

Table 15: Progression-free Survival and Overall Survival from Randomization in MM Maintenance Studies 1 and 2 (ITT Post-Auto-HSCT Population)

	Maintenance Study 1		Maintenance Study 2	
	REVLIMID N = 231	Placebo N = 229	REVLIMID N = 307	Placebo N = 307
PFS at Unblinding				
PFS Events n (%)	46 (20)	98 (43)	103 (34)	160 (52)
Median in months [95% CI]	33.9 [NE, NE]	19 [16.2, 25.6]	41.2 [38.3, NE]	23.0 [21.2, 28.0]
Hazard Ratio [95% CI]	0.38 [0.27, 0.54]		0.50 [0.39, 0.64]	
Log-rank Test p-value	<0.001		<0.001	
PFS at Updated Analysis 1 March 2015 (Studies 1 and 2)				
PFS Events n (%)	97 (42)	116 (51)	191 (62)	248 (81)
Median in months [95% CI]	68.6 [52.8, NE]	22.5 [18.8, 30.0]	46.3 [40.1, 56.6]	23.8 [21.0, 27.3]
Hazard Ratio [95% CI]	0.38 [0.28, 0.50]		0.53 [0.44, 0.64]	
OS at Updated Analysis 1 Feb 2016 (Studies 1 and 2)				
OS Events n (%)	82 (35)	114 (50)	143 (47)	160 (52)
Median in months [95% CI]	111 [101.8, NE]	84.2 [71.0, 102.7]	105.9 [88.8, NE]	88.1 [80.7, 108.4]
Hazard Ratio [95% CI]	0.59 [0.44, 0.78]		0.90 [0.72, 1.13]	

Date of Unblinding in Maintenance Study 1 and 2 = 17 December 2009 and 7 July 2010, respectively.

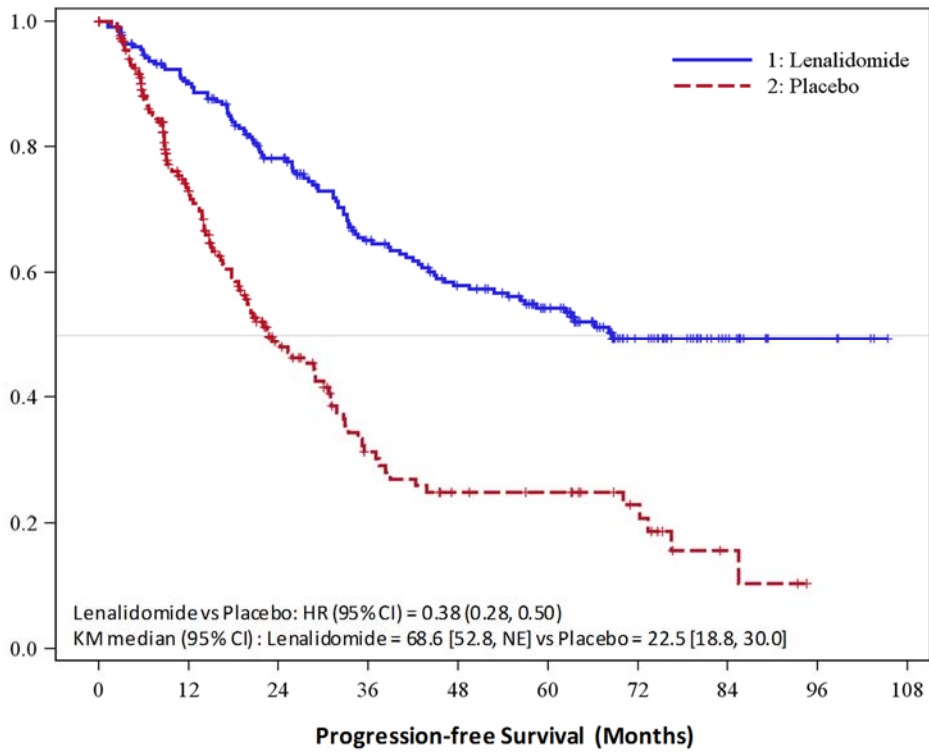
Auto-HSCT = autologous hematopoietic stem cell transplantation; CI = confidence interval; ITT = intent to treat; NE = not estimable;

PFS = progression-free survival.

PFS at time of unblinding for Maintenance Study 2 was based on assessment by an Independent Review Committee. All other PFS analyses were based on assessment by investigator.

Note: The median is based on Kaplan-Meier estimate, with 95% CIs about the median overall PFS time. Hazard ratio is based on a proportional hazards model stratified by stratification factors comparing the hazard functions associated with treatment arms (REVLIMID:placebo).

Kaplan-Meier Curves of Progression-free Survival from Randomization (ITT Post-Auto-HSCT Population) in MM Maintenance Study 1 between REVLIMID and Placebo Arms (Updated Cutoff Date 1 March 2015)



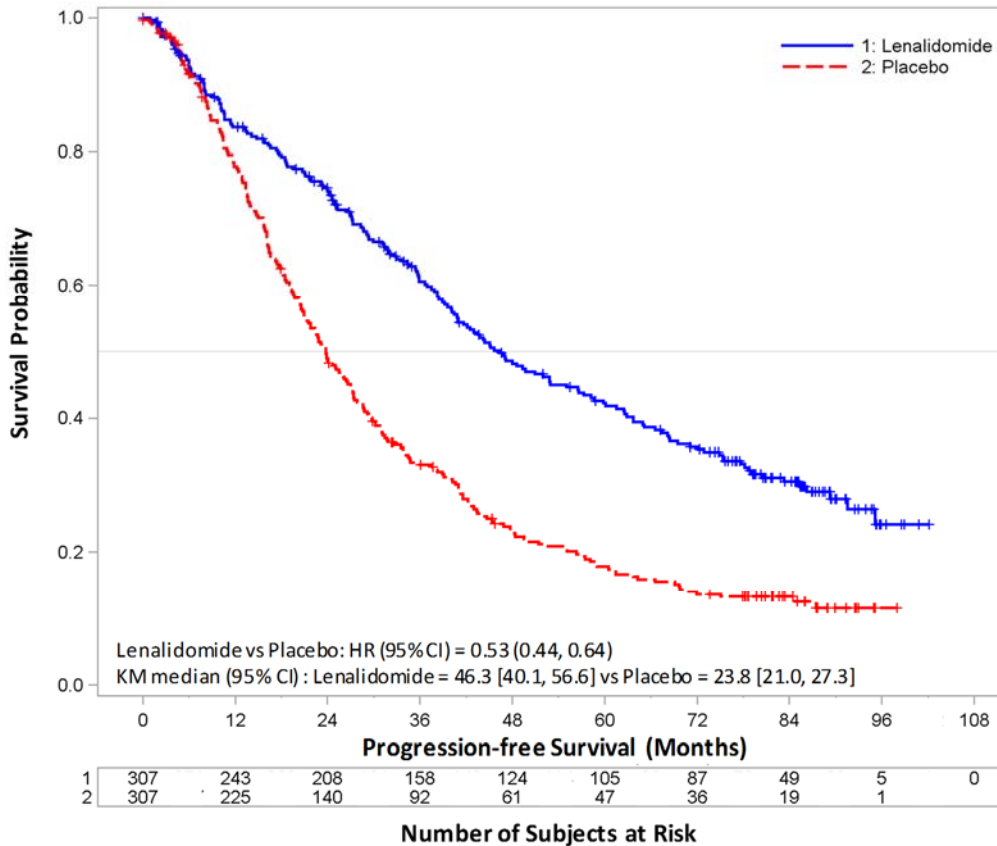
1	231	194	158	121	102	82	40	16	5	0
2	229	116	57	29	20	18	11	3	0	0

Number of Subjects at Risk

PFS Events: Lenalidomide = 97/231 (42%), Placebo = 116/229 (51%)

Auto-HSCT = autologous hematopoietic stem cell transplantation; CI = confidence interval; HR = hazard ratio; ITT = intent to treat; KM = Kaplan-Meier; PFS = progression-free survival; vs = versus.

Kaplan-Meier Curves of Progression-free Survival from Randomization (ITT Post-Auto-HSCT Population) in MM Maintenance Study 2 between REVLIMID and Placebo Arms (Updated Cutoff Date 1 March 2015)



PFS Events: Lenalidomide = 191/307 (62%), Placebo = 248/307 (81%)

Auto-HSCT = autologous hematopoietic stem cell transplantation; CI = confidence interval; HR = hazard ratio; ITT = intent to treat; KM = Kaplan-Meier; NE = not estimable; PFS = progression-free survival; vs = versus.

Randomized, Open-Label Clinical Studies in Patients with MM After At Least One Prior Therapy

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 MM who had received at least one prior treatment. These studies enrolled patients with absolute neutrophil counts (ANC) $\geq 1000/\text{mm}^3$, platelet counts $\geq 75,000/\text{mm}^3$, serum creatinine ≤ 2.5 mg/dL, serum SGOT/AST or SGPT/ALT $\leq 3 \times$ 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 16 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 16: Baseline Demographic and Disease-Related Characteristics – MM 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	64	62	63	64
Min, Max	36, 86	37, 85	33, 84	40, 82
Sex				
Male	106 (60%)	104 (59%)	104 (59%)	103 (59%)
Female	71 (40%)	72 (41%)	72 (41%)	72 (41%)
Race/Ethnicity				
White	141(80%)	148 (84%)	172 (98%)	175 (100%)
Other	36 (20%)	28 (16%)	4 (2%)	0 (0%)
ECOG Performance				
Status 0-1	157 (89%)	168 (95%)	150 (85%)	144 (82%)
Disease Characteristics				
Multiple Myeloma Stage (Durie-Salmon)				
I	3%	3%	6%	5%
II	32%	31%	28%	33%
III	64%	66%	65%	63%
β2-microglobulin (mg/L)				
≤ 2.5 mg/L	52 (29%)	51 (29%)	51 (29%)	48 (27%)
> 2.5 mg/L	125 (71%)	125 (71%)	125 (71%)	127 (73%)
Number of Prior Therapies				
1	38%	38%	32%	33%
≥ 2	62%	62%	68%	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%

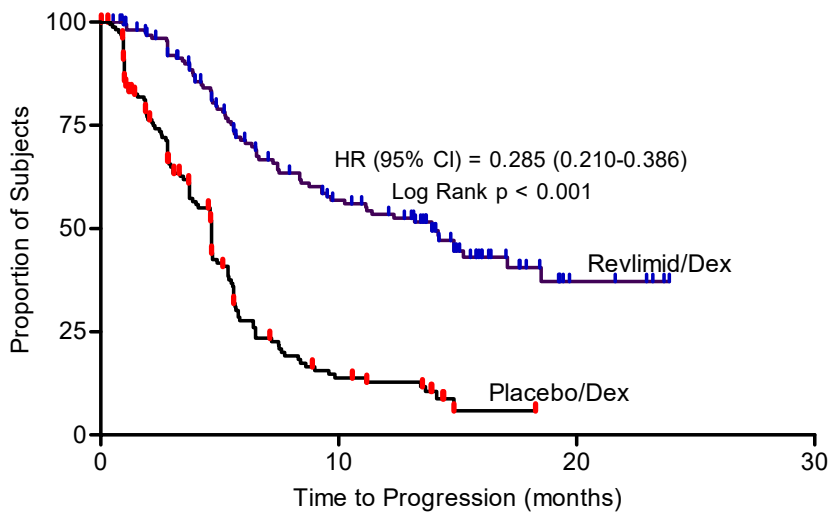
The primary efficacy endpoint in both studies was time to progression (TTP). TTP was defined as the time from randomization to the first occurrence of progressive disease.

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).

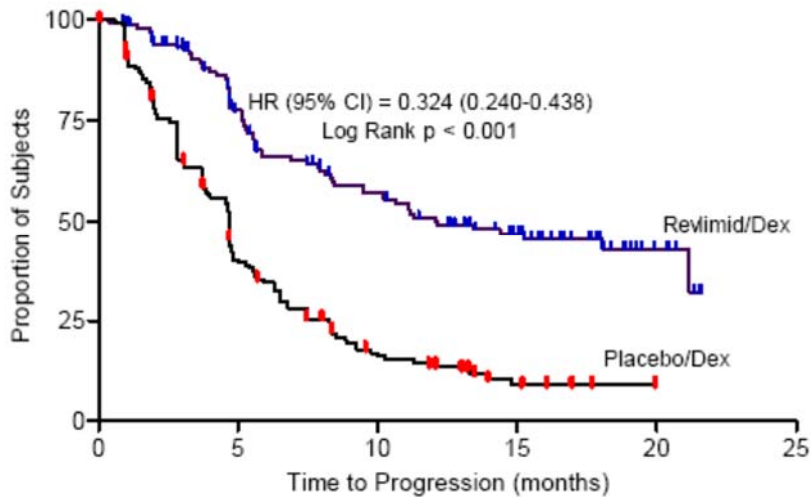
Table 17: TTP Results in MM Study 1 and Study 2

	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]	

Kaplan-Meier Estimate of Time to Progression — MM Study 1



Kaplan-Meier Estimate of Time to Progression — MM 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) $\geq 500/\text{mm}^3$, platelet counts $\geq 50,000/\text{mm}^3$, serum creatinine ≤ 2.5 mg/dL, serum SGOT/AST or SGPT/ALT $\leq 3 \times$ 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 18.

Table 18: Baseline Demographic and Disease-Related Characteristics in the MDS Study

Overall (N=148)		
Age (years)		
Median	71	
Min, Max	37, 95	
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)
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)
RARS	16	(10.8)
RAEB	30	(20.3)
CMML	3	(2)

^a IPSS Risk Category: Low (combined score = 0), Intermediate-1 (combined score = 0.5 to 1), 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 REVLIMID was conducted to evaluate the safety and efficacy of REVLIMID 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 REVLIMID 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 REVLIMID 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 /mm³, platelet counts $\geq 60,000$ /mm³, serum SGOT/AST or SGPT/ALT ≤ 3 x 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 19: 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)
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 ≥ 7 cm 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 20. The median time to response was 2.2 months (range 1.8 to 13 months).

Table 20: 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)

14.4 Follicular and Marginal Zone Lymphoma

The efficacy of REVLIMID with rituximab in patients with relapsed or refractory follicular and marginal zone lymphoma was evaluated in the AUGMENT (NCT01938001) and MAGNIFY (NCT01996865) trials.

AUGMENT is a randomized, double-blind, multicenter trial (n=358) in which patients with relapsed or refractory follicular or marginal zone lymphoma were randomized 1:1 to receive REVLIMID and rituximab or rituximab and placebo. AUGMENT included patients diagnosed with Grade 1, 2, or 3a follicular lymphoma, who received at least 1 prior systemic therapy, were refractory or relapsed, not rituximab-refractory, had at least one measurable nodal or extranodal lesion by CT or MRI scan, and had adequate bone marrow, liver, and renal function. Randomization was stratified by follicular versus marginal zone lymphoma, previous rituximab therapy, and time since other anti-lymphoma therapy. In AUGMENT, REVLIMID was administered orally 20 mg once daily for Days 1 to 21 of repeating 28-day cycles for a maximum of 12 cycles or until unacceptable toxicity. The dose of rituximab was 375 mg/m² every week in Cycle 1 (Days 1, 8, 15, and 22) and on Day 1 of every 28-day cycle from Cycles 2 through 5. All dosage calculations for rituximab were based on the patient's body surface area (BSA), using actual patient weight. Dose adjustments for REVLIMID were allowed based on clinical and laboratory findings. A patient with moderate renal insufficiency (≥30 to <60 mL/minute) received a lower REVLIMID starting dose of 10 mg daily on the same schedule. After 2 cycles, the REVLIMID dose could be increased to 15 mg once daily on Days 1 to 21 of each 28-day cycle if the patient tolerated the medication.

MAGNIFY is an open-label, multicenter trial (n=232) in which patients with relapsed or refractory follicular, marginal zone, or mantle cell lymphoma received 12 induction cycles of REVLIMID and rituximab. MAGNIFY included patients diagnosed with Grade 1, 2, 3a, 3b follicular (including transformed), marginal zone, or mantle cell lymphoma Stage I to IV who were previously treated for their lymphoma, had been refractory or had a relapse after their last treatment, had at least one measurable nodal or extranodal lesion by CT or MRI scan, and had adequate bone marrow, liver, and renal function. Patients refractory to rituximab were also included. The information from the subjects who received at least 1 dose of initial therapy in the first 12 induction cycles (n=222) in the MAGNIFY trial was included in the evaluation of the efficacy of REVLIMID/rituximab in patients with relapsed or refractory follicular and marginal zone lymphoma. In MAGNIFY, REVLIMID 20 mg was given on Days 1-21 of repeated 28-day cycles for up to 12 cycles or until unacceptable toxicity, progression, or withdrawal of consent. The dose of rituximab was 375 mg/m² every week in Cycle 1 (Days 1, 8, 15, and 22) and on Day 1 of every other 28-day cycle (Cycles 3,5,7,9, and 11) up to 12 cycles therapy. All dosage calculations for rituximab were based on the patient BSA and actual weight. Dose adjustments were allowed based on clinical and laboratory findings.

The demographic and disease-related baseline characteristics in the AUGMENT and MAGNIFY trials are shown in the following table.

Table 21: Baseline Demographics and Disease-Related Characteristics of Patients with FL and MZL in AUGMENT and MAGNIFY Trials

Parameter	AUGMENT Trial		MAGNIFY Trial
	REVLIMID + Rituximab (N=178)	Rituximab + Placebo (Control Arm) (N=180)	REVLIMID + Rituximab (N=222)
Age (years)			
Median (Max, Min)	64 (26, 86)	62 (35, 88)	65 (35, 91)
Age distribution, n (%)			
<65 years	96 (54)	107 (59)	103 (46)
≥65 years	82 (46)	73 (41)	119 (54)
Sex, n (%)			
Male	75 (42)	97 (54)	122 (55)
Female	103 (58)	83 (46)	100 (45)
Race			
White	118 (66)	115 (64)	206 (93)
Other races	54 (30)	64 (36)	14 (6)
Not collected or reported	6 (3)	1 (0.6)	2 (1)
Body Surface Area (BSA, m ²)			
Median (Max, Min)	1.8 (1.4, 3.1)	1.8 (1.3, 2.7)	2 (1.3, 2.6)
Disease Type FL or MZL			
Follicular lymphoma	147 (83)	148 (82)	177 (80)
Marginal zone lymphoma	31 (17)	32 (18)	45 (20)
MZL subtype at diagnosis (investigator), n (%)			
MALT	14 (45)	16 (50)	10 (22)
Nodal	8 (26)	10 (31)	25 (56)
Splenic	9 (29)	6 (19)	10 (22)
FL stage at diagnosis (investigator), n (%)			
FL Grade 1-2	125 (85)	123 (83)	149 (84)
FL Grade 3a	22 (15)	25 (17)	28 (16)
FLIPI score at baseline (calculated), n (%)			Not Collected

Parameter	AUGMENT Trial		MAGNIFY Trial
	REVLIMID + Rituximab (N=178)	Rituximab + Placebo (Control Arm) (N=180)	REVLIMID + Rituximab (N=222)
Low risk (0,1)	52 (29)	67 (37)	
Intermediate risk (2)	55 (31)	58 (32)	
High risk (≥ 3)	69 (39)	54 (30)	
Missing	2 (1)	1 (0.6)	
ECOG score at baseline, n (%)			
0	116 (65)	128 (71)	102 (46)
1	60 (34)	50 (28)	113 (51)
2	2 (1)	2 (1)	7 (3)
High tumor burden ^a at baseline, n (%)			
Yes	97 (54)	86 (48)	148 (67)
No	81 (46)	94 (52)	74 (33)
Number of prior systemic antilymphoma therapies			
1	102 (57)	97 (54)	94 (42) ^b
>1	76 (43)	83 (46)	128 (58)

Data Cutoff: 22 June 2018 (AUGMENT) and 1 May 2017 (MAGNIFY).

^a Defined by GELF criteria.

^b Patient had either 0 (n=2) or 1 prior systemic therapy.

ECOG = Eastern Cooperative Oncology Group; FLIPI = follicular lymphoma international prognostic index

In AUGMENT, efficacy was established in the intent-to-treat (ITT) population based on progression-free survival by Independent Review Committee using modified 2007 International Working Group response criteria. Efficacy results are summarized in Table 22.

Table 22: Efficacy Results for Patients in the AUGMENT Trial (ITT FL and MZL Population)

Parameter	REVLIMID + Rituximab (N=178)	Rituximab + Placebo (N=180)
PFS		
Patients with event, n (%)	68 (38.2)	115 (63.9)
Death	6 (8.8)	2 (1.7)
Progression of disease	62 (91.2)	113 (98.3)
PFS, median ^a [95% CI] (months)	39.4 [22.9, NE]	14.1 [11.4, 16.7]
HR ^b [95% CI]	0.46 [0.34, 0.62]	
p-value ^c	<0.0001	
Objective response (CR+PR) , n(%) [95% CI] ^d	138 (77.5) [70.7, 83.4]	96 (53.3) [45.8, 60.8]

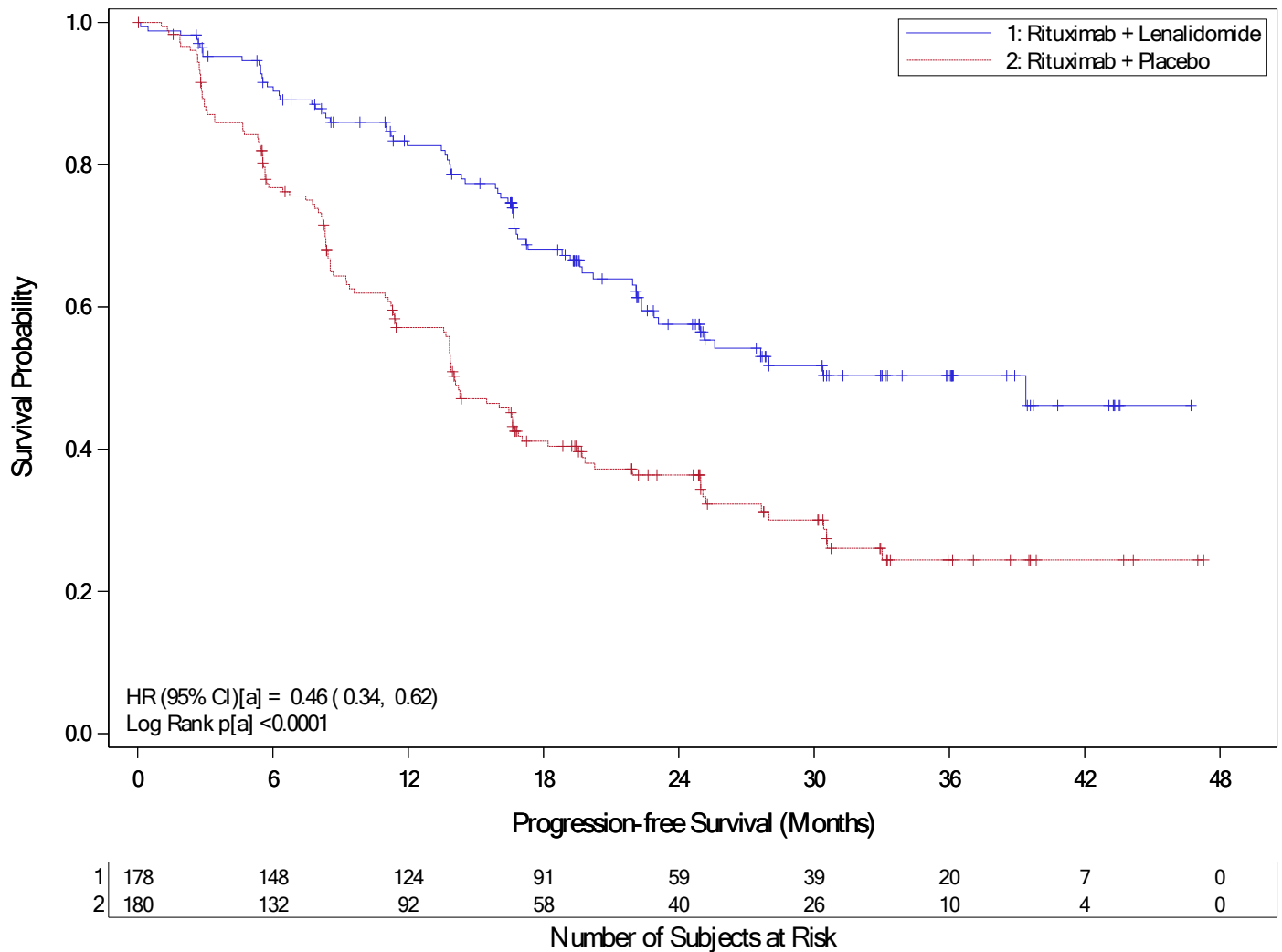
^a Median estimate is from Kaplan-Meier analysis.

^b hazard ratio and its CI were estimated from Cox proportional hazard model adjusting for the stratification 3: previous rituximab treatment (yes, no), time since last antilymphoma therapy (≤ 2 , > 2 years), and disease histology (FL, MZL).

^c p-value from log-rank test stratified by 3 factors noted above: previous rituximab treatment (yes, no), time since last antilymphoma therapy (≤ 2 , > 2 years), and disease histology (FL, MZL).

^d Exact confidence interval for binomial distribution.

Kaplan-Meier Curves of Progression-free Survival by IRC Assessment Between Arms in AUGMENT Trial (ITT FL and MZL Population)



a = Stratification factors included: previous rituximab treatment (y/n), time since last anti-lymphoma therapy (≤ 2 years, >2 years), and disease histology (FL or MZL). CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier; PFS = progression-free survival

Follicular Lymphoma

In AUGMENT, the objective response by IRC assessment for patients with follicular lymphoma was 80% (118/147) [95% CI: 73%, 86%] in REVLIMID with rituximab arm compared to 55% (82/148) [95% CI: 47, 64] in control arm.

In MAGNIFY, the overall response by investigator assessment was 59% (104/177) [95% CI: 51, 66] for patients with follicular lymphoma. Median duration of response was not reached with a median follow-up time of 7.9 months [95% CI: 4.6, 9.2].

Marginal Zone Lymphoma

In AUGMENT, the objective response by IRC assessment for patients with marginal zone lymphoma was 65% (20/31) [95% CI: 45%, 81%] in REVLIMID with rituximab arm compared to 44% (14/32) [95% CI: 26%, 62%] in control arm.

In MAGNIFY, the overall response by investigator assessment was 51% (23/45) [95% CI: 36, 66] for patients with marginal zone lymphoma. Median duration of response was not reached with a median follow-up time of 11.5 months [95% CI: 8.0, 18.9].

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

Advise the patient to read the FDA-approved Patient labeling (Medication Guide)

Embryo-Fetal Toxicity

Advise patients that REVLIMID is contraindicated in pregnancy [see *Boxed Warning and Contraindications (4.1)*]. REVLIMID is a thalidomide analogue 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 2 different forms of contraception including at least 1 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 healthcare provider 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 healthcare provider is not available, she should call Celgene Customer Care Center at 1-888-423-5436 [see *Warnings and Precautions (5.1) and Use in Specific Populations (8.3)*].
- 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 4 weeks 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 (8.3)*].
- All patients must be instructed to not donate blood while taking REVLIMID, during dose interruptions and for 4 weeks following discontinuation of REVLIMID [see *Warnings and Precautions (5.1)*].

REVLIMID REMS program

Because of the risk of embryo-fetal toxicity, REVLIMID is only available through a restricted program called the REVLIMID REMS 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 (8.3)*].
- 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.

Pregnancy Exposure Registry

Inform females there is a Pregnancy Exposure Registry that monitors pregnancy outcomes in females exposed to REVLIMID during pregnancy and that they can contact the Pregnancy Exposure Registry by calling 1-888-423-5436 [see *Use in Specific Populations (8.1)*].

Hematologic Toxicity

Inform patients that REVLIMID is associated with significant neutropenia and thrombocytopenia [see *Boxed Warning 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 Warning and Warnings 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 *Warnings 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 (5.8)*].

Severe Cutaneous Reactions

Inform patients of the potential risk for severe skin reactions such as SJS, TEN, and DRESS and report any signs and symptoms associated with these reactions to their healthcare provider for evaluation. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive REVLIMID [see *Warnings and Precautions (5.9)*].

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 (5.10)*].

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 (5.11)*].

Early Mortality in Patients with MCL

Inform patients with MCL of the potential for early death [see *Warnings and Precautions (5.14)*].

Hypersensitivity

Inform patients of the potential for severe hypersensitivity reactions such as angioedema and anaphylaxis to REVLIMID. Instruct patients to contact their healthcare provider right away for signs and symptoms of these reactions. Advise patients to seek emergency medical attention for signs or symptoms of severe hypersensitivity reactions [see *Warnings and Precautions (5.15)*].

Dosing Instructions

Inform patients how to take REVLIMID [see *Dosage and Administration (2)*]

- REVLIMID should be taken once daily at about the same time each day,
- REVLIMID may be taken 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
86 Morris Avenue
Summit, NJ 07901

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Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not take REVLIMID for conditions for which it was not prescribed. Do not give REVLIMID to other people, even if they have the same symptoms you have. It may harm them and may cause birth defects.

If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about REVLIMID that is written for health professionals.

What are the ingredients in REVLIMID?

Active ingredient: lenalidomide

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 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.

Manufactured for: Celgene Corporation, 86 Morris Avenue, Summit, NJ 07901

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For more information, call 1-888-423-5436 or go to www.CelgeneRiskManagement.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration
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