28 January 2016
EMA/CHMP/642878/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Revlimid

International non-proprietary name: lenalidomide

Procedure No. EMEA/H/C/000717/II/0079

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

ALT	Alanine transaminase/serum glutamic- pyruvic transaminase
AST	Serum glutamic-oxaloacetic transaminase (SGOT)
ASCT	Autologous stem cell transplant
ATE	Arterial thrombo-embolic event
BIC	Best investigator choice
CR	Complete response
DLBCL	Diffuse large B-cell lymphoma
ECOG	Eastern Cooperative Oncology Group
EMA	European medicine agency
FAS	Full Analysis Set
FLgr3	Grade 3 follicular lymphoma
IA	Interim analysis
IHC	Immunohistochemistry
IR	Incidence rate
Len	Lenalidomide
MCL	Mantle cell lymphoma
MDS	Myelodysplastic syndromes
MAH	Marketing authorisation holder
MI	Myocardial infarction
MM	Multiple myeloma
NA	Not applicable
NHL	Non Hodgkin lymphoma
NMSC	Non melanoma skin cancer
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
PK	Pharmacokinetic
PPS	Per Protocol Set
PR	Partial response
RRMCL	Relapsed/refractory Mantle cell lymphoma
RRMM	Relapsed/refractory Multiple Myeloma

RT	Readibility testing
SCT	Stem-cell transplantation
SmPC	Summary of product characteristics
SPM	Second primary malignancies
TEAE	Treatment emergent adverse event
TSF	Transformed lymphoma
TTF	Time to treatment failure
TTP	Time to progression
TTBR	Time to Best Response
TTFR	Time to First Response
VTE	Venous thrombo-embolic event

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Celgene Europe Limited submitted to the European Medicines Agency on 20 November 2014 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
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 relapsed and/ or refractory mantle cell lymphoma (MCL); as a consequence, SmPC sections 4.1, 4.2, 4.4, 4.7, 4.8, 5.1 and 5.2 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 25.0) was provided as part of this application.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Revlimid was designated as an orphan medicinal product EU/3/11/924 on 27/10/2011 in the following indication: Treatment of mantle cell lymphoma.

Following the CHMP positive opinion on the extension of indication for this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Revlimid as an orphan medicinal product in the newly approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/50/2011 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

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: Filip Josephson

Timetable	Actual dates
Submission date	20 November 2014
Start of procedure:	26 December 2014
CHMP Co-Rapporteur Assessment Report	16 February 2015
CXMP Rapporteur Assessment Report	16 February 2015
PRAC Rapporteur Assessment Report	24 February 2015
CHMP adopted Assessment Report for Revlimid on similarity with Torisel and Imbruvica	26 February 2015
Committees comments on PRAC Rapp Advice	2 March 2015
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	12 March 2015
CXMP comments	16 March 2015
Request for supplementary information (RSI)	26 March 2015
CXMP Rapporteur Assessment Report	29 June 2015
PRAC Rapporteur Assessment Report	30 June 2015
Committees comments on PRAC Rapp Advice	13 July 2015
PRAC Rapporteur Updated Assessment Report	8 July 2015
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	9 July 2015
CXMP comments	13 July 2015
CHMP Rapporteur Revised Assessment Report	20 July 2015
Request for supplementary information (RSI)	23 July 2015
PRAC Rapporteur Assessment Report	2 October 2015
CXMP Rapporteur Assessment Report	2 October 2015
Committees comments on PRAC Rapp Advice	6 October 2015
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	8 October 2015
CXMP comments	12 October 2015
Request for supplementary information (RSI)	22 October 2015
CXMP Rapporteur Assessment Report	18 December 2015
PRAC Rapporteur Assessment Report	31 December 2015
Committees comments on PRAC Rapp Advice	6 January 2016
PRAC Rapporteur Updated Assessment Report	7 January 2016
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	14 January 2016
CXMP comments	18 January 2016
Rapporteur Revised Assessment Report	21 January 2016
Opinion	28 January 2016

2. Scientific discussion

2.1. Introduction

Mantle cell lymphoma (MCL) is a histologic type of non-Hodgkin's lymphoma (NHL), a heterogeneous group of lymphoproliferative malignancies with differing clinical features and responses to treatment (Armitage, 1993). Morphologically, it is a distinct type of mature B-cell lymphoma usually infiltrating the mantle zone of lymph nodes or the area surrounding the lymphoid follicles. The 3 key components of the complex pathobiology of MCL are an aberrant cell cycle regulation due to overexpression of cyclin D1, abnormalities in deoxyribonucleic acid (DNA) damage responses leading to accumulation of genetic lesions, and constitutive activation of anti-apoptotic pathways (Alinari, 2012; Peréz-Galán, 2011).

Mantle cell lymphoma accounts for approximately 6% of all NHLs worldwide (Anon, 1997; Swerdlow, 2008). The annual incidence of MCL in Europe was estimated as on average 0.45/100,000 persons based on cancer registry data from 20 countries in the (Sant, 2010). Patients with MCL typically are predominantly male and Caucasian with a median age of > 60 years, and present with advanced stage disease. Despite intensive induction therapies in the front-line setting of young and fit patients, the clinical course is typically that of repeated relapses, and median survival of MCL is only 3 to 5 years (Abrahamsson, 2014; Salek, 2014).

Factors associated with adverse prognosis at the time of initial diagnosis are older age (≥ 65 years), advanced stage (stage III or IV) (Fisher, 1995; Norton, 1995; Teodorovic, 1995; Velders, 1996; Weigert, 2009), elevated lactate dehydrogenase (LDH) levels, poor Eastern Cooperative Oncology Group (ECOG) performance status, large tumour burden, bulky disease, and occurrence of B symptoms (Armitage, 1998; Tiemann, 2005). Age, ECOG, and LDH have been combined with white blood cell (WBC) count into a validated score for MCL, the mantle cell lymphoma International Prognostic Index (MIPI) providing a reliable risk stratification at initial diagnosis prior to therapy(Geisler, 2010a; Hoster, 2008). Another prognostic tool is the percentage of Ki-67 positive cells as a measure of cellular proliferation (Determann, 2008; Hoster, 2008), although the Ki-67 assay has not yet been standardized across laboratories.

In patients who have relapsed after initial therapy, the prognosis is poor (Ghielmini, 2009; Herrmann, 2009; Zaja, 2014; Zucca, 1995). This includes patients who received autologous stem cell transplantation (ASCT), which provides reasonable disease control only in a limited percentage of relapsed MCL patients. Median overall survival (OS) is < 1 year in early post-transplant relapse (Cassaday, 2013; Dietrich, 2011; Vose 2013). In the relapsed setting, additional important factors affecting the prognosis include refractoriness to prior therapy, number of prior therapies and responses thereto, types of prior therapies, and duration since last prior therapy.

In the European Union (EU) bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is approved for first line MCL in patients who are unsuitable to haematopoietic stem cell transplantation (HSCT) and temsirolimus and ibrutinib are the approved treatments for relapsed or refractory MCL.

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.

The marketing authorisation holder (MAH) applied for the following indication: Revlimid is indicated for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma.

The recommended indication for approval is: Revlimid is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma.

The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28- day cycles. Dosing is continued or modified based upon clinical and laboratory findings (SmPC section 4.2).

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity / environmental risk assessment

In Phase I environmental risk assessment, the $PEC_{SURFACEWATER}$ of lenalidomide has been determined by summing the three separate $PEC_{SURFACEWATER}$ values for each indication. The calculated market penetration factor for MM, MDS and MCL are 0.00013, 0.00015 and 0.00003 respectively and their respective $PEC_{SURFACEWATER}$ values are 0.0016 µg/L, 0.0008 µg/L and 0.0004 µg/L.

The total $PEC_{SURFACEWATER}$ of lenalidomide is 0.0028 µg/L and thus well below the action limit of 0.01 µg/L. A Phase II environmental assessment is not triggered

The partition coefficient (n-octanol/water) for lenalidomide was experimentally determined at several concentrations and pH values. The resulting logKow for lenalidomide was -0.34 (Kow 0.46) and hence below the trigger of 4.5. Therefore, a PBT assessment is not required.

2.2.2. Discussion on non-clinical aspects

The updated ERA consists of a newly determined $PEC_{SURFACEWATER}$ value which corresponds to the sum of the $PEC_{SURFACEWATER}$ for all three indications (see section 2.2.1). The resulting value is below the threshold and, therefore, lenalidomide is not expected to pose a risk to the environment. This is considered acceptable and the updated ERA does not change the conclusions drawn from ERA submitted with the initial MAA that lenalidomide is not expected to pose a risk to the environment.

2.2.3. Conclusion on the non-clinical aspects

Considering the above data, lenalidomide is not expected to pose a risk to the environment.

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

	Main Study	Supportive Studies		
	MCL-002	**MCL-001**	**NHL-003**	**NHL-002**
No. of subjects enrolled: planned/actual	250/254	133/134	200/218 (includes 57 MCL subjects)	40/50 (includes 15 MCL subjects)
No. of subjects treated with lenalidomide	167	134	217 (includes 57 MCL subjects)	49 (includes 15 MCL subjects)
Phase of study	2	2	2	2
Subject population	MCL relapsed/refractory	MCL relapsed/refractory to bortezomib	NHL, aggressive relapsed/refractory	NHL, aggressive relapsed/refractory
Control	Investigator's choice (IC): monotherapy with chlorambucil, cytarabine, rituximab, fludarabine, or gemcitabine	NA (single-arm study)	NA (single-arm study)	NA (single-arm study)
Lenalidomide dosing regimen	PO 25 mg QD[(1)] (21/28 days)	PO 25 mg QD[a] (21/28 days)	PO 25 mg QD (21/28 days)	PO 25 mg QD (21/28 days)
Duration of treatment	Until PD or unacceptable toxicity for lenalidomide; or various[(2)] for IC, or voluntary withdrawal	Until PD, unacceptable toxicity, or voluntary withdrawal	Until PD or unacceptable toxicity	52 weeks[(3)] or until PD or unacceptable toxicity
Primary efficacy endpoint(s)	PFS[(4),(5)]	ORR[d], DOR[d]	ORR[d]	ORR

2.4. Clinical efficacy

2.4.1. Dose response study

No dose-response studies were submitted. The claimed posology scheme (starting dose 25 mg orally once daily on days 1-21 of repeated 28-day cycles) is the same as the one already approved in the indication "multiple myeloma in adult patients who have received at least one prior therapy (RRMM)". The dose of lenalidomide selected for the clinical development program in MCL was based on results of two Phase 1 studies in RRMM (CDC-501-001 and CDC-501-002) that identified a dose of 25 mg as the Phase 2 dose. The activity of lenalidomide at this dose in MCL initially was shown in Studies NHL-003 and NHL-002. Based on these findings, the same dose schedule was selected for use in Study MCL-001 and then in the main Study MCL-002.

2.4.2. Main study

MCL 002 (SPRINT trial)

This was a multicenter, randomized, open-label, controlled Phase 2 study to compare the efficacy and safety of single-agent lenalidomide versus single agent of investigator's choice (IC) in patients with MCL who were refractory to their last regimen or had between 1 and 3 relapses.

Methods

Study participants

The target population was adult patients with relapsed/refractory MCL.

The main inclusion criteria included:

1. Patients with histologically proven mantle cell non-Hodgkin's lymphoma (including overexpression of cyclin D1 by IHC). In patients whose tumors were negative for cyclin D1 overexpression or translocation, evidence of overexpression of cyclin D2 or D3 by IHC was acceptable.

2. Patients who were refractory to their regimen or had relapsed once, twice, or three times and who had documented PD. Refractory to prior chemotherapy regimens was defined as not having reached a CR or partial response [PR] to prior treatment (best response was SD or PD). Relapse was defined as having reached best response to last treatment as CR, CRu, or PR.

3. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2.

4. Must have been ≥18 years of age at the time of signing the ICF.

5. Must have had at least one prior combination chemotherapy regimen with an alkylating agent, and comprising an anthracycline and/or cytarabine and/or fludarabine (with or without rituximab).

6. Prior SCT was allowed.

7. Must have been ineligible for intensive chemotherapy and/or transplant at time of inclusion in the study.

8. Must have had measurable disease on cross sectional imaging by CT, or MRI if CT was contraindicated, that was at least 2 cm in the longest diameter and measurable in 2 perpendicular dimensions.

9. Must have been able to adhere to the study visit schedule and other protocol requirements.

10. Life expectancy of greater than 3 months.

11. Females of childbearing potential (FCBP) must have:

- Had 2 negative medically supervised pregnancy tests prior to starting of study therapy. She must have agreed to ongoing pregnancy testing during the course of the study, and after end of study therapy. This applied even if the patient practiced complete and continued sexual abstinence.

- Either committed to continued abstinence from heterosexual intercourse (which had to be reviewed on a monthly basis) or agreed to use, and been able to comply with, effective contraception without interruption, 28 days prior to starting study drug, during the study therapy (including dose interruptions), and for 28 days after discontinuation of study therapy

12. Male patients must have:

- Agreed to use a condom during sexual contact with a FCBP, even if they had had a vasectomy, throughout study drug therapy, during any dose interruption and after cessation of study;

- Agreed to not donate semen or sperm during study drug therapy and for 28 days after end of study drug therapy

13. All patients must have:

- Had an understanding that the study drug could have a potential teratogenic risk.

- Agreed to abstain from donating blood while taking study drug therapy and for 28 days after end of study drug therapy

- Agreed not to share study medication with another person.

- Agreed to be counseled about pregnancy precautions and risks of fetal exposure

The main exclusion criteria included:

1. Diagnosis of lymphoma other than MCL.

2. Prior history of malignancies, other than MCL, unless the patient had been free of the disease for ≥ 5 years. Exceptions included the following:

- Basal cell carcinoma of the skin.
- Squamous cell carcinoma of the skin.
- Carcinoma in situ of the cervix.
- Carcinoma in situ of the breast.
- Incidental histological finding of prostate cancer (tumor-nodes-metastasis [TNM] stage of T1a or T1b).

3. Transformed lymphoma.

4. Prior use of lenalidomide.

5. Prior radiotherapy within 4 weeks prior to randomization.

6. Patients who were candidates for autologous or allogeneic transplantation at the time of inclusion into the study.

7. Prior allogeneic transplantation with persistent donor hematopoiesis.

8. Active central nervous system (CNS) lymphoma with the exception of those patients whose CNS lymphoma had been treated with chemotherapy, radiotherapy or surgery; had remained asymptomatic for 90 days (three months); and demonstrated no CNS lymphoma as shown by lumbar puncture, CT/brain MRI. Patients with a history of CNS involvement or CNS symptoms were required to have negative cerebrospinal fluid (CSF) cytology examination and a head CT during the Screening period (known and active CNS or lepto-meningeal involvement).

9. Known seropositive for or active viral infection with human immunodeficiency virus (HIV).

10. Known seropositive for or active viral infection with HBV:

- HBs Ag positive.
- HBs Ag negative, anti-HBs positive and/or anti-HBc positive and detectable viral deoxyribonucleic acid (DNA).
- Patients who were HBs Ag negative and viral DNA negative were eligible.
- Patients who had hepatitis B but had received an antiviral treatment and showed no detectable viral DNA for 6 months were eligible.
- Patients who were seropositive because of HBV vaccine were eligible.

11. Known seropositive for or active viral infection with HCV: Patients who had hepatitis C but had received an antiviral treatment and showed no detectable viral ribonucleic acid (RNA) for 6 months were eligible.

12. Patients who were not willing to take deep vein thrombosis (DVT) prophylaxis, if they were at risk.

13. Patients should not have received corticosteroids 7 days prior to randomization, except for prednisone ≤ 10 mg/day or equivalent for purposes other than treating MCL.

14. Pregnant or lactating females.

15. Any of the additional laboratory abnormalities.

- Absolute neutrophil count (ANC) < 1,500 cells/mm^3 (1.5 x 10^9/L).
- Platelet count < 60,000/ mm^3 (60 x 10^9/L)
- Serum aspartate transaminase/serum glutamic-oxaloacetic transaminase (AST/SGOT) or alanine transaminase/serum glutamic- pyruvic transaminase (ALT/SGPT)> 3.0 x upper limit of normal (ULN), except in patients with documented liver involvement by lymphoma.
- Serum total bilirubin > 1.5 x ULN, except in case of Gilbert's Syndrome and documented liver involvement by lymphoma.
- Calculated creatinine clearance (CrCl) of < 30 mL/min (Cockcroft-Gault estimation). Note: After Protocol Amendment No. 2 enrollment was no longer allowed with AST/SGOT or ALT/SGPT ≥ 5.0 x ULN, unless documented liver involvement by lymphoma. Similarly, total bilirubin > 2.0 mg/dL was no longer accepted but with the exceptions above.

16. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient from signing the ICF.

17. Participation in another clinical trial during the Screening/Baseline Phase and Treatment Phase of the study.

18. Any use of experimental drug during 4 weeks prior to randomization.

Treatments

Patients were randomized (2:1) to receive lenalidomide monotherapy (Lenalidomide Arm further referred as Len arm) or the single-agent treatment selected by the investigator (investigator's choice) on a by-patient basis during the Screening/Baseline Phase (Control arm). Lenalidomide was administered orally once daily on D1 to D21 in each 28-day cycle. The starting dose of lenalidomide was 25 mg or 10 mg based on renal function. Treatment was to continue until disease progression or unacceptable toxicity.

Patients in the Control arm were to receive investigator's choice single agent reference therapy. Dosing of the investigators choice single agents is provided in Table 1.

Table 1. Overview of Dosage of Investigators Choice Drugs (Study MCL 002)

Investigator's Choice (route)[a] (reference)	Dose	Dosing Days by Cycle	Cycle Duration	Maximum No. of Cycles
Chlorambucil (PO) (Rai, 2000; Ardeshna, 2003)	40 mg/m^2 (total monthly dose)	Split over 3-10 days	28 days	Until PD or toxicity
Rituximab (IV) (Ghielmini, 2000)	375 mg/m^2	D1, D8, D15, D22	56 days[b]	Until PD or toxicity
Cytarabine (IV) (Kantarjian, 1983)	1-2 g/m^2 once or twice per day	D1, D2	28 days	6 cycles
Gemcitabine (IV) (Dumontet, 2001)	1000 mg/m^2	D1, D8, D15	28 days	6 cycles
Fludarabine (IV) (Decaudin, 1998; Zinzani, 2000)	25 mg/m^2	D1 to D5	28 days	6 cycles
Fludarabine (PO) (Tobinai, 2006)	40 mg/m^2	D1 to D5	28 days	6 cycles

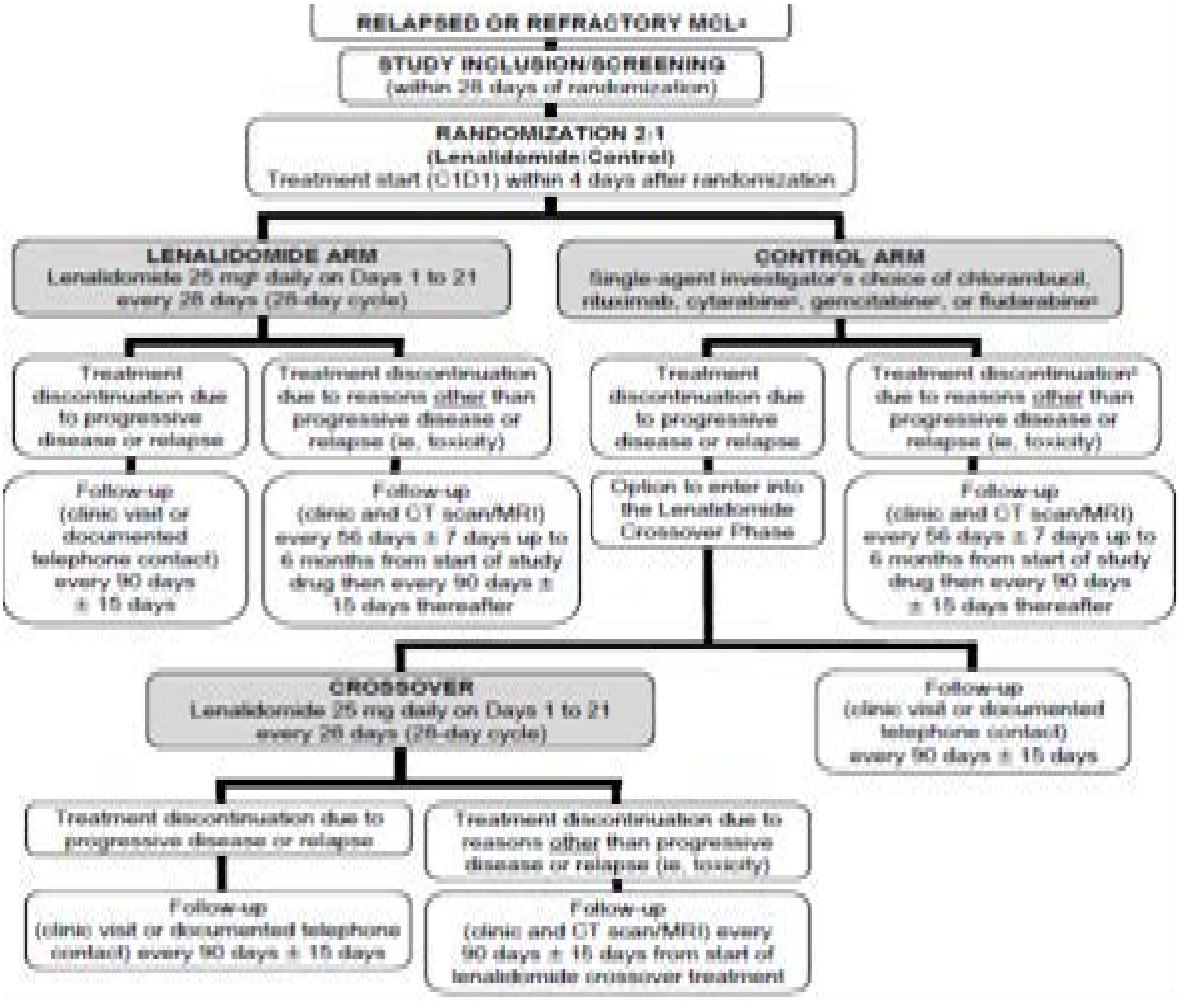
C = cycle; D = day; No. = number; PD = progressive disease; PO = orally; IV = intravenously; SmPC = summary of product characteristics.

[a] Investigator was to refer to the approved SmPCs, provided by Celgene, for complete prescribing information including administration, warnings, precautions, contraindications, and adverse reactions and follow institutional procedures for the administration of the agents, where applicable.

[b] Rituximab (single agent) was to be administered in 4 doses during the first 56 days, and was to be repeated every 56 days after D56 (given only on D1 of every 56 days cycle). Therefore, rituximab cycles are calculated as 56-day cycles past Cycle 1 (Appendix 16.2 of the SAP). For the prevention of cytokine release syndrome associated with the treatment of rituximab, methylprednisolone ≤ 125 mg or equivalent were accepted on C1D1.

The design of the trial is presented in the figure below.

Figure 1. Trial design-MCL 002



a Disease in subjects refractory to their prior regimen or who relapsed once, twice, or three times. Relapsed was defined as subjects with best response to last treatment as CR, CRu, or PR. Refractory was defined as subjects not having achieved a response to last treatment (best response was SD or PD).
b Initial dosing of lenalidomide was based on baseline renal function: 25 mg starting dose for subjects with normal renal function (CrCl ≥ 60 mL/min) and 10 mg starting dose for those with moderate renal insufficiency (CrCl < 60 mL/min but ≥ 30 mL/min).
c For subjects on cytarabine, fludarabine, or gemcitabine treatment was capped at 6 cycles. If treatment was completed as planned, this was considered the primary reason for treatment discontinuation in these subjects.

Objectives

The primary objective was to compare progression free survival (PFS) of lenalidomide monotherapy versus investigators choice single agent in patients with MCL who were refractory to their regimen or had relapsed once, twice or three times.

The secondary objectives were:

- To determine the Overall Response Rate (ORR) of lenalidomide monotherapy or investigator's choice single agent in patients with relapsed/refractory (R/R) MCL.
- To evaluate the safety of lenalidomide monotherapy or investigator's choice single agent in patients with R/R MCL.
- To determine the Time to Progression (TTP) and Overall Survival (OS) of patients with R/R MCL who had received treatment with lenalidomide or investigator's choice single agent.
- To investigate the health-related Quality of Life (QoL) of patients treated with lenalidomide or investigator's choice single agent.

Outcomes/endpoints

The primary endpoint was PFS defined as the time from randomization to the first observation of disease progression or death due to any cause.

The secondary endpoints were analyzed in an exploratory manner and included the following:

- ORR included best response of complete response (CR), CRu, or partial response (PR). Subjects who discontinued before any post-randomization efficacy assessments were considered non-responders.
- Duration of response was measured from the time of initial response (at least PR) until documented tumour progression or death. Tumour Control Rate (TCR) consisted of the rates for CR, CRu, PR, and Stable disease (SD).
- Duration of stable disease: Stable disease was defined as a response less than PR but that was not PD or relapsed disease. Duration of stable disease was calculated from the first SD date reported in the study to documented disease progression or documented response or death, whichever occurred first.
- TTP was defined as the time from randomization until objective tumour progression. Time to progression did not include deaths.
- Time to treatment failure (TTF) was defined as the time from the first dose of study drug to discontinuation of treatment for any reason, including disease progression, treatment toxicity, or death.
- Time to first response (TTFR) was defined as the time from randomization until initial response (CR + CRu + PR) if response had been confirmed.
- Time to best response (TTBR) was defined as the time from randomization until first date of best response (CR + CRu + PR) had been confirmed.
- OS defined as the time from randomization until death from any cause.
- Quality of life was analyzed using the instrument EORTC QLQ-C30 Version 3.0 which is a 30-item scale. The EORTC QLQ-C30 is composed of both multi-item scales and single-item measures. These include 5 functional scales, 3 symptom scales, a global health status/QoL scale, and 6 single items.

Sample size

Initially, it was calculated that 167 subjects were to be randomized to obtain 150 evaluable subjects, based on the width of the 95% CI around a certain point estimate for ORR that was considered significant clinical activity. After protocol amendment No. 2 (dated 14 December 2009) the primary endpoint was changed to PFS and the sample size was recalculated. For the primary efficacy variable, PFS, an improvement in median PFS from 2.5 months for the control arm to at least 4.25 months for lenalidomide was considered to be clinically relevant. Full information necessary for a one-sided log-rank test with an overall alpha of 0.025, to have 80% power, was to be achieved when approximately 128 patients had progressed or died.

After the third Data monitoring committee (DMC) held on 22 July 2011, the DMC recommended increasing the sample size from 174 (number of patients randomized at the time of the third DMC was held) to 250 patients and conducting the primary analysis 1 year after the last patient was randomized. Subsequently, the sample size changed to 250 patients following DMC recommendation (Protocol Amendment No. 4, dated 27 September 2011).

Randomisation

Subjects were randomized 2:1 to the lenalidomide or the control arm, and stratified according to:

- Time from diagnosis to first dose (< 3 years or ≥3 years)
- Time from end of last prior systemic anti-lymphoma therapy to first dose (< 6 months or ≥ 6 months)
- Prior stem cell transplantation (SCT) (yes or no).

Blinding (masking)

This was an open-label study.

Statistical methods

Efficacy analyses for the primary and secondary endpoints were performed on the intent-to-treat (ITT) population. Sensitivity analyses were conducted for the primary and secondary endpoints based on the full analysis set (FAS), Per Protocol Set (PPS), and As Treated (AT) populations.

Intent-to-Treat Population defined as all subjects who had been randomized, independently of whether they received study treatment or not.

Full Analysis Set Population included all randomized subjects who had received at least one single treatment dose with centrally confirmed histology of MCL as well as documented progression at entry.

Per Protocol Set Population included all randomized subjects who had received at least one single treatment dose, had centrally confirmed histology of MCL, as well as documented progression at entry, without any major protocol violation.

As Treated Population defined as all randomized subjects who had received at least 2 cycles of treatment regardless of the treatment arm allocation.

The sample size increase recommended by the DMC was not supported by any planned interim analyses; therefore, adjustment for controlling the α-level was not planned in the original protocol and is described in this section.

The final level was determined using an α-spending function of the O'Brien-Fleming type and a new group sequential test procedure was also to be used to preserve the type I error following the method developed by Cui et al (Cui, 1999), and adapted by Wassmer for time-to-event endpoints (Wassmer, 2006).

At the time of the third DMC, 67 events had been reported of the 128 needed for the final analysis. If one interim analysis had been planned at 52% of the information the upper boundary for superiority would have been based on an α-spending function of the O'Brien-Fleming type with overall α = 0.025, one-tailed.

Table 2. P-value for Rejecting Null Hypothesis (Superiority)

	P-Value for Rejecting Null Hypothesis (Superiority)
Interim 1 (52%)	0.002
Final	0.024

SAP = statistical analysis plan.

Kaplan-Meier (KM) survival analysis was performed (unadjusted for the stratification variables for all time-to-event endpoints). The median, 25th and 75th percentile time-to-event data were presented with 95% confidence intervals (CIs) unadjusted by strata and in addition, for the primary endpoint, within strata. The numerical difference (and CI of the difference) in the median, 25th, and 75th percentiles between lenalidomide and investigator's choice drug groups were presented for the unstratified analysis.

The groups were compared using the stratified log-rank test in order to assess superiority and the unstratified log-rank test as supportive analysis. A new statistical test was also conducted to take into

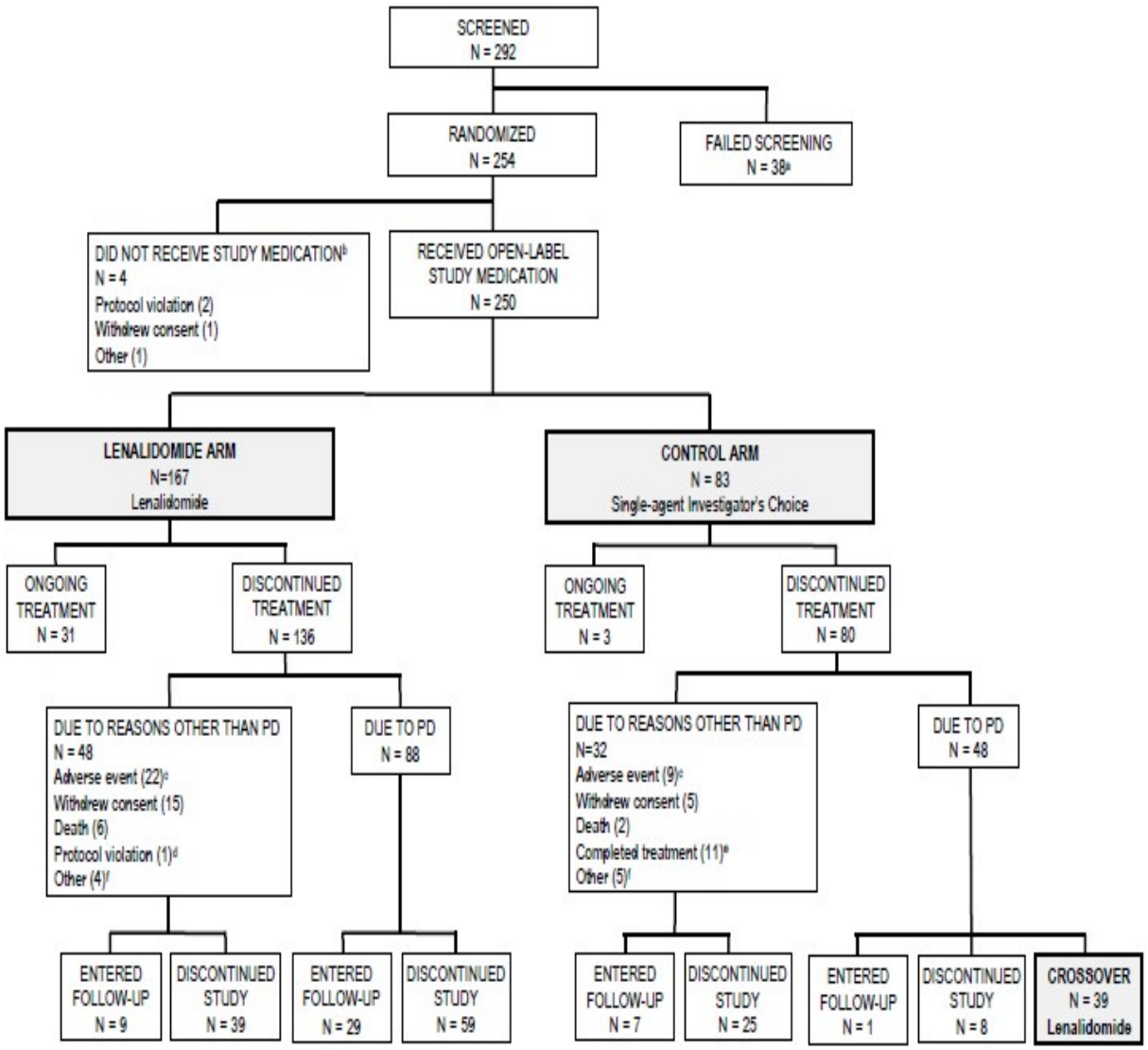
account the unplanned sample size reassessment recommended by the DMC and implemented after Protocol Amendment No. 4.

Subgroups included the stratification factors (time from diagnosis to first dose, time from end of last prior systemic anti-lymphoma therapy to first dose and prior SCT), demographic factors (sex and age) and relevant baseline disease characteristics (stage, MIPI, tumor burden, bulky disease, Ki 67 index).

The censoring rules for the main analysis are based on the FDA Guidance for Industry for Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA Guidance, 2007).

Results

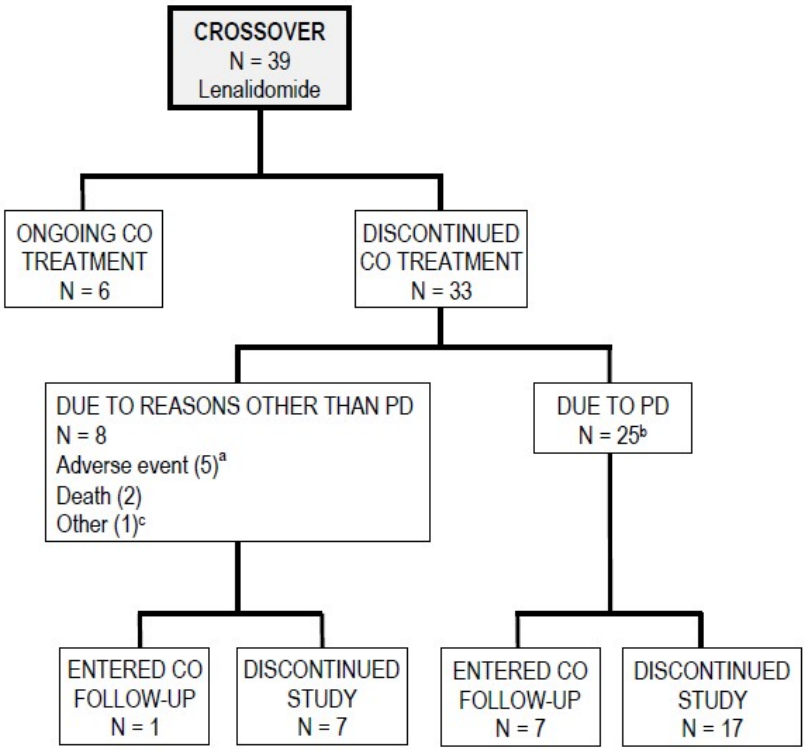
Participant flow



CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; PD = disease progression (as per investigators' assessment); PR = partial response; PS = performance status.

Thirty nine (46.4%) of the 84 patients who were randomized to the control arm crossed over to lenalidomide after having progressed on the control arm. At data cut-off, 33 of them had discontinued from crossover treatment, mainly due to disease progression (25 patients). The median time from randomization to crossover was 2.9 months (range: 0.7, 37.8). The disposition of crossover patients is presented in Figure 2.

Figure 2. Disposition of crossover patients – study MCL 002



AE = adverse event; CO = crossover; eCRF = electronic case report form; PD = disease progression (as per investigators' assessment).
[a] Discontinuations due to AEs in this figure were captured on eCRF page of treatment discontinuation.
[b] At the time of data cut off, Subject 6111006 who crossed over to Lenalidomide Arm, had just discontinued treatment due to PD and entered the Follow-up Phase; this subject is not presented as having entered CO follow -up.
[c] Subject 7151001 discontinued crossover lenalidomide due to deterioration of clinical status.
Source: Table 14.1.1, Table 14.1.1.1, Listing 16.2.1.1, and Listing 16.2.1.2.

Recruitment

The study is currently ongoing with a total of 254 subjects randomized at 67 sites in Belgium, Czech Republic, France, Germany, Israel, Italy, the Netherlands, Poland, Russia, Spain, Sweden, and UK. The first subject was randomized on 26 May 2009. The last subject was randomized on 7 March 2013.

Conduct of the study

The protocol was amended 5 times. The major changes to the conduct of the study are listed below:

- modification of primary endpoint from ORR to PFS,
- sample size increase to 250 patients,
- modification of type of analysis primary efficacy analysis was set 1 year after the last patient was randomized, instead of when 128 deaths or progressions had occurred. Thus, the event-driven analysis (128 events) was switched to a time-fixed analysis

- control of alpha error type to address the unplanned sample size change.

A summary of protocol violations is presented in Table 3.

Table 3. Summary of protocol violations (ITT population - study MCL 002)

Sponsor's Category Sponsor's Subcategory	Lenalidomide N=170 n (%)	Control N=84 n (%)	Overall N=254 n (%)
Number of Subjects with at Least one Protocol Violation	38 (22.4)	11 (13.1)	49 (19.3)
Received wrong tx or incorrect dose	20 (11.8)	7 (8.3)	27 (10.6)
Received the incorrect dose at any time for any reason	14 (8.2)	4 (4.8)	18 (7.1)
Began study medication despite dose-limiting toxicity (DLT)	9 (5.3)	1 (1.2)	10 (3.9)
Dispensed and/or dosed with incorrect supply of study medication	1 (0.6)	2 (2.4)	3 (1.2)
Entered study but subject did not satisfy entry criteria	13 (7.6)	4 (4.8)	17 (6.7)
Eligibility and Entry Criteria i.e. Subject enrolled violates inclusion/exclusion criteria	13 (7.6)	4 (4.8)	17 (6.7)
Other	6 (3.5)	1 (1.2)	7 (2.8)
Delayed signatures on revised / current version of informed consent form; other informed consent issues.	4 (2.4)	0 (0.0)	4 (1.6)
Improper handling of study medication; study drug not returned; other study drug administrative issues.	1 (0.6)	0 (0.0)	1 (0.4)
Subject has not taken an anti-thrombotic or an anti-tumor lysis medication as specified in protocol.	1 (0.6)	0 (0.0)	1 (0.4)
Failure to report serious adverse events or SUSARs in accordance with regulations.	0 (0.0)	1 (1.2)	1 (0.4)
Missing visit or assessment	4 (2.4)	1 (1.2)	5 (2.0)
Missing efficacy assessment	3 (1.8)	1 (1.2)	4 (1.6)
Missing safety assessment	1 (0.6)	0 (0.0)	1 (0.4)

Baseline data

The demographic and baseline disease characteristics are presented in Tables 4 and 5 respectively.

Table 4. Demographic characteristics (ITT Population - study MCL 002)

	Lenalidomide	Control
	N = 170	N = 84
Age (years)		
Mean ± StD	68.0 ± 9.4	67.5 ± 8.2
Median (min, max)	68.5 (44.0, 88.0)	68.5 (49.0, 87.0)
Age distribution, n (%)		
< 65 years	55 (32.4)	27 (32.1)
≥ 65 years	115 (67.6)	57 (67.9)
Sex, n (%)		
Male	123 (72.4)	63 (75.0)
Female	47 (27.6)	21 (25.0)
MCL stage at diagnosis, n (%)		
I	3 (1.8)	2 (2.4)
II	10 (5.9)	1 (1.2)
III	30 (17.6)	20 (23.8)
IV	123 (72.4)	59 (70.2)
MIPI score at diagnosis, n (%)		
Low risk	61 (35.9)	35 (41.7)
Intermediate risk	51 (30.0)	22 (26.2)
High risk	40 (23.5)	14 (16.7)
MIPI score at baseline (calculated[a]), n (%)		
Low risk	42 (24.7)	21 (25.0)
Intermediate risk	66 (38.8)	37 (44.0)
High risk	60 (35.3)	25 (29.8)
ECOG score at baseline[b], n (%)		
0 - 1	142 (83.5)	73 (86.9)
2 - 4	27 (15.9)	11 (13.1)

Table 5. Baseline disease characteristics (ITT Population-study MCL 002)

	Lenalidomide	Control
	N = 170	N = 84
MCL stage at diagnosis, n (%)		
I	3 (1.8)	2 (2.4)
II	10 (5.9)	1 (1.2)
III	30 (17.6)	20 (23.8)
IV	123 (72.4)	59 (70.2)
Missing	4 (2.4)	2 (2.4)
MIPI score at diagnosis, n (%)		
Low risk	61 (35.9)	35 (41.7)
Intermediate risk	51 (30.0)	22 (26.2)
High risk	40 (23.5)	14 (16.7)
Missing	18 (10.6)	13 (15.5)
MIPI score at baseline (calculated[a]), n (%)		
Low risk	42 (24.7)	21 (25.0)
Intermediate risk	66 (38.8)	37 (44.0)
High risk	60 (35.3)	25 (29.8)
Missing	2 (1.2)	1 (1.2)
ECOG score at baseline[b], n (%)		
0 - 1	142 (83.5)	73 (86.9)
2 - 4	27 (15.9)	11 (13.1)
Missing	1 (0.6)	0 (0.0)
LDH level[c] at baseline, n (%)		
< LLN	2 (1.2)	2 (2.4)
Normal	94 (55.3)	51 (60.7)
> ULN	73 (42.9)	30 (35.7)
Missing	1 (0.6)	1 (1.2)
WBC at baseline, n (%)		
$< 6.7 \times 10^9$/L	79 (46.5)	46 (54.8)
$6.7 - < 10 \times 10^9$/L	56 (32.9)	27 (32.1)
$10 - < 15 \times 10^9$/L	19 (11.2)	7 (8.3)
$\geq 15 \times 10^9$/L	15 (8.8)	4 (4.8)
Missing	1 (0.6)	0 (0.0)
Bone marrow involvement[d] at baseline, n (%)		
Negative	27 (15.9)	11 (13.1)
Indeterminate	4 (2.4)	3 (3.6)
Positive	21 (12.4)	13 (15.5)
Missing	118 (69.4)	57 (67.9)
Tumor burden[e] at baseline, n (%)		
High	81 (47.6)	28 (33.3)
Low	78 (45.9)	50 (59.5)
Missing	11 (6.5)	6 (7.1)
Bulky disease[f] at baseline, n (%)		
Yes	37 (21.8)	13 (15.5)
No	122 (71.8)	65 (77.4)
Missing	11 (6.5)	6 (7.1)

	Lenalidomide	Control
	N = 170	N = 84
Renal function[g] at baseline, n (%)		
Normal	134 (78.8)	63 (75.0)
Moderate insufficiency	34 (20.0)	21 (25.0)
Severe insufficiency	2 (1.2)	0 (0.0)
Time from diagnosis to first dose, n (%)		
< 3 years	91 (53.5)	44 (52.4)
≥ 3 years	76 (44.7)	39 (46.4)
Missing[h]	3 (1.8)	1 (1.2)
Ki-67 index[i], n (%)		
< 10%	60 (35.3)	25 (29.8)
10% - 30%	59 (34.7)	27 (32.1)
> 30%	31 (18.2)	19 (22.6)
Missing	20 (11.8)	13 (15.5)

CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; ITT = intent-to-treat; LDH = lactate dehydrogenase; LLN = lower limit of normal; MCL = mantle cell lymphoma; Max = maximum; Min = minimum; MIPI = Mantle Cell Lymphoma International Prognostic Index; ULN = upper limit of normal; WBC = white blood cell.

[a] MIPI score = 0.03535 * age + 0.6978 * (if ECOG > 1) + 1.367 * $\log_{10}$(LDH/ULN) + 0.9393 * $\log_{10}$(WBC per 10^6/L). MIPI score: low, 0 – 3 points; intermediate, 4 - 5 points; high, 6 – 11 points (Hoster, 2008).

[b] Subject 2171005 had missing ECOG score at baseline. All subjects met the inclusion criterion of ECOG score 0 to 2 (ie, no subjects had ECOG score > 2 at baseline).

[c] Level of LDH: low (LLN), 1.8 ukat/L; high (ULN), 3.4 ukat/L for subjects aged ≤ 60 years and 3.5 ukat/L for subjects aged > 60 years.

[d] Bone marrow involvement (biopsy score) was categorized according to the following observations (Cheson, 1999): (i) positive, if unequivocal cytologic or architectural evidence of malignancy, (ii) negative, if no aggregates or only a few well-circumscribed lymphoid aggregates, or (iii) indeterminate, if increased number or size of aggregates without cytologic or architectural atypia.

[e] High tumor burden: ≥ 1 lesion that was ≥ 5 cm in diameter or 3 lesions each ≥ 3 cm in diameter by central radiology review.

[f] Bulky disease: ≥ 1 lesion that is ≥ 7 cm in the longest diameter by central radiology review.

[g] Renal function: normal, CrCl ≥ 60 mL/min; moderate insufficiency, CrCl < 60 but ≥ 30 mL/min and not requiring dialysis; severe insufficiency, CrCl < 30 mL/min. Two randomized subjects (1041001 and 6111005) had calculated CrCl (Cockcroft-Gault estimation) values < 30 mL/min during screening, of whom one (6111005) was never treated.

[h] Time from diagnosis to first dose was missing in the 4 subjects who never received randomized treatment.

[i] Ki-67 index: labeling in the original pathology specimen at diagnosis, if available at time or at time of relapse.

Numbers analysed

Table 6 summarises the analysis sets.

Table 1. Analysis sets-All subjects (Study MCL 002)

	Lenalidomide	Control
Subjects in each set	**N = 170**	**N = 84**
Intent-to-treat (ITT), n (%)	170 (100.0)	84 (100.0)
Full Analysis Set (FAS), n (%)	164 (96.5)	81 (96.4)
Per Protocol Set (PPS), n (%)	129 (75.9)	70 (83.3)
As Treated (AT), n (%)	141 (82.9)	68 (81.0)
Safety, n (%)	167 (98.2)	83 (98.8)

Outcomes and estimation

Primary endpoint- PFS

- *Progression-free survival Based on central Review*

The efficacy results in terms of the primary endpoint of Progression free survival (cut-off date 7 March 2014), based on central review, are summarised in Table 7 and Figure 3.

Table 7. Progression Free Survival by Central Review (ITT population-Study MCL 002)

	Lenalidomide	Control
	N = 170	N = 84
Subjects with event, n (%)	106 (62.4)	59 (70.2)
Progression	92 (54.1)	55 (65.5)
Death	14 (8.2)	4 (4.8)
Censored, n (%)	64 (37.6)	25 (29.8)
PFS, median[a] [95% CI][b] (weeks)	**37.6** [24.0, 52.6]	**22.7** [15.9, 30.1]
20 weeks event-free, % (SE)	61 (4.0)	52 (5.9)
24 weeks event-free, % (SE)	58 (4.0)	49 (6.0)
56 weeks event-free, % (SE)	41 (4.1)	21 (5.3)
80 weeks event-free, % (SE)	31 (4.2)	11 (4.3)
104 weeks event-free, % (SE)	26 (4.1)	11 (4.3)
160 weeks event-free, % (SE)	22 (4.2)	8 (4.2)
208 weeks event-free, % (SE)	11 (5.8)	0 (0.0)
232 weeks event-free, % (SE)	11 (5.8)	0 (0.0)
Stratified HR [95% CI][c]	**0.63 [0.43, 0.90]**	
Stratified log-rank test, p-value[c]	0.012	
Unstratified log-rank test, p-value	0.003	
Sequential HR [95% CI][d]	**0.61 [0.44, 0.84]**	
Sequential log-rank test, p-value[d]	0.004	

CI = confidence interval; DMC =Data Monitoring Committee; HR = hazard ratio; ITT = intent-to-treat; KM = Kaplan-Meier; MIPI = Mantle Cell Lymphoma International Prognostic Index; PFS =progression-free survival; SAP = statistical analysis plan; SCT = stem cell transplantation; SE = standard error.

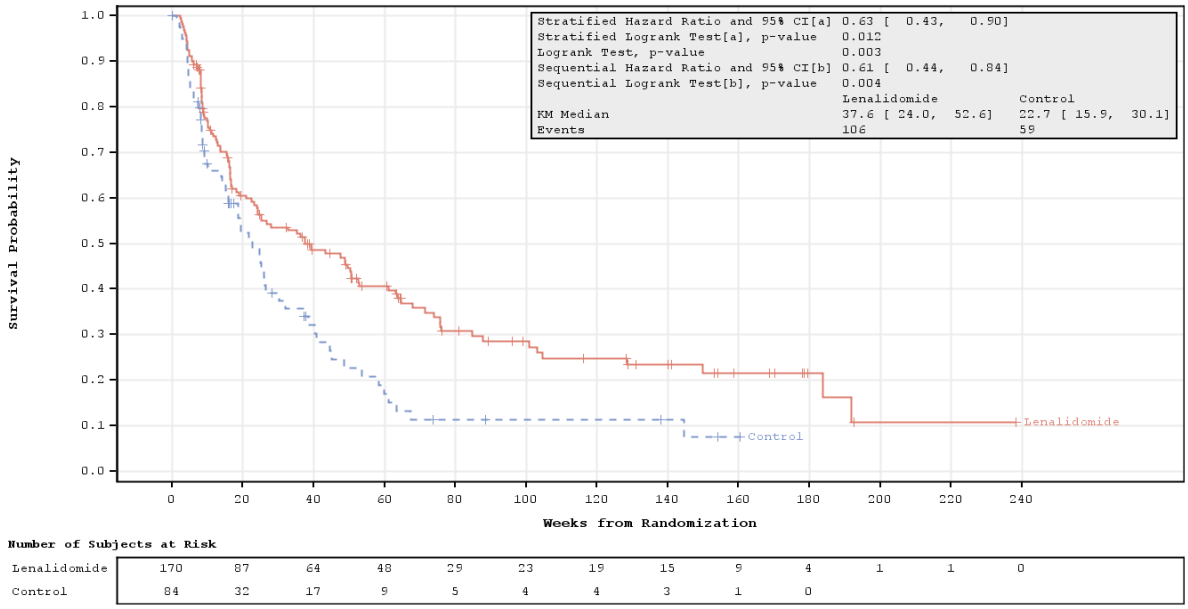
[a] The median was based on the KM estimate.

[b] Range was calculated as 95% CIs about the median survival time.

[c] The stratification variables included time from diagnosis to first dose (< 3 years and ≥ 3 years), time from last prior systemic anti-lymphoma therapy to first dose (< 6 months and ≥ 6 months), prior SCT (yes or no), and MIPI at baseline (low, intermediate, and high risk). As planned in the SAP, stratification factors were included in the stratified test and, as requested by the DMC, MIPI at baseline was added in the stratified test.

[d] Sequential test was based on a weighted mean of a log-rank test statistic using the unstratified log-rank test for sample size increase and the unstratified log-rank test of the primary analysis. The weights are based on observed events at the time the third DMC meeting was held and based on the difference between observed and expected events at the time of the primary analysis. The associated sequential HR and the corresponding 95% CI are presented.

Figure 3. Kaplan- Meier Curve for progression free survival by Central review (ITT population-Study MCL 002)



PFS Based on investigator's assessment

The results of the PFS analyses based on data from investigators' assessments showed a 37% reduction in the risk of disease progression or death for patients in the Len arm compared with those in the Control arm (HR = 0.63; 95% CI: 0.45, 0.86); using the sequential log-rank test, a statistically significant longer PFS in the Len arm than in the Control arm (p = 0.006) was observed.

The stratified analysis indicated a 41% reduction in the risk favouring the Len arm (HR = 0.59; 95% CI: 0.42, 0.85). A statistically significant longer PFS in the Len arm was seen by both the stratified (p = 0.003) and the unstratified (p = 0.004) log-rank tests.

The number of events analysed as per investigator's assessment was 178 compared to 165 in the primary analysis. Of the 178 patients who had progressed or died, 67.1% of patients in the Len arm had PFS events compared with 76.2% in the Control arm (data not shown).

Sensitivity analyses

When progression or death under a new anti-lymphoma treatment or under crossover lenalidomide was considered as an event, the risk reduction in favour of the Len Arm was maintained (HR = 0.60; 95% CI: 0.42, 0.84).

When death or progression after an extended lost-to-follow-up time (≥ 2 missed assessments) was considered as an event, no patients had been censored according to that situation, so results exactly replicate the primary analysis (HR = 0.63; 95% CI: 0.43, 0.90).

When the earliest date of documented progression determined either by the IRC or the investigator's assessment (instead of only IRC) was considered the date of the event, a greater number of events was collected than in any of the previous analyses, both in the Len Arm (n = 123; 72.4%) and in the Control arm (n = 71; 84.5%) and the risk reduction favouring the Len Arm was 40% (HR = 0.60; 95% CI: 0.42, 0.84) (data not shown).

Multivariate Analysis Using Cox Regression on Progression-free Survival

The stratified Cox proportional hazard regression model was used to estimate the HR and associated 95% CIs. Based on centrally reviewed data and after correction for several prognostic factors using this model, a risk reduction in PFS of 62% (HR = 0.38; 95% CI: 0.25, 0.58; p < 0.001) was observed in the Len Arm.

Beside the treatment effect, the Cox proportional hazards multivariate model of PFS for treatment arms estimated the following prognostic factors significant (p < 0.050): low or normal LDH at baseline, < 3 prior systemic anti lymphoma therapies, time since last rituximab to first dose ≥ 230 days, no bulky disease at baseline, low or normal Ki-67 index (Table 8).

Table 8. Summary of Multivariate Analysis Using Cox Regression on Progression Free Survival by Central Review ITT Population

	Univariate Analysis			Multivariate Analysis		
Variable	Hazard Ratio	95% CI	P-Value	Hazard Ratio	95% CI	P-Value
Events/All Subjects: 165/254						
Treatment Group (Len. vs Control)	0.619	[0.448, 0.855]	0.004	0.384	[0.254, 0.580]	<.001
Age Distribution (year) (>=65 vs <65)	0.825	[0.598, 1.137]	0.240			
Sex (Female vs Male)	0.996	[0.705, 1.407]	0.981			
MCL Stage Group at Diagnosis (III+IV vs I+II)	0.799	[0.444, 1.441]	0.456			
ECOG Group at Baseline (2-4 vs 0-1)	1.406	[0.923, 2.141]	0.112			
LDH at Baseline (High vs Low, Normal) [a]	1.821	[1.334, 2.486]	<.001	1.801	[1.198, 2.710]	0.005
WBC at Baseline (x10^9/L) (>=10 vs <10)	1.498	[1.011, 2.221]	0.044			
MIPI Score Group at Diagnosis (High vs Low, Intermediate)	1.137	[0.776, 1.667]	0.510			
MIPI Score Group at Baseline (High vs Low, Intermediate) [b]	1.726	[1.252, 2.380]	<.001	1.444	[0.941, 2.216]	0.093
No of Prior Systemic Anti-Lymphoma Th. (>=3 vs <3)	1.594	[1.148, 2.213]	0.005	1.897	[1.274, 2.825]	0.002
Relapsed vs Refractory to Last Prior Therapy [c]	0.846	[0.618, 1.158]	0.297			
Time from Last Prior Th. (month) (>=6 vs <6) to First Dose	0.775	[0.571, 1.053]	0.104			
Time since Last Rituximab to First Dose (>= 230 vs <230 days)	0.716	[0.521, 0.985]	0.040	0.588	[0.406, 0.851]	0.005
Prior High-Dose Therapy (Yes vs No) [d]	0.983	[0.661, 1.461]	0.931			
Prior Stem Cell Transplantation (Yes vs No)	0.956	[0.640, 1.429]	0.826			
Bone Marrow Assessment (Negative vs Intermediate, Positive)	0.925	[0.540, 1.584]	0.776			
Tumor Burden at Baseline (Low vs High) [e]	0.717	[0.522, 0.983]	0.039			
Time from MCL Diagnosis to First Dose (year) (>=3 vs <3)	0.924	[0.679, 1.257]	0.614			
Renal Function at Bsl (Normal Insuff. vs Moderate, Severe) [f]	0.726	[0.503, 1.047]	0.086			
Bulky Disease at Baseline (Yes vs No) [g]	1.430	[0.983, 2.081]	0.061	1.569	[1.027, 2.396]	0.037
KI67 Index Group (High vs Low, Normal) [h]	2.627	[1.746, 3.953]	<.001	2.908	[1.762, 4.800]	<.001

Note(s): Variables with p-value < 0.20 in the univariate analysis were used to select for the multivariate. Final variables were selected using a stepwise selection method with entry level = 0.20 and stay level = 0.15.
[a] Low<1.8 ukat/L; High>3.4 ukat/L for subjects aged <=60 years; High>3.5 ukat/L for subjects aged >60 years. Normal range are per local lab.
[b] MIPI score=0.03535 * AGE + 0.6978*(if ECOG > 1)+ 1.367 * log10(LDH/ULN) + 0.9393 * log10(WBC per 10^(-6) L).
[c] Relapse:Subjects With Best Response to Last Treatment as CR, CRu, or PR
[d] Defined as stem cell transplant, hyper-CVAD or R-hyper-CVAD.
[e] High tumor burden is defined as at least one lesion that is >=5 cm in diameter or 3 lesions that are >=3 cm in diameter by central radiology review.
[f] Normal= Creatinine clearance >=60 ml/min; Moderate = Creatinine clearance >=30 ml/min but <60 ml/min and not requiring dialysis; Severe insufficiency <30 ml/min.
2 subjects (1041001, 6111005) with severe renal insufficiency are included in the study.
[g] Bulky disease is defined as at least one lesion that is >= 7cm in the longest diameter by central radiology review.
[h] Low=<10%; Normal= 10-30%; High= >30%.

More events of progressive disease (PD) and death occurred in the high tumour burden than in the low tumour burden subgroup (Table 9).

Table 9. Summary of Progression-free Survival by Tumour Burden at Baseline Based on Central Review – ITT Population (Study MCL-002)

	Low Tumour Burden			**High Tumour Burden[a]**		
Progression-free Survival	**Len N = 78**	**Control N = 50**	**Overall N = 128**	**Len N = 81**	**Control N = 28**	**Overall N = 109**
Non censored, n (%)	**43 (55.1)**	**33 (66.0)**	**76 (59.4)**	**56 (69.1)**	**22 (78.6)**	**78 (71.6)**
Progressive disease	38 (48.7)	30 (60.0)	68 (53.1)	47 (58.0)	21 (75.0)	68 (62.4)
Death	5 (6.4)	3 (6.0)	8 (6.3)	9 (11.1)	1 (3.6)	10 (9.2)
Censored, n (%)	**35 (44.9)**	**17 (34.0)**	**52 (40.6)**	**25 (30.9)**	**6 (21.4)**	**31 (28.4)**

ITT = intent-to-treat; Len = lenalidomide.

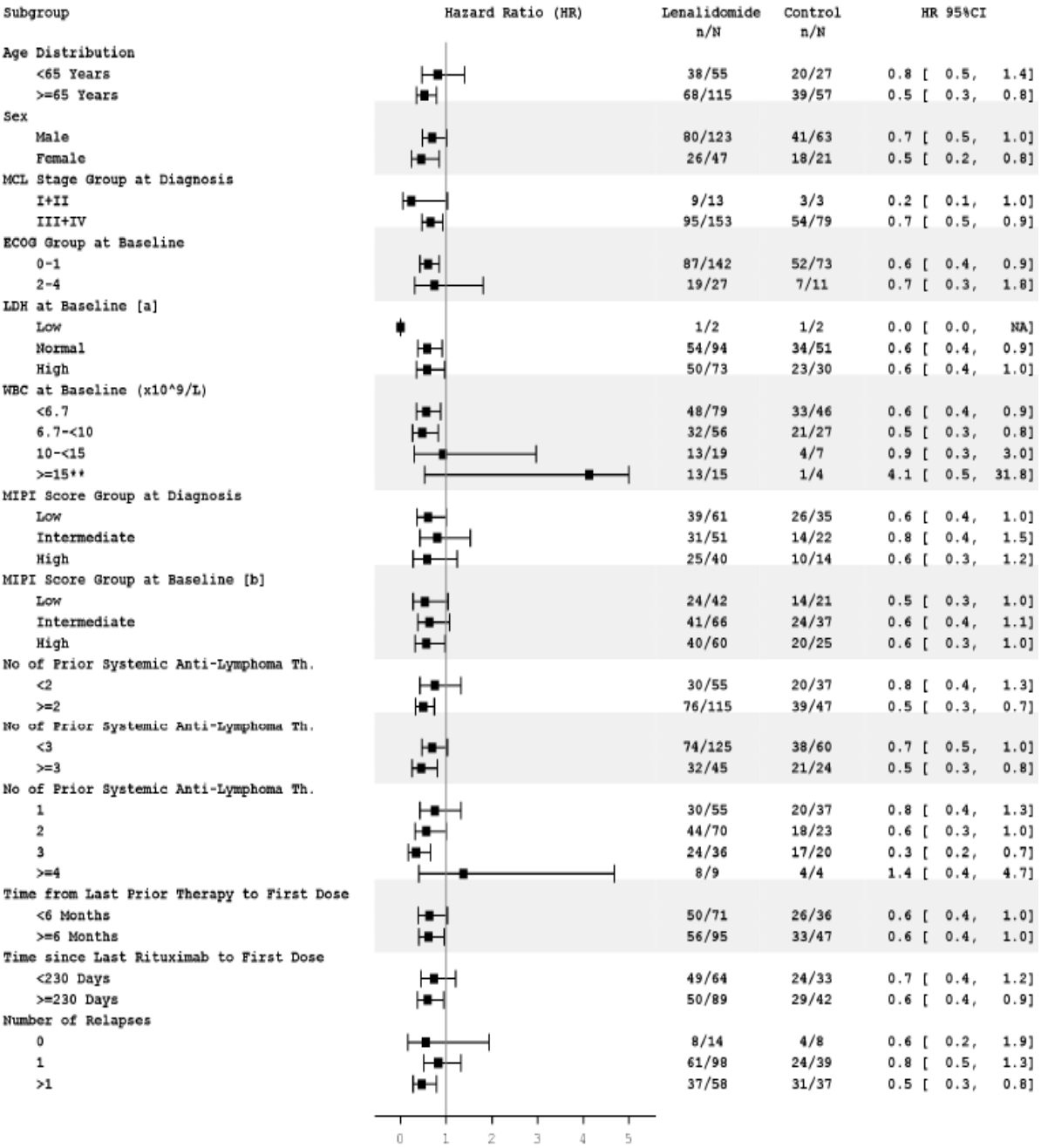
a High tumour burden is defined as at least one lesion that is ≥ 5 cm in diameter or 3 lesions that are ≥ 3 cm in diameter by central review.
Note: Data cutoff date is 07 Mar 2014. A total of 17 subjects did not have data on high or low tumor burden at baseline (CSR MCL-002 Table 14.1.3). Source: Table 1.1.1.

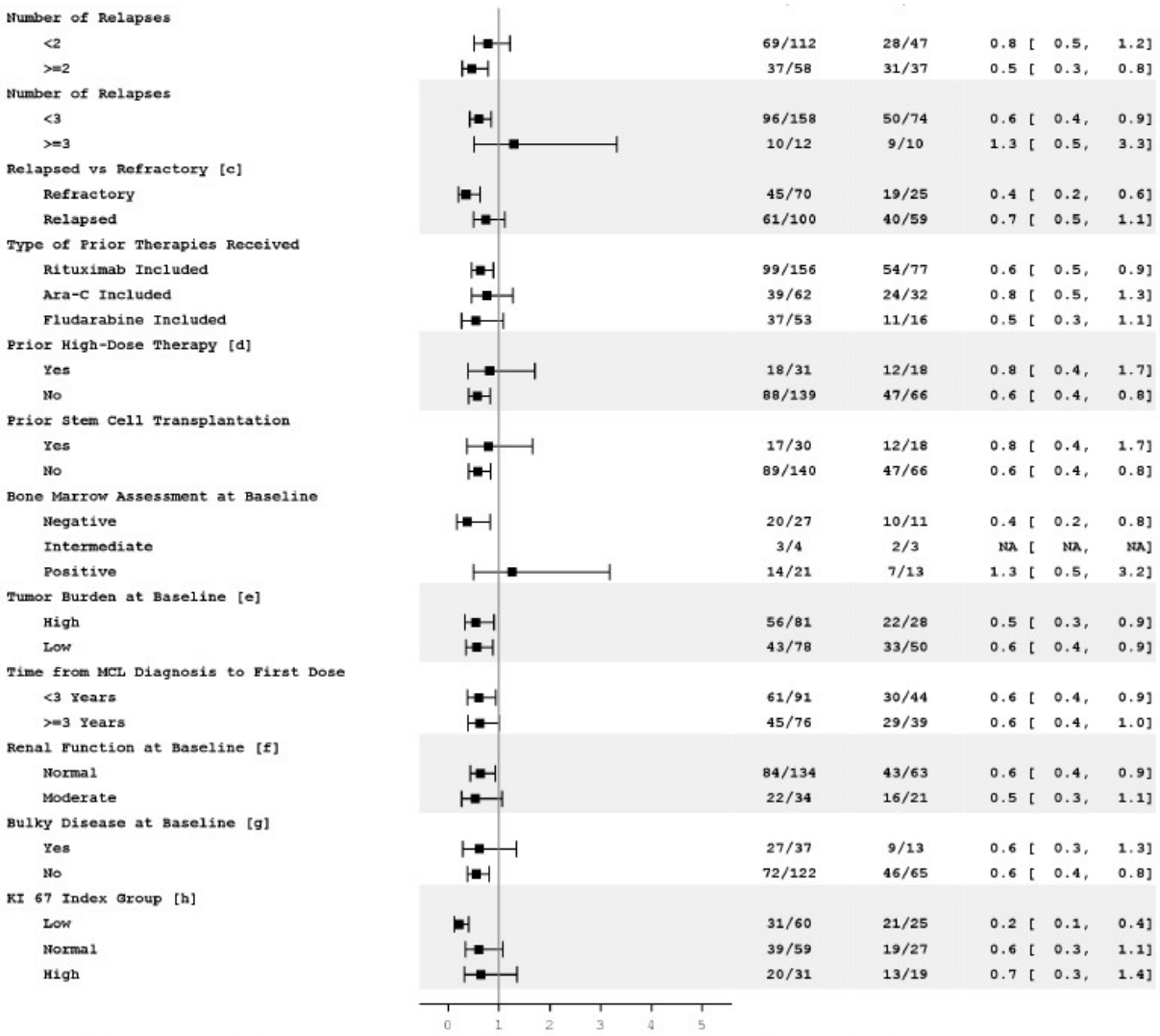
In multivariate logistic regression analyses of progression, high tumour burden was associated with higher risk of progression within 20 weeks (but not after 20 weeks) while lenalidomide treatment was associated with lower risk of progression in both subgroups .

Subgroup analyses of PFS

A Forest plot of the HRs by subgroups for the primary comparison of PFS by central review (ITT population) between Len arm and Control arm is shown in Figure 4.

Figure 4. Subgroup analysis of Progression Free survival by Central Review (ITT population-MCL 002 study)





CI = confidence interval; CR = complete response; CrCl = creatinine clearance; CRu = complete response unconfirmed; ECOG = Eastern Cooperative Oncology Group; HDT: high-dose therapy; hyper-CVAD = hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; ITT = intent-to-treat; LDH = lactate dehydrogenase; LLN = lower limit of normal; MCL = mantle cell lymphoma; Max = maximum; Min = minimum; MIPI = Mantle Cell Lymphoma International Prognostic Index; PD = progressive disease; PR = partial response; R-hyper-CVAD = rituximab plus hyper-CVAD; SCT = stem cell transplantation; SD = stable disease; StD = standard deviation; ULN = upper limit of normal; WBC = white blood cell.

[a] Level of LDH: low (LLN), 1.8 ukat/L; high (ULN), 3.4 ukat/L for subjects aged ≤ 60 years and 3.5 ukat/L for subjects aged > 60 years.

[b] MIPI score = 0.03535 * age + 0.6978 * (if ECOG > 1) + 1.367 * $\log_{10}$(LDH/ULN) + 0.9393 * $\log_{10}$(WBC per 10^6/L). MIPI score: low, 0 – 3 points; intermediate, 4 - 5 points; high, 6 – 11 points (Hoster, 2008).

[c] Relapsed: subjects with best response to last treatment as CR, CRu, or PR. Refractory: subjects not having achieved a response to last treatment (best response was SD or PD).

[d] Prior HDT: SCT, hyper-CVAD or R-hyper-CVAD.

[e] High tumor burden: ≥ 1 lesion that was ≥ 5 cm in diameter or 3 lesions each ≥ 3 cm in diameter by central radiology review.

[f] Renal function: normal, CrCl ≥ 60 mL/min; moderate insufficiency, CrCl < 60 but ≥ 30 mL/min and not requiring dialysis. The two subjects (1041001 and 6111005) with severe renal insufficiency (CrCl < 30 ml/min) at baseline are not included in the analysis.

[g] Bulky disease: ≥1 lesion that is ≥ 7 cm in the longest diameter by central radiology review.

[h] Ki-67 index: Low ≤ 10; Normal = 10 to 30; High > 30.

Note: ** indicates upper boundary is out of graph's range.

Source: Graph 14.2.1.5.

Secondary endpoints

- **Overall survival**

The efficacy results in terms of the secondary endpoint of Overall Survival (cut-off date 7 March 2014) are summarised in Table 10 and Figure 5.

Table 10. Overall Survival (ITT population-Study MCL 002)

	Lenalidomide	Control
	N = 170	N = 84
Subjects with events, n (%)	**83 (48.8)**	**45 (53.6)**
Death	83 (48.8)	45 (53.6)
Censored, n (%)	**87 (51.2)**	**39 (46.4)**
OS, median[a] [95% CI][b] (weeks)	**121.0** [86.7, 160.4]	**91.7** [69.4, 125.6]
20 weeks event-free, % (SE)	86 (2.7)	93 (2.9)
24 weeks event-free, % (SE)	83 (3.0)	91 (3.1)
56 weeks event-free, % (SE)	70 (3.6)	70 (5.2)
72 weeks event-free, % (SE)	63 (3.9)	60 (5.7)
104 weeks event-free, % (SE)	56 (4.2)	44 (6.3)
128 weeks event-free, % (SE)	50 (4.4)	37 (6.5)
144 weeks event-free, % (SE)	47 (4.5)	35 (6.5)
160 weeks event-free, % (SE)	42 (4.6)	35 (6.5)
184 weeks event-free, % (SE)	36 (5.0)	35 (6.5)
232 weeks event-free, % (SE)	31 (6.4)	26 (7.1)
HR [95% CI][c]	**0.89** [0.62, 1.28]	
Log-rank test, p-value	0.519	
Mantel-Byar test, p-value[c]	0.448	

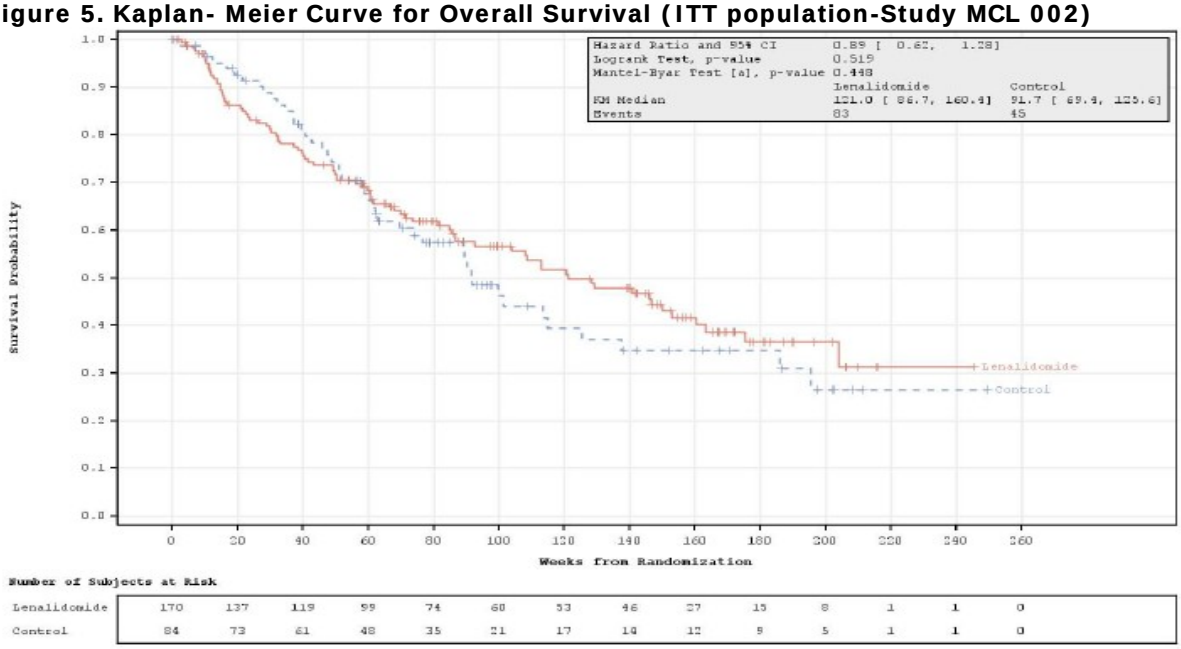
CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; KM = Kaplan-Meier; OS = overall survival; SE = standard error.

[a] The median was based on the KM estimate.

[b] Range was calculated as 95% CIs about the median survival time.

[c] Mantel-Byar test was used to evaluate the effect of crossover on OS.

Figure 5. Kaplan- Meier Curve for Overall Survival (ITT population-Study MCL 002)



High tumour burden was among the baseline disease characteristics with a higher incidence in the lenalidomide group than in the control group (47.6% [81/170] versus 33.3% [28/84]).

For OS, a HR of 0.71 (95% CI: 0.42, 1.19; p = 0.196) was observed in the subgroup of low tumour burden at baseline, and a HR of 1.17 (95% CI: 0.66, 2.08; p = 0.583) was seen in the high tumour burden subgroup for lenalidomide compared to control (Figure 6). Caution should be exercised when interpreting the results due to the smaller numbers of subjects at risk in the control group (n = 28) and in the lenalidomide group (n = 81).

Early deaths

In the ITT population, there was an overall apparent increase in deaths within 20 weeks in the lenalidomide arm 22/170 (13%) versus 6/84 (7%) in the control arm. Patients with high tumour burden at baseline are at increased risk of early death, 16/81 (20%) early deaths in the lenalidomide arm and 2/28 (7%) early deaths in the control arm. Within 52 weeks corresponding figures were 32/81 (39.5%) and 6/28 (21%).

In a multivariate logistic analysis of early deaths (within 20 weeks post randomization) in both treatment arms (n = 28) high tumour burden at baseline was a significant prognostic factor after correction for several risk factors (OR = 0.262; p = 0.007).

Table 11. Multivariate analysis on subjects who died within 20 weeks from randomisation (ITT population-Study MCL-002)

Multivariate Analysis on Subjects Who Died Within 20 Weeks From Randomization
ITT Population

	Univariate Analysis			Multivariate Analysis		
Variable	Odds Ratio	95% CI	P-Value	Odds Ratio	95% CI	P-Value
Events/All Subjects: 28/238						
Treatment Group (Len. vs Control)	1.954	[0.758, 5.033]	0.165			
MCL Stage Group at Diagnosis (III+IV vs I+II)	0.357	[0.106, 1.200]	0.096			
MIPI Score Group at Diagnosis (High vs Low, Intermediate)	2.415	[1.000, 5.831]	0.050	2.513	[0.967, 6.531]	0.059
WBC at Baseline (x10^9/L) (>=10 vs <10)	2.438	[1.017, 5.843]	0.046	2.472	[0.898, 6.803]	0.080
Bulky Disease at Baseline (Yes vs No) [a]	2.149	[0.894, 5.162]	0.087			
Tumor Burden at Baseline (Low vs High) [b]	0.367	[0.157, 0.858]	0.021	0.262	[0.099, 0.690]	0.007
History of Embolic and Thrombolic Events (Yes vs No)	0.609	[0.258, 1.434]	0.256			
History of Infections and Infestations (Yes vs No)	1.207	[0.464, 3.138]	0.700			
History of Cardiac Events (Yes vs No)	1.091	[0.440, 2.706]	0.851			
Extranodal Involvment at Enrollment (Yes vs No)	0.623	[0.271, 1.433]	0.265			
CIRS (>=7 vs 0-6) [c]	0.576	[0.234, 1.417]	0.229			

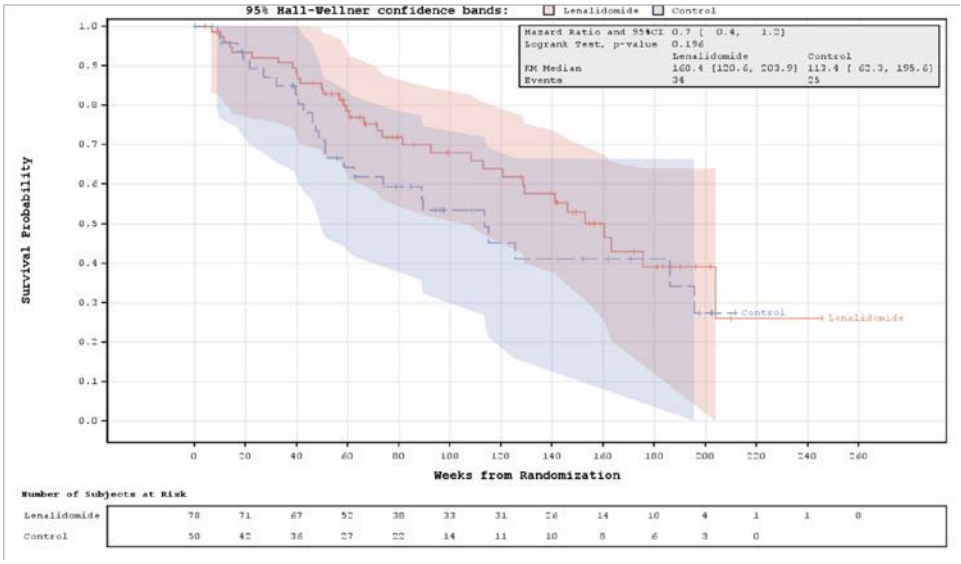
Multivariate Analysis on Subjects Who Died After 20 Weeks From Randomization
ITT Population

	Univariate Analysis			Multivariate Analysis		
Variable	Odds Ratio	95% CI	P-Value	Odds Ratio	95% CI	P-Value
Events/All Subjects: 100/238						
Treatment Group (Len. vs Control)	0.638	[0.370, 1.101]	0.106	0.646	[0.374, 1.118]	0.118
MCL Stage Group at Diagnosis (III+IV vs I+II)	1.190	[0.418, 3.394]	0.744			
MIPI Score Group at Diagnosis (High vs Low, Intermediate)	1.371	[0.728, 2.584]	0.328			
WBC at Baseline (x10^9/L) (>=10 vs <10)	0.776	[0.393, 1.532]	0.465			
Bulky Disease at Baseline (Yes vs No) [a]	1.225	[0.638, 2.354]	0.542			
Tumor Burden at Baseline (Low vs High) [b]	0.937	[0.549, 1.599]	0.810			
History of Embolic and Thrombolic Events (Yes vs No)	0.655	[0.358, 1.195]	0.168			
History of Infections and Infestations (Yes vs No)	0.714	[0.394, 1.295]	0.268			
History of Cardiac Events (Yes vs No)	1.043	[0.581, 1.870]	0.889			
Extranodal Involvment at Enrollment (Yes vs No)	0.832	[0.467, 1.482]	0.532			
CIRS (>=7 vs 0-6) [c]	1.535	[0.897, 2.627]	0.118	1.516	[0.883, 2.602]	0.131

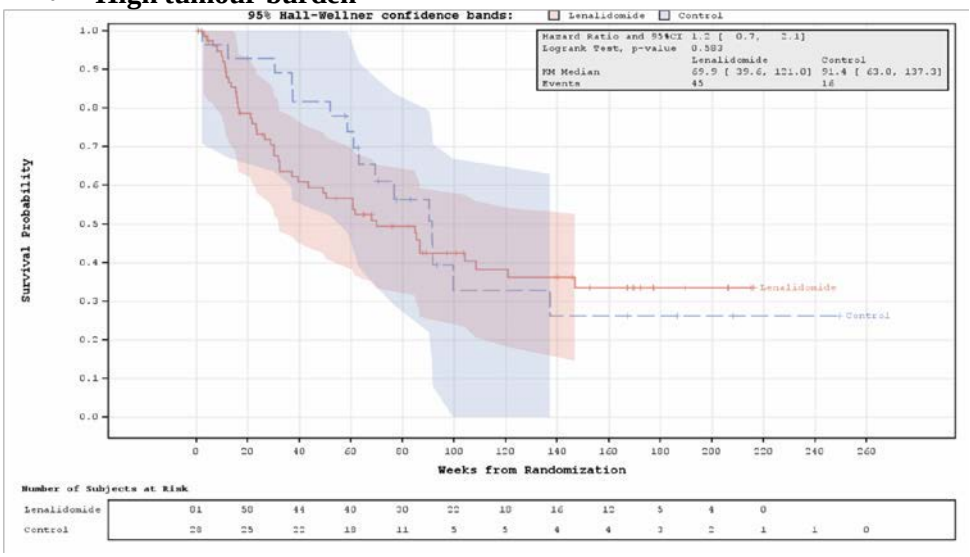
Note(s): Variables with p-value < 0.20 in the univariate analysis were used to select for the multivariate. Final variables were selected using a stepwise selection method with entry level = 0.20 and stay level = 0.15.
Multivariate analysis using Logistic regression model was estimated using 194 subjects.
[a] Bulky disease is defined as at least one lesion that is >= 7cm in the longest diameter by central radiology review.
[b] High tumor burden is defined as at least one lesion that is >=5 cm in diameter or 3 lesions that are >=3 cm in diameter by central radiology review.
[c] CIRS Cumulative Illness Rating Scale. Score 0-6: low comorbidity - score = 7: high comorbidity

Figure 6. Kaplan-Meier Curves of Overall Survival by Tumour Burden at Baseline ITT Population (Study MCL-002- cut-off date 7 March 2014

- **Low tumour burden**



- **High tumour burden**



CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; KM = Kaplan-Meier

- **Response and tumour control rate**

Best response rate and complete response rate by central review on ITT Population are presented in Table 12.

Table 12. Best response rate and complete response rate by central review (ITT Population-Study MCL 002)

	Lenalidomide	Control
	N = 170	N = 84
Response[a], n (%)		
Complete response (CR)	8 (4.7)	0 (0.0)
Partial response (PR)	60 (35.3)	9 (10.7)
Stable disease (SD)[b]	50 (29.4)	44 (52.4)
Progressive disease (PD)	34 (20.0)	26 (31.0)
Not done/Missing	18 (10.6)	5 (6.0)
ORR (CR, CRu, PR), n (%) [95% CI][c]	**68 (40.0)** [32.58, 47.78]	**9 (10.7)**[d] [5.02, 19.37]
p-value[e]	< 0.001	
CRR (CR, CRu), n (%) [95% CI][c]	**8 (4.7)** [2.05, 9.06]	**0 (0.0)** [0.00, 4.30]
p-value[e]	0.043	
TCR (CR, CRu, PR, SD), n (%) [95% CI][c]	**118 (69.4)** [61.89, 76.24]	**53 (63.1)** [51.87, 73.37]
p-value[e]	0.313	

- **Duration of stable disease**

The KM curves based on central review showed no difference in the estimated duration of SD between treatment arms (p = 0.884, log-rank test); similarly, results obtained in the FAS, PPS, and AT Populations did not show a clear trend in the comparison of SD between arms (data not shown).

- **Time to progression**

The TTP results by central review on ITT population are presented in Table 13.

Table 13. Time to progression by central review (ITT Population-MCL 002 study)

	Lenalidomide	Control
Subjects	**N = 170**	**N = 84**
Non-censored, n (%)	**98 (57.6)**	**56 (66.7)**
Progression	**98 (57.6)**	**56 (66.7)**
Censored, n (%)	**72 (42.4)**	**28 (33.3)**
TTP, median[a] [95% CI][b] (weeks)	**39.3** [24.3, 52.9]	**24.7** [15.9, 30.1]
20 weeks event-free, % (SE)	61 (4.0)	52 (6.0)
24 weeks event-free, % (SE)	59 (4.1)	50 (6.0)
56 weeks event-free, % (SE)	41 (4.3)	23 (5.7)
80 weeks event-free, % (SE)	32 (4.3)	13 (4.7)
104 weeks event-free, % (SE)	28 (4.4)	13 (4.7)
152 weeks event-free, % (SE)	25 (4.5)	8 (4.7)
208 weeks event-free, % (SE)	12 (6.6)	0 (0.0)
232 weeks event-free, % (SE)	12 (6.6)	0 (0.0)
HR [95% CI]	**0.62** [0.45, 0.87]	
Log-rank test, p-value	0.005	

- **Time to treatment failure**

The TTF was longer in Len arm than in the Control arm (p = 0.046, log-rank test). The improvement in median TTF between the Len arm, 24.4 weeks (5.6 months), and the Control arm, 17.9 weeks (4.1 months), was 6.5 weeks (1.5 months). Similarly, TTF by investigator's assessment is longer in Len arm than in Control arm but still without statistical significance (data not shown).

- **Time to first response (TTFR) and time to best response (TTBR)**

Analysis of TTFR by central review shows a rapid increase in the number of responders in the Len arm compared with the Control arm (HR = 3.91, 95% CI 1.95-7.85; p < 0.001).

The median time to first response was 18.7 weeks (4.3 months) in the Len arm and had not been reached for the Control arm at the data cut-off date.

The median TTBR was 26.7 weeks (6.2 months) in the Lenalidomide Arm and had not been reached for the Control Arm at the data cut-off date (data not shown).

- **Quality of life**

The QoL assessment was performed using the EORTC QLQ-C30 (a 30-item oncology-specific questionnaire). QoL are assessed at 6 time points: screening, after cycle 2 (C3D1), after cycle 4 (C5D1), after cycle 6 (C7D1), after cycle 8 (C9D1) and time of discontinuation from treatment (TxDC).

Table 14. Quality of Life Improvement Based on EORTC QLQ-30 Questionnaire (Change from Baseline) – ITT Population- Study MCL-002

	EORTC QLQ-30 Questionnaire Score			
	At Least 5-point Improvement		At Least 10-point Improvement[a]	
Subjects with Change in Each Category	Lenalidomide n (%)	Control n (%)	Lenalidomide n (%)	Control n (%)
Physical Functioning	59 (34.7)	21 (25.0)	41 (24.1)	7 (8.3)
Role Functioning	40 (23.5)	23 (27.4)	40 (23.5)	23 (27.4)
Emotional Functioning	65 (38.2)	26 (31.0)	42 (24.7)	14 (16.7)
Cognitive Functioning	35 (20.6)	14 (16.7)	35 (20.6)	14 (16.7)
Social Functioning	41 (24.1)	14 (16.7)	41 (24.1)	14 (16.7)
Fatigue	56 (32.9)	21 (25.0)	55 (32.4)	21 (25.0)
Pain	50 (29.4)	15 (17.9)	50 (29.4)	15 (17.9)
Nausea/Vomiting	17 (10.0)	4 (4.8)	17 (10.0)	4 (4.8)
Constipation	21 (12.4)	10 (11.9)	21 (12.4)	10 (11.9)
Diarrhea	30 (17.6)	11 (13.1)	30 (17.6)	11 (13.1)
Insomnia	42 (24.7)	19 (22.6)	42 (24.7)	19 (22.6)
Dyspnoea	36 (21.2)	15 (17.9)	36 (21.2)	15 (17.9)
Appetite Loss	30 (17.6)	14 (16.7)	30 (17.6)	14 (16.7)
Financial Problems	32 (18.8)	8 (9.5)	32 (18.8)	8 (9.5)
Global Health Status	55 (32.4)	26 (31.0)	40 (23.5)	20 (23.8)

EORTC QLQ-30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; ITT = intent-to-treat.

[a] A 10-point change in the scoring is considered to be a meaningful change in QoL (Osoba, 1998).

Overall, compliance declined over the course of the study, with higher non-compliance rates typically seen among patients in the control arm versus patients in the Len arm.

Among patients in the Len arm at treatment discontinuation, scores trended towards deterioration for the majority of scales, although scores for emotional functioning, pain, nausea/vomiting, insomnia, and financial problems improved slightly among patients in this arm (data not shown).

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 15. Summary of Efficacy for trial MCL-002

Title: A multicenter, randomized, open-label, controlled Phase 2 study designed to compare the efficacy and safety of single-agent lenalidomide versus single agent of investigator' choice (IC) in patients with MCL who were refractory to their last regimen or had between 1 and 3 relapses.			
Study identifier	MCL-002		
Design	Randomized, open-label, multicenter, controlled Phase 2 study		
Treatments groups	Len arm		Orally once daily on D1 to D21 in each 28-day cycle. The starting dose of lenalidomide was 25 mg or 10 mg based on renal function.
	Control arm		Investigator's choice single agent among following: Chlorambucil, Rituximab, Cytarabine, Gemcitabine, Fludarabine IV, Fludarabine p.o.
Endpoints and definitions	Primary endpoint	Progression Free Survival (PFS) based on central review	time from randomization to the first observation of disease progression or death due to any cause.
	Secondary endpoints	Overall Response Rate (ORR)	Included best response of CR, CRu, or PR
		Duration of Response (DOR)	time of initial response (at least PR) until documented tumour progression or death
		Time to progression (TTP)	time from randomization until objective tumor progression
		Overall survival (OS)	time from randomization until death from any cause

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent To Treat (ITT) Population (Clinical cut-off of 04 March 2014) N=254		
Descriptive statistics and estimate variability	Treatment group	Len arm	Control arm
	Number of subject	170	84
	Median PFS (weeks)	37.6	22.7
	95% CI	24.0, 52.6	15.9, 30.1

	Sequential HR* [95% CI] Sequential Log-rank test, p-value	0.61 [0.44, 0.84] 0.004	
	DOR (Weeks) 95% CI	69.6 41.1, 86.7	45.1 36.3, 80.9
	TTP (Weeks) 95% CI	39.3 24.3, 52.9	24.7 15.9, 30.1
	ORR (%) 95% CI	68 (40%) 32.58, 47.78	9 (10.7%) 5.02, 19.37
	OS (weeks) 95% CI	121 86.7, 160.4	91.7 69.4, 125.6
	HR [95% CI] Log-rank test, p-value	0.89 [0.62, 1.28] 0.520	
Effect estimate per comparison	Primary endpoint: PFS (Central review)	Comparison groups	Len vs. Control arm
		hazard ratio	0.63
		95% CI	(0.43;0.90)
		P-value	0.012
	Secondary endpoint: DOR	Comparison groups	Len vs. Control arm
		hazard ratio	0.70
		95% CI	(0.29, 1.68)
		P-value	0.421
	Secondary endpoint: TTP	Comparison groups	Len vs. Control arm
		hazard ratio	0.62
		95% CI	(0.45, 0.87)
		P-value	0.005
	Secondary endpoint: OS	Comparison groups	Len vs. Control arm
		hazard ratio	0.89
		95% CI	(0.62, 1.28)
		P-value	0.519
Notes	Stratification factors: Time from diagnosis to first dose (< 3 years or ≥ 3 years), time from end of last prior systemic anti-lymphoma therapy to first dose (< 6 months or ≥ 6 months) and prior stem cell transplantation (SCT) (yes or no). * Sequential test was based on a weighted mean of a log-rank test statistic using the unstratified log-rank test for sample size increase and the unstratified log-rank test of the primary analysis. The weights are based on observed events at the time the third DMC meeting was held and based on the difference between observed and expected events at the time of the primary analysis. The associated sequential HR and the corresponding 95% CI are presented.		

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

N/A

Supportive studies

MCL 001 study (EMERGE)

Study MCL 001 was a phase 2, multicenter, single-arm, open-label study to determine the efficacy and safety of single-agent lenalidomide in patients with mantle cell NHL who have relapsed or progressed after treatment with bortezomib or are refractory to bortezomib.

This study was comprised of 3 phases: a pretreatment phase, a treatment phase, and a follow-up phase. During pretreatment phase, potential study patients were screened for protocol eligibility within 28 days of Cycle 1, Day 1 (unless otherwise specified) prior to the start of lenalidomide therapy.

Patients continued participation in the treatment phase until disease progression, development of unacceptable AEs, or voluntary withdrawal. Patients who experienced disease progression or relapsed or who stopped treatment for other reasons entered the follow-up phase.

The follow-up phase of this study will continue until either 70% of the patients have died or a maximum of 4 years from enrollment of the last patient, whichever occurs first. Note that patients were to be followed for the occurrence of SPMs through 5 years after enrollment of the last patient.

Primary efficacy endpoints were the overall response rate (ORR) and duration of response (DOR).

The planned sample size was 133 patients. As of the data cut-off date of 20 March 2013, enrollment is complete with 117 (87%) of the 134 treated patients off study treatment and 17 patients (13%) ongoing on treatment. Table 16 summarises the main efficacy results on ITT population.

Table 16. Response Rates and Duration of Response Based on IRC and Investigators' Assessments (ITT Population)- MCL-001

Efficacy Endpoint	IRC Assessment (N = 134)	Investigators' Assessments (N = 134)
Best Response[a] Category, n (%)		
Overall Response Rate (CR+CRu+PR)	38 (28.4) [20.91, 36.79][b]	43 (32.1) [24.29, 40.70][b]
Complete Response (CR+CRu)	11 (8.2) [4.17, 14.21][b]	23 (17.2) [11.20, 24.63][b]
CR	4 (3.0)	8 (6.0)
CRu	7 (5.2)	15 (11.2)
Partial Response (PR)	27 (20.1)	20 (14.9)
Stable Disease (SD)	39 (29.1)	36 (26.9)
Progressive Disease (PD)	34 (25.4)	43 (32.1)
No Response Assessment (NRA)/Missing[c]	23 (17.2)	12 (9.0)
Duration of Overall Response (CR + CRu + PR) (months)		
n	38	43
Median [95% CI][d]	16.64 [9.173, 26.729]	18.48 [12.921, 35.244]
Minimum, Maximum	0.03+, 33.34+	0.99, 35.24
Number of Events, n (%)	20 (52.6)	23 (53.5)
Censored Observations, n (%)	18 (47.4)	20 (46.5)

+ = censored observation; CI = confidence interval; CR = complete response; CRu = complete response unconfirmed; IRC = Independent Review Committee; ITT = intent to treat.

[a] Best response during the study (ie, from the first dose date until the start of new anti-lymphoma therapy; if no anti-lymphoma therapy, then there was no end date).

[b] 95% exact CI based on binomial distribution.

[c] Insufficient efficacy data to determine response; included as non-responders in the analysis.

[d] Median was based on the Kaplan-Meier estimate and its 95% CI.

NHL 002 study

NHL 002 was a phase 2, multicenter, single-arm, open-label study to evaluate the safety and efficacy of single-agent lenalidomide in patients with relapsed or refractory aggressive Non-Hodgkin's Lymphoma. This trial was conducted in 2 phases: a treatment phase and a follow-up phase.

The treatment phase began on Day 1 of Cycle 1. Patients meeting all inclusion/exclusion criteria were enrolled to receive oral lenalidomide starting on Day 1 of Cycle 1, at a dose of 25 mg once daily to be taken on Days 1 to 21 every 28-day cycle. Treatment continued up to 52 weeks or until disease progression developed, lenalidomide treatment was discontinued for any reason, or the study was terminated.

Primary efficacy endpoint was response rate.

A total of 50 patients were enrolled in the study of which only 15 were MCL.

Table 17 summarises the efficacy results on ITT population.

Table 17. Summary of efficacy analyses (ITT population-NHL-002 study)

Efficacy Variable	All Subjects (N = 49)	Subgroup			
		NHL Subtype		Prior SCT	
		DLBCL Subjects (N = 26)	MCL Subjects (N = 15)	SCT Subjects (N = 14)	Non-SCT Subjects (N = 35)
Response rate (%) [a] (95% CI)	**34.7** (21.7, 49.6)	**19.2** (6.6, 39.4)	**53.3** (26.6, 78.7)	**50.0** (23.0, 77.0)	**28.6** (14.6, 46.3)
Tumor control rate (%) [b] (95% CI)	**59.2** (44.2, 73.0)	**50.0** (29.9, 70.1)	**66.7** (38.4, 88.2)	**85.7** (57.2, 98.2)	**48.6** (31.4, 66.0)
Duration of response (%), Median [c] (95% CI)	**10.2** (4.0, 16.3)	**7.0** (2.5, 10.4)	**13.7** (4.0, NE)	**7.0** (1.8, 16.3)	**10.4** (4.8, NE)
PFS time (%), Median [c] (95% CI)	**3.6** (2.0, 6.3)	**3.0** (1.8, 4.5)	**5.6** (2.6, 18.2)	**4.1** (2.6, 11.0)	**3.0** (1.8, 7.2)

CI = confidence interval DLBCL = diffuse large B-cell lymphoma; ITT = intent-to-treat; MCL = mantle cell lymphoma; NE = not estimable; PFS = progression-free survival; SCT = stem cell transplant.
[a] Response rate = CR + CRu + PR.
[b] Tumor control rate = CR + CRu + PR + SD.
[c] In months.

NHL 003 study

NHL 003 was a phase 2, multicenter, single-arm, open-label, study to evaluate the safety and efficacy of single-agent lenalidomide in patients with relapsed or refractory aggressive non-hodgkin's lymphoma. Patients were either diagnosed with diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), grade 3 follicular lymphoma (FLgr3) or transformed lymphoma (TSF).

The primary efficacy endpoint was ORR. A total of 218 patients were enrolled in the study of which 57 were MCL. For patients with MCL (N = 57), median treatment duration was 317+/- 397 day.

Table 18 summarises the efficacy results on ITT population.

Table 18. Summary of efficacy analyses (ITT population-NHL-003 study)

Efficacy Variable	All Subjects (N = 217)	NHL Subtype			
		MCL Subjects (N = 57)	DLBCL Subjects (N = 108)	FLgr3 Subjects (N = 19)	TSF Subjects (N = 33)
Response rate (%) [a], (95% CI)[b]	**31.3** (25.23, 37.96)	**35.1** (22.91, 48.87)	**24.1** (16.37, 33.25)	**42.1** (20.25, 66.50)	**42.4** (25.48, 60.78)
Complete response rate (%)[c], (95% CI)[b]	**12.9** (8.75, 18.11)	**12.3** (5.08, 23.68)	**9.3** (4.53, 16.37)	**15.8** (3.38, 39.58)	**24.2** (11.09, 42.26)
DoR, Median (months) [d], (95% CI)	**18.4** (6.51, 34.06)	**16.3** (7.10, NE)	**4.1** (2.14, 18.4)	**21.0** (4.27, NE)	**26.9** (18.71, NE)
DoC, Median (months) [d], (95% CI)	**28.3** (19.20, NE)	**NE** (9.70, NE)	**NE** (5.33, NE)	**23.7** (19.20, 28.27)	**21.4** (9.53, NE)
PFS time, Median (months) [d], (95% CI)	**4.5** (3.68, 6.28)	**8.8** (5.49, 22.98)	**3.6** (1.94, 3.91)	**7.5** (5.59, 36.03)	**4.3** (1.87, 25.02)
TTP time, Median (months) [d], (95% CI)	**4.5** (3.68, 6.28)	**8.8** (5.49, 22.98)	**3.6** (1.94, 3.91)	**7.5** (5.59, 36.03)	**4.3** (1.87, 28.77)
Time to first response, Median (months) [e], (Min, Max)	**1.9** (1.4, 43.4)	**1.9** (1.6, 24.2)	**1.9** (1.7, 43.4)	**1.9** (1.4, 2.1)	**2.0** (1.7, 3.9)
OS time, Median (months) [f], (95% CI)	**25.8** (20.09, NE)	**NE** (NE, NE)	**12.5** (7.40, NE)	**NE** (16.21, NE)	**25.0** (18.54, NE)

CI = confidence interval; CR = complete response; CRu = complete response unconfirmed; DLBCL = diffuse large B-cell lymphoma; DoC = duration of complete response; DoR = duration of response; FLgr3 = follicular lymphoma, grade 3; ITT = intent-to-treat; MCL = mantle cell lymphoma; Max = maximum; Min = minimum; NE = not estimable; NHL = non-Hodgkin lymphoma; OS = overall survival; PR = partial response; PFS = progression-free survival; TSF = transformed lymphoma; TTP = time to progression.
[a] Response rate = CR + CRu + PR.
[b] CI is an exact confidence interval from the binomial distribution.
[c] Complete response rate = CR + CRu.
[d] The median is based on the Kaplan-Meier estimate.
[e] Time to first response = time to first CR or CRu or PR.
[f] Overall survival is based on Investigator data.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal study MCL-002 was an open-label randomised (2:1) study in which single lenalidomide (n=170) was compared to investigator's pre-randomisation choice of chlorambucil, rituximab, cytarabine, gemcitabine or fludarabine (po/iv) single therapy (n=84). Although the chosen comparators are considered acceptable in the setting of R/R disease in patients not amenable for intensive chemotherapy, it would have been appropriate to include temsirolimus and bortezomib. However, efficacy in patients who had relapsed or progressed following, or were refractory to bortezomib is supported by the results obtained in the single arm MCL-001 study (n=134), which recruited a heavily pre-treated patient population including previous exposure to bortezomib. Additional supportive data are available from the NHL-003 and NHL-002 studies which included 57 and 15 patients with R/R MCL, respectively.

Current therapies such as ibrutinib or bortezomib may challenge lenalidomide position in the sequence of second or further line of treatment. In order to study the efficacy of lenalidomide use subsequent to ibrutinib treatment, the MAH is currently conducting the non-interventional Study CC-5013-MCL-004 in patients with MCL who have relapsed or progressed after treatment with ibrutinib or are refractory or intolerant to ibrutinib, and who are subsequently treated with lenalidomide monotherapy or a lenalidomide-containing regimen. The CHMP recommended the applicant to submit the results of study CC-5013-MCL-004 post approval.

The patient population enrolled into MCL-002 study is representative of the patient population of R/R MCL encountered in general clinical practice. Patients were mainly elderly, male, and had advanced disease stage.

Efficacy data and additional analyses

The results of the PFS analysis in study MCL-002 showed a statistically significant improvement in median PFS (HR =0.61; 95% CI 0.44-0.84, p=0.004) of 14.9 weeks (3.4 months) in patients treated with lenalidomide versus those treated with best investigator choice (BIC).

All secondary analyses of PFS, including sensitivity analyses showed significantly longer PFS with lenalidomide compared to BIC, with a consistent HR, thus confirming the robustness of the PFS data in the pivotal study. The effect on PFS was consistent across the investigated subgroups, which are considered relevant for the claimed indication.

During the assessment, the CHMP raised a major objection on the proposed indication to be restricted to RRMCL patients who are not eligible to high dose therapy and/or transplantation as soon as the first relapse happens. Moreover, as advanced stage is a factor associated with adverse/worse prognosis, the potential restriction of the target population to stage III or IV MCL patients was discussed. Allogeneic transplantation is an appropriate option for patients with relapsed or refractory disease who are in remission following second line therapy. In the subset of patients who relapsed after SCT, responses have been observed with lenalidomide, including the achievement of CR. Therefore patients having received prior HDT/SCT in first relapse should not be excluded from subsequent treatment with lenalidomide since they may miss the opportunity to benefit from it. Finally stage as a prognostic factor is not applicable to RRMCL therefore the CHMP agreed with the indication initially proposed by the applicant.

The median OS for single-agent lenalidomide treatment was 27.9 months (2.3 years) compared with 21.2 months (1.8 years) for BIC single-agent treatment however this survival advantage of 6.7 months was not statistically significant (HR =0.89; 95% CI 0.62, 1.28, p=0.519). Moreover, 22 patients in the Lenalidomide arm died during the first 20 weeks after randomization. An analysis on OS by tumour burden at baseline was provided by the applicant showing an increased proportion of early death prior to progression in the high

tumour burden group in the lenalidomide arm (see discussion on clinical safety). Although a definitive association has not been established in view of the potential confounders and small numbers in these subgroup analyses, lenalidomide is not recommended for the treatment of patients with high tumour burden if alternative treatment options are available (see section 4.4 of the SmPC and benefit-risk balance, unfavourable effects).

Regarding the other secondary endpoints, higher ORR was observed in lenalidomide arm (40.0%) which was statistically significant compared to the Control arm (10.7%). A higher quality of response was also observed in the Len arm, with a CR rate of 4.7%, compared to 0.0% in the Control arm (p = 0.043). Tumour control rate was comparable between arms. Responses were also seen earlier in the Len arm of Study MCL 002 compared to the Control arm, with a median time to first response and to best response of 18.7 weeks (4.3 months) and 26.7 weeks (6.2 months), respectively. The median time to first and best response was not reached in the Control arm. The DOR was 6 months longer in the Len arm compared to the Control arm although not statistically significant. Improvement of TTP confirms improvement of PFS. However due to the small number of patients achieving a response, results from the TTP analysis should be interpreted with caution.

Durable response was seen across all four studies presented, which is of major clinical importance, as RRMCL patients continuously relapse and the response rates and duration of response to next-line treatment usually get shorter. Study NHL 003 showed a PFS benefit consistent with that observed in the main study (median PFS of 8.8 and 8.7 months, respectively). In Study NHL 002, median PFS was 5.6 months, however, this study included only a small number of patients with MCL. In study MCL 001, ORR and DOR results have shown activity in bortezomib-exposed patients; important, as bortezomib recently was authorised for combination therapy in 1st line disease.

2.4.4. Conclusions on the clinical efficacy

The results of the pivotal MCL-002 trial are considered of clinical relevance. The statistically significant and clinically relevant improvement in PFS together support a clinical benefit associated with lenalidomide treatment in the target population.

2.5. Clinical safety

The safety analysis included data from the following studies:

- main randomized Study CC-5013-MCL-002 (cut-off date7 March 2014), with 170 subjects randomized into the Lenalidomide Arm and 84 subjects randomized into the Control Arm (investigator's choice);
- Study CC-5013-MCL-001 (cut-off date of 20 March 2013) (n = 134 subjects);
- Study CC-5013-NHL-003 (n = 57 MCL subjects);
- Study CC-5013-NHL-002 (n = 15 MCL subjects).

Patient exposure

Table 19. Treatment Exposure (safety population)

Parameter / Statistic	Analysis Group			
	MCL-002 Len (N = 167) n (%)	MCL-002 Control (N = 83) n (%)	MCL Subjects (MCL-001, NHL-003, NHL-002) (N = 206) n (%)	All MCL Len Subjects (MCL-002 Len, MCL-001, NHL-003, NHL-002) (N = 373) n (%)
Duration of Treatment Exposure (weeks)[a]				
Mean ± StD	46.6 ± 53.5	21.8 ± 31.3	35.5 ± 44.6	40.5 ± 49.1
Median	24.3	13.1	15.1	17.0
Minimum, Maximum	0.4, 241.9	0.1, 157.9	0.1, 208.4	0.1, 241.9
Number of Cycles				
≥ 1 cycle	167 (100.0)	83 (100.0)	206 (100.0)	373 (100.0)
≥2 cycles	141 (84.4)	68 (81.9)	169 (82.0)	310 (83.1)
≥ 3 cycles	119 (71.3)	51 (61.4)	127 (61.7)	246 (66.0)
≥ 4 cycles	102 (61.1)	41 (49.4)	107 (51.9)	209 (56.0)
≥ 6 cycles	83 (49.7)	28 (33.7)	88 (42.7)	171 (45.8)
≥ 12 cycles	62 (37.1)	7 (8.4)	54 (26.2)	116 (31.1)
≥ 18 cycles	37 (22.2)	3 (3.6)	33 (16.0)	70 (18.8)
≥ 24 cycles	28 (16.8)	0 (0.0)	18 (8.7)	46 (12.3)
≥ 30 cycles	18 (10.8)	0 (0.0)	13 (6.3)	31 (8.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cumulative Dose (mg)[b]				
Mean ± StD	4495.3 ± 5736.3	NA	3489.4 ± 4742.3	3939.8 ± 5227.6
Median	2057.5	NA	1575.0	1640.0
Minimum, Maximum	30.0, 25750	NA, NA	25.0, 26250	25.0, 26250
Dose Intensity (mg/day)[c]				
Mean ± StD	17.4 ± 6.8	NA	20.6 ± 5.9	19.2 ± 6.5
Median	18.9	NA	24.1	21.5
Minimum, Maximum	1.4, 25.0	NA, NA	5.3, 25.1	1.4, 25.1
Relative Dose Intensity (%)[d]				
Mean ± StD	0.8 ± 0.2	NA	0.9 ± 0.2	0.9 ± 0.2
Median	0.8	NA, NA	1.0	0.9
Minimum, Maximum	0.1, 1.4	NA	0.3, 1.5	0.1, 1.5
Dose Exposure (day)[e]				
Mean ± StD	229.6 ± 261.2	NA	172.4 ± 216.1	198.0 ± 238. 7
Median	105.0	NA, NA	67.5	84.0
Minimum, Maximum	3.0, 1030.0	NA	1.0, 1050.0	1.0, 1050.0

Len = lenalidomide; MCL = mantle cell lymphoma; NA = not applicable; NHL = non-Hodgkin's lymphoma; StD = standard deviation.
[a] Treatment duration = (date of last dose – date of first dose +1) / 7.
[b] Cumulative dose (mg) is the sum of all doses taken across the treatment period.
[c] Dose intensity (mg/day) = cumulative dose (mg) / number of days dosed (day). Dose intensity during the treatment is not defined for the MCL-002 Control analysis group, as it comprised several drugs with different regimens.
[d] Relative dose intensity = dose intensity / planned dose).
[e] Number of days dosed.

Adverse events

An overview of frequencies for all categories of adverse events is presented by analysis group in Table 20.

Table 20. Overview of AEs and deaths

Category	Analysis Group			
	MCL-002 Len Arm (N=167) n (%)	MCL-002 Control Arm (N=83) n (%)	MCL Subjects (MCL-001, NHL-002,NHL-003) (N=206) n (%)	All MCL Len Subjects (MCL-002 Len,MCL-001,NHL-002, NHL-003) (N=373) n (%)
Subjects With at Least 1–				
Adverse event	159 (95.2)	69 (83.1)	204 (99.0)	363 (97.3)
Adverse event related to study drug	140 (83.8)	50 (60.2)	182 (88.3)	322 (86.3)
Grade 3-4 adverse event	123 (73.7)	55 (66.3)	158 (76.7)	281 (75.3)
Grade 3-4 adverse event related to study drug	104 (62.3)	41 (49.4)	132 (64.1)	236 (63.3)
Serious adverse event	72 (43.1)	22 (26.5)	102 (49.5)	174 (46.6)
Serious adverse event related to study drug	36 (21.6)	12 (14.5)	44 (21.4)	80 (21.4)
Adverse event leading to	25 (15.0)	13 (15.7)	43 (20.9)	68 (18.2)

discontinuation of study drug				
Adverse event leading to dose interruption/reduction	111 (66.5)	33 (39.8)	124 (60.2)	235 (63.0)
Overall Number of Deaths	83 (49.7)	22 (26.5)[i)]	94 (45.6)	177 (47.5)
Death on Treatment[b]	15 (9.0)	2 (2.4)	26 (12.6)	41 (11.0)
Death During Follow-up[c]	68 (40.7)	20 (24.1)	68 (33.0)	136 (36.5)

Summary of Treatment-emergent Adverse Events (TEAEs)

Definition of TEAEs in the safety population:

- Study MCL-002: Any AE occurring or worsening on or after the first treatment of study drug and within 30 days after the last dose of study drug.
- Study MCL-001: Any AE occurring or worsening on or after the first dose of study drug and within 28 days after the last dose of study drug.
- Study NHL-003: Any AE occurring from the time of signature of informed consent through 30 days after the last dose of study drug.
- Study NHL-002: Any AE occurring on study or within 30 days after the last dose of study drug.

A tabular summary of study drug-related TEAEs, per investigator assessment, experienced by ≥ 2% of all subjects in any analysis group, by MedDRA SOC and Preferred Term (PT) is presented in Table 21.

Table 21. Treatment-related TEAEs Experienced by ≥ 2% in any Analysis Group, by SOC and PT

MedDRA System Organ Class / Preferred Term[a]	Analysis Group			
	MCL-002 Len (N = 167) n (%)	MCL-002 Control (N = 83) n (%)	MCL Subjects (MCL-001, NHL-003, NHL-002) (N = 206) n (%)	All MCL Len Subjects (MCL-002 Len, MCL-001, NHL-003, NHL-002) (N = 373) n (%)
Subjects With ≥ 1 TEAE Related To Study Drug	**140 (83.8)**	**50 (60.2)**	**182 (88.3)**	**322 (86.3)**
Blood and lymphatic system disorders	99 (59.3)	41 (49.4)	126 (61.2)	225 (60.3)
Neutropenia	75 (44.9)	27 (32.5)	97 (47.1)	172 (46.1)
Thrombocytopenia	51 (30.5)	27 (32.5)	72 (35.0)	123 (33.0)
Anaemia	30 (18.0)	14 (16.9)	40 (19.4)	70 (18.8)
Leukopenia	24 (14.4)	15 (18.1)	24 (11.7)	48 (12.9)
Febrile neutropenia	7 (4.2)	2 (2.4)	9 (4.4)	16 (4.3)
Lymphopenia	6 (3.6)	5 (6.0)	8 (3.9)	14 (3.8)
Gastrointestinal disorders	**45 (26.9)**	**15 (18.1)**	**86 (41.7)**	**131 (35.1)**
Diarrhoea	19 (11.4)	4 (4.8)	40 (19.4)	59 (15.8)
Constipation	14 (8.4)	2 (2.4)	28 (13.6)	42 (11.3)
Nausea	6 (3.6)	9 (10.8)	37 (18.0)	43 (11.5)
Abdominal pain	4 (2.4)	0 (0.0)	9 (4.4)	13 (3.5)
Dyspepsia	3 (1.8)	3 (3.6)	1 (0.5)	4 (1.1)
Stomatitis	2 (1.2)	3 (3.6)	1 (0.5)	3 (0.8)
Abdominal pain upper	1 (0.6)	3 (3.6)	1 (0.5)	2 (0.5)
Dry mouth	1 (0.6)	0 (0.0)	5 (2.4)	6 (1.6)
Vomiting	1 (0.6)	6 (7.2)	17 (8.3)	18 (4.8)
Skin and subcutaneous tissue disorders	**40 (24.0)**	**3 (3.6)**	**71 (34.5)**	**111 (29.8)**
Rash	13 (7.8)	2 (2.4)	39 (18.9)	52 (13.9)
Pruritus	10 (6.0)	1 (1.2)	20 (9.7)	30 (8.0)

MedDRA System Organ Class / Preferred Term[a]	Analysis Group			
	MCL-002 Len (N = 167) n (%)	MCL-002 Control (N = 83) n (%)	MCL Subjects (MCL-001, NHL-003, NHL-002) (N = 206) n (%)	All MCL Len Subjects (MCL-002 Len, MCL-001, NHL-003, NHL-002) (N = 373) n (%)
Dermatitis allergic	6 (3.6)	1 (1.2)	0 (0.0)	6 (1.6)
Rash generalised	6 (3.6)	0 (0.0)	1 (0.5)	7 (1.9)
Dry skin	3 (1.8)	0 (0.0)	6 (2.9)	9 (2.4)
General disorders and administration site conditions	**38 (22.8)**	**12 (14.5)**	**79 (38.3)**	**117 (31.4)**
Fatigue	20 (12.0)	4 (4.8)	52 (25.2)	72 (19.3)
Asthenia	12 (7.2)	4 (4.8)	9 (4.4)	21 (5.6)
Pyrexia	5 (3.0)	2 (2.4)	17 (8.3)	22 (5.9)
Oedema peripheral	4 (2.4)	0 (0.0)	14 (6.8)	18 (4.8)
Nervous system disorders	**24 (14.4)**	**2 (2.4)**	**37 (18.0)**	**61 (16.4)**
Lethargy	5 (3.0)	1 (1.2)	2 (1.0)	7 (1.9)
Peripheral sensory neuropathy	5 (3.0)	0 (0.0)	1 (0.5)	6 (1.6)
Paraesthesia	4 (2.4)	0 (0.0)	5 (2.4)	9 (2.4)
Neuropathy peripheral	2 (1.2)	1 (1.2)	8 (3.9)	10 (2.7)
Dysgeusia	1 (0.6)	1 (1.2)	7 (3.4)	8 (2.1)
Investigations	**20 (12.0)**	**8 (9.6)**	**35 (17.0)**	**55 (14.7)**
Alanine aminotransferase increased	6 (3.6)	3 (3.6)	4 (1.9)	10 (2.7)
Weight decreased	5 (3.0)	2 (2.4)	7 (3.4)	12 (3.2)
Aspartate aminotransferase increased	3 (1.8)	2 (2.4)	5 (2.4)	8 (2.1)
White blood cell count decreased	3 (1.8)	1 (1.2)	11 (5.3)	14 (3.8)
Blood creatinine increased	1 (0.6)	1 (1.2)	5 (2.4)	6 (1.6)
Infections and infestations	**19 (11.4)**	**10 (12.0)**	**43 (20.9)**	**62 (16.6)**
Upper respiratory tract infection	6 (3.6)	2 (2.4)	5 (2.4)	11 (2.9)
Pneumonia	4 (2.4)	2 (2.4)	9 (4.4)	13 (3.5)
Bronchitis	1 (0.6)	1 (1.2)	6 (2.9)	7 (1.9)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**18 (10.8)**	**0 (0.0)**	**17 (8.3)**	**35 (9.4)**
Tumour flare	16 (9.6)	0 (0.0)	14 (6.8)	30 (8.0)
Metabolism and nutrition disorders	**15 (9.0)**	**5 (6.0)**	**32 (15.5)**	**47 (12.6)**
Decreased appetite	6 (3.6)	3 (3.6)	16 (7.8)	22 (5.9)
Hypokalaemia	3 (1.8)	0 (0.0)	6 (2.9)	9 (2.4)
Respiratory, thoracic and mediastinal disorders	**15 (9.0)**	**2 (2.4)**	**35 (17.0)**	**50 (13.4)**
Pulmonary embolism	7 (4.2)	0 (0.0)	4 (1.9)	11 (2.9)
Cough	1 (0.6)	1 (1.2)	12 (5.8)	13 (3.5)
Dyspnoea	1 (0.6)	1 (1.2)	9 (4.4)	10 (2.7)
Dysphonia	0 (0.0)	0 (0.0)	5 (2.4)	5 (1.3)
Musculoskeletal and connective tissue disorders	**9 (5.4)**	**2 (2.4)**	**34 (16.5)**	**43 (11.5)**
Muscle spasms	4 (2.4)	0 (0.0)	12 (5.8)	16 (4.3)
Arthralgia	2 (1.2)	1 (1.2)	6 (2.9)	8 (2.1)
Myalgia	0 (0.0)	1 (1.2)	5 (2.4)	5 (1.3)
Vascular disorders	**9 (5.4)**	**1 (1.2)**	**18 (8.7)**	**27 (7.2)**
Deep vein thrombosis	3 (1.8)	0 (0.0)	6 (2.9)	9 (2.4)
Ear and labyrinth disorders	**5 (3.0)**	**0 (0.0)**	**2 (1.0)**	**7 (1.9)**
Vertigo	4 (2.4)	0 (0.0)	2 (1.0)	6 (1.6)

A tabular summary of Grade 3 and 4 TEAEs is presented for all analysis groups by MedDRA SOC and PT in Table 22.

Table 22. TEAEs of Grade 3 or 4 Experienced by ≥ 2% of Subjects in any Analysis Group by SOC and PT

MedDRA System Organ Class / Preferred Term[a]	Analysis Group			
	MCL-002 Len (N = 167) n (%)	MCL-002 Control (N = 83) n (%)	MCL Subjects (MCL-001, NHL-003, NHL-002) (N = 206) n (%)	All MCL Len Subjects (MCL-002 Len , MCL-001, NHL-003, NHL-002) (N = 373) n (%)
Subjects With ≥ 1 Grade 3 or 4 TEAE	**123 (73.7)**	**55 (66.3)**	**158 (76.7)**	**281 (75.3)**
Blood and lymphatic system disorders	**94 (56.3)**	**42(50.6)**	**119(57.8)**	**213 (57.1)**
Neutropenia	73 (43.7)	28 (33.7)	90 (43.7)	163 (43.7)
Thrombocytopenia	30 (18.0)	23 (27.7)	59 (28.6)	89 (23.9)
Anaemia	14 (8.4)	6 (7.2)	22 (10.7)	36 (9.7)
Febrile neutropenia	10 (6.0)	2 (2.4)	12 (5.8)	22 (5.9)
Lymphopenia	2 (1.2)	5 (6.0)	5 (2.4)	7 (1.9)
Infections and infestations	**27 (16.2)**	**7 (8.4)**	**40 (19.4)**	**67 (18.0)**
Pneumonia	6 (3.6)	2 (2.4)	8 (3.9)	14 (3.8)
Cellulitis	1 (0.6)	2 (2.4)	3 (1.5)	4 (1.1)
Respiratory, thoracic and mediastinal disorders	**16 (9.6)**	**3 (3.6)**	**28 (13.6)**	**44 (11.8)**
Pulmonary embolism	7 (4.2)	0 (0.0)	3 (1.5)	10 (2.7)
Dyspnoea	3 (1.8)	2 (2.4)	11 (5.3)	14 (3.8)
Pleural effusion	2 (1.2)	0 (0.0)	6 (2.9)	8 (2.1)
Gastrointestinal disorders	**14 (8.4)**	**3 (3.6)**	**25 (12.1)**	**39 (10.5)**
Diarrhoea	6 (3.6)	0 (0.0)	12 (5.8)	18 (4.8)
Abdominal pain	3 (1.8)	0 (0.0)	7 (3.4)	10 (2.7)
General disorders and administration site conditions	**14 (8.4)**	**1 (1.2)**	**30 (14.6)**	**44 (11.8)**
Pyrexia	4 (2.4)	1 (1.2)	3 (1.5)	7 (1.9)
Asthenia	2 (1.2)	0 (0.0)	7 (3.4)	9 (2.4)
Fatigue	2 (1.2)	0 (0.0)	16 (7.8)	18 (4.8)
Cardiac disorders	**11 (6.6)**	**2 (2.4)**	**7 (3.4)**	**18 (4.8)**
Atrial fibrillation	0 (0.0)	2 (2.4)	1 (0.5)	1 (0.3)
Metabolism and nutrition disorders	**10 (6.0)**	**2 (2.4)**	**14 (6.8)**	**24 (6.4)**
Dehydration	1 (0.6)	0 (0.0)	5 (2.4)	6 (1.6)
Investigations	**7 (4.2)**	**5 (6.0)**	**13 (6.3)**	**20 (5.4)**
Alanine aminotransferase increased	3 (1.8)	2 (2.4)	0 (0.0)	3 (0.8)
White blood cell count decreased	0 (0.0)	1 (1.2)	6 (2.9)	6 (1.6)
Vascular disorders	**7 (4.2)**	**2 (2.4)**	**13 (6.3)**	**20 (5.4)**
Hypertension	2 (1.2)	2 (2.4)	2 (1.0)	4 (1.1)
Deep vein thrombosis	1 (0.6)	0 (0.0)	6 (2.9)	7 (1.9)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**6 (3.6)**	**5 (6.0)**	**12 (5.8)**	**18 (4.8)**
Squamous cell carcinoma of skin	1 (0.6)	0 (0.0)	7 (3.4)	8 (2.1)
Mantle cell lymphoma	0 (0.0)	4 (4.8)	1 (0.5)	1 (0.3)
Musculoskeletal and connective tissue disorders	**5 (3.0)**	**0 (0.0)**	**12 (5.8)**	**17 (4.6)**
Immune system disorders	**1 (0.6)**	**2 (2.4)**	**0 (0.0)**	**1 (0.3)**

Adverse reactions

Table 23. ADRs reported in clinical trials in patients with mantle cell lymphoma treated with lenalidomide

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3–4 ADRs/Frequency
Infections and Infestations	Very Common Bacterial, viral and fungal infections (including opportunistic infections), Nasopharyngitis, Pneumonia Common Sinusitis	Common Bacterial, viral and fungal infections (including opportunistic infections)[◇], Pneumonia[◇]
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Common Tumour flare reaction	Common Tumour flare reaction, Squamous skin cancer[◇], Basal cell Carcinoma[◇]
Blood and Lymphatic System Disorders	Very Common Thrombocytopenia^, Neutropenia^, Leucopenias, Anaemia Common Febrile neutropenia	Very Common Thrombocytopenia, Neutropenia[◇], Anaemia[◇] Common Febrile neutropenia[◇], Leucopenias[◇]
Metabolism and Nutrition Disorders	Very Common Decreased appetite, Weight decreased, Hypokalaemia Common Dehydratation,	Common Dehydration[◇], Hyponatraemia, Hypocalcaemia
Psychiatric Disorders	Common Insomnia	
Nervous System Disorders	Common Dysgeuesia, Headache, neuropathy peripheral	Common Peripheral sensory neuropathy, Lethargy
Ear and Labyrinth Disorders	Common Vertigo	
Cardiac Disorders		Common Acute myocardial infarction (including acute)[◇], Cardiac failure
Vascular Disorders	Common Hypotension	Common Deep vein thrombosis[◇], pulmonary embolism[◇], Hypotension[◇]
Respiratory, Thoracic and Mediastinal Disorders	Very Common Dyspnoea	Common Dyspnoeia[◇]
Gastrointestinal Disorders	Very Common Diarrhoea, Nausea[◇], Vomiting[◇], Constipation Common Abdominal pain	Common Diarrhoea[◇], Abdominal pain[◇], Constipation
Skin and Subcutaneous Tissue Disorders	Very Common Rashes (including dermatitis allergic), Pruritus Common Night sweats, Dry skin	Common Rashes
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms, Back pain– Common Arthralgia, Pain in extremity, Muscular weakness	Common Back pain, Muscular weakness[◇], Arthralgia, Pain in extremity
Renal and Urinary Disorders		Common Renal failure[◇]
General Disorders and Administration Site Conditions	Very Common Fatigue, Asthenia, Peripheral oedema, Influenza like illness syndrome (including pyrexia, cough) Common Chills	Common Pyrexia[◇], Asthenia[◇], Fatigue

◊Adverse events reported as serious in mantle cell lymphoma clinical trials

Adverse Events of special interest

AEs of special interest include infections, cardiac events (cardiac arrhythmias, cardiac failure and ischemic heart disease), venous thromboembolism, arterial thromboembolism, tumour flare reaction, second primary malignancies, tumour lysis syndrome, thrombocytopenia, bleeding and peripheral neuropathy.

Infections

In MCL 002, infections were reported in 53.9% of patients in the Len arm thereof about 16% grade 3 or higher. Lower respiratory tract infections including pneumonia was the most commonly reported. Two (1.2%) patients in the Len arm had Grade 5 TEAEs of infections. One patients died due to neutropenic sepsis. The second patient (who was confirmed after study start to have CLL/SLL, not MCL) had Grade 5 AEs of septic shock and multiorgan failure, which were not considered related to study drug; the primary cause of death was listed as toxicity/multiorgan failure due to R-HAD chemotherapy that had been started as new anti-lymphoma therapy after lenalidomide treatment was discontinued.

Cardiac events

In MCL 002, cardiac arrhythmias were reported in 9.6% of patients in the Len arm and 4.8% of patients in the Control arm. Grade 3 to 5 AEs of cardiac arrhythmias were reported in 4.2% of patients in the Len arm and 2.4% of patients in the Control arm, with Grade 5 TEAEs being reported in 3 patients in the Len arm. Three (1.8%) patients in the Len arm had Grade 5 TEAEs of cardiac arrhythmias; no patients in the Control arm had Grade 5 cardiac arrhythmia events. Two patients had Grade 5 TEAEs of cardiac arrest; cause of death was specified as “other cause” (cardiac arrest and suspected cardiac arrest). None of these Grade 5 AEs was suspected by the investigator to be related to study drug. No patients in the Control arm had Grade 5 cardiac arrhythmia events. The only TEAE that led to treatment discontinuation was atrial fibrillation in 1 patient (1.2%) in the Control arm compared to no patients in the Len arm. Treatment-emergent AEs of cardiac arrhythmias led to dose interruption or reduction in 4 patients (2.4%) in the Len arm and in 1 patient (1.2%) in the Control arm.

In MCL 002, cardiac failure was reported in 5.4% of patients in the Len arm and in 2.4% of patients in the Control arm. The frequencies of Grade 3 to 5 cardiac failure events were similar between the Len arm (3.0%) and the Control arm (2.4%), with Grade 5 TEAEs reported in 1 patient in the Len arm and 2 patients in the Control arm. One (0.6%) patient in the Len arm and 2 (2.4%) patients in the Control arm had Grade 5 cardiac failure events. None of these Grade 5 AEs was suspected by the investigator to be related to study drug.None of the selected TEAEs in the selected AE category of cardiac failure led to treatment discontinuation in either treatment arm, and the only TEAE leading to dose interruption or dose reduction was cardiac failure, in 1 (0.6%) patient in the Len arm. In supportive studies, the frequencies of TEAEs, Grade 3 to 5 TEAEs, and SAEs of cardiac failure were 2.4%, 0.5%, and 0.5%, respectively.

In MCL 002, ischemic heart disease was reported in 4.2% of patients in the Len arm and 0.0% of patients in the Control arm. Grade 3 to 5 ischemic heart disease events were reported in 4 (2.4%) patients in the Len arm, with a Grade 5 TEAE reported in 1 patient. With the exception of the PT of blood creatine phosphokinase increased, all of the Grade 3 to 5 ischemic heart disease events in the Len arm was also SAEs. One (0.6%) patient in the Len arm had a Grade 5 TEAE of acute coronary syndrome. This patient’s death was attributed to “other cause” and theTEAE of acute coronary syndrome was not suspected by the investigator to be related to study drug. None of the TEAEs in the selected AE category of ischemic heart disease led to treatment discontinuation and the only PT leading to dose reduction or interruption was myocardial

infarction, in 1 (0.6%) patient in the Len arm. In supportive studies, the frequencies of TEAEs and Grade 3 to 5 TEAEs, of ischemic heart disease were 2.4% and 1.5% respectively.

Venous Thromboembolism

In MCL 002, venous thrombo-embolic events (VTE) were reported in 7.2% of patients in the Len arm and 1.2% of patients in the Control arm. All events were considered Grade 3 to 4, no Grade 5 was reported. In the Lenalidomide Arm, pulmonary embolism was the most frequently reported VTE (7 subjects, 4.2%), followed by deep vein thrombosis (3 subjects, 1.8%), with none of the events being Grade 5 in severity. Most of these subjects had no prior thromboembolic events or risk factors, and 4 of the 9 subjects with pulmonary embolism or deep vein thrombosis were not receiving thromboembolic prophylaxis prior to the event.

Arterial Thromboembolism

ATEs were reported in 2.4% of patients in the Len arm and 0.0% of patients in the Control arm. All events were considered Grade 3 to 4 AEs (no Grade 5 AEs reported) and SAEs. None of the ATE events except the ischemic stroke was considered related to study drug and did not lead to study drug discontinuation.

Tumour flare reaction (TFR)

In MCL 002, TFR was reported in 9.6% of patients in the Len arm and in 0.0% of patients in the Control arm. Of these TFR events in the Len arm, those in 3 (1.8%) patients were classified as Grade 3 to 4 events (no Grade 5 AEs reported) , 1 event was an SAE (0.6%), 1 event resulted in treatment discontinuation, and events in 2 patients (1.2%) led to dose interruption or reduction. All TFR events were considered related to study drug. Of the 16 patients in the Len arm with a TFR event, 11 patients received various therapies during the TFR episode (most frequently corticosteroids, analgesics, and antibacterials) and 13 patients did not have any change to study drug. In the supportive study MCL-001, approximately 10% of subjects experienced TFR; all reports were Grade 1 or 2 in severity and all were assessed as treatment-related. The majority of the events occurred in cycle 1 (SmPC section 4.8).

Tumour lysis syndrome (TLS)

In MCL 002, TLS was reported for one patient in each of the two treatment arms. There were no reports of TLS in study MCL-001 (SmPC section 4.8).

Second primary malignancies (SPM)

The incidence rates of second primary malignancies in Study MCL-002 are presented in Table 24.

Table 24. Incidence Rates of Second Primary Malignancies in Study MCL-002 as of the Data Cut-off Date of 7 March 2014 (Safety Population)

SPM Category	Lenalidomide (N = 167)		Control[a] (N = 83)	
	IR/ 100 PY[b]	95% CI	IR/ 100 PY[b]	95% CI
Hematologic malignancies	0.73	(0.12 – 2.40)	0.77	(0.04 – 3.80)
Solid tumors	1.47	(0.47 – 3.54)	2.36	(0.06 – 6.41)
Invasive SPMs	**2.20**	**(0.89 – 4.58)**	**3.17**	**(1.01 – 7.64)**
Non-invasive SPMs (Non-melanoma skin cancer)	1.88	(0.69 – 4.16)	0.77	(0.04 - 3.78)
Total SPMs	**3.78**	**(1.92 – 6.74)**	**3.98**	**(1.46 – 8.81)**

CI = confidence interval; IR = incidence rate; PY = person-year; SPM = second primary malignancy.
[a] The investigator's choice (control arm) was monotherapy with one of the following: chlorambucil, cytarabine, rituximab, fludarabine, or gemcitabine.
[b] Person-year is defined as the time from the date of the first dose of study drug to the onset date of the first SPM for subjects with SPMs and to the date of last follow-up for subjects without SPMs.

A summary of frequency and incidence rates of second primary malignancies in study MCL-001 is presented in Table 25.

Table 25. Summary of Frequency and Incidence Rates of Second Primary Malignancies in Study MCL-001 as of the Data Cutoff Date of 21 Mar 2014 (Safety Population)

SPM Category	Lenalidomide (N = 134)		
	n (%)	Incidence Rate (per 100 PY)[a]	95% CI
Hematologic malignancies	2 (1.5)	0.96	(0.24 – 3.85)
AML	0 (0.0)	--	--
Myeloproliferative disorder to AML	1 (0.7)	--	--
MDS	1 (0.7)	0.57	(0.08 – 4.07)
Hodgkin's/B-ALL/other B-cell	0 (0.0)	--	--
Solid tumors	5 (3.7)	2.46	(1.02 – 5.91)
Invasive SPMs	**7 (5.2)**	**3.47**	**(1.65 – 7.28)**
Non-invasive SPMs (Non-melanoma skin cancers)	7 (5.2)[b]	3.54	(1.69 – 7.42)
TOTAL SPMs	**12 (9.0)[c,d]**	**6.23**	**(3.54 – 10.97)**

AML = acute myeloid leukemia; B-ALL = B-cell acute lymphocytic leukemia; CI = confidence interval; MDS = myelodysplastic syndrome; PY = person-years; SPM = second primary malignancy.
a Person-years are defined as the time from the date of first dose of study drug to the onset date of the first SPM for subjects with an SPM and to the date of last follow-up for subjects without an SPM.
b Subject was diagnosed with squamous cell carcinoma of the skin on his left forehead prior to the first dose of lenalidomide. He had a relapse of this non-melanoma skin cancer in the same location after receiving lenalidomide. Thus, the squamous cell carcinoma of the skin is not considered to be an SPM and is excluded from all analyses of SPMs.
c Subject had a non-melanoma skin cancer (squamous cell carcinoma of skin) that became an invasive solid tumor because it metastasized to the cervical lymph nodes. In addition to this invasive solid tumor (metastatic squamous cell carcinoma), this subject had non-melanoma skin cancers (squamous cell carcinoma of skin). This subject is counted only once in the total SPM row.
d Subjectwas diagnosed with a solid tumor SPM (meningioma) and non-melanoma skin cancers (basal cell carcinoma and squamous cell carcinoma of skin). This subject is counted only once in the total SPM row.

Thrombocytopenia

In MCL-002 study thrombocytopenia was reported in 36.5% of subjects in the Lenalidomide Arm and 39.8% of subject in the Control Arm. Grade 3 to 5 TEAEs of thrombocytopenia were reported in 27.7% of subjects in the Control Arm and in 18.0% of subjects in the Lenalidomide Arm. There were no Grade 5 TEAEs of thrombocytopenia. The frequencies of SAEs of thrombocytopenia were 1.8% in the Lenalidomide Arm and 2.4% in the Control Arm.

The frequency of TEAEs of thrombocytopenia was similar between MCL subjects from the supportive studies (40.8%) and those in the Lenalidomide Arm of the main study (36.5%), with a higher frequency of Grade 3 to 5 AEs reported in the supportive studies (28.6%) than in the main study (18.0%).

Neutropenia

In MCL patients, lenalidomide is associated with a higher incidence of grade 3 or 4 neutropenia (43.7% in lenalidomide-treated patients compared with 33.7% in patients in the control arm in the Phase II study). Grade 3 or 4 febrile neutropenia episodes were observed in 6.0% of lenalidomide-treated patients compared with 2.4% in patients on control arm (see section 4.8 of the SmPC).

Bleeding

In MCL-002 study bleeding was reported in 11.4% of subjects in the Lenalidomide Arm and 10.8% of subjects in the Control Arm. The most common bleeding event in both treatment arms was epistaxis (3.6% in the Lenalidomide Arm, 2.4% in the Control Arm). Grade 3 to 5 bleeding events were reported at the same frequency in both treatment arms (3.6% each arm), with 1 Grade 5 TEAE being reported in the Lenalidomide Arm only. Most Grade 3 to 5 bleeding events occurred in the SOC of gastrointestinal disorders for both treatment arms. One (0.6%) subject in the Lenalidomide Arm had a Grade 5 bleeding event (cerebral haemorrhage) which was not considered related to study drug. No subjects in the Control Arm had Grade 5 bleeding events. All of the Grade 3 to 5 bleeding events reported in the Lenalidomide Arm was SAEs, whereas in the Control Arm the only Grade 3 to 5 bleeding event that was an SAE was abdominal wall hematoma.

The frequency of TEAEs of bleeding was similar among MCL subjects from the supportive studies (14.6%) and those in the Lenalidomide Arm of the main study (11.4%), with similar frequencies of Grade 3 to 5 AEs and SAEs reported in the supportive studies (3.9% and 3.4%, respectively) and in the main study (3.6% and 3.6%, respectively).

Peripheral Neuropathy

In MCL 002, peripheral neuropathy was reported in 7.8% of patients in the Len arm and 1.2% of patients in the Control arm. Grade 3 to 4 peripheral neuropathy (no Grade 5 AEs reported) was reported in 3 (1.8%) patients in the Len arm and in no patients in the Control arm. These events were not SAEs and did not result in study drug discontinuation.

In supportive studies, the frequency of TEAEs of peripheral neuropathy was higher among MCL patients from the supportive studies (11.2%) than in the Len arm of the main study (7.8%), with a similar frequency of Grade 3 to 5 AEs reported in the supportive studies (1.9%) and the main study (1.8%), while no SAEs of peripheral neuropathy were reported in patients in the supportive studies.

Serious adverse event / deaths / other significant events

Serious Adverse Events (SAEs)

Table 26. Grade 5 TEAEs, by Analysis Group and SOC and PT

MedDRA System Organ Class / Preferred Term[a]	Analysis Group			
	MCL-002 Len (N = 167) n (%)	MCL-002 Control (N = 83) n (%)	MCL Subjects (MCL-001, NHL-003, NHL-002) (N = 206) n (%)	All MCL Len Subjects (MCL-002 Len, MCL-001, NHL-003, NHL-002) (N = 373) n (%)
Subjects with ≥ 1 Grade 5 TEAE	**15 (9.0)**	**2 (2.4)**	**26 (12.6)**	**41 (11.0)**
General disorders and administration site conditions	**6 (3.6)**	**0 (0.0)**	**8 (3.9)**	**14 (3.8)**
General physical health deterioration	2 (1.2)	0 (0.0)	2 (1.0)	4 (1.1)
Multi-organ failure	2 (1.2)	0 (0.0)	2 (1.0)	4 (1.1)
Death	1 (0.6)	0 (0.0)	1 (0.5)	2 (0.5)
Sudden death	1 (0.6)	0 (0.0)	1 (0.5)	2 (0.5)
Asthenia	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Disease progression	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Mucosal inflammation	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Pyrexia	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Cardiac disorders	**4 (2.4)**	**2 (2.4)**	**1 (0.5)**	**5 (1.3)**
Cardiac arrest	2 (1.2)	0 (0.0)	0 (0.0)	2 (0.5)
Acute coronary syndrome	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.3)
Cardiac failure congestive	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.3)
Cardiac failure	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
Cardiac failure acute	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
Cardio-respiratory arrest	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Infections and infestations	**2 (1.2)**	**0 (0.0)**	**6 (2.9)**	**8 (2.1)**
Neutropenic sepsis	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.3)
Septic shock	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.3)
Enterococcal sepsis	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Pneumonia	0 (0.0)	0 (0.0)	3 (1.5)	3 (0.8)
Pseudomonal sepsis	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Sepsis	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Metabolism and nutrition disorders	**1 (0.6)**	**0 (0.0)**	**0 (0.0)**	**1 (0.3)**
Cachexia	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.3)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**1 (0.6)**	**0 (0.0)**	**5 (2.4)**	**6 (1.6)**
Mantle cell lymphoma	1 (0.6)	0 (0.0)	5 (2.4)	6 (1.6)
Nervous system disorders	**1 (0.6)**	**0 (0.0)**	**0 (0.0)**	**1 (0.3)**
Cerebral haemorrhage	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	**1 (0.6)**	**0 (0.0)**	**5 (2.4)**	**6 (1.6)**
Respiratory distress	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.3)
Dyspnoea	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Pleural effusion	0 (0.0)	0 (0.0)	2 (1.0)	2 (0.5)
Respiratory failure	0 (0.0)	0 (0.0)	2 (1.0)	2 (0.5)
Blood and lymphatic system disorders	**0 (0.0)**	**0 (0.0)**	**2 (1.0)**	**2 (0.5)**
Leukocytosis	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Lymphocytosis	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Gastrointestinal disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.5)**	**1 (0.3)**
Intestinal ischaemia	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Vascular disorders	**0 (0.0)**	**0 (0.0)**	**2 (1.0)**	**2 (0.5)**
Hypotension	0 (0.0)	0 (0.0)	2 (1.0)	2 (0.5)

Table 27. Treatment-emergent Serious Adverse Events Occurring in ≥ 2% of Subjects in any Analysis Group by SOC and PT

MedDRA System Organ Class / Preferred Term[a]	Analysis Group			
	MCL-002 Len (N = 167) n (%)	MCL-002 Control (N = 83) n (%)	MCL Subjects (MCL-001, NHL-003, NHL-002) (N = 206) n (%)	All MCL Len Subjects (MCL-002 Len, MCL-001, NHL-003, NHL-002) (N = 373) n (%)
Subjects with ≥ 1 SAE	**72 (43.1)**	**22 (26.5)**	**102 (49.5)**	**174 (46.6)**
Infections and infestations	**22 (13.2)**	**7 (8.4)**	**41 (19.9)**	**63 (16.9)**
Pneumonia	6 (3.6)	2 (2.4)	9 (4.4)	15 (4.0)
Blood and lymphatic system disorders	**17 (10.2)**	**5 (6.0)**	**20 (9.7)**	**37 (9.9)**
Anaemia	6 (3.6)	2 (2.4)	4 (1.9)	10 (2.7)
Febrile neutropenia	6 (3.6)	2 (2.4)	11 (5.3)	17 (4.6)
Neutropenia	6 (3.6)	0 (0.0)	5 (2.4)	11 (2.9)
Thrombocytopenia	3 (1.8)	2 (2.4)	4 (1.9)	7 (1.9)
Respiratory, thoracic and mediastinal disorders	**16 (9.6)**	**2 (2.4)**	**21 (10.2)**	**37 (9.9)**
Pulmonary embolism	6 (3.6)	0 (0.0)	2 (1.0)	8 (2.1)
Dyspnoea	3 (1.8)	1 (1.2)	6 (2.9)	9 (2.4)
Pleural effusion	2 (1.2)	0 (0.0)	6 (2.9)	8 (2.1)
Gastrointestinal disorders	**11 (6.6)**	**3 (3.6)**	**22 (10.7)**	**33 (8.8)**
Diarrhoea	6 (3.6)	0 (0.0)	5 (2.4)	11 (2.9)
Abdominal pain	1 (0.6)	0 (0.0)	5 (2.4)	6 (1.6)
General disorders and administration site conditions	**11 (6.6)**	**3 (3.6)**	**26 (12.6)**	**37 (9.9)**
Pyrexia	5 (3.0)	2 (2.4)	9 (4.4)	14 (3.8)
General physical health deterioration	3 (1.8)	1 (1.2)	5 (2.4)	8 (2.1)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**7 (4.2)**	**5 (6.0)**	**15 (7.3)**	**22 (5.9)**
Squamous cell carcinoma of skin	2 (1.2)	0 (0.0)	6 (2.9)	8 (2.1)
Mantle cell lymphoma	1 (0.6)	3 (3.6)	6 (2.9)	7 (1.9)
Vascular disorders	**5 (3.0)**	**0 (0.0)**	**10 (4.9)**	**15 (4.0)**
Hypotension	2 (1.2)	0 (0.0)	7 (3.4)	9 (2.4)
Metabolism and nutrition disorders	**4 (2.4)**	**1 (1.2)**	**7 (3.4)**	**11 (2.9)**
Dehydration	1 (0.6)	0 (0.0)	5 (2.4)	6 (1.6)

Deaths

A summary of deaths is presented in Table 28.

Table 28. All Deaths (Including Crossover) – Safety Population (Study MCL-002)

Deaths Primary Cause[a]	Data Cutoff 07 Mar 2015 Lenalidomide N = 167 n (%)	 Control N = 83 n (%)	 Overall N = 250 n (%)
Deaths reported[b]	**100 (59.9)**	**53 (63.9)**	**153 (61.2)**
Death during treatment[c] with lenalidomide or investigator's choice	**15 (9.0)**	**2 (2.4)**	**17 (6.8)**
Death from malignant disease	8 (4.8)	2 (2.4)	10 (4.0)
Death from other cause	4 (2.4)	0 (0.0)	4 (1.6)
Cause of death unknown	2 (1.2)	0 (0.0)	2 (0.8)
Early death from toxicity	1 (0.6)[d]	0 (0.0)	1 (0.4)[d]
Death post treatment[e] with lenalidomide or investigator's choice	**85 (50.9)**	**51 (61.4)**	**136 (54.4)**
Death from malignant disease	64 (38.3)	12 (14.5)	76 (30.4)
Death from other cause	10 (6.0)	5 (6.0)	15 (6.0)
Early death from toxicity	0 (0.0)	1 (1.2)	1 (0.4)
Cause of death unknown	10 (6.0)	4 (4.8)	14 (5.6)
Missing	1 (0.6)	0 (0.0)	1 (0.4)
Death during crossover treatment[f]	NA	2 (2.4)	2 (0.8)
Death post crossover treatment[g]	NA	27 (32.5)	27 (10.8)

eCRF = electronic case report form; MCL = mantel cell lymphoma; NA = not applicable.
a Each death broadly categorized into progression of MCL as the underlying disease, treatment toxicity, other causes (not related to malignant disease or toxicity), and unknown (not assessable or insufficient data), as selected by the investigator on the eCRF page DEATH.
b One death occurred prior to randomization and is not included in this table .
c Any death occurring on treatment and within 30 days after the last dose of initial treatment in the Lenalidomide or the Control Arm.
d Subject died due to toxicity from subsequent treatment [data cutoff date 07 Mar 2015].
e Death occurred after the last treatment dosing date plus 30 days for subjects treated with lenalidomide in the Lenalidomide Arm or with the investigator's choice in the Control Arm (including subjects who later crossed over to lenalidomide).
f Death occurred after the first crossover treatment dosing date and before the last crossover treatment dosing date plus 30 days.
g Death occurred after the last crossover treatment dosing date plus 30 days.

The rate of PD-related deaths within 64 weeks (when half of off-treatment death had occurred), was 75.6% (31/41) in the Lenalidomide Arm and 70.3% (19/27) in the Control Arm.

Table 29: Death on Treatment Versus Off Treatment by Treatment Arm and Malignant Disease as Cause of Death – Safety Population (Study MCL-002)

Death Primary Cause[a]	Data Cutoff 07 Mar 2015							
	On Treatment[b]				Off Treatment[c]			
	PD related		Not related to PD		PD related		Not related to PD	
Time Period[d] (weeks)	Len n (%)	Control n (%)	Len n (%)	Control n (%)	Len n (%)	Control n (%)	Len n (%)	Control n (%)
0 to < 4	1 (0.6)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4 to < 8	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
8 to < 12	3 (1.8)	1 (1.2)	3 (1.8)	0 (0.0)	1 (0.6)	1 (1.2)	1 (0.6)	0 (0.0)
12 to <16	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	6 (3.6)	1 (1.2)	0 (0.0)	0 (0.0)
16 to < 20	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	2 (2.4)	0 (0.0)	0 (0.0)
20 to < 24	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.4)	0 (0.0)	1 (0.6)	1 (1.2)
24 to < 28	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (1.2)	0 (0.0)	1 (1.2)
28 to < 32	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.8)	1 (1.2)	1 (0.6)	0 (0.0)
32 to < 36	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.8)	1 (1.2)	0 (0.0)	1 (1.2)
36 to < 40	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	3 (3.6)	1 (0.6)	0 (0.0)
40 to < 44	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.8)	1 (1.2)	0 (0.0)	1 (1.2)
44 to < 48	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	1 (1.2)
48 to < 52	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.4)	2 (2.4)	1 (0.6)	1 (1.2)
52 to < 56	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
56 to < 60	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	1 (1.2)	1 (0.6)	1 (1.2)
60 to < 64	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	3 (3.6)	3 (1.8)	1 (1.2)
64 to < 68	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
68 to < 72	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)	1 (1.2)
72 to < 76	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (1.2)
76 to < 80	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
80 to < 84	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
84 to < 88	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.4)	1 (1.2)	0 (0.0)	0 (0.0)
88 to < 92	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (4.8)	0 (0.0)	1 (1.2)
92 to < 96	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
96 to < 100	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	2 (1.2)	2 (2.4)
100 to < 104	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	1 (0.6)	0 (0.0)
104 to < 108	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
108 to < 112	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
112 to < 116	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	2 (2.4)	1 (0.6)	0 (0.0)
116 to < 120	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
120 to < 124	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
124 to < 128	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (1.2)
128 to < 132	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
132 to < 136	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
136 to < 140	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
140 to < 144	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
144 to < 148	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (1.2)	1 (0.6)	0 (0.0)
148 to < 152	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)
152 to < 156	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
156 to < 160	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
160 to < 164	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	1 (1.2)	0 (0.0)	0 (0.0)
164 to < 168	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
168 to < 172	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
172 to < 176	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (1.2)	0 (0.0)	0 (0.0)
176 to < 180	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
180 to < 184	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
184 to < 188	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
188 to < 192	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
192 to < 196	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
196 to < 200	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Death Primary Cause[a]	Data Cutoff 07 Mar 2015							
	On Treatment[a]				Off Treatment[b]			
	PD related		Not related to PD		PD related		Not related to PD	
Time Period[d] (weeks)	Len n (%)	Control n (%)	Len n (%)	Control n (%)	Len n (%)	Control n (%)	Len n (%)	Control n (%)
200 to < 204	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.6)**	0 (0.0)
204 to < 208	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
208 to < 212	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
212 to < 216	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.6)**	0 (0.0)	0 (0.0)	0 (0.0)
216 to < 220	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
220 to < 224	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (1.2)**	0 (0.0)	0 (0.0)
224 to < 228	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (1.2)**	0 (0.0)	0 (0.0)
228 to < 232	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
232 to < 236	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
236 to < 240	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
240 to < 244	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
244 to < 248	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
248 to < 252	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.6)**	0 (0.0)	0 (0.0)	0 (0.0)
Total (N = 153)	**8 (5.2)**	**2 (1.3)**	**7 (4.6)**	**0 (0.0)**	**64 (41.8)**	**34 (22.2)**	**21 (13.7)**	**17 (11.1)**

eCRF = electronic case report form; Len = lenalidomide; MCL = mantel cell lymphoma; PD = progressive disease.

[a] Each death broadly categorized into progression of MCL as the underlying disease, treatment toxicity, other causes (not related to malignant disease or toxicity), and unknown (not assessable or insufficient data), as selected by the investigator on the eCRF page DEATH. Not PD related comprises toxicity, other, and unknown.

[b] Any death occurring on treatment and within 30 days after the last dose in the Lenalidomide or the Control Arm (including crossover).

[c] Death occurred after the last treatment dosing date plus 30 days for subjects in the Lenalidomide or Control Arm (including crossover).

[d] Four-week periods do not strictly correspond to actual cycle length, as delaying the start of next cycle due to dose interruption was allowed per protocol.

Table 30. Key baseline characteristics of subjects with early death and the complementary group – ITT Population (Study MCL-002)

Data Cutoff Date 07 Mar 2014	**Early Death** (Within 20 Weeks From Randomization)				**Complementary Group**			
	Lenalidomide		**Control**		**Lenalidomide**		**Control**	
Key Baseline Characteristics	**D**	**n (%)**	**D**	**n (%)**	**D**	**n (%)**	**D**	**n (%)**
MCL stage at diagnosis								
I	3	0 (0.0)	2	0 (0.0)	3	3 (100.0)	2	2 (100.0)
II	10	4 (40.0)	1	0 (0.0)	10	6 (60.0)	1	1 (100.0)
III	30	3 (10.0)	20	0 (0.0)	30	27 (90.0)	20	20 (100.0)
IV	123	15 (12.2)	59	5 (8.5)	123	108 (87.8)	59	54 (91.5)
Missing	4	0 (0.0)	2	1 (50.0)	4	4 (100.0)	2	1 (50.0)
MIPI score at diagnosis								
Low Risk	61	9 (14.8)	35	0 (0.0)	61	52 (85.2)	35	35 (100)
Intermediate Risk	51	5 (9.8)	22	0 (0.0)	51	46 (90.2)	22	22 (100)
High Risk	40	5 (12.5)	14	5 (35.7)	40	35 (87.5)	14	9 (64.3)
Missing	18	3 (16.7)	13	1 (7.7)	18	15 (83.3)	13	12 (92.3)
WBC count at baseline (x								
< 6.7	79	7 (8.9)	46	3 (6.5)	79	72 (91.1)	46	43 (93.5)
6.7 to < 10	56	6 (10.7)	27	3 (11.1)	56	50 (89.3)	27	24 (88.9)
10 to < 15	19	4 (21.1)	7	0 (0.0)	19	15 (78.9)	7	7 (100.0)
≥ 15	15	5 (33.3)	4	0 (0.0)	15	10 (66.7)	4	4 (100.0)
Missing	1	0 (0.0)	0	0 (0.0)	1	1 (100.0)	0	0 (0.0)
Tumor burde..[a] at baseline								
High	81	16 (19.8)	28	2 (7.1)	81	65 (80.2)	28	26 (92.9)

Data Cutoff Date 07 Mar 2014	**Early Death** (Within 20 Weeks From Randomization)				**Complementary Group**			
	Lenalidomide		**Control**		**Lenalidomide**		**Control**	
Key Baseline Characteristics	**D**	**n (%)**	**D**	**n (%)**	**D**	**n (%)**	**D**	**n (%)**
Low	78	5 (6.4)	50	4 (8.0)	78	73 (93.6)	50	46 (92.0)
Missing	11	1 (9.1)	6	0 (0.0)	11	10 (90.9)	6	6 (100.0)
Bulky disease[b] at baseline								
Yes	37	7 (18.9)	13	2 (15.4)	37	30 (81.1)	13	11 (84.6)
No	122	14 (11.5)	65	4 (6.2)	122	108 (88.5)	65	61 (93.8)
Missing	11	1 (9.1)	6	0 (0.0)	11	10 (90.9)	6	6 (100.0)
Extranodal involvement[c] at enrollment								
Yes	45	9 (20.0)	25	1 (4.0)	45	36 (80.0)	25	24 (96.0)
No	125	13 (10.4)	59	5 (8.5)	125	112 (89.6)	59	54 (91.5)
CIRS-G score[d] at baseline								
Low comorbidity	115	17 (14.8)	52	4 (7.7)	115	98 (85.2)	52	48 (92.3)
High comorbidity	55	5 (9.1)	32	2 (6.3)	55	50 (90.9)	32	30 (93.8)
History of TE[e]	40	7 (17.5)	18	2 (11.1)	40	33 (82.5)	18	16 (88.9)
History of infections[f]	41	4 (9.8)	20	2 (10.0)	41	37 (90.2)	20	18 (90.0)
History of cardiac event	46	5 (10.9)	21	2 (9.5)	46	41 (89.1)	21	19 (90.5)

[a] High tumor burden: ≥ 1 lesion that was ≥ 5 cm in diameter or 3 lesions each ≥ 3 cm in diameter by central radiology review.

[b] Bulky disease: ≥ 1 lesion that is ≥ 7 cm in the longest diameter by central radiology review.

[c] Extranodal disease of liver, spleen, bone marrow, or other.

[d] Comorbidity burden category: Low, CIRS-G score 0 to 6; High, CIRS-G score ≥ 7.

[e] History of arteriovenous thromboembolic events (based on SMQ "embolic and thrombotic event").

[f] History of infections (based on SMQ "infection").

D: Denominator, number of subjects used to calculate the percentage

Laboratory findings

Haematology

In MCL 002, the majority of the patients with baseline and post-baseline data had normal, Grade 1 or Grade 2 haematology values at baseline.

More patients in the Control arm exhibited shifts in ALC to a worst post-baseline Grade 3 or 4 than in the Len arm(shifts to Grade 3: 28.0% versus 14.0%; shifts to a worst post-baseline Grade 4 value: 17.1% versus 5.5%). More patients in the Len arm exhibited shifts in ANC to a worst post-baseline Grade 3 value than in the Control arm (24.8% versus 15.7%), shifts to a worst post-baseline Grade 4 value being comparable (21.8% and 20.5%, respectively). There were no notable differences in the pattern of shifts in haemoglobin, platelets, or WBC between the 2 treatment arms.

In supportive trials, the majority of the patients with baseline and post-baseline data had normal, Grade 1 or Grade 2 haematology values at baseline. More patients in the Len arm from the main study exhibited shifts in ANC to a worst post-baseline Grade 4 value compared with the MCL patients from the supportive studies (21.8% versus 12.9%).

Serum Chemistry

In MCL 002, few patients exhibited shifts in chemistry parameters to a worst post baseline Grade 3 value in either treatment arm. The most common of these shifts pertained to uric acid (14.3% of the patients in the Len arm and 18.5% in the Control arm). Shifts to a worst post baseline Grade 4 value were relatively rare, and included uric acid (8.1% of patients in the Lenalidomide Arm and 9.9% of patients in the Control arm), calcium (3.7% and 2.4%, respectively), glucose (1.3% and 1.2%, respectively), potassium (1.2% in each

arm), and sodium (1.2% and 0.0%, respectively). Shifts in chemistry parameters to a worst post baseline value were essentially comparable between the 2 treatment arms.

In supportive trials, except for uric acid, the shifts in chemistry parameters observed in MCL patients from the supportive studies were essentially consistent with those observed in lenalidomide-treated patients from the main study. Shifts in uric acid to a worst post baseline Grade 3 or 4 value, however, were less frequently observed in MCL patients from the supportive studies than in lenalidomide-treated patients from the main study (shifts to a worst post baseline Grade 3: 0.0% versus 14.3%; shifts to a worst post baseline Grade 4: 2.5% versus 8.1%). A larger proportion of lenalidomide-treated patients in the main study had uric acid Grade 3 baseline values compared with MCL patients from the supportive studies (38/161 [23.6%] versus 0/200 [0.0%]).

Electrocardiograms

In MCL 002, two patients had abnormal, clinically significant ECG results post-baseline at unscheduled visits. One patient in the reported TEAEs of supraventricular tachycardia, atrial fibrillation, cardiac failure congestive, and angina pectoris and one in the Control arm reported atrial fibrillation. Both had medical history significant for cardiac conditions.

Safety in special populations

Age

Table 31. TEAEs Grade 3 or 4 Reported in ≥ 2% of Subjects in Any Analysis Group, by Age Group

MedDRA System Organ Class / Preferred Term[a]	NCI CTCAE[b] Grade 3 or 4 TEAEs							
	MCL-002 Len (N = 167)		MCL-002 Control (N = 83)		MCL Subjects (MCL-001, NHL-003, NHL-002) (N = 206)		All MCL Len Subjects (MCL-002 Len, MCL-001, NHL-003, NHL-002) (N = 373)	
	< 65 years (N = 54) n (%)	≥ 65 years (N = 113) n (%)	< 65 years (N = 27) n (%)	≥ 65 years (N = 56) n (%)	< 65 years (N = 76) n (%)	≥ 65 years (N = 130) n (%)	< 65 years (N = 130) n (%)	≥ 65 years (N = 243) n (%)
Subjects with ≥ 1 Grade 3 or 4 TEAE	**37 (68.5)**	**86 (76.1)**	**18 (66.7)**	**37 (66.1)**	**56 (73.7)**	**102 (78.5)**	**93 (71.5)**	**188 (77.4)**
Blood and lymphatic system disorders	**29 (53.7)**	**65 (57.5)**	**12 (44.4)**	**30 (53.6)**	**47 (61.8)**	**72 (55.4)**	**76 (58.5)**	**137 (56.4)**
Neutropenia	25 (46.3)	48 (42.5)	9 (33.3)	19 (33.9)	35 (46.1)	55 (42.3)	60 (46.2)	103 (42.4)
Thrombocytopenia	8 (14.8)	22 (19.5)	6 (22.2)	17 (30.4)	24 (31.6)	35 (26.9)	32 (24.6)	57 (23.5)
Anaemia	5 (9.3)	9 (8.0)	1 (3.7)	5 (8.9)	11 (14.5)	11 (8.5)	16 (12.3)	20 (8.2)
Leukopenia	4 (7.4)	9 (8.0)	4 (14.8)	5 (8.9)	8 (10.5)	7 (5.4)	12 (9.2)	16 (6.6)
Febrile neutropenia	1 (1.9)	9 (8.0)	0 (0.0)	2 (3.6)	2 (2.6)	10 (7.7)	3 (2.3)	19 (7.8)
Lymphopenia	0 (0.0)	2 (1.8)	1 (3.7)	4 (7.1)	2 (2.6)	3 (2.3)	2 (1.5)	5 (2.1)
Infections and infestations	**8 (14.8)**	**19 (16.8)**	**2 (7.4)**	**5 (8.9)**	**14 (18.4)**	**26 (20.0)**	**22 (16.9)**	**45 (18.5)**
Pneumonia	1 (1.9)	5 (4.4)	1 (3.7)	1 (1.8)	3 (3.9)	5 (3.8)	4 (3.1)	10 (4.1)
Respiratory, thoracic and mediastinal disorders	**4 (7.4)**	**12 (10.6)**	**0 (0.0)**	**3 (5.4)**	**10 (13.2)**	**18 (13.8)**	**14 (10.8)**	**30 (12.3)**
Pulmonary embolism	3 (5.6)	4 (3.5)	0 (0.0)	0 (0.0)	2 (2.6)	1 (0.8)	5 (3.8)	5 (2.1)
Dyspnoea	0 (0.0)	3 (2.7)	0 (0.0)	2 (3.6)	4 (5.3)	7 (5.4)	4 (3.1)	10 (4.1)
Pleural effusion	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)	1 (1.3)	5 (3.8)	1 (0.8)	7 (2.9)
Gastrointestinal disorders	**5 (9.3)**	**9 (8.0)**	**0 (0.0)**	**3 (5.4)**	**7 (9.2)**	**18 (13.8)**	**12 (9.2)**	**27 (11.1)**
Diarrhoea	3 (5.6)	3 (2.7)	0 (0.0)	0 (0.0)	2 (2.6)	10 (7.7)	5 (3.8)	13 (5.3)
Abdominal pain	2 (3.7)	1 (0.9)	0 (0.0)	0 (0.0)	1 (1.3)	6 (4.6)	3 (2.3)	7 (2.9)
General disorders and administration site conditions	**3 (5.6)**	**11 (9.7)**	**1 (3.7)**	**0 (0.0)**	**10 (13.2)**	**20 (15.4)**	**13 (10.0)**	**31 (12.8)**
Pyrexia	2 (3.7)	2 (1.8)	1 (3.7)	0 (0.0)	2 (2.6)	1 (0.8)	4 (3.1)	3 (1.2)
Asthenia	1 (1.9)	1 (0.9)	0 (0.0)	0 (0.0)	1 (1.3)	6 (4.6)	2 (1.5)	7 (2.9)
Fatigue	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)	4 (5.3)	12 (9.2)	4 (3.1)	14 (5.8)

Cardiac disorders	**1 (1.9)**	**10 (8.8)**	**0 (0.0)**	**2 (3.6)**	**2 (2.6)**	**5 (3.8)**	**3 (2.3)**	**15 (6.2)**
Atrial fibrillation	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)	1 (1.3)	0 (0.0)	1 (0.8)	0 (0.0)
Metabolism and nutrition disorders	**3 (5.6)**	**7 (6.2)**	**1 (3.7)**	**1 (1.8)**	**8 (10.5)**	**6 (4.6)**	**11 (8.5)**	**13 (5.3)**
Dehydration	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	3 (3.9)	2 (1.5)	3 (2.3)	3 (1.2)
Investigations	**2 (3.7)**	**5 (4.4)**	**1 (3.7)**	**4 (7.1)**	**5 (6.6)**	**8 (6.2)**	**7 (5.4)**	**13 (5.3)**
Alanine aminotransferase increased	1 (1.9)	2 (1.8)	1 (3.7)	1 (1.8)	0 (0.0)	0 (0.0)	1 (0.8)	2 (0.8)
White blood cell count decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	3 (3.9)	3 (2.3)	3 (2.3)	3 (1.2)
Vascular disorders	**0 (0.0)**	**7 (6.2)**	**1 (3.7)**	**1 (1.8)**	**6 (7.9)**	**7 (5.4)**	**6 (4.6)**	**14 (5.8)**
Hypertension	0 (0.0)	2 (1.8)	1 (3.7)	1 (1.8)	1 (1.3)	1 (0.8)	1 (0.8)	3 (1.2)
Deep vein thrombosis	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	3 (3.9)	3 (2.3)	3 (2.3)	4 (1.6)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**1 (1.9)**	**5 (4.4)**	**2 (7.4)**	**3 (5.4)**	**3 (3.9)**	**9 (6.9)**	**4 (3.1)**	**14 (5.8)**
Squamous cell carcinoma of skin	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	7 (5.4)	0 (0.0)	8 (3.3)
Mantle cell lymphoma	0 (0.0)	0 (0.0)	2 (7.4)	2 (3.6)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)
Musculoskeletal and connective tissue disorders	**2 (3.7)**	**3 (2.7)**	**0 (0.0)**	**0 (0.0)**	**3 (3.9)**	**9 (6.9)**	**5 (3.8)**	**12 (4.9)**
Back pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.6)	3 (2.3)	2 (1.5)	3 (1.2)
Immune system disorders	**0 (0.0)**	**1 (0.9)**	**1 (3.7)**	**1 (1.8)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.4)**
Drug hypersensitivity	0 (0.0)	1 (0.9)	1 (3.7)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)

Gender

Table 32. TEAEs Grade 3 or 4 Reported in ≥ 2% of Subjects in Any Analysis Group, by SOC and Sex

	NCI CTCAE[b] Grade 3 or 4 TEAEs							
	MCL-002 Len (N = 167)		MCL-002 Control (N = 83)		MCL Subjects (MCL-001, NHL-003, NHL-002) (N = 206)		All MCL Len Subjects (MCL-002 Len, MCL-001, NHL-003, NHL-002) (N = 373)	
MedDRA System Organ Class / Preferred Term[a]	Male (N = 122) n (%)	Female (N = 45) n (%)	Male (N = 62) n (%)	Female (N = 21) n (%)	Male (N = 160) n (%)	Female (N = 46) n (%)	Male (N = 282) n (%)	Female (N = 91) n (%)
Subjects with ≥ 1 Grade 3 or 4 TEAE	**88 (72.1)**	**35 (77.8)**	**42 (67.7)**	**13 (61.9)**	**122 (76.3)**	**36 (78.3)**	**210 (74.5)**	**71 (78.0)**
Blood and lymphatic system disorders	**65 (53.3)**	**29 (64.4)**	**34 (54.8)**	**8 (38.1)**	**92 (57.5)**	**27 (58.7)**	**157 (55.7)**	**56 (61.5)**
Neutropenia	50 (41.0)	23 (51.1)	21 (33.9)	7 (33.3)	69 (43.1)	21 (45.7)	119 (42.2)	44 (48.4)
Thrombocytopenia	23 (18.9)	7 (15.6)	22 (35.5)	1 (4.8)	50 (31.3)	9 (19.6)	73 (25.9)	16 (17.6)
Anaemia	10 (8.2)	4 (8.9)	5 (8.1)	1 (4.8)	20 (12.5)	2 (4.3)	30 (10.6)	6 (6.6)
Leukopenia	9 (7.4)	4 (8.9)	6 (9.7)	3 (14.3)	11 (6.9)	4 (8.7)	20 (7.1)	8 (8.8)
Febrile neutropenia	5 (4.1)	5 (11.1)	2 (3.2)	0 (0.0)	12 (7.5)	0 (0.0)	17 (6.0)	5 (5.5)
Lymphopenia	1 (0.8)	1 (2.2)	4 (6.5)	1 (4.8)	3 (1.9)	2 (4.3)	4 (1.4)	3 (3.3)
Infections and infestations	**22 (18.0)**	**5 (11.1)**	**3 (4.8)**	**4 (19.0)**	**33 (20.6)**	**7 (15.2)**	**55 (19.5)**	**12 (13.2)**
Pneumonia	4 (3.3)	2 (4.4)	1 (1.6)	1 (4.8)	8 (5.0)	0 (0.0)	12 (4.3)	2 (2.2)
Respiratory, thoracic and mediastinal disorders	**11 (9.0)**	**5 (11.1)**	**2 (3.2)**	**1 (4.8)**	**22 (13.8)**	**6 (13.0)**	**33 (11.7)**	**11 (12.1)**
Pulmonary embolism	4 (3.3)	3 (6.7)	0 (0.0)	0 (0.0)	3 (1.9)	0 (0.0)	7 (2.5)	3 (3.3)
Dyspnoea	2 (1.6)	1 (2.2)	2 (3.2)	0 (0.0)	9 (5.6)	2 (4.3)	11 (3.9)	3 (3.3)
Pleural effusion	1 (0.8)	1 (2.2)	0 (0.0)	0 (0.0)	2 (1.3)	4 (8.7)	3 (1.1)	5 (5.5)
Gastrointestinal disorders	**12 (9.8)**	**2 (4.4)**	**2 (3.2)**	**1 (4.8)**	**22 (13.8)**	**3 (6.5)**	**34 (12.1)**	**5 (5.5)**
Diarrhoea	5 (4.1)	1 (2.2)	0 (0.0)	0 (0.0)	11 (6.9)	1 (2.2)	16 (5.7)	2 (2.2)
Abdominal pain	2 (1.6)	1 (2.2)	0 (0.0)	0 (0.0)	6 (3.8)	1 (2.2)	8 (2.8)	2 (2.2)
General disorders and administration site conditions	**11 (9.0)**	**3 (6.7)**	**1 (1.6)**	**0 (0.0)**	**26 (16.3)**	**4 (8.7)**	**37 (13.1)**	**7 (7.7)**
Pyrexia	4 (3.3)	0 (0.0)	1 (1.6)	0 (0.0)	3 (1.9)	0 (0.0)	7 (2.5)	0 (0.0)
Asthenia	1 (0.8)	1 (2.2)	0 (0.0)	0 (0.0)	6 (3.8)	1 (2.2)	7 (2.5)	2 (2.2)
Fatigue	2 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	14 (8.8)	2 (4.3)	16 (5.7)	2 (2.2)

Cardiac disorders	**10 (8.2)**	**1 (2.2)**	**0 (0.0)**	**2 (9.5)**	**5 (3.1)**	**2 (4.3)**	**15 (5.3)**	**3 (3.3)**
Atrial fibrillation	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.5)	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)
Metabolism and nutrition disorders	**8 (6.6)**	**2 (4.4)**	**2 (3.2)**	**0 (0.0)**	**12 (7.5)**	**2 (4.3)**	**20 (7.1)**	**4 (4.4)**
Dehydration	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	5 (3.1)	0 (0.0)	6 (2.1)	0 (0.0)
Investigations	**4 (3.3)**	**3 (6.7)**	**4 (6.5)**	**1 (4.8)**	**10 (6.3)**	**3 (6.5)**	**14 (5.0)**	**6 (6.6)**
Alanine aminotransferase increased	2 (1.6)	1 (2.2)	1 (1.6)	1 (4.8)	0 (0.0)	0 (0.0)	2 (0.7)	1 (1.1)
White blood cell count decreased	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	4 (2.5)	2 (4.3)	4 (1.4)	2 (2.2)
Vascular disorders	**4 (3.3)**	**3 (6.7)**	**2 (3.2)**	**0 (0.0)**	**11 (6.9)**	**2 (4.3)**	**15 (5.3)**	**5 (5.5)**
Hypertension	0 (0.0)	2 (4.4)	2 (3.2)	0 (0.0)	1 (0.6)	1 (2.2)	1 (0.4)	3 (3.3)
Deep vein thrombosis	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	5 (3.1)	1 (2.2)	5 (1.8)	2 (2.2)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**3 (2.5)**	**3 (6.7)**	**2 (3.2)**	**3 (14.3)**	**11 (6.9)**	**1 (2.2)**	**14 (5.0)**	**4 (4.4)**
Squamous cell carcinoma of skin	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	7 (4.4)	0 (0.0)	8 (2.8)	0 (0.0)
Mantle cell lymphoma	0 (0.0)	0 (0.0)	2 (3.2)	2 (9.5)	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)
Musculoskeletal and connective tissue disorders	**2 (1.6)**	**3 (6.7)**	**0 (0.0)**	**0 (0.0)**	**9 (5.6)**	**3 (6.5)**	**11 (3.9)**	**6 (6.6)**
Back pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.9)	2 (4.3)	3 (1.1)	2 (2.2)
Immune system disorders	**0 (0.0)**	**1 (2.2)**	**2 (3.2)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (1.1)**
Drug hypersensitivity	0 (0.0)	1 (2.2)	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)

Renal impairment

There were altogether 34 individuals with moderate renal impairment vs. 132 classified as normal. In 24% of the patients with impaired renal function, Grade 3+ infections were observed in patients vs. 14% of those with normal function.

Tumour burden

At the preferred term level, the following differences in the reporting of Grade 3 or 4 TEAEs were observed between treatment arms:

- In the low tumour burden subgroup: there was a higher incidence of Grade 3 or 4 neutropenia (37.2% versus 30.6%) and febrile neutropenia (5.1% versus 0.0%) in the lenalidomide group, while in the control group more Grade 3 or 4 leukopenia (16.3% versus 6.4%), lymphopenia (6.1% versus 0.0%), and anemia (10.2% versus 5.1%) were noted.
- In the high tumour burden subgroup: there was a higher incidence of Grade 3 or 4 anaemia (10.1% versus 3.6%) and pulmonary embolism (6.3% versus 0.0%) in the lenalidomide group, while in the control group more Grade 3 or 4 thrombocytopenia (32.1% versus 13.9%), MCL (10.7% versus 0.0%), and lymphopenia (7.1% versus 1.3%) were noted.

Table 33. Treatment Discontinuations During Cycle 1 Due to Adverse Events or Consent Withdrawal by Tumour Burden at Baseline - Safety Population (Study MCL-002)

	Lenalidomide	**Control**
Treatment discontinuation during Cycle 1	**N = 15**	**N = 2**
Adverse event, n (%)	10 (66.7)	1 (50.0)
High tumour burden[a] at baseline	7 (46.7)	0 (0.0)
Low tumour burden at baseline	3 (20.0)	1 (50.0)
Consent withdrawal, n (%)	5 (33.3)	1 (50.0)

High tumour burden[a] at baseline	4 (26.7)	1 (50.0)
Low tumour burden at baseline	1 (6.7)	0 (0.0)

[a] High tumour burden is defined as at least one lesion that is ≥ 5 cm in diameter or 3 lesions that are ≥ 3 cm in diameter by central review.
Note: Data cut-off date is 07 Mar 2014.

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to adverse events
Table 34. TEAEs Leading to Study Drug Discontinuation in ≥ 2% of Subjects in any Analysis Group by SOC and PT

MedDRA System Organ Class / Preferred Term[a]	Analysis Group			
	MCL-002 Len (N = 167) n (%)	MCL-002 Control (N = 83) n (%)	MCL Subjects (MCL-001, NHL-003, NHL-002) (N = 206) n (%)	All MCL Len Subjects (MCL-002 Len, MCL-001, NHL-003, NHL-002) (N = 373) n (%)
Subjects With ≥ 1 TEAE Leading to Study Drug Discontinuation	**25 (15.0)**	**13 (15.7)**	**43 (20.9)**	**68 (18.2)**
Blood and lymphatic system disorders	**5 (3.0)**	**5 (6.0)**	**21 (10.2)**	**26 (7.0)**
Thrombocytopenia	2 (1.2)	4 (4.8)	12 (5.8)	14 (3.8)
Neutropenia	2 (1.2)	1 (1.2)	8 (3.9)	10 (2.7)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**4 (2.4)**	**4 (4.8)**	**1 (0.5)**	**5 (1.3)**
Mantle cell lymphoma	0 (0.0)	3 (3.6)	0 (0.0)	0 (0.0)

Post marketing experience

N/A

2.5.1. Discussion on clinical safety

The overall safety profile of Revlimid in patients with mantle cell lymphoma is based on data from 254 patients from a Phase II randomized, controlled study MCL-002. Additionally, ADRs from supportive study MCL-001 have been included in table 3 ''ADRs reported in clinical trials in patients with mantle cell lymphoma treated with lenalidomide

The most frequently observed adverse reactions which occurred more frequently in the lenalidomide arm compared with the control arm in Study MCL-002 were neutropenia (50.9%), anaemia (28.7%), diarrhoea (22.8%), fatigue (21.0%), constipation (17.4%), pyrexia (16.8%), and rash (including dermatitis allergic) (16.2%) (SmPC section 4.8).

The serious adverse reactions observed more frequently in Study MCL-002 (with a difference of at least 2 percentage points) in the lenalidomide arm compared with the control arm were: Neutropenia (3.6%); pulmonary embolism (3.6%) and diarrhoea (3.6%) (SmPC section 4.8). The recommended blood cell count monitoring scheme applicable to MCL has been reflected in section 4.4 of the SmPC to be performed every 2 weeks in Cycles 3 and 4, and then at the start of each cycle.

In Study MCL-002, TFR was reported in the lenalidomide arm only (16 subjects, 9.6%) thereof in 3 (1.8%) subjects classified as Grade 3 to 4 events (no Grade 5 AEs reported). One event was an SAE (0.6%), 1 event resulted in treatment discontinuation, and events in 2 subjects (1.2%) led to dose interruption or reduction.

Demographic and baseline characteristic of subjects with and without treatment-emergent TFR were generally similar, although those subjects in the lenalidomide arm with TFR appeared to include a higher percentage of males, slightly younger, and a higher percentage with high tumour burden (62.5% versus 45.7%) and with bulky disease ≥ 7 cm at baseline (43.8% versus 18.5%) than those subjects without TFR (SmPC section 4.4).

Tumour flare reaction was thus generally of mild to moderate severity, and often manageable with concomitant therapy and with no dose change or through dose interruption/reduction only.

Careful monitoring and evaluation for TFR is recommended. Patients with high MIPI at diagnosis or bulky disease (at least one lesion that is ≥ 7 cm in the longest diameter) at baseline may be at risk of TFR. Tumour flare reaction may mimic progression of disease (PD). Patients in studies MCL-002 and MCL-001 that experienced Grade 1 and 2 TFR were treated with corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and/or narcotic analgesics for management of TFR symptoms. The decision to take therapeutic measures for TFR should be made after careful clinical assessment of the individual patient (See section 4.4 of the SmPC).

Tumor flare reaction is the only new adverse reaction observed in patients treated for MCL (but has also been seen in patients with CLL) and has been classified as identified risk in the Risk Management Plan. To further investigate and characterize the association of lenalidomide and TFR the applicant will conduct a PASS on RRMCL patients treated with lenalidomide whose objective is to monitor incidence in “real world” situation (see Risk Management Plan).

In study MCL-002 there was overall an apparent increase in early (within 20 weeks) deaths in the lenalidomide group. During treatment cycle 1, patients with high tumour burden were more likely to be withdrawn from therapy in the lenalidomide group vs. the control group group. The main reason for treatment withdrawal for patients with high tumour burden during treatment cycle 1 in the lenalidomide arm was adverse events. However, in terms of grade 3 and 4 events up to week 20, there was no obvious interaction between tumour burden and adverse events (see benefit-risk balance, unfavourable effects). Patients with high tumour burden should therefore be closely monitored for adverse reactions including signs of tumour flare reaction (see sections 4.4 and 4.8 of the SmPC).

In MCL 002 study, the incidence rate of total second primary malignancies (SPMs), in the lenalidomide arm and control arm are similar. For invasive SPMs, the incidence rate in the lenalidomide arm is inferior to the one of control arm because of solid tumours occurring less frequently in the lenalidomide arm. Therefore, the excess of risk in the lenalidomide arm is driven by the occurrence of non-invasive SPMs. Patients in the lenalidomide arm had a 2.44-fold increased risk (1.88/0.77) of developing a Non Melanoma Skin Cancer (NMSC) compared to patients in the control arm. Time to onset of SPM is 30 months in lenalidomide arm while it is 6 months in Control arm. The solid tumours involve various fields: hepatic, breast, lung and skin for the lenalidomide arm and colon lung, NSC, renal for the control arm. Risk factors for SPM in the RRMCL population have not been identified. In this respect, AML, B-cell malignancies and NMSC have been included as important potential risks related to the indication/target population in the Risk Management Plan. The applicant committed to provide updated information on SPM in patients with MCL in future PSURs. Specific targeted follow-up questionnaires to study the relation between lenalidomide and SPMs will be implemented (see Risk Management Plan). All these safety items will be reported and assessed at each PSUR evaluation.

In MCL 002, frequencies and incidence rates of venous as well as arterial thromboembolic events were higher in the lenalidomide arm than in the control arm. Most events of pulmonary embolism or deep vein thrombosis occurred within the first 5 cycles of treatment. Most of patients with venous VTE had no prior thrombo-embolic events or risk factors; half had received thromboembolic prophylaxis prior to the event. Although incidence of VTEs observed in lenalidomide-treated patients of Study MCL-002 did not exceed the incidence in MM patients (where lenalidomide is used in combination), it is similar to that of MDS (where lenalidomide is used as single agent). As such, the warning about the increased risk of VTE in MCL

population is covered by the existing wording in SmPC currently applicable to MM and MDS population. The decision to take antithrombotic prophylactic measures in MCL indication should be made after careful assessment of an individual patient's underlying risk factors and with the same caution as in other indications (MM, MDS). Specific targeted follow-up questionnaires to study the relation between lenalidomide and ATE/ VTE will be implemented (see Risk Management Plan). All these safety items will be reported and assessed at each PSUR evaluation.

Among TEAEs reported at a lower frequency (< 10%), the following were also reported more frequently (≥ 5 percentage points) in the lenalidomide arm than in the control arm: pain in extremity, headache, TFR, and vertigo. Sections 4.7 and 4.8 of the SmPC have been updated accordingly.

In MCL 002, infections were reported in 53.9% of patients in the Len arm with 16% grade 3 or higher and lower respiratory tract infections including pneumonia being the most commonly reported. There were two deaths. The risk of infection is classified as an important identified risk for lenalidomide in the current RMP and is adequately reflected in the sections 4.4 and 4.8 of the SmPC.

2.5.2. Conclusions on clinical safety

Safety results for patients with RRMCL treated with lenalidomide were in general consistent with the known safety profile of lenalidomide with tumour flare reaction being only new adverse reaction observed in patients treated for MCL. Toxicity was generally manageable with dose reductions and/or interruptions.

To further investigate and characterize the association of lenalidomide and TFR the applicant will conduct a PASS on RRMCL patients treated with lenalidomide whose objective is to monitor incidence in "real world" situation (see Risk Management Plan).

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 PRAC considered that the risk management plan version 28.0 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC advice.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC and/or CHMP.

The CHMP endorsed the Risk Management Plan version 29.0 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)

Summary of safety concerns	
	Important Identified Risks Related to Indication/Target Population -For mantle-cell lymphoma (MCL): Tumour flare reaction (TFR)
	-For newly diagnosed multiple myeloma (NDMM): acute myeloid leukaemia (AML) and B-cell malignancies[a] -For relapsed and/or reflactory 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 Important Potential Risks Related to Indication/Target Population -For NDMM: NMSC[b] -For RRMM: AML and B-cell malignancies[a] -For myelodysplastic syndrome (MDS) and MCL: AML and B-cell 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)**
RRMCL PASS *Category 3*	To further investigate and characterise the associations of lenalidomide with TFR/high tumour burden.	TFR/high tumour burden	To start	The full protocol should be provided within 4 months after positive opinion on RRMCL extension of indication. Safety updates submitted with future PSURs. The final study report could be available in 2022.

Connect® MM Registry *Category 3*	The primary objectives of the registry are to describe practice patterns of common first-line and subsequent treatment regimens (including lenalidomide based) in patients with previously untreated MM, whether or not eligible for	SPM (AML and B-cell malignancies, NMSC and other SPM), cardiac events (cardiac	Ongoing	Safety updates submitted with future PSURs.

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)
	transplant, as well as diagnostic patterns and second primary	failure, cardiac		
	malignancy occurrence in a "real world" population.	arrhythmias, ischaemic heart disease [including MI]), renal failure, neutropenia and infection.		
Revlimid TNE NDMM Registry *Noninterventional: Category 1*	The primary objective is to further assess the safety profile of lenalidomide, including but not limited to cardiovascular safety and the effect of potential risk factors on early cardiovascular events (including MI/ischaemic heart disease) in adult patients with previously untreated MM not eligible for transplant.	Cardiac events (cardiac failure, cardiac arrhythmias, ischaemic heart disease [including MI]).	Planned Protocol synopsis has been submitted and was provided in Annex 6 of RMP version 26.0	The final study report could be available in 2022. Safety updates submitted with future PSURs.
RRMM PASS *Non-interventional: Category 3*	To monitor safety in a "real world" situation.	Celgene PPP. Safety profile in a 'real world' setting.	Ongoing	Safety updates submitted with future PSURs.
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 and a retrospective drug utilisation study of Revlimid in MDS).	AML and survival. Safety profile in a 'real world' setting.	Planned Protocols were provided in Annex 6 of RMP version 24.0	Safety updates submitted with future PSURs.
Pooled analysis of data from clinical trials of Revlimid. *Category 3*	To determine the incidence of VTEs and ATEs in patients with MM, with consideration of the thromboprophylactic agents used.	TEEs	Ongoing	Final Report submitted 31 Mar 2014 to the FDA. The label was formally approved on 12 Sep 2014. Submitted 04 March 2015 to the EMA with PSUR 11 (cut-off date 26 Dec 2014).

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)
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.

*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	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk		
Teratogenicity	Routine risk minimisation activities (SmPC and PL). Section 4.3: Contraindicated in pregnant women and in women of childbearing potential unless all the conditions of the Celgene PPP are met. Section 4.4: Warnings and precautions for use -Criteria for women of non childbearing potential -Counselling -Contraception -Pregnancy testing -Precautions for men -Additional precautions -Reference to educational materials. Section 4.6: Fertility, pregnancy and lactation Sections 4.8 and 5.3: The potential teratogenic effects of lenalidomide are highlighted.	-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 -Patient card to document

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Specific pregnancy reporting form	childbearing status, counselling and pregnancy testing
Thrombocytopenia and Bleeding	-Section 4.2 of SmPC: dose reduction advice for thrombo- cytopenia. Section 4.4 of SmPC: warning of thrombocytopenia and bleeding, and advice for monitoring by blood testing. -Listed as ADRs in Section 4.8 of SmPC. -Advice to patients in PL	-'Dear HCP' letter prior to launch. -HCP Kit. -Patient Brochure.
Neutropenia and Infection	-Section 4.2 of SmPC: dose reduction advice for neutropenia. -Section 4.4 of SmPC: warning of neutropenia and advice for monitoring by blood testing. Advice that patients should report febrile incidences promptly. -Listed as ADRs in Section 4.8 of SmPC. -Advice to patients in PL.	-'Dear HCP' letter prior to launch. -HCP Kit. -Patient Brochure
Thromboembolic Events	-Section 4.4 of SmPC warning. -Listed as ADRs in Section 4.8 of SmPC. -Advice to patients in PL.	-'Dear HCP' letter prior to launch -HCP Kit -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.	-HCP Kit
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 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.	-HCP Kit
Diarrhoea and Constipation	-Listed as ADRs in Section 4.8 of SmPC and in the PL.	None
Tumour lysis Syndrome	-Section 4.4 of SmPC warning. -Listed as an ADR in Section 4.8 of SmPC.	-HCP Kit
Acute Myeloid Leukaemia and B-cell Malignancies	-Section 4.4 of SmPC warning. -Listed as ADRs in Section 4.8 of SmPC. -Advice to patients provided in PL. -Event specific questionnaire for the collection of the AE and follow-up.	-'Dear HCP' letter prior to launch. o 'Dear HCP' letter following EC Approval for MDS o 'Dear HCP' letter after CHMP opinion of Article 20 procedure EMEA/H/C/717/A20/048 received 22 Sep 2011. -HCP Kit.
Non-melanoma Skin Cancers	-Section 4.4 of SmPC warning. -SPM listed as ADRs in Section 4.8 of SmPC. -Advice to patients provided in PL. -Event specific questionnaire for the collection of the AE and follow-up.	-'Dear HCP' letter prior to launch. o 'Dear HCP' letter following EC Approval for MDS o 'Dear HCP' letter after CHMP opinion of Article 20 procedure EMEA/H/C/717/A20/048 received 22 Sep 2011. -HCP Kit.
Tumour Flare Reaction	-Section 4.2 of SmPC: dose interruption advice for TFR. -Section 4.4 of SmPC warning. -Listed as an ADR in Section 4.8 of SmPC. -Event specific questionnaire for the collection of the AE and follow-up.	-HCP Kit
Important potential risks		
Peripheral Neuropathy	-Section 4.4 of SmPC warning. -Listed as an ADR in Section 4.8 of SmPC.	-'Dear HCP' letter prior to launch -HCP Kit

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Cardiac Failure and Cardiac Arrhythmias	-Listed as ADRs in Section 4.8 of SmPC. -Listed in PL.	None
Renal Failure	-Listed as an ADR in Section 4.8 of SmPC.	None
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	-The possible occurrence of hepatic disorders is detailed in Section 4.4 and Section 4.8 of SmPC.	-Dear HCP letter after EC approval of variation EMEA/H/C/00717/058 received 19 Nov 2012.
Other SPM	-Section 4.4 of SmPC warning. -SPM listed as ADRs in Section 4.8 of SmPC. -Advice to patients provided in PL. -Event specific questionnaire for the collection of the AE and follow-up.	-'Dear HCP' letter prior to launch. o 'Dear HCP' letter following EC Approval for MDS o 'Dear HCP' letter after CHMP opinion of Article 20 procedure EMEA/H/C/717/A20/048 received 22 Sep 2011. -HCP Kit.
Off-label Use	-Collection of off-label use data detailed in Section 4.4 of SmPC	-'Dear HCP' letter prior to launch. o Dear HCP letter following EC Approval for MDS -HCP Kit.
Missing information		
Paediatric Use	-Section 4.2: advice to not use in the paediatric age group. -Advice to patients in PL.	None
Use in Moderate and Severe Hepatic Impairment	- Section 4.2: no specific dose recommendations.	None
Use in Breastfeeding	-Section 4.6: advice to discontinue breastfeeding during therapy with lenalidomide. -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, 4.7, 4.8, 5.1 and 5.2 of the SmPC have been updated. Particularly, a new warning with regard to tumour burden and tumour flare reaction has been added to the product information. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

- Changes to the PL were considered not affecting readability.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The primary efficacy endpoint, PFS, was met as a statistically significant improvement in median PFS of 3.4 months was reached in patients treated with lenalidomide versus those treated with investigator's choice of therapy in the Control arm. Results showed a 39% reduction in the risk of disease progression or death for patients in the Len arm compared with those in the Control arm (HR =0.61; 95% CI 0.44-0.84, p = 0.004). The robustness of the PFS effect is supported by several sensitivity analyses, the results of which are in line with the primary analysis. A consistent risk reduction for disease progression with lenalidomide was observed in the analysis of subgroups by number of prior treatment lines, by response to last treatment line (relapsed versus refractory), and by number of relapses, suggesting that the treatment benefit of lenalidomide was independent of prior treatment lines.

This effect was further substantiated by results in ORR. A higher ORR was observed with lenalidomide which was statistically significant compared to the Control arm (40.0% vs 10.7%). A greater quality of response was also observed in the Len arm, with a CR rate of 4.7%, compared to 0.0% in the Control arm (p = 0.043). Responses were also seen earlier in the Len arm compared to the Control arm, with a median time to first response and to best response of 18.7 weeks (4.3 months) and 26.7 weeks (6.2 months), respectively.

The median OS for single-agent lenalidomide treatment was 27.9 months (2.3 years) compared with 21.2 months (1.8 years) for BIC single-agent treatment.

Uncertainty in the knowledge about the beneficial effects

A favourable overall survival trend was observed, however OS results of MCL 002 do not support the PFS results since the survival advantage of Len arm over Control arm is not statistically significant. The absence of difference in terms of OS could be attributed to the massive switch from Control arm to Len arm.

The positive effect of lenalidomide treatment on PFS remains consistent, with HRs of 0.56 (95% CI: 0.35, 0.88) and 0.54 (95% CI: 0.33, 0.90) in subjects with low and high tumour burden at baseline, respectively. In the high burden group, OS curves are crossing. Whilst HR is not optimal in case of crossing curves, it is 1.2 (p=0.6) in the high burden group vs. 0.7 (p=0.20) in the low burden group. Numbers are small, especially in the high burden control group; however the erratic behaviour of the OS curves in the ITT population is explained by what happens in the high burden group.

Risks

Unfavourable effects

The most frequently observed adverse reactions which occurred more frequently in the lenalidomide arm compared with the control arm in Study MCL-002 were neutropenia (50.9%), anaemia (28.7%), diarrhoea (22.8%), fatigue (21.0%), constipation (17.4%), pyrexia (16.8%), and rash (including dermatitis allergic) (16.2%).

The serious adverse reactions observed more frequently in Study MCL-002 (with a difference of at least 2 percentage points) in the lenalidomide arm compared with the control arm were: Neutropenia (3.6%); pulmonary embolism (3.6%) and diarrhoea (3.6%).

In general, tolerability is considered moderate in severity, but manageable and the only new event refers to tumour flare.

In MCL 002, frequencies and incidence rates of venous as well as arterial thromboembolic events were higher in the lenalidomide arm than in the control arm. Most events of pulmonary embolism or deep vein thrombosis occurred within the first 5 cycles of treatment. Most of patients with venous VTE had no prior thromboembolic events or risk factors; half had received thromboembolic prophylaxis prior to the event. Since the incidence of VTEs observed in lenalidomide-treated patients of Study MCL-002 did not exceed the incidence in MM patients (where lenalidomide is used in combination) and it is similar to that of MDS (where lenalidomide is used as single agent), the existing wording in the SmPC satisfactorily addresses this safety concern. In addition, specific targeted follow-up questionnaires to study the relation between lenalidomide and ATE/ VTE will be implemented. All these safety items will be reported and assessed at each PSUR evaluation.

Uncertainty in the knowledge about the unfavourable effects

In study MCL-002 there was an increased proportion of early deaths in the high tumour burden group in the lenalidomide arm. High tumour burden was defined as at least one lesion ≥5 cm in diameter or 3 lesions ≥3 cm (SmPC sections 4.4 and 4.8). In addition, a high rate of discontinuations in the lenalidomide arm during cycle 1 was observed. In a multivariate analysis high tumour burden but not treatment group was identified as a significant risk factor for early death. However, due to small number of patients, especially after having split the population in sub-groups for post-hoc analyses, data should be interpreted with caution. Although a definitive association has not been established in view of the potential confounders and small numbers in these subgroup analyses, lenalidomide is not recommended for the treatment of patients with high tumour burden if alternative treatment options are available (SmPC sections 4.4 and 4.8). Patients with high tumour burden should be closely monitored for adverse reactions including signs of tumour flare reaction (see Risk Management Plan). Furthermore, in order to further investigate and characterize the association of lenalidomide and TFR, the applicant will conduct a PASS on RRMCL patients treated with lenalidomide whose objective is to monitor incidence in “real world” situation (see Risk Management Plan).

Patients in the lenalidomide arm had a 2.44-fold increased risk (1.88/0.77) of developing a Non melanoma skin cancer (NMSC) compared to patients in the control arm. In this respect, AML, B-cell malignancies and NMSC have been included as important potential risks related to the indication/target population of MCL in the Risk Management Plan.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The clinical efficacy results observed for lenalidomide in RRMCL population are considered of a magnitude that is of clinical relevance both in absolute (3.4 months difference in median PFS) and relative terms (HR=0.61), in delaying progression of the disease.

The safety profile of lenalidomide in patients with RRMLC is overall consistent with what is already known in lenalidomide treated patients with MM and MDS with tumour flare being the only new safety signal.

Benefit-risk balance

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 and uncertainties. Therefore, the benefit-risk balance is considered positive.

Discussion on the Benefit-Risk Balance

Few alternative therapies are available for RRMCL patients. Because MCL iteratively relapses and relapsed patients may switch from one to another therapy, the availability of new medicinal products in second and further line treatment in RRMCL patients who are not eligible to high dose therapy and/or transplantation is considered of great clinical interest. Nevertheless, single-agent lenalidomide could provide an additional option and address the medical need in this rare disease with limited treatment options.

In patients with high tumour burden, the apparent early disadvantage of lenalidomide in terms of survival must be interpreted with caution, keeping in mind that the pivotal trial used active comparators. As a consequence, lenalidomide is not recommended for the treatment of patients with high tumor burden if alternative treatment options are available. However, on a case-by-case basis, the activity of lenalidomide may bring some benefit to some patients with high tumour burden who must be closely followed to limit tolerability issues.

Treatment with lenalidomide provided clinical benefit to patients with RRMCL in the form of prolonged PFS with durable complete and partial responses to treatment. The lack of difference in OS is not due to lack of antitumoral efficacy. The overall clinical benefit of the treatment has been demonstrated.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Revlimid (lenalidomide) is not similar to Torisel (temsirolimus) or Imbruvica (ibrutinib) 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 variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation requested		**Type**	**Annexes affected**
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 relapsed or refractory mantle cell lymphoma (MCL); as a consequence, SmPC sections 4.1, 4.2, 4.4, 4.7, 4.8, 5.1 and 5.2 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 29.0) has been approved as part of this application.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

5. EPAR changes

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

Scope

Extension of Indication to add treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL); as a consequence, SmPC sections 4.1, 4.2, 4.4, 4.7, 4.8, 5.1 and 5.2 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 29.0) has been approved as part of this application.

Summary

Please refer to the Scientific Discussion Revlimid-II-79.

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