CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Enasidenib (Idhifa) for Acute Myeloid Leukemia

October 31, 2019

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Celgene Inc. compared enasidenib to conventional care regimen (CCR) for patients with relapsed or refractory acute myeloid leukemia (R/R AML) with an isocitrate dehydrogenase 2 (IDH2) mutation.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	Funding request and patient population modelled are consistent, adult R/R AML with IDH2 mutation.
Type of Analysis	Cost Utility Analysis ($/QALY), Cost effectiveness Analysis ($/LY)
Type of Model	Partitioned-survival model
Comparator	Conventional care regimen (CCR) includes weighted mixture of AML treatments in Canadian context: 27.6%: Azacitidine 17.4%: 7-days cytarabine,3-days daunorubicin (7+3) 14.4%: Low dose cytarabine (LDAC) 40.6%: Best supportive care only
Year of costs	2019
Time Horizon	10-year
Perspective	Canadian public health care payer perspective
Cost of enasidenib	Recommended dose of enasidenib is one 100mg tablet daily, for at least 6 months until disease progression or unacceptable toxicity. Cost per 100mg tablet (and daily cost) of enasidenib: $1,216. 28-day cost: $34,048. (assumes no wastage).
Cost of conventional care regimen (CCR) * *Price Source: published pCODR submission, Cancer care monographs*	CCR weighted mixture within a typical Canadian clinical practice of available treatments for AML in Canada (see tables 2,3 below) 28-day cost: $1,556.90.
Discount Rate	1.5% annually for costs and effects
Model Structure	Patients in the model were assigned to one of three health states: event free survival (EFS), progressed disease (PD), and death. Overall survival (OS) was partitioned into EFS and PD states, and modelled with extrapolated regression curves. In each cycle of the model, the proportion of patients in the PD state was calculated as the difference between OS and EFS.
Key Data Sources	Enasidenib efficacy outcomes (OS, EFS) were based on enasidenib using only Phase I/II trial clinical trial AG221-C-001 (n=214).

	CCR efficacy outcomes (OS, EFS) were based on France chart review (n=71) receiving mixture of conventional care regimen with R/R AML IDH2. Relative efficacy was derived from an indirect treatment comparison using propensity score matching methodology of enasidenib compared to CCR (n=69 per treatment arm). The treatment mix selected from CCR matched the current Canadian context. Rates of adverse events were obtained from AG221-C-001 and literature for AML for CCR. Health-related quality of life for health-states and adverse events were based on estimates identified from a literature review. Costs for health-states, adverse events, and subsequent therapy (1 per patient) were based on Ontario unit costs and clinical opinion for resource utilization.

Table 2. Conventional Care Regimen Recommend Dosage

Regimen	Drug	Dose (mg)	Dosing	Schedule	Route	Number of Cycles (28 day)	Sources
LDAC	Low dose cytarabine	40	Fixed	Days 1-10, q12h	SC	4	Clinical Advisor Opinion; Alberta Health Services.
Azacitidine	Azacitidine	75	/m^2	Days 1-7	SC	3	Cancer Care Ontario Regimen Monograph; Median number of cycles (Pleyer 2014)
7+3	Daunorubicin	60	/m^2	Days 1-3	IV	1	Cancer Care Ontario Regimen Monograph
	Cytarabine	200	/m^2	Days 1-7	IV	1	Cancer Care Ontario Regimen Monograph

Table 3. 28-day cost for Conventional Care Regimen

	Conventional Care Regimen	Low dose cytarabine	Azacitidine	7+3	Best Supportive Care Only*
weeks	Weighted Average	14%	28%	17%	41%
1	$1,551.07	$94.50	$4,396.00	$1,863.00	$0.00
2	$5.83	$40.50	$0.00	$0.00	$0.00
3	$0.00	$0.00	$0.00	$0.00	$0.00
4	$0.00	$0.00	$0.00	$0.00	$0.00
total (28 days)	$1,556.90				

*Best Supportive Care Only assumed zero to be conservative due to uncertain pricing of generics.

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison to CCR (27.6% azacitidine, 17.4% 7+3, 14.4% LDAC, and 40.6% best supportive care only) is appropriate for the economic model because it uses the therapies that are currently provided for AML, although there is no current targeted therapy for R/R AML. The CGP considered effectiveness, safety, burden and need.

Effectiveness. There is significant uncertainty on the extent of the therapeutic effect of enasidenib given the limitations of the available studies. In making the above conclusions, the CGP took into the consideration the following: 1) results were derived from a single arm study, 2) in the absence of control arm, it is not possible to differentiate the treatment effect from other determinants of response or survival, 3) there are no long-term data and no direct data on health related QoL, and 4) there were limitations of the ITC using propensity matching. The ITC was built on a small subset of patients who were treated with enasidenib.

Safety. Enasidenib is 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 often included clinical laboratory values such as hyperbilirubinemia (12% of patients) and differentiation syndrome that occurred in 7% of patients.

Burden. There were 1509 new diagnosis cases of AML in Canada in 2017 and approximately 12% of these cases harbor the IDH2 mutation. Up to 50% of patients with AML have either refractory disease or relapse after having achieved remission. Thus, the estimate of the number of new cases year eligible for enasidenib would be 90 (1509 * 12% * 50%).

Need. Patients with relapse and refractory (R/R) AML have a poor prognosis with only 5-10% of patients being alive after 5 years. The current treatments are rarely effective and there is a significant unmet need for effective treatment options.

Clinician Input

Current Treatment(s) for the Indication Under Review:

- 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.

- *EGP comment: There are no specific comparators for IDH2 mutated AML approved in this setting, while azacitidine would be a comparator for AML and is not a targeted comparator for the IDH2 mutation.*

Eligible Patient Population

- Clinicians indicated that there is a clear unmet need in the population specified in the AG221-C001 trial and in the reimbursement request, and that this population corresponds to a small group in clinical practice 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

available to them. Treatment with enasidenib would offer patients with an IDH2 mutation a chance of response and prolongation of overall survival.

- Clinicians agreed 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.

➢ *EGP comment: The treatment for IHD2 R/R AML is an unmet need.*

Relevance to Clinical Practice

- One of the three clinicians had experience with using enasidenib. It was noted that only patients with a confirmed IDH2 mutation would be eligible for enasidenib. According to the clinicians, enasidenib is an oral therapy that is well tolerated with side effects comparable to other therapies used in this setting and no significant contraindications.
- Clinician with experience: In younger fit patients, the drug would be continued while responding and if stem cell transplant was feasible then this option should be considered. In older and unfit patients who are not eligible for stem cell transplant, the drug would be continued while patients are responding. There are no other Health Canada approved treatments for patients with R/R AML and the best option for these patients is currently enrollment on clinical trial. After patients are refractory to 1-2 cycles of intensive chemotherapy they are very unlikely to enter a remission with further intensive chemotherapy or gain benefit from this. In older unfit patients who do not respond or progress on a hypomethlyating agent there a few other options than best supportive care. On average, the median OS in patients with R/R AML is ~2-3 months so this treatment does appear to offer a significant OS benefit acknowledging that the available data is from a single arm trial. I do not think there are specific contraindications to the new drug and the drug appears to be well tolerated. It has a risk of differentiation syndrome similar to ATRA and ATO, but this appears to be manageable as well as a risk of indirect hyperbilirubinemia. It has less risk of myelosuppression and tissue/gut toxicity than conventional AML salvage chemotherapy

➢ *EGP comment: The economic model includes cost and impact on quality of life for adverse events, although no quality of life data was collected in the enasidenib studies. The CGP stated that the drug enasidenib may have acceptable tolerability compared to other drugs for AML.*

Sequencing and Priority of Treatments

- 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.

➢ *EGP comment: The drug enasidenib would be used for second line AML who are either Relapsed or Refractory, and sequencing was not investigated in the economic model. CGP noted it is reasonable to offer enasidenib at any point in relapsed or refractory setting (i.e., first, second, or later relapsed), however, the model only considered second line AML who are either Relapsed or Refractory. The enasidenib Phase I/II data suggest that there is similar EFS for differing lines of AML therapy (2^{nd}, 3^{rd}, 4^{th}).*

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.

- *EGP comment: IDH2 is tested as part of NGS when diagnosing AML, and clinicians suggest that IHD2 should be retested when R/R. The economic model considered testing at R/R for a proportion of patients, but not all.*

Implementation Questions
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.

    - *EGP comment: Clinicians noted a proportion of patients in the study proceed to transplant (a curative treatment). Enasidenib can be used a bridge to transplant, with increased EFS leading to increased likelihood of receiving s stem cell transplant. Among patients who proceeded to transplant during the study, median OS was 23.6 months (95% CI, 10.6 to not reached). the median OS among all patients with R/R AML who received enasidenib 100 mg/day (n = 214) was 8.8 months (95% CI, 7.7-9.6). The economic model does not evaluate the potential of using enasidenib as a bridge to stem cell transplantation.*

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.

- *EGP comment: IDH2 is relatively stable, but due to slight variability over time, IDH2 should be retested when R/R.*

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.

➢ *EGP comment: The economic model was built on event-free survival (EFS). EFS was defined the interval between first enasidenib dose and AML relapse (≥5% bone marrow blasts, reappearance of blasts in blood, or development of extramedullary disease), disease progression, or death. CGP stated that this was a reasonable output.*

Patient Advocacy Group Input

An online survey was posted on Leukemia & Lymphoma Society of Canada (LLSC) Facebook page and distributed by the LLSC staff asking for input from patients who are currently in treatment or in remission from AML. Overall, 12 individuals who had experience with AML completed online survey was posted on Leukemia & Lymphoma Society of Canada (LLSC) 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.

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. According to LLSC, most patients reported various 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. From a patient perspective, patients value managing disease-related symptoms and improving quality of life.

- *EGP comment: R/R AML affects all ages, while the current economic model focuses on adults to be consistent with the funding request. The cost and impact on quality of life from the listed adverse events were included in the economic model, including thrombocytopenia, fatigue, anemia and infections.*

Patients' Experience with Current Therapy

- 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.
- Patients were also asked to rate what side effects they were willing to tolerate with a new medication. The information indicated that they would be more willing to deal with short-term side effects like nausea; diarrhea; edema; loss of appetite as opposed to tolerating more severe side effects like pain and bruising and bleeding. The general consensus was that if the benefits outweighed the side-effects, they would all be willing to tolerate the effects in the short-term.

- *EGP comment: Respondents were more worried about pain, bruising and bleeding (thrombocytopenia). The economic model reported increased rates of adverse events with enasidenib for: anemia (+18%), febrile neutropenia (+17%), pneumonia (+13%), sepsis (+8%), dyspnea (+5%), thrombocytopenia (+5%), but decreased rates of neutropenia (-6%).*

Provincial Advisory Group 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 included eligible patient population, and economic factors included additional monitoring and management of treatment-related toxicities.

Currently Funded Treatments.

- PAG identified that for older patients, there is no standard of care for R/R 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 IDH2 mutation.

- *EGP comment: The economic model includes a weighted mix of comparators: azacitidine, low dose cytarabine, 7+3, and best supportive care. Hydroxyurea was not included as a comparator but was included as an option within best supportive care.*

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.

- *EGP comment: The submitted economic model did not included subgroups.*

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.

- *EGP comment: The economic model includes enasidenib as second line only (R/R AML).*

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.

- *EGP comment: The economic model does not include transplant options. Subsequent care following progression following enasidenib includes only the costs of pharmacotherapy.*

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.

- *EGP comment: According to CGP, there are no data to inform switching to new agent if patients are responding to current treatment. Most physician would continue current treatment and not switch patients if patient is responding and has no evidence of progression, with acceptable toxicity.*

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.

- *EGP comment: The budget impact analysis and economic model assumes the full cost of prescribed dosages (100mg daily without wastage).*

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.

- *EGP comment: The submitted economic model assumes the treatment duration which occurred in the trial until disease progression (4.14 months or 17 weeks), while a scenario analysis assumed the enasidenib treatment duration in the trial (7.45 months).*

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.

- *EGP comment: The economic model includes the costs of ongoing monitoring during different disease states.*

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.

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).

- *EGP comment: The economic model was built solely on patients who became R/R after failed first line therapy, which is limited by finding a historical cohort for matching with only history of one line of AML therapy. However, the duration of EFS was similar in the enasidenib study for patients with different lines of AML therapy.*

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.

- *EGP comment: The economic model assumed that IDH2 testing was conducted as part of AML testing in NGS. Additional IDH2 testing should occur when R/R occurs, due to variability in IDH2.*

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.

- *EGP comment: The economic model does not address if enasidenib could be used in first-line therapy, when IDH2 is first detected positive.*

1.3 Submitted and EGP Reanalysis Estimates

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

There were limitations with the submitted economic evaluation that could not be addressed in reanalysis. First, the economic model was built on comparative data that was not generated with RCT evidence. The propensity matched analysis used only about 1/3 (69/214) of the patients that were treated with enasidenib because of the inability to match all patients to the small sample size of the comparator CCR data (n=71). Also, the matched analysis only included patients who have had one prior lines of AML therapy whereas the funding request is for all R/R patients, at any point in the R/R disease setting. But, on the other hand, the EFS for patients treated with enasidenib have similar rates of EFS for different numbers of prior lines of AML therapy. The ongoing phase III trial can provide context since it includes patients for of R/R after second or third-line however the final analysis date is expected in 2020 (NCT02577406).

Second, there is an absence of long term data for overall survival. Meanwhile, the time period for EFS is short and the trial period captured most of the EFS events.

Third, the economic model does not incorporate the full experience of the patient. This includes having more than 1 extra line of subsequent therapy (the model only allows 1 subsequent therapy and only costs are included), or using enasidenib to extend time and stabilizing the patient to allow for the curative stem cell transplantation. Thus, the model in the current form cannot address sequencing or the potential economic benefit of creating a bridge to stem cell transplantation.

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the submitted economic model:

First, in reanalysis the enasidenib treatment duration was increased from median EFS to the actual enasidenib treatment duration which occurred in the trial. The submitted economic model used 4.14 cycles (3.8 months) for enasidenib treatment duration, based on median EFS. However, enasidenib can be continued if there is a clinical benefit (lack of disease progression and acceptable toxicity) and in the clinical trial the actual enasidenib treatment duration was 32.30 weeks (mean 7.45 months). This increases the ΔC from $142,124 to $213,893 which increased the ICUR +$134,803/QALY.

Second, in reanalysis EFS was modelled with individual Weibull curves instead of the submitted use of hazard rate models of EFS (i.e., hazard model includes one curve with a covariate for treatment to generate 2 results). The proportional hazard assumption was violated with EFS but not for OS. Thus, the use of OS hazard models by the sponsor was accepted. In addition, Weibull curves is the most common

type of curve for AML modelling. This increases the ΔC from $142,124 to $158,449 and reduces ΔE (QALYs) from 0.53 to 0.47, which increases the ICUR +$70,931/QALY.

Third, in reanalysis the time horizon of the model was reduced from 10 years to 5 years, which was supported by CGP based on the expected time horizon in clinical practice for this patient population. A 10-year time horizon was selected in the submission, given that in the reference case analysis <1% of CCR-treated patients and 2.5% of enasidenib-treated patients are alive at 10 years. However, most of this benefit was created by the tail of the extrapolated survival curves and is not established with long term OS data. This reduction in time horizon was considered appropriate given the uncertainty in the long tern OS data, and the supported evidence was based on a median follow-up time was 7.8 months. This decreases ΔC from $142,124 to $126,652 and reduces ΔE (QALYs) from 0.53 to 0.41, which increases the ICUR +$39,404/QALY.

Fourth, in reanalysis, the economic model would include the cost of all patients who are R/R AML would be receiving NGS panel at least one time to identify the IDH2 mutation. Including the costs for all patients will account for all resources in the treatment of R/R AML IDH2. In the submitted model, only reanalysis of 20% of the patients generated a cost for NGS ($1000/test). After R/R, some patients may receive PCR testing ($500/test) which is not often performed during AML diagnosis instead of NGS ($1,000/test). Because there is provincial variation in choices of tests (PCR, NGS), rates of retesting, and there is wide variation in prices of each tests, the average price for NGS was analyzed and assumed to occur at least once for each patient. This decreases ΔC from $142,124 to $142,023 and leaves ΔE (QALYs) unchanged, which reduces the ICUR -$188/QALY.

Fifth, in reanalysis, the local current price for a day in the hospital was used instead of a literature value. In the submitted economic model, the costs for cancer palliative care were $509.21/day, instead in reanalysis, the Ontario current cost was $1,258.20/day for cancer palliative care based on OCCI admission data for ICD10 CA codes Z54.1 (Convalescence following radiotherapy) and Z54.2 (Convalescence following chemotherapy). This decreases ΔC from $142,124 to $139,253 and leaves ΔE (QALYs) unchanged, which reduces the ICUR -$5,392/QALY.

Overall, the changes made in EGP reanalysis increased the ΔC from $142,124 to $204,090 (difference = +$61,966) and decreased the ΔE (QALYs) from 0.53 QALYs to 0.36 QALYs (difference = -0.17 QALYs) from the submitted base. This resulted in a change in the ICUR from $266,947/QALY to $566,858/QALY (difference = +$299,911/QALY).

Table 5. Submitted and EGP Estimates

Estimates (range/point)	Submitted	EGP Reanalysis	Change
ΔE (LY)	0.85	0.64	-0.21
Progression-free	0.44	0.09	-0.35
Post-progression	0.40	0.55	0.15
ΔE (QALY)	0.53	0.36	-0.17
Progression-free	0.33	0.08	-0.25
Post-progression	0.21	0.28	0.07
Adverse events	<0.01	<0.01	0
ΔC ($)	$142,124	$204,090	$61,966
Progression-free	$109,592	$159,843	$50,251
Post-progression	$32,892	$45,199	$12,307
End-of-Life	$-361	$-952	-$591
ICER estimate ($/QALY)	$266,947/QALY	$566,858/QALY	$299,911

Table 6. EGP Reanalysis Estimates, probabilistic results (5,000 iterations) (submitted and EGP reanalysis)

EGP's Reanalysis for the Best Case Estimate					
Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR ($/QALY)	Δ from baseline submitted ICER
Sponsor's reference case	$142,124	0.53	0.85	$266,947	--
1.Enasidenib treatment duration	$213,893	0.53	0.85	$401,750	$134,803
2. Modelling of EFS (hazard to individual curves)	$158,449	0.47	0.85	$337,878	$70,931
3.Time horizon reduced 10 to 5 years	$126,652	0.41	0.64	$306,351	$39,404
4. Include NGS cost for all patients	$142,023	0.53	0.85	$266,759	-$188
5. Hospital day costs changed to local prices	$139,253	0.53	0.85	$261,555	-$5,392
Best case estimate of above [1,2,3,4,5] parameters					
EGP Reanalysis	$204,090	0.36	0.64	$566,858	$299,911

1.5 Evaluation of Submitted Budget Impact Analysis

The budget impact analysis was based on a national payer perspective. Inputs that had a large increase in the budget impact were increased IDH2 mutation prevalence rate, increased enasidenib treatment duration and increased AML prevalence.

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

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for enasidenib when compared to conventional care regimen is:

- $566,858/QALY
- The extra cost of enasidenib is $204,090. The main source of extra costs is for enasidenib drug treatment and increased transfusion of blood products in prolonged progressive state.
- The extra clinical effect of enasidenib is 0.36 QALYs. The increased QALYs occur because of prolonged event free survival and prolonged period in the progressed state.

Overall conclusions of the submitted model:
The economic model was limited in its scope due to limited available evidence. This includes not having enough published evidence to support building a more complex model that captures the patient's life-time horizon experience of drug sequencing with one than 1 line of AML therapy, and stem cell transplantation. In addition, the main efficacy outcomes were estimated without RCT evidence, but instead were generated with an indirect comparison after propensity score matching and regression analysis of a small sample size.
Within the submitted economic model, the assumptions that lead to large changes in the ICUR estimates were choice of extrapolation model for long term overall survival, enasidenib treatment duration, and choice of utility values for disease states.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Leukemia Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of enasidenib for AML. A full assessment of the clinical evidence of [drug name and indication] is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR 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 Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

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

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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