PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

Ixazomib (Ninlaro) for Multiple Myeloma

June 29, 2017

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Ninlaro_for_relapsed_refractory__multiple_myeloma
Role in Review (Submitter and/or Manufacturer):	Manufacturer
Organization Providing Feedback	Takeda Canada Inc.

**pCODR 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 Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

____ agrees ____ agrees in part _x___ disagree

Please explain why the Submitter (or the Manufacturer of the drug under review, if not the Submitter) *agrees, agrees in part or disagrees with the initial recommendation.*

1) Takeda fundamentally disagrees with pERC's statistical approach for assessing the final PFS effect of ixazomib. pERC's approach is inconsistent with how pCODR has reviewed carfilzomib, another proteasome inhibitor (PI).

- pCODR issued a positive clinical recommendation for carfilzomib based only on the first PFS analysis of ASPIRE and no subsequent exploratory PFS analysis was done. Clinical PFS significance for carfilzomib was met at the initial comparative PFS analysis and was considered final and subsequently led to regulatory filing and approval. Ixazomib followed a similar path. Ixazomib met its primary PFS endpoint at the first comparative analysis (IA1) and subsequently achieved regulatory approval based on these significant IA1 results.
- There should be consistency for pERC's review of the TOURMALINE MM1 study and clinical conclusions should be based on the first and final PFS analysis which demonstrated statistical and clinical significance.
- As per the CGP review, PFS at IA2 was an exploratory and non-inferential assessment. It was conducted based on a request from the FDA during the initial MM1 study design.
- Health Canada (priority review), FDA and EU CHMP acknowledged the safety and efficacy of ixazomib and granted regulatory approval based on the validity of the MM1 IA1 data. In addition, ixazomib is the only PI studied using a randomized **double blind** study design in MM1 and is included as a triplet therapy in the NCCN 2016 Guidelines as a preferred treatment regimen, based on Level 1 evidence.

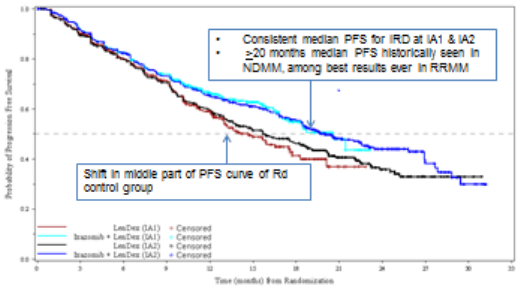
Key Aspects of the MM1 Study Design

- The MM1 Study employed a well-established and commonly used group-sequential design as published in the Statistical Analysis Plan[i]. The methodology has been extensively developed, evaluated, and documented [ii],[iii], [iv] which allows for valid analyses of interim data so that a trial can be stopped early in case of overwhelming efficacy.
- The interim analysis (IA) points were pre-specified and both analyses were potential time points for final PFS. The efficacy data determined that IA1 was the final analysis because the IA1 threshold for PFS was met. This O'Brien-Fleming group sequential monitoring approach is similar to the IA plan used in the ASPIRE study[v].
- The MM1 protocol provided 2 opportunities to test the study's hypothesis. The pre-specified boundary was crossed at the planned first PFS analysis, 286 events, with 40% of patients having achieved a PFS event (Figure 1), thus making the first IA the final analysis for PFS for statistical testing purposes. In fact, the observed p-value of 0.012 (HR=0.742) was well below the more stringent O'Brien Fleming boundary of 0.0227 for claiming statistical significance.
- The study continued in a blinded fashion, with a planned second IA for OS. Per protocol and as requested by the US FDA, the applicant took the opportunity to conduct a non-inferential (i.e. not to be used for making

statistical conclusions about whether the study is significant or not) sensitivity analysis for PFS at IA2.

- Although methodologically inappropriate to be drawing conclusions from the exploratory IA2 analysis, we understand that there are questions raised around the magnitude of benefit observed. There are several considerations when assessing the exploratory PFS IA2 analysis, most notably those affecting the placebo regimen:
  - Clinical benefit continued to be maintained in the IRd arm demonstrating consistency and certainty (20.6 and 20.0 months) (see graph)
  - There was asymmetric (unbalanced) censoring between the 2 treatment groups at IA2 analysis due to a greater number of patients in the Rd arm starting alternate therapy [redacted] **[This information was removed because it was out of scope]** (22 patients in IRd / 32 in Rd). As a result, the PFS curve for the placebo arm shifted up. Had the censoring patterns for the two arms been balanced at IA2, a treatment benefit similar to IA1 would have been observed.

Changes in IRC PFS results between primary and non-inferential analyses were mainly driven by changes in the control arm.



  - [redacted] **[This information was removed because it was out of scope.]**
  - Similar evidence was provided to the European Scientific Advisory Group informing the ixazomib CHMP review and they reached the following conclusion: *"The fact that a subsequent exploratory analysis showed some uncertainty about the level of statistical significance is not enough to change the conclusions about a clear beneficial effect in terms of PFS on the basis of the pre-planned analysis"* [vi]

- We challenge the committee's concern regarding the likelihood of false positive result at IA1. Requiring PFS results to pass the threshold for statistical significance at both IA1 and IA2, would be equivalent to subjecting the trial to an overall type I error rate of 0.0074 (1-sided). Under the null hypothesis of no treatment efficacy, the probability of observing HRs at or more extreme than what was observed at IA1 (HR=0.74) and IA2 (HR=0.82) is 0.0047. This means there is less than a 0.5% chance that IA1 was a false positive.

2) The pERC determination that all of the sub-group analyses were post-hoc is inaccurate and should not create uncertainty around the assessment of clinical benefit in these patient populations

- PFS in patients with high-risk cytogenetics was apriori classified as secondary efficacy endpoint per protocol
- Prior lines of therapy (1 vs 2-3) was a pre-specified stratification factor due to its prognostic relevance.
- Thus, these subgroups are not post hoc analyses and can be prospectively analysed and are valid.

High risk cytogenetic group:

- We acknowledge the committee's comments regarding the lack of consistency in the definition of the high-risk cytogenetic group. The science of high-risk cytogenetics was evolving at the time of the original MM1 protocol. The definition of high-risk used in the MM1 study included the 5 cytogenetic abnormalities. At the time of data analysis and publication, the accepted definition was the 3 abnormalities, Del(17), t(4,14) and t(14,16) [vii] as included in the NEJM 2015 MM1 publication[i]. Subsequent to the publication, the IMWG 2016 recommendations[viii] now include +1q21, which formed the basis of the pCODR submission.
- As published in the NEJM, the greatest clinical benefit was seen in the del(17), t(4,14) and t(14,16) group of high-risk cytogenetics. The results show an 11.7 month difference in PFS with ixazomib treatment, which is greater than that seen in the ASPIRE subgroup analysis[ix] (9.2 months difference) and with a better tolerability profile and an all oral treatment regimen."*KRd [carfilzomib + Ld] improves but does not abrogate the poor prognosis associated with high risk cytogenetics in patients with relapsed MM.*[v]"
- Clinician input also reflected the importance of ixazomib in this pre specified subgroup; a positive recommendation for this subgroup would be appropriate and addresses the high unmet medical need in this

subpopulation.

Table 1. PFS Results at IA1, IA2 and OS for the high risk cytogenetics patient

Subgroup	N		Median PFS (months)						Median OS(months)		
			Primary Analysis			12 July 2015 Analysis			12 July 2015 Analysis		
	P+Ld	I+Ld	P+Ld	I+Ld	HR (p value)	P+Ld	I+Ld	HR (p value)	P+Ld	I+Ld	HR (p value)
High-risk cytogenetics [del(17), t(4;14), or (14;16)]	62	75	9.7	21.4	0.543 (0.021)	9.3	18.7	0.625 (0.037)	28.6	NE	0.576 (0.113)
Expanded-risk cytogenetics del(17), t(4;14), t(14;16), or 1q21+	154	155	11.1	17.5	0.664 (0.016)	11.3	18.0	0.702 (0.019)	28.6	NE	0.620 (0.032)

Table 2. Summary of efficacy data in high risk cytogenetic patients

Adverse risk characteristics	Ixa +Ld vs Ld IA1		Ixa+Ld vs. Ld IA2		Carfilz. +Ld vs. Ld	
Elevated Cytogenetic Risk Groups	PFS (IRD vs RD)	HR (95% CI)	PFS (IRD vs RD)	HR (95% CI)	PFS (IRD vs RD)	HR (95% CI)
High risk genetic group: del (17p), t(4;14), or t(14;16)	21.4 vs 9.7	0.543	18.7 vs 9.3	0.625	23.1 vs 13.9	0.703
Elevated genetic risk group: del(17p),t(4;14); t(14;16), or 1q21+	17.5 vs11.1	0.664	18.0 vs 11.3	0.702	No data	No data

Source: ASPIRE: Avet-Loiseau H et al. Blood 2016[ix].

Two or more prior lines of therapy:

- As per the MM1 protocol, the subgroup of patients who had 2-3 prior therapies was a pre-specified subgroup and a stratification factor. **Thus, there is no uncertainty associated with the interpretation of the data from these analyses. The results are clinically and statistically compelling and are not likely to be chance findings.**
- This subgroup represents a high percentage (41%) of the entire study population, establishing a robust sample size. For the PFS data, 118 of 297 events (38%) had occurred at IA1. At IA1, the median PFS was already reached in the placebo regimen (12.9 months) but not yet reached in the ixazomib regimen, yielding a HR of 0.580 (p=0.003). This improvement in median PFS which is considered clinically meaningful.
- Although there is little rationale to adjust for multiple testing or to perform interaction testing, should the subgroup analysis of patients with 2+ prior line therapy (a stratification variable for randomization) be adjusted for multiple testing of all 6 subgroups defined by the 3 stratification variables, the p-value of .003*6=.018 would still be considered statistically significant under the group sequential framework. **While both patient subgroups 1 and 2-3 prior line therapy benefited from treatment, testing for interaction found that patients who had 2-3 prior therapies experienced more pronounced treatment benefit compared to patients who had 1 prior therapy (p-value for 2-sided test=0.0599)**; conventionally p<0.10 is considered significant for testing interaction[x].

PERC : "*Furthermore, no adjustments were made for multiple testing in the subgroups…..*" *page 2, para 3)*

- For the MM1 study, achieving statistical significance in the ITT population means evidence already exists for an overall positive treatment benefit in the ITT population. Therefore, there is little or no rationale to adjust for multiple testing when the purpose is to identify subgroups experiencing the most pronounced treatment effect.

3) Ensuring Options for Patients and MM Management

Consistent with the NCCN guidelines, CGP states that "*from a purely clinical perspective a reasonable option is to make both these agents available to patients and clinicians, and give them the option to choose one of these two drugs to add to len/dex.*"

PERC acknowledged that ixazomib is partially aligned with patient values as it offers patients with MM an alternative treatment option with tolerable side effects and an oral route of administration, which is consistent with the CGP and clinician's opinion. However, pERC's assessment of the benefits of the oral administration of ixazomib is not reflective and is inconsistent with the value placed by pERC in other MM product recommendations. pERC noted in its 2015 review of lenalidomide, "*the importance of oral therapies to patients and their caregivers with respect to convenience and the comfort of taking treatment at home. This is especially important when long travel distances are otherwise required to receive treatment and manage side*

effects."[xi] pERC's position regarding the burden of IV therapies as compared to orals is also reflected in its 2016 recommendation of daratumumab[xii].

There is a clear segment of patients with an unmet need that cannot benefit from currently available PI. This includes patients who are challenged get to the clinic for frequent treatment administration due to mobility issues or geography (especially rural settings), patients who are frail and/or elderly and those who suffer from comorbidities such as cardiovascular disease or renal impairment that may not be candidates to use carfilzomib.

	Ixazomib-Rd	Carfilzomib-Rd
Route of Admin	PO	IV
Minimum clinic visits based on 18 cycles	18	95
Dosing schedule	One capsule once a week at home + oral RD	Days 1,2,8,9,15 and 16 of 28-cycle + oral
Hospital/clinic visit	Every 4 weeks	Twice a week
Mandated prehydration	No	Additional IV hydration needed
Administration/clinic/hospital time per visit	0 hours	Over 2 hours (130 minutes)

This need in Canada for ixazomib, despite availability of other PIs has also been demonstrated with the high number of patients accessing the ixazomib's compassionate and patient support program.

Takeda recognises the systemic cost challenges and sustainability of cancer drug funding, however, there is a place in therapy for ixazomib for a certain segment of patients as outlined above. In order to achieve payer value, Takeda looks forward to working together to find the best value for patients, if afforded the opportunity.

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur two (2) Business Days after the end of the feedback deadline date.

____ Support conversion to final recommendation.

Recommendation does not require reconsideration by pERC.

_x___ Do not support conversion to final recommendation.

Recommendation should be reconsidered by pERC.

c) Please provide feedback on the initial recommendation. 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 Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity

3.2 Comments Related to Submitter or Manufacturer-Provided Information

Please provide feedback on any issues not adequately addressed in the initial recommendation based on any information provided by the Submitter (or the Manufacturer

of the drug under review, if not the Submitter) in the submission or as additional information during the review.

Please note that new evidence will be 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 providing is eligible for a Resubmission, please contact the pCODR Secretariat.

Page Number	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer-Provided Information

3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments

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

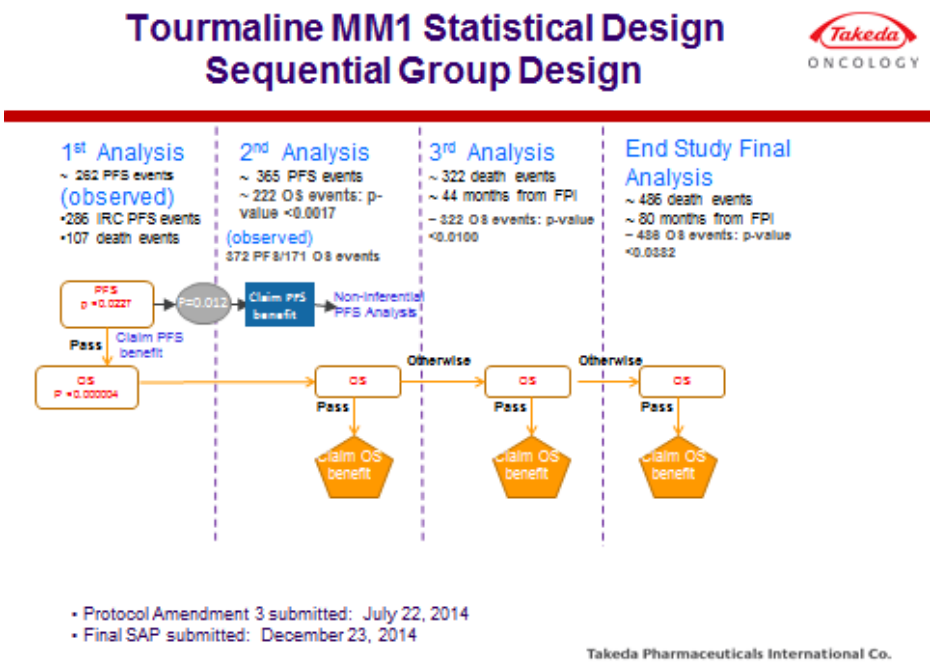
paragraph). Opinions from experts and testimonials should not be provided. Comments should be restricted to the content of the initial recommendation.

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.



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[ii] Jennison C, Turnbull B. Group Sequential Methods with Application to Clinical Trials: Chapman & Hall; 2000.

[iii] Proschan M, Lan K, Wittes J. Statistical Monitoring of Clinical Trials: A Unified Approach: Springer; 2006.

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[ix] Avet-Loiseau H, Fonseca R, Siegel D, Dimopoulos MA, et al . Carfilzomib significantly improves the progression-free survival of high-risk patients in multiple myeloma. Blood. 2016 Sep 1;128(9):1174-80. doi: 10.1182/blood-2016-03-707596. Epub 2016 Jul 20.

[x] Zelen M. The analysis of several 2 × 2 contingency tables. Biometrika 1971;58(1):129-37.

[xi] Pan-Canadian Oncology Drug Review. pCODR Expert Drug Review Committee Final Recommendation. Lenalidomide (Revlimid) ND MM. Published: Dec 3, 2015. https://www.cadth.ca/sites/default/files/pcodr/pcodr_lenalidomide_revlimid_nd-mm_fn_rec.pdf

[xii] Pan-Canadian Oncology Drug Review. pCODR Expert Drug Review Committee Final Recommendation. Daratumumab (Darzalex) Multiple Myeloma.Published: Dec 1, 2016. https://www.cadth.ca/sites/default/files/pcodr/pcodr_daratumumab_darzalex_mm_fn_rec.pdf