CADTH

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

Glasdegib (Daurismo) for Acute Myeloid Leukemia

January 8, 2021

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Glasdegib (with LDAC)/previously untreated AML in adult patients, who are age ≥ 75 years or who are not eligible to receive intensive induction chemotherapy
Eligible Stakeholder Role	Registered clinician feedback
Organization Providing Feedback	Ontario Health (Cancer Care Ontario) Hematology 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 OH-CCO Hematology DAC disagrees with the pCODR negative recommendation. Despite the small sample size and other issues around the randomized phase 2 trial, it did measure/suggest some benefit in OS for those randomized to glasdegib/LDAC over LDAC alone. Although the magnitude of benefit may be small with glasdegib and LDAC, there are some good responses and it provides a very reasonable option for unfit patients. Azacitidine is very challenging in this group of patients and there is an unmet need for a LDAC combination treatment and an oral option makes it easier to administer and less burdensome to the patients.

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

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.

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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

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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?**

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

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   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.

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2 Instructions for Providing Feedback

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- 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

CADTH

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

Glasdegib (Daurismo) for Acute Myeloid Leukemia

January **8, 2021**

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Glasdegib (Daurismo) in combination with low-dose cytarabine for the treatment of newly diagnosed and previously untreated acute myeloid leukemia in adult patients, who are age ≥ 75 years or who are not eligible to receive intensive induction chemotherapy
Eligible Stakeholder Role	Registered clinician(s) who have provided input on the drug submission
Organization Providing Feedback	Canadian Leukemia Study Group (CLSG)

** 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

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☐ 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 Canadian Leukemia Study Group (CLSG) represents acute leukemia treating physicians from every Canadian province. We disagree on several grounds with the pERC recommendation regarding the glasdegib/low dose cytarabine (LDAC) combination in AML:

i. Net Clinical Benefit of Glasdegib + LDAC Based on the BRIGHT 1003 Study
Yes, this was a phase II study, but nevertheless we believe that the data strongly support the use of the glasdegib + LDAC combination over LDAC alone.

An important consideration here is the patient composition in the BRIGHT 1003 study. This study is unique in that it defined explicitly the high risk (not suitable for induction chemotherapy) population eligible for this study. Criteria included:

- **Adults ≥55 years with newly-diagnosed AML, with one or more of the following criteria:**
  - **Age ≥75 years**
  - **Severe cardiac disease (baseline EF < 45%)**
  - **ECOG≥2**
  - **Baseline serum creatinine >1.3 mg/dl**

While seemingly trivial, as a result of this definition, the patients in the BRIGHT 1003 study were of considerably higher risk clinically than were the patients in the reference or comparative studies:

1. **MRC AML14** (LDAC vs. Hydroxyurea); Burnett A *et al*., *Cancer* 2007:109:1114

2. **AZA-MDS-001** (Azacitidine vs. BSC, LDAC, or induction chemotherapy [included AML with 20-30% blasts]); Fenaux P *et al*., *JCO* 2010 28:562-9
3. **AZA-AML-001** (Azacitidine vs. BSC, LDAC, or induction chemotherapy [AML with >30% blasts]); Dombret H, *et al*. *Blood* 2015; 126:291-299
4. **Viale-A** (Azacitidine +/- Venetoclax); DiNardo C, *et al*. *NEJM* 2020; 383: 617
5. **Viale-C** (LDAC +/- Venetoclax); Wei A, *et al*. *Blood* 2020; 135: 2137

The BRIGHT 1003 study specifically sought out higher risk patients (to ensure that they truly were not intensive chemotherapy candidates). Consistent with this, compared to studies 1-4 above, the BRIGHT 1003 study enrolled patients with a worse PS, a larger proportion of secondary vs. *de novo* AML, and a higher proportion of cases with high risk cytogenetics. In addition, fully ~67% of patients had 'severe' cardiac disease (baseline EF <45%), and ~20% had baseline renal function abnormalities. Overall, 71% and 27% of patients met ≥2 and ≥3 high risk criteria, respectively. These are not patients that would normally be considered for a clinical trial.

Similar to study 5 above (and in contrast to studies 1-4), the BRIGHT 1003 study also included patients who had received prior hypomethylating agents. These patients define another high risk group.

Consistent with the above higher risk patient status, the LDAC alone arm of the BRIGHT 1003 study (median age, 76 [range 68-83]) demonstrated a CR rate of only 2.3%, compared with 18% in the MRC AML14 study (median age, 74 [range 54-90]). In this light, the CR rate of the BRIGHT 1003 glasdegib + LDAC arm (median age, 77 [range 64-92]) - 17% - is quite remarkable in comparison. Similarly, median OS in the glasdegib + LDAC group (8.8 m) was > 2X longer than in MRC AML14, and the proportion of patients surviving at 6 and 12 months were 59.8% and 39.5%, respectively, compared to 36.3% and 22.7% in MRC AML 14.

Another notable observation in the BRIGHT 1003 and MRC AML 14 studies, is that the glasdegib + LDAC combination is more effective in poor risk cytogenetics cases than is LDAC alone, suggesting that glasdegib is able to expand the spectrum of activity of LDAC to patients with higher cytogenetic risk.

So while BRIGHT 1003 was a phase II study, with relatively small numbers, the differences in CR rates and survival in the LDAC vs. glasdegib + LDAC arms were clinically and statistically significant. In addition, while we acknowledge that comparisons among trials are only suggestive at best, the outcomes observed in the BRIGHT 1003 glasdegib + LDAC arm were much better than would be expected in such a high risk AML population.

We would argue, therefore, that in contrast to the pERC conclusion, there is actually a clear net clinical benefit of glasdegib in combination with LDAC, compared with LDAC alone, in adult patients with newly diagnosed and previously untreated AML, who are 75 years or older or who are not eligible to receive intensive induction chemotherapy. Moreover, speaking as leukemia treaters, we suggest that the magnitude of this OS benefit is highly relevant clinically.

ii. Quality-of-Life (QoL)

We agree that the toxicities of glasdegib in combination with LDAC are similar to those of LDAC alone, and are quite manageable. We also acknowledge the lack of formal QoL data. However, as leukemia treaters, we are absolutely certain that the benefit of glasdegib + LDAC extends to improved QoL.

First, in AML care, it is axiomatic that the achievement of CR is accompanied by improved QoL Thus, the >7X higher CR rate in the glasdegib + LDAC arm is associated with improved QoL in the patients achieving CR.

Second, improved QoL is also commonly seen in a subset of patients not achieving CR. A recent *post-hoc* analysis of BRIGHT 1003 study data (Cortes J *et al*. *J Hematol Oncol* 2020; 13:92) reports that In patients who did not achieve CR, the addition of glasdegib to LDAC improved OS compared to LDAC alone (5.0 m vs 4.1 m, respectively (p= 0.0182). Additionally, more non-CR patients receiving glasdegib + LDAC achieved durable recovery of absolute neutrophil count (≥ 1000/µl, 45.6% vs 35.5%), hemoglobin (≥ 9 g/dl, 54.4% vs 38.7%), and platelets (≥ 100,000/µl, 29.8% vs 9.7%). Overall, transfusion independence was achieved by 15.0% and 2.9% of non-CR patients receiving glasdegib + LDAC and LDAC alone, respectively.

To leukemia treaters, it is clear that improvement in cytopenias and transfusion independence are associated with improved QoL (fewer infections, fewer hospital admissions, fewer clinic/transfusion unit visits, decreased travel time, etc.).

iii. Glasdegib + LDAC vs. Azacitidine

We acknowledge that there are no direct comparisons of glasdegib + LDAC vs. azacitidine. A number of indirect comparisons have been presented, however. For example, an indirect comparison of glasdegib + LDAC (BRIGHT 1003) vs. Azacitidine alone (AZA-MDS-001, and AZA-AML-001 [see i. above]), that takes into account the higher risk status of the BRIGHT 1003 patients, suggests that glasdegib + LDAC may be preferable to azacitidine as a treatment option for previously untreated, chemotherapy-ineligible, acute myeloid leukaemia patients, irrespective of bone marrow blasts count (Abstract #EP626; 25th European Hematology Association Annual Congress (EHA25 Virtual), June 11-14, 2020).

Another consideration in this regard, is that 14% of the patients in BRIGHT 1003 (and 29% of patients in Viale-C [see i. above]) had received prior treatment for MDS with a hypomethylating agent (azacitidine or decitabine), and thus would not be candidates for azacitidine after progression to AML. For such patients, azacitidine would not be 'another relevant treatment option'.

So while there are no direct comparisons of glasdegib + LDAC vs. venetoclax, indirect comparisons do not support the notion that azacitidine is preferable (rather, the opposite conclusion is supported), and in any case, only a subset of patients receiving glasdegib + LDAC would even be candidates for azacitidine.

iv. Unmet Need

We disagree with the pERC statement that it was unclear whether glasdegib in combination with LDAC addresses an unmet need, 'given the availability of azacitidine'.

We would argue strongly that the glasdegib + LDAC combination does address an unmet need.
First, we disagree with the term 'availability of azacitidine'. Azacitidine is not approved in Canada for AML with >30% marrow blasts. So it is not available for a large proportion of patients. While LDAC is generally available for patients with >30% marrow blasts, based on the MRC AML14 study [see i. above] it has only little efficacy as a single agent in cases with high risk cytogenetics (37% of patients in BRIGHT 1003).

Second, as azacitidine is a standard treatment for higher risk MDS, many patients with secondary AML will already have failed prior azacitidine (in some reports >20% overall), and thus are not candidates for further drug. For such patients, an approach containing LDAC is generally the only option, and as stated above, LDAC + glasdegib is clearly superior to LDAC alone.
Third, LDAC + glasdegib offers a number of additional, important advantages that should not be dismissed. Specifically, Canadian physicians would be particularly likely to choose LDAC in patients,

i. who are intolerant of azacitidine;

ii. who have received azacitidine for an antecedent hematological disorder such as a myelodysplastic syndrome, and subsequently progressed to AML;
iii. for whom distance and travel issues are problematic. While LDAC can be given at home, either by home care, or via self-administration, azacitidine can be given only in a hospital or clinic setting. The travel and caregiver requirements needed to attend the cancer clinic 7 days in a row on a monthly basis are often prohibitory, especially for older patients living at a distance. That the ability of LDAC to facilitate hospital avoidance in older patients is an added advantage, has become apparent during the recent COVID-19 pandemic;
iv. who express a preference for LDAC

And in addition, for the glasdegib + LDAC combination

v. toxicities are manageable;
vi. eligibility for use is not restricted by patient age;
vii. can be used in frail patients with cardiac and renal issues, and poor performance status

We would argue that taken together, points i. - vii. clearly indicate that the glasdegib + LDAC combination does address an unmet need.

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Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
No editorial comments to provide			

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