Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis

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Published at jco.org on July 25, 2017.

Processed as a Rapid Communication manuscript.

Clinical trial information: NCT00551928, NCT00551928, NCT00430365.

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0732-183X/17/3529w-3279w/\$20.00

ABSTRACT

Purpose

Lenalidomide maintenance therapy after autologous stem-cell transplantation (ASCT) demonstrated prolonged progression-free survival (PFS) versus placebo or observation in several randomized controlled trials (RCTs) of patients with newly diagnosed multiple myeloma (NDMM). All studies had PFS as the primary end point, and none were powered for overall survival (OS) as a primary end point. Thus, a meta-analysis was conducted to better understand the impact of lenalidomide maintenance in this setting.

Patients and Methods

The meta-analysis was conducted using primary-source patient-level data and documentation from three RCTs (Cancer and Leukemia Group B 100104, Gruppo Italiano Malattie Ematologiche dell'Adulto RV-MM-PI-209, and Intergroupe Francophone du Myélome 2005-02) that met the following prespecified inclusion criteria: an RCT in patients with NDMM receiving ASCT followed by lenalidomide maintenance versus placebo or observation with patient-level data available and achieved database lock for primary efficacy analysis.

Results

Overall, 1,208 patients were included in the meta-analysis (605 patients in the lenalidomide maintenance group and 603 in the placebo or observation group). The median PFS was 52.8 months for the lenalidomide group and 23.5 months for the placebo or observation group (hazard ratio, 0.48; 95% CI, 0.41 to 0.55). At a median follow-up time of 79.5 months for all surviving patients, the median OS had not been reached for the lenalidomide maintenance group, whereas it was 86.0 months for the placebo or observation group (hazard ratio, 0.75; 95% CI, 0.63 to 0.90; $P = .001$). The cumulative incidence rate of a second primary malignancy before disease progression was higher with lenalidomide maintenance versus placebo or observation, whereas the cumulative incidence rates of progression, death, or death as a result of myeloma were all higher with placebo or observation versus lenalidomide maintenance.

Conclusion

This meta-analysis demonstrates a significant OS benefit and confirms the PFS benefit with lenalidomide maintenance after ASCT in patients with NDMM when compared with placebo or observation.

J Clin Oncol 35:3279-3289. © 2017 by American Society of Clinical Oncology

ASSOCIATED CONTENT

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Data Supplements
DOI: <https://doi.org/10.1200/JCO.2017.72.6679>

DOI: <https://doi.org/10.1200/JCO.2017.72.6679>

INTRODUCTION

After induction therapy, patients with newly diagnosed multiple myeloma (NDMM) may be treated with high-dose melphalan (HDM) and autologous stem-cell transplantation (ASCT).¹⁻⁴ ASCT is not curative, and most patients will experience progressive disease (PD),⁵⁻⁸ even patients

who attain a complete response.⁹⁻¹¹ Strategies to delay PD include achieving a deep response after ASCT¹²⁻¹⁵ and sustaining response with maintenance therapy to provide long-term disease control.^{9,16,17}

Effective maintenance therapy should be convenient for the patient, extend remission, and have a tolerable safety profile.^{3,18} The immunomodulatory drug lenalidomide has been shown to

improve progression-free survival (PFS) and overall survival (OS) in patients with NDMM and relapsed or refractory multiple myeloma (MM).^{2,19-24} Lenalidomide modulates the immune response, inhibits MM growth, and is suitable for maintenance therapy after ASCT.^{1,3,18,25} In three studies,^{2,19,20} lenalidomide maintenance after ASCT reduced the risk of progression or death by 50% to 58% versus placebo or observation, and one of these studies showed a significant OS improvement.¹⁹ The primary end point of these studies was PFS, and the studies were not powered for a primary OS end point. In addition, second primary malignancies (SPMs) were reported in patients receiving lenalidomide maintenance after HDM and ASCT.^{19,20} A meta-analysis was conducted at the request of the US Food and Drug Administration to evaluate the effect of post-ASCT lenalidomide maintenance on outcomes, including OS, in patients with NDMM.

PATIENTS AND METHODS

Study Identification and Selection

We examined all randomized controlled trials (RCTs) evaluating maintenance treatment with lenalidomide after HDM and ASCT. Inclusion criteria included RCT in patients with NDMM receiving post-ASCT lenalidomide before progression; maintenance comparing a lenalidomide arm to a placebo or observation arm; achieved database lock for the primary efficacy analysis; and primary-source patient-level data or available documentation. A search of the PubMed database using the keywords “lenalidomide,” “maintenance,” and “myeloma” found no other studies. We identified 17 studies (Data Supplement) and the following three studies met the prespecified inclusion criteria: Cancer and Leukemia Group B (CALGB) 100104 (A Phase III Randomized, Double-Blind Study of Maintenance Therapy With Lenalidomide or Placebo Following Autologous Stem Cell Transplantation for Multiple Myeloma)¹⁹; Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) RV-MM-PI-209 (A Phase III, Multicenter, Randomized, Controlled Study to Determine the Efficacy and Safety of Lenalidomide, Melphalan, and Prednisone Versus Melphalan (200 mg/m²) Followed by Stem Cell Transplant in Patients with Newly Diagnosed Multiple Myeloma)²; and Intergroupe Francophone du Myélome (IFM) 2005-02 (Relevance of Maintenance Therapy Using Lenalidomide After Autologous Stem Cell Transplantation Patients Under the Age of 65)²⁰. The Myeloma XI trial (Use of Thalidomide, Lenalidomide, Carfilzomib, Bortezomib and Vorinostat in the Initial Treatment of Newly Diagnosed Multiple Myeloma Patients)²⁶ had not completed accrual at the data cutoff date, and the other 13 studies did not compare lenalidomide maintenance with placebo or observation. Additional study details are provided in the Data Supplement.

The human investigations for the CALGB study were performed after approval by a local or central human investigations committee and in accordance with an assurance filed with and approved by the Department of Health and Human Services. The IFM and GIMEMA studies were performed after approval by a local or central human investigations committee in accordance with the European Medicines Agency. All data were anonymized to protect the identities of patients involved in the research. All investigators obtained informed consent from each participant or each participant's guardian.

Outcome Measures

The primary end point for the meta-analysis was OS. Other analyses included PFS, PFS after next therapy (PFS2), duration of maintenance treatment, time to second antineoplastic treatment, and safety. Individual analyses of OS, PFS, and PFS2 for each study were performed. All analyses used patient-level data from each study. Additional end point analytic details are provided in the Data Supplement.

Statistical Analysis

A 20-month improvement in median OS from 70 months for the placebo or observation control group to 90 months in the lenalidomide maintenance group, representing a hazard ratio (HR) of 0.78, was considered clinically relevant. March 1, 2015 was the cutoff date for the meta-analysis on the basis of number of events required. All patients were evaluated on an intent-to-treat (ITT) basis after ASCT. Additional methods, including sensitivity, heterogeneity, and exploratory analytic details, are presented in the Data Supplement.

RESULTS

Patient Demographics

A total of 1,208 patients composed the ITT population; 605 patients were in the lenalidomide maintenance group, and 603 patients were in the placebo or observation group (Data Supplement). The ITT population included all patients who were randomly assigned to lenalidomide versus placebo or observation and who received HDM or ASCT, regardless of whether they received maintenance therapy.

As of the March 1, 2015, data cutoff, the median follow-up time for all surviving patients was 79.5 months (range, 0.0 to 114.3 months). Patient demographics and disease-related characteristics were generally balanced based on available data, except for International Staging System (ISS) disease stage, cytogenetics, and renal function, which favored the placebo or observation group ($P < .1$; Table 1). The median age was approximately 58 years. Additional details on patient demographics and disease evaluation after ASCT and before maintenance therapy are provided in the Data Supplement. Maintenance treatment duration was affected by study changes within the CALGB study (allowing crossover from placebo to lenalidomide at unblinding before PD) and the IFM study (stopping maintenance in 119 patients without PD). Maintenance therapy durations are listed in Table 2. The percentages of patients receiving lenalidomide for ≥ 4 years were 24.1% in CALGB, 3.6% in IFM (which includes 2 cycles of lenalidomide consolidation), and 42.9% in the GIMEMA study. The mean treatment duration was 28 months with lenalidomide maintenance and 22 months with placebo or observation (Table 2).

PFS

In this meta-analysis, the significant PFS improvement observed with lenalidomide maintenance versus placebo or observation was confirmed. The median PFS time was 52.8 months for the lenalidomide group and 23.5 months for the placebo or observation group. The risk of progression or death was reduced by 52% with lenalidomide maintenance versus placebo or observation (HR, 0.48; 95% CI, 0.41 to 0.55; Fig 1A). Results were consistent when alternative censoring rules were applied (Data Supplement). The PFS improvement with lenalidomide maintenance versus placebo or observation was confirmed in each study (Fig 1B) and was seen in all subgroups that had data available from all three studies (Fig 1C). Subgroup analysis of data not available from all three studies is presented in the Data Supplement. Lenalidomide maintenance improved PFS in all subgroups, including patients with high-risk cytogenetics; however, the majority of patients did not have available cytogenetic data.

Table 1. Demographics and Disease-Related Characteristics at Diagnosis (intent-to-treat population)

Characteristic*	No. of Patients (%)							
	CALGB		IFM		GIMEMA		Pooled	
	Len Maintenance (n = 231)	Placebo (n = 229)	Len Maintenance (n = 307)	Placebo (n = 307)	Len Maintenance (n = 67)	Observation (n = 67)	Len Maintenance (n = 605)	Placebo or Observation (n = 603)
Age, year [†]								
Median (range)	58.0 (29.0-71.0)	58.0 (39.0-71.0)	57.5 (22.7-68.3)	58.1 (32.3-67.0)	57.9 (35.5-65.1)	56.2 (40.1-66.0)	58.0 (22.7-71.0)	57.9 (32.3-71.0)
≤ 59	131 (56.7)	133 (58.1)	198 (64.5)	194 (63.2)	43 (64.2)	48 (71.6)	372 (61.5)	375 (62.2)
≥ 60	100 (43.3)	96 (41.9)	109 (35.5)	113 (36.8)	24 (35.8)	19 (28.4)	233 (38.5)	228 (37.8)
Male	121 (52.4)	129 (56.3)	169 (55.0)	181 (59.0)	32 (47.8)	39 (58.2)	322 (53.2)	349 (57.9)
Race								
White	175 (75.8)	171 (74.7)	—	—	65 (97.0)	67 (100)	240 (39.7)	238 (39.5)
Nonwhite	42 (18.2)	47 (20.5)	—	—	2 (3.0)	0	44 (7.3)	47 (7.8)
Missing data	14 (6.1)	11 (4.8)	307 (100)	307 (100)	0	0	321 (53.1)	318 (52.7)
ISS stage ^{‡§}								
I	62 (26.8)	85 (37.1)	128 (41.7)	143 (46.6)	35 (52.2)	41 (61.2)	225 (37.2)	269 (44.6)
II	58 (25.1)	46 (20.1)	104 (33.9)	107 (34.9)	24 (35.8)	17 (25.4)	186 (30.7)	170 (28.2)
III	39 (16.9)	35 (15.3)	66 (21.5)	46 (15.0)	8 (11.9)	9 (13.4)	113 (18.7)	90 (14.9)
Missing data	72 (31.2)	63 (27.5)	9 (2.9)	11 (3.6)	0	0	81 (13.4)	74 (12.3)
Extramedullary disease								
Yes	54 (23.4)	69 (30.1)	30 (9.8)	28 (9.1)	10 (14.9)	10 (14.9)	94 (15.5)	107 (17.7)
No	160 (69.3)	149 (65.1)	277 (90.2)	278 (90.6)	57 (85.1)	57 (85.1)	494 (81.7)	484 (80.3)
Missing data	17 (7.4)	11 (4.8)	0	1 (0.3)	0	0	17 (2.8)	12 (2.0)
Adverse-risk cytogenetics, t(4;14) or del17p [¶]								
Yes	—	—	41 (13.4)	24 (7.8)	15 (22.4)	12 (17.9)	56 (9.3)	36 (6.0)
No	—	—	202 (65.8)	216 (70.4)	30 (44.8)	27 (40.3)	232 (38.3)	243 (40.3)
Missing data	—	—	64 (20.8)	67 (21.8)	22 (32.8)	28 (41.8)	317 (52.4)	324 (53.7)
Lactate dehydrogenase								
Normal	—	—	208 (67.8)	220 (71.7)	62 (92.5)	63 (94.0)	270 (44.6)	283 (46.9)
> ULN	—	—	40 (13.0)	41 (13.4)	5 (7.5)	4 (6.0)	45 (7.4)	45 (7.5)
Missing data	—	—	59 (19.2)	46 (15.0)	0	0	290 (47.9)	275 (45.6)
Creatinine clearance, mL/min ^{¶¶}								
< 50	11 (4.8)	9 (3.9)	45 (14.7)	25 (8.1)	4 (6.0)	3 (4.5)	60 (9.9)	37 (6.1)
≥ 50	60 (26.0)	64 (27.9)	204 (66.4)	232 (75.6)	63 (94.0)	64 (95.5)	327 (54.0)	360 (59.7)
Missing data	160 (69.3)	156 (68.1)	58 (18.9)	50 (16.3)	0	0	218 (36.0)	206 (34.2)

NOTE. Dash indicates not reported.

Abbreviations: CALGB, Cancer and Leukemia Group B; GIMEMA, Gruppo Italiano Malattie Ematologiche dell'Adulto; IFM, Intergroupe Francophone du Myélome; ISS, International Staging System; Len, lenalidomide; ULN, upper limit of normal.

*Race was not collected in the IFM 2005-02 study, and lactate dehydrogenase and cytogenetics data were not available for the CALGB 100104 study.

†For the CALGB 100104 and IFM 2005-02 studies, age at random assignment was available or used. For the GIMEMA study, only age at diagnosis was available.

‡ $P < .1$ for the comparison of ISS stages I, II, and III individually. The ISS stage was based on β_2 -microglobulin and albumin at diagnosis for the GIMEMA RV-MM-PI-209 and IFM 2005-02 studies and at registration for the CALGB 100104 study.§ $P < .1$ for the comparison between the lenalidomide maintenance arm and placebo arm in the CALGB study using the t test for continuous variables and Fisher's exact test for categorical variables.¶ $P < .1$ for the comparison between the lenalidomide maintenance group and placebo or observation group in the pooled analysis using the t test for continuous variables and Fisher's exact test for categorical variables.¶¶ $P < .1$ for the comparison between the lenalidomide maintenance arm and placebo arm in the IFM 2005-02 study using the t test for continuous variables and Fisher's exact test for categorical variables.

OS

As of the March 1, 2015, data cutoff, 490 deaths occurred in both cohorts. Median OS was not reached in the lenalidomide maintenance group and was 86.0 months in the placebo or observation group (HR, 0.75; 95% CI, 0.63 to 0.90; $P = .001$), representing a 25% reduction in the risk of death with lenalidomide maintenance versus placebo or observation (Fig 2A). Fisher's combination test confirmed the significant OS benefit with lenalidomide maintenance versus placebo or observation ($P = .001$). The 7-year survival rate was 62% with lenalidomide maintenance and 50% with placebo or observation. At the median follow-up time

of 79.5 months, 64% and 54% of patients were alive in the lenalidomide maintenance and placebo or observation groups, respectively. The proportional hazards (PH) assumption was tested using the time-dependent covariate in the PH Cox model; the proportionality was not significant ($P = .21$). The graphical check of the PH assumption using the $-\log(-\log)$ plot of the estimated survival function for each treatment group revealed the same results. The OS subgroup analyses are shown in Figure 2B. Except for patients with ISS disease stage III, the HRs for the subgroup analyses favor lenalidomide maintenance. Patients with better responses ($\geq$ very good partial response) after HDM or ASCT seemed to have

Table 2. Duration of Maintenance Therapy (safety population)

Treatment Duration	CALGB			IFM*			GIMEMA		Pooled	
	Len Maintenance (n = 224)	Placebo (n = 221)		Len Maintenance (n = 306)		Placebo (n = 302)	Len Maintenance (n = 56)	Observation (n = 67)	Len Maintenance (n = 586)	Placebo or Observation (n = 590)
		Placebo Up to Crossover (n = 221)	Len After Crossover (n = 76)†	All Patients (n = 306)	Cohort Treatment Stopped Jan 2011 (n = 119)‡					
Mean, months (range)§	30 (0-108)	13 (0-51)	25 (0-61)	25 (0-55)	39 (27-55)	20 (0-49)	35 (2-71)	29 (0-75)	28 (0-108)	22 (0-86)
Duration category, No. (%)										
≥ 1 year	150 (67.0)	95 (43.0)	46 (60.5)	217 (70.9)	119 (100)	211 (69.9)	44 (78.6)	51 (76.1)	411 (70.1)	391 (66.3)
≥ 2 years	116 (51.8)	32 (14.5)	33 (43.4)	170 (55.6)	119 (100)	121 (40.1)	33 (58.9)	36 (53.7)	319 (54.4)	230 (39.0)
≥ 3 years	82 (36.6)	6 (2.7)	24 (31.6)	88 (28.8)	74 (62.2)	32 (10.6)	29 (51.8)	23 (34.3)	199 (34.0)	95 (16.1)
≥ 4 years	54 (24.1)	1 (0.5)	18 (23.7)	11 (3.6)	11 (9.2)	2 (0.7)	24 (42.9)	17 (25.4)	89 (15.2)	44 (7.5)

NOTE. Safety population includes patients who received at least one dose of study drug.

Abbreviations: CALGB, Cancer and Leukemia Group B; GIMEMA, Gruppo Italiano Malattie Ematologiche dell'Adulto; IFM, Intergroupe Francophone du Myélome; Len, lenalidomide.

*In the IFM study, data from two cycles of lenalidomide consolidation are included.

†In the CALGB study, after study unblinding on December 17, 2009, patients randomly assigned to the placebo arm were allowed to cross over to lenalidomide before progressive disease.

‡In the IFM study, treatment was stopped in the lenalidomide arm in January 2011 for 119 patients (minimum treatment duration of 27 months) after observing an imbalance of second primary malignancies in the lenalidomide arm.

§Only mean values are reported due to treatment time truncation from the IFM 2005-02 study and median times cannot be given for the IFM 2005-02 study.

more favorable outcomes with lenalidomide maintenance. The most favorable OS benefit with lenalidomide maintenance was observed in patients who received a lenalidomide-based induction treatment (Fig 2C). Subgroup analysis of data not available for all three studies is presented in the Data Supplement. An OS improvement with lenalidomide maintenance was not seen in the following diagnostic subgroups: elevated lactate dehydrogenase, low creatinine clearance, and adverse-risk cytogenetics; however, not all patients had available information.

Heterogeneity and Exploratory Analyses

The Pignon heterogeneity test indicated a significant difference in quantitative treatment effect across studies ($P = .047$). No qualitative heterogeneity in OS was found using the Gail-Simon test ($P = .75$), indicating no directional difference in treatment effect. Thus, the HRs of the individual studies all favored lenalidomide maintenance treatment (Fig 2D). The heterogeneity observed is driven by the difference in magnitude of the treatment effect among the studies. A simplified multivariate analysis with treatment, study, and treatment by study interaction in the model revealed similar results; the heterogeneity in OS was mainly a result of differences between the CALGB and IFM studies ($P = .015$ for treatment by study [CALGB ν IFM] interaction). There was no significant heterogeneity in OS between CALGB and GIMEMA ($P = .525$ for treatment by study [CALGB ν GIMEMA] interaction). There were differences between the three studies regarding pre- and post-ASCT patient characteristics and treatment. These differences include prestudy patient characteristics, induction regimens, consolidation therapies (Data Supplement), and second-line therapies (Data Supplement), as well as changes in study conduct such as post-ASCT lenalidomide consolidation in the IFM trial, crossover from placebo to lenalidomide after unblinding in the CALGB trial, and stopping of lenalidomide maintenance therapy in the IFM trial (Data Supplement). With extended follow-up (February 1, 2016), lenalidomide maintenance reduced the risk

of death by 23% compared with placebo or observation (HR, 0.77; 95% CI, 0.65 to 0.91; $P = .002$). The median OS time was 111.0 months with lenalidomide maintenance compared with 86.9 months with placebo or observation. The median duration of follow-up among all surviving patients was 88.8 months (range, 0 to 119.8 months). Heterogeneity in OS across studies was not detected by the Pignon test with the longer follow-up ($P = .10$).

PFS2

Median PFS2 was 73.3 months with lenalidomide maintenance compared with 56.7 months with placebo or observation (HR, 0.72; 95% CI, 0.62 to 0.84; Data Supplement). Lenalidomide maintenance reduced the risk of a PFS2 event (progression on second-line treatment or death) by 28% compared with placebo or observation. The PFS2 HRs in all studies favored lenalidomide maintenance versus placebo or observation (Data Supplement).

Second-Line Antimyeloma Treatment

Time to second-line antimyeloma treatment was prolonged with lenalidomide maintenance versus placebo or observation (HR, 0.57; 95% CI, 0.49 to 0.66; Data Supplement). Fewer patients in the lenalidomide maintenance group (52.6%) started second-line antimyeloma therapy compared with patients in the placebo or observation group (70.8%). The most common second-line antimyeloma treatment was lenalidomide based (27.9%) in the placebo or observation group and bortezomib based (19.5%) in the lenalidomide maintenance group.

Safety

Treatment-emergent adverse events (TEAEs) were analyzed for patients in the CALGB and IFM trials. Data were not available from GIMEMA. Rates of treatment discontinuation as a result of TEAEs were 29.1% in the lenalidomide maintenance group and 12.2% in the placebo or observation group (Table 3). The most

Fig 1. Progression-free survival (PFS) analysis (intent-to-treat population). For analyses of PFS, patients who started another antimyeloma therapy before documented disease progression or patients with missing assessments are censored. (A) Kaplan-Meier estimates of PFS. (B) Hazard ratios (HRs) for PFS by individual study. (C) HRs for PFS by subgroup. (*) The size of each blue box corresponds to the size of the individual study. The CI is a function of the overall sample size. (†) Age at random assignment was available and used for the Cancer and Leukemia Group B (CALGB) 100104 study¹⁹ and the Intergroupe Francophone du Myélome (IFM) 2005-02 study²⁰. Only age at diagnosis was available for the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) RV-MM-PI-209 study². (‡) The International Staging System (ISS) stage was based on β_2 -microglobulin and albumin at diagnosis for the GIMEMA and IFM studies and at registration for the CALGB study. (§) Upon central review, four patients did not meet the criteria for stable disease (SD). ASCT, autologous stem-cell transplantation; CR, complete response; Len, lenalidomide; PR, partial response; VGPR, very good partial response.

common TEAEs leading to treatment discontinuation in the lenalidomide maintenance and placebo or observation groups were blood and lymphatic system disorders (4.3% v 2.1%, respectively)

and general disorders and administration site conditions (4.7% v 1.5%, respectively). Consistent with previous CALGB and IFM reports, this analysis showed a higher frequency of SPMs with

Fig 2. Overall survival (OS) analysis (intent-to-treat population). (A) Kaplan-Meier estimates of OS. (B) Hazard ratios (HRs) for OS by subgroup. (C) HRs for OS by prior induction subgroup. (D) HRs for OS by individual study. (*) Age at random assignment was available or used for the Cancer and Leukemia Group B (CALGB) 100104 study¹⁹ and the Intergroupe Francophone du Myélome (IFM) 2005-02 study²⁰. Only age at diagnosis was available for the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) RV-MM-PI-209 study². (†) The International Staging System (ISS) stage was based on β_2 -microglobulin and albumin at diagnosis for the GIMEMA and IFM studies and at registration for the CALGB study. (§) Upon central review, four patients did not meet the criteria for stable disease (SD). (§) All patients in the GIMEMA study received lenalidomide-based induction, which could be used in combination with any other drug. The size of each blue box corresponds to the size of the individual study. The CI is a function of the overall sample size. ASCT, autologous stem-cell transplantation; CR, complete response; Len, lenalidomide; NR, not reached; PR, partial response; TD, thalidomide and dexamethasone; VAD, vincristine, doxorubicin, and dexamethasone; VD, bortezomib and dexamethasone; VGPR, very good partial response.

lenalidomide maintenance versus placebo or observation. Frequencies of hematologic SPMs occurring before PD (5.3% and 0.8% for lenalidomide and placebo or observation, respectively) and before and after PD (6.1% and 2.8% for lenalidomide and placebo or observation, respectively) were reported for both groups. In the lenalidomide maintenance and placebo or observation groups, frequencies of solid tumor SPMs occurring before

PD (5.8% and 2.0%, respectively) and before and after PD (7.3% and 4.2%, respectively) were also reported. The cumulative incidence curves for hematologic and solid tumor SPMs are shown in Figures 3A and 3B. Time to invasive SPMs occurring before PD or start of second-line therapy was shorter in the lenalidomide maintenance group versus the placebo or observation group (HR, 2.67; 95% CI, 1.54 to 4.62; $P < .001$), whereas time to PD or

Table 3. Discontinuations as a Result of TEAEs (safety population)

TEAE	No. of Patients (%)					
	CALGB		IFM*		Pooled	
	Len Maintenance (n = 224)	Placebo (n = 221)	Len Maintenance (n = 306)	Placebo (n = 302)	Len Maintenance (n = 530)†	Placebo (n = 523)†
≥ 1 TEAE leading to discontinuation	63 (28.1)	19 (8.6)	91 (29.7)	45 (14.9)	154 (29.1)	64 (12.2)
TEAEs leading to discontinuation (≥ 1% of all patients)‡						
Blood and lymphatic system disorder	11 (4.9)	4 (1.8)	12 (3.9)	7 (2.3)	23 (4.3)	11 (2.1)
Neutropenia	5 (2.2)	0	7 (2.3)	1 (0.3)	12 (2.3)	1 (0.2)
Thrombocytopenia	6 (2.7)	1 (0.5)	3 (1.0)	5 (1.7)	9 (1.7)	6 (1.1)
General disorders and administration site conditions	12 (5.4)	5 (2.3)	13 (4.2)	3 (1.0)	25 (4.7)	8 (1.5)
Adverse event not specified	10 (4.5)	4 (1.8)	0	0	10 (1.9)	4 (0.8)
Neoplasms: benign, malignant, and unspecified§	16 (7.1)	3 (1.4)	7 (2.3)	2 (0.7)	23 (4.3)	5 (1.0)
Skin and subcutaneous tissue disorders	6 (2.7)	1 (0.5)	12 (3.9)	9 (3.0)	18 (3.4)	10 (1.9)
Nervous system disorders	5 (2.2)	3 (1.4)	13 (4.2)	6 (2.0)	18 (3.4)	9 (1.7)
GI disorders	5 (2.2)	0	13 (4.2)	1 (0.3)	18 (3.4)	1 (0.2)
Diarrhea	5 (2.2)	0	6 (2.0)	0	11 (2.1)	0
Infections and infestations	4 (1.8)	0	5 (1.6)	4 (1.3)	9 (1.7)	4 (0.8)
Musculoskeletal and connective tissue disorders	1 (0.4)	1 (0.5)	5 (1.6)	6 (2.0)	6 (1.1)	7 (1.3)

NOTE. Safety population includes patients who received at least one dose of study drug.

Abbreviations: CALGB, Cancer and Leukemia Group B; GIMEMA, Gruppo Italiano Malattie Ematologiche dell'Adulto; IFM, Intergroupe Francophone du Myélome; Len, lenalidomide; TEAE, treatment-emergent adverse event.

*In the IFM study, data from two cycles of lenalidomide consolidation are included.

†Data from the IFM and CALGB studies only.

‡System organ class presented with preferred terms nested below.

§Includes cysts and polyps.

second-line therapy was longer with lenalidomide maintenance versus placebo or observation (HR, 0.51; 95% CI, 0.45 to 0.59; $P < .001$; Fig 3C). The risk of developing PD was higher than the risk of developing an invasive SPM in both groups. In the lenalidomide maintenance and placebo or observation groups, the cumulative incidence rates of PD or second-line therapy were consistently higher than that of invasive SPM over time (Data Supplement). The time to death as a result of MM was significantly longer in the lenalidomide maintenance group versus the placebo or observation group (HR, 0.66; 95% CI, 0.53 to 0.81; $P < .001$; Fig 3D). For time to death as a result of SPM or adverse event, there were no differences between the two groups.

DISCUSSION

An improved PFS with lenalidomide maintenance versus placebo or observation after HDM and ASCT in patients with NDMM was previously reported in the three studies analyzed in this report.^{2,19,20} The studies were not powered for OS, and OS data were not mature at the time of their initial publications. One trial, the CALGB trial, showed an early significant improvement in OS with lenalidomide maintenance. As a result of the increased SPM incidence with lenalidomide maintenance versus placebo reported in two of the trials, the CALGB and IFM trials, it was important to understand the risks and benefits of long-term lenalidomide maintenance after HDM and ASCT for patients with NDMM. The meta-analysis was planned to demonstrate a 20-month improvement in median OS based on an estimated median OS of 70 months with placebo or observation, approximating an HR of 0.78. The OS analysis was planned before identifying studies for data collection. Primary-source patient data from the three studies

meeting the prespecified inclusion criteria were analyzed. The three studies consisted of generally similar patient populations, study designs, and maintenance approaches. The aggregate patient population provided sufficient power for the OS end point. A limitation of this analysis is the small number of studies included. Nevertheless, the meta-analysis was adequately powered to detect a treatment effect and demonstrated that lenalidomide maintenance versus placebo or observation after HDM and ASCT significantly prolonged OS and reduced the risk of death by 25%.

A 29.3-month PFS improvement was observed with lenalidomide maintenance versus placebo or observation on an ITT basis; these results are not adjusted for the crossover of placebo arm patients without PD in the CALGB study. The PFS2 benefit with lenalidomide maintenance versus placebo or observation indicated that lenalidomide maintenance did not induce PD resistant to salvage treatment. The PFS improvements observed with lenalidomide maintenance in each study were similar despite different dosing schedules (days 1 to 28 of a 28-day schedule for CALGB and IFM and days 1 to 21 of a 28-day schedule for GIMEMA). The recently presented results from the Myeloma XI trial demonstrated a similar PFS improvement with lenalidomide maintenance versus observation (HR, 0.47; 95% CI, 0.38 to 0.60) after ASCT using a treatment schedule of 21 days of treatment in a 28-day schedule.²⁶

The PFS subgroup analyses consistently favored lenalidomide maintenance versus placebo or observation, with differences in the magnitude of benefit. For the OS subgroup analyses, the benefit with lenalidomide maintenance was heterogeneous. The OS benefit with lenalidomide maintenance was less pronounced for patients older than age 60 years and for women. Patients with ISS disease stage III did not experience an OS benefit. The risk of death was reduced by 30% and 37% with lenalidomide maintenance versus placebo or observation in patients achieving very good partial

Fig 3. Second primary malignancy and mortality analyses. (A) Cumulative incidence curve of time to hematologic second primary malignancy (SPM) onset (as-treated population). Patients who were randomly assigned but not treated with lenalidomide maintenance are included in the control group. (B) Cumulative incidence of time to solid tumor SPM onset (as-treated population). Patients who were randomly assigned but not treated with lenalidomide maintenance are included in the control group. (C) Cumulative incidence curves of time to disease progression and time to invasive SPM onset before disease progression. (D) Kaplan-Meier (KM) curve of time to death by cause of death. AE, adverse event; Len, lenalidomide; MM, multiple myeloma; PD, progressive disease.

response or complete response, respectively. The induction subgroup analyses for OS favored lenalidomide maintenance versus placebo or observation. The effect was less favorable in patients who received a thalidomide-containing induction regimen or a vincristine, doxorubicin, and dexamethasone induction regimen. A PFS benefit, but not an OS benefit was seen with lenalidomide maintenance versus placebo or observation in patients with high-risk cytogenetics. Only a small number of patients had adverse-risk cytogenetics ($n = 92$). The Myeloma XI trial demonstrated improved PFS with lenalidomide maintenance versus observation in patients with high-risk cytogenetics, which included patients who had and had not received ASCT as a result of eligibility. The data are not yet mature enough for an OS analysis.²⁶

The heterogeneity analysis demonstrated that all three studies contributed to the positive results of the meta-analysis. The HRs for each study are consistent with an OS improvement with lenalidomide maintenance versus placebo or observation. The quantitative heterogeneity results from the differences in magnitude of the treatment effect among the studies, particularly between the CALGB and IFM studies. Possible reasons for this heterogeneity include differences in and incomplete data for some patient demographics, different induction regimens, number of ASCTs, consolidation therapy after ASCT in the IFM study, discontinuation of lenalidomide maintenance before PD in the IFM study, crossover from placebo to lenalidomide maintenance in the CALGB study for patients without progression, and differences in frequency and type of second-line therapy.

There were differences in the length of maintenance therapy in the three studies. The IFM study stopped lenalidomide maintenance at a mean duration of approximately 2 years. For the IFM study patients who stopped lenalidomide maintenance without progression ($n = 119$) the mean duration of maintenance was 3.3 years. The mean durations of maintenance in the CALGB and GIMEMA studies were 2.5 and 3 years, respectively. The proportions of patients on lenalidomide maintenance across the three studies are similar in the treatment duration categories of ≥ 1 , ≥ 2 , and ≥ 3 years. The cessation of lenalidomide maintenance in the IFM study is the primary reason for the smaller percentage of patients on lenalidomide maintenance at ≥ 4 years compared with the other studies. These duration differences may have influenced the magnitude of improvement in PFS, OS, and PFS2 but did not seem to reduce salvage treatment efficacy after PD. A recent retrospective analysis showed a correlation between length of lenalidomide maintenance therapy after ASCT and length of OS in patients with NDMM.²⁷ None of these studies examined a predetermined maintenance duration. Future study designs may evaluate different lengths of maintenance therapy, particularly in patients who achieve minimal residual disease-negative status.

In this analysis, the incidence rates of hematologic and solid tumor SPMs with lenalidomide maintenance were higher compared with placebo or observation. At a median follow-up time of 79.5 months, the rates of hematologic and solid tumor SPMs with lenalidomide maintenance before PD were 5.3% and 5.8%,

respectively. These results are comparable to a previous meta-analysis of lenalidomide therapy in patients with NDMM that showed cumulative 5-year incidence rates of hematologic and solid tumor SPMs of 3.1% and 3.8%, respectively.²⁸ The cumulative incidence rate of developing an SPM before PD is higher for patients who received lenalidomide maintenance, and the cumulative incidence rates of PD and death as a result of MM are higher for patients who received placebo or observation. Overall, the risk of developing PD is greater than that of developing an SPM.

An important treatment goal for patients with NDMM is to achieve and maintain remission or long-term disease control.^{29,30} Maintenance therapy after ASCT can be considered a valid approach toward achieving long-term disease control, delaying time to relapse and second-line treatment, and prolonging survival. A previously published meta-analysis of RCTs comparing thalidomide- or lenalidomide-based maintenance versus thalidomide- and lenalidomide-free maintenance or no maintenance therapy showed in stratified analyses that both maintenance therapies improve PFS, but not OS, in the transplantation setting.³¹ The study used published data from 2012 and 2014 of the same three trials in this analysis. The OS data were less mature, and the analysis did not use primary-source, patient-level data.

This study demonstrates a statistically significant and clinically meaningful improvement in OS with lenalidomide maintenance. With new, highly active, triplet induction regimens enhancing depth and duration of response as well as ongoing studies evaluating the optimal timing of ASCT,³²⁻³⁶ the use of lenalidomide maintenance for transplantation-eligible patients can be considered a standard of care. The costs of maintenance therapy should be weighed against the costs of shorter survival, earlier progression, and earlier use of subsequent lines of therapies for patients without maintenance. Understanding the role of minimal residual disease detection and immune reconstitution after ASCT, as well as developing early end points as surrogates for long-term outcomes, should allow us to develop clinical strategies to further improve OS.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Conception and design: All authors

Collection and assembly of data: All authors

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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Support

Supported by Celgene Corporation. The Cancer and Leukemia Group B 100104 trial was funded by the National Cancer Institute and National Heart, Lung, and Blood Institute and conducted by the Alliance for Clinical Trials in Oncology, Eastern Cooperative Oncology Group, and Blood and Marrow Transplant Clinical Trials Network. The Gruppo Italiano Malattie Ematologiche dell'Adulto RV-MM-PI-209 trial was funded by Celgene Corporation. The Intergroupe Francophone du Myélome 2005-02 trial was funded by the Programme Hospitalier de Recherche Clinique, the Swiss Group for Clinical Cancer Research, and a grant from Celgene Corporation.

Prior Presentation

Presented in part at the 52nd Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 3-7, 2016, and the 21st Congress of the European Hematology Association, Copenhagen, Denmark, June 9-12, 2016.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/iffc.

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Patents, Royalties, Other Intellectual Property: C4 Therapeutics, Oncopep, Acetylon

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Research Funding: Genmab (Inst), Janssen-Cilag (Inst), Takeda (Inst)

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No relationship to disclose

Acknowledgment

We thank Kristina Hernandez and Peter Simon for medical writing assistance, which was sponsored by Celgene Corporation.