Original Article

Results of a Multicenter, Randomized, Double-Blind, Dose-Evaluating Phase 2/3 Study of Lenalidomide in the Treatment of Metastatic Malignant Melanoma

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BACKGROUND: There are currently no systemic treatments for stage IV melanoma, which have been proven in randomized trials to benefit overall survival (OS). Lenalidomide has efficacy against melanoma in animal models and safety in phase 1 trials. The authors reported the results of a phase 2/3 study comparing the safety and efficacy of 2 doses of lenalidomide in patients with relapsed metastatic melanoma disease refractory to previous treatment with dacarbazine, temozolomide, interleukin-2, or interferon-α. **METHODS:** A total of 294 patients were randomized to oral lenalidomide at 5 mg or 25 mg dose. Tumor response, time to progression, and OS were evaluated. Treatment continued until disease progression or unacceptable adverse events. **RESULTS:** No significant differences in response rate, OS, or time to progression were observed between lenalidomide 25 mg versus 5 mg (overall response rate: 5.5% vs 3.4%, $P = .38$; median OS: 6.8 months vs 7.2 months, $P = .71$; and median time to progression: 2.2 months vs 1.9 months, $P = .24$). Myelosuppression was observed in 37.0% of patients in the 25 mg group and 13.7% of patients in the 5 mg group. Treatment-related serious adverse events were seen in 39.0% of patients at the 25 mg dose and 35.4% of patients at the 5 mg dose. **CONCLUSIONS:** Despite the occurrence of treatment-related serious adverse events, ~80% of patients continued treatment. The higher dose of lenalidomide did not improve response rate, time to progression, or OS of patients with relapsed/refractory stage IV melanoma. A parallel placebo-controlled study has been conducted to further assess the efficacy of lenalidomide in stage IV melanoma patients. **Cancer 2009;115:5228–36. © 2009 American Cancer Society.**

KEY WORDS: metastatic malignant melanoma, lenalidomide, phase 2/3, dose evaluation.

The worldwide incidence of melanoma is increasing, with the number of cases doubling in the past 20 years.[1] The American Cancer Society estimates that in 2008 approximately 60,000 new cases of melanoma will be diagnosed in the United States and over 8000 Americans are expected to die from the condition.[2]

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When it is diagnosed early, melanoma is characterized by a high cure rate by surgical resection. However, once distant metastases/stage IV disease is documented the prognosis is poor, with a median survival rate of 6-8 months and a 5-year survival rate of less than 5%.[3,4] There is some evidence that a minority of patients with stage IV disease treated with high doses of interleukin-2 (IL-2) have long-term survival (7%). For this reason, IL-2 treatment is approved by the US Food and Drug Administration for this population; however, the high level of toxicity limits its application.[5] Although surgery can have a role in some patients with stage IV disease, for most the presence of multiple metastatic sites and/or comorbidities limits the applicability of this approach.[6,7] Consequently, most patients with stage IV melanoma are currently treated with either dacarbazine or temozolomide, or with supportive care alone.[7,8] Neither dacarbazine nor high-dose IL-2 has been proven in randomized clinical trials to produce an overall survival (OS) benefit.[7,8] Furthermore, in a phase 3 trial of intravenous dacarbazine versus oral temozolomide in advanced metastatic melanoma patients, temozolomide was as effective as dacarbazine with a median OS of 7.7 months compared with 6.4 months for dacarbazine.[9]

Some potential new therapies that target specific signaling pathways involved in the progression of metastatic melanoma have been tested in clinical trials. These include the proteasome inhibitor bortezomib, the endothelin receptor antagonist bosentan, the multikinase inhibitor sorafenib, the angiogenesis inhibitor ABT-510, and the immunomodulatory drug thalidomide.[10-16] None of these drugs have exhibited a higher response rate than treatment with dacarbazine or IL-2, and no treatment has been established to increase median OS.[7] Thus, new systemic treatments for patients with stage IV melanoma are urgently needed. Currently, the National Comprehensive Cancer Network recommends enrollment in a clinical trial, over other existing treatments, as either first-line therapy or second-line therapy for patients with unresectable stage IV metastatic malignant melanoma.[7,17]

Lenalidomide has shown antitumor activity against metastatic malignant melanoma in an animal model.[18] The safety and tolerability of this drug were demonstrated in phase 1 studies, which also indicated the possibility of clinical activity of lenalidomide in the treatment of refractory metastatic malignant melanoma.[19,20] Here, we report the results from a phase 2/3 trial, MEL-001. The objective of MEL-001 was to compare the efficacy and safety of lenalidomide 5 mg with 25 mg in the treatment of patients with stage IV melanoma, whose disease had progressed after treatment with dacarbazine, temozolomide, IL-2, or interferon (IFN)-α.

MATERIALS AND METHODS

Study Design

MEL-001 was an international, multicenter, randomized, double-blind, dose-evaluating, parallel-group study. The protocols were designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. Institutional review boards or ethics committees at each participating center approved the study protocol. Patients from Canada and the United States were enrolled in the study. All patients provided written informed consent. All eligible patients who signed an informed consent were admitted to the study. Patients were randomized using an Interactive Voice Response System. Data from all randomized patients who received at least 1 dose of lenalidomide were included in the safety analyses. Response was determined using Response Evaluation Criteria in Solid Tumors (RECIST). The response assessment was scheduled for the fourth week of the second cycle. Disease progression was defined according to the RECIST criteria. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.

Patient Selection

Adult patients aged $\geq$18 years with stage IV melanoma were selected. A total of 294 subjects were enrolled as the intent-to-treat population. All patients had to have relapsed or refractory disease after treatment with dacarbazine, temozolomide, IL-2, and/or IFN-α for stage IIIb, IIIc, or IV disease, and an Eastern Cooperative Oncology Group (ECOG) performance status of $\leq$2. Patients were excluded if they had received cancer treatments within the preceding 28 days, were pregnant, had serious mental illness, significant comorbid disease, HIV, hepatitis, or hypersensitivity to thalidomide, known brain metastases, or had been treated previously with lenalidomide.

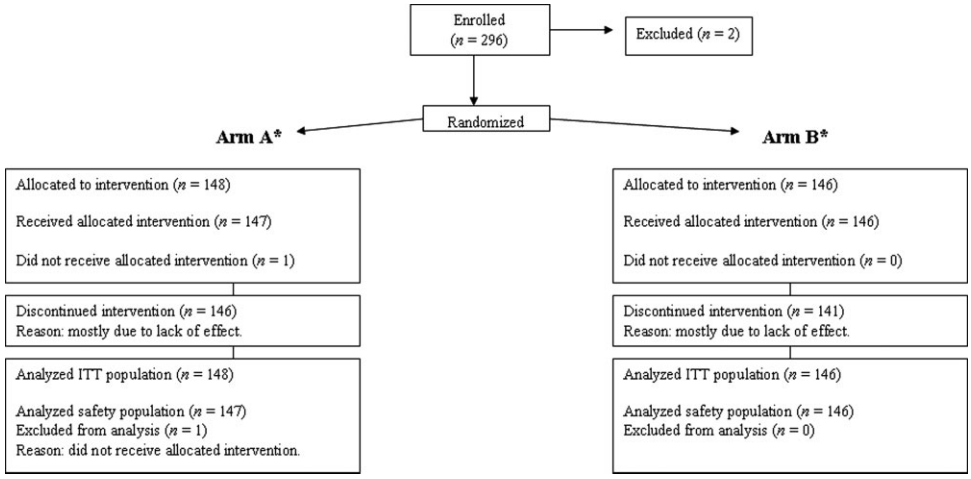

FIGURE 1. Patient flow is illustrated with. *Study Arm A = 5 mg lenalidomide and Study Arm B = 25 mg lenalidomide. ITT indicates intent to treat.

Treatment

Based on previously published prognostic indicators for metastatic malignant melanoma,[21] patients were stratified for randomization based on the following variables: gender, ECOG performance status, metastatic sites of stage IV melanoma (M1: metastases to skin, subcutaneous tissue, or distant lymph nodes; M2: metastases to lung; and M3: metastases to all other visceral sites),[22] serum lactate dehydrogenase (LDH), serum albumin, alkaline phosphatase, and platelet count. Patients in study arm A were treated with oral lenalidomide 5 mg plus placebo, looking identical to the 25 mg dose, administered daily for 28 days. Patients in study arm B were treated with oral lenalidomide 25 mg administered for 21 days of every 28 days and placebo for the remaining 7 days. Pill distribution was administered in a double-blind fashion as same number and pill appearance for all subjects in study, regardless of dose. Treatment continued until disease progression or unacceptable adverse events. Concurrent treatment with filgrastim for neutropenia was recommended, and patients received full supportive care, including transfusions, antibiotics, and antiemetics, when appropriate. Patients were monitored for adverse events and treatment withheld for serious adverse events (NCI-CTC grade 3 or higher nonhematological events and grade 4 or higher hematological events) until they resolved to grade 2. Dose reductions may be necessary for grade 4 neutropenia and grade 4 thrombocytopenia. The dose reduction schedule mandated a reduction to placebo for the 5 mg group and a reduction to 15 mg for the 25 mg group.

Statistical Methods

The primary outcome was OS with secondary endpoints of time to progression, tumor response rate, and safety. OS and time to progression endpoints were assessed using the Kaplan-Meier product limit method. Cox proportional hazards were used to assess the variable effects on treatment. Comparisons for response between subgroups were assessed using the Fisher exact test. Comparisons for the time to progression and OS curves were assessed using unstratified log-rank tests. All comparisons were 1-tailed at the 0.025 level (adjusted for 1 interim analysis).

RESULTS

Patient Characteristics

Of the 294 patients randomized to treatment, 293 patients were included in the data analyses. Figure 1 shows the patient flow through the study, and patient characteristics are summarized in Table 1. Overall, baseline patient characteristics were well balanced. Both study arms had a higher percentage of males than females (lenalidomide 5 mg [study arm A] 64.2% males vs 59.6% males lenalidomide 25 mg [study arm B]). This was consistent with the gender distribution of metastatic melanoma. Study arms were similar for median ECOG performance status

Table 1. Patient Characteristics

Characteristic	Lenalidomide 5 mg n=148	Lenalidomide 25 mg n=146
Median age, y	59.0	56.0
Male/female, No. (%)	95/53 (64.2/35.8)	87/59 (59.6/40.4)
Prior radiation, No. (%)		
Yes	62 (41.9)	52 (35.6)
No	12 (8.1)	9 (6.2)
Data not available	74 (50.0)	85 (58.2)
Prior cancer surgery, No. (%)		
Yes	147 (99.3)	146 (100.0)
No	1 (0.7)	0
ECOG performance status score, No. (%)		
0	73 (49.3)	65 (44.5)
1	60 (40.5)	68 (46.6)
2	14 (9.5)	13 (8.9)
Data not available	1 (0.7)	0
Metastatic site classification of stage IV melanoma, No. (%)		
M1	18 (12.2)	16 (11.0)
M2	23 (15.5)	25 (17.1)
M3	107 (72.3)	105 (71.9)
LDH level, No. (%)		
Normal	91 (61.5)	85 (58.2)
Elevated	57 (38.5)	61 (41.8)
No. of prior antineoplastic regimens, No. (%)		
1	35 (23.6)	40 (27.4)
2	56 (37.8)	51 (35.0)
3	22 (14.9)	25 (17.1)
4	19 (12.8)	18 (12.3)
5	9 (6.1)	5 (3.4)
≥6	7 (4.7)	6 (4.1)
Data not available	0	1 (0.7)

ECOG indicates Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

scores, sites of metastatic disease, mean LDH levels, and the number of prior treatment regimens.

Overall Survival

Figure 2 shows the Kaplan-Meier product limit estimation plot of OS. There were no significant differences in OS observed between the 2 treatment groups ($P = .71$; Table 2). Median OS for patients in the lenalidomide 25 mg dose was 6.8 months versus 7.2 months for the 5 mg dose. A lower ECOG performance status score, normal LDH levels, and a lower metastatic site classification positively affected OS in both treatment arms (Table 2). Nevertheless, there were no significant differences between the 2 doses for the OS in these subgroups of patients (Table 2).

Tumor Response Rate

Twenty-one patients in the 25 mg group and 18 patients in the 5 mg group were not evaluable for response. Of these patients who could not be evaluated, 11 patients in the 25 mg group and 7 patients in the 5 mg group had died before the scheduled date of response assessment. There were no significant differences in overall RECIST response rate observed between lenalidomide 25 mg versus 5 mg treatment groups (5.5% vs 3.4%, respectively; $P = .38$) (Table 2). The majority of patients exhibited disease progression at the first tumor assessment 61 (41.8%) patients of the 25 mg cohort and 80 (54.1%) patients of the 5 mg cohort. Stable disease was observed in 56 (38.4%) patients in the lenalidomide 25 mg cohort compared with 45 (30.4%) patients in the 5 mg group.

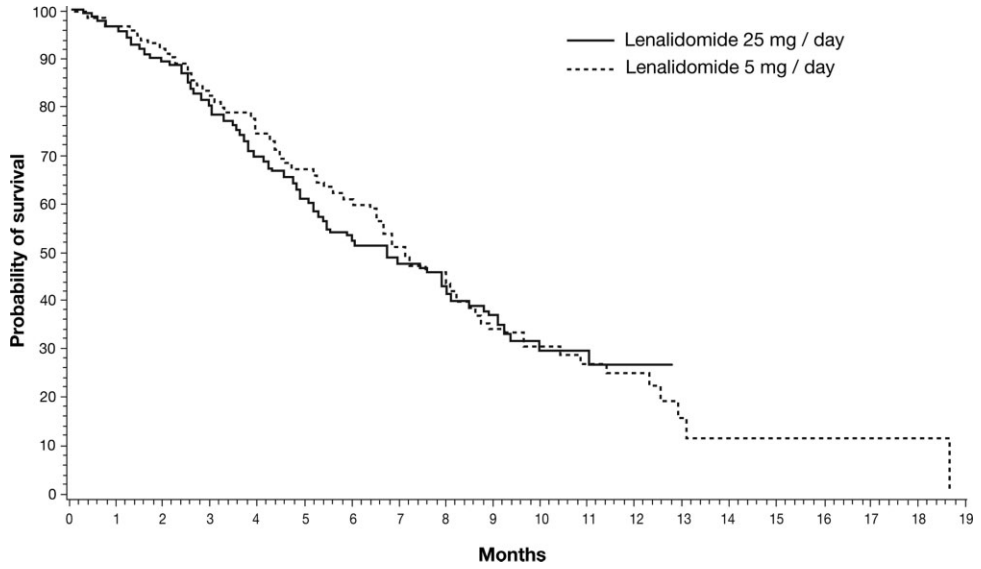

FIGURE 2. Kaplan-Meier product limit estimation plot of overall survival is shown.

Table 2. RECIST Response, Overall Survival, and Time to Progression

	Lenalidomide		
Parameters	5 mg n=148	25 mg n=146	*P*
RECIST response, No. (%)			
Overall response	5 (3.4)	8 (5.5)	.38*
Complete response	0	1 (0.7)	—
Partial response	5 (3.4)	7 (4.8)	—
Stable disease	45 (30.4)	56 (38.4)	—
Progression of disease	80 (54.1)	61 (41.8)	—
Missing/indeterminate	18 (12.2)	21 (14.4)	—
Overall survival			.71†
Median, mo (95% CI)	7.2 (6.5-8.2)	—	—
Hazard ratio (95% CI)	0.95 (0.70-1.27)		—
Subgroup median, mo			
ECOG performance status score			.72†
0 or 1	7.9	7.4	.61‡
2	3.0	3.9	.74‡
Metastatic site classification			.79†
M1	11.4	6.8	.62‡
M2	10.4	9.4	.58‡
M3	6.6	5.9	.95‡
LDH level			.89†
Normal	9.7	9.1	.38‡
Elevated	4.4	3.7	.33‡
Time to progression			.24‡
Median, mo (95% CI)	1.9 (1.8-2.0)	2.2 (1.8-3.1)	—
Hazard ratio (95% CI)	1.16 (0.9-1.5)		—

CI indicates confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; RECIST, Response Evaluation Criteria in Solid Tumors.

*The *P* value is based on a chi-square test of differences between groups.

†The *P* value is based on a one-tailed, log-rank test of curve differences between groups.

‡The *P* value is based on a one-tailed, unstratified log-rank test of curve differences between groups.

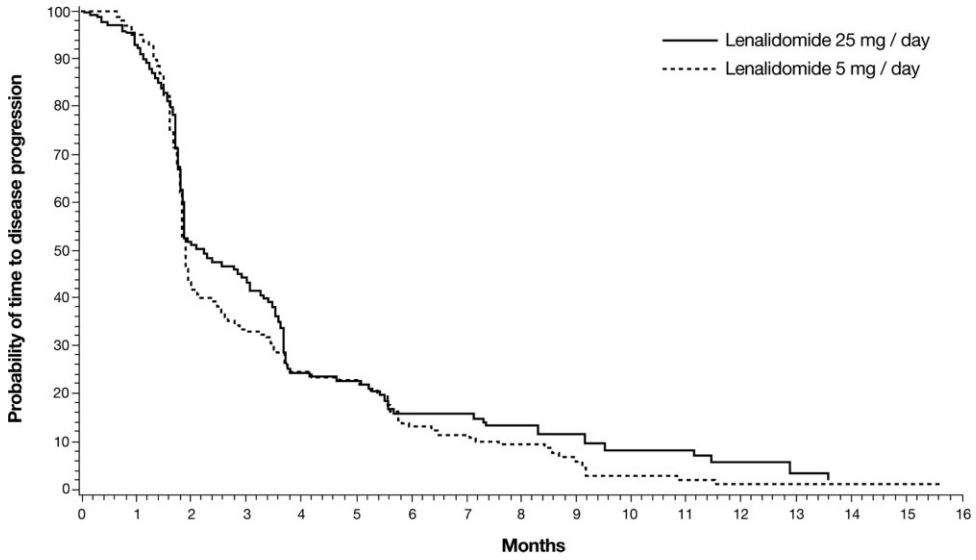

FIGURE 3. Kaplan-Meier product limit estimation plot of time to progression is shown.

Time to Progression

Figure 3 shows the Kaplan-Meier product limit estimation plot of time to progression. Median time to progression was 2.2 months for the lenalidomide 25 mg group and 1.9 months for the 5 mg group. No significant differences in time to progression were observed between the 2 lenalidomide regimens ($P = .24$) (Table 2). There were no differences between the 2 doses of lenalidomide for the time to progression in subgroups of patients stratified by their ECOG performance status score, LDH level, and metastatic site classification (ECOG [0 or 1, 2] $P = .24$; LDH [normal, elevated] $P = .17$, metastatic site classification [M1, M2, M3] $P = .23$).

Adverse Events

Adverse events of all grades are detailed in Table 3. At least 1 adverse event was observed in 98.6% and 97.3% of patients in the lenalidomide 25 mg and 5 mg treatment groups, respectively. Discontinuation of treatment due to adverse events was seen in 22.6% and 18.4% of patients in the 25 mg and 5 mg treatment groups, respectively. Adverse events leading to dose reduction were not observed in the 25 mg treatment group but were seen in 1.4% of patients in the 5 mg group. Myelosuppression was observed in 37.0% of patients in the 25 mg group and 13.6% in the 5 mg treatment group (Table 4). At least 1 treatment-related serious adverse event was observed in 39.0% and 35.4% of patients in the 25 mg and 5 mg treatment groups, respectively (Table 5 shows those occurring in $\geq$1% of patients per group). Frequently observed treatment-related serious adverse events were pulmonary embolism (3.4% of patients in the 5 mg lenalidomide study arm) and neutropenia (2.7% of patients in the 25 mg lenalidomide study arm). No clear treatment-related NCI-CTC grade 4 or 5 adverse events were noted.

Patient Disposition

More than half of the patients in each study arm had discontinued treatment with lenalidomide before the start of cycle 3; 45.2% of patients in the 25 mg study arm started cycle 3 compared with 33.8% of those in the 5 mg study arm. Throughout all cycles, the median dose received by patients was 25 mg in the 25 mg lenalidomide study arm and 5 mg in the 5 mg lenalidomide study arm, with only 2 (1.4%) patients in the 5 mg lenalidomide study arm and none in the 25 mg lenalidomide study arm requiring a dose reduction.

DISCUSSION

Currently approved treatments for metastatic malignant melanoma have significant toxicity and have not been

Table 3. Adverse Events of All Grades Occurring in ≥10% of Patients by Group

Adverse Events	Lenalidomide 5 mg n=147 No. (%)	Lenalidomide 25 mg n=146 No. (%)
Blood and lymphatic system disorders		
Anemia NOS	12 (8.2)	22 (15.1)
Gastrointestinal disorders		
Abdominal pain NOS	15 (10.2)	21 (14.4)
Constipation	35 (23.8)	34 (23.3)
Diarrhea NOS	38 (25.9)	45 (30.8)
Dyspepsia	14 (9.5)	16 (11.0)
Nausea	49 (33.3)	45 (30.8)
Vomiting NOS	30 (20.4)	25 (17.1)
General disorders and administration site conditions		
Asthenia	10 (6.8)	8 (5.5)
Fatigue	58 (39.5)	65 (44.5)
Edema peripheral	19 (12.9)	29 (19.9)
Pyrexia	22 (15.0)	24 (16.4)
Metabolism and nutrition disorders		
Anorexia	13 (8.8)	21 (14.4)
Appetite decreased NOS	6 (4.1)	16 (11.0)
Musculoskeletal and connective tissue disorders		
Arthralgia	16 (10.9)	23 (15.8)
Back pain	15 (10.2)	21 (14.4)
Muscle cramp	13 (8.8)	19 (13.0)
Pain in limb	15 (10.2)	17 (11.6)
Neoplasms benign, malignant, and unspecified		
Cancer pain	12 (8.2)	7 (4.8)
Nervous system disorders		
Dizziness	18 (12.2)	21 (14.4)
Headache	16 (10.9)	25 (17.1)
Psychiatric disorders		
Insomnia	20 (13.6)	16 (11.0)
Respiratory, thoracic, and mediastinal disorders		
Cough	23 (15.6)	28 (19.2)
Dyspnea NOS	20 (13.6)	26 (17.8)
Pharyngitis	12 (8.2)	16 (11.0)
Skin and subcutaneous tissue disorders		
Pruritus	19 (12.9)	37 (25.3)
Rash NOS	36 (24.5)	43 (29.5)

NOS, not otherwise specified.

shown to be effective in increasing OS. This disease is, therefore, particularly vexing and there is a clear unmet medical need for an effective treatment. There are interesting preclinical data suggesting that lenalidomide may have efficacy in this disease, and it is being tested in a randomized, placebo-controlled trial. However, even if lenalidomide is shown to be effective in improving outcomes such as time to progression or OS, the optimal dose will remain an important question. We report the results of a randomized trial of 2 doses of lenalidomide to determine their relative efficacy and safety for patients with metastatic malignant melanoma.

In this study, there were no significant differences observed in tumor response rates, time to progression, or OS between the 2 dose levels. A time to progression of about 2 months and an OS of about 7 months were observed after lenalidomide treatment, independent of the dose used.

The 25 mg dose of lenalidomide was associated with greater myelosuppression compared with the 5 mg dose. In all, myelosuppression was a common adverse event, as is the case in patients with hematological malignancies treated with lenalidomide.[23] As the patients in the present study had limited prior cytotoxic therapy and, thus, presumably normal bone marrow function, the results suggest that the observed myelosuppression is a result of treatment with lenalidomide.

The current study does not suggest that either dose of lenalidomide (5 mg or 25 mg) has significant activity in this disease. Despite the occurrence of treatment-related serious adverse events, ~80% of patients continued treatment The results for both treatment arms were similar to those of 68 inactive regimens in an ECOG phase 2 study population trial.[24] Perhaps the use of this agent in previously untreated patients, or in combination with other active agents, might produce more favorable results. Ultimately, the efficacy of lenalidomide as a single agent for the treatment of patients with metastatic melanoma will be determined in the randomized, placebo-controlled clinical trial which has completed accrual.

Table 4. Myelosuppression of All Grades

	Lenalidomide	
	5 mg n=147	25 mg n=146
	No. (%)	No. (%)
Anemia NOS	12 (8.2)	22 (15.1)
Anemia NOS aggravated	1 (0.7)	6 (4.1)
Leukopenia NOS	1 (0.7)	5 (3.4)
Neutropenia	2 (1.4)	13 (8.9)
Thrombocytopenia	4 (2.7)	8 (5.5)
Total	20 (13.6)	54 (37.0)

NOS, not otherwise specified.

Table 5. Treatment-Related Serious* Adverse Events Occurring in ≥1% of Patients by Group

	Lenalidomide	
Adverse Events	5 mg n=147	25 mg n=146
	No. (%)	No. (%)
Blood and lymphatic system disorders		
Anemia NOS	1 (0.7)	3 (2.1)
Neutropenia	0	4 (2.7)
Gastrointestinal disorders		
Intestinal obstruction NOS	3 (2.0)	3 (2.1)
Nausea	3 (2.0)	0
Vomiting NOS	4 (2.7)	0
General disorders and administration site conditions		
Asthenia	1 (0.7)	2 (1.4)
Pyrexia	2 (1.4)	0
Infections and infestations		
Cellulitis	2 (1.4)	0
Pneumonia NOS	2 (1.4)	1 (0.7)
Metabolism and nutrition disorders		
Anorexia	0	2 (1.4)
Dehydration	3 (2.0)	3 (2.1)
Neoplasms benign, malignant, and unspecified		
Cancer pain	1 (0.7)	2 (1.4)
Respiratory, thoracic, and mediastinal disorders		
Dyspnea NOS	4 (2.7)	3 (2.1)
Hemoptysis	2 (1.4)	1 (0.7)
Pleural effusion	3 (2.0)	3 (2.1)
Pulmonary embolism	5 (3.4)	3 (2.1)
Vascular disorders		
Deep vein thrombosis	4 (2.7)	3 (2.1)

NOS indicates not otherwise specified.
* Grade 4 hematological toxicity or nonhematological toxicity of grade 3-4.

Conflict of Interest Disclosures

Michael B. Atkins, is a consultant for Novartis and Schering-Plough.

Robert D. Knight and J. Ulf Jungnelius are Celgene employees.

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