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Clinical or biochemical progression of Myeloma: when patients need treatment

DISCLOSURE

Francesco Di Raimondo

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Current Hematologic Malignancy Reports (2019) 14:187–196
https://doi.org/10.1007/s11899-019-00507-x

MULTIPLE MYELOMA (P KAPOOR, SECTION EDITOR)

Expert Panel Consensus Statement for Proper Evaluation of First Relapse in Multiple Myeloma

M. Offidani[1] · M. Boccadoro[2] · F. Di Raimondo[3] · M. T. Petrucci[4] · P. Tosi[5] · M. Cavo[6]

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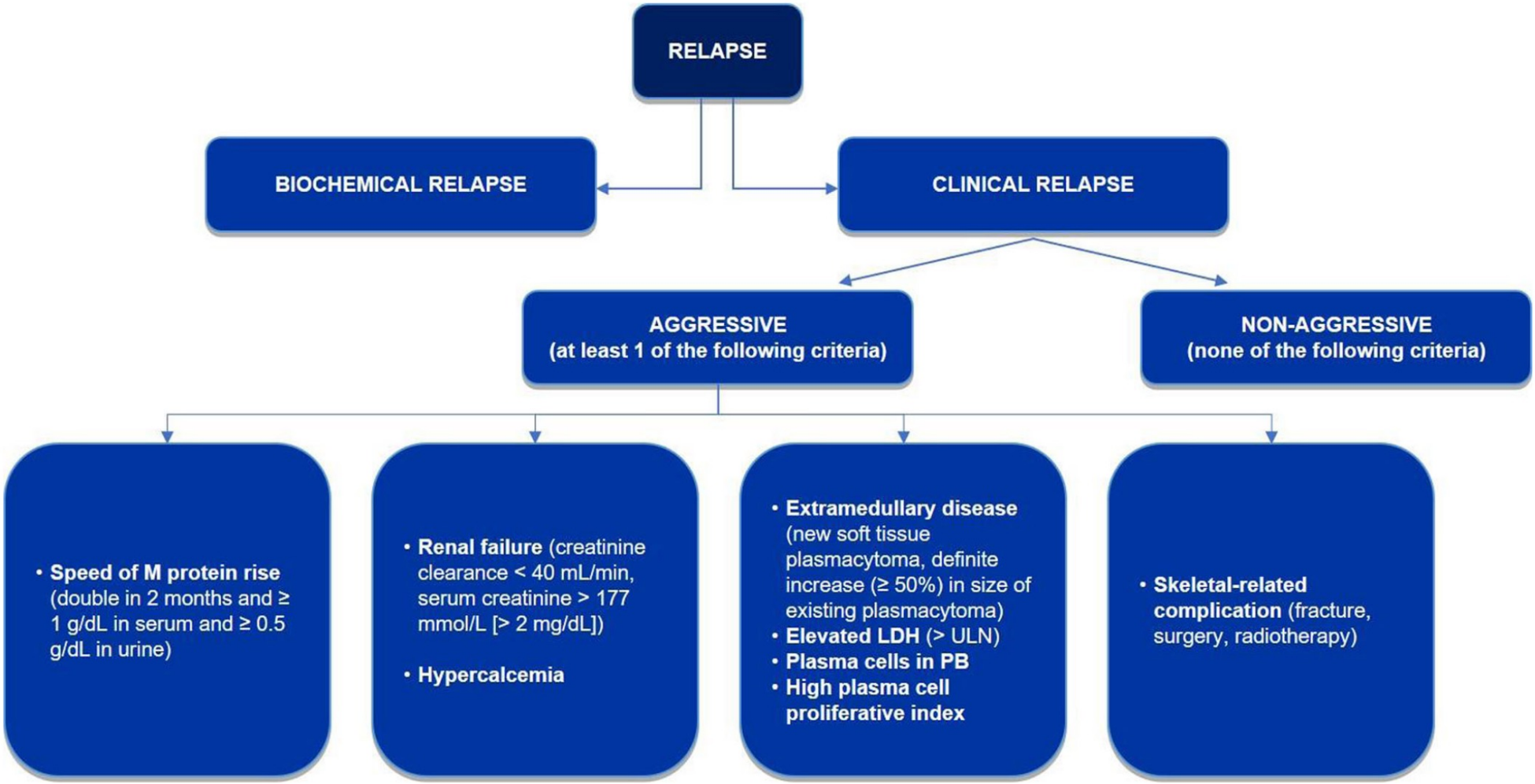
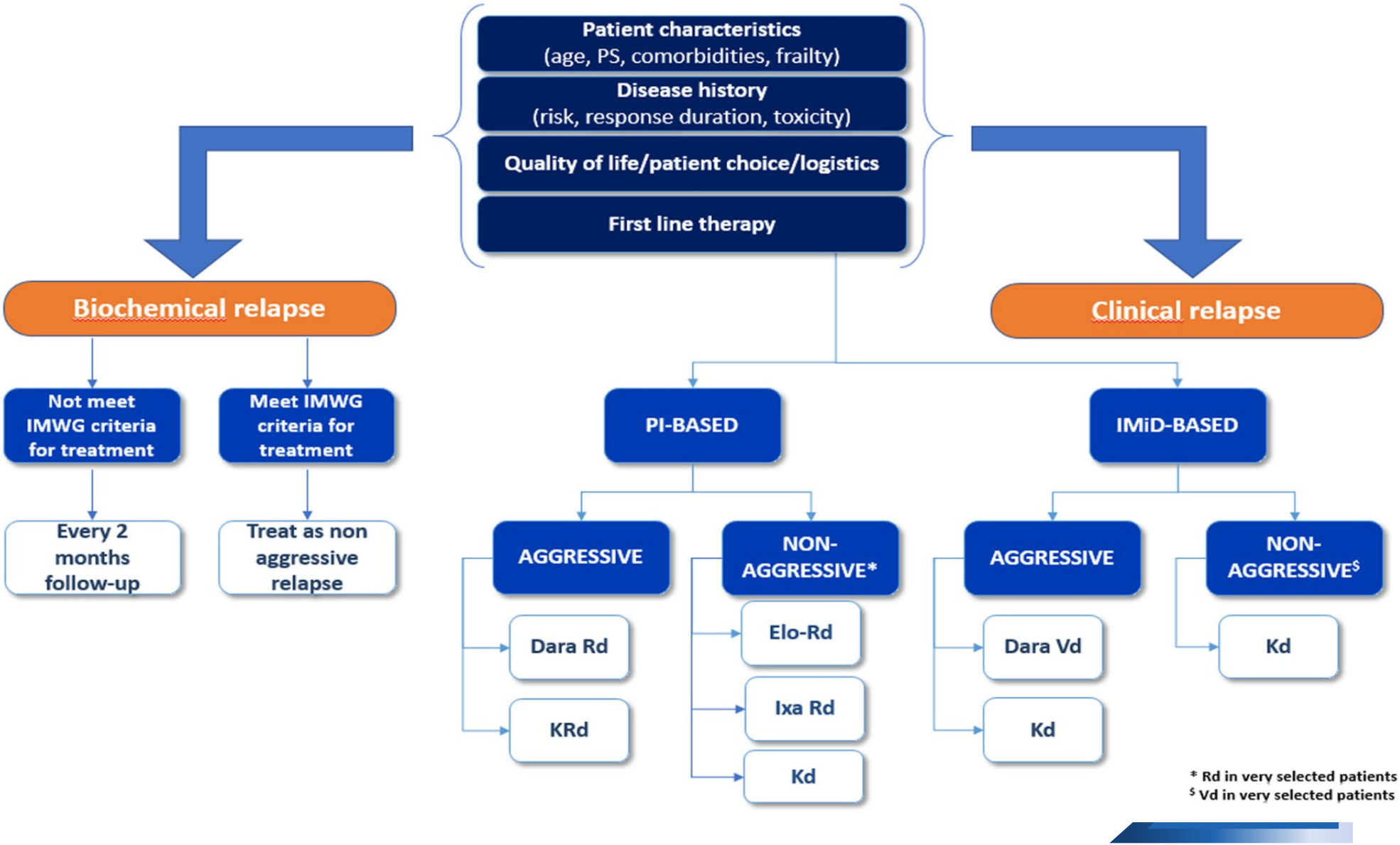
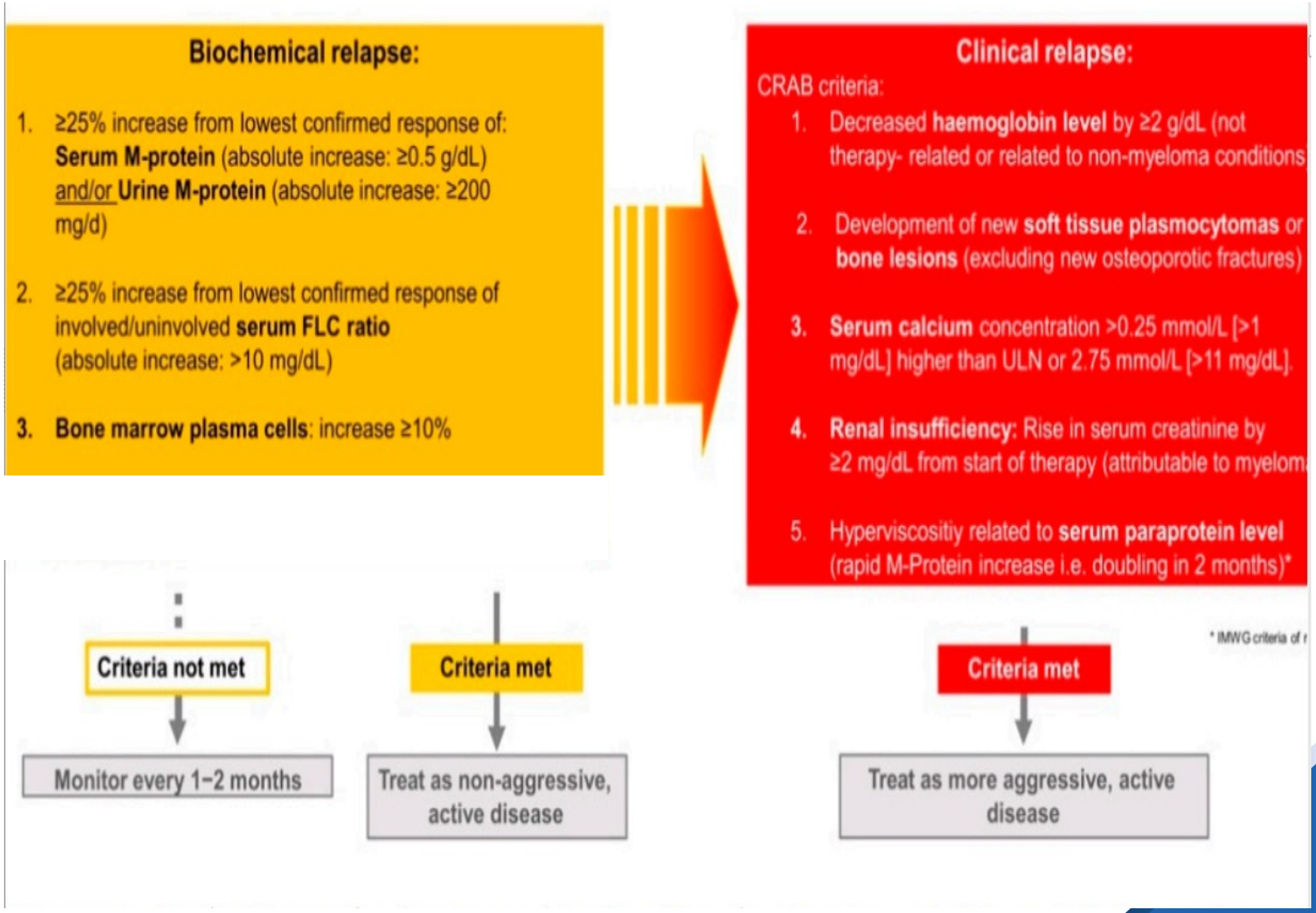
Abstract

Purpose of Review A working group of six expert physicians convened to assess the spectrum of relapse presentations, discussed the features that can define the disease as aggressive and n


RELAPSE
BIOCHEMICAL RELAPSE
CLINICAL RELAPSE
AGGRESSIVE
(at least 1 of the following criteria)
NON-AGGRESSIVE
(none of the following criteria)
• Speed of M protein rise (double in 2 months and ≥ 1 g/dL in serum and ≥ 0.5 g/dL in urine)
• Renal failure (creatinine clearance < 40 mL/min, serum creatinine > 177 mmol/L [> 2 mg/dL])
• Hypercalcemia
• Extramedullary disease (new soft tissue plasmacytoma, definite increase (≥ 50%) in size of existing plasmacytoma)
• Elevated LDH (> ULN)
• Plasma cells in PB
• High plasma cell proliferative index
• Skeletal-related complication (fracture, surgery, radiotherapy)


Patient characteristics
(age, PS, comorbidities, frailty)
Disease history
(risk, response duration, toxicity)
Quality of life/patient choice/logistics
First line therapy
Biochemical relapse
Clinical relapse
Not meet IMWG criteria for treatment
Meet IMWG criteria for treatment
Every 2 months follow-up
Treat as non aggressive relapse
PI-BASED
IMiD-BASED
AGGRESSIVE
NON-AGGRESSIVE*
AGGRESSIVE
NON-AGGRESSIVE$
Dara Rd
KRd
Elo-Rd
Ixa Rd
Kd
Dara Vd
Kd
Kd
* Rd in very selected patients
$ Vd in very selected patients



Gengenbach C, Cancers 2021

STATE OF ART

It is unclear whether starting treatment for biochemical progression provides any survival benefit to patients compared with initiation of therapy for symptomatic progression presenting with bone disease or other end-organ damage

Most consensus guidelines recommend initiating treatment at symptomatic relapse or in the event of rapidly rising paraprotein levels, largely based on expert opinion

Bone Marrow Transplantation (2014) **49,** 223–227
© 2014 Macmillan Publishers Limited All rights reserved 0268-3369/14
www.nature.com/bmt

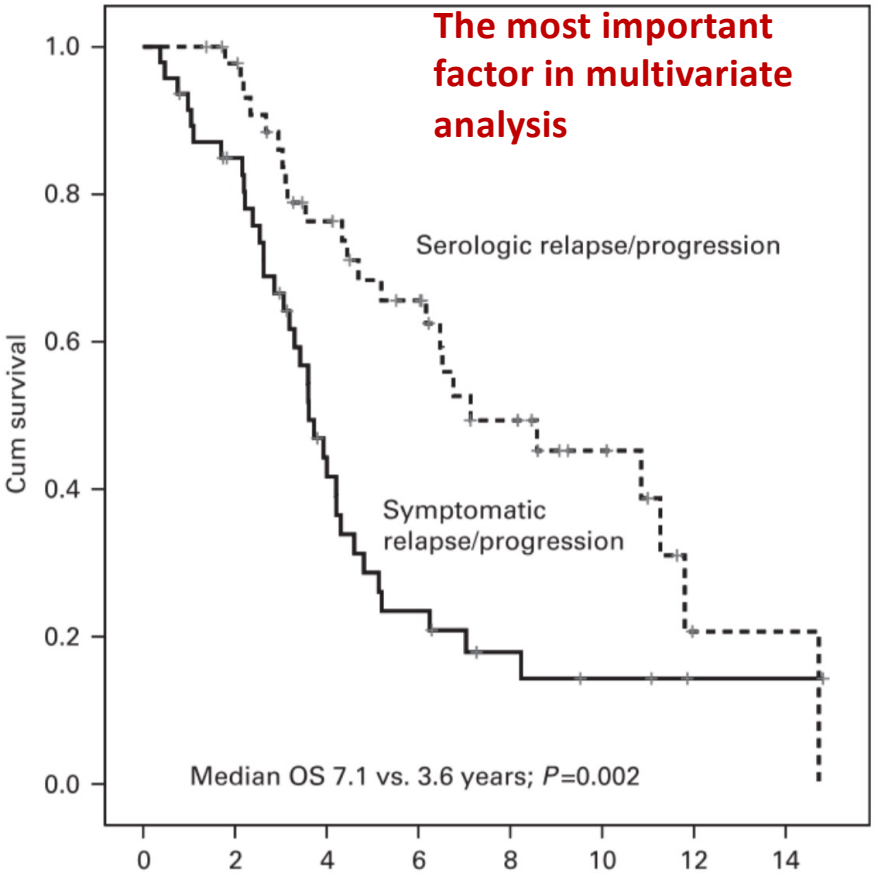
ORIGINAL ARTICLE

Pattern of relapse and progression after autologous SCT as upfront treatment for multiple myeloma

C Fernández de Larrea, R Jiménez, L Rosiñol, E Giné, N Tovar, MT Cibeira, F Fernández-Avilés, C Martínez, M Rovira and J Bladé

- **170 pts**
- **Symptomatic relapse 49,5%**
- **Biochemical relapse 50,5%**

OS in relapsed/progressing patients with MM after ABMT according to pattern of relapse



- Patients with asymptomatic relapse achieved a higher rate of response (69% vs 43% p= 0.016)
- Median time between asymptomatic relapse and treatment was only 5.6 months
- However, in 26% of pts with asymptomatic relapse, treatment was not initiated within the first 2 yrs. All these pts had ISS I or II at diagnosis

Fernandez de Larrea C, BMT 2014

Annals of Hematology (2018) 97:1671–1682
https://doi.org/10.1007/s00277-018-3361-2

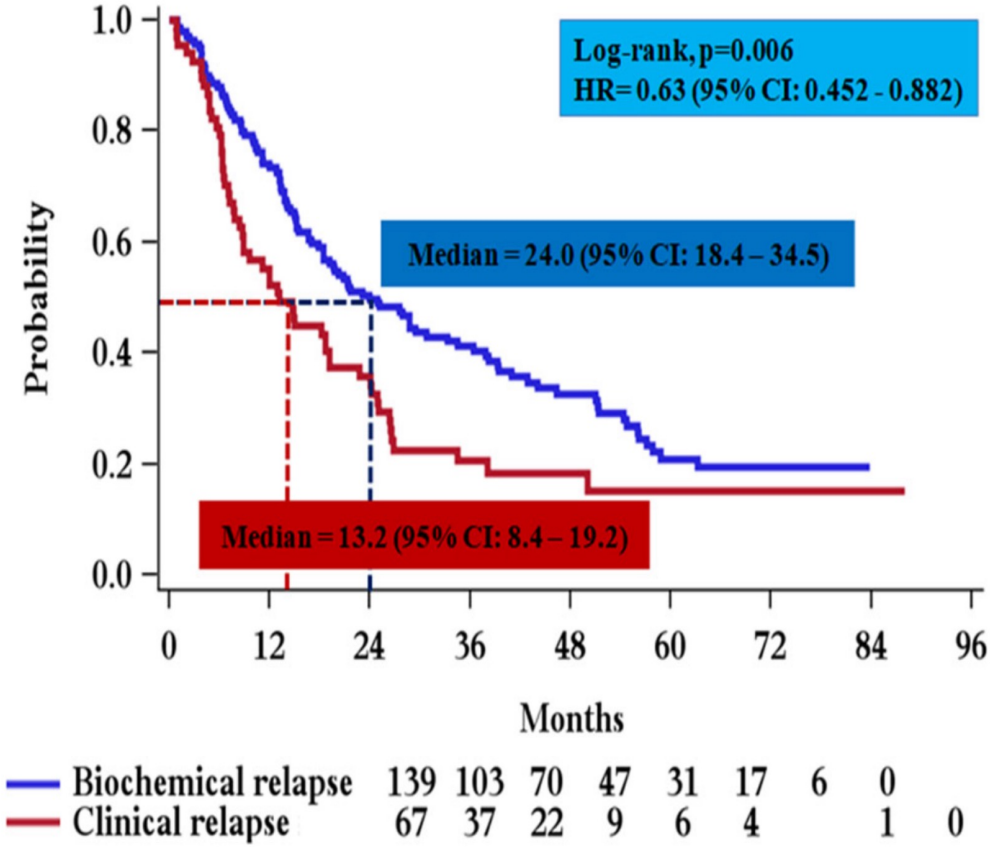
ORIGINAL ARTICLE

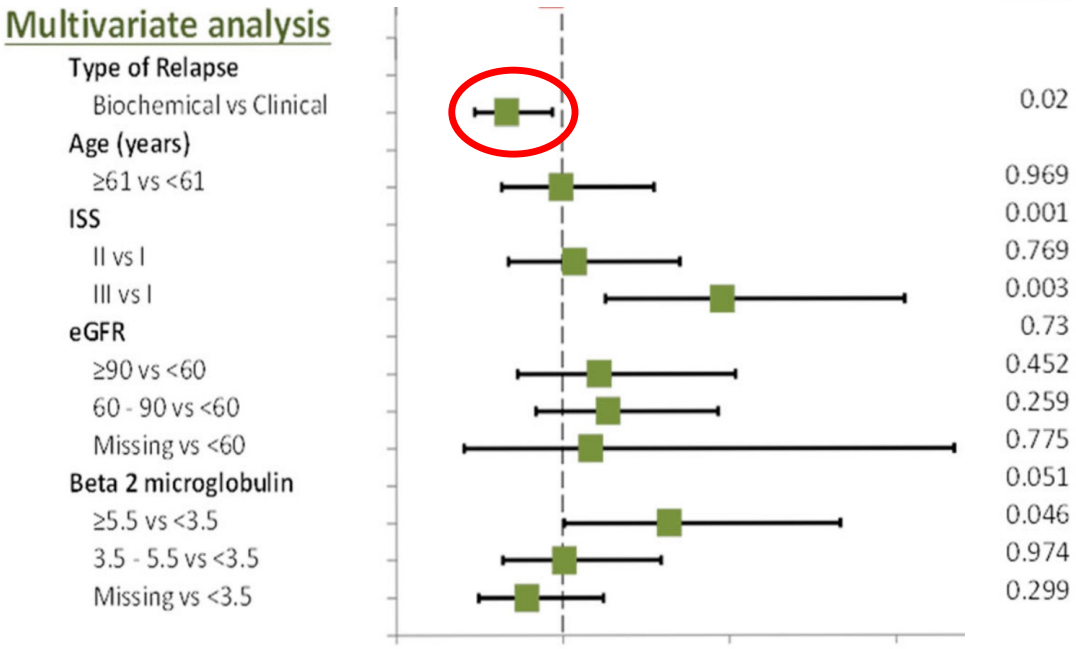
Real-world data on Len/Dex combination at second-line therapy of multiple myeloma: treatment at biochemical relapse is a significant prognostic factor for progression-free survival

Eirini Katodritou[1] · Marie-Christine Kyrtsonis[2] · Sosana Delimpasi[3] · Despoina Kyriakou[4] · Argiris Symeonidis[5] · Emmanouil Spanoudakis[6] · Georgios Vasilopoulos[7] · Achilles Anagnostopoulos[8] · Anna Kioumi[9] · Panagiotis Zikos[10] · Anthi Aktypi[11] · Evangelos Briasoulis[12] · Aikaterini Megalakaki[13] · Panayiotis Repousis[13] · Ioannis Adamopoulos[14] · Dimitrios Gogos[15] · Maria Kotsopoulou[13] · Vassiliki Pappa[16] · Eleni Papadaki[17] · Despoina Fotiou[18] · Eftychia Nikolaou[2] · Evlambia Giannopoulou[1] · Eleftheria Hatzimichael[12] · Nikolaos Giannakoulas[7] · Vassiliki Douka[8] · Kyriaki Kokoviadou[9] · Despoina Timotheatou[18] · Evangelos Terpos[19]

- **207 consecutive myeloma patients treated with Len/Dex in second line**
- **median age was 67 years**

PFS curves for patients who started second line treatment on clinical relapse or on biochemical relapse





The type of relapse was the strongest prognostic factor for PFS (p = 0.02)

Received: 13 October 2018 | Revised: 26 December 2018 | Accepted: 7 January 2019

DOI: 10.1002/ajh.25415

WILEY AJH

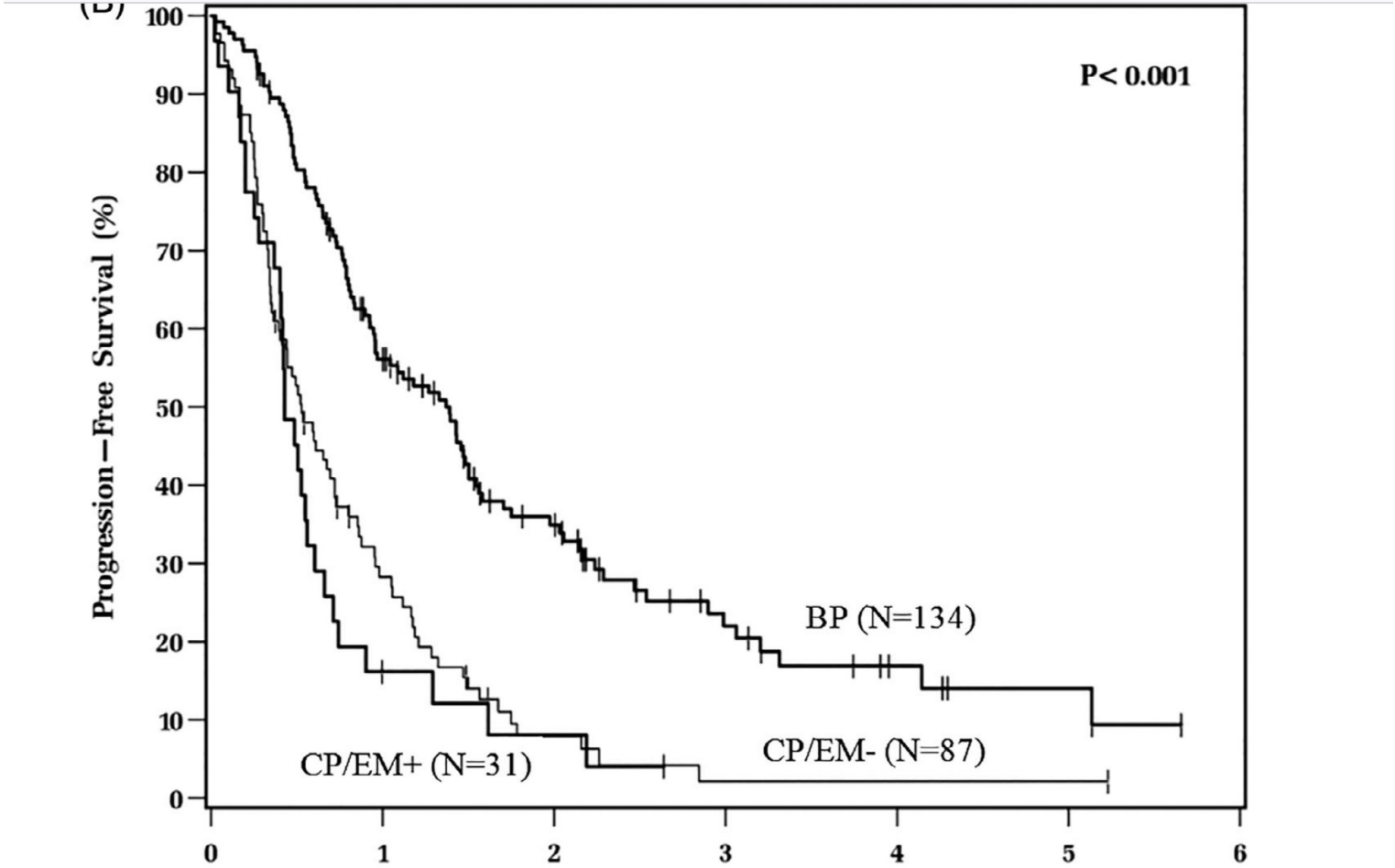
RESEARCH ARTICLE

Progression with clinical features is associated with worse subsequent survival in multiple myeloma

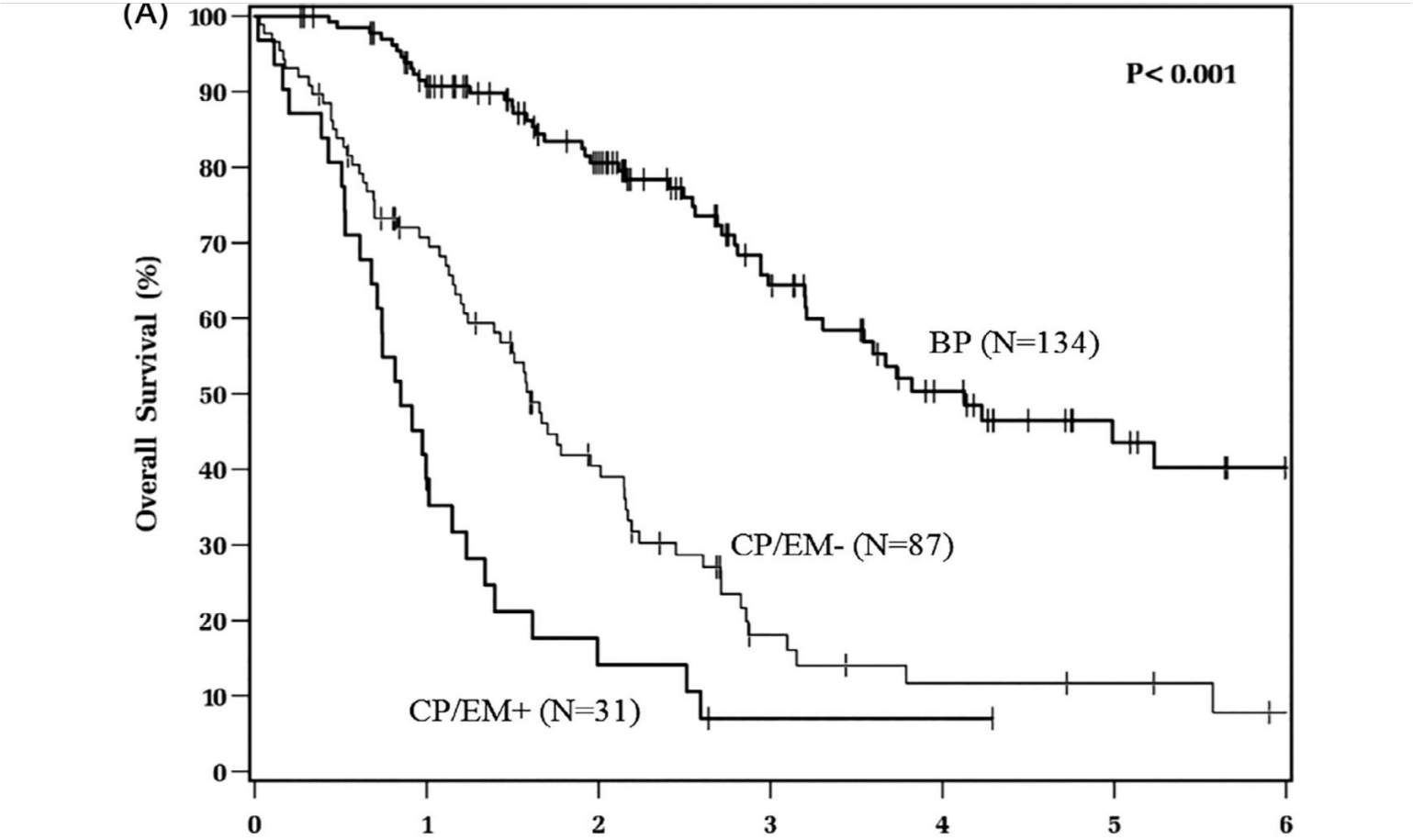
Rajshekhar Chakraborty[1] | Hien D. Liu[2] | Lisa Rybicki[1] | Jacqulyn Tomer[1] | Jack Khouri[1] | Robert M. Dean[1] | Beth M. Faiman[1] | Matt Kalaycio[1] | Christy J. Samaras[1] | Navneet S. Majhail[1] | Jason Valent[1]

- 134 patients (53%) had *BP* and 118 (47%) had clinical features at the time of disease progression. (*CP/EM-*: 35% and *CP/EM+*: 12%)
- At our institution, the general consensus is to initiate a new line of therapy whenever patients meet criteria for IMWG-defined "*Progressive disease*" or "*Clinical relapse*".

Kaplan-Meier curve for progression-free survival in groups with different patterns of progression.



Kaplan–Meier curve for overall survival in groups with different patterns of progression.



Leukemia (2019) 33:730–738
https://doi.org/10.1038/s41375-018-0271-1

ARTICLE

Multiple myeloma gammopathies

Relapse after complete response in newly diagnosed multiple myeloma: implications of duration of response and patterns of relapse

Surbhi Sidana[1] · Nidhi Tandon[1] · Angela Dispenzieri[1] · Morie A. Gertz[1] · Francis K. Buadi[1] · Martha Q. Lacy[1] · David Dingli[1] · Amie L. Fonder[1] · Suzanne R. Hayman[1] · Miriam A. Hobbs[1] · Wilson I. Gonsalves[1] · Rahma M. Warsame[1] · Taxiarchis Kourelis[1] · Yi Lisa Hwa[1] · Prashant Kapoor[1] · Robert A. Kyle[1] · Nelson Leung[1,2] · Ronald S. Go[1] · S. Vincent Rajkumar[1] · Shaji K. Kumar[1]

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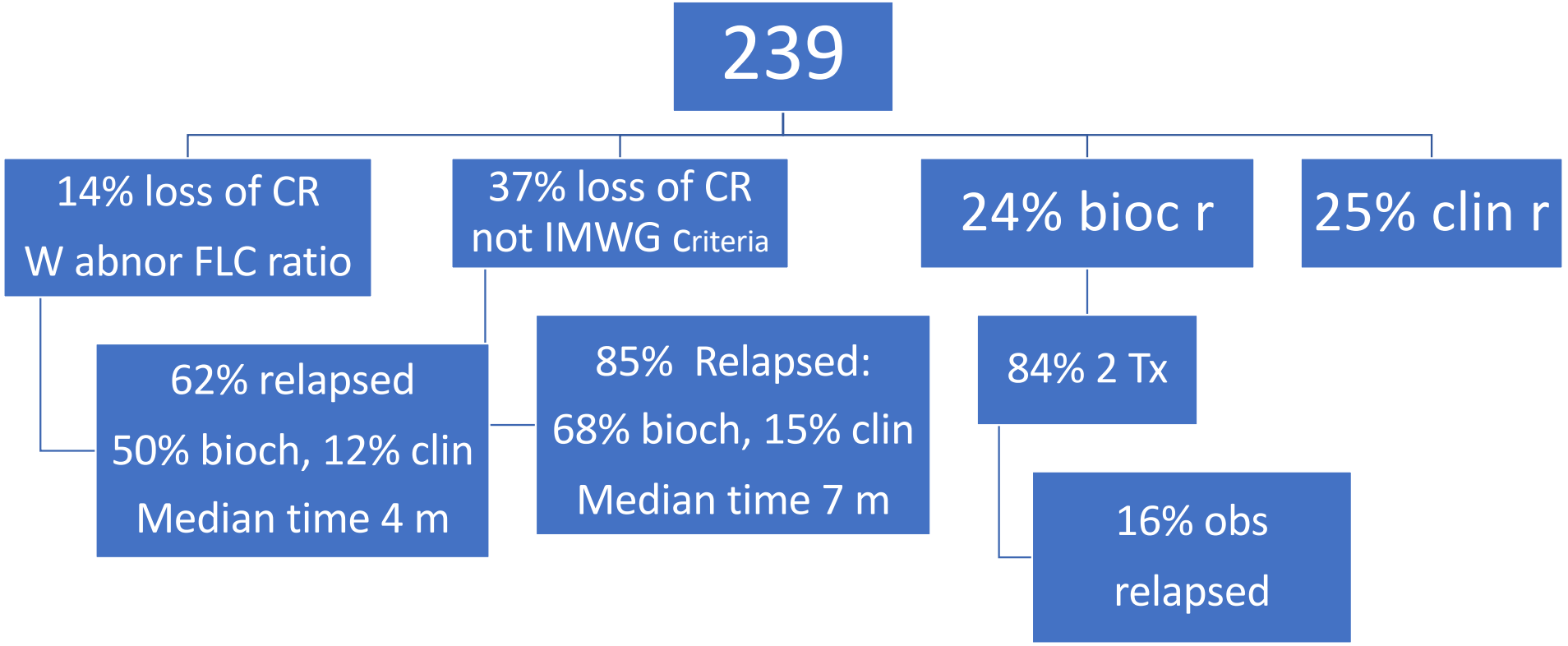
© Springer Nature Limited 2018

Type of relapse

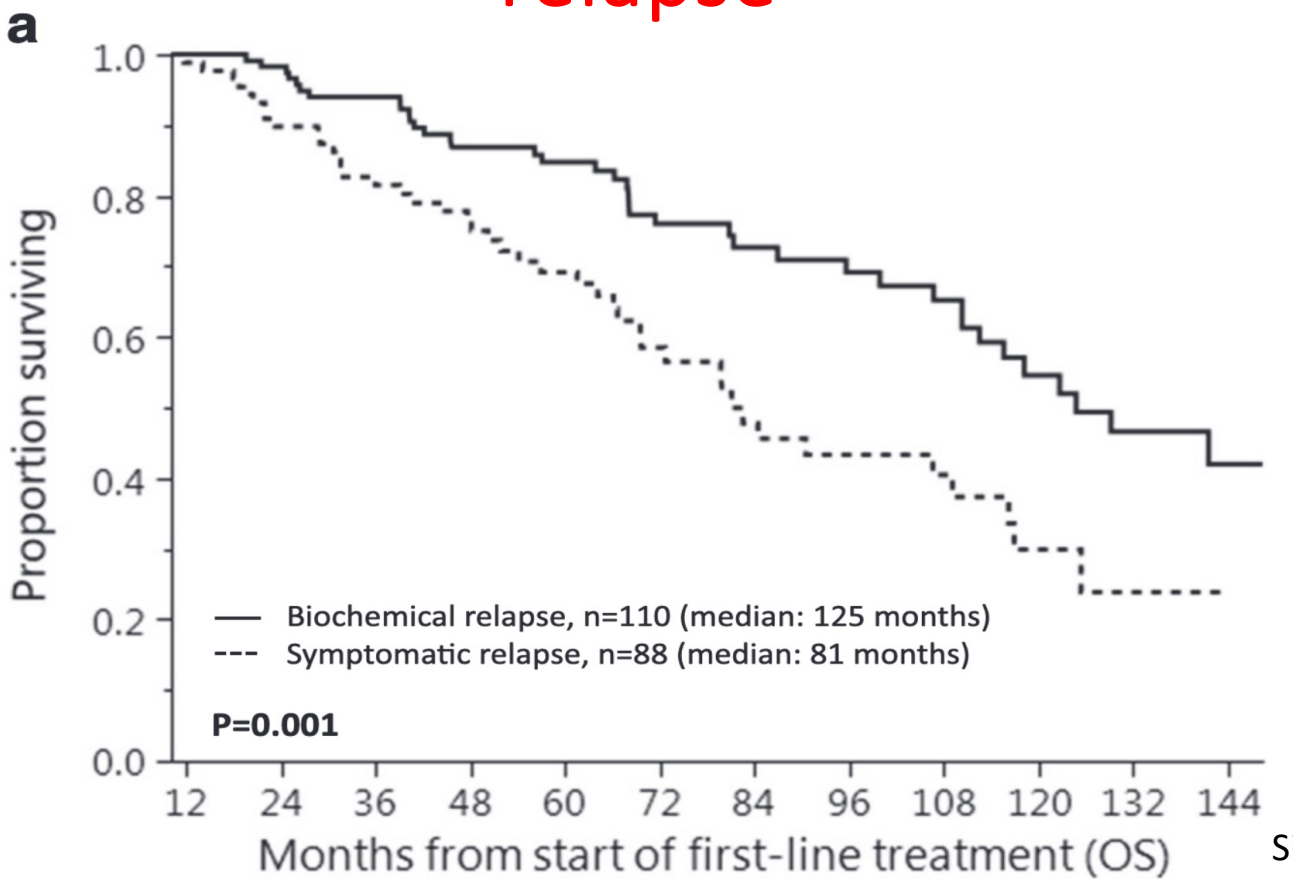
- 1) Symptomatic relapse/progression
- 2) Biochemical relapse/progression
- 3) Biochemical loss of CR with re-emergence of monoclonal protein: two consecutive positive immunofixation values in serum/urine or rise in monoclonal protein not meeting IMWG sympto-matic or biochemical progression criteria
- 4) Biochemical loss of CR with abnormal FLC ratio only

Sidana S,. Leukemia 2019



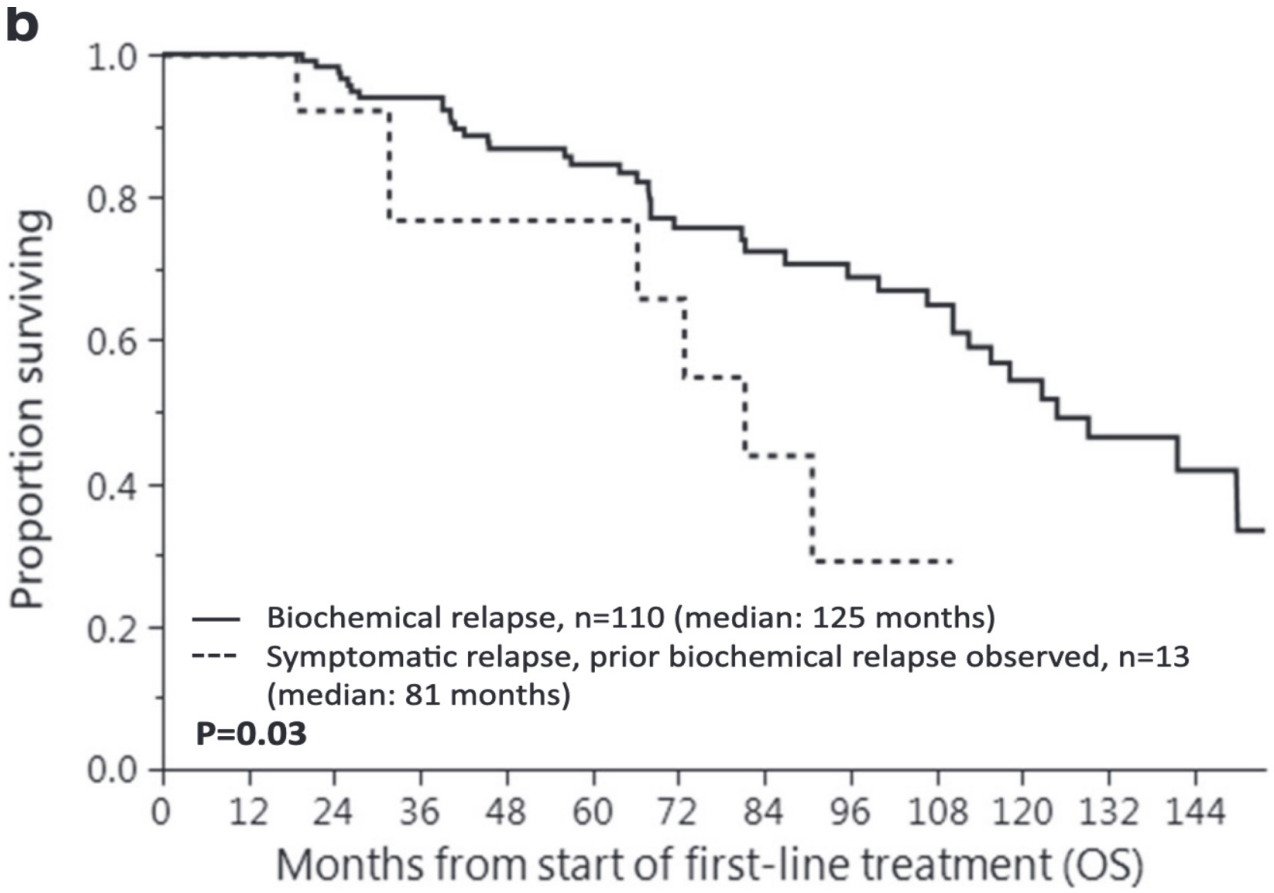
Sidana S, Leukemia 2019

Overall survival from start of first-line therapy in patients with relapse from complete response starting treatment for biochemical vs. symptomatic relapse



Sidana S,. Leukemia 2019

OS in patients with relapse from complete response starting treatment for BR vs. those who were observed with BR and started treatment for SR



Sidana S,. Leukemia 2019

EBMT

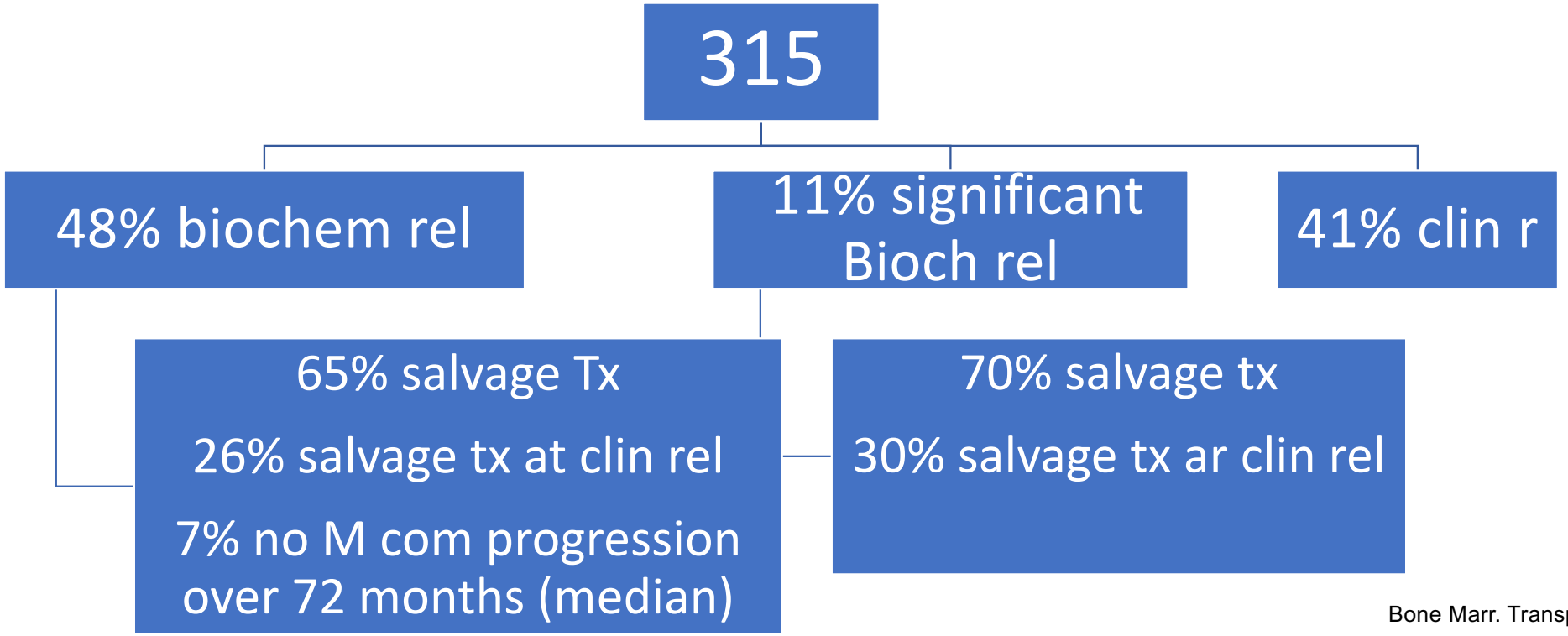
www.nature.com/bmt

ARTICLE

Check for updates

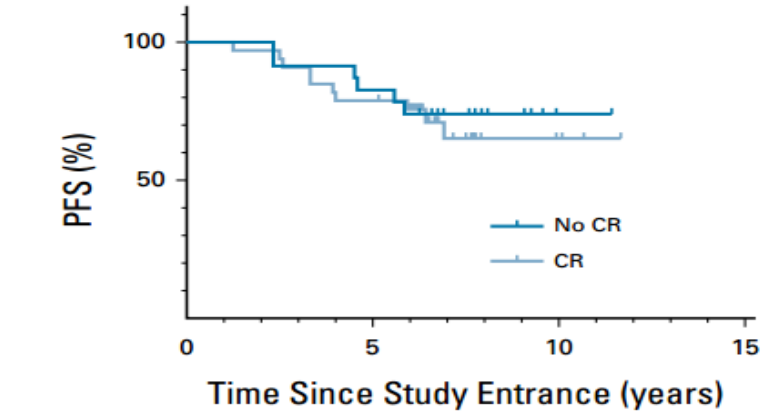
Optimal timing of treatment at relapse after autologous stem cell transplantation in patients with multiple myeloma: a study of the Korean Multiple Myeloma Working Party (KMM-1909)

Sung-Hoon Jung[1], Chang-Ki Min[2], Jae Hoon Lee[3], Yeung-Chul Mun[4], Soo-Mee Bang[5], Dok Hyun Yoon[6], Ho Sup Lee[7], Kihyun Kim[8]✉ and Je-Jung Lee[1]✉



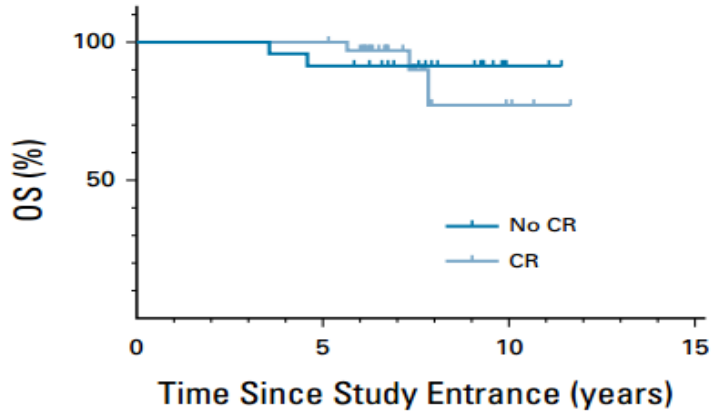
Bone Marr. Transpl. 2022

Of the 1,525 patients with active MM enrolled in PETHEMA/GEM clinical trials, 105 (7%) were classified as MGUS-like



No. at risk:

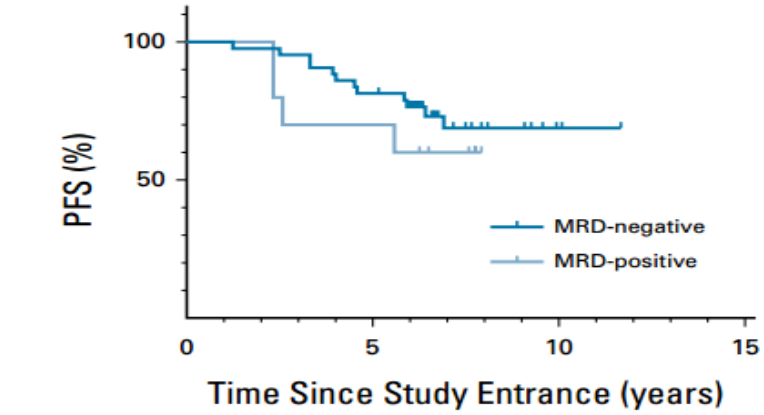
CR	33	27	4	-
No CR	23	20	2	-



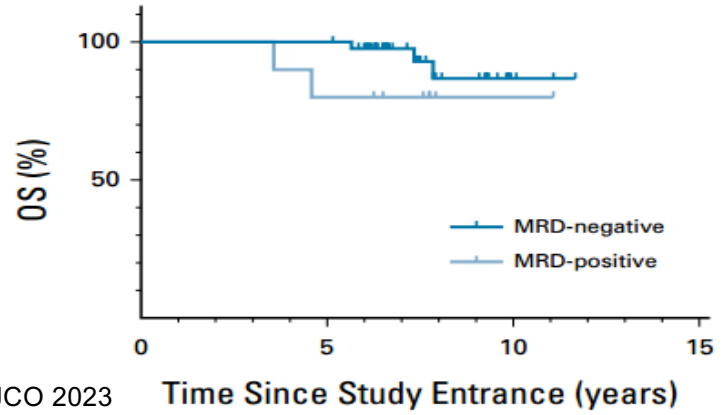
No. at risk:

CR	33	33	4	-
No CR	23	22	4	-

C

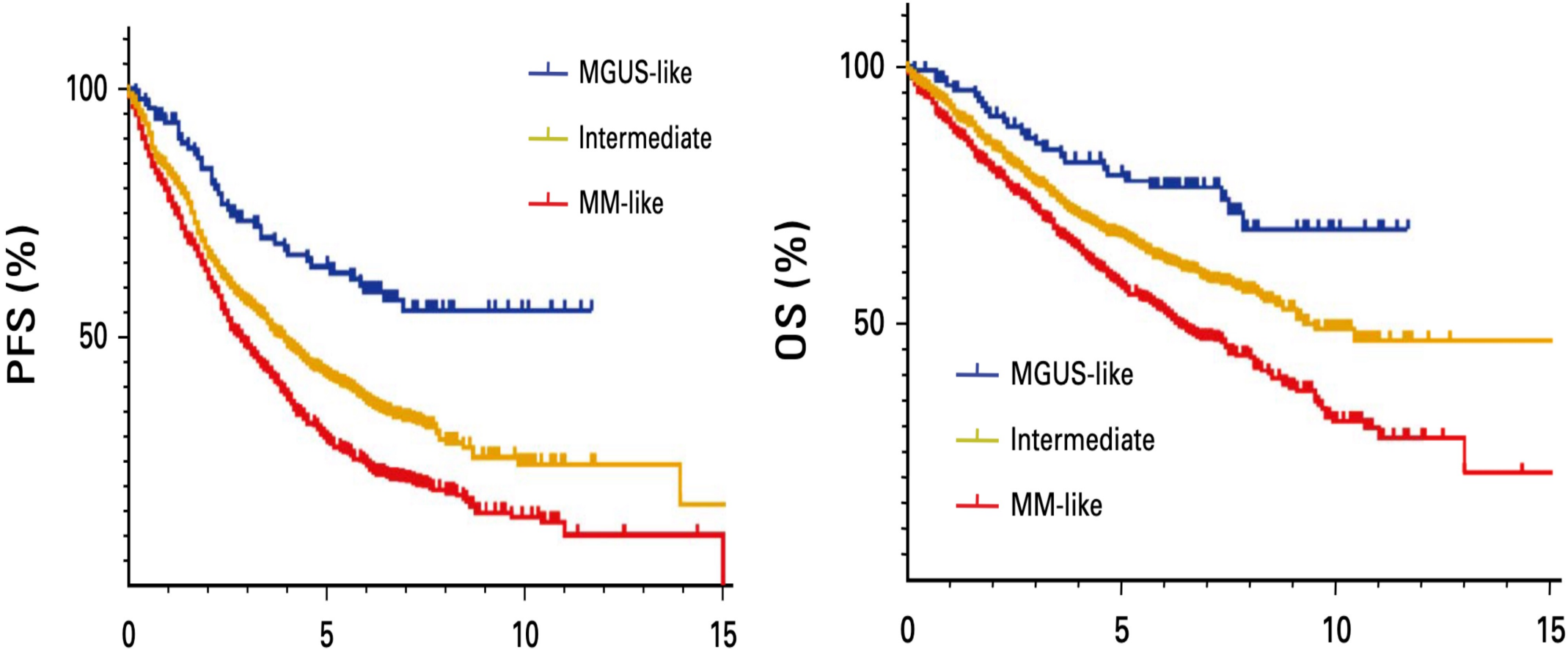


D



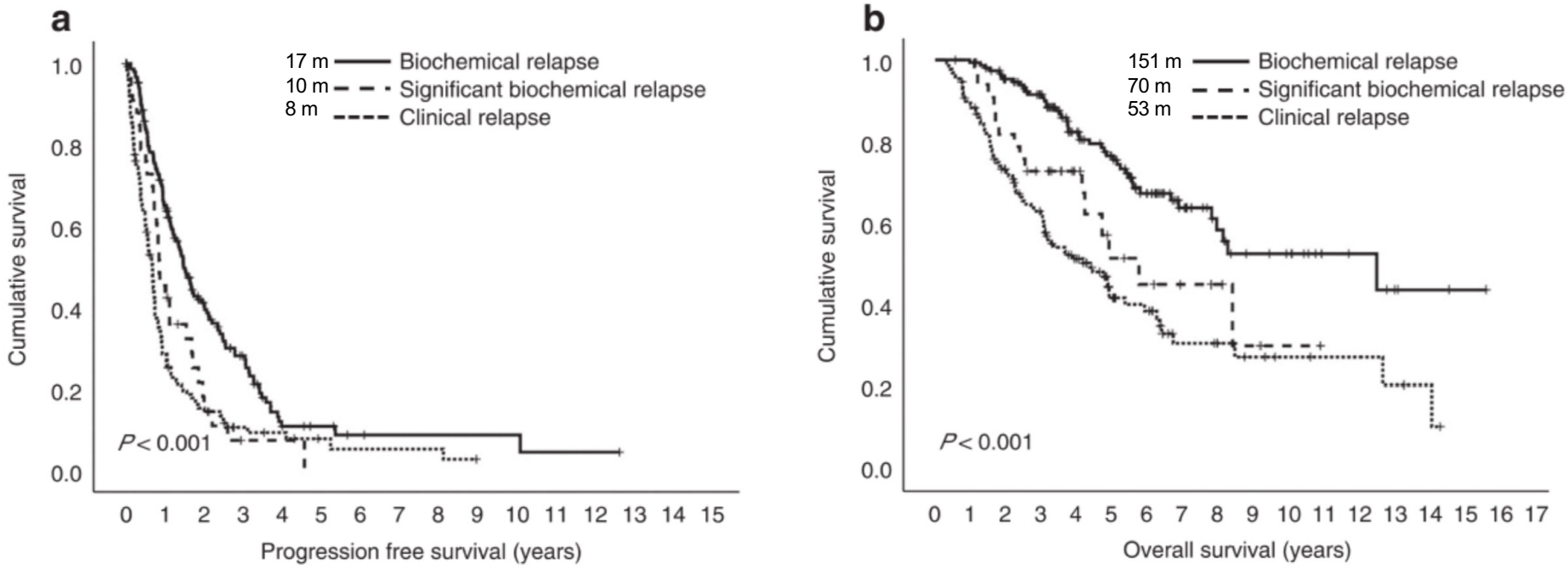
Burgos L, JCO 2023

Clinical Significance of the Monoclonal Gammopathy of Undetermined Significance–Like Phenotype

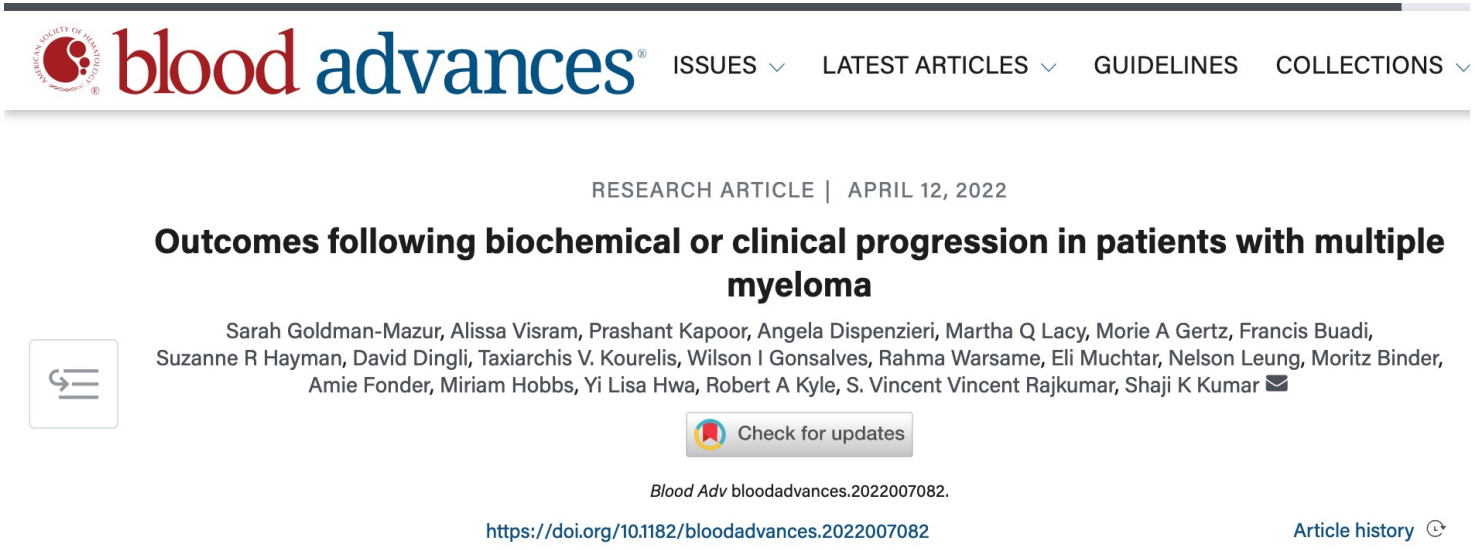


Burgos L, JCO 2023

Survival outcome by relapse type after ABMT

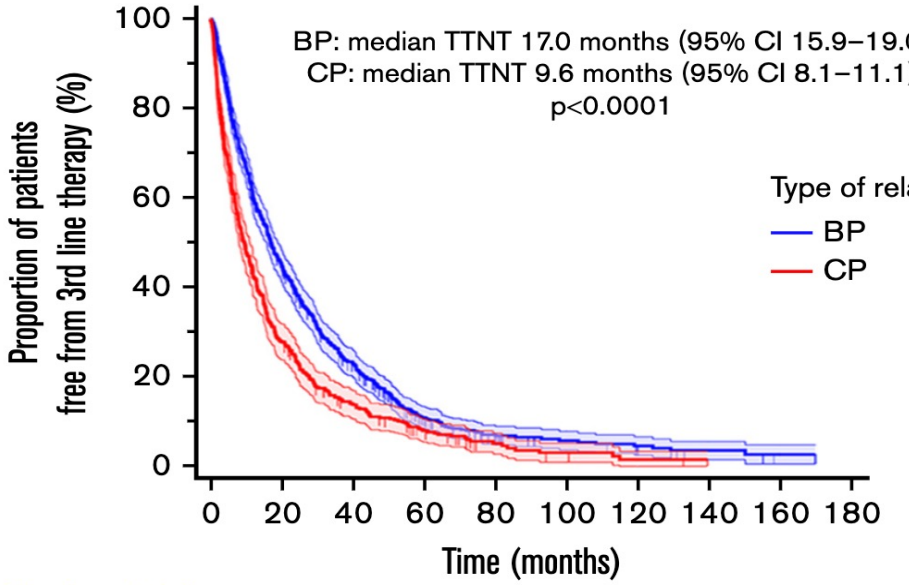


Jung S-H, Bone Marr. Transpl. 2022



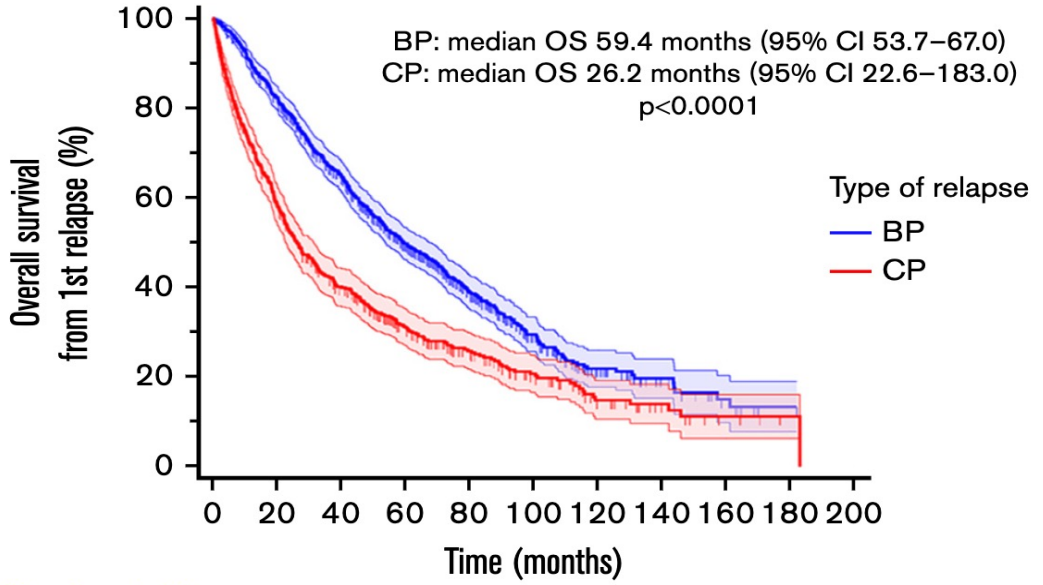
- BP was defined as increase in serum or urine monoclonal protein leading to initiation of a new line of therapy without meeting criteria for CP according to IMWG recommendations
- 1347 patients. 60.4% experienced BP, and 39.6% had CP
- Patients in the CP group were more likely to have high risk features at MM diagnosis

TTNT from 2nd line treatment and OS from 1st relapse in 1347 MM patients stratified by pattern of relapse into biochemical progression (BP) and clinical progression (CP)



Number at risk

Group: BP	754	334	162	60	27	15	10	4	1	0
Group: CP	485	133	59	28	10	5	2	0	0	0



Number at risk

Group: BP	813	657	489	322	187	93	39	20	9	1	0
Group: CP	534	308	195	122	76	43	21	10	4	1	0

Goldman-Mazur S, Blood Advances 2022

Mina et al. *Blood Cancer Journal* (2020)10:58
https://doi.org/10.1038/s41408-020-0326-1

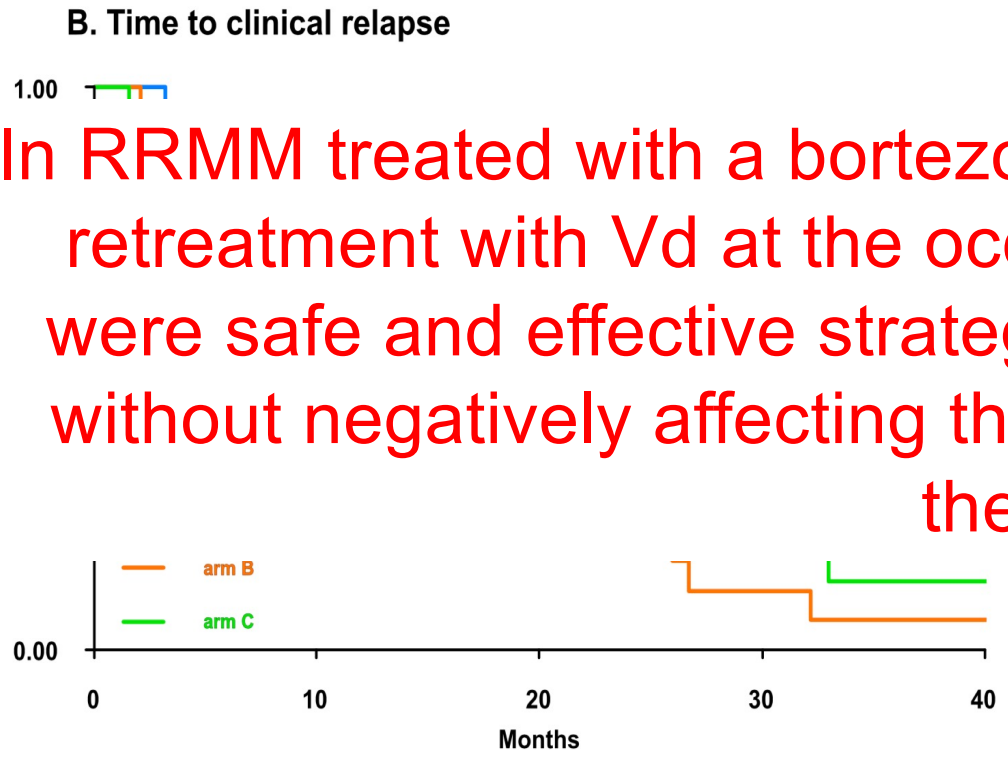
Blood Cancer Journal

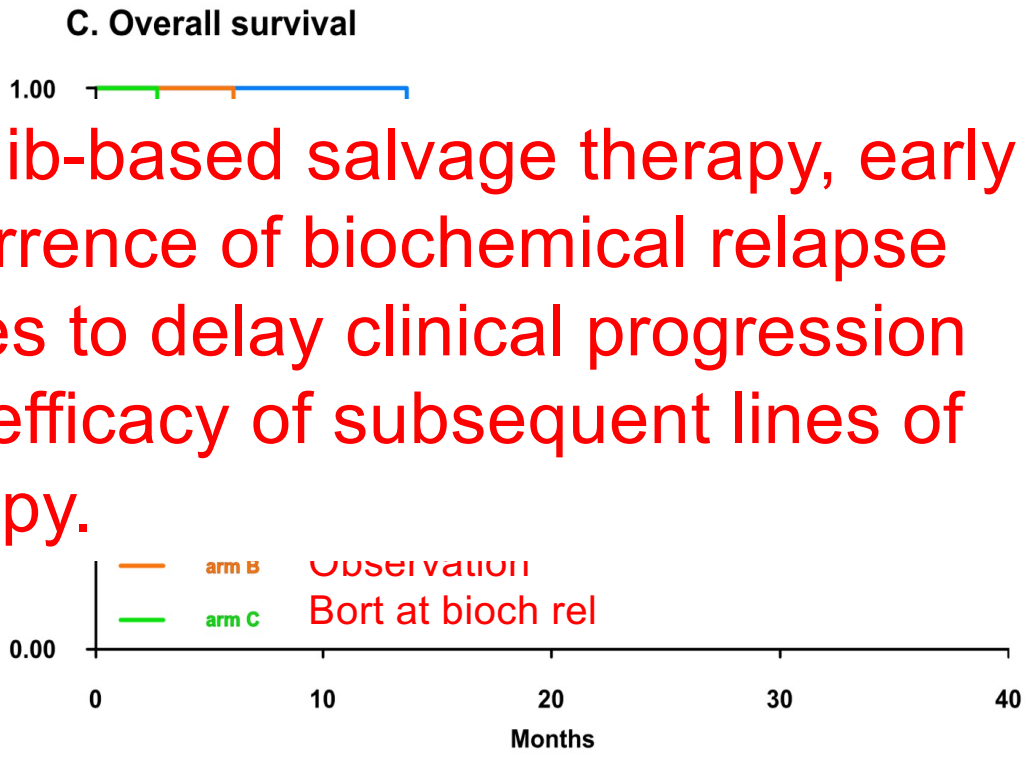
CORRESPONDENCE Open Access

Bortezomib-dexamethasone as maintenance therapy or early retreatment at biochemical relapse versus observation in relapsed/refractory multiple myeloma patients: a randomized phase II study

Roberto Mina[1], Angelo Belotti[2], Maria Teresa Petrucci[3], Renato Zambello[4], Andrea Capra[1], Giacomo Di Lullo[1], Sonia Ronconi[5], Norbert Pescosta[6], Mariella Grasso[7], Federico Monaco[8], Claudia Cellini[9], Marco Gobbi[10], Stelvio Ballanti[11], Paolo de Fabritiis[12], Maria Letizia Mosca-Siez[13], Monia Marchetti[14,15], Anna Marina Liberati[16], Massimo Offidani[17], Nicola Giuliani[18], Roberto Ria[19], Pellegrino Musto[20,21], Alessandra Romano[22], Pieter Sonneveld[23], Mario Boccadoro[1] and Alessandra Larocca[1]

Arm A: continuous treatment with subcutaneous bortezomib
Arm B: observation until clinical relapse
Arm C: six 28-day cycles of bortezomib at biochemical relapse

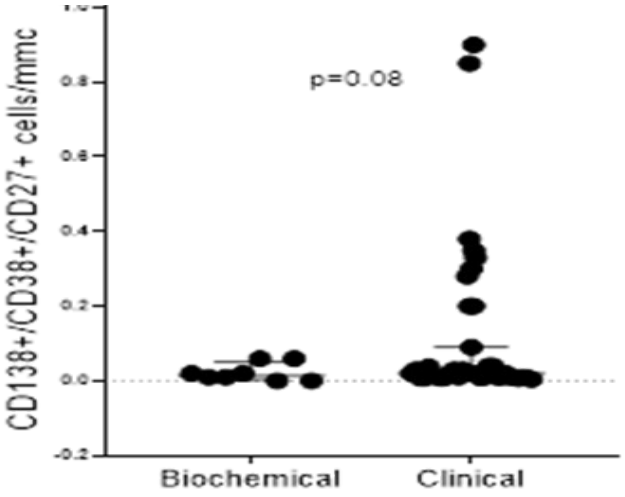


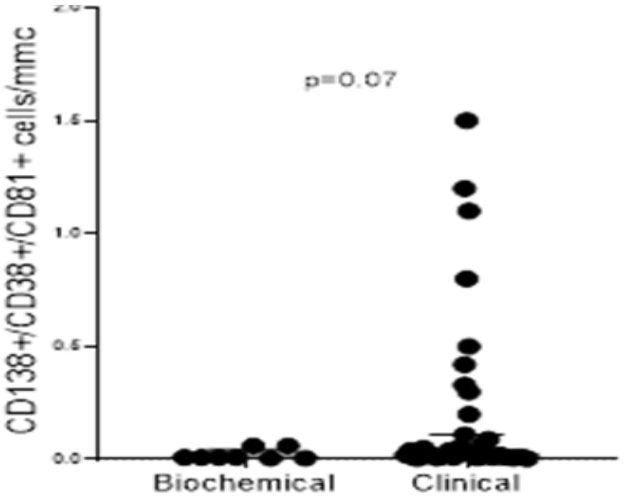


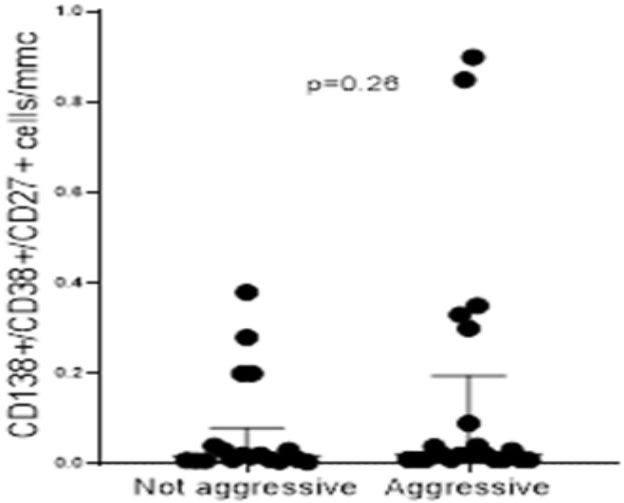
In RRMM treated with a bortezomib-based salvage therapy, early retreatment with Vd at the occurrence of biochemical relapse were safe and effective strategies to delay clinical progression without negatively affecting the efficacy of subsequent lines of therapy.

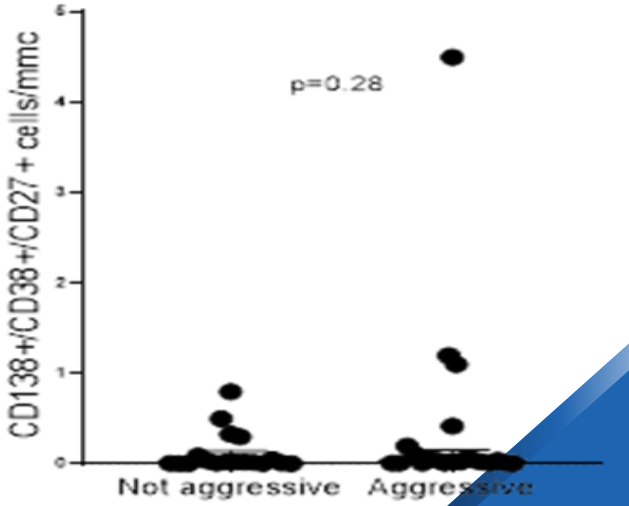
PATIENTS	N° 128	%
MALE	74	58%
FEMALE	54	42%
MEDIAN AGE	62 YEARS (RANGE 45- 78)	
RELAPSE	76	57%
RELAPSE/REFRACTORY	52	41%
PATIENTS TREATED AT BIOCHEMICAL RELAPSE	87	68%
PATIENTS TREATED AT CLINICAL RELAPSE	41	32%
MEDIAN NUMBER OF	PREVIOUS LINES 3 (1 -13)	
PREVIOUS ASCT	64	50%

Markovic U, EHA 2021

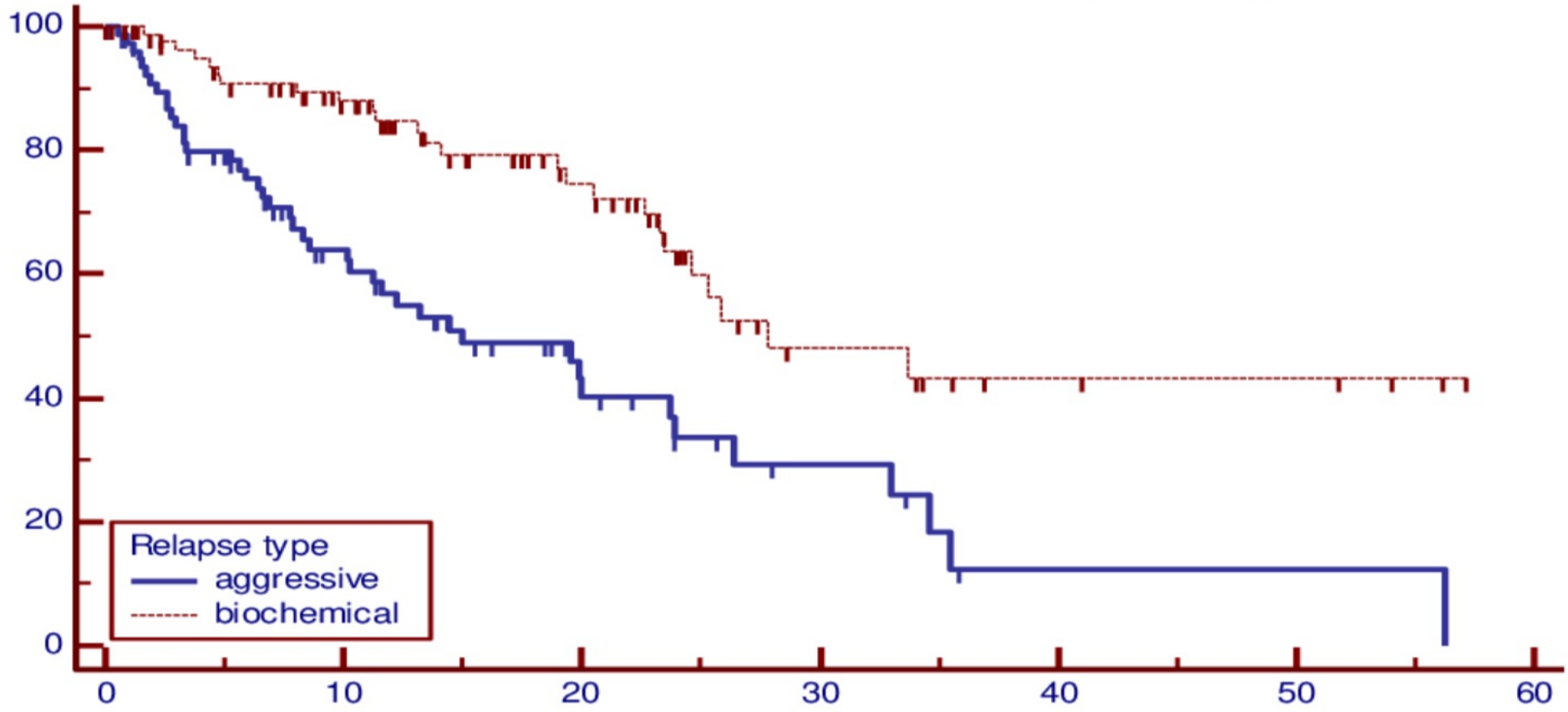

CD138+/CD38+/CD27+ cells/mmc
p=0.08
Biochemical
Clinical


CD138+/CD38+/CD81+ cells/mmc
p=0.07
Biochemical
Clinical


CD138+/CD38+/CD27+ cells/mmc
p=0.28
Not aggressive
Aggressive

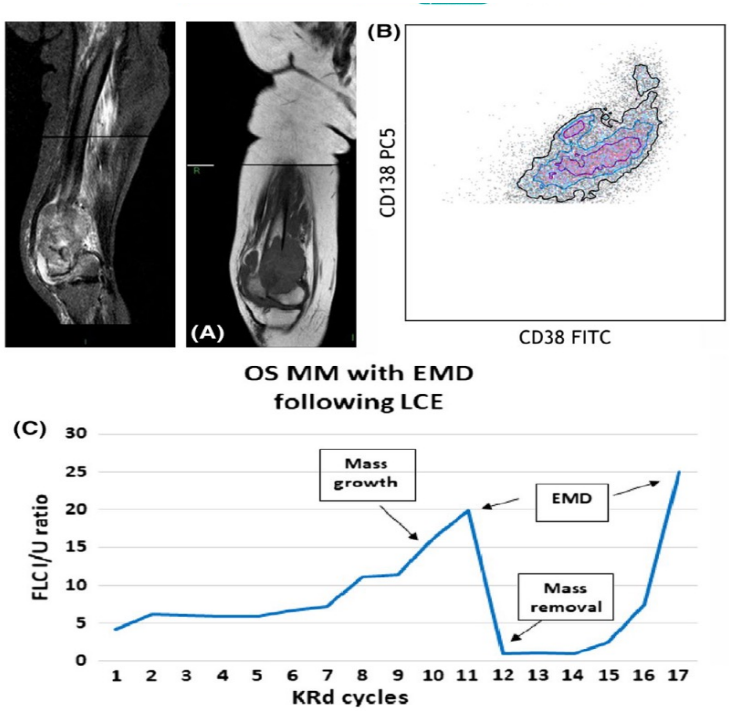

CD138+/CD38+/CD27+ cells/mmc
p=0.28
Not aggressive
Aggressive

Overall survival based on relapse type

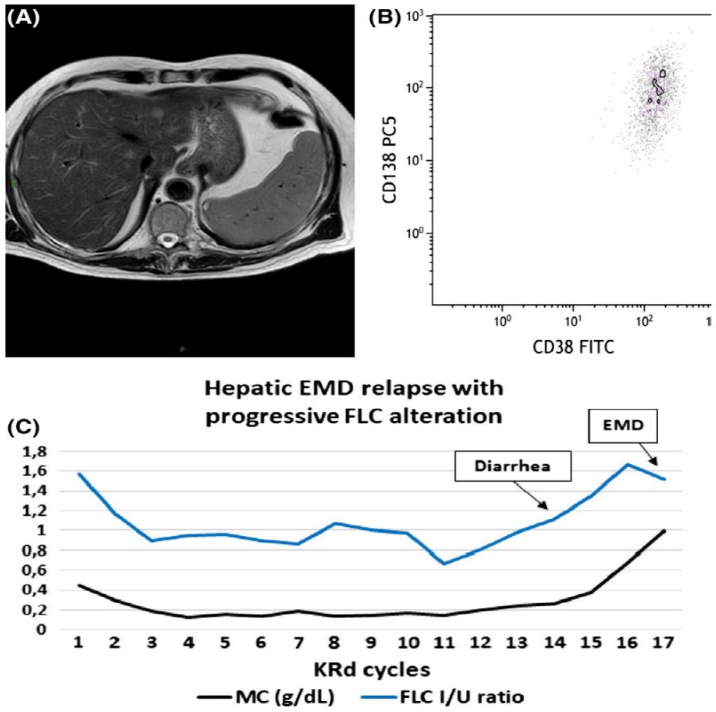


Number at risk						
Group: aggressive						
79	36	14	6	1	1	0
Group: biochemical						
86	57	32	10	5	4	0

sFLC assay can anticipate the extramedullary relapse



The alteration of both the FLC κ
and the rFLC has preceded at least by 1 month
the aggressive growth of the EMD mass



A progressive rise of the rFLC was noticed 5
months prior to the first increase of MC

Markovic U. Clin Case Rep. 2020

Received: 7 March 2023 | Revised: 6 July 2023 | Accepted: 10 July 2023

DOI: 10.1111/ejh.14057

European Journal of Haematology

ORIGINAL ARTICLE

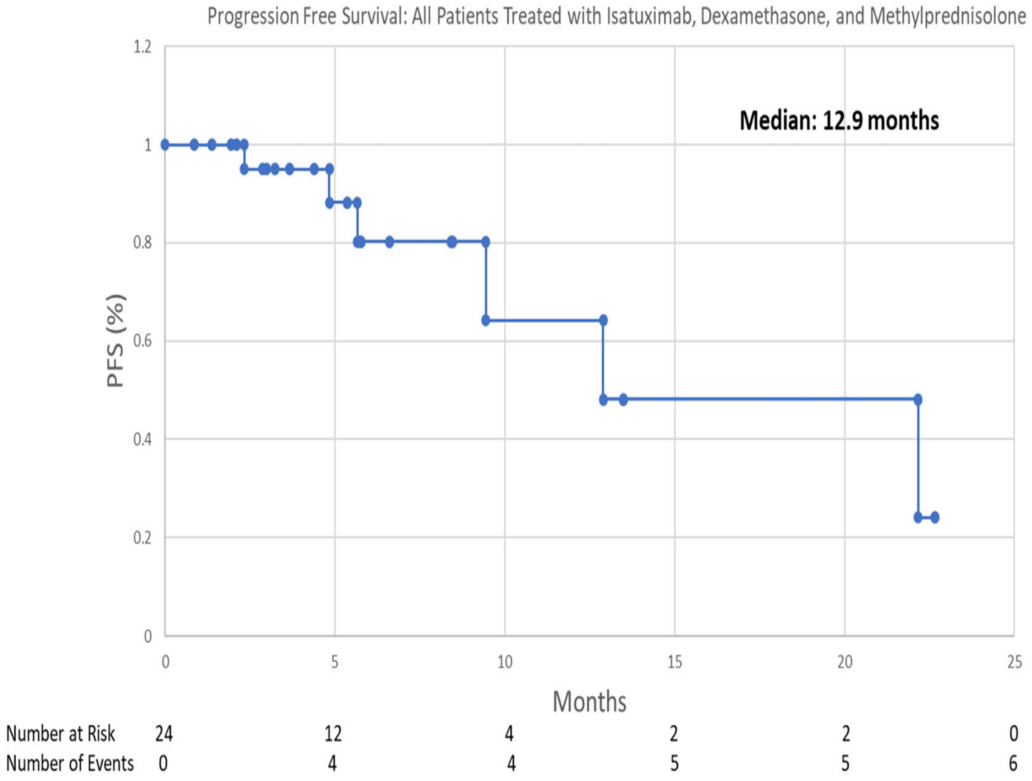
Efficacy of isatuximab in combination with steroids for the treatment of relapsed/refractory multiple myeloma patients exhibiting only biochemical progression—A single center retrospective study

Bernard Sean Regidor[1] | Scott Jew[1,2] | Marissa-Skye Goldwater[2] | Bethany Marie Beatty[1] | Sean Bujarski[1,2] | Adam ElSayed[1,2] | Ryan Danis[1] | Susanna Kim[3] | Regina Swift[1] | Gary Schwartz[1] | James R. Berenson[1,2,3]

24 pts, median 3 PLOT

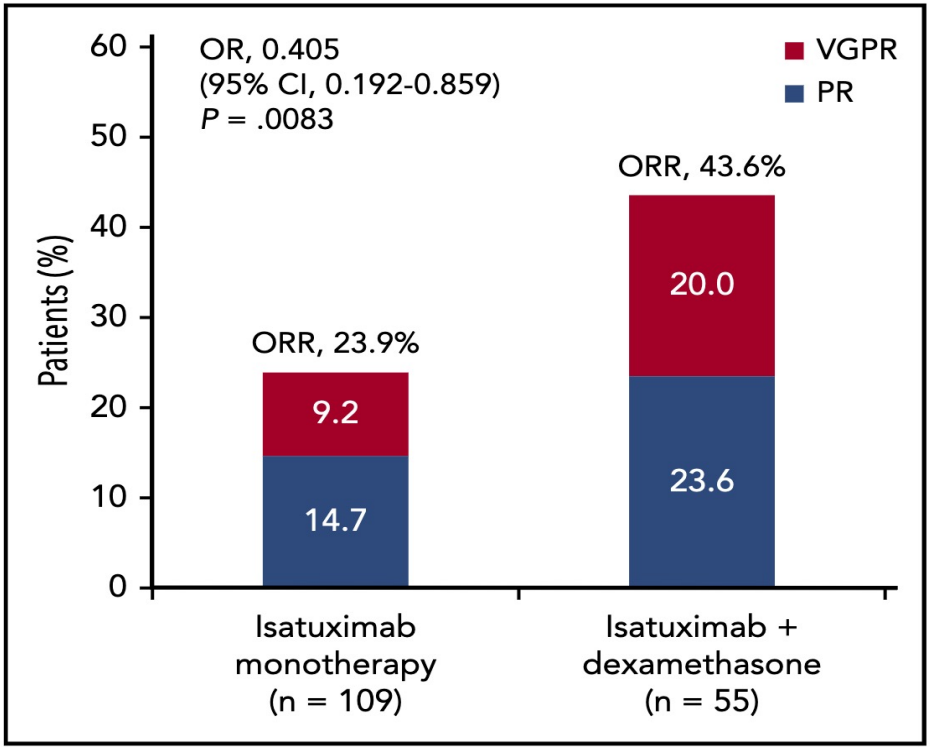
Efficacy of isatuximab in combination with steroids (ISAdm) for the treatment of relapsed/refractory MM pts exhibiting only biochemical progression

Response	Number of patients (%)
PR	12 (50)
CR	3 (13)
MR	4 (17)
ORR	**15 (63)**
CBR	**19 (79)**
SD	5 (21)
[a]Responders with high-risk cytogenetics	6 (100)

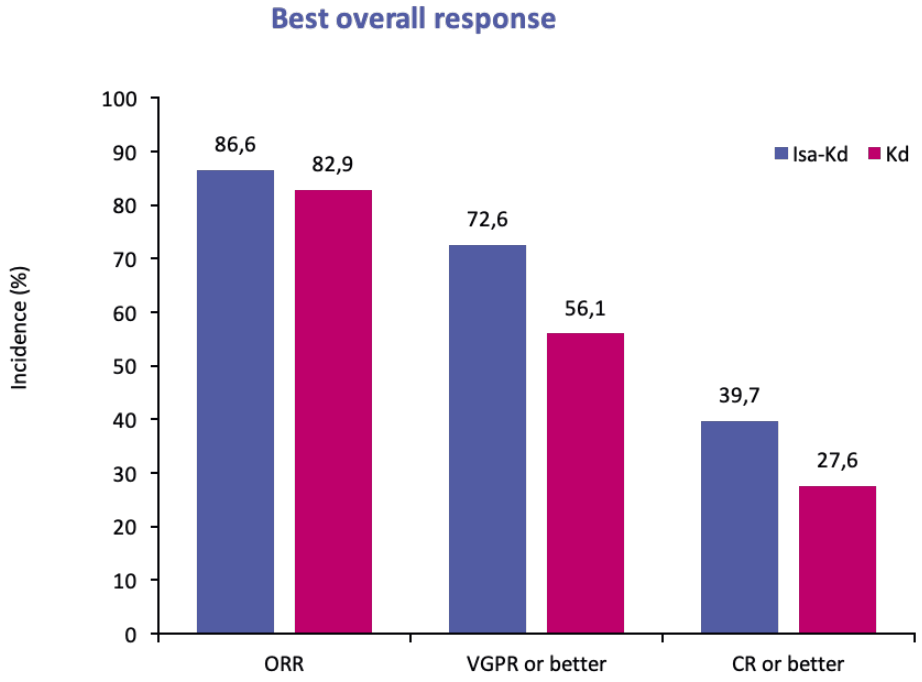


Regidor BS, Eur J Haematol. 2023;111:628–635.

BP treated with IsAdm have a higher ORR (83%) compared to Isa-dex but lower compared to IsaKd used in the treatment of RRMM patients regardless of BP or CP

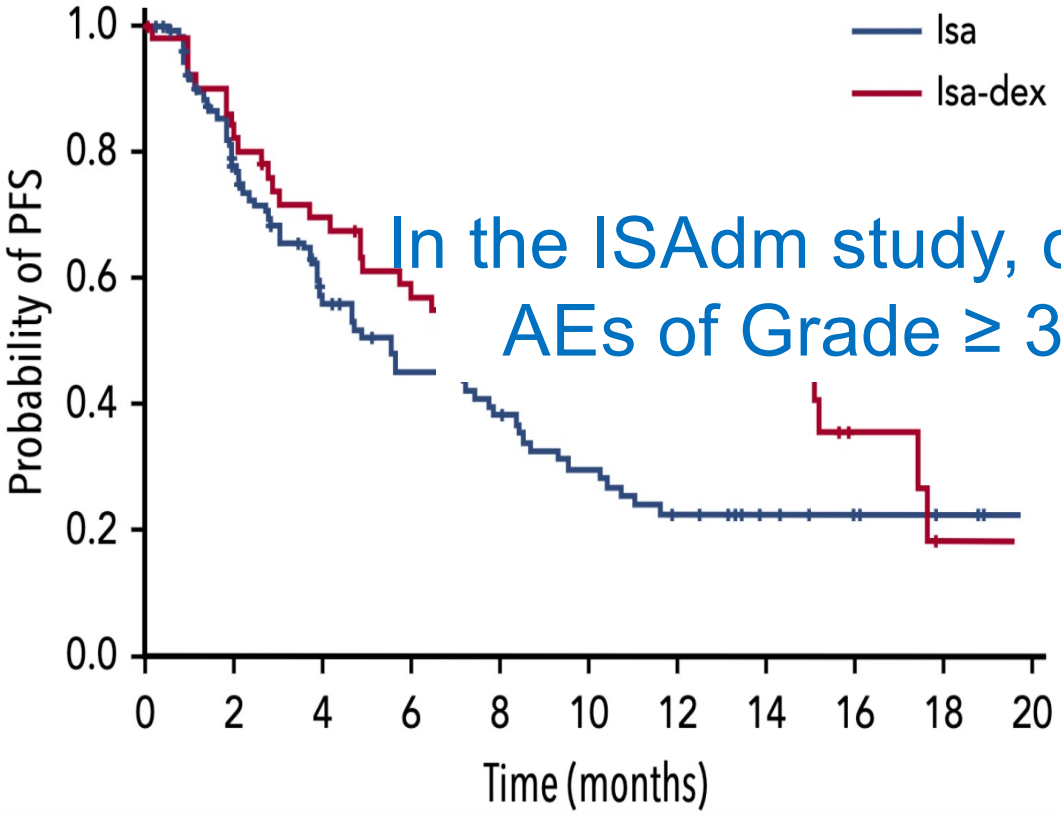


Dimopoulos M, Blood 2021

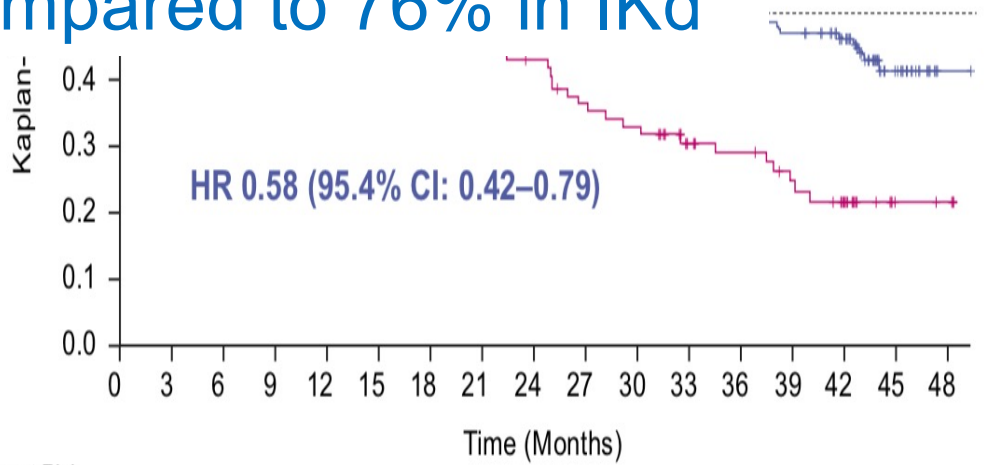


Moreau P, Lancet 2021

BP treated with ISAdm have a longer PFS (12.9 m) compared to Isa-dex but much shorter compared to IsaKd used in the treatment of RRMM patients regardless of BP or CP



In the ISAdm study, only 21% of pts experienced AEs of Grade ≥ 3 compared to 76% in IKd



Median PFS was 4.9 m. in the Isa arm and 10.2 m. in the Isa-dex arm

Median PFS 35.7 m

Conclusion

Patients with asymptomatic relapse have a clear advantage in terms of outcome. This is probably due to a more indolent disease biologically, higher sensitivity to treatment or both

Very few patients with biochemical relapse show no further progression

If the treatment is determined early in biochemical relapse, BAT may be appropriate

Early retreatment at biochemical relapse, can delay the onset of significant myeloma- related comorbidities, thus improving patients' quality of life

Pattern of relapse/progression (clinical vs biochemical) at study entry should be reported in clinical trials and could be considered as a stratification factor for randomization

sFLC assay may increases the accuracy of disease evaluation