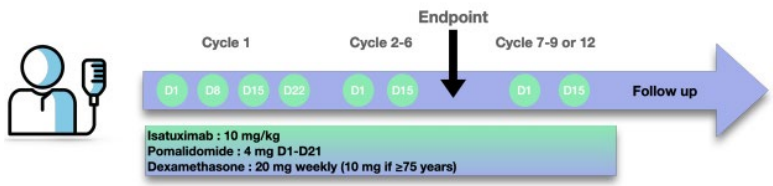


- N=27, No patients with prior Dara exposure
- HR reached **at day 8 in 20/27 (74%)** cases
- Primary endpoint: CR+VGPR HR after 6 cycle
- AE: mainly cytopenia (G-CSF)

Paolo Milani, ISA 2024

Efficacy and safety of isatuximab, pomalidomide and dexamethasone (IPd) in relapsed AL amyloidosis: interim results of the IsaMYP study

K. Queru (1) ; L. Tabone (2) ; S. Bender (3) ; B. Royer (4), M. Macro (5), G. Olombel (3) ; V. Pascal (3) ; MO. Petillon (2) ; J. Corre (6); F. Bridoux (3,7); A. Jaccard (1,3) ; M. Roussel (1,3)
(1) Hématologie Clinique, CHU Dupuytren 1, Limoges; (2) Coordination, IFM, Paris; (3) Immunologie, CRIBL U1262, Université de Limoges, Limoges; (4) Service d'immunoHématologie, CHU St Louis, APHP, Paris; (5) Hématologie Clinique, CHU Cote de Nacre, Caen; (6) Génétique des Hémopathies, IUC-Oncopole, Toulouse; (7)Service de Néphrologie et Transplantation Rénale, CHU La miletrie, Poitiers



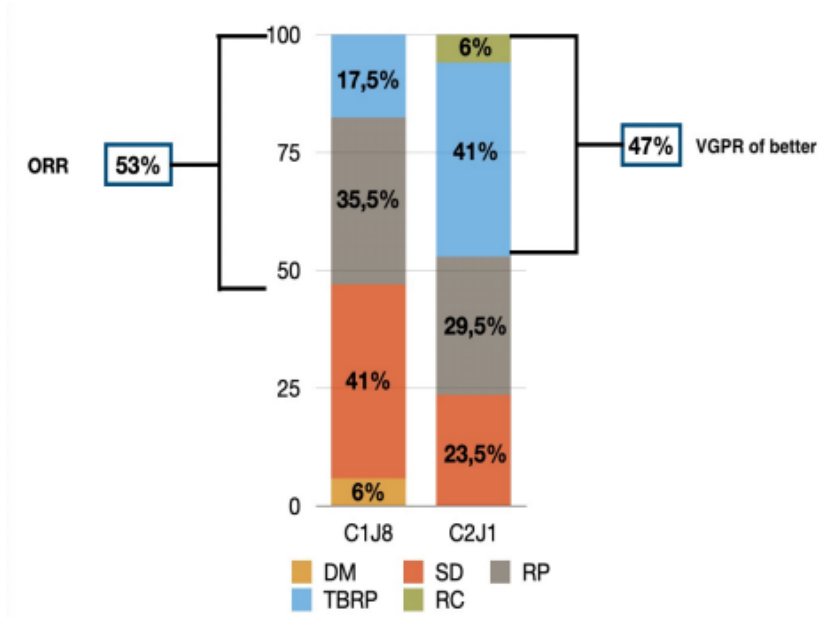


Figure 3 : Hematological responses at D8C1 and D1C2

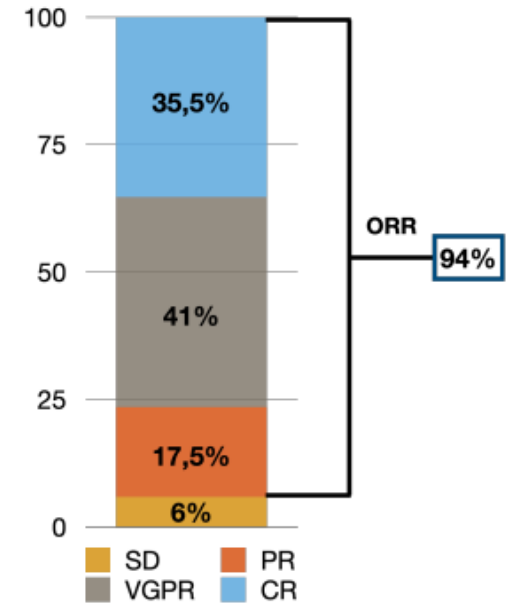
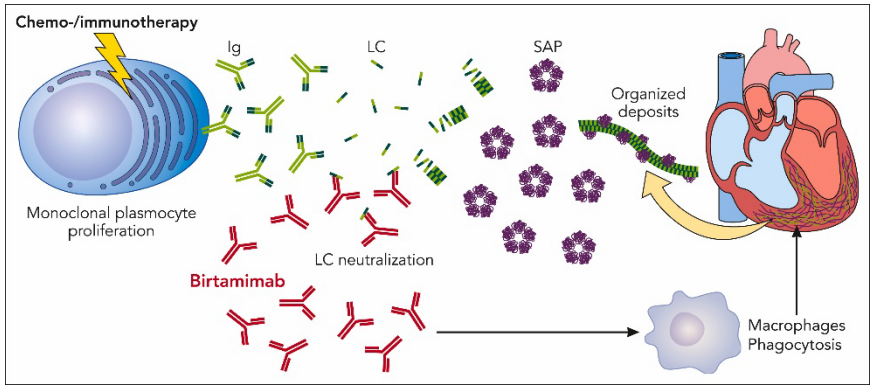


Figure 4 : Overall hematological responses at D1C5

News from NEOD001?

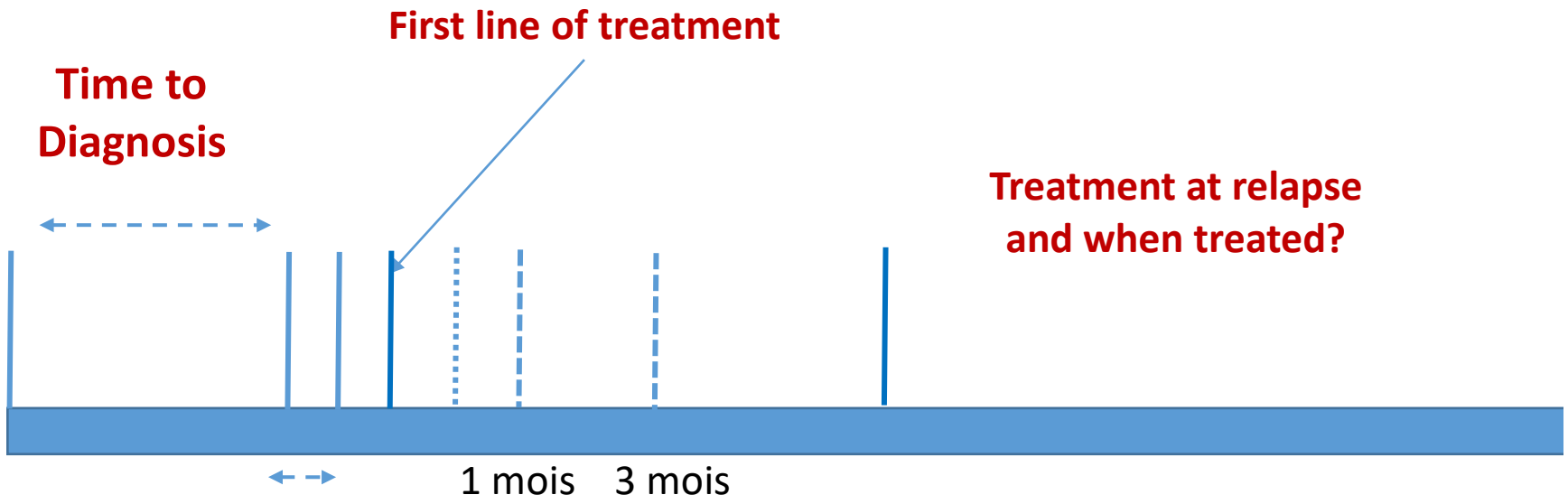


- Phase 3 VITAL trial, newly diagnosed treatment-naïve patients with AL amyloidosis received birtamimab + standard of care (SoC) or placebo + SoC

Conclusions: Treatment with birtamimab + SoC in patients with Mayo Stage IV AL amyloidosis was associated with significantly less decline in HRQoL versus placebo + SoC in several SF-36v2 domains

MG Gertz, IMS2024

Management of AL amyloidosis



Hope

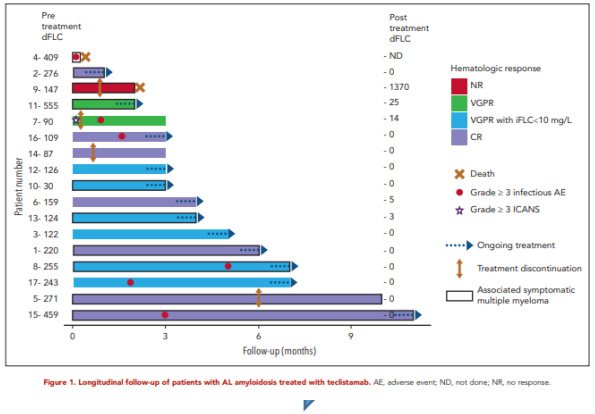


Figure 1. Longitudinal follow-up of patients with AL amyloidosis treated with teclistamab. AE, adverse event; ND, not done; NR, no response.

Controversies in the Management of Cardiac Amyloidosis (Sponsored by an unrestricted grant from BridgeBio) 1. Digoxin: Wrongfully Accused? 2. Beta-Blockers: Always Bad? 3. Entresto: Should We Ever Use It? 4. Mineralocorticoids: Yes, No? 5. SGLT2i for All? 6. Watchman: Wait a Minute? 7. Panel Discussion Q & A	*T. Damy (moderator)* *R. Cheng* *A. Masri* *M. Lyle*

Still subject to debate on different levels, so let's get started.