APOPC 2010

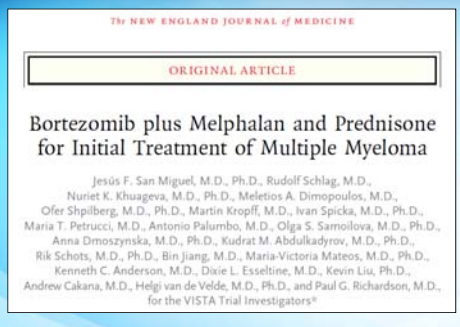
Significant papers in oncology

- Multiple Myeloma -

Ae-Ryoung PARK
Seoul St. Mary's Hospital
The Catholic University of Korea

1

Original article - 1



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bortezomib plus Melphalan and Prednisone for Initial Treatment of Multiple Myeloma

Jesús F. San Miguel, M.D., Ph.D., Rudolf Schlag, M.D., Nuriet K. Khuageva, M.D., Ph.D., Meletios A. Dimopoulos, M.D., Ofer Shpilberg, M.D., Ph.D., Martin Kropff, M.D., Ivan Spicka, M.D., Ph.D., Maria T. Petrucci, M.D., Antonio Palumbo, M.D., Olga S. Samoilova, M.D., Ph.D., Anna Dmoszynska, M.D., Ph.D., Kudrat M. Abdulkadyrov, M.D., Ph.D., Rik Schots, M.D., Ph.D., Bin Jiang, M.D., Maria-Victoria Mateos, M.D., Ph.D., Kenneth C. Anderson, M.D., Dixie L. Esseltine, M.D., Kevin Liu, Ph.D., Andrew Cakana, M.D., Helgi van de Velde, M.D., Ph.D., and Paul G. Richardson, M.D., for the VISTA Trial Investigators*

San Miguel JF, et al. *N Engl J Med.* 2008;359(9):906-917

San Miguel JF, et al. *N Engl J Med.* 2008;359(9):906-917

Original article

- **Title**
  Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma
- **Authors**
  Jesus F. San Miguel, M.D., Ph.D. et al
  The **VISTA**(Velcade as Initial Standard Therapy in multiple myeloma : Assessment with melphalan and prednisone) trial investigators
- **Journal**
  The New England Journal of Medicine 2008;359:906-17
- **Study type**
  International **phase Ⅲ trial** for patients NOT considered to be candidates for SCT

☞ **Bortezomib/melphalan/prednisone (b-MP)**
: Induction therapy for non-transplant candidates *(NCCN category 1)*

3

San Miguel JF, et al. *N Engl J Med.* 2008;359(9):906-917

Introduction

- Multiple Myeloma Therapy -

- **Melphalan/prednisone(MP)**
  - Standard care for patients with newly diagnosed multiple myeloma for more than 40 years
  - Median survival : 29-37 months
- **High-dose therapy with HSCT**
  - Preferred treatment for patients under the age of 65 years
  - Since the median age at diagnosis of myeloma is 70 years, more than half the patients with newly diagnosed myeloma may not be eligible for high-dose therapy.
- **Bortezomib**
  - Proteasome inhibitor bortezomib is active in relapsed or refractory myeloma.
  - In preclinical studies, bortezomib sensitized melphalan-sensitive and melphalan-resistant myeloma cell lines to melphalan.

4

San Miguel JF, et al. *N Engl J Med.* 2008;359(9):906-917

Introduction

- Mechanism of Bortezomib(Proteasome inhibitor) -

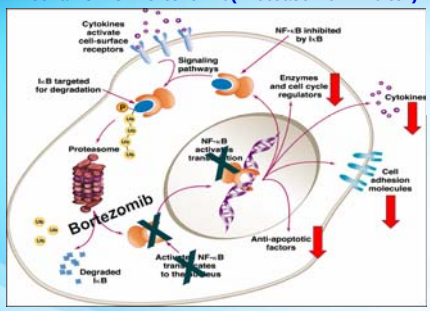


Figure from Armand JP, et al. Oncologist 2007;12:281-290
Copyright © Millennium Pharmaceuticals Inc.

San Miguel JF, et al. *N Engl J Med.* 2008;359(9):906-917

Patients & Methods

Newly diagnosed, untreated MM patients (transplant ineligible)
(151 centers in 22 countries)
(Dec 2004 ~ Sep 2006, N=682)

Randomized Allocation

Bortezomib Group (N=344)
Melphalan
9 mg/m², days 1-4
Prednisone
60 mg/m², days 1-4
Bortezomib 1.3 mg/m²
days 1,4,8,11,22,25,29,32 cycles 1-4
days 1,8,22,29 cycles 5-9
(Nine 6-week cycles)

Control Group (N=338)
Melphalan
9 mg/m², days 1-4
Prednisone
60 mg/m², days 1-4
(Nine 6-week cycles)

6

San Miguel JF, et al. *N Engl J Med.* 2008;359(9):906-917

Patients & Methods

- **Primary end point**
  - Time to disease progression
- **Secondary end point**
  - Complete response rate
  - Duration of response
  - Time to subsequent myeloma therapy
  - Overall survival
- **Response assessment**
  - Disease progression : determined by EBMT criteria
  - Relapse from complete response was defined as the reappearance of M protein on immunofixation.

7

San Miguel JF, et al. *N Engl J Med.* 2008;359(9):906-917

Results

Table. Baseline Characteristics of the Patients

	Bortezomib (N=344)	Control (N=338)		Bortezomib (N=344)	Control (N=338)
Age			International Staging System		
Median – yr	71	71	stage - %		
Range – yr	57-90	48-91	I	19	19
Subgroup – no.(%)			II	47	47
<65 yr	14(4)	9(3)	III	35	34
≥75 yr	107(31)	101(30)	Serum β2-microglobulin		
Male sex – no.(%)	175(51)	166(49)	Median – mg/L	4.2	4.3
Race – no.(%)			Range – mg/L	1.7-21.6	0.6-60.9
White	304(88)	295(87)	Subgroup - %		
Asian	33(10)	36(11)	<2.5 mg/L	12	12
Black	5(1)	7(2)	2.5-5.5 mg/L	55	55
Other	2(1)	0	>5.5 mg/L	33	33
Region - %			Albumin level		
Europe	79	78	Median – g/dL	3.3	3.3
North America	9	9	Range – g/dL	1.3-4.7	1.4-5.0
Other	11	13	Subgroup - %		
Karnofsky PS≤70 – no.(%)	122(35)	111(33)	<3.5 g/dl	58	62
Type of myeloma - %			≥3.5 g/dl	42	38
IgG	64	62	Hemoglobin – g/L		
IgA	24	26	Median	104	106
IgD	1	1	Range	64-159	73-165
IgM	1	1	Platelet count/mm³		
Light chain	8	8	Median	221.5k	221.5k
Biclonal	2	2	Range	68k-515k	33k-587k
Lytic bone lesions – no./total no.(%)	224/323(65)	222/336(66)	CrCL(calculated) - %		
Median plasma cells on bone marrow biopsy - %	40	41	<30 ml/min	6	5
			30-60 ml/min	48	50
			> 60ml/min	46	46
			Hx of cardiac condition – no.(%)	121(35)	105(31)

San Miguel JF, et al. *N Engl J Med.* 2008;359(9):906-917

Results : Time to Progression

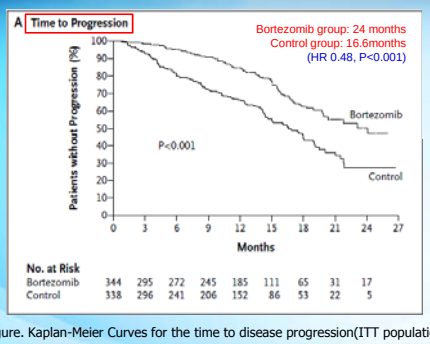
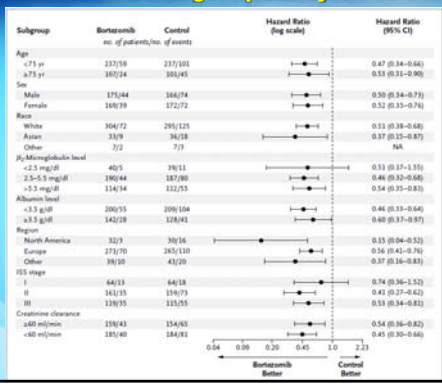


Figure. Kaplan-Meier Curves for the time to disease progression(ITT population)

9

San Miguel JF, et al. *N Engl J Med.* 2008;359(9):906-917

Results : Subgroup Analyses of TTP



10

San Miguel JF, et al. *N Engl J Med.* 2008;359(9):906-917

Results : Overall Survival

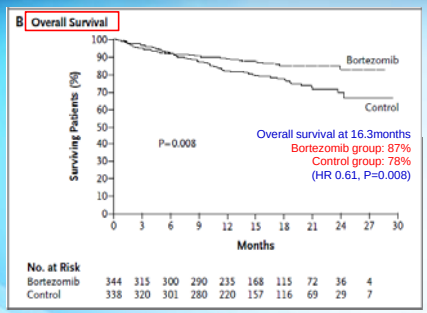


Figure. Kaplan-Meier Curves for Overall Survival(ITT population)
Median survival was not reached in either group.

11

San Miguel JF, et al. *N Engl J Med.* 2008;359(9):906-917

Results : Best Response to Treatment and Time-to-Event

Table. Best response to treatment and time-to-event data

	Bortezomib (N=337)	Control (N=331)	P value
Best response – no.(%)(EBMT criteria)			
Complete or partial response	238(71)	115(35)	<0.001
Complete response	102(30)	12(4)	<0.001
Partial response	136(40)	103(31)	NR
Median duration of response – months			
Complete or partial response	19.9	13.1	NR
Complete response	24.0	12.8	NR

12

San Miguel JF, et al. *N Engl J Med.* 2008;359(9):906-917

Results : Adverse Events

Table 3. Adverse Events (Safety Population).*

Events	Bortezomib Group (N=340)			Control Group (N=337)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
	number of patients (percent)					
Any event	338 (99)	181 (53)	96 (28)	326 (97)	148 (44)	92 (27)
Hematologic events†						
Thrombocytopenia	178 (52)	68 (20)	58 (17)	159 (47)	55 (16)	47 (14)
Neutropenia	165 (49)	102 (30)	34 (10)	155 (46)	79 (23)	49 (15)
Anemia	147 (43)	53 (16)	9 (3)	187 (55)	66 (20)	26 (8)
Leukopenia	113 (33)	67 (20)	10 (3)	100 (30)	55 (16)	13 (4)
Lymphopenia	83 (24)	49 (14)	18 (5)	58 (17)	30 (9)	7 (2)
Gastrointestinal events						
Nausea	164 (48)	14 (4)	0	94 (28)	1 (<1)	0
Diarrhea	157 (46)	23 (7)	2 (1)	58 (17)	2 (1)	0
Constipation	125 (37)	2 (1)	0	54 (16)	0	0
Vomiting	112 (33)	14 (4)	0	55 (16)	2 (1)	0
Infections						
Pneumonia	56 (16)	16 (5)	6 (2)	36 (11)	13 (4)	4 (1)
Herpes zoster	45 (13)	11 (3)	0	14 (4)	6 (2)	0
Nervous system disorders						
Peripheral sensory neuropathy	151 (44)	43 (13)	1 (<1)	16 (5)	0	0
Neuralgia	121 (36)	28 (8)	2 (1)	5 (1)	1 (<1)	0
Dizziness	56 (16)	7 (2)	0	37 (11)	1 (<1)	0

13

San Miguel JF, et al. *N Engl J Med.* 2008;359(9):906-917

Results : Adverse Events

- **Grade 3 events** occurred in higher proportion of patients in the bortezomib group than in the control group(53% vs 44%, P=0.02).
- There were no significant differences in grade 4 events(28% and 27%).
- Hematologic toxic effects were similar in the two groups.
- **Peripheral sensory neuropathy** was more frequent in the bortezomib group.
- All **grade 3 or 4 gastrointestinal symptoms** were more frequent in the bortezomib group than in the control group(19% vs 5%).
- Any grade of **herpes zoster** were more frequent in the bortezomib group than in the control group(13% vs 4%).
- The rate of **serious adverse events** in the bortezomib group was higher than that in the control group(46% vs 36%).

14

San Miguel JF, et al. *N Engl J Med.* 2008;359(9):906-917

Conclusion

- **Bortezomib/melphalan/prednisone(b-MP)**
  : Valuable front-line treatment for patients with newly diagnosed myeloma who are ineligible for high-dose therapy.
  - ✓ Median time to progression
  - ✓ Rate of complete response
  - ✓ Time to subsequent myeloma therapy
  - ✓ Median duration of response
  - ✓ Overall survival
- **Melphalan and prednisone alone can no longer be considered the standard of care in patients who are 65 years of age or older.**

15

Original article - 2

Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial

S Vincent Rajkumar, Susanna Jacobus, Natalie S Callander, Rafael Fonseca, David H Vesole, Michael E Williams, Rafat Abonour, David S Siegel, Michael Katz, Philip R Greipp, for the Eastern Cooperative Oncology Group

Summary

Background High-dose dexamethasone is a mainstay of therapy for multiple myeloma. We studied whether low-dose dexamethasone in combination with lenalidomide is non-inferior to and has lower toxicity than high-dose dexamethasone plus lenalidomide.

Rajkumar SV, et al. *Lancet Oncol.* 2010;11(1):29-37

16

Rajkumar SV, et al. *Lancet Oncol.* 2010;11(1):29-37

Original article

- **Title**
  Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial
- **Authors**
  S Vincent Rajkumar, et al: Division of Hematology, Mayo Clinic
  Funded and sponsored by the US National Cancer Institute(NCI)
- **Journal**
  Lancer Oncology 2010;11(1):29-37
- **Study type**
  Open-label non-inferiority randomised controlled trial

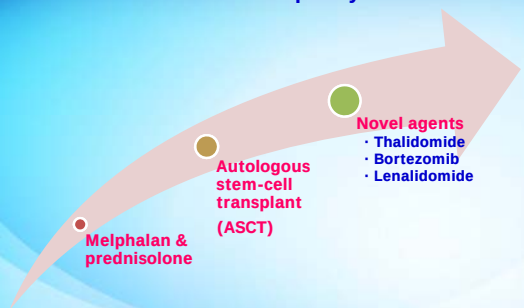
☞ **Lenalidomide/low-dose dexamethasone**
: Induction therapy for non-transplant candidates *(NCCN category 1)*

17

Rajkumar SV, et al. *Lancet Oncol.* 2010;11(1):29-37

Introduction

- Treatment of Multiple Myeloma -



18

Rajkumar SV, et al. *Lancet Oncol.* 2010;11(1):29-37

Introduction

High-dose dexamethasone
- Combination with infusional vincristine & doxorubicin
- Incorporated in various pre-transplant induction regimens

☞ **Significant toxicity**

Lenalidomide
- Analogue of thalidomide
- Lenalidomide plus high-dose dexa. showed high response rate than thalidomide and dexamethasine OR dexamethasone alone (preliminary results)

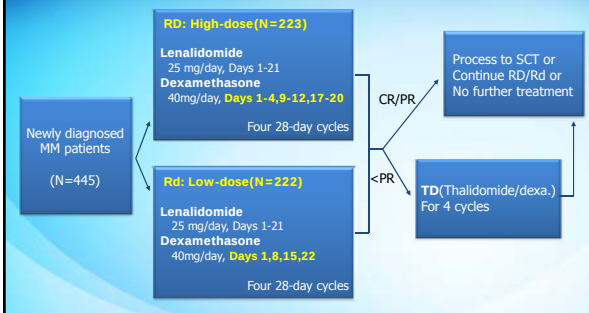
• Objectives •

Low-dose dexamethasone with lenalidomide is **non-inferior** to and has **lower toxicity** than **high-dose** dexamethasone plus lenalidomide.

19

Rajkumar SV, et al. *Lancet Oncol.* 2010;11(1):29-37

Methods



20

Rajkumar SV, et al. *Lancet Oncol.* 2010;11(1):29-37

Methods

- Additional Treatment -

- Allow to interrupt therapy for growth-factor-supported stem cell mobilization.
- **Dose adjustments** were allowed for **toxicity**.
- **Bisphosphonates** monthly
  : Pamidronate 90mg over 2-4 h every 4 weeks or Zoledronic acid 4mg IV over 15 min every 4 weeks.
- **Thromboprophylaxis**
  : After the first 266 patients were enrolled, mandatory thromboprophylaxis was added for all patients d/t high rates of deep-vein thrombosis.

21

Rajkumar SV, et al. *Lancet Oncol.* 2010;11(1):29-37

Methods

- **Primary end point**
  - Overall response rate in the first 4 cycles
- **Additional end points**
  - Best overall response
  - Time to progression
  - Progression-free survival
  - Overall survival
- **Response assessment**
  - Standard European Group for Blood and Bone Marrow Transplant(Blade) criteria
- **Non-inferiority margin**
  - Absolute difference of 15% in response rate
  - Odds ratio for response : 1.91

22

Rajkumar SV, et al. *Lancet Oncol.* 2010;11(1):29-37

Results : Overall Response Rates

Table. Response to therapy in first 4 cycles

	RD (N=214)	Rd (N=208)	Odds ratio	P value
Overall response rate (complete or partial)	79%	68.3%	1.75 (80% CI, 1.30-2.32)	0.008

☞ Although the difference(10.7%) in response rates is lower than 15%, the odds ratio for response of 1.75 indicates that low-dose therapy is inferior **in terms of overall response rate** because the preplanned inferiority odds ratio of 1.91 is well within the CI.

23

Rajkumar SV, et al. *Lancet Oncol.* 2010;11(1):29-37

Results : Overall Survival

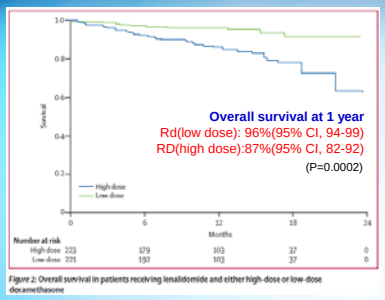


Figure 2: Overall survival in patients receiving lenalidomide and either high-dose or low-dose dexamethasone

☞ As a result, the trial was stopped and patients on high-dose therapy were crossed over to low-dose therapy.

24

Rajkumar SV, et al. *Lancet Oncol.* 2010;11(1):29-37

Results : Overall Survival

Table. Multivariate analysis of overall survival

	Hazard ratio (95% CI)	p value
Low dose vs high dose	0·40 (0·23-0·70)	0·001
ISS stage*		0·02
Stage II/III vs stage I	3·51 (1·49-8·28)	
Stage missing vs stage I	2·68 (0·80-8·95)	
ECOG performance status (1 or 2 vs 0)	1·65 (0·95-2·89)	0·08
Age (≥65 vs <65 years)	2·02 (1·15-3·57)	0·02
Race (white vs non-white)	2·69 (0·97-7·47)	0·06

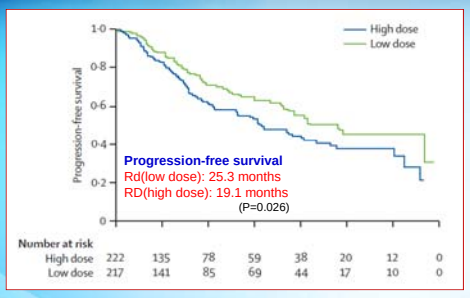
*Global p value. ISS=international staging system.

Table 2: Multivariate analysis of overall survival

25

Rajkumar SV, et al. *Lancet Oncol.* 2010;11(1):29-37

Results : Progression-free Survival



Progression-free survival
Rd(low dose): 25.3 months
RD(high dose): 19.1 months
(P=0.026)

☞ The higher response rates for high-dose dexamethasone did not translate into superior progression-free survival.

26

Rajkumar SV, et al. *Lancet Oncol.* 2010;11(1):29-37

Results : Toxicities

Table. Major grade 3 or higher toxicity

	High dose (N=223)	Low dose (N=220)	P value
Any grade 3 or higher in first 4 months	117(52%)	76(35%)	0.0001
Early mortality(first 4 months)	12(5%)	1	0.003
Deep-vein thrombosis or pulmonary embolism	57(26%)	27(12%)	0.0003
Infection or pneumonia	35(16%)	20(9%)	0.04
Fatigue	33(15%)	20(9%)	0.08

27

Rajkumar SV, et al. *Lancet Oncol.* 2010;11(1):29-37

Conclusion

- **Low-dose dexamethasone**
  - Time to progression
  - Progression-free survival
  - Overall survival
- Overall survival at 1 year was significantly better with low-dose than with high-dose dexamethasone, resulting in **early closure of the study** and **crossover to low-dose dexamethasone**.
- **High-dose** vs. low-dose dexamethasone
  - More toxic
  - More early deaths in the first 4 months
  - Increased risk of thromboembolic complications
  - Higher overall risk of serious adverse events

28

Rajkumar SV, et al. *Lancet Oncol.* 2010;11(1):29-37

Conclusion

- **Lenalidomide plus low-dose dexamethasone**
  : better short-term overall survival and with lower toxicity than lenalidomide plus high-dose dexamethasone in patients with newly diagnosed myeloma.

☞ ***Active regimen for newly diagnosed myeloma with acceptable toxicity and low early mortality***

29

Multiple Myeloma: Induction therapy

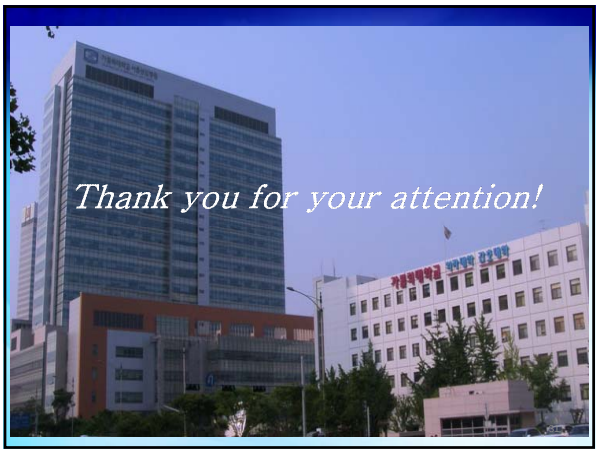
▪ Transplant eligible

- Bortezomib/dexa
- Bortezomib/doxorubicin/dexa
- Bortezomib/lenalidomide/dexa
- Bortezomib/thalidomide/dexa
- Lenalidomide/dexa
- Thalidomide/dexa
- Liposomal doxorubicin/vincristine /dexa

▪ Transplant ineligible

- Melphalan/prednisone
- Melphalan/prednisolone/bortezomib
- Melphalan/prednisolone/thalidomide
- Lenalidomide/low-dose dexa
- Doxorubicin/vincristine/dexa
- Thalidomide/dexa
- Liposomal doxorubicin/vincristine /dexa

NCCN Practice Guidelines in Oncology. Multiple Myeloma. V.3.2010


Thank you for your attention!