CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Enasidenib (Idhifa) for Acute Myeloid Leukemia

October 31, 2019

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding enasidenib for acute myeloid leukemia (AML). The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding enasidenib for AML conducted by the Leukemia Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on enasidenib for AML, a summary of submitted Provincial Advisory Group Input on enasidenib for AML, and a summary of submitted Registered Clinician Input on enasidenib for AML, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

Enasidenib (IDHIFA) is indicated for the treatment f adult patients with relapsed or refractory Acute Myeloid Leukemia (R/R AML) with an isocitrate dehydrogenase-2 (IDH2) mutation; Health Canada has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit.[1]

The reimbursement request is in line with the Health Canada approved indication.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

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.[2-4]

Phase I dose escalation, which was primarily conducted to determine the safety and the maximum tolerated dose (MTD) of enasidenib in patients with advanced hematologic malignancies, was followed by an expansion phase that included four cohorts of patients with relapsed or refractory acute myeloid leukemia (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 1-3

The primary objective of Phase II (single arm design) was to assess the efficacy of enasidenib for 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.

The primary analysis was performed using data from the 15-April-2016 cut-off date, when 173 out of 176 patients with R/R AML had completed at least 6 cycles of treatment or discontinued earlier (i.e., met the protocol-specified duration of follow up for the primary analysis). An updated analysis of the study data was performed at the data cut- off date of 01-September-2017. The efficacy analyses at this data cut-off used data from the combined Phase I/II population for efficacy (i.e., patients who received 100 mg/day of enasidenib in phase I or II). Safety analysis used data from all patients from the Phase I/II study.

Between 20-September-2013 and 01-September-2017, 345 patients were enrolled in the study and received ≥ 1 dose of enasidenib. A total of 280 patients with R/R AML and an IDH2 mutation participated in the study; of whom, 214 (76.2%) patients received 100 mg of enasidenib daily (in the Phase I expansion and Phase II parts of the study).[3] 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 to100) years, with the majority being White (76.6%), had a baseline Eastern Cooperative Oncology Group (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.

As of the 01-September-2017data cut-off date, 329 (95.4%) of 345 study participants discontinued treatment and 16 (4.6%) patients were still receiving treatment. Of the 105 patients in Phase II, 99 (94.3%) patients discontinued treatment. The most common reasons for treatment discontinuation in phase II included disease progression (41.4%), AEs (16.2%), death (15.2%), and bone marrow transplant (9.1%).

Efficacy

The pooled efficacy analyses used data from the 01-September-2017 data cut-off, with a median treatment duration of 4.6 (range 0.3 to 34.1) months, and a median follow-up duration of 7.8 (range 0.4 to 43.6) months.[5] The most common reasons for treatment discontinuation included disease progression (41.4%), AEs (16.2%), death (15.2%), and bone marrow transplant (9.1%).

A summary of the key efficacy results from the pooled analyses of AG221-C-001 are presented in Table 1.1. Data are presented using the 01-September-2017 data cut-off date unless otherwise specified.

Overall Response Rate (ORR)

The investigator-assessed ORR was the primary efficacy endpoint in the AG221-C-001 study. In the in the Phase I/II pooled population (N=214), the ORR was 38.8% with a duration of response (DOR) of 5.6 months. The estimated ORR met the pre-specified criteria outlined in the Sponsors statistical analysis plan for clinically meaningful activity, as the lower bound of the 95% CI was higher than 25%.[3,5] The median time to first response was 1.9 (range 0.5 to 9.4) months, and median time to best response was 3.7 (range 0.6 to14.7) months.[3]

Complete Remission (CR) Rate

The CR rate was estimated to be 19.6% in 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 CR rate plus the rate of complete remission with incomplete hematologic response (Cri/CRp) was 29.0% in the Phase I/II pooled population, with a median DOR of 6.7 months. For the Phase II population, the CR+ CRi/CRp rate was 31.4% with a median DOR of 6.75 months.[3,5]

Event-Free Survival (EFS)

The median duration of EFS was reported to be 4.7 months (95% CI 3.7, 5.6) in the Pooled Phase I/II population.[3]

Overall Survival

At the 01-September-2017 data cut-off, after a median follow-up of 7.8 months, the median OS for the pooled phase I/II population was 8.8 months (95% CI 7.7, 9.6).[3] In the Phase II population, with a median follow-up of 5.8 months, the median OS was estimated to be 7.0 months (95% CI 4.9, 8.8).[5]

Transfusion Independence

Of the 214 study participants, a total of 106 patients (49.5%) remained or became RBC independent of RBC transfusions, and 115 patients (53.7%) remained or became platelet transfusion independent, while receiving enasidenib treatment.[3,5]

Quality of Life (QOL)

No data on the patient-reported/QoL outcomes were collected in the AG221-C-001 study.[5]

Harms Outcomes

The median duration of treatment for patients with R/R AML who received 100 mg enasidenib was 4.6 months.[5]

Of the 214 patients treated with the 100 mg dose, a total of 91 (42.5%) patients had ≥ 1 suspected treatment-related Grade 3 or 4 TEAE (Table 6.9). The most frequently reported enasidenib-related Grade 3 or 4 TEAEs were IDH differentiation syndrome (6.5%), anemia (5.6%), blood bilirubin increased (5.1%), dyspnea (4.2%), thrombocytopenia (3.3%), platelet count decreased (2.3%), tumor lysis syndrome (1.9%). TEAEs leading to permanent discontinuation of the study treatment were reported for 36 (16.8%) patients; 9 (4.2%) of which were assessed by investigators as enasidenib-related. The most frequently reported TEAEs that led to discontinuation (occurring in ≥ 1.0% of patients) were sepsis (2.3%), leukocytosis (1.9%), and respiratory failure (1.4%). Deaths due to AEs were not reported.[5]

Table 1.1: Highlights of Key Outcomes

Study Outcomes	Study AG221-C-001	
	Pooled Phase I/II (N= 214)†	Phase II (N= 105)††
Primary Outcome, ORR		
% (95% CI)	38.8 (32.2, 45.7)	37.1 (27.9, 47.1)
DOR (months), median (95% CI)	5.6 (3.8, 7.4)	5.6 (3.7, 7.4)
Key Secondary Outcomes		
CR rate		
% (95% CI)	19.6 (14.5, 25.6)	20.0 (12.8, 28.9)
DOR (months), median (95% CI)	7.4 (6.5, 16.3)	6.7 (3.7, 7.4)
Time to first response (months)		
median (95% CI)	2.8 (0.5, 9.4)	2.7 (0.9, 7.5)
Time to best response (months)	3.8, (0.6, 14.7)	3.7 (0.9, 12.8)
median (95% CI)		
EFS		
Median, months (95% CI)	4.7 (3.7, 5.6)	NR
OS		
Events, n (%)	157 (73.4)	79 (75.2)
Median, months (95% CI)	8.8 (7.7, 9.6)	7.0 (4.9, 8.8)
Transfusion independence, n (%)		
RBC	106 (49.5%)	50 (47.6%)
Platelet	115 (53.7%)	53 (50.5%)
Patient-Reported Outcomes/ HRQoL	NR	

Harm Outcomes, n (%)		
Grade ≥3 TEAEs	91 (42.5%)	NR
Grade ≥3 TRAEs	91 (42.5%)	NR
TEAEs leading to permanent discontinuation	36 (16.8%)	NR
Death due to AE	NR	NR

AE = adverse event; **CI =** confidence interval; **CR** = complete remission; **EFS** = event-free survival; **HRQoL =** health-related quality of life, **NR** = not reported; OS = overall survival; **RBC** = red blood cell; **TEAEs** = treatment-emergent adverse events; **TRAE** = treatment-related adverse event
† median duration of follow up = 7.8 months
†† median duration of follow up = 5.8 months

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

One patient input was provided to pCODR through a patient advocacy group submission from the Leukemia & Lymphoma Society of Canada (LLSC) for enasidenib for the treatment of adult patients with R/R AML with IDH2 mutation. Information was obtained via an online survey publicized on LLSC's Facebook accounts and sent to individuals on their mailing list. Overall, 12 individuals with experience with AML completed the survey: three responses from patients currently on treatment and nine from patients no longer receiving treatment. All respondents were Canadian and ranged from 20-29 to 70-79 years of age. One respondent was a caregiver of a ~10 year-old patient. It is unknown if these patients had refractory or relapsed AML or if they were found positive for the IDH2 mutation, as this was not captured in the survey.

From a patient's perspective, fatigue was the most commonly reported (reported by all survey respondents) symptom related to AML that has an impact on their day-to-day living. Other reported symptoms resulting from AML included pain, skin problems, loss of appetite and sexual/intimacy issues. Patients with AML value managing disease-related symptoms and improving quality of life.

At the time of completing the survey, all respondents reported receiving or having received chemotherapy, with some also getting a stem cell transplant. Temporary side effects were experienced by patients under treatment, with infections being particularly noted. Patients had no experience with or knowledge of enasidenib. They expected that most of the cancer-related symptoms they experienced would be managed by the new drug. Overall, they were willing to tolerate short-term side effects from the drug if the benefits outweighed the risks.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Eligible patient population

Economic factors:

- Additional monitoring and management of treatment-related toxicities

Registered Clinician Input

Three clinician inputs were provided for enasidenib for adult patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation. All three inputs were submitted by individual clinicians. A summary of the input is provided below.

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 R/R AML patients with the IDH2 gene mutation, who normally show very poor prognosis. According to clinician 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 to other treatments. Clinician inputs indicate that testing with next generation sequencing to identify IDH2 mutations would be required for eligibility; it may be performed at diagnosis and/or at relapse.

Feedback on the initial recommendation from a registered clinician was received; the registered clinician agreed with the initial recommendation and expressed that enasidenib would be nice to have an option for the IDH2 mutated population but recognizes the issues with the costs and the nature of the phase 2 data. The CGP agree with the registered clinician's comment in that there is a need for effective therapeutic options for patients with R/R IDH2-mutated AML. This is acknowledged by the CGP in the initial clinical guidance report. As noted previously, the ongoing phase 3 clinical trial will allow one to better define the role that enasidenib may play in the management of patients with R/R IDH2-mutated AML, since the present phase I/II study does not include QOL evaluation and does not provide a comparator.

Summary of Supplemental Questions

The following supplemental issue was identified as relevant to the pCODR review of enasidenib in patients with R/R AML and an IDH2 mutation:

- Issue 1: Summary and critical appraisal of the propensity score matching analysis of enasidenib using the AG221-C-001 trial versus conventional care regimen using a France chart review of refractory or relapsed acute myeloid leukemia patients with an IDH2 mutation

In the absence of a trial directly comparing enasidenib with a relevant comparator, the Sponsor conducted an indirect treatment comparison using a propensity score matching (PSM) analysis to compare the efficacy of enasidenib in Study AG221-C-001 (n= 214)[3] to the efficacy of conventional care regimens in the France chart review study (n=103). The France Chart Review retrospective, observational, multicentre study of adult patients with R/R AML and an IDH2 mutation.[6,7] 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 CCR groups. The PMS analysis results suggest that treatment with

enasidenib could result in a statistically significant improvements in OS (HR: 0.62, 95% CI: 0.40 – 0.95) and EFS (average HR: 0.66, 95% CI: 0.44 – 0.99) as compared to CCR. The results suggest that enasidenib may offer clinically relevant benefits for patients with R/R AML and an IDH2 mutation when compared to CCR. However, these results should be interpreted with caution due to the following limitations:

- 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 ≥ 2 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 (T0) 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 [NCCN] risk stratification, etc.) 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, since the ATU represents the effect of the drug (enasidenib) on patients France Chart review population that 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).[5]

- Patients with missing data were excluded from the PSM analyses, and no imputation for missing data. The submitted report indicated that missing data 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.

See section 7.1 for more information.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for enasidenib

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="5">Population</td><td>Performance Status</td><td>The AG221-C-001 trial limited eligibility to ECOG PS 0-2. Approximately 92% of patients had ECOG PS of 0 or 1.
<table><tr><th>ECOG PS at Baseline (%)</th><th>Pooled Phase I/II population</th></tr><tr><td>0</td><td>22.9</td></tr><tr><td>1</td><td>61.7</td></tr><tr><td>2</td><td>15.0</td></tr><tr><td>Missing</td><td>0.4</td></tr></table></td><td>Does performance status limit the interpretation of the trial results (efficacy or safety) with respect to the target population (in Canadian clinical practice)?</td><td>Exclusion criteria based on PS are very reasonable and reflect what would be done clinically.
Treatment with enasidenib would be restricted to patients with ECOG PS 0-2.</td></tr>
<tr><td>Age</td><td>The median age was 68 (range 19 to 100) years.</td><td>Do the trial results apply to all adult patients?</td><td>From a clinical and pathophysiological perspective, it is reasonable to assume that the results of the trial apply to all adult patients. The trial included patients aged 19 to 100.</td></tr>
<tr><td>Cytogenic risk status</td><td>The cytogenetic risk status was intermediate risk in 50.5% and poor-risk in 25.78%.
<table><tr><th>Cytogenic Risk Status (%)</th><th>Pooled Phase I/II population</th></tr><tr><td>Intermediate</td><td>50.5</td></tr><tr><td>Poor</td><td>25.7</td></tr><tr><td>Failure</td><td>3.3</td></tr><tr><td>Missing</td><td>20.6</td></tr></table></td><td>Does the proportion of patients with various cytogenetic risk levels in the trial limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice patients)?</td><td>The proportion of patients with the various cytogenetics mutations enrolled in the trial reflect what we would have observed in the clinical setting.</td></tr>
<tr><td>Eligibility for other curative therapies</td><td>Patients who were eligible for potentially curative therapies, such as stem cell transplant, were excluded from the AG221-C-001 trial enrollment.</td><td>Did the exclusion of patients who were potential candidates for standard therapy or bone marrow transplantation limit the interpretation of the trial results with respect to the target population?</td><td>It is not specified in the manuscript what proportion of patients with R/R AML were excluded from the study because they were eligible to other treatment (e.g. targeted therapy, SCT, etc.). This leaves place to selection bias which may affect the validity and generalizability of the results. However, only a fraction of the patients with R/R AML have effective alternatives so that the CGP feel that the effect of this bias is likely marginal.</td></tr>
<tr><td>Relapsed or refractory status</td><td>In the AG221-C-001 trial, 39.3% of patients were primary refractory, and 60.7% had a</td><td>Does the proportion and age of patients</td><td>Although the proportion of</td></tr>
</table>

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		relapsed disease. Patients who were refractory to induction chemotherapy were reported to be younger (median age 60.5 years) than patients who were refractory to lower intensity regimens and those who relapsed following prior AML therapy. Patients who were refractory to non-intensive regimens were older (median age 74.0 years) and more likely to have had a prior diagnosis of MDS.	with relapsed and refractory disease in the trial limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice patients)?	**patients with relapsed or refractory disease reported in the trial is may differ to what is found in the Canadian setting, the AG221-C-001 trial does not find statistically significant different in OS results between patients who had primary refractory vs relapse disease, suggesting that these differences are unlikely to affect the results** **The difference in age for patients who had primary refractory disease after induction chemotherapy compared to those who received low-dose chemotherapy introduces potential confounding variable that may have biased the study results.** **It is likely that the age as well as the proportions of patients with refractory and relapsed AML in the AG221-C-001 trial differs to that in the found in the real world setting, which could affect the external validity of the study results.** **The proportion and demographics, including age, of patients with relapse of refractory AML in the trial is likely to differ compared to that**

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
				reported in the clinical trial. This creates uncertainty on the results. It is not possible for the CGP to quantify the impact of these differences on the results. The phase III study currently conducted would address these limitations.
	Number of prior therapies	In the AG221-C-001 trial, 47.2% of patients received one prior regimen, 30.4% received two prior regimens, and 22.4% received three or more prior therapies. Patients who were in relapse were most likely to have received multiple prior AML regimens.	Does the proportions of prior AML treatments received by patients in the trial limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice patients)?	**The study found statistically significant differences in median OS (See figure 3 of supplemental) between patients who had received 1 vs 2 vs ≥ 3 prior regimens. It is reasonable to imagine that the proportion of patients who have received prior number of regimens differs from that of the Canadian general population and that this may have affect the external validity of the results.**
Comparator	Standard of care	AG221-C-001 was a single-arm trial (i.e., no comparator). The sponsor provided an indirect treatment comparison (propensity score analysis) of enasidenib with standard of care including number of therapies used to treat R/R AML in a chart review study that was conducted in France.[5] These included: 5-azacytidine, 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.	Is the comparator used in the **France Chart Review study** applicable in the Canadian setting?	**The sponsor relied on the use of a Propensity Score analysis matching characteristics of the study patients to ones that were collected in the France Chart Review study.[5] In the absence of a comparator population derived from a randomized clinical trial, the France Chart Review offers the best comparison for the AG221-C-001 study patients. The France Chart**

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
				Review data included patients who had recently been treated, in a country where the management of patients with R/R AML is comparable. The CGP did highlight the fact that there will be variation in regiments at different sites based on availability, institutional preference and funding, although these differences are not likely to have a significant impact of the outcomes. **Because significant differences in the characteristics between the AG221-C-001 and the France Chart Review patients, this led to a low number of matched patients which affects the validity of the results.**
Outcomes	Appropriateness of primary and secondary outcomes	The primary efficacy endpoint of the AG221-C-001 trial was overall response rate (ORR)†. The secondary CR rate, duration of response, time to response, event-free survival, overall survival, transfusion dependence rate, and safety.	Were the primary and secondary outcomes appropriate for the trial design?	**OS is an appropriate outcome and is of paramount importance clinically. However, ORR (CR rate and duration of response) are not felt by the CGP to be a clinically significant outcomes by themselves since they have not been showed to correlate with either OS nor QoL.**

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Setting		The AG221-C-001 trial was conducted in 21 centres in the United States and France.	Do the trial results apply to patients from Canadian centres? Are different treatment practices expected in Asian countries which may impact the generalizability of the overall trial results in Canada?	**The management of R/R AML in the USA, France and Canada are very similar although there are the subtle regional differences in the use of second- and third-line chemotherapy which are unlikely to have a significant impact on the results.**

1.2.3 Interpretation

1. Burden of Illness and need:

There were 1509 new diagnosis cases of AML in Canada in 2017[8] and approximately 12% of these cases harbor the IDH2 mutation.[9] Up to 50% of patients with AML have either refractory disease or relapse after having achieved remission. Patients with relapse and refractory (R/R) AML have a poor prognosis with only 5-10% of patients being alive after 5 years.[10,11] The management of patients with R/R AML is very resource intensive and is associated with a poor quality of life (QoL) for affected patients. The current treatments are rarely effective and there is a significant unmet need for effective treatment options.

Enasidenib is a selective inhibitor of isocitrate dehydrogenase-2 (IDH 2) that is approved by Health Canada for the treatment of patients with relapse/refractory AML who have the IDH2 mutation. The notice of compliance is with conditions, pending the results of trials to verify its clinical benefit.

2. EFFECTIVENESS:

The evidence of the effectiveness of enasidenib in the treatment of patients with R/RIDH2-mutated AML is derived from a single arm, Phase I-II clinical trial. There currently does not exist any completed randomized study comparing the effectiveness of enasidenib with the standard of care in this patient population. The phase III RCT (AG-221-AML-004) comparing the effectiveness of enasidenib to conventional care regimen will only be completed in 2020.[12] The data of the patients included in the AG221-C-001 Phase I expansion and Phase II study will be reviewed below.

The phase I expansion consisted of 4 cohorts of patients with R/R AML harboring the IDH2 mutation:
Cohort 1: 60 years or age or older with R/R AML, or any age if they relapsed after hematopoietic stem cell transplantation
Cohort 2: younger than 60 years with R/R AML and no prior transplantation
Cohort 3: 60 year of age or older with untreated AML and ineligible for induction chemotherapy
Cohort 4: patients who were not eligible for Cohorts 1-3.
The AG221-C-001 phase II study is a single arm design of patients with R/R AML harboring the IDH2 mutation aimed to assess the efficacy of enasidenib for patients with R/R AML harboring the IDH2 mutation. The study enrolled patients with R/R AML who were 18 years or older and who harbored the IDH2 mutation. The patients included had relapsed after stem cell transplantation, received 2 or more treatments, failed induction or re-induction

and relapsed before 1 year. The subjects included in the AG221-C-001 study correspond to the adult patient population for which this submission was prepared.

Patients were treated with enasidenib 100 mg daily until disease progression or unacceptable toxicity. A total of 214 patients with R/R AML and harboring the IDH2 mutation received enasidenib 100 mg daily. The average age was 68 (range 19-100) years and most had an ECOG score of 1 (61.7%) and 15% had an ECOG of 2. There were 50.5% percent of the patients who had intermediate risk cytogenetics and 25.78% with poor-risk cytogenetics. All patients had received at least one prior anticancer therapy with a median of 2.0 (range 1.0 to 5.0) anticancer regiments. Patients received a median of 4.6 months of treatment (range 0.3 to 34.1) and a median follow-up duration of 7.8 (range 0.4 to 43.6) months.

The measurement of overall response rate was done as a primary objective, however as noted previously, ORR are not felt by the CGP to be a clinically significant outcomes by themselves since they have not been showed to correlate with either OS nor QoL.

The measurement of the overall survival was done as a secondary objective and the study found that the median OS for the patients enrolled in the study was 8.8 months (95% CI 7.7-9.6). This is significant and compares favorably with that of historical data documenting OS of 2-3 months as noted by the registered clinicians in adult patients with R/R AML.

The measurement of complete remission was also done as a secondary objective. The AG221-C-001 trial showed impressively that up to 19.6% that of these heavily pretreated patients achieved complete remission after treatment with enasidenib with a median duration of remission of 7.4 months. There are no completed randomized studies directly comparing the efficacy of enasidenib in patients with IDH2-mutated AML. The sponsor presented an indirect treatment comparison analysis to inform the comparative efficacy in terms of EFS and OS of enasidenib as compared with conventional care for the management of IDH2-mutated R/R AML. Real world evidence (RWE) using individual patient data from chart audit from 9 centers in France were collected for 103 patients. These patients had received a variety of different therapies, including 5-azacitidine, 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.

Using a propensity score matching (PSM) method, the clinical impact of enasidenib derived from the AG221-C-001 trial was compared to outcomes from patients treated by conventional care regimen from the France chart review study. The sponsor did match the patients’ characteristics to ensure that the demographics were well balanced for a large number of covariates for the two groups.

The PSM was used to generate OS and EFS KM curves with matched data sets for both enasidenib and CCR and found that the survival rates were clinically significantly much better in patients who were treated with enasidenib (3 and 12 months survival rates of 82% and 51% in the enasidenib group vs 71% and 35% in the CCR group). The survival times were also substantially better in patients treated with enasidenib with median survival times of 12.42 months (95% CI: 8.25-19.90) and 6.77 months (95% CI: 4.27-10.90) for patients treated with enasidenib vs CCR.

The size of the effect of enasidenib compared to CCR in terms of OS is substantial and clinically significant but the results need to be interpreted with caution given the

limitations of the method used; The limitations are described in detail in the method section. Most importantly, the PSM analysis rely on very few subjects since patients that were not matching were excluded from the analysis, including all those with ≥ 2 prior treatments. Also, a significant limitation is that there remains important imbalance in the patients' characteristics; a list of important potential confounders that were not included in the matching and clinically important characteristic such as the cytogenetic did not match (e.g. patients that were treated with enasidenib had worst cytogenetic profiles) possibly introducing a selection bias that can affect the measured effect size. Finally, the AG221-C-001 trial only had a short follow-up (median follow-up 9.7 months, range 3.7-20.8 months) so that there remains significant uncertainly on the long-term benefits of enasidenib. The patients included in the study had a median age of 68 and this corresponds to what is expected clinically in the real-world setting. However, the comorbidity profile is not specified, and this could potentially affect the external validity of the study.

Despite the uncertainly around the effect size of the treatment with enasidenib in patients with IDH2-mutated R/R AML, the improvement in overall survival in treated patients compares very favorably to what has been described historically and it most probable that treatment with enasidenib has clinically significant effects.

There was no data on patient-reported QoL outcomes, however, the study did look at transfusion independence and found that up to 106 (49.5%) of patients treated with enasidenib remained or became RBC-transfusion independent and 115 (53.7%) remained or became platelet transfusion independent. This, along with the fact that enasidenib is an oral medication with a toxicity profile that is favorable leads the clinical guidance panel to believe that enasidenib may have a favourable QoL as a result of this. It is not feasible for the CGP to specify the impact of enasidenib of QoL.

The ongoing phase III (AG-221-AML-004) clinical trial comparing the efficacy of enasidenib to CCR in patients with IDH2-mutated R/R AML will allow a determination of the therapeutic effect of enasidenib in the treatment of patients with IDH2-mutated R/R AML.[12]

3. Safety:
Enasidenib was overall well tolerated in the trial, with only 36 patients (16.8%) needing to terminate treatment because of treatment-related side-effects, mostly due to sepsis (in 2.3% of treated patients). Grade 3 and 4 toxicities included hyperbilirubinemia (12% of patients) and differentiation syndrome that occurred in 7% of patients.

4. Need:
Patients with IDH2-mutated R/R AML have a very poor prognosis and there is no standard approach to manage of these patients. Based on historical data, patient with R/R AML have a very poor prognosis and there is a clear need for effective therapy to improve patient's health outcomes.

1.3 Conclusions

The Clinical Guidance Panel concluded that there may be a net clinical benefit to enasidenib compared to conventional care for the treatment in patients with IDH2-mutated R/R AML based on a small Phase I/II clinical trial which demonstrated clinically significant OS benefit, impressive CR response in highly pretreated patients, and favourable transfusion independence.

No data on QoL were collected but enasidenib was well tolerated with a toxicity profile that was acceptable in this patient population. Patients with IDH2-mutated R/R AML who are eligible for further treatment are relatively rare but there is a clear unmet need in the treatment of these patient and enasidenib would partially fill that need. The requested reimbursement criteria align with the patient population included in the Phase I-II trial and with the NOC/c from Health Canada. According to clinician 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 can also be used as a bridge to stem cell transplant. The CGP made the above conclusions based on the points outlined below.

- There is significant uncertainty on the degree and nature of the therapeutic benefit of enasidenib given the absence of phase III clinical trial. In making the above conclusions, the Clinical Guidance Panel took into the consideration the following:
- There results are derived from a single arm, phase II study. In the absence of control arm, it is not possible to differentiate the treatment effect from other determinants of response or survival.
- This was an open label study and is prone to reporting and performance biases by virtue of being open.
- There are no long-term data available
- There are no data on health related Qol.
- There is an ongoing Phase III trial comparing the efficacy of enasidenib to CCR in patients with IDH2-mutated R/R AML which may answer the question regarding the therapeutic effect of enasidenib compared with CCR.

Feedback on the initial recommendation from the sponsor was received; the sponsor disagreed with the initial recommendation and stated that 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; and noted 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. The CGP disagree with the sponsor's comment that the clinical evidence are "very mature and associated with a high degree of certainty". For one, the median follow-up duration was short at 7.8 months (range 0.4 to 43.6). Second, as detailed in the clinical guidance report, the results are derived from a single non-randomized phase I/II trial clinical that enrolled a relatively small number of patient. This introduces the number of biases that can't be controlled for in a phase I/II trial. Third, the results do not allow the comparison to treatment that are used routinely in this patient population (e.g. azacitidine).
Fourth, the study did not include any data on HRQOL, an important consideration in patients with AML. Although CGP feel that enasidenib quite possibly may have a favorable impact on survival, there remains significant uncertainty on the effect of enasidenib on patients with R/R IDH2-mutated AML.

Feedback on the initial recommendation from the sponsor was received; the sponsor noted that for patients achieving a CR, the median OS was 22.9 months (13.2, NE) and those achieving a CR+CRi/CRp (31.4%), the median OS was 18.2 months (11.8, 25.6). The sponsor stated that these were clinically significant results given that the 5-year OS after first relapse is approximately 6% for those > 55 years of age (Forman, 2013). The CGP reminds the sponsor of their conclusions that 'there may be clinical benefit to enasidenib,' recognizing the limitations of the data available (Phase I-II study). The CGP does acknowledge that the results suggest that patients with IDH2-mutated R/R AML who have achieved CR/CRi seem to derive significant benefit and that these effect size estimated in the study when comparing to historical survival. However, there results are derived from a small number of patients (<100) and the fact remains that there is very significant uncertainty around the therapeutic effect of enasidenib in this patient population (see

CGP response in paragraph above to Sponsor's feedback). Moreover, there was no comparator (e.g. azacitidine) and so it is unclear how these results might compare to other treatment options. Certainly, the therapeutic impact of enasidenib in patients who achieve CR/CRi will be examined in the ongoing Phase III clinical trial and this should allow one to better assess the therapeutic effect of enasidenib in patients with R/R IDH2-mutated AML.

Additional implementation considerations requested by the Provincial Advisory Group (PAG):

1. If enasidenib use in first-line for previously untreated mutant-IDH2 AML is appropriate, PAG is seeking guidance on whether enasidenib would be given with standard first-line treatment, recognizing that this may be out of scope of the current review of enasidenib in the relapsed or refractory setting.
    - Based on the funding request and reviewed submission information (Phase I/II study), the new treatment seems appropriate for the target population and may be sequenced after relapse and before the currently used conventional therapies. There is no evidence that enasidenib is better than standard of care in the first line setting in patients with mutant-IDH2 AML. Enasidenib in the first line setting in patients with mutant-IDH2 AML would need to be empirically tested for CGP to provide recommendation.
2. PAG is also seeking guidance on the use of enasidenib for patients with relapsed or refractory AML with an IDH2 mutation in second relapse as a bridge to transplant or after transplant following a relapse.
    - Among the 19 patients who proceeded to transplant, median OS was 23.6 months (95% CI, 10.6 to not reached; there were 4 EFS events and the median EFS was calculated to be 9.6 months (95% CI, 8.4, 9.6) based on the 4 events. Based on this evidence presented, CGP believe that enasidenib can be used as a bridging agent.

3. If recommended for reimbursement, PAG noted that patients currently on other treatments for relapsed/refractory AML (e.g., chemotherapy) who have not progressed, would need to be addressed on a time-limited basis.

    - If patients are responding to treatment (i.e. without evidence of progression), most physicians would continue current treatment and not switch patients if patient is responding and has no evidence of progression. There are no data to inform switching to enasidenib if patients are responding to current treatment.

4. PAG noted the dosing schedule for enasidenib is until disease progression or unacceptable toxicity. For patients without disease progression or unacceptable toxicity, enasidenib is recommended for a minimum of six months to allow time for clinical response. PAG is seeking clarity on treatment duration and definition of disease progression.
    - CGP reiterated that enasidenib should be given at the minimum of six months to allow for clinical response; there does not exist data supporting longer treatment duration. The results of the ongoing phase III trial will provide clarity on the duration of treatment. Of note, the median treatment duration was 4.6 (range 0.3 to 34.1) months, and the median follow-up duration was 7.8 (range 0.4 to 43.6) months (01-September-2017 data cut-off).
    - Upon feedback on the initial recommendation the sponsor stated that the duration of treatment is mature with a high degree of certainty and thus, the reported duration of treatment is a very robust estimate. CGP reiterates that enasidenib should be given at the minimum of six months to allow for clinical

response and there does not exist data supporting longer treatment duration. The results of the ongoing phase III trial will provide clarity on the duration of treatment.

5. PAG noted that there is no standard of care for this patient population and limited treatment options are available. PAG noted in the pivotal trial, the majority of patients had received two or more prior AML-directed regimens. PAG is seeking confirmation that it is reasonable to offer enasidenib at any point in the relapsed or refractory setting (i.e., first, second, or later relapse).

    - Yes. The trial allowed for patients to receive one prior regimen, two prior regimens, and three prior regimens or more.

6. PAG had concerns related to the turnaround time for IDH2 testing, how testing is performed, and whether IDH2 is a de novo mutation or an acquired mutation. PAG is seeking clarity if patients tested positive for the IDH2 mutation at diagnosis, whether treatment with enasidenib would be reserved until the relapsed setting. With respect to IDH2 testing, how are patients currently being testing for IDH2 mutations? When should testing be completed (i.e., at diagnosis or at time of relapse)? Please identify other considerations for implementation of IDH2 testing (i.e., turnaround time).

    - CGP recognize that there is variability in access to IDH2 testing across Canada. It would be advisable to retest at the time of relapse, but this should not be mandatory. As such, eligible patients only need to have been shown to be positive for the IDH2 mutation at any point during the course of their disease.

7. Are patients with mutant IDH2 Myelodysplastic syndromes (MDS) with excess blasts and who are refractory be eligible to treatment with enasidenib as these patients were not outlined in the reimbursement request? Are patients 60 years and over with untreated AML and ineligible for induction chemotherapy eligible as these patients were not outlined in the reimbursement request.

    - Based on the study protocol:

    a. Patients with mutant-IDH2 MDS who had refractory anemia with excess blasts were part of the inclusion criteria for phase I dose escalation. MDS patients were also included in phase I expansion and phase II parts, but there is no mention of refractory anemia with excess blast.

    b. Untreated AML, ≥60 years of age and are not candidates for, or declined, standard therapy were eligible for inclusion in phase I dose escalation and expansion parts. Patients included in phase II were disease relapsed or refractory.

    - There does not exist any data suggesting that enasidenib is more effective than BSC in patients with IDH2-mutated AML that have not been treated prior. Likewise, there are no data showing clinical efficacy of enasidenib in patients with MDS. However, the CGP does note that, from a pathophysiology perspective, patients with MDS excess blasts would be likely to respond to treatment with enasidenib. This conclusion is based on a clinical opinion and not from empirical data.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Leukemia Tumour Group Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

AML is an aggressive hematological malignancy that presents with signs or symptoms of bone marrow failure (fatigue, dyspnea, bleeding, bruising or infection), organ infiltration, central nervous system and systemic complaints (chiefly fevers, fatigue, night sweats). Patients typically present to hospital acutely ill. The diagnosis of AML is confirmed by bone marrow histology and ancillary tests like cytogenetics and molecular testing.

In Canada the age adjusted incidence of AML is approximately $3.75/10^5$. In 2017 there were 1509 new cases of AML reported in Canada with a median age at diagnosis of 66 years, with just over a quarter of diagnoses in those over the age of 75. AML is uncommon in children with an age adjusted incidence of $7.2/10^6$.[8]

AML represents a heterogenous group of disorders with similar clinical presentations but variable prognosis. AML is classified according to the World Health Organization (WHO)Classification of Tumors of the Haematopoetic and Lymphoid Tissues.[13] The WHO classification is a combined clinicopathological and molecular genetic classification. One subtype of AML, Acute Promyelocytic Leukemia, is sufficiently distinct from a prognostic and therapeutic perspective that it will not be further discussed in this background section. Commonly associated mutations in AML include mutations in *FMS-Like Tyrosine Kinase 3 (FLT3)* FLT3 gene and mutations in Nucleophosmin 1 (NPM1) both of which are found in approximately 30% of AML patients. Approximately 12% of adult patients harbor a mutation in isocitrate dehydrogenase 2 (IDH2).[9]

The prognosis of patients with AML is primary driven by age at diagnosis, such that patients who are older tend to fair less well and the molecular genetic risk category of the AML. AML patients are stratified into those with favorable, intermediate and adverse risk primarily mediated by the molecular genetic profile of the AML.[14]

2.2 Accepted Clinical Practice

Left untreated, AML is uniformly fatal with survival ranging from weeks to months. The back bone of successful therapy remains intensive multidisciplinary supportive care including transfusion support, antimicrobial prophylaxis and management of tumor lysis syndrome.

While there are no overarching national Canadian guidelines on the management of AML several international guidelines harmonize with practice in Canada.[14-16] In younger fit patients initial induction remission involves combination chemotherapy (7 days of cytarabine and 3 days of anthracycline therapy (7+3)). There is evidence to support the combination of gemtuzumab ozogamicin with 7+3 in prolonging progression free and overall survival in patients with AML.[17] Gemtuzumab ozogamicin for this indication is under review by PCODR. For patients that harbor a FLT3 mutation combining midostaurin with standard remission induction (7+3) and consolidation chemotherapy is associated with an overall survival benefit. Midostaurin has been reviewed by pCODR and is funded in Canada for this indication.[18]

In younger fit patients the goal of remission induction therapy is to achieve a complete remission (CR1). A risk adapted approach is utilized to optimize the likelihood of a curative outcome. For those with favorable risk post remission therapy involves 3-4 cycles of high dose cytarabine (HIDAC) consolidation. Approximately 60% of patients are cured in this fashion.[14-16] For patients

with intermediate and adverse risk, AML results with HIDAC consolidation are unsatisfactory, consequently in younger fit patients allogeneic transplantation is pursued as a consolidation strategy in CR1. Allogeneic transplantation for AML in CR1 is associated with a probability of long term survival of 50% however the procedure is associated with a high risk of morbidity and mortality.[19] For patients that are not candidates for intensive therapy (remission induction, allogeneic stem cell transplant) because of advanced age or frailty, in those with intermediate or favorable risk cytogentics treatment with either low dose cytarabine or azacytidine are reasonable treatment options. For patients with adverse risk cytogenetics azacytidine treatment is preferred.[20] Outcomes for relapsed or refractory AML are inferior as compared to patients treated initially for their AML. The likelihood of obtaining a durable CR2 is far lower than for a durable CR1. The goal of AML treatment is therefore to optimize the probability of obtaining a CR1.

The approach to treatment of younger fit patients with relapsed or refractory AML may involve an experimental therapy, remission induction with treatments such as 7+3 or regimens such as fludarabine, cytarabine and idarubicin or less intensive regimens such as azacytidine. Consolidation may or may not involve an allogeneic stem cell transplant. In older, less fit patients who have relapsed or refractory AML, treatments may involve an experimental therapy or less intensive therapies such as an alternative hypomethylating agent (decitabine).[14-16]

2.3 Evidence-Based Considerations for a Funding Population

The evidence to support the use of Enasidenib in AML primarily arises from the results of a recently published phase I-II trial.[2]) A phase III study is anticipated to completed in 2020. The phase I-II study accrued adult patients (18-100) with relapsed or refractory AML harboring an IDH2 mutation. Study participants included those over 60 with relapsed refractory AML or those at any age who relapsed after allogeneic stem cell transplant. Patients were treated with Enasidenib 100 mg daily until disease progression or unacceptable toxicity. A total of 214 patients with R/R AML and harboring the IDH2 mutation received enasidenib 100 mg daily. Patients had received at least one prior anticancer therapy with a median of 2.0 (range 1.0 to 5.0) anticancer regiments. Patients received a median of 4.6 months of treatment (range 0.3 to 34.1). Median OS for the patients enrolled in the study was 8.8 months (95% CI 7.7-9.6) which is significantly longer than for a comparable historical cohort. 19.6% of patients enrolled were able to obtain a complete remission which is significant given the pre-treatment history.

Enasidenib is indicated for relapsed and refractory AML that harbors an IDH2 mutation. IDH2 mutation testing may be determined by a polymerase chain reaction assay or by next generation sequencing. Testing platforms are not routinely offered in all regions in Canada currently.

2.4 Other Patient Populations in Whom the Drug May Be Used

Enasidenib is currently licensed in Canada (NOC Feb 2019) for the treatment of adult patients with relapsed or refractory AML harboring an IDH2 mutation. Other patient populations in whom the drug could be considered include:

- Patients <18 years of age who would otherwise meet the Health Canada NOC
- Patients with de novo AML harboring an IDH2 mutation but are felt not to be candidates for other therapies due to frailty or other co-morbidities.
- While not explicitly explored in the phase II study of enasidenib for relapsed/refractory AML,[2] in younger fit patients enasidenib may also be used as a bridging strategy to allogeneic stem cell transplantation.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient input was provided to pCODR through a patient advocacy group submission from the Leukemia & Lymphoma Society of Canada (LLSC) for enasidenib for the treatment of adult patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation. Information was obtained via an online survey publicized on LLSC's Facebook accounts and sent to individuals on their mailing list. Overall, 12 individuals who had experience with AML completed the survey: three responses from patients currently on treatment and nine from patients no longer receiving treatment. It is unknown if these patients had refractory or relapsed AML or if they were found positive for the IDH2 mutation, as this was not captured in the survey. All respondents were Canadian and ranged from 20-29 to 70-79 years of age. One respondent was a caregiver of a ~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 has an impact on their day-to-day living. Other reported symptoms resulting from AML included pain, skin problems, loss of appetite and sexual/intimacy issues.

At the time of completing the survey, all respondents reported receiving or having received chemotherapy, with some also having received a stem cell transplant. Temporary side effects were experienced by patients under treatment, with infections being particularly noted. Patients had no experience with or knowledge of enasidenib. They expected that most of the cancer-related symptoms they experienced would be managed by the new drug. Overall, they were willing to tolerate short-term side effects from the drug if the benefits outweighed the risks. Patients with AML value managing disease-related symptoms and improving quality of life.

Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient advocacy groups.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with AML

Eleven of the twelve respondents were diagnosed as adults between 2011 and 2018, and one patient was diagnosed in 2012 at the age of 30 months. It is unknown if these patients had refractory or relapsed AML or if they were found positive for the IDH2 mutation, as this was not captured in the survey. According to LLSC, most patients reported a constellation of minor symptoms including pale complexion, signs of bleeding and bruising, fever, fatigue, frequent minor infections, gum bleeding, discomfort in bones or joints, enlarged spleen, liver or lymph nodes and shortness of breath. All patients experienced disruptions in their daily lives, as listed in Table 1.

Table 1: AML Symptoms Affecting Day-to-Day Living, n=12

Symptom	Proportion of respondents who rated 4 or more (%)	# of respondents	Rating average[a]
Fatigue	100	12	5.75
Loss of appetite/weight loss	58	12	5.5
Numbness and tingling	0	11	2.3

Table 1: AML Symptoms Affecting Day-to-Day Living, n=12			
Symptom	**Proportion of respondents who rated 4 or more (%)**	**# of respondents**	**Rating average[a]**
Fever/Night sweats	33	12	4.8
Pain	50	12	5.2
Lumps	0	3	1.3
Bruising and/or bleeding	25	12	6.0
Rashes/skin changes	67	12	5.6
Other[b]	86	7	5.5

[a] Ranked on a scale of 1 (no impact) to 7 (extremely large impact)

[b] Brain fog (2), loose bowels (1), hemorrhoids (1), constipation (1), digestive issues (1), vision loss & nail loss (1)

Fatigue was experienced by all respondents and was the symptom with the most impact on daily life; it impacted their daily routines and led to a disruption in activities, sleeping patterns and physical and emotional intimacy. One patient stated that she was "just more fatigued, doing too much in a day or too much stimulation has me feeling sick by about 5 or 6 pm, and I always go to bed early now. More forgetful and a bit irritable." Another patient stated that they have "no endurance & lack of energy."

Loss of appetite and/or weight were also experienced by all patients. Two patients experienced weight loss as a result of nausea and vomiting. However, patients did not cite nausea as an AML symptom, so it is unclear if these events were caused by the disease or its treatment (e.g., chemotherapy). One patient experienced weight gain due to hospitalization and lack of physical activity during treatment.

LLSC mentioned other commonly reported symptoms related to physical and emotional intimacy. Challenges were ascribed to similar factors including "vaginal dryness" (one patient) and "lack of sex drive" (two patients). One patient said intimacy was "decreased" due to "difficulties with transition from husband/wife team to patient/caregiver mentality" whilst another patient claimed that "intercourse [was] slightly painful after chemo."

3.1.2 Patients' Experiences with Current Therapy for AML

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

All of the patients surveyed reported that they had easy access to treatment options. More than 75% of patients indicated that, in their opinion, the current treatment did do a sufficient job in managing their cancer symptoms, although all patients reported having some variation of side effects associated with their treatments and therapies.

The most common side effects that were reported by patients include pain, nausea and vomiting, fatigue, infections or non-cancer illness, and fertility and sexual side effects.

Seven respondents experienced infections or other non-cancer illness 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 other viral infections.

3.1.3 Impact of AML and Current Therapy on Caregivers

The caregiver who responded to the LLSC survey did not report their personal perspective with regard to AML and its treatment.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Enasidenib

None of the survey respondents had experience with or knowledge of enasidenib. It is not clear if any of the patients who responded to the survey were eligible to receive enasidenib as per the proposed indication, that is, having refractory or relapsed AML with an IDH2 mutation.

Surveyed patients mentioned various expectations for the new drug. When asked to rate cancer symptoms that enasidenib should manage on a scale of 1 (extremely unimportant) to 7 (extremely important), patients rated the following with an average of 4 or more:

- Fatigue (8 out of 9 responses)
- Loss of appetite (7 out of 9 responses)
- Pain (7 out of 9 responses)
- Rashes or skin changes (7 out of 9 responses)
- Fever and/or night sweats (6 out of 9 responses)
- Bruising and/or bleeding (6 out of 9 responses)
- Numbness or tingling (6 out of 9 responses)

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, 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.

3.3 Additional Information

None

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Eligible patient population

Economic factors:

- Additional monitoring and management of treatment-related toxicities

Please see below for more details.

4.1 Currently Funded Treatments

PAG identified that for older patients, there is no standard of care for relapsed or refractory acute myeloid leukemia (AML), and current treatments include azacitidine, hydroxyurea, low-dose cytarabine, and best supportive care. For younger, fit patients, FLAG-IDA is a standard re-induction relapsed or refractory treatment. Patients are not routinely tested in all provinces for the isocitrate dehydrogenase-2 (IDH2) mutation.

4.2 Eligible Patient Population

The AG221-C-001 trial included patients with mutant-IDH2 myelodysplastic syndromes (MDS) with refractory anemia with excess blasts, as well as in the dose escalation phase, patients aged 60 years or older with untreated AML and ineligible for induction chemotherapy. PAG is seeking clarity on whether these subgroups of patients would be eligible for enasidenib as they are not outlined in the reimbursement request.

PAG noted that there may be interest to use enasidenib for patients with IDH2 mutations, who have previously untreated AML or relapsed/refractory AML who are not eligible for chemotherapy. If enasidenib use in first-line for previously untreated mutant-IDH2 AML is appropriate, PAG is seeking guidance on whether enasidenib would be given with standard first-line treatment, recognizing that this may be out of scope of the current review of enasidenib in the relapsed or refractory setting.

PAG is also seeking guidance on the use of enasidenib for patients with relapsed or refractory AML with an IDH2 mutation in second relapse as a bridge to transplant or after transplant following a relapse.

If recommended for reimbursement, PAG noted that patients currently on other treatments for relapsed/refractory AML (e.g., chemotherapy) who have not progressed, would need to be addressed on a time-limited basis.

4.3 Implementation Factors

There is a potential for drug wastage with enasidenib given dose modifications for adverse events would be managed with switching from 100mg to 50mg tablets.

PAG noted the dosing schedule for enasidenib is until disease progression or unacceptable toxicity. For patients without disease progression or unacceptable toxicity, enasidenib is recommended for a minimum of six months to allow time for clinical response. PAG is seeking clarity on treatment duration and definition of disease progression.

Additional nursing and pharmacy resources will be required for drug dispensing as well as monitoring and management of toxicities (e.g., differentiation syndrome, tumor lysis syndrome, hyperbilirubinemia, and nausea). Monitoring may also require additional healthcare resources such as laboratory, clinic visits, and hospitalization. If differentiation syndrome is suspected, hospitalization for close observation and monitoring of patients with pulmonary and/or renal manifestation is recommended.

As an oral option, chemotherapy chair time and nursing time would not be required. PAG identified the oral route of administration is an enabler to implementation.

However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

4.4 Sequencing and Priority of Treatments

PAG noted that there is no standard of care for this patient population and limited treatment options are available. PAG noted in the pivotal trial, the majority of patients had received two or more prior AML-directed regimens. PAG is seeking confirmation that it is reasonable to offer enasidenib at any point in the relapsed or refractory setting (i.e., first, second, or later relapse).

4.5 Companion Diagnostic Testing

PAG recognized that IDH2 testing would be required to determine the subset of patients with the IDH2 mutation. PAG noted that IDH2 is not routinely tested in all provinces and implementation of IDH2 testing would be required. There is no formalized testing process or funding in place for IDH2 in jurisdictions. Health care resources and coordination to conduct the IDH2 testing in the relapsed or refractory setting will be required. The potential significant increase in costs for IDH2 testing is a barrier to implementation.

PAG had concerns related to the turnaround time for IDH2 testing, how testing is performed, and whether IDH2 is a de novo mutation or an acquired mutation. PAG is seeking clarity if patients tested positive for the IDH2 mutation at diagnosis, whether treatment with enasidenib would be reserved until the relapsed setting.

4.6 Additional Information

None provided.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Three clinician inputs were provided for enasidenib for adult patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation. All three inputs were submitted by individual clinicians: one clinician from Ontario with membership to Cancer Care Ontario Hematology Drug Advisory Committee (DAC); one clinician from British Columbia (BC) with memberships to College of Physicians and Surgeons of BC, Royal College of Physicians and Surgeons of Canada, and Canadian Bone Marrow Transplant Group; and one clinician from Alberta with membership to Tom Baker Cancer Centre (TBCC), Canadian Cancer Trials Group (CCTG), Canadian Hemophilia Society (CHS). A summary of the input is provided below.

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 R/R AML patients with the IDH2 gene mutation, who normally present with 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 to other treatments. Clinician inputs indicate that testing with next generation sequencing to identify IDH2 mutations would be required for eligibility; it may be performed at diagnosis and/or at relapse.

Please see below for a summary of specific input received from the registered clinicians.

5.1 Current Treatment(s) for Adult Patients with R/R AML

Clinicians agreed that in older patients, there is no standard of care for relapsed or refractory acute myeloid leukemia (AML); current treatments include azacitidine, hydroxyurea, low-dose cytarabine, and best supportive care. For younger, fit patients, FLAG-IDA is a standard re-induction strategy for relapsed or refractory cases. One clinician added that the latter may also receive an allotransplant if they respond to re-induction. Patients not eligible for transplant would receive palliative treatment. Another clinician suggested that etoposide/cyclophosphamide may also be considered for younger patients.

5.2 Eligible Patient Population

Clinicians indicated that there is a clear unmet need in the population specified in the AG221-C001trial and in the reimbursement request, and that this population corresponds in clinical practice to a small group for which access to the therapy under review would be desirable. According to a clinician, patients with R/R AML have a very poor prognosis and have few effective treatments at their disposal. Treatment with enasidenib would offer patients with an IDH2 mutation a chance of response and prolongation of overall survival.

Clinicians agreed that that the trial's inclusion and exclusion criteria and age distribution are relevant to clinical practice. One clinician suggested that patients who relapse post-allotransplant should be eligible for funding, while another mentioned the possibility of using this drug as a bridge to stem cell transplant. Clinicians did not suggest limiting treatment to a specific subgroup of the target population.

5.3 Relevance to Clinical Practice

One input from a clinician who had experience with enasidenib noted that the drug should be used in patients with R/R AML with IDH2 mutant. In younger fit patients, enasidenib would be continued while responding and if stem cell transplant was feasible then this option should be considered. In older patients and less fit patients, the drug would be given to patients who are refractory or progressed after initial treatment with a hypomethylating agent (azacitidine or decitabine) and would be continued while patients are responding.

The clinician added that there is no other Health Canada-approved treatment for patients with R/R AML, so their best option is enrollment in a clinical trial. Patients refractory to 1–2 cycles of intensive chemotherapy are very unlikely to further benefit from it. Older unfit patients who do not respond to a hypomethylating agent have few options other than best supportive care. The clinician appreciates the significant OS benefit from enasidenib given that median OS is normally around 2–3 months in this population.

The other inputs from clinicians who do not have experience using the drug agreed that it should be given to patients matching the study population, i.e., patients with relapsed and/or refractory AML with an IDH2 mutation. All clinicians regarded the therapy as similar in safety compared to other treatments, with no significant contraindications. One clinician remarked that the drug has less risk of myelosuppression and tissue/gut toxicity than conventional AML salvage chemotherapy.

5.4 Sequencing and Priority of Treatments with Enasidenib

One clinician indicated that in the absence of a comparable treatment in the target population, the sequencing question does not apply. The other clinicians believed that the treatment would be given to the population of interest as second line (i.e., at time of relapse), replacing non-specific palliative therapies. It would be given as an add-on to supportive care but not with other induction treatments.

5.5 Companion Diagnostic Testing

Clinicians indicated that next generation sequencing (NGS) is required for this drug. According to a clinician, NGS is becoming standard of care for diagnosis and management of AML. When available, it is robust and can be turned around rather quickly, ideally in less than 1–2 weeks when a therapeutic decision depends on it. One clinician explained that although IDH2 mutations are fairly stable, the mutation status can change from time of diagnosis to time of relapse. Therefore, testing should be performed at both times. In contrast, another clinician suggested that initial diagnostic testing would be sufficient.

5.6 Additional Information

None.

5.7 Implementation Questions

5.7.1 In clinical practice, if enasidenib was available, is there evidence to use enasidenib in this setting as a bridge to transplant?

Clinician inputs noted that about 10% of the patients in the enasidenib clinical trial proceeded to stem cell transplant, which is a potentially curative treatment. One clinician

mentioned that the Hematology Drug Advisory Committee is unsure whether it would be preferred to use enasidenib or an aggressive re-induction regimen for transplant patients.

5.7.2 With respect to IDH2 testing, how are patients currently being testing for IDH2 mutations? When should testing be completed (i.e., at diagnosis or at time of relapse)? Please identify other considerations for implementation of IDH2 testing (i.e., turnaround time).

Two clinicians answered that testing should be done at diagnosis and repeated at time of relapse, while one clinician deemed it sufficient to use test results obtained at diagnosis or when treatment eligibility is being considered (i.e., at relapse).

Clinicians agreed that testing is relatively standard, robust and rapid; but one clinician considered that turnaround time at relapse may be a concern for some jurisdictions.

5.7.3 In clinical practice, what definition of disease progression is used?

Clinicians generally defined disease progression as an increase in the percentage of blasts in the bone marrow or in absolute circulating blasts in peripheral blood despite adequate therapy. One clinician also included peripheral blood cytopenias as an element of the definition.

One clinician explained that in patients treated with hypomethlyating agents, a complete response is often not achieved, but patients can have disease control with hematological improvement or a partial response. In this instance, disease progression is considered loss of this response.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety 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.

Note: Supplemental issues most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and will be outlined in section 7.

- Issue 1: Summary and critical appraisal of the propensity score matching analysis of enasidenib using the AG221-C-001 trial versus conventional care regimen using a France chart review of refractory or relapsed acute myeloid leukemia patients with an IDH2 mutation

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in Table 6.1.

Table 6.1: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators	Outcomes
• Randomized and non-randomized controlled trials • Single arm trials (in the absence of comparative evidence)	Adult patients with R/R AML who have an IDH2 mutation Subgroups: – Age – Sex – ECOG PS – Line of therapy – Previous treatment protocols – Prior SCT for AML – Time form diagnosis – Current co-morbidities	Enasidenib	In the absence of standard treatment options: • Chemotherapy • Supportive care	Efficacy – ORR – Time to response – PFS – OS – Duration of response – Clinical benefit rate Patient-reported outcomes/HRQoL Safety – AEs – SAEs – WDAEs

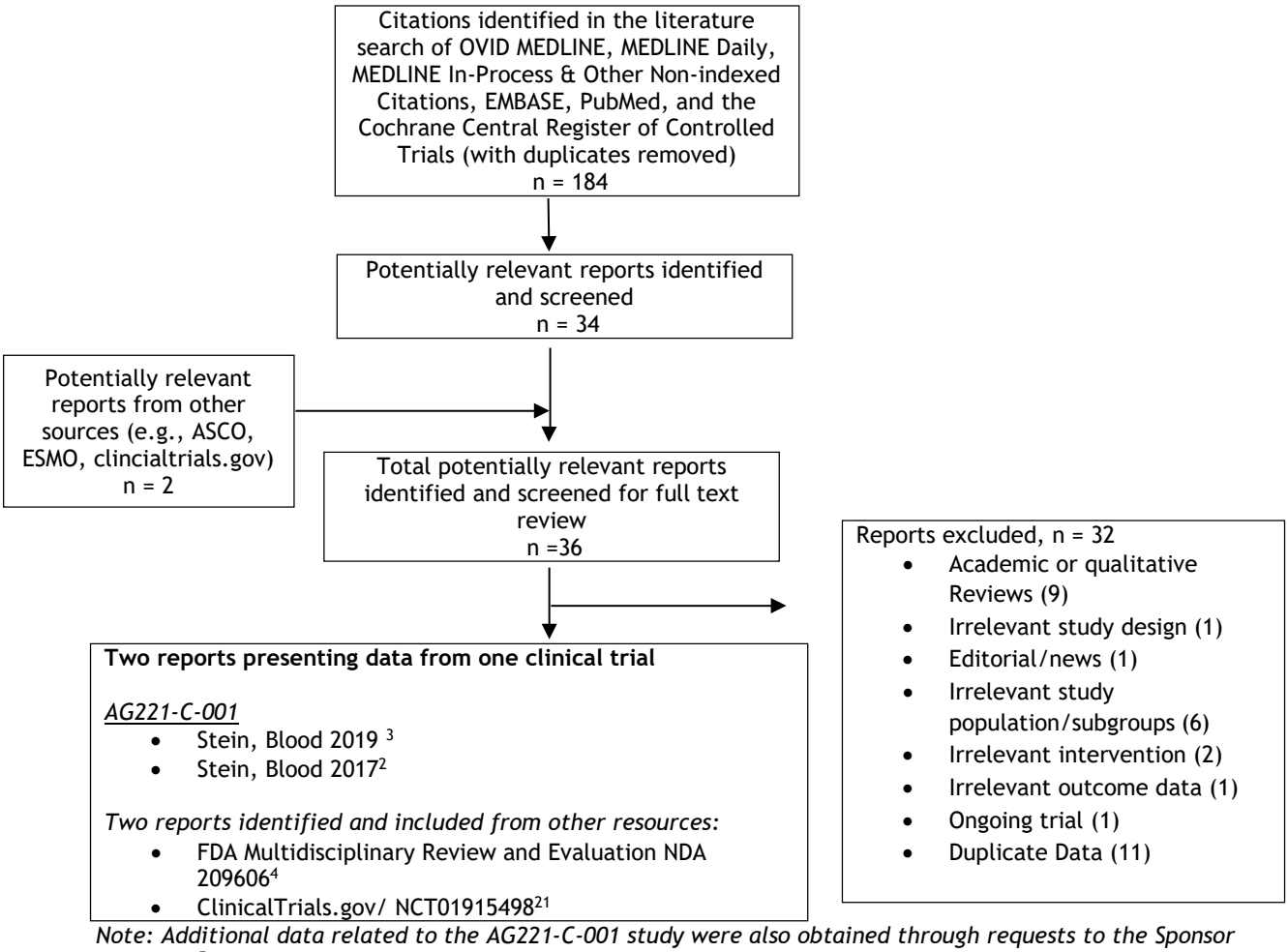
AE = adverse event; ECOG PS = Eastern Cooperative Oncology Group Performance Status Scale; HRQoL = health-related quality of life; IDH2 = isocitrate dehydrogenase-2; mg/m^2 = milligram per square meter of body surface; ORR = -overall response rate; OS = Overall survival; PFS = progression-free survival; R/R AML = relapsed or refractory acute myeloid leukemia; SAE = serious adverse events; SCT = stem cell transplant; WDAE = withdrawals due to adverse events.

6.3 Results

6.3.1 Literature Search Results

Of the 36 potentially relevant citations identified, four citations, reporting data from one clinical trial, were included in the pCODR systematic review,[2-4,21] and 32 citations were excluded. Studies were excluded because they were irrelevant study types,[22-31] or ongoing studies with no published results,[32] did not use the intervention of interest,[33,34] included irrelevant patient population or subgroups,[35-40] or if they reported irrelevant outcome data,[41] News items[42] as well as articles and conference abstracts reporting duplicate data from the included studies were also excluded.[2,43-52] Figure 6.1 illustrates the PRISMA flow Diagram for the study selection process.

Figure 6.1: PRISMA Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the AG221-C-001 study were also obtained through requests to the Sponsor by pCODR[5]

6.3.2 Summary of Included Studies

One phase I/II single arm trial met the selection criteria of this review. Relevant information on trial characteristics is summarized in Table 6.2.

6.3.2.1 Detailed Trial Characteristics

Table 6.2: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes†
Study: AG221-C-001[2,3] NCT01915498[21] **Characteristics:** Phase I/II, multicenter, open label, dose-escalation and expansion study **N treated:** Phase I Dose Escalation (N=113); Phase I Expansion (N=126); Phase II (N=105) **Number of centres and number of countries:** 21 sites in the United states and France **Patient Enrolment Dates:** Phase I Dose Escalation and Expansion initiated in September 2013 and is ongoing Phase II Expansion initiated in June 2015 and is Ongoing **Data cut-off dates** 15-April 2016 (primary analysis) 01-September 2017 **Primary completion date:**[21] 05-July-2019 **Final Analysis Date** Not available **Funding:** Celgene Inc.	<u>Key Inclusion Criteria:</u> • Adult (≥18 years of age) patients with advanced hematologic malignancies that harbor an IDH2 mutation • Documented IDH2 gene-mutated disease • ECOG PS 0 to 2 • Platelet count ≥20,000/μL • adequate hepatic and renal function <u>Key Exclusion Criteria:</u> • CNS leukemia • HSCT within 60 days prior to the first dose of enasidenib, post-HSCT immunosuppressive therapy at screening, or clinically significant graft-versus-host disease (GVHD) • systemic anticancer therapy or radiotherapy within 14 days prior to the first dose of enasidenib – Protocol-defined cardio-vascular conditions (details are provided in the text)	**Enasidenib** <u>Phase I Dose Escalation</u>: BID at 30, 50,75, 100, or 150 mg and QD at 50, 75, 100, 150, 200, 300, 450 and 650 mg (or as determined by the Clinical Study Team) on Days 1 to 28 of each 28-day cycle <u>Phase I Expansion</u>:†† A starting dose of 100 mg QD on Days 1 to 28 of each 28-day cycle <u>Phase II Expansion</u>:†† A starting dose of 100 mg QD on Days 1 to 28 of each 28-day cycle **No comparator**	<u>Primary:</u> • Safety/AEs • ORR <u>Secondary:</u> • CR • CR/CRH • PR • DoR • EFS • OS • TTR • TTBR • Transfusion independence

AE = adverse event; **BID** = twice daily; **CNS** = central nervous system; **CR** = complete remission; **CR/CRh**= complete remission with incomplete hematologic recovery; **DOR** = duration of response; **ECOG PS** = Eastern Cooperative Oncology Group Performance Status Scale; **EFS** = event-free survival; **HSCT** = hematopoietic stem cell transplant; **IDH2** = isocitrate dehydrogenase-2; **ORR** = -overall response rate; **OS** = Overall survival; **PR** = partial remission; **QD**= once daily; **TTBR** = time to best response; **TTR** = time to response

<u>† The results presented in this section focus on the phase I expansion and phase II results only.</u>
†† phase I expansion was conducted following the phase I dose escalation part of the study and included four cohorts of patients with IDH2 mutations. Phase II was a single arm study to assess the efficacy of enasidenib for treatment of patients with R/R AML harbouring an IDH2 mutation

a) Trials

Study AG221-C-001 was a Phase I/II, multicenter, open-label trial to evaluate the clinical activity, safety and pharmacokinetics/pharmacodynamics (PK/PD) of enasidenib in patients with advanced hematologic malignancies with an IDH2 mutation. The trial was conducted in 21 sites in the United States and France.

Trial design.[2-4]

The AG221-C-001 study design is illustrated in Figure 6.2. The trial consisted of two phases (three stages): Phase I Dose Escalation; Phase I Expansion; and Phase II.

Phase I: The objectives of Phase I Dose Escalation were to determine the safety and the maximum tolerated dose (MTD) of enasidenib, as well as characterizing PK/PD profiles and clinical activity of enasidenib.[2] Dose Escalation (standard 3+3 design) was followed by an expansion phase that included four cohorts of patients with IDH2 mutations:[2,4]

- 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 1-3

Phase II: The primary objective of Phase II (single arm design) was to assess the efficacy of enasidenib for treatment of patients with R/R AML harbouring an IDH2 mutation. The secondary objectives included identifying dose-limiting toxicities, evaluating safety outcomes, and characterizing the PK/PD profiles of enasidenib.

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. In all patients, the IDH2 mutation was identified prospectively.

Study endpoints and disease assessment[4,5]

Phase II was planned to be the pivotal part of the study. A pooled data from patients who received a 100 mg daily dose of enasidenib (in phase I expansion or Phase II parts of the study) were also presented by the sponsor; these pooled analyses were pre-planned.

The primary efficacy endpoint was overall response rate (ORR), defined as the rate of responses including complete remission (CR), CR with incomplete platelet recovery (CRp), CR with incomplete neutrophil recovery (CRi), morphologic leukemia-free state (MLFS), or partial remission (PR). Response to treatment and treatment decisions in all AML patients were determined by the investigators based on the 2003 modified International Working Group (IWG) criteria for AML,[53] or the 2006 modified IWG criteria for MDS.[54]

- CR was defined as < 5% blasts in the bone marrow, absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count >1.0 × 10^9/L (1000/μL); platelet count >100 × 10^9/L (100,000/μL); independence of red cell transfusions
- CRp was defined by all CR criteria except for residual thrombocytopenia (platelet counts <100 × 10^9/L [100,000/μL])
- Cri was defined by all CR criteria except for residual neutropenia (absolute neutrophil count <1.0 × 10^9/L [1000/μL])

- MLFS was defined as < 5% blasts in the bone marrow, absence of blasts with Auer rods; absence of extramedullary disease, no hematologic recovery required
- PR was defined by all hematologic criteria of CR; decrease of bone marrow blast percentage to 5% -25%; and decrease of pre-treatment bone marrow blast percentage by at least 50%

The key secondary endpoints included:

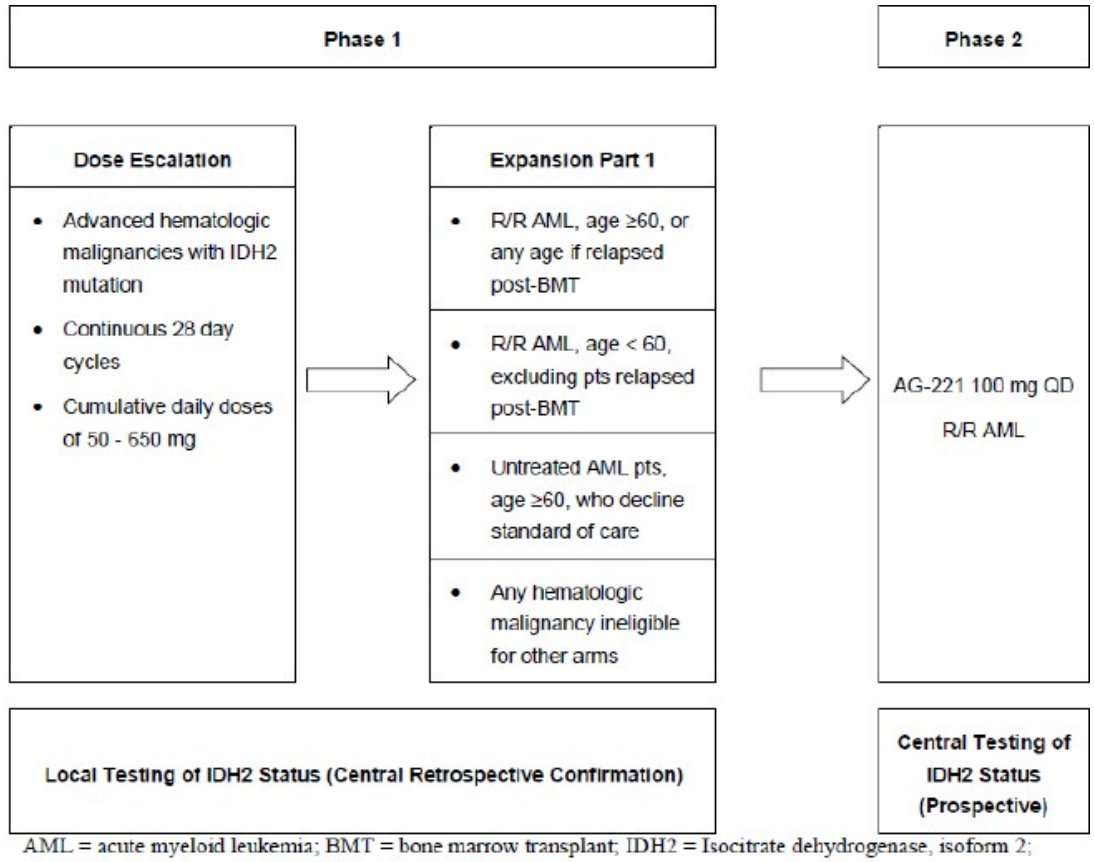
- Rate of CR with incomplete hematologic recovery (CR/CRh)
  - CRh was defined as < 5% blasts in the bone marrow and partial recovery of peripheral blood counts (platelets > 50 x 109/L and ANC > 0.5 x 109/L)
- Duration of response (DoR), defined as the date of the first documented response to the date of the first documented disease relapse, progression, or death due to any cause, whichever occurs first, in patients with a response of CR, CRi, CRp, PR or MLFS by investigator assessment (or CR, CRh, PR or MLFS by sponsor assessment).
- CR rate, defined as the rate of CR according to modified IWG response criteria
- Overall survival (OS), defined as the time from first dose to the date of death due to any cause
- Event-free survival (EFS), defined as the interval from the date of the first dose to the date of documented relapse, progression, or death due to any cause, whichever occurred first
- Time to response (TTR), defined as time from the date of first dose to the time until date of first occurrence of response, which included CR, CRi, CRp, PR and mCR (marrow complete response)/MLFS as determined by investigator (or CR, PR, and mCR/MLFS as determined by sponsor assessment)
- Time to best response (TTBR), defined as time from the date of first dose to the time until date of first occurrence of best response
- Time to complete response, defined as time from the date of first dose to the time until date of first CR, as determined by investigator
- Rate of conversion from transfusion dependence to transfusion independence
  - Baseline transfusion was defined as transfusion received 28 days before and 28 days after the first dose of treatment for Phase 1 subjects and 56 days before the first dose date for Phase 2

Bone marrow and peripheral blood samples for confirmation of disease status and IDH2 mutation screening were collected during the screening period (i.e., within 28 days prior to study start) for all patients. Data on patient history, physical exam including performance status, and adverse events were collected at the time of screening.

Responses were to be assessed retrospectively by Independent Response Adjudication Committee (IRAC). Disease assessments were to be performed at screening and on protocol-specified days (as per the phase of the study). An assessment was also to be conducted at the End of Treatment visit for patients who discontinued from the study due to reasons other than disease progression. For patients who underwent hematopoietic stem cell transplant (HSCT) following discontinuation of enasidenib, disease response assessments were to be conducted at least monthly until relapse or end of the study. At each disease response assessment, evaluations were to be performed for red blood cell (RBC) and platelet transfusion requirements as well as the associated hemoglobin levels and/or platelet counts.

Data on patient-reported outcomes were not collected in the AG221-C-001 trial.[5]

Figure 6.2: AG221-C-001 Study Design



AML = acute myeloid leukemia; BMT = bone marrow transplant; IDH2 = Isocitrate dehydrogenase, isoform 2; pts = patients; QD = once daily; R/R = relapsed/refractory.

Source: Applicant CSR Figure 1

***Source*:** [FDA Multidisciplinary Review and Evaluation NDA 209606; Figure 16, page 72][4]

Statistical analysis[4,5]

The sample size determination for each phase/stage of the study was as follows:

- Phase I Dose Escalation: number of patients required for the assessment of 13 dose levels/schedules, using a 3+3 design, was estimated to be approximately 66.
- Phase I Expansion: 25 subjects per cohort would provide 93% probability of detecting ≥1 adverse events with a true rate of 5%.
- Phase II: an ORR of at least 33.6% (at least 42 responses in 125 patients) will result in an exact binomial 95% confidence interval (CI) with a lower bound greater than 25%,which was considered to be clinically meaningful in this setting (based on the study by Roboz et al, 2014),[55] and exceeded the ORR expected with available therapies.

The Full Analysis Set (FAS) was used for the analysis of efficacy endpoints. This dataset included all patients who received ≥ 1 dose of study treatment. Response outcomes were summarized by the percentage of responses primarily in the FAS, with two-sided exact binomial 95% CIs. Time-to-

event outcomes (e.g., OS, EFS, TTR) were analyzed using Kaplan-Meir (KM) methods and KM curves. The 25th percentile, median, and 75th percentile with two-sided 95% CI were also provided for OS distribution in the FAS, and DOR in responders (within FAS).

All treated patients in study AG221-C-001, including those who underwent post-enasidenib transplant or subsequent anticancer therapies were included in the analyses of EFS and OS. For EFS, patients who received subsequent anticancer therapies were censored at the last disease assessment prior to subsequent therapies. However, the disease status was continuously assessed after post-enasidenib transplant. For OS, all treated patients were followed up until death (if the patients had died) or last date known alive for living patients, irrespective of receiving transplant or subsequent therapies.

The Safety Analysis Set (SAS) was used for the safety analysis. This dataset included all patients who received ≥ 1 dose of study treatment, with patients being classified according to the first dose level/schedule received.

Interim analyses and adjustment for multiplicity

Based on the AG221-C-001 study protocol, the end of the study was defined as the time at which:

- all patients had discontinued treatment with enasidenib and had been followed for survival for at least 12 months, or have died, been lost to follow-up, or withdrew consent; or
- the last data point from the last patient that was required for primary, secondary and/or exploratory analysis was received, whichever was later.

The primary analysis was performed using data from the 15-April-2016 cut-off date, when 173 out of 176 patients with R/R AML had completed at least 6 cycles of treatment or discontinued earlier (i.e., met the protocol-specified duration of follow up for the primary analysis).[2,4]

An updated analysis of the study data was performed at the data cut- off date of 01-September-2017. The efficacy analyses at this data cut-off used data from the combined Phase I/II population for efficacy (i.e., patients who received 100 mg/day of enasidenib in phase I or II). Safety analysis used data from all patients from the Phase I/II study. For patients who discontinued from study treatment to undergo HSCT and then restarted enasidenib, data after restarting enasidenib was excluded from all pooled analyses except for the mortality data.[5]

No adjustment was made for multiple comparisons/multiplicity.[5]

Protocol amendments

The original protocol was issued on 03-June- 2013, and was revised a total of 7 times between activation and the data cut-off date of October 14, 2016. Key protocol amendments are as follows:[4,5]

Amendment 3 (16-April-2014) added the Phase I expansion cohorts, added specific AML response criteria, allowed patients who had previously received enasidenib on this protocol to re-enter the study if they relapsed after HSCT, and added the recommendation to avoid the use of antacids, H1 blockers or proton pump inhibitors while taking enasidenib based on emerging PK data.

Amendment 4 (02-February-2015) added Phase II to the study and specified that information on red blood cell and platelet transfusions would be captured for subjects on Phase II for the 8-week period prior to first dose of study drug and during the treatment period. This amendment added an allowance for subjects who experience disease progression to continue on study drug if they are, in the opinion of the investigator, benefiting from treatment, and added guidelines for the management of QT prolongation and differentiation syndrome.

Amendment 6 (14-October- 2015) added additional guidance for differentiation syndrome in cases in which subjects were affected by presumed infections requiring hospitalization that did not respond to anti-infective treatments or worsened in the first 48 hours.

Amendment 7 (17-October-2017) updated the end of study definition (three years after the first dose of the last patient enrolled into Phase II), and reduced visit and assessment burden for ongoing study participants including those on treatment and those in long term follow up.

b) Populations

Eligibility criteria[4,5]

To be eligible for inclusion in the AG221-C-001 study, patients must meet the following criteria:

- ≥18 years of age,
- Diagnosis of advanced hematologic malignancy:

  Phase I Dose Escalation:

  - Diagnosis of AML according to World Health Organization (WHO) 2008 classificatyion[56]
  - Refractory or relapsed AML (defined as the reappearance of > 5% blasts in the bone marrow)
  - Untreated AML with age ≥ 60 years, if not candidates for standard therapy
  - Myelodysplastic syndrome (MDS) characterized by refractory anemia with excess blasts (RAEB) or considered high-risk by the Revised International Prognostic Scoring System (IPSS-R), if recurrent or refractory and not a candidate for regimens known to provide clinical benefit
  - Other relapsed or refractory hematologic cancers, with approval of the Medical Monitor

  Phase I Expansion:

  - Cohort 1: Relapsed or refractory AML and age ≥60 years, or any subject with AML who has relapsed following HSCT, regardless of age.
  - Cohort 2: Relapsed or refractory AML and age <60 years, excluding subjects with AML who have relapsed following a HSCT
  - Cohort 3: Untreated AML and age ≥60 years that decline standard of care chemotherapy
  - Cohort 4: IDH2-mutated advanced hematologic malignancies not eligible for expansion Cohorts 1 to 3.

  Phase II:

  Patients with relapsed or refractory AML who:

  - relapsed after allogeneic HSCT
  - were in second or later relapse
  - were refractory to initial induction or re-induction treatment
- Relapsed within one year of initial treatment, excluding patients with favorable-risk status according to the National Comprehensive Cancer Network Guidelines (NCCN 2015)
- Platelet count ≥ 20,000/μL (transfusions allowed) unless due to underlying malignancy
- Serum total bilirubin ≤ 1.5 x upper limit of normal (ULN), unless due to Gilbert's disease, a gene mutation in UGT1A1, or leukemic organ involvement
- AST, ALT and alkaline phosphatase ≤ 3.0 x ULN unless due to underlying malignancy

- Serum creatinine ≤ 2.0 x ULN or creatinine clearance > 40 mL/min based on the Cockroft-Gault formula

Patients were excluded if they had any of the following key exclusion criteria:

- Had central nervous system (CNS) leukemia
- Received HSCT within 60 days prior to the first dose of enasidenib, post-HSCT immunosuppressive therapy at screening, or clinically significant graft-versus-host disease (GVHD)
- Received systemic anticancer therapy or radiotherapy within 14 days prior to the first dose of enasidenib (hydroxyurea allowed for control of peripheral leukemic blasts in subjects with WBC > 30,000/μL)
- Had a New York Heart Association Class III or IV congestive heart failure, left ventricular ejection fraction < 40%, a history of myocardial infarction within the six months prior to screening, uncontrolled hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 100 mm Hg), uncontrolled angina pectoris, history of severe ventricular arrhythmias, or QTcF [QT corrected based on Fridericia's equation] ≥ 450 msec

Characteristics of the study population[3,5]

Between 20-September-2013 and 01-September-2017, 345 patients were enrolled at 21 sites and received ≥ 1 dose of enasidenib. A total of 280 patients with R/R AML and an IDH2 mutation participated in the study; of whom, 214 (76.2%) patients received 100 mg of enasidenib daily.[3] These 214 patients (with 105 in the Phase II study) were enrolled in the pooled Phase I/II analyses; these pooled analyses were pre-planned.

Baseline characteristics of the study population are presented in Table 6.3. The median age was 68 (range 19 to100) years. The majority of patients were White (76.6%), had a baseline Eastern Cooperative Oncology Group (ECOG) performance score of 1 (61.7%). The cytogenetic risk status was intermediate risk in 50.5% and poor-risk in 25.78%.

At baseline, 84 patients (39.3%) were primary refractory (40 patients refractory to induction therapy and 44 patients were refractory to lower intensity regimens), and 130 patients (60.7%) had a relapsed disease. Median time form initial diagnosis was 10.4 months. Patients who were refractory to induction chemotherapy were reported to be younger (median age 60.5 years) than patients who were refractory to lower intensity regimens and those who relapsed following prior AML therapy. Patients who were refractory to non-intensive regimens were older (median age 74.0 years) and more likely to have had a prior diagnosis of MDS. All patients had received prior systemic anticancer therapies, with a median of 2.0 (range 1.0 to 5.0) anticancer regimens. Overall, 47.2% of patients received one prior regimen, 30.4% received two prior regimens, and 22.4% received three or more prior therapies. Patients who were in relapse were most likely to have received multiple prior AML regimens.[3]

Table 6.3: Baseline patient and disease characteristics of patients in the AG221-C-001 Study

Characteristic	Phase II (N=105)	Pooled Phase I/II (N=214)
Age (median)	68.0	68.0
Sex (% male)	60	51
Weight (Kg)	77.4	74.7
BSA (m^2)	1.884	1.836
Race (%)		
White	74.3	76.6
Black	5.7	5.6
Native Hawaiian or Other Pacific Islander	1.0	0.5
Not provided	19.0	15.9
ECOG PS (%)		
0	22.9	22.9
1	61.0	61.7
2	15.2	15.0
Missing	1.0	0.4
Gene Mutation		
R140	75.2	75.7
R172	24.8	23.8
Prior MDS (%)	27.6	21.5
Primary refractory (%)	34.3	39.3
Primary relapsed (%)	65.7	60.7
Number of prior anti-cancer regimens (%)		
1	40.0	47.2
2	36.2	30.4
3	12.4	14.0
4	8.6	5.6
≥5	2.9	2.8
Prior SCT for AML (%)	16.2	13.6
Cytogenetic risk status (%)		
Intermediate risk	54.3	50.5
Poor risk	24.8	25.7
Failure	4.8	3.3
Missing	16.2	20.6
Time from initial diagnosis (months, median)	11.7	10.4
Patients receiving RBC transfusions (n (%))*	67 (63.8)	153 (71.5)
Number of RBC transfusions per patient (mean, median)*	3.8, 3.0	4.3, 3.0
Units of RBC transfused per patient (mean, median)*	5.4, 4.0	6.0, 5.0
Patients receiving platelet transfusions (n(%))*	59 (56.2)	132 (61.7)
Number of platelet transfusions per patient (mean, median)*	4.7, 4.0	6.0, 4.5
Units of platelets transfused per patient (mean, median)*	8.0, 5.0	12.5, 5.0

KEY: AML: acute myeloid leukemia; ECOG PS: Eastern Cooperative Oncology Group Performance Status; MDS: myelodysplastic syndrome; RBC: red blood cell; SCT: stem cell transplant

*Transfusion history based on 4 weeks prior to and after the first dose for Phase I and 8 weeks prior to the first dose for Phase II

Source: AG221-C-01 CSR Tables 14.1.6.6, 14.1.6.7, 14.1.7.6, 14.1.7.7

Note: 214 patients who received a 100 mg daily dose of enasidenib in either Phase I expansion or in Phase II were enrolled in the pooled Phase I/II analysis.

Source: [Celgene Submission document, Clinical Summary: IDHIFA® (Enasidenib) for the Treatment of R/R AML in Patients with Mutant IDH2, Table 5.2][5]

c) Interventions

Treatment Dosing Schedule

Phase I Dose Escalation: Enasidenib was administered orally in 30 mg, 50 mg, 75 mg, 100 mg, and 150 mg dose levels twice daily; or 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 300 mg, 450 mg, and 650 mg dose levels once daily on Days 1 to 28 in 28-day cycles.[2]

Phase I Expansion and Phase II: Enasidenib was administered orally 100 mg once daily on Days 1 to 28 in 28-day cycles. The treatment was continued until disease progression, the development of unacceptable toxicity, or withdrawal of consent. The median duration of treatment was 4.3 months (range 0.3 to 23.6).[3,4]

The first three patients in each cohort of Dose Escalation as well as the first 15 patients on each Phase 1 Expansion cohort received a single dose of enasidenib on Day -3 for pharmacokinetics testing. All patients then received enasidenib daily as monotherapy in continuous, 28-day cycles starting on Cycle 1 Day 1 and continuing until unacceptable toxicity, progressive disease, or withdrawal of consent. Following Amendment 4 (02-February-2015), patients who experienced disease progression who were benefitting from treatment (at the discretion of the investigator) were allowed to continue on study drug (with the approval of the Medical Monitor) until confirmation of progression upon repeat evaluation 28 days later. Patients who achieved an adequate response to enasidenib and met other criteria for HSCT were allowed to proceed to HSCT after discontinuation of study therapy. Patients who relapsed following HSCT were eligible to restart enasidenib with Medical Monitor approval, if they continued to meet other eligibility criteria and had received no other anti-cancer therapies after the last dose of enasidenib.[4,5]

As of the 01-September-2017 data cut-off date, the median treatment duration for all patients was 4.2 months and the median number of cycles of treatment was 5.0 (range 1 to 38), with 53.0% of subjects completing five or more cycles, and 15.9% completing more than 12 cycles. Patients with R/R AML who received 100 mg enasidenib had a median treatment duration of 4.6 months.[3,5]

Dose modifications

Dose escalations were permitted in the trial:[4]

- Phase I Dose Escalation: the enasidenib dose could be escalated to any higher dose that did not exceed the MTD, with approval of the Medical Monitor.
- Phase 1 Expansion: the enasidenib dose could be escalated to a higher dose one time, if the patient had suboptimal response at the first clinical response assessment or later, or evidence of relapse on enasidenib after a response in either the peripheral blood or marrow.
- Phase II: the enasidenib dose could be escalated to 200 mg daily if any of the following occurred:
  - ANC < 0.5×10^9/L after being on enasidenib for the first cycle without Grade ≥ 3 adverse events suspected by the investigator to be related to enasidenib; or
  - No PR or better achieved after being on enasidenib for ≥ 2 cycles without Grade ≥ 3 adverse events suspected by the investigator to be related to enasidenib; or
  - Evidence of morphologic relapse or progressive disease.

Dose reductions were allowed, in case of toxicity, in 50 mg increments. Any patient who was unable to tolerate 50 mg daily dose of enasidenib was removed from study treatment.[4]

Concomitant interventions

A summary of concomitant medications that were recommended, permitted, restricted, or prohibited in the trial are provided in Table 6.4.

Table 6.4: protocol defined concomitant treatments in the AG221-C-001 Study[4,5]

prohibited	restricted	Recommended/permitted
• Other anti-neoplastic therapy (except hydroxyurea) • Corticosteroids (except topical cutaneous, ophthalmic, nasal, and inhalational steroids). Short courses of steroids were permitted to treat co-morbidities (e.g., differentiation syndrome) • Medications known to prolong the QT interval • Sensitive CYP substrate medications that have a narrow therapeutic range • P-gp and BCRP transporter-sensitive substrates digoxin and rosuvastatin • Antacids, H2 blockers, and proton pump inhibitors	Drugs that are substrates for • UGT1A1 • OAT, OATP1B or OCT2 • CYP2C8, 2C9, 2C19, 2D6, 3A4 or 1A2 • P-gp or BCRP	Recommended • Hydroxyurea (orally) 2-3 g twice or three times daily, for patients with elevated WBC. • Furosemide and/or prompt initiation of leukapheresis, if clinically required Permitted • G-CSF, GM-CSF and erythropoiesis stimulating agents • other supportive care medications (e.g. anti-diarrheal or anti-nausea agents)

BCRP = Breast Cancer Resistance Protein; CYP2C8, 2C9, 2C19, 2D6, 3A4 or 1A2 = Cytochrome P_{450} isoenzymes; G-CSF = granulocyte-colony stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor ; OAT = organic-anion-transporter; OATP1B= organic-anion-transporting polypeptide 1B; OCT2 = Organic cation transporter 2; P-gp = P-glycoprotein; UGT1A1 = uridine diphosphoglucuronate-glucuronosyltransferase 1A1

All 214 subjects received at least 1 concomitant medication. The ATC drug classification of the concomitant medications used in at least 40% of patients are summarized in Table 6.5.

Table 6.5: Concomitant medications used in the AG221-C-001 Study

ATC Drug Classification of Concomitant Medication (≥ 40% of Subjects)	Overall N = 214	Proportion of Patients
Direct acting antivirals	184	86.0%
Antimycotics for systemic use	178	83.2%
Quinolone antibacterials	161	75.2%
Opioids	153	71.5%
Other analgesics and antipyretics	149	69.6%
Other beta-lactam antibacterials	139	65.0%
Antiemetics and antinauseants	133	62.1%
Corticosteroids for systemic use, plain	118	55.1%
Other antibacterials	116	54.2%
Beta-lactam antibacterials, penicillins	111	51.9%
Antihistamines for systemic use	109	50.9%
Drugs for peptic ulcer and gastroesophageal reflux disease	107	50.0%
Antigout preparations	106	49.5%
Intravenous solution additives	101	47.2%
Drugs for constipation	99	46.3%
Other antineoplastic agents*	96	44.0%
Anxiolytics	94	43.9%
Hypnotics and sedatives	90	42.1%
Potassium	87	40.7%

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*All 96 subjects: hydroxycarbamide (hydroxyurea)

Source: [Celgene Submission document, pCODR Checkpoint Meeting Responses; June 13, 2019][5]

Subsequent medications

Anticancer medication: sixty out of 214 patients (28%) received at least one post-treatment systemic medication for underlying malignancy (Table 6.6).[5]
A total of 32 patients received one or more post-treatment medication that belonged to the following ATC drug classes: antimycotics, corticosteroids, intravenous solution additives, opioids, other antibacterial agents, other beta-lactam antibacterial agents, and Quinolone antibacterials.[5]

Table 6.6: Post-treatment systemic medications for underlying malignancy

ATC Level Preferred Term*	100 mg (N=214) N (%)
Number of Subjects with at Least One Post-Treatment Systemic Medication for Underlying Malignancy†	60 (28.0)
Alkylating Agents (busulfan, cyclophosphamide, lomustine)	3 (1.4)
Antimetabolites	44 (20.6)
Azacitidine	13 (6.1)
Cytarabine	27 (12.6)
Fludarabine	10 (4.7)
Decitabine	12 (5.6)
Clofarabine	9 (4.2)
Other (cladribine, methotrexate)	6 (2.8)
Cytotoxic Antibiotics and Related Substances	16 (7.5)
Idarubicin	11 (5.1)
Other (daunorubicin, idarubicin HCl, mitoxantrone)	6 (2.8)
Investigational Drug	14 (6.5)
Other Antineoplastic Agents‡	23 (10.7)
Other (donor leukocyte infusion, filgrastim, etoposide)	6 (2.8)

A subject with multiple occurrences of a drug class or drug is counted only once in the specific ATC classification or preferred name, respectively.
*ATC Level and Preferred Term are based on WHO Drug Dictionary Enhanced March 1, 2017.
†Post-treatment medications are defined as non-study medications that were initiated on/after the end of the study treatment period. The end of the study treatment period is defined as the last dose of study drug +28 days or date of death, whichever occurs first. ATC level 3 is primarily used. if ATC level 3 is missing, the next available higher level is used.
‡ belinostat, combinations of antineoplastic agents, crenolanib, gilteritinib, hydoxycarbamide, nivolumab, other antineoplastic agents, protein kinase inhibitors, ruxolitinib, selinexor, sorafenib, topotecan, tretinoin, venetoclax)

Source: [Celgene Submission document, pCODR Checkpoint Meeting Responses; June 13, 2019][5]

d) Patient Disposition

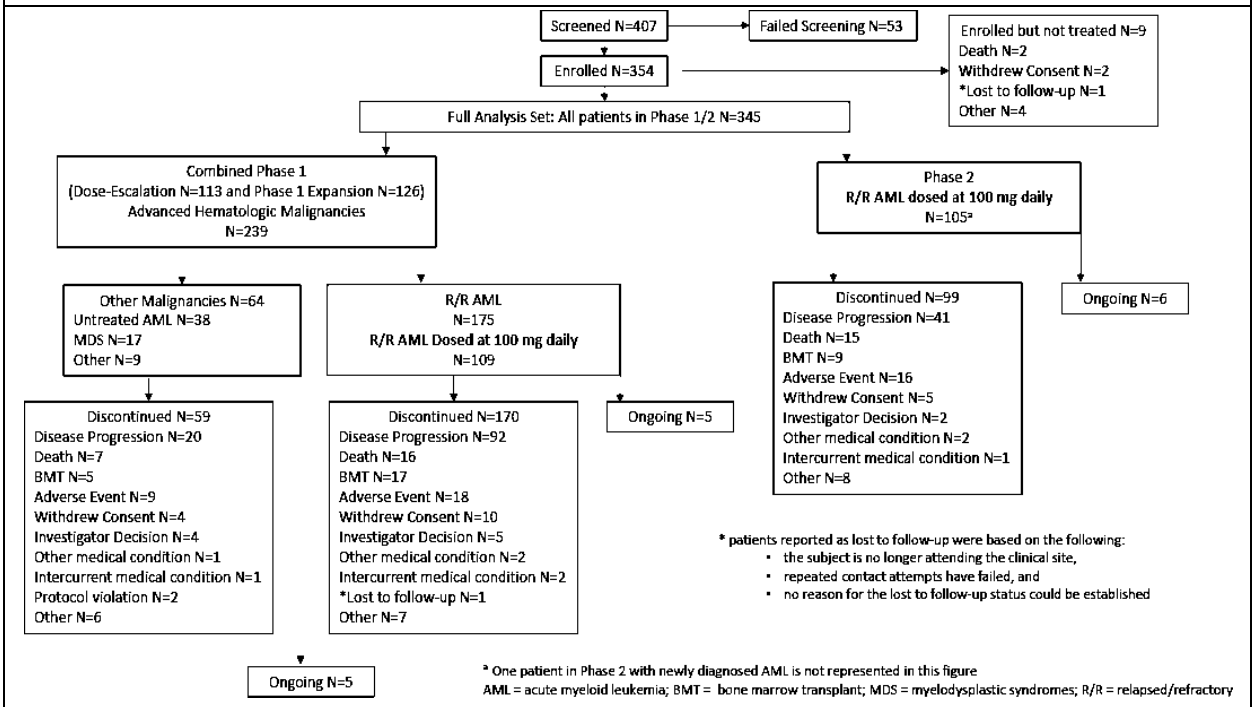
Figure 6.3 illustrates patient disposition in Study AG221-C-001.

As of the 01-September-2017 data cut-off date, a total of 345 patients were enrolled in the study, including 280 patients with R/R AML (105 patients in Phase II and 175 in Phase I). All of the 105 patients from Phase II and 109 (62.3%) of 175 patients from Phase I received 100mg daily dose of enasidenib.

Overall, 329 (95.4%) of 345 study participants discontinued treatment (including one newly diagnosed AML patient who is not presented in Figure 6.3), and 16 (4.6%) patients were still receiving treatment. Of the 105 patients in Phase II, 99 (94.3%) patients discontinued treatment.

The most common reasons for treatment discontinuation included disease progression (41.4%), AEs (16.2%), death (15.2%), and bone marrow transplant (9.1%). Of the 175 R/R AML patients in Phase I, 170 (97.1%) patients discontinued treatment. The most common reasons for treatment discontinuation included disease progression (54.1%), AEs (10.6%), bone marrow transplant (10.0%), death (9.4%), and patient consent withdrawal (5.9%).[5]

Figure 6.3: Patient disposition in Study AG221-C-001



Data cut-off: 01-September-2017

Source: [Celgene Submission documents – Consort Diagram][5]

Protocol violations/deviations[5]

A summary of major protocol deviations in the AG221-C-001 study is provided below:

In the Phase I Dose Escalation, 29/113 patients (25.7%) experienced at least one protocol violation; 25 patients had one violation, two patients had two violations, and two patients had more than violations. The most frequently observed violations included prohibited concomitant medications and/or procedures (16 patients;14.2%), and Good Clinical Practice (CGP) guidelines violations (8 patients; 7.1%), including 6 patients (5.3%) who experienced a violation related to the failure to report serious AEs or serious unexpected serious adverse reaction (SUSARs) in accordance with regulations.

In the Part I Expansion, 22/126 patients (17.5%) experienced at least one protocol violation; 16 patients had one violation, four patients had two violations, and two patients had more than two violations. The most frequently observed violations included prohibited concomitant medications and/or procedures (13 patients; 10.3%), and violations related to the failure to report serious AEs or SUSARs in accordance with regulations (6 patients; 4.8%).

In the Phase II FAS population, 17/106 patients (16.0%) experienced at least one protocol violation; 14 patients had one violation, two patients had two violations, and one patient had more than two violations. The most frequently observed violations included failure to satisfy the trial entry criteria (6 patients; 5.7%), violations related to the failure to report serious AEs or SUSARs in accordance with regulations (6 patients; 5.7%), and prohibited concomitant medications and/or procedures (4 patients;3.8%).

e) Limitations/Sources of Bias

- AG221-C-001 was a single arm study with no active treatment or placebo control groups. As a result, a direct comparison of the efficacy and safety of enasidenib relative to relevant comparators is not possible. However, the sponsor provided an indirect treatment comparison (propensity score matching analysis) of enasidenib versus conventional care regimens for patients with R/R AML with an IDH2 mutation, using an observational (chart review) study was conducted in France. The details of this analysis are discussed in section 7 of this report.
- The open label nature of the study might introduce 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 particularly be important in recruitment of patients, their subsequent care, attitudes of patients to the treatments, reporting of subjective outcomes (e.g., AEs) 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 analysing secondary endpoints or subgroup analyses. Therefore, these analyses are considered exploratory. Multiple testing can increase the probability of type 1 error and, therefore, lead to false positive conclusions.
- Patient-reported quality of life 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 endpoint in the AG221-C-001 study. Based on the evidence and discussions form the U.S. Food and Drug Administration (FDA) and American Society of Hematology (ASH) joint workshop,[57] the FDA reviewer suggested that achievement of a durable complete response (CR) was a more acceptable surrogate for clinical benefit, than ORR, in acute leukemias.[57]

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

As mentioned earlier, a total of 280 patients with R/R AML who had an IDH2 mutation participated in the AG221-C-001 study; of whom, 214 patients received a 100 mg daily dose of enasidenib. These 214 patients (with 105 in Phase II) were enrolled in the pooled Phase I/II analysis.

The pooled efficacy analyses used data from the 01-September-2017 data cut-off, with a median treatment duration of 4.6 (range 0.3 to 34.1) months, and a median follow-up duration of 7.8 (range 0.4 to 43.6) months.[5] A summary of the key efficacy results from the pooled analyses of AG221-C-001 are presented in Table 6.7.

The efficacy results are presented using the 01-September-2017 data cut-off date, unless otherwise specified.

ORR

The investigator-assessed ORR was the primary efficacy endpoint in the AG221-C-001 study. In the in the Phase I/II pooled population (N=214), the ORR was 38.8% with a DOR of 5.6 months. In the Phase II population (N=105), the ORR was 37.1% with a DOR of 5.6 months. The estimated ORR met the pre-specified criteria outlined in the Sponsors statistical analysis plan for clinically meaningful activity, as the lower bound of the 95% CI was higher than 25%.[3,5]

The median time to first response was 1.9 (range 0.5 to 9.4) months, and median time to best response was 3.7 (range 0.6 to14.7) months.[3],

Subgroup analysis results for ORR are as follows (Figure 6.4):

- Line of therapy – The ORR was 46.5% for patients who had received one prior AML treatment and 36.9% for those who had received two prior treatments. For patients who received ≥3 AML treatments prior to the study entry, the ORR was 25.0%. The Fisher exact test showed a statistically significant difference between the subgroups defined by the number of prior treatments (P = 0.040).
- Prior AML treatment outcome - The ORR was 37.5% for patients who were refractory to intensive chemotherapy (10.0% of patients who achieved a CR), 43.2% for patients who were refractory to lower intensity therapy (27.3% of patients who achieved a CR), and 37.7% for patients who relapsed to any prior therapy (20.0% of patients who achieved a CR). The ORR difference between the subgroups was not statistically significant.
- IDH2 mutations – ORR estimates were comparable between patients with IDH2-R140 mutations (35.8%; 95% CI 28.4, 43.7) and those with IDH2-R172 mutations (47.1%; 95% CI 32.9, 61.5).
- -Cytogenetic risk profile – The ORR was lower in patients with a poor-risk cytogenetic profile (18.2%) than patients with intermediate-risk cytogenetics (46.3%). The ORR difference between the two subgroups was statistically significant (P = 0.001.
- Other baseline variables including age, prior stem cell transplant, and ECOG performance status at entry had no significant effect on the likelihood of a response to enasidenib.[3]

Other key response outcomes (for definitions see section 6.3.2.1 and Table 6.7 footnotes)

Other response outcomes included complete remission (CR), CR with incomplete platelet recovery (CRp), CR with incomplete neutrophil recovery (CRi), morphologic leukemia-free state (MLFS), and partial remission (PR). These were included as secondary endpoints in the AG221-C-001 study.

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 CR+ CRi/CRp rate was 29.0% in the Phase I/II pooled population, with a median DOR of 6.7 months. For the Phase II population, the CR+ CRi/CRp rate was 31.4% with a median DOR of 6.75 months. A summary of non-CR response estimates (i.e., MLFS and PR) is presented in Table 6.7.[3,5]

Table 6.7: Efficacy Results from the AG221-C-001 study

Endpoint	Phase II (N=105)	Pooled Phase I/II (N=214)
Median Duration of Follow-up (months)	5.8	7.8
ORR n (%)	39 (37.1)	83 (38.8)
95% CI[a]	(27.9, 47.1)	(32.2, 45.7)
Median DOR[b] (months)	5.6	5.6
95% CI	(3.7, 7.4)	(3.8, 7.4)
CR[c] n (%)	21 (20.0)	42 (19.6)
95% CI[a]	(12.8, 28.9)	(14.5, 25.6)
Median DOR[d] (months)	6.7	7.4
95% CI	(3.7, 7.4)	(6.5, 16.3)
CRi /CRp[d] n (%)	12 (11.4)	20 (9.3)
CR+CRi/CRp n (%)	33 (31.4)	62 (29.0)
95% CI[a]	(22.7, 41.2)	(23.0, 35.5)
Median DOR (months)	6.5	6.7
95% CI	(3.7, 7.4)	(5.3, 9.7)
Specific Response Rates		
PR	4 (3.8)	9 (4.2)
MLFS	2 (1.9)	12 (5.6)
SD	44 (41.9)	98 (45.8)
PD	12 (11.4)	19 (8.9)
Summary of Overall Survival (OS)		
Number of events, n (%)	79 (75.2)	157 (73.4)
Median duration of OS (months)	7.0	8.8
95% CI	(4.9, 8.8)	(7.7, 9.6)
Median time to first response (Months) (95%CI)	2.7 (0.9, 7.5)	2.8 (0.5, 9.4)
Median time to best response (Months) (95%CI)	3.7 (0.9, 12.8)	3.8 (0.6, 14.7)

[a] 2-sided Exact Binomial 95% CI

[b] KM = Kaplan-Meier; Duration of response is calculated as the date of the first documented response to the date of the first documented disease relapse, progression or death due to any cause, whichever occurs first. Median, 25th, and 75th percentil estimates of median response duration are from an unstratified Kaplan-Meier analysis. Subjects missing response assessment are not included in any category.

[c] CR (complete remission) was defined as <5% of blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets >100,000/microliter and absolute neutrophil counts [ANC] >1,000/microliter).

[b] DOR (duration of response) was defined as time since first response to relapse or death, whichever is earlier.

[d] CRi/CRp (complete remission with incomplete hematological recovery) was defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets <100,000/microliter).

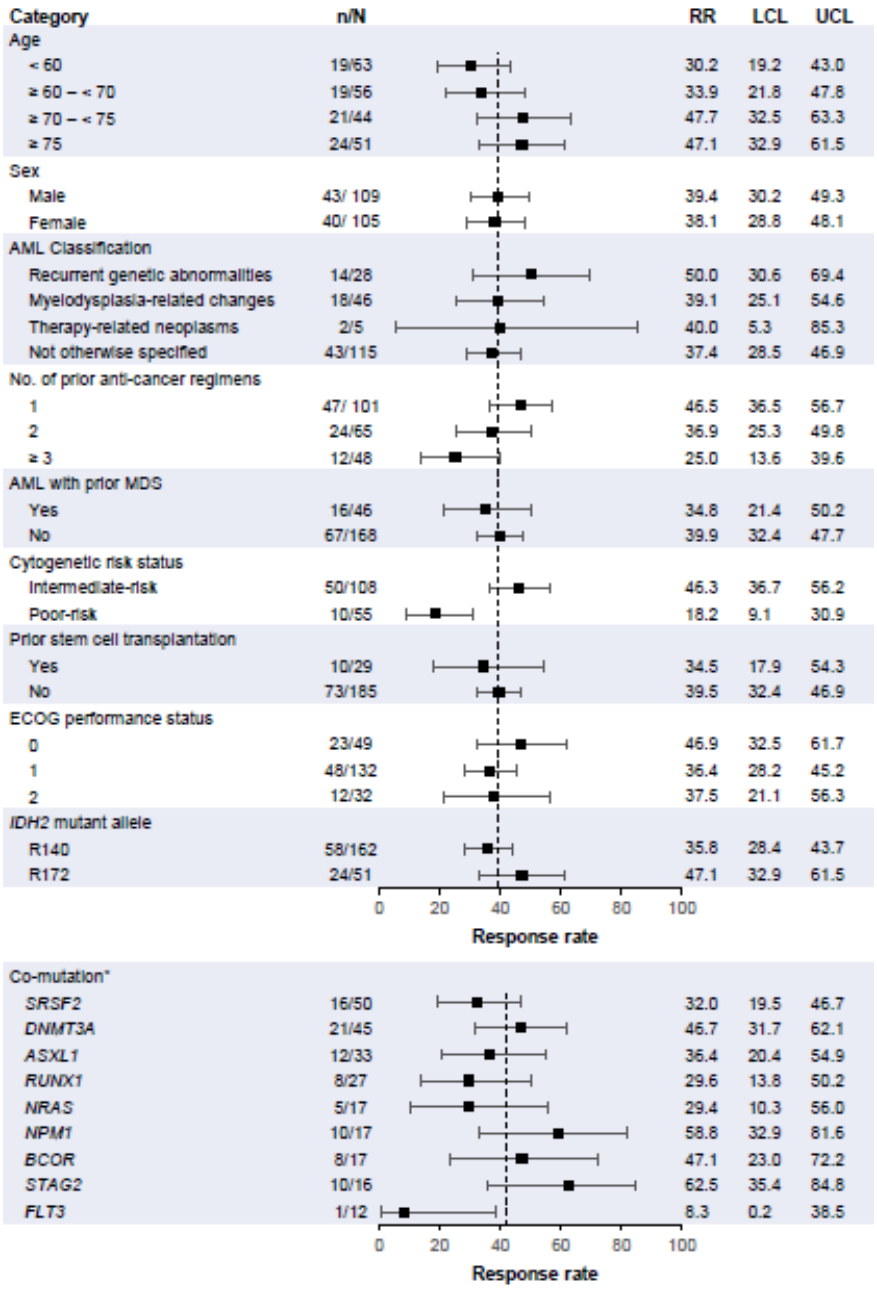
KEY: AML: acute myeloid leukemia; CI: confidence interval; CR: complete remission; Cri: complete remission with incomplete hematologic recovery; CRp: complete remission with incomplete platelet recovery; DOR: duration of response; MLFS: morphologic leukemia-free state; NA: not available; ORR: overall response rate; PD: progressive disease; PR: partial remission SD: stable disease.

Source: CSR Table 14.2.1.3, Table 14.2.1.6, Table 14.2.1.7, Table 14.2.13.12, Table 14.2.13.13.12, Table 14.2.13.14.12, Table 14.2.3.1.2, Table 14.2.3.1.5, Table 14.2.3.1.6, Table 14.2.4.1.2, Table 14.2.4.1.5 and Table 14.2.4.1.6.

Source: [Celgene Submission document, Clinical Summary: IDHIFA® (Enasidenib) for the Treatment of R/R AML in Patients with Mutant IDH2, Table 5.3][5]

Figure 6.4: Subgroup analyses of ORR based on baseline demographic and disease characteristics in the AG221-C-001 study - pooled Phase I/II population

For patients with relapsed/refractory AML who received enasidenib 100 mg/day (n=214).



*Co-mutations occurring in >10 patients; based on 127 patients with co-mutation data at baseline. Overall response rate in this subgroup was 41.7%
RR, response rate; LCL, 95% lower confidence limit; UCL, 95% upper confidence limit

Source: [Stein, Blood 2019; Supplementary Figure S2][3]

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Event-Free Survival (EFS)

EFS was a secondary outcome in the AG221-C-001 study. The median duration of EFS was reported to be 4.7 months (95% CI 3.7, 5.6) in the Pooled Phase I/II population.[3]

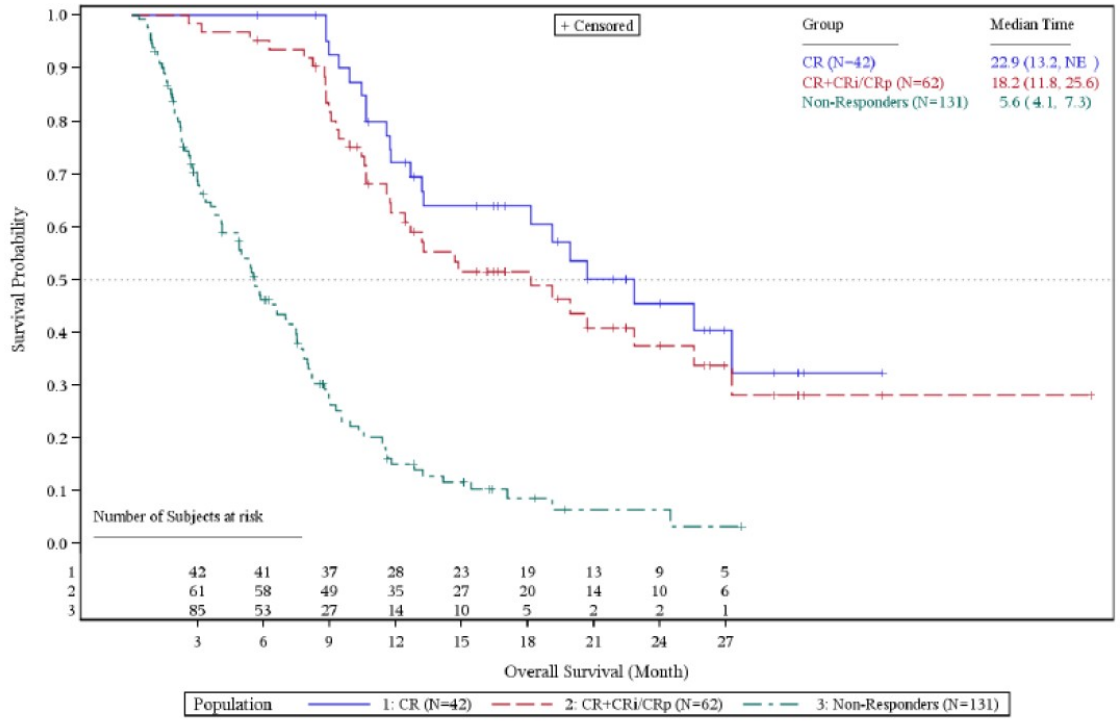
Overall Survival (OS)

At the 01-September-2017 data cut-off, after a median follow-up of 7.8 months, the median OS for the pooled phase I/II population was 8.8 months (95% CI 7.7, 9.6).[3]

The main subgroup analysis results for OS are as follows:

- Type of response to enasidenib- The median OS was estimated to be 22.9 months among the patients who achieved a CR, 18.2 months (95% CI 11.8, 25.6) among patients who achieved a CR+ CRi/CRp, 10.6 months among patients who achieved a non-CR response, and 5.6 months among non-responders.[3,5] In the Phase II population, median OS was not reached for patients who achieved a best response of CR at the time of data cut-off (Figure 6.5).[5]
- Post-treatment transplant- In patients who received bone marrow transplant during the study, the median OS was 23.6 months (95% CI 10.6, not estimable).[3]
- Line of therapy – The median OS was 11.8 months (95% CI, 8.3-15.4) for patients who had received one prior AML treatment, and 7.8 months (95% CI, 5.8-9.1) for those who had received two prior treatments. For patients who received ≥3 AML treatments prior to the study entry, the median OS was 7.0 months (95% CI, 4.9-8.8). The log-rank test showed a statistically significant difference between the subgroups defined by the number of prior treatments (P =0.001).[3]
- Prior AML treatment outcome- Overall, there was no significant difference in median OS among patient subgroups defined by response to prior AML treatment. The median OS was 12.4 months (95% CI 8.2, 22.9) for patients who were refractory to intensive chemotherapy prior to study entry, 8.0 months (95% CI 5.6, 11.7) for patients who were refractory to lower intensity therapy (e.g., hypomethylating agents or low-dose cytarabine), and 8.1 months (95% CI 7.0, 9.3) for patients who relapsed to any prior therapy.
- Cytogenetic risk profile – the median OS was 7.0 months for patients with poor-risk cytogenetics and 9.3 month among patients who had intermediate-risk cytogenetics. The survival difference between the two subgroups was found to be statistically significant (P =0.006).[3]

Figure 6.5: Kaplan-Meier Curves of OS in the AG221-C-001 study (CR, CR+Cri/CRp, and Non-Responders)



Key: AML: acute myeloid leukemia; CR: complete remission; CRi: complete remission with incomplete hematologic recovery; CRp: complete remission with incomplete platelet recovery; NE: not evaluable; OS: overall survival
Source: Phase I/II AG221-C-001 CSR Figure 17

Source: [Celgene Submission document, Clinical Summary: IDHIFA® (Enasidenib) for the Treatment of R/R AML in Patients with Mutant IDH2, Figure 5.1][5]

Transfusion Independence

Rate of conversion from transfusion dependence to transfusion independence was a secondary endpoint in the AG221-C-001 study.

Of the 214 patients in the pooled Phase I/II analysis, 153 patients were red blood cell (RBC) transfusion dependent and 132 patients were platelet transfusion dependent at baseline. Overall, 43.1% (66/153) of patients who required RBC transfusion and 40.2% (53/132) of those who required platelet transfusion at baseline became transfusion independent during any 56-day post-baseline period. In addition, 65.5% (40/61) of patients who were RBC transfusion independent and 75.6% (62/79) of those who were platelet transfusion independent at baseline maintained transfusion independence during any consecutive 56-day post-baseline (Table 6.8).

Of the 214 study participants, a total of 106 patients (49.5%) remained or became RBC independent of RBC transfusions, and 115 patients (53.7%) remained or became platelet transfusion independent, while receiving enasidenib treatment.[3,5]

Table 6.8 - Post baseline transfusion status in the AG221-C-001 study

	Phase II (N=105)			Pooled Phase I/II (N=214)		
Baseline Transfusion Status	N	Independent[b] N(%)	Dependent N(%)	N	Independent[b] N(%)	Dependent N(%)
Summary of RBC Transfusions						
Dependent[a]	67	28 (41.8)	39 (58.2)	153	66 (43.1)	87 (56.9)
Independent	38	22 (57.9)	16 (42.1)	61	40 (65.5)	21 (34.4)
Summary of Platelet Transfusions						
Dependent[a]	59	21 (35.6)	38 (64.4)	132	53 (40.2)	79 (59.8)
Independent	46	32 (69.6)	14 (30.4)	82	62 (75.6)	20 (24.4)

[a] With at least one transfusion during baseline.

[b] Defined as no transfusion required for at least 56 consecutive dates during the post baseline treatment period.

KEY: RBC: red blood cell

Source: Table 14.2.11.3.7, Table 14.2.11.3.8, Table 14.2.11.3.11, Table 14.2.11.3.12, Table 14.2.11.3.15 and Table 14.2.11.3.16.

Source: [Celgene Submission document, Clinical Summary: IDHIFA® (Enasidenib) for the Treatment of R/R AML in Patients with Mutant IDH2, Table 5.4][5]

Quality of Life (QOL)

No data on the patient-reported/QoL outcomes were collected in the AG221-C-001 study.[5]

Harms Outcomes

The submitted safety pooled analysis included all patients with R/R AML who at least one dose of 100 mg of enasidenib daily on study AG-221-C-001.[5] A larger dataset that included safety data form all patients with advanced hematologic malignancies who received enasidenib in the AG221-C-001 study (n=345) was used to support the safety analysis and to evaluate dose-toxicity relationships.[4]

Among all 345 patients, nearly all patients experienced a treatment-emergent adverse event (TEAE) during the course of the study treatment. The most frequent TEAEs (any grade) related to enasidenib treatment were indirect hyperbilirubinemia (40%), nausea (28%), and decreased appetite (17.7%) (Figure 6.9). The most frequent enasidenib-related grade 3 or 4 TEAEs were hyperbilirubinemia (10.4%), thrombocytopenia (6.7%), IDH differentiation syndrome (6.4%), and anemia (5.5%). TEAEs leading to discontinuation of the study treatment were reported for 43 (12.5%) patients[3]

Patients with R/R AML who received 100 mg enasidenib had a median treatment duration of 4.6 months. Of the 214 patients treated with the 100 mg dose, a total of 91 (42.5%) patients had ≥ 1 suspected treatment-related Grade 3 or 4 TEAE (Table 6.10). The most frequently reported enasidenib-related Grade 3 or 4 TEAEs were blood bilirubin increased (5.1%), IDH differentiation syndrome (6.5%), anemia (5.6%), thrombocytopenia (3.3%), platelet count decreased (2.3%), tumor lysis syndrome (1.9%), and dyspnea (4.2%). TEAEs leading to permanent discontinuation of the study treatment were reported for 36 (16.8%) patients; 9 (4.2%) of which were assessed by investigators as enasidenib-related. The most frequently reported TEAEs that led to discontinuation (occurring in ≥ 1.0% of patients) were sepsis (2.3%), leukocytosis (1.9%), and respiratory failure (1.4%).[5]

Table 6.9 - Treatment-related adverse events (any grade) in the AG221-C-001 study (in ≥5% of patients)

	Relapsed / refractory AML		
	Enasidenib 100 mg/day (n=214)	All doses (n=280)	All patients (N=345)
Preferred term	n (%)		
Hyperbilirubinemia*	71 (33)	97 (40)	139 (40)
Nausea	59 (28)	76 (27)	95 (28)
Decreased appetite	41 (19)	50 (18)	61 (18)
Vomiting	37 (17)	46 (16)	52 (15)
Diarrhea	33 (15)	45 (16)	52 (15)
Fatigue	31 (14)	41 (15)	51 (15)
IDH differentiation syndrome	27 (13)	33 (12)	38 (11)
Dysgeusia	22 (10)	26 (9)	34 (10)
AST increased	20 (9)	24 (9)	29 (8)
Dyspnea	20 (9)	21 (8)	27 (8)
Leukocytosis	16 (8)	22 (8)	25 (7)
Anemia	14 (7)	18 (6)	25 (7)
ALT increased	15 (7)	18 (6)	21 (6)
Rash	13 (6)	14 (5)	20 (6)
Hyperuricemia	12 (6)	14 (5)	18 (5)

*Contains multiple preferred terms under the Standardized MedDRA Query (SMQ) "Biliary system related investigations, signs and symptoms"
ALT, alanine aminotransferase; AST, aspartate aminotransferase; IDH, isocitrate dehydrogenase

Source: [Stein, Blood 2019; Supplementary Table S3][3]

Table 6.10 - Enasidenib-related Grade 3 or 4 TEAEs, Reported in ≥1% of patients in the AG221-C-001 study (pooled safety data set; R/R AML 100 mg dose, n= 214)

AE Preferred Term	Treatment Related TEAE (in ≥1%) N (%)	All TEAE N (%)
Subject With at Least 1 TEAE Reported as Treatment-related	91 (42.5)	91 (42.5)
Anemia	12 (5.6)	56 (26.2)
Febrile Neutropenia	8 (3.7)	76 (35.5)
Leukocytosis	4 (1.9)	22 (10.3)
Thrombocytopenia	7 (3.3)	39 (18.2)
Fatigue	2 (0.9)	17 (7.9)
Blood Bilirubin Increased	11 (5.1)	18 (8.4)
Platelet Count Decreased	5 (2.3)	18 (8.4)
Tumour Lysis Syndrome	4 (1.9)	11 (5.1)
Dyspnea	9 (4.2)	16 (7.5)
IDH Differentiation Syndrome	14 (6.5)	14 (6.5)
Nausea	5 (2.3)	11 (5.1)
Decreased appetite	4 (1.9)	9 (4.2)
Hyperbilirubinemia	4 (1.9)	5 (2.3)
Alanine aminotransferase increase	4 (1.9)	6 (2.8)
Neutrophil count decreased	3 (1.4)	6 (2.8)
Hyperuricemia	3 (1.4)	5 (2.3)

KEY: AE: adverse events; R/R: relapsed/ refractory; TEAE: treatment-emergent adverse event
Source: Table 14.3.1.10.6, 14.3.1.11.6

Source: [Celgene Submission document, Clinical Summary: IDHIFA® (Enasidenib) for the Treatment of R/R AML in Patients with Mutant IDH2, Table 6.1][5]

6.4 Ongoing Trials

The pCODR systematic review identified one relevant ongoing trial. More details about this trial are provided in Table 6.11.

Table 6.11: Ongoing trials of enasidenib in relapsed or refractory AML with an IDH2 mutation

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: AG221-AML-004 (IDHENTIFY)[32] NCT02577406[12] Characteristics: Phase III, multicenter, open label, randomized trial N (planned): 316 N (enrolled): 152 Number of centres and number of countries: 140 centres in US, Canada, Italy, Germany, UK, France, Spain, Austria, Belgium, Czech Republic, Denmark, Russia, Australia, Korea	<u>Key Inclusion Criteria:</u> • ≥ 60 years of age • primary or secondary AML according to WHO classification • Refractory to or relapsed after second- or third-line of intensive therapy or for AML or low-intensity AML therapy • ECOG PS of 0, 1 or 2 • Adequate organ function <u>Key Exclusion Criteria:</u> • Acute promyelocytic leukemia based on morphology, immunophenotype, molecular assay, or karyotype • AML secondary to chronic myelogenous leukemia	Enasidenib arm: Continuous 28-day cycles of Enasidenib 100 mg orally Conventional care regimen option: BSC only: continuous 28-day cycles of BSC; or azacitidine SC plus BSC: continuous 28-day cycles of azacitidine 75 mg/m2/day SC for 7 days, plus BSC; or LDAC SC plus BSC: continuous 28-day cycles of	<u>Primary:</u> OS <u>Secondary:</u> ORR EFS DOR TTR CR CR+Cri+ Crp HSCT rate Time to treatment failure HRQoL Safety Mortality

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Patient Enrolment Dates: Study initiated Oct 2015 and is ongoing Data cut-off: June 2020 (expected date) Final Analysis Date: March 31, 2020 (Final data collection date for primary outcome measure) Funding: Celgene	• History of targeted agent against an IDH2 mutation • History of systemic anticancer therapy or radiotherapy < 14 days prior to the start of study treatment	cytarabine 20 mg SC BID for 10 days, plus BSC; or IDAC IV plus BSC: 28-day cycles of cytarabine 0.5 to 1.5 g/m2/day IV for 3 to 6 days, plus BSC.	

AML = acute myeloid leukemia; **BID** = twice daily; **BSC** = best supportive care; **CR** = complete response; **CR+Cri+Crp** = complete remission with incomplete hematologic response; **DOR** = duration of response; **ECOG PS** = Eastern Cooperative Oncology Group Performance Status Scale; **EFS** = event-free survival; **HRQoL** = health-related quality of life; HSCT = hematopoietic stem cell transplant; **IDAC** = intermediate dose cytarabine; **IDH** = isocitrate dehydrogenase; **IV**= intravenous; **LDAC** = low dose cytarabine; **mg/m2/day** = milligram per square meter of body surface per day; **ORR** = overall response rate; **OS** = Overall survival; **SC** = subcutaneous; **TTR** = time to response; **UK** = United Kingdom; **US** = United States

7 SUPPLEMENTAL QUESTIONS

The following supplemental issue was identified during development of the review protocol as relevant to the pCODR review of enasidenib in patients with R/R AML and an IDH2 mutation.

- Issue 1: Summary and critical appraisal of the propensity score matching analysis of enasidenib using the AG221-C-001 trial versus conventional care regimen using a France chart review of refractory or relapsed acute myeloid leukemia patients with an IDH2 mutation

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Summary and critical appraisal of the propensity score matching analysis of enasidenib using the AG221-C-001 trial versus conventional care regimen using a France chart review of refractory or relapsed acute myeloid leukemia patients with an IDH2 mutation

7.7.1 Objective

The AG221-C-001 clinical trial was a single arm study, and therefore there are no comparative efficacy data available to inform comparisons with enasidenib. It is challenging to make naïve comparisons with published historical controls, as the trial includes a specific patient population (R/R with mutant *IDH2*). For this reason, indirect treatment comparison (ITC) analyses were undertaken to inform the comparative efficacy, specifically for EFS and OS, of enasidenib as compared with conventional care regimens (CCR) for R/R AML. Individual patient level data (IPD) from a France chart review study, focusing on patients with R/R AML and an *IDH2* mutation, was used to inform this comparison. This matching analysis was used to inform the submitted economic model and as a result, it has been critically appraised by the Methods Team.

7.7.2 Methods[5-7]

The objective of the propensity score matching (PSM) analysis was to compare the impact of enasidenib in Study AG221-C-001 to outcomes with conventional care regimens from the France chart review study. The France chart review was a retrospective, observational, multicentre study of adult patients with R/R AML and an IDH2 mutation. The chart review was carried out at nine centers in France that had inpatient diagnostic and treatment facilities for patients with AML. The study included patients aged ≥18 years who had been hospitalized with IDH2 positive R/R AML between September 2011 and September 2016.

As reported in Section 6, in Study AG221-C-001, 214 patients (received 100 mg/day of enasidenib. The France chart review included 103 patients who received a variety of different AML therapies, including 5-azacytidine, 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. Patients who had been treated with enasidenib were excluded from the chart review study. AG221-C-001 excluded patients who were eligible to receive hematopoietic stem cell transplant (HSCT) at enrolment, while the France Chart review did not have this exclusion criterion. To align patient populations between the two data sources, the PSM analysis excluded patients who underwent HSCT after baseline, as follows:

- For the France chart review, patients who received HSCT after date of the initiation of the second-line treatment were excluded due to the lack of data.
- For the AG221-C-001 study, patients eligible for HSCT at enrolment were excluded based on study exclusion criteria; however, to provide the most conservative analysis, 19 patients underwent HSCT after enasidenib treatment were also excluded from the PSM analysis population.

Patients in the AG221-C-001 trial were enrolled at various times since the diagnosis of their R/R AML. Similarly, data in the France chart review study were collected at the time of initial AML diagnosis and onwards. For the purpose of the PSM analysis, the study entry time (T0; baseline) was defined (post-hoc) for the France chart review study:

- For patients with two or more lines of therapy, T0 was defined as the time at which the patient started their second-line treatment after the initial relapsed or refractory (R/R) disease diagnosis.
- For patients who did not receive a second-line treatment, T0 was assumed to be the date of the initiation of the first-line treatment.
- For patients that did not receive any treatment after the R/R disease diagnosis, T0 was considered to be the date of the R/R event.

In order to balance baseline covariates and increase the homogeneity within the two study populations, the following five covariates were identified based on the expert advise (Four clinical advisors from US, Canada, Australia, and France), and included in the PSM analysis: history of HSCT before baseline (yes or no), baseline age category (<65 years or ≥65 years), number of prior lines of AML therapy at baseline (<2 or ≥2), cytogenetic risk at baseline (intermediate, poor, or failure), and history of MDS (yes or no). Patients with missing data for efficacy (i.e., OS and EFS) and one or more of the included covariates were excluded from the PSM analysis.

Patients in the two study groups were matched based on their individual propensity scores, which were estimated for all patients using a multivariable logistic regression model, using 1:1 optimal matching. The PSM was used to generate OS and EFS Kaplan-Meier (KM) curves with matched data sets for both enasidenib and CCR (the definitions of OS and EFS were consistent between the AG221-C-001 and France Chart Review studies). In addition, Cox proportional hazard models were used to estimate hazard ratios (HRs). Appropriateness of the proportional hazards assumption for Cox proportional hazards models was assessed through visual inspection of the KM curves, visual inspection of the Schoenfeld residuals plot, and a global test for non-proportion hazards of any covariate.

7.7.3 Findings

Table 7.1 shows the balance in covariates between the patients in the AG221-C-001 and France Chart Review studies, before and after propensity score matching. As shown in the table, a total of 195 patients from the AG221-C-001 study and 71 patients from the France Chart review were included in the PSM analysis. Before matching, considerable differences were observed for the number of prior treatment lines, prior HSCT, and cytogenetic risk profile (based on the standardized mean differences (SMDs) >0.10).

After optimal 1:1 matching, 69 patients remained in each of the enasidenib and CCR groups. The two study groups were balanced in terms of proportion of patients with prior HSCT; however, residual imbalance remained for the cytogenetic risk profile. After PSM, 83% of patients in the France Chart Review study appear to have had an intermediate cytogenetic risk profile, when compared to 59% of patients in trial population. In addition, no patients with ≥2 prior treatment lines were included in the analysis after matching.

Table 7.1: Overview of group demographic balance before and after PSM

Covariates	Pre-Matching Characteristics			Post-Matching Characteristics*		
	CCR	Enasidenib	SMD[ł]	CCR	Enasidenib	SMD
N	71	195	NA	69[‡]	69	NA
Prior HSCT, n (%)	10 (14%)	27 (14%)	0.01	10 (14%)	8 (12%)	0.09
≥2 Prior Lines of AML Therapy, n (%)	0 (0%)	104 (53%)	**1.51**	0 (0%)	0 (0%)	NA
Age ≥65 Years, n (%)	43 (61%)	124 (64%)	0.04	42 (61%)	41 (59%)	0.03
Cytogenetic Risk Profile, n (%)						
Intermediate	59 (83%)	96 (49%)	**0.38**	57 (83%)	41 (59%)	**0.32**
Poor	5 (7%)	52 (27%)	**0.54**	5 (7%)	13 (19%)	**0.35**
Failure/unevaluable	7 (10%)	47 (24%)	**0.76**	7 (10%)	15 (22%)	**0.52**
Prior MDS, n (%)	13 (19%)	43 (22%)	0.09	13 (19%)	11 (16%)	0.08

* PSM algorithm was based on optimal 1:1 matching and five covariates (history of HSCT at baseline, prior lines of therapy, age, cytogenetic risk factor, and prior MDS).

ł SMDs greater than 0.1 have been bolded.

‡ Two patients from the CCR group were excluded due to missing efficacy or covariate data.

Abbreviations: AML: acute myeloid leukemia; CCR: conventional care regimen; HSCT: hemopoietic stem cell transplant; MDS: myelodysplastic syndrome; NA: not applicable; PSM: propensity score matching; SMD: standard mean difference.

Source: [Celgene Submission document, PSM analysis report; Table 4][5]

The results of PMS analysis, after adjusting for covariates, are summarized below:[5]

- OS: The median survival rate was 12.42 months (95% CI: 8.25 – 19.90) for the enasidenib group and 6.77 months (95% CI 4.27 – 10.90) for the CCR group. The analysis results showed a statistically significant OS benefit in the enasidenib group than the CCR group (HR = 0.62, 95% CI 0.40, 0.95). At 3 and 12 months, the estimated OS rates were 82% and 51% in the enasidenib group, and 71% and 35% in the CCR group, respectively (Table 7.2).

- EFS: the proportional hazard assumption was violated for EFS curves; therefore, a weighted Cox regression analysis was used to calculate EFS HRs. The median EFS was 3.81 months (95% CI: 3.06 – 7.49) for the enasidenib group and 2.73 months (95% CI: 1.71 – 4.50) for the CCR group. At 3 and 12 months, the estimated EFS rates were 62% and 15% in the enasidenib group, and 47% and 17% in the CCR group, respectively (Table 7.3). Based on the weighted HR, a statistically significant EFS benefit was reported in the enasidenib group, after adjustment for covariates (average HR: 0.66, 95% CI: 0.44 – 0.99).

Table 7.2: Summary of PSM Results; KM analysis of OS

Parameter	Pre-Match Characteristics		Post-Match Characteristics*	
	CCR	Enasidenib	CCR	Enasidenib
Sample Size	70[†]	195	69[‡]	69
Number of Events	58	149	57	41
Median OS (months), 95% CI	6.77, 4.27 – 10.05	8.02, 7.03 – 9.03	6.77, 4.27 – 10.90	12.42, 8.25 – 19.90
3-month Survival Rate (%), 95% CI	70.2, 60.1 – 82.1	77.6, 71.9 – 83.7	71.3, 61.2 – 83.1	82.3, 73.6 – 91.9
12-month Survival Rate (%), 95% CI	34.0, 24.2 – 47.9	30.2, 24.1 – 38.0	34.5, 24.6 – 48.5	51.1, 39.8 – 65.7

* PSM algorithm was based on optimal 1:1 matching and five covariates (history of HSCT at baseline, prior lines of therapy, age, cytogenetic risk factor, and prior MDS).
[†] One patient was excluded due to missing efficacy data.
[‡] One patient from the CCR group was excluded due to missing covariate data.
Abbreviations: CCR: conventional care regimen; CI: confidence interval; HSCT: hemopoietic stem cell transplant; KM: Kaplan-Meier; MDS: myelodysplastic syndrome; OS: overall survival; PSM: propensity score matching.

Source: [Celgene Submission document, PSM analysis report; Table 5][5]

Table 7.3: Summary of PSM Results; KM analysis of EFS

Parameter	Pre-Match Characteristics		Post-Match Characteristics*	
	CCR	Enasidenib	CCR	Enasidenib
Sample Size	70[†]	195	69[‡]	69
Number of Events	62	145	61	53
Median EFS (months), 95% CI	2.30, 1.64 – 4.50	3.81, 3.68 – 5.36	2.73, 1.71 – 4.50	3.81, 3.06 – 7.49
3-month EFS Rate (%), 95% CI	46.3, 35.7 – 60.0	61.6, 54.9 – 69.1	47.0, 36.3 – 60.8	61.5, 50.9 – 74.3
12-month EFS Rate (%), 95% CI	17.2, 9.9 – 29.7	12.6, 8.1 – 19.6	17.4, 10.1 – 30.1	14.7, 7.6 – 28.6

* PSM algorithm was based on optimal 1:1 matching and five covariates (history of HSCT at baseline, prior lines of therapy, age, cytogenetic risk factor, and prior MDS).
[†] One patient was excluded due to missing efficacy data.
[‡] One patient from the CCR group was excluded due to missing covariate data.
Abbreviations: CCR: conventional care regimen; CI: confidence interval; EFS: event-free survival; HSCT: hemopoietic stem cell transplant; KM: Kaplan-Meier; MDS: myelodysplastic syndrome; PSM: propensity score matching.

Source: [Celgene Submission document, PSM analysis report; Table 6][5]

7.7.4 Summary and Conclusions

The results of the submitted PMS analysis indicate that treatment with enasidenib could result in a statistically significant improvements in OS (HR: 0.62, 95% CI: 0.40 – 0.95) and EFS (average HR: 0.66, 95% CI: 0.44 – 0.99) as compared to CCR. The results suggest that enasidenib may offer clinically relevant benefits for patients with R/R AML and an IDH2 mutation when compared to CCR. However, the results of the PSM analysis should be interpreted with caution due to the following limitations:

- 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 ≥ 2 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.

  Upon feedback on the initial recommendation, the sponsor disagreed with the statement above and expressed that 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.

  The Methods Team noted that the generalizability of the ATU results depends on the degree to which the untreated population is representative of the population that will be treated. As noted in the clinical guidance report, characteristics of the untreated sample (French Chart Review) were different from those who would be treated (i.e., trial population). 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 that 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 a better cytogenetic risk profile than the trial population, after matching. After propensity score matching, 83% of patients in the France Chart Review study appear to have had an intermediate cytogenetic risk profile when compared to 59% of patients in trial population (For more information refer to Section 7.3.3).
  - In the AG221-C-001 Study, 30.4% of patients received two prior regimens, and 22.4% received three or more prior therapies (Refer to Table 6.3). Treated patients with ≥2 prior treatment lines were excluded from the ATU analysis, as a result of matching.

- The definition of baseline (T0) 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 PMS analysis report as unmeasured confounders (such as IDH2 mutation location, creatinine clearance at baseline, National Comprehensive Cancer Network [NCCN] risk stratification, etc.) 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, since the ATU represents the effect of the drug (enasidenib) on patients France Chart review population that 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).[5]

- Patients with missing data were excluded from the PSM analyses, and no imputation for missing data. The submitted report indicated that missing data 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.

Upon reconsideration, the Sponsor noted that 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. The information included in Sponsor's comment had been acknowledged in the initial clinical guidance report that was reviewed by pERC.

8 COMPARISON WITH OTHER LITERATURE

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Leukemia Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on enasidenib for AML. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Leukemia Clinical Guidance Panel is comprised of four clinicians. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via Ovid platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** March 2019, **Embase** 1974 to 2019 April 09, **Ovid MEDLINE(R) ALL** 1946 to April 09, 2019
Search Strategy:

#	Searches	Results
1	(Idhifa* or enasidenib* or AG 221 or AG221 or CC 90007 or CC90007 or 3T1SS4E7AG).ti,ab,ot,kf,kw,hw,nm,rn.	372
2	1 use medall	80
3	1 use cctr	16
4	*enasidenib/	56
5	(Idhifa* or enasidenib* or AG 221 or AG221 or CC 90007 or CC90007).ti,ab,kw,dq.	252
6	or/4-5	254
7	6 use oemezd	162
8	7 not conference abstract.pt.	98
9	7 and conference abstract.pt.	64
10	limit 9 to yr=2014-current	63
11	2 or 3 or 8	194
12	remove duplicates from 11	127
13	10 or 12	190
14	limit 13 to english	177

2. Literature search via PubMed

A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

Search	Query	Items found
#5	Search **#3 AND publisher[sb]** Filters: **English**	6
#4	Search **#3 AND publisher[sb]**	6
#3	Search **(#1 OR #2)**	80
#2	Search **(Idhifa*[tiab] OR enasidenib*[tiab] OR AG 221[tiab] OR AG221[tiab] OR CC 90007[tiab] OR CC90007[tiab] OR 3T1SS4E7AG[rn])**	76
#1	Search **"AG-221" [Supplementary Concept]**	26

3. **Cochrane Central Register of Controlled Trials (CENTRAL)**
   (searched via Ovid)

4. **Grey literature search via:**

Clinical trial registries:

US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials

http://www.canadiancancertrials.ca/

Search: Idhifa/enasidenib, acute myeloid leukemia

Select international agencies including:

US Food and Drug Administration (FDA)

https://www.fda.gov/

European Medicines Agency (EMA)

https://www.ema.europa.eu/

Search: Idhifa/enasidenib, acute myeloid leukemia

Conference abstracts:

American Society of Clinical Oncology (ASCO)

https://www.asco.org/

European Society for Medical Oncology (ESMO)

https://www.esmo.org/

American Society of Hematology (ASH)

http://www.hematology.org/

Search: Idhifa/enasidenib, acute myeloid leukemia — last five years

Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the PRESS (Peer Review of Electronic Search Strategies) checklist (https://www.cadth.ca/resources/finding-evidence/press).[58]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Idhifa and enasidenib.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of July 31, 2019.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[59] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov and Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the

American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and the American Society of Hematology (ASH) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the CADTH Clinical Guidance Panel. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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