VOLUME 27 · NUMBER 22 · AUGUST 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

From the Centre Hospitalier Universitaire, Nancy; Centre Hospitalier Universitaire, Lille; Centre Hospitalier, Blois; Centre Hospitalier Universitaire, Grenoble; Centre Hospitalier Universitaire, Tours; Centre Hospitalier Universitaire, Angers; Centre Hospitalier Universitaire, Brest; Centre Hospitalier Chalon sur Saône; Centre Hospitalier Universitaire, Reims; Centre Henri Becquerel, Rouen; Centre Hospitalier Universitaire, Bobigny; Centre Hospitalier Universitaire, Poitiers; Centre Hospitalier Universitaire, Rennes; Centre Hospitalier Universitaire Saint-Antoine; Institut Curie, Paris; Centre Hospitalier Universitaire Besancon; Centre Hospitalier Universitaire, Dijon; Centre Hospitalier Universitaire, Nantes, France; and the Cliniques Universitaire de Mont-Godinne, Yvoir, Belgium.

Submitted November 18, 2008; accepted February 9, 2009; published online ahead of print at www.jco.org on May 18, 2009.

Written on behalf of the Intergroupe Francophone du Myelome.

Sponsored by the Centre Hospitalier Universitaire de Nancy; by a research grant from the French Ministry of Health (Projet Hospitalier de Recherche Clinique, CHRU Nancy 2001, No. 04.9702); by Laphal; by Pharmion; and by Celgene, which supplied free experimental treatment (thalidomide or placebo) for the study.

Presented in part in abstract format at the American Society of Clinical Oncology, Chicago, IL, June 1-5, 2007; XIth International Myeloma Workshop, Kos Island, Greece, June 25-30, 2007; and the American Society of Hematology, Atlanta, GA, December 8-11, 2007.

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: Cyrille Hulin, MD, Service d'Hématologie, rue du Morvan, Centre Hospitalier Universitaire de Nancy–Brabois, 54511 Vandoeuvre, France; e-mail: c.hulin@chu-nancy.fr.

The Acknowledgment is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

0732-183X/09/2722-3664/$20.00

DOI: 10.1200/JCO.2008.21.0948

Efficacy of Melphalan and Prednisone Plus Thalidomide in Patients Older Than 75 Years With Newly Diagnosed Multiple Myeloma: IFM 01/01 Trial

Cyrille Hulin, Thierry Facon, Philippe Rodon, Brigitte Pegourie, Lotfi Benboubker, Chantal Doyen, Mamoun Dib, Gaelle Guillerm, Bruno Salles, Jean-Paul Eschard, Pascal Lenain, Philippe Casassus, Isabelle Azaïs, Olivier Decaux, Laurent Garderet, Claire Mathiot, Jean Fontan, Ingrid Lafon, Jean Marc Virion, and Philippe Moreau

ABSTRACT

Purpose
Until recently, melphalan and prednisone were the standards of care in elderly patients with multiple myeloma. The addition of thalidomide to this combination demonstrated a survival benefit for patients age 65 to 75 years. This randomized, placebo-controlled, phase III trial investigated the efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed myeloma.

Patients and Methods
Between April 2002 and December 2006, 232 previously untreated patients with myeloma, age 75 years or older, were enrolled and 229 were randomly assigned to treatment. All patients received melphalan (0.2 mg/kg/d) plus prednisone (2 mg/kg/d) for 12 courses (day 1 to 4) every 6 weeks. Patients were randomly assigned to receive 100 mg/d of oral thalidomide (n = 113) or placebo (n = 116), continuously for 72 weeks. The primary end point was overall survival.

Results
After a median follow-up of 47.5 months, overall survival was significantly longer in patients who received melphalan and prednisone plus thalidomide compared with those who received melphalan and prednisone plus placebo (median, 44.0 *v* 29.1 months; $P = .028$). Progression-free survival was significantly prolonged in the melphalan and prednisone plus thalidomide group (median, 24.1 *v* 18.5 months; $P = .001$). Two adverse events were significantly increased in the melphalan and prednisone plus thalidomide group: grade 2 to 4 peripheral neuropathy (20% *v* 5% in the melphalan and prednisone plus placebo group; $P < .001$) and grade 3 to 4 neutropenia (23% *v* 9%; $P = .003$).

Conclusion
This trial confirms the superiority of the combination melphalan and prednisone plus thalidomide over melphalan and prednisone alone for prolonging survival in very elderly patients with newly diagnosed myeloma. Toxicity was acceptable.

J Clin Oncol 27:3664-3670. © 2009 by American Society of Clinical Oncology

INTRODUCTION

The incidence of multiple myeloma increases considerably with age, to more than 40 per 100,000/year in males older than 75 years.[1] At least half of all myeloma patients are older than 70 years of age and 20% are older than 80 years of age.[1-3] Within the past decade, the relative survival of patients younger than 60 years, has increased as a result of advancements made in autologous stem cell transplantation. However, only a moderate improvement in survival has been seen in patients between 60 years and 69 years of age and no improvement has been observed in older patients.[2,3] Until recently melphalan plus prednisone (MP) remained the most widely accepted treatment option for patients ineligible for high-dose therapy.[4-8] Because elderly patients (≥ 75 years) are usually under-represented in clinical trials,[1] further trials in elderly myeloma patients are necessary to delineate the best use of chemotherapy and novel agents, like thalidomide, bortezomib, and lenalidomide.

Thalidomide initially was shown to have substantial antimyeloma activity in relapsed and refractory disease.[9] Initial results of first-line therapy with MP plus thalidomide in elderly patients with

myeloma demonstrated increased response rates and progression-free survival.[10] More recently the Intergroupe Francophone du Myelome (IFM) 99-06 study demonstrated a significant overall survival advantage for MP plus thalidomide compared with MP alone.[11] Together these trials provided strong evidence indicating that the use of this combination should, at present, be a reference treatment for previously untreated elderly patients (65 to 75 years) with myeloma.[10,11] However, a survival benefit with MP plus thalidomide has not been demonstrated in patients older than 75 years. Therefore, we initiated a randomized, phase III trial (IFM 01-01) to evaluate whether the MP plus thalidomide combination prolonged survival in patients age 75 years or older with previously untreated multiple myeloma.

PATIENTS AND METHODS

Patients

Patients eligible for inclusion into this trial had stage II or III newly diagnosed multiple myeloma according to Durie-Salmon criteria and were at least 75 years of age.[12] In addition, patients with Durie-Salmon stage I multiple myeloma could be enrolled if they met the criteria of high-risk stage I disease.[6] Inclusion of nonsecretory or oligosecretory multiple myeloma was allowed.

Exclusion criteria included previous neoplasms (except basocellular cutaneous or cervical epithelioma); primary or associated amyloidosis; a WHO performance index of 3 or higher, if unrelated to multiple myeloma; substantial renal insufficiency with creatinine serum concentration of 50 mg/L or more; cardiac or hepatic clinically significant dysfunction; clinically significant peripheral neuropathy; history of venous thrombosis during the previous 6 months; or HIV infection, or hepatitis B or C infections. The institutional ethics committee of Nancy (Centre Hospitalier Régional Universitaire, Nancy, France) and the ethics committees from each of the participating hospitals in Belgium approved the protocol. All patients provided written informed consent before entering the trial.

Study Design

This multicenter, placebo-controlled, phase III trial randomly assigned patients centrally in a 1:1 ratio to receive either a 100 mg daily dose of thalidomide or placebo continuously for 72 weeks, administered at bedtime. In addition, all patients received 12 6-week cycles of MP: melphalan at 0.2 mg/kg on days 1 to 4; prednisone 2 mg/kg on days 1 to 4. A dose reduction to 50 mg per day of thalidomide or placebo was allowed at the investigator discretion in the event of patient intolerance to the 100 mg per day dose, especially in case of mild or moderate peripheral neuropathy (grade 1 or 2). No further dose reductions were allowed. In case of symptomatic peripheral neuropathy (grade 3 or 4) confirmed by electromyogram thalidomide was stopped. No maintenance treatment with thalidomide was allowed. In the event of any nonhematologic grade 3 or 4 adverse events or disease progression before 72 weeks, experimental treatment was stopped and unblinded. Clodronate was given orally at a dose of 1,040 mg per day continuously to all patients. No anticoagulation prophylaxis was prospectively planned. Transfusions of RBCs and platelets and the administration of neutrophil growth factors or erythropoiesis-stimulating agents were permitted as required. Plasmapheresis at initial treatment and radiotherapy to localized lesions to relieve symptoms during the treatment phase were also permitted.

Assessments and Efficacy End Points

The primary end point of this trial was overall survival. Secondary end points were safety, response rates, and progression-free survival. At inclusion, laboratory assessments included peripheral blood counts, chemistry analyses, and morphological interpretation of bone marrow aspirates. Furthermore, an electromyogram was planned at baseline. After inclusion, visits were scheduled every 6 weeks until treatment completion or study withdrawal. At every visit, safety issues related to thalidomide (ie, peripheral neuropathy, somnolence, constipation, nausea/vomiting, depression, and edema) were closely monitored. Response was assessed at 3, 6, 12, and 18 months. After end of treatment or withdrawal from the trial, patient status was assessed every 6 months. Response was assessed according to recent IFM trials conducted in elderly patients.[6,11] All clinical responses required documentation of improvement from baseline in bone pain and performans status, correction of hypercalcemia, and no increase in size or number of lytic bone lesions. A complete response required the absence of the original monoclonal protein in serum and urine by immunofixation, fewer than 5% of plasma cells in a bone-marrow aspirate, and the disappearance of soft tissue plasmocytomas. A very good partial response required a more than 90% decrease in monoclonal protein in serum and urine. A partial response required a reduction in the size of soft-tissue plasmocytomas, a more than 50% reduction in the concentration of serum monoclonal protein, and a more than 75% reduction in 24-hour urinary light chain excretion. After initial confirmation of complete, very good partial, or partial response, no subsequent verification was required. Progressive disease was defined as having at least one of the following: a higher than 25% increase in serum monoclonal protein concentration constituting an absolute increase of more than 5 g/L, confirmed by at least one repeated assessment; a higher than 50% increase in the 24-hour urinary light chain excretion, confirmed by at least one repeated assessment; a confirmed increase in the size of existing bone lesions or soft-tissue plasmocytomas; development of new bone lesions or soft-tissue plasmocytomas; or the development of hypercalcaemia, not attributable to any cause other than multiple myeloma. Patients not meeting the criteria of either complete response, partial response, or progressive disease were classified as having stable disease. The best response at 12 months was defined as the best improvement achieved by a patient at any time on treatment, from random assignment to month 15.

Statistical Methods

Assuming a median survival time of 22 months in the control (MP plus placebo) group and with a global type I error rate of 5%, the sample size was estimated to be 280 patients to guarantee, in a two-sided test, a power of 80% to detect an increase in the median survival time of 6 months. With this method, a P value of .05 at the final analysis would be regarded as significant. No interim analysis was initially planned. However, the IFM board decided to perform an interim analysis based on the confirmed efficacy of MP plus thalidomide in two other trials.[10,11] Recruitment into this trial was stopped on December 2006, due to the finding of a clear survival advantage with MP plus thalidomide in the IFM 99-06 trial,[11] and because MP plus thalidomide had been made available to newly diagnosed myeloma patients ineligible for high-dose therapy by the French Autorisation Temporaire d'Utilisation.

The distribution of parameters at inclusion or during follow-up was described overall or by treatment group through number and percentage of patients. Distributions of parameters assessed at inclusion were compared globally between treatment groups using χ^2 tests for categoric variables and Kruskal-Wallis rank test for continuous variables. Best response rates at 12 months were compared using the χ^2 test. Overall survival was calculated from random assignment to death from any cause. Data on patients who were alive at the time of analysis were censored in the survival analysis on the last date they were known to be alive. Progression-free survival was calculated from random assignment to progression or death. Data on patients who had not experienced disease progression were censored on the last date they were known to be alive and progression free. Survival was estimated with the Kaplan-Meier product limit method and curves were compared with the stratified log-rank test on an intention-to-treat basis. Hazard ratios were estimated with the use of the stratified Cox proportional hazards model for the intention-to-treat population. Adverse events rates were compared between groups using the χ^2 test.

RESULTS

Patients and Treatments

Between April 10, 2002, and December 22, 2006, at 44 IFM centers (39 in France; five in Belgium), a total of 232 patients were enrolled with 113 randomly assigned to MP plus thalidomide and 116 to MP plus placebo (Fig 1). Three patients failed inclusion criteria and received no protocol treatment. Baseline demographics and disease

characteristics were well balanced between the two groups except for sex (Table 1). Median age was 78.5 years (range, 75 to 89 years) with 36% of patients older than 80 years. According to local investigator assessment, 61% of patients had a significant comorbidity, and 7% presented at inclusion with a WHO index of 3 or 4. Severe renal failure (creatinine clearance $<$ 30 mL/min) was present in 13% of patients; β_2-microglobulin was above 3.5 mg/L in 69% of patients. An electromyogram was performed at baseline in half of the patients and of these, was abnormal in one third of patients, without clinically significant neuropathy. At the time of analysis in October 2008, the median follow-up time was 47.5 months.

Overall Survival

As of October 2008, a total of 134 (58.5%) of 229 patients had died: 58 (51%) and 76 (65.5%) in the MP plus thalidomide and MP plus placebo treatment groups, respectively, ($P = .03$). Myeloma progression was considered as the major cause of death in 90 patients (36 in the MP plus thalidomide group and 54 in the MP plus placebo group, respectively). There was one toxic death in each group, both due to intestinal perforation. The number of early deaths reported after 1 month and 3 months of treatment, respectively, were three and five in the MP plus thalidomide group and three and six in the MP plus placebo group.

Median overall survival was significantly prolonged in the MP plus thalidomide group (44.0 months; 95% CI, 33.4 to 58.7) compared with the MP plus placebo group (29.1 months; 95% CI, 26.4 to 34.9) (hazard ratio, 0.68 in favor of MP plus thalidomide; $P = .028$; Fig 2A). Median progression-free survival time was significantly longer in the MP plus thalidomide group (24.1 months; 95% CI, 19.4 to 29.0) compared with the MP plus placebo group (18.5 months; 95% CI, 14.6 to 21.3; hazard ratio, 0.62 in favor of MP plus thalidomide; $P = .001$; Fig 2B).

Rates of partial response, very good partial response, and complete response were also significantly higher in the MP plus thalidomide group compared with the MP plus placebo group ($P < .001$; Table 2). Disease progression occurred in 72 patients (64%) in the MP plus thalidomide group, and 84 patients (72%) in the MP plus placebo group. Rescue treatments were administered to 131 (84%) of 156 patients who presented with disease progression. This rate was similar in the two groups. Prescription of novel agents by treatment groups in this setting are presented in Table 3. Survival after progression was similar in the two groups (Fig 2C).

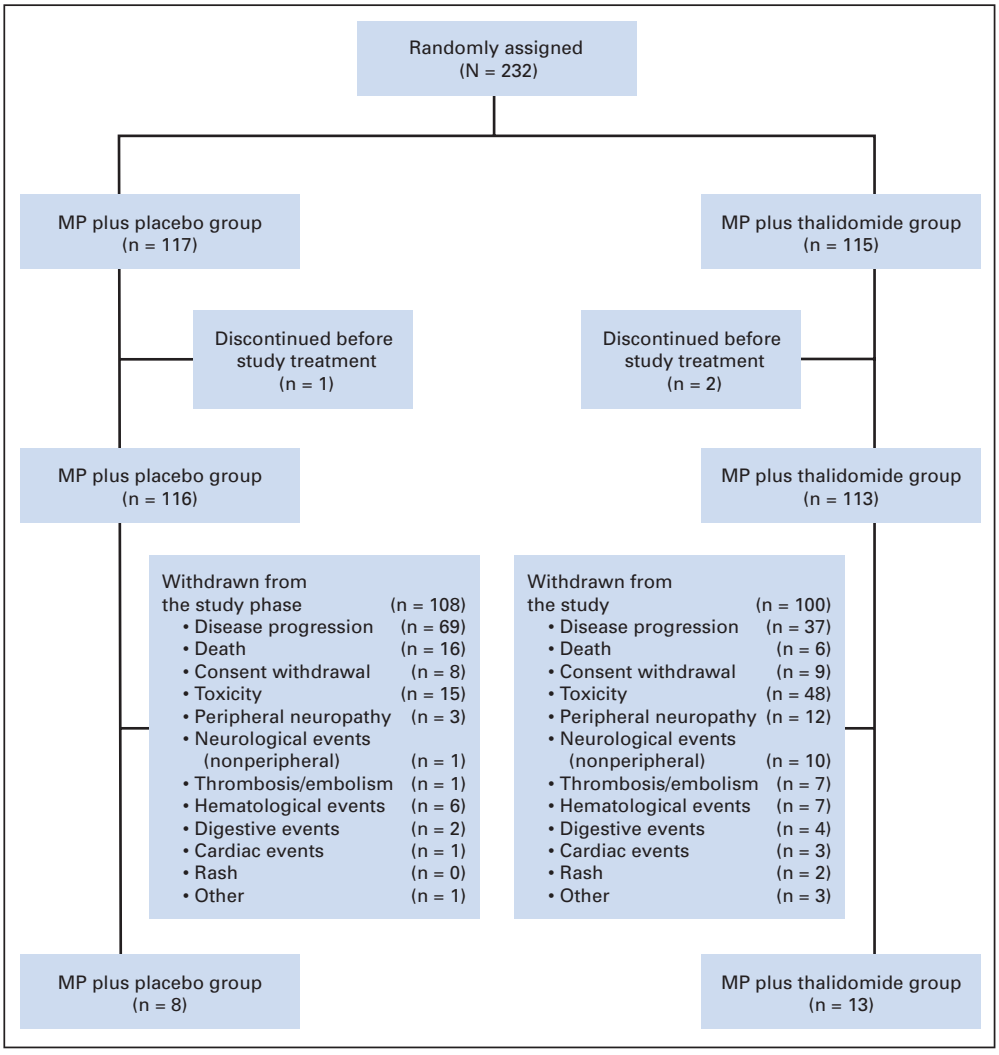

Fig 1. Trial profile. MP, melphalan and prednisone.

Table 1. Baseline Patient Demographics and Clinical Characteristics

Characteristic	All Patients (N = 229)		MP + Placebo (n = 116)		MP + Thalidomide (n = 113)	
	No.*	%	No.*	%	No.*	%
Age ≥ 80 years	83	36	40	34	43	38
Female sex	125	55	55	47	70	62
WHO performance index, 3-4	16	7	7	6	9	8
Bone lesions	180	80	93	82	87	78
Durie-Salmon stage II/III disease	207	91	107	93	100	89
Durie-Salmon substage B	22	10	14	12	8	7
International staging system						
1	51 of 202	25	26 of 104	25	25 of 98	25
2	86 of 202	43	47 of 104	45	39 of 98	40
3	65 of 202	32	31 of 104	30	34 of 98	35
IgA isotype	65	29	34	30	31	28
Albumin, < 3.5 g/dL	61 of 223	27	34 of 113	30	27 of 110	25
$Beta_2$-microglobulin, ≥ 3.5 mg/L	143 of 208	69	73 of 107	68	70 of 101	69
Clearance creatinine, ≤ 30 mL/min	27 of 210	13	16 of 105	15	11 of 105	11
Electromyogram abnormal	39 of 112	35	22 of 58	38	17 of 54	31
Significant comorbidity	139	61	69	60	70	62

NOTE. There were no significant differences between groups except for sex ($P = .03$).
Abbreviations: MP, melphalan and prednisone; IgA, immunoglobulin A.
*Total No. given when different from that listed at head of column.

Safety

Two adverse events were significantly increased in the MP plus thalidomide group: peripheral neuropathy and neutropenia (Table 4). Peripheral neuropathy was observed in 43 patients (39%) in the MP plus thalidomide group: grade 1 in 21 patients (19%), grade 2 in 20 patients (18%), and grade 3 in two patients (2%). In the MP plus placebo group, peripheral neuropathy was observed in 24 patients (16% grade 1, 3% grade 2, and 2% grade 3). No grade 4 peripheral neuropathy was reported. Neutropenia (grade 3 or 4) was observed in 25 patients (22%) in the MP plus thalidomide group and in 10 patients (9%) in the MP plus placebo group. Thrombosis occurred in seven patients (6%) in the MP plus thalidomide group and in four patients (3%) in the MP group (not significant). The occurrence of other adverse events was not statistically different between the two groups (Table 4).

In all, 48 patients in the MP plus thalidomide group and 15 patients in the MP plus placebo group discontinued the study drug because of adverse events. The adverse events that most frequently lead to discontinuation in the MP plus thalidomide group were peripheral neuropathy (12 patients), neurologic nonperipheral events (nine patients), venous thrombosis (seven patients), and hematologic toxicity (seven patients; Fig 1). This discontinuation for toxicity occurred within 3 months for nine patients, within 6 months for 23 patients, and within 12 months for 38 patients. The proportion of patients who required a dose reduction of the study treatment to 50 mg/d because of adverse events was higher in the MP plus thalidomide group than in the MP plus placebo group (20 *v* 3). The median duration of treatment with thalidomide or placebo was 13.5 and 18 months, respectively. The number of patients who withdrew consent was similar in the two groups: eight and nine patients, respectively.

DISCUSSION

In this randomized phase III study, we found that the addition of thalidomide to standard MP significantly extended both overall and progression-free survival compared with MP alone for this very elderly population with previously untreated multiple myeloma. We also observed that the MP plus thalidomide regimen was superior to the MP regimen in terms of increasing response rates, including complete response, progression-free survival, and overall survival. To our knowledge, until now no other prospective randomized study has focused on very elderly patients older than 75 years. This study fully confirms the impressive 18-month survival benefit previously reported in the IFM 99-06 trial dedicated to younger patients between the ages of 65 to 75 years.[11] In our trial, the superiority of MP plus thalidomide was not related to poor results of the MP plus placebo arm, since the median survival in this latter group was 29.1 months, similar to those achieved in our previous randomized trials in patients between 65 and 75 years of age,[6,11] and superior to those of others studies performed in very elderly patients (18 to 24 months).[13-17] The early death rate was low in the two groups as compared with historical data among elderly patients.[18]

Apart from the two IFM trials, three others comparing MP (or MP plus placebo) with MP plus thalidomide trials have been thus far reported: one from the Italian Multiple Myeloma Study group (GIMEMA [Groupe Italiano Malattie Ematologiche dell'Adulto]),[10,19] and two others in an abstract format (one from the Nordic Myeloma Study Group[20] and one from HOVON [the Dutch Belgian Cooperative Trial Group for Hematology Oncology][21]). These three studies have also shown superior results for response and either progression-free survival,[10,19,21] or time to progression,[20] with MP plus thalidomide compared with traditional MP. In the Italian study, overall survival in the MP plus thalidomide arm (median, 45.0 months) was not superior to that observed with MP, due to the apparent improvement of salvage therapy in the MP arm (median, 47.6 months). The good results of this latter arm could also be related to a short MP induction of 6 months followed by rapid cross-over with relapse treatment incorporating novel agents.[22] The lack of survival benefit observed in the MP plus thalidomide arm in the Nordic study (median survival 29 months *v* 33 months for MP alone)

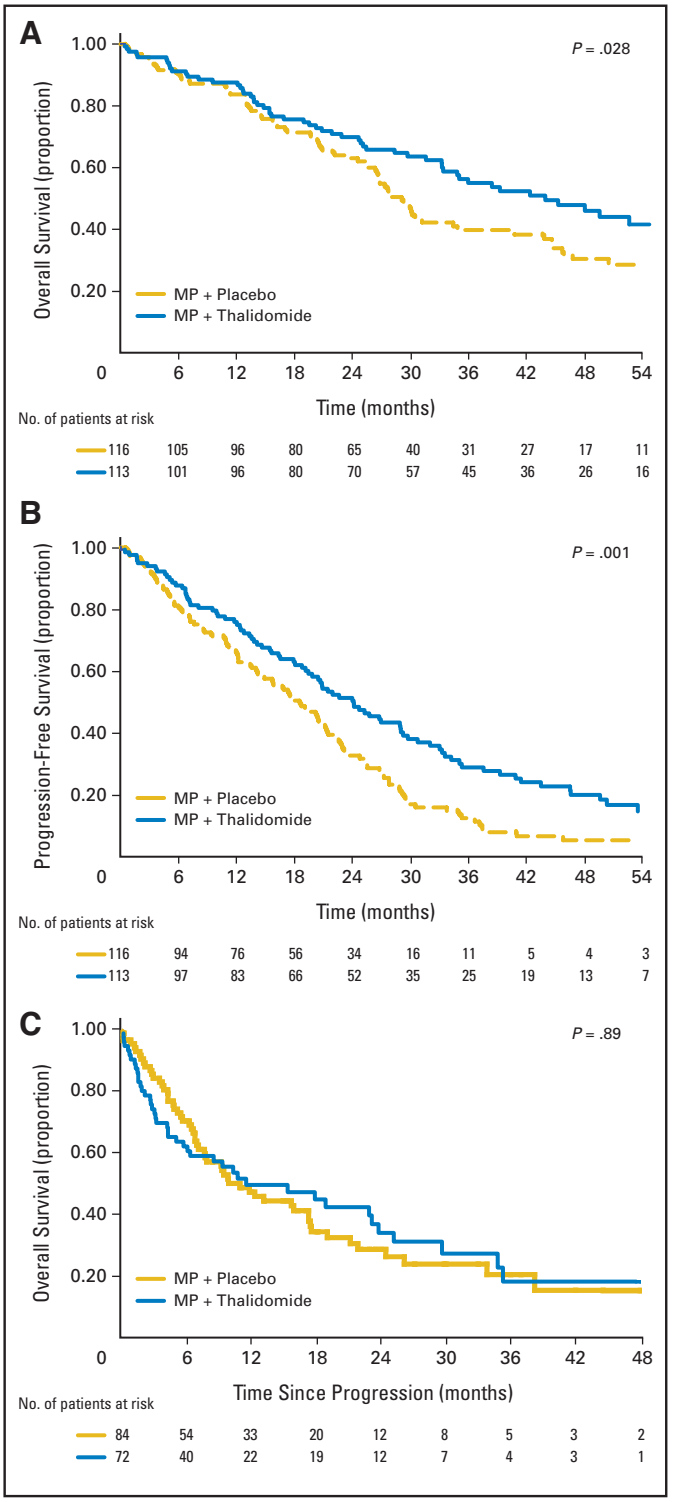

Fig 2. Kaplan-Meier curves for overall survival, progression-free survival, and survival after progression among all patients in an intention-to-treat population. (A) Estimates of median overall survival: melphalan and prednisone (MP) plus thalidomide group, blue curve (44.0 months; 95% CI, 33.4 to 58.7 months), and MP plus placebo group, gold curve (29.1 months; 95% CI, 26.4 to 34.9 months); hazard ratio of 0.68 in favor of MP plus thalidomide; $P = .028$. (B) Estimates of median time of progression-free survival: MP plus thalidomide group, blue curve (24.1 months; 95% CI, 19.4 to 29.0 months), and MP plus placebo group, gold curve (18.5 months; 95% CI, 14.6 to 21.3 months); hazard ratio of 0.62 in favor of MP plus thalidomide, $P = .001$. (C) Estimates of median survival time after progression: MP plus thalidomide group, blue curve (11.5 months), and MP plus placebo group, gold curve (9.9 months; log-rank $P = .89$).

Table 2. Best Response to Treatment (219 patients assessable)

Response	MP + Placebo (n = 112) No.	%	MP + Thalidomide (n = 107) No.	%	P
At least PR	35	31	66	62	< .001
At least VGPR	8	7	23	21	< .001
CR	1	1	7	7	< .001

Abbreviations: MP, melphalan and prednisone; PR, partial response; VGPR, very good partial response; CR, complete response.

maybe related to an increased toxic death rate in the early phase of treatment in patients older than 75 years.[20] In this specific study, the dose of both melphalan and thalidomide was not adjusted to age (thalidomide up to 400 mg/d and melphalan 0.25 mg/kg days 1 to 4 versus thalidomide 100 mg/d and melphalan 0.2 mg/kg days 1 to 4 in our trial). Moreover the proportion of patients with poor performance status was significantly higher in this study (WHO 3 or 4: 30% *v* 4% to 8% in other studies). These characteristics likely contributed to more frequent early deaths in the MP plus thalidomide group. Survival data in the HOVON trial are not yet interpretable due to the short follow-up.[21] The highest doses of drugs are not always optimal in elderly patients, as it has been demonstrated with dexamethasone.[6]

Despite the elderly population in the current trial, a substantial number of patients received subsequent treatment with novel agents at the time of relapse, especially in the MP arm in which more than 80% of the patients received at least one the three novel agents currently available. Survival time after progression was similar in the two groups, strongly suggesting that first-line treatment is of major importance in this population of elderly patients.

Toxicity in the MP plus thalidomide arm was acceptable, with a median thalidomide treatment duration longer than 1 year. Interestingly, no increase in thrombosis event rate was noted, possibly related

Table 3. Adverse Events

Adverse Event	MP + Placebo (n = 116) No.	%	MP + Thalidomide (n = 113) No.	%	P =
Peripheral neuropathy by grade					
1	19	17	20	18	.003
2	4	3	21	19	
3	2	2	2	2	
Neutropenia, grade 3 or 4	10	9	26	23	.003
Thrombosis or embolism, grade 3 or 4	4	3	7	6	.33
Somnolence, grade 2 to 4	3	3	7	6	.19
Depression, grade 2 to 4	3	3	8	7	.11
Constipation, grade 2 to 4	12	10	19	17	.16
Nausea/vomiting, grade 2 to 4	5	4	3	3	.5
Edema, grade 2 to 4	8	7	15	13	.11

Abbreviation: MP, melphalan and prednisone.

Table 4. Treatment After Disease Progression

Treatment	Progression After MP + Placebo (n = 84)		Progression After MP + Thalidomide (n = 72)	
	No.	%	No.	%
Any type	70	83	61	85
Thalidomide	53	63	16	22
Bortezomib	28	33	22	31
Lenalidomide	9	11	11	15
Thalidomide and/or lenalidomide	59	70	25	35
Thalidomide and/or lenalidomide and/or bortezomib	68	81	38	53

Abbreviation: MP, melphalan and prednisone.

to the more frequent use of antithrombotic treatments for comorbidities in this age group. Neutropenia and peripheral neuropathy were more common. However, the higher incidence of neutropenia did not translate into more frequent severe infections. Nevertheless, this 23% grade 3/4 neutropenia rate was lower than the 48% incidence found in the IFM 99-06 study, potentially due to the higher dose of melphalan (0.25 mg/kg days 1 to 4) and thalidomide (200 to 400 mg/day) used in this previous trial.[11] Consistent with the IFM 99-06 and GIMEMA studies,[10,11,19] the incidence of peripheral neuropathy in this trial was increased in patients receiving thalidomide, with most cases being mild (19% grade 1% and 18% grade 2). Severe neuropathy was rare (2% grade 3, no grade 4). Other adverse events commonly related to thalidomide, such as constipation, somnolence, edema, and depression, were not significantly increased.

In conclusion, our results strongly support the use of thalidomide in combination with melphalan and prednisone in previously untreated very elderly patients with multiple myeloma. The 100 mg dose of thalidomide was effective, and associated with acceptable toxicity. Although other promising combinations such as MP plus bortezomib,[23] MP plus lenalidomide,[24] or lenalidomide plus low-dose dexamethasone are currently being actively studied in these patients,[25] MP plus thalidomide should at this time be considered as the standard care in newly diagnosed myeloma patients older than 75 years.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(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: None **Consultant or Advisory Role:** Thierry Facon, Pharmion (C), Celgene (C), Janssen-Cilag (C); Philippe Moreau, Pharmion (C), Celgene (C), Janssen-Cilag (C) **Stock Ownership:** None **Honoraria:** Cyrille Hulin, Celgene, Pharmion, Janssen-Cilag; Thierry Facon, Pharmion, Celgene, Janssen-Cilag; Philippe Moreau, Pharmion, Celgene, Janssen-Cilag **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Cyrille Hulin, Thierry Facon, Isabelle Azaïs, Olivier Decaux, Claire Mathiot, Philippe Moreau
Administrative support: Claire Mathiot
Provision of study materials or patients: Cyrille Hulin, Thierry Facon, Philippe Rodon, Brigitte Pegourie, Lotfi Benboubker, Chantal Doyen, Mamoun Dib, Gaelle Guillerm, Bruno Salles, Jean-Paul Eschard, Pascal Lenain, Philippe Casassus, Isabelle Azaïs, Olivier Decaux, Laurent Garderet, Jean Fontan, Ingrid Lafon, Philippe Moreau
Collection and assembly of data: Cyrille Hulin, Jean Marc Virion
Data analysis and interpretation: Cyrille Hulin, Thierry Facon, Jean Marc Virion, Philippe Moreau
Manuscript writing: Cyrille Hulin, Thierry Facon, Jean Marc Virion, Philippe Moreau
Final approval of manuscript: Cyrille Hulin, Thierry Facon, Philippe Rodon, Brigitte Pegourie, Lotfi Benboubker, Chantal Doyen, Mamoun Dib, Gaelle Guillerm, Bruno Salles, Jean-Paul Eschard, Pascal Lenain, Philippe Casassus, Isabelle Azaïs, Olivier Decaux, Laurent Garderet, Claire Mathiot, Jean Fontan, Ingrid Lafon, Jean Marc Virion, Philippe Moreau

REFERENCES

1. Phekoo KJ, Schey A, Richards MA, et al: A population study to define the incidence and survival of multiple myeloma in a National Health Service Region in UK. Br J Hematol 127:299-304, 2004
2. Brenner H, Gondos A, Pulte A: Recent major improvment in long-term survival of younger patients with multiple myeloma. Blood 111:2521-2526, 2008
3. Kristinsson SY, Landgren O, Dickman PW, et al: Patterns of survival in multiple myeloma: A population-based study of patients diagnosed in Sweden from 1973 to 2003. J Clin Oncol 25:1993-1999, 2007
4. Alexanian R, Haut A, Khan AU, et al: Treatment for multiple myeloma: Combination chemotherapy with different melphalan dose regimens. JAMA 208:1680-1685, 1969
5. Myeloma Trialists' Collaborative Group: Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: An overview of 6633 patients from 27 randomized trials. J Clin Oncol 16:3832-3842, 1998
6. Facon T, Mary JY, Pegourie B, et al: Dexamethasone-based regimens versus melphalan-prednisone for elderly multiple myeloma patients ineligible for high-dose therapy. Blood 107:1292-1298, 2006
7. Kyle R, Rajkumar V: Multiple myeloma. Blood 111:2962-2972, 2008
8. Moreau P, Hulin C, Facon T: Frontline treatment of multiple myeloma in elderly patients. Blood Rev 22:303-309, 2008
9. Singhal S, Mehta J, Desikan R, et al: Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med 341:1565-1571, 1999
10. Palumbo A, Bringhen S, Caravita T, et al: Oral melphalan and prednisone chemotherapy plus thalidomide comparde with melphalan and prednisone alone in elderly patients with multiple myeloma: Randomized controlled trial. Lancet 367:825-8231, 2006
11. Facon T, Mary JY, Hulin C, et al: Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced–intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): A randomized trial. Lancet 370:1209-1218, 2007
12. Durie BG, Salmon SE: A clinical staging system for multiple myeloma: Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer 36:842-854, 1975
13. Bladé J, Munoz M, Fontanillas M, et al: Treatment of multiple myeloma in elderly people: Long-term results in 178 patients. Age Ageing 25:357-361, 1996
14. Rodon P, Linassier C, Gauvain JB, et al: Multiple myeloma in elderly patients: Presenting features and outcome. Eur J Hematol 66:11-17, 2001
15. Anagnostopoulos A, Gika D, Symeonidis A, et al: Multiple myeloma in elderly patients: Prognostic factors and outcome. Eur J Haematol 75:370-375, 2005
16. Mileshkin L, Prince HM: The adverse prognostic impact of advanced age in multiple myeloma. Leuk Lymphoma 46:951-966, 2005

17. Dimopoulos MA, Anagnostopoulos A, Terpos E, et al: Primary treatment with pulsed melphalan dexamethasone and thalidomide for elderly symptomatic patients with multiple myeloma. Haematologica 91:252-254, 2006

18. Augustson BM, Begum G, Dunn JA, et al: Early mortality after diagnosis of multiple myeloma: Analysis of patients entered onto the United Kingdom Medical Research Council trials between 1980 and 2002—Medical Research Council Adult Leukaemia Working Party. J Clin Oncol 23:919-926, 2005

19. Palumbo A, Bringhen S, Liberati AM, et al: Oral melphalan, prednisone and thalidomide in elderly patients with multiple myeloma: Updated results of a randomized controlled trial. Blood 112:3107-3114, 2008

20. Gulbrandsen N, Waage A, Gimsing I, et al: A randomized placebo controlled studywith melphalan/prednisone versus melphalan/prednisone/thalidomide: Quality of life and toxicity. Haematologica 93:84, 2008 (abstr 0209)

21. Wijermans P, Schaafsma M, Van Norden Y, et al: Melphalan + prednisone versus melphalan + prednisone + thalidomide induction therapy for multiple myelomain elderly patients: First interim results of the Dutch cooperative group HOVON. Haematologica 93:178, 2008 (abstr 0440)

22. Durie B: Crossover confusion: MPT still best. Blood 112:2998-2999, 2008

23. San Miguel JF, Schlag R, Khuageva NK, et al: Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 359:906-917, 2008

24. Palumbo A, Falco P, Corradini P, et al: Melphalan, prednisone, and lenalidomide treatment for newly diagnosed myeloma: A report from the GIMEMA-Italian Multiple Myeloma Network. J Clin Oncol 25:4459-4465, 2007

25. Rajkumar SV, Jacobus S, Callander N, et al: Randomized trial of lenalidomide plus high-dose dexamethasone (RD) versus lenalidomide plus low-dose dexamethasone (Rd) in newly diagnosed multiple myeloma (E4A03), a trial coordinated by the Eastern Cooperative Oncology Group: Analysis of response, survival, and outcome. J Clin Oncol 26: 455a, 2008 (suppl; abstr 8504)