pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Pomalidomide (Pomalyst) for Multiple Myeloma

July 31, 2014

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy of pomalidomide (Pomalyst) plus dexamethasone for patients with relapsed and/or refractory multiple myeloma who have previously failed on both bortezomib and lenalidomide, and who have received at least two prior treatment regimens, and have demonstrated disease progression on the last regimen.

Pomalidomide is an immunomodulatory agent with antineoplastic activity. Health Canada has approved the use of pomalidomide in combination with dexamethasone for use in patients with multiple myeloma for whom both bortezomib and lenalidomide have failed and who have received at least two prior treatment regimens and have demonstrated disease progression on the last regimen[31].

Pomalidomide is an oral capsule available as 1 mg, 2 mg, 3 mg and 4mg, and the Health Canada recommended dose is 4 mg daily for 21 out of 28 days in combination with low-dose dexamethasone 40 mg on days 1, 8, 15, and 22 of a 28-day cycle.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one open label multicentre randomized controlled trial, MM-003 (ref-San Miguel 2013), comparing the use of pomalidomide (4 mg/day on days 1-21) plus low dose dexamethasone (n=302, 40 mg/day on days 1, 8, 15, and 22) to high dose dexamethasone alone (n=153, 40 mg/day on days 1-4, 9-12, and 17-20). All drugs were oral.

The median age of patients in the study was 64 and 65 years in the pomalidomide plus low-dose dexamethasone group and high-dose dexamethasone group, respectively. Patients must have failed (progressive disease on or before 60 days of treatment, progressive disease ≤6 months after achieving partial response, or intolerance to bortezomib) treatment with bortezomib or lenalidomide. More than 94% of patients in both groups had failed on more than two previous treatments, and the median number of previous treatments for both groups was 5. Baseline characteristics were similar across both arms. Treatment was continued until progressive disease or unacceptable toxicity occurred. Patients were allowed to cross-over between the study groups following progression of disease.

Patients receiving pomalidomide were required to take thromboprophylaxis. Choice of thromboprophylaxis was left to the physician's discretion.

Efficacy

The primary outcome was progression free survival with overall survival as the secondary outcome.

After a median follow-up of 10 months (updated analysis), patients in the pomalidomide plus low-dose dexamethasone group had increased PFS compared with the high-dose dexamethasone group (4.0 months *vs* 1.9 months, respectively; HR 0.48 95% CI 0.39-0.60; p<0.0001). Analysis across subgroups for PFS demonstrated similar results. Median overall survival was also significantly longer in the pomalidomide plus low-dose dexamethasone

group than in the high-dose dexamethasone group (12.7 *vs* 8.1 months, respectively; HR 0.74 95% CI 0.56-0.97; p=0.0285).

Quality of Life

Pomalidomide plus low-dose dexamethasone significantly extended median time to meaningful worsening compared to high-dose dexamethasone for 2 of the 5 pre-selected domains for the EORTC QLQ-30: fatigue (113 *vs* 60 days, p=0.04) and emotional functioning (190 *vs* 124 days, p=0.02).

Harms

A similar number of deaths were reported in each arm respectively, 48% and 53% in the pomalidomide plus low-dose dexamethasone group and high-dose dexamethasone group. The most common cause of death was progression of disease (68% vs. 64%, respectively). Among these 4% and 5%, respectively were treatment-related deaths in the pomalidomide plus low-dose dexamethasone vs high-dose dexamethasone group.

Serious adverse events were reported in 61% vs 53% of patients in the pomalidomide plus low-dose dexamethasone group vs high-dose dexamethasone group, respectively. The most common grade 3-4 haematological adverse events were neutropenia (48% *vs* 16%), anaemia (33% *vs* 37%) and thrombocytopenia (22% *vs* 26%), in the pomalidomide plus low-dose dexamethasone and high-dose dexamethasone groups, respectively. The most common grade 3-4 non-haematological adverse events were pneumonia (13% *vs* 8%), bone pain (7% *vs* 5%) and fatigue (5% *vs* 6%) in the pomalidomide plus low-dose dexamethasone and high-dose dexamethasone groups, respectively.

1.2.2 Additional Evidence

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

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

1.2.3 Interpretation and Guidance

Burden of Illness and Need

Multiple myeloma is an incurable plasma cell neoplasm that makes up 1.2% of all new cancers in Canada.[15] In 2013, it is estimated that 2500 Canadians will be diagnosed with myeloma, and 1350 patients will die of this disease. Although there is significant heterogeneity within myeloma, the five-year survival for all patients is 43%.[16]

Chemotherapy is the primary modality of treatment for myeloma. Patients with myeloma will eventually become refractory or intolerant to the three classes of chemotherapy available to them: alkylators, bortezomib (a proteasome inhibitor), and lenalidomide (an immunomodulatory drug). When this scenario is reached, there is no clear standard of care. Commonly steroid therapy alone is used for palliation and symptom control to slow progressive disease without negatively impacting quality of life.

Effectiveness

The MM-003 trial demonstrated an overall survival and progression free survival advantage for patients receiving pomalidomide plus low-dose dexamethasone compared to dexamethasone alone. Although a secondary endpoint, the magnitude of survival benefit is both statistically and clinically significant. The survival analysis was also evident despite cross-over being allowed. PFS, as the primary endpoint was consistently improved across all subgroups analyzed. Although the absolute benefit in PFS was a modest (2.1 months), in this heavily pre-treated population with rapidly progressive disease, this would be considered a clinically significant improvement.

Compared to dexamethasone alone, the pomalidomide plus dexamethasone group had a statistically significant extension of time to meaningful worsening in the domains of fatigue, and emotional functioning. The remainder of the results showed no difference on QOL domains. These results are clinically relevant and are consistent with the patient experience as reported by the Patient Advocacy Groups.

Safety

The pomalidomide arm of the study was associated with a higher rate of neutropenia compared to dexamethasone alone. However, the rate of infection was similar between the two arms. All patients enrolled in the study required thromboprophylaxis. There was no difference in venous thromboembolic events between the two arms. All other safety and adverse event parameters were balanced, demonstrating that pomalidomide plus low-dose dexamethasone is a well-tolerated therapy compared to high-dose dexamethasone alone.

1.3 Conclusions

The pCODR Myeloma Clinical Guidance Panel concluded that there is a net overall clinical benefit to the use of pomalidomide plus low-dose dexamethasone compared to dexamethasone alone, in the treatment of relapsed and refractory myeloma. This is based on one high-quality randomized controlled trial that demonstrated a clinically and statistically significant benefit in overall survival and progression-free survival with adverse event profiles similar between the two arms of the study.

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

- The patient population included in this study had rapidly progressive disease, with either refractory disease on current therapy, or progression within 60 days of last therapy. The 60 day cut-off was used to define a patient group for the purpose of a clinical trial. However, the benefit of the drug likely extends to a broader population. The use of pomalidomide should not be limited to patients with rapidly progressive disease, but rather, used in patients with relapsed or refractory disease after treatment with both bortezomib and lenalidomide.

- There is no evidence to support or refute the role of retreatment with lenalidomide or bortezomib for patients with slowly progressing disease. Although some provinces allow for re-treatment of patients previously exposed to bortezomib and lenalidomide, this is not uniformly available. Demonstrating aggressive disease as outlined in the pivotal study may be difficult for these patients. The CGP thus agree that the decision to retreat versus moving to third-line therapy with pomalidomide should be made based on standard of practice within each province. Extending the availability of pomalidomide to slowly

progressing patients will thus ensure that provincial differences in availability of re-treatment will not hinder access of treatment to patients.

- Patients receiving lenalidomide in the maintenance setting are generally treated until disease progression and would consequently be considered to have relapsed or refractory disease at progression. Assuming that these patients meet the other eligibility requirement of having also progressed or been relapsed/refractory to bortezomib, it is reasonable to make pomalidomide available to patients that would have received lenalidomide in the maintenance setting and have subsequently progressed.

- This is the only phase III study in the third-line or greater setting to demonstrate an overall survival advantage.

- The federally mandated registration program required due to the teratogenicity of pomalidomide does not pose a barrier to implementation. All patients will have previously registered in this program at the time of therapy with lenalidomide.

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 pomalidomide (Pomalyst) 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 pomalidomide (Pomalyst) for multiple myeloma 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 pomalidomide (Pomalyst) for multiple myeloma and a summary of submitted Provincial Advisory Group Input on pomalidomide (Pomalyst) for multiple myeloma are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Pomalidomide has Health Canada approval for use in patients with multiple myeloma patients who have previously failed on both bortezomib and lenalidomide, and who have received at least two prior treatment regimens and have demonstrated disease progression on the last regimen. Pomalidomide is an oral capsule, available as 1 mg, 2 mg, 3 mg and 4mg. The Health Canada recommended dose is 4 mg daily for 21 out of 28 days in combination with low-dose dexamethasone 40 mg on days 1, 8, 15, and 22 of a 28-day cycle[31].

Pomalidomide is a thalidomide derivative and is the third member of a series of drugs known as immunomodulatory compounds, including thalidomide and lenalidomide.

2.1.2 Objectives and Scope of pCODR Review

The objective of this review is to evaluate the effect of pomalidomide plus low-dose dexamethasone on patient outcomes, including, progression-free survival, overall survival, and harms compared to high-dose dexamethasone or other standard treatments in patients with relapsed and/or refractory multiple myeloma who have previously failed on two treatments, including both bortezomib and lenalidomide, and demonstrated disease progression on the last treatment.

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.

The efficacy of pomalidomide plus low-dose dexamethasone (n=302) was compared to high-dose dexamethasone (n=153) in a single international multicentre randomized controlled trial (MM-003).[1] This was an open-label trial and therefore treatment

assignment was not masked. The trial procedures for randomisation were considered adequate. Patients assigned to the pomalidomide plus low-dose dexamethasone group were given 28-day cycles of pomalidomide (4 mg/day on days 1-21, orally) plus low-dose dexamethasone (40 mg/day on days 1, 8, 15, and 22, orally). Dexamethasone dose was reduced to 20 mg/day in all patients older than 75 years (regardless of treatment assignment). Patients assigned to the high-dose dexamethasone group were given 28-day cycles of high-dose dexamethasone (40 mg/day on days 1-4, 9-12, and 17-20).

This study recruited patients with relapsed and/or refractory multiple myeloma who had to have received at least two previous consecutive cycles of bortezomib and lenalidomide and had failed the previous treatment with bortezomib and lenalidomide. The median age of patients was 64 years (range 35 – 84) in the pomalidomide plus low-dose dexamethasone group and 65 years (range 35 – 87) in the high-dose dexamethasone group. The groups were equally distributed for all baseline characteristics. More than 94% of patients in both groups had failed on more than two previous treatments, and the median number of previous treatments for both groups was 5.

The primary endpoint was progression-free survival (PFS); secondary endpoints included overall survival, overall response rate, time to progression, duration of response, safety and quality of life. An interim survival analysis was planned for the same time as the final PFS analysis (242 PFS events) or when 106 deaths occurred. Quality of life was measured using three instruments: the EORTC QLQ-30, the QLQ-MY20 and the EQ-5D.

As per study protocol, patients were allowed to cross-over between the study groups upon disease progression: 76 patients in the high-dose dexamethasone group received pomalidomide after disease progression on their treatment assignment. However, 9 patients crossed over to the pomalidomide plus low-dose dexamethasone group *prior* to disease progression.

Based on the updated PFS analysis, where median follow-up was 10.0 months, patients in the pomalidomide plus low-dose dexamethasone group compared with the high-dose dexamethasone group had improved PFS (4.0 months [95% CI: 3.6-4.7] *vs* 1.9 months [95% CI: 1.9-2.2]; HR 0.48 [0.39-0.60]; p<0.0001). Median overall survival was also significantly longer in the pomalidomide plus low-dose dexamethasone group than in the high-dose dexamethasone group (12.7 months [95%CI: 10.4-15.5] *vs* 8.1 months [95% CI: 6.9 – 10.8]; HR 0.74 [0.56-0.97]; p=0.0285).

Pomalidomide plus low-dose dexamethasone significantly extended median time to meaningful worsening compared to high-dose dexamethasone for 2 of the 5 pre-selected domains for the EORTC QLQ-30: fatigue (113 *vs* 60 days, p=0.04) and emotional functioning (190 *vs* 124 days, p=0.02). Health utilities, as measured by the EQ-5D showed no differences between pomalidomide plus low-dose dexamethasone and high-dose dexamethasone, except in cycle 3. Of the two domains reported for the QLQ0-MY20, no differences were found between the two groups for disease symptoms.

The most common grade 3-4 haematological adverse events in the pomalidomide plus low-dose dexamethasone and high-dose dexamethasone groups were neutropenia (143 [48%] *vs* 24 [16%]), anaemia (99 [33%] *vs* 55 [37%]) and thrombocytopenia (67 [22%] *vs* 39 [26%]), respectively. The most common grade 3-4 non-haematological adverse events in the pomalidomide plus low-dose dexamethasone and high-dose dexamethasone groups included pneumonia (38 [13%] *vs* 12 [8%], respectively), bone pain (21 [7%] *vs* 7 [5%], respectively) and fatigue (16 [5%] *vs* 9 [6%], respectively). Serious adverse events, defined as grade 5, requiring hospitalisation, or resulting in disability or incapacity, were reported in 183 (61%) of patients in the pomalidomide plus low-dose dexamethasone group and 80 (53%) of patients in the high-dose dexamethasone group. 144 (48%) and 80 (53%) of

patients died in the pomalidomide plus low-dose dexamethasone group and high-dose dexamethasone group, respectively. The most common cause of death was progression of multiple myeloma, which accounted for 98 (68%) of deaths in the pomalidomide plus low-dose dexamethasone group and 51 (64%) of deaths in the high-dose dexamethasone group. There were 11 (4%) treatment-related deaths in the pomalidomide plus low-dose dexamethasone group and 7 (5%) treatment-related deaths in the high-dose dexamethasone group.

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

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, 94% of the respondents indicated that it is very important to have access to effective treatments for myeloma. 79% of the respondents noted that it was important to have a choice of drug based on known side effects of the drug. 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. Myeloma Canada reported that approximately 98.3% of the respondents used treatments other than pomalidomide to treat their myeloma. Respondents with experience using pomalidomide were asked about their overall experience, of which 46.3% of the respondents reported as being "much better", while 8.9% of the respondents reported as being "much worse". 53.6% of the respondents reported "fewer side effects" with the use of pomalidomide, while 10.3% reported "many more side effects". Respondents noted that the side effect experienced with pomalidomide that was the least tolerable was fatigue followed by back pain. 45.7% of respondents reported that pomalidomide was effective in controlling their myeloma, while approximately 10% of the respondents reported as being "not effective". 53% of the respondents found they have a good quality of life with pomalidomide, while approximately 7.7% of the respondents reported "poor quality of life".

PAG Input

From the PAG perspective, an enabler identified is that pomalidomide is an oral drug that can be easily used in the community.

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 pomalidomide including neutropenia and venous thromboembolism. In addition, the

requirement for physicians, pharmacists and patients to register with the federally mandated monitoring program is a barrier that may delay access.

Other

- There is an ongoing companion trial to the MM-003 examining pomalidomide as monotherapy for those that discontinued treatment with high dose dexamethasone due to disease progression.
- There are no other trials examining other appropriate comparators.
- There are two black box warnings for pomalidomide in the FDA product monograph: the first is that as a chemical analogue of thalidomide, it is known to cause birth defects in embryos exposed to the drug via either parent; the second is that patients treatment with pomalidomide are at risk of developing blood clots in the veins and lungs. Prophylaxis for deep vein thrombosis was given in the MM-003 trial for all patients treated with pomalidomide.
- In Canada, pomalidomide is only available through a controlled distribution program. Under this program, only prescribers and pharmacists registered with the program are able to prescribe and dispense the product. In addition, pomalidomide can only be dispensed to patients who are registered and meet all the conditions of this program.

2.2 Interpretation and Guidance

Burden of Illness and Need

Multiple myeloma is an incurable plasma cell neoplasm that makes up 1.2% of all new cancers in Canada.[15] In 2013, it is estimated that 2500 Canadians will be diagnosed with myeloma, and 1350 patients will die of this disease. The median age at presentation is 70 years old with a slightly higher incidence in males. Although there is significant heterogeneity within myeloma, the five year survival for all patients is 43%.[16]

Chemotherapy is the primary modality of treatment for myeloma. The three main classes of chemotherapy used, are alkylators (melphalan or cyclophosphamide), a proteasome inhibitor (bortezomib), or immunomodulatory drugs (thalidomide or lenalidomide). Patients with myeloma will eventually become refractory or intolerant of alkylators, bortezomib, and lenalidomide. When this scenario is reached, there is no clear standard of care. Commonly steroid therapy alone is used for palliation and symptom control to slow progressive disease without negatively impacting quality of life.

A previous phase II study with Pomalidomide demonstrated a respectable response rate in patients with relapsed or refractory myeloma.[17] Whether this response rate translated into a survival advantage was uncertain. To answer this question, the MM-003 Pomalidomide trial selected patients that had exhausted conventional therapy options. It is the first phase III myeloma study to demonstrate a survival advantage in the third-line setting for patients with relapsed and refractory disease after previously receiving lenalidomide, bortezomib and alkylator therapy.

Effectiveness

Overall Survival (OS):

The MM-003 trial demonstrated an overall survival advantage for patients receiving pomalidomide plus low-dose dexamethasone compared to dexamethasone alone. This was a secondary endpoint. The magnitude of the survival is both statistically and clinically significant. The analysis was based on intention to treat, and the benefit was still evident despite cross-over being allowed.

Progression-free survival (PFS):

The primary endpoint of this study was PFS. The analysis was done at a predetermined checkpoint demonstrating a statistically significant PFS. This difference was consistent across all subgroups analyzed. The absolute benefit in PFS was a modest 2.1 months. However, in this heavily pre-treated population with rapidly progressive disease, this would be considered a clinically significant improvement, supported by a HR of 0.48 (CI: 0.39-0.61).

Quality of life analysis:

Three QOL surveys were completed in this trial. Compared to dexamethasone alone, the pomalidomide plus dexamethasone group had a statistically significant extension of time to meaningful worsening in the domains of fatigue, and emotional functioning. The remainder of the results showed no difference on QOL domains. These results are clinically relevant and are consistent with the patient experience as reported by the Patient Advocacy Groups.

Safety

Toxicity:

The pomalidomide arm of the study was associated with a higher rate of neutropenia compared to dexamethasone alone. However, the rate of infection was similar between the two arms. All patients enrolled in the study required thromboprophylaxis. Choice of therapy was at the discretion of the treating physician. There was no difference in venous thromboembolic events between the two arms. All other safety and adverse event parameters were balanced, demonstrating that pomalidomide plus low-dose dexamethasone is a well-tolerated therapy compared to high-dose dexamethasone alone.

2.3 Conclusions

The pCODR Myeloma Clinical Guidance Panel concluded that there is a net overall clinical benefit to the use of pomalidomide plus low-dose dexamethasone compared to dexamethasone alone, in the treatment of relapsed and refractory myeloma. This is based on one high-quality randomized controlled trial that demonstrated a clinically and statistically significant benefit in overall survival and progression-free survival with adverse event profiles similar between the two arms of the study.

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

- The patient population included in this study had rapidly progressive disease, with either refractory disease on current therapy, or progression within 60 days of last therapy. The 60 day cut-off was used to define a patient group for the purpose of a clinical trial. However, the benefit of the drug likely extends to a broader population. The use of pomalidomide should not be limited to patients with rapidly progressive disease, but

rather, used in patients with relapsed or refractory disease after treatment with both bortezomib and lenalidomide.

- There is no evidence to support or refute the role of retreatment with lenalidomide or bortezomib for patients with slowly progressing disease. Although some provinces allow for re-treatment of patients previously exposed to bortezomib and lenalidomide, this is not uniformly available. Demonstrating aggressive disease as outlined in the pivotal study may be difficult for these patients. The CGP thus agree that the decision to retreat versus moving to third-line therapy with pomalidomide should be made based on standard of practice within each province. Extending the availability of pomalidomide to slowly progressing patients will thus ensure that provincial differences in availability of re-treatment will not hinder access of treatment to patients.

- Patients receiving lenalidomide in the maintenance setting are generally treated until disease progression and would consequently be considered to have relapsed or refractory disease at progression. Assuming that these patients meet the other eligibility requirement of having also progressed or been relapsed/refractory to bortezomib, it is reasonable to make pomalidomide available to patients that would have received lenalidomide in the maintenance setting and have subsequently progressed.

- This is the only phase III study in the third-line or greater setting to demonstrate an overall survival advantage.

- The federally mandated registration program required due to the teratogenicity of pomalidomide does not pose a barrier to implementation. All patients will have previously registered in this program at the time of therapy with lenalidomide.

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 an incurable plasma cell neoplasm that makes up 1.2% of all new cancers in Canada.[15] In 2013, it is estimated that 2500 Canadians will be diagnosed with myeloma, and 1350 patients will die of this disease. The median age at presentation is 70 years old with a slightly higher incidence in males. Although there is significant heterogeneity within myeloma, the five year survival for all patients is 43%.[16]

The diagnosis of myeloma is made based on excess clonal plasma cells in the bone marrow. Patients are further classified as having asymptomatic or symptomatic disease based on organ dysfunction caused by the excess plasma cells in the bone marrow or by the monoclonal proteins they produce. The hallmark features of symptomatic disease include hypercalcemia, renal insufficiency, anemia, and lytic bone disease. In the absence of symptoms, observation is appropriate and no therapy is required.[18]

3.2 Accepted Clinical Practice

Treatment of myeloma is reserved for patients with symptomatic disease. Chemotherapy is the primary modality of treatment, and radiation therapy is only used to help with symptom control due to painful bone involvement or a symptomatic plasmacytoma that cannot be controlled with chemotherapy alone. The three main classes of chemotherapy used to treat myeloma are alkylators (melphalan or cyclophosphamide), a proteasome inhibitor (bortezomib), or immunomodulatory drugs (thalidomide or lenalidomide). Various combinations of these drugs in combination with steroids (prednisone or dexamethasone) have proven to be highly effective therapy for myeloma, and the utilization of these drugs have improved the survival of myeloma patients.[19] There is no consensus with respect to the optimal sequencing or combination of drugs that should be used.

For patients under the age of 70, an autologous stem cell transplant (ASCT) can be considered in the initial therapy of myeloma. However, the toxicity of this treatment may preclude its use in some patients. Furthermore, combination chemotherapy may be equally effective with less toxicity particularly in patients over the age of 65.[18] Choosing the appropriate patients for ASCT is at the discretion of the treating physician. Although overall survival is the same if transplantation is performed at relapse or at time of diagnosis, early transplantation has a longer progression free survival, and less treatment related toxicity. For this reason, ASCT is not routinely used in the relapsed setting. Prior to receiving high dose melphalan chemotherapy conditioning for the transplant, three or four cycles of induction chemotherapy with a regimen containing bortezomib, lenalidomide or thalidomide is used to control the disease, improve the health of the patient, and clear the bone marrow to allow for easier stem cell collection.

There is considerable debate surrounding the role of maintenance therapy in myeloma post-ASCT. Recent studies using newer agents such as thalidomide, lenalidomide, and bortezomib have demonstrated improvement in progression free survival but there are conflicting studies with respect to a benefit in overall survival.[20] There are also concerns of tolerability of treatment, and long-term side effects of the maintenance therapy. For these reasons, use of maintenance

therapy has not been uniformly accepted across Canada. Further research is necessary to clarify questions with respect to appropriate patient selection, drug of choice, and safety.

Historically, melphalan and prednisone (MP) was the standard treatment for patients that were transplant ineligibly or had relapsed disease post-ASCT. More recently, using triplet therapy by adding bortezomib or thalidomide to MP has demonstrated a significant survival advantage compared to MP alone for newly diagnosed transplant ineligible patients. Regardless of the initial therapy, myeloma will relapse and further therapy will be required. Combination therapy with dexamethasone and either bortezomib or lenalidomide is the treatment of choice for second-line treatment. Upon relapse, resistance or intolerance, switching chemotherapy to an agent not previously used, is indicated. The efficacy of therapy may be enhanced by using triplet therapy by adding cyclophosphamide, melphalan, or doxorubicin to bortezomib or lenalidomide.[21]

Patients with myeloma will eventually become refractory or intolerant of alkylators, bortezomib, and lenalidomide. When this occurs, treatment options are limited, and until recently, supportive care was the only option. Palliative therapy often involves steroid therapy alone for symptom control and to try to slow progressive disease without negatively impacting quality of life. Other supportive measures include analgesics, transfusion support, radiation for symptomatic bone disease, and bisphosphonates for hypercalcemia or prevention of skeletal related events. More recently, pomalidomide and dexamethasone has demonstrated an improvement in progression free survival and overall survival in patients with relapsed and refractory disease after prior therapy with alkyators, bortezomib and lenalidomide.[1] This is the focus of this review.

3.3 Evidence-Based Considerations for a Funding Population

The population under consideration here includes patients with relapsed and/or refractory multiple myeloma, who have previously failed two treatments, including both bortezomib and lenalidomide, and demonstrating disease progression on the last treatment. All patients with progressive myeloma could be potential candidates for this therapy, assuming they are able to tolerate the toxicities of treatment.

3.4 Other Patient Populations in Whom the Drug May Be Used

Pomalidomide and low-dose dexamethasone could also be used in the setting of relapsed disease where administration of bortezomib was contraindicated or logistically impossible to administer. Instances where bortezomib cannot be administered logistically could include circumstances where a patient may not have access to adequate nursing and expertise for bortezomib administration and instances where patients are located in remote areas and administration of injectable chemotherapy by an oncology nurse is not feasible. In this instance, only oral chemotherapy is available. Previous phase II studies with pomalidomide and dexamethasone demonstrate significant response rates in this patient cohort.[22] This would be a small number of patients, with little impact of utilization of pomalidomide.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Myeloma Canada, provided input on pomalidomide (Pomalyst) in combination with low-dose dexamethasone for patients with multiple myeloma for whom both bortezomib and lenalidomide have failed and who have received at least two prior treatment regimens and have demonstrated disease progression on the last regimen, and their input is summarized below.

Myeloma Canada conducted two separate online surveys in February/March 2013 (herein referred to as "Survey 1") and in November/December 2013 (herein referred to as "Survey 2") to gather information from patients and caregivers about the impact of myeloma on their lives and the effect of treatments, particularly pomalidomide on their myeloma.

In Survey 1, Myeloma Canada reported a total of 619 respondents completed the survey. Responses from Survey 1 included 441 individuals living with multiple 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.

In Survey 2, Myeloma Canada reported a total of 406 respondents. 228 were from Canada with respondents from each province except PEI and no responses from the territories, 132 were from the United States, 3 from outside of North America and 43 did not respond. Of those who responded, 262 were patients and 104 were caregivers. A total of 151 respondents had experience with pomalidomide.

Both surveys 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, 94% of the respondents indicated that it is very important to have **access to effective treatments for myeloma**. 79% of the respondents noted that it was important to have **a choice of drug based on known side effects of the drug**. 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.** Myeloma Canada reported that approximately 98.3% of the respondents used treatments other than pomalidomide to treat their myeloma. Respondents with experience using pomalidomide were asked about their overall experience, of which 46.3% of the respondents reported as being "much better", while 8.9% of the respondents reported as being "much worse". 53.6% of the respondents reported "fewer side effects" with the use of pomalidomide, while 10.3% reported "many more side effects". Respondents noted that the side effect experienced with pomalidomide that was the least tolerable was fatigue followed by back pain. 45.7% of respondents reported that pomalidomide was effective in controlling their myeloma, while approximately 10% of the respondents reported as being "not effective". 53% of the respondents found they have a good quality of life with pomalidomide, while approximately 7.7% of the respondents reported "poor quality of life".

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

Based on the responses received from Survey 1, Myeloma Canada reported on patient experiences with multiple myeloma, including the importance of controlling symptoms/side-effects and the impact on the day-to-day activities.

Respondents rated on a scale of 1 - 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) noting this as 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 the respondents rated these aspects as a 10 "very important" to control. In all cases the rating average was greater than 8, which according to Myeloma Canada 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, diarrhoea and anaemia).

Symptom or problem related to myeloma	% of Respondents Rate "10"	Actual # of Respondents who rated "10"	Rating Average	N (total number of respondents received)
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". According to Survey 1, ability to work was impacted the most with 52.7% (271) of the 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".

Activity	% of Respondents (8 or higher)	Actual # of Respondents	Rating Average	N
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

4.1.2 Patients' Experiences with Current Therapy for Multiple Myeloma

Based on responses from Survey 1, 94.0% (503/535) of the respondents indicated that it is very important to have access to effective treatments for myeloma. 94.0% rated it as a 10 on a scale of 1 - 10, with 10 being "very important". The rating average was 9.90

According to Survey 2, 117 or 98.3% of the respondents used treatments other than pomalidomide to treat their myeloma.

The main treatments that the respondents have experienced are as follows:
bortezomib (N=108), lenalidomide (N=105), dexamethasone (N=105), autologous stem cell transplant (N=84), cyclophosphamide (N=65), thalidomide (N=55), melphalan + prednisone (N=49), vincristine, adriamycin/doxorubicin and dexamethasone (VAD) (N=26)

Treatment	% of Respondents	# of Respondents N = 116*
bortezomib (Velcade®)	93	108
lenalidomide (Revlimid®)	91	105
dexamethasone (Decadron®)	91	105
autologous stem cell transplant	72	84
cyclophosphamide (Cytoxan®)	56	65
thalidomide (Thalidomid ®)	47	55
melphalan + prednisone (MP)	42	49
VAD	22	26
allogeneic stem cell transplant	8	9

*The column exceeds the N of 116, because respondents selected more than one treatment.

According to Survey 2, respondents listed the side effects that they have experienced with these treatments as follows:

Side Effect	% of Respondents	# of Respondents N = 111
Fatigue	41	75
Neuropathy	36	66
Nausea	27	50
Stomach issues	14	27
Insomnia	11	21
Pain	11	21
Chemo Brain	10	19
Short of Breath	10	19
Low blood counts	8	16

Side Effect	% of Respondents	# of Respondents N = 111
Hair loss	8	16
Anaemia	5	10
Infections	4	9
Rash	4	9
Mouth sores	4	8
Mood swings/irritable	4	8
Dizziness	3	6
Weight loss/gain	3	7
Headache	3	7
Inflammation	2	5
Blood clot	2	4
Memory loss	2	5
Loss of appetite	1	2

A total of 111 respondents in Survey 2 with experience with these treatments responded to this open-ended question. The side effect mentioned by the most respondents was fatigue 41% (N=75), followed by neuropathy 36% (N=66), and then nausea 27% (N=50) and stomach issues 14% (N=27). Other side effects mentioned by 11% or fewer of the respondents included insomnia (11%), chemo brain (10%), short of breath (10%), low blood counts (8%), hair loss (8%).

Drawing from the responses in Survey 1, Myeloma Canada reported that the majority of patients and their caregivers (79%, 390/495) noted that it was important to have a choice of drug based on known side effects of the drug. 79% of the respondents 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.

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 multiple 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 Survey 1, Myeloma Canada reported that the 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% (n=146), 30.4% (n=144), 27.5% (n=131) 27.5% (n=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.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences to Date with Pomalidomide

Respondents were asked if they were to consider taking a new treatment for their myeloma, how important would it be to bring about improvement in their physical condition. Based on the

responses from Survey 1, 69.7% (342/491) of the respondents expressed that it is "extremely important" for a new treatment to bring about improvement in their physical condition. A total of 89.7% (440/491) gave this answer a rating of 8 or higher with 10 being "extremely important". The rating average for this question was 9.22

In addition to the above, 86.6% (425/491) of the respondents expressed that the expected benefit from taking a new drug is "extremely important". 98.6% (484/491) gave this a rating of 8 or higher with 10 being "extremely important". The rating average for this question was 9.77

The majority of respondents expressed that they would be willing to tolerate some level of side effects if the treatment was proven to be effective. As many as 177/491 (36%) of the respondents gave this a rating of 8 or higher, with 10 being "significant side effects", and 74/491 (15.1%) gave this a rating of 3 or lower, with 1 being "No side effects". According to Myeloma Canada, the rating average was 6.4, which meant that more respondents would tolerate side effects than those that would not tolerate any side effects.

The large majority of respondents (76.9%) in Survey 1 indicated that if they were to consider taking a new treatment for their myeloma, it is "very important to choose which drug would be better suited for me". 446/493 (90.5%) of respondents rated this 8 or higher, with 10 being "very important to choose which drug would be better suited for me", and 8 (1.6%) respondents rated this as 1, with 1 being "not important as long as there is a drug". The rating average for this question was 9.28

In Survey 2, respondents were asked about their personal experience with pomalidomide, in particular on how the respondent would rate their overall experience with pomalidomide. 46.3% (62/134) of the respondents rated this question as 8 or higher, with 10 being "much better", and 8.9% (12/134), rated this question 3 or lower, with 1 being "much worse". According to Myeloma Canada, the rating average for this question was 7.02, which meant that more people found pomalidomide to be a better experience than taking other drugs for their myeloma.

Much worse									Much better		
1 -	2	3	4	5	6	7	8	9	10 -	Rating Average	Rating Count
3.7% (5)	1.5% (2)	3.7% (5)	4.5% (6)	15.7% (21)	6.0% (8)	18.7% (25)	11.2% (15)	18.7% (25)	16.4% (22)	7.02	134

In addition to the above, respondents were asked to rate on how effective pomalidomide is in controlling their myeloma. 45.7% (63/113) of the respondents rated this question as 8 or higher, with 10 being "extremely effective," and 10% (14/113) rated this question as 3 or lower, with 1 being "not effective". A total of 19.6% or 27 rated this as a 10, "extremely effective". According to Myeloma Canada, the rating average for this question was 6.73, which meant that more people found pomalidomide to be effective in controlling their myeloma.

Not effective									Extremely effective		
1 -	2	3	4	5	6	7	8	9	10 -	Rating Average	Rating Count
6.5% (9)	6.5% (9)	0.7% (1)	2.9% (4)	14.5% (20)	11.6% (16)	11.6% (16)	13.8% (19)	12.3% (17)	19.6% (27)	6.73	113

In terms of side-effects, respondents were asked on how pomalidomide compares to the other treatments that respondents have taken. A total of 53.6% (73/136) of the respondents rated this question with a 3 or lower, with 1 being "fewer side effects". While 10.3% (14/136) of the respondents rated this as an 8 or higher, with 10 being "many more side effects". According to Myeloma Canada, the rating average for this question was 3.89, which meant that more people had "fewer side effects".

Fewer side effects									Many more side effects		
1 -	2	3	4	5	6	7	8	9	10 -	Rating Average	Rating Count
15.4% (21)	16.9% (23)	21.3% (29)	12.5% (17)	14.0% (19)	3.7% (5)	5.9% (8)	3.7% (5)	2.9% (4)	3.7% (5)	3.89	136

Respondents were also asked what the common side effects that respondents have experienced with pomalidomide. Respondents noted that the side effect that was the least tolerable was fatigue, which received an average rating of 6.74. 12.2% (17/139) of the respondents gave it a rating of 3 or lower with 1 being "completely intolerable". Fatigue was followed by back pain, which received an average rating of 6.88. 11.7% (13/136) gave it a rating of 3 or lower. The side effect that was the most tolerable was fever. It had an average rating of 7.5, which meant that most respondents found it to be tolerable. 10.7% (14/131) of the respondents rated fever as a 10 and 2.3% (3/131) of the respondents rated it as a one, with one being "completely intolerable" and 10 being "able to tolerate". According to Myeloma Canada, none of the choices of the side effects listed received an average rating less than 6.5, which means that more than half of the respondents were able to tolerate all the side effects.

Pomalidomide side effects	Completely intolerable									Able to tolerate			
	1 -	2	3	4	5	6	7	8	9	10 -	N/A	Rating Average	Rating Count
Fatigue	2.9% (4)	1.4% (2)	7.9% (11)	5.0% (7)	15.1% (21)	7.9% (11)	10.1% (14)	12.9% (18)	9.4% (13)	18.0% (25)	9.4% (13)	6.74	139
Back pain	2.2% (3)	5.1% (7)	5.1% (7)	1.5% (2)	11.0% (15)	4.4% (6)	6.6% (9)	8.8% (12)	8.8% (12)	18.4% (25)	27.9% (38)	6.88	136
Diarrhea	3.0% (4)	0.8% (1)	3.0% (4)	4.5% (6)	2.3% (3)	2.3% (3)	5.3% (7)	3.0% (4)	6.8% (9)	12.0% (16)	57.1% (76)	6.96	133
Neuropathy	2.3% (3)	3.0% (4)	6.8% (9)	3.0% (4)	7.5% (10)	5.3% (7)	9.0% (12)	6.0% (8)	8.3% (11)	21.8% (29)	27.1% (36)	7.04	133
Nausea	3.8% (5)	0.8% (1)	3.0% (4)	3.0% (4)	2.3% (3)	3.8% (5)	5.3% (7)	6.1% (8)	3.8% (5)	16.7% (22)	51.5% (68)	7.16	132
Shortness of Breath	4.4% (6)	1.5% (2)	2.2% (3)	2.2% (3)	6.6% (9)	3.7% (5)	5.1% (7)	8.1% (11)	3.7% (5)	20.6% (28)	41.9% (57)	7.19	136
Upper respiratory tract infection (sinusitis, cold)	3.0% (4)	2.2% (3)	1.5% (2)	5.2% (7)	3.7% (5)	3.7% (5)	3.7% (5)	6.7% (9)	11.2% (15)	15.7% (21)	43.3% (58)	7.25	134
Thrombocytopenia (low	1.5%	2.2%	5.9%	6.6%	2.9%	2.9%	6.6%	7.4%	8.8%	21.3	33.8	7.26	136

Pomalidomide side effects	Completely intolerable								Able to tolerate			
platelet count)	(2)	(3)	(8)	(9)	(4)	(4)	(9)	(10)	(12)	% (29)	% (46)		
Anaemia	1.5% (2)	0.0% (0)	5.2% (7)	3.7% (5)	10.4 % (14)	5.2% (7)	6.7% (9)	8.9% (12)	4.4% (6)	23.0 % (31)	31.1 % (42)	7.29	135
Dizziness and/or confusion	3.1% (4)	1.6% (2)	3.1% (4)	0.8% (1)	9.4% (12)	3.9% (5)	4.7% (6)	7.9% (10)	7.9% (10)	20.5 % (26)	37.0 % (47)	7.33	127
Neutropenia (low white blood cell count)	0.7% (1)	0.7% (1)	4.4% (6)	4.4% (6)	11.8 % (16)	5.9% (8)	7.4% (10)	11.8 % (16)	11.8 % (16)	21.3 % (29)	19.9 % (27)	7.39	136
Constipation	1.5% (2)	1.5% (2)	5.2% (7)	3.7% (5)	6.7% (9)	5.9% (8)	5.2% (7)	9.6% (13)	12.6 % (17)	20.7 % (28)	27.4 % (37)	7.41	135
Fever	2.3% (3)	0.0% (0)	0.8% (1)	0.8% (1)	5.3% (7)	2.3% (3)	0.8% (1)	2.3% (3)	6.9% (9)	10.7 % (14)	67.9 % (89)	7.50	131

Respondents were asked to report on their quality of life while taking pomalidomide. According to Myeloma Canada, the rating average for this question was 7.18, which meant that more people found they have a good quality of life with pomalidomide. 53% (75/141) of respondents rated this question as 8 or higher, with 10 being "excellent quality of life", and 7.7% (11/141), rated this question as 3 or lower, with 1 being "poor quality of life".

Poor quality of life									Excellent quality of life		
1 -	2	3	4	5	6	7	8	9	10 -	Rating Average	Rating Count
3.5% (5)	0.7% (1)	3.5% (5)	2.8% (4)	8.5% (12)	8.5% (12)	19.1% (27)	27% (38)	14.2% (20)	12.1% (17)	7.18	141

Respondents were asked to consider on how pomalidomide has changed or is expected to change their long-term health and well-being. A total of 27% or 33 respondents indicated that they expected the treatment to control their disease and 17% or 28 of the respondents expected the treatment to extend their life. Other responses included 12% (N=15) who said improved quality of life, 8% (N=10) said it was not effective, 7% (N=9) remissions, 6% (N=8), improved overall health, 5% (N=7) not well-tolerated, 5% (N=6) provided positive comments regarding side effects, 2% (N=3) commented on limited effectiveness, and 1 respondent expected to be able to continue to work.

Response	%	# of Respondents, N = 119
Control disease	27%	33
Don't know or NA	23%	28
Extend Life	17%	21
Improved Quality of Life	12%	15
Not effective	8%	10
Remission	7%	9
Improved overall health	6%	8
No longer on this treatment	5%	7
Not well tolerated	5%	7

Response	%	# of Respondents, N = 119
Positive comments re side effects	5%	6
Limited effectiveness	2%	3
Expect to continue to work	%	1

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

> *It is showing promise with a good reduction in the protein in the urine. My husband is at a point that all other treatments had failed and this is one of the last hopes. He is feeling well enough to work everyday and do some woodworking projects. This is a tremendous improvement from his health in the summer when he could hardly get out of bed. On drug trial his vision decreased, nausea was so bad he was on multiple drugs. He is diabetic, has high blood pressure, heart problems which all make the side effects worse."*
>
> *"In the seven months I have been on Pomalyst it has reduced my markers by an unbelievable amount. I use a computer program that track my results since I first came down with the disease 9 years ago. Pomalyst has given me the best markers since the beginning of the disease. Far beyond what I would have hoped for. This has been accomplished at 2Mg versus the standard 4Mg capsules."*
>
> *"Pomalyst has saved my life. I was hospitalized in July and told that I should be prepared to call in hospice. Pomalyst turned that situation around in a matter of one round of treatment. Yes, my quality of life could be a better, but without it I would have no life at all. Right now I am just trying to stay alive long enough to see a real, long-term treatment for MM."*
>
> *"I have been on a study of Pomalyst for five and a half years, and during that time have run 50 marathons. I cannot imagine any other treatment that would have allowed me to live my life so energetically. The myeloma is stable, and presents no obstacle to a full life."*

A total of 79 respondents who had experience with pomalidomide also responded to the open-ended question if there is anything else about pomalidomide that should be made known. Responses from Survey 2 are summarized below.

Response	%	# of Respondents, N = 79
Positive comments regarding the oral format	7	6
Cost of the drug was a factor	8	7
The drug did not work	1	1
The drug was more effective than other drugs	6	5
N/A answer (not related to the question)	13	11
Wouldn't do it again	1	1
Nothing further to add	15	12
Side effects were tolerable	10	8
Positive about the drug (thought it was the best drug, worked well with limited side effects, it should be an option for people with myeloma, etc.)	32	26
Mention of side effects	13	11

The following responses represent some of the comments provided that help to illustrate the table above.

> *"It just didn't work for me and couldn't control my myeloma."*

"After I had become drug tolerant of all the other medications, Pomalyst was my last option. It worked well for my treatment and I had a regression of the myeloma."

"Hair loss, diminished sex drive, occasional irritability."

"So thankful for this drug, it is the only thing that has worked for me."

"I am very glad I was eligible for the clinical trial and Pom gave me three years of stable disease and was able to work full time and enjoy a high QOL."

"Pomalyst is a good drug to take because of the limited side effects. I have upper respiratory infections and sinusitis, fatigue."

"The fact that it is an oral drug is really quite helpful for the quality of life-- it decreased the trips to go to the hospital/doctor's office for treatment and allows us to take some short trips."

"As I said before, the Pomalyst is taken with Dexamethasone with is awful. It is hard to distinguish which side effects are from that and which from the Pomalyst. Brain fog, dizziness. Weight gain feels particularly cruel."

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 pomalidomide (Pomalyst) in the treatment of relapsed and refractory multiple myeloma. 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 pomalidomide (Pomalyst) in the treatment of relapsed and refractory multiple myeloma was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From the PAG perspective, an enabler identified is that pomalidomide is an oral drug that can be easily used in the community.

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 pomalidomide including neutropenia and venous thromboembolism. In addition, the requirement for physicians, pharmacists and patients to register with the federally mandated monitoring program is a barrier that may delay access.

Please see below for more details.

5.1 Factors Related to Comparators

PAG noted that there are few treatment options for patients with multiple myeloma who have failed treatment with both bortezomib and lenalidomide. At this point in the disease, patients may receive palliative treatment with high-dose dexamethasone or cyclophosphamide/prednisone. Pomalidomide has progression-free survival and overall survival benefits and would be a new line of therapy that fills a gap in therapy for multiple myeloma patients who have failed both bortezomib and lenalidomide. This would be an enabler but PAG noted modest gains in progression free survival.

5.2 Factors Related to Patient Population

Multiple myeloma is considered an uncommon hematological cancer and the number of patients overall in the relapsed and refractory group would be small. Pomalidomide is a new line of treatment for these patients who have limited options which PAG identified as an enabler.

The standard of care is not well defined for relapse and refractory multiple myeloma patients who have failed both bortezomib and lenalidomide. Defining prior treatment has already been a challenge for lenalidomide, particularly as it relates to its use as induction therapy with or maintenance therapy after bone marrow transplantation. PAG has concerns in defining prior treatments and expects that clinicians may request for pomalidomide to be used in earlier lines of therapy, as maintenance therapy or for combination therapy. PAG would also like to know whether there is evidence for use of pomalidomide in patients who have received lenalidomide as maintenance therapy.

PAG noted that the U.S. Food and Drug Administration approval of pomalidomide is "for patients with multiple myeloma who have received at least two prior therapies including lenalidomide

and bortezomib and *have demonstrated disease progression on or within 60 days of completion of the last therapy*" (emphasis added) but the pCODR funding request does not include a statement regarding time to disease progression. PAG would like this issue addressed as this will impact implementation.

5.3 Factors Related to Accessibility

As an oral agent, PAG identified pomalidomide 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 to treatment in the community and not requiring clinic visits (chair time) for administration as enablers.

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

An enabler related to dosing of pomalidomide is the one tablet once daily regimen that would enhance patient compliance. There is the potential to confuse the dosing schedule of taking pomalidomide daily for 3 weeks and then 1 week off, however PAG noted this dosing schedule is the same as for lenalidomide with which patients with multiple myeloma would already be familiar.

Although the availability of four different strengths is an enabler for ease of dose adjustments, PAG expressed concerns if all tablet strengths are the same price, as is the case with lenalidomide. The flat pricing would be a barrier as there would be added costs for dose modifications. For example, a patient on a 4mg daily dose may be dispensed the smaller tablet strengths, to allow for the possible need of dose reductions. However, this dispensing strategy would cost more than dispensing the 4mg tablets. There are also concerns with the potential for drug wastage for patients who may be dispensed the 4mg tablets but do not tolerate and then have dose reduced 1mg, 2 mg or 3mg prior to finishing the amount of 4mg tablets dispensed.

5.5 Factors Related to Implementation Costs

Although providers and patients are familiar with the monitoring of lenalidomide, PAG noted that additional monitoring of 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 neutropenia and venous thromboembolism, associated with pomalidomide.

Patients will be required to receive anticoagulant drugs for prophylaxis or treatment of thrombotic events based on specific risk factors. This is a barrier as there would be additional costs for anticoagulant drugs and monitoring anticoagulant therapy.

Although the number of eligible patients may be small, PAG noted that there would be a budget impact for a new line of therapy since palliative treatment with high-dose dexamethasone or cyclophosphamide/prednisone is relatively inexpensive. This is a barrier to implementation given that these patients will now have a new treatment option for an unknown duration of time.

5.6 Other Factors

PAG noted that pomalidomide has black box warnings for embryo-fetal toxicity and venous thromboembolism. Due to these warnings, pomalidomide is only available through a federally mandated, restricted distribution program. Prescribers and pharmacists must be certified with the program and patients must agree to and comply with the requirements for monitoring. PAG has concerns on the significant time and logistical coordination required for the providers and the patients to register into the monitoring program.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effectiveness of pomalidomide (Pomalyst) in combination with dexamethasone for patients with relapsed and/or refractory multiple myeloma who have previously failed on both bortezomib and lenalidomide, and who have received at least two prior treatment regimens, and have demonstrated disease progression on the last regimen.

See Table 1 in section 6.2.1 for appropriate comparators and outcomes of interest.

No other supplemental questions 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 1. Selection criteria for systematic review

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators	Outcomes
Randomized controlled trials	Patients with relapsed and/or refractory multiple myeloma (rrMM), who have previously failed on two treatments, including both bortezomib and lenalidomide, and demonstrating disease progression on the last treatment • Sub-group analysis for patients >65 • Sub-group analysis by prior therapies	Pomalidomide in combination with dexamethasone as a third-line (or greater) treatment	• High-dose dexamethasone • Cyclophosphamide/ prednisone • Salvage regimens • Best supportive care (ie.no treatment; palliative care)	• **PFS** • **OS** • TTP • Duration of response • Overall response rate • **QoL** • **Safety** • Neutropenia • Anaemia • Thrombocytopenia • DVT • PE
PFS, progression free survival; OS, overall survival; TTP, time to progression; QoL, quality of life; DVT, deep vein thrombosis; PE, pulmonary embolism				

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 via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Pomalyst (pomalidomide) and multiple myeloma.

No filters were applied to limit the retrieval by study type. 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 was completed January 20, 2014 and was updated periodically during the review. The search is considered up to date as of May 1, 2014.

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 Canadian Cancer trials) along with relevant conference abstracts. Searches of conference abstracts included the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), American Society of Hematology (ASH), European School of Haematology (ESH) and the International Myeloma Workshop, based on input from the Clinical Guidance Panel. Conference abstract searches were limited to the last five years. The search was 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 any 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:

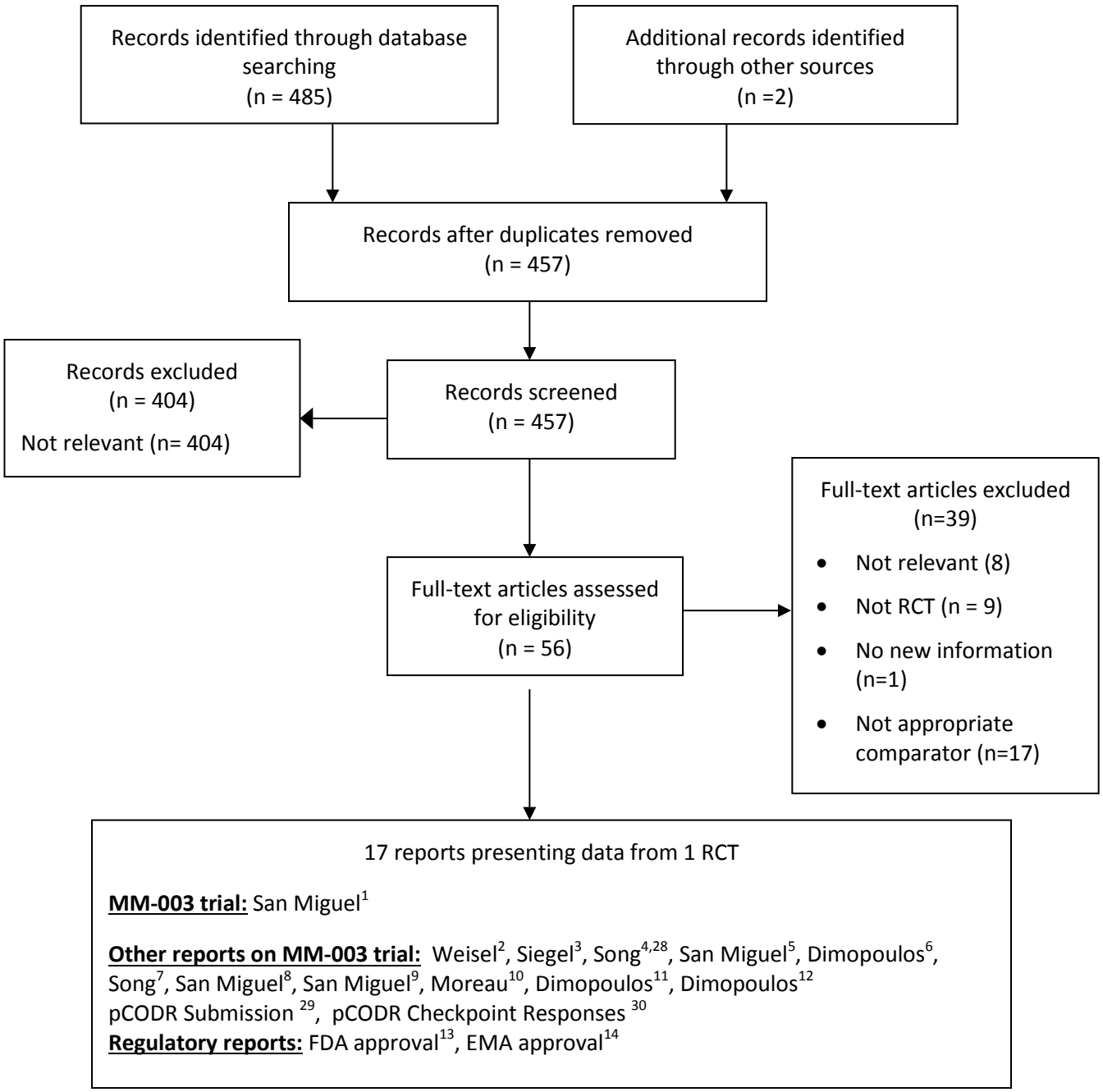
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental issues.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information, the interpretation of the systematic review and wrote guidance and conclusions for the report.
- The 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 457 potentially relevant reports identified, 14 were included in the pCODR systematic review[1-14] and 443 were excluded. Studies were excluded after full text review because they were not relevant (n=8), were not an appropriate study design (n=9), did not present new information (n=1) or did not examine an appropriate comparator (n=17).

Figure 1. PRISMA flow diagram for the inclusion and exclusion of studies



6.3.2 Summary of Included Studies

Table 2. Summary of trial characteristics of the included Study

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
MM-003 NCT01311687 93 centres in Europe, Russia, Australia, Canada and the USA March 18, 2011 - August 30, 2012 Open-label phase III RCT Randomized in a 2:1 ratio (pomalidomide + low-dose dexamethasone: high-dose dexamethasone) Randomized: n=455; all included in primary analysis Randomisation was stratified on • age (≤75 years *vs* >75 years) • disease status (refractory *vs* relapsed and refractory *vs* bortezomib intolerant) • number of previous treatments (two *vs* three or more) There is the currently an ongoing companion trial to the MM-003 evaluating the efficacy and safety of pomalidomide monotherapy in subjects with refractory or relapsed and refractory multiple myeloma who were enrolled in study CC-4047-MM-003 and discontinued treatment with high-dose dexamethasone due to disease progression. Funded by: Celgene **NOTE: Sponsor was involved in the data gathering,**	Patients had to be refractory to their previous treatment; judged to have refractory or relapsed/refractory disease; had received at least two previous consecutive cycles of bortezomib and lenalidomide (alone or in combination); had adequate aklylator treatment, and be older than 18 years Patients must have failed (progressive disease on or before 60 days of treatment, progressive disease ≤6 months after achieving partial response, or intolerance to bortezomib) treatment with bortezomib or lenalidomide -Patients who developed treatment intolerance after a minimum of two cycles of bortezomib and had developed progressive disease on or before 60 days after completing last treatment <u>Exclusion criteria:</u> • previously received pomalidomide • hypersensitivity to thalidomide, lenalidomide, or dexamethasone • resistance to high dexamethasone • peripheral neuropathy of grade 2 or more, substantial cardiac disease or laboratory abnormalities	<u>Intervention:</u> 28 day cycle of pomalidomide (4 mg/day on days 1-21, orally) plus low-dose dexamethasone (40 mg/day on days 1, 8, 15, and 22, orally) <u>Comparator:</u> 28 day cycle of high-dose dexamethasone (40 mg/day on days 1-4, 9-12, and 17-20). <u>NOTE:</u> for all patients over 75 years, regardless of treatment assignment, dexamethasone was reduced to 20 mg/day	<u>Primary</u> Progression-free survival <u>Secondary</u> Overall survival Overall response rate Time to progression Duration of response Safety Quality of life

Table 2. Summary of trial characteristics of the included Study			
Trial Design	**Key Inclusion Criteria**	**Intervention and Comparator**	**Outcomes**
analysis, review, interpretation and writing of the report.			
RCT= randomized controlled trial			

6.3.2.1 Detailed Trial Characteristics

a) Trials

The one randomized trial that met the inclusion criteria for this systematic review is summarized in Table 2. The study was an open-label trial, comparing pomalidomide + low-dose dexamethasone to high-dose dexamethasone at 93 centres across Europe, Russia, Australia, Canada and the USA.

The study included patients who were refractory to their previous treatment; judged to have refractory or relapsed and refractory disease; had to have received at least two previous consecutive cycles of bortezomib and lenalidomide, alone or in combination; had adequate akylator treatment (at least six cycles of alkylator treatment, or progressive disease after at least two cycles of alkylator treatment, or received alkylator treatment as part of a stem-cell trasnsplant); and be older than 18 years. Patients also must have failed (progressive disease on or before 60 days of treatment, progressive disease ≤ 6 months after achieving partial response, or intolerance to bortezomib) treatment with bortezomib or lenalidomide. Upon clarification at the checkpoint meeting, a patient would be excluded from the trial if they progressed after six months on their last bortezomib-containing regimen. In order for the patient to be included in the trial, the patient would require retreatment with a bortezomib-containing regimen in a subsequent line of therapy and meet the study entry criteria. Exclusion criteria included if patients had: a) previously received pomalidomide; b) had hypersensitivity to thalidomide, lenalidomide, or dexamethasone; c) had resistance to high-dose dexamethasone (progressive disease on or within 60 days of the last dose used in their previous treatment); d) had peripheral neuropathy of grade 2 or more; e) substantial cardiac disease (New York Heart Association Class II or IV, congestive heart failure, myocardial infarction on or within 12 months or unstable or poorly controlled angina); f) laboratory abnormalities: absolute neutrophil count of less than 1 x 10^9 per L, platelet count of less than 75 x 10^9 per L (<30 x 10^9 per litre if ≥50% of bone marrow nucleated cells were plasma cells); creatinine clearance of less than 45 mL/min according to the Cockrock-Gault formula or 24hr urine collection; corrected serum calcium greater than 3.5 µmol/L; haemoglobin less than 80g/L (4.9 mmol/L); or liver enzyme concentrations greater than three times the upper limit of normal.

Trial commenced enrolment on March 18, 2011 and finished on August 30, 2012. A total of 455 patients were enrolled and randomised. Target accrual was 426 patients. Sample size was calculated to have 242 PFS events (disease progression or death) with 85% power to detect a 50% improvement in median PFS (hazard ratio [HR] 1.5 for pomalidomide plus low-dose dexamethasone *vs* high-dose dexamethasone) at a two-sided significance level of 0.05. Final overall survival analysis was planned after 212 patients from both treatment groups died during the study. An interim survival analysis was also planned at either the same time as the final PFS analysis or when 106 deaths had occurred, whichever happened later. Efficacy

assessments were done in the intention-to treat population (all randomly assigned patients). Safety assessments were done in all patients who had received at least one dose of the study treatment.

Trial procedures for randomisation were considered adequate. Allocation to treatment was done randomly with a validated interactive voice and internet response system using a randomly permuted block within strata. As this was an open-label trial, treatment assignment was not masked. The sponsor reviewed the enrolment and screening. The implications of this are discussed in section (e). Patients were randomly assigned in a 2:1 ratio to pomalidomide plus low-dose dexamethasone: high-dose dexamethasone. Randomisation was stratified by age (≤75 years *vs* >75 years), disease status (refractory *vs* relapsed and refractory *vs* bortezomib intolerant), and number of previous treatments (two *vs* three or more). Upon clarification as the checkpoint meeting, "previous treatments" were not specified or outlined in the trial protocol. Stratification was not done by geographic region.

The primary endpoint was progression-free survival (PFS). The secondary endpoints were overall survival, overall response rate (proportion of patients who achieved at least a partial response according to the International Myeloma Working Group criteria[23] or European Group for Blood and Marrow Transplantation criteria for minor response only)[24], time to progression, duration of response, safety and quality of life. PFS and proportion of patients with an overall response presented in this report were based on investigator assessment of response and progressive disease. PFS has been determined to be an acceptable outcome for multiple myeloma.[23]

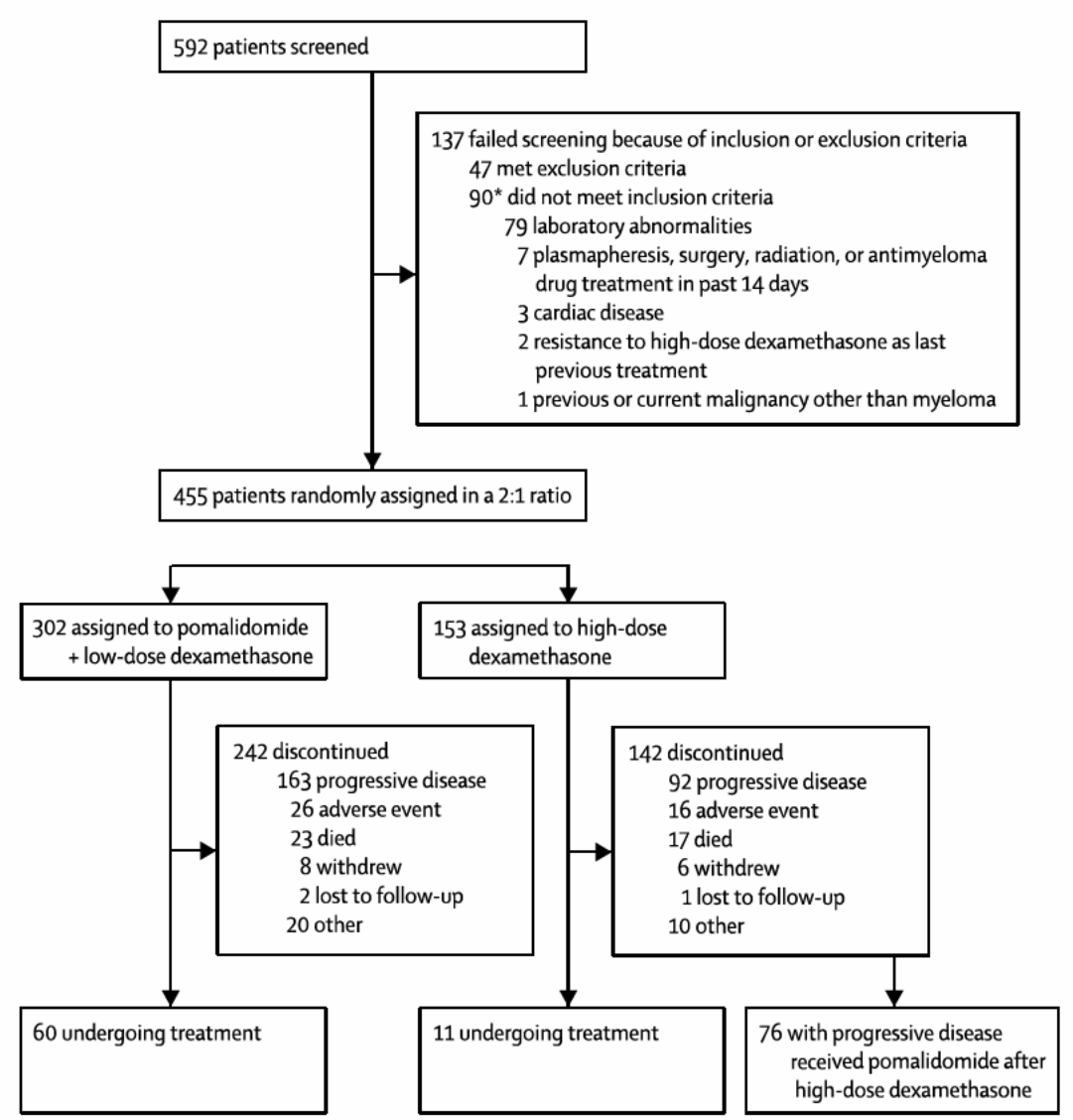
Quality of life was measured using the EORTC QLQ-C-30, a questionnaire developed to assess the quality of life of cancer patients. In addition, the QLQ-MY20 (myeloma tool) and the EQ-5D (health utility) tool were used. Analysis was done using the Kaplan-Meier method. A meaningful worsening was defined as a reduction in health-related quality of life (HRQOL) equal to or greater than the domain-specific minimally important difference, which was calculated using the standard error of measurement. HRQOL was analyzed both cross-sectionally and longitudinally through a mixed effects model.

b) Populations

Patients were classified on the basis of their disease status and were thought to be: a) refractory, if they had progressed on or within 60 days of treatment with bortezomib and lenalidomide (and had developed progressive disease on or within 60 days after completing their last treatment); b) relapsed and refractory, if they had achieved at least a partial response to previous treatment with bortezomib or lenalidomide, or both, but progressed within 6 months (and had developed progressive disease on or within 60 days after completing their last treatment); c) treatment intolerant to bortezomib, if they had developed treatment intolerance after a minimum of two cycles of bortezomib and had developed progressive disease on or before 60 days after completing their last treatment.

A total of 455 patients from the one randomized trial are included in this review. The following figure outlines the flow of patients in this trial.

Figure 2. Flow of patients in the MM-003 as taken from San Miguel et al.[1]



A total of 302 patients were randomized to pomalidomide + low-dose dexamethasone and 153 to high-dose dexamethasone. Groups were balanced for baseline characteristics and are summarized in the following table.

Table 3. Baseline characteristics of patients in the MM-003 trial as taken from San Miguel et al.[1]

	Pomalidomide plus low-dose dexamethasone (n=302)	High-dose dexamethasone (n=153)
Age (years)	64 (35–84)	65 (35–87)
>65	135 (45%)	72 (47%)
>75	24 (8%)	12 (8%)
Sex		
Male	181 (60%)	87 (57%)
Female	121 (40%)	66 (43%)
Time from diagnosis (years)	5·3 (0·6–30·0)	6·1 (0·9–21·1)
ECOG performance status score		
0–1	248 (82%)	122 (80%)
2–3	52 (17%)	28 (18%)
Missing	2 (<1%)	3 (2%)
International Staging System		
I–II	197 (65%)	93 (61%)
III	93 (31%)	54 (35%)
Missing	12 (4%)	6 (4%)
Creatinine clearance, <60 mL/min	95 (31%)	59 (39%)
Number of previous treatments	5 (2–14)	5 (2–17)
More than two	285 (94%)	145 (95%)
Previous treatments		
Dexamethasone	295 (98%)	152 (99%)
Thalidomide	173 (57%)	93 (61%)
Autologous stem-cell transplantation	214 (71%)	105 (69%)
Lenalidomide	302 (100%)	153 (100%)
Bortezomib	302 (100%)	153 (100%)
Refractory multiple myeloma	249 (82%)	125 (82%)
Intolerant to bortezomib	45 (15%)	23 (15%)
Refractory to lenalidomide	286 (95%)	141 (92%)
Refractory to bortezomib	238 (79%)	121 (79%)
Refractory to both bortezomib and lenalidomide	225 (75%)	113 (74%)

Data are median (range) or number (%). ECOG=Eastern Cooperative Oncology Group.

There were 135 (45%) patients in the pomalidomide plus low-dexamethasone group and 72 (47%) of patients in the high-dexamethasone group who were aged >65 years. Patients aged ≤65 years were more likely to have prior stem cell transplant (91% *vs* 45%), better renal function (creatinine clearance [CrCl]≥ 60 mL/min: 78% *vs* 51%), and less advanced disease (International Staging System stage III[25]: 28% *vs* 38%) compared with patients >65 years. Due to low numbers, there were no sub-group analyses for patients based on the 75 years cut-off. Sub-group analyses have been presented for greater and less than 65 years cut-off.

No information was provided for baseline characteristics by geographic region.

c) Interventions

Patients assigned to the pomalidomide plus low-dose dexamethasone group were given 28-day cycles of pomalidomide (4 mg/day on days 1-21, orally) plus low-dose dexamethasone (40 mg/day on days 1, 8, 15, and 22, orally). Patients assigned to the high-dose dexamethasone group were given 28-day cycles of high-dose dexamethasone (40 mg/day on days 1-4, 9-12, and 17-20). Dexamethasone dose was reduced to 20 mg/day in all patients older than 75 years. Treatment was continued until progressive disease or unacceptable toxicity occurred. The protocol stated that

pomalidomide was to be withheld for grade 4 and greater neutropenia, febrile neutropenia, and thrombocytopenia, grade 3 and greater venous thromboembolism, constipation, peripheral neuropathy, rash and all other grade 3 or greater treatment-related adverse events. The protocol also dictated that pomalidomide was to be withheld for grade 2 or greater hypothyroidism or hyperthyroidism. As per the protocol, the dose reduction was to be done on day 1 of the next cycle, and was reduced by 1 mg. The protocol stated that pomalidomide was to be discontinued for grade 4 rash or rash with blistering or grade 4 peripheral neuropathy. Dose modifications for dexamethasone were done according to institutional guidelines.

Note that patients receiving pomalidomide were required to take thromboprophylaxis. Choice of thromboprophylaxis and use of myeloid and erythroid growth factors was left to the physician's discretion.

d) Patient Disposition

The intention to treat population included 455 patients who were randomized to either pomalidomide plus low-dose dexamethasone (n=302) or high-dose dexamethasone (n=153). The safety population, defined as those who received at least one dose of pomalidomide, consisted of 300 patients in the pomalidomide plus low-dose dexamethasone group and 150 in the high-dose dexamethasone group.

As per study protocol patients were allowed to cross-over between the study groups. 76 patients in the high-dose dexamethasone group received pomalidomide plus low-dose dexamethasone after disease progression on their treatment assignment.

Disease progression was the most common reason for discontinuation of therapy in both groups (Figure 2). In the pomalidomide plus low-dose dexamethasone group, of the 242 patients that discontinued the study treatment, 8 withdrew consent and 2 were lost to follow-up. In the high-dose dexamethasone group, of the 142 patients who discontinued the study treatment, 6 withdrew consent and 1 was lost to follow-up.

e) Limitations/Sources of Bias

There were several limitations and potential sources of bias in this trial. The first was the open-label design of the trial. Neither the patients, nor the investigators were masked to the treatment assignment. Therefore, the investigators assessing outcome response were not blinded to the treatment assignment and detection bias could be present in assessing the efficacy of the drug.

The method of allocation concealment was not well described in the trial. As the sponsor was involved in reviewing the enrolment and screening of the patients, it is not clear what methods were undertaken to ensure adequate allocation concealment. Methods of reducing bias in the trial were raised as a concern at checkpoint, but no further information was provided.

Patients were allowed to cross over between the treatment arms upon disease progression. However, 9 patients crossed over to the pomalidomide plus low-dose dexamethasone group prior to disease progression on high-dose dexamethasone for the updated PFS analysis. Though, the authors of the trial estimate that this would favour the high-dose dexamethasone group at the updated PFS analysis, since the overall magnitude of difference in survival would be reduced.

An important potential source of bias was the high level of involvement of the sponsor in data collection, analysis, review, interpretation and writing of the report. It is unclear what role the sponsor played in each of these steps. The submitter provided no further information following the checkpoint meeting.

Baseline characteristics between groups were similar with the exception of time since diagnosis. Those in the high-dexamethasone group had a slightly longer time since diagnosis (median 6.1 years; range 0.9 - 21.1) compared to the pomalidomide plus low-dexamethasone group (median 5.3 years; range 0.6 - 30.0) although the significance of this difference is unclear.

There may be publication bias as not all the data collected for quality of life through the three instruments was made publicly available, or was included in the final trial publication.

Results are also not presented by geographic area. It is difficult to know if the results were consistent across all centres or how generalizable results are to different geographic settings.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Only an intention-to-treat analysis is presented, which includes all randomized patients. Follow-up for overall survival was planned to occur every 84 days for up to 5 years after randomisation. Progression-free survival and overall survival estimates were with the Kaplan-Meier product-limit method, along with a log-rank test. A final PFS analysis and an interim survival analysis were planned at the pre-specified data cut-off or when 106 deaths occurred. A final overall survival analysis was to be done after 212 patients from both treatment groups died during the study.

At the pre-specified data cut-off (September 7, 2012), 267 PFS events had occurred. The interim survival analysis was done at this time, when 134 deaths had occurred. An independent data monitoring committee indicated that the trial had met the primary endpoint for PFS and that the upper boundary for superior overall survival had been crossed, despite 45 patients in the high-dose dexamethasone group crossing over and receiving pomalidomide. The safety analysis included patients who received at least one dose of pomalidomide (n=450). 448 patients had completed at least 1 questionnaire for assessing HRQOL and were include in the analysis.

The following table summarizes the key outcomes.

Table 4. Summary of key outcomes[1,2,4]

EFFICACY (ITT)				
Outcome	**Study group**	**Events (%)**	**HR (95% CI)**	**p value**
Overall survival[a]	Pom + low-dex	145/302	0.74	0.0285
	High-dex	82/153	(0.56, 0.97)	
Outcome	**Study group**	**Median months (95% CI)**	**HR (95% CI)**	**p value**
Progression free survival[b]	Pom + low-dex	4.0 (3.6, 4.7)	0.48	<0.0001
	High-dex	1.9 (1.9, 2.2)	(0.39, 0.60)	
Time to progression	Pom + low-dex	4.7 (4.0, 6.0)	0.46	<0.0001
	High-dex	2.1 (1.9, 2.5)	(0.36, 0.59)	
Duration of response	Pom + low-dex	7.0 (5.8, 9.0)	0.52	0.0631
	High-dex	6.1 (1.4, 8.5)	(0.25, 1.05)	
Outcome	**Study group**	**Events (%)**	**OR (95% CI)**	**p value**
Overall response rate	Pom + low-dex	95 (31%)	4.22	<0.0001
	High-dex	15 (10%)	(2.35, 7.58)	

QUALITY OF LIFE EORTC QLQ-C30				
Outcome	**Study group**	**n**	**Median days to meaningful worsening (95% CI)**	**p value**
Global health status	Pom + low-dex	302	114 (71,143)	0.06
	High-dex	153	85 (37, 140)	
Physical functioning	Pom + low-dex	302	174 (123,288)	0.09
	High-dex	153	106 (57, NE)	
Fatigue	Pom + low-dex	302	113 (71, 169)	0.04
	High-dex	153	60 (57, 113)	
Emotional functioning	Pom + low-dex	302	190 (145, 361)	0.02
	High-dex	153	124 (64, 235)	
Pain	Pom + low-dex	302	147 (89, NE)	0.2
	High-dex	153	113 (58, NE)	
HARMS				
Outcome	**Study group**	**n/N**	**%**	**p value**
Dose interruption	Pom + low-dex	201/300	67%	NR
	High-dex	42/150	28%	
Dose reduction	Pom + low-dex	82/300	27%	NR
	High-dex	48/150	32%	
Permanent discontinuation[c]	Pom + low-dex	11/300	4%	NR
	High-dex	9/150	6%	
Grade 3 or 4 Neutropenia	Pom + low-dex	152/300	51%	NR
	High-dex	31/150	21%	
Grade 3 or 4 Anaemia	Pom + low-dex	157/300	52%	NR
	High-dex	76/150	51%	
Grade 3 or 4 Thrombocytopenia	Pom + low-dex	90/300	30%	NR
	High-dex	44/150	29%	
Deep vein thrombosis[d]	Pom + low-dex	6/300	2%	NR
	High-dex	2/150	1%	
Serious adverse events[e]	Pom + low-dex	183/300	61%	
	High-dex	80/150	53%	
Deaths, any cause	Pom + low-dex	144/300	48%	NR
	High-dex	80/150	53%	
Treatment-related deaths	Pom + low-dex	11/300	4%	NR
	High-dex	7/150	5%	

ITT = intention to treat; pom = pomalidomide; low-dex = low-dose dexamethasone; high-dex = high-dose dexamethasone; HR = hazard ratio; CI = confidence interval; OR = odds ratio; NR = not reported; NE = not estimable

[a]final overall survival analysis; [b]updated PFS analysis; [c]permanent discontinuation due to treatment-related adverse events; [d]reported as deep-vein thrombosis and pulmonary embolism; [e]defined as grade 5, requiring hospitalisation, or resulting in disability or incapacity

Efficacy Outcomes

a) Overall Survival

Overall survival was a secondary end-point and was only to be tested if the difference in PFS between treatment groups was significant. Following clarification from the checkpoint meeting, the submitter specified that patients were monitored for overall survival every 84 days after treatment until phase discontinuation. The overall survival data presented is considered a final analysis, and was done at the time of the updated PFS analysis. At the time of the final overall survival analysis, median follow-up was 10.0 months.

Median overall survival was significantly longer in the pomalidomide plus low-dose dexamethasone group than in the high-dose dexamethasone group (12.7 months [95%CI: 10.4-15.5] *vs* 8.1 months [95% CI: 6.9 – 10.8]; HR 0.74 [0.56-0.97]; p=0.0285).

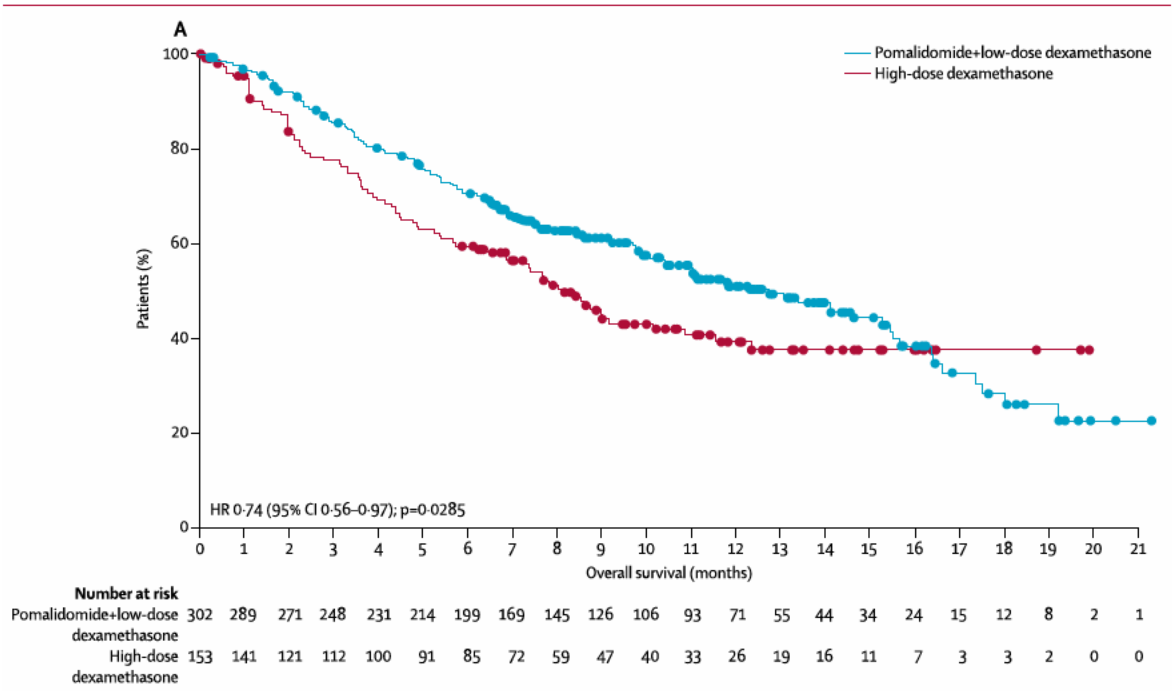
It should be noted that at a median follow-up of 10.0 months, 76 (50%) of 153 patients in the high-dose dexamethasone group had received pomalidomide. The authors estimated that all patients in the high-dose dexamethasone group would have received pomalidomide after 16 months of follow-up.

Sub-group analyses for overall survival

There were no significant differences between the two treatment group for patients who were refractory to both lenalidomide and bortezomib (11.1 months [9.2-15.5] *vs* 7.7 months [5.4-10.1], p=0.0957). Median overall survival was also similar in patients 65 years and younger (12.7 months, 95% CI: 10.08 – 16.41) and those older than 65 years (13.1 months, 95% CI: 9.78 – 15.53) receiving pomalidomide plus low-dose dexamethasone. In patients who had received more than two previous treatments, there was no significant difference in overall survival (HR 0.76, 95% CI: 0.58-1.01).

The following figure taken from San Miguel et al. shows that although there was a significant difference in the median overall survival between the two groups, the survival curves do cross, and therefore the proportionality assumptions appear to not have been met. Based on the Sept 2013 data from the submitter, overall survival results were more mature and showed that the curves do not cross at that point (HR was also similar to the median OS results). This updated data reflected an additional 5.4 months in median follow up and increase in the number of patients at risk (POM+LD-DEX increased from 145 to 176 of 302 events and HD-Dex increased from 82 to 101 of 153 events).

Figure 3. Kaplan-Meier overall survival as taken from San Miguel et al.[1]



b) Progression-free survival

The results presented here are from the updated PFS analysis (median follow-up 10.0 months).

Patients in the pomalidomide plus low-dose dexamethasone group compared with the high-dose dexamethasone group had increased PFS (4.0 months [95% CI: 3.6-4.7] *vs* 1.9 months [95% CI: 1.9-2.2]; HR 0.48 [0.39-0.60]; p<0.0001).

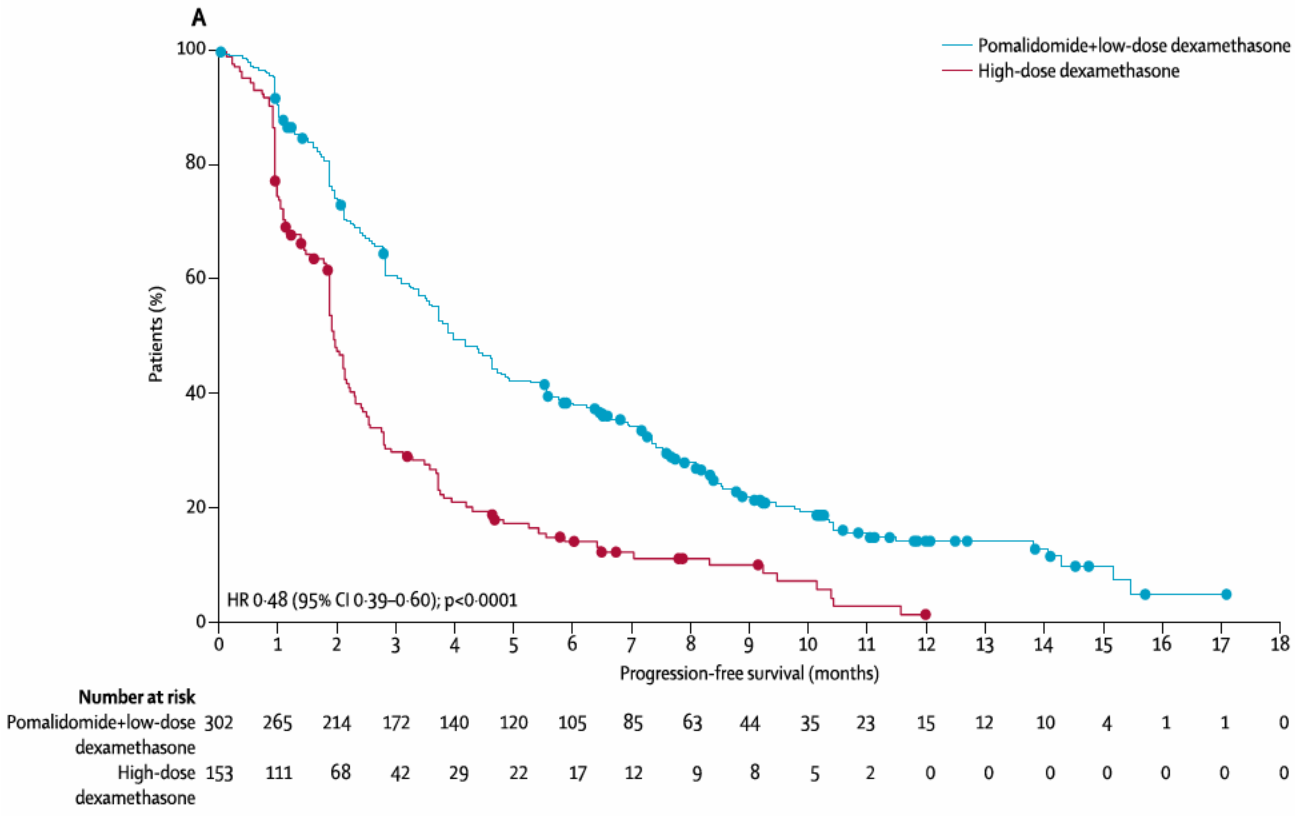
As above, it should be noted that at a median follow-up of 10.0 months, 76 (50%) of 153 patients had received pomalidomide.

<u>Sub-group analyses for progression-free survival</u>

There was a significant difference between the two treatment groups for patients who were refractory to both lenalidomide and bortezomib (HR 0.52; 95% CI: 0.41-0.68, p<0.0001), in those patients 65 years and younger (HR 0.47, p < .001) and those older than 65 years (HR 0.52, p < .001). In patients who had received more than two previous treatments, there was a significant difference in progression-free survival as well (HR 0.48, 95% CI: 0.39-0.61).

The following figure taken from San Miguel et al. shows the progression-free survival between the two groups.

Figure 4. Kaplan-Meier progression-free survival as taken from San Miguel et al.[1]



c) Time to progression

Time to progression was a secondary end-point. Upon clarification at the checkpoint meeting, time to progression was calculated as the time from randomization to the first documented progression confirmed by a blinded, Independent Response Adjudication Committee (IRAC). Time to progression was longer for those in the pomalidomide plus low-dose dexamethasone group (median 4.7 months [95% CI: 4.0 - 6.0]) than those in the high-dose dexamethasone group (median 2.1 months [95% CI: 1.9-2.5]), HR 0.46 (0.36-0.59), p<0.0001.

d) Duration of response

In patients with at least a partial response, there was no significant difference in median response duration for those in the pomalidomide plus low-dose dexamethasone group vs the high-dose dexamethasone group (7.0 months (5.8 - 9.0) vs 6.1 months (1.4 - 8.5), respectively; HR 0.52 (0.25 - 1.05), p=0.0631).

e) Overall response rate

Overall best response was determined at every cycle on Day 1 starting at Cycle 2 and at the treatment discontinuation visit. Response rate was done in accordance with the International Myeloma Working Group criteria[26] for all responses except for minor responses, which were in accordance with the European Group for Blood and Marrow Transplantation criteria.[27]

There were 95 (31%) overall responses in the pomalidomide plus low-dose dexamethasone group and 15 (10%) overall responses in the high-dose dexamethasone group (p<0.0001). There were 3 (1%) complete responses in the pomalidomide plus low-dose dexamethasone group and no complete responses in the high-dose dexamethasone group.

Quality of Life Outcomes

Upon clarification from the checkpoint meeting, 433 patients were included in the HRQOL analysis.

EORTC QLQ-C30[7]

Health-related quality of life (HRQOL) was analyzed for 5 predefined EORTC QLQ-C30 domains: global health status, physical functioning, fatigue, emotional functioning, and pain.

a) Time to clinically meaningful worsening

Analyses on time to clinically meaningful worsening showed that pomalidomide plus low-dose dexamethasone significantly extended median time to meaningful worsening compared to high-dose dexamethasone for the 2 of the 5 pre-selected domains: fatigue (113 *vs* 60 days, p=0.04) and emotional functioning (190 *vs* 124 days, p=0.02). Pomalidomide plus low-dose dexamethasone also extend the median time to meaningful worsening in HRQOL for the other 3 domains of global health status, physical functioning and pain, but these results were not statistically significant.

EQ-5D

b) Health utility index scores[28]

There were no differences in quality of life between the pomalidomide + low-dexamethasone group and the high-dexamethasone group, except at Cycle 3. Time to first worsening was not different. Time to first worsening was not different between the two groups.

c) Item responses[30]

The submitter, following checkpoint, provided more detailed EQ5-D data, including item responses. A repeated measured mixed model was created for all cycles where n≥20 for each arm, however, as stated by the submitter, the endpoints that did not converge could not be estimated.

Overall very few statistically significant differences were found between the groups, by item and by cycle.

QLQ-MY20[28]

Two domains were deemed clinically relevant from the QLQ-MY20: disease symptoms and side effects of treatment. Only patients with ≥1 study drug dose and ≥1 HRQoL item measured were included in this analysis (n=433).

There were no differences in disease symptoms between the pomalidomide+low-dexamethasone and the high-dexamethasone group over the course of the trial. Neither of the domains were different in time to first worsening between the groups

Harms Outcomes

The safety population (all patients receiving at least one dose of pomalidomide) consisted of 300 patients randomized to the pomalidomide plus low-dose dexamethasone group and 150 in the high-dose dexamethasone group. All adverse events were recorded by the investigator from the time the subject signed informed consent to 28 days after treatment discontinuation.

a) Deaths, any cause

144 (48%) and 80 (53%) of patients died in the pomalidomide plus low-dose dexamethasone group and high-dose dexamethasone group, respectively. The most common cause of death

was progression of multiple myeloma, which accounted for 98 (68%) of deaths in the pomalidomide plus low-dose dexamethasone group and 51 (64%) of deaths in the high-dose dexamethasone group. Infection was the second most common cause of death, and accounted for more deaths in the high-dose dexamethasone group 15 (19%) than in the pomalidomide plus low-dose dexamethasone group 14 (10%).

b) Treatment-related deaths

There were 11 (4%) treatment-related deaths in the pomalidomide plus low-dose dexamethasone group: 8 cases of infections and infestations, 2 cases of multiorgan failure or sudden death, and one nervous system disorder. There were 7 (5%) treatment-related deaths in the high-dose dexamethasone group; all 7 were due to infections and infestations.

c) Serious adverse events

Serious adverse events, defined as grade 5, requiring hospitalisation, or resulting in disability or incapacity, were reported in 183 (61%) of patients in the pomalidomide plus low-dose dexamethasone group and 80 (53%) of patients in the high-dose dexamethasone group.

d) Grade 3-4 adverse events

The grade 3-4 adverse events occurring in more than 10% of the safety population for both groups is shown in the following table.

e) Secondary Malignancies

Second primary malignancies were reported in both arms of the trial with 4 patients in the pomalidomide plus low-dose dexamethasone group (2 with invasive solid cancers and 2 with noninvasive (basal-cell) skin cancers) and 1 in the high-dose dexamethasone group (1 with noninvasive (basal-cell) skin cancer).

Table 5. Summary of the most commonly reported adverse events occurring in more than 10% of the safety population, as taken from San Miguel et al.[1]

	Pomalidomide plus low-dose dexamethasone (n=300)				High-dose dexamethasone (n=150)			
	Total	Grade 3	Grade 4	Grade 5	Total	Grade 3	Grade 4	Grade 5
Infections and infestations	203 (68%)	72 (24%)	19 (6%)	11 (4%)	79 (53%)	28 (19%)	8 (5%)	13 (9%)
Anaemia	157 (52%)	93 (31%)	6 (2%)	..	76 (51%)	48 (32%)	7 (5%)	..
Neutropenia	152 (51%)	77 (26%)	66 (22%)	..	31 (21%)	13 (9%)	11 (7%)	..
Fatigue	103 (34%)	16 (5%)	..	..	41 (27%)	9 (6%)	..	..
Thrombocytopenia	90 (30%)	27 (9%)	40 (13%)	..	44 (29%)	13 (9%)	26 (17%)	..
Pyrexia	80 (27%)	8 (3%)	1 (<1%)	..	34 (23%)	5 (3%)	2 (1%)	..
Diarrhoea	66 (22%)	3 (1%)	..	..	28 (19%)	2 (1%)	..	..
Constipation	65 (22%)	7 (2%)	..	..	22 (15%)	..	..	..
Cough	61 (20%)	1 (<1%)	1 (<1%)	..	15 (10%)	1 (<1%)	..	..
Back pain	59 (20%)	13 (4%)	2 (1%)	..	24 (16%)	5 (3%)	1 (<1%)	..
Dyspnoea	59 (20%)	13 (4%)	2 (1%)	..	21 (14%)	7 (5%)	..	..
Bone pain	52 (17%)	20 (7%)	1 (<1%)	..	19 (13%)	7 (5%)	..	..
Peripheral oedema	52 (17%)	4 (1%)	..	..	17 (11%)	3 (2%)	..	..
Upper respiratory tract infection	48 (16%)	5 (2%)	..	..	12 (8%)	2 (1%)	..	..
Asthenia	48 (16%)	10 (3%)	1 (<1%)	..	26 (17%)	9 (6%)	..	..
Muscle spasms	47 (16%)	1 (<1%)	..	..	11 (7%)	1 (<1%)	..	..
Pneumonia	46 (15%)	30 (10%)	8 (3%)	4 (1%)	16 (11%)	10 (7%)	2 (1%)	3 (2%)
Nausea	45 (15%)	2 (1%)	..	..	16 (11%)	2 (1%)	..	..
Leukopenia	38 (13%)	20 (7%)	6 (2%)	..	8 (5%)	2 (1%)	3 (2%)	..
Dizziness	37 (12%)	4 (1%)	..	..	12 (8%)	2 (1%)	..	..
Decreased appetite	36 (12%)	2 (1%)	..	..	12 (8%)	2 (1%)	..	..
Insomnia	31 (10%)	3 (1%)	..	..	30 (20%)	5 (3%)	..	..
Bronchitis	30 (10%)	3 (1%)	..	..	8 (5%)	..	..	..
Febrile neutropenia	29 (10%)	23 (8%)	5 (2%)	..	1 (<1%)	..	..	..
Epistaxis	28 (9%)	2 (<1%)	1 (<1%)	..	15 (10%)	2 (1%)	1 (<1%)	..
Hypercalcaemia	21 (7%)	6 (2%)	7 (2%)	..	16 (11%)	6 (4%)	2 (1%)	..
Muscle weakness	11 (4%)	3 (1%)	..	..	19 (13%)	5 (3%)	..	..

Data are number (%).

The most common grade 3-4 haematological adverse events in the pomalidomide plus low-dose dexamethasone and high-dose dexamethasone groups were neutropenia (143 [48%] *vs* 24 [16%]), anaemia (99 [33%] *vs* 55 [37%]) and thrombocytopenia (67 [22%] *vs* 39 [26%]), respectively. Occurrence of neutropenia did not seem to affect the incidence of infections and grade 3-4 infections occurred in 91 (30%) of patients in the pomalidomide plus low-dose dexamethasone group and 36 (24%) in the high-dose dexamethasone group. The majority of infections of any grade occurred in the absence of neutropenia: 133 [66%] of 203 patients in the pomalidomide plus low-dose dexamethasone group and 68 [86%] of 79 patients in the high-dose dexamethasone group.

The most common grade 3-4 non-haematological adverse events in the pomalidomide plus low-dose dexamethasone and high-dose dexamethasone groups included pneumonia (38 [13%] *vs* 12 [8%], respectively), bone pain (21 [7%] *vs* 7 [5%], respectively) and fatigue (16 [5%] *vs* 9 [6%], respectively).

Given that patients in the pomalidomide group or those at high-risk were provided with thromboprophylaxis, deep-vein thrombosis and pulmonary embolism were infrequent in both groups (any grade): 6 [2%] in the pomalidomide plus low-dose dexamethasone group and 2 [1%] in the high-dose dexamethasone group. Median time to onset of deep-vein thrombosis or pulmonary embolism was 4.0 months (1.0-6.2) in the pomalidomide plus low-dose dexamethasone group and 2.3 months (1.1-3.5) in the high-dose dexamethasone group. As of time of publication, 1 patient in each group has died of deep-vein thrombosis or pulmonary embolism as a consequence of disease progression.

f) Dose modifications

In the pomalidomide plus low-dose dexamethasone group, 201 (67%) of 300 patients required pomalidomide dose interruptions and 82 (27%) required pomalidomide dose reductions. Relative dose intensity was defined as the actual dose taken compared to the planned (i.e. starting) dose. The median relative dose intensity was 0.9 (0.3 – 1.3). In the high-dose dexamethasone group, 42 (38%) of 150 patients had dose interruptions and 48 (32%) had dose reductions. The median relative dose intensity was 1.0 (0.3-2.0).

Discontinuation of treatment due to treatment-related adverse events occurred in 11 (4%) patients in the pomalidomide plus low-dose dexamethasone group and 9 (6%) of patients in the high-dose dexamethasone group.

6.4 Ongoing Trials

No additional on-going and/or unreported trials were identified that would have been included had they been completed.

7 Supplemental Questions

No supplemental issues were identified as relevant to the pCODR review of pomalidomide for relapsed/refractory multiple myeloma.

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 on pomalidomide (Pomalyst) 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.

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

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations AND Ovid MEDLINE(R) 1946 to Present, Ovid MEDLINE(R) Daily Update January 17, 2014

Date: January 20, 2014

Number of unique records: 176

#	Search	Results
1	(Pomalyst$ or pomalidomide$ or "CC4047" or "CC 4047").ti.ot.ab.sh.rn.hw.nm.	195
2	(19171-19-8 or D2UX06XLB5).rn,nm.	114
3	or/1-2	196
4	limit 3 to english language	189
5	exp animals/	16943522
6	exp animal experimentation/	6106
7	exp models animal/	400208
8	exp animal experiment/	6106
9	nonhuman/	0
10	exp vertebrate/	16448805
11	or/5-10	16951435
12	exp humans/	13078281
13	exp human experimentation/	11580
14	or/12-13	13078916
15	11 not 14	3873125
16	4 not 15	180

Database: Embase 1974 to 2014 January 17

Date: January 20, 2014

Number of unique records: 262

#	Search	Results
1	*pomalidomide/	223
2	(Pomalyst$ or pomalidomide$ or "CC4047" or "CC 4047").ti,ab.	431
3	1 or 2	443
4	limit 3 to english language	429
5	exp animals/	19687294
6	exp animal experimentation/ or exp animal experiment/	1744832
7	exp models animal/	734063
8	nonhuman/	4205111
9	exp vertebrate/ or exp vertebrates/	19241847
10	or/5-9	20898257
11	exp humans/	15299687
12	exp human experimentation/ or exp human experiment/	320324
13	or/11-12	15301130
14	10 not 13	5598107
15	**4 not 14**	**412**

Database: EBM Reviews - Cochrane Central Register of Controlled Trials December 2013, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to December 2013

Date: January 20, 2014

Number of unique records: 3

Searches	Results	Search Type
1	*pomalidomide/	0
2	(Pomalyst$ or pomalidomide$ or "CC4047" or "CC 4047").ti,ab.	7
3	1 or 2	7
4	limit 3 to english [Limit not valid in CCTR,CDSR; records were retained]	7
5	exp animals/	410680
6	exp animal experimentation/ or exp animal experiment/	2
7	exp models animal/	304
8	nonhuman/	0
9	exp vertebrate/ or exp vertebrates/	410677
10	or/5-9	410680
11	exp humans/	410676
12	exp human experimentation/	108
13	or/11-12	410676
14	10 not 13	4
15	4 not 14	7

Database: PubMed

Date searched: January 20, 2014

Number of unique records: 29

1	pomalyst[All Fields] OR pomalidomide[All Fields]OR"CC4047"[All FIelds] OR "CC 4047"[All Fields] OR D2UX06XLB5 [rn]	205

Grey literature

a) www.clinicaltrials.gov

(Pomalyst or pomalidomide) AND (MM)

Nothing to report

b) www.canadiancancertrials.ca
(Pomalyst or pomalidomide)
Nothing found

c) Ontario Institute for Cancer Research
www.ontariocancertrials.ca

c) http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

(Pomalyst or pomalidomide)

Approval recommendation found

d) http://www.ema.europa.eu/ema/index.jsp?curl=/pages/home/Home_Page.jsp

(Pomalyst or pomalidomide)

Nothing found

Conference abstracts (2008-2014) via Web of Science:

1. American Society of Clinical Oncology (ASCO)— 2 identified
Topic=(Pomalyst or pomalidomide) AND Language=(English) AND Conference=(ASCO)

2. American Society of Hematology (ASH)- 52 identified (13 unique)
Topic=(Pomalyst or pomalidomide) AND Language=(English) AND Conference=(ASH)

3. European Society for Medical Oncology (ESMO) – no records found
Topic=(Pomalyst or pomalidomide) AND Language=(English) AND Conference=(ESMO)

4. European School of Haematology (ESH) – no records found
Topic=(Pomalyst or pomalidomide) AND Language=(English) AND Conference=(ESH)

5. International Myeloma Workshop – 1 identified (no unique)
Topic=(Pomalyst or pomalidomide) AND Language=(English) AND Conference=(ESH)

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