CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Ixazomib (Ninlaro) for Multiple Myeloma

June 29, 2017

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1 GUIDANCE IN BRIEF

1.1 Introduction

The objective of this review is to evaluate the safety and efficacy of ixazomib in combination with lenalidomide and dexamethasone (ILd) on patient outcomes compare to lenalidomide and dexamethasone (Ld) in patients with multiple myelomas (MM) that had at least two prior therapies or one prior therapy and have high-risk cytogenetic feature.

The appropriate comparators for ILd is Ld. Other appropriate comparators include carfilzomib plus lenalidomide and dexamethasone (CLd). The patient population under review is narrower than the Health Canada approved indication in that market authorization has been granted by Health Canada for patients with multiple myeloma who have received at least one prior therapy. The scope of the pCODR review only focuses on patients with multiple myelomas (MM) that had at least two prior therapies OR one prior therapy and have high-risk cytogenetic feature.

Ixazomib is a novel, orally administered, proteasome inhibitor. The recommended starting dose of ixazomib is 4 mg (one capsule) administered orally once a week on Days 1, 8, and 15 of a 28-day treatment cycle. Ixazomib in combination with Ld is administered until disease progression or unacceptable toxicity.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One randomized double-blind placebo-controlled trial (TOURMALINE-MM1) met the inclusion criteria.[1-5] TOURMALINE-MM1 was a phase III trial funded by Millennium Pharmaceuticals, a subsidiary of Takeda Pharmaceuticals. The aim of this trial was to examine the effect of adding ixazomib to lenalidomide and dexamethasone (ILd) combination compared to adding placebo on efficacy and safety outcomes in patients with relapsed/refractory multiple myelomas. The trial enrolled 722 patients from 26 countries with relapse or refractory multiple myelomas that had at least one prior treatment. Patients were randomized in a 1:1 ratio to receive ILd combination or placebo, Ld combination. Randomization was stratified according to the number of prior therapies, previous exposure to proteasome inhibitors, and International Staging System disease stage. Patients, investigators and independent assessors were blinded to the treatment allocation. Treatment was continued until disease progression or unacceptable toxicity.

Among 722 patient enrolled in the trial, 43% (309) had high risk cytogenetics [del(17p), t(4,14), t(14,16) and +1q21] and one prior line of treatment. As the +1q21 chromosome abnormality was added to the 2014 update of the IMWG guidelines, the +1q21 chromosome abnormality was not included in the high risk subgroup analysis within the TOURMALINE-MM1 trial publication. However, the subgroup analysis presented in this report include the +1q21 chromosome abnormality, unless otherwise stated, and therefore presents a large number of patients. Among 722 patients enrolled, 41% (297) had received at least two prior therapies. Patients in the TOURMALINE-MM1 trial were stratified based on prior lines of therapy but not based on cytogenetic features.

The baseline characteristics were well balanced in terms of age, race, ECOG status, ISS disease stage, cytogenetic profile, creatinine clearance, number of prior therapy, the proportion of patients who had stem cell transplant within the ITT population and in the subgroup analysis for the expanded high risk cytogenetics and patients who have had at

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least two prior lines of treatment. Nearly 70% of patients had prior treatment with a proteasome inhibitor, mostly with bortezomib. Fifty-five percent of patients in the ITT analysis and subgroup of patients with high risk cytogenetics had been treated with an immunomodulatory drug before. This number rose to nearly 70% in the subgroup of patients who had received at least 2 prior lines of therapy. Thalidomide was the immunomodulatory agent used in most patients. In the ITT analysis, 23% of patients were refractory to an immunomodulatory drug and 2% were refractory to a proteasome inhibitor.

ITT Results

Based on the statistical design of the trial, the first interim analysis (IA) for PFS was considered to be the final analysis in the ITT population as statistical significance was reached. This analysis was performed after a median follow-up of 14.8 months. There were 129/360 (36%) events of disease progression or death occurred in the ixazomib arm and 157/362 (43%) events in the placebo arm at the time of data cut-off on October 30, 2014. The median progression-free survival was 20.6 months in the ixazomib arm and 14.7 months in the placebo arm. The hazard ratio (HR) for disease progression or death was 0.74 [95% CI 0.59-0.94, p=0.01]. However, the supplemental appendix to the main publication (and also referenced in the FDA report) provided results from the second IA conducted after a median follow-up period of 23 months. At this second IA the hazard ratio for PFS was 0.82 [95% CI 0.67-1.0, p=0.0548].[2,6,33] Based on the statistical design of the trial, the second IA is considered to be non-inferential. The EMA report presented an analysis for PFS from IA2 that censored patients who had received alternative therapy. This additional analysis provided similar results PFS HR 0.818 95% CI 0.66-1.0), p=0.054] as the planned PFS analysis at IA2 that did not censor these patients.

After a median follow-up period of 23 months, 81/360 (23%) patients from the ixazomib arm and 90/362 (25%) patients from placebo arm have died. The hazard ratio of death was 0.87 [95% CI 0.64-1.18]. The number of deaths had not reached the level required for final analysis pre-specified by the protocol at this point of time.

The quality of life was assessed by EORTC-QLQ-C30 and EORTC-QLQ-MY20 questionnaires. The EORTC-QLQ-C30 global health score was not different between the treatment arms.

Subgroup results[7, 31]

Patients with a high-risk cytogenetic feature or had two prior therapies were the focus of this review. The key outcome summary of these two subgroups can be found in table 1. Results are based on the final analysis for PFS (first IA at 14.8 months) and IA2 (23 months) for OS. The submitter reported that median OS was not estimable at IA1 or IA2.

Table 1: Highlights of Key Outcomes based on results from the first interim analysis

	Expanded high risk cytogenetic and at least 1 prior therapy		**2+ prior therapies**	
	ILd (N=155)	**Ld (N=154)**	**ILd (N=148)**	**Ld (N=149)**
Progression-free survival, median	17.5 months	11.1 months	NE	12.9 months
HR (95%CI)	0.66 (0.47-0.93)		0.58 (0.4-0.84)	
p-value	0.02		0.003	
Overall survival, median	NE	28.6	NE	NE
HR (95%CI)	0.62 (0.4-0.96)		0.65 (0.41-1.02)	
p-value	0.03		0.057	
HrQoL				
Global health status difference from baseline (SD)	-5.59 (21.474)	-5.81 (27.589)	-7.51 (24.42)	-3.23 (27.80)
Least square mean difference (95% CI)	0.22 (-7.81 to 8.24, p=0.9573)		-4.29 (-13.62 to 5.06, p=0.366)	
Harms Outcome, n (%)				
AE grade ≥3	107 (69%)	103 (67%)	114 (77%)	113 (76%)
AE (any grade)	153 (99%)	153 (99%)	147 (99%)	148 (99%)

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	Expanded high risk cytogenetic and at least 1 prior therapy		2+ prior therapies	
	ILd (N=155)	Ld (N=154)	ILd (N=148)	Ld (N=149)
WDAE	26 (17%)	23 (15%)	24 (16%)	30 (20%)
AE = adverse event, **CI** = confidence interval, **HR** = hazard ratio, **HRQoL** = health-related quality of life, **NE** = not estimated, **SD** = standard deviation, **WDAE** = withdrawal due to adverse event *HR < 1 favours ixazomib arm				

Key Limitations/Sources of Bias

Trial Design:

- Baseline characteristics were well balanced. The only noted difference between the ITT treatment groups was the cytogenetic feature, where the ixazomib arm enrolled slightly more patients with high-risk cytogenetic abnormalities (excluding the +1q21 abnormality which was not included in the analysis presented in the main publication). However, once +1q21 patients were added into the analysis, presented in an unpublished clinical summary, the number of patients with high risk cytogenetics in the subgroup became more balanced.

Analysis of results:

- The hazard ratio for progression-free survival analysis of the ITT population was 0.74 [95% CI 0.59-0.94, p=0.01] at the first interim analysis. However, the effect size was reduced at the second interim analysis (hazard ratio 0.82, p=0.0548). Although the point estimate showed the same direction of effect, the data suggested a substantial amount of variation was still present in the data during interim analyses. Ideally we would then examine if the overall survival results corroborate with the progression-free survival analysis. However, at this time, the overall survival analysis for the ITT population was not statistically significant. Following the posting of the pERC initial recommendation, feedback was received from the submitter regarding the second interim analysis (IA2) for PFS. A new, previously un-submitted and unpublished analysis was provided by the submitter through the feedback which included censoring of data based on two factors which were considered to have contributed to the non-significant results at IA2. Censoring based on one of the factors was available to the review team in the published EMA report, while the analysis based on the combined analysis of the two factors could not be considered because these were new data previously unavailable to the review team. According to the *pCODR Procedures*, new data are not admissible at this stage in the pCODR review. Therefore the reviewers did not consider the rationale within the feedback. For the data available within the EMA report, the submitter explained that the presence of 22 (ILd) and 32 (Ld) patients who had received an alternative therapy may have contributed to the non-significant results at IA2. The Methods team reviewed these data from the EMA report. This group of patients were likely censored because they were considered to have had a protocol violation. Overall, the evidence provided in the EMA report is not very different [PFS HR 0.818 95% CI 0.67-1.0), p=0.054] from what was reported in the planned PFS analysis at IA2 that did not censor these patients. The Methods Team re-iterates the same concerns previously expressed. Mainly that, although the point estimate for PFS showed the same direction of effect, the data at IA2 suggested a substantial amount of variation is still present in the magnitude of effect in the ITT population.
- Furthermore, the magnitude of progression-free survival benefit was greater in the expanded high-risk cytogenetic and 2+ prior therapies subgroups. In both subgroups, the effect estimates were statistically significant at both interim analyses. In addition, the overall survival analysis in the expanded high-risk cytogenetic subgroup was also statistically significant. However, since the trial was not originally designed to detect

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differences within these subgroups of patients, it is difficult to determine whether the observed results were found by chance or can be reproduced in a bigger trial for this specific population. The subgroup analyses conducted in this trial should be considered hypothesis-generating, and therefore interpreted with caution.

- Given that the subgroup analyses were based on subgroups of baseline characteristics, patient overlap could occur between the subgroups. In this case, 20% of patients that had at least two prior therapies also had high-risk cytogenetic features. This suggested that part of the effect size was contributed by overlapping patients in the two subgroups.

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1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

From a patient's perspective, infections, followed by kidney problems, mobility, pain, fatigue, neuropathy, and shortness of breath are important aspects of myeloma to control. The ability to work, followed by the ability to exercise, travel, volunteer, concentrate, conduct household chores, fulfill family obligations, and spend time with family are symptoms associated with myeloma that impact or limit day-to-day activity and quality of life. According to Myeloma Canada, when it comes to treating myeloma, it is important for patients: to maintain quality of life or normal life, manage/minimize side effects, control the disease, have access to effective treatments, control symptoms, achieve or maintain remission, and prolong survival, among others. Based on no experience using ixazomib, patients responded that they were willing to tolerate some side effects. Main treatments patients used other than carfilzomib included: dexamethasone, bortezomib, lenalidomide, autologous stem cell transplant, melphalan, cyclophosphamide, pomalidomide, thalidomide, vincristine-doxorubicin-dexamethasone, and allogenic stem cell transplant. The side effects experienced with these treatments included: fatigue, neuropathy, insomnia, stomach issues, nausea, shortness of breath, pain, confusion, among others. Based on experiences to date with ixazomib, patients indicated that the side effects were tolerable. In an open-ended question, respondents were asked whether ixazomib has changed or is expected to change their long-term health and well-being. There were positive responses which included comments about being in remission, improved numbers (i.e., "*blood counts improved*"), and disease control. Responses about expectations of the treatment were also mentioned, which included comments about disease control and extended life. There were also responses stating that it was too early to tell and one response that the patient respondent is off treatment.

Provincial Advisory Group (PAG) Input

Clinical factors:

- Clarity on patients who would eligible for treatment
- Sequencing of currently available treatment and upcoming treatments

Economic factors:

- Potentially large prevalent patient population eligible for treatment

Registered Clinician Input

The clinicians identified that ixazomib would be an oral treatment option for patients with relapsed multiple myeloma. They noted that the addition of ixazomib to lenalidomide/ dexamethasone improves progression free survival, although overall survival is not yet known.

Summary of Supplemental Questions

The pCODR Clinical Guidance Panel (CGP) identified that carfilzomib, lenalidomide, dexamethasone (CLd) combination therapy is a relevant comparator for ixazomib, lenalidomide, dexamethasone (ILd) combination therapy. In the absence of head to head trials comparing these two treatment regimens, the CADTH-pCODR Methods team provided a critical appraisal of a manufacturer provided network meta-analysis that evaluated the

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relative efficacy of ILd versus other selected therapies based on the outcomes such as progression-free survival (PFS) and overall survival (OS) in patients with relapsed/refractory multiple myelomas that were treated with at least one prior therapy. Given the reimbursement request submitted to CADTH-pCODR, the focus of this critical appraisal was on indirect evidence related to patients with 1) high-risk cytogenetic and who have had at least one prior line of therapy and 2) patients who had at least 2 prior lines of therapy. Within the submitted NMA, results specific to the subgroup of patients high risk cytogenetics were available for PFS. Overall survival results were only available based on ITT analysis of the available trials included in the network. There was no direct or indirect evidence provided addressing the subgroup of patients who have had at least 2 prior lines of therapies.

Two RCTs (ASPIRE and TOURMALINE-MM1) were included in the indirect comparison between ILd combination and CLd combination to determine comparative efficacy in the subgroup of patients with high-risk cytogenetic. Based on the ASPIRE trial publication 13% (n=100 total) of patients were reported to have high risk cytogenetics (patients with the genetic subtype t(4;14) or t(14;16) or with deletion 17p in 60% or more of plasma cells, according to central review of bone marrow samples obtained at study entry)[37]. Therefore the comparison in this subgroup of patients is based on a small number of patients. Nine RCTs were included in the NMA for analysis for overall survival. The evidence used to estimate the hazard ratio was based on the subgroup of patients with high risk cytogenetics but rather the use of the ITT population from the included RCTs.

The results reported that there was no significant difference between ILd combination and CLd combination in terms of PFS. The results of this analysis were made non disclosable by the manufacturer. No significant difference in overall survival was observed comparing ILd with CLd.

The results of this analysis were also made non disclosable by the manufacturer.
There was only one trial included per direct comparison and only one path to indirectly compare carfilzomib with ixazomib. Therefore, it was not possible to assess heterogeneity and inconsistency. Due to the concern of effect modification in some transitivity criteria, in addition to the absence of heterogeneity and inconsistency assessments, the quality of evidence was low for the indirect comparison of carfilzomib and ixazomib. The 95% credible interval in the progression-free survival and overall survival analyses were quite wide, which suggested a high level of uncertainty and the lack the statistical power to detect any differences between carfilzomib and ixazomib in both analyses. On the other hand, this indirect comparison did not provide any additional information for the clinical effectiveness assessment.

See section 7.2 for more information.

Comparison with Other Literature

Both the FDA and EMA evaluated adding ixazomib to Lenalidomide and dexamethasone combination in multiple myeloma patients with at least one prior therapy. Both agencies included only TOURMALINE-MM1 in their report. The findings were similar to the findings in this report. Both agencies raised concern about the level of uncertainty in progression-free survival between the first and second interim analyses. However, both agencies concluded that the evidence was sufficient to support the clinical efficacy of ixazomib in patients with multiple myeloma that had at least one prior therapy regardless of the cytogenetic feature and conclusions were not made specifically for the subgroup of patients with high risk cytogenetics or patients who have had at least two prior lines of therapy.

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Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

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1.2.3 Factors Related to Generalizability of the Evidence

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="2">Population</td><td>Performance status</td><td>The majority of patients (94%) had ECOG score of 0 or 1 in both treatment groups. A small minority of patients had an ECOG PS of 2.

<table>
<tr><td colspan="3">ECOG score, n(%)</td></tr>
<tr><td></td><td>Ixazomib n=360</td><td>Placebo n=362</td></tr>
<tr><td>0</td><td>180/354 (51%)</td><td>170/358 (47%)</td></tr>
<tr><td>1</td><td>156/354 (44%)</td><td>164/358 (46%)</td></tr>
<tr><td>2</td><td>18/354 (5%)</td><td>24/358 (7%)</td></tr>
<tr><td colspan="3">Expanded High risk cytogenetics, n(%)</td></tr>
<tr><td>0</td><td>83 (54)</td><td>72 (47)</td></tr>
<tr><td>1</td><td>63 (41)</td><td>69 (45)</td></tr>
<tr><td>2</td><td>7 (5)</td><td>9 (6)</td></tr>
<tr><td colspan="3">Two prior lines of therapy, n(%)</td></tr>
<tr><td>0</td><td>59 (40)</td><td>58 (39)</td></tr>
<tr><td>1</td><td>77 (52)</td><td>74 (50)</td></tr>
<tr><td>2</td><td>10 (7)</td><td>15 (10)</td></tr>
</table></td><td>Is the trial result generalizable to patients with an ECOG score of 2 or higher?</td><td>While data on the efficacy and safety of using ixazomib combination therapy in patients with an ECOG PS of 2 or greater was limited, the CGP agreed that use of this combination therapy in this population may be appropriate. Patients with relapsed/refractory multiple myeloma often have symptoms related to the disease which may improve with reduction of disease burden. If that symptoms is a fracture, or symptomatic anemia, then ECOG can drop to 3 very easily. Myeloma often responds to therapy, and as hemoglobin can rise, or pain settle from fracture, patients PS can likewise improve with treatment.</td></tr>
<tr><td>Renal function</td><td>Patients with severe renal impairment were excluded from the TOURMALINE-MM1 trial.</td><td>Does the exclusion of patients with severe renal impairment limit the interpretation of trial results with the respect to target population?</td><td>Although the study limited enrollment to patients with a CrCl of ≥ 30 ml/min per 1.73 m^2 of body-surface area, use of ixazomib in patients with renal impairment would be a reasonable consideration. Ixazomib is not renally excreted, and therefore, adding this drug to dose-adjusted lenalidomide would be appropriate.[8] A priori ixazomib dose reduction may be required depending on the severity of renal impairment, as per the product monograph.[9] Lenalidomide dosing would need to be adjusted as per the product monograph.</td></tr>
</table>

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	Hepatic function	Patients with inadequate hepatic function were excluded.	Does the exclusion of patients with inadequate hepatic function limit the interpretation of trial results with the respect to target population?	It would be reasonable to allow clinicians to cautiously select patients with hepatic dysfunction to access this treatment, recognizing that such patients would have been ineligible for the key trial but might still benefit from this therapy.[10] *A priori* ixazomib dose reduction may be required depending on the severity of hepatic impairment, as per the product monograph.[9]
	Cytogenetic feature	One of the proposed population require test of cytogenetic feature	Is the test of cytogenetic feature reliable? Is it routinely performed in current practice?	The t(4;14), t(14;16), del(17p) and +1q FISH assays are reliable and are routinely performed in clinical practice.
	Expended cytogenetic feature	The definition of high-risk cytogenetic was expanded after the publication to include +1q21	Does the expanded definition align with the definition commonly accepted in Canada?	The International Myeloma Working Group has most recently defined high-risk cytogenetic features of myeloma to include one or more of the following: FISH –detected t(4;14), t(14;16), t(14;20), del(17p), or gain(1q); non-hyperdiploid karyotype; high risk gene expression profile signature; and del(13) detected by conventional cytogenetics[12].

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Comparator	**Standard of care**	Only Len-dex combination was used as the comparator in the trial.	Can the result be used to compare with other current therapy options?	Other drugs have been studied in combination with lenalidomide and dexamethasone to treat relapsed and refractory myeloma, including carfilzomib which has previously been reviewed by pCODR and other drugs (e.g. daratumumab, elotuzumab) which have not yet been reviewed by pCODR in this setting. Given the absence of direct comparison, it is not clear that one of these agents is superior to another, and in particular it is not clear whether ixazomib or carfilzomib is the more efficacious agent of the two. A Network meta-analysis was presented to help determine the comparative efficacy of ixazomib combination therapy compared to carfilzomib combination therapy. A number of limitations were identified in the presented results and therefore caution must be used in interpreting these results.
Outcomes	**Composite outcome**	PFS is a composite outcome of progression and death.	MM patients might live for an extended period of time after the first relapse. Does combining death and disease progression in this outcome affect the interpretation of result?	Progression-free survival is felt to be a clinically relevant and valid endpoint for myeloma trials, given that the use of subsequent therapy is likely to impact overall survival. PFS has been used in several previous pCODR myeloma drug reviews.

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1.2.4 Interpretation

Multiple myeloma is an incurable plasma cell neoplasm that makes up 1.3% of all new cancers in Canada. In 2016, it is estimated that 2700 Canadians were diagnosed with myeloma, and 1450 patients died 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 age-standardized five-year net survival rate for Canadian patients between 2006-2008 (excluding Quebec) was 42%.[11]

Patients can be stratified into groups with differing prognosis based on clinical and laboratory parameters. To date there has not been definitive evidence from randomized trials that has identified a superior treatment strategy which differs based on patient risk stratification. While existing evidence suggests that proteasome inhibitors and newer immunomodulatory drugs partly overcome the adverse prognostic significance of high risk disease features, especially when used in combination, the same therapies are generally recommended for patients without high-risk disease features.[12]

Regardless of the choice and duration of initial therapy, myeloma will eventually relapse in the vast majority and further therapy will be required. There is no single clear choice of therapy in relapsed and/or refractory myeloma. The choice of agents used in this setting will depend on the outcomes with the regimens used in prior lines of therapy, the condition of the patient, the expected tolerance of adverse effects, and the availability of treatment options.

One large, randomized trial comparing lenalidomide and dexamethasone with ixazomib or placebo for patients with relapsed and refractory myeloma has demonstrated a statistically and clinically significant improvement in progression-free survival (PFS) with the addition of ixazomib. This finding was published as the "final" analysis in the *New England Journal of Medicine*. Subsequently, a second interim analysis for PFS was done which showed a smaller PFS benefit which was of borderline statistical significance, lessening certainty regarding the magnitude of benefit of ixazomib. Although the trial did not demonstrate an overall survival benefit to ixazomib, progression-free survival is considered a clinically important and valid primary endpoint in studies of myeloma therapy and the use of subsequent lines of therapy in this incurable malignancy makes it difficult to discern an overall survival benefit from one line of therapy.

Subsets of patients in the trial with high risk disease (based on a post hoc analysis) and patients with more than one prior line of therapy were found to have a progression-free survival benefit and trended towards overall survival benefit with the addition of ixazomib. The published manuscript defined high risk cytogenetics to include at least one of del(17p), t(4;14) and t(14;16); in the submission, the high risk group was expanded to include previously unpublished data incorporating +1q21 in addition to the other three markers. These markers are reliably used in Canadian clinical practice for patient risk stratification. The study was not powered for these subset analyses, and cautious interpretation is required given the number and iterative nature of the subset analyses presented in the submission. Additionally, there is about 20% overlap between these two subsets, and the extent to which the overlap population drives the result in each subgroup is not presented. With these caveats, it appears that these subsets of patients derive benefit to the three-drug regimen relative to the ITT study population and that the benefit of ixazomib was consistent across most of the subgroups presented. Data (again from post hoc analysis for the expanded high risk population) presented in the submission suggest that the benefit is greater in these two subsets of patients relative to those without high risk cytogenetics and with only one prior line of therapy, but this comparison is not definitive. Additionally, the CGP agreed that the subgroup of patients with 2 or more prior lines of therapy was pre-specified, as patients were stratified on this factor, while the

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subgroup with expanded high risk was not. Despite this, pre-specifying for a subset analyses does not mean that the study was adequately powered to detect a true difference in these populations neither does it mean those analyses have been adjusted for multiple comparisons. The CGP therefore agreed that uncertainty remained related to the true magnitude of benefit in these two subgroups.

The addition of ixazomib to lenalidomide and dexamethasone was reasonably well tolerated in this trial, with manageable toxicity and no obvious detrimental impact on quality of life.

There are several other drug therapies for relapsed myeloma that have been demonstrated in randomized trials to improve PFS when added to lenalidomide (Revlimid) and dexamethasone (Rd). These include intravenous (IV) carfilzomib (KRd), IV elotuzumab and IV daratumumab. In the front line setting, the addition of IV bortezomib to lenalidomide and dexamethasone (VRd) has been shown to improve overall survival in one randomized trial. It is not clear whether one of these regimens is superior to another. Direct randomized comparisons between these various regimens are unlikely to take place in the setting of relapsed myeloma, although the KRd and VRd regimens are being compared in the front line setting. Carfilzomib and dexamethasone has been compared to bortezomib and dexamethasone in a randomized trial, demonstrating superiority for the carfilzomib regimen, but no direct comparisons of these regimens with ixazomib-containing or three-drug regimens have taken place.

Ixazomib, lenalidomide and dexamethasone is an oral drug regimen, distinguishing it from other proven three-drug combinations involving lenalidomide and dexamethasone in terms of patient convenience and resource utilization ("chair time").

1.3 Conclusions

The Clinical Guidance Panel concluded that there ***may be*** a net overall clinical benefit to adding ixazomib in combination with lenalidomide and dexamethasone in the treatment of relapsed and refractory myeloma, with 1-3 prior lines of therapy and regardless of cytogenetic risk profile, based on one high-quality randomized controlled trial that demonstrated a clinically and statistically significant benefit in progression-free survival as compared to the previous standard regimen of lenalidomide and dexamethasone, with a manageable adverse event profile and a convenient oral route of administration. A second interim analysis for PFS performed subsequent to the one in the published manuscript demonstrated a smaller PFS benefit to ixazomib, of borderline statistical significance for the ITT population.

Based on the submitted request, it has been requested that the evidence for this regimen be reviewed specifically for patients who have had at least one prior line of therapy and high risk cytogenetic abnormalities or patients who have had at least two prior lines of therapy. The available evidence in these subgroups is limited to a post hoc subset analysis of the aforementioned trial. The results of this analysis suggests that these subsets of patients derive PFS and possibly OS benefit from ixazomib. The Clinical Guidance Panel concluded that there ***may be*** a net overall clinical benefit to adding ixazomib to lenalidomide and dexamethasone for these subsets of patients based on this post hoc analysis. While the various analyses presented all trend in the same direction showing better PFS for the ixazomib treated patients, there is uncertainty regarding the magnitude of the effect in the subgroup analysis given the multiple analyses done and the post hoc nature of the subset analyses in the expanded high risk subgroup.

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

- Other drugs have been studied in combination with lenalidomide and dexamethasone to treat relapsed and refractory myeloma, including carfilzomib which has previously been

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reviewed by pCODR and other drugs (e.g. daratumumab, elotuzumab) which have not yet been reviewed by pCODR in this setting. Given the absence of direct comparisons, it is not clear that one of these agents is superior to another, and in particular it is not clear whether ixazomib or carfilzomib is the more efficacious agent of the two. A Network meta-analysis was presented to help determine the comparative efficacy of ixazomib combination therapy compared to carfilzomib combination therapy. A number of limitations were identified in the presented results and therefore caution must be used in interpreting these results. From a purely clinical perspective, a reasonable option is to make both agents available to patients and clinicians, and give them the option to choose one of these two drugs to add to lenalidomide and dexamethasone. It would be reasonable to allow patients to switch from one regimen to the other if there were adverse effects that it was thought could be ameliorated by the switch, but to otherwise restrict access to one regimen or the other in the relapse setting.

- The CGP re-iterated that while the various analyses presented (both ITT and subgroup analysis) all trend in the same direction showing better PFS for the ixazomib treated patients, there is uncertainty regarding the magnitude of the effect in the subgroup analysis given the multiple analyses done and the post hoc nature of the subset analyses.
- Treatment with ixazomib in combination with lenalidomide and dexamethasone could reasonably be restricted to patients whose disease is not demonstrably refractory to lenalidomide (including lenalidomide maintenance therapy) or a proteasome inhibitor.
- It would be reasonable to allow clinicians to cautiously select patients with hepatic or renal dysfunction or with poor performance status to access this treatment, recognizing that such patients would have been ineligible for the key trial but might still benefit from this therapy.
- Induction, stem cell transplant, plus post-transplant consolidation and/or maintenance treatment is all considered as one line of therapy.
- Patients who were eligible for transplant and who then relapse would be eligible for ixazomib combination therapy.

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2 BACKGROUND CLINICAL INFORMATION

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

2.1 Description of the Condition

Multiple myeloma is an incurable plasma cell neoplasm that makes up 1.3% of all new cancers in Canada. In 2016, it is estimated that 2700 Canadians were diagnosed with myeloma, and 1450 patients died 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 age-standardized five-year net survival rate for Canadian patients between 2006-2008 (excluding Quebec) was 42%.[11]

The diagnosis of myeloma is made based on excess clonal plasma cells in the bone marrow and/or very high levels of secreted monoclonal protein in the blood. 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. For some patients without end organ damage, observation is appropriate and no therapy is initially required. Most patients are either symptomatic at diagnosis or are highly likely to soon develop symptoms; these patients require immediate therapy.[13]

Patients can be stratified into groups with differing prognosis based on clinical and laboratory parameters. The International Myeloma Working Group has most recently defined high-risk cytogenetic features of myeloma to include one or more of the following: FISH –detected t(4;14), t(14;16), t(14;20), del(17p), or gain(1q); non-hyperdiploid karyotype; high risk gene expression profile signature; and del(13) detected by conventional cytogenetics.[12] Other clinical features of high risk myeloma include elevated serum beta-2-microglobulin and LDH levels. The current, revised international staging system (R-ISS) for myeloma identifies three stages, the highest risk stage being those 10% of patients with Beta-2-microglobulin >/=5.5 mg/L and at least one of the following: elevated serum LDH, t(4;14), t(14;16), del(17p).[14]

To date there has not been definitive evidence from randomized trials that has identified a superior treatment strategy which differs based on patient risk stratification. While existing evidence suggests that proteasome inhibitors and newer immunomodulatory drugs partly overcome the adverse prognostic significance of high risk disease features, especially when used in combination, the same therapies are generally recommended for patients without high-risk disease features.[12] Nevertheless, some expert clinicians have interpreted the existing evidence to recommend treating patients differently based on cytogenetic profile, for example offering bortezomib rather than lenalidomide as maintenance therapy for patients with t(4;14) myeloma;[15] this practice is applied by some Canadian clinicians.

2.2 Accepted Clinical Practice

Systemic therapy is the primary modality of treatment. Alkylators (melphalan or cyclophosphamide), proteasome inhibitors (ixazomib, bortezomib or carfilzomib), immunomodulatory drugs (thalidomide, pomalidomide or lenalidomide) and corticosteroids (prednisone or dexamethasone) have proven to be highly effective therapies for myeloma, and the utilization of these drugs have improved survival of myeloma patients.[16] There is no consensus with respect to the optimal sequencing or combination of drugs that should be used.

For fit patients, an autologous stem cell transplant (ASCT) can be considered as part of the initial therapy of myeloma and substantially improves life expectancy. However, the toxicity of this treatment precludes its use in less fit patients. Choosing the appropriate patients for ASCT is at

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the discretion of the treating physician and approximately half of patients are transplant eligible. Prior to receiving high dose melphalan chemotherapy conditioning for the transplant, three or four cycles of systemic induction therapy is used to control the disease, improve the health of the patient, and clear the bone marrow to allow for easier stem cell collection. In Canada, induction is usually with bortezomib, cyclophoaphamide and dexamethasone. Patients receive one or sometimes two cycles of high dose chemotherapy with stem cell rescue as part of front line treatment. Following stem cell transplant, further consolidation therapy is sometimes given; an indefinite course of maintenance therapy with lenalidomide or bortezomib is often given with the intent to prolong remission duration and survival.[17,18] The administration of induction therapy, high dose chemotherapy with autologous stem cell transplant, and post-transplant consolidation and/or maintenance therapy is all considered as being part of first-line treatment.

Current standard frontline systemic therapy regimens in Canada for transplant-ineligible patients include combinations of bortezomib with an alkylating agent (melphalan or cyclophosphamide) and a corticosteroid; or lenalidomide and dexamethasone.[19] While recent evidence supports the use of bortezomib, lenalidomide and dexamethasone as a standard 3-drug frontline regimen, this combination has not yet been evaluated by pCODR and is not yet routinely available in most jurisdictions.[20]

It seems generally that continuous therapy prolongs remission duration as compared to a more defined duration of therapy.[21] Many patients will therefore continue with frontline therapy until the disease demonstrates itself to be relapsed and/or refractory to the current treatment. Other patients will discontinue frontline therapy while still in remission, without the disease being demonstrably refractory to any drugs, in order to have a reprieve from the adverse effects of treatment.

Regardless of the choice and duration of initial therapy, myeloma will eventually relapse in the vast majority and further therapy will be required. There is no single clear choice of therapy in relapsed and/or refractory myeloma. The choice of agents used in this setting will depend on the outcomes with the regimens used in prior lines of therapy, the condition of the patient, the expected tolerance of adverse effects, and the availability of treatment options. Although patients are often not offered therapy with drugs that have been part of a regimen to which the disease has become refractory, there is evidence that combining such agents sometimes induces responses, particularly in the case of combining proteasome inhibitors and immunomodulatory drugs.[22]

2.3 Evidence-Based Considerations for a Funding Population

Ixazomib is currently approved by Health Canada for use in patients with relapsed multiple myeloma, in combination with lenalidomide and dexamethasone, who have received at least one prior therapy. The population studied in the key clinical trial under consideration here includes patients with relapsed and/or refractory multiple myeloma who have previously failed one to three lines of systemic therapy and have an ECOG score of 0 to 2. Patients were required to have adequate renal function (creatinine clearance of at least 30 mL/min/1.73 m2) and limited or no peripheral neuropathy (grade 0 or grade I without pain). Patients could not have disease that was refractory to a proteasome inhibitor or lenalidomide. Patients would previously have been considered eligible for standard therapy with lenalidomide and dexamethasone. Here, we are considering whether such patients should be treated with the combination of lenalidomide, dexamethasone and ixazomib. We are reviewing the efficacy of this treatment in the entire population of patients that were enrolled in this clinical trial, as well as the subset of patients with specific high-risk features including at least 2 prior lines of therapy and/or high risk cytogenetic markers (t(4;14), t(14;16), del(17p) and/or gain(1q21)).[2] Takeda has requested that we review their request for funding of ixazomib specifically in this high-risk subset.

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2.4 Other Patient Populations in Whom the Drug May Be Used

The combination of ixazomib, lenalidomide and dexamethasone could potentially be considered as treatment for patients who have received more than 3 prior lines of therapy; for those with an ECOG performance status of greater than 2; for those with creatinine clearance of less than 30 mL/min/1.73 m2; for those with neuropathy that is painful or greater than grade I; and for patients whose disease is refractory to another proteasome inhibitor and/or lenalidomide. It is reasonable to consider these patient populations within the scope of this review.

Ixazomib is being investigated, alone or in combination with many other drugs, in various other settings for the treatment of myeloma, including as pre-transplant induction therapy; post-transplant consolidation or maintenance therapy; and as part of frontline therapy for transplant-ineligible patients. Ixazomib is also being considered, alone or in combinations other than with lenalidomide and dexamethasone, for relapsed or refractory myeloma. At present, data from phase III trials is not available for evaluation of the efficacy of ixazomib in these settings; evaluating the use of ixazomib for these indications is beyond the scope of this review.

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3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Myeloma Canada provided input on ixazomib (Ninlaro) for the treatment of adult patients with multiple myeloma who have received at least one prior therapy and have high-risk cytogenetics, or have received at least two prior therapies. Their input is summarized below.

Unless otherwise specified, the information in this report under sections: 3.1.1 Experiences Patients Have with Multiple Myeloma, 3.1.2 Patients' Experiences with Current Therapy for Multiple Myeloma, and 3.2.1 Patient Expectations for Ixazomib are derived from a Myeloma Canada survey directed to patients (Survey 1) and the information under section 3.1.3 Impact of Multiple Myeloma on Caregivers is based on a Myeloma Canada survey directed to caregivers (Survey 2). The surveys were conducted online from August 15-31, 2016. The surveys asked questions about the impact of myeloma on the lives of patients and caregivers and the effect of treatments on their myeloma. The surveys also included specific questions directed to patients and caregivers who have used carfilzomib (Kyprolis) to treat their myeloma; however, the responses to these questions were not included in this report.

A total of 344 patients responded to the patient survey (Survey 1). Among these respondents, 238 were from Canada (representing each province, except New Brunswick and none of the respondents were from the territories), 104 were from the United States and 2 were from Israel.

A total of 123 caregivers responded to the caregiver survey (Survey 2). Among these respondents, 82 were from Canada (representing each province, except New Brunswick, Prince-Edward-Island and none of the respondents were from the territories), 40 were from the United States and 1 was from Australia.

Two additional online Myeloma Canada surveys (Survey 3 and Survey 4) were conducted from May 24 to June 10, 2016 and then another from November 15 to December 2, 2016. One survey was directed to myeloma patients (Survey 3) who had experience with ixazomib and the other survey was directed to caregivers of patients who have used the treatment (Survey 4). These two additional surveys were sent to myeloma patient mailing lists (Myeloma Canada and International Myeloma Foundation) in the Canada and the US.

The patient survey (Survey 3) had a total of 35 respondents, who used ixazomib in combination with dexamethasone and lenalidomide; of which 26 respondents were from the United States, 5 from Alberta, 2 from British Columbia and 1 each from New Brunswick and Newfoundland. The analysis of Survey 3 is reflected in section 3.2.1 Patient Expectations for and Experiences to Date with Ixazomib.

The caregiver survey (Survey 4) had a total of 4 respondents, who provided care to a patient who used ixazomib; of which 3 respondents were from the United States and 1 from Newfoundland. The analysis of these 4 respondents is included in section 3.1.3 Impact of Multiple Myeloma on Caregivers.

In addition to the online survey, a total of 7 patients who had experience with ixazomib and provided their email address, were interviewed by telephone. A summary of their responses is provided in this report.

Note: In all open-ended questions, the responses have been grouped into categories with the percentage of responses indicated. In some cases, the total does not add up to 100% due to responses falling into more than one category (i.e., the total is more than 100% as respondents were able to select more than one answer).

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From a patient's perspective, infections, followed by kidney problems, mobility, pain, fatigue, neuropathy, and shortness of breath are important aspects of myeloma to control. The ability to work, followed by the ability to exercise, travel, volunteer, concentrate, conduct household chores, fulfill family obligations, and spend time with family are symptoms associated with myeloma that impact or limit day-to-day activity and quality of life. According to Myeloma Canada, when it comes to treating myeloma, it is important for patients: to maintain quality of life or normal life, manage/minimize side effects, control the disease, have access to effective treatments, control symptoms, achieve or maintain remission, and prolong survival, among others. Based on no experience using ixazomib, patients responded that they were willing to tolerate some side effects. Main treatments patients used other than carfilzomib included: dexamethasone, bortezomib, lenalidomide, autologous stem cell transplant, melphalan, cyclophosphamide, pomalidomide, thalidomide, vincristine-doxorubicin-dexamethasone, and allogenic stem cell transplant. The side effects experienced with these treatments included: fatigue, neuropathy, insomnia, stomach issues, nausea, shortness of breath, pain, confusion, among others. Based on experiences to date with ixazomib, patients indicated that the side effects were tolerable. In an open-ended question, respondents were asked whether ixazomib has changed or is expected to change their long-term health and well-being. There were positive responses which included comments about being in remission, improved numbers (i.e., "*blood counts improved*"), and disease control. Responses about expectations of the treatment were also mentioned, which included comments about disease control and extended life. There were also responses stating that it was too early to tell and one response that the patient respondent is off treatment.

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

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Multiple Myeloma

When Myeloma Canada asked patient respondents to rate on a scale of 1-5, how important it is to control various aspects of myeloma, patient respondents indicated that infections were the most important, followed by kidney problems, mobility, pain, fatigue, neuropathy and shortness of breath. Based on the responses below, Myeloma Canada expressed that all aspects were important to very important.

	1 - Not important	2	3	4	5 - Very important	N/A	Total
Infections	0.34% 1	1.34% 4	4.36% 13	10.40% 31	83.22% 248	0.34% 1	298
Kidney problems	2.01% 6	1.34% 4	3.68% 11	9.36% 28	80.60% 241	3.01% 9	299
Mobility	0.34% 1	1.01% 3	4.70% 14	21.14% 63	70.81% 211	2.01% 6	298
Pain	0.67% 2	1.67% 5	9.03% 27	20.07% 60	66.56% 199	2.01% 6	299
Fatigue	0.00% 0	1.71% 5	10.92% 32	20.48% 60	65.87% 193	1.02% 3	293

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	1 - Not important	2	3	4	5 - Very important	N/A	Total
Neuropathy	0.33% 1	2.34% 7	9.70% 29	21.07% 63	64.55% 193	2.01% 6	299
Shortness of breath	1.01% 3	2.03% 6	13.85% 41	18.92% 56	62.16% 184	2.03% 6	296

When Myeloma Canada asked patient respondents to rate on a scale of 1-5, how much symptoms associated with myeloma impact or limit day-to-day activity and quality of life, patient respondents indicated that their ability to work was most affected, followed by the ability to exercise, travel, volunteer, concentrate, conduct household chores, fulfill family obligations, and spend time with family. Based on the responses below, Myeloma Canada expressed that symptoms associated with myeloma have a higher than neutral impact.

Ability to:	1 - Not at all	2	3	4	5 - Significant impact	N/A	Total
Work	10.23% 31	14.19% 43	16.83% 51	14.19% 43	29.70% 90	14.85% 45	303
Exercise	8.61% 26	19.21% 58	24.17% 73	24.83% 75	21.85% 66	1.32% 4	302
Travel	13.25% 40	16.23% 49	27.15% 82	17.88% 54	24.17% 73	1.32% 4	302
Volunteer	16.33% 49	18.00% 54	23.33% 70	18.33% 55	19.00% 57	5.00% 15	300
Concentrate	12.67% 38	24.33% 73	23.00% 69	21.00% 63	17.33% 52	1.67% 5	300
Conduct household chores	14.62% 44	22.26% 67	29.24% 88	20.60% 62	12.62% 38	0.66% 2	301
Fulfill family obligations	18.94% 57	25.58% 77	27.91% 84	13.62% 41	11.96% 36	1.99% 6	301
Spend time with family and friends	22.85% 69	25.17% 76	24.83% 75	14.57% 44	11.92% 36	0.66% 2	302

The following are quotes reported by Myeloma Canada help to illustrate the effect of myeloma on patients:

- *"Extra care when going out into the public to minimize the potential exposure to disease and germs - easier to get sick, takes longer to get better."*
- *"My emotional well being is significantly impacted due to treatment which includes steroids."*
- *"The impact is cyclical depending on where I am in my disease control, sometimes all of these things (the list above) see(m) very difficult and sometimes not as much."*
- *"Diarrhea limits my day plan - have to plan around it all the time."*

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- *"Ability to work n/a as Retired, but often unable to do what I used to enjoy e.g. Woodworking, "outside chores".*
- *Certainly could not have done my job - renovations, building etc."*

3.1.2 Patients' Experiences with Current Therapy for Multiple Myeloma

When Myeloma Canada asked patient respondents in an open-ended question, "what is important to you when it comes to treating your myeloma?" A total of 261 patients provided a response. According to Myeloma Canada, the responses fell into the following categories (starting with the most popular): to maintain quality of life or normal life (36%), (followed by) manage/minimize side effects (20%), control the disease (19%), access to effective treatments (15%), control symptoms (13%), achieve or maintain remission (7%), prolong survival (7%), access to a skilled medical team (6%), to be cured (5%), affordable treatments (3%), disease status (2%), maintain physical fitness (1%), minimal use of drugs (0.5%), and (lastly) to feel hopeful (0.5%).

In an open-ended question from Survey 3, when Myeloma Canada asked patients who used ixazomib in combination with dexamethasone and lenalidomide what is important, when it comes to treating myeloma, a total of 21 patients responded: maintain quality of life (n=7), live normal life (n=4), disease control (n=4), extended life (n=3), minimal side effects (n=3), to get better (n=2), avoid another transplant (n=1), convenience (n=1), results over side effects (n=1), and effective treatment (n=1). Of note, the total is more than 21, because some respondents provided more than one item. Below are verbatim quotes to illustrate their responses:

- *"Results. I will take any side effects to achieve results."*
- *"Quality of life - hoping to manage the disease for a long time. I was diagnosed in 12/12 at age 54. I did not have any bone disease or organ damage but very high m spike and a lot of bad proteins in my blood. I am higher risk and know I need aggressive treatment and monitoring but so far quality of life as been very high."*
- *"Minimal side effects while killing cancer! "*
- *"That I can live as normal as possible."*

Also, when Myeloma Canada asked patient respondents to rate the importance of access to effective treatments for myeloma on a scale of 1-5, with 1 being "not important" and 5 being "very important", a total of 97% of patients selected 5 – "very important". N = 294.

In addition, when Myeloma Canada asked patient respondents to rate the importance for the respondent and his/her physician to have choice based on each drug's known side effects on a scale of 1 -5, with 1 being "not important" and 5 being "very important", a total of 86% of patients selected 5 – "very important". N = 294.

Moreover, a total of 89% of patient respondents reported that "improvement to quality of life" was a "very important" consideration with any treatment for myeloma. N = 294.

When Myeloma Canada asked Canadian patient respondents in a multiple choice question about the financial implications of their treatment for myeloma, a total of 51% of patients selected drug costs, as well as, parking costs, followed by travel costs (33%), lost income due to work absence (32%), drug administration fees (17%), medical supply costs (16%), and accommodations costs (15%). A total of 25% of patients responded that they had no financial implications related to treatment for myeloma. N = 202. Of note, the total is greater than 100%, since respondents were able to select more than one answer; as well, only Canadian respondents were included in this question analysis.

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When Myeloma Canada asked Canadian patient respondents in an open-ended question about hardships accessing treatment for myeloma, the responses fell into the following categories: (starting with the most popular) no, not that I'm aware of, not so far and not yet (74%), yes (23%), too soon to tell (1%) and N/A (2%). The "yes" responses included: denied treatment (6%), drug not covered (5%), limited to covered treatments (3%), travel to treatment (2%), cost of drugs (2%), access to physician (1%), access to available bed (1%), treatment not available (1%), and waited for treatment approval(1%). N = 155. Of note, only Canadian responses were included in this question analysis.

Myeloma Canada reported that the main treatments patients used other than carfilzomib included: dexamethasone (84%), bortezomib (77%), lenalidomide (71%), autologous stem cell transplant (60%), melphalan (57%), cyclophosphamide (44%), pomalidomide (17%), thalidomide (16%), vincristine-doxorubicin-dexamethasone (9%), and allogenic stem cell transplant (9%). N = 295. Of note, the total is greater than 100%, since respondents were able to select more than one answer. Selected from a list, the side effects experienced by patients with these treatments included: fatigue (88%), neuropathy (62%), insomnia (57%), stomach issues (48%), nausea (46%), shortness of breath (43%), pain (38%), confusion (30%), does not apply to me as I have yet to be treated (2%), and I don't know or can't remember (0.3%). Under "other" an additional 7% of patient respondents cited stomach related issues (such as diarrhea and constipation) as a side effect, followed by skin rash (3%), cramps (2%), and emotional issues (2%). N = 295. Of note, the total is greater than 100%, since respondents were able to select more than one answer.

3.1.3 Impact of Multiple Myeloma and Current Therapy on Caregivers

When Myeloma Canada asked caregiver respondents in Survey 2 to rate on a scale of 1-5, with 1 = "not at all" and 5 = "significant impact", how much caring for someone with myeloma limits their day-to-day activity and quality of life, caregivers indicated that their ability to travel was most affected, followed by the ability to volunteer, spend time with family and friends, to concentrate, fulfill family obligations, to work, exercise, and to conduct household chores. The total number of caregiver respondents for this answer ranged from 115 to 120.

When Myeloma Canada asked caregiver respondents in Survey 4 in an open ended question about challenges encountered while helping to manage treatment side effects for the person they are caring for, the caregiver respondents provided the following verbatim responses:

- *"Doesn't seem to have any major side effects the dexamethasone is worse."*
- *"Tired so I give it to him at night."*
- *"My husband developed shortness of breath. Not sure if this is from Ninlaro since it developed after taking Carfilzomib and didn't go away."*
- *"Two to Three days after taking Ninlaro and Dex while taking Revlimid she crashes and is very tired for 2 days."*

Of note, Ninlaro = ixazomib, Dex = dexamethasone, and Revlimid = lenalidomide.

In another open ended question in Survey 4, caregiver respondents were asked if there is anything else about ixazomib that they would like Myeloma Canada to know and include. Two respondents provided the following responses:

- *"great that it can be taken by pill at home"*
- *"it gives us a sense of control, like the cancer is not controlling our life"*
- *"He has an aggressive form of Multiple Myeloma and this drug is being prescribed after three stem cell transplants. It gives us hope because it's keeping his disease in check."*

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3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Ixazomib

Based on no experience using ixazomib

In Survey 1, patient respondents were asked if they were to consider taking a new treatment for their myeloma, to rate on a scale of 1-5 how important it is to bring about improvement in their physical condition. A total of 82% patient respondents rated this as "extremely important". N = 251.

A total of 93% of patient respondents also reported that the expected benefit (such as lack of disease progression) from a new treatment was "extremely important". N = 250.

When Myeloma Canada asked patient respondents to rate on a scale of 1–5, if you were to consider taking a new treatment for your myeloma, how important it is for you and your physician to have choice in deciding which drug to take? A score of 1 was "not important as long as there is a drug" and 5 was "very important to choose which drug would be better suited for me, a total of 91% patient respondents selected 5. N = 251.

Patient respondents were asked to rate on a scale of 1 – 5, if you were to consider taking a treatment proven to be effective for your myeloma what severity of side effects are you willing to tolerate (for example: nausea, fatigue, diarrhea, fever, shortness of breath, constipation, anemia, and neuropathy). A score of 1 was "no side effects" and 5 was "significant side effects." According to Myeloma Canada, patients responded that they were willing to tolerate some side effects. N = 253.

Based on experiences to date with ixazomib

When Myeloma Canada asked patient respondents how long they have been on ixazomib, the responses were as follows, with N = 29:

- 1 to 6 months, 24 (83%)
- 7 to 12 months, 2 (7%)
- 1 to 2 years, 3 (10%)

When asked to rate ixazomib's effectiveness in controlling their myeloma on a scale of 1 – 5, 1 was "not effective" and 5 was "extremely effective", twelve (43%) patient respondents rated it a 5, six (21%) respondents rated it a 4 and none of the patient respondents rated it a 1 "not effective". N = 28.

When Myeloma Canada asked patient respondents to rate the comparable effectiveness of ixazomib in treating myeloma to other therapies taken, on a scale of 1 – 5, 1 was "not as effective" and 5 was "far more effective", a total of five (18%) respondents rated it a 5, ten (36%) patient respondents rated it a 4 and one respondent (4%) rated it a 1 "not as effective". N = 28.

When asked to rate ixazomib side effects on a scale of 1 – 5, 1 was "completely intolerable" and 5 was "very tolerable", a total of nine (32%) respondents rated it a 5, ten respondents (36%) rated it a 4 and the lowest rating was a 2 by three (13%) respondents. N = 28.

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Respondents were asked to rate the list of side effects with ixazomib provided from 1 – 5, 1 was "completely intolerable" and 5 was "very tolerable". The results are shown in the table below. According to Myeloma Canada, respondents indicated that the side effects with ixazomib were tolerable. In many cases, the side effect was not applicable as indicated by the number of responses in the "N/A" column.

	1 - Completely intolerable	2	3	4	5 - Very tolerable	N/A	Total
Nerve problems (tingling, numbness, burning in feet or hands, weakness in arms or legs)	**4.2%** 1	**29.1%** 7	**12.5%** 3	**25%** 6	**8.3%** 2	**20.8%** 5	24
Pain	**8.3%** 2	**4.2%** 1	**25%** 6	**20.8%** 5	**16.7%** 4	**25%** 6	24
Low platelet counts (bleeding and bruising)	**8.3%** 2	**4.2%** 1	**12.5%** 3	**20.8%** 5	**16.7%** 4	**37.5%** 9	24
Nausea/ vomiting	**0%** 0	**20.8%** 5	**4.2%** 1	**25%** 6	**25%** 6	**25%** 6	24
Diarrhea	**4%** 1	**4%** 1	**24%** 6	**20%** 5	**24%** 6	**24%** 6	25
Skin reactions (new or worsening rash)	**4.4%** 1	**4.4%** 1	**13%** 3	**8.7%** 2	**21.7%** 5	**47.8%** 11	23
Constipation	**8.7%** 2	**0%** 0	**17.4%** 4	**26.1%** 6	**30.4%** 7	**17.4%** 4	23
Back pain	**0.00%** 0	**0.00%** 0	**29.17%** 7	**20.83%** 5	**20.83%** 5	**29.17%** 7	24
Swelling (arms, hands, legs, ankles, or feet)	**0%** 0	**4%** 1	**20%** 5	**8%** 2	**24%** 6	**44%** 11	25
Liver problems (yellowing of skin or whites of your eyes, pain in upper right stomach area)	**4.8%** 1	**0%** 0	**4.8%** 1	**4.8%** 1	**33.3%** 7	**52.4%** 11	21

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Below are additional comments provided by patient respondents:

- *"More fatigue since I have been on it".*
- *"I got a headache lasting about 24 hours, started within an hour or two of taking. Have been taken off now do to neuropathy increasing."*
- *"Hard to tell because drug is being taken in conjunction with a number of other pharmaceuticals whose side effects are above. My sense is that I am tolerating the ninlaro well and that it is not contributing substantially to what I am experiencing."*
- *"Bronchial problems bleeding."*
- *"Not experience any side effects at this stage in treatment with this drug."*

When asked to rate how ixazomib side effects compare with other treatments for myeloma, on a scale of 1 – 5, 1 was "many more side effects" and 5 was "far fewer side effects", four (14%) patient respondents rated it a 5, eleven (39%) patient respondents rated it a 4, and none of the respondents rated it a 1. N=28.

Respondents were asked to rate on a scale of 1 – 5, how convenient they found it to take ixazomib (for example, does it interfere with your day-to-day activities; does it cause immediate or intolerable side effects). A score of 1 was "not at all convenient" and 5 was "extremely convenient". A total of eighteen respondents (64%) rated it a 5, six (21%) patient respondents rated it a 4, one respondent (4%) rated it a 1. N = 28. Below are additional comments provided by six patient respondents:

- *"Just need to take the same morning as my Dex only without food for this drug as part of morning routine. Day 1, 8, 15 of cycle is not major change to the current cycle."*
- *"Pill first thing in am wait an hour before other pills."*
- *"I had no additional side effects from Ninlaro. I was taking it in a study with Revlimid and Dex. Previous to that I had been on Rev and Dex, which gave me diarrhea (my worst side effect). That continued but is pretty much under control."*
- *"Nausea and headache day of and after taking."*
- *"I take 3 mg one day per week for 3 weeks and then a week off."*
- *"1 pill per wk 3 wks on, 1 wk off no more shots of Velcade in stomach, reduced labs x 2 per month."*

Of note, Ninlaro = ixazomib, Dex = dexamethasone, Revlimid = lenalidomide, *Velcade* = bortezomib.

Respondents were also asked to rate their quality of life while taking ixazomib on a scale of 1 – 5. A score of 1 was "poor quality of life" and 5 was "excellent quality of life". A total of five respondents (19%) rated it a 5, fifteen (56%) respondents rated it a 4, and none of the respondents rated it a 1. N = 27.

In an open-ended question, respondents were asked whether ixazomib has changed or is expected to change their long-term health and well-being. There were 22 responses. Twelve were positive responses, which included comments about being in remission, improved numbers (i.e., "*blood counts improved*"), and disease control. Seven responses were about expectations of the treatment, which included comments about disease control and extended life. Three patients responded that it was too early to tell and one patient respondents is off treatment. Of note, one respondent included comments that were about a positive outcome and an expectation.

Below are some verbatim quotes to illustrate the responses:
Positive examples:

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- *"I was becoming refractory to Rev/Dex. When Ninlaro was added to Rev/Dex 2.5 months ago my blood counts improved dramatically after one month and again after the second month."*
- *"My cancer numbers are coming down (light chains) so I know it's working!"*
- *"I am now in remission after 6 months of Ninlaro 3mg. 1 dose each week of 21 day cycle."*

Expectation examples:

- *"Hoping to keep the disease in check."*
- *"Hope to live longer."*
- *"Drug is expected to contribute to bringing my M-spike down. Spike has in fact been coming down at a relatively modest pace but not leaps and bounds."*

Of note, Ninlaro = ixazomib, Dex = dexamethasone, Rev = lenalidomide.

When asked whether ixazomib met their expectations, a 23 (85%) patients responded "yes", and four (15%) patients responded "no" (N = 27).

A total of 17 patients responded to the open-ended question, "what were your expectations of ixazomib". The following are their responses: wanted improved numbers ([n=3]; i.e., *"markers normal", "to lower numbers", "quicker and more pronounced reduction in M=Spike"),* were expecting remission (n=3), were expecting fewer side effects (n=3), more effective than bortezomib (n=1), hoping for the best (n=1), new medication not tried before (n=1), 5th relapse (n=1), wanted disease control (n=1), had high expectations (n=1), still in progress (n=1), "too soon" (n=1), and "as advertised" (n=1). Of note, the total is greater than 17, since respondents provided more than one answer.

In addition to the online survey, a total of seven patients were interviewed between May 24 and June 21, 2016. Below provides a description of the patients interviewed as well as their responses:

- Patient 1 has been on the treatment for 6 years – as a single agent. When asked about expectations, Patient 1 replied: "*To stop the progression. Yes, Ninlaro has been a life saver for me. I had a prognosis of 2 years and I'm 8 years in. It's been a lot easier to use, the side effects are minimal. It's kept the cancer low and steady."*
- Patient 2 has been on the treatment for 4 months. Their expectation was to extend life. Patient 2 stated: "*Yes, I'm considered to be in remission."*
- Patient 3 has been on treatment for 5 months. Patient 3's expectation was "*to be tolerable in terms of side-effects. I was hoping that it would work, but I didn't know. So far it is keeping the disease in check. I still have to go in once a month. Quality of life is a huge aspect for me. It's much more convenient than Velcade. It's a physical and emotional disruption to go to the hospital for treatment. You see a lot of people who are very sick and you wonder, is that going to be me. Every time you go in there, you relive that you are living with this fatal illness. You can travel and you're free.*"
- Patient 4 was on the treatment for 3 cycles, and no longer on treatment. Patient 4 stated: "*no improvement with treatment. I'm as high risk as you can get. I often respond a-typically to drugs. I wouldn't put a lot of weight on my experience."*
- Patient 5 has been on treatment for 4 months. Patient 5 commented: "*More than met my expectations. Thought it would knock the numbers down, but not to the degree that is has worked, Astonished at how fast it worked. Numbers are better than they were following my transplant. After 4th round of treatment, they couldn't find any trace of myeloma. They are now saying "complete remission". I work full time and go to the gym 3 times per week. It has not affected my quality of life."*
- For patient 6, it the second month on treatment. Patient 6's expectation was to buy time to wait for next therapy. Patient 6 expressed: "*I'm not the average patient, I know a lot about treatments. I went on Ninlaro to buy time to wait for the next therapy – engineered*

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t-cell therapy in all likelihood. Ninlaro has been a good experience so far. I was extremely anxious about the side effects. I'm taking Zofran prophylactically. The reality is, I don't feel any side effects. I follow the protocol diligently. The clinical benefits of Ninlaro have been very good. I'm in remission with my numbers."

- Patient 7 has been on treatment for 3 months. Patient 7 stated: "*I expect it to keep my myeloma under control for the coming months. So far it has been very effective in knocking the numbers back down, down 50%. I expect to have continued good numbers with another blood test through the next round."*

Of note, Ninlaro = ixazomib and Velcade = bortezomib.

3.3 Additional Information

None.

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4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

Input was obtained from all of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact implementation of ixazomib for previously treated multiple myeloma:

Clinical factors:

- Clarity on patients who would eligible for treatment
- Sequencing of currently available treatment and upcoming treatments

Economic factors:

- Potentially large prevalent patient population eligible for treatment

Please see below for more details.

4.1 Factors Related to Comparators

Lenalidomide plus dexamethasone is the current standard of care for previously treated multiple myeloma. However, when lenalidomide plus dexamethasone is funded for previously untreated multiple myeloma patients, patients who are given this treatment option in the first line setting will require other treatment combinations in the relapsed setting. PAG noted that ixazomib combination therapy appears to be better tolerated than bortezomib but has added toxicities when compared to lenalidomide plus dexamethasone alone. PAG is seeking information on whether comparison data is available comparing ixazomib combination therapy to carfilzomib combination therapy or bortezomib.

4.2 Factors Related to Patient Population

PAG is seeking clarity on the patient population who would be eligible for treatment with ixazomib/lenalidomide/dexamethasone, if recommended for funding:

- For patients who have been treated with lenalidomide plus dexamethasone in the first-line setting and progress, is there data to support the use of ixazomib/lenalidomide/dexamethasone?
- Would the addition of ixazomib be appropriate for patients who are already on lenalidomide plus dexamethasone for relapsed/refractory disease but have not yet progressed?
- For patients with relapsed/refractory multiple myeloma, would stem cell transplant be considered a previous line of therapy or are only patients who have been treated with at least two systemic treatments eligible?
- Since most patients who receive an autologous stem cell transplant receive maintenance lenalidomide following their transplant, is their data to support the use of ixazomib in combination with lenalidomide/dexamethasone after progression on maintenance lenalidomide? Would maintenance lenalidomide be considered as one

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line of prior systemic therapy? Would consistency with the carfilzomib recommendation be appropriate?

PAG noted that there may be interest to use the ixazomib/lenalidomide/dexamethasonet combination therapy in newly diagnosed patients but noted that there are ongoing trials for newly diagnosed multiple myeloma and that it is out of scope of this review.

Given the multiple treatments that will be available, PAG is seeking guidance on the appropriate place in therapy of ixazomib in combination with lenalidomide and dexamethasone and sequencing of all treatments available.

4.3 Factors Related to Dosing

Ixazomib is taken once weekly for three weeks with one week off and is an add-on to current oral treatments. PAG noted that the administration schedule may be challenging for some patients to adhere to as this is different than the lenalidomide.

PAG noted that there are multiple strengths available for ease of dose adjustment.

4.4 Factors Related to Implementation Costs

PAG noted that the prevalent number of patients with multiple myeloma who have received at least one prior line of therapy is significant. As ixazomib is an add-on therapy to current therapy, there will be a large budget impact.

PAG noted that the cost of bortezomib has been significantly reduced with generic products being available and bortezomib re-treatment in second-line and beyond treatment settings would be an option in most provinces, particularly for patients who have already been previously treated with lenalidomide.

4.5 Factors Related to Health System

PAG noted that ixazomib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. As an oral option, chemotherapy chair time and nursing time would not be required. PAG identified the oral route of administration is an enabler to implementation.

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

4.6 Factors Related to Manufacturer

At the time of the PAG input, price of ixazomib capsules was not available. PAG indicated that a flat pricing structure would be a barrier to implementation.

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5 SUMMARY OF REGISTERED CLINICIAN INPUT

One clinician input was received as a joint submission by six clinicians who are members of Myeloma Canada Research Network.

The clinicians identified that ixazomib would be an oral treatment option for patients with relapsed multiple myeloma. They noted that the addition of ixazomib to lenalidomide/dexamethasone improves progression free survival, although overall survival is not yet known.

Please see below for details from the clinician input.

5.1 Current Treatment(s) for this Multiple Myeloma

The clinicians providing input identified that the current treatments for relapsed/refractory multiple myeloma include lenalidomide, cyclophosphamide, dexamethasone, bortezomib, pomalidomide and melphalan. They noted that lenalidomide/dexamethasone has been the most common second-line therapy in myeloma. They also noted that carfilzomib and daratumumab are desirable but availability of these treatments at this time is limited.

5.2 Eligible Patient Population

Clinicians providing input estimated that 20% to 60% of the patient population would be defined by the funding request. They noted that the number of patients eligible for ixazomib will vary amongst the provinces, depending on what treatments are publicly funded in each province for relapsed multiple myeloma.

5.3 Identify Key Benefits and Harms with Ixazomib

Clinicians providing input identified that ixazomib offers patients the convenience of oral proteasome inhibitor treatment. Patients are not physically bound by recurrent chemotherapy clinic appointments, can travel or go on holiday without missing treatment, and can have a lifestyle that more closely resembles wellness. Oral treatment is cognitively less intrusive and less of a reminder of the cancer diagnosis than intravenous or subcutaneous treatment, and many patients appreciate this.

The clinicians providing input noted that ixazomib needs to be given with caution to patients with pre-existing peripheral neuropathy. They noted that the potential benefits of therapy outweighs the risks for thrombocytopenia and neuropathy.

5.4 Advantages of Ixazomib Over Current Treatments

Clinicians providing input noted that ixazomib improved progression free survival compared with lenalidomide/dexamethasone alone, although the impact on overall survival is not known yet. They noted that median progression-free survival improved from 14,7 months to 20,6 months; High quality response (VGPR or better) improving from 39% to 48%; faster median time of response from 1,9 months to 1,1 months; longer duration of response from 15 months to 20,5 months. In addition, they noted lenalidomide and dexamethasone has limited benefit in high-risk patients and ixazomib is particularly good for del17p myeloma. Ixazomib contributes to an important all-oral combination for myeloma and would fill the unmet need for re-treatment of relapsed myeloma with a proteasome inhibitor as well as the need for a funded triplet regimen

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more effective than the lenalidomide/dexamethasone doublet.

5.5 Sequencing and Priority of Treatments with Ixazomib

The clinicians providing input indicated that ixazomib/lenaldiomide/dexamethasone should not be used in patients who are refractory to lenalidomide or proteasome inhibitors. They feel that that ixazomib/lenaldiomide/dexamethasone would be appropriate for patients in whom lenaldiomide/dexamethasone would be considered at time of at least first the first relapse or later. They noted that Ixazomib/lenaldiomide/dexamethasone may displace pomalidomide/dexamethasone, which is currently the preferred third line therapy, or would be preferred over carfilzomib/lenalidomide/dexamethasone.

They noted that ixazomib/lenaldiomide/dexamethasone would be an excellent second-line regimen for patients relapsing after ASCT who have received 4-6 cycles of CyBorD as induction therapy, particularly if they are high-risk. Also, elderly patients treated with VMP who have high-risk disease would benefit from this regimen at the time of first relapse.

However, the increased cost compared with older agents such as bortezomib would make it unlikely to replace current first-line therapies at this time. It would not necessarily replace but would be a much needed added regimen in our armamentarium.

5.6 Companion Diagnostic Testing

No companion diagnostic identified.

5.7 Additional Information

No additional information related to ixazomib for multiple myeloma was provided. However, it was noted that these clinicians appreciated the opportunity for those who treat myeloma to provide input into the review.

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6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of ixazomib in combination with lenalidomide and dexamethasone on patient outcomes compare to appropriate comparators in patients with multiple myelomas (MM) that had at least two prior therapies OR one prior therapy and have high-risk cytogenetic feature.

Supplemental Questions and Comparison with Other Literature most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7 and section 8.

- Critical appraisal of a network meta-analysis assessing the relative efficacy of ixazomib versus other selected therapies in patients with relapsed/refractory multiple myelomas that were treated with at least one prior therapy.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP 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. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 2: Selection Criteria

Clinical Trial Design	Patient Population	Intervention‡	Appropriate Comparators†‡	Outcomes
Published or unpublished RCTs	Patients with MM that had at least two prior therapies OR one prior therapy accompanying with high-risk cytogenetic feature*	In a 28-day treatment cycle, the combination of Ixazomib 4 mg administered orally on Days 1, 8, and 15 AND lenalidomide 25 mg administered daily on Days 1 through 21 AND Dexamethasone 40 mg administered on Days 1, 8, 15, and 22.	Lenalidomide 25 mg administered daily on Days 1 through 21 AND dexamethasone 40 mg administered on Days 1, 8, 15, and 22 (with or without placebo) OR Carfilzomib in combination with lenalidomide and dexamethasone OR Bortezomib and dexamethasone	**Overall survival (All-cause mortality)** **Progression free survival** **Quality of life** Response rate Grade 3 and 4 adverse events Withdrawal due to adverse effects Any adverse effects
RCT: Randomized control trial; MM: Multiple myelomas				

** High risk cytogenetic feature was defined as patients with del(17p), t(4,14), t(14,16) and +1q21 genetic abnormalities*
† Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)
‡ Dosages listed are recommended starting dose. Dosage may be adjusted in trial according to individual needs

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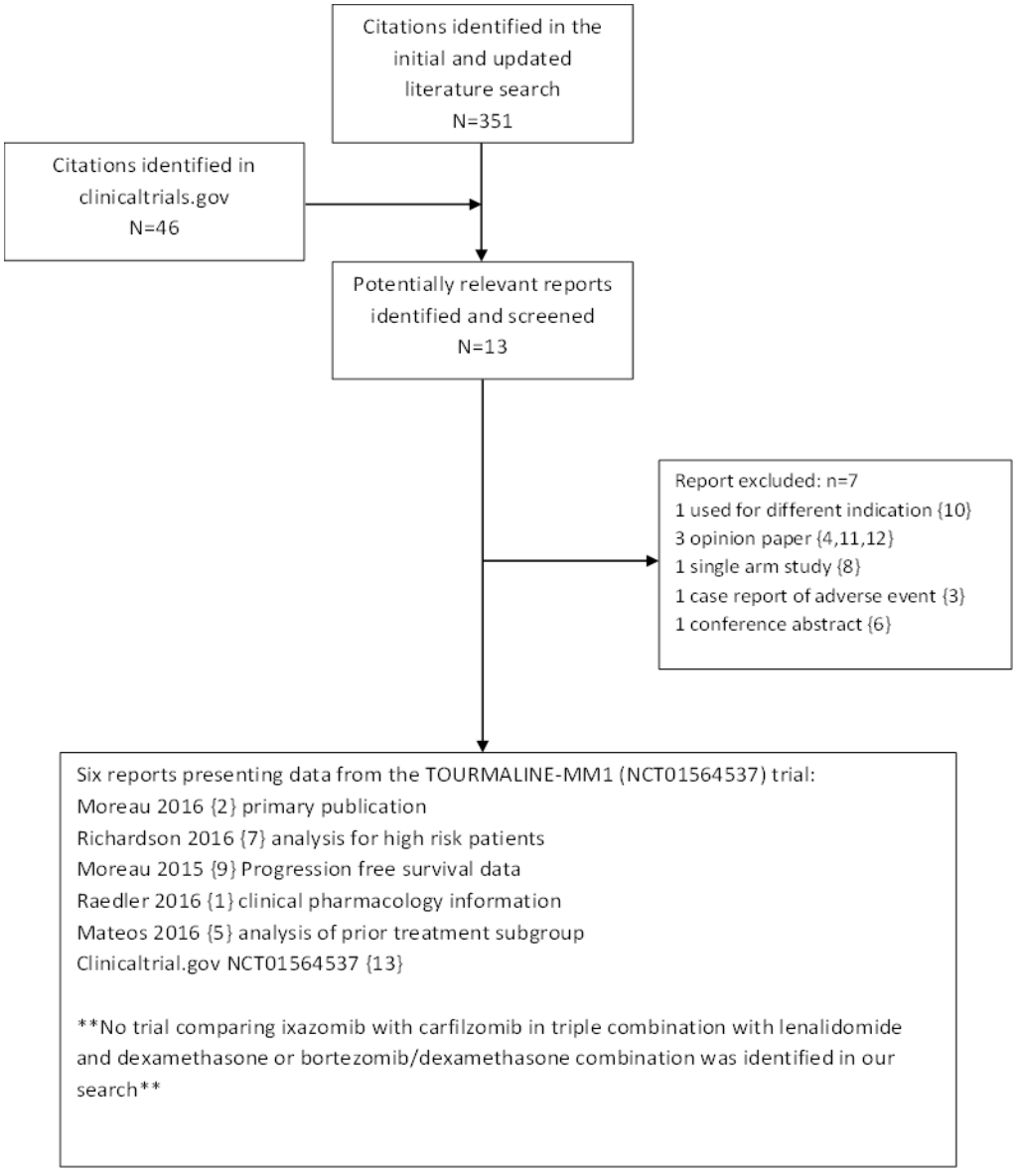
6.3 Results

6.3.1 Literature Search Results

Among the 13 potentially relevant reports identified by the search, six reports from the same study were included in the pCODR systematic review[1-5,23] while seven reports were excluded. Reports were excluded because they were opinion paper;[24-26] single arm study;[27] case report of an adverse event;[28] conference abstract;[29] used Ixazomib, lenalidomide, dexamethasone combination for a different indication.[30] The search is considered up to date as of April 3, 2017.

Figure 1: QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to studies TOURMALINE-MM1 were also obtained through requests to the Submitter by pCODR.[31]

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6.3.2 Summary of Included Studies

One clinical trial (TOURMALINE-MM1[1-5,23]) was included in this systematic review. The key characteristics of this trial are summarized in table 4.

6.3.2.1 Detailed Trial Characteristics

Table 3: Summary of Trial Characteristics of the Included Study

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
TOURMALINE-MM1[1-5,23] (NCT01564537) Phase III International multicenter 1:1 randomized double blind placebo controlled trial N=722 (Enrolment between August 28, 2012 to May 27, 2014) 147 sites in 26 countries Data cut-off date: Oct 30, 2014 Funded by Millennium Pharmaceuticals, a wholly owned subsidiary of Takeda Pharmaceuticals.	<u>Key Inclusion Criteria:</u> • Adult patients were eligible for enrollment if they had relapsed, refractory, or both relapsed and refractory multiple myelomas • had measurable levels of disease (even if measurable by serum free light-chain assay only) • had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2 • had received one to three prior therapies • had adequate hematologic and hepatic function • Patients with mild-to-moderate impairment of renal function (i.e., patients with a calculated creatinine clearance of at least 30 ml per minute per 1.73 m2 of body-surface area) were eligible <u>Key Exclusion Criteria:</u> • Patients were not eligible if they had peripheral neuropathy of grade 1 with pain or grade 2 or higher or had disease that was refractory to prior lenalidomide therapy or proteasome inhibitor–based therapy	In 28-day cycles, either 4 mg of oral ixazomib or matching placebo on days 1, 8, and 15; in addition, all patients received 25 mg of oral lenalidomide on days 1 through 21 (10 mg for patients with a creatinine clearance of ≤60 or ≤50 ml per minute per 1.73 m2, with the cut-off point determined according to the local prescribing information) and 40 mg of oral dexamethasone on days 1, 8, 15, and 22.	<u>Primary:</u> Progression free survival <u>Secondary:</u> Overall survival Overall survival in patients with del17p mutation PFS in patients with high risk cytogenic abnormalities Overall response rate Rate of complete response and VGPR Duration of response Time to diseases progression Safety Change in global health status

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Table 4: Select quality characteristics of included studies of Ixazomib in combination with lenalidomide and dexamethasone in patients with relapsed or refractory multiple myelomas[32]

Study	TOURMALINE-MM1
Treatment vs. Comparator	IRd vs Rd
Primary outcome	PFS
Required sample size	The study was powered to detect the superiority of ixazomib over placebo with respect to progression-free survival. Assuming a hazard ratio of 0.728 365 PFS events will be needed (85% power and 2-sided alpha of 0.05) with 2 planned IAs and the second IA as the final PFS analysis. An O'Brien–Fleming stopping boundary for efficacy was calculated with the use of a Lan–DeMets alpha-spending function on the basis of the number of events observed at the time of data cutoff. The total sample size was calculated based on maintaining 80% power to test the OS. The study is also adequately powered to test PFS. Assuming a hazard ratio of 0.77 (median survival of 30 months in control arm versus 39 months in treatment arm), the number of death events needed is 486 (80% power and 2-sided alpha of 0.05). A total of approximately 703 patients will need to be randomized in a 1:1 ratio into those 2 arms. Although the total sample size was calculated based on maintaining 80% power to test the OS, the study is also adequately powered to test PFS, the primary outcome. Sequential testing procedure will be used to test PFS and OS sequentially both at a 2-sided alpha level of 0.05 where OS would be tested only if there is significance based on the O'Brien Fleming alpha spending function at the first and second IA for PFS.
Sample size	360 vs. 362
Randomization method	1:1 stratified
Allocation concealment	matching placebo
Blinding	Double-blind, assessor blind
ITT Analysis	Yes
Final analysis	No
Early termination	Results were from interim analysis, study is ongoing
Ethics Approval	Yes

IRd: Ixazomib, lenalidomide, dexamethasone combination; Rd: lenalidomide, dexamethasone combination; PFS: progression-free survival.

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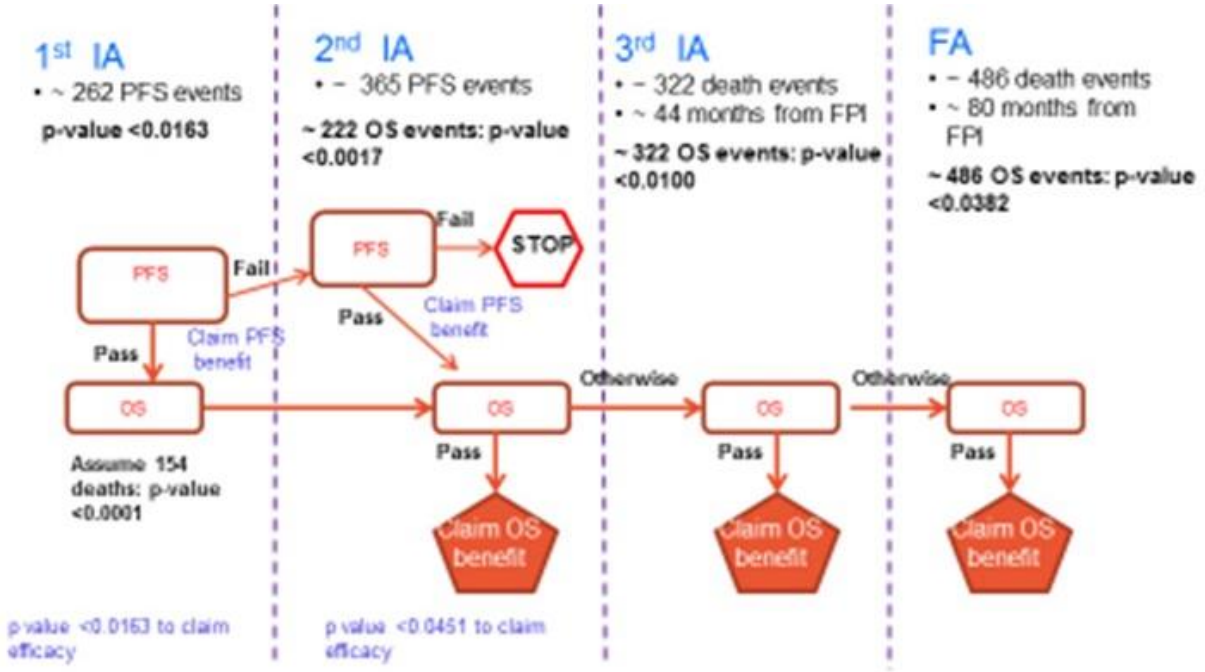
Figure 2. Final Statistical Plan Leading to PFS Analysis[31]



The first IA for PFS will be performed when approximately 262 events have occurred. This will be the first analysis for PFS for statistical testing purpose. If the test for PFS is statistically significant at the first IA, a non-inferential analysis of PFS will be performed at the second IA where the PFS data is considered mature. The alpha level at the first IA and second IA on PFS would be 0.0163 and 0.0337, respectively, if the number of PFS events at the first IA is exactly 262. If the observed p value is less than 0.0163 and 0.0451 at the first IA and the second IA, respectively, the test for PFS will be claimed to be statistically significant.

The trial will not be stopped for overwhelming evidence of efficacy or futility at the first IA for OS. A third IA will be conducted for OS when approximately 322 deaths (two-thirds of the total expected deaths) have occurred, with the opportunity to stop the study for overwhelming evidence of efficacy or futility. Based on the O'Brien-Fleming stopping boundary, the alpha levels at the 3 planned OS IAs and final analysis would be 0.00014, 0.0017, 0.0100, and 0.0382, respectively if the numbers of events at these analysis time points are exactly 154, 222, 322, and 486.(41) Correspondingly, if the nominal p value is less than 0.0001, 0.0018, 0.0112, and 0.0462, respectively, at the first, second, and third IAs, and the final analysis, the test for OS will be claimed to be statistically significant. However, the study will not be stopped after the first IA based on the test for OS.

a) Trials

One randomized double-blind placebo-controlled trial (TOURMALINE-MM1) met the inclusion criteria.[1-5,23] TOURMALINE-MM1 (MM1) was a phase III trial funded by Millennium Pharmaceuticals, a subsidiary of Takeda Pharmaceuticals. The aim of this trial was to examine the effect of adding ixazomib to lenalidomide and dexamethasone combination compared to lenalidomide and dexamethasone double combination alone on efficacy and safety outcomes in patients with relapsed/refractory multiple myeloma that had at least one prior therapy. The MM1 trial enrolled 722 patients from 26 countries with relapse or refractory multiple myeloma that had at least one prior treatment. Patients were randomized in a 1:1 ratio to receive Ixazomib, lenalidomide and dexamethasone triple combination (ILd) or placebo (lenalidomide and dexamethasone combination, Ld). Randomization scheme were to be generated by an independent statistician at Millennium who is not on the study team. Prior to dosing, a randomization number were to be

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assigned to each patient. The randomization assignment will be implemented by an interactive voice response system (IVRS). Randomization was stratified according to the number of prior therapies, previous exposure to proteasome inhibitors, and International Staging System disease stage. Patients, investigators and the independent assessors were blinded to the treatment allocation. Patients were treated until disease progression or unacceptable toxicity.

The primary outcome of TOURMALINE-MM1 was progression-free survival defined as the time from randomization to the date of first documented disease progression or death from any cause. The outcome was assessed by an independent review committee which was blinded to treatment allocation.

Key secondary outcomes included overall survival in intention-to-treat population and in patients with chromosome 17p deletion. Other secondary outcomes included overall response rate, complete response rate plus very good response rate, the time to disease progression, progression-free survival and overall survival in patients with high-risk cytogenetic abnormalities, safety, and change in global health status. Health-related quality of life in global health status was assessed by using the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 module (EORTC QLQ-C30) and the myeloma-specific module (EORTC QLQ-MY20). The EORTC QLQ-C30 is a validated questionnaire for evaluation of the quality of life in cancer patients. The questionnaire comprises of five functional scales, three symptoms scales, 6 single item symptom scales and a global health/quality of life scale. The score ranges from 0 to 100 with a higher score indicating better health status. A change of 10 points on this scale is considered to be clinically meaningful.

Of note, there is a lack of consistency for the definition of high risk cytogenetics.

- First, based on the published review protocol, PFS and OS in high risk cytogenetics (defined as including the t(4; 14), t(14; 16), + lq, del(13), or del(17) translocations) were pre-specified secondary endpoints.
- Secondly, based on the TOURMALINE-MM1 trial publication and accompanying supplemental appendix, high risk cytogenetics was indeed identified as a secondary endpoint. Although, not specifically defined, the only reference to the types of cytogenic abnormalities measured were for the del(17p), t(4;14), and t(14;16) translocations.
- Lastly, the Clinical Summary provided as part of the pCODR submission and including information on the expanded high risk subgroup of patients, indicated that the TOURMALINE-MM1 publication did not include +1q21 translocation in the high risk group, as this translocation was added to the 2014 update of the IMWG guidelines. Thus the analysis presented in the Clinical Summary include the t(4; 14), t(14; 16), + lq, del(13), or del(17) translocations.

Based on the sum of this information, the Methods team concluded that the analysis presented with the expanded high risk cytogenetics feature was post hoc. Following the receipt of feedback from the submitter on whether or not the two subgroups of interest were pre-specified or post hoc, the Methods team can confirm that the subgroup analysis with patients who have received 2+ prior subgroup existed at randomization, therefore it is not post hoc. However, it is clear that the definition of the high-risk subgroup changed since the publication. Therefore, the expanded high-risk subgroup remains a post hoc analysis.

The first interim analysis (IA1) was performed when median follow-up reached 15 months with data cut-off date on October 30, 2014. This interim analysis was the first and final analysis for progression-free survival. The second interim analysis (IA2) was performed

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when median follow-up reached 23 months with data cut-off date on July 12, 2015. The second interim analysis was performed primarily to evaluate overall survival. However, an additional analysis of progression-free survival was also performed at this time. Based on the design of the trial, the second IA would be non-inferential if the results of the first IA were significant.

b) Populations

TOURMALINE-MM1 randomized 722 patients to ixazomib or placebo group. The baseline characteristics were well balanced in terms of age, race, ECOG status, ISS disease stage, cytogenetic profile, creatinine clearance, the number of prior therapy, the proportion of patients who had stem cell transplant. Among all randomised patients 70% had been treated with a proteasome inhibitor before, mostly with bortezomib. Two percent of patients were refractory to proteasome inhibitor. Fifty-five percent of patients had been treated with an immunomodulatory drug before, mostly with thalidomide. Twenty-three percent of patients were refractory to an immunomodulatory drug. The baseline characteristics of patients can be found in table 6.

Table 5: Baseline characteristics

Characteristics	ILd n=360	Ld n=362	Total n=722
Median age (range)	66 year (38–91)	66 year (30–89)	66 year (30–91)
Male sex — n (%)	207 (58%)	202 (56%)	409 (57%)
White race — n (%)	310 (86%)	301 (83%)	611 (85%)
ECOG score n/N (%)			
0	180/354 (51%)	170/358 (47%)	350/712 (49%)
1	156/354 (44%)	164/358 (46%)	320/712 (45%)
2	18/354 (5%)	24/358 (7%)	42/712 (6%)
ISS disease stage n (%)			
I	226 (63%)	233 (64%)	459 (64%)
II	89 (25%)	87 (24%)	176 (24%)
III	45 (12%)	42 (12%)	87 (12%)
Median creatinine clearance (range)	78.4 ml/min per 1.73m^2 (20–233)	78.4 ml/min per 1.73m^2 (27–233)	78.4 ml/min per 1.73m^2 (20–233)
Median time since initial diagnosis	44.2 months (3–281)	42.2 months (4–306)	42.8 months (3–306)
Cytogenetic features			
Standard-risk cytogenetic abnormalities n (%)	199 (55%)	216 (60%)	415 (57%)
High-risk cytogenetic abnormalities* n (%)	75 (21%)	62 (17%)	137 (19%)
Data not available n (%)	86 (24%)	84 (23%)	170 (24%)
No. of prior therapies n (%)			
1	224 (62%)	217 (60%)	441 (61%)
2	97 (27%)	111 (31%)	208 (29%)
3	39 (11%)	34 (9%)	73 (10%)
Prior stem cell transplantation	212 (59%)	199 (55%)	411 (57%)
Prior proteasome inhibitor therapy n (%)	249 (69%)	253 (70%)	502 (70%)
Disease refractory to any prior proteasome inhibitor therapy n (%)	4 (1%)	8 (2%)	12 (2%)
Prior immunomodulatory drug therapy n (%)	193 (54%)	204 (56%)	397 (55%)
Disease refractory to any prior immunomodulatory drug therapy n/N (%)	41/193 (21%)	50/204 (25%)	91/397 (23%)

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Characteristics	ILd n=360	Ld n=362	Total n=722
*High risk cytogenic abnormality is defined as chromosome 17p deletion [del(17p)], translocation between chromosomes 4 and 14 [t(4;14)], and translocation between chromosomes 14 and 16 [t(14;16)]			

c) Interventions

TOURMALINE-MM1 randomized 360 patients to ixazomib arm and 362 patients to the placebo arm. In a 28-day cycle, all patients received 25 mg of lenalidomide on day 1-21 and 40 mg of dexamethasone on days 1, 8, 15 and 22. Patients received 4 mg ixazomib or matched placebo on days 1, 8, and 15. All drugs were administrated in oral form. Dose adjustment for toxicity was done according to guideline specified in the protocol. Treatment was continued until disease progression, unacceptable toxicity or death. The median follow-up was 14.7 months at the first interim analysis and 23 months at the second interim analysis.

d) Patient Disposition

Table 6: Patient disposition[33]

Category	ILd	Ld
Randomized	360	362
Received treatment	358	359
Total withdrawal	222	229
Withdrawal due to disease progression	124	146
Withdrawal due to adverse event	60	50
Withdraw consent	7	11
Protocol violation	0	1
Lost to follow-up	1	0
Withdrawal due to other reasons	30	21
Patients remain on treatment	136	133
ITT population for efficacy	360	362
Population for safety analysis*	361	359
*Three patients from placebo group received ixazomib by error for 1-2 cycles. These patients were added to the ixazomib group for safety analysis.		

e) Limitations/Sources of Bias

Trial Design:

- Baseline characteristics were well balanced. The only noted difference between the ITT treatment groups was the cytogenetic feature, where the ixazomib arm enrolled slightly more patients with high-risk cytogenetic abnormalities (excluding the +1q21 abnormality which was not included in the analysis presented in the main publication). However, once +1q21 patients were added into the analysis, presented in an unpublished clinical summary, the number of patients with high risk cytogenetics in the subgroup became more balanced.

Analysis of results:

- The hazard ratio for progression-free survival analysis of the ITT population was 0.74 [95% CI 0.59-0.94, p=0.01] at the first interim analysis. However, the effect size was reduced at the second interim analysis (hazard ratio 0.82, p=0.0548). Although the point estimate showed the same direction of effect, the data suggested a substantial

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amount of variation was still present in the data during interim analyses. Ideally, one would then examine if the overall survival results corroborate with the progression-free survival analysis. However, at this time, the overall survival analysis for the ITT population was not statistically significant both at IA1 and IA2. Following the posting of the pERC initial recommendation, feedback was received from the submitter regarding the second interim analysis (IA2) for PFS. A new, previously un-submitted and unpublished analysis was provided by the submitter through the feedback which included censoring of data based on two factors which were considered to have contributed to the non-significant results at IA2. Censoring based on one of the factors was available to the review team in the published EMA report, while the analysis based on the combined analysis of the two factors could not be considered because these were new data previously unavailable to the review team. According to the *pCODR Procedures*, new data are not admissible at this stage in the pCODR review. Therefore the reviewers did not consider the rationale within the feedback. For the data available within the EMA report, the submitter explained that the presence of 22 (ILd) and 32 (Ld) patients who had received an alternative therapy may have contributed to the non-significant results at IA2. The Methods team reviewed these data from the EMA report. This group of patients were likely censored because they were considered to have had a protocol violation. Overall, the evidence provided in the EMA report is not very different [PFS HR 0.818 95% CI 0.67-1.0), p=0.054] from what was reported in the planned PFS analysis at IA2 that did not censor these patients. The Methods Team re-iterates the same concerns previously expressed. Mainly that, although the point estimate for PFS showed the same direction of effect, the data at IA2 suggested a substantial amount of variation is still present in the magnitude of effect in the ITT population.

- Furthermore, the magnitude of progression-free survival benefit was greater in the two subgroups of interest 1) expanded high-risk cytogenetic + at least one prior line of therapy and 2) at least 2 prior therapies subgroups. In both subgroups, the effect estimates for PFS were statistically significant at both interim analyses and significant for OS only in the high risk subgroup. In addition, the overall survival analysis in the expanded high-risk cytogenetic subgroup was also statistically significant. However, since the trial was not designed to detect differences within these subgroups of patients, it is difficult to determine whether the observed results were found by chance or can be reproduced in a bigger trial for this specific population. Therefore all interpretation of testing for significance within these analysis should be done with caution. The subgroup analyses conducted in this trial should be considered hypothesis-generating, and therefore interpreted with caution.
- Given that the subgroup analyses were based on subgroups of baseline characteristics, patient overlap could occur between the subgroups. In this case, 20% of patients that had at least two prior therapies also had high-risk cytogenetic features. This suggested that part of the effect size was contributed by overlapping patients in the two subgroups.

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6.3.2.2 Detailed Outcome Data and Summary of Outcomes for ITT population

Efficacy Outcomes

Overall survival

Overall survival was defined as the time from the date of randomization to the date of death.[2] After a median follow-up period of 23 months, the second interim analysis (IA2) was conducted when 171 events had occurred. This was based on 81/360 (23%) patients from the ixazomib arm and 90/362 (25%) patients from placebo arm who died. The hazard ratio of death was 0.87 [95% CI 0.64-1.18, p=0.36]. The number of deaths had not reached the level required for final analysis pre-specified by the protocol at this point of time. The study continues in double-blind manner until overall survival data is matured and crossover is not permitted. The first interim analysis was conducted after 107 events had occurred and results were not significant (HR 0.9, 95% CI 0.62-1.32, p=0.59, taken from FDA Statistical Review page 22[6]). Notably, IA1 and IA2 were conducted before a sufficient number of events had occurred. Conducting an analysis early results in data that lacks power to detect a difference.

Overall survival in the subgroup of patients with the del17p mutation was a pre-specified analysis. Although results were not available, the FDA Medical Review noted that results for this subgroup analysis were not significant at the IA1.

Table 8. PFS and OS analysis plan and results in ITT population

	Required Events	Observed Events	Alpha after the analysis	Test Value	Observed p-value
	PFS Analysis				
IA1	262	286	0.0163	0.0163	0.01
IA2	365	372	0.0337	0.0451	0.0548
	OS Analysis[6]				
IA1	154	107	0.00014	0.0001	0.59
IA2	222	171	0.00170	0.0018	0.36
IA3	322	-	0.01000	0.0112	-
Final Analysis	486	-	0.03820	0.0462	-

Progression free survival

Progression-free survival was defined as the time from the date of randomization to the date of first documentation of disease progression or death from any cause as assessed by an independent review committee.[2] The assessment of disease progression was based on central laboratory results and International Myeloma Working Group 2011 criteria.[2]

The planned 1st interim analysis of PFS per IRC, was based on 286 progression or death events (~ 78% of planned 365 events) observed at the data cut-off date. This analysis for progression-free survival was performed after a median follow-up of 14.8 months in the ixazomib arm and 14.6 months in the placebo arm. There were 129/360 (36%) events of disease progression or death occurred in the ixazomib arm and 157/362 (43%) events in the placebo arm at the time of data cut-off on October 30, 2014. The median progression-free survival was 20.6 months in the ixazomib arm and 14.7 months in the placebo arm. The hazard ratio (HR) for disease progression or death was 0.74 [95% CI 0.59-0.94, p=0.01]. Based on the statistical design of the trial, this was the final analysis of progression-free survival analysis in the trial because it has reached a significant result. However, the

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supplemental appendix to the main publication (and also referenced in the FDA report) provided results from the second planned interim analysis after the occurrence of 372 events 177 and 195 in the ixazomib and placebo groups, respectively).[33] At this second (IA2) and final analysis point, the hazard ratio for progression-free survival was 0.82 [95% CI 0.67-1.0, p=0.0548].[2,6] The median progression-free survival became 20 months in the ixazomib arm, and 15.9 months in the placebo arm. It was not clear whether the estimate would change if progression-free survival were analyzed after all patients experienced disease progression.

Following the posting of the initial recommendation, feedback was received from the submitter regarding the second interim analysis for PFS and the limitations identified by the pCODR reviewers. A new, previously un-submitted and unpublished analysis was provided by the submitter through the feedback which included censoring of data based on two factors which were considered to have contributed to the non-significant results at IA2. The submitter explained that the presence of 22 (ILd) and 32 (Ld) patients who had received an alternative therapy was one of two factors which may have contributed to the non-significant results at IA2. Censoring based on one of the factors (patients who received an alternate therapy) was available to the review team in the published EMA report, while the analysis based on the combined analysis of the two factors could not be considered because these were new data previously unavailable to the review team. According to the *pCODR Procedures*, new data are not admissible at this stage in the pCODR review. Therefore the reviewers did not consider the rationale within the feedback.

It is notable that the EMA report has not defined what these alternative therapies are and why patients would have received alternative therapies. The evidence provided in the EMA report is not very different [PFS HR 0.818 95% CI 0.67-1.0), p=0.054] from what was reported in the planned PFS analysis at IA2 that did not censor these patients.

Sample	IA1 (PFS)	IA2 (PFS)	Adjusted IA2 (PFS)
ITT	HR: 0.74 [95% CI 0.59-0.94, p=0.01]	HR: 0.82 [95% CI 0.67-1.0, p=0.0548]	HR: 0.818 [95% CI 0.67-1.0, p=0.054]
Expanded high-risk subgroup	HR: 0.66 [95% CI 0.47-0.93, p=0.02]	HR: 0.7 [95% CI 0.52-0.95, p=0.02]	--
2+ prior therapy subgroup	HR: 0.58 [95%CI 0.4-0.84, p=0.003]	HR: 0.62 [95%CI NR, p=0.003]	--

IA1: first interim analysis; IA2 second interim analysis; HR: hazard ratio; 95% CI: 95% confidence interval; NR: not reported; PFS: progression free survival

Overall, the Methods Team re-iterates the same concerns previously expressed. Mainly that although the point estimate for PFS showed the same direction of effect, the data at IA2 suggested a substantial amount of variation is still present in the magnitude of effect in the ITT population.

Table 9: Progression-free survival subgroup analysis[31]

Subgroup	ILd	Ld	Hazard ratio	95% CI
Age 65 and younger, n	168	176	0.68	0.48-0.97
Age 66-75, n	145	125	0.83	0.55-1.25
Age 75 and older, n	47	61	0.87	0.46-1.63
ISS stage I and II, n	314	318	0.75	0.58-0.96
ISS stage III, n	46	44	0.72	0.39-1.31
Non-high risk[&], n Standard risk[#], n	285 199	300 216	0.79 0.64	0.61-1.04 Not available
High cytogenetic risk*, n	75	62	0.54	0.32-0.92
One prior therapy, n	224	217	0.83	0.62-1.12

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Two prior therapies, n	97	111	0.75	0.48-1.16
Three prior therapies, n	39	34	0.37	0.17-0.79
Previous PI treatment, n	250	253	0.74	0.56-0.97
No previous PI treatment, n	110	109	0.75	0.48-1.17
Previous immunomodulatory drug therapy, n	193	204	0.74	0.54-1.03
No previous immunomodulatory drug therapy, n	167	158	0.7	0.49-1.00
Refractory to last prior therapy, n	59	55	0.71	0.38-1.34
Not refractory to last prior therapy, n	301	307	0.74	0.58-0.96
Relapse patients, n	276	280	0.77	0.59-1.00
Refractory patients, n	42	40	0.78	0.39-1.58
Relapse and refractory patients, n	41	42	0.51	0.24-1.07

PI: proteasome inhibitor; ISS: International staging system. 95% CI: 95% confidence interval.
*high risk was defined as comprising of the t(4;14), t(14;16), and/or del(17) mutations.
#Standard risk is defined as patients confirmed not to have the t(4;14), t(14;16), and/or del(17) mutations.
&Non-high risk is defined as patients with standard risk plus patients for which no cytogenetic testing is available.

Quality of Life

The quality of life was measured by EORTC-QLQ-C30 and EORTC-QLQ-MY20. The completion rate for EORTC-QLQ-C30 from baseline to end of treatment was 70% of expected (157/225) in the ixazomib arm and 72% of expected (163/225) in the placebo arm. The completion rate for EORTC-QLQ-MY20 from baseline to end of treatment was 70% of expected (157/225) in the ixazomib arm and 71% of expected (160/225) in the placebo arm. After a median follow-up of 23 months, there was no significant difference in health-related quality of life score between the two treatment arms.[2] The least square mean difference of change in global health score from baseline to end of treatment was 1.6 (SE=1.85, p=0.393) between the two arms. Other quality of life score are summarized in the table below.

Table 10: Quality of life score from EORTC QLQ-30[31]

EORTC QLQ-30 categories	Least square mean difference between the two arms (SE)	p-value
Physical functioning	0.8 (1.60)	0.619
Role functioning	0.6 (2.39)	0.813
Emotional functioning	3.7 (1.72)	0.031
Cognitive functioning	0.5 (1.76)	0.768
Social functioning	0.6 (2.20)	0.793

Although between group differences were not meaningful, a clinically meaningful improvement from baseline (defined as a change of 10 points on the EORTC QLQ-C30), was reported at a few individual time points for appetite loss (end of treatment, only in the LD group) and constipation (cycle 2, both treatment groups). Clinically meaningful decline from baseline was also reported at individual time points for role functioning (end of treatment) and social functioning (end of treatment for both treatment groups). Clinically

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meaningfully improvements from baseline in diarrhea was reported in both treatment groups from cycle 10 to 24. At cycle 26, the difference was significant between groups and in favour of the ILd treatment group.[31]

Table 11: Quality of life score from EORTC QLQ-MY20[31]

EORTC QLQ-MY20 categories	Score in ixazomib arm, mean change from baseline to the end of treatment (95% confidence interval)	Score in placebo arm, mean change from baseline to the end of treatment (95% confidence interval)
Disease symptoms	-2.20 (-5.6, 1.2)	-2.52 (-5.8, 0.7)
Side effects of treatment	3.66 (1.3, 6.0)	4.12 (1.9, 6.4)
Body image	-1.49 (-6.4, 3.4)	2.19 (-2.3, 6.7)
Future perspective	-3.16 (-6.7, 0.4)	0.54 (-3.2, 4.3)

Overall response rate

The overall response rate in the ixazomib arm (78%) was significantly better than placebo arm (72%, p=0.04).[2] The number of patients who had a complete response or very good partial response was also significantly higher in the ixazomib arm (48%) than placebo arm (39%, p=0.01). The median time to response was shorter in the ixazomib arm (1.1 months) compared with the placebo arm (1.9 months).

Time to progression

The median time to disease progression was 21.4 months in the ixazomib arm and 15.7 months in the placebo arm.

Harms Outcomes

All adverse events and grade 3 & 4 adverse events

After a median follow-up of 23 months, 355/361 (98%) of patients in the ixazomib arm and 357/359 (99%) of patients in the placebo arm experienced at least one adverse event of any grade. Among these patients, 267/361 (74%) of patients in the ixazomib arm and 247/359 (69%) of patients in placebo arm experienced at least one grade 3 or more adverse event. Summary of some common adverse events can be found on the list below.[2]

Withdrawal due to adverse event

Sixty patients (17%) from the ixazomib arm and 50 patients (14%) from the placebo arm withdrew due to an adverse event.[2]

Table 12: Highlight of adverse events

Adverse event	ILd (n=361)		Ld (n=359)	
	Any grade	Grade 3 & 4	Any grade	Grade 3 & 4
Neutropenia	118 (33%)	81 (22%)	111 (31%)	85 (24%)
Thrombocytopenia	112 (31%)	69 (19%)	57 (16%)	32 (9%)
Anemia	103 (29%)	34 (9%)	98 (27%)	48 (13%)
Peripheral neuropathy	97 (27%)	9 (2%)	78 (22%)	6 (2%)
Arrhythmias	56 (16%)	20 (6%)	53 (15%)	11 (3%)
Thromboembolism	29 (8%)	11 (3%)	38 (11%)	12 (3%)
Liver impairment	26 (7%)	7 (2%)	21 (6%)	4 (1%)
Heart failure	16 (4%)	9 (2%)	14 (4%)	6 (2%)

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Acute renal failure	31 (9%)	9 (2%)	41 (11%)	16 (4%)
Myocardial infarction	5 (1%)	3 (<1%)	8 (2%)	4 (1%)
New primary malignant tumor	17 (5%)	NA	14 (4%)	NA

Peripheral neuropathy

At baseline, 197 patients (88 in the ixazomib arm, 109 in the placebo arm) reported having peripheral neuropathy as a pre-existing condition. Overall, 175 patients reported experiencing peripheral neuropathy during the study. Among these patients, 27/175 (15%) (14 (14%) in the ixazomib arm, 13 (17%) in the placebo arm) reported worsening of their baseline peripheral neuropathy. Among the patients who had peripheral neuropathy, 5 in the ixazomib arm and 4 in placebo arm discontinued the treatment agents.

6.3.2.3 Detailed Outcome Data and Summary of Outcomes for high-risk cytogenetics results

The detail results from this section came from unpublished data submitted by Takeda Canada Inc.[7] The expanded high risk cytogenetic patients subgroup included del(17p), t(4,14), t(14,16) and +1q21. The +1q21 chromosome abnormality was not included in the MM1 trial, as guidelines did not define it as high risk at the time of the publication, and therefore the sample size for the high-risk cytogenetic population was larger than the sample size reported in MM1. There were 155 high-risk cytogenetic patients in the ixazomib arm and 154 in the placebo arm (43% of ITT patients). The MM1 trial did not stratify according to cytogenetic feature.

Table 13: Baseline Characteristics for Patients in the Expanded High Risk Cytogenetics Subgroup

Characteristics	ILd (N=155) n (%)	Ld (N=154) n (%)
Median age, years (range)	67.0 (39, 91)	66.0 (43, 89)
Age >65 years, n (%)	85 (55)	79 (52)
Male sex	85 (55)	76 (49)
White race	136 (88)	125 (81)
ECOG PS 0 1 2	 83 (54) 63 (41) 7 (5)	 72 (47) 69 (45) 9 (6)
ISS Stage at study entry I or II III	 136 (88) 19 (12)	 131 (85) 23 (15)
Creatinine clearance, mL/min, n (%) <30 30-50 ≥50	 2 (1) 8 (5) 145 (94)	 1 (< 1) 21 (14) 132 (86)
Median time since initial diagnosis of MM, months (range)	39.59 (3.0, 174.5)	39.92 (4.2, 306.3)
Prior SCT	95 (61)	72 (47)

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Characteristics	ILd (N=155) n (%)	Ld (N=154) n (%)
Line of prior therapy 1 2 3	 101 (65) 42 (27) 12 (8)	 94 (61) 46 (30) 14 (9)
Relapsed Refractory relapsed and refractory primary refractory	116 (75) 18 (12) 21 (14) 11 (7)	110 (71) 28 (18) 16 (10) 7 (5)
Prior PI therapy	106 (68)	105 (68)
Prior IMD therapy, n (%)	94 (61)	84 (55)
Lenalidomide-containing	20 (13)	16 (10)
Thalidomide-containing	76 (49)	72 (47)
ECOG: European Cooperative Oncology Group; IMD: immunomodulatory drug; PI: proteasome inhibitor; PS = performance status		

Overall survival

At 23 months, 35/155 ixazomib patients (23%) and 53/154 placebo patients (34%) had died from any cause. The hazard ratio of death was 0.62 [95% CI 0.4, 0.96, p=0.03]. The data had not reached maturity to compare median overall survival.

Progression free survival

At 14.8 months, 62/155 (40%) in the ixazomib arm and 83/154 (54%) in the placebo arm experienced a progression event. The median progression-free survival was 17.5 month in the ixazomib arm and 11.1 months in the placebo arm. The hazard ratio (HR) was 0.66 [95% CI 0.47-0.93, p=0.02]. At 23 months, the hazard ratio was 0.7 [95% CI 0.52-0.95, p=0.02]. While the hazard ratio of progression-free survival for patients not identified as high risk (non-high risk) were 0.83 (p=0.28) at 15 months (IA1) and 0.92 (p=0.56) at 23 months (IA2).

Quality of life

The EORTC QLQ-30 global health status score in the ixazomib arm was not different compared with the placebo arm. The change of global health status score (standard deviation) from baseline was -5.59 (21.47) in the ixazomib arm (n=73/155) and -5.81 (27.59) in placebo arm (n=76/154). The least square mean difference between the treatment arms was 0.22 (95%CI -7.81 to 8.24, p=0.9573). The manufacturer has reported that results for quality of life were similar in the subgroup analysis compared to the ITT analysis. It should be noted that the global health status score is representative of one aspect of the EORTC QLQ C30 questionnaire. Results for the functional scales, symptom scales and single item symptom scales were not presented for the subgroup analysis.

Overall response rate

The overall response rate in the ixazomib arm (75%) was higher than placebo arm (65%).[7] The number of patients who had a complete response or very good partial response was also higher in the ixazomib arm (45%) than placebo arm (32%). No comparative statistics was reported.

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Time to progression

The median time to disease progression was 18.5 months in the ixazomib arm and 12.1 months in the placebo arm.

Safety profile

At 23 months, 103/155 (67%) of ixazomib patients and 110/154 (71%) of placebo patients discontinued treatment. The most common reason for discontinuation was disease progression (39% of ixazomib patients and 52% of placebo patients).

Table 14: Safety profile for expanded high-risk cytogenetic subgroup[31]

Variable	ILd, n=154	Ld, n=154
Any adverse event	153 (99%)	153 (99%)
Any grade ≥3 adverse event	107 (69%)	103 (67%)
Serious adverse events	71 (46%)	76 (49%)
On study death	4 (3%)	13 (8%)
Withdrawal due to adverse event	26/155 (17%)	23/154 (15%)

Table 15: Adverse events that occurred in ≥5% of patients in expanded high-risk cytogenetic subgroup

Primary System Organ Class, n (%) Preferred Term, n (%)	ILd, n=154	Ld, n=154
Infections and infestations	116 (75)	113 (73)
Upper respiratory tract infection	38 (25)	29 (19)
Nasopharyngitis	33 (21)	26 (17)
Gastrointestinal disorders	104 (68)	106 (69)
Diarrhoea	51 (33)	61 (40)
Constipation	48 (31)	45 (29)
General disorders and administration site conditions	95 (62)	96 (62)
Fatigue	42 (27)	42 (27)
Oedema peripheral	37 (24)	35 (23)
Musculoskeletal and connective tissue disorders	96 (62)	98 (64)
Back pain	37 (24)	28 (18)
Muscle spasms	21 (14)	34 (22)
Nervous system disorders	88 (57)	80 (52)
Peripheral sensory neuropathy	25 (16)	23 (15)
Dizziness	17 (11)	15 (10)
Headache	17 (11)	15 (10)
Neuropathy peripheral	17 (11)	9 (6)
Blood and lymphatic system disorders	72 (47)	83 (54)
Neutropenia	42 (27)	46 (30)
Anaemia	39 (25)	48 (31)
Thrombocytopenia	39 (25)	23 (15)
Skin and subcutaneous tissue disorders	69 (45)	62 (40)
Pruritus	20 (13)	12 (8)
Rash macular	14 (9)	8 (5)
Rash maculo-papular	10 (6)	8 (5)
Respiratory, thoracic and mediastinal disorders	62 (40)	61 (40)
Cough	24 (16)	27 (18)
Dyspnoea	12 (8)	12 (8)
Metabolism and nutrition disorders	53 (34)	54 (35)

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Primary System Organ Class, n (%) Preferred Term, n (%)	ILd, n=154	Ld, n=154
Decreased appetite	25 (16)	12 (8)
Hypokalaemia	19 (12)	15 (10)
Psychiatric disorders	53 (34)	60 (39)
Insomnia	32 (21)	39 (25)
Depression	10 (6)	5 (3)
Investigations	45 (29)	44 (29)
Platelet count decreased	16 (10)	8 (5)
Neutrophil count decreased	9 (6)	9 (6)
Eye disorders	41 (27)	37 (24)
Conjunctivitis	11 (7)	2 (1)
Vision blurred	8 (5)	8 (5)
Cataract	6 (4)	15 (10)
Vascular disorders	39 (25)	41 (27)
Hypertension	11 (7)	5 (3)
Hypotension	9 (6)	7 (5)
Injury, poisoning and procedural complications	34 (22)	38 (25)
Contusion	8 (5)	10 (6)
Fall	7 (5)	15 (10)
Cardiac disorders	29 (19)	26 (17)
Palpitations	6 (4)	1 (<1)
Atrial fibrillation	5 (3)	11 (7)
Cardiac failure	4 (3)	2 (1)
Cardiac failure congestive	4 (3)	2 (1)
Renal and urinary disorders	19 (12)	32 (21)
Renal failure acute	4 (3)	5 (3)
Renal failure chronic	3 (2)	9 (6)
Ear and labyrinth disorders	14 (9)	14 (9)
Vertigo	6 (4)	6 (4)
Hearing impaired	3 (2)	1 (<1)
Tinnitus	3 (2)	3 (2)
Endocrine disorders	8 (5)	7 (5)
Hyperthyroidism	4 (3)	1 (<1)
Hypothyroidism	0	3 (2)
Cushingoid	3 (2)	3 (2)
Hepatobiliary disorders	3 (2)	8 (5)
Hyperbilirubinaemia	0	4 (3)
Cholelithiasis	1 (<1)	2 (1)
Cholecystitis acute	0	2(1)

6.3.2.4 Detailed Outcome Data and Summary of Outcomes for patients with two or more prior therapies

There were 148 ixazomib patients and 149 placebo patients who had at least two prior therapies (41% of ITT population).[7] Patients were stratified according to the number of prior therapy at randomization. Twenty percent of patients in this subgroup also had high-risk cytogenetic features.

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Table 16: Baseline Patient Characteristics for the Subgroup of Patients who had 2+ Prior Therapies

Characteristics	ILd (N=148) N (%)	Ld (N=149) N (%)
Median age, years (range)	67.0 (44, 91)	66.0 (42, 88)
Age >65 years	80 (54)	77 (52)
Male sex	81 (55)	86 (58)
White race	125 (84)	120 (81)
ECOG PS 0 1 2	 59 (40) 77 (52) 10 (7)	 58 (39) 74 (50) 15 (10)
ISS Stage at study entry I or II III	 128 (86) 20 (14)	 131 (88) 18 (12)
Creatinine clearance, mL/min, n (%) <30 30-50 ≥50	 3 (2) 16 (11) 129 (87)	 2 (1) 21 (14) 125 (84)
Median time since initial diagnosis of MM, months (range)	57.76 (6.0, 281.1)	55.13 (4.9, 306.3)
Patients with high-risk cytogenetic abnormalities	30 (20)	28 (19)
Prior SCT	86 (58)	81 (54)
Relapsed refractory relapsed and refractory primary refractory	93 (63) 15 (10) 40 (27) 11 (7)	90 (60) 19 (13) 40 (27) 10 (7)
Prior PI therapy	111 (75)	113 (76)
Prior IMD therapy, n (%)	100 (68)	102 (68)
Lenalidomide-containing	18 (12)	21 (14)
Thalidomide-containing	82 (55)	81 (54)
ECOG: European Cooperative Oncology Group; IMD: immunomodulatory drug; PI: proteasome inhibitor; PS = performance status		

Overall survival

At 23 months, 33 of 148 ixazomib patients (22%) and 45 of 149 placebo patients (30%) had died. The hazard ratio of overall survival at 15 and 23 months were 0.62 (p=0.09) and 0.65 [95% CI 0.41-1.02, p=0.057] respectively. The median overall survival was not estimated as the data was not yet matured.

Progression-free survival

At 15 months, 41% (123/297) of patients experienced disease progression. The hazard ratio of disease progression was 0.58 [95%CI 0.4-0.84, p=0.003]. The hazard ratio was 0.62 [95%CI not reported, p=0.003] at 23 months. The median progression-free survival was 22 months for ixazomib patients and 13 months for placebo patients at the 23 months interim analysis.

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Quality of life

The EORTC QLQ-30 global health status score in the ixazomib arm was not different compared with the placebo arm. The change of global health status score (standard deviation) from baseline was -7.51 (24.42) in the ixazomib arm (61/136) and -3.23 (27.80) in placebo arm (n=62/145). The least square mean difference between the treatment arms was -4.29 (95%CI -13.63 to 5.06, p=0.3656). The manufacturer has reported that results for quality of life were similar in the subgroup analysis compared to the ITT analysis. It should be noted that the global health status score is representative of one aspect of the EORTC QLQ C30 questionnaire. Results for the functional scales, symptom scales and single item symptom scales were not presented for the subgroup analysis.

Overall response rate

The overall response rate in the ixazomib arm (80%) was higher than placebo arm (67%).[7] The number of patients who had a complete response or very good partial response was also higher in the ixazomib arm (53%) than placebo arm (32%).

Time to progression

The median time to progression was only estimated for placebo arm (13 months). The data was not yet mature to perform comparative statistics.

Safety profile

At 23 months, 88/149 (59%) of ixazomib patients and 103/148 (69%) of placebo patients discontinued treatment. The most common reason for discontinuation was disease progression (31% of ixazomib patients and 38% of placebo patients).

Table 17: Safety profile for the subgroup of patients with at least 2 prior therapies

Variable	ILd, n=149	Ld, n=148
Any adverse event	147 (99%)	148 (100%)
Any grade ≥3 adverse event	114 (77%)	113 (76%)
Serious adverse events	69 (46%)	83 (56%)
On study deaths	5 (3%)	13 (9%)
Withdrawal due to adverse event	24/149 (16%)	30/148(20%)

Table 18: Adverse events that occurred in ≥5% of patients with at least 2 prior therapies

	ILd	Ld
	N=149 n (%)	N=148 n (%)
Primary System Organ Class Preferred Term		
Infections and infestations	114 (77)	102 (69)
Upper respiratory tract infection	41 (28)	27 (18)
Nasopharyngitis	32 (21)	19 (13)
Gastrointestinal disorders	115 (77)	91 (61)
Diarrhoea	68 (46)	47 (32)
Constipation	53 (36)	34 (23)
Nausea	51 (34)	34 (23)
General disorders and administration site conditions	100 (67)	91 (61)
Fatigue	44 (30)	37 (25)
Oedema peripheral	42 (28)	28 (19)
Nervous system disorders	94 (63)	80 (54)

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	ILd	Ld
	N=149 n (%)	N=148 n (%)
Peripheral sensory neuropathy	26 (17)	20 (14)
Headache	21 (14)	23 (16)
Musculoskeletal and connective tissue disorders	94 (63)	93 (63)
Muscle spasms	29 (19)	36 (24)
Back pain	28 (19)	27 (18)
Skin and subcutaneous tissue disorders	85 (57)	48 (32)
Pruritus	21 (14)	10 (7)
Rash maculo-papular	17 (11)	3 (2)
Rash macular	16 (11)	9 (6)
Blood and lymphatic system disorders	81 (54)	73 (49)
Anaemia	47 (32)	44 (30)
Neutropenia	41 (28)	39 (26)
Respiratory, thoracic and mediastinal disorders	64 (43)	59 (40)
Cough	24 (16)	21 (14)
Dyspnoea	16 (11)	13 (9)
Psychiatric disorders	54 (36)	56 (38)
Insomnia	27 (18)	38 (26)
Anxiety	7 (5)	8 (5)
Confusional state	6 (4)	8 (5)
Metabolism and nutrition disorders	54 (36)	41 (28)
Hypokalaemia	18 (12)	12 (8)
Decreased appetite	17 (11)	15 (10)
Investigations	49 (33)	43 (29)
Platelet count decreased	15 (10)	7 (5)
Neutrophil count decreased	10 (7)	11 (7)
Weight decreased	10 (7)	8 (5)
Eye disorders	47 (32)	32 (22)
Cataract	12 (8)	18 (12)
Conjunctivitis	11 (7)	1 (<1)
Dry eye	10 (7)	5 (3)
Injury, poisoning and procedural complications	44 (30)	40 (27)
Fall	16 (11)	11 (7)
Contusion	8 (5)	6 (4)
Vascular disorders	35 (23)	33 (22)
Hypotension	10 (7)	3 (2)
Hypertension	9 (6)	8 (5)
Cardiac disorders	21 (14)	25 (17)
Atrial fibrillation	7 (5)	8 (5)
Palpitations	3 (2)	4 (3)
Sinus tachycardia	3 (2)	1 (<1)
Renal and urinary disorders	18 (12)	25 (17)
Renal failure acute	4 (3)	6 (4)
Urinary incontinence	4 (3)	3 (2)
Neoplasms begin, malignant, and unspecified (incl cysts and polyps)	15 (10)	19 (13)
Plasma cell myeloma	3 (2)	3 (2)
Plasmacytoma	2 (1)	0
Squamous cell carcinoma (skin)	2 (1)	1 (<1)
Ear and labyrinth disorders	12 (8)	11 (7)
Tinnitus	4 (3)	1 (<1)

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	ILd	Ld
	N=149 n (%)	N=148 n (%)
Hypoacusis	1 (<1)	3 (2)
Vertigo	1 (<1)	3 (2)
Hepatobiliary disorders	7 (5)	5 (3)
Hyperbilirubinaemia	1 (<1)	3 (2)
Biliary colic	1 (<1)	0
Cholecystitis acute	1 (<1)	0
Cholecystitis chronic	0	1 (<1)
Cholestasis	1 (<1)	0
Drug induced liver injury	1 (<1)	0
Hepatic function abnormal	1 (<1)	0
Hepatic steatosis	1 (<1)	0
Hepatotoxicity	1 (<1)	0
Cholelithiasis	0	1 (<1)

6.4 Ongoing Trials

None was identified.

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7 SUPPLEMENTAL QUESTIONS

7.1 Critical appraisal of the network meta-analysis

7.1.1 Objective

The pCODR Clinical Guidance Panel (CGP) identified that carfilzomib, lenalidomide, dexamethasone (CLd) combination therapy is a relevant comparator for ixazomib, lenalidomide, dexamethasone (ILd) combination therapy. In the absence of head to head trials comparing these two treatment regimens, the CADTH-pCODR Methods team provided a critical appraisal of a manufacturer provided network meta-analysis that evaluated the relative efficacy of ILd versus other selected therapies based on the outcomes such as progression-free survival (PFS) and overall survival (OS) in patients with relapsed/refractory multiple myelomas that were treated with at least one prior therapy. Given the reimbursement request submitted to CADTH-pCODR, the focus of this critical appraisal was on indirect evidence related to patients with 1) high-risk cytogenetic and who have had at least one prior line of therapy and 2) patients who had at least 2 prior lines of therapy. Within the submitted NMA, results specific to the subgroup of patients high risk cytogenetics were available for PFS. Overall survival results were only available based on ITT analysis of the available trials included in the network. There was no direct or indirect evidence provided addressing the subgroup of patients who have had at least 2 prior lines of therapies.

7.1.2 Findings

Two RCTs (ASPIRE and TOURMALINE-MM1) [34, 2] were included in the indirect comparison between ILd combination and CLd combination to determine comparative efficacy in the subgroup of patients with high-risk cytogenetic. Based on the ASPIRE trial publication 13% (n=100 total) of patients were reported to have high risk cytogenetics (patients with the genetic subtype t(4;14) or t(14;16) or with deletion 17p in 60% or more of plasma cells, according to central review of bone marrow samples obtained at study entry.)[34] Therefore the comparison in this subgroup of patients is based on a small number of patients.

The results reported that there was no significant difference between ILd combination and CLd combination in terms of PFS. The results of this analysis were made non disclosable by the manufacturer.

Nine RCTs were included in the NMA for analysis for overall survival. The evidence used to estimate the hazard ratio was based on the subgroup of patients with high risk cytogenetics but rather the use of the ITT population from the included RCTs.

No significant difference in overall survival was observed comparing ILd with CLd. The results of this analysis were also made non disclosable by the manufacturer.

7.1.3 Summary

The Bucher method was used to indirectly compare ILd to CLd combination through Ld only treatment in terms of PFS, which was the common comparator. The Bucher method is a simple, easy way to indirectly compare interventions. However, the Bucher method would only be valid if the transitivity assumption is true. Transitivity assesses the similarity between studies in terms of methodology, baseline characteristics, inclusion and exclusion criteria, intervention and comparators. If the trial is significantly different in any of these criteria, then the transitivity assumption may not be true.

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Baseline characteristics were not available based on the high-risk cytogenetic subgroups for the ASPIRE trial. Therefore only the comparison of ITT population between ASPIRE trial (CLd vs Ld) and TOURMALINE-MM1 (ILd vs Ld) was possible.

- ASPIRE was an open label trial. Since the patients and investigators were not blinded to treatment assignment, it was more prone to performance bias which might lead to better compliance within the carfilzomib arm.[37]
- Patient enrolled in TOURMALINE-MM1 were fitter than the patient enrolled in ASPIRE in terms of ISS stage at diagnosis (88% at stage I & II vs 42% at stage I & II) and percentage of patient who had only one prior therapy (61% vs 43%).[34, 2]
- The comparator was the same in both trials in term of dose and frequency. [34, 2]
- ASPIRE trial had a longer median follow-up (32.3 months in carfilzomib arm, 31.5 months in the placebo arm) compared with TOURMALINE-MM1 (14.8 months in the ixazomib arm, 14.6 months in the placebo arm). [34, 2]

These differences could affect the effect estimate of the indirect comparison and should be considered when interpreting the result, but they were not strong enough to indicate that the indirect comparison was not appropriate in this case.

There was only one trial included per direct comparison and only one path to indirectly compare carfilzomib with ixazomib. Therefore, it was not possible to assess heterogeneity and inconsistency. Due to the concern of effect modification in some transitivity criteria, in addition to the absence of heterogeneity and inconsistency assessments, the quality of evidence was low for the indirect comparison of carfilzomib and ixazomib. The 95% credible interval in the progression-free survival and overall survival analyses were quite wide, which suggested a high level of uncertainty and the lack the statistical power to detect any differences between carfilzomib and ixazomib in both analyses. The effect estimate can be used in the economic models to explore the uncertainty. On the other hand, this indirect comparison did not provide any additional information for the clinical effectiveness assessment.

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8 COMPARISON WITH OTHER LITERATURE

The FDA evaluated ILd combination for relapsed/refractory multiple myeloma patient with at least one prior therapy. The FDA clinical report included one RCT (TOURMALINE-MM1) in their report.[6] The result reported in the FDA clinical/statistical review was similar to the ITT findings in this CADTH-pCODR report. The FDA concluded that ILd showed benefit compared to Ld treatment only. However, the reviewers also raised concerns about the variation in progression-free survival analysis between the first and second interim analysis. The FDA review did not assess efficacy based on the expanded high risk subgroup or the subgroup of patients with 2 or more prior lines of treatments.

The European Medicines Agency (EMA) also evaluated ILd combination for relapsed/refractory multiple myeloma patient with at least one prior therapy. The EMA review included one RCT (TOURMALINE-MM1) in their report.[35] The result reported by the clinical efficacy section was similar to the findings of this CADTH review. The EMA initially concluded that the evidence was insufficient to support the clinical efficacy of ILd citing differences in the first and second interim analyses. However, upon re-examination, the EMA reversed its decision and concluded that ILd was clinically effective in the examined population. Although the EMA acknowledged that subsequent exploratory analysis showing some uncertainty is not enough to change the conclusions about a clear beneficial effect in terms of PFS, the EMA noted that the uncertainty observed in the IA2 suggests the size of the treatment effect observed in the primary analysis might be an over-estimation.[35] The EMA committee did not agree about drawing firm conclusion from subgroups data of high risk or 2+ prior therapies. They considered the evidence was insufficient without multiplicity adjustment for multiple subgroup analyses and lacked clinical and/or biological rational to explain the supposed greater efficacy observed in these subgroups of patients.

No study comparing CLd combination to ILd combination in relapsed/refractory multiple myeloma patients was found. Carfilzomib plus Ld combination for relapsed/refractory multiple myeloma patients with at least one prior therapy was evaluated by CADTH in May 2016.[36] The clinical review included one open label RCT (ASPIRE trial) that randomized 792 relapsed/refractory multiple myeloma patients to CLd (n=396) or Ld only (n=396) therapy. The review found CLd combination reduced the risk of progression or death when compared with Ld only therapy (Hazard ratio of progression-free survival = 0.69, 95%CI 0.57-0.83, p=0.0001). When compared with the patients in TOURMALINE-MM1, the patients in ASPIRE trial had more advanced disease as 44% was diagnosed at stage III in ASPIRE compared to 12% in TOURMALINE-MM1, and 56% of patients in ASPIRE had two or more prior therapies compared to 39% in TOURMALINE-MM1.

No other review was found comparing bortezomib/dexamethasone combination to ILd combination.

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9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Lymphoma/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 ixazomib (Ninlaro) 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 CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

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.

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APPENDIX A: LITERATURE SEARCH STRATEGY

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** November 2016, **Embase** 1974 to 2016 December 19, **Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

Line #	Searches	Results
1	*Ixazomib/ or *Ixazomib citrate/	171
2	(Ixazomib* or MLN2238 or MLN 2238 or MLN9708 or MLN 9708 or Ninlaro*).ti,ab,kw.	492
3	or/1-2	497
4	3 not conference abstract.pt.	315
5	3 and conference abstract.pt.	182
6	limit 5 to yr="2011 -Current"	165
7	4 or 6	480
8	7 use oemezd	309
9	(Ixazomib* or MLN2238 or MLN 2238 or MLN9708 or MLN 9708 or Ninlaro*).ti,ab,kf,kw,hw,rn,nm.	793
10	(1072833-77-2 or 71050168A2 or 1239908-20-3 or 46CWK97Z3K).rn,nm.	412
11	or/9-10	793
12	11 use ppez,cctr	188
13	8 or 12	497
14	limit 13 to english language	479

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15	remove duplicates from 14	338

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#2	Search **#1 AND publisher [sb]**	10
#1	Search **Ixazomib* OR MLN2238 OR MLN 2238 OR MLN9708 OR MLN 9708 OR Ninlaro* OR 1072833-77-2 OR 71050168A2 OR 1239908-20-3 OR 46CWK97Z3K**	133

3. Cochrane Central Register of Controlled Trials (Central)

Searched via Ovid

4. Grey Literature search via:

Clinical trial registries:

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

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

Search: ixazomib/Ninlaro, multiple myeloma

Select international agencies including:

U.S. Food and Drug Administration (FDA)
http://www.fda.gov/

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

Search: ixazomib/Ninlaro

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

American Society of Hematology
http://www.hematology.org/

Search: ixazomib/Ninlaro, multiple myeloma - last 5 years

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APPENDIX B: DETAILED METHODOLOGY OF LITERATURE REVIEW

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 Epub ahead of print, in-process records & daily updates via Ovid; Embase (1974-) via Ovid; the Cochrane Central Register of Controlled Trials (Nov. 2016) 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 ixazomib and Ninlaro.

No filters were applied to limit the retrieval by study type. The search was limited to English-language documents, but not limited by publication year, except for the limiting of conference abstracts to the past five years.

The search is considered up to date as of April 3, 2017.

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

Study Selection

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

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

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.

Data Analysis

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

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Writing of the Review Report

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

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

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