SYNOPSIS

Study CC-5013-MDS-004 (hereafter referred to as MDS-004) included a double-blind (DB) treatment phase, an open-label extension phase (hereafter referred to as the OL phase), and a follow-up phase (ie, no study drug treatment). During the follow-up phase, all subjects were to be followed for survival, progression to acute myeloid leukemia (AML), and second primary malignancies (SPMs; added with Amendment 6) for up to 3 years after the last subject had completed or discontinued from the OL phase; information regarding subsequent antineoplastic therapies (after discontinuation of lenalidomide) also was to be collected.

The MDS-004 clinical study report (CSR) dated 20 Oct 2010 included data for the DB and OL phases of the study and covered 08 Jul 2005 to 14 Jun 2010. At the time of the data cutoff for the MDS-004 CSR, all subjects had completed or discontinued from the DB or OL treatment phases.

The purpose of this follow-up synoptic report for Study MDS-004 is to summarize the data for progression to AML, survival, subsequent antineoplastic therapies, and SPMs reported during the entire study, including the DB, OL, and follow-up phases. The 3-year follow-up phase was planned to end on 21 Jun 2013; the actual date of the last subject's last visit was 09 Jul 2013. Thus, this synoptic report covers 08 Jul 2005 to 09 Jul 2013 and represents the final follow-up data for this study.

Name of Sponsor/Company: Celgene Corporation	**Name of Finished Product:** Revlimid® Capsules	**Name of Active Ingredient:** Lenalidomide
Title of Study: A multicenter, randomized, double-blind, placebo-controlled, 3-arm study of the efficacy and safety of 2 doses of lenalidomide versus placebo in red blood cell (RBC) transfusion-dependent subjects with low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion (del) 5q[31] cytogenetic abnormality.		
Coordinating Principal Investigator: . **Investigators:** The investigators and their institutional affiliations are listed in		
Study Centers: 38 sites		
Publications (References): Fenaux P, Giagounidis A, Selleslag D, et al. A randomized phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with Low-/Intermediate-1-risk myelodysplastic syndromes with del5q. *Blood*. 2011;118(14):3765-3776. Giagounidis A, Mufti GJ, Mittelman M, et al. Outcomes in RBC transfusion-dependent patients with Low-Intermediate-1-risk myelodysplastic syndromes with isolated deletion 5q treated with lenalidomide: a subset analysis from the MDS-004 study [published ahead of print 10 May 2014]. *Eur J Haematol*. 2014. Kuendgen A, Lauseker M, List AF, et al. Lenalidomide does not increase AML progression risk in RBC transfusion-dependent patients with low- or intermediate-1-risk MDS with del(5q): a comparative analysis. *Leukemia*. 2013;27(5):1072-1079. Revicki DA, Brandenburg NA, Muus P, Yu R, Knight R, Fenaux P. Health-related quality of life outcomes of lenalidomide in transfusion-dependent patients with Low- or Intermediate-1-risk myelodysplastic syndromes with a chromosome 5q deletion: results from a randomized clinical trial. *Leuk Res*. 2013;37(3):259-265. Saft L, Karimi M, Ghaderi M, et al. p53 protein expression independently predicts outcome in patients with lower-risk myelodysplastic syndromes with del(5q). *Haematologica*. 2014;99(6):1041-1049.		

Studied Period (years):	**Phase of development:** 3
Date first subject enrolled: 08 Jul 2005 Date of last subject's last visit (follow-up): 09 Jul 2013	

Objectives:

Primary:

To compare the efficacy of 2 doses (10 mg and 5 mg) of lenalidomide to that of placebo in subjects with RBC transfusion-dependent low- or intermediate-1 (INT-1)–risk International Prognostic Scoring System (IPSS) MDS associated with a del 5q[31] cytogenetic abnormality.

Secondary:

To compare the safety of 2 doses of lenalidomide (10 mg and 5 mg) to that of placebo in subjects with RBC transfusion-dependent low- or INT-1–risk IPSS MDS associated with a del 5q[31] cytogenetic abnormality.

Methodology:

This multicenter, randomized, DB, placebo-controlled, 3-arm study of 2 doses of oral lenalidomide versus placebo administered to RBC transfusion-dependent adult subjects with low- or INT-1–risk IPSS MDS associated with a del 5q[31] cytogenetic abnormality was conducted in 3 phases: a prerandomization phase, a DB treatment phase, and an OL phase.

Double-blind treatment phase: The DB treatment phase was to start (Day 1) within 3 days of randomization, and could continue for up to 52 weeks (until Day 365 of the DB treatment phase). On Day 1, all subjects began treatment with 5 mg lenalidomide, 10 mg lenalidomide, or placebo. Subjects who had evidence of at least a minor erythroid response after 16 weeks of treatment phase participation were able to continue therapy in the DB treatment phase for up to 52 weeks (Day 365 of the DB treatment phase) unless there was disease progression or erythroid relapse. Subjects who did not have evidence of at least a minor erythroid response after 16 weeks of DB treatment phase participation were to be discontinued from the DB treatment phase for lack of therapeutic efficacy and unblinded. Subjects discontinued from the DB treatment phase of the study for disease progression were not eligible for inclusion in the OL phase (see below). Subjects who had an erythroid relapse following the achievement of at least a minor erythroid response were discontinued from the DB treatment phase for lack of therapeutic efficacy and their assigned treatment arm was unblinded. Subjects who completed the total duration of 52 weeks in the DB treatment phase without disease progression or erythroid relapse were unblinded after Week 52 and entered the OL phase at their current dose of lenalidomide.

Open-label phase: Subjects were permitted to continue lenalidomide therapy in the OL phase for up to 156 weeks of total study participation. Subjects who did not achieve at least a minor erythroid response within 16 weeks of OL treatment, or who developed an erythroid relapse without low thyroid-stimulating hormone (all subjects) or testosterone (male subjects only) levels following the achievement of a minor or major erythroid response, were treated as follows:

- Subjects assigned to the placebo arm were eligible to receive lenalidomide 5 mg once daily in the OL phase for up to 140 weeks (for a total of up to 156 weeks of study participation).
- Subjects assigned to the lenalidomide 5 mg treatment arm and who tolerated therapy without undergoing dose reduction were eligible to receive lenalidomide 10 mg QD on Days 1 to 21 every 28 days in the OL phase for up to 140 weeks (for a total of up to 156 weeks of study participation).
- Subjects assigned to the lenalidomide 5 mg treatment arm who previously required a dose reduction were not eligible for OL treatment and were discontinued from the study.
- Subjects assigned to the lenalidomide 10 mg treatment arm and who did not have evidence of at least a minor erythroid response were not eligible for OL treatment and were discontinued from the study.

Additional details regarding the study design are provided in .

Subjects who discontinued study treatment for any reason were to be followed every 4 months (directly via telephone or information obtained from their treating physician) for survival and/or to collect any events of progression to AML; information regarding subsequent antineoplastic therapies (after discontinuation of lenalidomide) also was to be collected. The survival follow-up phase lasted up to 3 years after the last subject had completed/discontinued from the OL phase. Follow-up for SPMs was added with Amendment 6.

Number of Subjects (Planned and Analyzed):

Planned: Enrollment was expanded from 162 to 205 subjects to achieve the prespecified 135 evaluable subjects.

Analyzed: 205 (intent to treat [ITT] and safety). The ITT population included all randomized subjects. The safety population included all subjects who received ≥ 1 dose of study drug. For this study, the ITT population equals the safety population. All analyses in this synoptic report use data for the 205 subjects.

Diagnosis and Main Criteria for Inclusion:

Red blood cell transfusion-dependent adult subjects with low- or INT-1–risk IPSS MDS associated with a del 5q[31] cytogenetic abnormality (subjects with MDS clones that have a del 5q[31] cytogenetic abnormality with additional cytogenetic abnormalities remained eligible for enrollment into this study).

Test Product, Dose and Mode of Administration, Batch Numbers:

Celgene Corporation supplied lenalidomide 5 mg capsules and placebo capsules in blister packs during the DB treatment phase. The placebo capsules were identical in appearance to the 5 mg lenalidomide capsules. For the OL phase, Celgene supplied lenalidomide 5 mg capsules in bottles. The batch numbers are listed in .

Duration of Treatment:

Subjects could receive study treatment up to 156 weeks of total study participation unless the following occurred: 1) at least a minor erythroid response was not achieved within 16 weeks of OL treatment, 2) PD developed, or 3) the RBC transfusion requirement returned to baseline in the absence of hypothyroidism in female subjects or hypothyroidism and hypogonadism in male subjects. (See Methodology for additional details.) The rationale for the duration of treatment (ie, up to 156 weeks [3 years]) in this study is provided in .

Reference Therapy, Dose and Mode of Administration, Batch Number: Not applicable

Criteria for Evaluation (for this Synoptic Report):

Efficacy: Progression to AML and overall survival (OS)

Safety: Subsequent antineoplastic therapies (after discontinuation of lenalidomide), deaths, and SPMs

Statistical Methods:

A summary of the statistical and analytical plans is provided in . A brief summary of the statistical methods used for the analyses summarized in this synoptic report follows.

Descriptive analyses were performed to summarize subject disposition and treatment duration.

The AML follow-up time was calculated from the date of randomization to the date of AML diagnosis, death, or last known contact (for non-AML survivors), whichever was earlier.

Cumulative incidence of progression to AML was calculated from the date of the first dose of study drug. For subjects who switched from placebo to OL 5 mg lenalidomide (Pbo/5 mg), the cumulative incidence of progression to AML was calculated from the first dose of 5 mg lenalidomide.

Time to progression to AML was calculated from the date of randomization to the date of the first diagnosis of AML and analyzed by original randomized group. For subjects who switched from placebo to OL 5 mg lenalidomide (Pbo/5 mg), the time to progression to AML also was calculated from the first dose of 5 mg lenalidomide.

The survival follow-up time was calculated from the date of randomization to the date of death or last known contact and analyzed by original randomized group. Time to death was calculated from the date of randomization to the date of death from any cause. For subjects who switched from placebo to OL 5 mg lenalidomide (Pbo/5 mg), time to death also was calculated from the first dose of 5 mg lenalidomide and analyzed.

The frequency of subjects who were diagnosed with SPMs was summarized by SPM category. Incidence rate per 100 person-years was summarized by SPM category; person-years were calculated as the time from the first dose date of the study treatment to the onset date of the first SPM in each subcategory for subjects with an SPM, and to the date of last follow-up for subjects without an SPM.

The final database lock date for this synoptic report was 14 Aug 2013.

SUMMARY – CONCLUSIONS

This synoptic report presents the progression to AML, survival, subsequent antineoplastic therapies, and SPM data reported during the entire study, including the DB, OL, and follow-up phases. The 3-year follow-up phase was planned to end on 21 Jun 2013; the actual date of the last subject's last visit was 09 Jul 2013. Thus, this synoptic report covers 08 Jul 2005 to 09 Jul 2013 and represents the final follow-up data for this study.

Subject Disposition

At the time of the data cutoff for the MDS-004 CSR (14 Jun 2010), all subjects had completed or discontinued from the DB or OL phases); subject disposition reported in and is unchanged from the data reported in and .

The brief overview below provides clarification regarding the different subject groups included in the analyses in this report, particularly regarding the subjects who crossed over from the DB phase to receive different treatment in the OL phase. A summary of subject distribution by treatment regimen is provided in . The subject listings for subject disposition are provided in (DB treatment phase) and (OL phase).

A total of 205 subjects were enrolled in the DB treatment phase: 67 in the placebo arm, 69 in the 5 mg lenalidomide arm, and 69 in the 10 mg lenalidomide arm ( ). A total of 145 subjects entered the OL phase ( ), 141 of whom received ≥ 1 dose of OL lenalidomide ( ). Of those 141 subjects:

- 56 subjects crossed over from placebo in the DB treatment phase to receive 5 mg lenalidomide in the OL phase (Pbo/5 mg),
- 27 subjects who received a starting dose of 5 mg in the DB treatment phase continued to receive 5 mg in the OL phase (5 mg/5 mg),
- 14 subjects who received a starting dose of 5 mg in the DB treatment phase crossed over to receive 10 mg in the OL phase (5 mg/10 mg),
- 28 subjects who received a starting dose of 10 mg in the DB treatment phase dose-reduced to 5 mg in the OL phase (10 mg/5 mg), and
- 16 subjects who received a starting dose of 10 mg in the DB treatment phase continued to receive 10 mg in the OL phase (10 mg/10 mg) ( ).

Of note, an Extended Access Phase (EAP) was initiated in France (per local Protocol Amendment 6.1) to allow continued treatment of responding subjects. As of 09 Jul 2013, 1 subject ( ) was still receiving lenalidomide as subsequent antineoplastic therapy ( ). The EAP is planned to continue as long as the subject benefits.

EFFICACY RESULTS:

All results below include progression to AML and OS data from the DB, OL, and follow-up phases.

Two types of analyses are presented for time to progression to AML and OS:

1. The primary ITT analyses examine the data according to the original randomized treatment assignment.
2. The as-treated analyses separate the placebo group to examine those subjects who received only placebo versus those who crossed over to receive lenalidomide.

Subject listings of progression to AML and AML start date are provided in and , respectively. Narratives for subjects who had progression to AML at any time during the study are provided in

Time to Progression to AML

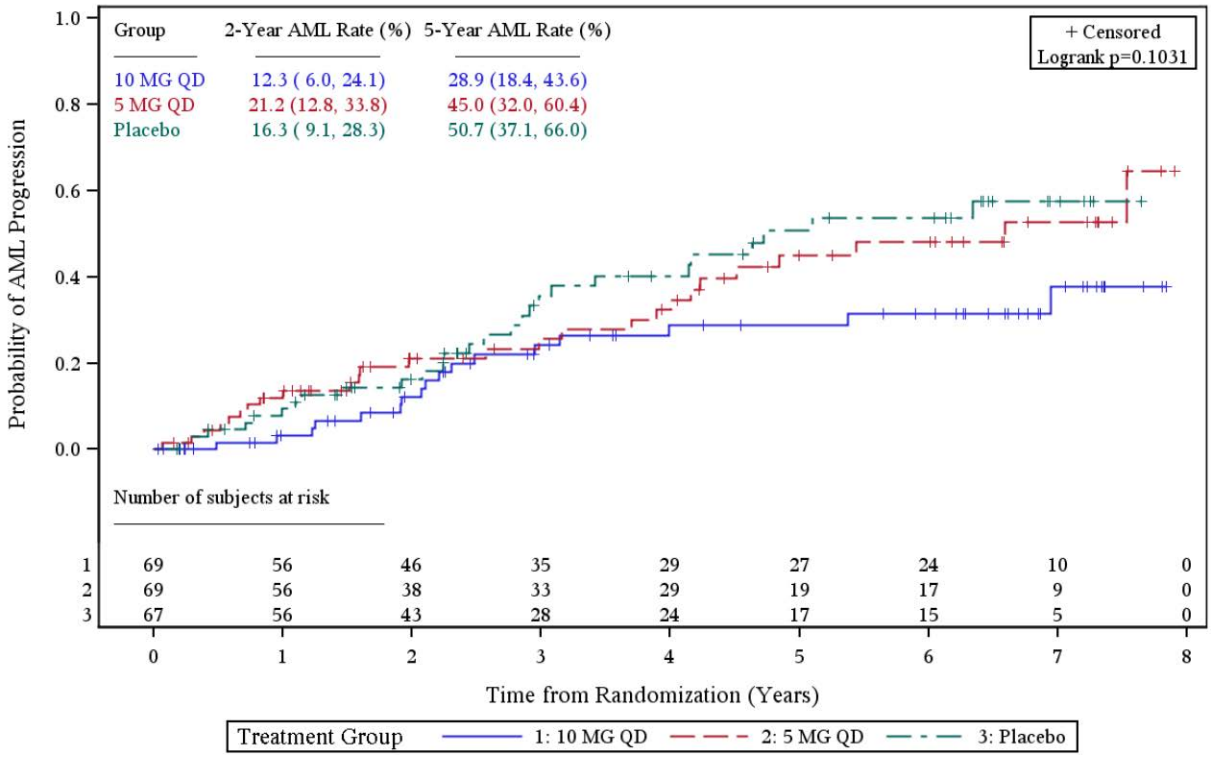
Progression to AML is part of the natural course of MDS and is a manifestation of disease progression. Thus, the possible impact of lenalidomide on the natural history of MDS and analyses of possible effects of lenalidomide on progression to AML are included here in the analysis of efficacy.

ITT Analyses

The median follow-up for time to progression to AML was 34.9 months (range = 0.4 to 95.4 months) for all randomized subjects, 30.9 months (range = 2.1 to 92.3 months) for the placebo group (including lenalidomide exposures for those subjects who switched from placebo to OL lenalidomide), 31.8 months (range = 0.8 to 95.4 months) for the 5 mg lenalidomide group, and 36.9 months (range = 0.4 to 94.6 months) for the 10 mg lenalidomide group ( ). Maximum duration of follow-up was almost 8 years (95.4 months).

Progression to AML was reported for 40.3% (27/67) of subjects randomized to placebo, 37.7% (26/69) of subjects randomized to 5 mg lenalidomide, and 24.6% (17/69) of subjects randomized to 10 mg lenalidomide ( ). Overall, the 10 mg lenalidomide group had the lowest overall rate of progression to AML ( ), although these differences were not statistically significant (Figure 1). The median time to progression was 57.0 months for the placebo group, 79.6 months for the 5 mg lenalidomide group, and not reached for the 10 mg lenalidomide group ( ). The 2-year rate for progression to AML was 16.3% in the placebo group, 21.2% in the 5 mg lenalidomide group, and 12.3% in the 10 mg lenalidomide group (p = 0.1031) (Figure 1). The 5-year rates were 50.7%, 45.0%, and 28.9%, respectively; again, the 10-mg dose was associated with the lowest cumulative rate of progression to AML.

Figure 1: Time to Progression to AML by Randomized Treatment Group (DB, OL, and Follow-up Phases)



AML = acute myeloid leukemia; DB = double blind; OL = open label; QD = once daily.
Note: The protocol-specified follow up for reporting of progression to AML for Study MDS-004 was completed on 21 Jun 2013, which was 3 years after the last subject completed/discontinued from the OL phase of this study per protocol.

As-treated Analyses

To examine the effect of lenalidomide exposure on progression to AML, time to progression of AML was analyzed considering the crossover of placebo subjects to lenalidomide. In the "as-treated" analyses, the median follow-up for progression to AML was 9.4 months (range = 2.1 to 55.1 months) for the placebo group (ie, 11 subjects who never switched from placebo to lenalidomide), 32.1 months (range = 1.4 to 88.6 months) for the subjects in the placebo group who subsequently crossed over to receive 5 mg lenalidomide (Pbo/5 mg), 31.8 months (range = 0.8 to 95.4 months) for the 5 mg lenalidomide group, and 36.9 months (range = 0.4 to 94.6 months) for the 10 mg lenalidomide group ( ). Maximum duration of follow-up was almost 8 years (95.4 months).

The proportion of subjects who had progression to AML was 24.6% for the 10 mg lenalidomide group, 37.7% for the 5 mg lenalidomide group, 41.1% for the Pbo/5 mg group, and 36.4% for the placebo group (never received lenalidomide) ( ). The median time to progression to AML was not reached for the 10 mg group, 79.6 months for the 5 mg group, 57.9 months for the Pbo/5 mg group, and 25.1 months for the placebo group ( ).

Cumulative incidence of progression to AML from the first dose of study drug is summarized in .

Overall Survival

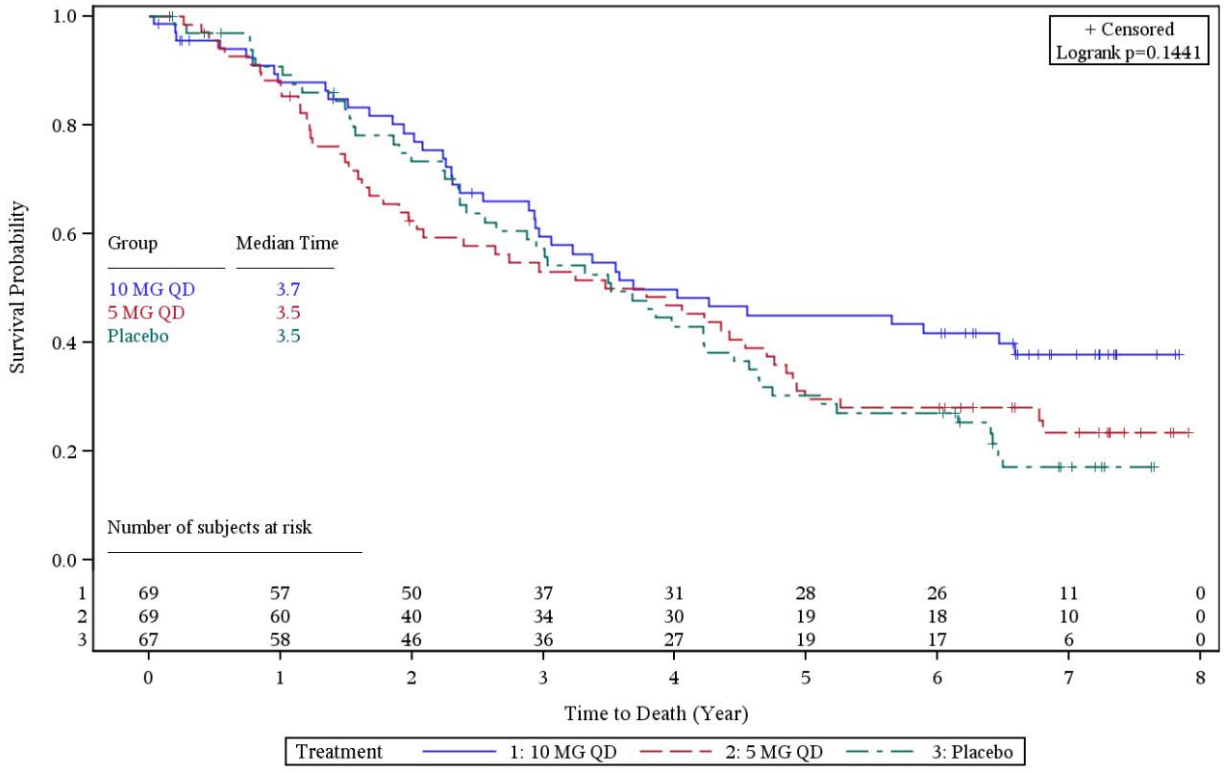
A subject listing of survival is provided in .

ITT Analyses

The median follow-up for OS was 39.2 months (range = 0.4 to 95.4 months) for all randomized subjects, 40.0 months (range = 2.1 to 92.3 months) for placebo, 35.8 months (range = 1.9 to 95.4 months) for the 5 mg lenalidomide group, and 40.7 months (range = 0.4 to 94.6 months) for the 10 mg lenalidomide group ( ). Maximum duration of follow-up was almost 8 years (95.4 months).

The percentage of subjects who died during the study was lower in the 10 mg lenalidomide group (56.5%) than in the 5 mg lenalidomide (71.0%) or placebo (76.1%) groups ( ), although these differences were not statistically significant (Figure 2). The median OS was 3.5 years in the placebo and 5 mg lenalidomide groups and 3.7 years in the 10 mg lenalidomide group (Figure 2). Thus, the risk of death over time was similar among the 3 treatment arms.

Figure 2: Overall Survival by Randomized Treatment Group (DB, OL, and Follow-up Phases)



DB = double blind; OL = open label; QD = once daily.

Note: The protocol-specified follow up for reporting of survival for Study MDS-004 was completed on 21 Jun 2013, which was 3 years after the last subject completed/discontinued from the OL phase of this study per protocol.

As-treated Analyses

Considering the crossover of placebo subjects to lenalidomide, the median follow-up for OS was 9.6 months (range = 2.1 to 55.1 months) for the placebo group (11 subjects who never received lenalidomide), 42.5 months (range =1.4 to 88.6 months) for the placebo group who subsequently crossed over to 5 mg (Pbo/5 mg), 35.8 months (range = 1.9 to 95.4 months) for the 5 mg lenalidomide group, and 40.7 months (range = 0.4 to 94.6 months) for the 10 mg lenalidomide group ( ). Maximum duration of follow-up was almost 8 years (95.4 months).

The proportion of subjects who died was lowest in the 10 mg lenalidomide group (56.5%), followed by the 5 mg lenalidomide group (71.0%), the Pbo/5 mg group (73.2%), and the placebo group (90.9%). The median time to death was 44.5 months for the 10 mg group, 41.9 months for the 5 mg group, 43.7 months for the Pbo/5 mg group, and 13.8 months for the placebo group.

SAFETY RESULTS:

Results below include survival, subsequent antineoplastic therapies, and SPM data from the DB, OL, and follow-up phases.

Treatment Duration

At the time of the data cutoff for the MDS-004 CSR (14 Jun 2010), all subjects had completed or discontinued from the DB or OL phases ( ); treatment duration reported in and is unchanged from the data reported in and . A brief overview is provided below. The subject listing for study drug dosing is provided in .

A total of 194 subjects received ≥ 1 dose of lenalidomide during the entire study. In the DB treatment phase, 69 subjects each received 5 mg or 10 mg lenalidomide, respectively ( ). In the OL phase, an additional 56 subjects, who had received placebo in the DB treatment phase, received 5 mg lenalidomide ( ).

Of note, in the DB treatment phase, subjects in the 10 mg lenalidomide group tended to continue treatment longer: 42.0% of subjects in the 10 mg lenalidomide group received treatment for ≥ 52 weeks (median = 50.3 weeks) compared with 21.7% of subjects in the 5 mg lenalidomide group (median = 18.0 weeks) ( ).

In the OL phase, the shortest median duration of treatment was in the 5 mg/10 mg lenalidomide group (15.7 weeks; range 2.3 to 136.0 weeks), the group that crossed over to receive a higher dose in the OL phase ( ). This short duration may reflect subjects who did not achieve transfusion independence or at least a minor erythroid response, and subsequently stopped at 16 weeks during the DB treatment phase ( ).

Considering duration of exposure to lenalidomide for the entire study (DB and OL treatment phases), the median duration of treatment was 72.9 weeks for the 10 mg lenalidomide group compared with 39.0 weeks for the 5 mg lenalidomide group ( ). Similarly, a greater proportion of subjects remained on treatment for ≥ 52 weeks in the 10 mg lenalidomide group (60.9%) compared with the 5 mg lenalidomide group (43.5%).

Subsequent Antineoplastic Therapy

A subject listing of subsequent antineoplastic therapy is provided in . A total of 114 subjects received subsequent antineoplastic therapy after discontinuation of the OL phase; 59 subjects received subsequent lenalidomide after discontinuation of the OL phase.

Deaths

Overall, 139 subjects (67.8%) died during the study (Table 1). Ten of the 139 deaths occurred within 30 days of the subject's last dose of study drug (4 in the placebo group [including 3 subjects who crossed over to receive lenalidomide 5 mg in the OL phase – Pbo/5 mg]) (Table 2).

Table 1: Overview of Deaths by Initial Randomized Treatment Group (DB, OL, and Follow-up Phases; Safety Population)

	Placebo[a] QD (N = 67) n (%)	Len 5 mg QD (N = 69) n (%)	Len 10 mg QD (N = 69) n (%)	Total (N = 205) n (%)
All Subjects Who Died During the Study	**51 (76.1)**	**49 (71.0)**	**39 (56.5)**	**139 (67.8)**
Subjects who died ≤ 30 days after the last dose of study drug	4 (6.0)	2 (2.9)	4 (5.8)	10 (4.9)
Subjects who died > 30 days after the last dose of study drug	47 (70.1)	47 (68.1)	35 (50.7)	129 (62.9)

DB = double blind; Len = lenalidomide; OL = open label; QD = once daily.
[a] Includes subjects who received placebo in the DB phase and who subsequently crossed over to receive lenalidomide in the OL phase.
Note: The protocol-specified follow up for reporting of survival for Study MDS-004 was completed on 21 Jun 2013, which was 3 years after the last subject completed/discontinued from the OL phase of this study per protocol.
Source:

Of the 10 subjects who died within 30 days after the last dose of study drug, 2 subjects each died due to adult respiratory distress syndrome and septic shock (Table 2). The causes of death for the other 6 subjects who died were reported in 1 subject each.

Table 2: Deaths That Occurred Within 30 days After the Last Dose of Study Drug (DB, OL, and Follow-up Phases; Safety Population)

Subject Number	Treatment Regimen	Age (y)/ Sex	Study Day of Death (Days After Last Dose)	Cause of Death
Placebo				
	Placebo		104 (14)	Adult respiratory distress syndrome
	Placebo (DB)/Len 5 mg (OL)		518 (2)	Acute respiratory distress syndrome
	Placebo (DB)/Len 5 mg (OL)		695 (23)	Myocardial infarction
	Placebo (DB)/Len 5 mg (OL)		882 (28)	Multiple organ failure, bronchopneumonia
Len 5 mg				
	Len 5 mg (DB)/Len 10 mg (OL)		145 (4)	Thrombosis – pulmonary embolism
	Len 5 mg		40 (2)	Aspiration pneumonia
Len 10 mg				
	Len 10 mg		72 (18)	Cerebral hemorrhage due to MDS progression
	Len 10 mg (DB)/Len 5 mg (OL)		824 (29)	Septic shock
	Len 10 mg		12 (2)	Septic shock (respiratory origin)
	Len 10 mg		198 (22)	Acute myeloid leukemia

DB = double blind; F = female; Len = lenalidomide; M = male; MDS = myelodysplastic syndromes; OL = open label; y = year.
Note: The protocol-specified follow up for reporting of survival for Study MDS-004 was completed on 21 Jun 2013, which was 3 years after the last subject completed/discontinued from the OL phase of this study per protocol.
Sources: and

A subject listing of deaths is provided in . Subject narratives for deaths that occurred during the survival follow-up phase (ie, up to 3 years after the last subject had completed or discontinued from the OL phase), as well as narratives of deaths included in the CSR that have been revised per data updates since 14 Jun 2010 (data cutoff for MDS-004 CSR), are provided in

Second Primary Malignancies

The follow-up for reporting of SPMs for this study was completed on 21 Jun 2013, 3 years after the last subject completed/discontinued from the OL phase of this study per protocol, with a final database lock date of 14 Aug 2013. The occurrence of AML in subjects with MDS is considered to be disease progression of MDS and, therefore, is not considered to be an SPM. Subjects with MDS who progressed to AML are summarized separately in this report.

Of the 67 subjects in the placebo arm, 56 crossed over to lenalidomide treatment. Of the 11 subjects in the placebo arm who did not crossover to lenalidomide treatment, none developed an SPM. Therefore, the frequencies of subjects with SPMs for this study are summarized as lenalidomide-treated subjects, which includes the 138 subjects in both lenalidomide arms plus the 56 placebo subjects who crossed over to lenalidomide treatment (N = 194) ( ).

Two subjects were excluded from the analysis of SPMs as follows ( ):

- Subject (5 mg lenalidomide arm) with chronic lymphocytic leukemia not otherwise specified (NOS) had evidence of malignancy prior to the start of study medication.
- Subject (placebo arm) with lip neoplasm NOS had no histologic confirmation of malignancy.

The frequencies of lenalidomide-treated subjects who experienced at least 1 SPM and incidence rates of SPMs in Study MDS-004 as of the 21 Jun 2013 completion date are shown in Table 3. Three subjects developed 2 solid tumor SPMs each after lenalidomide treatment and are counted only once in the solid tumor category (Subject [brain neoplasm and renal cancer], Subject [oropharyngeal cancer stage III and rectal cancer stage II], and Subject [colorectal cancer and breast cancer invasive]) ( ).

A total of 12 (6.2%) lenalidomide-treated subjects experienced at least 1 SPM as of the 21 Jun 2013 completion date for this study (Table 3). No hematologic SPMs were reported during this study. Of the 12 subjects who had an SPM, 10 (5.2%) subjects developed solid tumor SPMs including: bladder cancer, brain neoplasm, breast cancer (2 subjects), breast cancer stage I, colon cancer, colorectal cancer, endometrial cancer, hepatic neoplasm malignant, lung cancer metastatic, oropharyngeal cancer stage III, rectal cancer stage II, and renal cancer ( ).
Two (1%) subjects were diagnosed with at least 1 non-melanoma skin cancer (Table 3).

The incidence rate of developing an invasive SPM was 1.42 per 100 person-years as of the 21 Jun 2013 completion date for this study (Table 3).

The median time to diagnosis of the 10 solid tumors was 14.6 months (range: 0.7 to 66.9 months) ( ). The median time to diagnosis of the 2 non-melanoma skin cancers was 6.9 months (range: 0.3 to 13.4 months).

A listing of subjects who experienced an invasive SPM (hematologic or solid tumor SPM) in this study is provided in , and a narrative for each subject with an SPM can be found in .

Table 3: Summary of Frequency and Incidence Rates for Second Primary Malignancies (DB, OL, and Follow-up Phases; Safety Population)

SPM Category	Lenalidomide-treated (N = 194)[a] n (%)	Incidence Rate (per 100 PY)[b]	95% CI
Hematologic malignancies	0 (0.0)	--	--
Hodgkin's/B-ALL/other B-cell	0 (0.0)	--	--
Other	0 (0.0)	--	--
Solid tumors	10 (5.2)	1.42	(0.76 – 2.64)
Invasive SPMs	**10 (5.2)**	**1.42**	**(0.76 – 2.64)**
Non-invasive SPMs (Non-melanoma skin cancer)	2 (1.0)	0.28	(0.07 – 1.13)
TOTAL SPMs	**12 (6.2)**	**1.74**	**(0.99 – 3.06)**

B-ALL = B-cell acute lymphocytic leukemia; CI = confidence interval; DB = double blind; OL = open label; PY = person-years; SPM = second primary malignancy.

[a] In Study MDS-004, there were 56 subjects in the placebo group who crossed over to receive lenalidomide per protocol study design. Only the lenalidomide-treated subjects, which includes the 138 subjects in both lenalidomide arms plus the 56 placebo subjects who crossed over to lenalidomide treatment (N = 194), are summarized in this table for Study MDS-004. For those placebo subjects who crossed over to lenalidomide treatment, the start date of exposure was calculated from the date of the first open-label lenalidomide dose.

[b] Person-years are defined as the time from the date of first dose of study drug to the onset date of the first SPM for subjects with an SPM and to the date of last follow-up for subjects without an SPM.

Notes: 1) The follow up for reporting of SPMs for Study MDS-004 was completed on 21 Jun 2013, which was 3 years after the last subject completed/discontinued from the open-label extension phase of this study per protocol.
2) No hematologic malignancies were reported during this study.
3) "—" denotes that incidence rates were not calculated for these SPM categories.

Sources: and

CONCLUSIONS:

Based on a median follow-up of ≥ 3 years (maximum duration of follow-up of almost 8 years), there was no evidence in the ITT or as-treated analyses to suggest treatment with lenalidomide was associated with an increase in the rate of progression to AML or negatively affected OS (consistent with the conclusions reported in the MDS-004 CSR). Rates of progression to AML and deaths were lowest in the 10 mg compared with the other treatment groups. Overall, the incidence rate of developing an invasive SPM was low (1.42 per 100 person-years).

Date of the report: 08 Jul 2014