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ORIGINAL ARTICLE

Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma

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We present a pooled update of two large, multicenter MM-009 and MM-010 placebo-controlled randomized phase III trials that included 704 patients and assessed lenalidomide plus dexamethasone versus dexamethasone plus placebo in patients with relapsed/refractory multiple myeloma (MM). Patients in both studies were randomized to receive 25 mg daily oral lenalidomide or identical placebo, plus 40 mg oral dexamethasone. In this pooled analysis, using data up to unblinding (June 2005 for MM-009 and August 2005 for MM-010), treatment with lenalidomide plus dexamethasone significantly improved overall response (60.6 vs 21.9%, $P<0.001$), complete response rate (15.0 vs 2.0%, $P<0.001$), time to progression (median of 13.4 vs 4.6 months, $P<0.001$) and duration of response (median of 15.8 months vs 7 months, $P<0.001$) compared with dexamethasone-placebo. At a median follow-up of 48 months for surviving patients, using data up to July 2008, a significant benefit in overall survival (median of 38.0 vs 31.6 months, $P=0.045$) was retained despite 47.6% of patients who were randomized to dexamethasone-placebo receiving lenalidomide-based treatment after disease progression or study unblinding. Low β_2-microglobulin and low bone marrow plasmacytosis were associated with longer survival. In conclusion, these data confirm the significant response and survival benefit with lenalidomide and dexamethasone.

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Introduction

Multiple myeloma (MM) is an incurable plasma-cell malignancy that causes approximately 20% of all deaths attributed to all hematological malignancies and 2% of deaths caused by all types of cancer.[1] The median survival of patients with MM was approximately 33 months before the advent of new therapies.[2] On the basis of surveillance, epidemiology and end result estimates, nearly 20 000 individuals (11 190 men and 8730 women) were expected to be diagnosed with myeloma, and approximately 11 000 patients were expected to die from the disease in the United States during 2008.[3] Recent benefits in survival for patients with MM have been demonstrated after treatment with novel agents (for example, thalidomide, bortezomib and lenalidomide) administered alone or in combination.[4–7] In MM patients diagnosed between 1997 and 2006, the median survival for patients treated with one or more of these novel agents after relapse is more than double than that of patients not treated with the novel agents (30.9 months vs 14.8 months; $P<0.001$).[8]

Lenalidomide (Revlimid; Celgene Corporation, Summit, NJ, USA) is an oral IMiD classified as an immunomodulatory drug that has undergone rapid clinical development in MM.[9–11] After phase I and II trials showed promising activity of lenalidomide alone or in combination with dexamethasone,[12–13] two large, multicenter, randomized, placebo-controlled phase III trials were initiated: MM-009 in North America and MM-010 in Europe, Australia and Israel. These studies already demonstrated the superiority of lenalidomide plus dexamethasone over dexamethasone-placebo in relapsed or refractory patients at the preplanned interim analysis, at which time the data monitoring committee decided to unblind the study and allow patients to cross-over. Near identical results from these phase III trials in patients with previously treated myeloma showed that the addition of lenalidomide to dexamethasone, compared with dexamethasone alone, significantly improved overall response rate, progression-free survival (PFS), time to progression (TTP) and overall survival (OS).[6,7]

On the basis of the MM-009 and MM-010 trials, lenalidomide in combination with dexamethasone has been approved by the US Food and Drug Administration and European Medicines Agency for the treatment of MM in patients who have received at least one earlier therapy. Results were initially published with a median follow-up of 17.6 months for the MM-009 trial and 16.4 months for the MM-010 trial. We now report an updated pooled data analysis of 704 patients from the MM-009 and MM-010 phase III trials with an extended median follow-up of 48 months for OS.

Materials and methods

For the purposes of the present analysis, we evaluated pooled data from patients enrolled in the MM-009 and MM-010 phase

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III clinical trials. Protocols have been described in detail in the primary publications.[6,7]

Patient selection

Patient selection has been previously described.[6,7] In brief, eligible patients were aged at least 18 years, had progressive MM after one or more treatments, a serum creatinine level of less than 2.5 mg per 100 ml and a measurable disease that was not resistant to a total monthly dexamethasone dose of >200 mg.

Treatment

Patients were randomized to receive either oral lenalidomide 25 mg per day or placebo on days 1–21 of each 28-day cycle. All patients received 40 mg oral dexamethasone on days 1–4, 9–12 and 17–20 of each 28-day cycle (for 4 cycles) until disease progression. After four cycles, dexamethasone (40 mg/day) was limited to days 1–4 only. As the O'Brien–Fleming boundary for superiority of lenalidomide over placebo was crossed at the preplanned interim analysis by the data monitoring committee, the study was unblinded and patients originally randomized to receive dexamethasone-placebo were allowed to receive lenalidomide or lenalidomide plus dexamethasone either immediately or after disease progression occurred. If patients experienced grade 3 or 4 adverse events, lenalidomide was held until the adverse events were resolved and treatment was restarted with a dose reduced to 15 mg/day, with further reductions at decrements of 5 mg/day. For grade 3 or 4 neutropenia without other toxicity, patients received a subcutaneous injection of granulocyte colony-stimulating factor 5 μg/kg/day with the first dose-modification step. The dexamethasone dose was adjusted for adverse events at the discretion of the investigator. Dexamethasone reductions were 40 mg/day for 4 days every 2 weeks, then 40 mg/day for 4 days every 4 weeks, then 20 mg daily for 4 days every 4 weeks.

Response

Complete response, very good partial response and partial response (PR) of progressive disease were assessed every 4 weeks according to modified European Group for Blood and Marrow Transplantation criteria.[14] TTP was measured from the date of randomization to the date of the first assessment showing progression. For patients who were given another anti-myeloma therapy without documented disease progression, TTP was censored at the last adequate response assessment date before taking another anti-myeloma therapy. OS was calculated as time from randomization until death from any cause. OS was censored at the last date of patient follow-up. Data for OS were updated up to 23 July 2008 for MM-009 and 2 March for MM-010 (median follow-up of 48 months for surviving patients). Overall response rate, TTP and PFS were assessed up to unblinding, which occurred in June 2005 for study MM-009 and in August 2005 for study MM-010, for a median follow-up of 17.5 months for ongoing patients. Toxic effects were graded according to the National Cancer Institute's Common Toxicity Criteria, version 2.

Statistical analysis

Baseline characteristics were compared between groups using a pooled *t*-test for continuous variables (that is, age, time since diagnosis) and Fisher's exact test for categorical variables (all other variables). Fisher's exact tests were used to compare response rates; TTP, PFS and OS were estimated by Kaplan–Meier methods and compared between treatment groups using log-rank tests stratified by study. Exploratory analysis was performed to identify the predictors of OS among patients treated with lenalidomide plus dexamethasone. The univariate Cox proportional hazards model was used to determine potential prognostic variables predictive for OS. Variables assessed in the univariate analysis included age, gender, race, number of earlier therapies, earlier use of thalidomide, radiation therapy, dexamethasone and other baseline disease characteristics such as β_2-microglobulin, disease duration, lytic bone lesion, ECOG performance status, Durie–Salmon disease stage and percentage of plasma cells in bone marrow samples. Cytogenetic abnormalities were not routinely recorded and were therefore not included in the analysis. Only those variables that differed at the 0.20 level by the univariate analysis were included in the multivariate Cox regression model. For the multivariate analysis, a forward selection stepwise procedure was used to identify the subset of relevant factors. Statistical significance was determined at the 0.05 alpha level. TTP was the primary efficacy end point specified in the protocol. Other analyses were considered secondary without adjustment for multiplicity. Analyses were performed using Statistical Analysis Software (SAS) Version 9.1 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Baseline characteristics were well balanced between patients treated with lenalidomide plus dexamethasone and those treated with dexamethasone-placebo ($P>0.05$ for all; Table 1).

Efficacy

Up to study unblinding, TTP was significantly longer in patients treated with lenalidomide plus dexamethasone than in those treated with dexamethasone-placebo (median of 13.4 vs 4.6 months, respectively; $P<0.001$; Figure 1; Table 2). PFS was significantly longer in patients treated with lenalidomide plus dexamethasone than in those treated with dexamethasone-placebo (median of 11.1 vs 4.6 months, respectively; $P<0.001$; Figure 2; Table 2). The time to first response was similar in patients treated with lenalidomide plus dexamethasone than in those treated with dexamethasone-placebo (median of 1.9 vs 2.0 months, respectively); however, patients treated with lenalidomide plus dexamethasone had a substantially longer duration of response than did those treated with dexamethasone-placebo (median of 15.8 vs 7.0 months, $P<0.001$; Table 2). The median duration of treatment was 10.1 months for patients treated with lenalidomide plus dexamethasone compared with 5.3 months for patients treated with dexamethasone-placebo ($P<0.0001$). The pooled overall response rate was significantly higher in patients treated with lenalidomide plus dexamethasone than in those treated with dexamethasone-placebo (60.6 vs 21.9%, respectively; $P<0.001$; Table 2). Among patients treated with lenalidomide plus dexamethasone, complete response was observed in 15.0% and very good partial response in 17.3%, which was significantly higher compared with treatment with dexamethasone-placebo (2.0 and 2.8%, respectively; $P<0.001$ for the comparison of complete response + very good partial response between treatment groups).

After a median follow-up of 48 months, 199 patients (56.4%) died in the lenalidomide plus dexamethasone group and 219 patients (62.4%) died in the dexamethasone monotherapy

Table 1 Baseline characteristics

Characteristic, n *(%)*	*Lenalidomide+ dexamethasone (n = 353)*	*Dexamethasone+ placebo (n = 351)*
Age, years		
Median	63.0	63.0
Range	33–86	37–85
Sex		
Male	210 (59.5)	207 (59.0)
Female	143 (40.5)	144 (41.0)
Time since diagnosis, years		
Median	3.2	3.5
Range	0.4–15.7	0.0–26.6
Durie–Salmon stage		
I	17 (4.8)	13 (3.7)
II	106 (30.0)	112 (31.9)
III	229 (64.9)	226 (64.4)
Eastern Cooperative Oncology Group performance status		
0	152 (43.1)	150 (42.7)
1	155 (43.9)	162 (46.2)
2	37 (10.5)	33 (9.4)
Number of earlier therapies/stem cell transplantations		
1	65 (18.4)	73 (20.8)
⩾2	288 (81.6)	278 (79.2)
Earlier thalidomide treatment	127 (36.0)	147 (41.9)
Earlier bortezomib treatment	27 (7.6)	27 (7.7)
Earlier stem cell transplantation	206 (58.4)	203 (57.8)
β_2-Microglobulin level, mg/l		
⩽2.5	103 (29.2)	99 (28.2)
>2.5	250 (70.8)	252 (71.8)

No significant differences between the two groups for any of the characteristics ($P > 0.05$) were found based on pooled *t*-test for continuous variables (age, time since diagnosis) and Fisher's exact test for categorical variables (all other variables in the table).

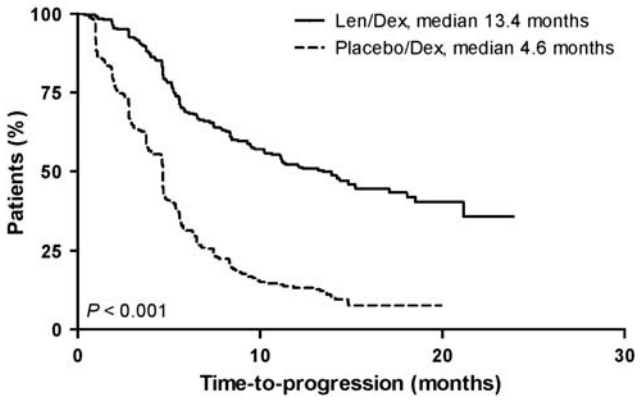

Figure 1 The Kaplan–Meier estimate of time-to-progression for the intent-to-treat population. The estimate of time-to-progression for the intent-to-treat population of the lenalidomide plus dexamethasone-placebo groups. Len/Dex denotes lenalidomide plus dexamethasone; Placebo/Dex denotes dexamethasone-placebo. Survival curves were compared using log-rank test stratified by study ($P < 0.001$).

group. OS was significantly longer in patients treated with lenalidomide plus dexamethasone than in those treated with dexamethasone-placebo (median of 38.0 vs 31.6 months, respectively; $P = 0.045$; Table 3; Figure 3).

The Cox proportional hazards regression model for multivariate analysis showed that treatment remained a highly significant predictor of OS ($P = 0.0008$, in favor of lenalidomide plus dexamethasone). In addition, baseline β_2-microglobulin levels higher than 2.5 mg/l, a baseline ISS (International Staging System) score >1, a high baseline percentage of plasma cells and more than one earlier anti-myeloma were among significant predictors of short OS after controlling for treatment factor (Table 3).

Of the 351 patients treated with dexamethasone-placebo, 167 (47.6%) received lenalidomide-based therapy after unblinding of the study or after disease progression. Of those, 147 (41.9%) patients crossed over to lenalidomide alone (as part of the MM-012 trial) after disease progression before study unblinding and 20 (5.7%) crossed over to lenalidomide plus dexamethasone after official study unblinding of the study; median time to crossover was 9.6 months. Among the 20 patients who received lenalidomide plus dexamethasone after study unblinding, 6 (30.0%) did so immediately after study unblinding and the remaining 14 (70.0%) crossed over after disease progression. Of the 32 patients in the placebo-dexamethasone arm ongoing at study unblinding, 12 did not cross-over to lenalidomide plus dexamethasone. Of these 12 patients, three patients remained on the dexamethasone regimen and then progressed, and the remaining patients were either responding or in the plateau phase at the time of data cutoff. After the crossover to a lenalidomide-based therapy, a ⩾ PR was achieved in 53 (31.7%) patients who were previously randomized to dexamethasone-placebo.

Safety

At least one grade 3 or 4 adverse event was observed in 83.3% of patients treated with lenalidomide plus dexamethasone and in 69.7% of those treated with dexamethasone-placebo ($P < 0.0001$). Neutropenia and thrombocytopenia were the most common grade 3 or 4 adverse events among those treated with lenalidomide plus dexamethasone and were significantly higher than in patients treated with dexamethasone-placebo ($P < 0.001$); grade 3 or 4 hyperglycemia was the most common event noted among those treated with dexamethasone-placebo (Table 4). As previously reported, thromboembolic events were significantly higher in patients treated with lenalidomide plus dexamethasone in the absence of a prophylactic use of an anticoagulant ($P < 0.001$). Patients treated with lenalidomide plus dexamethasone experienced grade 2 (1.4%) and grade 3 (1.4%) peripheral neuropathy. Patients in the dexamethasone group experienced grade 2 (1.7%) and grade 3 (0.6%) peripheral neuropathy and there were no grade 4 events in both groups.

Dosing

The median dose of lenalidomide or placebo was 25 mg and 40 mg for dexamethasone. Among the patients treated with lenalidomide plus dexamethasone, 38.8% had at least one dose reduction of lenalidomide and 30.9% had at least one dose reduction of dexamethasone; 15.7% of patients treated with dexamethasone-placebo required at least one dose reduction.

Discussion

Initial publication of MM-009 and MM-010, two randomized, placebo-controlled, phase III trials reported a significant benefit in response and TTP for patients with relapsed or refractory MM

Table 2 Response rates, time-to-progression, progression-free survival and overall survival

	Lenalidomide+dexamethasone (n = 353)	*Dexamethasone+placebo (n = 351)*	*P-value*
Up to Unblinding (median FU = 17.5 months)			
Response rate, %			
ORR	60.6	21.9	<0.001
CR	15.0	2.0	<0.001
VGPR	17.3	2.8	
PR	28.3	17.1	
Median TTP, months	13.4	4.6	<0.001
Median DOR, months	15.8	7.0	<0.001
Median PFS, months	11.1	4.6	<0.001
Extended FU (Median FU = 48 months)	38.0	31.6	0.045
Median OS, months			

Abbreviations: CR, complete response; DOR, duration of response; FU, follow-up; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; TTP, time-to-progression; VGPR, very good partial response.

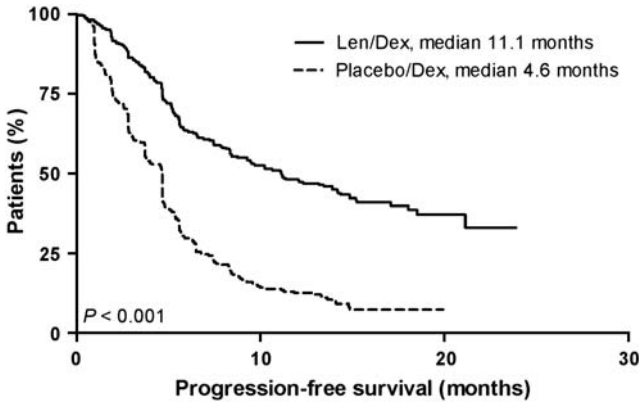

Figure 2 The Kaplan–Meier estimate of progression-free survival for the intent-to-treat population. The estimate of progression-free survival for the intent-to-treat population of the lenalidomide plus dexamethasone-placebo groups. Len/Dex denotes lenalidomide plus dexamethasone; Placebo/Dex denotes dexamethasone-placebo. Survival curves were compared using log-rank test stratified by study ($P<0.001$).

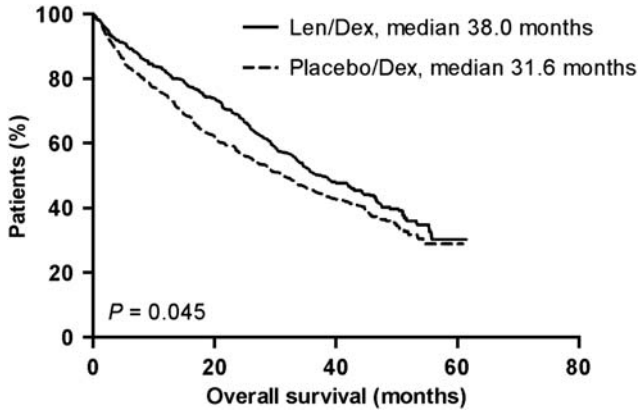

Figure 3 The Kaplan–Meier estimate of overall survival for the intent-to-reat population. The estimate of overall survival for the intent-to-treat population of the lenalidomide plus dexamethasone and dexamethasone-placebo groups. Len/Dex denotes lenalidomide plus dexamethasone; Placebo/Dex denotes dexamethasone-placebo. Survival curves were compared using log-rank test stratified by study ($P=0.045$).

Table 3 Predictors of overall survival in patients treated using the Cox regression model

	Hazard ratio (95% CIs)	*P-value*
Treatment (dexamethasone+placebo vs lenalidomide+dexamethasone treatment)	1.4 (1.2–1.7)	0.0008
Baseline plasma cells percentage (high vs low)	1.0 (1.0–1.0)	<0.0001
High baseline β_2-microglobulin (>2.5 vs ⩽2.5 mg/l)	1.6 (1.2–2.1)	<0.0022
Duration of multiple myeloma	0.9 (0.9–1.0)	0.0008
Lytic bone lesion at baseline (Y vs N)	1.3 (1.0–1.6)	0.064
Number of earlier anti-myeloma therapies	1.2 (1.0–1.3)	0.026
Previously treated with HDT/SCT (Y vs N)	1.2 (1.0–1.5)	0.053
Earlier dexamethasone therapy (Y vs N)	1.3 (1.1–1.7)	0.017
ISS score at baseline (III vs II vs I)	1.5 (1.3–1.7)	<0.0001

Abbreviations: HDT, high-dose therapy; ISS, International Staging System; SCT, stem cell transplant.

Table 4 Grade ⩾3 adverse events occurring in more than 5% of patients

Adverse event, n (%)	*Lenalidomide+ dexamethasone (n = 353)*	*Dexamethasone+ placebo (n = 351)*
Neutropenia	125 (35.4)**	12 (3.4)
Thrombocytopenia	46 (13.0)**	22 (6.3)
Anemia	38 (10.8)*	21 (6.0)
Pneumonia	32 (9.1)	19 (5.4)
All thromboembolic events	56 (15.9)**	19 (5.4)
Hyperglycemia	27 (7.6)	27 (7.7)
Fatigue	23 (6.5)	17 (4.9)
Muscle weakness	20 (5.7)	11 (3.1)
Hypokalemia	20 (5.7)	5 (1.4)
Asthenia	17 (4.8)	18 (5.1)

* $P<0.001$; ** $P<0.05$.

treated with lenalidomide plus dexamethasone compared with treatment with dexamethasone.[6,7] OS was also significantly longer for patients treated with lenalidomide plus dexamethasone in both trials; however, the median follow-up was short at 17.6 and 16.4 months for the MM-009 and MM-010 phase III

trials, respectively. Both studies were unblinded early by the data monitoring committee when the O'Brien–Fleming boundary for superiority of lenalidomide over placebo was crossed at the first planned interim analysis. We now present a pooled analysis of the MM-009 and MM-010 phase III trials with a median follow-up of 48 months for OS, which demonstrates a continued prolongation of OS for the lenalidomide and dexamethasone arm versus the dexamethasone single-agent arm, despite a crossover of almost half of the patients to either lenalidomide or lenalidomide plus dexamethasone as subsequent salvage therapies.

Patients experienced improved responses, with a total of 32.3% of patients achieving very good partial response or better with lenalidomide plus dexamethasone versus 4.8% with dexamethasone-placebo. The median duration of response of 15.8 months with lenalidomide plus dexamethasone was shown to be nearly twice as long as that noted with dexamethasone-placebo. The TTP of 13.4 months with lenalidomide plus dexamethasone was also almost thrice as long as with dexamethasone-placebo. The PFS of 11.1 months with lenalidomide plus dexamethasone was more than twice as long as with dexamethasone-placebo.

With a median follow-up of 17.6 months, an approximately 9 month improvement was observed in the median OS in patients treated with lenalidomide plus dexamethasone compared with that in patients treated with dexamethasone in the MM-009 trial (median OS 29.6 vs 20.2 months, respectively; $P<0.001$).[7] The median OS was not reached in the MM-010 trial at the 17.6 month follow-up; however, a similar significant improvement in OS was observed.[6] In the current analysis with a longer follow-up of 48 months, we now report an improvement in the median OS to 38.0 months for patients treated with lenalidomide plus dexamethasone versus 31.6 months for those receiving dexamethasone-placebo ($P=0.045$). Low serum β_2-microglobulin, a low ISS score at baseline and low plasma cell infiltration of the bone marrow were associated with longer survival.

As an IMiD immunomodulatory compound, the effect of lenalidomide might be more pronounced at the early stages of disease management when the cellular immune system and stroma are less compromised by other therapeutic agents. A recent subset analysis of the MM-009 and MM-010 trials demonstrated a significant clinical benefit in patients with one earlier therapy compared with those with $\geqslant 2$ earlier therapies, further supporting the earlier use of lenalidomide and dexamethasone.[15] On the basis of the above results, investigation of lenalidomide plus dexamethasone combination is also ongoing in patients with newly diagnosed MM. As current therapies are achieving response rates approaching 100% and an impressive OS (1–year OS, 86–96%) in MM patients, the challenge in this disease is to understand the function of immunomodulation in long-term therapy.[16,17,18]

In conclusion, results from this pooled analysis of data from the MM-009 and MM-010 trials, with a median extended follow-up of 48 months, confirm significant response outcomes and significant OS benefit with manageable toxicities for patients treated with lenalidomide and dexamethasone in relapsed or refractory MM. In addition, these data show for the first time that this significant OS benefit was still achieved despite nearly half of the patients in the control arm of the study receiving lenalidomide at the time of disease progression or study unblinding. These data, together with the results recently reported by Stadtmauer *et al*.,[15] indicate that the greatest benefit occurs with early use of lenalidomide and dexamethasone in patients with relapsed or refractory MM, and demonstrate the long-term significant clinical benefit of lenalidomide treatment.

Conflict of interest

MAD, CC and RN had a consultant role and have received honoraria from Celgene Corporation; CC and RN received research funding from Celgene Corporation; EAS and AS have received consulting and lecture fees from Celgene Corporation; MA is a member of the Board of Directors or Advisory Committee for Celgene Corporation; MTP has no relevant conflicts of interest to disclose; ZY, MO, JBZ and RDK are employed by Celgene Corporation; DMW received honoraria from and has been an occasional speaker for Celgene Corporation.

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