pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Enasidenib (Idhifa) **Submitted Reimbursement Request:** For the treatment of adult patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation	
Submitted By: Celgene Inc.	**Manufactured By:** Celgene Inc.
NOC Date: February 6, 2019	**Submission Date:** April 5, 2019
Initial Recommendation: August 29, 2019	**Final Recommendation:** October 31, 2019

Approximate per Patient Drug Costs, per Month (28 Days)	Cost per 100 mg tablet (and daily cost) of enasidenib: $1,216.00 28-day cost: $34,048.00

pERC RECOMMENDATION

☐ **Reimburse**

☐ **Reimburse with clinical criteria and/or conditions***

☒ **Do not reimburse**

* If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC does not recommend the reimbursement of enasidenib for the treatment of adult patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation.

pERC made this recommendation because it was unable to conclude, based on the available non-randomized non-comparative trial, that there is a net clinical benefit of enasidenib compared with other treatments. While pERC noted that there is a need for effective treatments in this setting and that enasidenib produces some anti-tumour activity, the Committee noted that there was a high level of uncertainty in the magnitude of benefit of enasidenib compared with available treatment options with regard to outcomes important to decision-making, such as overall survival (OS), event-free survival (EFS), and quality of life (QoL).

The Committee concluded that enasidenib aligns with patient values in that it manages some disease-related symptoms and offers ease of administration. However, pERC noted that the impact of enasidenib on patients' QoL compared with other treatments is uncertain.

pERC concluded that, at the submitted price, enasidenib was not cost-effective compared with conventional care regimens (CCRs) (azacitidine; seven-days cytarabine and three-days daunorubicin; low-dose cytarabine; best supportive care only). Additionally, there was considerable uncertainty in the cost-effectiveness estimates because of the lack of robust direct or indirect comparative effectiveness data in the submitted economic evaluation.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Possibility of Resubmission to Support Reimbursement** pERC noted that there is an ongoing phase III, multi-centre, open-label, randomized study comparing the efficacy and safety of enasidenib versus CCRs in patients 60 years or older with R/R AML after second- or third-line AML therapy and positive for an IDH2 mutation. pERC noted that data from this trial could form the basis of a resubmission to pCODR if comparative efficacy data important to decision-making such as OS, QoL, complete remission (CR) and EFS are available.

SUMMARY OF pERC DELIBERATIONS

There were 1,509 newly diagnosed cases of AML in Canada in 2017, and approximately 12% of these cases harbour the IDH2 mutation. Up to 50% of patients with AML have refractory disease or have relapsed after achieving remission. Patients with R/R AML have a poor prognosis, with only 5% to 10% of patients being alive after five years. If left untreated, the median OS may be two to three months. Younger, fit patients may receive re-induction chemotherapy with 7 + 3 (cytarabine and daunorubicin) or fludarabine-cytarabine-filgrastim-idarubicin (FLAG-IDA), followed by allogeneic transplantation. Treatment options are limited for older patients and include low-dose cytarabine, azacitidine, or best supportive care. Therefore, pERC acknowledged that there is a need for effective treatment options to improve patient health outcomes in this setting.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated on one single-arm, open-label phase I/II trial (AG221-C-001) that evaluated the safety and efficacy of enasidenib for the treatment of adult patients with R/R AML with an IDH2 mutation; specifically, pERC reviewed pooled data from patients in the phase I expansion (who met the eligibility criteria of phase II [i.e., cohorts 1 and 2]) or phase II parts of the study who received a 100 mg daily dose of enasidenib. pERC noted that limited conclusions could be drawn because of the lack of a comparator arm in the trial and the uncertainty of the long-term benefit of enasidenib given the short follow-up. pERC considered that the rate and duration of CR, duration of EFS, the proportion of patients who proceeded to stem cell transplant, and the OS for the pooled phase I/II population and for those who proceeded to stem cell transplant observed in Study AG221-C 001 appeared to be promising; however, pERC noted that there was uncertainty around the magnitude of the clinical benefit because of the limitations from the non-comparative trial. Furthermore, pERC noted that the impact of enasidenib on QoL is unknown, as it was not measured in Study AG221-C-001. Additionally, pERC discussed the safety profile of enasidenib and noted that the most frequently reported enasidenib-related Grade 3 or 4 treatment-emergent adverse events (TEAEs) were (less than 7%): IDH differentiation syndrome, anemia, increase in blood bilirubin, dyspnea, thrombocytopenia, decrease in platelet count, and tumour lysis syndrome. pERC considered enasidenib to be well tolerated. pERC also noted favourable transfusion independence with enasidenib, which pERC felt translated to less hospitalization, less fatigue, and less bruising. Overall, pERC could not confidently conclude that the available evidence demonstrated a net clinical benefit of treatment with enasidenib. Although pERC agreed there is anti-tumour activity with enasidenib, there was considerable uncertainty in the magnitude of benefit given the lack of comparative data and long-term outcome data on outcomes important for decision-making, such as OS, QoL, CR, and EFS. pERC agreed with the Clinical Guidance Panel (CGP) that overall response rate (ORR) was not felt to be a clinically significant outcome by itself as there is no evidence that a favourable ORR translates to improved OS. Upon reconsideration, pERC discussed the feedback from the sponsor regarding the maturity and certainty of the clinical evidence submitted and agreed with the CGP. Both pERC and the CGP noted the short median follow-up and that results were derived from a single non-randomized phase I/II trial with a relatively small number of patients, a number of biases that could not be controlled, no comparison with commonly used treatments (e.g., azacitidine), and no QoL data. pERC also discussed the sponsor's feedback regarding the maturity and certainty of the duration of treatment and agreed with the CGP that enasidenib should be given for a minimum of six months to allow for clinical response and that the results of the ongoing phase III trial will provide clarity on the duration of treatment. Furthermore, pERC discussed the sponsor's feedback noting that the OS results of patients achieving CR, CR with incomplete hematologic response, and CR with incomplete platelet recovery should be considered clinically significant. pERC noted the CGP's response, which reiterated its overall conclusion that there may be clinical benefit to enasidenib. pERC agreed that the patients with IDH2-mutated R/R AML who have achieved CR or CR with incomplete hematologic response seem to derive benefit when comparing the effect estimated in the study with historical survival rates; however, the Committee reiterated the limitations of the phase I/II study. In addition, pERC discussed the sponsor's feedback related to ORR and red blood cell and platelet transfusion independence. pERC reiterated that ORR was not felt to be a clinically significant outcome by itself as it has not been shown to correlate with either OS or QoL. pERC acknowledged that achievement of a durable CR was a more accepted surrogate

for clinical benefit than ORR in acute leukemias. With respect to transfusion independence, pERC reiterated that transfusion independence rates were favourable and acknowledged the importance of this outcome for patients. Overall, pERC reiterated that it could not confidently conclude that the available evidence demonstrated a net clinical benefit of treatment with enasidenib.

pERC discussed the sponsor's indirect comparison, which used a propensity score matching (PSM) analysis to compare the efficacy of enasidenib with CCRs in the France chart review study: a retrospective, observational, multi-centre study of adult patients with R/R AML and an IDH2 mutation. pERC noted that the PSM analysis results suggested that treatment with enasidenib could result in a statistically significant improvement in OS and EFS as compared with CCRs. pERC noted that there were a variety of chemotherapy combinations used in the PSM analysis (5-azacitadine, cytarabine, '7+3' chemotherapy, cytarabine and clofarabine, cytarabine and amsacrine, cytarabine with mitoxantrone and gemtuzumab ozogamicin, cytarabine with daunorubicin and gemtuzumab, clofarabine, decitabine, mercaptopurine, and no treatment), some of which are not currently used in Canada, however, the treatment mix selected from the PSM analysis [CCRs: azacitidine, 7-days cytarabine and 3-days daunorubicin (7+3), low-dose cytarabine; best supportive care only] for the economic model matched the current Canadian context. pERC also noted that a key limitation of the analysis was that the generalizability of the reported results was extremely limited due to the loss of patients in the treatment arm as a result of the matching process (e.g., trial patients with two or more prior treatments were excluded). As a result, pERC concluded that limited conclusions can be drawn from the PSM analysis. pERC discussed the feedback from the sponsor regarding the generalizability of the reported results and limitations of the PSM analysis noted by the Methods team and pERC agreed with the Methods team's specific concerns related to the generalizability of the reported results and noted that the sponsor's comments about missing data were acknowledged in the Initial Clinical Guidance report which noted that missing data were minimal despite the fact that there were no imputation analyses performed for missing data. Overall, pERC reiterated that limited conclusions can be drawn from the PSM analysis.

pERC also discussed that it is feasible to conduct a randomized controlled trial (RCT) of enasidenib versus currently available treatment options in the R/R setting as there is an ongoing phase III, multi-centre, open-label, randomized study (AG-221-AML-004) comparing the efficacy and safety of enasidenib with CCRs (azacitidine, cytarabine, or best supportive care) in patients 60 years or older with R/R AML after second- or third-line AML therapy and positive for an IDH2 mutation. pERC acknowledged that this ongoing phase III study will provide comparative efficacy data important to decision-making and noted that data from this trial could form the basis of a resubmission to pCODR. Upon reconsideration, pERC discussed the sponsor's feedback regarding the availability of the phase III study data and agreed with the CGP that results from the ongoing phase III clinical trial will help better define the role of enasidenib for patients with R/R IDH2-mutated AML.

pERC discussed the registered clinician input that noted that enasidenib would be a much-needed option for patients with R/R AML with IDH2 gene mutation. pERC also noted that both registered clinicians and the CGP stated that enasidenib may be used as a bridge to stem cell transplant. pERC discussed that a proportion of patients proceeded to transplant, and that the median survival of these patients was more favourable than the pooled phase I/II cohort in Study AG221-C-001 (23.6 months versus 8.8 months). pERC considered this to be promising evidence. pERC noted the registered clinician's feedback that enasidenib would be a nice-to-have option, and also noted that it acknowledged the limitations in the submitted non-randomized trial.

pERC deliberated on patient group input, which indicated that patients with AML value treatments that can manage disease-related symptoms and improve QoL. pERC noted that patients who provided input had no experience with or knowledge of enasidenib but understood that patients expected that most of the cancer-related symptoms they experienced would be managed by enasidenib. pERC discussed that enasidenib is an oral treatment, which may be easier to take and would not require as much personal and caregiver time and as many resources (e.g., trips to the hospital) compared with receiving IV or subcutaneous chemotherapies. pERC acknowledged that the favourable transfusion independence with enasidenib may translate to less hospitalization, less fatigue, and less bruising for patients. pERC concluded that enasidenib aligns with patient values as it manages some disease-related symptoms and offers ease of administration, which may translate to improved QoL. However, pERC noted that the impact of enasidenib on patients' QoL compared with other treatments is unknown. pERC discussed the feedback from the patient group regarding the benefit of enasidenib and noted patients' desire for additional treatment options for this patient population. pERC acknowledged that the results of the phase

I/II trial are promising and agreed that there is a need for effective therapeutic options for patients with R/R IDH2-mutated AML. pERC reiterated that the results from the phase III clinical trial will help better define the role of enasidenib and identified the possibility of resubmission in the future to support reimbursement for patients with R/R IDH2-mutated AML.

pERC deliberated upon the cost-effectiveness of enasidenib and concluded that enasidenib is not cost-effective when compared with CCRs. pERC noted that the Economic Guidance Panel's (EGP's) incremental cost-effectiveness ratio (ICER) estimate was substantially greater than the sponsor's base case as a result of the changes made by the EGP using the actual enasidenib treatment duration from the trial, the EFS modeled with individual Weibull curves, a five-year time horizon, the costs of all patients with R/R AML receiving next-generation sequencing (NGS) panel at least one time to identify the IDH2 mutation, and the local current price for a day in the hospital. pERC noted several limitations in the submitted analysis, particularly, the indirect comparison informing the economic model had considerable limitations, the uncertainty of treatment duration with enasidenib, and the lack of robust indirect or direct comparative effectiveness estimates for OS, all of which resulted in uncertainty in the ICER estimate. pERC also considered that enasidenib has an extremely high cost and would need a substantial price reduction to improve the cost-effectiveness.

pERC considered the feasibility of implementing a positive funding recommendation for enasidenib. In terms of the patient population, pERC noted that enasidenib in the first-line setting was out of scope, although evidence to use enasidenib as a bridge to transplant was promising. In terms of the implementation factors, pERC agreed with PAG that the oral route of administration is an enabler to implementation. As well, pERC noted that although there is a very small population of R/R AML patients with an IDH2 mutation, the potential budget impact could be large given the high cost of enasidenib. pERC noted that CGP and registered clinicians indicated that testing to identify IDH2 mutations would be required for eligibility and would be performed at diagnosis and/or at relapse. pERC acknowledged that IDH2 is not routinely tested in all provinces and implementation of IDH2 testing would be required if enasidenib were to be reimbursed.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated:

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis (BIA)
- guidance from the pCODR clinical and economic review panels
- input from one patient group: Leukemia & Lymphoma Society of Canada
- input from three individual registered clinicians: one clinician from Ontario; one clinician from British Columbia; and one clinician from Alberta
- input from PAG.

Feedback on the pERC Initial Recommendation was also provided by:

- one patient group: Leukemia & Lymphoma Society of Canada
- one clinician from Ontario
- PAG
- the sponsor: Celgene Inc.

The pERC Initial Recommendation was to not recommend reimbursement of enasidenib for the treatment of adult patients with R/R AML with an IDH2 mutation. Feedback on the pERC Initial Recommendation indicated that PAG and the registered clinician agreed with the recommendation and both support early conversion to the Final Recommendation. The sponsor and the patient group disagreed with the Initial Recommendation and did not support early conversion to the Final Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of enasidenib for the treatment of adult patients with R/R AML with an IDH2 mutation.

Studies included: One single-arm trial — Study AG221-C-001

The pCODR systematic review included one single-arm trial.

Study AG221-C-001 consisted of two phases (three stages): phase I dose escalation, phase I expansion, and phase II. Phase I dose escalation (which was primarily conducted to determine the safety and the maximum tolerated dose of enasidenib in patients with advanced hematologic malignancies) was followed by an expansion phase that included four cohorts of patients with R/R AML harbouring IDH2 mutations, including:

- Cohort 1: 60 years of age or older with R/R AML, or any age if they relapsed after hematopoietic cell transplantation
- Cohort 2: younger than 60 years with R/R AML and no prior transplantation
- Cohort 3: 60 years of age or older with untreated AML and ineligible for induction chemotherapy
- Cohort 4: patients who were ineligible for cohorts 1 to 3

The primary objective of phase II (single-arm design) was to assess the efficacy of enasidenib for the treatment of patients with R/R AML harbouring an IDH2 mutation. Patients in the phase I expansion and phase II cohorts were treated with a 100 mg daily dose of enasidenib until disease progression or unacceptable toxicity.

Patient populations: Adults 18 years and older with IDH2 mutation

Key inclusion criteria included adult (18 years of age or older) patients with advanced myeloid malignancies (AML or MDS with refractory anemia), have documented IDH2 gene-mutated disease, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, a platelet count of 20,000/μL or higher, and adequate hepatic and renal function. Key exclusion criteria included central nervous system leukemia; hematopoietic stem cell transplant within 60 days prior to the first dose of enasidenib,

post- hematopoietic stem cell transplant immunosuppressive therapy at screening, or clinically significant graft-versus-host disease; systemic anticancer therapy or radiotherapy within 14 days prior to the first dose of enasidenib; and protocol-defined cardiovascular conditions.

Between September 20, 2013, and September 01, 2017, 345 patients were enrolled in the study and received one or more doses of enasidenib. A total of 280 patients with R/R AML and an IDH2 mutation participated in the study; of these, 214 (76.2%) patients received 100 mg of enasidenib daily (in the phase I expansion and phase II parts of the study). These 214 patients were enrolled in the pooled phase I/II analyses. The median age of patients in the pooled analysis was 68 (range, 19 to 100) years, with the majority being white (76.6%) and having a baseline ECOG performance score of 1 (61.7%). The cytogenetic risk status was intermediate risk in 50.5% and poor-risk in 25.78%. All patients had received prior systemic anticancer therapies, with a median of 2.0 (range, 1.0 to 5.0) anticancer regimens.

Key efficacy results: Promising evidence from phase I/II study

The median treatment duration for the phase I/II pooled population was 4.6 months, and mean treatment duration was 7.45 months. The median follow-up was 7.8 months for the phase I/II pooled population, and the median follow-up was 5.8 months for the phase II population.

The key efficacy outcomes (data cut-off September 01, 2017) deliberated by pERC included CR, EFS, duration of response (DOR), OS, and transfusion independence.

The CR rate was estimated to be 19.6% in the phase I/II pooled population, with a median DOR of 7.4 months. For the phase II population, the CR rate was 20.0%, with a median DOR of 6.7 months.

The median duration of EFS was reported to be 4.7 months (95% confidence interval [CI], 3.7 to 5.6) in the pooled phase I/II population. Among the 19 patients who proceeded to transplant, there were four EFS events and the median EFS was calculated to be 9.6 months (95% CI, 8.4 to 9.6) based on the four events.

The median OS for the pooled phase I/II population was 8.8 months (95% CI, 7.7 to 9.6). In the phase II population, the median OS was estimated to be 7.0 months (95% CI, 4.9 to 8.8). Among the 19 patients who proceeded to transplant, median OS was 23.6 months (95% CI, 10.6 to not reached).

Of the 214 study participants, a total of 106 (49.5%) remained or became red blood cell independent of red blood cell transfusions, and 115 (53.7%) remained or became platelet transfusion independent, while receiving enasidenib treatment.

The ORR for the phase I/II pooled population was 38.8%; ORR was not felt by the CGP to be a clinically significant outcome by itself as it has not been shown to correlate with either OS or QoL.

pERC noted that the CGP disagreed with the sponsor's statement that the clinical evidence is "very mature and associated with a high degree of certainty." First, the CGP noted that the median follow-up duration was short at 7.8 months (range, 0.4 to 43.6). Second, CGP detailed in the clinical guidance report that the results are derived from a single non-randomized phase I/II clinical trial that enrolled a relatively small number of patients. This introduces a number of biases that cannot be controlled for in a phase I/II trial. Third, the CGP acknowledged that the results do not allow a comparison with treatments that are routinely used in this patient population (e.g., azacitidine). Fourth, the CGP noted that the study did not include any data on health-related QoL, an important consideration in patients with AML. Although the CGP feels that enasidenib may possibly have a favourable impact on survival, it stated that there remains significant uncertainty about the effect of enasidenib for patients with R/R IDH2-mutated AML.

As well, the sponsor stated that OS results for patients achieving a CR, those achieving a CR with incomplete hematologic response, and those achieving a CR with incomplete platelet recovery were clinically significant. pERC noted that in the CGP's response to the sponsor, it reminded the sponsor of its conclusion that "there may be clinical benefit to enasidenib," recognizing the limitations of the data available (phase I/II study). The CGP acknowledged that the results suggest that patients with IDH2-mutated R/R AML who have achieved CR or CRi or with incomplete hematologic response may derive significant benefit when comparing the effect estimated in the study to historical survival rates. However, the results are derived from a small number of patients and the fact remains that there is very significant uncertainty around the therapeutic effect of enasidenib in this patient population. Moreover,

there was no comparator group (e.g., azacitidine), so it is unclear how these results might compare with other treatment options. The CGP reiterated that the therapeutic impact of enasidenib in patients who achieve CR/CRi will be examined in the ongoing phase III clinical trial and this should help to better define the therapeutic effect of enasidenib in patients with R/R IDH2-mutated AML. pERC reiterated that the results from the phase III clinical trial will help better define the role of enasidenib and identified the possibility of resubmission in the future to support reimbursement for patients with R/R IDH2-mutated AML.

Patient-reported outcomes: Not collected

No data on the patient-reported/QoL outcomes were collected in the AG221-C-001 study.

Limitations: Ongoing single-arm, open-label study with no adjustment for multiplicity, no patient-reported outcomes collected

- AG221-C-001 was a single-arm study with no active treatment or placebo control groups.
- The open-label nature of the study could have introduced the risk of reporting and performance biases, as the study participants and the investigators were aware of the study intervention (i.e., enasidenib). This could be particularly important in recruitment of patients, their subsequent care, attitudes of patients to the treatments, reporting of subjective outcomes (e.g., adverse events) by the patients and care providers, handling of withdrawals and protocol violations, or exclusion of data from analysis.
- No adjustments were made for multiplicity introduced by analyzing secondary end points or subgroup analyses. Therefore, these analyses are considered exploratory. Multiple testing can increase the probability of type I error and, therefore, lead to false-positive conclusions.
- Patient-reported QoL outcomes have not been measured in the AG221-C-001 study.
- AG221-C-001 is an ongoing trial; therefore, the duration of follow-up for a proportion of patients might not be lengthy enough to make an inference on long-term survival benefits.
- The investigator-assessed ORR was the primary efficacy end point in the AG221-C-001 study. Based on the evidence and discussions from the FDA and American Society of Hematology joint workshop, the FDA reviewer suggested that achievement of a durable CR was a more acceptable surrogate for clinical benefit than ORR in acute leukemias.

In the absence of a trial directly comparing enasidenib with a relevant comparator, the sponsor conducted an indirect treatment comparison using a PSM analysis to compare the efficacy of enasidenib in Study AG221-C-001 (n = 214) with the efficacy of CCRs in the France chart review study (n = 103). This study was a retrospective, observational, multi-centre study of adult patients with R/R AML and an IDH2 mutation. The results of this analysis were used to inform the sponsor's pharmacoeconomic evaluation.

Patients in the two study groups were matched based on their individual propensity scores, using 1:1 optimal matching. After matching, 69 patients remained in each of the enasidenib and CCRs groups. The PSM analysis results suggest that treatment with enasidenib could result in statistically significant improvements in OS (hazard ratio: 0.62; 95% CI, 0.40 to 0.95) and EFS (average hazard ratio: 0.66; 95% CI, 0.44 to 0.99) as compared with CCRs. The results suggest that enasidenib may offer clinically relevant benefits for patients with R/R AML and an IDH2 mutation when compared with CCRs. However, these results should be interpreted with caution.

PSM Analysis Limitations:

- The generalizability of the reported results is extremely limited due to the loss of patients in the treatment arm as a result of the matching process (e.g., trial patients with two or more prior treatments were excluded).
- The method used for the PSM analysis was based on the estimation of average treatment effect among the untreated (ATU) population (i.e., France chart review population). This might also limit the generalizability of the results, as the trial population (treated with enasidenib) is the population of interest for this review.
- The definition of baseline for the untreated sample does not match well with the baseline status of patients in the treatment group regarding the number of previous treatments.
- Bias due to imbalance in unmeasured confounders is a potential limitation to these results. Key factors that are listed in the submitted PSM analysis report as unmeasured confounders (such as IDH2 mutation location, creatinine clearance at baseline, National Comprehensive Cancer Network risk stratification) were not included in the matching.

- Imbalance remained after matching for the cytogenetic risk profile. Patients in the France chart review study appear to have a better cytogenetic risk profile than the trial population, after matching. The results of the analysis can be misleading, given that the ATU represents the effect of the drug (enasidenib) on patients in the France chart review population that tend to be more likely to respond to enasidenib (due to a better cytogenetic risk profile). It was suggested in the submitted PSM analysis report that the residual imbalance was attributable to the small number of patients available for the PSM analysis and patient characteristics (predominantly older patients with advanced stage disease). pERC noted that the Methods team was specifically concerned about the following generalizability issues:
  - The submitted ATU analysis represents the effect of the enasidenib on patients in the France chart review population who tend to be more likely to respond to enasidenib (due to a better cytogenetic risk profile). Patients in the France chart review study appear to have had a better cytogenetic risk profile than the trial population, after matching. After PSM, 83% of patients in the France chart review study appear to have had an intermediate cytogenetic risk profile when compared with 59% of patients in the trial population.
  - In the AG221-C-001 study, 30.4% of patients received two prior regimens and 22.4% received three or more prior therapies. Treated patients with two or more prior treatment lines were excluded from the ATU analysis as a result of matching.
- Patients with missing data were excluded from the PSM analysis, and there were no imputations for missing data. The submitted report indicated that missing data were minimal, as none of the patients in Study AG221-C-001 and only two patients in the France chart review study were excluded due to missing data.

Safety: Well tolerated but considered preliminary given non-comparative study design

Of the 214 patients treated with the 100 mg dose, a total of 91 (42.5%) patients had one or more suspected treatment-related Grade 3 or 4 TEAEs. The most frequently reported enasidenib-related Grade 3 or 4 TEAEs were IDH differentiation syndrome (6.5%), anemia (5.6%), increase in blood bilirubin (5.1%), dyspnea (4.2%), thrombocytopenia (3.3%), decrease in platelet count (2.3%) and tumour lysis syndrome (1.9%). TEAEs leading to permanent discontinuation of the study treatment were reported for 36 (16.8%) patients; nine (4.2%) of which were assessed by investigators as enasidenib-related. The most frequently reported TEAEs that led to discontinuation (occurring in 1.0% or more of patients) were sepsis (2.3%), leukocytosis (1.9%), and respiratory failure (1.4%). No deaths due to adverse events were reported.

Need and burden of illness: Need for effective treatment options

There were 1,509 newly diagnosed cases of AML in Canada in 2017, and approximately 12% of these cases harbour the IDH2 mutation. Up to 50% of patients with AML have refractory disease or have relapsed after achieving remission. Patients with R/R AML have a poor prognosis, with only 5% to 10% of patients being alive after five years. If left untreated, the median OS may be 2 to 3 months. Younger, fit patients may receive re-induction chemotherapy with 7 + 3 (cytarabine and daunorubicin) or fludarabine-cytarabine-filgrastim-idarubicin (FLAG-IDA), followed by allogeneic transplantation. Treatment options are limited for older patients and include low-dose cytarabine, azacitidine, or best supportive care.

Registered clinician input: Much-needed option for patients with R/R AML with IDH2 gene mutation and may be used as a bridge to transplant

Treatment options are limited in older patients with R/R AML, while younger, fit patients may receive re-induction chemotherapy with allogenic transplant. Clinicians agreed that enasidenib would be a much-needed option for patients with R/R AML with the IDH2 gene mutation who normally show very poor prognosis. According to clinicians providing input, the new treatment seems appropriate for the target population and may be sequenced after relapse and before the currently used conventional therapies. It may also be used as a bridge to stem cell transplant. Efficacy is regarded as favourable, while toxicity appears comparable with other treatments. Clinician input indicated that testing with NGS to identify IDH2 mutations would be required for eligibility; it may be performed at diagnosis and/or at relapse.

pERC noted that the registered clinician said that enasidenib would be a nice-to-have option for the IDH2-mutated population but recognized the issues with the costs and the nature of the phase II data. pERC noted that the CGP agreed with the registered clinician's comment that there is a need for effective therapeutic options for patients with R/R IDH2-mutated AML. As noted previously, the ongoing phase III clinical trial will help better define the role that enasidenib may play in the management of patients with R/R IDH2-mutated AML, as the present phase I/II study does not include QoL evaluation or a comparator.

PATIENT-BASED VALUES

Values of patients with AML: Managing disease-related symptoms and improving QoL

A total of 12 individuals who had experience with AML participated in the online survey. It was unknown if these patients had R/R AML or if they had the IDH2 mutation. All respondents were adult Canadians, and one respondent was a caregiver for an approximately 10-year-old patient.

From a patient's perspective, fatigue was the most commonly reported (reported by all survey respondents) symptom related to AML that had an impact on their day-to-day living. Other reported symptoms resulting from AML included pain, bruising and/or bleeding, rashes/skin changes, loss of appetite, and physical and emotional intimacy issues. Patients with AML value managing disease-related symptoms and improving QoL.

All of the patients who responded to the Leukemia & Lymphoma Society of Canada survey had received treatment. Three patients were on induction or consolidation therapy and nine patients were off treatment. All respondents had received chemotherapy; four had also received a stem cell transplant, and two were waiting for a stem cell transplant. No further details on the chemotherapy regimens were provided.

The most common treatment side effects that were reported by patients included pain, nausea and vomiting, fatigue, infections or non-cancer illness, and fertility and sexual side effects. Seven respondents experienced infections or other non-cancer illnesses during treatment, presumably due to immunosuppression. The youngest patient reported a serious case of anthracycline-induced cardiomyopathy, while other respondents reported staph infections, skin infections, gum infections, or viral infections.

Patient values on treatment: No patients with experience with enasidenib

None of the survey respondents had experience with or knowledge of enasidenib. They expected that most of the cancer-related symptoms (e.g., fatigue, loss of appetite, pain, rashes or skin changes, fever and/or night sweats, bruising and/or bleeding, and numbness or tingling) they experienced would be managed by the new drug. With respect to expectations of side effects, patients indicated that they would be more willing to tolerate short-term side effects like nausea, diarrhea, edema and loss of appetite, as opposed to more severe side effects like pain, bruising, and bleeding. In general, patients were prepared to tolerate short-term side effects if the benefits outweighed the risks.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analysis

The cost-effectiveness and cost-utility analysis submitted to pCODR by Celgene Inc. compared enasidenib with CCRs (27.6%, azacitidine; 17.4%, 7-days cytarabine and 3-days daunorubicin (7+3); 14.4%, low-dose cytarabine; 40.6%, best supportive care only) for patients with R/R AML with an IDH2 mutation.

Basis of the economic model: partitioned-survival model

The submitted model was a partitioned-survival model. Patients in the model were assigned to one of three health states: EFS, progressed disease (PD), and death. OS was partitioned into EFS and PD states, and modeled with extrapolated regression curves. In each cycle of the model, the proportion of patients in the PD state was calculated as the difference between OS and EFS.

Enasidenib efficacy outcomes (OS and EFS) were based on enasidenib using only data from the phase I/II clinical trial AG221-C-001 (n = 214). CCRs efficacy outcomes (OS and EFS) were based on the France chart review (n = 71), where patients were receiving a mixture of CCRs for the treatment of R/R AML IDH2. Relative efficacy was derived from an indirect treatment comparison using PSM methodology of enasidenib compared with CCRs (n = 69 per treatment arm). There were a variety of chemotherapy combinations used in the PSM analysis (5-azacitadine, cytarabine, '7+3' chemotherapy, cytarabine and clofarabine, cytarabine and amsacrine, cytarabine with mitoxantrone and gemtuzumab ozogamicin, cytarabine with daunorubicin and gemtuzumab, clofarabine, decitabine, mercaptopurine, and no treatment), some of which are not currently used in Canada, however, the treatment mix selected from the PSM analysis [CCRs: azacitidine, 7-days cytarabine and 3-days daunorubicin (7+3), low-dose cytarabine; best supportive care only] for the economic model matched the current Canadian context. Rates of adverse events were obtained from Study AG221-C-001 and literature for AML for CCRs. Health-

related QoL for health states and adverse events were based on estimates identified from a literature review. Costs for health states, adverse events, and subsequent therapy (one per patient) were based on Ontario unit costs and clinical opinion for resource utilization.

Drug costs: High cost of enasidenib compared with CCRs

Recommended dosage of enasidenib is one 100 mg tablet daily for at least six months until disease progression or unacceptable toxicity.

Cost per 100 mg tablet (and daily cost) of enasidenib: $1,216.
28-day cost: $34,048.

CCRs weighted mixture within a typical Canadian clinical practice of available treatments for AML in Canada
28-day cost: $1,556.90.

Cost-effectiveness estimates: Uncertainty in the clinical effectiveness estimates

The main cost drivers are the cost of enasidenib based on treatment duration, and the costs for blood product transfusions in the progressed state. The main benefit for enasidenib in terms of QoL are the increased time until disease progression and increased OS. The parameters with the largest effect on the ICUR based on assumptions and tested in sensitivity analysis by the sponsor were choice of extrapolation survival model for OS and EFS, enasidenib treatment duration, time horizon, and choice of utility values for PD state and off treatment.

Limitations with the submitted economic evaluation that could not be addressed in reanalysis include:

- The economic model was built on comparative data that was not generated with RCT evidence.
- There is an absence of long-term data for OS. Meanwhile, the time period for EFS is short and the trial period captured most of the EFS events.
- The economic model does not incorporate the full experience of the patient. This includes having more than one extra line of subsequent therapy (the model only allows one subsequent therapy and only costs are included), or using enasidenib to extend time and stabilizing the patient to allow for the curative stem cell transplantation.

The EGP's best estimate of incremental cost and incremental effect for enasidenib when compared with conventional care regimen is $566,858 per quality-adjusted life-year (QALY). The extra cost of enasidenib is $204,090. The main source of extra costs is for enasidenib drug treatment and increased transfusion of blood products in the prolonged progressive state of the disease. The extra clinical effect of enasidenib is 0.36 QALYs. The increased QALYs occur because of prolonged EFS and prolonged period in the progressed state.

EGP's overall conclusions of the submitted model: The economic model was limited in its scope due to limited available evidence. This includes not having enough published evidence to support building a more complex model that captures the patient's life-time horizon experience of drug sequencing with more than one line of AML therapy, and stem cell transplantation. In addition, the main efficacy outcomes were estimated without RCT evidence, but instead were generated with an indirect comparison after PSM and regression analysis of a small sample size. Within the submitted economic model, the assumptions that lead to large changes in the incremental cost-utility ratio estimates were choice of extrapolation model for long-term OS, enasidenib treatment duration, and choice of utility values for disease states.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Very small population, but potentially large budget impact given the high cost of enasidenib

The BIA was based on a national payer perspective. Inputs that greatly increased in the budget impact were: increased IDH2 mutation prevalence rate, increased enasidenib treatment duration, and increased AML prevalence.

pERC discussed the sponsor's feedback which stated that the duration of treatment is mature with a high degree of certainty; thus, the reported duration of treatment is a very robust estimate. pERC agreed with the CGP that enasidenib should be given at a minimum of six months to allow for clinical response and

currently data supporting a longer treatment duration does not exist. As a result, both pERC and CGP believed that the results of the ongoing phase III trial will provide clarity on the duration of treatment.

Key limitations of the BIA included: uncertain estimation of the prevalence of R/R AML and possible changes in the rates of IDH2 testing. In addition, the degree of market uptake is unknown because this would be the first targeted therapy for this patient population. These parameters were tested in the sensitivity analysis in the sponsor's BIA.

pERC considered the feasibility of implementing a positive funding recommendation for enasidenib. In terms of the patient population, pERC noted that enasidenib in the first-line setting was out of scope, although evidence to use enasidenib as a bridge to transplant was promising. In terms of the implementation factors, pERC agreed with PAG that the oral route of administration is an enabler to implementation. As well, pERC noted that although there is a very small population of R/R AML patients with an IDH2 mutation, the potential budget impact could be large given the high cost of enasidenib. pERC noted that CGP and registered clinicians indicated that testing to identify IDH2 mutations would be required for eligibility and would be performed at diagnosis and/or at relapse. pERC acknowledged that IDH2 is not routinely tested in all provinces and implementation of IDH2 testing would be required if enasidenib were to be reimbursed.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. At the time of the Initial Recommendation, pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Henry Conter, Dr. Avram Denburg, Dr. Christian Kollmannsberger, Dr. W. Dominika Wranik, and Dr. Matthew Cheung, who were not present for the meeting
- Daryl Bell, who did not vote due to his role as a patient member alternate.

At the time of the Final Recommendation, pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Michael Crump, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Final Recommendation, except:

- Dr. Maureen Trudeau and Dr. Kelvin Chan, who were not present for the meeting
- Daryl Bell, who did not vote due to his role as a patient member alternate.

Avoidance of conflicts of interest

All members of the pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of enasidenib for AML, through their declarations, seven members had a real, potential, or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members was excluded from voting.

Information sources used

pERC is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient group and Provincial Advisory Group input, as well as original patient group input submissions, to inform its deliberations. pCODR Guidance Reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR Guidance Reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this recommendation document.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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