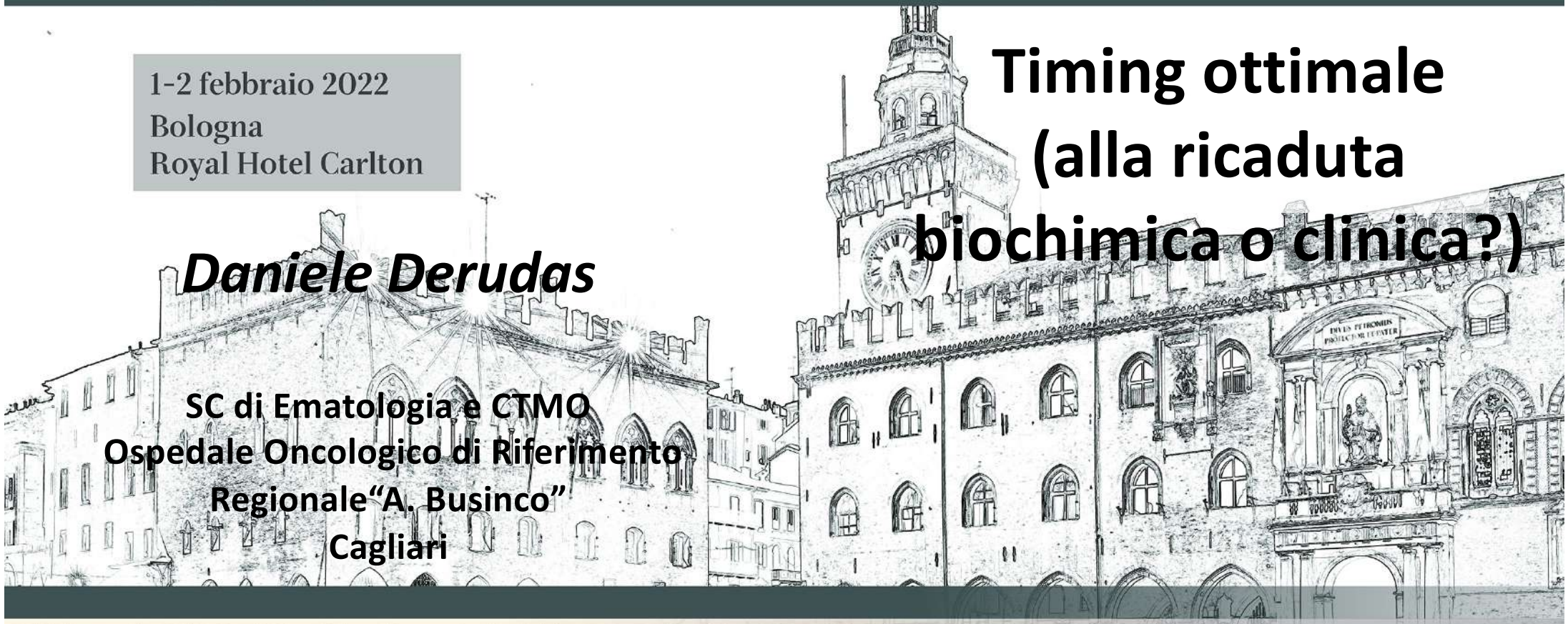
Highlights from IMW 2021

1-2 febbraio 2022
Bologna
Royal Hotel Carlton



Timing ottimale (alla ricaduta biochimica o clinica?)

Daniele Derudas

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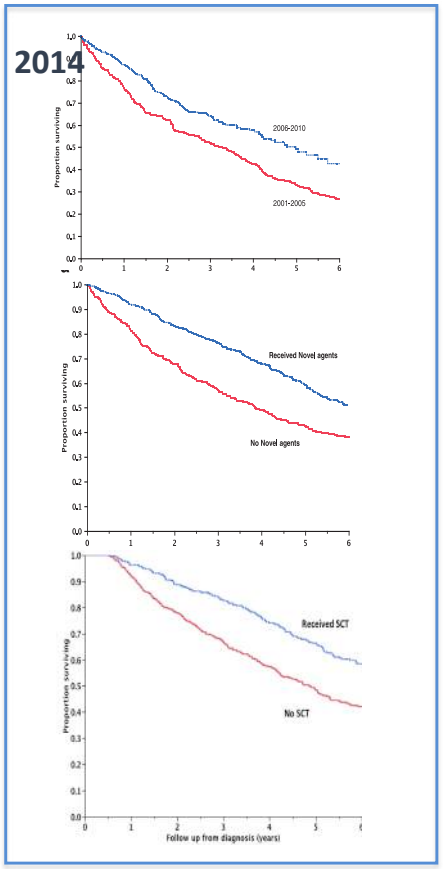
Comitato Scientifico
Michele CAVO
Maria Teresa PETRUCCI

Disclosures

No conflict of interest

2014



Kumar, Leukemia 2014

2020

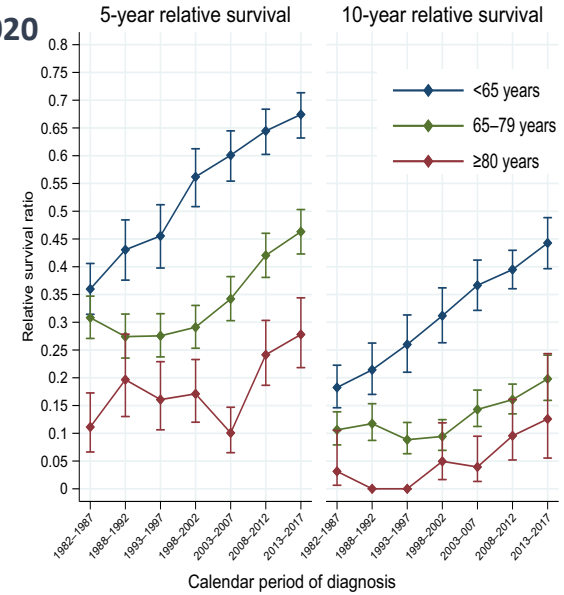


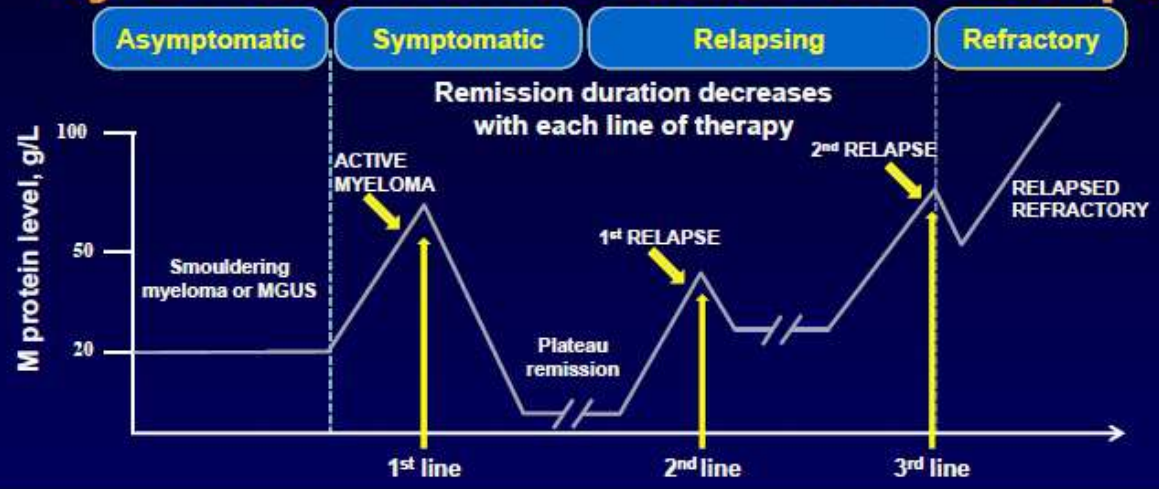
Table 1. The 5- and 10-year relative survival ratios (RSRs) across all calendar periods and age groups

		Calendar period of diagnosis						
	Age at diagnosis, years	1982–1987	1988–1992	1993–1997	1998–2002	2003–2007	2008–2012	2013–2017
5-year RSR (95% CI)	<65	0·36 (0·31–0·41)	0·43 (0·38–0·48)	0·46 (0·40–0·51)	0·56 (0·51–0·61)	0·60 (0·55–0·65)	0·65 (0·60–0·68)	0·67 (0·63–0·71)
	65–79	0·31 (0·27–0·35)	0·27 (0·24–0·32)	0·28 (0·24–0·32)	0·29 (0·25–0·33)	0·34 (0·30–0·38)	0·42 (0·38–0·46)	0·46 (0·42–0·50)
	≥80	0·11 (0·07–0·17)	0·20 (0·13–0·28)	0·16 (0·11–0·23)	0·17 (0·12–0·23)	0·10 (0·07–0·15)	0·24 (0·19–0·30)	0·28 (0·22–0·34)
10-year RSR (95% CI)	<65	0·18 (0·15–0·22)	0·21 (0·17–0·26)	0·26 (0·21–0·31)	0·31 (0·26–0·36)	0·37 (0·32–0·41)	0·40 (0·36–0·43)	0·44 (0·40–0·49)
	65–79	0·11 (0·08–0·14)	0·12 (0·09–1·15)	0·09 (0·06–0·12)	0·09 (0·07–0·13)	0·14 (0·11–0·18)	0·16 (0·14–0·19)	0·20 (0·16–0·24)
	≥80	0·03 (0·01–0·11)	0·00 (0·00–0·00)	0·00 (0·00–0·00)	0·05 (0·02–0·12)	0·04 (0·01–1·00)	0·10 (0·05–0·16)	0·13 (0·06–0·24)

RSR, relative survival ratio; CI, confidence interval.

Langseth,BJH 2020

Course of Disease: MM is Characterised by a Pattern of Remission and Relapse

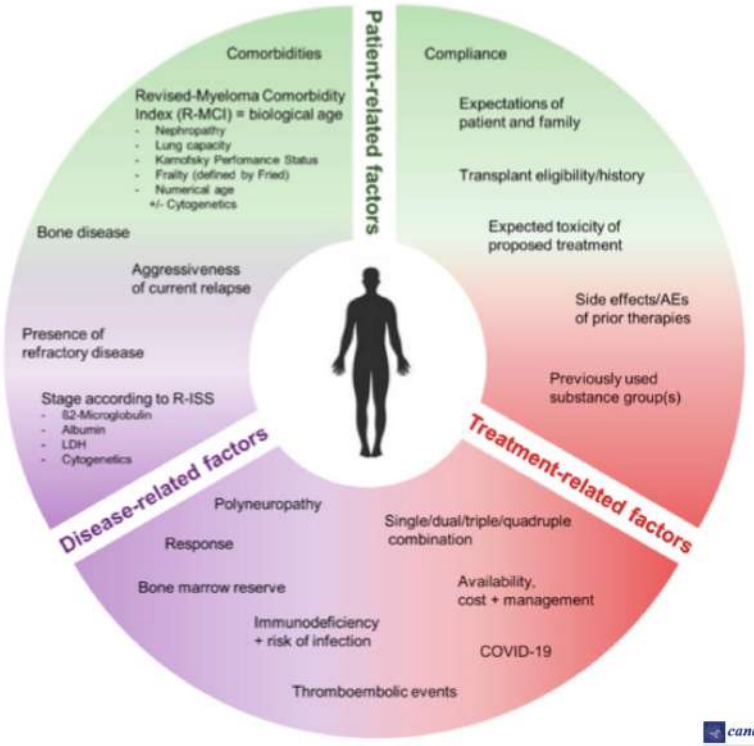


	1st line	2nd line	>3rd line
Median OS, months	20–50	14–16	6–10
Sensitivity to chemotherapy	Sensitive	Resistant	Resistant
Adverse events	Lower risk SAE	High risk SAE	High risk SAE

MGUS, monoclonal gammopathy of unknown significance; MM, multiple myeloma; OS, overall survival; SAE, serious adverse event

Adapted from: Durie BGM. 2008/2009 edition. North Hollywood, CA: International Myeloma Foundation; 2008.

Relevant parameters for treatment selection in RRMM patients



cancers

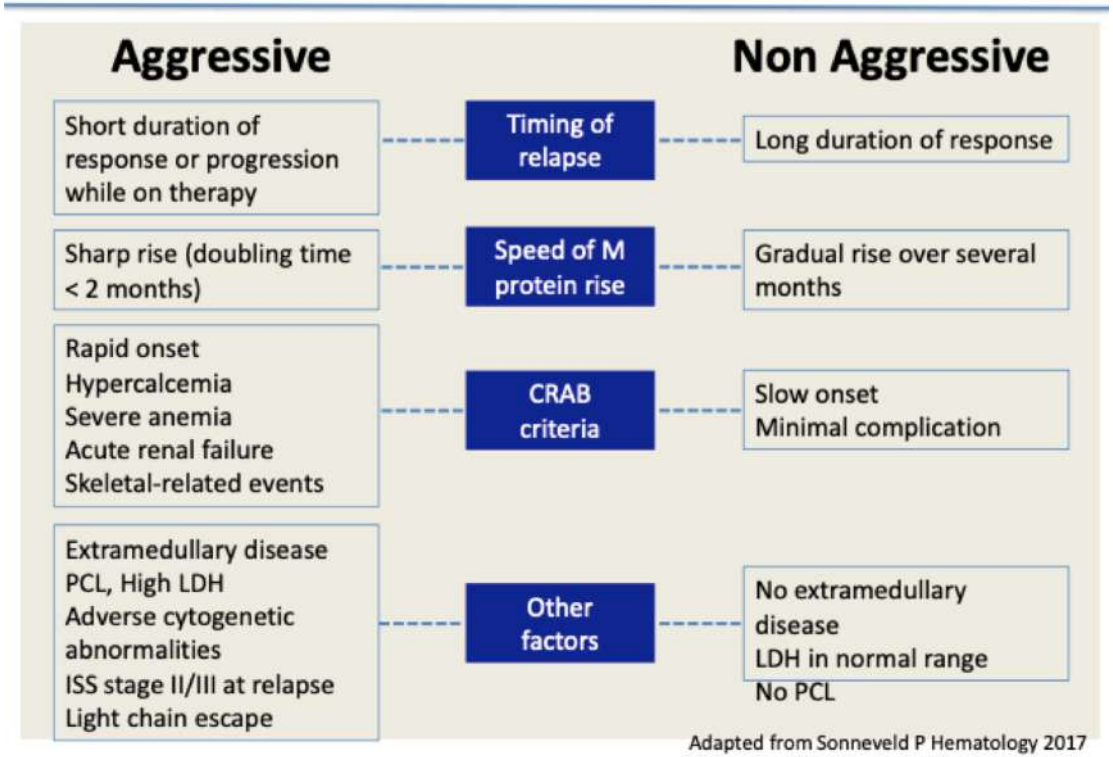
MDPI

Review

Choosing the Right Therapy for Patients with Relapsed/Refractory Multiple Myeloma (RRMM) in Consideration of Patient-, Disease- and Treatment-Related Factors

Laura Gengenbach *, Giulia Graziani *, Heike Reinhardt, Amelie Rösner, Magdalena Braun, Mandy-Deborah Müller, Christine Greil, Ralph Wäsch and Monika Engelhardt *

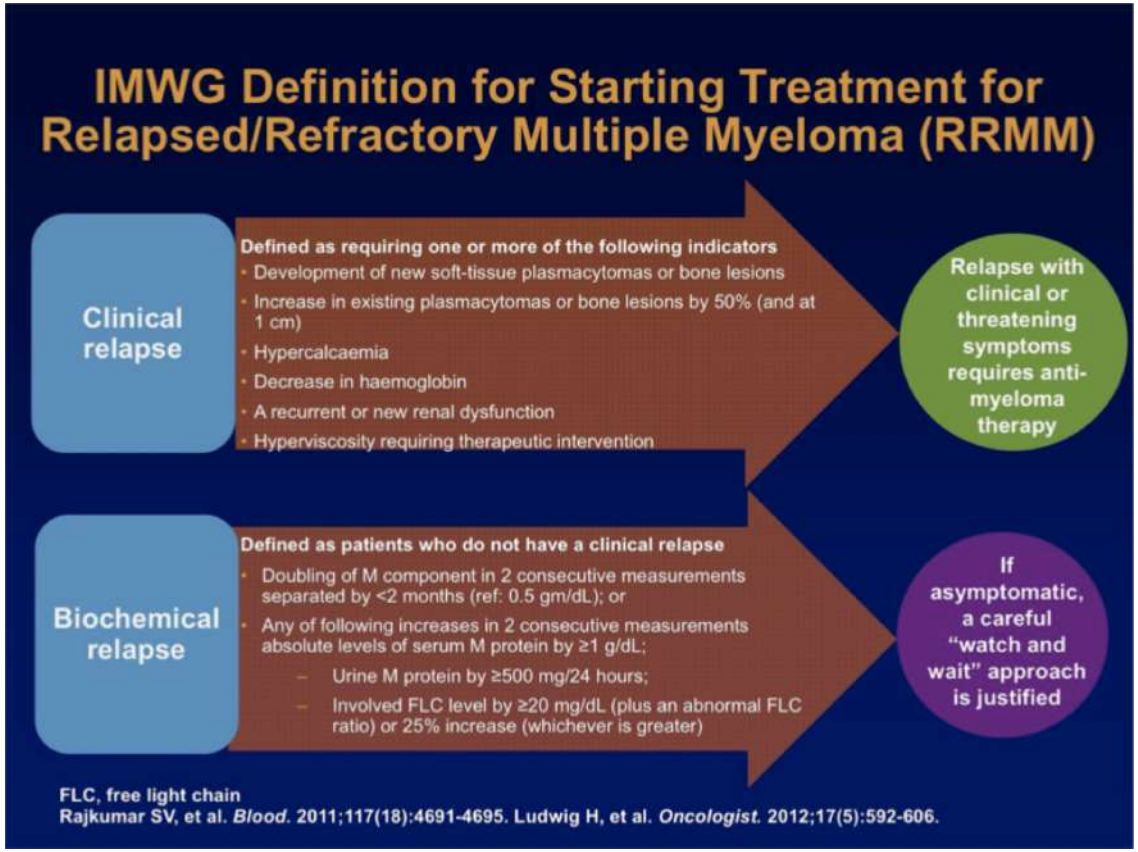
Not All Relapses in Multiple Myeloma are the Same[1-7]



*CRAB, calcium elevation, renal insufficiency, anemia, bone lesions.8 LDH, lactate dehydrogenase.

1. Mikhael JR. *Hematology Am Soc Hematol Educ Program.* 2014;2014:262-267. 2. Laubach J et al. *Leukemia.* 2016;30:1005-1017. 3. Lopez A et al. *Leuk Res Rep.* 2015;4:64-69. 4. Karlin L et al. *Leuk Lymphoma.* 2011;52:238-246. 5. Bladé J et al. *Ann Oncol.* 2010; 21(suppl 7):vii313-vii319. 6. Nooka AK et al. *Blood.* 2015;125: 3085-3099. 7. Mohty B et al. *Leukemia.* 2012;26:73-85. 8. Rajkumar SV et al. *Lancet Oncol.* 2014;15:e538-e548.

When to start treatment



Advantages for treatment at CRAB compared with biochemical relapse

- ✓ Patients could maintain active life between treatments
- ✓ Treatment toxicity could be spared
- ✓ The Health System could spare money
- ✓ Longer interruptions between treatments could prevent the development of clonal resistance
- ✓ Immune system could control indolent biochemical relapses prolonging time to next treatment

Limits for treatment at CRAB compared with biochemical relapse

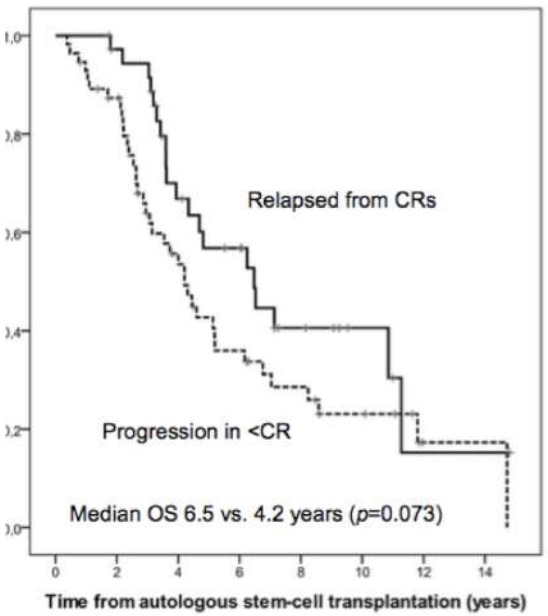
- ✓ Wait and watch; strategy can produce anxiety in patients and doctors
- ✓ A larger MM burden can be more difficult to be treated
- ✓ No prevention of organ damage
- ✓ More effective and safe treatment combinations available

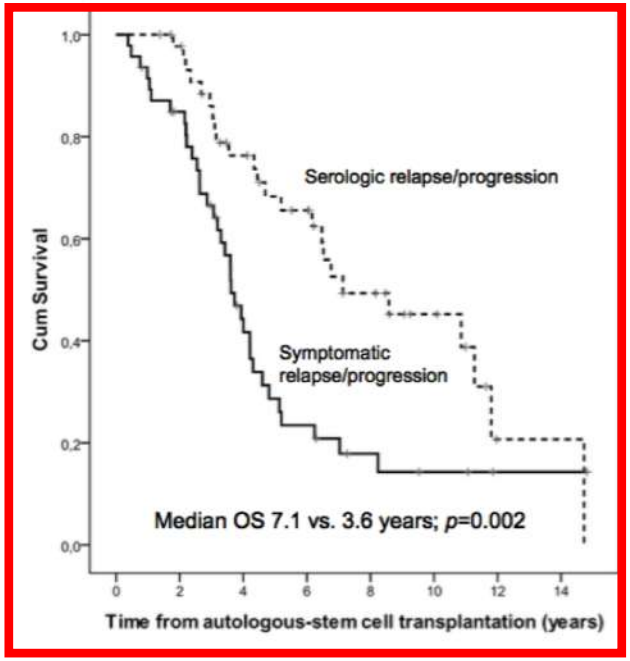
Relapse/progression pattern after front-line ASCT*

- Asymptomatic (M-protein increase) → 50%
- Symptomatic → 50%
- Similar to the initial clinical presentation (renal failure, ↑Ca, urine-M protein excretion, EMPs)

*Fernández de Larrea C *et al*, BMT 2014; 49:223-227.

Relapse/progression pattern after front-line ASCT*





*Fernández de Larrea C *et al*, BMT 2014; 49:223-227.

Treatment of relapse/progression after front-line ASCT*

26% of asymptomatic patients did not require therapy within 2 years

- ISS I or II at diagnosis, M-protein type was IgG (58%), only one extramedullary involvement
- Infrequent clinical features of aggressiveness (renal failure, hypercalcemia or anemia)
- All patients had received combination chemotherapy, with no novel agents pre-autologous SCT, except one
- Median OS after relapse/progression was 8.5 years, only four deaths
- Three of these 12 patients had not received any rescue therapy at 2, 3 and 4 years from relapse

Treatment of relapse/progression after front-line ASCT*

- Median time to rescue therapy: 2 months
  - Symptomatic patients → immediate therapy
  - Asymptomatic patients → 5.6 months

*Fernández de Larrea C *et al*, BMT 2014; 49:223-227.

653. MYELOMA: THERAPY, EXCLUDING TRANSPLANTATION: POSTER II | NOVEMBER 29, 2018

Subgroup Analysis of Patients with Biochemical or Symptomatic Relapse at the Time of Enrollment in the Endeavor Study

Philippe Moreau,[*,1] David S Siegel, MD PhD,[2] Hartmut Goldschmidt, MD,[3] Ruben Niesvizky, MD,[4] Sara Bringhen, MD,[5] Robert Z Orlowski, MD PhD,[*,6] Julie Blaedel,[7] Zhao Yang,[7] Meletios A Dimopoulos, MD[5]

Efficacy outcomes and adverse events by type of relapsed disease at study randomization.

	Biochemical (no CRAB symptoms at baseline)		Symptomatic (CRAB symptoms at baseline)	
Efficacy outcomes	**Kd56 (n=60)[a]**	**Vd (n=57)**	**Kd56 (n=404)[b]**	**Vd (n=408)**
Median PFS, months (95% CI)	NE (18.7–NE)	13.7 (12.1–NE)	17.7 (14.8–NE)	8.8 (7.4–10.1)
HR for Kd56 vs Vd (95% CI)	0.462 (0.232–0.922)		0.539 (0.439–0.662)	
Median OS, months (95% CI)	NE (NE–NE)	NE (39.8–NE)	44.0 (38.0–51.3)	36.8 (29.4–41.8)
HR for Kd56 vs Vd (95% CI)	0.768 (0.350–1.683)		0.801 (0.653–0.982)	
Safety outcomes	**Kd56 (n=60)**	**Vd (n=56)**	**Kd56 (n=403)**	**Vd (n=400)**
TEAEs, n (%)	58 (96.7)	56 (100.0)	399 (99.0)	395 (98.8)
Grade ≥3 TEAEs, n (%)	47 (78.3)	33 (58.9)	330 (81.9)	291 (72.8)
TEAEs leading to treatment discontinuation, n (%)	17 (28.3)	11 (19.6)	116 (28.8)	107 (26.8)
TEAEs leading to death, n (%)	0	1 (1.8)	32 (7.9)	20 (5.0)

[a]For PFS, n=61.

[b]For PFS, n=403.

CI, confidence interval; CRAB, hypercalcemia, renal impairment, anemia, or bone lesions; HR, hazard ratio; Kd56, carfilzomib (56 mg/m^2) and dexamethasone; OS, overall survival; NE, not estimable; PFS, progression-free survival; TEAE, treatment-emergent adverse event; Vd, bortezomib and dexamethasone.

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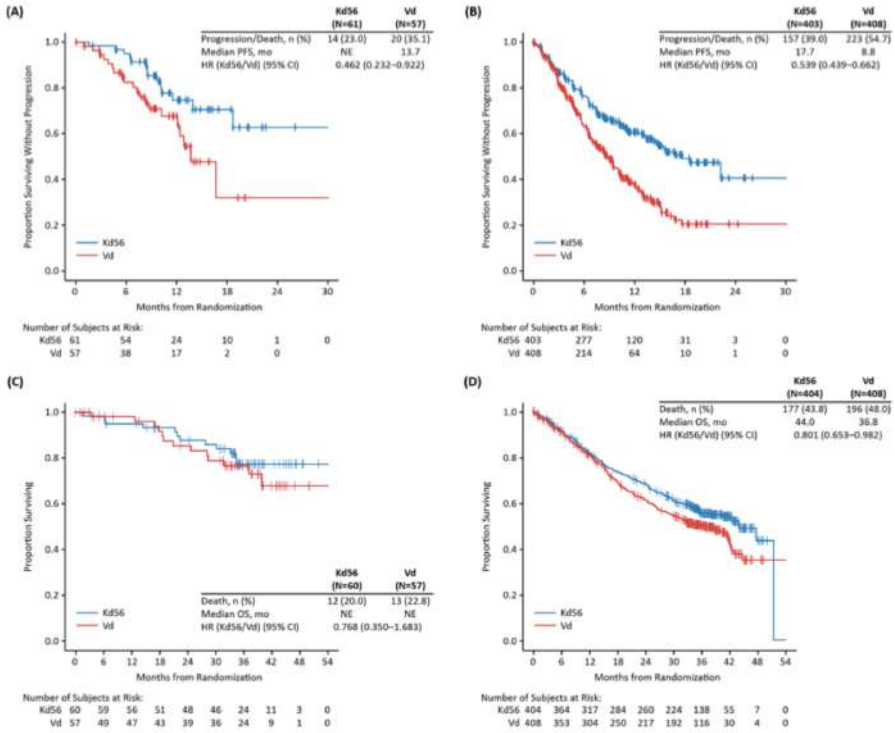

Figure. Kaplan–Meier PFS and OS curves for Kd56 and Vd by type of relapse at randomization: (A) PFS in patients with biochemical relapse, (B) PFS in patients with symptomatic relapse, (C) OS in patients with biochemical relapse, and (D) OS in patients with symptomatic relapse

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Leukemia (2019) 33:730–738
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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]

Received: 23 May 2018 / Revised: 28 August 2018 / Accepted: 3 September 2018 / Published online: 15 October 2018

Variable	$N = 351$, Median (IQR) or n (%)
Age, years	61 (54–66)
Males	198 (56)
High-risk cytogenetics: del17p, t(4;14),t (14;16) and t(14;20)	58/283 (21)
ISS (Data available in N = 295)	115/96/84 (39/33/28)
R-ISS (Data available in N = 230)	61/141/28 (27/61/12)
BMPCs	50% (30–70)
ASCT with initial therapy	271 (77)
Maintenance therapy	135 (39)
Time to CR	8 months (5–10)
Median duration of CR	24 months (13–42)
Duration of CR	
Less than 6 months	33 (9)
6–12 months	41 (12)
12–18 months	50 (14)
18–24 months	48 (14)
24 months or more	179 (51)
Loss of CR	239/351 (68)
Type of CR loss	
Symptomatic relapse/progression	59 (25)
Biochemical relapse/progression	58 (24)
Positive immunofixation with or without rise in monoclonal protein, not meeting criteria for progression	88 (37)
Abnormal FLC ratio in patients with light chain evaluable disease	34 (14)

ISS International Staging System, *R-ISS* Revised International Staging System, *BMPCs* bone marrow plasma cells, *ASCT* autologous stem cell transplantation, *CR* complete response

Loss of complete response

Loss of CR was defined as "(1) Symptomatic relapse/progression" (for example, progression with lytic lesions or soft tissue plasmacytoma or other symptoms of end-organ damage from myeloma); "(2) Biochemical relapse/progression" as defined by the IMWG criteria with 25% or more increase in monoclonal protein, with at least 0.5 g/dL absolute increase. For light chain evaluable patients, absolute increase in difference in involved and uninvolved FLC (dFLC) should be at least 10 mg/dL; "(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 symptomatic or biochemical progression criteria; "(4) Biochemical loss of CR with abnormal FLC ratio only [light chain myeloma only]:" Two consecutive abnormal FLC ratios in patients with light chain evaluable multiple myeloma who do not otherwise meet criteria for loss of CR with re-emergence of monoclonal protein as described in (3).

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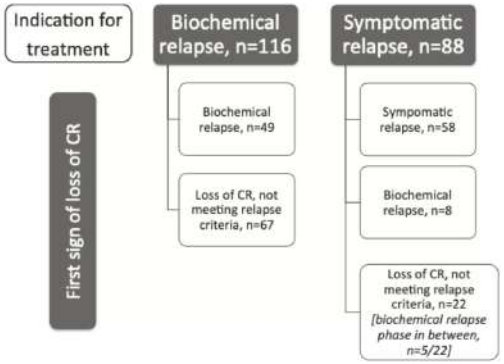

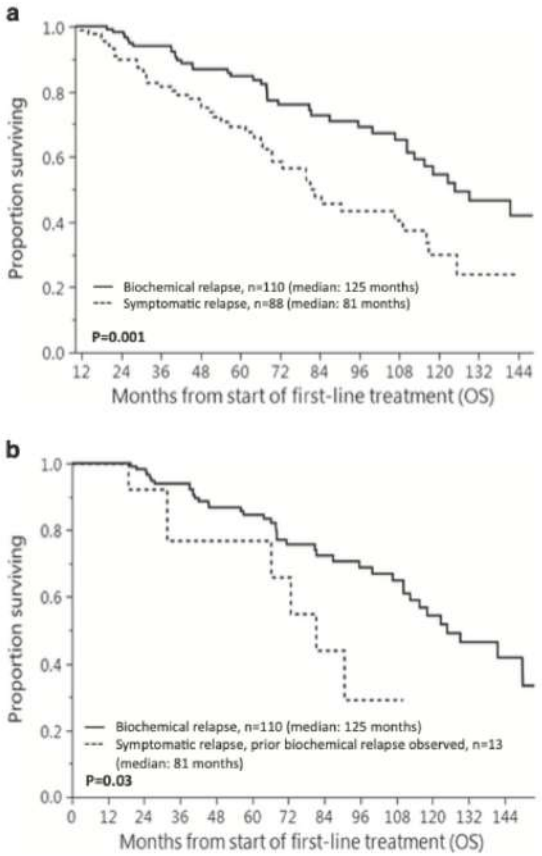

Overall survival from start of first-line therapy in patients with relapse from complete response starting treatment for (**a**) biochemical vs. symptomatic relapse and (**b**) biochemical relapse vs. those who were observed with biochemical relapse and started treatment for symptomatic disease

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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[15] · Vassiliki Pappa[16] · Eleni Papadaki[17] · Despoina Fotiou[16] · Eftychia Nikolaou[2] · Evlambia Giannopoulou[1] · Eleftheria Hatzimichael[13] · Nikolaos Giannakoulas[7] · Vassiliki Douka[9] · Kyriaki Kokoviadou[9] · Despoina Timotheatou[18] · Evangelos Terpos[19]

Received: 25 January 2018 / Accepted: 2 May 2018 / Published online: 13 May 2018

Response rates of second line treatment

	Total sample[a] ($N = 207$)	Relapse at the start of second-line treatment		p value
		Biochemical ($N = 139$)	Clinical ($N = 67$)	
Response	N (%)	N (%)	N (%)	0.021
sCR[b]	10 (4.8)	6 (4.3)	4 (6.0)	
CR[c]	27 (13.0)	15 (10.8)	12 (17.9)	
VGPR[d]	49 (23.7)	36 (25.9)	13 (19.4)	
PR[e]	66 (31.9)	51 (36.7)	15 (22.4)	
MR[f]/SD[g]	16 (7.7)	12 (8.6)	4 (6.0)	
Other	39 (18.9)	19 (13.7)	19 (28.4)	
ORR[h]	152 (73.4)	108 (77.7)	44 (65.7)	0.066

[a] Type of relapse unknown for one patient
[b] Stringent complete response
[c] Complete response
[d] Very good partial response
[e] Partial response
[f] Minor response
[g] Stable disease
[h] Overall response rate

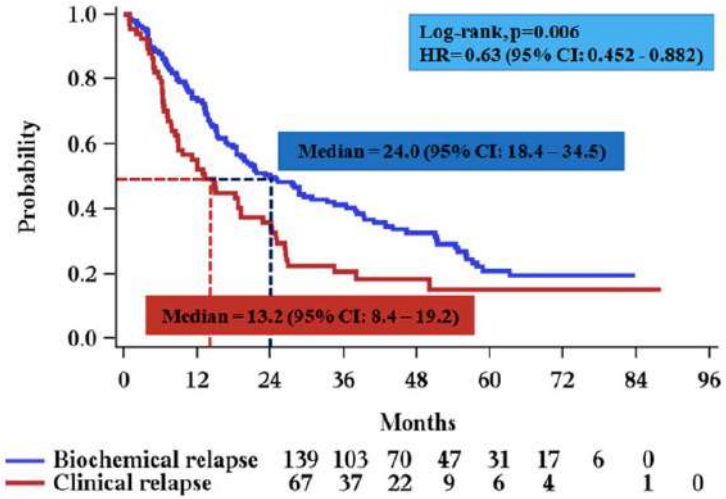

Fig. 2 PFS curves for patients who started second line treatment on clinical relapse (median 13.2 months), and for patients that started second line treatment on biochemical relapse (median 24 months)

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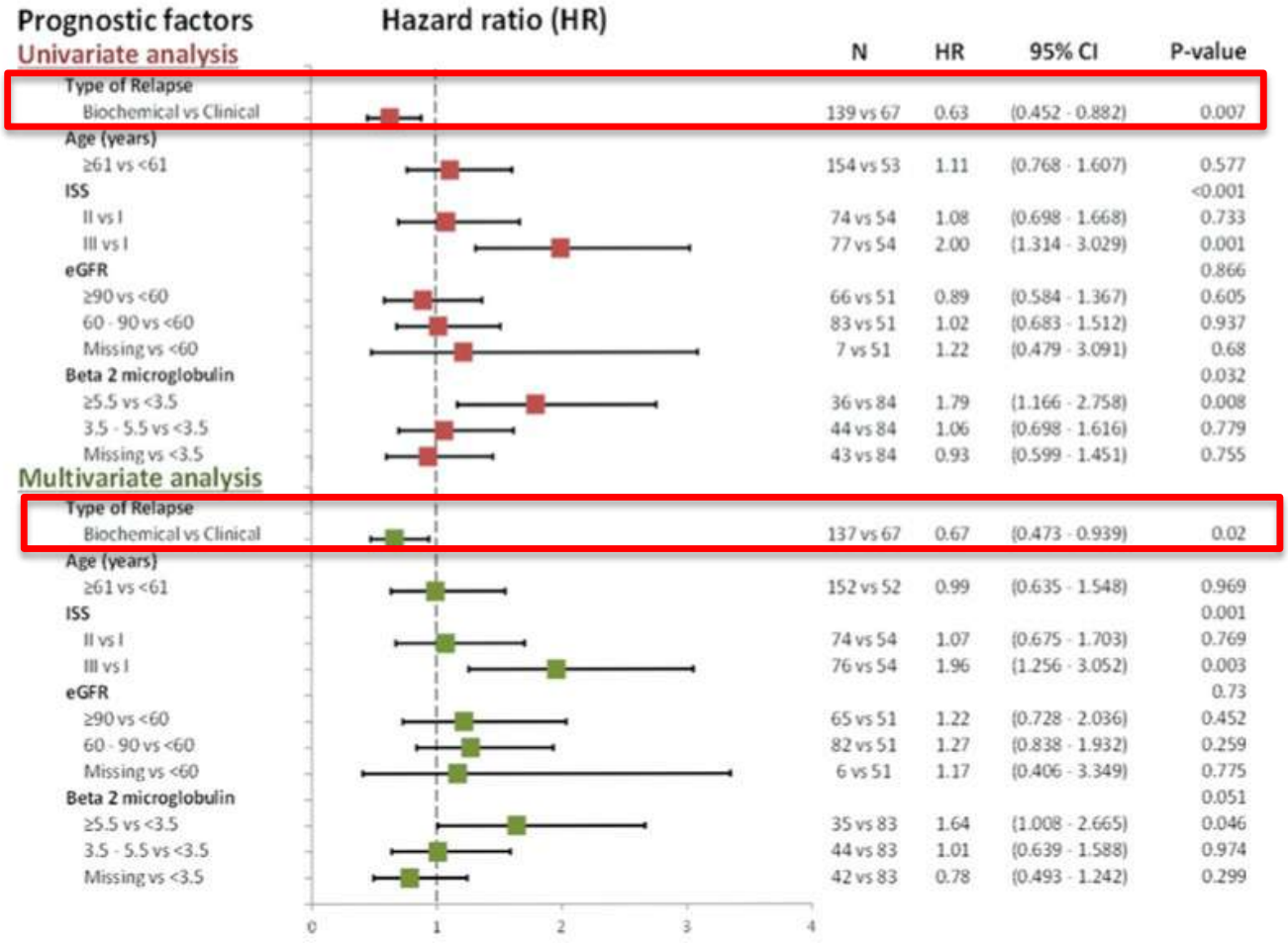

Prognostic factors	N	HR	95% CI	P-value
Univariate analysis				
Type of Relapse				
Biochemical vs Clinical	139 vs 67	0.63	(0.452 - 0.882)	0.007
Age (years)				
≥61 vs <61	154 vs 53	1.11	(0.768 - 1.607)	0.577
ISS				<0.001
II vs I	74 vs 54	1.08	(0.698 - 1.668)	0.733
III vs I	77 vs 54	2.00	(1.314 - 3.029)	0.001
eGFR				0.866
≥90 vs <60	66 vs 51	0.89	(0.584 - 1.367)	0.605
60 - 90 vs <60	83 vs 51	1.02	(0.683 - 1.512)	0.937
Missing vs <60	7 vs 51	1.22	(0.479 - 3.091)	0.68
Beta 2 microglobulin				0.032
≥5.5 vs <3.5	36 vs 84	1.79	(1.166 - 2.758)	0.008
3.5 - 5.5 vs <3.5	44 vs 84	1.06	(0.698 - 1.616)	0.779
Missing vs <3.5	43 vs 84	0.93	(0.599 - 1.451)	0.755
Multivariate analysis				
Type of Relapse				
Biochemical vs Clinical	137 vs 67	0.67	(0.473 - 0.939)	0.02
Age (years)				
≥61 vs <61	152 vs 52	0.99	(0.635 - 1.548)	0.969
ISS				0.001
II vs I	74 vs 54	1.07	(0.675 - 1.703)	0.769
III vs I	76 vs 54	1.96	(1.256 - 3.052)	0.003
eGFR				0.73
≥90 vs <60	65 vs 51	1.22	(0.728 - 2.036)	0.452
60 - 90 vs <60	82 vs 51	1.27	(0.838 - 1.932)	0.259
Missing vs <60	6 vs 51	1.17	(0.406 - 3.349)	0.775
Beta 2 microglobulin				0.051
≥5.5 vs <3.5	35 vs 83	1.64	(1.008 - 2.665)	0.046
3.5 - 5.5 vs <3.5	44 vs 83	1.01	(0.639 - 1.588)	0.974
Missing vs <3.5	42 vs 83	0.78	(0.493 - 1.242)	0.299

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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

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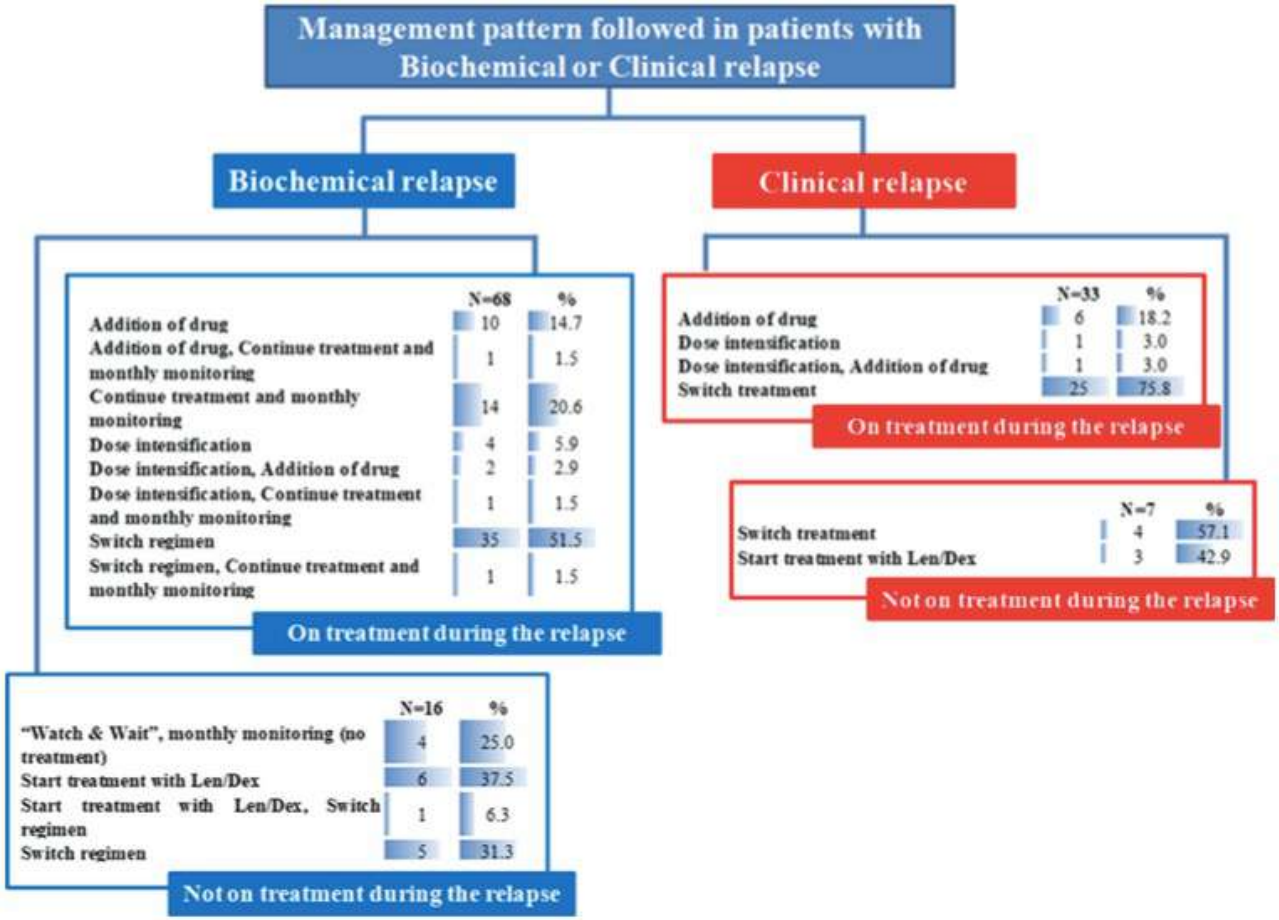

Blood Cancer Journal

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

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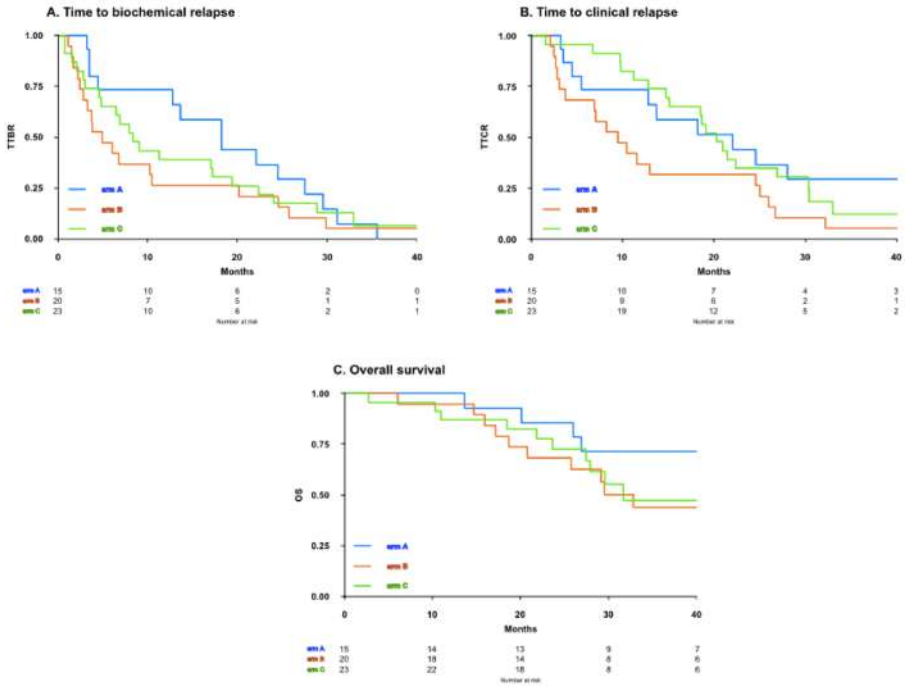

Survival outcomes: Time to biochemical relapse (**a**), time to clinical relapse (**b**) and overall survival (**c**) in the examined population. **TTBR** time to biochemical relapse, **TTCR** time to clinical relapse, **OS** overall survival, **ARM A** bortezomib and dexamethasone until progression, **ARM B** observation until clinical relapse, **ARM C** early retreatment at biochemical relapse with bortezomib and dexamethasone.

Highlights from IMW 2021

1-2 Febbraio 2022
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BENEFICIAL EFFECT ON OVERALL SURVIVAL OF EARLY SALVAGE TREATMENT WITH SECOND-GENERATION NOVEL AGENTS AT BIOCHEMICAL RELAPSE: A REAL-WORLD SINGLE CENTER EXPERIENCE

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INTRODUCTION

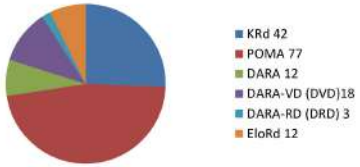
Despite therapeutic advances, multiple myeloma (MM) remains largely incurable and patients invariable develop relapsed or refractory (R/R) disease. Relapse can be characterized according to disease aggressiveness and the presence of clinical symptoms. Aggressive relapse can occur at biochemical level, due to rapid and relevant increase of monoclonal component or LDH, or at clinical level, defined by the presence of extramedullary disease, acute renal injury or progression to secondary plasma cell leukemia.

OBJECTIVE

To identify the clinical outcome upon treatment with second generation novel agents (pomalidomide, carfilzomib) and monoclonal antibodies (elotuzumab, daratumumab), we collected evidence of the best timing in providing early salvage treatment to RRMM.

METHODS

According to regulatory Italian laws, patients (N=128) received one of the following regimens:



Among second generation novel agents-treated patients (N=128), 100 pts were exposed to POMA alone (N=77), DARA alone (N=4), DVD (N=6), DRD (N=1), EloRd (N=8), KRD (N=24); 20 pts were exposed to two second generation of novel agents (POMA and KRd N=4, poma and DARA N=4, poma and EloRd N=2, poma and DVD N=3, KRd and DARA N=1, KRd and DVD N=5, EloRd and DVD N=1), 7 patients to three combination (POMA and KRd and DARA N=4, poma and KRd and DVD N=2, KRd and DARA and DVD N=1), 1 patient to POMA, DARA, EloRd and KRd.

RESULTS

From July 2014 to January 2019 we evaluated 166 R/R MM treatments of 128 patients. Table 1 shows patients characteristics.

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%

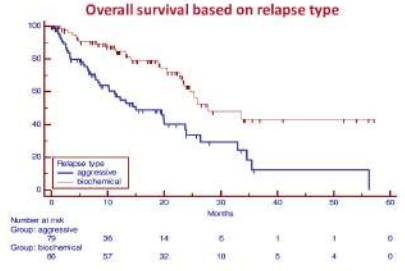
Table 1. Clinical characteristics

FISH was repeated before starting the second-generation drugs, and it was available in 53 cases: 11 carried on high-risk (del 17p, t4;14 or t14;16) and 42 standard-risk cytogenetics, without any additional marker compared to the matched sample at diagnosis.

For the whole cohort, longer overall survival (OS) was associated to treatment at biochemical relapse (27.8 vs 15.2 months, p=0.0005), to relapsed vs relapsed and refractory patients (34.1 vs 19.3 months, p=0.0004), to patients who received less than 3 lines of therapy (33.6 vs 19.1 months, p=0.002), carrying standard vs high-risk cytogenetics (20.4 vs 11.2 months, p-value not significant for low numbers in two groups. Figure 2) without any significant difference due to previous ASCT or the type of second-generation treatment.

In multivariable analysis only type of relapse (biochemical versus clinical) and refractory status were independent predictors of overall survival (p<0.0001).

Overall survival based on relapse type



CONCLUSION

In our community setting data, heavily pretreated patients achieved improvement of outcome obtaining a median OS >12 months, using second generation novel agents. Earlier treatment at biochemical asymptomatic relapse is associated with longer OS, suggesting that the most efficacious combinations should be anticipated as soon as possible to prolong OS

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- Offidani M, **Expert Panel Consensus Statement for Proper Evaluation of First Relapse in Multiple Myeloma** Curr Hematol Malig Rep. 2019 May 10. doi: 10.1007/s11899-019-00507-x.

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When to start treatment in patients with relapsed/progressed multiple myeloma?

Asymptomatic (M-protein) Relapse vs. Clinical Relapse

Current practice/recommendation (2011) → Delay treatment until:

✓**Clinical relapse**

✓**Significant paraprotein relapse***

- Any of the following criteria in 2 consecutive measurements separated by ≤ 2 months:
- Doubling of the M-component
  ↑ serum M protein by ≥ 10 g/L
  ↑ urine M protein by ≥ 500 mg/24h
  ↑ involved FLC level by ≥ 200 mg/L (plus abnormal ratio)

*Rajkumar *et al*, Blood 2011; 117: 4691-5.

Indications for treatment at relapse

Indications for treatment at relapse

Clinical relapse

- Development of new soft-tissue plasmacytomas or bone lesions
- Definite increase (≥50%) in size of existing plasmacytomas or bone lesions
- Hypercalcemia (≥11.5 mg/dL; 2.875 mmol/L)
- Decrease in hemoglobin of ≥2 g/dL (1.25 mmol/L), or to < 10g/dL because of myeloma
- Rise in serum creatinine by ≥2 mg/dL or more (≥177 mmol/L), due to myeloma
- Hyperviscosity requiring therapeutic intervention

Significant biochemical relapse in patients without clinical relapse

- Doubling of the M-component in two consecutive measurements separated by 2 months with the reference value of 5 g/L, or
- In two consecutive measurements any of the following increases:
  - o the absolute levels of serum M protein by ≥10 g/L, or
  - o an increase of urine M protein by ≥500 mg per 24 hours, or
  - o an increase of involved FLC level by ≥20 mg/dL (plus an abnormal FLC ratio) or 25% increase (whichever is greater)

When do we start treatment ?

- ✓ Patients in clinical relapse or in rapid and significant biochemical relapse
- ✓ In first relapse there is still a possibility of achieving a good and lasting response, especially in standard risk patients.
- ✓ In these patients, an increasing M-protein should be closely followed and, in case of (rapid) increase, immediate treatment should be initiated
- ✓ In high-risk patients treatment should always be started
- ✓ There is a small category of patients with slow indolent biochemical relapse who may experience a period of asymptomatic disease with observation only

Sonneveld P et al Haematologica 2016; Ludwig H ESH, Paris 2017

Indicators for Treatment in Relapsed Myeloma

Consider early treatment if:

- ✓ Previous aggressive presentation/ clinical behaviour
- ✓ Clearly increasing M-protein, particularly light chains in urine
- ✓ Decreasing Hb level

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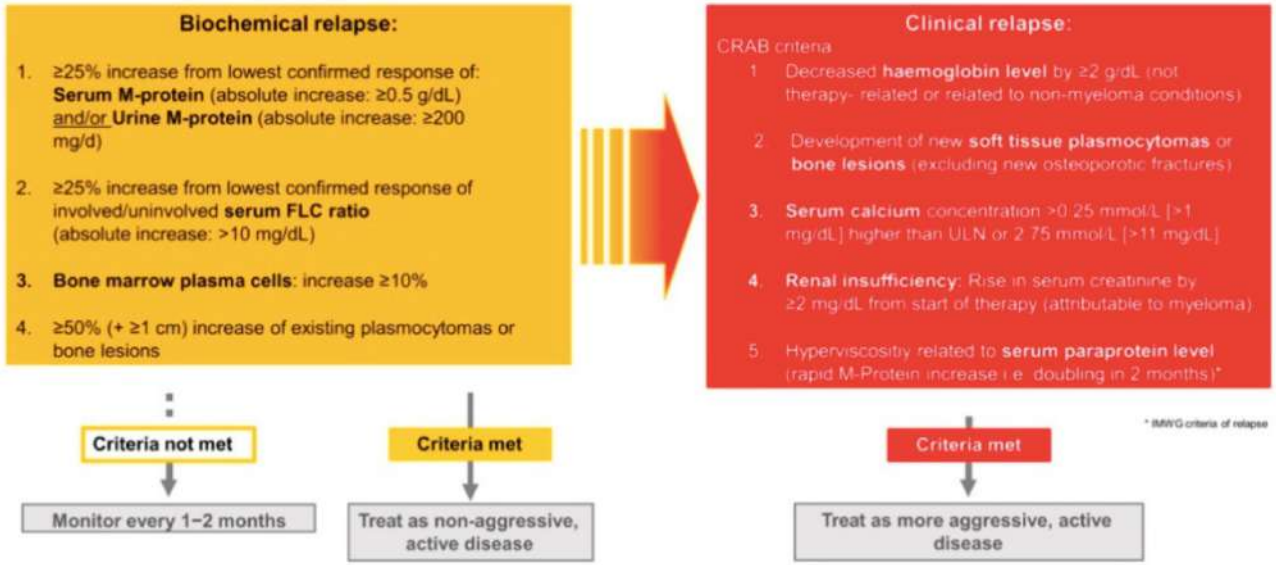
Review

Choosing the Right Therapy for Patients with Relapsed/Refractory Multiple Myeloma (RRMM) in Consideration of Patient-, Disease- and Treatment-Related Factors

Laura Gengenbach [†], Giulia Graziani [†], Heike Reinhardt, Amelie Rösner, Magdalena Braun, Mandy-Deborah Möller, Christine Greil, Ralph Wäsch and Monika Engelhardt [*,†]



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

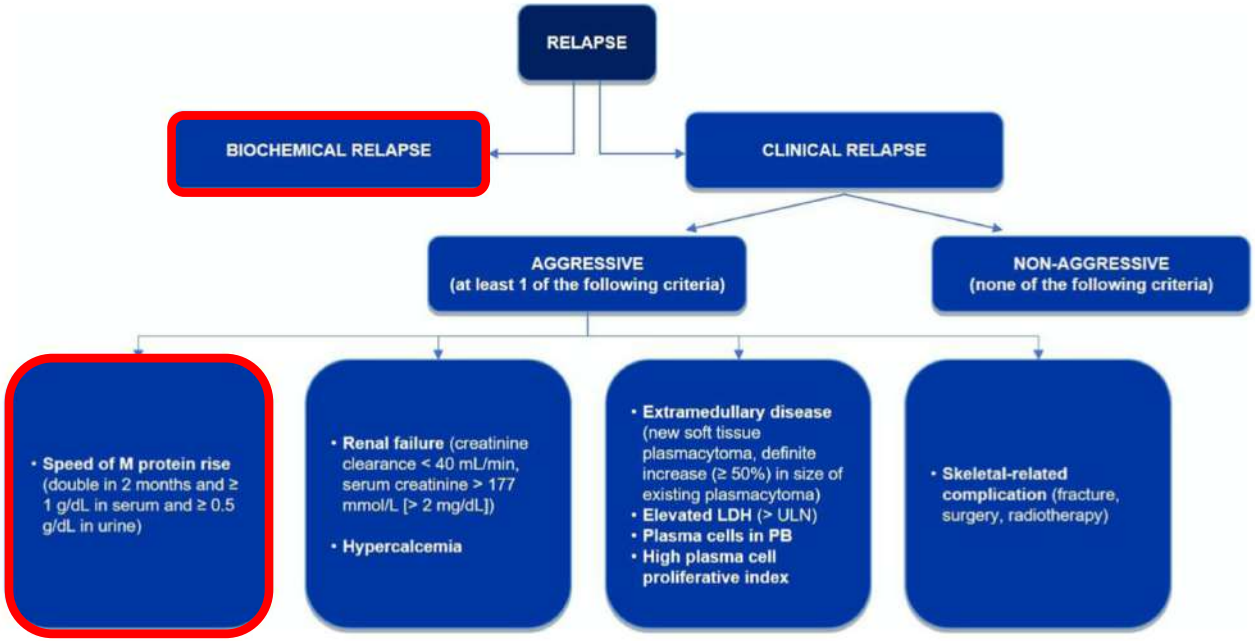
MULTIPLE MYELOMA (P KAPOOR, SECTION EDITOR)

Check for updates

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]

Published online: 10 May 2019



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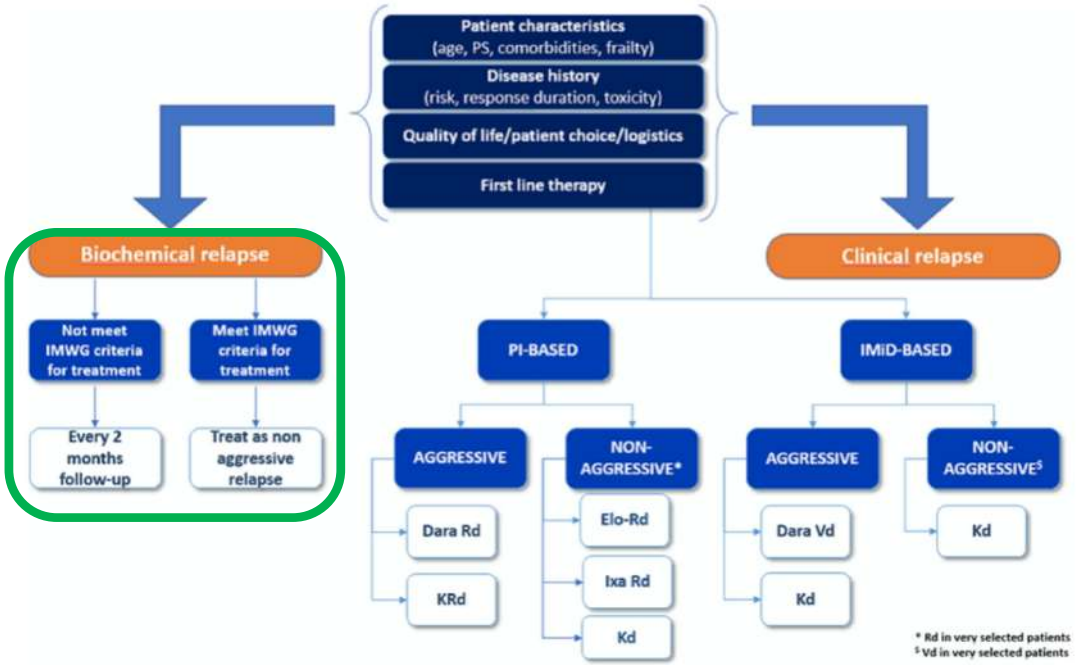

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Clinical implications of loss of bone marrow minimal residual disease negativity in multiple myeloma

Minimal Residual Disease (MRD) Relapse Patterns

	MRD Status		
Clinical End Point	**MRD Negative (n = 344)**	**MRD conversion (n = 224)**	***P*-value***
No clinical relapse	330 (95.9)	61 (27.2)	*<0.0001*
Relapse†	14 (4.1)	163 (72.8)	*<0.0001*
Clinical relapse‡	14 (4.1)	118 (52.7)	*<0.0001*
Biochemical relapse§	0 (0.0)	45 (20.1)	*<0.0001*

NOTE. Data are no. (%) unless otherwise noted.

* *P*-value determined by Fisher's exact test.

† Relapse defined using IMWG criteria, reappearance of serum or urine M-protein by immunofixation or electrophoresis, development of > 5% plasma cells in the bone marrow or appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcaemia)[14]

‡ Clinical relapse defined as relapse with any one of the following more than 30% BM involvement, presence of focal lesion on imaging (PET-CT, MRI DWIBS), presence CRAB criteria, presence of high-risk gene expression profile (GEP) signature at relapse or abnormal metaphase cytogenetics due to multiple myeloma.

§ Biochemical relapse defined as relapse with any one of the following a rising M-protein or free light chains, less than 30% BM involvement, focal lesion on imaging (PET-CT, MRI DWIBS), no CRAB criteria, no high-risk gene expression profile (GEP) signature at relapse, no abnormal metaphase cytogenetics due to MM.

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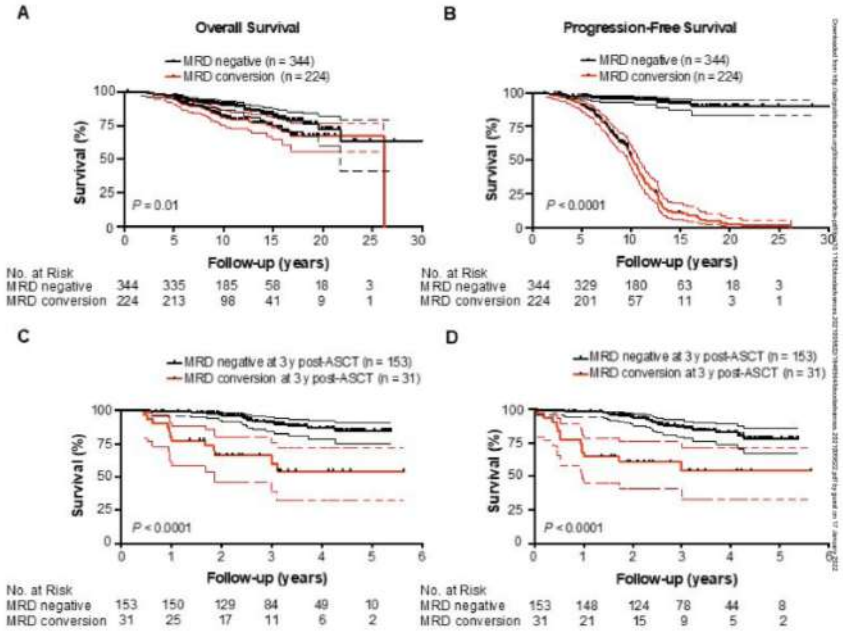

A) Overall survival of patients with MRD conversion is worse compared to patients with sustained MRD negativity (Hazard Ratio, 1.7; 95% Confidence Interval (CI), 1.1-1.7, P = 0.01).

B) Progression free survival of patients with MRD conversion versus patients with sustained MRD negativity is significantly inferior (Hazard Ratio, 18.9; 95% CI, 13.2-27.0, P < 0.0001). In a landmark analysis at 3 years post-ASCT,

C) Overall survival was significantly worse for patients that converted from MRD negative to positive compared to patients with sustained MRD negativity (Hazard Ratio, 20.0; 95% CI, 6.3-63.0, P < 0.0001).

D) Progression free survival of patients with MRD conversion is significantly worse than patients with sustained MRD negativity (Hazard Ratio, 4.5; 95% CI, 4.3-33.7, P < 0.0001).

OAB-058

Predictive relevance of sustained MRD negativity and of early loss of MRD negativity during maintenance therapy after transplant in newly diagnosed Multiple Myeloma patients

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- The worst PFS (24.7 months) was observed in pts with early loss of MRD negativity (< 1 year) and was significantly inferior if compared both to pts with sustained MRD negativity ($p < 0.0001$, HR 0.06 ; 0.01-0.54) and to MRD positive pts before maintenance (p 0.03, HR 0.35; 0.11-0.16), with significantly different outcome of the three subgroups ($p < 0.0001$)
- The worst OS observed in pts with early loss of MRD negativity (< 1 year) was significantly inferior if compared both to pts with sustained MRD negativity ($p < 0.0001$, HR 0.05; 0.003-0.80) and to MRD positive pts before maintenance (p 0.020, HR 0.21; 0.035- 1.26).
- We confirm the predictive value of MRD assessment after ASCT and therefore the importance of achieving sustained MRD negativity regardless of different treatment strategies. Moreover, the detection of early loss of MRD negativity can help the physician to identify pts with particularly poor prognosis

Conclusions

- Most patients with biochemical relapse will progress to clinical relapse, with a median time of approximately 5 months. However, a small fraction of patients—approximately 20%—may remain in biochemical relapse without progression for several years;
- Earlier intervention is generally best for the patient: by contrast, waiting may allow the malignant clone to expand, making the MM cells more resistant to subsequent therapy;
- Patients with confirmed biochemical relapse should receive therapy, especially in case of early, aggressive relapse, rapid increase in myeloma parameters and high-risk cytogenetics. If the criteria of biochemical relapse are not met or in case of an asymptomatic, very slow increase in biochemical markers (evolving MM), close monitoring of myeloma parameters at least every 2–3 months is recommended

Grazie per l' attenzione