CADTH

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

Niraparib (Zejula) for Ovarian Cancer

September 3, 2020

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	ZEJULA (niraparib) as monotherapy for the maintenance treatment of female adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy
Eligible Stakeholder Role	Manufacturer (Sponsor)
Organization Providing Feedback	GlaxoSmithKline Inc.

** 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.

GlaxoSmithKline Inc. (GSK) agrees with pERC's initial recommendation of niraparib as monotherapy for the maintenance treatment of female adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (hereinafter referred to as ovarian cancer) who are in a complete or partial response to platinum-based chemotherapy, and supports conversion of the initial recommendation to a final recommendation.

Clinical Feedback

- GSK is pleased to receive this recommendation from pERC on the basis of the net clinical benefit observed with niraparib regardless of biomarker status, per the NOVA trial results. pERC's acknowledgment that
  > *"a treatment benefit with niraparib was observed regardless of BRCA status; therefore, all patients should be offered niraparib maintenance therapy based on the evidence from the NOVA trial"* (page 19)

  provides confidence in the robustness of the NOVA study as well as niraparib's clinically meaningful improvement in PFS in all patients included in the trial.
- GSK agrees as well that "HRD testing should not be required to receive niraparib", given the benefit seen across biomarker subgroups in the NOVA trial and "as this test has not yet been clinically validated".
- GSK is also in agreement that treatment with niraparib is aligned with patient values, helping to fulfil an unmet need in patients' current maintenance treatment options (need for new treatments, importance of extending PFS while maintaining QoL).

Economic Feedback

We acknowledge CADTH's fulsome review of GSK's submitted health economic models, however, GSK is not in complete agreement and would like to comment on the critical appraisal of the economic models in the initial recommendation and the Economic Report.

Willingness to Pay (WTP) Threshold (page 12):

CADTH's assessment of the price reduction required in order to meet a $50,000/QALY WTP threshold should be interpreted with caution. There is broad recognition of the unique challenges in health economic modeling of cancer and rare diseases therapies and of certain caveats in demonstrating health economic value in these therapy areas. As such, it is a common sentiment across health economists that a WTP of $50,000/QALY may not be the appropriate threshold in all cases[1,2].

There is clear inconsistency across stakeholders on appropriate WTP thresholds for medicines. Recent Patented Medicines Pricing Review Board (PMPRB) June 2020 draft guidelines have highlighted the need for flexible willingness-to-pay (WTP) thresholds in order to reflect the cost-effectiveness of medicines across a variety of diseases[3].; per these recently proposed PMPRB draft guidelines, the "Pharmacoeconomic Value Threshold" is between $150,000/QALY - $200,000/QALY[3]. CADTH, however, puts focus in the initial recommendation on the reduction of the list price niraparib that would allow for a $50,000/QALY ICER to be achieved, rather than price reductions that would be required to achieve other commonly used willingness to pay thresholds such as $100,000/QALY or higher.

Within other CADTH review reports, where a price reduction is proposed, multiple WTP thresholds are indicated, and the final conclusion in the Pharmacoeconomic Review Report includes the percent reduction in the list price of the manufacturer's product to achieve all thresholds.[4] It is therefore important to note that the CADTH Reanalysis ICER of $98,913 was obtained with a 20% discount of the list price of niraparib in the gBRCAmut population compared to active surveillance and $99,603/QALY was obtained with a 50% discount in the list price of niraparib in the non-gBRCAmut population compared to active surveillance.

Decision Analytic Model (page 5, 11-12):

In terms of the modeling approach for the cost-utility analysis, although partitioned survival models (PSM) are widely considered to be robust and transparent and are commonly used in economic models of oncology treatments, a PSM was not used for the economic evaluation presented herein for two reasons. Firstly, overall survival (OS) data for niraparib and active surveillance from the NOVA trial were immature, and therefore robust estimation of long-term OS for patients receiving niraparib was not feasible. A benefit of the decision analytic model is that it does not require extrapolations of OS for niraparib. Secondly, the modeling approach used in the submission has been employed in previous submissions to HTA bodies, including the submission to NICE in the United Kingdom (TA528). While the economic review group for the UK submission expressed concerns about the approach, the NICE Appraisal Committee for this file ultimately determined that this decision analytic modeling approach was adequate for decision making, understanding that cost-effectiveness results based on a PSM approach would differ by less than £1,000 from those using the decision analytic approach[5]. While GSK recognizes the concerns about the modeling approach utilized, GSK believes the benefits of a decision analytic model combined with the alignment between the decision modeling approach and PSM results makes this type of model an appropriate choice for decision makers.

OS:PFS Ratio (page 5, 11-12):

GSK is in agreement that there is substantial uncertainty in the terms of the ratio of the gain in OS to the gain in progression free survival (PFS) with niraparib. Accordingly, in the submission, a ratio of 2:1 was used in the base case and a ratio of 1:1 was evaluated in a scenario analysis. While the uncertainty associated with this assumption was recognized as a limitation in the submission report, it should also be noted that there were no other data on the relationship between gains in PFS and OS with PARP inhibitors when used as second-line maintenance therapy other than those from Study 19 at the time of the submission. Given the paucity of OS data from NOVA and the limited ability to extrapolate OS data, this innovative approach was used by GSK to estimate OS.

Indirect Treatment Comparisons (ITC) (11-12):

GSK is also in agreement that the results of the two ITCs and the ITC/ network meta-analyses (NMA) should be interpreted cautiously due to the limitations identified by the Clinical Guidance Report. Further, GSK recognizes that this could lead to uncertainty with respect to the modeled assumption that the PFS of niraparib and olaparib are equivalent. However, it is reassuring that the clinical experts consulted support the conclusions from the ITC/NMA and believe the assumption of equal efficacy for PFS between niraparib and olabarib may be reasonable.

Dosing (page 12):

While the manufacturer submitted cost-utility model utilized the mean daily dosage of niraparib from NOVA, starting with a 300mg dose, GSK recognizes that, "pERC agreed with the CGP that a starting dose of 200mg should be considered for patients who are at risk for AEs, including patients with body weight less than 77 kg and low platelet count (<150,000/μL)" (page 4). It is important to note that the manufacturer submitted ICER estimates would be considered conservative if, in practice, more patients started with a 200mg dose instead of a 300mg dose.

While GSK appreciates the thorough review and critical appraisal of the manufacturer submitted cost-utility analysis, we are not in complete agreement and believe that the above concerns are important to highlight.

Budget Impact (page 12-13):

GSK acknowledges that for the calculation of the size of the model population, patients with high-grade serous histology were excluded from the budget impact model initially submitted to pCODR. This issue, however, was identified during initial consultations with CADTH and the submitted model was revised to not include this criterion.

GSK recognizes that the Guidelines for Conducting Pharmaceutical Budget Impact Analyses for Submission to Public Drug Plans in Canada published by the PMPRB recommends all forecasts and results should be presented on a 12-month basis for a minimum of three years[6]. The use of quarterly (3-month) intervals for projecting the number of patients who would initiate and continue with treatment over the course of each year is not inconsistent with these recommendations. This approach carefully takes into account that not all patients are likely to initiate treatment on the first day of every calendar year, and therefore, is an accurate representation of the budget impact for introducing a new therapy.

Section 6.6 of the PMPRB Budget Impact Analysis Guidelines recommends that budget impact be estimated with the annual cost calculated as the "*annual number of patients multiplied by the annual market share multiplied by the annual drug cost per patient*" [6]; this approach could yield inaccurate estimates of the budget impact when durations of treatment may exceed one year, and the proportion of patients receiving various treatments is changing over time. In particular, when a new drug is introduced and its use is increasing over the forecast period, assigning the full annual cost

to all patients who initiate treatment in the first year of the projection may substantially over- or under-estimate the budget impact (the latter if the new drug is displacing more costly treatments).

Notwithstanding the comments above on the health economic and budget impact models, GSK agrees with the initial recommendation – in particular, with the recommended clinical population outlined in the recommendation – and commends pERC for recognizing the value of niraparib regardless of biomarker status. This represents an important step towards the public reimbursement of niraparib, a maintenance treatment option for all platinum-sensitive recurrent ovarian cancer patients.

References:

1. Marseille E, Larson B, Kazi DS, Kahn JG, Rosen S. Thresholds for the cost–effectiveness of interventions: alternative approaches. Bulletin of the World Health Organization. 2014 Dec 15;93:118-24.

2. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness—the curious resilience of the $50,000-per-QALY threshold. New England Journal of Medicine. 2014 Aug 28;371(9):796-7.

3. PMPRB Draft Guidelines 2020. Available from: https://www.canada.ca/en/patented-medicine-prices-review/services/consultations/draft-guidelines.html. Accessed July 13, 2020.

4. Common Drug Review. Pharmacoeconomic Review Report for Nucala (mepolizumab). March 2019.

5. Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer. Available from: https://www.nice.org.uk/guidance/ta528. Accessed July 13, 2020.

6. Budget Impact Analysis Guidelines: Guidelines for Conducting Pharmaceutical Budget Impact Analyses for Submission to Public Drug Plans in Canada. Available from: http://www.pmprb-cepmb.gc.ca/cmfiles/bia-may0738lvv-5282007-5906.pdf. Accessed July 15, 2020.

b) Please indicate if the stakeholder agrees, agrees in part, or disagrees with the provisional algorithm:

☐ Agrees ☐ Agrees in part ☐ Disagrees

N/A

c) 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 or provisional algorithm) 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 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, including the provisional algorithm, 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 pERC initial recommendation, including the provisional algorithm.

As part of the CADTH's pCODR review 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, including the provisional algorithm, 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), including the provisional algorithm as part of the feasibility of adoption into the health system, 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. If the substantive comments relate specifically to the provisional algorithm, it will be shared with CADTH's Provincial Advisory Group (PAG) for a reconsideration. 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. Please also note that substantive comments on the provisional algorithm will preclude early conversion of the initial recommendation to a final 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. Similarly if the feedback relates specifically to the provisional algorithm and can be addressed editorially, CADTH staff will consult with PAG.

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

a) 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)

b) The following stakeholders are eligible to submit Feedback on the provisional algorithm:
   - 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
   - The Board of Directors of the Canadian Association of Provincial Cancer Agencies

- 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 pcodrsubmissions@cadth.ca