

**HOT
NEWS**

NELLE SINDROMI LINFOPROLIFERATIVE: la storia continua

Casi clinici: Macroglobulinemia di Waldenstrom

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Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Beigene						X	x
Abbvie						X	x
Janssen						X	x
AstraZeneca							x

Clinical case (1)

- 60 yrs old
- Obesity
- 2007 WM diagnosis, regular follow up with progressive slow IgM increase

May 2020 (*phone consultation due to COVID19 restrictions*)

Normal CBC

IgM 4900 mg/dl

No WM-related symptoms

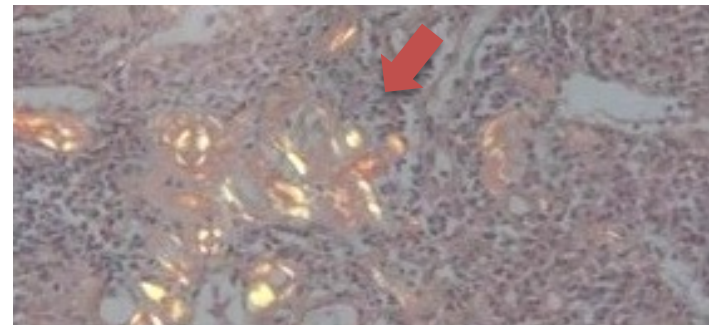
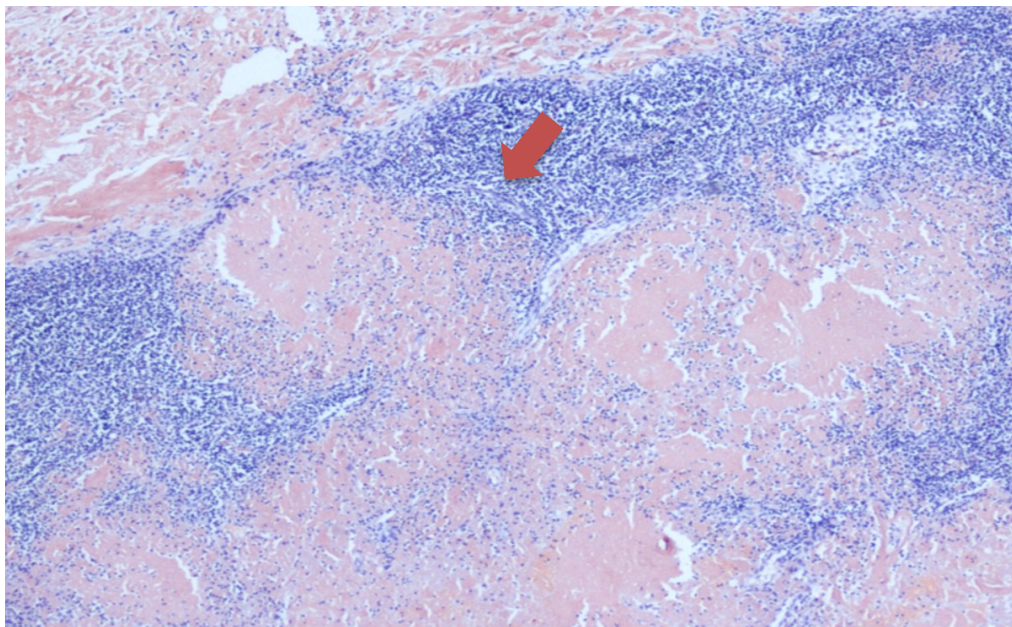
Clinical case (2)

Aug 2020: first aid access due to anasarca and dyspnea

- Normal CBC; IgM 5320 mg/dl; no hypoalbuminemia
- CT scan:
 - massive bilateral **pleural effusion**;
 - abdominal effusion**
 - diffuse **subcutaneous imbibition**
 - macroglossia**
 - upper/below diaphragm adenopathies **max 3.8 cm**
- PET: SUVmax 6
- Thoracentesis: 1700 ml, no neoplastic cells

Lymph node biopsy

Lymph node hystology



Diagnostic algorithm

Suspected systemic amyloidosis

- Nephrotic range proteinuria
- Heart failure with preserved ejection fraction
- Nondiabetic neuropathy (50% have carpal tunnel syndrome)
- Hepatomegaly and/or non-infectious diarrhoea
- Atypical MGUS or smoldering myeloma
- MGUS with abnormal free light chain ratio and elevated NT-proBNP and/or proteinuria

- Fat aspirate (sensitivity 80%)
- BM biopsy (sensitivity 70%)
- Lip/minor salivary gland (sensitivity 80%)

biopsy for Congo red

Negative

(amyloidosis excluded in 80%)

Positive

AL

ATTR

If continuous suspicious:

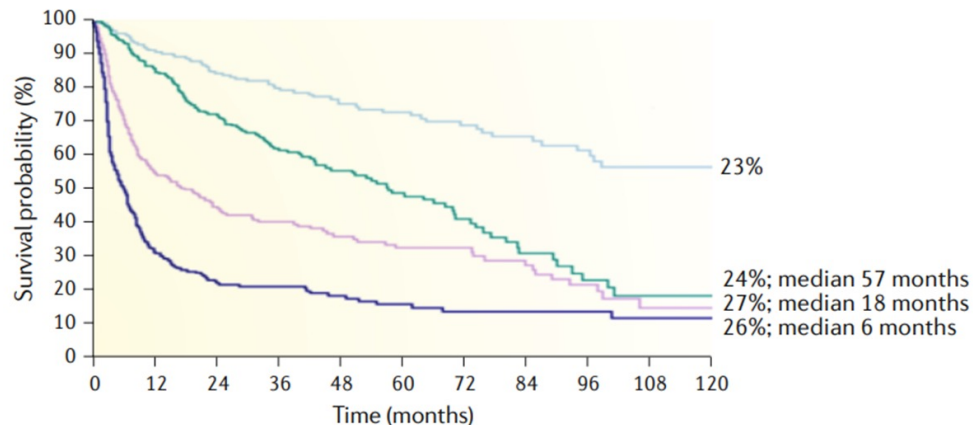
- Cardiac MRI (if clinical symptoms)
- Organ biopsy

Staging and measurement of FLC, NT-proBNP and troponin

Staging, clinical case (3)

Target	Tests	
Clone	<ul style="list-style-type: none"> • BM biopsy • MYD88, CXCR4 mutation • CT scan • sELF, uELF, FLC, Ig 	⇒ BM: 40% LPL infiltrate, positive Congo Red
		⇒ MYD88mut/CXCR4wt; No t(11;14)
		⇒ dFLC (lambda-kappa) 48; k/l ratio 17
Heart	<ul style="list-style-type: none"> • NT-proBNP or BNP if renal failure, cTn • Echocardiography (cardiac MRI, scintigraphy) • ECG 	⇒ NT-proBNP: 566; TnT: 21
		⇒ Normal echo (EF 60%), MRI
Kidney	<ul style="list-style-type: none"> • 24 h proteinuria, s creatinine, eGRF 	⇒ 24/h proteinuria 0.2 g/24h Neg uIMF
Liver	<ul style="list-style-type: none"> • Liver function tests • Liver imaging (echo, TC) 	⇒ Normal
Other	(if clinically indicated) EMG Gastroscopy	⇒ Normal EMG

Staging, clinical case (4)



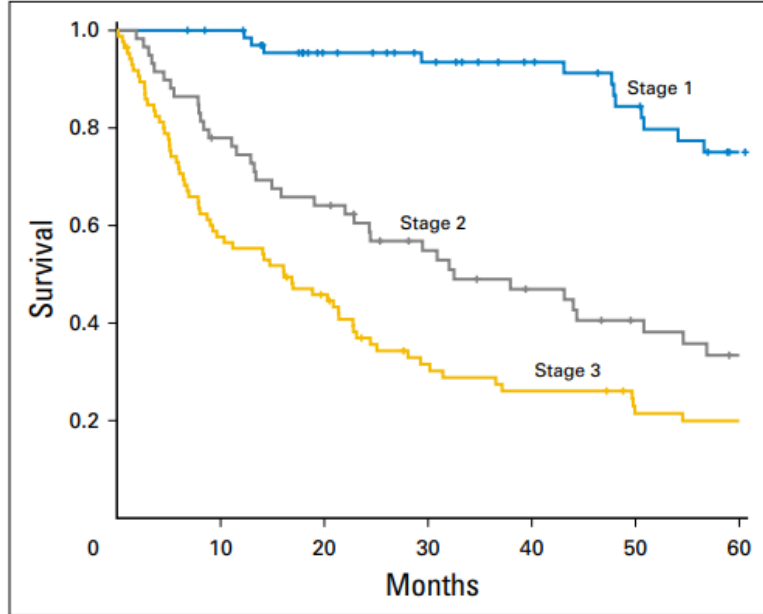
Revised Mayo Staging System:

- NT-proBNP > 1800 ng/L
- cTnT > 0.025 ng/mL
- dFLC > 180 mg/L



rev Mayo SS: stage I

Staging IgM-related amyloidosis



- **NT-proBNP >332 ng/L**
- **Cardiac troponin T > 0.035 mg/L or cardiac troponin I >0.1 mg/L**
- **Liver involvement and involvement of neuropathy**

Stage 1, no abn features

Stage 2, one or more features

Stage 3, two or more features

IgM-rel amyloidosis SS: stage 2

IgM vs non-IgM amyloidosis

	IgM	Non IgM
N of pts	644	1727
Male	59%	60%
Renal	58%	68%
Cardiac	41%	82%
Neuropathy	23%	13%
Liver	16%	14%
Soft tissue	27%	17%
Lymphnodes	22%	9%
GI tract	10%	12%



Therapeutic implications:

- ↑ eligibility to ASCT
- ↓ eligibility to bortezomib-based tx

Clinical case (5)

- **Reduce the levels of the amyloid light chain as deeply and as quickly as possible**
 - Eliminate toxicity and block the proteotoxic cascade

- **Accelerating the removal of amyloid deposits may:**
 - Allow to partially recover organ damage and extend survival
 - ↓ the formation of fibrils

NB: treatment must be:

- **Risk adapted (cardiac staging, neurologic evaluation)**
- **Response tailored (evaluate every second cycle)**

Case-specific therapeutic considerations

➤ **Reduce the levels of the amyloid light chain as deeply and as quickly as possible**

- Eliminate toxicity and block the proteotoxic cascade

➤ **Accelerating the removal of amyloid deposits may:**

- Allow to partially recover organ damage and extend survival
- ↓ the formation of fibrils

NB: treatment must be:

- **Risk adapted (cardiac staging, neurologic evaluation)**
- **Response tailored (evaluate every second cycle)**

➤ **No PN**

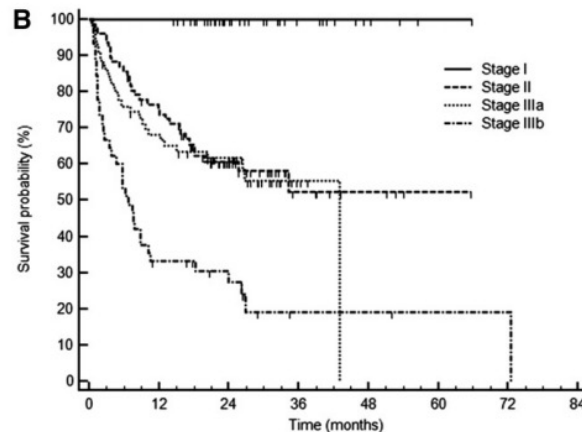
➤ **No bulky disease**

➤ **Need of rapid disease control**

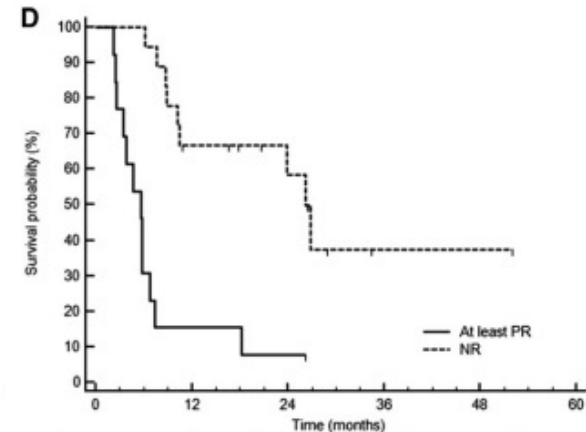
➤ **Effective on both WM and amyloidosis**

Bor-Cy-Dex

Impact of staging on OS



OS according to hematologic response (\geq PR)



230 pts
ORR 62%
VGPR+CR 43%

Cardiac response 17%
Renal response 25%

~20% of pts became ASCT-eligible after Bor-Cy-Dex

Clinical case (7)

Mo/year	Regimen	WM response	Amyloidosis response
June-July 2020	Bor-Cy-Dex 2 cycles	PR	SD
Aug-Sep 2020	Bor-Cy-Dex 2 cycles	PR	PR
Dec 2020- Jan 2021	Bor-Dexa-Rituximab 1 cycles	PR	PR

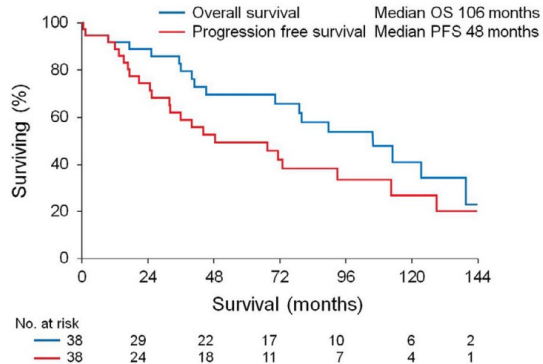
← Covid pneumonia

← Recurrence of symptomatic pleural effusion managed with diuretics

- 60 years old
- Partial hematologic response
- Clinical improvement
- Need to consolidate clinical response and improve survival**

ASCT in AL amyloidosis

Center	Criteria
Amyloidosis Center Boston	>70 years, >NYHA II, PS>2, sBP<90 mmHg, symptomatic pleural effusions, EF<40%
Mayo Clinic	>70 years, >NYHA II, PS >2, cTNT >0.06 ng/ml, Crea-cl <30 ml/min (unless on chronic dialysis), >2 organs
Amyloidosis Center Pavia	>65y, >NYHA II, PS>2, NT-proBNP>5000 ng/L, cTnT>0.06 ng/mL, EF<45%, sBP<90 mmHg, eGFR<50 mL/min, DLCO <50%
Memorial Sloan Kettering, NY	> 60 years, >3 organs involved, advanced cardiac disease
HOVON Study Group	PS >2, >NYHA III, EF <45%, other severe diseases
French Study group	Inadequate organ function, elevated NT-ProBNP and TNT
NAC, London	>2 organs, PS >1, eGFR <50 ml/min, significant cardiac involvement, autonomic neuropathy or gastrointestinal involvement, TNT >0.06 ng/mL.
Amyloidosis Center Heidelberg	>70 years, >NYHA II, PS>2, sBP <90 mmHg, symptomatic pleural effusions. Crea-cl < 30 ml/min (unless on chronic dialysis).



38 pts

- Renal 63%
- Neurologic 32%
- Cardiac 26%

ORR 92%

VGPR+CR 72%

Clinical case (8)

Mo/year	Regimen	WM response	Amyloidosis response
June-July 2020	Bor-Cy-Dex 2 cycles	PR	SD
Aug-Sep 2020	Bor-Cy-Dex 2 cycles	PR	PR
Dec 2020- Jan 2021	Bor-Dexa-Rituximab 1 cycles	PR	PR
May 2021	CTX HD+plerixafor	PR	VGPR
Aug 2021	ASCT	PR	VGPR

← Covid pneumonia

← Recurrence of symptomatic pleural effusion managed with diuretics

- Significant clinical improvement, no changes in pleural effusion or LN size
- Baseline dFLC 48 → pre-ASCT dFLC 5

What's next?

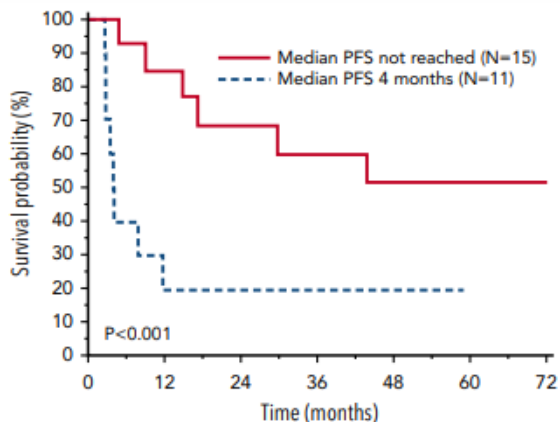
Bendamustine-rituximab in IgM-systemic amyloidosis

ORR 59%
CR+VGPR 22%

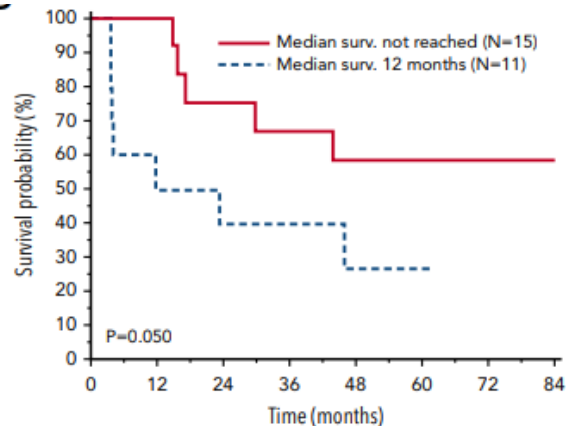
36 pts (TN+RR), m FU 18 mo

Cardiac involv 58%

PFS according to heme resp

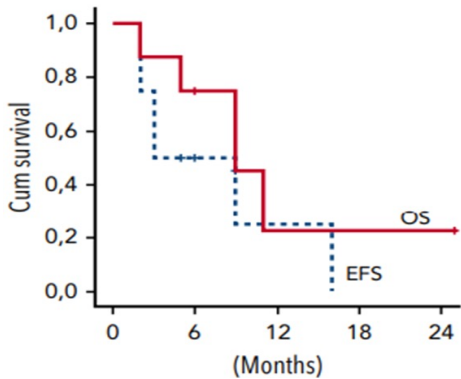
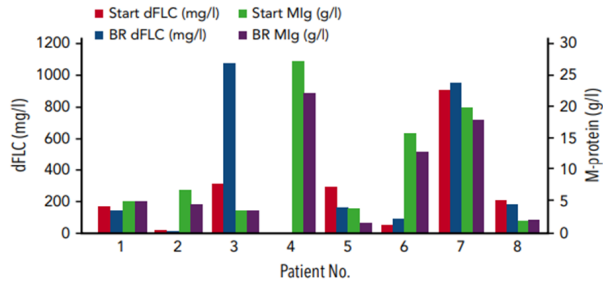


OS according to heme resp



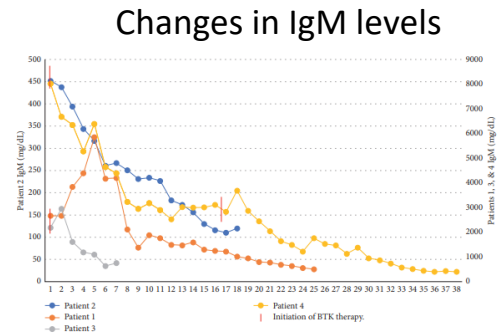
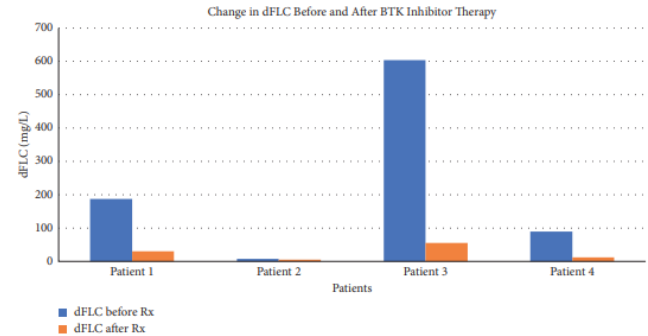
What's next? BTKi in IgM-systemic amyloidosis

M tx duration 4 mo (2-16)
Response in 2/8 pts



Pika Blood 2019

Changes in dFLC before and after iburtinib/acala



Zerdan Adv Hematol 2022

Conclusions

- **Rare complication of a rare disease**
 - importance of early recognition
- **Importance of rapid elimination of amyloid precursor**
- **Different treatment goals: QuoL, survival**
- **Need of new drugs/salvage treatments**