CADTH

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

Enasidenib (Idhifa) for Acute Myeloid Leukemia

October 31, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	IDHIFA® for the treatment of adult patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) with isocritrate dehydrogenase-2 (IDH-2) mutation
Eligible Stakeholder Role in Review (Sponsor and/or Manufacturer, Patient Group, Clinical Organization Providing Feedback	Submitter and Manufacturer Celgene Inc.

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

3.1 Comments on the Initial Recommendation

a) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the Initial Recommendation:

☐ Agrees ☐ agrees in part ☒ Disagree

After review of the Initial Recommendation and the Initial Clinical and Economic Guidance Reports, we request that pERC reconsider their recommendation based on the following:

1. A very lengthy delay in patient access will result from a resubmission based on an on-going Phase 3 RCT expected to be completed (data read out) in Q3 2020 and a Clinical Study Report will not be available until at least Q1 2021. Accounting for the additional time required to develop the pCODR submission, pCODR review and pCPA negotiations, we project that realistically, Canadian patients relying on provincial reimbursement would not have access until at least late 2023. The pCODR review, pCPA negotiation and provincial funding processes can, in itself, take up to 2 years to complete. We note that early experience in Canada since approval (~6 months) suggests a strong preference for enasidenib over existing options with ~40 patients receiving treatment where ~150 annually are estimated to be eligible for this treatment. Thus, waiting for a resubmission will result in lost opportunity for many patients to benefit given the very short survival of these patients.
2. The clinical evidence is very mature for long-term outcomes of interest and has a high degree of certainty, although the absolute duration of follow up is short. In Table 6.7 of the CGP report, it is reported that more than 73% of patients in the Phase II (75.2%) or Pooled Phase I/II (73.4%) data have experienced an OS event. This is a very high rate of observed OS events compared to what is usually seen from other oncology evaluations. Given the context of the disease where survival is very short, the evidence submitted for a highly relevant outcome, i.e. OS, is quite mature and does indicate a higher degree of certainty more so than simply looking at the numerical value of median duration of follow up alone.

3. The corresponding OS benefit in patients achieving a CR was not recognized within the Key Efficacy results section. For patients achieving a CR, the median OS was 22.9 months (13.2, NE). In addition, those achieving a CR+CRi/CRp (31.4%), the median OS was 18.2 months (11.8, 25.6). These are clinically significant results given that the 5-year OS after first relapse is approximately 6% for those > 55 years of age (Forman, 2013). We also note that CGP commented that enasidenib "impressively" achieved a 19.6% CR rate in this heavily pretreated, heterogenous, patient population. This observation was also echoed by Health Canada because in comparison, "the CR rate with available therapies can be expected to be approximately 10.5% in the general R/R AML population." (Health Canada, 2019)
4. The duration of treatment is mature with a high degree of certainty. As seen in Figure 6.3 of the CGP report, greater than 94% of patients were off treatment at the time of data cut-off. Thus, the reported duration of treatment is a very robust estimate.
5. A number of statements regarding the PSM in the EGP and CGP reports are inaccurate and may have impacted pERC's interpretation of the results.
    - Optimal 1:1 PSM was complete (i.e., residual differences after PSM do not indicate an incomplete match). Additionally, regression adjustments were not required to achieve statistically significant results. It was decided *a priori* to adhere to best practices in the conduct of PSM analyses and conduct adjustments post-match to reduce the bias that may arise due to residual imbalances between treatment groups and obtain an adjusted hazard ratio.
    - Given that there were a greater number of patients in the AG221-C-001 trial than the France chart review study, optimal 1:1 matching analysis estimated the average treatment effect on the untreated (ATU) rather than the average treatment effect on the treated (ATT) population. The ATU population is generalizable and should be of interest for supporting reimbursement decisions.
    - Missing data in the PSM was minimal as none of the patients in the AG221-C-001 trial and only two patients in the France chart review study were excluded due to missing data.
6. Although CR has historically been accepted as a surrogate of clinical benefit in the intensive treatment setting, achieving CR may not be required for an improvement in survival when considering newer, non-cytotoxic therapies (non-DNA damaging therapies) (Smith, 2009). A broader definition of response, i.e. overall response rate, was employed to ensure that a broader spectrum of responses (e.g., MLFS and PR) are employed to fully represent clinical benefit in this population based on the modified International Working Group (IWG) 2003 revised criteria for AML (Cheson, 2003). This approach is aligned with the recent ELN 2017 Guidelines (Döhner, 2017) which state that with newer agents (e.g., differentiating agents) response may be quite delayed, and hematologic improvement/transfusion independence may occur without a morphologic response. Hematologic improvements result in decreased transfusion requirements and an associated decrease in complications such as iron overload, and development of anti-red blood cell and/or anti-platelet antibodies (Smith, 2009). In addition to the association with improvement in OS, achieving RBC and platelet transfusion independence has been accepted as an important measure of clinical benefit. Given the MOA of enasidenib therapy, specifically an agent that induces differentiation of leukemic cells, and the ability to deliver repeated, chronic dosing, a different treatment response is observed with enasidenib compared with cytotoxic chemotherapies used to treat AML. Specifically, rather than a morphologic response being observed in a finite number of patients in a short period of time, qualitative improvement of response is observed in most responding subjects over time.

With the additional perspective presented above, the characterization of the clinical benefit for enasidenib is well supported by mature, robust evidence that provides a higher degree of

certainty in outcomes of importance, e.g. OS, for decision making than originally considered. As noted by the clinician input, the OS outcomes are "…significant and compares favourably with that of historical data documenting OS of 2-3 months…" and "enasidenib would be a much-needed option for patients with R/R AML with IDH2 gene mutation". Moreover, the CGP notes "the improvement in overall survival in treated patients compares favourably to what has been described historically and it most probable that treatment with enasidenib has clinically significant effects." Additionally, pERC "considered enasidenib to be well tolerated" and "concluded that enasidenib aligns with patient values, as it manages some disease-related symptoms and offer ease of administration, which may translate to improved QoL". Balancing the urgent, unmet need, and the strength of the evidence, we believe that any remaining uncertainty in the evidence is within an acceptable range to merit a recommendation to conditionally fund enasidenib. A conditional funding recommendation will enable Celgene to work with provincial payers to further reduce areas of uncertainty and address the economic aspects to provide patients with timely and sustainable access.

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

☐ agrees ☐ agrees in part ☐ disagree

Not applicable as no algorithm was identified in the initial recommendation.

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, line 22	Instead of "objective", it should be "overall". The primary endpoint was the overall response rate.
6	Key Clinical Efficacy Results	7, line 2	Remove "(CR rate and DOR)". The relevance of including this is unclear in the context of the ORR.

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 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.

☒ 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 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 program.

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

References

Cheson BD, Bennett JM, Kopecky KJ, Büchner T, Willman CL, Estey EH, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol. 2003;21(24):4642-9.

Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-47.

Forman SJ, Row JM. The myth of the second remission of acute leukemia in the adult. Blood. 2013;121(7):1077-1082).

Health Canada. Summary Basis for Decision – Idhifa. Issued August 19, 2019. Accessed September 13, 2019 at https://hpr-rps.hres.ca/reg-content/summary-basis-decision-detailTwo.php?linkID=SBD00441.

Smith BE, Karp JE. What are the endpoints of therapy for acute leukemias? Old definitions and new challenges. Clin Lymphoma Myeloma. 2009;9(Suppl 3):S296—301.

1 About Stakeholder Feedback

pCODR invites eligible stakeholders to provide feedback and comments on the Initial Recommendation made by the pCODR Expert Review Committee (pERC), including the provisional algorithm. (See www.cadth.ca/pcodr for information regarding review status and feedback deadlines.)

As part of the 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. (See www.cadth.ca/pcodr for a description of the pCODR process.) The Initial Recommendation is then posted for feedback from eligible stakeholders. All eligible stakeholders have 10 (ten) 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.

pERC 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 disagrees with the Initial Recommendation, and to provide a rational for their response.

   Please note that if a stakeholder agrees, agrees in part or disagrees with the Initial Recommendation, the stakeholder 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 pCODR's key guiding principles. 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 *pCODR Procedures* are met, the Final Recommendation will be posted on the CADTH website two (2) 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 PAG for a reconsideration. Please note that if any one of the eligible stakeholders does not support the Initial Recommendation proceeding to a Final pERC 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 the pERC chair and pERC members, 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 the PAG chair and PAG members.

The Final pERC 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

b) The following stakeholders are eligible to submit Feedback on the Initial Recommendation:

- The Sponsor making the pCODR Submission, 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 Provincial Advisory Group (PAG)

c) The following stakeholders are eligible to submit Feedback on the provisional algorithm:

- The Sponsor making the pCODR Submission, 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 Provincial Cancer Agencies

d) 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.

e) The template for providing *Stakeholder Feedback on pERC Initial Recommendation* can be downloaded from the pCODR section of the CADTH website. (See www.cadth.ca/pcodr for a description of the pCODR process and supporting materials and templates.)

f) At this time, 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.

g) 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 provided to the pERC for their consideration.

h) 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.

i) 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 program.

j) The comments must be submitted via a Microsoft Word (not PDF) document to pCODR by the posted deadline date.

k) If you have any questions about the feedback process, please e-mail pcodrsubmissions@cadth.ca

Note: 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 will be posted on the CADTH website (www.cadth.ca/pcodr). The submitted information in the feedback template will be made fully disclosable.