26 January 2017
EMA/CHMP/108277/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Revlimid

International non-proprietary name: lenalidomide

Procedure No. EMEA/H/C/000717/II/0089/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Explanation
A	Melphalan, prednisone, and lenalidomide; Arm A (A1 + A2) in the GIMEMA study
A1	Melphalan, prednisone, and lenalidomide intensified induction/no maintenance; Arm A1 in the GIMEMA study;
A2	Melphalan, prednisone, and lenalidomide intensified induction/lenalidomide maintenance; Arm A2 in the GIMEMA study
AdEERS	Adverse Event Expedited Reporting System
ADR	Adverse drug reaction
AE	Adverse event
AML	Acute myeloid leukemia
AMT	Antimyeloma therapy
ANC	Absolute neutrophil count
ASCT	Autologous stem-cell transplant
ATE	Arterial thromboembolic event
B	High-dose melphalan (MEL200) with ASCT; Arm B (B1 + B2) in the GIMEMA study
B1	Melphalan 200 mg/m² followed by ASCT/no maintenance; Arm B1 in the GIMEMA study, also referred to as “ASCT/no maintenance”
B2	Melphalan 200 mg/m² followed by ASCT/lenalidomide maintenance; Arm B2 in the GIMEMA study, also referred to as “ASCT/lenalidomide”
β2M	β2 microglobulin
B-ALL	B-cell acute lymphocytic leukemia
CALGB	Cancer and Leukemia Group B
CC-5013 or CDC-501	Lenalidomide
CCDS	Company Core Data Sheet
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CR	Complete response
CrCl	Creatinine clearance
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCEP	Dexamethasone, cyclophosphamide, etoposide, and cisplatin
del 13	Deletion in chromosome 13
del 17p	Deletion in chromosome 17p
DMC	Data Monitoring Committee
DSMB	Data and Safety Monitoring Board

Abbreviation	Explanation
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
FO.NE.SA Onlus	Fondazione Neoplasie Sangue Onlus
GCP	Good Clinical Practice
GIMEMA	Gruppo Italiano Malattie EMatologiche dell'Adulto
HDM	High-dose melphalan
HR	Hazard ratio
ICH	International Conference for Harmonisation
IFM	Intergroupe Francophone du Myélome
Ig	Immunoglobulin
IMWG	International Myeloma Working Group
IR	Incidence rate
ISS	International Staging System
ITT	Intent to treat
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
M-protein	Monoclonal protein
MAH	Marketing Authorisation Holder
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MEL200	Melphalan 200 mg/m^2
MM	Multiple myeloma
MPp+p	Melphalan, prednisone, and placebo for induction followed by placebo for maintenance (Arm C in the Study MM-015)
MPR	Melphalan, prednisone, and lenalidomide (Arm A in the GIMEMA study)
MPR+R	Melphalan, prednisone, and lenalidomide for induction followed by lenalidomide for maintenance; (Arm A in the Study MM-015)
MPT	Melphalan, prednisone, and thalidomide; (Arm C in the Study MM-020)
NCCN	National Comprehensive Cancer Network
NDMM	Newly diagnosed multiple myeloma
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PFS2	Progression-free survival after next-line therapy
PR	Partial response
PT	Preferred term
QD	Once daily

Abbreviation	Explanation
R10	Starting maintenance dose of lenalidomide 10 mg once daily on Days 1 to 28 of repeated 28-day cycles
Rd	Lenalidomide and low-dose (weekly) dexamethasone
RD	Lenalidomide and standard-dose (high-dose) dexamethasone
RMP	Risk Management Plan
SAE	Serious adverse event
SCS	Summary of Clinical Safety
SD	Stable disease
SmPC	Summary of Product Characteristics
SOC	System organ class
SPM	Second primary malignancy
t(4;14)	Translocation involving chromosomes 4 and 14
t(14;16)	Translocation involving chromosomes 14 and 16
TE	Transplant eligible
TEAE	Treatment-emergent adverse event
TNE	Transplant noneligible
TTP	Time to treatment progression
ULN	Upper limit of normal
US	United States
VAD	Vincristine, doxorubicin, and dexamethasone
VD	Bortezomib and dexamethasone
VGPR	Very good partial response

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Celgene Europe Limited submitted to the European Medicines Agency on 27 May 2016 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
B.II.e.5.a.2	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	Type IB	I, IIIA, IIIB and A
B.II.e.5.a.2	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	Type IB	I, IIIA, IIIB and A
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to add treatment of adult patients with newly diagnosed multiple myeloma (NDMM) who have undergone autologous stem cell transplantation (ASCT). Consequently SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 have been updated with the efficacy and safety data. The Package Leaflet and the RMP have been updated accordingly. Furthermore, the MAH introduced 7-day pack sizes for the 10 mg and 15 mg strengths with subsequent changes to the Product Information.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Labelling, Package Leaflet and Annex A and to the Risk Management Plan (RMP).

Revlimid, was designated as an orphan medicinal product EU/3/03/177 on 12/12/2003. Revlimid was designated as an orphan medicinal product in the following indication: treatment of multiple myeloma.

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011on the granting of a class waiver.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised

orphan medicinal products.

Protocol assistance

The applicant did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Pierre Demolis Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	27 May 2016
Start of procedure:	18 June 2016
CHMP Rapporteur Assessment Report	12 August 2016
PRAC Rapporteur Assessment Report	19 August 2016
PRAC Outcome	2 September 2016
CHMP members comments	5 September 2016
Updated CHMP Rapporteur(s) (Joint) Assessment Report	9 September 2016
Request for supplementary information (RSI)	15 September 2016
CHMP Rapporteur Assessment Report	5 January 2017
PRAC Rapporteur Assessment Report	5 January 2017
PRAC members comments	6 January 2017
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	12 January 2017
Similarity Assessment Report	13 January 2017
CHMP members comments	16 January 2017
Updated CHMP Rapporteur Assessment Report	24 January 2017
Opinion	26 January 2017

2. Scientific discussion

2.1. Introduction

Multiple myeloma (MM) is a B-cell neoplasm that stems from the malignant transformation of plasma cells in the bone marrow and is characterized by the accumulation of clonal plasma cells in the bone marrow (Boyd, 2012; Palumbo, 2011). Multiple myeloma accounts for approximately 10% to 18% of haematologic cancers (Mateos, 2014; Siegel, 2016). In Europe, 38,900 new cases of MM and 24,300 deaths due to MM were estimated in 2012 (Ferlay, 2013). Multiple myeloma is a disease of the elderly

(San Miguel, 2013a), with an overall median age at manifestation of approximately 70 years (Ludwig, 2014).

Currently no drug has been approved in the post-ASCT setting (TE NDMM) by the European Medicines Agency (EMA) or by the US Food and Drug Administration (FDA).

The most recent NCCN guidelines, define lenalidomide and thalidomide as Category 1 therapies for maintenance therapy post-ASCT (NCCN, 2016).

The lenalidomide mechanism of action includes anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties. Specifically, lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including multiple myeloma [MM] plasma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK T cells, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. In MDS Del (5q), lenalidomide was shown to selectively inhibit the abnormal clone by increasing the apoptosis of Del (5q) cells (SmPC section 5.1).

The current indication for Revlimid is as follows:

Revlimid is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant (see section 4.2).

Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

Revlimid is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

Revlimid is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (see sections 4.4 and 5.1).

The marketing authorisation holder (MAH) applied for the following indication: Revlimid is indicated for the treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.

The recommended indication for approval is: Revlimid as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.

Lenalidomide maintenance should be initiated after adequate haematologic recovery following ASCT. Lenalidomide must not be started if the Absolute Neutrophil Count (ANC) is $< 1.0 \times 10^9$/L, and/or platelet counts are $< 75 \times 10^9$/L.

The recommended starting dose is lenalidomide 10 mg orally once daily continuously (on days 1-28 of repeated 28-day cycles) given until disease progression or intolerance. After 3 cycles of lenalidomide maintenance, the dose can be increased to 15 mg orally once daily if tolerated. Dosing is continued or modified based upon clinical and laboratory findings (SmPC section 4.2).

In this application, the MAH submitted 2 type IB variations to add 7-day pack sizes for the 10 mg and 15 mg strengths in order to support the starting dose and dose modifications. These changes are acceptable to the CHMP.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

No ERA was submitted in this application (see Discussion and Conclusion on the non-clinical aspects).

2.2.2. Discussion and Conclusion on the non-clinical aspects

An ERA was submitted for a previous extension of indication, covering MDS population and the overall Multiple Myeloma (MM) population regardless of the stage of the disease. Revlimid was considered to pose negligible risk to the environment and no updated ERA was required by CHMP for this current extension of indication. The new/extended indication does not lead to a significant increase in environmental exposure further to the use of Revlimid.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Identifier	Primary Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Duration of Treatment	Study Status; Type of Report

CALGB 100104	To determine the efficacy of len in prolonging time to disease progression in patients with MM after ASCT; in particular, to investigate if len maintenance would prolong time to progression or death (ie, PFS) following single ASCT	Phase 3, multicenter, randomized, double-blind, placebo-controlled study Subjects were enrolled before ASCT (postinduction) and randomized after ASCT (1:1) to 2 arms for maintenance therapy: Len vs Placebo Randomization stratified by: 1.β2M at registration 2.Prior therapy with thalidomide 3.Prior therapy with len	**Maintenance:** 28-day cycles of len 10 mg PO or placebo, QD on Days 1-28/cycle Dose of len was to be increased to 15 mg QD after 3 months, if no dose-limiting toxicity was experienced.	**Registered:** 568 **ITT:** 460 (R=231, pbo=229)	Treatment until PD, or subject withdrawal for another reason	**Study unblinded:** 17 Dec 2009 **Study ongoing:** for subjects without PD. Subjects who have discontinued study treatment continue to be followed for progression, second-line therapy, survival, and SPMs. Full report issued 26Jan2016 (data cutoff: 1 Mar 2015)
IFM 2005-02	To evaluate the efficacy of len in extending posttransplantation PFS.	Phase 3, multicenter, randomized, double-blind, placebo-controlled study Subjects included after ASCT and randomized (1:1) to 2 arms: 1.Len consolidation/placebo maintenance 2.Len consolidation/ len maintenance Randomization stratified by: 1.β2M at diagnosis 2.Presence of del 13 at diagnosis 3.Response to last ASCT Recommended interval from ASCT to start of therapy: ≤6 months	**Consolidation:** 2 x 28-day cycles of len 25 mg PO on Days 1-21/cycle; consolidation was introduced with Amendment 2 (after randomization of 32 subjects). **Maintenance:** 28-day cycles of len 10 mg PO or placebo, QD on Days 1-28/cycle Dose of len was to be increased to 15 mg QD after 3 months, if no dose-limiting toxicity	**ITT**: 614 (R=307, pbo=307)	**Consolidation:** 2x 28-day cycles **Maintenance:** Treatment until PD, death, introduction of new anticancer treatment, obligatory treatment discontinuation in January 2011, (Amendment 9), or subject withdrawal for another reason	**Study unblinded:** 07 Jul 2010 **Len treatment discontinued:** January 2011 **Study ongoing:** All subjects continue to be followed for progression, second-line therapy, survival, and SPMs. Full report issued 29Apr2016 (data cutoff 01Mar2015)
GIMEMA	To compare the efficacy of the combination of len, prednisone, and low-dose melphalan (MPR)	Phase 3, multicenter, randomized, openlabel, 2x2 factorial, controlled study All subjects received Rd induction, followed by their assigned	**Induction:** 4x28-day cycles of Rd: Len 25 mg PO D1-21/cycle. Dex 40 mg PO D1, 8, 15, and 22 **ASCT/Intensified Induction:**	**ITT Maintenance post-ASCT:** 135 (67 R maintenance, 68 no maintenance)	**Induction:** Rd: 4x 28-day cycles **ASCT or Intensified**	**Study ongoing:** Study treatment ongoing for subjects without PD. Subjects who have discontinued study treatment continue to be

	versus highdose melphalan (MEL200) and ASCT in newly diagnosed, symptomatic MM subjects who were ≤65 years	ASCT or intensified induction and maintenance regimen. 2x2 randomization was performed at enrollment. Subjects were randomly assigned in a 1:1:1:1 ratio to 1 of 4 gps: A1: MPR/no maintenance A2: MPR/len; B1: MEL200 (ASCT)/ no maintenance B2: MEL200 (ASCT)/len Random code concealed until subject reached next phase of study. Randomization stratified by: 1. ISS stage (at diagnosis) 2. Age Recommended interval from ASCT to start of maintenance: 2 to 3 months	MPR: 6x28-day cycles: Melphalan 0.18 mg/kg PO D1- 4/cycle Predn 2 mg/kg PO D1-4/cycle Len 10 mg PO D1- 21/cycle, or MEL200: Melphalan 200 mg/m² IV followed by ASCT (to be repeated after 4 months if subject did not achieve a near VGPR response after first ASCT) **Maintenance:** No therapy or 28-day cycles of len 10 mg PO D1-21/cycle		**Induction[c]:** MPR: 6x 28day cycles MEL200 : ~ 4 months or repeated **Maintenance:** Treatment until PD or development of unacceptable adverse effects	followed for progression, second-line therapy, survival, and SPMs. No change in no-therapy arm after final analysis. Demographic, OS and SPM data included in the efficacy meta-analysis and SPM document (data cutoff 01Mar2015)

2.4. Clinical efficacy

2.4.1. Dose response study

No dose-response studies were submitted. The recommended starting dose for adult patients with NDMM who have undergone ASCT is lenalidomide 10 mg orally once daily continuously (on Days 1-28 of repeated 28-day cycles) given until disease progression or intolerance. After 3 cycles of lenalidomide maintenance, the dose can be increased to 15 mg orally.

2.4.2. Main studies

Study CALGB 100104

CALGB 100104 study is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, 2-arm parallel group study of maintenance therapy with lenalidomide or placebo following ASCT for NDMM.

Methods

Study participants

Main Inclusion Criteria:

- Active MM requiring treatment (Durie-Salmon stage ≥1) and stable disease or responsiveness to at least 2 months of any induction therapy;
- Peripheral blood stem cell collection of ≥ 2.10^6 CD34+ cells/kg (body weight) and preferably 5.10^6 cells/kg (body weight);
- At least 18, and no more than 70 years of age;
- ECOG Performance Status of 0 to 1;
- Diffusion capacity of the lung for carbon monoxide (DLCO) greater than 50% predicted with no symptomatic pulmonary disease;
- Left ventricular ejection fraction of at least 40% by multigated acquisition scan (MUGA) or echocardiogram.

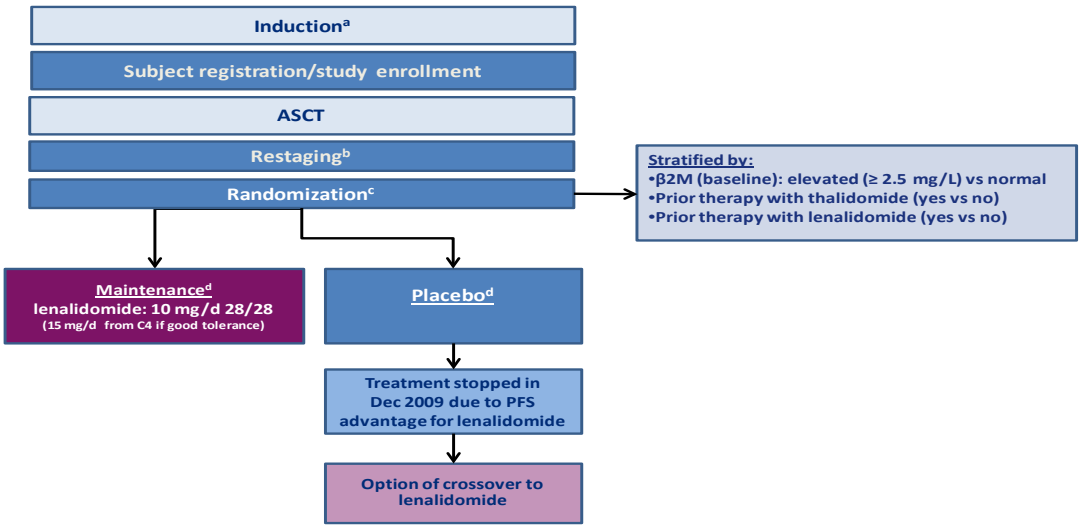
Main Exclusion Criteria:

- Smoldering myeloma, unless the disease had progressed to ≥ stage 1;
- Prior therapy, including with lenalidomide and thalidomide, for a duration of more than 12 months;
- More than 12 months from initiation of induction therapy;
- Prior progression after initial therapy. In addition, no more than two regimens were allowed excluding dexamethasone alone.
- Prior peripheral blood, bone marrow, or solid organ transplant;
- Uncontrolled diabetes mellitus;
- Any active serious infection;
- Human immunodeficiency virus (HIV), hepatitis B surface antigen (HBSAg), or hepatitis C (Hep C) positive;
- Pregnant or nursing;
- Had any of the following laboratory values:
    - ANC < 1000/µL
    - PLT < 100,000/µL
    - Creatinine clearance (CrCl) < 40 mL/min
    - Serum creatinine (SCr) > 2 mg/dL
    - Total bilirubin > 2 mg/dL
- Aspartate aminotransferase (AST) or Alkaline Phosphatase (Alk Phos) > 3x ULN
- Urine-human chorionic gonadotropin (U-HCG) or serum human chorionic gonadotropin (HCG) positive in patients of childbearing potential

Treatments

Patients were randomized to receive continuously once a day lenalidomide (experimental arm) or placebo (control arm) as maintenance therapy between Day 100 and Day 110 post-transplantation. The starting dose was 10 mg/day, escalated to 15 mg/day after 3 months if the subjects was able to tolerate the treatment, and continued until disease progression. Maintenance treatment was stopped and/or dose reduced as needed to manage toxicity.

Upon unblinding, patients who were receiving placebo were allowed to cross over to lenalidomide before progressive disease (PD), and patients who were receiving lenalidomide could continue treatment per the original protocol.



[a] Induction therapy was chosen at the investigator's discretion.
[b] Subjects underwent disease and response evaluation between Day +90 and Day +100 after transplant and before randomization.
[c] Before randomization, subjects must have had adequate organ function (ANC ≥ 1000/μL, PLT ≥ 75,000/μL, serum creatinine ≤ 2 mg/dL, bilirubin ≤ 2 mg/dL, AST ≤ 3 □ ULN, and alkaline phosphatase ≤ 3 x ULN) and must have had no evidence of PD. Randomization to study drug occurred between Day +90 to Day +100 after transplant. Initiation of maintenance therapy began between Day +100 and Day +110 after transplant.
[d] Study drug (lenalidomide or placebo) was started at a dose of 10 mg PO daily (2 capsules per day). After 3 months, the dose was to be increased to 15 mg PO daily (3 capsules per day), provided ANC ≥ 1000/μL, PLT ≥ 75,000/μL, and all nonhematologic toxicity was ≤ Grade 1. Doses could be reduced to 5 mg PO daily or 5 mg PO daily every 21 of 28 days if not tolerated at higher doses. Dosing could continue until PD or treatment intolerance.

Objectives

The primary objective was to determine the efficacy of lenalidomide in prolonging time to disease progression in patients with multiple myeloma after ASCT; in particular, to investigate if maintenance lenalidomide would prolong time to progression or death (ie, PFS) following single ASCT.Secondary objectives were (i) to determine if lenalidomide increases the complete response (CR) rate in patients with MM following ASCT, (ii) to compare overall survival (OS) in patients with MM who underwent ASCT and then were randomized to either lenalidomide or placebo; and (iii) to determine the feasibility of long-term administration of lenalidomide to MM patients who underwent ASCT.

Outcomes/endpoints

The primary endpoint was PFS. This endpoint was referred to as time to progression (TTP) in the protocol; however, as defined in the protocol, the analysis of TTP was equivalent to a standard PFS analysis, ie, defined as PD or death due to any cause.

The secondary endpoints were overall survival, rates for the various types of responses at prerandomization (3 months post-ASCT) and 12 months post-ASCT, and the improvement in response (e.g., PR to CR) over the aforementioned time points.

Exploratory efficacy endpoints include PFS2, type of second-line therapies, and second progression-free survival (second-line PFS).

Sample size

The plan was to randomize N = 462 subjects over a period of 33 months (targeted number of events= 309). It was anticipated that this would require, to account for a drop-out rate of 15%, about N = 544 subjects registered over this period. Under an equal allocation randomization scheme (i.e., 231 subjects randomized to each arm) and a planned follow-up period of 30 months at the α = 0.05 level of significance, this design would have had a power of at least 0.9 for the one-sided log-rank test. The total study period was expected to be 63 months.

The study was opened on 15 December 2004. Accrual to the study did not begin until April 2005. The protocol amendment (version 7, 15 Jun 2008) continued accrual to the study for an additional 30 months, starting April 2007. It was assumed that the accrual rate would remain constant at 16 per month for another 21 months. Given that the study had been open for 28 months (December 2004 through March 2007), and that the plan was to accrue for another 30 months (starting April 2007) and to follow the last subject for 30 months, the total study period would be 28+30+30 = 88 months (compared to 63 months in the original design). A total of 117 subjects were accrued through March 2007. An additional 421 subjects would be accrued, for a total of 538 subjects (compared to 544 in the original design). The revised total study period was 88 months, and the revised accrual goal was 538.

Randomisation

Patients were randomised 1:1 within 90-100 days after ASCT to receive either lenalidomide or placebo maintenance. Patients were stratified by β2 microglobulin (elevated [≥ 2.5 mg/L] versus normal), prior therapy with thalidomide (yes versus no), and prior therapy with lenalidomide (yes versus no).

Blinding (masking)

This was a double-blind trial.

Statistical methods

The ITT post-ASCT population was defined as all subjects who were randomized to receive lenalidomide maintenance (lenalidomide) versus placebo/no maintenance treatment (placebo). This population is used for all efficacy analyses.

The safety population was used for the analysis of treatment duration and included all subjects who received at least 1 dose of study drug. This population is used for all safety analyses.

Statistical Methodology

Table 1 : Summary of Key Primary and Secondary Efficacy Analyses

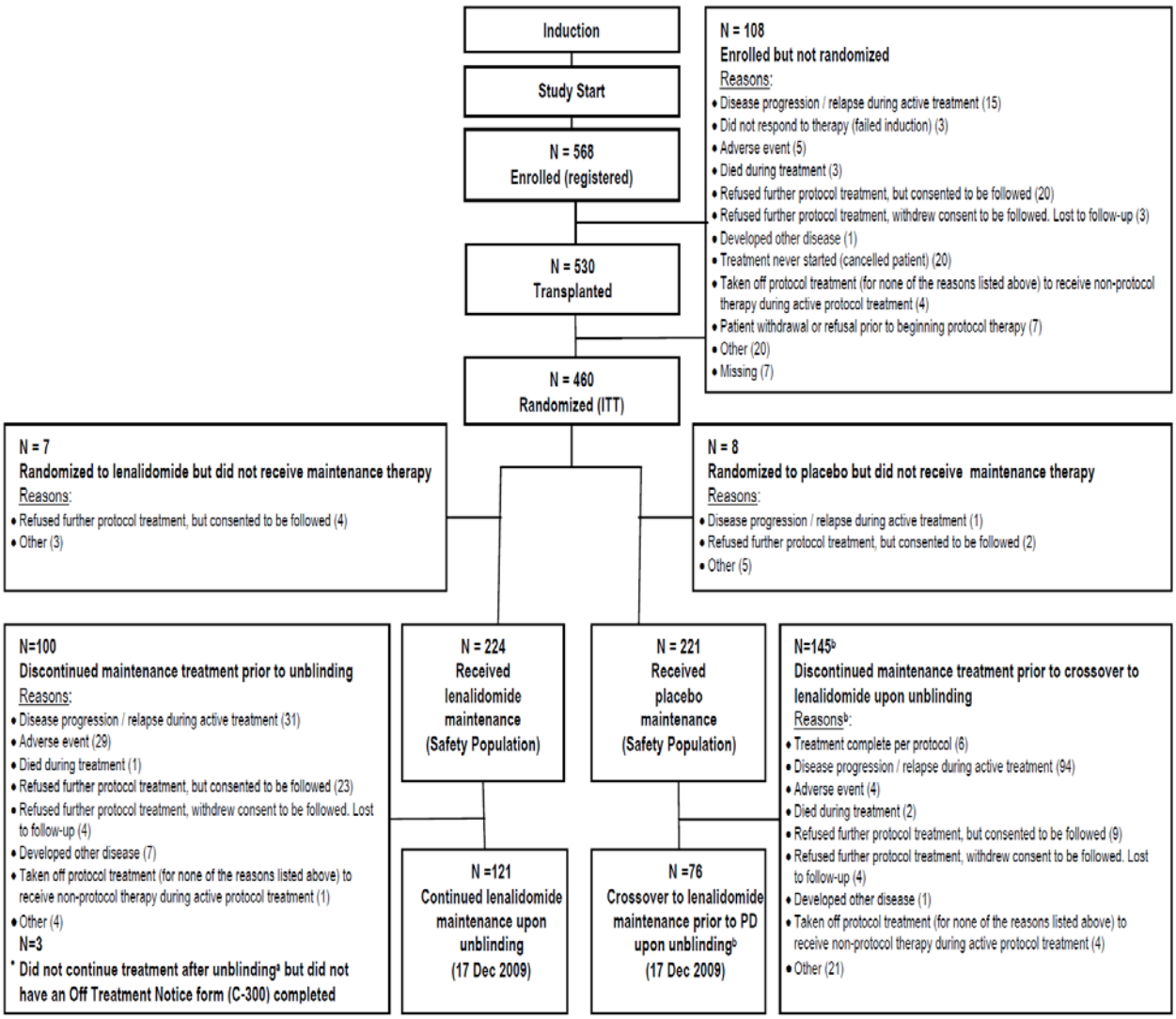
Type of Analysis	Endpoint	Analysis Set	Statistical Method
Primary Analysis	PFS	ITT	• Stratified log-rank test (stratified by β2-microglobulin level, prior therapy with thalidomide or lenalidomide), • Censoring rules based on EMA or FDA guidance • K-M method (median and 95% CIs) • HR and two-sided 95% CIs from the Cox model
Secondary analysis Secondary analyses	OS	ITT	• Unstratified log-rank test • K-M method (median and 95% CIs) • HR and two-sided 95% CIs from the Cox model
	Response rate: response at post-ASCT (3 months) and 12 months after ASCT	ITT	
Exploratory Analyses	PFS2	ITT	• Unstratified log-rank test • K-M method (median and 95% CIs) • HR and two-sided 95% CIs from the Cox model
	Second line PFS	ITT	
	Subsequent Anti-myeloma Therapies	ITT	

The first planned interim analysis was reviewed by the data and safety monitoring board (DSMB) in June 2009. After reviewing interim analysis results, the DSMB requested an updated analysis. The updated analysis was reviewed by the DSMB and included an estimated 28% of the expected number of events (progression or death) at a data cut-off date of 09 September 2009. The DSMB found that the study showed a significantly longer PFS following ASCT for those subjects receiving lenalidomide than those receiving placebo. This led to the release of the results on 17 December 2009. Treatment assignments were unblinded on 17 December 2009 and the randomization was stopped. Those subjects who were unblinded and determined to be on lenalidomide, continued on maintenance therapy with lenalidomide until progression as planned. For subjects who were receiving placebo at the time of unblinding, it was recommended by the DSMB that the placebo therapy be stopped and the subjects be given the opportunity to initiate lenalidomide therapy.

A PFS analysis from randomization was performed based on the EMA censoring rules, with the additional censoring of the 76 subjects in the placebo arm at the time of crossover. Censoring at the time of lenalidomide crossover was intended to remove any possible effect of lenalidomide after crossover. Due to the additional censoring, subjects with an original PFS event became censored or censoring dates were moved to an earlier date for these 76 subjects.

Results

Participant flow



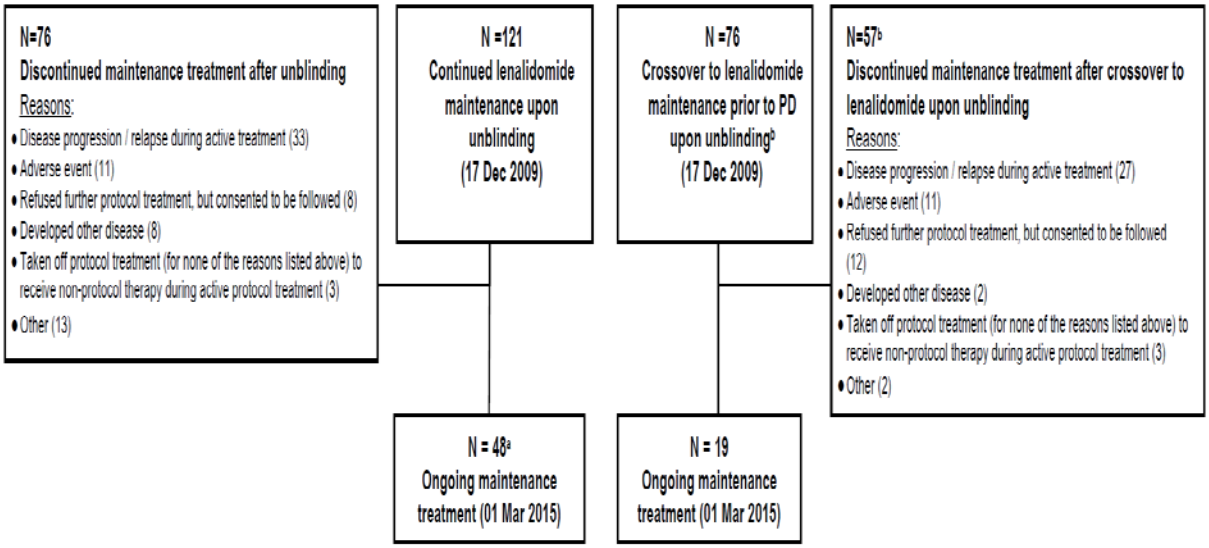
ITT = intent to treat; PD = progressive disease.

[a] According to the Continuation of Therapy (Unblinding) Form (Form C-1970; Appendix 16.1.2).

[b] Two subjects in the placebo arm started receiving lenalidomide upon unblinding despite PD; these 2 subjects are tabulated among the subjects who discontinued prior to crossover.

Data cutoff date = 01 Mar 2015.

Figure1: Disposition of subjects – Up to unblinding (17 Dec 2009) (All Registered Subjects)



PD = progressive disease.

[a] Three subjects in the lenalidomide arm who did not continue treatment after unblinding (according to the Continuation of Therapy [Unblinding] Form [Form C-1970; Appendix 16.1.2]) but did not have an Off Treatment Notice form (C-300) completed were included as subjects ongoing in maintenance treatment as of the 01 Mar 2015 data cutoff date, because they were not formally discontinued from the study.

[b] Two subjects in the placebo arm started receiving lenalidomide upon unblinding despite PD; these 2 subjects are not included.

Data cutoff date = 01 Mar 2015.

Figure 2: Disposition of subjects – After unblinding (17 Dec 2009) (Subjects who crossed over prior to PD or continued lenalidomide)

Recruitment

The first patient was randomized on the 19th August 2005. The study was unblinding on 17 December 2009 and the last patient was randomized on the 27th November 2009.

Conduct of the study

Nineteen protocol amendments or revisions were made throughout the period covered by this study report. Significant protocol changes to the clinical study report are outlined below:

- Amendment 3, dated 15 May 2006, reduced the time requirement for stable or responsive disease in the eligibility criteria from 4 months to 2 months. The prior treatment criterion of at least 4 weeks since prior chemotherapy, radiation therapy, or surgery to be eligible for the study was deleted. Cyclophosphamide dosing for the ASCT procedure was modified.
- Amendment 5, dated 15 May 2007, allowed the mobilization of autologous stem cells to be performed according to institutional guidelines and allowed for additional dosing options for melphalan for the ASCT procedure. Cyclophosphamide was removed from the treatment plan, allowing for institutions to follow their own local procedures for stem cell mobilization.
- Amendment 7, dated 15 June 2008, added a new eligibility criterion specifying a required number of stem cells to be collected. The schedule for stem cell collection and transplant was revised. The statistical section was revised to address accrual and interim analyses.
- Amendment 8, dated 15 August 2009, revised the eligibility criteria so that no more than 2 prior therapy regimens (not including dexamethasone alone) were allowed, and patients who underwent peripheral blood stem cell collection before or after study registration were eligible. Instructions for dosing by corrected body weight were changed so that only melphalan therapy

(rather than all transplant therapy) and growth factor drug doses were to be determined using a corrected body weight formula. Subjects with relapsed disease (recurrence of disease after attaining a CR) should continue on treatment if they do not fulfill criteria for PD.

- Amendment 10, dated 15 February 2010, noted the recent unblinding of treatment assignments and recommendations for continuation of therapy. Continuation of Therapy Form (Unblinding) was introduced to capture the subjects who continued on or crossed over to lenalidomide maintenance therapy.
- Amendment 12, dated 13 May 2011, required collection of data on SPMs. Cancer Screening Form was introduced for this purpose and was to be submitted every 6 months, beginning 6 months after randomization, until death. Instructions for reporting SPMs were revised, and all SPMs were to be reported through AdEERS.
- Amendment 17, dated 15 October 2012, allowed for the continued collection of certain subject data to accommodate the subjects who remain on study treatment longer than the 10-year mark. Data will continue to be collected as long as the subject is on study treatment.

The subsequent changes in the statistical analyse plan (dated 19 August 2015) are described below:

- Additional analyses of PFS using FDA censoring rules based; the PFS analysis for the original CSR dated 04 Jan 2013 was performed using EMA censoring rules.
- For PFS and OS, additional subgroup analyses have been added.
- Analysis of PFS2, an additional efficacy endpoint proposed by the EMA particularly valuable in the maintenance setting.
- Analysis of second-line PFS, measured as time from start of second line therapy to second PD or start of third line therapy.
- Summary of second line therapy and subsequent therapies.
- Response post-ASCT will be based on the central review, instead of investigator assessments, as VGPR could not be marked by investigator following the IMWG response criteria for majority of the post-ASCT assessments (mistaken change of CRF).
- Based on study unblinding in 17 December 2009 and the option for subjects to cross-over from placebo to lenalidomide safety will be analyzed according to the following cohorts: i) randomized to lenalidomide and treated ii) randomized to placebo but treated with lenalidomide after study unblinding (and prior to PD) iii) randomized to placebo and not treated with lenalidomide (prior to PD) iv) randomized to placebo and treated.

Baseline data

Demographic and baseline disease characteristics of patients from the Study CALGB 100104 in the Intent-to-treat Post-ASCT population are presented in the tables below.

Table 2: Demographics and Disease-related Characteristics at Diagnosis – Study CALGB 100104 (ITT Post-ASCT Population)

CALGB 100104	Lenalidomide (N = 231)	Placebo (N = 229)
Age (years)		
Median	58.0	58.0
(Min, Max)	(29.0, 71.0)	(39.0, 71.0)
Age Category, n (%)		
< 60 years	131 (56.7)	133 (58.1)
≥ 60 years	100 (43.3)	96 (41.9)
Sex, n (%)		
Male	121 (52.4)	129 (56.3)
Female	110 (47.6)	100 (43.7)
Race, n (%)		
White	175 (75.8)	171 (74.7)
Non-white	42 (18.2)	47 (20.5)
Missing	14 (6.1)	11 (4.8)
ISS Stage at Diagnosis, n (%)*		
Stage I or II	120 (51.9)	131 (57.2)
Stage I	62 (26.8)	85 (37.1)
Stage II	58 (25.1)	46 (20.1)
Stage III	39 (16.9)	35 (15.3)
Missing	72 (31.2)	63 (27.5)
Extramedullary Disease at Diagnosis, n (%)		
Yes	54 (23.4)	69 (30.1)
No	160 (69.3)	149 (65.1)
Missing	17 (7.4)	11 (4.8)
CrCl at Diagnosis, n (%)		
< 50 mL/min	11 (4.8)	9 (3.9)
≥ 50 mL/min	60 (26.0)	64 (27.9)
Missing	160 (69.3)	156 (68.1)

Notes: Percentages are calculated using the total number of subjects as the denominator. An asterisk ("*") denotes a p-value < 0.1 for the comparison between lenalidomide maintenance and placebo/no maintenance using the T-test for continuous variables and the Fisher's exact test for categorical variables in the CALGB 100104 study.

Prior therapy and Response after last ASCT

Prior therapy (induction and HDM/ASCT) and response after last ASCT of the subjects in the ITT post-ASCT population are summarized by treatment arm in Table .

Table 3 : Prior Therapy (Induction and HDM/ASCT) and Response After Last ASCT – Study CALGB 100104 (ITT Post-ASCT Population)

CALGB 100104	Lenalidomide (N = 231) n (%)	Placebo (N = 229) n (%)
Induction Therapy Containing:		
Lenalidomide	80 (34.6)	78 (34.1)
Thalidomide	102 (44.2)	104 (45.4)
Bortezomib	99 (42.9)	90 (39.3)
Anthracycline	44 (19.0)	31 (13.5)
Other	14 (6.1)	17 (7.4)
Change of Induction Regimen	56 (24.2)	43 (18.8)
Number of ASCTs		
1	231 (100.0)	229 (100.0)
Response After ASCT (Before Maintenance Therapy)		
CR/VGPR	128 (55.4)	153 (66.8)
CR	48 (20.8)	53 (23.1)
PR/SD/PD	86 (37.2)	60 (26.2)
Not evaluable	17 (7.4)	16 (7.0)

Second-line antimyeloma therapy

Second-line AMTs taken after the study treatment were categorized by type of treatment: bortezomib based, lenalidomide based, other novel drugs (other than bortezomib or lenalidomide) or several novel drugs (including bortezomib and lenalidomide), treatment without any novel drug(s), or stem-cell transplant. Lenalidomide received by subjects in the placebo arm who crossed over prior to PD upon study unblinding was not considered a second-line therapy.

Table 4: Second-line Antimyeloma Therapy on 1 March 2015– Studies CALGB 100104 (ITT Post-ASCT Population)

	CALGB 100104		
Subjects Who Received:	Lenalidomide (N = 231) n (%)	Placebo [a, b] (N = 229) n (%)	Placebo (crossover [b, c]) (N=76) n (%)
Any Second-line AMT	**106 (45.9)**	**144 (62.9)**	**37 (48.7)**
Bortezomib ± dexamethasone	38 (16.5)	29 (12.7)	12 (15.8)
Lenalidomide ± dexamethasone[a]	29 (12.6)	61 (26.6)	12 (15.8)
Other novel drugs[b] or several novel drugs	27 (11.7)	43 (18.8)	7 (9.2)
Treatment without any novel drug	8 (3.5)	6 (2.6)	3 (3.9)
Stem-cell transplant	4 (1.7)	5 (2.2)	3 (3.9)
No Second-line AMT	**125 (54.1)**	**85 (37.1)**	**39 (51.3)**
Not progressed on first line therapy	88 (38.1)	50 (21.8)	31 (40.8)
Died brfore receiving second-line therapy	17 (7.4)	4 (1.7)	0 (0.0)
Other reasons	20 (8.7)	31 (13.5)	8 (10.5)

[a] Second-line AMT in subjects who crossed over to lenalidomide prior to PD upon study unblinding is included in the Placebo column.
[b] Lenalidomide received by subjects in the placebo arm who crossed over prior to PD upon study unblinding is not considered as second-line therapy.

[c] Subjects in the placebo arm who crossed over to lenalidomide prior to PD upon study unblinding

Numbers analysed

Table 5 : Analysis Populations - Study CALGB 100104

Outcomes and estimation

CALGB 100104			
Analysis Set	**Len**	**Placebo**	**Total**
ITT post-ASCT Population	231	229	460
Safety Population	224	221	445

Primary efficacy endpoint: Progression-free-Survival

Table 6 : Summary of Progression-free Survival – Study CALGB 100104 (ITT Post-ASCT Population)

CALGB 100104 Endpoint / Data Cutoff Date	Censoring Rules	Statistics	Lenalidomide (N = 231)	Placebo (N = 229)
PFS from transplant 17 Dec 2009	EMA	PFS events (% N)	46 (19.9)	99 (43.2)
		Median (months)[a] (95% CI)[b]	37.2 (NE, NE)	22.2 (18.40, 28.93)
		HR (95% CI)[c]	0.38 (0.27, 0.54)	
		p-value	< 0.001	
PFS from randomization 17 Dec 2009	EMA	PFS events (% of N)	46 (19.9)	98 (42.8)
		Median (months)[a] (95% CI)[b]	33.9 (NE, NE)	19.0 (16.2, 25.6)
		HR (95% CI)[c]	0.38 (0.27, 0.54)	
		p-value	< 0.001	
PFS from randomization 1 Mar 2015	EMA	PFS events (% of N)	126 (54.5)	162 (70.7)
		Median (months)[a] (95% CI)[b]	58.4 (42.7, 82.0)	28.9 (21.0, 35.4)
		HR (95% CI)[c]	0.58 (0.46, 0.73)	
		p-value	< 0.001	
	FDA	PFS events (% of randomized)	97 (42.0)	116 (50.7)
		Median (months)[a] (95% CI)[b]	68.6 (52.8, NE)	22.5 (18.8, 30.0)
		HR (95% CI)[c]	0.38 (0.28, 0.50)	
		p-value	< 0.001	
PFS from randomization 1 Feb 2016	EMA	PFS events (% of N)	66.3	
		Median (months) (95% CI)	56.9 (41.9, 71.7)	29.4 (20.7, 35.5)
		HR (95% CI)[c]	0.61 (0.48, 0.76)	
		p-value	< 0.001	

[a] The median is based on Kaplan-Meier estimate.
[b] 95% CIs about the median overall PFS time.
[c] Based on a proportional hazards model comparing the hazard functions associated with treatment arms (lenalidomide:placebo).

Table 7. Summary of Progression-free Survival Based on the Investigator Assessments and FDA Censoring Rules ITT Population - CALGB Study (cut-off 1 Feb 2016)

	Statistics	Lenalidomide (N=231)	Placebo (N=229)	Overall (N=460)
Progression free survival (PFS)	N	231	229	460
Progressed/Died	n (%)	104 (45.0)	117 (51.1)	221 (48.0)
Progressed	n (%)	89 (38.5)	106 (46.3)	195 (42.4)
Died	n (%)	15 (6.5)	11 (4.8)	26 (5.7)
Censored	n (%)	127 (55.0)	112 (48.9)	239 (52.0)
Overall PFS time (Months)	Median [a]	68.6	24.3	38.9
	95% CI [b]	(49.47, NE)	(18.76, 30.91)	(33.28, 52.76)
	12 Months Event-Free(SE) %	89.96 (2.03)	73.01 (3.24)	82.09 (1.89)
	24 Months Event-Free(SE) %	78.44 (2.82)	50.40 (3.99)	66.20 (2.43)
	36 Months Event-Free(SE) %	65.35 (3.35)	32.94 (4.25)	52.09 (2.71)
	48 Months Event-Free(SE) %	57.70 (3.53)	26.57 (4.15)	45.17 (2.75)
	60 Months Event-Free(SE) %	54.25 (3.59)	26.57 (4.15)	42.94 (2.77)
	72 Months Event-Free(SE) %	48.99 (3.69)	22.56 (4.12)	38.34 (2.80)
	84 Months Event-Free(SE) %	47.40 (3.74)	16.11 (4.05)	35.35 (2.84)
	96 Months Event-Free(SE) %	43.96 (4.20)	13.43 (4.17)	32.20 (3.12)
	108 Months Event-Free(SE) %	37.68 (6.84)	NE(NE)	28.18 (4.65)
	Mean [c]	46.4	20.3	33.4
	SD	31.57	21.64	30.04
	Median [c]	40.2	12.6	21.4
	Min, Max	0.0, 118.0	0.0, 106.4	0.0, 118.0
Hazard rate ratio (HR)	HR (95% CI) [d]	0.399 (0.303, 0.524)		
Log rank test	p-value [e]	< 0.001		

Subgroup Analyses of Progression-Free Survival

Table 8 : Subgroup Analyses of Progression-free Survival From Randomization Using EMA Censoring Rules – Study CALGB 100104 (ITT Post-ASCT Population)

	Lenalidomide (N = 231)		Placebo (N = 229)		Statistics		
CALGB 100104 PFS Subgroup	**N**	**Median PFS[a]** (months)	**N**	**Median PFS[a]** (months)	**p-value**	**HR[b]**	**95% CI**
Age[c]							
< 60	131	63.0	133	19.8	< 0.001	0.49	0.36, 0.67
≥ 60	100	56.3	96	37.2	0.066	0.72	0.50, 1.02
Sex							
Male	121	54.6	129	28.7	< 0.001	0.58	0.43, 0.79
Female	110	72.0	100	37.0	0.002	0.58	0.41, 0.82
ISS Stage at diagnosis							
I	62	63.5	85	35.4	0.054	0.66	0.43, 1.01
II	58	72.0	46	19.5	< 0.001	0.32	0.19, 0.53
III	39	31.3	35	28.9	0.587	0.87	0.52, 1.46
β2M[d] at randomization							
≥ 2.5 mg/L	64	44.0	62	30.0	0.036	0.63	0.40, 0.97
< 2.5 mg/L	167	63.0	167	28.7	< 0.001	0.56	0.42, 0.74
Prior lenalidomide[d]							
Yes	84	NE	82	26.3	< 0.001	0.48	0.32, 0.74
No	147	44.0	147	30.0	0.002	0.64	0.48, 0.85
Prior thalidomide[d]							
Yes	96	49.5	94	30.0	0.010	0.63	0.44, 0.90
No	135	62.3	135	26.3	< 0.001	0.55	0.40, 0.75
Post-ASCT Response (Central review)							
CR/VGPR	128	72.0	153	31.8	< 0.001	0.51	0.37, 0.70

Not CR/VGPR	103	36.5	76	23.9	0.010	0.63	0.44, 0.90
Post-ASCT Response (Central review)							
CR	48	72.0	53	35.4	0.057	0.60	0.36, 1.02
Not CR	183	54.6	176	25.8	< 0.001	0.57	0.44, 0.74

ASCT = autologous stem-cell transplant; β2M = β2 microglobulin; CI = confidence interval; CR = complete response; EMA = European Medicines Agency; HR = hazard ratio; ISS = International Staging System; NE = not estimable; PFS = progression-free survival; VGPR = very good partial response.

[a] The median is based on Kaplan-Meier estimate.

[b] Based on a proportional hazards model comparing the hazard functions associated with treatment groups (lenalidomide:placebo).

[c] Age at randomization.

[d] Stratification factors.

Data cutoff date = 1 Mar 2015

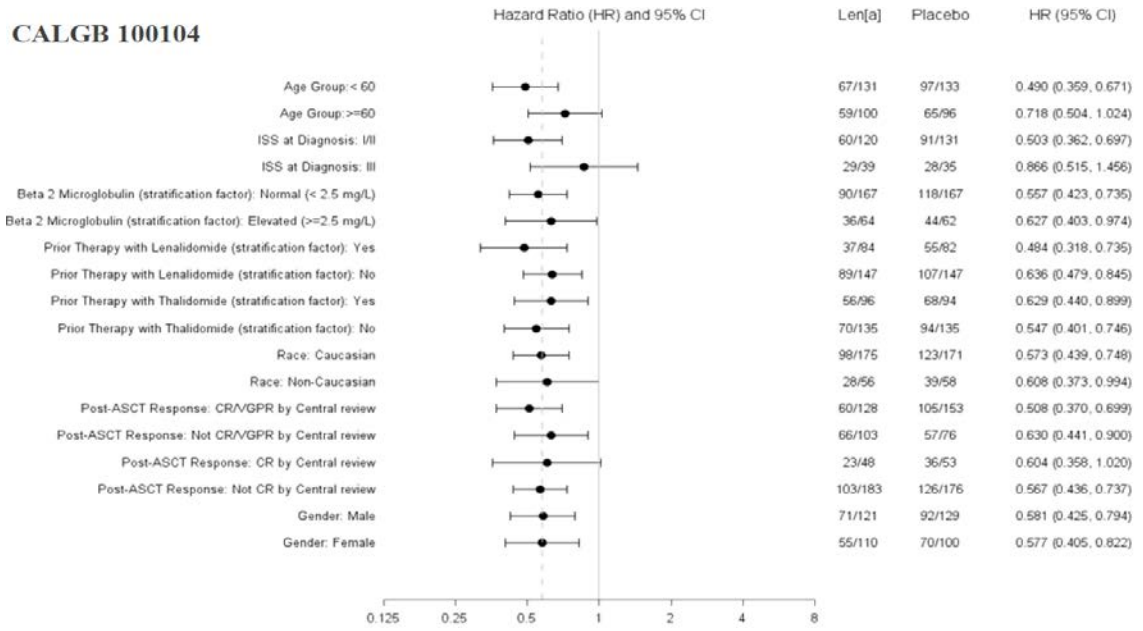


Figure 3 : Hazard Ratios by Subgroup for the Comparison of PFS – 1 March 2015 – Study CALGB 100104 (ITT Post-ASCT Population)

Table 9 : Progression-free Survival from Randomization Using EMA Censoring Rules and Crossover Adjustment – 1 March 2015 (ITT Population)

		CALGB 100104	
	Statistic	**Lenalidomide (N = 231)**	**Placebo (N = 229)**
Progressed / died	n (%)	126 (54.5)	129 (56.3)
Censored	n (%)	105 (45.5)	100 (43.7)
PFS time from randomization (months)	Median [b]	58.4	22.5
	(95% CI) [c]	(42.71, 82.00)	(18.63, 29.99)
	36 months event-free (SE) %	60.01 (3.25)	33.55 (3.99)
	48 months event-free (SE) %	53.30 (3.32)	25.81 (3.81)
	60 months event-free (SE) %	49.03 (3.34)	23.07 (3.72)
	72 months event-free (SE) %	44.40 (3.47)	19.25 (3.71)
	84 months event-free (SE) %	41.52 (3.87)	14.15 (3.82)
	96 months event-free (SE) %	31.71 (7.06)	NE (NE)
Comparison between arms	HR (95% CI) [d]	0.446 (0.347, 0.574)	
	Log-rank Test p-value[e]	< 0.001	

[a] For subjects who crossed over from placebo to lenalidomide prior to PD, PFS was censored at the date of crossover.
[b] The median is based on Kaplan-Meier estimate.
[c] 95% CIs about the median overall PFS time.
[d] Based on a proportional hazards model comparing the hazard functions associated with treatment arms (lenalidomide: placebo).
[e] The p-value is based on unstratified log rank test of Kaplan-Meier curve differences between the treatment arms.

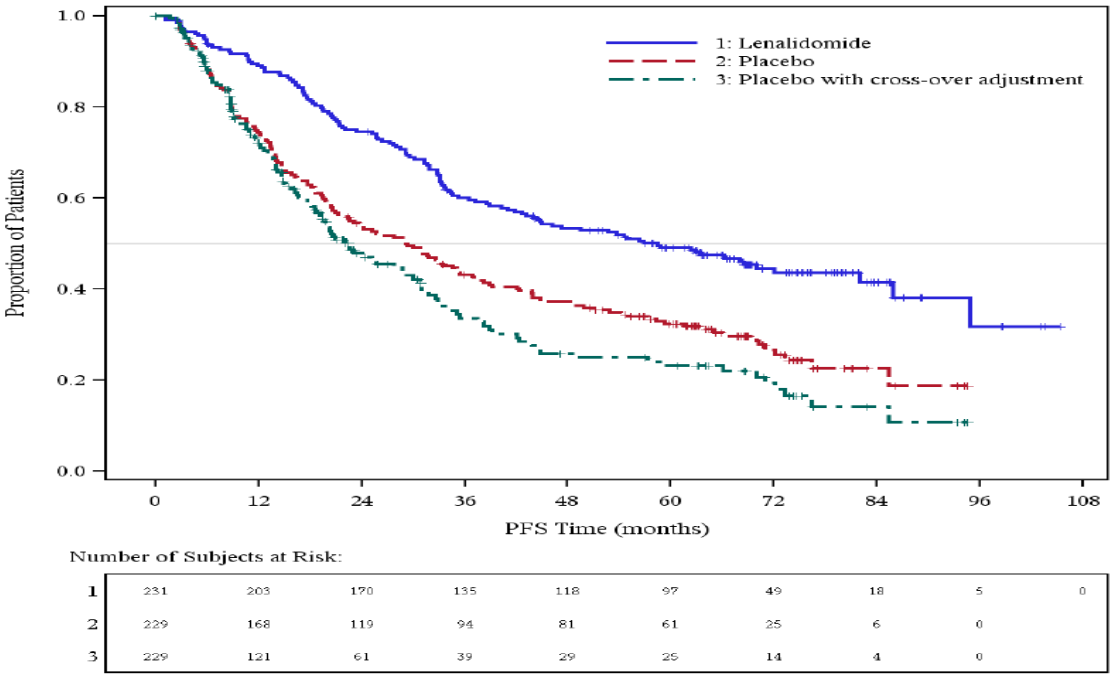


Figure 4 : Kaplan-Meier Curve for PFS from Randomization based on EMA Censoring Rules and Cross-over Adjustment – 01 Mar 2015 (ITT Population)

Secondary efficacy endpoint: Overall Survival

As of the 1 March 2015 data cutoff date, the median follow-up time from randomization was, overall, 72.4 months in the CALGB study. Between the date of unblinding (17 December 2009) and the data cutoff date for this submission (1 March 2015), the rate of death events overall increased from 8.0% to 39.3%.

Table 10 : Summary of Overall Survival From Randomization – Study CALGB 100104 (ITT Post-ASCT Population)

CALGB 100104 Endpoint / Data Cutoff Date	Statistics	Lenalidomide (N = 231)	Placebo (N = 229)
Overall Survival **17 Dec 2009**	OS events (% of N)	13 (5.6)	24 (10.5)
	Median (months) (95% CI)	NE	NE
	HR (95% CI) p-value	0.52 (0.26, 1.01) 0.050	
Overall Survival **1 Mar 2015**	OS events (% of N)	72 (31.2)	109 (47.6)
	Median (months)[a] (95% CI)	NE (NE, NE)	79.0 (70.2, 88.4)
	HR (95% CI) p-value	0.57 (0.42, 0.76) < 0.001	
Overall Survival **1 Feb 2016**	OS events (% of N)	42.6	
	Median (months)[a] (95% CI)	111.0 (101.8, NE)	84.2 (71.0, 102.7)
	HR (95% CI) p-value	0.61 (0.46, 0.81) < 0.001	

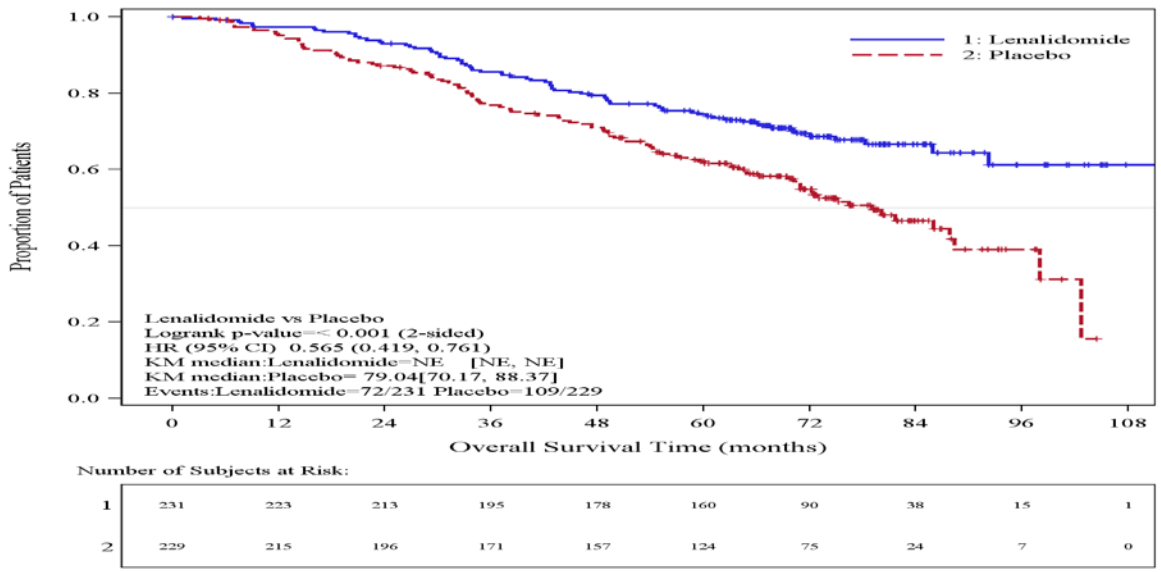


Figure 5 : Kaplan-Meier Plots of Overall Survival From Randomization – Study CALGB 100104 – 1 March 2015 (ITT Post-ASCT Population)

Exploratory efficacy endpoint: Progression-free Survival (PFS2)

Table 11 : Progression-free Survival 2 From Randomization Using EMA Censoring Rules – Studies CALGB 100104 – 1 March 2015 (ITT Post-ASCT Population)

CALGB 100104

	Statistic	Lenalidomide (N = 231)	Placebo (N = 229)
2nd PD/start of 3rd line/died	n (%)	114 (49.4)	142 (62.0)
2nd PD	n (%)	42 (18.2)	60 (26.2)
Start of 3rd line	n (%)	33 (14.3)	40 (17.5)
Died	n (%)	39 (16.9)	42 (18.3)
Censored	n (%)	117 (50.6)	87 (38.0)
PFS2 time from randomization (months)	Median[a]	78.3	52.8
	(95% CI)[b]	(63.0, 98.1)	(40.7, 62.7)
	36 months event-free (SE) %	76.37 (2.81)	63.13 (3.22)
	48 months event-free (SE) %	67.99 (3.09)	52.80 (3.34)
	60 months event-free (SE) %	59.76 (3.27)	47.16 (3.35)
	72 months event-free (SE) %	53.14 (3.39)	39.20 (3.41)
	84 months event-free (SE) %	47.41 (3.77)	31.88 (3.78)
	96 months event-free (SE) %	41.99 (4.46)	21.86 (6.48)
Comparison between arms	HR (95% CI)[c]	0.64 (0.50, 0.82)	
	p-value	< 0.001	

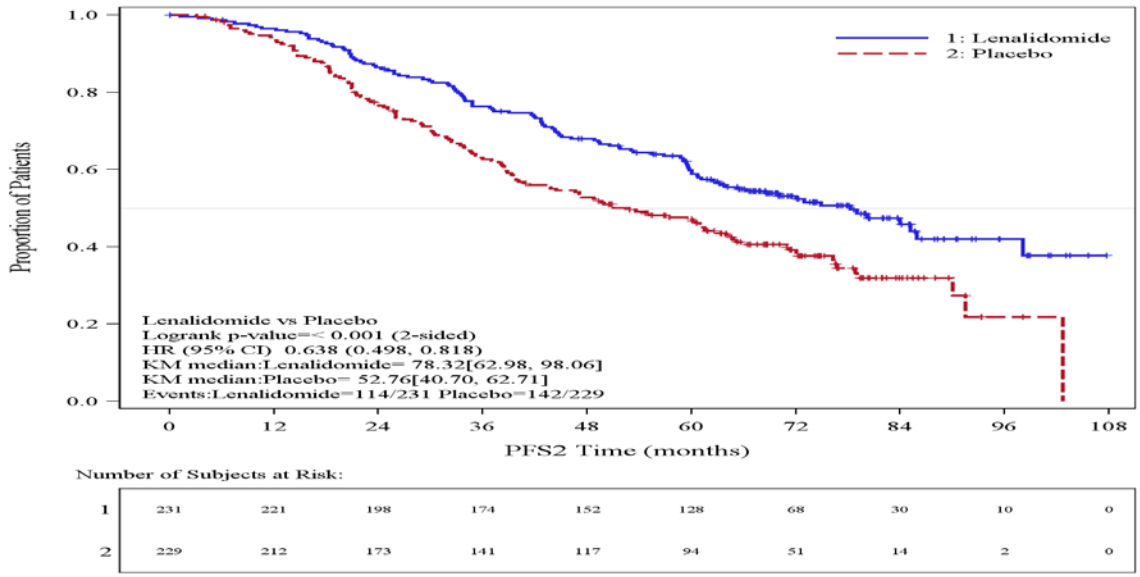


Figure 6 : Kaplan-Meier Plots of Progression-free Survival After Next-line Therapy (PFS2) – Study CALGB 100104 – 1 March 2015 (ITT Post-ASCT Population)

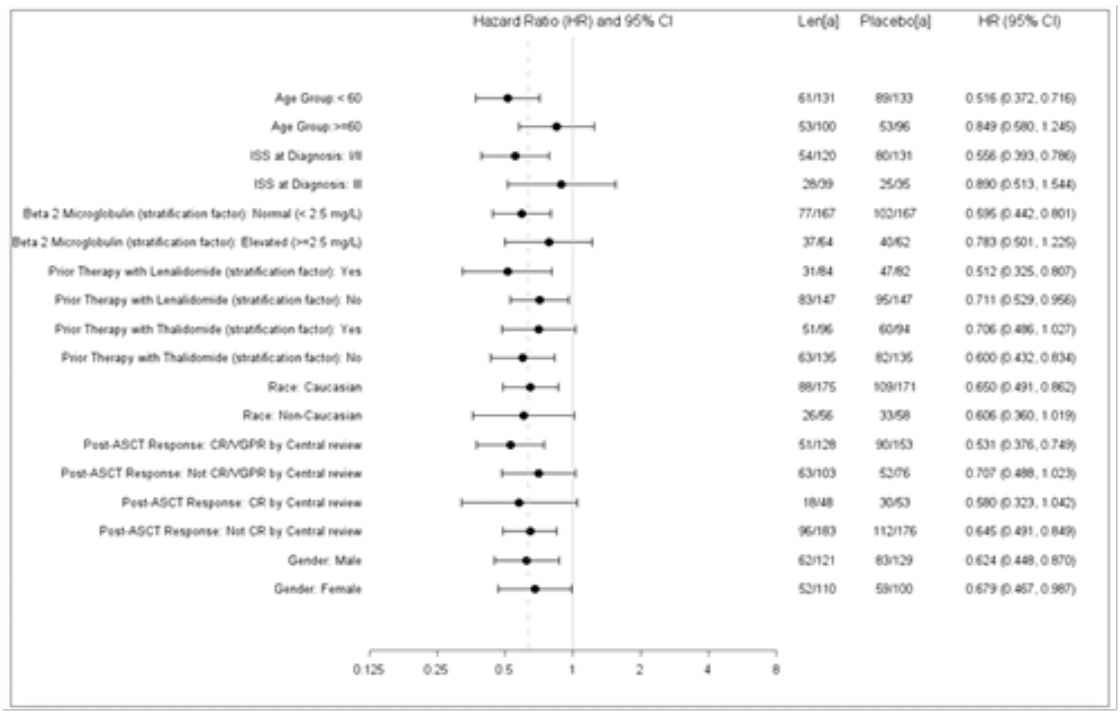
As of the 01 February 2016 data cutoff date, the PFS2 analysis indicates a 39% reduction in the risk of PD after starting second-line AMT, death, or starting a third-line AMT for subjects in the lenalidomide arm compared with those in the placebo arm (HR = 0.61; 95% CI, 0.48 to 0.78). The improvement in median PFS2 was 27.4 months (80.2 months in the lenalidomide arm versus 52.8 months in the placebo arm).

Table 12 Sensitivity Analyses of PFS2 by Taking Lenalidomide after Crossover from Placebo Following Unblinding as Second Line Therapy ITT Population - CALGB study (1 February 2016)

	Statistics	Lenalidomide (N=231)	Placebo (N=229)	Overall (N=460)
Progression-free Survival2 (PFS2)	N	231	229	460
2nd PD/3rd Line/Died	n (%)	120 (51.9)	172 (75.1)	292 (63.5)
2nd PD	n (%)	44 (19.0)	80 (34.9)	124 (27.0)
3rd Line	n (%)	35 (15.2)	55 (24.0)	90 (19.6)
Died	n (%)	41 (17.7)	36 (15.7)	77 (16.7)
Censored	n (%)	111 (48.1)	57 (24.9)	168 (36.5)
Overall time (Months)	Median [a]	80.2	38.7	59.7
	95% CI [b]	(63.30, 101.84)	(34.76, 49.93)	(50.99, 64.78)
	12 Months Event-Free(SE) %	96.50 (1.22)	91.61 (1.84)	94.07 (1.11)
	24 Months Event-Free(SE) %	86.41 (2.27)	71.68 (3.00)	79.08 (1.91)
	36 Months Event-Free(SE) %	76.71 (2.80)	54.67 (3.32)	65.76 (2.23)
	48 Months Event-Free(SE) %	68.29 (3.09)	45.70 (3.33)	57.07 (2.33)
	60 Months Event-Free(SE) %	60.15 (3.26)	38.42 (3.26)	49.34 (2.36)
	72 Months Event-Free(SE) %	52.77 (3.35)	31.28 (3.13)	42.09 (2.35)
	84 Months Event-Free(SE) %	48.72 (3.43)	23.90 (3.01)	36.41 (2.36)
	96 Months Event-Free(SE) %	45.09 (3.63)	16.24 (3.65)	31.24 (2.62)
	108 Months Event-Free(SE) %	35.94 (5.85)	NE(NE)	25.28 (3.52)
	Mean [c]	82.2	75.9	80.1
	SD	20.28	23.45	21.55
	Median [c]	82.3	79.8	81.5
	Min, Max	0.0, 119.8	4.1, 107.9	0.0, 119.8
Hazard rate ratio (HR)	HR (95% CI) [d]	0.497 (0.393, 0.628)		
Log rank test	p-value [e]	< 0.001		

Subgroup Analyses of Progression-Free Survival after Next-line Therapy

Figure 7 : Hazard Ratios by Subgroup for the Comparison of PFS2 – Study CALGB 100104 – 1 March 2015 (ITT Post-ASCT Population)



Ancillary analyses

N/A

Study IFM 2005-02

This was a phase III, multicenter, randomised, double-blind, placebo-controlled, 2-arm parallel study

investigating lenalidomide therapy following ASCT for the treatment of multiple myeloma.

Methods

Study participants
Main inclusion criteria:

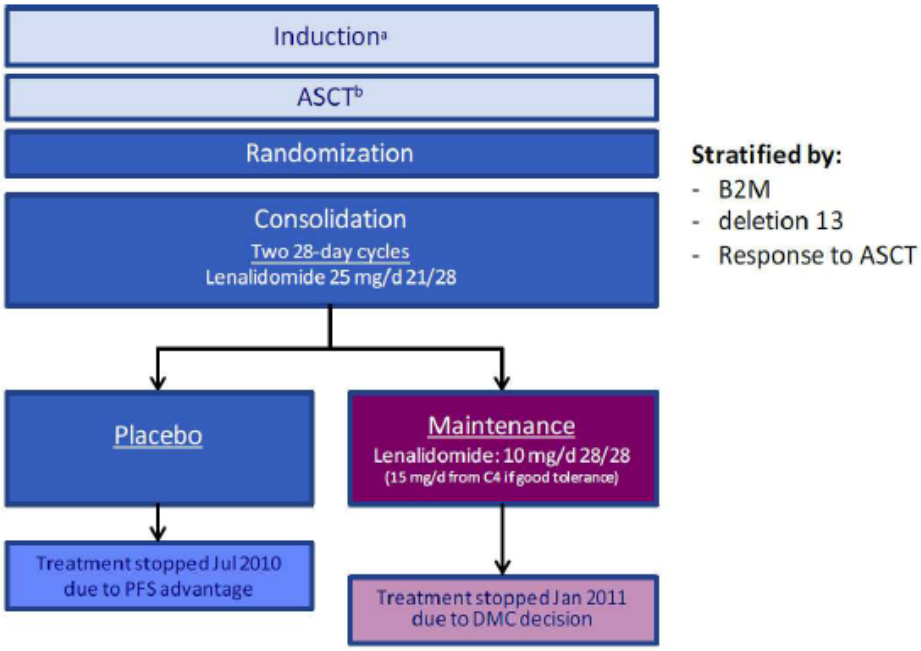
- Diagnosis of de novo myeloma before ASCT
- Age 18 to 65 years
- Post-transplantation period ≤6 months
- Effective contraception and negative pregnancy test if necessary
- Satisfactory restoration of the haematological parameters defined by: PNN >1,000/mm^3 and Platelets > 75,000/mm^3
- Bilirubin < 35 µmol/l and AST/ALT/AP< 3N
- Creatinine < 160 µmol/l

Main exclusion criteria:

- Pregnant women or women of childbearing potential not using a reliable contraceptive method
- Past or current history of malignancy
- Symptomatic cardiac failure or coronary disease, and VEF >40%
- Liver disorders
- Lung disorders: ventilation tests and DLCO <50% N
- History of renal disorder not related to the disease and defined by a creatinine level>160 µmol/L
- Active chronic and severe infection
- Signs of progression after transplant

Treatments
The study consists of 2 treatment phases for each subject: a consolidation phase after undergoing 1 to 2 ASCT (proposed to all patients after the amendment 2), and a maintenance phase.

Following confirmation of inclusion criteria and within 6 months after ASCT, patients were randomised to receive in maintenance phase continuous daily orally placebo or lenalidomide 10 mg/day for 28 days per 28-day cycle. For patients showing good tolerance to maintenance therapy, the dose of lenalidomide could be increased to 15 mg/day. Prior to starting maintenance treatment, the patients were also to receive 2 cycles of consolidation treatment with lenalidomide (25 mg/day for 21 consecutive days of a 28-day cycle).



[a] Free choice, but the recommendation was to include subject in IFM 2005-01 protocol. IFM 2005-01 Arm A1 = VAD (4 cycles) followed by DCEP (2 cycles); IFM 2005-01 Arm A2 = VAD (4 cycles) followed by DCEP (2 cycles); IFM 2005-01 Arm B1 = bortezomib and dexamethasone (4 cycles); IFM 2005-01 Arm B2 = bortezomib and dexamethasone (4 cycles) followed by DCEP (2 cycles).
[b] A second ASCT was recommended if response to first transplant was not VGPR or better.

Objectives

The primary objective of this study was to evaluate the efficacy of a maintenance treatment with lenalidomide following autologous stem cell transplantation in extending post-transplantation PFS.

Secondary objectives were to assess progression free survival (PFS) from the date of diagnosis, overall survival (OS), time to progression (TTP), response assessment and safety of lenalidomide in post-transplantation consolidation and maintenance treatment chemotherapy.

Outcomes/endpoints

The primary efficacy endpoint was PFS (defined as the period from randomization to the date of progression or death whatever the cause).

Secondary endpoints were:

- PFS from diagnosis calculated for all patients from the date of diagnosis to the date of progression or death (whatever the cause).
- OS calculated from the date of randomisation to the date of death.
- Response duration calculated for all randomised patients with a complete or partial response from the date of randomisation to the date of progression.
- Complete response duration calculated for all randomised patients with a complete response from the date that complete response criteria were first met to the date of progression.
- TTP calculated for all patients from the date of randomisation to the date of progression.
- Time to the best response calculated for all patients from the date of randomisation to the date of the best response.

Sample size

For the primary efficacy variable, PFS, sample size calculation were based on the assumption that a 42% improvement in median time to progression from 37.5% at 4 years after randomisation for placebo to 50% at 4 years for lenalidomide was to be considered clinically relevant. The initial calculation evaluated that approximately 267 subjects in each treatment group would have 90% power to detect the difference in 2 survivorship functions with a hazard rate ratio of 1.42 (placebo arm vs. lenalidomide arm) using a one-sided log rank test with overall significance level of 0.05 (adjusted for 4 interim analyses). Expecting a drop out rate of 15%, 614 subjects were to be enrolled. Full information necessary for a log-rank test to have 90% power would be achieved when approximately 300 subjects had progressed or died (PFS).

Approximately 614 subjects would also have 85% power to detect the difference in 2 survivorship functions with a hazard rate ratio of 1.42 (placebo arm vs. lenalidomide arm) using a one-sided logrank test with overall significance level of 0.025 (adjusted for one interim analysis) with a final alpha equal to 2.4%. Full information necessary for a log-rank test to have 85% power would be achieved when approximately 300 subjects had progressed or died (PFS).

Randomisation

After transplantation, patients were randomised (1:1) to lenalidomide arm or placebo arm.

Randomisation was stratified based on 3 parameters: beta2-microglobulin at diagnosis (≤ or > 3 mg/l), chromosome 13 deletion (present or absent) and response after transplant (CR; VGPR /PR;SD).

Initial stratification also comprised the number of transplants (one or two). The amendment number 4 modified this stratum which became response after transplant. The number of subjects randomized before the amendment 4 was 312.

Blinding (masking)

This was a double blind study until amendment 8.

Statistical methods

This study was designed to have 1 interim analysis performed after 60% of events (progression and/or deaths) had been observed. An independent DMC evaluated safety and efficacy data at the time of the interim analysis. Upper and lower bounds based on O'Brien-Fleming stopping rules were used in the interim efficacy analysis. The primary efficacy variable PFS, was compared between arms using a group sequential log-rank test corresponding to 2 analyses one interim at 60% information and one final at 100% information. The upper boundary for superiority of lenalidomide over placebo was based on an α spending function of the O'Brien-Fleming type with overall one-sided α=0.025. If at the interim analysis (at 60%), a log rank statistic is above the upper boundary, a recommendation to stop the study and claim superiority for the lenalidomide to be considered.

Definition of Analysis Sets

Intent-to-Treat Population (ITT)

The intent-to-treat (ITT) population was defined as all subjects who were randomized, independently of whether they received study treatment or not. Patients were analysed according to the treatment they were randomized to receive and not according to what they actually received, if different.

Treated Population/Safety Population

The treated population was defined as all randomized subjects who received at least 1 dose of the study treatment (either lenalidomide or placebo). Patients were analyzed according to the treatment they were randomized to receive and not according to what they actually received, if different.

Per-Protocol Population (PP)

Per-protocol population was defined as all randomized subjects who met eligibility criteria, who received at least 1 dose of study treatment and who had at least 1 valid post-baseline response assessment without any major protocol violation. Patients were to be analysed according to the initial treatment they actually received.

Consolidation population

The consolidation population was defined as all randomized subjects who received at least 1 dose of the study treatment (lenalidomide) during the consolidation period. Patients were analyzed according to the treatment they were randomized to receive and not according to what they actually received, if different.

Maintenance population

The maintenance population was defined as all randomized subjects who received at least 1 dose of the study treatment (either lenalidomide or placebo) during the maintenance period. It included all patients in the consolidation population who continued the treatment in the maintenance period and all patients without consolidation period who began the treatment with a maintenance treatment.

Efficacy analyses were performed on the ITT population and safety analyses were performed on the treated population.

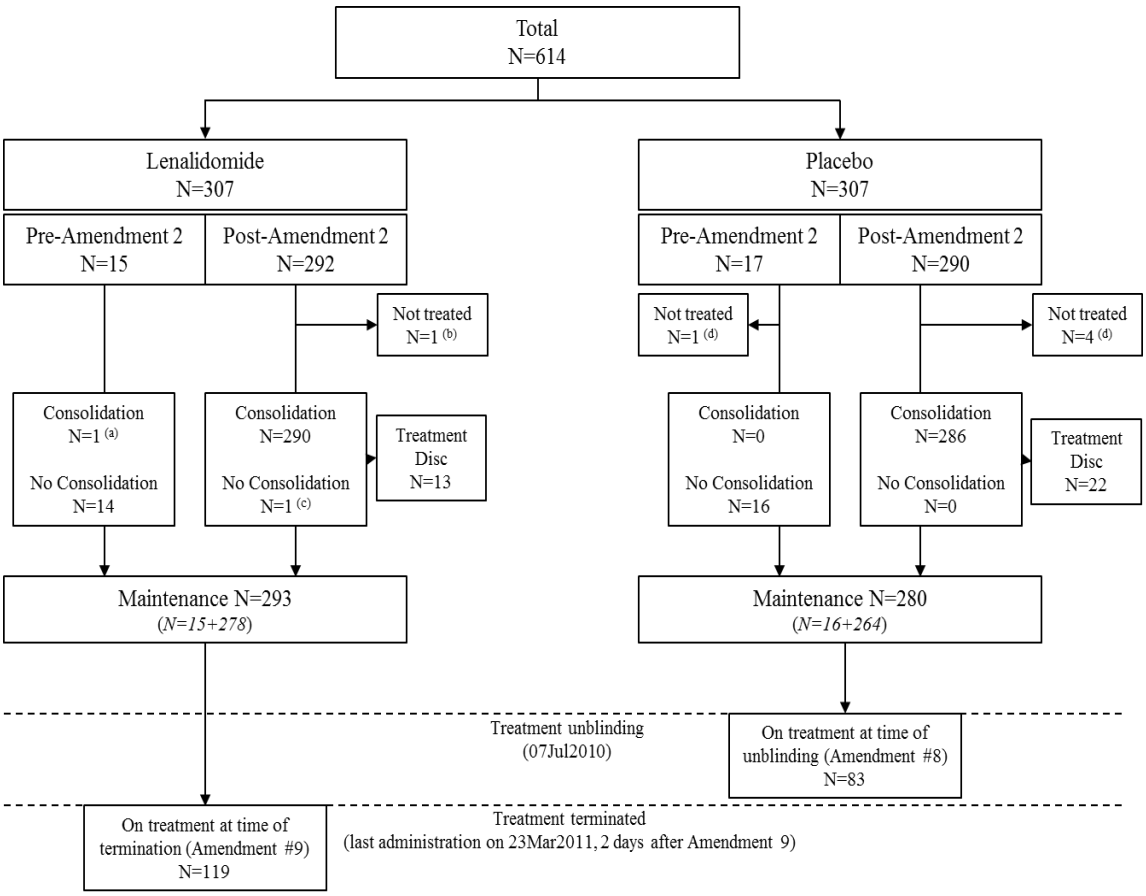
Statistical Methodology

Table 13 : Summary of Key Primary and Secondary Efficacy Analyses

Type of Analysis	Endpoint	Analysis Set	Statistical Method
Primary Analysis	PFS	ITT	• Unstratified log-rank test • Censoring rules based on EMA or FDA guidance • K-M method (median and 95% CIs) • HR and two-sided 95% CIs from the Cox model
Secondary analysis Secondary analyses	OS	ITT	• Unstratified log-rank test • K-M method (median and 95% CIs) • HR and two-sided 95% CIs from the Cox model
Exploratory Analyses	PFS2	ITT	• Unstratified log-rank test • K-M method (median and 95% CIs) • HR and two-sided 95% CIs from the Cox model

Results

Participant flow



a) 1 patient randomized just before Amendment #2 approval asked to receive the consolidation treatment at the time the amendment was approved
b) 1 patient did not receive any treatment due to grade 4 thrombocytopenia
c) 1 patient randomized after Amendment #2 approval did not receive the consolidation treatment due to elapsed time between the date of approval and the date of written receipt of the approval
d) 5 patients did not receive any treatment: three patients for disease progression and two patients for consent withdrawal

Recruitment

The study started on 12 June 2006 and the last patient was enrolled in 29 August 2008. The last dose of lenalidomide maintenance treatment was administered on March 2011.

Conduct of the study

Twelve amendments to the study protocol were made. Significant protocol changes are outlined below:

- Amendment 2, dated 4 October 2006, included a post-transplant consolidation step. Under this amendment, all patients were to receive 2 cycles of consolidation therapy with lenalidomide 25 mg/day for 21 consecutive days of a 28-day cycle, prior to starting maintenance treatment in the arm to which they were randomized.

- Amendment 4, dated 20 August 2007, stratified the randomization by “post-transplantation response” rather than “number of transplantations”.
- Amendment 7, dated 24 August 2009, planned an interim analysis of efficacy when 60% information fraction had been reached (60% of events required for primary PFS analysis). If the p-value from the logrank test was less than 0.004, then the independent DMC could consider stopping and/or unblinding the study and declaring the lenalidomide arm superior.
- Amendment 8, dated 26 August 2010, added Data Monitoring Committee (DMC) recommendation to unblind the study, following the results of a pre-planned interim analysis (September 2009 dataset) that showed significant benefit in the lenalidomide arm. First unblinding occurred on 7 July 2010; patients in the placebo group were recommended to not cross over to lenalidomide treatment;
- Amendment 9, dated 21 March 2011, added the decision to stop treatment for all patients still on therapy after reports showed a higher level of second primary malignancies (SPMs) in the lenalidomide arm;
- Amendment 12, dated 18 December 2014, extended the duration of the study of a further 3 years (up to December 2017) in order to evaluate precisely the risk of second cancers.

Baseline data

Table 14 : Demographics and Disease-related Characteristics at Diagnosis – Study IFM 2005-02 (ITT Post-ASCT Population)

IFM 2005-02	Len (N = 307)	Placebo (N = 307)
Age (years)		
Median	57.5	58.1
(Min, Max)	(22.7, 68.3)	(32.3, 67.0)
Age Category, n (%)		
< 60 years	198 (64.5)	194 (63.2)
≥ 60 years	109 (35.5)	113 (36.8)
Sex, n (%)		
Male	169 (55.0)	181 (59.0)
Female	138 (45.0)	126 (41.0)
ISS Stage at Diagnosis, n (%)		
Stage I or II	232 (75.6)	250 (81.4)
Stage I	128 (41.7)	143 (46.6)
Stage II	104 (33.9)	107 (34.9)
Stage III	66 (21.5)	46 (15.0)
Missing	9 (2.9)	11 (3.6)
Extramedullary Disease at Diagnosis, n (%)		
Yes	30 (9.8)	28 (9.1)
No	277 (90.2)	278 (90.6)
Missing	0	1 (0.3)
Adverse risk Cytogenetics at Diagnosis: t(4;14) or del 17p, n (%)**		
Yes	41 (13.4)	24 (7.8)
No	202 (65.8)	216 (70.4)
Missing	64 (20.8)	67 (21.8)
LDH at Diagnosis, n (%)		
≤ ULN	208 (67.8)	220 (71.7)
> ULN	40 (13.0)	41 (13.4)
Missing	59 (19.2)	46 (15.0)
CrCl at Diagnosis, n (%)**		
< 50 mL/min	45 (14.7)	25 (8.1)
≥ 50 mL/min	204 (66.4)	232 (75.6)
Missing	58 (18.9)	50 (16.3)

Notes: Percentages are calculated using the total number of subjects as the denominator. A double asterisk ("**") denotes a p-value < 0.1 for the comparison between lenalidomide maintenance and placebo/no maintenance using the T-test for continuous variables and the Fisher's exact test for categorical variables in the IFM study.

Prior therapy and Response after last ASCT

Table 15 : Prior Therapy (Induction and HDM/ASCT) and Response After Last ASCT – Study IFM 2005-02 (ITT Post-ASCT Population)

IFM 2005-02	Lenalidomide (N = 307) n (%)	Placebo (N = 307) n (%)
Induction Therapy Containing:**		
TD	10 (3.3)	10 (3.3)
VD	140 (45.6)	135 (44.0)
VAD	141 (45.9)	157 (51.1)
Other	16 (5.2)	5 (1.6)
Intensification (DCEP)	80 (26.1)	74 (24.1)
Number of ASCTs		
1	243 (79.2)	243 (79.2)
2	64 (20.8)	64 (20.8)
Missing	0	0
Response After ASCT (Before Maintenance Therapy)		
CR/VGPR	162 (52.8)	160 (52.1)
CR	13 (4.2)	21 (6.8)
PR/SD/PD	104 (33.9)	114 (37.1)
Not evaluable	28 (9.1)	27 (8.8)
Missing	13 (4.2)	6 (2.0)

Notes: Percentages are calculated using the total number of subjects as the denominator. A double asterisk ("**") denotes a p-value < 0.1 for the comparison between lenalidomide maintenance and placebo/no maintenance using the T-test for continuous variables and the Fisher's exact test for categorical variables in the IFM study.

Second-line antimyeloma therapy

Table 16 : Second-line Antimyeloma Therapy by Category – Studies IFM 2005-02 – 1 March 2015 (ITT Post-ASCT Population)

Subjects Who Received:	IFM 2005-02 Lenalidomide (N = 307) n (%)	IFM 2005-02 Placebo (N = 307) n (%)
Any Second-line AMT	184 (59.9)	235 (76.5)
Bortezomib ± dexamethasone	71 (23.1)	35 (11.4)
Lenalidomide ± dexamethasone	34 (11.1)	103 (33.6)
Other novel drugs or several novel drugs	28 (9.1)	37 (12.1)
Treatment without any novel drug	10 (3.3)	6 (2.0)
Stem-cell transplant[d]	41 (13.4)	54 (17.6)
No Second-line AMT	123 (40.1)	72 (23.5)

Numbers analysed

Table 17 : Data sets analyzed - Study IFM 2005-05

		Placebo N = 307	Lenalidomide N = 307	Total N =614
Randomized	Yes	307 (100.0%)	307 (100.0%)	614 (100.0%)
ITT population	Yes	307 (100.0%)	307 (100.0%)	614 (100.0%)
	No	9 (2.9%)	13 (4.2%)	22 (3.6%)

Per Protocol population	Yes	298 (97.1%)	294 (95.8%)	592 (96.4%)
Treated population	No	5 (1.6%)	1 (0.3%)	6 (1.0%)
	Yes	302 (98.4%)	306 (99.7%)	608 (99.0%)
Consolidation	No	21 (6.8%)	16 (5.2%)	37 (6.0%)
	Yes	286 (93.2%)	291 (94.8%)	577 (94.0%)
Maintenance	No	27 (8.8%)	14 (4.6%)	41 (6.7%)
	Yes	280 (91.2%)	293 (95.4%)	573 (93.3%)

Outcomes and estimation

Primary efficacy endpoint: Progression-free survival

Table 18 : Summary of Progression-free Survival – Study IFM 2005-02 (ITT Post-ASCT Population)

IFM 2005-02 Endpoint / Data cutoff date	**Censoring Rules**	**Statistics**	**Lenalidomide (N = 307)**	**Placebo (N = 307)**
PFS from randomization 4 Sep 2009	EMA	PFS events (% of N)	72 (23.5)	141 (45.9)
		Median (months)[a] (95% CI)[b]	NE (NE, NE)	23.0 (20.6, 26.3)
		HR (95% CI)[c] p-value	0.45 (0.34,0.60) < 0.001	
	FDA	PFS events (% of N)	71 (23.1)	139 (45.3)
		Median (months)[a] (95% CI)[b]	NE (NE, NE)	23.0 (20.6, 27.6)
		HR (95% CI)[c] p-value	0.45 (0.34,0.60) < 0.001	
PFS from randomization 1 Mar 2015	EMA	PFS events (% of N)	209 (68.1)	255 (83.1)
		Median (months)[a] (95% CI)[b]	44.4 (39.6, 52.0)	23.8 (21.2, 27.3)
		HR (95% CI)[c] p-value	0.55 (0.46, 0.66) < 0.001	
	FDA	PFS events (% of N)	191 (62.2)	248 (80.8)
		Median (months)[a] (95% CI)[b]	46.3 (40.4, 56.6)	23.8 (21.0, 27.3)
		HR (95% CI)[c] p-value	0.53 (0.43, 0.64) < 0.001	
PFS from randomization 1 Feb 2016	EMA	PFS events (% of N)	218 (71.0)	257 (83.7)
		Median (months)[a] (95% CI)[b]	44.4 (39.6, 52.0)	23.8 (21.2, 27.3)
		HR (95% CI)[c] p-value	0.57 (0.47, 0.68) < 0.001	

[a] The median is based on Kaplan-Meier estimate.
[b] 95% CIs about the median overall PFS time.
[c] Based on a proportional hazards model comparing the hazard functions associated with treatment arms (lenalidomide:placebo).

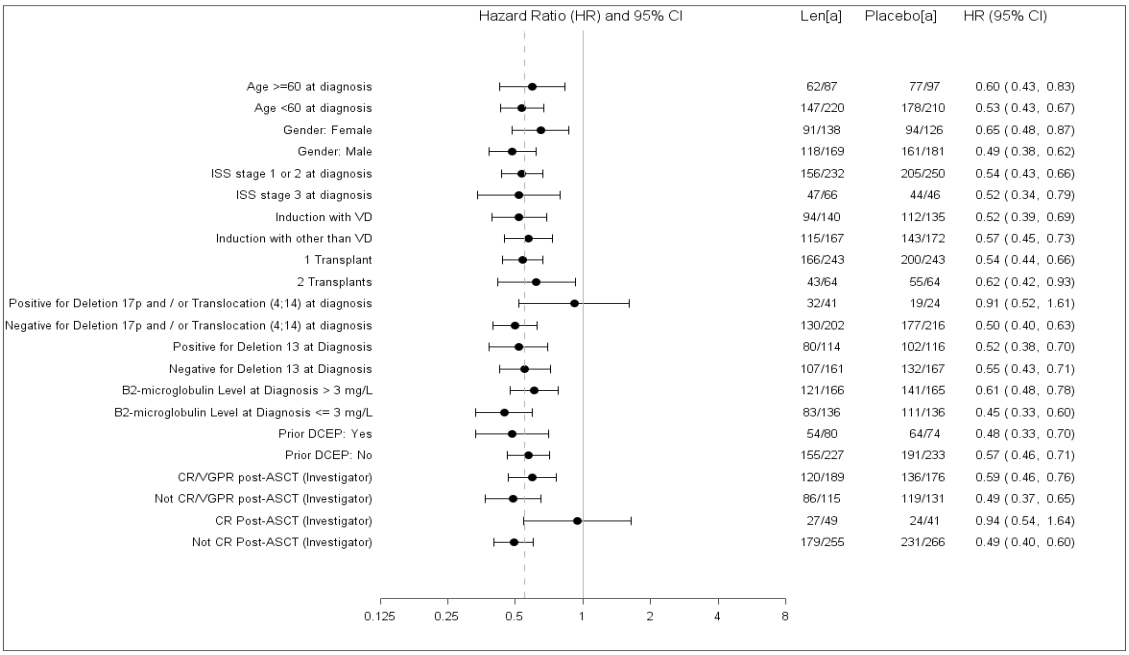
Table 19. Progression-free Survival from Randomization Based on the Investigator Assessments and FDA Censoring Rules (Cut off Date – 1 February 2016) ITT Population - Study IFM 2005-02

	Statistics	Lenalidomide (N=307)	Placebo (N=307)	Overall (N=614)
Progression Free Survival (PFS)	N	307	307	614
Censored	n (%)	108 (35.2)	57 (18.6)	165 (26.9)
Progression	n (%)	193 (62.9)	249 (81.1)	442 (72.0)
Died	n (%)	6 (2.0)	1 (0.3)	7 (1.1)
PFS Time (Months)	Median [a]	46.3	23.8	32.9
	95% CI [b]	(40.44, 56.61)	(20.96, 27.27)	(29.17, 37.78)
	6 Months Event-Free(SE) %	92.61 (1.52)	91.56 (1.62)	92.08 (1.11)
	12 Months Event-Free(SE) %	83.68 (2.16)	77.75 (2.44)	80.72 (1.63)
	18 Months Event-Free(SE) %	79.15 (2.38)	62.55 (2.84)	70.84 (1.88)
	24 Months Event-Free(SE) %	74.24 (2.57)	48.65 (2.94)	61.40 (2.02)
	30 Months Event-Free(SE) %	66.57 (2.79)	39.55 (2.88)	52.96 (2.09)
	36 Months Event-Free(SE) %	60.53 (2.92)	33.13 (2.78)	46.70 (2.10)
	48 Months Event-Free(SE) %	48.57 (3.03)	23.17 (2.52)	35.73 (2.04)
	60 Months Event-Free(SE) %	42.25 (3.02)	17.56 (2.29)	29.73 (1.96)
	72 Months Event-Free(SE) %	35.78 (2.96)	13.45 (2.06)	24.43 (1.86)
	84 Months Event-Free(SE) %	30.80 (2.88)	13.08 (2.04)	21.83 (1.80)
	96 Months Event-Free(SE) %	26.12 (2.84)	11.85 (1.97)	18.80 (1.76)
	108 Months Event-Free(SE) %	23.20 (2.99)	NE(NE)	17.28 (1.83)
	120 Months Event-Free(SE) %	NE(NE)	NE(NE)	NE(NE)
Censored	Mean [c]	65.9	58.6	63.4
	SD	39.15	42.94	40.52
	Median [c]	88.1	85.1	87.6
	Min, Max	0.0, 115.0	0.0, 107.1	0.0, 115.0
Hazard rate ratio (HR)	HR (95% CI) [d]	0.541 (0.448,0.653)		
Log rank test	p-value [e]	< 0.001		

Table 20 : PFS according to IRC assessment, using EMA censoring rules – 7 July 2010 (ITT population) Study IFM 2005-02

		IFM 2005-02	
	Statistics	**Lenalidomide (N = 307)**	**Placebo (N = 307)**
Censored	n (%)	190 (61.9)	136 (44.3)
Progressed	n (%)	101 (32.9)	165 (53.7)
Died	n (%)	16 (5.2)	6 (2.0)
PFS time from randomization (months)	Median	40.1	22.8
	(95% CI)	(35.7, 42.4)	(20.7, 27.4)
	12 months event-free (SE) %	84.3 (2.1)	77.6 (2.5)
	24 months event-free (SE) %	72.0 (2.7)	47.6 (3.1)
	36 months event-free (SE) %	55.6 (3.6)	33.1 (3.5)
	48 months event-free (SE) %	34.6 (6.5)	18.3 (6.0)
Comparison between arms	HR (95% CI)	0.52 (0.41, 0.66)	
	Log-rank Test p-value	< 0.0000001	

Figure 8 : Hazard Ratios by Subgroup for the Comparison of Progression-free Survival – 1 March 2015- Study IFM 2005-02 (ITT Post-ASCT Population)



ASCT = autologous stem-cell transplant; CI = confidence interval; CR = complete response; DCEP = dexamethasone, cyclophosphamide, etoposide, and cisplatin; del 17p = deletion in chromosome 17p; HR = hazard ratio; ISS = International Staging System; ITT = intent-to-treat; Len = lenalidomide; PD = progressive disease; PR = partial response; SD = stable disease; t(4;14) = translocation involving chromosomes 4 and 14; VD = bortezomib and dexamethasone; VGPR = very good partial response.

[a] No. of events/no. of subjects.

Note: The dashed line represents the HR of the ITT population.

Table 21 : Subgroup Analyses of Progression-free Survival From Randomization Using EMA Censoring Rules – Study IFM 2005-02 – 1 March 2015 (ITT Post-ASCT Population)

	Lenalidomide (N = 307)		Placebo (N = 307)		Statistics		
IFM 2005-02 PFS Subgroup	N	Median PFS[a] (months)	N	Median PFS[a] (months)	p-value	HR[b]	95% CI
Age[c]							
< 60	220	45.1	210	23.9	< 0.001	0.53	0.43, 0.67
≥ 60	87	40.9	97	23.2	0.002	0.60	0.43, 0.84
Sex							
Male	169	44.4	181	22.6	< 0.001	0.49	0.38, 0.62
Female	138	44.2	126	26.2	0.003	0.65	0.49, 0.87
ISS Stage at diagnosis							
I	128	60.1	143	26.0	< 0.001	0.47	0.35, 0.62
II	104	40.1	107	20.5	0.002	0.62	0.46, 0.85
III	66	32.7	46	21.7	0.002	0.52	0.34, 0.79
β2M[d] at diagnosis							
≤ 3 mg/L	136	63.7	136	26.6	< 0.001	0.45	0.33, 0.60
> 3 mg/L	166	36.9	165	20.7	< 0.001	0.61	0.48, 0.78
Adverse cytogenetics at diagnosis							
Yes	41	31.8	24	24.5	0.755	0.91	0.52, 1.61
No	202	49.7	216	27.3	< 0.001	0.50	0.40, 0.63
Del 13[d]							
Negative	161	52.0	167	27.4	< 0.001	0.55	0.43,0.71
Positive	114	39.6	116	21.8	< 0.001	0.52	0.38,0.70
Prior DCEP							
Yes	80	39.2	74	22.3	< 0.001	0.48	0.33, 0.70
No	227	46.9	233	26.2	< 0.001	0.57	0.46, 0.71
Prior VD							
VD	140	49.7	135	26.2	< 0.001	0.52	0.39, 0.69
Other	167	40.8	172	22.4	< 0.001	0.57	0.45,0.74
ASCT							
1	243	46.9	243	23.9	< 0.001	0.54	0.44, 0.66
2	64	40.4	64	23.2	0.019	0.62	0.42, 0.93
Post-ASCT Response[d] (Investigator Assessment)							
CR/VGPR	189	51.0	176	26.6	< 0.001	0.60	0.46, 0.76
Not CR/VGPR	115	40.4	131	21.0	< 0.001	0.49	0.37, 0.65
Post-ASCT Response (Investigator Assessment)							
CR	49	62.6	41	50.6	0.841	0.95	0.55, 1.64
Not CR	255	43.0	266	22.6	< 0.001	0.49	0.40, 0.60

ASCT = autologous stem-cell transplant; β2M = β2 microglobulin; CI = confidence interval; CR = complete response; CSR = clinical study report; DCEP = dexamethasone, cyclosphosphamide, etoposide, cisplatin; EMA = European Medicines Agency; HR = hazard ratio; ISS = International Staging System; PFS = progression-free survival; VD = bortezomib and dexamethasone; VGPR = very good partial response.

[a] The median is based on Kaplan-Meier estimate.

[b] Based on a proportional hazards model comparing the hazard functions associated with treatment groups (lenalidomide:placebo).

[c] Age at randomization.

[d] Stratification factors.

Note: Subgroups of post-ASCT response are shown as per investigator assessment in the comparison of PFS since response to last ASCT per investigator assessment was a stratification factor.

Secondary efficacy endpoint: Overall Survival

Between the date of the interim analysis (4 September 2009) and the data cutoff date for this submission (1 March 2015), the rate of death events overall increased from 8.1% to 44.3%. As of the

1 March 2015 data cutoff date, the median OS follow-up time from randomization for all surviving subjects was 86.0 months.

Table 22 : Summary of Overall Survival From Randomization – Study IFM 2005-02 (ITT Post-ASCT Population)

IFM 2005-02 Endpoint / Data Cutoff Date	Statistics	Lenalidomide (N = 307)	Placebo (N = 307)
OS	OS events (% of N)	24 (7.8)	26 (8.5)
04 Sep 2009	Median (months) (95% CI)[b]	NE (NE, NE)	NE (NE, NE)
	HR (95% CI) p-value	0.95 (0.54, 1.65) 0.854	
OS	OS events (% of N)	128 (41.7)	144 (46.9)
01 Mar 2015	Median (months) (95% CI)[b]	NE (90.6, NE)	90.9 (81.0, NE)
	HR (95% CI) p-value	0.91 (0.72, 1.15) 0.423	

Figure 7 : Kaplan-Meier Plots of Overall Survival From Randomization – Study IFM 2005-02 (ITT Post-ASCT Population) Cut-off 1 March 2015

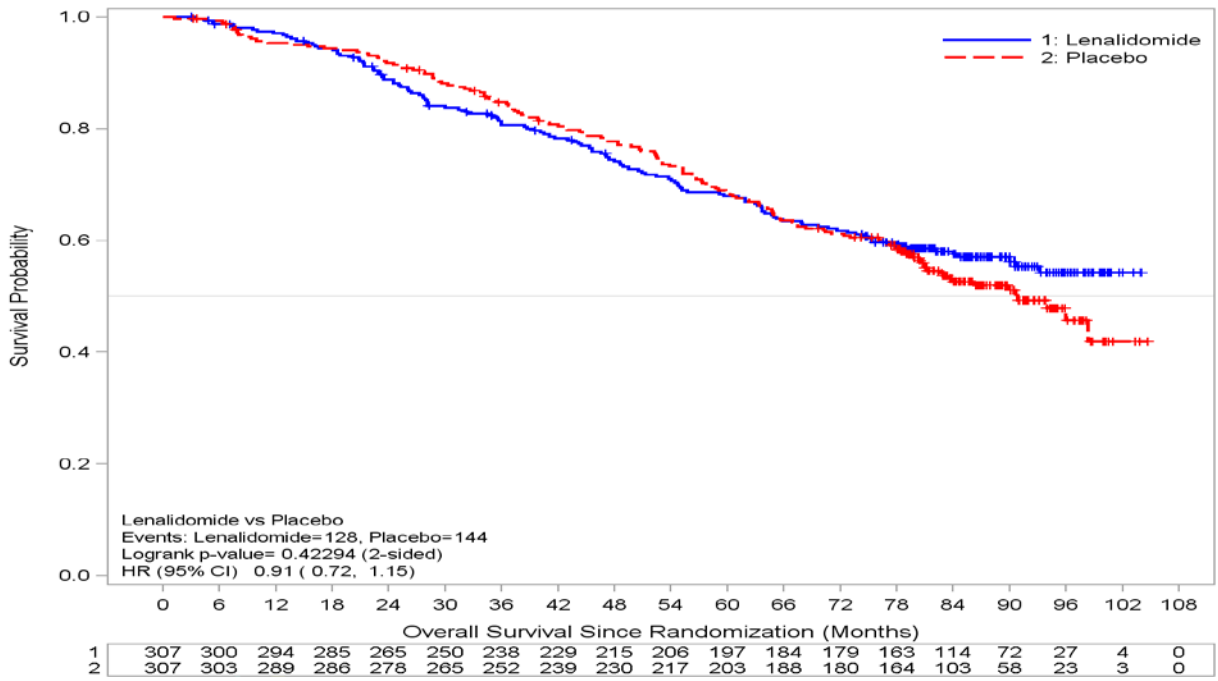


Table 22 : Summary of Overall Survival– Study IFM 2005-02 (ITT Post ASCT Population- Cut-off 1 February 2016)

	Statistics	Lenalidomide (N=307)	Placebo (N=307)	Overall (N=614)
Overall Survival	N	307	307	614
Censored	n (%)	164 (53.4)	147 (47.9)	311 (50.7)
Died	n (%)	143 (46.6)	160 (52.1)	303 (49.3)
Overall Survival Time (Months)	Median [a]	105.9	88.1	94.5
	95% CI [b]	(88.77, NE)	(80.66, 108.39)	(86.24, NE)
	6 Months Event-Free(SE) %	98.69 (0.65)	99.35 (0.46)	99.02 (0.40)
	12 Months Event-Free(SE) %	97.03 (0.97)	95.38 (1.21)	96.21 (0.78)
	18 Months Event-Free(SE) %	94.38 (1.32)	94.39 (1.32)	94.38 (0.94)
	24 Months Event-Free(SE) %	88.69 (1.83)	91.74 (1.58)	90.22 (1.21)
	30 Months Event-Free(SE) %	83.95 (2.12)	88.08 (1.87)	86.03 (1.41)
	36 Months Event-Free(SE) %	80.89 (2.28)	84.73 (2.07)	82.83 (1.54)
	48 Months Event-Free(SE) %	74.06 (2.55)	77.64 (2.41)	75.87 (1.75)
	60 Months Event-Free(SE) %	67.87 (2.72)	68.53 (2.69)	68.20 (1.91)
	72 Months Event-Free(SE) %	61.67 (2.84)	61.09 (2.83)	61.38 (2.00)
	84 Months Event-Free(SE) %	57.17 (2.89)	52.53 (2.90)	54.83 (2.05)
	96 Months Event-Free(SE) %	52.80 (2.96)	46.36 (2.98)	49.60 (2.10)
	108 Months Event-Free(SE) %	48.69 (3.32)	44.16 (3.10)	46.34 (2.30)
Censored	Mean [c]	91.6	91.9	91.8
	SD	24.01	21.80	22.95
	Median [c]	97.5	95.8	96.7
	Min, Max	3.0, 115.5	3.3, 115.5	3.0, 115.5
Hazard rate ratio (HR)	HR (95% CI) [d]	0.899 (0.717,1.127)		
Log rank test	p-value [e]	0.355		

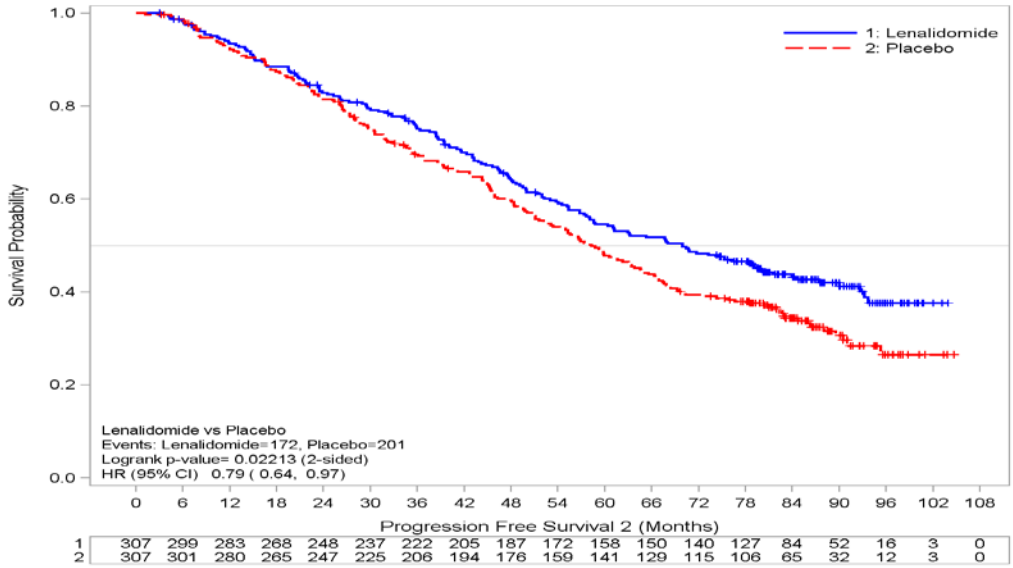
Exploratory efficacy endpoint: Progression-free Survival (PFS2)

Table 23 : Progression-free Survival 2 From Randomization Using EMA Censoring Rules – Study IFM 2005-02 – 1 Mar 2015 (ITT Post-ASCT Population)

	Statistic	IFM 2005-02	
		Lenalidomide (N = 307)	Placebo (N = 307)
2nd PD/start of 3rd line/died	n (%)	172 (56.0)	201 (65.5)
2nd PD	n (%)	130 (42.3)	166 (54.1)
Start of 3rd line	n (%)		
Died	n (%)	42 (13.7)	35 (11.4)
Censored	n (%)	135 (44.0)	106 (34.5)
PFS2 time from randomization (months)	Median[a]	70.0	58.4
	(95% CI)[b]	(58.1, 80.1)	(51.6, 64.9)
	36 months event-free (SE) %	75.4 (2.5)	69.6 (2.6)
	48 months event-free (SE) %	64.2 (2.8)	59.7 (2.8)
	60 months event-free (SE) %	54.5 (2.9)	47.8 (2.9)
	72 months event-free (SE) %	48.3 (2.9)	39.4 (2.8)
	84 months event-free (SE) %	43.2 (2.9)	34.3 (2.8)
	96 months event-free (SE) %	37.6 (3.4)	26.5 (3.5)
Comparison between arms	HR (95% CI)[c]	0.79 (0.64,0.97)	
	p-value	0.0221261	

[a] The median is based on Kaplan-Meier estimate.
[b] 95% confidence intervals about the median overall PFS2 time.
[c] Based on a proportional hazards model comparing the hazard functions associated with treatment arms (lenalidomide:placebo).

Figure 10 : Kaplan-Meier Plots of Progression-free Survival After Next-line Therapy (PFS2) – Study IFM 2005-02 – 1 March 2015 (ITT Post-ASCT Population)



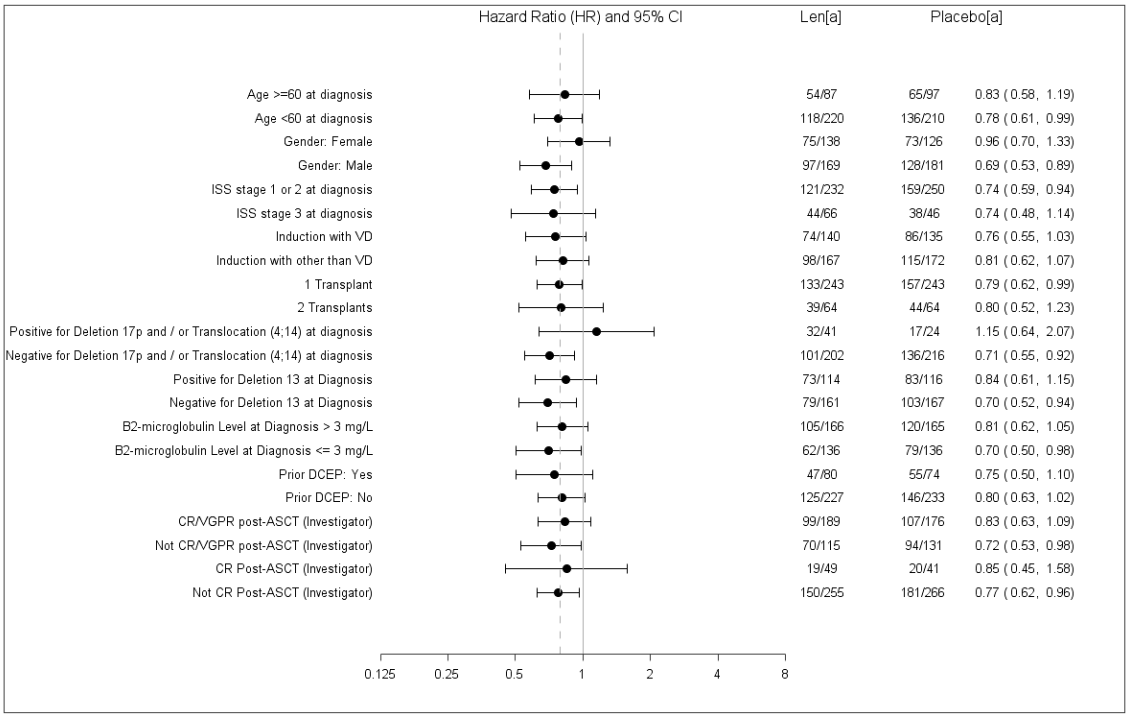
ASCT = autologous stem-cell transplant; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; PFS2 = progression-free survival after next-line therapy; vs =versus.
Note: The median is based on Kaplan-Meier estimate and 95% CIs about the median overall PFS2 time. Hazard ratio is based on a proportional hazards model comparing the hazard functions associated with treatment arms (lenalidomide:placebo).
Data cutoff date = 1 March 2015.

Table 24: Summary of Progression-free Survival on Next-line Therapy from Randomization (PFS2) Study IFM 2005-02 (Cutoff Date – 1 February 2016)

	Statistics	Lenalidomide (N=307)	Placebo (N=307)	Overall (N=614)
Progression Free Survival (PFS)	N	307	307	614
Censored	n (%)	116 (37.8)	91 (29.6)	207 (33.7)
Progression	n (%)	145 (47.2)	176 (57.3)	321 (52.3)
Died	n (%)	46 (15.0)	40 (13.0)	86 (14.0)
PFS Time (Months)	Median [a]	69.9	58.4	61.6
	95% CI [b]	(58.09, 80.03)	(51.12, 64.92)	(56.84, 67.91)
	6 Months Event-Free(SE) %	98.36 (0.73)	98.69 (0.65)	98.52 (0.49)
	12 Months Event-Free(SE) %	93.40 (1.43)	92.40 (1.52)	92.90 (1.04)
	18 Months Event-Free(SE) %	88.43 (1.84)	87.44 (1.91)	87.94 (1.32)
	24 Months Event-Free(SE) %	82.75 (2.18)	81.48 (2.23)	82.12 (1.56)
	30 Months Event-Free(SE) %	79.38 (2.33)	74.82 (2.50)	77.09 (1.71)
	36 Months Event-Free(SE) %	75.31 (2.49)	69.45 (2.66)	72.37 (1.83)
	48 Months Event-Free(SE) %	64.06 (2.79)	59.63 (2.84)	61.83 (1.99)
	60 Months Event-Free(SE) %	54.43 (2.90)	47.77 (2.90)	51.08 (2.05)
	72 Months Event-Free(SE) %	48.23 (2.92)	39.29 (2.84)	43.73 (2.04)
	84 Months Event-Free(SE) %	42.34 (2.89)	35.17 (2.78)	38.72 (2.01)
	96 Months Event-Free(SE) %	36.33 (2.87)	28.13 (2.72)	32.27 (1.98)
	108 Months Event-Free(SE) %	30.63 (3.31)	22.76 (3.39)	26.79 (2.34)
	120 Months Event-Free(SE) %	NE(NE)	NE(NE)	NE(NE)
Censored	Mean [c]	89.2	87.0	88.2
	SD	26.64	25.82	26.24
	Median [c]	97.4	94.0	95.3
	Min, Max	3.0, 115.0	3.3, 113.9	3.0, 115.0
Hazard rate ratio (HR)	HR (95% CI) [d]	0.802 (0.660,0.975)		
Log rank test	p-value [e]	0.026		

Subgroup Analyses of Progression-Free Survival after Next-line Therapy

Figure 8 : Hazard Ratios by Subgroup for the Comparison of PFS2 – Study IFM 2005-02 – 1 March 2015 (ITT Post-ASCT Population)



Ancillary analyses

N/A

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 25 : Summary of Efficacy for trial CALGB 100104

Title: A phase III randomized, double-blind study of maintenance therapy with lenalidomide or placebo following autologous stem cell transplantation for multiple myeloma			
Study identifier	CALGB 100104 / ECOG 100104		
Design	Phase 3, multicenter, randomized, double-blind, placebo-controlled, 2-arm parallel group study		
	Duration of main phase:		until disease progression or treatment intolerance
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Superiority		
Treatments groups	Placebo = Arm A		Placebo: days 1-28 of a 28 days cycle
	Lenalidomide = Arm B		Maintenance: Lenalidomide 10mg/day (days 1-28 of a 28 days cycle, to be increased at 15mg/day from C4 if good tolerance)
Endpoints and definitions	Primary endpoint	Progression-free survival (PFS)	Time from randomization to progression (PD or death from any cause after transplant) based on EMA censuring rules, by IRC assessment
	Secondary endpoint	Overall survival (OS)	Time from the date of randomization to the date of death
	Exploratory endpoint	Progression-free survival-2 PFS2	Time from randomisation to second objective disease progression, or death from any cause, whichever occurs first

Analysis description	**Primary Analysis with cut-off at unblinding (17 December 2009)**		
Analysis population and time point description	Intent to treat Post-ASCT		
Descriptive statistics and estimate variability	Treatment group	Lenalidomide	Placebo
	Number of subject	231	229
	PFS events (N)	46 (19.9 %)	98 (42.8%)
	PFS event rate (%)	31.3%	
	PFS Median (months)	33.9	19.0
	[95% CI]	[NE, NE]	[16.2, 25.6]
	OS events (N)	13 (5.6%)	24 (10.5%)
	OS Median (months)	NE	NE
	[95% CI]		
Effect estimate per comparison	Primary endpoint (Post-	Comparison groups	Lenalidomide vs Placebo
		HR	0.38

	transplantation PFS)	[95% CI]	[0.27, 0.54]
		P-value	<0.001
	Secondary endpoint (OS)	Comparison groups	Lenalidomide vs Placebo
		HR	0.52
		[95% CI]	[0.26, 1.01]
		P-value	0.050
Analysis description	**Adhoc Analysis with an updated cut-off at 1 March 2015**		
Analysis population and time point description	Intent to treat Post-ASCT		
Descriptive statistics and estimate variability	Treatment group	Lenalidomide	Placebo
	PFS events (N)	126 (54.5 %)	162 (70.7%)
	PFS event rate (%)	62.6%	
	PFS Median (months)	58.4	28.9
	[95% CI]	[42.7, 82.0]	[21.0, 35.4]
	OS events (N)	72 (31.2%)	109 (47.6%)
	OS event rate (%)	39.3%	
	OS Median (months)	NE	79.0
	[95% CI]	[NE, NE]	[70.2, 88.4]
	PFS2 events (N)	114	142
	PFS2 Median (months)	78.3	52.8
	[95% CI]	[63.0, 98.1]	[40.7, 62.7]
Effect estimate per comparison	Primary endpoint (Post-transplantation PFS)	Comparison groups	Lenalidomide vs Placebo
		HR	0.58
		[95% CI]	[0.46, 0.73]
		P-value	<0.001
	Secondary endpoint (OS)	Comparison groups	Lenalidomide vs Placebo
		HR	0.57
		[95% CI]	[0.42, 0.76]
		P-value	<0.001
	Exploratory endpoint (PFS2)	Comparison groups	Lenalidomide vs Placebo
		HR	0.64
		[95% CI]	[0.50, 0.82]
		P-value	<0.001
Analysis description	**Adhoc Analysis with an updated cut-off at 1 February 2016**		
Analysis population and time point description	Intent to treat Post-ASCT		
Descriptive statistics and estimate variability	Treatment group	Lenalidomide	Placebo
	PFS Median (months)	56.9	29.4
	[95% CI]	[41.9, 71.7]	[20.7, 35.5]
	OS Median (months)	111.0	84.2
	[95% CI]	[101.84, NE]	[70.96, 102.69]

	PFS2 Median (months)	80.2	52.8
	[95% CI]	[63.3, 101.8]	[41.3, 64.0]
Effect estimate per comparison	Primary endpoint (Post-transplantation PFS)	Comparison groups	Lenalidomide vs Placebo
		HR	0.61
		[95% CI]	[0.48, 0.76]
		P-value	<0.001
	Secondary endpoint (OS)	Comparison groups	Lenalidomide vs Placebo
		HR	0.61
		[95% CI]	[0.46, 0.81]
		P-value	<0.001
	Exploratory endpoint (PFS2)	Comparison groups	Lenalidomide vs Placebo
		HR	0.61
		[95% CI]	[0.48, 0.78]
		P-value	<0.001

Table 26 : Summary of Efficacy for trial IFM 2005-02

Title: A phase III, multicenter, randomised, double-blind, placebo-controlled, 2-arm parallel study investigating lenalidomide therapy following ASCT for the treatment of multiple myeloma			
Study identifier	Protocol 04.004.01 / IFM 2005-02		
Design	Phase III, multicentre, randomised, double-bind, placebo-controlled 2-arm parallel study		
	Duration of main phase:	Consolidation phase (2 cycles of 28 days) followed by maintenance phase until relapse	
	Duration of Run-in phase:	not applicable	
	Duration of Extension phase:	not applicable	
Hypothesis	Superiority		
Treatments groups	Placebo = Arm A		Consolidation: lenalidomide 25 mg/day (days 1-21 of a 28-day cycle, 2 cycles) Maintenance: placebo (days 1-28 of a 28-day cycle, until PD)
	Lenalidomide = Arm B		Consolidation: lenalidomide 25 mg/day (days 1-21 of a 28-day cycle, 2 cycles) Maintenance: Lenalidomide 10 mg/day, increased to 15 mg/day at C4 if good tolerance (days 1-28 of a 28-day cycle, until PD)
Endpoints and definitions	Primary endpoint	Post-transplantation progression-free survival (PFS)	Time from the date of randomisation to the date of progression or death (whatever the cause), based on EMA censuring rules and by IRC assessment

	Secondary endpoint	Overall survival (OS)	Time from the date of randomisation to the date of death
	Exploratory endpoint	Progression-free Survival after next-line therapy (PFS2)	Time from randomization to second disease progression or death

Analysis description	**Primary Analysis with cut-off at unblinding (7 July 2010)**		
Analysis population and time point description	Intent to treat Post-ASCT		
Descriptive statistics and estimate variability	Treatment group	Lenalidomide	Placebo
	Number of subject	307	307
	PFS events (N)	117 (38.1 %)	171 (55.7%)
	PFS event rate (%)	46.9%	
	PFS Median (months)	40.1	22.8
	[95% CI]	[35.7, 42.4]	[20.7, 27.4]
	OS event rate (%)	15.3%	
	OS Median (months)	*Not provided*	*Not provided*
	[95% CI]		
Effect estimate per comparison	Primary endpoint (Post-transplantation PFS)	Comparison groups	Lenalidomide vs Placebo
		HR	0.52
		[95% CI]	[0.41, 0.66]
		P-value	<0.001
Analysis description	**Ad-hoc Analysis with an updated cut-off at 1 March 2015**		
Analysis population and time point description	Intent to treat Post-ASCT		
	PFS events (N)	209 (68.1 %)	255 (83.1%)
	PFS event rate (%)	75.6%	
	PFS Median (months)	44.4	23.8
	[95% CI]	[39.6, 52.0]	[21.2, 27.3]
	OS event rate (%)	44.3%	
	OS Median (months)	NE	90.9
	[95% CI]	[90.6, NE]	[81.0, NE]
	PFS2 Median (months)	70.0	58.4
	[95% CI]	[58.1, 80.1]	[51.6, 64.9]
Effect estimate per comparison	Primary endpoint (Post-transplantation PFS)	Comparison groups	Lenalidomide vs Placebo
		HR	0.55
		[95% CI]	[0.46, 0.66]
		P-value	<0.001

	Secondary endpoint (OS)	Comparison groups	Lenalidomide vs Placebo
		HR	0.91
		[95% CI]	[0.72, 1.15]
		P-value	0.423
	PFS2	Comparison groups	Lenalidomide vs Placebo
		HR	0.79
		[95% CI]	[0.64, 0.97]
		P-value	0.022
Analysis description	**Adhoc Analysis with an updated cut-off at 1 February 2016**		
Analysis population and time point description	Intent to treat Post-ASCT		
Descriptive statistics and estimate variability	Treatment group	Lenalidomide	Placebo
	PFS Median (months)	44.4	23.8
	[95% CI]	[39.6, 52]	[21.2, 27.3]
	OS Median (months)	105.9	88.1
	[95% CI]	[88.8, NE]	[80.7, 108.4]
	PFS2 Median (months)	69.9	58.4
	[95% CI]	[58.1, 80.0]	[51.1, 65.0]
Effect estimate per comparison	Primary endpoint (Post-transplantation PFS)	Comparison groups	Lenalidomide vs Placebo
		HR	0.57
		[95% CI]	[0.47, 0.68]
		P-value	<0.001
	Secondary endpoint (OS)	Comparison groups	Lenalidomide vs Placebo
		HR	0.90
		[95% CI]	[0.72, 1.13]
		P-value	0.355
	Exploratory endpoint (PFS2)	Comparison groups	Lenalidomide vs Placebo
		HR	0.80
		[95% CI]	[0.66, 0.98]
		P-value	0.026

Analysis performed across trials (pooled analyses and meta-analysis)

Table 27 : Study Conduct – Studies CALGB 100104, IFM 2005-02, and GIMEMA

Study Design/Conduct	CALGB 100104	IFM 2005-02	GIMEMA
Enrollment Period[a]	Aug 2005 to Nov 2009	Jun 2006 to Aug 2008	Nov 2007 to Jul 2009
Study Blinding	Double blind	Double blind	Open label
Randomization (Timing Relative to the Start of Maintenance Treatment)	Randomized (1:1) post-ASCT, with lenalidomide maintenance or placebo started immediately after randomization	Randomized (1:1) post-ASCT, with 2 cycles of lenalidomide consolidation received by both treatment arms before either lenalidomide maintenance or placebo (Amendment 2 after enrollment of 32 subjects)	2 × 2 randomization at enrollment, before induction Randomized (1:1:1:1) to A1: MPR/no maintenance A2: MPR/lenalidomide B1: MEL200 (ASCT)/ no maintenance B2: MEL200 (ASCT)/ lenalidomide Only Arms B1 and B2 were included in the meta-analysis of OS (lenalidomide maintenance in the post-ASCT setting)
Post-ASCT Consolidation		Consolidation (lenalidomide, 2 cycles, 25 mg/day for 21/28 days) added for both study arms after enrollment of 32 subjects	
Stratification Factors	1. β2M at registration 2. Prior therapy with thalidomide 3. Prior therapy with lenalidomide	1. β2M at diagnosis 2. Presence of del 13 at diagnosis 3. Response to last ASCT[b]	1. ISS stage (at diagnosis) 2. Age
Interim Analysis/ Early Unblinding Due to DSMB Recommendation	Study unblinded on 17 Dec 2009 following an interim analysis crossing the prespecified superiority boundary for PFS (decision based on 28% of the expected ~ 309 PFS events)	Study unblinded on 07 Jul 2010 following an interim analysis crossing the prespecified superiority boundary for PFS (decision based on 60% of the expected 300 PFS events)	Interim analysis did not meet prespecified stopping rules
Crossover Before PD	Crossover before PD: 76 subjects randomized to placebo crossed over to receive lenalidomide maintenance treatment before PD	No crossover before PD	
Limited Treatment Duration with Lenalidomide Maintenance		119 subjects in the lenalidomide arm stopped maintenance in January 2011 (Amendment 9)	
Study Status/ Follow-up	FPI: Aug 2005 LPI: Nov 2009 Treatment ongoing for subjects without PD Subjects who have discontinued treatment continue to be followed for progression, second-line therapy, survival, and SPMs	FPI: Jun 2006 LPI: Aug 2008 No subject on treatment All subjects continue to be followed for progression, second-line therapy, survival, and SPMs	FPI: Nov 2007 LPI: Jul 2009 Treatment ongoing for subjects without PD Subjects who have discontinued treatment continue to be followed for progression, second-line therapy, survival, and SPMs

Clinical studies in special populations

N/A

Supportive study

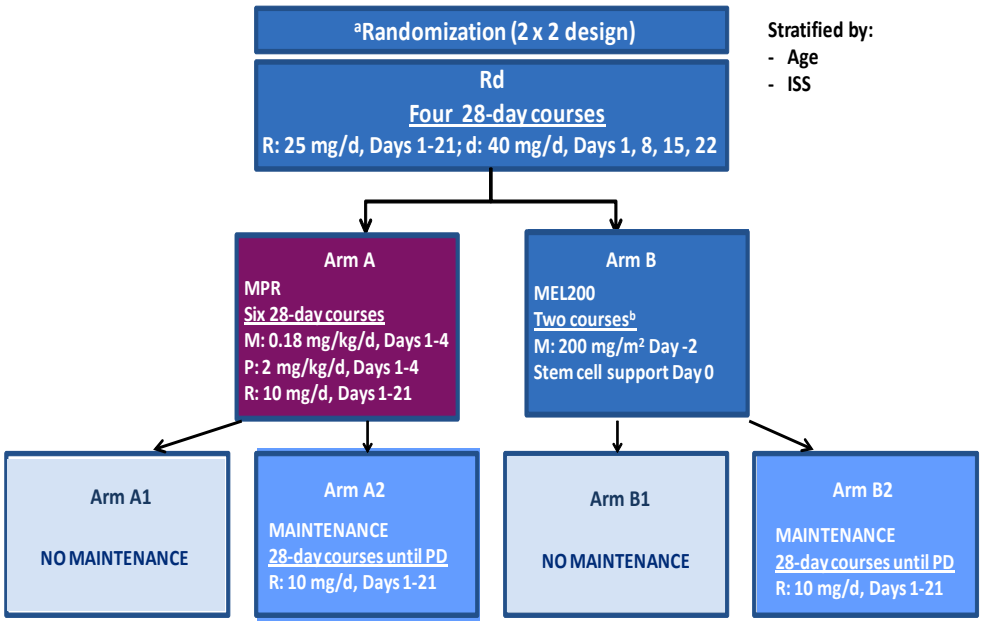
GINEMA study

Study GIMEMA was a Phase 3, multicenter, open-label, 2 × 2 factorial, controlled study conducted by Fondazione Neoplasie Sangue Onlus (FO.NE.SA Onlus), an independent Italian cooperative group, in the first-line setting of transplant-eligible NDMM. The primary objective of the study was to determine (after induction treatment with a standard lenalidomide-dexamethasone regimen) the efficacy and safety of MPR (Melphalan-Prednisone-Lenalidomide) versus High Dose Melphalan (MEL200: melphalan 200 mg/m^2) followed by ASCT in NDMM subjects in extending PFS, the primary endpoint.

Overall, subjects were randomized (1:1:1:1 ratio) at enrollment and prior to induction into 1 of 4 groups:

ASCT *versus* intensified induction: Arm A (MPR) or Arm B (2 courses of HDM [MEL200] and ASCT unless at least VGPR was achieved after 1 course).

Maintenance: Arms A1 (no maintenance) and A2 (maintenance with lenalidomide), Arms B1 (no maintenance) and B2 (maintenance with lenalidomide).



[a] MPR versus MEL200 (ASCT); R maintenance versus no maintenance; + antithrombotic substudy: aspirin versus low molecular weight heparin.
[b] One course of MEL200 (ASCT) if subject achieved VGPR after Cycle 1.

Prerandomization stratification factors included ISS disease stage (I or II versus III) and age (≤ 60 versus > 60 years). Maintenance therapy was initiated within 2 to 3 months following completion of intensified induction or ASCT. Subjects received maintenance treatment with lenalidomide at a dosage of 10 mg/day or no maintenance treatment. Subjects continued to receive maintenance treatment until PD or development of unacceptable adverse effects.

The primary comparison was between HDM/ASCT and MPR (Arms B and A, respectively). A total of 402 subjects were registered in the study between November 2007 and July 2009 at 62 centers in Italy and Israel . Of the 402 subjects, 399 entered the common induction/mobilization phase (4 courses of Rd), and 273 remained eligible for random assignment to receive intensified induction with HDM/ASCT or MPR (Arms B versus A). At the end of intensified induction, 251 subjects also were eligible for the randomized comparison between maintenance and no maintenance (Arms 2 versus 1), but only 231 subjects received treatment/no treatment.

Efficacy results (Data cut-off Date: 30 April 2013)

The median duration of follow-up from the time of enrollment was 51.2 months.

Table 28 : **Progression-Free Survival and Overall Survival – GIMEMA (ITT Maintenance-phase Population)**

GIMEMA Endpoint	**Statistics**	**Lenalidomide (Arms A2 + B2) (N = 126)**	**Placebo (Arms A1 + B1) (N = 125)**
PFS from start of maintenance	Median (months)	41.9	21.6
	HR (95% CI) p-value	0.47 (0.33, 0.65) < 0.001	
OS from start of maintenance	HR (95% CI) p-value	0.64 (0.36, 1.15) 0.14	

CI = confidence interval; HR = hazard ratio; HR = hazard ratio; ITT = intent-to-treat; OS = overall survival; PFS = progression-free survival.
Note: The maintenance-phase population comprised all subjects who were eligible to receive lenalidomide maintenance therapy (Arms A2 and B2) or no maintenance therapy (Arms A1 and B1); the starting time of the analyses was the date of clinical evaluation after the consolidation phase.
Data cutoff date = 30 Apr 2013.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical data package for the new indication consists of 2 pivotal studies: CALGB 100104 and IFM 2005-02. The design of both studies had some substantial differences in term of patient management. IFM 2005-02 study was performed in an EU population and included a consolidation and a maintenance phase while CALGB 100104 was performed exclusively in US patients with only a maintenance phase. Consolidation is not a standard of care approach to myeloma therapy. There is no approved drug in this particular setting. The administration of a higher dose of lenalidomide over a few weeks to achieve further reduction in myeloma tumour burden is debatable. Based on this, the indication was restricted to maintenance treatment of adult patients with newly diagnosed multiple myeloma who have

undergone autologous stem cell transplantation

In study CALGB 100104, the DSMB, after reviewing the interim analysis results, requested an updated analysis. The updated analysis was reviewed by the DSMB and included an estimated 28% of the expected number of events at a data cut-off date of 9 September 2009. The DSMB found that the study demonstrated a significantly longer PFS following ASCT for those subjects receiving lenalidomide than those receiving placebo. This led to the release of the results on 17 December 2009. Treatment assignments were unblinded on 17 December 2009 and the randomization was stopped.

In IFM 2005-02 study treatment assignments were unblinded on 7 July 2010 and the randomization was stopped. Those subjects who were unblinded and determined to be on lenalidomide, continued on maintenance therapy with lenalidomide until progression as planned. For subjects who were receiving placebo at the time of unblinding, it was recommended by the DSMB that the placebo therapy be stopped (cross over before PD not recommended).

After observing an imbalance of SPMs in the lenalidomide arm, a safety measure was initiated on 26 January 2011, which provided for the immediate treatment discontinuation of patients in the lenalidomide arm who were still receiving study maintenance treatment at that time.

Efficacy data and additional analyses

CALGB 100104

At the time of unblinding, CALGB 100104 has provided convincing evidence of efficacy of lenalidomide with a clinically meaningful and statistically significant improvement in the primary endpoint PFS, compared to placebo. The risk of disease progression or death was reduced by 62% (HR=0.38, 95% CI [0.27 to 0.54]; log-rank p value < 0.001).

The finding of interim analysis was supported by the updated analyses: at the March 2015 data cut-off, the risk of disease progression or death was reduced by 42% (HR=0.58; 95% CI [0.46 to 0.73]; log-rank p value < 0.001); at the February 2016 data cut-off, the risk of disease progression or death was reduced by 39% (HR= 0.61, 95% CI [0.48 to 0.76]; log-rank p value < 0.001).

Overall survival data was still immature at the time of the interim analysis. In the updated analysis (1 March 2015 data cut-off date) the median OS was not reached in the lenalidomide arm however the HR remained statistically significant, in favour of the lenalidomide arm (HR=0.57; 95% CI [0.42 to 0.76]; log-rank p value < 0.001). In the second updated analysis (1 February 2016 data cut-off date) the median OS for lenalidomide treatment was 111.0 months compared with 84.2 months for placebo treatment and this survival advantage of 26.8 months was statistically significant (HR=0.61; 95% CI [0.46 to 0.81]; log-rank p value < 0.001).

PFS2 analysis demonstrated an HR of 0.61 (95% CI [0.46 to 0.81] log-rank p value < 0.001) in favour of lenalidomide arm, confirming the benefit of the maintenance therapy.

Study IFM 2005-002

The primary endpoint, PFS, showed a highly significant HR of 0.45 (0.34 to 0.60, log-rank p value < 0.001). The median PFS was 23 months in the placebo arm while not reached in the lenalidomide arm. The updated analyses support the interim analysis: at the March 2015 data cut-off, the risk of disease progression or death was reduced by 45% (HR=0.55; 95% CI [0.46 to 0.66]; log-rank p value < 0.001); at the February 2016 data cut-off, the risk of disease progression or death was reduced by 43% (HR= 0.57, 95% CI [0.47 to 0.68]; log-rank p value < 0.001).

Additional analysis of PFS was conducted in the ITT population restricted to 573 patients who received maintenance treatment, i.e., excluding patients who entered the consolidation phase of the study but were discontinued from treatment before beginning maintenance treatment. According to this analysis in maintenance population (cut-off date of 1 March 2015), the estimated PFS HR was 0.54 (95% CI: 0.44 to 0.65). Median PFS was 24.1 months (95% CI: 21.3 to 27.5) in the placebo arm and 46.9 months (95% CI: 40.8 to 55.1) in the lenalidomide arm.

Overall survival was not mature at the time of the interim analysis (4 September 2009). Based on the updated data set (1 February 2016) the HR remained not statistically significant (p=0.355). However this was not associated with any negative trend.

The PFS2 analysis demonstrated an HR of 0.80 (95% CI, 0.66 to 0.98) in favor of lenalidomide maintenance, resulting in an improvement of 11.5 months in the KM median for PFS2 (69.9 versus 58.4 months in the lenalidomide and placebo arms, respectively).

Study GIMEMA

In study GIMEMA, the subgroup analysis showed a significantly longer PFS following ASCT for those subjects receiving lenalidomide than those receiving placebo (HR= 0.42; 95% CI [0.24 to 0.73]). However, the HR of OS was not statistically significant (HR = 0.62; 95% CI [0.21-1.59]).

Efficacy results, although potentially in favour of Revlimid, have to be interpreted with caution since the study was not powered for any comparison between maintenance and no maintenance (Arms B2 and B1, respectively). Therefore, it is believed that no significant conclusion could be drawn from such data.

2.4.4. Conclusions on the clinical efficacy

Study CALGB 100104 has provided convincing evidence of clinical efficacy of lenalidomide in terms of the primary endpoint PFS, compared to placebo in patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation. This was supported by a statistical significant survival benefit in favour of lenalidomide.

In study IFM 2005-002, lenalidomide maintenance resulted in a clinically meaningful and statistically significant improvement in the primary endpoint of PFS and secondary endpoint PFS2 compared to placebo.

2.5. Clinical safety

Introduction

The evaluation of safety in maintenance therapy post ASCT in TE NDMM patients was primarily based on data from studies CALGB 100104 (“CALGB” study) and IFM 2005-02 (“IFM” study), which started in 2005 and 2006, respectively. In both CALGB and IFM studies, TE NDMM subjects received local standard of induction and HDM/ASCT (High Dose Melphalan/ Autologous stem-cell transplantation) therapy followed by protocol-specified maintenance therapy until disease progression.

In addition, results were supported with data taken from MM-15 Study, in non-transplant eligible patients.

The analyses of AEs generally focused on TEAEs during maintenance treatment, defined as any AEs that occurred/worsened on or after the first dose of maintenance study drug and within 30 days after the last dose (as defined in the CALGB and IFM).

Patient exposure

In CALGB and IFM studies, the maintenance safety population included all subjects who received at least 1 dose of Lenalidomide or placebo in the maintenance phase.

Placebo-controlled studies	Population	Number of subjects	Patients in lenalidomide arm	Patients in placebo arm	Patients in lenalidomide arm with long term safety data
CALGB 100104	29.0 - 71.0 years	445	224	221	224
IFM 2005-02	21.9-67.0 years	608	306	302	293

CALGB: Review of the first planned interim analysis by the DSMB in June 2009 and then with a data cut-off on 09 Sep 2009 led to early unblinding of the results on 17 Dec 2009. Based on their review of data, the DSMB noted that the analysis demonstrated a significantly longer time to progression or death following ASCT (ie, the primary endpoint) in subjects in the lenalidomide arm versus placebo. After unblinding, this study continued, with ongoing subjects in the placebo arm (who had not yet progressed) being given the option to crossover to lenalidomide maintenance therapy. Ongoing subjects in the Lenalidomide arm could continue their maintenance treatment.

Upon study unblinding (17 Dec 2009), 121 subjects in the lenalidomide arm continued protocol maintenance therapy and 76 subjects in the placebo arm who had not yet progressed crossed over to receive lenalidomide maintenance treatment. To be noted, as of the 01 Mar 2015 data cutoff date, 48 subjects in the lenalidomide arm and 19 subjects in the placebo arm (who had crossed over to receive lenalidomide) are still receiving maintenance therapy.

In placebo subjects, TEAEs recorded after crossover to lenalidomide were excluded from the SCS analyses, except second primary malignancies, which are presented regardless of crossover.

In the CALGB study, the initial planned maintenance dose of 10mg lenalidomide QD was to be increased to 15 mg QD (3 capsules per day) according to study design after 3 months, provided the absolute neutrophil count (ANC) was $\geqslant$ 1000/mcL and platelet count $\geqslant$ 75,000/mcL and all non-hematologic toxicity was $\leqslant$ Grade 1 . The placebo arm followed the same dosing schedule as the R10 arm, including the potential increase to 3 capsules daily.

In the IFM study, patients who met all eligibility criteria were randomized (1:1) to 1 of 2 treatment arms but they all first received 2 cycles of consolidation treatment with lenalidomide 25 mg/day for 21 consecutive days of a 28-day cycle, followed by single-agent lenalidomide 10 mg/day 28/28 days or placebo maintenance therapy. TEAEs recorded during the 2 cycles of consolidation lenalidomide therapy prior to maintenance (amendment 2) were excluded from the SCS analyses in both R10 and placebo subjects, with the exception of SPM analyses.

In the IFM study, if there were no signs of toxicity, the initial maintenance dose of 10 mg lenalidomide QD was to be increased to 15 mg QD according to study design after 3 months of maintenance. The placebo arm followed the same dosing schedule as the R10 arm, including the potential to increase the number of capsules.

Treatment duration and extent of exposure for studies CALGB 100104 and IFM 2005-02 are presented in Table 29.

Table 29 : Treatment Duration and extent of exposure (CALGB 100104 and IFM 2005-02)

	Trial and Study Arm (Lenalidomide Starting QD Dose)			
	CALGB 100104		**IFM 2005-02**	
	R10 (10 mg)[a]	**Placebo[b]**	**R10[c] (10 mg)[a]**	**Placebo[c]**
Treatment intent / schedule (days)	**MNT (28/28)**	**MNT (28/28)**	**MNT (28/28)**	**MNT (28/28)**
Variable	**(N = 224)**	**(N = 221)**	**(N = 293)**	**(N = 280)**
Treatment duration (weeks)				
Mean	131.6	57.3	104.6	85.6
SD	110.59	41.93	63.14	48.03
Median	110.3	47.6	113.6	88.6
Min, Max	1.4, 467.6	1.7, 220.6	0.6, 240.0	1.0, 212.3
Treatment duration (months)				
Mean	30.3	13.2	24.0	19.7
SD	25.43	9.64	14.52	11.05
Median	25.4	10.9	26.1	20.4
Min, Max	0.3, 107.5	0.4, 50.7	0.1, 55.2	0.2, 48.8
Treatment duration				
n (%) ≥ 1 year Tx	150 (67.0)	95 (43.0)	212 (72.4)	200 (71.4)
n (%) ≥ 2 years Tx	116 (51.8)	32 (14.5)	159 (54.3)	99 (35.4)
n (%) ≥ 3 years Tx	82 (36.6)	6 (2.7)	71 (24.2)	23 (8.2)
n (%) ≥ 4 years Tx	54 (24.1)	1 (0.5)	4 (1.4)	2 (0.7)
Person-years of exposure	565.06	242.70	587.17	459.47

21/28 = Days 1 to 21 of 28-day cycles; 28/28 = Days 1 to 28 of 28-day cycles; IND = induction; M = melphalan; Max = maximum; Min = minimum; MNT = maintenance; P = prednisone; QD = once daily; R = lenalidomide; SD = standard deviation; Tx = treatment.

[a] The starting lenalidomide maintenance dose (R 10 mg QD 28/28) could be raised to 15 mg QD (28/28), according to the study design.

[b] In Study CALGB 100104, data were excluded for placebo subjects crossing over to lenalidomide after the unblinding of the study.

[c] In Study IFM 2005-02, data were excluded from all subjects for the 2 cycles of lenalidomide consolidation (R 25 mg QD 21/28).

[d] In Study MM-015, the planned induction treatment for Arm MPR+R was up to nine, 28-day cycles of 0.18 mg/kg melphalan + 2 mg/kg prednisone oral QD (on Days 1-4) with lenalidomide 10 mg oral QD (on Days 1-21).

Data cutoff: 01 Mar 2015 for CALGB and IFM studies; 30 Apr 2013 for Study MM-015

Demographics

Table 30 : Demographics and Subject Characteristics (CALGB 100104 and IFM 2005-02)

		Trial and Study Arm (Lenalidomide Starting QD Dose)			
		CALGB 100104		IFM 2005-02	
		R10(10 mg)[a]	Placebo[b]	R10[c](10 mg)[a]	Placebo[c]
Treatment intent / schedule (days)		MNT (28/28)	MNT (28/28)	MNT (28/28)	MNT (28/28)
Variable	**Statistic**	**(N = 224)**	**(N = 221)**	**(N = 293)**	**(N = 280)**
Age (years)	Mean	57.4	57.1	55.4	55.3
	SD	8.06	7.58	7.06	7.19
	Median	58.0	58.0	56.7	57.2
	Minimum, Maximum	29.0, 71.0	39.0, 71.0	21.9, 67.0	31.7, 66.3
Age category 1 (years), n (%)	< 60	126 (56.3)	128 (57.9)	209 (71.3)	192 (68.6)
	≥ 60	98 (43.8)	93 (42.1)	84 (28.7)	88 (31.4)
Age category 2 (years), n (%)	< 65	176 (78.6)	180 (81.4)	284 (96.9)	272 (97.1)
	≥ 65	48 (21.4)	41 (18.6)	9 (3.1)	8 (2.9)
Sex, n (%)	Male	117 (52.2)	125 (56.6)	164 (56.0)	163 (58.2)
	Female	107 (47.8)	96 (43.4)	129 (44.0)	117 (41.8)
Race, n (%)	White or Caucasian	169 (75.4)	167 (75.6)	NA	NA
	Black or African American	39 (17.4)	41 (18.6)	NA	NA
	Asian	2 (0.9)	1 (0.5)	NA	NA
	Other	0	2 (0.9)	NA	NA
	Missing	14 (6.3)	10 (4.5)	NA	NA
ISS disease stage at diagnosis, n (%)	I or II	117 (52.2)	126 (57.0)	221 (75.4)	228 (81.4)
	III	37 (16.5)	34 (15.4)	64 (21.8)	42 (15.0)
	Missing	70 (31.3)	61 (27.6)	8 (2.7)	10 (3.6)

		Trial and Study Arm (Lenalidomide Starting QD Dose)			
		CALGB 100104		IFM 2005-02	
		R10(10 mg)[a]	Placebo[b]	R10[c](10 mg)[a]	Placebo[c]
Treatment intent / schedule (days)		MNT (28/28)	MNT (28/28)	MNT (28/28)	MNT (28/28)
Variable	**Statistic**	**(N = 224)**	**(N = 221)**	**(N = 293)**	**(N = 280)**
Creatinine clearance post-ASCT or post-induction for MM-015, n (%)	< 50 mL/min	22 (9.8)	14 (6.3)	9 (3.1)	8 (2.9)
	< 30	3 (1.3)	0	0	1 (0.4)
	≥ 30 to < 50	19 (8.5)	14 (6.3)	9 (3.1)	7 (2.5)
	≥ 50 mL/min	195 (87.1)	198 (89.6)	173 (59.0)	185 (66.1)
	Missing	7 (3.1)	9 (4.1)	111 (37.9)	87 (31.1)
Time from Transplant to Maintenance (months)	Mean	3.6	3.6	5.9	6.0
	SD	0.24	0.28	1.44	1.42
	Median	3.5	3.5	5.8	5.8
	Minimum, Maximum	3.0, 5.0	2.7, 5.4	1.8, 10.7	2.2, 10.7

28/28 = Days 1 to 28 of 28-day cycles; IND = induction; ISS = International Staging System; M = melphalan; Max = maximum; Min = minimum; MNT = maintenance; NA = not available; P = prednisone; QD = once daily; R = lenalidomide; SD = standard deviation.

[a] The starting lenalidomide maintenance dose (R 10 mg QD 28/28) could be raised to 15 mg QD (28/28), according to the study design; [b] In Study CALGB 100104, data were excluded for placebo subjects crossing over to lenalidomide after the unblinding of the study; [c] In Study IFM 2005-02, data were excluded from all subjects for the 2 cycles of lenalidomide consolidation; [d] In Study MM-015, the planned induction treatment for Arm MPR+R was up to nine, 28-day cycles of 0.18 mg/kg M + 2 mg/kg P oral QD (on Days 1-4) with R 10 mg oral QD (on Days 1-21).

Adverse events

Table 31: Overview of TEAEs by trial and study arm: within study and interstudy comparisons for CALGB 100104 and IFM 2005 02 Maintenance Pooled and Non-pooled (Safety Population)

	Trial and Study Arm (Lenalidomide Starting QD Dose)					
	CALGB 100104		IFM 2005-02		CALGB 100104 + IFM 2005-02	
	R10 (10 mg)[a]	Placebo[b]	R10[c] (10 mg)[a]	Placebo[c]	R10 Pool[c] (10 mg)[a]	Placebo Pool[b,c]
Number (%) of Subjects With ≥ 1:	**(N = 224) n (%)**	**(N= 221) n (%)**	**(N = 293) n (%)**	**(N= 280) n (%)**	**(N= 517) n (%)**	**(N= 501) n (%)**
TEAE	215 (96.0)	188 (85.1)	291 (99.3)	272 (97.1)	NA[d]	NA[d]
Grade 3 or 4 TEAE	178 (79.5)	122 (55.2)	220 (75.1)	90 (32.1)	398 (77.0)	212 (42.3)
Grade 5 TEAEs	3 (1.3)	4 (1.8)	7 (2.4)	2 (0.7)	10 (1.9)	6 (1.2)
Treatment-emergent SAE[e]	63 (28.1)	27 (12.2)	131 (44.7)	64 (22.9)	194 (37.5)	91 (18.2)
TEAEs leading to discontinuation	63 (28.1)	6 (2.7)	81 (27.6)	28 (10.0)	144 (27.9)	34 (6.8)

21/28 = Days 1 to 21 of 28-day cycles; 28/28 = Days 1 to 28 of 28-day cycles; AdEERS = Adverse Event Expedited Reporting System; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; NA = not applicable; QD = once daily; R = lenalidomide; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] The starting lenalidomide maintenance dose (R 10 mg QD 28/28) could be raised to 15 mg QD (28/28), according to the study design.

[b] In Study CALGB 100104, for placebo subjects, only AEs up to crossing over to lenalidomide are included.

[c] In Study IFM 2005-02, data were excluded from all subjects for the 2 cycles of lenalidomide consolidation (R 25 mg QD 21/28).

[d] Due to differences in safety data collection methods between CALGB and IFM, overall TEAEs were not pooled for analysis.

[e] For Study CALGB 100104, SAEs refer to AEs from AdEERS.

Note:. A subject with multiple occurrences of a TEAE is counted only once in that TEAE category. Severity is assessed according to CTCAE Version 3.0 or most current version.

Data cutoff: 1 March 2015

Table 32: TEAEs by System Organ Class Reported for at Least 2% of Subjects in Any Treatment Arm by Trial and Study Arm: Within Study and Interstudy Comparisons for CALGB 100104 and IFM 2005-02 Maintenance (Safety Population)

System Organ Class	Trial and Study Arm (Lenalidomide Starting QD Dose)			
	CALGB 100104		IFM 2005-02	
	R10 (10 mg)[a]	Placebo[b]	R10[c] (10 mg)[a]	Placebo[c]
	(N = 224) n (%)	**(N = 221) n (%)**	**(N = 293) n (%)**	**(N = 280) n (%)**
Subjects with ≥ 1 TEAE	215 (96.0)	188 (85.1)	291 (99.3)	272 (97.1)

System Organ Class	Trial and Study Arm (Lenalidomide Starting QD Dose)			
	CALGB 100104		IFM 2005-02	
	R10 (10 mg)[a] (N = 224) n (%)	Placebo[b] (N = 221) n (%)	R10[c] (10 mg)[a] (N = 293) n (%)	Placebo[c] (N = 280) n (%)
Blood and Lymphatic System Disorders	189 (84.4)	118 (53.4)	206 (70.3)	68 (24.3)
Cardiac Disorders	11 (4.9)	7 (3.2)	9 (3.1)	20 (7.1)
Ear and Labyrinth Disorders	1 (0.4)	3 (1.4)	23 (7.8)	19 (6.8)
Endocrine Disorders	3 (1.3)	2 (0.9)	3 (1.0)	11 (3.9)
Eye Disorders	8 (3.6)	9 (4.1)	32 (10.9)	32 (11.4)
Gastrointestinal Disorders	130 (58.0)	94 (42.5)	198 (67.6)	120 (42.9)
General Disorders and Administration Site Conditions	75 (33.5)	42 (19.0)	185 (63.1)	139 (49.6)
Hepatobiliary Disorders	37 (16.5)	19 (8.6)	29 (9.9)	7 (2.5)
Immune System Disorders	1 (0.4)	0	14 (4.8)	11 (3.9)
Infections and Infestations	122 (54.5)	84 (38.0)	235 (80.2)	218 (77.9)
Injury, Poisoning and Procedural Complications	24 (10.7)	15 (6.8)	36 (12.3)	37 (13.2)
Investigations	50 (22.3)	37 (16.7)	39 (13.3)	32 (11.4)
Metabolism and Nutrition Disorders	55 (24.6)	51 (23.1)	51 (17.4)	37 (13.2)
Musculoskeletal and Connective Tissue Disorders	40 (17.9)	51 (23.1)	194 (66.2)	179 (63.9)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	27 (12.1)	8 (3.6)	25 (8.5)	11 (3.9)
Nervous System Disorders	53 (23.7)	53 (24.0)	137 (46.8)	109 (38.9)
Psychiatric Disorders	21 (9.4)	14 (6.3)	60 (20.5)	44 (15.7)
Renal and Urinary Disorders	9 (4.0)	6 (2.7)	17 (5.8)	26 (9.3)
Reproductive System and Breast Disorders	3 (1.3)	4 (1.8)	22 (7.5)	21 (7.5)
Respiratory, Thoracic and Mediastinal Disorders	46 (20.5)	35 (15.8)	141 (48.1)	97 (34.6)
Skin and Subcutaneous Tissue Disorders	79 (35.3)	63 (28.5)	116 (39.6)	87 (31.1)
Surgical and Medical Procedures	0	0	34 (11.6)	41 (14.6)
Vascular Disorders	22 (9.8)	9 (4.1)	43 (14.7)	34 (12.1)

21/28 = Days 1 to 21 of 28-day cycles; 28/28 = Days 1 to 28 of 28-day cycles; AE = adverse event; Incl = Including; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily; R = lenalidomide; TEAE = treatment-emergent adverse event.

[a] The starting lenalidomide maintenance dose (R 10 mg QD 28/28) could be raised to 15 mg QD (28/28), according to the study design.

[b] In Study CALGB 100104, for placebo subjects, only AEs up to crossing over to lenalidomide are included.

[c] In Study IFM 2005-02, data were excluded from all subjects for the 2 cycles of lenalidomide consolidation (R 25 mg QD 21/28).

Note: A subject with multiple occurrences of a TEAE within a system organ class is counted only once in that system organ class. System organ classes are coded using MedDRA Version 15.1 and are listed alphabetically

Data cutoff: 1 March 2015

Table 33: TEAEs reported for at least 10% of subjects in any treatment arm by trial and study arm: within study and interstudy comparisons for CALGB 100104 and IFM 2005-02 Maintenance (Safety Population)

System Organ Class Preferred Term	Trial and Study Arm (Lenalidomide Starting QD Dose)			
	CALGB 100104		IFM 2005-02	
	R10 (10 mg)[a] (N = 224) n (%)	Placebo[b] (N = 221) n (%)	R10[c] (10 mg)[a] (N = 293) n (%)	Placebo[c] (N = 280) n (%)
Subjects with ≥ 1 TEAE	215 (96.0)	188 (85.1)	291 (99.3)	272 (97.1)
Blood and Lymphatic System Disorders	189 (84.4)	118 (53.4)	206 (70.3)	68 (24.3)
Anaemia	47 (21.0)	27 (12.2)	26 (8.9)	15 (5.4)
Febrile neutropenia[d]	39 (17.4)	34 (15.4)	7 (2.4)	1 (0.4)
Leukopenia	51 (22.8)	25 (11.3)	93 (31.7)	21 (7.5)
Lymphopenia	40 (17.9)	29 (13.1)	13 (4.4)	3 (1.1)
Neutropenia[d]	177 (79.0)	94 (42.5)	178 (60.8)	33 (11.8)
Thrombocytopenia[d]	162 (72.3)	101 (45.7)	69 (23.5)	29 (10.4)
Gastrointestinal Disorders	130 (58.0)	94 (42.5)	198 (67.6)	120 (42.9)
Abdominal pain	8 (3.6)	7 (3.2)	31 (10.6)	15 (5.4)
Constipation	12 (5.4)	8 (3.6)	37 (12.6)	25 (8.9)
Diarrhoea[d]	122 (54.5)	83 (37.6)	114 (38.9)	34 (12.1)
Gastrointestinal disorder	2 (0.9)	2 (0.9)	36 (12.3)	8 (2.9)
Nausea	33 (14.7)	22 (10.0)	31 (10.6)	28 (10.0)
General Disorders and Administration Site Conditions	75 (33.5)	42 (19.0)	185 (63.1)	139 (49.6)
Asthenia	0	1 (0.5)	87 (29.7)	53 (18.9)
Fatigue	51 (22.8)	30 (13.6)	31 (10.6)	15 (5.4)
Pain	3 (1.3)	4 (1.8)	31 (10.6)	33 (11.8)
Pyrexia	17 (7.6)	10 (4.5)	60 (20.5)	26 (9.3)
Hepatobiliary Disorders	37 (16.5)	19 (8.6)	29 (9.9)	7 (2.5)
Hyperbilirubinaemia[d]	34 (15.2)	19 (8.6)	4 (1.4)	1 (0.4)
Infections and Infestations	122 (54.5)	84 (38.0)	235 (80.2)	218 (77.9)
Bronchitis	10 (4.5)	9 (4.1)	139 (47.4)	104 (37.1)
Gastroenteritis	0	0	66 (22.5)	55 (19.6)
Influenza	8 (3.6)	5 (2.3)	39 (13.3)	19 (6.8)
Nasopharyngitis	5 (2.2)	2 (0.9)	102 (34.8)	84 (30.0)

System Organ Class Preferred Term	Trial and Study Arm (Lenalidomide Starting QD Dose)			
	CALGB 100104		IFM 2005-02	
	R10 (10 mg)[a] (N = 224) n (%)	Placebo[b] (N = 221) n (%)	R10[c] (10 mg)[a] (N = 293) n (%)	Placebo[c] (N = 280) n (%)
Neutropenic infection[d]	40 (17.9)	19 (8.6)	0	0
Rhinitis	2 (0.9)	0	44 (15.0)	19 (6.8)
Sinusitis	8 (3.6)	3 (1.4)	41 (14.0)	26 (9.3)
Upper respiratory tract infection	60 (26.8)	35 (15.8)	32 (10.9)	18 (6.4)
Investigations	50 (22.3)	37 (16.7)	39 (13.3)	32 (11.4)
Weight increased[d]	19 (8.5)	24 (10.9)	11 (3.8)	16 (5.7)
Metabolism and Nutrition Disorders	55 (24.6)	51 (23.1)	51 (17.4)	37 (13.2)
Hypokalaemia	24 (10.7)	13 (5.9)	12 (4.1)	1 (0.4)
Musculoskeletal and Connective Tissue Disorders	40 (17.9)	51 (23.1)	194 (66.2)	179 (63.9)
Arthralgia	11 (4.9)	14 (6.3)	41 (14.0)	47 (16.8)
Back pain	17 (7.6)	25 (11.3)	76 (25.9)	79 (28.2)
Muscle spasms	0	1 (0.5)	98 (33.4)	43 (15.4)
Pain in extremity	10 (4.5)	12 (5.4)	27 (9.2)	28 (10.0)
Nervous System Disorders	53 (23.7)	53 (24.0)	137 (46.8)	109 (38.9)
Paraesthesia	2 (0.9)	0	39 (13.3)	30 (10.7)
Peripheral sensory neuropathy	27 (12.1)	26 (11.8)	2 (0.7)	2 (0.7)
Respiratory, Thoracic and Mediastinal Disorders	46 (20.5)	35 (15.8)	141 (48.1)	97 (34.6)
Cough	23 (10.3)	12 (5.4)	80 (27.3)	56 (20.0)
Lung disorder	1 (0.4)	0	34 (11.6)	10 (3.6)
Skin and Subcutaneous Tissue Disorders	79 (35.3)	63 (28.5)	116 (39.6)	87 (31.1)
Dry skin	9 (4.0)	4 (1.8)	31 (10.6)	21 (7.5)
Rash[d]	71 (31.7)	48 (21.7)	22 (7.5)	17 (6.1)

21/28 = Days 1 to 21 of 28-day cycles; 28/28 = Days 1 to 28 of 28-day cycles; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily; R = lenalidomide; TEAE = treatment-emergent adverse event.

[a] The starting lenalidomide maintenance dose (R 10 mg QD 28/28) could be raised to 15 mg QD (28/28), according to the study design.

[b] In Study CALGB 100104, for placebo subjects, only AEs up to crossing over to lenalidomide are included.

[c] In Study IFM 2005-02, data were excluded from all subjects for the 2 cycles of lenalidomide consolidation (R 25 mg QD 21/28).

[d] This term corresponds to a preprinted CTCAE term or prompt on the case report form of Study CALGB 100104.

Data cutoff: 1 Mar 2015

Table 34: Grade 3 or 4 TEAEs reported for at least 2% of subjects in any treatment arm by trial and study arm: within study and interstudy comparisons for CALGB 100104 and IFM 2005-02 Maintenance – Pooled and Non-pooled (Safety Population)

	Trial and Study Arm (Lenalidomide Starting QD Dose)					
	CALGB 100104		IFM 2005-02		CALGB 100104 + IFM 2005-02	
	R10 (10 mg)[a]	Placebo[b]	R10[c] (10 mg)[a]	Placebo[c]	R10 Pool[c] (10 mg)[a]	Placebo Pool[b,c]
System Organ Class Preferred Term	(N= 224) n (%)	(N= 221) n (%)	(N= 293) n (%)	(N= 280) n (%)	(N= 517) n (%)	(N= 501) n (%)
Subjects with ≥ 1 Grade 3 or 4 TEAE	178 (79.5)	122 (55.2)	220 (75.1)	90 (32.1)	398 (77.0)	212 (42.3)
Blood and Lymphatic System Disorders	145 (64.7)	80 (36.2)	178 (60.8)	32 (11.4)	323 (62.5)	112 (22.4)
Anaemia	23 (10.3)	18 (8.1)	11 (3.8)	3 (1.1)	34 (6.6)	21 (4.2)
Febrile neutropenia[d]	39 (17.4)	34 (15.4)	5 (1.7)	1 (0.4)	44 (8.5)	35 (7.0)
Leukopenia	45 (20.1)	22 (10.0)	71 (24.2)	5 (1.8)	116 (22.4)	27 (5.4)
Lymphopenia	37 (16.5)	26 (11.8)	11 (3.8)	2 (0.7)	48 (9.3)	28 (5.6)
Neutropenia[d]	133 (59.4)	73 (33.0)	158 (53.9)	21 (7.5)	291 (56.3)	94 (18.8)
Pancytopenia	0	0	7 (2.4)	1 (0.4)	7 (1.4)	1 (0.2)
Thrombocytopenia[d]	84 (37.5)	67 (30.3)	38 (13.0)	8 (2.9)	122 (23.6)	75 (15.0)
Gastrointestinal Disorders	44 (19.6)	32 (14.5)	14 (4.8)	4 (1.4)	58 (11.2)	36 (7.2)
Diarrhoea[d]	22 (9.8)	17 (7.7)	7 (2.4)	0	29 (5.6)	17 (3.4)
Nausea	16 (7.1)	10 (4.5)	0	0	16 (3.1)	10 (2.0)
Vomiting	8 (3.6)	5 (2.3)	1 (0.3)	0	9 (1.7)	5 (1.0)
General Disorders and Administration Site Conditions	24 (10.7)	14 (6.3)	16 (5.5)	4 (1.4)	40 (7.7)	18 (3.6)
Asthenia	0	0	10 (3.4)	2 (0.7)	10 (1.9)	2 (0.4)
Fatigue	21 (9.4)	9 (4.1)	3 (1.0)	0	24 (4.6)	9 (1.8)
Infections and Infestations	66 (29.5)	34 (15.4)	40 (13.7)	13 (4.6)	106 (20.5)	47 (9.4)
Bronchitis	1 (0.4)	5 (2.3)	4 (1.4)	1 (0.4)	5 (1.0)	6 (1.2)
Gastroenteritis	0	0	6 (2.0)	0	6 (1.2)	0
Herpes zoster	3 (1.3)	2 (0.9)	6 (2.0)	2 (0.7)	9 (1.7)	4 (0.8)
Infection	9 (4.0)	5 (2.3)	0	0	9 (1.7)	5 (1.0)
Lower respiratory tract infection	6 (2.7)	4 (1.8)	0	2 (0.7)	6 (1.2)	6 (1.2)
Lung infection	19 (8.5)	2 (0.9)	1 (0.3)	0	20 (3.9)	2 (0.4)
Neutropenic infection[d]	27 (12.1)	14 (6.3)	0	0	27 (5.2)	14 (2.8)
Pneumonia	15 (6.7)	4 (1.8)	2 (0.7)	2 (0.7)	17 (3.3)	6 (1.2)
Upper respiratory tract infection	7 (3.1)	9 (4.1)	1 (0.3)	0	8 (1.5)	9 (1.8)
Injury, Poisoning and Procedural Complications	14 (6.3)	9 (4.1)	4 (1.4)	2 (0.7)	18 (3.5)	11 (2.2)
Radiation mucositis[d]	6 (2.7)	6 (2.7)	0	0	6 (1.2)	6 (1.2)

Investigations	21 (9.4)	6 (2.7)	3 (1.0)	9 (3.2)	24 (4.6)	15 (3.0)
Alanine aminotransferase increased	8 (3.6)	0	0	1 (0.4)	8 (1.5)	1 (0.2)
Aspartate aminotransferase increased	6 (2.7)	0	0	0	6 (1.2)	0
Prothrombin time prolonged	5 (2.2)	0	0	0	5 (1.0)	0
Metabolism and Nutrition Disorders	32 (14.3)	36 (16.3)	6 (2.0)	4 (1.4)	38 (7.4)	40 (8.0)
Dehydration	7 (3.1)	3 (1.4)	0	0	7 (1.4)	3 (0.6)
Hyperglycaemia	4 (1.8)	11 (5.0)	0	0	4 (0.8)	11 (2.2)
Hypocalcaemia	5 (2.2)	8 (3.6)	0	1 (0.4)	5 (1.0)	9 (1.8)
Hypokalaemia	16 (7.1)	12 (5.4)	2 (0.7)	0	18 (3.5)	12 (2.4)
Hypophosphataemia	13 (5.8)	14 (6.3)	0	0	13 (2.5)	14 (2.8)
Musculoskeletal and Connective Tissue Disorders	17 (7.6)	20 (9.0)	14 (4.8)	12 (4.3)	31 (6.0)	32 (6.4)
Arthralgia	5 (2.2)	3 (1.4)	2 (0.7)	5 (1.8)	7 (1.4)	8 (1.6)
Back pain	4 (1.8)	7 (3.2)	5 (1.7)	4 (1.4)	9 (1.7)	11 (2.2)
Myalgia	3 (1.3)	5 (2.3)	2 (0.7)	1 (0.4)	5 (1.0)	6 (1.2)
Nervous System Disorders	19 (8.5)	20 (9.0)	10 (3.4)	9 (3.2)	29 (5.6)	29 (5.8)
Headache	5 (2.2)	1 (0.5)	0	0	5 (1.0)	1 (0.2)
Peripheral sensory neuropathy	6 (2.7)	6 (2.7)	0	0	6 (1.2)	6 (1.2)
Respiratory, Thoracic and Mediastinal Disorders	22 (9.8)	15 (6.8)	24 (8.2)	4 (1.4)	46 (8.9)	19 (3.8)
Dyspnoea	8 (3.6)	4 (1.8)	2 (0.7)	0	10 (1.9)	4 (0.8)
Hypoxia	6 (2.7)	6 (2.7)	0	0	6 (1.2)	6 (1.2)
Lung disorder	1 (0.4)	0	19 (6.5)	3 (1.1)	20 (3.9)	3 (0.6)
Pneumonitis[d]	10 (4.5)	5 (2.3)	0	0	10 (1.9)	5 (1.0)
Skin and Subcutaneous Tissue Disorders	15 (6.7)	7 (3.2)	16 (5.5)	3 (1.1)	31 (6.0)	10 (2.0)
Rash[d]	11 (4.9)	5 (2.3)	3 (1.0)	0	14 (2.7)	5 (1.0)
Vascular Disorders	15 (6.7)	6 (2.7)	7 (2.4)	7 (2.5)	22 (4.3)	13 (2.6)
Hypotension	5 (2.2)	3 (1.4)	0	0	5 (1.0)	3 (0.6)
Thrombosis	5 (2.2)	2 (0.9)	0	0	5 (1.0)	2 (0.4)

21/28 = Days 1 to 21 of 28-day cycles; 28/28 = Days 1 to 28 of 28-day cycles; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily; R = lenalidomide; TEAE = treatment-emergent adverse event.

[a] The starting lenalidomide maintenance dose (R 10 mg QD 28/28) could be raised to 15 mg QD (28/28), according to the study design.

[b] In Study CALGB 100104, for placebo subjects, only AEs up to crossing over to lenalidomide are included.

[c] In Study IFM 2005-02, data were excluded from all subjects for the 2 cycles of lenalidomide consolidation (R 25 mg QD 21/28).

[d] This term corresponds to a preprinted CTCAE term or prompt on the case report form of Study CALGB 100104.

Note: System organ classes and preferred terms are coded using MedDRA Version 15.1 and are listed alphabetically. A subject with multiple occurrences of a TEAE is counted only once in that TEAE category. Severity is assessed according to CTCAE Version 3.0 or most current version.

Data cutoff: 1 Mar 2015

Serious adverse event / deaths / other significant events

Serious adverse event

Table 35: Treatment emergent SAEs Reported for at least 1% of subjects in any treatment arm by trial and study arm: within study and interstudy comparisons for CALGB 100104 and IFM 2005 02 Maintenance – Pooled and Non-pooled (Safety Population)

System Organ Class Preferred Term	Trial and Study Arm (Lenalidomide Starting QD Dose)					
	CALGB 100104		IFM 2005-02		CALGB 100104 + IFM 2005-02	
	R10 (10 mg)[a] (N= 224) n (%)	Placebo[b] (N= 221) n (%)	R10[c] (10 mg)[a] (N= 293) n (%)	Placebo[c] (N= 280) n (%)	R10 Pool[c] (10 mg)[a] (N= 517) n (%)	Placebo Pool[b,c] (N= 501) n (%)
Subjects with ≥ 1 treatment-emergent SAE[d]	63 (28.1)	27 (12.2)	131 (44.7)	64 (22.9)	194 (37.5)	91 (18.2)
Blood and Lymphatic System Disorders	17 (7.6)	4 (1.8)	25 (8.5)	4 (1.4)	42 (8.1)	8 (1.6)
Febrile neutropenia[e]	6 (2.7)	1 (0.5)	7 (2.4)	1 (0.4)	13 (2.5)	2 (0.4)
Leukopenia	4 (1.8)	0	0	0	4 (0.8)	0
Neutropenia[e]	10 (4.5)	1 (0.5)	10 (3.4)	0	20 (3.9)	1 (0.2)
Pancytopenia	0	0	4 (1.4)	0	4 (0.8)	0
Thrombocytopenia[e]	6 (2.7)	2 (0.9)	4 (1.4)	2 (0.7)	10 (1.9)	4 (0.8)
Gastrointestinal Disorders	5 (2.2)	9 (4.1)	5 (1.7)	5 (1.8)	10 (1.9)	14 (2.8)
Diarrhoea[e]	2 (0.9)	3 (1.4)	2 (0.7)	0	4 (0.8)	3 (0.6)
Nausea	1 (0.4)	3 (1.4)	0	0	1 (0.2)	3 (0.6)
Vomiting	1 (0.4)	3 (1.4)	0	1 (0.4)	1 (0.2)	4 (0.8)
General disorders and Administration Site Conditions	6 (2.7)	2 (0.9)	6 (2.0)	0	12 (2.3)	2 (0.4)
Pyrexia	4 (1.8)	2 (0.9)	2 (0.7)	0	6 (1.2)	2 (0.4)
Infections and Infestations	36 (16.1)	11 (5.0)	40 (13.7)	10 (3.6)	76 (14.7)	21 (4.2)

Bronchitis	1 (0.4)	4 (1.8)	6 (2.0)	0	7 (1.4)	4 (0.8)
Gastroenteritis	0	0	3 (1.0)	0	3 (0.6)	0
Herpes zoster	1 (0.4)	0	5 (1.7)	0	6 (1.2)	0
Infection	3 (1.3)	0	0	0	3 (0.6)	0
Influenza	1 (0.4)	0	3 (1.0)	0	4 (0.8)	0
Lung infection	21 (9.4)	2 (0.9)	1 (0.3)	1 (0.4)	22 (4.3)	3 (0.6)
Pneumonia pneumococcal	0	0	4 (1.4)	2 (0.7)	4 (0.8)	2 (0.4)
Staphylococcal sepsis	0	0	3 (1.0)	0	3 (0.6)	0
Upper respiratory tract infection	4 (1.8)	2 (0.9)	1 (0.3)	0	5 (1.0)	2 (0.4)
Urinary tract infection	3 (1.3)	0	0	0	3 (0.6)	0
Musculoskeletal and Connective Tissue Disorders	5 (2.2)	3 (1.4)	7 (2.4)	8 (2.9)	12 (2.3)	11 (2.2)
Back pain	0	1 (0.5)	2 (0.7)	3 (1.1)	2 (0.4)	4 (0.8)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	6 (2.7)	1 (0.5)	17 (5.8)	6 (2.1)	23 (4.4)	7 (1.4)
Basal cell carcinoma	2 (0.9)	0	3 (1.0)	1 (0.4)	5 (1.0)	1 (0.2)
Myelodysplastic syndrome	2 (0.9)	0	3 (1.0)	0	5 (1.0)	0
Respiratory, Thoracic and Mediastinal Disorders	10 (4.5)	8 (3.6)	26 (8.9)	4 (1.4)	36 (7.0)	12 (2.4)
Cough	3 (1.3)	0	0	0	3 (0.6)	0
Dyspnoea	6 (2.7)	2 (0.9)	0	0	6 (1.2)	2 (0.4)
Lung disorder	0	0	20 (6.8)	3 (1.1)	20 (3.9)	3 (0.6)
Pneumonitis[e]	4 (1.8)	5 (2.3)	0	0	4 (0.8)	5 (1.0)
Pulmonary embolism	0	0	3 (1.0)	0	3 (0.6)	0
Surgical and Medical Procedures	0	0	10 (3.4)	14 (5.0)	10 (1.9)	14 (2.8)
Vertebroplasty	0	0	0	4 (1.4)	0	4 (0.8)
Vascular Disorders	2 (0.9)	4 (1.8)	8 (2.7)	4 (1.4)	10 (1.9)	8 (1.6)
Deep vein thrombosis	0	0	3 (1.0)	0	3 (0.6)	0

21/28 = Days 1 to 21 of 28-day cycles; 28/28 = Days 1 to 28 of 28-day cycles; AdEERS = Adverse Event Expedited Reporting System; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; Incl = Including; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily; R = lenalidomide; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] The starting lenalidomide maintenance dose (R 10 mg QD 28/28) could be raised to 15 mg QD (28/28), according to the study design.

[b] In Study CALGB 100104, for placebo subjects, only AEs up to crossing over to lenalidomide are included.

[c] In Study IFM 2005-02, data were excluded from all subjects for the 2 cycles of lenalidomide consolidation (R 25 mg QD 21/28).

[d] For Study CALGB 100104, SAEs refer to AEs from AdEERS.

[e] This term corresponds to a preprinted CTCAE term or prompt on the case report form of Study CALGB 100104.

Data cutoff: 1 Mar 2015

Overall, Grade 5 TEAEs were reported in 3 (1.3%) subjects in the CALGB lenalidomide arm and 4 (1.8%) subjects in the CALGB placebo arm.

The Grade 5 TEAEs reported in the CALGB lenalidomide arm included: sepsis (n = 2) and sudden death (n = 1). Of the 3 subjects in the CALGB lenalidomide arm who experienced Grade 5 TEAEs, 1 subject with a Grade 5 TEAE of sepsis died of sepsis on treatment. The 2 other subjects in the CALGB lenalidomide arm who experienced Grade 5 TEAEs (sepsis [n = 1] and sudden death [n = 1]) died more than 30 days after the last dose; therefore, these 2 subjects were not considered to have on-treatment deaths despite having a treatment-emergent Grade 5 event.

In the CALGB placebo arm, Grade 5 TEAEs included: multiple myeloma (n =2); acute respiratory distress syndrome (n = 1); atrioventricular block (n = 1); and sepsis (n = 1). Of the 4 subjects in the CALGB placebo arm who experienced Grade 5 TEAEs, 3 subjects died on treatment. These CALGB placebo subjects who died on treatment included: 1 subject with Grade 5 TEAEs of atrioventricular block and sepsis who died of sepsis; 1 subject with a Grade 5 TEAE of multiple myeloma who died of multiple myeloma; and 1 subject with a Grade 5 TEAE of acute respiratory distress syndrome who died of H1N1 influenza. The other subject in the CALGB placebo arm who experienced a Grade 5 TEAE (multiple myeloma) died more than 30 days after the last dose; therefore, this subject was not considered to have an on-treatment death despite having a treatment-emergent Grade 5 event.

Overall, Grade 5 TEAEs were reported in 7 (2.4%) subjects in the IFM lenalidomide arm and 2 (0.7%) subjects in the IFM placebo arm. The SOC with the most subjects who experienced a Grade 5 TEAE was the neoplasms benign, malignant and unspecified (including cysts and polyps) SOC (4 [1.4%] subjects in the IFM lenalidomide arm).

The Grade 5 TEAEs reported in the IFM lenalidomide arm included: acute myeloid leukemia (n = 1); colon cancer metastatic (n = 1); esophageal carcinoma (n = 1); ischemia (n = 1), myelodysplastic syndrome (n = 1); staphylococcal sepsis (n = 1); and sudden death (n =1). Of the 7 subjects in the IFM lenalidomide arm who experienced Grade 5 TEAEs, 4 subjects died between the first dose and 30 days after the last dose of maintenance treatment. The Grade 5 TEAEs reported for these 4 IFM lenalidomide subjects included: 1 subject with acute myeloid leukemia; 1 subject with ischemia (acute mesenteric and colonic ischemia); 1 subject with staphylococcal sepsis; and 1 subject with sudden death. The 3 other IFM lenalidomide subjects who experienced a Grade 5 TEAEs died more than 30 days after the last dose. The Grade 5 TEAEs reported (days from last dose to death) for these 3 IFM lenalidomide subjects included: 1 subject with colon cancer metastatic (227 days); 1 subject with esophageal carcinoma (325 days); and 1 subject with myelodysplastic syndrome (544 days).

The Grade 5 TEAEs reported in the IFM placebo arm included: renal failure (n =1); road traffic accident (n = 1); and staphylococcal infection (n = 1). The 2 subjects in the IFM placebo arm who experienced Grade 5 TEAEs died between the first dose and 30 days after the last dose of maintenance treatment. The Grade 5 TEAEs reported for these 2 IFM placebo subjects included: 1 subject with a road traffic accident and 1 subject with a staphylococcal infection and renal failure.

Second Primary Malignancies

In late 2010, a safety concern arose with regard to SPMs based on the emerging results of 3 prospective, randomized, double-blind, placebo-controlled lenalidomide studies in subjects with NDMM (Studies MM-015, IFM 2005-02, and CALGB 100104) leading to an evaluation of SPMs across the entire MAH's lenalidomide safety database, including all investigational indications.

Two cohort studies of SPMs after ASCT for multiple myeloma have been reported. The first analysis is a retrospective cohort study of 841 consecutive patients with multiple myeloma who underwent ASCT at City of Hope between 1989 and 2009 (Krishnan, 2013). The cumulative incidences of SPMs were 7.4%

at 5 years and 15.9% at 10 years. Older age (≥ 55 years) and race (non-Hispanic white) were associated with an increased risk for SPMs by multivariate analysis. The risk for SPMs in patients receiving lenalidomide could not be assessed because too few patients in this population were treated with lenalidomide. A second cohort analysis studied patients who received a first ASCT within 18 months of diagnosis of multiple myeloma and were reported to the Center for International Blood and Bone Marrow Transplant Research (CIBMTR). This study included 4161 patients receiving an ASCT for multiple myeloma in the US from 1990 to 2010 (Mahindra, 2015). Post-ASCT maintenance therapy in this population included thalidomide (15%), lenalidomide (11%), bortezomib (9%), and interferon (6%). The cumulative incidences of SPMs were 2.6%, 4.2%, and 6.1% at 3, 5, and 7 years, respectively. The incidence rate of SPMs was 1.2 new cancers per 100 person-years. Obesity, older age, and male gender were associated with increased risks of SPMs in multivariate analyses.

CALGB 100104

As of the data cut-off date of 1 February 2016 for Study CALGB 100104, the median follow-up time for surviving subjects was 81.6 months (range: 3.4 to 119,8 months). SPM analysis was split into invasive and non-invasive SPM. Invasive SPM include hematologic malignancies and solid tumors.

Table 36: Number and percentage of subjects with second primary malignancies in Study CALGB 100104 as of the 1 March15 and 1 February 2016 Data Cut-off Dates (SPM Safety Analysis Population)

	Lenalidomide (N = 224)		**Placebo (N = 221)**	
SPM Category	**Data as of 1 Mar 2015 n (%)**	**Data as of 1 Feb 2016 n (%)**	**Data as of 1 Mar 2015 n (%)**	**Data as of 1 Feb 2016 n (%)**
Hematologic Malignancies	15 (6.7)	19 (8.5)	8 (3.6)	8 (3.6)
AML	6 (2.7)	6 (2.7)	0 (0.0)	0 (0.0)
MDS to AML	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
MDS	4 (1.8)	4 (1.8)	4 (1.8)	4 (1.8)
B-cell malignancies (B-ALL and Hodgkin's disease)	4 (1.8)[a]	8 (3.6)[b]	3 (1.4)[a]	3 (1.4)[b]
Other[c]	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)
Solid Tumors	17 (7.6)[d]	18 (8.0)[d]	10 (4.5)[e]	11 (5.0)[e]
Invasive SPMs	32 (14.3)	36 (16.1)[f]	17 (7.7)[g]	18 (8.1)[g]
Non-Invasive SPMs (Non-melanoma skin cancer)	12 (5.4)	12 (5.4)	9 (4.1)	10 (4.5)
TOTAL SPMs	42 (18.8)[h,i]	46 (20.5)[f,h,i]	24 (10.9)[g,j,k]	26 (11.8)[g,j,k]

AML = acute myeloid leukemia; B-ALL = B-cell acute lymphocytic leukemia; MDS = myelodysplastic syndromes; SPM = second primary malignancy.

[a] B-cell malignancies in the lenalidomide arm include 2 cases of B-cell type acute leukemia, 1 case of Hodgkin's disease, and 1 case of acute lymphocytic leukemia; the placebo arm includes 3 cases of B-cell type acute leukemia.

[b] B-cell malignancies in the lenalidomide arm include 2 cases of B-cell type acute leukemia, 2 cases of Hodgkin's disease, 2 cases of acute lymphocytic leukemia, 1 case of B precursor type acute leukemia, and 1 case of Waldenstrom's macroglobulinemia; the placebo arm includes 3 cases of B-cell type acute leukemia.

[c] Other includes 1 case of malignant histiocytosis (placebo arm).

[d] One Subject (lenalidomide arm) had 2 solid tumor SPMs (endometrial cancer and breast cancer) and is only counted once in the solid tumor category.

[e] One Subject (placebo arm) had 2 solid tumor SPMs (endometrial cancer and ovarian cancer) and is only counted once in the solid tumor category.

[f] One Subject (lenalidomide arm) had 1 hematologic SPM (MDS) and 1 solid tumor SPM (colon cancer) and is only counted once in the invasive category and in the total.

[g] One Subject (placebo arm) had both a hematologic SPM (MDS) and solid tumor SPM (malignant melanoma) and is counted only once in the invasive SPM category and the total.

[h] One Subject (lenalidomide arm) had both a hematologic SPM (AML) and 2 non-melanoma skin cancers. This subject is counted only once in the total.

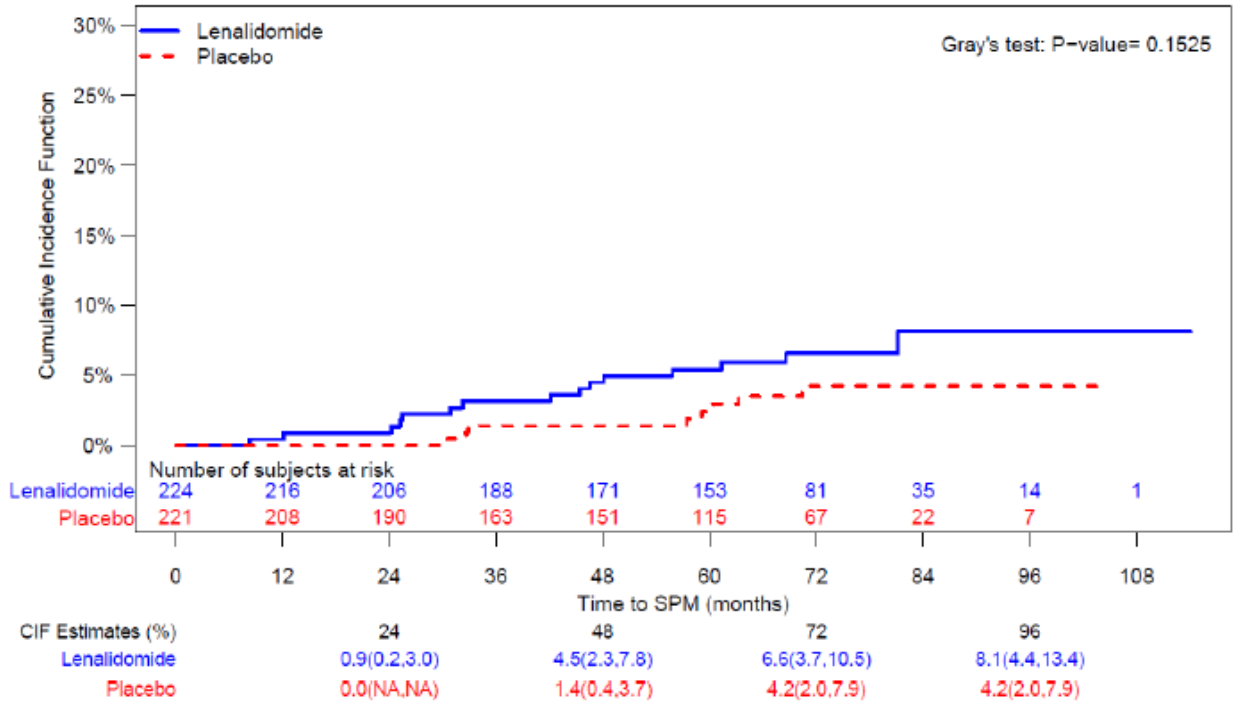
[i] One Subject (lenalidomide arm) had both a solid tumor SPM (prostate cancer) and a non-melanoma skin cancer. This subject is counted only once in the total.

[j] One Subject (placebo arm) had both a solid tumor SPM (metastatic squamous cell carcinoma) and a non-melanoma skin ancer. This subject is counted only once in the total.

[k] One Subject (placebo arm) had both a solid tumor SPM (endometrial cancer) and a non-melanoma skin cancer. This subject is counted only once in the total.

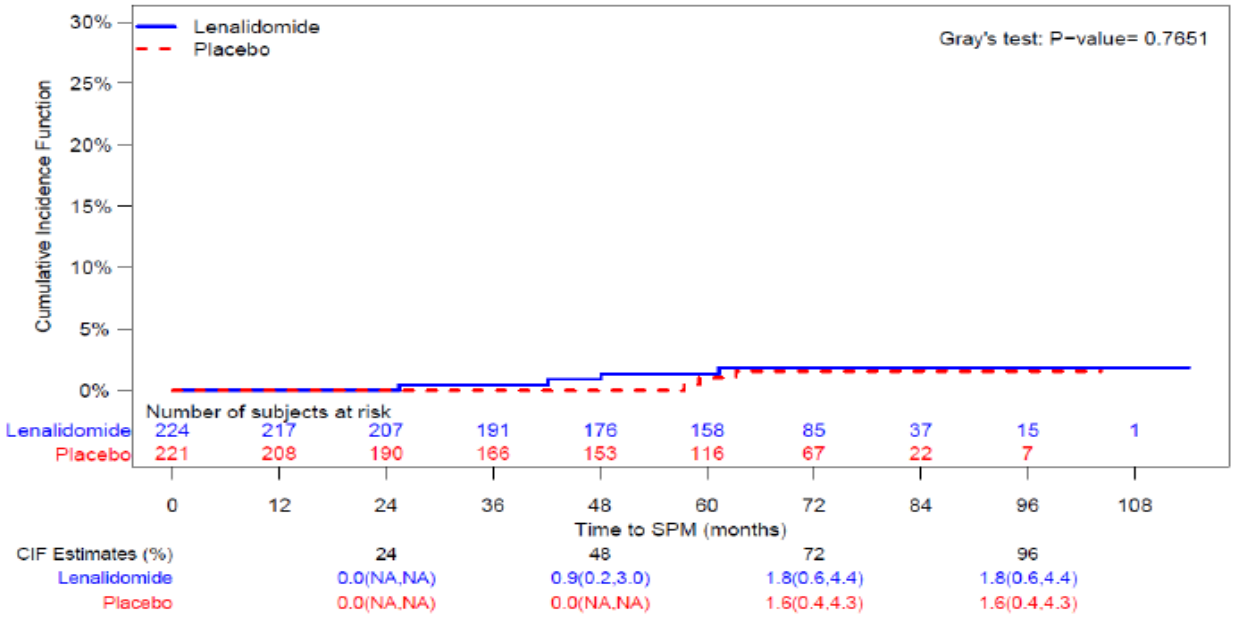
Subjects with SPM in the placebo arm: Following study unblinding on 17 Dec 2009, a total of 76 of the 221 subjects in the placebo arm had crossed over to receive lenalidomide treatment prior to disease progression. As of cut-off date on 1 March 2016, 85 subjects in the placebo arm received lenalidomide salvage therapy after disease progression. Only 60 of the 221 subjects who were randomized and received placebo maintenance were not exposed to lenalidomide post-ASCT prior to (crossover) or after (salvage) progressive disease. Among the 76 placebo subjects who crossed over to lenalidomide treatment prior to disease progression, 12 subjects were diagnosed with an SPM after the start of lenalidomide therapy, including 9 patients with invasive SPM. Among the 85 placebo subjects who received lenalidomide salvage therapy after disease progression, 8 subjects were diagnosed with SPM after the start of lenalidomide salvage therapy. Among the 60 placebo subjects who were not exposed to lenalidomide post-ASCT during this study, 1 subject developed a solid tumor SPM (carcinoid tumor pulmonary).

Figure 9: Cumulative Incidence of Hematologic Second Primary Malignancy With Death as the Competing Risk in Study CALGB 100104 as of the 1 March 2015 Data Cut-off Date (SPM Safety Analysis Population)



CIF = cumulative incidence function; NA = not applicable; SPM = second primary malignancy.
Source: Figure 14.11.3.1.1

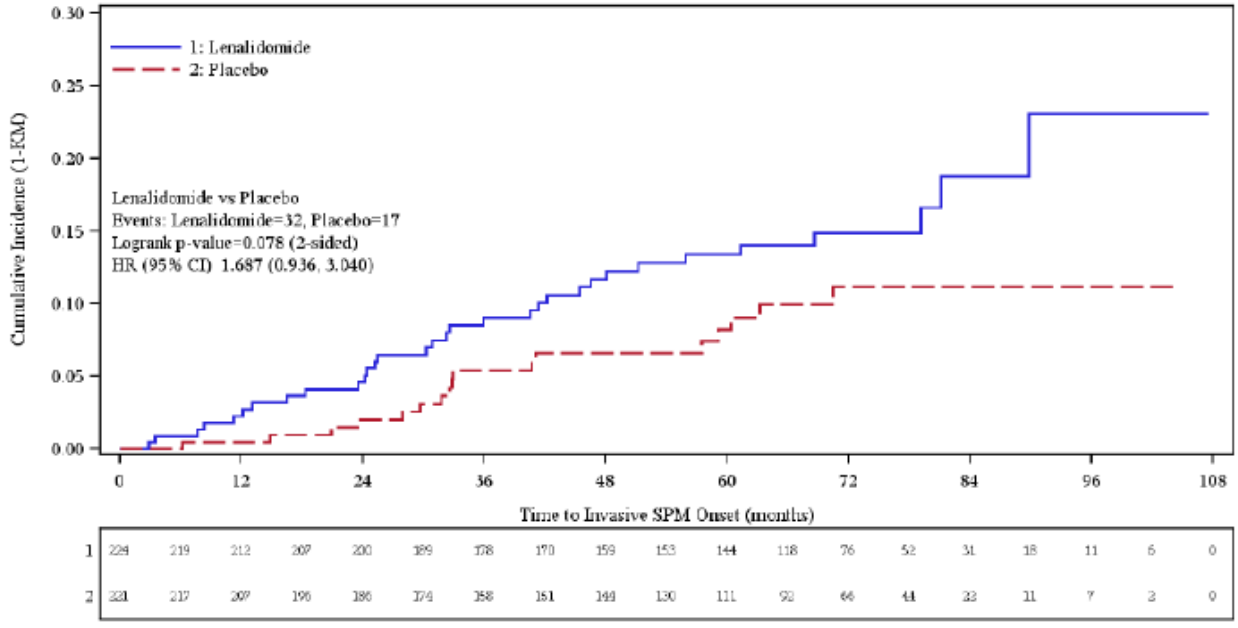
Figure 10: Cumulative Incidence of B-Cell Second Primary Malignancy With Death as the Competing Risk in Study CALGB 100104 as of the 01 Mar 2015 Data Cutoff Date (SPM Safety Analysis Population)



B-ALL = B-cell acute lymphocytic leukemia; CIF = cumulative incidence function; NA = not applicable; SPM = second primary malignancy.
Note: For Study CALGB 100104, B-cell malignancies include B-ALL and Hodgkin's disease.
Source: Figure 14.11.3.1.3

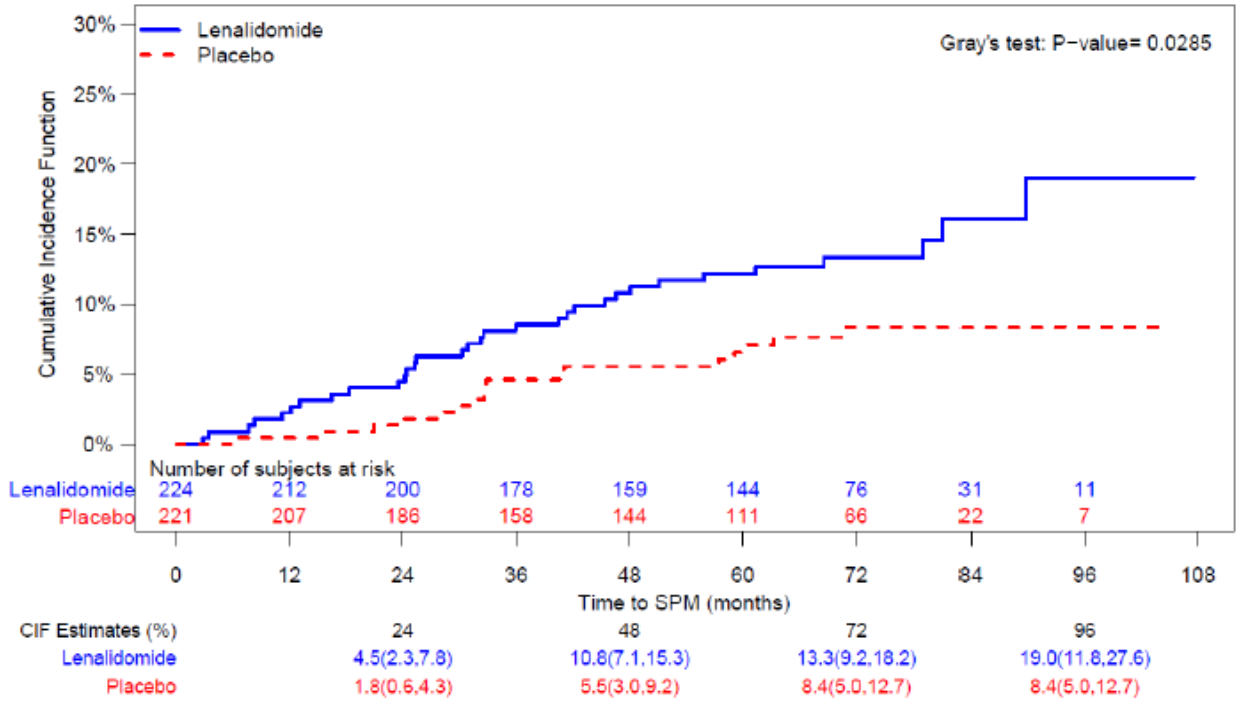
Invasive SPM

Figure 11: Cumulative Incidence Curves Using the Kaplan-Meier Method for Time to Onset of Invasive Second Primary Malignancy for Study CALGB 100104 Cutoff Date 1 March 2015 (SPM Safety Analysis Population)



CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier; SPM = second primary malignancy.
Source: Figure 14.11.2.1.5

Figure 12: Cumulative incidence of invasive SPM with Death as the Competing Risk in Study CALGB 100104 as of the 1 March 2015 Data Cutoff Date (SPM Safety Analysis Population)



CIF = cumulative incidence function; SPM = second primary malignancy.
Source: Figure 14.11.3.1.5

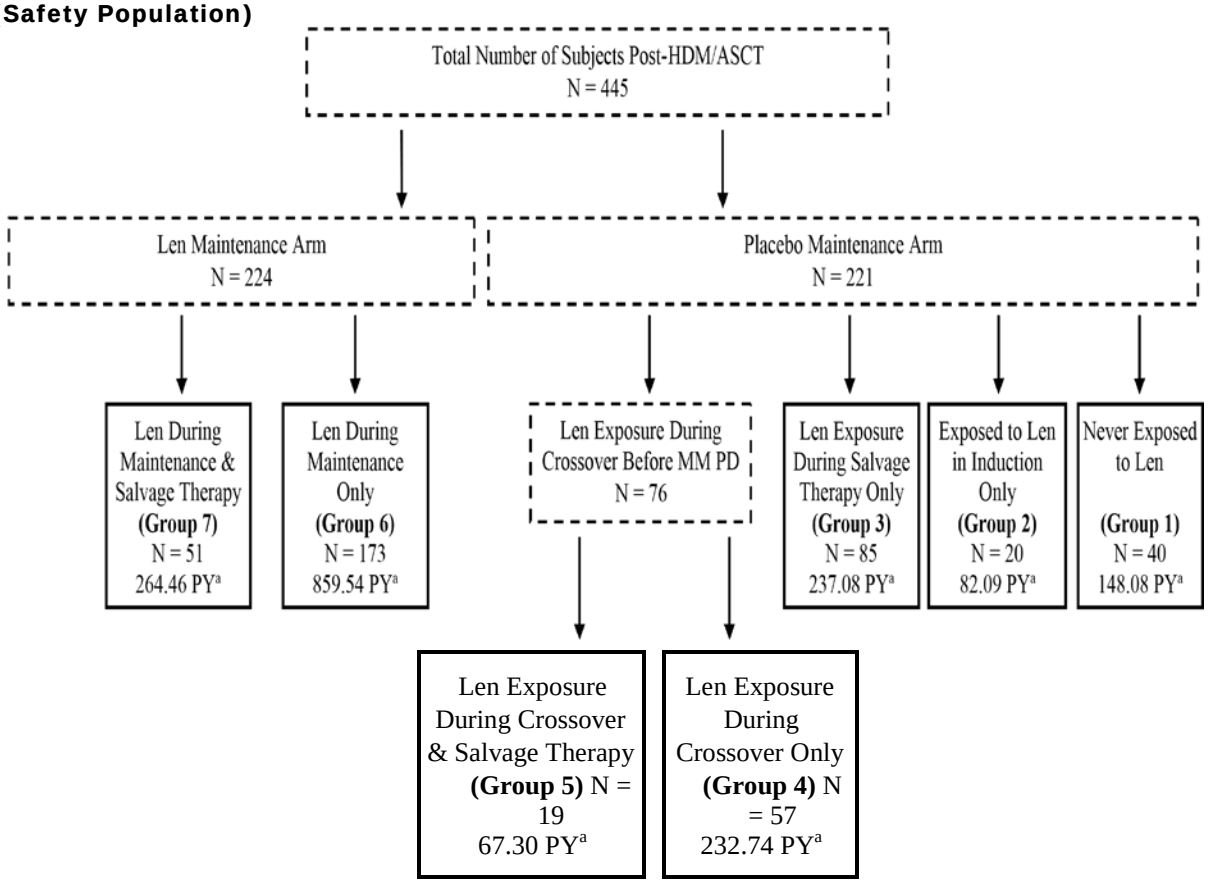
Analysis of SPM in lenalidomide exposed versus non-exposed patients (1 March 2015)

Table 37: Lenalidomide Exposure for Subjects in Study CALGB 100104 (Safety Population)

Group	Lenalidomide Therapy During			Start of Lenalidomide Exposure	Number of Subjects (N = 445)	Number of Subjects With Invasive SPMs
	Maintenance	Crossover Prior to PD[a]	Salvage After PD			
1	No	No	No	No exposure	40[b]	1
2	No	No	No	Induction only	20[c]	0
3	No	No	Yes	Salvage	85	7[d]
4	No	Yes	No	Crossover	57	7
5	No	Yes	Yes	Crossover	19	2
6	Yes	No	No	Maintenance	173	28
7	Yes	No	Yes	Maintenance	51	4

PD = progressive disease; SPM = second primary malignancy.
[a] After the study was unblinded (17 Dec 2009), subjects in the placebo arm whose multiple myeloma had not progressed were allowed to cross over to receive lenalidomide treatment prior to disease progression at the treating physician's discretion. [b] Excludes subjects exposed to lenalidomide during the induction period. [c] Subjects exposed to lenalidomide during the induction period only.
[d] Two subjects were diagnosed with invasive SPMs (solid tumor SPMs) prior to receiving lenalidomide-containing salvage therapy; One subject was diagnosed with 2 solid tumor SPMs (endometrial cancer stage II and ovarian cancer) and one subject was diagnosed with lentigo maligna. These 2 subjects received lenalidomide-containing salvage therapy; however, their solid tumor SPMs were diagnosed during placebo maintenance and thus, these solid tumor SPMs are not included in the "lenalidomide exposed group." Data cutoff date= 1 March 2015.

Figure 13: Disposition of Lenalidomide Exposure for Subjects in Study CALGB 100104 (Safety Population)



ASCT = autologous stem cell transplant; HDM = high-dose melphalan; Len = lenalidomide; MM PD = multiple myeloma progressive disease; PY = person-years of observation time; SPMs = second primary malignancies.

[a] Person-years is observation time of the subject group. Observation time was calculated as time from the first dose of lenalidomide for the lenalidomide exposed group or first dose of placebo for the lenalidomide non-exposed group to the first invasive SPM, death, or data cutoff date, whichever occurred first, for each subject.

Data cutoff date = 1 March 2015.

Table 38: Frequencies and incidence rates of invasive second primary malignancies including invasive subcategories: subjects exposed and not exposed to lenalidomide in study CALGB 100104 (Safety Population)

Invasive SPMs	Subjects Exposed to Lenalidomide After HDM and ASCT						Subjects Not Exposed to Lenalidomide After HDM and ASCT	
	Len Starting at Salvage Therapy After PD[a] (Group 3) (N = 85)	Len Starting at Crossover Prior to PD[b]		Len Starting at Maintenance		All Len Exposed (Groups 3 to 7) (N = 385)	No Len Exposure (Group 1) (N = 40)	Len During Induction Only (Group 2) (N = 20)
		No Len Salvage (Group 4) (N = 57)	Len Salvage (Group 5) (N = 19)	No Len Salvage (Group 6) (N = 173)	Len Salvage (Group 7) (N = 51)			
Number of subjects (%)	5 (5.9)	7 (12.3)	2 (10.5)	28 (16.2)	4 (7.8)	**46 (11.9)**	**1 (2.5)**	0 (0.0)
Person-years	237.08	232.74	67.30	859.54	264.46	**1661.12**	**148.08**	82.09
Incidence rate/100 PY (95% CI)	**2.11 (0.88 – 5.07)**	**3.01 (1.43 – 6.31)**	**2.97 (0.74 – 11.88)**	**3.26 (2.25 – 4.72)**	**1.51 (0.57 – 4.03)**	**2.77 (2.07 – 3.70)**	**0.68 (0.10 – 4.79)**	--
Hematologic malignancies	3	3	2	14	1	23	0	0
AML	0	0	0	6	0	6	0	0
MDS to AML	0	0	0	1	0	1	0	0
MDS	2	1	1	3	1	8	0	0
B-cell malignancies (B=ALL and Hodgkin's disease)	0	2	1	4	0	7	0	0
Other	1	0	0	0	0	1	0	0
Solid tumors	2	5	0	14	3	24	1	0
Invasive SPMs	**5**	**7**	**2**	**28**	**4**	**46**	**1**	**0**

AML = acute myeloid leukemia; ASCT = autologous stem cell transplant; B-ALL = B-cell acute lymphocytic leukemia; CI = confidence interval; HDM = high-dose melphalan; Len = lenalidomide; MDS = myelodysplastic syndromes; PD = progressive disease; PY = person-years; SPM = secondary primary malignancy.

[a] Non-crossover subjects with an invasive SPM that was diagnosed on or after the start of lenalidomide salvage therapy after PD. [b] Crossover subjects with an invasive SPM that was diagnosed on or after the start of lenalidomide therapy prior to PD. Data cutoff date = 1 Mar 2015.

Invasive SPM

- *Hematologic*: Globally, 23 cases of hematologic malignancies were observed in CALGB study, exclusively in the lenalidomide exposed arm:

  o *AML/MDS:* Among these 23 cases of hematologic malignancies, 15 were AML/MDS SPMs.

  o *B-cell malignancies*: Among these 23 cases of hematologic malignancies, 7 were B-cell malignancies.

- *Solid tumors:* As of the 1 March 2015 data cutoff date, a total of 25 subjects were diagnosed with solid tumor SPMs; 24 subjects in the lenalidomide exposed arm and 1 subject in the no lenalidomide exposure arm.

IFM 2005-02

As of the data cut-off date of 1 February 2016 for Study IFM, the median follow-up time for surviving subjects was 96.7 months (range: 3.0 to 115.5 months).

Table 39: Number and percentage of subjects with second primary malignancies in Study IFM 2005-02 as of the 1 March 2015 and 1 February 2016 Data Cutoff Dates (SPM Safety Analysis Population)

	Lenalidomide (N = 306)		Placebo (N = 302)	
SPM Category	**Data as of 1 Mar 2015 n (%)**	**Data as of 1 Feb 2016 n (%)**	**Data as of 1 Mar 2015 n (%)**	**Data as of 1 Feb 2016 n (%)**
Hematologic Malignancies	21 (6.9)[a]	21 (6.9)[a]	9 (3.0)	9 (3.0)
AML	2 (0.7)	2 (0.7)	3 (1.0)	3 (1.0)
MDS to AML	4 (1.3)	4 (1.3)	0 (0.0)	0 (0.0)
MDS	4 (1.3)	4 (1.3)	3 (1.0)	3 (1.0)
B-ALL and Hodgkin's disease[b]	11 (3.6)	11 (3.6)	2 (0.7)[c]	2 (0.7)[c]
Other[d]	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Solid Tumors	21 (6.9)	23 (7.5)	13 (4.3)	19 (6.3)
Invasive SPMs	41 (13.4)[e]	43 (14.1)[e]	22 (7.3)	28 (9.3)
Non-Invasive SPMs (Non-melanoma skin cancer)	10 (3.3)	10 (3.3)	7 (2.3)	7 (2.3)
TOTAL SPMs	49 (16.0)[e,f]	51 (16.7)[e,f]	27 (8.9)[g,h]	33 (10.9)[g,h]

ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia; B-ALL = B-cell acute lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; MDS = myelodysplastic syndromes; SPM = second primary malignancy.

[a] One Subject (lenalidomide arm) had 2 hematologic SPMs (AML and DLBCL) and is counted only once in the hematologic malignancies category.

[b] B-cell malignancies in the lenalidomide arm include 4 cases of Hodgkin's disease, 3 cases of B-cell type acute leukemia, 3 cases of DLBCL, and 1 case of ALL; the placebo arm includes 1 case of Hodgkin's disease and 1 case of ALL.

[c] One Subject (placebo arm) received approximately 43 months of second-line lenalidomide therapy prior to diagnosis of ALL.

[d] Other includes 1 case of acute biphenotypic leukemia (lenalidomide arm) and 1 case of T-cell lymphoma (placebo arm).

[e] One Subject (lenalidomide arm) had 3 SPMs: a hematologic SPM (B-cell type acute leukemia), a solid tumor SPM (prostate cancer), and 4 non-melanoma skin cancers. This subject is counted only once in the invasive SPM category and the total.

[f] One Subject (lenalidomide arm) had both a hematologic SPM (Hodgkin's disease) and a non-melanoma skin cancer. This subject is counted only once in the total.

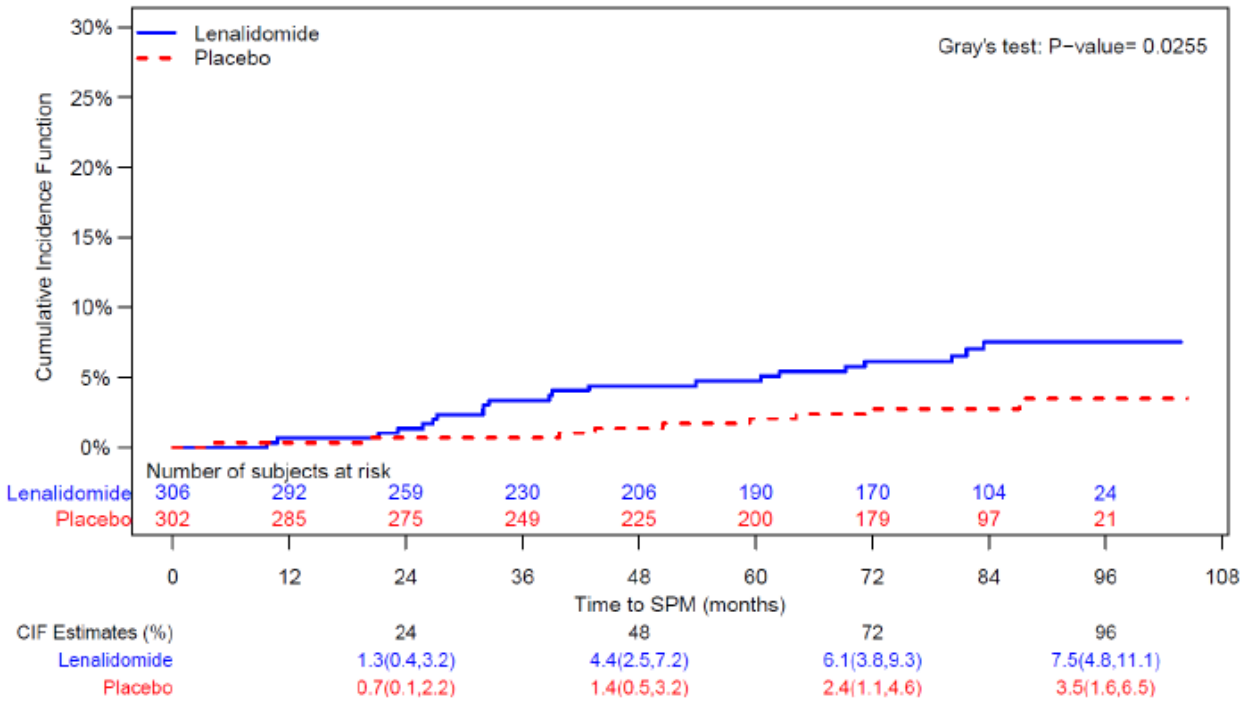
[g]

Consistent with the frequencies of subjects with SPMs, the incidence rates of invasive, hematologic, and solid tumor SPMs were higher for the lenalidomide arm compared with the placebo arm. The incidence rates of developing an invasive SPM were 2.51 and 1.59 per 100 person-years in the lenalidomide and placebo arms, respectively.

Subjects with SPM in the placebo arm

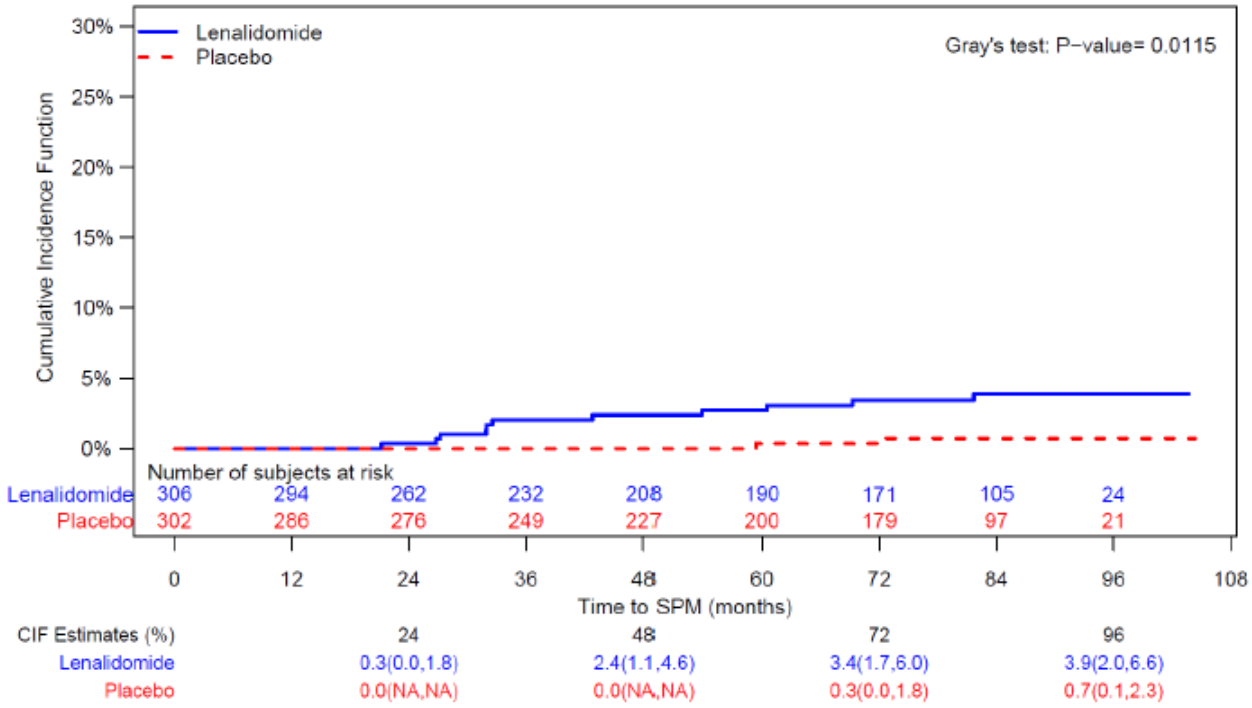
Globally, 27 of the 302 patients in the placebo arm presented with SPM, including 22 (7.3%) invasive SPM. Among these, 13(4.3) were solid tumors and 9 (3%) were hematologic malignancies. Of the 103 placebo subjects in the placebo group who received lenalidomide salvage treatment, 7 subjects were diagnosed with an invasive SPM (3 hematologic and 4 solid tumor SPMs) after the start of lenalidomide salvage therapy. In addition, 2 subjects were diagnosed with a non-melanoma skin cancer prior to the start of lenalidomide salvage therapy. Of the 199 subjects in the placebo arm who were not exposed to lenalidomide after consolidation, 13 subjects developed an invasive SPM (6 hematologic malignancies and 7 solid tumors) and 3 subjects developed a non-melanoma skin cancer.

Figure 14: Cumulative Incidence of Hematologic Second Primary Malignancy With Death as the Competing Risk in Study IFM 2005-02 as of the 1 March 2015 Data Cut-off Date (SPM Safety Analysis Population)



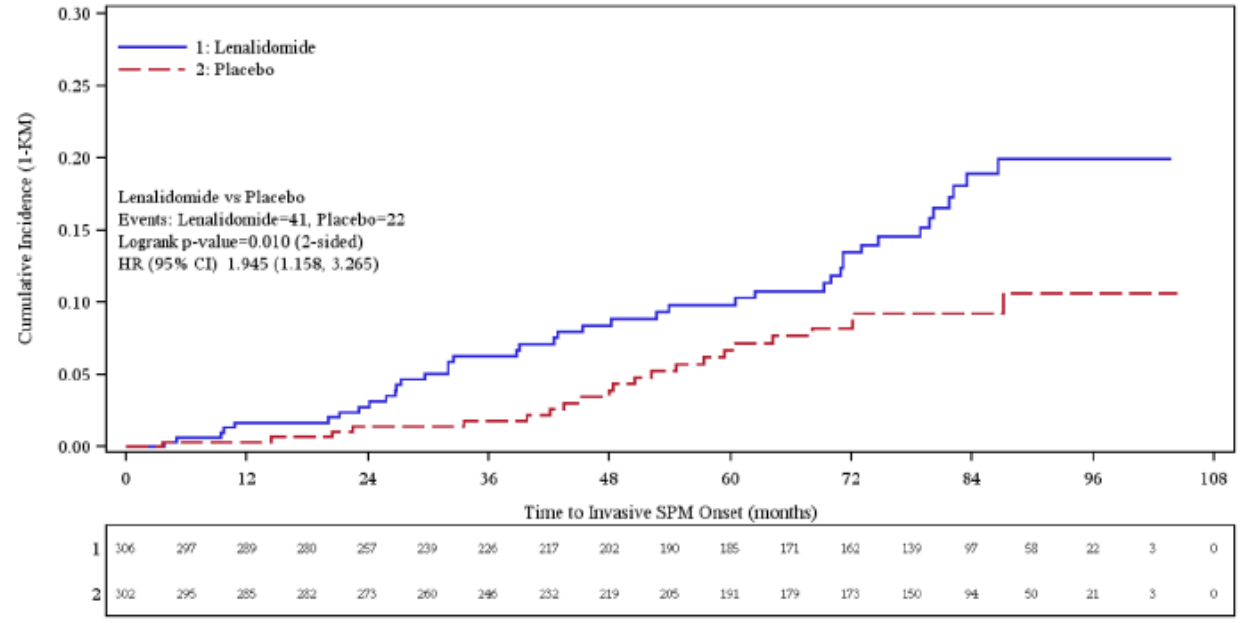
CIF = cumulative incidence function; SPM = second primary malignancy.
Source: Figure 14.11.3.2.1

Figure 15: Cumulative Incidence of B-Cell Second Primary Malignancy With Death as the Competing Risk in Study IFM 2005-02 as of the 01 Mar 2015 Data Cutoff Date (SPM Safety Analysis Population)



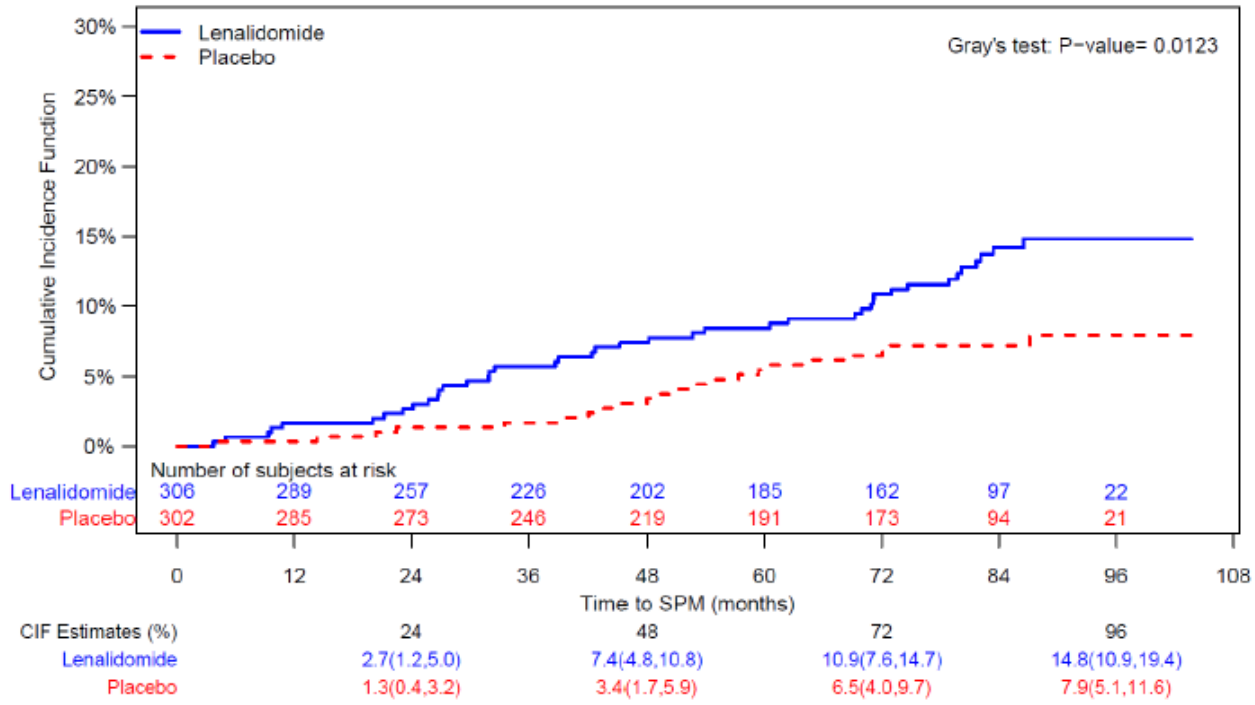
Invasive SPM

Figure 16: Cumulative Incidence Curves Using the Kaplan-Meier Method for Time to Onset of Invasive Second Primary Malignancy for Study IFM 2005-02 Cutoff Date 1 March 2015 (SPM Safety Analysis Population)



CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier; SPM = second primary malignancy.
Source: Figure 14.11.2.2.5

Figure 17: Cumulative incidence of invasive SPM with death as the Competing Risk in Study IFM 2005-02 as of the 1 March 2015 Data Cutoff Date (SPM Safety Analysis Population)



CIF = cumulative incidence function; SPM = second primary malignancy.
Source: Figure 14.11.3.2.5

Analysis of SPM in lenalidomide exposed versus non-exposed patients (1 March 2015)

For Study IFM 2005-02, the number of subjects with invasive SPMs was higher for the lenalidomide exposed population compared with the lenalidomide non-exposed population (61 [10.3%] versus 2 [14.3%], respectively). The number of person-years of observation time was much greater (43.48-fold) for the lenalidomide exposed population compared with the lenalidomide non-exposed population (3164.71 versus 72.78 person-years, respectively), since only a small minority of subjects did not receive lenalidomide consolidation treatment. A total of 2 subjects developed hematologic SPMs (AML and MDS [1 subject each]) among the small number of lenalidomide non-exposed subjects, resulting in an IR for invasive SPMs of 2.75 per 100 person-years (95% CI 0.69, 10.99) compared with an IR of 1.93 per 100 person-years (95% CI 1.50, 2.48) in subjects exposed to lenalidomide; however, the 95% CIs of the respective IRs overlap.

Table 40: Lenalidomide Exposure for Subjects in Study IFM 2005-02 (Safety Population)

Group	Lenalidomide Therapy During			Start of Lenalidomide Exposure	Number of Subjects (N = 608)	Number of Subjects With Invasive SPMs
	Consolidation[a]	Maintenance	Salvage[b]			
1	No	No	No	No exposure	14	2
2	No	No	Yes	Salvage	2	0
3	No	Yes	No	Maintenance	15	4
4	Yes	No	No	Consolidation	196	11

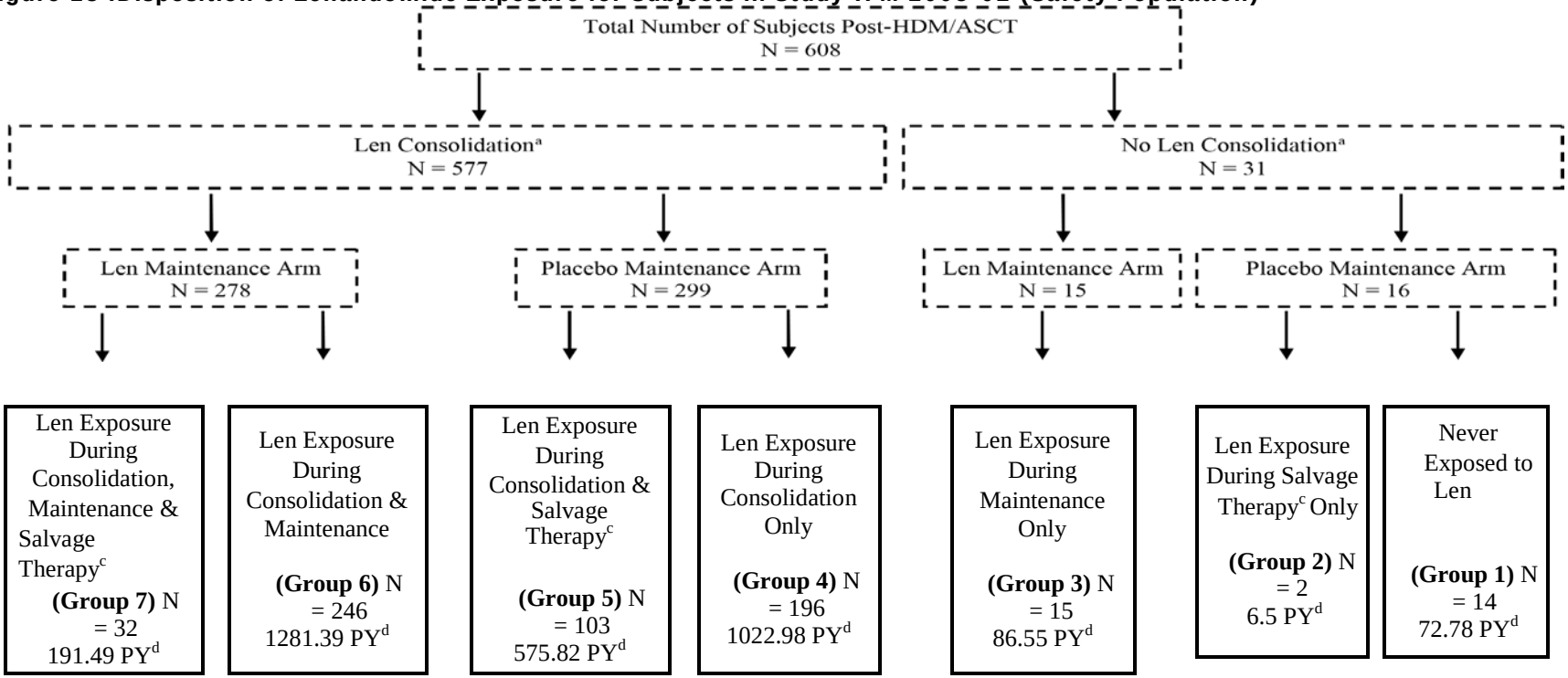
5	Yes	No	Yes	Consolidation	103	9
6	Yes	Yes	No	Consolidation	246	27
7	Yes	Yes	Yes	Consolidation	32	0

SPM = second primary malignancy.

[a] Following Protocol Amendment 2, all subjects in both treatment arms received 2 cycles of consolidation treatment with 25 mg/day lenalidomide posttransplantation on Days 1 to 21 of a 28-day cycle before initiation of maintenance treatment with placebo or lenalidomide at a dose of 10 mg/day, which could be increased to 15 mg/day if tolerable.

[b] Only data for the first salvage regimen were collected. Data cutoff date = 1 Mar 2015

Figure 18 :Disposition of Lenalidomide Exposure for Subjects in Study IFM 2005-02 (Safety Population)



ASCT = autologous stem cell transplant; HDM = high-dose melphalan; Len = lenalidomide; MM PD = multiple myeloma progressive disease; PY = person-years of observation time; SPMs = second primary malignancies.

[a] Following Protocol Amendment 2, all subjects in both treatment arms received 2 cycles of consolidation treatment with 25 mg/day lenalidomide post-ASCT on Days 1 to 21 of a 28 day cycle before initiation of maintenance treatment with placebo or lenalidomide at a dose of 10 mg/day, which could be increased to 15 g/day if tolerable.

[b] Prior to Protocol Amendment 2, subjects did not receive consolidation treatment.

[c] Only data for the first salvage regimen were collected.

[d] Person-years is observation time of the subject group. Observation time was calculated as **time from** the first dose of lenalidomide for the lenalidomide exposed group or first dose of placebo for the lenalidomide non-exposed group **to** the first invasive SPM, death, or data cutoff date, whichever occurred first, for each subject.
Data cutoff date = 1 Mar 2015.

Table 41: Frequencies and Incidence Rates of Invasive Second Primary Malignancies Including Invasive Subcategories: Subjects Exposed and Not Exposed to Lenalidomide in Study IFM 2005-02 (Safety Population)

	Subjects Exposed to Lenalidomide							Subjects Not Exposed to Lenalidomide
			Len Starting at Consolidation Placebo Maintenance		Len Starting at Consolidation Len Maintenance			
Invasive SPMs	Len Starting at Salvage Therapy[a] (Group 2) (N = 2)	Len During Maintenance Only (Group 3) (N = 15)	No Len Salvage (Group 4) (N = 196)	Len Salvage (Group 5) (N = 103)	No Len Salvage (Group 6) (N = 246)	Len Salvage (Group 7) (N = 32)	All Len Exposed (Groups 2 to 7) (N = 594)	No Len Exposure (Group 1) (N = 14)
Number of subjects (%)	0 (0.0)	4 (26.7)	11 (5.6)	9 (8.7)	37 (15.0)	0 (0.0)	**61 (10.3)**	**2 (14.3)**
Person-years	6.50	86.55	1022.98	575.82	1281.39	191.49	**3164.71**	**72.78**
Incidence rate/100 PY (95% CI)	--	**4.62 (1.73 – 12.31)**	**1.08 (0.60 – 1.94)**	**1.56 (0.81 – 3.00)**	**2.89 (2.09 – 3.99)**	--	**1.93 (1.50 – 2.48)**	**2.75 (0.69 – 10.99)**
Hematologic malignancies	0	2	4	3	19	0	28	2
AML	0	1	1	1	1	0	4	1
MDS to AML	0	0	0	0	4	0	4	0
MDS	0	0	1	1	4	0	6	1
B-cell malignancies (B=ALL and Hodgkin's disease)	0	2	1	1	9	0	13	0
Other	0	0	1	0	1	0	2	0
Solid tumors	0	2	7	6	19	0	34	0
Invasive SPMs	**0**	**4**	**11**	**9**	**37**	**0**	**61**	**2**

AML = acute myeloid leukemia; B-ALL = B-cell acute lymphocytic leukemia; CI = confidence interval; Len = lenalidomide; MDS = myelodysplastic syndromes; PY = person-years; SPM = secondary primary malignancy.

[a] Subjects with an invasive SPM that was diagnosed **on or after** the start of lenalidomide salvage therapy.

Data cutoff date = 01 Mar 2015.

Studies CALGB100104 and IFM 2005-02 pooled data

A total of 156 (14.8%) of the 1053 subjects in the pooled Studies CALGB 100104 and IFM 2005-02 experienced at least 1 SPM as of the 01 Feb 2016 data cutoff date. Of these, a higher frequency of subjects with SPMs was observed in the pooled lenalidomide arm compared with the pooled placebo arm (97 [18.3%] versus 59 [11.3%], respectively).

The frequency of subjects with invasive SPMs (hematologic and solid tumor SPMs) was higher in the pooled lenalidomide arm compared with the pooled placebo arm (79 [14.9%] versus 46 [8.8%], respectively). Of those with invasive SPMs, 40 (7.5%) of the 57 subjects with hematologic SPMs were in the pooled lenalidomide arm, while 17 (3.3%) subjects were in the pooled placebo arm. The frequency of subjects with solid tumor SPMs was also higher in the pooled lenalidomide arm compared with the pooled placebo arm (41 [7.7%] versus 30 [5.7%], respectively). The incidence rate of hematologic malignancies, most notably AML, MDS and B-cell malignancies (including Hodgkin's lymphoma), was 1.31 per 100 person-years for the lenalidomide arms and 0.58 per 100 person-years for the placebo arms (1.02 per 100 person-years for patients exposed to lenalidomide after ASCT and 0.60 per 100 person-years for patients not-exposed to lenalidomide after ASCT). The incidence rate of solid tumour SPMs was 1.36 per 100 person-years for the lenalidomide arms and 1.05 per 100 person-years for the placebo arms (1.26 per 100 person-years for patients exposed to lenalidomide after ASCT and 0.60 per 100 person-years for patients not-exposed to lenalidomide after ASCT).
The incidence rates of developing a non-melanoma skin cancer were similar for the pooled lenalidomide and pooled placebo arms (0.72 versus 0.59 per 100 person-years, respectively).

Table 42: **Number and percentage of subjects with second primary malignancies as of the 1 March 2015 data cutoff date – Pooled Data for Studies CALGB 100104 and IFM 2005-02 (SPM Safety Analysis Population)**

	Pooled Studies CALGB 100104 and IFM 2005-02			
	Lenalidomide (N = 530)		Placebo (N = 523)	
SPM Category	Data as of 1 Mar 2015 n (%)	Data as of 1 Feb 2016 n (%)	Data as of 1 Mar 2015 n (%)	Data as of 1 Feb 2016 n (%)
Hematologic Malignancies	36 (6.8)[a]	40 (7.5)[a]	17 (3.3)	17 (3.3)
AML	8 (1.5)	8 (1.5)	3 (0.6)	3 (0.6)
MDS to AML	5 (0.9)	5 (0.9)	0 (0.0)	0 (0.0)
MDS	8 (1.5)	8 (1.5)	7 (1.3)	7 (1.3)
B-cell malignancies (B-ALL and Hodgkin's disease)	15 (2.8)	19 (3.6)	5 (1.0)	5 (1.0)
Other[b]	1 (0.2)	1 (0.2)	2 (0.4)	2 (0.4)
Solid Tumors	38 (7.2)[c]	41 (7.7)	23 (4.4)[d]	30 (5.7)
Invasive SPMs	73 (13.8)[e]	79 (14.9)[e,f]	39 (7.5)[g]	46 (8.8)[g]
Non-Invasive SPMs (Non-melanoma skin cancer)	22 (4.2)	22 (4.2)	16 (3.1)	17 (3.3)
TOTAL SPMs	91 (17.2)[e,h,i,j]	97 (18.3)[e,f,h,i,j]	51 (9.8)[g,k,l,m,n]	59 (11.3)[g,k,l,m,n]

AML = acute myeloid leukemia; B-ALL = B-cell acute lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; MDS = myelodysplastic syndromes; SPM = second primary malignancy.

[a] One Subject (lenalidomide arm in Study IFM 2005-02) had 2 hematologic SPMs (AML and DLBCL) and is counted only once in the hematologic malignancies category.

[b] Other includes 1 case of acute biphenotypic leukemia (lenalidomide arm in Study IFM 2005-02), 1 case of malignant histiocytosis (placebo arm in Study CALGB 100104), and 1 case of T-cell lymphoma (placebo arm in Study IFM 2005-02).

[c] One Subject (lenalidomide arm in Study CALGB 100104) had 2 solid tumor SPMs (endometrial cancer and breast cancer) and is counted only once in the solid tumor category.

[d] One Subject (placebo arm in Study CALGB 100104) had 2 solid tumor SPMs (endometrial cancer stage II and ovarian cancer) and is counted only once in the solid tumor category.

[e] One Subject (lenalidomide arm in Study IFM 2005-02) had 3 SPMs: a hematologic SPM (B-cell type acute leukemia), a solid tumor SPM (prostate cancer), and 4 non-melanoma skin cancers. This subject is counted only once in the invasive SPM category and the total.

[f] One Subject (lenalidomide arm in Study CALGB 100104) had both a hematologic SPM (MDS) and solid tumor SPM (colon cancer). This subject is counted only once in the invasive SPM category and the total.

[g] One Subject (placebo arm in Study CALGB 100104) had both a hematologic SPM (MDS) and solid tumor SPM (malignant melanoma). This subject is counted only once in the invasive SPM category and the total.

[h] One Subject (lenalidomide arm in Study CALGB 100104) had both a hematologic SPM (AML) and 2 non-melanoma skin cancers. This subject is counted only once in the total. [i] One Subject (lenalidomide arm in Study CALGB 100104) had both a solid tumor SPM (prostate cancer) and a non-melanoma skin cancer. This subject is counted only once in the total.

[j] One Subject (lenalidomide arm in Study IFM 2005-02) had both a hematologic SPM (Hodgkin's disease) and a non-melanoma skin cancer. This subject is counted only once in the total.

[k] One Subject (placebo arm in Study CALGB 100104) had both a solid tumor SPM (metastatic squamous cell carcinoma) and 3 non-melanoma skin cancers. This subject is counted only once in the total. [l] One Subject (placebo arm in Study CALGB 100104) had both a solid tumor SPM (endometrial cancer) and a non-melanoma skin cancer. This subject is counted only once in the total.

[m] One Subject (placebo arm in Study IFM 2005-02) had both a solid tumor SPM (malignant melanoma) and a non-melanoma skin cancer. This subject is counted only once in the total.

[n] One Subject (placebo arm in Study IFM 2005-02) had both a solid tumor SPM (superficial spreading melanoma stage unspecified) and 13 non-melanoma skin cancers. This subject is counted only once in the total.

Table 43: Incidence rates of second primary malignancies as of the 1 March 2015 data cutoff date pooled data for studies CALGB 100104 and IFM 2005-02 (SPM Safety Analysis Population)

	Incidence Rate per 100 person-years[a] (95% Confidence Intervals)			
	Lenalidomide (N = 530)		**Placebo (N = 523)**	
SPM Category	**Data as of 01 Mar 2015 n (%)**	**Data as of 01 Feb 2016 n (%)**	**Data as of 01 Mar 2015 n (%)**	**Data as of 01 Feb 2016 n (%)**
Hematologic Malignancies	1.28 (0.93 - 1.78)	1.31 (0.96 – 1.79)	0.63 (0.39 - 1.01)	0.58 (0.36 – 0.94)
Solid Tumors	1.36 (0.99 - 1.87)	1.36 (1.00 – 1.85)	0.86 (0.57 – 1.29)	1.05 (0.73 – 1.50)
Invasive SPMs	2.69 (2.14 - 3.38)	2.69 (2.16 – 3.35)	1.46 (1.07 – 2.00)	1.61 (1.21 – 2.15)
Non-Invasive SPMs (Non-melanoma skin cancer)	0.78 (0.52 - 1.19)	0.72 (0.48 – 1.10)	0.60 (0.36 - 0.97)	0.59 (0.37 – 0.95)
TOTAL SPMs	3.42 (2.79 - 4.21)	3.39 (2.78 – 4.13)	1.94 (1.47 - 2.55)	2.09 (1.62 – 2.70)

SPM = second primary malignancy.

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

Analysis of SPM in lenalidomide exposed versus non-exposed patients (01 March 2015)

Table 44: Frequencies and incidence rates of invasive second primary malignancies including invasive subcategories: subjects exposed and not exposed to lenalidomide in Studies CALGB 100104 and IFM 2005-02 (Pooled Data Safety Population)

	As Treated Population			As Randomized Population[a]	
		No Exposure to Lenalidomide			
Invasive SPMs	**Exposure to Lenalidomide (N = 979)**	**No Exposure to Lenalidomide (N = 54)**	**Exposure to Lenalidomide During Induction Only(N = 20)**	**Lenalidomide (N = 530)**	**Placebo (N = 523)**
Number of subjects (%)	107 (10.9)	3 (5.6)	0 (0.0)	73 (13.8)	39 (7.5)
Person-years	4825.83	220.86	82.09	2717.95	2662.64
Incidence rate/100 PY (95% CI)	2.22 (1.83 – 2.68)	1.36 (0.44 – 4.21)	--	2.69 (2.14 - 3.38)	1.46 (1.07 – 2.00)
Hematologic malignancies	51	2	0	36	17
AML	10	1	0	8	3
MDS to AML	5	0	0	5	0
MDS	14	1	0	8	7
B-cell malignancies (B=ALL and Hodgkin's disease)	20	0	0	15	5
Other	3	0	0	1	2
Solid tumors	58	1	0	38	23
Invasive SPMs	**107**	**3**	**0**	**73**	**39**

AML = acute myeloid leukemia; B-ALL = B-cell acute lymphocytic leukemia; CI = confidence interval; MDS = myelodysplastic syndromes; PY = person-years; SPM = secondary primary malignancy. [a] The as randomized safety population is defined as all randomized subjects who received at least 1 dose of lenalidomide or placebo therapy.
Data cutoff date = 1 Mar 2015.
Note: "--" denotes that incidence rates were not calculated.

Deaths

Due to differences in the data collected for cause of death between the IFM study (death categories) and the CALGB study (verbatim terms), a comparison of cause of death by frequency of PTs is not possible. On-treatment deaths are defined as deaths occurring between the first dose and 30 days after the last dose of maintenance treatment.

Table 45: Summary of Causes of Death by Categories During and After Study Treatment for the CALGB 100104 (Excluding Deaths after Cross Over) and IFM 2005-02 Studies (Safety Population)

Death Category	Trial and Study Arm (Lenalidomide Starting QD Dose)			
	CALGB 100104		IFM 2005-02	
	R10 (10 mg)[a]	PBO[b]	R10[c] (10 mg)[a]	Placebo[c]
	(N = 224) n (%)	(N = 221) n (%)	(N = 293) n (%)	(N = 280) n (%)
AE (deaths due to toxicity ≤ 30 days after last dose)	1 (0.4)	2 (0.9)	3 (1.0)	0
MM or MM-related	48 (21.4)	79 (35.7)	82 (28.0)	95 (33.9)
Post-treatment toxicity (for deaths due to toxicity > 30 days after last dose)	5 (2.2)	5 (2.3)	13 (4.4)	16 (5.7)
SPM or SPM-treatment related	8 (3.6)	2 (0.9)	14 (4.8)	11 (3.9)
Other (for those causes of death that were unknown or missing)	6 (2.7)	3 (1.4)	5 (1.7)	4 (1.4)

21/28 = Days 1 to 21 of 28-day cycles; 28/28 = Days 1 to 28 of 28-day cycles; AE = adverse event; MM =multiple myeloma; PBO = placebo; QD = once daily; R = lenalidomide; SPM = second primary malignancy.

[a] The starting lenalidomide maintenance dose (R 10 mg QD 28/28) could be raised to 15 mg QD (28/28), according to the study design.

[b] In Study CALGB 100104, data were excluded for placebo subjects crossing over to lenalidomide after the unblinding of the study.

[c] In Study IFM 2005-02, data were excluded from all subjects for the 2 cycles of lenalidomide consolidation (R 25 mg QD 21/28).

Laboratory findings

In CALGB study, changes from baseline for any of the parameters examined were small in both treatment arms, with no consistent pattern suggesting any differences.

In IFM study, the frequency of subjects with Grade 3 or 4 WBC levels was higher in the lenalidomide arm than in the placebo arm (44.1% versus 9.6%), although the frequency of Grade 4 events was comparable between the two arms (2.0% and 1.3%, respectively). It follows that the frequency of subjects with Grade 3 or 4 neutrophils levels was also higher in the lenalidomide arm than in the placebo arm (71.9% versus 28.8%). The proportion of subjects with Grade 3 or 4 thrombocytopenia was higher in the lenalidomide than the placebo arm (15.0% versus 8.3%).

The number of subjects with elevated total bilirubin, AP, GGT levels was slightly higher (>5%) in lenalidomide group. The same for ALT and AST levels (≥ 10%)

Safety in special populations

Elderly

In each age subgroup (Age Subgroup < 65years or ≥ 65 years; and Age Subgroup < 60 years or ≥ 60 years), the difference in the lenalidomide safety profile between the 2 studies is generally consistent with the overall safety profile.

Renal impairment

In both studies, subjects were included with adequate renal function pre-ASCT (exclusion criteria: CrCl < 40 mL/min (before ASCT) in CALGB study and history of renal disorder not related to the disease and defined by serum creatinine > 160 µmol in IFM).

In each subgroup (creatinine clearance < 50 mL/min or ⩾ 50 mL/min), the lenalidomide safety profile in both studies was generally consistent with the overall safety profile.

Hepatic impairment

Patients with hepatic impairment were excluded

Safety related to drug-drug interactions and other interactions

N/A.

Discontinuation due to adverse events

Overall, TEAEs leading to discontinuation of study drug were reported more frequently in the lenalidomide pool than the placebo pool (27.9% versus 6.8%, respectively). With the exception of neutropenia (2.3%), the frequencies of individual TEAEs leading to discontinuation of study drug were low (< 2%) in the lenalidomide pool.

Table 46: TEAEs Leading to Discontinuation of Study Drug Reported for at Least 1% of Subjects in Any Treatment Arm by Trial and Study Arm: Within Study and Interstudy Comparisons for CALGB 100104 and IFM 2005 02 Maintenance – Pooled and Non-pooled (Safety Population)

	Trial and Study Arm (Lenalidomide Starting QD Dose)					
	CALGB 100104		IFM 2005-02		CALGB 100104 + IFM 2005-02	
	R10 (10 mg)[a]	Placebo[b]	R10[d] (10 mg)[a]	Placebo[d]	R10 Pool[d] (10 mg)[a]	Placebo Pool[b,d]
System Organ Class Preferred Term	**(N= 224) n (%)**	**(N= 221)[c] n (%)**	**(N= 293) n (%)**	**(N= 280) n (%)**	**(N= 517) n (%)**	**(N= 501) n (%)**
Subjects with ≥ 1 TEAE leading to discontinuation	63 (28.1)	6 (2.7)	81 (27.6)	28 (10.0)	144 (27.9)	34 (6.8)
Blood and Lymphatic System Disorders	11 (4.9)	0	12 (4.1)	3 (1.1)	23 (4.4)	3 (0.6)
Neutropenia[e]	5 (2.2)	0	7 (2.4)	0	12 (2.3)	0
Thrombocytopenia[e]	6 (2.7)	0	3 (1.0)	2 (0.7)	9 (1.7)	2 (0.4)
Gastrointestinal Disorders	5 (2.2)	0	12 (4.1)	0	17 (3.3)	0
Diarrhoea[e]	5 (2.2)	0	5 (1.7)	0	10 (1.9)	0
Gastrointestinal disorder	0	0	4 (1.4)	0	4 (0.8)	0
General Disorders and Administration Site Conditions	12 (5.4)	1 (0.5)	10 (3.4)	1 (0.4)	22 (4.3)	2 (0.4)
Adverse event[f]	10 (4.5)	1 (0.5)	0	0	10 (1.9)	1 (0.2)
Asthenia	0	0	4 (1.4)	0	4 (0.8)	0
Pyrexia	1 (0.4)	0	3 (1.0)	0	4 (0.8)	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	16 (7.1)	1 (0.5)	7 (2.4)	2 (0.7)	23 (4.4)	3 (0.6)
Acute myeloid leukaemia	3 (1.3)	0	1 (0.3)	1 (0.4)	4 (0.8)	1 (0.2)
Breast cancer	3 (1.3)	0	0	0	3 (0.6)	0
Myelodysplastic syndrome	5 (2.2)	0	1 (0.3)	0	6 (1.2)	0
Nervous System Disorders	5 (2.2)	2 (0.9)	13 (4.4)	4 (1.4)	18 (3.5)	6 (1.2)
Neuropathy peripheral	1 (0.4)	1 (0.5)	5 (1.7)	0	6 (1.2)	1 (0.2)
Respiratory, Thoracic and Mediastinal Disorders	1 (0.4)	0	5 (1.7)	1 (0.4)	6 (1.2)	1 (0.2)
Lung disorder	0	0	4 (1.4)	0	4 (0.8)	0
Vascular Disorders	1 (0.4)	0	4 (1.4)	3 (1.1)	5 (1.0)	3 (0.6)
Deep vein thrombosis	0	0	3 (1.0)	0	3 (0.6)	0

21/28 = Days 1 to 21 of 28-day cycles; 28/28 = Days 1 to 28 of 28-day cycles; AE = adverse event; CRF = case report form; CTCAE = Common Terminology Criteria for Adverse Events; Incl = Including; MedDRA = Medical Dictionary for Regulatory Activities; PD = progressive disease; PT = preferred term; QD = once daily; R = lenalidomide; TE = transplant eligible; TEAE = treatment-emergent adverse event; TNE = transplant

noneligible.[a] The starting lenalidomide maintenance dose (R 10 mg QD 28/28) could be raised to 15 mg QD (28/28), according to the study design.

[b] In Study CALGB 100104, for placebo subjects, only AEs up to crossing over to lenalidomide are included.

[c] N = 145 is for placebo subjects in CALGB who did not cross over prior to PD upon study unblinding.

[d] In Study IFM 2005-02, data were excluded from all subjects for the 2 cycles of lenalidomide consolidation (R 25 mg QD 21/28).

[e] This term corresponds to a preprinted CTCAE term or prompt on the CRF of Study CALGB 100104.

[f] Due to CRF layout in CALGB, specific AEs that led to treatment discontinuation were not collected. Subjects with "AE," "other disease," or "other, specify" as the reason for treatment discontinuation were retrospectively queried for a specific adverse event term that may have led to discontinuation. For those subjects with terms not provided, PT of "adverse event" was utilized.

Note: System organ classes and preferred terms are coded using MedDRA Version 15.1 and are listed alphabetically. A subject with multiple occurrences of a TEAE is counted only once in that TEAE category.
Data cutoff: 1 March 2015

Post marketing experience

During the most recent PSUR reporting interval, 2 safety signals were identified from the literature (Epstein-Barr virus [EBV] reactivation and serious hypocalcemia), and 1 was identified from a health authority (pulmonary alveolar hemorrhage [PAH]). Safety topic reviews were completed for all 3 signals. For EBV reactivation and PAH, no changes to the reference safety information were required. Serious hypocalcemia is a listed event in the Revlimid Company Core Data Sheet (CCDS); no additional labeling was warranted. PAH remain under close monitoring.

In addition, an in-depth analysis of peripheral neuropathy in patients treated with lenalidomide was performed in response to the PRAC recommendation adopted on 09 Jul 2015 for the lenalidomide PSUR 11 (covering 27 Dec 2013 to 26 Dec 2014). The MAH was requested to discuss whether peripheral neuropathy remains an important potential risk for lenalidomide, or, if considering MDS and NDMM studies, this risk should be considered as an identified risk in the EU RMP. This review was provided in the next PSUR 12 (covering 27 Dec 2014 to 26 Dec 2015). Overall, the analysis of peripheral neuropathy has confirmed the established safety profile of lenalidomide and the status of this important potential risk remained unchanged.

During the assessment of the previous PSUR 11, the MAH had planned to update the EU SmPC for Revlimid to align with the CCDS version 12 by including acute graft versus host disease (aGvHD) after allogeneic hematopoietic transplant as a new ADR based on post-marketing/literature reports, which was a confirmed signal during the reporting period of PSUR 11. However, the PRAC did not agree to update the EU SmPC to include the ADR of aGvHD for the time being and recommended that the signal be kept ongoing and that evidence of off-label use of lenalidomide in this unapproved indication in EU be further investigated in the next PSUR.

2.5.1. Discussion on clinical safety

The evaluation of safety is primarily based on data from study CALGB 100104 and study IFM 2005-02. These two studies randomized 1074 subjects; 1018 of those subjects started maintenance treatment (517 subjects received lenalidomide and 501 subjects received placebo). As of the 1 March 2015 data cutoff date, lenalidomide treatment remains ongoing in the CALGB study for 67 subjects (48 from the lenalidomide arm and 19 who crossed over from the placebo arm), as well as long-term safety follow-up (including follow-up for SPMs) for all subjects. Treatment was discontinued in the IFM study in January 2011, but long-term follow-up for deaths and SPMs for all subjects remains ongoing.

The serious adverse reactions observed more frequently (⩾5%) with lenalidomide maintenance than placebo were: Pneumonias (10.6%; combined term) from IFM 2005-02 and Lung infection (9.4%) from CALGB 100104 (SmPC section 4.8).

In the IFM 2005-02 study, the adverse reactions observed more frequently with lenalidomide maintenance than placebo were neutropenia (60.8%), bronchitis (47.4%), diarrhoea (38.9%), nasopharyngitis (34.8%), muscle spasms (33.4%), leucopenia (31.7%), asthenia (29.7%), cough (27.3%), thrombocytopenia (23.5%), gastroenteritis (22.5%) and pyrexia (20.5%) (SmPC section 4.8).

In the CALGB 100104 study, the adverse reactions observed more frequently with lenalidomide maintenance than placebo were neutropenia (79.0%), thrombocytopenia (72.3%), diarrhoea (54.5%), rash (31.7%), upper respiratory tract infection (26.8%), fatigue (22.8%), leucopenia (22.8%) and anaemia (21.0%) (SmPC section 4.8).

The observed *TEAEs* were mainly expected. In both studies, there were about twice more serious TEAE in lenalidomide arms vs placebo. The main concerned SOCs with SAE were “Blood and Lymphatic System Disorders” with 7.6% and 8.5 % in lenalidomide arms in CALGB and IFM study respectively, vs (1.8 % and 1.4%) in placebo arms in CALGB and IFM study respectively; and “infections and infestations” with 16.1% and 13.7 % in lenalidomide arms in CALGB and IFM study respectively, vs (5.0 % and 3.6%) in placebo arms in CALGB and IFM study respectively. Reported serious infections were mainly respiratory infections, considering the main reported PT Bronchitis, Lung infection and Upper respiratory tract infection. It should also be noted that PT “lung disorders” reported in IFM study is related to infections (6.8% in lenalidomide arm). Similar trends in these serious TEAE are observed when comparing both studies. These serious TEAE are coherent with the known safety profile of lenalidomide.

The overall frequency of subjects with Grade 3 or 4 TEAEs during CALGB lenalidomide maintenance was 70.1% compared with 75.1% in IFM lenalidomide during maintenance. The most commonly reported Grade 3 or 4 TEAEs in the CALGB lenalidomide arm were neutropenia, thrombocytopenia, and leukopenia (> 15% of subjects each), followed by lymphopenia, neutropenic infection, lung infection, fatigue, febrile neutropenia, diarrhea, and pneumonia (> 5% of subjects each). The most commonly reported Grade 3 or 4 TEAEs in the IFM lenalidomide arm were neutropenia and leukopenia (> 15% of subjects each), followed by thrombocytopenia and lung disorder (> 5% of subjects each).

Grade 5 TEAEs were reported in 3 (1.3%) subjects in the lenalidomide arm of the CALGB study, of which 2 of 3 subjects died > 30 days after last treatment, and in 7 (2.4%) subjects in the lenalidomide arm of the IFM study, of which 3 of 7 subjects died > 30 days after last treatment . All individual Grade 5 TEAEs occurred in < 1% of CALGB lenalidomide subjects and in ≤ 0.4% of IFM lenalidomide subjects.

In late 2010, a safety concern arose with regard to SPMs based on the emerging results of 3 prospective, randomized, double-blind, placebo-controlled lenalidomide studies in subjects with NDMM (Studies MM-015, IFM 2005-02, and CALGB 100104) leading to an evaluation of SPMs across the entire MAH lenalidomide safety database, including all investigational indications.

Previous analyses of the CALGB and IFM studies (data cutoff of May 2013; median follow-up of surviving subjects of 46.7 and 60.9 months, respectively) showed that subjects treated with lenalidomide maintenance therapy post-HDM/ASCT had a statistically significant increased risk for hematologic SPMs, and solid tumour SPMs (negative trend only) compared with subjects given placebo. Based on safety data provided in studies IFM and CALGB (data cut-off of Feb 2016), a higher frequency of SPM was observed in patients in lenalidomide arm: CALGB: 20.5% versus 11.8%, respectively, and IFM: 16.7% versus 10.9%.

To better characterize the potential risk increase of SPM associated with lenalidomide maintenance treatment, the MAH re-analysed the SPM results from both IFM and CALGB studies according to the lenalidomide exposure. PY was calculated as the time from the first dose date to the onset date of the first SPM for subjects with a SPM and the time from the first dose date to the date of last follow-up for subjects without an SPM. Duration of exposure was not taken into account in this calculation. IR also relied on the assumption that event rate per time unit is constant over time, e.g. that the risk is the same early and late after high dose therapy. This is less likely for, e.g. EBV associated Hodgkin.

A small minority of subjects in Studies CALGB 100104 and IFM 2005-02 (N = 54) were never exposed to lenalidomide during these studies. A total of 74 subjects were non-exposed to lenalidomide after ASCT. The pooled data included 979 subjects who were exposed to lenalidomide during 1 or more of the treatment phases of these studies. Cross-over to lenalidomide whether prior to progression (after unblinding), after progression or as late salvage is not random driven but subject to investigator decision where time after ABMT is of relevance. Early progression after ABMT reflects poor prognosis and probably a more complex genotype and higher mutation burden. Higher mutation burden probably is reflected in a higher mutation burden in non-myeloma cells and a higher likelihood of SPM. As lenalidomide is non-mutagenic, but acts as a "facilitator" for SPM development, precise mechanisms to be defined, it is probably not possible to define the add-on risk of lenalidomide over time for SPM development in patients crossing-over.

For the pooled CALGB and IFM studies, the frequency of subjects with invasive SPMs was higher for the lenalidomide exposed population compared with the lenalidomide non-exposed population (107 [10.9%] versus 3 [5.6%], respectively).

The increased risk of secondary primary malignancies associated with lenalidomide is relevant also in the context of NDMM after stem cell transplantation. Though this risk is not yet fully characterized, it should be kept in mind when considering and using Revlimid in this setting.

The incidence rate of hematologic malignancies, most notably AML, MDS and B-cell malignancies (including Hodgkin's lymphoma), was 1.31 per 100 person-years for the lenalidomide arms and 0.58 per 100 person-years for the placebo arms (1.02 per 100 person-years for patients exposed to lenalidomide after ASCT and 0.60 per 100 person-years for patients not-exposed to lenalidomide after ASCT). The incidence rate of solid tumour SPMs was 1.36 per 100 person-years for the lenalidomide arms and 1.05 per 100 person-years for the placebo arms (1.26 per 100 person-years for patients exposed to lenalidomide after ASCT and 0.60 per 100 person-years for patients not-exposed to lenalidomide after ASCT) (SmPC section 4.4).

Overall, grade 4 neutropenia was observed at a higher frequency in the lenalidomide maintenance arms compared to the placebo maintenance arms in the 2 studies evaluating lenalidomide maintenance in NDMM patients who have undergone ASCT (32.1% vs 26.7% in CALGB 100104 and 16.4% vs 0.7% in IFM 2005-02, respectively). Treatment-emergent AEs of neutropenia leading to lenalidomide discontinuation were reported in 2.2% of patients in CALGB 100104 and 2.4% of patients in IFM 2005-02, respectively. Grade 4 febrile neutropenia was reported at similar frequencies in the lenalidomide maintenance arms compared to placebo maintenance arms in both studies (0.4% vs 0.5% in CALGB 100104 and 0.3% vs 0% in IFM 2005-02, respectively). Patients should be advised to promptly report febrile episodes, a treatment interruption and/or dose reductions may be required (SmPC sections 4.2, 4.4, 4.8).

Grade 3 or 4 thrombocytopenia was observed at a higher frequency in the lenalidomide maintenance arms compared to the placebo maintenance arms in studies evaluating lenalidomide maintenance in NDMM patients who have undergone ASCT (37.5% vs 30.3% in CALGB 100104 and 13.0% vs 2.9% in IFM 2005-02, respectively). Patients and physicians are advised to be observant for signs and

symptoms of bleeding, including petechiae and epistaxis, especially in patients receiving concomitant medicinal products susceptible to induce bleeding (SmPC sections 4.4, 4.8).

2.5.2. Conclusions on clinical safety

Safety results for patients with NNMM treated with lenalidomide were in general consistent with the known safety profile of lenalidomide. The SmPC has been updated with the risk of increase of SPM associated with lenalidomide maintenance treatment.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The applicant implemented the changes in the RMP as requested by PRAC and/or CHMP. The PRAC considered that the risk management plan version 34.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 34.0 with the following content (new text marked as underlined, deletions marked as strikethrough):

Safety concerns

Summary of safety concerns	
Important identified risks	-Teratogenicity -Thrombocytopenia and bleeding -Neutropenia and infection -Thromboembolic events -Cutaneous reactions -Hypersensitivity and angioedema -Diarrhoea and constipation -Tumour lysis syndrome (TLS) <u>Important Identified Risks Related to Indication/Target Population</u> <u>-For mantle-cell lymphoma (MCL): Tumour flare reaction (TFR)</u> -For newly diagnosed multiple myeloma (NDMM): acute myeloid leukaemia (AML) and B-cell malignancies[a] -For relapsed and/or refractory multiple myeloma (RRMM): non melanoma skin cancer (NMSC[b])
Important potential risks	-Peripheral neuropathy -Cardiac failure -Cardiac arrhythmias -Renal failure -Ischaemic heart disease (including myocardial infarction) -Interstitial lung disease (interstitial pneumonitis) -Hepatic disorders -Off-label use <u>Important Potential Risks Related to Indication/Target Population</u> -For NDMM: NMSC[b] -For RRMM: AML and B-cell malignancies[a] -For myelodysplastic syndrome (MDS) <u>and MCL</u>: AML and B-cell

Summary of safety concerns	
	malignancies[a]; NMSC[b] -Other second primary malignancies (SPM) (ie, those not detailed above for the RRMCL, NDMM, RRMM and MDS populations)
Missing information	-Paediatric use -Use in moderate and severe hepatic impairment -Use in breastfeeding

[a] The risk of AML and B-cell malignancies is an identified risk for the NDMM population, and a potential risk for the MCL, RRMM and MDS populations

[b] The risk of NMSC is an identified risk for the RRMM population, and a potential risk for the MCL, NDMM and MDS populations

Pharmacovigilance plan

Study/Activity **Type, Title and Category (1 to 3)**	**Objectives**	**Safety Concerns Addressed**	**Status (planned, started)**	**Date for Submission of Interim or Final Reports (planned or actual)**
MDS PASSes *Non-interventional: observational Category 1*	To gather safety data on the use of lenalidomide in MDS patients and monitor off-label use (prospective disease registry in transfusion-dependent low- and INT-1-risk MDS with an isolated del 5q [MDS-010] and a retrospective drug utilisation study of Revlimid in MDS [MDS-012]).	AML and survival. Safety profile in a 'real world' setting.	Ongoing	Safety updates submitted with future PSURs. The final study report for MDS-010 could be available in 2022.
Connect® MDS/AML Disease Registry *Non-interventional: observational Category 3*	The primary objectives of the registry are to describe practice patterns of common first-line treatment regimens (including lenalidomide-based) in the community and academic settings. Additionally, the registry will provide insight into treatment regimens and therapy sequence in clinical practice as they relate to clinical outcomes (response, OS, PFS) in patients with symptomatic MDS. Data regarding SPM are also being collected.	AML and B-cell malignancies NMSC Other SPM	Ongoing	Safety updates submitted with future PSURs.
RRMCL PASS *Category 3*	To further investigate and characterise the associations of lenalidomide with TFR/high tumour burden.	TFR/high tumour burden	Planned	The final study report could be available in 2022. Safety updates submitted with future PSURs.

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional pharmacovigilance activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Specific targeted follow-up questionnaires to study the relation between lenalidomide and TFR/high tumour burden, ATE, VTE and SPMs should be implemented. All these safety items should be reported and assessed at each PSUR evaluation.

The PRAC also considered that the studies in the post-authorisation development plan are sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Safety Concern	**Proposed Routine Risk Minimisation Measures**	**Proposed Additional Risk Minimisation Measures**
Important Identified Risk		
Teratogenicity	Routine risk minimisation activities (SmPC and PL). Sections 4.3. 4.4, 4.6, 4.8, 5.3 of SmPC: Specific pregnancy reporting form	– Celgene PPP – Educational Programme o Direct HCP communication prior to launch o Direct HCP communication with findings from CC-501-TOX-004 o HCP kit to include booklet o Treatment algorithm, pregnancy reporting form, patient card, patient brochure and checklists. – Therapy management o Criteria for determining women of childbearing potential, Contraceptive measures and pregnancy testing for women of childbearing potential o Advice in SmPC, Dear HCP letter and educational materials – System to ensure appropriate measures have been completed o Patient card to document childbearing status, counselling and pregnancy testing
Thrombocytopenia and Bleeding	– Section 4.2, 4.4, 4.8 of SmPC – Advice to patients in PL.	– 'Dear HCP' letter prior to launch. – HCP Kit o HCP Brochure – Patient Brochure.
Neutropenia and Infection	– Section 4.2, 4.4, 4.8 of SmPC – Advice to patients in PL.	– 'Dear HCP' letter prior to launch. – HCP Kit o HCP Brochure – Patient Brochure.
Thromboembolic Events	– Sections 4.4 and 4.8 of SmPC. – Advice to patients in PL.	– 'Dear HCP' letter prior to launch. – HCP Kit o HCP Brochure – Patient Brochure.

Cutaneous Reactions	– Rash, Stevens-Johnson syndrome and toxic epidermal necrolysis discussed in Sections 4.2, 4.4 and 4.8 of SmPC and in the PL.	– 'Dear HCP' letter prior to launch. – HCP Kit o HCP Brochure
Hypersensitivity and Angioedema	– SmPC Section 4.3: contraindicated in patients who are hypersensitive to the active substance or any of the excipients. – Allergic reactions discussed in SmPC Section 4.4. – Hypersensitivity listed as an ADR in Section 4.8 of SmPC and in PL. – Angioedema discussed in Sections 4.2 and 4.8 of SmPC and in the PL.	– 'Dear HCP' letter prior to launch. – HCP Kit o HCP Brochure
Diarrhoea and Constipation	- Section 4.8 of SmPC and PL	– 'Dear HCP' letter prior to launch
Tumour Lysis Syndrome	– Sections 4.4 and 4.8 –	– 'Dear HCP' letter prior to launch.
Acute Myeloid Leukaemia and B-cell Malignancies	– Section 4.4 and 4.8 of SmPC – Advice to patients provided in PL.	– Dear HCP letter following EC Approval for MDS – 'Dear HCP' letter after CHMP opinion of Article 20 procedure EMEA/H/C/717/A20/048 received 22 Sep 2011. – HCP Kit. o HCP Brochure.
Non-melanoma Skin Cancers	– Section 4.4 and 4.8 of SmPC – Advice to patients provided in PL.	None
Tumour Flare Reaction	– Section 4.2, 4.4, 4.8 of SmPC –	– HCP Kit
Important Potential Risk		
Peripheral Neuropathy	– Section 4.4 and 4.8 of SmPC	– HCP Kit o HCP Brochure.
Cardiac Failure and Cardiac Arrhythmias	– Section 4.8 of SmPC. – Listed in PL.	None
Renal Failure	– Section 4.8 of SmPC.	– HCP Kit o HCP Brochure.
Ischaemic Heart Disease (including myocardial infarction)	The association between ischaemic heart disease and lenalidomide is unknown. Close monitoring will continue. – Myocardial infarction is included in Sections 4.4 and 4.8 of the SmPC.	None
Interstitial Lung Disease (interstitial pneumonitis)	– Listed as an ADR in Section 4.8 of SmPC.	None

Hepatic Disorders	– Sections 4.4 and 4.8 of SmPC.	– Dear HCP' letter prior to launch. – Dear HCP letter after EC approval of variation EMEA/H/C/00717/058 received 19 Nov 2012. – HCP Kit o HCP Brochure
Other SPM	– Section 4.4 and 4.8 of SmPC – Advice to patients provided in PL.	– ''Dear HCP' letter after CHMP opinion of Article 20 procedure EMEA/H/C/717/A20/048 received 22 Sep 2011. – HCP Kit o HCP Brochure
Off-label Use	– Collection of off-label use data detailed in Section 4.4 of SmPC.	None
Missing Information		
Paediatric Use	– Section 4.2 of SmPC – Advice to patients in PL.	None
Use in Moderate and Severe Hepatic Impairment	– Section 4.2 of SmPC:	– HCP Kit o HCP Brochure.
Use in Breastfeeding	– Section 4.6 of SmPC: – Advice to patients in PL.	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Furthermore, the MAH introduced 7-day pack sizes for the 10 mg and 15 mg strengths with subsequent changes to the Product Information.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Multiple myeloma accounts for about 10% to 18% of hematologic malignancies. It is a disease of the elderly, with an overall median age at manifestation of approximately 70 years. The prognosis of patients with MM depends on a variety of factors at time of diagnosis. Induction therapy with subsequent HDM supported by ASCT is considered the standard for first-line treatment for young and fit MM patients. Despite improvements in therapeutic options and long-term outcome during the past years, most patients still experience disease relapse or have progressive disease.

3.1.2. Available therapies and unmet medical need

Revlimid (lenalidomide) is already indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant. Revlimid is also indicated in combination with dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

No drug has currently been approved in the post-ASCT setting (TE NDMM) however the European Myeloma Network recommendations on the evaluation and treatment of NDMM include the use of lenalidomide, thalidomide, or bortezomib as maintenance therapy post-ASCT for patients with NDMM.

3.1.3. Main clinical studies

Study CALGB 100104 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, 2-arm parallel group study of maintenance therapy with lenalidomide or placebo following ASCT for NDMM.

Study IFM 2005-002 was a phase III, multicenter, randomized, double-blind, pharmacological study designed to test the benefit of maintenance after consolidation therapy with lenalidomide versus placebo in prolonging response after ASCT.

3.2. Favourable effects

In study CALGB 100104 the primary efficacy endpoint, PFS, was met as a statistically significant improvement in median PFS was observed in patients treated with lenalidomide maintenance. The risk of disease progression or death was reduced by 39% (HR=0.61, 95% CI [0.48 to 0.76]; log-rank p value < 0.001). The robustness of the PFS effect is supported by the updated and subgroup analyses, the results of which are in line with the interim analysis.

This effect was further substantiated by results in OS. Overall survival data was still immature at the time of the interim analysis however in the updated analysis (1 February 2016 data cut-off date) the median OS for lenalidomide treatment was 111.0 months compared with 84.2 months for placebo treatment and this survival advantage of 26.8 months was statistically significant (HR=0.61; 95% CI [0.46 to 0.81]; log-rank p value < 0.001).

Statistically significant improvements were observed in PFS2 (HR of 0.61, 95% CI [0.48 to 0.78] log-rank p value < 0.001) confirming the benefit of the maintenance therapy.

Based on the results from study IFM 2005-02, the primary endpoint, PFS, showed a highly significant HR of 0.45 (0.34 to 0.60, log-rank p value < 0.001). The updated analyses supported the interim analysis: at the March 2015 data cut-off, the risk of disease progression or death was reduced by 45% (HR=0.55; 95% CI [0.46 to 0.66]; log-rank p value < 0.001); at the February 2016 data cut-off, the risk of disease progression or death was reduced by 43% (HR= 0.57, 95% CI [0.47 to 0.68]; log-rank p value < 0.001). PFS2 data are supportive of the favourable effects of lenalidomide maintenance treatment. OS data was not statistically significant however there is evidence of a survival benefit for patients.

3.3. Uncertainties and limitations about favourable effects

One uncertainty was identified during the assessment regarding the initially proposed broad indication, however the indication was restricted to maintenance treatment and this uncertainty was satisfactorily addressed (see discussion on clinical efficacy).

3.4. Unfavourable effects

In both studies, there were about twice more serious TEAE in lenalidomide arms vs placebo. In both lenalidomide arms, the main concerned SOCs was “infections and infestations” with 16.1% and 13,7 % in lenalidomide arms in CALGB and IFM study respectively, vs (5.0 % and 3.6%) in placebo arms in CALGB and IFM study respectively. Reported serious infections were mainly respiratory infections, considering the main reported PT bronchitis, lung infection and upper respiratory tract infection. Similar trends in these serious TEAE are observed when comparing both studies. These serious TEAE are coherent with the known safety profile of lenalidomide.

The most commonly reported Grade 3 or 4 TEAEs in the CALGB lenalidomide arm were neutropenia, thrombocytopenia, and leukopenia (> 15% of subjects each), followed by lymphopenia, neutropenic infection, lung infection, fatigue, febrile neutropenia, diarrhea, and pneumonia (> 5% of subjects each). The most commonly reported Grade 3 or 4 TEAEs in the IFM lenalidomide arm were neutropenia and leukopenia (> 15% of subjects each), followed by thrombocytopenia and lung disorder (> 5% of subjects each). Grade 5 TEAEs were reported in 3 (1.3%) subjects in the lenalidomide arm of the CALGB study, of which 2 of 3 subjects died > 30 days after last treatment, and in 7 (2.4%) subjects in the lenalidomide arm of the IFM study, of which 3 of 7 subjects died > 30 days after last treatment . All individual Grade 5 TEAEs occurred in < 1% of CALGB lenalidomide subjects and in ⩽ 0.4% of IFM lenalidomide subjects.

3.5. Uncertainties and limitations about unfavourable effects

Previous analyses of the CALGB and IFM studies (data cut-off of May 2013) showed that subjects treated with lenalidomide maintenance therapy post-HDM/ASCT had a statistically significant increased risk for hematologic SPMs and solid tumour SMPs (negative trend only) compared with subjects given placebo. Based on safety data provided in studies IFM and CALGB (data cut-off of Feb 2016), a higher frequency of SPM was observed in patients in lenalidomide arm compared to placebo arm: CALGB: 20.5% versus 11.8%, respectively, and IFM: 16.7% versus 10.9%.

Based on the analysis according to the lenalidomide exposure, the frequency of subjects (pooled CALGB and IFM studies) with invasive SPMs was higher for the lenalidomide exposed population compared with the lenalidomide non-exposed population (107 [10.9%] versus 3 [5.6%], respectively). The incidence rate of hematologic malignancies, most notably AML, MDS and B-cell malignancies (including Hodgkin’s lymphoma), was 1.31 per 100 person-years for the lenalidomide arms and 0.58 per 100 person-years for the placebo arms (1.02 per 100 person-years for patients exposed to

lenalidomide after ASCT and 0.60 per 100 person-years for patients not-exposed to lenalidomide after ASCT). The incidence rate of solid tumour SPMs was 1.36 per 100 person-years for the lenalidomide arms and 1.05 per 100 person-years for the placebo arms (1.26 per 100 person-years for patients exposed to lenalidomide after ASCT and 0.60 per 100 person-years for patients not-exposed to lenalidomide after ASCT)This has been adequately reflected in the SmPC (see sections 4.4 and 4.8). Furthermore, AML and B-cell malignancies are classified as an important identified risk in the Risk Management Plan.

3.6. Effects Table

Table 47: Effects Table for Revlimid for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation (data cut-off: 1 February 2016)

Effect	Short Description	Unit	Placebo	Lenalidomide	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS	Median time from randomization to progression or death	Months	29.4 (20.7, 35.5)	56.9 (41.9, 71.7)	The PFS effect was supported by the PFS results of study IFM 2005-02	Numbers presented were taken from the CALGB 100104 study(see 'clinical efficacy' section)
OS	Median time from randomization to death of any cause	Months	84.2 (71.0, 102.7)	111 (101.8, NE)	Not supported by the OS results in study IFM 2005-02	
Unfavourable Effects						
Diarrhoea	Incidence of grade 3 or 4 events	%	5.6	3.4		Numbers presented were taken from the CALGB 100104 and IFM 2005 02 studies – Pooled Safety Population (see 'clinical safety' section)
Neutropenia	Incidence of grade 3 or 4 events	%	18.8	56.3		
Thrombocytopenia	Incidence of grade 3 or 4 events	%	15.0	23.6		
Leukopenia	Incidence of grade 3 or 4 events	%	5.4	22.4		
Neutropenic infection	Incidence of grade3 or 4 events	%	2.8	5.2		
Lung infection	Incidence of grade 3 or 4 events	%	0.4	3.9		
SPM	Incidence	%	11.3	18.3		

Abbreviations: AE: adverse event; HR: hazard ratio; NE: not estimable; OS: overall survival; PFS: progression-free survival

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the CALGB study a statistically highly significant survival benefit, was demonstrated without identified factors biasing the result in favour of the experimental arm. These favourable results were not replicated in the IFM study, but PFS and PFS2 data are supportive of favourable effects of lenalidomide maintenance therapy.

The safety profile of lenalidomide in maintenance treatment is overall consistent with what is already known in lenalidomide NNMM treated patients. SPM is an important safety concern and an approximate doubling of the risk is a reasonable risk estimate. No new risks of lenalidomide were identified.

3.7.2. Balance of benefits and risks

The efficacy of lenalidomide in the target population is considered clinically relevant and, in the view of the safety profile, the benefits are considered to outweigh the combined risks.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

Conclusions

The overall B/R of Revlimid for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Revlimid (lenalidomide) is not similar to Imnovid (pomalidomide), Thalidomide Celgene (thalidomide), Kyprolis (carfilzomib), Farydak (panobinostat), Darzalex (Daratumumab) and Ninlaro (ixazomib) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See Appendix 1.

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends by consensus the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
B.II.e.5.a.2	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	Type IB	I, IIIA, IIIB and A
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition	Type II	I and IIIB

	of a new therapeutic indication or modification of an approved one		
B.II.e.5.a.2	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	Type IB	I, IIIA, IIIB and A

Extension of indication to add maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation; as a consequence, SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC and Package Leaflet. A revised version of the RMP (version 34.0) has been approved as part of this application. Furthermore, the MAH introduced 7-day pack sizes for the 10 mg and 15 mg strengths with subsequent changes to the Product Information.

The group of variations leads to amendments to the Summary of Product Characteristics, Labelling, Package Leaflet and Annex A and to the Risk Management Plan (RMP).

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to add maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation; as a consequence, SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC and Package Leaflet. A revised version of the RMP (version 34.0) has been approved as part of this application. Furthermore, the MAH introduced 7-day pack sizes for the 10 mg and 15 mg strengths with subsequent changes to the Product Information.

Summary

Please refer to the Scientific Discussion Revlimid-II-89/G.