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 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.

Drug: Ixazomib (Ninlaro)	
Submitted Reimbursement Request: In combination with lenalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.	
Submitted By: Takeda Pharmaceutical Company Limited	**Manufactured By:** Takeda Pharmaceutical Company Limited
NOC Date: August 4, 2016	**Submission Date:** November 30, 2018
Initial Recommendation: May 3, 2019	**Final Recommendation:** July 05, 2019

Approximate per Patient Drug Costs, per Month (28 Days)	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 cycle.

pERC RECOMMENDATION ☐ **Reimburse** ☐ **Reimburse with clinical criteria and/or conditions*** ☒ **Do not reimburse** *If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.	pERC does not recommend reimbursement of ixazomib (Ninlaro) in combination with lenalidomide and dexamethasone (ILd) for patients with multiple myeloma who have received at least one prior treatment. pERC made this recommendation because the Committee was not confident that there is a net clinical benefit of ILd treatment compared with lenalidomide and dexamethasone (Ld), due to concerns about the evidence presented from the TOURMALINE-MM1 trial. The Committee concluded that there was considerable uncertainty in 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 aligned with patient values because it offers an alternative oral treatment with 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 compared with Ld, both at the submitted and the reanalysis estimates.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Possibility of Resubmission to Support Reimbursement** pERC acknowledged that the phase III randomized controlled trial (RCT), TOURMALINE-MM1 is still pending a final analysis for OS. The estimated analysis date for this to occur is after 486 events. pERC noted that confirmatory results demonstrating an OS benefit could form the basis of a resubmission to pCODR when the full data are available. pERC further acknowledged that any new randomized controlled trials with demonstrated OS benefit and/or confirming the PFS benefit observed in the TOURMALINE-MM1 trial could form the basis of a resubmission.

SUMMARY OF pERC DELIBERATIONS

Multiple myeloma is an incurable plasma cell neoplasm that represents 1.3% to 1.5% of all new cancers in Canada with an estimated 2,900 new cases and 1,450 deaths annually. The median age of diagnosis is 69 years with a five-year overall survival estimated at 42%. Regardless of the choice and duration of initial therapy, myeloma will eventually relapse in the vast majority of patients and further therapy will be required. There is no single clear choice of therapy in relapsed and/or refractory myeloma. Based on expert opinion from the Clinical Guidance Panel (CGP) and registered clinicians, pERC noted that daratumumab triplet combination regimens or carfilzomib triplet combinations are likely to be the preferred second-line treatment option. For patients who are not eligible to receive a triplet therapy, carfilzomib plus dexamethasone doublet therapy is also available. 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.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

The pCODR systematic review included one randomized double-blind, placebo-controlled trial, TOURMALINE-MM1, which evaluated ILd compared with Ld on efficacy and safety outcomes in patients with relapsed or refractory multiple myeloma. pERC discussed the results of the two interim analyses for the primary outcome of PFS and the three analyses for the secondary outcome of OS. pERC stated that uncertainty remained in the magnitude of benefit detected in the intention-to-treat (ITT) analysis for PFS, 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. The committee further noted a sensitivity analysis that adjusted for possible confounding factors and other rationales provided which aimed to explain why there was a non-significant result at IA2. Overall, pERC expressed concern that the magnitude of benefit on the length of time patients live without their disease progressing appeared to reduce after longer follow-up. pERC felt 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. Therefore, the Committee was concerned that the statistically significant PFS results from IA1 may represent a false-positive as IA2 showed a diminished effect and there was a large amount of variance around the effect estimate, including no effect (upper bound of 95% CI was 1). Based on this, pERC concluded that there is considerable uncertainty in the magnitude of PFS benefit reported for the trial results in the overall ITT population. Investigators for the TOURMALINE-MM1 trial made adjustments for multiple testing of both PFS and OS; however, significance was not demonstrated at IA1, IA2 nor for the most recent analysis for OS. The final OS analysis is still pending. The available evidence demonstrated that quality of life was not diminished for patients treated with ILd compared with Ld. pERC deliberated on the toxicity of ILd and noted that it was generally well tolerated. The committee had a robust discussion on the clinical benefit of ILd in this setting and the uncertainty in the clinical evidence presented. Overall, having considered the totality of the clinical evidence, pERC lacked confidence that there is a net clinical benefit of ILd treatment compared with Ld in the treatment of patients with relapsed or refractory multiple myeloma.

Following the posting of the pERC initial recommendation, feedback was received from the submitter on several factors. First, the submitter highlighted two data sources that were not RCTs (one prospective observational study and a registry of patients) that provided data on a subgroup of patients for whom the submitter noted that there is greater need for an oral treatment option (e.g., elderly and frail patients). These studies were not included in the pCODR systematic review based on the pre-specified review protocol that only included RCTs. pERC further noted that the efficacy and safety of ILd in patients who have had at least two prior lines of treatment was previously evaluated by pERC. Based on the evidence at the time, which was using subgroup analysis results of the TOURMALINE-MM1 trial, pERC did not recommend reimbursement in this population. pERC concluded that a resubmission would be required to

re-evaluate any new or additional analysis available for this subgroup of patients. Second, pERC agreed with the submitter that there is difficulty in demonstrating an OS advantage in a setting where patients would receive multiple lines of treatments. Notwithstanding, other agents, such as the daratumumab combination treatments, have demonstrated an OS advantage in this setting. Last, pERC reiterated that although the second interim analysis was non-inferential, subsequent interim analyses with more mature data should not demonstrate a weakened magnitude of PFS benefit. Based on this, pERC concluded that there is considerable uncertainty in the magnitude of PFS benefit reported for the trial results in the overall ITT population.

pERC noted that a network meta-analysis (NMA) was submitted that compared ILd with a number of agents currently available or expected to be widely available. These included combination agents that were recently conditionally recommended for reimbursement by pERC [daratumumab plus lenalidomide plus dexamethasone (DLd), daratumumab plus bortezomib plus dexamethasone (DVd) and carfilzomib plus lenalidomide plus dexamethasone (CLd)]. The results of this NMA reported that DVd and DLd are superior to ILd in terms of PFS but not OS. Furthermore, no differences in PFS and OS were reported between ILd, CLd, and Cd. Despite the absence of direct or robust indirect evidence, pERC noted the CGP's clinical opinion which indicated that preferred treatment options would include DVd or DLd in the second-line followed by CLd in the third line setting. Input from registered clinicians indicated that CLd is the preferred comparator for ILd, although acknowledging that DVd/DLd were only recently recommended for reimbursement. Overall, the committee noted that there were limitations identified by the pCODR reviewers with regards to the results of the NMA and agreed that caution must be used in interpreting the results.

pERC deliberated upon input from one patient advocacy group and noted that patients value disease control, prolonged life, remission, improved quality of life, fewer side effects and managing key symptoms (infections, kidney problems, mobility, pain, fatigue, neuropathy and shortness of breath). Overall, pERC concluded that ixazomib aligned with the patient values of having an oral treatment option for patients, tolerable side effects, and quality of life that was not diminished. However, considerable uncertainty remained about the magnitude of effect achieved with ILd. Following the posting of the pERC initial recommendation, feedback was received from patient groups expressing disappointment that a subgroup of patients that could benefit from ILd was not identified (e.g., patients for whom tolerability and ease of administration is important). pERC reiterated that patients who have had two or more lines of therapy, who tend to be frailer and have tolerability issues with treatments, were previously evaluated in this setting based on the TOURMALINE-MM1 trial data. Based on this evaluation pERC had issued a recommendation to not reimburse ILd in these subgroups of patients due to considerable uncertainty in the evidence. pERC further acknowledged feedback from patients commending the representation of patients' voices into the initial recommendation. pERC appreciated this feedback and reiterated the value the lived experience of patients has in guiding pERC's deliberations and recommendation.

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). pERC noted that the submitted model assumed an OS advantage for ILd when compared with Ld despite no OS benefit having been demonstrated through the TOURMALINE-MM1 trial. In their reanalysis, the EGP explored the impact of removing this predicted OS benefit with ILd along with reducing the time horizon to 15 years (25 years in the base case) and using utility estimates for Canadian populations (UK general public tariffs were used to estimate utilities in the base case). Based on these changes, the incremental cost-effectiveness ratio (ICER) increased from $466,388/QALY in the base case to $711,726/QALY. pERC further agreed that there is considerable uncertainty in the clinical effect estimates derived through the NMA when comparing ILd to relevant comparators (DVd, DLd, and CLd). After the cost-effectiveness estimates were adjusted by modifying the model inputs (time horizon reduction to 15 years, removing the OS benefit and the use of Canadian specific utility values), ILd was compared to other treatments in a sequential analysis which found that ILd was more effective and more costly than Ld, CLd, and DVd while it was less effective and more costly than DLd. According to the cost-effectiveness acceptability curves, which illustrate the uncertainty in the cost-effectiveness estimates for the different combination agents, in all of the probabilistic analysis iterations, ILd is never the most cost-effective option at any level of willingness to pay. pERC, therefore, concluded that ILd is not cost-effective at either the submitted estimate or the EGP's reanalysis estimate. Following the posting of the pERC initial recommendation, feedback was received from the submitter regarding the EGP's removal of the predicted OS benefit from the analysis. The submitter commented that this analysis ignores the NMA, which is being used to inform the relative effectiveness of agents in the sequential analysis. pERC noted feedback from the EGP clarifying that the intent of its analysis was to explore the uncertainty in the

estimated OS benefit, given that the TOURMALINE-MM1 trial did not demonstrate an OS advantage in favour of ILd. The EGP noted that the NMA is still being used to inform other comparisons.

pERC considered the feasibility of implementing a funding recommendation for ILd. Given the negative reimbursement recommendation of ILd, pERC agreed that it was not necessary to address implementation questions related to generalizability of the trial results, such as sequencing and indication creep. pERC further noted the absence of direct evidence comparing ILd with DVd, DLd, and CLd, which are relevant comparators in this setting. Although indirect evidence was made available in the submitter's NMA, limitations were identified in this analysis, limiting the conclusions that could be drawn from the reported results and the resulting ICERs. pERC agreed with pCODR's Provincial Advisory Group that the addition of ixazomib to Ld would have a large budget impact, as there is a large prevalent population of patients who have received one prior therapy.

EVIDENCE IN BRIEF

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

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis
- Guidance from the pCODR clinical and economic review panels
- Input from one patient advocacy group (Myeloma Canada (MC)
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- One patient advocacy group, [Myeloma Canada]
- One clinician group, [Cancer Care Ontario Hematology DAC]
- PAG
- The submitter [Takeda Canada Inc.].

The pERC Initial Recommendation was to not recommend reimbursement of ixazomib (Ninlaro) in combination with lenalidomide and dexamethasone (ILd) for patients with multiple myeloma who have received at least one prior treatment. Feedback on the pERC Initial Recommendation indicated that the manufacturer disagreed with the Initial recommendation, the patient advocacy group agreed in part while PAG and registered clinician group agreed 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 one prior therapy.

Studies included: Randomized controlled trial and Network Meta-Analysis

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.

Evidence was also available from the China Continuation study which enrolled 115 patients, 57 patients to ILd and 58 to the Ld group. The study was conducted to fulfill regulatory requirements in China with the intention to assess consistency with the global TOURMALINE-MM1 study.

A pooled analysis was also available of Asian patients from the TOURMALINE-MM1 and China Continuation study of 138 patients, 67 patients randomized to the ILd group and 71 to Ld group.

The pCODR review also provided contextual information on a critical appraisal of a manufacturer-provided network meta-analysis that evaluated the relative efficacy of ILd versus various other relevant comparators [DLd, DVd, CLd, carfilzomib + dexamethasone (Cd), pomalidomide + dexamethasone (Pom-Dex), bortezomib (V), dexamethasone (Dex)] 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. The results demonstrated that ILd was associated with significantly improved PFS and OS compared to Ld, V, Dex, and Pom-Dex. In addition, there was a statistically significant better overall response rate in favour of ILd compared with Ld, V, and Dex. Statistically significantly longer PFS was reported for DLd compared with ILd. pERC considered the results of this NMA and limitations identified by the pCODR reviewers and agreed that caution must be used in drawing conclusions from this indirect comparison.

Patient populations: Well Balanced Baseline Characteristics in TOURMALINE-MM1

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. The majority of patients had an Eastern Cooperative Oncology Group 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). The majority of patients (70%) had been treated with a proteasome inhibitor before (mostly with bortezomib) and had one (61%) or two (29%) prior lines of therapy. About half of patients (55%) had received prior immunomodulatory agents. Very few patients were refractory to prior proteasome inhibitors (2%) while 23% were refractory to prior immunomodulatory agents.

In the China continuation study, the majority of patients had an ECOG PS of 0 (44%) or 1(52%), had one (44%) or two (38%) prior lines of therapy, and had received prior bortezomib (61%) and/or an immunomodulatory agent (86%). All patients had received prior corticosteroids.

Although there were some differences in the baseline characteristics between the TOURMALINE-MM1 trial and China Continuation study, the baseline characteristics of patients included in the pooled analysis were balanced between the treatment groups.

Key efficacy results: Statistically Significant PFS at IA1 with Efficacy Diminishing at IA2

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. A sensitivity analysis was conducted to remove patients who started subsequent therapy prior to progression. In the analysis, these patients were counted as having progressed at start of new therapy (22 ILd and 32Ld). Based on this analysis, median PFS was 18.4 versus 13.6 months; HR = 0.792; *P* = 0.017. It was unclear what the confidence interval on the HR was. Furthermore, the submitter noted that extended study enrolment in Japan may have contributed to the diminished treatment effect at IA2. The submitter noted that 17% of new PFS events at IA2 were from Japan vs 4% of original PFS event at IA1. It was noted that later enrolled patients had more dose adjustments. Lastly the submitter noted that a release in February 2015 indicating primary analysis had been met may have biased results as it may have affected the treatment decisions of physicians. The Committee considered these rationales and noted that subsequent IAs with more mature data should be confirmatory of earlier analyses regardless of the abovementioned clarifications. 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, or with the latest analysis. The final analysis is still pending.

pERC considered the results of the China continuation study and pooled analysis and noted that they were consistent with the results of the TOURMALINE trial in reporting results in favour of ILd [58% reduction in risk of death for patients treated with ILd group compared to the Ld (HR 0.419; 95% CI 0.242–0.726; p = 0.001)]. pERC noted that there was no statistical analysis plan for the China Continuation study and that the sample size of the trial was small. Although acknowledging the need for this data to fulfill regulatory requirements in China, pERC agreed that there is no biological rationale to expect different responses in Asian patients as compared with the general public. pERC was not convinced that the overall survival benefit seen in the China continuation trial was a true result, given the small sample size in the trial, the lack of a formal statistical analysis plan and that the larger TOURAMALINE trial wasn't showing an overall survival benefit.

Following the posting of the pERC initial recommendation, feedback was received from the submitter on two data sources that were not RCTs (one prospective observational study and a registry of patients) providing data on a subgroup of patients for whom the submitter noted that there is greater need for an oral treatment option (e.g., elderly and frail patients). These studies were not included in the pCODR systematic review based on the pre-specified review protocol that only included RCTs. pERC further noted that the efficacy and safety of ILd in patients who have had at least two prior lines of treatment was previously evaluated by pERC. Based on the evidence at the time, which was using subgroup analysis results of the TOURMALINE-MM1 trial, pERC did not recommend reimbursement in this population. pERC concluded that a resubmission would be required to re-evaluate any new or additional analysis available

for this subgroup of patients. Feedback from the submitter also highlighted the difficulty in demonstrating an OS advantage in a setting where patients would receive multiple lines of treatments. pERC acknowledged this difficulty but noted that other agents, such as the daratumumab combination treatments, have demonstrated an OS advantage in this setting. Last, pERC reiterated that although the second interim analysis was non-inferential, subsequent interim analyses with more mature data should not demonstrate a weakened magnitude of PFS benefit. Based on this, pERC concluded that there is considerable uncertainty in the magnitude of PFS benefit reported for the trial results in the overall ITT population.

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) scores between the two treatment arms. No differences were reported for the global health status compared with the placebo arm. The available evidence demonstrated that QoL was not diminished for patients treated with ILd compared with Ld and baseline values.

Safety: Manageable toxicity profile

pERC deliberated on the toxicity of ILd and noted that ILd was generally well tolerated. At the 23-month analysis, similar number of patients experienced at least one adverse event (AE) and at least one grade 3 or worse AE. Withdrawal due to AE's was also similar between treatment groups. Although 197 patients reported peripheral neuropathy as a baseline comorbidity, 175 patients reported experiencing peripheral neuropathy during the study. Among these patients, 27(15%) (14 in the ILd group, 13 in the Ld group) reported worsening of their baseline peripheral neuropathy. Among the patients who had peripheral neuropathy, five in the ixazomib arm and four in placebo arm discontinued the treatment agents. The proportion of adverse events occurring in ≥ 10% of patients in either the ILd group or the Ld regimen (all grades, grade 3 and grade 4) remained consistent at the 23-month follow-up and the latest analysis. Overall, pERC concluded that the toxicity profile of ILd is manageable.

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.

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 2018, it was estimated that 2,900 Canadians were diagnosed with myeloma and 1,450 patients died of this disease. The median age at presentation is approximately 69 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 for Canadian patients (excluding Quebec) was 42%.

Regardless of the initial therapy, patients with myeloma will relapse 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. Patients will ultimately be offered all possible available effective chemotherapeutic options sooner or later and in various combinations. Based on clinical opinion, 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. For patients who are not eligible for a triplet therapy, carfilzomib plus dexamethasone doublet therapy is an option. 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 offer patients the potential for a triplet regimen entirely administered via the oral route.

Registered clinician input: Advantage of oral therapy for the elderly and patients unable to travel long distance for treatment

Input was received from Myeloma Cancer Research Network and the Drug Advisory Committee for Hematology from Cancer Care Ontario. Clinicians noted that currently funded treatment options for previously treated multiple myeloma include CLd, Cd, Ld, V, and Pom-Dex. DLd and DVd were recently

approved for reimbursement. CLd was noted to be the most appropriate currently reimbursed comparator, but some patients are unable to receive CLd due to heart failure or transportation required to receive intravenous treatment of carfilzomib.

In alignment with the TOURMALINE-MM1 trial, eligible patients include those with relapsed myeloma who have received between one and three prior lines of therapy. Clinicians noted an unmet need in large geographic provinces where patients may travel long distances such as three to six hours to the clinic for treatment. There was agreement among the clinicians that elderly patients, especially those with a heart condition or patients living at a great distance from treatment centres, may benefit particularly from the oral treatment. 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 proteasome inhibitor (PI) alternatives. Clinicians agreed 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. Switching would however be appropriate if there is intolerance. Clinicians also noted that some patients with high cytogenetic risk – such as those with del(17p) disease – could benefit from ILd treatment.

Both clinician groups agreed that ixazomib would not replace current therapies but would be an option should patients be unable to or unwilling to take carfilzomib. Clinicians further noted that they would consider a number of factors before a choice of therapy is made, such as age, myelosuppression, convenience of administration, heart failure, renal failure, other comorbidities and tolerability. It is expected that patients with previous exposure to carfilzomib would not be good candidates for ixazomib. Those who were refractory to lenalidomide would also not qualify for ILd therapy.

pERC considered this input from Clinicians and agreed that as an all-oral treatment regimen, ILd would offer patients the convenience of home-based treatment particularly in patients that live far away from treatment centres. pERC however agreed that there are a number of other triplet agents that have demonstrated efficacy in this setting which offer treatment options to patients and clinicians.

PATIENT-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, Myeloma Canada, which included collated input from surveys and interviews conducted between 2016 and 2018 for three pCODR reviews. Key symptoms patients with myeloma wished to control include infections, kidney problems, mobility, pain, fatigue, neuropathy, and shortness of breath. Patients noted that myeloma most affects the ability to work, followed by the ability to exercise, travel, volunteer, concentrate, conduct household chores, fulfill family obligations and spend time with family.

Patients had experience with a number of agents including bortezomib, lenalidomide, autologous stem cell transplant, melphalan, cyclophosphamide, pomalidomide, thalidomide, VAD and allogenic stem cell transplant. Side effects of treatment include fatigue, neuropathy, insomnia, stomach issues, nausea, shortness of breath, pain, and confusion.

The majority of patients indicated that they did not or have not yet experienced hardship in accessing treatment while 23% did. Hardships included being denied treatment, drug not being covered, having to travel for treatment and costs of drugs. Patients expressed that the greatest financial implication from treatment is the drug cost followed by parking costs, travel for treatment, lost income due to work absence and accommodations cost.

Caregivers indicated that caring for a loved one with myeloma has affected their ability to travel and spend time with family and friends.

pERC concluded that the results of the TOURMALINE-MM1 trial align with the patient values of having additional treatment options with a manageable toxicity profile and maintenance of quality of life. 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.

Following the posting of the pERC initial recommendation, feedback was received from patient groups expressing disappointment that a subgroup of patients that could benefit from ILd was not identified (e.g., patients for whom tolerability and ease of administration is important). pERC reiterated that patients who have had two or more lines of therapy, who tend to be frailer and have tolerability issues with treatments, were previously evaluated in this setting based on the TOURMALINE-MM1 trial data. Based on this evaluation pERC had issued a recommendation to not reimburse ILd in these subgroups of patients due to considerable uncertainty in the evidence. pERC further acknowledged feedback from patients commending the representation of patients' voices into the initial recommendation. pERC appreciated this feedback and reiterated the value the lived experience of patients has in guiding pERC's deliberations and recommendation.

Patient values on treatment: QoL maintenance, disease and symptom control

Patients' expectations for the drug under review include improving or maintaining quality of life, managing/minimizing side effects, controlling the disease, having access to effective treatments, and controlling symptoms. The majority of patients (97%) felt it was very important to have access to effective treatments while 86% felt it was very important to have choice of treatment based on a drug's known side effects. Among patients responding to a more recent 2018 survey, patients' expectations of ILd include disease control, prolonged life, remission and fewer side effects.

Thirty-two patients providing input had experience receiving ILd as a treatment. Among 16/32 patients responding, 75% reported that ILd was effective in controlling their disease, prolonging life (62.5%), inducing a remission (56.25%), improving quality of life (43.75%), they had fewer side effects than with other treatments (37.5%) and this treatment allowed them to enjoy a normal life (37.5%). The majority of patients (86%) felt they had positive outcomes. When asked about how effective ILd was in controlling their myeloma, 44% noted it was very effective, 25% said it was effective and 19% felt it was extremely effective. These responses were comparable to patient input collected in 2016 for a review of ILd in patients with ≥ 2 prior treatments or 1 prior treatment + high risk cytogenetics. The majority of patients (62.5%) noted that the administration of ILd was associated with no negative effects while 37.5% felt there were negative effects. Most patients (75%) indicated that ILd was very tolerable or tolerable. A quarter of patients who had experience using ILd rated their quality of life as excellent, while 31.25% rated it as good, 18.75% rated it as fair, 12.5% rated a very good and 12.5% rated a poor quality of life.

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. Overall, pERC concluded that ILd aligned with patient values of having an additional treatment option that is fully oral, maintains patients' quality of life and has a manageable toxicity profile.

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 relevant comparators (Ld, CLd, DVd, DLd) for the treatment of patients with multiple myeloma who have had at least one prior line of treatment.

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 medications, hospitalization, drug administration and monitoring, adverse event management, post progression therapies and palliative care.

The clinical effects considered in the analysis were based on IA1 for PFS and the most recent analysis for OS from the TOURMALINE-MM1 trial and extrapolation beyond the trial period. An NMA was used to derive clinical effect estimates for the comparison to other relevant comparators. In addition, other clinical effect estimates considered include time on treatment, adverse events and health utilities derived from the trial.

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

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 cycle, ixazomib costs $317.64 per day and $8,893.95 per 28-day cycle.

Carfilzomib costs $1,533.33 per single-use vial of 60 mg.

- For cycle 1, at the recommended dose of 20-27mg/m^2 for cycle 1 administered on days 1, 2, 8, 9, 15, and 16, carfilzomib costs $328.57 per day and $9,199.98 per 28-day cycle.
- For cycles 2 to 12, at the recommended dose of 27 mg/m^2 for cycle 2 to 12 administered on days 1, 2, 8, 9, 15, and 16, carfilzomib costs $328.57 per day and $9,199.98 per 28-day cycle.
- For cycles 13 to 18, at the recommended dose of 27 mg/m^2 for cycle 13 up to 18 administered on days 1, 2, 15, and 16, carfilzomib costs $219.05 per day and $6,133.32 per 28-day cycle.

Lenalidomide costs $8,904.00 per pack (25 mg per capsule and 21 capsules per pack). 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.

Dexamethasone costs $30.00 per pack (4 mg tablets and 50 tablets per pack). 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.

Daratumumab costs $2,392.08 per 400 mg unit. At the recommended dose of 16mg/kg administered on days 1, 8, 15, and 22 for cycles 1 and 2, 16mg/kg administered on days 1 and 15 for cycles 3 to 6 and 16mg/kg administered on days 1 for cycles 7 and beyond, daratumumab costs:

- For cycles 1 and 2: $1,366.90 per day and $38,273.28 per 28-day cycle.
- For cycles 3 to 6: $683.45 per day and $19,136.64 per 28 day-cycle.
- For cycles 7 or more: $341.73 per day and $9,568.32 per 28-day cycle.

Bortezomib costs $1,402.42 per pack of 3.5mg. At the recommended dose of 1.3 mg/m^2 administered on days 1, 4, 8, and 11, bortezomib costs $200.35 per day and $5,609.68 per 28-day cycle.

Pomalidomide costs $500.00 per 4mg capsule. At the recommended dose of 4 mg administered every day on days 1-21, pomalidomide costs $375.00 per day and $10,500.00 per 28-day cycle.

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 based on the results of the TOURMALINE-MM1 trial and the cost-effectiveness of ILd compared with other relevant comparators based on a manufacturer submitted NMA. 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). pERC noted that the model assumed an OS advantage for ILd when compared with Ld despite no OS benefit having been demonstrated through the TOURMALINE-MM1 trial thus far. In their reanalysis, the EGP explored the impact of removing this predicted OS benefit with ILd along with reducing the time horizon to 15 years (25 years in the base case) and using utility estimates for Canadian populations (UK general public tariffs used to estimate utilities in the base case). Based on these changes, the ICER increased from $466,388/QALY in the base case to $711,726/QALY. For the comparison to other relevant treatment options (DVd, DLd, and CLd), pERC noted that there is considerable uncertainty in the clinical effect estimates derived through the NMA. After the cost-effectiveness estimates were adjusted by modifying the model inputs (time horizon reduction to 15 years, removing the OS benefit and the use of Canadian specific utility values), ILd was compared to other treatments in a sequential analysis which found that ILd was more effective and more costly than Ld, CLd, and DVd while it was less effective and more costly than DLd. According to the cost-effectiveness acceptability curves, which illustrate the uncertainty in the cost-effectiveness estimates for the different combination agents, in all of the probabilistic analysis iterations, ILd is never the most cost-effective option at any level of willingness to pay. Having discussed the submitted and EGP's reanalysis estimates, pERC concluded that ILd is not cost-effective at either the submitted estimate or EGP's reanalysis estimate.

Following the posting of the pERC initial recommendation, feedback was received from the submitter regarding the EGP's removal of the predicted OS benefit from the analysis. The submitter commented that this analysis ignores the NMA, which is being used to inform the relative effectiveness of agents in the

sequential analysis. pERC noted feedback from the EGP clarifying that the intent of its analysis was to explore the uncertainty in the estimated OS benefit, given that the TOURMALINE-MM1 trial did not demonstrate an OS advantage in favour of ILd. The EGP noted that the NMA is still being used to inform other comparisons.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Oral administration, indirect comparison with other relevant triplet agents

pERC considered the feasibility of implementing a funding recommendation for ILd. Given the negative reimbursement recommendation of ILd, pERC agreed that it was not necessary to address implementation questions related to generalizability of the trial results, such as sequencing and indication creep. pERC agreed that the oral route of administration is an enabler. The Committee noted concerns raised by pCODR's Provincial Advisory Group about potential requests to use ILd in the first-line setting, and agreed that assessing this request is out of scope for this current review. pERC further noted the absence of direct evidence comparing ILd with DVd, DLd, and CLd, which are relevant comparators in this setting. Although indirect evidence was made available in the submitter's NMA, limitations were identified in this analysis, limiting the conclusions that could be drawn from the reported results and the resulting ICERs. 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.

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)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Daryl Bell, who did not vote due to his role as a patient member alternate.

All members participated in deliberations and voting on the Final Recommendation, except:

- Dr. Avram Denburg who was not present for the meeting
- Daryl Bell who did not vote due to his role as a patient member alternate

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 ixazomib (Ninlaro) for multiple myeloma through their declarations, five members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members was 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 the pCODR Expert Review Committee 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.

Disclaimer

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided “as is” and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report. This document is composed of interpretation, analysis, and opinion on the basis of

information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR document).