CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Ixazomib (Ninlaro) for Multiple Myeloma

July 5, 2019

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List of Abbreviations

AE(s)	Adverse Events
CI	Confidence interval
CGP	Clinical Guidance Panel
DOR	Duration of Response
DLd	Daratumumab + lenalidomide + dexamethasone
DVd	Daratumumab + bortezomib + dexamethasone
ELd	Elotuzumab + lenalidomide + dexamethasone
HR	Hazard ratio
ILd	Ixazomib + lenalidomide + dexamethasone
Kd	Carfilzomib + dexamethasone
CLd	Carfilzomib + lenalidomide + dexamethasone
Ld	Lenalidomide + dexamethasone
MM	Multiple Myeloma
NMA	Network meta-analysis
ORR	Overall response rate
OS	Overall survival
pCODR	pan-Canadian Oncology Drug Review
PFS	Progression free survival
V	Bortezomib
VLd	Bortezomib + lenalidomide + dexamethasone
Vd	Bortezomib + dexamethasone

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 compared to appropriate comparators in patients with multiple myelomas (MM) who have received at least one prior therapy. The funding request is for ILd for the treatment of adult patients with MM who have received at least one prior therapy. A previous pCODR review evaluated the safety and efficacy of ILd on patient outcomes compared to lenalidomide and dexamethasone (Ld) in patients with MM that had at least two prior therapies or one prior therapy and have high-risk cytogenetic features.[1] The previous funding request was for adult patients with MM who have received at least one prior therapy and have high-risk cytogenetics or have received at least two prior therapies. The current review provided subsequent analysis results for overall survival and safety.

Ixazomib is a novel, orally administered, proteasome inhibitor.[1] 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]

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.[2] 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 safety and efficacy of adding ixazomib to lenalidomide and dexamethasone (ILd) combination compared to lenalidomide and dexamethasone (Ld) combination alone on efficacy and safety outcomes in patients with relapsed, refractory or relapsed and refractory multiple myeloma (MM). The MM1 trial enrolled 722 patients from 26 countries across 4 continents with relapsed, refractory or relapsed and refractory MM that had at least one to three prior lines of treatment.[3] Patients were randomized in a 1:1 ratio to receive ILd triple combination or Ld.[4] Randomization was stratified according to the number of prior therapies (1 versus 2 or 3), previous exposure to proteasome inhibitors (exposed versus not exposed), and International Staging System disease stage (Stage I or II versus Stage III).[2] Patients, investigators and the independent assessors were blinded to the treatment allocation. Patients were treated until disease progression or unacceptable toxicity.[5]

The primary outcome of TOURMALINE-MM1 was progression-free survival (PFS) assessed by an independent review committee which was blinded to treatment allocation.[4]

Key secondary outcomes included overall survival (OS) in intention-to-treat population (ITT). Other secondary outcomes included overall response rate, complete response rate plus very good partial response rate, duration of response, 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. [4]

Efficacy Results

In the first interim analysis of the TOURMALINE-MM1 trial, the hazard ratio (HR) for PFS of the ITT population was 0.74 (95% confidence interval [CI] 0.59-0.94, p=0.012) based on 129 events in the ILd group compared to 157 events in the Ld group.[4] The effect size was reduced at the second interim analysis which is a non-inferential PFS analysis (HR: 0.82, 95% CI 0.67-1.00, p=0.055). The first interim analysis for OS was conducted after a median follow-up of 15 months when 107 events had occurred and results were not significant (HR: 0.90, 95% CI: 0.62-1.32, p=0.59). [1] The second interim analysis for OS was conducted after a median follow-up period of 23 months when 171 deaths had occurred. This was based on 81/360 (23%) patients from the ixazomib arm and 90/362 (25%) patients from the Ld arm. The HR was 0.87 [95% CI: 0.64-1.18, p=0.36]. A subsequent analysis for OS was conducted following the second interim analysis after [redacted] deaths had occurred at [redacted] months follow-up. *(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until January 31, 2020 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*.) The results were not statistically significant (HR=[redacted], 95% CI: [redacted], p=[redacted]) and the [redacted] OS benefit was [redacted]% in the ILd arm vs. [redacted]% in the Ld arm.[6] *(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until January 31, 2020 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*.) Although the statistical boundary to reach significance (p <0.011) for OS was not met at this analysis, the trial will continue in a blinded fashion towards the final analysis at 486 death events (expected in March 2020).[4]

Based on results from the China Continuation study, conducted to fulfill regulatory requirements in China with the intention to assess consistency with the global TOURMALINE-MM1 study, Hou et al[7] reported 67 PFS events (30 and 37 in the ILd and Ld arms respectively) and a 40% reduction in the risk of PFS in patients randomized to the ILd arm compared to Ld (HR 0.598, 95% CI: 0.367–0.972; p = 0.035). For OS, there was a 58% improvement in patients randomized in the ILd group compared to the Ld group (HR 0.419; 95% CI 0.242–0.726; p = 0.001). Notably, there was no statistical analysis plan for this study.

A pooled analysis of the TOURMALINE-MM1 trial and China Continuation study conducted on a subgroup of Asian patients found that the median PFS was 7.3 months and 4.6 months in the ILd and Ld treatment groups respectively (HR=0.559, 95% CI no reported). In addition, the median OS in the ITT was 25.8 months and 15.8 months in the ILd and Ld treatment groups, respectively (HR=0.346, 95% CI 0.196-0.611).[8]

Safety Results

Overall, the proportion of adverse events occurring ≥10% of patients in either the ILd group or the Ld regimen (all grades, grade 3 and grade 4) were similar at 23 months follow-up and at the latest analysis.[2,6]

In the China Continuation Study, 38 (67%) and 43 (74%) patients reported grade ≥3 adverse events. Thrombocytopenia, neutropenia and anemia were the most frequent grade 3/4 adverse events.[7]

In the pooled analysis of the TOURMALINE-MM1 trial and China Continuation study conducted on a subgroup of Asian patients, grade 3/4 treatment-emergent adverse events were reported in 74% of patients in the ILd group compared to 73% of patients in the Ld group.[8]

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

One patient advocacy group, Myeloma Canada (MC), provided input on the pCODR submission of ixazomib (I) in combination with lenalidomide (L) and dexamethasone (d) submission for adult patients with multiple myeloma who have had at least one prior therapy.

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. Patients with myeloma value disease control, prolonged life, remission, improved quality of life, fewer side effects and managing key symptoms, such as, infections, kidney problems, problems with mobility, pain, fatigue, neuropathy and shortness of breath. Myeloma Canada noted that cure would be the most important value, but patients understand there are no cures at the moment. 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 concerns associated with myeloma that impact or limit day-to-day activity and quality of life. Patients who responded to the survey questions noted disease control as the most important consideration followed by prolonged life and remission, and fewer side effects. Patients who had experience with ixazomib noted disease control as an expectation fulfilled, followed by prolonged life, remission, improved quality of life, fewer side effects than other treatments and enjoying a normal life. Patients also noted that ILd as providing an excellent quality of life (25% of respondents), followed by good (31.25% of respondents), very good (12.5% of respondents) fair (18.75% of respondents) and poor (12.5% of respondents). Of the patient respondents, 50% noted that ILd improved their long-term health outlook, 12.5% noted that the treatment did not improve their long term health outcome and 37.5% of respondents noted that it was too soon to tell.

Please see Section 3 for a summary of specific input received from Patient groups.

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 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 Section 4 for a summary of specific input received from PAG.

Registered Clinician Input

Two joint clinician input submissions (Myeloma Cancer Research Network and DAC for Hematology, Cancer Care Ontario) were made from a total of nine clinicians. The registered clinicians provided input on ixazomib in combination with lenalidomide and dexamethasone for adult patients with multiple myeloma who have at least one prior therapy.

Carfilzomib combination therapy was stated to be the most appropriate comparator for ixazomib. Clinicians agreed the clinical trial criteria were applicable to the Canadian context. There were several advantages of ixazomib being an oral therapy, including benefits for patients for whom traveling long distances to cancer centres is a challenge. Elderly patients were highlighted in particular as potentially benefiting the most from ixazomib, due to its oral formulation and tolerability.

There was consensus that carfilzomib in combination with lenalidomide and dexamethasone would remain as the preferred proteasome inhibitor (PI) for patients in this setting. However, the choice of treatment (i.e., carfilozimib or ixazomib) is dependent on patient factors and preferences. Switching to a different PI upon progression, i.e., from carfilzomib to ixazomib, or vice versa, was not supported by the clinicians. Overall, ixazomib would most likely be considered as second-line treatment or for patients who received one to three prior treatments. An ideal sequencing path was not provided, as both clinician inputs highlighted the lack of currently available evidence to inform such a decision, and the complex nature of multiple myeloma. While carfilzomib, bortezomib and ixazomib were stated to be relatively interchangeable, their therapeutic profiles were acknowledged to affect their utility in practice.

Please see Section 5 for a summary of specific input received from the registered clinician(s).

Summary of Supplemental Questions

The objective of the network meta-analysis (NMA) was to evaluate the relative efficacy and safety of ixazomib versus other selected regimens for the treatment of relapsed refractory multiple myelomas (MM) based on the outcome of progression free survival (PFS), overall survival (OS) and overall response rate (ORR). A systematic search of EMBASE and PubMed/Medline using Ovid was performed along with searches on the 2016-2017 European Hematology Association (EHA) and American Society of Hematology (ASH) conference websites. The current NMA incorporated results from the second interim analysis for PFS and ORR and subsequent interim analyses for OS from the TOURMALINE MM-1 trial to perform an indirect comparison with other treatments of interest.[9]

A total of 17 studies, including 13 peer-reviewed randomized controlled trials (RCTs) (from 26 full text publications and 12 conference abstracts) and 4 observational studies (from 3 full text publications and 1 conference abstract) were included in the analysis.

Fifteen RCTs in the extended NMA network provided results for PFS including three observational studies.

- ILd was associated with a statistically significantly improvement in PFS as compared to Ld, V, Dex and Pom-dex however statistically significantly shorter PFS compared to DVd and DLd.
- There was no statistically significant difference in PFS for ILd compared to Vd, PVd, VLd, ELd, Cd or CLd.

Fifteen RCTs which included 13 treatment comparisons reported results for OS in the NMA extended network.

- There was a statistically significant improvement in OS for ILd compared to Ld, V, Dex and Pom-Dex.
- There was no statistically significant difference in OS for ILd compared to Vd, PVd, VLd, ELd, Cd, CLd, DLd and DVd.

Seventeen studies which included 13 treatment comparisons reported results for ORR in the NMA extended network.

- There was a statistically significant improvement in ORR for ILd compared to Ld, V and Dex.
- While ORR was statistically significantly improved for ILd compared to CLd and DLd, the magnitude of effect for ORR was decreased.
- There was no statistically significant difference in ORR for ILd compared to Vd, Pom-Dex, PVd, VLd, ELd, Cd and DVd.

The pCODR review team noted that the submitted NMA incorporated treatment regimens that are not reimbursed in the Canadian setting or anticipated to be reimbursed in the near future, namely panobinostat + bortezomib + dexamethasone and elotuzumab + lenalidomide + dexamethasone. Upon exclusion of the trails (ELOQUENT-2 and PANORAMA1) that encompassed the aforementioned treatment regimes, the results of the NMA remained similar. Furthermore, the exclusion of ELOQUENT-2 and PANORAMA1 showed tighter 95% CrIs.[10]

Conclusions

The NMA was conducted using a Bayesian framework. The results from the NMA demonstrated that ILd was associated with significantly improved PFS and OS compared to Ld, V, Dex, and Pom-Dex. Additionally, statistically significantly shorter PFS was reported when compared to DLd and DVd. In addition, there was a statistically significant improvement in ORR in favour of ILd compared to Ld, V, and Dex.

The submitter noted that the network was not well connected and sparse, therefore only fixed effects models were conducted for this study. The inclusion of observational studies in the NMA extended network for PFS violates the assumption of homogeneity. Furthermore, there was heterogeneity across study populations due to different inclusion and exclusion criteria. The sample size of the underlying studies may have contributed towards the imprecision of the estimates. Thus, the width of the credible intervals was wide. Therefore the results for PFS, OS and ORR should be interpreted with caution. Other outcomes of interest (e.g., health related quality of life and safety) were not explored in this NMA.

See section 7.2 for more information.

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="3">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.[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>
</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 symptom 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.[53] A priori ixazomib dose reduction may be required depending on the severity of renal impairment, as per the product monograph.[54] Lenalidomide dosing would need to be adjusted as per the product monograph.</td></tr>
<tr><td>Hepatic function</td><td>Patients with inadequate hepatic function were excluded.</td><td>Does the exclusion of patients with inadequate hepatic function limit the interpretation of trial results with the respect to target population?</td><td>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.[55] A priori ixazomib dose reduction may be required depending on the severity of hepatic impairment, as per the product monograph.[54]</td></tr>
</table>

1.2.3 Factors Related to Generalizability of the Evidence

	Other populations	No evidence was identified within the current review to support the used of ILd in the following populations: Waldenstrom's macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome	Is there evidence to support the use of ILd in patients with Waldenstrom's macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome	There is insufficient evidence to know the effectiveness of ILd in patients with of Waldenstrom's macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome. The one exception would be plasma cell leukemia, as this is a rare disoLder managed in the same fashion as myeloma. This regimen would be a reasonable consideration in this circumstance.

1.2.4 Interpretation

Burden of Illness and Need

Multiple myeloma is an incurable plasma cell neoplasm representing 1.3% of all new cancers in Canada. In 2018, it is estimated that 2,900 Canadians were diagnosed with myeloma with 1,450 patients dying from myeloma.[11] The median age at diagnosis is 69 years with a slight male preponderance. Although there is significant heterogeneity within myeloma, the age-standardized five-year net survival rate for Canadian patients is 42%.[11]

With better understanding of the biology of multiple myeloma, it is now widely accepted that effective early combination novel therapies should be embraced early and continuously while paying attention to side effect profile. Alkylators, immunomodulatory agents (IMiD, proteasome Inhibitors (PI), and monoclonal antibodies are the 4 main "currently" available/approved classes of chemotherapeutics in Canada. An agent from different therapeutic class is often used in combination with an agent from another in conjunction with steroids such as dexamethasone to enhance efficacy.

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 chemotherapy considers the: 1) outcomes with the regimens used in prior lines of therapy, 2) condition of the patient, 3) expected tolerance of adverse effects, 4) availability of treatment options, and 5) personal and geographical considerations.

Taken together, patients will ultimately receive all possible available effective chemotherapeutic options sooner or later and in various combinations subject to early mortality. It is important to emphasize that the use of effective, superior and safe combination therapy early is preferred as opposed to "saving them for later". In general, the former approach leads to better PFS, OS and health-related quality of life.

It is within this context that ixazomib in combination with lenalidomide and dexamethasone for relapsed myeloma is assessed at the Clinical Guidance Panel. Within the pCODR framework of reviews, the reviewers identified one Randomized Control Trial [12] addressing the submitter, Takeda Canada's request for funding.

Interpretation

Overall [12]

The identified randomized trial comparing lenalidomide and dexamethasone with ixazomib (ILd) or placebo (Ld) for patients with relapsed and refractory myeloma, demonstrating a statistically and clinically significant improvement in progression-free survival (PFS) with the addition of ixazomib to lenalidomide and dexamethasone ILd (0.74 95% CI 0.59-0.94, p=0.01) with a median follow-up of 14.8 months. This finding was published as the "final" analysis in the *New England Journal of Medicine*. Following this publication, an additional analysis for PFS was performed with a median follow-up of 23 months – which demonstrates a smaller PFS benefit (0.82 95% CI 0.67-1.0, p=0.0548). [13] With the longer follow-up time, data from IA2 suggest that there is less certainty in the estimate of PFS benefit with ixazomib. However, the absolute difference between ILd and Ld remains >4 months and clinically significant. PFS is considered a clinically important and valid primary endpoint in studies of myeloma therapy where an absolute improvement of >4-6 months is considered clinically meaningful from a patient's perspective. Overall survival (OS) remains an important endpoint in myeloma studies but the use of subsequent lines of therapy in this incurable malignancy often makes it difficult to discern an OS benefit from one line of

therapy. The trial did not demonstrate an OS benefit with ILd at the first or second planned interim analysis. A recent analysis based on a median follow up of [redacted] months also demonstrated no statistically significant benefit for OS. The Final analysis for OS is still outstanding. *(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until January 31, 2020 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*.)

Tolerability

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 (by EORTC QLQC30 and MY20 scales) nor improvements.

Comparative Therapies

There are several recent drug therapies for relapsed myeloma that have been demonstrated in randomized trials to improve PFS when added to lenalidomide (Revlimid) and dexamethasone (Ld). These include intravenous (IV) carfilzomib (CLd), IV elotuzumab and IV daratumumab. Additionally, in the front-line setting, the addition of IV bortezomib to lenalidomide and dexamethasone (VLd) has been shown to improve overall survival in one randomized trial. It is unclear which triple therapy regimen is superior, but it is clear that a triple therapy combination is superior to only dual therapy in both front line or relapsed settings. Direct randomized comparisons between these various regimens are unlikely to take place in the setting of relapsed myeloma, although the CLd and VLd regimens are being compared in the front-line setting. Carfilzomib and dexamethasone has been compared to bortezomib and dexamethasone in a randomized trial in the relapsed setting.[14] Similarly CLd has been compared to Ld at the time of relapse.[15] In both of these studies, the carfilzomib regimen demonstrated superiority in both PFS and OS. No direct comparisons of these regimens with ixazomib-containing or three-drug regimens have being evaluated.

A Network Meta-Analyses (NMA) was provided by the submitter[13] to compare ILd with relevant comparators, the results are to be interpreted with caution given the limitations of the available data. Ultimately, NMA seeks to ascertain indirectly which agent is superior. However, in the care of patients with myeloma, a "new" medication is not a replacement for another, rather an additional option for care. Based on the presented indirect evidence, DVd and DLd are superior to CLD which is in turn superior to ILD with respect to PFS and OS. As such and based on the opinion of the CGP, the preferred 2nd line choice is likely either DVd or DLd based on efficacy, followed by carfilzomib/dex as 3rd line. This means that ILd cannot be used as 2nd line, as this would disqualify the use of a daratumumab combination in the later line. Additionally, ILd may not be used in third line as patients may have a progressed on both lenalidomide and bortezomib, making them ineligible for this therapy. This does not however imply that ixazomib has no therapeutic value especially in a disease where multiple relapses occur. The CGP agrees that the added value of ILD is in its convenience of oral dosing, distinguishing it from other proven three-drug combinations involving lenalidomide and dexamethasone in terms of patient convenience, acceptance, quality of life and resource utilization ("chair time"). This would be valuable in those patients who cannot travel to receive IV therapy and/or who are intolerant to daratumumab and/or carfilzomib as either 2nd or 3Ld line in specific cases. Currently, one would use Pom/dex as the last line as there are less restrictions on its funding and can still be considered in patients with resistance to lenalidomide.

The sequencing of therapies may also be determined based on what combinations are funded provincially. The standard approach is to maximize a particular regimen before

switching to the next. This may affect the choices available to patients once resistance occurs.

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 (ILd) in the treatment of relapsed and refractory myeloma, with 1-3 prior lines of therapy and regardless of cytogenetic risk profile. This is based on one high-quality randomized controlled trial that demonstrates a clinically and statistically significant benefit in progression-free survival as compared to the previous standard regimen of lenalidomide and dexamethasone (Ld), with a manageable adverse event profile and a convenient oral route of administration. Notably, a second interim analysis for PFS performed subsequent to the data from the published manuscript demonstrates a smaller PFS benefit to ixazomib. With the longer follow-up time, data from IA2 suggest that there is less certainty in the estimate of PFS benefit with ixazomib.

Nonetheless, the CGP acknowledges that ixazomib represents an important therapeutic option (given its oral nature and weekly dosing). In particular, it may be the preferred option by patients and/or clinicians looking to utilize an oral proteasome inhibitor in the care of patients with relapsed myeloma.

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 and daratumumab which has previously been reviewed by pCODR and other drugs (e.g. 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 other agent's currently reimbursed (eg. Daratumumab or carfilzomib combination agents) 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 these relevant therapies. A number of limitations were identified in the presented results and therefore caution must be used in interpreting these results as discussed.
- Treatment with ixazomib in combination with lenalidomide and dexamethasone (ILd) could reasonably be restricted to patients whose disease is not demonstrably clinically refractory (as opposed to biochemical progression) 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 considered one line of therapy.
- Patients who were eligible for transplant and who progress on induction therapy prior to transplant would be eligible for ixazomib combination therapy if clinically appropriate. The issue regarding ILd re-induction prior to a planned transplant cannot be answered with the provided data.
- There is insufficient evidence to know the effectiveness of ILd in patients with Waldenstrom's macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome. The one exception would be plasma cell leukemia, as this is a rare disorder managed in the same fashion as myeloma. This regimen would be a reasonable consideration in this circumstance.

- The CGP agreed that it is reasonable to use ILd in the following patients as long as patients still have sensitivity to both a proteasome inhibitor and lenalidomide:
    - Patients previously treated with other combination therapies such as daratumumab/bortezomib/dexamethasone
    - Patients previously treated with bortezomib or lenalidomide maintenance post autologous stem cell transplant
    - Patients who received more than 3 lines of prior therapy
    - Patients who have been treated with lenalidomide/dexamethasone in the first-line setting and progress.
- If a patient is already on triplet therapy (e.g., carfilzomib/lenalidomide/dexamethasone, lenalidomide/dexamethasone), responding and tolerating the regimen, the CGP agreed that there would be no reason to switch to ILd aside for patient preference. Furthermore, there is insufficient data to support one triplet regimen after the other, at the present time.
- The CGP noted concerns for indication creep and noted the following:
    - It is unlikely that a patient in fourth or fifth line therapy would still be sensitive to both lenalidomide and bortezomib. If resistance has occurred, then ILd would not be considered based on the current level of evidence and the inclusion and exclusion criteria of the trial
    - At the present time, there is insufficient evidence to support the use of ILd in the first line setting.
    - In patients with minor biochemical progression of multiple myeloma while receiving lenalidomide/dexamethasone in the second-line setting or during lenalidomide maintenance post autologous stem cell transplant, there is evidence that supports triplet therapy. Consequently, ILd would be a reasonable consideration should minor biochemical progression occur.
- The CGP noted a number of requests to guide the sequencing of currently available agents in this setting. The CGP agreed that there is insufficient data to know the appropriate sequencing of these drugs in the first or second line setting. Furthermore, there have not been any randomized controlled trials to determine whether or not there is preference for a particular proteasome inhibitor or other novel agent (i.e., ixazomib, carfilzomib, or daratumumab) and whether or not ixazomib is equivalent or superior to carfilzomib or daratumumab. Additionally, any proposed sequencing of myeloma therapies is likely biased due to current funding of medications and combinations which has been provincially determined. It would be impossible to disentangle the preferred sequencing based on data and clinical judgement as opposed to availability. That being said, the CGP note that the preferred 2nd line choice is either DVd or DLd followed by carfilzomib/dex as 3rd line. The added value of ILd is in its convenience of oral dosing, distinguishing it from other proven three-drug combinations involving lenalidomide and dexamethasone in terms of patient convenience, acceptance, quality of life and resource utilization ("chair time"), particularly in those patients who cannot travel to receive IV therapy and/or who are intolerant to daratumumab and/or carfilzomib as either 2nd or 3Ld line in specific cases.
- The CGP agreed that if there is excess toxicity to ILd, then a clinician could either treat with Id alone, or switch to CLd if the patient is still sensitive to a proteasome inhibitors. Similarly, for patients still sensitive to proteasome inhibitors, but unable to tolerate carfilzomib, it would be appropriate to consider ILd.

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 represents 1.3-1.5% of all new cancers in Canada with an estimated 2900 new cases annually with 1,450 patients dying from myeloma.[11] The median age of diagnosis is 69 years with a 5-year overall survival estimated at 42%.[11]

The morbidity and mortality from myeloma stem from direct and indirect effects of the malignant plasma cells and its monoclonal protein. The diagnosis of symptomatic multiple myeloma (myeloma that necessitates treatment) is made based on the International Myeloma Working Group (IMWG) recommendations [16]. Specifically, one must document Clonal bone marrow plasma cells ≥ 10% and any one of the following: 1) Hypercalcemia, 2) Renal insufficiency, 3) Anemia, 4) Bone lesions or 5) Clonal bone marrow plasma cells ≥ 60%, Involved: uninvolved serum free light chain ratio ≥100 or > 1 focal lesions on MRI studies.
Without effective therapy, the illness results in a significant decrease in quality of life and is universally fatal. The management of symptomatic myeloma is reliant on effective systemic chemotherapy and supportive measures (pain control, antibiotics, kyphoplasty, radiation therapy, dialysis and psychosocial supports). The median survival of symptomatic myeloma has significantly improved over the last 20 years with concurrent improvements in Health Related Quality of Life (HRQOL) [17-20]. Improvements in outcomes, including overall survival have been predominantly attributed to improvements in chemotherapeutics [18,21].

2.2 Accepted Clinical Practice

Based on understanding of myeloma biology and clinical observations, there has been a paradigm shift in the "philosophy" of symptomatic myeloma chemotherapeutic management. Previously, there has been a reluctance to use more effective medications or medication combinations sooner and/or upfront [22]. Rather, clinicians were saving therapeutic options in the relapsed and/or refractory setting. This approach was rational when the chemotherapeutics "tool-box" was limited, less efficacious and was associated with significant side effect profile. However, with better understanding of biology such as clonal tiding [23-26], emergence of more targeted therapies [27], indirect data from multiple randomized trials [28], it is now widely accepted that effective early combination novel therapies should be embraced early and continuously while paying attention to side effect profile.

The optimal chemotherapeutic management of symptomatic myeloma remains elusive. Radiation therapy remains supportive and reserved for management of pain and localized symptomology from plasmacytomas (localized myeloma). Given that myeloma is incurable, patients will ultimately receive all possible effective chemotherapeutic options. However, there remains no consensus on the optimal sequencing of effective therapies.

There are 4 main "currently" available/approved classes of chemotherapeutics in Canada include: 1) Alkylators such as melphalan, cyclophosphamide, liposomal doxorubicin, 2) Immunomodulatory agents (IMiD) such as thalidomide, lenalidomide and pomolidomide, 3) Proteosome Inhibitors (PI) such as bortezomib and carfilzomib, and 4) Monoclonal antibodies such as daratumumab.

In principal, an agent from different therapeutic class is often used in combination with an agent from another. All these combinations are often employed in conjunction with steroids such as dexamethasone to enhance efficacy. The current chemotherapeutic management can be

conceptualized as follows in Transplant eligible and ineligible patients with symptomatic myeloma:

Various combinations of chemotherapeutics are utilized at each stage with the chemotherapeutic goal of suppressing the malignant clone(s), achieving complete remission and maintaining the remission/suppression, while paying attention to chemotherapeutic side effects [29].

Taken together, a strategy of early, effective and continuous therapy result in better outcomes of Overall Survival [28], Progression Free Survival 1 & 2 [28], HRQOL [30,31] and possibly economics [32] than a strategy of intermittent therapies based on symptoms.

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 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. [33,34] 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.[35] 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.[36]

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.[37]

Other considerations:

Although it is tempting from the current framework for methodologic and funding evaluation for chemotherapeutics to define a clear sequence of therapy for patients with myeloma, in practice this is rarely practical or possible. It should be recognized that clinical trials evaluate patients in

aggregate without individual and personal considerations. As such, the funding framework necessitates clinicians to choose their preferred therapy without a clear option of "changing one's mind" once therapy is started, allowing a more individualized evaluation after several cycles of therapy. This issue cannot be understated where choosing a specific line of therapy may negate the possibility of availing of a subsequent effective therapy, resulting in "choice remorse". This framework restricts and impedes the personalized care for patients suffering from myeloma.

Taken together, patients will ultimately receive all possible available effective chemotherapeutic options sooner or later and in various combinations subject to early mortality. It is important to emphasize that the use of effective, superior and safe combination therapy early is preferred as opposed to "saving them for later". In general, the former approach leads to better PFS, OS and health-related quality of life. Separately in the absence of curative therapy, the presence and access of a "new" agent in myeloma is not considered a replacement for another approved and/or available agent. Rather, new agents are additional therapeutic options that can be utilized in combination with relatively older myeloma agents to optimize the chemotherapeutic care.

In principle, the treating clinician should be afforded as many effective chemotherapeutic options in dynamic fashion, as opposed to a linear choice of therapy in oLder to care for the patients. This would negate the consternation that often arises how best to navigate "approved" medications and/or combinations as opposed to "what is best for patient".

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 m^2) 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 with relapsed myeloma 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 triple combination of lenalidomide, dexamethasone and ixazomib instead of dual therapy lenalidomide with dexamethasone.

We are reviewing the efficacy of this treatment in the entire population of patients that were enrolled in this submitted 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] The submitter, Takeda has requested a reimbursement review of ixazomib in combination with lenalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

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, peer-reviewed published 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.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Myeloma Canada (MC), provided input on the pCODR submission of ixazomib in combination with lenalidomide (L) and dexamethasone (d) submission for adult patients with multiple myeloma who have had at least one prior therapy.

Two online surveys, one for patients and one for caregivers, were conducted and made available to Canadians between September 12, 2018 and October 1, 2018. Surveys were directed to respondents through MC support group networks. A total of 32 respondents indicated having experience with ILd, and 25 reported having used at least one prior treatment; of these, six were from Alberta, seven from British Columbia, five from Ontario, three from Quebec, two from New Brunswick, one from Manitoba, and one from Saskatchewan. It is unclear whether patients that responded to the survey are located geographically far from treatment centres as this information was not collected. Twelve caregivers providing care to patients with experience with ixazomib responded to MC's survey. These surveys were used to inform the section of this summary speaking to experience with ixazomib.

To inform the Disease Experience, Experiences with Currently Available Treatments, and Improved Outcomes sections of this summary, MC referred to previous patient advocacy submissions they had made to pCODR for carfilzomib (Kyprolis) and ixazomib (Ninlaro) in 2016 and 2017, respectively. MC stated that they do not think the results they provided for the "Condition and Current Therapy Information" section of this summary would differ from their previous patient advocacy input submissions. MC acknowledged that there have been advancements in treatments since those submissions, however, they stated that myeloma has continued to be a serious disease, impacting both patients and caregivers. In addition, MC stated that current treatments still present patients with inconvenient side effects and that new treatments provide both patients and caregivers with a greater sense of hope.

For the pCODR 10084 Carfilzomib (Kyprolis) submission, Myeloma Canada conducted two online surveys between August 15, 2016 and August 31, 2016. A total of 344 responded to the patient survey (Survey 1) and a total of 123 responded to the caregiver survey (Survey 2). For the pCODR 10088 Ixazomib (Ninlaro) submission, Myeloma Canada conducted two additional surveys from May 24 to June 10, 2016 (survey directed to patients – Survey 3) and then another from November 15 to December 2, 2016 (survey directed to caregivers – Survey 4). The patient survey had a total of 35 respondents and the caregiver survey had a total number of 4 respondents. In addition to the online survey, a total of 7 patients who had experience with ixazomib and who had provided their email address, were interviewed by telephone. A summary of their responses is provided in this report

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. Patients with myeloma value disease control, prolonged life, remission, improved quality of life, fewer side effects and managing key symptoms, such as, infections, kidney problems, problems with mobility, pain, fatigue, neuropathy and shortness of breath. Myeloma Canada noted that cure would be the most important value, but patients understand there are no cures at the moment. 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 concerns associated with myeloma that impact or limit day-to-day activity and quality of life. Patients who responded to the survey questions noted disease control as the most important consideration followed by prolonged life and remission, and fewer side effects. Patients who had experience with ixazomib noted disease control as an expectation fulfilled, followed by prolonged life, remission, improved quality of life, fewer side effects than other treatments and enjoying a normal life. Patients also noted that ILd as providing an excellent quality of life (25% of respondents), followed by good

(31.25% of respondents), very good (12.5% of respondents) fair (18.75% of respondents) and poor (12.5% of respondents). Of the patient respondents, 50% noted that ILd improved their long-term health outlook, 12.5% noted that the treatment did not improve their long term health outcome and 37.5% of respondents noted that it was too soon to tell.

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. Please see below for a summary of specific input received from the patient advocacy groups.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Multiple Myeloma

As per the input submitted by Myeloma Canada, this section is taken from the previous patient input summary for the submission of Ixazomib (Ninlaro) for Multiple Myeloma (pCODR 10088).

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 aspect to control 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
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

Ability to:	1 - Not at all	2	3	4	5 - Significant impact	N/A	Total
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 which 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."*
- *"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

As per the input submitted by Myeloma Canada, this section is taken from the previous patient input summary for the submission of Ixazomib (Ninlaro) for Multiple Myeloma (pCODR 10088).

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.

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.

At the time of the input for the submission for Ixazomib (Ninlaro) in Multiple Myeloma (pCODR 10088, 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

As per the input submitted by Myeloma Canada, this section is taken from the previous patient input summary for the submission of Ixazomib (Ninlaro) for Multiple Myeloma (pCODR 10088).

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."*

3.2 Information about the Drug Being Reviewed

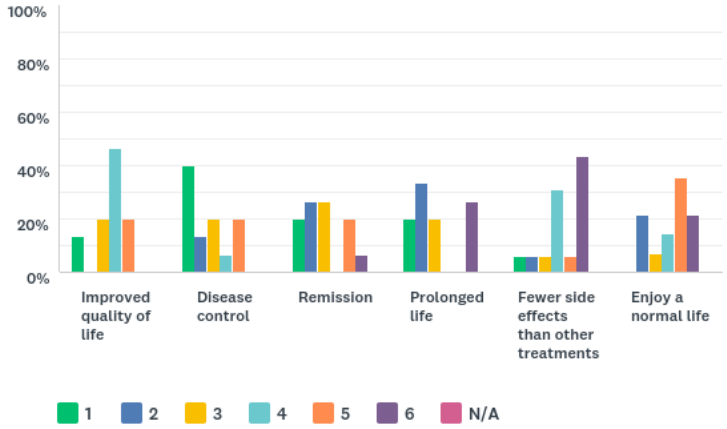
3.2.1 Patient Expectations for and Experiences To Date with Ixazomib

For the current submission, Myeloma Canada provided input on patient experiences from online surveys conducted between September 12 and October 1, 2018. A total of 32 patient respondents had experience with ixazomib as per the indication under review. Of these 32 patients, 25 patient respondents who had experience with ILdnoted that it was not their first treatment regimen.

Among the 25 patient respondents who used ILd, 8 were on the treatment from 1 – 6 months, 4 were on treatment for 7 – 12 months, and 4 for 1 – 2 years. It is to be noted that 9 respondents did not answer this question.

Patient respondents were asked to rank their expectations of ixazomib before using the treatment combination. Chart 1 below summarizes the responses. In summary, among the respondents who answered the question, 40% ranked disease control as the most important expectation, followed by prolonged life and remission each with 10% and fewer side effects with 6.25%.

Chart 1 – Patient expectations of treatment combinations



Patient respondents were also asked which expectations ILd fulfilled. Chart 2 summarizes the responses. In summary, among the 16 respondents, the majority of respondents (75%) selected disease control as an expectation fulfilled, followed by prolonged life 62.5%, remission (56.25%), improved quality of life (43.75%), fewer side effects than other treatments (37.5%) and enjoy a normal life (37.5%).

Chart 2 – Expectations fulfilled by treatment combination under review.

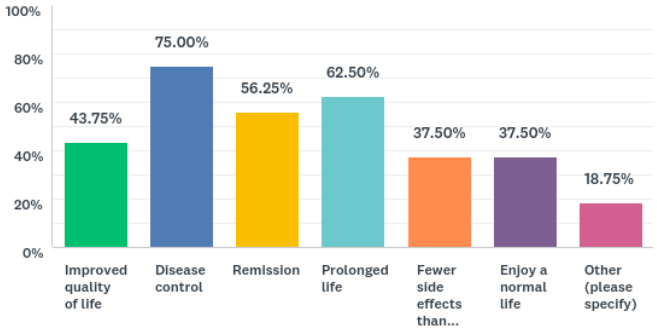
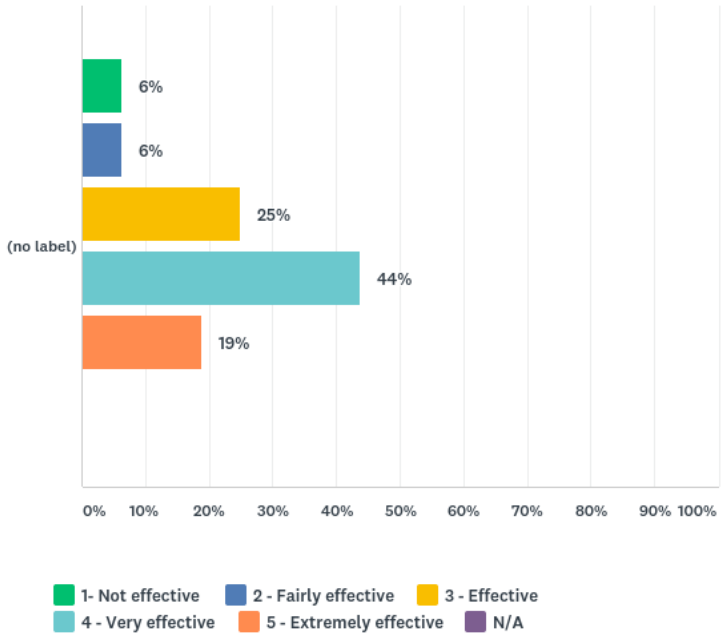


Chart 3 below indicates that among the 16 patient respondents who replied to this question, 44% responded that the treatment was very effective, followed by 25% who responded effective and 19% extremely effective in controlling their myeloma.

Chart 3 – Effectiveness rating in controlling myeloma of treatment combination under review



When patients were asked if they experienced positive outcomes with ixazomib in combination with Ld, 86% (of 14 total patient respondents) responded yes. Verbatim comments under "please explain" were as follows:

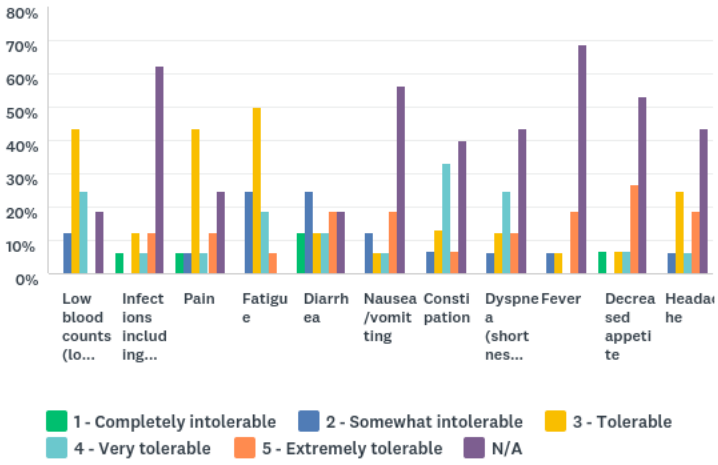
- *"The only other treatment I had was CyBorD and then an autologous stem cell transplant, all were positive outcomes. --- Only other treatment was prior to SCT.--- SPE is down significantly – yeah ---*
- *This was my second regimen with Revlimid and Dex plus ixazomib. Compared favourably with Rev and Dex alone.--- I don't know as I came out of remission after going on this protocol.--- Positive Response/remission--- Only been on regime 4 months so hard to tell--- Side effects are getting worse. M protein number is slowly coming down."*

When patients were asked if they experienced negative outcomes with the ixazomib combination treatment, 47% responded no, 7% responded yes, and 47% provided a comment under "please explain" among the 15 respondents. Those verbatim comments were as follows:

- *"I don't know as I came out of remission after going on this protocol.--- Valcade caused a lot of nausea.--- Had to use the lower mg. dosage during the first round but things are better now --- massive blood clots--- I don't know as I came out of remission after going on this protocol--- High dose of Revlimid (25mg) caused severe gastral problems, am now on 5mg Revlimid, less side effects--- Fatigue, pain, blurred vision are making it difficult to enjoy life as much as I should and to continue the treatment."*

When patients were asked if the administration of ILd had a negative effect, 62.5% of respondents said no, 37.5% said yes among the 16 respondents. Additionally, when asked to rate the overall side effects of ILd, 50% responded that side effects were tolerable, followed by 25% very tolerable, 12.5% completely intolerable, 6.25% somewhat intolerable and extremely tolerable. Chart 4 below illustrates that the majority of side effects were tolerable, very tolerable or extremely tolerable. It was noted by MC that 13% of the 16 patient respondents rated diarrhea as completely intolerable, 6% found pain, decreased appetite and infections including pneumonia as completely intolerable.

Chart 4 – Tolerability of side effects of Ninlaro® (ixazomib) in combination



Myeloma Canada also asked respondents to rate their quality of life since starting ILd on a scale of 1 (poor quality of life) to 5 (excellent quality of life). Of the 16 respondents, 25% gave it a rating of excellent quality of life, followed by 31.25% good quality of life, 18.75% fair quality of life, 12.5% very good quality of life and 12.5% poor quality of life.

When patients were asked if ILd met their expectations, 68.75% responded yes, 12.5% responded no, and 18.75% provided a comment to "please explain" among the 16 respondents. Their verbatim responses were:

- *"Slowed progression of myeloma as evidenced by Paraprotein numbers reduced--- I don't know as I came out of remission after going on this protocol.--- You always hope that you will feel ´normal' again but you know that this will never happen again. "*

When patients were asked if ILd improved their health and well-being, of the 16 patients who responded to this question 37.5% responded yes, 18.75% responded no, 25% responded I'm not sure, and 18.75% responded too soon to tell among the 16 respondents.

When asked if ILd improved their long-term health outlook, of the 16 patients who responded 50% responded yes, 12.5% responded no and 37.5% responded too soon to tell.

When asked if there was anything else about ILd that they would like others to know, the following verbatim responses were given by patients:

- *"Although it seems counterintuitive, regular exercise really seems to help manage my symptoms. Also, I am not on dexamethasone, just Ninlaro and Revlimid. My hematologist did not prescribe it as I had difficulty with it while I was on CyBorD. The day I took the dex, I was hyper, the next day mean and angry and the third day, I just slept."*
- *"dexamthasone screws with my brain"*
- *"The pill form of the medication is wonderful, it is unfortunate that it did not control my aggressive myeloma."*
- *"My platelets are more sensitive to chemo since coming out of remission and have been consistently lower since starting this Ninlaro protocol. Now I cannot do chemo every week like I did when diagnosed and the only difference would have been the addition of Ninlaro in the second protocol regimen. I now can only do chemo every second week instead of weekly to try and get back into remission before another stem cell transplant."*

- *"Too soon to say, so far very optimistic for returning to normal "*
- *"The side effects weren't too bad at the beginning but seem to get worse or last longer at every cycle. The cost is also excessive and I couldn't afford it if I didn't have health insurance."*

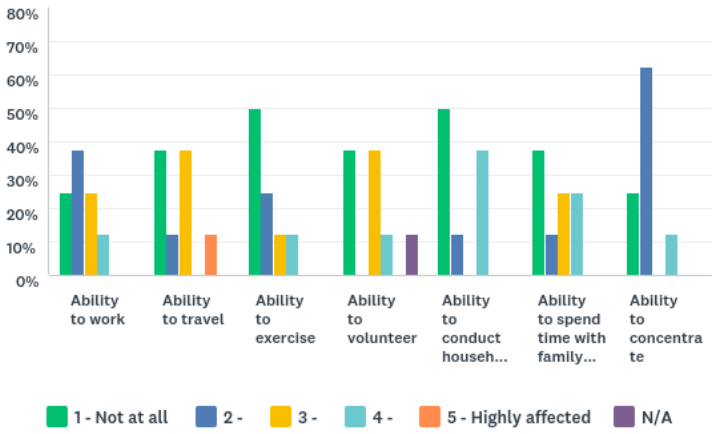
3.2.2 Caregiver Experiences to Date with Ixazomib

A total of 12 caregivers provided care to patients who took the ILd and 11 responded that it was not the first treatment combination "regimen".

When asked if the caregiver experienced any challenges while helping to manage side effects of ILd for the person with myeloma they care for, of the 7 total caregiver respondents, 4 replied no and 3 replied yes.

Chart 5 summarizes the responses of 8 caregivers of how their activities of daily living were affected. Ability to travel and ability to spend time with family and friends were the most affected.

Chart 5 – Effects on activities of daily living



3.3 Additional Information

None.

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

Currently funded treatment options for previously treated multiple myeloma include carfilzomib/lenalidomide/ dexamethasone, carfilzomib/dexamethasone, lenalidomide/dexamethasone, bortezomib, and pomalidomide/dexamethasone. PAG noted that daratumumab (with lenalidomide/dexamethasone or bortezomib/dexamethasone) was recently reviewed at pCODR, for the treatment of patients with multiple myeloma who have received at least one prior therapy.

PAG noted that the comparator in the TMM1 trial was lenalidomide/dexamethasone, which is a treatment option for previously treated multiple myeloma. However, lenalidomide/dexamethasone is also 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 is seeking information on whether comparison data is available comparing ixazomib combination therapy to carfilzomib combination therapy.

4.2 Factors Related to Patient Population

PAG is seeking guidance on the use of ixazomib/lenalidomide/dexamethasone for:

- Patients with diagnosis of Waldenstrom's macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, plasma cell leukemia, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome, as these patients were excluded from the TMM1 trial
- Patients previously treated with other combination therapies such as daratumumab/bortezomib/dexamethasone
- Patients previously treated with bortezomib or lenalidomide maintenance post autologous stem cell transplant
- Patients who received more than 3 lines of prior therapy

PAG is also seeking clarity on whether autologous stem cell transplant or maintenance lenalidomide would be considered as one line of prior therapy. Specifically, whether consistency with the carfilzomib recommendation would be appropriate.

If recommended for reimbursement, PAG noted the following groups of patients would need to be addressed on a time-limited basis:

- Patients currently treated with alternative relapsed/refractory regimens (e.g., carfilzomib/lenalidomide/dexamethasone, lenalidomide/dexamethasone) but who have not yet progressed
- Patients who have been treated with lenalidomide/dexamethasone in the first-line setting and progress

PAG noted there are concerns for indication creep with ixazomib as clinicians use ixazomib/dexamethasone as fourth or fifth line of therapy for relapsed/refractory multiple myeloma. There also may be a potential for indication creep to use ixazomib triplet therapy in patients with minor biochemical progression of multiple myeloma while receiving lenalidomide/dexamethasone in the second-line setting or during lenalidomide maintenance post autologous stem cell transplant.

PAG noted that there may be interest to use the ixazomib/lenalidomide/dexamethasone 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.

4.3 Implementation Factors

Ixazomib's dosing schedule is orally once daily a week on days 1, 8, and 15 of a 28-day treatment cycle. Lenalidomide is recommended daily on days 1 through 21 while dexamethasone is recommended on days 1, 8, 15, and 22 of a 28-day treatment cycle. PAG noted the different dosing schedules for the three oral medications may be difficult for patients and may lead to patient confusion. Processes would need to be in place, prior to implementation of ixazomib, to minimize dosing errors and patient confusion.

PAG had concerns for incremental costs due to drug wastage with dose adjustments, particularly when dose modifications are completed mid cycle. PAG also noted that additional monitoring would be required for toxicities such as rash and diarrhea.

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 and a barrier to implementation.

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.

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.

4.4 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.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two joint clinician input submissions (Myeloma Cancer Research Network and DAC for Hematology, Cancer Care Ontario) were made from a total of nine clinicians. The registered clinicians provided input on ixazomib in combination with lenalidomide and dexamethasone for adult patients with multiple myeloma who have at least one prior therapy.

Carfilzomib combination therapy was stated to be the most appropriate comparator for ixazomib. Clinicians agreed the clinical trial criteria were applicable to the Canadian context. There were several advantages of ixazomib being an oral therapy, including benefits for patients for whom traveling long distances to cancer centres is a challenge. Elderly patients were highlighted in particular as potentially benefiting the most from ixazomib, due to its oral formulation and tolerability.

There was consensus that carfilzomib in combination with lenalidomide and dexamethasone would remain as the preferred proteasome inhibitor (PI) for patients in this setting. However, the choice of treatment (i.e., carfilozimib or ixazomib) is dependent on patient factors and preferences. Switching to a different PI upon progression, i.e., from carfilzomib to ixazomib, or vice versa, was not supported by the clinicians. Overall, ixazomib would most likely be considered as second-line treatment or for patients who received one to three prior treatments. An ideal sequencing path was not provided, as both clinician inputs highlighted the lack of currently available evidence to inform such a decision, and the complex nature of multiple myeloma. While carfilzomib, bortezomib and ixazomib were stated to be relatively interchangeable, their therapeutic profiles were acknowledged to affect their utility in practice.

Please see below for details from the clinician input.

5.1 Current Treatment(s) for this Multiple Myeloma

Currently funded treatment options for previously treated multiple myeloma include carfilzomib/lenalidomide/ dexamethasone, carfilzomib/dexamethasone, lenalidomide/dexamethasone, bortezomib, and pomalidomide/dexamethasone. Daratumumab (with lenalidomide/dexamethasone or bortezomib/dexamethasone) was recently reviewed at pCODR, for the treatment of patients with multiple myeloma who have received at least one prior therapy. Clinician input agreed with the abovementioned treatments, one of the joint clinician inputs stated that they agreed with the funding algorithm, except that pomalidomide/dexamethasone is not available for patients who have only received one prior line of therapy.

There was agreement by clinicians that carfilzomib/lenalidomide/ dexamethasone was the most appropriate currently funded comparator for ixazomib. However, they noted that some patients are unable to receive this treatment due to heart failure and transportation required to receive treatment. One of the clinicians stated that the treatment combination of ixazomib, lenalidomide and dexamethasone is advantageous to provinces with a large geographical area as it offers patients the option of an oral regimen.

5.2 Eligible Patient Population

Both joint clinician inputs agreed that the clinical trial criteria can be applied to Canadian practice. Based on the clinical trial, eligible patients include those with relapsed myeloma who have received between one and three prior lines of therapy.

One of the clinicians stated there is an unmet need; large geographic provinces, such as Saskatchewan, require patients to travel long distances such as three to six hours to the clinic in Saskatoon. An oral treatment would eliminate complicated and time-consuming travel. There was agreement among the clinicians that ixazomib treatment would be used for patients who live far away from their treatment centres. Elderly patients, especially those with a heart condition or those unable to come often to the hospital, and some patients with high cytogenic risk, were suggested as patient populations that may benefit particularly from the oral treatment.

The preferred treatment for patients is carfilzomib/lenalidomide/dexamethasone. Another clinician stated that while ixazomib treatment is advantageous due to its oral delivery system, treatment may not be limited to patients who are unable to access intravenous alternatives as many factors may impact the treatment decision. Overall, the consensus was that ixazomib would be used for patients who have relapsed and had one to three prior lines of therapy. It would be the preferred treatment for patients who would require travelling long distances to their cancer centre, patients who may benefit from an all oral treatment, or for who carfilzomib is not appropriate due to cardiac conditions.

5.3 Relevance to Clinical Practice

Both of the joint clinician inputs highlighted the convenience of ixazomib treatment as it is a take home oral drug. Elderly patients were a subgroup of particular interest for use with ixazomib, studies showed ixazomib had similar efficacy among elderly patients, was well tolerated, and had minimal side effects. Elderly patients also face greater challenges travelling to cancer centres.

Other patients for whom ixazomib was stated to be preferred included frail patients who have no contraindications to using ixazomib and patients with comorbidities or intolerances that may preclude other PI alternatives. For example, neuropathy that may preclude bortezomib or cardiac history that may preclude carfilzomib. Ixazomib is a favourable treatment choice for patients with severe underlying disease, as it is better tolerated than carfilzomib which has increased cardiac and renal toxicities.

The safety profile and tolerability of ixazomib in clinical practice was stated to be consistent with available evidence. Ixazomib was is a comparable alternative to approved agents/regimens in the same treatment space based on clinical trials, ixazomib was stated to be similar to carfilzomib in terms of efficacy.

5.4 Sequencing and Priority of Treatments with Ixazomib

There was agreement among clinicians that if a patient was refractory to a PI-lenalidomide-dexamethasone combination, they should not be switched to another PI-lenalidomide-dexamethasone based treatment approach. For example, a patient who progressed while receiving carfilzomib would not then receive ixazomib. However, if intolerance to a PI developed, it was stated that switching to another PI treatment may be considered if the disease remained under control or was not refractory.

Both group clinician inputs agreed that ixazomib would not replace current therapies, but would be an option when a PI-lenalidomide-dexamethasone regimen was being considered. While ixazomib would not replace carfilzomib, it would serve as another option should patients be unable to, or unwilling to take carfilzomib. However, one clinician stated that ixazomib would replace carfilzomib for many Saskatchewanians, based on geographical limitations imposed on many patients in this province.

In terms of sequencing, the following were stated as being relevant considerations for prescribing ixazomib:

- Patients who received bortezomib induction
- Patients who have not progressed on, or have been exposed to lenalidomide
- Patients have received one to three prior lines of therapy

Overall, patients with previous exposure to lenalidomide or carfilzomib were stated not to be good candidates for ixazomib. However, one of the inputs highlighted that it is difficult to make blanket statements regarding sequencing and priority of treatments, as myeloma is a very heterogeneous disease. A number of factors are necessary for a clinician to consider before a choice of therapy is made, such as age, myelosuppression, convenience, renal failure, other comorbidities and tolerability. Finally, it was noted that eligibility for treatment with pomalidomide should be available, for patients who fail ixazomib.

5.5 Companion Diagnostic Testing

No companion diagnostic identified.

5.6 Additional Information

No additional information related to ixazomib for multiple myeloma was provided.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of ixazomib in combination with lenalidomide and dexamethasone on patient outcomes compared to appropriate comparators in adult patients with multiple myeloma (MM) who have received at least one prior therapy.

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.

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 1: 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 OR Daratumaab in combination with Lendalidamide 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 Patient preference for treatment Access for treatment options

Clinical Trial Design	Patient Population	Intervention‡	Appropriate Comparators†‡	Outcomes
			OR Daratumabab in combination with bortezomib and dexamethasone	
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

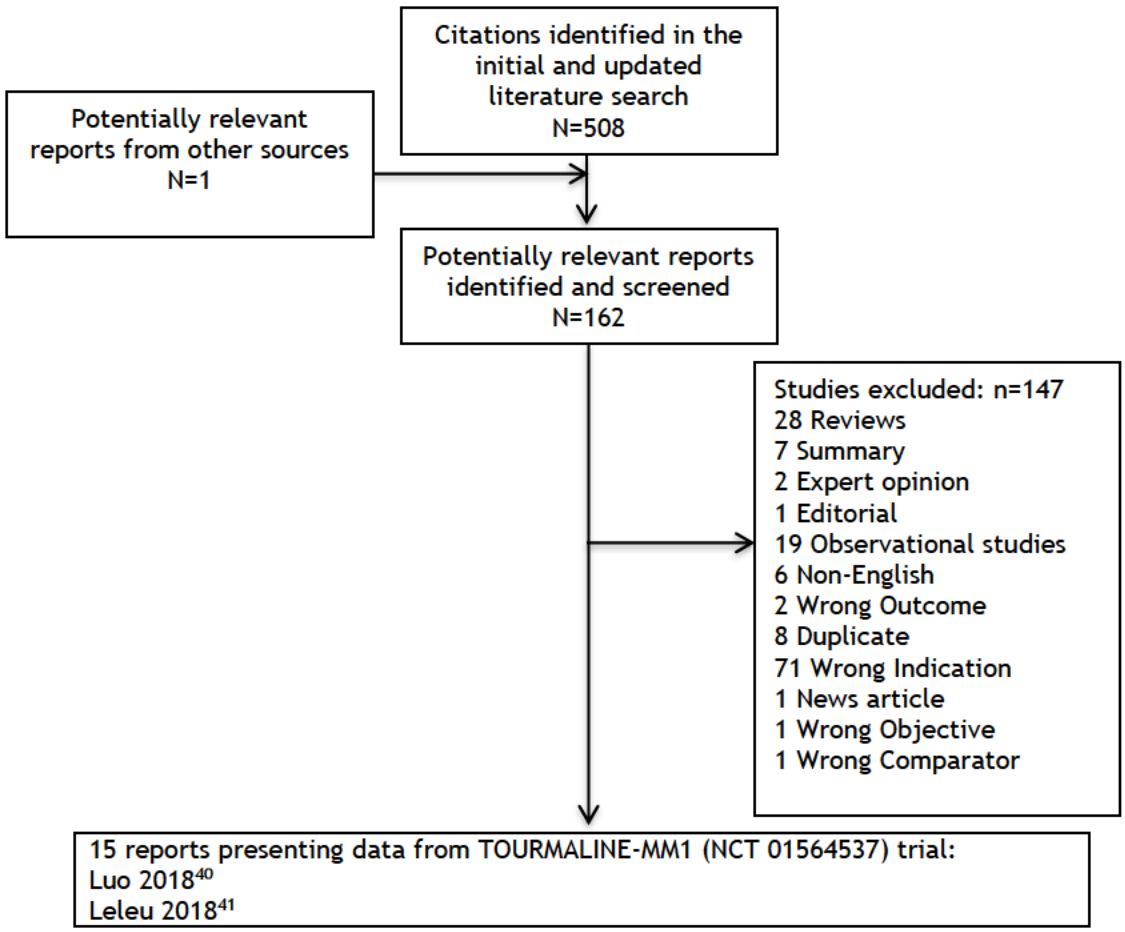
6.3 Results

6.3.1 Literature Search Results

Among the 161 potentially relevant reports identified by the search, 14 reports presenting data from TOURMALINE-MM1 ((NCT 01564537) trial were identified. The TOURMALINE-MM1[2] ((NCT 01564537) trial data is reported along with the China Continuation Study[7]. There were 147 studies excluded and the reasons are outlined in Figure 1.

The submitter provided feedback on pERC's Initial Recommendation and described two studies they felt should be considered as part of the evidence brief in the following review. These included one prospective observational study INSIGHT[38] and a Czech registry[39] of patients, both of which did not meet the study design inclusion criteria outlined in the protocol (see section 6.2.1). Based on consultation with members of the clinical guidance panel, the selection criteria for this review were decided a priori in a protocol. Specifically, randomized controlled trials were part of the inclusion criteria as this study design is methodologically more robust than nonrandomized studies in assessing the efficacy and safety of ixazomib in combination with lenalidomide and dexamethasone compared with relevant standards of treatment. A systematic literature search of randomized controlled trials was conducted. Thus, reporting results from the two nonrandomized studies would introduce bias. Based on this assessment, these two studies were excluded from this review and not considered any further.

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



Betts 2017[42]
Gupta 2017[43]
Hanley 2017[44]
Richardson 2016[45]
Hou 2016[46],Hou 2017 [7]
Mateos 2016[47], Mateos 2017[48]
Moreau 2016 [2], Moreau 2015
Avet-Loiseau 2016[50]
Di Bacco 2016[51]
Fu 2018[8]
Clincialtrial.gov NCT01564537

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

6.3.2 Summary of Included Studies

One clinical trial (TOURMALINE-MM[2,52]) 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 2: Summary of Trial Characteristics of the Included Study

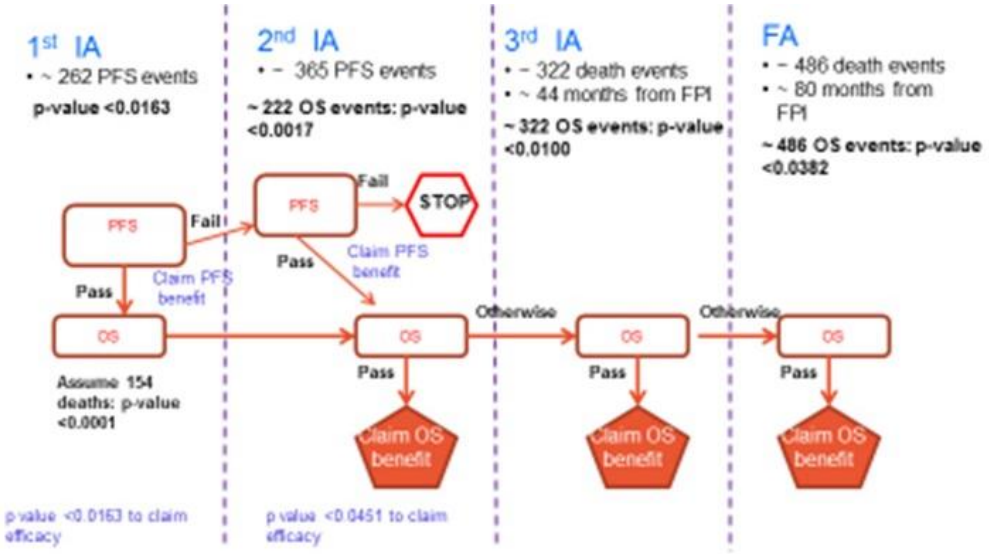
Trial Design	Inclusion Criteria	Intervention	Comparator	Trial Outcomes
TOURMALINE-MM1[2,52] (NCT01564537) Phase III International multicenter 1:1 randomized double blind placebo controlled trial N=722 (Enrolment between August 28, 2012 to May 27, 2014) 147 sites in 26 countries Data cut-off date: Oct 30, 2014 Funded by Millennium Pharmaceuticals, a wholly owned subsidiary of Takeda Pharmaceuticals. Hou et al[7] (2017)* N=115 (Enrolment between May 8, 2014 to May 8, 2015) 11 centres in China Data cut-off date for PFS final analysis: Jul 12, 2015 Data cut-off date for OS final analysis: Jul 19, 2015	<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.	Lenalidomide 15 mg administered daily on Days 1 though 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 OR Daratumumab in combination with lenalidomide and dexamethasone OR Daratumumab in combination with bortezomib and dexamethasone	<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

Table 3: Select quality characteristics of included studies of Ixazomib in combination with lenalidomide and dexamethasone in patients with relapsed or refractory multiple myelomas [2,7]

Study	TOURMALINE-MM1
Treatment vs. Comparator	ILd vs Ld
Primary outcome	PFS
Required sample size	The study was powered to detect the superiority of ILd 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 for PFS. 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 or second IA for PFS.
Sample size	ILd (n=360) vs. Ld (n=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 Data cut-off for the final analysis for OS*
Ethics Approval	Yes
ILd: Ixazomib combined with lenalidomide, dexamethasone; Ld: lenalidomide and dexamethasone combination; PFS: progression-free survival.	

A second trial, the China Continuation study, was conducted to fulfill regulatory requirements in China with the intention to assess consistency with the global TOURMALINE-MM1 study. The authors of the study, Hou et al (2017),[53] did not perform any formal power calculation for the outcomes assessed. In addition, the results from TOURMALINE-MM1 were not used to determine the sample size in the China Continuation study nor demonstrate non-inferior or equivalent efficacy. The sample size of 115 patients [ILd (n =57) vs. Ld (n=58)] was intended to assess consistency in the global TOURMALINE-MM1 study.[53]

Figure 2. Final Statistical Plan Leading to PFS Analysis[1]



As outlined in a previously submitted pCODR review, the first IA for PFS will be performed when approximately 262 events have occurred.[1] 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.[1] 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.[1]

a) Trials

One randomized double-blind placebo-controlled trial (TOURMALINE-MM1) met the inclusion criteria.[2,52,54] 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 (ILd) combination compared to lenalidomide and dexamethasone (Ld) on efficacy and safety outcomes in patients with relapsed, refractory or relapsed and refractory multiple myeloma (MM). The MM1 trial enrolled 722 patients from 26 countries across 4 continents with relapse or refractory MM that had at least one to three prior lines of treatment. Patients were randomized in a 1:1 ratio to receive ILd or Ld.[2] 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 assigned to each patient. The randomization assignment will be implemented by an interactive voice response system (IVRS).[5] 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[2]. Patients were treated until disease progression or unacceptable toxicity.[5]

The primary outcome of TOURMALINE-MM1 was progression-free survival (PFS) 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.[2]

Key secondary outcomes included overall survival (OS) in intention-to-treat population. Other secondary outcomes included overall response rate, complete response rate plus very good partial response rate, duration of response, 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 on the functional scales and global quality of life indicating better health status in contrast to a higher score on the symptom scales indicative of more complaints.[4] A change of 10 points on this scale is considered to be clinically meaningful.[56]

Group sequential design statistical methodology was applied for 3 interim analyses and a final analysis.[4] The first interim analysis (IA1) for PFS was performed when median follow-up reached 15 months with a data cut-off date on October 30, 2014. The non-inferential second interim analysis (IA2) for PFS was performed at the request of the FDA when median follow-up reached 23 months with data cut-off date on July 12, 2015. This IA2 of PFS was performed primarily to evaluate OS and thus no inferences can be made with respect to PFS based on IA2.[4] Based on the design of the trial, IA2 would be non-inferential if the results of IA1 were significant.[13] A subsequent analysis [redacted] was performed on [redacted] and the final analysis includes will be determined at 486 death events.[6] *(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until January 31, 2020 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.*)

b) Populations

TOURMALINE-MM1 randomized 722 patients to ILd or Ld. The baseline characteristics were 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.[1] Among all randomized 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.[1] The baseline characteristics of patients can be found in table 4.

Table 4: Baseline characteristics for TOURMALINE-MM1 [7]

Characteristic	Ixazomib Group (N = 360)	Placebo Group (N = 362)	Overall (N = 722)
Age			
Median (range) — yr	66 (38–91)	66 (30–89)	66 (30–91)
>65 yr — no. (%)	192 (53)	186 (51)	378 (52)
Male sex — no. (%)	207 (58)	202 (56)	409 (57)
White race — no. (%)†	310 (86)	301 (83)	611 (85)
ECOG performance status score — no./total no. (%)‡			
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 at study entry — no. (%)§			
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) — ml/min per 1.73 m^2	78.4 (20–233)	78.4 (27–233)	78.4 (20–233)
Creatinine clearance — no. (%)			
<30 ml/min per 1.73 m^2	5 (1)	5 (1)	10 (1)
30 to <60 ml/min per 1.73 m^2	74 (21)	95 (26)	169 (23)
60 to <90 ml/min per 1.73 m^2	155 (43)	129 (36)	284 (39)
≥90 ml/min per 1.73 m^2	126 (35)	132 (36)	258 (36)
Median time since initial diagnosis of multiple myeloma (range) — mo	44.2 (3–281)	42.2 (4–306)	42.8 (3–306)
Cytogenetic features — no. of patients (%)¶			
Standard-risk cytogenetic abnormalities	199 (55)	216 (60)	415 (57)
High-risk cytogenetic abnormalities	75 (21)	62 (17)	137 (19)
Data not available	86 (24)	84 (23)	170 (24)
No. of prior therapies — no. of patients (%)‖			
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)
Disease category — no./total no. (%)			
Relapsed	276/359 (77)	280/362 (77)	556/721 (77)
Refractory	42/359 (12)	40/362 (11)	82/721 (11)
Relapsed and refractory	41/359 (11)	42/362 (12)	83/721 (12)
Primary refractory	24/359 (7)	22/362 (6)	46/721 (6)
Prior proteasome inhibitor therapy — no. (%)	249 (69)	253 (70)	502 (70)
Bortezomib	248 (69)	250 (69)	498 (69)
Carfilzomib	1 (<1)	4 (1)	5 (1)
Disease refractory to any prior proteasome inhibitor therapy — no. (%)**	4 (1)	8 (2)	12 (2)

Table 1. (Continued.)

Characteristic	Ixazomib Group (N=360)	Placebo Group (N=362)	Overall (N=722)
Prior immunomodulatory drug therapy — no./total no. (%)	193/360 (54)	204/362 (56)	397/722 (55)
Lenalidomide	44/360 (12)	44/362 (12)	88/722 (12)
Thalidomide	157/360 (44)	170/362 (47)	327/722 (45)
Disease refractory to any prior immunomodulatory drug therapy††	41/193 (21)	50/204 (25)	91/397 (23)

* There were no significant differences at baseline between the two groups in the characteristics shown.
† Race was self-reported.
‡ Eastern Cooperative Oncology Group (ECOG) performance status is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability related to tumor.
§ The International Staging System (ISS) consists of three stages: stage I, serum β_2-microglobulin level lower than 3.5 mg per liter (300 nmol per liter) and albumin level 3.5 g per deciliter or higher; stage II, neither stage I or III; and stage III, serum β_2-microglobulin 5.5 mg per liter or higher (470 nmol per liter). Higher stages indicate more severe disease.
¶ High-risk cytogenetic abnormalities were detected by fluorescence in situ hybridization (FISH) analysis and were 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)]. A total of 36 patients in the ixazomib group and 33 patients in the placebo group had del(17p) alone or in combination with either t(4;14) or t(14;16) or both; 36 and 25 patients, respectively, had t(4;14) alone; and 3 and 4 patients, respectively, had t(14;16) alone. Standard-risk cytogenetic abnormalities were defined as the absence of high-risk abnormalities in the samples that were available for evaluation; samples from some patients were not available for testing because the sample was missing or clotted or for other reasons. In accordance with the protocol, the cutoff values for defining the presence of high-risk cytogenetic abnormalities were established by the central diagnostic laboratory on the basis of the false positive rates (or technical cutoff values) of the FISH probes that we used. These cutoff points were 5% positive cells for del(17p), 3% positive cells for t(4;14), and 3% positive cells for t(14;16).
‖ The number of prior therapies was determined by the sponsor in a blinded medical review of data on prior therapy.
** Refractoriness to any prior proteasome inhibitor therapy was determined by the sponsor in a blinded medical review.
†† All the patients had disease that had been refractory to prior therapy with thalidomide, except for one patient in the placebo group, who, on further blinded medical review by the sponsor, was determined to have disease that had been refractory to prior therapy with lenalidomide. Percentages are shown are those patients who received prior therapy with immunomodulatory drugs.

Table 6. Baseline characteristics for China Continuation Study[7]

Baseline characteristics	Ixazomib-Rd (*n* = 57)	Placebo-Rd (*n* = 58)	Overall (*n* = 115)
Median age, years (range)	61.0 (30–76)	61.5 (36–80)	61.0 (30-
Patient age, *n* (%)			
≤65 years	42 (74)	41 (71)	83 (72)
>65–75 years	14 (25)	14 (24)	28 (24)
>75 years	1 (2)	3 (5)	4 (3)
Male sex, *n* (%)	41 (72)	38 (66)	79 (69)
Baseline ECOG performance status, *n* (%)			
0	25 (44)	26 (45)	51 (44)
1	31 (54)	29 (50)	60 (52)
2	1 (2)	3 (5)	4 (3)
MM subtype at study entry, *n* (%)			
IgG	29 (51)	31 (53)	60 (52)
IgA	11 (19)	14 (24)	25 (22)
Light chain only	13 (23)	8 (14)	21 (18)
Other	4 (7)	5 (9)	9 (8)
ISS stage at initial diagnosis, *n* (%)			
I	11 (19)	11 (19)	22 (19)
II	17 (30)	14 (24)	31 (27)
III	21 (37)	21 (36)	42 (37)
Unknown	8 (14)	12 (21)	20 (17)
ISS stage at study entry, *n* (%)			
I	31 (54)	38 (66)	69 (60)
II	21 (37)	16 (28)	37 (32)
III	5 (9)	4 (7)	9 (8)
Creatinine clearance, mL/min, *n* (%)			
<30	0	1 (2)	1 (<1)
30–<60	4 (7)	8 (14)	12 (10)
60–<90	28 (49)	23 (40)	51 (44)
≥90	25 (44)	26 (45)	51 (44)
Median time since initial MM diagnosis, months (range)	29.5 (3–143)	28.6 (1–141)	28.7 (1–
Lines of prior therapy, *n* (%)			
1	25 (44)	26 (45)	51 (44)
2	20 (35)	24 (41)	44 (38)
3	12 (21)	8 (14)	20 (17)
Disease status at study entry, *n* (%)			
Relapsed[a]	15 (26)	13 (22)	28 (24)
Refractory[b]	28 (49)	33 (57)	61 (53)
Relapsed and refractory[c]	14 (25)	12 (21)	26 (23)
Prior therapy exposure, *n* (%)			
Prior proteasome inhibitor (all bortezomib)	34 (60)	36 (62)	70 (61)
Prior immunomodulatory drug therapy	52 (91)	47 (81)	99 (86)
Lenalidomide	3 (5)	7 (12)	10 (9)
Thalidomide	52 (91)	45 (78)	97 (84)
Thalidomide-refractory	37 (65)	35 (60)	72 (63)
Prior corticosteroids	57 (100)	58 (100)	115 (100)
Dexamethasone	56 (98)	57 (98)	113 (98)
Prednisone	17 (30)	20 (34)	37 (32)
Prior melphalan	24 (42)	24 (41)	48 (42)
Prior stem cell transplant	8 (14)	12 (21)	20 (17)

patients enrolled in the C16010 China Continuation Study *(Continued)*

Abbreviations: *ECOG* Eastern Cooperative Oncology Group, *ISS* International Staging System, *MM* multiple myeloma
[a]Patients who had relapsed from at least one previous treatment but were not refractory to any previous treatment
[b]Patients who were refractory to at least one previous treatment but were not relapsed to any previous treatment
[c]Patients who were relapsed from at least one previous treatment and additionally were refractory to at least one previous treatment. Refractory disease was defined as disease progression on treatment or progression within 60 days after the last dose of a given therapy

Following randomization of patients, there were 360 patients in the ILd arm and 362 patients to the Ld 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.[2] 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. [1]

In the China Continuation study of 115 patients, 57 patients were randomized to ILd and 58 patients to the Ld arm. Hou et al[7] reported that baseline characteristics were well balanced between the groups.

In a pooled analysis of the TOURMALINE-MM1 and China Continuation study of 138 patients, 67 patients were randomized to the ILd group and 71 patients to the Ld group.[8] Fu et al reported that the baseline characteristics were balanced between the groups.[8]

d) Patient Disposition

Table 5: Patient disposition[3]

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
Withdrawal by patient	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.		

In the China Continuation study, 39 and 38 patients withdrew from the study due to disease progression in the ILd and Ld arms respectively. In addition, there were 26 patients that experienced common adverse events in the ILd arm that led to treatment discontinuation compared to 18 patients in the Ld arm. Two patients in the Ld arm withdrew from the treatment due to other reasons. Withdrawal by patient was documented by 3 patients in the ILd arm compared to 2 patients in the Ld arm.[7]

e) Limitations/Sources of Bias

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=0.012) at the first interim analysis (129 events in the ILd group compared to 157 events in the Ld group). However, the effect size was reduced at the second interim analysis (hazard ratio 0.82, 95% CI 0.67-1.00, 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. Overall

survival remained not statistically significant in IA3 and the risk of death was lower in the latest analysis compared to IA1 and IA2, and the study continues.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes for ITT population

Efficacy Outcomes

Overall survival

Overall survival (OS) was defined as the time from the date of randomization to the date of death.[2] The first interim analysis (IA1) was conducted after 107 events had occurred and results were not significant (HR 0.90, 95% CI 0.62-1.32, p=0.59). [1] The second interim analysis (IA2) was conducted after a median follow-up period of 23 months when 171 deaths had occurred. This was based on 81/360 (23%) patients from the ILd arm and 90/362 (25%) patients from Ld arm who died. The HR was 0.87 [95% CI 0.64-1.18, p=0.36].[4] A subsequent analysis was conducted after the second interim analysis to test for overall survival after [redacted] deaths had occurred after [redacted] months follow-up. *(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until January 31, 2020 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.)* The results were found to be not statistically significant (HR=[redacted], 95% CI: [redacted], p=[redacted]) and the [redacted] OS benefit was [redacted]% in the ILd arm vs. [redacted]% in the Ld arm.[6] *(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until January 31, 2020 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.)* Although the statistical boundary to reach significance (p <0.011) for OS was not met at this analysis, the trial will continue in a blinded fashion towards the final analysis at 486 death events (expected in March 2020). [4]

Based on results from the China Continuation study, there was a 58% reduction in risk of death for patients randomized in the ILd group compared to the Rd group (HR 0.419; 95% CI 0.242-0.726; p = 0.001).[7]

A pooled analysis of the TOURMALINE-MM1 trial and China Continuation study conducted on a subgroup of Asian patients found that the median OS in the ITT was 25.8 months and 15.8 months in the ILd and Rd treatment groups, respectively (HR=0.346, 95% CI 0.196-0.611).[8]

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
Subsequent Analysis	322	[redacted]	0.01000	0.0112	[redacted]
Final Analysis	486	-	0.03820	0.0462	-

Note: Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until January 31, 2020 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.

Progression free survival (PFS)

Progression-free survival (PFS) 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 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 PFS was performed after a median follow-up of 14.8 months in the ILd and 14.6 months in the Ld arm. There were 129/360 (36%) events of disease progression or death which occurred in the ILd arm and 157/362 (43%) events in the Ld arm at the time of the October 30, 2014 data cut-off.[4] The median PFS was 20.6 months in the ILd arm and 14.7 months in the Ld arm. The HR for PFS was 0.74 [95% CI 0.59-0.94, p=0.01]. Based on the statistical analysis plan in the trial protocol, this was the final analysis of PFS and served as the basis for assessing efficacy of ILd in this population. At this second non-inferential (IA2), the HR for progression-free survival was 0.82 [95% CI 0.67-1.0, p=0.0548].{Moreau, 2016 #477}{, 2018 Nov #783} [6]

Hou et al reported the median follow-up as 7.4 months in patients randomized to receive ILd compared to a median follow-up of 6.9 months in the Ld arm. Based on 67 PFS events (30 and 37 in the ILd and Ld arms respectively), there was a 40% reduction in the risk of disease progression in patients randomized to the ILd arm compared to Ld (HR 0.598, 95% CI 0.367–0.972; p = 0.035, logrank test).[8]

A pooled analysis of the TOURMALINE-MM1 trial and China Continuation study conducted on a subgroup of Asian patients found that the median PFS was 7.3 months and 4.6 months in the ILd and Ld treatment groups respectively (HR=0.559, 95% CI no reported).

Sensitivity analysis for PFS:

The submitter conducted a sensitivity analysis to explore possible factors that may have resulted in a diminished PFS at IA2. The submitter noted that slightly more patients in the Ld group started post progression therapy prior to progression (n=22 ILd and n=32 Ld). Based on this analysis, median PFS was 18.4 versus 13.6 months for ILd compared to Ld, respectively with a HR=0.792; p=0.017. It was unclear what the confidence interval on the HR was.

Furthermore, the submitter notes that more Japanese patients had late enrolled onto the study, where 17% of the new PFS events at IA2 were from these late enrolled Japanese patients, while 4% of the original PFS events at IA1 were Japanese.

Lastly, the submitter noted that a press release in Feb 2015 indicating that the primary analysis had been met may have biased results as it may have impacted the physician treatment decisions.

Quality of Life

Quality of life was measured by using EORTC-QLQ-C30 and EORTC-QLQ-MY20 questionnaires.[4] 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.[1] 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.[1] Other quality of life score are summarized in the table below.

Table 10: Quality of life score based on the EORTC QLQ-30[1]

EORTC QLQ-C30 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 CLd 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 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.[1]

Table 11: Quality of life score from EORTC QLQ-MY20 for Mean change from baseline to End of Treatment[1]

EORTC QLQ-MY20 categories	Ixazomib	Placebo
Disease symptoms, (95% CI)	-2.20 (-5.6, 1.2)	-2.52 (-5.8, 0.7)
Side effects of treatment, (95% CI)	3.66 (1.3, 6.0)	4.12 (1.9, 6.4)
Body image, (95% CI)	-1.49 (-6.4, 3.4)	2.19 (-2.3, 6.7)
Future perspective, (95% CI)	-3.16 (-6.7, 0.4)	0.54 (-3.2, 4.3)

Overall response rate

In IA1, the odds of ORR in patients randomized to ILd was 1.44 times higher compared to Ld (odds ratio (OR)=1.44, 95% CI 1.03-2.03; p = 0.04).[4] In IA2, the odds of ORR in patients randomized to ILd was 1.35 times higher compared to Ld (OR=1.35, 95% CI 0.96-1.91; p = 0.089).[4]

The number of patients who had a complete response or very good partial response was also significantly higher in the ILd arm (48%) than Ld arm (39%, p=0.01).[2]

A pooled analysis of the TOURMALINE-MM1 trial and China Continuation study conducted on a subgroup of Asian patients found that the ORR was 57% in the ILd group versus 37% in the Ld group.[8]

Duration of Response (DOR)

Hou et al[7] reported that the median DOR was 7.4 months among responding patients in the ILd arm versus 5.6 months in the Ld arm.[2]

Time to progression (TTP)

In IA1, the median time to disease progression was significantly longer in the ILd arm at 21.4 months compared to 15.7 months in the Ld arm (HR: 0.71, 95% CI: 0.56-0.91, p=0.007).[4] At IA2, the median time to disease progression was significantly longer in the ILd arm at 22.4 months compared to 17.6 months in the Rd arm (HR: 0.79, 95% CI: 0.64-0.98, p=0.034).[4] At the final data cut-off, there was a 71.5% improvement in TTP with ILd versus Ld (HR 0.583; 95% CI 0.353-0.963; p = 0.032); median TTP was 7.3 months (95% CI 4.70-9.53) versus 4.1 months (95% CI 2.99-5.52).[7]

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 Ld arm experienced at least one adverse event of any grade. Among these patients, 267/361 (74%) of patients in the ILd 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.

Withdrawal due to adverse event

Sixty patients (17%) from the ILd arm and 50 patients (14%) from the Ld arm withdrew due to an adverse event.[1]

Table 12: Adverse events at 23 months follow-up[1]

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%)
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 ILd arm, 109 in the Ld 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.[1]

At the latest analysis, there was no concern of cumulative toxicity in the ITT populations or increase in cardiovascular disorders. Adverse events are summarized in the table below

Table 13: Adverse events at the latest analysis (months follow-up)[6]

	ILd arm	Ld arm
GI SOC		
Diarrhea	( )	( )
Nausea	( )	( )
Vomiting	( )	( )
Rash	( )	( )
Rashes, eruptions and exanthems NEC (HLT)	( )	( )
Thrombocytopenia	( )	( )
Peripheral Neuropathy	( )	( )
Cardiac disorders SOC	( )	( )
Cardiac arrhythmias	( )	( )
Heart Failure	( )	( )
Myocardial Infarction	( )	( )
Renal impairment	( )	( )
Liver impairment	( )	( )
Encephalopathy	( )	( )
Other AEs		
Pneumonia	( )	( )
Neutropenia	( )	( )
Anemia	( )	( )
Embolic and Thrombotic events, venous	( )	( )
Hypertension	( )	( )
GI SOC = ; NEC = HLT = ; AE = adverse event		

Note: *Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until January 31, 2020 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.*

Overall, the proportion of adverse events occurring ≥10% of patients in either the ILd group or the Ld regimen (all grades, grade 3 and grade 4) remained consistent at 23 months follow-up and at the latest analysis.[6]

Hou et al[7] reported that there were 67% of patients in the ILd arm and 74% of patients in the Ld arm that had at least one grade ≥3 adverse events and 33 and 31% reported at least one serious adverse event. Overall, there were lower rates of anemia reported among patients in the ILd arm compared to Ld (35 vs 53%; grade 3/4 12%/0 vs 26%/2The incidence of gastrointestinal events were higher in patients that were in the ILd arm versus Ld arm.

The pooled analysis of the TOURMALINE-MM1 and China Continuation study conducted on a subgroup of Asian patients found that the tolerability of the side effects was consistent with the safety results of the large global study.[8]

6.4 Ongoing Trials

No relevant ongoing studies were identified.

7 SUPPLEMENTAL QUESTIONS

7.1 Critical appraisal of the network meta-analysis (NMA) comparing the efficacy and safety of at least one prior therapy of relapsed refractory multiple myeloma

Background

The pCODR-conducted literature search identified only one RCT that assessed the efficacy and safety of ixazomb in combination with lenalidamide and dexamethasone (ILd) versus lenalidamide and dexamethasone (Ld) in patients who had relapsed, refractory or relapsed and refractory multiple myeloma.[2] Given that panobinostat + bortezomib + dexamethasone and elotuzumab + lenalidomide + dexamethasone are not currently reimbursed in the Canadian setting, the submitter provided an updated NMA that removes these two comparators.

Review of published NMA

Objectives of NMA

The objective of the NMA was to evaluate the relative efficacy and safety of ixazomib versus other selected regimens for the treatment of relapsed refractory multiple myeloma based on the outcome of progression free survival (PFS), overall survival (OS) and overall response rate (ORR).[9]

Methods

Search and study selection

The Manufacturer conducted a systematic review to identify eligible studies for the NMA. The inclusion and exclusion criteria are presented in Table 1.[9]

Table 1: Inclusion and exclusion criteria for systematic review

Clinical effectiveness	Inclusion Criteria	Exclusion Criteria
Study design	Interventional study Observational study	• Review article • Meta-analysis • Case report • Animal experiment study • Non-pharmaceutical intervention or non-human study
Number of study arms	Multi-arm studies	Single-arm studies
Publication type	Only publications or reports with sufficient results suited for evaluation	letters, editorials, press releases
Population	Adult patients aged 18 years and older with relapsed or refractory MM following at least 1 prior line of therapy	• Pediatric patients (<18 years) • Non-relapsed or non-refractory MM • Newly diagnosed, previously untreated patients
Intervention	Studies includes interventions of interest: Ld, ILd, V, Vd, PVd, CLd, Cd, Pom-Dex, ELd, VLd, DLd, DVd	Study that does not include interventions of interest

Clinical effectiveness	Inclusion Criteria	Exclusion Criteria
Outcomes	At least one of the following efficacy outcomes is reported: Progression free survival (PFS; measured by hazard ratio [HR]), Overall survival (OS; measured by HR), and Overall Response Rate (ORR; measured by odds ratio [OR])	Study that does not report an outcome of interest
Language restrictions	Only English language records were included	
Post-hoc analysis:	Only studies that presented post-hoc analyses for original studies (e.g., extended follow-up) were included	
Abbreviations: Ld: lenalidomide + dexamethasone, ixazomib + lenalidomide + dexamethasone, V: bortezomib monotherapy, Vd: bortezomib + dexamethasone, PVd: panobinostat + bortezomib + dexamethasone, CLd: carfilzomib + lenalidomide + dexamethasone, Cd: carfilzomib + dexamethasone, Pom-Dex: pomalidomide + dexamethaonse, ELd: elotzumab + lenalidomide + dexamethasone, VLd: bortezomib + lenalidomide + dexamethasone, DLd: daratumumab + lenalidomide + dexamethasone, DVd: daratumumab + bortezomib + dexamethasone		

A systematic search of EMBASE and PubMed/Medline using Ovid was performed. The searches were conducted on February 21, 2018. Publications through December 31, 2017 were considered and no limitations were placed on outcomes as abstracts may not have reported all outcomes evaluated in a study. The 2016-2017 European Hematology Association (EHA) and American Society of Hematology (ASH) conferences. Additional targeted literature searches were conducted to identify other studies that may present the outcome data stratified by subgroups of interest. Two reviewers independently screened the titles/abstracts of studies to assess eligibility. Full-texts of eligible studies were retrieved and independently reviewed by the two reviewers. Data was also extracted by two independent reviewers. Discrepancies were resolved by discussion with additional reviewers.[9]

NMA methodology

The current NMA incorporated results from the second (PFS and ORR) and subsequent (OS) interim analyses of the TOURMALINE MM-1 trial to perform an indirect comparison against other treatments of interest.

The actual estimation of the NMA was conducted under a Bayesian framework. As the network was sparse and did not contain sufficient information, fixed effects models were conducted for this NMA. Random effects models were not conducted as these types of model fits contribute towards high variance and large confidence intervals when the network is sparse. The best model fit was determined based on the residual deviance and Deviance Information Criterion (DIC). The analyses were estimated using Bayesian Markov Chain Monte Carlo (MCMC).[9]

In the current study, the NMA base case analysis included peer-reviewed RCTs only. Additional sensitivity analyses based on an extended network that included observational studies was conducted to assess the robustness of the base case findings.[9]

Results

Included Studies

The systematic literature search provided by the submitter identified a total of 7,554 citations from EMBASE and Medline databases as well as 54 abstracts from ASH and 400 conference abstracts from EHA. A total of 17 studies, including 13 peer-reviewed RCTs (from 26 full text

publications and 12 conference abstracts) and 4 observational studies (from 3 full text publications and 1 conference abstract) were included in the analysis. [9]

Trial characteristics

Details of the populations, interventions and comparators used in the NMA are reported in Table 2.

Table 2: Assessment of the similarity between identified studies and availability of outcomes and subgroup results

Trial Name	Study type	N	No of prior therapies	Treatment Arms Evaluated
APEX	RCT: Yes Phase: III Double blinded: Open-label	333 336	1	Bortezomib dexamethasone
ASPIRE	RCT: Yes Phase: III Double blinded: Open-label	396 396	2 2	Carfilzomib+lenalidomide+dexamethasone Lenalidomide+dexamethasone
Bruno	Observational Retrospective	9 14	-	Bortezomib Bortezomib +dexamethasone
CASTOR	RCT: Yes Phase: III Double blinded: Open-label	251 247	2 2	Daratumumab +bortezomib +dexamethasone Bortezomib +dexamethasone
Dimopoulos 2010 a	Phase: III Observational Prospective	49 50	2 2	Bortezomib + dexamethasone + lenalidomide Dexamethasone + lenalidomide
Dimopoulos 2010b	Conference abstract	106 326	-	Bortezomib Bortezomib + dexamethasone
Dimopolous 2015	Observational Propensity Score Matched-pairs	109 109	-	Bortezomib Bortezomib + dexamethasone
ELOQUENT-2	RCT: Yes Phase: III Open-label	321 325	2 2	Elotzumab + lenalidomide+dexamethasone Lenalidomide +dexamethasone
ENDEAVOR	RCT: Yes Phase: III	464 465	-	Carfilzomib+dexamethasone Bortezomib+dexamethasone
Hellmann 20	Open Label Pharmakinetic Two-stage	301 813	-	Bortezomib Bortezomib+dexamethasone Bortezomib+rifampicin
MM-003	Phase III Randomized Open-label	302 153	5 5	Pomalidomide Dexamethasone Dexamethasone
MM-009	Phase III Double -blind Placebo-controlled Randomized	177 176	2 2	Lenalidomide Dexamethasone Plaebo+dexamethasone Cycle length
MM-010	Phase III Double -blind Placebo-controlled Randomized	176 175	2 2	Lenalidomide + dexamethasone Placebo
PANORAMA 1	Phase III Double -blind Placebo-controlled	387 381	-	Panobinostat + bortezomib + dexamethasone Placebo +bortezomib +dexamethasone

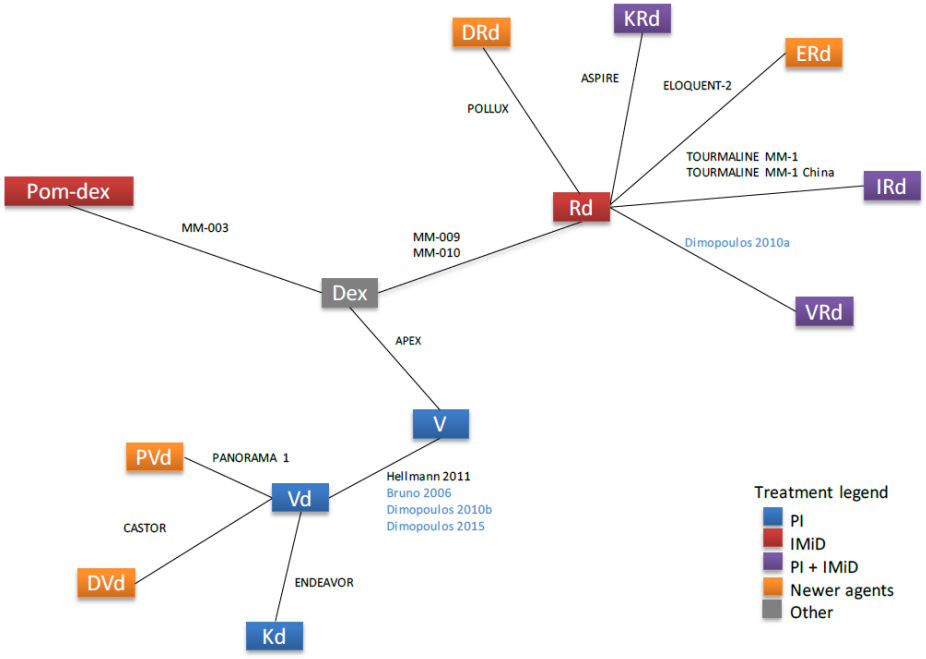
	Randomized			
POLLUX	Phase III Conference Abstract Open-label Randomized	286 283	1 1	Daratmumab+lenalidomide+dexamethasone Lenalidomide +dexamethasone
TOURMALINE MM-1	Phase III Placebo-controlled Randomized Double-blind	360 362	–	Ixazomib + lenalidomide +dexamethasone Placebo + lenalidomide + dexamethasone
TOURMALINE MM-1	Double-blind Multicentre	360 362	-	Ixazomib + lenalidomide + dexamethasone Placebo + lenalidomide + dexamethasone

Based on the previously submitted NMA and evolving treatment landscape, the following regimens were removed: thalidomide, thalidomide + dexamethasone, thalidomide + dexamethasone + bortezomib, pegylated liposomal doxorubicin + bortezomib, bortezomib _ dexamethasone + cyclophosphamide, and elotuzumab + bortezomib + dexamethasone.

NMA Results

A graphical representation of the NMA is presented in Figure 1.

Figure 1. Network diagram of all studies included in the NMA [9]



Progression Free Survival (PFS)

Fifteen RCTs in the NMA provided results for PFS including three observational studies. ILd was associated with a statistically significantly longer PFS as compared to Ld, V, Dex and Pom-dex however statistically significantly shorter PFS compared to DLd and DVd. There was no statistically significant difference in PFS for ILd compared to Vd, PVd, VLd, ELd, Kd or CLd.[9] Table 3 presents results for PFS in the extended network.

Table 3. NMA hazard ratios (95% credible intervals) for PFS-extended network[9]

Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until January 31, 2020 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.

Overall Survival (OS)

Fifteen studies which included 13 treatment comparisons reported results for OS in the NMA extended network. There was a statistically significant longer OS for ILd compared to Ld, V, Dex and Pom-Dex. There was no statistically significant difference in OS for ILd compared to Vd, PVd, VLd, ELd, Kd, CLd, DLd and DVd.[9] Table 4 presents results for OS in the extended network.

Table 4. NMA hazard ratios (95% credible intervals) for OS-extended network[9]

Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until January 31, 2020 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.

Overall Response Rate (ORR)

Seventeen studies which included 13 treatment comparisons reported results for ORR in the NMA extended network. There was a statistically significant better ORR for ILd compared to Ld, V and Dex. While ORR was statistically significant for ILd compared to CLd and DLd, the magnitifue of effect for ORR was decreased. There was no statistically significant difference in ORR for ILd compared to Vd, Pom-Dex, PVd, VLd, ELd, Kd and DVd.[9] Table 5 presents results for ORR in the extended network.

Table 5. NMA odds ratios (95% credible intervals) for ORR-extended network[9]

Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until January 31, 2020 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.

The NMA included two trials (ELOQUENT-2 and PANORAMA1) which encompass treatment regiments not currently reimbursed in the Canadian setting. Upon the exclusion of these trials, for PFS and OS, the hazard ratio changed slightly from [redacted] to [redacted] for ILd vs. VLd for OS, and no changes were made to statistically significant findings. *(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until January 31, 2020 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.)* Similarly, for ORR, the odds ratio changed from [redacted] to [redacted] for ILd vs. Vd, and no changes were made to statistically significant findings.[10] *(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until January 31, 2020 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.)*

Critical Appraisal of the ITC

The quality of the NMA provided by the Submitter was assessed according to the recommendations made by the ISPOR Task Force on Indirect Treatment Comparisons.[55] Details of the critical appraisal are presented below.

Table 6: Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis Jansen et al[55]

ISPOR Questions	Details and Comments‡
1. Is the population relevant?	**Yes.** The study populations of all the included trials in the NMA matched in review indication (e.g., the treatment of adult patients with multiple myeloma who have received at least one prior therapy).
2. Are any critical interventions missing?	**No.** The Submitter included all relative interventions for this patient population. While the review team noted that the submitted NMA incorporated treatment regimens that are not reimbursed in the Canadian setting or anticipated to be reimbursed in the near future, the submitter provide an updated NMA that excluded the treatment regimens not reimbursed in the Canadian setting.
3. Are any relevant outcomes missing?	**No.** The following outcomes were assessed: PFS, OS and ORR.
4. Is the context (e.g., settings and circumstances) applicable to your population?	**Yes.**
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	**Yes.** A summary of the systematic literature review used to conduct the NMA was reported. The information sources, search strategy and study selection criteria were clearly described.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	**No.** There were no closed loops in the NMA.
7. Is it apparent that poor quality studies were included thereby leading to bias?	**Unclear.** Information on the tools used to assess the quality of studies were not available.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	**No.** There was no selective reporting of outcomes.
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	**Yes.** There were differences in study inclusion and exclusion criteria. Thus, study populations were different across studies.
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	**Yes.** The submitter did acknowledge that there was heterogeneity across the study trials and due to a sparse network that did not contain sufficient information, a fixed effects model was used.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	The use of a Bayesian framework preserves within study randomization.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	**Not possible.** There was no closed loop and the network was sparse.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	**Not applicable.**
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	**Yes.** There is an imbalance in the distribution of treatment effect modifiers across different types of comparisons in the network of trials. It is unclear if the researchers attempted to minimize the bias with the analysis.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	**Yes.** The Submitter stated that only fixed models were conducted for this study since the network was not well-connected and very sparse.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	**Not applicable.** Fixed effects models were used.

ISPOR Questions	Details and Comments‡
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	While subgroup analyses were conducted for the primary outcome of PFS for patients stratified by high-risk genetic subtype of MM, number of prior lines of therapy, ISS reported at study entry, age category and renal impairment using creatinine clearance categories, meta-regression was not undertaken.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	**Yes.** The NMA is presented in Figure 1.
19. Are the individual study results reported?	**Yes.** The Submitter provided the base case for PFS and OS used in the NMA.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	**Yes.** The Submitter provided the direct comparisons for PFS,OS and ORR across all of the trials included in the NMA.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	**Yes.** Measures of uncertainty were reported for each hazard ratio.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	**No.**
23. Is the impact of important patient characteristics on treatment effects reported?	**No.**
24. Are the conclusions fair and balanced?	**Yes.** The overall conclusions of the NMA are fair and the relevant comparators identified by CGP and PAG are included.
25. Were there any potential conflicts of interest?	**No.**
26. If yes, were steps taken to address these?	**Not applicable.** There were no potential conflicts of interest.

The review team noted that the submitted NMA incorporated treatment regimens that are not reimbursed in the Canadian setting or anticipated to be reimbursed in the near future, namely panobinostat + bortezomib + dexamethasone and elotuzumab + lenalidomide + dexamethasone. Upon exclusion of ELOQUENT-2 and PANORAMA1, the results of the NMA remained almost identical. The exclusion of ELOQUENT-2 and PANORAMA1 showed tighter 95% CrIs.[10]

While the NMA base case analysis included peer-reviewed RCTs only, the extended network included observational studies also.[9]

An additional NMA was conducted by Lou et al[40] 2018 and the search time period was from January 1, 2000 to June 30, 2017. PubMed database was searched using a search strategy adopted by Botta et al. The outcomes of interest were nonresponse rate (NRR), time to progression (TTP), PFS and OS. The studies included in the NMA were limited to RCTs where at least 2 different regimens were compared (studies that entailed different dosing schemes or modes of administration being compared were excluded). The results of the NMA demonstrated that daratumumab combined with lenalidomide, and dexamethasone was the most effective therapy in terms of NRR, TTP, and PFS (NRR: OR =0.046, 95% CrI =[0.024, 0.085]; TTP: HR =0.14, 95% CrI =[0.092, 0.2]; PFS: HR =0.12, 95% CrI =[0.077, 0.18], compared with dexamethasone singlet. In addition, ixazomib combined with lenalidomide, and dexamethasone was the most effective therapy in terms of OS (HR =0.12, 95%CrI =0.17, 0.54).[40]

Conclusions

The NMA was conducted using a Bayesian framework. The results from the NMA demonstrated that ILd was associated with significantly improved PFS and OS than Ld, V, Dex, and Pom-Dex, but statistically significantly shorter PFS than DLd. In addition, there was a statistically significant better ORR in favour of ILd compared to Rd, V, and Dex.

Due to concerns of a sparse network, only fixed effects models were conducted for this study. The inclusion of observational studies in the NMA extended network for PFS violates the assumption of homogeneity. Furthermore, there was heterogeneity across study populations due to different inclusion and exclusion criteria. The sample size of the underlying studies may have also contributed towards the imprecision of the estimates. Thus, the width of the credible intervals was wide. Therefore the results for PFS, OS and ORR should be interpreted with caution. Other outcomes of interest (e.g., health related quality of life and safety) were not explored in this NMA.

8 COMPARISON WITH OTHER LITERATURE

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

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. The manufacturer, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

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.

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

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

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.

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.

REFERENCES

1. Pan-Canadian Oncology Drug Review final clinical guidance report: ixazomib (Ninlaro) for muptiple myeloma. Ottawa (ON): CADTH; 2017 June 29: https://www.cadth.ca/sites/default/files/pcodr/pcodr_ixazomib_ninlaro_mm_fn_cgr.pdf. Accessed 2019 Apr 9.

2. Moreau P, Masszi T, Grzasko N, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;374(17):1621-1634.

3. Moreau P MT, Grzasko N, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma Suplementary Appendix. *N Engl J Med [supplementary appendix on the Internet]*. 2016;374:1621-1634.

4. Clinical summary: NINLARO [ixazomib (as ixazomib citrate)]. Oakville (ON): Takeda Canada; 2018 Nov.

5. Moreau P MT, Grzasko N, et al. Protocol for Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. (374):1621-1634.

6. TOURMALINE-MM1 (TMM1) data and information: interim analysis 3 (IA3)[CONFIDENTIAL]. Oakville (ON): Takeda Canada; 2018.

7. Hou J, Jin J, Xu Y, et al. Randomized, double-blind, placebo-controlled phase III study of ixazomib plus lenalidomide-dexamethasone in patients with relapsed/refractory multiple myeloma: China continuation study. *J Hematol Oncol*. 2017;10(1):137.

8. Fu W, Lu J, Jin J, et al. Overall survival (OS) benefit of oral ixazomib in combination with lenalidomide and dexamethasone (IRd) vs lenalidomide and dexamethasone (Rd) in Asian patients (pts) with relapsed and/or refractory multiple myeloma (RRMM): pooled-analysis from the tourmaline-MM1 and the China continuation studies. *Blood*. 2018;132(Suppl. 1).

9. Analysis Group Inc. Systematic literature review and network meta-analysis in relapsed/refractory multiple myeloma: updated results [CONFIDENTIAL]. Boston (MA): Analysis Group, Inc.; 2018 Oct 29.

10. Takeda Canada response to pCODR checkpoint meeting questions on ixazomib (Ninlaro). Oakville (ON): Takeda Canada; 2019 Feb 6.

11. Canadian Cancer Statistics Advisory Committee. Canadian cancer statistics 2018. Canadian Cancer Society: Toronto (ON); 2018: http://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2018-EN.pdf?la=en. Accessed 2019 Apr 9.

12. Moreau P, Hulin C, Caillot D, et al. Ixazomib-lenalidomide-dexamethasone (IRd) combination before and after autologous stem cell transplantation (ASCT) followed by ixazomib maintenance in patients with newly diagnosed multiple myeloma (NDMM): A phase 2 study from the intergroupe Francophone Du MyeLome (IFM). *Blood*. 2016;128(22).

13. pan-Canadian Oncology Drug Review manufacturer submission: Ninlaro (ixazomib as ixazomib citrate), 4 mg capsule. Oakville (ON): Takeda Canada Inc; 2018 Nov 29.

14. Dimopoulos MA, Goldschmidt H, Niesvizky R, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2017;18(10):1327-1337.

15. Siegel DS, Dimopoulos MA, Ludwig H, et al. Improvement in overall survival with carfilzomib, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma. *J Clin Oncol*. 2018;36(8):728-734.

16. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15(12):e538-548.

17. Kristinsson SY, Landgren O, Dickman PW, Derolf AR, Bjorkholm M. Patterns of survival in multiple myeloma: a population-based study of patients diagnosed in Sweden from 1973 to 2003. *J Clin Oncol*. 2007;25(15):1993-1999.

18. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood*. 2008;111(5):2516-2520.

19. Pozzi S, Marcheselli L, Bari A, et al. Survival of multiple myeloma patients in the era of novel therapies confirms the improvement in patients younger than 75 years: a population-based analysis. *Br J Haematol*. 2013;163(1):40-46.

20. Ahuja A, Attri S, Kamra S, Kalra M. Hrqol and health utility impact on patients with newly diagnosed multiple myeloma In Us and Europe: a systematic literature review. *Value Health*. 2015;18(7):A468.

21. Warren JL, Harlan LC, Stevens J, Little RF, Abel GA. Multiple myeloma treatment transformed: a population-based study of changes in initial management approaches in the United States. *J Clin Oncol*. 2013;31(16):1984-1989.

22. Rajkumar SV, Gahrton G, Bergsagel PL. Approach to the treatment of multiple myeloma: a clash of philosophies. *Blood*. 2011;118(12):3205-3211.

23. Bahlis NJ. Darwinian evolution and tiding clones in multiple myeloma. *Blood*. 2012;120(5):927-928.

24. Anderson KC. The 39th David A. Karnofsky Lecture: bench-to-bedside translation of targeted therapies in multiple myeloma. *J Clin Oncol*. 2012;30(4):445-452.

25. Corre J, Munshi N, Avet-Loiseau H. Genetics of multiple myeloma: another heterogeneity level? *Blood*. 2015;125(12):1870-1876.

26. Boise LH, Kaufman JL, Bahlis NJ, Lonial S, Lee KP. The Tao of myeloma. *Blood*. 2014;124(12):1873-1879.

27. Blade J, de Larrea CF, Rosinol L. Incorporating monoclonal antibodies into the therapy of multiple myeloma. *J Clin Oncol*. 2012;30(16):1904-1906.

28. San Miguel J, Moreau P, Rajkumar V, et al. Four phase 3 studies of the oral proteasome inhibitor (PI) ixazomib for multiple myeloma in the newly-diagnosed, relapsed/refractory, and maintenance settings: tOURMALINE-MM1, -MM2, -MM3, and -MM4. *Clin Lymphoma Myeloma Leuk*. 2015;15.

29. Chanan-Khan AA, Giralt S. Importance of achieving a complete response in multiple myeloma, and the impact of novel agents. *J Clin Oncol*. 2010;28(15):2612-2624.

30. Dimopoulos MA, Palumbo A, Hajek R, et al. Factors that influence health-related quality of life in newly diagnosed patients with multiple myeloma aged >/= 65 years treated with melphalan,

prednisone and lenalidomide followed by lenalidomide maintenance: results of a randomized trial. *Leuk Lymphoma*. 2014;55(7):1489-1497.

31. Delforge M, Minuk L, Eisenmann JC, et al. Health-related quality-of-life in patients with newly diagnosed multiple myeloma in the FIRST trial: lenalidomide plus low-dose dexamethasone versus melphalan, prednisone, thalidomide. *Haematologica*. 2015;100(6):826-833.

32. Garrison LP, Jr., Wang ST, Huang H, et al. The cost-effectiveness of initial treatment of multiple myeloma in the U.S. with bortezomib plus melphalan and prednisone versus thalidomide plus melphalan and prednisone or lenalidomide plus melphalan and prednisone with continuous lenalidomide maintenance treatment. *Oncologist*. 2013;18(1):27-36.

33. Cavo M, Rajkumar SV, Palumbo A, et al. International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation. *Blood*. 2011;117(23):6063-6073.

34. Ludwig H, Durie BG, McCarthy P, et al. IMWG consensus on maintenance therapy in multiple myeloma. *Blood*. 2012;119(13):3003-3015.

35. Palumbo A, Rajkumar SV, San Miguel JF, et al. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. *J Clin Oncol*. 2014;32(6):587-600.

36. Durie BG, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet*. 2017;389(10068):519-527.

37. Laubach J, Garderet L, Mahindra A, et al. Management of relapsed multiple myeloma: recommendations of the International Myeloma Working Group. *Leukemia*. 2016;30(5):1005-1017.

38. U.S. National Library of Medicine. An Observational Study of Presentation, Treatment Patterns, and Outcomes in Multiple Myeloma Participants. 2019; https://clinicaltrials.gov/ct2/show/NCT02761187. Accessed Jun 5, 2019.

39. Czech Myeloma Group. RMG | Registry of Monoclonal Gammopathies. https://rmg.healthregistry.org/index.php. Accessed Jun 5, 2019.

40. Luo XW, Du XQ, Li JL, Liu XP, Meng XY. Treatment options for refractory/relapsed multiple myeloma: an updated evidence synthesis by network meta-analysis. *Cancer Manag Res*. 2018;10:2817-2823.

41. Leleu X, Masszi T, Bahlis NJ, et al. Patient-reported health-related quality of life from the phase III TOURMALINE-MM1 study of ixazomib-lenalidomide-dexamethasone versus placebo-lenalidomide-dexamethasone in relapsed/refractory multiple myeloma. *Am J Hematol*. 2018;04:04.

42. Betts K, Chen C, Zichlin M, Brun A, Signorovitch J, Makenbaeva D. Relative progression-free survival over time of novel triplet regimens for the treatment of relapsed/refractory multiple myeloma. *Haematologica*. 2017;102 (Supplement 2):533.

43. Gupta N, Diderichsen PM, Hanley MJ, et al. Population pharmacokinetic analysis of ixazomib, an oral proteasome inhibitor, including data from the phase III TOURMALINE-MM1 study to inform labelling. *Clin Pharmacokinet*. 2017;56(11):1355-1368.

44. Hanley MJ, Gupta N, Hou J, et al. Characterization of the pharmacokinetics of ixazomib in Chinese patients with relapsed/refractory multiple myeloma in the China continuation of the tourmaline-MM1 study. *Clin Pharmacol Ther*. 2017;101 (Supplement 1):S31.

45. Richardson PG, Avet-Loiseau H, Palumbo A, et al. Efficacy and safety of ixazomib plus lenalidomide-dexamethasone (IRd) vs placebo-rd in patients (pts) with relapsed/refractory multiple myeloma (RRMM) by cytogenetic risk status in the global phase III Tourmaline-MM1 study. *J Clin Oncol*. 2016;34(Supplement 15):8018-8018.

46. Hou J, Jin J, Xu Y, et al. Ixazomib plus lenalidomide-dexamethasone (IRD)vs placebo-RD in patients (PTS) with relapsed/refractory multiple myeloma (RRMM): China continuation of tourmaline-MM1. *Haematologica*. 2016;101 (Supplement 1):540.

47. Mateos MV, Masszi T, Grzasko N, et al. Efficacy and safety of oral ixazomib-lenalidomide-dexamethasone (IRD) vs placebo-RD in relapsed/refractory multiple myeloma patients: impact of prior therapy in the phase 3 tourmaline-MM1 study. *Haematologica*. 2016;101 (Supplement 1):527.

48. Mateos MV, Masszi T, Grzasko N, et al. Impact of prior therapy on efficacy and safety of oral ixazomib-lenalidomide-dexamethasone (IRd) vs placebo-Rd in patients (pts) with relapsed/refractory multiple myeloma (RRMM) in TOURMALINE-MM1. *J Clin Oncol*. 2016;34(Supplement 15):8039-8039.

49. Moreau P, Masszi T, Grzasko N, et al. Ixazomib, an investigational oral proteasome inhibitor (PI), in combination with lenalidomide and dexamethasone (IRD), significantly extends progression-free survival (PFS) for patients (PTS) with relapsed and/or refractory multiple myeloma (RRMM): The phase 3 tourmaline-MM1 study (NCT01564537). *Blood*. 2015;126 (23):727.

50. Avet-Loiseau H, Bahlis N, Chng WJ, et al. Impact of cytogenetic risk status on efficacy and safety of ixazomib-lenalidomide-dexamethasone (IRD) vs placebo-rd in relapsed/refractory multiple myeloma patients in the global tourmaline-MM1 study. *Haematologica*. 2016;101 (Supplement 1):80.

51. Di Bacco A, Bahlis NJ, Munshi NC, et al. Higher c-MYC expression is associated with ixazomib-lenalidomide-dexamethasone (IRd) progression-free survival (PFS) benefit versus placebo-rd: biomarker analysis of the phase 3 tourmaline-mm1 study in relapsed/refractory multiple myeloma (RRMM). *Blood*. 2016;128(22).

52. Millennium Pharmaceuticals Inc. NCT01564537: A phase 3 study comparing oral ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with relapsed and/or refractory multiple myeloma. Bethesda (MD): U.S. National Library of Medicine; 2018: https://clinicaltrials.gov/ct2/show/NCT01564537. Accessed 2019 Apr 9.

53. al He. Supplementary Methods for Randomized, double-blind, placebo-controlled phase III study of ixazomib plus

lenalidomide-dexamethasone in patients with relapsed/refractory multiple

myeloma: China Continuation study. *J Hematol Oncol*. 2017.

54. Moreau P MT, Grzasko N, et al. . Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma *N Engl J Med [supplementary appendix on the Internet]*. 2017:1621-1634.

55. Jansen JP, Trikalinos T, Cappelleri JC, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value Health*. 2014;17(2):157-173.