PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Lenalidomide (Revlimid) for Multiple Myeloma

October 22, 2013

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy of maintenance treatment with single-agent lenalidomide following autologous stem cell transplantation (ASCT), compared to an appropriate comparator, in patients with newly diagnosed multiple myeloma (MM).

Although lenalidomide does not have Health Canada regulatory approval for this indication, the manufacturer is requesting funding as maintenance treatment for newly diagnosed multiple myeloma in patients after stem-cell transplantation. In the two pivotal trials included in the pCODR systematic review, lenalidomide was administered at 10 mg/day for the first 3 months and then increased to 15 mg/day if tolerated.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included two randomised, double-blind, placebo-controlled, phase 3 trials, IFM 2005-02[1] and CALGB 100104[2] that assessed the efficacy and safety of lenalidomide maintenance therapy compared to placebo maintenance in patients with newly diagnosed MM following treatment with ASCT.

- IFM 2005-02 randomized patients (n=307) to lenalidomide maintenance (10 mg/day for the first 3 months, increased to 15 mg/day if tolerated, thereafter) or placebo maintenance (n=307). Patients had a mean age of 55 and had received 1 or 2 prior ASCT (75% and 21%, respectively). Almost all patients had received prior consolidation treatment with lenalidomide 25 mg/day on days 1-21 of a 28-day cycle for 2 cycles following single or double ASCT.
- CALGB 100104 randomised patients (n=231) to maintenance therapy with lenalidomide (10 mg/day for the first 3 months, increased to 15 mg/day if tolerated, thereafter) or to maintenance therapy with placebo (n=229). Patients had a mean age of 59 and the majority had received induction therapy with a regimen containing lenalidomide, thalidomide, or bortezomib, or a combination of the three. All patients in CALGB 100104 had received prior single-ASCT.

In the IFM 2005-02 study, the final efficacy analysis was conducted in July 2010 and the study was unblinded but cross-over was not permitted. Patients stopped receiving lenalidomide as of January 2011 due to safety concerns related to an increased incidence of second primary malignancies in patients receiving lenalidomide.

The CALGB 100104 study was however terminated early (December 17, 2009, following a median follow-up of 18 months) due to the demonstration of statistically significant improvements in the primary efficacy outcome of TTP after a pre-planned interim analysis. Patients were then allowed to crossover to lenalidomide.

Efficacy

IFM 2005-02

The primary end-point for the IFM 2005-02 study was progression free survival (PFS). Key secondary outcomes included overall survival (OS). The IFM 2005-02 study demonstrated a statistically significant improvement in the primary outcome, PFS, at the data cut-off dates of July 2010 and October 2011. At the October 2011 cut-off, the median PFS was 44 vs 24 months in the lenalidomide compared to placebo arms, respectively (HR=0.50 95% CI: not reported p<0.001).[1,3] For the secondary outcome of OS, the study did not demonstrate a statistically significant difference in OS.

CALGB 100104

The primary end-point for the CALGB 100104 study was time to progression (TTP). Key secondary outcomes included overall survival (OS). The CALGB 100104 study demonstrated a statistically significant improvement in the primary outcome, TTP, at the December 2009 and October 2011 pre-planned interim analysis.[2,4] The January 2013 updated analysis also demonstrated a median TTP of 50 vs 27 months in the lenalidomide compared to placebo arms (HR= 0.51 95% CI: 0.39-0.66 p=NR). A statistically significant difference in OS in favour of the lenalidomide maintenance was also reported at the January 2013 updated analysis (analysis was based on 116 deaths out of 460 randomized patients).[4]

Quality of life data were not reported in either trial.

Harms

IFM 2005-02

A statistically significantly higher rate of grade 3 or 4 thromboembolic events and hematologic adverse events were observed in the lenalidomide maintenance arm compared to the placebo maintenance arm.[1] More patients in the lenalidomide arm discontinued treatment due to adverse events compared to the placebo arm (27.1% vs 14.6%, respectively).

The incidence of second primary malignancies was statistically significantly higher in the lenalidomide maintenance arm compared to the placebo maintenance arm (3.1 vs 1.2 per 100 patient-years; p=0.002, respectively).[1] In the lenalidomide arm, 32 second primary malignancies occurred in 26 patients compared to 12 second primary malignancies in 11 patients assigned to the placebo maintenance arm which resulted in the termination of the trial as of January 2011.

CALGB 100104

The CALGB 100104 study reported statistically significantly higher rates of grade 3 or 4 hematologic adverse events, neutropenia, anemia, and thrombocytopenia in the lenalidomide maintenance arm than in the placebo arm (see Table 3 for rates and p-values).[2] In the CALGB study, 10.0% and 1.4% of patients (from the 143 patients who did not crossover to lenalidomide) discontinued therapy due to an adverse in the lenalidomide and placebo arms, respectively.[2] Of the 86 patients who crossed over to receive lenalidomide maintenance, five patients (5.8%) discontinued therapy due to an adverse event. As of the January 2013 updated analysis, a total of 29/231 (12.6%) and 15/229 (6.6%) patients developed second primary malignancies in the lenalidomide and placebo arms, respectively.[4]

1.2.2 Additional Evidence

pCODR received input on lenalidomide for multiple myeloma from one patient advocacy group, (Myeloma Canada). Provincial Advisory group input was obtained from nine of the nine provinces participating in pCODR.

No supplemental issues were identified during the development of the review process

Comparison with other Literature

Two studies were identified that did not meet the systematic review inclusion criteria but were considered to provide relevant additional data. One study assessed the benefit of lenalidomide maintenance in transplant-ineligible patients.[5] The other study assessed lenalidomide maintenance versus no maintenance in both transplanted and non-transplanted patients but results were presented at an aggregate level and could not be reported separately for the population of interest.[6,7] The results of these two studies were consistent with the PFS benefit observed in the IFM 2005-02 and CALGB 100104 trials.

1.2.3 Interpretation and Guidance

Burden of Illness and Need

Multiple myeloma is a cancer of the bone marrow with an incidence of approximately 2500 new cases per year in Canada.[8] Myeloma increases in incidence with age, with a median age at presentation of 70 years[9], and is present in slight excess in males relative to females. Myeloma is incurable in the vast majority of cases, with 1350 deaths from the disease expected in Canada in 2013.[8]

Autologous stem cell transplant is frequently performed as part of front line myeloma therapy in patients with multiple myeloma. This treatment is not curative and improving patient survival, remission duration and quality of life are important goals. For patients in whom high dose melphalan and autologous stem cell transplantation is the planned treatment, strategies to further increase therapeutic efficacy have been explored including the incorporation of novel agents into treatment before (induction), during (conditioning), or after (consolidation, maintenance) high dose melphalan therapy. Older drug classes such as chemotherapy agents, corticosteroids and cytokines have not been found to significantly improve patient outcomes in the maintenance setting. Thalidomide has been shown to prolong remission when administered as maintenance therapy post transplant, with some studies showing an overall survival advantage.[10] The role of bortezomib in the maintenance post-transplant setting has not been clearly defined.

Effectiveness

The CALGB 100104 trial demonstrated an overall survival advantage to the use of lenalidomide maintenance following autologous stem cell transplant for myeloma patients as compared to observation. The magnitude of survival benefit seen in this study was both statistically and clinically significant. An overall survival benefit for lenalidomide maintenance was not seen post transplant in the IFM 2005-02 trial.

Both studies, CALGB 100104 and IFM 2005-02, demonstrated a statistically and clinically significant improvement in disease control as measured with PFS or the very similar endpoint, TTP, with the addition of lenalidomide maintenance following autologous stem cell transplant. These results are consistent with the PFS benefit seen in a published trial of lenalidomide maintenance in transplant-ineligible patients[5], and in a trial presented in

abstract form only that looked at lenalidomide maintenance versus no maintenance in both transplanted and non-transplanted patients.[6,7] A substantial PFS improvement should be regarded as the basis for a change in standard of care as prolongation of progression-free survival is arguably a meaningful endpoint in myeloma trials due to the considerable morbidity that can occur with progression.[11]

Safety

While the addition of lenalidomide has been associated with increased toxicity, the degree of toxicity appears to be manageable. The absolute percentage of patients discontinuing protocol therapy due to adverse events was only 10-15% higher in the lenalidomide arms compared to patients receiving placebo in the control arms for both trials while the increased adverse hematological toxicities seen with lenalidomide in the two trials were expected and acceptable.

Although lenalidomide has been associated with an increased risk of second malignancies in myeloma patients, the increase in the rate of second malignancies in the two trials was relatively small and did not lead to decreased survival in the treatment arms of the trials. Based on the two trials, the Clinical Guidance Panel considered the second malignancy risk to be acceptable.

1.3 Conclusions

The pCODR Myeloma Clinical Guidance Panel concluded that there is a net clinical benefit to the use of lenalidomide maintenance as part of front line therapy that includes high dose melphalan and autologous hematopoietic stem cell transplantation for patients with multiple myeloma. This conclusion is based on two fully published, high quality randomized controlled trials (CALGB 100104 and IFM 2005-02) showing improvement in PFS or TTP with lenalidomide with increased but manageable toxicity, and one of which demonstrated an overall survival advantage with lenalidomide following autologous stem cell transplant.

In making this conclusion, the Clinical Guidance Panel also considered that:

- Progression-free survival is a meaningful endpoint in myeloma trials due to the considerable morbidity that can occur with progression, and that a substantial PFS improvement should be regarded as the basis for a change in standard of care.[11]
- 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.
- Results are consistent with the PFS benefit seen with the use of lenalidomide in transplant-ineligible patients[5] and in both transplanted and non-transplanted patients.[6,7]
- A manageable degree of toxicities and a relatively low rate of second malignancies were observed.

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 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 (Revlimid) conducted by the 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 (Revlimid) and a summary of submitted Provincial Advisory Group Input on lenalidomide (Revlimid) are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Multiple myeloma is a cancer of the bone marrow with an incidence of approximately 2500 new cases per year in Canada.[8]

Patients with symptomatic myeloma are treated primarily with anti-myeloma drug therapy. For eligible patients high dose melphalan and autologous stem cell transplant is generally prescribed as part of the initial treatment, rather than deferring this therapy until relapse, in order to maximize the duration of the first remission.

For patients in whom high dose melphalan and autologous stem cell transplantation is the planned treatment, strategies to further increase therapeutic efficacy have been explored including the incorporation of novel agents, including bortezomib, thalidomide, and lenalidomide, into treatment before (induction), during (conditioning), or after (consolidation, maintenance) high dose melphalan therapy. Older drug classes such as chemotherapy agents, corticosteroids and cytokines have not been found to significantly improve patient outcomes in the maintenance setting. Thalidomide has been shown to prolong remission when administered as maintenance therapy post transplant, with some studies showing an overall survival advantage.[10] Thalidomide maintenance has not been widely implemented in Canada, in part over concerns about toxicity including peripheral neuropathy. At present, access to thalidomide as post-transplant maintenance therapy is somewhat limited in Canada. The role of bortezomib maintenance post-transplant has not been clearly defined. Studies incorporating bortezomib both pre- and post-transplant have demonstrated improved patient outcomes, but the design of these studies did not permit the determination of the efficacy or cost-effectiveness of bortezomib specifically in the maintenance setting.

Allogeneic stem cell transplantation is used infrequently to treat myeloma because of high treatment related morbidity and mortality, but can achieve long term disease control in some patients.[12]

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effectiveness of maintenance treatment with single-agent lenalidomide following autologous stem cell transplantation (ASCT), compared to an appropriate comparator, in patients with newly diagnosed multiple myeloma (MM).

See Table 4 in Section 6.2.1 for outcomes of interest and appropriate comparators.

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.

Two randomized controlled trials comparing the use of lenalidomide maintenance therapy to placebo maintenance in patients with newly diagnosed MM following treatment with ASCT were identified and included in this clinical guidance report.[1,2] A brief summary of key trial quality characteristics can be found in Table 1. For a more detailed description of the trial design and patient characteristics, please see Table 5 in the *Systematic Reivew* (Section 6.3.2.1). The trials were similar in design with a few exceptions: The IFM 2005-02 study included 614 patients and administered consolidation treatment with lenalidomide 25 mg/day on days 1-21 of a 28-day cycle for 2 cycles to all patients following either single or double ASCT.[1] Patients randomized to the lenalidomide maintenance arm received lenalidomide at 10 mg/day for the first 3 months, increased to 15 mg/day if tolerated, thereafter. Patients randomized to the placebo maintenance arm received placebo. Both arms were administered until patient withdrew consent, disease progression, or unacceptable toxic effects. The CALGB 100104 study randomized 460 patients, following single ASCT, to receive maintenance therapy with lenalidomide at 10 mg/day for the first 3 months, increased to 15 mg/day if tolerated, thereafter or to receive maintenance placebo.[2] Both arms were administered until disease progression.

Table 1. Select quality characteristics of included RCTs of lenalidomide maintenance following ASCT in newly diagnosed MM.

Study	Treatment	Primary outcome	Required sample size (80% power, α=0.05)	Sample size N	Randomization method	Allocation concealment	Blinding	ITT analysis	Final analysis	Early termination	Ethical Approval
IFM 2005-02[1]	LEN maintenance Vs. placebo	PFS	614 patients required to provide 85% power to detect a HR 0.704 (in favour of LEN) using a one-sided overall alpha=0.025, assuming 4-year PFS of 50% for the LEN arm and 37.5% for the placebo arm.	LEN: 307 Placebo: 307	Central[A], stratified[B]	Yes	Double[C]	Yes	Yes	Yes[D]	Yes
CALGB 100104[2]	LEN maintenance Vs. placebo	TTP	460 patients with 309 events to provide 90% power to detect a HR 0.714 (in favour of LEN) using a one-sided alpha=0.05, assuming a median TTP of 33.6 months for LEN and 24 months for placebo.	LEN: 231 Placebo: 229	Central, stratified[E]	Yes	Double[F]	Yes	Yes	Yes[G]	Yes

Notes: ITT = intention-to-treat; LEN=lenalidomide; N= number of patients randomized; NR = not reported; PFS = progression-free survival; TTP=time-to-progression.

[A]The use of central randomization was confirmed in the submitter's response to the checkpoint meeting questions.[3]

[B]Stratification was by baseline 13q deletion (presence vs. absence), serum β_2-microglobulin (≤3 mg/L vs. >3 mg/L), and by response after transplantation achieved at the time of randomization (complete response/very good partial respoinse vs. partial response/stable disease).

[C]Patients and response assessors (independent review committee) were blinded to treatment allocation. The study used an independent data and safety monitoring committee.[1]

[D]The In January 2010, an interim analysis was conducted for PFS that indicated the pre-specified level of significance (p<0.004) for stopping the study had been reached; however, the independent data and safety monitoring committee recommended that the study be continued, unblinded and without crossover of patients. In January 2011, an increased incidence of second primary cancers was observed in the lenalidomide group and the independent data and safety monitoring committee recommended that treatment with lendalidomide be stopped and that follow-up continue to determine survival and to detect second primary cancers.

[E]Stratification was by baseline serum β_2-microglobulin (≤2.5 mg/L vs. >2.5 mg/L), prior use of thalidomide during induction therapy (yes vs. no), and prior use of lenalidomide during induction therapy (yes vs. no).

[F]Although the study was described as double-blind, other than for patients, it was not clear exactly who was blinded to treatment allocation. The study had an independent data and safety monitoring committee.[2]

[G]With a data-cut-off of December 17, 2009, the independent data and safety monitoring committee released the study data to the investigators as the pre-specified boundary for efficacy had been crossed.[1] Treatment assignment was unblinded and patients were allowed to cross over to the lenalidomide arm.[13]

No serious limitations or potential sources of bias were identified in either study. Of note, the OS results of the CALGB 100104 study need to be interpreted with caution given the relatively small number of events (88 out of 460 patients at the October 2011 analysis[2] and 116 events out of 460 patients for the January 2013 analysis[4]), until more mature OS data are available. In addition, both studies were terminated early: the IFM 2005-02 study due to an increased incidence of second primary malignancies and the CALGB study after a pre-planned interim analysis demonstrated a statitistically significant improvement in the primary outcome, TTP. The IFM 2005-02 study also demonstrated a statistically significant improvement in primary outcome, PFS, at a pre-planned interim analysis; however, the data and safety monitoring committee recommended continuation of the study, unblinded and without allowing crossover, in order to collect additional survival data.

The key efficacy results for both studies are summarized in Table 2. Both studies reported statistically significant differences in PFS (IFM 2005-02) or in TTP (CALGB 100104) in favour of lenalidomide maintenance compared to placebo maintenance (see Table 2 for estimates of effect and hazard ratios [HR]). The IFM 2005-02 study[1] did not demonstrate a statistically significant difference in OS (Table 2), whereas the CALGB 100104 study[2] reported a statistically significant difference in OS in favour of lenalidomide maintenance compared to placebo maintenance at the updated October 2011 analysis (Table 2); however the analysis was based on 88 deaths out of 460 randomized patients, with the median OS not reached in either arm. An updated analysis conducted in January 2013 also reported a statistically significant difference in OS in favour of the lenalidomide maintenance arm compared to the placebo maintenance arm (Table 2).[4] That analysis was based on 116 deaths out of 460 randomized patients.[4]

Key grade 3 or 4 adverse event outcomes can be found in Table 3. The CALGB 100104 study reported statistically significantly higher rates of grade 3 or 4 hematologic adverse events, neutropenia, anemia, and thrombocytopenia in the lenalidomide maintenance arm than in the placebo arm (see Table 3 for rates and p-values).[2] The IFM 2005-02 study also reported a statistically significantly higher rate of grade 3 or 4 hematologic adverse events in the lenalidomide maintenance arm compared to the placebo maintenance arm as well as a statistically significantly higher rate of grade 3 or 4 thromboembolic events in the lenalidomide arm compared to the placebo arm (see Table 3 for rates and p-value).[1]

In the IFM 2005-02 study, treatment was discontinued due to adverse events in 83 patients (27.1%) in the lenalidomide maintenance arm and in 44 patients (14.6%) in the placebo maintenance arm.[1] In the CALGB study, 23 patients (10.0%) in the lenalidomide maintenance arm discontinued therapy due to an adverse event compared to 2 (1.4%) (from among 143 patients in the placebo arm who did not cross over to receive lenalidomide maintenance).[2] Of the 86 patients placebo arm patients who crossed over to receive lenalidomide maintenance, five patients (5.8%) discontinued therapy due to an adverse event.

Table 2. Efficacy outcomes reported in included studies of lenalidomide maintenance following ASCT in newly diagnosed MM.

Study	Date of Analysis	Treatment arms	OS, median (mos)	PFS[A]/TTP[B], median (mos)	Follow-up, median (mos)
IFM 2005-02[1]	July 2010	LEN, n=307 Placebo, n=307	NYR NYR HR=1.25 95%CI=not reported p=0.29	41[A] 23[A] HR=0.50 95%CI=not reported p<0.001	30
	October 2011	LEN, n=307 Placebo, n=307	NYR NYR HR=1.06 95%CI=not reported p=0.70	44[A,D] 24[A,D] HR=0.50 95%CI=not reported p<0.001	45
CALGB 100104[2,4]	December 17, 2009	LEN, n=231 Placebo, n=229	NYR NYR HR=0.52 95%CI=0.26-1.02 p=0.05	39[B] 21[B] HR=0.37 95%CI=0.26-0.53 p<0.001	18
	October 31, 2011	LEN, n=231 Placebo, n=229	NYR NYR HR=0.62 95%CI=0.40-0.95 p=0.03	46[B] 27[B] HR=0.48 95%CI=0.36-0.63 p<0.001	34
	OS update January 7, 2013[E]	LEN, n=231 Placebo, n=229	NYR 73 HR=0.61 95% CI=0.41-0.87 p=0.008	50 27 HR=0.51 95% CI=0.39-0.66 p=NR	48

Notes: 95%CI=95% confidence interval; **ASCT**=autologous stem cell transplantation; **HR**=hazard ratio with HR<1 favouring lenalidomide maintenance; **LEN**=lenalidomide; **mos**=months; **NYR**=not yet reached; **PFS**=progression-free survival; **TTP**=time-to-progression.

[A]The IFM 2005-02 trial reported PFS.
[B]The CALGB 100104 trial reported TTP.
[D]Median PFS values were estimated from the published Kaplan-Meier survival curves.
[E]Data on median OS, the 95% CI for the OS HR, and all of the data for TTP were obtained from the submitter's response at the pCODR Checkpoint Meeting.[3]

In the IFM 2005-02 study, 32 second primary malignancies occurred in 26 patients in the lenalidomide maintenance arm compared to 12 second primary malignancies in 11 patients assigned to the placebo maintenance arm. The incidence of second primary malignancies

was statistically significantly higher in the lenalidomide maintenance arm (3.1 per 100 patient-years) compared to the placebo maintenance arm (1.2 per 100 patient-years; p=0.002).[1] In the CALGB 100104 study, the following second primary malignancies were reported: in the lenalidomide arm, eight patients had a hematologic cancer, 10 patients had a solid-tumour cancer, two patients had a basal-cell carcinoma, and two patients had a squamous-cell carcinoma; whereas in the placebo arm, one patient had a hematologic cancer, five patients had a solid-tumour cancer, one patient had a basal-cell carcinoma, and two patients had a squamous-cell carcinoma.[2] In the January 2013 analysis reported at the 14th Annual International Myeloma Workshop, a total of 29 out of 231 patients (12.6%) who received lenalidomide maintenance and 15 out of 229 patients (6.6%) who received placebo maintenance developed a second primary malignancy.[4]

Table 3. Number of patients (percent) with Grade 3 or 4 adverse events that occurred in 5% or more of patients in either arm of the included studies of lenalidomide maintenance following ASCT in newly diagnosed MM.

Grade 3 or 4 Adverse Event	IFM 2005-02[1]			CALGB 100104[2]		
	LEN, n=306	Placebo, n=302	p-value	LEN, n=231	Placebo, n=229	p-value
Any adverse event, n (%)	225 (74)	130 (43)	NR	136 (58.9)	68 (29.7)	NR
Hematologic, n (%)	179 (58)	68 (22)	p<0.001	110 (47.6)	39 (17.0)	p<0.001
Neutropenia, n (%)	157 (51)	53 (18)	NR	104 (45.0)	34 (14.9)	p<0.001
Febrile neutropenia, n (%)	4 (1)	1 (<1)	NR	13 (5.6)	3 (1.3)	NR
Anemia, n (%)	10 (3)	7 (2)	NR	11 (4.8)	1 (0.4)	p=0.006
Thrombocytopenia, n (%)	44 (14)	20 (7)	NR	32 (13.9)	11 (4.8)	p=0.001
Thromboembolic events, n (%)	NR (6)	NR (2)	p=0.01	3 (1.3)	1 (0.4)	NR
General Disorders, n (%)	18 (6)	8 (3)	NR	NR	NR	NR
Fatigue, n (%)	15 (5)	8 (3)	NR	13 (5.6)	7 (3.1)	NR
Infections, n (%)	41 (13)	15 (5)	NR	14 (6.1)	6 (2.6)	NR
Skin disorders, n (%)	21 (7)	11 (4)	NR	NR	NR	NR
Diarrhea, n (%)	5 (2)	1 (<1)	NR	11 (4.8)	4 (1.7)	NR

Notes: LEN=lenalidomide; **n**=number of patients.

2.1.4 Comparison with Other Literature

Relevant literature identified jointly by the pCODR Clinical Guidance Panel and Methods Team and providing supporting information to the systematic review is summarized below. This information has not been systematically reviewed.

Two studies were identified that did not meet the systematic review inclusion criteria but were considered to provide relevant additional data. One study assessed the benefit of lenalidomide maintenance in transplant-ineligible patients.[5] The other study assessed lenalidomide maintenance versus no maintenance in both transplanted and non-transplanted patients but results were presented at an aggregate level and could not be reported separately for the population of interest.[6,7]

One study, reported by Boccadoro et al[6] and Cavallo et al[7], was identified that did not meet the eligibility criteria for the systematic review as separate data for the maintenance portion of the trial for the study population of interest to this systematic review were not reported; however, the study was included in the *Ongoing Trials* section (Section 6.4) as the study has only been reported in abstract form and a full publication may provide additional relevant data. The study was an open-label randomized trial using a 2X2 factorial design. Patients with newly diagnosed multiple myeloma, aged 65 years or less, were initially randomized to receive melphalan, prednisone, and lenalidomide every 28 days for 6 cycles (with no ASCT) or to receive high-dose melphalan followed by ASCT (see Table 8 in the *Ongoing Trials* section for additional details). Patients underwent a second randomization to receive maintenance therapy with lenalidomide (no dose or schedule details were reported) or to no maintenance treatment. It is unknown whether the results reported in the abstract publications were from an interim or a final analysis. Boccadoro et al reported that the primary endpoint was PFS and that 170 patients were required per arm to demonstrate a 15% improvement in PFS at 2-years with a power of 80%; although it was not clear whether the improvement referred to induction therapy or to maintenance therapy.[6] No other details regarding study quality were available and no data were available separately for the group of patients who received high-dose melphalan followed by ASCT followed by randomization to lenalidomide maintenance compared to no maintenance. Without this information, it is difficult to determine the quality of the study. The study results must be interpreted with caution. The median PFS for all patients who received lenalidomide maintenance was 37.5 months compared to 25.7 months for all patients who received no maintenance (p=0.0008).[6] The 4-year OS was 76% for maintenance lenalidomide compared to 68% for no maintenance (p=0.08).[6] The rate of second primary malignancies was 2% in both maintenance arms.[7]

Another study, the Multiple Myeloma 015 (MM-015) Study, randomly assigned patients who were ineligible for transplantation to one of three treatment arms in a 1:1:1 ratio: 1) melphalan, prednisone, and lenalidomide followed by lenalidomide maintenance (MPR-R); 2) melphalan, prednisone, and lenalidomide without maintenance therapy (MPR), or; 3) melphalan and prednisone without maintenance therapy (MP).[5] In each arm, melphalan was administered at a dose of 0.18 mg/kg on days 1-4, prednisone at 2 mg/kg on days 1-4, lenalidomide (or placebo) at 10 mg on days 1-21 of each 28-day cycle for up to nine cycles, followed by maintenance therapy with placebo (MP and MPR arms) or lenalidomide at 10 mg on days 1-21 of each 28-day cycle until disease progression or unacceptable adverse effects (MPR-R arm). The trial was a double-blind multicentre study conducted in Europe, Australia, and Israel from February 2007 to September 2008. The study was funded by Celgene. The primary endpoint was PFS (from randomization to progression or death from any cause) as compared between the MPR-R arm and MP, with disease progression assessed by European Group for Blood and Marrow Transplantation (EBMT) criteria. With 450 patients (150 per arm), the study would have 80% power to detect a 50% improvement in median PFS (15 months in the MP arm to 22.5 months in the MPR-R arm).[5] Pre-planned interim analyses were conducted using a pre-specified O'Brien-Fleming superiority boundary. The first of the interim analyses (April 2009) crossed the boundary (two-sided alpha of 0.003 at 50% of the required events) and the data and safety monitoring committee recommended unblinding of the study.[5] Importantly, the study planned a 'landmark analysis' of PFS (from start of maintenance therapy) for the MPR-R arm compared to the MPR arm, only for those patients who started the maintenance phase of the trial in order to define the contribution of maintenance therapy to PFS. The treatment arms were balanced for a number of baseline characteristics. A total of two patients in the MPR-R arm were lost to follow-up, while no patients in the MPR or MP arms were lost to follow-up.[5] Of 152 patients assigned to the MPR-R arm, 88 entered the maintenance phase of the study. Of the 153 patients assigned to the MPR arm, 94 entered

the maintenance phase of the study, and of 154 patients assigned to the MP arm, 102 entered the maintenance phase of the study. PFS was statistically significantly longer for MPR-R (median 31 months) compared to MPR (14 months; HR 0.49; p<0.001) and compared to MP (13 months; HR 0.40; p<0.001) after a median follow-up of 30 months. The landmark analysis demonstrated statistically significantly longer PFS from the start of maintenance therapy for the MPR-R arm (lenalidomide maintenance, median 26 months) compared to the MPR arm (placebo maintenance, median 7 months; HR 0.34; p<0.001). The authors reported that the difference in PFS associated with MPR-R was consistent across all subgroups of patients defined by stratification factors (age and International Staging System) and baseline characteristics.[5] A total of 43 patients (28%) died in the MPR-R arm, 52 (34%) in the MPR arm, and 45 (29%) in the MP arm. The 3-year OS was 70% for MPR-R, 62% for MPR, and 66% for MP. The incidence of new or worsened adverse events during the maintenance phase of the trial as low: Grade 3 or 4 neutropenia and thrombocytopenia occurred in six (6.8%) and five (5.7%) of 88 patients in the MPR-R arm and in none (0%) and 2 (2.1%) of 94 patients in the MPR arm. No patients had grade 3 or 4 febrile neutropenia or bleeding during maintenance therapy in any arm. The 3-year rate of second primary malignancies was 7% in the MPR-R arm, 7% in the MPR arm, and 3% in the MP arm.[5] Second primary malignancies included acute myeloid leukemia (MPR-R, n=4; MPR, n=2), myelodysplastic syndromes (MPR-R, n=1; MPR, n=3; MP, n=1), T-cell acute lymphoblastic leukemia (MPR-R, n=1), chronic myelomonocytic leukemia (MPR-R, n=1), and solid tumours (MPR-R, n=5; MPR, n=4; MP, n=3).[5]

2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in this review

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 majority of respondents (79%) noted that it was important to have choice of drug for their myeloma based on known side effects of the drug. Respondents reported symptoms associated with myeloma impacted or limited their own or their caregiver's day-to-day activity and quality of life. Respondents ranked infections as the most important aspect to control myeloma. Infections were followed by kidney problems, pain, mobility, neuropathy, shortness of breath and fatigue. Respondents reported side effects, including fatigue, neuropathy and stomach upset with current therapies. Respondents were asked about their personal experience with lenalidomide, of which a majority of the respondents reported that the product was a better experience than taking other drugs for their myeloma. Of those who responded, 45.9% of the respondents reported "fewer side effects" while 11.8% reported "many more side effects" with lenalidomide compared to other treatments.

PAG Input

Input on lenalidomide (Revlimid) as maintenance treatment for newly diagnosed multiple myeloma patients after stem cell transplant was obtained from all of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From the PAG

perspective, lenalidomide as an oral drug already available on the market and easily used in the community were identified as enablers.

There are several barriers to implementation identified. PAG noted that additional health care resources will be required to vigilantly monitor and treat toxicities associated with lenalidomide. In addition, the requirement for physicians, pharmacists and patients to register with the RevAid® monitoring program is a barrier that may delay access. There would be additional drug costs due to use of lenalidomide maintenance therapy over several years in a patient population who previously did not receive maintenance drug therapy. PAG raised concerns around the flat pricing of all strengths and the potential for drug wastage with dose adjustments. PAG is requesting clarification around the need for dose adjustments.

Other

The draft product monograph provided by the manufacturer (Celgene Inc.) provides the following serious warnings and precautions:[14]

- Potential for human birth defects, stillbirths, and spontaneous abortions.
- Neutropenia and thrombocytopenia.
- Deep vein thrombosis and pulmonary embolism.
- Available only under a controlled distribution program called RevAid®.

2.2 Interpretation and Guidance

Burden of Illness and Need

Multiple myeloma is a cancer of the bone marrow with an incidence of approximately 2500 new cases per year in Canada.[8] Myeloma increases in incidence with age, with a median age at presentation of 70 years[9], and is present in slight excess in males relative to females. Myeloma is incurable in the vast majority of cases, with 1350 deaths from the disease expected in 2013.[8] The five and ten year survival rates for all patients are approximately 30% and 17% respectively; for those younger than 60 years of age the ten year survival rate is 30%.[15]

Multiple myeloma is relatively common and autologous stem cell transplant is frequently performed as part of front line myeloma therapy. This treatment is not curative and improving patient survival, remission duration and quality of life are important goals. While improvement in response rate is seen as a positive sign of the activity of a drug, it is not considered as sufficient evidence to adopt a change in practice without evidence of benefit in the other aforementioned domains.

Effectiveness

Overall survival impact of incorporating lenalidomide maintenance into front line therapy for transplant-eligible myeloma:

The CALGB 100104 trial demonstrated an overall survival advantage to the use of lenalidomide maintenance following autologous stem cell transplant for myeloma patients as compared to observation. The magnitude of survival benefit seen in this study was both statistically and clinically significant. An overall survival benefit for lenalidomide maintenance was not seen post transplant in the IFM 2005-02 trial. In neither trial was overall survival the primary outcome.

Improvement in progression-free survival with the incorporation of lenalidomide maintenance into front line therapy for transplant-eligible patients

It can be argued 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 can also be argued that prolongation of progression-free survival is a meaningful endpoint in myeloma trials due to the considerable morbidity that can occur with progression, and that a substantial PFS improvement should be regarded as the basis for a change in standard of care.[11]

Two fully published, randomized controlled trials (CALGB 100104, IFM 2005-02) have demonstrated a statistically and clinically significant improvement in disease control as measured with PFS or the very similar endpoint, TTP, with the addition of lenalidomide maintenance following autologous stem cell transplant. These results are consistent with the PFS benefit seen in a published trial of lenalidomide maintenance in transplant-ineligible patients[5], and in a trial presented in abstract form only that looked at lenalidomide maintenance versus no maintenance in both transplanted and non-transplanted patients in randomized trial using a 2 x 2 design.[6,7]

Safety

Toxicity is increased but manageable

While the addition of lenalidomide has been associated with increased toxicity, the degree of toxicity appears to be manageable. The absolute percentage of patients discontinuing protocol therapy due to adverse events in the CALGB 100104 and IFM 2005-02 trials was only 10-15% higher in the lenalidomide arms compared to patients receiving placebo in the control arms. The increased adverse hematological toxicities seen with lenalidomide in the two trials were expected and acceptable. The thrombosis rates were acceptably low with appropriate prophylaxis. Non-hematological toxicities were not dramatically increased in patients on lenalidomide. Quality of life data were not reported in either trial.

Second malignancies

Lenalidomide has been associated with an increased risk of second malignancies in myeloma patients. In the CALGB 100104 and IFM 2005-02 studies, there were more second malignancies seen in patients taking lenalidomide versus placebo. The increase in the rate of second malignancies in the two trials was relatively small, and did not lead to decreased survival in the treatment arms of the trials. The second malignancy risk is felt by the Clinical Guidance Panel to be acceptable based on these data.

2.3 Conclusions

The pCODR Myeloma Clinical Guidance Panel concluded that there is a net clinical benefit to the use of lenalidomide maintenance as part of front line therapy that includes high dose melphalan and autologous hematopoietic stem cell transplantation for patients with multiple myeloma. This conclusion is based on two fully published, high quality randomized controlled trials (CALGB 100104 and IFM 2005-02) showing improvement in PFS or TTP with lenalidomide with increased but manageable toxicity, and one of which demonstrated an overall survival advantage with lenalidomide following autologous stem cell transplant.

In making this conclusion, the Clinical Guidance Panel also considered that:

- Due to the considerable morbidity that can occur with progression, progression-free survival is a meaningful endpoint in myeloma trials and a substantial PFS improvement should be regarded as the basis for a change in standard of care.[11]
- 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.
- Results are consistent with the PFS benefit seen with the use of lenalidomide in transplant-ineligible patients[5] and in both transplanted and non-transplanted patients.[6,7]
- A manageable degree of toxicities and a relatively low rate of second malignancies were observed.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR 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 a cancer of the bone marrow with an incidence of approximately 2500 new cases per year in Canada.[8] Characteristic disease features include the presence of excess, malignant bone marrow plasma cells; bone disease including osteolytic lesions, osteoporosis and pathological fractures; anemia and other cytopenias; and hypercalcemia. The malignant plasma cells usually secrete monoclonal immunoglobulin into the blood and urine that can be used as a measure of disease burden, including detection of disease progression (rising monoclonal protein levels) or response to therapy (falling levels). Monoclonal immunoglobulin light chains can deposit in the kidneys, leading to renal insufficiency.[9]

Myeloma increases in incidence with age, with a median age at presentation of 70 years[9], and is present in slight excess in males relative to females. Myeloma is incurable in the vast majority of cases, with 1350 deaths from the disease expected in Canada in 2013.[8] The five and ten year survival rates for all patients are approximately 35% and 17%, respectively; for those younger than 60 years of age the ten year survival rate is 30%.[15]

3.2 Accepted Clinical Practice

A subset of patients with multiple myeloma are diagnosed in an asymptomatic phase, with no clinical manifestations of organ damage and no symptoms attributable to the disease. These patients are generally not treated immediately but rather are observed closely for the development of symptoms or signs of disease before embarking on treatment.

Patients with symptomatic myeloma are treated primarily with anti-myeloma drug therapy. For many years the mainstay of myeloma treatment was a combination of oral melphalan (chemotherapy) and prednisone (corticosteroid therapy). Other, older drug combinations did not improve survival in comparison to melphalan and prednisone, and median survival was approximately 2.5 years regardless of the therapy chosen.[16]

High dose intravenous melphalan supported by autologous hematopoietic stem cell transplantation has improved survival for myeloma patients who are eligible for this treatment. Eligibility criteria generally include good performance status and sufficient organ function and is generally reserved for patients aged less than about 70 years but the decision to use this treatment is ultimately left to the discretion of the treating physician, in discussion with the patient. For eligible patients high dose melphalan and autologous stem cell transplant is generally prescribed as part of the initial treatment, rather than deferring this therapy until relapse, in order to maximize the duration of the first remission. Delaying the transplant until relapse can produce similar long-term survival rates but has been associated with inferior symptom control. Sufficient stem cells are usually collected in order to allow more than one autologous transplant; this approach can facilitate the administration of two consecutive cycles of high dose melphalan with stem cell transplant support, an approach known as tandem transplantation, or can be used to allow high dose melphalan to be administered again at the time of relapse in patients who benefited from a prior autologous transplant. The advantage of tandem transplantation relative to a single transplant up front is not clearly established.

High dose melphalan is generally preceded by a three to four month course of induction therapy with conventional doses of anti-myeloma drugs. The goals are to improve the functional status of the patient prior to high dose therapy and to clear sufficient amounts of myeloma cells from the

bone marrow to facilitate hematopoietic stem cell collection. Care must be taken to choose induction therapy which will not impair the ability to collect hematopoietic stem cells for autologous transplantation.

Newer anti-myeloma drugs have further improved the survival of myeloma patients, including bortezomib, thalidomide and lenalidomide. These drugs are generally used in combination with corticosteroids and/or chemotherapy agents, and are of proven benefit in both newly diagnosed patients not eligible for transplant and those with relapsed disease.[17]

For patients in whom high dose melphalan and autologous stem cell transplantation is the planned treatment, strategies to further increase therapeutic efficacy have been explored including the incorporation of novel agents into treatment before (induction), during (conditioning), or after (consolidation, maintenance) high dose melphalan therapy. Older drug classes such as chemotherapy agents, corticosteroids and cytokines have not been found to significantly improve patient outcomes in the maintenance setting. Thalidomide has been shown to prolong remission when administered as maintenance therapy post transplant, with some studies showing an overall survival advantage.[10] Thalidomide maintenance has not been widely implemented in Canada, in part over concerns about toxicity including peripheral neuropathy. At present the access to thalidomide as post-transplant maintenance therapy is somewhat limited in Canada. Neither thalidomide nor lenalidomide has been clearly shown to prolong remission when incorporated into induction therapy pre-transplant, although response rates are increased as compared to the use of older induction regimens like VAD (vincristine, adriamycin, dexamethasone). So far, there is no evidence that incorporation of agents other than high dose melphalan into the conditioning regimen improves outcome, although this subject continues to be investigated.

The use of bortezomib as part of initial therapy for myeloma patients undergoing high dose melphalan and autologous stem cell transplantation is the subject of a recent pCODR review. The role of bortezomib maintenance post-transplant has not been clearly defined. Studies incorporating bortezomib both pre- and post-transplant have demonstrated improved patient outcomes, but the design of these studies did not permit the determination of the efficacy or cost-effectiveness of bortezomib specifically in the maintenance setting.

Allogeneic stem cell transplantation is used infrequently to treat myeloma because of high treatment related morbidity and mortality, but can achieve long term disease control in some patients.[12]

When patients relapse following initial treatment, therapy is generally given again incorporating either previously effective agents and/or those that have not yet been administered. Novel agents are expanding the therapeutic armamentarium. Multiple myeloma eventually relapses repeatedly following courses of effective therapy, and eventually patients succumb to progressive disease and its complications. Resistance to treatment and the cumulative adverse effects of both disease and treatment have adverse effects on patient quality of life. Important supportive measures can have a positive impact on both quality of life and survival, including medical pain management, the use of palliative radiotherapy for symptomatic bone lesions, prevention and treatment of infections and venous thrombosis, hematopoietic support with blood products and growth factors, bisphosphonates for hypercalcemia and bone disease, and dialysis for renal failure.[9]

3.3 Evidence-Based Considerations for a Funding Population

The population under consideration here includes patients with newly diagnosed, symptomatic multiple myeloma who have been treated with front line high dose chemotherapy and autologous hematopoietic stem cell transplantation, and whose myeloma has not progressed since the transplant. The randomized trials supporting this indication included patients up to 6 months post-transplant. This population comprises less than half of all newly diagnosed myeloma patients.

3.4 Other Patient Populations in Whom the Drug May Be Used

It would be reasonable to consider lenalidomide maintenance therapy for patients whose myeloma has not progressed since receiving a front-line autologous stem cell transplant, even if more than 6 months has elapsed since the transplant. Although there is no evidence in support of this use of lenalidomide, it would seem fair to provide access particularly for those patients who are unable to access the drug in Canada within 6 months of the transplant due to the time lines of drug approval and funding processes.

Lenalidomide is already widely available in Canada as therapy for multiple myeloma patients whose disease has progressed after at least one prior line of therapy. There is also an indication in Canada for its use in the treatment of myelodysplasia associated with deletion of 5q.

Lenalidomide has demonstrated efficacy as a treatment for several types of lymphoma, although there is not yet any randomized trial demonstrating its equivalence or superiority to other standard lymphoma treatment regimens.

The use of lenalidomide could potentially be considered as part of induction therapy for previously untreated myeloma patients undergoing high dose chemotherapy and autologous stem cell transplantation, although there is no randomized trial demonstrating this approach to be superior to other standard induction regimens. Lenalidomide could also be used as part of the initial therapy for myeloma patients who are not candidates for a stem cell transplant. There is some high level evidence already published in support of this indication. The drug could reasonably also be used in induction or maintenance for those few myeloma patients who are treated with allogeneic transplantation, based on extrapolation of the data in autologous transplant recipients.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Multiple Myeloma Canada, provided input on lenalidomide (Revlimid) for the maintenance treatment of patients with newly diagnosed multiple myeloma after stem-cell transplantation and their input is summarized below.

Multiple Myeloma Canada conducted an anonymous online survey to gather information from patients and caregivers about the impact of myeloma on their lives and the effect of treatments, particularly lenalidomide on their myeloma. The survey link was sent by e-mail to myeloma patients and caregivers across Canada. Multiple Myeloma Canada reported a total of 619 respondents completed the survey, of this total 441 were individuals living with myeloma, 160 were caregivers and 20 did not specify if they were a patient or a caregiver.

Respondents were from across Canada with each province represented. There were no respondents from the territories. The survey had a combination of multiple choice, rating and open-ended questions. Certain open responses that reflected the sentiment of a majority of the respondents are included verbatim to provide a deeper understanding of the patient and caregiver perspective.

From a patient perspective, the majority of respondents (79%) noted that it was important to have choice of drug for their myeloma based on known side effects of the drug. Respondents reported symptoms associated with myeloma impacted or limited their own or their caregiver's day-to-day activity and quality of life. Respondents ranked infections as the most important aspect to control myeloma. Infections were followed by kidney problems, pain, mobility, neuropathy, shortness of breath and fatigue. Respondents reported side effects, including fatigue, neuropathy and stomach upset with current therapies. Respondents were asked about their personal experience with lenalidomide, of which a majority of the respondents reported that the product was a better experience than taking other drugs for their myeloma. Of those who responded, 45.9% of the respondents reported "fewer side effects" while 11.8% reported "many more side effects" with lenalidomide compared to other treatments.

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 and have not been corrected.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients Have with Multiple Myeloma

Respondents rated on a scale of 1 – 10 on how important it is to control various aspects of myeloma with 1 being "not important" and 10 being "very important". Those who completed the survey ranked infections as the highest score with 71.8% (382) rating it as 10, a "very important" aspect of myeloma to control. Infections were followed by kidney problems, pain, mobility, neuropathy, shortness of breath and fatigue. In all cases, more than 50% of respondents rated these aspects as a 10 "very important" to control. In all cases the rating average was greater than 8, which meant that all listed symptoms were considered important.

Additional aspects that were provided under "other" included concerns about: bones (fractures, density), emotional (depression, mood swings), dizziness, bowel and stomach issues (constipation and diarrhoea and anaemia).

Symptom or problem related to myeloma	% of Respondents Rate "10"	# of Respondents	Rating Average	N (Total # of Respondents)
Infections	71.8%	382	9.17	532
Kidney problems	68.2%	361	9.06	529
Pain	64.3%	342	9.03	532
Mobility	59.7%	318	8.95	533
Neuropathy	56.7%	299	8.75	527
Shortness of breath	51.0%	269	8.42	527
Fatigue	50.9%	273	8.69	536

Respondents also rated on a scale of 1 – 10 on how much the symptoms associated with myeloma impact or limit the day-to-day activity and the quality of life, with 1 being "not at all" and 10 being "significant impact".

Symptom or problem related to myeloma	% of Respondents Rate "8"or Higher	# of Respondents	Rating Average	N (Total # of Respondents)
Ability to work	52.7%	271	6.63	514
Ability to travel	40.9%	218	6.04	533
Ability to exercise	39.7%	209	6.12	526
Ability to volunteer	37.2%	195	5.73	526
Ability to conduct household chores	29.4%	156	5.47	529
Ability to fulfil family obligations	29.1%	154	5.32	528
Ability to spend time with family and friends	24.4%	128	4.84	528

According to the survey, ability to work was impacted the most with 52.7% (271) of respondents who rated this as 8 or higher in terms of significance of impact, with 10 being "significant impact". The survey indicated that in every situation about 25% or more of the respondents rated their impact as 8 or higher with 10 being "significant impact".

All elements with the exception of ability to spend time with family and friends had a rating average greater than 5, which meant that the responses were closer to "significant impact" than "not at all". Ability to spend time with family and friends had a rating average of 4.84, which meant that the responses were closer to "not at all".

4.1.2 Patients' Experiences with Current Therapy for Multiple Myeloma

The main treatments that the respondents have experienced are as follows: dexamethasone (84.2%, 368), lenalidomide (72.1%, 315), autologous stem cell transplant (ASCT) (69.9%, 301), melphalan with prednisone (41.9%, 183), cyclophosphamide (40.0%, 175) and VAD (16.7%, 73). Under "Other", 12% (55) respondents indicated that they had used thalidomide to treat their myeloma.

Side Effect	% of Respondents	# of Respondents (N=437*)
Dexamethasone	84.2%	368
Lenalidomide	72.1%	315

Autologous stem cell transplant (ASCT)	68.9%	301
Melphalan + Prednisone (MP)	41.9%	183
Cyclophosphamide	40.0%	175
VAD	16.7%	73

*column exceeds N of 437 because respondents selected more than one treatment.

Respondents listed the side effects that they have experienced with these treatments as follows:

Treatment	% of Respondents*	# of Respondents (N=437*)
Fatigue/weak/tired	55%	228
Neuropathy	38%	161
Stomach upset, including constipation/diarrhoea	38%	158

**** Only the top 3 have been listed***

Respondents were asked that if they have a choice of drugs for the treatment of myeloma to rate on a scale of 1 – 10 on how important it was for them to make that choice based upon each different drug's known side effects, with 1 being "not important" and 10 being "very important". The majority of individuals with myeloma and their caregivers (79%, 390) reported that it was important to have choice of drug for their myeloma based on known side effects of the drug, N = 495. 79% gave this a rating of 8 or higher with 10 being "very important" and 57.2% gave this a rating of 10. The rating average was 8.55, which meant that a large proportion felt that choice was important based on side effects.

Respondents were also asked if they or their doctor experienced any hardships in accessing treatment for myeloma. In this open-ended question, 28% (111 respondents) of individuals living with myeloma and their caregivers indicated that they did experience some hardship in accessing treatment for their myeloma, N = 413. Hardships included: lack of access to treatment/limited choice of treatment, cost or financial issues, delayed treatment usually due to lack of access initially, administration or paper work required to receive the treatment, travel to receive treatment.

Hardship	% of Respondents*	# of Respondents (N=437*)
Lack of access to treatment, limited choice of treatment	13%	55
Cost or financial issues	6%	27
Delayed treatment usually due to lack of access initially	6%	27
Administration or paper work required to receive the treatment	3%	16
Travel to receive treatment	1%	7

4.1.3 Impact of Multiple Myeloma and Current Therapy on Caregivers

Respondents were asked to rate on a scale of 1 – 10 on how much the symptoms associated with myeloma impact or limit the caregiver's day-to-day activity and quality of life, with 1 being "not

at all", and 10 being "significant impact". According to the survey, ability to travel was impacted the most with 39.2% of respondents who rated this as 8 or higher in terms of significance of impact. The survey indicated that in every situation about 20% or more of the respondents rated their impact as 8 or higher with 10 being "significant impact".

On the other hand, 30.6% (146), 30.4% (144), 27.5% (131) 27.5% (128) indicated that there was no impact (a rating of 1 "not at all") on ability to exercise, ability to volunteer, ability to conduct household chores, and ability to work, respectively.

Ability to travel and ability to work were the only two aspects that received a rating average of 5 or more, which meant that these two aspects had a greater than neutral impact and all the others had a less than neutral impact.

Symptom or problem related to myeloma	% of Respondents Rate "8"or Higher	# of Respondents	Rating Average	N (Total # of Respondents)
Ability to travel	39.2%	187	5.77	476
Ability to work	31.1%	145	5.00	466
Ability to volunteer	27.1%	128	4.56	473
Ability to spend time with family and friends	22.0%	105	4.44	477
Ability to exercise	22.2%	106	4.42	477
Ability to fulfil family obligations	21.8%	104	4.43	477
Ability to conduct household chores	19.5%	93	4.25	476

Respondents also reported symptoms associated with myeloma impact or limited the caregiver's day-to-day activity and quality of life as follows:

> *"I am the daughter providing care for the patient who is my dad. so he is my family obligation. Taking care of him is a full-time job."*

> "Mental health issues related to stress. Family physician referred me to psychologist."

> "as caregiver, my health has suffered considerably, I am exhausted"

Respondents were asked to describe the challenges that their caregivers face as a result of the side effects of the treatment. A total of 370 individuals provided a response to this question. Out of that total, 238 indicated that there were challenges to the caregiver as a result of side effects of treatment. The other 132 respondents indicated that they either did not have a caregiver, did not currently have side effects of disease or felt that there were no challenges to the caregiver. The single biggest challenge (33%) was the stress and anxiety (emotional issues) of dealing with mood swings caused by treatment and the uncertainty with the disease and the treatments. N = 370.

Challenges	% of Respondents	# of Respondents (N=370)
Emotional issues	33%	123
Household chores, personal support	16%	63
Fatigue, tired, weak, sleep affected	13%	52

Challenges	% of Respondents	# of Respondents (N=370)
Limited activity – travel, difficulty making plans, limited family time	9%	39
Work, financial	7%	29

The following responses represent some of the comments provided that help to illustrate the challenges listed in the table above:

> *"Living with fear creates anxiety, fatique and dealing with loss of income from both of us is extremely challenging. Our decisions were basesd on lots of things out of our control. Husband and wife roles were reverse for several years and as his mobility became more comprimised, difficultly controlling his temper along with coping with the drugs and their effects. Disese has ups and downs. Pain management, intestinal difficulties and eating require learning curves and prep from the caregiver. All my energy goes into building up a positive environment for my husband and I for the other family members. I had to be vigilant at the drop of a pin for several infections and be the one to notice when he needed medical attention. This requires me to be present and working outside the home would be difficult. Patient was mostly in denial and did not seek information or communicate his pain level accurately to medical staff without me in attendance. I walked the fence to know when to provide patient with information from 'Myeloma resources'."*

> *"I am the caregiver - and it sometimes is hard to see a loved one (the patient) suffering the effects of this disease and treatments. He was diagnosed in November of 2004 and so it has been 8 and a half years and it does get a bit wearing (for me) but I am very glad that he is being so well looked after and very much appreciate that Revlimid came along just when he needed it."*

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences to Date with Lenalidomide

Respondents were asked about their personal experience with lenalidomide, in particular how has lenalidomide changed or is expected to change their long-term health and well being. There were a total of 223 open-ended responses to this question. In this open-ended question respondents reported that they are experiencing or have experienced the following changes: extended life (24%), disease and/or side effect control (21%), remission (17%), improved quality of life (13%), improved blood counts (9%). 6% reported that lenalidomide was not effective for them and 2% reported that they are no longer taking the drug. 22% were not sure what to expect or what changes they may have had, often because the drug was taken in combination with other treatments.

Change or Expected Change	# of Responses	% of Responses
Extend life	54	24%
Control disease and side effects	46	21%
Remission	38	17%
Contribute to Quality of Life	28	13%
Improve blood counts	19	9%
Revlimid was not good – side effects or not effective	13	6%

Change or Expected Change	# of Responses	% of Responses
No longer taking	4	2%
Not sure	48	22%

The following responses represent some of the comments provided that help to illustrate the changes or expected changes listed in the table above.

"It has given me hope. My expected remission time has been increased from 2 yr to 5 and beyond. I hope to be alive to see a cure."

"Revlimid is increasing my life expectancy, changing the disease from one that would have killed me by now to one that can be controlled."

"Revlimid has surpassed my expectations for the entire single year I have been taking the drug. Side effects have been at times quite challenging, but for the most part, the results of the treatment have made the side effects quite tolerable. My sense of well-being while taking this drug has resulted in a much more active, "normal" life experience. My Iga levels have been normal for at least the last nine months; my kidney function has remained stable."

"It has totally changed my life. Now I can walk normally; sleep reasonably well with sleeping pills; and have a social life. I have gained much of my memory back. I am constantly surprised that both relatives and friends think that I am cured. It has made a tremendous difference in my life."

"Revlimid brought me into a quick remission. I have stayed that way for almost 2 years. I like the fact that it is available as an oral medication. This means that I save a great deal of time with the administration of the drug and it gives me the flexibility to travel."

"So far this has been the ideal solution for me. The disease is complete remission (no M-protein on monthly blood tests for about 3 years now) and I have no side effects at all (other than slightly low blood counts but very manageable). I lead a perfectly normal life and I am disease free."

Respondents were asked how long they have been on lenalidomide. Below is a summary Table of the responses received.

Change or Expected Change	# of Responses	% of Responses (N= 272 open-ended responses)
Less than one year	40.1%	109
1 to 2 years	41.2%	112
3 to 4 years	11.4%	31
5 to 7 years	4.8%	13
More than 7 years	2.6%	7

Respondents were asked on how lenalidomide compared in terms of side effects to the other treatments they have taken and to rate on a scale of 1 - 10, with 1 being "fewer side effects" and 10 being "many more side effects". The rating average for this question was 4.19, which meant that more people had "fewer side effects". A total of 45.9% (105), rated this question with a 3 or lower, with 1 being "fewer side effects".

While 11.8% (27) rated this 8 or higher, with 10 being "many more side effects", N = 229.

Respondents were asked on how they would rate their overall experience with lenalidomide based on any experience they have had with taking other drugs for myeloma on a scale of 1 – 10, with 1 being "much worse" and 10 being "much better". The rating average for this question was 7.29, which meant that more people found lenalidomide to be a better experience than taking other drugs for their myeloma. 54.8% (126), rated this question as 8 or higher, with 10 being "much better", and 9.1% (21), rated this question 3 or lower, with 1 being "much worse", N = 230. Respondents also provided the following comments below.

"I was diagnosed with multiple myeloma a few days after giving birth to my third child. It was incomprehensible to think that I might die from cancer when I had a family that needed me. Fortunately, my specialists were able to start me in a drug trial which included Revlimid, and control my myeloma very quickly, so that I went into the transplant with very low levels. That was in 2009 and I am still in remission, though the spectre of relapse hangs over any plans we make for our family."

"After recovering from the ASCT I was symptom free for 5 yrs. Even though my doctor always warned that eventually the myeloma would come back, I never thought it would. So when I had the relapse last year, this was a huge blow, and it made me very insecure. Now being on Revlimid for a while, I feel better about the disease, even though it is not pleasant to be on pills all the time. I realize that, had I been diagnosed 10 years ago, the outcome would have been very different, and I might not even be here, so I am grateful for that. Am also very grateful that the government is paying for this very expensive drug."

4.3 Additional Information

No information was provided in this section by Myeloma Canada.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group as factors that could affect the feasibility of implementing a funding recommendation for lenalidomide (Revlimid) as maintenance treatment for newly diagnosed multiple myeloma patients after stem cell transplant. 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.pcodr.ca).

Overall Summary

Input on lenalidomide (Revlimid) as maintenance treatment for newly diagnosed multiple myeloma patients after stem cell transplant was obtained from all of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From the PAG perspective, lenalidomide as an oral drug already available on the market and easily used in the community were identified as enablers.

There are several barriers to implementation identified. PAG noted that additional health care resources will be required to vigilantly monitor and treat toxicities associated with lenalidomide. In addition, the requirement for physicians, pharmacists and patients to register with the RevAid® monitoring program is a barrier that may delay access. There would be additional drug costs due to use of lenalidomide maintenance therapy over several years in a patient population who previously did not receive maintenance drug therapy. PAG raised concerns around the flat pricing of all strengths and the potential for drug wastage with dose adjustments. PAG is requesting clarification around the need for dose adjustments.

Please see below for more details.

5.1 Factors Related to Comparators

PAG noted that lenalidomide for maintenance treatment after ASCT for multiple myeloma patients will be a new treatment regimen. Currently there are no other drugs funded drugs for use in this setting and these patients are typically observed post transplant.

There are no drugs approved by Health Canada for maintenance therapy in multiple myeloma patients who are post stem cell transplant. However, bortezomib was recently reviewed and thalidomide may be used in some jurisdictions. PAG questioned how lenalidomide would compare to bortezomib and/or thalidomide.

5.2 Factors Related to Patient Population

Lenalidomide is already funded by the jurisdictions for treatment of multiple myeloma patients who have received prior systemic therapy. PAG noted that there is already indication creep in this setting. PAG has concerns for increase demand for continued use beyond disease progression post ASCT and for use in the pre-transplant setting. PAG requested clarity regarding use of maintenance therapy beyond disease progression.

Multiple myeloma is considered an uncommon hematological cancer, the number of patients overall would be small. However, PAG noted that these patients who previously would not have any maintenance treatment could potentially be on lenalidomide for more than three years.

5.3 Factors Related to Accessibility

As an oral agent, PAG identified lenalidomide as a treatment that can be delivered to patients more easily than intravenous therapy in both rural and urban settings. As such, PAG identified the ease in accessibility of treatment for patients as an enabler.

However, as pharmacies are required to be registered with the RevAid® program to dispense lenalidomide, PAG noted that many community pharmacies would not likely be registered and patients can only obtain their prescription from a limited number of registered pharmacies.

PAG noted that in some jurisdictions, oral medications are not covered in the same way as intravenous cancer medications, which may limit accessibility of treatment to patients. For these jurisdictions, patients 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 since maintenance treatment could span over several years.

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.

5.4 Factors Related to Dosing

PAG requested clarification on the need to increase the dose of lenalidomide in maintenance therapy. The dose in one of the trials is 10mg daily for first 3 months, with increase to 15mg, if tolerated. The dose is 10mg daily in the other trial.

PAG also noted that monitoring this patient population for toxicities may be a new issue presenting a challenge to implementation. Additional health care resources are required for vigilant monitoring and treatment of the significant toxicities, including secondary malignancies, associated with lenalidomide. Currently, this group of patients may not be on any maintenance drug therapy.

5.5 Factors Related to Implementation Costs

PAG expressed concern with the flat pricing for the four strengths of lenalidomide. A patient on 10mg tablets whose dose is increased to 15mg but the 10mg tablets + 5 mg tablets were dispensed, to allow for further dose adjustments, would cost twice that of the 15mg tablets. There are concerns with drug wastage for patients who may be dispensed the 15mg tablets but do not tolerate and then have dose reduced back to 10mg.

In addition, the packaging size of 21 or 28 count blister packs may be an issue for dispensing in the maintenance setting where treatment is continuous. This could lead to dispensing errors.

5.6 Other Factors

"To avoid embryo-fetal exposure, REVLIMID® and THALOMID® are only available through a controlled distribution program called RevAid®. RevAid® monitors critical activities and ensures all program requirements are met before the drug is released to a patient." [www.revaid.ca]

- Only prescribers who are registered and agree to meet all the conditions of the RevAid® program will have access to REVLIMID® and THALOMID®.

• Only patients who are enrolled in RevAid® by their registered physician, and agree to comply with the requirements of the RevAid® program will receive REVLIMID® or THALOMID®.
• Only pharmacists registered with the RevAid® can dispense REVLIMID® or THALOMID®. Pharmacists must meet the certification requirements on an ongoing basis in order to dispense these drugs.

PAG has concerns on the significant time and logistical coordination required to register the patients into the RevAID monitoring program. The controlled drug distribution mandated by Health Canada will require additional physician and pharmacy resources for longer period of time.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effectiveness of maintenance treatment with single-agent lenalidomide following autologous stem cell transplantation compared to an appropriate comparator, in patients with newly diagnosed MM.

See Table 4 in Section 6.2.1 for outcomes of interest and appropriate comparators.

- Note: No Supplemental Questions relevant to the pCODR review or to the Provincial Advisory Group were identified.

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 4. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCT	Patients with newly diagnosed MM who have received autologous stem cell transplantation (either single or double)	Lenalidomide maintenance 10-15 mg/d orally, until progression or unmanageable toxicity	Placebo OR Best supportive care OR Bortezomib maintenance OR Thalidomide maintenance	**OS** **PFS** **QOL** **Adverse events** Second primary malignancy

Abbreviations: OS=overall survival; PFS=progression-free survival; QOL=quality of life; RCT=randomized controlled trial.

** 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-) with in-process records & daily updates via Ovid; EMBASE (1980-) via Ovid; The Cochrane Central Register of Controlled Trials (2013, Issue 8) via Wiley; 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 lenalidomide (Kadcyla), maintenance therapy, 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. Retrieval was not limited by publication year. Retrieval was limited to the English language.

The search is considered up to date as of September 5, 2013.

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 – clinicatrials.gov and Ontario Institute for Cancer Research – Ontario 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 information as required by the pCODR Review Team.

6.2.3 Study Selection

One member 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.

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.

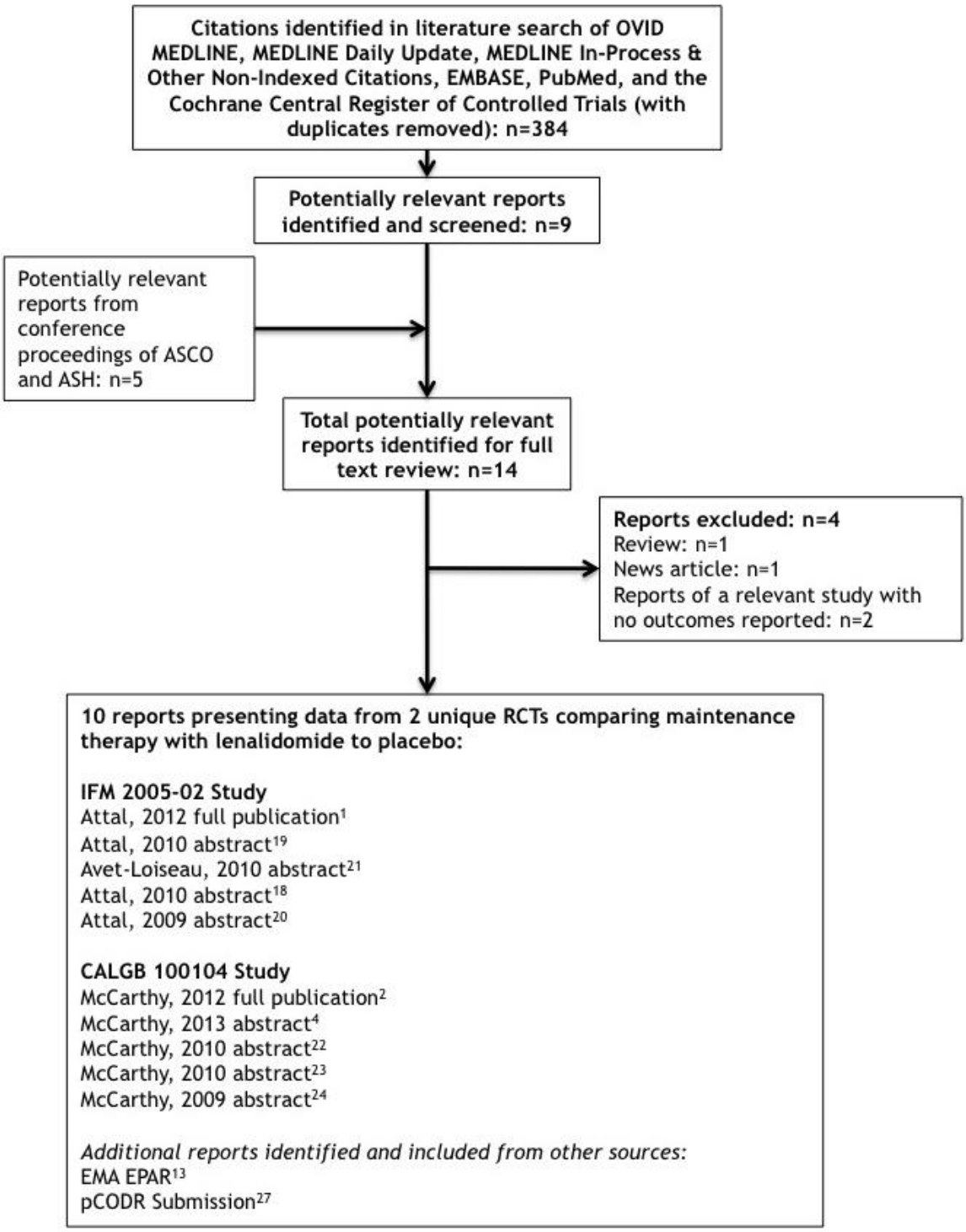
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided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

6.3 Results

6.3.1 Literature Search Results

Of the 384 potentially relevant reports identified (with duplicate citations removed), 10 reports, representing two studies, were included in the pCODR systematic review[1,2,4,18-24] and four studies were excluded. Studies were excluded because they were a news article[25], a review article[26], or they were abstract publications of the same ongoing randomized trial that did not report data for the subgroup of patients who received ASCT prior to randomization to maintenance therapy with lenalidomide or to no maintenance[6,7]—please see section 6.4 *Ongoing Trials* for details regarding the trial design. In addition, one report from the European Medicines Agency[13] was identified and included as was the submission by the manufacturer to pCODR.[27]

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of Studies.



Note: Additional data related to the IFM 2005-02 and the CALGB 100104 studies were also obtained through requests to the Submitter by pCODR.[3]

6.3.2 Summary of Included Studies

Two randomized controlled trials were identified that met the eligibility criteria of this systematic review Tables 1 & 5).

6.3.2.1 Detailed Trial Characteristics

a) Trials

Two randomized trials met the inclusion criteria for this systematic review. Specific design characteristics of those trials can be found in Table 5. Both trials used similar designs: both randomized newly diagnosed patients with multiple myeloma 1:1 to maintenance therapy with lenalidomide alone versus (vs.) placebo, following autologous stem cell transplantation (ASCT). Both trials were described as double-blind. The IFM 2005-02 study blinded patients and outcome assessors to treatment allocation and used an independent data and safety monitoring committee.[1] The CALGB 100104 study blinded patients and used an independent data and safety monitoring committee, but was unclear from the published reports, whether study personnel, treating physicians, outcome assessors, or some combination of these were blinded to treatment allocation.[2] The submitter clarified that all of the aforementioned study personnel were blinded, with the exception of the statisticians at the Duke Statistical Centre.[3]

Both trials were multicentre studies: the IFM 2005-02 study was conducted in France, Belgium, and Switzerland and the CALGB 100104 study was conducted in the U.S. The IFM study was funded by the Programme Hospitalier de Recherche Clinique, the Swiss Group for Clinical Research (SAKK), and by a grant from Celgene. The CALGB study was funded by the National Cancer Institute (NCI). Celgene provided the study drugs in both trials.

An appropriate method of randomization was used in each study. The IFM study stratified randomization by baseline serum β_2-microglobulin ($\leq$3 mg/L vs. >3 mg/L), 13 q deletion (presence or absence), and by response after SCT.[1] The CALGB study also stratified randomization by baseline serum β_2-microglobulin but by different threshold ($\leq$2.5 mg/L vs. >2.5 mg/L).[2] The investigators also stratified by prior use of thalidomide during induction and by prior use of lenalidomide during induction.[2]

The IFM 2005-02 study used progression-free survival (PFS) as the primary study endpoint, defined as the time from randomization to first documentation of progressive disease or death from any cause.[1] The CALGB study used time-to-progression (TTP) as the primary endpoint, defined as time to progressive disease or death from any cause after transplantation.[2] The IFM 2005-02 study used an independent review committee to assess response/progression[1], as did the CALGB study, although this was not reported in any publication but was confirmed by the submitter.[3] The International Myeloma Working Group (IMWG) criteria were used to assess response/progression in both studies.[1,2] Both trials included overall survival and adverse events as secondary outcomes. The IFM study also included response rate and event-free survival as secondary outcomes, while the CALGB study investigated response after transplantation as a secondary outcome.

Table 5. Summary of Trial characteristics of the included studies of lenalidomide maintenance therapy following ASCT in patients with newly diagnosed MM

IFM2005-02 Study[1,18-21]

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
NCT00430365 IFM2005-02 Study 77 sites in 3 countries (France, Belgium, Switzerland) Patients enrolled from July 2006 through August 2008 Data cutoff: October 1, 2011 Enrolled: n=614 Randomized: n=614 Double-blind, placebo-controlled Phase 3 RCT Randomized in a 1:1 ratio (lenalidomide:placebo) Randomization was stratified by: A) Baseline levels of serum β_2-microglobulin B) Presence or absence of 13q deletion on basis of FISH C)Response after transplantation Funded by: Programme Hospitalier de Recherche Clinique; Swiss Group for Clinical Cancer Research (SAKK); grant from Celgene; study drug also provided by Celgene	Age <65 years Received autologous SCT (single or double) after induction therapy and had not progressed between first-line autologous SCT (one or two procedures) done within the previous 6 months and randomization Serum aspartate aminotransferase or alanine aminotransferase level ≤3 ULN Serum bilirubin ≤ 35 µmol/L Serum creatinine <160 µmol/L Absolute neutrophil count ≥1000/mm^3 Platelet counts > 75,000/mm^3 Negative pregnancy test before enrolment and agreement to use contraception Written informed consent **Exclusion criteria:** None specified	**Intervention:** Consolidation treatment (following SCT) with Lenalinomide 25 mg/day on days 1 to 21 of a 28 day cycle for 2 cycles, followed by maintenance therapy with Lenalidomide 10 mg/day for the first 3 months, increased to 15/mg/day if tolerated **Control:** Consolidation treatment (following SCT) with Lenalinomide 25 mg/day on days 1 to 21 of a 28 day cycle for 2 cycles, followed by maintenance therapy with placebo Both arms were administered until patient withdrew consent, disease progression or unacceptable toxic effects	**Primary:** Progression-free survival **Secondary:** Overall survival RR Event-free Survival AEs

Summary of Trial characteristics of the CALGB100104 Study[2,4,22-24]

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
NCT00114101 CALGB100104 Study 47 sites in 1 country (U.S.) Patients enrolled from April 2005 through July 2009 Data cutoff: October 31, 2011 (for evaluation of long term outcomes Data unblinded: December 17, 2009 Enrolled: n=568 Randomized: n=460 Double-blind, placebo-controlled Phase 3 RCT Randomized in a permuted-block design Randomization was stratified by: A) Levels of serum β_2-microglobulin at registration B) Prior use of thalidomide during induction C)Prior use of lenalidomide during induction Funded by: NCI; study drug provided by Celgene	Age 18 - 70 years, ECOG 0-1 Symptomatic disease requiring treatment (Durie-Salmon stage ≥I) Any induction regimen of 2-12 months duration. No more than 2 inducation regimens (excluding dexamethasone) Received autologous SCT (single) after induction therapy Peripheral-blood stem cells (CD34+ cells) for transplantation ≥$2x10^6$/kg body weight Stable disease or a marginal partial or complete response in the first 100 days after SCT Adequate pulmonary, cardiac, renal and hepatic functions Registered before transplantation Written informed consent **Exclusion criteria:** Serious coexisting conditions (ex. uncontrolled diabetes, serious infection, immune dysfunction) Pregnancy	**Intervention:** Maintenance therapy (following SCT) with Lenalidomide starting at 10 mg/day **Control:** Maintenance therapy (following SCT) with placebo Both arms were administered until disease progression	**Primary:** Time to progression **Secondary:** Overall survival Response after transplantation AEs
Notes: AEs = adverse events; **ECOG** = Eastern Cooperative Oncology Group; **SCT** = stem cell transplantation; **ULN** = upper limit of normal.			

Sample size calculations and requirements for each study can be found in Table 1—both studies were superiority designs and both were terminated early.

The CALGB 100104 study was terminated early for benefit, after the third interim analysis, with a data cut-off of December 17, 2009.[2] The study had pre-planned interim analyses using a group sequential design, with seven planned analyses for TTP using a one-sided p=0.005.[2] The final analysis included data from that cut-off, or follow-up data submitted as of October 31, 2011 for evaluations of long-term outcomes.[2] TTP and overall survival curves were analyzed using the methods of Kaplan-Meier with the use of a stratified log-rank test. A Cox proportional hazards model was used to estimate hazard ratio (HR) and the 95% confidence intervals (95% CI). Comparisons between groups for adverse events

were made using the chi-square or Fisher's exact test. The incidence rates of second primary cancers were calculated as the ratio of the number of second primary cancers to the number of patient-years at risk and were compared with the use of the binomial exact text.

The IFM 2005-02 study had one pre-planned interim analysis that was to be conducted when 180 events had occurred. That analysis was adjusted using the methods of Lan-DeMets using an O'Brien-Fleming alpha-spending function.[1] The interim analysis was conducted in January 2010 and the independent data and safety monitoring committee recommended that the study be unblinded, but that treatment continue as assigned, without allowing crossover. The final analysis was conducted with a data cut-off of July 7, 2010 (date of unblinding). In January 2011, an increase in the incidence of second primary cancers was observed in the lenalidomide maintenance arm and the independent data and safety monitoring committee recommended that lenalidomide maintenance therapy be discontinued, but that follow-up of the study participants continue in order to determine overall survival and to detect second primary cancers.[1] PFS and overall survival curves were estimated using the methods of Kaplan-Meier. A Cox proportional hazards model was used to estimate the HR and 95% CI. Subgroups analyses of TTP and overall survival using the pre-defined the randomization strata were also conducted. Comparisons of differences between groups for adverse events were made using Fisher's exact test.

b) Populations

A total of 614 patients in the IFM study and 460 patients in the CALGB study were randomized to receive either lenalidomide maintenance or placebo following ASCT. The baseline patient characteristics in each of the studies were similar between the study groups. See Table 6 for select baseline patient characteristics. Of note, the IFM 2005-02 study noted a higher proportion of patients in the lenalidomide group than the placebo group for both t(4;14) translocation and for t(4;14) or deletion of chromosome 17.[1]

Table 6. Baseline Patient Characteristics in the included studies of lenalidomide maintenance after ASCT in newly diagnosed MM.				
Characteristic	**IFM 2005-02[1]**		**CALGB 100104[2]**	
	LEN	**Placebo**	**LEN**	**Placebo**
n	307	307	231	229
Age (years) Mean/Median Range	 Mean: 55 22-67	 55 32-66	 Median: 59 29-71	 58 40-71
Sex, n (%) Male	 169 (55)	 181 (59)	 121 (52.4)	 129 (56.3)
Type of Myeloma, n (%) IgG IgA Light-chain Other	 192 (63) 62 (20) 47 (15) 6 (2)	 169 (55) 78 (25) 55 (18) 5 (2)	<u>Serum</u> IgG kappa: 70 (30) IgG lambda: 43 (19) IgA kappa: 21 (9) IgA lambda: 13 (6) IgM kappa: 2 (1) IgM lambda: 0 <u>Urine</u> Kappa LC only: 13 (6) Lambda LC only: 4 (2) Data missing: 35 (15)	 76 (33) 31 (14) 20 (9) 13 (6) 1 (<1) 1 (<1) 12 (5) 10 (4) 41 (18)
International Staging System, n (%) I II III Data Missing	 NR (43) NR (35) NR (22) -	 NR (49) NR (36) NR (15) -	 177 (77) 11 (5) 4 (2) 39 (17)	 170 (74) 16 (7) 3 (1) 40 (17)
Serum β_2-microglobulin level, n (%) ≤ level > level Data missing	 ≤3 mg/L: NR (45) >3 mg/L: NR (55) -	 NR (45) NR (55) -	 ≤2.5 mg/L: 170 (74) >2.5 mg/L: 50 (22) 11 (5)	 163 (71) 55 (24) 11 (5)
Response, n (%)	<u>At randomization</u> >VGPR: 192 (63) ≤PR: 115 (37)	 176 (57) 131 (43)	<u>To ASCT at day 100</u> CR: 67 (29) PR: 115 (50) Marginal: 11 (5) SD: 38 (16) PD: 0 Data Missing: 0	 79 (34) 109 (48) 5 (2) 32 (14) 3 (1) 1 (<1)
Abbreviations: ASCT=autologous stem cell transplantation; **LEN**=lenalidomide; **n**=number of patients randomized; **n**=number of patients; **NR**=not reported.				

c) Interventions

In the IFM 2005-02 study, patients could receive either a single or double ASCT.[1] The IFM 2005-02 study treated all patients with consolidation therapy following ASCT, with lenalidomide at 25 mg/d, orally, on days 1-21 of a 28-day cycle for 2 cycles, followed by their randomly allocated maintenance treatment (lenalidomide or placebo). Lenalidomide maintenance was given as 10 mg/day, orally for the first 3 months then increased to 15 mg/d if tolerated. Treatment with lenalidomide maintenance or placebo was continued

until the patient withdrew consent, disease progression, or unacceptable toxic effects occurred.[1] The use of intravenous bisphosphonates was not recommended. Treatment with lenalidomide could be reduced to 10 mg/d or subsequently 5 mg/d or eventually discontinued permanently based on the patient's platelet and neutrophil counts.[1] The median relative dose intensity of lenalidomide as maintenance therapy (administered dose divided by the target dose) was 83% in the lenaliodmide arm and 94% in the placebo arm.[1]

In the CALGB 100104 study, patients were registered prior to ASCT. All patients received a single ASCT.[2] The CALGB 100104 trial did not treat patients with a consolidation therapy following ASCT. Following ASCT, patients received lenalidomide maintenance at a dose of 10 mg/d, orally for the first 3 months, and then increased to 15 mg/d if tolerated. Treatment with lenalidomide maintenance or placebo was continued until disease progression or unacceptable toxic effects. Similarly to the IFM 2005-02 study, treatment with lenalidomide could be reduced to 10 mg/d, 5 mg/d or eventually discontinued based on the patient's platelet and absolute neutrophil counts. In addition, dose modifications could be made based on occurrence of grade ≥3 neurologic toxicity, grade ≥2 cardiac toxicity, or other grade 3 or higher non-hematologic toxicities.[2]

d) Patient Disposition

The IFM 2005-02 study had one patient in the lenalidomide arm and five in the placebo arm who did not receive the assigned study treatment. Sixteen patients (5.2%) in the lenalidomide arm and 21 patients (6.8%) in the placebo arm did not receive consolidation therapy prior to maintenance therapy. The available publications did not report the number of patients who withdrew from the study. In a response to this question, the submitter reported that 32 patients withdrew consent, six died, 15 sought new treatment, three patients did not want to continue on the study's follow-up schedule (but were followed-up at their local appointments) and for one patient the reason for withdrawal was missing. And 279 patients withdrew due to progressive disease.[3] The intent-to-treat population included all 614 randomized patients with 307 in the lenalidomide arm and 307 in the placebo arm. The safety population included 306 patients in the lenalidomide arm and 302 patients in the placebo arm who received the study drug.

In the CALGB 100104 study included all randomized patients in the intent-to-treat analysis: 231 in the lenalidomide arm and 229 in the placebo arm. Twenty-nine patients (12.6%) in the lenalidomide arm and 16 patients (7.0%) in the placebo arm withdrew consent.[2] No reasons for withdrawal were reported and it was not possible to determine the number of patients lost to follow-up from the publication; however, the submitter reported that no patients in either arm were lost to follow-up at the checkpoint meeting.[3] A total of 86 patients in the placebo arm crossed over to receive lenalidomide following adverse events (harms) were also analyzed on the basis of the intent-to-treat population.

e) Limitations/Sources of Bias

IFM 2005-02 Study

No significant limitations or sources of bias were noted in the IFM 2005-02 study. The study was described as being 'double-blind.' The submitter provided confirmation that this included all patients and study personnel including, data collectors, treating physicians, adjudicators of outcome, and data analysts.[3] The study's primary outcome was TTP for which the assessment of disease progression can be subjective and could be a potential source of bias; however, the assessments were conducted by an independent

review committee using the IMWG criteria, thus mitigating the potential for bias. The study used an independent data and safety monitoring committee.

The number of patients lost to follow-up was not reported in the published literature.

The study was unblinded early due to the interim analysis demonstrating that maintenance lenalidomide had crossed the pre-specified efficacy boundary for PFS; however, the study continued unblinded on the recommendation of the data and safety monitoring committee. Patients were not allowed to cross over to the lenalidomide arm after unblinding, therefore the impact on the results would have been limited. In addition, the study was terminated early due to the detection of a higher incidence of second primary cancers in patients in the lenalidomide arm.

CALGB 100104 Study

Similarly to the IFM trial, no significant limitations or potential sources of bias were noted in the CALGB 100104 study. The study was described as 'double-blind.' The submitter provided confirmation that this included all patients and study personnel including, data collectors, treating physicians, adjudicators of outcome, and data analysts (except statisticians at Duke Statistical Centre).[3] The study's primary outcome was PFS for which the assessment of disease progression can be subjective and could be a potential source of bias; however, the assessments were conducted by an independent review committee using the IMWG criteria, thus mitigating the potential for bias. The study used an independent data and safety monitoring committee.

The number of patients lost to follow-up was not reported in the published literature; however, the submitter reported that no patients in either arm were lost to follow-up.[3]

The study was terminated early for benefit, based on the pre-specified boundary for efficacy for TTP. In any study stopped early for benefit, there is a risk that the effect size may be over-estimated. In addition, although a significant difference in OS was noted at the October 2011 analysis, only 88 deaths had occurred (35 in the lenalidomide arm and 53 in the placebo arm) out of a total of 460 patients (231 in the lenalidomide arm and 229 in the placebo arm).[2] A later analysis of OS conducted in January 2013, included 116 deaths (47 in the lenalidomide arm and 69 in the placebo arm).[4] Given the small number of events, the OS results should be interpreted with caution until more mature data are available.

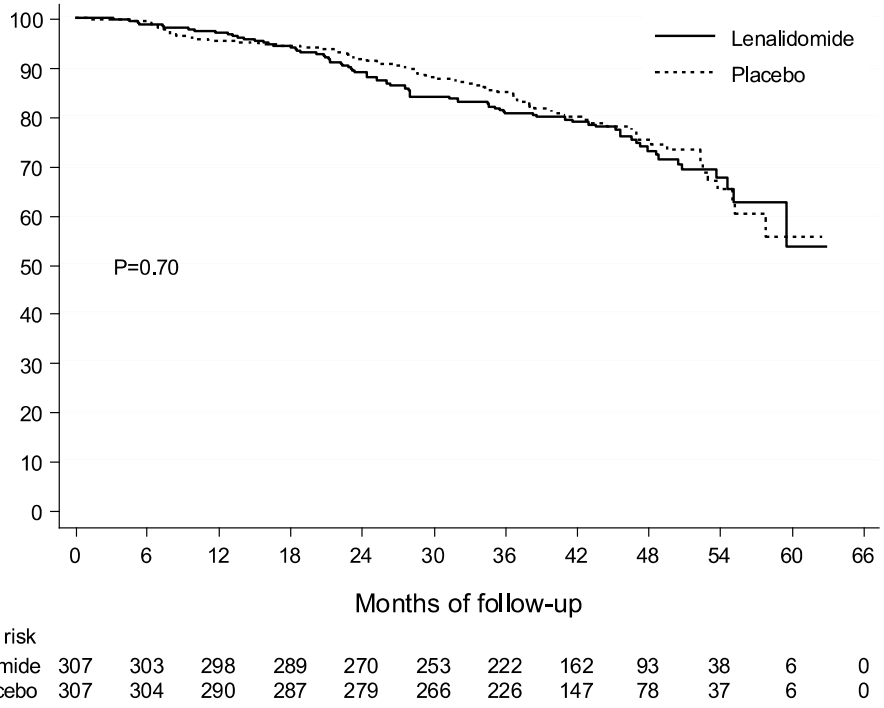
6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Overall Survival

The IFM 2005-02 study reported no statistically significant differences in overall survival at either data cut-off (Table 2). The 4-year overall survival at the October 2011 data cut-off was 73% of 307 patients in the lenalidomide arm and 75% of 307 patients in the placebo arm.[1] Figure 2 shows the Kaplan-Meier survival curve for overall survival at the October 2011 data cut-off, published in the Supplementary Materials to Attal et al.[1]

Figure 2. Overall Survival Kaplan-Meier survival curves from the IFM 2005-02 study for lenalidomide maintenance compared to placebo following ASCT in newly diagnosed MM from the October 2011 analysis.[1]

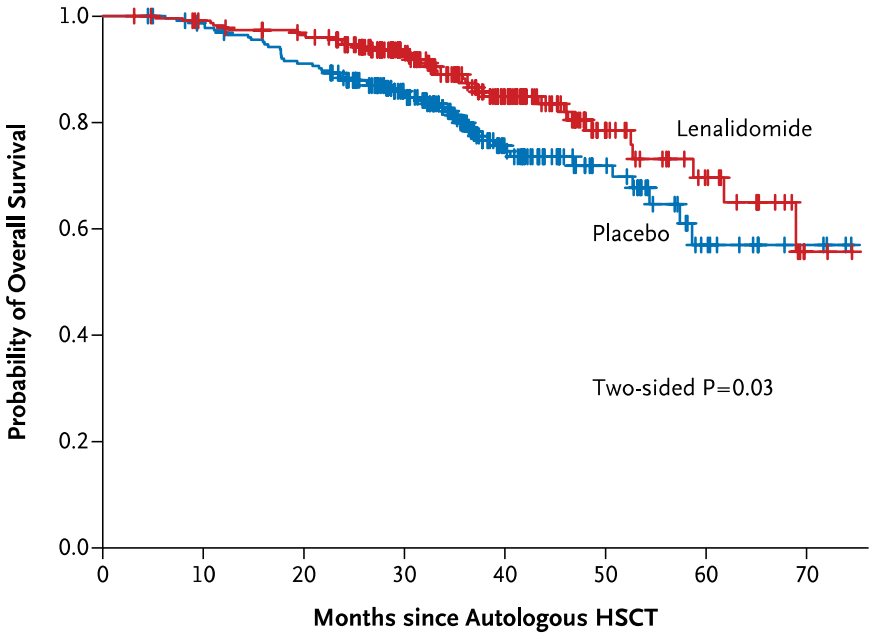


N at risk												
Lenalidomide	307	303	298	289	270	253	222	162	93	38	6	0
Placebo	307	304	290	287	279	266	226	147	78	37	6	0

Source: Attal et al (supplementary appendix).[1]

The CALGB 100104 study reported a statistically significant difference in overall survival in favour of the lenalidomide arm compared to the placebo arm (median not reached in either arm, HR=0.62, 95% CI 0.40-0.95, p=0.03) at the October 31, 2011 data cut-off.[2] At that time a total of 35 of 231 patients had died in the lenalidomide arm and 53 of 229 had died in the placebo arm after a median follow-up of 34 months. Figure 3 shows the Kaplan-Meier survival curve for overall survival at the October 2011 data cut-off, published in McCarthy et al.[2]

Figure 3. Overall Survival Kaplan-Meier survival curves from the CALGB 100104 study for lenalidomide maintenance compared to placebo following ASCT in newly diagnosed MM from the October 2011 analysis.[2]



Source: McCarthy et al.[2]

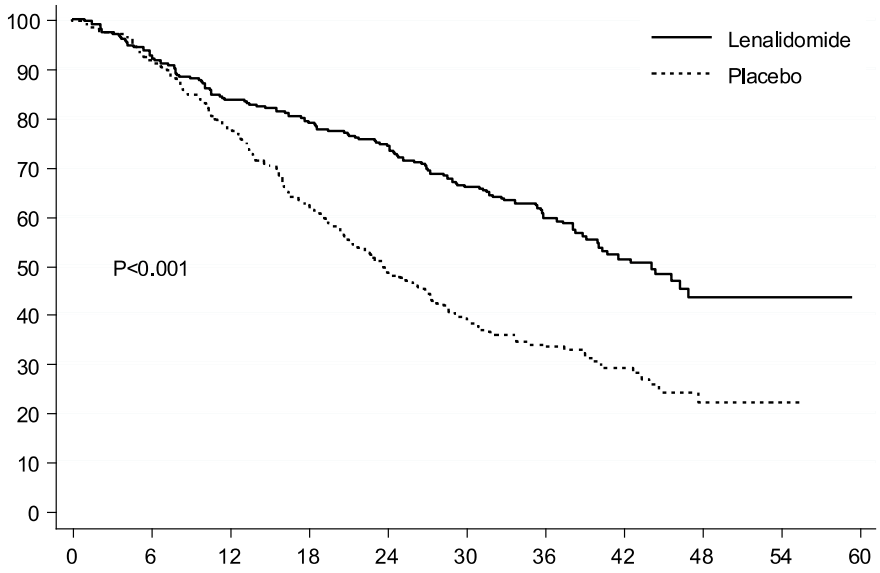
The results of an updated analysis, conducted on January 7, 2013 and presented in abstract form at the 14th Annual International Myeloma Workshop[4], demonstrated a statistically significant difference in OS in favour of the lenalidomide arm (median not reached[3]) compared to the placebo maintenance arm (median 73 months[3]), with HR=0.61[4] (95% CI 0.41-0.87[3]); p=0.008[4]), after a median follow-up of approximately 48 months.[4] Sixty-nine of 229 (30%) patients had died on the placebo arm compared to 47 of 231 (20%) patient deaths on the lenalidomide arm.[4]

Progression-Free Survival and Time-to-Progression

The IFM 2005-02 study reported PFS, defined as the time from randomization to disease progression or death from any cause.[1] Statistically significant differences in PFS in favour of the lenalidomide arm compared to placebo were demonstrated in both the July 2010 analysis (study was unblinded after this analysis) and in the October 2011 analysis (after the study was unblinded) (Table 2). The median PFS at the July 2010 analysis was 41 months in the lenalidomide arm and 23 months in the placebo arm, with a HR 0.50, p<0.001. The 3-year PFS was 59% of 307 patients in the lenalidomide arm and 35% of 307 patients in the placebo arm. The authors reported that age, sex, isotype of the monoclonal component, International Staging System stage, induction regimen, or the number of transplantations did not change the PFS benefit.[1] The October 2011 analysis demonstrated very similar results, with median PFS (estimated from the published Kaplan-Meier survival curves) of 44 months in the lenalidomide arm and 24 months in the placebo arm, with HR=0.50, p<0.001. The 4-year PFS was 43% of 307 patients in the lenalidomide arm and 22% of 307 patients in the placebo arm. Figure 4 shows the Kaplan-Meier curves

of PFS at the October 2011 data cut-off, published in the Supplementary Materials to Attal et al.[1]

Figure 4. Progression-free survival Kaplan Meier survival curves from the IFM 2005-02 study for lenalidomide maintenance compared to placebo following ASCT in newly diagnosed MM from the October 2011 analysis.[1]

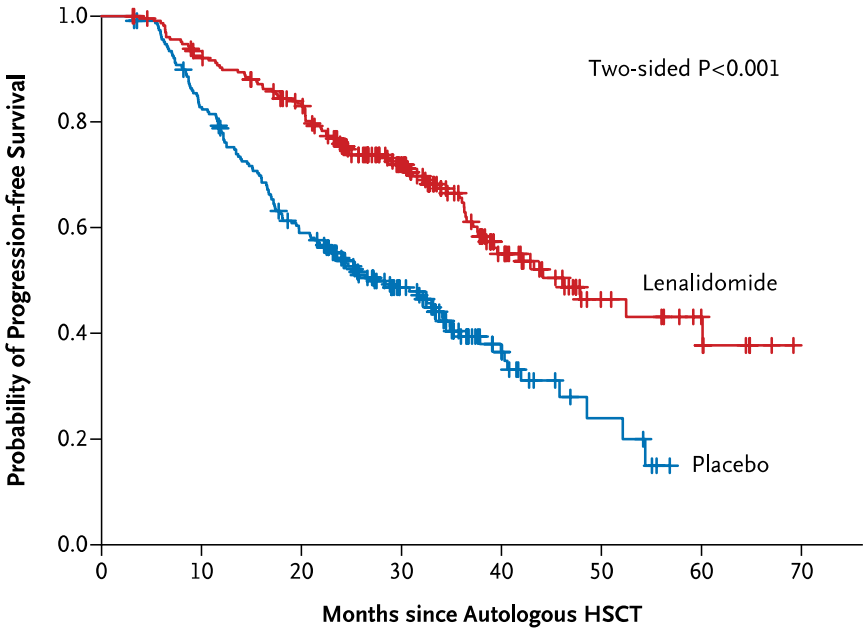


N at risk											
Lenalidomide	307	271	243	228	207	171	115	58	22	5	0
Placebo	307	268	225	179	138	100	62	30	11	1	0

Source: Attal et al (supplementary appendix).[1]

The CALGB 100104 study reported TTP, defined as the time to progressive disease or death from any cause after transplantation.[2] Statistically significant differences in TTP were reported at both the December 2009 analysis and the October 2011 analysis (Table 2). At the October analysis, median TTP was 46 months in the lenalidomide arm compared to 27 months in the placebo arm (HR=0.48, 95% CI 0.36-0.63, p<0.001) with 86 events out of 231 patients in the lenalidomide arm and 132 events out of 229 patients in the placebo arm after a median follow-up of 34 months. The earlier December 2009 analysis had similar results (see Table 2) but with 47 events and 101 events in the lenalidomide and placebo arms, respectively. In addition, the January 2013 updated analysis also had similar results (see Table 2) as the October 2011 analysis, but with 104 events out of 231 patients in the lenalidomide arm and 146 events out of 229 patients in the placebo arm after a median follow-up of approximately 48 months.[3] Figure 5 shows the Kaplan-Meier curves of TTP at the October 2011 data cut-off, published in McCarthy et al[2].

Figure 5. Time-to-Progression Kaplan Meier survival curves from the CALGB 100104 study for lenalidomide maintenance compared to placebo following ASCT in newly diagnosed MM from the October 2011 analysis.[2]



Source: McCarthy et al.[2]

Harms Outcomes

Any Grade Adverse Events

Both studies reported the incidences of adverse events following randomization to lenalidomide maintenance or placebo maintenance.[1,2] Table 7 presents data on the reported rates of any Grade of adverse event that occurred in 20% or more of patients in either arm of each study. Almost all patients in both arms had an adverse event of any grade: lenalidomide, 305 out of 306 patients; and placebo, 297 out of 302 patients. Higher rates of the following adverse events (of any grade) were reported in the lenalidomide arm than in the placebo arm: hematologic (69% vs. 35%, respectively), neutropenia (59% vs. 26%), thrombocytopenia (24% vs. 15%), diarrhea (40% vs. 20%), pyrexia (20% vs. 11%), skin disorders (57% vs. 48%), and muscle spasms (39% vs. 23%). Attal et al did not report statistical comparisons between treatment arms for those adverse events.[1] The incidence of thromboembolic events was statistically significantly higher in the lenalidomide arm (6% of 306 patients) compared to the placebo arm (2% of 302 patients; $p<0.01$).[1] The rates of any grade adverse events were not reported for the CALGB 100104 study.[2]

Table 7. Number of patients (percent) with any Grade adverse events that occurred in 20% of more of patients in either arm of the included studies of lenalidomide maintenance following ASCT in newly diagnosed MM.

Adverse Event	IFM 2005-02[1]		CALGB 100104[2]	
	LEN, n=306	Placebo, n=302	LEN, n=231	Placebo, n=229
Any adverse event, n (%)	305 (>99)	297 (98)	NR	NR
Hematologic, n (%) **Neutropenia**, n (%) **Thrombocytpenia**, n (%)	210 (69) 180 (59) 74 (24)	107 (35) 78 (26) 45 (15)	NR	NR
Gastrointestinal disorders, n (%) **Nausea and vomiting**, n (%) **Constipation**, n (%) **Diarrhea**, n (%)	222 (72) 48 (16) 61 (20) 123 (40)	171 (57) 54 (18) 58 (19) 61 (20)	NR	NR
General Disorders, n (%) **Fatigue**, n (%) **Pyrexia**, n (%)	209 (68) 145 (47) 62 (20)	184 (61) 122 (40) 33 (11)	NR	NR
Infection, n (%) **Upper respiratory infection**, n (%)	252 (82) 215 (70)	232 (77) 194 (64)	NR	NR
Nervous System Disorders, n (%) **Peripheral neuropathy**, n (%)	156 (51) 71 (23)	130 (43) 49 (16)	NR	NR
Skin disorders, n (%) **Rash**, n (%)	176 (57) 61 (20)	146 (48) 51 (17)	NR	NR
Back pain, n (%)	80 (26)	83 (27)	NR	NR
Muscle spasms, n (%)	119 (39)	70 (23)	NR	NR

Notes: LEN=lenalidomide; **n**=number of patients.

Grade 3 or 4 Adverse Events

Table 3 presents data on the reported rates of Grade 3 or 4 adverse events that occurred in 5% of more of patients in either arm of each study. In the IFM 2005-02 study, the incidence of Grade 3 or 4 thromboembolic events was statistically significantly higher in the lenalidomide arm (6% of 306 patients) compared to the placebo arm (2% of 302 patients; p=0.01).[1] In addition, the incidence of grade 3 or 4 hematologic adverse events was also statistically significantly higher for the lenalidomide arm (58% of 306 patients) compared to the placebo arm (22% of 302 patients; p<0.001).[1] Similarly, in the CALGB 100104 study, the incidence of Grade 3 or 4 hematologic adverse events was also statistically significantly higher for lenalidomide (58.9% of 231 patients) compared to placebo (29.7% of 229 patients; p<0.001).[2] In addition, the incidences of the following Grade 3 or 4 adverse events were statistically significantly higher in the lenalidomide arm compared to the placebo arm: neutropenia (45.0% vs. 14.9%; p<0.001), anemia (4.8% vs. 0.4%; p=0.006), thrombocytopenia (13.9% vs. 4.8%; p=0.001), leukocytopenia (11.7% vs. 3.5%; p=0.001), and lymphopenia (6.9% vs. 1.7%; p=0.01).[2] No other statistical comparisons were reported.[2]

Discontinuation of Therapy Due to Adverse Events

In the IFM 2005-02 study, treatment was discontinued due to adverse events in 83 patients (27.1%) in the lenalidomide arm and in 44 patients (14.6%) in the placebo arm.[1] Of the 88 patients in the lenalidomide arm, patients discontinued due to the following: blood disorders (n=10), gastrointestinal disorders (n=13), general disorders (n=13), neoplasms (n=8), nervous system disorders (n=11), skin and subcutaneous tissue disorders (n=12), vascular disorders (n=6), infections (n=4), or other events (n=17). Of the 44 patients in the placebo arm, reasons for discontinuation included: blood disorders (n=7), gastrointestinal disorders (n=3), general disorders (n=3), neoplasms (n=2), nervous system disorders (n=6), skin and subcutaneous tissue disorders (n=8), vascular disorders (n=3), infections (n=4), or other events (n=17). Patients in either arm could have more than one adverse event leading to discontinuation.[1]

In the CALGB 100104 study, 10.0% of 231 patients in the lenalidomide arm discontinued therapy due to an adverse event. Of the 143 patients in the placebo arm who did not cross over to lenalidomide, 1.4% discontinued therapy due to an adverse event. Of the 86 patients who crossed over to receive lenalidomide, 5.8% discontinued therapy due to an adverse event.[2]

Second Primary Malignancies

In the IFM 2005-02 study, 32 second primary malignancies occurred in 26 patients in the lenalidomide arm compared to 12 second primary malignancies in 11 patients in the placebo group.[1] The incidence of second primary malignancies was statistically significantly higher in the lenalidomide arm (3.1 per 100 patient-years) compared to the placebo arm (1.2 per 100 patient-years; p=0.002).[1]

In the CALGB 100104 study, the following second primary malignancies were reported: in the lenalidomide arm, eight patients had a hematologic cancer, 10 patients had a solid-tumour cancer, two patients had a basal-cell carcinoma, and two patients had a squamous-cell carcinoma; whereas in the placebo arm, one patient had a hematologic cancer, five patients had a solid-tumour cancer, one patient had a basal-cell carcinoma, and two patients had a squamous-cell carcinoma.[2] In the January 2013 analysis, a total of 29 out of 231 patients (12.6%) who received lenalidomide maintenance and 15 out of 229 patients (6.6%) who received placebo maintenance developed a second primary malignancy.[4] The cumulative incidence risk of developing a second primary malignancy was higher for the lenalidomide maintenance arm compared to the placebo maintenance arm (p=0.03).[4]

6.4 Ongoing Trials

Only one ongoing study investigating the use of lenalidomide maintenance therapy in newly diagnosed MM met the eligibility criteria for this review: NCT00551928. Details of this trial can be found in Table 8 and in Section 2.1.4 *Comparison with Other Literature*.

Table 8. Study NCT00551928: A phase 3, multicentre, randomized, controlled study to determine the efficacy and safety of lenalidomide, melphalan, and prednisone (MPR) versus melphalan (200 mg/m^2) followed by stem cell transplantation in newly diagnosed multiple myeloma subjects.[6,7,28]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT00551928 Active control, multicentre, open-label, 2x2 factorial randomized phase III trial. Start date: June 2007 Expected completion date: August 2011 Last verified in March 2010—active. Estimated enrolment: 402 Sponsor: Fondazione Neoplasie Sangue Onlus Note: The ClinicalTrials.gov record does not indicate that a 2x2 factorial design was used for this study; however, abstract publications by Boccadoro et al[6] and Cavallo et al[7] report otherwise.	Newly diagnosed multiple myeloma. Karnofsky PS ≥60 Age ≤65 years ***Excluded:*** Previous treatment with anti-myeloma therapy.	**Randomization 1:** MPR: melphalan 0.18 mg/kg d1-4 + prednisone 2 mg/kg d1-4 + lenalidomide 10 mg/d d1-21, every 28 days for 6 cycles (no ASCT) ***OR*** High-dose melphalan 200 mg/m^2 for 2 cycles every 4 months followed by ASCT **Both arms above were included in Randomization 2:** Lenalidomide maintenance (no further details available) ***OR*** No maintenance treatment	<u>Primary outcomes:</u> Progression-free survival <u>Secondary outcomes:</u> Overall survival

Notes: ASCT=autologous stem cell transplantation; d=day; PS=performance status.
Available from: http://clinicaltrials.gov/ct2/show/NCT00551928?term=mpr+AND+lenalidomide&rank=6.

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review

8 ABOUT THIS DOCUMENT

This Final Clinical Guidance Report was prepared by the pCODR 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 lenalidomide (Revlimid) for multiple myeloma. 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.pcodr.ca).

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. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The 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.pcodr.ca). 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.

APPENDIX A: LITERATURE SEARCH STRATEGY

1. Literature Search via OVID Platform.

Ovid MEDLINE (R), Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations, and Ovid MEDLINE (R) Daily Update.

1. (lenalidomide: or revlimid: or CC-5013:).ti,ab,rn,nm,sh,hw,ot.
2. 191732-72-6.rn,nm.
3. 1 or 2
4. multiple myeloma:.ti,ab,sh,hw,ot.
5. Exp multiple myeloma/
6. 4 or 5
7. exp maintenance chemotherapy/
8. (maintenance: or continu:).ti,ab,sh,hw,ot.
9. 7 or 8
10. 3 and 6 and 9

Ovid EMBASE

1. *lenalidomide/
2. (lenalidomide: or revlimid: or CC-5013:).ti,ab.
3. 1 or 2
4. exp *multiple myeloma/
5. multiple myeloma:.ti,ab.
6. 4 or 5
7. exp *maintenance therapy/
8. (maintenance: or continu:).ti,ab.
9. 7 or 8
10. 3 and 6 and 9

    Human Filter

11. exp animals/
12. exp animal experimentation/
13. exp models animal/
14. exp animal experiment/
15. nonhuman/
16. exp vertebrate/
17. animal.po.
18. or/11-17
19. exp humans/
20. exp human experiment/
21. human.po.
22. or/19-21
23. 18 not 22
24. 10 not 23

    RCT filter

25. (Randomized Controlled Trial or Controlled Clinical Trial).pt.
26. Randomized Controlled Trial/
27. Randomized Controlled Trials as Topic/
28. Controlled Clinical Trial/
29. Controlled Clinical Trials as Topic/
30. Randomization/

31. Random Allocation/
32. Double-Blind Method/
33. Double Blind Procedure/
34. Double-Blind Studies/
35. Single-Blind Method/
36. Single Blind Procedure/
37. Single-Blind Studies/
38. Placebos/
39. Placebo/
40. Control Groups/
41. Control Group/
42. (random* or sham or placebo*).ti,ab,hw.
43. ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
44. ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
45. (control* adj3 (study or studies or trial*)).ti,ab.
46. (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.
47. allocated.ti,ab,hw.
48. ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.
49. or/25-48
50. 24 and 50

2. Literature Search via PubMed

PubMed

1. lenalidomide* OR revlimid* OR CC-5013*
2. multiple myeloma*
3. maintenance* OR continu*
4. publisher[sb]
5. 1 AND 2 AND 3 AND 4

3. Literature Search via Cochrane Central Register of Controlled Trials (CENTRAL)

Search terms: ((lenalidomide* OR revlimid* OR CC-5013*) AND (maintenance* OR continu*)) in Cochrane Central Register of Controlled Trials.

4. Grey Literature Searches

Clinical Trial Registries:

U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov

Ontario Institute for Cancer. Ontario Cancer trials
www.ontariocancertrials.ca

Search terms: lenalidomide, revlimid, multiple myeloma

Select International Agencies:

Food and Drug Administration (FDA):
www.fda.gov

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

Search terms: lenalidomide, revlimid

Conference Abstracts:

American Society of Clinical Oncology (ASCO)
via the *Journal of Clinical Oncology* search portal: http://jco.ascopubs.org/search

Search terms: myeloma and (lenalidomide or revlimid)

American Society of Hematology (ASH)
via the *Blood* search portal: http://bloodjournal.hematologylibrary.org/search

Search terms: myeloma and (lenalidomide or revlimid) and (maintenance or continuous or continued)

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