VOLUME 30 · NUMBER 20 · JULY 10 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Superiority of the Triple Combination of Bortezomib-Thalidomide-Dexamethasone Over the Dual Combination of Thalidomide-Dexamethasone in Patients With Multiple Myeloma Progressing or Relapsing After Autologous Transplantation: The MMVAR/IFM 2005-04 Randomized Phase III Trial From the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation

Laurent Garderet, Simona Iacobelli, Philippe Moreau, Mamoun Dib, Ingrid Lafon, Dietger Niederwieser, Tamas Masszi, Jean Fontan, Mauricette Michallet, Alois Gratwohl, Giuseppe Milone, Chantal Doyen, Brigitte Pegourie, Roman Hajek, Philippe Casassus, Brigitte Kolb, Carine Chaleteix, Bernd Hertenstein, Francesco Onida, Heinz Ludwig, Nicolas Ketterer, Christian Koenecke, Marleen van Os, Mohamad Mohty, Andrew Cakana, Norbert Claude Gorin, Theo de Witte, Jean Luc Harousseau, Curly Morris, and Gösta Gahrton

See accompanying editorial on page 2434; listen to the podcast by Dr Richardson at www.jco.org/podcasts

Author affiliations appear at the end of this article.

Submitted June 7, 2011; accepted March 1, 2012; published online ahead of print at www.jco.org on May 14, 2012.

Written on behalf of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation.

Supported by Johnson & Johnson and Celgene.

Presented at the 37th Annual Meeting of the European Group for Blood and Marrow Transplantation, Paris, France, April, 3-6, 2011.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

Corresponding author: Laurent Garderet, MD, Hôpital Saint Antoine, Département d'hématologie, 184, rue du Faubourg Saint Antoine, 75012 Paris, France; e-mail: laurent.garderet@sat.aphp.fr.

0732-183X/12/3020-2475/$20.00

DOI: 10.1200/JCO.2011.37.4918

ABSTRACT

Purpose
This prospective multicenter phase III study compared the efficacy and safety of a triple combination (bortezomib-thalidomide-dexamethasone [VTD]) versus a dual combination (thalidomide-dexamethasone [TD]) in patients with multiple myeloma (MM) progressing or relapsing after autologous stem-cell transplantation (ASCT).

Patients and Methods
Overall, 269 patients were randomly assigned to receive bortezomib (1.3 mg/m^2 intravenous bolus) or no bortezomib for 1 year, in combination with thalidomide (200 mg per day orally) and dexamethasone (40 mg orally once a day on 4 days once every 3 weeks). Bortezomib was administered on days 1, 4, 8, and 11 with a 10-day rest period (day 12 to day 21) for eight cycles (6 months), and then on days 1, 8, 15, and 22 with a 20-day rest period (day 23 to day 42) for four cycles (6 months).

Results
Median time to progression (primary end point) was significantly longer with VTD than TD (19.5 *v* 13.8 months; hazard ratio, 0.59; 95% CI, 0.44 to 0.80; $P = .001$), the complete response plus near-complete response rate was higher (45% *v* 21%; $P = .001$), and the median duration of response was longer (17.9 *v* 13.4 months; $P = .04$). The 24-month survival rate was in favor of VTD (71% *v* 65%; $P = .093$). Grade 3 peripheral neuropathy was more frequent with VTD (29% *v* 12%; $P = .001$) as were the rates of grades 3 and 4 infection and thrombocytopenia.

Conclusion
VTD was more effective than TD in the treatment of patients with MM with progressive or relapsing disease post-ASCT but was associated with a higher incidence of grade 3 neurotoxicity.

J Clin Oncol 30:2475-2482. © 2012 by American Society of Clinical Oncology

INTRODUCTION

Patients with multiple myeloma (MM) often respond to initial therapy; however, the disease ultimately recurs and, over the course of time, becomes refractory to further treatment. Median survival is 5 years. There is thus an urgent need for more effective therapies in both first-line and relapsed settings.[1-3]

Thalidomide, an immunomodulatory drug, was the first new drug to bring about an improvement in

the therapy of MM after the introduction of melphalan and prednisone in the 1960s and of vincristine, doxorubicin, and dexamethasone in the 1980s.[4,5] In patients with relapsed or refractory MM receiving thalidomide, the complete response plus partial response (CR + PR) rate was 29%, and the 12-month event-free and overall survival (OS) rates were 34% and 59%, respectively.[6] Addition of dexamethasone to thalidomide enhanced response rates to within the range of 45% to 57%.[7]

Bortezomib ((Velcade; Millennium Pharmaceuticals, Cambridge, MA, and Johnson & Johnson Pharmaceutical Research & Development, Raritan, NJ) is a first-in-class proteasome inhibitor. Approval in the relapsed setting was based on the international phase III APEX trial of bortezomib versus high-dose dexamethasone in patients with MM who had received one to three prior therapies.[8,9] Bortezomib demonstrated superior time to progression (TTP) and a 6-month survival benefit over dexamethasone alone, despite more than 62% of patients crossing over from the dexamethasone arm to receive bortezomib. The bortezomib response rate (CR + PR), based on European Group for Blood and Marrow Transplantation (EBMT) criteria, was 43%, with 9% CR, 7% near-CR (nCR), and 27% PR. Furthermore, combining bortezomib and dexamethasone (VD) showed added benefit, even in patients refractory to prior dexamethasone treatment.[10]

Preclinical studies have shown synergistic effects on adding an immunomodulatory drug (eg, thalidomide or lenalidomide) to bortezomib.[11] These two types of drug have different but overlapping mechanisms of anti-MM activity. In addition, both bortezomib and immunomodulatory drugs are able to enhance dexamethasone activity during all phases of MM. The results of small clinical trials have shown that even better response rates are achieved with a triple-drug combination that includes bortezomib, dexamethasone, and an immunomodulatory drug or an alkylator (eg, cyclosphosphamide) than with a two-drug combination (thalidomide-dexamethasone or bortezomib-dexamethasone).[12-14]

Available studies so far have not specifically addressed the subpopulation of patients with MM progressing or relapsing after autologous stem-cell transplantation (ASCT). We report the results of a multicenter phase III prospective randomized trial comparing the efficacy and safety of the triple combination of bortezomib-thalidomide-dexamethasone (VTD) versus the standard two-drug combination of thalidomide-dexamethasone (TD) in these patients. The primary end point was TTP.

PATIENTS AND METHODS

Patients

Patients with confirmed MM and measurable disease were eligible if they had progressed or relapsed after at least one ASCT and provided it was their first progression or relapse. Previous allogeneic transplantation was prohibited. A Karnofsky performance status above 50%, platelets at or higher than 40,000/μL, absolute neutrophil count at or higher than 1,000/μL, and creatinine clearance at or higher than 30 mL/min were required. Exclusion criteria included grade 2 or higher peripheral neuropathy. On retrospective analysis, 31 patients did not meet these criteria, that is, 15 patients had neuropathy above grade 1, six had impaired hematopoiesis, four had impaired kidney function, five patients were in second relapse, and one had nonsecretory MM. These deviations were evenly distributed in both arms and, since the deviations were considered minor, all patients originally included were analyzed. Women of childbearing age had to use a method of birth control and have a negative serum or urine beta-human chorionic gonadotropin pregnancy test at screening and throughout the study. Men had to use contraception. Review boards at participating institutions and regulatory authorities approved the study, which was conducted according to the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice Guidelines. All patients provided written informed consent.

Study Design and Treatment

This international randomized, controlled, open-label study enrolled 269 patients from 60 centers and randomly assigned them to the triple combination VTD or to the dual combination TD (CONSORT diagram; Fig 1). Patients were stratified by number of previous ASCTs and by center at screening. All patients received thalidomide scheduled at 200 mg per day orally for 1 year and dexamethasone 40 mg per day orally for four days every 3 weeks for 1 year. Patients assigned to VTD received 1.3 mg/m^2 bortezomib as an intravenous bolus on days 1, 4, 8, and 11 followed by a 10-day rest period (day 12 to day 21) for eight cycles (6 months) and then on days 1, 8, 15, and 22 followed by a 20-day rest period (day 23 to day 42) for four cycles (6 months). Antithrombotic prophylaxis was mandatory in both arms. Enoxaparin (40 mg per day subcutaneously) was used for primary prophylaxis, and warfarin was used for secondary prophylaxis. Prophylaxis against herpes zoster infection was highly recommended in the VTD arm. Transfusion support as well as neutrophils and erythropoietic growth factors were allowed. Bisphosphonates were used according to established guidelines. Dose reduction strategies were recommended for significant toxicities.

Study treatment continued for 1 year. Treatment was withheld on withdrawal of the patient's consent, disease progression, or the occurrence of any grade 4 toxic effects. Patients who were still responding after 1 year of treatment could continue, provided that treatment was tolerated. A new transplantation, either autologous or allogeneic, could be performed only in patients who completed the planned 1-year treatment. The study did not allow crossover from the TD arm to the VTD arm.

The primary end point was TTP, defined as the interval from random assignment to disease progression, and was assessed on the intent-to-treat (ITT) population. Secondary end points included progression-free survival (PFS), defined as time from random assignment to progression or death from any cause, OS, defined as the interval from random assignment to death from any cause, overall response rate (CR + PR), and safety.

Assessments

Progression and response were determined according to EBMT criteria[15] with reference to investigator-reported TTP or response reports. Two additional PR subcategories were defined. The nCR category was a PR subcategory meeting all CR criteria except for a positive immunofixation. The very good partial response (VGPR) subcategory (International Myeloma Working Group [IMWG] criteria) was a PR subcategory attained by patients who had had a 90% or greater reduction in their serum M-component since diagnosis. All patients, including those who discontinued treatment, were followed up for progression every 3 weeks for the first 6 months and every 6 weeks thereafter. Safety, assessed in all patients who received one or more drug doses until 30 days after the last dose, was graded according to National Cancer Institute Common Toxicity Criteria (NCI CTC, version 3).

Statistical Analysis

The study was designed to provide 90% power to detect a hazard ratio (HR) of 0.67 (VTD *v* TD) for TTP at a one-sided overall significance level of 0.025. Four interim analyses were planned to test for efficacy and futility using an alpha-spending function as for O'Brien-Fleming–type boundaries (for details, see Fig 1; implementation in EAST v 3.1.0, Cambridge, MA). The trial was stopped for superiority of VTD over TD after the second interim analysis performed after 134 events and a median follow-up of 24 months.

Median TTP was estimated from the cumulative incidence curve for progression (death without progression was a competing risk). The adjusted analysis was performed on the stratified Cox regression for the cause-specific hazard. Similar methods for competing risk end points were used to calculate time to achievement of response (with death and progression as competing events). The Kaplan-Meier probability estimator and Cox models were used to

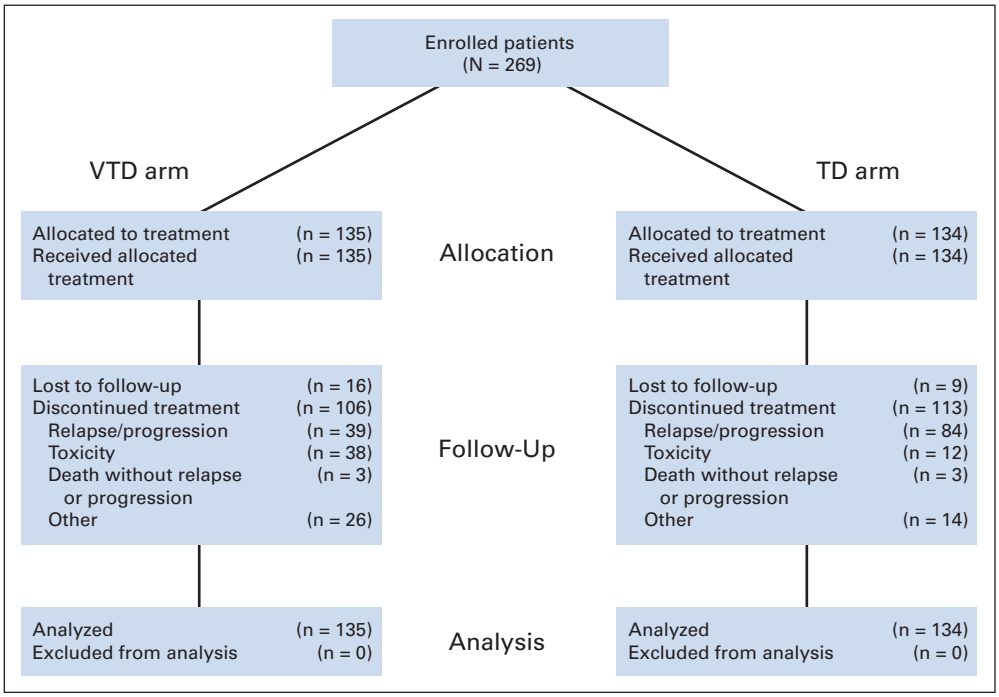

Fig 1. CONSORT diagram for MMVAR (Multiple Myeloma Velcade At Relapse) trial. TD, thalidomide-dexamethasone; VTD, bortezomib-thalidomide-dexamethasone.

calculate PFS, OS, and duration of response (DOR). All analyses were performed using R v 2.10.0 software (http://www.r-project.org).

RESULTS

Patients and Treatment

From January 2006 to July 2010, 135 and 134 patients were randomly assigned to VTD and TD, respectively (Fig 1). Their baseline demographic data and other characteristics, including number of prior ASCTs, were well balanced (Table 1). Median follow-up at the last update (March 2, 2011) was 30 months (range, 1 to 62 months) with 22 patients still being treated (11 in each arm).

Efficacy (ITT population)

Median TTP was longer in patients receiving VTD than TD (19.5 *v* 13.8 months). VTD reduced the risk of developing disease progression by 40% (HR, 0.59; 95% CI, 0.44 to 0.80; $P = .001$; Fig 2A). Median PFS was significantly longer for VTD than TD (18.3 months [95% CI, 15.5 to 20.6 months] *v* 13.6 months [95% CI, 9.9 to 16.1 months]; HR, 0.61; 95% CI, 0.45 to 0.81; $P = .001$; Fig 2B). During the 1-year treatment period (cutoff, March 2, 2011), we recorded 14 deaths for VTD and 20 deaths for TD, 11 cases versus 17 cases of relapse/progression, three cases versus one case of infection, and zero cases versus two cases of secondary malignancy. The 24-month OS rates were not significantly different (71% [95% CI, 63% to 81%] for VTD *v* 65% [95% CI, 57% to 75%] for TD; $P = .093$; Fig 2C). Median TTP was longer in patients receiving VTD than TD regardless of the number of previous ASCTs (one or more; Fig 3).

Complete response (CR + nCR) rate was higher for VTD than for TD (45% *v* 25%; $P = .001$), and the median DOR was longer (17.2 *v* 13.4 months; $P = .03$). If the VGPRs were included with the complete responders (CR + nCR), the response rate rose to 56% for VTD and 35% for TD ($P < .001$; Table 2). Median time to first response (PR or better) was significantly shorter in patients treated with VTD than in those treated with TD (1.5 *v* 2.6 months; $P \leq .001$).

In a multivariate analysis of the overall study population, randomization to receive VTD was the key independent variable positively related to a better TTP (HR, 0.47; 95% CI, 0.31 to 0.72; $P < .001$). The variables related to a worse TTP were high β2-microglobulin (for the logarithm: HR, 2.41; 95% CI, 1.63 to 3.58; $P < .001$), high International Staging System score (HR, 1.53; 95% CI, 1.16 to 2.02; $P = .02$), and a chromosome 13 deletion (HR, 2.3; 95% CI, 1.49 to 3.57; $P < .001$). A secondary analysis showed that early relapse, within 1 year from last ASCT, remained a bad prognosis parameter, but this risk factor had a lower impact in the VTD group.

Drug Exposure, Patient Disposition, and Safety

The median number of treatment cycles received was 6.25 (6.25 of 8; 78%) in the VTD arm and 6.88 (6.88 of 8; 86%) in the TD arm during the first 6 months of treatment. It was 7.56 (7.56 of 12; 63%) for VTD and 9.93 (9.93 of 16; 62%) for TD at the end of the 1-year treatment period. The percentage of patients receiving planned doses was as follows: 46.6% bortezomib, 40.6% thalidomide, and 78.9% dexamethasone when randomly assigned to VTD therapy and 55.8% thalidomide and 76.7% dexamethasone when randomly assigned to TD. The percentage of patients in whom doses were reduced ($\leq$ 1.0 mg/m^2 bortezomib, $\leq$ 100 mg per day thalidomide) was as follows: in the VTD arm, 6% for bortezomib, 22% for thalidomide, and 28% for both bortezomib and thalidomide; in the TD arm, 30% for thalidomide. The highest toxicity occurred after cycle 4 in the VTD arm and after cycle 6 in the TD arm. Because of AEs, 38 patients (28%) discontinued VTD treatment and 12 patients (9%) discontinued TD before the end of the planned 1-year treatment period.

Table 1. Baseline Characteristics of Patients With Multiple Myeloma According to Treatment Group

Characteristic	VTD (n = 135)		TD (n = 134)		Total (N = 269)	
	No.	%	No.	%	No.	%
No. of previous autologous transplantations						
1	71	53	71	53	142	53
≥ 2	64	47	63	47	127	47
Age, years						
Median	60.0		62.6		61.2	
Range	29-76		39-75		29-76	
Sex						
Male	86	64	83	62	169	63
Female	49	36	51	38	100	37
Type of myeloma						
IgG	86	66	77	61	163	64
IgA	23	18	31	25	54	21
Light chain	21	16	17	14	38	15
Interval from diagnosis to random assignment, years						
Median	2.97		3.24		3.10	
Range	0.7-13.3		0.7-18.1		0.7-18.1	
Interval from transplantation to random assignment, months						
Median	24.75		24.21		24.55	
Range	2.2-122.5		3.4-153.6		2.2-153.6	
Karnofsky status*						
≤ 80	44	36	46	39	90	37
> 80	78	64	73	61	151	63
Prior treatment						
Bortezomib	26	20	28	21	54	20
Thalidomide	14	10	8	6	22	8
Cytogenetics*						
Normal	32	36	39	48	71	41
Abnormal	58	64	43	52	101	59
FISH deletion 13*						
Absent	56	55	60	67	116	61
Present	45	45	29	33	74	39
Serum β_2-microglobulin, mg/L*						
< 3.5	72	65	63	62	135	64
3.5-5.5	23	21	20	20	43	20
≥ 5.5	15	14	18	18	33	16
ISS score*						
I	63	59	56	56	119	58
II	28	27	26	26	54	26
III	15	14	18	18	33	16
Disease status at transplantation						
CR	15	12	16	13	31	12
PR	95	77	89	71	184	74
MR	8	6	7	6	15	6
Stable or progressive disease	6	5	13	10	19	8
Hemoglobin, g/dL						
Median	11.9		12.0		11.9	
Range	7.9-15.8		6.9-16.5		6.9-16.5	
Platelet count × 10^9/L						
Median	195		198		196	
Range	34-419		45-394		34-419	
Serum creatinine, μmol/L						
Median	79.6		80.0		79.6	
Range	2.3-857		3.2-663		2.3-857	

Abbreviations: CR, complete response; FISH, fluorescent in situ hybridization; Ig, immunoglobulin; ISS, International Staging System; MR, minimal response; PR, partial response; TD, thalidomide-dexamethasone; VTD, bortezomib-thalidomide-dexamethasone.
*More than 10% of data missing.

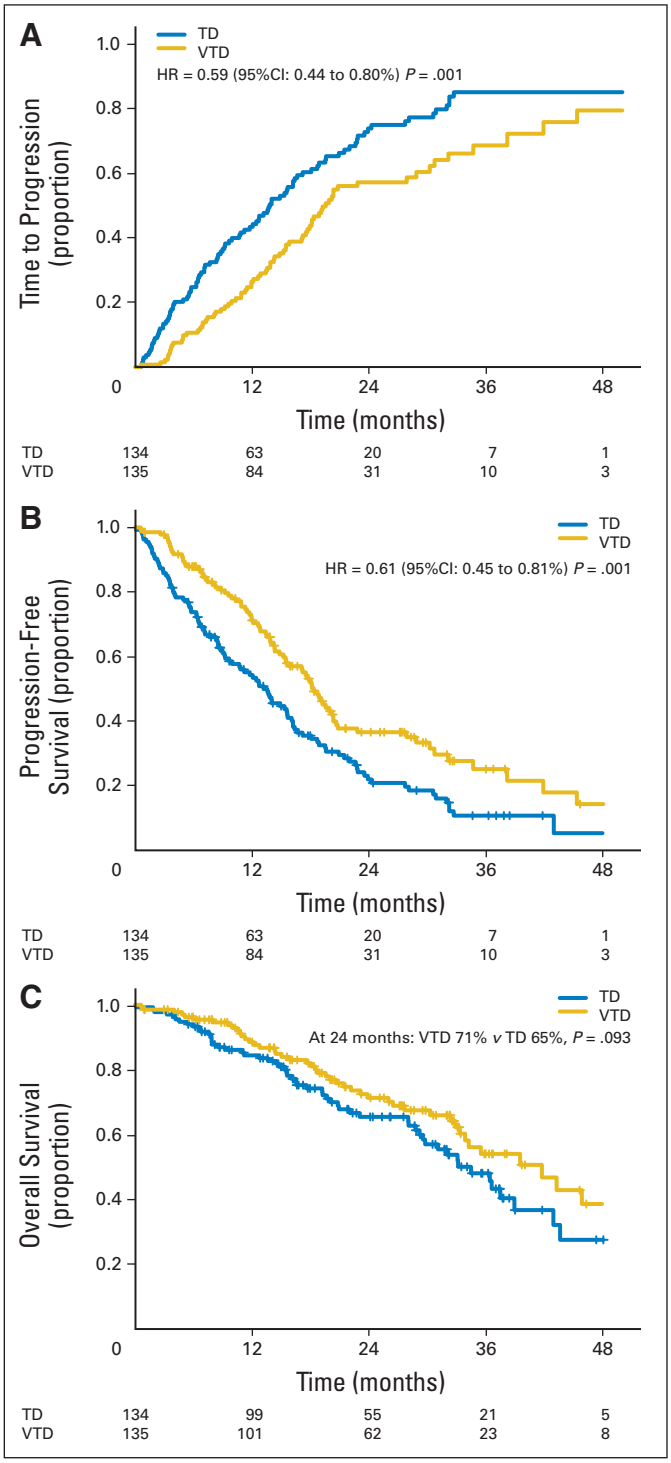

Fig 2. Comparison of the triple (bortezomib-thalidomide-dexamethasone) and dual (thalidomide-dexamethasone) treatment groups. (A) Cumulative incidence for time to progression; (B and C) Kaplan-Meier plots for progression-free survival and overall survival. HR, hazard ratio (from the stratified Cox model); TD, thalidomide-dexamethasone; VTD, bortezomib-thalidomide-dexamethasone.

The incidence of AEs is given in Table 3. The incidence of grade 4 AEs was relatively low. Severe myelosuppression was uncommon, and grade 4 neutropenia, related febrile neutropenia, and sepsis were rare. The most clinically significant AE was cumulative, dose-related, peripheral sensory neuropathy (Table 4). Thrombocytopenia was transient and was not associated with serious bleeding complications. Thromboembolic events were rare: five cases versus 10 cases of deep vein thrombosis and five cases versus two cases of pulmonary embolism for VTD versus TD. Most AEs responded to standard management.

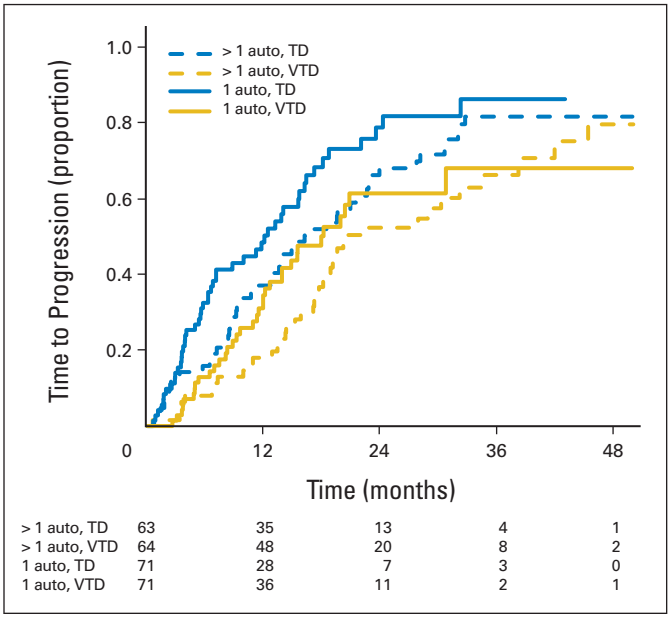

Fig 3. Cumulative incidence curve for time to progression according to the number of previous autologous (auto) transplantations (one or more). TD, thalidomide-dexamethasone; VTD, bortezomib-thalidomide-dexamethasone.

DISCUSSION

This study has shown that patients with MM progressing or relapsing after ASCT have significantly better outcomes if they receive VTD rather than TD. Median TTP was significantly longer (19.5 *v* 13.8

Table 2. Response Rates

Response	VTD (n = 124) No.	VTD (n = 124) %	TD (n = 120) No.	TD (n = 120) %	*P*
CR	35	28	16	13	
Near CR	21	17	9	8	
VGPR	13	11	17	14	
PR	39	32	44	37	
MR	8	6	10	8	
Stable disease	8	6	17	14	
Progressive disease	0	0	7	6	
Test for comparison					
CR		28		13	.004
nCR or better		45		21	< .001
VGPR or better		56		35	.001
PR or better		87		72	.003

Abbreviations: CR, complete response; MR, minimal response; nCR, near-complete response; PR, partial response; TD, thalidomide-dexamethasone; VGPR, very good partial response; VTD, bortezomib-thalidomide-dexamethasone.

Table 3. Overview of Treatment Emergent AEs

Characteristic	VTD (n = 133) No	VTD (n = 133) %	TD (n = 129) No	TD (n = 129) %	P
Any AE	131	98	125	97	.387
Drug-related AE	124	93	108	84	.024
Serious AE	55	41	46	36	.343
Drug-related serious AE	38	29	24	19	.057
Grade 3 or 4 AE	94	71	74	57	.024
Drug-related grade 3 or 4 AE	79	59	47	36	< .001

Abbreviations: AE, adverse event; TD, thalidomide-dexamethasone; VTD, bortezomib-thalidomide-dexamethasone.
Drug-related AE: relationship to study drug(s) either possible, probable, or definite.

months; $P = .001$) as were PFS and DOR ($P = .001$ and $P = .04$, respectively). The hazard of disease progression was reduced by 40% when using the triple combination.

The long TTP (19.5 months) in patients receiving VTD compares favorably with published findings on single or dual bortezomib therapy. The TTP for bortezomib was only 6 months in the APEX trial[9] and 9 months for the combination of bortezomib plus a liposomal anthracycline.[16] Our 19-month TTP is, in fact, even longer than the longest TTP recorded so far, namely for lenalidomide-dexamethasone (13 months in the MM-009 and MM-010 trials).[17,18] However, trial comparisons must be viewed with caution because of differences in study populations, dose intensity, or use of maintenance therapy. Published studies often refer to patient mixes (relapsed and refractory patients with MM), with or without ASCT. All our patients had undergone at least one ASCT. None had refractory disease. These two things together could explain our better results.

A higher efficacy of the VTD combination was observed, even after adjusting for factors for high risk of disease progression (eg, advanced age, increased β2-microglobulin level, prior thalidomide or bortezomib treatment, and chromosome 13 deletion), thus demonstrating that bortezomib provides extra benefit in both good- and poor-prognosis patients.

Table 4. Grade 3 to 4 Adverse Events in Patients Receiving VTD or TD

Adverse Event	VTD (n = 133) Total	VTD (n = 133) Grade 3 to 4 (%)	TD (n = 129) Total	TD (n = 129) Grade 3 to 4 (%)	P
Peripheral neuropathy					
Grade 3	38	29	16	12	.001
Grade 4	3	2	2	2	.676
Infection	18	14	9	7	.08
Thrombocytopenia	22	17	9	7	.016
Neutropenia	15	11	21	16	.239
Anemia	10	8	6	5	.332
Thromboembolism	8	6	7	5	.837
Herpes zoster	1	1	0	0	.323
Gastrointestinal	1	1	1	1	.982
Cardiac	2	2	1	1	.579
Constipation	9	7	7	5	.650
Fatigue	10	8	4	3	.111

Abbreviations: TD, thalidomide-dexamethasone; VTD, bortezomib-thalidomide-dexamethasone.

We observed no significant difference in OS between VTD and TD over a median follow-up of 30 months. Two phase III trials of induction regimens before ASCT have also established superiority of VTD over TD (higher CR rate and lower progressive disease rate, longer TTP and PFS) but not in terms of OS.[19,20] Reasons for the lack of a difference in OS may be a follow-up that is too short, a sample size that is too small, and/or post progression therapy, including bortezomib. However, OS for VTD may yet prove to be greater than that for TD if the follow-up period is prolonged, even in the ITT analysis. An improved OS was observed after prolonged follow-up in the phase III trials of lenalidomide-dexamethasone (MM-009 and MM-010).[21]

Addition of bortezomib to TD more than doubled the CR + nCR rate in our study. An almost three-fold increase in response has been reported in the first-line setting.[20] A CR, or at least a VGPR, in the first-line setting is associated with improved outcomes.[22] Response rates may differ between the first-line and relapsed settings because of differences in tumor biology at diagnosis and relapse after ASCT.

The safety profile of VTD was consistent with the known toxicities of bortezomib and thalidomide. The overall incidence of grade 3 and 4 AEs was greater for VTD than for TD (71% *v* 57%). Severe myelosuppression was uncommon. Grade 4 neutropenia, related febrile neutropenia, and sepsis were rare. Thrombocytopenia was transient and not associated with serious bleeding complications. Appropriate prophylaxis resulted in few thromboembolic events and virtually abrogated the risk of reactivation of varicella-zoster virus infection associated with bortezomib-based therapies.

The most clinically significant AE was cumulative, dose-related peripheral sensory neuropathy (grade 3), which occurred in 29% of patients on VTD and 12% on TD. This was a higher incidence than expected. Above grade 2 neurotoxicity was twice as high in our study (31%) as that reported for thalidomide (6%) or bortezomib (13%).[6-8] Risk factors for peripheral neuropathy include prior occurrence, prior chemotherapy, and age. In the VTD and TD arms of our study, 10% and 6% of patients, respectively, had received thalidomide before inclusion, 20% and 21% had received bortezomib, and 15% and 19% had grade 1 or 2 neuropathy. The high starting doses and the duration of treatment were probably the main causes for higher neurotoxicity. In the patients still receiving VTD after 1 year, 70% were receiving a reduced dose of thalidomide and 54% a reduced dose of bortezomib.

To reduce peripheral neuropathy, it may be prudent to adjust the bortezomib dose or schedule. There are several ways of doing this without having an impact on efficacy. The first is by reducing both bortezomib and thalidomide starting dose: The IFM (Intergroupe Francophone du Myélome) 2007-02 study compared a reduced dose of bortezomib (1 *v* 1.3 mg/m^2 per injection) in a low-dose VTD versus high-dose VD protocol, in which thalidomide (100 mg per day) was given as induction treatment before ASCT. Four cycles of VTD were more effective than four cycles of VD, since the CR + VGPR rate was higher both before and after ASCT. The incidence of polyneuropathy was markedly reduced in the VTD arm despite the addition of thalidomide.[23] The second method—switching from twice-a-week to once-a-week bortezomib—has been shown to markedly reduce the incidence of grades 3 and 4 peripheral neuropathy (from 28% to 8%; $P < .001$) and associated discontinuations (from 15% to 5%; $P < .001$), without having a large impact on CR rate (decrease from 35% to 30%; $P = .27$) or without greatly affecting long-term

outcomes.[24] Third, subcutaneous bortezomib is as effective as intravenous bortezomib and is less neurotoxic.[25,26] In the future, genetic predisposition analysis may help identify patients at greater risk of neuropathy and in whom dose adjustment would be advisable.[27]

An alternative to bortezomib dose reduction is substituting lenalidomide for thalidomide in the triple combination (ie, lenalidomide-bortezomib-dexamethasone) in patients with newly diagnosed MM. The reported incidence of grade 3 neurologic toxic effects after a median of eight cycles of therapy was only 6%.[28] In the relapsed setting, grade 3 to 4 toxicities included 30% neutropenia, 22% thrombocytopenia, and 3% neuropathy. Median TTP was 9.5 months, median PFS was 9.5 months, and the 2-year OS rate was 55%.[29]

To enhance DOR in our study, the first 6 months of bortezomib treatment were followed by a relatively short (6-month) maintenance phase at a lower dose. The maintenance phase may have contributed to the high TTP and prolonged DOR. In three major trials, thalidomide maintenance post-ASCT enhanced response rates and extended event-free survival, PFS, and OS.[30-32] Two prospective randomized studies have shown that post-ASCT maintenance therapy with lenalidomide prolongs PFS and TTP compared with placebo. No improvement has yet been observed in OS.[33,34] Two trials of bortezomib-thalidomide have confirmed the feasibility and efficacy of maintenance therapy.[35,36]

In conclusion, our study has demonstrated the superiority of the triple-combination VTD over the dual TD combination in the treatment of patients with MM progressing or relapsing post-ASCT. However, neurotoxicity is an issue of concern and requires appropriate dose reduction. In light of our experience, we suggest a starting dose of 100 mg per day thalidomide for the VTD combination. This combination may be considered a new standard of care for this subpopulation of patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Andrew Cakana, Johnson & Johnson (C) **Consultant or Advisory Role:** Chantal Doyen, Celgene (C), Janssen-Cilag (C); Mohamad Mohty, Celgene (C), Janssen Pharmaceuticals (C); Gösta Gahrton, Fujimoto Pharmaceutical (C) **Stock Ownership:** Andrew Cakana, Johnson & Johnson **Honoraria:** Philippe Moreau, Celgene, Janssen Pharmaceuticals, Millennium Pharmaceuticals; Heinz Ludwig, Janssen-Cilag; Mohamad Mohty, Celgene, Janssen Pharmaceuticals; Curly Morris, Celgene, Janssen Pharmaceuticals **Research Funding:** Mohamad Mohty, Celgen, Janssen Pharmaceuticals **Expert Testimony:** None **Other Remuneration:** Curly Morris, Celgene, Janssen Pharmaceuticals

AUTHOR CONTRIBUTIONS

Conception and design: Laurent Garderet, Mauricette Michallet, Alois Gratwohl, Christian Koenecke, Jean Luc Harousseau
Administrative support: Marleen van Os, Mohamad Mohty
Provision of study materials or patients: Laurent Garderet, Philippe Moreau, Mamoun Dib, Ingrid Lafon, Dietger Niederwieser, Tamas Masszi, Jean Fontan, Mauricette Michallet, Alois Gratwohl, Giuseppe Milone, Chantal Doyen, Brigitte Pegourie, Roman Hajek, Philippe Casassus, Brigitte Kolb, Carine Chaleteix, Bernd Hertenstein, Francesco Onida, Heinz Ludwig, Nicolas Ketterer, Christian Koenecke, Mohamad Mohty
Collection and assembly of data: Marleen van Os
Data analysis and interpretation: Laurent Garderet, Simona Iacobelli, Philippe Moreau, Mamoun Dib, Ingrid Lafon, Dietger Niederwieser, Tamas Masszi, Jean Fontan, Mauricette Michallet, Alois Gratwohl, Giuseppe Milone, Chantal Doyen, Brigitte Pegourie, Roman Hajek, Philippe Casassus, Brigitte Kolb, Carine Chaleteix, Bernd Hertenstein, Francesco Onida, Heinz Ludwig, Nicolas Ketterer, Mohamad Mohty, Andrew Cakana, Norbert Claude Gorin, Theo de Witte, Curly Morris, Gösta Gahrton
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Kumar SK, Rajkumar SV, Dispenzieri A, et al: Improved survival in multiple myeloma and the impact of novel therapies. Blood 111:2516-2520, 2008
2. Laubach JP, Mahindra A, Mitsiades CS, et al: The use of novel agents in the treatment of relapsed and refractory multiple myeloma. Leukemia 23: 2222-2232, 2009
3. Kastritis E, Palumbo A, Dimopoulos MA: Treatment of relapsed/refractory multiple myeloma. Semin Hematol 46:143-157, 2009
4. Hus I, Dmoszynska A, Manko J, et al: An evaluation of factors predicting long-term response to thalidomide in 234 patients with relapsed or resistant multiple myeloma. Br J Cancer 91:1873-1879, 2004
5. Cibeira MT, Rosiñol L, Ramiro L, et al: Long-term results of thalidomide in refractory and relapsed multiple myeloma with emphasis on response duration. Eur J Haematol 77:486-492, 2006
6. Glasmacher A, Hahn C, Hoffmann F, et al: A systematic review of phase-II trials of thalidomide monotherapy in patients with relapsed or refractory multiple myeloma. Br J Haematol 132:584-593, 2006
7. von Lilienfeld-Toal M, Hahn-Ast C, Furkert K, et al: A systematic review of phase II trials of thalidomide/dexamethasone combination therapy in patients with relapsed or refractory multiple myeloma. Eur J Haematol 81:247-252, 2008
8. Richardson PG, Barlogie B, Berenson J, et al: A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med 348:2609-2617, 2003
9. Richardson PG, Sonneveld P, Schuster MW, et al: Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 352:2487-2498, 2005
10. Jagannath S, Richardson PG, Barlogie B, et al: Bortezomib in combination with dexamethasone for the treatment of patients with relapsed and/or refractory multiple myeloma with less than optimal response to bortezomib alone. Haematologica 91: 929-934, 2006
11. Richardson PG, Mitsiades C, Ghobrial I, et al: Beyond single-agent bortezomib: Combination regimens in relapsed multiple myeloma. Curr Opin Oncol 18:598-608, 2006
12. Ciolli S, Leoni F, Gigli F, et al: Low dose Velcade, thalidomide and dexamethasone (LD-VTD): An effective regimen for relapsed and refractory multiple myeloma patients. Leuk Lymphoma 47: 171-173, 2006
13. Pineda-Roman M, Zangari M, van Rhee F, et al: VTD combination therapy with bortezomib-thalidomide-dexamethasone is highly effective in advanced and refractory multiple myeloma. Leukemia 22:1419-1427, 2008
14. Ladetto M, Pagliano G, Ferrero S, et al: Major tumor shrinking and persistent molecular remissions after consolidation with bortezomib, thalidomide, and dexamethasone in patients with autografted myeloma. J Clin Oncol 28:2077-2084, 2010
15. Bladé J, Samson D, Reece D, et al: Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation:

Myeloma Subcommittee of the EBMT, European Group for Blood and Marrow Transplant. Br J Haematol 102:1115-1123, 1998

16. Orlowski RZ, Nagler A, Sonneveld P, et al: Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: Combination therapy improves time to progression. J Clin Oncol 25:3892-3901, 2007

17. Weber DM, Chen C, Niesvizky R, et al: Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 357:2133-2142, 2007

18. Dimopoulos M, Spencer A, Attal M, et al: Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 357: 2123-2132, 2007

19. Rosiñol L, Cibeira MT, Martinez J, et al: Thalidomide/dexamethasone (TD) vs. bortezomib (Velcade)/thalidomide/dexamethasone (VTD) vs VBMCP/VBAD/Velcade as induction regimens prior autologous stem cell transplantation (ASCT) in multiple myeloma (MM): Results of a phase III PETHEMA/GEM trial. Blood 114:59a, 2009 (abstr 130)

20. Cavo M, Tacchetti P, Patriarca F, et al: Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: A randomized phase 3 study. Lancet 376:2075-2085, 2010

21. Dimopoulos MA, Chen C, Spencer A, et al: Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia 23:2147-2152, 2009

22. Chanan-Kahn AA, Giralt S: Importance of achieving a complete response in multiple myeloma, and the impact of novel agents. J Clin Oncol 28:2612-2624, 2010

23. Moreau P, Facon T, Attal M, et al: Comparison of reduced-dose bortezomib plus thalidomide plus dexamethasone (vTD) to bortezomib plus dexamethasone (VD) as inductions treatment prior to ASCT in de novo multiple myeloma (MM): Results of IFM2007-02 study. J Clin Oncol 28:576s, 2010 (suppl; abstr 8014)

24. Bringhen S, Larocca A, Rossi D, et al: Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. Blood 116:4745-4753, 2010

25. Moreau P, Coiteux V, Hulin C, et al: Prospective comparison of subcutaneous versus intravenous administration of bortezomib in patients with multiple myeloma. Haematologica 93:1908-1911, 2008

26. Moreau P, Pylypenko H, Grosicki S, et al: Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: A randomised, phase 3, non-inferiority study. Lancet Oncol 12:431-440, 2011

27. Johnson DC, Corthals SL, Walker BA, et al: Genetic factors underlying the risk of thalidomide-related neuropathy in patients with multiple myeloma. J Clin Oncol 29:797-804, 2011

28. Richardson PG, Weller E, Lonial S, et al: Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood 116:679-686, 2010

29. Richardson PG, Jagannath S, Jakubowiak AJ, et al: Phase II trial of lenalidomide, bortezomib, and dexamethasone in patients (pts) with relapsed and relapsed/refractory multiple myeloma (MM): Updated efficacy and safety data after > 2 years of follow-up. Blood 116, 2010 (abstr 3049)

30. Attal M, Harousseau JL, Leyvraz S, et al: Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood 108:3289-3294, 2006

31. Barlogie B, Tricot G, Anaissie E, et al: Thalidomide and hematopoietic-cell transplantation for multiple myeloma. N Engl J Med 354:1021-1030, 2006

32. Spencer A, Prince HM, Roberts AW, et al: Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. J Clin Oncol 27:1788-1793, 2009

33. Attal M, Cristini C, Marit G, et al: Lenalidomide maintenance after transplantation for myeloma. J Clin Oncol 28:577s, 2010 (suppl; abstr 8018)

34. McCarthy PL, Owzar K, Anderson KC, et al: Phase III intergroup study of lenalidomide versus placebo maintenance therapy following single autologous stem cell transplant (ASCT) for multiple myeloma (MM): CALGB 100104. J Clin Oncol 28:577s, 2010 (suppl; abstr 8017)

35. Palumbo A, Bringhen S, Rossi D, et al: Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: A randomized controlled trial. J Clin Oncol 28:5101-5109, 2010

36. Mateos MV, Oriol A, Martínez-López J, et al: Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: A randomised trial. Lancet Oncol 11:934-941, 2010

Affiliations

Laurent Garderet and Norbert Claude Gorin, University Hospital Saint-Antoine, Paris; Philippe Moreau, Mohamad Mohty, and Jean Luc Harousseau, University Hospital Nantes, Nantes; Mamoun Dib, University Hospital Angers, Angers; Ingrid Lafon, University Hospital Dijon, Dijon; Jean Fontan, University Hospital Besançon, Besançon; Mauricette Michallet, University Hospital Lyon, Lyon; Brigitte Pegourie, University Hospital Grenoble, Grenoble; Philippe Casassus, University Hospital Bobigny, Bobigny; Brigitte Kolb, University Hospital Reims, Reims; Carine Chaleteix, University Hospital Clermont-Ferrand, Clermont-Ferrand, France; Simona Iacobelli, Centro Biostatistica e Bioinformatica, Università di Roma Tor Vergata, Rome; Giuseppe Milone, Ospedale Ferrarotto Catania, Catania; Francesco Onida, University Hospital Milano, Milano, Italy; Dietger Niederwieser, University of Leipzig, Leipzig; Bernd Hertenstein, University Hospital Bremen, Bremen; Christian Koenecke, University Hospital Hannover, Hannover, Germany; Tamas Masszi, St István and St Laszlo Hospital of Budapest, Budapest, Hungary; Alois Gratwohl, University Hospital Basel, Basel; Nicolas Ketterer, University Hospital of Lausanne, Lausanne, Switzerland; Chantal Doyen, University Hospital Mont Godinne, Yvoir; Andrew Cakana, Johnson & Johnson, Beerse, Belgium; Roman Hajek, University Hospital Brno, Brno, Czech Republic; Heinz Ludwig, Wilhelminenspital Vienna, Vienna, Austria; Marleen van Os, Leiden University Medical Center, Leiden; Theo de Witte, University of Nijmegen, Nijmegen, the Netherlands; Curly Morris, The Queen's University Belfast, Belfast, Ireland; and Gösta Gahrton, Karolinska University Hospital, Huddinge, Sweden.

