CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Registered Clinician Feedback on a pCODR Expert Review Committee Initial Recommendation

Ixazomib (Ninlaro) for Multiple Myeloma

June 29, 2017

1. Feedback on pERC Initial Recommendation

Name of the drug indication(s):	Ixazomib (Ninlaro) for the treatment of adult patients with multiple myeloma who have received at least one prior therapy including and have high-risk cytogenetics or have received at least two prior therapies.
Name of registered clinician(s):	Myeloma Canada Research Network

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

2. Comments on the Initial Recommendation

a) Please indicate if the registered clinician(s) agrees or disagrees with the initial recommendation:

____ agrees ____ agrees in part X disagree

Ixazomib added to lenalidomide and dexamethasone (IRd) has been demonstrated in a well-designed phase III study to be superior to lenalidomide and dex alone, with respect to PFS, particularly in high-risk patients. The reviewers are respectfully requested to re-consider the negative recommendation on the basis of the 4 following points:

1) This is the only trial of which I am aware that included assessment of **high-risk myeloma as a predefined endpoint**. Most studies just perform post-hoc subgroup analyses when possible.

2) The PFS at the second interim analysis (IA)--which was not the formal endpoint of the study-- appears to have yielded less robust benefit for the triplet than observed initially. My understanding is that this IA was performed **after the results showing the benefit of the triplet were publically announced**, and this may have affected the behavior of the control group. I also understand that the high-risk group continued to show a solid PFS benefit at the second IA, and this is the most relevant subgroup for whom the triplet is requested. These considerations and other potential factors affecting the second IA deserve careful reassessment before rejecting this drug.

3) The benefit of IRd in high-risk patients must also be interpreted in the context of the other triplets approved by Health Canada for this indication, and in the context of the patient population we face in the real world. The alternative triplet containing a proteasome inhibitor and approved by pCODR with efficacy in high-risk relapsed myeloma is KRd, i.e., CRD (carfilzomib + lenalidomide + dex)

but this regimen is just **not feasible for many elderly and relatively immobile patients,** due to its potential toxicity profile and dose schedule (it requires 6 IV treatments per month).

The **vascular and cardiac toxicity from carfilzomib**, as emphasized by the results reported recently from the CLARION trial of melphalan, prednisone and carfilzomib (compared to VMP) in older myeloma patients, is not inconsequential and in practice leads to avoidance of this proteasome inhibitor in many older patients with even mild cardiac co-morbidity.

Moreover, for patients who are in great pain from myeloma-related skeletal destruction, who live a distance from a cancer centre, or who have transportation/financial issues, **carfilzomib-based therapy is simply not an option.** The inability of these high-risk patients to receive a convenient well-tolerated **oral** proteasome inhibitor-based triplet (IRd) of documented benefit compared to lenalidomide and dex alone **seems to discriminate against an important segment of the myeloma population**. Are patients unable to manage carfilzomib just left with suboptimal treatment--lenalidomide and dex alone--due to circumstances beyond their control?

4) It must also be kept in mind **that Ontario patients who cannot receive carfilzomib will have NO funded re-treatment with a proteasome inhibitor for relapse since bortezomib is not funded either.** This is a travesty that continues to compromise the treatment options for many Ontario myeloma patients compared to those in other provinces.

The refusal to recommend IRd for high risk relapsed myeloma, if upheld, would place an undue and difficult-to-justify burden on high-risk patients in whom carfilzomib is not a reasonable choice

but who might do well with a more convenient oral triplet proteasome-inhibitor based regimen.

Thank you for considering these critical issues.

b) Notwithstanding the feedback provided in part a) above, please indicate if the registered clinician(s) would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur within 2(two) business days of the end of the consultation period.

____	Support conversion to final recommendation.	X	Do not support conversion to final recommendation.
	Recommendation does not require reconsideration by pERC.		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?

No comments

3. Comments Related to the Registered Clinician(s) Input

No comments

4. 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

- The following template form should be used by the registered clinician(s) to submit input at the beginning of a drug review. Please note that there is a separate template for providing feedback on an initial recommendation.

- The clinician(s) **must be registered with the pCODR program** to provide input. (See https://www.cadth.ca/pcodr/registration for information on eligibility and registration.)

- The registered clinician(s) must also complete the *pCODR Clinician Conflict of Interest Declarations Template* when providing input at the beginning of a drug review (see Appendix A of this document). While CADTH encourages collaboration among registered clinicians and that feedback submitted for a specific drug or indication be made jointly, each registered clinician must complete their own separate *pCODR Clinician Conflict of Interest Declarations Template*.

- Please ensure that the input is in English, and that it is succinct and clear. Please use a minimum 11-point font and do not exceed six (6) typed, 8 ½″ by 11″ pages. If a submission exceeds six pages, only the first six will be considered.

- The registered clinician(s) 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 registered clinician(s) should not feel restricted by the space allotted on the form and can expand the tables in the template as required. The categories and questions outlined are only examples, to guide identification of relevant clinical factors for pERC's consideration. Please note that comments may be attributed to a specific individual clinician and that registered clinicians who submit input will be identified as a contributor to the specific input. CADTH's pCODR program maintains the discretion to remove any information that may be out of scope of the review.

- It is important to note that scientific published references are not required, as pCODR has access to current scientific literature through the manufacturer's submission, tumour groups, and a rigorous, independent literature search.

- The registered clinician(s) must be submitted by the **deadline date** for this drug, posted on the pCODR section of the CADTH website under *Find a Review* so that it can be available in time to be fully used in the pCODR review process. If more than one submission is made by the same registered clinician(s), only the first submission will be considered.

- In addition to its use in the pCODR process, the information provided in this submission may be shared with the provincial and territorial ministries of health and Provincial cancer agencies that participate in pCODR, to use in their decision-making.

Should you have any questions about completing this form, please email submissions@pcodr.ca