Final Recommendation for Ixazomib (Ninlaro) for Multiple Myeloma
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pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada’s provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
This pCODR Expert Review Committee (pERC) Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

pERC does not recommend reimbursement of ixazomib (Ninlaro) in combination with lenalidomide and dexamethasone (ILD) for the requested subgroup of patients with multiple myeloma who have received at least one prior treatment and have high-risk cytogenetics or who have received at least two prior therapies. (Note: The submitter’s funding request was based on a subset of patients from the Health Canada-approved indication.)

pERC made this recommendation because the Committee was not confident that there is a net clinical benefit of ILD treatment in the requested patient population compared with lenalidomide and dexamethasone (Ld), due to concerns about the evidence presented from the available subgroup analyses from the TOURMALINE-MM1 trial. The Committee concluded that there was considerable uncertainty about the magnitude of clinical benefit of ILd compared with Ld with regard to outcomes important to decision-making, such as overall survival (OS) and progression-free survival (PFS). pERC concluded that ILd partially aligned with patient values because it offers an alternative treatment in this group of patients (i.e., the subgroup of patients from the TOURMALINE-MM1 trial who received at least one prior treatment and have high-risk cytogenetics (as per the expanded definition of high-risk), or who have received at least two prior therapies) with an oral route of administration, tolerable side effects and quality of life that was not diminished, however, its clinical effect is uncertain.

The Committee noted that, based on the high level of uncertainty in the available clinical data, ILd could not be considered cost-effective in this population compared with Ld both at the submitted and the reanalysis estimates.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS

No next steps were identified.
SUMMARY OF pERC DELIBERATIONS

Despite significant advancements in the treatment and life expectancy of patients with multiple myeloma, it remains an incurable disease, and most patients will relapse following initial therapy. Bortezomb-based or lenalidomide-based therapies are currently the standard treatment options in the second-line setting; however, superiority of one regimen over the other has not been conclusively demonstrated. With the recent pERC reimbursement recommendation for carfilzomib triplet therapy, treatment patterns are likely to shift toward the use of upfront bortezomb-based regimens followed by carfilzomb plus lenalidomide and dexamethasone (CLd). For patients who are not eligible to receive the triplet therapy, carfilzomib plus dexamethasone doublet therapy has also recently been recommended for reimbursement by pERC. In reconsideration of the pERC Initial Recommendation, pERC considered feedback from the registered clinicians, who see a need for effective oral treatment combinations for patients for whom carfilzomib-based therapy is not an option. pERC agreed with the registered clinicians that there are limited effective treatment options for patients who cannot tolerate carfilzomib-based therapies. pERC noted that treatment options in multiple myeloma are changing rapidly as new agents are being introduced. Given that all available therapies involve intravenous or subcutaneous administration or both, pERC noted that ixazomib is the first in the class of proteasome inhibitors to offer patients the potential for an all-oral triplet regimen administered entirely via the oral route.

The pCODR systematic review included one open-label randomized controlled trial, TOURMALINE-MM1, which evaluated ILd compared with Ld on efficacy and safety outcomes in patients with relapsed or refractory multiple myeloma. pERC stated that uncertainty remained in the magnitude of benefit detected in the intention-to-treat (ITT) analysis, which limited their confidence in the results. pERC noted that the overall trial results reported statistically significant improvements in PFS at the first interim analysis (IA1), whereas a second interim analysis (IA2) reported non-significant PFS results. pERC acknowledged that the design of the trial specified that IA1 would be the final analysis and that IA2 would be non-inferential. In discussion, the Committee noted that the subsequent data are more mature and should be confirmatory of earlier analyses; however, the more mature data resulted in a diminishing effect. Therefore, the Committee was concerned that the statistically significant PFS results from IA1 may represent a false-positive given the non-significant results of IA2. Based on this, pERC agreed that there is considerable uncertainty in the magnitude of PFS benefit reported for the trial results in the overall ITT population. Investigators made adjustments for multiple testing of both PFS and OS; however, significance was not demonstrated at IA1 or IA2 for OS. A third interim analysis and a final analysis are still pending.

In reconsideration of the Initial Recommendation, pERC discussed the feedback received from the submitter and registered clinicians regarding the second interim analysis (IA2) for PFS. pERC discussed the submitter’s claim that assessing the PFS results of ixazomib based on IA2 is inconsistent with how the Committee previously reviewed another proteasome inhibitor (carfilzomib). pERC acknowledged that the overall trial results reported statistically significant improvements in PFS at IA1, the specified final analysis for PFS in the TOURMALINE-MM1 trial. However, pERC reiterated that subsequent interim analyses with more mature data should be confirmatory of earlier analyses. Instead, the more mature data from IA2 resulted in a weakened magnitude of PFS benefit. The Committee felt that the magnitude of benefit on the length of time patients live without their disease progressing appeared to reduce after longer follow-up based on the results reported in the ITT population in the TOURMALINE-MM1 trial. pERC also discussed additional analyses provided by the submitter in their feedback. The submitter provided new, previously unsubmitted and unpublished analyses that were considered out of scope for the review and, as a result, were not considered by the Review Team and not provided to pERC for reconsideration. An additional analysis that was previously published in a European Medicines Agency (EMA) report was also provided by the submitter in their feedback. pERC discussed the data available within the EMA report (censoring based on patients who received an alternate therapy) and noted that it explained a possible reason for a non-significant result in IA2. However, pERC noted that the result from this analysis was similar to the reported planned PFS analysis at IA2, and was still non-significant. pERC also acknowledged...
that the published EMA report stated that the uncertainty observed in the IA2 suggests that the size of the treatment effect observed in IA1 might be an over-estimation. Overall, the Committee reiterated their original concerns about the evidence and that there is considerable uncertainty in the magnitude of PFS benefit reported in the trial results in the ITT population.

In considering the patient population requested for reimbursement by the submitter, pERC specifically deliberated upon the results of a subgroup analysis in patients with at least one prior therapy and high-risk cytogenetics and a second subgroup of patients who had received at least two prior therapies in the TOURMALINE-MM1 trial. pERC had many concerns that limited their confidence in the results of subgroup analyses presented from TOURMALINE-MM1. While PFS and overall survival (OS) were reported to be significant in the two subgroups of patients (significance reported only for PFS in patients with at least two prior lines of treatment), the post hoc nature of these analyses resulted in considerable uncertainty in the interpretation. Furthermore, no adjustments were made for multiple testing in the subgroups, and there was no information available about whether tests for interaction had been conducted to confirm that the subgroups identified were indeed effect modifiers. Adjusting for multiple testing in the subgroup analysis using the design employed in the ITT analysis indicated that the PFS results for the subgroup of patients with at least one prior therapy and high-risk cytogenetics is no longer significant at IA1. Therefore, the Committee was unable to draw any conclusions on the PFS and OS results within the two subgroups of interest and concluded that the results were, at best, hypothesis-generating. The Committee agreed that the results in the subgroups of interest are exploratory and that further studies are required to confirm the magnitude of benefit achieved with ixazomib with respect to outcomes important to decision-making, such as OS and PFS.

In reconsideration of the Initial Recommendation, pERC discussed feedback from the submitter regarding whether the two subgroup analyses were pre-specified or post hoc in nature. The Clinical Guidance Panel (CGP) and the Methods Team clarified and confirmed that the subgroup analyses of patients who received at least two prior therapies were pre-specified at the time of randomization; therefore, the analyses were not considered post hoc in nature. However, the subgroup of patients with at least one prior therapy and high-risk cytogenetics was not pre-specified, as the definition of high-risk cytogenetics was updated since the time of data analysis and publication, therefore that subgroup analysis was considered post hoc in nature. Although pERC noted that analyses of patients who received at least two prior lines of therapies were considered pre-specified, the Committee agreed with the Methods Team and the CGP that this does not mean the trial was adequately powered to detect a true difference in this subpopulation; nor does it mean that those analyses have been adjusted for multiple comparisons. pERC emphasized that there was considerable uncertainty about the magnitude of clinical benefit of ILd compared with Ld in the two subgroups of patients with regard to outcomes important to decision-making, such as OS and PFS.

pERC noted that limited data were available on patient-reported outcomes within the subgroups of interest. The available evidence both in the ITT and within the subgroups of interest demonstrated that quality of life was not diminished for patients treated with ILd compared with Ld and baseline values. pERC deliberated on the toxicity of ILd and noted that ILd was generally well tolerated. The Committee discussed potential concerns for thrombocytopenia with the use of ILd as it occurred more frequently in patients treated with ILd both in the ITT analysis and within the subgroup of patients with at least one prior therapy and high-risk cytogenetics. pERC considered input from registered clinicians which stated that the benefit of ixazomib outweighs the risks associated with thrombocytopenia but acknowledged that frequent blood work would be required to monitor for risk of this adverse event. Overall, due to considerable limitations in the evidence from the available subgroup analyses of the TOURMALINE-MM1 trial, pERC lacked confidence that there is a net clinical benefit of ILd treatment compared with Ld in the treatment of patients with at least one prior therapy and high-risk cytogenetics or patients who had received at least two prior therapies. pERC noted that indirect evidence was presented making a comparison to Ld. The Committee considered the limitations identified by the CGP and agreed that caution must be used in interpreting the results of this indirect comparison of the two triplet-therapies.

pERC deliberated upon input from a patient advocacy group. pERC noted that the oral route of administration with ixazomib aligned with patient values as it would allow for the entire treatment regimen to be administered at home. However, it is likely patients would require frequent blood work, at least at the beginning of treatment, to monitor for thrombocytopenia. In reconsideration of the Initial Recommendation, pERC considered feedback from the patient group regarding the need for and value of oral treatment options. The patient group expressed that pERC did not truly appreciate the value and benefits of oral treatment options for patients and their impact on patients’ lives. pERC discussed the need for oral treatment as an option for patients. The Committee appreciated that having a treatment regimen that is administered orally would potentially allow patients to remain at home, thus reducing...
both the emotional burden and the inconvenience of frequent hospital visits for patients and for those accompanying them to receive intravenous treatments in a cancer centre. Overall, pERC acknowledged that although ixazomib offers an oral regimen as a treatment option, its clinical benefit remains uncertain.

The Committee also noted that adherence to the administration schedule of the triplet therapy may be challenging for some patients as the administration schedule of ixazomib is different from that of lenalidomide and dexamethasone. In reconsideration of the Initial Recommendation, pERC considered feedback from the patient group regarding adherence to the administration schedule of triplet therapy. The patient group felt that adherence to the administration schedule for the triplet therapy would not be difficult for patients. pERC emphasized that their recommendation not to reimburse ixazomib was not based on their concerns about patients’ adherence to the ixazomib dosing schedule. pERC discussed that the administration schedule of the triplet therapy may be challenging for some patients, since the dosing regimen is complex. The Committee discussed that the concern about adherence to the triplet therapy was mainly about safety, given the complexity of the administration schedule. (Ixazomib is taken once weekly for three weeks, with one week off, and is an add-on to current oral treatments.) The Committee noted that the Provincial Advisory Group shared the same concerns about adherence due to the complexity of the administration schedule and the Committee noted that dispensing the medications and monitoring patients would require the participation of a multidisciplinary health care team, both in the clinic and in the community setting. Overall, pERC concluded that ixazomib partially aligned with patient values, because even though ixazomib is a potential oral treatment option for patients, with tolerable side effects and quality of life that was not diminished, considerable uncertainty remained in the magnitude of effect achieved with ixazomib.

pERC deliberated upon the cost-effectiveness of ILd compared with Ld. pERC considered that ILd is not cost-effective both at the submitted estimates and at the reanalysis estimates provided by the pCODR Economic Guidance Panel (EGP). The main limitation identified by the EGP and CGP, and which impacted the incremental cost-effectiveness ratio (ICER), was the uncertainty in the estimates for long-term survival gained through ILd. Given pERC’s lack of confidence in the clinical effect estimates derived from the subgroup analyses, the Committee agreed that considerable uncertainty existed in the extrapolation of this benefit over a long time horizon, as was done in the submitter’s base case results. Despite this, pERC noted that the submitted base case ICERs were high for both subgroups. Given the absence of alternative evidence to use as inputs for OS, the Committee agreed with the EGP’s method to quantify uncertainty in the clinical effect estimates. The EGP explored a range that included the submitter’s estimates for OS as the lower estimate and the removal of OS benefit beyond the trial period as the upper estimate. This had a substantial impact on the ICER. The EGP also changed the time horizon to reflect input from the CGP that confirmed that patients at this stage of disease are likely to live another 10 years and not 20 years as posited in the submitted base case. When these two inputs were combined, the ICER increased to nearly $1M per quality-adjusted life-year (QALY) in the subgroup of patients with at least one prior therapy and high-risk cytogenetics and $1.7M/QALY in the subgroup with at least two prior lines of treatment. pERC, therefore, concluded that ixazomib is not cost-effective at either the submitted estimate or EGP’s reanalysis estimate.

pERC considered the feasibility of implementing a funding recommendation for ixazomib and agreed that the oral route of administration is an enabler to implementation, although there may be some logistical considerations that affect cost and access. However, pERC noted that adherence to the administration schedule may be challenging for some patients, as it is different from both lenalidomide and dexamethasone. pERC agreed that the Ld regimen may introduce additional workload for pharmacy and clinic staff to ensure appropriate counselling, adherence, dispensing, and monitoring. In reconsideration of the Initial Recommendation, pERC discussed the feedback from the patient group regarding the potential additional workload of pharmacy and clinic staff to counsel patients on ixazomib. The patient group felt that an oral treatment regimen would be less resource-intensive compared with intravenous treatment in a cancer centre. While pERC acknowledged that ixazomib is an oral treatment option that would not require chemotherapy chair time and nursing time, they reiterated that the complex administration schedule of the triplet therapy would require additional workload for pharmacy and clinic staff to ensure that patients receive appropriate counselling, dispensing, follow-up and monitoring while being treated with ixazomib. The Committee noted that dispensing the regimen may also include logistical concerns, as ixazomib is taken once weekly and has considerable cost per capsule. This may lead some pharmacies to elect to dispense only one dose at a time. pERC discussed that lenalidomide must be dispensed through a controlled distribution program from only registered pharmacies; however, the same restrictions would not apply to dispensing ixazomib and dexamethasone. pERC concluded that
implementing a reimbursement recommendation for ixazomib would require additional workload of the health care team (e.g., oncologists/hematologists, pharmacists, nurses, etc.) and that logistical considerations would include ongoing patient support programs.

pERC noted the absence of direct evidence comparing ILd with CLd, a relevant comparator in this setting. Indirect evidence was made available by the submitter; however, significant limitations were identified in this comparison, limiting the conclusions that could be drawn from the reported results. pERC agreed with pCODR’s Provincial Advisory Group that the addition of ixazomib to Ld would have a large budgetary impact, as there is a large prevalent population of patients who have received one prior therapy. Based on registered clinician input, between 20% and 60% of patients with multiple myeloma would be eligible based on the funding request.
EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- A pCODR systematic review
- An evaluation of the manufacturer’s economic model and budget impact analysis
- Guidance from pCODR clinical and economic review panels
- Input from one patient advocacy group (Myeloma Canada)
- Input from pCODR’s Provincial Advisory Group (PAG)
- Input from registered clinicians

Feedback on the pERC Initial Recommendation was also provided by:

- One patient advocacy group, (Myeloma Canada)
- The PAG
- The submitter (Takeda Pharmaceutical Company Limited)
- Registered clinicians

The pERC Initial Recommendation was to not recommend reimbursement of ixazomib in combination with lenalidomide and dexamethasone (ILD) in the treatment of patients with multiple myeloma who have had at least two prior therapies or who have had at least one prior therapy and high-risk cytogenetic features. Feedback on the pERC Initial Recommendation indicated that PAG agreed with the Initial Recommendation; the submitter, registered clinicians, and the patient advocacy group disagreed with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope
The purpose of the review is to evaluate the safety and efficacy of ixazomib in combination with lenalidomide and dexamethasone (ILD) in the treatment of patients with multiple myeloma who have had at least two prior therapies or who have had at least one prior therapy and high-risk cytogenetic features.

Studies included: Randomized controlled trial
The pCODR systematic review included one randomized double-blind placebo-controlled trial, TOURMALINE-MM1, which randomized 722 patients in a 1:1 ratio to receive ILD or lenalidomide and dexamethasone (Ld). The TOURMALINE-MM1 trial was designed with two interim analyses (IAs) for progression-free survival (PFS) and four analyses (three interim analyses plus one final analysis) for overall survival (OS). Based on the design, if PFS was significant at the first IA (IA1), it would be considered as the final analysis and the second IA (IA2) would be non-inferential. OS was to be assessed once significance was achieved for PFS. Adjustments were made for multiple testing for both PFS and OS in the intention-to-treat (ITT) analysis but not in the subgroup analyses. Information was not provided on whether or not tests for interaction had been conducted for the subgroups of patients with at least one prior therapy and high-risk cytogenetics and patients who had at least two prior lines of therapies.

The pCODR review also provided a critical appraisal of a manufacturer-provided network meta-analysis that evaluated the relative efficacy of ILD versus carfilzomib plus lenalidomide plus dexamethasone (CLd) based on outcomes such as PFS and OS in patients with relapsed or refractory multiple myeloma who were treated with at least one prior therapy. While results specific to the subgroup of patients with at least one prior therapy and high-risk cytogenetics were available for PFS, OS results were only available based on ITT analysis of the available trials included in the network analysis. Furthermore, there was no direct or indirect evidence provided addressing the subgroup of patients who have had at least two prior lines of therapies. Although the overall results of the indirect comparison reported no differences between ILD and CLd in patients with at least one prior therapy and high-risk cytogenetics, there were a number of limitations identified which greatly limited the ability to interpret the findings. pERC therefore agreed that caution must be used to draw conclusions from this indirect comparison.

Patient populations: Analysis of two subgroups from full trial
Among 722 patients enrolled in the trial, 43% (309) had at least one prior therapy and high-risk cytogenetics — del(17p), t(4,14), t(14,16) and +1q21 — and one prior line of treatment, while 41% (297)
had received at least two prior therapies. As the +1q21 chromosome abnormality was added to the 2014 update of the International Myeloma Working Group guidelines, the +1q21 chromosome abnormality was not included in the high-risk subgroup analysis within the TOURMALINE-MM1 trial publication. The analysis presented in this report, however, includes the updated definition for high risk. Patients in the TOURMALINE-MM1 trial were stratified based on prior lines of therapy but not based on cytogenetic features. Treatment was continued until disease progression or unacceptable toxicity. pERC noted that the analysis presented on the subgroup of patients who received at least two prior lines of therapies was pre-specified, however, the subgroup of patients with at least one prior therapy and high-risk cytogenetics was not pre-specified, as the definition of high-risk cytogenetics was changed since the time of data analysis and publication, therefore that subgroup analysis was post hoc in nature. pERC also noted that there was overlap in the two patient populations requested by the submitter; where 20% of patients in the subgroup of patients who had at least one prior therapy and high-risk cytogenetics were also counted a second time in the group of patients with at least two prior therapies. pERC noted that the potential impact on the reported results of this overlap within the two subgroups is unknown.

Baseline characteristics were well balanced in terms of age, race, Eastern Cooperative Oncology Group (ECOG) status, International Staging System (ISS) disease stage, cytogenetic profile, creatinine clearance, number of prior lines of therapy, and the proportion of patients who had stem cell transplant within the ITT population, and in the subgroup analysis for the expanded high-risk cytogenetics and patients who had at least two prior lines of treatment. In the ITT population, the majority of patients had an ECOG performance status of 0 (51% and 47%) or 1 (44% and 46%) in the ILd and Ld groups, respectively. A minority of patients had an ECOG performance status of 2 (5% and 7%, respectively). Similar proportions were reported for the subgroup of patients with at least one prior therapy and high-risk cytogenetics and patients who had received at least two prior lines of therapy.

Key efficacy results: Post hoc analysis, unadjusted for multiplicity, absence of tests for interaction

The key efficacy outcome deliberated on by pERC was PFS, the primary outcome of the TOURMALINE-MM1 trial. Key secondary outcomes included OS and patient-reported outcomes.

Based on the overall trial results in the ITT analysis, statistically significant improvements in PFS were reported at IA1 (0.74; 95% confidence interval [CI], 0.59 to 0.94; \( P = 0.01 \)), whereas IA2 (0.82; 95% CI, 0.67 to 1.0; \( P = 0.0548 \)) reported non-significant results. The Committee noted that subsequent IAs with more mature data should be confirmatory of earlier analyses. pERC considered the impact of the diminished effect at IA2 and considered whether the magnitude of effect observed at IA1 is reliable. Based on this, the Committee agreed that there is uncertainty in the magnitude of PFS benefit reported for the overall trial results. For key secondary outcomes, significance was not demonstrated for OS at IA1 or IA2, with a third IA and final IA still pending.

In reconsideration of the Initial Recommendation, pERC considered the feedback received from the submitter regarding the second interim analysis (IA2) for PFS. The submitter provided new, previously unsubmitted and unpublished analyses that were considered out of scope for the review and, as a result, were neither considered by the Review Team nor provided to pERC for reconsideration. An additional analysis that was previously published in a European Medicines Agency (EMA) report was also provided by the submitter in their feedback. pERC noted that censoring based on patients who received an alternate therapy was available to the Review Team in the published EMA report. For the data available within the EMA report, pERC noted that the submitter explained that the presence of 22 (ILd) and 32 (Ld) patients who had received an alternative therapy may have contributed to the non-significant results at IA2. pERC noted that the Methods Team concluded that these patients were likely censored because they were considered to have had a protocol violation. Furthermore, the Methods Team reported that overall, the evidence provided in the EMA report is similar (PFS HR 0.818; 95% CI, 0.67 to 1.0; \( P = 0.054 \)) to what was reported in the planned PFS analysis at IA2 that did not censor these patients (PFS HR 0.82; 95% CI, 0.67 to 1.0; \( P = 0.0548 \)). pERC noted the same concerns previously expressed: mainly that, although the point estimate for PFS showed the same direction of effect, the data at IA2 suggested a substantial amount of uncertainty is present in the magnitude of effect in the ITT population.

In the subgroup of patients with at least one prior therapy and high-risk cytogenetics at IA1, median PFS was 17.5 months and 11.1 months in the ILd and Ld groups, respectively, with a hazard ratio (HR) of 0.66 (95% CI, 0.46 to 0.93; \( P = 0.03 \)). At IA2 (23 months), median OS was not estimable in for ILd and 28.6 months for Ld with a significant difference reported HR 0.62 (95% CI, 0.40 to 0.96; \( P = 0.03 \)) in favour of...
ILD. Within the subgroup of patients who have had at least two prior lines of therapy, median PFS was not estimable and 12.9 months in the ILd and Ld groups, respectively, with HR 0.58 (95% CI, 0.40 to 0.84; \( P = 0.003 \)). Median OS was also not estimable in both groups, with HR 0.65 (95% CI, 0.41 to 1.02; \( P = 0.057 \)). pERC deliberated upon these results and agreed that the post hoc nature of the analysis, the lack of information on tests for interaction, and the absence of adjusting for multiple testing resulted in considerable uncertainty in the interpretation. The use of adjustments for multiple testing based on the design employed in the ITT analysis indicates that the PFS results for the subgroup of patients with at least one prior therapy and high-risk cytogenetics is no longer significant at IA1. Therefore, the Committee was unable to draw any conclusions on the PFS and OS results within the two subgroups of interest and concluded that the results were, at most, hypothesis-generating.

In reconsideration of the Initial Recommendation, pERC noted the feedback from the submitter regarding whether the two subgroup analyses were pre-specified or post hoc in nature. The Clinical Guidance Panel (CGP) and the Methods Team confirmed that the subgroup analysis of patients who received at least two prior therapies were pre-specified at the time of randomization; therefore, this analysis is not considered post hoc in nature. However, the subgroup of patients with at least one prior therapy and high-risk cytogenetics was not pre-specified, as the definition of high-risk cytogenetics was changed since the time of data analysis and publication, therefore that subgroup analysis is still considered post hoc in nature. Despite this, pERC noted that pre-specifying for a subset analysis does not mean that the study was adequately powered to detect a true difference in these subpopulations. Furthermore, it does not mean that those analyses have been adjusted for multiple comparisons. Therefore, the Committee noted that there remains considerable uncertainty about the magnitude of clinical benefit of ILd within the two subgroups of interest.

**Patient-reported outcomes: Maintained in both treatment groups**

Patient-reported outcomes were assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 module (EORTC QLQ-C30) and myeloma-specific module (EORTC QLQ-MY20). After a median follow-up of 23 months, there was no significant difference in health-related quality-of-life (QoL) score between the two treatment arms in the ITT analysis. Only global health status scores for the EORTC QLQ-C30 questionnaire were available in the subgroup analyses. No differences were reported for the global health status compared with the placebo arm for both the subgroups. pERC noted that limited data were available on patient-reported outcomes within the subgroups of interest. The available evidence both in the ITT and within the subgroups of interest demonstrated that QoL was not diminished for patients treated with ILd compared with Ld and baseline values.

**Safety: Management of thrombocytopenia**

pERC deliberated on the toxicity of ILd and noted that ILd was generally well tolerated. There were fewer on-study deaths in the ILd group compared to Ld group for both the subgroup of patients with at least one prior therapy and high-risk cytogenetics (3% and 8%, respectively) and those with two prior lines of treatment (3% and 9%, respectively). Data were available only for on study deaths. Serious adverse events also occurred less frequently in the subgroup of patients who had had at least two prior lines of treatment (46% and 56%, respectively). pERC noted input from registered clinicians advising that careful administration would be needed in patients with pre-existing peripheral neuropathy. Although data were not available on the number of study patients with pre-existing peripheral neuropathy while on treatment, the incidence of this adverse event was similar between groups in the ITT analysis as well as in subgroups of interest. The Committee discussed the increased frequency of thrombocytopenia in the ILd groups compared with Ld groups. In the ITT analysis, grade 3 or grade 4 thrombocytopenia occurred in 19% and 9% of patients in the ILd and Ld groups, respectively. Among the subgroup of patients with at least one prior therapy and having high-risk cytogenetics, 35% and 15% in the ILd and Ld groups, respectively, experienced thrombocytopenia. pERC acknowledged that frequent blood work to monitor for thrombocytopenia would be required at least at the start of treatment with ILd.

**Need and burden of illness: Oral treatment regimen**

Despite significant advancements in the treatment and life expectancy of patients with multiple myeloma, it remains an incurable disease, and most patients will relapse following initial therapy. In 2016, it was estimated that 2,700 Canadians were diagnosed with myeloma and 1,450 patients died of this disease. The median age at presentation is 70 years, and there is a slightly higher incidence in males. Although there is significant heterogeneity within myeloma, the age-standardized five-year net survival rate (2006-2008) for Canadian patients (excluding Quebec) was 42% (excluding Quebec).
Regardless of the initial therapy, patients with myeloma will relapse and further therapy will be required. Second-line therapy using either a bortezomib-based or lenalidomide-based therapy has been the standard of care, and choice of therapy largely depends on which regimen was not used in the first-line setting as the superiority of one regimen over the other has not been conclusively demonstrated. With the recent availability of carfilzomib triplet therapy, treatment patterns are likely to shift to bortezomib-based regimens into upfront options to be followed by CLd subsequently. In the first-line setting, younger patients (i.e., less than 70 years) may also be eligible for bortezomib-based induction followed by autologous stem cell transplant followed by maintenance low-dose lenalidomide. For patients who are not eligible for the triplet therapy, carfilzomib plus dexamethasone doublet therapy is an option. Both these regimens recently received approval for reimbursement by pERC. The Committee noted that treatment options in multiple myeloma have been changing rapidly as new agents are being introduced. Given that all available therapies involve intravenous or subcutaneous administration or both, pERC noted that ixazomib is the first in the class of proteasome inhibitors to offers patients the potential for a triplet regimen entirely administered via the oral route.

In reconsideration of the pERC Initial Recommendation, pERC considered feedback from the registered clinicians that there is a need for effective treatments for patients for whom carfilzomib-based therapy is not an option. pERC noted that the clinicians expressed concerns that patients who are unable to tolerate carfilzomib currently have limited treatment options. Specifically, the registered clinicians noted that the carfilzomib triplet regimen is not feasible for many elderly and relatively immobile patients due to its potential toxicity profile and dose schedule, as it requires multiple intravenous treatments per month. While pERC appreciated the need for oral treatment options in this high-risk population, pERC noted that there was considerable uncertainty about the magnitude of clinical benefit of ILd compared with Ld in the two subgroups of patients with regard to outcomes important to decision-making, such as OS and PFS.

Registered clinician input: Need in del(17p) mutation-positive patients, advantage of oral therapy
Clinicians providing input noted that Ld has been the most common second-line therapy in myeloma although Ld has limited benefit in high-risk patients, while ixazomib is effective for patients with del17p myeloma. pERC appreciated the need for treatment in this del17p population and noted that OS in the subgroup of patients with the del(17p) mutation was pre-specified. Notwithstanding the small sample size and the limitation in interpreting results from subgroup analysis, significant improvements were reported for PFS but not OS. pERC therefore agreed that caution must be used in interpreting these results. pERC further noted that all other subgroup analyses were post hoc and were not sufficient to inform pERC’s decision on net clinical benefit with the use of ixazomib in the subgroup of patients with at least one prior therapy and high-risk cytogenetics. Clinicians also indicated that carfilzomib-based and daratumumab-based regimens are desirable treatment options in this setting but the availability of these treatments at this time is limited. Clinicians identified that ixazomib offers patients the convenience of oral proteasome inhibitor treatment. pERC considered this input and agreed that as an all-oral treatment regimen, ILd would offer patients the convenience of home-based treatment. Related to the safety profile of ixazomib, clinicians identified that ixazomib needs to be given with caution to patients with pre-existing peripheral neuropathy and that the potential benefits of therapy with ixazomib outweigh the risks for thrombocytopenia and neuropathy. pERC acknowledged this input but agreed that there would be a need for frequent blood work to monitor for thrombocytopenia at least at the start of treatment.

VALUES-BASED VALUES

Values of patients with multiple myeloma: Effective oral option, management of symptoms and treatment side effects, improved quality of life
pERC reviewed input from one patient advocacy group. Symptoms most important to control were infections, followed by kidney problems, mobility, pain, fatigue, neuropathy, and shortness of breath. Patients also reported that their disease limited their ability to work (the most significant limitation in ability), followed by their abilities to travel, exercise, volunteer, conduct household chores, fulfill family obligations, and spend time with family.

Given the impact of the disease on patients’ QoL, patients valued access to effective treatments, the ability to choose between effective treatment options based on their side effect profiles, and having options that improve QoL and physical condition. Most patients indicated a willingness to tolerate some
side effects with new, effective treatments. pERC concluded that the results of the TOURMALINE-MM1 trial align with the patient value of having additional treatment options. pERC also noted that the oral route of administration aligned with patient values as it would allow for the entire treatment regimen to be administered at home. However, there would be a need for frequent blood work at least at the beginning of treatment to monitor for thrombocytopenia. The Committee also identified that the administration schedule of this triplet therapy may be challenging for some patients to adhere to, as the dosing schedule for ixazomib is different than the schedule used for both lenalidomide and dexamethasone. In reconsideration of the Initial Recommendation, pERC considered feedback from the patient group regarding the need for oral treatment options. The patient group felt that pERC did not truly appreciate the value and benefits of oral treatment options for patients and its impact on patients’ lives. pERC noted that having a treatment regimen that is administered orally would potentially allow patients to remain at home, thus reducing both the emotional burden and the inconvenience of frequent hospital visits for patients and those accompanying them when receiving intravenous treatments in a cancer centre. Overall, the uncertainty in the magnitude of clinical benefit led pERC to conclude that ixazomib partially aligned with patient values.

Caregivers indicated that their ability to travel was most affected in their duties of caring for someone with myeloma. This was followed by their abilities to volunteer, spend time with family and friends, concentrate, fulfill family obligations, work, exercise, and conduct household chores.

Patient values on treatment: Quality-of-life maintenance, survival, remission, symptom control
The most frequently experienced side effects of currently available treatments were reported to be fatigue, neuropathy, insomnia, stomach issues, nausea, shortness of breath, pain, and confusion, among others. The majority of patients reported that they did not experience hardship in accessing current treatments. Patients expressed that it is important to have access to new treatments that maintain QoL or normal life, manage or minimize side effects, control the disease, control symptoms, achieve or maintain remission, and prolong survival, among others.

Thirty-five patients who had experience with ixazomib reported that the side effects were tolerable. Among 28 patients who had experience taking ixazomib, nearly half reported that it was extremely effective in controlling their myeloma. On a scale of 1 to 5 (5 = far more effective to 1 = not as effective), most patients ranked ixazomib as a 4 or 5 (36% and 18%, respectively) in effectiveness compared with other treatments they had taken. On a similar scale (5 = very tolerable to 1 = completely intolerable), most patients ranked the tolerability of ixazomib as being a 4 or 5 (36% and 32%, respectively). Most patients (64%) also found ixazomib extremely convenient to take. Patients rated their QoL on ixazomib (5 = excellent QoL to 1 = poor QoL), and the majority noted their QoL to be 4 or 5 (56% and 19%, respectively). pERC noted that the input of patients who had experience using ixazomib aligns with the results of the TOURMALINE-MM1 trial, which indicated that patients’ QoL was not diminished and that ixazomib had a manageable toxicity profile. However, pERC agreed that considerable uncertainty remained in the clinical effect estimates for ixazomib in relation to PFS and OS both in the ITT and the subgroup analyses of interest. Therefore, pERC concluded that ixazomib partially aligned with patient values.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analysis
The pCODR Economic Guidance Panel (EGP) conducted a cost-effectiveness analysis and cost-utility analysis comparing ILd with Ld for the treatment of patients with multiple myeloma who have had at least one prior line of treatment and have a high-risk cytogenetic abnormality, or patients who have received at least two prior therapies.

Basis of the economic model: Clinical inputs derived from subgroup analysis and intention-to-treat analysis
Costs considered in the analysis include drug acquisition, concomitant medication, hospitalization, subsequent treatment, drug administration and monitoring, adverse event management, and palliative care.
The clinical effects considered in the analysis were based on IA1 for OS and PFS from the TOURMALINE-MM1 trial and extrapolation beyond the trial period. The submitter noted that OS results for the requested subgroups were not available at IA1, therefore data from the ITT analysis were used for the analyses presented in the two subgroups of interest. Given that there was an overlap of 20% of patients who had at least one prior therapy and high-risk cytogenetics with the subgroup of patients who have had at least two prior lines of treatment, adjustments were made to account for the data used in the economic analysis. In addition, other clinical effects estimates considered include time-to-treatment duration and adverse events and health utilities derived from the trial. Adverse events and health utilities were based on the ITT analysis.

**Drug costs: Flat pricing of ixazomib, potentially complex dosing of ixazomib triplet**

At the list price, ixazomib costs 2,964.65 per 4 mg, 3 mg, or 2.3 mg capsule. At the recommended dosage of 4 mg (one capsule) orally once a week on days 1, 8, and 15 of a 28-day treatment cycle, ixazomib costs $317.64 per day and $8,893.95 per 28-day course.

At the list price, carfilzomib costs $1,533.33 per single-use vial of 60 mg.

- For cycle 1, at the recommended starting dosage of 20 mg/m² on days 1 and 2 and target dosage of 27 mg/m² thereafter (days 8, 9, 15, and 16), carfilzomib costs $229.63 per day and $6,429.76 per 28 days. When wastage is considered, carfilzomib costs $273.81 per day and $7,666.65 per 28 days.
- For cycles 2 to 12, at the recommended dosage of 27 mg/m² on days 1, 2, 8, 9, 15, and 16, carfilzomib costs $251.36 per day and $7,037.98 per 28 days. When wastage is considered, carfilzomib costs $273.81 per day and $7,666.65 per 28 days.
- For cycles 13 to 18, at the recommended dosage of 27 mg/m² on days 1, 2, 15, and 16, carfilzomib costs $167.57 per day and $4,691.99 per 28 days. When wastage is considered, carfilzomib costs $219.05 per day and $6,133.32 per 28 days.

At the list price, lenalidomide costs $340.00 per 5 mg, $361.00 per 10 mg, $382.00 per 15 mg, $403.00 per 20 mg, and $424.00 per 25 mg capsule. At the recommended dosage of 25 mg orally on days 1 to 21 per 28-day cycle, lenalidomide costs $318.00 per day and $8,904.00 per 28-day cycle.

At the list price, dexamethasone costs $3.00 per 40 mg orally. At the recommended dosage of 40 mg per day on days 1, 8, 15, and 22 of a 28-day cycle, dexamethasone costs $0.44 per day and $12.18 per 28 days.

pERC discussed the dosing regimen of ixazomib, lenalidomide, and dexamethasone and noted that the dosing schedules and requirements are different among the therapies. pERC considered that there would need to be clear communication between pharmacists, clinicians, and patients on strategies to manage the complexity of the dosing schedule.

**Cost-effectiveness estimates: Not cost-effective by submitter’s or Economic Guidance Panel’s estimates**

pERC deliberated upon the cost-effectiveness of ILd compared with Ld and agreed that ILd is not cost-effective at either the submitted estimate or at the reanalysis estimate provided by the pCODR EGP. The main limitation identified by the EGP and which impacted the incremental cost-effectiveness ratio (ICER) was uncertainty in the estimates for long-term survival gained through ILd, which were derived from both the ITT population and post hoc subgroup analyses. Although OS was derived from the ITT analysis, the TOURMALINE-MM1 trial had not demonstrated a survival advantage at any of the IAs. Therefore, the Committee agreed that there is considerable uncertainty in using this evidence to subsequently extrapolate benefit over a long time horizon. Based on this extrapolation, nearly 60% and 40% of the benet modelled in the subgroup of patients with at least one prior therapy and high-risk cytogenetics and at least two prior lines of therapies, respectively, was accrued in the post-progression period, despite the absence of evidence to support such a post-progression gain in quality-adjusted life-years (QALYs). Despite these substantial estimated gains, pERC noted that the submitted base case ICERs were high for both subgroups. In the absence of alternative evidence to use as inputs for OS, the EGP explored a range of estimates, which includes the submitter’s estimates of OS as the lower estimate and removal of OS benefit beyond the trial period as the upper estimate. This change had a substantial impact on the ICER. The EGP also changed the time horizon to reflect input from the Clinical Guidance Panel, which confirmed that the expected benefit to be accrued by patients at this stage of disease is likely to be captured by a time horizon of 10 years and not 20 years. When these two inputs were combined, the ICER increased to nearly $1M/QALY and $1.7M/QALY in the subgroup of patients with at least one prior therapy and high-risk cytogenetics and subgroup with at least two prior lines of treatment, respectively.
pERC therefore concluded that ixazomib is not cost-effective either at the submitted estimate or at the EGP’s reanalysis estimate. pERC also noted the EGP’s discussion of several errors, a concern that brought into question the face validity of the submitted model.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Oral administration, different administration schedule, indirect comparison with carfilzomib triplet

pERC considered the feasibility of implementing a funding recommendation for ixazomib and agreed that the oral route of administration is an enabler. However, pERC noted that the administration schedule may be challenging for some patients to adhere to as it differs from the lenalidomide schedule. Dispensing of the regimen may also present logistical considerations as ixazomib is taken once weekly and has considerable cost per capsule. This may lead to some pharmacies electing to dispense only one dose at a time. Additionally, lenalidomide must be dispensed via a controlled distribution program from only registered pharmacies, but the same restrictions would not apply to dispensing of ixazomib and dexamethasone. Overall, the regimen may introduce additional workload for pharmacy and clinic staff to ensure appropriate counselling, adherence, dispensing, and monitoring. The Committee noted concerns by pCODR’s Provincial Advisory Group for potential requests to use ILd in the first-line setting, agreeing that this is out of scope for this current review. pERC noted the absence of direct evidence comparing ILd with CLd, a relevant comparator in this setting. Indirect evidence was made available by the submitter; however, significant limitations were identified in this comparison limiting the conclusions that could be drawn from the reported results. (See Clinical Guidance Report, Section 7.)
DRUG AND CONDITION INFORMATION

Drug Information
- Third-generation proteasome inhibitor
- 4 mg, 3 mg, or 2.3 mg capsule
- 4 mg orally on days 1, 8, and 15 of a 28-day cycle

Cancer Treated
- Multiple myeloma

Burden of Illness
- 2,700 Canadians diagnosed, and 1,450 patients will die of this disease in 2016
- Despite significant advancement, remains an incurable disease

Current Standard Treatment
- Lenalidomide plus dexamethasone
- Carfilzomib plus lenalidomide plus dexamethasone (recently recommended for reimbursement by pERC)

Limitations of Current Therapy
- Subcutaneous or intravenous administration
- Life expectancy is limited with current therapies
- Continued need for novel therapies that can improve life expectancy

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee
Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)  Don Husereau, Health Economist
Dr. Paul Hoskins, Oncologist (Vice-Chair)  Dr. Anil Abraham Joy, Oncologist
Dr. Scott Berry, Oncologist  Carole McMahon, Patient Member
Dr. Kelvin Chan, Oncologist  Valerie McDonald, Patient Member Alternate
Dr. Matthew Cheung, Oncologist  Dr. Catherine Moltzan, Oncologist
Dr. Craig Earle, Oncologist  Jo Nanson, Patient Member
Dr. Allan Grill, Family Physician  Karen MacCurdy Thompson, Pharmacist
Dr. Marianne Taylor, Oncologist  Danica Wasney, Pharmacist

All members participated in deliberations and voting on the Initial Recommendation, except:
- Dr. Matthew Cheung, Dr. Allan Grill, and Dr. Anil Abraham Joy, who were not present for the meeting
- Valerie McDonald, who did not vote due to her role as a patient member alternate.

All members participated in deliberations and voting on the Final Recommendation, except:
- Dr. Scott Berry, Dr. Matthew Cheung, Dr. Allan Grill, and Jo Nanson who were not present for the meeting

Avoidance of conflicts of interest
All members of the pCODR Expert Review Committee must comply with the pCODR Conflict of Interest Guidelines; individual conflict of interest statements for each member are posted on the pCODR website, and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of
ixazomib (Ninlaro) for multiple myeloma, through their declarations, six members had a real, potential, or perceived conflict, and based on application of the pCODR Conflict of Interest Guidelines, none of these members were excluded from voting.

Information sources used
pERC is provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR Guidance Reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR Guidance Reports for more detail on their content.

Consulting publicly disclosed information
pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to pERC for its deliberations was handled in accordance with the pCODR Disclosure of Information Guidelines.

Use of this Recommendation
This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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