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Adverse event management in patients with relapsed and refractory multiple myeloma taking pomalidomide plus low-dose dexamethasone: a pooled analysis

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ABSTRACT

Objectives: Heavily pretreated patients with relapsed and refractory multiple myeloma are susceptible to treatment-related adverse events (AEs). Managing AEs is important to ensure patients continue therapy long enough to receive the best clinical benefit. Data from the MM-002, MM-003, and MM-010 trials were pooled to further characterize the safety profile of pomalidomide plus low-dose dexamethasone and AE management.

Methods: This analysis included 1088 patients who received ≥ 2 prior therapies, including lenalidomide and bortezomib, and progressed ≤ 60 days of last therapy. Patients received 28-day cycles of pomalidomide 4 mg/day on days 1-21 and low-dose dexamethasone 40 mg (20 mg if aged > 75 years) weekly until disease progression or unacceptable toxicity. Thromboprophylaxis was required.

Results: The most common grade 3/4 AEs were neutropenia (56.2%), anemia (32.3%), and thrombocytopenia (25.8%), which occurred within the first few cycles of treatment. Grade 3/4 infections occurred in 33.7% patients, of whom 13.9% had pneumonia and 40.3% had neutropenia. Pomalidomide dose reductions or interruptions were reported in 24.2% and 66.0% of patients, respectively. AEs were managed by dose modifications and/or supportive care.

Conclusions: Pomalidomide plus low-dose dexamethasone showed an acceptable safety profile and AEs were well managed according to study protocols and established guidelines.

Key Words

Relapsed and refractory multiple myeloma, safety, pomalidomide, dexamethasone, pooled analysis

Clinicaltrials.gov identifier: NCT00833833 (MM-002), NCT01311687 (MM-003), and NCT01712789 (MM-010)

INTRODUCTION

Patients with relapsed and refractory multiple myeloma (RRMM) are usually older, have advanced disease, and may present with disease-related comorbidities, such as myelosuppression, bone disease, or renal impairment, which may make further treatment and adverse event (AE) management difficult.(1-3) Because of a high disease burden, lasting effects of prior treatment, and comorbidities, patients with RRMM are more susceptible to treatment-related AEs than patients with newly diagnosed MM.(2-6) This is in part due to exposure to multiple prior therapies, resulting in an increased risk for common treatment-related AEs, including neutropenia, peripheral neuropathy, thrombocytopenia, anemia, and infection.(1-3, 7-11) Infection is a particularly challenging treatment-emergent AE because it is a leading cause of morbidity and death in patients with RRMM.(12, 13) Another potentially serious AE is venous thromboembolism, which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), but DVT and PE are infrequent due to active prophylaxis.(1-3, 5, 9, 12) Given the advanced nature of disease, patients with RRMM should be monitored closely and carefully managed during treatment.

A recently published population-based study in over 9000 patients showed that the risk of bacterial infections (pneumonia and septicemia in particular) and viral infections (such as herpes zoster and influenza) was much higher in patients with MM than in controls, and that the risk of infection had increased in recent years.(14) The risk of infection-related death was also shown to be higher in patients with MM. These findings reflect that patients are reaching increasingly advanced and more heavily pretreated disease stages with prolonged survival through the use of treatment maintenance and novel therapies. Managing the complications of the disease and of its treatment, such as infections, thrombosis, myelotoxicity, and neuropathy, is crucial to ensure that patients remain on therapy for as long as possible to maximize the clinical benefit.

Pomalidomide is a distinct immunomodulatory agent with tumoricidal and immunoregulatory effects. In the United States and European Union, pomalidomide plus low-dose dexamethasone is approved for the treatment of patients with RRMM who have had ≥ 2 prior therapies, including lenalidomide and a proteasome inhibitor (bortezomib in the EU).(15-17) When given orally at 4 mg for 21 of 28 days in combination with low-dose dexamethasone, pomalidomide is both efficacious and safe in patients with RRMM, with a predictable and manageable adverse event profile.(8, 18, 19) Three clinical trials have demonstrated the efficacy and safety of pomalidomide plus low-dose dexamethasone in patients with RRMM.(20-22) Progression-free survival was 4.0 to 4.6 months and median overall survival was 11.9 to 16.5 months in the MM-002, MM-003 (NIMBUS), and MM-010 (STRATUS) trials. Hematologic AEs and infections were the most common grade ≥ 3 AEs reported in these trials. Recently published analyses of these trials demonstrated that pomalidomide plus low-dose dexamethasone is also safe and effective in patients with moderate renal impairment.(23, 24)

Here we report a pooled analysis from these 3 clinical trials (MM-002, MM-003, and MM-010) that further examined the safety profile of pomalidomide plus low-dose dexamethasone—including the incidence and time to onset of the AEs of interest (hematologic AEs, infections, neuropathy, and thrombotic events)—in patients with RRMM and to assess AE management in this population.

METHODS

Study Identification and Selection

MM-002, MM-003, and MM-010 were multicenter studies that, as previously described, evaluated pomalidomide plus low-dose dexamethasone in patients with RRMM.(20-22) The

trials were registered with ClinicalTrials.gov as NCT00833833 (MM-002), NCT01311687 (MM-003), and NCT01712789 (MM-010) and with EudraCT as 2010-019820-30 (MM-003) and 2012-001888-78 (MM-010); approved by institutional review boards or independent ethics committees at each participant site; and conducted in accordance with the Helsinki Declaration of 1975, as revised in 2008.

The inclusion and exclusion criteria were similar among the trials. Eligible adults with documented RRMM had progressive disease ≤ 60 days of their last prior antimyeloma therapy after having received ≥ 2 prior treatments, including ≥ 2 cycles of lenalidomide and bortezomib (alone or in combination). Refractoriness to lenalidomide and bortezomib (or intolerance of bortezomib) was allowed (MM-002) or required (MM-003 and MM-010).

Key exclusion criteria were absolute neutrophil count < 1.0×10^9/L (MM-002, MM-003) or < 0.8×10^9/L (MM-010); platelet count < 75×10^9/L (< 30×10^9/L for patients with ≥ 50% plasma cells of nucleated bone marrow cells); creatinine clearance < 45 mL/min (MM-003 and MM-010) according to the Cockcroft-Gault formula (25); and serum creatinine ≥ 3.0 mg/dL (MM-002). Patients were excluded from the studies if they had peripheral neuropathy grade ≥ 2.

All patients included in this analysis received 28-day cycles of pomalidomide 4 mg/day on days 1-21 plus low-dose dexamethasone 40 mg (20 mg if aged > 75 years) weekly until disease progression or unacceptable toxicity. Thromboprophylaxis with low-dose aspirin, low-molecular-weight heparin, or the equivalent was required for all patients. The instructions for pomalidomide dose reductions, interruptions, and discontinuations were similar among the 3 trials and are described in the supplement (Table S1).

Assessments

Grouped AE terms were used for this pooled analysis to enhance AE detection and to present clinically relevant AE terms. AEs were coded using Medical Dictionary for Regulatory Activities version 14.0. A patient with multiple occurrences of an AE was counted only once in that AE category.

Peripheral neuropathy included the preferred terms peripheral sensory neuropathy, paresthesia, neuropathy peripheral, hypoesthesia, polyneuropathy, peripheral motor neuropathy, dysesthesia, and peripheral sensorimotor neuropathy. Thrombocytopenia included the preferred terms thrombocytopenia, platelet count decreased, and heparin-induced thrombocytopenia. Neutropenia included the preferred terms neutropenia, leukopenia, febrile neutropenia, neutrophil count decreased, and white blood cell count decreased. Anemia included the preferred terms anemia and hemoglobin decreased. Infections included any infection or infestation. Deep vein thrombosis/pulmonary embolism included the preferred terms deep vein thrombosis and pulmonary embolism.

AE severity was graded and recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, v4.0.

RESULTS

Patients

The pooled safety population consisted of 1088 patients (Table 1). Patient demographics and disease-related characteristics were well balanced and similar across the 3 trials. The median age was 66.0 years (range 34.0-88.0 years) for the pooled group, and 57.1% of patients were

male. The median time from initial diagnosis was 5.3 years (range 0.6-30.0 years). Most patients (87.8%) had an Eastern Cooperative Oncology Group performance status of 0-1. International Staging System stage III disease at baseline was noted in nearly one-third of patients (29.8%), and 41.0% of patients had a history of peripheral neuropathy. The median number of prior regimens was 5 across all trials, with a range of 2.0-18.0 in the pooled population, and 68.1% of patients had undergone prior stem cell transplants. All patients had received prior treatment with lenalidomide and bortezomib; 93.8% were refractory to lenalidomide, 81.0% were refractory to bortezomib, and 76.7% were refractory to both lenalidomide and bortezomib.

Pomalidomide Dosing and Modifications

The median treatment duration was 4.8 months (range 0.1-47.8 months), with a median relative dose intensity of 0.9 (Table 2).

Pomalidomide dose reductions or interruptions occurred in 24.2% and 66.0% of patients, respectively (Table 2). In the pooled safety population, 13.4% of patients required dose reduction and 33.3% needed dose interruption because they had 1 or more AEs of interest. Treatment-emergent AEs most commonly leading to dose reductions of pomalidomide were neutropenia (8.1%), thrombocytopenia (5.4%), and infections (3.9%). The AEs most frequently leading to dose interruptions were infections (29.8%), neutropenia (25.9%), and thrombocytopenia (10.6%). Peripheral neuropathy that resulted in pomalidomide dose reduction or interruption was infrequent (0.9% in each case). Thromboembolism (DVT or PE) that led to reductions or interruptions of pomalidomide dose was also not common (0.4% for dose reductions, 1.5% for interruptions).

Treatment-emergent AEs leading to discontinuation of pomalidomide were infrequent, occurring in 74 patients (6.8%) in the total safety population (Table 2). Infections (1.7%) and

thrombocytopenia (0.7%) were the most common treatment-emergent AEs leading to discontinuation.

Safety

Among the 1088 patients included in our analysis, the most frequently reported grade 3/4 treatment-emergent AEs (≥ 5%) were hematologic, and included neutropenia (56.2%), anemia (32.3%), thrombocytopenia (25.8%), and febrile neutropenia (6.2%) (Table 3).

The most common grade 3/4 nonhematologic treatment-emergent AEs (≥ 5%) were infections (33.7%); pneumonia was reported in 13.9% of patients and concurrent neutropenia in 40.3% of patients with infections. The majority of grade 3/4 infections (59.7%) occurred in the absence of neutropenia. Other grade 3/4 infections included lower respiratory infection (2.6%) and sepsis (2.2%), and 3 patients (< 1%) had herpes zoster. Grade 3/4 fatigue was observed in 6.6% of patients. Of the treatment-emergent AEs of special interest, grade 3/4 DVT and PE were infrequent (1.7%). The incidence of grade 3/4 peripheral neuropathy was noted in fewer than 2% of patients, presumably because grade ≥ 2 peripheral neuropathy was an exclusion criterion. Treatment-emergent peripheral neuropathy of any grade was reported in 16.7% of patients, with a median time to onset of 6.8 weeks. The incidence of any grade DVT/PE was 2.8% in the pooled population.

Overall, the median time to AE onset for the most frequent hematologic AEs ranged from 2.1 weeks for thrombocytopenia to 3.7 weeks for anemia (Fig 1). In general, nonhematologic AEs had a longer median time to onset, with DVT/PE having the longest time to onset, 16.4 weeks.

Invasive secondary primary malignancies were noted in 9 patients in the overall patient population (8 patients had solid tumors and 1 patient had acute myeloid leukemia). The incidence rate per 100 person-year for invasive secondary primary malignancies was 0.9 (95%

CI, 0.50-1.84) for all patients, 0.85 for patients with solid tumors, and 0.11 for patients with hematologic malignancies.

Supportive Care

In addition to pomalidomide dose modification, supportive care was used to manage AEs. Granulocyte colony-stimulating factor (G-CSF) therapy was administered to patients experiencing neutropenia and febrile neutropenia (72.2% and 79.7%, respectively). Anti-infective agents were used in all patients with febrile neutropenia and 96.0% of patients with infections. Red blood cell transfusions were required in 68.7% of patients with anemia, and 34.9% of patients with thrombocytopenia received platelet transfusions (Table 4).

DISCUSSION

This study analyzed the occurrence and management of AEs in over 1000 heavily pretreated patients with RRMM enrolled in 3 clinical trials. Pomalidomide, administered orally at 4 mg for 21 of 28 days in combination with low-dose dexamethasone, was generally well tolerated. Consistent with the results of the individual trials (MM-002, MM-003, and MM-010), the most common grade 3/4 treatment-emergent AEs in the pooled analysis were hematologic (neutropenia, anemia, and thrombocytopenia); these occurred within the first few cycles of treatment based on a median time to onset of less than 4 weeks. Infections were mostly respiratory, with a median time to onset of 5.9 weeks (range, 0.1 to 70.4 weeks). Consistent with previous observations, the majority of infections occurred in the absence of neutropenia. The median time to onset of peripheral neuropathy and DVT or PE was 6.8 weeks (range, 0.1 to 86.1 weeks) and 16.4 weeks (range, 0.4 to 47.6 weeks), respectively.

Overall, the studies in this pooled analysis followed the recommended guidelines for AE management in MM.(11, 12, 26-28) AEs were effectively managed with dose modifications and supportive care. Pomalidomide dose reductions and interruptions caused by 1 or more AEs of interest occurred in 13.4% and 33.3%, respectively, and were primarily due to neutropenia, thrombocytopenia, and infections. Given that the patient population was heavily pretreated, the bone marrow function in these patients was most likely compromised. In this context, G-CSF was allowed within the protocol and used in over 70% of patients with neutropenia, consistent with recommended guidelines.(3, 5, 12) Patients with febrile neutropenia also received anti-infective agents. Anemia and thrombocytopenia were managed with the administration of red blood cell transfusion and platelet transfusion, respectively. Infections were primarily managed with anti-infectives and pomalidomide dose interruptions. Use of mandatory thromboprophylaxis is considered to have contributed to the maintenance of very low rates of grade 3/4 DVT or PE.(5, 8, 12, 17) Based on the low rate of discontinuations due to neutropenia and infections, this study supports the use of G-CSF and antibiotic prophylaxis for patients with low blood counts or a previous history of infection in order to optimize the duration of pomalidomide treatment.

Recommended guidelines for the management and treatment of infections in patients with MM include the use of broad spectrum antibiotics and antiviral prophylaxis, such as acyclovir and valacyclovir for herpes-zoster or antiviral agents for neutropenia, depending on risk.(5, 7, 12-14, 26-28) Because patients with RRMM—particularly those with low blood counts or a previous history of infection or both—are at high risk for infections, they should be carefully monitored and managed. Therefore, in addition to withholding pomalidomide during active infection, antibiotic prophylaxis should be considered for the complete duration of pomalidomide treatment.(5) Also, these patients and their contacts should receive routine vaccinations against the influenza virus, *Streptococcus pneumoniae*, and *Haemophilus influenzae*.(5, 20)

In general, the characteristics of the patients with RRMM in this analysis were comparable to those in patients seen outside the clinical trial setting.(29-31) Although these patients were heavily pretreated and the majority were refractory to lenalidomide, bortezomib, or both, their general health status was good (88% with an Eastern Cooperative Oncology Group performance status ≤ 1), which should be considered when interpreting the results.

This analysis confirms the acceptable safety profile of pomalidomide plus low-dose dexamethasone in patients with RRMM in the MM-002, MM-003, and MM-010 studies and, supporting the established guidelines, demonstrates that treatment-emergent AEs were appropriately managed during these studies.

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Table 1. Baseline characteristics.

Characteristic	MM-002 (n = 112)	MM-003 (n = 300)	MM-010 (n = 676)	Overall (N = 1088)
Male, n (%)	61 (54.5)	180 (60.0)	380 (56.2)	621 (57.1)
Age, median (range), y	64.0 (34.0-88.0)	64.0 (35.0-84.0)	66.0 (37.0-88.0)	66.0 (34.0-88.0)
Time since diagnosis, median (range), y	5.4 (1.1-18.1)	5.3 (0.6-30.0)	5.3 (0.6-28.2)	5.3 (0.6-30.0)
ECOG PS, n (%)				
0	32 (28.6)	110 (36.7)	293 (43.3)	435 (40.0)
1	67 (59.8)	136 (45.3)	317 (46.9)	520 (47.8)
2	13 (11.6)	52 (17.3)	65 (9.6)	130 (11.9)
3	0	0	1 (0.1)	1 (0.1)
Missing	0	2 (0.7)	0	2 (0.2)
ISS at baseline, n (%)				
I	0	81 (27.0)	146 (21.6)	227 (20.9)
II	0	113 (37.7)	266 (39.3)	379 (34.8)
III	0	92 (30.7)	232 (34.3)	324 (29.8)
Missing	112 (100)	14 (4.7)	32 (4.7)	158 (14.5)
Number of prior Tx regimens, median (range)	5.0 (2.0-13.0)	5.0 (2.0-14.0)	5.0 (2.0-18.0)	5.0 (2.0-18.0)
BORT, n (%)	112 (100)	300 (100)	676 (100)	1088 (100)
LEN, n (%)	112 (100)	300 (100)	676 (100)	1088 (100)
DEX, n (%)	111 (99.1)	293 (97.7)	660 (97.6)	1064 (97.8)
THAL, n (%)	77 (68.8)	172 (57.3)	368 (54.4)	617 (56.7)
SCT, n (%)	81 (72.3)	213 (71.0)	447 (66.1)	741 (68.1)
LEN-refractory, n (%)	87 (77.7)	285 (95.0)	648 (95.9)	1020 (93.8)
BORT-refractory, n (%)	79 (70.5)	236 (78.7)	566 (83.7)	881 (81.0)
LEN- and BORT-refractory, n (%)	69 (61.6)	224 (74.7)	542 (80.2)	835 (76.7)

BORT, bortezomib; DEX, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; LEN, lenalidomide; SCT, stem cell transplant; THAL, thalidomide; Tx, treatment.

Table 2. Pomalidomide exposure.

	Safety Population (N = 1088)
Average POM daily dose, median (range), mg	4.0 (1.6-4.2)
POM relative dose intensity, median (range)[a]	0.9 (0.2-1.3)
Treatment duration, median (range), months	4.8 (0.1-47.8)
Dose reductions	
≥ 1 dose reduction, n (%)	263 (24.2)
≥ 1 AE of interest leading to dose reduction, n (%)	146 (13.4)
Neutropenia[b]	88 (8.1)
Thrombocytopenia[b]	59 (5.4)
Infections[b]	42 (3.9)
Peripheral neuropathy[b]	10 (0.9)
Anemia[b]	9 (0.8)
DVT/PE	4 (0.4)
Dose interruptions	
≥ 1 dose interruption, n (%)	718 (66.0)
≥ 1 AE of interest leading to dose interruption, n (%)	362 (33.3)
Infections[b]	324 (29.8)
Neutropenia[b]	282 (25.9)
Thrombocytopenia[b]	115 (10.6)
Anemia[b]	50 (4.6)
DVT/PE	16 (1.5)
Peripheral neuropathy[b]	10 (0.9)
Discontinuations	
≥ 1 AE leading to discontinuation, n (%)	74 (6.8)
Infections[b]	18 (1.7)
Thrombocytopenia[b]	8 (0.7)
Pneumonia	5 (0.5)

AE, adverse event, DVT, deep vein thrombosis; PE, pulmonary embolism; POM, pomalidomide.

[a] Relative dose intensity is the ratio of administered dose intensity vs planned dose intensity.

[b] Grouped AE term.

Table 3. Grade 3/4 treatment-emergent adverse events ≥ 5% overall and treatment-emergent adverse events of interest.

	MM-002 (n = 112)	MM-003 (n = 300)	MM-010 (n = 676)	Overall (N = 1088)
Hematologic treatment-emergent AEs, n (%)				
Neutropenia[a]	56 (50.0)	170 (56.7)	385 (57.0)	611 (56.2)
Febrile neutropenia	3 (2.7)	28 (9.3)	36 (5.3)	67 (6.2)
Leukopenia	11 (9.8)	27 (9.0)	54 (8.0)	92 (8.5)
Anemia[a]	27 (24.1)	99 (33.0)	225 (33.3)	351 (32.3)
Thrombocytopenia[a]	23 (20.5)	73 (24.3)	185 (27.4)	281 (25.8)
Nonhematologic treatment-emergent AEs, n (%)				
Infections[a]	50 (44.6)	90 (30.0)	227 (33.6)	367 (33.7)
Pneumonia	26 (23.2)	38 (12.7)	87 (12.9)	151 (13.9)
Fatigue	16 (14.3)	16 (5.3)	40 (5.9)	72 (6.6)
Treatment-emergent AEs of special interest, n (%)				
Peripheral neuropathy[a]	0	5 (1.7)	10 (1.5)	15 (1.4)
DVT/PE	3 (2.7)	4 (1.3)	11 (1.6)	18 (1.7)

AE, adverse event; DVT, deep vein thrombosis; PE, pulmonary embolism.

[a] Grouped AE term.

Table 4. Supportive care.

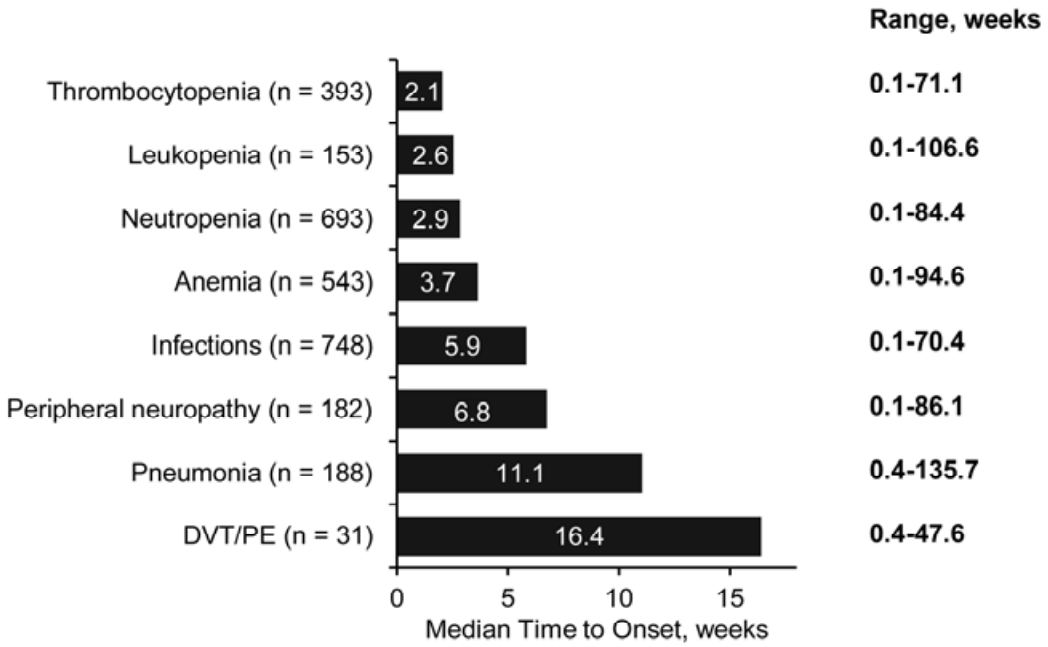
	G-CSF, n (%)	Anti-Infectives, n (%)	Platelet Transfusion, n (%)	RBC Transfusion, n (%)
Any-grade hematologic treatment-emergent AE				
Neutropenia (n = 693)[a]	500 (72.2)	N/A	N/A	N/A
Febrile neutropenia (n = 69)	55 (79.7)	69 (100)	N/A	N/A
Anemia (n = 543)[a]	N/A	N/A	N/A	373 (68.7)
Thrombocytopenia (n = 393)[a]	N/A	N/A	137 (34.9)	N/A
Any-grade nonhematologic treatment-emergent AE				
Infections (n = 748)[a]	N/A	718 (96.0)	N/A	N/A

AE, adverse event; G-CSF, granulocyte colony-stimulating factor; N/A, not applicable; RBC, red blood cell.

[a] Grouped AE term.

FIGURE LEGEND

Figure 1. Time to onset of any-grade adverse event. Bar graph shows the median time to onset of adverse events of interest and range in weeks.



DVT, deep vein thrombosis; PE, pulmonary embolism.

[a] Thrombocytopenia, neutropenia, anemia, infections, peripheral neuropathy were grouped AE terms.