pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Lenalidomide (Revlimid) for Multiple Myeloma

December 3, 2015

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1 GUIDANCE IN BRIEF

1.1 Background

The objective of this review is to evaluate the efficacy and safety of lenalidomide (Revlimid) as a combination therapy in the first-line treatment of patients with newly diagnosed multiple myeloma who are not candidates for stem cell transplant.

Lenalidomide (LEN) is an immunomodulatory drug analogous to thalidomide with anti-angiogenic and anti-inflammatory properties. While LEN has Health Canada approval in other indications[3], the indication in the current review, has not been approved by Health Canada.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included two open label randomised controlled trials (RCT), [FIRST (n=1623), MM-015 (n=459)] and one double blind RCT, [E1A06 (n=306)]. Baseline characteristics were well balanced between groups across the three trials. The median age of patients ranged from 71 to 76 years across the three trials. The majority of patients in the FIRST and E1A06 trials had and eastern cooperative oncology group performance status (ECOG PS) of 0 (~30%), 1(~50%) or 2 (~20%). In the MM-015 trial the median Karnofsky performance status scale (KPSS) ranged from 80 to 100.

- The FIRST trial randomised patients 1:1:1 to melphalan + prednisone + thalidomide (MPT) regimen or LEN (L) in combination with dexamethasone (d), either continuously until progression (con-Ld) or for 18 cycles of 4 weeks (Ld18). The primary objective of the study was to assess the superiority of con-Ld for progression-free survival (PFS) in comparison with MPT.
- The MM-015 trial randomised patients 1:1:1 to a melphalan + prednisone + LEN (MPL) regimen for induction followed by maintenance with LEN (MPL-L) or to MPL or melphalan + prednisone (MP) for induction without maintenance therapy. To maintain the blinding, LEN was replaced by placebo for both the induction therapy and the maintenance therapy. The primary objective of the study was to evaluate the superiority of MPL-L for PFS in comparison with MP.
- The E1A06 trial randomised patients 1:1 to receive induction with MPT followed by maintenance with thalidomide (MPT-T) to induction with MPL followed by maintenance with LEN (MPL-L). The primary objective of the study was to assess whether MPL-L was non-inferior to MPT-T for PFS.

Efficacy

The primary outcome for the FIRST trial was progression-free survival (PFS). The median PFS was 25.5 vs. 20.7 vs. 21.2 months in the con-Ld, Ld18 and MPT arms, respectively. There was a statistically significant improvement in PFS in patients with con-Ld compared to MPT treatment (HR 0.72, 95% CI 0.61 to 0.85, P < 0.001) and compared to Ld18 treatment (HR 0.70, 95% CI 0.60 to 0.82, P < 0.001). PFS was not different between the MPT and Ld18 arms.

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In MM-015 median PFS was statistically significantly higher in the MPL-L vs. MPL group (31 vs. 14 months, respectively HR 0.49, P < 0.001) and MPL-L vs. MP (31 vs. 13 months, respectively HR 0.40, P < 0.001). In E1A06, the median PFS were similar between the MPT-T and MPL-L arms (21 vs. 18.7 months, respectively HR 0.84 95% CI 0.64 to 1.09 P = 0.19).

Overall survival (OS) was a secondary outcome in all three studies. In FIRST, the OS rates at 3 years were 70% vs. 66% vs. 62% with con-Ld, Ld18 and MPT, respectively (see Table 3). There was a statistically significant reduction of death risk between the con-Ld and MPT arms (HR 0.78, 95% CI 0.64 to 0.96, P = 0.02), but the difference in OS did not cross the pre-specified superiority boundary. At 4 years, the OS rates were 59 %, 56 % and 51 % for the same groups, respectively. At 4 years (interim analysis performed March 3, 2014), the median OS in the con-Ld and MPT groups was 58.9 months and 48.5 months, respectively (HR = 0.75, 95% CI 0.62 to 0.90). In MM-015, risks of death were not statistically different between groups. For the E1A06 study, OS rates after 3 years were 63% for both arms.

In the FIRST trial, quality of life was statistically and clinically significant from baseline but not between groups at 18 months for EQ-5D index score and pain (QLQ-C30) for both treatment groups. Of note, compliance rates for HR-QoL questionnaires were higher for the con-Ld group than the MPT group at 12 months (91 vs. 81%; P ≤ 0.002) and at 18 months (89 vs. 67%; P ≤ 0.002). In MM-015, the MPL-L group achieved statistically and clinically significant change from baseline for disease symptoms, global health status, physical functioning, fatigue, and pain at 64 weeks. The MP group also achieved a statistically and clinically different change from baseline in pain. For the E1A06 study, the change from baseline in FACT-Ntx TOI score at 12 months favored MPL-L over MPT-T.

Harms

In the FIRST trial, the overall occurrence of grade 3-4 adverse events (AE's) were similar between groups. In comparison with MPT, treatment with con-Ld was associated with fewer hematological AEs, especially neutropenia (28 vs. 45%), and fewer peripheral sensory neuropathies (1 vs. 9%), but con-Ld was also associated with an increase of infections (29 vs. 17%). The numbers of second primary cancers were similar between groups, but numerically lower for hematologic malignancies in the con-Ld group. In MM-015, a treatment with LEN was associated with more grade 3-4 hematological AEs compared to MP. After long-term follow-up on maintenance, occurrences of second primary cancers were found to be higher with MPL-L and MPL than with MP. Three deaths in the MPL-L group (2%) and one death in the MPL group (0.7%) were considered to be related to lenalidomide. The E1A06 trial reported more grade 3-4 AEs with MPT-T (73%) than with MPL-L (58%) (P = 0.007). More specifically, grade 3-4 non hematological AEs rates were higher in the MPT-T arm (59%) than in the MPL-L arm (40%) (P = 0.001). Incidence rates of second primary cancers were also higher with MPT-T.

1.2.2 Additional Evidence

pCODR received input on lenalidomide (Revlimid) for patients with newly diagnosed MM who are not candidates for stem cell transplant from one patient advocacy group, Myeloma Canada. Provincial Advisory group input was obtained from eight of the nine provinces participating in pCODR.

In addition, one supplemental question was identified during development of the review protocol as relevant to the pCODR review of lenalidomide (Revlimid) and is discussed as supporting information:

- Summary of manufacturer-submitted network meta-analysis comparing lenalidomide with other first-line treatments for patient with newly diagnosed multiple myeloma who are not candidates for stem cell transplantation.

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1.2.3 Interpretation and Guidance

Multiple myeloma is relatively common and incurable. While conventional therapy is high dose chemotherapy and autologous hematopoietic stem cell transplantation, approximately half of newly diagnosed patients are not eligible for this treatment due to advanced age, comorbidities and/or impaired functional status. There is no strict definition of a "transplant-eligible" or "transplant-ineligible" myeloma patient, and this distinction is made individually for each patient by the treating hematologist or oncologist. New treatments are needed to further prolong remission duration, extend survival and improve the quality of life of transplant-ineligible myeloma patients as compared to currently available treatments.

The FIRST study demonstrated a clinically and statistically significant improvement in progression free survival with the continuous use of con-Ld as compared to a planned 72 weeks of MPT, a previous standard of care. A clinically significant overall survival advantage was also seen with con-Ld compared to MPT, although it did not meet the pre-specified criteria for statistical superiority. The MM-015 trial also demonstrated significant PFS improvement for continuous lenalidomide therapy (MPL-L) as compared to MPL or MP alone. Likewise, the E1A06 trial showed no difference in PFS or OS for MPT-T compared to MPL-L. Again, demonstrating that continuous lenalidomide-containing regimen is a reasonable first-line choice in transplant-ineligible patients. While both con-Ld and MPL-L are felt to be acceptable first line options, con-Ld is likely to emerge as the more widely adopted regimen in Canada compared to MPL-L.

Quality of life for patients treated with continuous lenalidomide-containing regimens in FIRST, MM-015 and E1A06 was comparable or superior to the comparator arms in each trial. Toxicity profiles for the continuous lenalidomide-containing regimens were also comparable or superior to the comparators. There was no increase in second malignancies with continuous lenalidomide-containing regimens in these trials, however this will need to be evaluated with longer follow up data as other trials with lenalidomide have shown incidence of second primary malignancies. Overall, there is no loss of safety or quality of life with continuous lenalidomide-based therapy found in these trials.

A network meta-analysis was presented to indirectly compare con-Ld and melphalan, prednisone and bortezomib (MPB), the most relevant treatment option in the Canadian setting. The limitations in the analysis however made it difficult to draw any conclusions on the comparative efficacy between the two regimens. In the absence of direct comparative evidence (through an RCT), the CGP agreed that it is difficult to determine the true comparative efficacy between these regimens. Based on the available evidence, the CGP however agreed that both options should be made available to patients and treating oncologists and use of one over the other should depend on the entire clinical scenario. Access to both con-Ld and MPB may vary for patients depending on individual geographical and financial constraints; the toxicity profiles differ between the regimens (e.g. thrombosis with lenalidomide, neuropathy with bortezomib). Con-Ld also has the advantage of being a convenient oral therapy that, in contrast to MPB, does not require the resources of a chemotherapy suite and can be taken by patients entirely at home. One regimen therefore may be more suitable than the other for a given patient depending on the clinical circumstances (e.g. prescribing MPB to a patient without financial coverage for lenalidomide who has a history of pulmonary embolism and lives near a center that can administer bortezomib, versus prescribing con- Ld to a patient with pre-existing peripheral neuropathy whose drug plan funds lenalidomide and who lives far from a center that can administer bortezomib). It would therefore be clinically valuable to have the ability to

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choose which regimen to prescribe to a given patient in the frontline setting, rather than to conclude that one regimen is sufficient for all patients.

1.3 Conclusions

The Clinical Guidance Panel concludes that there is a net overall clinical benefit with the use of lenalidomide as part of front line therapy for transplant-ineligible patients with newly diagnosed multiple myeloma. This conclusion is based on a fully published randomized trial showing improvement in PFS and possibly OS with continuous lenalidomide and dexamethasone as compared to 72 weeks of either lenalidomide and dexamethasone or the previous standard MPT regimen; a fully published randomized trial demonstrating improved PFS with the continuous MPL-L regimen as compared to either a defined course of MPL or MP; a fully published randomized trial finding no difference in PFS or OS between MPL-L and MPT-T, with quality of life favoring the MPL-L regimen;

In making this conclusion, the Clinical Guidance Panel considered:

- There is comparable or favorable safety and quality of life profiles for the continuous lenalidomide-containing regimens versus the comparators in each of these three trials.
- con-Ld and MPL-L are both reasonable standard front line regimens incorporating lenalidomide into continuous therapy for transplant-ineligible myeloma patients, with net clinical benefit as compared to a limited duration of lenalidomide-containing therapy and to previous standard therapies.
- The MPB regimen that is currently available to these patients in Canada does not incorporate lenalidomide; MPB is a very reasonable standard front line treatment and should remain as an option for this population in addition to con-Ld and MPL-L.
- While a network meta-analysis was presented comparing con-Ld and MPB, the limitations in the analysis made it difficult to draw any conclusions on the comparative efficacy between the two regimens. In the absence of an RCT, the CGP agreed that it is difficult to determine the true comparative efficacy of lenalidomide to MPB.
- In addition to the cost of the drug itself, lenalidomide prescription incurs additional costs to the health care system because of the Health Canada mandated RevAid controlled drug distribution program

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2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding lenalidomide (Revlimid) for newly diagnosed multiple myeloma. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website, www.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature regarding lenalidomide conducted by the Lymphoma and Myeloma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on lenalidomide and a summary of submitted Provincial Advisory Group Input on lenalidomide are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Multiple Myeloma (MM) is a cancer of the bone marrow which features malignant bone marrow plasma cells and causes osteolytic lesions, osteoporosis, pathological fractures, anemia, cytopenias and hypercalcemia. Renal insufficiency may also be a result of MM. MM accounts for approximately 13% of hematological cancers. MM is incurable in the vast majority of cases.[1]

The median age at diagnosis is approximately 70 years.[1] Upon diagnosis and the presence of symptoms, patients may be candidates for stem cell transplantation (SCT) depending on their age and performance status. There is no strict definition of a "transplant-eligible" or "transplant-ineligible" myeloma patient, and this distinction is made individually for each patient by the treating hematologist or oncologist. The pharmacological therapy strategy will differ according to the decision to undergo SCT or not. For newly diagnosed MM (ND-MM) patients ineligible for SCT, treatment with melphalan and prednisone (MP) have been the standard of care for many years. More recently, antimyeloma drugs such as bortezomib and thalidomide have been used in combination with corticosteroids and chemotherapy agents with improved benefits over MP. The most common treatment regimens are melphalan + prednisone + thalidomide (MPT), melphalan + prednisone + bortezomib (MPB).[1] The MPT treatment regimen is however not commonly used in the Canadian setting.

Lenalidomide (LEN) is an immunomodulatory drug analogous to thalidomide with anti-anti-angiogenic and anti-inflammatory properties. The mechanism of action of LEN on MM include induction of apoptosis, decreased production of pro-inflammatory cytokines, inhibition of angiogenesis, blocked binding of MM cells to bone marrow stromal cells and stimulating natural killer cells.[2-5]

Health Canada has approved LEN, in combination with dexamethasone, for the treatment of MM patients who have received at least one prior therapy. LEN is also approved for the treatment of myelodysplasia with 5q deletion.[6] The indication reviewed here, i.e. as first-line treatment of ND-MM in patients who are not candidates for SCT, has not been approved by Health Canada.

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2.1.2 Objectives and Scope of pCODR Review

The objective of the review was to evaluate the efficacy and safety of LEN as first-line treatment of ND-MM in patients who are not candidates for SCT. In addition to studies included in the systematic review, a summary of manufacturer-submitted network meta-analysis comparing LEN with other first-line treatments for patient with ND-MM who are not candidates for SCT was provided.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

Three clinical trials, the FIRST trial[7-11] the MM-015 trial,[12-16] and the E1A06 trial,[17,18] met the inclusion criteria for this systematic review. The three studies randomised patients to a lenalidomide containing regimen (con-Ld vs Ld18 vs MPT, MPL-L vs MPL vs MP and MPL-L vs MPT-T, respectively) See Table 4, 5 and 6 in Section 6.3 for details on Trial Characteristics.

A total of 2388 patients were randomized in the FIRST (N = 1623), the MM-015 (N = 459) and the E1A06 (N = 306) trials. Across FIRST and MM-015, baseline characteristics were well balanced between groups. The baseline characteristics of patients enrolled in the E1A06 were not detailed. There was no significant difference between groups at baseline that could favor the study drug. The median age of patients was ranging from 71 to 75.7 years. FIRST was the only study to enroll patients under 65 years old, but these patients represented less than 6 % of its population. The proportion of males and females were balanced. In terms of performance status, 30 % of the patients in FIRST had a score of 0, half had an ECOG score of 1, and 20% had a score of 2. In MM-015, the median KPSS was ranging from 80 to 100. In terms of disease severity, from 40 % to 51 % of patients were of ISS stage III across groups. Details on randomization can be found in Section 6.3.2.1.For all included trials, doses reductions were allowed as pre-specified in the protocol and all patients received protocol-specified anti-thrombotic prophylaxis.

Key Outcomes:

In FIRST, the overall survival (OS) rates at 3 years were 70 % with con- Ld, 66 % with Ld18 and 62 % with MPT (see Table 1). At 4 years, those rates were 59 %, 56 % and 51 % for the same groups, respectively. At 3 years, there was a statistically significant reduction of death risk between the con-Ld and the MPT groups (HR = 0.78, 95% CI 0.64 to 0.96, P = 0.02), but the difference in OS did not cross the pre-specified superiority boundary. At 4 years (interim analysis performed March 3, 2014), the median OS in the con-Ld and MPT groups was 58.9 months and 48.5 months, respectively (HR = 0.75, 95% CI 0.62 to 0.90).[46]

In MM-015, risks of death were not statistically different between groups. For the E1A06 study, OS rates after 3 years were 63 % for both arms.

PFS was the primary endpoint for the FIRST and the MM-015 studies. The median PFS in the FIRST trial was 25.5 months with con-Ld, 20.7 months with Ld18, and 21.2 months with MPT. Patients who had con-Ld had a statistically significant improvement in PFS compared to those who had MPT (HR = 0.72, 95% CI 0.61 to 0.85, P < 0.001) and compared to those who had Ld18 (HR = 0.70, 95% CI 0.60 to 0.82, P < 0.001). PFS was not different between the MPT group and the Ld18 group. In MM-015, the median PFS was statistically significantly higher in the MPL-L group (median of 31 months) compared to the MPL-L (median of 14 months, HR = 0.49, P < 0.001) and MP (median of 13 months, HR = 0.40, P < 0.001). Subgroup analyses showed that benefits in PFS were not maintained in patients aged over 75 years. A significant treatment-by-age interaction was found (P = 0.001). In E1A06, the median PFS were similar with 21 months for MPT-T and 18.7 months for MPL-L (P = 0.19). The HR for progression between these two groups was 0.84 (95%CI 0.64 to 1.09), which was within the pre-specified non-inferiority margin.

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Overall responses rates (ORR) in the FIRST trial were statistically significantly (P < 0.001) greater with con-Ld (75 %) and Ld18 (73 %) compared to MPT (62 %). The response rates for complete response and very good partial response numerically favored patients randomized to con-Ld and Ld18. For MM-015, ORRs statistically significantly favored MPL-L (77 %, P < 0.001) and MPL (68 %, P = 0.002) compared to MP (50 %). Numbers also appeared to favor MPL-L and LEN-based regimens for complete response rates and very good partial response rates, respectively. For the E1A06 study, response rates were based on a per protocol analysis. Rates for partial response and for the combination of complete and very good partial responses were similar for both treatment arms.

HR-QoL data for the FIRST and MM-015 trials are summarized in Table 11 (Section 6.3.2.2). For the FIRST study, results for the con- Ld and Ld 18 groups were pooled post-hoc. Changes from baseline at 18 months were statistically and clinically significant for EQ-5D index score and pain (QLQ-C30) for both treatment groups. For all the QoL endpoints at 18 months, no statistically significant differences were observed between groups. In MM-015, the MPL-L group achieved statistically and clinically significant change from baseline for disease symptoms (QLQ-MY20), global health status (QLQ-C30), physical functioning (QLQ-C30), fatigue (QLQ-C30), and pain (QLQ-C30) at 64 weeks. The MP group also achieved a statistically and clinically different change from baseline in pain. For the E1A06 study, the change from baseline in FACT-Ntx TOI score at 12 months favored MPL-L (3.3) over MPT-T (−2.8) (P = 0.007).

In the FIRST trial, the overall occurrence of grade 3-4 AEs were similar between groups. AEs leading to dose interruptions occurred in 77 %, 59 % and 69 % and AEs leading to withdrawal occurred in 27 %, 17 % and 20 % of patients who received MPT, Ld 18 and con- Ld, respectively. In comparison with MPT, treatment with con- Ld was associated with fewer hematological AEs, especially neutropenia (28 vs. 45 %), and fewer peripheral sensory neuropathies (1 vs. 9 %), but con- Ld was also associated with an increase of infections (29 vs. 17 %). The numbers of second primary cancers were similar between groups, but numerically lower for hematologic malignancies in the con- Ld group. In MM-015, a treatment with LEN was associated with more grade 3-4 hematological AEs compared to MP. Granulocyte colony-stimulating factor was used in 35 % of patients in the MPL-L group, 32 % of patients in the MPL group and 8 % of patients in the MP group. Platelet transfusions were required by 34 %, 27 % and 16 % of patients, for the same groups, respectively. Grade 3-4 deep-vein thrombosis (DVT) occurred in 3% of patients treated with LEN and 1% of patients treated with MP. After long-term follow-up on maintenance, occurrences of second primary cancers were found to be higher with MPL-L and MPL than with MP. Three deaths in the MPL-L group (2%) and one death in the MPL group (0.7%) were considered to be related to lenalidomide. The manufacturer also provided data on peripheral sensory neuropathy at their last data cut-off showing an incidence rate of 8 % for MPL-L, 5.9 % for MPL and 3.3 % for MP. The E1A06 trial reported more grade 3-4 AEs with MPT-T (73 %) than with MPL-L (58 %) (P = 0.007). More specifically, grade 3-4 non hematological AEs rates were higher in the MPT-T arm (59 %) than in the MPL-L arm (40 %) (P = 0.001). Incidence rates of second primary cancers were also higher with MPT-T.

Table 1: Summary of Key Efficacy Outcomes

	FIRST,[7,9]			MM-015,[14]			E1A06,[17,18]	
	MPT N = 547	Ld18 N = 541	con-Ld N = 535	MPL-L N = 152	MPL-placebo N = 153	MP + placebo-placebo N = 154	MPL-L	MPT-T
Overall survival rates								
At 3 years, %	62	66	70	70	62	66	63	63
HR (95% CI), P value	3-year analysis con- Ld vs. MPT: 0.78 (0.64 to 0.96), P = 0.02			MPL-L vs. MPL: 0.79 (NR), P = 0.25 MPL-L vs. MP: 0.95 (NR), P = 0.81			NR	

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Table 1: Summary of Key Efficacy Outcomes								
	FIRST,[7,9]			MM-015,[14]			E1A06,[17,18]	
	MPT N = 547	Ld18 N = 541	con-Ld N = 535	MPL-L N = 152	MPL-placebo N = 153	MP + placebo-placebo N = 154	MPL-L	MPT-T
	4-year analysis con- Ld vs. MPT: 0.75 (0.62 to 0.90)							
Progression-free survival								
Median, months	21.2	20.7	25.5	31	14	13	18.7	21
HR (95% CI), P value	con-Ld vs. MPT: 0.72 (0.61 to 0.85), P < 0.001 con- Ld vs. Ld 18: 0.70 (0.60 to 0.82), P < 0.001 con- Ld vs. MPT: 1.03 (0.89 to 1.20), P = 0.70			MPL-L R vs. MPL: 0.49 (NR), P < 0.001 MPL-L vs. MP: 0.40 (NR), P < 0.0 01			MPT-T vs. MPL-L: 0.84 (0.64 to 1.09)	
Response rates								
Overall Response rates, n (%)	341 (62)	397 (73)	402 (75)	117 (77)	104 (68)	77 (50)	NR	NR
P values	con- Ld vs. MPT: P < 0.001 Ld 18 vs. MPT: P < 0.001			MPL-L vs. MP: P < 0.001 MPL vs. MP: P = 0.002			NR	
Harms of interest	N = 541	N = 540	N = 532	N = 150		N = 152		N = 153		NR	NR
				Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4		
DVT, PE or both, n (%)	29 (5)	30 (6)	42 (8)	2 (1)	0	6 (4)	1 (1)	1 (1)	0	NR (6.7)	NR (8.8)
Peripheral sensory neuropathy, n(%)	51 (9)	2 (<1)	6 (1)	NR	NR	NR	NR	NR	NR	NR	NR
Cardiac disorders	46 (9)	39 (7)	63 (12)	5 (3)	3 (2)	4 (3)	4 (3)	5 (3)	0	NR	NR
Neutropenia, n (%)	243 (45)	143 (26)	148 (28)	100 (67)	52 (35)	97 (64)	49 (32)	45 (29)	12 (8)	NR	NR
Thrombocytopenia, n (%)	60 (11)	43 (8)	44 (8)	53 (35)	17 (11)	58 (38)	19 (12)	18 (12)	6 (4)	NR	NR
Infections	93 (17)	118 (22)	154 (29)	14 (9)	1 (1)	20 (13)	3 (2)	11 (7)	0	NR	NR
Second primary cancers, Incidence rate per 100 person-years (95%CI)	3.68 (2.76-4.89)	3.33 (2.48-4.48)	2.76 (2.00-3.81)	3.04 (NR)		2.57 (NR)		0.98 (NR)		2.01 (NR)	3.47 (NR)
CI = confidence interval; con- Ld = continuous lenalidomide + dexamethasone; DVT = Deep vein thrombosis; HR = hazard ratio; HR-QoL = Health-related Quality of Life; Ld 18 = lenalidomide+dexamethasone for 18 cycles; MP = melphalan + prednisone; MPL = melphalan + prednisone + Revlimid (lenalidomide); MPL-L = MPL for induction therapy + Revlimid (lenalidomide) as maintenance therapy; MPT = melphalan + prednisone + thalidomide; NR = not reported; PE = pulmonary embolism.											
* Statistically significant difference reaching MCID See section 6.3.2.2 for more details											

Some limitations were noted among studies. The FIRST and E1A06 studies were open label trials and were therefore prone to bias for subjective measures such as HR-QoL. In addition, completion rates of HR-QoL questionnaires were imbalanced between groups in FIRST, likely biasing in favor

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of LEN. Studies were not powered to detect difference in OS and differences in OS were likely to be biased toward the null by post-progression treatment with LEN. Studies had a multiplicity of secondary outcomes, increasing risks of type I error.

2.1.4 Comparison with Other Literature

Three meta-analyses were conducted to assess the efficacy and safety of LEN in ND-MM patients.[19-21] Those meta-analyses included from 7 to 10 studies and concluded in improved PFS, ORR and complete response rates, but unchanged OS, when ND-MM patient were treated with LEN. The counterparts were higher risks of cytopenias, DVT, infections, diarrhea and hematologic cancer.[19-21] Another meta-analysis reviewed the effect of LEN on the occurrence of second primary malignancies in patient with ND-MM.[22] By pooling the individual patient data from seven trials reporting on 3254 patients, patients who received LEN were found to have an increased risk of developing haematological second primary malignancies, especially when LEN was combined to melphalan.[22]

2.1.5 Summary of Supplemental Questions

Summary of manufacturer-submitted and poster-reported network meta-analysis comparing lenalidomide with other first-line treatments for patient with newly diagnosed multiple myeloma who are not candidates for stem cell transplantation.

The Clinical Guidance Panel confirmed that, in the Canadian setting, a bortezomib containing regimen is the most clinically relevant treatment option for patients with newly diagnosed MM and who are not candidates for stem cell transplant. In the absence of head-to-head trial data for lenalidomide compared to melphalan + prednisone + bortezomib (MPB) in patients with newly diagnosed multiple myeloma (ND-MM) who are not candidates for stem cell transplantation (SCT), a network meta-analysis (NMA) comparing lenalidomide with other first-line treatments in this patient population was conducted. Using fixed effects analyses, continuous lenalidomide + dexamethasone appeared to have a lower risk of progression and death compared to MPT and VMP. Limitations of this NMA included additional criteria for study inclusion which excluded studies that used continuous thalidomide maintenance treatment and some differences in inclusion criteria between included studies that resulted in minor heterogeneity in patient baseline characteristics. In addition, the network was small and comprised of few studies, with no direct linkage connecting lenalidomide to MPB, increasing uncertainty in the results.

See section 7.1 for more information.

2.1.6 Other Considerations

See Section 4 and Section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) Input, respectively.

Patient Advocacy Group Input

From a patient perspective, the level of impact of multiple myeloma varies depending on how long the patient has been diagnosed, whether or not they have had treatment, and whether their symptoms are under control. Respondents indicated that it is very important to have access to effective treatments for myeloma and to have a choice of drug based on known side effects of the drug. Respondents who did not receive the drug under review reported that the expected benefit such as lack of disease progression from a new treatment was extremely important. For respondents who have experienced with lenalidomide, the following were reported: 62% (N=16) respondents reported that it had provided remission or extended life, 12%

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(n=3) indicated that it had improved their quality of life, 15% (n=4) that it had been positive in terms of long-term health and well-being, 12% (n=3) were unsure, 4% (n=1) stopped treatment because of side effects, 4% (n=1) felt that he or she were no longer getting benefit from treatment, and 4% (n=1) wasn't getting better or worse. The most common side effects of lenalidomide included skin rash, fatigue, constipation, neutropenia and diarrhea. The majority of respondents reported that these side effects were tolerable.

PAG Input

Input was obtained from the eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could be impact implementation of lenalidomide in the first-line treatment of multiple myeloma in patients who are not eligible for stem cell transplantation (SCT):

Clinical factors:

- Mephalan/prednisone/thalidomide is not the relevant Canadian comparator
- Long-term benefits compared to risk of secondary cancers
- Treatment sequencing
- Oral administration of two drugs instead of the current intravenous drug in combination with two oral drugs

Economic factors:

- Unknown duration of therapy
- High cost of lenalidomide relative to the standard of care
- Additional resources to monitor adverse effects, monthly, prior to drug distribution (Revaid program)

Lower cost of bortezomib due to recently available generic product

2.2 Interpretation and Guidance

Burden of Illness and Need

Multiple myeloma is relatively common and is still incurable. While conventional therapy is high dose chemotherapy and autologous hematopoietic stem cell transplantation, approximately half of newly diagnosed patients are not eligible for this treatment due to advanced age, comorbidities and/or impaired functional status. There is no strict definition of a "transplant-eligible" or "transplant-ineligible" myeloma patient, and this distinction is made individually for each patient by the treating hematologist or oncologist. New treatments are needed to further prolong remission duration, extend survival and improve the quality of life of transplant-ineligible myeloma patients as compared to currently available treatments.

As with previous pCODR reports, it is argued here that it is increasingly difficult to demonstrate an overall survival advantage in multiple myeloma due in large part to the number of treatment options that can be applied subsequent to the initial therapy. It is also argued that prolongation of progression-free survival is a meaningful endpoint in myeloma trials, and that a substantial PFS improvement should be regarded as the basis for a change in standard of care.

Effectiveness of front-line lenalidomide containing regimens for transplant-ineligible myeloma

Overall and progression-free survival:

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The three-arm FIRST randomized trial has demonstrated a clinically and statistically significant improvement in progression free survival with the continuous use of lenalidomide and dexamethasone (con- Ld) as compared to a planned 72 weeks of MPT, a previous standard of care (thalidomide is not widely available in Canada), or a planned 72 weeks of lenalidomide and dexamethasone. A clinically significant overall survival advantage was seen with con- Ld compared to MPT, which did not meet pre-specified criteria for statistical superiority with a p-value of 0.02. In this trial, 72 weeks of Ld was associated with superior PFS compared to 72 weeks of MPT, showing that the choice of regimen is important and not just the duration of therapy.

The three-arm MM-015 trial results demonstrated significant PFS improvement for continuous therapy with MPL followed by R maintenance (MPL-L) as compared to MPL alone (which was in turn superior to MP alone), supporting the concept of continuous lenalidomide-containing front line therapy as compared to a limited duration of therapy. This trial also showed that, like MPT or MPB, MPL-L is superior to MP and can therefore be considered a standard frontline regimen.

The E1A06 trial showed no difference in PFS or OS for MPT-T compared to MPL-L. Again, this trial demonstrates a continuous lenalidomide-containing regimen to be a reasonable first-line choice in transplant-ineligible patients.

Lenalidomide-containing regimens such has con- Ld and MPL-L have not been compared directly to MPB. While a network meta-analysis was presented by Celgene to indirectly compare con- Ld and MPB, the limitations in the analysis made it difficult to draw any conclusions on the comparative efficacy between the two regimens. In the absence of direct comparative evidence (through an RCT), the CGP agreed that it is difficult to determine the true comparative efficacy between these regimens. Based on the available evidence, the CGP however agreed that both options should be made available to patients and treating oncologists and use of one over the other should depend on the entire clinical scenario. con- Ld has the advantage of being convenient oral therapy that, in contrast to MPB, does not require the resources of a chemotherapy suite and can be taken by patients entirely at home. Access to both con- Ld and MPB may vary for patients depending on individual geographical and financial constraints; the toxicity profiles differ between the regimens (e.g. thrombosis with lenalidomide, neuropathy with bortezomib). One regimen therefore may be more suitable than the other for a given patient depending on the clinical circumstances (e.g. prescribing MPB to a patient without financial coverage for lenalidomide who has a history of pulmonary embolism and lives near a center that can administer bortezomib, versus prescribing con- Ld to a patient with pre-existing peripheral neuropathy whose drug plan funds lenalidomide and who lives far from a center that can administer bortezomib). It would therefore be clinically valuable to have the ability to choose which regimen to prescribe to a given patient in the frontline setting, rather than to conclude that one regimen is sufficient for all patients.

Con-Ld and MPL-L have not been directly compared to one another and an RCT would be required to determine the comparative efficacy. A large randomized trial has demonstrated con-Ld to be superior to MPT, whereas MPL-L has been proven superior to MPL or MP but not MPT-T. Con-Ld has become the standard arm of many subsequent global randomized trials in the front line setting and is a backbone regimen with which novel agents are being combined. Cross trial comparisons of con-Ld and MPL-L would suggest more hematological toxicity with MPL-L. Con-Ld has long been widely used as a standard regimen in the relapse setting, whereas MPL-L is not widely used in Canada. Con-Ld is therefore likely to emerge as the more widely adopted regimen in Canada compared to MPL-L. However, both con-Ld and MPL-L are felt to be acceptable first line options.

Safety

Quality of Life is acceptable and toxicity is manageable

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Quality of life for patients treated with continuous lenalidomide-containing regimens in FIRST, MM-015 and E1A06 was comparable or superior to the comparator arms in each trial. Toxicity profiles for the continuous lenalidomide-containing regimens were also comparable or superior to the comparators. There was no increase in second primary malignancies (SPM) with continuous lenalidomide-containing regimens in these trials. While second primary malignancies have not been observed in these trials thus far, other trials with lenalidomide have demonstrated SPM's and therefore long term data is needed to understand the incidence of SPM for the use of lenalidomide in newly diagnosed patients. There is no loss of safety or quality of life with continuous lenalidomide-based therapy found in these trials.

2.3 Conclusions

The Clinical Guidance Panel concludes that there is a net overall clinical benefit with the use of lenalidomide as part of front line therapy for transplant-ineligible patients with newly diagnosed multiple myeloma. This conclusion is based on a fully published randomized trial showing improvement in PFS and possibly OS with continuous lenalidomide and dexamethasone as compared to 72 weeks of either lenalidomide and dexamethasone or the previous standard MPT regimen; a fully published randomized trial demonstrating improved PFS with the continuous MPL-L regimen as compared to either a defined course of MPL or MP; a fully published randomized trial finding no difference in PFS or OS between MPL-L and MPT-T, with quality of life favoring the MPL-L regimen.

In making this conclusion, the Clinical Guidance Panel considered:

- There is comparable or favourable safety and quality of life profiles for the continuous lenalidomide-containing regimens versus the comparators in each of these three trials.
- con- Ld and MPL-L are both reasonable standard front line regimens incorporating lenalidomide into continuous therapy for transplant-ineligible myeloma patients, with net clinical benefit as compared to a limited duration of lenalidomide-containing therapy and to previous standard therapies.
- The MPB regimen that is currently available to these patients in Canada does not incorporate lenalidomide; MPB is a very reasonable standard front line treatment and should remain as an option for this population in addition to con-Ld and MPL-L.
- While a network meta-analysis was presented comparing con-Ld and MPB, the limitations in the analysis made it difficult to draw any conclusions on the comparative efficacy between the two regimens. In the absence of an RCT, the CGP agreed that it is difficult to determine the true comparative efficacy of lenalidomide to MPB.
- In addition to the cost of the drug itself, lenalidomide prescription incurs additional costs to the health care system because of the Health Canada mandated RevAid controlled drug distribution program

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3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Lymphoma/Myeloma Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

Multiple myeloma is an incurable cancer characterized by increased plasma cells in the bone marrow that can cause osteolytic lesions, hypercalcemia, impaired hematopoiesis, and secretion of monoclonal immunoglobulin that can cause renal dysfunction. Myeloma is diagnosed in approximately 2700 new cases annually with 1400 deaths from the disease expected in Canada in 2015.{69} Median age at presentation is 70 years.{60} Median survival is 4-5 years for patients who are ineligible for high dose chemotherapy and autologous hematopoietic stem cell transplant, and 7-8 years for patients who are eligible for transplant.{60}

3.2 Accepted Clinical Practice

The mainstay of myeloma treatment is anti-cancer drug therapy. Patients with good performance status, preserved organ function and limited comorbidities are potentially eligible for high dose chemotherapy and autologous hematopoietic stem cell transplantation, which improves median survival by 2-3 years in comparison to conventional dose therapy. Approximately half of these patients will not eligible for this treatment due to advanced age, comorbidities and/or impaired functional status.{60}

Two regimens that do not include lenalidomide have been shown in randomized trials to improve patient outcomes in comparison to the previous melphalan and prednisone (MP) standard regimen for transplant-ineligible myeloma: the addition of thalidomide to MP (the MPT regimen){70} and the addition of bortezomib to MP (the MPB regimen).{71} MPT and MPB have not been directly compared in randomized trials and it is therefore not clear if one is superior; both are considered standard front line therapies for transplant-ineligible myeloma, however thalidomide is not readily available in Canada. MPT has been compared to MP in several high quality trials, consistently showing improved PFS for MPT and with evidence of improved OS in both an individual trial and in meta-analyses. MPB has been compared to MP in one high quality trial, in which both PFS and OS were improved with MPB.

In both clinical trials and clinical practice, MPT and MPB are usually given for defined periods of time (on the order of 12-18 months) rather than being administered continuously until disease progression, because cumulative toxicity limits the duration of therapy that is tolerable by most patients.{70, 71} Maintenance therapy with thalidomide has been found to improve PFS in both transplant and non-transplant containing frontline regimens,{72} but toxicity has prevented the widespread uptake of this approach in clinical practice.{73} Bortezomib maintenance shows some promise but has not yet been adequately studied to rigorously determine its role in myeloma therapy.{73}

While MPB is widely available in Canada, MPT is not. Clinical trials have not directly compared MPB to lenalidomide-containing regimens. MPT has been compared to lenalidomide-based therapy in randomized trials and is an acceptable standard regimen for such a comparison. A lenalidomide-containing regimen that is demonstrably superior to MP

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is also worthy of consideration as a standard frontline therapy for transplant-ineligible patients, given that this is the level of evidence currently available for both MPT and MPB.

In this review, the use of lenalidomide-containing regimens as initial therapy for transplant-ineligible myeloma patients is being considered, as well as the question of whether such therapy should be prescribed until disease progression or unacceptable toxicity occurs ("continuous therapy") or whether a pre-defined duration of lenalidomide-containing treatment should be given, as is currently the standard approach with MPT or MPB.

3.3 Evidence-Based Considerations for a Funding Population

Of the 2700 new myeloma diagnoses are made in Canada each year,{69} the vast majority will need immediate therapy, and approximately half of these patients are transplant-ineligible.{60} Therefore, approximately 1350 transplant-ineligible myeloma patients per year are potentially under consideration to receive frontline lenalidomide-containing therapy. Ineligibility for transplant may be due to advanced age, comorbidities and/or impaired functional status. There is no strict definition of a "transplant-eligible" or "transplant-ineligible" myeloma patient, and this distinction is made individually for each patient by the treating hematologist or oncologist.{74}

Studies in transplant-eligible patients demonstrate improvement in outcomes with continuous lenalidomide as part of front line therapy. The trial published by Palumbo and colleagues{75} randomized patients initially treated with 4 cycles of induction with Ld to consolidation with MPL versus autologous stem cell transplant consolidation, followed by a second randomization to lenalidomide maintenance or no maintenance. In the Palumbo trial, maintenance therapy significantly improved PFS regardless of the consolidation regimen used (MPL or transplant). Two other frontline trials in the post-autologous transplant setting have also shown lenalidomide maintenance to improve PFS, with OS being prolonged in one trial.{76, 77} Taken together, the use of continuous lenalidomide therapy for myeloma patients has consistently improved PFS, with some evidence of improved OS, as part of frontline therapy in both transplant-eligible and transplant-ineligible patients.

Continuous lenalidomide and dexamethasone (con-Ld) is likely to be prescribed to many of these patients if it is available. Some patients might still be prescribed the MPB regimen, either if they pay for their oral cancer drugs with third-party drug plans that do not fund lenalidomide, or if the treating physician feels that MPB is a better choice than a lenalidomide-containing regimen on the basis of clinical factors. The MPL-L regimen might also be chosen for some patients. In the absence of direct comparisons amongst con-Ld, MPL-L and MPB in randomized trials, it is reasonable for all three regimens to be made available to patients and their treating physicians.

3.4 Other Patient Populations in Whom the Drug May Be Used

Lenalidomide and dexamethasone is already widely available in Canada to treat relapsed and refractory multiple myeloma. This regimen is used in some countries as induction therapy prior to autologous stem cell transplantation.{78, 79} It is also sometimes considered as a treatment for smouldering multiple myeloma or AL amyloidosis, another plasma cell dyscrasia;{80} lenalidomide is an established treatment for myelodysplastic

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syndrome, a bone marrow disorder unrelated to myeloma.{81} All of these indications are reasonable, but are not the subject of this review. Ongoing randomized trials in the frontline therapy of transplant-ineligible are comparing lenalidomide and dexamethasone with vs. without the addition of newer therapies such as daratumumab, elotuzumab, ixazomib and carfilzomib; the results of these trials might prompt a future change in practice, and some of these regimens have already emerged as superior to con-Ld in the relapse setting. Lenalidomide is under evaluation as a treatment for other hematologic malignancies including chronic lymphocytic leukemia,{82} Waldenstrom's macroglobulinemia,{83} and various lymphomas.{84}

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4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Myeloma Canada, provided input on lenalidomide (Revlimid) in combination with low-dose dexamethasone, for treatment of newly diagnosed multiple myeloma patients who are not candidates for stem cell transplantation, and their input is summarized below.

Myeloma Canada conducted an online survey from April 9 to April 24, 2015 to gather information from myeloma patients and caregivers about the impact of myeloma on their lives and the effect of treatments on their myeloma. The survey included specific questions directed to patients who have not had a stem cell transplant nor are candidates for stem cell transplantation. Within this group, specific questions were asked about the expectations of lenalidomide from patients that **have not used** the treatment and 2) questions about the treatment experiences from patients that **have used** lenalidomide.

Myeloma Canada reported a total of 713 responded to the survey. Of this total, 653 respondents were from Canada, 56 were from the United States, 2 were from Italy and 2 were from the UK. Among the respondents, 518 were individuals living with myeloma and the remaining 195 were caregivers. A total of 181 respondents did not receive a stem cell transplant nor were they candidates; among this cohort of respondents, 33 respondents had used lenalidomide.

From a patient perspective, the level of impact of multiple myeloma varies depending on how long the patient has been diagnosed, whether or not they have had treatment, and whether their symptoms are under control. Respondents indicated that it is very important to have access to effective treatments for myeloma and to have a choice of drug based on known side effects of the drug. Respondents who did not receive the drug under review reported that the expected benefit such as lack of disease progression from a new treatment was extremely important. For respondents who have experienced with lenalidomide, the following were reported: 62% (N=16) respondents reported that it had provided remission or extended life, 12% (n=3) indicated that it had improved their quality of life, 15% (n=4) that it had been positive in terms of long-term health and well-being, 12% (n=3) were unsure, 4% (n=1) stopped treatment because of side effects, 4% (n=1) felt that he or she were no longer getting benefit from treatment, and 4% (n=1) wasn't getting better or worse. The most common side effects of lenalidomide included skin rash, fatigue, constipation, neutropenia and diarrhea. The majority of respondents reported that these side effects were tolerable.

Please see below for a summary of specific input received from the patient advocacy group. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that was reported have also been reproduced as is according to the submission, without modification.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with multiple myeloma

Myeloma Canada reported on patient experiences with multiple myeloma, including the importance of controlling symptoms/side-effects and the impact on the day-to-day activities.

Respondents rated on a scale of 1-5 how important it is to control various aspects of myeloma, patients indicated that infections were the most important, followed by kidney

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problems, mobility, pain, fatigue, neuropathy and shortness of breath. Each response received a weighted average of 4.34 or higher, which according to Myeloma Canada meant that all aspects were considered to be important to very important.

	1 - Not important	2	3	4	5 - Very important	N/A	Total	Weighted Average
Infections	2% 9	1% 6	5%21	6% 28	85% 383	1% 6	453	4.72
Kidney problems	3% 12	3% 13	4%18	10% 46	76% 344	4%19	452	4.61
Mobility	2% 10	4% 17	6% 26	18% 82	66% 299	4%16	450	4.48
Pain	3% 11	4%18	7%33	16% 70	68% 304	3% 13	449	4.46
Fatigue	0.9% 4	3% 15	10% 46	20% 89	64% 287	0.90% 4	445	4.45
Neuropathy	2% 9	3% 14	11% 47	18% 82	62% 277	4% 17	446	4.41
Shortness of breath	2% 11	5% 21	11% 47	18% 80	60% 267	4%19	445	4.34

Respondents also rated on a scale of 1-5 how much symptoms associated with myeloma impact or limit day-to-day activity and quality of life. Respondents indicated that their ability to work was most affected, followed by ability to exercise, travel, volunteer, conduct household chores, fulfill family obligations, spend time with family. All responses received a 2.64 - 3.43 weighted average, which indicated a higher than neutral impact.

Ability to:	1 - Not at all	2	3	4 -	5 - Significant impact	N/A	Total -	Weighted Average -
Work	13% 61	13% 59	15% 71	12% 57	32% 148	15%69	465	3.43
Travel	14% 65	17% 78	21% 97	19% 88	27% 125	2% 11	464	3.29
Exercise	12% 55	16% 74	24%112	24%111	23%105	1% 6	463	3.30
Volunteer	18% 84	16% 75	20% 94	17% 80	21% 98	7% 31	462	3.08
Conduct household chores	17% 77	25%117	25% 117	19% 86	13% 62	0.86%4	463	2.87
Fulfill family obligations	20% 93	23% 104	22% 101	19% 88	13% 59	3% 15	460	2.81
Spend time with family and friends	27% 126	24% 110	18% 82	18% 83	12% 57	1% 5	463	2.64

Myeloma Canada noted the level of impact varies depending on how long the patient has been diagnosed, whether or not they have had treatment, and whether their symptoms are under control. To provide greater clarity regarding the answers to this question, respondents reported the following:

> *"this is based on when I was very sick. Am in remission now and have healthy respect for disease"*

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"Ability to enjoy life, (& loved ones), no quality of life at times. Depression, constant pain because of shingles in mouth that turned into Neuralgia"

"depends entirely on current position in cycle"

"Currently my myeloma is in remission and the vertebral damage is controlled. However, when I was in the midst of my symptoms, every one of these would have been 5"

4.1.2 Patients' Experiences with Current Therapy for Newly Diagnosed Mutilple Myeloma

Myeloma Canada reported that the main treatments patients used included: dexamethasone (n=102), bortezomib (n=98), melphalan (n=62), cyclophosphamide (n=40), thalidomide (n=23).

Below were the side-effects experienced that were reported by respondents as a result of the treatments:

Side Effect	%	N
Fatigue	80	120
Neuropathy	55	83
Pain	41	62
Insomnia	37	56
Shortness of Breath	36	54
Nausea	35	53
Stomach Issues	33	49
Confusion	29	44
Does not apply to me as I have yet to be treated	5	8
I don't know or can't remember	2	3

According to Myeloma Canada, of the 430 respondents, 98% of the respondents indicated that it is very important to have access to effective treatments for myeloma. 98% of respondents rated it as a 5 on a scale of 1 - 5, with 5 being "very important". The weighted average was 4.89.

Drawing from the responses, Myeloma Canada reported that the majority of respondents noted that it was important to have a choice of drug based on known side effects of the drug. Of the 442 respondents, 89% of the respondents gave this a rating of 5 being "very important". The weighted average was 4.98.

In addition, of the 430 respondents, 87% of respondents reported that "improvement to quality of life" was a very important consideration with any treatment for myeloma. The weighted average was 4.89.

When asked about hardships accessing treatment for myeloma, of the 389 respondents, 87% respondents indicated that they did not experience hardships or not so far in accessing treatments. 12% (n=44) respondents reported hardships that included delays in treatment, overall lack of access to treatment, costs related, special access. It was reported that 2% (n=8) respondents were on clinical trials.

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4.1.3 Impact of Multiple Myeloma and Current Therapy on Caregivers

Respondents were asked to rate on a scale of 1 – 5 on how much the symptoms associated with multiple myeloma impact or limit the caregiver's day-to-day activity and quality of life, with 1 being "not at all", and 5 being "significant impact". Myeloma Canada reported that the ability to travel was impacted the most with weighted average of 3.21, followed by ability to work (2.46); spending time with family and friends (2.43); fulfilling family obligations (2.41); volunteering (2.32); exercise (2.24); and conducting household chores (2.23). Total caregiver respondents for this answer ranged from 179 – 183.

Myeloma Canada received a total of 177 caregivers who responded to an open question asking about the challenges they face as a result of the side effects of treatment. The following responses were given: 38% (n=35) have experienced stress/anxiety/depression, 13% (n=12) have more work to do around the home, 12% (n=11) find it difficult to deal with the mood swings of the patient, 12% (n=11) experienced fatigue, 11% (n=10) have had a negative effect on their quality of life, 11% (n=10) reported no challenges or no challenges yet, 4% (n=4) reported "yes" with no explanation, 2% (n=2) found it difficult to deal with the side effect of diarrhea, and 1% (n=1) had to inject pain medication.

Below were some of the comments gathered from caregiver respondents:

> *"A significant impact on all aspects but we were probably the happiest and most appreciative of life during this time. I will never regret our choices and my role as caregiver. Before he passed he said it was "sensational" that we were able to get more time and live it out in such a transending way. I always wonder if he had had the revimind sooner if things would be different."*
>
> *"Trying to provide meals when my husband is nauseous and doing all the driving when he is in pain or too tired or* confused"
>
> "*my husband's mobility was hampered as well has his cognitive function when he was on the refectory drugs. He wasn't able to sleep at night for more than two or three hours which meant I was up every time with him as well. I was running on love and adrenalin, not sleep."*
>
> *"yes, side effects impact tempermen of patient in turn (really) impact my feelings and outlook"*
>
> *"It greatly limits travel, affects intimency, affects ability to exercise, go for walks, travel"*
>
> *"Additional requirement to assist patient with personal care. Unable to leave patient for extended time."*

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Lenalidomide

Respondents who had not had a stem cell transplant nor did they qualify for transplantation were asked if they were to consider taking a new treatment for their myeloma, to rate on a scale of 1-5 how important it is to bring about improvement in their physical condition. Of the 140

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respondents, a total of 82% of respondents rated this as (extremely important). The weighted average was 4.77.

Moreover, of the 139 respondents, 90% of this respondent group also reported that the expected benefit (such as lack of disease progression) from a new treatment was extremely important. The weighted average was 4.90.

When asked to rate on a scale of 1 - 5, with 1 being "no side effects" and 5 being "significant side effects", this respondent group responded that they are willing to tolerate some side effects. Of the 142 respondents, 12% of respondents selected "significant side effects, and 10% selected "no side effects"; the overall weighted average was 3.10, which is according to Myeloma Canada is higher than neutral.

According to Myeloma Canada, 33 respondents had used lenalidomide who have not had a stem cell transplant nor qualified for stem cell transplant.

Of the 29 respondents who responded to the open-ended question about how lenalidomide changed or is expected to change long-term health and well-being, 62% of respondents (n=16) reported that it had provided remission or extended life, 12% (n=3) indicated that it had improved their quality of life, 15% (n=4) that it had been positive in terms of long-term health and well-being, 12% (n=3) were unsure, 4% (n=1) stopped treatment because of side effects, 4% (n=1) felt that he or she were no longer getting benefit from treatment, and 4% (n=1) wasn't getting better or worse.

Based on responses from 31 respondents, lenalidomide was very effective in controlling their myeloma. On a scale of 1 - 5, with being "not effective" and 5 being "extremely effective", 52% of respondents (n=16) rated it is a "5" and 3% of respondents (n=1) rated is as a "1".
The weighted average was 4.27.

Respondents were also asked to rate how tolerable the side effects of lenalidomide on a scale of 1 - 5, with 1 being "completely intolerable" and 5 "very tolerable". Of the 31 respondents, 58% of respondents (n=18) rated it is a "4" or higher and 3% of respondents (n=1) rated it is a "1".
The weighted average was 3.67.

The most common side effects with reported for lenalidomide were:

-	1 - Completely intolerable	2	3	4	5 - Very tolerabl	N/A	Total	Weighted Average
Skin rash	4%(1)	4%(1)	17%(4)	13%(3)	17% (4)	43% (10)	23	3.62
Fatigue	0%	11%(3)	52%(14)	15%(4)	15%(4)	7%(2)	27	3.36
Constipation	0%	12%(3)	36%(9)	16%(4)	12%(3)	24%(6)	25	3.37
Neutropenia	0%	14%(3)	33%(7)	19%(4)	10%(2)	24%(5)	21	3.31
Diarrhea	0%	11%(3)	35% (9)	15%(4)	4%(1)	35%(9)	26	3.18

When asked on a scale of 1 - 5, to rate their quality of life while taking lenalidomide with 1 was "poor quality of life" and 5 "excellent quality of life"; the majority of respondents rated this as a "3" or higher. Of the 31 respondents who answered the question, 48% of respondents (n=15) rated it as a "4" or higher. The weighted average was 3.53.

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When asked in an open-ended question about anything else about lenalidomide that respondents wanted us to know and include, the 18 respondents who answered this question reported the following: 28% of respondents (n=5) were grateful for the treatment, 11% of respondents (n=2) identified negative side effects, 6% of respondents (n=1) indicated that it extends life, 5% of respondents (n=1) said that it was a necessary treatment, 5% of respondents (n=1) thought it was expensive and 5% of respondents (n=1) thought "It's a cure".

The following responses represent some of the comments provided that help to illustrate respondents' experiences with lenalidomide:

> *It has kept me alive for close to 4 years now, and my blood tests improve gradually with each test.*
> *My cancer is relatively stabilized at about 30% of what it was. I expect it (w) ill stay that way.*
>
> *Revlimid has changed my health from very poor to completely tolerable. My quality of life has improved so much since taking Revlimid. This is my second round of Revlimid. I was in a study for l8 months of Revlimid and dexamethasone. I was then in remission for 3 years. I started a second study with Revlimid and dex and another drug MLN9708/placebo. My m-protein in again very low and I am tolerating it well.*
>
> *I have gone from not being able to get out of bed on my own to being able to take care of all my personal needs.*
>
> Doesn't seem to be getting better or worse
>
> *It has lowered by m-protein from 1.7 to 0.2*
>
> *If you can tolerate the side effects than you can expect to live longer and have many good days*
>
> *It's darn expensive.*
>
> *For me, it has been extremely effective (combined with dexa) going into remission after 10 months of treatment*

4.3 Additional Information

No information was provided in this section by Myeloma Canada.

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5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from the eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could be impact implementation of lenalidomide in the first-line treatment of multiple myeloma in patients who are not eligible for stem cell transplantation (SCT):

Clinical factors:

- Mephalan/prednisone/thalidomide is not most the relevant Canadian comparator
- Long-term benefits compared to risk of secondary cancers
- Treatment sequencing
- Oral administration of two drugs instead of the current intravenous drug in combination with two oral drugs

Economic factors:

- Unknown duration of therapy
- High cost of lenalidomide relative to the standard of care
- Additional resources to monitor adverse effects, monthly, prior to drug distribution (Revaid program)
- Lower cost of bortezomib due to recently available generic product

Please see below for more details.

5.1 Factors Related to Comparators

For patients with multiple myeloma who are not eligible for SCT, the standard of care in most provinces is melphalan/prednisone/ bortezomib (MPB), cyclophosphamide/ bortezomib/dexamethasone (CBD) or bortezomib/cyclophosphamide/prednisone. PAG noted that while melphalan/prednisone/thalidomide (MPT) is available in 2 provinces, the combination of MPT is seldom used due to the poor tolerance to thalidomide and would not be the relevant comparator in Canadian practice.

PAG is seeking information on comparative efficacy to MPB.

5.2 Factors Related to Patient Population

PAG noted that the number of patients would be relatively small. PAG is seeking guidance on determining patients who would not be eligible for SCT and therefore, could be eligible for treatment with lenalidomide plus dexamethasone.

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In addition, PAG is seeking information on treating patients after they have progressed on lenalidomide plus dexamethasone therapy and whether re-treatment as third-line treatment of later would be appropriate. PAG noted that some patients who progress would then be treated with intravenous chemotherapy and is seeking information on re-treatment with lenalidomide after treatment with intravenous chemotherapy.

5.3 Factors Related to Dosing

PAG indicated that lenalidomide in combination with dexamethasome would be more acceptable to patients over travelling to chemotherapy clinics for administration of an intravenous drug and also taking two other oral drugs at home. This is an enabler to implementation. PAG also indicated the once daily dosing would enhance treatment compliance but patients would need to be informed of the 21 day treatment cycle.

5.4 Factors Related to Implementation Costs

As lenalidomide is administered orally, PAG identified that chemotherapy units and chair time would not be required. In addition, health care professionals are familiar with the administration and monitoring of lenalidomide. These are enablers to implementation.

PAG noted that although the number of patients may be small, the cost of lenalidomide is high and duration of therapy is indefinite since it is assumed patients will be treated until progression. The budget impact may be significant but there is uncertainty in the degree of the impact. PAG also noted that bortezomib is less costly with the availability of its generic product in 2015.

5.5 Factors Related to Health System

PAG noted that lenalidomide is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. PAG identified the oral route of administration is an enabler to implementation.

However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

PAG has concerns on the significant time and logistical coordination required for the RevAID monitoring program. The controlled drug distribution program mandated by Health Canada will require additional pharmacy and health care resources for monthly monitoring and for longer period of time. PAG noted that the overall time for coordinating distribution lenalidomide and monitoring could be more than the time for the preparation, administration and monitoring of bortezomib.

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5.6 Other Factors

PAG identified that the high cost and flat pricing of the different strengths of lenalidomide tablets is a barrier to implementation.

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6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of lenalidomide (LEN) as a combination therapy in the treatment of newly diagnosed multiple myeloma (ND-MM) in patients who are not candidates for stem cell transplantation (SCT). (See Table 1 in Section 6.2.1 for outcomes of interest).

A Supplemental Question most relevant to the pCODR review and to the Provincial Advisory Group was identified while developing the review protocol and is outlined in section 7.

- Summary of manufacturer-submitted network meta-analysis comparing lenalidomide with other first-line treatments for patient with newly diagnosed multiple myeloma who are not candidates for stem cell transplantation

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 2: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs	Patients with ND-MM who are not candidates for SCT **Subgroups:** Age Performance status	Lenalidomide (10 to 25 mg on days 1 to 21 of a 28-day cycle)	Melphalan/ prednisone/ thalidomide (MPT) melphalan/ prednisone/bortezomib (MPB) Cyclophosphamide/ bortezomib/ dexamethasone (CyBorD) Cyclophosphamide/ bortezomib/ prednisone	Efficacy OS HR-QoL PFS TTP Duration of response Overall response rate Safety SAE AE WDAE Death AEs of interest Deep vein thrombosis Pulmonary embolism Hepatotoxicity Cardiac disorders

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Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
				Second primary malignancies Neuropathy Neutropenia Thrombocytopenia
AE = adverse event; HR-QoL= health-related quality of life; ND-MM = newly diagnosed multiple myeloma; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; SAE = serious adverse event; SCT = stem cell transplantation; TTP = time to progression; WDAE = withdrawal due to adverse event				

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-2015 May 19) with in-process records & daily updates via Ovid; Embase (1974-2015 May19) via Ovid; The Cochrane Central Register of Controlled Trials (April 2015) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Revlimid, lenalidomide and Multiple Myeloma.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. Where possible, retrieval was limited to the human population. The search was also limited to English language documents, but not limited by publication year. The search is considered up to date as of September 4, 2015.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health - clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

6.2.3 Study Selection

Two members of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

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6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

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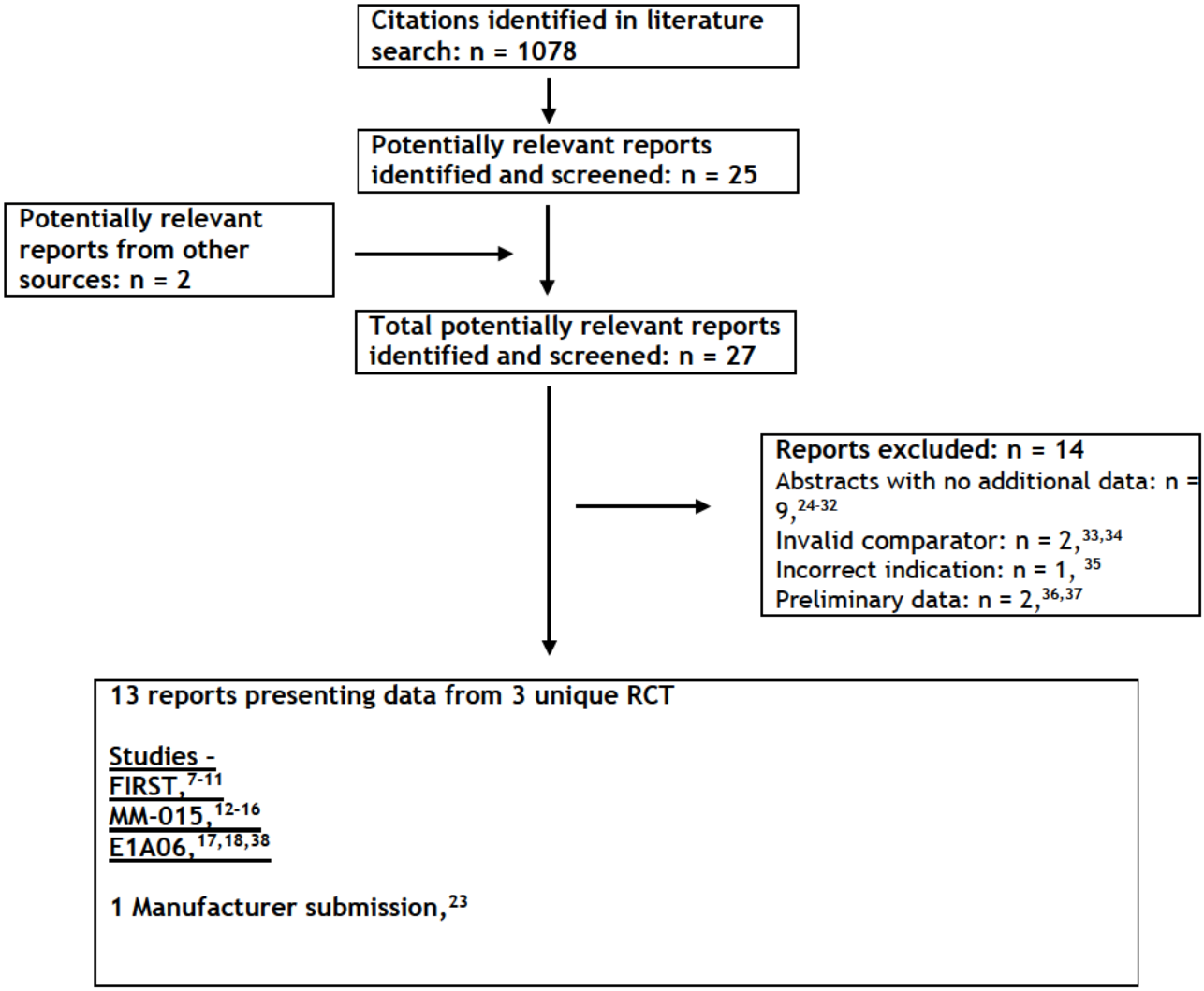
6.3 Results

6.3.1 Literature Search Results

Of the 1078 potentially relevant reports identified through literature search, 25 were considered potentially relevant. Thus, with the manufacturer's submission[23] and another document found on the web,[18] a total of 27 potentially references were identified. Thirteen reports presenting data from 3 studies were included in the pCODR systematic review[7-18,23] and fourteen studies were excluded. Studies were excluded because they were abstracts which provided no additional data[24-32], had an invalid comparator[33,34], was investigating an incorrect indication[35], or provided preliminary data.[36,37]

QUOROM Flow Diagram for Inclusion and Exclusion of studies



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Note: Additional data related to the FIRST and MM-015 studies were also obtained through requests to the Submitter by pCODR at the Checkpoint Meeting.[67]

6.3.2 Summary of Included Studies

Three clinical trials, the FIRST trial[7-11] the MM-015 trial,[12-16] and the E1A06 trial[17,18] met the inclusion criteria for this systematic review. All were multicenter, phase III RCTs which evaluated LEN as first-line treatment for ND-MM in patients who were not candidates for SCT. The FIRST trial compared the melphalan + prednisone + thalidomide (MPT) regimen to LEN in combination with dexamethasone (Ld), either continuously (con-Ld) or for 18 cycles of 4 weeks (Ld18). In the MM-015 trial, the melphalan + prednisone + LEN (MPL) regimen for induction followed by maintenance with LEN (MPL-L) was compared to MPL or melphalan + prednisone (MP) for induction without maintenance therapy. The E1A06 trial compared induction with MPT followed by maintenance with thalidomide (MPT-T) to induction with MPL followed by maintenance with LEN (MPL-L). Table 3 presents a summary of the included studies.

6.3.2.1 Detailed Trial Characteristics

Table 3. Summary of Trials Characteristics

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
FIRST trial[7-11] Phase III, active controlled, open-label, RCT 246 centres in 18 countries, including Canada Patient enrollment: August 2008 through March 2011 N = 1623 randomized, N = 1613 treated Funded by: Intergroupe Francophone du Myelome and Celgene	Patients with previously untreated, symptomatic and measurable multiple myeloma who were ineligible for stem cell transplantation. Patients did not have restriction for age. <u>Exclusion criteria:</u> • Prior antimyeloma treatment, except for radiotherapy and treatment with bisphosphonates or a single course of glucocorticoids. • ECOG PS > 2 • Renal failure requiring dialysis • ANC < 1000/mm^3, platelet count < 50,000/mm^3 • AST or ALT levels more than 3 times the upper limit of the normal range • Peripheral neuropathy of grade 2 or higher	MPT (N = 547), melphalan (0.25 mg/kg/day on days 1 to 4), prednisone (2 mg/kg/day on days 1 to 4), thalidomide (200 mg/day) on 42-day cycles for 12 cycles (72 weeks) 2 groups with lenalidomide (25 mg per day on days 1 to 21 of each cycle) in combination with dexamethasone (40 mg on days 1, 8, 15 and 22) administered on 28-day cycles: • Ld18 (N = 541), treated for 18 cycles (72 weeks) • con-Ld (N = 535), treated until disease progression All patients were on antithrombotic prophylaxis.	<u>Primary</u> PFS <u>Secondary</u> OS ORR Time to response Duration of response Time to treatment failure Time to second line therapy HR-QoL Safety <u>Exploratory</u> Time to disease progression PFS after next line of treatment
MM-015 trial[12-16] Phase III, placebo-controlled, double blind, RCT 82 centers in Europe, Australia and Israel Patient enrollment:	Patients with symptomatic, measurable, newly diagnosed multiple myeloma who are not candidates for transplantation (≥65 years of age) <u>Exclusion criteria:</u> • ANC < 1500/mm^3 • Platelet count < 75,000/mm^3 • Hemoglobin level < 8.0 g/dL • Renal insufficiency, i.e., serum creatinine level of > 2.5 mg/dL	Group MPL-L (N = 152), MPL induction with nine 28-day cycles of: melphalan (at a dose of 0.18 mg/kg on days 1 through 4), prednisone (2 mg/kg on days 1 through 4), lenalidomide (10 mg/day on days 1 through 21). This is followed by lenalidomide maintenance using the same regimen.	<u>Primary</u> PFS <u>Secondary</u> OS ORR Time to response Duration of response Response quality HR-QoL Safety

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February 2007 through September 2008 N = 459 randomized Funded by Celgene	• Peripheral neuropathy of grade 2 or higher	Group MPL(N = 153), same MPL induction, followed by placebo maintenance Group MP (N = 154), MP induction using the same regimens as in the MPL induction, with placebo during induction and maintenance. All patients received aspirin (75 to 100 mg daily) antithrombotic prophylaxis during induction, and could be continued during maintenance.	
E1A06 trial,[38] abstracts[17,18] Phase III, active-controlled, open label, non-inferiority RCT Patient enrollment: February 2008 through November 2011 N = 306 patients randomized The study was sponsored by the National Cancer Institute	Symptomatic, transplant ineligible patients who were previously untreated (≥65 years and declined alternative treatment or <65 years and not a candidate for SCT or declined transplant) **Exclusion criteria:** • ECOG PS > 2 • ANC < 1000/mm^3 • Platelet count < 75,000/mm^3 • Renal insufficiency, i.e., serum creatinine level of > 2.5 mg/mL and creatinine clearance < 60 mL/min • AST and ALT levels more than 2.5 times the upper limit of the normal range	Group MPT-T: melphalan (9 mg/m^2 on days 1 through 4), prednisone (100 mg on days 1 through 4) and thalidomide (100 mg daily) for twelve 28-day cycles, followed by maintenance with thalidomide (100 mg daily) alone until relapse Group MPL-L: melphalan (5 mg/m^2 on days 1 through 4), prednisone (100 mg on days 1 through 4) and lenalidomide (10 mg on days 1 to 21) for twelve 28-day cycles, followed by maintenance with lenalidomide (10 mg daily) alone until relapse. Aspirin anti-thrombotic prophylaxis was used.	Primary PFS Secondary OS ORR Depth of response QoL Toxicity
ALT = alanine aminotransferase; **ANC** = absolute neutrophil count; **AST** = aspartate aminotransferase; **con-** Ld = continuous lenalidomide+dexamethasone; **HR-QoL** = health related quality of life; **Ld 18** = lenalidomide+dexamethasone for 18 cycles; **ORR** = overall response rate; **OS =** overall survival; **MP** = Melphalan+prednisone; **MPL** = Melphalan-prednisone-Revlimid; **MPT** = melphalan+prednisone+thalidomide; **PFS** = progression-free survival; **L** = Revlimid (lenalidomide); **RCT**= randomized controlled trial; **T** = thalidomide.			
Note: In the MM-015 study, patients in whom progressive disease developed during induction therapy were proposed to enroll in an open-label extension phase to receive lenalidomide (25 mg/day on days 1 through 21 of a 28-day cycle) alone or in combination with dexamethasone (40 mg/day on days 1 to 4, 9 to 12, and 17 to 20 of a 28-day cycle).			

a) Trials

Three trials met the inclusion criteria for review. The FIRST trial was a multicentre, active-controlled, open-label, phase III RCT. This trial was conducted in 246 treatment centres in 18 countries, including Canada, in Europe, North America and the Asia-pacific region. The MM-015 trial was a multicentre, randomized, double-blind, phase III, placebo-controlled trial. The trial was conducted in 82 centers across Europe, Australia and Israel. The E1A06 trial was a phase III multicentre, active-controlled, open-label, phase III RCT reported in two conference abstracts and recently published. Study center locations were not mentioned. Major eligibility criteria for screened patients in both studies have been listed in Table 3. Briefly, in the FIRST trial, patients were of all ages, had previously untreated symptomatic and measurable ND-MM, and were

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ineligible for SCT. A low performance status (ECOG PS > 2), low neutrophil or platelet counts, renal failure, high hepatic enzymes levels, and moderate to severe peripheral neuropathy were exclusion criteria. Radiotherapy, treatment with bisphosphonates or a single course of glucocorticoids were allowed. The MM-015 trial enrolled similar patients but those were restricted for age ≥ 65 years. Exclusion criteria for this study were low neutrophil or platelet counts, low hemoglobin level, renal insufficiency, and moderate to severe peripheral neuropathy. Both studies were sponsored by Celgene. The E1A06 study enrolled patients with untreated, symptomatic ND-MM ≥ 65 years that had declined alternative treatment and patients < 65 years who were not candidates for SCT or refused transplant. This study was sponsored by the National Cancer Institute.

The FIRST and the MM-015 studies randomized patients at a 1:1:1 ratio between three treatment groups with an interactive voice-response system. Patients were stratified according to age (≤75 years vs. >75 years), International Staging System (ISS) disease stage (I or II vs. III), and country in the FIRST trial. For MM-015, patients were stratified for age and disease stage only. Treatment allocation was not concealed in the FIRST trial. MM-015 had treatment allocations concealed for patients and investigators. The E1A06 trial randomized patients at a 1:1 ratio between two treatment groups using permuted blocks within strata with dynamic balancing within main institution and their affiliate networks. Patients were stratified for ISS disease stage (Stage I-II vs. III) and age (< 65 vs. ≥65). Allocation of treatment was not concealed for this trial.

The primary objectives of the included trials were: to assess the superiority of con-Ld for progression-free survival (PFS) in comparison with MPT in the FIRST trial; to evaluate the superiority of MPL-L for PFS in comparison with MP in the MM-015 trial; and to assess whether MPL-L was non-inferior to MPT-T for PFS in the E1A06 trial.

The FIRST study had more than 80 % power to detect a hazard ratio (HR) of 0.80 for disease progression or death, using a two-sided log-rank test and a significance level of 0.05, including one interim analysis. The O'Brien-Fleming boundary was used for PFS, and the Pocock boundary was used for OS. The MM-015 study had more than 80 % statistical power to detect a 50 % improvement in median PFS from 15 months to 22.5 months using a one-sided log rank test with a significance level of 0.024 for the final analysis. MM-015 was not powered to assess OS. In the E1A06 trial, a difference of 0.18 or more in HR was used as a non-inferiority threshold, which corresponded to a median PFS for MPT-T or 25 months and 20.5 months for MPL-L, incorporating 8 interim analyses and one final analysis. The E1A06 trial had 86% power to detect a HR of at least 1.2 using a one-side significance level of 0.05 for the primary non-inferiority test.

b) Populations

A total of 2388 patients were randomized in the FIRST (N = 1623), the MM-015 (N = 459) and the E1A06 (N = 306) trials. The baseline characteristics of patients enrolled in the E1A06 trial were not specified, except for the median age of patients which was 75.7 years. Across FIRST, MM-015, and E1A06, baseline characteristics were well balanced between groups (Table 4, Table 5 and Table 6). There was no significant difference between groups at baseline, except for the median Karnofsky performance status score (KPSS) in the MM-015 study that was lower for patients randomized to MPL-L compared to patients randomized to MP. The median age of patients in the studies was ranging from 71 to 77 years, with 24 % to 60 % of them aged over 75 years. Indeed, FIRST and E1A06 were the only studies to enroll patients under 65 years old, but these patients represented less than 6 % of its population. Patients enrolled in E1A06 were older than the other two studies. The proportion of males and females were balanced. In terms of performance status, 30 % of the patients in FIRST and E1A06 had a score of 0, half had an ECOG score of 1, and 20% had a score of 2. In MM-015, the median KPSS was ranging from 80 to 100. In terms of disease severity, from 30 % to 51 % of patients were of ISS stage III across groups.

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Table 4. Summary of Patients' Baseline Characteristics: FIRST trial			
Characteristics	FIRST[7,9]		
	MPT N = 547	Ld18 N = 541	con-Ld N = 535
Age			
Median, year	73	73	73
Range, year	51 to 92	40 to 89	44 to 91
≥65 years, n (%)	520 (95)	507 (94)	504 (94)
65 to 75, n (%)	NR	NR	NR
>75 years, n (%)	188 (34)	193 (36)	186 (35)
Sex (n, %)			
Male	287 (52)	273 (50)	294 (55)
Race or ethnic group			
White	491 (90)	480 (89)	474 (89)
Asian	44 (8)	43 (8)	40 (7)
Black	5 (1)	6 (1)	9 (2)
Other	4 (1)	11 (2)	7 (1)
Undisclosed	3 (1)	1 (<1)	5 (1)
ECOG performance status score, n (%)			
0	156 (29)	163 (30)	155 (29)
1	272 (50)	263 (49)	257 (48)
2	111 (20)	113 (21)	119 (22)
3*	2 (<1)	2 (<1)	2 (<1)
Not available	3 (1)	0	2 (<1)
International Staging System stage, n (%)			
I or II	323 (59)	322 (60)	319 (60)
III	224 (41)	219 (40)	216 (40)
Myeloma subtype, n (%)			
IgA	123 (22)	142 (26)	138 (26)
IgD	4 (1)	7 (1)	4 (1)
IgG	350 (64)	331 (61)	334 (62)
IgM	1 (<1)	1 (<1)	3 (1)
IgA and IgG	8 (1)	6 (1)	7 (1)
IgA and IgM	1 (<1)	0	0
Light chain only	57 (10)	54 (10)	46 (9)
Not available	3 (1)	0	3 (1)
Lactate dehydrogenase, n (%)			
<200 U/liter	434 (79)	442 (82)	448 (84)
≥200 U/liter	112 (20)	99 (18)	86 (16)
Missing data	1 (<1)	0	1 (<1)
Creatinine clearance, n (%)			
<30 mL/min	55 (10)	47 (9)	45 (8)
<60 mL/min	258 (47)	254 (47)	267 (50)
≥60 mL/min	289 (53)	287 (53)	268 (50)
History of bone lesions, n (%)			
Present	394 (72)	382 (71)	380 (71)
Absent	153 (28)	158 (29)	154 (29)
Unknown	0	1 (<1)	1 (<1)
High-risk cytogenetic profile†			
n/N (%)	47/253 (19)	52/261 (20)	43/248 (17)

con-Ld = continuous lenalidomide + dexamethasone; Ig = immunoglobulin; Ld18 = lenalidomide+dexamethasone for 18 cycles; MPT = melphalan + prednisone + thalidomide; U = Unit;

* Six patients had worsening of their ECOG PS score from 2 to 3 during the screening period
† A high-risk cytogenetic profile was define was defined as translocations (4;14) or (14;16) or deletion 17p.

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Table 5. Summary of Patients' Baseline Characteristics: MM-015 trial			
Characteristics	MM-015		
	MPL-L N = 152	MPL-placebo N = 153	MP + placebo-placebo N = 154
Age			
Median, year	71	71	72
Range, year	65 to 87	65 to 86	65 to 91
65 to 75, n (%)	116 (76.3)	116 (75.8)	116 (75.3)
>75 years, n (%)	36 (23.7)	37 (24.2)	38 (24.7)
Sex (n, %)			
Male	71 (46.7)	82 (53.6)	75 (48.7)
Karnofsky performance status score, n (%)			
Median	80*	80	90
Range	60 to 100	60 to 100	60 to 100
International Staging System stage, n (%)			
I	28 (18.4)	32 (20.9)	28 (18.2)
II	50 (32.9)	47 (30.7)	48 (31.2)
III	74 (48.7)	74 (48.4)	78 (50.6)
Lytic bone lesions, n (%)			
Present	108 (71.1)	110 (71.9)	101 (65.6)
Absent	43 (28.3)	40 (26.1)	51 (33.1)
Missing data or not determined	1 (0.7)	3 (2.0)	2 (1.3)
Creatinine clearance, n (%)			
≥ 60 mL/min	72 (47.4)	83 (54.2)	77 (50.0)
< 60 mL/min	78 (51.3)	69 (45.1)	76 (49.4)
Missing data	2 (1.3)	1 (0.7)	1 (0.6)
Cytogenetic features, n (%)			
Adverse			
Deletion 17p	6 (3.9)	6 (3.9)	7 (4.5)
Translocation (4;14)	6 (3.9)	2 (1.3)	3 (1.9)
Translocation (14;16)	0	1 (0.7)	0
Favorable†	14 (9.2)	19 (12.4)	13 (8.4)
Deletion 13q	38 (25.0)	45 (29.4)	38 (24.7)
Normal	1 (0.7)	4 (2.6)	2 (1.3)
Could not be evaluated	61 (40.1)	61 (39.9)	59 (38.3)
Missing data	32 (21.1)	21 (13.7)	41 (26.6)

MP = melphalan + prednisone; MPL = melphalan + prednisone + Revlimid (lenalidomide); MPL-L = MPL for induction therapy + Revlimid (lenalidomide) as maintenance therapy; U = Unit;

* There was a statistically significant difference (P = 0.03) compared to the MP group.
† A favorable prognosis was defined as the presence of a hyperdiploid karyotype and translocation t(11;14)(p13;q32)

Table 6. Summary of Patients' Baseline Characteristics: E1A06 trial		
Characteristics	E1A06	
	MPT-T N = 154	MPL-L N = 152
Age		
Median, year	75.8	76.6
Range, year	54.3 to 91.9	62.7 to 91.6
< 65 years, n (%)	9 (5.8)	6 (4.0)
<75 years, n (%)	61 (39.6)	63 (41.5)
Sex (n, %)		
Male	86 (55.8)	81 (53.3)
International Staging System stage, n (%)		
I	45 (29.6)	36 (23.7)

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II	58 (38.2)	70 (46.0)
III	49 (32.2)	46 (30.3)
ECOG Performance Status Score, n (%)		
0	51 (33.1)	49 (32.2)
1	74 (48.1)	74 (48.7)
2	29 (18.8)	29 (19.1)
Creatinine clearance, n (%)		
> 1.5 mg/dL	16 (10.4)	16 (10.5)
Myeloma subtype, n (%)		
IgG	92 (71.3)	90 (72.6)
IgA	32 (24.8)	32 (25.8)
IgM/IgD/Biclonal	5 (3.9)	2 (1.6)

MPL-L = melphalan + prednisone + Revlimid (lenalidomide) for induction therapy + Revlimid (lenalidomide) as maintenance therapy; **MPT-T** = melphalan + prednisone + thalidomide for induction therapy + thalidomide as maintenance therapy

c) Interventions

In FIRST, 547 patients were randomized to MPT: melphalan (0.25 mg/kg/day on days 1 to 4), prednisone (2 mg/kg/day on days 1 to 4), thalidomide (200 mg/day) on 42-day cycles for 12 cycles (72 weeks); 541 patients were randomized to LEN (25 mg per day on days 1 to 21 of each cycle) in combination with dexamethasone (40 mg on days 1, 8, 15 and 22) administered on 28-day cycles for 18 cycles (Ld 18); and 535 patients were randomized to continuous LEN therapy in combination with dexamethasone (con- Ld) using the same treatment regimen as Ld 18.

In MM-015, 152 patients were randomized to receive MPL-L which consisted of MPL induction with nine 28-day cycles of melphalan (at a dose of 0.18 mg/kg on days 1 through 4), prednisone (2 mg/kg on days 1 through 4), and LEN (10 mg/day on days 1 through 21), followed by LEN maintenance using the same regimen until disease progression or the development of unacceptable rates of adverse effects. The 153 patients randomized to the MPL group had the same MPL induction followed by placebo maintenance. The last group of 154 patients was allocated MP using the same melphalan and prednisone regimens as for the MPL regimen for induction. To maintain the blinding of these latter patients, LEN was replaced by placebo for both the induction therapy and the maintenance therapy. Specifically for this study, patients in whom progressive disease developed during induction therapy were proposed to enroll in an open-label extension phase to receive LEN (25 mg/day on days 1 through 21 of a 28-day cycle) alone or in combination with dexamethasone (40 mg/day on days 1 to 4, 9 to 12, and 17 to 20 of a 28-day cycle).

In E1A06, 306 patients were enrolled, with 154 patients randomized to MPT and 152 patients randomized to MPL. The MPT group received melphalan (9 mg/m^2 on days 1 through 4), prednisone (100 mg on days 1 through 4) and thalidomide (100 mg daily) for twelve 28-day cycles, followed by maintenance with thalidomide (100 mg daily) alone until relapse. The MPL group received melphalan (5 mg/m^2 on days 1 through 4), prednisone (100 mg on days 1 through 4) and lenalidomide (10 mg on days 1 to 21) for twelve 28-day cycles, followed by maintenance with lenalidomide (10 mg daily) alone until relapse. Maintenance was not given in patients discontinuing therapy during induction.

For FIRST, MM-015 and E1A06, doses reductions were allowed as pre-specified in the protocol. All patients received protocol-specified anti-thrombotic prophylaxis which included low dose (70 to 325 mg/day) aspirin in all three trials, but also low molecular weight heparin, heparin or warfarin in the FIRST trial. Bisphosphonates, other supportive therapies, hematopoietic or myeloid growth factors were allowed in the FIRST trial. In all trials, concomitant medications uses were not detailed.

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d) Outcome Measures

Efficacy Outcomes

All included studies evaluated PFS as the primary endpoint. The FIRST trial compared con- Ld with MPT, the MM-015 trial compared MPL-L with MP, and the E1A06 trial compared MPL with MPT.

Secondary endpoints for FIRST included overall survival (OS), overall response rate (ORR), time to response, duration of response, time to treatment failure, time to second-line antimyeloma therapy, and HR-QoL. HR-QoL was evaluated with the myeloma specific QLQ-MY20 questionnaire, the general oncology-related QLQ-C30 and the generic EuroQoL-5 dimensions (EQ-5D) instruments. The investigators focused on seven pre-specified measures and subdomains from these questionnaires. For the QLQ-MY20, the "disease symptoms" and "sides effects of treatment" domains were analysed and reported on a scale from 0 (better health) to 100 (worst health). Reported minimal clinically important differences (MCIDs) for these domains were of 10 and 6 points, respectively.[8] For QLQ-C30, the global health status and the "physical functioning", "fatigue" and "pain" subdomains were analysed on a scale from 0 to 100. A score of 100 represent the best health for global health status and physical functioning scores, but the worst health for fatigue and pain scores. Reported MCIDs for these measures were of 7, 9, 10 and 12 points, respectively. Finally, the EQ-5D index score was reported on a scale from –0.594, the worst health state, to 1.000, the best health state. A MCID of 0.07 points was used.[8] In the FIRST trial, disease progression was determined every 28 days for patients treated with LEN and every 42 days for patients treated with MPT, by an Independent Response Adjudication Committee based on the International Myeloma Work Group (IMWG) response criteria. Time to progression was calculated as the time between randomization and disease progression. In that study, time to treatment failure was defined as the time between randomization and discontinuation of study treatment for any reason, including disease progression, treatment toxicity, start of another antimyeloma therapy, or death.

Secondary endpoints for MM-015 were OS, ORR, time to response, duration of response, response quality and HR-QoL. In that study, response to treatment and disease progression were assessed with the European Group for Blood and Marrow Transplantation criteria. A very good partial response was defined according to the International uniform Response Criteria for Multiple Myeloma. In that study, PFS was calculated from the time of randomization until the date of progression or death from any cause during treatment or until data censoring at the last date at which the patient was known to be progression-free. The same HR-QoL measures as in the FIRST study were investigated, except for EQ-5D that was not used in MM-015.

Secondary endpoints for E1A06 included OS, ORR, depth of response, QoL assessed Functional Assessment of Cancer Therapy-Neurotoxicity (FACT-Ntx) Trial Outcome Index (TOI), and toxicity. Response evaluation was based on the International Myeloma Working Group response criteria. PFS was defined as the time from randomization to the earliest documentation of disease progression or death from any cause without regard for timing of disease evaluation. Patients who were alive without evidence of disease progression were censored at the date of last disease assessment.

Safety Outcomes

Safety and toxicity were secondary outcomes for all included studies. AEs were graded according to the National Cancer Institute Common Terminology Criteria for AEs (version 3.0). The safety analyses included patients who received at least one dose of the assigned treatment. In the FIRST trial, an independent monitoring committee monitored safety throughout the study.

e) Drug Exposure

In FIRST, the median duration of treatment was 18.4 months with con- Ld, 16.6 months with Ld 18 and 15.4 months with MPT.

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For the MM-015 study, median durations of treatment in the MPL-L arm was similar to that seen in the con- Ld arm of the FIRST trial and nearly 1/3 longer than what was seen in the MPL and MP arms of the MM-015 study. In the MPL-L and MPL groups, the LEN dose during induction was reduced in 39 % of patients aged between 65 and 75, and in 53 % of patients who were older than 75. The MP group received the highest dose intensities of melphalan and prednisone, i.e. less dose reductions, compared to the MPL-Land MPL groups.

In E1A06, the overall median time on induction therapy was 12 months and the median time on therapy for patients who had maintenance therapy was 23 months. Median time on maintenance was 10.5 months. According to authors, drug exposure was not different between arms.

f) Patient Disposition

Patient disposition for FIRST is summarized in Table 7. In the FIRST study, a total of 1623 patients were randomized. The majority of patients who discontinued treatment in all three arms did so due to disease progression while the second most common reasons were adverse events, death and 'other'. The overall and per category number of patients discontinuing treatment were relatively similar between arms although discontinuations were numerically lower in patients who received con- Ld compared to those who received MPT. Lower discontinuations due to AEs and disease progression appeared to be the reason for that difference.

Table 7:Patient Population and Disposition in the FIRST trial

	FIRST[7,9]		
	MPT	Ld 18	con- Ld
Randomized	547	541	535
Received treatment, n (%)	541 (98.9)	540 (99.8)	532 (99.4)
Efficacy (ITT) analysis, n (%)	547 (100)	541 (100)	535 (100)
Safety analysis, n (%)	541 (98.9)	540 (99.8)	532 (99.4)
Discontinued treatment at 72 weeks, n (%)	301 (55.0)	259 (47.9)	ND
Discontinued treatment at data cutoff, n (%)	ND	ND	ND
• AEs	ND	ND	ND
• Disease progression	ND	ND	ND
• Withdrew consent	ND	ND	ND
• Death	ND	ND	ND
• Lost to follow up	ND	ND	ND
• Protocol violation	ND	ND	ND
• Other	ND	ND	ND

AE = adverse event; con- Ld = continuous lenalidomide + dexamethasone; ITT = intention to treat; Ld 18 = lenalidomide+dexamethasone for 18 cycles; MPT = melphalan + prednisone + thalidomide; NR = not reported; ND = Not Disclosed by Celgene

In the MM-015 trial, approximately 62 % of patients completed the induction phase (see Table 8). A slightly higher number of patients who received LEN discontinued before the end of induction compared to MP. This tendency was reversed at the end of maintenance. More patients who received LEN discontinued because of AEs compared to the MP group. However, fewer patients in the MPL-L group discontinued because of disease progression, compared to MPL or MP.

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Table 8:Patient Population and Disposition in the MM-015 trial			
	MM-015[14]		
	MPL-L	MPL-placebo	MP + placebo-placebo
Randomized	152	153	154
Efficacy (ITT) analysis, n (%)	152 (100)	153 (100)	154 (100)
Safety analysis, n (%)	150 (98.7)	152 (99.3)	153 (99.4)
Discontinued induction treatment, n (%)	64 (42.1)	59 (38.6)	52 (33.8)
• AEs	24	22	8
• Disease progression	14	20	24
• Withdrew consent	13	8	9
• Died	4	4	4
• Lack of therapeutic effect	1	4	2
• Lost to follow-up	1	NR	NR
• Protocol violation	1	NR	2
• Other	6	1	3
Entered maintenance phase, n	88	94	102
Discontinued maintenance treatment, n(%)	55 (62.5)	80 (85.1)	93 (91.2)
• AEs	8	5	4
• Disease progression	40	67	86
• Lost to follow-up	1	NR	NR
• Other	5	4	2
• Missing data	1	3	1
• Withdrawal of consent	NR	1	NR
AE = adverse event; ITT = intention to treat; MP = melphalan + prednisone; MPL = melphalan + prednisone + Revlimid (lenalidomide); MPL-L = MPL for induction therapy + Revlimid (lenalidomide) as maintenance therapy; NR = not reported			

The E1A06 trial randomized 306 patients, of which 51 % reached maintenance therapy. After a median follow-up of 40.7 months, 275 patients were off-treatment: 42 % due to AEs; 34 % due to progressive disease; and 10 % withdrawn from study. The authors of the E1A06 stated that no differences in discontinuations were observed between studies.

g) Limitations/Sources of Bias

- In the FIRST and E1A06 studies, the allocated study treatment was not blinded from the patients or the investigators. In open-label trials, the assessment of subjective measures, such as HR-QoL, and the reporting of adverse events were likely to be biased. Although disease progression or survival are objective measures and less prone to bias, they may be biased by an unblinded investigator. The possibility that investigators may undergo unplanned assessment of disease progression, e.g. after an AE, cannot be ruled out. This might be in favor of the LEN efficacy.
- In addition to the concerns around allocation concealment, the validity of HR-QoL outcomes in the FIRST trial was impaired by the statistically significant lower completion of questionnaires in the MPT arm (67 %) than in the con- Ld arm (89 %). The lower

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compliance might be explained by poor performance status, hence a lower QoL. Thus, the lower compliance to HR-QoL questionnaires in the MPT group could be in favor of LEN. In addition, missing data were not imputed. Less than half of randomized patients had data for analysis.

- The FIRST and MM-015 studies were adequately powered (> 80 %) to detect a difference in PFS, but not powered to detect a difference in the secondary outcomes, including OS. For all studies, a hierarchical step-down approach for the analysis of the secondary outcomes was not mentioned and the multiplicity of secondary outcomes had increased the risk of type I error.
- Baseline characteristics of FIRST and MM-015 were similar between their respective groups. Only the median KPSS in the MM-015 study was statistically significantly lower for patients randomized to MPL-L compared to patients randomized to MP. This difference could potentially disfavored LEN. Of note, in the FIRST trial, the highest frequency of assessment of disease progression in patients who received LEN was also likely to disfavor LEN.
- All included studies were randomized. However, only the FIRST study randomized its participants according to the country of their study centre. Therefore, in MM-015 it is not known whether confounders were equally distributed between the study arms at different study sites.
- Pre-specified subgroup analyses were reported for FIRST and MM-015. The patients enrolled in these studies were not stratified in function of most of the parameters used for subgrouping. Also, subgroups lacked power to detect a difference. Hence their relevance is unclear. However, patients in MM-015 were stratified according to age and a difference was found for older patients vs. patients aged between 65 and 75 years.
- Different post-progression therapies could have influenced the results for overall survival. Patients who did not have LEN as first-line treatment were likely to receive LEN as second-line therapy. This could have biased the results for OS toward the null.
- As the studies investigated an elderly population, comorbidities might have influenced study results. The manufacturer provided data for comorbidities for the FIRST and MM-015 studies. These appeared to be evenly distributed among groups.
- For Canadian clinical practice, where the use of thalidomide is very restricted, comparison of LEN with MP or MPB is of higher relevance than comparison with MPT. Thalidomide was also used as post-progression therapy in FIRST and MM-015, which may have limited generalizability to the Canadian context.
- All efficacy results were analysed with an ITT approach, except for E1A06 which analysed some efficacy results with a per protocol approach, in line with its non-inferiority objective.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

a) Efficacy Outcomes

In the FIRST study, the median duration of follow-up among surviving patients was 37.0 months. In the MM-015 trial, mean durations of follow-up was 30 months, with an update of safety events after a median follow-up of 53 months. In E1A06, the median follow-up duration was 40.7 months. Efficacy results for survival, progression and response are displayed in Table 10.

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Overall survival (OS) rates

In FIRST, the overall survival rates at 3 years were 70 % with con- Ld , 66 % with Ld 18 and 62 % with MPT. At 4 years, those rates were 59 %, 56 % and 51 % for the same groups, respectively. At 3 years, there was a statistically significant reduction of death risk between the con- Ld and the MPT groups (HR = 0.78, 95% CI 0.64 to 0.96, P = 0.02), but the difference in OS did not cross the pre-specified superiority boundary. At 4 years (interim analysis performed March 3, 2014), the median OS in the con-Ld and MPT groups was 58.9 months and 48.5 months, respectively (HR = 0.75, 95% CI 0.62 to 0.90).[46]

In MM-015, overall survival rates at 3 years were 70 % with MPL-L, 62 % with MPL and 66 % with MP. Risks of death were not statistically different between groups.

For the E1A06 study, OS rates after 3 years were 63 % for both arms. After 41 months of follow-up, median OS were not statistically significantly different between the MPL-L arm (47.7 months) and the MPT-T arm (52.6 months) (HR = 0.88, 95% CI 0.63 to 1.24).

Health-Related Quality of Life

HR-QoL was assessed in the three included studies. HR-QoL data for the FIRST and MM-015 trials are summarized in Table 9.

For the FIRST study, results for the con- Ld and Ld 18 groups were pooled post-hoc. Changes from baseline at 18 months were statistically significant for EQ-5D index score, disease symptoms (QLQ-MY20), global health status (QLQ-C30), physical functioning (QLQ-C30) and pain (QLQ-C30) for both treatment groups. The changes from baseline reached the MCID for EQ-5D index score and pain, but not for disease symptoms, global health status and physical functioning. Changes in fatigue (QLQ-C30) from baseline were not statistically significant. Change in side effects of treatments (QLQ-MY20) was statistically significantly worsened for the MPT group, but not statistically different with Ld, although numerically worsened as well. Those degradations did not reach the MCID for this domain. For all the QoL endpoints at 18 months, no statistically significant differences were observed between groups. Of note, compliance rates for HR-QoL questionnaires were higher for the con- Ld group than the MPT group at 12 months (91 vs. 81%; $P \leq 0.002$) and at 18 months (89 vs. 67%; $P \leq 0.002$).

In MM-015, the MPL-L group achieved statistically significant change from baseline for disease symptoms (QLQ-MY20) and global health status (QLQ-C30) at 64 weeks. Both changes reached the MCID. For physical functioning (QLQ-C30), both the MPL-L and the MPL groups had statistically significant improvements from baseline after 64 weeks, but only the MPL-L group reached the MCID. For fatigue (QLQ-C30), only the MPL group did not show a statistically significant change from baseline. The MPL-L group reached the MCID for fatigue, the MPL group was very close and the MP group did not meet the MCID. All groups had statistically significant improvement from baseline for pain (QLQ-C30), with MPL-L and MP reaching MCID, while MPL was close. No groups had a statistically significant difference for side effects of treatment (QLQ-MY20). Compliance to questionnaires were generally high (i.e.>76 % at time points and > 65 % at progression of disease or discontinuation) and consistent across treatment groups. In addition, the manufacturer provided HR-QoL data after 19 cycles and their results did not show any statistical difference between treatments.

For the E1A06 study, the change from baseline in FACT-Ntx TOI score at 12 months favored MPL-L (3.3) over MPT-T (–2.8) (P = 0.007), but there was no statistically significant difference at end of treatment in change from baseline between MPL-L (-3.4) and MPT-T (-5.9) (P = 0.256)

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Table 9: Summary of Health-Related Quality of Life Outcomes					
	FIRST[8] after 18 months		MM- 015[13] after 16 cycles (64 weeks)		
	MPT N = 547	Ld N = 1076	MPL-L N = 152	MPL-placebo N = 153	MP + placebo-placebo N = 154
EQ-5D Index Score					
n at baseline	490	982	NR	NR	NR
Baseline, mean (SD)	0.5 (0.4)	0.5 (0.4)	NR	NR	NR
n at endpoint	182	473	NR	NR	NR
Mean at endpoint (SD)	0.7 (0.2)	0.7 (0.2)	NR	NR	NR
Change from baseline (SD)	0.1 (0.4)*	0.1 (0.3)*	NR	NR	NR
P value from baseline	< 0.0001	< 0.0001	NR	NR	NR
Intergroup P value	0.4632		NR		
QLQ-MY20					
Disease symptoms					
n at baseline	511	1022	138	142	148
Baseline, mean (SD)	30.3 (22.7)	30.1 (22.3)	34.0 (23.6)	32.1 (21.5)	32.3 (22.4)
n at endpoint	188	508	65	55	64
Mean at endpoint (SD)	21.8 (18.0)	21.0 (18.4)	23.7 (20.4)	26.7 (18.5)	29.4 (19.8)
Change from baseline (SD)	–7.9 (21.3)	–7.5 (23.4)	–11.4 (23.2)*	–5.9 (25.8)	–3.4 (20.7)
P value from baseline	< 0.0001	< 0.0001	< 0.01	NS	NS
Intergroup P value	0.8399		NR		
Side effects of treatment					
n at baseline	510	1020	138	141	147
Baseline, mean (SD)	20.1 (15.9)	19.8 (15.6)	20.6 (15.0)	19.0 (15.8)	17.1 (14.4)
n at endpoint	187	507	65	55	64
Mean at endpoint (SD)	21.7 (14.9)	19.9 (14.6)	17.8 (12.9)	15.4 (14.5)	16.0 (12.5)
Change from baseline (SD)	4.3 (16.4)	2.2 (16.5)	–2.6 (14.5)	–2.9 (14.2)	–0.9 (12.2)
P value from baseline	0.0006	0.1530	NS	NS	NS
Intergroup P value	0.1530		NR		
QLQ-C30					
Global health status					
n at baseline	508	1015	137	142	147
Baseline, mean (SD)	50.8 (24.2)	51.7 (24.4)	49.6 (23.5)	53.2 (23.5)	52.8 (22.8)

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Table 9: Summary of Health-Related Quality of Life Outcomes					
	FIRST[8] after 18 months		MM- 015[13] after 16 cycles (64 weeks)		
	MPT N = 547	Ld N = 1076	MPL-L N = 152	MPL-placebo N = 153	MP + placebo-placebo N = 154
n at endpoint	184	505	64	54	65
Mean at endpoint (SD)	60.6 (18.0)	61.8 (20.2)	62.2 (17.1)	63.3 (18.4)	61.9 (18.9)
Change from baseline (SD)	4.8 (27.1)	6.0 (26.5)	11.3 (25.1)*	7.0 (26.5)*	8.1 (25.1)*
P value from baseline	0.0196	< 0.0001	< 0.01	NS	NS
Intergroup P value	0.5873		NR		
Physical functioning					
n at baseline	509	1025	140	146	148
Baseline, mean (SD)	59.9 (28.8)	61.5 (27.0)	57.5 (25.3)	64.0 (24.3)	65.5 (23.8)
n at endpoint	189	507	65	56	65
Mean at endpoint (SD)	73.4 (18.8)	72.6 (20.3)	72.6 (20.3)	73.2 (17.3)	67.6 (20.2)
Change from baseline (SD)	8.3 (27.1)	6.8 (25.2)	10.2 (25.2)*	7.6 (22.7)	1.1 (19.3)
P value from baseline	< 0.0001	< 0.0001	< 0.01	< 0.05	NS
Intergroup P value	0.5062		NR		
Fatigue					
n at baseline	512	1025	140	146	147
Baseline, mean (SD)	46.0 (28.4)	44.8 (27.8)	49.3 (25.6)	44.2 (27.1)	42.6 (27.4)
n at endpoint	189	503	65	55	65
Mean at endpoint (SD)	36.3 (23.3)	38.4 (23.5)	35.2 (22.4)	31.3 (20.4)	37.3 (21.8)
Change from baseline (SD)	−4.3 (30.1)	−1.5 (29.5)	−10.1 (27.0)*	−9.7 (28.8)	−4.1 (26.3)
P value from baseline	0.0512	0.2492	< 0.05	NS	< 0.05
Intergroup P value	0.2748		NR		
Pain					
n at baseline	512	1025	140	146	148
Baseline, mean (SD)	45.3 (35.4)	44.7 (33.7)	48.8 (34.8)	44.9 (30.2)	43.5 (33.0)
n at endpoint	188	507	65	55	65
Mean at endpoint (SD)	28.0 (26.1)	28.6 (26.6)	28.0 (24.5)	33.6 (22.8)	31.3 (25.4)
Change from baseline (SD)	−14.7 (32.8)*	−13.4 (35.1)*	−21.4 (33.0)*	−11.0 (33.0)	−12.2 (30.0)*
P value from baseline	< 0.0001	< 0.0001	< 0.001	< 0.05	< 0.01
Intergroup P value	0.6733		NR		

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Table 9: Summary of Health-Related Quality of Life Outcomes					
	FIRST[8] after 18 months		MM- 015[13] after 16 cycles (64 weeks)		
	MPT N = 547	Ld N = 1076	MPL-L N = 152	MPL-placebo N = 153	MP + placebo-placebo N = 154
con- Ld = continuous lenalidomide + dexamethasone; EQ-5D = Euro quality of life-5 domain; Ld 18 = lenalidomide+dexamethasone for 18 cycles; MP = melphalan + prednisone; MPL = melphalan + prednisone + Revlimid (lenalidomide); MPL-L = MPL for induction therapy + Revlimid (lenalidomide) as maintenance therapy; MPT = melphalan + prednisone + thalidomide; NR = not reported, NS = not significant; SD = standard deviation					
Note: Changes from baseline that reached the MCID are marked with an asterisk "*"					

Progression free survival (PFS)

PFS was the primary endpoint for the FIRST and the MM-015 studies. The median PFS in the FIRST trial was 25.5 months with con- Ld , 20.7 months with Ld 18, and 21.2 months with MPT. Patients who had con- Ld had a statistically significant improvement in PFS compared to those who had MPT (HR = 0.72, 95% CI 0.61 to 0.85, P < 0.001) and compared to those who had Ld 18 (HR = 0.70, 95% CI 0.60 to 0.82, P < 0.001). PFS was not different between the MPT group and the Ld 18 group.

Subgroup analyses were performed for PFS and OS in the FIRST study. The benefits of con- Ld on PFS and OS were observed for most of the subgroups. The benefits of con- Ld were questionable in patients with high-risk cytogenetic profile or a high level of lactate deshydrogenase. When patients were subgrouped for the quality of their response, results in patients who had a very good partial response or a complete response showed that PFS was improved in patients who had con- Ld compared to those who received Ld.

In MM-015, the median PFS was statistically significantly higher in the MPL-L group (median of 31 months) compared to the MPL (median of 14 months, HR = 0.49, P < 0.001) and MP (median of 13 months, HR = 0.40, P < 0.001). By using a pre-specified landmark analysis, patients who had MPL-L statistically significantly extended their PFS from the start of maintenance therapy (median of 26 months) compared to patients who received MPL (median of 7 months, HR = 0.34, P < 0.001). Subgroup analyses showed that benefits in PFS were maintained in all subgroups (gender, disease staging, renal function, microglobulin levels, albumin levels and KPSS), except patients aged over 75 years. A significant treatment-by-age interaction was found (P = 0.001).

In E1A06, after ITT analysis, the median PFS were similar with 21 months with MPT-T and 18.7 months with MPL-L (P = 0.19). The HR for progression between these two groups was 0.84 (95%CI 0.64 to 1.09).This difference in HR was within the pre-specified non-inferiority margin. Subgroup analyses for PFS showed no statistically significant difference between treatment arms.

Time to progression

In FIRST, the time to progression was statistically significantly longer with con- Ld (32.5 months) compared with Ld18 (21.9 months, HR = 0.62, P < 0.001) and MPT (23.9 months, HR = 0.68, P < 0.001).

Duration of response

The duration of the response in the FIRST study was statistically significantly longer with con- Ld (35.0 months) than with Ld (22.1 months, HR = 0.60, P < 0.001) or MPT (22.3 months, HR = 0.63, P < 0.001).

In MM-015, duration of response was statistically significantly higher (P < 0.001) for the MPL-L group (29 months) compared to the MPL (13 months) and the MP groups (13 months)

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Response rates

Overall responses rates in the FIRST trial were statistically significantly (P < 0.001) greater with con- Ld (75 %) and Ld 18 (73 %) compared to MPT (62 %). The response rates for complete response and very good partial response numerically favored patients randomized to con- Ld and Ld 18.

For MM-015, ORRs statistically significantly favored MPL-L (77 %, P < 0.001) and MPL (68 %, P = 0.002) compared to MP (50 %). Numbers also appeared to favor MPL-L and LEN-based regimens for complete response rates and very good partial response rates, respectively.

For the E1A06 study, response rates were based on a per protocol analysis. Rates for partial response (59.9 % for MPL-L vs. 63.6 % for MPT-T) and for the combination of complete and very good partial responses (23.0 % for MPL-L vs. 18.8 % for MPT-T) were similar for both treatment arms.

Other efficacy outcomes

The following efficacy outcomes were not included in the review protocol. In FIRST, the median time to response was statistically significantly shorter with con- Ld (1.8 months, P < 0.001) and Ld 18 (1.8 months, P < 0.001) compared to MPT (2.8 months). The median time to treatment failure was longer with con- Ld (16.9 months) and Ld 18 (17.2 months) compare to MPT (14.1 months).

In MM-015, the median time to response was statistically significantly shorter with MPL-L and MPL (2 months for both) compared to MP (3 months, P < 0.001 for both comparisons).

Table 10: Summary of Key Efficacy Outcomes

	FIRST,[7,9]			MM-015,[14]			E1A06,[17,18]	
	MPT N = 547	Ld 18 N = 541	con- Ld N = 535	MPL-L N = 152	MPL-placebo N = 153	MP + placebo-placebo N = 154	MPL-L	MPT-T
Overall survival rates								
At 3 years, %	62	66	70	70	62	66	63	63
At 4 years, %	51	56	59	NR	NR	NR	NR	NR
HR (95% CI), P value	3-year analysis con- Ld vs. MPT: 0.78 (0.64 to 0.96), P = 0.02 4-year analysis con- Ld vs. MPT: 0.75 (0.62 to 0.90)			MPL-L vs. MPL: 0.79 (NR), P = 0.25 MPL-L vs. MP: 0.95 (NR), P = 0.81			NR	
Progression-free survival								
Median, months	21.2	20.7	25.5	31	14	13	18.7	21
HR (95% CI), P value	con- Ld vs. MPT: 0.72 (0.61 to 0.85), P < 0.001 con- Ld vs. Ld 18: 0.70 (0.60 to 0.82), P < 0.001 Ld 18 vs. MPT: 1.03 (0.89 to 1.20), P = 0.70			MPL-L R vs. MPL: 0.49 (NR),P < 0.001 MPL-L vs. MP: 0.40 (NR),P < 0.001			MPT-T vs. MPL-L: 0.84 (0.64 to 1.09)	

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Table 10: Summary of Key Efficacy Outcomes								
	FIRST,[7,9]			MM-015,[14]			E1A06,[17,18]	
	MPT N = 547	Ld 18 N = 541	con- Ld N = 535	MPL-L N = 152	MPL-placebo N = 153	MP + placebo-placebo N = 154	MPL-L	MPT-T
Time to progression								
Median, months	23.9	21.9	32.5	NR	NR	NR	NR	NR
HR (P value)	con- Ld vs. MPT: 0.68 (P < 0.001) con- Ld vs. Ld 18: 0.62 (P < 0.001)			NR			NR	
Duration of response								
Median, months	22.3	22.1	35.0	29	13	13	NR	NR
HR (P value)	con- Ld vs. MPT: 0.63 (P < 0.001) con- Ld vs. Ld 18: 0.60 (P < 0.001)			MPL-L vs. MPL: NR (P < 0.001) MPL-L vs. MP: NR (P < 0.001)			NR	
Response rates								
Overall Response rates, n (%)	341 (62)	397 (73)	402 (75)	117 (77)	104 (68)	77 (50)	NR	NR
P values	con- Ld vs. MPT: P < 0.001 Ld 18 vs. MPT: P < 0.001			MPL-L vs. MP: P < 0.001 MPL vs. MP: P = 0.002			NR	
Complete response rate, n (%)	51 (9)	77 (14)	81 (15)	15 (10)	5 (3)	5 (3)	NR (9)	NR (5)
Very good partial response rate, n (%)	103 (19)	154 (28)	152 (28)	35 (23)	45 (29)	14 (9)	NR (23)*	NR (18.8)*
Partial response rate, n (%)	187 (34)	166 (31)	169 (32)	102 (67)	99 (65)	72 (47)	NR (59.9)*	NR (63.6)*
Stable disease rate, n (%)	145 (27)	111 (21)	101 (19)	28 (18)	40 (26)	70 (46)	NR	NR
Progressive disease rate, n (%)	19 (3)	12 (2)	7 (1)	0	2 (1)	0	NR	NR
Response could not be evaluated, n (%)	42 (8)	21 (4)	25 (5)	7 (5)	7 (5)	7 (5)	NR	NR

CI = confidence interval; con- Ld = continuous lenalidomide + dexamethasone; HR = hazard ratio; Ld 18 = lenalidomide+dexamethasone for 18 cycles; MP = melphalan + prednisone; MPL = melphalan + prednisone + Revlimid (lenalidomide); MPL-L = MPL for induction therapy + Revlimid (lenalidomide) as maintenance therapy; MPT = melphalan + prednisone + thalidomide; NR = not reported.

* Based on a per protocol analysis

Post-progression therapy

Details of post-progression therapies were reported in the FIRST and the MM-015 studies (Table 11). In FIRST, a lower proportion of patients in the con- Ld group received second line therapy compared to the Ld18 and MPT groups. Patients in the con- Ld group had a longer time to second-line therapy compared with Ld18 and MPT (P < 0.001 vs. both groups) and also a longer PFS2

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compared to MPT (P = 0.005). In MM-015, the MPL-L group had the lowest proportion of patients which received second-line therapy. Post-progression death risks were not statistically significantly different between MPL-L, MPL and MP groups.

Table 11: Summary of Post Progression Therapy

	FIRST[7,9]			MM-015[15]		
	MPT N = 547	Ld18 N = 541	con- Ld N = 535	MPL-L N = 152	MPL-placebo N = 153	MP + placebo-placebo N = 154
Received second-line therapy						
n, (%)	309 (56)	299 (55)	231 (43)	70 (46)	109 (69)	117 (76)
Open-label lenalidomide (in extension phase)	NR	NR	NR	21 (13.8)	52 (34.0)	76 (49.4)
Other second-line therapy	NR	NR	NR	49 (32.2)	54 (35.3)	41 (26.2)
Time to second-line antimyeloma therapy						
Median, months	26.7	28.5	39.1	NR	NR	NR
P-value	con- Ld vs. MPT: P < 0.001 con- Ld vs. Ld 18: P < 0.001			NR		
Post-progression overall survival						
Median, months	NR	NR	NR	30.3	25.6	NE
3-year survival rate, %	NR	NR	NR	48.3	48.9	58.2
HR (P value)	NR			MPL-L vs. MP: 1.40 (P = 0.184)		
Progression -free survival 2						
Median, months	36.3	39.4	42.9	39.7	NR	28.5
HR (P value)	con- Ld vs. MPT: 0.78 (P = 0.005)			MPL-L vs. MP: 0.71 (P = 0.013)		
Second-line treatment, n(%)						
Bortezomib-based regimens	150 (48.5)	168 (56.2)	143 (61.9)	30 (19.7)	29 (19.0)	23 (14.9)
Lenalidomide-based regimens	106 (34.3)	61 (20.4)	27 (11.7)	2 (1.3)	10 (6.5)	8 (5.2)
Thalidomide-based regimens	22 (7.1)	22 (7.4)	29 (12.6)	11 (7.2)	9 (5.9)	6 (3.9)
Lenalidomide or thalidomide in combination with bortezomib-based regimens	3 (1.0)	8 (2.7)	0 (0)	NR	NR	NR
Glucocorticoids	NR	NR	NR	36 (23.7)	39 (25.5)	32 (20.8)
Other regimens	28 (9.1)	40 (13.4)	32 (13.9)	27 (17.8)	18 (11.8)	20 (13.0)
Regimens containing alkylating agents	76 (24.6)	133 (44.5)	125 (54.1)	NR	NR	NR

con- Ld = continuous lenalidomide + dexamethasone; HR = hazard ratio; Ld 18 = lenalidomide+dexamethasone for 18 cycles; MP = melphalan + prednisone; MPL = melphalan + prednisone +

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Table 11: Summary of Post Progression Therapy						
	FIRST[7,9]			MM-015[15]		
	MPT N = 547	Ld18 N = 541	con- Ld N = 535	MPL-L N = 152	MPL-placebo N = 153	MP + placebo-placebo N = 154
Revlimid (lenalidomide); MPL-L = MPL for induction therapy + Revlimid (lenalidomide) as maintenance therapy; MPT = melphalan + prednisone + thalidomide; NE = not estimable; NR = not reported.						

b) Harms Outcomes

In the FIRST trial, the overall occurrence of grade 3-4 AEs were similar between groups (89%, 80 % and 85 % for MPT, Ld18 and con- Ld , respectively) (see Table 12). AEs leading to dose interruptions occurred in 77 %, 59 % and 69 % and AEs leading to withdrawal occurred in 27 %, 17 % and 20 % of patients who received MPT, Ld 18 and con- Ld , respectively. In comparison with MPT, treatment with con- Ld was associated with fewer hematological AEs, especially neutropenia (28 vs. 45 %), and fewer peripheral sensory neuropathies (1 vs. 9 %), but con- Ld was also associated with an increase of infections (29 vs. 17 %). The numbers of second primary cancers were similar between groups, but numerically lower for hematologic malignancies in the con- Ld group (0.4 vs. 2.2 %, see Table 14).

In MM-015, a treatment with LEN was associated with more grade 3-4 hematological AEs (see Table 12). Granulocyte colony-stimulating factor was used in 35 % of patients in the MPL-L group, 32 % of patients in the MPL group and 8 % of patients in the MP group. Platelet transfusions were required by 34 %, 27 % and 16 % of patients, for the same groups, respectively. Grade 3-4 deep-vein thrombosis (DVT) occurred in 3% of patients treated with LEN and 1 % of patients treated with MP. During induction therapy, discontinuation rates from treatments due to AEs were 16 % for MPL-L, 14 % for MPL and 5 % for MP. During the maintenance phase, the incidence of grade3-4 AEs was low. After long-term follow-up on maintenance, occurrences of second primary cancers were found to be higher with MPL-L (16 %) and MPL (12 %) than with MP (5 %) (see Table 13). Three deaths in the MPL-L group (2 %) and one death in the MPL group (0.7%) were considered to be related to lenalidomide. The manufacturer also provided data on peripheral sensory neuropathy at their last data cutpoint showing an incidence rate of 7.3% for MPL-L, 5.9 % for MPL and 3.3 % for MP.

The E1A06 trial reported more grade 3-4 AEs with MPT-T (73 %) than with MPL-L (58 %) (P = 0.007). More specifically, grade 3-4 non hematological AEs rates were higher in the MPT-T arm (59 %) than in the MPL-L arm (40 %) (P = 0.001) Incidence rates of second primary cancers were also higher with MPT-T (18 patients) compared with MPL-L (14 patients).

Table 12: Summary of Key Harms Outcomes												
	FIRST[7,9]			MM-015[14]†						E1A06[17,18]	
	MPT N = 541	Ld18 N = 540	con-Ld N = 532	MPL-L N = 150		MPL-placebo N = 152		MP + placebo-placebo N = 153		MPL-L	MPT-T
				Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4		
Any grade 3 or 4 event*, n(%)	480 (89)	433 (80)	453 (85)	NR	NR	NR	NR	NR	NR	NR (58)	NR (73)
Hematological adverse event, n (%)											
Neutropenia	243 (45)	143 (26)	148 (28)	100 (67)	52 (35)	97 (64)	49 (32)	45 (29)	12 (8)	43	41
Anemia	102 (19)	85 (16)	97 (18)	36 (24)	4 (3)	40 (26)	4 (3)	21 (14)	2 (1)	NR	NR

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Table 12: Summary of Key Harms Outcomes											
	FIRST[7,9]			MM-015[14]†						E1A06[17,18]	
	MPT N = 541	Ld18 N = 540	con-Ld N = 532	MPL-L N = 150		MPL-placebo N = 152		MP + placebo-placebo N = 153		MPL-L	MPT-T
				Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4		
Thrombocytopenia	60 (11)	43 (8)	44 (8)	53 (35)	17 (11)	58 (38)	19 (12)	18 (12)	6 (4)	NR	NR
Lymphopenia	37 (7)	18 (3)	30 (6)	NR	NR	NR	NR	NR	NR	10	21
Leukopenia	53 (10)	30 (6)	24 (5)	35 (23)	6 (4)	39 (26)	8 (5)	21 (14)	2 (1)	NR	NR
Febrile neutropenia	NR (3)	NR (3)	NR (1)	7 (5)	3 (2)	2 (1)	2 (1)	0	0	NR	NR
Non-hematologic adverse event, n (%)											
Infection	93 (17)	118 (22)	154 (29)	14 (9)	1 (1)	20 (13)	3 (2)	11 (7)	0	NR	NR
Cardiac disorder	46 (9)	39 (7)	63 (12)	5 (3)	3 (2)	4 (3)	4 (3)	5 (3)	0	NR	NR
Pneumonia	31 (6)	45 (8)	43 (8)	NR	NR	NR	NR	NR	NR	NR	NR
DVT, PE or both	29 (5)	30 (6)	42 (8)	2 (1)	0	6 (4)	1 (1)	1 (1)	0	NR (6.7)	NR (8.8)
Asthenia	32 (6)	33 (6)	41 (8)	NR	NR	NR	NR	NR	NR	NR	NR
Fatigue	31 (6)	46 (9)	39 (7)	8 (5)	0	2 (1)	2 (1)	5 (3)	0	NR	NR
Back pain	28 (5)	34 (6)	37 (7)	NR	NR	NR	NR	NR	NR	NR	NR
Hypokalemia	11 (2)	20 (4)	35 (7)	NR	NR	NR	NR	NR	NR	NR	NR
Hyperglycemia	9 (2)	23 (4)	28 (5)	NR	NR	NR	NR	NR	NR	NR	NR
Rash	28 (5)	28 (5)	33 (6)	7 (5)	0	7 (5)	0	2 (1)	0	NR	NR
Cataracts	3 (1)	14 (3)	31 (6)	NR	NR	NR	NR	NR	NR	NR	NR
Dyspnea	18 (3)	22 (4)	30 (6)	NR	NR	NR	NR	NR	NR	6	12
Constipation	29 (5)	10 (2)	12 (2)	NR	NR	NR	NR	NR	NR	0	8
Peripheral sensory neuropathy	51 (9)	2 (<1)	6 (1)	NR	NR	NR	NR	NR	NR	NR	NR
Diarrhea	8 (1)	18 (3)	21 (4)	3 (2)	1 (1)	2 (1)	0	0	0	NR	NR

con-Ld = continuous lenalidomide + dexamethasone; **DVT** = deep vein thrombosis; **Ld18** = lenalidomide+dexamethasone for 18 cycles; **MP** = melphalan + prednisone; **MPL** = melphalan + prednisone + Revlimid (lenalidomide); **MPL-L** = MPL for induction therapy + Revlimid (lenalidomide) as maintenance therapy; **MPT** = melphalan + prednisone + thalidomide; **NR** = not reported; **PE** = pulmonary embolism.

* Occuring in at least 5 % of any study group

† AEs reported during the induction therapy of MM-015 are reported in this table. See Table 13 for AEs reported during the maintenance phase.

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Table 13: Summary of adverse events for the maintenance phase of MM-015						
	MM-015[14,16]					
	MPL-L N = 88		MPL-placebo N = 94		MP + placebo-placebo N = 102	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Maintenance therapy after a median follow-up of 30 months						
Hematological adverse event, n (%)						
Neutropenia	4 (5)	2 (2)	0	0	1 (1)	0
Thrombocytopenia	0	5 (6)	0	2 (2)	2 (2)	0
Anemia	2 (2)	2 (2)	2 (2)	1 (1)	5 (5)	0
Nonhematologic adverse event, n (%)						
Infection	3 (3)	2 (2)	2 (2)	0	1 (1)	2 (2)
Fatigue	2 (2)	1 (1)	0	0	1 (1)	0
Deep-vein thrombosis	2 (2)	0	1 (1)	0	0	0
Diarrhea	3 (3)	1 (1)	0	0	0	0
Bone pain	4 (5)	0	1 (1)	0	4 (4)	1 (1)
Diabetes mellitus	2 (2)	0	0	0	0	0
Maintenance therapy after a median follow-up of 53 months[16]						
Neutropenia*, n (%)	6 (7)		0		1 (1)	
Anemia*, n (%)	7 (8)		3 (3)		5 (5)	
Thrombocytopenia*, n (%)	8 (9)		3 (3)		2 (2)	
Invasive second primary malignancies, n (%)	14 (16)		11 (12)		5 (5)	
Patients with ≥ 1 AE leading to dose reduction of lenalidomide or PBO	29 (33)		5 (5)		2(2)	
Patients with ≥ 1 AE leading to discontinuation of lenalidomide or PBO	18 (21)		4 (4)		4 (4)	

MP = melphalan + prednisone; **MPL** = melphalan + prednisone + Revlimid (lenalidomide); **MPL-L** = MPL for induction therapy + Revlimid (lenalidomide) as maintenance therapy; **NR** = not reported; **PBO** = placebo

* Grade 3-4 AEs

Table 14: Second primary cancers								
	FIRST[7,9]			MM-015[14]†			E1A06,[17,18]	
	MPT N = 541	Ld18 N = 540	con-Ld N = 532	MPL-L N = 150	MPL-placebo N = 152	MP + placebo-placebo N = 153	MPL-L	MPT-T
Any								

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Table 14: Second primary cancers								
	FIRST[7,9]			MM-015[14]†			E1A06,[17,18]	
	MPT N = 541	Ld18 N = 540	con-Ld N = 532	MPL-L N = 150	MPL-placebo N = 152	MP + placebo-placebo N = 153	MPL-L	MPT-T
n (%)	47 (9)	44 (8)	37 (7)	NR	NR	NR	NR	NR
Incidence rate per 100 person-years (95% CI)	3.68 (2.76-4.89)	3.33 (2.48-4.48)	2.76 (2.00-3.81)	3.04 (NR)	2.57 (NR)	0.98 (NR)	2.01 (NR)	3.47 (NR)
Invasive, n (%)	27 (5)	30 (6)	17 (3)	NR	NR	NR	14 (NR)	17 (NR)
Hematologic cancers, n (%)	12 (2)	2 (<1)	2 (<1)	7 (5)	5 (3)	1 (1)	NR	NR
Solid tumors, n (%)	15 (3)	29 (5)	15 (3)	5 (3)	4 (3)	3 (2)	NR	NR
Non-invasive, n (%)	21 (4)	17 (3)	22 (4)	NR	NR	NR	NR	NR
con-Ld = continuous lenalidomide + dexamethasone; **Ld18** = lenalidomide+dexamethasone for 18 cycles; **MP** = melphalan + prednisone; **MPL** = melphalan + prednisone + Revlimid (lenalidomide); **MPL-L** = MPL for induction therapy + Revlimid (lenalidomide) as maintenance therapy; **MPT** = melphalan + prednisone + thalidomide; **NR** = not reported.								
* Occuring in at least 5 % of any study group † AEs reported during the induction therapy of MM-015 are reported in this table. See Table 13 for AEs reported during the maintenance phase.								

6.4 Ongoing Trials

Two not yet completed studies that could be relevant to this review were found. A multicenter phase III RCT.

NCT01093196 sponsored by the Fondazione Neoplasie Sangue Onlus) planned to compare lenalidomide + dexamethasone vs. melphalan + prednisone + lenalidomide vs. Cyclophosphamide + prednisone + lenalidomide in patients with ND-MM patients aged 65 years or older. The status of the study is deemed unknown by clinicaltrails.gov since the recruitment status was last verified in December 2011 as active, not recruiting.

Another multicenter phase III study (NCT02215980 sponsored by the Fondazione Neoplasie Sangue Onlus) planned to compare lenalidomide + dexamethasone until disease progression or intolerance vs. induction lenalidomide + dexamethasone followed by lenalidomide maintenance until disease progression or intolerance in elderly and unfit ND-MM patients. In July 2014, the study was recruiting patients.

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7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review of lenalidomide for patients with newly diagnosed multiple myeloma who are not candidates for stem cell transplantation:

- Summary of manufacturer-submitted network meta-analysis comparing lenalidomide with other first-line treatments for patient with newly diagnosed multiple myeloma who are not candidates for stem cell transplantation
- Summary of a poster-reported network meta-analysis comparing lenalidomide with other first-line treatments for patient with newly diagnosed multiple myeloma who are not candidates for stem cell transplantation

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

NOTE: The critical appraisal of two NMA's below are reporting on a poster-reported and the manufacturer-submitted NMA. Of particular importance is the absence of results in the critical appraisal of the manufacturer-submitted NMA (Section 7.1). As the information was deemed to be non-disclosable by Celgene, it could not be reported in this critical appraisal. The results from this report were also used in the economic analysis submitted by Celgene. The results of the poster presentation (Section 7.2) are however reported and were considered, by the pCODR Methods team, to be similar to the results reported in the manufacturer-submitted NMA.

7.1 Summary of manufacturer-submitted NMA comparing lenalidomide with other first-line treatments for patient with ND-MM who are not candidates for SCT

7.1.1 Objective

To summarize and critically appraise the methods and findings of the manufacturer-submitted network meta-analysis (NMA) comparing lenalidomide with other first-line treatment for patients with newly diagnosed multiple myeloma (ND-MM) who are not candidates for stem cell transplantation (SCT).

7.1.2 Findings

Methods

Systematic Review

The manufacturer provided an NMA based on a systematic review to evaluate the relative efficacy of lenalidomide compared with other first-line agents for the treatment of ND-MM in patients who are not eligible for SCT (Table 15). The MEDLINE, EMBASE, and Cochrane databases were searched and supplemented with conference proceedings. Abstracts and full-text articles were screened by one investigator and decisions to exclude abstracts or articles were confirmed by a second investigator, with discrepancies being resolved by a third investigator. The main inclusion criteria for the systematic review were randomized controlled trials (RCTs) in untreated adult patients with MM who were ineligible for SCT. Studies that evaluated first-line treatment of MM in which only responders to induction therapy were randomized to maintenance treatment were excluded, as these patients were no longer treatment-naïve at the time of randomization. Interventions included lenalidomide, thalidomide, bortezomib, interferon, or bendamustine as monotherapy or part of a combination therapy, or melphalan

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plus prednisone combination therapy, and comparators included placebo, another drug, or the same drug at a different dose level or with additional active agent or adjuvant-therapy agent. Outcomes of interest were clinical efficacy, safety, of quality of life (QoL) endpoints.

Table 15: PICOS Criteria for Study Selection

Patients	Untreated adult multiple myeloma patients who are newly diagnosed or untreated, and aged 65 years or older or ineligible for stem cell transplantation
Interventions	Lenalidomide, thalidomide, bortezomib, interferon, or bendamustine as monotherapy or as part of a combination therapy, or melphalan plus prednisone combination therapy
Comparators	Placebo or the same drug at a different dose level or with additional active agent or adjuvant-therapy agent, or another drug
Outcomes	Clinical efficacy, safety, or quality of life endpoints
Study Design	Randomized controlled trials

Additional Criteria

Additional criteria were applied to the included trials in order to minimize between-trial heterogeneity and include trials that would contribute to a network that was both clinically and statistically robust. First, since the systematic review and MTC was conducted to inform the economic model assessing the cost-effectiveness and cost-utility of lenalidomide vs VMP (primary comparator) and lenalidomide vs MPT, trials providing evidence around these interventions were included and other treatments were included only if they contributed to an otherwise closed network of lenalidomide vs MPT or lenalidomide vs VMP. Second, only trials with a treatment duration of at least 48 weeks with similar dosing schedules were included to minimize potential heterogeneity. Third, only trials in which thalidomide maintenance treatment was given over a fixed period (e.g., maximum 12 six-week cycles) were included, while trials that continuously administered thalidomide during the maintenance phase until disease progression were excluded. This was done because this treatment regimen is in line with thalidomide's label in Europe, where a maximum of 12 six-week cycles of therapy is recommended, and this was also consistent with the thalidomide dosing used in the FIRST trial.

Network Meta-Analysis

The evidence on survival endpoints (OS and PFS) identified from the systematic review was assessed quantitatively using an NMA to evaluate the comparative efficacy of lenalidomide and VMP. Fixed-effects and random-effects Bayesian mixed-treatment comparison (MTC) meta-analyses were conducted and compared all treatments of interest using hazard ratios (HR) for overall survival (OS) and progression-free survival (PFS). Random effects MTC analyses used a uniform prior for the square root(tau) of [0, 0.4] based on research suggesting that relative effects on mortality are low. All analyses involved a 50,000 run-in iteration phase and a 50,000 iteration phase for parameter estimation. Convergence was confirmed through the use of three-chain Brooks-Gelman-Rubin plots and the inspection of the ratios of Monte Carlo error to the standard deviations of the posteriors.

No sensitivity analyses were pre-specified in the protocol. However, one of the included studies used a duration of thalidomide treatment that differed from those in other studies with a fixed duration of MPT treatment, and so this study was included in a sensitivity analysis. It also was noted that in the case where there is little heterogeneity between studies in a network, the use of fixed-effects analyses is appropriate and random-effects analyses can be regarded as a sensitivity analysis. Statistical heterogeneity was assessed using I^2.

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In the MTC, a quality assessment of the included RCTs was performed to evaluate potential bias in terms of randomization, concealment, inclusion criteria, blinding, patient characteristics, and the use of an intention-to-treat (ITT) population analysis using questions derived from the Cochrane Handbook for systematic reviews of interventions.[39]

Results

Study and Patient Characteristics

Sixteen trials were identified in the systematic review that reported HR data (adjusted or unadjusted) for OS or PFS. Eleven trials were excluded either because they did not contribute to a closed network of lenalidomide vs MPT or lenalidomide vs VMP, they were less than 48 weeks in duration, or they used continuous thalidomide dosing during the maintenance phase (five trials). In the remaining five trials, one used a thalidomide treatment duration that differed to that from the other studies (28-day cycles for 6 to 12 weeks; NCT01274403),[40] and was only included in the network as a sensitivity analysis. In total, four studies were included in the network for the primary analysis (Figure 2 and Table 16).[7,41-43] The dosing of thalidomide used in the trials that evaluated treatment with the MPT regimen ranged from 100 mg/day to up to 400 mg/day. The median duration of follow-up in all included studies ranged from 30 months to 60 months.

The median age of the patients enrolled in the five trials ranged from 71 years to 78.5 years. Four trials allowed the inclusion of patients younger than 65 years if they were ineligible for high-dose therapy plus SCT due to comorbidities.[7,40,42,43] However, patients under the age of 65 years were included only in the VISTA (range 48 to 91 years) and FIRST (range 44 to 92 years) trials. There were differences in the enrollment criteria for age, as the IFM 01/01 trial included patients that were at least 75 years, while the IFM 99/06 trial included patients younger than 75 years. Gender distributions were consistent across studies and across treatment arms, with an approximately 50/50 divide between genders. The exception was the IFM 01/01 study, where 38% of the patients in the MPT arm were male, compared to 53% in the MP arm.

The disease stage varied among the five trials using the Durie-Salmon staging system, the International Staging System (ISS), and the ECOG-PS. The majority of patients (89% to 100%) in the three MPT vs. MP trials reporting Durie-Salmon stage were assessed as having stage II or III disease.[40,41,43] The proportion of patients distributed into the three categories of the ISS were consistent across all five trials. ECOG-PS was measured in two trials: in the NCT01274403 trial, there was a higher proportion of patients with an ECOG of 3 to 4 than in the FIRST trial (> 9% versus < 1%). The myeloma isotype was similar among the five trials, with the majority of patients having the IgG isotype. The frequency of bone lesions was markedly lower in the IFM 01/01 trial, with only 7% of patients having this characteristic at enrollment, compared to 65% in the VISTA trial and 71% in the FIRST trial.

A summary of the quality assessment of individual studies is presented in **Table 16**. Only the IFM 01/01 trial was blinded, although it was unclear how concealment was maintained. All of the included studies had appropriate randomization, reported inclusion and exclusion criteria, provided a description of patient characteristics, and used an ITT-based analysis.

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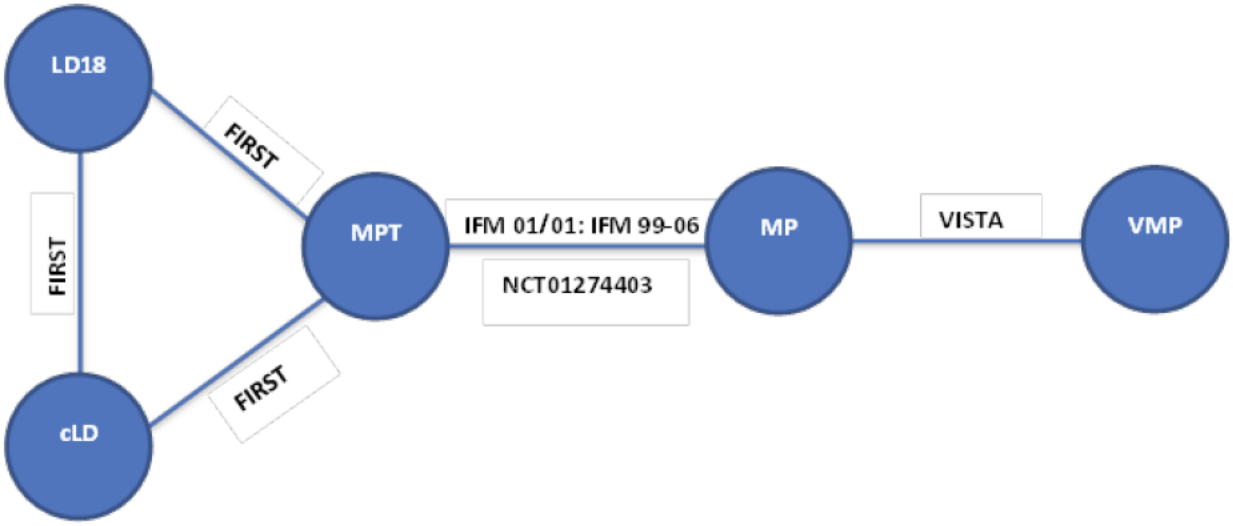
Figure 1: Network diagram of primary analysis and sensitivity analysis networks



cLD = continuous lenalidomide + dexamethasone; LD18 = lenalidomide + dexamethasone for 18 cycles; MP = melphalan + prednisone; MPT = melphalan + prednisone + thalidomide; VMP = bortezomib + melphalan + prednisone

Table 16: Summary of studies used in the NMA

Trial, Publications	Study design and median duration of follow-up	Patient population	Intervention and comparator (number randomized) used in NMA	Outcomes used in NMA
Primary analysis				
FIRST Benboubker et al. 2014[7]	Multinational, Multicentre, Phase III OL RCT 37 months (range 0 to 56.7)	Patients with previously untreated, symptomatic and measurable MM who were ≥ 65 years or < 65 years and ineligible for SCT	**MPT (n = 547)** melphalan (0.25 mg/kg/day on days 1 to 4), prednisone (2 mg/kg/day on days 1 to 4), thalidomide (200 mg/day) on 42-day cycles for 12 cycles (72 weeks) 2 groups of LD (25 mg per day on days 1 to 21 of each cycle) in combination with dexamethasone (40 mg on days 1, 8, 15 and 22) administered on 28-day cycles: **LD18 (n = 541)** treated for 18 cycles (72 weeks) **cLD (n = 535)** treated until disease progression	Primary: PFS Secondary: OS
IFM 01/01 Hulin et al. 2009[41]	European, Multicentre, Phase III RCT 47.5 months	Patients with stage II or III ND-MM according to Durie-Salmon criteria who were ≥ 75 years. Patients with Durie-Salmon stage I MM could be enrolled if they met the criteria of high-risk stage I disease.	**MPT (n = 115)** melphalan (0.2 mg/kg/day on days 1 to 4), prednisone (2 mg/kg/day on days 1 to 4), thalidomide (100 mg/day) on 42-day cycles for 12 cycles (72 weeks) **MP+placebo (n = 117)**	Primary: OS Secondary: PFS

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Trial, Publications	Study design and median duration of follow-up	Patient population	Intervention and comparator (number randomized) used in NMA	Outcomes used in NMA
			melphalan (0.2 mg/kg/day on days 1 to 4), prednisone (2 mg/kg/day on days 1 to 4), placebo on 42-day cycles for 12 cycles (72 weeks)	
IFM 99-06 Facon et al. 2007[40]	European, Multicentre, Phase III OL RCT 51.5 months (IQR 34.4 to 63.2)	Patients with previously untreated stage II or III MM according to Durie-Salmon criteria who were between 65 and 75 years. Patients < 65 years were included if they were ineligible for high-dose treatment. Patients with Durie-Salmon stage I MM could be enrolled if they met the criteria of high-risk stage I disease.	**MPT (n = 125)** melphalan (0.25 mg/kg/day on days 1 to 4), prednisone (2 mg/kg/day on days 1 to 4), thalidomide (200-400 mg/day) on 42-day cycles for 12 cycles (72 weeks) **MP (n = 196)** melphalan (0.2 mg/kg/day on days 1 to 4), prednisone (2 mg/kg/day on days 1 to 4) on 42-day cycles for 12 cycles (72 weeks)	Primary: OS Secondary: PFS
VISTA San Miguel et al. 2012[42]	Multinational, Multicentre, Phase III OL RCT 60.1 months (range 0 to 74)	Patients with newly diagnosed, untreated, symptomatic, measurable MM who were not candidates for high-dose therapy plus SCT because of age (≥ 65 years) or coexisting conditions.	**VMP (n = 344)** bortezomib (1.3 mg/m^2/day on days 1, 4, 8, 11, 22, 25, 32 during cycles 1 to 4 and days 1, 8, 22, 29 during cycles 5 to 9), melphalan (9 mg/m^2/day on days 1 to 4), prednisone (60 mg/m^2/day on days 1 to 4) on 42-day cycles for 9 cycles (54 weeks) **MP (n = 338)** melphalan (9 mg/m^2/day on days 1 to 4), prednisone (60 mg/m^2/day on days 1 to 4) on 42-day cycles for 9 cycles (54 weeks)	Primary: TTP Secondary: OS
Sensitivity analysis				
NCT01274403 Sacchi et al. 2011[43]	Italian, Multicentre, Phase II OL RCT 30 months	Patients > 65 years and younger patients who were ineligible for high-dose treatment with newly diagnosed stage II or III MM.	**MPT (n = 70)** melphalan (0.25 mg/kg/day on days 1 to 4), prednisone (60 mg/m^2/day on days 1 to 4), thalidomide (100 mg/day) on 28-day cycles for 6 to 12 cycles **MP (n = 65)** melphalan (0.25 mg/kg/day on days 1 to 4), prednisone (60 mg/m^2/day on days 1 to 4) on 28-day cycles for 6 to 12 cycles	OS, PFS

cLD = continuous lenalidomide+dexamethasone; IQR = interquartile range; LD18 = lenalidomide+dexamethasone for 18 cycles; MM = multiple myeloma; MP = melphalan + prednisone; MPT = melphalan + prednisone + thalidomide; ND-MM = newly diagnosed multiple myeloma; OL = open label; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; SCT = stem cell transplantation; TTP = time to progression; VMP = bortezomib + melphalan + prednisone

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Table 17: Quality assessment of studies included in the primary analysis and sensitivity analysis network

TRIAL	Randomization	Concealment	Inclusion/ exclusion criteria	Blinding	Description of patient characteristics	Use of ITT-based analysis?
FIRST Benboubker et al. 2014[7]	Yes	Unclear	Yes	Yes	Yes	Yes
IFM 01/01 Hulin et al. 2009[41]	Yes	NA	Yes	No	Yes	Yes
IFM 99-06 Facon et al. 2007[40]	Yes	NA	Yes	No	Yes	Yes
VISTA San Miguel et al. 2012[42]	Yes	NA	Yes	No	Yes	Yes
NCT01274403 Sacchi et al. 2011[43]	Yes	NA	Yes	No	Yes	Yes

Results of the Network Meta-Analysis

The results of this NMA were not disclosable, and are therefore not presented here.

Critical Appraisal of Network Meta-Analysis

The quality of the manufacturer-submitted NMA was assessed according to recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[44] Details and commentary for each of the relevant items identified by the ISPOR group are provided in Table 18.

Strengths

The NMA was based on a systematic review to identify all relevant studies, and the validity of included studies was individually assessed. Baseline characteristics of patients were compared across studies included in the network and appeared to be similar across studies despite different inclusion criteria. The analyses were conducted using appropriate and clearly reported methodology (i.e., Bayesian analysis models created with OpenBugs 3.2.2). The outcome measures assessed (PFS and OS) were appropriate and used to inform the pharmacoeconomic model. One sensitivity analysis was performed including one study that used a different MPT regimen than the other MPT studies.

Limitations

A limitation of the NMA was the use of additional study selection criteria to generate the final network. The exclusion of studies that used continuous thalidomide dosing may not have been appropriate, as the main intervention of interest was continuous lenalidomide + dexamethasone treatment. The manufacturer provided feedback to the initial pCODR Clinical Guidance Report and noted that the inclusion of this study would have added heterogeneity to the network due to the different dosing regimens of thalidomide. However, the pCODR Methods team agreed that the use of a sensitivity analyses that included the studies looking at continuous thalidomide maintenance dosing would have been appropriate to explore the impact of this study on the results of the NMA. The primary and sensitivity networks were small, limiting the power of the

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network. For the included studies, different doses of thalidomide were used in the MPT regimens, but there was no statistical heterogeneity across the studies comparing MPT to MP. In addition, the follow-up duration differed between the studies included in the network, ranging from 37 months to 60 months in the primary network, and 30 months to 60 months in the sensitivity network. While follow up analysis was available for the FIRST study, the pCODR Methods team was not able to comment on the impact of follow up results in the other studies. The inclusion criteria differed among the included studies, which resulted in some differences among the age of patients between trials and disease stage, but overall these differences were not major and statistical heterogeneity was low. There was no assessment of model fit performed, therefore it is unknown how a fixed effect model compared to a random effects model and whether it was the most appropriate model to use. Following the posting of the pCODR Initial Clinical Guidance Report, the submitter provided information on assessment of model fit. The Deviance Information Criterion (DIC) values provided by the manufacturer were reported to be -3.755 for the fixed effect model and -3.086 for the random effect model, suggesting that the fixed effect model yielded a better fit.

Table 18. Appraisal of the indirect comparison analyses using ISPOR criteria[44]

ISPOR Checklist Item		Details and Comments
1.	Are the rationale for the study and the objectives stated clearly?	• The rationale for conducting a network meta-analysis and the study objectives were clearly stated.
2.	Does the methods section include the following? • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity of individual studies	• The eligibility criteria for individual RCTs were clearly stated. • Information sources and search strategy were well reported. • Methods for selection process, data extraction were clearly reported. • The list of excluded studies was provided. • Validity of individual studies was assessed using criteria derived from the Cochrane Handbook for systematic reviews of interventions.
3.	Are the outcome measures described?	• Outcomes assessed in the network meta-analysis were clearly stated.
4.	Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• A description of the statistical model was provided. • Both fixed effects and random effects analyses were presented, and heterogeneity was assessed to determine that the use of a fixed effect analyses was appropriate • The majority of trials were open-label in design, but this may not influence outcomes such as OS and PFS. • Differences in patient population were highlighted.
5.	Are sensitivity analyses presented?	• One sensitivity analysis was presented in which one additional study was included in the primary network analysis, as this study had a different dosing regimen of MPT compared to the other MPT studies. • Additional sensitivity analyses would have been more appropriate, such as including trials that used continuous thalidomide dosing.
6.	Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• A table of study characteristics was provided, in addition to individual tables comparing specific baseline characteristics. • A figure showing the network of studies was provided.
7.	Does the study describe an assessment of model fit? Are competing models being compared?	• Both fixed effects and random-effects analyses were performed. • No assessment of model fit was performed.
8.	Are the results of the evidence synthesis presented clearly?	• Results of the NMA were clearly presented in the report.

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7.1.3 Summary

In the absence of head-to-head trial data for lenalidomide compared to bortezomib + melphalan + prednisone (VMP) in patients with newly diagnosed multiple myeloma (ND-MM) who are not candidates for stem cell transplantation (SCT), the manufacturer submitted a network meta-analysis (NMA) comparing lenalidomide with other first-line treatments in this patient population. Results of this NMA were non-disclosable. Limitations of this NMA included additional criteria for study inclusion which excluded studies that used continuous thalidomide maintenance treatment and some differences in inclusion criteria between included studies that resulted in minor heterogeneity in patient baseline characteristics. In addition, the network was small and comprised of few studies, limiting the power of the network.

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7.2 Summary of poster-reported NMA comparing lenalidomide with other first-line treatments for patient with ND-MM who are not candidates for SCT

7.2.1 Objective

To summarize and critically appraise the methods and findings of a poster-reported NMA comparing lenalidomide with other first-line treatment for patients with ND-MM who are not candidates for SCT.[45] As the results of the full NMA report provided by the manufacturer were non-disclosable, this NMA reported in a poster format was also summarized.

7.2.2 Findings

Methods

Systematic Review

An NMA based on a systematic review to evaluate the relative efficacy of lenalidomide compared with other first-line agents for the treatment of ND-MM in patients who are not eligible for SCT was presented in a poster format. The EMBASE, Pubmed, and CENTRAL databases were searched and supplemented with conference proceedings. Interventions included lenalidomide, thalidomide, bortezomib, interferon, or bendamustine as monotherapy or part of a combination therapy, or melphalan plus prednisone combination therapy.

Additional Criteria

Additional criteria were applied to the included trials in order to determine the trials that would be included in the NMA. Only studies providing evidence to compare continuous lenalidomide + dexamethasone (cLD) treatment to VMP, using MPT as a common comparator were included. Only trials with a treatment duration of at least 48 weeks were included. Only trials in which thalidomide maintenance treatment was given over a fixed period (e.g., maximum 12 six-week cycles) were included, as per the thalidomide summary of product characteristics and current clinical practice.

Network Meta-Analysis

The evidence on survival endpoints (OS and PFS) identified from the systematic review was assessed quantitatively using an NMA to evaluate the comparative efficacy of lenalidomide and VMP. Fixed-effects and random-effects Bayesian mixed-treatment comparison (MTC) meta-analyses were conducted and compared all treatments of interest using hazard ratios (HR) for overall survival (OS) and progression-free survival (PFS).

No sensitivity analyses were pre-specified in the protocol. However, one of the included studies used a duration of thalidomide treatment that differed from those in other studies with a fixed duration of MPT treatment, and so this study was removed in a sensitivity analysis. A separate sensitivity analysis was conducted to evaluate the effect of combining the studies with a fixed duration of MPT treatment with 6 additional studies that either included thalidomide maintenance or had a study comparator with a 1- to 2-degree linkage to either MPT or MPT with maintenance thalidomide treatment in the network.

In the MTC, a quality assessment of the included RCTs was performed to evaluate potential bias in terms of randomization, concealment, inclusion criteria, blinding, patient characteristics, and the use of an intention-to-treat (ITT) population analysis using questions derived from the Cochrane Handbook for systematic reviews of interventions.[39] Assessments were validated by independent investigators and discrepancies were resolved by a senior investigator through reaching a consensus.

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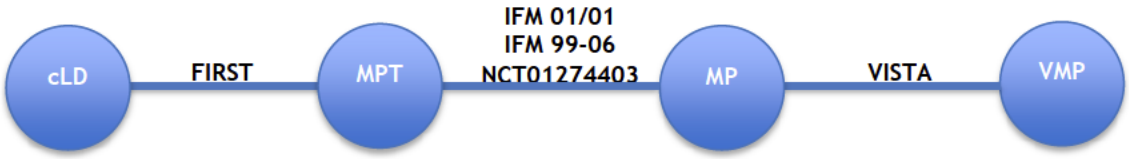
Results

Study and Patient Characteristics

Eighty-two articles were selected for inclusion in the review representing 48 trials. On the basis of clinical relevance and treatment schedule, the primary analysis for the NMA was based on five trials evaluating continuous lenalidomide, VMP, MP, and MPT (Figure 2).[7,40-43] The included trials were identical to the trials included in the full NMA report summarized in Section 7.1. However, Study NCT01274403 was included in the primary analysis instead of in a sensitivity analysis, and was removed in a sensitivity analysis.

Figure 2: Network diagram of primary analysis and sensitivity analysis networks



cLD = continuous lenalidomide + dexamethasone; MP = melphalan + prednisone; MPT = melphalan + prednisone + thalidomide; VMP = bortezomib + melphalan + prednisone

Results of the Network Meta-Analysis

In the poster, only hazard ratios using fixed-effects analyses were presented for OS and PFS based on the primary analysis network of five studies. Comparisons were evaluated using continuous lenalidomide (cLD) as the reference treatment.

Overall Survival

Using fixed-effects analyses, cLD was associated with a significantly lower risk of death compared to VMP (HR 0.63, 95% CrI 0.44 to 0.92), MPT (HR 0.75, 95% CrI 0.62 to 0.90), and MP (HR 0.44, 95% CrI 0.32 to 0.60) (Table **19**). There was no difference between cLD and LD18.

Table 19: Results of the MTC analysis - Overall Survival

	Primary Network Analysis (5 studies)
cLD versus Comparators	**OS Fixed-Effects HR [95% CrI]**
VMP	0.63 [0.44, 0.92]
MPT	0.75 [0.62, 0.90]
MP	0.44 [0.32, 0.60]

cLD = continuous lenalidomide + dexamethasone; CrI = credible interval; HR = hazard ratio; OS = overall survival; MP = melphalan + prednisone; MPT = melphalan + prednisone + thalidomide; VMP = bortezomib + melphalan + prednisone

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Progression-Free Survival

Using fixed-effects analyses, cLD was associated with a significantly lower risk of disease progression death compared to LD18 (HR 0.69, 95% CI 0.49 to 0.98), VMP (HR 0.68, 95% CrI 0.48 to 0.97), MPT (HR 0.69, 95% CrI 0.59 to 0.80), and MP (HR 0.39, 95% CrI 0.31 to 0.49) (

Table 20).

Table 20: Results of the MTC analysis - Progression-Free Survival

	Primary Network Analysis (5 studies)
cLD versus Comparators	PFS Fixed-Effects HR [95% CrI]
VMP	0.69 [0.49, 0.98]
MPT	0.69 [0.59, 0.80]
MP	0.39 [0.31, 0.49]
cLD = continuous lenalidomide + dexamethasone; CrI = credible interval; HR = hazard ratio;; PFS = progression-free survival; MP = melphalan + prednisone; MPT = melphalan + prednisone + thalidomide; VMP = bortezomib + melphalan + prednisone	

Sensitivity Analyses

When Study NCT01274403[43] was removed from the network, the point estimates for OS and PFS did not vary to a high degree (data not reported).

The sensitivity analysis that included 6 additional studies with thalidomide maintenance or had a study comparator with a 1- to 2-degree linkage to either MPT or MPT with maintenance thalidomide treatment in the network showed nearly identical results to the primary analysis (data not reported).

Critical Appraisal of Network Meta-Analysis

The quality of the manufacturer-submitted NMA was assessed according to recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[44] Due to the similarity of this poster-reported NMA and the manufacturer-submitted NMA, the critical appraisal points do not differ much. However, the reporting in this poster NMA was sparse, with a lack of details on study selection criteria and methodologies used to conduct the NMA.

7.2.3 Summary

In the absence of head-to-head trial data for lenalidomide compared to bortezomib + melphalan + prednisone (VMP) in patients with newly diagnosed multiple myeloma (ND-MM) who are not candidates for stem cell transplantation (SCT), a network meta-analysis (NMA) comparing lenalidomide with other first-line treatments in this patient population was conducted and presented in a poster format. Using fixed effects analyses, continuous lenalidomide + dexamethasone appeared to have a lower risk of progression and death compared to MPT and VMP. Limitations of this NMA included additional criteria for study inclusion which excluded studies that used continuous thalidomide maintenance treatment and some differences in inclusion criteria between included studies that resulted in minor heterogeneity in patient baseline characteristics. In addition, the network was small and comprised of few studies, with no direct linkage connecting lenalidomide to VMP, increasing uncertainty in the results.

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8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Lymphoma and Myeloma Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on lenalidomide for ND-MM. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

The Lymphoma and Myeloma Clinical Guidance Panel is comprised of three medical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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APPENDIX A: LITERATURE SEARCH STRATEGY

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** April 2015, **Embase** 1974 to 2015 May 19, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

#	Searches	Results
1	(Revlimid* or Revimid* or lenalidomide* or CC 5013 or CDC 501 or CDC501 or CDC5013 or CC5013 or CDC 5013 or "ENMD 0997" or ENMD0997 or IMiD 3 or IMiD3).ti,ot,ab,sh,rn,hw,nm,au,kw. or (191732-72-6 or 443912-14-9 or 346670-73-3 or F0P408N6V4).rn,nm.	13450
2	exp Multiple Myeloma/ or (myelom* or kahler disease or morbus kahler).ti,ab.	141170
3	1 and 2	7842
4	3 use pmez	1491
5	3 use cctr	186
6	4 or 5	1677
7	*lenalidomide/ or (Revlimid* or Revimid* or lenalidomide* or CC 5013 or CDC 501 or CDC501 or CDC5013 or CDC 5013 or CC5013 or "ENMD 0997" or ENMD0997 or IMiD 3 or IMiD3).ti,ab.	8706
8	exp Multiple Myeloma/ or (myelom* or kahler disease or morbus kahler).ti,ab.	141170
9	7 and 8	5547
10	9 use oemezd	4009
11	6 or 10	5686
12	(Randomized Controlled Trial or Controlled Clinical Trial).pt.	912909
13	Randomized Controlled Trial/	768945
14	Randomized Controlled Trials as Topic/	176502
15	"Randomized Controlled Trial (topic)"/	73067
16	Controlled Clinical Trial/	480231

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17	Controlled Clinical Trials as Topic/	9309
18	"Controlled Clinical Trial (topic)"/	4185
19	Randomization/	170171
20	Random Allocation/	170171
21	Double-Blind Method/	359184
22	Double Blind Procedure/	122742
23	Double-Blind Studies/	320404
24	Single-Blind Method/	53373
25	Single Blind Procedure/	20181
26	Single-Blind Studies/	53373
27	Placebos/	323592
28	Placebo/	268819
29	Control Groups/	76441
30	Control Group/	76353
31	(random* or sham or placebo*).ti,ab,hw.	2921067
32	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	600989
33	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	1494
34	(control* adj3 (study or studies or trial*)).ti,ab.	949528
35	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.	69744
36	allocated.ti,ab,hw.	122228
37	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.	68969
38	or/12-37	3691820
39	11 and 38	1338
40	remove duplicates from 39	1092

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41	limit 40 to english language	1052

2. Literature search via PubMed

Search	Query	Items found
#8	Search **#4 OR #7**	41
#7	Search **#1 AND #2** Filters: **Publication date from 2015/05/14 to 2015/12/31; English**	5
#5	Search **#1 AND #2**	1433
#6	Search **#1 AND #2** Filters: **Publication date from 2015/05/14 to 2015/12/31**	5
#4	Search **#1 AND #2 AND #3**	38
#3	Search **publisher[sb]**	472738
#2	Search **Multiple myeloma[mh] OR multiple myeloma*[tiab] OR kahler disease[tiab] OR morbus kahler*[tiab]**	39653
#1	Search **((lenalidomide[Supplementary Concept] OR Revlimid*[tiab] OR Revimid*[tiab] OR lenalidomide*[tiab] OR CC 5013[tiab] OR CDC 501[tiab] OR CDC501[tiab] OR CC5013[tiab] OR CDC5013[tiab] OR CDC 5013[tiab] OR IMiD3 cpd[tiab] OR ENMD 0997[tiab] OR ENMD0997 OR imid 3[tiab] OR imid3[tiab])**	2522

3. Cochrane Central Register of Controlled Trials (Central)

Searched via Ovid

4. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search terms: Revlimid/lenalidomide and Multiple myeloma

Select international agencies including:

Food and Drug Administration (FDA):

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http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search terms: **Revlimid**

Conference abstracts:

American Society of Clinical Oncology (ASCO)
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Search terms: Revlimid/lenalidomide and Multiple Myeloma / last 5 years

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