pan-Canadian Oncology Drug Review Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation (Manufacturer)

Ixazomib (Ninlaro) for Multiple Myeloma

July 5, 2019

Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Ninlaro in combination with lenalidomide and dexamethasone for patients with multiple myeloma who have received at least one prior line of therapy
Eligible Stakeholder Role in Review (Submitter and/or Manufacturer, Patient Organization Providing Feedback	Manufacturer Takeda Canada Inc

**The pCODR program may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by pCODR.*

3.1 Comments on the Initial Recommendation

a) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the Initial Recommendation:

☐ agrees ☐ agrees in part ☒ disagree

Takeda believes in the benefit of Ninlaro for the treatment of patients with RRMM, principally supported by two placebo-controlled RCTs and robust RWE, all of which demonstrated that the addition of ixazomib to len-dex (ILd) results in increased efficacy. With over 800 Canadians being treated with ILd since NOC, there is clearly a need for this treatment option. Nevertheless, we respect the interpretation by pCODR, and to reduce the level of uncertainty regarding the magnitude of treatment effect, Takeda proposes limiting the reimbursement of Ninlaro.
Takeda requests pERC consider conditionally listing Ninlaro today for patients who have failed two or more previous therapies (3L+) contingent on significant overall survival (OS) benefit in the 3L+ population from the MM1 trial. Takeda commits to provide the final analysis of TMM1 with over 6 years of follow-up confirming the OS advantage of ILd over Ld in the 3L+ population.
Takeda firmly believes that the totality of this evidence package, along with the commitment to provide confirmatory long-term OS data, addresses the clinical uncertainty raised in the initial recommendation.
This 3L+ population is well-defined and addresses pCODR's question of appropriate place in therapy for ILd where both efficacy and tolerability are paramount. Further, this 3L+ population is clearly aligned with the unmet medical need recognized by pCODR and identified by physicians, patients and payers. In terms of the pCODR deliberative framework:
- ILd has demonstrated Clinical Benefit with significant PFS and OS in the 3L+ patient population across all interim analyses (IA) including the latest analysis of TMM1, the randomized placebo-controlled China Continuation Study, the prospective INSIGHT study and Czech registry Name Patient Program (NPP).
- It addresses the Patient-Based Values of having additional treatment options, especially for patients with co-morbidities, with a tolerable side effect profile, while maintaining QoL. The oral route of administration allows for the entire treatment to be administered at home, ensuring treatment for patients who may not be eligible for other injectable treatments (e.g., difficulty accessing IV treatment centres, lack of caregiver support, poor venous access).
- Takeda is committed to working with all drug plans to address their Economic concerns by ensuring that we can increase the treatment options available to patients with MM, and offer an

all-oral triplet therapy, at no incremental cost to drug plan budgets over current branded triplet therapies for RRMM in the 3L+ setting.
- Ixazomib's oral route of administration is an enabler to Adoption [Feasibility]. Also, the later line of therapy addresses PAG's concern of a large prevalent population, as the 3L+ population is relatively smaller and more manageable, and thus, reduces the risk of a large budgetary impact. pERC indicated that the most likely 2L treatment would be DLd/DVd, leaving CLd and ILd to later lines of therapy. However, as patients and physicians indicated, there is a need for additional treatments even in this setting. As such, we urge pERC to also consider access for patients who also began 2L treatment with a triplet therapy (either carfilzomib-based or daratumumab-based) and need to switch to another triplet regimen due to toxicity, intolerance or difficulty accessing IV treatment centres. This is consistent with the recent CCO Funding Announcement regarding daratumumab.

b) Please provide editorial feedback on the Initial Recommendation to aid in clarity. Is the Initial Recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

Page No.	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
Page 3	Summary of pERC deliberations	Paragraph 2, line 15	The PFS from IA2 was non-inferential and should not be used to support decision making. The OS is still unknown and the study is still ongoing. Furthermore, demonstrating OS can be challenging due to subsequent therapies.
Page 3	Summary of pERC deliberations	Paragraph 2, line 1	Please correct statement to reflect that TMM1 is not an open-label study and is the only placebo controlled randomized triplet study in MM.

3.2 Comments Related to Eligible Stakeholder Provided Information

☐ Support conversion to Final Recommendation.

Recommendation does not require reconsideration by pERC.

☒ Do not support conversion to Final Recommendation.

Recommendation should be reconsidered by pERC.

Page No.	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information
Page 1	pERC Rec	Paragraph 2, line 5 "…uncertainty in the magnitude of clinical benefit of ILd vs Ld with regard to outcomes important to decision making, such as OS and PFS"	To reduce the level of uncertainty regarding the magnitude of treatment effect, the evidence supporting 3L+ that was included in the submission should be considered for the following reasons: - Within the TMM1 study, the 3L+ population has consistently shown significant benefit in PFS at IA1 and IA2 and OS at IA1, IA2 and the latest analysis.

	mPFS (ILd vs Ld)	OS (ILd vs Ld)
IA1	NE vs 12.9	NE vs NE

Page 3	Summary of pERC Deliberations	Paragraph 2, line 25 (and throughout) "…pERC lacked the confidence that there is a net clinical benefit of ILd…"	<table><tr><td>(15mo)</td><td>HR=0.58</td><td>HR=0.618 (P=0.094)</td></tr><tr><td>IA2 (23mo)</td><td>22 vs 13.0 HR=0.62</td><td>NE vs NE HR=0.645 (P=0.057)</td></tr><tr><td>Latest Analysis (>4y)</td><td>NA</td><td>52.4 vs 43 HR=0.682(P=0.0228)</td></tr></table>*NE=not estimable - The clinical value of the 3L+ is also demonstrated in the RWE from the INSIGHT and NPP analysis (81 3L+ patients of 163 ILd RRMM patients), and is comparable to the results from TMM1 (median PFS= 23.0 mo at a median follow up of 9.6 mo). - The findings in the 3L+ population in TMM1 are more probable to represent true drug effect and not chance findings: - Number of lines of therapy was a predefined stratification factor of the study; - The subgroup represents a high percentage of the entire study: 41%; - ILd shows PFS advantage over Ld, which varied minimally, after ~2y follow-up, and continued OS benefit after over 4y follow-up Takeda commits to provide the final analysis of TMM1 with > 6 years of follow-up confirming the OS advantage of ILd over Ld in the 3L+ population.
Page 3 Page 7	Summary of pERC deliberations Registered Clinician Input: Advantage of oral therapy for the elderly and patients unable to travel long distance for treatment	Paragraph 3, line 6 "..no differences in PFS and OS were reported between ILd and CLd and Cd…" Paragraph 1, line 3: "CLd was noted to be the most appropriate comparator, but some patients are unable to receive CLd due to heart failure or transportation required…" Paragraph 2, line 2: "Clinicians noted an	- The submitted NMA showed non-SS OS between ILd and DLd/DVd, and non-SS PFS between ILd and DLd, DVd, CLd and Cd. This is the best available evidence that considers all relevant comparators. - The NMA is aligned with physician input that daratumumab combination treatment is likely to become the standard of care, leaving CLd and ILd as options in 3L. In fact, ILd would be the better treatment option given the improved OS in the 3L+ setting seen in the MM1 trial vs ASPIRE (HR=0.682 vs HR=0.79, respectively). - Despite access to DLd, DVd, CLd and Cd, as stated by patients and physicians, additional treatment options are needed. - With advancing disease and accumulating morbidity, patients with multiple prior therapies may become more frail and susceptible to toxicity of chemotherapy (eg, peripheral neuropathy, bone marrow suppression, cardiovascular events, renal toxicity, new primary malignancies), and the impact of MM itself (eg, fatigue, bone fractures, renal impairment). - There is a need for new multi-drug treatment regimens that would improve efficacy in patients

		unmet need in large geographic provinces…" and "elderly patients, especially those with a heart condition or patients living a great distance from treatment centers may benefit…"	later in their myeloma treatment course while having a manageable toxicity profile and simple route of administration. - Currently available options have dose-limiting toxicities that reduce the ability of patients to continue therapy (e.g., peripheral neuropathy with bortezomib, cardiac toxicity with carfilzomib) or more complex methods of administration (eg, IV infusions, injections, more frequent monitoring) that require visits to a hospital or clinic. This may have negative consequences on outcomes for patients who progress on these treatments. - The high frequency administration of parenteral agents coupled with the complexity of oral/parenteral combination treatment regimens adds to patient, caregiver, and health systems burden. - DLd, DVd, CLd, Cd are highly care-intensive, requiring frequent return to the chemotherapy suite, adding to this already-burdensome disease. This contrasts to an all oral treatment regimen, which requires far fewer clinic visits and lowers the patient/ systems burden.
Page 4	Summary of pERC deliberations	Paragraph 6, line 8: "…there is a large prevalent population of patients who have received one prior therapy…"	- Clinicians agreed that ILd would not replace current therapies, but would be an option should patients be unable to or unwilling to take carfilzomib. - Takeda is committed to working with all drug plans to ensure no incremental cost. - the 3L+ population it is relatively smaller and more manageable population.
Page 10	Economic Evaluation	Para 1, Lines 2-3: "In their reanalysis, the EGP explored the impact of removing this predicted OS benefit with ILd…"	Given this reanalysis is being completed in the context of the sequential analysis, it ignores the NMA informing the relative effectiveness of comparators. If the intention is to complete a pair-way analysis of ILd to Ld, pERC should examine those results in the context of the analysis that adjusts, i.e. censors, for post-progression therapies.

About Completing This Template

pCODR invites the Submitter, or the Manufacturer of the drug under review if they were not the Submitter, to provide feedback and comments on the initial recommendation made by pERC. (See www.cadth.ca/pcodr for information regarding review status and feedback deadlines.)

As part of the pCODR review process, the pCODR Expert Review Committee makes an initial recommendation based on its review of the clinical, economic and patient evidence for a drug. (See www.cadth.ca/pcodr for a description of the pCODR process.) The initial recommendation is then posted for feedback and comments from various stakeholders. The pCODR Expert Review Committee welcomes comments and feedback that will help the members understand why the Submitter (or the Manufacturer of the drug under review, if not the Submitter), agrees or disagrees with the initial recommendation. In addition, the members of pERC would like to know if there is any lack of clarity in the document and if so, what could be done to improve the clarity of the information in the initial recommendation. Other comments are welcome as well.

All stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation and rationale. If all invited stakeholders agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation by 2 (two) business days after the end of the consultation (feedback) period. This is called an "early conversion" of an initial recommendation to a final recommendation.

If any one of the invited stakeholders does not support the initial recommendation proceeding to final pERC recommendation, pERC will review all feedback and comments received at the next possible pERC meeting. Based on the feedback received, pERC will consider revising the recommendation document as appropriate. It should be noted that the initial recommendation and rationale for it may or may not change following consultation with stakeholders.

The final pERC recommendation will be made available to the participating provincial and territorial ministries of health and cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

Instructions for Providing Feedback

a) Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.

b) Feedback or comments must be based on the evidence that was considered by pERC in making the initial recommendation. No new evidence will be considered at this part of the review process, however, it may be eligible for a Resubmission.

c) The template for providing *Submitter or Manufacturer Feedback on pERC Initial Recommendation* can be downloaded from the pCODR website. (See www.cadth.ca/pcodr for a description of the pCODR process and supporting materials and templates.)

d) At this time, the template must be completed in English. The Submitter (or the Manufacturer of the drug under review, if not the Submitter) should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply. Similarly, the Submitter (or the Manufacturer of the drug under review, if not the Submitter) should not feel restricted by the space allotted on the form and can expand the tables in the template as required.

e) Feedback on the pERC Initial Recommendation should not exceed three (3) pages in length, using a minimum 11 point font on 8 ½″ by 11″ paper. If comments submitted exceed three pages, only the first three pages of feedback will be forwarded to the pERC.

f) Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts and testimonials should not be provided. Comments should be restricted to the content of the initial recommendation.

g) References to support comments may be provided separately; however, these cannot be related to new evidence. New evidence is not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are considering to provide is eligible for a Resubmission, please contact the pCODR Secretariat.

h) The comments must be submitted via a Microsoft Word (not PDF) document to the pCODR Secretariat by the posted deadline date.

i) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca.

Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.