PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

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

Trabectedin (Yondelis) for Liposarcoma or Leiomyosarcoma

August 5, 2016

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	YONDELIS® (trabectedin) for advanced soft tissue sarcoma
Role in Review (Submitter and/or Manufacturer):	Manufacturer
Organization Providing Feedback	Janssen 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

Janssen disagrees with the pERC initial recommendation based on four critical aspects and has provided the rationale below.

1) Janssen disagrees that the magnitude of the absolute benefit in progression-free survival (PFS) was modest for trabectedin compared with dacarbazine.

At multiple times, the clinical guidance report (CGR) acknowledged the clinically important and statistically significant difference in PFS for trabectedin compared to dacarbazine. (CGR, 2016, pp 2,3) Additionally, as stated in the FDA medical review, the clinical reviewers considered this magnitude of improvement in PFS (i.e., HR=0.55; p<0.001) to be clinically meaningful. (FDA Medical Review, 2015, pp 13, 38)

2) Janssen disagrees that more patients in the trabectedin group may have had a better prognosis than patients in the dacarbazine group due to a seven month difference from the time of diagnosis to the time of treatment.

First, the correlation between having a better prognosis on treatment and time between diagnosis and treatment is uncertain. To date, no study addressed the prognostic significance of having a longer time from initial diagnosis to treatment in metastatic soft tissue sarcoma. Additionally, if this correlation were true and longer time did bias the results, we would expect to see differences in benefit by tumor subtype, as some are more rapidly progressing than others. However, based on the forest plot, the benefit across subgroups appears uniform. (Demetri et al., 2015, pp 4)

Secondly, the seven month difference between treatment groups (comparing time from diagnosis to treatment initiation) as stated in the initial recommendation represents the median value as obtained from the interim clinical data cut-off date. (Demetri et al, 2015, pp 3) However, given the large range in time from diagnosis to initial treatment in both the trabectedin and dacarbazine groups, it is important to consider the mean values, as median values may not be truly representative of differences in time from diagnosis to treatment. To note, at the time of the interim clinical cut-off, the difference in median time from diagnosis to treatment was 7 months (as noted above) and the difference in mean time from diagnosis to treatment was only 1.1 months. (Interim CSR, 2014, pp 57)

3) Janssen disagrees that the subsequent therapies following progression did not affect the potential to observe an overall survival (OS) benefit with trabectedin. Specifically, pERC made this statement as these therapies have not previously shown OS benefits.

The CGR notes that although OS is considered the most unbiased endpoint, there is acknowledgment that any difference in OS is impossible when subsequent lines of therapy are allowed in the study. The CGR indicates that PFS is a clinically acceptable endpoint for metastatic sarcomas. (CGR, 2016, pp 3,15) Furthermore, a meta-analysis that included 52 published studies and 9,762 patients found that both PFS and response rate were found to be appropriate surrogates for OS. (Zer et al., 2016) Hence, it is likely that post-progression treatments contributed to the loss in OS signal.

Additionally, in the Phase 3 clinical trial of trabectedin vs. dacarbazine (SAR-3007), a greater proportion of patients received gemcitabine and docetaxel post-progression in the dacarbazine group compared to the trabectedin group (27% vs. 15%, respectively). (Demetri et al, 2015, pp 6) Gemcitabine +/- docetaxel has been shown to improve PFS, especially with docetaxel, and since most patients would be treated with the combination, this may have further confounded OS, especially since a larger proportion of patients in the dacarbazine group received the combination. (Maki et al., 2007)

Similarly, the proportion of patients receiving pazopanib post-progression is larger in the dacarbazine group (28% in the dacarbazine group and 18% in the trabectedin group). (Demetri et al., 2015, pp 6) Based on the clinical reviewer report, Pazopanib was considered to provide a net clinical benefit. (Pazopanib CGR, 2012, pp 3) Hence, the addition of pazopanib post-progression may have further confounded OS, especially with the discrepancy between the dacarbazine and trabectedin post-progression treatment mixes.

4) Janssen disagrees that quality of life (QoL) data is lacking for trabectedin.

Quality of life data was measured using the MD Anderson Symptom Index in both groups and demonstrated that there was no difference in QoL between the two groups, despite higher incidences of various toxicities in the trabectedin group. This was important as this patient population was ECOG PS 0-1, asymptomatic/minimally asymptomatic, and would therefore be very unlikely to observe improvement in disease-related symptoms. The absence of symptom deterioration mirrored the absence of progression of sarcoma and can be considered as clinically meaningful to patients and physicians. (CGR, 2016, pp 8)

Hence, not only was adequate QoL data provided to assess the symptom severity experienced by patients on trabectedin and dacarbazine, the absence of symptom deterioration between groups can be considered clinically meaningful.

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 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?

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.