A Noninterventional, Observational, European Post-Authorization Safety Study of Patients With Relapsed/Refractory Multiple Myeloma Treated With Lenalidomide

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Abstract

Given the key role of lenalidomide in the treatment of relapsed/refractory multiple myeloma, it is important to evaluate the safety of lenalidomide in real-world populations of patients who may not qualify for clinical trial participation. This noninterventional, European post-authorization safety study confirms that the real-world safety profile of lenalidomide is similar to what has been reported in clinical trials.

Introduction: Lenalidomide plus dexamethasone is effective and well tolerated in relapsed/refractory multiple myeloma (RRMM). In this observational, noninterventional European post-authorization safety study, the safety profile of lenalidomide plus dexamethasone was investigated and compared with that of other agents in the treatment of RRMM in a real-world setting. **Patients and Methods:** Patients had received $\geq$ 1 prior antimyeloma therapy; prior lenalidomide was excluded. Treatment was per investigator's routine practice. Adverse events were analyzed by incidence rates per 100 person-years to account for differences in observation length and treatment duration. **Results:** In total, 2150 patients initiated lenalidomide, and 1479 initiated any other antimyeloma therapy, predominately bortezomib (80.3%), which was primarily administered intravenously (74.3%). The incidence rate of neuropathy was lower with lenalidomide (10.5) than with bortezomib (78.9) or thalidomide (38.7). Lenalidomide also had a lower incidence rate of infections (68.7) versus bortezomib (95.9) and thalidomide (76.0). Conversely, the incidence rate of neutropenia was higher with lenalidomide (38.0) than with bortezomib (18.2) or thalidomide (25.7). The incidence rates of thrombocytopenia were 24.4, 40.4, and 14.4 with lenalidomide, bortezomib, and thalidomide, respectively.

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Conclusion: No new safety signals for lenalidomide were identified in this study, which is the largest prospective real-world European study of lenalidomide in patients with RRMM to date. These results confirm that the safety profile of lenalidomide plus dexamethasone in RRMM in a real-world setting is comparable to that reported in clinical trials.

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Introduction

Patient outcomes in multiple myeloma (MM) have improved since the introduction of effective, novel treatments, but the disease is still not considered curable, and most patients will experience relapse or progressive disease (PD) even after autologous stem cell transplant.[1-4] Furthermore, the disease course of MM is characterized by the development of drug resistance and increased genetic heterogeneity.[5-10] Thus, recurrent myeloma tends to become more aggressive with each relapse and is associated with worse patient outcomes.[11]

The immunomodulatory drug lenalidomide is an established agent in MM pharmacotherapy.[12] Lenalidomide exerts direct immunomodulatory and tumoricidal effects by modulating the E3 ligase protein cereblon.[13-16] This triggers proteasomal degradation of the transcription factors Ikaros and Aiolos, leading to downregulation of *IRF4* and *c-MYC* and upregulation of interleukin 2.[14,16,17] The efficacy of lenalidomide plus dexamethasone is greater than that of lenalidomide alone.[18-20] Indeed, this regimen is effective and well tolerated in patients with relapsed/refractory MM (RRMM), as demonstrated by 2 large, randomized, double-blind, phase III trials (MM-009 and MM-010).[18,19,21] In both trials, time to progression and overall survival were prolonged with lenalidomide plus dexamethasone versus placebo plus dexamethasone. These trials led to the approval of the combination by the United States Food and Drug Administration and the European Commission for the treatment of MM in patients who have received $\geq$ 1 prior therapy.[13,22,23]

Given the key role of lenalidomide in the treatment of RRMM,[2,12] accurate understanding of its safety profile, particularly in patient populations that may not qualify for clinical trial participation or have access to clinical trials, is critical for clinicians. Indeed, differences in both patient and disease characteristics between MM clinical trial and real-world populations can impact reported outcomes.[24] Because real-world safety findings regarding the use of lenalidomide in patients with RRMM are limited, there is a need for such data. Moreover, because lenalidomide is typically administered until PD, many patients will receive long-term treatment with lenalidomide. This prolonged exposure may confound interpretation of safety data. Specifically, adverse events (AEs) are often reported as percentages, which cannot take into account length of time on treatment. Thus, incidence rates—the frequency of events observed over a definite time period—provide enhanced context for the safety of long-term treatments, especially in comparison with fixed-duration therapies.

In this observational, noninterventional European Post-Authorization Safety Study (EU PASS), the safety of lenalidomide plus dexamethasone in the treatment of RRMM was investigated in a real-world setting comprising 269 sites across 17 countries in the European Union. This is the largest prospective real-world European study of lenalidomide in RRMM undertaken to date. Following are detailed safety data regarding AEs of special interest with lenalidomide treatment (including both overall percentages and incidence rates) and comparisons with data from a non-lenalidomide background cohort comprising primarily patients who received bortezomib but also thalidomide and other agents.

Patients and Methods

Study Design

The study included a lenalidomide cohort and a background cohort. Patients in both cohorts had received $\geq$ 1 prior anti-myeloma therapy and were required to have never received lenalidomide. Enrolled patients who were treated on the study with lenalidomide for off-label indications were kept in the study. To achieve a patient population reflective of those treated in real-world clinical practice, there were few restrictions on eligibility. Exclusion criteria were refusal to participate in the study, concurrent participation in an interventional clinical trial, and previous exposure to lenalidomide. Patients in the lenalidomide cohort commenced lenalidomide treatment, whereas those in the background cohort commenced a therapy other than lenalidomide. Patients previously enrolled in the background cohort who were subsequently prescribed lenalidomide as a new line of treatment could re-enter the study as new patients in the lenalidomide cohort.

Recruitment began in August 2008 and ended once 1500 patients in the lenalidomide cohort began the third treatment cycle; up to 1500 patients could be enrolled in the background cohort. The sample size was determined based on incidences of AEs of special interest reported in the MM-009 and MM-010 RRMM clinical trials.[18,19] Data from these trials indicated that 83% of patients completed $\geq$ 3 months of study intervention. Thus, it was estimated that enrolling approximately 1800 patients would provide for 1500 patients at 3 months. Treatment was per the routine practice of the investigator, and all participating patients provided written informed consent. The study protocol was approved by the Committee for Medicinal Products for Human Use and each center's institutional review board or independent ethics committee, as applicable. The final data cutoff was August 31, 2017.

Study Objectives

The primary objectives of the study were to characterize and assess the incidence of AEs of special interest in patients with RRMM treated with lenalidomide in a real-world setting and compare this with the incidence of these AEs in a non-lenalidomide background cohort. The AEs of special interest represent those

Table 1 Demographic and Baseline Characteristics

Characteristic	Lenalidomide Cohort, n (%)	Background Cohort, n (%)			
	Lenalidomide (n = 2150)	Bortezomib (n = 1187)	Thalidomide (n = 137)	Other (n = 155)	Total (n = 1479)
Age, y					
Median (range)	70.0 (25.0-95.0)	69.0 (30.0-93.0)	71.0 (38.0-95.0)	75.0 (44.0-90.0)	70.0 (30.0-95.0)
≤65	781 (36.3)	416 (35.0)	44 (32.1)	24 (15.5)	484 (32.7)
66-75	794 (36.9)	461 (38.8)	54 (39.4)	54 (34.8)	569 (38.5)
≥76	575 (26.7)	310 (26.1)	39 (28.5)	77 (49.7)	426 (28.8)
Male	1150 (53.5)	649 (54.7)	77 (56.2)	82 (52.9)	808 (54.6)
Indication for treatment					
MM	2080 (96.7)	1185 (99.8)	137 (100)	154 (99.4)	1476 (99.8)
Other[a]	70 (3.3)	2 (0.2)	0	1 (0.6)	3 (0.2)
Time since MM diagnosis, y[b]	(n = 2148)	(n = 1187)	(n = 137)	(n = 155)	(n = 1479)
Median (range)	2.9 (0.0-36.9)	3.0 (0.0-28.7)	3.1 (0.1-23.3)	3.1 (0.1-16.1)	3.0 (0.0-28.7)
ECOG PS					
0-2	1734 (80.7)	926 (78.0)	99 (72.3)	106 (68.4)	1131 (76.5)
3-4	60 (2.8)	44 (3.7)	10 (7.3)	6 (3.9)	60 (4.1)
Unknown/missing	356 (16.6)	217 (18.3)	28 (20.4)	43 (27.7)	288 (19.5)
Patients with prior therapies	2127 (98.9)	1176 (99.1)	133 (97.1)	155 (100)	1464 (99.0)
No. prior therapies					
0	23 (1.1)[c]	11 (0.9)	4 (2.9)	0	15 (1.0)
1	950 (44.2)	840 (70.8)	77 (56.2)	82 (52.9)	999 (67.5)
2	685 (31.9)	219 (18.4)	33 (24.1)	46 (29.7)	298 (20.1)
3	271 (12.6)	67 (5.6)	13 (9.5)	16 (10.3)	96 (6.5)
4	126 (5.9)	29 (2.4)	6 (4.4)	8 (5.2)	43 (2.9)
5	53 (2.5)	15 (1.3)	4 (2.9)	3 (1.9)	22 (1.5)
6	42 (2.0)	6 (0.5)	0	0	6 (0.4)
Previous treatment before study drug[d]					
Alkylating agents (including high-dose treatment)[e]	1863 (86.7)	1084 (91.3)	117 (85.4)	133 (85.8)	1334 (90.2)
Bortezomib	1436 (66.8)	282 (23.8)	62 (45.3)	72 (46.5)	416 (28.1)
Thalidomide	870 (40.4)	640 (53.9)	36 (26.3)	44 (28.4)	720 (48.7)
Topoisomerase inhibitors	766 (35.6)	323 (27.2)	31 (22.6)	22 (14.2)	376 (25.4)
Thalidomide and bortezomib	172 (8.0)	40 (3.4)	1 (0.7)	11 (7.1)	52 (3.5)
Chemotherapy assigned at baseline in combination with study drug					
Cyclophosphamide	67 (3.1)	175 (14.7)	39 (28.5)	61 (39.4)	275 (18.6)
Doxorubicin	13 (0.6)	58 (4.9)	3 (2.2)	10 (6.5)	71 (4.8)
Melphalan[f]	7 (0.3)	130 (11.0)	33 (24.1)	68 (43.9)	231 (15.6)
Vincristine	2 (0.1)	2 (0.2)	0	16 (10.3)	18 (1.2)
Other	120 (5.6)	144 (12.1)	21 (15.3)	57 (36.8)	222 (15.0)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; IgG = immunoglobulin G; MM = multiple myeloma.
[a]For the lenalidomide cohort, "Other" includes 55 patients with off-label indications as well as 15 patients with myeloma-related (on-label) indications, such as "plasma cell myeloma," "plasmacytoma," "plasma cell leukemia," and "blood IgG increased."
[b]Time since MM diagnosis is calculated as (date of informed consent − date of diagnosis) + 1; when day is missing, it is estimated as 1; when the month is missing, it is estimated as June.
[c]Three patients in the lenalidomide cohort with MM had no previous therapies; most of the patients who received lenalidomide with no previous therapies received the study drug for indications other than MM.
[d]Previous treatment exposure at any time before starting study drug.
[e]More commonly prescribed alkylating agents included such drugs as melphalan, cyclophosphamide, lomustine, and carmustine.
[f]Melphalan includes drugs named Melphalan or Alkeran.

reported with lenalidomide treatment (and listed in the summary of product characteristics), including neutropenia, thrombocytopenia, infections, bleeding events, venous thromboembolism (VTE), cardiac failure, cardiac arrhythmias, QT prolongation, neuropathy, rash, hypersensitivity, hypothyroidism, and renal failure. Secondary objectives included monitoring neuropathy in patients with baseline

neuropathy taking lenalidomide, compliance with pregnancy testing requirements in women of childbearing potential taking lenalidomide, and identification of new safety signals with lenalidomide treatment.

Assessments

Assessments were conducted per routine clinical practice. AEs were coded per Medical Dictionary for Regulatory Activities version 18.0. AE severity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 whenever possible. Treatment-emergent AEs (TEAEs) were defined as AEs occurring on or after the first treatment and within 30 days after the last dose.

Patients were followed for up to 36 months for second primary malignancy (SPM) assessments per a protocol amendment modifying the design of the study 3 years after trial start. Follow-up occurred 30 days after ending active treatment and was subsequently scheduled for every 6 months. SPMs were identified using the Medical Dictionary for Regulatory Activities terms under the "Neoplasms benign, malignant, and unspecified" System Organ Class. SPMs were assessed as medically important events and reported as serious AEs.

Analyses

Analyses were performed using the safety population (patients who received $\geq$ 1 dose of treatment). The sample size of 1500 in the lenalidomide cohort would permit evaluation of AEs with an incidence of 1/500 to be detected with a 95% CI.

Results

Patients and Treatment

At the data cutoff of August 31, 2017, the safety population included 3629 patients from 269 sites in 17 European countries. Of these patients, 2150 (59.2%) were in the lenalidomide cohort, and 1479 (40.8%) were in the background cohort. As permitted by protocol, 126 (5.9%) patients in the lenalidomide cohort were previously enrolled in the background cohort. In the background cohort, 1187 (80.3%) patients received bortezomib, 137 (9.3%) received thalidomide, and 155 (10.5%) received other agents. Of the 1187 patients who received bortezomib, 882 (74.3%) received it intravenously.

Baseline characteristics for the treatment cohorts are shown in Table 1. The median age was 70.0 years, and most patients had an Eastern Cooperative Oncology Group performance status of 0 to 2. The median number of treatments received prior to enrollment was 1, but a smaller proportion of patients in the lenalidomide cohort (44.2%) than in the bortezomib (70.8%) or thalidomide (56.2%) subcohort had only 1 prior treatment. Alkylating agents were the most common previously received antimyeloma medications (including high-dose treatments) before study enrollment.

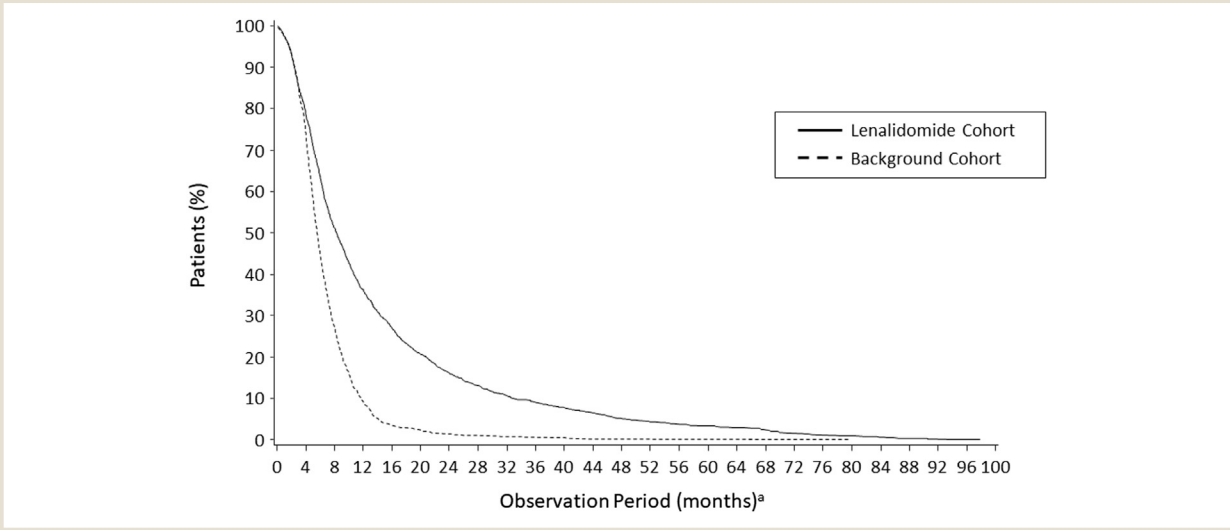
The median for the highest dose of lenalidomide achieved was 25 mg, and the median final dose was 15 mg. The average daily dose was 18.6 mg. The median duration of treatment was 6.6 months (range, 0.1-97.9 months) for lenalidomide, 4.1 months for bortezomib (range, 0-79.4 months), and 4.6 months for thalidomide (range, 0.2-36.9 months). Figure 1 displays patients under observation by time for both the lenalidomide and background cohorts. The lenalidomide cohort had an observation period of 2525 person-years versus 652, 92, and 91 person-years for patients treated with bortezomib, thalidomide, and other therapies, respectively. At the time of data cutoff, all patients had discontinued treatment (see Supplemental Table 1 in the online version). The most common reason for discontinuation was PD in the lenalidomide cohort (32.3%) and the thalidomide subcohort (25.5%); in the bortezomib subcohort, the most common reason was completion of planned treatment course (35.7%). Treatment discontinuation owing to AEs appeared similar among patients in the lenalidomide cohort (22.7%) and the bortezomib (20.1%) and thalidomide (21.2%) subcohorts. The median time to discontinuation owing to an AE was 4.4 months in the lenalidomide cohort, 3.5 months in the bortezomib subcohort, and 2.8 months in the thalidomide subcohort. The mean time to discontinuation owing to an AE was 9.2, 4.2, and 4.1 months, respectively. The disparities in observation length, duration of treatment, and primary causes of treatment discontinuation between the lenalidomide cohort and bortezomib subcohort are likely attributable to the intended courses of treatment for each drug. Per labeled posology, lenalidomide should be given until PD or intolerance in patients with RRMM.[13,22] Conversely, bortezomib, which was the most commonly received drug in the background cohort, is given as a fixed-duration treatment.[25,26]

Adverse Events of Special Interest

To account for differences in observation length and treatment duration, AEs of special interest were analyzed using incidence rates per 100 person-years (Table 2). The AEs with the highest incidence rates overall were infections, neutropenia, thrombocytopenia, and neuropathy. The incidence rate of neuropathy was much lower in the lenalidomide cohort (10.5) than in the bortezomib (78.9) or thalidomide (38.7) subcohort. Likewise, lenalidomide had a lower incidence rate of infections (68.7) than bortezomib (95.9) or thalidomide (76.0). Conversely, the incidence rate of neutropenia was higher with lenalidomide (38.0) than with bortezomib (18.2) or thalidomide (25.7). The incidence rate of thrombocytopenia was 24.4 in the lenalidomide cohort, which was lower than that in the bortezomib subcohort (40.4) but higher than that in the thalidomide subcohort (14.4). For the remaining AEs of special interest, incidence rates were generally low irrespective of cohort.

The frequencies of grade 3/4 cardiac failure, cardiac arrhythmias, bleeding events, renal failure, and rash were low regardless of intervention (ranging from 0.4% to 4.1% in the lenalidomide cohort, 0% to 2.6% in the bortezomib subcohort, and 0% to 2.9% in the thalidomide subcohort) (Table 3). In addition, across all patients, grade 3/4 VTE was reported infrequently (2.9% in the lenalidomide cohort, 0.5% in the bortezomib subcohort, and 0% in the thalidomide subcohort). An apparently similar proportion of patients across treatment cohorts had $\geq$ 1 previous thromboembolic event in their medical histories (11.6% in the lenalidomide cohort and 10.2% in the bortezomib and thalidomide subcohorts). Thromboembolic prophylaxis was given to patients based on physician discretion, history of thromboembolism, and recommended use of thromboembolic prophylaxis with lenalidomide. Medication for thromboembolic prophylaxis (eg, warfarin, aspirin, low-molecular-weight heparin, and others) was taken at baseline by

Figure 1 Percentage of Patients in the Lenalidomide Cohort Versus the Background Cohort Under Observation by Time. The Lenalidomide Cohort Experienced a Longer Observation Period Compared With the Background Cohort



[a]The period of observation is from day of consent to last contact or last known date alive

71.0% of patients in the lenalidomide cohort compared with 31.5% of patients in the bortezomib subcohort and 64.2% in the thalidomide subcohort. Among all patients, hypothyroidism, hypersensitivity, and QT prolongation were rarely reported.

Neuropathy Status

In the lenalidomide cohort, 806 (37.5%) patients had pre-existing neuropathy (motor and/or sensory) at baseline: 35 (4.3%) had grade 3 or 4 motor neuropathy and 46 (5.7%) had grade 3 or 4 sensory neuropathy at baseline (see Supplemental Table 2 in the online version). Neuropathy in patients receiving lenalidomide was mostly mild to moderate throughout the study, and sensory neuropathy was more common than motor neuropathy. Among patients with neuropathy, the frequency of grade 3 or 4 motor or sensory neuropathy was $\leq$ 5% during the first 12 months of treatment. Moreover, grade 4 events were recorded infrequently throughout the study. Indeed, after baseline, grade 4 motor neuropathy was only reported in 1 patient each at months 2, 4, and 6. Similarly, grade 4 sensory neuropathy was only reported in 1 patient each at months 1, 7, 14, and 24. As previously noted, the incidence rate of neuropathy was markedly lower in the lenalidomide cohort than in the bortezomib and thalidomide subcohorts. The findings suggest that pre-existing neuropathy did not worsen in patients treated with lenalidomide.

Adverse Events

In the lenalidomide cohort, 1999 (93.0%) patients experienced $\geq$ 1 any-grade TEAE and 1245 (57.9%) experienced $\geq$ 1 grade 3/4 TEAE (see Supplemental Table 3 in the online version). In the bortezomib and thalidomide subcohorts, respectively, 973 (82.0%) and 122 (89.1%) patients experienced $\geq$ 1 any-grade TEAE, and 486 (40.9%) and 60

Table 2 Incidence Rates of AEs of Special Interest

MedDRA SMQ or HLT, IR per 100 PY (95% CI)	Lenalidomide (n = 2150)	Bortezomib (n = 1187)	Thalidomide (n = 137)	Other (n = 155)
Infections	68.7 (64.5-73.2)	95.9 (86.8-106.0)	76.0 (56.2-102.8)	83.5 (62.6-111.5)
Neutropenia	38.0 (35.2-41.1)	18.2 (14.8-22.5)	25.7 (16.0-41.4)	39.6 (27.0-58.2)
Thrombocytopenia	24.4 (22.2-26.7)	40.4 (35.0-46.8)	14.4 (7.7-26.7)	32.8 (21.6-49.8)
Neuropathy	10.5 (9.2-12.0)	78.9 (70.9-87.8)	38.7 (26.0-57.8)	2.7 (0.7-10.6)
Venous thromboembolism	6.2 (5.2-7.3)	3.0 (1.8-5.0)	–[a]	4.0 (1.3-12.5)
Cardiac failure	2.9 (2.3-3.7)	2.4 (1.4-4.2)	1.4 (0.2-9.7)	4.0 (1.3-12.3)
Bleeding events	6.8 (5.8-8.0)	10.2 (7.7-13.4)	5.6 (2.1-14.8)	4.0 (1.3-12.3)
Rash	5.8 (4.8-6.9)	4.7 (3.1-7.0)	8.4 (3.8-18.7)	2.7 (0.7-10.9)
Cardiac arrhythmias	2.9 (2.3-3.7)	4.4 (2.9-6.7)	–[a]	4.0 (1.3-12.3)

Abbreviations: AE = adverse event; CI = confidence interval; HLT = high-level term; IR = incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; PY = person-years; SMQ = Standardized MedDRA Query.
[a]No patients reported AEs for these categories, so IRs and CIs were not calculated.

Table 3 Frequencies of AEs of Special Interest[a]

MedDRA SMQ or HLT, n (%)	Lenalidomide Cohort		Background Cohort							
	Lenalidomide (n = 2150)		Bortezomib (n = 1187)		Thalidomide (n = 137)		Other (n = 155)		Total (n = 1479)	
	All TEAEs	Grade 3/4 TEAEs	All TEAEs	Grade 3/4 TEAEs	All TEAEs	Grade 3/4 TEAEs	All TEAEs	Grade 3/4 TEAEs	All TEAEs	Grade 3/4 TEAEs
Infections	965 (44.9)	308 (14.3)	386 (32.5)	119 (10.0)	42 (30.7)	19 (3.9)	46 (29.7)	12 (7.7)	474 (32.0)	150 (10.1)
Neutropenia	629 (29.3)	433 (20.1)	87 (7.3)	53 (4.5)	17 (12.4)	10 (7.3)	26 (16.8)	18 (11.6)	130 (8.8)	81 (5.5)
Thrombo-cytopenia	464 (21.6)	216 (10.0)	180 (15.2)	100 (8.4)	10 (7.3)	5 (3.6)	22 (14.2)	6 (3.9)	212 (14.3)	111 (7.5)
Neuropathy	210 (9.8)	30 (1.4)	337 (28.4)	65 (5.5)	24 (17.5)	3 (2.2)	2 (1.3)	0	363 (24.5)	68 (4.6)
Renal failure	176 (8.2)	88 (4.1)	46 (3.9)	31 (2.6)	5 (3.6)	4 (2.9)	5 (3.2)	5 (3.2)	56 (3.8)	40 (2.7)
Bleeding events	144 (6.7)	25 (1.2)	50 (4.2)	11 (0.9)	5 (3.6)	2 (1.5)	3 (1.9)	2 (1.3)	58 (3.9)	15 (1.0)
VTE	132 (6.1)	63 (2.9)	15 (1.3)	6 (0.5)	0	0	3 (1.9)	0	18 (1.2)	6 (0.4)
Rash	122 (5.7)	8 (0.4)	23 (1.9)	0	6 (4.4)	0	2 (1.3)	0	31 (2.1)	0
Cardiac failure	65 (3.0)	28 (1.3)	12 (1.0)	6 (0.5)	1 (0.7)	1 (0.7)	3 (1.9)	3 (1.9)	16 (1.1)	10 (0.7)
Cardiac arrhythmias	64 (3.0)	23 (1.1)	22 (1.9)	10 (0.8)	0	0	3 (1.9)	2 (1.3)	25 (1.7)	12 (0.8)
Hypothyroidism	6 (0.3)	1 (< 0.1)	1 (0.1)	0	0	0	0	0	1 (0.1)	0
Hypersensitivity	5 (0.2)	0	4 (0.3)	0	0	0	0	0	4 (0.3)	0
QT prolongation	0	0	0	0	0	0	0	0	0	0

Abbreviations: AE = adverse event; HLT = high-level term; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardized MedDRA Query; TEAE = treatment-emergent adverse event; VTE = venous thromboembolism.
[a]Data may have been affected by the longer median duration of treatment in the lenalidomide cohort versus the bortezomib and thalidomide subcohorts.

(43.8%) patients experienced ≥ 1 grade 3/4 TEAE. The most frequently reported TEAEs of any grade in the lenalidomide cohort were hematologic (neutropenia, anemia, thrombocytopenia), followed by the nonhematologic TEAEs of diarrhea, pyrexia, fatigue, asthenia, constipation, and peripheral neuropathy (see Supplemental Table 4 in the online version). Peripheral neuropathy was reported in 4.6% of patients taking lenalidomide versus 16.8% of those taking bortezomib and 8.0% of those taking thalidomide. Likewise, hematologic TEAEs (neutropenia, thrombocytopenia, anemia, and leukopenia) were the most commonly occurring grade 3/4 TEAEs (Table 4), and pneumonia, asthenia, peripheral neuropathy, and renal failure were the most common nonhematologic grade 3/4 TEAEs.

Dose Modifications

The proportion of patients with ≥ 1 related TEAE that led to treatment discontinuation was similar between the lenalidomide cohort (19.0%) and the bortezomib subcohort (17.1%). In the thalidomide subcohort, 21.2% of patients had ≥ 1 related TEAE that led to treatment discontinuation. The most common related TEAEs that led to discontinuation were thrombocytopenia (2.5%), neutropenia (2.3%), and infections (2.0%) in the lenalidomide cohort, peripheral neuropathy (5.3%) and peripheral sensory neuropathy (2.1%) in the bortezomib subcohort, and dizziness (2.9%), infections (2.9%), polyneuropathy (2.2%), and constipation (2.2%) in the thalidomide subcohort. The proportion of patients with a TEAE leading to dose interruption was higher in the lenalidomide cohort (46.2%) than in the bortezomib (31.2%) and thalidomide (29.2%) subcohorts.

Short-Term Exposure Safety Analysis

A post hoc analysis was performed to compare the safety profiles for patients in both cohorts for up to 4 months of treatment (see Supplemental Table 5 in the online version) owing to the difference in median treatment duration for observation of TEAEs in the cohorts (6.6 months for the lenalidomide cohort, 4.1 months for the bortezomib subcohort, and 4.6 months for the thalidomide subcohort). A period of 4 months was chosen because it corresponds to the approximate median duration of treatment in the background cohort and the end of the first 3 cycles of lenalidomide treatment. For the AEs of special interest, the rate of any-grade TEAEs and grade 3/4 TEAEs within the first 4 months of study treatment were generally comparable between the lenalidomide and the background cohorts as a whole. Grade 3/4 neutropenia was reported more frequently in the lenalidomide cohort (12.6%) than in the bortezomib (4.0%), thalidomide (5.8%), and other (10.3%) subcohorts. Conversely, grade 3/4 neuropathy was reported less frequently in the lenalidomide cohort (0.7%) than in the bortezomib (4.3%) and thalidomide (2.2%) subcohorts; no instances of grade 3/4 neuropathy were reported with other treatments. The rate of grade 3/4 VTE was low overall; it was reported in 1.2% of the lenalidomide cohort and 0.4% of the bortezomib subcohort. No instances of grade 3/4 VTE were reported in the thalidomide or other subcohorts. In summation, no unexpected differences were noted in the frequencies of AEs of special interest with short-term treatment exposure between the lenalidomide and background cohorts.

Long-Term Lenalidomide Exposure Safety Analysis

An additional post hoc analysis was performed to assess the safety of prolonged lenalidomide administration by comparing the frequencies of AEs of special interest during short-term treatment (≤ 6 months) versus long-term exposure (> 6 months) in the lenalidomide cohort (see Supplemental Table 6 in the online version). For each AE of special interest, the frequencies of patients reporting any-grade TEAEs and grade 3/4 TEAEs were higher within 6 months of the start of treatment and lower or stable after > 6 months on treatment.

Second Primary Malignancies

SPM incidence rates per 100 person-years are reported in Table 5. Among all patients, the incidence rate of all SPMs was 4.1. Despite overlap of 95% confidence interval (CI) limits between the lenalidomide cohort and the subcohorts for some SPM categories, generalized comparisons may be observed. The incidence rate of all SPMs was highest in the other (6.5) and bortezomib (6.0) subcohorts. Relative to the bortezomib subcohort, the lenalidomide cohort had lower incidence rates for all SPMs and invasive SPMs (including both hematologic and solid tumor SPMs separately) but a higher incidence rate of noninvasive SPMs. Patients treated with lenalidomide had a similar incidence rate of invasive SPMs compared with those treated with thalidomide (2.2 vs. 2.7, respectively), but higher incidence rates for all other categories; the thalidomide subcohort had no reported hematologic or noninvasive SPMs. SPM incidence rates were generally lower with lenalidomide than with the other therapies, but there were no reported hematologic SPMs in the other subcohort.

Lenalidomide Pregnancy Counseling and Contraception

There were 24 (1.1%) women of childbearing potential in the lenalidomide cohort. All received counseling at baseline, and 23 reported using some form of contraception, having a tubal sterilization, or having a vasectomized male partner at baseline and during the study. No pregnancy or potential fetal exposure to lenalidomide was reported in women of childbearing potential in the lenalidomide cohort.

Discussion

To make better informed treatment decisions, physicians need safety data on lenalidomide use in patients with RRMM who may not qualify for clinical trials but are still encountered in clinical practice, especially given that many patients in the real world will receive long-term treatment. This observational, noninterventional EU PASS investigated the safety of lenalidomide plus dexamethasone in a real-world setting and compared it with that of bortezomib and other non-lenalidomide agents. When evaluating safety, duration of treatment is an important consideration; in this study, patients treated with lenalidomide had a longer duration of treatment than those treated with non-lenalidomide therapies. Moreover, although the median duration of treatment in the lenalidomide cohort was 6.6 months, some patients remained on lenalidomide treatment for much longer (up to 97.9 months). Another key factor in safety analyses is the length of observation, which was also longer

Table 4 Most Common (≥ 2% of Patients) Grade 3/4 TEAEs in Either Treatment Cohort

	Lenalidomide Cohort		Background Cohort					
	Lenalidomide (n = 2150)		Bortezomib (n = 1187)		Thalidomide (n = 137)		Other (n = 155)	
System Organ Class Preferred Term, n (%)[a,b]	Grade 3/4 TEAEs[c]	Related Grade 3/4 TEAEs[c]	Grade 3/4 TEAEs[c]	Related Grade 3/4 TEAEs[c]	Grade 3/4 TEAEs[c]	Related Grade 3/4 TEAEs[c]	Grade 3/4 TEAEs[c]	Related Grade 3/4 TEAEs[c]
Hematologic	594 (27.6)	509 (23.7)	152 (12.8)	125 (10.5)	16 (11.7)	7 (5.1)	26 (16.8)	21 (13.5)
Neutropenia	371 (17.3)	342 (15.9)	42 (3.5)	38 (3.2)	6 (4.4)	4 (2.9)	14 (9.0)	13 (8.4)
Thrombocytopenia	198 (9.2)	161 (7.5)	87 (7.3)	79 (6.7)	5 (3.6)	1 (0.7)	6 (3.9)	6 (3.9)
Anemia	185 (8.6)	113 (5.3)	38 (3.2)	18 (1.5)	7 (5.1)	1 (0.7)	11 (7.1)	5 (3.2)
Leukopenia	70 (3.3)	59 (2.7)	18 (1.5)	18 (1.5)	0	0	1 (0.6)	1 (0.6)
Infections and infestations	307 (14.3)	110 (5.1)	119 (10.0)	50 (4.2)	19 (13.9)	4 (2.9)	12 (7.7)	6 (3.9)
Pneumonia	104 (4.8)	41 (1.9)	36 (3.0)	18 (1.5)	10 (7.3)	1 (0.7)	3 (1.9)	2 (1.3)
General disorders and administration-site conditions	187 (8.7)	86 (4.0)	56 (4.7)	25 (2.1)	4 (2.9)	2 (1.5)	14 (9.0)	5 (3.2)
Asthenia	43 (2.0)	26 (1.2)	17 (1.4)	4 (0.3)	0	0	5 (3.2)	2 (1.3)
Nervous system disorders	113 (5.3)	57 (2.7)	89 (7.5)	71 (6.0)	9 (6.6)	5 (3.6)	1 (0.6)	0
Peripheral neuropathy	13 (0.6)	12 (0.6)	40 (3.4)	39 (3.3)	2 (1.5)	1 (0.7)	0	0
Renal and urinary disorders	100 (4.7)	21 (1.0)	40 (3.4)	7 (0.6)	5 (3.6)	0	6 (3.9)	1 (0.6)
Renal failure	44 (2.0)	13 (0.6)	21 (1.8)	2 (0.2)	1 (0.7)	0	2 (1.3)	0

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
[a]Patient with multiple occurrences of an AE is counted only once in the AE category.
[b]System organ classes and preferred terms are coded using MedDRA version 18.0. System organ classes and preferred terms are listed in descending order of frequency for all TEAEs for the lenalidomide cohort.
[c]Reported in ≥ 2% of patients in either the lenalidomide cohort or background cohort as a whole.

Table 5 Incidence Rates of SPMs

SPM, IR per 100 PY (95% CI)[a]	Lenalidomide (n = 2150)	Bortezomib (n = 1187)	Thalidomide (n = 137)	Other (n = 155)
Total SPMs[b]	3.6 (2.9-4.5)	6.0 (4.3-8.5)	2.7 (0.7-10.9)	6.5 (2.7-15.6)
Invasive SPMs	2.2 (1.6-2.9)	5.3 (3.7-7.7)	2.7 (0.7-10.9)	3.9 (1.2-12.0)
Solid tumors	1.6 (1.2-2.2)	4.2 (2.8-6.4)	2.7 (0.7-10.9)	3.9 (1.2-12.0)
Hematologic	0.6 (0.3-1.0)	1.2 (0.5-2.6)	—[c]	—[c]
AML	0.1 (0.0[d]-0.4)	1.0 (0.4-2.4)	—[c]	—[c]
MDS	0.4 (0.2-0.8)	0.2 (0.0[e]-1.4)	—[c]	—[c]
Other hematologic[f]	0.0[d] (0.0[g]-0.3)	—[c]	—[c]	—[c]
Noninvasive SPMs	1.5 (1.1-2.1)	0.8 (0.3-2.1)	—[c]	3.9 (1.3-12.0)

Abbreviations: AML = acute myeloid leukemia; CI = confidence interval; IR = incidence rate; MDS = myelodysplastic syndrome; PY = person-years; SPM = second primary malignancy.
[a]Patients who experienced > 1 SPM (eg, 2 types of SPMs) or > 1 episode of an SPM are counted once in each SPM category and once in the total row.
[b]Total includes the number of patients with ≥ 1 SPM.
[c]No patients reported SPMs in these categories, so IRs and CIs were not calculated.
[d]Rounded down from 0.04.
[e]Rounded down from 0.03.
[f]Adult T-cell lymphoma/leukemia.
[g]Rounded down from 0.01.

with lenalidomide compared with bortezomib, thalidomide, or other agents. These differences may be attributed to the treatment schedules of each agent. Per the drug label, lenalidomide is administered until PD or intolerance, whereas bortezomib (the most commonly received treatment of the non-lenalidomide therapies in this study) is typically administered for a fixed treatment period.[22,25] To account for the increased length of time that patients received lenalidomide versus the therapies in the background cohort, incidence rates of the AEs of special interest were assessed in addition to their raw frequencies.

Compared with bortezomib and thalidomide, lenalidomide had a lower incidence rate of infections but a higher incidence rate of neutropenia. The incidence rate of thrombocytopenia with lenalidomide was lower than that with bortezomib but higher than that with thalidomide. Most other AEs of special interest—such as cardiac failure, hypothyroidism, bleeding events, hypersensitivity, and others—were rarely reported across cohorts. Notably, patients receiving lenalidomide reported a lower incidence rate of neuropathy than did patients receiving non-lenalidomide therapies, and lenalidomide-treated patients with baseline neuropathy generally did not report worsening throughout the study. Based on these results, the present status of peripheral neuropathy as an important potential risk for patients starting a new line of treatment with lenalidomide may require reassessment.

The incidence rates of SPMs in the lenalidomide cohort align with what has been previously reported with lenalidomide. In a pooled analysis of the MM-009 and MM-010 RRMM clinical trials, the overall SPM incidence rate was higher in the lenalidomide group (3.98; 95% CI, 2.51-6.31) than in the placebo group (1.38; 95% CI, 0.44-4.27).[27] The authors attributed this difference to the increased incidence of nonmelanoma skin carcinomas in the lenalidomide group (2.40 [95% CI, 1.33-4.33] vs. 0.91 [95% CI, 0.23-3.66]); the incidence rate of invasive SPMs was not higher in the lenalidomide group (1.71; 95% CI, 0.86-3.43) than in the placebo group (0.91; 95% CI, 0.23-3.66). The rates of overall SPM incidence (3.6; 95% CI, 2.9-4.5) and invasive SPM incidence (2.2; 95% CI, 1.6-2.9) reported in the lenalidomide cohort of this EU PASS are similar to those reported in the lenalidomide group of the pooled analysis. A review of SPMs by the International Myeloma Working Group provides additional context, noting no increase in SPM incidence with lenalidomide plus dexamethasone (without melphalan).[28]

Data from analyses by time on treatment are also consistent with the established safety profile of lenalidomide. The short-term exposure safety analysis, conducted for better comparability of treatments owing to the differences in median treatment duration for observation of TEAEs across the treatment cohorts, revealed no unexpected differences between the lenalidomide and background cohorts in rates of grade 3/4 AEs of special interest within the first 4 months of study treatment. The long-term lenalidomide exposure analysis revealed that, across all AEs of special interest, the frequencies of grade 3/4 TEAEs after 6 months of lenalidomide treatment were lower than or similar to those reported within the first 6 months. Diarrhea occurred after 6 months in 13.9% (any grade) and 0.9% (grade 3/4) of patients in the lenalidomide cohort. Diarrhea was also a related TEAE that led to discontinuation (at any point during treatment) in 1.1% of patients in the lenalidomide cohort. It has been hypothesized that late onset of lenalidomide-related diarrhea may be related to immune-mediated antimyeloma activity,[29] highlighting the need for appropriate AE management throughout treatment. Overall, these results underscore the long-term tolerability of lenalidomide and are consistent with its established safety profile. Without the strict inclusion and exclusion criteria of randomized clinical studies, this EU PASS provides data on the real-world use and safety of lenalidomide plus dexamethasone, offering a more complete perspective of the safety profile. The results of this EU PASS are consistent with the recently published results of a smaller (n = 98 at 16 sites), German, noninterventional, observational study of lenalidomide plus dexamethasone in patients with RRMM.[30]

Although cross-trial comparisons must be interpreted with caution, it is valuable to compare the real-world results from the lenalidomide cohort of the EU PASS with those from the

lenalidomide groups of the MM-009 and MM-010 clinical trials. Grade 3/4 neutropenia was lower in the EU PASS than in both MM-009 and MM-010 (20.1% vs. 41.2% and 29.5%, respectively), whereas grade 3/4 thrombocytopenia was similar (10.0% vs. 14.7% and 11.4%, respectively). Grade 3/4 infections were reported in 14.3% of patients in the EU PASS, which is lower than the frequency reported for "any infection" in MM-009 (21.5%) but higher than the frequencies of "upper respiratory infection" (1.7%) and "all other infection" (11.4%) in MM-010. Grade 3/4 VTE was reported markedly less frequently in the EU PASS than in MM-009 and MM-010 (2.9% vs. 14.7% and 11.4%, respectively). This is likely attributable to differences in thromboembolic prophylaxis use. Per standard treatment practices at the times of the studies, thromboprophylaxis was not required in MM-009 and not recommended in MM-010. Recommendations have since changed,[31] and 71.0% of patients in the lenalidomide cohort of the EU PASS were receiving thromboembolic prophylaxis at baseline. Overall, the frequencies of AEs of special interest reported in the lenalidomide cohort of the EU PASS were mostly lower than or similar to those reported in the lenalidomide groups of the MM-009 and MM-010 clinical trials.

As per the nature of observational research, there was no randomization of treatments, and the decision to treat a patient was made prior to the decision to include a patient in this study. Therefore, different factors may have affected treatment allocation and contributed to bias. For instance, the severity of a patient's disease may have influenced the investigator's treatment choice. Additionally, a higher proportion of patients in the lenalidomide cohort (54.7%) than in the background cohort (28.3%) had received $\geq$ 2 therapies prior to study enrollment, which likely correlates to a greater morbidity and susceptibility to AEs among those patients, because disease severity typically increases with subsequent lines of therapy.

Conclusion

In conclusion, no new safety signals for lenalidomide were identified in the EU PASS, which is the largest prospective real-world European study of lenalidomide in RRMM undertaken to date. The results of this study demonstrate that the safety profile of lenalidomide plus dexamethasone in patients with RRMM in a real-world setting is comparable to that seen in clinical trials of lenalidomide in the RRMM setting. These findings have confirmed the established safety profile of lenalidomide for patients with RRMM in a real-world setting.

Clinical Practice Points

- Lenalidomide is an approved agent and a standard treatment option for patients with RRMM based on the results of multiple clinical trials
- There is a need to explore outcomes in patients with RRMM who may not qualify for clinical trial participation but are routinely encountered in clinical practice, especially because many will receive long-term treatment
- The real-world findings observed in patients with RRMM in this prospective European post-authorization safety study confirm the established toxicity profile of lenalidomide; no new safety signals were observed
- These results will provide clinicians with better insight regarding the use of lenalidomide in their patients, many of whom will have different patient and disease characteristics than those included in clinical trials

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Supplemental Data

Supplemental tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.clml.2020.05.006.

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Supplemental Table 1 Treatment Discontinuation[a]

Reason for Discontinuation	Lenalidomide Cohort, n (%)	Background Cohort, n (%)			
	Lenalidomide (n = 2150)	Bortezomib (n = 1187)	Thalidomide (n = 137)	Other (n = 155)	Total (n = 1479)
Discontinuations	2150 (100)	1187 (100)	137 (100)	155 (100)	1479 (100)
Owing to disease progression[b]	695 (32.3)	189 (15.9)	35 (25.5)	40 (25.8)	264 (17.8)
Owing to adverse events	487 (22.7)	238 (20.1)	29 (21.2)	16 (10.3)	283 (19.1)
Other[c]	504 (23.4)	162 (13.6)	24 (17.5)	28 (18.1)	214 (14.5)
Death	167 (7.8)	43 (3.6)	5 (3.6)	11 (7.1)	59 (4.0)
Owing to lack of therapeutic effect[d]	90 (4.2)	69 (5.8)	9 (6.6)	14 (9.0)	92 (6.2)
Patient in remission	88 (4.1)	42 (3.5)	6 (4.4)	4 (2.6)	52 (3.5)
Completed course of treatment as planned[e]	45 (2.1)	424 (35.7)	27 (19.7)	35 (22.6)	486 (32.9)
Patient lost to follow-up	38 (1.8)	12 (1.0)	2 (1.5)	3 (1.9)	17 (1.1)
Withdrawal of consent	36 (1.7)	6 (0.5)	0	1 (0.6)	7 (0.5)
Missing	0	2 (0.2)	0	3 (1.9)	5 (0.3)

[a]Data reflect the primary reason for treatment discontinuation as selected by the investigator. Adverse events may have contributed to treatment discontinuation without being selected as the primary reason for discontinuation.
[b]Only the patients in the lenalidomide cohort were to be observed until progressive disease or death.
[c]"Other" reasons (free text responses) included such categories as physician decisions, moving to transplant, or empty field on case record form.
[d]Other than disease progression.
[e]"Completed course of treatment as planned" is applicable for background cohort patients, who had a defined treatment duration; for lenalidomide cohort patients, this applied to those patients who received the drug as induction therapy before stem cell transplant or those from terminated sites where queries could not be issued.

Supplemental Table 2 Neuropathy Status of Patients in the Lenalidomide Cohort During the First 12 Months of Study Participation

Time of Assessment[a]	Lenalidomide Cohort (n = 2150)				
	Patients With Neuropathy, n[b]	Motor Neuropathy[c]		Sensory Neuropathy[c]	
		Grade 1 or 2, n (%)[d,e]	Grade 3 or 4, n (%)[d,e]	Grade 1 or 2, n (%)[d,e]	Grade 3 or 4, n (%)[d,e]
Baseline	806	267 (33.1)	35 (4.3)	653 (81.0)	46 (5.7)
Month 1	671	209 (31.1)	22 (3.3)	515 (76.8)	29 (4.3)
Month 2	589	179 (30.4)	16 (2.7)	456 (77.4)	21 (3.6)
Month 3	487	142 (29.2)	9 (1.8)	377 (77.4)	17 (3.5)
Month 4	427	120 (28.1)	8 (1.9)	328 (76.8)	12 (2.8)
Month 5	349	103 (29.5)	6 (1.7)	269 (77.1)	13 (3.7)
Month 6	293	88 (30.0)	7 (2.4)	226 (77.1)	12 (4.1)
Month 7	252	72 (28.6)	9 (3.6)	190 (75.4)	11 (4.4)
Month 8	215	56 (26.0)	7 (3.3)	162 (75.3)	7 (3.3)
Month 9	195	52 (26.7)	5 (2.6)	149 (76.4)	6 (3.1)
Month 10	171	44 (25.7)	4 (2.3)	123 (71.9)	7 (4.1)
Month 11	155	46 (29.7)	4 (2.6)	115 (74.2)	6 (3.9)
Month 12	131	40 (30.5)	4 (3.1)	100 (76.3)	6 (4.6)

[a]Relative to time of enrollment for each patient.
[b]Patients with both motor and sensory neuropathy were counted once.
[c]For each row, the combined amount of patients reported in the Motor Neuropathy and Sensory Neuropathy columns may not equal the value reported in the Patients With Neuropathy column because some patients reported both motor and sensory neuropathy, and some patients had neuropathy of unknown grading.
[d]Percentages based off value in the Patients with Neuropathy column in the same row.
[e]National Cancer Institute—Common Terminology Criteria version 3.0 was used for grading the status of neuropathy.

Supplemental Table 3 Overview of TEAEs

Patients With ≥ 1 TEAE in the TEAE Category, n (%)[b]	Lenalidomide Cohort[a]	Background[a]			
	Lenalidomide (n = 2150)	Bortezomib (n = 1187)	Thalidomide (n = 137)	Other (n = 155)	Total (n = 1479)
TEAE	1999 (93.0)	973 (82.0)	122 (89.1)	112 (72.3)	1207 (81.6)
Related TEAE	1615 (75.1)	745 (62.8)	92 (67.2)	66 (42.6)	903 (61.1)
Grade 3/4 TEAE	1245 (57.9)	486 (40.9)	60 (43.8)	61 (39.4)	607 (41.0)
Related grade 3/4 TEAE	829 (38.6)	292 (24.6)	22 (16.1)	29 (18.7)	343 (23.2)
TEAE leading to death (grade 5 TEAE)[c]	300 (14.0)	64 (5.4)	10 (7.3)	14 (9.0)	88 (5.9)
Serious TEAE	973 (45.3)	335 (28.2)	46 (33.6)	49 (31.6)	430 (29.1)
Related serious AE	393 (18.3)	114 (9.6)	15 (10.9)	16 (10.3)	145 (9.8)
TEAE leading to discontinuation	739 (34.4)	298 (25.1)	47 (34.3)	25 (16.1)	370 (25.0)
Related TEAE leading to discontinuation	409 (19.0)	203 (17.1)	29 (21.2)	15 (9.7)	247 (16.7)
TEAE leading to dose reduction	516 (24.0)	254 (21.4)	24 (17.5)	23 (14.8)	301 (20.4)
TEAE leading to dose interruption	993 (46.2)	370 (31.2)	40 (29.2)	39 (25.2)	449 (30.4)
TEAE leading to dose interruption and reduction	229 (10.7)	69 (5.8)	5 (3.6)	3 (1.9)	77 (5.2)

Abbreviations: AE = adverse event; TEAE = treatment-emergent adverse event.
[a]Treatment cohorts are defined according to the starting treatment, but patients could have taken other drugs in combination with the main assigned drug.
[b]A patient with multiple occurrences of an AE is counted only once in the AE category.
[c]Includes any death occurring for any reason, including progressive disease, on or after the first treatment of the study medication and within 30 days after the last dose.

Supplemental Table 4 Most Common (≥ 10% of Patients) Any Grade TEAEs in the Lenalidomide Cohort or Background Cohort

System Organ Class Preferred Term, n (%)[a,b]	Lenalidomide Cohort		Background Cohort					
	Lenalidomide (n = 2150)		Bortezomib (n = 1187)		Thalidomide (n = 137)		Other (n = 155)	
	All TEAEs	Related TEAEs	All TEAEs	Related TEAEs	All TEAEs	Related TEAEs	All TEAEs	Related TEAEs
Hematologic	968 (45.0)	829 (38.6)	274 (23.1)	214 (18.0)	31 (22.6)	20 (14.6)	51 (32.9)	36 (23.2)
Neutropenia	534 (24.8)	488 (22.7)	69 (5.8)	63 (5.3)	14 (10.2)	11 (8.0)	22 (14.2)	19 (12.3)
Anemia	471 (21.9)	335 (15.6)	114 (9.6)	67 (5.6)	17 (12.4)	7 (5.1)	26 (16.8)	10 (6.5)
Thrombocytopenia	425 (19.8)	365 (17.0)	154 (13.0)	134 (11.3)	10 (7.3)	5 (3.6)	22 (14.2)	18 (11.6)
General disorders and administration-site conditions	938 (43.6)	509 (23.7)	346 (29.1)	193 (16.3)	49 (35.8)	31 (22.6)	41 (26.5)	16 (10.3)
Fatigue	287 (13.3)	214 (10.0)	108 (9.1)	85 (7.2)	27 (19.7)	24 (17.5)	12 (7.7)	6 (3.9)
Pyrexia	291 (13.5)	72 (3.3)	90 (7.6)	24 (2.0)	11 (8.0)	3 (2.2)	14 (9.0)	6 (3.9)
Asthenia	266 (12.4)	139 (6.5)	94 (7.9)	46 (3.9)	10 (7.3)	3 (2.2)	14 (9.0)	5 (3.2)
Gastrointestinal disorders	770 (35.8)	438 (20.4)	353 (29.7)	222 (18.7)	44 (32.1)	30 (21.9)	27 (17.4)	11 (7.1)
Diarrhea	338 (15.7)	194 (9.0)	138 (11.6)	85 (7.2)	8 (5.8)	3 (2.2)	9 (5.8)	3 (1.9)
Constipation	213 (9.9)	124 (5.8)	137 (11.5)	82 (6.9)	28 (20.4)	23 (16.8)	7 (4.5)	3 (1.9)
Nervous system disorders	620 (28.8)	395 (18.4)	478 (40.3)	418 (35.2)	55 (40.1)	45 (32.8)	19 (12.3)	9 (5.8)
Peripheral neuropathy	98 (4.6)	79 (3.7)	200 (16.8)	192 (16.2)	11 (8.0)	10 (7.3)	1 (0.6)	1 (0.6)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
[a]A patient with multiple occurrences of an AE is counted only once in the AE category.
[b]System organ classes and preferred terms are coded using MedDRA version 18.0. System organ classes and preferred terms are listed in descending order of frequency for all TEAEs for the lenalidomide cohort.

Supplemental Table 5 AEs of Special Interest Occurring Within 4 Months of Start of Study Treatment

MedDRA SMQ or HLT, n (%)	Lenalidomide Cohort		Background Cohort							
	Lenalidomide (n = 2150)		Bortezomib (n = 1187)		Thalidomide (n = 137)		Other (n = 155)		Total (n = 1479)	
	All TEAEs	Grade 3/4 TEAEs	All TEAEs	Grade 3/4 TEAEs	All TEAEs	Grade 3/4 TEAEs	All TEAEs	Grade 3/4 TEAEs	All TEAEs	Grade 3/4 TEAEs
Infections	624 (29.0)	175 (8.1)	320 (27.0)	100 (8.4)	29 (21.2)	10 (7.3)	36 (23.2)	10 (6.5)	385 (26.0)	120 (8.1)
Neutropenia	397 (18.5)	271 (12.6)	78 (6.5)	47 (4.0)	15 (10.9)	8 (5.8)	22 (14.2)	16 (10.3)	115 (7.8)	71 (4.8)
Thrombocytopenia	327 (15.2)	144 (6.7)	167 (14.1)	95 (8.0)	8 (5.8)	3 (2.2)	19 (12.3)	6 (3.9)	194 (13.1)	104 (7.0)
Neuropathy	121 (5.6)	14 (0.7)	300 (35.3)	51 (4.3)	16 (11.7)	3 (2.2)	2 (1.3)	0	318 (21.5)	54 (3.7)
Renal failure	111 (5.2)	49 (2.3)	39 (3.3)	25 (2.1)	4 (2.9)	3 (2.2)	5 (3.2)	5 (3.2)	48 (3.2)	33 (2.2)
Rash	92 (4.3)	7 (0.3)	20 (1.7)	0	5 (3.6)	0	1 (0.6)	0	26 (1.8)	0
Bleeding events	72 (3.3)	11 (0.5)	42 (3.5)	9 (0.8)	4 (2.9)	2 (1.5)	2 (1.3)	1 (0.6)	48 (3.2)	12 (0.8)
Venous thromboembolism	63 (2.9)	26 (1.2)	11 (0.9)	5 (0.4)	0	0	3 (1.9)	0	14 (0.9)	5 (0.3)
Cardiac failure	38 (1.8)	13 (0.6)	12 (1.0)	6 (0.5)	1 (0.7)	1 (0.7)	2 (1.3)	2 (1.3)	15 (1.0)	9 (0.6)
Cardiac arrhythmias	33 (1.5)	12 (0.6)	18 (1.5)	9 (0.8)	0	0	3 (1.9)	2 (1.3)	21 (1.4)	11 (0.7)
Hypersensitivity	2 (0.1)	0	3 (0.3)	0	0	0	0	0	3 (0.2)	0
Hyperthyroidism	1 (<0.1)	0	1 (0.1)	0	0	0	0	0	1 (0.1)	0
QT prolongation	0	0	0	0	0	0	0	0	0	0

Abbreviations: AE = adverse event; HLT = high-level term; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardized MedDRA Query; TEAE = treatment-emergent adverse event.

Supplemental Table 6 AEs of Special Interest Occurring Within 6 Months and After 6 Months of Initiation of Study Treatment in the Lenalidomide Cohort

	Lenalidomide (n = 2150)			
	≤6 Months		>6 Months[a]	
SMQ or HLT, n (%)	All TEAEs	Grade 3/4 TEAEs	All TEAEs	Grade 3/4 TEAEs
Infections	724 (33.7)	212 (9.9)	424 (19.7)	113 (5.3)
Neutropenia	478 (22.2)	321 (14.9)	286 (13.3)	179 (8.3)
Thrombocytopenia	381 (17.7)	172 (8.0)	154 (7.2)	61 (2.8)
Neuropathy	150 (7.0)	20 (0.9)	76 (3.5)	10 (0.5)
Renal failure	131 (6.1)	60 (2.8)	52 (2.4)	29 (1.3)
Rash	97 (4.5)	8 (0.4)	30 (1.4)	0
Bleeding events	94 (4.4)	19 (0.9)	57 (2.7)	6 (0.3)
Venous thromboembolism	90 (4.2)	43 (2.0)	46 (2.1)	20 (0.9)
Cardiac failure	45 (2.1)	17 (0.8)	23 (1.1)	11 (0.5)
Cardiac arrhythmias	38 (1.8)	14 (0.7)	28 (1.3)	9 (0.4)
Hypersensitivity	2 (0.1)	0	3 (0.1)	0
Hypothyroidism	2 (0.1)	0	4 (0.2)	1 (<0.1)

Abbreviations: AE = adverse event; HLT = high-level term; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardized MedDRA Query; TEAE = treatment-emergent adverse event.
[a]Includes any AE that started or worsened > 6 months after treatment began. AEs that started within the first 6 months of treatment but worsened > 6 months after treatment began are only counted as occurring > 6 months after treatment began. Percentages are based on the total safety population in the lenalidomide cohort (n = 2150). For the lenalidomide cohort, 1143 patients were still receiving treatment after 6 months.