CADTH

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

Niraparib (Zejula) for first line Ovarian Cancer

April 29, 2021

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Niraparib Maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy
Eligible Stakeholder Role	Registered Clinician Feedback
Organization Providing Feedback	Members of Ontario Health (Cancer Care Ontario) Gynecologic Cancers Drug Advisory Committee

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

3.1 Comments on the Initial Recommendation

a) Please indicate if the stakeholder agrees, agrees in part, or disagrees with the initial recommendation:

☐ Agrees ☒ Agrees in part ☐ Disagrees

Please explain why the stakeholder agrees, agrees in part or disagrees with the initial recommendation. If the stakeholder agrees in part or disagrees with the initial recommendation, please provide specific text from the recommendation and rationale. Please also highlight the applicable pERC deliberative quadrants for each point of disagreement. The points are to be numbered in order of significance.

The DAC noted that the patient population who would derive the most benefit from niraparib treatment was inadequately addressed. Though the HR-proficient/*BRCA*-negative population was not part of the primary analysis determined *a priori,* there was a subgroup analysis performed reporting only a 2.7 month PFS in these patients (Table S6 – Key Subgroup Analyses). The DAC felt that in order to have a fulsome/informed discussion on benefit and risk for the use of PARPi in *BRCA* wildtype patients the HR status is essential. This medication requires intensive surveillance to monitor toxicities and patients need to be able to decide whether the toxicity and additional surveillance required is worth a 2.7 month PFS. This can only be done if HRD status is known.

1. The PRIMA trial was designed in such a way (i.e., how the primary efficacy groups were defined) that made it difficult to evaluate the true benefit of niraparib in the HR-proficient/*BRCA*-negative population. They evaluated the overall population and the HRD population (*BRCA* positive + HRD score ≥ 42) as primary outcomes but the PFS in those that were HR-proficient (HRP) was a secondary subgroup analysis.

2. The DAC expressed concern with offering niraparib to HRP/*BRCA*-negative patients with PFS improvement of only 2.7 months. While this is statistically significant in the trial it is not clinically meaningful. In addition the DAC felt niraparib is associated with significant toxicities, intensive surveillance for toxicities, and huge expense without meaningful clinical benefit. The HRP/*BRCA*-negative population will make up a large percentage (50%) of the patient

population who would be eligible for niraparib under this initial recommendation. In addition, the benefit in PFS (5.6 months) in the overall population was due to the enrichment of HRD (BRCA positive myChoice score ≥ 42) patients which made up over 50 percent of the entire study population.

3. The availability of a validated HRD testing method would be essential for clinicians and patients to make informed treatment decisions; i.e., to identify patients who would derive the most benefit from treatment with niraparib (HRD and *BRCA*-positive patients). The DAC did not agree with the conclusion that the HRD test (Myriad myChoice score ≥ 42) used in PRIMA trial was not validated. It was used in an *a priori* fashion and showed a significant improvement in PFS (11.2 months) in those that were HRD (*BRCA* positive or myChoice ≥42).

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 Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
18	Companion diagnostic testing	2nd paragraph, last line	"pERC agreed with the CGP that until further studies are performed to validate the test, HRD testing should not be required to receive niraparib." The DAC disagrees strongly that further studies are needed to validate myChoice Myriad HRD test. This study defined HRD as including pathogenic variants in *BRCA1/2* and Myriad myChoice score ≥ 42 or both. The Myriad myChoice test is a genomic assessment of HRD that includes loss of heterozygosity, telomeric allelic imbalance and large scale state transitions and has been described in publications. This randomized controlled trial (PRIMA) using this test as an *a priori* subgroup is the highest level of validation of a predictive biomarker. This study was powered to assess a difference for this HRD subgroup and therefore confirms the use of this as predicting response to niraparib. In addition they showed that the PFS in patients with pathogenic variant in *BRCA* (PFS=11.2 months) was similar to those with an HRD score of ≥ 42 (PFS=11.4), highlighting the importance of knowing the HRD score for those who are *BRCA* wildtype (Supplement Table S6). In contrast those that were HRP only had a PFS of 2.7 months which is not clinically meaningful even if statistically significant. Our DAC would want all patients to know what type of benefit they would expect if they were HRP with the additional toxicities and surveillance required. In addition, patients and clinicians may be more inclined to accept the additional toxicities and inconvenience of additional follow up if they knew

			there was a 11.4 month PFS benefit if they knew they were HRD positive but *BRCA* wildtype The OH-CCO Gyne DAC feels strongly that the results of these tests are important to determine who would benefit most from this maintenance therapy and to inform risk/benefit discussions with patients. The DAC feels an HRD test is necessary in order to offer this drug in *BRCA* wildtype patients.

3.2 Comments Related to Eligible Stakeholder Provided Information

Notwithstanding the feedback provided in part a) above, please indicate if the stakeholder would support this initial recommendation proceeding to final recommendation ("early conversion"), which would occur two business days after the end of the feedback deadline date.

☐ 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.

If the eligible stakeholder does not support conversion to a final recommendation, please provide feedback on any issues not adequately addressed in the initial recommendation based on any information provided by the stakeholder 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.

Additionally, if the eligible stakeholder supports early conversion to a final recommendation; however, the stakeholder has included substantive comments that requires further interpretation of the evidence, the criteria for early conversion will be deemed to have not been met and the initial recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting.

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information

Template for Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation

1 About Stakeholder Feedback

CADTH invites eligible stakeholders to provide feedback and comments on the pan-Canadian Oncology Drug Review Expert Review Committee (pERC) initial recommendation.

As part of the CADTH's pan-Canadian Oncology Drug Review (pCODR) process, pERC makes an initial recommendation based on its review of the clinical benefit, patient values, economic evaluation and adoption feasibility for a drug. The initial recommendation is then posted for feedback from eligible stakeholders. All eligible stakeholders have 10 business days within which to provide their feedback on the initial recommendation. It should be noted that the initial recommendation may or may not change following a review of the feedback from stakeholders.

CADTH welcomes comments and feedback from all eligible stakeholders with the expectation that even the most critical feedback be delivered respectfully and with civility.

A. Application of Early Conversion

The stakeholder feedback document poses two key questions:

1. **Does the stakeholder agree, agree in part, or disagree with the initial recommendation?**

   All eligible stakeholders are requested to indicate whether they agree, agree in part, or disagree with the initial recommendation, and to provide a rationale for their response. Please note that if a stakeholder agrees, agrees in part or disagrees with the initial recommendation, they can still support the recommendation proceeding to a final recommendation (i.e. early conversion).

2. **Does the stakeholder support the recommendation proceeding to a final recommendation ("early conversion")?**

   An efficient review process is one of the key guiding principles for CADTH's pCODR process. If all eligible stakeholders support the initial recommendation proceeding to a final recommendation and that the criteria for early conversion as set out in the *Procedures for the CADTH Pan-Canadian Oncology Drug Review* are met, the final recommendation will be posted on the CADTH website two business days after the end of the feedback deadline date. This is called an "early conversion" of an initial recommendation to a final recommendation.

   For stakeholders who support early conversion, please note that if there are substantive comments on any of the key quadrants of the deliberative framework (e.g., differences in the interpretation of the evidence), the criteria for early conversion will be deemed to have **not** been met and the initial recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting. Please note that if any one of the eligible stakeholders does not support the initial recommendation proceeding to a final recommendation, pERC will review all feedback and comments received at a subsequent pERC meeting and reconsider the initial recommendation.

B. Guidance on Scope of Feedback for Early Conversion

Information that is within scope of feedback for early conversion includes the identification of errors in the reporting or a lack of clarity in the information provided in the review documents. Based on the feedback received, pERC will consider revising the recommendation document, as appropriate and to provide clarity.

If a lack of clarity is noted, please provide suggestions to improve the clarity of the information in the initial recommendation. If the feedback can be addressed editorially this will done by the CADTH staff, in consultation with pERC, and may not require reconsideration at a subsequent pERC meeting.

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

2 Instructions for Providing Feedback

- The following stakeholders are eligible to submit feedback on the initial recommendation:
    - The sponsor and/or the manufacturer of the drug under review;
    - Patient groups who have provided input on the drug submission;
    - Registered clinician(s) who have provided input on the drug submission; and
    - CADTH's Provincial Advisory Group (PAG)
- 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.
- The template for providing stakeholder is located in section 3 of this document.
- The template must be completed in English. The stakeholder 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.
- Feedback on the initial recommendation should not exceed three 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 provided to the pERC for their consideration.
- 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, and should not contain any language that could be considered disrespectful, inflammatory or could be found to violate applicable defamation law.
- References may be provided separately; however, these cannot be related to new evidence.
- CADTH is committed to providing an open and transparent cancer drug review process and to the need to be accountable for its recommendations to patients and the public. Submitted feedback must be disclosable and will be posted on the CADTH website.
- The template must be filed with CADTH as a Microsoft Word document by the posted deadline.
- If you have any questions about the feedback process, please e-mail requests@cadth.ca