# LENALIDOMIDE
# RISK MANAGEMENT PLAN

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| Term | Definition |
|---|---|
| AdEERS | Adverse Event Expedited Reporting System |
| ADR | Adverse drug reaction |
| AE | Adverse event |
| AFSSAPS | Agence Française de Sécurité Sanitaire des Produits de Santé |
| ALF | Acute liver failure |
| AMI | Acute myocardial infarction |
| AML | Acute myeloid leukaemia |
| ANC | Absolute neutrophil count |
| ANSM | Agence nationale de sécurité du médicament et des produits de santé |
| ASCT | Autologous stem cell transplantation |
| ASR | Age-standardised incidence rates |
| AST | Aspartate aminotransferase |
| ATC | Anatomical Therapeutic Chemical Classification |
| ATE | Arterial thromboembolic event |
| ATLL | Adult T-cell leukaemia-lymphoma |
| AUC | Area under the curve |
| BCRP | Breast cancer resistance protein |
| BID | Twice daily |
| BMS | Bristol Myers Squibb |
| BSEP | Bile salt export pump |
| BUMEL | Busulfan with melphalan |
| CALGB | Cancer and Leukaemia Group B |
| CCDS | Company Core Data Sheet |
| CD | Clusters of differentiation |
| CDC | Centers for Disease Control and Prevention |
| CHD | Coronary heart disease |
| CHF | Congestive heart failure |
| CHMP | Committee for Medicinal Products for Human Use |
| CHOP | Cyclophosphamide, doxorubicin, vincristine and prednisolone |
| CI | Confidence interval |
| CLcr | Creatinine clearance |
| CL/F | Apparent clearance |
| CLL | Chronic lymphocytic leukaemia |
| $C_{max}$ | Maximum concentration |

| Term | Definition |
|---|---|
| CML | Chronic myeloid leukaemia |
| CMML | Chronic myelomonocytic leukaemia |
| CNS | Central nervous system |
| CPRD | Clinical Practice Research Datalink |
| CRF | Case report form |
| CSC | Corrected serum calcium |
| CSF | Cerebrospinal fluid |
| CSR | Clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CVA | Cerebrovascular accident |
| CYP | Cytochrome P450 |
| Del 5q | Deletion 5q |
| Del 13q | Deletion 13q |
| Del 17p | Deletion 17p |
| Dex | Dexamethasone |
| DHPC | Direct Healthcare Professional Communication |
| DILI | Drug-induced liver injury |
| DLBCL | Diffuse large B-cell lymphoma |
| DLP | Data lock point |
| DNA | Deoxyribonucleic acid |
| DSUR | Development Safety Update Report |
| DVT | Deep vein thrombosis |
| E | Evaluation |
| EBMT | European Society for Bone and Marrow Transplantation |
| EBV | Epstein-Barr virus |
| EC | European Commission |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| EEA | European Economic Area |
| EMA/EMEA | European Medicines Agency |
| EPAR | European public assessment report |
| EPITT | European Pharmacovigilance Issues Tracking Tool |
| EPO | Erythropoietin |
| ESA | Erythropoiesis-stimulating agent |
| ESMO | European Society for Medical Oncology |

| Term | Definition |
|---|---|
| EU | European Union |
| FAB | French-American-British |
| FCBP | Females of childbearing potential |
| FDA | Food and Drug Administration |
| FL | Follicular lymphoma |
| FLIPI | Follicular Lymphoma International Prognostic Index |
| G-CSF | Granulocyte colony-stimulating factor |
| GLSG | German Low Grade Lymphoma Study Group |
| GvHD | Graft versus host disease |
| GVP | Good pharmacovigilance practices |
| HBV | Hepatitis B virus |
| (β-)hCG | (β-)human chorionic gonadotropin |
| HCP | Healthcare professional |
| HCV | Hepatitis C virus |
| HDM | High dose melphalan |
| HDT | High-dose therapy |
| HHV-8 | Human herpes virus-8 |
| HIV | Human immunodeficiency virus |
| HLGT | High Level Group Term |
| HLT | Higher Level Term |
| HMRN | Haematological Malignancy Research Network |
| hpf | High-power field |
| HR | Hazard ratio |
| HRQoL | Health related quality of life |
| HSC | Haematopoietic stem cell |
| (auto-)HSCT | (autologous) Haematopoietic stem cell transplantation |
| ICUS | Idiopathic cytopenia of undetermined significance |
| IFI | Invasive fungal infection |
| IFM | Intergroupe Francophone du Myelome |
| Ig | Immunoglobulin |
| IHC | Immunohistochemistry |
| IHD | Ischaemic heart disease |
| IIT | Investigator-initiated trial |
| IL | Interleukin |
| IMiD | Immunomodulatory drug |

| Term | Definition |
|---|---|
| INN | International Nonproprietary Name |
| INR | International normalised ratio |
| INT | Intermediate |
| INT-1/INT-2 | Intermediate-1/Intermediate-2 |
| IPSS | International Prognostic Scoring System |
| IQR | Interquartile range |
| ISS | International Staging System |
| ITT | Intent-to-treat |
| IV | Intravenous(ly) |
| KLSG | Kiel Lymphoma Study Group |
| LEG | Legally binding measure |
| Len | Lenalidomide |
| LFS | Leukaemia-free survival |
| LMWH | Low-molecular-weight heparin |
| MAA | Marketing Authorisation Application |
| MAH | Marketing Authorisation Holder |
| MALT | Mucosa-associated lymphoid tissue |
| MATE | Multi antimicrobial extrusion protein |
| MCL | Mantle cell lymphoma |
| MDS | Myelodysplastic syndrome(s) |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MEL200 | Melphalan 200 mg/$m^2$ |
| MGUS | Monoclonal gammopathy of undetermined significance |
| LMWH | Low-molecular-weight heparin |
| MAA | Marketing Authorisation Application |
| MAH | Marketing Authorisation Holder |
| MALT | Mucosa-associated lymphoid tissue |
| MATE | Multi antimicrobial extrusion protein |
| MCL | Mantle cell lymphoma |
| MDS | Myelodysplastic syndrome(s) |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MEL200 | Melphalan 200 mg/$m^2$ |
| MGUS | Monoclonal gammopathy of undetermined significance |
| MI | Myocardial infarction |
| MIPI | Mantle cell lymphoma International Prognostic Index |

| Term | Definition |
|---|---|
| MM | Multiple myeloma |
| MPp+p | Induction therapy (up to 9 cycles) with melphalan/prednisone plus placebo followed by maintenance therapy with single-agent placebo |
| MPR+p | Induction therapy (up to 9 cycles) with melphalan/prednisone plus lenalidomide followed by maintenance therapy with single-agent placebo |
| MPR+R | Induction therapy (up to 9 cycles) with melphalan/prednisone plus lenalidomide followed by maintenance therapy with single-agent lenalidomide |
| MPT | Melphalan, prednisone and thalidomide |
| MRP | Multidrug resistance-associated protein |
| MTD | Maximum tolerated dose |
| MZL | Marginal zone lymphoma |
| N/A | Not applicable |
| N/n | Number of patients |
| NA | Not available |
| NC | Not calculated/not collected |
| NCA(s) | National Competent Authority(ies) |
| NCI | National Cancer Institute |
| NCCN | National Comprehensive Cancer Network |
| NDMM | Newly diagnosed multiple myeloma |
| NEC | Not elsewhere classified |
| NHL | Non-Hodgkin’s lymphoma |
| NK | Natural killer |
| NMSC | Non-melanoma skin cancer |
| NOAEL | No observed adverse effect level |
| NOL | No Objection Letter |
| NOS | Not otherwise specified |
| OAT | Organic anion transporter |
| OCT | Organic cation transporter |
| ONJ | Osteonecrosis of the jaw |
| OS | Overall survival |
| PASS/PASSes | Postauthorisation Safety Study/Studies |
| PBO | Placebo |
| PD | Progressive disease |
| PDCO | Paediatric Committee |
| PFS | Progression-free survival |
| P-gp | P-glycoprotein |

| Term | Definition |
|---|---|
| PI | Prescribing information |
| PK | Pharmacokinetic(s) |
| PL | Package leaflet |
| PMC | Postmarketing Commitment |
| PPP | Pregnancy Prevention Programme |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PSUR | Periodic Safety Update Report |
| PT | Preferred term |
| PTLD | Post-Transplant Lymphoproliferative Disorders |
| QD | Once daily |
| QOD | Every other day |
| QPPV | Qualified Person Responsible for Pharmacovigilance |
| QTc | Corrected QT interval |
| R | Reporting |
| RA | Refractory anaemia |
| RAEB | Refractory Anaemia with Excess Blasts |
| RARS | Refractory Anaemia with Ringed Sideroblasts |
| RBC | Red blood cell |
| R-CHOP | Rituximab, cyclophosphamide, doxorubicin, vincristine and predniso(lo)ne |
| RCMD | Refractory cytopenia with multilineage dysplasia |
| R-CVP | Rituximab, cyclophosphamide, vincristine and prednisolone |
| Rd | Lenalidomide and low-dose dexamethasone given in 28-day cycles until documentation of progressive disease |
| Rd18 | Lenalidomide and low-dose dexamethasone given in 28-day cycles for up to 18 cycles (72 weeks) |
| REMS | Risk Evaluation and Mitigation Strategies |
| Rit | Rituximab |
| RMP | Risk Management Plan |
| RRMCL | Relapsed or refractory MCL |
| RRMM | Relapsed or refractory MM |
| RSI | Request for Supplementary Information |
| RVd | Lenalidomide, bortezomib and dexamethasone |
| SAE | Serious adverse event |
| SC | Subcutaneous |
| SCS | Summary of Clinical Safety |
| SD | Standard deviation |

| Term | Definition |
|---|---|
| SEER | Surveillance, Epidemiology and End Results |
| SIR | Standardised incidence ratio |
| SmPC | Summary of Product Characteristics |
| SMQ | Standardised MedDRA Query |
| SMR | Standardised Mortality Ratio |
| SOC | System Organ Class |
| SPM | Second primary malignancies |
| STR | Safety topic review |
| SUSAR | Suspected unexpected serious adverse reaction |
| SWOG | Southwest Oncology Group (until 2010; thereafter referred to as SWOG) |
| $t_{1/2}$ | Half-life |
| $t_{1/2,z}$ | Terminal half-life |
| tAML | Therapy-associated AML |
| TBD | To be determined |
| TCL | T-cell lymphoma |
| TD | Thalidomide and dexamethasone |
| TE | Transplant eligible |
| TEAE | Treatment-emergent adverse event |
| TFR | Tumour flare reaction |
| TLS | Tumour lysis syndrome |
| $t_{max}$ | Time to maximum concentration |
| tMDS | Therapy-associated MDS |
| TNE | Transplant non-eligible |
| TP | Tumour protein |
| TTP | Time to disease progression |
| UGT | 5'-diphospho-glucuronosyltransferase |
| UK | United Kingdom |
| ULN | Upper limit of normal |
| US/USA | United States/United States of America |
| VCD | Cyclophosphamide, bortezomib and dexamethasone |
| VD | Bortezomib and dexamethasone |
| VMP | Bortezomib, melphalan and prednisone |
| VTD | Bortezomib, thalidomide and dexamethasone |
| VTE | Venous thromboembolic event |
| WHO | World Health Organization |

| Term | Definition |
|---|---|
| WPSS | WHO Classification-based Prognostic Scoring System |

# EU RISK MANAGEMENT PLAN (RMP) FOR LENALIDOMIDE

**RMP version to be assessed as part of this application:**

Version Number: 41.1Data-lock Point for this RMP: 22-Sep-2023Date of Final Sign-off: 21-Oct-2024

Rationale for submitting an updated RMP:

- Updated the status of Study MDS-012 and the Connect® MDS/AML Disease Registry from ongoing to completed throughout the RMP.
- Administrative update to the routine risk minimisation measures in Table 5.3-1 to remove the statement that "The association between ischaemic heart disease and lenalidomide is unknown" (related to Procedure no. EMEA/H/C/000717/IB/0129/G).
- Administrative update of the Post-Authorization Exposure.

## Summary of Significant Changes in this RMP

| Part/Module | Summary of Major Changes | Version # / Date of Positive Opinion for Module Update |
|---|---|---|
| **Part II Safety Specification** | | |
| **SI** Epidemiology of the indication(s) and target population(s) | N/A | V37.0 / 18-Dec-2019 |
| **SII** Non-clinical part of the safety specification | N/A | V40.1/ 04-Jan-2024 |
| **SIII** Clinical trial exposure | N/A | V37.0 / 18-Dec-2019 |
| **SIV** Populations not studied in clinical trials | N/A | V37.0 / 18-Dec-2019 |
| **SV** Post-authorization experience | Administrative update | V41.1 / pending |
| **SVI** Additional EU requirements for the safety specification | N/A | V37.0 / 18-Dec-2019 |
| **SVII** Identified and potential risks | N/A | V40.1/ 04-Jan-2024 |
| **SVIII** Summary of the safety concerns | N/A | V40.1/ 04-Jan-2024 |
| **Part III Pharmacovigilance Plan** | Updated the status of Study MDS-012 and the Connect® MDS/AML Disease Registry from ongoing to completed. | V41.1 / pending |
| **Part IV Plan for post-authorization efficacy studies** | N/A | V37.0 / 18-Dec-2019 |
| **Part V Risk Minimisation Measures** | Administrative update to the routine risk minimisation measures in Table 5.3-1 to remove the statement that "The association between ischaemic heart disease and lenalidomide is unknown" (related to Procedure | V41.1 / pending |

## Summary of Significant Changes in this RMP

| Part/Module | Summary of Major Changes | Version # / Date of Positive Opinion for Module Update |
|---|---|---|
| | no. EMEA/H/C/000717/IB/0129/G).<br>pdated the status of Study MDS-012 and the Connect® MDS/AML Disease Registry from ongoing to completed. | |
| **Part VI Summary of the Risk Management Plan** | Updated to align with changes made in the RMP. | V41.1 / pending |
| **Part VII Annexes** | | |
| **ANNEX 2**<br>Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme | Updated the status of Study MDS-012 and the Connect® MDS/AML Disease Registry from ongoing to completed. | V41.1 / pending |
| **ANNEX 3**<br>Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan | Updated to remove protocols for completed studies. | V41.1 / pending |
| **ANNEX 4**<br>Specific adverse drug reaction follow-up forms | N/A | V38.3 / 08-Jun-2023 |
| **ANNEX 5**<br>Protocols for proposed and on-going studies in RMP Part IV | N/A | V37.0 / 18-Dec-2019 |
| **ANNEX 6**<br>Details of proposed additional risk minimisation activities | Updated to remove statements related to completed Study MDS-012 | V41.1 / pending |
| **ANNEX 7**<br>Other supporting data | N/A | V40.1/ 04-Jan-2024 |
| **ANNEX 8**<br>Summary of changes to the risk management plan over time | Updated to reflect changes in the RMP. | V41.1 / pending |

Other RMP versions under evaluation:

| RMP Version Number | Submitted on | Procedure Number |
|---|---|---|
| None | | |

## Details of the currently approved RMP:

Version number: 40.1

Approved with procedure: EMEA/H/C/000717/IB/0129/G

Date of approval: 04-Jan-2024

**EU RMP Contact Person: Priv. Doz. Dr. Stefan Kaehler, EU QPPV**

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

# 1 PART I: PRODUCT OVERVIEW

## Table 1-1: Product Details

| | |
|---|---|
| **Active substance(s) (INN or common name)** | Lenalidomide |
| **Pharmacotherapeutic group(s) (ATC Code)** | Other immunosuppressants<br>L04 AX04 |
| **Marketing Authorisation** | Bristol-Myers Squibb Pharma EEIG |
| **Medicinal products to which this RMP refers** | 1 |
| **Invented name(s) in the EEA** | Revlimid® |
| **Marketing authorization procedure** | Centralised - EMA; Procedure Number EMEA/H/C/717 |
| **Brief description of the product** | Lenalidomide [3-(4'-amino-1,3-dihydro-1-oxo-2H-isoindol-2y1)-2-6-piperidinedione] is an immunomodulatory agent and belongs to a class of drugs known as IMiD. The mechanism of action of lenalidomide includes direct cytotoxic and immunomodulatory effects. Specifically, lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including MM plasma tumour cells, FL tumour cells and those with deletions of chromosome 5), enhances T-cell- and NK cell-mediated immunity and increases the number of NK, T and NK T cells. In MDS associated with a del 5q cytogenetic abnormality, lenalidomide selectively inhibits the abnormal clone by increasing the apoptosis of del 5q cells. The combination of lenalidomide and rituximab increases antibody-dependent cellular cytotoxicity and direct tumour apoptosis in FL cells.<br>The lenalidomide mechanism of action also includes additional activities such as anti-angiogenic and pro-erythropoietic properties. Lenalidomide inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by cells expressing CD34+ haematopoietic stem cells, and inhibits production of pro inflammatory cytokines (eg, tumour necrosis factor alpha and IL-6) by monocytes.<br>Direct tumour cytotoxic effects of lenalidomide have also been shown to result from actin polymerisation and relocalisation of membrane proteins leading to cytoskeletal reorganisation, cell cycle arrest, and alterations in gene expression. The cytoskeletal effects play a key role in the restoration of a defective immune synapse in MCL. In MCL, lenalidomide treatment induced formation of F-actin and polarisation of F-actin-rich structures to the plasma membrane within minutes and induced the polarisation of antigen-presenting proteins, such as CD1c, and the increase of co-stimulatory molecules, such as CD54. |
| **Hyperlink to the Product Information** | Refer to proposed PI |

## Table 1-1: Product Details

| | |
|---|---|
| **Indication(s) in the EEA** | **Current:**<br>NDMM in TE Patients<br>Revlimid as monotherapy is indicated for the maintenance treatment of adult patients with NDMM who have undergone ASCT.<br>NDMM in TNE Patients<br>Revlimid as combination therapy with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone is indicated for the treatment of adult patients with previously untreated MM who are not eligible for transplant.<br>RRMM<br>Revlimid in combination with dexamethasone is indicated for the treatment of MM in adult patients who have received at least one prior therapy.<br>MDS<br>Revlimid as monotherapy is indicated for the treatment of adult patients with transfusion-dependent anaemia due to low- or INT-1 risk MDS associated with an isolated del 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.<br>MCL<br>Revlimid as monotherapy is indicated for the treatment of adult patients with RRMCL.<br>FL<br>Revlimid in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated FL (Grade 1 – 3a).<br>**Proposed:**<br>None. |
| **Dosage in the EEA** | **Current:**<br>For all indications described below, dosing is modified based upon clinical and laboratory findings.<br>NDMM in TE Patients Who Have Undergone ASCT<br>The recommended starting dose is lenalidomide 10 mg orally QD continuously (on Days 1 to 28 of repeated 28-day cycles) given until disease progression or intolerance. After 3 cycles of lenalidomide maintenance, the dose can be increased to 15 mg orally QD if tolerated.<br>NDMM in TNE Patients<br>Combination with dexamethasone until disease progression or intolerance in patients who are not eligible for transplant<br>The recommended starting dose of lenalidomide is 25 mg QD on Days 1 to 21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally QD on Days 1, 8, 15 and 22 of repeated 28-day cycles. Patients may continue lenalidomide and dexamethasone therapy until disease progression or intolerance. |

| Table 1-1: | Product Details |
|---|---|
| | Initial treatment: Lenalidomide in combination with bortezomib and dexamethasone<br>The recommended starting dose is lenalidomide 25 mg orally QD on Days 1 to 14 of each 21-day cycle, in combination with bortezomib and dexamethasone. Bortezomib should be administered via subcutaneous injection (1.3 mg/m$^2$ body surface area) twice weekly on Days 1, 4, 8 and 11 of each 21-day cycle. Up to eight 21-day treatment cycles (24 weeks of initial treatment) are recommended.<br>Continued treatment: Lenalidomide in combination with dexamethasone<br>Continue lenalidomide 25 mg orally QD on Days 1 to 21 of repeated 28-day cycles in combination with dexamethasone. Treatment should be continued until disease progression or unacceptable toxicity.<br>Combination with melphalan and prednisone followed by lenalidomide maintenance in patients who are not eligible for transplant<br>The recommended starting dose is lenalidomide 10 mg orally QD on Days 1 to 21 of repeated 28-day cycles for up to 9 cycles, melphalan 0.18 mg/kg orally on Days 1 to 4 of repeated 28-day cycles, and prednisone 2 mg/kg orally on Days 1 to 4 of repeated 28-day cycles. Patients who complete 9 cycles or who are unable to complete the combination therapy due to intolerance are treated with lenalidomide monotherapy as follows: 10 mg orally QD on Days 1 to 21 of repeated 28-day cycles given until disease progression.<br>RRMM<br>In combination with dexamethasone: The recommended starting dose of lenalidomide is 25 mg orally QD on Days 1 to 21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally QD on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg QD on Days 1 to 4 every 28 days for all subsequent cycles.<br>MDS<br>Del 5q MDS: The recommended starting dose of lenalidomide is 10 mg orally QD on Days 1 to 21 of repeated 28-day cycles.<br>MCL<br>The recommended starting dose of lenalidomide is 25 mg orally QD on Days 1 to 21 of repeated 28-day cycles.<br>FL<br>The recommended starting dose of lenalidomide is 20 mg, orally QD on Days 1 to 21 of repeated 28-day cycles for up to 12 cycles of treatment. The recommended starting dose of rituximab is 375 mg/m$^2$ IV every week in Cycle 1 (Days 1, 8, 15, and 22) and Day 1 of every 28-day cycle for Cycles 2 through 5.<br>**Proposed:**<br>None |
| **Pharmaceutical form (s) and strength(s)** | **Current:**<br>Hard capsules, available in 2.5, 5, 7.5, 10, 15, 20, and 25 mg.<br>**Proposed:**<br>None |
| **Is/will the product be subject to additional monitoring in the EU?** | Yes |

# 2 PART II: SAFETY SPECIFICATION

## 2.1 Module SI: Epidemiology of the Indication(s) and Target Population(s)

### *2.1.1 Module SI.1: Follicular Lymphoma*

The incidence, prevalence, mortality, and demographics of the population of patients with FL are summarised in Table 2.1.1-1.

**Table 2.1.1-1: Epidemiologic Characteristics of Follicular Lymphoma**

| **Follicular Lymphoma** | |
|---|---|
| Incidence and Prevalence | • FL is the second most common form of indolent lymphoma in the US and Europe, and accounts for about 10% to 20% of NHL.[1]<br>• Age-adjusted incidence rate of FL in the US was 3.4 per 100,000 person-years from 2011 to 2012, and estimated new cases of FL was 13,960 in 2016.[2] In the UK, the crude incidence rate from the HMRN from 2004 to 2012 was 3.23% (95% CI: 3.03-3.45) per 100,000; age-standardised (European 2013) incidence rate was 2.81 (95% CI: 2.74-2.88) per 100,000.[3]<br>• The 3-, 5-, and 10-year prevalence rates per 100,000 estimated from the UK HMRN database were 9.7 (95% CI: 8.7-10.7), 14.8 (95% CI: 13.6-16.1), and 25.2 (95% CI: 23.5-26.9) respectively.[3] |
| Demographics of the population: age, gender, racial and/or ethnic origin | • The median age at diagnosis is 60 to 65 years, and there is a slight female predominance. In the US, African-Americans have a higher incidence than Caucasians.[4]<br>• In the UK HMRN population, median age at diagnosis was 64.9 (IQR 55.8-73.3).[3] Similarly, in the EUROCARE study, the median age at diagnosis was 62 years (IQR 51 to 72) and females accounted for 53% of all 13,988 cases.[5] |
| Risk factors for the disease | • Risk factors for FL are poorly understood. Other than age, gender and ethnicity, environmental and occupational exposure to benzenes and pesticides have been implicated, but a clear association has not been established. Lifestyle factors such as smoking, alcohol use, and obesity have also been implicated in various studies, but conflicting results have not established a clear association with increased risk of FL.[4]<br>• Genetic risk factors include variants at the 6p21.32 region of the Major Histocompatibility Complex II locus, polymorphisms of the DNA repair gene XRCC3, and ultraviolet exposure in individuals with certain polymorphisms of the vitamin D receptor.[6]<br>• Risk factors for transformation to DLBCL have been controversial. Clinical risk factors include elevated β2-microglobulin levels, high international prognostic index, high FLIPI score, and advanced stage (III and IV). Some studies suggest that time and treatment approach (watch and wait as first-\line therapy versus treatment with rituximab) are possible risk factors for transformation. However, due to the variable follow-up time, inclusion criteria and treatments, findings in various studies have been inconsistent.[1] |
| Main treatment options | • Treatment options are currently recommended for patients with FL by the ESMO[7] and NCCN.[8] |

## Table 2.1.1-1: Epidemiologic Characteristics of Follicular Lymphoma

| Follicular Lymphoma | |
|---|---|
| | • In the EU, approved firstline treatment options include rituximab, interferon alpha, Y90 ibritumomab tiuxetan, bendamustine, and obinutuzumab.<br>• At relapse, the selection of salvage treatment depends on the patient's prior regimens. In symptomatic cases with low tumour burden, rituximab monotherapy may be utilized. In early relapses, (< 12 to 24 months), consideration should be given to a non-cross resistant therapy, such as CHOP followed by bendamustine. Fludararabine, platinum or alkylator based regimens are other treatment options. Rituximab may be added if the previous antibody containing regimen achieved a duration of remission > 6 to 12 months. In rituximab refractory cases, obinutuzumab may be used. In patients with short lived remissions (< 2 to 3 years), high dose chemotherapy followed by ASCT, should be considered. In late relapses, monotherapy is considered palliative treatment, eg idelalisib. Other subsequent treatment options recommended by the NCCN include idelalisib and copanilisib, as well as the following regimens: cyclophosphamide, vincristine and prednisone with obinutuzumab or rituximab, and lenalidomide with or without rituximab. For elderly patients whose treatment options may be limited by comorbidities, radioimmunotherapy (Y90 ibritumomab tiuxetan) may be an effective treatment option. Additional treatment options recommended by the NCCN for the elderly patient population include R-CHOP; R-CVP; and bendamustine and rituximab. |
| Mortality and morbidity (natural history) | • The natural history of FL is indolent in nature, with most patients developing several relapses over their lifetime. As the disease progresses, subsequent relapses can become progressively aggressive and refractory, and some cases may transform into aggressive lymphoma.[9]<br>• According to the WHO criteria, FL tumours are histologically divided into three grades: Grade 1 (< 5 centroblasts per hpf), Grade 2 (6 to 15 centroblasts/hpf) and Grade 3 (> 15 centroblasts/hpf). Grade 3 is further subdivided into Grade 3A (centrocytes still present) and Grade 3B (the follicles consist almost entirely of centroblasts). Grades 1 through 3A are considered to be indolent and incurable, whereas Grade 3B is considered an aggressive but curable disease similar to DLBCL.[4] The Ann Arbor staging system includes: Stage I (IE) – single lymph node region or extralymphatic site; Stage 2 (IIE) – multiple lymph node regions or at least one lymph node region plus a localised extralymphatic site on the same side of the diaphragm; Stage 3 (IIIE, IIIS) – multiple lymph node regions or lymphoid structures (eg, thymus, Waldeyer's ring) on both sides of the diaphragm with optional localised extranodal site (IIIE) or spleen (IIIS); Stage 4 – diffuse or disseminated extralymphatic organ involvement. The FLIPI risk factors include: number of nodal sites or long diameter of largest lymph node; age > 60 years; elevated lactate dehydrogenase or elevated β2-microglobulin; Ann Arbor Stage III to IV or bone marrow involvement; and haemoglobin < 12 g/dL.[7]<br>• The overwhelming majority of FL patients have advanced stage disease at diagnosis, whereas less than 10% of patients have Stage 1/2 disease at diagnosis. Studies have reported that 10% to 70% of patients transform to DLBCL over time, with an estimated risk of 3% per year. Common symptoms include rapid progression of lymphadenopathy, extranodal disease, B symptoms (fever, night sweats, and weight loss) and elevated serum lactate dehydrogenase.[10]<br>• 5-year relative survival rates (the ratio of observed survival in the patient group to expected survival in a comparable group of the general population assumed to be |

**Table 2.1.1-1: Epidemiologic Characteristics of Follicular Lymphoma**

| Follicular Lymphoma | |
|---|---|
| | free of the cancer of interest) for patients with FL ranged from 81% in black males to 87% in white females in the US.[2]<br>• 5-year overall and relative survival rates in the UK HMRN patients diagnosed between 2004 and 2012, and followed through to 2014 were 75.6% (95% CI: 72.4-78.5) and 86.5% (95% CI: 83.0-89.4), respectively.[3] |
| Important co-morbidities | • Comorbidities associated with FL are usually due to the advanced age of the patient. Such patients are more likely to develop cardiovascular, neurological, kidney injuries and complications as well as mucositis.[11] |

### *2.1.2 Module SI.2: Multiple Myeloma*

The incidence, prevalence, mortality, and demographics of the population of patients with MM are summarised in Table 2.1.2-1.

**Table 2.1.2-1: Epidemiologic Characteristics of Multiple Myeloma**

| Multiple Myeloma | |
|---|---|
| Incidence and Prevalence | • MM accounts for about 10% to 18% of haematologic malignancies.[12,13]<br>• The prevalence of MM varies from country to country in the EU. Overall, the estimated prevalence of MM in the EU in 2018 ranges from 1.79 to 3.61 in 10,000 persons (data on file). In Europe, 38,900 new cases of MM and 24,300 deaths due to MM were estimated in 2012. [14]<br>• Crude and age-standardised incidence rates (ASR) of MM in the population of the EU – 28 states are 6.6 and 3.0 per 100,000, respectively, based upon estimates obtained from GLOBOCAN 2012 data.[14]<br>• The 1-year, 3-year, and 5-year number of persons with MM and prevalence proportions of MM (ages 15 years and older) in the EU-28 countries were 5.8 per 100,000 persons, 13.4 per 100,000 persons and 18.0 per 100,000 persons, respectively.[14]<br>• Gains in survivorship associated with new therapies will increase the prevalence of MM. |
| Demographics of the population: age, gender, racial and/or ethnic origin | • MM incidence rates among males and females in Europe rise with increasing age intervals: 0.0 (ages 0 to 14 years), 0.2 (ages 15 to 39 years), 1.3 (ages 40 to 44 years), 2.9 (ages 45 to 49 years), 5.2 (ages 50 to 54 years), 8.1 (ages 55 to 59 years), 12.3 (ages 60 to 64 years), 17.9 (ages 65 to 69 years), 24.6 (ages 70 to 74 years), 31.0 (ages 75 years and older).[14]<br>• The ASR incidence of MM in men in the EU-28 countries is 3.7, based upon the diagnosis of MM in 18,043 men. MM accounted for 1.3% of all malignancies in men .[14]<br>• The ASR incidence of MM in women in the EU-28 countries is 2.5, based upon the diagnosis of MM in 15,599 women. MM accounts for 1.4% of all malignancies in women.[14] |

**Table 2.1.2-1: Epidemiologic Characteristics of Multiple Myeloma**

| **Multiple Myeloma** | |
|---|---|
| | • Analysing 18,824 MM registrations with ethnicity obtained by linkage to the English Hospital Episodes Statistics Database,[15] reported markedly higher incidence rates of MM in Black African men (ASR 8.6 per 100,000) and Black Caribbean men (8.3) relative to White men (3.7). Similar results were obtained with MM incidence rates in Black African women (5.8) and Black Caribbean women (5.7) were compared to White women (2.4). This pattern is similar to that reported in the US, where incidence rates of MM are markedly higher in Black men compared to White men (15.9 versus 7.8 per 100,000) and in Black women compared to White women (11.4 versus 4.6 per 100,000, respectively).[16] Racial differences in rates were also observed in the US population.[17] |
| Risk factors for the disease | • Age is the most important risk factor for MM, although race and gender are also important. While strong familial clustering of MM suggests that underlying genetic factors are important, findings from studies of lifestyle, dietary, occupational and environmental risk factors have been inconsistent.[17,18] |
| Main treatment options | • Treatment options are currently recommended for patients with NDMM by ESMO,[19] EMN ([TNE][20]; [TE][21]; [elderly][22]); and NCCN.[23]<br>In the EU, treatment options available for NDMM approved for TE NDMM include VD and VTD. Regimens approved for TNE NDMM include lenalidomide; Rd; induction therapy with lenalidomide, melphalan prednisone followed by single-agent lenalidomide (MPR+R); bortezomib; VMP; MPT; bendamustine. In addition, although not regulatory authorised, currently recommended per European clinical treatment guidelines and widely accepted as a standard of care and pending market authorisation is the combination of lenalidomide, bortezomib and dexamethasone (RVd), in the TE and TNE populations.[19,21,22]<br>• Treatment should be initiated in all patients with MM according to the updated definition proposed by the International Myeloma Working Group in 2014.[24]<br>***Newly diagnosed MM***<br>• For patients with NDMM, the choice of initial therapy is determined by the patient's age, fitness/frailty status, and the presence of comorbidities, and thus the ability to undergo auto-HSCT.[19,23,25,26,27]<br>• The current ESMO MM guidelines recommend auto-HSCT for patients < 65 years or fit patients < 70 years in good clinical condition.[19] Similarly, the EMN guideline for TE MM patients recommends auto-HSCT for non-frail patients < 65 years; auto-HSCT should still be considered for patients < 65 years who have reduced performance status or comorbidities when the benefit of transplant outweighs the risk.[21] The recently published EMN guidelines for elderly MM patients note that non-frail, elderly MM patients up to the age of 70 years (or even 75 years) without prohibitive comorbidities and adequate organ function may benefit from HDM followed by auto-ASCT.[22]<br>• In Europe, TE NDMM patients are most often treated with bortezomib-containing triplet regimens such as VTD (27%) and VCD (23%).[28] In addition, a proportion of patients still receive the bortezomib-containing doublet regimen, VD (10%). |

**Table 2.1.2-1: Epidemiologic Characteristics of Multiple Myeloma**

| **Multiple Myeloma** | |
|---|---|
| | • For non-transplant candidates with NDMM, the choice of treatment is more heterogeneous, with VMP (24%), VD (15%), and Rd (10%) the most commonly used regimens.[28]<br>***Relapsed/Refractory MM***<br>• The choice of therapy in the relapse setting depends on several parameters such as age, performance status, comorbidities, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options, the interval since the last therapy and the type of relapse (ie, clinical versus biochemical relapse; in the case of biochemical relapse, treatment can be delayed).[29]<br>Major treatment regimens in MM for R/R disease include: carfilzomib, lenalidomide and dexamethasone; bortezomib, dexamethasone and panobinostat; carfilzomib and dexamethasone; lenalidomide, dexamethasone and elotuzumab; lenalidomide, dexamethasone and ixazomib; bortezomib, dexamethasone and daratumumab; lenalidomide, dexamethasone and daratumumab.[19]<br>• In young patients (< 65 years of age), a second ASCT may be considered, provided the patient responded well to the previous ASCT and had a PFS of more than 24 months.[30]<br>In the relapse setting, allogenic stem cell transplant should only be carried out in the context of a clinical trial. In RRMM, the EMA has approved lenalidomide in combination with dexamethasone[31,32] and bortezomib either alone as a single agent [33] or in combination with pegylated doxorubicin. [34] Nevertheless, bortezomib is mostly used in combination with dexamethasone in the relapse setting. Thalidomide and bendamustine are effective drugs, often used, but not approved.[35] Triplet combinations have proved effective in Phase 2 trials, but only one single randomised trial has shown the superiority of VTD over TD for PFS in patients relapsing following ASCT.[36]<br>• Thalidomide is also used in multiple combinations with clinical benefit in patients with relapsed and/or refractory myeloma.[37]<br>• When possible, patients should be offered participation in clinical trials. Pomalidomide,[35] the third-in-class IMiD, and carfilzomib,[35] the second-in-class proteasome inhibitor, both are approved in the US and the EU.<br>• Other drugs or classes of drugs such as histone-deacetylase inhibitors, monoclonal antibodies and other CAR-T therapy are currently under development. |
| Mortality and morbidity (natural history) | • Crude and age-standardised mortality rates of MM in the EU-28 population are 4.0 and 1.6 per 100,000, respectively, based upon estimates obtained from GLOBOCAN 2012.[14] Within the EU-28 population, 20,462 men and women died with MM in 2012.[14] The cumulative mortality risk of MM (ages 0 to 74 years) is 0.17%.<br>• According to GLOBOCAN 2012 data, MM accounts for 1.2% of all deaths among persons with invasive malignancy in the European population.[14] |

**Table 2.1.2-1: Epidemiologic Characteristics of Multiple Myeloma**

| **Multiple Myeloma** | |
|---|---|
| | • Between 1989 and 2009, 1206 patients with MM were identified through the Modena Cancer Registry,[38] corresponding to periods of conventional therapy (1988 to 1996), high dose melphalan (HDM) and ASCT (1997 to 2005) and novel agents (2006 to 2009). Relative survival and OS improved over the years, with little change noted for patients aged ≥ 75 years. The survival of MM patients aged < 65 years and, in particular, 65 to 74 years improved over time, especially after 2006.<br>• The most recent data from the EBMT registry (2006 to 2010) reported 5 year OS in MM transplant recipients as follows: 61.5% (< 40 years of age), 62.8% (40 to 49 years). 59.9% (50 to 59 years), 58.8% (60 to 64 years), 53.3% (65 to 69 years), 49.7% (≥ 70 years).[39]<br>• In a retrospective analysis of MM patients who received HSCT, median OS was 79.5 months in those < 60 years of age and 63.4 months in those ≥ 60 years of age.[40] |
| Important co-morbidities | • Renal impairment.[41,42,43]<br>• Peripheral neuropathy.[44,45,46]<br>• Thromboembolic events.[47,48,49,50]<br>• Anaemia, leucopenia and infection.[43,51,52]<br>• Secondary primary malignancies.[53,54,55,56,57,58]<br>• GvHD.[59,60]<br>• Bone diseases.[61,62,63]<br>• Gastrointestinal haemorrhage.[64,65] |

### *2.1.3 Module SI.3: Myelodysplastic Syndrome*

The incidence, prevalence, mortality, and demographics of the population of patients with MDS are summarised in Table 2.1.3-1.

**Table 2.1.3-1: Epidemiologic Characteristics of Myelodysplastic Syndrome**

| **Myelodysplastic Syndrome** | |
|---|---|
| Incidence and Prevalence | • Among 216 patients newly diagnosed with MDS (WHO subtypes) during the interval 1996 to 2005 and identified on the Düsseldorf Registry, the overall crude incidence rate (per 100,000 personyears-) was 3.78 (95% CI: 3.314.32). The overall -agestandardised incidence was 2.51 per 100,000 -person-years.[66]<br>• In an analysis of data from the North American Association of Central Cancer Registries (encompassing 82% of the US population), the average annual ageadjusted incidence rate for MDS in 2001 to 2003 was 3.3 per -100,000.[67] MDS incidence rates were highest among whites and nonHispanics-.<br>• There are no prevalence data for MDS from the US and EU cancer registry databases. Using data from the Düsseldorf MDS Registry, in which the point |

**Table 2.1.3-1: Epidemiologic Characteristics of Myelodysplastic Syndrome**

| Myelodysplastic Syndrome | |
|---|---|
| | prevalence of MDS was assessed, an age-standardised prevalence of approximately 7 per 100,000 persons was reported. Given the similar incidence and no known differences in disease duration or treatment options between Western European countries, the prevalence of MDS is expected to be similar throughout the EU.[66] |
| Demographics of the population: age, gender, racial and/or ethnic origin | • The overall ASR was 4.30 and 3.32 per 100,000 personyears- for men and women, respectively, in the Düsseldorf MDS Registry. The incidence rate ratio comparing men to women was 1.78 .[66] However, the incidence of MDS with the del 5q cytogenetic abnormality is greater in women than men. On the Düsseldorf MDS Registry in 2003, 2 (7%) female patients had the del 5q cytogenetic abnormality compared with no male patients.[66]<br>• Using data from the Düsseldorf MDS Registry, in 2003 the median age of prevalent male and female patients was 69 and 78 years, respectively.[66]<br>• In an analysis of data from the North American Association of Central Cancer Registries, age adjusted incidence of MDS was significantly higher among males and a sharp increase was observed with age; rates were 5 times greater among those aged 80 years and older (35.5 per 100,000) compared with those aged 60 to 69 years (7.1 per 100,000).[67] |
| Risk factors for the disease | • Although the aetiology of MDS remains unclear, risk factors for the disease include gender, age and exposure to ionising radiation, chemicals, drugs or other environmental agents.[68] |
| Main treatment options | • The only potentially curative approach that currently exists for treating MDS patients is allogeneic HSCT.[69] This approach is typically only employed in younger patients with higher-risk disease because of morbidity/mortality and the lack of a suitable donor in older patients; hence, allogeneic HSCT is only a potential solution in a small subset (approximately 5%) of MDS patients.[68,69]<br>• Other than transfusion support and iron chelation, the treatment options for low- or INT-1-risk MDS, include ESAs (EPO or darbepoetin-α) alone or in combination with G-CSF; immunosuppressive therapies such as antithymocyte globulin or cyclosporin A; and lenalidomide.[69,70,71] ESAs are unlikely to be effective for patients with transfusion-dependent anaemia due to low- or INT-1 risk del 5q MDS as (1) these patients commonly have increased EPO levels, and ESAs have less effect in patients who already have adequate or high levels of EPO, (2) ESAs have been found to be less effective in patients who have a significant transfusion requirement, and (3) ESAs may be less effective in patients with del 5q MDS. Sanna and colleagues have reported that patients with del 5q MDS may have higher endogenous EPO levels and reduced sensitivity to treatment with EPO.[72] Patients with higher endogenous EPO levels and more substantial transfusion requirements have a relatively low likelihood of responding to treatment with EPO.[73,74,75] |
| Mortality and morbidity (natural history) | • In the Multicentre Registry study, the median time of survival from diagnosis was 75 months (range, 1.7 to 350). The 2- and 5year survival probabilities were 86% and 61%, respectively. -Transfusiondependent patients had a median survival of 44 months compared to 97 months for -transfusionindependent -patients.[76] |

**Table 2.1.3-1: Epidemiologic Characteristics of Myelodysplastic Syndrome**

| Myelodysplastic Syndrome | |
|---|---|
| | • Among MDS patients reported to the SEER 17 regions database during 2001to 2003, the 3year observed survival was 35%. Age and sex were significantly associated with survival, whereas race was not. Younger patients demonstrated better survival, and men with MDS were 25% more likely to die than -women.[77]<br>• Progression to AML occurs at a variable rate depending on the presence of adverse prognostic risk factors. In the Multicentre Registry study, the cumulative AML progression risk was 4.7% after 2 years of diagnosis and 14.7% (competing risk method). In the first 2 years following diagnosis, the probability of developing AML was 11% for patients presenting with transfusion dependency compared with 2% among patients without transfusion dependency.[76] |
| Important co-morbidities | • Anaemia.[78,79]<br>• Neutropenia and Infections.[79,80]<br>• Thrombocytopenia and Bleeding.[79,80]<br>• Other Neoplasms, Including Progression to AML.[81] |

### *2.1.4 Module SI.4: Mantle Cell Lymphoma*

The incidence, mortality, and demographics of the population of patients with MCL are summarised in Table 2.1.4-1.

**Table 2.1.4-1: Epidemiologic Characteristics of Mantle Cell Lymphoma**

| Mantle Cell Lymphoma | |
|---|---|
| Incidence and Prevalence | • The HAEMACARE project has identified 1012 cases of MCL, which were diagnosed in 2000 to 2002 and archived in 44 European cancer registries.[82] Based on these cases, the crude incidence of MCL is 0.45 per 100,000 (95% CI: 0.42-0.48). The estimated prevalence of MCL is 1 per 25,000.[83] |
| Demographics of the population: age, gender, racial and/or ethnic origin | • According to the HAEMACARE project, the incidence of MCL in Europe is 0.64 (95% CI: 0.60-0.69) in males and 0.27 (95% CI: 0.24–0.30) in females. Typically, patients with MCL are predominantly male, with a median age of > 60 years and present with advanced stage disease at diagnosis, as well as extranodal involvement.[84,85,86] |
| Risk factors for the disease | • Given the rarity of MCL, large-scale epidemiologic studies of risk factors for NHL frequently do not include sufficient numbers of MCL patients to adequately assess risk factors for this disease. Little evidence exists to link MCL with environmental or occupational exposures, and lifestyle factors (eg, cigarette smoking, alcohol intake, body mass index) have not been implicated in the aetiology of MCL.<br>• Unlike other lymphomas where immune suppression and exposure to specific infectious agents increase lymphoma risk, evidence for association between specific infectious agents and MCL is scarce. However, some studies have shown that the Ig gene repertoire in MCL is restricted and features precisely targeted, and probably functionally driven, somatic hypermutation. |

**Table 2.1.4-1: Epidemiologic Characteristics of Mantle Cell Lymphoma**

| **Mantle Cell Lymphoma** | |
|---|---|
| | • Family history of haematopoietic malignancies has been linked with a two-fold increased risk of MCL. In the context of genetic susceptibility to NHL, there is little evidence of highly penetrant genetic traits in association with the disease. Instead, candidate gene studies focusing on low-penetrance polymorphic variants in the risk of NHL and its subtypes have consistently revealed associations with variants in genes encoding the proinflammatory cytokines tumour necrosis factor, lymphotoxin-alpha and interleukin-10.[87] |
| Main treatment options | • In the front-line setting, MCL is a chemosensitive disease, and (immuno-) chemotherapy regimens (particularly rituximab, cyclophosphamide, doxorubicin, vincristine, predniso(lo)ne [R-CHOP]) can achieve high response rates. However, almost all patients will eventually relapse.<br>• Treatment strategies generally depend on the individual risk profile and the patient's comorbidities, as indicated in the recommendations of the European MCL Network and ESMO.[88,89]<br>• Subsequent to the completion of enrollment and analysis of data in Study MCL002, updated Clinical Practice Guidelines for diagnosis, treatment, and follow-up of newly diagnosed and relapsed MCL were approved by the ESMO Guidelines Working Group in Aug -2014.[90]<br>• According to the European MCL Network Guidelines[88] and the ESMO recommendations,[89] there is no single standard treatment for patients with relapsed disease.[91] In first relapse in younger fit patients (< 65 years of age, without severe comorbidities), the treatment goal is to achieve the best possible remission as a bridge to stem cell transplantation, whereas in transplant-ineligible patients, the objective is to induce long-lasting remissions.<br>• The treatment guidelines of the European MCL Network,[88] ESMO,[89] Spain,[92] and the UK,[91] recommend that patients with multiple relapses and elderly frail patients should be treated with single-agent therapy. The European MCL Network Guidelines and the current ESMO therapeutic recommendations[89] recommend treatment with temsirolimus, lenalidomide, bortezomib, and ibrutinib preferably in combination (excluding elderly, frail patients). Other single agents such as fludarabine[93,94] gemcitabine,[95] rituximab,[96] cytarabine,[97] or chlorambucil[98,99] can also be considered. These agents are typically used sequentially. If a patient relapses or is refractory to one agent, then that patient is treated with another agent from this list of available agents.<br>• Temsirolimus is approved for the treatment of RRMCL in the EU.[100] In Feb 2012, pixantrone received a conditional Marketing Authorisation in the EU for the treatment of adults with multiple relapsed and/or refractory aggressive NHL, but is not included in any of the MCL treatment guidelines. Ibrutinib was authorised in the EU for MCL in Oct 2014, indicated for the treatment of adult patients with RRMCL.<br>• In the US, ibrutinib is approved for MCL patients who have received at least one prior therapy. This was an accelerated approval.<br>• The treatment guidelines also recommend bortezomib in patients with multiple relapses.[89,91] This agent is approved in the US and several other countries for the treatment of MCL. In Jan 2015, bortezomib was authorised in combination with |

**Table 2.1.4-1: Epidemiologic Characteristics of Mantle Cell Lymphoma**

| Mantle Cell Lymphoma | |
|---|---|
| | rituximab, cyclophosphamide, doxorubicin and prednisone, for the treatment of adult patients with previously untreated MCL who are unsuitable for HSCT.<br>• In the EU, lenalidomide is currently available for MCL via clinical trials. Lenalidomide single agent treatment is included in the treatment guidelines for MCL,[88,89,92] which is in line with the indication. |
| ortality and morbidity (natural history) | • 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 patients with MCL is only 3 to 5 years.[101,102] Following the initial relapse, the median OS decreases to 1 to 2 years.[103]<br>• Based on a 2004 to 2012 analysis of the UK's population-based HMRN, a registry with 5796 lymphoma patients and 247 MCL patients, the 5-year OS was 25% and relative survival was 31.4%.[3]<br>• Among 150 patients with advanced-stage nonblastoid MCL identified either in the KLSG (1975 to 1986) or in the GLSG (1996 to 2004), median OS has almost doubled over the past 30 years. Five-year survival rates were 22% in the KLSG and 47% in the GLSG. Poor performance status, elevated serum lactate dehydrogenase and higher age negatively influenced mortality. |
| Important co-morbidities | • Second Primary Malignancies.[53,104,105,106]<br>• Thromboembolic Events.[107,108,109] |

## 2.2 Module SII: Nonclinical Part of the Safety Specification

Full details of the nonclinical safety data for lenalidomide are presented in the Nonclinical Overview ( MAA, Module 2, Section 2.4 Nonclinical Overview).

A summary of the nonclinical findings and their relevance to human usage is outlined in Table 2.2-1.

**Table 2.2-1: Nonclinical Risks and Relevance to Human use**

| Key Safety Findings (from Nonclinical Studies) | Relevance to human usage |
|---|---|
| **Toxicity Including:**<br>• Single and Repeat-dose Toxicity<br>Lenalidomide has a low potential for acute toxicity; minimum lethal doses after single-dose oral administration were > 2000 mg/kg in rodents.<br>Chronic administration of lenalidomide to rats resulted in kidney pelvis mineralisation, most notably in females. The changes were minor and did not affect renal function, and were not considered to be adverse.<br>In the rat, reports of crystals in the urine and kidneys are likely to be due to drug or drug metabolites that have crystallised during renal elimination due to the | The primary toxicities observed in the nonclinical studies following repeated oral administrations of lenalidomide were associated with the haematopoietic/lymphoreticular systems and the kidneys.<br>Dose adjustments to be made in case of haematological toxicity are described in Section 4.2 of the SmPC. Monitoring of complete blood counts is included in Section 4.4 and haematological events are described in Section 4.8 of the SmPC. |

**Table 2.2-1: Nonclinical Risks and Relevance to Human use**

| Key Safety Findings (from Nonclinical Studies) | Relevance to human usage |
|---|---|
| high doses used. The histological changes in the kidney were reversible, and therefore appear to be of limited clinical relevance. NOAEL in rats was determined to be 300 mg/kg/day.<br>In monkeys, repeated oral administration of lenalidomide resulted in a dose-dependent decrease in neutrophil count, an effect that is related to the pharmacodynamic effect of the drug. Repeated oral administration of 4 and 6 mg/kg/day to monkeys produced mortality and significant toxicity (marked weight loss, reduced red and white blood cell and platelet counts, multiple organ haemorrhage, gastrointestinal tract inflammation, lymphoid, and bone marrow atrophy). Monkeys dosed with 1 and 2 mg/kg/day for up to 52 weeks exhibited changes in bone marrow cellularity, a slight decrease in myeloid: erythroid cell ratio, and thymic atrophy. Mild suppression of the white blood cell count was observed at 1 mg/kg/day. The NOAEL in monkeys was 1 mg/kg, based on the minimal severity, lack of associated toxicologically significant haematologic effect, and expected recovery of thymic atrophy at this dose as demonstrated by a recovery at higher doses.[a] | Dose adjustments to be made in patients with impaired renal function are described in Section 4.2 of the SmPC. Careful dose selection and monitoring of renal function in patients with renal impairment is included in Section 4.4 of the SmPC.<br>Renal and urinary disorders are described in Section 4.8 of the SmPC. |
| • Reproductive and Developmental Toxicity<br>Reproductive and developmental toxicity studies with lenalidomide have been conducted in rats, rabbits and monkeys.<br>Embryofoetal developmental toxicity studies were conducted in rats, rabbits, and monkeys. In monkeys, malformations occurred in the foetuses at 0.5 mg/kg, the lowest lenalidomide dose tested. Exposure in monkeys at this dose (AUC of 378 ng•hr/mL) was 0.17 to 0.41 times the exposure from a human clinical dose of 25 mg/day (AUC of 2262 ng•hr/mL) and 10 mg/day (933 ng•hr/mL), respectively.<br>Malformations ranged from stiff and slightly malrotated hindlimbs at 0.5 mg/kg/day to severe external malformations, such as bent, shortened, malformed, malrotated and/or partially absent parts of extremities, oligo- and/or polydactyly and/or non patent anus at 4 mg/kg/day. Limb and digital defects correlated with skeletal findings at ≥ 1 mg/kg/day. These malformations were similar to those seen with the positive control thalidomide, a known human teratogen.<br>In rats, oral doses up to 500 mg/kg lenalidomide did not affect embryofoetal development. In the definitive embryofoetal development study in rabbits conducted at doses up to 20 mg/kg/day, maternal toxicity was seen at ≥ 10 mg/kg/day, and a dose of 20 mg/kg/day | Lenalidomide is structurally related to thalidomide, a known human teratogenic active substance that causes severe life-threatening birth defects (Sections 4.4, 4.6 and 4.8). In monkeys, lenalidomide induced malformations similar to those described with thalidomide (SmPC, Sections 4.4, 4.6, 4.8 and 5.3).<br>If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected (SmPC, Sections 4.4, 4.6 and 4.8).<br>For details, see Section 2.7 and Section 3. |

## Table 2.2-1: Nonclinical Risks and Relevance to Human use

| Key Safety Findings (from Nonclinical Studies) | Relevance to human usage |
|---|---|
| resulted in a single abortion. At ≥ 10 mg/kg/day, developmental toxicity consisted of increased postimplantation loss (early and late resorptions and intrauterine deaths), reduced foetal body weights, increased incidence of gross external findings in foetuses associated with morbidity, and soft tissue and skeletal variations. The NOAEL for maternal and developmental toxicity was 3 mg/kg/day. Exposure of rabbits at this dose (AUC of 2836 ng•hr/mL) was 1.3 to 3 times the exposure from a human clinical doses of 25 mg/day (AUC of 2262 ng•hr/mL) or 10 mg/day (933 ng•hr/mL), respectively.<br>Studies in rats administered lenalidomide at doses of up to 500 mg/kg/day indicated that it has no effects on male or female reproductive performance or fertility, or pre- and postnatal reproductive toxicity. | |
| • Nephrotoxicity<br>Included as part of single and repeat-dose toxicity findings above. | As above. |
| • Genotoxicity/Carcinogenicity<br>Carcinogenicity studies have not been conducted with lenalidomide as its intended use is in the treatment of advanced cancer. In rats administered lenalidomide orally for 26 weeks (up to 300 mg/kg/day), no hyperplastic or proliferative lesions were identified at the dosing phase or the recovery phase necropsies (4 weeks after last dose). In monkeys administered lenalidomide orally for 52 weeks (up to 2 mg/kg/day), no neoplastic or pre-neoplastic changes were identified at the dosing phase necropsy. In vitro and in vivo genotoxicity studies indicated no mutagenic or clastogenic potential for lenalidomide. In addition, lenalidomide spiked with up to 5% of the predominant impurity RC4 and was not genotoxic in a reverse mutation (Ames) test. | Many antineoplastic agents are mutagenic and/or test positive in rodent carcinogenicity assays. The negative results achieved in genotoxicity studies of lenalidomide alone or spiked with the impurity RC4 suggest that a risk of mutagenic or clastogenic potential is absent and provides some assurance that lenalidomide is not carcinogenic. In addition, there were no observations of pre-neoplastic lesions in the chronic rat and monkey studies. |
| **General Safety Pharmacology**<br>• Evaluation of the safety pharmacology of lenalidomide showed no behavioural or physiological changes in rats treated with up to 2000 mg/kg lenalidomide compared to control animals. | None |
| • Cardiovascular<br>• The potential for cardiovascular effects was evaluated in vitro and in vivo. Lenalidomide has a low potential to block the human Ether-à-go-go-Related Gene channel. The in vivo effects were evaluated in anaesthetised dogs following IV administration of lenalidomide at doses of 2, 10, and 20 mg/kg. No biologically | Cardiac failure and cardiac arrhythmia are described in Section 4.8 of the SmPC. Ischmeic heart disease is described in Sections 4.4 and 4.8 of the SmPC. |

## Table 2.2-1: Nonclinical Risks and Relevance to Human use

| Key Safety Findings (from Nonclinical Studies) | Relevance to human usage |
|---|---|
| important changes were observed in any of the haemodynamic parameters measured. | |
| • Nervous System<br>Lenalidomide did not induce behavioural, autonomic, or motor activity changes when administered orally to rats at doses up to 2000 mg/kg. | Effects on the nervous system are described in Section 4.8 of the SmPC. |
| **Mechanisms for Drug Interactions**<br>Lenalidomide is not a substrate of human cytochrome P450 (CYP) enzymes, and hence is not likely to be subject to drug-drug interactions when co-administered with CYP inhibitors or inducers. Lenalidomide did not significantly inhibit CYP1A2, 2C9, 2C19, 2D6, 2E1, or 3A4 isoforms and was not a CYP inducer in vitro. Hence, lenalidomide is not likely to precipitate clinically relevant drug-drug interactions when co-administered with CYP substrates. Furthermore, at concentrations up to 150 µM, lenalidomide is not an inhibitor of the BSEP, human MRP2, human OAT1 and OAT3, OATP1B1 and OATP1B3, and OCT2. Lenalidomide is not a substrate of MRP1, MRP2, or MRP3 efflux transporters, or OAT1, OAT3, OATP1B1 (OATP2), OCT1, OCT2, OCTN1, OCTN2, or MATE1. Lenalidomide is a weak substrate but not an inhibitor of P-gp. Lenalidomide is not a substrate or inhibitor (at concentrations up to 150 µM) of BCRP. Therefore, clinically relevant drug-drug interactions are unlikely between lenalidomide and substrates or inhibitors of these transporters.<br>• Lenalidomide is not an inhibitor of bilirubin glucuronide formation mediated by UGT1A1 genotypes UGT1A1*1/*1, UGT1A1*1/*28, and UGT1A1*28/*28. Therefore, lenalidomide is not anticipated to cause any drug-drug interactions due to UGT1A1 inhibition. | As lenalidomide is not metabolised by CYP enzymes, administration with medicinal products that inhibit CYP enzymes is not likely to result in metabolic medicinal product interactions in man (SmPC, Section 5.2).<br>Furthermore, clinically relevant drug-drug interactions are unlikely between lenalidomide and substrates/inhibitors of the following transporters: BSEP; MRP1, MRP2 and MRP3 efflux transporters; human OAT1, OAT3, OATP1B1 (OATP2), OATP1B3, OCT1, OCT2, OCTN1, OCTN2 and MATE1; P-gp, and BCRP.<br>Lenalidomide is not anticipated to cause any drug-drug interactions due to UGT1A1 inhibition. |
| **Other Toxicity-related Information or Data**<br>• Pre-clinical Pharmacokinetics<br>In rats and monkeys, lenalidomide pharmacokinetics and disposition are characterised by moderate clearance, rapid absorption, and good oral bioavailability, with excretion of unchanged parent as the major clearance pathway. Protein-protein binding was low (19% to 29% bound) in all species. In rhesus monkeys, lenalidomide distributed into CSF with a CSF-to-plasma exposure ratio of 0.11. 14C-Lenalidomide derived radioactivity distributes widely into rat tissues, except brain. Distribution of radioactivity to the foetus is limited after oral administration to pregnant rats. | Lenalidomide is eliminated predominantly through urinary excretion and patients with renal impairment may require dose adjustment. Low lenalidomide protein binding suggests limited potential for pharmacokinetic variability in patients with abnormal plasma protein concentrations. Lenalidomide distribution into rhesus monkey CSF suggests the potential for lenalidomide to cross the human blood brain barrier.<br>Despite limited distribution of 14C-lenalidomide into the foetus of pregnant rats, lenalidomide is structurally related to thalidomide, a known human teratogenic active substance that causes severe life-threatening birth defects (Sections 4.4, 4.6 and 4.8). In monkeys, lenalidomide |

**Table 2.2-1: Nonclinical Risks and Relevance to Human use**

| Key Safety Findings (from Nonclinical Studies) | Relevance to human usage |
|---|---|
| Lenalidomide was excreted largely as unchanged drug and hydrolysis of the glutarimide ring in both rats and monkeys. In these species, the major route of elimination of radioactivity following IV administration was renal. Following oral administration to rats and monkeys, radioactivity was eliminated in almost equal proportions in urine and faeces. | induced malformations similar to those described with thalidomide (SmPC, Sections 4.4, 4.6, 4.8 and 5.3). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected (SmPC, Section 4.4, 4.6 and 4.8). |

[a] The NOAEL previously provided was incorrect due to typographical error and has been corrected.

## 2.3 Module SIII: Clinical Trial Exposure

### *2.3.1 Module SIII.1: Clinical Study Information*

The data presented in this section represent the main studies supporting the FL, TE NDMM, TNE NDMM, RRMM, del 5q MDS and MCL indications. Data from Studies MDS-001, MDS-002 and MDS-007 are not included in this RMP. MDS-001 and MDS-002 represent a broader indication which does not reflect the target population in detail and would therefore dilute safety signals. These clinical trials are not related to the approved indication (which would be in accordance with the GVP as only proposed and approved indications should be pooled and not studies in different indications under development ie, paediatrics). MDS-007 represents the approved indication, but represents solely the Japanese population. This study was considered for the overall safety of lenalidomide and no differences in risk due to ethnic origin have been identified.

In addition, data from Study CC-5013-MCL-003 have not been presented in this RMP. Study MCL-003 was a Phase 3, multi-centre, randomised, double-blind, placebo-controlled, first-line maintenance study of lenalidomide in patients with newly diagnosed mantle cell lymphoma (the "RENEW" trial), that was stopped prematurely for reasons other than safety concerns after only nine patients had been enrolled (four in the lenalidomide arm, five in the placebo arm).

Data published subsequent to the time of the study planning suggested that the duration of remission and OS time after a response to R-CHOP were significantly shorter among patients who were not assigned to any maintenance therapy, as compared with those who received maintenance therapy (rituximab or interferon alpha).[110] In light of these findings, the MCL-003 study design, which included a placebo control arm, was no longer considered clinically appropriate.

The study population in Study MCL-003 was different to those in Studies MCL-002 and MCL-001 as it consisted of newly diagnosed MCL patients achieving a complete response or partial response after first-line induction chemoimmunotherapy (anthracycline based, fludarabine based, or rituximab-bendamustine combination). In addition, the starting dose of lenalidomide maintenance treatment in Study MCL-003 was 15 mg compared to a lenalidomide starting dose of 25 mg in the other studies. Finally, all four patients in the lenalidomide arm had short treatment durations.

Details of the main FL, TE NDMM, TNE NDMM, RRMM, del 5q MDS and MCL clinical studies included in this RMP are listed below.

**FL:**

- **CC-5013-NHL-007:** Phase 3, double-blind, randomised study to compare the efficacy and safety of rituximab plus lenalidomide versus rituximab plus placebo for relapsed/refractory indolent lymphoma (follicular lymphoma and marginal zone lymphoma) (AUGMENT).
- **CC-5013-NHL-008:** Phase 3, randomised study of lenalidomide plus rituximab followed by lenalidomide single agent maintenance versus rituximab maintenance for relapsed/refractory follicular, marginal zone or mantle cell lymphoma (MAGNIFY).

**TE NDMM (post-autologous stem cell transplant):**

- **Cancer and Leukaemia Group B (CALGB) 100104:** Phase 3, multi-centre, randomised, double-blind, placebo-controlled, 2-arm study to evaluate the efficacy and safety of continuous lenalidomide maintenance following single ASCT in patients ≥ 18 to 70 years of age with NDMM.
- **Intergroupe Francophone du Myélome (IFM) 2005-02:** Phase 3, multi-centre, randomised, double-blind, placebo-controlled, 2-arm study to evaluate the efficacy and safety of continuous lenalidomide maintenance therapy in patients < 65 years of age with MM after induction therapy followed by a single ASCT or tandem ASCT.

In addition, data from GIMEMA are included for the risks relating to SPM only (Section 2.7) and are only included in the total exposure data in this module.

**TNE NDMM:**

- **SWOG S0777:** A randomised Phase 3 trial of lenalidomide, dexamethasone versus bortezomib, lenalidomide and dexamethasone for induction, in patients with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant.
- **CC-5013-MM-020:** Phase 3, multi-centre, randomised, open label, 3-arm efficacy and safety study of lenalidomide and low-dose dexamethasone compared to MPT in patients with NDMM, who were either 65 years of age or older or not candidates for stem cell transplantation.
- **CC-5013-MM-015:** Phase 3, multi-centre, randomised, double-blind, placebo-controlled, 3-arm parallel group, safety and efficacy study of lenalidomide in combination with melphalan and prednisone in NDMM patients who are not stem cell transplant candidates.

**RRMM:**

- **CC-5013-MM-009:** Phase 3, multi-centre, randomised, parallel-group, double-blind, placebo-controlled, safety and efficacy study of lenalidomide plus dexamethasone.
- **CC-5013-MM-010:** Phase 3, multi-centre, randomised parallel group, double-blind, placebo-controlled, safety and efficacy study of lenalidomide plus dexamethasone.

**Del 5q MDS:**

- **CC-5013-MDS-003:** Phase 2, multi-centre, single arm, open label, safety and efficacy study (including extension Study CC-5013-MDS-003E/009, which was intended to provide further long-term outcomes for OS/vital status and the possible occurrence of progression to AML).
- **CC-5013-MDS-004:** Phase 3, multi-centre, randomised, double-blind, placebo-controlled, 3-arm safety and efficacy study.

**MCL:**

- **CC-5013-MCL-002:** A Phase 2, multi-centre, randomised, open-label study to determine the efficacy of lenalidomide versus Investigator's choice in patients with relapsed or refractory mantle cell lymphoma (the "SPRINT" trial).
- **CC-5013-MCL-001:** A Phase 2, multi-centre, 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 (the "EMERGE" trial).
- **CC-5013-NHL-002:** A Phase 2, multi-centre, single-arm, open-label study to evaluate the safety and efficacy of single-agent lenalidomide in patients with relapsed or refractory aggressive NHL.
- **CC-5013-NHL-003:** A Phase 2, multi-centre, single-arm, open-label study to evaluate the safety and efficacy of single-agent lenalidomide in patients with relapsed or refractory aggressive NHL.

### *2.3.2 Module SIII.2: Clinical Studies in Follicular Lymphoma*

The safety data presented are primarily based on data from 2 BMS-sponsored studies, CC-5013-NHL-007 (NHL-007) and CC-5013-NHL-008 (NHL-008).

In Study NHL-007, patients were aged ≥ 18 with histologically confirmed MZL or FL previously treated with at least one prior systemic chemotherapy, immunotherapy or chemoimmunotherapy and had received at least 2 previous doses of rituximab. Only data from patients with FL are included in this RMP. Patients had documented relapsed, refractory or progressive disease after treatment with systemic therapy and were not rituximab-refractory. Patients were randomised (1:1 ratio) to treatment with either:

- lenalidomide 20 mg QD orally (Days 1 to 21 in each 28 day cycle) for up to 12 cycles plus rituximab 375 mg/m$^2$ IV (Days 1, 8, 15 and 22 in Cycle 1 and Day 1 in Cycles 2 to 5 of each 28-day cycle) or,
- matching placebo (QD) plus rituximab 375 mg/m$^2$ IV (Days 1, 8, 15 and 22 in Cycle 1 and Day 1 in Cycles 2 to 5 of each 28-day cycle).

Study NHL-008 recruited patients aged ≥ 18 with histologically confirmed FL Grades 1 to 3b or transformed FL, MZL, or MCL who had received ≥ 1 prior therapy and had Stage I to IV, measurable disease. Only data from patients with FL are included in this RMP. Patients had documented relapsed, refractory or progressive disease after last treatment with systemic therapy. Patients received induction therapy (ie, initial treatment period) of lenalidomide 20 mg QD orally (Days 1 to 21 in each 28-day cycle) for 12 cycles plus IV rituximab 375 mg/m$^2$, Days 1, 8, 15, and 22 of Cycle 1 and Day 1 of Cycles 3, 5, 7, 9, and 11 (28-day cycles). Patients were then randomised (1:1 ratio) to maintenance (ie, extended treatment) lenalidomide 10 mg/day on Days 1 to 21 of

each 28-day cycle, for Cycles 13 to 30, plus rituximab 375 mg/m$^2$ IV on Day 1 of Cycles 13, 15, 17, 19, 21, 23, 25, 27, and 29, or rituximab 375 mg/m$^2$ alone (same schedule). Safety data included for NHL-008 were based on the initial treatment period (induction phase) in patients with FL Grade 1 to 3a, only.

The demographics and baseline characteristics of FL patients in Studies NHL-007 and NHL-008 are presented in Table 2.3.2-1, while duration of exposure to study medication is presented in Table 2.3.2-2.

In both studies, approximately half of the safety population were younger than 65 years of age, the majority of patients were white and non-Hispanic and the proportion of males to females was balanced in both studies. The majority of FL patients in both studies had a histological diagnosis of Grade 1 to 2. In Study NHL-007, a higher proportion of patients had an Ann Arbor Stage I or II at diagnosis compared with Study NHL-008, whereas a higher proportion of patients in Study NHL-008 had an Ann Arbor Stage IV. In both studies, the majority of patients did not have elevated lactate dehydrogenase and had no B symptoms at baseline.

The median treatment duration was longer in Study NHL-007 (11.0 and 11.2 months in the rituximab plus placebo and lenalidomide plus rituximab arms, respectively) compared to Study NHL-008 (7.4 months). Consistent with this trend, the median number of treatment cycles was higher in Study NHL-007 (12.0 in both arms) compared with Study NHL-008 (7.0), and the majority of patients in both the lenalidomide and placebo arms of Study NHL-007 received 12 cycles (72.6% and 60.1%, respectively) compared with around a third of patients in Study NHL-008 (29.4%). Per the data lock point for this FL RMP, data from Study NHL-008 are based on an ongoing actively enrolling study. Hence, the proportion of the patients who completed all 12 cycles of lenalidomide plus rituximab is less than in Study NHL-007.

Overall, no clinically meaningful differences in demographic and disease-related characteristics were observed, and the treatment arms in NHL-007 were generally balanced with regard to the demographic and disease-related characteristics.

**Table 2.3.2-1: Demographic and Baseline Characteristics of FL Patients in Studies NHL-007 and NHL-008 (Safety Population)**

| **Demographic/Baseline Characteristic** | **NHL-007** | | **NHL-008** | **Pooled NHL-007 and NHL-008** |
|---|---|---|---|---|
| | **PBO+Rit (N = 148)** | **Len+Rit (N = 146)** | **Len+Rit (N = 177)** | **Len+Rit (N = 323)** |
| **Age (Years)** | | | | |
| Mean (SD) | 60.7 (11.08) | 61.6 (11.34) | 64.5 (10.70) | 63.2 (11.07) |
| Median (Range) | 61.0 (35.0 to 88.0) | 62.0 (26.0 to 86.0) | 65.0 (35.0 to 91.0) | 64.0 (26.0 to 91.0) |
| < 65 (n [%]) | 94 (63.5) | 86 (58.9) | 84 (47.5) | 170 (52.6) |
| ≥ 65 (n [%]) | 54 (36.5) | 60 (41.1) | 93 (52.5) | 153 (47.4) |

**Table 2.3.2-1: Demographic and Baseline Characteristics of FL Patients in Studies NHL-007 and NHL-008 (Safety Population)**

| Demographic/Baseline Characteristic | NHL-007 | | NHL-008 | Pooled NHL-007 and NHL-008 |
|---|---|---|---|---|
| | PBO+Rit (N = 148) | Len+Rit (N = 146) | Len+Rit (N = 177) | Len+Rit (N = 323) |
| **Sex (n [%])** | | | | |
| Male | 80 (54.1) | 61 (41.8) | 97 (54.8) | 158 (48.9) |
| Female | 68 (45.9) | 85 (58.2) | 80 (45.2) | 165 (51.1) |
| **Ethnicity (n [%])** | | | | |
| White | 92 (62.2) | 90 (61.6) | 164 (92.7) | 254 (78.6) |
| Non-white | 55 (37.2) | 52 (35.6) | 11 (6.2) | 63 (19.5) |
| Missing | 1 (0.7) | 4 (2.7) | 2 (1.1) | 6 (1.9) |
| Hispanic | 13 (8.8) | 19 (13.0) | 10 (5.6) | 29 (9.0) |
| Non-Hispanic | 133 (89.9) | 122 (83.6) | 164 (92.7) | 286 (88.5) |
| Missing | 2 (1.4) | 5 (3.4) | 3 (1.7) | 8 (2.5) |
| **Histological Diagnosis (n [%])** | | | | |
| FL | | | | |
| Grade 1 to 2 | 123 (83.1) | 124 (84.9) | 149 (84.2) | 273 (84.5) |
| Grade 3a | 25 (16.9) | 22 (15.1) | 28 (15.8) | 50 (15.5) |
| **Ann Arbor Stage at Enrollment (n [%])** | | | | |
| I | 13 (8.8) | 13 (8.9) | 3 (1.7) | 16 (5.0) |
| II | 29 (19.6) | 21 (14.4) | 17 (9.6) | 38 (11.8) |
| III | 60 (40.5) | 69 (47.3) | 50 (28.2) | 119 (36.8) |
| IV | 46 (31.1) | 43 (29.5) | 107 (60.5) | 150 (46.4) |
| **FL International Prognostic Index (n [%])** | | | | |
| 0 to 1 | 53 (35.8) | 45 (30.8) | - | - |
| 2 | 48 (32.4) | 46 (31.5) | - | - |
| 3 to 5 | 46 (31.1) | 54 (37.0) | - | - |
| Missing | 1 (0.7) | 1 (0.7) | - | - |
| **LDH Elevated at Baseline (n [%])** | | | | |
| Yes | 33 (22.3) | 33 (22.6) | 50 (28.2) | 83 (25.7) |
| No | 114 (77.0) | 112 (76.7) | 126 (71.2) | 238 (73.7) |
| Missing | 1 (0.7) | 1 (0.7) | 1 (0.6) | 2 (0.6) |
| **B Symptoms** | | | | |

**Table 2.3.2-1: Demographic and Baseline Characteristics of FL Patients in Studies NHL-007 and NHL-008 (Safety Population)**

| Demographic/Baseline Characteristic | NHL-007 | | NHL-008 | Pooled NHL-007 and NHL-008 |
|---|---|---|---|---|
| | PBO+Rit (N = 148) | Len+Rit (N = 146) | Len+Rit (N = 177) | Len+Rit (N = 323) |
| Yes | 11 (7.4) | 12 (8.2) | 23 (13.0) | 35 (10.8) |
| No | 137 (92.6) | 134 (91.8) | 154 (87.0) | 288 (89.2) |

**Table 2.3.2-2: Duration of Exposure in FL Studies NHL-007 and NHL-008 (Safety Population)**

| Parameter | NHL-007 | | NHL-008 | Pooled NHL-007 and NHL-008 |
|---|---|---|---|---|
| | PBO+Rit (N = 148) | Len+Rit (N = 146) | Len+Rit (N = 177) | Len+Rit (N = 323) |
| **Treatment Duration (Months)** | | | | |
| Mean (SD) | 9.3 (2.93) | 10.0 (2.82) | 7.3 (3.75) | 8.5 (3.62) |
| Median | 11.0 | 11.2 | 7.4 | 11.0 |
| Range | 0.9 to 13.1 | 0.9 to 15.0 | 1.2 to 13.1 | 0.9 to 15.0 |
| **Number of Cycles** | | | | |
| Mean (SD) | 9.9 (3.10) | 10.4 (2.94) | 7.1 (4.29) | 8.6 (4.09) |
| Median | 12.0 | 12.0 | 7.0 | 11.0 |
| Range | 1.0 to 12.0 | 1.0 to 12.0 | 0.0 to 12.0 | 0.0 to 12.0 |
| **Number of Cycles Received (n [%])** | | | | |
| 1 | 1 (0.7) | 3 (2.1) | 14 (7.9) | 17 (5.3) |
| 2 | 4 (2.7) | 2 (1.4) | 6 (3.4) | 8 (2.5) |
| 3 | 5 (3.4) | 3 (2.1) | 26 (14.7) | 29 (9.0) |
| 4 | 4 (2.7) | 2 (1.4) | 3 (1.7) | 5 (1.5) |
| 5 | 3 (2.0) | 3 (2.1) | 12 (6.8) | 15 (4.6) |
| 6 | 10 (6.8) | 7 (4.8) | 8 (4.5) | 15 (4.6) |
| 7 | 7 (4.7) | 7 (4.8) | 16 (9.0) | 23 (7.1) |
| 8 | 4 (2.7) | 3 (2.1) | 4 (2.3) | 7 (2.2) |
| 9 | 13 (8.8) | 5 (3.4) | 9 (5.1) | 14 (4.3) |
| 10 | 4 (2.7) | 4 (2.7) | 2 (1.1) | 6 (1.9) |

**Table 2.3.2-2: Duration of Exposure in FL Studies NHL-007 and NHL-008 (Safety Population)**

| Parameter | NHL-007 | | NHL-008 | Pooled NHL-007 and NHL-008 |
|---|---|---|---|---|
| | PBO+Rit (N = 148) | Len+Rit (N = 146) | Len+Rit (N = 177) | Len+Rit (N = 323) |
| 11 | 4 (2.7) | 1 (0.7) | 15 (8.5) | 16 (5.0) |
| 12 | 89 (60.1) | 106 (72.6) | 52 (29.4) | 158 (48.9) |
| **Relative Dose Intensity (%)** | | | | |
| Mean (SD) | 95.5 (15.21) | 85.0 (18.57) | 77.9 (23.96) | 81.1 (21.94) |
| Median | 98.5 | 92.1 | 82.9 | 88.1 |
| Range | 4.8 to 195.0 | 39.0 to 139.9 | 4.8 to 175.0 | 4.8 to 175.0 |

### *2.3.3 Module SIII.3: Clinical Studies in Transplant Eligible Newly Diagnosed Multiple Myeloma Post-autologous Stem Cell Transplantation Maintenance*

The safety data presented are primarily based on data from 2 independently-conducted cooperative group studies, CALGB 100104 and IFM 2005-02.

In Study CALGB 100104, patients were aged ≥ 18 to 70 years with active MM requiring treatment and stable disease or responsiveness to at least 2 months of any induction therapy who were candidates and willing to undergo HDM with ASCT rescue. Ninety to 100 days post-ASCT, patients underwent disease and response evaluation and received treatment after stratification and randomisation (1:1 ratio) to maintenance treatment with either lenalidomide or placebo on Days 1 to 28 of a 28-day cycle (28/28 days) until disease progression or treatment intolerance. Randomisation was stratified by baseline β2 microglobulin (elevated, ≥ 2.5 mg/L versus normal), prior therapy with thalidomide (yes/no), and prior therapy with lenalidomide (yes/no). The starting dose of lenalidomide or placebo was 10 mg/day (28/28 days) for the first 3 months, increased to 15 mg/day if the patient's ANC ≥ 1000/µL, platelet count ≥ 75,000/µL, and any nonhaematologic toxicity was no greater than Grade 1.

In Study IFM 2005-02, patients were < 65 years of age with MM who had received an initial treatment with induction therapy and ASCT. Within ≤ 6 months after ASCT and randomisation, all patients (ie, after enrolment of the first 32 patients) received 2 cycles of consolidation treatment with lenalidomide 25 mg QD orally (21/28 days) before their assigned maintenance treatment with either lenalidomide or placebo until disease progression. The starting dose of lenalidomide or placebo was 10 mg once a day for the first 3 months, increased to 15 mg/day if tolerated.

The AE data collection methodologies differed in several ways between the 2 studies and appeared to result in noticeable differences in the reported frequencies and severities of several TEAEs both

in the lenalidomide and the placebo treatment arms. Many of these disparities can be attributed to the lack of collection of AE start and stop dates on the AE CRF in Study CALGB 100104, for which instead AE reporting periods were used for estimation of AE onset (EU SCS Section 1.2.1.1), and differences between the 2 studies in how AEs were reported via the design of the AE and other safety-related CRF pages. In Study CALGB 100104 only, the AE CRF reporting form had 8 preprinted Common Terminology Criteria for Adverse Events (CTCAE) terms: "ANC," "platelets," "febrile neutropenia," "weight gain," "rash," "bilirubin," "diarrhea," and "pneumonitis/pulmonary infiltrates". Investigators were instructed to report AEs of all grades for these 8 preprinted AEs, and to report AEs other than these 8 if they were of Grade ≥ 3 severity (other events of Grade 1 or 2 severity could be reported, but this was not a protocol requirement). Also, this CRF page contained prompts and reminders for reporting infections with Grade 3 or 4 neutrophils, mucositis/stomatitis, and new malignancies (SPM) (EU SCS Section 1.2.1.2.1). In Study CALGB 100104, start dates were reported for SAEs; SAEs represented expedited events in the AdEERS.

Recognising these differences, the primary data presentation is the evaluation of side-by-side comparisons of individual study arms from both studies to provide a clinically meaningful review of the overall safety data of lenalidomide 10 mg QD maintenance in the post-ASCT setting. Grade 3 or 4 TEAEs occurred more frequently in both treatment arms of Study CALGB 100104 compared to Study IFM 2005-02. Those differences in Grade 3 or 4 TEAE frequencies observed in the placebo arms (55.2% in Study CALGB 100104 versus 32.1% in Study IFM 2005-02; EU SCS, Table 24) suggest a potential carryover effect from HDM/ASCT in Study CALGB 100104 (ie, close proximity of transplant to start of maintenance). Based on this observation and to further investigate this impact, analyses were conducted comparing the frequencies of all AEs collected post-transplant during maintenance therapy versus the frequencies when AEs possibly occurring before start of maintenance (ie, during the "post-ASCT period") are excluded. The latter analysis was done for TEAEs of all grades and Grade 3 or 4 TEAEs although these 2 categories were possibly impacted by carryover effect of HDM/ASCT due to collection of AE using reporting periods, and not specific stop/start dates.

The median time from ASCT to the start of treatment was 3.3 months for Study CALGB 100104 and 3.4 months for Study IFM 2005-02 (EU Summary of Clinical Efficacy, Table 33). In Study IFM 2005-02, patients in both the lenalidomide and placebo arms underwent 2 cycles of lenalidomide (25 mg/day for 21 of 28 day cycles) consolidation therapy immediately prior to the start of maintenance therapy.

The demographics and baseline characteristics of patients in Studies CALGB 100104 and IFM 2005-02 are presented in Table 2.3.3-1, while duration of exposure to study medication is presented in Table 2.3.3-2.

In Studies CALGB 100104 and IFM 2005-02, the majority of the safety population were younger than 60 years of age, and the proportion of males to females was balanced in both studies. The majority of patients in Study CALGB 100104 were white or Caucasian; race and ethnicity data were not collected in Study IFM 2005-02. In both studies, the majority of patients had an International Staging System (ISS) Stage I or II at diagnosis. In Study CALGB 100104, 3 patients

(1.3%) in the lenalidomide arm (no patients in the placebo arm) and in Study IFM 2005-02, no patients in the lenalidomide arm and only one patient in the placebo arm (0.4%) had severe renal insufficiency (creatinine clearance [CLcr] < 30 mL/min) post-ASCT. The proportions of patients with moderate renal impairment (CLcr ≥ 30 mL/min to < 50 mL/min) were 8.5% and 6.3% in the lenalidomide and placebo arms of Study CALGB 100104, respectively, and 3.1% and 2.5% in the lenalidomide and placebo arms of Study IFM 2005-02, respectively, post-ASCT.

Overall, no clinically meaningful differences in demographic and disease-related characteristics were observed, and the treatment arms were balanced with regard to the demographic and disease-related characteristics. In Study IFM 2005-02, at diagnosis there was an imbalance between treatment arms in the distribution of the ISS stage categories, and patients with a reduced CLcr (< 50 mL/min).

**Table 2.3.3-1: Demographic and Baseline Characteristics of TE NDMM Patients in Studies CALGB 100104 and IFM 2005 02 (Safety Population; Data Cutoff: 01 Mar 2015)**

| Demographic/Baseline Characteristic | CALGB 100104 Maintenance | | IFM 2005-02 Maintenance | |
|---|---|---|---|---|
| | Lenalidomide (N = 224) | Placebo (N = 221) | Lenalidomide (N = 293) | Placebo (N = 280) |
| **Age (Years)** | | | | |
| Mean (SD) | 57.4 (8.06) | 57.1 (7.58) | 55.4 (7.06) | 55.3 (7.19) |
| Median (Range) | 58.0 (29.0 to 71.0) | 58.0 (39.0 to 71.0) | 56.7 (21.9 to 67.0) | 57.2 (31.7 to 66.3) |
| < 60 (n [%]) | 126 (56.3) | 128 (57.9) | 209 (71.3) | 192 (68.6) |
| ≥ 60 (n [%]) | 98 (43.8) | 93 (42.1) | 84 (28.7) | 88 (31.4) |
| < 65 (n [%]) | 176 (78.6) | 180 (81.4) | 284 (96.9) | 272 (97.1) |
| ≥ 65 (n [%]) | 48 (21.4) | 41 (18.6) | 9 (3.1) | 8 (2.9) |
| **Sex (n [%])** | | | | |
| Male | 117 (52.2) | 125 (56.6) | 164 (56.0) | 163 (58.2) |
| Female | 107 (47.8) | 96 (43.4) | 129 (44.0) | 117 (41.8) |
| **Race (n [%])** | | | | |
| White or Caucasian | 169 (75.4) | 167 (75.6) | NR | NR |
| Black or African American | 39 (17.4) | 41 (18.6) | NR | NR |
| Asian | 2 (0.9) | 1 (0.5) | NR | NR |
| Other | 0 (0.0) | 2 (0.9) | NR | NR |
| Missing | 14 (6.3) | 10 (4.5) | NR | NR |
| **ISS Stage at Diagnosis (n [%])** | | | | |
| I or II | 117 (52.2) | 126 (57.0) | 221 (75.4) | 228 (81.4) |
| III | 37 (16.5) | 34 (15.4) | 64 (21.8) | 42 (15.0) |

**Table 2.3.3-1: Demographic and Baseline Characteristics of TE NDMM Patients in Studies CALGB 100104 and IFM 2005 02 (Safety Population; Data Cutoff: 01 Mar 2015)**

| Demographic/Baseline Characteristic | CALGB 100104 Maintenance | | IFM 2005-02 Maintenance | |
|---|---|---|---|---|
| | Lenalidomide (N = 224) | Placebo (N = 221) | Lenalidomide (N = 293) | Placebo (N = 280) |
| Missing | 70 (31.3) | 61 (27.6) | 8 (2.7) | 10 (3.6) |
| **Creatinine Clearance at Diagnosis (n [%])**[a] | | | | |
| < 30 mL/min | NR | NR | 15 (6.0) | 5 (1.9) |
| ≥ 30 to < 50 mL/min | NR | NR | 30 (12.0) | 20 (7.8) |
| ≥ 50 to < 80 mL/min | NR | NR | 86 (34.5) | 86 (33.5) |
| ≥ 80 mL/min | NR | NR | 118 (47.4) | 146 (56.8) |
| < 50 mL/min | 11 (4.9) | 9 (4.1) | NR | NR |
| ≥ 50 mL/min | 57 (25.4) | 61 (27.6) | NR | NR |
| Missing | 156 (69.6) | 151 (68.3) | 58 | 50 |
| **Creatinine Clearance at Post-ASCT (n [%])** | | | | |
| < 50 mL/min | 22 (9.8) | 14 (6.3) | 9 (3.1) | 8 (2.9) |
| < 30 mL/min | 3 (1.3) | 0 (0.0) | 0 (0.0) | 1 (0.4) |
| ≥ 30 to < 50 mL/min | 19 (8.5) | 14 (6.3) | 9 (3.1) | 7 (2.5) |
| ≥ 50 mL/min | 195 (87.1) | 198 (89.6) | 173 (59.0) | 185 (66.1) |
| Missing | 7 (3.1) | 9 (4.1) | 111 (37.9) | 87 (31.1) |
| **Time from Transplant to Maintenance (Months)** | | | | |
| Mean (SD) | 3.6 (0.24) | 3.6 (0.28) | 5.9 (1.44) | 6.0 (1.42) |
| Median (Range) | 3.5 (3.0 to 5.0) | 3.5 (2.7 to 5.4) | 5.8 (1.8 to 10.7) | 5.8 (2.2 to 10.7) |

[a] Data are from the ITT Population for Study IFM 2005-02 (lenalidomide N = 307; placebo N = 307).
Source: ISS Table 2.1; Study CALGB 100104 CSR, Table 14.1.3.2; Study IFM 2005-02 CSR, Table 14.2-7.

In Study CALGB 100104, exposure for patients in the lenalidomide arm during maintenance was more than double than in the placebo arm prior to cross over to lenalidomide as reflected in the mean treatment duration. The duration of placebo maintenance treatment was limited by the interim unblinding (EU SCS Section 1.1.4.1.1.1). In Study IFM 2005-02, the mean treatment duration of maintenance therapy of lenalidomide was 24.0 months compared to 19.7 months in the placebo arm. The duration of maintenance treatment in both arms was limited due to changes in the study conduct (EU SCS Section 1.1.4.1.1.2).

Of the 221 patients in Study CALGB 100104 and 280 patients in Study IFM 2005-02 who received placebo maintenance, mean treatment duration for placebo patients was more than 6 months longer in Study IFM 2005-02 compared to Study CALGB 100104 (19.7 months versus 13.2 months,

respectively). The shorter exposure in placebo patients can be explained by the timing of the interim analysis and study unblinding (17 Dec 2009) relative to the prolonged enrolment period. These patients either discontinued the study or crossed over to lenalidomide. For Study IFM 2005-02, treatment was also unblinded (07 Jul 2010) and treatment discontinued (with no option for crossover to lenalidomide) for placebo patients.

Of the 224 patients in Study CALGB 100104 and 293 patients in Study IFM 2005-02 who received lenalidomide maintenance, mean treatment duration for lenalidomide exposed patients was about 6 months longer in Study CALGB 100104 compared to Study IFM 2005-02 (30.3 months versus 24.0 months, respectively). The shorter exposure in Study IFM 2005-02 lenalidomide patients was due to termination of the study in Jan 2011.

**Table 2.3.3-2: Duration of Exposure in TE NDMM Studies CALGB 100104 and IFM 2005 02 (Safety Population; Data Cutoff: 01 Mar 2015)**

| Parameter | CALGB 100104 Maintenance | | IFM 2005-02[a] Maintenance | |
|---|---|---|---|---|
| | Lenalidomide (N = 224) | Placebo[b] (N = 221) | Lenalidomide (N = 293) | Placebo (N = 280) |
| **Treatment Duration (Weeks)** | | | | |
| Mean (SD) | 131.6 (110.59) | 57.3 (41.93) | 104.6 (63.14) | 85.6 (48.03) |
| Median | 110.3 | 47.6 | 113.6 | 88.6 |
| Range | 1.4 to 467.6 | 1.7 to 220.6 | 0.6 to 240.0 | 1.0 to 212.3 |
| **Treatment Duration (Months)** | | | | |
| Mean (SD) | 30.3 (25.43) | 13.2 (9.64) | 24.0 (14.52) | 19.7 (11.05) |
| Median | 25.4 | 10.9 | 26.1 | 20.4 |
| Range | 0.3 to 107.5 | 0.4 to 50.7 | 0.1 to 55.2 | 0.2 to 48.8 |
| **Years on Treatment (n [%])** | | | | |
| ≥ 1 year Tx | 150 (67.0) | 95 (43.0) | 212 (72.4) | 200 (71.4) |
| ≥ 2 years Tx | 116 (51.8) | 32 (14.5) | 159 (54.3) | 99 (35.4) |
| ≥ 3 years Tx | 82 (36.6) | 6 (2.7) | 71 (24.2) | 23 (8.2) |
| ≥ 4 years Tx | 54 (24.1) | 1 (0.5) | 4 (1.4) | 2 (0.7) |
| **Cumulative Dose (mg)** | | | | |
| Mean (SD) | NR | NR | 7919.5 (5670.80) | 7721.6 (4782.89) |
| Median | NR | NR | 7200.0 | 7965.0 |
| Range | NR | NR | 40.0 to 24360 | 70.0 to 21,510 |
| **Dose Intensity (mg/day)** | | | | |
| Mean (SD) | NR | NR | 10.5 (3.20) | 12.4 (2.35) |
| Median | NR | NR | 10.1 | 13.5 |
| Range | NR | NR | 2.3 to 15.0 | 4.8 to 15.0 |

**Table 2.3.3-2: Duration of Exposure in TE NDMM Studies CALGB 100104 and IFM 2005 02 (Safety Population; Data Cutoff: 01 Mar 2015)**

| Parameter | CALGB 100104 Maintenance | | IFM 2005-02[a] Maintenance | |
|---|---|---|---|---|
| | Lenalidomide (N = 224) | Placebo[b] (N = 221) | Lenalidomide (N = 293) | Placebo (N = 280) |
| **Person-years of Exposure** | | | | |
| | 565.06 | 242.70 | 587.17 | 459.47 |

[a] The data for 2 cycles of lenalidomide consolidation therapy are excluded.

[b] For placebo patients, only dosing data up to crossing over to lenalidomide are included.

Source: ISS Table 3.1.

### *2.3.4 Module SIII.4: Clinical Studies in Transplant Non-eligible Newly Diagnosed Multiple Myeloma*

Study SWOG S0777 (RVd initial treatment)

Study SWOG S0777 was a cooperative group study. A total of 523 patients with NDMM who had received no prior chemotherapy were randomised in a 1:1 ratio to 1 of 2 treatment arms:

- **Arm A:** Six 28-day cycles (24 weeks) of Rd (initial treatment); patients who completed ≥ 4 cycles of Rd initial treatment continued Rd therapy until PD.
  - Lenalidomide 25 mg/day administered orally on Days 1 to 21
  - Dexamethasone 40 mg/day administered orally on Days 1, 8, 15, and 22
- **Arm B:** Eight 21-day cycles (24 weeks) of RVd (initial treatment); patients who completed ≥ 6 cycles but were not able to tolerate a total of 8 cycles of initial treatment continued Rd (same regimen as for treatment therapy for Arm A) until PD.
  - Lenalidomide 25 mg/day administered orally on Days 1 to 14
  - Bortezomib 1.3 mg/m2 IV on Days 1, 4, 8, and 11
  - Dexamethasone 20 mg/day administered orally on Days 1, 2, 4, 5, 8, 9, 11, and 12.

Patients were stratified at progression by ISS stage (I, II, III), and by intent to transplant at progression (yes versus no). As of the 01 Dec 2016 data cutoff date, five patients (one in the RVd arm and four in the Rd arm) were randomised but not treated. Of the 518 treated patients, 201 patients (110 in the RVd arm and 91 in the Rd arm) received initial treatment but did not continue on to the continued Rd treatment phase of the study treatment (ie, discontinued from the study treatment during initial treatment).

#### *2.3.4.1 Module SIII.4.1: Safety Data Collection*

Adverse events were recorded on paper AE summary forms (teleforms), which contained 80 preprinted CTCAE terms. In addition, investigators were instructed to report all other AEs in the free-text field at the end of AE summary form. The teleform data submission was replaced by

an online form that allowed the investigator to select the CTCAE term from a dropdown list of all CTCAE 3.0 terms; the option for a free-text entry was no longer needed.

Per the study protocol, safety assessments were recorded every 3 months while the patient was on protocol treatment and within 14 days after completion of initial treatment and completion of continued Rd therapy. For AEs reported via the original AE paper forms (teleform data submission), specific AE start and stop dates were not collected; only the start date of the 3-month AE reporting period was collected. BMS used the start date of the corresponding 3-month AE reporting period as the start date for each individual AE; stop dates were not imputed. For AEs reported electronically via the online form, specific AE start and stop dates were not collected; however, the start and end dates of the AE reporting period for routine AEs were collected. The Off Treatment Notice form provided the information for AEs leading to discontinuation.

The demographics and baseline characteristics of patients are presented in Table 2.3.4.1-1, while duration of exposure to study medication is presented in Table 2.3.4.1-2.

Patients ranged in age from 28.0 to 87.0 years, with a median age of 63.0 years in each treatment arm. Overall, there were slightly more male patients (57.5%) than female patients (42.5%), and the majority of patients were Caucasian (79.7%). No clinically meaningful differences in demographics were observed, and the treatment arms were generally balanced.

**Table 2.3.4.1-1: Demographic and Baseline Characteristics of TNE NDMM Patients in Study SWOG S0777 (Safety Population; Data Cutoff: 01 Dec 2016)**

| Demographic/Baseline Characteristic | Arm B (RVd) (N = 262) | Arm A (Rd) (N = 256) |
|---|---|---|
| **Age (Years)** | | |
| Mean (SD) | 62.2 (10.48) | 62.6 (10.39) |
| Median (Range) | 63.0 (35.0 to 85.0) | 63.0 (28.0 to 87.0) |
| ≤ 65 (n [%]) | 167 (3.7) | 149 (8.2) |
| > 65 (n [%]) | 95 (36.3) | 107 (41.8) |
| > 65 and ≤ 75 (n [%]) | 67 (25.6) | 83 (32.4) |
| > 75 (n [%]) | 28 (10.7) | 24 (9.4) |
| **Sex (n [%])** | | |
| Male | 163 (62.2) | 121 (47.3) |
| Female | 99 (37.8) | 135 (52.7) |
| **Race (n [%])** | | |
| American Indian or Alaska Native | 2 (0.8) | 1 (0.4) |
| Asian | 7 (2.7) | 5 (2.0) |
| Black or African American | 34 (13.0) | 37 (14.5) |
| Native Hawaiian or other Pacific Islanders | 3 (1.1) | 3 (1.2) |

**Table 2.3.4.1-1: Demographic and Baseline Characteristics of TNE NDMM Patients in Study SWOG S0777 (Safety Population; Data Cutoff: 01 Dec 2016)**

| Demographic/Baseline Characteristic | Arm B (RVd) (N = 262) | Arm A (Rd) (N = 256) |
|---|---|---|
| White or Caucasian | 209 (79.8) | 204 (79.7) |
| Unknown | 7 (2.7) | 6 (2.3) |
| **ISS Stage at Diagnosis (n [%])** | | |
| I | 78 (29.8) | 75 (29.3) |
| II | 98 (37.4) | 96 (37.5) |
| III | 86 (32.8) | 85 (33.2) |
| **Creatinine Clearance at Diagnosis (n [%])** | | |
| < 60 mL/min | 78 (29.8) | 76 (29.7) |
| ≥ 60 mL/min | 184 (70.2) | 179 (69.9) |
| < 50 mL/min | 46 (17.6) | 43 (16.8) |
| ≥ 50 mL/min | 216 (82.4) | 212 (82.8) |
| Missing | 0 | 1 (0.4) |

Source: SCS Table 1.2

**Table 2.3.4.1-2: Duration of Exposure in TNE NDMM Study SWOG-S0777 - Initial Treatment (Safety Population; Data Cutoff; 01 Dec 2016)**

| Duration (Weeks) | Arm B (RVd) (N = 262) | Arm A (Rd) (N = 256) |
|---|---|---|
| **Duration of Exposure of Initial Therapy (Weeks)** | | |
| Mean (SD) | 21.3 (8.09) | 22.4 (7.51) |
| Median | 24.0 | 24.1 |
| Range | 0.4 to 36.6 | 1.3 to 35.1 |
| **Treatment Duration Time Period Distribution from 0 to** | **n (%)** | |
| ≤ 3 weeks | 14 (5.3) | 9 (3.5) |
| ≤ 6 weeks | 20 (7.6) | 17 (6.6) |
| ≤ 9 weeks | 28 (10.7) | 27 (10.5) |
| ≤ 12 weeks | 47 (17.9) | 34 (13.3) |
| ≤ 15 weeks | 61 (23.3) | 40 (15.6) |
| ≤ 18 weeks | 81 (30.9) | 53 (20.7) |
| ≤ 21 weeks | 99 (37.8) | 60 (23.4) |

**Table 2.3.4.1-2: Duration of Exposure in TNE NDMM Study SWOG-S0777 - Initial Treatment (Safety Population; Data Cutoff; 01 Dec 2016)**

| Duration (Weeks) | Arm B (RVd) (N = 262) | Arm A (Rd) (N = 256) |
|---|---|---|
| ≤ 24 weeks | 137 (52.3) | 128 (50.0) |
| ≤ 27 weeks | 201 (76.7) | 199 (77.7) |
| ≤ 30 weeks | 244 (93.1) | 240 (93.8) |
| ≤ 33 weeks | 258 (98.5) | 251 (98.0) |
| ≤ 36 weeks | 261 (99.6) | 256 (100) |
| ≤ 40 weeks | 262 (100) | 256 (100) |

Source: SCS Table 2.1

As of the data cutoff date of 01 Dec 2016, the medium treatment duration was 24.0 weeks (range 0.4 to 36.6) with RVd and 24.1 weeks (range 1.3 to 35.1) with Rd during initial treatment. For 48% of patients treated with RVd and 50% of patients treated with Rd, the duration of initial treatment was > 24 weeks.

Study CC-5013-MM-020

In Study CC-5013-MM-020 (hereafter referred to as Study MM-020), a total of 1613 patients from Europe (Austria, Belgium, France, Germany, Greece, Italy, Portugal, Spain, Sweden, Switzerland, and UK), Asia (China, Taiwan, and Republic of Korea), and North America/Pacific (US, Canada, Australia, and New Zealand) regions were randomised in a 1:1:1 ratio to 1 of 3 treatment arms:

- Treatment Arm A (Rd), lenalidomide (25 mg/day) and low-dose dexamethasone (given on Days 1, 8, 15 and 22) in repeated 28-day cycles until documentation of PD;
- Treatment Arm B (Rd18), lenalidomide (25 mg/day) and low-dose dexamethasone (given on Days 1, 8, 15 and 22) in repeated 28-day cycles for up to 18 cycles (72 weeks);
- Treatment Arm C (MPT), melphalan, prednisone (given on Days 1 to 4) and thalidomide in a 42-day cycle for up to 12 cycles (72 weeks).

Patients were stratified at randomisation by age (≤ 75 years versus > 75 years), stage (ISS Stages I or II versus Stage III), and country.

Of the 1613 enrolled patients, 535 were randomised to Arm Rd, 541 to Arm Rd18, and 547 to Arm MPT; of those, 3 in Arm Rd, 1 in Arm Rd18, and 6 in Arm MPT were never treated. The demographics and baseline characteristics of patients are presented in Table 2.3.4.1-3, while duration of exposure to study medication is presented in Table 2.3.4.1-4.

The majority of the study population are elderly patients. The median age is 73.0 years across all 3 treatment arms; 65.2% are ≤ 75 years and 34.9% are > 75 years. The study population also included 92 patients (5.7%) who were < 65 years; these patients were deemed ineligible for stem cell transplant but the reasons for the ineligibility were not systematically captured.

Overall, the intent-to-treat (ITT) population included a balanced proportion of males (52.6%) to females (47.4%) and the majority were white or Caucasian (89.0%), non-Hispanic or Latino (92.8%), and from Europe (68.6%). In general, study patients had advanced stage disease. Of the total study population, 40.6% had ISS Stage III, approximately half had some degree of renal insufficiency (CLcr < 60 mL/min), 71.2% had a history of bone disease, and 13.5% had radiation for MM prior to treatment in the study (see Table 14.1.1.1.1, MM-020 clinical study report [CSR]).

Overall, no clinically meaningful differences in demographic and disease-related characteristics were observed, and the treatment arms were balanced with regard to the demographic and disease-related characteristics. The medical history includes a number of comorbidities and manifestations of the disease for this elderly population: hypertension (59.8%), anaemia (57.5%), back pain (32.3%), bone pain (22.6%), hypercholesterolemia (17.6%), diabetes ("Type 2 diabetes mellitus," 7.6%; "diabetes mellitus," 6.5%), gastroesophageal reflux disease (7.5%), and obesity (2.3%). Of the total patients, 29.3% had a history of cardiac disorders including atrial fibrillation (7.7%), coronary artery disease (4.1%), and myocardial infarction (MI; 4.0%) (see Table 14.1.3.2.1, MM-020 CSR). Other important comorbidities were DVT (1.5%), pulmonary embolism (1.8%), and CVA (2.6%). History of invasive malignancies was also documented in 10.4% of the total patients (Table 14.1.4.2.1.4, MM-020 CSR).

**Table 2.3.4.1-3: Demographic and Baseline Characteristics of TNE NDMM Patients in Study MM 020 (ITT Population; Data Cutoff: 24 May 2013)**

| Demographic/Baseline Characteristic | Rd (N = 535) | Rd18 (N = 541) | Rd and Rd18 (N = 1076) | MPT (N = 547) |
|---|---|---|---|---|
| **Age (Years)** | | | | |
| Mean (SD) | 73.2 (6.57) | 72.9 (6.50) | 73.0 (6.53) | 73.1 (6.32) |
| Median (Range) | 73.0 (44.0 to 91.0) | 73.0 (40.0 to 89.0) | 73.0 (40.0 to 91.0) | 73.0 (51.0 to 92.0) |
| ≤ 75 (n [%]) | 349 (65.2) | 348 (64.3) | 697 (64.8) | 359 (65.6) |
| > 75 (n [%]) | 186 (34.8) | 193 (35.7) | 379 (35.2) | 188 (34.4) |
| **Sex (n [%])** | | | | |
| Male | 294 (55.0) | 273 (50.5) | 567 (52.7) | 287 (52.5) |
| Female | 241 (45.0) | 268 (49.5) | 509 (47.3) | 260 (47.5) |
| **Race (n [%])** | | | | |
| Asian | 40 (7.5) | 43 (7.9) | 83 (7.7) | 44 (8.0) |
| Black or African American | 9 (1.7) | 6 (1.1) | 15 (1.4) | 5 (0.9) |
| Native Hawaiian or other Pacific Islanders | 1 (0.2) | 0 | 1 (0.1) | 1 (0.2) |
| Other | 6 (1.1) | 11 (2.0) | 17 (1.6) | 3 (0.5) |
| White or Caucasian | 474 (88.6) | 480 (88.7) | 954 (88.7) | 491 (89.8) |
| Undisclosed | 5 (0.9) | 1 (0.2) | 6 (0.6) | 3 (0.5) |
| **Ethnicity (n [%])** | | | | |
| Hispanic or Latino | 37 (6.9) | 33 (6.1) | 70 (6.5) | 36 (6.6) |
| Not Hispanic or Latino | 493 (92.1) | 505 (93.3) | 998 (92.8) | 508 (92.9) |
| Undisclosed | 5 (0.9) | 3 (0.6) | 8 (0.7) | 3 (0.5) |
| **ISS Stage (n [%])** | | | | |
| I | 115 (21.5) | 112 (20.7) | 227 (21.1) | 108 (19.7) |
| II | 195 (36.4) | 204 (37.7) | 399 (37.1) | 205 (37.5) |
| III | 225 (42.1) | 224 (41.4) | 449 (41.7) | 234 (42.8) |
| Missing | 0 | 1 (0.2) | 1 (0.1) | 0 |
| **ECOG Performance Status (n [%])** | | | | |
| 0 | 155 (29.0) | 163 (30.1) | 318 (29.6) | 156 (28.5) |
| 1 | 257 (48.0) | 263 (48.6) | 520 (48.3) | 275 (50.3) |
| 2 | 119 (22.2) | 113 (20.9) | 232 (21.6) | 111 (20.3) |

**Table 2.3.4.1-3: Demographic and Baseline Characteristics of TNE NDMM Patients in Study MM 020 (ITT Population; Data Cutoff: 24 May 2013)**

| Demographic/Baseline Characteristic | Rd (N = 535) | Rd18 (N = 541) | Rd and Rd18 (N = 1076) | MPT (N = 547) |
|---|---|---|---|---|
| ≥ 3 | 2 (0.4) | 2 (0.4) | 4 (0.4) | 2 (0.4) |
| Missing | 2 (0.4) | 0 | 2 (0.2) | 3 (0.5) |

**Table 2.3.4.1-4: Duration of Exposure in TNE NDMM Study MM 020 (Safety Population; Data Cutoff: 24 May 2013)**

| Duration (Weeks) | Rd (N = 532) | Rd18 (N = 540) | MPT (N = 541) |
|---|---|---|---|
| **Treatment Duration Time Period Distribution from 0 to** | **(n %)** | | |
| ≤ 4 weeks | 24 (4.5) | 27 (5.0) | 19 (3.5) |
| ≤ 12 weeks | 50 (9.4) | 54 (10.0) | 81 (15.0) |
| ≤ 24 weeks | 98 (18.4) | 102 (18.9) | 131 (24.2) |
| ≤ 36 weeks | 141 (26.5) | 146 (27.0) | 175 (32.3) |
| ≤ 48 weeks | 179 (33.6) | 186 (34.4) | 212 (39.2) |
| ≤ 52 weeks (1 year) | 194 (36.5) | 195 (36.1) | 225 (41.6) |
| ≤ 60 weeks | 219 (41.2) | 217 (40.2) | 248 (45.8) |
| ≤ 72 weeks | 241 (45.3) | 315 (58.3) | 332 (61.4) |
| ≤ 84 weeks | 281 (52.8) | 533 (98.7) | 529 (97.8) |
| ≤ 96 weeks | 309 (58.1) | 539 (99.8) | 538 (99.4) |
| ≤ 104 weeks (2 years) | 324 (60.9) | 540 (100.0) | 539 (99.6) |
| ≤ 108 weeks | 330 (62.0) | 540 (100.0) | 540 (99.8) |
| ≤ 120 weeks | 347 (65.2) | 540 (100.0) | 541 (100.0) |
| ≤ 132 weeks | 372 (69.9) | 540 (100.0) | 541 (100.0) |
| ≤ 144 weeks | 401 (75.4) | 540 (100.0) | 541 (100.0) |
| ≤ 156 weeks (3 years) | 434 (81.6) | 540 (100.0) | 541 (100.0) |
| ≤ 168 weeks | 455 (85.5) | 540 (100.0) | 541 (100.0) |
| ≤ 180 weeks | 476 (89.5) | 540 (100.0) | 541 (100.0) |
| ≤ 192 weeks | 493 (92.7) | 540 (100.0) | 541 (100.0) |
| ≤ 200 weeks | 505 (94.9) | 540 (100.0) | 541 (100.0) |
| > 200 weeks | 532 (100.0) | 540 (100.0) | 541 (100.0) |
| **Duration of Exposure** | | | |

**Table 2.3.4.1-4: Duration of Exposure in TNE NDMM Study MM 020 (Safety Population; Data Cutoff: 24 May 2013)**

| | | | |
|---|---|---|---|
| Mean (SD) | 89.8 (63.45) | 54.8 (25.53) | 51.9 (27.64) |
| Median | 80.2 | 72.0 | 67.1 |
| Range | 0.7 to 246.7 | 0.9 to 102.6 | 0.2 to 110.0 |

The median treatment duration in Arm Rd, 80.2 weeks (range: 0.7, 246.7), was longer than in either Arm Rd18 (72.0 weeks [range: 0.9, 102.6]) or Arm MPT (67.1 weeks [range: 0.1, 110.0]) owing to the study design, which proposed treatment in Arm Rd to continue until disease progression. Treatments in Arm Rd18 and Arm MPT were both capped at 72 weeks (eighteen 28-day cycles and six 42-day cycles, respectively). Overall, 58.3% (Arm Rd18) and 61.4% (Arm MPT) of patients were treated for 72 weeks or less, including patients who discontinued treatment.

As of the 24 May 2013 cutoff, 208 patients in Arm Rd (39%) were treated for > 2 years and 98 patients (18%) were treated for > 3 years.

The total number of person-years on study treatment in each treatment arm was 921 in Arm Rd, 587 in Arm Rd18, and 549 in Arm MPT.

Study CC-5013-MM-015

In Study CC-5013-MM-015 (hereafter referred to as Study MM-015), a total of 459 stem cell TNE patients were randomised to treatment in the double-blind treatment phase of the study in a 1:1:1 ratio of:

- Induction therapy (up to 9 cycles) with melphalan/prednisone plus lenalidomide followed by maintenance therapy with single-agent lenalidomide (hereafter referred to as MPR+R); 10 mg/day on Days 1 to 21 of repeated 28-day cycles, given until disease progression.
- Induction therapy (up to 9 cycles) with melphalan/prednisone plus lenalidomide followed by maintenance therapy with single-agent placebo (hereafter referred to as MPR+p).
- Induction therapy (up to 9 cycles) with melphalan/prednisone plus placebo (p) followed by maintenance therapy with single-agent placebo (hereafter referred to as MPp+p).

Patients were stratified at randomisation by age (≤ 75 years versus > 75 years) and disease stage (ISS; Stages I and II versus Stage III).[111]

Of the 459 patients randomised to treatment, 152, 153 and 154 patients were randomised to receive MPR+R, MPR+p and MPp+p, respectively. Overall, 455 patients were included in the safety population (150, 152 and 153 in the MPR+R, MPR+p and MPp+p arms, respectively). The demographics and baseline characteristics of patients are presented in Table 2.3.4.1-5, while duration of exposure to study medication is presented in Table 2.3.4.1-6.

The ITT population included approximately equal numbers of females (50.3%) and males (49.7%), and almost all patients were white (98.7%). Patients ranged in age from 65.0 to 91.0 years (median,

71.0 years), and approximately half of patients in each treatment arm were ISS Stage III. Overall, the three treatment arms were well balanced. The only notable exception was baseline Karnofsky performance status, which was significantly different between the MPR+R and MPp+p arms (median, 80% and 90%, respectively).

In general, no clinically notable differences in medical histories were observed between the three treatment arms. The majority of the patients had a history of musculoskeletal and connective tissue disorders (73.0% of patients; eg, osteoporosis, back pain, bone pain, and osteoarthritis); and vascular disorders (65.7% of patients; eg, hypertension); and blood and lymphatic system disorders (65.3% of patients; eg, anaemia) (see Table 14.1.5, MM-015 CSR). Thirty-one percent (31.4%) of patients had a history of cardiac disorders, the most common of which included myocardial ischemia (8.4%) and atrial fibrillation (5.7%). Few patients had a history of venous thromboembolism: DVT (1.5%), pulmonary embolism (1.3%), thrombophlebitis (0.9%), and venous thrombosis (< 0.2%). A total of 31/455 patients (6.8%) had a history of prior invasive malignancy that had been inactive for ≥ 3 years prior to screening, with the exception of 1 patient who had prostate cancer diagnosed 1 year and 9 months prior to entering the study. Approximately half of the patients in each treatment arm had CLcr < 60 mL/min.

**Table 2.3.4.1-5: Demographic and Baseline Characteristics of TNE NDMM Patients in Study MM 015 (ITT Population; Data Cutoff: 30 Apr 2013)**

| Demographic/Baseline Characteristic | MPR+R (N = 152) | MPR+p (N = 153) | MPp+p (N = 154) |
|---|---|---|---|
| **Age (Years)** | | | |
| Mean (SD) | 72.0 (5.33) | 72.1 (5.20) | 72.0 (5.26) |
| Median (Range) | 71.0 (65.0 to 87.0) | 71.0 (65.0 to 86.0) | 72.0 (65.0 to 91.0) |
| ≤ 75 (n [%]) | 116 (76.3) | 116 (75.8) | 116 (75.3) |
| > 75 (n [%]) | 36 (23.7) | 37 (24.2) | 38 (24.7) |
| **Sex (n [%])** | | | |
| Male | 71 (46.7) | 82 (53.6) | 75 (48.7) |
| Female | 81 (53.3) | 71 (46.4) | 79 (51.3) |
| **Race (n [%])** | | | |
| White | 151 (99.3) | 151 (98.7) | 151 (98.1) |
| Black | 1 (0.7) | 0 | 0 |
| Hispanic | 0 | 0 | 1 (0.6) |
| Other | 0 | 2 (1.3) | 2 (1.3) |
| **ISS Stage (n [%])** | | | |
| I | 28 (18.4) | 32 (20.9) | 28 (18.2) |
| II | 50 (32.9) | 47 (30.7) | 48 (31.2) |
| III | 74 (48.7) | 74 (48.4) | 78 (50.6) |

**Table 2.3.4.1-5: Demographic and Baseline Characteristics of TNE NDMM Patients in Study MM 015 (ITT Population; Data Cutoff: 30 Apr 2013)**

| Demographic/Baseline Characteristic | MPR+R (N = 152) | MPR+p (N = 153) | MPp+p (N = 154) |
|---|---|---|---|
| **Karnofsky Performance Scale (n [%])** | | | |
| 60 | 13 (8.6) | 16 (10.5) | 11 (7.1) |
| 70 | 40 (26.3) | 20 (13.1) | 22 (14.3) |
| 80 | 37 (24.3) | 54 (35.3) | 43 (27.9) |
| 90 | 40 (26.3) | 40 (26.1) | 51 (33.1) |
| 100 | 21 (13.8) | 23 (15.0) | 27 (17.5) |
| **Demographic/Baseline Characteristic** | **MPR+R (N = 152)** | **MPR+p (N = 153)** | **MPp+p (N = 154)** |
| Missing | 1 (0.7) | 0 | 0 |
| Median | 80.0 | 80.0 | 90.0 |

**Table 2.3.4.1-6: Duration of Exposure in TNE NDMM Study MM 015 (Induction+Maintenance Phase; Safety Population; Data Cutoff: 30 Apr 2013)**

| Duration (Weeks) | MPR+R (N = 150) | MPR+p (N = 152) | MPp+p (N = 153) |
|---|---|---|---|
| **Treatment Duration (n [%])**[a] | | | |
| 0 to ≤ 4 | 5 (3.3) | 7 (4.6) | 8 (5.2) |
| > 4 to ≤ 8 | 8 (5.3) | 2 (1.3) | 3 (2.0) |
| > 8 to ≤ 12 | 4 (2.7) | 2 (1.3) | 9 (5.9) |
| > 12 to ≤ 16 | 5 (3.3) | 7 (4.6) | 4 (2.6) |
| > 16 to ≤ 20 | 10 (6.7) | 5 (3.3) | 6 (3.9) |
| > 20 to ≤ 24 | 5 (3.3) | 10 (6.6) | 6 (3.9) |
| > 24 to ≤ 28 | 10 (6.7) | 2 (1.3) | 1 (0.7) |
| > 28 to ≤ 32 | 6 (4.0) | 5 (3.3) | 7 (4.6) |
| > 32 to ≤ 36 | 4 (2.7) | 8 (5.3) | 4 (2.6) |
| > 36 to ≤ 40 | 3 (2.0) | 11 (7.2) | 2 (1.3) |
| > 40 to ≤ 44 | 1 (0.7) | 3 (2.0) | 6 (3.9) |
| > 44 to ≤ 48 | 3 (2.0) | 5 (3.3) | 8 (5.2) |
| > 48 to ≤ 52 | 3 (2.0) | 7 (4.6) | 11 (7.2) |
| > 52 to ≤ 56 | 1 (0.7) | 8 (5.3) | 5 (3.3) |
| > 56 to ≤ 60 | 4 (2.7) | 7 (4.6) | 6 (3.9) |
| > 60 to ≤ 64 | 5 (3.3) | 9 (5.9) | 8 (5.2) |
| > 64 to ≤ 68 | 3 (2.0) | 3 (2.0) | 6 (3.9) |
| > 68 to ≤ 72 | 1 (0.7) | 10 (6.6) | 9 (5.9) |
| > 72 to ≤ 76 | 3 (2.0) | 2 (1.3) | 4 (2.6) |
| > 76 to ≤ 80 | 4 (2.7) | 1 (0.7) | 3 (2.0) |
| > 80 to ≤ 84 | 0 | 2 (1.3) | 1 (0.7) |
| > 84 to ≤ 88 | 3 (2.0) | 2 (1.3) | 4 (2.6) |
| > 88 to ≤ 92 | 2 (1.3) | 6 (3.9) | 3 (2.0) |
| > 92 to ≤ 96 | 3 (2.0) | 2 (1.3) | 2 (1.3) |
| > 96 to ≤ 100 | 4 (2.7) | 3 (2.0) | 3 (2.0) |
| > 100 to ≤ 104 | 2 (1.3) | 2 (1.3) | 4 (2.6) |
| ≥ 104 | 48 (32.0) | 21 (13.8) | 20 (13.1) |
| **Duration of Exposure** | | | |
| Mean (SD) | 90.0 (81.83) | 58.5 (37.67) | 57.7 (36.62) |

**Table 2.3.4.1-6: Duration of Exposure in TNE NDMM Study MM 015 (Induction+Maintenance Phase; Safety Population; Data Cutoff: 30 Apr 2013)**

| Duration (Weeks) | MPR+R (N = 150) | MPR+p (N = 152) | MPp+p (N = 153) |
|---|---|---|---|
| Median | 62.6 | 53.0 | 53.0 |
| Range | 3.4 to 297.0 | 2.0 to 162.7 | 1.0 to 160.3 |

[a] Treatment duration is calculated from the first of the dosing start dates to the last of the last cycle end dates of the 3 study drugs.

It should be noted that dosing information in the maintenance period is difficult to compare between arms due to patients in Arms MPR+p and MPp+p stopping treatment (placebo) following unblinding of the study. As a result, the median cumulative dose in the maintenance phase was 3146.3 mg of lenalidomide in Arm MPR+R, 1325.0 mg of placebo in Arm MPR+p, and 1670.0 mg of placebo in Arm MPp+p.

### *2.3.5 Module SIII.5: Clinical Studies in Relapsed or Refractory Multiple Myeloma*

A total of 353 patients were randomised to treatment with lenalidomide/dexamethasone and 350 patients received placebo/dexamethasone in Studies CC-5013-MM-009 and CC-5013-MM-010 (hereafter referred to as Studies MM-009 and MM-010). Patient populations in the controlled RRMM studies are shown in Table 2.3.5-1, while duration of exposure to study medication is presented in Table 2.3.5-2.

The safety population was approximately 60% male and 40% female, with patients ranging in age from 33 to 86 years (median, 63 years). There was significant comorbidity and cardiac risk factors within this safety population (see Table 14.1.4.1A, MM-009 and MM-010 CSRs), including a history of cardiac disorders (28.6% lenalidomide/dexamethasone and 29.0% placebo/dexamethasone), hypertension (43.4% lenalidomide/dexamethasone and 43.2% placebo/dexamethasone) and hypercholesterolaemia (10.7% lenalidomide/dexamethasone and 10.4% placebo/dexamethasone).

**Table 2.3.5-1: Demographic and Baseline Characteristics in the Controlled RRMM Studies (Pooled Studies MM 009 and MM 010; Data Cutoff: 31 Dec 2005)**

| Demographic/Baseline Characteristic | Len/Dex (N = 353) | PBO/Dex[a] (N = 351) |
|---|---|---|
| **Age (Years)** | | |
| N | 353 | 351 |
| Mean (SD) | 62.7 (9.98) | 62.7 (9.30) |

**Table 2.3.5-1: Demographic and Baseline Characteristics in the Controlled RRMM Studies (Pooled Studies MM 009 and MM 010; Data Cutoff: 31 Dec 2005)**

| Demographic/Baseline Characteristic | Len/Dex (N = 353) | PBO/Dex[a] (N = 351) |
|---|---|---|
| Median | 63.0 | 63.0 |
| Range | 33.0 to 86.0 | 37.0 to 85.0 |
| 18 to 24 (n [%]) | 0 | 0 |
| 25 to 34 (n [%]) | 1 (0.3) | 0 |
| 35 to 44 (n [%]) | 14 (4.0) | 7 (2.0) |
| 45 to 54 (n [%]) | 56 (15.9) | 70 (19.9) |
| 55 to 64 (n [%]) | 121 (34.3) | 121 (34.5) |
| 65 to 74 (n [%]) | 118 (33.4) | 114 (32.5) |
| > 74 (n [%]) | 43 (12.2) | 39 (11.1) |
| **Sex (n [%])** | | |
| Male | 210 (59.5) | 207 (59.0) |
| Female | 143 (40.5) | 144 (41.0) |
| **Race/Ethnicity (n [%])** | | |
| White | 313 (88.7) | 323 (92.0) |
| Black | 27 (7.6) | 17 (4.8) |
| Hispanic | 3 (0.8) | 5 (1.4) |
| Asian/Pacific islander | 6 (1.7) | 2 (0.6) |
| American Indian/Alaska native | 0 | 0 |
| Other | 4 (1.1) | 4 (1.1) |
| **Prior Antimyeloma Regimens/Stem Cell Transplantation (n [%])[b]** | | |
| 0 | 0 | 0 |
| 1 | 65 (18.4) | 73 (20.8) |
| 2 | 138 (39.1) | 134 (38.2) |
| 3 | 114 (32.3) | 106 (30.2) |
| > 3 | 36 (10.2) | 38 (10.8) |

[a] One patient randomised to placebo/dexamethasone did not receive treatment; thus 350 patients treated with placebo/dexamethasone.

[b] Any number of stem cell transplant procedures is considered as one regimen.

Source: Variation II/34

**Table 2.3.5-2: Duration of Exposure in the Controlled RRMM Studies (Pooled Studies MM 009 and MM 010; Data Cutoff: 31 Dec 2005)**

| Duration (Weeks)[a] | Len/Dex (N = 353) | PBO/Dex (N = 350) |
|---|---|---|
| **Treatment Duration (n [%])** | | |
| < 1 | 1 (0.3) | 2 (0.6) |
| 1 to < 4 | 14 (4.0) | 14 (4.0) |
| 4 to < 8 | 14 (4.0) | 38 (10.9) |
| 8 to < 12 | 27 (7.6) | 42 (12.0) |
| 12 to < 16 | 15 (4.2) | 28 (8.0) |
| 16 to < 20 | 18 (5.1) | 31 (8.9) |
| 20 to < 24 | 16 (4.5) | 23 (6.6) |
| 24 to < 28 | 19 (5.4) | 38 (10.9) |
| 28 to < 32 | 19 (5.4) | 27 (7.7) |
| 32 to < 36 | 10 (2.8) | 12 (3.4) |
| 36 to < 40 | 11 (3.1) | 15 (4.3) |
| 40 to < 44 | 12 (3.4) | 14 (4.0) |
| 44 to < 48 | 8 (2.3) | 8 (2.3) |
| 48 to < 52 | 6 (1.7) | 4 (1.1) |
| 52 to < 56 | 6 (1.7) | 6 (1.7) |
| 56 to < 60 | 12 (3.4) | 6 (1.7) |
| 60 to < 64 | 7 (2.0) | 2 (0.6) |
| 64 to < 68 | 4 (1.1) | 2 (0.6) |
| 68 to < 72 | 5 (1.4) | 3 (0.9) |
| 72 to < 76 | 7 (2.0) | 2 (0.6) |
| 76 to < 80 | 6 (1.7) | 3 (0.9) |
| 80 to < 84 | 4 (1.1) | 2 (0.6) |
| 84 to < 88 | 3 (0.8) | 0 |
| 88 to < 92 | 5 (1.4) | 1 (0.3) |
| 92 to < 96 | 2 (0.6) | 0 |
| 96 to < 100 | 6 (1.7) | 1 (0.3) |
| 100 to < 104 | 4 (1.1) | 2 (0.6) |
| ≥ 104 | 92 (26.1) | 24 (6.9) |
| **Duration of Exposure** | | |

**Table 2.3.5-2: Duration of Exposure in the Controlled RRMM Studies (Pooled Studies MM 009 and MM 010; Data Cutoff: 31 Dec 2005)**

| Duration (Weeks)[a] | Len/Dex (N = 353) | PBO/Dex (N = 350) |
|---|---|---|
| Mean (SD) | 72.3 (69.13) | 35.0 (44.29) |
| Median | 44.0 | 23.1 |
| Range | 0.1 to 254.9 | 0.3 to 238.1 |

[a] Treatment duration is number of weeks from day of the first dose to day of the last dose of study drug.

Source: Variation II/34

### *2.3.6 Module SIII.6: Clinical Studies in Del 5q MDS with or without Additional Cytogenetic Abnormalities*

In Study CC-5013-MDS-003 (hereafter referred to as Study MDS-003), which includes extension Study CC-5013-MDS-003E/009 (hereafter referred to as Study MDS-003E/009), where no additional treatment was given, rather as explained below, additional information was captured, patients with a diagnosis of low- or INT-1-risk del 5q MDS and RBC-transfusion-dependent anaemia were treated with lenalidomide 10 mg orally QD. Initially, this was as a syncopated dosage regimen in which patients received lenalidomide 10 mg orally QD on Days 1 to 21 of a 28-day cycle. Following a protocol amendment, a continuous dosage regimen (ie, 10 mg orally on Day 1 to 28 of a 28-day cycle) was used in which there was no planned rest period. The decision to change the dosing regimen from a syncopated regimen to a continuous regimen was taken when additional data from a Phase 1/2 study (Study MDS-501-001) became available to suggest that a continuous regimen of lenalidomide (10 mg of lenalidomide QD without a planned rest period) produced an earlier response, with no additional safety concerns.

After the MDS-003 study was closed, the need for longer-term follow-up was identified. The MDS-003E (Germany)/MDS-009 (US) (MDS-003E/MDS-009) study was a non-interventional (no study drug was provided under the protocol), multi-centre, follow-up extension study of patients previously enrolled in MDS-003. It was conducted specifically to provide further long-term outcomes for OS/vital status (including date of death or last known date alive, primary underlying cause of death, and other significant conditions contributing to death) and the possible occurrence of progression to AML for patients previously enrolled in the MDS-003 study and to further analyse these outcomes based on the long-term follow-up data obtained.

Overall, 148 patients were enrolled into Study MDS-003, all of whom received lenalidomide and completed the study. Forty-six patients started with the syncopated dosage regimen of which 6 patients switched to a continuous dosage regimen; 102 patients started with the continuous dosage regimen. Study MDS-003 was completed on 27 Aug 2008 and the extension Study MDS-003E/009 was completed on 01 Oct 2010. Study MDS-003E/009 was only intended to collect follow-up data as described above from Study MDS-003. The demographics and

baseline characteristics of patients are summarised in Table 2.3.6-1, while duration of exposure to study medication is presented in Table 2.3.6-2.

The study population reflected that observed in clinical practice, and included more females (65.5%) than males (34.5%), as would be expected for this patient population. Patients ranged in age from 37 to 95 years, with a median age of 71.0 years. Overall 9 (6.1%) patients had INT-2 or high-risk del 5q MDS according to the central review. One hundred and ten (74.3%) patients had an MDS clone with an isolated del 5q cytogenetic abnormality, 25 (16.9%) patients had intermediate cytogenetic complexity, and 12 (8.1%) patients had complex cytogenetic abnormalities.

Overall, the median duration of treatment was 52.5 weeks (range, 0.4 to 253.0 weeks) and 62.8% (93/148) of patients received treatment for at least 32 weeks, indicating a long duration of lenalidomide treatment in the study patients.

**Table 2.3.6-1: Demographic and Baseline Characteristics of Del 5q MDS Patients in Study MDS 003 (ITT Population; Data Cutoff: 27 Aug 2008)**

| Demographic/Baseline Characteristic | Lenalidomide 10 mg (Continuous[a]; N = 102) | Lenalidomide 10 mg (Syncopated[b]; N = 46) | Overall (N = 148) |
|---|---|---|---|
| **Age (Years)** | | | |
| Mean (SD) | 69.3 (11.0) | 71.4 (9.4) | 70.0 (10.5) |
| Median (Range) | 71.0 (37.0 to 95.0) | 72.0 (51.0 to 91.0) | 71.0 (37.0 to 95.0) |
| ≤ 65 (n [%]) | 35 (34.3) | 13 (28.3) | 48 (32.4) |
| > 65 (n [%]) | 67 (65.7) | 33 (71.7) | 100 (67.6) |
| **Sex (n [%])** | | | |
| Male | 33 (32.4) | 18 (39.1) | 51 (34.5) |
| Female | 69 (67.6) | 28 (60.9) | 97 (65.5) |
| **Race (n [%])** | | | |
| White | 99 (97.1) | 44 (95.7) | 143 (96.6) |
| Hispanic | 2 (2.0) | 1 (2.2) | 3 (2.0) |
| Asian/Pacific Islander | 1 (1.0) | 1 (2.2) | 2 (1.4) |
| **5q(-) (31-33) Chromosomal Abnormality (n [%])[c]** | | | |
| Yes | 102 (100) | 46 (100) | 148 (100) |
| No | 0 | 0 | 0 |
| **IPSS Score (Central Review)[d] (n [%])** | | | |
| Low (0) | 36 (35.3) | 13 (28.3) | 49 (33.1) |
| INT-1 (0.5 to 1.0) | 44 (43.1) | 25 (54.3) | 69 (46.6) |
| INT-2 (1.5 to 2.0) | 4 (3.9) | 3 (6.5) | 7 (4.7) |

**Table 2.3.6-1: Demographic and Baseline Characteristics of Del 5q MDS Patients in Study MDS 003 (ITT Population; Data Cutoff: 27 Aug 2008)**

| Demographic/Baseline Characteristic | Lenalidomide 10 mg (Continuous[a]; N = 102) | Lenalidomide 10 mg (Syncopated[b]; N = 46) | Overall (N = 148) |
|---|---|---|---|
| High risk (≥ 2.5) | 1 (1.0) | 1 (2.2) | 2 (1.4) |
| Missing | 17 (16.7) | 4 (8.7) | 21 (14.2) |
| **FAB Classification (Central Haematologic Review) (n [%])** | | | |
| RA | 52 (51.0) | 26 (56.5) | 78 (52.7) |
| RARS | 13 (12.7) | 3 (6.5) | 16 (10.8) |
| RAEB | 18 (17.6) | 12 (26.1) | 30 (20.3) |
| CMML | 2 (2.0) | 1 (2.2) | 3 (2.0) |
| Acute Leukaemia | 0 | 1 (2.2) | 1 (0.7) |
| Unable to classify | 17 (16.7) | 3 (6.5) | 20 (13.5) |
| **Cytogenetic Complexity (n [%])[d]** | | | |
| Isolated 5q | 80 (78.4) | 30 (65.2) | 110 (74.3) |
| INT (5q + 1 Abnormality) | 14 (13.7) | 11 (23.9) | 25 (16.9) |
| Complex | 7 (6.9) | 5 (10.9) | 12 (8.1) |
| Unknown | 1 (1.0) | 0 | 1 (0.7) |
| **ECOG Performance Status (n [%])** | | | |
| 0 | 43 (42.2) | 16 (34.8) | 59 (39.9) |
| 1 | 49 (48.0) | 26 (56.5) | 75 (50.7) |
| 2 | 10 (9.8) | 4 (8.7) | 14 (9.5) |

[a] 10 mg on Days 1 to 28 of a 28-day cycle.

[b] 10 mg on Days 1 to 21 of a 28-day cycle.

[c] Standard cytogenic studies were performed and centrally reviewed by an independent cytogenic reviewer to confirm the patient's cytogenic eligibility at baseline.

[d] IPSS Score = Sum of narrow blast + karyotype + cytopenia score. Intermediate: +1 abnormality. Complex: ≥ 2 abnormalities.

Source: Study MDS-003 CSR, Table 11.

**Table 2.3.6-2: Duration of Exposure of Del 5q MDS Patients in Study MDS 003 (Data Cutoff: 27 Aug 2008)**

| | Lenalidomide 10 mg (Continuous[a]; N = 102) | Lenalidomide 10 mg (Syncopated[b]; N = 46) | Overall (N = 148) |
|---|---|---|---|
| **Treatment Duration (Weeks)** | | | |

**Table 2.3.6-2: Duration of Exposure of Del 5q MDS Patients in Study MDS 003 (Data Cutoff: 27 Aug 2008)**

| | Lenalidomide 10 mg (Continuous[a]; N = 102) | Lenalidomide 10 mg (Syncopated[b]; N = 46) | Overall (N = 148) |
|---|---|---|---|
| Mean (SD) | 94.6 (85.1) | 74.8 (75.5) | 88.5 (82.5) |
| Median | 52.0 | 55.0 | 52.5 |
| Range | 0.4 to 250.6 | 2.0 to 253.0 | 0.4 to 253.0 |
| **Distribution of Treatment Duration (n [%])** | | | |
| At least 4 weeks | 98 (96.1) | 40 (87.0) | 138 (93.2) |
| At least 8 weeks | 95 (93.1) | 36 (78.3) | 131 (88.5) |
| At least 16 weeks | 86 (84.3) | 34 (73.9) | 120 (81.1) |
| At least 24 weeks | 76 (74.5) | 30 (65.2) | 106 (71.6) |
| At least 32 weeks | 67 (65.7) | 26 (56.5) | 93 (62.8) |

[a] 10 mg on Days 1 to 28 of a 28-day cycle.

[b] 10 mg on Days 1 to 21 of a 28-day cycle.

Source: Study MDS-003 CSR, Table 35.

Of the 148 patients who were enrolled in Study MDS-003, 76 had died at the time of writing the final MDS-003 CSR and 18 did not participate in the extension study. Thus, 54 patients were included in the extension study follow-up cohort. The median duration of follow-up for all patients in Study MDS-003 at the time of the final MDS-003 CSR was 2.8 years (33.9 months; range, 0.3 to 58.2 months). Following completion of the extension study (intended to collect follow-up data only), the median duration of follow-up for all MDS-003 patients was 3.2 years (38.4 months; range, 0.3 to 81.9 months).

In Study CC-5013-MDS-004 (hereafter referred to as Study MDS-004), patients were randomised in a 1:1:1 ratio to one of three treatment arms:

- **Lenalidomide 10 mg:** oral lenalidomide 10 mg (two 5 mg capsules) QD on Days 1 to 21 and 2 placebo capsules QD on Days 22 to 28, every 28 days.
- **Lenalidomide 5 mg:** oral lenalidomide 5 mg (one 5 mg capsule) plus 1 placebo capsule QD, every 28 days.
- **Placebo:** 2 placebo capsules QD, every 28 days.

In Study MDS-004, all 205 enrolled patients received at least 1 dose of double-blind study medication and were included in the safety population (69, 69 and 67 patients received lenalidomide 10 mg, lenalidomide 5 mg and placebo, respectively). Of the 67 placebo patients, 56 crossed-over to lenalidomide 5 mg; however, 11 received only placebo (ie, the patients received no lenalidomide). The demographics and baseline characteristics of patients are summarised in Table 2.3.6-3, while duration of exposure to study medication is presented in Table 2.3.6-4.

In the safety population, there were more females than males (71.0% to 80.6% of patients were female across the three treatment groups), consistent with the expected demographics for a del 5q MDS population. The mean age was 66.2 to 68.2 years across the treatment groups, with the majority of patients (60.0% overall) over the age of 65 years. Of the 205 patients in the safety population, 191 had a del 5q (31 to 33) chromosomal abnormality and 4 patients did not; these demographic data were missing for 10 patients. The majority of patients were in the IPSS MDS low and INT-1 risk groups (70 and 74 patients overall, respectively). In addition, the majority of patients had or presented with RA based on central review for FAB classification, with comparable percentages across treatment groups. The median transfusion burden was 6 units/8 weeks in all 3 treatment groups.

**Table 2.3.6-3: Demographic and Baseline Characteristics of Del 5q MDS Patients in Study MDS 004 (Double blind Safety Population; Data Cutoff: 11 Oct 2010)**

| Demographic/Baseline Characteristic | Lenalidomide 10 mg (N = 69) | Lenalidomide 5 mg (N = 69) | Placebo (N = 67)[a] |
|---|---|---|---|
| **Age (Years)** | | | |
| Mean (SD) | 67.6 (11.68) | 66.2 (10.54) | 68.2 (9.70) |
| Median (Range) | 68 (36 to 86) | 66 (40 to 86) | 69 (39 to 85) |
| ≤ 65 (n [%]) | 29 (42.0) | 32 (46.4) | 21 (31.3) |
| > 65 (n [%]) | 40 (58.0) | 37 (53.6) | 46 (68.7) |
| **Sex (n [%])** | | | |
| Male | 20 (29.0) | 16 (23.2) | 13 (19.4) |
| Female | 49 (71.0) | 53 (76.8) | 54 (80.6) |
| **Race/Ethnicity (n [%])** | | | |
| White | 69 (100.0) | 67 (97.1) | 66 (98.5) |
| Other | 0 | 2 (2.9) | 1 (1.5) |
| **5q(-) (31-33) Chromosomal Abnormality (n [%])**[b] | | | |
| Yes | 64 (92.8) | 64 (92.8) | 63 (94.0) |
| No | 1 (1.4) | 2 (2.9) | 1 (1.5) |
| Missing | 4 (5.8) | 3 (4.3) | 3 (4.5) |
| **IPSS Score (Central Review) (n [%])** | | | |
| Low (0) | 20 (29.0) | 20 (29.0) | 30 (44.8) |
| INT-1 (0.5 to 1.0) | 23 (33.3) | 29 (42.0) | 22 (32.8) |
| INT-2 (1.5 to 2.0) | 3 (4.3) | 5 (7.2) | 2 (3.0) |
| High risk (≥ 2.5) | 1 (1.4) | 0 | 0 |
| Missing | 22 (31.9) | 15 (21.7) | 13 (19.4) |
| **FAB Classification (Central Review) (n [%])** | | | |

**Table 2.3.6-3: Demographic and Baseline Characteristics of Del 5q MDS Patients in Study MDS 004 (Double blind Safety Population; Data Cutoff: 11 Oct 2010)**

| Demographic/Baseline Characteristic | Lenalidomide 10 mg (N = 69) | Lenalidomide 5 mg (N = 69) | Placebo (N = 67)[a] |
|---|---|---|---|
| RA | 32 (46.4) | 38 (55.1) | 37 (55.2) |
| RARS | 9 (13.0) | 7 (10.1) | 8 (11.9) |
| RAEB | 9 (13.0) | 9 (13.0) | 4 (6.0) |
| CMML | 0 | 2 (2.9) | 1 (1.5) |
| RAEB-T | 0 | 0 | 1 (1.5) |
| CML | 1 (1.4) | 0 | 0 |
| Specimen not adequate/Other/Missing | 17 (24.6) | 11 (15.9) | 12 (17.9) |
| **Transfusion Burden (Units/8 Weeks)** | | | |
| Median (Range) | 6 (2 to 12) | 6 (1 to 25) | 6 (2 to 12) |

[a] Including placebo patients who cross over to lenalidomide 5 mg after 16 weeks of double-blind phase.

[b] Standard cytogenic studies were performed and centrally reviewed by an independent cytogenetic reviewer to confirm the patient's cytogenic eligibility at baseline.

Source: Study MDS-004 CSR, Table 14.1.3.2.

Across the three treatment groups, there was significant comorbidity (see Table 14.1.4, MDS-004 CSR), which included a history of hypertension (20.3% to 27.5%), osteoarthritis (8.7% to 13.4%), hypercholesterolaemia (7.2% to 11.6%), constipation (5.8% to 10.4%) and atrial fibrillation (8.7% to 10.1%).

The mean duration of exposure was comparable across the lenalidomide groups and slightly lower in the placebo group (including the patients who crossed over to lenalidomide; Table 2.3.6-4), which is consistent with the smaller proportion of patients in the placebo group continuing with treatment beyond 24 weeks. Of note, the study design stipulated that patients with no evidence of at least a minor erythroid response after 16 weeks double-blind treatment were to be discontinued from the double-blind phase and if they had received placebo treatment could enter the open-label phase.

The median daily dose of lenalidomide received per cycle for the first 6 cycles ranged from 5.0 mg to 2.5 mg in the 5 mg group and from 10.0 mg to 5.0 mg in the 10 mg group, and was consistently higher in the 10 mg group. The respective median daily doses remained stable through Month/Cycle 12 (Study MDS-004 CSR, Section 12.1.1).

**Table 2.3.6-4: Duration of Exposure of Del 5q MDS Patients in Study MDS 004 (Double blind Safety Population; Data Cutoff: 11 Oct 2010)**

| Duration (Weeks)[a] | Lenalidomide 10 mg (N = 69) | Lenalidomide 5 mg (N = 69) | Placebo (N = 67) |
|---|---|---|---|
| **Treatment Duration (n [%])** | | | |
| ≥ 4 weeks | 63 (91.3) | 67 (97.1) | 63 (94.0) |
| ≥ 8 weeks | 59 (85.5) | 62 (89.9) | 62 (92.5) |
| ≥ 16 weeks | 54 (78.3) | 50 (72.5) | 42 (62.7) |
| ≥ 24 weeks | 41 (59.4) | 30 (43.5) | 6 (9.0) |
| ≥ 32 weeks | 39 (56.5) | 29 (42.0) | 4 (6.0) |
| ≥ 52 weeks | 29 (42.0) | 15 (21.7) | 3 (4.5) |
| **Duration of Exposure** | | | |
| Mean (SD) | 34.7 (20.22) | 28.6 (17.71) | 17.4 (9.65) |
| Median | 50.3 | 18.0 | 16.0 |
| Range | 1.4 to 56.3 | 2.4 to 53.1 | 1.3 to 54.4 |

[a] Treatment duration = (date of last dose = date of first dose + 1)/7

Source: Study MDS-004 CSR, Table 14.3.1.1.

## *2.3.7 Module SIII.7: Clinical Studies in Mantle Cell Lymphoma*

Study CC-5013-MCL-002

A total of 254 patients were enrolled and randomised in a 2:1 ratio to the lenalidomide arm (n = 170) or the control arm (n = 84). Of all patients randomised, 250 (98.4%) received at least 1 dose of study medication, either lenalidomide (n = 167; 98.2%) or Investigator's choice (n = 83; 98.8%). The mean and median treatment duration in the lenalidomide arm were 46.6 and 24.3 weeks, respectively, and ranged from 0.4 to 241.9 weeks as of the data cutoff date 07 Mar 2014 (1 year after the last patient was randomised). The proportion of patients on study in the 2 treatment arms was comparable over time, with > 40% of patients remaining on study for ≥ 80 weeks (≥ 18.5 months) in each arm. Demographics and baseline characteristics of patients are summarised in Table 2.3.7-1, while duration of exposure to study medication is presented in Table 2.3.7-2.

The majority of the safety population (67.6%) were elderly patients (≥ 65 years old), and the median age was 68.5 years. Overall, the study included more men (73.6%) than women (26.4%), in line with distribution of the disease by sex (2.3:1) in Europe (Sant, 2010). Most patients were white or Caucasian (95.2%); race was not reported in the remaining patients (4.8%). Overall, no clinically meaningful differences in demographic characteristics were observed between treatment arms. Review of baseline disease characteristics showed that, in general, patients had advanced relapses, as evidenced by a median of 2 prior systemic anti-lymphoma therapies and a significant number of patients with 2 or more prior relapses.

**Table 2.3.7-1: Demographic and Baseline Characteristics of MCL Patients in Studies MCL-002, MCL-001, NHL-002 and NHL-003 (Safety Population)**

| Demographic/ Baseline Characteristic | MCL-002 | | All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003) (N = 373) |
|---|---|---|---|
| | Lenalidomide (N = 167) | Control (N = 83) | |
| **Age (Years)** | | | |
| Mean (SD) | 68.1 (9.37) | 67.4 (8.22) | 67.4 (9.27) |
| Median (Range) | 69.0 (44.0 to 88.0) | 68.0 (49.0 to 87.0) | 68.0 (33.0 to 88.0) |
| < 65 (n [%]) | 54 (32.3) | 27 (32.5) | 130 (34.9) |
| ≥ 65 (n [%]) | 113 (67.7) | 56 (67.5) | 243 (65.1) |
| **Sex (n [%])** | | | |
| Male | 122 (73.1) | 62 (74.7) | 282 (75.6) |
| Female | 45 (26.9) | 21 (25.3) | 91 (24.4) |
| **Race (n [%])** | | | |
| White or Caucasian | 159 (95.2) | 79 (95.2) | 353 (94.6) |
| Black or African American | 0 | 0 | 1 (0.3) |
| Asian/Pacific Islander | 0 | 0 | 3 (0.8) |
| Hispanic | 0 | 0 | 4 (1.1) |
| Other | 0 | 0 | 4 (1.1) |
| Missing | 8 (4.8) | 4 (4.8) | 8 (2.1) |
| **MCL Stage at Diagnosis (n [%])** | | | |
| I | 3 (1.8) | 2 (2.4) | 8 (2.1) |
| II | 10 (6.0) | 1 (1.2) | 20 (5.4) |
| III | 29 (17.4) | 20 (24.1) | 57 (15.3) |
| IV | 121 (72.5) | 58 (69.9) | 279 (74.8) |
| Missing | 4 (2.4) | 2 (2.4) | 9 (2.4) |
| **ECOG Performance Status (n [%])** | | | |
| 0 | 65 (38.9) | 35 (42.2) | 144 (38.6) |
| 1 | 76 (45.5) | 37 (44.6) | 178 (47.7) |
| 2 | 25 (15.0) | 11 (13.3) | 49 (13.1) |
| 3 | 0 | 0 | 1 (0.3) |
| Missing | 1 (0.6) | 0 | 1 (0.3) |

Data cutoff dates: Studies MCL-002 (07 Mar 2014); MCL-001 (20 Mar 2013); NHL-002 (23 Jun 2008); NHL-003 (27 Apr 2011).

**Table 2.3.7-2: Duration of Exposure in MCL Studies MCL 002, MCL 001, NHL 002 and NHL 003 (Safety Population)**

| Demographic/ Baseline Characteristic | MCL-002 | | All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003) (N = 373) |
|---|---|---|---|
| | Lenalidomide (N = 167) | Control (N = 83) | |
| **Number of Cycles** | | | |
| ≥ 1 | 167 (100.0) | 83 (100.0) | 373 (100.0) |
| ≥ 2 | 141 (84.4) | 68 (81.9) | 310 (83.1) |
| ≥ 3 | 119 (71.3) | 51 (61.4) | 246 (66.0) |
| ≥ 4 | 102 (61.1) | 41 (49.4) | 209 (56.0) |
| ≥ 6 | 83 (49.7) | 28 (33.7) | 171 (45.8) |
| ≥ 12 | 62 (37.1) | 7 (8.4) | 116 (31.1) |
| ≥ 18 | 37 (22.2) | 3 (3.6) | 70 (18.8) |
| ≥ 24 | 28 (16.8) | 0 | 46 (12.3) |
| ≥ 30 | 18 (10.8) | 0 | 31 (8.3) |
| **Duration (Weeks)** | | | |
| Mean (SD) | 46.6 (53.53) | 21.8 (31.30) | 40.5 (49.05) |
| Median | 24.3 | 13.1 | 17.0 |
| Range | 0.4 to 241.9 | 0.1 to 157.9 | 0.1 to 241.9 |

Data cutoff dates: Studies MCL-002 (07 Mar 2014); MCL-001 (20 Mar 2013); NHL-002 (23 Jun 2008); NHL-003 (27 Apr 2011).

The study populations in the TE and TNE NDMM, RRMM, del 5q MDS and MCL studies are representative of the patient populations for each condition in terms of age and likely comorbidity.

## 2.4 Module SIV: Populations Not Studied in Clinical Trials

### *2.4.1 Module SIV.1: Exclusion Criteria in Pivotal Clinical Studies within the Development Programme*

The important exclusion criteria in the pivotal clinical studies across the development programme are described in Table 2.4.1-1.

**Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies**

| Exclusion Criteria | Reason for exclusion | Is it considered to be included as missing information? | Rationale (if not included as missing information) |
|---|---|---|---|
| **Studies SWOG S0777, CALGB 100104, IFM 2005-02, MM-020, MM-015, MM-009, MM-010, MDS-003, MDS-004, MCL-002, MCL-001, NHL-003, NHL-002, NHL-007 and NHL-008** | | | |
| Pregnant and lactating women | Lenalidomide is contraindicated in pregnant | No | Section 4.3 of the SmPC clearly states that |

**Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies**

| Exclusion Criteria | Reason for exclusion | Is it considered to be included as missing information? | Rationale (if not included as missing information) |
|---|---|---|---|
| | women based on malformations seen in an embryofoetal developmental toxicity study in monkeys. Malformations similar to those resulting from thalidomide administration occurred in the offspring of female monkeys who received lenalidomide at doses as low as 0.5 mg/kg/day on gestational days 20 to 50 of pregnancy.<br>It is unknown if lenalidomide is secreted in human milk. There is a potential for adverse reactions in nursing infants from lenalidomide.<br>Pregnant and lactating females are excluded to avoid potential harm to the unborn fetus or breastfeeding newborn. | | lenalidomide is contraindicated in pregnant women and Section 4.4 includes a pregnancy warning.<br>Section 4.6 of the SmPC recommends that female patients must not breastfeed when taking lenalidomide, as it is not known if lenalidomide passes into human milk. |
| Known human immunodeficiency virus (HIV) positivity or seropositive/ active viral infections (hepatitis B antigen, hepatitis B virus [HBV], hepatitis C virus [HCV] or active infectious hepatitis) | IMiD drugs exert various effects on the immune system, altering cytokine production, regulating T cell costimulation and enhancing NK cell cytotoxicity. Particularly, IMiDs inhibit tumour necrosis factor-alpha, playing an important role in immune response against bacterial and viral infections. Moreover, lenalidomide causes myelosuppression, mainly neutropenia, which is an important risk factor for infections. In addition, patients are at an increased risk of lethal infections when treated with a combination of drugs that have a bone marrow suppressive effect. | No | Warnings on infection with or without neutropenia and viral reactivation have been included in Section 4.4 of the SmPC. Hepatic disorder in the context of pre-existing viral disease is also included in Section 4.4 of the SmPC.<br>Guidelines for dose adjustment for patients with neutropenia and MM, MDS, MCL or FL are outlined in Section 4.2 of the SmPC. |
| Prior history of malignancies | Due to the risk of SPM observed with the use of lenalidomide (monotherapy, combination therapy and with or without the use of | No | The safety outcome variable was incidence of SPM with the use of lenalidomide. |

**Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies**

| Exclusion Criteria | Reason for exclusion | Is it considered to be included as missing information? | Rationale (if not included as missing information) |
|---|---|---|---|
| | alkylating agent and prior ASCT), patients with a history of SPM (except for basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix or breast or incidental finding of prostate cancer stage T1a or T1b) were excluded unless the patient had been free of the disease for ≥ 5 years, due to the risk of SPM. | | Based on the diseases treated, the age of the target population, and the treatment regimens used (prior alkylating agents/auto ASCT), and SPM follow-up in clinical trials, SPM is an important identified risk. Section 4.4 of the SmPC includes warnings about SPM. |
| Patients who are unable or unwilling to undergo thromboprophylaxis | Data have shown that patients who do not undergo thromboprophylaxis, especially high risk patients, are at a higher risk for thromboembolism when lenalidomide is given in combination with dexamethasone. | No | Section 4.4 of the SmPC includes a warning to minimise all modifiable risk factors, to closely monitor patients with known risk factors, and a recommendation for prophylactic antithrombotics in patients with additional risk factors. |
| Chronic steroid use or immunosuppressive treatment | Patients with conditions requiring chronic steroid or immunosuppressive treatment, such as rheumatoid arthritis, multiple sclerosis and lupus, are likely to need additional steroid or immunosuppressive treatments in addition to the study treatment (lenalidomide in combination with dexamethasone or prednisone). Chronic steroid or immunosuppressive agents can compromise the immune system even more, thus putting the patients at increased risk for infections. | No | Experience to date has indicated that treatment with lenalidomide has been well tolerated by patients receiving physiological and high doses of dexamethasone. Use of other immunosuppressive medications in the target population is not anticipated to lead to an increased risk of common AEs known to be associated with lenalidomide. |
| Known hypersensitivity to thalidomide | A possible cross-reaction between lenalidomide and thalidomide has been reported in the literature. | No | Section 4.4 of the SmPC includes a warning that cases of allergic reaction/hypersensitivity reactions have been reported in patients treated with lenalidomide. |

**Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies**

| Exclusion Criteria | Reason for exclusion | Is it considered to be included as missing information? | Rationale (if not included as missing information) |
|---|---|---|---|
| | | | Patients who had previous allergic reactions while treated with thalidomide should be monitored closely, as a possible cross-reaction between lenalidomide and thalidomide has been reported in the literature. |
| Active central nervous system (CNS) lymphoma | Patients with active CNS lymphoma conditions have significantly worse prognoses and are excluded from the clinical development programme to ensure interpretability of efficacy. | No | Patients whose CNS lymphoma had been treated with chemotherapy, radiotherapy or surgery; had remained asymptomatic for 90 days (3 months); and demonstrated no CNS lymphoma were not excluded. Lenalidomide does not cross the blood-brain barrier. |
| **Studies CALGB 100104, IFM 2005-02, MM-020, MM-015, MM-009, MM-010, MDS-003, MDS-004, MCL-002, MCL-001, NHL-003, NHL-002** | | | |
| Moderate to severe hepatic impairment | Lenalidomide has not formally been studied in patients with impaired hepatic function.<br>No detectable in vitro metabolism of lenalidomide was observed in human liver microsomes, recombinant CYP enzymes, or isolated human hepatocytes, indicating that hepatic metabolism is not a major clearance pathway. | No | Hepatic metabolism is not a major clearance pathway for lenalidomide.<br>Section 4.2 of the SmPC states that lenalidomide has not been formally studied in patients with impaired hepatic function and there are no specific dose recommendations (for patients with hepatic impairment).<br>Section 5.2 of the SmPC states that population pharmacokinetic analyses included patients with mild hepatic impairment (N = 16, total bilirubin > 1 to ≤ 1.5 x upper limit of normal [ULN] or aspartate aminotransferase [AST] > ULN) and indicate that mild hepatic impairment does not influence |

**Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies**

| Exclusion Criteria | Reason for exclusion | Is it considered to be included as missing information? | Rationale (if not included as missing information) |
|---|---|---|---|
| | | | lenalidomide clearance (exposure in plasma). There are no data available for patients with moderate to severe hepatic impairment. |
| Moderate to severe renal insufficiency | Approximately 65% to 85% of lenalidomide is eliminated unchanged through urinary excretion in subjects with normal renal function. The elimination half-life is approximately 3 to 5 hours at clinical doses (5 to 50 mg/day). Steady-state levels are achieved within 4 days.<br>Pharmacokinetic analyses in subjects with impaired renal function indicate that, as renal function decreases, the total drug clearance decreases proportionally, which is reflected by increased AUC. The terminal half-life (t1/2,z) of lenalidomide was longer by approximately 6 to 12 hours in subjects with moderate or worse renal insufficiency. However, renal insufficiency did not alter the oral absorption of lenalidomide. The maximum concentration (Cmax) was similar between healthy subjects and subjects with renal insufficiency. | No | Renal excretion is the major clearance pathway for lenalidomide.<br>Recommended dose adjustments in patients with impaired renal function are described in Section 4.2 of the SmPC. No dose adjustments are required for patients with mild renal impairment.<br>Warnings and information regarding the use of lenalidomide in patients with renal insufficiency are provided in Sections 4.4 and 5.2 of the SmPC. |
| Inadequate marrow reserve<br>Neutropenia (≥ Grade 3) | Study patients may be at risk of significant neutropenia through effects of the study drug. | No | Guidelines for dose adjustment for patients with neutropenia and MM, MDS, MCL or FL are outlined in Section 4.2 of the SmPC. Warnings regarding the risk of neutropenia in patients treated with lenalidomide are provided in Sections 4.4 and 4.8 of the SmPC. |

**Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies**

| Exclusion Criteria | Reason for exclusion | Is it considered to be included as missing information? | Rationale (if not included as missing information) |
|---|---|---|---|
| Inadequate marrow reserve<br>Thrombocytopenia (≥ Grade 2 or ≥ Grade 3 per indication) | Study patients may be at risk of significant thrombocytopenia through effects of the study drug. | No | Guidelines for dose adjustment for patients with thrombocytopenia and MM, MDS, MCL or FL are outlined in Section 4.2 of the SmPC. Warnings regarding the risk of thrombocytopenia in patients treated with lenalidomide are provided in Sections 4.4 and 4.8 of the SmPC. |

### *2.4.2 Module SIV.2: Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes*

The clinical development programme is unlikely to detect rare adverse reactions. Patients with FL, relapsed or refractory MM, del 5q MDS and MCL have overall a limited survival time meaning that the trial programme may be limited in its ability to assess cumulative effects, and those effects with a long latency. Furthermore, these patients are, to a great extent, elderly with a limited natural life expectancy.

### *2.4.3 Module SIV.3: Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes*

To ensure patient safety, specific populations of patients were excluded from the clinical studies (Table 2.4.3-1). Thus, experience in these populations is limited.

**Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Development Programmes**

| Type of special population | Exposure |
|---|---|
| Pregnant women | Not included in the clinical development programme. |
| Lactating women | Not included in the clinical development programme. |
| Patients with renal impairment | **FL studies**<br>In Studies NHL-007 and NHL-008, patients were required to have a baseline CLcr of ≥ 30 mL/min. In Study NHL-007, 13.7% and 10.8% of FL patients in the lenalidomide plus rituximab and rituximab plus placebo arms, respectively, had a baseline CLcr of ≥ 30 mL/min but < 60 mL/min. In Study NHL-008, 20.9% of FL patients had a baseline CLcr of ≥ 30 mL/min but < 60 mL/min.<br>**TE NDMM studies**<br>The TE NDMM studies had entry criteria for renal function, measured by either serum creatinine or CLcr. |

## Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Development Programmes

| Type of special population | Exposure |
|---|---|
| | In Study CALGB 100104, patients were required to have CLcr ≥ 30 mL/min (after ASCT) prior to receiving maintenance therapy. In Study IFM 2005-02, patients were required to have serum creatinine < 160 µmol/L before and after ASCT, and serum creatinine < 250 µmol/L during ASCT. In both TE NDMM studies, there were no starting dose adjustments based on renal function specified for lenalidomide maintenance. The majority of patients in both studies had CLcr ≥ 50 mL/min at post-ASCT.<br><br>In Study CALGB 100104, 3 patients (1.3%) in the lenalidomide arm (no patients in the placebo arm) and in Study IFM 2005-02, no patients in the lenalidomide arm and only one patient in the placebo arm (0.4%) had severe renal insufficiency (CLcr < 30 mL/min) post-ASCT. The proportions of patients with moderate renal impairment (CLcr ≥ 30 mL/min to < 50 mL/min) were 8.5% and 6.3% in the lenalidomide and placebo arms of Study CALGB 100104, respectively, and 3.1% and 2.5% in the lenalidomide and placebo arms of Study IFM 2005-02, respectively.<br><br>**TNE NDMM studies**<br><br>In Study SWOG S0777, patients were required to have a calculated or measured CLcr > 30 cc/min. Across both arms (RVd and Rd), approximately 70% of patients had baseline creatinine values of ≥ 60 mL/min, while 30% entered with a baseline creatinine value of < 60 mL/min and 17.7% of patients entered had a CLcr < 50 mL/min.<br><br>Approximately half of patients enrolled in TNE NDMM Studies MM-020 and MM-015 had some degree of renal insufficiency (CLcr < 60 mL/min).<br><br>**RRMM studies**<br><br>In Study MM-009, 22.4% of patients in each treatment arm had relevant medical history/concomitant disease in the renal and urinary disorder system organ class (SOC). In Study MM-010, 12.5% of patients in the lenalidomide/dexamethasone arm and 14.9% of patients in the placebo/dexamethasone arm had relevant medical history/concomitant disease in the renal and urinary disorder SOC.<br><br>**MDS studies**<br><br>In total, 17.6% of patients in Study MDS-003, and 11.6%, 5.8% and 6.0% of patients in the lenalidomide 10 mg, 5 mg and placebo groups, respectively, in Study MDS-004 had relevant medical history/concomitant disease in the renal and urinary disorder SOC.<br><br>**MCL studies**<br><br>Patients with severe renal impairment (CLcr < 30 mL/min) were excluded from the clinical studies in MCL. In Study MCL-002, 77.6% of all enrolled patients had normal renal function or mild renal impairment at baseline whereas 21.7% had moderate renal impairment (30 mL/min ≤ CLcr < 60 mL/min).<br><br>**PK study**<br><br>A multi-centre study (CC-5013-PK-001) has been performed with lenalidomide 25 mg daily as a single oral dose in 5 groups of patients (total 30 patients) with non-malignant conditions and defined by renal function (normal, mild impairment, moderate impairment, severe impairment and end-stage renal disease).<br><br>Dose adjustment for patients with moderate or severe impaired renal function or end stage renal disease are provided in Section 4.2 the SmPC. |

## Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Development Programmes

| Type of special population | Exposure |
|---|---|
| Patients with moderate to severe hepatic impairment | These patients were excluded from the clinical development programme. |
| Patients with uncontrolled cardiovascular disorders (including congestive heart failure, hypertension, or cardiac arrhythmia) and MI within 6 months prior to enrollment | These patients were excluded from the clinical development programme. |
| Immunocompromised patients | The target population used in the clinical trial development programme were immunocompromised patients. |
| Patients with a disease severity different from inclusion criteria in clinical trials | **FL studies**<br>In Study NHL-007, patients were required to have documented relapsed, refractory, or progressive disease after previous treatment with at least one prior systemic chemotherapy, immunotherapy or rituximab plus chemotherapy and had to have received at least 2 previous doses of rituximab. Overall, 74.1% of FL patients in Study NHL-007 had advanced disease (Ann Arbor Stage III/IV) and 34.0% had high-risk FLIPI scores. In Study NHL-008, 88.7% of FL patients had advanced disease (Ann Arbor Stage III/IV).<br>**TE NDMM studies**<br>In Studies CALGB 100104 and IFM 2005-02, of the patients treated with lenalidomide, 16.5% and 21.8% of patients, respectively, had ISS Stage III at diagnosis. In Study CALGB 100104, 3 patients (1.3%) in the lenalidomide arm (no patients in the placebo arm) and in Study IFM 2005-02, no patients in the lenalidomide arm and only one patient in the placebo arm (0.4%) had severe renal insufficiency (CLcr < 30 mL/min) post-ASCT.<br>**TNE NDMM studies**<br>In Study SWOG S0777, patients in general had distribution of disease severity that was similar to what is reported and expected in studies of NDMM. Of note, at baseline, 33.1% of patients were ISS Stage III; 12.6% of patients had cytogenic risk classified as high; 3.3% of patients had an ECOG performance status of 3, and 14.5% of patients presented with a high lactate dehydrogenase value (> 280 IU/L).<br>In general, patients in Study MM-020 had advanced-stage disease: of the total study population, 40.6% had ISS Stage III, 9.1% had severe renal insufficiency (CLcr < 30 mL/min), 71.2% had a history of bone disease, and 13.5% had radiation for MM prior to treatment in the study. About a third (33.5%) of the study patients had cytogenetic profiles associated with adverse risk (defined as t[4;14], t[14;16], del[13q] or monosomy 13, del[17p], or 1q gain), while 18.3% of patients overall presented with baseline lactate dehydrogenase values of 200 U/L or higher.<br>In Study MM-015, it is noteworthy that approximately half of the patients in each treatment arm were ISS Stage III; and approximately half had CLcr < 60 mL/min.<br>**RRMM studies** |

**Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Development Programmes**

| Type of special population | Exposure |
|---|---|
| | Participants in Studies MM-009 and MM-010 had a history of disease progression after at least one prior antimyeloma regimen (with at least 2 cycles of treatment), measurable levels of serum (> 0.5 mg/dL) and urine (≥ 0.2 g excreted in a 24 hour collection sample) M-paraprotein, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2. The majority of patients had Stage II or III MM; however, a small but comparable proportion of patients in each treatment group of both studies had Stage I disease (1.8% and 6.3% in the lenalidomide/dexamethasone arm versus 2.3% and 4.6% in the placebo/dexamethasone arm of Studies MM-009 and MM-010, respectively).<br>**MDS studies**<br>In Study MDS-003, all 148 patients had a del 5q cytogenetic abnormality, and the majority had low or INT-1-risk MDS (118/148; 79.7%). Seven (4.7%) and two (1.4%) patients had INT-2 and high-risk MDS, respectively. In Study MDS-004, 93.2% of patients overall had a del 5q cytogenetic abnormality, and the majority had low or INT-1-risk MDS (144/205; 70.2%). Ten (4.9%) patients overall had INT-2 risk-MDS, and a single patient in the lenalidomide 10 mg group had high-risk MDS. IPSS score was missing for 50 of the 205 patients (24.4%). Therefore, limited data are available for the use of lenalidomide in the higher risk group. It should be noted that patients with INT-2 and high-risk MDS have a poor prognosis, with median survival durations of 1.2 and 0.4 years, respectively.[81]<br>**MCL studies**<br>In Study MCL-002, patients generally had advanced stage disease: 91.3% of all patients randomised had MCL Stage III or IV at diagnosis. Furthermore, 33.5% of patients had high-risk Mantle cell lymphoma International Prognostic Index (MIPI) score at baseline, 42.9% had high tumour burden at baseline, and 19.7% had bulky disease. For 79 patients, data on bone marrow were available at baseline. For 34 (43.0%) of these patients, disease involvement in the bone marrow was positive (ie, the biopsy showed unequivocal cytologic or architectural evidence of malignancy). Few patients (15.0%) had an ECOG performance score of 2 at baseline. Patients with ECOG performance scores of 3 or 4 were excluded. |
| Population with relevant different ethnic origin | The PK and safety of lenalidomide were compared between healthy Japanese and Caucasian subjects in a Phase 1, randomised, double-blind, placebo-controlled, single-dose study. The concentration-time profiles for the Japanese and Caucasian subjects were similar at all 3 lenalidomide dose levels (5 mg, 10 mg, and 20 mg). There were no statistically significant differences ($p > 0.05$) in the PK parameters between Japanese and Caucasian subjects at each dose level. Cmax and AUC extrapolated to time infinity increased proportionally with doses from 5 mg to 20 mg in both ethnic groups. No ethnicity-related trends were observed in AEs, clinical laboratory tests, vital signs, and ECGs.<br>In Study NHL-007, patients were predominantly white with 90 (61.6%) and 92 (62.2%) white FL patients receiving treatment with lenalidomide plus rituximab and rituximab plus placebo, respectively. In Study NHL-008, 164 (92.7%) FL patients who received lenalidomide plus rituximab were white.<br>In the TE NDMM Study CALGB 100104, patients were predominantly of white or Caucasian race with 169 (75.4%) and 167 (75.6%) white/Caucasian patients receiving maintenance treatment with lenalidomide and placebo, respectively. Data on race were not collected in Study IFM 2005-02. |

**Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Development Programmes**

| Type of special population | Exposure |
|---|---|
| | In the TNE NDMM study SWOG S0777, 79.7% of patients were Caucasian, 13.7% were Black or African-American, 2.3% were Asian, 1.1% were Native Hawaiian or other Pacific Islander, 0.6% were American Indian or Alaska Native, and 2.5% were of Unknown race. Patients were predominantly of white or Caucasian (89.0%) race, non-Hispanic or Latino (92.8%) ethnicity, and recruited in Europe (68.6%) in Study MM-020, and the majority of patients were of white or Caucasian (98.7%) race and non-Hispanic or Latino (99.8%) ethnicity in Study MM-015.<br><br>In the RRMM studies performed in the USA, Canada, Australia, Europe, Israel and Ukraine, 88.7% of patients in the lenalidomide/dexamethasone arm were categorised as white, 7.6% of these patients were categorised as black, 0.8% were categorised as Hispanic, 1.7% were categorised as Asian/Pacific Islander and 1.1% were categorised as other.<br><br>The lenalidomide PK in Asian RRMM patients (Studies CC-5013-MM-017 and CC-5013-MM-021) are comparable to that historically observed in Caucasian RRMM patients.<br><br>In the del 5q MDS studies, which were performed in the USA, Europe and Israel, the majority of patients were white (96.6% and 98.5% for Studies MDS-003 and MDS-004, respectively).<br><br>The PK of lenalidomide in Japanese patients with del 5q MDS (Study CC-5013-MDS-007-PK) were comparable to that historically observed in the Caucasian MM or MDS patients.<br><br>In the studies in MCL, the majority of patients were of white or Caucasian race. In Study MCL-002, 94.9% of all patients randomised were of white race. |
| Subpopulations carrying relevant genetic polymorphisms | Lenalidomide is not metabolised by the CYP enzymes. Genetic polymorphisms have not been studied in the lenalidomide clinical trial population.<br><br>A tumour protein (TP) 53 mutation is present in approximately 20% to 25% of lower-risk MDS del 5q patients and is associated with a higher risk of progression to AML. In a post-hoc analysis of a clinical trial of Revlimid in low- or INT-1-risk MDS (Study MDS-004), the estimated 2-year rate of progression to AML was 27.5% in patients with immunohistochemistry (IHC)-p53 positivity and 3.6% in patients with IHC-p53 negativity (p = 0.0038) (SmPC, Sections 4.4 and 4.8). |
| Other | **Paediatric Population:**<br><br>Lenalidomide is not authorised for use in children in the EU/EEA or elsewhere in the world. Class waivers for MM and all mature B cell neoplasms in paediatrics and product-specific waivers for MCL, MDS and all mature B cell neoplasms in paediatrics have been granted by the Paediatric Committee (PDCO) at the EMA (Decision dated 04 Oct 2017).<br><br>There is limited experience with lenalidomide from investigator-initiated trials (IITs) in children. Lenalidomide should not be used in the paediatric age group (0 to 17 years) outside of a clinical trial.<br><br>Data for cumulative paediatric exposure in the EU/EEA Member States from product launch to 26 Dec 2017 (where such data are available) are presented in Section 2.5.1. The cumulative paediatric commercial exposure for lenalidomide is 257 patients as of 26 Dec 2017. In total, 17 paediatric patients with relapsed/refractory AML were treated with lenalidomide in the BMS-sponsored Study CC-5013-AML-002, which was |

**Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Development Programmes**

| Type of special population | Exposure |
|---|---|
| | conducted in the US and Canada, and accounts for all known paediatric exposure within the clinical trial setting. |

## 2.5 Module SV: Post-Authorization Experience

### *2.5.1 Module SV.1: Post-authorization Exposure*

#### *2.5.1.1 Module SV.1.1: Method Used to Calculate Exposure*

The cumulative value for exposure represents the estimated number of unique patients exposed to the product from 27-Dec-2005 through 26-Dec-2022.

The methodology for estimating commercial patient exposure utilizes up to 3 data sources:

1) The Company's Sales/Shipment Data – this data consists of all shipments of BMS product to all applicable countries and includes commercial and free-of-charge units for both branded and generic product (as applicable). The data are used to determine the units (eg, milligrams) of a product that were sold to a geography to estimate the number of patients who would have been exposed to that product, based on expected dosing in the geography. Shipment data are used to estimate the active patients for a period of time by dividing the total units sold by the average units per patient (note that average units per patient is derived from epidemiologic and market research).
2) Claims Data – these data consist of 2 distinct sources of electronic health care claims data in the USA: Optum Clinformatics Datamart and Symphony Claims for Hem/Onc. Claims data consisting of distinct patient IDs and prescription fill rates for each product are used to understand usage patterns. For newly approved products, until sufficient claims data are available, patterns are based on discontinuation rates derived from clinical trial experience.
3) Controlled Distribution Database – this data source provides detailed patient exposure including demographics, indication for use, and dosing information in the USA.

#### *2.5.1.2 Module SV.1.2: Exposure*

Cumulatively, as of 26-Dec-2022, approximately 959,466 patients have been exposed to commercial lenalidomide.[112] This excludes subjects enrolled in IITs who receive lenalidomide in the [redacted] through the REVLIMID REMS® program (19,282 subjects) and in [redacted] through RevAid® (385subjects) to avoid double counting these exposures.

**Table 2.5.1.2-1: Summary of Worldwide Commercial Exposure**

| Location | Cumulative |
|---|---|
| [redacted] | 366,800[a] |
| [redacted][b] | 265,374 |

**Table 2.5.1.2-1: Summary of Worldwide Commercial Exposure**

| Location | Cumulative |
|---|---|
| [redacted] | 90,911 |
| [redacted] | 40,672 |
| [redacted] | 24,091[a] |
| [redacted] / [redacted] | 24,853 |
| [redacted] | 22,210 |
| Rest of World[c] | 124,555 |
| **TOTAL** | 959,466 |

[a] Since IIT subjects in the [redacted] receive lenalidomide through commercial sources, the cumulative total is reduced by the number of these subjects to avoid double-counting these exposures.

[b] Includes the [redacted].

[c] Includes countries and regions not otherwise specified in the table.

### *2.5.1.3 Exposure within the EU/EEA Member States*

As of 26 Dec 2022, lenalidomide has been approved in 31 EU/EEA Member States and the UK: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, The Netherlands and the UK.[112]

Data on [redacted] and the [redacted] as pertains to cumulative exposure up to 26-Dec-2022 in adults, FCBP, and paediatric use (where such data are available) are presented in Table 2.5.1.3-1 and Table 2.5.1.3-2. In the [redacted] the most common indications for which lenalidomide has been used up to 26-Dec-2022 are presented in Table 2.5.1.3-3 and Table 2.5.1.3-4.

**Table 2.5.1.3-1: [redacted] Lenalidomide Estimated Patient Exposure by Country from Implemented Controlled Access Programme**

| Country | Number of Patients (%) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Exposure Cumulative Period | | | | | | | | | | | | | | | |
| | MM | | MDS | | MCL | | Off-label | | Adults | | FCBP | | Children | | Total Exposure | |
| | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| [redacted] | 0 | 0 | 0 | 0 | 0 | 0 | 10,768 | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 10,768 | 100 |
| [redacted] | 11,449 | 93 | 398 | 3 | 28 | 0 | 376 | 3 | 11,856 | 97 | 79 | 1 | 3 | 0 | 12,251 | 100 |
| [redacted] | 300 | 96 | 7 | 2 | 0 | 0 | 5 | 2 | 312 | 100 | 1 | 0 | 0 | 0 | 312 | 100 |
| [redacted] | 189 | 97 | 3 | 2 | 0 | 0 | 2 | 1 | 166 | 86 | 0 | 0 | 0 | 0 | 194 | 100 |
| [redacted] | 2,819 | 94 | 184 | 6 | 4 | 0 | 4 | 0 | 3,011 | 100 | NA | NA | 0 | 0 | 3,011 | 100 |
| [redacted] | 336 | 92 | 30 | 8 | 0 | 0 | 0 | 0 | 366 | 100 | 7 | 2 | 0 | 0 | 366 | 100 |
| [redacted] | 6,089 | 90 | 455 | 7 | 61 | 1 | 161 | 2 | 6,766 | 100 | 92 | 1 | 0 | 0 | 6,766 | 100 |
| [redacted] | 965 | 80 | 136 | 11 | 2 | 0 | 105 | 9 | 1,208 | 100 | 5 | 0 | 0 | 0 | 1,208 | 100 |
| [redacted] | 4,628 | 87 | 78 | 1 | 37 | 1 | 587 | 11 | 5,338 | 100 | 191 | 4 | 4 | 0 | 5,330 | 100 |
| [redacted] | 50,334 | 84 | 2,293 | 4 | 1,063 | 2 | 6,376 | 11 | NA | NA | NA | NA | NA | NA | 60,066 | 100 |
| [redacted] | 9 | 90 | 1 | 10 | 0 | 0 | 0 | 0 | 10 | 100 | 0 | 0 | 0 | 0 | 10 | 100 |
| [redacted] | 185 | 96 | 4 | 2 | 0 | 0 | 4 | 2 | 185 | 96 | 0 | 0 | 0 | 0 | 193 | 100 |
| [redacted] | 545 | 91 | 24 | 4 | 3 | 1 | 27 | 5 | 551 | 92 | 12 | 2 | 0 | 0 | 599 | 100 |
| [redacted] | 98 | 87 | 0 | 0 | 1 | 1 | 14 | 12 | 113 | 100 | 2 | 2 | 0 | 0 | 113 | 100 |
| [redacted] | 4,947 | 93 | 347 | 7 | 3 | 0 | 31 | 1 | 5,328 | 100 | 141 | 3 | 0 | 0 | 5,328 | 100 |
| [redacted] | 1,471 | 83 | 63 | 4 | 1 | 0 | 227 | 13 | NA | NA | NA | NA | NA | NA | 1,762 | 100 |
| [redacted] | 1,044 | 98 | 22 | 2 | 0 | 0 | 0 | 0 | 1,066 | 100 | NA | NA | 0 | 0 | 1,066 | 100 |
| [redacted] | 12,244 | 80 | 325 | 2 | 49 | 0 | 2,630 | 17 | 15,224 | 100 | 176 | 1 | 4 | 0 | 15,248 | 100 |
| **Total** | 97,652 | 78 | 4,370 | 4 | 1,252 | 1 | 21,317 | 17 | 51,500 | 41 | 706 | 1 | 11 | 0 | 124,591 | 100 |

[redacted] [redacted] exposure data are only available until and including 30-Nov-2020.

[redacted] As from 04-Mar-2020, patient ID code is no longer collected, therefore patient counts for the current period (27-Dec-2020 through 26-Dec-2022) are not possible. Cumulative data: age category included 3 children, 11,856 confirmed adult patients, 390 unknown and 2 inconclusive; risk category included 6,728 male patients, 5,443 female patients (79 FCBP) and 79 inconclusive patients and 1 unknown.

[redacted] Exposure data no longer collected for [redacted] The cumulative data includes data up to the date of 26 Dec 2018.

[redacted] Please be informed that [redacted] is no longer capturing exposure data for lenalidomide, given that the initials of the patients and the status of the prescription (initial or repeated) are no longer collected and thus we are not able to know the number of patients exposed to the medication for the current period (27-Dec 2020 through 26-Dec-2022).

[redacted] The cumulative data includes data up to the date of 26-Dec-2018. [redacted] no longer collects this data per agreement with the NCA in May 2019.

[redacted] Please note: The cumulative data include data up to 05-Feb-2020. After this date, [redacted] no longer collects this data as per agreement with the NCA.

[redacted] The cumulative data includes data up to the date of 26-Dec-2018. After this date, [redacted] no longer collects this data per agreement with the NCA in August 2019.

[redacted] Edited for period 27-Dec-2020 through 26-Dec-2022: off-label - 55 (all indications were provided); patient type: 1,610 adults, 943 male patients, 40 FCBP, 631 FNCBP, 2 unknown. Newly indicated follicular lymphoma - 14 patients. Total exposure – 1,614 patients. Cumulative period: off-label - 587 (77 indications not provided); patient type: 2,117 male patients, 191 FCBP, 2,040 FNCBP, 146 unknown. Unknown age = 12 patients. Children = 4 patients (3 male and 1 FNCBP). Newly indicated follicular lymphoma - 24 patients. Total exposure – 5,354.

[redacted] Data regarding number of patients, sex, and age are only available for off-label use. For the following indications data are underestimated because starting from 01-Jan-2013 the AIFA National Oncology Registry was changed and the updated information are not available: second line MM (in label), MDS 5q- isolated (in label), MDS 5q- not isolated (Law 648), MCL and DLBCL (Law 648), and amyloidosis (Law 648). Starting from 18-Nov-2021 (Official Journal n. 274 dated 17-Nov-2021) off-label data will be collected by the NCA through the PPP AIFA registry directly and will not be available for the reporting above.

[redacted] Lenalidomide is not commercially available in [redacted]

[redacted] Exposure data were collected until 01-Jul-2019. After this date, data collection was impossible due to lenalidomide generics on the market.

[redacted] As of 04-Mar-2020, patient ID code was no longer collected, therefore patient count for the current period (27-Dec-2020 through 26-Dec-2022) was not possible. For cumulative data: age category included 551 confirmed adult patients and 48 patients of unknown age; of 599 patients, 14 patients were prescribed lenalidomide for an unknown indication and 12 patients for an inconclusive indication (counted as off-label).

[redacted] The cumulative data includes data up to the date of 26-Dec-2019. Due to the new SOF adopted earlier this year, it is not possible to supply the lenalidomide exposure data as previously done, since the information required to compile the data is no longer being collected.

[redacted] The cumulative data includes data up to the date of 26-Dec-2018. The cumulative reporting period was from 11-Sep-2009 to 26-Dec-2018. Exposure data is no longer being collected for [redacted] as of 06-Jun-2019, as agreed with the corresponding NCA.

[redacted] The cumulative data includes data up to the date of 26-Dec-2018. After this date, [redacted] no longer collects this data per agreement with NCA in July 2018.

[redacted] The cumulative data includes data up to the date of 26-Dec-2018. After this date, [redacted] no longer collects this data, as agreed with the corresponding NCA.

[redacted] The implemented controlled distribution system does not capture real time data linked to medicinal product dispense. Data are collected retrospectively and presented in annual reports with a defined period covered. These annual reports are provided in the EU-specific Annex of the PBRER per period covered. The cumulative data that is provided reflects data up to 26-Dec-2016; there were 20 patients of unknown age.

No exposure data collected for the following countries:

[redacted] No study was conducted to collect information on patient exposure and used indications during the covered period. No cumulative data are available. No lenalidomide patient exposure data are available for [redacted] for the period 27-Dec-2020 through 26-Dec-2022.

[redacted] Exposure data originating from the implemented controlled distribution system are not collected.

[redacted] The implemented controlled distribution system in the [redacted] does not provide patient exposure data. The data provided is from Company supported supply on NPP basis for off-label indications only.

[redacted] PPP Revlimid in place in [redacted] does not collect exposure data.

[redacted] Exposure data are not available for lenalidomide in [redacted]

[redacted] There are no changes for [redacted] as there are no data for the cumulative/interval exposure period from the marketed use of lenalidomide for [redacted] The requested exposure data are not available for [redacted]

**Table 2.5.1.3-2: [redacted] Lenalidomide Estimated Exposure by Country Based on Surrogates[a] for Off-label Use**

| Country | Number of Patients (%) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Exposure Cumulative Period | | | | | | | | | | | | | | | |
| | MM | | MDS | | MCL | | Off-label | | Adults | | FCBP | | Children | | Total Exposure | |
| | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| [redacted] | 1 | 8 | 3 | 23 | 1 | 8 | 8 | 62 | 13 | 100 | NA | NA | 0 | 0 | 13 | 100 |
| [redacted] | 6 | 33 | 0 | 0 | 1 | 6 | 11 | 61 | 18 | 100 | NA | NA | 0 | 0 | 18 | 100 |
| [redacted] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | NA | NA | 0 | 0 | 0 | 0 |
| [redacted] | 2 | 11 | 2 | 11 | 1 | 6 | 13 | 72 | 18 | 100 | NA | NA | 0 | 0 | 18 | 100 |
| [redacted] | 4 | 13 | 4 | 13 | 2 | 6 | 21 | 68 | 30 | 97 | NA | NA | 1 | 3 | 31 | 100 |
| **Total** | 13 | 16 | 9 | 11 | 5 | 6 | 53 | 66 | 79 | 99 | 0 | 0 | 1 | 1 | 80 | 100 |

[a] Surrogates: medical inquiries or free of charge supply requests received by BMS

[redacted] From the date of launch of lenalidomide in [redacted] on 03 Dec 2007 until 26 Dec 2018, in total 13 queries have been received regarding the use in MM maintenance treatment (1), MDS (3), myelofibrosis (2), Richter's syndrome (1), Prurigo Nodulus Hyder (1), dermatological condition (1), chronic myeloproliferative syndrome (1), MCL (1), PC (1), lymphomas (1). No cumulative data available from 27 Dec 2018 as this is no longer a requirement by the NCA due to low numbers of queries. Off-label use will be monitored via AEs/ADRs received in off-label indications as surrogate markers.

[redacted] From the date of launch of lenalidomide in [redacted] on 26 May 2008 until 26 Dec 2018, in total 18 queries have been received regarding the use in MM maintenance treatment (3), myelofibrosis (2), CLL (2), AML (2), combination therapy of azacitidine plus lenalidomide in AML (1), plasmacytoma (1), MCL (1), allo-SCT in MM (1), combination regimens with lenalidomide in MM (lenalidomide plus chemotherapy and lenalidomide plus bendamustine) (1), VRD combination in MM (1) and dermatology (1), use of lenalidomide in amyloidosis (1) and combination therapy lenalidomide plus rituximab for CLL (1). No cumulative data available from 27 Dec 2018 as this is no longer a requirement by the NCA due to low numbers of queries. Off-label use will be monitored via AEs/ADRs received in off-label indications as surrogate markers.

[redacted] From the date of launch of lenalidomide in [redacted] on 05 Mar 2010 until 26 Dec 2018, no queries about off-label use have been received. No cumulative data available from 27 Dec 2018 as this is no longer a requirement by the NCA due to low numbers of queries. Off-label use will be monitored via AEs/ADRs received in off-label indications as surrogate markers.

[redacted] From the date of launch of lenalidomide in [redacted] on 03 Dec 2007 until 26 Dec 2018, in total 18 queries have been received regarding the use of VRD as induction and maintenance/consolidation therapy for myeloma (1), plasma cell leukaemia (2), amyloidosis (2), myelofibrosis (3), consolidation therapy after auto-SCT for MM (1), MCL (1), and FL (1), the combination therapy lenalidomide plus bendamustine plus rituximab (1), combination therapy lenalidomide plus romidepsin (1), pre-allo-SCT use of lenalidomide plus azacitidine in MDS (1), combination therapy lenalidomide plus bevacizumab (1), use

in ovarian cancer (2) and use of lenalidomide high-risk MDS non del(5q) in combination with azacitidine (1). No cumulative data available from 27 Dec 2018 as this is no longer a requirement by the NCA due to low numbers of queries. Off-label use will be monitored via AEs/ADRs received in off-label indications as surrogate markers.

[redacted] From the date of launch of lenalidomide in [redacted] on 14 Mar 2008 until 26 Dec 2018, in total 31 queries have been received regarding the use in newly diagnosed MM (1), plasma cell leukaemia (1), malignant B-cell lymphoma (1), MCL (2), low lenalidomide dose pre-allo-SCT (1), MM maintenance (1), MDS (4), amyloidosis (2), AML (2) and lenalidomide in combination with radiation therapy (1), PC (1), NHL (2), polycythaemia vera (1), stem cell mobilisation (1) children (1), combination therapy lenalidomide plus cyclophosphamide (1), colon cancer (1), consolidation/maintenance treatment (2), novel treatment combinations in MM (1), in lymphoma (1), transplant-eligible patient (1), plasmacytoma (1) and as induction and maintenance treatment in Auto-SCT myeloma (1). No cumulative data available from 27 Dec 2018 as this is no longer a requirement by the NCA due to low numbers of queries. Off-label use will be monitored via AEs/ADRs received in off-label indications as surrogate markers.

**Table 2.5.1.3-3: [redacted] Lenalidomide Estimated Patient Exposure by Country and Indication from Implemented Controlled Access Programme**

| Country | Number of Patients (%) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Exposure Cumulative Period | | | | | | | | | | | | | | | |
| | MM | | MDS | | MCL | | Amyloidosis | | Myelofibrosis | | CLL | | Other | | Total Exposure | |
| | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| [redacted] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 10,768 | 100 | 10,768 | 100 |
| [redacted] | 11,449 | 93 | 398 | 3 | 28 | 0 | 11 | 0 | 7 | 0 | 4 | 0 | 354 | 3 | 12,251 | 100 |
| [redacted] | 300 | 96 | 7 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 2 | 312 | 100 |
| [redacted] | 189 | 97 | 3 | 2 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 194 | 100 |
| [redacted] | 2,819 | 94 | 184 | 6 | 4 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 3 | 0 | 3,011 | 100 |
| [redacted] | 336 | 92 | 30 | 8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 366 | 100 |
| [redacted] | 6,089 | 90 | 455 | 7 | 61 | 1 | 8 | 0 | 3 | 0 | 4 | 0 | 146 | 2 | 6,766 | 100 |
| [redacted] | 965 | 80 | 136 | 11 | 2 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 103 | 9 | 1,208 | 100 |
| [redacted] | 4,628 | 87 | 78 | 1 | 37 | 1 | 23 | 0 | 35 | 1 | 35 | 1 | 494 | 9 | 5,330 | 100 |
| [redacted] | 50,334 | 84 | 2,293 | 4 | 1,063 | 2 | 64 | 0 | 0 | 0 | 114 | 0 | 6,198 | 10 | 60,066 | 100 |
| [redacted] | 9 | 90 | 1 | 10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 10 | 100 |
| [redacted] | 185 | 96 | 4 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 2 | 193 | 100 |
| [redacted] | 545 | 91 | 24 | 4 | 3 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 26 | 4 | 599 | 100 |
| [redacted] | 98 | 87 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 13 | 12 | 113 | 100 |
| [redacted] | 4,947 | 93 | 347 | 7 | 3 | 0 | 1 | 0 | 3 | 0 | 3 | 0 | 24 | 0 | 5,328 | 100 |
| [redacted] | 1,471 | 83 | 63 | 4 | 1 | 0 | 227 | 13 | NA | NA | NA | NA | NA | NA | 1,762 | 100 |
| [redacted] | 1,044 | 98 | 22 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | NA | NA | 0 | 0 | 1,066 | 100 |
| [redacted] | 12,244 | 80 | 325 | 2 | 49 | 0 | 9 | 0 | 121 | 1 | 21 | 0 | 2,479 | 16 | 15,248 | 100 |
| **Total** | 97,652 | 78 | 4,370 | 4 | 1,252 | 1 | 346 | 0 | 172 | 0 | 181 | 0 | 20,618 | 17 | 124,591 | 100 |

[redacted] Due to the cut-off date of this report, [redacted] exposure data are only available until and including 30-Nov-2020.

[redacted] As from 04-Mar-2020 patient ID code is no longer collected, therefore patient counts are not possible. As a result, the exposure for the current period (27-Dec-2020 through 26-Dec-2022) is zero. Cumulative data: amongst 12,251 patients, 45 have inconclusive indications and are counted in the "other" category. Interval data: amongst 1,944 patients, 3 have inconclusive indications and are counted in the "other" category

[redacted] The cumulative data includes data up to the date of 26-Dec-2018. After this date, [redacted] no longer collects this data as agreed with the corresponding NCA.

[redacted] Please be informed that due to the retrospective collection nature of the SOF forms data for the period 27-Dec-2019 through 30-Nov-2020 have been provided. The data for December 2020 will be included in the table for the next reporting period. [redacted] is no longer capturing exposure data for lenalidomide, given that the initials of the patients and the status of the prescription (initial or repeated) are no longer collected and thus we are not able to know the number of patients exposed to the medication.

[redacted] The cumulative data includes data up to the date of 26-Dec-2018. [redacted] no longer collects this data per agreement with NCA in May 2019.

[redacted] Please note: The current and cumulative data include data up to 05-Feb-2020. After this date. [redacted] no longer collects this data as per agreement with NCA.

[redacted] The cumulative data includes data up to the date of 26-Dec-2018. After this date, [redacted] no longer collects this data per agreement with NCA in August 2019.

[redacted] Edited for period 27-Dec-2020 through 26-Dec-2022: off-label - 55 (all indications were provided); patient type: 1,610 adults, 943 M, 40 FCBP, 631 FNCBP, 2 unknown. Newly indicated follicular lymphoma - 14 patients. Total exposure – 1,614 patients. Cumulative period: off-label - 587 (77 indications not provided); patient type: 2,117 M, 191 FCBP, 2,040 FNCBP 2,040, 146 unknown. Unknown age = 12 patients. Children = 4 patients (3 male and 1 FNCBP). Newly indicated follicular lymphoma - 24 patients. Total exposure – 5,354.

[redacted] For the following indications data are underestimated because starting from 01-Jan-2013 the AIFA National Oncology Registry was changed and the updated information are not available: second line MM (in label), MDS 5q- isolated (in label), MDS 5q- not isolated (Law 648), MCL and DLBCL (Law 648), and amyloidosis (Law 648). Starting from 18-Nov-2021 (Official Journal n. 274 dated 17-Nov-2021) off-label data will be collected by the NCA through the PPP AIFA registry directly and will not be available for the reporting above.

[redacted] Lenalidomide is not commercially available in [redacted]

[redacted] Exposure data were collected until 01-Jul-2019. After this date data collection was impossible due to lenalidomide generics on the market.

[redacted] DLP 03-Mar-2020. From 04-Mar-2020 patient ID code was no longer collected, therefore patient count was not possible. As a result exposure for current period (27-Dec-2020 to 26-Dec-2022) is zero. For cumulative data: of 599 patients, 14 patients were prescribed lenalidomide for an unknown indication and 12 patients for an inconclusive indication.

[redacted] The cumulative data includes data up to the date of 26-Dec-2019. Due to the new SOF adopted earlier this year, it is not possible to supply the lenalidomide exposure data as previously done, since the information required to compile the data is no longer being collected.

[redacted] The cumulative data includes data up to the date of 26-Dec-2018. The cumulative reporting period was from 11-Sep-2009 to 26-Dec-2018. Exposure Data is no longer being collected for [redacted] as of 06-Jun-2019.

[redacted] The cumulative data includes data up to the date of 26-Dec-2018. [redacted] no longer collects this data per agreement with NCA in July 2018.

[redacted] The cumulative data includes data up to the date of 26-Dec-2018. [redacted] no longer collects this data, as agreed with the corresponding NCA.

[redacted] The implemented controlled distribution system does not capture real time data linked to medicinal product dispense. Data are collected retrospectively and presented in annual reports with a defined period covered. These annual reports are provided in the EU-specific Annex of the PBRER per period covered. The cumulative data that is provided reflects data up to 26-Dec-2016; there were 20 patients of unknown age.

No exposure data collected for the following countries:

[redacted] No study was conducted to collect information on patient exposure and used indications during the covered period. No cumulative data are available. No lenalidomide patient exposure data are available for [redacted] for the period 27-Dec-2020 through 26-Dec-2022.

[redacted] The implemented controlled distribution system in the [redacted] does not provide patient exposure data. Data provided is from Company supported supply on NPP basis for off-label indications only.

[redacted] PPP Revlimid in place in [redacted] does not collect exposure data.

[redacted] There are no changes for [redacted] as there are no data for the cumulative/interval exposure period from the marketed use of lenalidomide for [redacted] The requested exposure data are not available for [redacted]

.

**Table 2.5.1.3-4: [redacted] Lenalidomide Estimated Exposure by Country and Indication based on Surrogates[a] for Off-label Use**

| Country | Number of Patients (%) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Exposure Cumulative Period | | | | | | | | | | | | | | | |
| | MM | | MDS | | MCL | | Amyloidosis | | Myelofibrosis | | CLL | | Other | | Total Exposure | |
| | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| [redacted] | 1 | 8 | 3 | 23 | 1 | 8 | 0 | 0 | 2 | 15 | 0 | 0 | 6 | 46 | 13 | 100 |
| [redacted] | 6 | 33 | 0 | 0 | 1 | 6 | 1 | 6 | 2 | 11 | 3 | 17 | 5 | 28 | 18 | 100 |
| [redacted] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [redacted] | 2 | 11 | 2 | 11 | 1 | 6 | 2 | 11 | 3 | 17 | 0 | 0 | 8 | 44 | 18 | 100 |
| [redacted] | 4 | 13 | 4 | 13 | 2 | 6 | 2 | 6 | 0 | 0 | 0 | 0 | 19 | 61 | 31 | 100 |
| Total | 13 | 16 | 9 | 11 | 5 | 6 | 5 | 6 | 7 | 5 | 3 | 4 | 38 | 48 | 80 | 100 |

[a] Surrogates: medical inquiries or free of charge supply requests received by BMS

[redacted] From the date of launch of lenalidomide in [redacted] on 03 Dec 2007 until 26 Dec 2018, in total 13 queries have been received regarding the use in MM maintenance treatment (1), MDS (3), myelofibrosis (2), Richter's syndrome (1), Prurigo Nodulus Hyder (1), dermatological condition (1), chronic myeloproliferative syndrome (1), MCL (1), PC (1), lymphomas (1). No cumulative data available from 27 Dec 2018 as this is no longer a requirement by the NCA due to low numbers of queries. Off-label use will be monitored via AEs/ADRs received in off-label indications as surrogate markers.

[redacted] From the date of launch of lenalidomide in [redacted] on 26 May 2008 until 26 Dec 2018, in total 18 queries have been received regarding the use in MM maintenance treatment (3), myelofibrosis (2), CLL (2), AML (2), combination therapy of azacitidine plus lenalidomide in AML (1), plasmacytoma (1), MCL(1), allo-SCT in MM (1), combination regimens with lenalidomide in MM (lenalidomide plus chemotherapy and lenalidomide plus bendamustine) (1), VRD combination in MM (1) and dermatology (1), use of lenalidomide in amyloidosis (1) and combination therapy lenalidomide plus rituximab for CLL (1). No cumulative data available from 27 Dec 2018 as this is no longer a requirement by the NCA due to low numbers of queries. Off-label use will be monitored via AEs/ADRs received in off-label indications as surrogate markers.

[redacted] From the date of launch of lenalidomide in [redacted] on 05 Mar 2010 until 26 Dec 2018, no queries about off-label use have been received. No cumulative data available from 27 Dec 2018 as this is no longer a requirement by the NCA due to low numbers of queries. Off-label use will be monitored via AEs/ADRs received in off-label indications as surrogate markers.

[redacted] From the date of launch of lenalidomide in [redacted] on 03 Dec 2007 until 26 Dec 2018, in total 18 queries have been received regarding the use of VRD as induction and maintenance/consolidation therapy for myeloma (1), plasma cell leukaemia (2), amyloidosis (2), myelofibrosis (3), consolidation therapy after auto-SCT for MM (1), MCL (1), and FL (1), the combination therapy lenalidomide plus bendamustine plus rituximab (1), combination therapy lenalidomide plus romidepsin (1), pre-allo-SCT use of lenalidomide plus azacitidine in MDS (1), combination therapy lenalidomide plus bevacizumab (1), use in ovarian cancer (2) and use of lenalidomide high-risk MDS non del(5q) in combination with azacitidine (1). No cumulative data available from 27 Dec 2018

as this is no longer a requirement by the NCA due to low numbers of queries. Off-label use will be monitored via AEs/ADRs received in off-label indications as surrogate markers.

[redacted] From the date of launch of lenalidomide in [redacted] on 14 Mar 2008 until 26 Dec 2018, in total 31 queries have been received regarding the use in newly diagnosed MM (1), plasma cell leukaemia (1), malignant B-cell lymphoma (1), MCL (2), low lenalidomide dose pre-allo-SCT (1), MM maintenance (1), MDS (4), amyloidosis (2), AML (2) and lenalidomide in combination with radiation therapy (1), PC (1), NHL (2), polycythaemia vera (1), stem cell mobilisation (1) children (1), combination therapy lenalidomide + cyclophosphamide (1), colon cancer (1), consolidation/maintenance treatment (2), novel treatment combinations in MM (1), in lymphoma (1), transplant-eligible patient (1), plasmacytoma (1) and as induction and maintenance treatment in ASCT myeloma (1). No cumulative data available from 27 Dec 2018 as this is no longer a requirement by the NCA due to low numbers of queries. Off-label use will be monitored via AEs/ADRs received in off-label indications as surrogate markers.

## 2.6 Module SVI: Additional EU Requirements for the Safety Specification

### *2.6.1 Module SVI.1: Potential for Misuse for Illegal Purposes*

Lenalidomide has not been systematically studied in humans for its potential for abuse, tolerance or physical dependence. Based on its pharmacological properties, there is no anticipated risk of abuse or misuse for illegal purposes. To date, no safety signal has been identified relating to the misuse or abuse of lenalidomide.

## 2.7 Module SVII: Identified and Potential Risks

### *2.7.1 Module SVII.1: Identification of Safety Concerns in the Initial RMP Submission*

The summary of the safety concerns in the initial RMP submission (Version 5.0) at time of authorisation (14-Jun-2007) is presented in Table 2.7.1-1. A description of the changes to the list of safety concerns in the approved RMPs is presented in Annex 8.

**Table 2.7.1-1: Safety Concerns in the Initial RMP Submission**

| | |
|---|---|
| ***Important identified risks*** | Neutropenia and thrombocytopenia |
| | Infection |
| | Bleeding events |
| | Thrombosis/thromboembolism |
| ***Important potential risks*** | Foetal exposure |
| | Peripheral neuropathy |
| | Cardiac failure |
| | Cardiac arrhythmias |
| | QT prolongation |
| | Hypersensitivity |
| | Rash |
| | Hypothyroidism |
| | Renal failure |
| ***Missing information*** | Long-term use |
| | Change in death rate |
| | Change in rate of progression of MDS to AML |
| | Use in renal failure |

#### *2.7.1.1 Module SVII.1.1: Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP*

Adverse reactions with minimal clinical impact on patients and not associated with any relevant risk (in relation to the life-threatening haematologic diseases being treated) include low grade

abdominal pain, dyspepsia, nausea, dry mouth, stomatitis, dysphagia, toothache, vomiting, low grade colitis and low grade caecitis, fatigue, asthenia, pyrexia, oedema, influenza-like syndrome, chest pain, chills, cough, dyspnoea, rhinorrhoea, ataxia, balance impaired, headache, tremor, dysgeusia, lethargy, tinnitus and dizziness, muscle spasms, bone pain, musculoskeletal pain (including back pain and pain in extremity) and connective tissue pain and discomfort, arthralgia, myalgia, muscular weakness, joint swelling, insomnia, altered mood, loss of libido, haematuria, urinary retention, urinary incontinence, hyperhidrosis, skin hyperpigmentation, erythema, night sweats, skin discoloration, photosensitivity reaction, decreased appetite, weight decreased, C-reactive protein increased, hypomagnesemia, iron overload, and low grade hypertension.

Adverse reactions such as low grade blurred vision, reduced visual acuity, deafness, erectile dysfunction and higher grades of cataract and depression could have an impact on the quality of life; however, the clinical impact of these reactions is considered minimal in relation to the severity of the underlying life-threatening malignancy being treated. Other reactions such as haemolysis, autoimmune haemolytic anaemia, acquired hemophilia, acquired fanconi syndrome, somnolence, hyperthyroidism and hypothyroidism are not considered important because only low grades were reported with the lenalidomide treatment group. Low grade events are not considered to have significant impact on the benefit-risk profile of lenalidomide in the target population.

Adverse reactions of higher grade with acceptable clinical impact on patients treated for life-threating oncologic diseases include renal tubular necrosis, gout, vasculitis, ischaemia, peripheral ischaemia, hemolytic anaemia, hypokalaemia, hypocalcaemia, hyperglycaemia, hyperuricaemia, hypophosphataemia, dehydration, syncope, rhabdomyolysis, pancreatitis, gastrointestinal perforations (including diverticular, intestinal and large intestine perforations), diabetes mellitus, hypotension, and respiratory distress. Some of the above reactions may have serious consequences but occur with a low frequency, such as rhabdomyolysis. These reactions are not considered to impact the benefit-risk profile of lenalidomide in the target population. The most current product information does not advise on specific clinical actions to be taken to minimise the risk and no additional risk minimisation measures are in place for these reactions. They are not considered to be important for the target population. These ADRs are included in Section 4.8 of the SmPC.

Haematological toxicities such as febrile neutropenia, anaemia, leucopenia, lymphopenia, and pancytopenia are already well known to HCPs. The HCPs have appropriate measures in place as part of routine clinical practice for prevention and treatment of these haematological toxicities. These reactions are included in Section 4.8 of the SmPC.

### 2.7.1.2 Module SVII.1.2: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

**Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP**

| Risk Type | Risk-Benefit Impact |
|---|---|
| ***Important identified risks*** | |
| Teratogenicity | Lenalidomide is a chemical analogue of thalidomide, a known human teratogen that causes severe life-threatening birth defects. In addition, lenalidomide induced malformations in the offspring of pregnant monkeys similar to those described with thalidomide. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.<br>Please see Section 2.7.3.1 for further details.<br>Lenalidomide is contraindicated in pregnant women. Lenalidomide is subject to controlled access due to potential off-label use to treat malignancies in younger populations than the target population, and FCBP have to meet all the conditions of the PPP, which is intended to prevent the risk of embryofoetal exposure and thus reduce the potential teratogenic effects of lenalidomide exposure.<br>The teratogenic effects in humans can be potentially serious or life-threatening to the foetus or unborn baby. |
| Serious Infection due to Neutropenia | In the FL studies, lenalidomide plus rituximab treatment was associated with a higher frequency of neutropenia AEs compared to rituximab plus placebo. In Study NHL-007, of the 50.7% lenalidomide-rituximab treated patients with ≥ Grade 3 neutropenia, 2.7% of the patients had concurrent serious infection. In Study NHL-008, of the 31.6% lenalidomide-rituximab treated patients with ≥ Grade 3 neutropenia, 10.7% of the patients had concurrent serious infection.<br>Overall, in pooled Studies NHL-007 and NHL-008, of the 45.8% lenalidomide-rituximab treated patients with treatment-emergent neutropenia, 9.5% and 7.4%, experienced concurrent treatment-emergent Grade 3 or 4 and serious infection, respectively (Table 2.7.3.1-2).<br>In NDMM, lenalidomide maintenance after ASCT is associated with a higher frequency of Grade 4 neutropenia compared to placebo maintenance.<br>The combination of lenalidomide with dexamethasone in NDMM patients is associated with a lower frequency of Grade 4 neutropenia compared with MPT.<br>In patients treated with lenalidomide in Study IFM 2005-02, of the 14.1% of patients with ≥ Grade 3 infection, only one-fourth (25.6%) of the patients had concurrent neutropenia and both of the patients (0.7%) who had ≥ Grade 4 infection had concurrent neutropenia (IFM 2005-02 CSR, Table 14.3-60 and Table 14.3-62).<br>The combination of lenalidomide with melphalan and prednisone in NDMM patients is associated with a higher frequency of Grade 4 neutropenia compared with MPp+p. There was a higher frequency of Grade 4 febrile neutropenia observed.<br>In patients treated with lenalidomide in NDMM Study MM-020, of the 29.3% of patients with ≥ Grade 3 infection, one-fifth (20.5%) of the patients had concurrent neutropenia (any grade); and of the 6.8% of patients with ≥ Grade 4 infection, less than one-fourth (22.2%) of the patients had concurrent neutropenia of any grade (MM-020 CSR, Table 14.3.2.3.22.2).<br>The combination of lenalidomide with dexamethasone in MM patients is associated with a higher incidence of Grade 4 neutropenia. |

**Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP**

| Risk Type | Risk-Benefit Impact |
|---|---|
| | In MDS and MCL, lenalidomide is associated with a higher incidence of Grade 3 or 4 neutropenia.<br>Severe/serious infections in the context of neutropenia may put the patient at an unacceptable risk of death and are considered important.<br>Please see Section 2.7.3.1 for further details. |
| SPM | In NDMM patients receiving lenalidomide in combination with bortezomib and dexamethasone, the haematologic SPM incidence rate was 0.00 to 0.16 per 100 person-years and the incidence rate of solid tumour SPM 0.21 to 1.04 per 100 person-years.<br>In clinical trials of newly diagnosed MM patients not eligible for transplant, a 4.9-fold increase in incidence rate of haematologic SPM (cases of AML, MDS) has been observed in patients receiving lenalidomide in combination with melphalan and prednisone until progression (1.75 per 100 person-years) compared with melphalan in combination with prednisone (0.36 per 100 person-years). A 2.12-fold increase in incidence rate of solid tumour SPM has been observed in patients receiving lenalidomide (9 cycles) in combination with melphalan and prednisone (1.57 per 100 person-years) compared with melphalan in combination with prednisone (0.74 per 100 person-years).<br>The increased risk of SPM associated with lenalidomide is relevant also in the context of NDMM after stem cell transplantation. The incidence rate of haematologic malignancies, most notably AML, MDS and B-cell malignancies (including<br>Hodgkin's lymphoma), was 1.31 per 100 person-years for the lenalidomide arms and 0.58 per 100 person-years for the placebo arms (1.02 per 100 person-years for patients exposed to lenalidomide after ASCT and 0.60 per 100 person-years for patients not-exposed to lenalidomide after ASCT). The incidence rate of solid tumour SPM was 1.36 per 100 person-years for the lenalidomide arms and 1.05 per 100 person-years for the placebo arms (1.26 per 100 person-years for patients exposed to lenalidomide after ASCT and 0.60 per 100 person-years for patients not-exposed to lenalidomide after ASCT).<br>In clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls, mainly comprising of basal cell or squamous cell skin cancers.<br>In clinical trials other than MM, SPM risk has been lower (MDS, MCL).<br>In a relapsed/refractory study which included FL patients, no increased risk of SPM was observed in the lenalidomide/rituximab arm compared to the placebo/rituximab arm. Haematologic SPM of AML occurred in 0.29 per 100 person-years in the lenalidomide/rituximab arm compared with 0.29 per 100 person-years in patients receiving placebo/rituximab. The incidence rate of haematologic plus solid tumour SPMs was 0.87 per 100 person-years in the lenalidomide/rituximab arm, compared to 1.17 per 100 person-years in patients receiving placebo/rituximab.<br>The diagnosis of a new malignancy is one of the most serious events experienced by a cancer survivor, and the identification of SPM and their treatment are critical.<br>Please see Section 2.7.3.1 for further details. |
| Important Identified Risk Related to Indication/Target Population | |
| For MCL and FL: Tumour Flare Reaction (TFR) | In Study NHL-007, the proportion of FL patients experiencing at least one TFR event was higher among lenalidomide plus rituximab-treated patients than patients treated with rituximab plus placebo (risk ratio = 19.3 [95% CI: 2.6-143.9]). Tumour flare reaction AEs were reported for 7 lenalidomide plus rituximab-treated patients in Study NHL-008. In pooled Studies NHL-007 and NHL-008, TFR SAEs were reported for 2/323 (0.6%) lenalidomide plus rituximab-treated patients, both of which resolved. No TFR SAEs had an outcome of death. Less than 2% of lenalidomide plus rituximab-treated patients |

**Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP**

| Risk Type | Risk-Benefit Impact |
|---|---|
| | experienced Grade 3 or 4 AEs of TFR and TFR AEs leading to dose interruption. No patients experienced TFR AEs leading to dose discontinuation or reduction.<br>TFR has been reported in MCL patients receiving lenalidomide. In Study MCL-002, approximately 10% of lenalidomide-treated patients experienced TFR compared with 0% in the control arm. The majority of the events occurred in Cycle 1, all were assessed as treatment-related, and the majority of the reports were Grade 1 or 2. Patients with high MIPI at diagnosis or bulky disease (at least one lesion ≥ 7 cm in the longest diameter) at baseline may be at risk of TFR. A Postauthorisation Safety Study (PASS) is being carried out to quantify and characterise the event of TFR by tumour burden and the proportion of early deaths by tumour burden in RRMCL patients receiving lenalidomide in a 'real world' setting.<br>Please see Section 2.7.3.1 for further details. |
| ***Important potential risks*** | |
| Cardiac Failure | In Study NHL-007, no cardiac failure events occurred in the lenalidomide plus rituximab arm. In Study NHL-008, cardiac failure AEs were reported in one (0.6%) lenalidomide plus rituximab-treated patient. In Studies NHL-007 and NHL-008, no cardiac failure SAEs were reported and no patients died due to an event of cardiac failure.<br>Cardiac failure events occurred at a similar frequency in Arm MPT and Arm Rd18 (5.0% and 5.2%, respectively) but occurred with higher frequency in Arm Rd (8.8%) in TNE NDMM Study MM-020. When adjusted for treatment duration, the incidence of events was similar between Arm Rd (6.19 events per 100 PY,) Arm Rd18 (5.62), and Arm MPT (6.19). The incidence rate of events was highest and similar across arms during the first 6 months of treatment indicating that more events occurred in the first 6 months of treatment. Deaths due to cardiac disorders on study treatment were low and similar in Arms Rd, Rd18 and MPT. A PASS is being conducted to further characterise this safety concern in the recently added target population of TNE NDMM patients by investigating the aetiology of cardiovascular events in a 'real world' setting.<br>Please see Section 2.7.3.1 for further details. |
| Cardiac Arrhythmias | In Study NHL-007, the proportion of patients experiencing at least one cardiac arrhythmia event was slightly higher in the lenalidomide plus rituximab arm than the rituximab plus placebo arm (8.8% and 11.6%, respectively; risk ratio = 1.3 [95% CI: 0.6-2.7]). Deaths due to cardiac arrhythmia were low: there was one death (0.7%) reported for a lenalidomide plus rituximab-treated patient in Study NHL-007 (PT: arrhythmia). In Study NHL-008, cardiac arrhythmia AEs were reported for 6.8% lenalidomide plus rituximab treated patients. One patient in this study died due to an event of cardiac arrhythmia (PT: cardio-respiratory arrest).<br>Cardiac arrhythmia events occurred more frequently in Arm Rd compared with Arm Rd18 and MPT (25.0% versus 17.4% and 22.7%, respectively) in TNE NDMM Study MM-020. When adjusted for treatment duration, the incidence of events was higher in Arm MPT than Arm Rd and Arm Rd18. Grade 3 or 4 cardiac arrhythmias and SAEs of cardiac arrhythmias also occurred with generally similar frequencies across all arms. A PASS is being conducted to further characterise this safety concern by investigating the incidence and mortality associated with cardiovascular events and to utilise extensive risk factor information among TNE NDMM patients treated with a lenalidomide-containing regimen in a 'real world' setting.<br>Please see Section 2.7.3.1 for further details. |

**Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP**

| Risk Type | Risk-Benefit Impact |
|---|---|
| Ischaemic Heart Disease (Including Myocardial Infarction) | In Study NHL-007, IHD events occurred at a low frequency in both the rituximab plus placebo and lenalidomide plus rituximab arms (1.4% and 0.7%, respectively). In Study NHL-008, IHD events were reported for 4.0% of lenalidomide plus rituximab-treated patients. There were no deaths due to IHD in the FL studies.<br>Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors. The overall frequency of myocardial infarction/ischaemic heart disease (MI/IHD) was slightly higher in Study MM-015 than in Study MM-020. In Study MM-020, an imbalance in the incidence of MI/IHD between the two lenalidomide-containing arms (Rd/Rd18) was observed during the first 6 months of treatment. Further investigation into the potential risk factors for MI/IHD did not yield an explanation for the difference in frequency of MI/IHD between arms with identical treatment during the first 6 months of the study. Therefore, such a difference may have resulted from unmeasured confounders before or after baseline, or due to some combination of different risk factors that have not yet been fully understood. Fatal outcomes have been observed although these were of low frequency. A PASS is being conducted to further characterise this safety concern by investigating the incidence and mortality associated with cardiovascular events and to utilise extensive risk factor information among TNE NDMM patients treated with a lenalidomide-containing regimen in a 'real world' setting.<br>Please see Section 2.7.3.1 for further details. |
| Off-label Use | The risk of off-label use is monitored through the MDS PASS.<br>Further characterisation of this risk is warranted and, therefore, this risk remains important.<br>Please see Section 2.7.3.1 for further details. |
| ***Missing Information*** | None. |

## 2.7.2 Module SVII.2: New Safety Concerns and Reclassification with a Submission of an Updated RMP

There are no new safety concerns or reclassification of safety concerns with the submission of the updated RMP.

## 2.7.3 Module SVII.3: Details of Important Identified Risks, Important Potential Risks, and Missing Information

This section presents information on identified and potential risks that require further characterisation or evaluation. Section 2.7.3.1 provides the clinical data for the respective indications.

**Main and Supporting Studies**

**MM indication:**

- NDMM-TE/TNE (RVd initial/induction therapy): Study SWOG S0777;
- NDMM-TE (maintenance post-autologous stem cell transplant): Studies CALGB 100104 and IFM 2005-02;
- NDMM-TNE: Studies MM-020 and MM-015.

**RRMM indication:** Studies MM-009 and MM-010.

**Del 5q MDS indication:** Studies MDS-003 and MDS-004.

**MCL indication:** Studies MCL-002, MCL-001, NHL-002 and NHL-003.

**FL indication:** Studies NHL-007 and NHL-008

Study MCL-003 (described in Section 2.3.1) was stopped prematurely for reasons other than safety concerns after only nine patients had been enrolled (four in the lenalidomide arm, five in the placebo arm). No data from this study have been presented in the RMP.

**RMP Search Strategy for Adverse Events Presentation**

The RMP search criteria have been defined for each study based on the MedDRA version as noted in Table 2.7.3-1. Due to the different MedDRA versions used for each clinical study's database, the terms were used based on the MedDRA version used to code AEs in the clinical database. The MedDRA PTs for each of the Important Identified Risks and Important Potential Risks are shown in the respective tables in Section 2.7.3.1.

**Table 2.7.3-1: RMP Search Criteria**

| Study | RMP Search Criteria[a] | MedDRA Version Used to Code AEs in Clinical Database |
|---|---|---|
| SWOG S0777 | 15.1 | 15.1 |
| IFM 2005-02 | 15.1 | 15.1 |
| CALGB 100104 | 15.1 | 15.1 |
| GIMEMA[b] | 15.1 | 15.1 |
| MM-015 | 15.1 | 10.0 |
| MM-020 | 15.1 | 15.1 |
| MM-009 | 13.0[c] | 13.0 |
| MM-010 | 13.0c | 13.0 |
| MDS-003 | 13.0 | 5.1 |
| MDS-004 | 13.0 | 5.1 |
| MCL-001 | 16.1 | 16.1 |
| MCL-002 | 16.1 | 16.1 |
| NHL-002 | 16.1 | 16.1 |
| NHL-003 | 16.1 | 16.1 |
| NHL-007 | 21.0 | 21.0 |
| NHL-008 | 21.0 | 21.0 |

[a] For the risk of SPM, the RMP search criteria for each study were consistent to the MedDRA version used to code AEs in the clinical database.

[b] The GIMMEA study was only included for the SPM-related risks.

[c] For the RRMM studies MM-009 and MM-010, the search criteria for the important identified risks of Serious Infection due to Neutropenia, and the important risks of Cardiac Failure, Cardiac Arrhythmias, and Ischaemic Heart Disease (Including Myocardial Infarction) were defined in MedDRA Versions 5.1 and/or 11.0.

In Section 2.7.3.1, the definition of "risk" of each event of interest is based on cumulative incidence (ie, the proportion of patients experiencing each event, or group of events), and also relative risk, where indicated.

**SPM Search Strategy**

A search for SPM from the clinical and safety databases was performed by retrieving and manually reviewing all MedDRA PTs in the Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps) SOC. Events deemed to not represent an SPM were excluded. Thus, events in the high level group terms (HLGTs) of metastases and neoplasm-related morbidities (eg, tumour lysis syndrome, tumour flare, and cancer pain); reports of most neoplasms clearly identifiable as benign except for meningioma, which was considered to be a solid tumour malignancy because the clinical course is not benign; events of disease progression of the underlying indication (eg, MM in a study investigating treatment for MM); and reports of pre-existing SPM were not included as SPM events in presentations or analyses in this RMP.

**Data Collection**

**TEAEs:**

Typically all AEs in BMS-sponsored clinical studies are collected for 28 days post discontinuation of active treatment and 30 days post discontinuation of active treatment in the cooperative studies (CALGB 100104, IFM 2005-02 and RVd study SWOG S0777).

**SPM:**

Collection of SPM in clinical trials is continuing for the duration of the studies, from the time of signing the Informed Consent Document up to the time all patients have been followed for at least 5 years (a maximum of 6 years for SWOG S0777) from randomisation or have died. Due to the long-term nature of the SPM data collection and the different follow up times in the studies, these events are better understood through incidence rates rather than frequency only. For this reason, both frequencies and incidence rates have been included for the SPM risk assessment. For each SPM category, the incidence rate per 100 person-years was calculated as: (the number of patients with any SPM in the SPM category/total person-years)*100.

**Data Presentation**

It is important to note that pooling across indications (TE and TNE NDMM, RRMM, MDS, MCL and FL) for this section was not performed because of the basic differences in the pathophysiology of the indications, patient populations, treatment regimens, dose/dose intensity and schedules (cycle length) and route of administration across the indications. Treatment regimen for RVd as initial treatment in NDMM: 25 mg lenalidomide QD orally on Days 1 to 14 of a 21-day cycle for

up to eight 3-week cycles with 1.3 mg/m$^2$ bortezomib IV on Days 1, 4, 8 and 11 and 20 mg dexamethasone QD orally on Days 1, 2, 4, 5, 8, 9, 11, and 12 (SWOG S0777); lenalidomide 25 mg QD orally 21/28 days cyclic regimen with dexamethasone or lenalidomide 10 mg QD orally 21/28 days cyclic regimen with melphalan and prednisone induction followed by lenalidomide maintenance with 10 mg QD orally 21/28 days cyclic regimen for TNE NDMM; lenalidomide maintenance 10 mg QD orally 28/28 days continuous regimen for TE NDMM; lenalidomide 25 mg QD orally 21/28 days cyclic regimen for RRMM, and lenalidomide 10 mg QD orally 21/28 days cyclic regimen, 10 mg QD orally 28/28 days cyclic regimen or 5 mg QD orally 28/28 days continuous regimen for MDS.

**Pooling of Studies**

Pooling was not performed for the MM indication primarily due to the different patient populations (TE versus TNE), disease setting, study designs, study treatment regimen (monotherapy, doublet versus triplet), dose/dose intensity and cycle length:

- In TE NDMM Study CALGB 100104, patients received maintenance treatment with either lenalidomide or placebo until disease progression. The starting dose of lenalidomide was 10 mg/day for the first 3 months, increased to 15 mg/day if tolerated. A conservative approach was applied to determine the adverse reactions from CALGB 100104. The adverse reactions included events reported post-HDM/ASCT as well as events from the maintenance treatment period.
- In TE NDMM Study IFM 2005-02, patients received maintenance treatment with either lenalidomide or placebo until relapse. The starting dose of lenalidomide was 10 mg/day for the first 3 months, increased to 15 mg if tolerated. With the exception of the SPM risks (SPM safety analysis population), data are presented for the maintenance period only in Study IFM 2005-02, and include AEs reported during the start of the maintenance period.
- The TNE RVd NDMM Study SWOG S0777 compared initial (induction) treatment with RVd versus Rd followed by continued Rd for all patients.
- The TNE NDMM Study MM-020 compared 3 regimens: lenalidomide with low-dose dexamethasone given until disease progression (Rd), or Rd given for eighteen 28-day cycles (Rd18 = 72 weeks); versus MPT given for twelve 6-week cycles (72 weeks).
- The TNE NDMM Study MM-015 compared the combination of melphalan/prednisone with or without lenalidomide during 9 cycles of induction followed by a maintenance phase comparing lenalidomide with placebo.

Pooling within the MDS indication (MDS-003 and MDS-004 studies), was not done because of the differences in the duration of exposure to lenalidomide and dosing. The median duration of exposure was 52.5 weeks for the 10 mg dose in MDS-003, and 50.3 weeks for the 10 mg dose, 18 weeks for the 5 mg dose, and 16 weeks for the placebo arm in MDS-004. Unless otherwise indicated, the data presented from Study MDS-004 are from the double-blind phase (N = 69 patients each in the 10 mg and 5 mg lenalidomide groups; N = 67 in the placebo group), and so do not include open-label phase results (during which placebo-treated patients could cross over to lenalidomide 5 mg) or the follow-up phase of Study MDS-004. The double-blind phase was 52 weeks including the first 16 weeks of which the patients in the placebo arm who did not achieve

a minor response by Week 16 were given the option to cross over to the 5 mg lenalidomide arm. Details of the clinical study design for MDS-003 and MDS-004 are found in Section 2.3.

It is worth noting that in Study MCL-002, as of the 07 Mar 2014 data cutoff, the median treatment duration in the lenalidomide arm (24.3 weeks; range: 0.4, 241.9) was longer than in the control arm (13.1 weeks; range: 0.1, 157.9). This longer time on treatment was partially due to the fact that three of the investigator's choice drugs in the control arm (cytarabine, gemcitabine and fludarabine) were administered up to a maximum of 6 cycles (per protocol, based on standard of care), while lenalidomide was administered until PD or unacceptable toxicity.

### *2.7.3.1 Module SVII.3.1: Presentation of Important Identified and Important Potential Risks*

**Important Identified Risks**

- Teratogenicity (Table 2.7.3.1-1)
- Serious infection due to neutropenia (Table 2.7.3.1-2)
- SPM (Table 2.7.3.1-3)
- Tumour Flare Reaction (MCL and FL Indications) (Table 2.7.3.1-16)
- Cardiac failure (Table 2.7.3.1-17)
- Cardiac arrhythmias (Table 2.7.3.1-18)
- Ischaemic heart disease (including myocardial infarction) (Table 2.7.3.1-19)

**Important Potential Risks**

- Off-label use (Table 2.7.3.1-20)

**Missing Information**

- None

**Important Identified Risk: Teratogenicity**

**Table 2.7.3.1-1: Important Identified Risk: Teratogenicity**

| Important Identified Risk Teratogenicity | |
|---|---|
| Potential mechanisms | No mechanism by which lenalidomide may cause teratogenicity has been established. |
| Evidence source and strength of evidence | Lenalidomide is structurally related to thalidomide, which is known to cause serious birth defects and death of the foetus. In nonclinical studies, lenalidomide induced malformations similar to those described with thalidomide. Therefore, a teratogenic effect of lenalidomide is expected and lenalidomide is contraindicated during pregnancy. |

## Table 2.7.3.1-1: Important Identified Risk: Teratogenicity

| Important Identified Risk Teratogenicity | |
|---|---|
| Characterization of risk | Not applicable. There were no cases of pregnancy in Studies SWOG 0777, CALGB 100104, IFM 2005-02, MM-020, MM-015, MM-009, MM-010, MDS-003, MDS-004, MCL-002, MCL-001, NHL-002, NHL-003, NHL-007 or NHL-008.<br><br>As of 26 Dec 2017, there have been a total of 13 confirmed reports of possible maternal exposure during pregnancy from clinical trials, of which 5 were reports from non-US trials [redacted] Five of the pregnancies were in female patients receiving lenalidomide and 8 pregnancies were in the female partners of male patients receiving lenalidomide. Two of the 5 reports of pregnancy in female patients on lenalidomide arose from a BMS-sponsored study for complex regional pain syndrome. The remaining 3 reports in female patients receiving lenalidomide were from investigator-led studies (two in MM and one in Hodgkin's lymphoma). Of the 8 reports of pregnancy in the female partner of a male patient receiving lenalidomide, two reports arose from a BMS-sponsored study for complex regional pain syndrome, two reports arose from an investigator-led study in MM and one report arose from an investigator-led study in chronic lymphocytic leukaemia (CLL). The remaining 3 reports of pregnancy in female partners of male patients receiving lenalidomide were in a follicular lymphoma study. |
| Risk factors and risk groups | The 'at risk' group comprises FCBP or female partners of male patients treated with lenalidomide and there are no risk factors. |
| Preventability | To avoid any risk of foetal exposure to lenalidomide, the drug is contraindicated in women who are pregnant and in FCBP unless all of the conditions of the PPP are met (SmPC, Section 4.3). Women of childbearing potential should use an effective method of contraception (SmPC, Sections 4.4 and 4.6). Male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and not using effective contraception, even if the man has had a vasectomy (SmPC, Sections 4.4 and 4.6) and should not donate semen throughout treatment duration, during dose interruption and for 1 week after cessation of treatment. It is not known whether lenalidomide is excreted in human milk. Therefore, breastfeeding should be discontinued during therapy with lenalidomide (SmPC, Section 4.6). |
| Impact on the risk-benefit balance of the product | Lenalidomide is structurally related to thalidomide, a known human teratogen, inducing a high frequency (about 30%) of severe and life-threatening birth defects such as: ectromelia (amelia, phocomelia, haemimelia) of the upper and/or lower extremities, microtia with abnormality of the external acoustic meatus (blind or absent), middle and internal ear lesions (less frequent), ocular lesions (anophthalmia, microphthalmia), congenital heart disease and renal abnormalities.<br><br>Potentially severe or life-threatening defects/disability, or foetal death. |
| Public health impact | Lenalidomide is an analogue of a known human teratogenic compound. It was shown to be present in the semen of healthy male subjects in Phase 1 studies and a developmental toxicity study in monkeys indicated that lenalidomide produced malformations in the monkeys' offspring. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected (SmPC, Sections 4.4, 4.6 and 4.8). |
| Data source | Clinical trials, RRMM PASS, spontaneous reports. |
| MedDRA Terms | See Annex 7 |

## Important Identified Risk: Serious Infection due to Neutropenia

### Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

| **Important Identified Risk Serious Infection due to Neutropenia** | |
|---|---|
| Potential mechanisms | The pathogenesis of lenalidomide-induced neutropenia has not been elucidated. |
| Evidence source and strength of evidence | In clinical trials, neutropenia has been reported as a consequence of lenalidomide treatment; ≥ Grade 4 and ≥ Grade 3 infections have occurred in the context of neutropenia (any grade). |
| Characterization of risk | **Frequency with 95% CI**<br>**FL Studies:** |

| **Neutropenia/ Infection** | **NHL-007** | | **NHL-008** | **Pooled NHL-007 and NHL-008** |
|---|---|---|---|---|
| | **PBO+Rit** | **Len+Rit** | **Len+Rit** | **Len+Rit** |
| Total number of patients | 148 | 146 | 177 | 323 |
| **Patients with ≥ 1 SAE** | | | | |
| Neutropenia | 0 | 6 | 9 | 15 |
| Infection | 5 | 14 | 20 | 34 |
| **Patients with ≥ 1 AE** | | | | |
| Neutropenia | 33 | 85 | 63 | 148 |
| Infection | 68 | 92 | 90 | 182 |
| **Incidence (% of patients) with ≥ 1 AE (95% CI)** | | | | |
| Neutropenia | 22.3 (15.9 to 29.9) | 58.2 (49.8 to 66.3) | 35.6 (28.6 to 43.1) | - |
| Infection | 45.9 (37.7 to 54.3) | 63.0 (54.6 to 70.8) | 50.8 (43.2 to 58.4) | - |

Overall, in pooled Studies NHL-007 and NHL-008, neutropenia AEs were reported for 148 lenalidomide plus rituximab-treated patients and infection AEs were reported for 182 lenalidomide plus rituximab-treated patients.

In Study NHL-007, the proportion of FL patients experiencing at least one neutropenia event was higher among lenalidomide plus rituximab-treated patients than patients treated with rituximab plus placebo (risk ratio = 2.6 [95% CI: 1.7 to 3.9]). The proportion of FL patients experiencing at least one infection event was higher among lenalidomide plus rituximab-treated patients than patients treated with rituximab plus placebo (risk ratio = 1.4 [95% CI: 1.0 to 1.9]).

In Study NHL-008, 35.6% and 50.8% FL patients who received lenalidomide plus rituximab experienced at least one AE of neutropenia or infection, respectively.

To further elucidate the relationship between neutropenia and infection, a stratified analysis of infection in neutropenic patients was performed.

**Infection Events in Patients with Concurrent Infection After Treatment-emergent Neutropenia (Studies NHL-007 and NHL-008)**

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

| AE Category[a,b] | Statistic[c] | NHL-007 | | | | NHL-008 | | Pooled NHL-007 and NHL-008 | |
|---|---|---|---|---|---|---|---|---|---|
| | | PBO+Rit | | Len+Rit | | Len+Rit | | Len+Rit | |
| | | M/N or n/M (%) | 95% CI[d] | M/N or n/M (%) | 95% CI[d] | M/N or n/M (%) | 95% CI[d] | M/N or n/M (%) | 95% CI[d] |
| **Total Neutropenia (Any Grade)** | **M/N (%)** | **33/148 (22.3)** | **(15.9, 29.9)** | **85/146 (58.2)** | **(49.8, 66.3)** | **63/177 (35.6)** | **(28.6, 43.1)** | **148/323 (45.8)** | **(40.3, 51.4)** |
| With concurrent infection (Grade 3 or 4) | n/M (%) | | | 5/85 (5.9) | (1.9, 13.2) | 9/63 (14.3) | (6.7, 25.4) | 14/148 (9.5) | (5.3, 15.4) |
| Without concurrent infection (Grade 3 or 4) | n/M (%) | | | 80/85 (94.1) | (86.8, 98.1) | 54/63 (85.7) | (74.6, 93.3) | 134/148 (90.5) | (84.6, 94.7) |
| With concurrent infection (serious) | n/M (%) | | | 3/85 (3.5) | (0.7, 10.0) | 8/63 (12.7) | (5.6, 23.5) | 11/148 (7.4) | (3.8, 12.9) |
| Without concurrent infection (serious) | n/M (%) | | | 82/85 (96.5) | (90.0, 99.3) | 55/63 (87.3) | (76.5, 94.4) | 137/148 (92.6) | (87.1, 96.2) |
| **Total Neutropenia ≥ Grade 3** | **M/N (%)** | **19/148 (12.8)** | **(7.9, 19.3)** | **74/146 (50.7)** | **(42.3, 59.0)** | **56/177 (31.6)** | **(24.9, 39.0)** | **130/323 (40.2)** | **(34.9, 45.8)** |
| With concurrent infection (Grade 3 or 4) | n/M (%) | | | 3/74 (4.1) | (0.8, 11.4) | 7/56 (12.5) | (5.2, 24.1) | 10/130 (7.7) | (3.8, 13.7) |
| Without concurrent infection (Grade 3 or 4) | n/M (%) | | | 71/74 (95.9) | (88.6, 99.2) | 49/56 (87.5) | (75.9, 94.8) | 120/130 (92.3) | (86.3, 96.2) |
| With concurrent infection (serious) | n/M (%) | | | 2/74 (2.7) | (0.3, 9.4) | 6/56 (10.7) | (4.0, 21.9) | 8/130 (6.2) | (2.7, 11.8) |
| Without concurrent infection (serious) | n/M (%) | | | 72/74 (97.3) | (90.6, 99.7) | 50/56 (89.3) | (78.1, 96.0) | 122/130 (93.8) | (88.2, 97.3) |
| **Total Neutropenia ≥ Grade 4** | **M/N (%)** | **5/148 (3.4)** | **(1.1, 7.7)** | **32/146 (21.9)** | **(15.5, 29.5)** | **30/177 (16.9)** | **(11.7, 23.3)** | **62/323 (19.2)** | **(15.0, 23.9)** |
| With concurrent infection (Grade 3 or 4) | n/M (%) | | | 3/32 (9.4) | (2.0, 25.0) | 1/30 (3.3) | (0.1, 17.2) | 4/62 (6.5) | (1.8, 15.7) |
| Without concurrent infection (Grade 3 or 4) | n/M (%) | | | 29/32 (90.6) | (75.0, 98.0) | 29/30 (96.7) | (82.8, 99.9) | 58/62 (93.5) | (84.3, 98.2) |
| With concurrent infection (serious) | n/M (%) | | | 2/32 (6.3) | (0.8, 20.8) | 1/30 (3.3) | (0.1, 17.2) | 3/62 (4.8) | (1.0, 13.5) |
| Without concurrent infection (serious) | n/M (%) | | | 30/32 (93.8) | (79.2, 99.2) | 29/30 (96.7) | (82.8, 99.9) | 59/62 (95.2) | (86.5, 99.0) |

[a] Definition of concurrent infection: the start date of any infection is within 2 weeks after the start date, but before or on the end date of neutropenia. Neutropenia and

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

infection are considered as concurrent if either of them had both missing start and end date or both of them had missing start date. Otherwise, if neutropenia start date is missing, infection is concurrent if its start date is before neutropenia end date; if neutropenia end date is missing, infection is considered as concurrent if its start date is within 2 weeks after the neutropenia start date; if infection start date is missing, it is considered as concurrent if its end date is on or after the neutropenia start date.

[b] Graded using CTCAE version 4.03 or higher.

[c] N = number of subjects in the designated population; M = number of subjects with neutropenia in specific AE grade; n = number of subjects with concurrent infection. Confidence interval is 95% Clopper-Pearson CI for the percentage.

**NDMM RVd Study:**

| Neutropenia/ Infection | SWOG S0777 | |
|---|---|---|
| | **Arm B (RVd)** | **Arm A (Rd)** |
| Total number of patients | 262 | 256 |
| **Patients with ≥ 1 SAE** | | |
| Neutropenia | 3 | 6 |
| Infection | 28 | 17 |
| **Patients with ≥ 1 AE** | | |
| Neutropenia | 78 | 101 |
| Infection | 92 | 74 |
| **Incidence (% of patients) with ≥ 1 AE (95% CI)** | | |
| Neutropenia | 29.8 (24.3 to 35.7) | 39.5 (33.4 to 45.7) |
| Infection | 35.1 (29.3 to 41.2) | 28.9 (23.4 to 34.9) |

In Study SWOG S0777, the proportion of patients experiencing at least one neutropenia event was smaller among patients treated with RVd than patients treated with Rd (risk ratio = 0.75 [95% CI: 0.59-0.96]). The proportion of patients experiencing at least one infection event was greater among patients treated with RVd than patients treated with Rd (risk ratio = 1.21 [95% CI: 0.94-1.56]).

**TE NDMM Studies:**

| Neutropenia/ Infection | CALGB 100104 Maintenance | | IFM 2005-02 Maintenance | |
|---|---|---|---|---|
| | **Len** | **Placebo** | **Len** | **Placebo** |
| Total number of patients | 224 | 221 | 293 | 280 |
| **Patients with ≥ 1 SAE** | | | | |
| Neutropenia | 15 | 2 | 17 | 1 |

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

| | | | | |
|---|---|---|---|---|
| Infection | 36 | 11 | 40 | 10 |
| **Patients with ≥ 1 AE** | | | | |
| Neutropenia | 179 | 100 | 178 | 34 |
| Infection | 122 | 84 | 235 | 219 |
| **Incidence (% of patients) with ≥ 1 AE (95% CI)[a]** | | | | |
| Neutropenia | 79.9 (74.1 to 85.0) | 45.2 (38.6 to 52.1) | 60.8 (54.9 to 66.4) | 12.1 (8.6 to 16.6) |
| Infection | 54.5 (47.7 to 61.1) | 38.0 (31.6 to 44.8) | 80.2 (75.2 to 84.6) | 78.2 (72.9 to 82.9) |

[a] Incidence was not adjusted for time on treatment.

In Study CALGB 100104, the proportion of patients experiencing at least one neutropenia event was greater among lenalidomide-treated patients than patients treated with placebo (risk ratio = 1.77 [95% CI: 1.51-2.07]; $p < 0.001$). The proportion of patients experiencing at least one infection event was greater among lenalidomide-treated patients than patients treated with placebo (risk ratio = 1.43 [95% CI: 1.17-1.76]; $p < 0.001$). Of note, "ANC" and "febrile neutropenia" (CTCAE) were preprinted terms on the CRF in Study CALGB 100104 (EU SCS, Section 1.2.1.2.1).

In Study IFM 2005-02, the proportion of patients experiencing at least one neutropenia event was greater among lenalidomide-treated patients than patients treated with placebo (risk ratio = 5.00 [95% CI: 3.60-6.95]; $p < 0.001$). The proportion of patients experiencing at least one infection event was similar among lenalidomide-treated patients and patients treated with placebo (risk ratio = 1.03 [95% CI: 0.94-1.12]; $p = 0.558$).

To further elucidate the relationship between neutropenia and infection a stratified analysis of infection in neutropenic and non-neutropenic patients was performed in Study IFM 2005-02. This relationship could not be analysed for Study CALGB 100104, as the start dates for regular AEs were not collected in the study; only the reporting periods were collected and they are either 3- or 6-month intervals.

**Infection Events in Patients with Neutropenia (Study IFM 2005-02)**

| **Infection Events** | **Number (%) of Patients with Neutropenia (N = 119)** | | **Number (%) of Patients without Neutropenia (N = 454)** | |
|---|---|---|---|---|
| | **Len N = 105** | **Placebo N = 14** | **Len N = 188** | **Placebo N = 266** |
| With infection | 78 (74.3) | 10 (71.4) | 157 (83.5) | 209 (78.6) |
| Without infection | 27 (25.7) | 4 (28.6) | 31 (16.5) | 57 (21.4) |

These data demonstrate that in the presence of neutropenia, no notable trend in infection risk is noted in lenalidomide-treated patients compared with placebo in the TE NDMM Study IFM 2005-02.

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

**TNE NDMM Studies:**

| Neutropenia/ Infection | MM-020 | | | MM-015 | | |
|---|---|---|---|---|---|---|
| | Rd | Rd18 | MPT | MPR+R | MPR+p | MPp+p |
| Total number of patients | 532 | 540 | 541 | 150 | 152 | 153 |
| **Patients with ≥ 1 SAE** | | | | | | |
| Neutropenia | 16 | 12 | 21 | 14 | 6 | 1 |
| Infection | 163 | 129 | 89 | 23 | 20 | 19 |
| **Patients with ≥ 1 AE** | | | | | | |
| Neutropenia | 190 | 181 | 338 | 128 | 122 | 81 |
| Infection | 399 | 378 | 305 | 96 | 87 | 98 |
| **Incidence (% of patients) with ≥ 1 AE (95% CI)**[a] | | | | | | |
| Neutropenia | 35.7 (31.6 to 40.0) | 33.5 (29.5 to 37.7) | 62.5 (58.2 to 66.6) | 85.3 (78.6 to 90.6) | 80.3 (73.0 to 86.3) | 52.9 (44.7 to 61.1) |
| Infection | 75.0 (71.1 to 78.6) | 70.0 (65.9 to 73.8) | 56.4 (52.1 to 60.6) | 64.0 (55.8 to 71.7) | 57.2 (49.0 to 65.2) | 64.1 (55.9 to 71.6) |

[a] Incidence was not adjusted for time on treatment.

In Study MM-020, the proportion of patients experiencing at least one neutropenia event was lower among lenalidomide-treated patients than patients treated with control (risk ratio = 0.55 [95% CI: 0.50-0.62]; $p < 0.001$). The proportion of patients experiencing at least one infection event was greater among lenalidomide-treated patients than patients treated with control (risk ratio = 1.29 [95% CI: 1.18-1.40]; $p < 0.001$).

In Study MM-015, the proportion of patients experiencing at least one neutropenia event was greater among lenalidomide-treated patients than patients treated with control (risk ratio = 1.56 [95% CI: 1.34-1.83]; $p < 0.001$). The proportion of patients experiencing at least one infection event was lower among lenalidomide-treated patients than patients treated with control (risk ratio = 0.95 [95% CI: 0.81-1.10]; $p = 0.467$).

To further elucidate the relationship between neutropenia and infection a stratified analysis of infection in neutropenic and non-neutropenic patients was performed.

**Infection Events in Patients with Neutropenia (Study MM-020)**

| Infection Events | Number (%) of Patients with Neutropenia (N = 463) | | | Number (%) of Patients without Neutropenia (N = 1150) | | |
|---|---|---|---|---|---|---|
| | Rd N = 119 | Rd18 N = 111 | MPT N = 233 | Rd N = 413 | Rd18 N = 429 | MPT N = 308 |

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

| | | | | | | |
|---|---|---|---|---|---|---|
| With infection | 85 (71.4) | 72 (64.9) | 100 (42.9) | 314 (76.0) | 306 (71.3) | 205 (66.6) |
| Without infection | 34 (28.6) | 39 (35.1) | 133 (57.1) | 99 (24.0) | 123 (28.7) | 103 (33.4) |

**Infection Events in Patients with Neutropenia (Study MM-015)**

| **Infection Events** | **Number (%) of Patients with Neutropenia (N = 245)** | | | **Number (%) of Patients without Neutropenia (N = 210)** | | |
|---|---|---|---|---|---|---|
| | **MPR+R N = 101** | **MPR+p N = 96** | **MPp+p N = 48** | **MPR+R N = 49** | **MPR+p N = 56** | **MPp+p N = 105** |
| With infection | 57 (56.4) | 44 (45.8) | 22 (45.8) | 39 (79.6) | 43 (76.8) | 75 (71.4) |
| Without infection | 44 (43.6) | 52 (54.2) | 26 (54.2) | 10 (20.4) | 13 (23.2) | 30 (28.6) |

These data demonstrate that in the presence of neutropenia, no notable trend in infection risk is noted in lenalidomide-treated patients compared with control in the TNE NDMM studies.

**RRMM Studies:**

| **Neutropenia/Infection** | **MM-009 and MM-010** | |
|---|---|---|
| | **Len/Dex** | **PBO/Dex** |
| Total number of patients | 353 | 350 |
| **Patients with ≥ 1 SAE** | | |
| Neutropenia | 11 | 1 |
| Infection | 81 | 59 |
| **Patients with ≥ 1 AE** | | |
| Neutropenia | 157 | 23 |
| Infection | 243 | 200 |
| **Incidence (% of patients) with ≥ 1 AE (95% CI)**[a] | | |
| Neutropenia | 44.5 (39.2 to 49.8) | 6.6 (4.2 to 9.7) |
| Infection | 68.8 (63.7 to 73.6) | 57.1 (51.8 to 62.4) |

[a] Incidence between arms was not adjusted for actual time on treatment (mean treatment duration 44 weeks [Len/Dex] versus 23 weeks [PBO/Dex]).

In the RRMM clinical studies, the risk of patients experiencing at least one event of neutropenia was greater among lenalidomide/dexamethasone-treated patients (157/353; 44.5%) than that observed among placebo/dexamethasone-treated patients (23/350; 6.6%). The risk ratio for neutropenia of lenalidomide versus placebo is 6.77 (95% CI: 4.38–9.71; $p < 0.0001$).

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

The risk of experiencing at least one episode of infection was comparable for lenalidomide/dexamethasone-treated and placebo/dexamethasone-treated patients (243/353 [68.8%] and 200/350 [57.1%], respectively). The risk ratio is 1.21 (95% CI: 1.07–1.35; p = 0.001).

To further elucidate the relationship between neutropenia and infection in patients in the RRMM studies, a stratified analysis of the risk of infection in the presence or absence of neutropenia in this population was performed and is presented in the table below.

**Infection Events in Patients with and without Neutropenia (Studies MM-009 and MM-010)**

| Infection Events | Number (%) of Patients with Neutropenia N = 180 | | Number (%) of Patients without Neutropenia N = 523 | |
|---|---|---|---|---|
| | Len/Dex N = 157 | PBO/Dex N = 23 | Len/Dex N = 196 | PBO/Dex N = 327 |
| With infection | 129 (82.2) | 17 (73.9) | 114 (58.2) | 183 (56.0) |
| Without infection | 28 (17.8) | 6 (26.1) | 82 (41.8) | 144 (44.0) |

Among neutropenic patients in the lenalidomide/dexamethasone arm, the risk of infection was 82.2% (129/157); among neutropenic patients in the placebo/dexamethasone arm, the risk was 73.9% (17/23). The risk ratio contrasting infection risk between these two groups was 1.11 (95% CI: 0.86–1.43; p = 0.36).

There were 196 patients in the lenalidomide/dexamethasone arm without neutropenia and 327 patients in the placebo/dexamethasone arm without neutropenia. The risk of infection within these two arms was 58.2% and 56.0%, respectively. The risk ratio was 1.04 (95% CI: 0.89–1.21; p = 0.63).

The Breslow-Day test for interaction of the risk ratio between strata was 0.91 (p = 0.34), indicating no significant statistical difference. After controlling for the effect of neutropenia, there is no increased risk of infection among lenalidomide-treated patients (adjusted risk ratio 1.05; 95% CI: 0.92–1.21, p = 0.45). However, the greater risk of infection may be understood by the greater proportion of patients with neutropenia.

**Del 5q MDS Studies:**

| Neutropenia/Infection | MDS-003[a] Len (10 mg) | MDS-004[b] | | |
|---|---|---|---|---|
| | | Len (10 mg) | Len (5 mg) | PBO[c] |
| Total number of patients | 148 | 69 | 69 | 67 |
| **Patients with ≥ 1 SAE** | | | | |
| Neutropenia | 17 | 5 | 6 | 0 |
| Infection | 35[d] | 9[e] | 8[f] | 3[g] |

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

| | | | | |
|---|---|---|---|---|
| **Patients with ≥ 1 AE** | | | | |
| Neutropenia | 101 | 53 | 54 | 12 |
| Infection | 117 | 45 | 41 | 23 |
| **Incidence (% of patients) with ≥ 1 AE (95% CI)** | | | | |
| Neutropenia | 68.2 (60.1 to 75.6) | 76.8 (65.1 to 86.1) | 78.3 (66.7 to 87.3) | 17.9 (9.6 to 29.2) |
| Infection | 79.1 (71.6 to 85.3) | 65.2 (52.8 to 76.3) | 59.4 (46.9 to 71.1) | 34.3 (23.2 to 46.9) |

[a] Median time on treatment was 52.5 weeks.

[b] Median time on treatment was 50.3 weeks on the 10 mg group, 18.0 weeks in the 5 mg group and 16.0 weeks in the PBO group.

[c] Data in PBO group is from the first 16 weeks of the double-blind phase.

[d] Includes PTs of pneumonia NOS (15), sepsis NOS (6), and bacteraemia, cellulitis, infection NOS and urinary tract infection NOS (2 each). All other PTs reported for ≤ 1 patient.

[e] Includes PTs of pneumonia (2), and bronchopneumonia, anal abscess, cellulitis, erysipelas, gastroenteritis, pyelonephritis, septic shock and urinary tract infection (1 each).

[f] Includes PTs of pneumonia (2), and erysipelas, infection, lower respiratory tract infection, respiratory tract infection, staphylococcal sepsis and urinary tract infection (1 each).

[g] Includes PTs of arthritis bacterial, bronchopneumonia and pneumonia (1 each).

In Study MDS-004, the risk of neutropenia was comparable in the lenalidomide 10 mg and 5 mg groups (53/69; 76.8% and 54/69; 78.3%, respectively) and greater than in the placebo group (12/67; 17.9%). For the combined group (5 mg and 10 mg) versus placebo, the risk ratio is 4.33 (95% CI: 2.57–7.28).

The risk of infection was similar in the lenalidomide 10 mg and 5 mg groups (45/69; 65.2% and 41/69; 59.4%, respectively), and greater than in the placebo group (23/67; 34.3%). For the combined group (5 mg and 10 mg) versus placebo, the risk ratio is 1.81 (95% CI: 1.27–2.59).

A stratified analysis of infection with and without neutropenia in this population is presented below.

**Infection Events in Patients with and without Neutropenia (Study MDS-004)**

| **Infection Events** | **Number (%) of Patients with Neutropenia N = 137** | | | **Number (%) of Patients without Neutropenia N = 68** | | |
|---|---|---|---|---|---|---|
| | **Len (10 mg) N = 62** | **Len (5 mg) N = 59** | **PBO N = 16** | **Len (10 mg) N = 7** | **Len (5 mg) N = 10** | **PBO N = 51** |

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

| | | | | | | |
|---|---|---|---|---|---|---|
| With infection | 40 (64.5) | 35 (59.3) | 5 (31.3) | 5 (71.4) | 6 (60.0) | 18 (35.3) |
| With related infection | 27 (43.5) | 23 (39.0) | 2 (12.5) | 0 | 0 | 0 |

Temporally related infection was defined as infection that occurred within 2 weeks of an AE of neutropenia.

It can be concluded that the risk of infection with lenalidomide is probably related to the risk of neutropenia in this population.

**MCL Studies:**

| **Neutropenia/ Infection** | **MCL-002** | | **All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003)** |
|---|---|---|---|
| | **Len** | **Control** | |
| Total number of patients | 167 | 83 | 373 |
| **Patients with ≥ 1 SAE** | | | |
| Neutropenia | 11 | 2 | 25 |
| Infection | 22 | 7 | 63 |
| **Patients with ≥ 1 AE** | | | |
| Neutropenia | 89 | 29 | 201 |
| Infection | 90 | 31 | 211 |
| **Incidence (% of patients) with ≥ 1 AE (95% CI)** | | | |
| Neutropenia | 53.3 (45.4 to 61.0) | 34.9 (24.8 to 46.2) | 53.9 (48.7 to 59.0) |
| Infection | 53.9 (46.0 to 61.6) | 37.3 (27.0 to 48.7) | 56.6 (51.4 to 61.7) |

In Study MCL-002, the proportion of patients experiencing at least one neutropenia event was greater among lenalidomide-treated patients than patients treated with control (risk ratio = 1.53 [95% CI: 1.10-2.11]; p = 0.011).

The proportion of patients experiencing at least one infection event was also greater among lenalidomide-treated patients than patients treated with control (risk ratio = 1.44 [95% CI: 1.06-1.97]; p = 0.021).

To further elucidate the relationship between neutropenia and infection a stratified analysis of infection in neutropenic and non-neutropenic patients was performed.

**Infection Events in Patients with Neutropenia**

| | **Number (%) of Patients with Neutropenia** | **Number (%) of Patients without Neutropenia** |
|---|---|---|

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

| | **MCL-002** | | **All MCL Len Patients (MCL-002, MCL-001, NHL-002, NHL-003)** | **MCL-002** | | **All MCL Len Patients (MCL-002, MCL-001, NHL-002, NHL-003)** |
|---|---|---|---|---|---|---|
| | **Len N = 89** | **Control N = 29** | **Len N = 201** | **Len N = 78** | **Control N = 54** | **Len N = 172** |
| With infection | 27 (30.3) | 5 (17.2) | 54 (26.9) | 28 (35.9) | 18 (33.3) | 75 (43.6) |
| Without infection | 62 (69.7) | 24 (82.8) | 147 (73.1) | 50 (64.1) | 36 (66.7) | 97 (56.4) |

These data demonstrate that in the presence of neutropenia, no notable trend in infection risk is noted in lenalidomide-treated patients compared with infection events in the absence of neutropenia in the studies in MCL.

**Seriousness/Outcomes**

**FL Studies:**

SAE outcomes reported in the FL studies are summarised below.

| **Neutropenia/Infection** | **NHL-007** | | **NHL-008** | **Pooled NHL-007 and NHL-008** |
|---|---|---|---|---|
| | **PBO+Rit** | **Len+Rit** | **Len+Rit** | **Len+Rit** |
| Total number of patients | 148 | 146 | 177 | 323 |
| **Patients with ≥ 1 SAE** | | | | |
| Neutropenia | 0 | 6 (4.1) | 9 (5.1) | 15 (4.6) |
| Infection | 5 (3.4) | 14 (9.6) | 20 (11.3) | 34 (10.5) |
| **Death** | | | | |
| Neutropenia | 0 | 0 | 0 | 0 |
| Infection | 0 | 0 | 0 | 0 |
| **Resolved** | | | | |
| Neutropenia | 0 | 6 (4.1) | 9 (5.1) | 15 (4.6) |
| Infection | 5 (3.4) | 14 (9.6) | 16 (9.0) | 30 (9.3) |
| **Resolved with Sequelae** | | | | |
| Neutropenia | 0 | 0 | 0 | 0 |

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

| | | | | |
|---|---|---|---|---|
| Infection | 0 | 0 | 3 (1.7) | 3 (0.9) |
| **Not Recovered/Not Resolved** | | | | |
| Neutropenia | 0 | 0 | 0 | 0 |
| Infection | 0 | 0 | 0 | 0 |
| **Ongoing at Time of Death** | | | | |
| Neutropenia | 0 | 0 | 0 | 0 |
| Infection | 0 | 0 | 1 (0.6) | 1 (0.3) |

In Study NHL-007, neutropenia SAEs were reported for 6/146 (4.1%) lenalidomide plus rituximab-treated patients (PTs reported were febrile neutropenia and neutropenia) and 0/148 rituximab plus placebo-treated patients. No neutropenia SAEs had an outcome of death. Infection SAEs were reported for 14/146 (9.6%) lenalidomide plus rituximab-treated patients and for 5/148 (3.4%) rituximab plus placebo-treated patients. No infection SAEs had an outcome of death.

In Study NHL-008, neutropenia SAEs were reported for 9/177 (5.1%) lenalidomide plus rituximab-treated patients (PTs reported were febrile neutropenia and neutropenia). No neutropenia SAEs had an outcome of death. Infection SAEs were reported for 20/177 (11.3%) lenalidomide plus rituximab-treated patients (PTs reported in 2 or more patients were pneumonia, sepsis and cellulitis). No infection SAEs had an outcome of death.

**NDMM RVd Study**

SAE outcomes reported in Study SWOG S0777 are summarised below.

| **Outcome** | **SWOG S0777** | |
|---|---|---|
| | **Arm B (RVd)** | **Arm A (Rd)** |
| Total number of patients | 262 | 256 |
| **Patients with ≥ 1 SAE** | | |
| Neutropenia | 3 (1.1) | 6 (2.3) |
| Infection | 28 (10.7) | 17 (6.6) |
| **Death** | | |
| Neutropenia | 0 | 0 |
| Infection | 0 | 0 |
| **Recovered/Resolved** | | |
| Neutropenia | 1 (0.4) | 4 (1.6) |
| Infection | 8 (3.1) | 4 (1.6) |
| **Recovered/Resolved with Sequelae** | | |
| Neutropenia | 0 | 0 |
| Infection | 2 (0.8) | 1 (0.4) |

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

| | | |
|---|---|---|
| **Recovering/Resolving** | | |
| Neutropenia | 1 (0.4) | 0 |
| Infection | 13 (5.0) | 9 (3.5) |
| **Not Recovered/Not Resolved** | | |
| Neutropenia | 1 (0.4) | 2 (0.8) |
| Infection | 3 (1.1) | 3 (1.2) |
| **Ongoing at Death** | | |
| Neutropenia | 0 | 0 |
| Infection | 1 (0.4) | 0 |
| **Unknown** | | |
| Neutropenia | 0 | 0 |
| Infection | 1 (0.4) | 0 |

In Study SWOG S0777, neutropenia SAEs were experienced by 3/262 (1.1%) patients treated with RVd and 6/256 (2.3%) patients treated with Rd (PTs reported were febrile neutropenia and neutropenia). Infection SAEs were reported in 28/262 (10.7%) patients treated with RVd (PTs reported in 2 or more patients were urinary tract infection, lung infection, sepsis and Enterocolitis infectious) and 17/256 (6.6%) patients treated with Rd (PTs reported in 2 or more patients were urinary tract infection and lung infection). No neutropenia or infection SAEs had an outcome of death in Study SWOG S0777.

**TE NDMM Studies:**

SAE outcomes reported in the TE NDMM studies are summarised below.

| **Outcome** | **CALGB 100104 Maintenance** | | **IFM 2005-02 Maintenance** | |
|---|---|---|---|---|
| | **Len** | **Placebo** | **Len** | **Placebo** |
| Total number of patients | 224 | 221 | 293 | 280 |
| **Patients with ≥ 1 SAE** | | | | |
| Neutropenia | 15 (6.7) | 2 (0.9) | 17 (5.8) | 1 (0.4) |
| Infection | 36 (16.1) | 11 (5.0) | 40 (13.7) | 10 (3.6) |
| **Death** | | | | |
| Neutropenia | 0 | 0 | 0 | 0 |
| Infection | 1 (0.4) | 0 | 0 | 0 |
| **Recovered/Resolved** | | | | |
| Neutropenia | 5 (2.2) | 0 | 12 (4.1) | 0 |
| Infection | 11 (4.9) | 4 (1.8) | 16 (5.5) | 3 (1.1) |

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

| | | | | |
|---|---|---|---|---|
| **Recovering/Resolving** | | | | |
| Neutropenia | 3 (1.3) | 0 | 4 (1.4) | 0 |
| Infection | 15 (6.7) | 2 (0.9) | 6 (2.0) | 0 |
| **Not Recovered/Not Resolved** | | | | |
| Neutropenia | 6 (2.7) | 0 | 0 | 0 |
| Infection | 6 (2.7) | 0 | 0 | 0 |
| **Recovered with Sequelae** | | | | |
| Neutropenia | 1 (0.4) | 0 | 0 | 0 |
| Infection | 3 (1.3) | 2 (0.9) | 1 (0.3) | 0 |
| **Missing** | | | | |
| Neutropenia | 0 | 2 (0.9) | 1 (0.3) | 1 (0.4) |
| Infection | 0 | 3 (1.4) | 17 (5.8) | 7 (2.5) |
| **Ongoing at Death** | | | | |
| Neutropenia | 0 | 0 | 0 | 0 |
| Infection | 0 | 0 | 0 | 0 |

In Study CALGB 100104, neutropenia SAEs were reported for 15/224 (6.7%) lenalidomide-treated patients (PTs reported were febrile neutropenia, neutropenia and neutropenic infection). No neutropenia SAEs had an outcome of death in Study CALGB 100104. Infection SAEs were reported for 36/224 (16.1%) lenalidomide-treated patients in Study CALGB 100104. PTs reported in the lenalidomide group in 2 or more patients were appendicitis, infection, lung infection, meningitis, upper respiratory tract infection, and urinary tract infection. An infection SAE (PT: sepsis) had an outcome of death in 1 (0.4%) lenalidomide-treated patient in Study CALGB 100104.

In Study IFM 2005-02, neutropenia SAEs were reported for 17/293 (5.8%) lenalidomide-treated patients (PTs reported were febrile neutropenia and neutropenia). Infection SAEs were reported for 40/293 (13.7%) lenalidomide-treated patients. PTs reported in the lenalidomide group in 2 or more patients were bacterial sepsis, bronchitis, bronchopneumonia, gastroenteritis, herpes zoster, influenza, pneumonia, pneumonia pneumococcal and staphylococcal sepsis. No neutropenia and infection SAEs had an outcome of death in Study IFM 2005-02.

**TNE NDMM Studies:**

SAE outcomes reported in the TNE NDMM studies are summarised below.

| **Outcome** | **MM-020** | | | **MM-015** | | |
|---|---|---|---|---|---|---|
| | **Rd** | **Rd18** | **MPT** | **MPR+R** | **MPR+p** | **MPp+p** |
| Total number of patients | 532 | 540 | 541 | 150 | 152 | 153 |
| **Patients with ≥ 1 SAE** | | | | | | |

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

| | | | | | | |
|---|---|---|---|---|---|---|
| Neutropenia | 16 (3.0) | 12 (2.2) | 21 (3.9) | 14 (9.3) | 6 (3.9) | 1 (0.7) |
| Infection | 163 (30.6) | 129 (23.9) | 89 (16.5) | 23 (15.3) | 20 (13.2) | 19 (12.4) |
| **Death** | | | | | | |
| Neutropenia | 0 | 1 (0.2) | 1 (0.2) | 0 | 0 | 0 |
| Infection | 21 (3.9) | 12 (2.2) | 10 (1.8) | 3 (2.0) | 1 (0.7) | 0 |
| **Recovered/Resolved** | | | | | | |
| Neutropenia | 14 (2.6) | 10 (1.9) | 14 (2.6) | 11 (7.3) | 3 (2.0) | 0 |
| Infection | 111 (20.9) | 92 (17.0) | 61 (11.3) | 14 (9.3) | 15 (9.9) | 0 |
| **Not Recovered/Not Resolved** | | | | | | |
| Neutropenia | 0 | 0 | 1 (0.2) | 1 (0.7) | 0 | 0 |
| Infection | 3 (0.6) | 4 (0.7) | 1 (0.2) | 0 | 0 | 0 |
| **Recovered with Sequelae** | | | | | | |
| Neutropenia | 1 (0.2) | 0 | 1 (0.2) | 0 | 0 | 0 |
| Infection | 14 (2.6) | 5 (0.9) | 6 (1.1) | 6 (4.0) | 1 (0.7) | 1 (0.7) |
| **Missing** | | | | | | |
| Neutropenia | 1 (0.2) | 0 | 1 (0.2) | 1 (0.7) | 2 (1.3) | 1 (0.7) |
| Infection | 9 (1.7) | 9 (1.7) | 6 (1.1) | 0 | 3 (2.0) | 18 (11.8) |
| **Ongoing at Death** | | | | | | |
| Neutropenia | 0 | 1 (0.2) | 3 (0.6) | 1 (0.7) | 1 (0.7) | 0 |
| Infection | 5 (0.9) | 7 (1.3) | 4 (0.7) | 0 | 0 | 0 |
| **Recovering/Resolving** | | | | | | |
| Neutropenia | 0 | 0 | 0 | 0 | 0 | 0 |
| Infection | 0 | 0 | 1 (0.2) | 0 | 0 | 0 |

In Study MM-020, SAEs of neutropenia were reported more frequently in the MPT arm of the study compared with the Rd and Rd18 arms (MPT: 3.9% versus Rd: 3.0%, Rd18: 2.2%). (PTs were febrile neutropenia, neutropenia and neutropenic sepsis). Neutropenia (neutropenic sepsis) was Grade 5 (fatal) in 3 patients: 1 in each treatment

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

arm of the study. In Study MM-015, SAEs of neutropenia were reported more frequently in the lenalidomide-containing arms of the study (MPR+R: 9.3%; MPR+p: 3.9%) compared with placebo-treated patients (MPp+p: 0.7%). Among patients receiving induction with melphalan, prednisone and lenalidomide, the frequency of these events was higher in patients receiving continuous treatment with lenalidomide following induction than in patients receiving placebo.

No neutropenia SAEs had an outcome of death in Study MM-015.

In Study MM-020, infection SAEs were experienced by more patients in the lenalidomide arms: 163/532 (30.6%) and 129/540 (23.9%) patients in Arm Rd and Arm Rd18, respectively, compared with 89/541 (16.5%) patients in Arm MPT. PTs reported for 5 or more patients overall (in descending order of frequency) were pneumonia (135 patients), sepsis (33), bronchitis (20), upper respiratory tract infection, respiratory tract infection and lobar pneumonia (17 each), urinary tract infection and lung infection (16 each), septic shock and lower respiratory tract infection (15 each), cellulitis (13), influenza (10), infection and bronchopneumonia (9 each), pneumonia pneumococcal (7), bacteraemia (6), and staphylococcal sepsis, pyelonephritis, herpes zoster, gastroenteritis, erysipelas and arthritis bacterial (5 each). Infection SAEs with an outcome of death were reported for 21 (3.9%), 12 (2.2%) and 10 (1.8%) patients, respectively. In Study MM-015, infection SAEs were experienced by slightly fewer patients in the control arm: 23/150 (15.3%), 20/152 (13.2%) and 19/153 (12.4%) patients in the MPR+R, MPR+p and MPp+p arms, respectively. PTs reported for more than 2 patients overall were bronchitis, lower respiratory tract infection, pneumonia, sepsis, and urinary tract infection). A total of 3 (2.0%), 1 (0.7%) and 0 patients with infection SAEs in the MPR+R, MPR+p and MPp+p arms, respectively, had outcomes of death.

**RRMM Studies:**

The SAEs reported in the RRMM studies are summarised below.

| **Outcome** | **Number (%) of Patients**[a] | |
|---|---|---|
| | **MM-009 and MM-010** | |
| | **Len/Dex N = 353** | **PBO/Dex N = 350** |
| **Patients with ≥ 1 SAE** | | |
| Neutropenia | 11 (3.1) | 1 (0.3) |
| Infection | 81 (22.9) | 59 (16.9) |
| **Death** | | |
| Neutropenia | 0 | 0 |
| Infection | 1 (0.3) | 3 (0.9) |
| **Resolved/Recovered with/without Sequelae (MM-009 and MM-010)** | | |
| Neutropenia | 8 (2.3) | 1 (0.3) |
| Infection | 21 (5.9) | 14 (4) |
| **Not Recovered/Not Resolved (MM-009 and MM-010)** | | |
| Neutropenia | 1 (0.3) | 0 |

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

| | | |
|---|---|---|
| Infection | 1 (0.3) | 0 |
| **Unknown/Missing (MM-009 and MM-010)** | | |
| Neutropenia | 4 (1.1) | 0 |
| Infection | 68 (19.2) | 44 (12.5) |

[a] Patients may be counted more than once.

A total of 14 serious neutropenia events were experienced by 11/353 (3.1%) lenalidomide/dexamethasone-treated patients. These SAEs were febrile neutropenia (6 patients), neutropenia (5 patients), and neutropenic sepsis (one patient). A total of 116 infection SAEs were experienced by 81 (22.9%) lenalidomide/dexamethasone-treated patients. SAEs of pneumonia NOS were experienced by 34 patients, all other SAEs were experienced by 4 or fewer patients. A total of 4 patients were reported with both SAEs of infection and leucopenia/neutropenia.

Of the 14 neutropenia SAEs experienced by lenalidomide/dexamethasone-treated patients, all 14 were of Grade 3 or 4 intensity and 12 were considered to be related to treatment. In 13 of the 14 SAEs, the dose of lenalidomide was reduced or interrupted, or treatment was permanently discontinued. A neutropenia SAE was reported in 1 out of 350 (0.3%) placebo/dexamethasone-treated patients.

Of the 116 infection SAEs experienced by lenalidomide/dexamethasone-treated patients, 98 were of Grade 3 or 4 intensity and 41 were considered to be related to treatment. In 61 of the 116 SAEs, the dose of lenalidomide was reduced or interrupted, or treatment was permanently discontinued. One patient died as a result of septic shock not related to lenalidomide/dexamethasone. Infection SAEs were experienced by 59 out of 350 (16.9%) placebo/dexamethasone-treated patients.

**Del 5q MDS Studies:**

The outcomes of the SAEs reported in Studies MDS-003 and MDS-004 are summarised below.

| **Outcome** | **Number (%) of Patients**[a] | | | |
|---|---|---|---|---|
| | **MDS-003**[b] | **MDS-004**[c] | | |
| | **Len (10 mg) N = 148** | **Len (10 mg) N = 69** | **Len (5 mg) N = 69** | **PBO**[d] **N = 67** |
| **Patients with ≥ 1 SAE** | | | | |
| Neutropenia | 17 (11.5) | 5 (7.2) | 6 (8.7) | 0 |
| Infection | 35 (23.6)[e] | 9 (13.0)[f] | 8 (11.6)[g] | 3 (4.5)[h] |
| **Death** | | | | |
| Neutropenia | 0 | 0 | 0 | 0 |
| Infection | 4 (2.7) | 1 (1.4) | 0 | 0 |
| **Not Recovered/Not Resolved** | | | | |
| Neutropenia | 2 (1.4) | 0 | 0 | 0 |

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

| | | | | |
|---|---|---|---|---|
| Infection | 2 (1.4) | 1 (1.4) | 0 | 0 |
| **Resolved/Recovered with/without Sequelae** | | | | |
| Neutropenia | 12 (8.1) | 5 (7.2) | 5 (7.2) | 0 |
| Infection | 27 (18.2) | 7 (10.1) | 6 (8.7) | 2 (3.0) |
| **Unknown/Missing** | | | | |
| Neutropenia | 3 (2.0) | 1 (1.4) | 1 (1.4) | 0 |
| Infection | 7 (4.7) | 1 (1.4) | 2 (2.9) | 1 (1.5) |

[a] Patients may be counted more than once

[b] Median time on treatment was 52.5 weeks.

[c] Median time on treatment was 50.3 weeks in the 10 mg group, 18.0 weeks in the 5 mg group and 16.0 weeks in the PBO group.

[d] Data in PBO group is from the first 16 weeks of the double-blind phase.

[e] Includes PTs of pneumonia NOS (15), sepsis NOS (6), and bacteraemia, cellulitis, infection NOS and urinary tract infection NOS (2 each). All other PTs reported for ≤ 1 patient.

[f] Includes PTs of pneumonia (2), and bronchopneumonia, anal abscess, cellulitis, erysipelas, gastroentiritis, pyelonephritis, septic shock and urinary tract infection (1 each).

[g] Includes PTs of pneumonia (2), and erysipelas, infection, lower respiratory tract infection, respiratory tract infection, staphylococcal sepsis, urinary tract infection and urosepsis (1 each).

[h] Includes PTs of arthritis bacterial, bronchopneumonia and pneumonia (1 each).

In Study MDS-004, neutropenia-related SAEs were PT neutropenia in 4 patients each in the lenalidomide groups, and the PT of febrile neutropenia, which was experienced by 1 and 2 patients in the lenalidomide 10 mg and 5 mg groups, respectively. All of the neutropenia SAEs were considered related to treatment.

In Study MDS-004, treatment-related SAEs of infection included cellulitis in the lenalidomide 10 mg group and erysipelas, infection, lower respiratory tract infection and pneumonia in the lenalidomide 5 mg group. One patient in the lenalidomide 10 mg group died due to septic shock (respiratory origin).

In Study MDS-003, 4 patients experienced infection SAEs that resulted in death. These SAEs were sepsis in 2 patients, which were considered not related to study medication, and Klebsiella sepsis and pneumonia in 1 patient each, which were considered treatment related.

**MCL Studies:**

SAE outcomes reported in the studies in MCL are summarised below.

| **Outcome** | **MCL-002** | |
|---|---|---|

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

| | Len | Control | All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003) |
|---|---|---|---|
| Total number of patients | 167 | 83 | 373 |
| **Patients with ≥ 1 SAE** | | | |
| Neutropenia | 11 (6.6) | 2 (2.4) | 25 (6.7) |
| Infection | 22 (13.2) | 7 (8.4) | 63 (16.9) |
| **Death** | | | |
| Infection | 0 | 0 | 5 (1.3) |
| **Ongoing at Death** | | | |
| Neutropenia | 2 (1.2) | 0 | 2 (0.5) |
| Infection | 1 (0.6) | 0 | 4 (1.1) |
| **Recovered with Sequelae** | | | |
| Neutropenia | 1 (0.6) | 0 | 1 (0.3) |
| Infection | 3 (1.8) | 0 | 7 (1.9) |
| **Recovered/Resolved** | | | |
| Neutropenia | 8 (4.8) | 2 (2.4) | 22 (5.9) |
| Infection | 17 (10.2) | 7 (8.4) | 44 (11.8) |
| **Unknown** | | | |
| Neutropenia | 0 | 0 | 0 |
| Infection | 1 (0.6) | 0 | 3 (0.8) |

In Study MCL-002, neutropenia SAEs were experienced more frequently by lenalidomide-treated patients (11/167 [6.6%]) than by patients in the control group (2/83 [2.4%]); PTs reported in the lenalidomide group were febrile neutropenia, neutropenia and neutropenic sepsis). No patients experienced SAEs of neutropenia that had an outcome of death.

In the combined MCL Studies MCL-002, MCL-001, NHL-002 and NHL-003, neutropenia SAEs were experienced by 25/373 (6.7%) lenalidomide-treated patients (PTs reported were febrile neutropenia, neutropenia and neutropenic sepsis). No patients experienced SAEs of neutropenia that had an outcome of death.

In Study MCL-002, infection SAEs were experienced by more patients in the lenalidomide group (22/167 [13.2%]) than in the control group (7/83 [8.4%]). PTs reported in the lenalidomide group in 2 or more patients were pneumonia, bronchitis, urinary tract infection, lower respiratory tract infection, and lung infection. No patients experienced SAEs of infection that had an outcome of death.

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

In the combined MCL Studies MCL-002, MCL-001, NHL-002 and NHL-003, infection SAEs were experienced by 63/373 (16.9%) lenalidomide-treated patients. PTs reported in 2 or more patients were pneumonia, bronchitis, urinary tract infection, cellulitis, lower respiratory tract infection, pneumonia bacterial, pneumonia streptococcal, sepsis, staphylococcal sepsis, bronchopneumonia, bronchopulmonary aspergillosis, bacteraemia, clostridium difficile colitis, lung infection, respiratory tract infection, septic shock, staphylococcal bacteraemia and urosepsis. A total of 5 (1.3%) patients experienced SAEs of infection that had an outcome of death.

**Severity and Nature of Risk**

**FL Studies:**

Details of AEs pertaining to neutropenia and infection that were reported in the FL studies are summarised below.

| Neutropenia/Infection | NHL-007 | | NHL-008 | Pooled NHL-007 and NHL-008 |
|---|---|---|---|---|
| | PBO+Rit | Len+Rit | Len+Rit | Len+Rit |
| Total number of patients | 148 | 146 | 177 | 323 |
| **All AEs** | | | | |
| Neutropenia | 33 (22.3) | 85 (58.2) | 63 (35.6) | 148 (45.8) |
| Infection | 68 (45.9) | 92 (63.0) | 90 (50.8) | 182 (56.3) |
| **Grade 3 or 4** | | | | |
| Neutropenia | 19 (12.8) | 74 (50.7) | 56 (31.6) | 130 (40.2) |
| Infection | 7 (4.7) | 22 (15.1) | 23 (13.0) | 45 (13.9) |
| **AEs Leading to Dose Discontinuation** | | | | |
| Neutropenia | 0 | 5 (3.4) | 10 (5.6) | 15 (4.6) |
| Infection | 0 | 1 (0.7) | 5 (2.8) | 6 (1.9) |
| **AEs Leading to Dose Interruption** | | | | |
| Neutropenia | 13 (8.8) | 59 (40.4) | 32 (18.1) | 91 (28.2) |
| Infection | 12 (8.1) | 29 (19.9) | 30 (16.9) | 59 (18.3) |
| **AEs Leading to Dose Reduction** | | | | |
| Neutropenia | 4 (2.7) | 28 (19.2) | 38 (21.5) | 66 (20.4) |
| Infection | 0 | 0 | 5 (2.8) | 5 (1.5) |

In Study NHL-007, a greater proportion of FL patients treated with lenalidomide plus rituximab than those treated with rituximab plus placebo experienced Grade 3 or 4 AEs of neutropenia (50.7% versus 12.8%), and neutropenia AEs leading to dose interruption (40.4% versus 8.8%), dose reduction (19.2% versus 2.7%) and study treatment discontinuation (3.4% versus 0%). A greater proportion of patients treated with lenalidomide plus rituximab than those treated with rituximab plus placebo

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

experienced Grade 3 or 4 AEs of infection (15.1% versus 4.7%), and infection AEs leading to dose interruption (19.9% versus 8.1%). Less than 1% of patients treated with lenalidomide plus rituximab experienced infection AEs leading to study treatment discontinuation. No patients in either treatment arm experienced infection AEs leading to dose reduction.

In Study NHL-008, Grade 3 or 4 AEs of neutropenia were reported for 31.6% lenalidomide plus rituximab-treated patients, and neutropenia AEs leading to dose interruption, dose reduction and study treatment discontinuation were reported for 18.1%, 21.5% and 5.6% lenalidomide plus rituximab-treated patients, respectively. Grade 3 or 4 AEs of infection were reported for 13.0% lenalidomide plus rituximab-treated patients, and infection AEs leading to dose interruption, dose reduction and study treatment discontinuation were reported for 16.9%, 2.8% and 2.8% lenalidomide plus rituximab-treated patients, respectively.

**NDMM RVd Study:**

Details of AEs pertaining to neutropenia and infection that were reported in Study SWOG S0777 are summarised below.

| **Neutropenia/Infection** | **SWOG S0777** | |
|---|---|---|
| | **Arm B (RVd)** | **Arm A (Rd)** |
| Total number of patients | 262 | 256 |
| **All AEs** | | |
| Neutropenia | 78 (29.8) | 101 (39.5) |
| Infection | 92 (35.1) | 74 (28.9) |
| **Grade 3 or 4** | | |
| Neutropenia | 27 (10.3) | 45 (17.6) |
| Infection | 36 (13.7) | 24 (9.4) |
| **AEs Leading to Dose Withdrawn Permanently** | | |
| Neutropenia | NC | NC |
| Infection | NC | NC |
| **AEs Leading to Dose Interruption** | | |
| Neutropenia | NC | NC |
| Infection | NC | NC |
| **AEs Leading to Dose Reduction** | | |
| Neutropenia | NC | NC |
| Infection | NC | NC |

NC = not collected.

In Study SWOG S0777, the incidences of Grade 3 or 4 AEs of neutropenia (10.3% versus 17.6%) and infection (13.7% versus 9.4%) were comparable for patients in the RVd and Rd arms. Adverse events leading to study treatment withdrawal, interruption and dose reduction were not collected in this study.

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

**TE NDMM Studies:**

Details of AEs pertaining to neutropenia and infection that were reported in the TE NDMM studies are summarised below.

| Neutropenia/ Infection | CALGB 100104 Maintenance | | IFM 2005-02 Maintenance | |
|---|---|---|---|---|
| | Len | Placebo | Len | Placebo |
| Total number of patients | 224 | 221 | 293 | 280 |
| **All AEs** | | | | |
| Neutropenia | 179 (79.9) | 100 (45.2) | 178 (60.8) | 34 (12.1) |
| Infection | 122 (54.5) | 84 (38.0) | 235 (80.2) | 219 (78.2) |
| **Grade 3 or 4** | | | | |
| Neutropenia | 140 (62.5) | 78 (35.3) | 158 (53.9) | 22 (7.9) |
| Infection | 66 (29.5) | 34 (15.4) | 40 (13.7) | 13 (4.6) |
| **AEs Leading to Dose Withdrawn Permanently**[a] | | | | |
| Neutropenia | 5 (2.2) | 0 | 8 (2.7) | 0 |
| Infection | 4 (1.8) | 0 | 5 (1.7) | 2 (0.7) |
| **AEs Leading to Dose Interruption**[b] | | | | |
| Neutropenia | NC | NC | 72 (24.6) | 1 (0.4) |
| Infection | NC | NC | 52 (17.7) | 20 (7.1) |
| **AEs Leading to Dose Reduction**[c] | | | | |
| Neutropenia | NC | NC | 42 (14.3) | 2 (0.7) |
| Infection | NC | NC | 4 (1.4) | 2 (0.7) |

[a] In Study CALGB100104, actions taken due to AEs (eg, treatment discontinued, dose reduced, dose interrupted) were not collected on the CRF. AEs leading to treatment discontinuation were derived retrospectively from the Off Treatment Notice form.

NC = not collected per study design.

In Study CALGB 100104, greater proportions of patients treated with lenalidomide than those treated with placebo experienced Grade 3 or 4 AEs of neutropenia (62.5% versus 35.3%) and infection (29.5% versus 15.4%). AEs of neutropenia and infection led to permanent withdrawal of study treatment in 2.2% and 1.8% of patients treated with lenalidomide, respectively; there were no AEs of neutropenia or infection leading to permanent withdrawal of study treatment in patients treated with placebo.

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

In Study IFM 2005-02, greater proportions of patients treated with lenalidomide than those treated with placebo experienced Grade 3 or 4 AEs of neutropenia (53.9% versus 7.9%), and neutropenia AEs leading to dose interruption (24.6% versus 0.4%), dose reduction (14.3% versus 0.7%) and study treatment withdrawal (2.7% versus 0%). Greater proportions of patients treated with lenalidomide than those treated with placebo experienced Grade 3 or 4 AEs of infection (13.7% versus 4.6%), and infection AEs leading to dose interruption (17.7% versus 7.1%). Less than 2% of patients in both treatment arms experienced infection AEs leading to dose reduction or study treatment withdrawal.

There was no evidence of an increased frequency of onset of neutropenia or infection over time across studies (EU SCS, Section 2.1.11).

**TNE NDMM Studies**

Details of AEs pertaining to neutropenia and infection that were reported in the TNE NDMM studies are summarised below.

| Neutropenia/ Infection | MM-020 | | | MM-015 | | |
|---|---|---|---|---|---|---|
| | Rd | Rd18 | MPT | MPR+R | MPR+p | MPp+p |
| Total number of patients | 532 | 540 | 541 | 150 | 152 | 153 |
| **All AEs** | | | | | | |
| Neutropenia | 190 (35.7) | 181 (33.5) | 338 (62.5) | 128 (85.3) | 122 (80.3) | 81 (52.9) |
| Infection | 399 (75.0) | 378 (70.0) | 305 (56.4) | 96 (64.0) | 87 (57.2) | 98 (64.1) |
| **Grade 3 or 4** | | | | | | |
| Neutropenia | 152 (28.6) | 147 (27.2) | 252 (46.6) | 114 (76.0) | 102 (67.1) | 48 (31.4) |
| Infection | 154 (28.9) | 118 (21.9) | 93 (17.2) | 17 (11.3) | 22 (14.5) | 15 (9.8) |
| **AEs Leading to Dose Withdrawn Permanently** | | | | | | |
| Neutropenia | 7 (1.3) | 2 (0.4) | 13 (2.4) | 4 (2.7) | 6 (3.9) | 2 (1.3) |
| Infection | 23 (4.3) | 15 (2.8) | 6 (1.1) | 4 (2.7) | 1 (0.7) | 1 (0.7) |
| **AEs Leading to Dose Interruption** | | | | | | |
| Neutropenia | 119 (22.4) | 104 (19.3) | 268 (49.5) | 95 (63.3) | 76 (50.0) | 31 (20.3) |
| Infection | 164 (30.8) | 113 (20.9) | 67 (12.4) | 28 (18.7) | 30 (19.7) | 15 (9.8) |
| **AEs Leading to Dose Reduction** | | | | | | |
| Neutropenia | 15 (2.8) | 7 (1.3) | 57 (10.5) | 23 (15.3) | 14 (9.2) | 3 (2.0) |

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

| | | | | | | |
|---|---|---|---|---|---|---|
| Infection | 10 (1.9) | 4 (0.7) | 5 (0.9) | 1 (0.7) | 1 (0.7) | 0 |

In Study MM-020, more patients in the MPT arm of the study experienced Grade 3 or 4 neutropenia compared with the Rd and Rd18 arms of the study (MPT: 46.6% versus Rd: 28.6% and Rd18: 27.2%). Neutropenia AEs led to lenalidomide withdrawal or dose reduction for ≤ 2.8% of patients in the lenalidomide treatment arms. In patients in Arm MPT, neutropenia AEs led to dose withdrawal in 2.4% of patients and to dose reduction in 10.5% of patients. Neutropenia led to dose interruption for 22.4%, 19.3% and 49.5% of patients in Arms Rd, Rd18 and MPT, respectively. In Study MM-015, more patients in the lenalidomide-containing arms of the study experienced Grade 3 or 4 neutropenia (MPR+R: 76.0%; MPR+p: 67.1%) compared with placebo-treated patients (MPp+p: 31.4%). Among patients receiving induction with melphalan, prednisone and lenalidomide, the frequency of these events was higher in patients receiving continuous treatment with lenalidomide following induction than in patients receiving placebo. Neutropenia AEs led to lenalidomide withdrawal and dose reduction for < 4% and < 16.0% of patients, respectively, in each of the 3 treatment arms. Neutropenia led to dose interruption for 63.3%, 50.0% and 20.3% of patients in the MPR+R, MPR+p and MPp+p arms, respectively.

In Study MM-020, Grade 3 or 4 AEs of infection were reported for more patients in Arm Rd and Arm Rd18 (28.9% and 21.9% of patients, respectively) than patients in Arm MPT (17.2% of patients). Infection AEs led to treatment withdrawal and dose reduction for ≤ 4.3% of patients in all treatment arms. Infection led to dose interruption for 30.8%, 20.9% and 12.4% of patients in Arms Rd, Rd18 and MPT, respectively. In Study MM-015, Grade 3 or 4 infection AEs were reported for 11.3% and 14.5% of patients in the MPR+R and MPR+p arms, and 9.8% of patients in the MPp+p arm. Infection AEs led to lenalidomide withdrawal or dose reduction for ≤ 30% of patients in each treatment arm. Infection AEs led to dose interruption for 18.7%, 19.7% and 9.8% of patients in the MPR+R, MPR+p and MPp+p arms, respectively.

**RRMM Studies:**

Details of neutropenia and infection AEs reported in the RRMM studies are summarised below.

| **Neutropenia/Infection** | **Number (%) of Patients** | |
|---|---|---|
| | **MM-009 and MM-010** | |
| | **Len/Dex N = 353** | **PBO/Dex N = 350** |
| **All AEs** | | |
| Neutropenia | 157 (44.5) | 23 (6.6) |
| Infection | 243 (68.8) | 200 (57.1) |
| **Grade 3 or 4** | | |
| Neutropenia | 130 (36.8) | 12 (3.4) |
| Infection | 88 (24.9) | 57 (16.3) |
| **AEs Leading to Discontinuation** | | |

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

| | | |
|---|---|---|
| Neutropenia | 12 (3.4)[a] | 2 (0.6) |
| Infection | 7 (2.0)[b] | 10 (2.9)[c] |
| **AEs Leading to Dose Interruption** | | |
| Neutropenia | 89 (25.2)[d] | 13 (3.7) |
| Infection | 79 (22.4)[e] | 38 (10.9)[f] |
| **AEs Leading to Dose Reduction** | | |
| Neutropenia | 16 (4.5) | 0 |
| Infection | 11 (3.1)[g] | 1 (0.3)[h] |

[a] Includes PT of febrile neutropenia (1).

[b] Includes PTs of pneumonia NOS (3), sepsis NOS (2), all other PTs experienced by 1 patient each.

[c] Includes PTs of pneumonia NOS (4), all other PTs experienced by 1 patient each.

[d] Includes PT of febrile neutropenia (6).

[e] Includes PTs of pneumonia NOS (20), upper respiratory tract infection NOS (12), urinary tract infection NOS (5), all other PTs experienced by ≤ 4 patients.

[f] Includes PTs of pneumonia NOS, respiratory tract infection NOS, all other PTs experienced by 3 patients or less

[g] Includes PT of oral fungal infection NOS (2). All other PTs reported for ≤ 1 patient.

[h] Includes PT of pneumonia NOS (1).

A total of 130/353 (36.8%) and 88/353 (24.9%) lenalidomide/dexamethasone-treated patients experienced a Grade 3 or 4 neutropenia and infection AE, respectively. Of the neutropenia Grade 3 or 4 events, neutropenia (PT) was the most commonly reported event (125 patients). Of note, Grade 3 or 4 febrile neutropenia and granulocytopenia were reported in only 8 (2.3%) patients and 1 (0.3%) patient, respectively. Infection AEs reported included pneumonia NOS (32 patients), sepsis NOS and urinary tract infection NOS (6 patients each). For placebo/dexamethasone-treated patients, 23/350 (6.6%) experienced a neutropenia AE, with 12/350 (3.4%) experiencing a Grade 3 or 4 AE. A total of 200/350 (57.1%) placebo/dexamethasone-treated patients experienced an infection AE, with 57/350 (16.3%) experiencing a Grade 3 or 4 AE.

**Del 5q MDS Studies:**

Details of neutropenia and infection AEs reported in Studies MDS-003 and MDS-004 are summarised below.

| **Neutropenia/Infection** | **Number (%) of Patients** | |
|---|---|---|
| | | **MDS-004**[b] |

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

| | MDS-003 [a] Len (10 mg) N = 148 | Len (10 mg) N = 69 | Len (5 mg) N = 69 | PBO[c] N = 67 |
|---|---|---|---|---|
| **All AEs** | | | | |
| Neutropenia | 101 (68.2) | 53 (76.8) | 54 (78.3) | 12 (17.9) |
| Infection | 117 (79.1) | 45 (65.2) | 41 (59.4) | 23 (34.3) |
| **Grade 3 or 4** | | | | |
| Neutropenia | 99 (66.9) | 52 (75.4) | 51 (73.9) | 10 (14.9) |
| Infection | 46 (31.1) | 11 (15.9) | 6 (8.7) | 3 (4.5) |
| **AEs Leading to Discontinuation** | | | | |
| Neutropenia | 6 (4.1) | 1 (1.4) | 1 (1.4) | 0 |
| Infection | 4 (2.7) | 1 (1.4)[d] | 1 (1.4)[e] | 0 |
| **AEs Leading to Dose Interruption** | | | | |
| Neutropenia | 38 (25.7) | 16 (23.2) | 8 (11.6) | 0 |
| Infection | 0 | 1 (1.4)[f] | 0 | 1 (1.5)[g] |
| **AEs Leading to Dose Reduction** | | | | |
| Neutropenia | 0 | 23 (33.3) | 20 (29.0)[h] | 0 |
| Infection | 0 | 2 (2.9)[i] | 1 (1.4)[j] | 0 |

[a] Median time on treatment was 52.5 weeks.

[b] Median time on treatment was 50.3 weeks in the 10 mg group, 18.0 weeks in the 5 mg group and 16.0 weeks in the PBO group.

[c] Data in PBO group is from the first 16 weeks of the double-blind phase.

[d] Includes PT of pneumonia (both 1)

[e] Includes PT of rash pustular (1)

[f] Includes PT of gastroenteritis (1)

[g] Includes PT of pneumonia (both 1)

[h] Includes PT of febrile neutropenia (2)

[i] Includes PTs of cellulitis and nasopharyngitis (1 each)

[j] Includes PT of lower respiratory tract infection (1)

In Study MDS-004, the risk of Grade 3 or 4 neutropenia and infection AEs was higher in the lenalidomide groups than the placebo group. Similarly, the risks of neutropenia

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

**Important Identified Risk Serious Infection due to Neutropenia**

leading to treatment interruption or dose reduction were higher in the lenalidomide groups than the placebo group.

**MCL Studies:**

| Neutropenia/ Infection | MCL-002 | | All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003) (N = 373) |
|---|---|---|---|
| | Len (N = 167) | Control (N = 83) | |
| **All AEs** | | | |
| Neutropenia | 89 (53.3) | 29 (34.9) | 201 (53.9) |
| Infection | 90 (53.9) | 31 (37.3) | 211 (56.6) |
| **Grade 3 or 4** | | | |
| Neutropenia | 78 (46.7) | 28 (33.7) | 173 (46.4) |
| Infection | 27 (16.2) | 8 (9.6) | 67 (18.0) |
| **AEs Leading to Discontinuation** | | | |
| Neutropenia | 2 (1.2) | 1 (1.2) | 10 (2.7) |
| Infection | 2 (1.2) | 2 (2.4) | 5 (1.3) |
| **AEs Leading to Dose Interruption** | | | |
| Neutropenia | 42 (25.1) | 9 (10.8) | 87 (23.3) |
| Infection | 31 (18.6) | 6 (7.2) | 55 (14.7) |
| **AEs Leading to Dose Reduction** | | | |
| Neutropenia | 13 (7.8) | 6 (7.2) | 28 (7.5) |
| Infection | 0 | 0 | 5 (1.3) |
| **AEs Leading to Dose Reduction and Interruption** | | | |
| Neutropenia | 41 (24.6) | 2 (2.4) | 83 (22.3) |
| Infection | 2 (1.2) | 1 (1.2) | 7 (1.9) |

In Study MCL-002, Grade 3 or 4 neutropenia AEs were reported in a greater proportion of patients in the lenalidomide group (46.7%) than the control group (33.7%). The proportions of patients with neutropenia leading to study treatment being permanently withdrawn, or the dose reduced were the same (1.2% and 1.2%) and similar (7.8% versus 7.2%), respectively, in both treatment groups. A greater proportion of patients in the lenalidomide group than in the control group experienced neutropenia AEs leading to dose interruption (25.1% versus 10.8%, respectively) and to dose reduction and interruption (24.6% versus 2.4%). This might be attributed to the strict dose-modification protocol requirements and the longer treatment duration for the lenalidomide arm compared to the control arm.

## Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia

| Important Identified Risk Serious Infection due to Neutropenia | |
|---|---|
| | In Study MCL-002, Grade 3 or 4 infection AEs were reported in a greater proportion of patients in the lenalidomide group (16.2%) than the control group (9.6%). The proportions of patients with infection AEs leading to study treatment being permanently withdrawn were similar in the lenalidomide and control groups (1.2% versus 2.4%, respectively), whereas a greater proportion of patients in the lenalidomide group than the control group experienced infection AEs leading to dose interruption (18.6% versus 7.2%). The proportions of patients with infection AEs leading to dose reduction and interruption were the same (1.2%) in both groups. No patients had their dose reduced as a result of infection AEs. |
| Risk factors and risk groups | Haematologic malignancies by themselves or by virtue of their therapeutic strategies, chemotherapy, radiation or haematopoietic stem cell transplant put patients at risk of infections.[113] The introduction of stem cell transplantation and novel anti-myeloma agents has improved the outcome of patients with MM. These advances have transformed MM into a chronic condition, with multiple relapses and salvage therapies, all of which results in cumulative immunosuppression and higher risk of infection. For example, application of stem cell transplantation has broadened the spectrum of infection to include those caused by Clostridium difficile, cytomegalovirus, and opportunistic moulds. Risk factors include myeloma-related innate immunodeficiency, which involves various arms of the immune system and includes B-cell dysfunction (manifested as hypogammaglobulinemia). Polyclonal hypogammaglobulinemia has been classically associated with infection by encapsulated bacteria, such as Streptococcus pneumoniae and Haemophilus influenzae. Myeloma and treatment-associated organ dysfunctions and comorbidities also increase the risk of infection. These dysfunctions and comorbidities include (1) renal failure (cast nephropathy, hypercalcemia, deposition disease, and others), respiratory compromise, caused by collapse of thoracic vertebra and opiate therapy (which may depress the central nervous system) given to patients with painful fractures (3) severe alimentary mucosal damage (caused by chemotherapy, radiation therapy, or graft-versus-host disease) (4) hyperglycemia induced by dexamethasone (5) transfusional iron overload and (6) the multisystem involvement by myeloma-associated deposition diseases (AL-amyloidosis and light chain deposit disease). Indeed, levels of CD4+ T cells, particularly naive and activated subsets, decrease significantly with increasing cycles of chemotherapy, a decrease strongly associated with opportunistic infections. Finally, myeloma typically affects an older population, with a median age of 62 to 73 years. These patients frequently experience an age-related decline in physiologic reserve of various organs and from other age-related conditions, including frailty, geriatric syndromes, cognitive dysfunction, and social isolation, all of which may increase the risk of infection.[114]<br><br>Lenalidomide treatment in combination with dexamethasone in MM patients with at least one prior therapy is associated with a higher incidence of Grade 4 neutropenia compared to placebo-dexamethasone treated patients (SmPC, Section 4.4). The combination of lenalidomide with melphalan and prednisone in clinical trials of NDMM patients is associated with a higher incidence of Grade 4 neutropenia than MPp+p treated patients (SmPC, Section 4.4).<br><br>The proportion of patients who experienced Grade 3 or 4 myelosuppression in one study of lenalidomide-treated patients with MM was significantly higher for patients who had prior high-dose chemotherapy and stem cell transplantation, compared with |

**Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia**

| Important Identified Risk Serious Infection due to Neutropenia | |
|---|---|
| | those that did not.[115] Impairment of antibody response, neutropenia, treatment with glucocorticoids, and reduction of normal Ig all increase the likelihood of infection. While a much greater proportion of lenalidomide/dexamethasone patients experienced neutropenia relative to placebo/dexamethasone patients, this increased risk did not translate into an infection risk of the same magnitude in either the total study population or in the study population restricted to Grade 3 or 4 toxicities.<br>Lenalidomide treatment in MDS patients is associated with a higher incidence of Grade 3 or 4 neutropenia compared with patients on placebo (SmPC, Section 4.4). In patients with MDS, those experiencing neutropenia while receiving lenalidomide may be at increased risk for infections. |
| Preventability | The major dose-limiting toxicities of lenalidomide include neutropenia.<br>Neutropenia can be managed with dose reduction (Richardson, 2006b).[115] Dosing recommendations in the event of neutropenia can be found in Section 4.2 of the SmPC. The use of growth factors in the management of neutropenia should be considered (SmPC, Section 4.2 and 4.4).<br>Monitoring of lenalidomide-treated patients, particularly in the initial weeks of treatment, is important to reduce the risk of myelosuppression-related complication.[116] Patients should be advised to promptly report febrile episodes and dose reductions may be required (SmPC, Section 4.4). A complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and haematocrit should be performed at baseline, every week for the first 8 weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias. In MCL patients, the monitoring scheme should be every 2 weeks in Cycles 3 and 4, and then monthly thereafter. In FL patients, the monitoring scheme should be weekly for the first 3 weeks of Cycle 1 (28 days), every 2 weeks during Cycles 2 through 4, and then at the start of each cycle thereafter (SmPC, Section 4.4).<br>Hepatitis B virus status should be established before initiating treatment with lenalidomide. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Patients previously infected with HBV should be closely monitored for signs and symptoms of active HBV infection throughout therapy (SmPC, Section 4.4). In patients with repeated infectious complications, long-term administration of antibiotic or antiviral medication or use of IV Ig may be recommended (as recommended by Ludwig).[117] |
| Impact on the risk-benefit balance of the product | Infections in the presence of neutropenia may contribute significantly to morbidity and mortality. |
| Public health impact. | Severe neutropenia is more prevalent in del 5q MDS patients, than in non-del 5q MDS and MM patients.[118] In one study of relapsed MM patients, infections were reported in a higher proportion of lenalidomide-treated patients (67.8%), compared to the placebo group (44.0%).[31]<br>Neutropenia is associated with lenalidomide treatment, and is a very common ADR of lenalidomide treatment (SmPC, Section 4.8). All lenalidomide-treated patients should be monitored for myelosuppression to reduce the risk of myelosuppression-related complications. Infections should be treated aggressively in MM patients, as these contribute significantly to morbidity and mortality.[117] These infections may necessitate treatment with antibiotics and/or G-CSF for neutropenic infection. The majority of patients with MDS die from bleeding or infection due to |

**Table 2.7.3.1-2: Important Identified Risk: Serious Infection due to Neutropenia**

| Important Identified Risk Serious Infection due to Neutropenia | |
|---|---|
| | bone marrow failure.[68] All lenalidomide-treated patients should be monitored for events of infection. |
| Data source | Studies NHL-007 and NHL-008 (13 Aug 2018), Study SWOG S0777 (01 Dec 2016); Study CALGB 100104 (01 Mar 2015); Study IFM 2005-02 (01 Mar 2015); Study MM-020 (24 May 2013); Study MM-015 (30 Apr 2013); Integrated Summary of Safety (Dec 2005) for Studies MM-009 and MM-010; Study MDS-003 CSR; Study MDS-004 CSR; Study MCL-001 (20 Mar 2013); Study MCL-002 (07 Mar 2014); Study NHL-002 (23 Jun 2008); Study NHL-003 (27 Apr 2011). |
| MedDRA Terms | See Annex 7 |

### Important Identified Risk: Second Primary Malignancies

Second primary malignancies are identified risks with the use of lenalidomide particularly when lenalidomide is given in combination with oral melphalan or following HDM supported by ASCT or after a prior alkylating therapy. The data from NDMM trials suggest there may be an increased incidence of invasive SPM, especially haematologic SPM, when lenalidomide or thalidomide are given in combination with oral melphalan or as maintenance therapy following HDM supported by ASCT.

The SPM that have been observed include invasive (haematologic [AML, B-cell malignancies, other haematologic malignancies] and solid tumours) and non-invasive (non-melanoma skin cancer [NMSC]) that are identified risks with lenalidomide. Studies NHL-007 and NHL-008 (FL), Study SWOG S0777 (NDMM RVd), Studies IFM 2005-02, CALGB 100104 and GIMEMA (TE NDMM), Studies MM-020 and MM-015 (TNE NDMM), Studies MM-009 and MM-010 (RRMM), Studies MDS-003 and MDS-004 (MDS) and Studies MCL-001, MCL-002, NHL-002 and NHL-003 (MCL) were included in the analysis of these risks. Information concerning this identified risk is summarised in Table 2.7.3.1-3 using the following data cutoff dates:

FL Studies

- NHL-007: 22 Jun 2018.
- NHL-008: 01 May 2017.

NDMM RVd Study

- SWOG S0777: 01 Dec 2016.

TE NDMM Studies

- IFM 2005-02: 01 Mar 2015.
- CALGB 100104: 01 Mar 2015.
- GIMEMA: 01 Mar 2015.

TNE NDMM Studies

- MM-020: 24 May 2013.

- MM-015: 30 Apr 2013.

RRMM Studies

- MM-009: 23 Jul 2008.
- MM-010: 02 Mar 2008.

MDS Studies

- MDS-003: 27 Aug 2008.
- MDS-004: 26 Nov 2012.

MCL Studies

- MCL-001: 21 Mar 2014.
- MCL-002: 07 Mar 2014.
- NHL-002: 23 Jun 2008.
- NHL-003: 25 Mar 2013.

**Table 2.7.3.1-3: Important Identified Risk: Second Primary Malignancies**

| **Important Identified Risk Second Primary Malignancies** | |
|---|---|
| Potential mechanisms | No mechanism whereby lenalidomide may cause SPM has been identified.<br>While none of the following may be exclusive there may be several explanations why patients with MM might develop secondary haematopoietic and lymphatic cancers, including:<br>• **Treatment-related**<br>Change of natural disease history as a result of improved survival in recent years.<br>As a consequence of the use of alkylating agents<br>– Prolonged immunosuppression (cytopenias).<br>– Use of G-CSF, especially in combination with high-dose chemotherapy.<br>– Increased surveillance of cancer patients.<br>– As a consequence of selective reporting<br>• **Syndromic**<br>Cytogenetic factors associated with MM.<br>• **Heredity**<br>• **Shared aetiologic factors**<br>Human herpes virus-8 (HHV-8) infection in the case of Kaposi sarcoma.<br>EBV infection in the case of PTLD.<br>Exposure to environmental agents. |
| Evidence source and strength of evidence | Patients treated with lenalidomide may be at increased risk of developing new cancers. The reason for this is not clear, but investigations are being undertaken. |

## Table 2.7.3.1-3: Important Identified Risk: Second Primary Malignancies

| Important Identified Risk Second Primary Malignancies | |
|---|---|
| Characterization of risk | **Frequency with 95% CI (Invasive SPM [Haematologic Malignancies])**<br>The frequency of haematologic malignancies is summarised in Table 2.7.3.1-4 for the NDMM RVd study, Table 2.7.3.1-5 for the NDMM studies, Table 2.7.3.1-6 for the RRMM studies, and Table 2.7.3.1-7 for the MDS and lymphoma studies. The risk of SPM associated with lenalidomide is dependent on tumour type and context. In randomised Phase 3 study NHL-007 in FL, there was no increased risk of SPM for lenalidomide plus rituximab compared to rituximab plus placebo.<br>**FL Studies:**<br>Study NHL-007<br>AML was experienced by 1 (0.29 events per 100 person-years) patient in both the lenalidomide plus rituximab and rituximab plus placebo arms. The AML malignancies were PT acute myeloid leukaemia in both patients. No patients in either treatment arm experienced MDS, B-cell or other haematologic malignancies.<br>Study NHL-008<br>Other haematologic malignancies were experienced by 1 (0.55 events per 100 person-years) lenalidomide plus rituximab-treated patient. The event of other haematologic malignancies was PT leukaemia granulocytic. No lenalidomide plus rituximab-treated patients experienced AML, MDS or B-cell malignancies.<br>**NDMM RVd Study**<br>Study SWOG S0777<br>There were no reports of AML in the RVd and Rd arms of Study SWOG S0777. MDS (PT: Myelodysplastic syndrome) was reported in 2 (0.16 events per 100 person-years) patients in the RVd arm and 1 (0.09 events per 100 person-years) patient in the Rd arm. B-cell malignancies were reported in 2 (0.8 events per 100 person-years) patients in the Rd arm (PTs: B-cell type acute leukaemia and diffuse large B-cell lymphoma) and no patients in the RVd arm. There were no reports of other haematologic malignancies in the RVd and Rd arms.<br>**TE NDMM Studies**<br>Study IFM 2005-02<br>In Study IFM 2005-02, AML was experienced by 6 (0.36 events per 100 person-years) and 3 (0.18 events per 100 person-years) patients in the lenalidomide and placebo arms, respectively. B-cell malignancies were experienced by 11 (0.67 events per 100 person-years) and 2 (0.12 events per 100 person-years) patients in the lenalidomide and placebo arms, respectively. The AML malignancies were acute myeloid leukaemia in 2 (0.7%) patients in the lenalidomide group and 3 (1.0%) patients in the placebo group, and MDS to AML reported in 4 (1.3%) patients in the lenalidomide group. The B-cell malignancies were Hodgkin's disease (4 [1.3%] patients in the lenalidomide group and 1 [0.3%] patient in the placebo group); B-cell type acute leukaemia (3 [1.0%] patients in the lenalidomide group); DLBCL (3 [1.0%] patients in the lenalidomide group) and acute lymphocytic leukaemia (1 [0.3%] patient each in the lenalidomide and placebo groups). MDS was experienced by 4(0.24 events per 100 person-years) patients in the lenalidomide arm and 3 (0.18 events per 100 person-years) patients in the placebo arm. The MDS events were myelodysplastic syndrome in 4 (1.3%) patients in the lenalidomide arm and 2 (0.7%) patients in the placebo group, and refractory anaemia with an excess of blasts in 1 (0.3%) patient in the placebo arm. Other haematologic malignancies were experienced by 1 (0.06 events per 100 person-years) patient in the lenalidomide arm and 1 (0.06 events per |

## Table 2.7.3.1-3: Important Identified Risk: Second Primary Malignancies

| Important Identified Risk Second Primary Malignancies |
|---|

100 person-years) patient in the placebo arm (events of acute biphenotypic leukaemia and TCL, respectively).

Study CALGB 100104

In Study CALGB 100104, in the lenalidomide group, the haematologic malignancies of AML and B-cell malignancies were reported for 7 (0.59 events per 100 person-years) and 4 (0.33 events per 100 person-years) patients, respectively. B-cell malignancies were reported in 3 (0.29 events per 100 person-years) patients in the placebo group. The AML malignancies were acute myeloid leukaemia in 5 (2.2%) patients, and MDS to AML and erythroleukaemia each reported in 1 (0.4%) patient in the lenalidomide group. The B-cell malignancies were B-cell type acute leukaemia, reported in 1 (0.4%) patient in the lenalidomide group and 3 (1.4%) patients in the placebo group, and acute lymphocytic leukaemia, B precursor type acute leukaemia and Hodgkin's disease, reported in 1 (0.4%) patient each in the lenalidomide group. Four patients in both the lenalidomide group and the placebo group experienced MDS (0.33 and 0.39 events per 100 person-years, respectively). Other haematologic malignancies were experienced by 1 (0.10 events per 100 person-years) patient in the placebo arm (malignant histiocytosis).

Study GIMEMA

There were no reports of AML, MDS, other haematologic malignancies or B-cell malignancies in Study GIMEMA.

**TNE NDMM Studies**

Study MM-020

In Study MM-020, AML was experienced by 1 (0.07 events per 100 person-years), 1 (0.07 events per 100 person-years) and 6 (0.46 events per 100 person-years) patients in Arms Rd, Rd18 and MPT, respectively. There were no reports of B-cell malignancies in Study MM-020. MDS was experienced by 1 (0.07 events per 100 person-years) patient each in Arm Rd and Arm Rd18, and 6 (0.45 events per 100 person-years) patients in Arm MPT. No patients had other haematologic malignancies in Study MM-020.

Study MM-015

In Study MM-015, AML was experienced by 5 (0.96 events per 100 person-years), 5 (0.98 events per 100 person-years) and 1 (0.18 events per 100 person-years) patients in Arms MPR+R, MPR+p and MPp+p, respectively. There were no reports of B-cell malignancies in Study MM-015. MDS was experienced by 3 (0.58 events per 100 person-years), 2 (0.39 events per 100 person-years) and 1 (0.18 events per 100 person-years) patients in Arms MPR+R, MPR+p and MPp+p, respectively. Other haematologic malignancies were experienced by 1 (0.19 events per 100 person-years) patient in Arm MPR+R. This other haematologic malignancy was T-cell type acute leukaemia.

**RRMM Studies**

Studies MM-009 and MM-010

There were no reports of AML or B-cell malignancies in Studies MM-009 and MM-010. MDS was reported in 2 (0.6%) patients in the lenalidomide/dexamethasone group.

**Del 5q MDS Studies**

For Study MDS-004, the analysis of B-cell malignancies and AML include the double-blind phase of 52 weeks including the first 16 weeks of which the patients in the placebo arm who did not achieve a minor response by Week 16 were given the

**Table 2.7.3.1-3: Important Identified Risk: Second Primary Malignancies**

| Important Identified Risk Second Primary Malignancies | |
|---|---|
| | option to cross over to the 5 mg lenalidomide arm. In MDS, AML is considered disease progression; however, it is also viewed as an important potential risk when taking lenalidomide that will be monitored closely.<br>Study MDS-004<br>There were no reports of B-cell malignancies in Study MDS-004. AML was reported for 17 (6.50 events per 100 person-years) patients in the lenalidomide 10 mg group, 26 (11.16 events per 100 person-years) patients in the lenalidomide 5 mg group and 27 (12.35 events per 100 person-years) patients in the placebo group (27 patients included 23 patients who crossed over to lenalidomide 5 mg after 16 weeks of placebo treatment).<br>Study MDS-003<br>B-cell lymphoma was reported for 1 (0.21 events per 100 person-years) patient and AML was reported for 37 (7.86 events per 100 person-years) patients in Study MDS-003. The only other haematologic malignancy reported was MM (1 [0.21 events per 100 patient-years] patient).<br>**MCL Studies**<br>Study MCL-002<br>There were no reports of AML in Study MCL-002. In Study MCL-002, B-cell malignancies were experienced by 1 (0.36 events per 100 person-years) patient (0.6%) in the lenalidomide group and 1 (0.77 events per 100 person-years) patient (1.2%) in the control group. The B-cell malignancies were acute lymphocytic leukaemia in the patient in the lenalidomide group and DLBCL in the patient in the control group. MDS was experienced by 1 (0.36 events per 100 person-years) patient (0.6%) in the lenalidomide group and no patients in the control group. No patients had other haematologic malignancies in Study MCL-002.<br>Study MCL-001<br>In Study MCL-001, AML (PT: myeloproliferative disorder) was experienced by 1 (0.48 events per 100 person-years) patient (0.7%) treated with lenalidomide. There were no reports of B-cell malignancies in Study MCL-001. MDS was experienced by 1 (0.48 events per 100 person-years) lenalidomide-treated patient (0.7%). No patients had other haematologic malignancies in Study MCL-001.<br>Study NHL-002<br>There were no reports of AML, MDS, other haematologic malignancies, or B-cell malignancies in Study NHL-002.<br>Study NHL-003<br>In Study NHL-003, AML (PT: acute myeloid leukaemia) was reported in 1 (0.5%) patient treated with lenalidomide. There were no reports of B-cell malignancies in Study NHL-003. MDS was reported in 1 (0.5%) patient treated with lenalidomide. There were no reports of other haematologic malignancies in Study NHL-003.<br>**Frequency with 95% CI (Invasive SPM [Solid Tumours])**<br>The frequency of solid tumours is summarised in Table 2.7.3.1-4 for the RVd study, Table 2.7.3.1-5 for the NDMM studies, Table 2.7.3.1-6 for the RRMM studies, and Table 2.7.3.1-7 for the MDS and lymphoma studies.<br>**FL Studies:**<br>Study NHL-007<br>Solid tumours were reported for 2 (0.58 events per 100 person-years) and 3 (0.89 events per 100 person-years) patients in the lenalidomide plus rituximab and |

## Table 2.7.3.1-3: Important Identified Risk: Second Primary Malignancies

| Important Identified Risk Second Primary Malignancies |
|---|

rituximab plus placebo arms, respectively. Solid tumours in the lenalidomide plus rituximab arm were carcinoid tumour of the gastrointestinal tract and squamous cell carcinoma of lung (1 [0.7%] patient each). Solid tumours in the rituximab plus placebo arm were invasive ductal breast carcinoma, malignant melanoma and transitional cell cancer of the renal pelvis and ureter localised (1 [0.7%] patient each).

Study NHL-008

Solid tumours were reported for 1 (0.55 events per 100 person-years) lenalidomide plus rituximab-treated patient. This was an event of transitional cell carcinoma (1 [0.6%] patient).

**NDMM RVd Study**

Study SWOG S0777

Solid tumours were reported in 8 (0.66 events per 100 person-years) patients in the RVd arm and 10 (0.90 events per 100 person-years) patients in the Rd arm in Study SWOG S0777. The solid tumours reported in the RVd and Rd arms were all single reports (by PT).

**TE NDMM Studies**

Study IFM 2005-02

Solid tumours were reported for 21 (1.28 events per 100 person-years) and 13 (0.78 events per 100 person-years) patients in the lenalidomide and placebo arms, respectively. The most frequently reported solid tumours (experienced by ≥ 2 patients overall) were breast cancer (3 [1.0%] patients in the lenalidomide arm and 1 [0.3%] patient in the placebo arm); hypopharyngeal cancer (2 [0.7%] patients in the lenalidomide arm); malignant melanoma (1 [0.3%] patient in the lenalidomide arm and 2 [0.7%] patients in the placebo arm); prostate cancer (3 [1.0%] patients in the lenalidomide arm and 4 [1.3%] patients in the placebo arm); rectal cancer (1 [0.3%] patient each in the lenalidomide and placebo arms), and renal cell carcinoma (1 [0.3%] patient each in the lenalidomide and placebo arms).

Study CALGB 100104

Solid tumours were reported for 17 (1.48 events per 100 person-years) and 10 (0.98 events per 100 person-years) patients in the lenalidomide and placebo groups, respectively. The most frequently reported solid tumours (experienced by ≥ 2 patients overall) were breast cancer (experienced by 3 [1.3%] patients in the lenalidomide group and 1 [0.5%] patient in the placebo group); breast cancer in situ (experienced by 2 [0.9%] patients in the lenalidomide group); endometrial cancer (experienced by 2 [0.9%] patients in the lenalidomide group and 1[0.5%] patient in the placebo group); malignant melanoma (1 [0.4%] patient in the lenalidomide group and 2 [0.9%] patients in the placebo group), and prostate cancer (3 [1.3%] patients in the lenalidomide group only).

Study GIMEMA

Solid tumours were reported for 5 (2.21 events per 100 person-years) and 2 (0.68 events per 100 person-years) in the lenalidomide and no maintenance groups, respectively. The solid tumours reported in the lenalidomide group were adenocarcinoma sigma, breast cancer, colon adenocarcinoma, K prostate, and left breast carcinoma, each reported in 1 (1.8%) patient. The solid tumours reported in the placebo group were ‘breast cancer: carcinoma infiltrante con aspetti lobulare G2’, K lung, and ‘tumor endometrial cancer: adenocarcinoma endometriale IIstadio G2-3’, each reported in 1 (1.3%) patient.

**TNE NDMM Studies**

## Table 2.7.3.1-3: Important Identified Risk: Second Primary Malignancies

| Important Identified Risk Second Primary Malignancies |
|---|
| Study MM-020<br>Solid tumours were reported for 15 (1.09 events per 100 person-years), 29 (2.15 events per 100 person-years) and 15 (1.15 events per 100 person-years) patients in Arms Rd, Rd18 and MPT, respectively. The most frequently reported solid tumours (experienced by ≥ 3 patients overall) were prostate cancer (1 [0.2%] patient in Arm Rd, 3 [0.6%] patients in Arm Rd18 and 2 [0.4%] patients in Arm MPT), breast cancer (1 [0.2%] patient in Arm Rd, 3 [0.6%] patients in Arm Rd18 and 1 [0.2%] patient in Arm MPT), lung squamous cell carcinoma Stage 1 (3 [0.6%] patients in Arm Rd18).<br>Study MM-015<br>Solid tumours were reported for 5 (0.97 events per 100 person-years), 11 (2.16 events per 100 person-years) and 4 (0.74 events per 100 person-years) patients in Arms MPR+R, MPR+p and MPp+p, respectively. The most frequently reported solid tumours (experienced by ≥ 2 patients overall) were breast cancer (2 [1.3%] patients in Arm MPp+p), hepatic neoplasm malignant (reported for 1 [0.7%] patient each in Arms MPR+p and MPp+p), prostate cancer and rectal cancer (both reported for 1 patient [0.7%] each in Arms MPR+R and MPR+p).<br>**RRMM Studies**<br>Solid tumours were reported for 6 (1.7%) patients in the lenalidomide/dexamethasone group. The solid tumours were reported for single patients each (fibrous histiocytoma, breast cancer in situ, bronchioalveolar carcinoma, glioblastoma multiforme, lung adenocarcinoma NOS, prostate cancer NOS and transitional cell carcinoma). In the placebo/dexamethasone group, 2 patients (0.6%) developed a solid tumour (fibrous histiocytoma and malignant melanoma).<br>Analyses were performed to present incidence rates per 100 person-years, with person-years being the time in years from first dose date to last dose date for patients without an SPM, and the time from first dose date to SPM onset for patients with an SPM. The incidence rates of solid tumours were similar for the lenalidomide/dexamethasone and placebo/dexamethasone groups (1.28 versus 0.91 per 100 person-years, respectively).<br>**Del 5q MDS Studies**<br>For Study MDS-004, the analysis of SPM includes data from the open-label phase as well as the double-blind phase (the double-blind phase was 52 weeks including the first 16 weeks of which the patients in the placebo arm who did not achieve a minor response by Week 16 were given the option to cross over to the 5 mg lenalidomide arm).<br>Study MDS-004<br>In Study MDS-004, solid tumours were reported for 4 (1.52 events per 100 patient-years) patients in the 10 mg lenalidomide group, 4 (1.69 events per 100 patient-years) patients in the 5 mg lenalidomide group and 2 (0.85 events per 100 patient-years) patients in the placebo group (including patients who crossed over from placebo to lenalidomide 5 mg). Two patients (1 patient in the 10 mg lenalidomide group and 1 in the placebo group) had 2 SPM each; therefore a total of 12 AEs of SPM have been reported to date. Two of the 12 events of SPM were diagnosed a few days after the patients were randomised on the study and were not therefore considered related to treatment.<br>Study MDS-003<br>Solid tumours were reported for 7 (1.49 events per 100 patient-years) patients, and comprised carcinoid tumour of the small bowel, colon cancer, endometrial cancer, |

## Table 2.7.3.1-3: Important Identified Risk: Second Primary Malignancies

| Important Identified Risk Second Primary Malignancies |
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lung cancer metastatic, ovarian cancer, thymoma and vulval cancer, which were experienced by single (0.7%) patients each.

**MCL Studies**

Study MCL-002

Solid tumours were reported in 4 (1.47 events per 100 person-years) patients (2.4%) in the lenalidomide group and 3 (2.37 events per 100 person-years) patients (3.6%) in the control group. The solid tumours reported in the lenalidomide group were adenocarcinoma gastric, liposarcoma, metastatic squamous cell carcinoma and transitional cell carcinoma, each reported in 1 (0.6%) patient. The solid tumours reported in the control group were colon cancer, meningioma benign and metastatic renal cell carcinoma, each reported in 1 (1.2%) patient.

Study MCL-001

Solid tumours were reported in 5 (2.46 events per 100 person-years) patients (3.7%) and comprised bladder cancer, colon cancer metastatic, meningioma, metastases to liver, metastatic squamous cell carcinoma and transitional cell carcinoma, each reported in 1 (0.7%) patient.

Study NHL-002

Solid tumours were reported in 2 (7.29 events per 100 person-years) patients (4.1%) treated with lenalidomide and comprised breast cancer and small cell lung cancer stage unspecified, each reported in 1 (2.0%) patient.

Study NHL-003

Solid tumours were reported in 4 (1.8%) patients treated with lenalidomide in Study NHL-003, and comprised gastric cancer, oesophageal carcinoma, prostate cancer and renal cell carcinoma stage unspecified in 1 (0.5%) patient each.

**Frequency with 95% CI (Non-invasive SPM [NMSC])**

The frequency of NMSC is summarised in Table 2.7.3.1-4 for the RVd study, Table 2.7.3.1-5 for the NDMM studies, Table 2.7.3.1-6 for the RRMM studies, and Table 2.7.3.1-8 for the MDS and lymphoma studies.

**FL Studies:**

Study NHL-007

Non-melanoma skin cancers were experienced by 3 (0.88 events per 100 person-years) and 2 (0.59 events per 100 person-years) patients in the lenalidomide plus rituximab and rituximab plus placebo arms, respectively. Non-melanoma skin cancers reported in the lenalidomide plus rituximab arm comprised squamous cell carcinoma of skin (2 [1.4%] patients) and basal cell carcinoma (1 [0.7%] patient). Non-melanoma skin cancers reported in the rituximab plus placebo arm comprised basal cell carcinoma and squamous cell carcinoma of skin (1 [0.7%] patient each).

Study NHL-008

Non-melanoma skin cancers were experienced by 8 (4.57 events per 100 person-years) lenalidomide plus rituximab-treated patients. The NMSCs reported comprised basal cell carcinoma (5 [2.8%] patients) and squamous cell carcinoma of skin (4 [2.3%] patients).

**NDMM RVd Study**

Study SWOG S0777

In Study SWOG S0777, NMSC was reported in 11 (0.92 events per 100 person-years) patients in the RVd arm and 7 (0.62 events per 100 person-years) patients in the Rd

## Table 2.7.3.1-3: Important Identified Risk: Second Primary Malignancies

| Important Identified Risk Second Primary Malignancies |
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| arm. NMSC reported in the RVd arm comprised basal cell carcinoma (6 [2.3%] patients) and squamous cell carcinoma of skin (8 [3.1%] patients). NMSC reported in the Rd arm were basal cell carcinoma (6 [2.3%] patients) and squamous cell carcinoma of skin (2 [0.8%] patients).<br>**TE NDMM Studies**<br>Study IFM 2005-02<br>In Study IFM 2005-02, NMSC was experienced by 10 (0.61 events per 100 person-years) and 7 (0.42 events per 100 person-years) patients in the lenalidomide and placebo arms, respectively. NMSC reported in the lenalidomide group comprised basal cell carcinoma (8 [2.6%] patients), squamous cell carcinoma (1 [0.3%] patient), and squamous cell carcinoma of skin (4 [1.3%] patients). NMSC reported in the placebo group comprised basal cell carcinoma (2 [0.7%] patients), keratoacanthoma (1 [0.3%] patient), squamous cell carcinoma (2 [0.7%] patients), and squamous cell carcinoma of skin (2 [0.7%] patients).<br>Study CALGB 100104<br>In Study CALGB 100104, in the lenalidomide group, NMSC was reported for 12 patients (1.02 events per 100 person-years). A similar incidence was reported in the placebo group (9 patients [0.88 events per 100 person-years]). The NMSC comprised squamous cell carcinoma of skin (9 [4.0%] patients in the lenalidomide group and 5 [2.3%] patients in the placebo group), and basal cell carcinoma (7 [3.1%] patients in the lenalidomide group and 5 [2.3%] patients in the placebo group).<br>Study GIMEMA<br>In Study GIMEMA, NMSC was reported for 1 (0.42 events per 100 person-years) patient treated with lenalidomide (basalioma) and 1 (0.34 events per 100 patient-years) patient not receiving maintenance treatment ('squamous cell cancer of the skin left leg skin (upon tibia)').<br>**TNE NDMM Studies**<br>Study MM-020<br>In Study MM-020, NMSC was experienced by 22 (1.62 events per 100 person-years), 17 (1.25 events per 100 person-years) and 21 (1.62 events per 100 person-years) patients in Arms Rd, Rd18 and MPT, respectively.<br>Study MM-015<br>In Study MM-015, NMSC was experienced by 4 (0.77 events per 100 person-years), 6 (1.19 events per 100 person-years) and 8 (1.51 events per 100 person-years) patients in Arms MPR+R, MPR+p and MPp+p, respectively.<br>**RRMM Studies**<br>NMSC was reported for 3.1% of lenalidomide-treated patients, including basal cell carcinoma and squamous cell carcinoma (1.7% of patients each), and Bowen's disease (0.6% of patients). In the placebo/dexamethasone group, 2 patients each (0.6%) developed a NMSC (basal cell carcinoma and squamous cell carcinoma).<br>Analyses were performed to present incidence rates per 100 person-years, with person-years being the time in years from first dose date to last dose date for patients without an SPM, and the time from first dose date to SPM onset for patients with an SPM. The incidence rates of NMSC were 2.40 versus 0.91 per 100 person-years for the lenalidomide/dexamethasone and placebo/dexamethasone groups, respectively.<br>**Del 5q MDS Studies**<br>For Study MDS-004, the analysis of SPM includes data from the open-label as well as the double-blind phase (the double-blind phase was 52 weeks including the first |

## Table 2.7.3.1-3: Important Identified Risk: Second Primary Malignancies

| Important Identified Risk Second Primary Malignancies |
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| 16 weeks of which the patients in the placebo arm who did not achieve a minor response by Week 16 were given the option to cross over to the 5 mg lenalidomide arm).<br>Study MDS-004<br>One patient each in the lenalidomide 10 mg (0.38 events per 100 person-years) and 5 mg groups (0.42 events per 100 person-years) developed a NMSC (basal cell carcinoma). No placebo-treated patients experienced a NMSC.<br>Study MDS-003<br>In Study MDS-003, 6 (1.30 events per 100 person-years) patients developed a NMSC. The NMSC comprised squamous cell carcinoma of skin (3 [2.0%] patients), basal cell carcinoma and squamous cell carcinoma (2 [1.4%] patients each) and keratocanthoma (1 [0.7%] patient). NMSC was experienced by 6 (4.1%) patients in total.<br>**MCL Studies**<br>Study MCL-002<br>In Study MCL-002, NMSC was reported in 5 (1.88 events per 100 person-years) lenalidomide-treated patients (3.0%) and 1 (0.77 events per 100 person-years) control patient (1.2%). For lenalidomide-treated patients, the NMSC comprised squamous cell carcinoma of skin in 4 (2.4%) patients and basal cell carcinoma, squamous cell carcinoma and squamous cell carcinoma of the oral cavity in 1 (0.6%) patient each. In the control group, the NMSC was squamous cell carcinoma of skin in 1 (1.2%) patient.<br>Study MCL-001<br>In Study MCL-001, NMSC was experienced by 7 (3.54 events per 100 person-years) patients (5.2%) treated with lenalidomide, and comprised squamous cell carcinoma of skin in 6 (4.5%) patients and basal cell carcinoma in 4 (3.0%) patients.<br>Study NHL-002<br>There were no reports of NMSC in Study NHL-002.<br>Study NHL-003<br>In Study NHL-003, NMSC was reported in 6 (2.8%) patients treated with lenalidomide, and comprised squamous cell carcinoma in 3 (1.4%) patients, basal cell carcinoma in 2 (0.9%) patients, basosquamous carcinoma in 1 (0.5%) patient and squamous cell carcinoma of skin in 1 (0.5%) patient.<br>**Seriousness/Outcomes (Invasive SPM [Haematologic Malignancies])**<br>The outcome of haematologic malignancies is summarised in Table 2.7.3.1-8 for the NDMM RVd study, Table 2.7.3.1-9 for the NDMM studies, Table 2.7.3.1-10 for the RRMM studies, and Table 2.7.3.1-11 for the MDS and lymphoma studies.<br>**FL Studies:**<br>Study NHL-007<br>In Study NHL-007, one lenalidomide plus rituximab-treated patient with an event of AML had an outcome of not recovered/not resolved. One event of AML in the rituximab plus placebo arm had an outcome of death.<br>Study NHL-008<br>In Study NHL-008, no haematologic malignancies had an outcome of death. One (0.6%) lenalidomide plus rituximab-treated patient with an event of leukaemia granulocytic had an outcome of not recovered/not resolved.<br>**NDMM RVd Study** |

## Table 2.7.3.1-3: Important Identified Risk: Second Primary Malignancies

| Important Identified Risk Second Primary Malignancies |
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| Study SWOG S0777<br>In Study SWOG S0777, there were no reports of AML in the RVd and Rd arms, and no reports of B-cell malignancy in the RVd arm. B-cell malignancies with outcomes of not recovered/not resolved were reported in 2 (0.8%) patients in the Rd arm. Outcomes of not recovered/not resolved were recorded for MDS in 2 (0.8%) patients in the RVd arm and 1 (0.4%) patient in the Rd arm. There were no reports of other haematologic malignancies in the RVd and Rd arms.<br>**TE NDMM Studies**<br>Study IFM 2005-02<br>In the lenalidomide arm of Study IFM 2005-02, AML had an outcome of death in 5 (1.6%) patients and ongoing at death in 1 (0.3%) patient; B-cell malignancy had an outcome of death in 3 (1.0%) patients; and MDS had an outcome of death in 1 patient (0.3%). In the placebo arm, an outcome of death was reported for 3 (1.0%) patients with AML and 1 (0.3%) patient with B-cell malignancy.<br>In the lenalidomide arm, B-cell malignancy had an outcome of recovering/resolving for 2 (0.7%) patients; not recovered/not resolved for 2 (0.7%) patients; and missing for 4 (1.3%) patients. An outcome of not recovered/not resolved was recorded for 3 patients (1.0%) with MDS and 1 (0.3%) patient with other haematologic malignancies.<br>In the placebo arm, outcome was missing for 1 (0.3%) patient with a B-cell malignancy. An outcome of death was recorded for 2 patients (0.7%) with MDS and 1 patient (0.3%) with other haematologic malignancies.<br>Study CALGB 100104<br>In Study CALGB 100104, an outcome of death was reported for AML in 1 (0.4%) patient in the lenalidomide arm. In the lenalidomide arm, AML had an outcome of not recovered/not resolved for 2 (0.9%) patients, and missing for 4 (1.8%) patients. In the lenalidomide arm, B-cell malignancy had an outcome of not recovered/not resolved for 1 (0.4%) patient, and missing for 3 (1.3%) patients. For patients with MDS in the lenalidomide arm, an outcome of not recovered/not resolved was reported for 1 (0.4%) patient, and the outcome was missing for 3 (1.3%) patients.<br>In the placebo group, B-cell malignancy had an outcome of missing for 2 (0.9%) patients and not recovered/not resolved for 1 (0.5%) patient; MDS had an outcome of death for 1 (0.5%) patient.<br>Study GIMEMA<br>There were no reports of AML or B-cell malignancies in Study GIMEMA.<br>**TNE NDMM Studies**<br>Study MM-020<br>In Study MM-020, AML had an outcome of death for 2 (0.4%) patients in Arm MPT, not recovered/not resolved for 1 (0.2%) patient each in Arm Rd and Arm Rd18 and 2 (0.4%) patients in Arm MPT and missing for 2 (0.4%) patients in Arm MPT. MDS had an outcome of death in 1 (0.2%) patient in Arm Rd and 1 (0.2%) patient in Arm MPT. Other outcomes for other haematologic malignancies were not recovered/not resolved for 1 (0.2%) and 5 (0.9%) patients with MDS in Arms Rd18 and MPT, respectively.<br>There were no reports of B-cell malignancies in Study MM-020.<br>Study MM-015<br>AML had an outcome of death for 3 (2.0%) patients each in Arms MPR+R and MPR+p, not recovered/not resolved for 1 (0.7%) patient each in Arms MPR+R and |

## Table 2.7.3.1-3: Important Identified Risk: Second Primary Malignancies

| Important Identified Risk Second Primary Malignancies | |
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MPp+p, and ongoing at death for 1 (0.7%) patient in Arm MPR+R. MDS had an outcome of death in 1 (0.7%) patient each in Arm MPR+R, Arm MPR+p, and Arm MPp+p. Other outcomes for haematologic malignancies were not recovered/not resolved for 2 (1.3%) patients with MDS in Arm MPR+R and 1 (0.7%) patient in Arm MPR+p, and recovered/resolved for 1 (0.7%) patient with other haematologic cancer in Arm MPR+R.

There were no reports of B-cell malignancies in Study MM-015.

**RRMM Studies**

Studies MM-009 and MM-010

There were no reports of AML or B-cell malignancies in Studies MM-009 and MM-010.

The outcomes of the other haematologic malignancies in Studies MM-009 and MM-010 were unknown.

**Del 5q MDS Studies**

For Study MDS-004, the analysis of SPM includes data from the open-label phase as well as the double-blind phase (the double-blind phase was 52 weeks including the first 16 weeks of which the patients in the placebo arm who did not achieve a minor response by Week 16 were given the option to cross over to the 5 mg lenalidomide arm).

Study MDS-004

There were no reports of B-cell malignancies or other haematologic malignancies in Study MDS-004. Of the patients with AML, 14 out of 16 patients in the lenalidomide 10 mg group, 23 out of 24 patients in the lenalidomide 5 mg group and 25 out of 26 patients in the placebo group have died.

Study MDS-003

In Study MDS-003, no patients had an outcome of death from B-cell malignancies. The outcome of B-cell malignancy in Study MDS-003 was recovered/resolved. Of the 37 patients with AML, 35 had died at the data cutoff and 2 were alive. The cause of death for the 35 patients is not known. An outcome of not recovered/not resolved was reported for a single patient with other haematologic malignancy.

**MCL Studies**

Study MCL-002

There were no reports of AML in Study MCL-002. In the lenalidomide group, the outcome of the B-cell malignancy was death in 1 (0.6%) patient, and the outcome of the B-cell malignancy was not recovered/not resolved in 1 (1.2%) patient in the control group. MDS had an outcome of not recovered/not resolved in 1 (0.6%) lenalidomide-treated patient. No patients had other haematologic malignancies.

Study MCL-001

In Study MCL-001, AML had an outcome of not recovered/not resolved in 1 (0.7%) lenalidomide-treated patient. There were no reports of B-cell malignancies in Study MCL-001. MDS had an outcome of ongoing at death in 1 (0.7%) lenalidomide-treated patient. No patients had other haematologic malignancies in Study MCL-001.

Study NHL-002

There were no reports of AML, MDS, other haematologic malignancies and B-cell malignancies in Study NHL-002.

Study NHL-003

## Table 2.7.3.1-3: Important Identified Risk: Second Primary Malignancies

| Important Identified Risk Second Primary Malignancies | |
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| | In Study NHL-003, AML had an outcome of recovered/resolved in 1 (0.5%) lenalidomide-treated patient. MDS had an outcome of not recovered/not resolved in 1 (0.5%) lenalidomide-treated patient. No patients had other haematologic malignancies in Study NHL-003.<br>**Seriousness/Outcomes (Invasive SPM [Solid Tumours])**<br>The outcome of solid tumours is summarised in Table 2.7.3.1-8 for the NDMM RVd study, Table 2.7.3.1-9 for the NDMM studies, Table 2.7.3.1-10 for the RRMM studies, and Table 2.7.3.1-11 for the MDS and lymphoma studies.<br>**FL Studies:**<br>Study NHL-007<br>In Study NHL-007, in the lenalidomide plus rituximab arm an outcome of recovered/resolved and not recovered/not resolved was reported for 1 (0.7%) patient each. In the rituximab plus placebo arm, an outcome of recovered/resolved was reported for 3 (2.0%) patients.<br>Study NHL-008<br>In Study NHL-008, an outcome of not recovered/not resolved was reported for 1 (0.6%) lenalidomide plus rituximab-treated patient.<br>**NDMM RVd Study**<br>Study SWOG S0777<br>For patients in the RVd arm with solid tumours, the outcomes were death (1 [0.4%] patient), recovered/resolved (4 [1.5%] patients), recovering/resolving (1 [0.4%] patient) and not recovered/not resolved (2 [0.8%] patients). For patients in the Rd arm with solid tumours, the outcomes were recovered/resolved (4 [1.6%] patients), recovered with sequela (1 [0.4%] patient), not recovered/not resolved (3 [1.2%] patient) and missing (2 [0.8%] patients).<br>**TE NDMM Studies**<br>Study IFM 2005-02<br>In the lenalidomide arm of Study IFM 2005-02, an outcome of death was recorded for 2 patients (0.7%) with solid tumours. In the placebo arm, an outcome of death was recorded for 1 patient (0.3%) with solid tumours. For patients with solid tumours in the lenalidomide arm, an outcome of recovered/resolved was reported for 6 patients (2.0%), recovering/resolving was reported for 5 (1.6%) patients, not recovered/not resolved was reported for 7 (2.3%) patients, and ongoing at death was reported for 1 (0.3%) patient.<br>Study CALGB 100104<br>In Study CALGB 100104, an outcome of death was reported for 1 (0.4%) patient with solid tumour in the lenalidomide arm. For patients with solid tumours in the lenalidomide arm, an outcome of not recovered/not resolved was reported for 1 (0.4%) patient, and the outcome was missing for 15 (6.7%) patients.<br>Study GIMEMA<br>In Study GIMEMA, an outcome of death was reported for 1 (1.8%) patient with solid tumour in the lenalidomide group. In the lenalidomide group, outcomes of recovered/resolved, recovering/resolving and not recovered/not resolved were reported for 2 (3.6%), 1 (1.8%) and 1 (1.8%) patients with solid tumour, respectively. In patients not receiving maintenance treatment, outcomes of not recovered/not resolved and recovered/resolved were each reported for 1 (1.3%) patient with solid tumour. |

## Table 2.7.3.1-3: Important Identified Risk: Second Primary Malignancies

| Important Identified Risk Second Primary Malignancies | |
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| | **TNE NDMM Studies**<br>Study MM-020<br>In Study MM-020, solid tumours had an outcome of death in 3 (0.6%) patients each in Arms Rd and Rd18, and in 5 (0.9%) patients in Arm MPT. Other outcomes for solid tumours were not recovered/not resolved for 5 (0.9%), 5 (0.9%) and 3 (0.6%) patients in Arms Rd, Rd18 and MPT, respectively; recovered/resolved for 3 (0.6%), 9 (1.7%) and 5 (0.9%) patients, respectively; ongoing at death for 1 (0.2%), 2 (0.4%) and 2 (0.4%) patients, respectively; recovered with sequelae for 0, 3 (0.6%) and 0 patients, respectively, and missing for 3 (0.6%), 7 (1.3%) and 0 patients, respectively.<br>Study MM-015<br>In Arm MPR+R, solid tumour had an outcome of death in 2 (1.3%) patients and in Arm MPR+p, solid tumour had an outcome of death in 4 (2.6%) patients. Other outcomes for solid tumours in Arms MPR+R, MPR+p and MPp+p were not recovered/not resolved for 1 (0.7%), 3 (2.0%) and 0 patients, respectively; ongoing at death for 1 (0.7%), 1 (0.7%) and 0 patients, respectively; and missing for 1 (0.7%), 3 (2.0%) and 4 (2.6%) patients, respectively.<br>**RRMM Studies**<br>Studies MM-009 and MM-010<br>For solid tumours in the lenalidomide/dexamethasone and placebo/dexamethasone groups the outcomes were unknown for 2 (0.6%) and 0 patients, respectively; recovered/resolved for 1 (0.3%) and 0 patients, respectively; and not recovered/not resolved for 3 (0.8%) and 0 patients, respectively.<br>**Del 5q MDS Studies**<br>Study MDS-004<br>In Study MDS-004, one (1.4%) patient in the lenalidomide 5 mg group and 1 (1.5%) patient in the placebo group had an outcome of death from a solid tumour. The outcomes in the lenalidomide 10 mg group were recovered/resolved (2 [2.9%] patients), recovered with sequelae (1 [1.4%] patient) and not recovered/resolved (1 [1.4%] patient). The outcomes for the single patients with solid tumours in the lenalidomide 5 mg group and placebo groups were not recovered/resolved.<br>Study MDS-003<br>In Study MDS 003, the outcome was death for 2 (1.4%) patients, resolved/recovered with/without sequelae for 2 (1.4%) patients and unknown/missing for 3 (2.0%) patients, all due to solid tumours.<br>**MCL Studies**<br>Study MCL-002<br>Outcomes for solid tumours were recovered/resolved in 2 (1.2%) patients, not recovered/not resolved in 1 (0.6%) patient and recovered with sequelae in 1 (0.6%) patient in the lenalidomide group. Outcomes for solid tumours in the control group were death, not recovered/not resolved and recovered/resolved in 1 (1.2%) patient each.<br>Study MCL-001<br>Outcomes for solid tumours were not recovered/not resolved in 3 (2.2%) patients, recovered/resolved in 1 (0.7 %) patient, and recovered with sequelae in 1 (0.7%) patient treated with lenalidomide.<br>Study NHL-002 |

## Table 2.7.3.1-3: Important Identified Risk: Second Primary Malignancies

| Important Identified Risk Second Primary Malignancies |
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| Outcomes for solid tumours were not recovered/not resolved in 2 (4.1%) patients treated with lenalidomide.<br>Study NHL-003<br>One patient (0.5%) had a fatal outcome for solid tumour; the outcomes for the remaining solid tumours were ongoing at death in 1 (0.5%) patient and missing in 2 (0.9%) patients treated with lenalidomide in Study NHL-003.<br>**Seriousness/Outcomes (Non-invasive SPM [NMSC])**<br>The outcome of NMSC is summarised in Table 2.7.3.1-8 for the NDMM RVd study, Table 2.7.3.1-9 for the NDMM studies, Table 2.7.3.1-10 for the RRMM studies, and Table 2.7.3.1-11 for the MDS and lymphoma studies.<br>**FL Studies:**<br>Study NHL-007<br>In Study NHL-007, an outcome of recovered/resolved was reported for 2 (1.4%) patients and not recovered/not resolved for 1 (0.7%) patient in the lenalidomide plus rituximab arm. In the rituximab plus placebo arm, an outcome of recovered/resolved was reported for 2 (1.4%) patients with NMSC.<br>Study NHL-008<br>In Study NHL-008, no NMSC had an outcome of death. All reported events of NMSC had an outcome of recovered/resolved.<br>**NDMM RVd Study**<br>Study SWOG S0777<br>In Study SWOG S0777, the outcomes of NMSC in the RVd arm were recovered/resolved in 6 (2.3%) patients, recovered with sequela in 3 (1.1%) patients and recovering/resolving in 2 (0.8%) patients. The outcomes of NMSC in the Rd arm were recovered/resolved in 2 (0.8%) patients, not recovered/not resolved in 1 (0.4%) patient and missing in 4 (1.6%) patients.<br>**TE NDMM Studies**<br>Study IFM 2005-02<br>In the lenalidomide arm of Study IFM 2005-02, an outcome of recovered/resolved and recovering/resolving was reported for 8 (2.6%) and 2 (0.7%) patients with NMSC, respectively. In the placebo arm, NMSC had an outcome of recovered/resolved (5 [1.7%] patients), not recovered/not resolved (1 [0.3%] patient) and recovering/resolving (1 [0.3%] patient).<br>Study CALGB 100104<br>In Study CALGB 100104, in the lenalidomide arm, NMSC had an outcome of not recovered/not resolved for 3 (1.3%) patients, recovering/resolving for 1 (0.4%) patient, and recovered/resolved for 2 (0.9%) patients. The outcome was missing for 6 (2.7%) patients in the lenalidomide arm.<br>In the placebo arm, NMSC had an outcome of not recovered/not resolved for 1 (0.5%) patient, recovered/resolved for 4 (1.8%) patients, and the outcome was missing for 4 (1.8%) patients.<br>Study GIMEMA<br>In Study GIMEMA, in the lenalidomide group, an outcome of recovered/resolved was reported for 1 (1.8%) patient with NMSC. In patients not receiving maintenance treatment, an outcome of recovered/resolved was reported for 1 (1.3%) patient with NMSC. |

## Table 2.7.3.1-3: Important Identified Risk: Second Primary Malignancies

| Important Identified Risk Second Primary Malignancies | |
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| | **TNE NDMM Studies**<br>Study MM-020<br>In Arms Rd and Rd18, respectively, of Study MM-020, an outcome of recovered/resolved was reported for 18 (3.4%) patients and 13 (2.4%) patients with NMSC, not recovered/not resolved was reported for 1 (0.2%) patient and 2 (0.4%) patients, missing was reported for 2 (0.4%) patients each, and ongoing at death was reported for 1 (0.2%) patient and 0 patients. In Arm MPT, an outcome of recovered/resolved was reported for 17 (3.1%) patients with NMSC, not recovered/not resolved was reported for 2 (0.4%) patients, and missing was reported for 2 (0.4%) patients.<br>Study MM-015<br>For NMSC in Arms MPR+R, MPR+p and MPp+p, the outcomes were recovered/resolved for 1 (0.7%), 5 (3.3%) and 6 (3.9%) patients, respectively, and not recovered/not resolved for 1 (0.7%), 0 and 0 patients, respectively. The outcomes were missing for 2 (1.3%), 1 (0.7%) and 2 (1.3%) patients in Arms MPR+R, MPR+p and MPp+p, respectively.<br>**RRMM Studies**<br>Studies MM-009 and MM-010<br>The outcomes of the events of NMSC were recovered/resolved for 2 (0.6%) patients in the lenalidomide-treated patients and 1 [0.3%] patient in the placebo/dexamethasone group. The outcomes for the other events of NMSC were unknown.<br>**Del 5q MDS Studies**<br>For Study MDS-004, the analysis of SPM includes data from the open-label phase as well as the double-blind phase (the double-blind phase was 52 weeks including the first 16 weeks of which the patients in the placebo arm who did not achieve a minor response by Week 16 were given the option to cross over to the 5 mg lenalidomide arm).<br>Study MDS-004<br>In Study MDS-004, the outcome for all events of NMSC was unknown.<br>Study MDS-003<br>In Study MDS-003, no patients had an outcome of death from NMSC. The outcome for all events of NMSC was unknown.<br>**MCL Studies**<br>Study MCL-002<br>The outcomes of the events of NMSC were recovered/resolved in 4 (2.4%) patients and not recovered/not resolved in 1 (0.6%) patient treated with lenalidomide in Study MCL-002. The outcome of the event of NMSC was recovered/resolved in 1 (1.2%) patient treated with control.<br>Study MCL-001<br>The outcomes of the events of NMSC were recovered/resolved in 6 (4.5%) patients and not recovered/not resolved in 1 (0.7%) patient treated with lenalidomide in Study MCL-001.<br>Study NHL-002<br>There were no reports of NMSC in Study NHL-002.<br>Study NHL-003 |

## Table 2.7.3.1-3: Important Identified Risk: Second Primary Malignancies

| Important Identified Risk Second Primary Malignancies | |
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The outcomes of the events of NMSC were recovered/resolved in 3 (1.4%) patients and missing in 3 (1.4%) patients treated with lenalidomide in Study NHL-003.

**Severity and Nature of Risk (Invasive SPM [Haematologic Malignancies])**

The severity and nature of the haematologic malignancies are summarised in Table 2.7.3.1-12 for the NDMM RVd study, Table 2.7.3.1-13 for the NDMM studies, Table 2.7.3.1-14 for the RRMM studies, and Table 2.7.3.1-15 for the MDS and lymphoma studies.

**FL Studies:**

Study NHL-007

In Study NHL-007, the frequency of Grade 3 or 4 events was the same in the lenalidomide plus rituximab versus the rituximab plus placebo arm for AML (1 [0.7%] patient each).

Study NHL-008

In Study NHL-008, Grade 3 or 4 T-cell malignancy was reported in 1 (0.6%) lenalidomide plus rituximab-treated patient.

**NDMM RVd Study**

Study SWOG S0777

There were no reports of AML in the RVd and Rd arms of Study SWOG S0777. Grade 3 or 4 B-cell malignancies were reported in 2 (0.8%) patients in the Rd arm and no patients in the RVd arm. Grade 3 or 4 MDS was reported in 1 (0.4%) patient each in the RVd and Rd arms. There were no reports of other haematologic malignancies in the RVd and Rd arms.

**TE NDMM Studies**

Study IFM 2005-02

In Study IFM 2005-02, the frequency of Grade 3 or 4 events was higher in the lenalidomide versus the placebo group for B-cell malignancies (9 [2.9%] versus 1 [0.3%] patients). For AML, the frequency of Grade 3 or 4 events was comparable in the lenalidomide and placebo groups (4 [1.3%] versus 2 [0.7%] patients). Other haematologic cancer of Grade 3 or 4 intensity was reported for 1 (0.3%) patient each in the lenalidomide and placebo groups.

B-cell malignancies (1 [0.3%] patient in the lenalidomide group versus 0 patients in the placebo group) and AML (2 [0.7%] patients in each of the lenalidomide and placebo groups) led to dose discontinuation in Study IFM 2005-02. No patients experienced B-cell malignancies or AML leading to dose reduction or interruption. No patients experienced other haematologic malignancies leading to discontinuation and dose reduction or interruption.

Study CALGB 100104

In Study CALGB 100104, Grade 3 or 4 MDS was reported in 2 (0.9%) lenalidomide-treated patients and 1 (0.5%) placebo-treated patient. In Study CALGB 100104, actions taken due to AEs (eg, treatment discontinued, dose reduced, dose interrupted) were not collected on the CRF.

Study GIMEMA

There were no reports of AML, MDS, other haematologic malignancies or B-cell malignancies in Study GIMEMA. In Study GIMEMA, AE grade and actions taken due to AEs (eg, treatment discontinued, dose reduced, dose interrupted) were not collected on the CRF.

**TNE NDMM Studies**

## Table 2.7.3.1-3: Important Identified Risk: Second Primary Malignancies

| Important Identified Risk Second Primary Malignancies | |
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Study MM-020

Grade 3 or 4 AML was reported for 1 (0.2%) patient in Arm Rd, 0 patients in Arm Rd18, and 5 (0.9%) patients in Arm MPT. No events of B-cell malignancy were reported. AML leading to discontinuation was reported for 1 (0.2%) patient in Arm Rd, and no patients in Arms Rd18 and MPT. Grade 3 or 4 events of MDS were reported for 1 (0.2%), 0 and 5 (0.9%) patients in Arms Rd, Rd18 and MPT, respectively. Events leading to discontinuation were MDS in 1 (0.2%) patient in Arm Rd. No events led to dose reduction in any of the arms, and there were no events leading to dose interruption or discontinuation in Arm MPT.

Study MM-015

In Study MM-015, Grade 3 or 4 AML was reported for 4 (2.7%) patients in Arm MPR+R, 3 (2.0%) patients in Arm MPR+p, and 1 (0.7%) patient in Arm MPp+p. No events of B-cell malignancy were reported. AML leading to discontinuation was more frequently reported in Arm MPR+R (2.7% [4 patients]), than Arms MPR+p and MPp+p (0 patients each).

In Study MM-015, Grade 3 or 4 events of MDS were reported for 3 (2.0%), 1 (0.7%) and 0 patients in Arms MPR+R, MPR+p and MPp+p, respectively. Other haematologic cancer of Grade 3 or 4 intensity was reported for 1 (0.7%) patient in Arm MPR+R. Events leading to discontinuation were MDS in 1 (0.7%) patient each in Arms MPR+R and MPR+p and other haematologic cancer in 1 (0.7%) patient in Arm MPR+R. There were no events leading to dose interruption or reduction in any of the arms.

**RRMM Studies**

In Studies MM-009 and MM-010, no patients experienced Grade 3 to 5 AML or B-cell malignancies, or AML or B-cell malignancies that led to dose reduction or discontinuation. No patients experienced MDS or other haematologic malignancies that led to dose discontinuation, reduction, or interruption.

**Del 5q MDS Studies**

Severity of events is unknown for AML as most AML cases were captured during follow-up phase via phone contact.

Study MDS-004

There were no reports of B-cell malignancies or other haematologic malignancies in Study MDS-004.

Study MDS-003

In Study MDS-003, one (0.7%) patient had a Grade 3 or 4 B-cell malignancy which was resolved. None of the events of B-cell malignancies or other haematologic malignancies reported led to dose discontinuation, interruption or reduction. One (0.7%) patient had a Grade 3 or 4 other haematologic malignancy. None of the other haematologic malignancies led to dose discontinuation, reduction, or interruption.

**MCL Studies**

Study MCL-002

There were no reports of AML in Study MCL-002. Grade 3 or 4 B-cell malignancy was reported in 1 (0.6%) patient in the lenalidomide group and 1 (1.2%) patient in the control group. B-cell malignancy leading to discontinuation was reported in 1 (0.6%) patient in the lenalidomide group and no patients in the control group. There were no B-cell malignancies leading to dose reduction or interruption in Study MCL-002.

Grade 3 or 4 MDS was reported in 1 (0.6%) lenalidomide-treated patient and no patients in the control group. There were no events of MDS leading to discontinuation

## Table 2.7.3.1-3: Important Identified Risk: Second Primary Malignancies

| Important Identified Risk Second Primary Malignancies | |
|---|---|

or dose reduction or interruption in Study MCL-002. No patients had other haematologic malignancies in Study MCL-002.

Study MCL-001

In Study MCL-001, Grade 3 or 4 AML was reported in 1 (0.7%) lenalidomide-treated patient. There were no reports of AML leading to discontinuation or dose reduction or interruption. There were no reports of B-cell malignancies in Study MCL-001. There were no Grade 3 or 4 events of MDS. No events of MDS led to discontinuation or dose reduction or interruption. No patients had other haematologic malignancies in Study MCL-001.

Study NHL-002

There were no reports of AML, MDS, other haematologic malignancies, or B-cell malignancies in Study NHL-002.

Study NHL-003

In Study NHL-003, Grade 3 or 4 AML was reported in 1 (0.5%) lenalidomide-treated patient. AML leading to discontinuation was reported in 1 (0.5%) lenalidomide-treated patient. There were no reports of B-cell malignancies in Study NHL-003. Grade 3 or 4 MDS was reported in 1 (0.5%) lenalidomide-treated patient. There were no events of MDS leading to discontinuation, dose interruption or dose reduction. No patients had other haematologic malignancies in Study NHL-003.

**Severity and Nature of Risk (Invasive SPM [Solid Tumours])**

The severity and nature of the solid tumours are summarised in Table 2.7.3.1-12 for the NDMM RVd study, Table 2.7.3.1-13 for the NDMM studies, Table 2.7.3.1-14 for the RRMM studies, and Table 2.7.3.1-15 for the MDS and lymphoma studies.

**FL Studies:**

Study NHL-007

In Study NHL-007, the frequency of Grade 3 or 4 solid tumours was lower in the lenalidomide plus rituximab versus the rituximab plus placebo arm (1 [0.7%] patients versus 3 [2.0%] patients).

Study NHL-008

In Study NHL-008, Grade 3 or 4 solid tumours were reported in 1 (0.6%) lenalidomide plus rituximab-treated patient. One (0.6%) lenalidomide plus rituximab-treated patient had a solid tumour AE that led to study medication discontinuation.

**NDMM RVd Study**

Study SWOG S0777

Grade 3 or 4 solid tumours were reported in 5 (1.9%) patients in the RVd arm and 6 (2.3%) patients in the Rd arm in Study SWOG S0777.

**TE NDMM Studies**

Study IFM 2005-02

In Study IFM 2005-02, the frequency of Grade 3 or 4 events was similar in the lenalidomide and placebo groups for solid tumours (17 [5.6%] versus 10 [3.3%] patients). SPM leading to dose discontinuation were solid tumours (3 [1.0%] patients in the lenalidomide group versus 1 [0.3%] patient in the placebo group). Solid tumours leading to dose interruption were experienced by a single patient (0.3%) in the lenalidomide group.

Study CALGB 100104

## Table 2.7.3.1-3: Important Identified Risk: Second Primary Malignancies

| Important Identified Risk Second Primary Malignancies |
|---|
| In Study CALGB 100104, Grade 3 or 4 solid tumours were reported in 1 (0.5%) patient treated with placebo and no lenalidomide-treated patients. Actions taken due to AEs (eg, treatment discontinued, dose reduced, dose interrupted) were not collected on the CRF.<br><br>Study GIMEMA<br><br>In Study GIMEMA, AE grade and actions taken due to AEs (eg, treatment discontinued, dose reduced, dose interrupted) were not collected on the CRF.<br><br>**TNE NDMM Studies**<br><br>Study MM-020<br><br>Grade 3 or 4 solid tumours were reported for 12 (2.3%), 20 (3.7%) and 4 (0.7%) patients in Arms Rd, Rd18 and MPT, respectively. Events leading to discontinuation were solid tumours in 5 (0.9%) patients in Arm Rd and 3 (0.6%) patients in Arm Rd18. Solid tumours led to dose interruption in 2 (0.4%) and 4 (0.7%) patients in Arms Rd and Rd18, respectively. No events led to dose reduction in any of the arms, and there were no events leading to dose interruption or discontinuation in Arm MPT.<br><br>Study MM-015<br><br>Grade 3 or 4 solid tumours were reported for 4 (2.7%), 6 (3.9%) and 2 (1.3%) patients in Arms MPR+R, MPR+p and MPp+p, respectively. Events leading to discontinuation were solid tumours in 2 (1.3%) patients, 3 (2.0%) patients and 1 (0.7%) patient in Arms MPR+R, MPR+p and MPp+p, respectively. There were no events leading to dose interruption or reduction in any of the arms.<br><br>**RRMM Studies**<br><br>Studies MM-009 and MM-010<br><br>In Studies MM-009 and MM-010, Grade 3 or 4 solid tumours (6 [1.7%] and 1 [0.3%] patients, respectively) were reported. Solid tumours leading to discontinuation or dose interruption were infrequently observed in the lenalidomide/ dexamethasone group (3 [0.8%] or 1 [0.3%] patients overall, respectively) and were not observed in the placebo/ dexamethasone group.<br><br>**Del 5q MDS Studies**<br><br>Study MDS-004<br><br>In the lenalidomide 10 mg group of Study MDS-004, 3 (4.3%) patients had a Grade 3 or 4 solid tumour and in the lenalidomide 5 mg group, 1 (1.4%) patient had a Grade 3 or 4 solid tumour. Severity and nature of risk was unknown for 2 patients with solid tumours. None of the solid tumours reported led to dose discontinuation, interruption or reduction.<br><br>Study MDS-003<br><br>In Study MDS-003, 5 (3.4%) patients had a Grade 3 or 4 solid tumour. None of the solid tumours reported led to dose discontinuation, interruption or reduction.<br><br>**MCL Studies**<br><br>Study MCL-002<br><br>Grade 3 or 4 solid tumours were reported in 3 (1.8%) patients in the lenalidomide group and no patients in the control group in Study MCL-002. Events of solid tumours led to discontinuation in 1 (0.6%) patient in the lenalidomide group and no patients in the control group. There were no events of solid tumours leading to dose reduction or interruption in Study MCL-002.<br><br>Study MCL-001 |

## Table 2.7.3.1-3: Important Identified Risk: Second Primary Malignancies

| Important Identified Risk Second Primary Malignancies |
|---|
| In Study MCL-001, Grade 3 or 4 events of solid tumours were reported in 4 (3.0%) lenalidomide-treated patients, with events of solid tumours leading to discontinuation and to dose interruption in 1 (0.7%) patient each. No events of solid tumours led to dose reduction in Study MCL-001.<br>Study NHL-002<br>In Study NHL-002, Grade 3 or 4 events of solid tumours were reported in 1 (2.0%) lenalidomide-treated patient. No events of solid tumour led to dose discontinuation, interruption or reduction.<br>Study NHL-003<br>In Study NHL-003, Grade 3 or 4 events of solid tumours were reported in 2 (0.9%) lenalidomide-treated patients, and events of solid tumours led to discontinuation in 2 (0.9%) patients. There were no events of solid tumours that led to dose interruption or dose reduction.<br>**Severity and Nature of Risk (Non-Invasive SPM [NMSC])**<br>The severity and nature of the NMSC are summarised in Table 2.7.3.1-12 for the NDMM RVd study, Table 2.7.3.1-13 for the NDMM studies, Table 2.7.3.1-14 for the RRMM studies, and Table 2.7.3.1-15 for the MDS and lymphoma studies.<br>**FL Studies:**<br>Study NHL-007<br>In Study NHL-007, there were no Grade 3 or 4 events of NMSC in the lenalidomide plus rituximab or rituximab plus placebo arms.<br>Study NHL-008<br>In Study NHL-008, Grade 3 or 4 NMSC were reported in 3 (1.7%) lenalidomide plus rituximab-treated patients. One (0.6%) lenalidomide plus rituximab-treated patient had an AE of NMSC that led to study medication interruption.<br>**NDMM RVd Study**<br>Study SWOG S0777<br>In Study SWOG S0777, Grade 3 or 4 NMSC was reported in 6 (2.3%) patients in the RVd arm and 2 (0.8%) patients in the Rd arm.<br>**TE NDMM Studies**<br>Study IFM 2005-02<br>In Study IFM 2005-02, the frequency of Grade 3 or 4 events was higher in the lenalidomide versus the placebo group for NMSC (8 [2.6%] versus 5 [1.7%] patients). One (0.3%) patient in the placebo group had their study treatment interrupted due to events of NMSC.<br>No patients experienced NMSC leading to discontinuation or dose reduction.<br>Study CALGB 100104<br>In Study CALGB 100104, Grade 3 or 4 events of NMSC were reported for 1 (0.4%) patient treated with lenalidomide and 2 (0.9%) patients treated with placebo. In Study CALGB 100104, actions taken due to AEs (eg, treatment discontinued, dose reduced, dose interrupted) were not collected on the CRF.<br>Study GIMEMA<br>In Study GIMEMA, AE grade and actions taken due to AEs (eg, treatment discontinued, dose reduced, dose interrupted) were not collected on the CRF.<br>**TNE NDMM Studies** |

## Table 2.7.3.1-3: Important Identified Risk: Second Primary Malignancies

| Important Identified Risk Second Primary Malignancies |
|---|
| Study MM-020<br>In Study MM-020, Grade 3 or 4 NMSC was reported for 10 (1.9%), 12 (2.2%) and 3 (0.6%) patients in Arms Rd, Rd18 and MPT, respectively. NMSC leading to discontinuation was reported for 1 (0.2%) patient each in Arms Rd and Rd18, and 0 patients in Arm MPT. One (0.2%) patient in Arm Rd had NMSC leading to dose interruption.<br>Study MM-015<br>For NMSC, Grade 3 or 4 events were reported for 2 (1.3%), 4 (2.6%) and 5 (3.3%) patients in Arms MPR+R, MPR+p and MPp+p, respectively. Two (1.3%) patients in Arm MPp+p had NMSC leading to dose interruption, and 1 (0.7%) patient in Arm MPR+R had NMSC leading to discontinuation.<br>**RRMM Studies**<br>Studies MM-009 and MM-010<br>In Studies MM-009 and MM-010, Grade 3 or 4 NMSC was reported in 4 (1.1%) and 1 (0.3%) patients in the lenalidomide and placebo arms, respectively. Three (0.8%) patients in the lenalidomide arm had their dose interrupted due to events of NMSC.<br>**Del 5q MDS Studies**<br>Study MDS-004<br>In Study MDS-004, there were no Grade 3, 4 or 5 events of NMSC. No events of NMSC led to dose interruption, reduction or discontinuation.<br>Study MDS-003<br>In Study MDS-003, one (0.7%) patient had a Grade 3 or 4 NMSC. None of the events of NMSC reported led to dose discontinuation, interruption or reduction.<br>**MCL Studies**<br>Study MCL-002<br>In Study MCL-002, Grade 3 or 4 events of NMSC were reported in 3 (1.8%) lenalidomide-treated patients and 1 (1.2%) patient in the control group. There were no events of NMSC leading to discontinuation or dose reduction or interruption in Study MCL-002.<br>Study MCL-001<br>In Study MCL-001, Grade 3 or 4 events of NMSC were reported in 5 (3.7%) lenalidomide-treated patients. NMSC led to dose interruption in 1 (0.7%) patient. There were no events of NMSC leading to discontinuation or dose reduction in Study MCL-001.<br>Study NHL-002<br>There were no reports of NMSC in Study NHL-002.<br>Study NHL-003<br>In Study NHL-003, Grade 3 or 4 events of NMSC were reported in 5 (2.3%) lenalidomide-treated patients. There were no events of NMSC leading to discontinuation, dose interruption or dose reduction in Study NHL-003.<br>• **Lymphoproliferative disorders in ASCT patients**<br>The development of Post-Transplant Lymphoproliferative Disorders (PTLD) after solid organ transplantation is well recognised.[119] Most cases are due to EBV-driven tumour formation in B-cells. Other important risks include the use of potent and prolonged immunosuppressive medication, the age of donor (in the case of allogenic transplantation) and recipient, number and severity of rejection episodes and cytokine |

**Table 2.7.3.1-3: Important Identified Risk: Second Primary Malignancies**

| Important Identified Risk Second Primary Malignancies | |
|---|---|
| | gene polymorphisms.[119] In patients with MM a number of prospective, randomised trials have been conducted that compare conventional chemotherapy with high-dose therapy using ASCT. As a result of these studies, ASCT has nowadays become a standard of care in MM.[120] However, these patients are at risk of developing PTLD. Reports have demonstrated that HSCT patients with PTLD generally have higher concentrations of EBV deoxyribonucleic acid (DNA) in the peripheral blood than patients without PTLD.[121]<br>• **G-CSF therapy**<br>Guidelines for cancer care support the use of G-CSF prophylaxis in specific therapeutic circumstances.[122] Despite the usefulness of G-CSF therapy, increased risks of AML or MDS associated with G-CSF use have been described. Lyman[123] provided a systematic review of AML/MDS incidence among 6058 and 6746 patients randomly assigned to receive chemotherapy with and without initial G-CSF support in 25 randomised clinical trials. At mean and median follow-up across studies of 60 and 53 months, respectively, AML/MDS was reported in 22 control patients and 43 G-CSF patients, for an estimated risk ratio of 1.92 (95% CI: 1.19–3.07). Median follow-up time was 54 months.<br>The risk of AML/MDS was significantly increased in studies where G-CSF use was associated with higher total dose of chemotherapy (risk ratio = 2.334; 95% CI: 1.237–4.403). There was no significant difference in the risk ratio for mortality. Even though these findings do not establish a unique causal role associated with the use of G-CSF the median follow-up of about 5 years may be insufficient to provide a final quantification of AML/MDS.<br>• **Heredity**<br>Additional insight has also been obtained in elucidating the risk of malignancies in close family members of patients affected by MM. The available data show an increased risk of more than one malignancy in MM patients and first-degree relatives compared to the general population. The reason for this finding is still unclear but may involve risk conferred by shared genetic factors.[124,125] |
| Risk factors and risk groups | **MDS Populations (Haematologic Malignancies)**<br>A study to identify prognostic factors for progression to leukaemia (LFS) and OS was reported by Malcovati.[126] Four hundred seventy six patients first diagnosed with de novo MDS between 1992 and 2002 were evaluated. In one of the earliest studies to report the negative effects of developing a transfusion requirement, Malcovati reported an increased risk associated with transfusion burden when analysed as a time-dependent covariate in a combined group of patients with RA, RARS or MDS with del(5q) (HR = 3.46).<br>Further development of the WPSS a learning cohort of 426 Italian MDS patients and a validation cohort of 193 German MDS patients was reported by Malcovati and colleagues.[127] In a multivariable analysis of the Italian patients stratified by WHO subgroups, cytogenetics (HR = 1.48) and transfusion requirement (HR = 2.53) significantly affected OS and risk of AML (HR = 1.3 and HR = 2.4, respectively). These findings were corroborated in the subsequent multivariable analysis of German MDS patients stratified by WHO subgroups, with cytogenetics (HR = 1.84) and transfusion dependency (HR = 1.85) and risk of AML (HR = 2.27 and HR = 2.25, respectively). Mallo[128] reported the results of a cooperative study designed to assess |

**Table 2.7.3.1-3: Important Identified Risk: Second Primary Malignancies**

| Important Identified Risk Second Primary Malignancies |
|---|

prognostic factors for OS and progression to AML in 541 patients with de novo MDS and del 5q. In multivariate analyses the most important predictors of both OS and AML progression were number of chromosomal abnormalities ($p < 0.001$ for both outcomes), platelet count ($p < 0.001$ and $p = 0.001$, respectively) and proportion of bone marrow blasts ($p < 0.001$ and $p = 0.016$, respectively). Transfusion burden was not addressed in this study.

Knuendgen [129] assessed the risk of AML progression and death in 295 lenalidomide-treated MDS-003 and MDS-004 patients versus 125 MDS patients with del 5q from a large multicentre registry who had received best supportive care only including ESAs. In the final multivariate Cox proportional hazard models, lenalidomide treatment was not associated with progression to AML (HR 0.939; $p = 0.860$). Significant factors associated with an increased risk of AML progression were complex cytogenetics (del 5q plus > 1 abn; HR 3.627; $p = 0.002$), bone marrow blasts 5% to 10% (HR 2.215; $p = 0.016$), and higher transfusion burden (HR 1.097 [10% increase in risk per unit at baseline]; $p = 0.029$). Higher haemoglobin levels were associated with a reduced risk (HR 0.857; $p = 0.054$). Regarding survival, lenalidomide treatment was associated with a reduced risk of death (HR 0.597; $p = 0.012$).

Other factors associated with decreased mortality were higher haemoglobin levels (HR 0.883; $p = 0.028$), higher platelet counts (HR 0.999; $p = 0.035$), and female sex (HR 0.598; $p = 0.002$). Higher transfusion burden (HR 1.056; $p = 0.037$) and age (HR 1.049; $p < 0.001$) increased the risk of death.

Mutations in the TP53 gene have been well described as a poor prognostic variable and associated with chemotherapy resistance in a wide variety of malignancies including high-risk MDS and AML.[130,131]

**MCL Population (Haematologic Malignancies)**

There is no information available.

**NMSC**

Risk factors for NMSC include: increased sun or ultraviolet radiation exposure; physical factors such as fair skin, red or blond hair, and light eye colour; chemical carcinogens such as, arsenic, tobacco, and oral methoxsalen; ionising radiation; and previous history of NMSC.[132,133]

- **Prolonged survival as a result of improved therapies**

As previously noted, the 5-year relative survival among MM patients has increased from 24.6% among patients first diagnosed in 1975 to 1977 to 44.9% among patients first diagnosed between 2003 and 2009.[134]

Due to improvements in the care of patients with cancer, the number of cancer survivors has been increasing in recent years. Increased longevity increases the risk of developing second malignancy, including NMSC.

- **Immunosuppression associated with transplantation procedures**

Immunosuppression is a risk factor for NMSC.[133,132] Patients receiving immunosuppressive therapy following solid organ transplantation and those receiving bone marrow transplants have an increased risk of skin cancer. In a small series of patients (n = 43) receiving nonmyeloablated haematopoietic cell transplants, 6 patients developed squamous cell carcinoma (n = 3), basal cell carcinoma (n = 2), or malignant melanoma (n = 2).[135] In another study, the most frequently observed

## Table 2.7.3.1-3: Important Identified Risk: Second Primary Malignancies

| Important Identified Risk Second Primary Malignancies | |
|---|---|
| | secondary malignancies among patients (n = 557) receiving allogeneic bone marrow transplants were NMSC. Out of 31 secondary malignancies, 5 were basal cell carcinoma and 4 were squamous cell carcinoma skin cancers.[136] |
| Preventability | The risk of occurrence of haematologic SPM must be taken into account before initiating treatment with Revlimid either in combination with melphalan or immediately following HDM and ASCT. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated (SmPC, Section 4.4). TP53 and the risk of progression to AML is mentioned in Section 4.4 of the SmPC. |
| Impact on the risk-benefit balance of the product | SPM may result in significant morbidity and mortality depending on the type of SPM. It impacts the patient's activities of daily living.<br>AML and B-cell malignancies may result in an increase in mortality, and adversely affect quality of life.<br>NMSC is rarely fatal but impacts the patient's activities. |
| Public health impact | As survival after a diagnosis of cancer improves, identification and quantification of the late effects of cancer and its therapy have become critical. Generally, new cancer is considered to be one of the most serious events experienced by cancer survivors. The number of patients with multiple primary cancers is growing rapidly, with independent malignancies now comprising about 16% of incident cancers reported to the National Cancer Institute's (NCI) SEER Program in 2003. Moreover, second tumours may be a cause of mortality among several populations of long-term survivors.[58] It should be noted, however, that the risk of dying from MM is considerably higher than the risk of developing a second cancer.[137]<br>NMSC is rarely fatal but has adverse public health effects of high medical cost. The total cost of NMSC care in the US in the Medicare population is $426 million/year. The average cost per episode of NMSC when performed in a physician's office setting was found to be $492 and the cost per episode of care in inpatient and outpatient settings were $5537 and $1043, respectively.[138] |
| Data source | Studies NHL-007 (22 Jun 2018) and NHL-008 (01 May 2017); Study SWOG S0777 (01 Dec 2016); Study CALGB 100104 (01 Mar 2015); Study IFM 2005-02 (01 Mar 2015); Study GIMEMA (01 Mar 2015); Study MM-020 (24 May 2013); Study MM-015 (30 Apr 2013); Integrated Summary of Safety (Dec 2005) for Studies MM-009 and MM-010; Study MDS-003 CSR; Study MDS-004 CSR; Study MCL-001 (21 Mar 2014); Study MCL-002 (07 Mar 2014); Study NHL-002 (23 Jun 2008); Study NHL-003 (25 Mar 2013). NDMM Day 120 Responses. |
| MedDRA Terms | See Annex 7 |

**Table 2.7.3.1-4: Frequency and Incidence Rate of Second Primary Malignancies: NDM RVd**

| **SPM** | | **SWOG S0777** | |
|---|---|---|---|
| | | **Arm B (RVd) N = 262** | **Arm A (Rd) N = 256** |
| **INVASIVE** | | | |
| **Haematologic Malignancies** | | | |
| AML[a] | Patients with ≥ 1 SPM | 0 | 0 |
| | IR[b], 95% CI | 0 | 0 |
| MDS | Patients with ≥ 1 SPM | 2 | 1 |
| | IR[b], 95% CI | 0.16<br>0.04 to 0.65 | 0.09<br>0.01 to 0.63 |
| B-cell Malignancies | Patients with ≥ 1 SPM | 0 | 2 |
| | IR[b], 95% CI | 0 | 0.18<br>0.04 to 0.71 |
| Other haematologic malignancies | Patients with ≥ 1 SPM | 0 | 0 |
| | IR[b], 95% CI | 0 | 0 |
| Solid Tumours | Patients with ≥ 1 SPM | 8 | 10 |
| | IR[b], 95% CI | 0.66<br>0.33 to 1.32 | 0.90<br>0.48 to 1.67 |
| **NON-INVASIVE** | | | |
| **NMSC** | Patients with ≥ 1 SPM | 11 | 7 |
| | IR[b], 95% CI | 0.92<br>0.51 to 1.66 | 0.62<br>0.30 to 1.31 |

[a] Includes patients with the event of 'MDS to AML'.

[b] Incidence rates per 100 person-years.

Data cutoff: 01 Dec 2016.

Patients may be counted more than once across SPM subcategories.

**Table 2.7.3.1-5: Frequency and Incidence Rate of Second Primary Malignancies: NDMM Studies**

| SPM | | TE NDMM STUDIES | | | | | | TNE NDMM STUDIES | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | IFM 2005-02 | | CALGB 100104 | | GIMEMA | | MM-020 | | | MM-015 | | |
| | | Len N = 306 | Placebo N = 302 | Len N = 224 | Placebo N = 221 | Len N = 56 | Control N = 79 | Rd N = 532 | Rd18 N = 540 | MPT N = 541 | MPR+R N = 150 | MPR+p N = 152 | MPp+p N = 153 |
| **INVASIVE** | | | | | | | | | | | | | |
| **Haematologic Malignancies** | | | | | | | | | | | | | |
| AML[a] | Patients with ≥ 1 SPM | 6 | 3 | 7 | 0 | 0 | 0 | 1 | 1 | 6 | 6 | 5 | 1 |
| | IR[b], 95% CI | 0.36 (0.16 to 0.80) | 0.18 (0.06 to 0.55) | 0.59 (0.28 to 1.23) | 0 | 0 | 0 | 0.07 0.01 to 0.51 | 0.07 0.01 to 0.51 | 0.46 0.20 to 1.01 | 0.96 0.40 to 2.31 | 0.98 0.41 to 2.36 | 0.18 0.03 to 1.29 |
| MDS | Patients with ≥ 1 SPM | 4 | 3 | 4 | 4 | 0 | 0 | 1 | 1 | 6 | 3[c] | 2 | 1 |
| | IR[b], 95% CI | 0.24 0.09 to 0.64 | 0.18 0.06 to 0.55 | 0.33 0.13 to 0.89 | 0.39 0.14 to 1.03 | 0 | 0 | 0.07 0.01 to 0.51 | 0.07 0.01 to 0.51 | 0.45 0.20 to 1.01 | 0.58 0.19 to 1.79 | 0.39 0.10 to 1.57 | 0.18 0.03 to 1.29 |
| B-cell Malignancies | Patients with ≥ 1 SPM | 11 | 2 | 4 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | IR[b], 95% CI | 0.67 0.37 to 1.21 | 0.12 0.03 to 0.48 | 0.33 0.12 to 0.89 | 0.29 0.09 to 0.89 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Patients with ≥ 1 SPM | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |

**Table 2.7.3.1-5: Frequency and Incidence Rate of Second Primary Malignancies: NDMM Studies**

| SPM | | TE NDMM STUDIES | | | | | | TNE NDMM STUDIES | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | IFM 2005-02 | | CALGB 100104 | | GIMEMA | | MM-020 | | | MM-015 | | |
| | | Len N = 306 | Placebo N = 302 | Len N = 224 | Placebo N = 221 | Len N = 56 | Control N = 79 | Rd N = 532 | Rd18 N = 540 | MPT N = 541 | MPR+R N = 150 | MPR+p N = 152 | MPp+p N = 153 |
| Other haematologic malignancies[d] | IR[b], 95% CI | 0.06 0.01 to 0.42 | 0.06 0.01 to 0.42 | 0 | 0.10 0.01 to 0.68 | 0 | 0 | 0 | 0 | 0 | 0.19 0.03 to 1.37 | 0 | 0 |
| **Solid Tumours** | Patients with ≥ 1 SPM | 21 | 13 | 17 | 10 | 5 | 2 | 15 | 29 | 15 | 5 | 11 | 4 |
| | IR[b], 95% CI | 1.28 0.84 to 1.97 | 0.78 0.46 to 1.35 | 1.48 0.92 to 2.37 | 0.98 0.53 to 1.83 | 2.21 0.92 to 5.31 | 0.68 0.17 to 2.70 | 1.09 0.66 to 1.81 | 2.15 1.49 to 3.09 | 1.15 0.69 to 1.90 | 0.97 0.41 to 2.34 | 2.16 1.20 to 3.91 | 0.74 0.28 to 1.96 |
| **NON-INVASIVE** | | | | | | | | | | | | | |
| **NMSC** | Patients with ≥ 1 SPM | 10 | 7 | 12 | 9 | 1 | 1 | 22 | 17 | 21 | 4 | 6 | 8 |
| | IR[b], 95% CI | 0.61 0.33 to 1.14 | 0.42 0.20 to 0.88 | 1.02 0.58 to 1.80 | 0.88 0.46 to 1.70 | 0.42 0.06 to 2.99 | 0.34 0.05 to 2.41 | 1.62 1.07 to 2.46 | 1.25 0.78 to 2.02 | 1.62 1.05 to 2.48 | 0.77 0.29 to 2.06 | 1.19 0.54 to 2.65 | 1.51 0.75 to 3.02 |

[a] For all TE NDMM studies, patients with the event of 'MDS to AML' were included in this category.

[b] Incidence rates per 100 person-years.

[c] Two cases of MDS and one case of chronic myelomonocytic leukaemia.

[d] Other includes 1 case of acute biphenotypic leukaemia in the lenalidomide group and 1 case of T-cell lymphoma in the placebo group (Study IFM 2005-02); 1 case of malignant histiocytosis in the placebo group (Study CALGB 100104); 1 case reported as T cell type acute leukaemia (Study MM-015; ARM MPR+R).

Data cutoff: IFM 2005-02: 01 Mar 2015; CALGB 100104: 01 Mar 2015; GIMEMA: 01 Mar 2015; MM-020: 24 May 2013; MM-015: 30 Apr 2013.
Patients may be counted more than once across SPM subcategories.

**Table 2.7.3.1-6: Frequency and Incidence Rate of Second Primary Malignancies: RRMM Studies**

| **SPM** | | **MM-009 and MM-010a** | |
|---|---|---|---|
| | | **Len/Dex N = 352** | **Placebo/Dex N = 350** |
| **INVASIVE** | | | |
| **Haematologic Malignancies** | | | |
| AML | Patients with ≥ 1 SPM | 0 | 0 |
| | IR[a], 95% CI | 0.0 | 0.0 |
| MDS | Patients with ≥ 1 SPM | 2 | 0 |
| | IR[a], 95% CI | 0.6<br>0.07 to 2.03 | 0.0 |
| B-cell Malignancies | Patients with ≥ 1 SPM | 0 | 0 |
| | IR[a], 95% CI | 0.0 | 0.0 |
| Other haematologic malignancies | Patients with ≥ 1 SPM | 0 | 0 |
| | IR[a], 95% CI | 0.0 | 0.0 |
| Solid Tumours | Patients with ≥ 1 SPM | 6 | 2 |
| | IR[a], 95% CI | 1.7<br>0.63 to 3.66 | 0.6<br>0.07 to 2.05 |
| **NON-INVASIVE** | | | |
| **NMSC** | Patients with ≥ 1 SPM | 11 | 2 |
| | IR[a], 95% CI | 3.1, 1.57 to 5.51 | 0.6, 0.07 to 2.05 |

[a] Incidence rate between arms was not adjusted for actual time on treatment (mean treatment duration 44 weeks [Len/Dex] versus 23 weeks [Placebo/Dex].

Data cutoff: MM-009: 23 Jul 2008; MM-010: 02 Mar 2008.

Patients may be counted more than once across SPM subcategories.

**Table 2.7.3.1-7: Frequency and Incidence Rate of Second Primary Malignancies**

| SPM | | MDS | | | | Lymphoma | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | MDS-003[a] | MDS-004 (Dose Group as Randomised)[b] | | | MCL-002 | | MCL-001 | NHL-002 | NHL-003 | NHL-007[c] | | NHL-008 |
| | | Len (10 mg) N = 148 | Len (10 mg) N = 69 | Len (5 mg) N = 69 | Placebo N = 67 | Len N = 167 | Control N = 83 | Len N = 134 | Len N = 49 | Len N = 217 | PBO+Rit N = 148 | Len+Rit N = 146 | Len+Rit N = 177 |
| **INVASIVE** | | | | | | | | | | | | | |
| **Haematologic Malignancies** | | | | | | | | | | | | | |
| AML | Patients with ≥ 1 SPM | 37[d] | 17 | 26 | 27[e] | 0 | 0 | 1 | 0 | 1 | 1 | 1 | 0 |
| | IR[f], 95% CI | 7.86<br>5.69 to 10.85 | 6.50<br>4.04 to 10.46 | 11.16<br>7.60 to 16.39 | 12.35<br>8.47 to 18.00 | 0 | 0 | 0.7<br>0.0 to 4.1 | 0 | 0.5<br>0.0 to 2.5 | 0.29<br>0.04 to 2.09 | 0.29<br>0.04 to 2.06 | 0 |
| MDS | Patients with ≥ 1 SPM | NA | NA | NA | NA | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 |
| | IR,[g] 95% CI | NA | NA | NA | NA | 0.6<br>0.0 to 3.3 | 0 | 0.7<br>0.0 to 4.1 | 0 | 0.5<br>0.0 to 2.5 | 0 | 0 | 0 |
| B-cell Malignancies | Patients with ≥ 1 SPM | 1[bg] | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| | IR[h], 95% CI | 0.21<br>0.03 to 1.49 | 0.0 | 0.0 | 0.0 | 0.6<br>0.0 to 3.3 | 1.2<br>0.0 to 6.5 | 0 | 0 | 0 | 0 | 0 | 0 |

**Table 2.7.3.1-7: Frequency and Incidence Rate of Second Primary Malignancies**

| SPM | | MDS | | | | Lymphoma | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | MDS-003[a] | MDS-004 (Dose Group as Randomised)[b] | | | MCL-002 | | MCL-001 | NHL-002 | NHL-003 | NHL-007[c] | | NHL-008 |
| | | Len (10 mg) N = 148 | Len (10 mg) N = 69 | Len (5 mg) N = 69 | Placebo N = 67 | Len N = 167 | Control N = 83 | Len N = 134 | Len N = 49 | Len N = 217 | PBO+Rit N = 148 | Len+Rit N = 146 | Len+Rit N = 177 |
| Other haematologic malignancies | Patients with ≥ 1 SPM | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | IR[i], 95% CI | 0.21<br>0.03 to 1.47 | 0.0 | 0.0 | 0.0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.55<br>0.08 to 3.93 |
| **Solid Tumours** | Patients with ≥ 1 SPM | 7 | 4 | 4[j] | 2 | 4 | 3 | 5 | 2 | 4 | 3 | 2 | 1 |
| | IR[k], 95% CI | 1.49<br>0.71 to 3.13 | 1.52<br>0.57 to 4.04 | 1.69<br>0.63 to 4.49 | 0.85<br>0.21 to 3.39 | 2.4<br>0.7 to 6.0 | 3.6<br>0.8 to 10.2 | 3.7<br>1.2 to 8.5 | 4.1<br>0.5 to 14.0 | 1.8<br>0.5 to 4.7 | 0.89<br>0.29 to 2.76 | 0.58<br>0.15 to 2.32 | 0.55<br>0.08 to 3.93 |
| **NON-INVASIVE** | | | | | | | | | | | | | |
| **NMSC** | Patients with ≥ 1 SPM | 6 | 1 | 1 | 0 | 5 | 1 | 7 | 0 | 6 | 2 | 3 | 8 |
| | IR[l], 95% CI | 1.30<br>0.58 to 2.89 | 0.38<br>0.05 to 2.68 | 0.42<br>0.06 to 2.98 | 0.0 | 3.0<br>1.0 to 6.8 | 1.2<br>0.0 to 6.5 | 5.2<br>2.1 to 10.5 | 0 | 2.8<br>1.0 to 5.9 | 0.59<br>0.15 to 2.36 | 0.88<br>0.28 to 2.74 | 4.57<br>2.29 to 9.14 |

[a] Median time on treatment was 52.5 weeks.

[b] For Study MDS-004, the analysis of SPM includes data from the open label phase as well as the double blind phase.

[c] Patients could cross over to lenalidomide 5 mg after 16 weeks of placebo treatment.

[d] Patient [redacted] in MDS-003, who was identified as having AML at baseline by the central reviewer, was excluded in AML analyses.

[e] 27 patients included 23 patients who crossed over to lenalidomide 5 mg after 16 weeks of placebo treatment.

[f] Incidence rates per 100 person-years.

[g] B-cell lymphoma [redacted]

Data cutoff: MCL-001: 21 Mar 2014; MCL-002: 07 Mar 2014; NHL-002: 23 Jun 2008; NHL-003: 25 Mar 2013; MDS-003 27 Aug 2008; MDS-004: 26 Nov 2012; NHL-007: 22 Jun 2018; NHL-008: 01 May 2017.

Patients may be counted more than once across SPM subcategories.

## Table 2.7.3.1-8: Outcome of Second Primary Malignancies: NDMM RVd

| **SPM** | | **SWOG S0777** | |
|---|---|---|---|
| | | **Arm B (RVd) N = 262** | **Arm A (Rd) N = 256** |
| | | **n (%)** | |
| **INVASIVE** | | | |
| **Haematologic Malignancies** | | | |
| AML[a] | Death | 0 | 0 |
| | Recovered with sequela | 0 | 0 |
| B-cell Malignancies | Death | 0 | 0 |
| | Not recovered/not resolved | 0 | 2 (0.8) |
| MDS | Death | 0 | 0 |
| | Not recovered/not resolved | 2 (0.8) | 1 (0.4) |
| **Solid Tumours** | Death | 1 (0.4) | 0 |
| | Ongoing at death | 0 | 0 |
| | Recovered/resolved | 4 (1.5) | 4 (1.6) |
| | Recovered with sequela | 0 | 1 (0.4) |
| | Recovering/resolving | 1 (0.4) | 0 |
| | Not recovered/not resolved | 2 (0.8) | 3 (1.2) |
| | Missing | 0 | 2 (0.8) |
| **NON-INVASIVE** | | | |
| **NMSC** | Death | 0 | 0 |
| | Recovered/resolved | 6 (2.3) | 2 (0.8) |
| | Recovered with sequela | 3 (1.1) | 0 |
| | Recovering/resolving | 2 (0.8) | 0 |
| | Not recovered/not resolved | 0 | 1 (0.4) |
| | Missing | 0 | 4 (1.6) |

[a] Includes patients with the event of 'MDS to AML'.

n = number of patients.

Data cutoff: 01 Dec 2016.

Patients may be counted more than once across SPM subcategories.

**Table 2.7.3.1-9: Outcome of Second Primary Malignancies: NDMM Studies**

| SPM | | TE NDMM | | | | | | TNE NDMM | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | IFM 2005-02 | | CALGB 100104 | | GIMEMA | | MM-020 | | | MM-015 | | |
| | | Len N = 306 | Placebo N = 302 | Len N = 224 | Placebo N = 221 | Len N = 56 | Control N = 79 | Rd N = 532 | Rd18 N = 540 | MPT N = 541 | MPR+R N = 150 | MPR+p N = 152 | MPp+p N = 153 |
| | | n (%) | | | | | | | | | | | |
| **INVASIVE** | | | | | | | | | | | | | |
| **Haematologic Malignancies** | | | | | | | | | | | | | |
| AML[a] | Death | 5 (1.6) | 3 (1.0) | 1 (0.4) | 0 | 0 | 0 | 0 | 0 | 2 (0.4) | 3 (2.0) | 3 (2.0) | 0 |
| | Not recovered/ not resolved | 0 | 0 | 2 (0.9) | 0 | 0 | 0 | 1 (0.2) | 1 (0.2) | 2 (0.4) | 0 | 1 (0.7) | 1 (0.7) |
| | Ongoing at death | 1 (0.3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.7) | 0 | 0 |
| | Unknown/ missing | 0 | 0 | 4 (1.8) | 0 | 0 | 0 | 0 | 0 | 2 (0.4) | 1 (0.7) | 1 (0.7) | 0 |
| MDS | Death | Death | 1 (0.3) | 2 (0.7) | 0 | 1 (0.5) | 0 | 1 (0.2) | 0 | 1 (0.2) | 1 (0.7) | 1 (0.7) | 1 (0.7) |
| | Not recovered/ not resolved | Not recovered /not resolved | 3 (1.0) | 1 (0.3) | 1 (0.4) | 0 | 0 | 0 | 1 (0.2) | 5 (0.9) | 2 (1.3) | 1 (0.7) | 0 |
| | Recovered/ resolved | Recovered/ resolved | 0 | 0 | 0 | 1 (0.5) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Unknown/ missing | Unknown/ missing | 0 | 0 | 3 (1.3) | 2 (0.9) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Death | 3 (1.0) | 1 (0.3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Table 2.7.3.1-9: Outcome of Second Primary Malignancies: NDMM Studies**

| SPM | | TE NDMM | | | | | | TNE NDMM | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | IFM 2005-02 | | CALGB 100104 | | GIMEMA | | MM-020 | | | MM-015 | | |
| | | Len N = 306 | Placebo N = 302 | Len N = 224 | Placebo N = 221 | Len N = 56 | Control N = 79 | Rd N = 532 | Rd18 N = 540 | MPT N = 541 | MPR+R N = 150 | MPR+p N = 152 | MPp+p N = 153 |
| | | n (%) | | | | | | | | | | | |
| B-cell Malignancies | Recovering/ resolving | 2 (0.7) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Not recovered/ not resolved | 2 (0.7) | 0 | 1 (0.4) | 1 (0.5) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Unknown/ missing | 4 (1.3) | 1 (0.3) | 3 (1.3) | 2 (0.9) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Other haematologic malignancies | Death | 0 | 1 (0.3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Recovered/ resolved | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.7) | 0 | 0 |
| | Not recovered/ not resolved | 1 (0.3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Unknown/ missing | 0 | 0 | 0 | 1 (0.5) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Solid Tumours** | Death | 2 (0.7) | 1 (0.3) | 1 (0.4) | 0 | 1 (1.8) | 0 | 3 (0.6) | 3 (0.6) | 5 (0.9) | 2 (1.3) | 4 (2.6) | 0 |
| | Recovered with sequelae | 0 | 1 (0.3) | 0 | 0 | 0 | 0 | 0 | 3 (0.6) | 0 | 0 | 0 | 0 |

**Table 2.7.3.1-9: Outcome of Second Primary Malignancies: NDMM Studies**

| SPM | | TE NDMM | | | | | | TNE NDMM | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | IFM 2005-02 | | CALGB 100104 | | GIMEMA | | MM-020 | | | MM-015 | | |
| | | Len N = 306 | Placebo N = 302 | Len N = 224 | Placebo N = 221 | Len N = 56 | Control N = 79 | Rd N = 532 | Rd18 N = 540 | MPT N = 541 | MPR+R N = 150 | MPR+p N = 152 | MPp+p N = 153 |
| | | n (%) | | | | | | | | | | | |
| | Recovered/ resolved | 6 (2.0) | 3 (1.0) | 0 | 1 (0.5) | 2 (3.6) | 1 (1.3) | 3 (0.6) | 9 (1.7) | 5 (0.9) | 0 | 0 | 0 |
| | Recovering/ resolving | 5 (1.6) | 3 (1.0) | 0 | 0 | 1 (1.8) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Not recovered/ not resolved | 7 (2.3) | 4 (1.3) | 1 (0.4) | 0 | 1 (1.8) | 1 (1.3) | 5 (0.9) | 5 (0.9) | 3 (0.6) | 1 (0.7) | 3 (2.0) | 0 |
| | Ongoing at death | 1 (0.3) | 1 (0.3) | 0 | 0 | 0 | 0 | 1 (0.2) | 2 (0.4) | 2 (0.4) | 1 (0.7) | 1 (0.7) | 0 |
| | Unknown/ missing | 0 | 0 | 15 (6.7) | 9 (4.1) | 0 | 0 | 3 (0.6) | 7 (1.3) | 0 | 1 (0.7) | 3 (2.0) | 4 (2.6) |
| **NON-INVASIVE** | | | | | | | | | | | | | |
| **NMSC** | Death | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Recovered/ resolved | 8 (2.6) | 5 (1.7) | 2 (0.9) | 4 (1.8) | 1 (1.8) | 1 (1.3) | 18 (3.4) | 13 (2.4) | 17 (3.1) | 1 (0.7) | 5 (3.3) | 6 (3.9) |
| | Recovering/ resolving | 2 (0.7) | 1 (0.3) | 1 (0.4) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Not recovered/not resolved | 0 | 1 (0.3) | 3 (1.3) | 1 (0.5) | 0 | 0 | 1 (0.2) | 2 (0.4) | 2 (0.4) | 1 (0.7) | 0 | 0 |
| | Ongoing at death | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.2) | 0 | 0 | 0 | 0 | 0 |
| | Missing | 0 | 0 | 6 (2.7) | 4 (1.8) | 0 | 0 | 2 (0.4) | 2 (0.4) | 2 (0.4) | 2 (1.3) | 1 (0.7) | 2 (1.3) |

[a] For all TE NDMM studies, patients with the event of 'MDS to AML' were included in this category.

Data cutoff: IFM 2005-02: 01 Mar 2015; CALGB 100104: 01 Mar 2015; GIMEMA: 01 Mar 2015.
n = number of patients. Patients may be counted more than once across SPM subcategories.

## Table 2.7.3.1-10: Outcome of Second Primary Malignancies: RRMM

| **SPM** | | **MM-009 and MM-010**[a] | |
|---|---|---|---|
| | | **Len/Dex N = 352** | **Len/Dex N = 352** |
| | | **n (%)** | |
| **INVASIVE** | | | |
| **Haematologic Malignancies** | | | |
| MDS | Unknown | 2 (0.6) | 0 |
| **Solid Tumours** | Recovered/resolved | 1 (0.3) | 0 |
| | Recovering/resolving | 0 | 0 |
| | Not recovered/not resolved | 3 (0.8) | 0 |
| | Unknown | 2 (0.6) | 2 (0.6) |
| **NON-INVASIVE** | | | |
| **NMSC** | Death | 0 | 0 |
| | Recovered/resolved | 2 (0.6) | 1 (0.3) |
| | Recovering/resolving | 0 | 0 |
| | Not recovered/not resolved | 0 | 0 |
| | Unknown | 9 (2.5) | 1 (0.3) |

[a] Incidence between arms was not adjusted for actual time on treatment (mean treatment duration 44 weeks [Lex/Dex]).

n = number of patients.

Data cutoff: MM-009: 23 Jul 2008; MM-010: 02 Mar 2008

**Table 2.7.3.1-11: Outcome of Second Primary Malignancies: MDS and Lymphoma Studies**

| SPM | | MDS | | | | Lymphoma | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | MDS-003[a] | MDS-004 (Dose Group as Randomised)[b] | | | MCL-002 | | MCL-001 | NHL-002 | NHL-003 | NHL-007 | | NHL-008 |
| | | Len (10 mg) N = 148 | Len (10 mg) N = 69 | Len (5 mg) N = 69 | Placebo[c] N = 67 | Len N = 167 | Control N = 83 | Len N = 134 | Len N = 49 | Len N = 217 | PBO+ Rit N = 148 | Len+ Rit N = 146 | Len+ Rit N = 177 |
| | | n (%) | | | | | | | | | | | |
| **INVASIVE** | | | | | | | | | | | | | |
| **Haematologic Malignancies** | | | | | | | | | | | | | |
| AML | Patient died[d] | 35 (23.8) | 14 (20.3) | 23 (33.3) | 25 (37.3) | NA | NA | NA | NA | NA | 1 (0.7) | 0 | 0 |
| | Patient alive[e] | 2 (1.4) | 2 (2.9) | 1 (1.4) | 1 (1.5) | NA | NA | NA | NA | NA | 0 | 1 (0.7) | 0 |
| | Not recovered/not resolved | NA | NA | NA | NA | 0 | 0 | 1 (0.7) | 0 | 0 | 0 | 1 (0.7) | 0 |
| | Recovered/ resolved | NA | NA | NA | NA | 0 | 0 | 0 | 0 | 1 (0.5) | 0 | 0 | 0 |
| MDS | Not recovered/not resolved | NA | NA | NA | NA | 1 (0.6) | 0 | 0 | 0 | 1 (0.5) | 0 | 0 | 0 |
| | Ongoing at death | NA | NA | NA | NA | 0 | 0 | 1 (0.7) | 0 | 0 | 0 | 0 | 0 |
| | Death | 0 | 0 | 0 | 0 | 1 (0.6) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Table 2.7.3.1-11: Outcome of Second Primary Malignancies: MDS and Lymphoma Studies**

| SPM | | MDS | | | | Lymphoma | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | MDS-003[a] | MDS-004 (Dose Group as Randomised)[b] | | | MCL-002 | | MCL-001 | NHL-002 | NHL-003 | NHL-007 | | NHL-008 |
| | | Len (10 mg) N = 148 | Len (10 mg) N = 69 | Len (5 mg) N = 69 | Placebo[c] N = 67 | Len N = 167 | Control N = 83 | Len N = 134 | Len N = 49 | Len N = 217 | PBO+ Rit N = 148 | Len+ Rit N = 146 | Len+ Rit N = 177 |
| | | n (%) | | | | | | | | | | | |
| B-cell Malignancies | Resolved/recovered with/without sequelae | 1 (0.7) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Not recovered/not resolved | 0 | 0 | 0 | 0 | 0 | 1 (1.2) | 0 | 0 | 0 | 0 | 0 | 0 |
| | Unknown/ missing | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Other haematologic malignancies | Death | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Resolved/ recovered with/without sequelae | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Not recovered/not resolved | 1 (0.7) | 0 | 0 | 0 | | | | | | 0 | 0 | 1 (0.6) |
| | Ongoing at death | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.7) | 0 | 0 | 0 | 0 | 0 |

**Table 2.7.3.1-11: Outcome of Second Primary Malignancies: MDS and Lymphoma Studies**

| SPM | | MDS | | | | Lymphoma | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | MDS-003[a] | MDS-004 (Dose Group as Randomised)[b] | | | MCL-002 | | MCL-001 | NHL-002 | NHL-003 | NHL-007 | | NHL-008 |
| | | Len (10 mg) N = 148 | Len (10 mg) N = 69 | Len (5 mg) N = 69 | Placebo[c] N = 67 | Len N = 167 | Control N = 83 | Len N = 134 | Len N = 49 | Len N = 217 | PBO+ Rit N = 148 | Len+ Rit N = 146 | Len+ Rit N = 177 |
| | | n (%) | | | | | | | | | | | |
| | Unknown/ missing | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Solid Tumours** | Death | 2 (1.4) | 0 | 1 (1.4) | 1 (1.5) | 0 | 1 (1.2) | 0 | 0 | 1 (0.5) | 0 | 0 | 0 |
| | Resolved/ recovered with/without sequelae | 2 (1.4) | 2 (2.9) | 0 | 0 | NA | NA | NA | NA | NA | 0 | 0 | 0 |
| | Recovered/ resolved | NA | NA | NA | NA | 2 (1.2) | 1 (1.2) | 1 (0.7) | 0 | 0 | 3 (2.0) | 1 (0.7) | 0 |
| | Recovered with sequelae | 0 | 1 (1.4) | 0 | 0 | 1 (0.6) | 0 | 1 (0.7) | 0 | 0 | 0 | 0 | 0 |
| | Not recovered/not resolved | 0 | 1 (1.4) | 1 (1.4) | 1 (1.5) | 1 (0.6) | 1 (1.2) | 3 (2.2) | 2 (4.1) | 0 | 0 | 1 (0.7) | 1 (0.6) |
| | Unknown/missing | 3 (2.0) | 0 | 2 (2.9) | 0 | 0 | 0 | 0 | 0 | 2 (0.9) | 0 | 0 | 0 |
| **NMSC** | Death | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Resolved/recovered with/without sequelae | 0 | 0 | 0 | 0 | NA | NA | NA | NA | NA | 0 | 0 | 8 (4.5) |

## Table 2.7.3.1-11: Outcome of Second Primary Malignancies: MDS and Lymphoma Studies

| SPM | | MDS | | | | Lymphoma | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | MDS-003[a] | MDS-004 (Dose Group as Randomised)[b] | | | MCL-002 | | MCL-001 | NHL-002 | NHL-003 | NHL-007 | | NHL-008 |
| | | Len (10 mg) N = 148 | Len (10 mg) N = 69 | Len (5 mg) N = 69 | Placebo[c] N = 67 | Len N = 167 | Control N = 83 | Len N = 134 | Len N = 49 | Len N = 217 | PBO+ Rit N = 148 | Len+ Rit N = 146 | Len+ Rit N = 177 |
| | | n (%) | | | | | | | | | | | |
| | Recovered/resolved | NA | NA | NA | NA | 4 (2.4) | 1 (1.2) | 6 (4.5) | 0 | 3 (1.4) | 2 (1.4) | 2 (1.4) | 0 |
| | Not recovered/not resolved | 0 | 0 | 0 | 0 | 1 (0.6) | 0 | 1 (0.7) | 0 | 0 | 0 | 1 (0.7) | 0 |
| | Unknown/missing | 6 (4.1) | 1 (1.4) | 1 (1.4) | 0 | 0 | 0 | 0 | 0 | 3 (1.4) | 0 | 0 | 0 |

[a] Median time on treatment was 52.5 weeks.

[b] For Study MDS-004, the analysis of SPM includes data from the open label phase as well as the double blind phase.

[c] Patients could cross over to lenalidomide 5 mg after 16 weeks of placebo treatment.

[d] Survival status is provided for 147 patients because 1 patient in MDS-003 had AML at baseline and is therefore not included in the analysis.

N = number of patients; NA = not applicable.

Note: there were no AEs of B-cell malignancy in Study MDS-004.

Data cutoff: MCL-001: 21 Mar 2014; MCL-002: 07 Mar 2014; NHL-002: 23 Jun 2008; NHL-003: 25 Mar 2013; MDS-003 27 Aug 2008; MDS-004: 26 Nov 2012; NHL-007: 22 Jun 2018; NHL-008: 01 May 2017.

Patients may be counted more than once across SPM subcategories.

## Table 2.7.3.1-12: Severity and Nature of Risk of Second Primary Malignancies: NDMM RVd

| **SPM** | | **SWOG S0777** | |
|---|---|---|---|
| | | **Arm B (RVd) N = 262** | **Arm A (Rd) N = 256** |
| | | **n (%)** | |
| **INVASIVE** | | | |
| **Haematologic Malignancies** | | | |
| AML[a] | All SPM | 0 | 0 |
| | Grade 3 or 4 | 0 | 0 |
| | SPM leading to discontinuation | NC | NC |
| | SPM leading to dose interruption | NC | NC |
| | SPM leading to dose reduction | NC | NC |
| B-cell Malignancies | All SPM | 0 | 2 (0.8) |
| | Grade 3 or 4 | 0 | 2 (0.8) |
| | SPM leading to discontinuation | NC | NC |
| | SPM leading to dose interruption | NC | NC |
| | SPM leading to dose reduction | NC | NC |
| MDS | All SPM | 2 (0.8) | 1 (0.4) |
| | Grade 3 or 4 | 1 (0.4) | 1 (0.4) |
| | SPM leading to discontinuation | NC | NC |
| | SPM leading to dose interruption | NC | NC |
| | SPM leading to dose reduction | NC | NC |
| **Solid Tumours** | All SPM | 8 (3.1) | 10 (3.9) |
| | Grade 3 or 4 | 5 (1.9) | 6 (2.3) |
| | SPM leading to discontinuation | NC | NC |
| | SPM leading to dose interruption | NC | NC |
| | SPM leading to dose reduction | NC | NC |
| **NON-INVASIVE** | | | |
| **NMSC** | All SPM | 11 (4.2) | 7 (2.7) |
| | Grade 3 or 4 | 6 (2.3) | 2 (0.8) |
| | SPM leading to discontinuation | NC | NC |
| | SPM leading to dose interruption | NC | NC |
| | SPM leading to dose reduction | NC | NC |

[a] Includes patients with the event of 'MDS to AML'.

n = number of patients; NC = not collected.
Data cutoff: 01 Dec 2016.
Patients may be counted more than once across SPM subcategories.

**Table 2.7.3.1-13: Severity and Nature of Risk of Second Primary Malignancies: NDMM Studies**

| SPM | | TE NDMM | | | | | | TNE NDMM | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | IFM 2005-02 | | CALGB 100104 | | GIMEMA | | MM-020 | | | MM-015 | | |
| | | Len N = 306 | Placebo N = 302 | Len N = 224 | Placebo N = 221 | Len N = 56 | Control N = 79 | Rd N = 532 | Rd18 N = 540 | MPT N = 541 | MPR+R N = 150 | MPR+p N = 152 | MPp+p N = 153 |
| | | n (%) | | | | | | | | | | | |
| **INVASIVE** | | | | | | | | | | | | | |
| **Haematologic Malignancies** | | | | | | | | | | | | | |
| AML[a] | All SPM | 6 (2.0) | 3 (1.0) | 7 (3.1) | 0 | 0 | 0 | 1 (0.2) | 1 (0.2) | 6 (1.1) | 5 (3.3) | 5 (3.3) | 1 (0.7) |
| | Grade 3 or 4 | 4 (1.3) | 2 (0.7) | 0 | 0 | 0 | 0 | 1 (0.2) | 0 | 5 (0.9) | 4 (2.7) | 3 (2.0) | 1 (0.7) |
| | SPM leading to discontinuation | 2 (0.7) | 2 (0.7) | NC | NC | NC | NC | 1 (0.2) | 0 | 0 | 4 (2.7) | 0 | 0 |
| | SPM leading to dose interruption | 0 | 0 | NC | NC | NC | NC | 0 | 0 | 0 | 0 | 0 | 0 |
| | SPM leading to dose reduction | NC | NC | NC | NC | NC | NC | 0 | 0 | 0 | 0 | 0 | 0 |
| MDS | All SPM | 4 (1.3) | 3 (1.0) | 4 (1.8) | 4 (1.8) | 0 | 0 | 1 (0.2) | 1 (0.2) | 6 (1.1) | 3 (2.0) | 2 (1.3) | 1 (0.7) |
| | Grade 3 or 4 | 2 (0.7) | 2 (0.7) | 2 (0.9) | 1 (0.5) | 0 | 0 | 1 (0.2) | 0 | 5 (0.9) | 3 (2.0) | 1 (0.7) | 0 |
| | SPM leading to discontinuation | 0 | 0 | NC | NC | 0 | 0 | 1 (0.2) | 0 | 0 | 1 (0.7) | 1 (0.7) | 0 |
| | SPM leading to dose interruption | 0 | 0 | NC | NC | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | SPM leading to dose reduction | 0 | 0 | NC | NC | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Table 2.7.3.1-13: Severity and Nature of Risk of Second Primary Malignancies: NDMM Studies**

| SPM | | TE NDMM | | | | | | TNE NDMM | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | IFM 2005-02 | | CALGB 100104 | | GIMEMA | | MM-020 | | | MM-015 | | |
| | | Len N = 306 | Placebo N = 302 | Len N = 224 | Placebo N = 221 | Len N = 56 | Control N = 79 | Rd N = 532 | Rd18 N = 540 | MPT N = 541 | MPR+R N = 150 | MPR+p N = 152 | MPp+p N = 153 |
| | | n (%) | | | | | | | | | | | |
| B-cell Malignancies | All SPM | 11 (3.6) | 2 (0.7) | 4 (1.8) | 3 (1.4) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Grade 3 or 4 | 9 (2.9) | 1 (0.3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | SPM leading to discontinuation | 1 (0.3) | 0 | NC | NC | NC | NC | 0 | 0 | 0 | 0 | 0 | 0 |
| | SPM leading to dose interruption | 0 | 0 | NC | NC | NC | NC | 0 | 0 | 0 | 0 | 0 | 0 |
| | SPM leading to dose reduction | NC | NC | NC | NC | NC | NC | 0 | 0 | 0 | 0 | 0 | 0 |
| Other haematologic malignancies | All SPM | 1 (0.3) | 1 (0.3) | 0 | 1 (0.5) | 0 | 0 | 0 | 0 | 0 | 1 (0.7) | 0 | 0 |
| | Grade 3 or 4 | 1 (0.3) | 1 (0.3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.7) | 0 | 0 |
| | SPM leading to discontinuation | 0 | 0 | NC | NC | 0 | 0 | 0 | 0 | 0 | 1 (0.7) | 0 | 0 |
| | SPM leading to dose interruption | 0 | 0 | NC | NC | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | SPM leading to dose reduction | 0 | 0 | NC | NC | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Table 2.7.3.1-13: Severity and Nature of Risk of Second Primary Malignancies: NDMM Studies**

| SPM | | TE NDMM | | | | | | TNE NDMM | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | IFM 2005-02 | | CALGB 100104 | | GIMEMA | | MM-020 | | | MM-015 | | |
| | | Len N = 306 | Placebo N = 302 | Len N = 224 | Placebo N = 221 | Len N = 56 | Control N = 79 | Rd N = 532 | Rd18 N = 540 | MPT N = 541 | MPR+R N = 150 | MPR+p N = 152 | MPp+p N = 153 |
| | | n (%) | | | | | | | | | | | |
| **Solid Tumours** | All SPM | 21 (6.9) | 13 (4.3) | 17 (7.6) | 10 (4.5) | 5 (8.9) | 2 (2.5) | 15 (2.8) | 29 (5.4) | 15 (2.8) | 5 (3.3) | 11 (7.2) | 4 (2.6) |
| | Grade 3 or 4 | 17 (5.6) | 10 (3.3) | 0 | 1 (0.5) | NC | NC | 12 (2.3) | 20 (3.7) | 4 (0.7) | 4 (2.7) | 6 (3.9) | 2 (1.3) |
| | SPM leading to discontinuation | 3 (1.0) | 1 (0.3) | NC | NC | NC | NC | 5 (0.9) | 3 (0.6) | 0 | 2 (1.3) | 3 (2.0) | 1 (0.7) |
| | SPM leading to dose interruption | 1 (0.3) | 0 | NC | NC | NC | NC | 2 (0.4) | 4 (0.7) | 0 | 0 | 0 | 0 |
| | SPM leading to dose reduction | 0 | 0 | NC | NC | NC | NC | 0 | 0 | 0 | 0 | 0 | 0 |
| **NON-INVASIVE** | | | | | | | | | | | | | |
| **NMSC** | All SPM | 10 (3.3) | 7 (2.3) | 12 (5.4) | 9 (4.1) | 1 (1.8) | 1 (1.3) | 22 (4.1) | 17 (3.1) | 21 (3.9) | 4 (2.7) | 6 (3.9) | 8 (5.2) |
| | Grade 3 or 4 | 8 (2.6) | 5 (1.7) | 1 (0.4) | 2 (0.9) | NC | NC | 10 (1.9) | 12 (2.2) | 3 (0.6) | 2 (1.3) | 4 (2.6) | 5 (3.3) |
| | SPM leading to discontinuation | 0 | 0 | NC | NC | NC | NC | 1 (0.2) | 1 (0.2) | 0 | 1 (0.7) | 0 | 0 |
| | SPM leading to dose interruption | 0 | 1 (0.3) | NC | NC | NC | NC | 1 (0.2) | 0 | 0 | 0 | 0 | 2 (1.3) |

## Table 2.7.3.1-13: Severity and Nature of Risk of Second Primary Malignancies: NDMM Studies

| SPM | | TE NDMM | | | | | | TNE NDMM | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | IFM 2005-02 | | CALGB 100104 | | GIMEMA | | MM-020 | | | MM-015 | | |
| | | Len N = 306 | Placebo N = 302 | Len N = 224 | Placebo N = 221 | Len N = 56 | Control N = 79 | Rd N = 532 | Rd18 N = 540 | MPT N = 541 | MPR+R N = 150 | MPR+p N = 152 | MPp+p N = 153 |
| | | n (%) | | | | | | | | | | | |
| | SPM leading to dose reduction | 0 | 0 | NC | NC | NC | NC | 0 | 0 | 0 | 0 | 0 | 0 |

[a] Patients with the event of 'MDS to AML' were included in this category.

n = number of patients; NC = not collected per study design.

Data cutoff: IFM 2005-02: 01 Mar 2015; CALGB 100104: 01 Mar 2015; GIMEMA: 01 Mar 2015; MM-020: 24 May 2013; MM-015: 30 Apr 2013.

Actions taken due to AEs (eg, treatment discontinued, dose reduced, dose interrupted) in Studies CALGB 100104 and GIMEMA, and AE grade in Study GIMEMA, were not collected on the CRF.

Patients may be counted more than once across SPM subcategories.

## Table 2.7.3.1-14: Severity and Nature of Risk Second Primary Malignancies: RRMM

| SPM | | MM-009 and MM-010[a] | |
|---|---|---|---|
| | | Len/Dex N = 352 | Len/Dex N = 352 |
| | | n (%) | |
| **INVASIVE** | | | |
| **Haematologic Malignancies** | | | |
| MDS | All SPM | 2 (0.6) | 0 |
| | Grade 3 or 4 | 2 (0.6) | 0 |
| | SPM leading to discontinuation | 0 | 0 |
| | SPM leading to dose interruption | 0 | 0 |
| | SPM leading to dose reduction | 0 | 0 |
| Other haematologic malignancies | All SPM | 0 | 0 |
| | Grade 3 or 4 | 0 | 0 |
| | SPM leading to discontinuation | 0 | 0 |
| | SPM leading to dose interruption | 0 | 0 |
| | SPM leading to dose reduction | 0 | 0 |
| **Solid Tumours** | All SPM | 6 (1.7) | 2 (0.6) |
| | Grade 3 or 4 | 6 (1.7) | 1 (0.3) |
| | SPM leading to discontinuation | 3 (0.8) | 0 |
| | SPM leading to dose interruption | 1 (0.3) | 0 |
| | SPM leading to dose reduction | 0 | 0 |
| **NON-INVASIVE** | | | |
| **NMSC** | All SPM | 11 (3.1) | 2 (0.6) |
| | Grade 3 or 4 | 4 (1.1) | 1 (0.3) |
| | SPM leading to discontinuation | 0 | 0 |
| | SPM leading to dose interruption | 3 (0.8) | 0 |
| | SPM leading to dose reduction | 0 | 0 |

[a] Incidence between arms was not adjusted for actual time on treatment (mean treatment duration 44 weeks [Len/Dex] versus 23 weeks [Placebo/Dex]).

n = number of patients

Data cutoff: MM-009: 23 Jul 2008; MM-010: 02 Mar 2008

**Table 2.7.3.1-15: Severity and Nature of Risk of Second Primary Malignancies: MDS and Lymphoma Studies**

| SPM | | MDS | | | | Lymphoma | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | MDS-003[a] | MDS-004 (Dose Group as Randomised)[b] | | | MCL-002 | | MCL-001 | NHL-002 | NHL-003 | NHL-007 | | NHL-008 |
| | | Len (10 mg) N = 148 | Len (10 mg) N = 69 | Len (5 mg) N = 69 | Placebo[c] N = 67 | Len N = 167 | Control N = 83 | Len N = 134 | Len N = 49 | Len N = 217 | PBO+ Rit N = 148 | Len+ Rit N = 146 | Len+ Rit N = 177 |
| | | n (%) | | | | | | | | | | | |
| **INVASIVE** | | | | | | | | | | | | | |
| **Haematologic Malignancies** | | | | | | | | | | | | | |
| - AML | All SPM | [d] | [d] | [d] | [d] | 0 | 0 | 1 (0.7) | 0 | 1 (0.5) | 1 (0.7) | 1 (0.7) | 0 |
| | Grade 3 or 4 | [d] | [d] | [d] | [d] | 0 | 0 | 1 (0.7) | 0 | 1 (0.5) | 1 (0.7) | 1 (0.7) | 0 |
| | SPM leading to discontinuation | [d] | [d] | [d] | [d] | 0 | 0 | 0 | 0 | 1 (0.5) | NC | NC | 0 |
| | SPM leading to dose interruption | [d] | [d] | [d] | [d] | 0 | 0 | 0 | 0 | 0 | NC | NC | 0 |
| | SPM leading to dose reduction | [d] | [d] | [d] | [d] | 0 | 0 | 0 | 0 | 0 | NC | NC | 0 |
| - MDS | All SPM | NA | NA | NA | NA | 1 (0.6) | 0 | 1 (0.7) | 0 | 1 (0.5) | 0 | 0 | 0 |
| | Grade 3 or 4 | NA | NA | NA | NA | 1 (0.6) | 0 | 0 | 0 | 1 (0.5) | 0 | 0 | 0 |
| | SPM leading to discontinuation | NA | NA | NA | NA | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Table 2.7.3.1-15: Severity and Nature of Risk of Second Primary Malignancies: MDS and Lymphoma Studies**

| SPM | | MDS | | | | Lymphoma | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | MDS-003[a] | MDS-004 (Dose Group as Randomised)[b] | | | MCL-002 | | MCL-001 | NHL-002 | NHL-003 | NHL-007 | | NHL-008 |
| | | Len (10 mg) N = 148 | Len (10 mg) N = 69 | Len (5 mg) N = 69 | Placebo[c] N = 67 | Len N = 167 | Control N = 83 | Len N = 134 | Len N = 49 | Len N = 217 | PBO+ Rit N = 148 | Len+ Rit N = 146 | Len+ Rit N = 177 |
| | | n (%) | | | | | | | | | | | |
| | SPM leading to dose interruption | NA | NA | NA | NA | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | SPM leading to dose reduction | NA | NA | NA | NA | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| B-cell Malignancies | All SPM | 1 (0.7) | 0 | 0 | 0 | 1 (0.6) | 1 (1.2) | 0 | 0 | 0 | 0 | 0 | 0 |
| | Grade 3 or 4 | 1 (0.7) | 0 | 0 | 0 | 1 (0.6) | 1 (1.2) | 0 | 0 | 0 | 0 | 0 | 0 |
| B-cell Malignancies (Continued) | SPM leading to discontinuation | 0 | 0 | 0 | 0 | 1 (0.6) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | SPM leading to dose interruption | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | SPM leading to dose reduction | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Table 2.7.3.1-15: Severity and Nature of Risk of Second Primary Malignancies: MDS and Lymphoma Studies**

| SPM | | MDS | | | | Lymphoma | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | MDS-003[a] | MDS-004 (Dose Group as Randomised)[b] | | | MCL-002 | | MCL-001 | NHL-002 | NHL-003 | NHL-007 | | NHL-008 |
| | | Len (10 mg) N = 148 | Len (10 mg) N = 69 | Len (5 mg) N = 69 | Placebo[c] N = 67 | Len N = 167 | Control N = 83 | Len N = 134 | Len N = 49 | Len N = 217 | PBO+ Rit N = 148 | Len+ Rit N = 146 | Len+ Rit N = 177 |
| | | n (%) | | | | | | | | | | | |
| Other haematologic malignancies | All SPM | 1 (0.7) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.6) |
| | Grade 3 or 4 | 1 (0.7) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.6) |
| | SPM leading to discontinuation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | SPM leading to dose interruption | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | SPM leading to dose reduction | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Solid Tumours** | All SPM | 7 (4.7) | 4 (5.8) | 4 (5.8) | 2 (3.0) | 4 (2.4) | 3 (3.6) | 5 (3.7) | 2 (4.1) | 4 (1.8) | 3 (2.0) | 2 (1.4) | 1 (0.6) |
| | Grade 3 or 4 | 5 (3.4) | 3 (4.3) | 1 (1.4) | 0 | 3 (1.8) | 0 | 4 (3.0) | 1 (2.0) | 2 (0.9) | 3 (2.0) | 1 (0.7) | 1 (0.6) |

**Table 2.7.3.1-15: Severity and Nature of Risk of Second Primary Malignancies: MDS and Lymphoma Studies**

| SPM | | MDS | | | | Lymphoma | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | MDS-003[a] | MDS-004 (Dose Group as Randomised)[b] | | | MCL-002 | | MCL-001 | NHL-002 | NHL-003 | NHL-007 | | NHL-008 |
| | | Len (10 mg) N = 148 | Len (10 mg) N = 69 | Len (5 mg) N = 69 | Placebo[c] N = 67 | Len N = 167 | Control N = 83 | Len N = 134 | Len N = 49 | Len N = 217 | PBO+ Rit N = 148 | Len+ Rit N = 146 | Len+ Rit N = 177 |
| | | n (%) | | | | | | | | | | | |
| | SPM leading to discontinuation | 0 | 0 | 0 | 0 | 1 (0.6) | 0 | 1 (0.7) | 0 | 2 (0.9) | NC | NC | 1 (0.6) |
| | SPM leading to dose interruption | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.7) | 0 | 0 | NC | NC | 0 |
| | SPM leading to dose reduction | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | NC | NC | 0 |
| **NON-INVASIVE** | | | | | | | | | | | | | |
| **NMSC** | All SPM | 6 (4.1) | 1 (1.4) | 1 (1.4) | 0 | 5 (3.0) | 1 (1.2) | 7 (5.2) | 0 | 6 (2.8) | 2 (1.4) | 3 (2.1) | 8 (4.5) |
| | Grade 3 or 4 | 1 (0.7) | 0 | 0 | 0 | 3 (1.8) | 1 (1.2) | 5 (3.7) | 0 | 5 (2.3) | 0 | 0 | 3 (1.7) |
| | SPM leading to discontinuation | 0 | 0 | 0 | 0 | | | | | | NC | NC | 0 |

**Table 2.7.3.1-15: Severity and Nature of Risk of Second Primary Malignancies: MDS and Lymphoma Studies**

| SPM | | MDS | | | | Lymphoma | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | MDS-003[a] | MDS-004 (Dose Group as Randomised)[b] | | | MCL-002 | | MCL-001 | NHL-002 | NHL-003 | NHL-007 | | NHL-008 |
| | | Len (10 mg) N = 148 | Len (10 mg) N = 69 | Len (5 mg) N = 69 | Placebo[c] N = 67 | Len N = 167 | Control N = 83 | Len N = 134 | Len N = 49 | Len N = 217 | PBO+ Rit N = 148 | Len+ Rit N = 146 | Len+ Rit N = 177 |
| | | n (%) | | | | | | | | | | | |
| | SPM leading to dose interruption | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.7) | 0 | 0 | NC | NC | 1 (0.6) |
| | SPM leading to dose reduction | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | NC | NC | 0 |

[a] Median time on treatment was 52.5 weeks.

[b] For Study MDS-004, the analysis of SPM includes data from the open label phase as well as the double blind phase.

[c] Patients could cross over to lenalidomide 5 mg after 16 weeks of placebo treatment.

[d] Severity of events is unknown for AML as most AML cases were captured during follow-up phase via phone contact.

n = number of patients; NC = not calculable as action information is not available for most patients.

Note: there were no AEs of B-cell malignancy in Study MDS-004.

Data cutoff: MCL-001: 21 Mar 2014; MCL-002: 07 Mar 2014; NHL-002: 23 Jun 2008; NHL-003: 25 Mar 2013; MDS-003 27 Aug 2008; MDS-004: 26 Nov 2012; NHL-007: 22 Jun 2018; NHL-008: 01 May 2017.

Patients may be counted more than once across SPM subcategories.

## Important Identified Risk: Tumour Flare Reaction (MCL and FL Indications)

The important identified risk of TFR is specific to lenalidomide-treated patients with lymphomas. The risk described below in Table 2.7.3.1-16 reflects data from the studies in MCL and FL only. There were no reports of TFR in the MM or MDS pivotal studies.

**Table 2.7.3.1-16: Important Identified Risk: Tumour Flare Reaction (MCL and FL Indications)**

| **Important Identified Risk Tumour Flare Reaction (MCL and FL Indications)** | |
|---|---|
| Potential mechanisms | Immune mediated responses have been postulated as an underlying mechanism that may be related to antitumour activity. In a case review of four patients using lenalidomide[139] the aetiology of tumour flare is hypothesised to be mediated through upregulation of B-cell activation markers including CD40, CD80, CD86, HLA-DR and CD95 expression in CLL cells. The effect of 10 or 20 mg lenalidomide on upregulation of CD80 molecules was studied in vitro[140] in CLL with attention to TFR, also referred to as cytokine release syndrome. Strong CD80 upregulation and T-cell activation predicted more severe side effects, manifesting in 83% of patients as cytokine release syndrome within 8 to 72 hours after the first dose of lenalidomide, and neither the severity of the cytokine release syndrome nor the degree of T-cell activation correlated with clinical response. Tumour flare reaction may correlate with response to treatment,[141] although this has not been reproduced[142] across all clinical trials describing the phenomenon. |
| Evidence source and strength of evidence | Based on clinical trial data, lenalidomide may increase the risk of TFR in patients with CLL and other lymphomas. |
| Characterization of risk | **Frequency with 95% CI**<br>**FL Studies:** |

| **Tumour Flare Reaction** | **NHL-007** | | **NHL-008** | **Pooled NHL-007 and NHL-008** |
|---|---|---|---|---|
| | **PBO+Rit** | **Len+Rit** | **Len+Rit** | **Len+Rit** |
| Total number of patients | 148 | 146 | 177 | 323 |
| Patients with ≥ 1 SAE | 0 | 1 | 1 | 2 |
| Patients with ≥ 1 AE | 1 | 19 | 7 | 26 |
| Incidence (% of patients) with ≥ 1 AE (95% CI) | 0.7 (0.0 to 3.7) | 13.0 (8.0 to 19.6) | 4.0 (1.6 to 8.0) | - |

Overall, in pooled Studies NHL-007 and NHL-008, TFR AEs were reported for 26 lenalidomide plus rituximab-treated patients.

In Study NHL-007, the proportion of FL patients experiencing at least one TFR event was higher among lenalidomide plus rituximab-treated patients than patients treated with rituximab plus placebo (risk ratio = 19.3 [95% CI: 2.6-143.9]).

In Study NHL-008, TFR AEs were reported for 4.0% of lenalidomide plus rituximab-treated patients.

**MCL Studies:**

## Table 2.7.3.1-16: Important Identified Risk: Tumour Flare Reaction (MCL and FL Indications)

**Important Identified Risk Tumour Flare Reaction (MCL and FL Indications)**

| Tumour Flare Reaction | MCL-002 | | All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003) |
|---|---|---|---|
| | Len | Control | |
| Total number of patients | 167 | 83 | 373 |
| Patients with ≥ 1 SAE | 1 | 0 | 1 |
| Patients with ≥ 1 AE | 16 | 0 | 30 |
| Incidence (% of patients) with ≥ 1 AE (95% CI) | 9.6 (5.6 to 15.1) | 0 | 8.0 (5.5 to 11.3) |

In Study MCL-002, TFR AEs were reported in the lenalidomide treatment group (9.6%), whereas no events were reported in the control group.

**Seriousness/Outcomes**

**FL Studies:**

SAE outcomes reported in the FL studies are summarised below.

| Outcome | NHL-007 | | NHL-008 | Pooled NHL-007 and NHL-008 |
|---|---|---|---|---|
| | PBO+Rit | Len+Rit | Len+Rit | Len+Rit |
| Total number of patients | 148 | 146 | 177 | 323 |
| Patients with ≥ 1 SAE | 0 | 1 (0.7) | 1 (0.6) | 2 (0.6) |
| Resolved | 0 | 1 (0.7) | 1 (0.6) | 2 (0.6) |

In Study NHL-007, TFR SAEs were reported for 1/146 (0.7%) lenalidomide plus rituximab-treated patient and 0/148 rituximab plus placebo-treated patients. No TFR SAEs had an outcome of death.

In Study NHL-008, TFR SAEs were reported for 1/177 (0.6%) lenalidomide plus rituximab-treated patients. No TFR SAEs had an outcome of death.

**MCL Studies:**

The outcomes of the TFR SAEs are summarised below.

| Outcome | MCL-002 | | All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003) |
|---|---|---|---|
| | Len | Control | |

## Table 2.7.3.1-16: Important Identified Risk: Tumour Flare Reaction (MCL and FL Indications)

**Important Identified Risk Tumour Flare Reaction (MCL and FL Indications)**

| | | | |
|---|---|---|---|
| Total number of patients | 167 | 83 | 373 |
| Patients with ≥ 1 SAE | 1 (0.6) | 0 | 1 (0.3) |
| Ongoing at death | 1 (0.6) | 0 | 1 (0.3) |

In Study MCL-002, 1 (0.6%) lenalidomide-treatment patient experienced a TFR SAE (PT tumour flare) that was ongoing at the time of the patient's death.

**Severity and Nature of Risk**

**FL Studies:**

Details of AEs pertaining to TFR that were reported in FL studies are summarised below.

| **Tumour Flare Reaction** | **NHL-007** | | **NHL-008** | **Pooled NHL-007 and NHL-008** |
|---|---|---|---|---|
| | **PBO+Rit** | **Len+Rit** | **Len+Rit** | **Len+Rit** |
| Total number of patients | 148 | 146 | 177 | 323 |
| All AEs | 1 | 19 | 7 | 26 |
| Grade 3 or 4 | 0 | 1 (0.7) | 0 | 1 (0.3) |
| AEs leading to discontinuation | 0 | 0 | 0 | 0 |
| AEs leading to dose interruption | 0 | 2 (1.4) | 1 (0.6) | 3 (0.9) |
| AEs leading to dose reduction | 0 | 0 | 0 | 0 |

In Study NHL-007, 1.4% of lenalidomide plus rituximab-treated patients experienced TFR AEs leading to dose interruption, and 0.7% of lenalidomide plus rituximab-treated patients experienced Grade 3 or 4 AEs of TFR. No lenalidomide plus rituximab-treated patients experienced TFR AEs leading to dose discontinuation or dose reduction. In the rituximab plus placebo arm, no patients had Grade 3 or 4 AEs of TFR, or TFR AEs leading to dose interruption, dose reduction and study treatment discontinuation.

In Study NHL-008, no Grade 3 or 4 AEs of TFR, or AEs leading to dose reduction and study treatment discontinuation were reported. TFR AEs leading to dose interruption were reported for 0.6% of lenalidomide plus rituximab-treated patients.

**MCL Studies:**

| | **MCL-002** | |
|---|---|---|

## Table 2.7.3.1-16: Important Identified Risk: Tumour Flare Reaction (MCL and FL Indications)

**Important Identified Risk Tumour Flare Reaction (MCL and FL Indications)**

| Tumour Flare Reaction | Len (N = 167) | Control (N = 83) | All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003) (N = 373) |
|---|---|---|---|
| All AEs | 16 (9.6) | 0 | 30 (8.0) |
| Grade 3 or 4 | 3 (1.8) | 0 | 3 (0.8) |
| AEs leading to discontinuation | 1 (0.6) | 0 | 1 (0.3) |
| AEs leading to dose interruption | 1 (0.6) | 0 | 1 (0.3) |
| AEs leading to dose reduction | 1 (0.6) | 0 | 1 (0.3) |

In Study MCL-002, Grade 3 or 4 TFR AEs were reported in 3 (1.8%) patients in the lenalidomide group and no patients in the control group. Tumour flare reaction AEs led to study treatment being permanently withdrawn, dose interruption and dose reduction in 1 (0.6%) lenalidomide-treated patient each. No patients in the control group had TFR AEs.

Risk factors and risk groups

Tumour flare reaction has been associated with greater tumour burden in CLL.[142] In Study MCL-002, in the final multivariate model, high MIPI score at diagnosis (p=0.084) and bulky disease at baseline (p=0.020) appeared to be strong and independent risk factors for TFR.

Preventability

When using steroids in the first days in CLL, there was a decrease in severity, but not in TFR incidence.[138,141]The frequency of TFR also appears to be lower when lenalidomide is used in combination with rituximab[143] and higher sequential treatment with ofatumumab.[144] A recommendation regarding careful monitoring and evaluation for TFR is included in the SmPC (SmPC, Section 4.4).

Impact on the risk-benefit balance of the product

Clinical manifestations of TFR can include sudden onset of painful, tender swelling of disease-involved lymph nodes, spleen, and/or liver along with a low-grade fever. Also, rash and a rise in the peripheral blood white cell count can occur.[145]

Generally, interruption or modification of lenalidomide dosing is not required in MCL, and use of non-steroidal, analgesic and anti-inflammatory drugs has been shown to be effective in cases when TFR does develop.[146]

Public health impact.

Tumour flare reaction is a side effect of cancer treatment that may mimic disease progression. Within the realm of haematologic malignancies, TFR is specific to lenalidomide treatment of CLL and B-cell lymphomas. Among patients with CLL, Chanan-Khan[141] reported 58% of 45 patients experienced TFR and Ferrajoli[142] reported 30% of 44 patients were affected following lenalidomide starting doses of 25 mg/day and 10 mg/day, respectively. The frequency of TFR among MCL patients

### Table 2.7.3.1-16: Important Identified Risk: Tumour Flare Reaction (MCL and FL Indications)

| Important Identified Risk Tumour Flare Reaction (MCL and FL Indications) | |
|---|---|
| | in a small Phase II study of lenalidomide was reported by Eve (2010) to be 12% (3/25 patients). Among 134 MCL patients treated with lenalidomide at 25 mg, 13 (10%) experienced Grade 1 or 2 TFR.[146] In this study, lenalidomide 25 mg (10 mg for CLcr 30 to 60 mL/min) was self-administered orally on Days 1 through 21 of each 28-day cycle until PD, intolerance, or voluntary withdrawal.<br><br>Tumour flare reaction has been reported in Hodgkin's disease,[147] but not in association with MM or myelodysplasia.[148] Most TFRs develop very early in the course of therapy and may mimic progression of disease (including increased absolute lymphocyte count); however, they subside over time and resolve within 2 weeks.<br><br>Tumour flare reaction is a common ADR of lenalidomide treatment (SmPC, Section 4.8). Tumour flare reaction is an important, transient and manageable adverse effect that may mimic disease progression and clinicians therefore need to be aware of this specific complication. Tumour flare reaction, however, can be quite confidently distinguished from progressing MCL based on its timing and clinical grounds (including signs of inflammatory reaction and the lack of nights sweats and weight loss), so that lenalidomide treatment is not discontinued unnecessarily. |
| Data source | Study NHL-007 and Study NHL-008 (13 Aug 2018); Study MCL-001 (20 Mar 2013); Study MCL-002 (07 Mar 2014); Study NHL-002 (23 Jun 2008); Study NHL-003 (27 Apr 2011). |
| MedDRA Terms | See Annex 7 |

## Important Identified Risk: Cardiac Failure

### Table 2.7.3.1-17: Important Identified Risk: Cardiac Failure

| Important Identified Risk Cardiac Failure | |
|---|---|
| Potential mechanisms | A mechanism by which lenalidomide could cause cardiac failure has not been identified. |
| Evidence source and strength of evidence | Based on clinical trial data, a higher incidence of cardiac failure has been observed; the reason for this is not clear. |
| Characterization of risk | **Frequency with 95% CI**<br>**FL Studies:** |

| Cardiac Failure | NHL-007 | | NHL-008 | Pooled NHL-007 and NHL-008 |
|---|---|---|---|---|
| | PBO+Rit | Len+Rit | Len+Rit | Len+Rit |
| Total number of patients | 148 | 146 | 177 | 323 |
| Patients with ≥ 1 SAE | 0 | 0 | 0 | 0 |
| Patients with ≥ 1 AE | 2 | 0 | 1 | 1 |

## Table 2.7.3.1-17: Important Identified Risk: Cardiac Failure

**Important Identified Risk Cardiac Failure**

| | | | | |
|---|---|---|---|---|
| Incidence (% of patients) with ≥ 1 AE (95% CI) | 1.4 (0.2 to 4.8) | 0 | 0.6 (0.0 to 3.1) | - |

Overall, in pooled Studies NHL-007 and NHL-008, cardiac failure AEs were reported for 1 (0.3%) lenalidomide plus rituximab-treated patient.

In Study NHL-007, no FL patients treated with lenalidomide plus rituximab-treated patients experienced cardiac failure events.

In Study NHL-008, cardiac failure events were reported for 1(0.6%) lenalidomide plus rituximab-treated patient.

**NDMM RVd Study:**

| **Cardiac Failure** | **SWOG S0777** | |
|---|---|---|
| | **Arm B (RVd)** | **Arm A (Rd)** |
| Total number of patients | 262 | 256 |
| Patients with ≥ 1 SAE | 2 | 3 |
| Patients with ≥ 1 AE | 6 | 3 |
| Incidence (% of patients) with ≥ 1 AE (95% CI) | 2.3 (0.8 to 4.9) | 1.2 (0.2 to 3.4) |

In Study SWOG S0777, the proportion of patients experiencing at least one cardiac failure event was greater among patients treated with RVd than patients treated with Rd (risk ratio = 1.95 [95% CI: 0.49-7.73]).

**TE NDMM Studies:**

| **Cardiac Failure** | **CALGB 100104 Maintenance** | | **IFM 2005-02 Maintenance** | |
|---|---|---|---|---|
| | **Len** | **Placebo** | **Len** | **Placebo** |
| Total number of patients | 224 | 221 | 293 | 280 |
| Patients with ≥ 1 SAE | 0 | 0 | 0 | 1 |
| Patients with ≥ 1 AE | 0 | 1 | 0 | 2 |
| Incidence (% of patients) with ≥ 1 AE (95% CI)[a] | 0 | 0.5 (0.0 to 2.5) | 0 | 0.7 (0.1 to 2.6) |

[a] Incidence was not adjusted for time on treatment.

In Study CALGB 100104, cardiac failure AEs were reported in 1 (0.5%) patient treated with placebo and no lenalidomide-treated patients. In Study IFM 2005-02, cardiac failure AEs were reported in 2 (0.7%) patients treated with placebo; no lenalidomide-treated patients experienced cardiac failure AEs.

TNE **NDMM Studies:**

| | **MM-020** | **MM-015** |
|---|---|---|

## Table 2.7.3.1-17: Important Identified Risk: Cardiac Failure

**Important Identified Risk Cardiac Failure**

| Cardiac Failure | Rd | Rd18 | MPT | MPR+R | MPR+p | MPp+p |
|---|---|---|---|---|---|---|
| Total number of patients | 532 | 540 | 541 | 150 | 152 | 153 |
| Patients with ≥ 1 SAE | 26 | 21 | 17 | 6 | 2 | 2 |
| Patients with ≥ 1 AE | 47 | 28 | 27 | 7 | 4 | 4 |
| Incidence (% of patients) with ≥ 1 AE (95% CI)[a] | 8.8 (6.6 to 11.6) | 5.2 (3.5 to 7.4) | 5.0 (3.3 to 7.2) | 4.7 (1.9 to 9.4) | 2.6 (0.7 to 6.6) | 2.6 (0.7 to 6.6) |

[a] Incidence was not adjusted for time on treatment.

In Study MM-020, the proportion of patients experiencing at least one cardiac failure event was greater among lenalidomide-treated patients than patients treated with control (risk ratio = 1.40 [95% CI: 0.91-2.15]; p = 0.122). Note that treatment duration was longer in Arm Rd compared with Arms Rd18 and MPT (see Section 2.3.3). In Study MM-015, the proportion of patients experiencing at least one cardiac failure event was greater among lenalidomide-treated patients than patients treated with control (risk ratio = 1.39 [95% CI: 0.45-4.30]; p = 0.564).

**RRMM Studies:**

| Cardiac Failure | MM-009 and MM-010 | |
|---|---|---|
| | Len/Dex | PBO/Dex |
| Total number of patients | 353 | 350 |
| Patients with ≥ 1 SAE | 6 | 4 |
| Patients with ≥ 1 AE | 12 | 8 |
| Incidence (% of patients) with ≥ 1 AE (95% CI)[a] | 3.4 (1.8 to 5.9) | 2.3 (1.0 to 4.5) |

[a] Incidence between arms was not adjusted for actual time on treatment (mean treatment duration 44 weeks [Len/Dex] versus 23 weeks [PBO/Dex]).

The risk ratio versus placebo is 1.49 (95% CI: 0.62–3.59 p = 0.39).

**Del 5q MDS Studies:**

| Cardiac Failure | MDS-003[a] | MDS-004[b] | | |
|---|---|---|---|---|
| | Len (10 mg) | Len (10 mg) | Len (5 mg) | PBO[c] |
| Total number of patients | 148 | 69 | 69 | 67 |
| Patients with ≥ 1 SAE | 8 | 1 | 2 | 0 |
| Patients with ≥ 1 AE | 11 | 2 | 3 | 1 |

## Table 2.7.3.1-17: Important Identified Risk: Cardiac Failure

**Important Identified Risk Cardiac Failure**

| | | | | |
|---|---|---|---|---|
| Incidence (% of patients) with ≥ 1 AE (95% CI) | 7.4 (3.8 to 12.9) | 2.9 (0.4 to 10.1) | 4.3 (0.9 to 12.2) | 1.5 (0.0 to 8.0) |

[a] Median time on treatment was 52.5 weeks.

[b] Median time on treatment was 50.3 weeks in the 10 mg group, 18.0 weeks in the 5 mg group and 16.0 weeks in the PBO group.

[c] Data in PBO group is from the first 16 weeks of the double-blind phase.

In Study MDS-004, no appreciable difference in risk of cardiac failure was seen across all treatment groups (1.5% to 4.3%).

**MCL Studies:**

| **Cardiac Failure** | **MCL-002** | | **All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003)** |
|---|---|---|---|
| | **Len** | **Control** | |
| Total number of patients | 167 | 83 | 373 |
| Patients with ≥ 1 SAE | 4 | 2 | 5 |
| Patients with ≥ 1 AE | 9 | 2 | 14 |
| Incidence (% of patients) with ≥ 1 AE (95% CI) | 5.4 (2.5 to 10.0) | 2.4 (0.3 to 8.4) | 3.8 (2.1 to 6.2) |

In Study MCL-002, the proportion of patients experiencing at least one cardiac failure event was greater among lenalidomide-treated patients than patients treated with control (risk ratio = 2.24 [95% CI: 0.49-10.12]; p = 0.296).

**Seriousness/Outcomes**

**FL Studies:**

In FL patients in Studies NHL-007 and NHL-008, no cardiac failure SAE was reported.

**NDMM RVd Study:**

The outcomes of the cardiac failure SAEs are summarised below.

| **Outcome** | **SWOG S0777** | |
|---|---|---|
| | **Arm B (RVd)** | **Arm A (Rd)** |
| Patients with ≥ 1 SAE | 2 (0.8) | 3 (1.2) |
| Death | 0 | 0 |
| Ongoing at death | 0 | 1 (0.4) |
| Recovered/resolved | 1 (0.4) | 0 |
| Recovered/resolved with sequelae | 1 (0.4) | 0 |

## Table 2.7.3.1-17: Important Identified Risk: Cardiac Failure

**Important Identified Risk Cardiac Failure**

| | | |
|---|---|---|
| Recovering/resolving | 0 | 1 (0.4) |
| Unknown | 0 | 1 (0.4) |

In Study SWOG S0777, cardiac failure SAEs were reported for 2/262 (0.8%) patients treated with RVd (PTs: cardiac failure) and 3/256 (1.2%) patients treated with Rd (PTs: cardiac failure and cardiac failure congestive). No cardiac failure SAEs had an outcome of death.

**TE NDMM Studies:**

No cardiac failure SAEs were reported in Study CALGB 100104. One (0.4%) patient treated with placebo in Study IFM 2005-02 experienced a cardiac failure SAE, with an outcome of recovering/resolving.

**TNE NDMM Studies:**

The outcomes of the cardiac failure SAEs are summarised below.

| **Outcome** | **MM-020** | | | **MM-015** | | |
|---|---|---|---|---|---|---|
| | **Rd N = 532** | **Rd18 N = 540** | **MPT N = 541** | **MPR+R N = 150** | **MPR+p N = 152** | **MPp+p N = 153** |
| Patients with ≥ 1 SAE | 26 (4.9) | 21 (3.9) | 17 (3.1) | 6 (4.0) | 2 (1.3) | 2 (1.3) |
| Death | 5 (0.9) | 3 (0.6) | 2 (0.4) | 2 (1.3) | 0 | 0 |
| Ongoing at death | 2 (0.4) | 0 | 1 (0.2) | 0 | 1 (0.7) | 0 |
| Recovered/ resolved | 16 (3.0) | 12 (2.2) | 11 (2.0) | 3 (2.0) | 1 (0.7) | 0 |
| Recovered with sequelae | 0 | 1 (0.2) | 2 (0.4) | 1 (0.7) | 0 | 0 |
| Not recovered/not resolved | 1 (0.2) | 3 (0.6) | 0 | 0 | 0 | 0 |
| Missing | 2 (0.4) | 2 (0.4) | 1 (0.2) | 0 | 0 | 2 (1.3) |

In Study MM-020, cardiac failure SAEs were experienced by a comparable proportion of patients in the Rd18 and MPT arms of the study (3.9% and 3.1%, respectively) and a slightly higher proportion in the Rd arm of the study (4.9%). PTs reported for more than 2 patients overall were acute pulmonary oedema, cardiac failure, cardiac failure congestive, cardiogenic shock and pulmonary oedema. An outcome of death was reported for SAEs of cardiac failure in 5 (0.9%), 3 (0.6%) and 2 (0.4%) patients in Arms Rd, Rd18 and MPT, respectively.

In Study MM-015, cardiac failure SAEs were experienced by 6/150 (4.0%), 2/152 (1.3%) and 2/153 (1.3%) patients in the MPR+R, MPR+p and MPp+p arms, respectively. PTs reported for more than 2 patients overall were cardiac failure and cardiogenic shock. A total of 2 (1.3%) patients in the MPR+R arm had cardiac failure SAEs with outcomes of death.

**RRMM Studies:**

## Table 2.7.3.1-17: Important Identified Risk: Cardiac Failure

**Important Identified Risk Cardiac Failure**

The outcomes of the cardiac failure SAEs reported in the RRMM studies are summarised below.

| Outcome | Number (%) of Patients[a] | |
|---|---|---|
| | MM-009 and MM-010 | |
| | Len/Dex N = 353 | PBO/Dex N = 350 |
| Patients with ≥ 1 SAE | 6 (1.7) | 4 (1.1) |
| Death | 1 (0.3) | 1 (0.3) |
| Resolved/recovered with/without sequelae (MM-009 and MM-010) | 4 (1.1) | 0 |
| Not recovered/not resolved/ongoing | 0 | 0 |
| Unknown/missing (MM-009 and MM-010) | 1 (0.3) | 4 (1.1) |

[a] Patients can be counted more than once.

The SAEs reported for lenalidomide/dexamethasone-treated patients were cardiac failure congestive (5 patients) and pulmonary oedema NOS (one patient). Five of these SAEs were of Grade 3 or 4 intensity and 2 were considered related to treatment (Grade 3 CHF and Grade 2 congestive cardiac failure). In 3 of the 6 patients, the dose of lenalidomide/dexamethasone was interrupted (2 SAEs of cardiac failure congestive and 1 SAE of pulmonary oedema NOS). One patient died of CHF, which was not considered related to lenalidomide/dexamethasone by the investigator. The 6 SAEs reported for 4 placebo/dexamethasone-treated patients were pulmonary oedema NOS (4 patients), and cardiac failure acute and cardiac failure NOS (one patient each).

**Del 5q MDS Studies:**

The outcomes of the cardiac failure SAEs reported in Studies MDS-003 and MDS-004 are summarised below.

| Outcome | Number (%) of Patients[a] | | | |
|---|---|---|---|---|
| | MDS-003[b] | MDS-004[c] | | |
| | Len (10 mg) N = 148 | Len (10 mg) N = 69 | Len (5 mg) N = 69 | PBO[d] N = 67 |
| Patients with ≥ 1 SAE | 8 (5.4) | 1 (1.4) | 2 (2.9) | 0 |
| Death | 3 (2.0) | 0 | 0 | 0 |
| Not recovered/not resolved | 1 (0.7) | 0 | 0 | 0 |
| Resolved/recovered with/without sequelae | 3 (2.0) | 0 | 2 (2.9) | 0 |
| Unknown/missing | 1 (0.7) | 1 (1.4) | 0 | 0 |

[a] Patients may be counted more than once.

## Table 2.7.3.1-17: Important Identified Risk: Cardiac Failure

**Important Identified Risk Cardiac Failure**

[b] Median time on treatment was 52.5 weeks.

[c] Median time on treatment was 50.3 weeks in the 10 mg group, 18.0 weeks in the 5 mg group and 16.0 weeks in the PBO group.

[d] Data in PBO group is from the first 16 weeks of the double-blind phase.

In Study MDS-004, cardiac failure SAEs were experienced by 1/69 (1.4%) and 2/69 (2.9%) patients in the lenalidomide 10 mg and 5 mg groups, respectively, (all PTs were cardiac failure) compared with no patients in the placebo group. The SAEs were of Grade 3 intensity in the lenalidomide 5 mg group and of Grade 5 intensity in the lenalidomide 10 mg group. One patient each in the lenalidomide 10 mg and 5 mg groups experienced SAEs of cardiac failure considered related to treatment.

In Study MDS-003, 3 patients experienced cardiac failure SAEs that resulted in death (PTs: cardiac failure [2] and cardiac failure congestive [1]). The SAEs were considered not related to study medication.

**MCL Studies:**

The outcomes of the cardiac failure SAEs are summarised below.

| **Outcome** | **MCL-002** | | **All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003)** |
|---|---|---|---|
| | **Len** | **Control** | |
| Total number of patients | 167 | 83 | 373 |
| Patients with ≥ 1 SAE | 4 (2.4) | 2 (2.4) | 5 (1.3) |
| Death | 1 (0.6) | 2 (2.4) | 1 (0.3) |
| Recovered with sequelae | 1 (0.6) | 0 | 1 (0.3) |
| Recovered/resolved | 1 (0.6) | 0 | 2 (0.5) |
| Unknown | 1 (0.6) | 0 | 1 (0.3) |

In Study MCL-002, cardiac failure SAEs were experienced by 4/167 (2.4%) lenalidomide-treated patients and 2/83 (2.4%) patients in the control group. The SAEs (PTs) experienced by lenalidomide-treated patients were: cardiac failure (2 [1.2%] patients), cardiac failure congestive and left ventricular failure (1 [0.6%] patient each). The SAEs (PTs) experienced by patients in the control group were cardiac failure and cardiac failure acute (1 [1.2%] patient each). One patient in the lenalidomide group and two patients in the control group experienced a cardiac failure SAE that had an outcome of death.

In the combined MCL Studies MCL-002, MCL-001, NHL-002 and NHL-003, cardiac failure SAEs were experienced by 5/373 (1.3%) lenalidomide-treated patients. These SAEs (PTs) were cardiac failure, cardiac failure congestive (2 [0.5%] patients each) and left ventricular failure (1 [0.3%] patient). One patient experienced a cardiac failure SAE that had an outcome of death.

**Severity and Nature of Risk**

## Table 2.7.3.1-17: Important Identified Risk: Cardiac Failure

**Important Identified Risk Cardiac Failure**

**FL Studies:**

Details of AEs pertaining to cardiac failure that were reported in FL studies are summarised below.

| Cardiac Failure | NHL-007 | | NHL-008 | Pooled NHL-007 and NHL-008 |
|---|---|---|---|---|
| | PBO+Rit | Len+Rit | Len+Rit | Len+Rit |
| Total number of patients | 148 | 146 | 177 | 323 |
| All AEs | 2 | 0 | 1 | 1 |
| Grade 3 or 4 | 1 ( 0.7) | 0 | 0 | 0 |
| AEs leading to discontinuation | 1 ( 0.7) | 0 | 0 | 0 |
| AEs leading to dose interruption | 0 | 0 | 0 | 0 |
| AEs leading to dose reduction | 0 | 0 | 0 | 0 |

In Study NHL-007, less than 1% of patients in the rituximab plus placebo arm and no patients in the lenalidomide plus rituximab arm experienced Grade 3 or 4 AEs of cardiac failure. No patients in the lenalidomide plus rituximab arm experienced cardiac failure AEs leading to dose reduction, dose interruption and study treatment discontinuation.

In Study NHL-008, no Grade 3 or 4 AEs of cardiac failure were reported. No cardiac failure AEs led to dose reduction, dose interruption or study treatment discontinuation.

**NDMM RVd Study:**

Cardiac failure AEs reported in Study SWOG S0777 are summarised below.

| Cardiac Failure | SWOG S0777 | |
|---|---|---|
| | Arm B (RVd) | Arm A (Rd) |
| Patients with ≥ 1 AE | 6 (2.3) | 3 (1.2) |
| Grade 3 or 4 | 4 (1.5) | 3 (1.2) |
| AEs leading to dose withdrawn permanently | 1 (0.4) | 0 |
| AEs leading to dose interruption | NC | NC |
| AEs leading to dose reduction | NC | NC |

NC = not collected.

In Study SWOG S0777, the frequencies of Grade 3 or 4 cardiac failure AEs were < 2% in the RVd and Rd arms. In the RVd arm, a cardiac failure AE leading to study treatment withdrawal was reported in 1 (0.4%) patient (PT: cardiac failure congestive). No cardiac failure AEs led to study treatment withdrawal in the Rd arm.

## Table 2.7.3.1-17: Important Identified Risk: Cardiac Failure

**Important Identified Risk Cardiac Failure**

**TE NDMM Studies:**

Cardiac failure AEs reported in the TE NDMM studies are summarised below.

| Cardiac Failure | CALGB 100104 Maintenance | | IFM 2005-02 Maintenance | |
|---|---|---|---|---|
| | Len | Placebo | Len | Placebo |
| Patients with ≥ 1 AE | 0 | 1 (0.5) | 0 | 2 (0.7) |
| Grade 3 or 4 | 0 | 0 | 0 | 1 (0.4) |
| AEs leading to dose withdrawn permanently[a] | 0 | 0 | 0 | 1 (0.4) |
| AEs leading to dose interruption[a] | NC | NC | 0 | 0 |
| AEs leading to dose reduction[a] | NC | NC | 0 | 0 |

[a] In Study CALGB 100104, actions taken due to AEs (eg, treatment discontinued, dose reduced, dose interrupted) were not collected on the CRF. AEs leading to treatment discontinuation were derived retrospectively from the Off Treatment Notice Form.

NC = not collected per study design.

There were no Grade 3 or 4 cardiac failure AEs or cardiac failure AEs leading to permanent withdrawal of study treatment reported in Study CALGB 100104. In Study IFM 2005-02, no lenalidomide-treated patients experienced cardiac failure AEs. Grade 3 or 4 cardiac failure AEs and cardiac failure AEs leading to permanent withdrawal of study treatment were each reported in 1 (0.4%) patient treated with placebo; no placebo-treated patients had their dose interrupted or reduced due to AEs of cardiac failure.

**TNE NDMM Studies:**

Cardiac failure AEs reported in the TNE NDMM studies are summarised below.

| Cardiac Failure | MM-020 | | | MM-015 | | |
|---|---|---|---|---|---|---|
| | Rd N = 532 | Rd18 N = 540 | MPT N = 541 | MPR+R N = 150 | MPR+p N = 152 | MPp+p N = 153 |
| Patients with ≥ 1 AE | 47 (8.8) | 28 (5.2) | 27 (5.0) | 7 (4.7) | 4 (2.6) | 4 (2.6) |
| Grade 3 or 4 | 27 (5.1) | 16 (3.0) | 17 (3.1) | 3 (2.0) | 2 (1.3) | 0 |
| AEs leading to dose withdrawn permanently | 8 (1.5) | 7 (1.3) | 2 (0.4) | 2 (1.3) | 0 | 1 (0.7) |
| AEs leading to dose interruption | 10 (1.9) | 7 (1.3) | 4 (0.7) | 1 (0.7) | 1 (0.7) | 0 |

## Table 2.7.3.1-17: Important Identified Risk: Cardiac Failure

**Important Identified Risk Cardiac Failure**

| | | | | | | |
|---|---|---|---|---|---|---|
| AEs leading to dose reduction | 1 (0.2) | 2 (0.4) | 1 (0.2) | 0 | 0 | 0 |

In Study MM-020, Grade 3 or 4 cardiac failure AEs were reported for a greater proportion of patients in Arm Rd (5.1%) than Arm Rd18 and Arm MPT (3.0% and 3.1%, respectively). Cardiac failure AEs led to withdrawal of study treatment permanently or dose interruption in ≤ 1.9% of patients in all treatment arms. In Study MM-015, Grade 3 or 4 cardiac failure AEs were reported for 2.0% and 1.3% of patients in the MPR+R and MPR+p arms, respectively, and no patients in the MPp+p arm. Cardiac failure AEs led to dose interruption in single patients in the MPR+R and MPR+p arms, and to withdrawal of lenalidomide permanently in 1.3% patients in the MPR+R arm and 0.7 patients in the MPp+p arm.

**RRMM Studies:**

| **Cardiac Failure** | **Number (%) of Patients** | |
|---|---|---|
| | **MM-009 and MM-010** | |
| | **Len/Dex N = 353** | **PBO/Dex N = 350** |
| All AEs | 12 (3.4) | 8 (2.3) |
| Grade 3 or 4 | 6 (1.7) | 6 (1.7) |
| AEs leading to discontinuation | 1 (0.3)[a] | 3 (0.9)[b] |
| AEs leading to dose interruption | 3 (0.8)[c] | 1 (0.3)[d] |
| AEs leading to dose reduction | 0 | 0 |

[a] Includes PT of cardiac failure congestive (1)

[b] Includes PTs of pulmonary oedema NOS (3) and cardiac failure acute (1)

[c] Includes PTs of cardiac failure congestive (2) and pulmonary oedema NOS (2)

[d] Includes PT of pulmonary oedema NOS (1)

Overall, only 6/353 (1.7%) lenalidomide/dexamethasone-treated patients experienced a Grade 3 or 4 cardiac failure AE, with cardiac failure congestive and pulmonary oedema NOS accounting for the majority of these AEs (5 and 4 patients, respectively). The same proportion of placebo /dexamethasone-treated patients (6; 1.7%) experienced a Grade 3 or 4 cardiac failure AE.

**Del 5q MDS Studies:**

Details of cardiac failure AEs reported for patients in Studies MDS-003 and MDS-004 are summarised below.

| **Cardiac Failure** | **Number (%) of Patients** | | | |
|---|---|---|---|---|
| | **MDS-003**[a] | **MDS-004**[b] | | |
| | **Len (10 mg)** | **Len (10 mg) N = 69** | **Len (5 mg) N = 69** | **PBO**[c] **N = 67** |

## Table 2.7.3.1-17: Important Identified Risk: Cardiac Failure

**Important Identified Risk Cardiac Failure**

| | | | | |
|---|---|---|---|---|
| | **N = 148** | | | |
| All AEs | 11 (7.4) | 2 (2.9) | 3 (4.3) | 1 (1.5) |
| Grade 3 or 4 | 9 (6.1) | 1 (1.4) | 2 (2.9) | 0 |
| AEs leading to discontinuation | 1 (0.7) | 0 | 0 | 0 |
| AEs leading to dose interruption | 0 | 0 | 0 | 0 |
| AEs leading to dose reduction | 0 | 0 | 1 (1.4)[d] | 0 |

[a] Median time on treatment was 52.5 weeks.

[b] Median time on treatment was 50.3 weeks in the 10 mg group, 18.0 weeks in the 5 mg group and 16.0 weeks in the PBO group.

[c] Data in PBO group is from the first 16 weeks of the double-blind phase.

[d] Includes PT of cardiac failure (1).

In Study MDS-004, few patients experienced a Grade 3 or 4 cardiac failure AE or a cardiac failure AE leading to dose reduction. No patients reported a cardiac failure AE resulting in dose interruption or discontinuation.

**MCL Studies:**

Cardiac failure AEs reported in the studies in MCL are summarised below.

| **Cardiac Failure** | **MCL-002** | | **All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003) (N = 373)** |
|---|---|---|---|
| | **Len (N = 167)** | **Control (N = 83)** | |
| All AEs | 9 (5.4) | 2 (2.4) | 14 (3.8) |
| Grade 3 or 4 | 5 (3.0) | 0 | 6 (1.6) |
| AEs leading to dose interruption | 1 (0.6) | 0 | 2 (0.5) |

In Study MCL-002, Grade 3 or 4 cardiac failure AEs were reported in a greater proportion of patients in the lenalidomide group than the control group (3.0% versus 0%). The proportion of patients with cardiac failure AEs leading to dose interruption was greater in the lenalidomide group than the control group (0.6% versus 0%). No cardiac failure AEs led to discontinuation or dose reduction.

Risk factors and risk groups

No particular risk groups or risk factors have been identified for lenalidomide. In MM and MDS no differences in frequency, severity, serious outcomes and apparent risk level of cardiac failure AEs have been observed.

Cardiac symptoms in patients with MDS are often due to anaemia and may be due to iron overload and side effects of therapy.[149] In a study of 840 MDS patients, Della Porta[150] reported that heart failure (28% versus 18%, $p = 0.001$) and cardiac death (69% versus 55%, $p = 0.03$) were significantly more frequent in transfusion-dependent patients. In a Cox analysis with time-dependent covariates, transfusion-dependent patients showed an increased risk of non-leukemic death (HR = 2.12; $p \leq 0.001$), heart failure (HR = 1.34; $p = 0.03$), and cardiac death (HR

## Table 2.7.3.1-17: Important Identified Risk: Cardiac Failure

| Important Identified Risk Cardiac Failure | |
|---|---|
| | = 2.99; p = 0.01). The development of secondary iron overload significantly affected the risk of non-leukemic death and OS (HR = 1.25 and 1.16, respectively; p < 0.001), and this effect was maintained after adjusting for transfusion burden. Iron overload specifically increased the risk of developing heart failure (HR = 1.17, p < 0.001). General risk factors for CHF include increasing age, previous heart disease, diabetes, hypertension, amyloidosis, and previous anthracycline based chemotherapy treatment.[151] |
| Preventability | Careful monitoring of patients with known medical history that may be contributory to a cardiac failure event should be carried out. Additionally, if serious infection occurs in patients, they should be monitored carefully for cardiac failure events. |
| Impact on the risk-benefit balance of the product | Can have mild to severe to life-threatening or fatal impact. Symptoms can be mild with moderate activity or exertion to severe with minimal activity or at rest. |
| Public health impact. | Data concerning the incidence of cardiac failure in patients with MM and MDS are limited. However, high-output cardiac failure is one of the known cardiovascular issues associated with MM and is frequently seen in patients with extensive bone lesions.[152] Cardiac failure is a common cardiovascular event in the elderly. Based upon the prospective Rotterdam Study of 7983 participants ≥ 55 years of age, the point prevalence of CHF on 01 Jan 1999 was 7.0%. Prevalence was higher in males aged 55+ (8.0%) than in women similarly aged (6.0%). Prevalence increased rapidly with age, rising from 0.9% in patients aged 55 to 64, to 4.0% in patients aged 65 to 74, 9.7% in those aged 75 to 84, to 17.4% in those aged 85 years or older. Lifetime risk for CHF was 33% for men and 29% for women at the age of 55.[153] Based upon the most recent US statistics on CHF,[154] the overall prevalence of CHF is 2.1%, with 825,000 new cases annually. Prevalence is greater in males (2.5%) than females (1.8%), and rises dramatically with age. Among persons less than 60, the prevalence of CHF is less than 2.0%.<br><br>These prevalence proportions rise to 7.8% among males 60 to 79, and 8.6% among males aged 80+. Corresponding figures for females are 4.5% and 11.5%, respectively.<br><br>The prevalence of cardiac failure or ejection fraction ≤ 50% as a comorbid disorder was determined to be 19% among 840 consecutively diagnosed MDS patients seen at the Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, between 1992 and 2007, based upon detailed review of patients' medical charts and laboratory values at diagnoses and during the course of disease.[155]<br><br>In a study cohort of 23,855 MDS patients identified in the SEER-Medicare database, the overall baseline prevalence of CHF was 30.6%, based upon ICD-9-CM diagnoses in the 12 months prior to MDS diagnoses.[156]<br><br>An association between cardiac failure and lenalidomide combined with dexamethasone or lenalidomide alone cannot be established. |
| Data source | Studies NHL-007 and NHL-008 (13 Aug 2018); Study SWOG S0777 (01 Dec 2016); Study CALGB 100104 (01 Mar 2015); Study IFM 2005-02 (01 Mar 2015); Study MM-020 (24 May 2013); Study MM-015 (30 Apr 2013); Integrated Summary of Safety (Dec 2005) for Studies MM-009 and MM-010; Study MDS-003 CSR; Study MDS-004 CSR; Study MCL-001 (20 Mar 2013); Study MCL-002 (07 Mar 2014); Study NHL-002 (23 Jun 2008); Study NHL-003 (27 Apr 2011). |
| MedDRA Terms | See Annex 7 |

## Important Identified Risk: Cardiac Arrhythmias

### Table 2.7.3.1-18: Important Identified Risk: Cardiac Arrhythmias

| **Important Identified Risk Cardiac Arrhythmias** | |
|---|---|
| Potential mechanisms | No mechanisms by which lenalidomide may cause cardiac arrhythmias have been identified. |
| Evidence source and strength of evidence | Based on clinical trial data, a higher incidence of cardiac arrhythmia was observed in the lenalidomide arm. |
| Characterization of risk | **Frequency with 95% CI** |

**FL Studies:**

| **Cardiac Arrhythmias** | **NHL-007** | | **NHL-008** | **Pooled NHL-007 and NHL-008** |
|---|---|---|---|---|
| | **PBO+Rit** | **Len+Rit** | **Len+Rit** | **Len+Rit** |
| Total number of patients | 148 | 146 | 177 | 323 |
| Patients with ≥ 1 SAE | 3 | 4 | 1 | 5 |
| Patients with ≥ 1 AE | 13 | 17 | 12 | 29 |
| Incidence (% of patients) with ≥ 1 AE (95% CI) | 8.8 (4.8 to 14.6) | 11.6 (6.9 to 18.0) | 6.8 (3.6 to 11.5) | - |

Overall, in pooled Studies NHL-007 and NHL-008, cardiac arrhythmia AEs were reported for 29 lenalidomide plus rituximab-treated patients.

In Study NHL-007, the proportion of patients experiencing at least one cardiac arrhythmia event was slightly higher in the lenalidomide plus rituximab arm than the rituximab plus placebo arm (risk ratio = 1.3 [95% CI: 0.6-2.7]).

In Study NHL-008, cardiac arrhythmia events were reported for 6.8% lenalidomide plus rituximab-treated patients.

**NDMM RVd Study:**

| **Cardiac Arrhythmias** | **SWOG S0777** | |
|---|---|---|
| | **Arm B (RVd)** | **Arm A (Rd)** |
| Total number of patients | 262 | 256 |
| Patients with ≥ 1 SAE | 16 | 4 |
| Patients with ≥ 1 AE | 43 | 21 |
| Incidence (% of patients) with ≥ 1 AE (95% CI) | 16.4 (12.1 to 21.5) | 8.2 (5.1 to 12.3) |

In Study SWOG S0777, the proportion of patients experiencing at least one cardiac arrhythmia event was greater among patients treated with RVd than patients treated with Rd (risk ratio = 2.00 [95% CI: 1.22-3.27]).

**TE NDMM Studies:**

## Table 2.7.3.1-18: Important Identified Risk: Cardiac Arrhythmias

**Important Identified Risk Cardiac Arrhythmias**

| Cardiac Arrhythmias | CALGB 100104 Maintenance | | IFM 2005-02 Maintenance | |
|---|---|---|---|---|
| | Len | Placebo | Len | Placebo |
| Total number of patients | 224 | 221 | 293 | 280 |
| Patients with ≥ 1 SAE | 2 | 2 | 3 | 1 |
| Patients with ≥ 1 AE | 12 | 8 | 11 | 16 |
| Incidence (% of patients) with ≥ 1 AE (95% CI)[a] | 5.4 (2.8 to 9.2) | 3.6 (1.6 to 7.0) | 3.8 (1.9 to 6.6) | 5.7 (3.3 to 9.1) |

[a] Incidence was not adjusted for time on treatment.

In Study CALGB 100104, the proportion of patients experiencing at least one cardiac arrhythmia event was greater among lenalidomide-treated patients than patients treated with placebo (risk ratio = 1.48 [95% CI: 0.62-3.55]; p = 0.380). In Study IFM 2005-02, the proportion of patients experiencing at least one cardiac arrhythmia event was smaller among lenalidomide-treated patients than patients treated with placebo (risk ratio = 0.66 [95% CI: 0.31-1.39]; p = 0.272).

**TNE NDMM Studies:**

| Cardiac Arrhythmias | MM-020 | | | MM-015 | | |
|---|---|---|---|---|---|---|
| | Rd | Rd18 | MPT | MPR+R | MPR+p | MPp+p |
| Total number of patients | 532 | 540 | 541 | 150 | 152 | 153 |
| Patients with ≥ 1 SAE | 45 | 35 | 32 | 10 | 6 | 8 |
| Patients with ≥ 1 AE | 133 | 94 | 123 | 33 | 30 | 25 |
| Incidence (% of patients) with ≥ 1 AE (95% CI)[a] | 25.0 (21.4 to 28.9) | 17.4 (14.3 to 20.9) | 22.7 (19.3 to 26.5) | 22.0 (15.7 to 29.5) | 19.7 (13.7 to 27.0) | 16.3 (10.9 to 23.2) |

[a] Incidence was not adjusted for time on treatment.

In Study MM-020, the proportion of patients experiencing at least one cardiac arrhythmia event was similar among lenalidomide-treated patients and patients treated with control (risk ratio = 0.93 [95% CI: 0.77-1.13]; p = 0.472). In Study MM-015, the proportion of patients experiencing at least one cardiac arrhythmias event was slightly higher among lenalidomide-treated patients than patients treated with control (risk ratio = 1.28 [95% CI: 0.84-1.94]; p = 0.255).

The most frequent cardiac arrhythmia events in Study MM-020 were atrial fibrillation, reported for 37, 25 and 25 patients each in Arms Rd, Rd18 and MPT, followed by syncope (22, 17 and 27 patients in these respective arms) and bradycardia (20, 11 and 25 patients in these respective arms). In Study MM-015, the most frequent cardiac

## Table 2.7.3.1-18: Important Identified Risk: Cardiac Arrhythmias

**Important Identified Risk Cardiac Arrhythmias**

arrhythmia events were atrial fibrillation, reported for 8, 5 and 9 patients each in the MPR+R, MPR+p and MPp+p arms, followed by palpitations (6, 3 and 6 patients in these respective arms) and syncope (3, 5 and 2 patients in these respective arms).

**RRMM Studies:**

| Cardiac Arrhythmias | MM-009 and MM-010 | |
|---|---|---|
| | Len/Dex | PBO/Dex |
| Total number of patients | 353 | 350 |
| Patients with ≥ 1 SAE | 13 | 5 |
| Patients with ≥ 1 AE | 30 | 17 |
| Incidence (% of patients) with ≥ 1 AE (95% CI)[a] | 8.5 (5.8 to 11.9) | 4.9 (2.9 to 7.7) |

[a] Incidence between arms was not adjusted for actual time on treatment (mean treatment duration 44 weeks [Len/Dex] versus 23 weeks [PBO/Dex]).

In the RRMM clinical studies, cardiac arrhythmias were noted in 8.5% (30/353) of lenalidomide/dexamethasone-treated patients and in 4.9% (17/350) of the placebo/dexamethasone-treated patients. The risk ratio for cardiac arrhythmia was 1.75 (95% CI: 0.98 – 3.11; p = 0.055).

**Del 5q MDS Studies:**

| Cardiac Arrhythmias | MDS-003[a] | MDS-004[b] | | |
|---|---|---|---|---|
| | Len (10 mg) | Len (10 mg) | Len (5 mg) | PBO[c] |
| Total number of patients | 148 | 69 | 69 | 67 |
| Patients with ≥ 1 SAE | 8 | 1 | 1 | 1 |
| Patients with ≥ 1 AE | 30 | 5 | 4 | 4 |
| Incidence (% of patients) with ≥ 1 AE (95% CI) | 20.3 (14.1 to 27.7) | 7.2 (2.4 to 16.1) | 5.8 (1.6 to 14.2) | 6.0 (1.7 to 14.6) |

[a] Median time on treatment was 52.5 weeks.

[b] Median time on treatment was 50.3 weeks in the 10 mg group, 18.0 weeks in the 5 mg group and 16.0 weeks in the PBO group.

[c] Data in PBO group is from the first 16 weeks of the double-blind phase.

In Study MDS-004, the risk of cardiac arrhythmias was comparable across the lenalidomide and placebo groups (5.8% to 7.2%). For the combined group (5 mg and 10 mg) versus placebo, the risk ratio is 1.09 (95% CI: 0.35-3.42).

The most frequent cardiac arrhythmia events were palpitations, reported for 3 patients each in the lenalidomide 5 mg and placebo groups, and by 1 patient in the lenalidomide 10 mg group, followed by atrial fibrillation (1, 2 and 1 patients in these respective groups). The other cardiac arrhythmia events (atrial flutter, tachycardia and tachyarrhythmia) were reported for single patients.

**MCL Studies:**

## Table 2.7.3.1-18: Important Identified Risk: Cardiac Arrhythmias

**Important Identified Risk Cardiac Arrhythmias**

| Cardiac Arrhythmias | MCL-002 | | All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003) |
|---|---|---|---|
| | Len | Control | |
| Total number of patients | 167 | 83 | 373 |
| Patients with ≥ 1 SAE | 7 | 1 | 12 |
| Patients with ≥ 1 AE | 16 | 4 | 35 |
| Incidence (% of patients) with ≥ 1 AE (95% CI) | 9.6 (5.6 to 15.1) | 4.8 (1.3 to 11.9) | 9.4 (6.6 to 12.8) |

In Study MCL-002, the proportion of patients experiencing at least one cardiac arrhythmia event was greater among lenalidomide-treated patients than patients treated with control (risk ratio = 1.99 [95% CI: 0.69-5.76]; p = 0.205).

**Seriousness/Outcomes**

**FL Studies:**

Serious AE outcomes reported in the FL studies are summarised below.

| Outcome | NHL-007 | | NHL-008 | Pooled NHL-007 and NHL-008 |
|---|---|---|---|---|
| | PBO+Rit | Len+Rit | Len+Rit | Len+Rit |
| Total number of patients | 148 | 146 | 177 | 323 |
| Patients with ≥ 1 SAE | 3 (2.0) | 4 (2.7) | 1 (0.6) | 5 (1.5) |
| Death | 0 | 1 (0.7) | 1 (0.6) | 2 (0.6) |
| Resolved | 3 (2.0) | 3 (2.1) | 0 | 3 (0.9) |

In Study NHL-007, cardiac arrhythmia SAEs were reported for 4/146 (2.7%) lenalidomide plus rituximab-treated patients (PTs reported were atrial fibrillation, supraventricular tachycardia and arrhythmia) and 3/148 (2.0%) rituximab plus placebo-treated patients (PTs reported were atrial fibrillation, syncope and atrial flutter). One (0.7%) cardiac arrhythmia SAE of arrhythmia had an outcome of death in the lenalidomide plus rituximab arm.

In Study NHL-008, cardiac arrhythmia SAEs were reported for 1/177 (0.6%) lenalidomide plus rituximab-treated patient (PT reported was cardio-respiratory arrest). This SAE of cardio-respiratory arrest had an outcome of death.

**NDMM RVd Study:**

The outcomes of the cardiac arrhythmia SAEs are summarised below.

| Outcome | SWOG S0777 | |
|---|---|---|
| | Arm B (RVd) | Arm A (Rd) |
| Patients with ≥ 1 SAE | 16 (6.1) | 4 (1.6) |

## Table 2.7.3.1-18: Important Identified Risk: Cardiac Arrhythmias

**Important Identified Risk Cardiac Arrhythmias**

| | | |
|---|---|---|
| Death | 1 (0.4) | 0 |
| Recovered/resolved | 6 (2.3) | 1 (0.4) |
| Recovered/resolved with sequelae | 0 | 0 |
| Recovering/resolving | 7 (2.7) | 1 (0.4) |
| Not recovered/not resolved | 2 (0.8) | 1 (0.4) |
| Unknown | 0 | 1 (0.4) |

In Study SWOG S0777, cardiac arrhythmia SAEs were reported for 16/262 (6.1%) patients treated with RVd (PTs reported were atrial fibrillation, sudden death and syncope) and 4/256 (1.6%) patients treated with Rd (PTs reported were atrial fibrillation and syncope). One cardiac arrhythmia SAE in Study SWOG S0777 was fatal (PT: sudden death) and was reported in the RVd arm.

**TE NDMM Studies:**

The outcomes of the cardiac arrhythmia SAEs are summarised below.

| **Outcome** | **CALGB 100104 Maintenance** | | **IFM 2005-02 Maintenance** | |
|---|---|---|---|---|
| | **Len** | **Placebo** | **Len** | **Placebo** |
| Patients with ≥ 1 SAE | 2 (0.9) | 2 (0.9) | 3 (1.0) | 1 (0.4) |
| Death | 0 | 1 (0.5) | 0 | 0 |
| Resolved/recovered | 1 (0.4) | 0 | 1 (0.3) | 0 |
| Recovered with sequelae | 1 (0.4) | 0 | 0 | 0 |
| Missing | 0 | 0 | 2 (0.7) | 1 (0.4) |
| Not recovered/not resolved | 0 | 1 (0.5) | 0 | 0 |

In Study CALGB 100104, cardiac arrhythmia SAEs were reported for 2/224 (0.9%) lenalidomide-treated patients (PTs were sick sinus syndrome and syncope). An outcome of death was reported for 1 (0.5%) placebo-treated patient in Study CALGB 100104 (PT: atrioventricular block).

In Study IFM 2005-02, cardiac arrhythmia SAEs were reported for 3/293 (1.0%) lenalidomide-treated patients (PTs were atrial fibrillation and sudden death).

**TNE NDMM Studies:**

The outcomes of the cardiac arrhythmia SAEs are summarised below.

| **Outcome** | **MM-020** | | | **MM-015** | | |
|---|---|---|---|---|---|---|
| | **Rd N = 532** | **Rd18 N = 540** | **MPT N = 541** | **MPR+R N = 150** | **MPR+p N = 152** | **MPp+p N = 153** |

## Table 2.7.3.1-18: Important Identified Risk: Cardiac Arrhythmias

**Important Identified Risk Cardiac Arrhythmias**

| | | | | | | |
|---|---|---|---|---|---|---|
| Patients with ≥ 1 SAE | 45 (8.5) | 35 (6.5) | 32 (5.9) | 10 (6.7) | 6 (3.9) | 8 (5.2) |
| Death | 7 (1.3) | 4 (0.7) | 2 (0.4) | 1 (0.7) | 0 | 0 |
| Ongoing at death | 1 (0.2) | 3 (0.6) | 1 (0.2) | 0 | 0 | 0 |
| Not recovered/not resolved | 0 | 0 | 0 | 0 | 0 | 0 |
| Recovered/ resolved | 33 (6.2) | 24 (4.4) | 24 (4.4) | 8 (5.3) | 3 (2.0) | 0 |
| Recovered with sequelae | 3 (0.6) | 3 (0.6) | 4 (0.7) | 1 (0.7) | 3 (2.0) | 0 |
| Missing | 1 (0.2) | 1 (0.2) | 1 (0.2) | 0 | 0 | 8 (5.2) |

In Study MM-020, cardiac arrhythmia SAEs were experienced by a comparable proportion of patients in the Rd18 and MPT arms of the study (6.5% and 5.9%, respectively), and a slightly higher proportion in the Rd arm of the study (8.5%). In descending order of frequency, PTs reported for more than 2 patients overall were atrial fibrillation, syncope, cardiac arrest, sudden death, atrial flutter, bradycardia, supraventricular tachycardia, tachycardia, arrhythmia, loss of consciousness and sinus bradycardia. SAEs of cardiac arrhythmia had an outcome of death in 7 (1.3%), 4 (0.7%) and 2 (0.4%) patients in Arms Rd, Rd18 and MPT, respectively. These were PTs of sudden death (7 patients), cardiac arrest (5 patients) and cardio-respiratory arrest (1 patient).

In Study MM-015, cardiac arrhythmia SAEs were experienced by a slightly higher proportion of patients in the MPR+R arm (6.7%) than in the MPR+p and MPp+p arms (3.9% and 5.2%, respectively). In descending order of frequency, PTs reported for more than 2 patients overall were atrial fibrillation, syncope, bradycardia and palpitations. One (0.7%) patient in the MPR+R arm had an SAE of cardiac arrhythmia with an outcome of death.

**RRMM Studies:**

The outcomes of the cardiac arrhythmia SAEs reported in the RRMM studies are summarised below.

| **Outcome** | **Number (%) of Patients**[a] | |
|---|---|---|
| | **MM-009 and MM-010** | |
| | **Len/Dex N = 353** | **PBO/Dex N = 350** |
| Patients with ≥ 1 SAE | 13 (3.7) | 5 (1.4) |
| Death | 1 (0.3) | 3 (0.9) |
| Resolved/recovered with/without sequelae (MM-009 and MM-010) | 6 (1.7) | 2 (0.6) |
| Not recovered/not resolved/ongoing | 0 | 0 |

## Table 2.7.3.1-18: Important Identified Risk: Cardiac Arrhythmias

**Important Identified Risk Cardiac Arrhythmias**

| | | |
|---|---|---|
| Unknown/missing (MM-009 and MM-010) | 6 (1.7) | 0 |

[a] Patients may be counted more than once.

Thirteen out of 353 (3.7%) lenalidomide/dexamethasone-treated patients experienced 14 cardiac arrhythmia SAEs. These SAEs were atrial fibrillation (11 patients), and cardio-respiratory arrest and tachycardia NOS (one patient each). Thirteen of these 14 SAEs were of Grade 3 or 4 intensity. Eight of these 14 SAEs (all events of atrial fibrillation) were considered related to lenalidomide/dexamethasone by the investigator, and of these 8 related SAEs, 2 led to discontinuation of lenalidomide/dexamethasone treatment, and 2 led to interruption of lenalidomide/dexamethasone treatment. One patient died as a result of cardio-respiratory arrest, which was not considered related to lenalidomide/dexamethasone by the investigator.

A total of 5 SAEs were reported in 5/350 (1.4%) patients treated with placebo/dexamethasone. These SAEs were atrial fibrillation (2 patients), and cardiac arrest, sinus tachycardia and cardio-respiratory arrest (one patient each).

**Del 5q MDS Studies:**

The outcomes of the cardiac arrhythmia SAEs reported in Studies MDS-003 and MDS-004 are summarised below.

| **Outcome** | **Number (%) of Patients[a]** | | | |
|---|---|---|---|---|
| | **MDS-003[b]** | **MDS-004[c]** | | |
| | **Len (10 mg) N = 148** | **Len (10 mg) N = 69** | **Len (5 mg) N = 69** | **PBO[d] N = 67** |
| Patients with ≥ 1 SAE | 8 (5.4) | 1 (1.4) | 1 (1.4) | 1 (1.5) |
| Death | 2 (1.4) | 0 | 0 | 0 |
| Not recovered/not resolved | 0 | 0 | 1 (1.4) | 0 |
| Resolved/recovered with/without sequelae | 5 (3.4) | 1 (1.4) | 0 | 1 (1.5) |
| Unknown/missing | 1 (0.7) | 0 | 0 | 0 |

[a] Patients may be counted more than once.

[b] Median time on treatment was 52.5 weeks.

[c] Median time on treatment was 50.3 weeks in the 10 mg group, 18.0 weeks in the 5 mg group and 16.0 weeks in the PBO group.

[d] Data in PBO group is from the first 16 weeks of the double-blind phase.

In Study MDS-004, a cardiac arrhythmia SAE was experienced by 1 patient each in the lenalidomide 10 mg (PT: tachyarrhythmia), lenalidomide 5 mg (PT: atrial fibrillation) and placebo (PT: atrial flutter) groups. These 3 patients all experienced cardiac arrhythmia SAEs of Grade 2 or 3 intensity. The SAEs were considered not related to treatment.

## Table 2.7.3.1-18: Important Identified Risk: Cardiac Arrhythmias

**Important Identified Risk Cardiac Arrhythmias**

In Study MDS-003, 2 patients experienced cardiac arrhythmia SAEs that resulted in death (PTs: atrial fibrillation and sudden death). The SAEs were considered not related to study medication.

**MCL Studies:**

The outcomes of the cardiac arrhythmia SAEs are summarised below.

| Outcome | MCL-002 | | All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003) |
|---|---|---|---|
| | Len | Control | |
| Total number of patients | 167 | 83 | 373 |
| Patients with ≥ 1 SAE | 7 (4.2) | 1 (1.2) | 12 (3.2) |
| Death | 3 (1.8) | 0 | 5 (1.3) |
| Recovered with sequelae | 1 (0.6) | 0 | 2 (0.5) |
| Recovered/resolved | 2 (1.2) | 1 (1.2) | 4 (1.1) |
| Unknown | 1 (0.6) | 0 | 1 (0.3) |

In Study MCL-002, cardiac arrhythmia SAEs were experienced by 7/167 (4.2%) lenalidomide-treated patients and 1/83 (1.2%) patient in the control group. The SAEs (PTs) experienced by lenalidomide-treated patients were cardiac arrest (2 [1.2%] patients), supraventricular tachycardia, atrial fibrillation, sudden death, atrioventricular block second degree and tachycardia (1 [0.6%] patient each). The SAE (PT) experienced by a single patient in the control group was atrial fibrillation. Three patients in the lenalidomide group experienced a cardiac arrhythmia SAE that had an outcome of death.

In the combined MCL Studies MCL-002, MCL-001, NHL-002 and NHL-003, cardiac arrhythmia SAEs were experienced by 12/373 (3.2%) lenalidomide-treated patients. These SAEs (PTs) were supraventricular tachycardia (3 [0.8%] patients); atrial fibrillation, cardiac arrest, sudden death (2 [0.5%] patients each); atrioventricular block second degree, bradycardia, cardio-respiratory arrest and tachycardia (1 [0.3%] patient each). Five patients experienced a cardiac arrhythmia SAE that had an outcome of death.

**Severity and Nature of Risk**

**FL Studies**

Details of AEs pertaining to cardiac arrhythmia that were reported in the FL studies are summarised below.

| Cardiac Arrhythmias | NHL-007 | | NHL-008 | Pooled NHL-007 and NHL-008 |
|---|---|---|---|---|
| | PBO+Rit | Len+Rit | Len+Rit | Len+Rit |
| Total number of patients | 148 | 146 | 177 | 323 |

## Table 2.7.3.1-18: Important Identified Risk: Cardiac Arrhythmias

**Important Identified Risk Cardiac Arrhythmias**

| | | | | |
|---|---|---|---|---|
| All AEs | 13 (8.8) | 17 (11.6) | 12 (6.8) | 29 (9.0) |
| Grade 3 or 4 | 2 (1.4) | 4 (2.7) | 3 (1.7) | 7 (2.2) |
| AEs leading to discontinuation | 1 (0.7) | 0 | 1 (0.6) | 1 (0.3) |
| AEs leading to dose interruption | 0 | 3 (2.1) | 4 (2.3) | 7 (2.2) |
| AEs leading to dose reduction | 0 | 0 | 0 | 0 |

In Study NHL-007, a greater proportion of patients treated with lenalidomide plus rituximab than those treated with rituximab plus placebo experienced Grade 3 or 4 AEs of cardiac arrhythmia (2.7% versus 1.4%). Three (2.1%) patients treated with lenalidomide plus rituximab experienced cardiac arrhythmia AEs leading to dose interruption. No patients treated with lenalidomide plus rituximab experienced cardiac arrhythmia AEs leading to study treatment discontinuation or dose reduction.

In Study NHL-008, 1.7% lenalidomide plus rituximab-treated patients experienced a Grade 3 or 4 AE of cardiac arrhythmia. Cardiac arrhythmia AEs leading to dose interruption and study treatment discontinuation were experienced by 2.3% and 0.6% lenalidomide plus rituximab-treated patients, respectively. No patients treated with lenalidomide plus rituximab experienced cardiac arrhythmia AEs leading to dose reduction.

**NDMM RVd Study:**

Cardiac arrhythmia AEs reported in Study SWOG S0777 are summarised below.

| **Cardiac Arrhythmias** | **SWOG S0777** | |
|---|---|---|
| | **Arm B (RVd)** | **Arm A (Rd)** |
| Patients with ≥ 1 AE | 43 (16.4) | 21 (8.2) |
| Grade 3 or 4 | 27 (10.3) | 9 (3.5) |
| AEs leading to dose withdrawn permanently | 1 (0.4) | 0 |
| AEs leading to dose interruption | NC | NC |
| AEs leading to dose reduction | NC | NC |

NC = not collected.

In Study SWOG S0777, the frequencies of Grade 3 or 4 cardiac arrhythmia AEs were 10.3% and 3.5% in the RVd and Rd arms, respectively. In the RVd arm only, a cardiac arrhythmia AE leading to study treatment withdrawal was reported in 1 (0.4%) patient (PT: syncope).

**TE NDMM Studies:**

Cardiac arrhythmia AEs reported in the TE NDMM studies are summarised below.

| **Cardiac Arrhythmias** | **CALGB 100104 Maintenance** | **IFM 2005-02 Maintenance** |
|---|---|---|

## Table 2.7.3.1-18: Important Identified Risk: Cardiac Arrhythmias

**Important Identified Risk Cardiac Arrhythmias**

| | Len | Placebo | Len | Placebo |
|---|---|---|---|---|
| Patients with ≥ 1 AE | 12 (5.4) | 8 (3.6) | 11 (3.8) | 16 (5.7) |
| Grade 3 or 4 | 8 (3.6) | 5 (2.3) | 1 (0.3) | 1 (0.4) |
| AEs leading to dose withdrawn permanently[a] | 0 | 0 | 1 (0.3) | 0 |
| AEs leading to dose interruption[b] | NC | NC | 0 | 0 |
| AEs leading to dose reduction[c] | NC | NC | 0 | 0 |

[a] In Study CALGB 100104, actions taken due to AEs (eg, treatment discontinued, dose reduced, dose interrupted) were not collected on the CRF. AEs leading to treatment discontinuation were derived retrospectively from the Off Treatment Notice form.

NC = not collected per study design.

In Study CALGB 100104, Grade 3 or 4 cardiac arrhythmia AEs were reported in 3.6% of lenalidomide-treated patients and 2.3% of placebo-treated patients. There were no cardiac arrhythmia AEs leading to permanent withdrawal of study treatment. In Study IFM 2005-02, Grade 3 or 4 cardiac arrhythmia AEs were reported in single lenalidomide-treated and placebo-treated patients. One patient treated with lenalidomide experienced at least one cardiac arrhythmia AE leading to withdrawal of study treatment permanently compared to no patients treated with placebo. No cardiac arrhythmia AEs leading to study treatment interruption or dose reduction were reported in Study IFM 2005-02.

**TNE NDMM Studies:**

Cardiac arrhythmia AEs reported in the TNE NDMM studies are summarised below.

| **Cardiac Arrhythmias** | **MM-020** | | | **MM-015** | | |
|---|---|---|---|---|---|---|
| | **Rd N = 532** | **Rd18 N = 540** | **MPT N = 541** | **MPR+R N = 150** | **MPR+p N = 152** | **MPp+p N = 153** |
| Patients with ≥ 1 AE | 133 (25.0) | 94 (17.4) | 123 (22.7) | 33 (22.0) | 30 (19.7) | 25 (16.3) |
| Grade 3 or 4 | 41 (7.7) | 30 (5.6) | 43 (7.9) | 9 (6.0) | 8 (5.3) | 5 (3.3) |
| AEs leading to dose withdrawn permanently | 6 (1.1) | 2 (0.4) | 6 (1.1) | 3 (2.0) | 0 | 0 |
| AEs leading to dose interruption | 21 (3.9) | 11 (2.0) | 23 (4.3) | 7 (4.7) | 2 (1.3) | 7 (4.6) |

## Table 2.7.3.1-18: Important Identified Risk: Cardiac Arrhythmias

**Important Identified Risk Cardiac Arrhythmias**

| | | | | | | |
|---|---|---|---|---|---|---|
| AEs leading to dose reduction | 2 (0.4) | 2 (0.4) | 6 (1.1) | 1 (0.7) | 0 | 0 |

In Study MM-020, Grade 3 or 4 cardiac arrhythmia AEs were reported for relatively few patients, with no consistent pattern between treatment arms (Rd: 7.7%, Rd18: 5.6%, MPT: 7.9%). Cardiac arrhythmia AEs led to withdrawal of study treatment permanently, dose interruption or dose reduction in ≤ 4.3% of patients in all treatment arms.

In Study MM-015, Grade 3 or 4 cardiac arrhythmia AEs were reported for 6.0%, 5.3% and 3.3% of patients in the MPR+R, MPR+p and MPp+p arms, respectively. Cardiac arrhythmia AEs led to the withdrawal of lenalidomide permanently in 2.0% of patients in the MPR+R arm; dose interruption in 4.7%, 1.3% and 4.6% of patients in the MPR+R, MPR+p and MPp+p arms, respectively; and to dose reduction in 0.7% of patients in the MPR+R arm only.

**RRMM Studies:**

Details of AEs of cardiac arrhythmias that were reported in the RRMM studies are summarised below.

| **Cardiac Arrhythmias** | **Number (%) of Patients** | |
|---|---|---|
| | **RRMM** | |
| | **Len/Dex N = 353** | **PBO/Dex N = 350** |
| All AEs | 30 (8.5) | 17 (4.9) |
| Grade 3 or 4 | 20 (5.7) | 8 (2.3) |
| AEs leading to discontinuation | 2 (0.6)[a] | 1 (0.3)[b] |
| AEs leading to dose interruption | 2 (0.6)[c] | 2 (0.6)[d] |
| AEs leading to dose reduction | 1 (0.3)[e] | 0 |

[a] Includes PT of atrial fibrillation (2)

[b] Includes PT of cardiac arrest (1)

[c] Includes PTs of atrial fibrillation (1) and tachycardia NOS (1)

[d] Includes PTs of atrial fibrillation (1) and tachycardia NOS (1)

[e] Includes PT of sinus tachycardia (1)

Overall, only 20/353 (5.7%) lenalidomide/dexamethasone-treated patients experienced Grade 3 or 4 AEs of cardiac arrhythmias, with atrial fibrillation and tachycardia NOS accounting for the majority of these AEs (14 and 6 patients, respectively). A comparable proportion of placebo/dexamethasone-treated patients (8/350; 2.3%) experienced a Grade 3 or 4 cardiac arrhythmia AE.

Less than 1% of the patients in both arms were withdrawn from the trial or had to temporarily interrupt their treatment due to cardiac arrhythmias. The dose was reduced in just one patient in the lenalidomide/dexamethasone arm.

**Del 5q MDS Studies:**

## Table 2.7.3.1-18: Important Identified Risk: Cardiac Arrhythmias

**Important Identified Risk Cardiac Arrhythmias**

Details of cardiac arrhythmia AEs reported for patients in Studies MDS-003 and MDS-004 are summarised below.

| **Cardiac Arrhythmia** | **Number (%) of Patients** | | | |
|---|---|---|---|---|
| | **MDS-003**[a] | **MDS-004**[b] | | |
| | **Len (10 mg) N = 148** | **Len (10 mg) N = 69** | **Len (5 mg) N = 69** | **PBO**[c] **N = 67** |
| All AEs | 30 (20.3) | 5 (7.2) | 4 (5.8) | 4 (6.0) |
| Grade 3 or 4 | 13 (8.8) | 2 (2.9) | 1 (1.4) | 0 |
| AEs leading to discontinuation | 2 (1.4) | 0 | 1 (1.4)[d] | 1 (1.5)[e] |
| AEs leading to dose interruption | 0 | 0 | 0 | 0 |
| AEs leading to dose reduction | 0 | 0 | 0 | 0 |

[a] Median time on treatment was 52.5 weeks.

[b] Median time on treatment was 50.3 weeks in the 10 mg group, 18.0 weeks in the 5 mg group and 16.0 weeks in the PBO group.

[c] Data in PBO group is from the first 16 weeks of the double-blind phase.

[d] Includes PT of atrial fibrillation (1).

[e] Includes PT of palpitations (1).

In Study MDS-004, few patients experienced a Grade 3 or 4 cardiac arrhythmia AE or a cardiac arrhythmia AE that resulted in dose discontinuation, interruption or reduction.

**MCL Studies:**

Cardiac arrhythmia AEs reported in the studies in MCL are summarised below.

| **Cardiac Arrhythmias** | **MCL-002** | | **All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003) (N = 373)** |
|---|---|---|---|
| | **Len (N = 167)** | **Control (N = 83)** | |
| All AEs | 16 (9.6) | 4 (4.8) | 35 (9.4) |
| Grade 3 or 4 | 4 (2.4) | 2 (2.4) | 7 (1.9) |
| AEs leading to discontinuation | 0 | 1 (1.2) | 1 (0.3) |
| AEs leading to dose interruption | 4 (2.4) | 1 (1.2) | 5 (1.3) |

## Table 2.7.3.1-18: Important Identified Risk: Cardiac Arrhythmias

| Important Identified Risk Cardiac Arrhythmias | |
|---|---|
| | In Study MCL-002, Grade 3 or 4 cardiac arrhythmia AEs were reported in the same proportion of patients in the lenalidomide and control groups (both 2.4%). The proportion of patients with cardiac arrhythmia AEs leading to discontinuation was lower in the lenalidomide group than the control group (0% versus 1.2%), whereas a greater proportion of patients in the lenalidomide group than the control group (2.4% versus 1.2%) experienced cardiac arrhythmia AEs leading to dose interruption. |
| Risk factors and risk groups | Standard risk factors for atrial fibrillation include advancing age, European ancestry, body size (greater height and body mass index), electrocardiography features (left ventricular hypertrophy, left atrial enlargement), diabetes, systolic blood pressure and presence of cardiovascular disease (ie, CHD, heart failure, valvular heart disease). Other factors include clinical and subclinical hyperthyroidism, chronic kidney disease, and heavy alcohol consumption. Familial aggregation studies have identified a role for genetic factors, although such factors probably account for a small proportion of cases.[154] In a case-control study of 385 eligible cases of new-onset atrial fibrillation embedded within the Rotterdam study, the risk of new-onset atrial fibrillation was significantly higher for persons who received a corticosteroid prescription within 1 month before the atrial fibrillation index date.[157] Only high-dose corticosteroid use was associated with increased risk (OR = 6.07; 95% CI: 3.90-9.42). The association of atrial fibrillation was independent of indication for use. Risks were increased not only in patients with asthma or chronic obstructive pulmonary disease, but also in patients with rheumatic, allergic, or malignant haematologic diseases. |
| Preventability | Patients with a known cardiac history should be carefully chosen for any chemotherapy and carefully monitored by their physician. |
| Impact on the risk-benefit balance of the product | Can have mild to severe life-threatening or fatal impact. Symptoms can be mild or moderate with no or minimal non-invasive medical intervention indicated. Severe or life-threatening symptoms may warrant invasive interventions (eg, pacemaker, ablation). |
| Public health impact. | Data concerning the incidence of cardiac arrhythmias in patients with MM, MDS, MCL and FL are limited. As reported from the Rotterdam study, a prospective cohort study among patients aged 55+, the prevalence of atrial fibrillation at baseline among 6808 participants was 5.5%.[158] Prevalence rose from 0.7% among those aged 55 to 59, to 17.8% among those aged 85 and above. The overall incidence rate was 9.9/1000 person-years. Prevalence and incidence were higher in men than women. Lifetime risks of atrial fibrillation at age 55 years were 23.8% in men and 22.2% in women.<br>The prevalence of cardiac arrhythmias (defined as atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias) was determined to be 7% among 840 consecutively diagnosed MDS patients seen at the Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, between 1992 and 2007, based upon detailed review of patients' medical charts and laboratory values at diagnoses and during the course of disease.[155]<br>Patients who develop atrial fibrillation are at increased risk of serious cardiovascular complications, such as heart failure and ischaemic stroke.[157] However, an association between cardiac arrhythmias and lenalidomide in combination with dexamethasone or lenalidomide alone cannot be established. Most cardiac arrhythmias observed with lenalidomide treatment in the clinical setting were non-serious. |

**Table 2.7.3.1-18: Important Identified Risk: Cardiac Arrhythmias**

| **Important Identified Risk Cardiac Arrhythmias** | |
|---|---|
| Data source | Studies NHL-007 and NHL-008 (13 Aug 2018); Study SWOG S0777 (01 Dec 2016); Study CALGB 100104 (01 Mar 2015); Study IFM 2005-02 (01 Mar 2015); Study MM-020 (24 May 2013); Study MM-015 (30 Apr 2013); Integrated Summary of Safety (Dec 2005) for Studies MM-009 and MM-010; Study MDS-003 CSR; Study MDS-004 CSR; Study MCL-001 (20 Mar 2013); Study MCL-002 (07 Mar 2014); Study NHL-002 (23 Jun 2008); Study NHL-003 (27 Apr 2011). |
| MedDRA Terms | See Annex 7 |

## Important Identified Risk: Ischaemic Heart Disease (Including Myocardial Infarction)

For the RRMM clinical studies the search criteria were based on the important identified risk of MI. However, for the FL, TE and TNE NDMM, del 5q MDS and MCL clinical studies, the search criteria were broadened to include ischaemic heart disease. Importantly, a number of patients experienced AEs pertaining to ischaemic heart disease in Studies SWOG S0777, CALGB 100104, IFM 2005-02, MM-020, MM-015, MDS-003, MDS-004 and MCL-002 using these broader search criteria (Table 2.7.3.1-19).

**Table 2.7.3.1-19: Important Identified Risk: Ischaemic Heart Disease (Including Myocardial Infarction)**

| **Important Identified Risk Ischaemic Heart Disease (Including Myocardial Infarction)** | |
|---|---|
| Potential mechanisms | A mechanism by which lenalidomide could cause MI has not been identified. |
| Evidence source and strength of evidence | In clinical trials, IHD has been reported in patients treated with lenalidomide. Myocardial infarction occurs relatively often in individuals of the older age groups that most often develop the target indications of MM, MDS, MCL and FL. |
| Characterization of risk | **Frequency with 95% CI**<br>**FL Studies:** |

| **Ischaemic Heart Disease** | **NHL-007** | | **NHL-008** | **Pooled NHL-007 and NHL-008** |
|---|---|---|---|---|
| | **PBO+Rit** | **Len+Rit** | **Len+Rit** | **Len+Rit** |
| Total number of patients | 148 | 146 | 177 | 323 |
| Patients with ≥ 1 SAE | 1 | 1 | 4 | 5 |
| Patients with ≥ 1 AE | 2 | 1 | 7 | 8 |
| Incidence (% of patients) with ≥ 1 AE (95% CI) | 1.4 (0.2 to 4.8) | 0.7 (0 to 3.8) | 4.0 (1.6 to 8.0) | - |

Overall, in pooled Studies NHL-007 and NHL-008, IHD AEs were reported for 8 lenalidomide plus rituximab-treated patients.

## Table 2.7.3.1-19: Important Identified Risk: Ischaemic Heart Disease (Including Myocardial Infarction)

**Important Identified Risk Ischaemic Heart Disease (Including Myocardial Infarction)**

In Study NHL-007, the proportion of patients experiencing at least one IHD event was low in both FL patients in the lenalidomide plus rituximab arm and rituximab plus placebo arm (risk ratio = 0.5 [95% CI: 0.0-5.6]).

In Study NHL-008, IHD events were reported for 4.0% of lenalidomide plus rituximab-treated patients.

**NDMM RVd Study:**

| Ischaemic Heart Disease | SWOG S0777 | |
|---|---|---|
| | Arm B (RVd) | Arm A (Rd) |
| Total number of patients | 262 | 256 |
| Patients with ≥ 1 SAE | 1 | 2 |
| Patients with ≥ 1 AE | 1 | 3 |
| Incidence (% of patients) with ≥ 1 AE (95% CI) | 0.4 (0.0 to 2.1) | 1.2 (0.2 to 3.4) |

In Study SWOG S0777, the proportion of patients experiencing at least one ischaemic heart disease event was smaller among patients treated with RVd than patients treated with Rd (risk ratio = 0.33 [95% CI: 0.03-3.11]).

**TE NDMM Studies:**

| Ischaemic Heart Disease | CALGB 100104 Maintenance | | IFM 2005-02 Maintenance | |
|---|---|---|---|---|
| | Len | Placebo | Len | Placebo |
| Total number of patients | 224 | 221 | 293 | 280 |
| Patients with ≥ 1 SAE | 1 | 2 | 0 | 2 |
| Patients with ≥ 1 AE | 1 | 2 | 2 | 2 |
| Incidence (% of patients) with ≥ 1 AE (95% CI)[a] | 0.4 (0.0 to 2.5) | 0.9 (0.1 to 3.2) | 0.7 (0.1 to 2.4) | 0.7 (0.1 to 2.6) |

[a] Incidence was not adjusted for time on treatment.

In Study CALGB 100104, the proportion of patients experiencing at least one IHD event was smaller among lenalidomide-treated patients than patients treated with placebo (risk ratio = 0.49 [95% CI: 0.05-5.40]; p = 0.563). In Study IFM 2005-02, the proportion of patients experiencing at least one IHD event was the same among lenalidomide-treated patients and patients treated with placebo (risk ratio = 0.96 [95% CI: 0.14-6.74]; p = 0.964).

**TNE NDMM Studies:**

| Ischaemic Heart Disease | MM-020 | | | MM-015 | | |
|---|---|---|---|---|---|---|
| | Rd | Rd18 | MPT | MPR+R | MPR+p | MPp+p |

## Table 2.7.3.1-19: Important Identified Risk: Ischaemic Heart Disease (Including Myocardial Infarction)

**Important Identified Risk Ischaemic Heart Disease (Including Myocardial Infarction)**

| | | | | | | |
|---|---|---|---|---|---|---|
| Total number of patients | 532 | 540 | 541 | 150 | 152 | 153 |
| Patients with ≥ 1 SAE | 30 | 6 | 10 | 5 | 3 | 3 |
| Patients with ≥ 1 AE | 43 | 17 | 17 | 14 | 7 | 10 |
| Incidence (% of patients) with ≥ 1 AE (95% CI)[a] | 8.1 (5.9 to 10.7) | 3.1 (1.8 to 5.0) | 3.1 (1.8 to 5.0) | 9.3 (5.2 to 15.2) | 4.6 (1.9 to 9.3) | 6.5 (3.2 to 11.7) |

[a] Incidence was not adjusted for time on treatment.

In Study MM-020, the proportion of patients experiencing at least one IHD event was greater among lenalidomide-treated patients than patients treated with control (risk ratio = 1.78 [95% CI: 1.05-3.02]; p = 0.032). In Study MM-015, the proportion of patients experiencing at least one IHD event was similar among lenalidomide-treated patients and patients treated with control (risk ratio = 1.06 [95% CI: 0.51-2.20]; p = 0.867).

**RRMM Studies:**

| **Myocardial Infarction** | **MM-009 and MM-010** | |
|---|---|---|
| | **Len/Dex** | **PBO/Dex** |
| Total number of patients | 353 | 350 |
| Patients with ≥ 1 SAE | 7 | 2 |
| Patients with ≥ 1 AE | 8 | 3 |
| Incidence (% of patients) with ≥ 1 AE (95% CI)[a] | 2.3 (0.7 to 3.8) | 0.9 (0.0 to 1.8) |

[a] Incidence between arms was not adjusted for actual time on treatment (mean treatment duration 44 weeks [Len/Dex] versus 23 weeks [PBO/Dex]).

In the RRMM clinical studies, the proportion of patients experiencing at least one MI meeting the criteria for an SAE was under 2% in both treatment arms. The proportion of patients affected was non-significantly higher (p = 0.11) among patients in the lenalidomide/dexamethasone arm (7/353; 1.98%) relative to the placebo/dexamethasone arm (2/350; 0.57%). The proportion of patients experiencing at least one MI event was greater in the lenalidomide/dexamethasone arm than in the placebo/dexamethasone arm (risk ratio 2.64 [95% CI: 0.71-9.88]).

**Del 5q MDS Studies:**

| **Ischaemic Heart Disease** | **MDS-003**[a] | **MDS-004**[b] | | |
|---|---|---|---|---|
| | **Len (10 mg)** | **Len (10 mg)** | **Len (5 mg)** | **PBO**[c] |
| Total number of patients | 148 | 69 | 69 | 67 |

## Table 2.7.3.1-19: Important Identified Risk: Ischaemic Heart Disease (Including Myocardial Infarction)

**Important Identified Risk Ischaemic Heart Disease (Including Myocardial Infarction)**

| | | | | |
|---|---|---|---|---|
| Patients with ≥ 1 SAE | 3 | 3 | 0 | 0 |
| Patients with ≥ 1 AE | 10 | 3 | 1 | 1 |
| Incidence (% of patients) with ≥ 1 AE (95% CI) | 6.8 (3.3 to 12.1) | 4.3 (0.9 to 12.2) | 1.4 (0.0 to 7.8) | 1.5 (0.0 to 8.0) |

[a] Median time on treatment was 52.5 weeks.

[b] Median time on treatment was 50.3 weeks in the 10 mg group, 18.0 weeks in the 5 mg group and 16.0 weeks in the PBO group.

[c] Data in PBO group is from the first 16 weeks of the double-blind phase.

In Study MDS-004, the risk of IHD was slightly higher in the lenalidomide 10 mg group (4.3%) than the lenalidomide 5 mg and placebo groups (1.4% and 1.5%, respectively).

**MCL Studies:**

| **Ischaemic Heart Disease** | **MCL-002** | | **All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003)** |
|---|---|---|---|
| | **Len** | **Control** | |
| Total number of patients | 167 | 83 | 373 |
| Patients with ≥ 1 SAE | 3 | 0 | 5 |
| Patients with ≥ 1 AE | 7 | 0 | 12 |
| Incidence (% of patients) with ≥ 1 AE (95% CI) | 4.2 (1.7 to 8.4) | 0 | 3.2 (1.7 to 5.6) |

In Study MCL-002, at least one IHD event was reported in 4.2% of lenalidomide-treated patients, whereas no patient treated with control experienced an event of IHD.

**Seriousness/Outcomes**

**FL Studies:**

SAE outcomes reported in the FL studies are summarised below.

| **Outcome** | **NHL-007** | | **NHL-008** | **Pooled NHL-007 and NHL-008** |
|---|---|---|---|---|
| | **PBO+Rit** | **Len+Rit** | **Len+Rit** | **Len+Rit** |
| Total number of patients | 148 | 146 | 177 | 323 |
| Patients with ≥ 1 SAE | 1 (0.7) | 1 (0.7) | 4 (2.3) | 5 (1.5) |

## Table 2.7.3.1-19: Important Identified Risk: Ischaemic Heart Disease (Including Myocardial Infarction)

**Important Identified Risk Ischaemic Heart Disease (Including Myocardial Infarction)**

| | | | | |
|---|---|---|---|---|
| Recovered with sequelae | 0 | 0 | 2 (1.1) | 2 (0.6) |
| Resolved | 1 (0.7) | 1 (0.7) | 2 (1.1) | 3 (0.9) |

In Study NHL-007, IHD SAEs were reported for 1/146 (0.7%) lenalidomide plus rituximab-treated patient (PT reported was angina pectoris) and 1/148 (0.7%) rituximab plus placebo-treated patients (PT reported was myocardial infarction). No IHD SAEs had an outcome of death.

In Study NHL-008, IHD SAEs were reported for 4/177 (2.3%) lenalidomide plus rituximab-treated patients (PTs reported were angina pectoris, acute coronary syndrome, acute myocardial infarction and troponin increased). No IHD SAEs had an outcome of death.

**NDMM RVd Study:**

The outcomes of the ischaemic heart disease SAEs are summarised below.

| **Outcome** | **SWOG S0777** | |
|---|---|---|
| | **Arm B (RVd)** | **Arm A (Rd)** |
| Patients with ≥ 1 SAE | 1 (0.4) | 2 (0.8) |
| Death | 0 | 0 |
| Recovered/ resolved | 1 (0.4) | 1 (0.4) |
| Recovering/ resolving | 0 | 1 (0.4) |

In Study SWOG S0777, ischaemic heart disease SAEs were reported for 1/262 (0.4%) patient treated with RVd (PT: myocardial infarction) and 2/256 (0.8%) patients treated with Rd (PTs: angina pectoris and myocardial infarction). None of the ischaemic heart disease SAEs in Study SWOG S0777 had a fatal outcome.

**TE NDMM Studies:**

The outcomes of the IHD SAEs are summarised below.

| **Outcome** | **CALGB 100104 Maintenance** | | **IFM 2005-02 Maintenance** | |
|---|---|---|---|---|
| | **Len** | **Placebo** | **Len** | **Placebo** |
| Patients with ≥ 1 SAE | 1 (0.4) | 2 (0.9) | 0 | 2 (0.7) |
| Death | 0 | 0 | 0 | 0 |
| Resolved/recovered | 0 | 1 (0.5) | 0 | 0 |
| Missing | 0 | 0 | 0 | 2 (0.7) |
| Not recovered/not resolved | 1 (0.4) | 1 (0.5) | 0 | 0 |

## Table 2.7.3.1-19: Important Identified Risk: Ischaemic Heart Disease (Including Myocardial Infarction)

**Important Identified Risk Ischaemic Heart Disease (Including Myocardial Infarction)**

In Study CALGB 100104, IHD SAEs were reported for 1/224 (0.4%) lenalidomide-treated patient (PT: blood creatine phosphokinase increased). In Study IFM 2005-02, no IHD SAEs were reported for lenalidomide-treated patients.

No IHD SAEs had an outcome of death in the TE NDMM Studies CALGB 100104 and IFM 2005-02.

**TNE NDMM Studies:**

The outcomes of the IHD SAEs are summarised below.

| Outcome | MM-020 | | | MM-015 | | |
|---|---|---|---|---|---|---|
| | Rd N = 532 | Rd18 N = 540 | MPT N = 541 | MPR+R N = 150 | MPR+p N = 152 | MPp+p N = 153 |
| Patients with ≥ 1 SAE | 30 (5.6) | 6 (1.1) | 10 (1.8) | 5 (3.3) | 3 (2.0) | 3 (2.0) |
| Death | 3 (0.6) | 2 (0.4) | 1 (0.2) | 0 | 0 | 0 |
| Ongoing at death | 3 (0.6) | 0 | 0 | 1 (0.7) | 0 | 0 |
| Resolved/ recovered | 19 (3.6) | 4 (0.7) | 8 (1.5) | 3 (2.0) | 2 (1.3) | 0 |
| Recovered with sequelae | 4 (0.8) | 0 | 1 (0.2) | 1 (0.7) | 1 (0.7) | 0 |
| Missing | 1 (0.2) | 0 | 0 | 0 | 0 | 3 (2.0) |

In Study MM-020, IHD SAEs were experienced by a greater proportion of patients treated with lenalidomide or dexamethasone until disease progression (30/532 [5.6%] patients) than those treated with lenalidomide and dexamethasone for 18 cycles or in patients treated with MPT for 12 cycles (6/540 [1.1%] and 10/541 [1.8%]). PTs reported for more than 2 patients overall were acute coronary syndrome, AMI, angina pectoris, coronary artery disease, coronary artery stenosis and MI. An outcome of death was reported for SAEs of IHD in 3 (0.6%), 2 (0.4%) and 1 (0.2%) patients in Arms Rd, Rd18 and MPT, respectively.

In Study MM-015, IHD SAEs were experienced by similar proportions of patients in the MPR+R, MPR+p and MPp+p arms, respectively: 5/150 (3.3%), 3/152 (2.0%) and 3/153 (2.0%). The PTs were acute coronary syndrome, AMI, angina pectoris, coronary artery disease, coronary artery occlusion and myocardial ischaemia. No IHD SAEs had an outcome of death in Study MM-015.

**RRMM Studies:**

The outcomes of the MI SAEs reported in the RRMM studies are summarised below.

| Outcome | Number (%) of Patients[a] | |
|---|---|---|
| | MM-009 and MM-010 | |
| | Len/Dex N = 353 | PBO/Dex N = 350 |
| Patients with ≥ 1 SAE | 7 (2.0) | 2 (0.6) |

## Table 2.7.3.1-19: Important Identified Risk: Ischaemic Heart Disease (Including Myocardial Infarction)

**Important Identified Risk Ischaemic Heart Disease (Including Myocardial Infarction)**

| | | |
|---|---|---|
| Death | 4 (1.1) | 0 |
| Resolved/recovered with/without sequelae (MM-009 and MM-010) | 3 (0.8) | 2 (0.6) |
| Not recovered/not resolved/ongoing | 0 | 0 |
| Unknown/missing (MM-009 and MM-010) | 0 | 0 |

[a] Patients can be counted more than once.

Seven out of 353 (0.2%) lenalidomide/dexamethasone-treated patients experienced 7 SAEs of MI. These SAEs were MI (5 patients), troponin I increased (one patient) and acute coronary syndrome (one patient). All of these SAEs were of Grade 3 or 4 intensity. Only one of the SAEs was considered related to lenalidomide and included a fatal report secondary to CVA. An outcome of death was reported for 4 patients and causes included MI (2) and CVA (1) and respiratory failure (1). In 3 of the 7 reports of SAEs lenalidomide/dexamethasone was withdrawn. Of these patients one recovered and 2 died. Dose was unchanged in 3 (1 SAE of acute coronary syndrome and 2 SAEs of acute MI); dose was interrupted in one patient who recovered (SAE of acute MI). A total of 3 SAEs (myocardial ischaemia and MI in one; MI in the other) were reported in 2 out of 350 (0.6%) placebo/dexamethasone-treated patients. In one patient who recovered the dose was interrupted and in the other patient the dose was unchanged and the patient recovered.

**Del 5q MDS Studies:**

The outcomes of the IHD SAEs reported in Studies MDS-003 and MDS-004 are summarised below.

| **Outcome** | **Number (%) of Patients**[a] | | | |
|---|---|---|---|---|
| | **MDS-003**[b] | **MDS-004**[c] | | |
| | **Len (10 mg) N = 148** | **Len (10 mg) N = 69** | **Len (5 mg) N = 69** | **PBO**[d] **N = 67** |
| Patients with ≥ 1 SAE | 3 (2.0) | 3 (4.3) | 0 | 0 |
| Death | 1 (0.7) | 0 | 0 | 0 |
| Not recovered/not resolved | 0 | 1 (1.4) | 0 | 0 |
| Resolved/recovered with/without sequelae | 2 (1.4) | 2 (2.9) | 0 | 0 |
| Unknown/missing | 0 | 0 | 0 | 0 |

[a] Patients may be counted more than once.

[b] Median time on treatment was 52.5 weeks.

[c] Median time on treatment was 50.3 weeks in the 10 mg group, 18.0 weeks in the 5 mg group and 16.0 weeks in the PBO group.

[d] Data in PBO group is from the first 16 weeks of the double-blind phase.

## Table 2.7.3.1-19: Important Identified Risk: Ischaemic Heart Disease (Including Myocardial Infarction)

**Important Identified Risk Ischaemic Heart Disease (Including Myocardial Infarction)**

In Study MDS-004, an IHD SAE was experienced by 3 patients in the lenalidomide 10 mg group (PTs: Acute MI [2 patients] and MI [1 patient]). All 3 patients experienced IHD SAEs of Grade 3 or 4 intensity and 1 patient experienced an IHD SAE considered related to treatment. No deaths were reported in Study MDS-004.

In Study MDS-003, a single patient experienced an SAE of MI (PT) that resulted in death. The SAE was considered not related to study medication.

**MCL Studies:**

The outcomes of the IHD SAEs are summarised below.

| Outcome | MCL-002 | | All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003) |
|---|---|---|---|
| | Len | Control | |
| Total number of patients | 167 | 83 | 373 |
| Patients with ≥ 1 SAE | 3 (1.8) | 0 | 5 (1.3) |
| Death | 1 (0.6) | 0 | 1 (0.3) |
| Recovered with sequelae | 0 | 0 | 1 (0.3) |
| Recovered/resolved | 2 (1.2) | 0 | 3 (0.8) |

In Study MCL-002, IHD SAEs were experienced by 3/167 (1.8%) lenalidomide-treated patients. The SAEs (PTs) experienced by lenalidomide-treated patients were acute myocardial infarction, myocardial infarction and acute coronary syndrome (1 [0.6%] patient each). One patient in the lenalidomide group experienced an IHD SAE that had an outcome of death.

In the combined MCL Studies MCL-002, MCL-001, NHL-002 and NHL-003, IHD SAEs were experienced by 5/373 (1.3%) lenalidomide-treated patients. These SAEs (PTs) were acute myocardial infarction, myocardial infarction (2 [0.5%] patients each) and acute coronary syndrome (1 [0.3%] patient). One patient experienced an IHD SAE that resulted in death.

**Severity and Nature of Risk**

**FL Studies:**

Details of AEs pertaining to IHD that were reported in the FL studies are summarised below.

| Ischaemic Heart Disease | NHL-007 | | NHL-008 | Pooled NHL-007 and NHL-008 |
|---|---|---|---|---|
| | PBO+Rit | Len+Rit | Len+Rit | Len+Rit |
| Total number of patients | 148 | 146 | 177 | 323 |
| All AEs | 2 (1.4) | 1 (0.7) | 7 (4.0) | 8 (2.5) |

## Table 2.7.3.1-19: Important Identified Risk: Ischaemic Heart Disease (Including Myocardial Infarction)

**Important Identified Risk Ischaemic Heart Disease (Including Myocardial Infarction)**

| | | | | |
|---|---|---|---|---|
| Grade 3 or 4 | 1 (0.7) | 1 (0.7) | 3 (1.7) | 4 (1.2) |
| AEs leading to discontinuation | 0 | 0 | 0 | 0 |
| AEs leading to dose interruption | 1 (0.7) | 0 | 1 (0.6) | 1 (0.3) |
| AEs leading to dose reduction | 0 | 0 | 1 (0.6) | 1 (0.3) |

In Study NHL-007, < 1% of patients experienced Grade 3 or 4 IHD AEs. No patients treated with lenalidomide plus rituximab had study treatment discontinued, dose reduction or dose interruption due to an IHD AE.

In Study NHL-008, 1.7% lenalidomide plus rituximab-treated patients experienced a Grade 3 or 4 AE of IHD. IHD AEs leading to dose interruption or reduction were experienced by < 1% lenalidomide plus rituximab-treated patients. No patients had study treatment discontinued due to IHD AEs.

**NDMM RVd Study:**

Ischaemic heart disease AEs reported in Study SWOG S0777 are summarised below.

| **Ischaemic Heart Disease** | **SWOG S0777** | |
|---|---|---|
| | **Arm B (RVd)** | **Arm A (Rd)** |
| Patients with ≥ 1 AE | 1 (0.4) | 3 (1.2) |
| Grade 3 or 4 | 1 (0.4) | 2 (0.8) |
| AEs leading to dose withdrawn permanently | 1 (0.4) | 0 |
| AEs leading to dose interruption | NC | NC |
| AEs leading to dose reduction | NC | NC |

NC = not collected.

In Study SWOG S0777, Grade 3 or 4 ischaemic heart disease AEs were reported in < 1% of patients in the RVd and Rd arms. Ischaemic heart disease AEs led to study treatment withdrawal of 1 (0.4%) patient in the RVd arm (PT: acute myocardial infarction); none lead to study treatment withdrawal in the Rd arm.

**TE NDMM Studies:**

Ischaemic heart disease AEs reported in the TE NDMM studies are summarised below.

| **Ischaemic Heart Disease** | **CALGB 100104 Maintenance** | | **IFM 2005-02 Maintenance** | |
|---|---|---|---|---|
| | **Len** | **Placebo** | **Len** | **Placebo** |
| Patients with ≥ 1 AE | 1 (0.4) | 2 (0.9) | 2 (0.7) | 2 (0.7) |
| Grade 3 or 4 | 1 (0.4) | 2 (0.9) | 0 | 1 (0.4) |

## Table 2.7.3.1-19: Important Identified Risk: Ischaemic Heart Disease (Including Myocardial Infarction)

**Important Identified Risk Ischaemic Heart Disease (Including Myocardial Infarction)**

| | | | | |
|---|---|---|---|---|
| AEs leading to dose withdrawn permanently[a] | 0 | 0 | 0 | 0 |
| AEs leading to dose interruptiona | NC | NC | 0 | 1 (0.4) |
| AEs leading to dose reductiona | NC | NC | 0 | 0 |

[a] In Study CALGB 100104, actions taken due to AEs (eg, treatment discontinued, dose reduced, dose interrupted) were not collected on the CRF. AEs leading to treatment discontinuation were derived retrospectively from the Off Treatment Notice form.

NC = not collected per study design.

Grade 3 or 4 IHD AEs were reported in 1 (0.4%) patient treated with lenalidomide and 2 (0.9%) patients treated with placebo in Study CALGB 100104. There were no IHD AEs leading to permanent withdrawal of study treatment. In Study IFM 2005-02, no lenalidomide-treated patients experienced Grade 3 or 4 IHD AEs. Grade 3 or 4 IHD AEs were reported in 1 (0.4%) patient treated with placebo. One patient treated with placebo experienced at least one IHD AE leading to study treatment interruption. No patients in the study had their study treatment withdrawn permanently or their dose reduced due to IHD AEs.

**TNE NDMM Studies:**

Ischaemic heart disease AEs reported in the TNE NDMM studies are summarised below.

| **Ischaemic Heart Disease** | **MM-020** | | | **MM-015** | | |
|---|---|---|---|---|---|---|
| | **Rd N = 532** | **Rd18 N = 540** | **MPT N = 541** | **MPR+R N = 150** | **MPR+p N = 152** | **MPp+p N = 153** |
| Patients with ≥ 1 AE | 43 (8.1) | 17 (3.1) | 17 (3.1) | 14 (9.3) | 7 (4.6) | 10 (6.5) |
| Grade 3 or 4 | 25 (4.7) | 8 (1.5) | 10 (1.8) | 5 (3.3) | 4 (2.6) | 1 (0.7) |
| AEs leading to dose withdrawn permanently | 2 (0.4) | 0 | 1 (0.2) | 0 | 1 (0.7) | 0 |
| AEs leading to dose interruption | 13 (2.4) | 3 (0.6) | 7 (1.3) | 4 (2.7) | 3 (2.0) | 3 (2.0) |
| AEs leading to dose reduction | 0 | 0 | 0 | 0 | 0 | 0 |

In Study MM-020, the frequency of Grade 3 or 4 IHD AEs was comparable in patients treated with lenalidomide and dexamethasone for 18 cycles or in patients treated with MPT for 12 cycles (1.5% and 1.8%, respectively), and was higher in patients treated with lenalidomide and dexamethasone until disease progression (4.7%). Ischaemic

## Table 2.7.3.1-19: Important Identified Risk: Ischaemic Heart Disease (Including Myocardial Infarction)

**Important Identified Risk Ischaemic Heart Disease (Including Myocardial Infarction)**

heart disease AEs led to withdrawal of study treatment permanently or dose interruption in ≤ 2.4% of patients in all treatment arms, with no IHD AEs resulting in dose reduction in any treatment arms.

In Study MM-015, Grade 3 or 4 IHD AEs were reported for a similar proportion of patients in Arms MPR+R and MPR+p (3.3% and 2.6%, respectively) and a lower proportion of patients in Arm MPp+p (0.7%).

Ischaemic heart disease AEs led to the withdrawal of lenalidomide permanently in a single patient in Arm MPR+p, and dose interruption in 2.7%, 2.0% and 2.0% of patients in Arms MPR+R, MPR+p and MPp+p, respectively. No patients in any treatment arms had their dose reduced as a result of IHD AEs.

**RRMM Studies:**

Details of MI AEs that were reported in the RRMM studies, respectively, are summarised below.

| **Myocardial Infarction** | **Number (%) of Patients** | |
|---|---|---|
| | **RRMM** | |
| | **Len/Dex N = 353** | **PBO/Dex N = 350** |
| All AEs | 8 (2.3) | 3 (0.9) |
| Grade 3 or 4 | 7 (2.0) | 3 (0.9) |
| AEs leading to discontinuation | 3 (0.8)[a] | 0 |
| AEs leading to dose interruption | 1 (0.3)[b] | 1 (0.3)[c] |
| AEs leading to dose reduction | 3 (0.8) | 1 (0.3) |

[a] Includes PT of MI (3)

[b] Includes PT of MI (1)

[c] Includes PT of MI (1)

Overall, 7/353 (2.0%) lenalidomide/dexamethasone-treated patients experienced a Grade 3 or 4 MI AE, with the PT MI accounting for the majority of these AEs (5 patients). Two patients (3 SAEs) in the placebo/dexamethasone-treated patients experienced a Grade 3 or 4 MI AE.

**Del 5q MDS Studies:**

Details of IHD AEs reported for patients in Studies MDS-003 and MDS-004 are summarised below.

| **Ischaemic Heart Disease** | **Number (%) of Patients** | | | |
|---|---|---|---|---|
| | **MDS-003[a]** | **MDS-004[b]** | | |
| | **Len (10 mg) N = 148** | **Len (10 mg) N = 69** | **Len (5 mg) N = 69** | **PBO[c] N = 67** |
| All AEs | 10 (6.8) | 3 (4.3) | 1 (1.4) | 1 (1.5) |

## Table 2.7.3.1-19: Important Identified Risk: Ischaemic Heart Disease (Including Myocardial Infarction)

**Important Identified Risk Ischaemic Heart Disease (Including Myocardial Infarction)**

| | | | | |
|---|---|---|---|---|
| Grade 3 or 4 | 4 (2.7) | 3 (4.3) | 0 | 0 |
| AEs leading to discontinuation | 0 | 1 (1.4)[d] | 0 | 0 |
| AEs leading to dose interruption | 0 | 1 (1.4)[e] | 0 | 0 |
| AEs leading to dose reduction | 0 | 0 | 0 | 0 |

[a] Median time on treatment was 52.5 weeks.

[b] Median time on treatment was 50.3 weeks in the 10 mg group, 18.0 weeks in the 5 mg group and 16.0 weeks in the PBO group.

[c] Data in PBO group is from the first 16 weeks of the double-blind phase.

[d] Includes PT of MI (1)

[e] Includes PT of acute MI (1)

In Study MDS-004, 4.3% of patients in the lenalidomide 10 mg group experienced Grade 3 or 4 IHD. Ischaemic heart disease resulted in dose discontinuation and interruption for 1.4% of patients.

**MCL Studies:**

Ischaemic heart disease AEs reported in the studies in MCL are summarised below.

| **Ischaemic Heart Disease** | **MCL-002** | | **All MCL Lenalidomide Patients (MCL-002, MCL-001, NHL-002, NHL-003) (N = 373)** |
|---|---|---|---|
| | **Len (N = 167)** | **Control (N = 83)** | |
| All AEs | 7 (4.2) | 0 | 12 (3.2) |
| Grade 3 or 4 | 3 (1.8) | 0 | 6 (1.6) |
| AEs leading to discontinuation | 0 | 0 | 1 (0.3) |
| AEs leading to dose interruption | 1 (0.6) | 0 | 1 (0.3) |

In Study MCL 002, Grade 3 or 4 IHD AEs were reported in 3 (1.8%) patients in the lenalidomide group. One (0.6%) patient experienced an AE that led to dose interruption.

Risk factors and risk groups

Risk factors for 10-year coronary risk based upon the Framingham Heart Study include elevated blood pressure, elevated cholesterol, high-density lipoprotein-C, presence of diabetes and cigarette smoking.[154] These factors are in addition to the well-known relationships between coronary risk and age and gender.

In Europe, smoking remains a major public health issue and about 20% of death from CVD in men and about 3% of deaths from CVD in women are due to smoking. Levels of obesity are high across Europe in both adults and children, although rates vary

**Table 2.7.3.1-19: Important Identified Risk: Ischaemic Heart Disease (Including Myocardial Infarction)**

| Important Identified Risk Ischaemic Heart Disease (Including Myocardial Infarction) | |
|---|---|
| | substantially between countries. Participation in physical activity is low. Increases in population body mass index over the interval 1980 to 2008 were noted in almost all countries. The prevalence of diabetes in Europe is high and has increased rapidly over the last ten years, increasing by more than 50% in many countries.[159] |
| Preventability | MI has been reported in patients receiving lenalidomide, particularly in those with known risk factors and within the first 12 months when used in combination with dexamethasone. Patients with known risk factors – including prior thrombosis – should be closely monitored, and action should be taken to try to minimise all modifiable risk factors (eg, smoking, hypertension and hyperlipidaemia) (SmPC, Section 4.4). |
| Impact on the risk-benefit balance of the product | Ischaemic heart disease can be life-threatening or fatal depending on the severity and impacts activities of daily living. |
| Public health impact. | Information on the incidence/prevalence of MI in the EU is limited. Among 5148 participants in the Rotterdam prospective cohort study of persons at least age 55 with no evidence of prevalent infarction, 141 recognised MIs occurred and the incidence rate of this event was 5.0 per 1000 person-years.[160] The incidence was higher in men (8.4) than in women (3.1). The incidence of unrecognised MI was 3.8 per 1000 person-years, with only small differences between men (4.2) and women (3.6). Rates generally increased with age for both recognised and unrecognised MI.<br><br>In a population-based cohort of 3729 people older than 64 years identified in three geographical areas of Spain and free of previous MI, adjusted incidence rates of MI were higher in men (957 per 100,000 person-years) than in women (546 per 100,000).[161] Thus, men showed a significantly ($p < 0.001$) higher cumulative incidence of MI at 10 years (7.2%) than women (3.8%). While cumulative incidence increased with age ($p < 0.05$), gender-differences tended to narrow.<br><br>Using linked Hospital Episode Statistics and mortality information, the Oxford Record Linkage studied English individuals of any age, who were admitted to hospital for AMI or who died suddenly from AMI in 2010.[162] They identified 82,252 AMI events. Age-standardised incidence of first AMI per 100,000 population was 130 (95% CI: 129–131) in men and 55.9 (95% CI: 55.3–56.6) in women. Incidence rates demonstrated a steep age gradient for both men and women, with about three-quarters of all AMIs occurring in individuals aged ≥ 65 years. About one in six AMIs are reinfarctions in both men and women, and this proportion increases with older age.<br><br>Disease of the heart and circulatory system (cardiovascular disease) is the main cause of death in the EU, accounting for 1.9 million deaths each year. Forty percent of all deaths in the EU (43% of deaths in women and 36% of deaths in men) are from cardiovascular disease – slightly less than for Europe as a whole. Over a third of deaths from cardiovascular disease in the EU are from CHD. CHD by itself is the single most common cause of death in Europe and death rates from CHD are generally higher in Central and Eastern Europe than in Northern, Southern and Western Europe. CHD is also the single most common cause of death in the EU, accounting for over 681,000 deaths in the EU each year: 15% of deaths among men, and 13% of deaths among women.[159]<br><br>The proportion of MDS patients with comorbid coronary artery disease or prevalent MI at baseline in the Pavia cohort was 8%. Coronary artery disease was defined as |

**Table 2.7.3.1-19: Important Identified Risk: Ischaemic Heart Disease (Including Myocardial Infarction)**

| Important Identified Risk Ischaemic Heart Disease (Including Myocardial Infarction) | |
|---|---|
| | one or more vessel-coronary artery stenosis requiring medical treatment, stent or bypass graft.[155]<br>In the SEER-Medicare cohort of 23,855 patients with MDS, the proportion of patients with ischemic heart disease was 41.1% and those with prevalent MI was 3.3%. Baseline comorbidities were identified in the 12 months prior to the MDS diagnosis.[156]<br>MI is a leading cause of morbidity and mortality. Many of the risk factors associated with MI can be modified eg, through a change in lifestyle.<br>An association between MI and lenalidomide combined with dexamethasone or lenalidomide alone is not established. |
| Data source | Studies NHL-007 and NHL-008 (13 Aug 2018); Study SWOG S0777 (01 Dec 2016); Study CALGB 100104 (01 Mar 2015); Study IFM 2005-02 (01 Mar 2015); Study MM-020 (24 May 2013); Study MM-015 (30 Apr 2013); Integrated Summary of Safety (Dec 2005) for Studies MM-009 and MM-010; Study MDS-003 CSR; Study MDS-004 CSR; Study MCL-001 (20 Mar 2013); Study MCL-002 (07 Mar 2014); Study NHL-002 (23 Jun 2008); Study NHL-003 (27 Apr 2011). |
| MedDRA Terms | See Annex 7 |

**Table 2.7.3.1-20: Important Potential Risk: Off-label Use**

| Important Potential Risk: Off-label Use |
|---|
| Off-label use (ie, outside the indication of patients with transfusion-dependent anaemia due to low- or INT-1-risk MDS associated with an isolated del 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate) is an important potential risk in other MDS patients.. Routine monitoring for off-label use includes the collection of detailed data relating to indication as part of the national controlled access programme, where possible per national regulation.<br>An increased risk of mortality in patients with CLL, a current non-approved indication, was observed after unblinded review of data from Study CC-5013-CLL-008. The Data Monitoring Committee found an imbalance of safety between the two study arms, specifically an increased number of deaths in the lenalidomide arm, and OS in favour of chlorambucil. Upon request, the MAH's Medical Information departments will provide available information and publications to physicians on the risk of the increase in mortality should a physician request information regarding use of lenalidomide in CLL.<br>Cumulative information on off label use from the US postmarketing population and details of the available data on off-label use in the EU are provided in Section 2.5. |

### *2.7.3.2 Module SVII.3.2: Presentation of the Missing Information*

Not applicable.

## 2.8 Module SVIII: Summary of the Safety Concerns

**Table 2.8-1: Summary of Safety Concerns**

| | |
|---|---|
| ***Important identified risks*** | Teratogenicity |
| | Serious infection due to neutropenia |
| | SPM |
| | Tumour Flare Reaction (MCL and FL Indications) |
| | Cardiac failure |
| | Cardiac arrhythmias |
| | Ischaemic heart disease (including myocardial infarction) |
| ***Important potential risks*** | Off-label use |
| ***Missing information*** | None |

# 3 PART III: PHARMACOVIGILANCE PLAN

## 3.1 Part III.1 - Routine Pharmacovigilance Activities

Routine Pharmacovigilance activities in BMS as described in the BMS Pharmacovigilance System Master File and Drug Safety's Standard Operating Procedures are in accordance with "Good Pharmacovigilance Practices in the European Union."

In addition to expedited reporting, BMS vigilantly undertakes follow-up on all ADRs, including serious ADRs that are provided to health authorities to ensure that all details of the case are captured for optimal clinical evaluation. This includes efforts to obtain all relevant information and to establish the final outcome of the ADRs.

### *3.1.1 Part III.1.1 - Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection*

#### *3.1.1.1 Part III.1.1.1 - Specific Adverse Reaction Follow-up Questionnaire*

For events of special interest, materials and tools (such as event specific questions) have been developed to ensure that consistent and good quality follow-up information is obtained.

Event specific questionnaires are used to collect adverse reaction and follow-up information for all of the important identified and potential risks (see Section 2.8). The forms are provided in Annex 4 of the RMP.

#### *3.1.1.2 Part III.1.1.2 - Other Forms of Routine Pharmacovigilance Activities*

#### *3.1.1.3 Part III.1.1.3 - Expedited Reporting and Follow-up of Pregnancy*

The pregnancy capture and follow-up procedure is detailed below.

The PPP aims to minimise the risks of teratogenicity by ensuring HCPs and patients are fully informed of and understand the risks of teratogenicity prior to starting their lenalidomide treatment. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic substance that causes severe life-threatening birth defects. If lenalidomide is taken

during pregnancy, a teratogenic effect can be expected. The core PPP for lenalidomide reflects advice, guidance and direction obtained from the Member States.

In order to ensure there is a consistent approach with the ability to capture all information globally, the same principles on obtaining follow-up data on pregnancies are implemented in all territories where lenalidomide is marketed whilst taking into account the legal and healthcare differences in those territories worldwide.

The objectives of the system are:

- To obtain information on all reported pregnancies of females exposed to lenalidomide.
- To obtain information on all reported pregnancies of female partners of male patients exposed to lenalidomide.
- To determine the root cause of all pregnancies and hence failures of the PPP.

In the EU BMS uses the following methods to enhance the capture of reports of pregnancy over and above reliance upon spontaneous reporting:

- The Educational Materials in the Educational HCP's Kit make reference to the requirement to report all suspected pregnancies to the local BMS office and where applicable to the NCA. The Patient Brochure also advises the patient to immediately seek medical advice if there is any risk or suspicion of possible risk of pregnancy. Similar advice is also provided with reference to female partners of male patients.

Database of Pregnancy Reports

All reports of pregnancies received by BMS are entered into BMS's Global Safety Database. This includes all Consumer reports in addition to HCP reports. Any abnormal pregnancy test result (eg, β-hCG) elevated and positive urine pregnancy test are immediately processed. EU Health Authorities are notified of these reports.

Follow-up

All reports of pregnancies are followed up. Follow-up is via the physician/obstetrician/ neonatologist/paediatrician as appropriate. In each country office, any report of pregnancy is followed up by the Drug Safety staff. All reports of pregnancy are also immediately notified to the EEA Qualified Person for Pharmacovigilance (QPPV) and QPPV deputies.

All reports of abnormal pregnancy test results are followed up with the prescriber and follow-up information sent to Health Authorities.

Frequency/Duration of Follow-up

Upon receipt of a notification of pregnancy, the pregnancy specific follow-up questionnaire is sent to the reporter. Upon receipt of this information by BMS, dates for further follow-up actions are tracked.

The HCP/Obstetrician is also sent a Follow-up and Outcome Form to be completed at the outcome of the Pregnancy.

An Infant follow-up form is available for use in the event that a birth defect is detected as an outcome.

Corresponding standard forms are available on request.

Root Cause of Failure of Pregnancy Prevention Programme

The Pregnancy Background Form includes questions to determine why the PPP was unsuccessful for the case in question.

Regulatory Reporting of Pregnancies

All initial pregnancy reports and follow-up information are reported on an expedited basis within 15 days.

Should any suspected teratogenic effect be reported following treatment with lenalidomide, this is expedited immediately.

Compliance with the PPP is monitored in each member state. Examples of methods to monitor compliance include keeping a record of counselling patients prior to prescription, a record of a negative pregnancy test within 3 days of prescription and a record of dispensing within 7 days of the prescription date, etc. The maximum interval of consecutive PPP compliance studies is agreed on between BMS and individual NCAs.

#### *3.1.1.4 Part III.1.1.4 - An Analysis of Adverse Drug Reactions of Special Interest within the Required PSURs*

Emerging potential safety signals can be detected by periodic and if appropriate, cumulative evaluation of the ADRs. The results are compiled in the PSUR, with summaries and conclusions submitted to the health authorities.

In addition, data regarding pregnancy exposure to lenalidomide is targeted for review and is specifically discussed in the PSUR document. These data include all pregnancy case reports collected during the specified period together with cumulative data. Non-medically confirmed case reports of suspected foetal exposure are also provided, whenever applicable. Occupational exposure in pregnant females (eg, a nurse opening the capsules, laboratory technician or carer) is also provided with the corresponding outcome in each PSUR.

PSURs are submitted in accordance with GVP in the EU. Periodicity of PSUR submissions is defined by the EURD-List.

## 3.2 Part III.2 - Additional Pharmacovigilance Activities

### *3.2.1 Part III.2.1 - Pregnancy Prevention Programme Implementation*

The pregnancy capture and follow-up procedure is detailed above.

Physicians are encouraged or required as per local legislation to report pregnancies to BMS or in accordance to local legislation to the NCA.

Additional monitoring of the implementation of the BMS PPP is carried out on a country basis in agreement with relevant NCA (Table 3.2.1-1).

The postmarketing surveillance study RRMM PASS (Annex 2) was also performed in Member States where this was feasible. This study monitored compliance to the process indicators of the implemented PPP and reporting of exposure during pregnancy was also stimulated through this study.

**Table 3.2.1-1: Pregnancy Prevention Programme Implementation**

| Study short name and title | Rationale and study objectives | Study design | Study population | Milestones |
|---|---|---|---|---|
| Monitoring of Pregnancy Prevention Programme implementation | Monitoring of implementation of PPP. | Additional monitoring implementation of BMS PPP on a country specific basis in accordance with local legal framework and with agreement of the relevant NCA (ie, monitoring of patient card completion, monitoring by external agency and surveys) | Patients in the EU receiving lenalidomide | Ongoing.<br>In line with the PSUR |

### *3.2.2 Part III.2.2 - Additional Studies*

**Connect® MM Registry**

BMS is currently sponsoring the Connect® MM registry, a US, multicentre, prospective, observational study that compiles data regarding treatment patterns and patient outcomes in patients with NDMM (both transplant eligible and non-eligible) (Table 3.2.2-1). 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 transplant, as well as diagnostic patterns and occurrence of SPM in a 'real world' population. All consecutive patients at more than 250 participating sites in community and academic settings in the US who have NDMM within 2 months of enrollment were eligible, with planned follow-up on a quarterly basis up to early discontinuation or study end, expected in 2024. This registry enrolled 3011 newly diagnosed MM patients in two cohorts. The first cohort (Cohort 1) consists of 1493 patients enrolled between Sep-2009 and Dec-2011. The extension cohort (Cohort 2) consists of 1518 patients enrolled between Dec-2012 and Apr-2016.

**Table 3.2.2-1: Connect® MM Registry**

| Study short name and title | Rationale and study objectives | Study design | Study population | Milestones |
|---|---|---|---|---|
| Connect® MM: The Multiple Myeloma Disease Registry | 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 transplant, as well as diagnostic patterns and occurrence of SPM in a 'real world' population. | A prospective, observational, longitudinal, multi-centre study | Patients with NDMM (both transplant eligible and non-eligible) | Enrollment completed and follow up ongoing. As of DLP (26-Dec-2017), 3011 patients were enrolled and 1727 patients were discontinued from the study.<br>Safety updates will be submitted with future PSURs. |

### Revlimid TNE NDMM Registry

The MAH proposed a PASS product registry with the primary objectives to compare the incidence of cardiovascular events between TNE NDMM patients treated with a first-line lenalidomide-containing regimen and those treated with a first-line non lenalidomide-containing regimen; and to identify, quantify, and characterise risk factors for cardiovascular events in this population of TNE NDMM patients (Table 3.2.2-2). The incidence of other treatment-emergent events will be examined to characterise the overall safety profile of lenalidomide among patients within the labelled indication. SPM follow-up will extend beyond active treatment.

The Revlimid TNE NDMM PASS (CC-5013-MM-034) is designed as a prospective non-interventional study to compare the incidence of cardiovascular events between TNE NDMM patients treated with a first-line lenalidomide-containing regimen and those treated with a first-line non-lenalidomide-containing regimen. The study will gather extensive risk factor information at baseline and throughout follow-up to aid in the interpretation of any observed differences in the incidence of cardiovascular events between the two cohorts. Other safety endpoints of interest will be characterised through standard follow-up procedures.

This study will be implemented in a selected number of countries in the EU. Sites will be selected based on their expertise in treating patients with NDMM, access to lenalidomide through local reimbursement options, sufficient resources to conduct observational research, and on their ability to collect and report data for this study at the required quality standards. In particular, sites will be

asked to confirm during the feasibility assessment that they are able to commit to liaise with other treating physicians (eg, cardiologists) to ensure sufficient follow-up with patients regarding any cardiovascular events; this may include, but is not limited to, tests, diagnoses, treatment, and outcome information. Site selection will attempt to cover multiple EU countries, urban and rural locations, as well as different types of medical centres (eg, public, private or university ownership).

It is anticipated that approximately 888 patients would be enrolled. The final study report could be available in 2027. Safety updates will be submitted with future PSURs.

**Table 3.2.2-2: Revlimid TNE NDMM Registry**

| Study short name and title | Rationale and study objectives | Study design | Study population | Milestones |
|---|---|---|---|---|
| Revlimid TNE NDMM Registry:<br>A prospective non-interventional PASS of lenalidomide in previously untreated adult MM patients who are not eligible for transplant ("transplant noneligible" [TNE]) ("Revlimid® TNE NDMM PASS"), CC-5013-MM-034. | The primary objectives are to compare the incidence of cardiovascular events between TNE NDMM patients treated with a first-line lenalidomide-containing regimen and those treated with a first-line non lenalidomide-containing regimen; and to identify, quantify, and characterise risk factors for cardiovascular events in this population of TNE NDMM patients. | A prospective non-interventional PASS | TNE NDMM patients | Ongoing<br>Protocol version 3.0 dated 10-May-2016 was endorsed by PRAC on 02-Sep-2016.<br>Protocol version 4.0 dated 30-Nov-2020 was submitted on 18-Dec-2020, and endorsed by PRAC on 08 Jul 2021<br>An interim study report is expected Q2 2025.<br>The final study report is expected Q1 2027.<br>Safety updates will be submitted with future PSURs. |

## RRMCL PASS

This RRMCL PASS (CC-5013-MCL-005) (Table 3.2.2-5) was designed to gather additional safety information as a multinational, non-interventional study following the request for further assessment of safety issues via postmarketing surveillance.

Potential sites will be identified where R/R MCL patients have been treated with lenalidomide. Site inclusion will be limited to countries where lenalidomide is reimbursed for this indication. Identification of sites will be done through partnerships such as, but not limited to that with the European Mantle Cell Lymphoma Registry. Other sources including knowledge of, or experience with sites can also be used for site identification purposes. Identified sites will then be assessed for feasibility and invited to participate in the study. All data will be collected retrospectively from

identified patients following the first dose of lenalidomide treatment for up to 6 months, including those patients who died within this data collection period.

**Table 3.2.2-3: RRMCL PASS**

| Study short name and title | Rationale and study objectives | Study design | Study population | Milestones |
|---|---|---|---|---|
| RRMCL PASS | The study is designed as a retrospective non-interventional study of patients with RRMCL with the objective to quantify and characterise the event of TFR by tumour burden and the proportion of early deaths by tumour burden in patients treated with lenalidomide in a 'real world' setting. | Multinational safety surveillance study, designed as a postauthorisation non-interventional study. | Patients with RRMCL. | Version 3 of the protocol was submitted on 14-Aug-2017, approved by PRAC on 26-Oct-2017 and endorsed by CHMP on 09-Nov-2017.<br>Version 4 of the protocol was submitted on 16-Sep-2019 and endorsed by CHMP on 28-May-2020<br>Amendment 2, Version 5 of the protocol was submitted on 20-Jun-2022 and approved by PRAC on 26-Jun-2023.<br>Safety updates will be submitted with future PSURs.<br>The final study report could is expected in Q4 2024. |

### *3.2.3 Part III.2.3 - Second Primary Malignancies Monitoring in Ongoing Studies*

Invasive SPM will be considered important medical events. BMS will perform long-term follow-up in ongoing clinical studies to monitor SPM for BMS-sponsored studies. For Study MCL-002: the follow-up phase is to continue until 70% of patients in the study have died, or the median follow-up for responding patients is > 2 years, or the median duration of response has been reached, or 4 years from the date the last patient was randomised is reached, whichever comes latest.

For Study MM-020, SPM was to be documented for 5 years following randomisation of the last patient. For Study MM-015, patients were contacted in the follow-up phase (for at least 5 years) to determine if the patient had been diagnosed with SPM.

## 3.3 Part III.3 - Summary Table of Additional Pharmacovigilance Activities

Links to the protocols are provided in Annex 3.

## Table 3.3-1: On-going and Planned Studies/Activities in the Postauthorisation Pharmacovigilance Development Plan

| Study / Activity Type, Title | Summary of objectives | Safety concerns addressed | Status (planned, started) | Date for Submission of Interim or Final Reports (planned or actual) |
|---|---|---|---|---|
| **Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation** | | | | |
| Revlimid TNE NDMM Registry<br>*Non-interventional: Category 1* | The primary objectives are to compare the incidence of cardiovascular events between TNE NDMM patients treated with a first-line lenalidomide-containing regimen and those treated with a first-line non lenalidomide-containing regimen; and to identify, quantify, and characterise risk factors for cardiovascular events in this population of TNE NDMM patients. | Cardiac events (cardiac failure, cardiac arrhythmias, IHD [including MI]). | Ongoing | An interim study report is expected Q2 2025.<br>The final study report is expected Q1 2027.<br>Safety updates will be submitted with future PSURs. |
| **Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances** | | | | |
| None. | | | | |
| **Category 3 - Required additional pharmacovigilance activities** | | | | |
| Monitoring of Pregnancy Prevention Programme implementation<br>*Category 3* | Monitoring of implementation of PPP. | Monitoring of pregnancy prevention. | Ongoing | Safety updates will be submitted with future PSURs. |
| Connect® MM Registry.<br>*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 | SPM (AML and B-cell malignancies, NMSC and other SPM), cardiac events (cardiac failure, cardiac arrhythmias, IHD [including MI]), Serious Infection due to Neutropenia. | Ongoing | Safety updates will be submitted with future PSURs. |

**Table 3.3-1: On-going and Planned Studies/Activities in the Postauthorisation Pharmacovigilance Development Plan**

| Study / Activity Type, Title | Summary of objectives | Safety concerns addressed | Status (planned, started) | Date for Submission of Interim or Final Reports (planned or actual) |
|---|---|---|---|---|
| | patients with previously untreated MM, whether or not eligible for transplant, as well as diagnostic patterns and occurrence of SPM in a 'real world' population. | | | |
| RRMCL PASS (CC-5013-MCL-005)<br>*Category 3* | The study is designed as a retrospective non-interventional study of patients with RRMCL with the objective to quantify and characterise the event of TFR by tumour burden and the proportion of early deaths by tumour burden in patients treated with lenalidomide in a 'real world' setting. | TFR/high tumour burden and early deaths | Ongoing | The final study report could is expected in Q4 2024.<br>Safety updates will be submitted with future PSURs. |

# 4 PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Protocols for imposed post-authorization efficacy studies are provided in Annex 5.

# 5 PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

The following sets out the basis of the Risk Minimisation Programme, where applicable for the safety concerns discussed in this document.

The same core requirements of the Risk Minimisation Programme apply across all indications for lenalidomide in the EU, since the Risk Minimisation Programme is product and not indication specific. Furthermore, the core requirements of the Risk Minimisation Programme apply across all Member States, however, the local implementation differs between Member States taking into account the local differences in healthcare system, legal framework and culture. Therefore, consultations have taken place with NCAs to determine the appropriate method of implementation of the Risk Minimisation Programme in each Member State.

Consultations also took place with haematology physicians, pharmacists and oncology nurses throughout Europe in order to determine the method of delivery of the Risk Minimisation Programme appropriate to each Member State. Thus, the local implementation of the Risk Minimisation Programme has taken into account the differing healthcare systems throughout the EU Member States.

For lenalidomide, the PPP is a key element of the Risk Minimisation Programme. However, it must also be noted that other activities aimed at minimising the risk of other adverse reactions, such as serious infection due to neutropenia and bleeding due to thrombocytopenia are also included in the Risk Minimisation Programme.

## 5.1 Part V.1: Routine Risk Minimisation Measures

Summaries of the routine risk minimisation measures for each safety concern included in Part II SVIII are provided in Table 5.1-1.

**Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern**

| Safety Concern | Routine risk minimisation activities |
|---|---|
| Teratogenicity | **Routine risk communication:**<br>**SmPC**<br>**Section 4.6 Fertility, pregnancy and lactation.**<br>**Section 4.8 Undesirable effects.**<br>**Section 5.3 Preclinical safety data.**<br>These sections highlight the potential teratogenic effects of lenalidomide.<br>**PL**<br>This document warns of the potential teratogenic effects of lenalidomide and the need to avoid pregnancy.<br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br>**SmPC**<br>**Section 4.3 Contraindications** |

## Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

| Safety Concern | Routine risk minimisation activities |
|---|---|
| | Lenalidomide is contraindicated in pregnant women and in FCBP unless all the conditions of the BMS PPP are met.<br>**Section 4.4 Special warnings and precautions for use**<br>This section highlights the potential teratogenic effects of lenalidomide. Stringent controls are required to ensure exposure of an unborn child to lenalidomide does not occur.<br>These include:<br>• Criteria for women of non-childbearing potential<br>• Counseling<br>• Contraception<br>• Pregnancy testing<br>• Precautions for men<br>• Additional precautions<br>• Reference to educational materials, prescribing and dispending restrictions.<br>**Other routine risk minimisation measures beyond the Product Information:**<br>Pack size:<br>The pack is based on a maximum 4-week supply of capsules to ensure that FCBP are required to obtain a new monthly prescription with a medically supervised pregnancy test.<br>Legal status:<br>Lenalidomide is subject to restricted medical prescription. |
| Serious Infection due to Neutropenia | **Routine risk communication:**<br>**SmPC**<br>**Section 4.8 Undesirable effects**<br>Listed as ADRs.<br>**PL**<br>This document warns that lenalidomide may cause neutropenia and infections, and that if a patient has, or has had a HBV infection, lenalidomide may cause the virus to become active again. Viral infections, including herpes zoster (shingles) and recurrence of hepatitis B infection, are listed as possible side effects<br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br>**SmPC**<br>**Section 4.2 Posology and method of administration**<br>Dose reduction advice for neutropenia.<br>**Section 4.4 Special warnings and precautions for use**<br>Warning of neutropenia, and infection with or without neutropenia, and advice for monitoring patients, including blood testing for neutropenia. Advice that patients should report febrile episodes promptly. |

**Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern**

| Safety Concern | Routine risk minimisation activities |
|---|---|
| | Advice that HBV status should be established before initiating treatment with lenaliomide and advice to exercise caution when lenalidomide is used in patients previously infected with HBV. In addition, advice that patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy.<br>**PL**<br>Advice to the doctor to check if the patient has ever had hepatitis B infection prior to lenalidomide treatment.<br>**Other routine risk minimisation measures beyond the Product Information:**<br>Legal status:<br>Lenalidomide is subject to restricted medical prescription. |
| SPM | **Routine risk communication:**<br>**SmPC**<br>**Section 4.8 Undesirable effects**<br>Listed as ADRs.<br>**PL**<br>Informs patients on:<br>• risk of SPM<br>• need for the doctor to carefully evaluate benefit and risk, and<br>• when lenalidomide is contraindicated.<br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br>**SmPC**<br>**Section 4.4 Special warnings and precautions for use**<br>This section highlights the risk of SPM, and advises standard cancer screening before and during lenalidomide use, with instigation of treatment as necessary.<br>**Other routine risk minimisation measures beyond the Product Information:**<br>Legal status:<br>Lenalidomide is subject to restricted medical prescription. |
| Tumour Flare Reaction (MCL and FL Indications) | **Routine risk communication:**<br>**SmPC**<br>**Section 4.8 Undesirable effects**<br>Listed as an ADR.<br>**PL**<br>This document details the risks associated with lenalidomide use, their symptoms, and any actions to be taken by the patient.<br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:** |

## Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

| Safety Concern | Routine risk minimisation activities |
|---|---|
| | **SmPC**<br>**Section 4.2 Posology and method of administration**<br>This section includes dose interruption advice for TFR.<br>**Section 4.4 Special warnings and precautions for use**<br>This section highlights the risk of TFR in lenalidomide-treated patients with CLL and other lymphomas, and warns that tumour flare may mimic disease progression.<br>**Other routine risk minimisation measures beyond the Product Information:**<br>Legal status:<br>Lenalidomide is subject to restricted medical prescription. |
| Cardiac Failure and Cardiac Arrhythmias | **Routine risk communication:**<br>**SmPC**<br>**Section 4.8 Undesirable effects**<br>Listed as ADRs.<br>**PL**<br>This document details the risks associated with lenalidomide use, their symptoms, and any actions to be taken by the patient.<br>Symptoms of cardiac failure and cardiac arrhythmia are listed as side effects.<br>**Routine risk minimisaion activities recommending specific clinical measures to address the risk:** None.<br>**Other routine risk minimisation measures beyond the Product Information:**<br>Legal status:<br>Lenalidomide is subject to restricted medical prescription. |
| Ischaemic Heart Disease (Including MI) | **Routine risk communication:**<br>**SmPC**<br>**Section 4.8 Undesirable effects**<br>Listed as ADRs.<br>**PL**<br>This document details the risks associated with lenalidomide use, their symptoms, and any actions to be taken by the patient.<br>Symptoms of MI are listed as side effects.<br>**Routine risk minimisaion activities recommending specific clinical measures to address the risk:**<br>**SmPC**<br>**Section 4.4 Special warnings and precautions for use**<br>This section highlights the possible occurrence of MI, and advises monitoring of patients with known risk factors. |

**Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern**

| Safety Concern | Routine risk minimisation activities |
|---|---|
| | **Other routine risk minimisation measures beyond the Product Information:**<br>Legal status:<br>Lenalidomide is subject to restricted medical prescription. |
| Off-label Use | **Routine risk communication:**<br>**SmPC**<br>**Section 4.4 Special warnings and precautions for use**<br>This section describes the collecting of detailed data relating to the indication in order to monitor closely the off-label use within the national territory.<br>**PL**<br>This document details the indications for which lenalidomide is approved.<br>**Routine risk minimisaion activities recommending specific clinical measures to address the risk:** None.<br>**Other routine risk minimisation measures beyond the Product Information:**<br>Legal status:<br>Lenalidomide is subject to restricted medical prescription. |

## 5.2 Part V.2: Additional Risk Minimisation Measures

Additional risk minimisation measures are presented in Table 5.2-1 and Annex 6.

**Table 5.2-1: Additional Risk Minimisation Measures**

| | |
|---|---|
| Pregnancy Prevention Programme (PPP) | **Objectives:**<br>The objectives of the BMS PPP are:<br>• Ensuring that exposure of an unborn child to lenalidomide does not occur.<br>• Ensuring early alert to the physician of any pregnancies.<br>• Educating patients and HCPs on the safe use of lenalidomide.<br>• Pregnancy testing and contraception requirements.<br>• A controlled access system to ensure that all appropriate measures have been performed prior to the drug being dispensed.<br>• Follow-up on the effectiveness of the PPP.<br>**Rationale for the additional risk minimisation activity:**<br>The BMS PPP is designed to minimise the risk of teratogenicity and provide education on the risk and the necessary steps to prevent foetal exposure.<br>**Target audience and planned distribution path:**<br>Proposed actions<br>The key elements of the BMS PPP are set out below and further details are provided as Annexes in previous RMPs. |

**Table 5.2-1: Additional Risk Minimisation Measures**

| | |
|---|---|
| | • Direct communication with the HCP prior to launch ('Dear HCP' letter).<br>• Educational Programme<br>• Therapy management<br>• Prescribing controls<br>• Dispensing controls<br>• Assessment.<br><br>**Plans to evaluate the effectiveness of the interventions and criteria for success:**<br><u>Proposed review period</u><br>The BMS PPP will be analysed on an ongoing basis and summarised at the time of the PSUR with respect to any pregnancy exposures. Additional information to be provided in the updates include:<br>• Status of the implementation in each Member State.<br>• Any adaptations to the PPP will be included as an update.<br>• The results of any compliance measurements as process indicators undertaken in individual countries according to country specific agreements with NCAs.<br>• Reports of pregnancy exposure to be reviewed on an ongoing basis and summarised at the time of the PSUR overall and by country.<br>• Root causes for pregnancy exposure.<br>• Outcome of pregnancy.<br>• Modifications and corrective action will be taken accordingly.<br><u>Criteria for Success:</u><br>Outcome indicator: pregnancy exposures. |
| Additional Patient Educational Materials<br>• Educational brochure for patients<br>• Patient card<br>• Risk awareness forms | **Objectives:**<br>Provision of information to the patients for the risk of:<br>• Teratogenicity<br><br>**Rationale for the additional risk minimisation activity:**<br>Patients to understand the occurrence of the risks specified above and the appropriate management of these risks.<br><br>**Target audience and planned distribution path:**<br>The target audience is patients who are prescribed lenalidomide and the planned distribution path is the provision of patient brochure by healthcare professionals.<br><br>**Plans to evaluate the effectiveness of the interventions and criteria for success:**<br>Expedited reporting (E+R) as per EU guidance, GVP<br>PSUR as per EU guidance, GVP (E+R)<br>[E = Evaluation; R = Reporting]<br><u>Methods of assessment</u><br>AE reports to be reviewed on an ongoing basis. AEs to be summarised at the time of the PSUR.<br>Assessment through PASSes.<br>Modifications and corrective action will be taken accordingly. |

**Table 5.2-1: Additional Risk Minimisation Measures**

| | |
|---|---|
| | Criteria for Success:<br>Outcome Indicator: Frequency and severity of events. No significant increase in frequency of reports in the postmarketing setting as presented in the SmPC.<br>Planned Dates for Assessment:<br>Next PSUR update with next data lock point (DLP) covered. |
| Direct HCP Communication Prior to Launch ('Dear HCP' Letter) | **Objectives:**<br>Provision of information to the patients for the risk of:<br>• Teratogenicity<br>• SPM<br>**Rationale for the additional risk minimisation activity:**<br>HCPs to understand the occurrence of the risks specified above and the appropriate management of these risks<br>**Target audience and planned distribution path:**<br>The target audience is HCPs who intend to prescribe lenalidomide.<br>**Plans to evaluate the effectiveness of the interventions and criteria for success:**<br>Expedited reporting (E+R) as per EU guidance, GVP<br>PSUR as per EU guidance, GVP (E+R)<br>[E = Evaluation; R = Reporting]<br>Methods of assessment<br>AE reports to be reviewed on an ongoing basis. AEs to be summarised at the time of the PSUR.<br>Assessment through PASSes.<br>Modifications and corrective action will be taken accordingly.<br>Criteria for Success:<br>Outcome Indicator: Frequency and severity of events. No significant increase in frequency of reports in the postmarketing setting as presented in the SmPC.<br>Planned Dates for Assessment:<br>Next PSUR update with next DLP covered. |
| Additional HCP Educational Materials:<br>• Educational Healthcare Professional brochure<br>• Information on where to find latest SmPC | **Objectives:**<br>Lenalidomide HCP Educational Materials to be provided to prescribing physicians and pharmacists for the risks of:<br>• Teratogenicity<br>• SPM<br>• TFR<br>**Rationale for the additional risk minimisation activity:**HCPs to understand the occurrence of the risks specified above and the appropriate management of these risks.<br>**Target audience and planned distribution path:**<br>The target audience is HCPs who intend to prescribe lenalidomide. |

**Table 5.2-1: Additional Risk Minimisation Measures**

| | |
|---|---|
| | **Plans to evaluate the effectiveness of the interventions and criteria for success:**<br>Expedited reporting (E+R) as per EU guidance, GVP<br>PSUR as per EU guidance, GVP (E+R)<br>[E = Evaluation; R = Reporting]<br>Methods of assessment<br>AE reports to be reviewed on an ongoing basis. AEs to be summarised at the time of the PSUR.<br>Assessment through PASSes.<br>Modifications and corrective action will be taken accordingly.<br>Criteria for Success:<br>Outcome Indicator: Frequency and severity of events. No significant increase in frequency of reports in the postmarketing setting as presented in the SmPC.<br>Planned Dates for Assessment:<br>Next PSUR update with next DLP covered. |

## 5.3 Part V.3:Summary of Risk Minimisation Measures

A summary of risk minimisation measures and pharmacovigilance activities by safety concern is provided in Table 5.3-1.

**Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities**

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| **Important Identified Risks** | | |
| Teratogenicity | **Routine risk minimisation measures:**<br>Section 4.3 of SmPC: contraindicated in pregnant women and in FCBP unless all the conditions of the BMS PPP are met.<br>Section 4.4 of SmPC: warnings and precautions for use<br>• Criteria for women of non-childbearing potential<br>• Counselling<br>• Contraception<br>• Pregnancy testing<br>• Precautions for men<br>• Additional precautions | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>• Expedited reporting of all pregnancies as a serious event.<br>• Contact details on reporting pregnancies in HCP Kit.<br>• Followup of all pregnancies until one year after delivery.<br>• Root cause analysis of failed BMS PPP as part of standard followup.<br>• Review of PSURs (periodic and cumulative). |

**Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities**

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| | • Reference to educational materials, prescribing and dispensing restrictions.<br>Section 4.6 of SmPC: fertility, pregnancy and lactation.<br>Sections 4.8 and 5.3 of SmPC: the potential teratogenic effects of lenalidomide are highlighted.<br>Pack size:<br>The pack is based on a maximum 4-week supply of capsules to ensure that FCBP are required to obtain a new monthly prescription with a medically supervised pregnancy test.<br>Legal status:<br>Lenalidomide is subject to restricted medical prescription. | |
| | **Additional risk minimisation measures:**<br>• BMS PPP<br>• Educational Programme<br>– Direct HCP communication prior to launch<br>– Direct HCP communication with findings from CC-501-TOX-004<br>– Educational Healthcare Professional brochure<br>– Educational brochures for patients<br>– Patient card<br>– Risk awareness forms<br>– Information on where to find latest SmPC<br>• Therapy management<br>• Criteria for determining FCBP, Contraceptive measures and pregnancy testing for FCBP<br>– Advice in SmPC, Dear HCP letter and educational materials | **Additional pharmacovigilance activities:**<br>• Additional monitoring of implementation of BMS PPP on a country specific basis in accordance with local legal network framework and with agreement of the relevant NCA (ie, monitoring of patient card completion, monitoring by external agency and surveys). |

**Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities**

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| | • System to ensure appropriate measures have been completed.<br>• Patient card to document childbearing status, counselling and pregnancy testing. | |
| Serious Infection due to Neutropenia | **Routine risk minimisation measures:**<br>• Section 4.2 of SmPC: dose reduction advice for neutropenia.<br>• Section 4.4 of SmPC: warning of neutropenia, and infection with or without neutropenia, and advice for monitoring patients, including blood testing for neutropenia. Advice that patients should report febrile episodes promptly. Advice regarding establishing HBV status before treatment, use in patients previously infected with HBV and monitoring for signs and symptoms of active HBV infection throughout therapy.<br>• Listed as ADRs in Section 4.8 of SmPC.<br>• Advice to patients in PL, including that the doctor is advised to check if the patient has ever had hepatitis B infection prior to starting lenalidomide treatment. | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>Event specific questionnaire for the collection of the AE and follow-up. |
| | **Additional risk minimisation measures:**<br>None. | **Additional pharmacovigilance activities:**<br>• Connect® MM Registry |
| SPM | **Routine risk minimisation measures:**<br>• Section 4.4 of SmPC warning of SPM and advice for cancer screening.<br>• Listed as ADRs in Section 4.8 of SmPC.<br>• Advice to patients provided in PL. | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>Event specific questionnaire for the collection of the AE and follow-up. |

**Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities**

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| | **Additional risk minimisation measures:**<br>• Dear HCP letter<br>• Educational Healthcare Professional brochure | **Additional pharmacovigilance activities:**<br>• Connect® MM Registry<br>• Long-term follow-up (at least 5 years from the date of the randomisation of the last patient in the study) for SPM in all BMS-sponsored clinical trials.<br>• Solicited reporting of SPM in all BMSsponsored clinical trials (status of trials will be updated with each PSUR and DSUR cycle). |
| Tumour Flare Reaction (MCL and FL Indications) | **Routine risk minimisation measures:**<br>• Section 4.2 of SmPC: dose interruption advice for TFR.<br>• Section 4.4 of SmPC warning.<br>• Listed as an ADR in Section 4.8 of SmPC.<br>**Additional risk minimisation measures:**<br>• Educational Healthcare Professional brochure | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>Event specific questionnaire for the collection of the AE and follow-up.<br>**Additional pharmacovigilance activities:**<br>• RRMCL PASS. |
| Cardiac Failure and Cardiac Arrhythmias | **Routine risk minimisation measures:**<br>• Listed as ADRs in Section 4.8 of SmPC.<br>• Listed in PL.<br>**Additional risk minimisation measures:**<br>None. | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>Event specific questionnaire for the collection of the AE and follow-up.<br>**Additional pharmacovigilance activities:**<br>• Connect® MM Registry.<br>• Revlimid TNE NDMM Registry |
| Ischaemic Heart Disease (including myocardial infarction) | **Routine risk minimisation measures:**<br>Close monitoring will continue.<br>• Myocardial infarction is included in Sections 4.4 and 4.8 of the SmPC. | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>Event specific questionnaire for the collection of the AE and follow-up. |

**Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities**

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| | **Additional risk minimisation measures:**<br>None. | **Additional pharmacovigilance activities:**<br>• Connect® MM Registry.<br>• Revlimid TNE NDMM Registry |
| **Important Potential Risk** | | |
| Off-label Use | **Routine risk minimisation measures:**<br>• Collection of off-label use data detailed in Section 4.4 of SmPC. | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>Collection of detailed data relating to indication as part of the national controlled aceess programme, where possible per national regulation. |
| | **Additional risk minimisation measures:**<br>None. | **Additional pharmacovigilance activities:**<br>• None |

# 6 PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for REVLMID (lenalidomide)

This is a summary of the risk management plan (RMP) for REVLIMID. The RMP details important risks of REVLIMID, how these risks can be minimised, and how more information will be obtained about REVLIMID 's risks and uncertainties (missing information).

REVLIMID's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how REVLIMID should be used.

This summary of the RMP for REVLIMID should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of REVLIMID's RMP.

## I. The medicine and what it is used for

REVLIMID is authorised in combination with rituximab for the treatment of adult patients with previously treated follicular lymphoma (FL); as monotherapy for the maintenance treatment of adult patients with newly diagnosed multiple myeloma (NDMM) who have undergone autologous stem cell transplantation (ASCT); in combination with dexamethasone for the treatment of MM in adult patients who have received at least one prior therapy; in combination with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone for the treatment of adult patients with previously untreated MM who are not eligible for transplant; as monotherapy for the treatment of adult patients with transfusion-dependent anaemia due to low- or intermediate 1 (INT-1) risk myelodysplastic syndrome (MDS) associated with an isolated deletion 5q (del 5q) cytogenetic abnormality when other therapeutic options are insufficient or inadequate; and as monotherapy for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (RRMCL) (see SmPC for the full indication). REVLIMID contains lenalidomide as the active substance and it is given by oral route of administration.

Further information about the evaluation of REVLIMID’s benefits can be found in REVLIMID’s EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine’s webpage: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000717/human_med_001034.jsp&mid=WC0b01ac058001d124.

## II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of REVLIMID, together with measures to minimise such risks and the proposed studies for learning more about REVLIMID's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk minimisation* measures.

In the case of REVLIMID, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of REVLIMID is not yet available, it is listed under 'missing information' below.

## *II.A List of important risks and missing information*

Important risks of REVLIMID are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of REVLIMID. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

**List of important risks and missing information**

| | |
|---|---|
| ***Important identified risks*** | Teratogenicity |
| | Serious infection due to neutropenia |
| | SPM |
| | Tumour Flare Reaction (MCL and FL Indications) |
| | Cardiac failure |
| | Cardiac arrhythmia |
| | Ischaemic heart disease (including myocardial infarction) |
| ***Important potential risks*** | Off-label use |
| ***Missing information*** | None |

## *II.B Summary of important risks*

### Important identified risks

| **Teratogenicity** | |
|---|---|
| Evidence for linking the risk to the medicine | Lenalidomide is structurally related to thalidomide, which is known to cause serious birth defects and death of the foetus. In nonclinical studies, lenalidomide induced malformations similar to those described with thalidomide. Therefore, a teratogenic effect of lenalidomide is expected and lenalidomide is contraindicated during pregnancy. |
| Risk factors and risk groups | The 'at risk' group comprises FCBP or female partners of male patients treated with lenalidomide and there are no risk factors. |
| Risk minimisation measures | Routine risk minimisation activities: Section 4.3 of SmPC: contraindicated in pregnant women and in FCBP unless all the conditions of the BMS PPP are met.<br>Section 4.4 of SmPC: warnings and precautions for use<br>• Criteria for women of non-childbearing potential<br>• Counselling<br>• Contraception<br>• Pregnancy testing<br>• Precautions for men<br>• Additional precautions<br>• Reference to educational materials, prescribing and dispensing restrictions.<br>Section 4.6 of SmPC: fertility, pregnancy and lactation.<br>Sections 4.8 and 5.3 of SmPC: the potential teratogenic effects of lenalidomide are highlighted.<br>Pack size:<br>The pack is based on a maximum 4-week supply of capsules to ensure that FCBP are required to obtain a new monthly prescription with a medically supervised pregnancy test.<br>Legal status: Lenalidomide is subject to restricted medical prescription.<br><br>Additional risk minimisation measures: BMS PPP<br>o Educational Programme<br>o Direct HCP communication prior to launch<br>o Direct HCP communication with findings from CC-501-TOX-004<br>o Educational HCP's kit to include: Educational Healthcare Professional brochure; Educational brochures for patients; Patient card; Risk awareness forms; Information on where to find latest SmPC<br>o Therapy management<br>o Criteria for determining FCBP, Contraceptive measures and pregnancy testing for FCBP<br>o Advice in SmPC, Dear HCP letter and educational materials<br>o System to ensure appropriate measures have been completed.<br>Patient card to document childbearing status, counselling and pregnancy testing. |

## Important identified risks

| | |
|---|---|
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>Additional monitoring of implementation of BMS PPP on a country specific basis in accordance with local legal framework and with agreement of the relevant NCA (ie, monitoring of patient card completion, monitoring by external agency and surveys). |
| **Serious Infection due to Neutropenia** | |
| Evidence for linking the risk to the medicine | In clinical trials, neutropenia has been reported as a consequence of lenalidomide treatment; ≥ Grade 3 and ≥ Grade 4 infections have occurred in the context of neutropenia (any grade). |
| Risk factors and risk groups | Haematologic malignancies by themselves or by virtue of their therapeutic strategies, chemotherapy, radiation or haematopoietic stem cell transplant put patients at risk of infections. The introduction of stem cell transplantation and novel anti-myeloma agents has improved the outcome of patients with MM. These advances have transformed MM into a chronic condition, with multiple relapses and salvage therapies, all of which results in cumulative immunosuppression and higher risk of infection. For example, application of stem cell transplantation has broadened the spectrum of infection to include those caused by Clostridium difficile, cytomegalovirus, and opportunistic moulds. Risk factors include myeloma-related innate immunodeficiency, which involves various arms of the immune system and includes B-cell dysfunction (manifested as hypogammaglobulinemia). Polyclonal hypogammaglobulinemia has been classically associated with infection by encapsulated bacteria, such as Streptococcus pneumoniae and Haemophilus influenzae. Myeloma and treatment-associated organ dysfunctions and comorbidities also increase the risk of infection. These dysfunctions and comorbidities include (1) renal failure (cast nephropathy, hypercalcemia, deposition disease, and others), respiratory compromise, caused by collapse of thoracic vertebra and opiate therapy (which may depress the central nervous system) given to patients with painful fractures (3) severe alimentary mucosal damage (caused by chemotherapy, radiation therapy, or graft-versus-host disease) (4) hyperglycemia induced by dexamethasone (5) transfusional iron overload and (6) the multisystem involvement by myeloma-associated deposition diseases (AL-amyloidosis and light chain deposit disease). Indeed, levels of CD4+ T cells, particularly naive and activated subsets, decrease significantly with increasing cycles of chemotherapy, a decrease strongly associated with opportunistic infections. Finally, myeloma typically affects an older population, with a median age of 62 to 73 years. These patients frequently experience an age-related decline in physiologic reserve of various organs and from other age-related conditions, including frailty, geriatric syndromes, cognitive dysfunction, and social isolation, all of which may increase the risk of infection.<br>Lenalidomide treatment in combination with dexamethasone in MM patients with at least one prior therapy is associated with a higher incidence of Grade 4 neutropenia compared to placebo-dexamethasone treated patients (SmPC, Section 4.4). The combination of lenalidomide with melphalan and prednisone in clinical trials of NDMM patients is associated with a higher incidence of Grade 4 neutropenia than MPp+p treated patients (SmPC, Section 4.4).<br>The proportion of patients who experienced Grade 3 or 4 myelosuppression in one study of lenalidomide-treated patients with MM was significantly higher for patients who had prior high-dose chemotherapy and stem cell transplantation, compared with those that did not. Impairment of antibody response, neutropenia, treatment with glucocorticoids, and reduction of normal |

## Important identified risks

| | |
|---|---|
| | Ig all increase the likelihood of infection. While a much greater proportion of lenalidomide/dexamethasone patients experienced neutropenia relative to placebo/dexamethasone patients, this increased risk did not translate into an infection risk of the same magnitude in either the total study population or in the study population restricted to Grade 3 or 4 toxicities.<br>Lenalidomide treatment in MDS patients is associated with a higher incidence of Grade 3 or 4 neutropenia compared with patients on placebo (SmPC, Section 4.4). In patients with MDS, those experiencing neutropenia while receiving lenalidomide may be at increased risk for infections. |
| Risk minimisation measures | Routine risk minimisation measures:<br>• Section 4.2 of SmPC: dose reduction advice for neutropenia.<br>• Section 4.4 of SmPC: warning of neutropenia, and infection with or without neutropenia, and advice for monitoring patients, including blood testing for neutropenia. Advice that patients should report febrile episodes promptly. Advice regarding establishing HBV status before treatment, use in patients previously infected with HBV and monitoring for signs and symptoms of active HBV infection throughout therapy.<br>• Listed as ADRs in Section 4.8 of SmPC.<br>• Advice to patients in PL, including that the doctor is advised to check if the patient has ever had hepatitis B infection prior to starting lenalidomide treatment.<br><br>Additional risk minimisation measures: None. |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• Connect® MM Registry |
| **SPM** | |
| Evidence for linking the risk to the medicine | In clinical trials, AML and B-cell malignancies have been reported in patients treated with lenalidomide.<br>Based on clinical trial data, lenalidomide may increase the risk of NMSC. Patients with MM also have an increased risk of NMSC.<br>Patients treated with lenalidomide may be at increased risk of developing new cancers. The reason for this is not clear, but further investigations are being undertaken. |
| Risk factors and risk groups | **MDS Populations (Haematologic Malignancies)**<br>A study to identify prognostic factors for progression to leukaemia (LFS) and OS was reported by Malcovati. Four hundred seventy six patients first diagnosed with de novo MDS between 1992 and 2002 were evaluated. In one of the earliest studies to report the negative effects of developing a transfusion requirement, Malcovati reported an increased risk associated with transfusion burden when analysed as a time-dependent covariate in a combined group of patients with RA, RARS or MDS with del(5q) (HR = 3.46).<br>Further development of the WPSS a learning cohort of 426 Italian MDS patients and a validation cohort of 193 German MDS patients was reported by Malcovati and colleagues. In a multivariable analysis of the Italian patients stratified by WHO subgroups, cytogenetics (HR = 1.48) and transfusion requirement (HR = 2.53) significantly affected OS and risk of AML (HR = 1.3 and HR = 2.4, respectively). These findings were corroborated in the subsequent multivariable analysis of German MDS patients stratified by WHO |

## Important identified risks

subgroups, with cytogenetics (HR = 1.84) and transfusion dependency (HR = 1.85) and risk of AML (HR = 2.27 and HR = 2.25, respectively). Mallo reported the results of a cooperative study designed to assess prognostic factors for OS and progression to AML in 541 patients with de novo MDS and del 5q. In multivariate analyses the most important predictors of both OS and AML progression were number of chromosomal abnormalities ($p < 0.001$ for both outcomes), platelet count ($p < 0.001$ and $p = 0.001$, respectively) and proportion of bone marrow blasts ($p < 0.001$ and $p = 0.016$, respectively). Transfusion burden was not addressed in this study.

Knuendgen assessed the risk of AML progression and death in 295 lenalidomide-treated MDS-003 and MDS-004 patients versus 125 MDS patients with del 5q from a large multicentre registry who had received best supportive care only including ESAs. In the final multivariate Cox proportional hazard models, lenalidomide treatment was not associated with progression to AML (HR 0.939; $p = 0.860$). Significant factors associated with an increased risk of AML progression were complex cytogenetics (del 5q plus > 1 abn; HR 3.627; $p = 0.002$), bone marrow blasts 5% to 10% (HR 2.215; $p = 0.016$), and higher transfusion burden (HR 1.097 [10% increase in risk per unit at baseline]; $p = 0.029$). Higher haemoglobin levels were associated with a reduced risk (HR 0.857; $p = 0.054$). Regarding survival, lenalidomide treatment was associated with a reduced risk of death (HR 0.597; $p = 0.012$).

Other factors associated with decreased mortality were higher haemoglobin levels (HR 0.883; $p = 0.028$), higher platelet counts (HR 0.999; $p = 0.035$), and female sex (HR 0.598; $p = 0.002$). Higher transfusion burden (HR 1.056; $p = 0.037$) and age (HR 1.049; $p < 0.001$) increased the risk of death.

Mutations in the TP53 gene have been well described as a poor prognostic variable and associated with chemotherapy resistance in a wide variety of malignancies including high-risk MDS and AML.

**MCL Population (Haematologic Malignancies)**

There is no information available.

**NMSC**

Risk factors for NMSC include: increased sun or ultraviolet radiation exposure; physical factors such as fair skin, red or blond hair, and light eye colour; chemical carcinogens such as, arsenic, tobacco, and oral methoxsalen; ionising radiation; and previous history of NMSC.

- **Prolonged survival as a result of improved therapies**

As previously noted, the 5-year relative survival among MM patients has increased from 24.6% among patients first diagnosed in 1975 to 1977 to 44.9% among patients first diagnosed between 2003 and 2009.

Due to improvements in the care of patients with cancer, the number of cancer survivors has been increasing in recent years. Increased longevity increases the risk of developing second malignancy, including NMSC.

- **Immunosuppression associated with transplantation procedures**

Immunosuppression is a risk factor for NMSC. Patients receiving immunosuppressive therapy following solid organ transplantation and those receiving bone marrow transplants have an increased risk of skin cancer. In a small series of patients (n = 43) receiving nonmyeloablated haematopoietic cell transplants, 6 patients developed squamous cell carcinoma (n = 3), basal cell carcinoma (n = 2), or malignant melanoma (n = 2). In another study, the most frequently observed secondary malignancies among patients (n = 557) receiving allogeneic bone marrow transplants were NMSC. Out of 31

## Important identified risks

| | |
|---|---|
| | secondary malignancies, 5 were basal cell carcinoma and 4 were squamous cell carcinoma skin cancers. |
| Risk minimisation measures | Routine risk minimisation measures:<br>• Section 4.4 of SmPC warning of SPM and advice for cancer screening.<br>• Listed as ADRs in Section 4.8 of SmPC.<br>• Advice to patients provided in PL.<br>Additional risk minimisation measures:<br>• Dear HCP letter.<br>• Educational HCP brochure. |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• Connect® MM Registry.<br>• Long-term follow-up (at least 5 years from the date of the randomisation of the last patient in the study) for SPM in all BMS-sponsored clinical trials.<br>• Solicited reporting of SPM in all BMS-sponsored clinical trials (status of clinical trials will be updated with each PSUR and DSUR cycle). |

**Tumour Flare Reaction (MCL and FL Indications)**

| | |
|---|---|
| Evidence for linking the risk to the medicine | Based on clinical trial data, lenalidomide may increase the risk of TFR in patients with CLL and other lymphomas. |
| Risk factors and risk groups | Tumour flare reaction has been associated with greater tumour burden in CLL In Study MCL-002, in the final multivariate model, high MIPI score at diagnosis ($p = 0.084$) and bulky disease at baseline ($p = 0.020$) appeared to be strong and independent risk factors for TFR. |
| Risk minimisation measures | Routine risk minimisation measures:<br>• Section 4.2 of SmPC: dose interruption advice for TFR.<br>• Section 4.4 of SmPC warning.<br>• Listed as an ADR in Section 4.8 of SmPC.<br>Additional risk minimisation measures:<br>Educational HCP brochure. |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>RRMCL PASS. |

**Cardiac Failure and Cardiac Arrhythmias**

| | |
|---|---|
| Evidence for linking the risk to the medicine | Based on clinical trial data, a higher incidence of cardiac failure has been observed; the reason for this is not clear.<br>Based on clinical trial data, a higher incidence of cardiac arrhythmias was observed in the lenalidomide arm. |
| Risk factors and risk groups | No particular risk groups or risk factors have been identified for lenalidomide. In MM and MDS no differences in frequency, severity, serious outcomes and apparent risk level of cardiac failure AEs have been observed.<br>Cardiac symptoms in patients with MDS are often due to anaemia and may be due to iron overload and side effects of therapy. In a study of 840 MDS patients, Della Porta reported that heart failure (28% versus 18%, $p = 0.001$) and cardiac death (69% versus 55%, $p = 0.03$) were significantly more frequent |

## Important identified risks

| | |
|---|---|
| | in transfusion-dependent patients. In a Cox analysis with time-dependent covariates, transfusion-dependent patients showed an increased risk of non-leukemic death (HR = 2.12; $p \leq 0.001$), heart failure (HR = 1.34; $p = 0.03$), and cardiac death (HR = 2.99; $p = 0.01$). The development of secondary iron overload significantly affected the risk of non-leukemic death and OS (HR = 1.25 and 1.16, respectively; $p < 0.001$), and this effect was maintained after adjusting for transfusion burden. Iron overload specifically increased the risk of developing heart failure (HR = 1.17, $p < 0.001$). General risk factors for CHF include increasing age, previous heart disease, diabetes, hypertension, amyloidosis, and previous anthracycline based chemotherapy treatment.<br>Standard risk factors for atrial fibrillation include advancing age, European ancestry, body size (greater height and body mass index), electrocardiography features (left ventricular hypertrophy, left atrial enlargement), diabetes, systolic blood pressure and presence of cardiovascular disease (ie, CHD, heart failure, valvular heart disease). Other factors include clinical and subclinical hyperthyroidism, chronic kidney disease, and heavy alcohol consumption. Familial aggregation studies have identified a role for genetic factors, although such factors probably account for a small proportion of cases. In a case-control study of 385 eligible cases of new-onset atrial fibrillation embedded within the Rotterdam study, the risk of new-onset atrial fibrillation was significantly higher for persons who received a corticosteroid prescription within 1 month before the atrial fibrillation index date. Only high-dose corticosteroid use was associated with increased risk (OR = 6.07; 95% CI: 3.90-9.42). The association of atrial fibrillation was independent of indication for use. Risks were increased not only in patients with asthma or chronic obstructive pulmonary disease, but also in patients with rheumatic, allergic, or malignant haematologic diseases. |
| Risk minimisation measures | Routine risk minimisation measures:<br>• Listed as ADRs in Section 4.8 of SmPC<br>• Listed in PL.<br><br>Additional risk minimisation measures: None. |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• Connect® MM Registry.<br>• Revlimid TNE NDMM Registry. |

**Ischaemic Heart Disease (Including Myocardial Infarction)**

| | |
|---|---|
| Evidence for linking the risk to the medicine | In clinical trials, ischaemic heart disease has been reported in patients treated with lenalidomide. Myocardial infarction occurs relatively often in individuals of the older age groups that most often develop the target indications of MM, MDS, MCL and FL. |
| Risk factors and risk groups | Risk factors for 10-year coronary risk based upon the Framingham Heart Study include elevated blood pressure, elevated cholesterol, high-density lipoprotein-C, presence of diabetes and cigarette smoking. These factors are in addition to the well-known relationships between coronary risk and age and gender.<br>In Europe, smoking remains a major public health issue and about 20% of death from CVD in men and about 3% of deaths from CVD in women are due to smoking. Levels of obesity are high across Europe in both adults and children, although rates vary substantially between countries. Participation in physical activity is low. Increases in population body mass index over the |

## Important identified risks

| | |
|---|---|
| | interval 1980 to 2008 were noted in almost all countries. The prevalence of diabetes in Europe is high and has increased rapidly over the last ten years, increasing by more than 50% in many countries. |
| Risk minimisation measures | Routine risk minimisation measures:<br>The association between ischaemic heart disease and lenalidomide is unknown. Close monitoring will continue.<br>Myocardial infarction is included in Sections 4.4 and 4.8 of the SmPC.<br><br>Additional risk minimisation measures: None. |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• Connect® MM Registry.<br>• Revlimid TNE NDMM Registry. |

## Important potential risks

| **Off-label Use** | |
|---|---|
| Evidence for linking the risk to the medicine | There is potential for the use of lenalidomide in indications other than the approved indications. |
| Risk factors and risk groups | Not applicable |
| Risk minimisation measures | Routine risk minimisation measures:<br>Collection of off-label use data detailed in Section 4.4 of SmPC.<br>Additional risk minimisation measures:<br>None. |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>None. |

## *II.C Post-authorisation development plan*

### *II.C.1 Studies which are conditions of the marketing authorisation*

The following studies are conditions of the marketing authorisation:

**Revlimid TNE NDMM Registry (CC-5013-MM-034)**

Purpose of the study: The primary objectives are to compare the incidence of cardiovascular events between TNE NDMM patients treated with a first-line lenalidomide-containing regimen and those treated with a first-line non lenalidomide-containing regimen; and to identify, quantify, and characterise risk factors for cardiovascular events in this population of TNE NDMM patients.

### *II.C.2 Other studies in post-authorisation development plan*

**Monitoring of Pregnancy Prevention Programme Implementation**

Purpose of the study: Monitoring implementation of the pregnancy prevention programme on a country specific basis as agreed with the relevant National Competent Authority..

**Connect® MM: The Multiple Myeloma Disease Registry**

Purpose of the study: 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 transplant, as well as diagnostic patterns and occurrence of SPM in a 'real world' population.

**RRMCL PASS (CC-5013-MCL-005)**

Purpose of the study: To quantify and characterise the event of tumour flare reaction (TFR) by tumour burden and the proportion of early deaths by tumour burden in patients treated with lenalidomide in a 'real world' setting.

# ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of Contents

Bristol Myers Squibb™
P.O BOX 4000, B.3140,
Princeton, NJ-08543-4000

**Event-Specific Questionnaire for HCP – Pregnancy Background**

**(Patient or Partner of Patient)**
**Telephone: 1-800-721-5072**
**Fax: 609-818-3804**
**Email: Worldwide.Safety@BMS.com**

| | | | |
|---|---|---|---|
| **Reporter Information** | | | |
| REPORTER NAME: | | | |
| ADDRESS: | | CITY, STATE, ZIP, COUNTRY: | |
| PHONE NO.: | | FAX NO.: | |
| **Obstetrician Information (Please provide)** | | | |
| OBSTETRICIAN NAME: | | | |
| ADDRESS: | | CITY, STATE, ZIP, COUNTRY: | |
| PHONE NO.: | | FAX NO.: | |
| **Patient Information** | | | |
| PATIENT ID: | DATE OF BIRTH: | ETHNICITY: ☐ WHITE ☐ BLACK ☐ ASIAN ☐ OTHER, SPECIFY: | |
| **Partner of Patient Information** ☐ Not applicable | | | |
| DATE OF BIRTH: | ETHNICITY: ☐ WHITE ☐ BLACK ☐ ASIAN ☐ OTHER, SPECIFY: | | |
| **Patient Treatment Information: [DRUG NAME]®** | | | |
| LOT NO.: | EXPIRY DATE: | DOSE: | FREQUENCY: |
| ROUTE: | START DATE: | STOP DATE: | |
| INDICATION FOR USE: | | | |
| CYTOGENETIC ABNORMALITIES: ☐ NO ☐ YES If Yes, specify: | | | |

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| **Current Pregnancy** | | | |
|---|---|---|---|
| Date of Last Menstrual Period: | | Estimated Delivery Date: | |
| PREGNANCY TEST | DATE | REFERENCE RANGE | RESULT |
| Urine qualitative | | | |
| Serum quantitative | | | |
| **Prenatal Tests** | | | |
| | DATE | RESULT | |
| Ultrasound | | | |
| Ultrasound | | | |
| Ultrasound | | | |
| Amniocentesis | | | |
| Maternal serum AFP | | | |

| **Pregnancy History** | | |
|---|---|---|
| No. of previous pregnancies:<br>Date of last pregnancy: | No. of full term births: | No. of preterm births: |
| No. of fetal deaths: | No. of living children: | No. of abortions:<br>Elective _____ Spontaneous _____ |

Type of delivery: ☐ Vaginal ☐ C-section

Did birth defect occur in any previous pregnancy? ☐ No ☐ Yes ☐ Unknown

If Yes,
specify: _____

Did a stillbirth or spontaneous abortion occur in any previous pregnancy? ☐ No ☐ Yes ☐ Unknown

1) If Yes, in what week of pregnancy did the stillbirth or spontaneous abortion occur?
Week: _____

2) Was there any birth defect noted? ☐ No ☐ Yes, If Yes, specify: _____

**Relevant Medical History**

☐ NO ☐ YES IF YES, SPECIFY:

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| Medical History | Date of Diagnosis | Medical History | Date of Diagnosis |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |

**Social History**

Alcohol Use ☐ No ☐ Yes, if yes, amount/unit consumed per day:

| Tobacco Use ☐ No ☐ Yes | IV or recreational drug use ☐ No ☐ Yes, If Yes, specify: |
|---|---|

**Family History:** Congenital Abnormalities ☐ No ☐ Yes, If Yes, specify:

If there is a family history of congenital abnormalities, was there a consultation with a Geneticist?

☐ No ☐ Yes, If Yes, specify:

**Environmental Exposure** (e.g. Radiation, Chemical EXPOSURE) ☐ No ☐ Yes, If Yes, specify:

**Medications/Treatments (including herbal, alternative and over-the-counter medicines and dietary supplements) During Pregnancy**

| Medication/Treatment | Start Date | Stop Date/ Ongoing | Indication |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

**Adverse Event(s) During Pregnancy**

| Event(s) | Onset Date | Stop Date / Ongoing | Serious | | Causal Relationship to [DRUG NAME] ® | |
|---|---|---|---|---|---|---|
| | | | Y/N | Serious Criteria[1] | Y/N | If no, what medications, disease states, etc, played a role in the event? |

| | | | | | | |
|---|---|---|---|---|---|---|
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| | | | | | | |

[1] Serious Criteria: **1**) death, **2**) life-threatening, **3**) required inpatient hospitalization or prolongation of existing hospitalization, **4**) a persistent or significant disability/incapacity, **5**) a congenital anomaly/birth defect, **6**) medically significant

**Root Cause of Pregnancy**

**1. What forms of birth control was your patient using while on [Drug Name] before becoming pregnant or impregnating their partner? Please check all that apply.**

| | | |
|---|---|---|
| Tubal ligation | ☐ Yes | ☐ No |
| IUD | ☐ Yes | ☐ No |
| Hormonal birth control | ☐ Yes | ☐ No |
| Partner's vasectomy | ☐ Yes | ☐ No |
| Male latex or synthetic condom | ☐ Yes | ☐ No |
| Diaphragm | ☐ Yes | ☐ No |
| Cervical cap or shield | ☐ Yes | ☐ No |
| Spermicide or sponge | ☐ Yes | ☐ No |
| Withdrawal | ☐ Yes | ☐ No |
| Abstinence | ☐ Yes | ☐ No |

**2. Was your patient or their partner without contraception for even one day at any time during use of** [DRUG NAME] **®?**

☐ No, please proceed to Question 5

☐ Yes, please answer Question 3, Question 4, Question 5, and Question 6

**3. If applicable per Question 2, how often did your patient have unprotected sexual intercourse?**

☐ Multiple times

☐ Once a week

☐ Once every 2 weeks

☐ Once a month

☐ Not at all

☐ Other, specify _____

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**4. If applicable per Question 2, why did your patient and/or their partner interrupt or stop using contraception?**

☐ Wanted a child

¨ Partner disapproved

☐ Side effects

☐ Health concerns

☐ Inconvenient to use

☐ Other, specify _____

**5. Please ask your patient if they received the [**Drug Name**]® Patient Information (e.g. Medication Guide or patient leaflet).**

☐ No, please proceed to Question 5.3

☐ Yes, please answer Question 5.1

**5.1 Please ask your patient if they read the [**Drug Name**]® Patient Information (e.g. Medication Guide or patient leaflet).**

☐ No, please proceed to Question 5.3

☐ Yes, please answer Question 5.2

**5.2 Please ask your patient if they understood the information in the [**Drug Name**]® Patient Information (e.g. Medication Guide or patient leaflet).**

☐ No, please proceed to Question 5.3

☐ Yes, please proceed to Question 5.3

**5.3 Please ask your patient where most of their knowledge about contraception during [**Drug Name**]® use came from.**

☐ Physician who prescribed [Drug Name]®

☐ Patient Guide to the [Drug Name] REMS® Program

☐ [Drug Name]® Patient Information (e.g. Medication Guide or patient leaflet)

☐ Other, specify: _____

**6. Please ask your patient if they felt that they and their partner had a good understanding of the risk of pregnancy during [**Drug Name**]® use.**

☐ No

☐ Yes

☐ Don't know

**SIGNATURE OF PERSON COMPLETING THIS FORM:** _____ **DATE:** _____

**MCN:**

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**Event-Specific Questionnaire for HCP – Pregnancy Follow-up**
**(Patient or Partner of Patient)**
**Telephone: 1-800-721-5072**
**Fax: 609-818-3804**
**Email: Worldwide.Safety@BMS.com**

| **Date:** | **Period Covered:** _____ (Date) to _____ (Date) |
|---|---|

| **Reporter Information** | |
|---|---|
| REPORTER NAME: | |
| ADDRESS: | CITY, STATE, ZIP, COUNTRY: |
| PHONE NO.: | FAX NO.: |
| **Name of Patient or Pregnant Partner of Male Patient:** | |
| **Current Pregnancy** | |

Prenatal Tests (If any additional medical records relating to these prenatal tests are available, please attach along with this form)

| TEST | DATE | RESULT |
|---|---|---|
| Ultrasound | | |
| Ultrasound | | |
| Ultrasound | | |
| Amniocentesis | | |
| Maternal Serum AFP | | |
| Other Tests, Specify: | | |

**Pregnancy Type**

☐ SINGLETON ☐ TWIN ☐ TRIPLET ☐ OTHER, SPECIFY: _____

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Princeton, NJ-08543-4000

**Medications/Treatments (including herbal, alternative and over-the-counter medicines and dietary supplements) During Pregnancy**

| MEDICATION/TREATMENT | START DATE | STOP DATE/ CONTINUING | INDICATION |
|---|---|---|---|
| | | | |
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**Adverse Event(s) During Pregnancy**

| EVENT(S) | ONSET DATE | STOP DATE / ONGOING | SERIOUS | | CAUSAL RELATIONSHIP TO [Drug Name] ® | |
|---|---|---|---|---|---|---|
| | | | Y/N | SERIOUS CRITERIA[1] | Y/N | IF NO, WHAT MEDICATIONS, DISEASE STATES, etc., PLAYED A ROLE IN THE EVENT? |
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[1] Serious Criteria: **1**) death, **2**) life-threatening, **3**) required inpatient hospitalization or prolongation of existing hospitalization, **4**) a persistent or significant disability/incapacity, **5**) a congenital anomaly/birth defect, **6**) medically significant

**DATE:**

**SIGNATURE OF PERSON COMPLETING THIS FORM:** _____ _____

**MCN:**

Bristol Myers Squibb™
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**Event-Specific Questionnaire for HCP – Pregnancy Follow-up**
**(Patient or Partner of Patient)**
**Telephone: 1-800-721-5072**
**Fax: 609-818-3804**
**Email: Worldwide.Safety@BMS.com**

| **Date:** | **Period Covered:** _____ (Date) to _____ (Date) |
|---|---|

| **Reporter Information** | |
|---|---|
| REPORTER NAME: | |
| ADDRESS: | CITY, STATE, ZIP, COUNTRY: |
| PHONE NO.: | FAX NO.: |
| **Name of Patient or Pregnant Partner of Male Patient:** | |
| **Current Pregnancy** | |
| Prenatal Tests (If any additional medical records relating to these prenatal tests are available, please attach along with this form) | |

| TEST | DATE | RESULT |
|---|---|---|
| Ultrasound | | |
| Ultrasound | | |
| Ultrasound | | |
| Amniocentesis | | |
| Maternal Serum AFP | | |
| Other Tests, Specify: | | |

**Pregnancy Type**

☐ SINGLETON ☐ TWIN ☐ TRIPLET ☐ OTHER, SPECIFY: _____

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Princeton, NJ-08543-4000

**Medications/Treatments (including herbal, alternative and over-the-counter medicines and dietary supplements) During Pregnancy**

| MEDICATION/TREATMENT | START DATE | STOP DATE/ CONTINUING | INDICATION |
|---|---|---|---|
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**Adverse Event(s) During Pregnancy**

| EVENT(S) | ONSET DATE | STOP DATE / ONGOING | SERIOUS | | CAUSAL RELATIONSHIP TO [Drug Name] ® | |
|---|---|---|---|---|---|---|
| | | | Y/N | SERIOUS CRITERIA[1] | Y/N | IF NO, WHAT MEDICATIONS, DISEASE STATES, etc., PLAYED A ROLE IN THE EVENT? |
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[1] Serious Criteria: **1**) death, **2**) life-threatening, **3**) required inpatient hospitalization or prolongation of existing hospitalization, **4**) a persistent or significant disability/incapacity, **5**) a congenital anomaly/birth defect, **6**) medically significant

**DATE:**

**SIGNATURE OF PERSON COMPLETING THIS FORM:** _____ _____

**MCN:**

Bristol Myers Squibb™
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Princeton, NJ-08543-4000

**Event-Specific Questionnaire for HCP – Pregnancy Follow-up**
**(Patient or Partner of Patient)**
**Telephone: 1-800-721-5072**
**Fax: 609-818-3804**
**Email: Worldwide.Safety@BMS.com**

| **Date:** | **Period Covered:** _____ (Date) to _____ (Date) |
|---|---|
| **Reporter Information** | |
| REPORTER NAME: | |
| ADDRESS: | CITY, STATE, ZIP, COUNTRY: |
| PHONE NO.: | FAX NO.: |
| **Name of Patient or Pregnant Partner of Male Patient:** | |
| **Current Pregnancy** | |
| Prenatal Tests (If any additional medical records relating to these prenatal tests are available, please attach along with this form) | |

| TEST | DATE | RESULT |
|---|---|---|
| Ultrasound | | |
| Ultrasound | | |
| Ultrasound | | |
| Amniocentesis | | |
| Maternal Serum AFP | | |
| Other Tests, Specify: | | |

**Pregnancy Type**

☐ SINGLETON ☐ TWIN ☐ TRIPLET ☐ OTHER, SPECIFY: _____

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Princeton, NJ-08543-4000

**Medications/Treatments (including herbal, alternative and over-the-counter medicines and dietary supplements) During Pregnancy**

| MEDICATION/TREATMENT | START DATE | STOP DATE/ CONTINUING | INDICATION |
|---|---|---|---|
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**Adverse Event(s) During Pregnancy**

| EVENT(S) | ONSET DATE | STOP DATE / ONGOING | SERIOUS | | CAUSAL RELATIONSHIP TO [Drug Name] ® | |
|---|---|---|---|---|---|---|
| | | | Y/N | SERIOUS CRITERIA[1] | Y/N | IF NO, WHAT MEDICATIONS, DISEASE STATES, etc., PLAYED A ROLE IN THE EVENT? |
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[1] Serious Criteria: **1**) death, **2**) life-threatening, **3**) required inpatient hospitalization or prolongation of existing hospitalization, **4**) a persistent or significant disability/incapacity, **5**) a congenital anomaly/birth defect, **6**) medically significant

**SIGNATURE OF PERSON COMPLETING THIS FORM:** _____ **DATE:** _____

**MCN:**

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Princeton, NJ-08543-4000

**Event-Specific Questionnaire for HCP – Pregnancy Outcome**
**(Patient or Partner of Patient)**
**Telephone: 1-800-721-5072**
**Fax: 609-818-3804**
**Email: Worldwide.Safety@BMS.com**

| **Reporter Information** | | | |
|---|---|---|---|
| REPORTER NAME: | | | |
| ADDRESS: | | | CITY, STATE, ZIP, COUNTRY: |
| PHONE NO.: | | | FAX NO.: |
| **Patient Information** | | | |
| PATIENT ID: | DATE OF BIRTH: | | ETHNICITY: ☐ WHITE ☐ BLACK ☐ ASIAN ☐ OTHER, SPECIFY: |
| **Partner of Patient Information** ☐ Not applicable | | | |
| DATE OF BIRTH: | ETHNICITY: ☐ WHITE ☐ BLACK ☐ ASIAN ☐ OTHER, SPECIFY: | | |
| **Pregnancy Type**<br>☐ SINGLETON ☐ TWIN ☐ TRIPLET ☐ OTHER, SPECIFY: _____ | | | |
| **Pregnancy Outcome** | | | |
| DATE OF DELIVERY: | | | GESTATION AGE AT DELIVERY: |
| DELIVERY DETAILS | NO | YES | ADDITIONAL COMMENTS |
| Normal | ☐ | ☐ | |
| C-section | ☐ | ☐ | |
| Induced | ☐ | ☐ | |
| Assisted (e.g., forceps) | ☐ | ☐ | |
| Elective Termination | ☐ | ☐ | Date: |
| Spontaneous Abortion (≤ 20 weeks) | ☐ | ☐ | Weeks from LMP: |
| Fetal Death/Stillbirth (> 20 weeks) | ☐ | ☐ | |
| Were the Products of Conception Examined? | ☐ | ☐ | If yes, was the fetus normal? ☐ Yes ☐ No ☐ Unknown<br>If no, describe: _____ |

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| **Obstetrics Information** | | | |
|---|---|---|---|
| | No | Yes | |
| Complications During Pregnancy | ☐ | ☐ | If Yes, specify: |
| Complications During Labor/Delivery | ☐ | ☐ | If Yes, specify: |
| Post-partum Maternal Complications | ☐ | ☐ | If Yes, specify: |
| **Fetal and Neonatal Status** | | | |
| | No | Yes | |
| Live Normal Infant | ☐ | ☐ | |
| Fetal Distress | ☐ | ☐ | If Yes, specify: |
| Intra-uterine Growth Retardation | ☐ | ☐ | If Yes, specify: |
| Neonatal Complications* | ☐ | ☐ | If Yes, specify: |
| Birth Defect Noted? | ☐ | ☐ | If Yes, specify: |

**Sex:** ☐ Male ☐ Female **Birth Weight:** ____ lbs ____ oz ***or*** ____ kg **Length:** ____ inches ***or*** ____ cm

| **Apgar Score:** | Unknown: | 1 min: | 5 mins: | 10 mins: |
|---|---|---|---|---|

***PLEASE PROVIDE A BRIEF SUMMARY OF THE MANAGEMENT OF THE COMPLICATIONS.**

**SIGNATURE OF PERSON COMPLETING THIS FORM:** _____ **DATE:** _____

**MCN:**

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**Event-Specific Questionnaire for Primary Care Physician or Pediatrician – Infant Follow-up**

**Telephone: 1-800-721-5072**
**Fax: 609-818-3804**
**Email: Worldwide.Safety@BMS.com**

Date of Assessment: _____

Age in Months: _____

Weight (at the time of this assessment): _____ lbs _____ oz ***or*** _____ kg

Length (at the time of this assessment): _____ inches ***or*** _____ cm

Name of Patient on [Drug Name]®: _____

Name of Infant (if known): _____

Please provide information for the period from _____ (Date) to _____ (Date)

**Birth Defects/Anomalies**:

New birth defects or anomalies noted since previous report? ☐ Yes ☐ No

If **Yes**, please list the birth defects/anomalies below:

| **BIRTH DEFECT/ANOMALY** | **WAS THE DEFECT/ ANOMALY ATTRIBUTED TO [Drug Name]® THERAPY?** (Y/N/UNKNOWN) | **FACTORS THAT MAY HAVE CONTRIBUTED TO THIS OUTCOME:** (e.g. FAMILY HISTORY, MATERNAL AGE, OBESITY, ALCOHOL CONSUMPTION DURING PREGNANCY, etc.) | **DEFECT/ ANOMALY NOTED PRIOR TO BIRTH?** (Y/N) | **INFANT AGE WHEN DEFECT/ ANOMALY WAS NOTED** (SPECIFY WEEKS OR MONTHS) |
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**Developmental Assessment**:

Is the child developing normally for his/her age? ☐ Yes ☐ No

If No, please define your concerns regarding any developmental issues or abnormalities:

_____

_____

_____

Diagnosis date of any developmental issues: _____

**Infant Illnesses, Hospitalizations, Drug Therapies:**

| Infant Illnesses | Hospitalized? | Drug Therapies |
|---|---|---|
| | ☐ Yes ☐ No | |
| | ☐ Yes ☐ No | |
| | ☐ Yes ☐ No | |
| | ☐ Yes ☐ No | |
| | ☐ Yes ☐ No | |
| | ☐ Yes ☐ No | |

**SIGNATURE OF PERSON COMPLETING THIS FORM:** _____ **DATE:** _____

**MCN:**

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Princeton, NJ-08543-4000

**Event-Specific Questionnaire for Primary Care Physician or Pediatrician – Infant Follow-up**

**Telephone: 1-800-721-5072**
**Fax: 609-818-3804**
**Email: Worldwide.Safety@BMS.com**

Date of Assessment: _____

Age in Months: _____

Weight (at the time of this assessment): _____ lbs _____ oz ***or*** _____ kg

Length (at the time of this assessment): _____ inches ***or*** _____ cm

Name of Patient on [Drug Name]®: _____

Name of Infant (if known): _____

Please provide information for the period from _____ (Date) to _____ (Date)

**Birth Defects/Anomalies**:

New birth defects or anomalies noted since previous report? ☐ Yes ☐ No

If **Yes**, please list the birth defects/anomalies below:

| **BIRTH DEFECT/ANOMALY** | **WAS THE DEFECT/ ANOMALY ATTRIBUTED TO [Drug Name] ® THERAPY?** (Y/N/UNKNOWN) | **FACTORS THAT MAY HAVE CONTRIBUTED TO THIS OUTCOME:** (e.g. FAMILY HISTORY, MATERNAL AGE, OBESITY, ALCOHOL CONSUMPTION DURING PREGNANCY, etc.) | **DEFECT/ ANOMALY NOTED PRIOR TO BIRTH?** (Y/N) | **INFANT AGE WHEN DEFECT/ ANOMALY WAS NOTED** (SPECIFY WEEKS OR MONTHS) |
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**Developmental Assessment**:

Is the child developing normally for his/her age? ☐ Yes ☐ No

If No, please define your concerns regarding any developmental issues or abnormalities:

Diagnosis date of any developmental issues: _____

**Infant Illnesses, Hospitalizations, Drug Therapies:**

| Infant Illnesses | Hospitalized? | Drug Therapies |
|---|---|---|
| | ☐ Yes ☐ No | |
| | ☐ Yes ☐ No | |
| | ☐ Yes ☐ No | |
| | ☐ Yes ☐ No | |
| | ☐ Yes ☐ No | |
| | ☐ Yes ☐ No | |

**SIGNATURE OF PERSON COMPLETING THIS FORM:** _____ **DATE:** _____

**MCN:**

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Princeton, NJ-08543-4000

**Event-Specific Questionnaire for Primary Care Physician or Pediatrician – Infant Follow-up**

**Telephone: 1-800-721-5072**
**Fax: 609-818-3804**
**Email: Worldwide.Safety@BMS.com**

Date of Assessment: _____

Age in Months: _____

Weight (at the time of this assessment): _____ lbs _____ oz ***or*** _____ kg

Length (at the time of this assessment): _____ inches ***or*** _____ cm

Name of Patient on [Drug Name]®: _____

Name of Infant (if known): _____

Please provide information for the period from _____ (Date) to _____ (Date)

**Birth Defects/Anomalies**:

New birth defects or anomalies noted since previous report? ☐ Yes ☐ No

If **Yes**, please list the birth defects/anomalies below:

| **BIRTH DEFECT/ANOMALY** | **WAS THE DEFECT/ ANOMALY ATTRIBUTED TO [Drug Name]® THERAPY?** (Y/N/UNKNOWN) | **FACTORS THAT MAY HAVE CONTRIBUTED TO THIS OUTCOME:** (e.g., FAMILY HISTORY, MATERNAL AGE, OBESITY, ALCOHOL CONSUMPTION DURING PREGNANCY, etc.) | **DEFECT/ ANOMALY NOTED PRIOR TO BIRTH?** (Y/N) | **INFANT AGE WHEN DEFECT/ ANOMALY WAS NOTED** (SPECIFY WEEKS OR MONTHS) |
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**Developmental Assessment**:

Is the child developing normally for his/her age? ☐ Yes ☐ No

If No, please define your concerns regarding any developmental issues or abnormalities:

_____

_____

_____

Diagnosis date of any developmental issues: _____

**Infant Illnesses, Hospitalizations, Drug Therapies:**

| Infant Illnesses | Hospitalized? | Drug Therapies |
|---|---|---|
| | ☐ Yes ☐ No | |
| | ☐ Yes ☐ No | |
| | ☐ Yes ☐ No | |
| | ☐ Yes ☐ No | |
| | ☐ Yes ☐ No | |
| | ☐ Yes ☐ No | |

**SIGNATURE OF PERSON COMPLETING THIS FORM:** _____ **DATE:** _____

**MCN:**

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P.O BOX 4000, B.3140,
Princeton, NJ-08543-4000

**Event-Specific Questionnaire for Primary Care Physician or Pediatrician – Infant Follow-up**

**Telephone: 1-800-721-5072**
**Fax: 609-818-3804**
**Email: Worldwide.Safety@BMS.com**

Date of Assessment: _____

Age in Months: _____

Weight (at the time of this assessment): _____ lbs _____ oz ***or*** _____ kg

Length (at the time of this assessment): _____ inches ***or*** _____ cm

Name of Patient on [Drug Name]®: _____

Name of Infant (if known): _____

Please provide information for the period from _____ (Date) to _____ (Date)

**Birth Defects/Anomalies**:

New birth defects or anomalies noted since previous report? ☐ Yes ☐ No

If **Yes**, please list the birth defects/anomalies below:

| **BIRTH DEFECT/ANOMALY** | **WAS THE DEFECT/ ANOMALY ATTRIBUTED TO [Drug Name]® THERAPY?** (Y/N/UNKNOWN) | **FACTORS THAT MAY HAVE CONTRIBUTED TO THIS OUTCOME:** (e.g., FAMILY HISTORY, MATERNAL AGE, OBESITY, ALCOHOL CONSUMPTION DURING PREGNANCY, etc.) | **DEFECT/ ANOMALY NOTED PRIOR TO BIRTH?** (Y/N) | **INFANT AGE WHEN DEFECT/ ANOMALY WAS NOTED** (SPECIFY WEEKS OR MONTHS) |
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**Developmental Assessment**:

Is the child developing normally for his/her age? ☐ Yes ☐ No

If No, please define your concerns regarding any developmental issues or abnormalities:

_____

_____

_____

Diagnosis date of any developmental issues: _____

**Infant Illnesses, Hospitalizations, Drug Therapies:**

| Infant Illnesses | Hospitalized? | Drug Therapies |
|---|---|---|
| | ☐ Yes ☐ No | |
| | ☐ Yes ☐ No | |
| | ☐ Yes ☐ No | |
| | ☐ Yes ☐ No | |
| | ☐ Yes ☐ No | |
| | ☐ Yes ☐ No | |

**SIGNATURE OF PERSON COMPLETING THIS FORM:** _____ **DATE:** _____

**MCN:**

Bristol Myers Squibb™
P.O BOX 4000, B.3140
Princeton, NJ-08543-4000

**[Case_ ID]**

**Adverse Event Report Questionnaire**
**TL Acute Myeloid Leukaemia AML or MDS in Non-MDS Indication Thalidomide Revlimid**

**INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM:**

**Patient Demographics:**

Patient's date of birth (DD-MMM-YYYY): _____ Gender: ☐ Male ☐ Female

Age: _____

Race/Ethnicity: _____ ☐ Aborginal ☐ African American ☐ Asian
☐ American Indian or Alaskan Native ☐ Native Hawaiian or other Pacific Islander
☐ Torres Strait Islander ☐ White ☐ Black ☐ Non Hispanic

Age Group:_____

Note: Please provide Age Group if Patient's Date of Birth or Age is not available.

Age Group Definition: Neonate: 0 - 27 days, Infant: 28 days to 23 months, Child: 2 years to 11years, Adolescent: 12 years to 18 years, Adult: More than 18 years and less than or equal to 65 years and Elderly: equal or greater than 66 years)

**Suspect Products:** Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events]:

| | Suspect Product #1 | Suspect Product #2 | Suspect Product #3 |
|---|---|---|---|
| Product name | | | |
| Daily dose and regimen | | | |
| Route of administration | | | |
| Indication | | | |
| Start date or treatment duration (DD-MMM-YYYY) | | | |
| Stop date (DD-MMM-YYYY) | | | |
| Lot/Batch number(s) | | | |
| Expiration date(s) | | | |
| Action Taken with the suspect product | | | |

(Choose from one of the following for action Taken with Suspect Product: Drug withdrawn, Dose reduced, Dose increased, Dose not changed, Unknown)

**Adverse Event (AE) Description:** Please provide diagnosis or symptoms/signs if diagnosis is unavailable.

| | Adverse Event #1 | Adverse Event #2 | Adverse Event #3 | Adverse Event #4 |
|---|---|---|---|---|

| Add Diagnosis Here → | | | | |
|---|---|---|---|---|
| Start Date (DD/MMM/YYYY) | | | | |
| Stop Date (DD/MMM/YYYY) | | | | |
| Time lag if AE occurred after cessation of treatment with the suspect product(s): | | | | |
| Required Hospitalization (Yes/No) | | | | |
| Life-Threatening (Yes/No) | | | | |
| Persistent or significant disability (Yes/No) | | | | |
| Congenital abnormality (Yes/No) | | | | |
| Cause of Death (Yes/No) | | | | |
| Treatment of Adverse Event | | | | |
| Outcome (recovery and sequelae, if any) | | | | |
| Did the event(s) abate after suspect Product was stopped or dose reduced? (Yes/No) | | | | |
| Did the event recur after reintroducing (Yes/No) | | | | |

**Please summarize course of reported events including signs and symptoms in chronological order**:

_____

_____

_____

**Diagnostic tests** (use additional pages if needed)**:** Please indicate test unit where applicable.

| Date | Test Name | Pre-treatment value | AE onset value | AE resolution value | Normal low | Normal high |
|---|---|---|---|---|---|---|
| | | | | | | |
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Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

_____

_____

**Concomitant Medications** (use additional pages if needed)**:**

Did the Patient take any concomitant medication? ☐ Yes (please complete below) ☐ No ☐ Unknown
Please include all concomitant medications including indications, therapy dates and dosing information. These should include concurrent anti-myeloma therapy, colony-stimulating factors, and/or ESAs.

| Medication Name | Daily dose and regimen | Route of administration | Indication | Start date DD-MMM-YYYY | Stop date DD-MMM-YYYY |
|---|---|---|---|---|---|

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**Other Etiological Factors:** ☐ Yes (please complete below) ☐ None ☐ Unknown

☐ Relevant medical and/or drug history (please specify), including start date or duration:
Please include familial history of malignancies, environmental exposure, blood transfusion dependence status.

_____

_____

_____

☐ Family history (please specify): _____
☐ Drug/alcohol/tobacco abuse: _____
☐ Other (please specify): _____

**Additional questions:**

Please provide the date [Revlimid/Thalidomide drug indication, e.g., AML or MDS] was initially diagnosed with stage/classification.

Please provide full bone marrow results as well as full cytogenetics at baseline and at the time of diagnosis of [MDS or AML] with dates. Please specify if this information is not available or not evaluable.

Please specify AML type if not included in the bone marrow or cytogenetics documents. Please specify if this information is not available or not evaluable.

Please also provide the [Revlimid/Thalidomide indication] stage/classification at the time of the MDS or AML diagnosis. Please specify if this information is not available or not evaluable. Is there evidence of progression of underlying disease? Please explain.

Please provide changes in transfusion dependence status during disease (Revlimid/Thalidomide indication) treatment with corresponding dates.

Please provide information on any antineoplastic treatments the patient may have received including radiotherapy with radiation zone for any malignant neoplasm, specifying the indication for this. Please provide duration of treatment with dates and also cumulative dose if available.

Please specify what treatment was received for the AML/MDS.

What was the outcome of AML/MDS? If fatal outcome, please provide circumstances surrounding the death.

_____

Health Practitioner Name (Print)

_____

Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:

Description of event: [narrative]

Bristol Myers Squibb™
P.O BOX 4000, B.3140
Princeton, NJ-08543-4000

**[Case_ ID]**

**Adverse Event Report Questionnaire**
**TL Cardiac Arrhythmia and ECG Changes Pomalyst Revlimid**

**INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM:**

**Patient Demographics:**

Patient's date of birth (DD-MMM-YYYY): _____ Gender: ☐ Male ☐ Female

Age: _____

Race/Ethnicity: _____ ☐ Aborginal ☐ African American ☐ Asian
☐ American Indian or Alaskan Native ☐ Native Hawaiian or other Pacific Islander
☐ Torres Strait Islander ☐ White ☐ Black ☐ Non Hispanic

Age Group:_____

Note: Please provide Age Group if Patient's Date of Birth or Age is not available.

Age Group Definition: Neonate: 0 - 27 days, Infant: 28 days to 23 months, Child: 2 years to 11years, Adolescent: 12 years to 18 years, Adult: More than 18 years and less than or equal to 65 years and Elderly: equal or greater than 66 years)

**Suspect Products:** Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events]:

| | Suspect Product #1 | Suspect Product #2 | Suspect Product #3 |
|---|---|---|---|
| Product name | | | |
| Daily dose and regimen | | | |
| Route of administration | | | |
| Indication | | | |
| Start date or treatment duration (DD-MMM-YYYY) | | | |
| Stop date (DD-MMM-YYYY) | | | |
| Lot/Batch number(s) | | | |
| Expiration date(s) | | | |
| Action Taken with the suspect product | | | |

(Choose from one of the following for action Taken with Suspect Product: Drug withdrawn, Dose reduced, Dose increased, Dose not changed, Unknown)

**Adverse Event (AE) Description:** Please provide diagnosis or symptoms/signs if diagnosis is unavailable.

| | Adverse Event #1 | Adverse Event #2 | Adverse Event #3 | Adverse Event #4 |
|---|---|---|---|---|

| Add Diagnosis Here → | | | | |
|---|---|---|---|---|
| Start Date (DD/MMM/YYYY) | | | | |
| Stop Date (DD/MMM/YYYY) | | | | |
| Time lag if AE occurred after cessation of treatment with the suspect product(s): | | | | |
| Required Hospitalization (Yes/No) | | | | |
| Life-Threatening (Yes/No) | | | | |
| Persistent or significant disability (Yes/No) | | | | |
| Congenital abnormality (Yes/No) | | | | |
| Cause of Death (Yes/No) | | | | |
| Treatment of Adverse Event | | | | |
| Outcome (recovery and sequelae, if any) | | | | |
| Did the event(s) abate after suspect Product was stopped or dose reduced? (Yes/No) | | | | |
| Did the event recur after reintroducing (Yes/No) | | | | |

**Please summarize course of reported events including signs and symptoms in chronological order**:

_____

_____

_____

**Diagnostic tests** (use additional pages if needed)**:** Please indicate test unit where applicable.

| Date | Test Name | Pre-treatment value | AE onset value | AE resolution value | Normal low | Normal high |
|---|---|---|---|---|---|---|
| | CPK | | | | | |
| | CPK-MB | | | | | |
| | Troponin | | | | | |
| | RBC | | | | | |
| | Hemoglobin | | | | | |
| | Metabolic Panel (specify) | | | | | |
| | Serum potassium | | | | | |
| | Serum magnesium | | | | | |
| | Phosphorus | | | | | |
| | Calcium | | | | | |
| | Uric acid | | | | | |
| | Creatinine | | | | | |
| | BUN | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
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| | | | | | | |

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

_____

_____

**Concomitant Medications** (use additional pages if needed)**:**

Did the Patient take any concomitant medication? ☐ Yes (please complete below) ☐ No ☐ Unknown
Please include any antiemetics.

| Medication Name | Daily dose and regimen | Route of administration | Indication | Start date DD-MMM-YYYY | Stop date DD-MMM-YYYY |
|---|---|---|---|---|---|
| | | | | | |
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**Other Etiological Factors:** ☐ Yes (please complete below) ☐ None ☐ Unknown

☐ Relevant medical and/or drug history (please specify), including start date or duration:

_____

_____

_____

☐ Family history (please specify): _____
☐ Drug/alcohol/tobacco abuse: _____
☐ Other (please specify): _____

**Additional questions:**

Please provide a brief description of the cardiac arrhythmia, or ECG change, including the type and the clinical signs/symptoms observed, including start and stop dates:

Please specify the type of arrhythmia/ECG change.

Clinical signs and symptoms, if present (if none please state)
Start date Stop date

Does this patient have a relevant cardiac history? If yes, please specify. If no, please state.

Does this patient have a history of cardiac risk factors (e.g. hypertension, hyperlipidemia, hypercholesterolemia, diabetes, sepsis, obesity, smoking, renal disease, cardio respiratory problems)? If yes, please specify below. If no, please state.

Please provide the available results of the diagnostic workup (include dates of baseline, event onset, and resolution results)

| Test Name | Pre-treatment results | AE onset results | AE resolution results |
|---|---|---|---|
| EKG findings | | | |
| Echocardiogram | | | |
| Chest x-ray | | | |
| Holter, Stress Test | | | |

Please describe specific treatments and interventions of the arrhythmia

_____

Health Practitioner Name (Print)

_____

Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:

Description of event: [narrative]

Bristol Myers Squibb™
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Princeton, NJ-08543-4000

**[Case_ ID]**

**Adverse Event Report Questionnaire**
**TL Cardiac Failure Pomalyst Revlimid**

**INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM:**

**Patient Demographics:**

Patient's date of birth (DD-MMM-YYYY): _____ Gender: ☐ Male ☐ Female

Age: _____

Race/Ethnicity: _____ ☐ Aborginal ☐ African American ☐ Asian
☐ American Indian or Alaskan Native ☐ Native Hawaiian or other Pacific Islander
☐ Torres Strait Islander ☐ White ☐ Black ☐ Non Hispanic

Age Group:_____

Note: Please provide Age Group if Patient's Date of Birth or Age is not available.

Age Group Definition: Neonate: 0 - 27 days, Infant: 28 days to 23 months, Child: 2 years to 11years, Adolescent: 12 years to 18 years, Adult: More than 18 years and less than or equal to 65 years and Elderly: equal or greater than 66 years)

**Suspect Products:** Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events]:

| | Suspect Product #1 | Suspect Product #2 | Suspect Product #3 |
|---|---|---|---|
| Product name | | | |
| Daily dose and regimen | | | |
| Route of administration | | | |
| Indication | | | |
| Start date or treatment duration (DD-MMM-YYYY) | | | |
| Stop date (DD-MMM-YYYY) | | | |
| Lot/Batch number(s) | | | |
| Expiration date(s) | | | |
| Action Taken with the suspect product | | | |

(Choose from one of the following for action Taken with Suspect Product: Drug withdrawn, Dose reduced, Dose increased, Dose not changed, Unknown)

**Adverse Event (AE) Description:** Please provide diagnosis or symptoms/signs if diagnosis is unavailable.

| | Adverse Event #1 | Adverse Event #2 | Adverse Event #3 | Adverse Event #4 |
|---|---|---|---|---|

| Add Diagnosis Here → | | | | |
|---|---|---|---|---|
| Start Date (DD/MMM/YYYY) | | | | |
| Stop Date (DD/MMM/YYYY) | | | | |
| Time lag if AE occurred after cessation of treatment with the suspect product(s): | | | | |
| Required Hospitalization (Yes/No) | | | | |
| Life-Threatening (Yes/No) | | | | |
| Persistent or significant disability (Yes/No) | | | | |
| Congenital abnormality (Yes/No) | | | | |
| Cause of Death (Yes/No) | | | | |
| Treatment of Adverse Event | | | | |
| Outcome (recovery and sequelae, if any) | | | | |
| Did the event(s) abate after suspect Product was stopped or dose reduced? (Yes/No) | | | | |
| Did the event recur after reintroducing (Yes/No) | | | | |

**Please summarize course of reported events including signs and symptoms in chronological order**:

_____

_____

_____

**Diagnostic tests** (use additional pages if needed)**:** Please indicate test unit where applicable.

| Date | Test Name | Pre-treatment value | AE onset value | AE resolution value | Normal low | Normal high |
|---|---|---|---|---|---|---|
| | Calcium | | | | | |
| | Magnesium | | | | | |
| | Total CPK | | | | | |
| | CK-MB | | | | | |
| | Troponins | | | | | |
| | BNP | | | | | |
| | WBC | | | | | |
| | RBC | | | | | |
| | Platelets | | | | | |
| | Hemoglobin | | | | | |
| | Hematocrit | | | | | |
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Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

_____

**Concomitant Medications** (use additional pages if needed)**:**

Did the Patient take any concomitant medication? ☐ Yes (please complete below) ☐ No ☐ Unknown

| Medication Name | Daily dose and regimen | Route of administration | Indication | Start date DD-MMM-YYYY | Stop date DD-MMM-YYYY |
|---|---|---|---|---|---|
| | | | | | |
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**Other Etiological Factors:** ☐ Yes (please complete below) ☐ None ☐ Unknown

☐ Relevant medical and/or drug history (please specify), including start date or duration:

_____

_____

_____

☐ Family history (please specify): _____
☐ Drug/alcohol/tobacco abuse: _____
☐ Other (please specify): _____

**Additional questions:**

Did the cardiac failure occur prior to therapy? ☐ Yes ☐ No

If the cardiac failure occurred prior to therapy, would you consider it an exacerbation?
☐ Yes ☐ No

Please provide the date the exacerbation was diagnosed_____

Please circle classification of cardiac failure:

a. Class I (mild) Patients with cardiac disease but without limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or angina pain

b. Class II (mild) Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina pain.

c. Class III (moderate) Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or angina pain.

d. Class IV (severe) Patients with cardiac disease resulting in the inability to carry on any physical activity without discomfort. Symptoms of heart failure or the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased

Please provide results for EKG, echocardiogram, angiogram, CT scan, MRI and ejection fraction.

Did the patient receive any recent blood transfusions or IV infusions? ☐ Yes ☐ No
If yes, please specify what was transfused and provide the amount transfused with dates.

Does the patient have other cardiac history including congenital heart disease, coronary artery disease, cardiac stents, myocardial infarction, valvular heart disease, cardiomyopathy, endocarditis, or myocarditis?

Please provide any associated risk factors including history of hyperlipidemia, obesity, hypertension COPD, renal disease, diabetes, sepsis, substance abuse, and family history of heart disease.

Any exposure to other chemotherapeutic agents (previous and/or ongoing)? Please specify.

Are there any concurrent events that contributed to or led up to the cardiac failure? Please specify.

What treatments/interventions were provided to the patient for the cardiac failure?

_____
Health Practitioner Name (Print)

_____
Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:

Description of event: [narrative]

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Princeton, NJ-08543-4000

**[Case_ ID]**

**Adverse Event Report Questionnaire**
**TL Myocardial infarction (Thalidomide_Revlimid)**

**INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM:**

**Patient Demographics:**

Patient's date of birth (DD-MMM-YYYY): _____ Gender: ☐ Male ☐ Female

Age: _____

Race/Ethnicity: _____ ☐ Aborginal ☐ African American ☐ Asian
☐ American Indian or Alaskan Native ☐ Native Hawaiian or other Pacific Islander
☐ Torres Strait Islander ☐ White ☐ Black ☐ Non Hispanic

Age Group:_____

Note: Please provide Age Group if Patient's Date of Birth or Age is not available.

Age Group Definition: Neonate: 0 - 27 days, Infant: 28 days to 23 months, Child: 2 years to 11years, Adolescent: 12 years to 18 years, Adult: More than 18 years and less than or equal to 65 years and Elderly: equal or greater than 66 years)

**Suspect Products:** Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events]:

| | Suspect Product #1 | Suspect Product #2 | Suspect Product #3 |
|---|---|---|---|
| Product name | | | |
| Daily dose and regimen | | | |
| Route of administration | | | |
| Indication | | | |
| Start date or treatment duration (DD-MMM-YYYY) | | | |
| Stop date (DD-MMM-YYYY) | | | |
| Lot/Batch number(s) | | | |
| Expiration date(s) | | | |
| Action Taken with the suspect product | | | |

(Choose from one of the following for action Taken with Suspect Product: Drug withdrawn, Dose reduced, Dose increased, Dose not changed, Unknown)

**Adverse Event (AE) Description:** Please provide diagnosis or symptoms/signs if diagnosis is unavailable.

| | Adverse Event #1 | Adverse Event #2 | Adverse Event #3 | Adverse Event #4 |
|---|---|---|---|---|

| Add Diagnosis Here → | | | | |
|---|---|---|---|---|
| Start Date (DD/MMM/YYYY) | | | | |
| Stop Date (DD/MMM/YYYY) | | | | |
| Time lag if AE occurred after cessation of treatment with the suspect product(s): | | | | |
| Required Hospitalization (Yes/No) | | | | |
| Life-Threatening (Yes/No) | | | | |
| Persistent or significant disability (Yes/No) | | | | |
| Congenital abnormality (Yes/No) | | | | |
| Cause of Death (Yes/No) | | | | |
| Treatment of Adverse Event | | | | |
| Outcome (recovery and sequelae, if any) | | | | |
| Did the event(s) abate after suspect Product was stopped or dose reduced? (Yes/No) | | | | |
| Did the event recur after reintroducing (Yes/No) | | | | |

**Please summarize course of reported events including signs and symptoms in chronological order**:

_____

_____

_____

**Diagnostic tests** (use additional pages if needed)**:** Please indicate test unit where applicable.

| Date | Test Name | Pre-treatment value | AE onset value | AE resolution value | Normal low | Normal high |
|---|---|---|---|---|---|---|
| | CPK | | | | | |
| | MB | | | | | |
| | Troponin | | | | | |
| | BNP | | | | | |
| | WBC | | | | | |
| | ANC | | | | | |
| | RBC | | | | | |
| | Hgb | | | | | |
| | Hct | | | | | |
| | Magnesium | | | | | |
| | Calcium | | | | | |
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| | | | | | | |
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Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

_____

**Concomitant Medications** (use additional pages if needed)**:**

Did the Patient take any concomitant medication? ☐ Yes (please complete below) ☐ No ☐ Unknown
Please include erythropoietin and thromboprophylactic medications and others as appropriate.

| Medication Name | Daily dose and regimen | Route of administration | Indication | Start date DD-MMM-YYYY | Stop date DD-MMM-YYYY |
|---|---|---|---|---|---|
| | | | | | |
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**Other Etiological Factors:** ☐ Yes (please complete below) ☐ None ☐ Unknown

☐ Relevant medical and/or drug history (please specify), including start date or duration:

☐ Family history (please specify): _____
☐ Drug/alcohol/tobacco abuse: _____
☐ Other (please specify): _____

**Additional questions:**

Did the patient have a history of cardiac disease such as coronary artery disease, myocardial infarction, arrhythmia, or congestive heart failure? Please provide the onset dates of diagnosis.

Please provide any risk factors for the myocardial infarction. (hyperlipidemia, hypercholesterolemia, obesity, hypertension, COPD, renal disease, diabetes, sepsis, substance abuse, sedentary life style, immobility, dehydration, etc.).

Please provide the following diagnostic results including the baseline and the most recent EKG, echocardiogram, stress test, and cardiac catheterization, if available.

Please provide the treatment and interventions that were administered due to the myocardial infarction.

Please provide concurrent events/circumstances surrounding the MI.

Did the patient have a history of chest pain?

Did the patient have a history of thromboembolic events? If yes, please specify type.

_____
Health Practitioner Name (Print)

_____
Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:

Description of event: [narrative]

Bristol Myers Squibb™
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Princeton, NJ-08543-4000

**[Case_ ID]**

**Adverse Event Report Questionnaire**
**TL Neutropenia Pomalyst Revlimid**

**INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM:**

**Patient Demographics:**

Patient's date of birth (DD-MMM-YYYY): _____ Gender: ☐Male ☐ Female

Age: _____

Race/Ethnicity: _____ ☐ Aborginal ☐African American ☐ Asian
☐ American Indian or Alaskan Native ☐ Native Hawaiian or other Pacific Islander
☐ Torres Strait Islander ☐ White ☐ Black ☐ Non Hispanic

Age Group:_____

Note: Please provide Age Group if Patient's Date of Birth or Age is not available.

Age Group Definition: Neonate: 0 - 27 days, Infant: 28 days to 23 months, Child: 2 years to 11years, Adolescent: 12 years to 18 years, Adult: More than 18 years and less than or equal to 65 years and Elderly: equal or greater than 66 years)

**Suspect Products:** Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events]:

| | Suspect Product #1 | Suspect Product #2 | Suspect Product #3 |
|---|---|---|---|
| Product name | | | |
| Daily dose and regimen | | | |
| Route of administration | | | |
| Indication | | | |
| Start date or treatment duration (DD-MMM-YYYY) | | | |
| Stop date (DD-MMM-YYYY) | | | |
| Lot/Batch number(s) | | | |
| Expiration date(s) | | | |
| Action Taken with the suspect product | | | |

(Choose from one of the following for action Taken with Suspect Product: Drug withdrawn, Dose reduced, Dose increased, Dose not changed, Unknown)

**Adverse Event (AE) Description:** Please provide diagnosis or symptoms/signs if diagnosis is unavailable.

| | Adverse Event #1 | Adverse Event #2 | Adverse Event #3 | Adverse Event #4 |
|---|---|---|---|---|

| Add Diagnosis Here → | | | | |
|---|---|---|---|---|
| Start Date (DD/MMM/YYYY) | | | | |
| Stop Date (DD/MMM/YYYY) | | | | |
| Time lag if AE occurred after cessation of treatment with the suspect product(s): | | | | |
| Required Hospitalization (Yes/No) | | | | |
| Life-Threatening (Yes/No) | | | | |
| Persistent or significant disability (Yes/No) | | | | |
| Congenital abnormality (Yes/No) | | | | |
| Cause of Death (Yes/No) | | | | |
| Treatment of Adverse Event | | | | |
| Outcome (recovery and sequelae, if any) | | | | |
| Did the event(s) abate after suspect Product was stopped or dose reduced? (Yes/No) | | | | |
| Did the event recur after reintroducing (Yes/No) | | | | |

**Please summarize course of reported events including signs and symptoms in chronological order**:

_____

_____

_____

**Diagnostic tests** (use additional pages if needed)**:** Please indicate test unit where applicable.

| Date | Test Name | Pre-treatment value | AE onset value | AE resolution value | Normal low | Normal high |
|---|---|---|---|---|---|---|
| | WBC | | | | | |
| | ANC | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

_____

_____

**Concomitant Medications** (use additional pages if needed)**:**

Did the Patient take any concomitant medication? ☐ Yes (please complete below) ☐ No ☐ Unknown

| Medication Name | Daily dose and regimen | Route of administration | Indication | Start date DD-MMM-YYYY | Stop date DD-MMM-YYYY |
|---|---|---|---|---|---|
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**Other Etiological Factors:** ☐ Yes (please complete below) ☐ None ☐ Unknown

☐ Relevant medical and/or drug history (please specify), including start date or duration:

_____

_____

_____

☐ Family history (please specify): _____
☐ Drug/alcohol/tobacco abuse: _____
☐ Other (please specify): _____

**Additional questions:**

What treatments were given for the neutropenia? Please include dates. Did the patient receive G-CSF? GM-CSF? Please provide details.

Did your patient experience an infection in association with the neutropenia?
☐ **Yes** ☐ **No**
If yes, please provide location of the infection.

Does the patient have a history of recurrent infection? ☐ **Yes** ☐ **No**
If yes, please explain.

Please provide the stage/classification of the patient's disease at the time of the infection.

Does your patient have a medical history of autoimmune disease, abnormal disease of spleen, bone marrow disease, etc.?

Has your patient received prior radiation therapy? If so, please provide treatment details including dates.

Does your patient have a medical history of cancer effecting bone marrow?

Please include culture / serology / bone marrow studies / x-ray results for the event of infection.

_____

Health Practitioner Name (Print)

_____

Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:

Description of event: [narrative]

Bristol Myers Squibb™
P.O BOX 4000, B.3140
Princeton, NJ-08543-4000

**[Case_ ID]**

**Adverse Event Report Questionnaire**
**TL Second Primary Malignancies (Pomalyst Revlimid Thalidomide)**

**INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM:**

**Patient Demographics:**

Patient's date of birth (DD-MMM-YYYY): _____ Gender: ☐Male ☐ Female
Age: _____

Race/Ethnicity: _____ ☐ Aborginal ☐African American ☐ Asian
☐ American Indian or Alaskan Native ☐ Native Hawaiian or other Pacific Islander
☐ Torres Strait Islander ☐ White ☐ Black ☐ Non Hispanic

Age Group:_____

Note: Please provide Age Group if Patient's Date of Birth or Age is not available.

Age Group Definition: Neonate: 0 - 27 days, Infant: 28 days to 23 months, Child: 2 years to 11years, Adolescent: 12 years to 18 years, Adult: More than 18 years and less than or equal to 65 years and Elderly: equal or greater than 66 years)

**Suspect Products:** Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events]:

| | Suspect Product #1 | Suspect Product #2 | Suspect Product #3 |
|---|---|---|---|
| Product name | | | |
| Daily dose and regimen | | | |
| Route of administration | | | |
| Indication | | | |
| Start date or treatment duration (DD-MMM-YYYY) | | | |
| Stop date (DD-MMM-YYYY) | | | |
| Lot/Batch number(s) | | | |
| Expiration date(s) | | | |
| Action Taken with the suspect product | | | |

(Choose from one of the following for action Taken with Suspect Product: Drug withdrawn, Dose reduced, Dose increased, Dose not changed, Unknown)

**Adverse Event (AE) Description:** Please provide diagnosis or symptoms/signs if diagnosis is unavailable.

| | Adverse Event #1 | Adverse Event #2 | Adverse Event #3 | Adverse Event #4 |
|---|---|---|---|---|

| Add Diagnosis Here → | | | | |
|---|---|---|---|---|
| Start Date (DD/MMM/YYYY) | | | | |
| Stop Date (DD/MMM/YYYY) | | | | |
| Time lag if AE occurred after cessation of treatment with the suspect product(s): | | | | |
| Required Hospitalization (Yes/No) | | | | |
| Life-Threatening (Yes/No) | | | | |
| Persistent or significant disability (Yes/No) | | | | |
| Congenital abnormality (Yes/No) | | | | |
| Cause of Death (Yes/No) | | | | |
| Treatment of Adverse Event | | | | |
| Outcome (recovery and sequelae, if any) | | | | |
| Did the event(s) abate after suspect Product was stopped or dose reduced? (Yes/No) | | | | |
| Did the event recur after reintroducing (Yes/No) | | | | |

**Please summarize course of reported events including signs and symptoms in chronological order**:

_____

_____

_____

**Diagnostic tests** (use additional pages if needed)**:** Please indicate test unit where applicable.

| Date | Test Name | Pre-treatment value | AE onset value | AE resolution value | Normal low | Normal high |
|---|---|---|---|---|---|---|
| | Calcium | | | | | |
| | Phosphate | | | | | |
| | Uric Acid | | | | | |
| | Creatinine | | | | | |
| | Potassium | | | | | |
| | LDH | | | | | |
| | Albumin | | | | | |
| | Protein | | | | | |

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

_____

_____

**Concomitant Medications** (use additional pages if needed)**:**

Did the Patient take any concomitant medication? ☐ Yes (please complete below) ☐ No ☐ Unknown
Please include drugs that are potentially nephrotoxic (NSAIDS, antibiotics) including over the counter drugs.

| Medication Name | Daily dose and | Route of | Indication | Start date | Stop date |
|---|---|---|---|---|---|

| | regimen | administration | | DD-MMM-YYYY | DD-MMM-YYYY |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

**Other Etiological Factors:** ☐ Yes (please complete below) ☐ None ☐ Unknown

☐ Relevant medical history (including history of malignancies) and/or drug history (please specify), including start date or duration:

_____

_____

_____

☐ Family history (please specify), including history of malignancies with estimated dates: _____
☐ Drug/alcohol/tobacco abuse: _____
☐ Other (please specify): _____

**Additional questions:**

*When querying about SPMs, specify the malignancy or diagnosis. Do not use the term SPM when diagnosis is known.*

**Core Questions for Follow-up of SPMs:**

1. Dates of the underlying disease's diagnosis.
2. Date of first clinical symptoms of SPM.
3. Stage of the underlying disease treated with [*BMS product*] at baseline, the end of treatment if applicable, and at the time of the event with supportive documentation if available.
4. Medical history of bone marrow transplant including dates, type, donor details, source, and conditioning regimens such as treatment with alkylating agents (i.e. Cyclophosphamide, Melphalan, etc.).
5. Environmental exposure e.g. atmospheric pollutants/toxic chemicals (pesticides, herbicides, benzene, solvents); occupation/hobbies.
6. Full SPM (*specify malignancy or diagnosis if known*) biopsy reports. If not available please provide the detailed results.

**In addition to the Core Questions, specific information should be requested based on the risk factors for individual types of cancer, including:**

**Hematologic Malignancies (including Lymphoma and B-cell malignancy):**

- ◊ Previous chemotherapy rounds (dates, type) and /or radiotherapy (zone, duration, cumulative dose) or subsequent ones if SPM (specify malignancy or diagnosis) detected after product discontinuation
- ◊ Medical conditions that compromise the immune system – HIV/AIDS, autoimmune diseases, diseases requiring immune suppressive therapy-organ transplant
- ◊ For lymphoma: Infection with HIV, Epstein-Barr virus+++, Helicobacter pylori, hepatitis B or C, human T-lymphotrophic virus type I, Burkitt's lymphoma

- Concurrent or medical/family history of inherited syndromes with genetic changes that raise the risk of acute lymphocytic leukemia (ALL) including: Down syndrome, Klinefelter syndrome, Fanconi anemia, Bloom syndrome, Ataxia-telangiectasia, Neurofibromatosis.
- Exposure to benzene (solvent used in the rubber industry, oil refineries, chemical plants, shoe manufacturing, and gasoline-related industries, and is also present in cigarette smoke, as well as some glues, cleaning products, detergents, art supplies, and paint strippers).
- Smoking history – Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of time, number of cigarettes/days or pack-years, age at starting
- Exposure to high levels of radiation
- Medical history of treated hematologic malignancies or concurrent leukemias or lymphomas including: Chronic Lymphocytic Leukemia (CLL), Richter transformation, and Diffuse Large B-cell lymphoma (DLBCL) such as Hodgkin's disease and plasmablastic lymphoma.
- Relevant diagnostic test results (if available), including: biopsy, immunohistochemistry, flow cytometry, cytogenetics, reverse transcriptase polymerase chain reaction, Fluorescence in situ hybridization (FISH), and next generation sequencing

**Lung Cancer:**

- Smoking history – Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of time, number of cigarettes/days or pack-years, age at starting
- Pre-existing pulmonary disease
- Family history of lung cancer

**Thyroid Cancer:**

- Personal or family history of thyroid and/or autoimmune diseases – hypo or hyperthyroidism, goiter, benign thyroid nodules, Hashimoto's disease, Graves disease
- Family history of familial medullary thyroid cancer, multiple endocrine neoplasia and familial adenomatous polyposis
- Living in iodine deficient area
- History of radiation exposure

**Breast Cancer:**

- Receptor status of the tumor – ER, PR, Her2/neu
- Age at onset of menses and age of menopause
- Number of pregnancies and age at first birth
- History of breastfeeding children
- Use of oral contraceptives or hormone replacement therapy
- Obesity
- Economic status, and dietary iodine deficiency

**Ovarian Cancer:**

- Number of pregnancies and childbearing status
- History of hormone replacement therapy
- History of breast cancer

**Uterine Cancer:**

- Age at onset of menses and age of menopause
- Number of pregnancies
- Use of oral contraceptives
- Obesity

**Colon Cancer:**

- Family or personal history of adenomatous polyposis (FAP), Lynch syndrome (Hereditary nonpolyposis colorectal cancer)
- Diet high in red meat and animal fat, refined carbohydrates, low-fiber diet, and low overall intake of fruits and vegetables
- Obesity and sedentary habits
- Any history of inflammatory conditions of digestive tract - Chronic ulcerative colitis, Crohn's disease longer duration, greater extent of colon involvement

**Anorectal Cancer:**

- History of infection with human papillomavirus, HIV, chronic fistulas, irradiated anal skin, leukoplakia, lymphogranulomatoma venereum, condyloma acuminatum

**Gastric Cancer:**

- Diet rich in pickled vegetables, salted fish, salt, and smoked meats
- Helicobacter pylori infection
- Obesity
- Previous gastric surgery
- Pernicious anemia, adenomatous polyps, gastric ulcer
- Chronic atrophic gastritis
- Radiation exposure
- History of alcohol use/smoking

**Oesophageal Cancer:**

- Genetic causes - tylosis (hyperkeratosis palmaris et plantaris)
- History of alcohol use/smoking
- History of chronic or acute inflammation (e.g. GERD, Barrett's esophagus, caustic ingestion), achalasia (esophageal motility disorder)
- Human papilloma virus
- Sclerotherapy
- Plummer-Vinson syndrome (dysphagia, associated with iron deficiency anemia)

**Liver cancer:**

- History of cirrhosis (including alcoholic, biliary cirrhosis), other chronic liver dysfunction
- History of alcohol use/smoking
- Hepatitis B, C
- Hemochromatosis
- Indigestion of food contaminated with fungal aflatoxins (in subtropical regions)

**Pancreatic Cancer:**

- History of alcohol use/smoking
- Obesity
- Diet (red meat)
- History of chronic pancreatitis or long-standing diabetes mellitus (primarily in women).
- Inherited predisposition (hereditary pancreatitis, familial adenomatous polyposis, etc.)

**Renal Cancer (renal cell carcinoma):**

- Smoking history – Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of time, number of cigarettes/days or pack-years, age at starting
- Obesity
- Hypertension
- Phenacetin-containing analgesics taken in large amounts

- History of renal transplantation
- Exposure to radiopaque dyes, asbestos, cadmium, and leather tanning and petroleum products
- Inherited von Hippel-Lindau disease (VHL) disease, Adult polycystic kidney disease, Tuberous sclerosis

**Bladder Cancer:**

- Smoking history – Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of time, number of cigarettes/days or pack-years, age at starting
- Industrial exposure to aromatic amines in dyes, paints, solvents, leather dust, inks, combustion products, rubber, and textiles
- Occupation - painting, driving trucks, and working with metal
- Prior spinal cord injuries with long-term indwelling catheters

**Prostate Cancer:**

- Smoking history – Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of time, number of cigarettes/days or pack-years, age at starting
- History of high-grade prostatic intraepithelial neoplasia (PIN)
- Genome changes-deletion of chromosome 3 and fusion of TMPRSS2 and ERG genes
- Testosterone level
- History of sexually transmitted diseases
- History of vasectomy
- History of exposure to cadmium
- History of genitor-urinary infections

**Head and Neck Cancer:**

- History of alcohol use/smoking
- Exposure to Human papilloma virus (HPV) or Epstein-Barr virus (EBV)
- History of poor oral hygiene and/or poor nutrition
- Exposure to asbestos, wood dust, paint fumes or chemicals
- History of Gastroesophageal reflux disease (GERD) or laryngopharyngeal reflux disease (LPRD)

**Brain tumors (gliomas and meningiomas):**

- Exposure to radiation
- Exposure to vinyl chloride, Pesticides
- Immune system disorders
- Hormone replacement therapy

**Larynx Cancer:**

- History of alcohol use/smoking
- Asbestos exposure
- Any activity requiring loud speech, exposure to sudden and frequent temperature changes
- Frequent hoarseness, frequent and persistent cough
- Persistently swollen neck glands
- Tonsillectomy and laryngeal surgery

**Nasal and Paranasal Sinus Cancer:**

- Woodworking, any dust/flour chronic exposure
- History of Infection with human papillomavirus (HPV)
- Smoking history – Product smoked (i.e. cigars, cigarettes, etc.) and depth of inhalation, length of time, number of cigarettes/days or pack-years, age at starting

**Mouth and Oropharyngeal Cancer:**

- ◊ History of alcohol use/smoking
- ◊ History of poor oral hygiene
- ◊ Chronic mucosal/gum irritation / ill-fitting dentures
- ◊ Betel-Nut Chewing (Indian populations)
- ◊ History of syphilis or viral infections
- ◊ Impaired immunity – AIDS, transplant with anti-rejection drugs
- ◊ Precancerous mouth plaques – Leukoplakia or erythroplasia
- ◊ History of cancer of the aero-digestive tract

**Melanoma, basal cell carcinoma, squamous cell carcinoma of skin:**

- ◊ History of prolonged sun exposure (UV radiation) – severe blistering sunburns, frequent tanning, use of sunlamps and tanning booths
- ◊ History of living close to equator or at high elevation
- ◊ History of skin conditions – Dysplastic nevus, Xeroderma pigmentosum, nevoid basal cell carcinoma syndromes
- ◊ Skin type – fair (pale) skin – burns easily, freckles
- ◊ Eye color – blue, green or gray, Hair color – blond or red
- ◊ Use of medication causing sensitivity to sun – antibiotics, hormones, antidepressants,
- ◊ Immune system depression – AIDS, leukemias, etc.
- ◊ Exposure to arsenic, coal tar or creosote
- ◊ For eye localization- history of oculodermal melanocytosis or Dysplastic nevus syndrome

_____

Health Practitioner Name (Print)

_____

Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:

Description of event: [narrative]

Bristol Myers Squibb™
P.O BOX 4000, B.3140
Princeton, NJ-08543-4000

**[Case_ ID]**

**Adverse Event Report Questionnaire**
**TL Tumour Flare Reaction (Revlimid)**

**INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM:**

**Patient Demographics:**

Patient's date of birth (DD-MMM-YYYY): _____ Gender: ☐ Male ☐ Female

Age: _____

Race/Ethnicity: _____ ☐ Aborginal ☐ African American ☐ Asian
☐ American Indian or Alaskan Native ☐ Native Hawaiian or other Pacific Islander
☐ Torres Strait Islander ☐ White ☐ Black ☐ Non Hispanic

Age Group:_____

Note: Please provide Age Group if Patient's Date of Birth or Age is not available.

Age Group Definition: Neonate: 0 - 27 days, Infant: 28 days to 23 months, Child: 2 years to 11years, Adolescent: 12 years to 18 years, Adult: More than 18 years and less than or equal to 65 years and Elderly: equal or greater than 66 years)

**Suspect Products:** Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events]:

| | Suspect Product #1 | Suspect Product #2 | Suspect Product #3 |
|---|---|---|---|
| Product name | | | |
| Daily dose and regimen | | | |
| Route of administration | | | |
| Indication | | | |
| Start date or treatment duration (DD-MMM-YYYY) | | | |
| Stop date (DD-MMM-YYYY) | | | |
| Lot/Batch number(s) | | | |
| Expiration date(s) | | | |
| Action Taken with the suspect product | | | |

(Choose from one of the following for action Taken with Suspect Product: Drug withdrawn, Dose reduced, Dose increased, Dose not changed, Unknown)

**Adverse Event (AE) Description:** Please provide diagnosis or symptoms/signs if diagnosis is unavailable.

| | Adverse Event #1 | Adverse Event #2 | Adverse Event #3 | Adverse Event #4 |
|---|---|---|---|---|

| Add Diagnosis Here → | | | | |
|---|---|---|---|---|
| Start Date (DD/MMM/YYYY) | | | | |
| Stop Date (DD/MMM/YYYY) | | | | |
| Time lag if AE occurred after cessation of treatment with the suspect product(s): | | | | |
| Required Hospitalization (Yes/No) | | | | |
| Life-Threatening (Yes/No) | | | | |
| Persistent or significant disability (Yes/No) | | | | |
| Congenital abnormality (Yes/No) | | | | |
| Cause of Death (Yes/No) | | | | |
| Treatment of Adverse Event | | | | |
| Outcome (recovery and sequelae, if any) | | | | |
| Did the event(s) abate after suspect Product was stopped or dose reduced? (Yes/No) | | | | |
| Did the event recur after reintroducing (Yes/No) | | | | |

**Please summarize course of reported events including signs and symptoms in chronological order**:

_____

_____

_____

**Diagnostic tests** (use additional pages if needed)**:** Please indicate test unit where applicable.

| Date | Test Name | Pre-treatment value | AE onset value | AE resolution value | Normal low | Normal high |
|---|---|---|---|---|---|---|
| | WBC | | | | | |
| | ANC | | | | | |
| | Lymphocytes | | | | | |
| | Hb | | | | | |
| | Platelets | | | | | |
| | LDH | | | | | |
| | Creatinine | | | | | |
| | Calcium | | | | | |
| | Phosphorus | | | | | |
| | Albumin | | | | | |
| | CRP | | | | | |
| | | | | | | |
| | | | | | | |

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

_____

**Concomitant Medications** (use additional pages if needed)**:**

Did the Patient take any concomitant medication? ☐ Yes (please complete below) ☐ No ☐ Unknown
Include at least other chemotherapies, higher dose chemotherapy, treatment with immuno-modulator, hormonotherapy.

| Medication Name | Daily dose and regimen | Route of administration | Indication | Start date DD-MMM-YYYY | Stop date DD-MMM-YYYY |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

**Other Etiological Factors:** ☐ Yes (please complete below) ☐ None ☐ Unknown

☐ Relevant medical and/or drug history (please specify), including start date or duration:

☐ Family history (please specify): _____
☐ Drug/alcohol/tobacco abuse: _____
☐ Other (please specify): _____

**Additional questions:**

Provide Revlimid dosing with therapy start date, and all doses prior to the tumor flare reaction.

Please confirm the chemotherapy indication.

Tumor burden (to specify) or disease stage at baseline and at the time of the event.

Details on the associated symptoms : (Fever <please provide temperature value>
, pain <to specify>, rash <details on zones>, tender lymph nodes/ swelling <specify location>, tender liver or spleen, elevated WBC counts, other <to specify>).

Any complication (to specify).

Imagery results (CT scan/MRI) at baseline and at the time of the event.

Infections work-up (serologies, cultures – blood/urine/sputum/stools), chest Xray.

Does this patient have a history of previous tumor flare?
☐ Yes ☐ No ☐ Unknown
If yes, please describe

Provide the action taken with Revlimid in response to the tumor flare reaction:

| | |
|---|---|
| None | |
| Permanently Discontinued | Stop date: _____ |
| Temporarily Interrupted | Stop date: _____ |
| Dose Reduced | Date and new dose:_____ |
| Dose Increased | Date and new dose:_____ |

Did the event abate after discontinuing Revlimid? Yes No

Was Revlimid product re-introduced? Yes No
Provide restart date and dosing:

Provide the action taken with concomitant chemotherapy (to specify):_____

| | |
|---|---|
| None | |
| Permanently Discontinued | Stop date: _____ |
| Temporarily Interrupted | Stop date: _____ |
| Dose Reduced | Date and new dose:_____ |
| Dose Increased | Date and new dose:_____ |

Did the event abate after discontinuing concomitant chemotherapy? Yes No
Was concomitant chemotherapy re-introduced? Yes No
Provide restart date and dosing:

Treatment of the tumor flare (details).

Response to treatment

_____
Health Practitioner Name (Print)

_____
Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:

Description of event: [narrative]

# ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

The MAH shall agree the details of a controlled access programme with the National Competent Authorities and must implement such programme nationally to ensure that:

- Prior to launch, all doctors who intend to prescribe Revlimid and all pharmacists who may dispense Revlimid receive a Direct Healthcare Professional Communication as described below.
- Prior to prescribing (where appropriate, and in agreement with the National Competent Authority, dispensing) all healthcare professionals who intend to prescribe (and dispense) Revlimid are provided with an Educational Healthcare Professional's Kit containing the following:
    - Educational Healthcare Professional brochure
    - Educational brochures for patients
    - Patient card
    - Risk awareness forms
    - Information on where to find latest Summary of Product Characteristics (SmPC)

The MAH shall implement a pregnancy prevention programme (PPP) in each Member State. Details of the PPP should be agreed with the National Competent Authorities in each Member State and put in place prior to the launch of the medicinal product.

The MAH should agree the final text of the Direct Healthcare Professional Communication and the contents of the Educational Healthcare Professional's Kit with the National Competent Authority in each Member State prior to launch of the medicinal product and ensure that the materials contain the key elements as described below.

The MAH should agree on the implementation of the controlled access programme in each Member State.

**Key elements to be included**

***Direct Healthcare Professional Communication (prior to launch)***

The Direct Healthcare Professional Communication shall consist of two parts:

- A core text as agreed by the CHMP.
- National specific requirements agreed with the National Competent Authority regarding:
    - Distribution of the medicinal product
    - Procedures to ensure that all appropriate measures have been performed prior to Revlimid being dispensed

***Educational Healthcare Professional's Kit***

The Educational Healthcare Professional's Kit shall contain the following elements:

**Educational Healthcare Professional brochure**

- Brief background on lenalidomide

- Maximum duration of treatment prescribed
  - 4 weeks for women with childbearing potential
  - 12 weeks for men and women without childbearing potential
- The need to avoid foetal exposure due to teratogenicity of lenalidomide in animals and the expected teratogenic effect of lenalidomide in humans
- Guidance on handling the blister or capsule of Revlimid for healthcare professionals and caregivers
- Obligations of the healthcare professionals who intend to prescribe or dispense Revlimid
  - Need to provide comprehensive advice and counselling to patients
  - That patients should be capable of complying with the requirements for the safe use of Revlimid
  - Need to provide patients with appropriate patient educational brochure, patient card and/or equivalent tool
- Safety advice relevant to all patients
  - Description of risk of tumour flare reaction in MCL and FL patients
  - Description of risk of SPM
  - Local country specific arrangements for a prescription for lenalidomide to be dispensed
  - That any unused capsules should be returned to the pharmacist at the end of the treatment
  - That the patient should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Revlimid
- Description of the PPP and categorisation of patients based on sex and childbearing potential
  - Algorithm for implementation of PPP
  - Definition of women of childbearing potential (WCBP) and actions the prescriber should take if unsure
- Safety advice for women of childbearing potential
  - The need to avoid foetal exposure
  - Description of the PPP
  - Need for effective contraception (even if the woman has amenorrhoea) and definition of effective contraception
  - That if she needs to change or stop using her method of contraception she should inform:
    - The physician prescribing her contraception that she is on lenalidomide
    - The physician prescribing lenalidomide that she has stopped or changed her method of contraception
  - Pregnancy test regime
    - Advice on suitable tests
    - Before commencing treatment
    - During treatment based on method of contraception
    - After finishing treatment
  - Need to stop Revlimid immediately upon suspicion of pregnancy
  - Need to tell treating doctor immediately upon suspicion of pregnancy
- Safety advice for men
  - The need to avoid foetal exposure
  - The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraception (even if the man has had a vasectomy)

        - During Revlimid treatment
        - For at least 7 days following final dose.
    - That he should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Revlimid treatment
    - That if his partner becomes pregnant whilst he is taking Revlimid or shortly after he has stopped taking Revlimid he should inform his treating doctor immediately
- Requirements in the event of pregnancy
    - Instructions to stop Revlimid immediately upon suspicion of pregnancy, if female patient
    - Need to refer patient to physician specialised or experienced in dealing with teratology and its diagnosis for evaluation and advice
    - Local contact details for reporting of any suspected pregnancy immediately
- Local contact details for reporting adverse reactions

**Educational Brochures for patients**

The Educational brochures for patients should be of 3 types:

- Brochure for women patients of childbearing potential and their partner
- Brochure for women patients who are not of childbearing potential
- Brochure for male patients

All educational brochures for patients should contain the following elements:

- That lenalidomide is teratogenic in animals and is expected to be teratogenic in humans
- Description of the patient card and its necessity
- Guidance on handling Revlimid for patients, caregivers and family members
- National or other applicable specific arrangements for a prescription for Revlimid to be dispensed
- That the patient must not give Revlimid to any other person
- That the patient should not donate blood during treatment (including during dose interruptions) and for at least 7 days after discontinuation of Revlimid treatment
- That the patient should tell their doctor about any adverse events
- That any unused capsules should be returned to the pharmacist at the end of the treatment

The following information should also be provided in the appropriate brochure:

Brochure for women patients with childbearing potential

- The need to avoid foetal exposure
- Description of the PPP
- The need for effective contraception and definition of effective contraception
- That if she needs to change or stop using her method of contraception she should inform:
    - The physician prescribing her contraception that she is on lenalidomide
    - The physician prescribing lenalidomide that she has stopped or changed her method of contraception
- Pregnancy test regime
    - Before commencing treatment

  - During treatment (including dose interruptions), at least every 4 weeks except in case of confirmed tubal sterilisation
  - After finishing treatment
- The need to stop Revlimid immediately upon suspicion of pregnancy
- The need to contact their doctor immediately upon suspicion of pregnancy

Brochure for male patients

- The need to avoid foetal exposure
- The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraception (even if the man has had vasectomy)
  - During Revlimid treatment (including dose interruptions)
  - For at least 7 days following final dose
- That if his partner becomes pregnant, he should inform his treating doctor immediately
- That he should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Revlimid treatment

**Patient Card or equivalent tool**

The patient card shall contain the following elements:

- Verification that appropriate counselling has taken place
- Documentation of childbearing potential status
- Check box (or similar) which physician ticks to confirm that patient is using effective contraception (if woman of childbearing potential)
- Pregnancy test dates and results

***Risk Awareness Forms***

There should be 3 types of risk awareness forms:

- Women of childbearing potential
- Women of non-childbearing potential
- Male patient

All risk awareness forms should contain the following elements:

- teratogenicity warning
- patients receive the appropriate counselling prior to treatment initiation
- affirmation of patient understanding of the risk of lenalidomide and the PPP measures
- date of counselling
- patient details, signature and date
- prescriber name, signature and date
- aim of this document i.e. as stated in the PPP: “The aim of the risk awareness form is to protect patients and any possible foetuses by ensuring that patients are fully informed of and understand the risk of teratogenicity and other adverse reactions associated with the use of

lenalidomide. It is not a contract and does not absolve anybody from his/her responsibilities with regard to the safe use of the product and prevention of foetal exposure."

Risk awareness forms for women of childbearing potential should also include:

- Confirmation that the physician has discussed the following:
  - the need to avoid foetal exposure
  - that if she is pregnant or plans to be, she must not take lenalidomide
  - that she understands the need to avoid lenalidomide during pregnancy and to apply effective contraceptive measures without interruption, at least 4 weeks before starting treatment, throughout the entire duration of treatment, and at least 4 weeks after the end of treatment
  - that if she needs to change or stop using her method of contraception she should inform:
    - the physician prescribing her contraception that she is taking Revlimid
    - the physician prescribing Revlimid that she has stopped or changed her method of contraception
  - of the need for pregnancy tests i.e. before treatment, at least every 4 weeks during treatment and after treatment
  - of the need to stop Revlimid immediately upon suspicion of pregnancy
  - of the need to contact their doctor immediately upon suspicion of pregnancy
  - that she should not share the medicinal product with any other person
  - that she should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Revlimid
  - that she should return the unused capsules to the pharmacist at the end of treatment

Risk awareness forms for women with no childbearing potential should also include:

- Confirmation that the physician has discussed the following:
  - that she should not share the medicinal product with any other person
  - that she should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Revlimid
  - that she should return the unused capsules to the pharmacist at the end of treatment

Risk awareness forms for male patients should also include:

- Confirmation that the physician has discussed the following:
  - the need to avoid foetal exposure
  - that lenalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a WCBP not on effective contraception (even if the man has had a vasectomy)
  - that if his partner becomes pregnant, he should inform his treating doctor immediately and always use a condom
  - that he should not share the medicinal product with any other person

- that he should not donate blood or semen during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Revlimid
- that he should return the unused capsules to the pharmacist at the end of treatment