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pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Midostaurin (Rydapt) for Acute Myeloid Leukemia

December 19, 2017

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by** Novartis Pharmaceuticals compared midostaurin (MIDO) with standard of care for adult patients with newly diagnosed *FLT3* mutation-positive acute myeloid leukemia (AML). The modelled population was identical to that of the RATIFY phase III randomized controlled trial[1]; namely previously untreated, *FLT3* mutation-positive AML patients and consistent with the patient population who would be considered eligible for MIDO in Canada. During the induction phase, in addition to the standard of care (SOC) of daunorubicin and cytarabine given intravenously, patients received MIDO or placebo orally.[1] Patients who achieved complete remission (CR) received consolidation therapy with cytarabine plus MIDO or placebo (Table 1). In the RATIFY trial, patients also received maintenance therapy with MIDO or placebo; however, as per the Health Canada approved indication for MIDO (i.e., administration at induction and consolidation phases only, and not at the maintenance phase), the health outcomes and costs associated with maintenance therapy were removed from the submitted model. Patients could receive stem cell therapy (SCT) during the study.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	Newly diagnosed, previously untreated, *FLT3* mutation-positive AML patients (modeled population is aligned with that of funding request)
Type of Analysis	*Cost-effectiveness and cost-utility analyses*
Type of Model	*Partitioned-survival model*
Comparator	*Standard of care consisting of induction therapy: IV daunorubicin (60 mg/m^2 on days 1-3) and IV cytarabine (200 mg/m^2 on days 1-7); re-treatment allowed if residual AML on a day 21 bone marrow exam; consolidation therapy: If patients achieved complete remission after induction therapy, patients received 4 x 28 day cycles of consolidation therapy with high-dose cytarabine (dose of 3000 mg/m^2, over a period of 3 hours every 12 hours on days 1, 3 and 5).*
Year of costs	*2017*
Time Horizon	*15 years*
Perspective	*Canadian public payer*
Cost of MIDO (This is an add-on therapy)	• $167.92 per 25 mg tablet • At the recommended dose of 50 mg twice per day:$671.70 per day • $9,402.40 per 21- day course on days 8 to 21 of each induction and consolidation cycle
Cost of standard treatment (before adding MIDO)	**Induction** Daunorubicin: • $93.00/20mg vial At the recommended dose of 60 mg/m^2 on days 1 to 3 of a 21-day cycle: • $67.75 per day

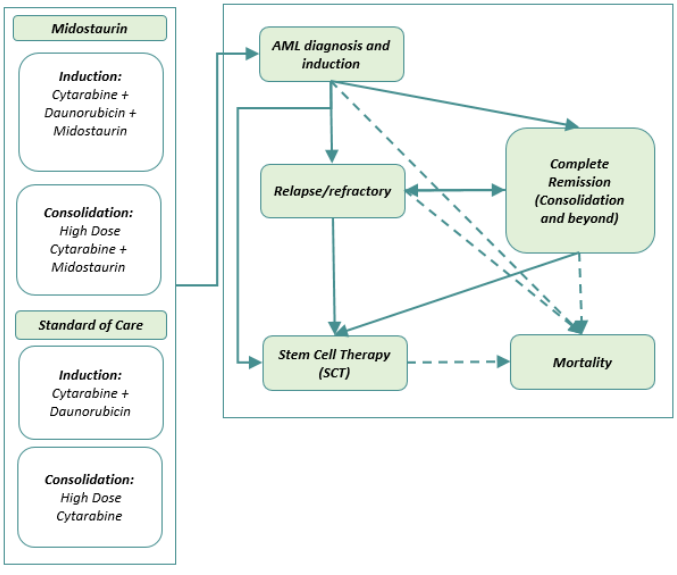
	• $1422.90 per 21-day course (used days 1-3 of each cycle) Cytarabine: • $6.75/100mg vial At the recommended dose of 200mg/m^2 daily by CIV for 7 days of 21-day cycle: • $7.65 per day • $160.65 per 21-day course **<u>Consolidation</u>** Cytarabine • $6.75/100mg vial At the recommended dose of 3000mg/m^2/day over 3 hours every 12 hours on days 1, 3, 5 twice per day: • $49.18 per day • $1,032.75 per 21-day course
Model Structure	A partitioned survival model was used with five health states: i) AML diagnosis/induction, ii) complete remission (CR) (including consolidation and beyond), iii) relapse/refractory (secondary therapy/reinduction), iv) stem cell therapy (SCT), and v) mortality. All patients started from the initial AML diagnosis/induction state and moved either to the CR, relapse or death state. Patients in the CR state could move to relapse/SCT/death states, but only these patients could receive SCT prior to relapse. SCT patients could move only to death (absorbing) state (i.e., no relapse/subsequent therapy after SCT was assumed) (Figure A). 

	Figure A. Model framework (excludes treatment during maintenance)
Key Data Sources	*Data on clinical effectiveness of MIDO and standard of care arms came from the RATIFY trial. The overall survival estimates were corrected to reflect the exclusion of the maintenance phase with midostaurin. Extrapolation was used to model overall and event-free survival beyond trial duration. Drug utilization information came from the trial with drug costs coming from Canadian sources. Resource utilization for routine care (all medical care costs except medications) came from a UK study. Unit costs for routine care came from Canadian sources but the total costs did not reflect the Canadian fee for service reimbursement structure. The occurrence of adverse events came from the RATIFY trial with unit costs coming from Canadian sources. Utilities were estimated outside the trial, using a TTO technique in a sample of UK general public.*
Note: ** Drug costs for all comparators in this table are based on costing information under license from IMS Health Canada Inc. concerning the following information service(s): DeltaPA and may be different from those used by the submitter in the economic model. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc. Quintile IMS DeltaPA– accessed on August 15, 2017. All calculations are based on = 70kg and body surface area (BSA) = 1.7m$^{2.}$*	

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate. The CGP concluded that there is a net clinical benefit to the incorporation of MIDO into the induction and consolidation treatment phases for these patients. Although some Canadian centres use a higher dose of daunorubicin than in the trial, use idarubicin instead of daunorubicin, or use variable consolidation therapy doses for high dose cytarabine (HIDAC) chemotherapy, these differences were not assumed to change the efficacy or safety of MIDO. Some Canadian centres use FLAG-IDA for induction but CGP did not support the combination of MIDO with this regimen. It was also noted that physicians prescribing concomitant CYP3A4 inhibitor antifungal agents may need to consider a dose reduction of MIDO. The latter would reduce MIDO costs.

Summary of registered clinician input relevant to the economic analysis
Registered clinicians stated that MIDO will improve survival and will allow for more patients to receive SCT. Steven-Johnson syndrome rash is one of the serious adverse events reported after MIDO use by registered clinicians. However, no such serious adverse event was reported in RATIFY trial; the economic model considered the costs of exfoliative dermatitis. Another concern was that *FLT3* testing should be conducted early so MIDO can be used from the 8th day of induction. The model population considered patients that were already *FLT3* mutation-positive. The current rate of *FLT3* testing that was incorporated into the budget impact analysis (BIA) was obtained from a survey of Canadian physicians.

Summary of patient input relevant to the economic analysis
Patients and caregivers that were surveyed for this evaluation had little experience with MIDO. In general, patients commented about the side effects of AML treatments but were also in support of drugs that extend survival (i.e., willing to tolerate side effects for survival benefits). The economic model considered the adverse events both when estimating the treatment

benefits and treatment costs. Grade 3/4 adverse events (AEs) with a prevalence of ≥5% in any of the treatment phases (induction, consolidation) were included in the model. Platelet count, neutrophil count, hemoglobin, febrile neutropenia, leukopenia NOS, lymphopenia, diarrhoea NOS, hypokalemia were the most frequent AEs. Patient input also noted that improvement in the ability to function and quality of life (QoL) was important. The RATIFY trial did not collect patient reported outcomes, including quality of life data. It is unknown how MIDO impacts a patient's QoL. Utilities were estimated outside the RATIFY trial, using a TTO technique in a sample of UK general public.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG noted that MIDO is an oral drug and would be an add-on therapy to intravenous chemotherapy; this is an enabling factor to uptake since patients can continue receiving MIDO at home without the need to travel to a treatment centre. PAG also mentioned that although *FLT3* testing is available in most provinces, the test would need to be available in all sites that will adopt the treatment. The BIA assumed that once diagnosed, all patients (100%) will have *FLT3* testing as soon as MIDO is adopted in clinical practice.

1.3 Submitted and EGP Reanalysis Estimates

In the cost-effectiveness analysis, the MIDO arm had higher life expectancy than SOC arm by 0.62 years with an increased cost equal to $18,049, and an ICER of $29,311/LY. In the cost-utility analysis, the difference in QALYs was 0.80 favoring MIDO and resulting in an ICUR of $22,579/QALY (Table 2).

Using trial data only, MIDO versus SOC resulted in 0.47 life years gained, contributing to 64% of life years gained when considering a 15-year time horizon (Note: the time horizon was considered adequate by CGP as most relapses will have occurred by 5 years). When looking at cost by category, MIDO had lower routine care costs, resulting in significant cost savings in the submitter's analysis. Routine care costs included physician, nurse, pharmacist and inpatient unit stay costs for all states. The higher routine care costs in the SOC arm compared with the MIDO arm are explained mostly by the high cost of routine care in the relapse state and a higher number of patients in the relapse state in the SOC arm.

The submitter conducted scenario, one-way and probabilistic sensitivity analysis (PSA). Using a lifetime horizon and resource utilization for conventional chemotherapy regimen arm instead of midpoint from the azacitidine study resulted in noticeably lower ICERs. Using utility values from published literature resulted in a higher ICER. One-way sensitivity analyses were sensitive to MIDO overall survival, CR rate and routine care costs after relapse, none of which changed the direction of the ICER.

Table 2. Submitted and EGP Estimates

Estimates (range/point)	Submitted	EGP Reanalysis
ΔE (LY)	0.62	
ΔE (QALY)	0.80	
ΔC ($)	$18,049	
ICER estimate ($/QALY)	$22,579/QALY	

The main assumptions and limitations with the submitted economic evaluation were:

The submitted model was based on a partitioned survival model with 5 states reflecting the disease progression in AML. This type of model structure comes with a limited flexibility in modifying the underlying hazard ratios for OS or EFS (Note: the submitter conducted sensitivity analysis using confidence intervals around the HRs and different survival distributions). The model

allowed for two cycles of secondary therapy which was considered adequate by the CGP since the survival gain represents a more significant treatment benefit. No relapse was assumed after SCT and no subsequent SCT, which was also considered adequate by the CGP. Other limitations included:

- No utility data were collected from the patients in RATIFY trial. Novartis sponsored a study (using TTO) to estimate utilities for the health states from the model in a convenience sample of general public members in the UK. We tested the effect of some of these values using utilities from the literature.
- The RATIFY trial did not capture resource utilization by the patients. The unit costs for drugs (except MIDO), SCT, routine care, adverse events and mortality came from Canadian sources. Resource utilization for the routine care came from a UK study that surveyed physicians on resource utilization for the NICE TA399 study. This is a major limitation since the population modeled for the evaluation of azacitidine for AML was older and sicker compared to the RATIFY study population. To obtain total costs for routine care the submitter multiplied the total minutes of service use/cycle by the cost for service/minute. This is not representative to Canadian healthcare service costs where the fee-for-service is the most accepted reimbursement structure. The effect of this limitation on the model is unclear, although there were more patients who received routine care in the SOC arm.
- The RATIFY trial did not capture post-SCT events. To calculate the total cost for SCT the submitter considered 1-year post-procedural costs of complications, i.e., the rate of graft versus host disease. The model assumed that this event will occur in 39% of patients. The parameter selection was not well justified and was tested in one-way sensitivity analysis by EGP.
- The submitter assigned a unit cost to mortality but did not justify the selection of its components. The submitter assigned zero costs to routine care and post-SCT recovery after 39th cycle considering the short treatment duration of the experimental treatment. Both parameters were tested in one-way sensitivity analysis by EGP.

1.4 Detailed Highlights of the EGP Reanalysis

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

- **Utility for SCT procedure**: The estimate used by the submitter was -0.210 based on the TTO study by Novartis and 0.61 based on a systematic review of QLQ-C30 scores[2] and EQ-5D mapping algorithm[3] as per the submitter. The change of this parameter resulted in a very small benefit gain by MIDO and a slightly lower ICER (Table 3).
- **Utility for induction period:** The estimate used by the submitter was 0.162 based on the TTO study. The 1998 study by Uyl-de Groot et al evaluated the quality of life of AML patients during induction phase (with either daunorubicin–cytosine arabinoside (control arm) or daunorubicin–cytosine arabinoside with GM-CSF).[4] The EuroQol instrument was used to assess the QoL among patients and among a representative panel of citizens in the Netherlands. The utility scores were 64.8 from patients and 77.4 from general population in the experimental arm. Testing of these values (instead of 0.162) resulted in very small benefit gains for MIDO and had almost no effect on the ICER.
- **Mortality costs:** The submitter assigned $13,996 to each mortality event. Since the amount of cost assigned to mortality was not justified, we explored the effects of assigning 0 cost to mortality and 25% and 50% higher costs than in the base case. The effect of changing the mortality cost on the overall ICER was minimal.
- **Routine care costs:** Since the routine care costs were estimated for a different patient population and resource utilization in the UK healthcare system, we tested the removal of all routine care costs, as well as assigning 25% higher and lower costs (Note: the submitter tested ±20% of this parameter). With higher routine care costs, the MIDO arm becomes more cost-saving resulting in a noticeably lower ICER.

- **Duration for routine care:** The submitter captured short-term routine care costs, up to the 39th week. We tested costs of routine care up to 6 years (based on trial duration) and 15 years (model time horizon). The increase in routine care duration to up to 15 years made MIDO a dominant arm.
- **SCT complication rate:** The submitter used an estimate for 1-year graft versus host disease rate (39%) from a study that had a different patient population (based on the study by Eapen et al).[5] This parameter was used twice, when calculating the SCT costs and the utility for post-SCT recovery. We tested the impact of this assumption by using a ±25% change in the estimate. Lower SCT complication rate slightly increased the ICER (higher costs for MIDO arm) and the opposite was observed with a lower SCT rates.
- We also calculated the ICER when reducing the unit cost of MIDO by 5% and 10%, respectively, to show how the ICER changes.

Table 3. Detailed Description of EGP Reanalysis

One-way and multi-way sensitivity analyses					
Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR ($/QALY)	Δ from baseline submitted ICER ($/QALY)
Base case	**$18,049**	**0.80**	**0.62**	**$22,579/QALY**	
SCT treatment utility = 0.61	$18,049	0.81	0.62	$22,312/QALY	-267
Induction utility = 0.648	$18,049	0.81	0.62	$22,611/QALY	32
Induction utility = 0.774	$18,049	0.80	0.62	$22,619/QALY	40
Mortality cost: 0	$18,752	0.80	0.62	$23,234/QALY	-345
Mortality cost: 25% higher	$17,918	0.80	0.62	$22,415/QALY	-164
Mortality cost: 50% higher	$17,787	0.80	0.62	$22,251/QALY	-328
Routine care costs (both arms): 0	$32,006	0.80	0.62	$40,039/QALY	17,460
Routine care costs (both arms): 25% higher	$14,599	0.80	0.62	$18,214/QALY	-4,365
Routine care costs (both arms): 25% lower	$21,538	0.80	0.62	$26,944/QALY	4,365
Duration of routine care: 6 years (75 cycles)	$13,751	0.80	0.62	$17,203/QALY	5376
Duration of routine care: 15 years (199 cycles)	-$4,280	0.80	0.62	-$5,712/QALY	Cost-saving
SCT complication rate: 25% higher	$18,307	0.76	0.62	$24,159/QALY	1,580
SCT complication rate: 25% lower	$17,790	0.84	0.62	$21,155/QALY	-1,424
MIDO cost decrease by 5%	$16,700	0.80	0.62	$20,892/QALY	-1,687
MIDO cost increase by 10%	$15,352	0.80	0.62	$19,205/QALY	-3,374
EGP's Reanalysis for the Best Case Estimate					
Description of Reanalysis	ΔC	ΔE		ICUR	Δ from baseline submitted ICER
Baseline (Submitter's best case)	**$18,049**	**0.80**	**0.62**	**$22,579/QALY**	

Best case estimate of above parameters
Since none of the parameters tested in EGP reanalysis offered satisfactory alternatives to the estimates used in the model, and none reversed or significantly changed the base case ICER, the EGP agrees with the submitter's ICER.

1.5 Evaluation of Submitted Budget Impact Analysis

The budget impact analysis (BIA) was conducted from the Canadian public payer perspective to provide a budget impact estimate across all Canadian provinces and territories. Midostaurin is intended to be administered as an add-on therapy, in combination with standard cytarabine and daunorubicin induction and HIDAC consolidation. Two hypothetical scenarios were evaluated: the world with and without MIDO reimbursement. Time horizon of BIA was three years. Parameters for BIA (size of the eligible population, costs, current market share and future uptake) came from different sources including Statistics Canada and physician surveys. Base-case analysis reflected drug utilization for both MIDO and SOC arms in the RATIFY trial. The base case analysis considered drug wastage. The cost of *FLT3* testing ($73.00) was considered separately.

The important parameters were tested in one-way sensitivity analysis by the submitter. The factors that most influence the budget impact analysis include the percentage of patients expected to receive each cycle of treatment as per the indication, the percentage of MIDO patients receiving consolidation, AML incidence and *FLT3* mutation incidence.

A potential limitation of the BIA model included the use of a drug cost for cytarabine that was different from the pharmacoeconomic model. Following an inquiry to the submitter by the EGP, this was explained by the lower cost per 100mg of drug if larger vials are considered. Additional sensitivity analysis that used a value similar to the economic model resulted in a very small increase in BIA.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for MIDO when compared to SOC is:

- The ICER is $22,579/QALY and the same as the submitter's original estimate;
- Considering the limited available evidence, the EGP agrees with the submitter's estimate that the extra cost of MIDO is $18,049. However, the true magnitude of the cost difference is uncertain due to the use of resource utilization data for routine care from a study with a population different from the RATIFY trial, and use of unit costs that are not representative of the Canadian setting in the submitted model.
- The extra clinical effect of MIDO is 0.80 QALY. There may be some uncertainty with this estimate as the utility values did not come from study patients.

Overall conclusions of the submitted model:

- *The use of a different population and different healthcare system from the Canadian setting to estimate routine care costs for AML patients is a limitation. Based on a comparison of CEA for azacitidine use in AML in the UK[6] and in Canada[7], the cost of the routine care could be overestimated (and the ICER underestimated) in the current submission. However, the variations of this parameter have a limited effect on the ICER.*
- *Other limitations include using utility estimates that did not come from AML patients and assuming no events (other than survival) after SCT. However, the over- or underestimation of these estimates have little impact on ICER, the latter been mostly driven by the incremental life years gained in MIDO arm.*

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 Final 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 midostaurin (Rydapt) for AML. A full assessment of the clinical evidence of midostaurin (Rydapt) for AML 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 information redacted from this publicly available Guidance Report.

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.

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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