LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

MYELOMA

Updates from the American Society of Hematology (ASH®) Annual Meeting

OUTLOOK on MYELOMA

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Welcome and Introduction

LAUREN BERGER, MPH
Senior Director, Patient Services Programs
The Leukemia & Lymphoma Society

New Approaches to the Management of Multiple Myeloma

Robert Z. Orlowski, Ph.D., M.D.

Director, Myeloma Section
Professor, Departments of Lymphoma/Myeloma & Experimental Therapeutics
Principal Investigator, M. D. Anderson SPORE in Multiple Myeloma
Chair, Southwest Oncology Group Myeloma Committee

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Outline

- **Disease biology & course**
- Asymptomatic multiple myeloma
- Therapy for transplant-ineligible patients
- Induction in patients eligible for transplant
- Transplant and post-transplant maintenance
- Relapsed and/or refractory multiple myeloma
- Developments in supportive care for myeloma

2011 ASH Abstract 994

Incidence and Prognostic Value of Chromosomal Abnormalities in Elderly Patients with Myeloma : The IFM Experience on 1095 Patients

Hervé Avet-Loiseau, Cyrille Hulin, Loic Campion, Murielle Roussel, Gerald Marit, Denis Caillot, Anne-Marie Stoppa, Brigitte Pegourie, Jean-Gabriel Fuzibet, Carine Chateleix, Bruno Royer, Catherine Traulle, Olivier Decaux, Lotfi Benboubker, Philippe Casassus, Margaret Macro, Claire Mathiot, Brigitte Kolb, Jean-Paul Fermand, and Thierry Facon

Chromosomal Changes & OS

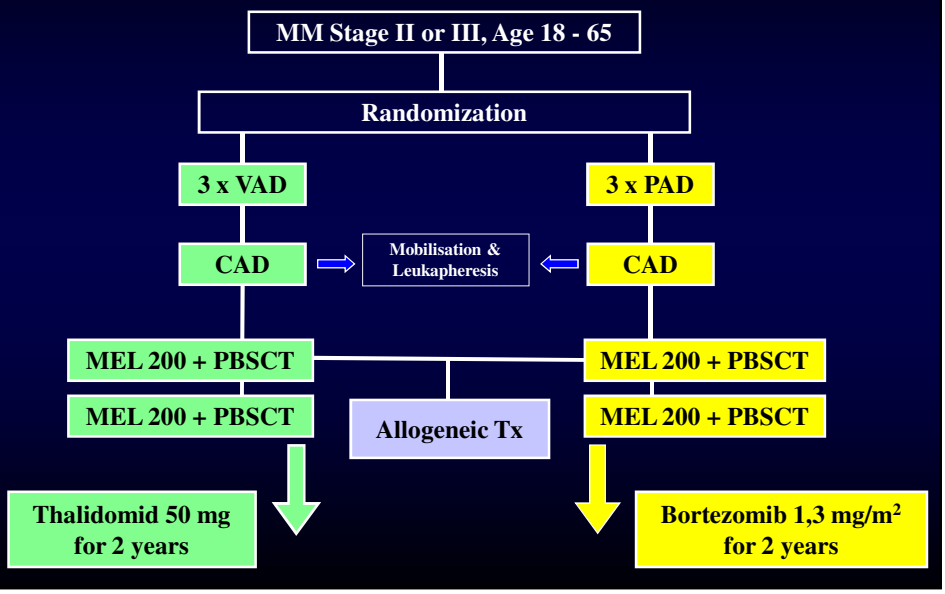
	Hazard-Ratio	p value
Del(13)	1.24 (1.01-1.53)	0.045
t(4;14)	1.85 (1.39-2.46)	$< 10^{-4}$
Del(17p)	2.38 (1.69-3.34)	$< 10^{-6}$

2011 ASH Abstract 332

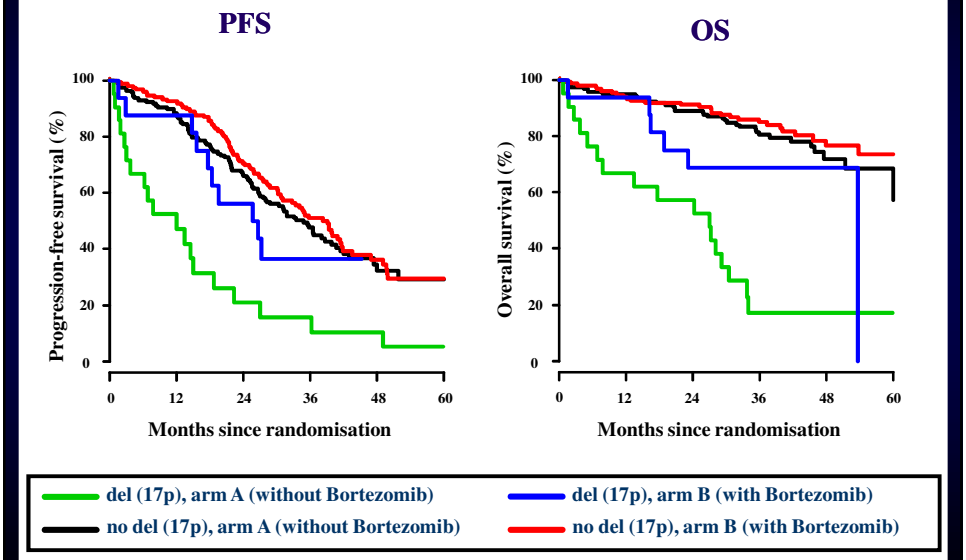
Combining Information Regarding Chromosomal Aberrations t(4;14), del(17p13) and the Copy Number of 1q21 with the International Staging System Classification Allows Stratification of Myeloma Patients Undergoing Autologous Stem Cell Transplantation : Results from the HOVON-65/GMMG-HD4 Trial

Kai Neben, Henk M. Lokhorst, Anna Jauch, Uta Bertsch, Thomas Hielscher, Christiane Heiss, Bronno van der Holt, Stefan Schmitt, Laila el Jarari, Hans J. Salwender, Igor W. Blau, Michael Pfreundschuh, Katja Weisel, Ulrich Duehrsen, Walter Lindemann, Christian Teschendorf, Hans Martin, Christof Scheid, Mathias Haenel, Hans Guenter Derigs, Ullrich Graeven, Ingo GH Schmidt-Wolf, Norma Peter, Mohammed Wattad, Steffen P Luntz, Annemiek Broyl, Joerg Schubert, Martin Hoffmann, Martin Goerner, Jochen Tischler, Martin Kaufmann, Marc S Raab, Anthony D. Ho, Helgi van de Velde, Dirk Hose, Pieter Sonneveld, and Hartmut Goldschmidt

Study Design



In Both Study Arms

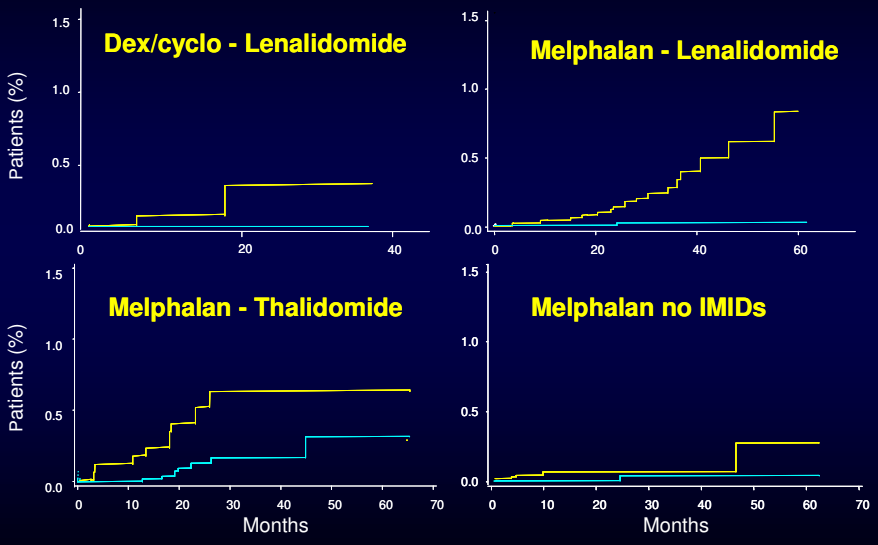


2011 ASH Abstract 996

Second Primary Malignancies in Newly Diagnosed Multiple Myeloma Patients Treated with Lenalidomide : Analysis of Pooled Data in 2459 Patients

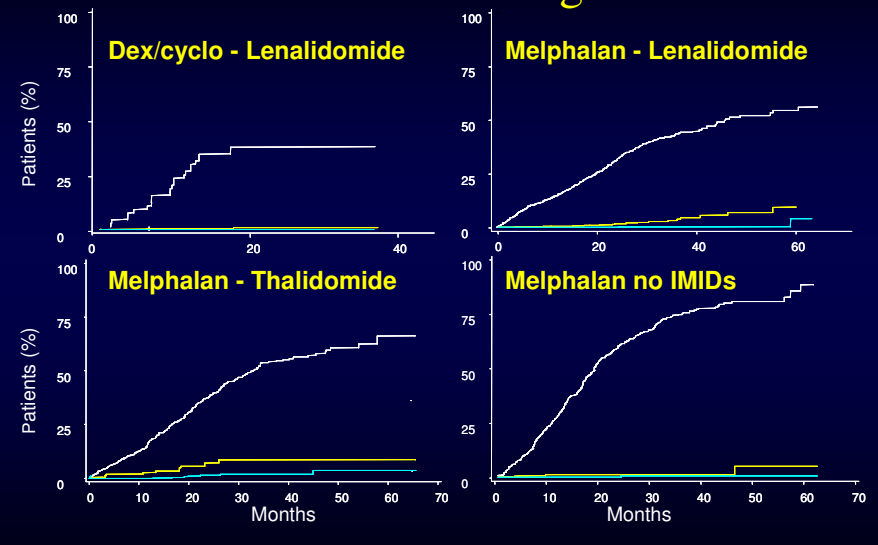
Antonio Palumbo, Alessandra Larocca, Sonja Zweegman, Giulia Lupparelli, Agostina Siniscalchi, Pellegrino Musto, Moshe Levin, Henk Lokhorst, Sara Grammatico, Lucio Catalano, Roberto Ria, Anna Marina Liberati, Francesca Patriarca, Giulia Benevolo, Antonietta Pia Falcone, Bronno van der Holt, Sylvia Verelst, Davide Rossi, Claudia Crippa, Sara Bringhen, Roman Hajek, Andrew Spencer, Mario Boccadoro, and Pieter Sonneveld

Cumulative Incidence of SPMs



SPMs, second primary malignancies

SPMs & Risk of Progression



SPMs, second primary malignancies

Observed vs. Expected SPMs

SMPs observed in Italian patients
SMPs expected from Italian Cancer Registry (age- and sex-adjusted)

All patients	Observed	Expected	SIR	95% CI
All patients	48	72	0.67	0.49-0.88
Male	29	35	0.83	0.55-1.19
Female	19	35	0.55	0.33-0.85

Therapy	Observed	Expected	SIR	95% CI
Dex/cyclo - Lenalidomide	2	6	0.31	0.04-1.13
Melphalan - Lenalidomide	23	24	0.96	0.61-1.44
Melphalan - Thalidomide	17	22	0.76	0.44-1.22
Melphalan no IMIDs	6	19	0.31	0.11-0.68

SPM, second primary malignancy; SIR, standardized incidence ratio; CI, confidence interval

Investigator Conclusions

- Caution ….. 48 SPM / 2283 analysed patients

Protocol	Incidence per 100 per year
Dex/cyclo - Lenalidomide	0.40
Melphalan - Lenalidomide	0.95
Melphalan - Thalidomide	1.05
Melphalan no IMIDs	0.42

- Observed and expected rates of SPMs → similar
- risk of death > risk of SPMs

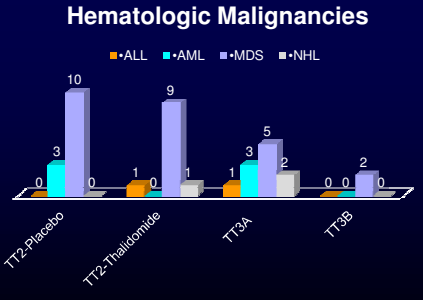
2011 ASH Abstract 823

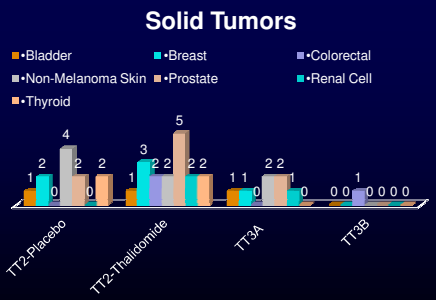
Second Malignancies in Total Therapy Trials for Newly Diagnosed Multiple Myeloma : Influence of Lenalidomide vs. Thalidomide in Maintenance Phases

Saad Z Usmani, Rachael Sexton, Antje Hoering, Christoph J. Heuck, Bijay Nair, Sarah Waheed, Yazan AlSayed, Nathan Petty, John Crowley, Bart Barlogie

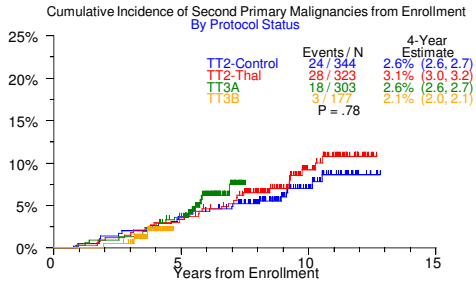
SPM Types

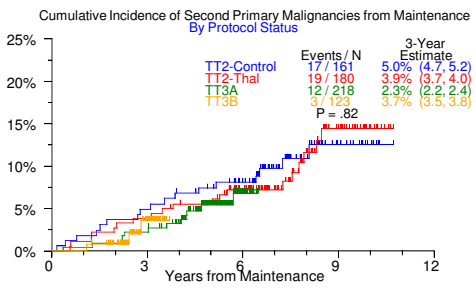
SPM Type	TT2-Placebo	TT2-Thalidomide	TT3A (n/%)	TT3B(n/%)
All Cancers	24 (6.9%)	28 (8.7%)	18 (5.9%)	3 (1.7%)
Hematologic Malignancies	13 (3.8%)	11 (3.4%)	11 (3.6%)	2 (1.1%)
Solid Tumors	11 (3.1%)	17 (5.3%)	7 (2.3%)	1 (0.6%)





Cumulative Incidence





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2011 ASH Abstract 991

A Multicenter, Randomised, Open-label, Phase III Study of Lenalidomide/Dexamethasone versus Therapeutic Abstention in High-risk Smoldering MM

MV Mateos, L López-Corral, MT Hernández, J de la Rubia, JJ Lahuerta, P Giraldo, J Bargay, L Rosiñol, A Oriol, J García-Laraña, l Palomera, F de Arriba, F Prósper, ML Martino, AI Teruel, J Hernández, G Estevez, M Mariz, A Alegre, JL Guzman, N Quintana, JL García, JF San Miguel.
On behalf of Spanish Myeloma Group (PETHEMA/GEM)

Study Design

Asymptomatic Myeloma Patients
PC ≥ 10% + MP ≥ 3.0
Or
PC ≥ 10% or MP ≥ 3.0 and ≥ 95% aberrant immunophenotype + immunoparesis

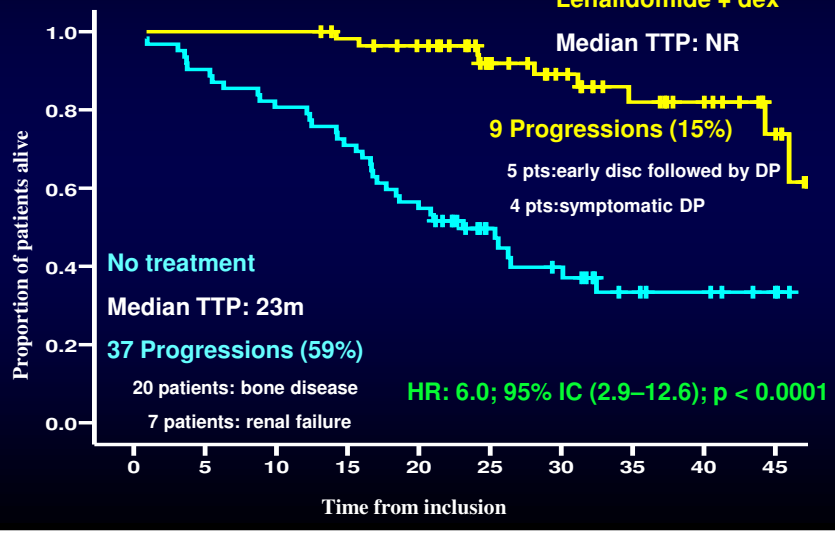
Standard
Observation

Treatment
Cycles 1-9: Lenalidomide 25 mg po days 1-21 of every 28-day cycle + dexamethasone 20 mg po on days 1-4 and 12-15
Later Cycles: Lenalidomide 10 mg po days 1-21 of every 2-month cycle

- 1º objective: TTP to symptomatic myeloma

TTP to Active Disease

Median follow-up: 32 months (range 12–49)



Second Primary Malignancies

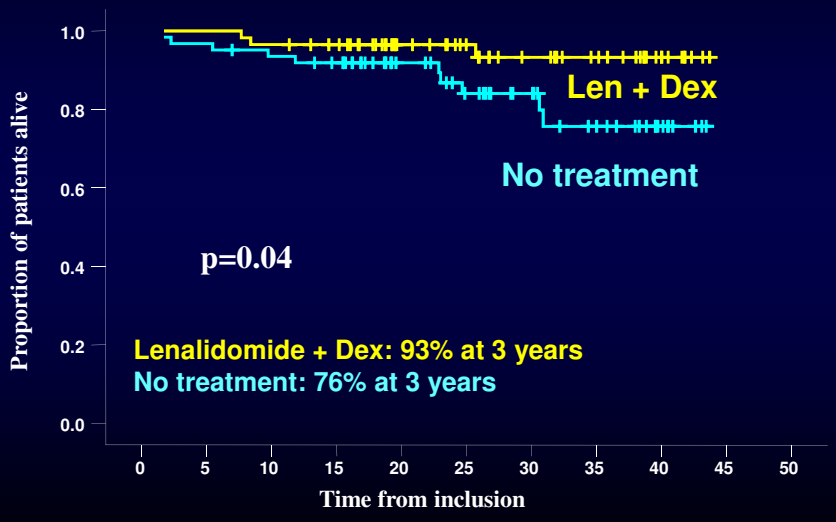
3 patients (5%)→ Polycythaemia vera and prostate cancer (2 pts)

54 yrs . After induction and 10 maint. Cycles Hb: 15g/dl→JAK2+ Polycythaemia Vera	Sample obtained at the moment of inclusion in the study (frozen DNA)→ JAK2+
68 yrs. After induction and 9 maint cycles PSA x2→Prostate enlargement Bx:Prostate Cancer	Medical records PSA x2 plus prostate hyperplasia since 2006 Follow-up by Urologist
61 yrs. After induction and 16 maint cycles PSA x3→Prostate enlargement with compression symptoms Bx:Prostate Cancer	Medical records prostate hyperplasia since 2003 Follow-up by Urologist

No SPM detected in the abstention arm

Overall Survival from Inclusion

Median follow-up: 32 months (range 12–49)



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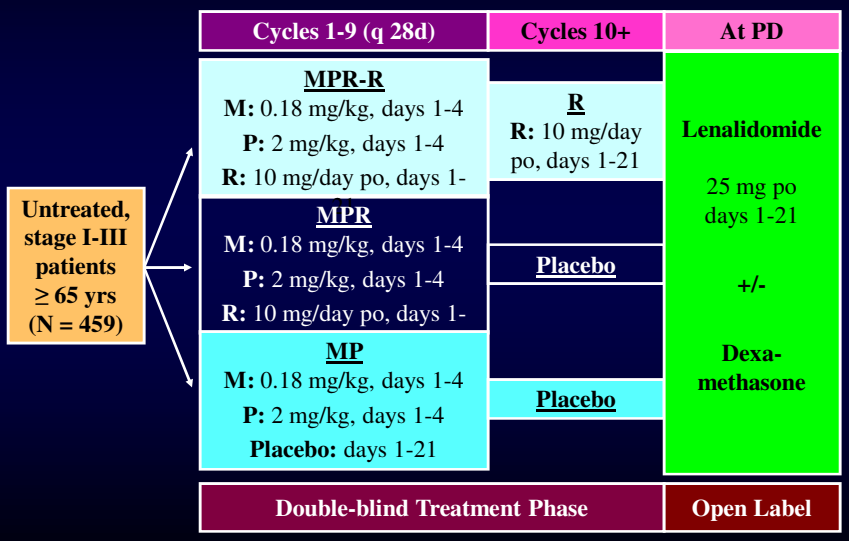
2011 ASH Abstract 475

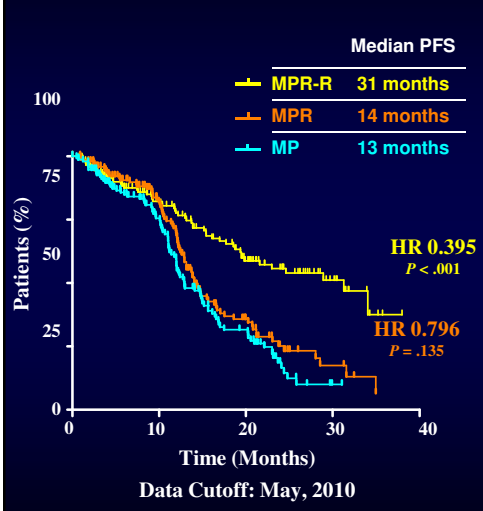
Continuous Lenalidomide Treatment for Newly Diagnosed Multiple Myeloma

Antonio Palumbo, Adam Zdenek, Martin Kropff, Robin Foà, John Catalano, Heinz Gisslinger, Wideslaw Wiktor-Jedrzejczak, Michel Delforge, Katja Weisel, Nicola Cascavilla, Jan Van Droogenbroeck, Genadi Iosava, Michele Cavo, Joan Blade, Meral Beksac, Ivan Spicka, Torben Plesner, Zhinuan Yu, Lindsay Herbein, Jay Mei, Christian J Jacques, Meletios Dimopoulos

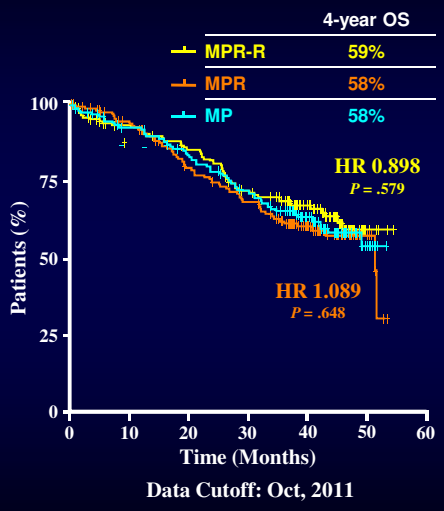
Study Design



Progression-free and Overall Survival



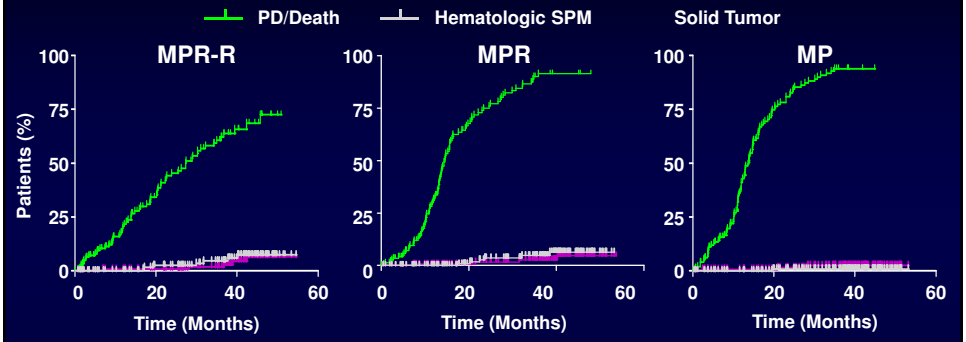
Data Cutoff: May, 2010



Data Cutoff: Oct, 2011

- TTP HR advantages similar: MPR-R vs MP = 0.337; MPR vs MP = 0.826

Second Primary Malignancies



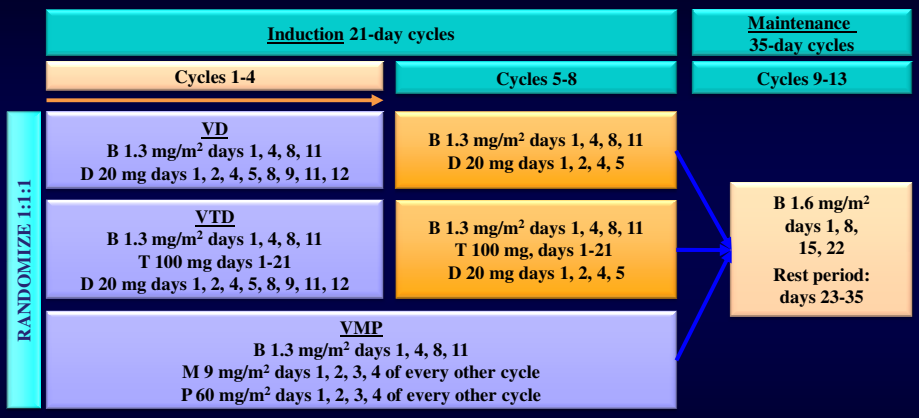
SPM, n (IR per 100 PY)	MPR-R (n = 150)	MPR (n = 152)	MP (n = 153)
Total Invasive SPMs	12 (3.04)	10 (2.57)	4 (0.98)
Hematologic	7 (1.75)	6 (1.54)	1 (0.24)
Solid tumors	5 (1.26)	5 (1.28)	3 (0.74)
Non-melanoma skin cancer	2 (0.50)	5 (1.29)	6 (1.50)

2011 ASH Abstract 478

Efficacy and Safety of Three Bortezomib-Based Combinations in Elderly, Newly Diagnosed Multiple Myeloma Patients : Results From All Randomized Patients in the Community-Based, Phase 3b UPFRONT Study

Ruben Niesvizky, Ian Flinn, Robert Rifkin, Nashat Gabrail, Veena Charu, Billy Clowney, James Essell, Yousuf Gaffar, Thomas Warr, Rachel Neuwirth, Deyanira Corzo, and James Reeves

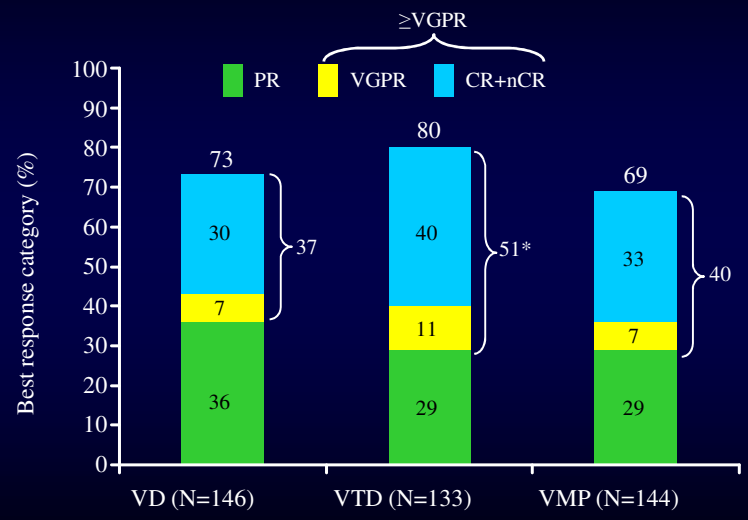
Study Design



BD and BTD: reduced dexamethasone dosing in cycles 5-8 vs 1-4

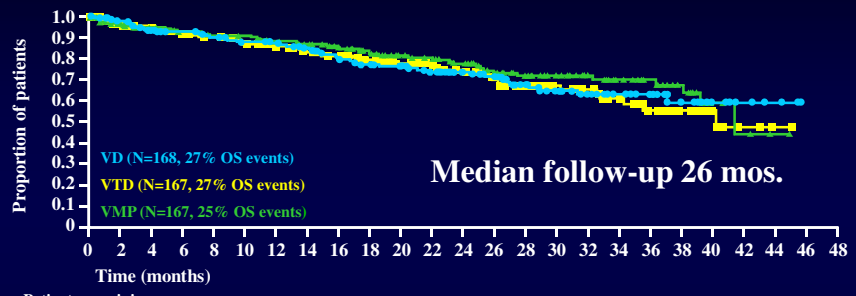
- **Endpoints**: primary – PFS; secondary – ORR, safety, QOL
- **Patients**: results reported after 100 patients in each arm had the opportunity to complete all 13 treatment cycles (8 induction cycles and 5 maintenance cycles)

Best Response Rates



*≥VGPR rate VTD > VD, p=0.0174

Overall Survival



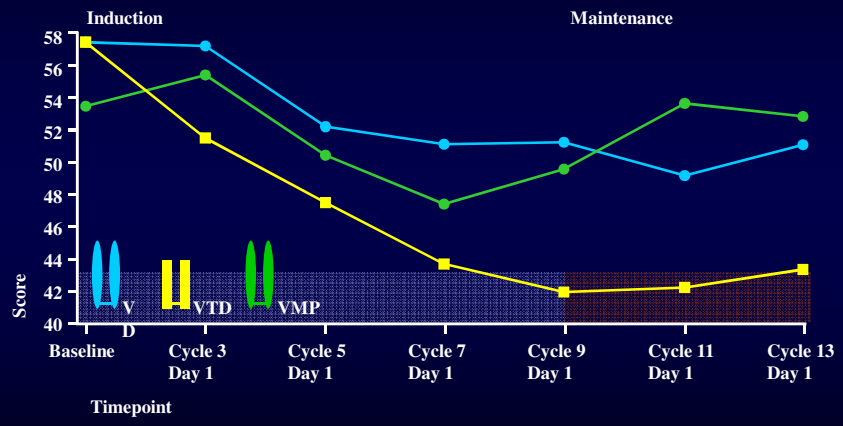
Patients remaining, n

VD	168	156	143	136	130	123	120	112	102	93	88	78	68	62	49	41	34	27	23	14	9	5	3
VTD	167	145	138	131	125	117	111	104	100	91	85	75	67	53	46	39	32	25	17	11	7	3	1
VMP	167	156	147	138	134	133	126	120	113	102	91	86	76	65	54	46	39	32	27	19	5	3	1

OS was assessed in the ITT population (N=502)
Although median follow-up is 26 months, OS data are preliminary as a significant number of patients are censored within the first 12 months

- 1-year OS estimates were 87.4% (VD), 86.1% (VTD), and 88.3% (VMP)
- 2-year OS estimates were 73.7% (VD), 73.6% (VTD), and 77.6% (VMP)
- There was no statistically significant difference in OS between the three arms

Patient-reported Quality of Life



UPFRONT QoL poster (Niesvizky et al., ASH 2011, abstract 1864)

2011 ASH Abstract 476

Continued Overall Survival Benefit After 5 Years' Follow-Up with Bortezomib-Melphalan-Prednisone (VMP) Versus Melphalan-Prednisone (MP) in Patients with Previously Untreated Multiple Myeloma, and No Increased Risk of Second Primary Malignancies : Final Results of the Phase 3 VISTA Trial

Jesús F. San Miguel, Rudolf Schlag, Nuriet K. Khuageva, Meletios A. Dimopoulos, Ofer Shpilberg, Martin Kropff, Ivan Spicka, Maria T. Petrucci, Antonio Palumbo, Olga S. Samoilova, Anna Dmoszynska, Kudrat M. Abdulkadyrov, Michel Delforge, Bin Jiang, Maria-Victoria Mateos, Kenneth C. Anderson, Dixie L. Esseltine, Kevin Liu, William Deraedt, Andrew Cakana, Helgi van de Velde, Paul G. Richardson

MMY-3002 Study Design

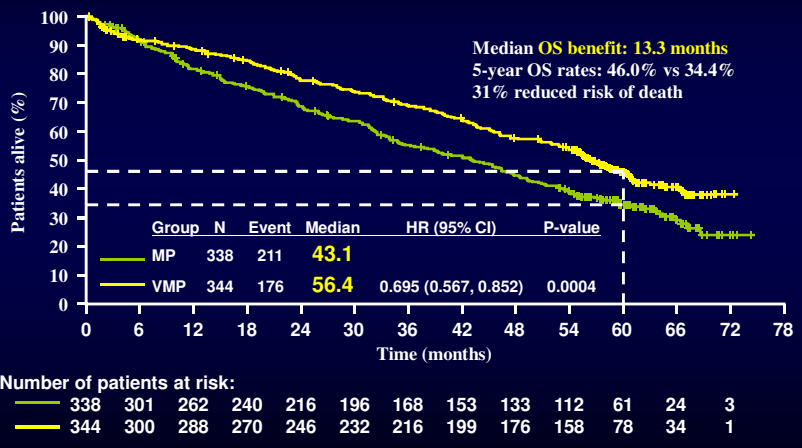
Untreated transplant-ineligible myeloma patients

Standard MP[1]
M 9 mg/m² + P 60 mg/m² days 1-4; q 6 weeks x 9 cycles
n = 331

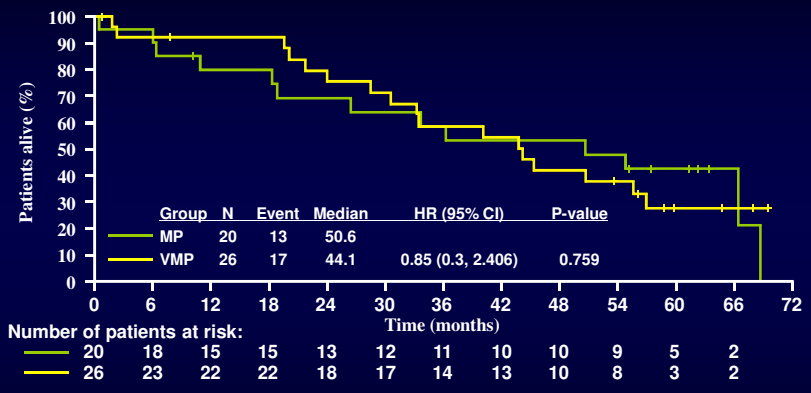
MP + V[1]
Cycles 1-4: MP as above + V 1.3 mg/m² days 1, 4, 8, 11, 22, 25, 29, and 32 q 6 weeks
Cycles 5-9: MP as above + V 1.3 mg/m² days 1, 8, 22, 29 and q 6 weeks
n = 336

[1]No VTE prophylaxis was given to all patients.

Overall Survival

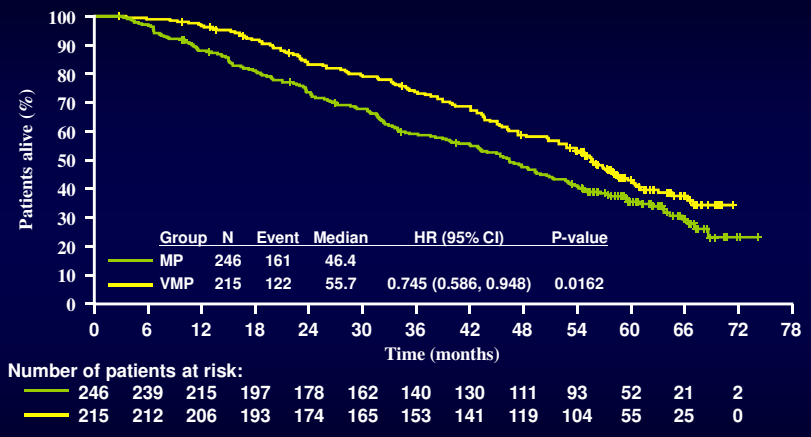


Impact of High-risk Cytogenetics



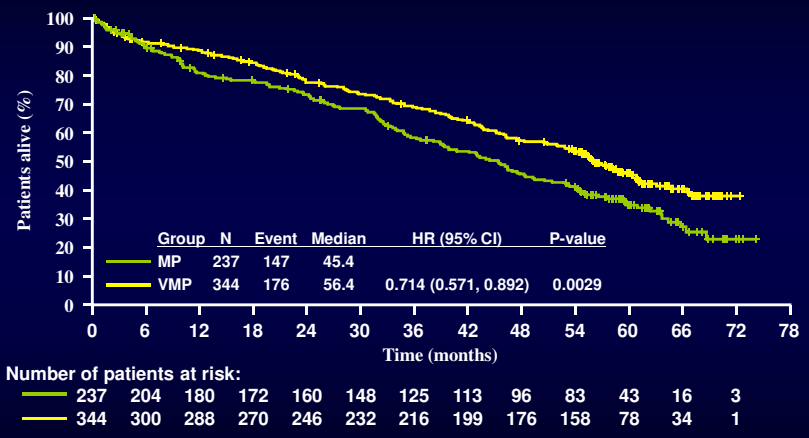
- Small subgroup (n=46; 26 VMP, 20 MP) with high-risk cytogenetics – any of t(4;14), t(14;16), del(17p)
- No significant difference in OS between arms
  - Curves cross following median time to second-line therapy with VMP
  - Lower proportion of VMP vs MP patients with high-risk cytogenetics received subsequent bortezomib-based therapy (38% vs 60%)

OS in Those Receiving Subsequent Therapies



- **Bias against VMP due to omission of higher proportion of VMP vs MP patients who experienced most benefit from treatment; i.e. those who had not yet required subsequent therapy (35% vs 23%)**

VMP Compared to MP Then V



- **Analysis includes all VMP patients, versus MP patients who have not received second-line therapy (due to not having relapsed, or due to death) plus those who received bortezomib salvage**

SPMs : Exposure-adjusted Incidence

SPM incidence rate, n per 100-patient-years	VMP (N=327)	MP (N=328)	RR (95% CI)
Exposure, patient-years	1167	1004	
Hematologic SPMs	0.26	0.30	0.862 (0.174, 4.269)
Fatal	0.17	0.30	0.574 (0.096, 3.436)
Non-hematologic SPMs	1.40	1.00	1.389 (0.630, 3.061)
Fatal	0.52	0.60	0.859 (0.277, 2.664)
Overall rate	1.66	1.30	
Background rate, all cancers, general US population aged 65-74 years, 2004–2008[1]	1.92		

- **No increased risk of SPMs with addition of bortezomib to MP**
- **Overall incidence rates in both arms consistent with background rate of all cancers in the general US population aged 65–74 years[1]**

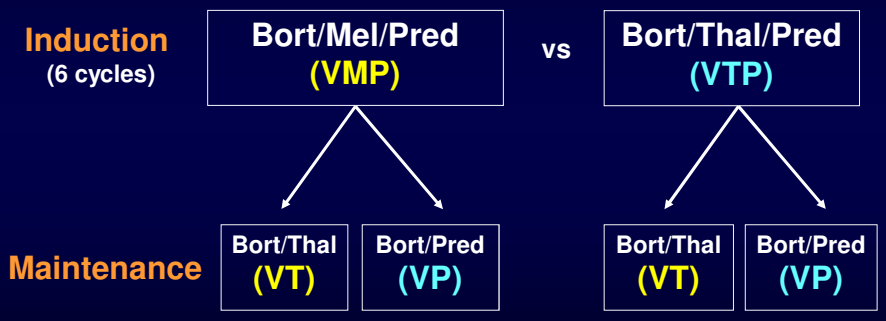
2011 ASH Abstract 477

Maintenance Therapy with Bortezomib plus Thalidomide (VT) or Bortezomib plus Prednisone (VP) in Elderly Myeloma Patients Included in the GEM2005MAS65 Spanish Randomized Trial

MV Mateos, A Oriol, J Martínez, AI Teruel, E Bengoechea, M Pérez, J López, J Díaz-Mediavilla, JM Hernández, Y González, Joan Blade, Juan-Jose Lahuerta, and Jesús F. San Miguel

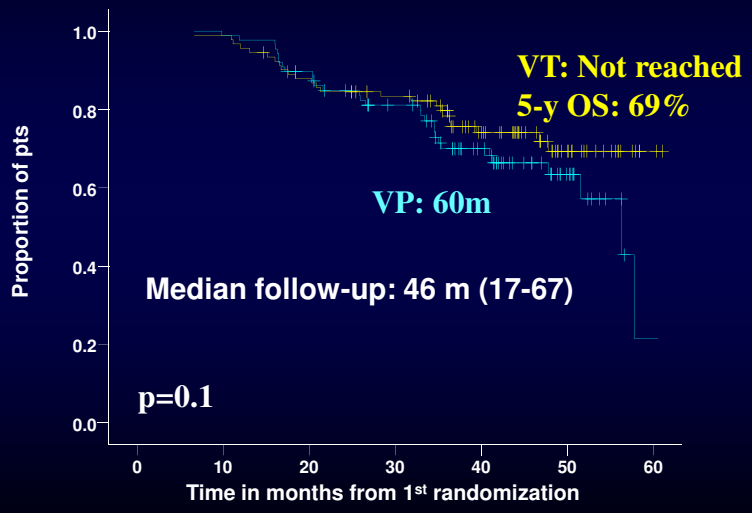
Study Design

Series of 260 elderly untreated MM patients included in the GEM2005 spanish trial



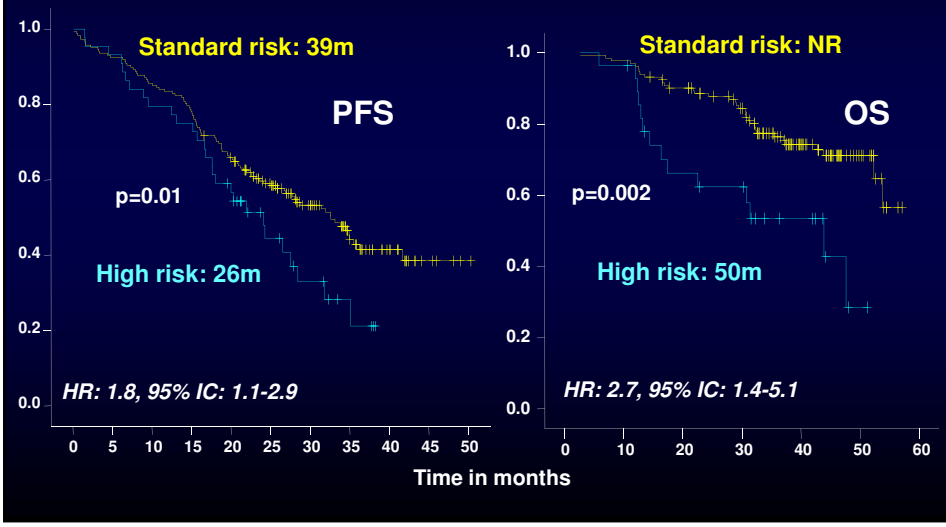
No significant differences in ORR between VMP and VTP (80% and 81%), and CR rate (20% and 27%)

OS According to Maintenance



Cytogenetics & Maintenance

Median follow-up: 46 m (17-67)



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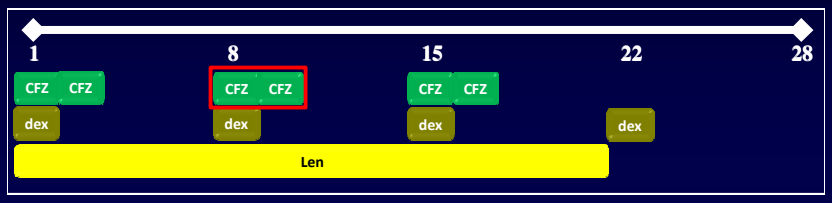
2011 ASH Abstract 631

Final Results of a Frontline Phase I/II Study of Carfilzomib, Lenalidomide, and Low-dose Dexamethasone (CRd) in Multiple Myeloma (MM)

AJ Jakubowiak, D Dytfeld, S Jagannath, DH Vesole, T Anderson, B Nordgren, K Detweiler-Short, D Lebovic, K Stockerl-Goldstein, K Griffith, T Jobkar, D Durecki, S Wear, R Ott, A Al-Zoubi, M Mietzel, M Hussein, D Couriel, H Yeganegi, R Vij

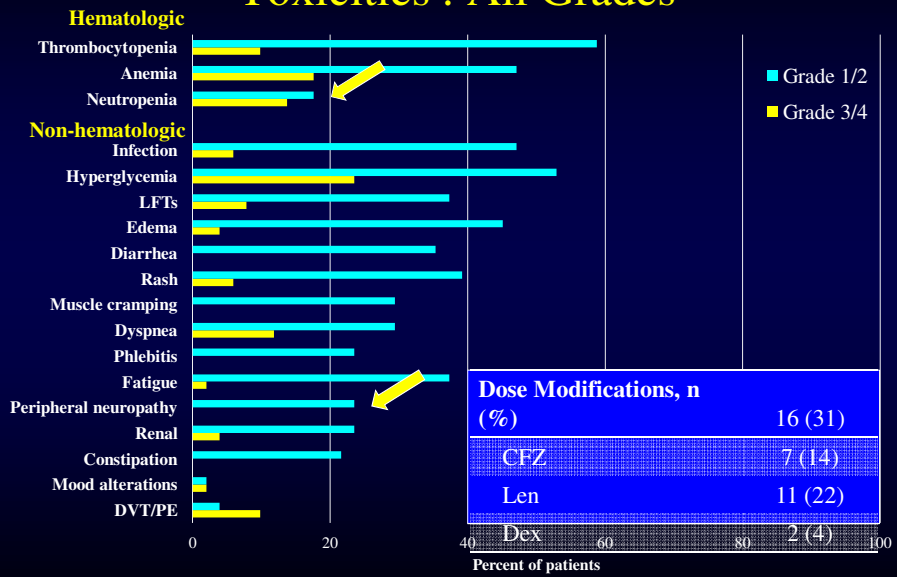
Schedule & Dosing

28-day cycles



Cycles 1–4	20, 27, or 36 mg/m²	40 mg	25 mg
Cycles 5–8	20, 27, or 36 mg/m²	20 mg	25 mg
Cycles 9+ (maintenance)	20, 27, or 36 mg/m²	20 mg	25 mg

Toxicities : All Grades



N= 51, Cycles 1–8 only, based on CTC v 3.0 . No neutropenic fevers, no treatment-related mortality.

Best Responses

Response,† n (%)	N	≥PR (ORR)	≥VGPR	sCR/CR/nCR
All Patients*				
(1–20 cycles)	49	46 (94)	32 (65)	26 (53)
ISS Stage				
I	20	18 (90)	13 (65)	10 (50)
II or III	29	28 (97)	19 (66)	16 (55)
Cytogenetics				
Normal/favorable	33	30 (91)	20 (61)	17 (52)
Unfavorable**	16	16 (100)	12 (75)	9 (56)

†Assessed by modified IMWG Uniform Criteria with an addition of nCR

* Based on 49 patients who completed 1 month of treatment as of cutoff date 6/30/11

** del 13 by metaphase or hypodiploidy or t(4;14) or t(14;16) or del 17p

Responses by Dose Level

Response, n (%)	N	≥PR (ORR)	≥VGPR	sCR/CR/nCR
CFZ 20 mg/m^2*	4	4 (100)	4 (100)	3 (75)
CFZ 27 mg/m^2*	13	13 (100)	13 (100)	11 (85)
CFZ 36 mg/m^2†	32	28 (88)	15 (47)	12 (38)

*Median number of cycles 16 (4–20)

†Median number of cycles 5 (1–14)

Response & Treatment Duration

Response, %	4+ cycles (n=35)	8+ cycles (n=28)	12+ cycles (n=19)
≥ PR	100	100	100
≥ VGPR	89	89	100
sCR/CR/nCR	71	75	79

2011 ASH Abstract 479

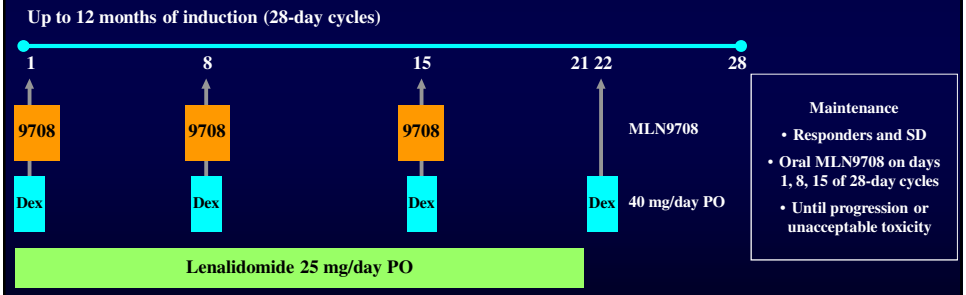
Phase 1/2 Study of Oral MLN9708, a Novel, Investigational Proteasome Inhibitor, in Combination with Lenalidomide and Dexamethasone in Patients with Previously Untreated Multiple Myeloma (MM)

Jesus G. Berdeja, Paul G. Richardson, Sagar Lonial, Ruben Niesvizky, Ai-Min Hui, Deborah Berg, Neeraj Gupta, Guohui Liu, Alessandra Di Bacco, Shaji K. Kumar[6]

Study Design

Dose escalation of oral MLN9708:
3+3 schema, based on cycle 1 DLTs

Starting dose based on dose-escalation portion of twice-weekly dosing study (C16003),[1] 33% dose increments
1.68 → 2.23 → 2.97 → 3.95 mg/m²



- **Transplant-eligible patients could undergo SCT after 6 cycles**
- **Mandatory thromboprophylaxis with aspirin or LMWH**

All Adverse Events

AE, n	MLN9708, mg/m²				Total
	1.68 (n=3)	2.23 (n=3)	2.97 (n=6)	3.95 (n=3)	(N=15)
Fatigue	1	2	3	3	9 (60%)
Rash*	2	1	4	1	8 (53%)
Vomiting	2	1	2	3	8 (53%)
Anemia	1	1	3	1	6 (40%)
Diarrhea	1	0	1	3	5 (33%)
Nausea	1	1	1	2	5 (33%)
Insomnia	1	1	2	0	4 (27%)
Peripheral edema	1	1	0	2	4 (27%)
Thrombocytopenia	0	0	2	2	4 (27%)

- **AEs transient and manageable with dose reduction, discontinuation, or standard supportive care**
- **Grade 1 drug-related peripheral neuropathy in 3 patients (2 at 1.68 mg/m² and 1 at 2.97 mg/m²)**
- **No grade >1 PN**

Preliminary Responses

- 15 evaluable patients, 100% ≥PR (through 4 cycles)
  - Best responses 3 CR, 6 VGPR, 6 PR
- Rapid time to response
  - 14/15 achieved PR in cycle 1 (15th had 48% reduction)
- Two discontinuations after cycle 6 for SCT
  - 1 in VGPR, 1 in CR
- MRD measurements showed molecular CR in 1/3 CRs

Outline

- Disease biology & course
- Asymptomatic multiple myeloma
- Therapy for transplant-ineligible patients
- Induction in patients eligible for transplant
- **Transplant and post-transplant maintenance**
- Relapsed and/or refractory multiple myeloma
- Developments in supportive care for myeloma

2011 ASH Abstract 333

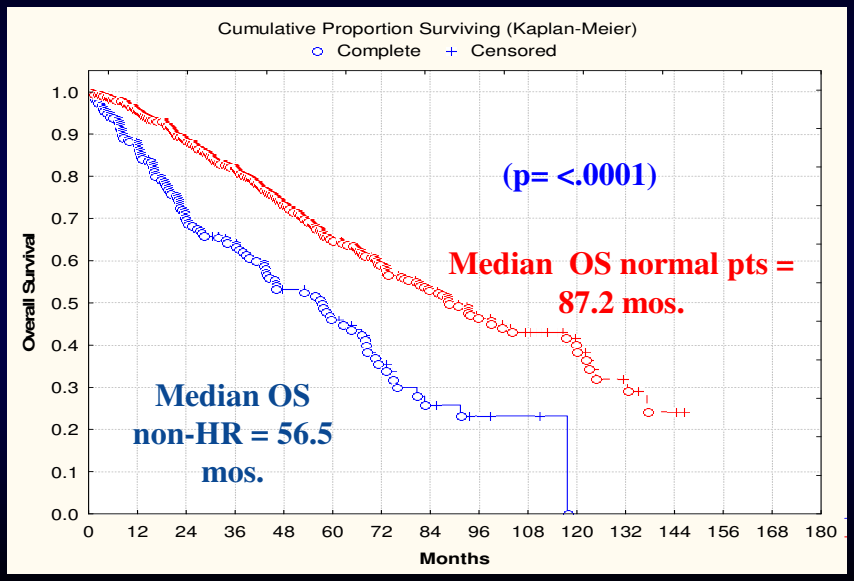
Impact of Non High-Risk Chromosomal Abnormalities on the Outcome of Autologous Hematopoietic Stem Cell Transplantation in Multiple Myeloma

Sairah Ahmed, Heather Lin, Veera Baladandayuthapani, Mubeen A. Khan, Gary Lu, Gabriela Rondon, Sofia Qureshi, Yvonne T. Dinh, Qaiser Bashir, Nina Shah, Simrit Parmar, Chitra M. Hosing, Uday Popat, Sergio A. Giralt, Robert Z. Orlowski, Jatin J. Shah, Richard Champlin, and Muzaffar H. Qazilbash

Non-high Risk Abnormalities & Outcomes

	Normal (n= 924)	Non-High Risk (n= 298)
Final Response	PD = 17 (1.8%) <PR = 132 (14%) PR = 278 (30%) VGPR = 194 (20%) CR = 221 (23%) sCR = 75 (8.1%) Unknown = 7	PD = 20 (6.7%) <PR = 45 (15%) PR = 103 (34%) VGPR = 73 (24%) CR = 34 (11%) sCR = 16 (5%) Unknown = 7
Progressed	447/924 (48%)	172/298 (57%)
Died	278/924 (30%)	123/298 (41%)

Overall Survival



2011 ASH Abstract 504

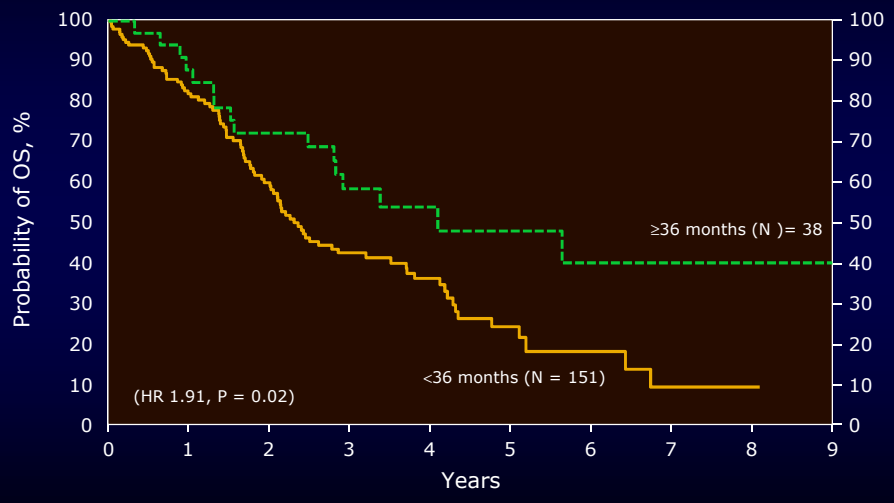
Second Autologous Transplant for Multiple Myeloma (MM) Relapse After a Prior Autologous Transplant (AHCT) – A Report from the Center for International Blood and Marrow Transplant Research (CIBMTR)

Ayman Saad, Laura Michaelis, David Vesole, Jennifer Le-Rademacher, Xiaobao Zhong, Angela Dispenzieri, Sagar Lonial, Gustavo Milone, Parameswaran Hari

Long-term Outcomes

AHCT2	AHCT1	AHCT2
Response at 1 year (%) - CR - PR	82 43 39	68 25 43
- Relapse at 3 years (%)	80	82
- Median time to relapse (months)	18	12

OS and Time to First Relapse

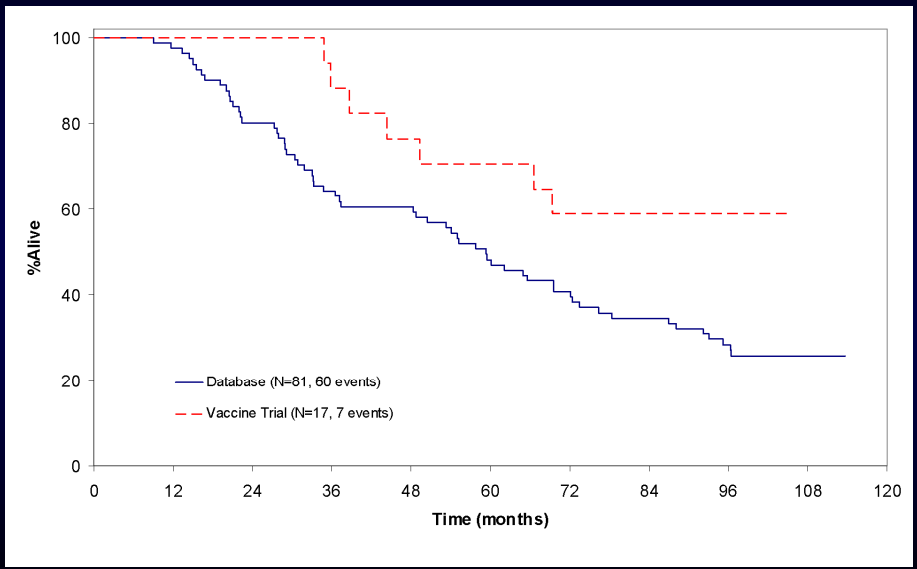


2011 ASH Abstract 636

Matched Case Control Analysis Comparing Long Term Survival of Multiple Myeloma Patients who Received Stem Cell Transplant with and without Idiotype-pulsed Antigen Presenting Cell Vaccine

Yi Lin, Morie A Gertz, Robert B Sims (Dendreon Corp), Sumithra Mandrekar, Kristina Laumann, Betsy LaPlant, Angela Dispenzieri, Suzanne Hayman, Francis Buadi, David Dingli, Douglas Padley, Dennis A Gastineau, Shaji K Kumar, Vincent Rajkumar, Martha Q Lacy

Study 2 : Overall Survival

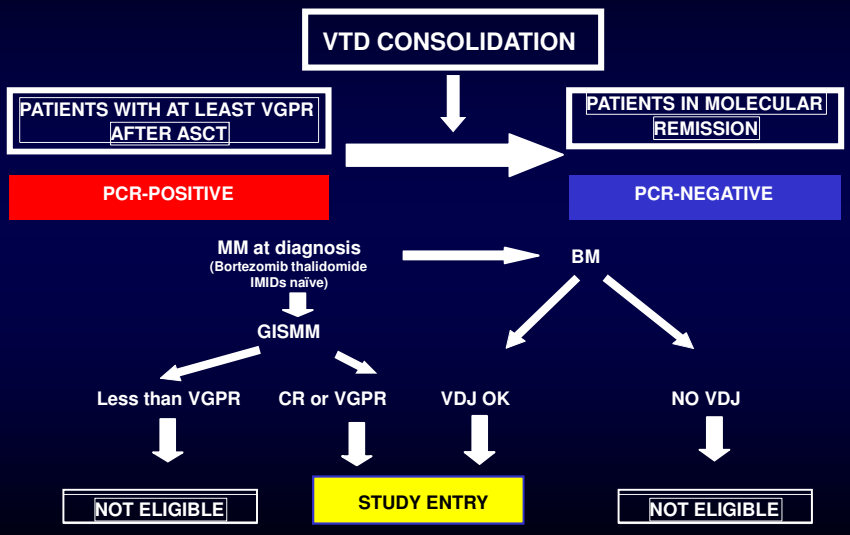


2011 ASH Abstract 827

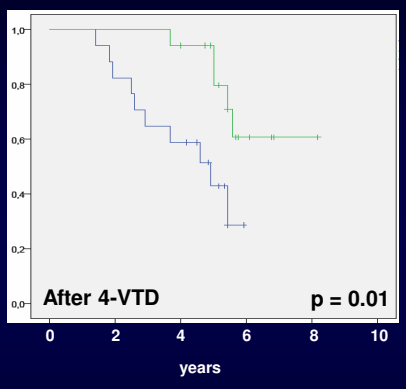
Long-term Results of the GIMEMA VTD Consolidation Trial in Autografted Multiple Myeloma Patients (VEL-03-096) : Impact of Minimal Residual Disease Detection by Real-time Quantitative PCR on Late Recurrences and Overall Survival

Marco Ladetto, Simone Ferrero, Daniela Drandi, Federica Cavallo, Luigia Monitillo, Paola Ghione, Sara Barbiero, Mariella Grasso, Fausto Rossini, Tommasina Guglielmelli, Clotilde Cangialosi, Anna Marina Liberati, Vincenzo Callea, Tommaso Carovita, Luca De Rosa, Francesco Pisani, Antonietta Pia Falcone, Patrizia Pregno, Alberto Rocci, Roberto Passera, Mario Boccadoro and Antonio Palumbo

Study Design

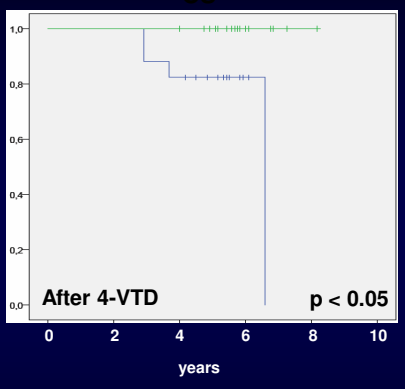


Survival by Molecular Tumor Burden



5-years projected PFS: 82% vs 42%

HTB vs LTB (median)



5-years projected OS: 100% vs 79%

- RQ-PCR value < median (LTB)
- RQ-PCR value > median (HTB)

Outline

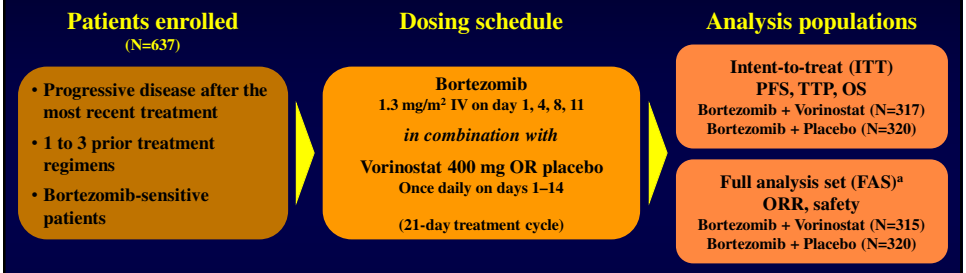
- Disease biology & course
- Asymptomatic multiple myeloma
- Therapy for transplant-ineligible patients
- Induction in patients eligible for transplant
- Transplant and post-transplant maintenance
- **Relapsed and/or refractory multiple myeloma**
- Developments in supportive care for myeloma

2011 ASH Abstract 811

VANTAGE 088 : An International, Multicenter, Randomized, Double-Blind Study of Vorinostat (MK-0683) or Placebo in Combination With Bortezomib in Patients With Multiple Myeloma

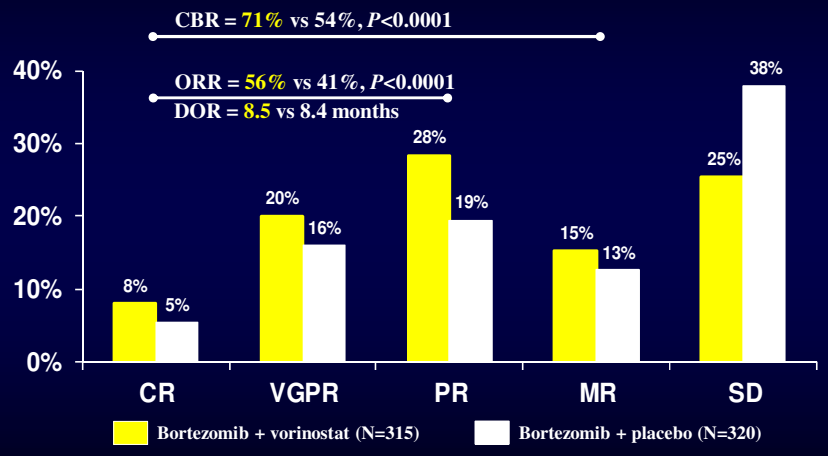
Meletios Dimopoulos, Sundar Jagannath, Sung-Soo Yoon, David S. Siegel, Sagar Lonial, Roman Hajek, Thierry Facon, Laura Rosinol, Hilary Blacklock, Hartmut Goldschmidt, Vania Hungria, Andrew Spencer, Antonio Palumbo, Donna Reece, Thorsten Graef, Jennifer Houp, Linda Sun, Joseph E. Eid, Kenneth C. Anderson

Trial Design



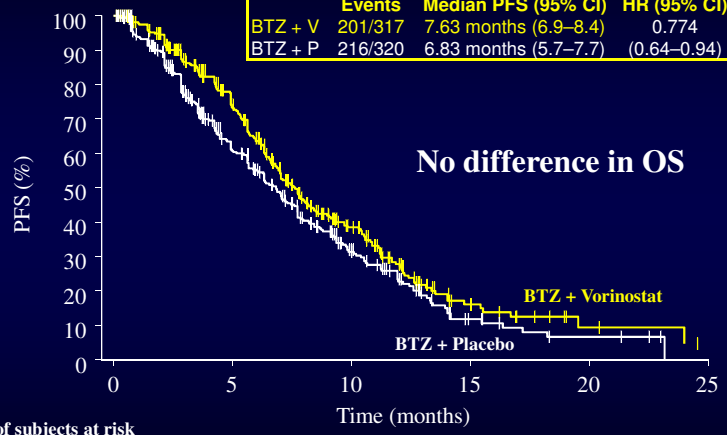
- Primary endpoint
  - PFS
- Secondary endpoints
  - OS, TTP, response rate (EBMT criteria), safety

Response by EBMT Criteria



Progression-free Survival

	Events	Median PFS (95% CI)	HR (95% CI)	*P* value
BTZ + V	201/317	7.63 months (6.9–8.4)	0.774 (0.64–0.94)	0.01
BTZ + P	216/320	6.83 months (5.7–7.7)		



Number of subjects at risk

BTZ + Vorinostat	317	196	75	14	3	0
BTZ + Placebo	320	157	58	12	4	0

Adverse Events

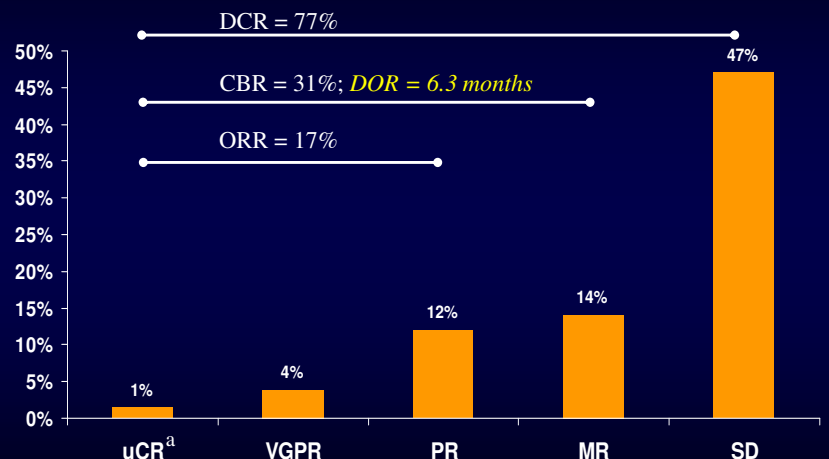
Adverse Event	Bortezomib + Vorinostat (N=315)		Bortezomib + Placebo (N=320)	
	All Grades, %	Grade 3-4, %	All Grades, %	Grade 3-4, %
Hematologic (≥15%)				
Anemia	29	17	25	13
Thrombocytopenia[a]	55	45	33	24
Neutropenia	36	28	30	25
Nonhematologic (≥25%)				
Constipation	20	2	27	1
Diarrhea[a]	62	17	43	9
Nausea[a]	61	8	39	4
Vomiting[a]	45	7	26	4
Other AEs of interest				
Neuropathy	42	8	45	8
Fatigue[a]	40	17	31	7

2011 ASH Abstract 480

VANTAGE 095 : An International, Multicenter, Open-Label Study of Vorinostat (MK-0683) in Combination with Bortezomib in Patients With Relapsed or Refractory Multiple Myeloma

David S. Siegel, Meletios Dimopoulos, Sung-Soo Yoon, Jacob P. Laubach, Jonathan L. Kaufman, Hartmut Goldschmidt, Donna Reece, Xavier Leleu, Simon Durrant, Fritz Offner, Michele Cavo, Arnon Nagler, Sundar Jagannath, Thorsten Graef, Jennifer Houp, Linda Sun, Jason Howe, Sandra Wear, Kenneth C. Anderson

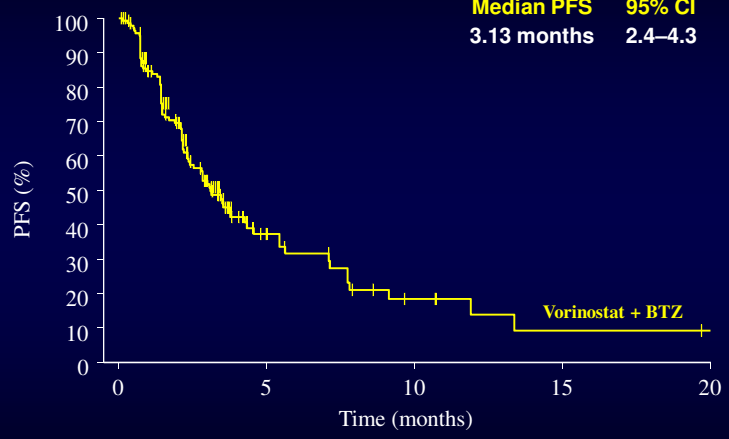
IMWG Response Data



Applying EBMT criteria:
ORR = 11%; DOR = 7.0 months

Progression-free Survival

Median PFS	95% CI
3.13 months	2.4–4.3



Number of subjects at risk					
Vorinostat + BTZ	143	20	6	2	0

2011 ASH Abstract 813

Final Results from the Bortezomib-naïve Group of PX-171-004, a Phase 2 Study of Single-agent Carfilzomib in Patients with Relapsed and/or Refractory Multiple Myeloma

Ravi Vij, Jonathan L. Kaufman, Andrzej J. Jakubowiak, Michael Wang, Sundar Jagannath, Vishal Kukreti, Kevin T. McDonagh, Melissa Alsina, Nizar J. Bahlis, Andrew Belch, Frederic J. Reu, Nashat Y. Gabrail, Jeffrey Matous, David H. Vesole, Robert Z. Orlowski, Sandra Wear, Lori Kunkel, Alvin Wong, Peter Lee, A. Keith Stewart

Study Design

Carfilzomib IV
QD x 2 for 3 weeks (28-day cycle for up to 12 cycles)

Study Population (N=165)
- Measurable disease
- Responsive to ≥1 prior therapy
- Relapsed and/or refractory MM following 1–3 prior regimens
- ECOG PS 0–2

Cohort 1
20 mg/m²

- BOR-treated* (n=35)
- BOR-naïve (n=59)

Cohort 2†
20 mg/m² cycle 1
Escalation to 27 mg/m² in all subsequent cycles

- BOR-naïve (n=70)

Primary endpoint: ORR (CR+VGPR+PR [IMWG criteria])

Secondary endpoints: CBR (ORR+MR [EBMT criteria]), DOR, PFS, TTP, OS, safety

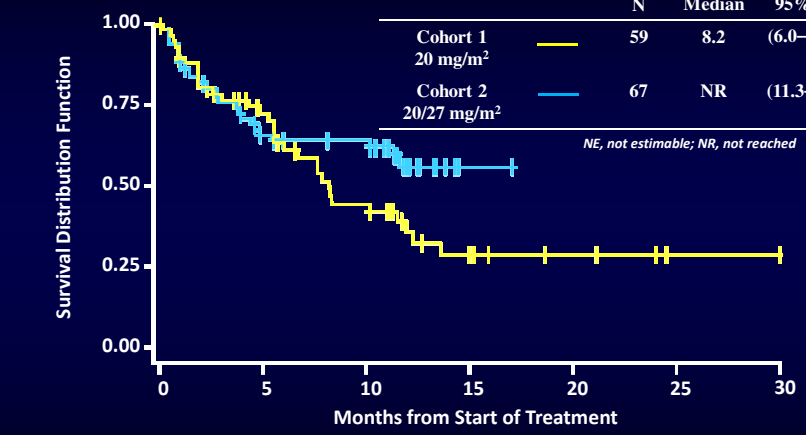
Carfilzomib Activity

	Cohort 1 20 mg/m^2 (n=59)	Cohort 2 20/27 mg/m^2 (n=67)*
Best Response, n (%)		
CR	2 (3)	1 (2)
VGPR	8 (14)	18 (27)
PR	15 (25)	16 (24)
MR	10 (17)	8 (12)
SD	13 (22)	10 (15)
PD	7 (12)	11 (16)
ORR (CR+VGPR+PR)	25 (42)	35 (52)
CBR (ORR+MR)	35 (59)	43 (64)

Response Durability

Median, months	Cohort 1 20 mg/m^2 (n=59)	Cohort 2 20/27 mg/m^2 (n=67)*
Duration of response Median, (95% CI)	n=25 13.1 (7.2–NE)	n=35 NR (NE–NE)
Duration of clinical benefit response Median, (95% CI)	n=35 11.5 (6.2–NE)	n=43 NR (NE–NE)
Time to progression Median, (95% CI)	n=59 8.3 (6.0–12.3)	n=67 NR (11.3–NE)
Time to response Median, (min, max)	n=25 1.0 (0.5, 3.7)	n=35 1.9 (0.5, 3.7)
Time to clinical benefit response Median, (min, max)	n=35 0.5 (0.5, 6.5)	n=43 0.5 (0.5, 5.9)

Progression-free Survival



Number at risk:

59	33	19	7	4
67	38	33	1	0

2011 ASH Abstract 302

Phase 1 Clinical Evaluation of Twice-Weekly Marizomib (NPI-0052), a Novel Proteasome Inhibitor, in Patients with Relapsed/Refractory Multiple Myeloma (MM)

Paul Richardson, Andrew Spencer, Paul Cannell, Simon J. Harrison, Laurence Catley, Craig Underhill, Todd M. Zimmerman, Craig Hofmeister, Andrzej Jakubowiak, Jacob Laubach, Jonathan Kaufman, Michael A. Palladino, Angie M. Longenecker, Ana Lay, Saskia Neuteboom, Sandra Wear, G. Kenneth Lloyd, Alison L. Hannah, Steven D. Reich, Matthew A. Spear, Kenneth C. Anderson

Responses at Full Dose Marizomib ± Dex

- In response-evaluable patients

All Pts		
EBMT		
≥ SD	11/20	55%
MR + PR	3/20	15%
Uniform Criteria		
≥ SD	12/21	57%
PR + VGPR	4/21	19%

Pts Refractory to Bortezomib		
EBMT		
≥ SD	8/12	67%
MR + PR	2/12	17%
Uniform Criteria		
≥ SD	8/12	67%
PR + VGPR	2/12	17%

Median Duration of Response (all Pts) = 133 days (~ 5 mos)

Pts Exposed to Bortezomib		
EBMT		
≥ SD	11/19	58%
MR + PR	3/19	16%
Uniform Criteria		
≥ SD	11/19	58%
PR + VGPR	3/19	16%

Pts Refractory to Lenalidomide		
EBMT		
≥ SD	8/13	62%
MR + PR	3/13	23%
Uniform Criteria		
≥ SD	9/14	64%
PR + VGPR	4/14	29%

2011 ASH Abstract 812

Phase 2 Randomised Open Label Study of 2 Modalities of Pomalidomide plus Low-dose Dexamethasone in Patients with Multiple Myeloma, Refractory to Both Lenalidomide and Bortezomib. IFM 2009-02.

Xavier Leleu, Michel Attal, Philippe Moreau, Bertrand Arnulf, Catherine Traulle, Mauricette Michalet, Gerald Marit, Claire Mathiot, Marie Odile Petillon, Margaret Macro, Murielle Roussel, Brigitte Pegourie, Brigitte Kolb, Anne Marie Stoppa, Sabine Brechignac, Laurent Garderet, Bruno Royer, Cyrille Hulin, Lotfi Benboubker, Olivier Decaux, Martine Escoffre-Barbe, Denis Caillot, Jean Paul Fermand, Herve Avet-Loiseau, Thierry Facon

Study Design

Arm A – Cycle 21 days
- Pomalidomide 4mg oral/d, 1–21
- Dexamethasone 40mg oral/w, 1, 8, 15, 22
- Aspirin/LMWH continue

Arm B – Cycle 28 days
- Pomalidomide 4 mg oral/d, d 1–28
- Dexamethasone 40 mg oral/w, 1, 8, 15, 22
- Aspirin/LMWH continue

Key inclusion criteria

- Relapsed MM
- Resistant or Refractory to len and bortez
- Measurable disease (central lab)
- ANC > 1 x10^9/L; Platelets ≥ 75 x10^9/L; Hb ≥ 8 g/dL
- Creatinine clearance ≥50 mL/min

6 pts per arm

DMC – TOLERANCE
Rule: no difference

17 pts per arm

DMC - EFFICACY
Rule: 4 ≥ PR /arm

40 pts per arm

Until Progression
(relapse or refractory)

- N=84 randomized

Primary objective

Response rate (PR and better) according to IMWG

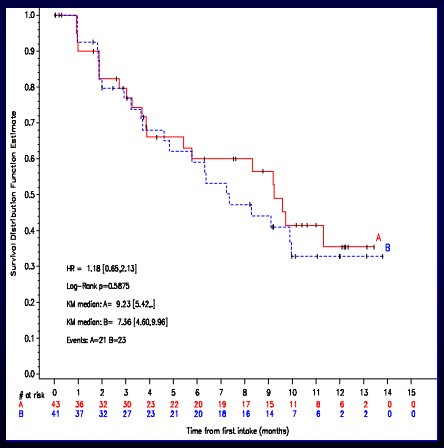
Response Data*

	21/28 N=43	28/28 N=41	Total
ORR (≥PR), %	35	34	34.5
CR, n	1	2	3
VGPR, n	1	1	2
PR, n	13	11	24
Stable disease, %	44	51	48
Progressive disease, %	12	7	9.5
Not evaluable, n	4	3	7
Median time to First response, months	2.7	1.1	1.8
Median Duration of response, months	10.5	7.2	8.1
≥ one year in responders, %	47.5	36	37.5

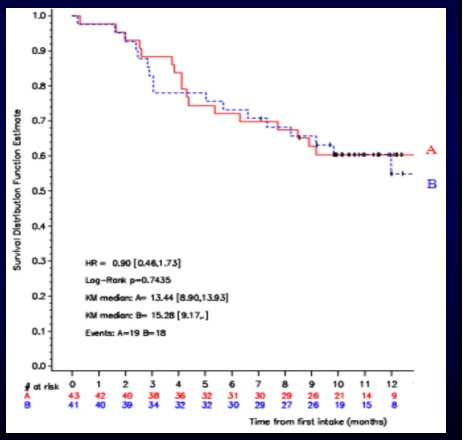
*Median follow-up 11.3 mos. in both arms

Time to Events

TTP: Median 9.1 mos.
(95% CI: 5.8;10.0)



OS: Median 13.4 mo.s
(95% CI: 9.8;-)



2011 ASH Abstract 303

A Phase 2 Study of Elotuzumab in Combination With Lenalidomide and Low-Dose Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma

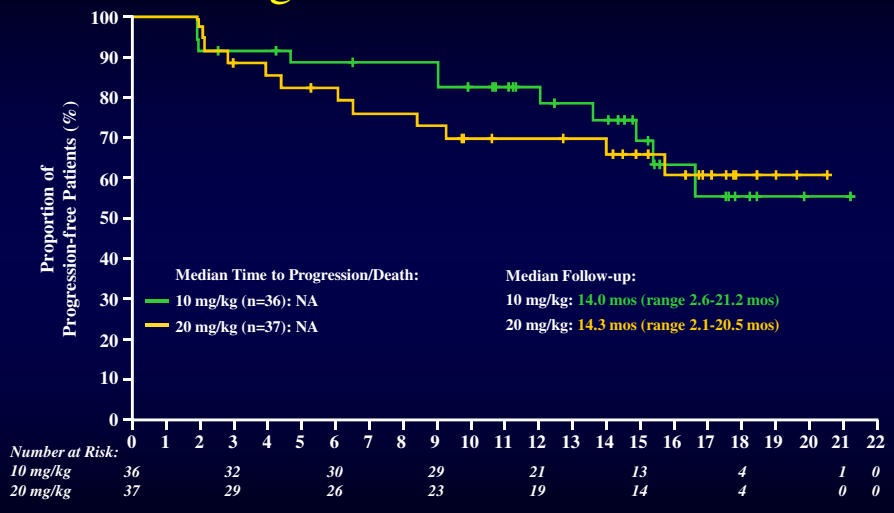
Sagar Lonial, Andrzej J. Jakubowiak, Sundar Jagannath, Marc S. Raab, Thierry Facon, Ravi Vij, Philippe Moreau, Donna E. Reece, Darrell White, Lotfi Benboubker, Jeffrey Zonder, Jean-Francois Rossi, Claire Tsao, Teresa Parli, Glenn Kroog, Anil K. Singhal, Paul G. Richardson, on behalf of the 1703 Study Investigators

Efficacy

	Elotuzumab 10 mg/kg	Elotuzumab 20 mg/kg	Total
Patients, n	36	37	73
ORR (≥PR), n (%)	33 (92)	27 (73)	60 (82)
CR/stringent CR, n (%)	5 (14)	4 (11)	9 (12)
VGPR, n (%)	14 (39)	12 (32)	26 (36)
PR, n (%)	14 (39)	11 (30)	25 (34)
<PR, n (%)	3 (8)	10 (27)	13 (18)

- **Median time to response: 1 month (range, 0.7-5.8)**
- **Median time to best response: 2.2 months (range, 0.7-17.5)**

Progression-free Survival



At a median follow-up of 14.1 months, the median PFS was not reached
PFS rate was 75% (10 mg/kg) and 65% (20 mg/kg)

Adverse Events

Preferred Term, n (%)	Elotuzumab 10 mg/kg, n=36	Elotuzumab 20 mg/kg, n=37	Total, N=73	
			Any Grade	Grade 3/4†
Muscle spasms	19 (53)	21 (57)	40 (55)	2 (3)
Diarrhea	20 (56)	19 (51)	39 (53)	4 (5)
Fatigue	19 (53)	16 (43)	35 (48)	5 (7)
Constipation	14 (39)	19 (51)	33 (45)	0
Nausea	16 (44)	15 (41)	31 (42)	1 (1)
Upper respiratory tract infection	17 (47)	13 (35)	30 (41)	2 (3)
Pyrexia	14 (39)	14 (38)	28 (38)	1 (1)
Anemia	13 (36)	10 (27)	23 (32)	8 (11)
Insomnia	9 (25)	13 (35)	22 (30)	1 (1)
Peripheral edema	12 (33)	9 (24)	21 (29)	1 (1)
Back pain	11 (31)	8 (22)	19 (26)	2 (3)
Hyperglycemia	7 (19)	12 (32)	19 (26)	7 (10)
Neutropenia	11 (31)	8 (22)	19 (26)	12 (16)
Thrombocytopenia	11 (31)	7 (19)	18 (25)	12 (16)
Lymphopenia	10 (28)	7 (19)	17 (23)	12 (16)
Leukopenia	7 (19)	5 (14)	12 (16)	6 (8)
Hypokalemia	5 (14)	6 (16)	11 (15)	4 (5)

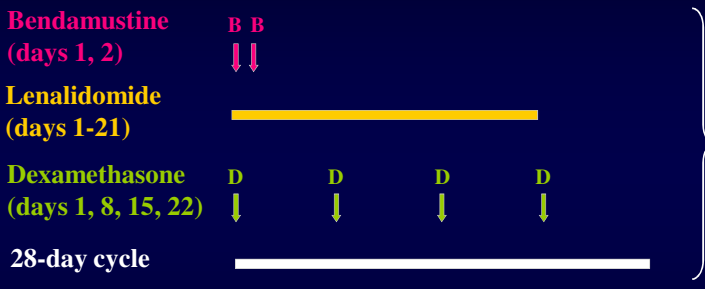
†Grade 5: 1 patient, pneumonia complicated by cellulitis, sepsis, multi-organ failure

2011 ASH Abstract 303

Combination of Bendamustine, Lenalidomide, and Dexamethasone (BLD) in Patients with Refractory or Relapsed Multiple Myeloma Is Safe and Highly Effective: Results of Phase I/II Open-Label, Dose Escalation Study

Suzanne Lentzsch, Amy O'Sullivan, Ryan Kennedy, Mohammad Abbas, Navkiranjit Gill, Lijun Dai, Carrie Andreas, Diane Gardner, Silvana Lalo Pregja, Steve Burt, Robert L. Redner, Robert Volkin, G. David Roodman, Markus Y. Mapara, J. Franklin Viverette, Mounzer Agha, John K. Waas, Yongli Shuai, Daniel Normolle, and Jeffrey A. Zonder

Study Design



2 cycles past best response

8 cycles max

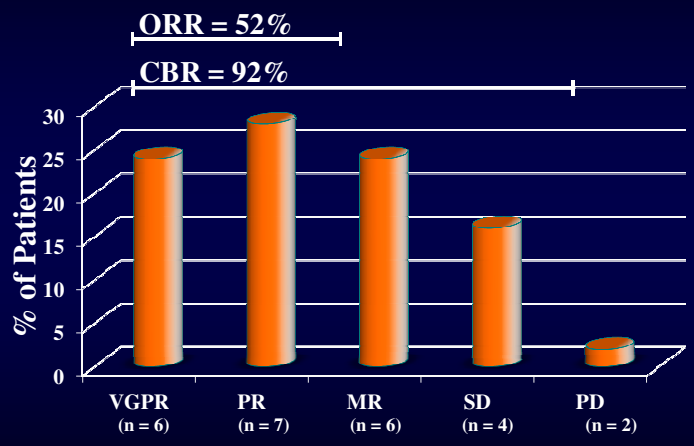
Additional treatments: prophylaxis with aspirin (325 mg/day) and an H-2 blocker or PPI were required; PCP antibiotic prophylaxis was recommended

Dose Limiting Toxicities

Dose level	Patients Treated	No. of DLTs Observed	Description
1	3	0	N/A
2	6	1	Grade 4 neutropenia (n = 1)
3	6	2	Grade 4 neutropenia (n = 1) Prolonged grade 3 thrombocytopenia (n = 1)

MTD: bendamustine 75 mg/m^2 plus lenalidomide 10 mg (dose level 2)

Response Rates (N = 25 Evaluable)



Time to VGPR+PR - median in months 1.6 (1.6, 3.5); 95% CI

Outline

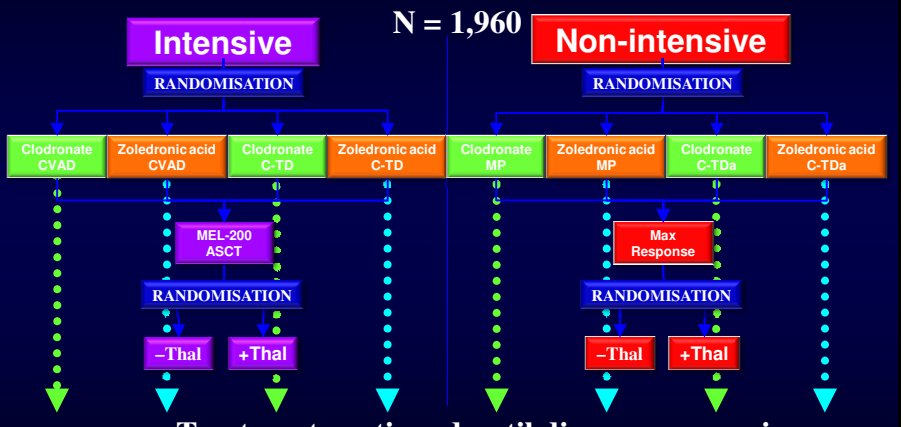
- Disease biology & course
- Asymptomatic multiple myeloma
- Therapy for transplant-ineligible patients
- Induction in patients eligible for transplant
- Transplant and post-transplant maintenance
- Relapsed and/or refractory multiple myeloma
- **Developments in supportive care for myeloma**

2011 ASH Abstract 993

MRC Myeloma IX :
6-Year Median Follow-up Highlights the Importance of Long-term Follow-up in Myeloma Clinical Trials and Differential Effects of Thalidomide in High- and Low-risk Disease

G.J. Morgan, F.E. Davie[1], W.M. Gregory, S.E. Bell, A.J. Szubert, G. Cook, M.T. Drayson, R.G. Owen, F.M. Ross, G.H. Jackson, J.A. Child

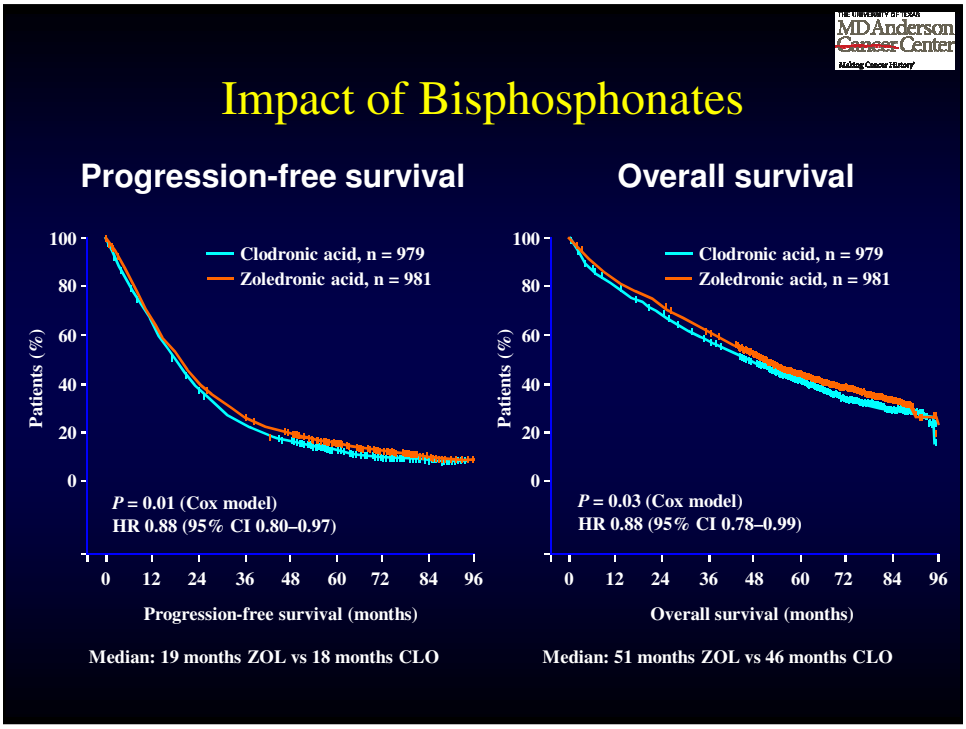
Trial Design



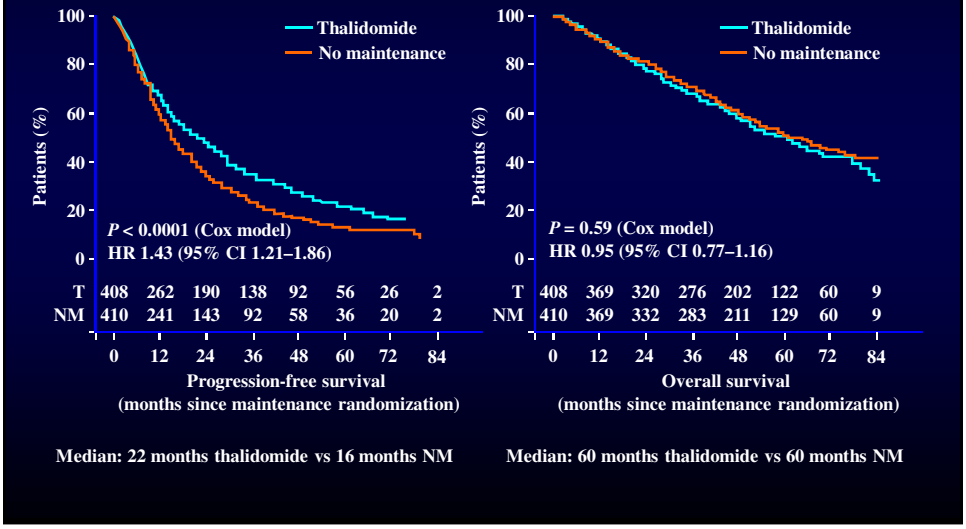
Primary endpoints: PFS, OS, Response
Secondary endpoints: SREs (Time to first SRE, SRE incidence), Safety, and QoL
Zoledronic acid (4 mg IV q 3-4 wk); Clodronate (1,600 mg/d PO)

ISRCTN68454111

Impact of Bisphosphonates



Impact of Maintenance Therapy



New Approaches to the Management of Patients with Multiple Myeloma : Summary

Robert Z. Orlowski, Ph.D., M.D.

Director, Myeloma Section
Professor, Departments of Lymphoma/Myeloma & Experimental Therapeutics
Principal Investigator, M. D. Anderson SPORE in Multiple Myeloma
Chair, Southwest Oncology Group Myeloma Committee

THE UNIVERSITY OF TEXAS
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What Have We Learned ?

- Asymptomatic multiple myeloma
  - Patients at high risk of progression to symptomatic disease can be differentiated from those with intermediate or low risk
  - High risk patients may benefit from early initiation of therapy with lenalidomide/dex
  - Data require longer follow-up, a larger study, and questions about impact on stem cells and induction of drug resistance remain

Induction Therapy

- Transplant-eligible patients
  - A better induction regimen pre-transplant improves the outcome post-transplant
    - VD > VAD and PAD > VAD
    - VTD > TD, and VRD may be even better
  - CRd and MLN9708 + Rd look attractive as well
  - What is optimal for high risk patients?
    - V with induction & maintenance for 17p

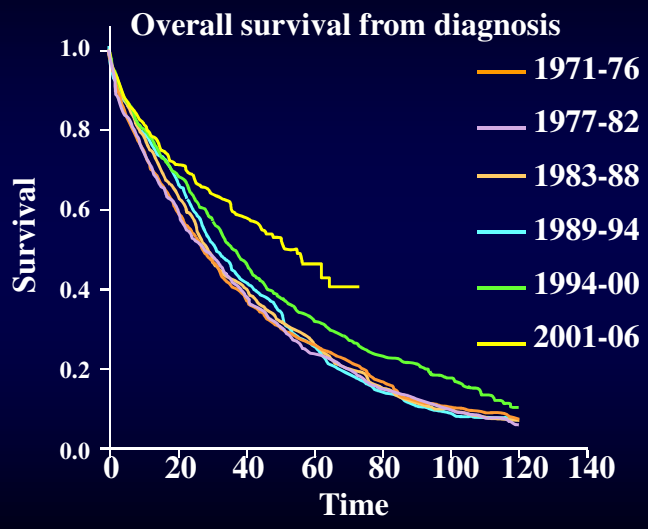
Transplant and Maintenance

- Early transplant still of value
- Autologous remains the standard of care
- Consolidation to molecular remission may improve outcomes
- Maintenance therapy consistently benefits PFS, and often OS as well
- SPM risk needs further scrutiny, but risk of myeloma-related death is still many fold higher

Other Pearls

- Patients not eligible for transplant
  - Earlier use of novel agents improves outcomes
  - Triplet combinations based on MP > MP alone
    - MPT > MP in most studies
    - MPR+R also better than MP
    - MPV maintains long-term superiority to MP as well
    - Early novel agent use better than reserving them for later
  - Greater use of consolidation & maintenance
  - Which regimen is best for which patient ?

Impact of Novel Agents Up-front

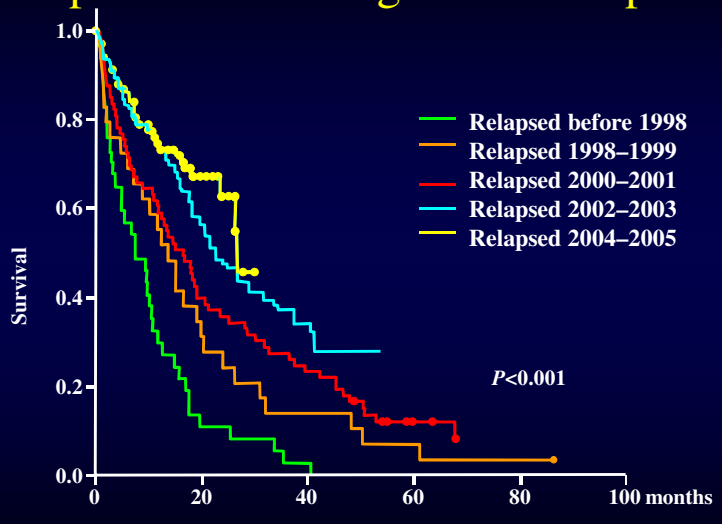


Kumar, S et al. Blood 111:2516, 2008.

Additional News

- Patients with relapsed and/or refractory disease
  - Len/Dex and BDox are the standards
  - Reusing drugs that worked before can be successful
  - Drugs with novel mechanisms of action are showing promise alone and in combination
  - Benefits of vorinostat + bortezomib unclear; other HDACi moving forward (panobinostat, ACY1215)
  - Next generation of proteasome inhibitors (carfilzomib, marizomib, MLN9708) and IMiDs (pomalidomide) are in/coming to registration studies

Impact of Novel Agents at Relapse



Kumar, S et al. Blood 111:2516, 2008.

A Cornucopia of New Drugs

- New small molecules
  - Novel signal transduction inhibitors
  - Second generation proteasome inhibitors
  - Second & third generation immunomodulators
  - Histone deacetylase & heat shock protein 90 inhibitors
- Monoclonal antibodies
  - Siltuximab
  - Elotuzumab
  - Lorvotuzumab mertansine

Lymphoma & Myeloma Center

- Lymphoma/Myeloma/Amyloidosis/ Waldenström's Referral Line : 1-855-MYELOMA
  - Karin L. Ewer, JD, MBA, PAS
  - Rommel I. Quiambao, BS, PAS
- Yolanda C. Villanueva, RN, BSN
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  - Dr. Sheeba Thomas
  - Dr. Michael Wang
  - Dr. Donna Weber






Question and Answer Session


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• TOLL-FREE PHONE: (877) LLS-COPAY
For more information about myeloma and other LLS programs, please contact an LLS Information Specialist.
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