Chronic treatment is better than intermittent treatment

Argument against:

Dr Holger Auner

Imperial College London

SUBGROUPS

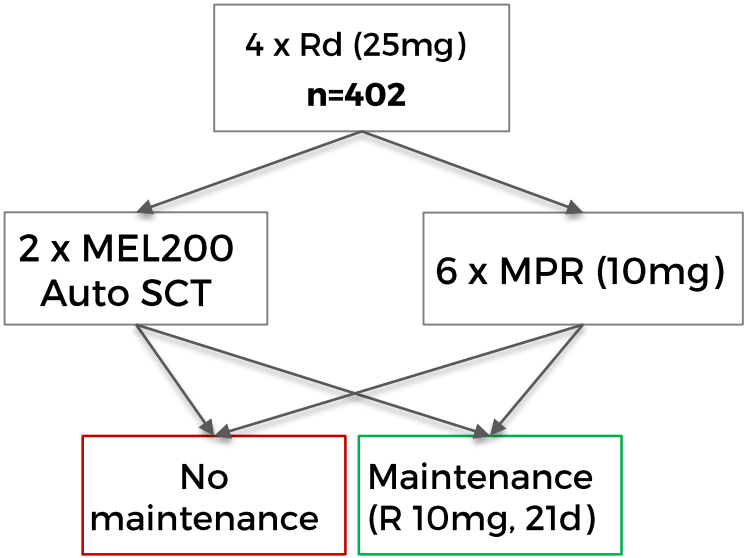
Continuous or maintenance therapy does not benefit all patients

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 4, 2014 VOL. 371 NO. 10

Autologous Transplantation and Maintenance Therapy in Multiple Myeloma

A. Palumbo, F. Cavallo, F. Gay, F. Di Raimondo, D.B. Yehuda, M.T. Petrucci, S. Pezzatti, T. Caravita, C. Cerrato, E. Ribakovsky, M. Genuardi, A. Cafro, M. Marcatti, L. Catalano, M. Offidani, A.M. Carella, E. Zamagni, F. Patriarca, P. Musto, A. Evangelista, G. Ciccone, P. Omedé, C. Crippa, P. Corradini, A. Nagler, M. Boccadoro, and M. Cavo



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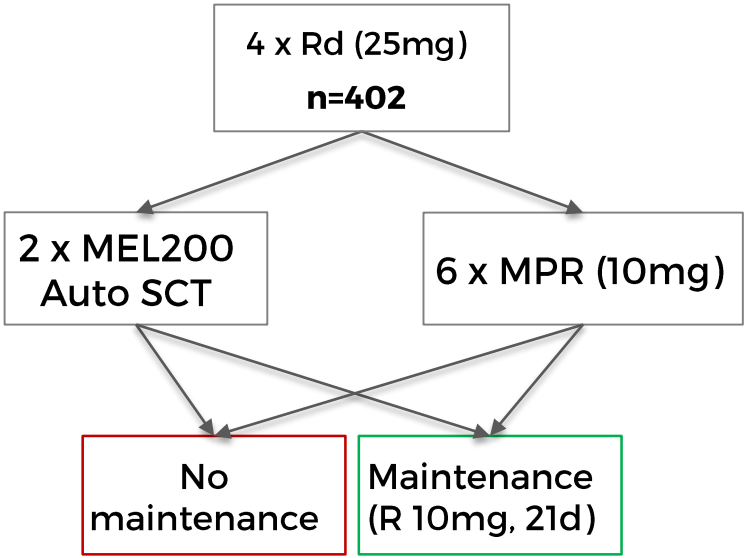
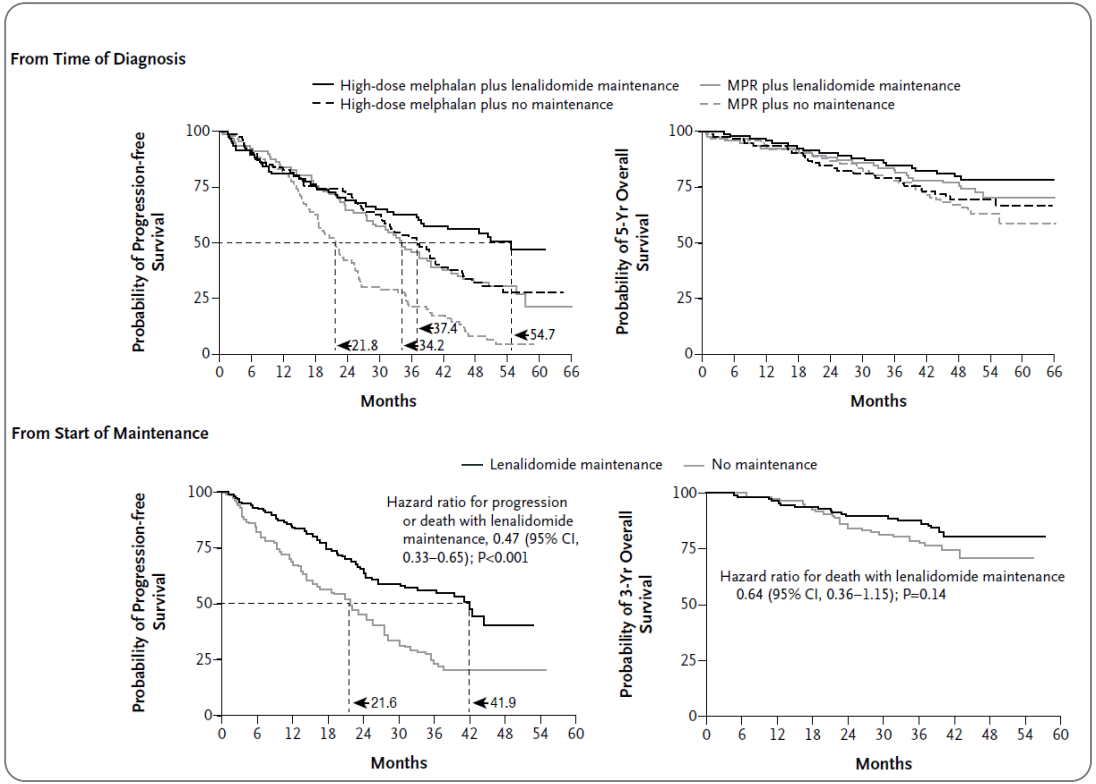
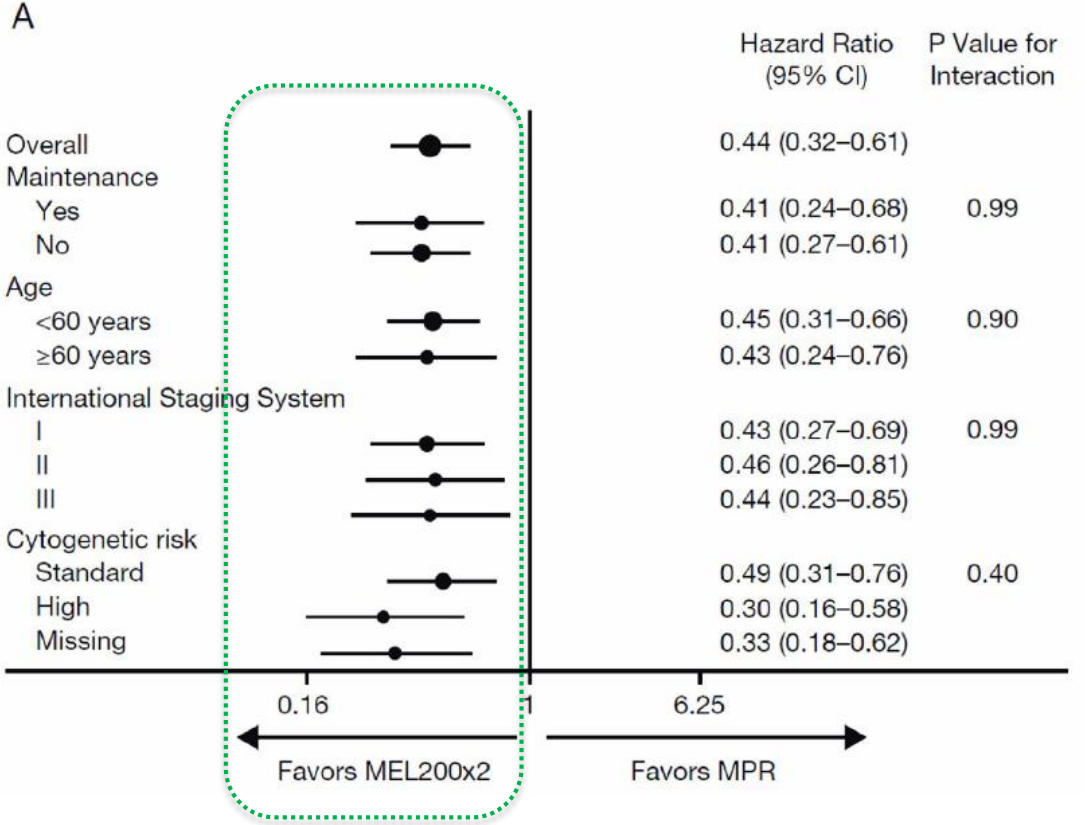




High-dose Mel plus ASCT (x2) benefits all patients

PFS



Maintenance does NOT benefit all patients

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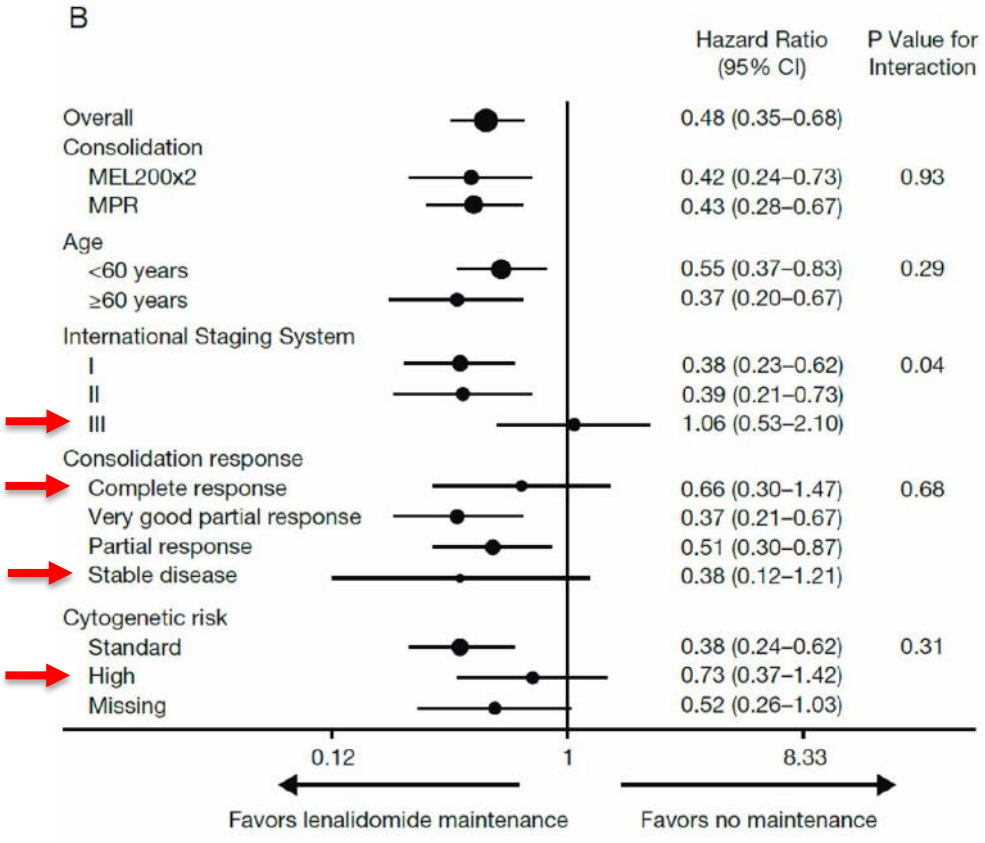
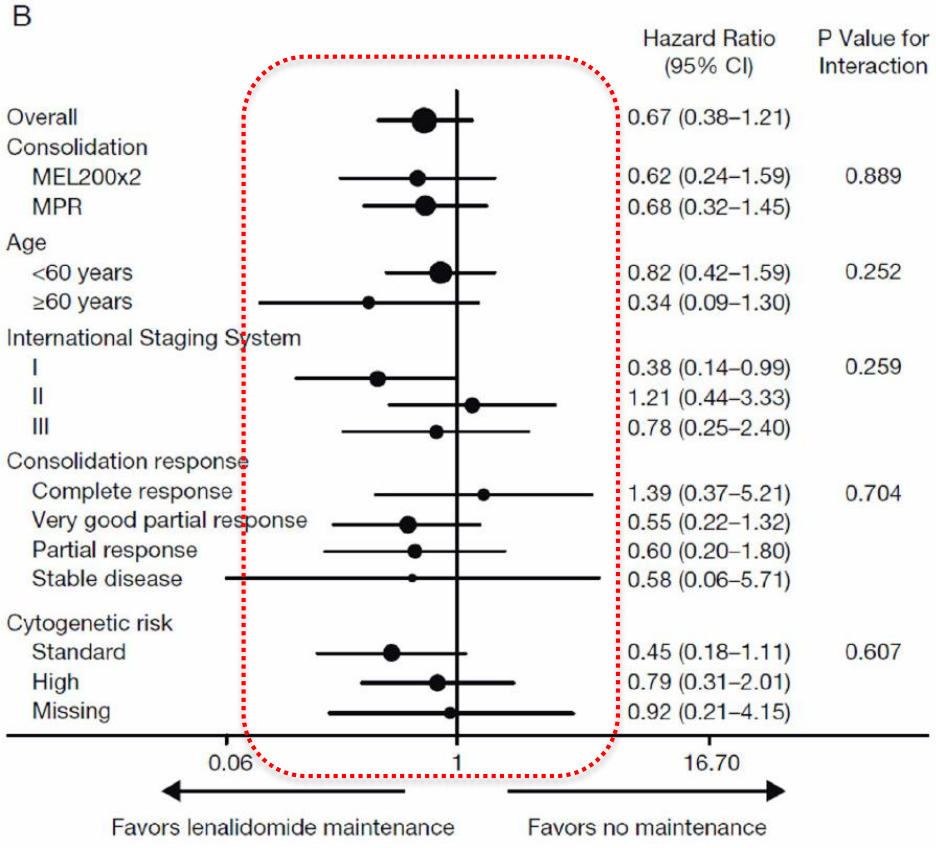


Maintenance does NOT benefit any patient subgroup

Overall survival

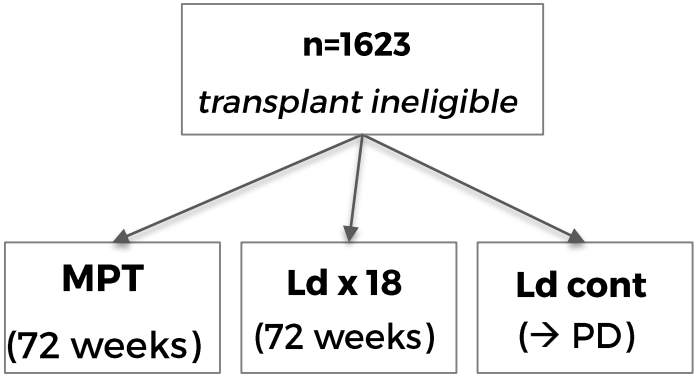


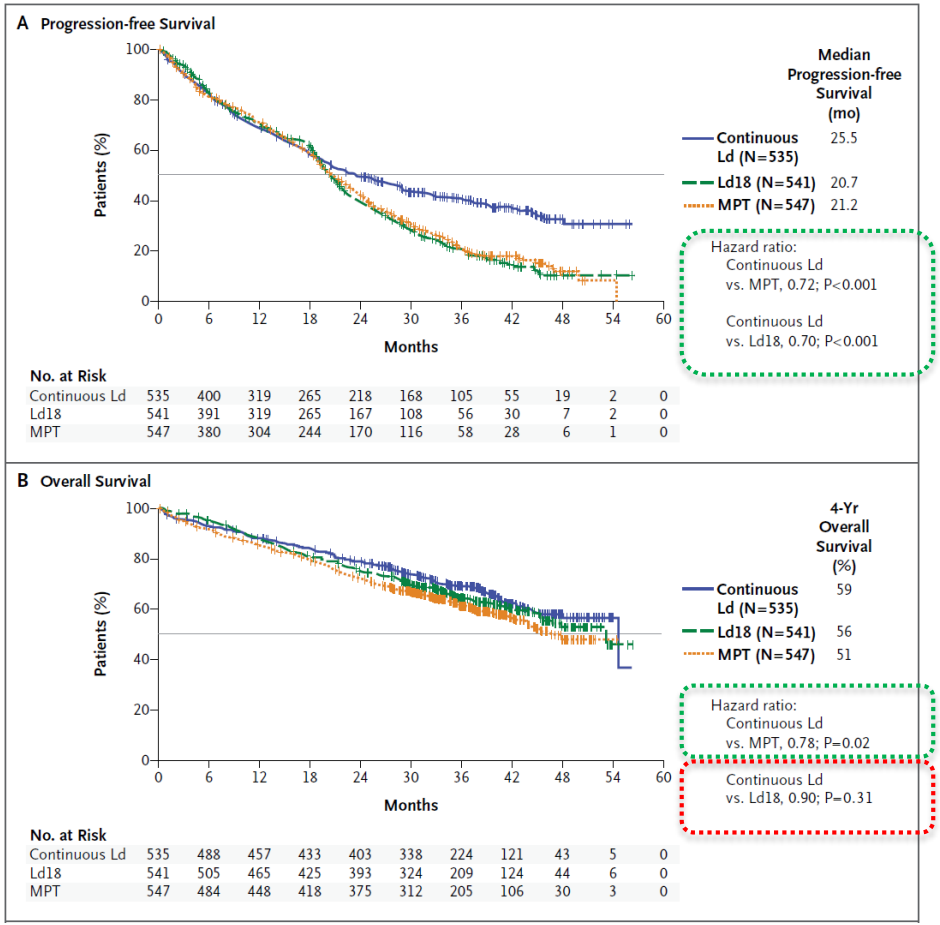
N ENGL J MED 371;10 NEJM.ORG SEPTEMBER 4, 2014

ORIGINAL ARTICLE

Lenalidomide and Dexamethasone in Transplant-Ineligible Patients with Myeloma

Lotfi Benboubker, M.D., Meletios A. Dimopoulos, M.D., Angela Dispenzieri, M.D., John Catalano, M.D., Andrew R. Belch, M.D., Michele Cavo, M.D., Antonello Pinto, M.D., Katja Weisel, M.D., Heinz Ludwig, M.D., Nizar Bahlis, M.D., Anne Banos, M.D., Mourad Tiab, M.D., Michel Delforge, M.D., Jamie Cavenagh, M.D., Catarina Geraldes, M.D., Je-Jung Lee, M.D., Christine Chen, M.D., Albert Oriol, M.D., Javier de la Rubia, M.D., Lugui Qiu, M.D., Darrell J. White, M.D., Daniel Binder, M.D., Kenneth Anderson, M.D., Jean-Paul Fermand, M.D., Philippe Moreau, M.D., Michel Attal, M.D., Robert Knight, M.D., Guang Chen, Ph.D., Jason Van Oostendorp, M.Sc., Christian Jacques, M.D., Annette Ervin-Haynes, D.O., Hervé Avet-Loiseau, M.D., Cyrille Hulin, M.D., and Thierry Facon, M.D., for the FIRST Trial Team*



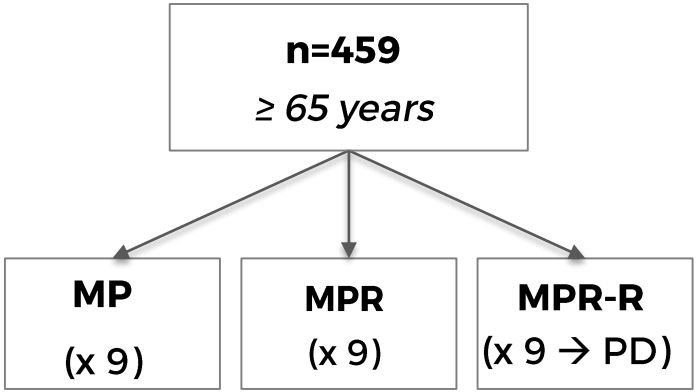


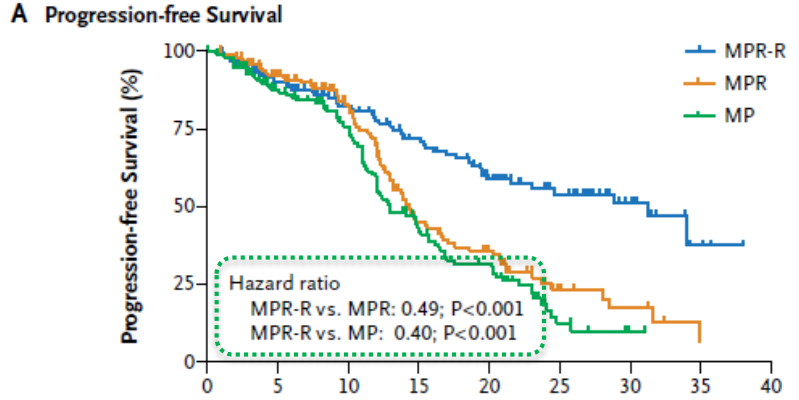
The NEW ENGLAND JOURNAL of MEDICINE

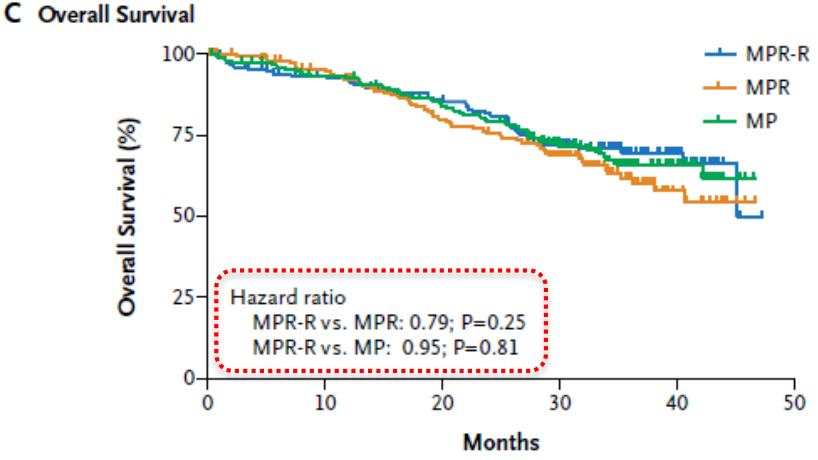
ESTABLISHED IN 1812 MAY 10, 2012 VOL. 366 NO. 19

Continuous Lenalidomide Treatment for Newly Diagnosed Multiple Myeloma

Antonio Palumbo, M.D., Roman Hajek, M.D., Ph.D., Michel Delforge, M.D., Ph.D., Martin Kropff, M.D., Maria Teresa Petrucci, M.D., John Catalano, M.B., B.S., Heinz Gisslinger, M.D., Wiesław Wiktor-Jędrzejczak, M.D., Ph.D., Mamia Zodelava, M.D., Ph.D., Katja Weisel, M.D., Nicola Cascavilla, M.D., Genadi Iosava, M.D., Michele Cavo, M.D., Janusz Kloczko, M.D., Ph.D., Joan Bladé, M.D., Meral Beksac, M.D., Ivan Spicka, M.D., Ph.D., Torben Plesner, M.D., Joergen Radke, M.D., Christian Langer, M.D., Dina Ben Yehuda, M.D., Alessandro Corso, M.D., Lindsay Herbein, B.S., Zhinuan Yu, Ph.D., Jay Mei, M.D., Ph.D., Christian Jacques, M.D., and Meletios A. Dimopoulos, M.D., for the MM-015 Investigators*







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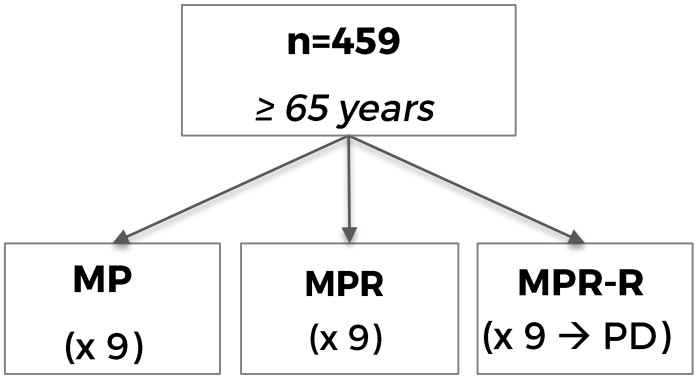

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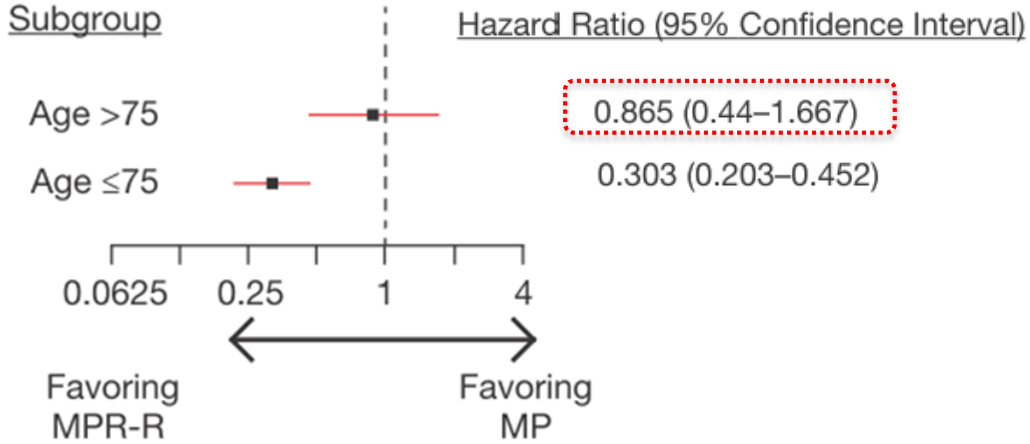

ADHERENCE

How adherent are patients going to be to ‘real life’ treatment?

May poor adherence affect treatment outcomes?

Do patients on oral chemotherapy have sufficient knowledge for optimal adherence? A mixed methods study

ARBER A., ODELIUS A., WILLIAMS P., LEMANSKA A. & FAITHFULL S. (2015) European Journal of Cancer Care

- UK myeloma patients on CTD (n=64)
- 92% *reported* being fully adherent
- 31% relied on partner/family member for help
- 58% knew when to take their meds

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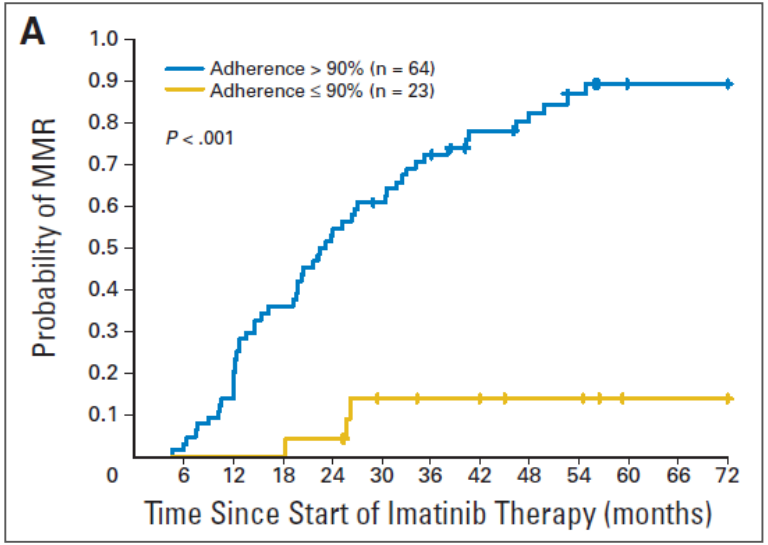
VOLUME 28 · NUMBER 14 · MAY 10 2010

JOURNAL OF CLINICAL ONCOLOGY

Adherence Is the Critical Factor for Achieving Molecular Responses in Patients With Chronic Myeloid Leukemia Who Achieve Complete Cytogenetic Responses on Imatinib

David Marin, Alexandra Bazeos, Francois-Xavier Mahon, Lina Eliasson, Dragana Milojkovic, Marco Bua, Jane F. Apperley, Richard Szydlo, Ritti Desai, Kasia Kozlowski, Christos Paliompeis, Victoria Latham, Letizia Foroni, Mathieu Molimard, Alistair Reid, Katy Rezvani, Hugues de Lavallade, Cristina Guallar, John Goldman, and Jamshid S. Khorashad



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Supportive care (anti-coagulants, anti-diabetics, anti-infectives…) ??

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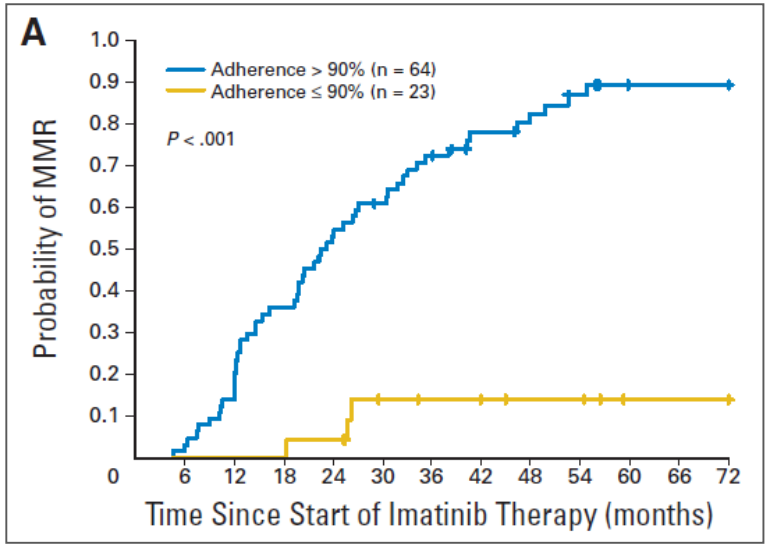


TOXICITIES

Are we considering all relevant toxicities?

Financial toxicity in insured patients with multiple myeloma: a cross-sectional pilot study

Scott F Huntington, Brendan M Weiss, Dan T Vogl, Adam D Cohen, Alfred L Garfall, Patricia A Mangan, Jalpa A Doshi, Edward A Stadtmauer

Lancet Haematol 2015
2: e408–16

Survey of individuals receiving at least 3 months of ongoing treatment at a tertiary academic medical centre in the USA

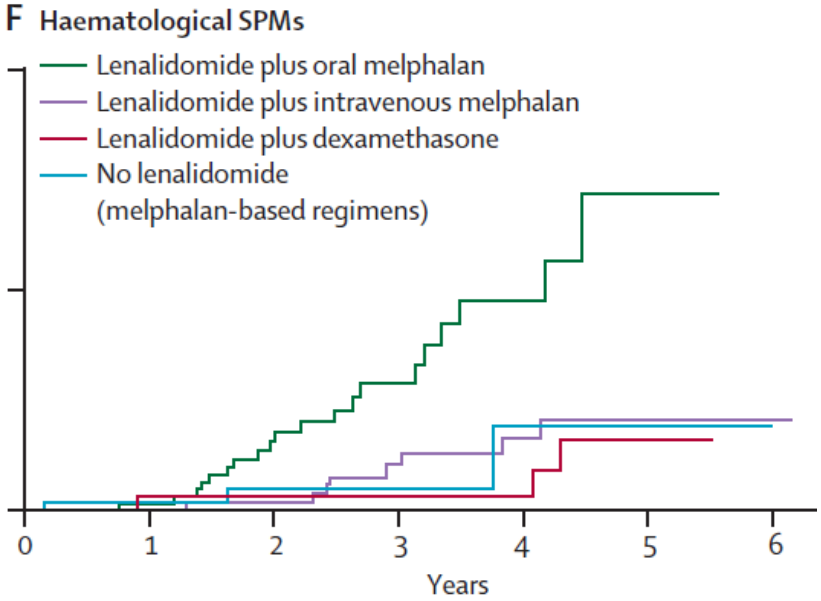
Self-reported level of financial burden	99	
Not a financial burden at all		29 (29%)
Minor financial burden		34 (34%)
Moderate financial burden		17 (17%)
Significant financial burden		19 (19%)
Decreased spending on		
Basic-goods like food and clothing	100	55 (55%)
Leisure activities	98	63 (64%)
Willingness to discuss costs with oncologist	100	
Already have or very likely to discuss		34 (34%)
Moderately likely to discuss		25 (25%)
Unlikely or would not discuss		41 (41%)

Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a meta-analysis of individual patient data

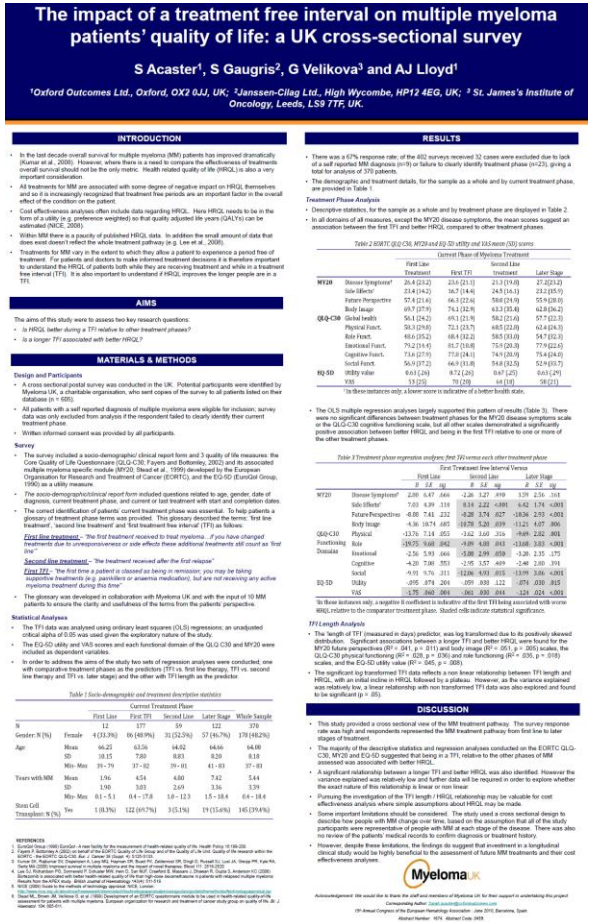
Antonio Palumbo, Sara Bringhen, Shaji K Kumar, Giulia Lupparelli, Saad Usmani, Anders Waage, Alessandra Larocca, Bronno van der Holt, Pellegrino Musto, Massimo Offidani, Maria T Petrucci, Andrea Evangelista, Sonja Zweegman, Ajay K Nooka, Andrew Spencer, Meletios A Dimopoulos, Roman Hajek, Michele Cavo, Paul Richardson, Sagar Lonial, Giovannino Ciccone, Mario Boccadoro, Kenneth Anderson, Bart Barlogie, Pieter Sonneveld, Philip L McCarthy

Lancet Oncol 2014; 15: 333–42

Cumulative incidence (95% CI)	3 years	5 years
Lenalidomide plus oral melphalan	2·8% (1·3–4·3)	7·2% (3·0–11·4)
Lenalidomide plus intravenous melphalan	1·0% (0·1–1·8)	2·0% (0·5–3·5)
Lenalidomide plus dexamethasone	0·3% (0·0–0·7)	1·3% (0·0–2·7)
No lenalidomide	0·3% (0·0–0·7)	1·3% (0·0–2·7)



Complexity of long-term toxicities i.e. in relation to concomitant or previous therapies



The impact of a treatment free interval on multiple myeloma patients' quality of life: a UK cross-sectional survey

S Acaster[1], S Gaugris[2], G Velikova[3] and AJ Lloyd[1]

[1]Oxford Outcomes Ltd., Oxford, OX2 0JJ, UK; [2]Janssen-Cilag Ltd., High Wycombe, HP12 4EG, UK; [3] St. James's Institute of Oncology, Leeds, LS9 7TF, UK.

INTRODUCTION

- In the last decade overall survival for multiple myeloma (MM) patients has improved dramatically (Kumar et al., 2008). However, where there is a need to compare the effectiveness of treatments overall survival should not be the only metric. Health related quality of life (HRQL) is also a very important consideration
- All treatments for MM are associated with some degree of negative impact on HRQL themselves and as it is increasingly recognized that treatment free periods are an important factor in the overall effect of the condition on the patient.
- Cost effectiveness analyses often include data regarding HRQL. Here HRQL needs to be in the form of a utility (e.g. preference weighted) so that quality adjusted life years (QALYs) can be estimated (NICE, 2008).
- Within MM there is a paucity of published HRQL data. In addition the small amount of data that does exist doesn't reflect the whole treatment pathway (e.g. Lee et al., 2008).
- Treatments for MM vary in the extent to which they allow a patient to experience a period free of treatment. For patients and doctors to make informed treatment decisions it is therefore important to understand the HRQL of patients both while they are receiving treatment and while in a treatment free interval (TFI). It is also important to understand if HRQL improves the longer people are in a TFI.

AIMS

The aims of this study were to assess two key research questions:

- *Is HRQL better during a TFI relative to other treatment phases?*
- *Is a longer TFI associated with better HRQL?*

MATERIALS & METHODS

Design and Participants

- A cross sectional postal survey was conducted in the UK. Potential participants were identified by Myeloma UK, a charitable organisation, who sent copies of the survey to all patients listed on their database (n = 605).
- All patients with a self reported diagnosis of multiple myeloma were eligible for inclusion; survey data was only excluded from analysis if the respondent failed to clearly identify their current treatment phase.
- Written informed consent was provided by all participants.

Survey

- The survey included a socio-demographic/ clinical report form and 3 quality of life measures: the Core Quality of Life Questionnaire (QLQ-C30; Fayers and Bottomley, 2002) and its associated multiple myeloma specific module (MY20; Stead et al., 1999) developed by the European Organisation for Research and Treatment of Cancer (EORTC), and the EQ-5D (EuroQol Group, 1990) as a utility measure.
- *The socio-demographic/clinical report form* included questions related to age, gender, date of diagnosis, current treatment phase, and current or last treatment with start and completion dates.
- The correct identification of patients' current treatment phase was essential. To help patients a glossary of treatment phase terms was provided. This glossary described the terms: 'first line treatment', 'second line treatment' and 'first treatment free interval' (TFI) as follows:

  First line treatment - *"the first treatment received to treat myeloma…if you have changed treatments due to unresponsiveness or side effects these additional treatments still count as 'first line'"*

  Second line treatment - *"the treatment received after the first relapse"*

  First TFI - *"the first time a patient is classed as being in remission; you may be taking supportive treatments (e.g. painkillers or anaemia medication), but are not receiving any active myeloma treatment during this time"*
- The glossary was developed in collaboration with Myeloma UK and with the input of 10 MM patients to ensure the clarity and usefulness of the terms from the patients' perspective.

Statistical Analyses

- The TFI data was analysed using ordinary least squares (OLS) regressions; an unadjusted critical alpha of 0.05 was used given the exploratory nature of the study.
- The EQ-5D utility and VAS scores and each functional domain of the QLQ C30 and MY20 were included as dependent variables.
- In order to address the aims of the study two sets of regression analyses were conducted; one with comparative treatment phase as the predictors (TFI vs. first line therapy, TFI vs. second line therapy and TFI vs. later stage) and the other with TFI length as the predictor.

Table 1 Socio-demographic and treatment descriptive statistics

		Current Treatment Phase				
		First Line	First TFI	Second Line	Later Stage	Whole Sample
N		12	177	59	122	370
Gender: N (%)	Female	4 (33.3%)	86 (48.9%)	31 (52.5%)	57 (46.7%)	178 (48.2%)
Age	Mean	66.25	63.56	64.02	64.66	64.00
	SD	10.15	7.80	8.83	8.20	8.18
	Min- Max	39 - 79	37 - 92	39 - 91	41 - 83	37 - 83
Years with MM	Mean	1.96	4.54	4.80	7.42	5.44
	SD	1.90	3.03	2.69	3.36	3.39
	Min- Max	0.1 - 5.1	0.4 – 17.8	1.0 – 12.3	1.5 – 18.4	0.4 – 18.4
Stem Cell Transplant: N (%)	Yes	1 (8.3%)	122 (69.7%)	3 (5.1%)	19 (15.6%)	145 (39.4%)

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RESULTS

- There was a 67% response rate; of the 402 surveys received 32 cases were excluded due to lack of a self reported MM diagnosis (n=9) or failure to clearly identify treatment phase (n=23), giving a total for analysis of 370 patients.
- The demographic and treatment details, for the sample as a whole and by current treatment phase, are provided in Table 1.

Treatment Phase Analysis

- Descriptive statistics, for the sample as a whole and by treatment phase are displayed in Table 2.
- In all domains of all measures, except the MY20 disease symptoms, the mean scores suggest an association between the first TFI and better HRQL compared to other treatment phases.

Table 2 EORTC QLQ-C30, MY20 and EQ-5D utility and VAS mean (SD) scores

		Current Phase of Myeloma Treatment			
		First Line Treatment	First TFI	Second Line treatment	Later Stage
MY20	Disease Symptoms[a]	26.4 (23.2)	23.6 (21.1)	23.3 (19.8)	27.2(23.2)
	Side Effects[a]	21.4 (14.2)	16.7 (14.4)	24.5 (16.1)	23.2 (15.9)
	Future Perspective	57.4 (21.6)	66.3 (22.6)	58.0 (21.9)	55.9 (20.0)
	Body Image	69.7 (27.9)	74.1 (32.9)	63.3 (35.4)	62.8 (34.2)
QLQ-C30	Global health	56.1 (24.2)	69.1 (21.9)	58.2 (21.6)	57.7 (22.3)
	Physical Funct.	58.3 (29.8)	72.1 (23.7)	68.5 (22.0)	62.4 (24.3)
	Role Funct.	48.6 (35.2)	68.4 (32.2)	58.5 (31.0)	54.7 (32.3)
	Emotional Funct.	79.2 (16.4)	81.7 (16.8)	75.9 (20.3)	77.9(22.6)
	Cognitive Funct.	73.6 (27.9)	77.8 (24.1)	74.9 (20.9)	75.4 (24.0)
	Social Funct.	56.9 (37.2)	66.9 (31.8)	54.8 (32.5)	52.9 (33.7)
EQ-5D	Utility value	0.63 (.26)	0.72 (.26)	0.67 (.25)	0.63 (.29)
	VAS	53 (25)	70 (20)	64 (18)	58 (21)

[a]In these instances only, a lower score is indicative of a better health state.

- The OLS multiple regression analyses largely supported this pattern of results (Table 3). There were no significant differences between treatment phases for the MY20 disease symptoms scale or the QLQ-C30 cognitive functioning scale, but all other scales demonstrated a significantly positive association between better HRQL and being in the first TFI relative to one or more of the other treatment phases.

Table 3 Treatment phase regression analyses: first TFI versus each other treatment phase

		First Treatment free Interval Versus								
		First Line			Second Line			Later Stage		
		B	S.E	sig	B	S.E	sig	B	S.E	sig
MY20	Disease Symptoms[a]	2.80	1.47	.066	-2.26	3.27	.490	3.59	2.56	.164
	Side Effects[a]	7.03	1.39	.116	8.34	2.22	<.001	6.42	1.74	<.001
	Future Perspectives	-8.88	7.41	.232	-9.28	3.74	.027	-10.36	2.93	<.001
	Body Image	-4.36	10.74	.685	-10.70	5.20	.039	-11.25	4.07	.006
QLQ-C30 Functioning Domains	Physical	-13.76	7.14	.055	-3.62	3.60	.316	-9.05	2.82	.001
	Role	-19.75	9.68	.042	-9.09	4.88	.063	-13.08	3.83	<.001
	Emotional	-2.56	5.93	.666	-5.08	2.99	.050	-3.26	2.35	.175
	Cognitive	-4.20	7.06	.553	-2.95	3.57	.409	-2.48	2.80	.391
	Social	-9.91	9.76	.311	-12.26	4.93	.015	-13.99	3.86	<.001
EQ-5D	Utility	-.095	.074	.204	-.059	.038	.122	-.076	.030	.015
	VAS	-1.75	2.60	.501	-.061	4.50	.044	-.124	.024	<.001

[a]In these instances only, a negative B coefficient is indicative of the first TFI being associated with worse HRQL relative to the comparator treatment phase. Shaded cells indicate statistical significance.

TFI Length Analysis

- The 'length of TFI' (measured in days) predictor, was log transformed due to its positively skewed distribution. Significant associations between a longer TFI and better HRQL were found for the MY20 future perspectives (R^2 = .041, p = .011) and body image (R^2 = .051, p = .005) scales, the QLQ-C30 physical functioning (R^2 = .028, p = .036) and role functioning (R^2 = .035, p = .018) scales, and the EQ-5D utility value (R^2 = .045, p = .008).
- The significant log transformed TFI data reflects a non linear relationship between TFI length and HRQL, with an initial incline in HRQL followed by a plateau. However, as the variance explained was relatively low, a linear relationship with non transformed TFI data was also explored and found to be significant (p < .05).

DISCUSSION

- This study provided a cross sectional view of the MM treatment pathway. The survey response rate was high and respondents represented the MM treatment pathway from first line to later stages of treatment.
- The majority of the descriptive statistics and regression analyses conducted on the EORTC QLQ-C30, MY20 and EQ-5D suggested that being in a TFI, relative to the other phases of MM assessed was associated with better HRQL.
- A significant relationship between a longer TFI and better HRQL was also identified. However the variance explained was relatively low and further data will be required in order to explore whether the exact nature of this relationship is linear or non linear.
- Pursuing the investigation of the TFI length / HRQL relationship may be valuable for cost effectiveness analysis where simple assumptions about HRQL may be made.
- Some important limitations should be considered. The study used a cross sectional design to describe how people with MM change over time, based on the assumption that all of the study participants were representative of people with MM at each stage of the disease. There was also no review of the patients' medical records to confirm diagnosis or treatment history.
- However, despite these limitations, the findings do suggest that investment in a longitudinal clinical study would be highly beneficial to the assessment of future MM treatments and their cost effectiveness analyses.

MyelomaUK

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Postal survey of 605 myeloma patients in the UK; 3 quality of life measures (EORTC QLQ-C30, MY20 and EQ-5D)

→ being in a treatment-free interval, relative to the other phases of MM assessed, was associated with better health-related quality of life (HRQoL)

CLONAL EVOLUTION

Could maintenance therapy alter myeloma cell biology and thus responses to treatment?

Spatially divergent clonal evolution in multiple myeloma: overcoming resistance to BRAF inhibition

Marc S. Raab,[1,2] Nicola Lehners,[1,2] Jing Xu,[1,2] Anthony D. Ho,[1] Peter Schirmacher,[3] Hartmut Goldschmidt,[1,4] and Mindaugas Andrulis[3]

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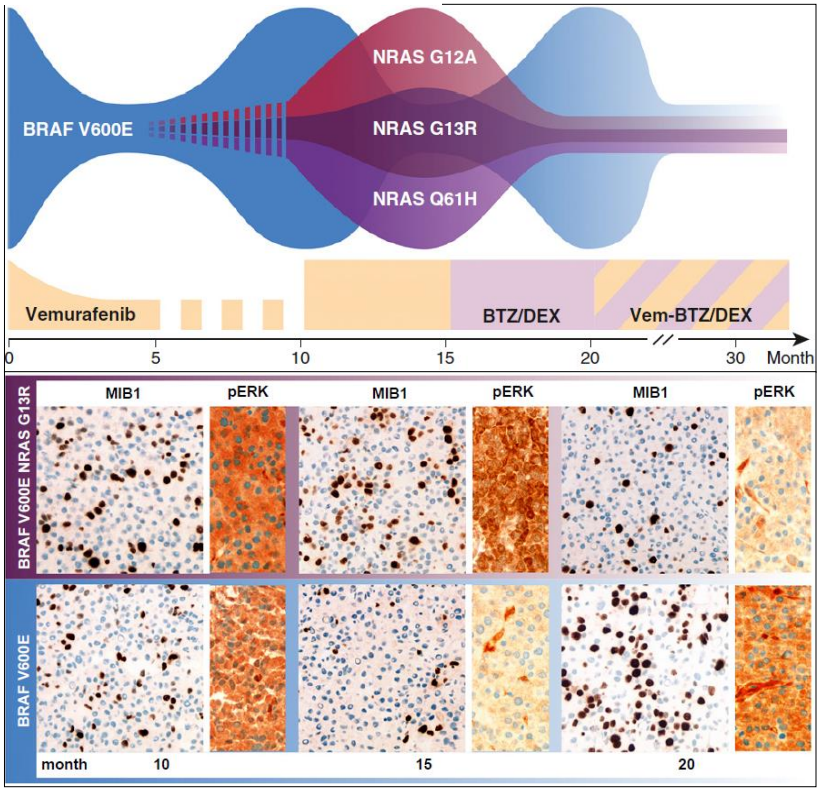

Clonal selection and double-hit events involving tumor suppressor genes underlie relapse in myeloma

Niels Weinhold,[1,*] Cody Ashby,[1,*] Leo Rasche,[1] Shweta S. Chavan,[1] Caleb Stein,[1] Owen W. Stephens,[1] Ruslana Tytarenko,[1] Michael A. Bauer,[1] Tobias Meissner,[2] Shayu Deshpande,[1] Purvi H. Patel,[1] Timea Buzder,[1] Gabor Molnar,[1] Erich A. Peterson,[1] Frits van Rhee,[1] Maurizio Zangari,[1] Sharmilan Thanendrarajan,[1] Carolina Schinke,[1] Erming Tian,[1] Joshua Epstein,[1] Bart Barlogie,[1] Faith E. Davies,[1] Christoph J. Heuck,[1] Brian A Walker,[1] and Gareth J. Morgan[1]

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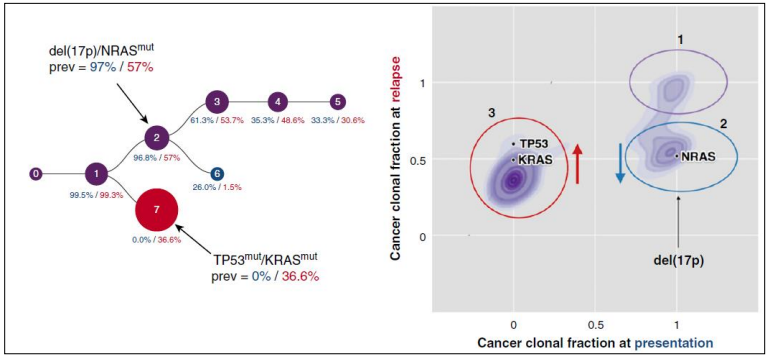
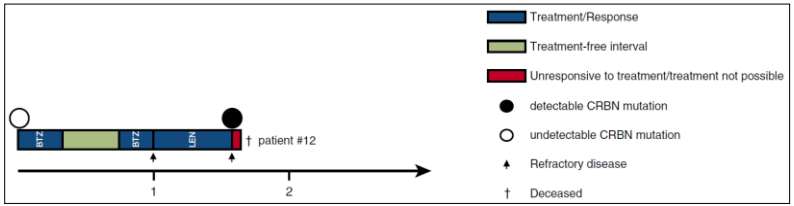


Targeted sequencing of refractory myeloma reveals a high incidence of mutations in *CRBN* and Ras pathway genes

K. Martin Kortüm,[1,2,*] Elias K. Mai,[3,4,*] Nur H. Hanafiah,[3,*] Chang-Xi Shi,[1] Yuan-Xiao Zhu,[1] Laura Bruins,[1] Santiago Barrio,[1] Patrick Jedlowski,[1] Maximilian Merz,[4] Jing Xu,[3,5] Robert A. Stewart,[1] Mindaugas Andrulis,[5] Anna Jauch,[6] Jens Hillengass,[4] Hartmut Goldschmidt,[4,7] P. Leif Bergsagel,[1] Esteban Braggio,[1] A. Keith Stewart,[1,8] and Marc S. Raab[3,4]

BLOOD, 1 SEPTEMBER 2016 • VOLUME 128, NUMBER 9



Drug costs to the NHS

Patient preference

Impact on day-care units

OTHER POTENTIAL ISSUES ?

Unexpected long-term toxicities

Geographically remote areas

'Real-life' benefit ?

Chronic treatment is better than intermittent treatment'

(personal opinion stained by blotches of evidence)

Maintenance with lenalidomide can benefit patients but we don't really know which patients after what treatment (treatment line) for how long and at what cost.

Maintenance will almost certainly play a role in improving myeloma outcomes but we need to figure out how to do it without harming patients and the NHS (*biomarkers*)