CLINICAL STUDY PROTOCOL

FHCRC # 9266
FRED HUTCHINSON CANCER RESEARCH CENTER
UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE
Millennium Study Number: X16064

Alternating the Administration of Ixazomib and Lenalidomide as Maintenance Therapy after Autologous Transplant for Treating Multiple Myeloma

Indication: **Maintenance therapy after autologous Tx for Multiple Myeloma**

Phase: **II**

Protocol History

Original	02 July 2015
Previous	30 October 2015
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Current	16 September 2019

Investigator and Study Center:

Principal Investigator

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This is an investigator-initiated study. The principal investigator Leona A Holmberg MD, PhD (who may also be referred to as the sponsor-investigator), is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.

PROTOCOL SUMMARY

Study Title: Alternating the Administration of Ixazomib and Lenalidomide as Maintenance Therapy after Autologous Transplant for Treating Multiple Myeloma
Phase: II
Number of Patients: 30
Study Objectives Primary • Evaluate the toxicity of the use of ixazomib and lenalidomide as maintenance therapy after autologous transplant Secondary • Evaluate the ability to deliver the planned therapy • Assess initial response to therapy • Evaluate the median time to disease progression • Assess overall survival

Overview of Study Design:

Hypothesis of this phase II study is that ixazomib and lenalidomide as maintenance therapy after autologous PBSC transplant for Multiple Myeloma will be safe and tolerable and prolong the time to disease progression post transplant. The treatment regimen is alternating ixazomib with lenalidomide every two months until disease progression, intolerable toxicity or maximum of 24 months of therapy. The dose of ixazomib is 4.0 mg po on days 1, 8 and 15 per each 28-day cycle given for two consecutive months, followed by then lenalidomide 10 mg po daily for two consecutive months, then ixazomib for two months etc. Dose reduction for toxicity will be incorporated. If >30 days off initially planned next cycle of therapy, then patient will be taken off study. Toxicity will be graded per CTCAE version 4.0. The first four months of therapy will be used as the time period to evaluate end point of toxicity for stopping rules. Toxicity that meets stopping rules will be determined based on the number of patients that are withdrawn from study for significant toxicity (grade IV, non-hematological, non-metabolic, non-peripheral neuropathy) and the number of patients who stop therapy for toxicity and are withdrawn from study as they could not recover adequately and resume therapy by 30 days from the initial stopping of the study drugs. We shall consider the withdrawal rate to be excessive, and hence the therapy to be too toxic, if the true withdrawal rate from the study exceeds 15% in the first four months. An interim analysis at 15 treated patients will be conducted. If > 50% of patients are unable to receive > 50% of planned therapy in first 12 months of treatment, the study will be terminated due to lack of feasibility. Another endpoint is time to disease progression. Patients will be followed for initial response and for progression of disease, response criteria will be determined by International Myeloma working group criteria. In patients with chemo-refractory disease at the time of ASCT, the therapy will be felt to be promising if median time to progression is >9 months. If chemo-sensitive disease at time of ASCT, the therapy will be felt to be promising if median time to progression is >41 months based on CALGB 10014 lenalidomide maintenance study post ASCT. Cytogenetic information will be collected and initial response rates and outcome will be descriptively reported. Patients will be followed for overall survival. The incidence of secondary cancers will also be collected. If this study regimen is deemed to be potentially efficacious and is not regarded as too toxic per stopping rules outlined above and observed EFS rate are consistent with rates that match or exceed historical benchmarks, then a phase III trial to show efficacy rate of this regimen over single agent therapy will be designed.

Study Population:

Adult Autologous Multiple Myeloma Transplant patients

Duration of Study:

Five years (2-3 years to enroll patients on study)

SCHEDULE OF EVENTS

Study Flow Chart

(Each cycle is 28 days) Cycle		1-4 cycles				5-24 cycles			
Day	Screening (Baseline within 30 days)	Predose Day (within 3 days) to Day 1 of Cycle 1-4	Day 8 (+/- 3 days) Week one	Day 15 and 22 (+/- 3 days) Weeks 2 and 3	Predose Day (within 3 days) to Day 1 of Cycle 5-24	Day 8 (+/- 3 day) Week one	Day 15 (+/- 3 days) Week 2	End of Study (Labs within 7 days and other tests within month after last dose of drug)	Survival Follow-up
Phase	Screening	Pretreatment	Treatment	Treatment		Treatment	Treatment	Post-Treatment	Post-Treatment
Study Procedures									
Obtain study informed consent	X								
Demographics	X								
Review Inclusion/Exclusion criteria	X								
Review/collect prior medications	X								
Collect medical history	X								
Enroll Revlimid REMS TM program pre cycle 3		X							
Safety Labs/ Measurements									
Collect serum β-hCG pregnancy test[b]	X	X[b]							
Collect CBC	X	**X**	**X**	**X**	**X**	**X**	X	X	X
Collect blood chemistry	X	**X**	**X**	**X**	**X**	**X**		X	X
Collect PT/INR & aPTT[a]	X								
Collect urinalysis (complete)	X								
Collect 24-hour urine creatinine clearance	X								

Cycle	------	1-4			5-24				--------
Day	Screening (Baseline) Within 30 days prior to first dose	Predose Day (within 3 days Day 1 of Cycle 1-4	Day X (+/- 3 days) Week one	Day X Cycle 1-24	Pre dose within 3 days	Day X (+/- 3 days Week one	Day X (+/- 3 days) Week 2	End of Study (within month after last dose of drug)	Survival Follow-up
Phase	Screening	Pretreatment	Treatment	Treatment	Treatment	Treatment		Post-treatment	Post-Treatment
Review concomitant medications	X	X			X				
Review adverse experiences		X			X			X	
ECOG Performance Status	X	X			X			X	X
Perform physical examination and collect vital signs (including height at screening and weight at all visits)	X	X			X			X	X
Efficacy Measurements									
MRI Bone Marrow and osseous survey								X	X (yearly)
BM aspirate and biopsy unilateral for pathology, flow, cytogenetics and myeloma FISH panel	X							X	X (yearly)
Serum free light or SPEP with IF	X			X (every 3 months				X	X (every 3 months)
24 hour urine for UPEP with IF, total protein, Bence Jones quantification	X (if abnormal pre TX)			X (every 3 months if abnormal pre Tx)				X	X (yearly)
Drug Administration & Accountability									
Administer premedication/prophylactic supportive care medications as specified		X			X				
Dispense ixazomib only for cycles 1-2, 5-6 , 9-10, 13-14, 17-18, 21-22 from IDS Pharmacy		X			X				
Dispense lenalidomide only for cycles, 3-4, 7-8, 11-12, 15-16, 19-20, 23-24 (commercial source)		X			X				
Perform ixazomib pill count as indicated		X			X				

a **PT/INR and aPTT should be collected at baseline and monitored throughout the study if the patient is being treated with warfarin or other anticoagulant therapy.**

b **Female patients of childbearing potential must have a negative serum pregnancy test (β-hCG pregnancy test) within 24 hours prior to receiving the first dose of study drug(s). Follow Revlimid REMS TM standard plan for follow-up testing.**

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Common abbreviations used in oncology protocols are provided below. Program-specific or protocol-specific abbreviations must be added to this list, and unnecessary abbreviations removed, as applicable. Abbreviations that are retained should not be changed.

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
ASCT	Autologous Peripheral Blood Stem Cell Transplant
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{24\ hr}$	area under the plasma concentration versus time curve from zero to 24 hours
AUC_{inf}	area under the plasma concentration versus time curve from zero to infinity
AUC_{τ}	area under the plasma concentration versus time curve from zero to next dose
βhCG	beta-human chorionic gonadotropin
BID	bis in die; twice a day
BM	bone marrow
BSA	body surface area
BUN	blood urea nitrogen
BZD	Benzodiazepines
CBC	complete blood count
CFR	Code of Federal Regulations
CL_P	plasma clearance
CL_{Total}	total clearance
C_{max}	single-dose maximum (peak) concentration
CNS	central nervous system

Abbreviation	Term
CO_2	carbon dioxide
CR	complete remission
C_{trough}	single-dose end of dosing interval (trough) concentration
CV	coefficient of variation
CYP	cytochrome P_{450}
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DME	drug metabolizing enzymes
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunosorbent assay
EOS	End of Study (visit)
EOT	End of Treatment (visit)
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GI	Gastrointestinal
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice
Hb	Hemoglobin
Hct	Hematocrit
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
ITT	intent-to-treat

Abbreviation	Term
IV	intravenous; intravenously
K_i	inhibition constant
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
LFT	liver function test(s)
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MRI	magnetic resonance imaging
MRU	medical resource utilization
MTD	maximum tolerated dose
MUGA	multiple gated acquisition (scan)
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NPO	nothing by mouth
NYHA	New York Heart Association
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease (disease progression)
Pgp	P-glycoprotein
PK	pharmacokinetic(s)
PO	*per os*; by mouth (orally)
PR	partial response
PRO	patient-reported outcome
QD	*quaque die*; each day; once daily
QOD	*quaque altera die*; every other day
RBC	red blood cell
SAE	serious adverse event
SD	stable disease
SmPC	Summary of Product Characteristics
$t_{1/2}$	terminal disposition half-life

Abbreviation	Term
TGI	tumor growth inhibition
T_{max}	single-dose time to reach maximum (peak) concentration
ULN	upper limit of the normal range
US	United States
V_z	volume of distribution in the terminal phase
VGPR	Very good partial response
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

Autologous transplants (ASCT) can cause remission in Multiple Myeloma (MM) patients, but relapse remains a major problem. Proteasome inhibitors and IMiDs are classes of drugs that are very active in treating Multiple Myeloma. Recently, at ASH 2013 Mateos et al [1] reported in a non-transplant setting on the use of an alternating schedule of VMP and lenalidomide plus Dex in elderly newly diagnosed non- transplant Multiple Myeloma patients. The alternating schedule was superior to sequential therapy with respect 18 month TTP and overall Survival in patients, especially those who achieved a CR/sCR. Post ASCT, the addition of maintenance therapy (i.e. bortezomib, thalidomide and lenalidomide) changes the outcome of transplant patients by consistently and significantly prolonging the time to disease progression. But, there is no universally accepted standard of care for maintenance therapy post ASCT. The purpose of this study is to determine if alternating the IMiD lenalidomide with the proteasome inhibitor ixazomib is a well-tolerated all oral maintenance regimen and if it is effective therapy in terms of changing the time to disease progression post ASCT. It is felt that the use of an alternating schedule may decrease the development of resistant clones to emerge dominant. If feasible to deliver this therapy and the therapy appears to be effective, then a larger randomized trial would be appropriate comparing alternating schedule with single agent therapy.

1.1.2 Ixazomib (MLN9708)

1.2 Preclinical Experience

Please refer to the current ixazomib Investigator's Brochure (IB) and Safety Management Attachment (SMA).

1.3 Clinical Experience

Ixazomib is a potent, reversible, and specific 20S proteasome inhibitor.
Ixazomib is the first orally bioavailable proteasome inhibitor to enter clinical development. The ixazomib clinical development program includes investigation of activity in both hematologic and nonhematologic malignancies, 2 routes of administration (IV and PO), and more convenient/less frequent dosing schedules than those currently used with commercially available proteasome inhibitors. There are no new studies planned using the IV formulation at this time, as only the oral formulation is currently being developed for commercialization. Data are available from 637 patients who have received at least 1 dose of ixazomib across the clinical development program; in addition, 817 patients have enrolled in phase 3 clinical trials, either in placebo-controlled Studies C16010 or C16014 (and received either ixazomib or placebo in combination with LenDex), or in Study C16011 (and received either ixazomib and dexamethasone, or physician's choice of a dexamethasone-containing regimen). Pharmacokinetic data demonstrate that the disposition of IV ixazomib is multi-exponential, with the rapid initial phase being largely over by 4 hours after the dose. The terminal halflife

after multiple doses ranges from 2.8 to 12.2 days. Oral ixazomib is rapidly absorbed with a median T_{max} of 1 hour. The terminal half-life after multiple doses ranges from 2.1 to 11.3 days. Population PK analyses demonstrated that oral ixazomib can be administered as a fixed dose rather than BSA-based dosing and starting dose adjustment is not required in patients with mild (60-90 mL/min) or moderate (30-60 mL/min) renal impairment. These findings have been incorporated into the summary of clinical studies with ixazomib (Table 1-1).

Clinical studies are ongoing to investigate the safety and activity of ixazomib, including further characterization of the clinical pharmacology aspects of the drug. Preliminary efficacy data suggest that ixazomib has early anti-tumor activity across all clinical studies. The preliminary safety data indicate that ixazomib is generally well tolerated with manageable and reversible AEs. Most of the AEs seen in the clinical studies to date were reversible at tolerated doses or with drug discontinuation and can be monitored in the clinic with routine clinical observations and tests. Enrollment continues in the ongoing studies to further characterize safety and efficacy.

Additional detailed information regarding the clinical experience of ixazomib may be found in the IB.

1.4 Pharmacokinetics and Drug Metabolism

The PK of ixazomib after IV dosing is characterized by a multi-exponential disposition profile in plasma with the terminal half-life after multiple doses ranging from 2.8 to 12.2 days. Plasma exposures increase proportionally over the dose range of 0.5 to 3.11 mg/m^2 (0.8-6.8 mg actual administered dose range). Renal elimination appears to be a minor clearance pathway for ixazomib as renal clearance is less than 5% of the total body clearance estimate from the population PK analysis.

After both once- and twice-weekly oral dosing, ixazomib is rapidly absorbed with a median T_{max} of 1 hour. The observed range for the terminal half-life after multiple doses is 2.1 to 11.3 days. Dose proportionality has been observed for doses between 0.48 and 3.95 mg/m^2 (0.8-8.9 mg actual administered dose range).

Pharmacokinetic parameters for ixazomib coadministered with LenDex (Studies C16005 and C16008), or MP (Study C16006), appear to be similar to those observed when ixazomib is administered as a single agent. This suggests that there is no readily apparent effect of coadministration of LenDex, or MP, on the clinical PK of ixazomib. Likewise, no apparent differences in the PK of ixazomib have been noted between patients with different malignancies.

After once-weekly dosing, Day 1 geometric mean dose-normalized ixazomib exposures in Japanese and Asian patients receiving ixazomib plus LenDex are similar to the observed values in Western patients (Studies C16004, C16005, and C16007). On Day 15, the geometric mean dose-normalized ixazomib $AUC_{0\text{-}168}$ in Asian patients is approximately 45% higher than the observed values in Western patients.

Ixazomib is neither a time-dependent nor a reversible inhibitor of CYP isozymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 (IC_{50} >30 μM). Treatment with up to 5000-ng/mL ixazomib citrate did not induce CYP1A2, 2B6, and 3A4/5 activity or corresponding immunoreactive protein levels in

cultured human hepatocytes. Therefore, the potential for CYP isozymes-mediated DDIs is low. However, there may be a potential for DDIs with a concomitant strong CYP3A4/5 or 1A2 inhibitor or inducer because CYP3A4/5 and 1A2 are the primary isozymes that contribute to the overall metabolism of ixazomib in HLMs. Clinical evaluation with a strong CYP3A4/5 inhibitor and a strong CYP3A4/5 inducer is ongoing (Study C16009). Ixazomib showed medium permeability in Caco-2 cells and may be a low-affinity substrate of P-gp, BCRP, and MRP2 efflux pump transporters. Ixazomib is not an inhibitor of P-gp, BCRP, and MRP2 ($IC_{50} > 100$ μM). Ixazomib citrate is not a substrate of OATPs and is not an inhibitor of OCT2, OAT1, OAT3, or OATPs. The contribution of efflux transporters to ixazomib transport is low (19% of total transport). Consequently, the potential for ixazomib to cause transporter-mediated DDIs is low. Results from these clinical pharmacology studies support the continued exclusion of strong CYP3A4 inhibitors in ongoing clinical trials [2]. A high-fat meal decreased both the rate and extent of absorption of ixazomib. Therefore, ixazomib should continue to be administered on an empty stomach (no food for 2 hours before and 1 hour after dosing) [3]. Based on clinical experience from the phase 1 studies, the dose selected for phase 3 studies is 4 mg given weekly.

Further details on these studies are provided in the IB.

1.5 Clinical Trial Experience Using the Oral Formulation of Ixazomib

As of March 2014, there are 18 ongoing clinical studies of ixazomib, 1 completed study, and 2 studies initiating clinical sites. Information regarding these ongoing studies, patient populations, and ixazomib doses investigated are included in Table 1-1.

Table 1-1 Clinical Studies of Oral Ixazomib

Trial/ Population	Description	Doses Investigated
C16003 RRMM N = 60	PO, TW, single agent 21-day cycle	0.24-2.23 mg/m^2 TW MTD: 2.0 mg/m^2 DLT: rash, thrombocytopenia Closed to enrollment
C16004 RRMM N = 60	PO, W, single agent 28-day cycle	0.24-3.95 mg/m^2 W MTD: 2.97 mg/m^2 DLT: rash, nausea, vomiting, diarrhea Closed to enrollment
C16005 NDMM N = 65	PO, W, combination with LenDex 28-day cycle	1.68-3.95 mg/m^2 W MTD: 2.97 mg/m^2 DLT: nausea, vomiting, diarrhea, syncope RP2D[a]: 4.0 mg fixed (switched to fixed dosing in phase 2, equivalent to 2.23 mg/m^2) Closed to enrollment
C16006 NDMM N = 55	PO, TW (Arm A- 42 day cycle), W (Arm B- 28 day cycle), W (Arm C- 42 day cycle), and W (Arm D-42 day cycle) combination with Melphalan and Prednisone	Arm A[a]: 3-3.7-mg fixed dose TW DLT: rash, thrombocytopenia, subileus Arm B[a]: 3-5.5-mg fixed dose, W DLT: Esophageal ulcer nausea, vomiting, hematemesis, thrombocytopenia, ileus, neurogenic bladder Arm C: 3-4–mg fixed dose, W Arm D: 4-mg, W MTD = 3.0 mg
C16007 RRAL N = 27	PO, W, single agent 28-day cycle	4-5.5-mg fixed dose[a] W DLT: thrombocytopenia, diarrhea, dyspnea, acute rise in creatinine, cardiac arrest MTD: 4.0 mg W
C16008 NDMM N = 64	PO, TW, combination with LenDex 21-day cycle	3.0-3.7-mg fixed dose[a] TW MTD: 3.0 mg Closed to enrollment
C16009 Solid tumors, Lymphomas N = 74	PO, W, 5-Arm sequentially enrolling trial, combination with ketoconazole, rifampin, or clarithromycin	2.5-5.5-mg fixed dose[a] W
C16010 RRMM N = 683	PO, W, with LenDex versus placebo-LenDex 28-day cycle	4.0 mg W
C16011 RRAL N = 42	PO, W, with Dex versus physician's choice of a Dex-based regimen 28-day cycle	4.0 mg W
C16013 RRMM N = 36	PO, W, with LenDex 28-day cycle	4.0 mg W

Trial/ Population	Description	Doses Investigated
C16014 Symptomatic MM N=92	PO, combination with LenDex	Ixazomib 4.0 mg or matching placebo on Days 1, 8, and 15, plus Len 25 mg on Days 1-21 (10 mg if low creatinine clearance, with escalation to 15 mg if tolerated) and Dex 40 mg (or 20 mg if >75 years old) on Days 1, 8, 15, and 22
C16015 Symptomatic MM with normal renal function or severe renal impairment N=6	PO, combination with Dex	Part A: Ixazomib 3.0 mg on Day 1 Part B: Ixazomib 4.0 mg on Days 1, 8, and 15, plus Dex 40 mg (or 20 mg if >75 years old) on Days 1, 8, 15 and 22 of a 28-day cycle

Trial/ Population	Description	Doses Investigated
C16017 RR follicular lymphoma N=6	PO, W	4.0, 5.3, and 7.0 mg, W Treatment at RP2D once determined.
C16018 Advanced solid tumors or hematologic malignancies with varying degrees of liver dysfunction N=24	Part A: PO, Day 1 of 15-day cycle Part B: PO, W	1.5 mg (severe hepatic impairment), 2.3 mg (moderate hepatic impairment), or 4.0 mg (normal hepatic function)
C16019 Adult patients with NDMM following standard-of-care specific induction therapy followed by HDT and ASCT N=652 planned, site initiation in progress	PO, W, single agent 28-day cycle	3.0-mg W (increased to 4.0mg at Cycle 5, if tolerated)
C16020 Treatment naiive adult patients with NDMM who are ineligible for high-dose therapy followed by ASCT due to age (≥65 years) or comorbidies N=2	Arm-A: PO, W with cyclo 300 mg/m^2 and dex 40 mg (or 20 mg if (≥75 years old) Arm-B: PO, W with cyclo 400 mg/m^2 and dex 40 mg (or 20 mg if (≥75 years old) 28-day cycle	4.0 mg fixed dose, W
TB-MC010034 RRMM N = 14	PO, W	4.0 mg, W Single agent: 4.0 mg Combination with Rd

Source: Clinical study protocols for all studies listed, and \biostatistics\MLNM9708\DSUR\2014\Tables\T14.1.1.1-Disposition; data cutoff 27 March 2014.

Abbreviations: ASCT = autologous stem cell transplant; BA = bioavailability; CSR = clinical study report; cyclo = cyclophosphamide; DDI = drug-drug interaction; dex = dexamethasone; HDT = high-dose therapy; IV = intravenous; keto = ketoconazole; len = lenalidominde; MTD = maximum tolerated dose; mel = melphalan; NDMM = newly diagnosed multiple myeloma; NSCLC = non-small cell lung cancer; ORR = overall response rate; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetics; pred = prednisone; RP2D = recommended phase 2 dose; RP3D = recommended phase 3 dose; RRAL = relapsed and/or refractory systemic light-chain amyloidosis;

RRMM = relapsed and/or refractory multiple myeloma; SCT = stem cell transplant; SD = stable disease; TBD = to be determined; thal = thalidomide; TW = twice weekly; US = United States; UK = United Kingdom.
Unless otherwise noted, patients may continue study treatment per protocol until disease progression or unacceptable toxicity. Study protocols C16001, C16002, C16003, C16004, C16007, C16009, C16015, C16017, C16018, and TB-MC010034 specify a maximum of 12 cycles unless it is determined that a patient would derive clinical benefit from continued therapy beyond 12 cycles. c Within this table, number of patients enrolled is defined as the safety population, ie, patients who received at least 1 dose of study drug.
[a]Approximate BSA and fixed dosing equivalence: 3 mg~ equivalent to 1.68 mg/m^2 BSA dosing; 4.0 mg ~ equivalent to 2.23 mg/m^2 BSA dosing; and 5.5 mg~ equivalent to 2.97 mg/m^2 BSA dosing.

Overview of the Oral Formulation of Ixazomib

The emerging safety profile indicates that ixazomib is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with VELCADE though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation. An overview of the most frequent (at least 10%) AEs occurring in the pooled safety population from single-agent ixazomib and ixazomib in combination with standard regimen oral ixazomib studies is shown in Tables 1-2 and 1-3.

Table 1-2 Overall Safety Population Oral Ixazomib: Most Common Treatment-Emergent Events (>20%) by MedDRA System Organ Class and Preferred Term

MedDRA SOC	Preferred Term Total Oral Studies (n = 491)[a]	Preferred Term Single-Agent Ixazomib (n = 153)[b]	Preferred Term Ixazomib in Combination with Standard Regimen (n = 220)[c]
Gastrointestinal disorders	Nausea (47%), diarrhea (47%), vomiting (37%), constipation (27%)	Nausea (48%), diarrhea (44%), vomiting (33%), constipation (19%)	Diarrhea (53%), nausea (42%), constipation (35%), vomiting (33%)
General disorders and administration site conditions	Fatigue (45%), pyrexia (23%), peripheral edema (25%)	Fatigue (51%), pyrexia (25%), peripheral edema (12%)	Fatigue (45%), peripheral edema (37%), pyrexia (22%)
Skin and subcutaneous tissue disorders	Rash (all terms; 40%)[d]	Rash (all terms; 36%)[d]	Rash (all terms; 53%)[d]
Blood and lymphatic system disorders	Thrombocytopenia (33%), anemia (23%), neutropenia (21%)	Thrombocytopenia (41%), anemia (21%), neutropenia (18%)	Thrombocytopenia (35%), neutropenia (29%), anemia (26%)
Metabolism and nutrition disorder	Decreased appetite (24%)	Decreased appetite (29%)	Decreased appetite (19%)
Nervous system	Dizziness (17%), Peripheral neuropathy (16%)	Dizziness (15%), peripheral neuropathy (13%)	Peripheral neuropathy (26%), dizziness (25%)
Infections and infestations	Upper respiratory tract infection (19%)	Upper respiratory tract infection (18%)	Upper respiratory tract infection (28%)

Table 1-2 Overall Safety Population Oral Ixazomib: Most Common Treatment-Emergent Events (>20%) by MedDRA System Organ Class and Preferred Term

MedDRA SOC	Preferred Term Total Oral Studies (n = 491)[a]	Preferred Term Single-Agent Ixazomib (n = 153)[b]	Preferred Term Ixazomib in Combination with Standard Regimen (n = 220)[c]
Musculoskeletal and connective tissue disorders	Back pain (15%), pain in extremity (13%)	Back pain (12%)	Back pain (27%), pain in extremity (21%)
Psychiatric disorders	Insomnia (18%)		Insomnia (29%)

Source: \biostatistics\MLNM9708\IB\2014\Tables\T14.1.3-TEAE_Pct10_Pooled, \biostatistics\MLNM9708\IB\2014\Tables\T14.1.4-TEAE_Pct10_OralSingle, and \biostatistics\MLNM9708\IB\2014\Tables\T14.1.5-TEAE_Pct10_OralComb; data cutoff 27 March 2014.
a Studies with oral formulation C16003/4/5/6/7/8/9/13/15/17/18/TB_MC010034) excluding ongoing phase 3 trials.
b Studies C16003, C16004, C16007, and C16017.
c Studies C16005 (w/ LenDex), C16006 (w/ MP), C16008 (w/ LenDex), and C16013 (w/ LenDex) (n = 220).
d Represents aggregate frequency as no individual preferred term reported at ≥ 20% frequency.

Table 1-3 Most Common (>10% of Total) Treatment-Emergent Adverse Events in Oral Studies

Primary System Organ Class Preferred Term	Oral Studies Total n = 491 n (%)
Subjects with at Least One Adverse Event	482 (98)
Gastrointestinal disorders	**400 (81)**
Nausea	230 (47)
Diarrhoea	230 (47)
Vomiting	181 (37)
Constipation	134 (27)
Abdominal pain	60 (12)
General disorders and administration site conditions	**363 (74)**
Fatigue	223 (45)
Pyrexia	112 (23)
Oedema peripheral	122 (25)
Asthenia	74 (15)
Nervous system disorders	**272 (55)**

Table 1-3 Most Common (>10% of Total) Treatment-Emergent Adverse Events in Oral Studies

Primary System Organ Class Preferred Term	Oral Studies Total n = 491 n (%)
Dizziness	85 (17)
Headache	74 (15)
Neuropathy peripheral	81 (16)
Metabolism and nutrition disorders	**267 (54)**
Decreased appetite	120 (24)
Dehydration	61 (12)
Hypokalaemia	57 (12)
Blood and lymphatic system disorders	**256 (52)**
Thrombocytopenia	161 (33)
Anaemia	114 (23)
Neutropenia	103 (21)
Lymphopenia	61 (12)
Skin and subcutaneous tissue disorders	**255 (52)**
Rash (all terms)	197 (40)
Rash maculo-papular[a]	60 (12)
Rash macular[a]	56 (11)
Musculoskeletal and connective tissue disorders	**249 (51)**
Back pain	88 (18)
Arthralgia	72 (15)
Pain in extremity	66 (13)
Respiratory, thoracic and mediastinal disorders	**228 (46)**
Cough	94 (19)
Dyspnoea	80 (16)
Infections and infestations	**244 (50)**
Upper respiratory tract infection	94 (19)
Psychiatric disorders	**151 (31)**
Insomnia	89 (18)

Table 1-3 Most Common (>10% of Total) Treatment-Emergent Adverse Events in Oral Studies

Primary System Organ Class Preferred Term	Oral Studies Total n = 491 n (%)

Source: Ixazomib Investigator's Brochure Edition 8

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, version 15.0.

Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator.

[a]Note that rash maculopapular and rash macular represent the 2 most common terms used to describe rash.

Modest transient increases in creatinine and infrequent (<8%) cases of reversible renal failure have also been reported.

As of 27 March 2014, there are 16 studies actively enrolling patients with Multiple Myeloma to investigate oral ixazomib in combination with standard combination regimens. The clinical experience with ixazomib also shows early signs of antitumor activity as evidenced by at least a 50% reduction in disease burden in some patients and prolonged disease stabilization in others across all ongoing trials. The antitumor activity has been seen with single-agent ixazomib, when combined with established therapies, and across the malignancies studied (advanced solid tumors [4], non-Hodgkin's disease, Hodgkin's disease[5], relapsed and/or refractory Multiple Myeloma RRMM[6][7], relapsed or refractory systemic light chain amyloidosis RRAL[8], and newly diagnosed Multiple Myeloma NDMM[9][10][11] to date.

Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports the ongoing development of ixazomib.

1.6 Relapsed and/or Refractory Multiple Myeloma

The development of ixazomib in patients with RRMM includes 2 phase 1 dose escalation single-agent studies (Studies C16003 and C16004) (see study details in IB). Across these studies, 120 patients were treated, 60 in each study (Study C16003 with the twice-weekly schedule and Study C16004 with the weekly schedule). The MTD in Study C16003 was 2 mg/m^2 twice-weekly dosing based on DLTs of macular rash and thrombocytopenia (platelet count = 10 x 10^9/L). The MTD in Study C16004 was 2.97 mg/m^2 given weekly based on DLTs of diarrhea, nausea, vomiting, and erythema multiforme.

At the data cutoff, with 3 patients remaining on study, the median number of cycles administered in Study C16003 was 4 (range 1-61) with 33 (55%) patients treated for ≥ 4 cycles, 17 (28%) for ≥ 8 cycles, and 11 (18%) for ≥ 12 cycles. Across all patients treated, including above and below the MTD, dose reductions were needed once in 57% of patients, with ≥ 2 reductions needed in 20% of patients.

At the data cutoff, all patients in Study C16004 have discontinued treatment. The median number of cycles administered was 2 (range 1-24) with 19 (32%) patients treated for ≥ 4 cycles, 12 (20%) for ≥ 8 cycles, and 2 (3%) for ≥ 12 cycles. Across all patients treated including above and below the MTD, dose reductions were needed once in 33% of patients, with ≥ 2 reductions needed in 13% of patients.

The development of ixazomib in patients with RRMM includes combinational studies (Studies C16010, C16013, and TB-MC010034). Study C16013 is a phase 1 study to characterize the PK and tolerability of 4 mg of PO ixazomib when administered in combination with LenDex in adult Asian patients with RRMM (see Table 1-1 for details). Two non-DLT evaluable patients reported AEs that, although they did not meet the protocol definition of DLT, were considered dose limiting by the investigator: ALT increase (Grade 3) with increased alkaline phosphatase and GGT (Grade 2) in one patient and diarrhea (Grade 3) in a second patient. At the data cutoff, the median number of cycles administered was 4.5 (range 1-15), with 20 (56%) patients treated for ≥ 4 cycles, 12 (33%) for ≥ 8 cycles, and 4 (11%) for ≥ 12 cycles. Across all patients treated including above and below the MTD, dose reductions were needed once in 28% of patients and no patient needed more than 1 reduction. Study TB-MC010034 is a phase 1/1b study in Japanese patients with RRMM. The study is designed to assess the tolerability, safety, and PK of oral ixazomib both as a single agent and in combination with LenDex in a Japanese patient population (see Table 1-1 for details). Ixazomib at 4 mg as a single agent and in combination with LenDex was considered tolerable because DLTs occurred in 1 of 6 DLT-evaluable patients in either cohort. Doselimiting toxicities included diarrhea, nausea, hypokalaemia, hypertension, thrombocytopenia, and hyponatraemia in the single-agent cohort and thrombocytopenia and neutropenia in combination with LenDex. At the data cutoff across both cohorts, the median number of cycles administered was 7 (range 1-23) with 9 (64%) treated for ≥ 4 cycles, 6 (43%) for ≥ 8 cycles, and 5 (36%) for ≥12 cycles. Across all patients treated, dose reductions were needed once in 14% of patients and 1 patient needed more than 1 reduction.

No dose adjustment is required for Asian patients based on PK and safety data.

Study C16010 is an ongoing, randomized, double-blind, multicenter, phase 3 study evaluating ixazomib or placebo once weekly for 3 weeks in 28-day cycles, in combination with LenDex in patients with RRMM. At the data cutoff, a total of 683 patients were randomized in a 1:1 ratio (see Table 1-1 for details). Because this study is ongoing, nonserious safety or efficacy data are not available. Serious safety data and deaths (blinded) are summarized.

1.7 Newly Diagnosed Multiple Myeloma (NDMM)

Three phase 1/ 2 studies are being conducted with ixazomib in combination with standard anti-myeloma regimens; 2 in combination with LenDex (Studies C16005 and C16008) and 1 in combination with MP (Study C16006). Study C16014 is a randomized, placebo controlled phase 3 study of ixazomib or placebo in combination with LenDex. (See Table 1-1 for details). Throughout this section, Studies C16005 and C16008 are presented first, followed by Study C16014 (SAEs and deaths only), and then Study C16006.

Study C16005 is a phase 1/2 study of weekly ixazomib in combination with LenDex in a 28-

day cycle during the induction phase followed by single-agent ixazomib during the maintenance phase [10] [12] [13][14]. The MTD was 2.97 mg/m2 given weekly with LenDex based on DLTs of urticaria rash, dizziness, nausea, orthostatic hypotension, vomiting, peripheral neuropathy, and syncope. The recommended phase 2 dose (RP2D) is 2.23 mg/m2 determined after evaluation of the available data from the phase 1 portion of the trial, which included but was not limited to analyses of both efficacy results and safety results. This RP2D has been translated into a fixed dose of 4.0 mg on the basis of the results of the population PK analysis (IB Section 5.4) [15] [16].

At the data cutoff, in Study C16005, 15 patients remained on study receiving ixazomib in the maintenance phase. The median number of cycles administered was 7 (range 1-39) with 59 (91%) patients treated for ≥ 4 cycles, 32 (49%) for ≥ 8 cycles, 26 (40%) for ≥12 cycles, and 14 (22%) for ≥ 25 cycles, including 1 patient who received 39 cycles. Across all patients treated including above and below the MTD, dose reductions of any drug in the combination were needed once in 20% of patients, with ≥ 2 reductions needed in 8% of patients.

Study C16008 is a phase 1/2 study of twice-weekly ixazomib in combination with LenDex in a 21-day cycle during the induction phase followed by single-agent ixazomib during the maintenance phase [13]. While there were no DLTs reported in this study, 3.0 mg was determined to be the RP2D following evaluation of the available data from the phase 1 portion of this trial including, but not limited to, analyses of efficacy results and toxicity characterization [17]. At the data cutoff, in Study C16008, 12 patients remained on study receiving ixazomib in the maintenance phase. The median number of cycles administered was 9 (range 1-39) with 59 (92%) patients treated for ≥ 4 cycles, 49 (77%) for ≥ 8 cycles, 24 (38%) for ≥12 cycles, and 5 (8%) for ≥ 25 cycles, including 1 patient who received 38 cycles. Across all patients treated including above and below the MTD, dose reductions were needed once in 30% of patients, with ≥ 2 reductions needed in 11% of patients. Study C16014 is an ongoing, randomized, double-blind, multicenter, phase 3 study conducted at more than 150 sites worldwide. As of 27 March 2014, a total of 92 patients were randomized in a 1:1 ratio (see Table 1-1 for details). Because this study is ongoing, nonserious safety or efficacy data are not available. Serious safety data and deaths (blinded) are summarized.

Study C16006 is a phase 1 study of ixazomib in combination with MP [11]. Multiple dosing schedules are being explored in this study as outlined in Table 1-1 and the IB. Arm A, twice-weekly ixazomib plus MP, was terminated due to nonhematologic toxicity findings. The MTD for Arm A is 3 mg twice weekly with MP in a 6-week cycle based on DLTs of rash, neutropenia, and thrombocytopenia. Although the MTD was established, Arm A, twice weekly ixazomib plus MP, was terminated due to nonhematologic toxicity findings in subsequent cycles. The MTD for Arm B, weekly ixazomib plus MP in a 28-day cycle, is 4 mg based on DLTs of ileus, neurogeneic bladder, diarrhea, hematoemesis, esophageal ulcer hemorrhage, thrombocytopenia, and vomiting. One patient has reported DLTs (thrombocytopenia and neutropenia) in Arm D, ixazomib 2 weeks on/1 week off × 2 plus MP in a 6-week cycle. Study C16006 is still enrolling patients. At the data cutoff, the median number of cycles administered was 8 (range 1-28) with 43 (78%) patients treated for ≥ 4 cycles, 29 (53%) for ≥ 8 cycles, 21 (38%) for ≥ 12 cycles, and 3 (5%) for ≥ 25 cycles, including 1 patient who has received 28 cycles. Across all patients treated including above and below the MTD, dose reductions were needed once in 35% of patients, with ≥ 2 reductions needed in 20% of patients.

Please refer to the ixazomib IB and SMA for further information.

1.8 Lenalidomide

1.8.1 Pharmacology and pharmacokinetics

Clinical pharmacokinetics studies have shown that lenalidomide when administered as a single 200-mg dose has a half-life of elimination that ranged from 3.2 hours to 8.7 hours. Initially, there is a rapid decrease in plasma levels, then there is a less rapid decline. Peak plasma levels occur between 0.6-1.5 hours post dose being given. Co-administration with food delays absorption but does not alter the extent of absorption. With multiple doses, steady state plasma concentrations were obtained within four days. Sixty-eight percent of the orally administered lenalidomide is excreted by the kidneys. No pharmacokinetic or pharmocodynamic interactions between lenalidomide and warfarin have been observed. The interaction with digoxin if any is small and digoxin levels should thus be followed based on clinical judgment in patients receiving both digoxin and lenalidomide.

1.8.2 Toxicity profile

Below are listed the side effects which occurred in patients treated with lenalidomide in other clinical trials.

Frequent (chance of 10-50% that this will happen) side effects include: fatigue, nausea, rash, diarrhea, constipation, vomiting, pyrexia, cough, insomnia, pruritis, peripheral edema, dyspnea, back pain, anorexia, abdominal pain and dizziness, headache.

In addition, the following severe adverse events have been reported in patients treated with lenalidomide in previous research studies.

Occasional (chance of 1-10% that this will happen) side effects include: thrombosis or pulmonary emboli, leucopenia, thrombocytopenia, neutropenia, dyspnea, pneumonia, anemia, dehydration, vomiting, asthenia, increased pain and kidney failure.

Rare (chance of less than 1% that this will happen) side effects include: pancytopenia, hyperuricemia, sinusitis, fatigue, arthritis, diffuse gastritis, diverticulitis, abnormal liver function test, blood transfusion reaction, thyroid disorders, myositis, myocarditis with congestive heart failure, respiratory failure, pulmonary edema, pulmonary hypertension, interstitial lung disease, ischemic colitis, hepatitis, arrhythmia, increased pressure in the eye, retinal hemorrhage, fainting, condition characterized by weight loss and malnutrition, encephalopathy, development of new cancer and anaphylaxis.

Recent data suggests that Multiple Myeloma patients receiving the combination of lenalidomide and Dexamethasone are at an increased risk for developing deep vein thrombosis.

1.8.3 Special toxicity considerations

Both men and women will enroll in the Revlimid REMS TM program and will follow appropriate precautions to avoid pregnancy.

1.8.4 Administration

Oral Route

Lenalidomide is FDA approved for treating Multiple Myeloma and is commercially available. Patients, prescribers and dispensing pharmacies must be registered in the FDA-mandated Revlimid REMS TM program.

1.8.5 Clinical non TX data

Two multicenter randomized studies evaluated the efficacy and safety of lenalidomide. The analysis showed superior outcome with lenalidomide arm, over the placebo arm. For both studies, extended follow-up and crossover were also analyzed.

Table 1.4. TTP, Response and Survival results

	Study 1		Study 2	
	Len/Dex (n=177)	Placebo/Dex (n-176)	Len/Dex (n=176)	Placebo/Dex (n=175)
TTP				
Median TTP in months (95% CI)	13.9 (9.5, 18.5)	4.7 (3.7, 4.9)	12.1 (9.5, NE)	4.7 (38, 4.8)
Hazard ratio (95% CI)	0.285 (.21,.386)		0.324 (.24,.438)	
Log rank Test, p value	<.001		<.001	
Response				
CR n (%)	23 (13)	1 (1)	27 (15)	7 (4)
PR n (%)	84 (48)	33 (19)	77 (44)	34 (19)
Overall response n (5)	107 (61)	34 (19)	104 (59)	41 (23)
p-value	<.001		<.001	

Odds ratio	6.38 (3.95, 10.32)		4.72 (2.98, 7.49)	
Survival				
Median months (95% CI)	39.4 (32.9, 47.4)	31.6 (24.1, 40.9)	37.5 (29.9, 46.6)	30.8 (23.5, 40.3)
Hazard ratio (95% CI)	0.79 (.61-1.03)		1.86 (.65-1.14)	

1.10 Study Rationale

1.10.1 Introduction/Background

Single agent high dose Melphalan combined with autologous stem cell rescue is well established as the standard of care for treating chemoresponsive and chemorefractory Multiple Myeloma. However, relapse continues to remain a major problem after a standard autologous transplant. Moreau, et al,[18] compared, in a prospective and randomized trial, the two most widely used autologous transplant conditioning regiments at that time for treatment of Multiple Myeloma. A total of 282 evaluable, newly-diagnosed, chemotherapy-responsive patients under the age of 65 years old were randomized. 142 patients received Melphalan 200mg/m^2 alone. The rest were treated with Melphalan 140 mg/m^2, Cytoxan, and total body radiation (TBI). The median duration of EFS was similar 21 vs. 20.5 months respectively, p=.6. The 45-month survival, though, was superior for Melphalan alone therapy, 65.8% vs. 45.5% (p=. 05). Vesole, et al,[19] reported on the SWOG experience in treating patients with chemorefractory Multiple Myeloma using high-dose Melphalan followed by autologous stem cell transplantation. Patients up to the age of 70 years were enrolled if they were refractory to VAD or other alkylating agents. All patients were given Cytoxan and GM-GSF for collection of peripheral blood stem cells. Upon recovery from autologous transplant, patients were treated with maintenance interferon alfa-2b until disease progression. Of 66 assessable patients, 56 patients went to transplant. The overall response rate to Melphalan of transplanted patients was 35% CR, 20% VGPR, and 39% PR. There were 4 deaths (7.1%) from regimen-related transplant toxicity. Overall, the median survival was 19 months based on intent to treat. Three-year actuarial PFS and S was 25% and 31%, respectively. Recently tandem autologous transplants are being offered to treat patients with Multiple Myeloma, yet, even tandem autologous transplants result in high relapse rates. Attal, et al,[20]showed at 4 years the EFS rate was still only 20%. Overall, Cavo, et al, [21] have shown that tandem autologous transplants prolong the EFS rate by 12 months (p=.001) and time to progression by 17 months (p=.0001). But, tandem autologous transplants work best in patients who do not achieve CR, near CR or VGPR with first autologous transplants.

Thus, strategies to prevent relapse after stem cell transplant have focused on adding novel treatment strategies as maintenance or consolidation therapy post ASCT.

They have fallen into different approaches of consolidation without or with maintenance therapy or maintenance therapy alone. Consolidation therapy regimens originally were more commonly used

in Europe and maintenance therapy alone in USA. Consolidation therapy has been defined as improving on response and accepting more toxicity and maintenance therapy has been defined as maintaining response with less toxicity. But, these are really artificial definitions for if one looks at other disease like ALL where maintenance therapy is also given to improve response and is given to patients in CR to prevent future relapses.

In the era before IMiDs and bortezomib, alpha interferon and glucosteroids were all studied post ASCT. The use of these drugs was limited by the question of efficacy and toxicity. Shustik C et al[22] questioned the benefit of steroid therapy. Meta-analysis of interferon showed a benefit but with a lot of toxicity[23] with interferon.

Thalidomide

As the first available novel agents, thalidomide was first studied as additional therapy post ASCT. See tables 1.5 and 1.6 for summary of response rates and summary of outcome of studies.

Table 1.5 Initial Disease Response Rates for Thalidomide Post ASCT

TRIAL	CR+VGPR (%) Thal vs control arm
Barlogie et al TT II[24]	62 vs. 43, p<.01
Attal et al[25]	76 vs. 55, p=.03
Spencer et al[26]	63 vs. 40, p=.001
Lokhorst et al[27]	66 vs. 54, p=.005

Table 1.6 Summary of Studies giving Thalidomide after ASCT

Study	Comparison	Duration Thal	PFS/EFS	OS(yrs)
Attal et al[25]	T vs. none	Prog	+	+ (4 yr)
Barlogie et al[24]	T vs. none	Prog	+	+ (8 yr)
Lokhorst et al[27]	T vs. inf	Prog	+	ND
Morgan et al[28]	T vs. none	Prog	+	ND (3 yr)
Spencer et al[26]	T/P vs. P	1 yr or Prog	+	+ (3 yr)
Maiolino et al[29]	T/D vs. D	1 yr or Prog	+	ND (2 yr)
Stewart et al[30]	T/P vs. none	Prog	+	ND (4 yr)

+ Statistical difference in favor thalidomide-containing therapy, ND not detected difference statistically

Differences in results may be due to differences in design of study, dose of thalidomide given, number of patients treated, use with steroids and type of steroid, comparison group, prior use of thalidomide in induction, duration of therapy and follow-up interval. In general, all have statically shown better event free survival (efs)/progressive free survival (pfs) in thalidomide arms of study, four reported increase in response rates, three studies had increase in OS. Thalidomide seems though to do best in standard risk disease. Peripheral neuropathy was an issue though in the studies and did result in discontinuation of drug. Little data about CR after ASCT and if those patients benefited by addition of thalidomide though was presented. IFM study 99-02 reported most benefit of thalidomide was in patients less than VGPR after ASCT[23] but MRC My IX study did not sees difference in benefit based on response to ASCT[27]. Recently, Rawstron AC et al[31] showed in clinical trial setting MRD can be used to track efficacy of maintenance therapy as 8 out of 29 patients with MRD positive after ASCT randomly assigned to thalidomide maintenance became MRD negative vs. only one out of 29 not receive maintenance therapy.

Combination therapy with thalidomide has also been studied as consolidation after ASCT. Cavo et al[32] reported that after tandem ASCT the PFS for VTD was superior to TD. The beneficial effect was most evident in patient not achieving at least near CR after ASCT in the initial report.

Lenalidomide

Lenalidomide was the next drug studied to be given after ASCT. The largest randomized studies has been CALGB[33] and the IFM study[34] that used maintenance or consolidation/maintenance approaches. See tables 1.7 and 1.8 for summary of design of studies, comparisons of studies and outcomes.

Table 1.7 CALGB vs. IFM Lenalidomide Studies

Study	# pts	Therapy	EFS	OS	Duration Therapy
CALGB 10014 [33]	462	Induction pre TX: Thal and Len 74%, and no progression during induction allowed All got single ASCT Cons: No Maint: 10 mg Len vs. Placebo	3 yr EFS 43 vs. 27 mos (p<.001)	85 vs. 77%, p=.028 Med fu 34 mos Superior S even with crossover	Crossover Range Len exposure 30-72 mos All continue on therapy
IFM 05-02[34]	605	Induction pre TX : VAD 52% and VD 44%, pre ASCT also 25% got DCEP One ASCT (79%) , 2 ASCT (21%) Cons: Len 2 mos pre day 100 Maint: Len 10 mg vs. placebo	4 yr EFS 40 vs. 23 mos P<.001)	74 vs. 75% (p=.7) Median fu 45 mos	No crossover Range Len exposure 32-59 mos All stopped therapy on Jan 2011 (concern about secondary cancers) Median 32 months therapy

Table 1.8 Comparisons of CALGB and IFM studies

Comparisons	CALGB[33]	IFM[34]
Stratification	Age < 71 years, Normal or elevated, beta 2 microglobulin Prior use of Thalid, Prior use of Len	Age < 65 years, CR/VGPR vs. PR or stable Beta 2 microglobulin ≤ 3 or > 3
Planned doses	Not reported	83% before stopped study
Median follow-up unblinded	18 months	33 months
Response to Therapy	Cytogenetic not reported but analysis is ongoing	Len arm had more t4,14 and 17p del (p=.006) Del 13 EFS 53% vs. 24%, (p<.001)
	CR post TX about 29-34%	CR post TX was 5-8%
	Did increase time to progression in patients not in CR.	Tandem ASCT not show different outcome then single ASCT. Conversion to CR/VGPR 58% - 69% in two groups with consolidation therapy
	No statistical difference in benefit between CR and not in CR at randomization in TTP and OS Induction and maintenance with Len and OS better (p=.03) even with cross over benefit from Len in TTP and OS	Conversion with Maintenance 84 vs. 76 % (p= .009) VGPR benefit 64 vs. 49%, p=.006 Less than VGPR 51 vs. 18%, p<.001 Del 13 53% vs. 24%, p<.001

Both studies reported secondary cancer risks about 3 X increased in CALGB and 2.6 X increased in IFM study in lenalidomide arms vs. placebo with increased AML/MDS in CALGB and increased ALL and HL in IFM.

A recent update at ASH 2013 Attal et al[35] showed in IFM study no OS advantage benefit for maintenance therapy at 68 vs. 67% for placebo (HR=1), at 5 years. In the update, 5 year PFS was 42% with lenalidomide vs. 18% with control arm, p, .0001. Median survival after first progression after ASCT was 10 months in lenalidomide arm vs. 19 months in placebo arm (p<.0001). Note it is important though to know how patients were treated when they relapsed as if bulk got lenalidomide again one would question how much benefit they would get as result. If one looked at alternative drugs then one might see better survival based on how treat at relapse for example if used carfilzomib salvage. Another major difference in the IFM and CALGB STUDY is the stopping of lenalidomide in the IFM study and this may mean that lenalidomide drug if only drug given is better used to maximize response if ones stay on it as long as tolerated or to disease progression. Since CALGB has not reported seeing increased secondary malignances after long term use of lenalidomide with longer follow-up, it argues all risk is early in use of drug and not with long term use for secondary cancers.

Recently, Gay et al[36], reported in a landmark analysis on the use of lenalidomide maintenance in patients that were < 65 years old (n=402). They found that lenalidomide therapy increased both PFS and OS rates. The 4 year OS rate from start of maintenance therapy was 80% for lenalidomide maintenance vs. 62% without maintenance therapy, p=.01.

Bortezomib

Bortezomib was the next novel agent studied post ASCT. Sonneveld P et al [37] looked at treating with PAD vs. VAD followed by auto TXs followed by thalidomide therapy in VAD group vs. bortezomib maintenance in PAD group. If adjust in multivariate analysis, the OS at 3 years was improved in all PAD arms. Patients with poor risk cytogenetic benefited especially del 17p13 with statistically significant differences in PFS (p=.0020 adj). But although patients presenting with higher beta 2 microglobulin levels at diagnosis benefited from PAD they did have less benefit then patients with lower risk beta 2 microglobulin. Also patients in renal failure at diagnosis had most benefit with bortezomib. Bortezomib therapy was reported to improve the CR/near CR rates after ASCT. Recently, Mellqvist et al[38] reported on single agent bortezomib vs. placebo after ASCT in bortezomib naïve patients. The TTP was 27 months vs. 20 months for placebo p=.05. Improvement in response was statistically different <p=.007. Most benefit was in patients in less than VGPR state. But, no difference in OS was reported.

Sahebi F et al[39] looked at the use of sequential therapy with bortezomib, dexamethasone for six cycles followed by thalidomide and dexamethasone for six cycles then thalidomide alone until progression as maintenance therapy after ASCT. Thirty-three percent of the patients upgrade their response after ASCT to CR after the addition of maintenance therapy.

As result of all these post ASCT studies NCCN guidelines recommend with category 1 evidence as standard of care after ASCT to treat with thalidomide or lenalidomide and bortezomib as category 2B.

Novel agents have increased the initial CR rates, and also it is known that getting into CR appears to increase survival post ASCT. But, it is also important not only to get into CR but also important to maintain the CR. Patients with sustained CR after ASCT > 3 years had longer median overall survival then those not in sustained CR (82 vs. 42 months), p<.001.

ASCT is a platform to build on in which you can amplify the disease response in the setting of reduced tumor burden and changed immune system and thus prolong the duration of responses. Long term disease control remains an important part of Multiple Myeloma treatment currently in the absence of curative potential. In the era of novel agents we have seen improved outcomes after ASCT. Prolong therapy with induction, ASCT, consolidation therapy/maintenance therapy appear to be the standard approach to induce remission status that improve outcomes. The data to date from prospective studies show that to achieve the higher CR rates and prolong duration of their duration is induction with novel agents, followed by ASCT then consolidation/maintenance therapy. This sequential approach seems the appropriate stage to upgrade responses. Overall effective induction therapy, consolidation and/or maintenance therapy have increased the efficacy of ASCT with CR/near CR of 36 to 70% and 5 year OS from 61 to 72% reported. But, there are many unanswered questions about how to optimize maintenance therapy post ASCT.

We are thus proposing a study of ixazomib and lenalidomide as maintenance therapy after autologous transplant for Multiple Myeloma with the proposed modified dosing schedule based on overlapping toxicity of the individual drugs and decreased marrow reserve early after autologous transplant. Since we do not know the best way to deliver maintenance therapy after ASCT, and the best regimen, it is possible this alternating schedule can decrease the duration of therapy and thus making it a more practical regimen for patients as well as overcome the development of cross resistance.

In summary, autologous transplants can cause remission in Multiple Myeloma patients, but relapse remains a major problem. Post-transplant maintenance therapy seems to change the outcome of transplant patients; however, the optimal regimen for maintenance therapy is not known. Ixazomib and lenalidomide are active drugs to treat Multiple Myeloma. Thus, it is reasonable to study the combination of lenalidomide and ixazomib as maintenance therapy after autologous transplants.

1.11 Potential Risks and Benefits

Please refer to the current ixazomib IB and SMA and FDA package insert for lenalidomide (See Section 12.3).

The clinical benefit of ixazomib continues to be studied in a comprehensive and global development plan that involves studies sponsored by Millennium. Ixazomib appears to show early signs of anti-tumor activity as evidenced by at least 50% reduction in disease burden in some patients, including patients that have been heavily pretreated as well as those with newly diagnosed Multiple Myeloma, and prolongs stabilization of the underlying disease in other patients across all ongoing trials. The preliminary findings are favorable when considering historical and currently available therapies for the patient populations evaluated. Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports expanded development of ixazomib for the treatment of patients with advanced malignancy.

This study will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonization (ICH) guidelines

2. STUDY OBJECTIVES

2.1 Primary Objectives

- Evaluate the toxicity of the use of ixazomib and lenalidomide as maintenance therapy after autologous transplant

2.2 Secondary Objectives

- Evaluate the ability to deliver the planned therapy
- Assess initial response to therapy
- Evaluate the median time to disease progression
- Assess overall survival

3. STUDY ENDPOINTS

3.1 Primary Endpoints

Toxicity

3.2 Secondary Endpoints

Time to progression of disease

4. STUDY DESIGN

4.1 Overview of Study Design

Treatment regimen

Alternating ixazomib 4.0 mg po on days 1, 8 and 15 per each 28- day cycle for two consecutive cycles, followed by then lenalidomide 10 mg po daily for two consecutive cycles until disease progression, intolerable toxicity or maximum of 24 cycles of therapy. Dose reduction for toxicity will be incorporated. If >30 days off initially planned next cycle of therapy, then patient will be taken off study. Toxicity will be graded per CTCAE version 4.0.

Therapy will start 30-120 days post autologous transplant when the patient is recovered from acute toxicity. See study flow chart on page 4 for scheduling of events for study.

4.2 Number of Patients

Thirty patients. First day of treatment will define enrolled on study therapy.

4.3 Duration of Study

Enroll 30 patients over 2-3 years with then two year follow-up of last patient who started treatment on the study.

5. STUDY POPULATION

5.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Male or female patients 18 years or older.
    a. Eastern Cooperative Oncology Group (ECOG) performance status and/or other performance status 0, 1, or 2.
    b. Any autologous patient who underwent high dose Melphalan ($\geq$140 mg/m^2) therapy/PBSC rescue for any stage of Multiple Myeloma and did not participate in another clinical transplant trial whose primary endpoint is also evaluating long-term, disease-free survival or survival. Consenting for study between 30 days to 120 days after transplant. Earliest can start therapy is 30 days post transplant after recovered from acute toxicity of ASCT.
2. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
3. Female patients who:
    a. Are postmenopausal for at least 1 year before the screening visit, OR
    b. Are surgically sterile, OR
    c. If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug, OR
    d. Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

4. Male patients, even if surgically sterilized (i.e., status post-vasectomy), must agree to one of the following:
    a. Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, OR

    b. Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

5. Patients must meet the following clinical laboratory criteria:

    a. Absolute neutrophil count (ANC) ≥ 1,000/mm^3 and platelet count (transfusion independent) ≥ 75,000/$mm^{3.}$

    b. Total bilirubin ≤ 1.5 × the upper limit of the normal range (ULN).

    c. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × ULN.

    d. Calculated creatinine clearance ≥ 30 mL/min (see appendix).

5.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Female patients who are lactating or have a positive serum pregnancy test during the screening period.

2. Failure to have fully recovered (i.e., ≤ Grade 1 toxicity) from the reversible effects of prior ASCT chemotherapy.

3. Major surgery within 14 days before enrollment.

4. Radiotherapy within 14 days before enrollment. If the involved field is small, 7 days will be considered a sufficient interval between treatment and administration of the ixazomib.

5. History of central nervous system multiple myeloma involvement.

6. Infection requiring systemic antibiotic therapy or other serious infection within 14 days before study enrollment.

7. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months.

8. Systemic treatment, within 14 days before the first dose of ixazomib, with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort.

9. Ongoing or active systemic infection, active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive.

10. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

11. Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent. Patient cannot be allergic to boron.

12. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib including difficulty swallowing.

13. Diagnosed or treated for another malignancy within 2 years before study enrollment or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

14. Patient has ≥ Grade 2 peripheral neuropathy, or Grade 1 with pain on clinical examination during the screening period.

15. Participation in other clinical trials, including those with other investigational agents not included in this trial, within 30 days of the start of this trial and throughout the duration of this trial.

16. Patients with history prior to transplant of progression on lenalidomide therapy.

6. STUDY DRUG

6.1 Description of Investigational Agents

Treatment regimen consists of alternating ixazomib 4.0 mg po on days 1, 8 and 15 per each 28- day cycle for two consecutive months, followed by then lenalidomide 10 mg po daily for two consecutive months until disease progression, intolerable toxicity or maximum of 24 months of therapy. Dose reduction for toxicity will be incorporated. If >30 days off initially planned next cycle of therapy, then the patient will be taken off study. Toxicity graded per CTCAE version 4. Patients will start therapy 30-120 days post autologous transplant.

6.1.1 Ixazomib Capsules

The ixazomib drug product is provided in strengths of 4.0-, 3.0-, and 2.3-mg capsules as the active boronic acid. The different dose strengths are differentiated by both capsule size and color

as described below:

Dose Strength	Capsule Size	Capsule Color
4.0 mg	Size 4	Ivory
3.0 mg	Size 3	Light gray
2.3 mg	Size 2	Light pink

For additional details, please see the ixazomib IB.

6.2 Study Drug Administration of Ixazomib

Ixazomib is stored in the IDS Pharmacy according to storage conditions detailed in the Investigator's Brochure and is dispensed by IDS Pharmacy for each cycle. Patients will keep diary to show took drugs. Patients should be instructed to swallow ixazomib capsules whole, with water, and not to break, chew, or open the capsules. Study drug should be taken on an empty stomach (no food for 2 hours before and 1 hour after dosing). Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.

Missed doses can be taken as soon as the patient remembers if the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

6.2.1 Ixazomib Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). Patients should be monitored for toxicity, as necessary, and doses of ixazomib should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of ixazomib dose (see Section 9.3).

Capsules of ixazomib will also be referred to as study drug. Study drug will be supplied by Millennium as capsules of 2.3-, 3.0- and 4.0 mg ixazomib. This is dependent on available ixazomib formulation.

The prescribed administration of ixazomib doses in this study is 4 mg ixazomib on days 1, 8 and 15 of each 28 day cycle for two cycles in a row followed then by lenalidomide therapy for two 28 day cycles for a total of 24 months of therapy.

6.2.2 Ixazomib Destruction

Ixazomib (expired or end of study) should be destroyed on site according to the institution's standard operating procedure. Be sure to document removal and destruction on drug accountability logs.

6.3 Lenalidomide

6.3.1 Administration of Lenalidomide

After first two 28 day cycles of ixazomib, the starting dose of lenalidomide will be 10 mg po daily on days 1-28, every 28 day cycles for two cycles alternating with ixazomib. Lenalidomide should be taken orally about the same time every day, either with or without food. The capsules should not be opened, broken or chewed.

6.3.2 How Supplied

Lenalidomide is commercially available. Patients, prescribers and dispensing pharmacies must be registered in the FDA-mandated Revlimid REMS TM program.

6.4 Dose-Modification Guidelines

6.4.1 Recommended Ixazomib Criteria for Beginning or Delaying a Subsequent Treatment Cycle & Dose Modifications for Treatment Associated Toxicity

Treatment with ixazomib will use a cycle length of 28 days. For a new cycle of treatment to begin, the patient must meet the following criteria:

- ANC must be $\geq 1{,}000/mm^3$.
- Platelet count must be $\geq 75{,}000/mm^3$.
- All other nonhematologic toxicity (except for alopecia) and peripheral neuropathy must have resolved to $\leq$ Grade 1 or to the patient's baseline condition.

If the patient fails to meet the above-cited criteria for initiation of the next cycle of treatment, dosing should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria have been met. If the patient continues to fail to meet the above-cited criteria, delay therapy and continue to reevaluate. The maximum delay before treatment should be discontinued will be 30 days or at the discretion of the Principal Investigator.

For dosing recommendations upon recovery, refer to Table 6-1, Table 6-2, and Table 6-3.

Table 6-1 Ixazomib Dose Adjustments

Dose Level	Dose (mg)
Starting Dose	4.0 mg
-1	3.0 mg
-2	2.3 mg
-3	Discontinue

Dosing adjustments for hematologic toxicity are outlined in Table 6-2.

Table 6-2 Ixazomib Dose Adjustments for Toxicities

Criteria	Action
Within-Cycle Dose Modifications	
• If platelet count ≤ 30×10^9/L or ANC ≤ 0.50×10^9/L on a ixazomib dosing day (other than Day 1)	• Ixazomib dose should be withheld. • Complete blood count (CBC) with differential should be repeated at least every other day until the ANC and/or platelet counts have exceeded the prespecified values (see Section 6.4.1) on at least 2 occasions. • Upon recovery, ixazomib may be reinitiated with 1 dose level reduction.
Dose Modifications for Subsequent Treatment Cycles	
• Delay of up to 4 weeks in the start of a subsequent cycle due to lack of toxicity recovery as defined in Section 6.4.1. • ANC < 1.0×10^9/L, platelet count < 75×10^9/L, or other nonperipheral neuropathy, nonhematologic toxicities (except for alopecia) > Grade 1 or not to the patient's baseline condition	• Hold ixazomib until resolution as per criteria Section 6.4.1. • Upon recovery, reduce ixazomib 1 dose level. • The maximum delay before treatment should be discontinued will be 30 days or at the discretion of the PI.
Dose Modifications for Subsequent Treatment Cycles	

Table 6-2 Ixazomib Dose Adjustments for Toxicities

Criteria	Action
• All hematologic toxicities	• For hematologic toxicity that occurs during a cycle but recover in time for the start of the next cycle: o If dose was reduced within the cycle, start the next cycle at that same dose. o If due to toxicity timing, i.e., after Day 15 dosing thus a dose reduction was not required at that point in the cycle, reduce ixazomib by 1 dose level at the start of that cycle. o Do not reduce the dose both within a cycle and at the start of the cycle for the same most severe toxicity.

Treatment modifications due to ixazomib-related AEs are outlined in Table 6-3.

Table 6-3 Ixazomib Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events (Non-Hematologic Toxicities)

Adverse Event (Severity)	Action on Study Drug	Further Considerations
Peripheral Neuropathy:		
Grade 1 peripheral neuropathy	No action	Grade 1 signs and symptoms: asymptomatic; without pain or loss of function; clinical or diagnostic observations only[7]
New or worsening Grade 1 peripheral neuropathy with pain or Grade 2	Hold ixazomib until resolution to Grade ≤ 1 without pain or baseline	Grade 2 signs and symptoms: Moderate symptoms; limiting instrumental activities of daily living (ADL)[7]
New or worsening Grade 2 peripheral neuropathy with pain or Grade 3	Hold ixazomib until resolution to Grade ≤ 1 without pain or baseline Reduce ixazomib to next lower dose upon recovery	Grade 3 signs and symptoms: severe symptoms; limiting self-care ADL; assistive device indicated[7]

Table 6-3 Ixazomib Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events (Non-Hematologic Toxicities)

Adverse Event (Severity)	Action on Study Drug	Further Considerations
New or worsening Grade 4 peripheral neuropathy	Discontinue ixazomib	
Grade 2 Rash	Symptomatic recommendations as per section 6.10	At the discretion of the investigator, may require dose modification.
Grade 3 Nonhematologic, nonperipheral neuropathy toxicity judged to be related to ixazomib	Hold ixazomib until resolution to Grade < 1 or baseline	Symptomatic recommendations noted in Section 6.10
If not recovered to < Grade 1 or baseline within 30 days	Reduce ixazomib to next lower dose upon return to < Grade 1 or baseline	
Subsequent recurrence Grade 3 that does not recover to < Grade 1 or baseline within 30 days	Hold ixazomib until resolution to Grade < 1 or baseline	
Grade 4 Nonhematologic nonperipheral neuropathy toxicities judged to be related to ixazomib	Consider permanently discontinuing ixazomib	Exceptions are cases in which the investigator determines the patient is obtaining a clinical benefit

Once ixazomib is reduced for any toxicity, the dose may not be re-escalated.

6.4.2 Recommended Dose Modifications for Lenalidomide Treatment Associated Toxicity

For a new cycle of treatment to begin, the patient must meet the following criteria:

- ANC must be ≥ 1,000/mm^3.
- Platelet count must be ≥ 75,000/mm^3.
- All other nonhematologic toxicity (except for alopecia) or peripheral neuropathy must have resolved to ≤ Grade 1 or to the patient's baseline condition.

The maximum delay before treatment should be discontinued will be 30 days post original planned start of the cycle or at the discretion of the Principal Investigator.

Dose reduction schemas for Lenalidomide

Table 6.4: Dose reduction schema for Lenalidomide cycles

Due to Adverse Events (Hematologic Toxicities)		
ANC $\leq$ 500 and/or platelets$\leq$ 30,000 cells/mm^3 (Other than Day 1)	Hold to ANC $\geq$ 1000 and platelets $\geq$ 75,000 cells/mm^3, then dose reduce	1stdose reduction(DR): 21 days instead of 28 days 2nd DR: 5 mg po 21 days on, 7 days off 3rd DR 5 mg po qod

Table 6.5: Dose reduction schema for Lenalidomide cycles, by Grade

Due to Adverse Events (Non-Hematologic Toxicities)			
Adverse Event (Severity)	Action on Study Drug	Further Considerations	Dose De-Escalation Schedule
Peripheral Neuropathy:			
Grade 1 peripheral neuropathy	No action	Grade 1 signs and symptoms: asymptomatic; without pain or loss of function; clinical or diagnostic observations only [7]	1st dose reduction(DR): 21 days instead of 28 days
New or worsening Grade 1 peripheral neuropathy with pain or Grade 2	Hold study drug until resolution to Grade ≤ 1 without pain or baseline	Grade 2 signs and symptoms: Moderate symptoms; limiting instrumental activities of daily living (ADL) [7]	2nd DR: 5 mg po 21 days on, 7 days off
New or worsening Grade 2 peripheral neuropathy with pain or Grade 3	Hold study drug until resolution to Grade ≤ 1without pain or baseline Reduce study drug to next lower dose upon recovery	Grade 3 signs and symptoms: severe symptoms; limiting self-care ADL; assistive device indicated [7]	3rd DR 5 mg po qod
New or worsening Grade 4 peripheral neuropathy	Discontinue study drug		
Rash Grade 2	Symptomatic recommendations as per Section 6.10	At the discretion of the investigator, may require dose modification.	
Grade 3 nonhematologic, nonperipheral neuropathy toxicity judged to be related to lenalidomide If not recovered to < Grade 1 or baseline within 30 days Subsequent recurrence Grade 3 that does not recover to < Grade 1 or baseline within 30 days	Hold study drug until resolution to Grade < 1 or baseline Reduce study drug 1 to next lower dose upon return to < Grade 1 or baseline Hold study drug until resolution to Grade < 1 or baseline Reduce study drug to next lower dose	Symptomatic recommendations noted in Section 6.7 Monitor closely, take appropriate medical precautions, and provide appropriate symptomatic care	
Grade 4 nonhematologic, nonperipheral neuropathy toxicities judged to be related to lenalidomide	Consider permanently discontinuing lenalidomide	Exceptions are cases in which the investigator determines the patient is obtaining a clinical benefit	

Once lenalidomide is reduced for any toxicity, the dose may not be re-escalated.

6.5 Additional medications

Supportive care

- IV Bisphosphonates therapy as clinically indicated per Standard Practice guidelines. VZV and PCP prophylaxis to continue for 2 additional months post stopping therapy.

6.6 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study.

Systemic treatment with any of the following metabolizing enzyme inhibitors is not permitted in this study. (A drug-drug interaction [DDI] with a strong inhibitor would increase the ixazomib exposure and could lead to a higher probability of an AE):

- Strong inhibitors of CYP1A2: fluvoxamine, enoxacin, ciprofloxacin
- Strong inhibitors of CYP3A: clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, and posaconazole

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided, unless there is no appropriate alternative medication for the patient's use (Rationale: Unlike with inhibitors, if there were to be a DDI with an inducer, ixazomib exposure would be less; therefore, there would be a reduced chance of an AE. However, there may be less chance for an antitumor effect, but that is not an absolute reason to be taken off ixazomib):

- Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital
- Excluded foods and dietary supplements include St. John's wort and Ginkgo biloba

The following procedures are prohibited during the study.

- Any antineoplastic treatment with activity against Multiple Myeloma, other than study drugs
- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates disease progression)
- Platelet transfusions to help patients meet eligibility criteria or prior to any dosing day are not allowed within 3 days prior to treatment administration (refer to eligibility criteria and criteria required prior to initiating next cycle of treatment or within cycle dose modifications).

6.7 Permitted Concomitant Medications and Procedures

The following medications and procedures are permitted during the study:

- Antiemetics, including 5-HT3 serotonin receptor antagonists, may be used at the discretion of the investigator.
- Loperamide or other antidiarrheal should be used for symptomatic diarrhea at discretion of the investigator. The dose and regimen will be according to institutional guidelines. IVF should be given to prevent volume depletion.
- Growth factors (e.g., granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoietin) are permitted. Their use should follow published guidelines and/or institutional practice.
- Patients should be transfused with red cells and platelets as clinically indicated and according to institutional guidelines.
- Patients who experience worsening neuropathy from baseline may be observed for recovery and have dose reductions/delays as indicated in the protocol, and any supportive therapy or intervention may be initiated as appropriate at the discretion of the investigator.
- Supportive measures consistent with optimal patient care may be given throughout the study.

6.8 Precautions and Restrictions

- Fluid deficit should be corrected before initiation of treatment and during treatment.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function.

Pregnancy

It is not known what effects ixazomib has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or

- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the informed consent form through 90 days after the last dose of study drug, or

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post ovulation methods] and withdrawal are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (i.e., status post vasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, or

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post ovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

6.9 **Patients will also enroll in Revlimid REMS TM program for Lenalidomide use and followed appropriately as Revlimid is associated with birth defects.**

Patients should not breastfeed on this study.

6.10 Management of Ixazomib Clinical Events

Adverse drug reactions such as thrombocytopenia, diarrhea, fatigue, nausea, vomiting, and rash have been associated with ixazomib treatment. Management guidelines regarding these events are outlined below. Further details of management of ixazomib AEs are described in Section 6 of the ixazomib IB.

Prophylaxis Against Risk of Reactivation of Herpes Infection

Patients may be at an increased risk of infection including reactivation of herpes zoster and herpes simplex viruses. Antiviral therapy such as acyclovir, valacyclovir, or other antivirals are to be given as clinically indicated in Section 6.5., i.e. acyclovir 800 mg po BID or valacyclovir 500 mg po BID.

Nausea and/or Vomiting

Standard anti-emetics including 5-hydroxytryptamine 3 serotonin receptor antagonists are recommended for emesis if it occurs once treatment is initiated; prophylactic anti-emetics may also be considered at the physician's discretion. Dexamethasone should not be administered as an anti-emetic. Fluid deficit should be corrected before initiation of study drug and during treatment.

Diarrhea

Prophylactic antidiarrheals will not be used in this protocol. However, diarrhea should be managed according to clinical practice, including the administration of antidiarrheals once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficit should be corrected before initiation of treatment and during treatment.

Erythematous Rash With or Without Pruritus

As with bortezomib, rash with or without pruritus has been reported with lenalidomide and also with ixazomib, primarily at the higher doses tested and when given with agents where rash is an overlapping toxicity. The rash may range from limited erythematous areas, macular and/or small papular bumps that may or may not be pruritic over a few areas of the body, to a more generalized eruption that is predominately on the trunk or extremities. Rash has been most commonly characterized as maculopapular or macular. To date, when it does occur, rash is most commonly reported within the first 3 cycles of therapy. The rash is often transient, self-limiting, and is typically Grade 1 to 2 in severity.

Symptomatic measures such as antihistamines or corticosteroids (oral or topical) have been successfully used to manage rash and have been used prophylactically in subsequent cycles. The use of a topical, IV, or oral steroid (e.g., prednisone $\leq$ 10 mg per day or equivalent) is permitted. Management of a Grade 3 rash may require intravenous antihistamines or corticosteroids. Administration of ixazomib or lenolidamide should be modified per protocol and re-initiated at a reduced level from where rash was noted (also, per protocol).

In line with clinical practice, dermatology consult and biopsy of Grade 3 or higher rash or any SAE involving rash is recommended. Prophylactic measures should also be considered if a patient has previously developed a rash (e.g., using a thick, alcohol-free emollient cream on dry areas of the body or oral or topical antihistamines). A rare risk is Stevens-Johnson Syndrome, a severe and potentially life-threatening rash with skin peeling and mouth sores, which should be managed symptomatically according to standard medical practice. Punch biopsies for histopathological analysis are encouraged at the discretion of the investigator.

Thrombocytopenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Ixazomib and lenalidomide administration should be modified as noted as per dose modification recommendations in the protocol when thrombocytopenia occurs (see Table 6-2). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. A rare risk is thrombotic thrombocytopenic purpura (TTP), a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. TTP should be managed symptomatically according to standard medical practice.

Neutropenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable. Growth factor support is not required but may be considered according to standard clinical practice. Ixazomib and lenolidomide administration should be modified as noted as per dose modification recommendations in the protocol when neutropenia occurs (see Table 6-2). Therapy can be reinitiated at a reduced level upon recovery of ANCs.

Fluid Deficit

Dehydration should be avoided since ixazomib may cause vomiting, diarrhea, and dehydration. Acute renal failure has been reported in patients treated with ixazomib, commonly in the setting of the previously noted gastrointestinal toxicities and dehydration.

Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

Hypotension

Symptomatic hypotension and orthostatic hypotension with or without syncope have been reported with ixazomib. Blood pressure should be closely monitored while the patient is on study treatment and fluid deficit should be corrected as needed, especially in the setting of concomitant symptoms such as nausea, vomiting, diarrhea, or anorexia. Patients taking medications and/or diuretics to manage their blood pressure (for either hypo- or hypertension) should be managed according to standard clinical practice, including considerations for dose adjustments of their concomitant medications during the course of the trial. Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

Posterior Reversible Encephalopathy Syndrome

One case of posterior reversible encephalopathy syndrome, which ultimately resolved, has been reported with ixazomib. This condition is characterized by headache, seizures and visual loss, as well as abrupt increase in blood pressure. Diagnosis may be confirmed by magnetic resonance imaging (MRI). If the syndrome is diagnosed or suspected, symptom-directed treatment should be maintained until the condition is reversed by control of hypertension or other instigating factors.

Transverse Myelitis

Transverse myelitis has also been reported with ixazomib. It is not known if ixazomib causes transverse myelitis; however, because it happened to a patient receiving ixazomib, the possibility that ixazomib may have contributed to transverse myelitis cannot be excluded.

Elevated Creatinine

Metabolism appears to be a major route of elimination for ixazomib. Urinary excretion of the parent compound is negligible. Modest transient increases in creatinine and infrequent (< 8%) cases of reversible renal failure have been reported. Two patients have required temporary dialysis for acute renal failure. One patient was treated above the MTD in Study C16001, where IV ixazomib was administered to patients with advanced solid tumors. The second patient required temporary dialysis due to ESRD related to progression of myeloma. Confounding factors include GI toxicities such as nausea, vomiting, and diarrhea, and concomitant dehydration and disease progression. As a

result of these events, all ongoing ixazomib clinical studies were amended to increase creatinine monitoring to include clinical chemistry during the week off therapy and patient management suggestions were enhanced. Dehydration should be avoided. Appropriate supportive care that includes IV fluids to prevent fluid deficits according to standard medical practice is recommended. Non-steroidal anti-inflammatory drugs (NSAIDs) are not recommended given they may, in and of themselves, have an association to renal dysfunction.

Cough, Dyspnea, and Headache

Cases of cough, dyspnea, and headache have been reported in the clinical studies; however, the relationship of onset to ixazomib is not yet completely established in humans. Standard medical care and additional monitoring should be performed as clinically indicated.

Peripheral Edema

Cases of peripheral edema have been reported in the clinical studies, primarily in the oral combination studies. Standard medical care and additional monitoring should be performed as clinically indicated.

6.11 Preparation, Reconstitution, and Dispensing

Ixazomib and lenalidomide are anticancer drugs and as with other potentially toxic compounds caution should be exercised when handling ixazomib or lenalidomide capsules.

6.12 Packaging and Labeling

The study drug ixazomib capsules will be provided by Millennium. The study drug will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations.

The capsules are individually packaged using cold-form foil-foil blisters that are in a child-resistant carton. There are 3 capsules in each wallet/carton.

Lenalidomide will be supplied as commercial product. Standard recommendations from package insert will be followed (See appendix 12.3).

6.13 Storage, Handling, and Accountability

Upon receipt at the investigative site, ixazomib should remain in the blister and carton provided until use or until drug is dispensed. The container should be stored at the investigative site according to storage conditions detailed in the Investigator's Brochure. Ensure that the drug is used before the retest expiry date provided by Millennium. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

In countries where local regulations permit, ixazomib capsules dispensed to the patient for take-home dosing should remain in the blister packaging and refrigerated as noted above until the point of use. The investigative site is responsible for providing the medication to the patient in the correct daily dose configurations. Comprehensive instructions should be provided to the patient in order to ensure compliance with dosing procedures. Patients who are receiving take-home medication

should be given only 1 cycle of medication at a time. Patients should be instructed to store the medication according to storage conditions detailed in the Investigator's Brochure for the duration of each cycle. Patients should be instructed to return their empty blister packs to the investigative site, rather than discarding them. Reconciliation will occur accordingly when the patient returns for their next cycle of take-home medication. Any extreme in temperature should be reported as an excursion and should be dealt with on a case-by-case basis.

Because ixazomib is an investigational agent, it should be handled with due care. Patients should be instructed not to chew, break, or open capsules. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful by inhalation, ingestion, or skin absorption. Gloves and protective clothing should be worn during cleanup and return of broken capsules and powder to minimize skin contact.

The area should be ventilated and the site washed with soap and water after material pick-up is complete. The material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations.

In case of contact with the powder (e.g., from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified. Patients are to be instructed on proper storage, accountability, and administration of ixazomib, including that ixazomib is to be taken as intact capsules.

Lenalidomide will be handled per package insert (see Section 12.3)

6.14 Study Compliance

Ixazomib study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

6.15 Termination of Treatment and/or Study Participation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Adverse event
- Protocol violation
- Lost to follow-up
- Progressive disease
- Study terminated
- The treatment appears detrimental in the judgment of primary physician

- They develop non-hematological, non-metabolic, non-peripheral neuropathy grade IV toxicity

- They are unable to resume therapy more than 30 days after initial stopping of therapy for toxicity or cannot tolerate lowest dose reduction level

- Repeated noncompliance to protocol in view of principal investigator

Patients who are withdrawn from the study will not be replaced.

At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed per study calendar (See Study Flow Chart). The primary reason for patient's withdrawal from the study should be recorded in the source documents and CRF.

7. STATISTICAL AND QUANTITATIVE ANALYSES

7.1 Statistical Methods

Research Description To see if alternating ixazomib with oral lenalidomide is well tolerated with acceptable toxicity profile post ASCT and if it provides equivalent or superior outcomes in terms of time to disease progression over lenalidomide alone.

7.1.1 Determination of Sample Size

Thirty Multiple Myeloma patients post ASCT are to be enrolled over 2-3 years. Expect to enroll 1-1.5 patients per month.

7.1.2 Randomization and Stratification

There is no randomization or stratification of patients on this study.

7.1.3 Populations for Analysis

Multiple Myeloma patients post ASCT.

7.1.4 Procedures for Handling Missing, Unused, and Spurious Data

Data collection will be evaluated quarterly for record completeness. Any missing data will be abstracted from primary source files. Study-specific case report forms (CRFs) will specifiy required data to be collected to ensure that patient safety and study objectives are accurately and completely captured. Primary source documents will be stored with all CRFs to provide validity for the abstracted data.

7.1.5 Demographic and Baseline Characteristics

Patients will be characterized as to whether they are chemo-sensitive or chemo-refractory disease at time of autologous transplant. All patients with PR or better response to last standard chemotherapy will be considered to have chemosensitive disease. Cytogenetic information will be collected.

7.1.6 Efficacy Analysis

An endpoint of the study is time to disease progression. Patients will be followed for initial response and for progression of disease. Response criteria will be determined by International Myeloma Working Group Criteria. In patients with chemo-refractory disease at the time of ASCT, the therapy will be felt to be promising if median time to progression is >9 months. If chemo-sensitive disease at time of ASCT the therapy will be felt to be promising if median time to progression is > 41 months based on CALGB 10014 lenalidomide maintenance study post ASCT. Initial response rates and outcome will be descriptively reported. Patients will be followed for overall survival.

7.1.7 Safety Analysis

The first endpoint is to evaluate the toxicity of the proposed therapy. The first four months of therapy will be used as the time period in which toxicity will be evaluated and stopping rules for unacceptable toxicity will be implemented. Rules for stopping therapy will be based on rate of withdrawal due to significant toxicity (grade IV, non-hematological, non-metabolic and non-peripheral neuropathy). A true withdrawal rate within first 4 months of 15% will be considered excessive. Withdrawal rate will be assessed after every ten patients are treated. Enrollment will not be held though until the 10th patient enrolled becomes evaluable. Sufficient evidence will be taken for a lower limit to the corresponding one sided 80% confidence interval that exceeds 15%. Operationally observed rates that say regimen is too toxic would be 2/5, 3/10, 4/15, 5/20, 6/25 and 7/30. If the true probability of withdrawal from the study is 5%, the probability of deeming this regimen as too toxic after 15 or 30 patients have been treated is approximately .03 and .03, respectively. If the true probability of withdrawal is 10%, these probabilities are approximately .13 and .15, respectively. On the other hand, if the true probability of withdrawal is .30, then the probability of judging this regimen as too toxic after 15 or 30 patients is approximately .78 and .91, respectively.

With the semi-continuous monitoring of the withdrawal rate, the estimate of this rate, should the study run to completion, will be biased slightly downward. Without consideration of this bias, 30 patients will allow us 80% confidence that the estimated withdrawal rate will be within approximately .094 of the true rate under the assumption that the true rate is 20%. The incidence of second cancers will also be collected.

7.1.8 Interim Analysis

An interim analysis at 15 treated patients will be conducted to assess feasibility for maintenanance therapy. If > 50% of patients are unable to receive > 50% of planned therapy in first 12 months of treatment, the study will be terminated due to lack of feasibility.

If this study regimen is deemed to be potentially efficacious and is not regarded as too toxic per stopping rules outlined above and observed EFS rate are consistent with rates that match or exceed historical benchmarks, then a phase III trial to show efficacy rate of this regimen over single agent therapy will be designed.

8. ADVERSE EVENTS

8.1 Definitions

8.1.1 Pretreatment definitions

Patients will only be evaluable for adverse event reporting after received first dose of study drug.

8.1.2 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

8.1.3 Serious Adverse Event Definition

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability or incapacity** (disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious

particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of $1000/mm^3$ to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

8.2 Procedures for Reporting Serious Adverse Events

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. For serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

AEs which are serious must be reported to Millennium Pharmacovigilance (or designee) from the first dose of study drug through 30 days after administration of the last dose of ixazomib. Any SAE that occurs at any time after completion of ixazomib treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Millennium Pharmacovigilance (or designee). In addition, new primary malignancies that occur during the follow-up periods must be reported, regardless of causality to study regimen, for a minimum of three years after the last dose of the investigational product, starting from the first dose of study drug. All new cases of primary malignancy must be reported to Millennium Pharmacovigilance (or designee).

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Since this is an investigator-initiated study, the principal investigator Leona Holmberg MD, PhD also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's EC or IRB.

Regardless of expectedness or causality, all SAEs (including serious pretreatment events) must also be reported in English to Millennium Pharmacovigilance (or designee) within the timelines outlined below:

Fatal and Life Threatening SAEs within 24 hours of the sponsor-investigator's observation or awareness of the event

All other serious (non-fatal/non-life threatening) events within 4 calendar days of the sponsor-investigator's observation or awareness of the event

See below for contact information for the reporting of SAEs to Millennium Pharmacovigilance.

The sponsor-investigator must fax or email the SAE Form per the timelines above. A sample of an SAE Form will be provided.

The SAE report must include at minimum:

- **Event term(s)**
- **Serious criteria**
- **Intensity of the event(s):** Sponsor-investigator's or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version specified in the protocol, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.
- **Causality of the event(s):** Sponsor-investigator's or sub-investigator's determination of the relationship of the event(s) to study drug administration.

Follow-up information on the SAE may be requested by Millennium.

Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version used at your institution, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Millennium Pharmacovigilance (or designee) from all sites participating in the study. Sub-investigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations to the required regulatory agencies and to Millennium Pharmacovigilance, unless otherwise agreed between the sponsor-investigator and sub-investigator(s).

Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

Sponsor-investigator must also provide Millennium Pharmacovigilance with a copy of all communications with applicable regulatory authorities related to the study product(s), as soon as possible but no later than 4 calendar days of such communication.

SAE and Pregnancy Reporting Contact Information

Fax Number: 1-800-963-6290
Email: TakedaOncoCases@cognizant.com

Suggested Reporting Form:

- SAE Report Form (provided by Millennium)
- US FDA MedWatch 3500A: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm
- Any other form deemed appropriate by the sponsor-investigator

8.3 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study or within 90 days after the last dose, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 8.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 8.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Suggested Pregnancy Reporting Form:

- Pregnancy Report Form (provided by Millennium)

In addition, reporting of lenalidomide toxicity will be per Revlimid REMS TM program.

9. ADMINISTRATIVE REQUIREMENTS

9.1 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained

in accordance with the label instructions pending further guidance from a Millennium Quality representative.

For Product Complaints,

- Phone: 1-877-TAKEDA7 (1-877-825-3327)
- E-mail: medicalinformation@tpna.com
- FAX: 1-800-247-8860
- Hours: Mon-Fri, 8 a.m. – 6 p.m. ET

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Millennium Pharmacovigilance (refer to Section 8.2).

10. DATA AND SAFETY MONITORING PLAN

The study will be independently monitored in accordance with the Institutional Data and Safety Monitoring Plan of the Fred Hutchinson/University of Washington Cancer Consortium as outlined in: http://www.cancerconsortium.org/content/dam/consortium/Resource-Documents/Data-Safety-Monitoring/13013S_Data_Safety_Monitoring_Plan.pdf.

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12. APPENDICES

12.1 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.

12.2 Cockcroft-Gault Equation

For males:

$$\text{Creatinine Clearance} = \frac{(140\text{-age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{(140\text{–age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[μmol/L]})}$$

For females:

$$\text{Creatinine Clearance} = \frac{0.85\,(140\text{-age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})} \text{ OR } \frac{0.85\,(140\text{-age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine [μmol/L]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

12.3 Package Insert for Lenalidomide

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use REVLIMID® safely and effectively. See full prescribing information for REVLIMID.

REVLIMID [lenalidomide] capsules, for oral use
Initial US Approval: 2005

WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM
See full prescribing information for complete boxed warning.

EMBRYO-FETAL TOXICITY
- **Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death.**
- **Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception (5.1).**

REVLIMID is available only through a restricted distribution program called the REVLIMID REMS™ program (formerly known as the "RevAssist® program") (5.2, 17).

HEMATOLOGIC TOXICITY. REVLIMID can cause significant neutropenia and thrombocytopenia (5.3).
- **For patients with del 5q myelodysplastic syndromes, monitor complete blood counts weekly for the first 8 weeks and monthly thereafter (5.3).**

VENOUS AND ARTERIAL THROMBOEMBOLISM
- **Significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with multiple myeloma receiving REVLIMID with dexamethasone. Anti-thrombotic prophylaxis is recommended (5.4).**

----------RECENT MAJOR CHANGES----------

Boxed Warning	09/14
Indication and Usage (1.1)	02/15
Dosage and Administration (2.1, 2.4)	02/15
Warnings and Precautions (5.3, 5.4, 5.6, 5.11)	02/15

----------INDICATIONS AND USAGE----------

REVLIMID is a thalidomide analogue indicated for the treatment of patients with:
- Multiple myeloma (MM), in combination with dexamethasone (1.1).
- Transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities (1.2).
- Mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib (1.3).

Limitations of Use:
- REVLIMID is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials (1.4).

----------DOSAGE AND ADMINISTRATION----------

- MM: 25 mg once daily orally on Days 1-21 of repeated 28-day cycles. Refer to section 14.1 for dexamethasone dosing (2.1, 14.1).
- MDS: 10 mg once daily (2.2).
- MCL: 25 mg once daily orally on Days 1-21 of repeated 28-day cycles (2.3).
- Continue or modify dosing based on clinical and laboratory findings (2.1, 2.2, 2.3).
- Renal impairment: Adjust starting dose in patients with moderate or severe renal impairment and on dialysis (CLcr<60 mL/min) (2.4).

----------DOSAGE FORMS AND STRENGTHS----------

- Capsules: 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg (3).

----------CONTRAINDICATIONS----------

- **Pregnancy** (Boxed Warning, 4.1, 5.1, 8.1).
- Demonstrated hypersensitivity to lenalidomide (4.2, 5.8).

----------WARNINGS AND PRECAUTIONS----------

- Increased mortality: serious and fatal cardiac adverse reactions occurred in patients with CLL treated with REVLIMID (5.5).
- Second Primary Malignancies (SPM): Higher incidences of SPM were observed in controlled trials of patients with multiple myeloma receiving REVLIMID (5.6).
- Hepatotoxicity: Hepatic failure including fatalities; monitor liver function. Stop REVLIMID and evaluate if hepatotoxicity is suspected (5.7).
- Allergic Reactions, including fatalities: Hypersensitivity, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis; discontinue REVLIMID if reactions are suspected. Do not resume REVLIMID if these reactions are verified (5.8).
- Tumor lysis syndrome (TLS) including fatalities: Monitor patients at risk of TLS (i.e., those with high tumor burden) and take appropriate precautions (5.9).
- Tumor flare reaction: Serious tumor flare reactions have occurred during investigational use of REVLIMID for chronic lymphocytic leukemia and lymphoma (5.10, 6.3).
- Impaired Stem Cell mobilization: A decrease in the number of CD34+ cells collected after treatment (> 4 cycles) with REVLIMID has been reported. Consider early referral to transplant center (5.11).

----------ADVERSE REACTIONS----------

- MM: Most common adverse reactions (≥20%) include diarrhea, fatigue, anemia, constipation, neutropenia, peripheral edema, insomnia, muscle cramp/spasms, back pain, nausea, asthenia, pyrexia, upper respiratory tract infection, cough, rash, dyspnea, dizziness, decreased appetite, thrombocytopenia, and tremor (6.1).
- MDS: Most common adverse reactions (>15%) include thrombocytopenia, neutropenia, diarrhea, pruritus, rash, fatigue, constipation, nausea, nasopharyngitis, arthralgia, pyrexia, back pain, peripheral edema, cough, dizziness, headache, muscle cramp, dyspnea, pharyngitis, and epistaxis (6.1).
- MCL: Most common adverse reactions (≥15%) include neutropenia, thrombocytopenia, fatigue, diarrhea, anemia, nausea, cough, pyrexia, rash, dyspnea, pruritus, constipation, peripheral edema and leukopenia (6.1).

To report SUSPECTED ADVERSE REACTIONS contact Celgene Corporation at 1-888-423-5436 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Digoxin: Periodic monitoring of digoxin plasma levels is recommended due to increased C_{max} and AUC with concomitant REVLIMID therapy (7.1).
- Patients taking concomitant therapies such as erythropoietin stimulating agents or estrogen containing therapies may have an increased risk of thrombosis (7.2).

----------USE IN SPECIFIC POPULATIONS----------

- Nursing Mothers: Discontinue drug or nursing taking into consideration the importance of the drug to the mother (8.3).
- Patients with Renal Insufficiency: Adjust the starting dose of REVLIMID with moderate or severe renal impairment and on dialysis (2.4).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 02/2015

FULL PRESCRIBING INFORMATION CONTENTS*
WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM

Embryo-Fetal Toxicity
Do not use REVLIMID during pregnancy. Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting REVLIMID® treatment. Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after REVLIMID treatment [*see Warnings and Precautions (5.1), and Medication Guide (17)*]. To avoid embryo-fetal exposure to lenalidomide, REVLIMID is only available through a restricted distribution program, the REVLIMID REMS™ program (formerly known as the "RevAssist®" program) (5.2).

Information about the REVLIMID REMS™ program is available at www.celgeneriskmanagement.com or by calling the manufacturer's toll-free number 1-888-423-5436.

Hematologic Toxicity (Neutropenia and Thrombocytopenia)
REVLIMID can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q myelodysplastic syndromes had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for del 5q myelodysplastic syndromes should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors *[see Dosage and Administration (2.2)]*.

Venous and Arterial Thromboembolism
REVLIMID has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with multiple myeloma who were treated with REVLIMID and dexamethasone therapy. Monitor for and advise patients about signs and symptoms of thromboembolism. Advise patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Thromboprophylaxis is recommended and the choice of regimen should be based on an assessment of the patient's underlying risks *[see Warnings and Precautions (5.4)]*.

1 INDICATIONS AND USAGE

1.1 Multiple Myeloma

REVLIMID in combination with dexamethasone is indicated for the treatment of patients with multiple myeloma (MM).

1.2 Myelodysplastic Syndromes

REVLIMID is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

1.3 Mantle Cell Lymphoma

REVLIMID is indicated for the treatment of patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.

1.4 Limitations of Use:

REVLIMID is not indicated and is not recommended for the treatment of patients with CLL outside of controlled clinical trials *[see Warnings and Precautions (5.5)]*.

2 DOSAGE AND ADMINISTRATION

REVLIMID should be taken orally at about the same time each day, either with or without food. REVLIMID capsules should be swallowed whole with water. The capsules should not be opened, broken, or chewed.

2.1 Multiple Myeloma

Multiple Myeloma

The recommended starting dose of REVLIMID is 25 mg orally once daily on Days 1-21 of repeated 28-day cycles in combination with dexamethasone. Refer to Section 14.1 for specific dexamethasone dosing. For patients > 75 years old, the starting dose of dexamethasone may be reduced *[see Clinical Studies (14.1)]*. Treatment should be continued until disease progression or unacceptable toxicity.

In patients who are not eligible for autologous stem cell transplantation (ASCT), treatment should continue until disease progression or unacceptable toxicity. For patients who are ASCT-eligible, hematopoietic stem cell mobilization should occur within 4 cycles of a REVLIMID-containing therapy *[see Warnings and Precautions (5.11)]*.

Dose Adjustments for Hematologic Toxicities During Multiple Myeloma Treatment

Dose modification guidelines, as summarized in Table 1 below, are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia or other Grade 3 or 4 toxicity judged to be related to REVLIMID.

Table 1: Dose Adjustments for Hematologic Toxicities for MM

Platelet counts

Thrombocytopenia in MM

When Platelets	Recommended Course
Fall to <30,000/mcL	Interrupt REVLIMID treatment, follow CBC weekly
Return to ≥30,000/mcL	Resume REVLIMID at next lower dose. Do not dose below 2.5 mg daily
For each subsequent drop <30,000/mcL Return to ≥30,000/mcL	Interrupt REVLIMID treatment Resume REVLIMID at next lower dose. Do not dose below 2.5 mg daily

Absolute Neutrophil counts (ANC)

Neutropenia in MM

When Neutrophils	Recommended Course
Fall to <1000/mcL	Interrupt REVLIMID treatment, follow CBC weekly
Return to ≥1,000/mcL and neutropenia is the only toxicity	Resume REVLIMID at 25 mg daily or initial starting dose
Return to ≥1,000/mcL and if other toxicity	Resume REVLIMID at next lower dose. Do not dose below 2.5 mg daily
For each subsequent drop <1,000/mcL Return to ≥1,000/mcL	Interrupt REVLIMID treatment Resume REVLIMID at next lower dose. Do not dose below 2.5 mg daily

Other Toxicities in MM

For other Grade 3/4 toxicities judged to be related to REVLIMID, hold treatment and restart at the physician's discretion at next lower dose level when toxicity has resolved to ≤ Grade 2.

Starting Dose Adjustment for Renal Impairment in MM:

[See Dosage and Administration (2.4)].

2.2 **Myelodysplastic Syndromes**

The recommended starting dose of REVLIMID is 10 mg daily. Treatment is continued or modified based upon clinical and laboratory findings.

Dose Adjustments for Hematologic Toxicities During MDS Treatment

Patients who are dosed initially at 10 mg and who experience thrombocytopenia should have their dosage adjusted as follows:

Platelet counts

If thrombocytopenia develops WITHIN 4 weeks of starting treatment at 10 mg daily in MDS

If baseline ≥100,000/mcL	
When Platelets	**Recommended Course**
Fall to <50,000/mcL	Interrupt REVLIMID treatment
Return to ≥50,000/mcL	Resume REVLIMID at 5 mg daily
If baseline <100,000/mcL	
When Platelets	**Recommended Course**
Fall to 50% of the baseline value	Interrupt REVLIMID treatment
If baseline ≥60,000/mcL and returns to ≥50,000/mcL	Resume REVLIMID at 5 mg daily
If baseline <60,000/mcL and returns to ≥30,000/mcL	Resume REVLIMID at 5 mg daily

If thrombocytopenia develops AFTER 4 weeks of starting treatment at 10 mg daily in MDS

When Platelets	Recommended Course
<30,000/mcL or <50,000/mcL with platelet transfusions	Interrupt REVLIMID treatment
Return to ≥30,000/mcL (without hemostatic failure)	Resume REVLIMID at 5 mg daily

Patients who experience thrombocytopenia at 5 mg daily should have their dosage adjusted as follows:

If thrombocytopenia develops during treatment at 5 mg daily in MDS

When Platelets	Recommended Course

<30,000/mcL or <50,000/mcL with platelet transfusions	Interrupt REVLIMID treatment
Return to ≥30,000/mcL (without hemostatic failure)	Resume REVLIMID at 2.5 mg daily

Patients who are dosed initially at 10 mg and experience neutropenia should have their dosage adjusted as follows:

Absolute Neutrophil counts (ANC)

If neutropenia develops WITHIN 4 weeks of starting treatment at 10 mg daily in MDS

If baseline ANC ≥1,000/mcL	
When Neutrophils	**Recommended Course**
Fall to <750/mcL	Interrupt REVLIMID treatment
Return to ≥1,000/mcL	Resume REVLIMID at 5 mg daily
If baseline ANC <1,000/mcL	
When Neutrophils	**Recommended Course**
Fall to <500/mcL	Interrupt REVLIMID treatment
Return to ≥500/mcL	Resume REVLIMID at 5 mg daily

If neutropenia develops AFTER 4 weeks of starting treatment at 10 mg daily in MDS

When Neutrophils	**Recommended Course**
<500/mcL for ≥7 days or <500/mcL associated with fever (≥38.5°C)	Interrupt REVLIMID treatment
Return to ≥500/mcL	Resume REVLIMID at 5 mg daily

Patients who experience neutropenia at 5 mg daily should have their dosage adjusted as follows:

If neutropenia develops during treatment at 5 mg daily in MDS

When Neutrophils	**Recommended Course**
<500/mcL for ≥7 days or <500/mcL associated with fever (≥38.5°C)	Interrupt REVLIMID treatment
Return to ≥500/mcL	Resume REVLIMID at 2.5 mg daily

Other Grade 3 / 4 Toxicities in MDS

For other Grade 3/4 toxicities judged to be related to REVLIMID, hold treatment and restart at the physician's discretion at next lower dose level when toxicity has resolved to ≤ Grade 2.

Starting Dose Adjustment for Renal Impairment in MDS:

[See Dosage and Administration (2.4)].

2.3 **Mantle Cell Lymphoma**

The recommended starting dose of REVLIMID is 25 mg/day orally on Days 1-21 of repeated 28-day cycles for relapsed or refractory mantle cell lymphoma. Treatment should be continued until disease progression or unacceptable toxicity.

Treatment is continued, modified or discontinued based upon clinical and laboratory findings.

Dose Adjustments for Hematologic Toxicities During MCL Treatment

Dose modification guidelines as summarized below are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia or other Grade 3 or 4 toxicities considered to be related to REVLIMID.

Platelet counts

Thrombocytopenia during treatment in MCL

When Platelets	**Recommended Course**
Fall to <50,000/mcL	Interrupt REVLIMID treatment and follow CBC weekly
Return to ≥50,000/mcL	Resume REVLIMID at 5 mg less than the previous dose. Do not dose below 5 mg daily

Absolute Neutrophil counts (ANC)

Neutropenia during treatment in MCL

When Neutrophils	**Recommended Course**
Fall to <1000/mcL for at least 7 days	Interrupt REVLIMID treatment and follow

OR Falls to < 1,000/mcL with an associated temperature ≥ 38.5°C OR Falls to < 500 /mcL	CBC weekly
Return to ≥1,000/mcL	Resume REVLIMID at 5 mg less than the previous dose. Do not dose below 5 mg daily

Other Grade 3 / 4 Toxicities in MCL

For other Grade 3/4 toxicities judged to be related to REVLIMID, hold treatment and restart at the physician's discretion at next lower dose level when toxicity has resolved to ≤ Grade 2.

Starting Dose Adjustment for Renal Impairment in MCL:

[See Dosage and Administration (2.4)].

2.4 **Starting Dose for Renal Impairment in MM, MDS or MCL**

Since REVLIMID is primarily excreted unchanged by the kidney, adjustments to the starting dose of REVLIMID are recommended to provide appropriate drug exposure in patients with moderate or severe renal impairment and in patients on dialysis. Based on a pharmacokinetic study in patients with renal impairment due to non-malignant conditions, REVLIMID starting dose adjustment is recommended for patients with CLcr < 60 mL/min. The recommendations for initial starting doses for patients with MDS or MCL, and MM are as follows:

Table 2: Starting Dose Adjustments for Patients with Renal Impairment in MDS or MCL

Category	Renal Function (Cockcroft-Gault)	Dose in MCL	Dose in MDS
Moderate Renal Impairment	CLcr 30-60 mL/min	10 mg Every 24 hours	5 mg Every 24 hours
Severe Renal Impairment	CLcr < 30 mL/min (not requiring dialysis)	15 mg Every 48 hours	2.5 mg Every 24 hours
End Stage Renal Disease	CLcr < 30 mL/min (requiring dialysis)	5 mg Once daily. On dialysis days, administer the dose following dialysis.	2.5 mg Once daily. On dialysis days, administer the dose following dialysis.

Table 3: Starting Dose Adjustments for Patients with Renal Impairment in MM

Category	Renal Function (Cockcroft-Gault)	Dose in MM
Moderate Renal Impairment	CLcr 30-50 mL/min	10 mg Every 24 hours
Severe Renal Impairment	CLcr < 30 mL/min (not requiring dialysis)	15 mg Every 48 hours
End Stage Renal Disease	CLcr < 30 mL/min (requiring dialysis)	5 mg Once daily. On dialysis days, administer the dose following dialysis.

Moderate renal impairment for MM: Consider escalating the dose to 15 mg after 2 cycles if the patient tolerates the 10 mg dose of lenalidomide without dose-limiting toxicity.

After initiation of REVLIMID therapy, subsequent REVLIMID dose increase or decrease is based on individual patient treatment tolerance, as described elsewhere *[See Dosage and Administration (2.1-2.3)].*

3 DOSAGE FORMS AND STRENGTHS

REVLIMID 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg and 25 mg capsules will be supplied through the REVLIMID REMS™ program.

REVLIMID is available in the following capsule strengths:

2.5 mg: White and blue-green opaque hard capsules imprinted "REV" on one half and "2.5 mg" on the other half in black ink
5 mg: White opaque capsules imprinted "REV" on one half and "5 mg" on the other half in black ink
10 mg: Blue/green and pale yellow opaque capsules imprinted "REV" on one half and "10 mg" on the other half in black ink
15 mg: Powder blue and white opaque capsules imprinted "REV" on one half and "15 mg" on the other half in black ink
20 mg: Powder blue and blue-green opaque hard capsules imprinted "REV" on one half and "20 mg" on the other half in black ink
25 mg: White opaque capsules imprinted "REV" on one half and "25 mg" on the other half in black ink

4 CONTRAINDICATIONS

4.1 **Pregnancy**

REVLIMID can cause fetal harm when administered to a pregnant female. Limb abnormalities were seen in the offspring of monkeys that were dosed with lenalidomide during organogenesis. This effect was seen at all doses tested. Due to the results of this developmental monkey study, and lenalidomide's structural similarities to thalidomide, a known human teratogen, lenalidomide is contraindicated in females who are pregnant [*see Boxed Warning*]. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus *[see Warnings and Precautions (5.1, 5.2), Use in Special Populations (8.1), (8.6)]*.

4.2 **Allergic Reactions**

REVLIMID is contraindicated in patients who have demonstrated hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide *[see Warnings and Precautions (5.8)]*.

5 WARNINGS AND PRECAUTIONS

5.1 **Embryo-Fetal Toxicity**

REVLIMID is a thalidomide analogue and is contraindicated for use during pregnancy. Thalidomide is a known human teratogen that causes life-threatening human birth defects or embryo-fetal death [*see Use in Specific Populations (8.1)*]. An embryo-fetal development study in monkeys indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy, similar to birth defects observed in humans following exposure to thalidomide during pregnancy.

REVLIMID is only available through the REVLIMID REMS™ program (formerly known as the "RevAssist® program") *[see Warnings and Precautions (5.2)]*.

Females of Reproductive Potential
Females of reproductive potential must avoid pregnancy for at least 4 weeks before beginning REVLIMID therapy, during therapy, during dose interruptions and for at least 4 weeks after completing therapy.

Females must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control, beginning 4 weeks prior to initiating treatment with REVLIMID, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of REVLIMID therapy.

Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing REVLIMID therapy and then weekly during the first month, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles *[see Use in Specific Populations (8.6)]*.

Males
Lenalidomide is present in the semen of patients receiving the drug. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID and for up to 28 days after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate sperm *[see Use in Specific Populations (8.6)]*.

Blood Donation
Patients must not donate blood during treatment with REVLIMID and for 1 month following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to REVLIMID.

5.2 **REVLIMID REMS™ Program**

Because of the embryo-fetal risk [*see Warnings and Precautions (5.1)*], REVLIMID is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS), the **REVLIMID REMS™** program **(formerly known as the "RevAssist®" program).**

Required components of the **REVLIMID REMS™** program include the following:
- Prescribers must be certified with the **REVLIMID REMS™** program by enrolling and complying with the REMS requirements.
- Patients must sign a Patient-Physician agreement form and comply with the REMS requirements. In particular, female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements *[see Use in Specific Populations (8.6)]* and males must comply with contraception requirements *[see Use in Specific Populations (8.6)]*.
- Pharmacies must be certified with the **REVLIMID REMS™** program, must only dispense to patients who are authorized to receive REVLIMID and comply with REMS requirements.

Further information about the **REVLIMID REMS™** program is available at www.celgeneriskmanagement.com or by telephone at 1-888-423-5436.

5.3 **Hematologic Toxicity**

REVLIMID can cause significant neutropenia and thrombocytopenia. Monitor patients with neutropenia for signs of infection. Advise patients to observe for bleeding or bruising, especially with use of concomitant medication that may increase risk of bleeding. Patients taking REVLIMID should have their complete blood counts assessed periodically as described below *[see Dosage and Administration (2.1, 2.2, 2.3)]*.

Patients taking REVLIMID in combination with dexamethasone for MM should have their complete blood counts (CBC) assessed every 7 days (weekly) for the first 2 cycles, on Days 1 and 15 of Cycle 3, and every 28 days (4 weeks) thereafter. A dose interruption and/or dose reduction may be required *[see Dosage and Administration (2.1)]*.

Patients taking REVLIMID for MDS should have their complete blood counts monitored weekly for the first 8 weeks and at least monthly thereafter. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the MDS study. In the 48% of patients who developed Grade 3 or 4 neutropenia, the median time to onset was 42 days (range, 14-411 days), and the median time to documented recovery was 17 days (range,

2-170 days). In the 54% of patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was 28 days (range, 8-290 days), and the median time to documented recovery was 22 days (range, 5-224 days) *[see Boxed Warning and Dosage and Administration (2.2)]*.

Patients taking REVLIMID for MCL should have their complete blood counts monitored weekly for the first cycle (28 days), every 2 weeks during cycles 2-4, and then monthly thereafter. Patients may require dose interruption and/or dose reduction. In the MCL trial, Grade 3 or 4 neutropenia was reported in 43% of the patients. Grade 3 or 4 thrombocytopenia was reported in 28% of the patients.

5.4 Venous and Arterial Thromboembolism

Venous thromboembolic events (deep venous thrombosis and pulmonary embolism) and arterial thromboses are increased in patients treated with REVLIMID. A significantly increased risk of DVT (7.4%) and of PE (3.7%) occurred in patients with multiple myeloma after at least one prior therapy who were treated with REVLIMID and dexamethasone therapy compared to patients treated in the placebo and dexamethasone group (3.1% and 0.9%) in clinical trials with varying use of anticoagulant therapies. In the newly diagnosed multiple myeloma (NDMM) study in which nearly all patients received antithrombotic prophylaxis, DVT was reported as a serious adverse reaction (3.6%, 2.0%, and 1.7%) in the Rd Continuous, Rd18, and MPT Arms, respectively. The frequency of serious adverse reactions of PE was similar between the Rd Continuous, Rd18, and MPT Arms (3.8%, 2.8%, and 3.7%, respectively) *[see Boxed Warning and Adverse Reactions (6.1)]*.

Myocardial infarction (1.7%) and stroke (CVA) (2.3%) are increased in patients with multiple myeloma after at least one prior therapy who were treated with REVLIMID and dexamethasone therapy compared to patients treated with placebo and dexamethasone (0.6%, and 0.9%) in clinical trials. In the NDMM study, myocardial infarction (including acute) was reported as a serious adverse reaction (2.3%, 0.6%, and 1.1%) in the Rd Continuous, Rd18, and MPT Arms, respectively. The frequency of serious adverse reactions of CVA was similar between the Rd Continuous, Rd18, and MPT Arms (0.8%, 0.6 %, and 0.6%, respectively) *[see Adverse Reactions (6.1)]*. Patients with known risk factors, including prior thrombosis, may be at greater risk and actions should be taken to try to minimize all modifiable factors (e.g. hyperlipidemia, hypertension, smoking).

In controlled clinical trials that did not use concomitant thromboprophylaxis, 21.5% overall thrombotic events (Standardized MedDRA Query Embolic and Thrombotic events) occurred in patients with refractory and relapsed multiple myeloma who were treated with REVLIMID and dexamethasone compared to 8.3% thrombosis in patients treated with placebo and dexamethasone. The median time to first thrombosis event was 2.8 months. In the NDMM study in which nearly all patients received antithrombotic prophylaxis, the overall frequency of thrombotic events was 17.4% in patients in the combined Rd Continuous and Rd18 Arms, and was 11.6% in the MPT Arm. The median time to first thrombosis event was 4.37 months in the combined Rd Continuous and Rd18 Arms. Thromboprophylaxis is recommended. The regimen of thromboprophylaxis should be based on an assessment of the patient's underlying risks. Instruct patients to report immediately any signs and symptoms suggestive of thrombotic events. ESAs and estrogens may further increase the risk of thrombosis and their use should be based on a benefit-risk decision in patients receiving REVLIMID *[see Drug Interactions (7.2)]*.

5.5 Increased Mortality in Patients with CLL

In a prospective randomized (1:1) clinical trial in the first line treatment of patients with chronic lymphocytic leukemia, single agent REVLIMID therapy increased the risk of death as compared to single agent chlorambucil. In an interim analysis, there were 34 deaths among 210 patients on the REVLIMID treatment arm compared to 18 deaths among 211 patients in the chlorambucil treatment arm, and hazard ratio for overall survival was 1.92 [95% CI: 1.08 – 3.41], consistent with a 92% increase in the risk of death. The trial was halted for safety in July 2013.

Serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiac failure occurred more frequently in the REVLIMID treatment arm. REVLIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials.

5.6 Second Primary Malignancies

In clinical trials in patients with multiple myeloma receiving REVLIMID an increase of invasive second primary malignancies notably AML and MDS have been observed. The increase of cases of AML and MDS occurred predominantly in NDMM patients receiving REVLIMID in combination with oral melphalan (frequency of 5.3%) or immediately following high dose intravenous melphalan and ASCT (frequency of up to 5.2%). The frequency of AML and MDS cases in the REVLIMID / dexamethasone arms was observed to be 0.4%. Cases of B-cell malignancies (including Hodgkin's Lymphomas) were observed in clinical trials where patients received lenalidomide in the post-ASCT setting.

Patients who received REVLIMID-containing therapy until disease progression did not show a higher incidence of invasive SPM than patients treated in the fixed duration REVLIMID-containing arms. Monitor patients for the development of second primary malignancies. Take into account both the potential benefit of REVLIMID and the risk of second primary malignancies when considering treatment with REVLIMID.

5.7 Hepatotoxicity

Hepatic failure, including fatal cases, has occurred in patients treated with lenalidomide in combination with dexamethasone. In clinical trials, 15% of patients experienced hepatotoxicity (with hepatocellular, cholestatic and mixed characteristics); 2% of patients with multiple myeloma and 1% of patients with myelodysplasia had serious hepatotoxicity events. The mechanism of drug-induced hepatotoxicity is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop REVLIMID upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

5.8 Allergic Reactions

Angioedema and serious dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. These events can be fatal. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive REVLIMID. REVLIMID interruption or discontinuation should be considered for Grade 2-3 skin rash. REVLIMID must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if SJS or TEN is suspected and should not be resumed following discontinuation for these reactions.

REVLIMID capsules contain lactose. Risk-benefit of REVLIMID treatment should be evaluated in patients with lactose intolerance.

5.9 Tumor Lysis Syndrome

Fatal instances of tumor lysis syndrome have been reported during treatment with lenalidomide. The patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

5.10 Tumor Flare Reaction

Tumor flare reaction has occurred during investigational use of lenalidomide for CLL and lymphoma, and is characterized by tender lymph node swelling, low grade fever, pain and rash. REVLIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials.

Monitoring and evaluation for tumor flare reaction (TFR) is recommended in patients with MCL. Tumor flare reaction may mimic progression of disease (PD). In the MCL trial, 13/134 (10%) of subjects experienced TFR; all reports were Grade 1 or 2 in severity. All of the events occurred in cycle 1 and one patient developed TFR again in cycle 11. Lenalidomide may be continued in patients with Grade 1 and 2 TFR without interruption or modification, at the physician's discretion. Patients with Grade 1 and 2 TFR may also be treated with corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and/or narcotic analgesics for management of TFR symptoms. In patients with Grade 3 or 4 TFR, it is recommended to withhold treatment with lenalidomide until TFR resolves to $\leq$ Grade 1. Patients with Grade 3 or 4 TFR may be treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR.

5.11 Impaired Stem Cell Mobilization

A decrease in the number of CD34+ cells collected after treatment (> 4 cycles) with REVLIMID has been reported. In patients who are ASCT candidates, referral to a transplant center should occur early in treatment to optimize the timing of the stem cell collection. In patients who received more than 4 cycles of a REVLIMID-containing treatment or for whom inadequate numbers of CD 34+ cells have been collected with G-CSF alone, G-CSF with cyclophosphamide or the combination of G-CSF with a CXCR4 inhibitor may be considered.

6 ADVERSE REACTIONS

The following adverse reactions are described in detail in other sections of the prescribing information:

- Embryo-Fetal Toxicity *[see Boxed Warnings, Warnings and Precautions (5.1, 5.2)]*
- Neutropenia and thrombocytopenia *[see Boxed Warnings, Warnings and Precautions (5.3)]*
- Venous and arterial thromboembolism *[see Boxed Warnings, Warnings and Precautions (5.4)]*
- Increased Mortality in Patients with CLL *[see Warnings and Precautions (5.5)]*
- Second Primary Malignancies *[see Warnings and Precautions (5.6)]*
- Hepatotoxicity *[see Warnings and Precautions (5.7)]*
- Allergic Reactions *[see Warnings and Precautions (5.8)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.9)]*
- Tumor Flare Reactions *[see Warnings and Precautions (5.10)]*
- Impaired Stem Cell Mobilization *[see Warnings and Precautions (5.11)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience

Specific Populations

Newly Diagnosed Multiple Myeloma:

Data were evaluated from 1613 patients in a large phase 3 study who received at least one dose of REVLIMID with low dose dexamethasone (Rd) given for 2 different durations of time (i.e., until progressive disease [Arm Rd Continuous; N=532] or for up to eighteen 28-day cycles [72 weeks, Arm Rd18; N=540] or who received melphalan, prednisone and thalidomide (Arm MPT; N=541) for a maximum of twelve 42-day cycles (72 weeks). The median treatment duration in the Rd Continuous arm was 80.2 weeks (range 0.7 to 246.7) or 18.4 months (range 0.16 to 56.7).

In general, the most frequently reported adverse reactions were comparable in Arm Rd Continuous and Arm Rd18, and included diarrhea, anemia, constipation, peripheral edema, neutropenia, fatigue, back pain, nausea, asthenia, and insomnia. The most frequently reported Grade 3 or 4 reactions included neutropenia, anemia, thrombocytopenia, pneumonia, asthenia, fatigue, back pain, hypokalemia, rash, cataract, lymphopenia, dyspnea, DVT, hyperglycemia, and leukopenia. The highest frequency of infections occurred in Arm Rd Continuous (75%) compared to Arm MPT (56%). There were more grade 3 and 4 and serious adverse reactions of infection in Arm Rd Continuous than either Arm MPT or Rd18.

In the Rd Continuous arm, the most common adverse reactions leading to dose interruption of REVLIMID were infection events (28.8%); overall, the median time to the first dose interruption of REVLIMID was 7 weeks. The most common adverse reactions leading to dose reduction of REVLIMID in the Rd Continuous arm were hematologic events (10.7%); overall, the median time to the first dose reduction of REVLIMID was 16 weeks. In the Rd Continuous arm, the most common adverse reactions leading to discontinuation of REVLIMID were infection events (3.4%).

In both Rd arms, the frequencies of onset of adverse reactions were generally highest in the first 6 months of treatment and then the frequencies decreased over time or remained stable throughout treatment, except for cataracts. The frequency of onset of cataracts increased over time with 0.7% during the first 6 months and up to 9.6% by the 2nd year of treatment with Rd Continuous.

Table 4 summarizes the adverse reactions reported for the Rd Continuous, Rd18, and MPT treatment arms.

Table 4: All Adverse Reactions in ≥5.0% and Grade 3/4 Adverse Reactions in ≥ 1.0% of Patients in the Rd Continuous or Rd18 Arms*

	All Adverse Reactions[a]			Grade 3/4 Adverse Reactions[b]		
System organ class Preferred term	Rd Continuous (N = 532)	Rd18 (N = 540)	MPT (N = 541)	Rd Continuous (N = 532)	Rd18 (N = 540)	MPT (N = 541)
General disorders and administration site conditions						
Fatigue[%]	173 (32.5)	177 (32.8)	154 (28.5)	39 (7.3)	46 (8.5)	31 (5.7)
Asthenia	150 (28.2)	123 (22.8)	124 (22.9)	41 (7.7)	33 (6.1)	32 (5.9)
Pyrexia[c]	114 (21.4)	102 (18.9)	76 (14.0)	13 (2.4)	7 (1.3)	7 (1.3)
Non-cardiac chest pain[f]	29 (5.5)	31 (5.7)	18 (3.3)	<1%	< 1%	< 1%
Gastrointestinal disorders						
Diarrhea	242 (45.5)	208 (38.5)	89 (16.5)	21 (3.9)	18 (3.3)	8 (1.5)
Abdominal pain[%,f]	109 (20.5)	78 (14.4)	60 (11.1)	7 (1.3)	9 (1.7)	< 1%
Dyspepsia[f]	57 (10.7)	28 (5.2)	36 (6.7)	<1%	< 1%	0 (0.0)
Musculoskeletal and connective tissue disorders						
Back pain[c]	170 (32)	145 (26.9)	116 (21.4)	37 (7)	34 (6.3)	28 (5.2)
Muscle spasms[f]	109 (20.5)	102 (18.9)	61 (11.3)	< 1%	< 1%	< 1%
Arthralgia[f]	101 (19.0)	71 (13.1)	66 (12.2)	9 (1.7)	8 (1.5)	8 (1.5)
Bone pain[f]	87 (16.4)	77 (14.3)	62 (11.5)	16 (3.0)	15 (2.8)	14 (2.6)
Pain in extremity[f]	79 (14.8)	66 (12.2)	61 (11.3)	8 (1.5)	8 (1.5)	7 (1.3)
Musculoskeletal pain[f]	67 (12.6)	59 (10.9)	36 (6.7)	< 1%	< 1%	< 1%
Musculoskeletal chest pain[f]	60 (11.3)	51 (9.4)	39 (7.2)	6 (1.1)	< 1%	< 1%
Muscular weakness[f]	43 (8.1)	35 (6.5)	29 (5.4)	< 1%	8 (1.5)	< 1%
Neck pain[f]	40 (7.5)	19 (3.5)	10 (1.8)	< 1%	< 1%	< 1%
Infections and infestations						
Bronchitis[c]	90 (16.9)	59 (10.9)	43 (7.9)	9 (1.7)	6 (1.1)	3 (0.6)
Nasopharyngitis[f]	80 (15)	54 (10)	33 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary tract infection[f]	76 (14.3)	63 (11.7)	41 (7.6)	8 (1.5)	8 (1.5)	< 1%
Upper respiratory tract infection[c%,f]	69 (13.0)	53 (9.8)	31 (5.7)	< 1%	8 (1.5)	< 1%
Pneumonia[c@]	93 (17.5)	87 (16.1)	56 (10.4)	60 (11.3)	57 (10.5)	41 (7.6)
Respiratory tract infection[%]	35 (6.6)	25 (4.6)	21 (3.9)	7 (1.3)	4 (0.7)	1 (0.2)
Influenza[f]	33 (6.2)	23 (4.3)	15 (2.8)	< 1%	< 1%	0 (0.0)
Gastroenteritis[f]	32 (6.0)	17 (3.1)	13 (2.4)	0 (0.0)	< 1%	< 1%
Lower respiratory tract infection	29 (5.5)	14 (2.6)	16 (3.0)	10 (1.9)	3 (0.6)	3 (0.6)
Rhinitis[f]	29 (5.5)	24 (4.4)	14 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Cellulitis[c]	< 5%	< 5%	< 5%	8 (1.5)	3 (0.6)	2 (0.4)
Sepsis[c@]	33 (6.2)	26-(4.8)	18 (3.3)	26 (4.9)	20 (3.7)	13 (2.4)
Nervous system disorders						
Headache[f]	75 (14.1)	52 (9.6)	56 (10.4)	< 1%	< 1%	< 1%
Dysgeusia[f]	39 (7.3)	45 (8.3)	22 (4.1)	< 1%	0 (0.0)	< 1%
Blood and lymphatic system disorders[d]						
Anemia	233 (43.8)	193 (35.7)	229 (42.3)	97 (18.2)	85 (15.7)	102 (18.9)
Neutropenia	186 (35.0)	178 (33)	328 (60.6)	148 (27.8)	143 (26.5)	243 (44.9)
Thrombocytopenia	104 (19.5)	100 (18.5)	135 (25.0)	44 (8.3)	43 (8.0)	60 (11.1)
Febrile neutropenia	7 (1.3)	17 (3.1)	15 (2.8)	6 (1.1)	16 (3.0)	14 (2.6)
Pancytopenia	5 (0.9)	6 (1.1)	7 (1.3)	1 (0.2)	3 (0.6)	5 (0.9)
Respiratory, thoracic and mediastinal disorders						

System organ class Preferred term	All Adverse Reactions[a]			Grade 3/4 Adverse Reactions[b]		
	Rd Continuous (N = 532)	Rd18 (N = 540)	MPT (N = 541)	Rd Continuous (N = 532)	Rd18 (N = 540)	MPT (N = 541)
Cough[f]	121 (22.7)	94 (17.4)	68 (12.6)	< 1%	< 1%	< 1%
Dyspnea[c,e]	117 (22.0)	89 (16.5)	113 (20.9)	30 (5.6)	22 (4.1)	18 (3.3)
Epistaxis[f]	32 (6.0)	31 (5.7)	17 (3.1)	< 1%	< 1%	0 (0.0)
Oropharyngeal pain[f]	30 (5.6)	22 (4.1)	14 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnea exertional[e]	27 (5.1)	29 (5.4)	< 5%	6 (1.1)	2 (0.4)	0 (0.0)
Metabolism and nutrition disorders						
Decreased appetite	123 (23.1)	115 (21.3)	72 (13.3)	14 (2.6)	7 (1.3)	5 (0.9)
Hypokalemia[%]	91 (17.1)	62 (11.5)	38 (7)	35 (6.6)	20 (3.7)	11 (2.0)
Hyperglycemia	62 (11.7)	52 (9.6)	19 (3.5)	28 (5.3)	23 (4.3)	9 (1.7)
Hypocalcemia	57 (10.7)	56 (10.4)	31 (5.7)	23 (4.3)	19 (3.5)	8 (1.5)
Dehydration[%]	25 (4.7)	29 (5.4)	17 (3.1)	8 (1.5)	13 (2.4)	9 (1.7)
Gout[e]	< 5%	< 5%	< 5%	8 (1.5)	0 (0.0)	0 (0.0)
Diabetes mellitus[%,e]	< 5%	< 5%	< 5%	8 (1.5)	4 (0.7)	2 (0.4)
Hypophosphatemia[e]	< 5%	< 5%	< 5%	7 (1.3)	3 (0.6)	1 (0.2)
Hyponatremia[%,e]	< 5%	< 5%	< 5%	7 (1.3)	13 (2.4)	6 (1.1)
Skin and subcutaneous tissue disorders						
Rash	139 (26.1)	151 (28.0)	105 (19.4)	39 (7.3)	38 (7.0)	33 (6.1)
Pruritus[f]	47 (8.8)	49 (9.1)	24 (4.4)	< 1%	< 1%	< 1%
Psychiatric disorders						
Insomnia	147 (27.6)	127 (23.5)	53 (9.8)	4 (0.8)	6 (1.1)	0 (0.0)
Depression	58 (10.9)	46 (8.5)	30 (5.5)	10 (1.9)	4 (0.7)	1 (0.2)
Vascular disorders						
Deep vein thrombosis[c%]	55 (10.3)	39 (7.2)	22 (4.1)	30 (5.6)	20 (3.7)	15 (2.8)
Hypotension[c%]	51 (9.6)	35 (6.5)	36 (6.7)	11 (2.1)	8 (1.5)	6 (1.1)
Injury, Poisoning, and Procedural Complications						
Fall[f]	43 (8.1)	25 (4.6)	25 (4.6)	< 1%	6 (1.1)	6 (1.1)
Contusion[f]	33 (6.2)	24 (4.4)	15 (2.8)	< 1%	< 1%	0 (0.0)
Eye disorders						
Cataract	73 (13.7)	31 (5.7)	5 (0.9)	31 (5.8)	14 (2.6)	3 (0.6)
Cataract subcapsular[e]	< 5%	< 5%	< 5%	7 (1.3)	0 (0.0)	0 (0.0)
Investigations						
Weight decreased	72 (13.5)	78 (14.4)	48 (8.9)	11 (2.1)	4 (0.7)	4 (0.7)
Cardiac disorders						
Atrial fibrillation[c]	37 (7.0)	25 (4.6)	25 (4.6)	13 (2.4)	9 (1.7)	6 (1.1)
Myocardial infarction (including acute)[c,e]	< 5%	< 5%	< 5%	10 (1.9)	3 (0.6)	5 (0.9)
Renal and Urinary disorders						
Renal failure (including acute)[c@,f]	49 (9.2)	54 (10.0)	37 (6.8)	28 (5.3)	33 (6.1)	29 (5.4)
Neoplasms benign, malignant and unspecified (Incl cysts and polyps)						
Squamous cell carcinoma[c,e]	< 5%	< 5%	< 5%	8 (1.5)	4 (0.7)	0 (0.0)
Basal cell carcinoma[c,f]	< 5%	< 5%	< 5%	< 1%	< 1%	0 (0.0)

Note: System organ classes (SOC) and preferred terms (PTs) reflect coding of adverse reactions using MedDRA. A subject with multiple occurrences of an adverse reaction is counted only once under the applicable SOC/PT.

[a] All treatment-emergent adverse reactions in at least 5.0% of subjects in the Rd Continuous or Rd18 Arms and at least a 2.0% higher frequency (%) in either the Rd Continuous or Rd18 Arms compared to the MPT Arm.

[b] All grade 3 or 4 treatment-emergent adverse reactions in at least 1.0% of subjects in the Rd Continuous or Rd18 Arms and at least a 1.0% higher frequency (%) in either the Rd Continuous or Rd18 Arms compared to the MPT Arm.

[c] Serious treatment-emergent adverse reactions in at least 1.0% of subjects in the Rd Continuous or Rd18 Arms and at least a 1.0% higher frequency (%) in either the Rd Continuous or Rd18 Arms compared to the MPT Arm.

[d] Preferred terms for the blood and lymphatic system disorders SOC were included by medical judgment as known adverse reactions for Rd Continuous/Rd18, and have also been reported as serious.

[e] Footnote "a" not applicable

[f] Footnote "b" not applicable.

[g] - adverse reactions in which at least one resulted in a fatal outcome

[%] - adverse reactions in which at least one was considered to be life threatening (if the outcome of the reaction was death, it is included with death cases)

*PTs for combined adverse reaction terms:

Abdominal Pain: Abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain

Pneumonias: Pneumonia, lobar pneumonia, pneumonia pneumococcal, bronchopneumonia, pneumocystis jiroveci pneumonia, pneumonia legionella, pneumonia staphylococcal, pneumonia klebsiella, atypical pneumonia, pneumonia bacterial, pneumonia escherichia, pneumonia streptococcal, pneumonia viral

Sepsis: Sepsis, septic shock, urosepsis, escherichia sepsis, neutropenic sepsis, pneumococcal sepsis, staphylococcal sepsis, bacterial sepsis, meningococcal sepsis, enterococcal sepsis, klebsiella sepsis, pseudomonal sepsis

Rash: Rash, rash pruritic, rash erythematous, rash maculo-papular, rash generalised, rash papular, exfoliative rash, rash follicular, rash macular, drug rash with eosinophilia and systemic symptoms, erythema multiforme, rash pustular

Deep Vein Thrombosis: Deep vein thrombosis, venous thrombosis limb, venous thrombosis

After At Least One Prior Therapy for MM

Data were evaluated from 703 patients in two studies who received at least one dose of REVLIMID/dexamethasone (353 patients) or placebo/dexamethasone (350 patients).

In the REVLIMID/dexamethasone treatment group, 269 patients (76%) had at least one dose interruption with or without a dose reduction of REVLIMID compared to 199 patients (57%) in the placebo/dexamethasone treatment group. Of these patients who had one dose interruption with or without a dose reduction, 50% in the REVLIMID/dexamethasone treatment group had at least one additional dose interruption with or without a dose reduction compared to 21% in the placebo/dexamethasone treatment group. Most adverse reactions and Grade 3/4 adverse reactions were more frequent in patients who received the combination of REVLIMID/dexamethasone compared to placebo/dexamethasone.

Tables 5, 6, and 7 summarize the adverse reactions reported for REVLIMID/dexamethasone and placebo/dexamethasone groups.

Table 5: Adverse Reactions Reported in ≥5% of Patients and with a ≥2% Difference in Proportion of Patients Between the REVLIMID/dexamethasone and Placebo/dexamethasone Groups

System Organ Class/ Preferred Term	REVLIMID/Dex* (N=353) n (%)	Placebo/Dex * (N=350) n (%)
Blood and lymphatic system disorders		
Neutropenia[%]	149 (42.2)	22 (6.3)
Anemia[g]	111 (31.4)	83 (23.7)
Thrombocytopenia[g]	76 (21.5)	37 (10.6)
Leukopenia	28 (7.9)	4 (1.1)
Lymphopenia	19 (5.4)	5 (1.4)
General disorders and administration site conditions		
Fatigue	155 (43.9)	146 (41.7)
Pyrexia	97 (27.5)	82 (23.4)
Peripheral edema	93 (26.3)	74 (21.1)
Chest Pain	29 (8.2)	20 (5.7)
Lethargy	24 (6.8)	8 (2.3)
Gastrointestinal disorders		
Constipation	143 (40.5)	74 (21.1)
Diarrhea[g]	136 (38.5)	96 (27.4)
Nausea[g]	92 (26.1)	75 (21.4)
Vomiting[g]	43 (12.2)	33 (9.4)

System Organ Class/ Preferred Term	REVLIMID/Dex* (N=353) n (%)	Placebo/Dex * (N=350) n (%)
Abdominal Pain[g]	35 (9.9)	22 (6.3)
Dry Mouth	25 (7.1)	13 (3.7)
Musculoskeletal and connective tissue disorders		
Muscle cramp	118 (33.4)	74 (21.1)
Back pain	91 (25.8)	65 (18.6)
Bone Pain	48 (13.6)	39 (11.1)
Pain in Limb	42 (11.9)	32 (9.1)
Nervous system disorders		
Dizziness	82 (23.2)	59 (16.9)
Tremor	75 (21.2)	26 (7.4)
Dysgeusia	54 (15.3)	34 (9.7)
Hypoaesthesia	36 (10.2)	25 (7.1)
Neuropathy[a]	23 (6.5)	13 (3.7)
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	83 (23.5)	60 (17.1)
Nasopharyngitis	62 (17.6)	31 (8.9)
Pharyngitis	48 (13.6)	33 (9.4)
Bronchitis	40 (11.3)	30 (8.6)
Infections[b] and infestations		
Upper respiratory tract infection	87 (24.6)	55 (15.7)
Pneumonia[g]	48 (13.6)	29 (8.3)
Urinary Tract Infection	30 (8.5)	19 (5.4)
Sinusitis	26 (7.4)	16 (4.6)
Skin and subcutaneous system disorders		
Rash[c]	75 (21.2)	33 (9.4)
Sweating Increased	35 (9.9)	25 (7.1)
Dry Skin	33 (9.3)	14 (4.0)
Pruritus	27 (7.6)	18 (5.1)
Metabolism and nutrition disorders		
Anorexia	55 (15.6)	34 (9.7)
Hypokalemia	48 (13.6)	21 (6.0)
Hypocalcemia	31 (8.8)	10 (2.9)
Appetite Decreased	24 (6.8)	14 (4.0)
Dehydration	23 (6.5)	15 (4.3)
Hypomagnesemia	24 (6.8)	10 (2.9)
Investigations		
Weight Decreased	69 (19.5)	52 (14.9)
Eye disorders		
Blurred vision	61 (17.3)	40 (11.4)
Vascular disorders		
Deep vein thrombosis[h]	33 (9.3)	15 (4.3)
Hypertension	28 (7.9)	20 (5.7)
Hypotension	25 (7.1)	15 (4.3)

Table 6: Grade 3/4 Adverse Reactions Reported in ≥2% Patients and With a ≥1% Difference in Proportion of Patients Between the REVLIMID/dexamethasone and Placebo/dexamethasone groups

System Organ Class/ Preferred Term	REVLIMID/Dex[#] (N=353) n (%)	Placebo/Dex[#] (N=350) n (%)
Blood and lymphatic system disorders		
Neutropenia[%]	118 (33.4)	12 (3.4)
Thrombocytopenia[@]	43 (12.2)	22 (6.3)
Anemia[@]	35 (9.9)	20 (5.7)
Leukopenia	14 (4.0)	1 (0.3)
Lymphopenia	10 (2.8)	4 (1.1)
Febrile Neutropenia[%]	8 (2.3)	0 (0.0)
General disorders and administration site conditions		
Fatigue	23 (6.5)	17 (4.9)
Vascular disorders		
Deep vein thrombosis[%]	29 (8.2)	12 (3.4)
Infections and infestations		
Pneumonia[@]	30 (8.5)	19 (5.4)
Urinary Tract Infection	5 (1.4)	1 (0.3)
Metabolism and nutrition disorders		
Hypokalemia	17 (4.8)	5 (1.4)
Hypocalcemia	13 (3.7)	6 (1.7)
Hypophosphatemia	9 (2.5)	0 (0.0)
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism[@]	14 (4.0)	3 (0.9)
Respiratory Distress[@]	4 (1.1)	0 (0.0)
Musculoskeletal and connective tissue disorders		
Muscle weakness	20 (5.7)	10 (2.9)
Gastrointestinal disorders		
Diarrhea[@]	11 (3.1)	4 (1.1)
Constipation	7 (2.0)	1 (0.3)
Nausea[@]	6 (1.7)	2 (0.6)
Cardiac disorders		
Atrial fibrillation[@]	13 (3.7)	4 (1.1)
Tachycardia	6 (1.7)	1 (0.3)
Cardiac Failure Congestive[@]	5 (1.4)	1 (0.3)
Nervous System disorders		
Syncope	10 (2.8)	3 (0.9)
Dizziness	7 (2.0)	3 (0.9)
Eye Disorders		
Cataract	6 (1.7)	1 (0.3)
Cataract Unilateral	5 (1.4)	0 (0.0)
Psychiatric Disorder		
Depression	10 (2.8)	6 (1.7)

Table 7: Serious Adverse Reactions Reported in ≥1% Patients and With a ≥1% Difference in Proportion of Patients Between the REVLIMID/dexamethasone and Placebo/dexamethasone Groups

System Organ Class/ Preferred Term	REVLIMID/Dex[&] (N=353) n (%)	Placebo/Dex[&] (N=350) n (%)
Blood and lymphatic system disorders		

System Organ Class/ Preferred Term	REVLIMID/Dex[A] (N=353) n (%)	Placebo/Dex[A] (N=350) n (%)
Febrile Neutropenia[%]	6 (1.7)	0 (0.0)
Vascular disorders		
Deep vein thrombosis[%]	26 (7.4)	11 (3.1)
Infections and infestations		
Pneumonia[@]	33 (9.3)	21 (6.0)
Respiratory, thoracic, and mediastinal disorders		
Pulmonary embolism[@]	13 (3.7)	3 (0.9)
Cardiac disorders		
Atrial fibrillation[@]	11 (3.1)	2 (0.6)
Cardiac Failure Congestive[@]	5 (1.4)	0 (0.0)
Nervous system disorders		
Cerebrovascular accident[@]	7 (2.0)	3 (0.9)
Gastrointestinal disorders		
Diarrhea [@]	6 (1.7)	2 (0.6)
Musculoskeletal and connective tissue disorders		
Bone Pain	4 (1.1)	0 (0.0)

For Tables 5, 6 and 7 above:
[@] - adverse reactions in which at least one resulted in a fatal outcome
[%] - adverse reactions in which at least one was considered to be life threatening (if the outcome of the reaction was death, it is included with death cases)
Median duration of exposure among patients treated with REVLIMID/dexamethasone was 44 weeks while median duration of exposure among patients treated with placebo/dexamethasone was 23 weeks. This should be taken into consideration when comparing frequency of adverse reactions between two treatment groups REVLIMID/dexamethasone vs. placebo/dexamethasone.

Venous and Arterial Thromboembolism [*see Boxed Warning, Warnings and Precautions (5.4)*]

Deep vein thrombosis (DVT) was reported as a serious (7.4%) or severe (8.2%) adverse drug reaction at a higher rate in the REVLIMID/dexamethasone group compared to 3.1 % and 3.4% in the placebo/dexamethasone group, respectively in the 2 studies in patients with at least 1 prior therapy with discontinuations due to DVT adverse reactions reported at comparable rates between groups. In the NDMM study, DVT was reported as an adverse reaction (all grades: 10.3%, 7.2%, 4.1%), as a serious adverse reaction (3.6%, 2.0%, 1.7%), and as a Grade 3/4 adverse reaction (5.6%, 3.7%, 2.8%) in the Rd Continuous, Rd18, and MPT Arms, respectively. Discontinuations and dose reductions due to DVT adverse reactions were reported at comparable rates between the Rd Continuous and Rd18 Arms (both <1%). Interruption of REVLIMID treatment due to DVT adverse reactions was reported at comparable rates between the Rd Continuous (2.3%) and Rd18 (1.5%) arms.

Pulmonary embolism (PE) was reported as a serious adverse drug reaction (3.7%) or Grade 3/4 (4.0%) at a higher rate in the REVLIMID/dexamethasone group compared to 0.9% (serious or grade 3/4) in the placebo/dexamethasone group in the 2 studies in patients with, at least 1 prior therapy, with discontinuations due to PE adverse reactions reported at comparable rates between groups. In the NDMM study, the frequency of adverse reactions of PE was similar between the Rd Continuous, Rd18, and MPT Arms for adverse reactions (all grades: 3.9%, 3.3%, and 4.3%, respectively), serious adverse reactions (3.8%, 2.8%, and 3.7%, respectively), and grade 3/4 adverse reactions (3.8%, 3.0%, and 3.7%, respectively).

Myocardial infarction was reported as a serious (1.7%) or severe (1.7%) adverse drug reaction at a higher rate in the REVLIMID/dexamethasone group compared to 0.6 % and 0.6% respectively in the placebo/dexamethasone group. Discontinuation due to MI (including acute) adverse reactions was 0.8% in REVLIMID/dexamethasone group and none in the placebo/dexamethasone group. In the NDMM study, myocardial infarction (including acute) was reported as an adverse reaction (all grades: 2.4%, 0.6%, and 1.1%), as a serious adverse reaction, (2.3%, 0.6%, and 1.1%), or as a severe adverse reaction (1.9%, 0.6%, and 0.9%) in the Rd Continuous, Rd18, and MPT Arms, respectively.

Stroke (CVA) was reported as a serious (2.3%) or severe (2.0%) adverse drug reaction in the REVLIMID/dexamethasone group compared to 0.9% and 0.9% respectively in the placebo/dexamethasone group. Discontinuation due to stroke (CVA) was 1.4% in REVLIMID/ dexamethasone group and 0.3% in the placebo/dexamethasone group. In the NDMM study, CVA was reported as an adverse reaction (all grades: 0.8%, 0.6%, and 0.6%), as a serious adverse reaction (0.8%, 0.6 %, and 0.6%), or as a severe adverse reaction (0.6%, 0.6%, 0.2%) in the Rd Continuous, Rd18, and MPT arms respectively.

Other Adverse Reactions: After At Least One Prior Therapy for MM

In these 2 studies, the following adverse drug reactions (ADRs) not described above that occurred at ≥1% rate and of at least twice of the placebo percentage rate were reported:

Blood and lymphatic system disorders: pancytopenia, autoimmune hemolytic anemia

Cardiac disorders: bradycardia, myocardial infarction, angina pectoris

Endocrine disorders: hirsutism

Eye disorders: blindness, ocular hypertension

Gastrointestinal disorders: gastrointestinal hemorrhage, glossodynia

General disorders and administration site conditions: malaise

Investigations: liver function tests abnormal, alanine aminotransferase increased

Nervous system disorders: cerebral ischemia

Psychiatric disorders: mood swings, hallucination, loss of libido

Reproductive system and breast disorders: erectile dysfunction

Respiratory, thoracic and mediastinal disorders: cough, hoarseness

Skin and subcutaneous tissue disorders: exanthem, skin hyperpigmentation

Myelodysplastic Syndromes:

A total of 148 patients received at least 1 dose of 10 mg REVLIMID in the del 5q MDS clinical study. At least one adverse event was reported in all of the 148 patients who were treated with the 10 mg starting dose of REVLIMID. The most frequently reported adverse events were related to blood and lymphatic system disorders, skin and subcutaneous tissue disorders, gastrointestinal disorders, and general disorders and administrative site conditions.

Thrombocytopenia (61.5%; 91/148) and neutropenia (58.8%; 87/148) were the most frequently reported adverse events. The next most common adverse events observed were diarrhea (48.6%; 72/148), pruritus (41.9%; 62/148), rash (35.8%; 53/148) and fatigue (31.1%; 46/148). Table 8 summarizes the adverse events that were reported in $\geq$ 5% of the REVLIMID treated patients in the del 5q MDS clinical study. Table 9 summarizes the most frequently observed Grade 3 and Grade 4 adverse reactions regardless of relationship to treatment with REVLIMID. In the single-arm studies conducted, it is often not possible to distinguish adverse events that are drug-related and those that reflect the patient's underlying disease.

Table 8: Summary of Adverse Events Reported in ≥5% of the REVLIMID Treated Patients in del 5q MDS Clinical Study

System organ class/Preferred term [a]	10 mg Overall (N=148)	
Patients with at least one adverse event	148	(100.0)
Blood and Lymphatic System Disorders		
Thrombocytopenia	91	(61.5)
Neutropenia	87	(58.8)
Anemia	17	(11.5)
Leukopenia	12	(8.1)
Febrile Neutropenia	8	(5.4)
Skin and Subcutaneous Tissue Disorders		
Pruritus	62	(41.9)
Rash	53	(35.8)
Dry Skin	21	(14.2)
Contusion	12	(8.1)
Night Sweats	12	(8.1)
Sweating Increased	10	(6.8)
Ecchymosis	8	(5.4)
Erythema	8	(5.4)
Gastrointestinal Disorders		
Diarrhea	72	(48.6)
Constipation	35	(23.6)
Nausea	35	(23.6)
Abdominal Pain	18	(12.2)
Vomiting	15	(10.1)
Abdominal Pain Upper	12	(8.1)
Dry Mouth	10	(6.8)
Loose Stools	9	(6.1)
Respiratory, Thoracic and Mediastinal Disorders		
Nasopharyngitis	34	(23.0)
Cough	29	(19.6)
Dyspnea	25	(16.9)
Pharyngitis	23	(15.5)
Epistaxis	22	(14.9)
Dyspnea Exertional	10	(6.8)
Rhinitis	10	(6.8)
Bronchitis	9	(6.1)
General Disorders and Administration Site Conditions		
Fatigue	46	(31.1)
Pyrexia	31	(20.9)
Edema Peripheral	30	(20.3)
Asthenia	22	(14.9)
Edema	15	(10.1)
Pain	10	(6.8)
Rigors	9	(6.1)
Chest Pain	8	(5.4)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	32	(21.6)
Back Pain	31	(20.9)
Muscle Cramp	27	(18.2)
Pain in Limb	16	(10.8)
Myalgia	13	(8.8)
Peripheral Swelling	12	(8.1)
Nervous System Disorders		
Dizziness	29	(19.6)
Headache	29	(19.6)
Hypoesthesia	10	(6.8)
Dysgeusia	9	(6.1)
Peripheral Neuropathy	8	(5.4)
Infections and Infestations		
Upper Respiratory Tract Infection	22	(14.9)
Pneumonia	17	(11.5)
Urinary Tract Infection	16	(10.8)
Sinusitis	12	(8.1)
Cellulitis	8	(5.4)
Metabolism and Nutrition Disorders		
Hypokalemia	16	(10.8)
Anorexia	15	(10.1)

Hypomagnesemia	9	(6.1)
Investigations		
Alanine Aminotransferase Increased	12	(8.1)
Psychiatric Disorders		
Insomnia	15	(10.1)
Depression	8	(5.4)
Renal and Urinary Disorders		
Dysuria	10	(6.8)
Vascular Disorders		
Hypertension	9	(6.1)
Endocrine Disorders		
Acquired Hypothyroidism	10	(6.8)
Cardiac Disorders		
Palpitations	8	(5.4)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Table 9: Most Frequently Observed Grade 3 and 4 Adverse Events [1] Regardless of Relationship to Study Drug Treatment

Preferred term [2]	10 mg (N=148)	
Patients with at least one Grade 3/4 AE	131	(88.5)
Neutropenia	79	(53.4)
Thrombocytopenia	74	(50.0)
Pneumonia	11	(7.4)
Rash	10	(6.8)
Anemia	9	(6.1)
Leukopenia	8	(5.4)
Fatigue	7	(4.7)
Dyspnea	7	(4.7)
Back Pain	7	(4.7)
Febrile Neutropenia	6	(4.1)
Nausea	6	(4.1)
Diarrhea	5	(3.4)
Pyrexia	5	(3.4)
Sepsis	4	(2.7)
Dizziness	4	(2.7)
Granulocytopenia	3	(2.0)
Chest Pain	3	(2.0)
Pulmonary Embolism	3	(2.0)
Respiratory Distress	3	(2.0)
Pruritus	3	(2.0)
Pancytopenia	3	(2.0)
Muscle Cramp	3	(2.0)
Respiratory Tract Infection	2	(1.4)
Upper Respiratory Tract Infection	2	(1.4)
Asthenia	2	(1.4)
Multi-organ Failure	2	(1.4)
Epistaxis	2	(1.4)
Hypoxia	2	(1.4)
Pleural Effusion	2	(1.4)
Pneumonitis	2	(1.4)
Pulmonary Hypertension	2	(1.4)
Vomiting	2	(1.4)
Sweating Increased	2	(1.4)
Arthralgia	2	(1.4)
Pain in Limb	2	(1.4)
Headache	2	(1.4)
Syncope	2	(1.4)

[1] Adverse events with frequency ≥1% in the 10 mg Overall group. Grade 3 and 4 are based on National Cancer Institute Common Toxicity Criteria version 2.
[2] Preferred Terms are coded using the MedDRA dictionary. A patient with multiple occurrences of an AE is counted only once in the Preferred Term category.

In other clinical studies of REVLIMID in MDS patients, the following serious adverse events (regardless of relationship to study drug treatment) not described in Table 8 or 9 were reported:

Blood and lymphatic system disorders: warm type hemolytic anemia, splenic infarction, bone marrow depression, coagulopathy, hemolysis, hemolytic anemia, refractory anemia

Cardiac disorders: cardiac failure congestive, atrial fibrillation, angina pectoris, cardiac arrest, cardiac failure, cardio-respiratory arrest, cardiomyopathy, myocardial infarction, myocardial ischemia, atrial fibrillation aggravated, bradycardia, cardiogenic shock, pulmonary edema, supraventricular arrhythmia, tachyarrhythmia, ventricular dysfunction

Ear and labyrinth disorders: vertigo

Endocrine disorders: Basedow's disease

Gastrointestinal disorders: gastrointestinal hemorrhage, colitis ischemic, intestinal perforation, rectal hemorrhage, colonic polyp, diverticulitis, dysphagia, gastritis, gastroenteritis, gastroesophageal reflux disease, obstructive inguinal hernia, irritable bowel syndrome, melena, pancreatitis due to biliary obstruction, pancreatitis, perirectal abscess, small intestinal obstruction, upper gastrointestinal hemorrhage

General disorders and administration site conditions: disease progression, fall, gait abnormal, intermittent pyrexia, nodule, rigors, sudden death

Hepatobiliary disorders: hyperbilirubinemia, cholecystitis, acute cholecystitis, hepatic failure

Immune system disorders: hypersensitivity

Infections and infestations infection bacteremia, central line infection, clostridial infection, ear infection, *Enterobacter* sepsis, fungal infection, herpes viral infection NOS, influenza, kidney infection, *Klebsiella* sepsis, lobar pneumonia, localized infection, oral infection, *Pseudomonas* infection, septic shock, sinusitis acute, sinusitis, *Staphylococcal* infection, urosepsis

Injury, poisoning and procedural complications: femur fracture, transfusion reaction, cervical vertebral fracture, femoral neck fracture, fractured pelvis, hip fracture, overdose, post procedural hemorrhage, rib fracture, road traffic accident, spinal compression fracture

Investigations: blood creatinine increased, hemoglobin decreased, liver function tests abnormal, troponin I increased

Metabolism and nutrition disorders: dehydration, gout, hypernatremia, hypoglycemia

Musculoskeletal and connective tissue disorders: arthritis, arthritis aggravated, gouty arthritis, neck pain, chondrocalcinosis pyrophosphate

Neoplasms benign, malignant and unspecified: acute leukemia, acute myeloid leukemia, bronchoalveolar carcinoma, lung cancer metastatic, lymphoma, prostate cancer metastatic

Nervous system disorders: cerebrovascular accident, aphasia, cerebellar infarction, cerebral infarction, depressed level of consciousness, dysarthria, migraine, spinal cord compression, subarachnoid hemorrhage, transient ischemic attack

Psychiatric disorders: confusional state

Renal and urinary disorders: renal failure, hematuria, renal failure acute, azotemia, calculus ureteric, renal mass

Reproductive system and breast disorders: pelvic pain

Respiratory, thoracic and mediastinal disorders: bronchitis, chronic obstructive airways disease exacerbated, respiratory failure, dyspnea exacerbated, interstitial lung disease, lung infiltration, wheezing

Skin and subcutaneous tissue disorders: acute febrile neutrophilic dermatosis

Vascular system disorders: deep vein thrombosis, hypotension, aortic disorder, ischemia, thrombophlebitis superficial, thrombosis

Mantle Cell Lymphoma:

In the MCL trial, a total of 134 patients received at least 1 dose of REVLIMID. Their median age was 67 (range 43-83) years, 128/134 (96%) were Caucasian, 108/134 (81%) were males and 82/134 (61%) had duration of MCL for at least 3 years.

Table 10 summarizes the most frequently observed adverse reactions regardless of relationship to treatment with REVLIMID. Across the 134 patients treated in this study, median duration of treatment was 95 days (1-1002 days). Seventy-eight patients (58%) received 3 or more cycles of therapy, 53 patients (40%) received 6 or more cycles, and 26 patients (19%) received 12 or more cycles. Seventy-six patients (57%) underwent at least one dose interruption due to adverse events, and 51 patients (38%) underwent at least one dose reduction due to adverse events. Twenty-six patients (19%) discontinued treatment due to adverse events.

Table 10: Incidence of Adverse Reactions (≥10%) or Grade 3 / 4 AE (in at least 2 patients) in Mantle Cell Lymphoma

System Organ Class/Preferred Term	All AEs[1] (N=134) n (%)	Grade 3/4 AEs[2] (N=134) n (%)
General disorders and administration site conditions		
Fatigue	45 (34)	9 (7)
Pyrexia[$]	31 (23)	3 (2)
Edema peripheral	21 (16)	0
Asthenia[$]	19 (14)	4 (3)
General physical health deterioration	3 (2)	2 (1)
Gastrointestinal disorders		
Diarrhea[$]	42 (31)	8 (6)
Nausea[$]	40 (30)	1 (<1)
Constipation	21 (16)	1 (<1)
Vomiting[$]	16 (12)	1 (<1)
Abdominal pain[$]	13 (10)	5 (4)
Musculoskeletal and connective tissue disorders		
Back pain	18 (13)	2 (1)
Muscle spasms	17 (13)	1 (<1)
Arthralgia	11 (8)	2 (1)
Muscular weakness[$]	8 (6)	2 (1)
Respiratory, thoracic and mediastinal disorders		
Cough	38 (28)	1 (<1)
Dyspnea[$]	24 (18)	8 (6)
Pleural Effusion	10 (7)	2 (1)
Hypoxia	3 (2)	2 (1)
Pulmonary embolism	3 (2)	2 (1)
Respiratory distress[$]	2 (1)	2 (1)

System Organ Class/Preferred Term	All AEs[1] (N=134) n (%)	Grade 3/4 AEs[2] (N=134) n (%)
Oropharyngeal pain	13 (10)	0
Infections and infestations		
Pneumonia[@ $]	19 (14)	12 (9)
Upper respiratory tract infection	17 (13)	0
Cellulitis[$]	3 (2)	2 (1)
Bacteremia[$]	2 (1)	2 (1)
Staphylococcal sepsis[$]	2 (1)	2 (1)
Urinary tract infection[$]	5 (4)	2 (1)
Skin and subcutaneous tissue disorders		
Rash [+]	30 (22)	2 (1)
Pruritus	23 (17)	1 (<1)
Blood and lymphatic system disorders		
Neutropenia	65 (49)	58 (43)
Thrombocytopenia[% $]	48 (36)	37 (28)
Anemia[$]	41 (31)	15 (11)
Leukopenia[$]	20 (15)	9 (7)
Lymphopenia	10 (7)	5 (4)
Febrile neutropenia[$]	8 (6)	8 (6)
Metabolism and nutrition disorders		
Decreased appetite	19 (14)	1 (<1)
Hypokalemia	17 (13)	3 (2)
Dehydration[$]	10 (7)	4 (3)
Hypocalcemia	4 (3)	2 (1)
Hyponatremia	3 (2)	3 (2)
Renal and urinary disorders		
Renal failure[$]	5 (4)	2 (1)
Vascular disorders		
Hypotension[@ $]	9 (7)	4 (3)
Deep vein thrombosis[$]	5 (4)	5 (4)
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Tumor flare	13 (10)	0
Squamous cell carcinoma of skin[$]	4 (3)	4 (3)
Investigations		
Weight decreased	17 (13)	0

[1]-MCL trial AEs – All treatment emergent AEs with ≥10% of subjects
[2]-MCL trial Grade 3/4 AEs – All treatment-emergent Grade 3/4 AEs in 2 or more subjects
[$]-MCL trial Serious AEs – All treatment-emergent SAEs in 2 or more subjects
[@]- AEs where at least one resulted in a fatal outcome
[%]- AEs where at least one was considered to be Life Threatening (if the outcome of the event was death, it is included with death cases)
[#]- All PTs under SOC of Infections except for rare infections of Public Health interest will be considered listed
[+]- All PTs under HLT of Rash will be considered listed

The following adverse events which have occurred in other indications and not described above have been reported (5%-10%) in patients treated with REVLIMID monotherapy for mantle cell lymphoma.

General disorders and administration site conditions: Chills
Musculoskeletal and connective tissue disorders: Pain in extremity
Nervous system disorders: Dysgeusia, headache, neuropathy peripheral
Infections and infestations: Respiratory tract infection, sinusitis, nasopharyngitis
Skin and subcutaneous tissue disorders: Dry skin, night sweats

The following serious adverse events not described above and reported in 2 or more patients treated with REVLIMID monotherapy for mantle cell lymphoma.

Respiratory, Thoracic, and Mediastinal Disorders: Chronic obstructive pulmonary disease
Infections and Infestations: *Clostridium difficile* colitis, sepsis
Neoplasms benign, malignant and unspecified (including cysts and polyps): Basal cell carcinoma
Cardiac Disorder: Supraventricular tachycardia

6.2 Postmarketing Experience

The following adverse drug reactions have been identified from the worldwide post-marketing experience with REVLIMID: Allergic conditions (angioedema, SJS, TEN), tumor lysis syndrome (TLS) and tumor flare reaction (TFR), pneumonitis, hepatic failure, including fatality, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis and transient abnormal liver laboratory tests. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure *[see Warnings and Precautions Section (5.7 to 5.10)]*.

Cases of hypothyroidism and hyperthyroidism have also been reported. Optimal control of thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.

7 DRUG INTERACTIONS

Results from human in vitro studies show that REVLIMID is neither metabolized by nor inhibits or induces the cytochrome P450 pathway suggesting that lenalidomide is not likely to cause or be subject to P450-based metabolic drug interactions.

7.1 Digoxin

When digoxin was co-administered with multiple doses of REVLIMID (10 mg/day) the digoxin C_{max} and $AUC_{0-\infty}$ were increased by 14%. Periodic monitoring of digoxin plasma levels, in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication, is recommended during administration of REVLIMID.

7.2 Concomitant Therapies That May Increase the Risk of Thrombosis

Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as estrogen containing therapies, should be used with caution after making a benefit-risk assessment in patients receiving REVLIMID *[see Warnings and Precautions (5.4)]*.

7.3 Warfarin

Co-administration of multiple dose REVLIMID (10 mg) with single dose warfarin (25 mg) had no effect on the pharmacokinetics of total lenalidomide or R- and S-warfarin. Expected changes in laboratory assessments of PT and INR were observed after warfarin administration, but these changes were not affected by concomitant REVLIMID administration. It is not known whether there is an interaction between dexamethasone and warfarin. Close monitoring of PT and INR is recommended in multiple myeloma patients taking concomitant warfarin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X *[see Boxed Warnings and Contraindications (4.1).]*

Risk Summary

REVLIMID can cause embryo-fetal harm when administered to a pregnant female and is contraindicated during pregnancy. REVLIMID is a thalidomide analogue.

Thalidomide is a human teratogen, inducing a high frequency of severe and life-threatening birth defects such as amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of bones, external ear abnormalities (including anotia, micropinna, small or absent external auditory canals), facial palsy, eye abnormalities (anophthalmos, microphthalmos), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations have also been documented and mortality at or shortly after birth has been reported in about 40% of infants.

Lenalidomide caused thalidomide-type limb defects in monkey offspring. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

If pregnancy does occur during treatment, immediately discontinue the drug. Under these conditions, refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure to REVLIMID must be reported to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436.

Animal data

In an embryo-fetal developmental toxicity study in monkeys, teratogenicity, including thalidomide-like limb defects, occurred in offspring when pregnant monkeys received oral lenalidomide during organogenesis. Exposure (AUC) in monkeys at the lowest dose was 0.17 times the human exposure at the maximum recommended human dose (MRHD) of 25 mg. Similar studies in pregnant rabbits and rats at 20 times and 200 times the MRHD respectively, produced embryo lethality in rabbits and no adverse reproductive effects in rats.

In a pre- and post-natal development study in rats, animals received lenalidomide from organogenesis through lactation. The study revealed a few adverse effects on the offspring of female rats treated with lenalidomide at doses up to 500 mg/kg (approximately 200 times the human dose of 25 mg based on body surface area). The male offspring exhibited slightly delayed sexual maturation and the female offspring had slightly lower body weight gains during gestation when bred to male offspring. As with thalidomide, the rat model may not adequately address the full spectrum of potential human embryo-fetal developmental effects for lenalidomide.

8.3 **Nursing Mothers**

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from lenalidomide, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 **Pediatric Use**

Safety and effectiveness in pediatric patients below the age of 18 have not been established.

8.5 **Geriatric Use**

REVLIMID has been used in multiple myeloma (MM) clinical trials in patients up to 91 years of age.

After At Least One Prior Therapy: Of the 703 MM patients who received study treatment in Studies 1 and 2, 45% were age 65 or over while 12% of patients were age 75 and over. The percentage of patients age 65 or over was not significantly different between the REVLIMID/dexamethasone and placebo/dexamethasone groups. Of the 353 patients who received REVLIMID/dexamethasone, 46% were age 65 and over. In both studies, patients > 65 years of age were more likely than patients ≤ 65 years of age to experience DVT, pulmonary embolism, atrial fibrillation, and renal failure following use of REVLIMID. No differences in efficacy were observed between patients over 65 years of age and younger patients.

NDMM: Overall, of the 1613 patients in the NDMM study who received study treatment, 94% (1521 /1613) were 65 years of age or older, while 35% (561/1613) were over 75 years of age. The percentage of patients over age 75 was similar between study arms (Rd Continuous: 33%; Rd18: 34%; MPT: 33%). Overall, across all treatment arms, the frequency in most of the AE categories (eg, all AEs, grade 3/4 AEs, serious AEs) was higher in older (> 75 years of age) than in younger (≤ 75 years of age) subjects. Grade 3 or 4 AEs in the General Disorders and Administration Site Conditions SOC were consistently reported at a higher frequency (with a difference of at least 5%) in older subjects than in younger subjects across all treatment arms. Grade 3 or 4 TEAEs in the Infections and Infestations, Cardiac Disorders (including cardiac failure and congestive cardiac failure), Skin and Subcutaneous Tissue Disorders, and Renal and Urinary Disorders (including renal failure) SOCs were also reported slightly, but consistently, more frequently (<5% difference), in older subjects than in younger subjects across all treatment arms. For other SOCs (e.g., Blood and Lymphatic System Disorders, Infections and Infestations, Cardiac Disorders, Vascular Disorders), there was a less consistent trend for increased frequency of grade 3/4 AEs in older vs younger subjects across all treatment arms Serious AEs were generally reported at a higher frequency in the older subjects than in the younger subjects across all treatment arms.

REVLIMID has been used in del 5q MDS clinical trials in patients up to 95 years of age.

Of the 148 patients with del 5q MDS enrolled in the major study, 38% were age 65 and over, while 33% were age 75 and over. Although the overall frequency of adverse events (100%) was the same in patients over 65 years of age as in younger patients, the frequency of serious adverse events was higher in patients over 65 years of age than in younger patients (54% vs. 33%). A greater proportion of patients over 65 years of age discontinued from the clinical studies because of adverse events than the proportion of younger patients (27% vs.16%). No differences in efficacy were observed between patients over 65 years of age and younger patients.

REVLIMID has been used in a mantle cell lymphoma (MCL) clinical trial in patients up to 83 years of age. Of the 134 patients with MCL enrolled in the MCL trial, 63% were age 65 and over, while 22% of patients were age 75 and over. The overall frequency of adverse events was similar in patients over 65 years of age and in younger patients (98% vs. 100%). The overall incidence of grade 3 and 4 adverse events was also similar in these 2 patient groups (79% vs. 78%, respectively). The frequency of serious adverse events was higher in patients over 65 years of age than in younger patients (55% vs. 41%). No differences in efficacy were observed between patients over 65 years of age and younger patients.

Since elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Monitor renal function.

8.6 **Females of Reproductive Potential and Males**

REVLIMID can cause fetal harm when administered during pregnancy *[see Use in Specific Populations (8.1)]*. Females of reproductive potential must avoid pregnancy 4 weeks before therapy, while taking REVLIMID, during dose interruptions and for at least 4 weeks after completing therapy.

Females
Females of reproductive potential must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control simultaneously (one highly effective form of contraception – tubal ligation, IUD, hormonal (birth control pills, injections, hormonal patches, vaginal rings or implants) or partner's vasectomy and one additional effective contraceptive method – male latex or synthetic condom, diaphragm or cervical cap. Contraception must begin 4 weeks prior to initiating treatment with REVLIMID, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of REVLIMID therapy. Reliable contraception is indicated even where

there has been a history of infertility, unless due to hysterectomy. Females of reproductive potential should be referred to a qualified provider of contraceptive methods, if needed.

Females of reproductive potential must have 2 negative pregnancy tests before initiating REVLIMID. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing REVLIMID. Once treatment has started and during dose interruptions, pregnancy testing for females of reproductive potential should occur weekly during the first 4 weeks of use, then pregnancy testing should be repeated every 4 weeks in females with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her menstrual bleeding. REVLIMID treatment must be discontinued during this evaluation.

Males
Lenalidomide is present in the semen of males who take REVLIMID. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID, during dose interruptions and for up to 28 days after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate sperm

8.7 **Renal Impairment**

Since lenalidomide is primarily excreted unchanged by the kidney, adjustments to the starting dose of REVLIMID are recommended to provide appropriate drug exposure in patients with moderate (CLcr 30-60 mL/min) or severe renal impairment (CLcr < 30 mL/min) and in patients on dialysis *[see Dosage and Administration (2.4)]*.

8.8 **Hepatic Impairment**

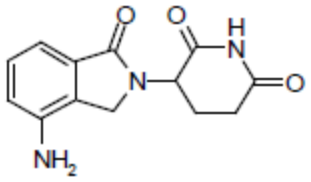
No dedicated study has been conducted in patients with hepatic impairment. The elimination of unchanged lenalidomide is predominantly by the renal route.

10 OVERDOSAGE

There is no specific experience in the management of lenalidomide overdose in patients with MM, MDS, or MCL. In dose-ranging studies in healthy subjects, some were exposed to up to 200 mg (administered 100 mg BID) and in single-dose studies, some subjects were exposed to up to 400 mg. Pruritus, urticaria, rash, and elevated liver transaminases were the primary reported AEs. In clinical trials, the dose-limiting toxicity was neutropenia and thrombocytopenia.

11 DESCRIPTION

REVLIMID, a thalidomide analogue, is an immunomodulatory agent with antiangiogenic and antineoplastic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:



3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione

The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3.

Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

REVLIMID is available in 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg and 25 mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The 5 mg and 25 mg capsule shell contains gelatin, titanium dioxide and black ink. The 2.5 mg and 10 mg capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide and black ink. The 15 mg capsule shell contains gelatin, FD&C blue #2, titanium dioxide and black ink. The 20 mg capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide and black ink.

12 CLINICAL PHARMACOLOGY

12.1 **Mechanism of Action**

Lenalidomide is an analogue of thalidomide with immunomodulatory, antiangiogenic, and antineoplastic properties. Lenalidomide inhibits proliferation and induces apoptosis of certain hematopoietic tumor cells including multiple myeloma, mantle cell lymphoma, and del (5q) myelodysplastic syndromes *in vitro*. Lenalidomide causes a delay in tumor growth in some *in vivo* nonclinical hematopoietic tumor models including multiple myeloma. Immunomodulatory properties of lenalidomide include activation of T cells and natural killer (NK) cells, increased numbers of NKT cells, and inhibition of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. In multiple myeloma cells, the combination of lenalidomide and dexamethasone synergizes the inhibition of cell proliferation and the induction of apoptosis.

12.2 **Pharmacodynamics**

The effect of lenalidomide on the QTc interval was evaluated in 60 healthy male subjects in a randomized, thorough QT study with placebo and positive controls. At a dose two times the maximum recommended dose, lenalidomide does not prolong the QTc interval to any clinically relevant extent. The largest upper bound of the 2-sided 90% CI for the mean differences between lenalidomide and placebo was below 10 ms.

12.3 **Pharmacokinetics**

Absorption

Lenalidomide is rapidly absorbed following oral administration. Following single and multiple doses of REVLIMID in patients with MM or MDS the maximum plasma concentrations occurred between 0.5 and 6 hours post-dose. The single and multiple dose pharmacokinetic disposition of lenalidomide is linear with AUC and C_{max} values increasing proportionally with dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

Systemic exposure (AUC) of lenalidomide in MM and MDS patients with normal or mild renal function (CLcr ≥ 60 mL/min) is approximately 60% higher as compared to young healthy male subjects.

Administration of a single 25 mg dose of REVLIMID with a high-fat meal in healthy subjects reduces the extent of absorption, with an approximate 20% decrease in AUC and 50% decrease in C_{max}. In the trials where the efficacy and safety were established for REVLIMID, the drug was administered without regard to food intake. REVLIMID can be administered with or without food.

Population pharmacokinetic analyses show that the oral absorption rate of lenalidomide in patients with MCL is similar to that observed in patients with MM or MDS.

Distribution

In vitro (^{14}C)-lenalidomide binding to plasma proteins is approximately 30%.

Lenalidomide is present in semen at 2 hours (1379 ng/ejaculate) and 24 hours (35 ng/ejaculate) after the administration of REVLIMID 25 mg daily.

Metabolism

Lenalidomide -undergoes limited metabolism. Unchanged lenalidomide is the predominant circulating component in humans. Two identified metabolites are 5-hydroxy-lenalidomide and N-acetyl-lenalidomide; each constitutes less than 5% of parent levels in circulation.

Elimination

Elimination is primarily renal. Following a single oral administration of [^{14}C]-lenalidomide (25 mg) to healthy subjects, approximately 90% and 4% of the radioactive dose is eliminated within ten days in urine and feces, respectively. Approximately 82% of the radioactive dose is excreted as lenalidomide in the urine within 24 hours. Hydroxy-lenalidomide and N-acetyl-lenalidomide represent 4.59% and 1.83% of the excreted dose, respectively. The renal clearance of lenalidomide exceeds the glomerular filtration rate.

The mean half-life of lenalidomide is 3 hours in healthy subjects and 3 to 5 hours in patients with MM, MDS or MCL.

Drug Interactions

Co-administration of single or multiple doses of dexamethasone (40 mg) has no clinically relevant effect on the multiple dose pharmacokinetics of REVLIMID (25 mg).

In vitro, lenalidomide is a substrate, but is not an inhibitor of P-glycoprotein (P-gp). In healthy volunteers, co-administration of REVLIMID (25 mg) after multiple doses of a P-gp inhibitor such as quinidine (600 mg twice daily) does not result in a clinically significant increase in the Cmax and AUC of REVLIMID. In healthy volunteers, co-administration of the P-gp inhibitor/substrate, temsirolimus (25 mg), with REVLIMID (25 mg) does not significantly alter the pharmacokinetics of REVLIMID, temsirolimus, or its metabolite, sirolimus.

In vitro studies demonstrated that REVLIMID is not a substrate of human breast cancer resistance protein (BCRP), multidrug resistance protein (MRP) transporters MRP1, MRP2, or MRP3, organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptide 1B1 (OATP1B1 or OATP2), organic cation transporters (OCT) OCT1 and OCT2, multidrug and toxin extrusion protein (MATE) MATE1, and organic cation transporters novel (OCTN) OCTN1 and OCTN2. Lenalidomide is not an inhibitor of bile salt export pump (BSEP), BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2. Lenalidomide does not inhibit bilirubin glucuronidation formation in human liver microsomes with UGT1A1 genotyped as UGT1A1*1/*1, UGT1A1*1/*28, and UGT1A1*28/*28.

Specific Populations

Patients with Renal Impairment: The pharmacokinetics of lenalidomide were studied in patients with renal impairment due to nonmalignant conditions. In this study, 5 patients with mild renal impairment (creatinine clearance 57-74 mL/min), 6 patients with moderate renal impairment (creatinine clearance 33-46 mL/min), 6 patients with severe renal impairment (creatinine clearance 17-29 mL/min), and 6 patients with end stage renal disease requiring dialysis were administered a single oral 25-mg dose of REVLIMID. As a control group comparator, 7 healthy subjects of similar age with normal renal function (creatinine clearance 83-145 mL/min) were also administered a single oral 25-mg dose of REVLIMID. As creatinine clearance decreased from mild to severe impairment, half-life increased and drug clearance decreased linearly. Patients with moderate and severe renal impairment had a 3-fold increase in half-life and a 66% to 75% decrease in drug clearance compared to healthy subjects. Patients on hemodialysis (n=6) given a single, 25-mg dose of lenalidomide has an approximate 4.5-fold increase in half-life and an 80% decrease in drug clearance compared to healthy subjects. Approximately 30% of the drug in body was removed during a 4-hour hemodialysis session.

In MM patients, those patients with mild renal impairment had an AUC 56% greater than those with normal renal function.

Adjustment of the starting dose of REVLIMID is recommended in patients with moderate or severe (CLcr < 60 mL/min) renal impairment and in patients on dialysis *[see Dosage and Administration (2.4)]*.

Elderly Patients: No dedicated clinical studies have been conducted to evaluate pharmacokinetics of lenalidomide in the elderly. Population pharmacokinetic analyses included patients with ages ranging from 39 to 85 years old and show that age does not influence the disposition of lenalidomide.

Patients with Hepatic Disease: Population pharmacokinetic analyses included patients with mild hepatic impairment (N = 16, total bilirubin >1 to ≤ 1.5 x ULN or AST > ULN) and show that mild hepatic impairment does not influence the disposition of lenalidomide. There are no data available for patients with moderate to severe hepatic impairment.

Pediatric: No pharmacokinetic data are available in patients below the age of 18 years.

Other Intrinsic Factors: Population pharmacokinetic analyses show that body weight (33-135 kg), gender, race, and type of hematological malignancies (MM, MDS or MCL) do not have a clinically relevant effect on lenalidomide clearance in adult patients.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with lenalidomide have not been conducted.

Lenalidomide was not mutagenic in the bacterial reverse mutation assay (Ames test) and did not induce chromosome aberrations in cultured human peripheral blood lymphocytes, or mutations at the thymidine kinase (tk) locus of mouse lymphoma L5178Y cells. Lenalidomide did not increase morphological transformation in Syrian Hamster Embryo assay or induce micronuclei in the polychromatic erythrocytes of the bone marrow of male rats.

A fertility and early embryonic development study in rats, with administration of lenalidomide up to 500 mg/kg (approximately 200 times the human dose of 25 mg, based on body surface area) produced no parental toxicity and no adverse effects on fertility.

14 CLINICAL STUDIES

14.1 Multiple Myeloma

Randomized, Open-Label Clinical Trial in Patients with Newly Diagnosed Multiple Myeloma:

A randomized multicenter, open-label, 3-arm trial of 1,623 patients, was conducted to compare the efficacy and safety of REVLIMID and low-dose dexamethasone (Rd) given for 2 different durations of time to that of melphalan, prednisone and thalidomide (MPT) in newly diagnosed multiple myeloma patients who were not a candidate for stem cell transplant. In the first arm of the study, Rd was given continuously until progressive disease [Arm Rd Continuous]. In the second arm, Rd was given for up to eighteen 28-day cycles [72 weeks, Arm Rd18]). In the third arm, melphalan, prednisone and thalidomide (MPT) was given for a maximum of twelve 42-day cycles (72 weeks). For the purposes of this study, a patient who was < 65 years of age was not a candidate for SCT if the patient refused to undergo SCT therapy or the patient did not have access to SCT due to cost or other reasons. Patients were stratified at randomization by age (≤75 versus >75 years), stage (ISS Stages I and II versus Stage III), and country.

Patients in the Rd Continuous and Rd18 arms received REVLIMID 25 mg once daily on Days 1 to 21 of 28-day cycles. Dexamethasone was dosed 40 mg once daily on Days 1, 8, 15, and 22 of each 28-day cycle. For patients over > 75 years old, the starting dose of dexamethasone was 20 mg orally once daily on days 1,8,15, and 22 of repeated 28-day cycles. Initial dose and regimens for Rd Continuous and Rd18 were adjusted according to age and renal function. All patients received prophylactic anticoagulation with the most commonly used being aspirin.

The demographics and disease-related baseline characteristics of the patients were balanced among the 3 arms. In general, study subjects had advanced-stage disease. Of the total study population, the median age was 73 in the 3 arms with 35% of total patients > 75 years of age; 59% had ISS Stage I/II; 41% had ISS stage III; 9% had severe renal impairment (creatinine clearance [CLcr] < 30 mL/min); 23% had moderate renal impairment (CLcr > 30 to 50 mL/min; 44% had mild renal impairment (CLcr > 50 to 80 mL/min). For ECOG Performance Status, 29% were Grade 0, 49% Grade 1, 21% Grade 2, 0.4% ≥ Grade 3.

The primary efficacy endpoint, PFS, was defined as the time from randomization to the first documentation of disease progression as determined by Independent Response Adjudication Committee (IRAC), based on International Myeloma Working Group [IMWG] criteria or death due to any cause, whichever occurred first during the study until the end of the PFS follow-up phase. For the efficacy analysis of all endpoints, the primary comparison was between Rd Continuous and MPT arms. The efficacy results are summarized in the table below. PFS was significantly longer with Rd Continuous than MPT: HR 0.72 (95% CI: 0.61-0.85 p <0.0001). A lower percentage of subjects in the Rd Continuous arm compared with the MPT arm had PFS events (52% versus 61%, respectively). The improvement in median PFS time in the Rd Continuous arm compared with the MPT arm was 4.3 months. The myeloma response rate was higher with Rd Continuous compared with MPT (75.1% versus 62.3%); with a complete response in 15.1% of Rd Continuous arm patients versus 9.3% in the MPT arm. The median time to first response was 1.8 months in the Rd Continuous arm versus 2.8 months in the MPT arm.

For the interim OS analysis with 03 March 2014 data cutoff, the median follow-up time for all surviving patients is 45.5 months, with 697 death events, representing 78% of prespecified events required for the planned final OS analysis (697/896 of the final OS events). The observed OS HR was 0.75 for Rd Continuous versus MPT (95% CI = 0.62, 0.90).

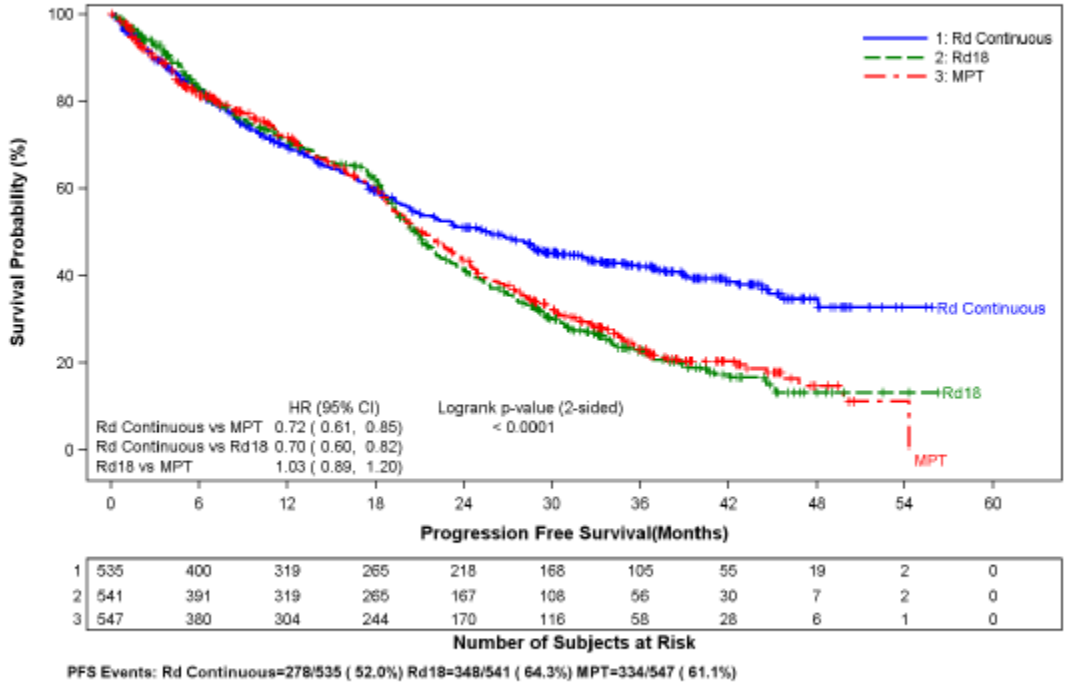
Table 11: Overview of Efficacy Results – Study MM-020 (Intent-to-treat Population)

	Rd Continuous (N = 535)	Rd18 (N = 541)	MPT (N = 547)
PFS – IRAC (months)[g]			
Number of PFS events	278 (52.0)	348 (64.3)	334 (61.1)
Median[a] PFS time, months (95% CI)[b]	25.5 (20.7, 29.4)	20.7 (19.4, 22.0)	21.2 (19.3, 23.2)
HR [95% CI][c]; p-value[d]			
Rd Continuous vs MPT	0.72 (0.61, 0.85); <0.0001		
Rd Continuous vs Rd18	0.70 (0.60, 0.82)		
Rd18 vs MPT	1.03 (0.89, 1.20)		
Overall Survival (months)[h]			
Number of Death events	208 (38.9)	228 (42.1)	261 (47.7)
Median[a] OS time, months (95% CI)[b]	58.9 (56.0, NE)[f]	56.7 (50.1, NE)	48.5 (44.2, 52.0)
HR [95% CI][c]			
Rd Continuous vs MPT	0.75 (0.62, 0.90)		
Rd Continuous vs Rd18	0.91 (0.75, 1.09)		
Rd18 vs MPT	0.83 (0.69, 0.99)		
Response Rate[e] – IRAC, n (%)[g]			
CR	81 (15.1)	77 (14.2)	51 (9.3)
VGPR	152 (28.4)	154 (28.5)	103 (18.8)
PR	169 (31.6)	166 (30.7)	187 (34.2)
Overall response: CR, VGPR, or PR	402 (75.1)	397 (73.4)	341 (62.3)

CR = complete response; d = low-dose dexamethasone; HR = hazard ratio; IRAC = Independent Response Adjudication Committee; M = melphalan; NE = not estimable; OS = overall survival; P = prednisone; PFS = progression-free survival; PR = partial response; R = lenalidomide; Rd Continuous = Rd given until documentation of progressive disease; Rd18 = Rd given for ≤ 18 cycles; T = thalidomide; VGPR = very good partial response; vs = versus.

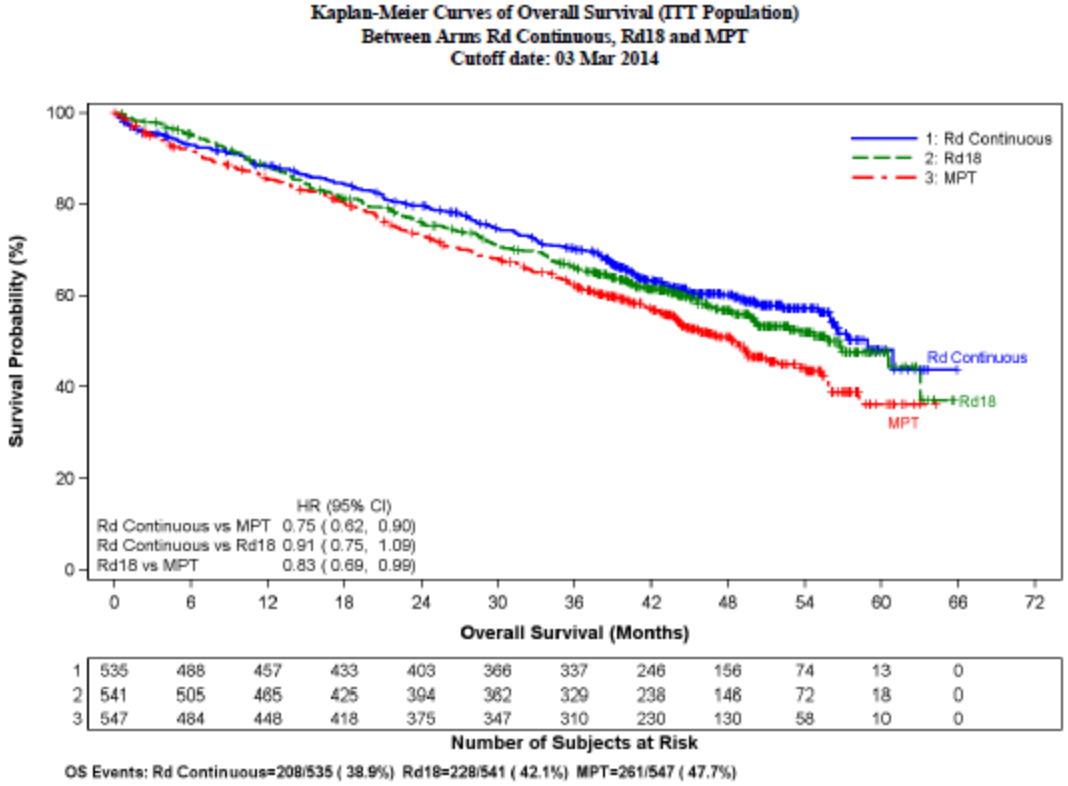
[a] The median is based on the Kaplan-Meier estimate.
[b] The 95% Confidence Interval (CI) about the median.
[c] Based on Cox proportional hazards model comparing the hazard functions associated with the indicated treatment arms.
[d] The p-value is based on the unstratified log-rank test of Kaplan-Meier curve differences between the indicated treatment arms.
[e] Best assessment of response during the treatment phase of the study
[f] Including patients with no response assessment data or whose only assessment was "response not evaluable."
[g] Data cutoff date = 24 May 2013.
[h] Data cutoff date = 3 March 2014.

Kaplan-Meier Curves of Progression-free Survival Based on IRAC Assessment (ITT Population)
Between Arms Rd Continuous, Rd18 and MPT
Cutoff date: 24 May 2013



PFS Events: Rd Continuous=278/535 (52.0%) Rd18=348/541 (64.3%) MPT=334/547 (61.1%)

CI = confidence interval; d = low-dose dexamethasone; HR = hazard ratio; IRAC = Independent Response Adjudication Committee; M = melphalan; P = prednisone; R = lenalidomide; Rd Continuous = Rd given until documentation of progressive disease; Rd18 = Rd given for ≤ 18 cycles; T = thalidomide.



CI = confidence interval; d = low-dose dexamethasone; HR = hazard ratio; M = melphalan; P = prednisone; R = lenalidomide; Rd Continuous = Rd given until documentation of progressive disease; Rd18 = Rd given for ≤18 cycles; T = thalidomide.

Randomized, Open-Label Clinical Studies in Patients with Previously Treated Multiple Myeloma

Two randomized studies (Studies 1 and 2) were conducted to evaluate the efficacy and safety of REVLIMID. These multicenter, multinational, double-blind, placebo-controlled studies compared REVLIMID plus oral pulse high-dose dexamethasone therapy to dexamethasone therapy alone in patients with multiple myeloma who had received at least one prior treatment. These studies enrolled patients with absolute neutrophil counts (ANC) ≥ 1000/mm^3, platelet counts ≥ 75,000/mm^3, serum creatinine ≤ 2.5 mg/dL, serum SGOT/AST or SGPT/ALT ≤ 3 x upper limit of normal (ULN), and serum direct bilirubin ≤ 2 mg/dL.

In both studies, patients in the REVLIMID/dexamethasone group took 25 mg of REVLIMID orally once daily on Days 1 to 21 and a matching placebo capsule once daily on Days 22 to 28 of each 28-day cycle. Patients in the placebo/dexamethasone group took 1 placebo capsule on Days 1 to 28 of each 28-day cycle. Patients in both treatment groups took 40 mg of dexamethasone orally once daily on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy.

The dose of dexamethasone was reduced to 40 mg orally once daily on Days 1 to 4 of each 28-day cycle after the first 4 cycles of therapy. In both studies, treatment was to continue until disease progression.

In both studies, dose adjustments were allowed based on clinical and laboratory findings. Sequential dose reductions to 15 mg daily, 10 mg daily and 5 mg daily were allowed for toxicity [*see Dosage and Administration (2.1)*].

Table 12 summarizes the baseline patient and disease characteristics in the two studies. In both studies, baseline demographic and disease-related characteristics were comparable between the REVLIMID/dexamethasone and placebo/dexamethasone groups.

Table 12: Baseline Demographic and Disease-Related Characteristics – Studies 1 and 2

	Study 1		Study 2	
	REVLIMID/Dex N=177	**Placebo/Dex N=176**	**REVLIMID/Dex N=176**	**Placebo/Dex N=175**
Patient Characteristics				
Age (years) Median Min, Max	 64 36, 86	 62 37, 85	 63 33, 84	 64 40, 82
Sex Male Female	 106 (60%) 71 (40%)	 104 (59%) 72 (41%)	 104 (59%) 72 (41%)	 103 (59%) 72 (41%)
Race/Ethnicity White Other	 141(80%) 36 (20%)	 148 (84%) 28 (16%)	 172 (98%) 4 (2%)	 175(100%) 0 (0%)
ECOG Performance Status 0-1	157 (89%)	168 (95%)	150 (85%)	144 (82%)
Disease Characteristics				
Multiple Myeloma Stage (Durie-Salmon) I II III	 3% 32% 64%	 3% 31% 66%	 6% 28% 65%	 5% 33% 63%
B2-microglobulin (mg/L) ≤ 2.5 mg/L > 2.5 mg/L	 52 (29%) 125 (71%)	 51 (29%) 125 (71%)	 51 (29%) 125 (71%)	 48 (27%) 127 (73%)
Number of Prior Therapies				
1 ≥ 2	38% 62%	38% 62%	32% 68%	33% 67%
Types of Prior Therapies				
Stem Cell Transplantation	62%	61%	55%	54%
Thalidomide	42%	46%	30%	38%
Dexamethasone	81%	71%	66%	69%
Bortezomib	11%	11%	5%	4%
Melphalan	33%	31%	56%	52%
Doxorubicin	55%	51%	56%	57%

The primary efficacy endpoint in both studies was time to progression (TTP). TTP was defined as the time from randomization to the first occurrence of progressive disease.

Preplanned interim analyses of both studies showed that the combination of REVLIMID/dexamethasone was significantly superior to dexamethasone alone for TTP. The studies were unblinded to allow patients in the placebo/dexamethasone group to receive treatment with the REVLIMID/dexamethasone combination. For both studies, the extended follow-up survival data with crossovers were analyzed. In study 1, the median survival time was 39.4 months (95%CI: 32.9, 47.4) in REVLIMID/dexamethasone group and 31.6 months (95%CI: 24.1, 40.9) in placebo/dexamethasone group, with a hazard ratio of 0.79 (95% CI: 0.61-1.03). In study 2, the median survival time was 37.5 months (95%CI: 29.9, 46.6) in REVLIMID/dexamethasone group and 30.8 months (95%CI: 23.5, 40.3) in placebo/dexamethasone group, with a hazard ratio of 0.86 (95% CI: 0.65-1.14).

Table 13: TTP Results in Study 1 and Study 2

	Study 1		Study 2	
	REVLIMID/Dex N=177	Placebo/Dex N=176	REVLIMID/Dex N=176	Placebo/Dex N=175
TTP				
Events n (%)	73 (41)	120 (68)	68 (39)	130 (74)
Median TTP in months [95% CI]	13.9 [9.5, 18.5]	4.7 [3.7, 4.9]	12.1 [9.5, NE]	4.7 [3.8, 4.8]
Hazard Ratio [95% CI]	0.285 [0.210, 0.386]		0.324 [0.240, 0.438]	
Log-rank Test p-value [3]	<0.001		<0.001	
Response				
Complete Response (CR) n (%)	23 (13)	1 (1)	27 (15)	7 (4)
Partial Response (RR/PR) n (%)	84 (48)	33 (19)	77 (44)	34 (19)
Overall Response n (%)	107 (61)	34 (19)	104 (59)	41 (23)
p-value	<0.001		<0.001	
Odds Ratio [95% CI]	6.38 [3.95, 10.32]		4.72 [2.98, 7.49]	

Figure 1: Kaplan-Meier Estimate of Time to Progression — Study 1

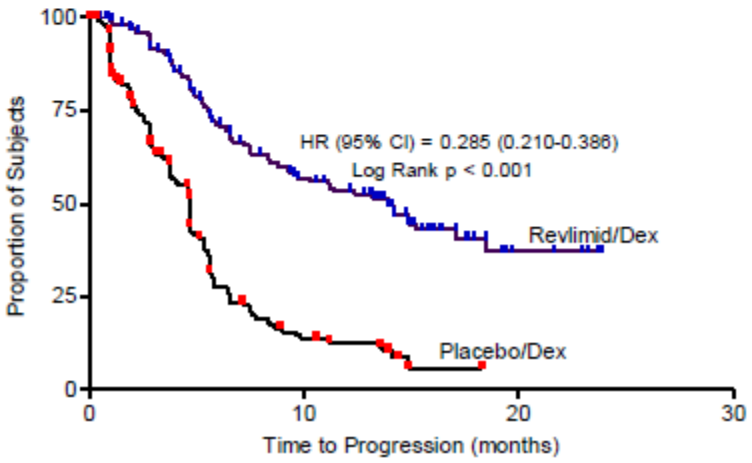
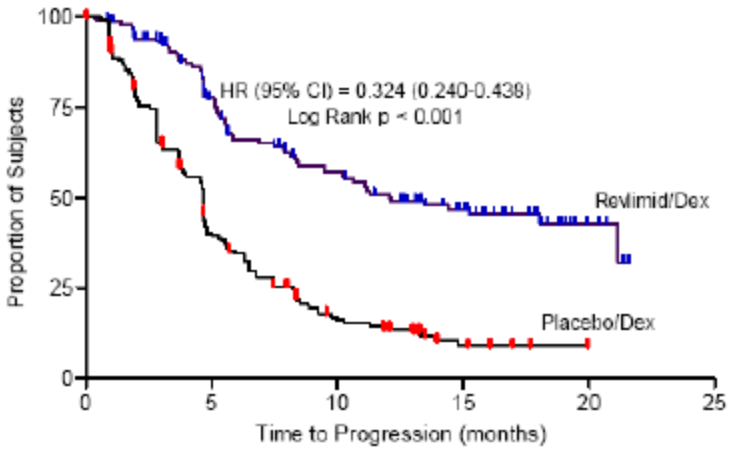


Figure 2: Kaplan-Meier Estimate of Time to Progression — Study 2



14.2 Myelodysplastic Syndromes (MDS) with a Deletion 5q Cytogenetic Abnormality

The efficacy and safety of REVLIMID were evaluated in patients with transfusion-dependent anemia in low- or intermediate-1- risk MDS with a 5q (q31-33) cytogenetic abnormality in isolation or with additional cytogenetic abnormalities, at a dose of 10 mg once daily or 10 mg once daily for 21 days every 28 days in an open-label, single-arm, multi-center study. The major study was not designed nor powered to prospectively compare the efficacy of the 2 dosing regimens. Sequential dose reductions to 5 mg daily and 5 mg every other day, as well as dose delays, were allowed for toxicity *[Dosage and Administration (2.2)]*.

This major study enrolled 148 patients who had RBC transfusion dependent anemia. RBC transfusion dependence was defined as having received ≥ 2 units of RBCs within 8 weeks prior to study treatment. The study enrolled patients with absolute neutrophil counts (ANC) ≥ 500/mm^3, platelet counts ≥ 50,000/mm^3, serum creatinine ≤ 2.5 mg/dL, serum SGOT/AST or SGPT/ALT ≤ 3 x upper limit of normal (ULN), and serum direct bilirubin ≤ 2 mg/dL. Granulocyte colony-stimulating factor was permitted for patients who developed neutropenia or fever in association with neutropenia. Baseline patient and disease-related characteristics are summarized in Table 14.

Table 14: Baseline Demographic and Disease-Related Characteristics in the MDS Study

	Overall (N=148)	
Age (years)		
Median	71.0	
Min, Max	37.0, 95.0	
Gender	**n**	**(%)**
Male	51	(34.5)
Female	97	(65.5)
Race	**n**	**(%)**
White	143	(96.6)
Other	5	(3.4)
Duration of MDS (years)		
Median	2.5	
Min, Max	0.1, 20.7	
Del 5 (q31-33) Cytogenetic Abnormality	**n**	**(%)**
Yes	148	(100.0)
Other cytogenetic abnormalities	37	(25.2)
IPSS Score [a]	**n**	**(%)**
Low (0)	55	(37.2)
Intermediate-1 (0.5-1.0)	65	(43.9)
Intermediate-2 (1.5-2.0)	6	(4.1)
High (≥2.5)	2	(1.4)
Missing	20	(13.5)
FAB Classification [b] from central review	**n**	**(%)**
RA	77	(52.0)
RARS	16	(10.8)
RAEB	30	(20.3)
CMML	3	(2.0)

[a] IPSS Risk Category: Low (combined score = 0), Intermediate-1 (combined score = 0.5 to 1.0),

Intermediate-2 (combined score = 1.5 to 2.0), High (combined score ≥ 2.5); Combined score = (Marrow blast score + Karyotype score + Cytopenia score)
[b] French-American-British (FAB) classification of MDS.

The frequency of RBC transfusion independence was assessed using criteria modified from the International Working Group (IWG) response criteria for MDS. RBC transfusion independence was defined as the absence of any RBC transfusion during any consecutive "rolling" 56 days (8 weeks) during the treatment period.

Transfusion independence was seen in 99/148 (67%) patients (95% CI [59, 74]). The median duration from the date when RBC transfusion independence was first declared (i.e., the last day of the 56-day RBC transfusion-free period) to the date when an additional transfusion was received after the 56-day transfusion-free period among the 99 responders was 44 weeks (range of 0 to >67 weeks). Ninety percent of patients who achieved a transfusion benefit did so by completion of three months in the study.

RBC transfusion independence rates were unaffected by age or gender.

The dose of REVLIMID was reduced or interrupted at least once due to an adverse event in 118 (79.7%) of the 148 patients; the median time to the first dose reduction or interruption was 21 days (mean, 35.1 days; range, 2-253 days), and the median duration of the first dose interruption was 22 days (mean, 28.5 days; range, 2-265 days). A second dose reduction or interruption due to adverse events was required in 50 (33.8%) of the 148 patients. The median interval between the first and second dose reduction or interruption was 51 days (mean, 59.7 days; range, 15-205 days) and the median duration of the second dose interruption was 21 days (mean, 26 days; range, 2-148 days).

14.3 Mantle Cell Lymphoma

A multicenter, single-arm, open-label trial of single-agent lenalidomide was conducted to evaluate the safety and efficacy of lenalidomide in patients with mantle cell lymphoma who have relapsed after or were refractory to bortezomib or a bortezomib-containing regimen. Patients with a creatinine clearance ≥60 mL/min were given lenalidomide at a dose of 25 mg once daily for 21 days every 28 days. Patients with a creatinine clearance ≥30 mL/min and <60 mL/min were given lenalidomide at a dose of 10 mg once daily for 21 days every 28 days. Treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent.

The trial included patients who were at least 18 years of age with biopsy-proven MCL with measurable disease by CT scan. Patients were required to have received prior treatment with an anthracycline or mitoxantrone, cyclophosphamide, rituximab, and bortezomib, alone or in combination. Patients were required to have documented refractory disease (defined as without any response of PR or better during treatment with bortezomib or a bortezomib-containing regimen), or relapsed disease (defined as progression within one year after treatment with bortezomib or a bortezomib-containing regimen). At enrollment patients were to have an absolute neutrophil counts (ANC) ≥1500/ mm^3, platelet counts ≥ 60,000/mm^3, serum SGOT/AST or SGPT/ALT ≤3x upper limit of normal (ULN) unless there was documented evidence of liver involvement by lymphoma, serum total bilirubin ≤1.5 x ULN except in cases of Gilbert's syndrome or documented liver involvement by lymphoma, and calculated creatinine clearance (Cockcroft-Gault formula) ≥30 mL/min.

The median age was 67 years (43-83), 81% were male and 96% were Caucasian. The table below summarizes the baseline disease-related characteristics and prior anti-lymphoma therapy in the Mantle Cell Lymphoma trial.

Table 15: Baseline Disease-related Characteristics and Prior Anti –Lymphoma Therapy in Mantle Cell Lymphoma Trial

Baseline Disease Characteristics and Prior Anti - Lymphoma Treatment	Total Patients (N=134)
ECOG Performance Status[a] n (%)	
0	43 (32)
1	73 (54)
2	17 (13)
3	1 (<1)
Advanced MCL Stage, n (%)	
III	27 (20)
IV	97 (72)
High or Intermediate MIPI Score[b], n (%)	90 (67)
High Tumor Burden[c], n (%)	77 (57)
Bulky Disease[d], n (%)	44 (33)
Extranodal Disease, n (%)	101 (75)
Number of Prior Systemic Anti-Lymphoma Therapies, n (%)	
Median (range)	4 (2, 10)
1	0 (0)
2	29 (22)
3	34 (25)
≥ 4	71 (53)
Number of Subjects Who Received Prior Regimen Containing, n (%):	
Anthracycline/mitoxantrone	133 (99)
Cyclophosphamide	133 (99)
Rituximab	134 (100)
Bortezomib	134 (100)

Baseline Disease Characteristics and Prior Anti - Lymphoma Treatment	Total Patients (N=134)
Refractory to Prior Bortezomib, n (%)	81 (60)
Refractory to Last Prior Therapy, n (%)	74 (55)
Prior Autologous Bone Marrow or Stem Cell Transplant, n (%)	39 (29)

[a] ECOG = Eastern Cooperative Oncology Group
[b] MIPI = MCL International Prognostic Index
[c] High tumor burden is defined as at least one lesion that is ≥5 cm in diameter or 3 lesions that are ≥3 cm in diameter
[d] Bulky disease is defined as at least one lesion that is ≥7cm in the longest diameter

The efficacy endpoints in the MCL trial were overall response rate (ORR) and duration of response (DOR). Response was determined based on review of radiographic scans by an independent review committee according to a modified version of the International Workshop Lymphoma Response Criteria (Cheson, 1999). The DOR is defined as the time from the initial response (at least PR) to documented disease progression. The efficacy results for the MCL population were based on all evaluable patients who received at least one dose of study drug and are presented in Table 16. The median time to response was 2.2 months (range 1.8 to 13 months).

Table 16: Response Outcomes in the Pivotal Mantle Cell Lymphoma Trial

Response Analyses (N = 133)		**N (%)**	**95% CI**
Overall Response Rate (IWRC) (CR + CRu +PR)		34 (26)	(18.4, 33.9)
Complete Response (CR + CRu)		9 (7)	(3.1, 12.5)
CR		1 (1)	
CRu		8 (6)	
Partial Response (PR)		25 (19)	
Duration of Response (months)		**Median**	**95% CI**
Duration of Overall Response (CR + CRu + PR)	(N = 34)	16.6	(7.7, 26.7)

15 REFERENCES

1. OSHA Hazardous Drugs. *OSHA* [Accessed on 29 January 2013, from http://www.osha.gov/SLTC/hazardousdrugs/index.html]

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

White and blue-green opaque hard capsules imprinted "REV" on one half and "2.5 mg" on the other half in black ink:

2.5 mg bottles of 28 (NDC 59572-402-28)

2.5 mg bottles of 100 (NDC 59572-402-00)

White opaque capsules imprinted "REV" on one half and "5 mg" on the other half in black ink:

5 mg bottles of 28 (NDC 59572-405-28)

5 mg bottles of 100 (NDC 59572-405-00)

Blue/green and pale yellow opaque capsules imprinted "REV" on one half and "10 mg" on the other half in black ink:

10 mg bottles of 28 (NDC 59572-410-28)

10 mg bottles of 100 (NDC 59572-410-00)

Powder blue and white opaque capsules imprinted "REV" on one half and "15 mg" on the other half in black ink:

15 mg bottles of 21 (NDC 59572-415-21)

15 mg bottles of 100 (NDC 59572-415-00)

Powder blue and blue-green opaque hard capsules imprinted "REV" on one half and "20 mg" on the other half in black ink.

20 mg bottles of 21 (NDC 59572-420-21)

20 mg bottles of 100 (NDC 59572-420-00)

White opaque capsules imprinted "REV" on one half and "25 mg" on the other half in black ink:

25 mg bottles of 21 (NDC 59572-425-21)

25 mg bottles of 100 (NDC 59572-425-00)

16.2 **Storage**

Store at 20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F) [See USP Controlled Room Temperature].

16.3 **Handling and Disposal**

Care should be exercised in the handling of REVLIMID. REVLIMID capsules should not be opened or broken. If powder from

REVLIMID contacts the skin, wash the skin immediately and thoroughly with soap and water. If REVLIMID contacts the mucous membranes, flush thoroughly with water.

Procedures for the proper handling and disposal of anticancer drugs should be considered. Several guidelines on the subject have been published.[1]

Dispense no more than a 28-day supply.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient labeling (Medication Guide)

Embryo-Fetal Toxicity
Advise patients that REVLIMID is contraindicated in pregnancy *[see Contraindications (4.1)]*. REVLIMID is a thalidomide analog and can cause serious birth defects or death to a developing baby *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.

- Advise females of reproductive potential that they must avoid pregnancy while taking REVLIMID and for at least 4 weeks after completing therapy.
- Initiate REVLIMID treatment in females of reproductive potential only following a negative pregnancy test.
- Advise females of reproductive potential of the importance of monthly pregnancy tests and the need to use two different forms of contraception including at least one highly effective form simultaneously during REVLIMID therapy, during dose interruption and for 4 weeks after she has completely finished taking REVLIMID. Highly effective forms of contraception other than tubal ligation include IUD and hormonal (birth control pills, injections, patch or implants) and a partner's vasectomy. Additional effective contraceptive methods include latex or synthetic condom, diaphragm and cervical cap.
- Instruct patient to immediately stop taking REVLIMID and contact her doctor if she becomes pregnant while taking this drug, if she misses her menstrual period, or experiences unusual menstrual bleeding, if she stops taking birth control, or if she thinks FOR ANY REASON that she may be pregnant.
- Advise patient that if her doctor is not available, she can call 1-888-668-2528 for information on emergency contraception *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)]*.
- Advise males to always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID and for up to 28 days after discontinuing REVLIMID, even if they have undergone a successful vasectomy.
- Advise male patients taking REVLIMID that they must not donate sperm *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)]*.
- All patients must be instructed to not donate blood while taking REVLIMID, during dose interruptions and for 1 month following discontinuation of REVLIMID *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)]*.

REVLIMID REMS™ program
Because of the risk of embryo-fetal toxicity, REVLIMID is only available through a restricted program called the REVLIMID REMS™ program **(formerly known as the "RevAssist® program)** *[see Warnings and Precautions (5.2)]*.

- Patients must sign a Patient-Physician agreement form and comply with the requirements to receive REVLIMID. In particular, females of reproductive potential must comply with the pregnancy testing, contraception requirements and participate in monthly telephone surveys. Males must comply with the contraception requirements *[see Use in Specific Populations (8.6)]*.
- REVLIMID is available only from pharmacies that are certified in REVLIMID REMS™ program. Provide patients with the telephone number and website for information on how to obtain the product.

Hematologic Toxicity

Inform patients that REVLIMID is associated with significant neutropenia and thrombocytopenia *[see Boxed Warnings and Warnings and Precautions (5.3)]*.

Venous and Arterial Thromboembolism

Inform patients of the risk of thrombosis including DVT, PE, MI, and stroke and to report immediately any signs and symptoms suggestive of these events for evaluation *[see Boxed Warnings and Warning and Precautions (5.4)]*.

Increased Mortality in Patients with CLL

Inform patients that REVLIMID had increased mortality in patients with CLL and serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiac failure *[see Warning and Precautions (5.5)]*.

Second Primary Malignancies

Inform patients of the potential risk of developing second primary malignancies during treatment with REVLIMID *[see Warnings and Precautions (5.6)]*.

Hepatotoxicity

Inform patients of the risk of hepatotoxicity, including hepatic failure and death, and to report any signs and symptoms associated with this event to their healthcare provider for evaluation *[see Warnings and Precautions (5.7)]*.

Allergic Reactions

Inform patients of the potential for allergic reactions including hypersensitivity, angioedema, Stevens-Johnson Syndrome, or toxic epidermal necrolysis if they had such a reaction to THALOMID and report symptoms associated with these events to their healthcare provider for evaluation *[see Warnings and Precautions (5.8)]*.

Tumor Lysis Syndrome

Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation *[see Warnings and Precautions (5.9)]*.

Tumor Flare Reaction

Inform patients of the potential risk of tumor flare reaction and to report any signs and symptoms associated with this event to their healthcare provider for evaluation *[see Warnings and Precautions (5.10)]*.

Dosing Instructions

Inform patients to take REVLIMID once daily at about the same time each day, either with or without food. The capsules should not be opened, broken, or chewed. REVLIMID should be swallowed whole with water.

Instruct patients that if they miss a dose of REVLIMID, they may still take it up to 12 hours after the time they would normally take it. If more than 12 hours have elapsed, they should be instructed to skip the dose for that day. The next day, they should take REVLIMID at the usual time. Warn patients to not take 2 doses to make up for the one that they missed.

Manufactured for: Celgene Corporation
Summit, NJ 07901

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REVLIMID REMS™ is a trademark of Celgene Corporation.

Pat. www.celgene.com/therapies

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12.4 Evaluation and Counseling of Patient

The patient will be completely evaluated. The protocol will be discussed thoroughly with the patient and family and the attending physicians will describe all known risks to the patient. Alternative forms of therapy will be presented as objectively as possible and the risks and hazards of the procedure explained to the patient. Consent will be obtained using forms approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center. A summary of the conference will be dictated for the medical record.

Study personnel must obtain documented consent from each potential patient prior to entering in a clinical study. Consent must be documented by obtaining the dated signature both of the patient and of the person conducting the consent discussion on the consent form.

If the patient is illiterate, an impartial witness should be present during the entire informed consent reading and discussion. Afterward, the patient should sign and date the informed consent, if capable. The impartial witness should also sign and date the informed consent along with the individual who read and discussed the informed consent (i.e., study staff personnel).

If the patient is legally incompetent (i.e., a minor or mentally incapacitated), the written consent of a parent, legal guardian or legal representative must be obtained. Depending on local law or review committee requirements such consent may also need to be signed by an impartial witness.

Patients who are non-English speaking will be consented per FHCRC standard procedure.

A copy of the signed and dated consent form should be given to the patient before participation in the study.

The initial informed consent form and any subsequent revised written informed consent form, and written information must receive the IRB/IEC's approval/favorable opinion in advance of use. The patient or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the trial. The communication of this information should be documented.

12.5 Protocol Registration

Patients will be assigned to the protocol by the attending physician and registered through the FHCRC Registration Office (206-667-4728), Monday through Friday, 8 a.m. to 4 p.m. Registration will be through the final clinical coordinator sheet. After hours, the Registration Office can be reached by paging 206-995-7437.