CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Midostaurin (Rydapt) for Acute Myeloid Leukemia

December 19, 2017

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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 midostaurin (Rydapt) 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 midostaurin (Rydapt) for AML conducted by the Leukemia Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy group; input from the Provincial Advisory Group and input from Registered Clinicians.

The systematic review is fully reported in Sections 6. A background Clinical Information provided by the CGP, a summary of submitted patient advocacy group Input on midostaurin (Rydapt) for AML a summary of submitted Provincial Advisory Group Input on midostaurin (Rydapt) for AML and a summary of submitted Registered Clinician Input on midostaurin (Rydapt) for AML, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is the evaluate the efficacy and safety of midostaurin (Rydapt) in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy compared with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy plus placebo for the treatment of adult patients with newly diagnosed *FLT3*-mutated acute myeloid leukemia (AML). A validated test is required to confirm the *FLT3* mutation status of AML. The funding request is in line with the Health Canada indication.

Midostaurin is available as 25 mg soft gelatin capsules. The recommended dose of midostaurin is 50 mg twice daily on Days 8 to 21 of each cycle of induction with cytarabine and daunorubicin and on Days 8 to 21 of each cycle of consolidation with cytarabine. Patients may be given up to 2 cycles of induction therapy with cytarabine and daunorubicin if complete remission is not observed at the end of the first induction cycle. Patients in complete remission after induction therapy should be given up to 4 cycles of consolidation therapy with cytarabine.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The search strategy identified one study, RATIFY, that met the inclusion criteria of the systematic review.[1] RATIFY is a randomized, double-blind, phase 3 superiority trial comparing standard chemotherapy plus midostaurin to standard chemotherapy plus placebo in patients aged 18-59 years with newly diagnosed acute myeloid leukemia (AML) with a fms-related tyrosine kinase 3 gene *FLT3* mutation. Patients (n=717) were enrolled from 225 centres in 17 countries between May 2008 and October 2011. Five centres in Canada participated[2] and 13 patients were enrolled and randomized.[3] RATIFY was funded by the Cancer Therapy Evaluation Program of the National Cancer Institute (North American sites) and Novartis (non-North American sites). The data cut for the published trial was March 7, 2016.[1] Please note that the data cut for the Clinical Study Report (CSR) was April 1, 2015.[2]

Patients (n=717) were randomized in block size of 6, 1:1, stratified by *FLT3* mutation subtype (tyrosine kinase domain (TKD), internal tandem duplication (ITD) high ratio, ITD low ratio), to receive either standard chemotherapy plus midostaurin (n=360) or standard chemotherapy plus placebo (n=357) in induction, consolidation and maintenance. Hematopoietic stem cell transplantation (SCT) was not protocolized in RATIFY. However, SCT "… was performed at the discretion of the investigator".[1]

Overall, baseline characteristics were fairly well balanced between the two groups. The median age at trial entry was 47.9 years (range 18.0-60.9). A summary of key outcomes identified in the systematic review protocol are highlighted in Table 1.

Median overall survival in the midostaurin group was 74.7 months (95% CI 31.5, not reached [NR]) and in the placebo group was 25.6 months (95% CI 18.6, 42.9). Due to few events occurring after 36 months in the midostaurin group, the K-M curve plateaued (hovering slightly above 50%) thus contributing to the large observed median survival in the midostaurin group and the resulting large difference between groups in median survival (49.1 months, confidence interval not provided). [1] Compared with the difference in median survival, the HR for death (HR 0.78 (95% CI 0.63, 0.96)) and the 4-year overall survival rate (51.4% midostaurin group and 44.3% placebo group: 4-year OS difference 7.1%, confidence interval not provided) more accurately reflect the magnitude of the efficacy of midostaurin.[1] Over the course of the trial, a large proportion of patients underwent SCT: 213 (59%) in the midostaurin group and 196 (55%) in the placebo group. This was significantly higher than the proportion of patients that were anticipated to undergo SCT in the planning stage of the trial (assumed 15% in the initial sample size calculation, amended to 25% in the revised calculation). Quality of life data were not collected in this trial.

All patients in RATIFY experienced at least one adverse event (AE) of any grade. All patients enrolled in the trial, but for one in the midostaurin group (i.e., n=716) experienced at least one Grade 3/4 AE.[2] Grade 3, 4 and 5 AEs are reported in Table 7. The rate of grade 3, 4, or 5 anemia was higher in the midostaurin group than in the placebo group (92.7% vs. 87.8%).[1] The rate of grade 3, 4 or 5 rash was also higher in the midostaurin group than in the placebo group (14.1% vs. 7.6%). The rate of grade 3, 4, or 5 nausea was higher in the placebo group than in the midostaurin group (9.6% vs. 5.6%).

Limitations/Sources of Bias

- The indication proposed by the submitter included a maintenance phase with midostaurin monotherapy following the consolidation therapy. The proposed Health Canada indication aligned with the clinical trial population in the RATIFY trial. However, Health Canada did not approve this indication because the submitter failed to provide convincing evidence of the benefit of maintenance therapy. Although maintenance therapy was an integral part of the pivotal study, the patients were not re-randomized prior to the start of the maintenance phase. When the small number of patients who entered this phase was considered, it was difficult to assess the contribution of this phase to the OS benefit.[4]

- The RATIFY trial demonstrated a benefit of midostaurin on survival (HR for death: 0.78, 95% CI 0.63-0.96, p=0.009); difference in 4-year overall survival 7.1%, (confidence interval not provided) .[1] In the RATIFY trial, midostaurin was used in three phases of treatment (induction, consolidation and maintenance);

approximately 29% of patients received maintenance therapy. The indication under review is for induction and consolidation only but, as pointed out by the Health Canada review, the observed survival benefit may not be influenced by the effect of midostaurin in the maintenance phase.

Assuming, as per Health Canada's review, that there is no effect of midostaurin in the maintenance phase, the HR for overall survival reported in the published trial can be interpreted as is. However, if there is an effect of midostaurin in the maintenance phase on overall survival, there is uncertainty in the interpretation of the HR. At the Checkpoint meeting (September 2017), the submitter provided the HR for death removing patients who received maintenance, to reflect the reimbursement request (for induction and consolidation only) (removed n=120 in midostaurin group and n=85 in placebo group): HR = 0.82 (95% CI 0.65, 1.04)[5] but this is no longer a comparison of randomized groups and is subject to differential selection bias. The direction and magnitude of differential selection bias is uncertain.

Patients who achieved remission after their first induction (21 days) went on to consolidation (four 28-day cycles), thus at approximately 4.5 months some patients will have begun maintenance with midostaurin. If we consider the pre-maintenance results, visual inspection of thecumulative incidence for death curves[6] suggests that the curves begin to separate at approximately 1 month (i.e., approximately after 1 cycle of induction), suggesting that the effect of midostaurin begins early in treatment. However, the submitter did not provide an estimate of the treatment effect from the cumulative incidence curves.

The HR (ITT analysis) reported in the published trial provides an unbiased estimate of the treatment effect (midostaurin compared with placebo) on overall survival. Assuming there is no benefit of midostaurin in maintenance the HR can be interpreted as is. However, if there is uncertainty regarding the contribution of midostaurin in the maintenance phase to overall survival, the HR should be interpreted with caution as the contribution of midostaurin in the maintenance phase to overall survival cannot be estimated with certainty.

- Although the enrolment target of 714 was met (n=717 enrolled), the number of events (death) was not reached (event target = 509, events observed = 377). This may be in part due to the much higher than anticipated occurrence of stem cell transplant (57% compared with the 25% assumed for sample size planning purposes).

- During study planning, the proportion of patients expected to undergo SCT was 15%. However, the observed proportion, when the sample size was amended, was 25%. Further, the observed rate at data cut-off March 7, 2016 was 57%.

- Overall, a large proportion of patients, 57%, in both treatment arms underwent SCT, a concomitant therapy that was not protocolized.[1] SCT occurred in 213 (59%) of patients in the midostaurin group and in 196 (55%) of patients in the placebo group. A similar proportion of patients in both groups underwent allogeneic SCT in CR1 (midostaurin group = 101 (28%) patients, placebo group = 81 (22%) patients). The effect of SCT is likely to diminish the magnitude of the effect between midostaurin and placebo on overall survival. This was considered in the revised sample size calculation ("The HR was lower [compared with the HR used for the original sample size calculation] since it

was assumed no treatment effect for patients who received an SCT".[2] Further, upon undergoing SCT, study treatment was stopped thus limiting the exposure to midostaurin (and therefore limiting its potential effect).

- At Checkpoint,[6] the submitter was asked to provide 1) a competing risk analysis for OS, where SCT was treated as a competing risk and 2) cumulative incidence curves for SCT and death by group. The HR for death where SCT was considered a competing risk was 0.813 (95% CI 0.592, 1.118). This is consistent in direction and magnitude with the HR for OS presented in the trial publication (HR 0.78, 95%: 0.63, 0.96). In addition, visual inspection of the cumulative incidence curves for SCT suggests that the proportion of patients in both groups who received SCT over time was not different (the curves overlap entirely from 0 months to 48 months).

- Median OS could not be reliability interpreted[4] (median OS in the midostaurin group was 74.7 months (95% CI 31.5, not reached [NR]) and in the placebo group was 25.6 months (95% CI 18.6, 42.9).[1] The difference in median OS was 49.1 months, however the confidence interval for the difference was not provided.[1] The 4-year survival rate was 51.4% in the midostaurin group and 44.3% in the placebo group.[1] The difference in 4-year survival rate was 7.1%, however the confidence interval for the difference was not provided.[1]

- The trial did not collect data on health-related QOL; thus, the magnitude and direction of the effect of midostaurin on patient-reported QoL in adult patients with FLT-mutation positive AML is unknown.

Table 1: Highlights of Key Outcomes

	RATIFY		Data cut-off date	Data source
	MIDO (N=360)	placebo (N=357)		
Overall survival (OS)				
Median months (95% CI)	74.7 (31.5-NR)	25.6 (18.6-42.9)	March 7, 2016	Stone NEJM 2017[1]
HR (95%CI)	0.78 (0.63-0.96)		March 7, 2016	Stone NEJM 2017[1]
p-value	0.009 (one-sided, stratified log rank)		March 7, 2016	Stone NEJM 2017[1]
HR (95% CI)	0.79 (0.64 - 0.97)		September 2016	Checkpoint 1[6]
Deaths (%)	171 (47.5%)	186 (52.1%)	April 1, 2015	CSR A230[2]
Death (%)	176 (48.9%)	189 (52.9%)	September 2016	Checkpoint 1[6]
Median follow-up time (months) from randomization to cut off on April 1, 2015) (min, max)	60.2 (42, 81)	60.2 (42, 79)	April 1, 2015	CSR A2301[2]
4-year overall survival rate	51.4%	44.3%	March 7, 2016	Stone NEJM 2017[1]

	RATIFY		Data cut-off date	Data source
	MIDO (N=360)	placebo (N=357)		
Difference, 4-year overall survival rate (95% CI)	7.1% (confidence interval not provided)		March 7, 2016	Stone NEJM 2017[1]
HR (95% CI), patients removed from analysis if received maintenance (n=120 midostaurin, n=85 placebo)	0.82 (0.65, 1.04)		April 1, 2015	Checkpoint 2[5]
Event free survival (EFS)				
Median months (95% CI)	8.2 (5.4 - 10.7)	3.0 (1.9 - 5.9)	March 7, 2016	Stone NEJM 2017[1]
HR (95%CI)	0.78 (0.66 - 0.93)		March 7, 2016	Stone NEJM 2017[1]
p-value	P=0.002 (one-sided, by stratified score test)		March 7, 2016	Stone NEJM 2017[1]
Failure to achieve remission by day 60	147 (40.8%)	166 (46.5%)	April 1, 2015	CSR A2301[2]
Relapse	91 (25.3%)	90 (25.2%)	April 1, 2015	CSR A2301[2]
Death	18 (5.0%)	24 (6.7%)	April 1, 2015	CSR A2301[2]
Disease free survival (DFS)				
Median months (95% CI)	26.7 (19.4 - NR)	15.5 (11.3 - 23.5)	March 7, 2016	Stone NEJM 2017[1]
HR (95% CI)	0.71 (0.55 - 0.91)		April 1, 2015	CSR A2301[2]
p-value	P=0.0051, 1-sided		April 1, 2015	CSR A2301[2]
Complete Remission (CR)				
Protocol-specified CR by day 60, no. (%)	212 (59%)	191 (54%)	March 7, 2016	Stone NEJM 2017[1]
Stem Cell Transplant (SCT)				
SCT after 1st CR	28.1%	22.7%	March 7, 2016	Stone NEJM 2017[1]

	RATIFY		Data cut-off date	Data source
	MIDO (N=360)	placebo (N=357)		
Allogeneic SCT in CR1, n (%)	101 (28.1%)	81 (22.7%)	March 7, 2016	Stone NJEM 2017[1]
SCT (overall)	213 (59%)	196 (55%)	March 7, 2016	Stone NEJM 2017, appendix[7]
HrQoL				
Quality of Life	**Not reported**	**Not reported**		
Harms Outcome, n (%)	**Arm (N=355)**	**Arm (N=354)**		
Grade ≥3	354 (99.7%)	354 (100%)		
AE (any grade), n (%)	355 (100%)	354 (100%)	April 1, 2015	CSR A2301 [2]
Stevens-Johnson syndrome	0	0	April 1, 2015	CSR A2301[2]
Fungal infections, any grade	4	1	April 1, 2015	Checkpoint 1[6]
WDAE**, n (%)	32 (9%)	22 (6.2%)	March 7, 2016	Stone NEJM 2017[1]
AE = adverse event, CI = confidence interval, HR = hazard ratio, HRQoL = health-related quality of life, NR = not reached, SD = standard deviation, WDAE = withdrawal due to adverse event, *HR < 1 favours midostaurin, **denominator is 360 for midostaurin, 357 for placebo.				

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

From a patient perspective, a diagnosis of AML is challenging and overwhelming experience for patients and their families as it impacts their relationships with their communities and family, and can have severe financial implications. Caregivers experience a huge emotional impact from their loved one going through cancer as well as a complete lifestyle change from the time spent caring for their loved one. The symptoms of ALL experienced by all patient respondents to certain a degree included loss of appetite, fever and/or night sweats, fatigue, pain, bruising and/or bleeding, dizziness and rashes/skin changes. LLSC noted that standard treatment for AML patients includes induction chemotherapy with a cytarabine/anthracycline combination, followed by up to four cycles of consolidation (post-remission) chemotherapy and either autologous stem transplantation or allogeneic stem cell transplantation. Patient input reported that eight out of nine respondents stated that the current treatments available did a sufficient job in managing their cancer symptoms; however, there are significant side effects that come with treatment that patient respondents have to manage. Patient respondents who have not had experience with midostaurin indicated that they would be willing to tolerate severe side effects for improved survival, and that the most important symptoms to manage were pain, fatigue, loss of appetite/weight loss, and rashes/skin changes. Patient input

indicated that the following were some of the benefits and challenges that respondents who received midostaurin reported: an increase in appetite, substantial improvement in daily activities, but causes fatigue and weakness.

Provincial Advisory Group (PAG) Input

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

Clinical factors:

- There is a clearly defined patient eligibility for adults 18 to 59 years of with previously untreated AML, where patients with AML treated outside the trial eligibility (e.g. pediatric patients, elderly or unfit patients treated with non-aggressive induction protocols) would be excluded

Economic factors:

- Implementation or access to *FLT3* testing, if not already available
- Add-on oral therapy to intravenous chemotherapy during induction and consolidation

Registered Clinician Input

Two clinician inputs were provided input on midostaurin for AML: one from an individual clinician who is a member of the Alberta Cancer Board and CCTG leukemia steering committee and one joint submission from 3 clinicians on behalf of the Hematology Drug Advisory Committee at Cancer Care Ontario (CCO). Midostaurin is to be used in combination with standard induction and consolidation chemotherapy for adult patients with newly diagnosed AMl who are *FLT3* mutation-positive.

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

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.

1.2.3 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 Midostaurin (Rydapt) AML

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	Age	Patients could be enrolled if they were between the ages of 18 to 59 years. The median age at trial entry was 47.9 years (range 18.0-60.9). The RATIFY trial did not include patients younger than 18 or older than 60 to determine whether they respond differently.	Does the age restriction in the trial limit the interpretation of the trial results with respect to the target population?	It is the opinion of the CGP that the lower and upper age ranges of age in the RATIFY trial are arbitrary, as there is likely to be a similar treatment effect in other individuals provided they are deemed fit to receive the intensive induction chemotherapy and midostaurin (e.g. AYA and adults 60-70), based on PS and organ function. This is supported by the interim-analyses results from the AMLSG 16-10 Trial[8]
	Performance Status	Patients could be included if they had an ECOG Status of 0-2. In the midostaurin group, 90% (323/360) were ECOG 0 or 1 and, in the placebo group 87% (310/357) were ECOG 0 or 1. The majority of remaining patients were ECOG 2[2,9]	Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population?	It is plausible that patients with ECOG 3 or even 4 may still derive benefit from induction plus midostaurin, especially when it is the illness itself that results in the reduced PS. If so, patients improve rapidly when their AML undergoes prompt treatment with the correct supportive care. Overall, the CGP recommends that if a patient is considered eligible for induction chemotherapy, the patient should also be eligible for

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
				treatment with midostaurin. This decision should be at the discretion of the treating team.
	Mutation Status	The requested population for reimbursement is for patients with *FLT3* mutation. A key inclusion criteria was *FLT3* mutation.	Are the overall trial results generalizable to a patient who are *FLT3* mutation positive?	A validated test is required to confirm the *FLT3* mutation status of AML. *FLT3* mutation testing results should be available prior to or within 1 week after commencing 7&3 as *FLT3* mutation testing is standard practice in Canada. Midostaurin would ideally commence 8 days after commencement of 7&3. *FLT3* mutational status is thus an elemental and time-sensitive companion test for midostaurin prescribing. Midostaurin should be given by day 8, or as soon as possible thereafter. Midostaurin should not be administered after the consolidation phase of treatment.
	Patients expected to undergo SCT	During study planning, the proportion of patients expected to undergo SCT in the RATIFY trial was 15%. However, the observed proportion, when the sample size was amended, was 25%. Further, the observed rate at data cut-off March 7, 2016 was 57%.	Are the rates of SCT in the RATIFY trial generalizable to the Canadian setting?	According to the CGP, the SCT rates in Canada are much higher than the observed rate in the RATIFY trial.
Intervention	MID Maintenance	MID was administered in induction, consolidation and maintenance therapy in RATIFY trial.	What is the role of MID in the maintenance setting?	The role of MID in post-remission maintenance was not analyzed by the CGP.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		Health Canada did not approve the MID maintenance phase of therapy. As such, the role of MID in this setting was not considered for this review.		Omission of MID in post-remission maintenance is not expected to affect net clinical benefit of MID that is administered in induction/consolidation phases.
Comparator	Dose and Schedule	Induction therapy: daunorubicin (dose of 60 mg/m^2 of body surface area per day, administered by rapid IV injection on days 1, 2, and 3) and cytarabine (dose of 200 mg/m^2, administered by continuous IV infusion on days 1 - 7). Midostaurin or placebo administered at dose of 50 mg orally twice daily on days 8 - 21. Day 21: bone marrow examination. If definitive evidence of clinically significant residual leukemia, 2nd cycle of induction therapy (identical to the first) was administered. Consolidation therapy: If patients achieved complete remission after induction therapy, 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). Midostaurin or placebo was administered at dose of 50 mg orally twice daily on days 8 -21.		There are minor differences in induction and consolidation practice in Canada. Doses and types of anthracycline differ (i.e. ida vs dauno) and dose of dauno 60-90mg/m^2/dose). However, this is not clinically significant. However, the use of FLAG-IDA (as compared to 7& 3) in addition to MID is uncertain. There is no evidence to support the use of midostaurin in combination with FLAG-IDA. HIDAC is given between 2 to 4 cycles in Canada, and at doses of 9-18g/m^2 total per cycle. This is not considered clinically significant.
Setting	Location of the participating centres	225 centres in 17 countries participated in the trial. Seven centres in Canada participated.	If the trial was conducted only in academic centres are the results applicable in the community setting?	In general, treatment with midostaurin should be restricted to acute leukemia referral centres that regularly see and treat younger adults with AML. The centre should be treating AML with 7&3.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
				In Canada there is no regulatory hoop to treat AML, as each province handle this differently. However, the vast majority of AML centres are based at university teaching hospitals.
	Supportive medications, procedures or care	Concomitant CYP3A4 inhibitor/inducer drugs. These patients were eligible for the RATIFY, although investigators were advised to exercise caution when evaluating such patients for the RATIFY trial.	Are the results of the trial generalizable to a setting where different supportive medications, procedures, or care are used?	In general the results are generalizable, as there was a reported wide spectrum antifungal use in patients in the RATIFY trial. However, a pre-emptive dose reduction of midostaurin in case of co-medication with strong CYP3A4 inhibitors (e.g. posaconazole) is considered reasonable by the CGP, and should be done on a case by case basis at the discretion of the treating oncologist.

1.2.4 Interpretation

The CGP concludes that, overall, there is a net clinical benefit to the incorporation of midostaurin (MID) into the remission induction and consolidation components during curative intent chemotherapy for adults with newly diagnosed *FLT3* mutated AML.

The incorporation of MID into 1st line remission induction and consolidation therapy for *FLT3* positive adults with AML results in clinically significant improvements in overall survival, irrespective of whether patients receive allogeneic blood/marrow transplantation (BMT) as post-remission therapy. The use of MID in this setting appears to result in a toxicity profile that is not substantially different to placebo, with the exception of higher rates of skin reactions and anemia after exposure to MID.

The CGP notes several limitations to the available data, as discussed below. However, these limitations do not substantially alter the CGP's conclusions about the net clinical benefit of MID.

(i) The RATIFY study restricted eligibility to patients aged 18-59 years. However, it is common practice in Canada to offer intensive chemotherapy to adults with AML until the age of 70, if not even higher and is supported by a recently published Canadian consensus statement[10] as well as phase II clinical trial data[8] which combined MID with intensive remission induction and consolidation chemotherapy until age 70 years. In the phase II trial by Schlenk *et al*, there was no signal that this older group of patients (age 60-70) experienced reduced efficacy or excess rates of adverse events or as compared to their younger counterparts. The CGP thus feels that a strict upper age range of eligibility is not relevant to the use of MID in Canada, but rather depends on the willingness of both patient and physician to proceed with intensive remission induction and consolidation chemotherapy, a reasonable surrogate for patient fitness. Provided there is intent to give such remission induction chemotherapy in adults, the addition of MID to this therapy would be seem acceptable at least until age 70 years.

(ii) Neither the RATIFY study nor any other study made available to CGP examined outcomes in patients younger than 18 years of age. The CGP is thus unable to make any conclusions about the net clinical benefit of MID for children and adolescents younger than 18 years. The CGP acknowledge that the scope of this review only considers adult patients with newly diagnosed *FLT3*-mutated AML.

(iii) The RATIFY study included MID or placebo as post-remission maintenance therapy for patients who completed consolidation therapy and did not proceed to allogeneic blood/marrow transplantation (BMT). The CGP notes that the specific indication for MID as post-remission maintenance therapy for AML could not be reviewed by pCODR. The CGP regards the role of MID during post-remission maintenance therapy as relatively small, and its exclusion from the current review does not impact the conclusion of a net clinical benefit for MID in induction/consolidation. Although it is impossible to separate accurately and reproducibly the effect of MID in induction/consolidation versus its role in maintenance, The CGP concludes that MID maintenance adds very little, if any, to the benefits already conferred by MID in induction/consolidation. Moreover, a substantial portion (estimated at 50% of patients) of *FLT3* mutated AML patients will proceed to allogeneic BMT in first complete remission (CR1), and thus these patients will not have the opportunity to be exposed to MID maintenance therapy anyway.

(iv) There is some variability to the dose and schedule of remission induction and consolidation cycles given in Canadian centres which are worthy of further discussion:

- Although the use of anthracycline/cytarabine remission induction chemotherapy is commonplace in Canada, some centres use daunorubicin 60mg/m^2/dose (as was used in the RATIFY trial), while others use a higher dose (90mg/m^2/dose), while others may use idarubicin in place of daunorubicin. The CGP is of the opinion that none of these differences are thought to change the efficacy, safety, and new clinical benefit of the addition of MID to induction chemotherapy.

- Registered Clinician input obtained during the pCODR review revealed that some leukemia centres in Ontario use a different remission induction regimen for high-risk subsets of AML patients (the "FLAG-IDA" regimen). The extent to which this regimen is used overall in Canada is unknown to the CGP. The CGP does not recommend MID in combination with FLAG-IDA remission induction, as the CGP are unaware of any evidence about the efficacy and safety of this therapeutic approach.

- In consolidation chemotherapy, the dose and schedule of high dose cytarabine (HIDAC) chemotherapy in Canada may differ to that given in the RATIFY trial. Overall, doses of HIDAC vary between 6g/m^2/cycle to 18g/m^2/cycle, while the number of planned cycles varies from as few as two and as many as four. However, the CGP is of the opinion that this variability in HIDAC dose and schedule will not affect the net clinical benefit of adding of MID to consolidation chemotherapy.

(v) Drug interactions with MID. The RATIFY trial did not specifically exclude patients who were taking concomitant strong CYP3A4 inducer or inhibitor drugs; instead, caution was advised in considering such patients for the clinical trial. The CGP is aware that an unspecified number of patients accrued onto the RATIFY trial were administered CYP3A4 inhibitor antifungal agents, such as those in the triazole class (e.g. voriconazole, high dose fluconazole, or posaconazole). However, it is not known whether these patients experienced unexpected toxicities as a result of high MID exposure. Overall adverse event rates in the trial were not higher in the MID arm with the exception of skin reactions (rashes) and anemia. It is plausible, that these excess adverse event may have occurred in those exposed to high levels of MID; The CGP thus recommends vigilance in the setting of possible drug interactions and consideration of MID dose reduction, as discussed below.

The phase II trial by Schlenk et al (ASH 2016) included a planned dose MID dose reduction of 87.5% (i.e. 12.5% of planned MID dose) for those taking strong CYP3A4 inhibitors.[8] The results of this single arm study showed that AML response rates and relapse rates were not inferior in those who were subjected to planned dose reductions of MID. Thus, it appears that pre-emptive dose reductions of MID in patients who are to receive concomitant CYP3A4 inhibitors is a safe and efficacious approach. This may secondarily reduce drug costs, as cumulative MID dosing would be considerably lower.

(vi) *FLT3* companion testing and turnaround time in Canada. *FLT3* testing is standard practice across Canada, however it is not performed in all facilities. In order to adhere as closely as possible to the treatment plan for MID as used in the RATIFY trial, diagnostic *FLT3* results should be reported as rapidly as possible, and preferably before day 8 of the initial remission induction regimen. This fast turnaround time may not be possible at the present time in Canada, even at some high volume leukemia centres. Some centres may use local laboratories whose processing and reporting times are unacceptably slow, while others may have to send specimens to other centres, other provinces, or even out-of country. However, the CGP expects that in anticipation of imminent MID availability, all centres in Canada who regularly treat adults with AML have, or are in the process of having

capacity to obtain timely *FLT3* results either by local laboratory testing or making arrangements for efficient processing at an outside laboratory.

In the uncommon scenario that a *FLT3* result is known only after day 8 of remission induction, the CGP recommends that MID be commenced as soon as possible, provided this occurs prior to the time of response assessment bone marrow biopsy, which usually occurs between day 21 and 28. If the *FLT3* result is delayed beyond this time, the CGP recommend starting MID at any time during subsequent cycles of chemotherapy (i.e. with second induction if first CR (CR1) in not achieved, or with consolidation chemotherapy if CR1 is achieved. The CGP does not recommend use of MID as post-BMT maintenance therapy in the absence of clinical data to support this approach.

1.3 Conclusions

The treatment of adults with AML associated with *FLT3* mutations represent an area of substantial unmet need in oncology. The CGP concludes that there is a net clinical benefit to the incorporation of midostaurin (MID) into the remission induction and consolidation components during curative intent chemotherapy for adults with newly diagnosed *FLT3* mutated AML.

The incorporation of MID into 1st line remission induction and consolidation therapy for *FLT3* positive adults with AML results in clinically significant improvements in overall survival, irrespective of whether patients receive allogeneic blood/marrow transplantation (BMT) as post-remission therapy. The use of MID in this setting appears to result in a toxicity profile that is not substantially different to placebo, with the exception of higher rates of skin reactions and anemia after exposure to MID.

The conclusions of the CGP are based primarily on the results of a single, large, high quality international randomized trial in which Canadian centres participated. The CGP also incorporated the results of another single arm phase II clinical trial, published only in abstract form, in order to generate conclusions about age eligibility for MID and dose modifications of MID in the setting of clinically significant drug interactions.[8]

The CGP has insufficient data to conclude on the use of MID in pediatrics although there is no reason to believe that this patient population would not respond to MID. The CGP acknowledge that the scope of this review only considers adult patients with newly diagnosed *FLT3*-mutated AML. The use of MID in children is out of scope for this review.

The CGP is also unable to conclude on the use of MID with different remission induction regimens for AML, most notably that of the FLAG-IDA regimen.Regarding companion testing, the CGP concludes that timely *FLT3* mutation analysis (for both ITD and TKD sub-types) is a vital and inseparable component to the use of MID for adults with AML.

2 BACKGROUND CLINICAL INFORMATION

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

2.1 Description of the Condition

Acute Myeloid Leukemia (AML) is a malignancy of the hematopoietic system, characterised by proliferation of immature white cells within the blood and bone marrow, with suppression of normal hematopoiesis, and subsequent bone marrow failure.

In Canada, the age-adjusted incidence of leukemia overall is 15.3/100 000, with AML consisting of approximately 25% of these cases, giving an incidence of 3.75/100 000. In 2016, there were 1475 new cases of AML in Canada. AML is diagnosed predominantly in adults, with median age at diagnosis of 66 years. At diagnosis, 29% of patients are over the age of 75. The disease may be seen in children, albeit at a much lower incidence (age standardised incidence of 7.2 per million, or approximately 20 new cases per year in Canada).[11]

AML is heterogeneous, with multiple different subtypes recognised by the World Health Organization (WHO). [12] One subtype of AML, acute promyelocytic leukemia (APL) is sufficiently distinct from a prognostic and therapeutic point of view that it will not be discussed in this summary of AML.

The majority of AML cases are of unknown cause. A minor proportion of AML cases evolve from preceding clonal hematological conditions such as myelodysplastic syndrome (MDS) or myeloproliferative neoplasms (MPN). AML may also arise as a complication of previous exposure to systemic DNA damaging agents such as radiation or chemotherapy given for an unrelated medical condition (therapy-related AML). A very small number of AML cases are familial, and these are predominantly seen in children.[12]

The AML classification system is based on clinical presentation combined with the microscopic and genetic characteristics of the AML cells. The most prognostically important categorisation of AML consists of (i) age at diagnosis, with older patients faring less well and (ii) diagnostic cytogenetics. Cytogenetic testing permit the stratification of AML patients into "better risk", "poor risk", and "intermediate groups". In addition to their prognostic importance, both age and cytogenetics at diagnosis are pivotal guides to therapeutic decisions.[12-14]

A more recently recognized AML prognostic sub-group is based on the molecular genetic signature of the leukemic cells: activating mutations of the *FMS-Like Tyrosine Kinase 3 (FLT3)* gene occur in ~30% of newly diagnosed AML patients, and can be broadly categorised into those with internal tandem duplications (ITD), whose negative prognostic value is the most powerful, and those with point mutations of the tyrosine kinase domain (TKD), where the negative prognostic implication is more controversial.[12,13] Patients with *FLT3* ITD mutations (of any level of quantitative allelic burden) experience higher relapse rates and poorer overall survival than *FLT3* negative patients. *FLT3* TKD mutational status is also considered a poor risk biomarker, despite more variable evidence to support this conclusion.[13]

2.2 Accepted Clinical Practice

Left untreated, AML is invariably lethal, as patients will succumb within a few days to weeks as a consequence of the effects of bone marrow failure or infiltration of vital organs by leukemia cells.

Supportive care remains the foundation of treatment for AML patients, including blood transfusions, treatment of opportunistic infections, and management of metabolic consequences such as tumour lysis syndrome. Without vigilant multi-disciplinary supportive care, attempts at remission induction and curative systemic therapy are unlikely to be successful. As a consequence, patients who receive active therapy for their AML should be managed in an experienced leukemia referral centre that is capable of offering prompt and comprehensive multi-specialty care.

Regarding AML-specific therapy, nationally accepted, peer-reviewed Canadian specific guidelines for the management of AML are not available. However, recent European and American guidelines have been widely adopted in Canada. [13,14] In addition, provincial guidelines such as Alberta Cancer Services' and CancerCare Ontario's evidence-based guidelines are used within those respective provinces; they are also likely to have been adopted in other Canadian jurisdictions.[15,16] The following general guidelines and approached to therapy are in use in Canada: In predominantly younger adults (younger than 60 to 70 years old) with preserved baseline levels of fitness and functional status, the standard of care in Canada is dual chemotherapy remission induction with an anthracycline for 3 days (daunorubicin or idarubicin) in combination with infusional cytarabine for 7 days at intermediate doses ("7 & 3"). Using this approach, first complete remission (CR1) occurs in 50-80% of patients.[13]

The addition of the anti-CD33 monoclonal antibody-chemotherapy conjugate gemtuzumab ozogamicin (GO) to standard remission induction therapy may be associated with reduced rates of relapse and improved overall survival (OS) in adults with newly diagnosed AML.[17] However, although recently FDA approved, GO is neither licensed nor available in Canada. As a result, standard of care in Canada remains 7&3 remission induction without adjunctive GO.

If CR1 is achieved, and a curative outcome remains the objective, post-remission therapy most commonly consists of consolidation with high dose cytarabine ("HIDAC") for 3 to 4 cycles. Approximately 60 to 70% of patients with "better risk" AML are cured in this fashion.[13,14] For patients without "better" or low risk biomarkers at diagnosis, including those with *FLT3* mutations, outcomes after HIDAC consolidation alone are disappointing (10-40%, depending on risk group and other clinical variables).[13,14] Consequently, in the absence of "better risk" biomarkers, allogeneic hematopoietic cell transplantation (HCT) is offered as soon as possible, provided a suitable donor can be identified.

For patients with intermediate or poor risk AML, long-term survival after allogeneic HCT is approximately 50%.[13,14] However, despite the relative success of HCT for AML, the procedure is complex, arduous, and associated with substantial treatment related mortality, morbidity, and expense. Chronic graft-vs-host-disease (GVHD) occurs in at least half of all HCT recipients, and can lead to significant debility and reduction in quality of life. Moreover, HCT is not available to all HCT eligible patients for the following reasons: AML may relapse while awaiting HCT; patients may develop co-morbidities that prevent safe delivery of HCT; a suitable donor may not be located in a timely manner.

In patients with *FLT3* (ITD or TKD) mutations, apart from the recommendation to undergo HCT in CR1, targeted, mutation specific interventions are under active development. The addition of the *FLT3* inhibitor sorafenib to standard frontline therapy in younger *FLT3* mutated AML patients failed to demonstrate improvements in survival.[14] When sorafenib was evaluated as part of frontline therapy in older patients, outcomes in the sorafenib arm were inferior.[18] Despite the disappointing outcomes after the incorporation of sorafenib, targeted treatment aimed at high-risk groups (including *FLT3* mutated AML) remains attractive, and represents an unmet need in Canada and elsewhere.

If a patient with AML is refractory to or relapses after intensive frontline therapy, the probability of achieving a second CR is lower than with frontline therapy (i.e. 30-50%), and the likelihood of a durable CR2drops dramatically.[13,14] Thus, the achievement and maintenance of CR1 represents the best chance of cure, and efforts to achieve a durable CR1 with safe therapy are of great importance.

2.3 Evidence-Based Considerations for a Funding Population

The evidence to support the use of Midostaurin in AML primarily arises from the results of the "RATIFY" trial, an international randomized placebo controlled trial (RCT) of 717 adults aged 18-59 with newly diagnosed untreated AML (excluding APL) of any cytogenetic subgroup with *FLT3* positivity (ITD or TKD).[1] In this trial, patients were assigned to receive 7&3 at standard doses partnered with either Midostaurin (MID) or placebo (PLA). MID or PLA were administered orally from day 8 to day 22 at 50 mg po bid. A second blinded remission induction course was allowed if residual AML was noted on a day 21 bone marrow examination. Those patients who achieved CR1 received 4 cycles of HIDAC consolidation at standard doses and schedule, plus MID or PLA (50 mg po bid, days 8-22), followed by one year of maintenance therapy with MID or PLA (50 mg po bid). HCT was allowed at any time point, at investigator and patient discretion.

RATIFY showed that although CR1 rates were not statistically different between the MID and PLA arms (58.9% vs 53.5%), MID was associated with superior OS with a Hazard Ratio [HR] of 0.78 (one-sided p = 0.009) and EFS HR of 0.78 (one-sided p = 0.002) after a median follow-up of 59 months in surviving patients. Superiority of MID vs. PLA was consistent across all *FLT3* ITD allelic ratio sub-groups, as well as in the *FLT3* TKD group.

MID was not associated with excess treatment related toxicities of substantial clinical concern. Grade 3-5 anemia was higher with MID (95% vs. 88%), as was rash (14% vs. 8%), but nausea was lower with MID (6% vs. 10%). There were no differences in the distribution of the 37 AEs that resulted in death (MID, 5.3%; PLA, 5.0%; p=1.0). Similarly, no difference in treatment-related mortality (TRM) was noted (MID, 3.1%; PLA, 2.5%; p=0.82).

In this trial, the CR, OS, EFS, and TRM rates in the standard of care arm would be in keeping with expected rates associated with intensive therapy for adult *FLT3* mutated AML; thus these results are reflective of the outcomes of regular clinical practice in Canada for younger adults. Several academic Canadian centres participated in this RCT, implying that the standard of care arm was acceptable to Canadian centres and that the question of whether the addition of MID to standard of care was a scientifically worthwhile and clinically practical one.

The RATIFY trial utilized MID in two major stages of treatment: (i) Remission induction/consolidation and (ii) maintenance therapy. As the trial did not incorporate a 2:2 factorial design, it is impossible to know exactly whether the survival benefits associated with MID were attributable to its use in stage (i) or (ii), or a combination of these treatment phases. However, as the median duration of exposure to MID was only 3 months it can be inferred the bulk of the benefits afforded by MID were in stage (i) of exposure to this drug.

The surprisingly large difference in median OS between the MID and PLA groups can likely be explained by the non-linear pattern of the survival curve, seen most prominently in the MID arm, with an plateau of this curve, with very few events after ~40 months of follow-up, and thus remaining above 50% OS for this period of time. In contrast, the PLA curve dropped below 50% at a sooner time point in follow-up, and only then appeared to plateau. A more clinically relevant and understandable estimate of effect size in this trial can be derived from 4-year OS rates: there was an absolute difference in OS of 51.4% vs. 44.3% in the MID and PLA arms, respectively, representing an absolute mortality reduction of 7.1% in favour of MID, with an associated number-needed-to-treat (NNT) of 14.

The eligible patient population for MID is those adult patients (>17years old) with newly diagnosed, untreated AML of any cytogenetic sub-type, who have identifiable mutations in *FLT3* (either the ITD mutation of any degree of allelic mutation, or the TKD variant) and who are otherwise eligible for remission induction with 7&3. If used, MID would be administered in remission induction and consolidation phases, but would be discontinued if and when HCT is administered. As the net clinical benefits of maintenance of therapy with MID remain unclear, MID is not expected to be used in this phase of treatment. Moreover, MID is not approved for maintenance chemotherapy in Canada.

The RATIFY trial studied patients age 18-59 years. However, older patients who are eligible to receive 7&3 should be offered MID, as the age cut point of 59 years is an arbitrary one. As MID appears to provide an overall survival benefit without excess toxicities, a strict upper age range for MID is not recommended. In general, the eligible population would constitute a younger (age <70years), fitter subgroup of AML patients, representing approximately half of all newly diagnosed AML patients in Canada. The inclusion patients up to age 70 is supported by a German multicentre clinical trial (AMLSG 16-10 trial), MID was combined with standard remission induction and consolidation chemotherapy for *FLT3* AML patients aged 18-70.[8] In this study, both efficacy and safety were not different between younger (<60 years) and older patients (60-70 years).

In general, such remission induction therapy, with or without MID, must be administered as an in-patient at an acute leukemia referral centre, with adequate haematology, oncology, critical care, infectious disease, nursing, pharmacy, and psychosocial supports.

FLT3 mutation analysis should be reported either qualitatively (positive or negative) or, if *FLT3* ITD positive, quantitatively (reported as an "allelic ratio"). It is expected that the majority of major Canadian leukemia centres have developed or will develop in-house testing for *FLT3* testing using multiplex PCR technology. Alternatively, this test can be sent out to the single US-based laboratory that is licensed by the FDA to perform this test.[19] *FLT3* mutation testing results should be available prior to or within 1 week after commencing 7&3, as MID would ideally commence 8 days after commencement of 7&3. *FLT3* mutational status is thus an elemental and time-sensitive companion test for MID prescribing.

2.4 Other Patient Populations in Whom the Drug May Be Used

1. Relapsed AML: It is foreseeable that in patients with *FLT3* mutated AML in relapse yet are MID naïve, prescribers may want to use MID in combination with second line remission induction chemotherapy. However, the evidence to support this is less strong that using MID in combination with systemic chemotherapy in the first-line setting.

2. *FLT3* negative AML. Even those patients with a low allelic burden of *FLT3* ITD experienced a benefit with MID, suggesting that MID, a multi-targeted kinase inhibitor, may confer benefits by inhibiting non-*FLT3* kinases. It would be tempting to prescribe MID AML patients regardless of *FLT3* mutation status, but this would be inappropriate in the absence of convincing clinical data.

3. Pediatric AML: It is foreseeable that in children and adolescents (<18 years old) with newly diagnosed *FLT3* mutated AML prescribers may want to use MID in combination with first line remission induction chemotherapy. This would seem reasonable based on the common biology of *FLT3* AML that is likely to be non-age specific. However, the tolerability of PK/PD of MID in the paediatric setting in not established.

4.Older/frailer AML patients: It is foreseeable that in older (>70 years) and/or less fit adult patients with newly diagnosed *FLT3* mutated AML who are ineligible for 7&3 remission induction, prescribers may want to use MID in combination low dose systemic chemotherapy (e. g. low dose

cytarabine [LDAC] or azacytidine [AZA]), or even as MID monotherapy. However, the effectiveness of MID in these settings is not established.

5. Drug-drug interactions: MID is a competitive inhibitor of cytochrome (CYP) 3A4, and may be subject to clinically significant drug interactions. High levels of MID exposure may result in excess toxicities such as QT interval prolongation, cardiac dysrhythmias as well as pulmonary or cutaneous toxicities. Within the RATIFY trial, the potential for major drug interactions was acknowledged within the clinical trial eligibility criteria, but such concomitant drugs did not constitute a reason for exclusion from the RATIFY trial. As an example, strong inhibitors of CYP3A4 such as triazole anti-fungal drugs (e.g. posaconazole) were permitted, but were to be used with caution. The incorporation of MID into any AML regimen needs to account for the potential risk of drug interactions; the use of supportive care or other drugs should adhere, as much as possible, to the recommendations outlined within the Health Canada approved monograph and the RATIFY trial.

6. As a bridge to allogenic HCT: Patients with AML who are refractory and/or who relapse have few therapeutic options and represent a high-risk patient population. These patients may benefit from treatment combination that include MID to increase the likelihood of achieving CR. The use of MID in this context remains poorly established and is supported by little evidence but is subject to ongoing studies.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Input on midostaurin (Rydapt) for treatment of newly diagnosed Acute Myeloid Leukemia (AML) in patients who are *FLT3* mutation-positive was provided by The Leukemia & Lymphoma Society of Canada (LLSC). Input provided by LLSC is summarized below.

The information was collected through two online surveys that were posted using Survey Monkey. The first survey was distributed by LLSC staff to patients who are currently receiving treatment or in remission from AML. The survey was distributed to known AML patients through email and responses were followed up by phone interviews as needed. There were nine respondents; seven from patients not currently receiving treatment (6 female and one male), and two responses from patients currently receiving treatment with midostaurin (1 female and 1 male).

The second online survey was distributed by healthcare professionals and LLSC staff asking for input from current and previous caregivers of patients with AML. LLSC received six responses (all female); three from caregivers whose patients are currently receiving treatment and three from caregivers whose patients are currently in remission.

Both surveys asked questions about the drug midostaurin, including whether or not patients or caregivers had heard about the drug, expectations they had about the drug, and what symptoms were most important to them for the drug to manage.

Below are tables describing the demographics of respondents who participated in survey 1 and 2:

Survey #1 -Patient Age Range (9 respondents)

Age at Diagnosis	Number of Patients
19 and younger	2
20-29	0
30-39	2
40-49	2
50-59	1
60-69	1
70-79	1
80 and older	0

Survey #2 -Caregiver Age Range (6 respondents)

Age Range	Number of Caregivers
19 and younger	1
20-29	1
30-39	0
40-49	1
50-59	1
60-69	0
70-79	2
80 and older	0

In order to supplement the information gathered in Survey #1, and to provide the most thorough evidence regarding the effects of an AML diagnosis on patients and caregivers, the LLSC used information from a Pharmerit qualitative study to understand challenges and unmet needs in AML patients. Pharmerit conducted one-on-one interviews with 10 patients (6 female, 4 male) comprised of concept elicitation and cognitive debriefing components with AML in Canada, Denmark and the United Kingdom. Subjects were recruited through patient advocacy groups and were all 18 years of age or older. Participation in the study involved patients taking part in a single, one-on-one 60 - 90 minute interviews. During the first part of the interview, subjects

answered open-ended questions about their experience being diagnosed with AML and the symptoms and impact of AML during treatments. The second part of the interview focused on cognitive debriefing.

In brief, LLSC received a total of 15 responses from the online surveys (9 patients and 6 caregivers), and supported these findings with supplemental information from 10 patients from the Pharmerit study.

From a patient perspective, a diagnosis of AML is challenging and overwhelming experience for patients and their families as it impacts their relationships with their communities and family, and can have severe financial implications. Caregivers experience a huge emotional impact from their loved one going through cancer as well as a complete lifestyle change from the time spent caring for their loved one. The symptoms of ALL experienced by all patient respondents to certain a degree included loss of appetite, fever and/or night sweats, fatigue, pain, bruising and/or bleeding, dizziness and rashes/skin changes. LLSC noted that standard treatment for AML patients includes induction chemotherapy with a cytarabine/anthracycline combination, followed by up to four cycles of consolidation (post-remission) chemotherapy and either autologous stem transplantation or allogeneic stem cell transplantation. In some cases, radiation therapy and a bone marrow transplant are also necessary. LLSC reported that eight out of nine respondents stated that the current treatments available did a sufficient job in managing their cancer symptoms; however, there are significant side effects that come with treatment that patient respondents have to manage, in particular during treatment these side effects can often be physically and emotionally debilitating. According to LLSC, patient respondents who have not had experience with midostaurin indicated that they would be willing to tolerate severe side effects for improved survival, and that the most important symptoms to manage were pain, fatigue, loss of appetite/weight loss, and rashes/skin changes. LLSC indicated that the following were some of the benefits and challenges that respondents who received midostaurin reported: an increase in appetite, substantial improvement in daily activities, but causes fatigue and weakness.

Please see below for a summary of specific input received from LLSC. 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.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with AML

According to LLSC, acute myeloid leukemia (AML) is one of the four major subtypes of leukemia, a rapidly progressing cancer of the bone marrow and blood. It affects the myeloid line of blood cells and occurs when a myeloblast (an immature cell of the bone marrow) goes through genetic changes and freezes in the immature stage. Even though the risk of AML diagnosis gets greater with age, it is also the most common type of leukemia diagnosed during infancy (20% of acute childhood leukemia cases).

LLSC reported that almost all patient respondents (n=8) were diagnosed between 2011 and 2016 as adults. One patient respondent was diagnosed in 2012 at the age of 3 (their parent/guardian was participating in the survey). According to LLSC, most patients who are diagnosed with AML show symptoms that are also associated with a number of other less serious diseases. Some of these include a 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. Many patients, including those surveyed, express a feeling of a complete

loneliness, or a "loss of well-being" expressed as an "overwhelming weakness that lasted for months".

LLSC indicated that a diagnosis of AML can turn a person's world upside down. It impacts their relationships with their communities and family and can have severe financial implications as well. All patient respondents indicated that, as a result of their diagnosis, their daily lives have been severely impacted by AML. The most common disruptions are listed in the chart below with the percentage of respondents who experienced them.

Disruption	Percentage of respondents (n=9)
Eating Habits (weight loss/loss of appetite)	77%
Physical Functioning	88%
Intimacy	88%
Daily Routines	88%
Financial	88%

Noticeable changes in eating habits were mentioned by seven respondents. These patients described substantial changes in appetite and unexplained weight fluctuations. One patient respondent lost 55 pounds during the first 3 months after diagnosis and another experienced *"digestive issues and pain"*. Eight respondents reported being less active and becoming tired more easily. This daily lack of energy can have a profound negative impact on a person's ability to function and their quality of life. One respondent stated that *"playing with the kids is harder the more physical it gets"* and another stated they had *"difficulty climbing and going down the stairs."* Other commonly reported side-effects of diagnosis were a complete loss of physical and emotional intimacy and financial hardships. As an example, one respondent, a 75 year old retiree, had to leave her family home and move to a different city in order to be close to treatment, another had to stop working entirely and was not eligible for disability. One patient respondent even stated that they *"lost ¼ of their annual salary"* as a result of being unable to work and another respondent stated that they could never return to work.

Common symptoms of AML such as loss of appetite, fever and/or night sweats, fatigue, pain, bruising and/or bleeding, dizziness and rashes/skin changes were experienced in some degree by all patient respondents. Each respondent ranked all the symptoms they were experiencing on a scale of 1 (no impact) to 7 (extreme impact). The highest ranked symptoms are listed in the chart below:

Symptom	Percentage of total patients who ranked 4+
Fever/night sweats	55%
Fatigue	100%
Pain	44%
Bruising and/or bleeding	33%
Light headedness	22%
Rashes/skin changes	66%
Numbness and tingling	44%

The information gathered in the Pharmerit survey further supported the findings and patient testimonials from Survey #1. The patients who were interviewed expressed the similar feelings of isolation and depression as a result of their diagnosis. One patient, diagnosed in 2011, stated *"I couldn't get myself off the couch"*, and another patient reported *"I had no energy to read or write"* and *"felt as weak as a kitten."* In regards to physical symptoms from the diagnosis, all 10 patients interviewed mentioned extreme fatigue and rashes/skin changes as being the most prominent symptoms before diagnosis and pre-induction treatment. One female patient who was diagnosed in January 2014 stated that she was *"tired for about 3 months before diagnosis. Every day getting worse and worse."* This same patient described experiencing severe skin changes, reporting, *"I got this weird rash all over my face and it spread to my legs. I thought I was getting acne and razor burn."* Patients commonly experience skin changes that appear as rashes and bruises prior to diagnosis. These are often caused by popping blood vessels, low platelets and a reduced clotting ability.

3.1.2 Patients' Experiences with Current Therapy for AML

LLSC stated that a number of factors affect the choice and outcome of the treatment for AML. These factors include AML subtype, the results of cytogenetic analysis (a type of test that looks at the number and size of the chromosomes in cells), medical history, where the AML is located in the body, age, and general health. Treatment usually needs to start as quickly as possible after diagnosis due to the rapid progression of the disease. The standard treatment for AML patients includes induction chemotherapy with a cytarabine/anthracycline combination, followed by up to four cycles of consolidation (post-remission) chemotherapy and either autologous stem transplantation or allogeneic stem cell transplantation. In some cases, radiation therapy and a bone marrow transplant are also necessary. The standard treatment protocol was experienced by LLSC's patient sample (Survey #1) with the exception of one who is presently waiting for a bone marrow transplant.

All of the patient respondents have received treatment; two are currently receiving treatment and are in the consolidation or "post-remission;" and seven are not currently receiving treatment. All patient respondents received induction and consolidation chemotherapy, two received stem cell transplants, and two are waiting on both bone marrow and stem cell transplantations. All respondents, with the exception of one, indicated that in their opinion, the current treatments available did do a sufficient job in managing their cancer symptoms, although all patients reported having some severe side effects associated with their treatments and therapies. One patient respondent specifically stated that her treatment *"came with quite a bit of side effects that were scary and painful,"* and another went from *"being a fit mother to needing 24 hour care because of neurological complications from treatment."*

According to LLSC, chemotherapy affects tissues that normally have a high rate of cell turnover. Therefore, the lining of the mouth, the intestines, the skin and the hair follicles may be affected. Most AML side effects are temporary and subside once the body adjusts to therapy or when therapy is complete. However, during treatment, these side effects are often physically and emotionally debilitating. One patient respondent reported *"needing to use diapers"* due to incontinence and that she *"couldn't even bathe herself."* Another had such severe neurological complications that she now is confined to a wheelchair; while others have become sterile and *"have zero sex drive."* The highest ranked side-effects experienced by our patient respondents were:

- Mouth ulcers
- Incontinence
- Anemia
- Cognitive changes (memory loss and neurological degeneration)

- Nausea and Vomiting
- Fatigue
- Pain
- Infections (non-cancer related)
- Fertility and Sexual Side Effects

Extreme fatigue was indicated by all patient respondents as being impacted by treatment. One patient respondent explained *"I was tired to the bone, so wiped out I couldn't even move."* Another patient reported that treatment makes you *"so extraordinarily weak that you just can't lift your hand or head."*

In addition to the above, LLSC indicated that one of the most serious side effects from treatment is an increased risk of contracting an illness or infection, not related to the cancer diagnosis. This is due to the deficiency of neutrophils and monocytes (types of white cells) in the body. A low blood cell count can lead to serious infection from common bacteria and fungi in the environment. The risk of infection is further elevated because chemotherapy damages the lining of the mouth and the intestines, making it easier for bacteria to enter blood. Five respondents in Survey #1 identified that they developed some form of infection or non-cancer illness during treatment. One patient respondent developed pneumonia staph streptococcus, another respondent had anthrocyclene induced cardiomyopathy, and the most serious side effect reported was heart failure.

The information from the Pharmerit survey is aligned with the patient testimonials from Survey #1. A female respondent from the study stated that she *"developed a fever and pneumonia whilst waiting for induction treatment in the hospital."* Another described her low immune level stating *that "it was tough because I just had no resistance to anything. If somebody came along and sneezed on me I was done".*

Other serious treatment side effects mentioned in the Pharmerit study were cognitive complications such as memory loss and nerve system damage, mouth ulcers, nausea and vomiting. For the subjects who reported developing ulcers, it was the most painful part of the treatment process. They couldn't swallow, eat or even drink without experience excruciating pain. Three patients from the Pharmerit study also reported neurological complications from chemotherapy, with one stating that as a result of treatment, they *"had to be in a wheelchair and then learn to walk again."* This was consistent with the experience of a patient respondent in Survey #1, who said that she went *"from a working mother to being wheelchair bound."* Nausea and vomiting were also reported and in many cases was so severe that antiemetics were not able to help. One patient respondent reported that everything tasted like metal and that even "*a whiff of food*" brought on hour-long nausea. This patient respondent remembers "losing 5 to 10 pounds in a week's period from not eating."

3.1.3 Impact of AML and Current Therapy on Caregivers

LLSC submits that caregivers are essential components of a patient's treatment and recovery. A diagnosis of blood cancer dramatically affects the lives of families and all others who have a relationship with the patient. All of the caregivers who responded to this survey are caring for a family member. These caregivers are a vital extension of the healthcare team and provide emotional and physical support to those suffering from the disease.

Of the six caregivers surveyed, four are currently caring from their spouse/partner and two are caring for their parent. Of the six patients, three were identified by their caregivers as being diagnosed with *FLT3*-mutated AML.

All of the caregivers' surveys expressed some degree of a negative emotional response to their loved one's diagnosis and all had their lives impacted by caring for someone with AML. In many cases, the emotional response and toll on the caregiver was quite severe. One respondent whose mother was diagnosed in April 2011 stated *"my mother being diagnosed with AML was probably one of the worst things that has ever happened in my life. Not a single day passes that I don't think about what she endured going through treatments."* All caregivers reported feeling overwhelmed with their loved one's diagnosis, coupled with anxiety, depression and stress.

The additional time commitment for the caregiver as they assume more of the household chores as well as ensuring the patient maintains their medical obligations does have a significant impact on their lifestyles, regardless of age.

One caregiver respondent, who is between 70 and 79, stated:

> *"My life changed significantly. For 6 months my partner was unable to do anything. I had to maintain all household chores for two months whilst she was in hospital. My sleep was disturbed because of worry. It was very stressful."*

Another caregiver respondent, between the ages of 20 and 29, said:

> *"your entire life is put on hold, you follow the patient's routine and you always feel emotionally exhausted."*

Caregiver respondents also experience a degree of loss of work and social life due to their loved one's diagnosis. This was best exemplified by a caregiver respondent who stated:

> *"managing his care is a full time job. I have missed all of my own appointments" and by another who stated they "could no longer visit with friends or dine out or just go shopping without being cautious about all the details."*

In addition to the above, caregiver respondents experience a degree of loss of work due to their loved one's diagnosis. Since patients are in hospitals for an extended period of time, their caregivers also spend much of their time there with their loved one. This was best exemplified by a caregiver who stated that *"mine and my mothers work was impacted as we rotated who was staying with my dad. Our days were centered on treatment schedules, meals and medication."*

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Midostaurin

LLSC submits that midostaurin is a novel targeted therapy for newly diagnosed *FLT3*-mutated AML and it is indicated for use in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy. FMS-like tyrosine kinase-3 (*FLT3*) is the most common molecular abnormality in AML affecting approximately one out of three patients. This mutation can result in faster disease progression, higher relapse rates and lower rates of survival than other forms of AML.

When patients were surveyed about their experience with midostaurin, patients who had never received the drug were asked a series of follow-up questions regarding their expectations for the new drug. Patients were asked "*What are the most important cancer symptoms for midostaurin to control?*" The most popular responses were highlighted below:

- Pain
- Fatigue
- loss of appetite/weight loss
- Rashes/skin changes.

Patients were also asked to rate what side effects they were willing to tolerate with the new medication. LLSC found that patients would be willing to deal with more severe side effects if there was an increase in survival. A quote illustrating this stated: *"If the outcome was survival rates being increased, there wouldn't be much of a choice tolerate or not tolerate. Life is too important."*

3.2.2 Patient Experiences to Date with Midostaurin

The survey asked both patients and caregivers about their knowledge and experience with midostaurin. Only one patient had experience with midostaurin. The patients reported that *"the study drug I was given* [referring to midostaurin] *is probably the reason I am still alive."*

One other patient had heard about midostaurin but was not able to obtain it for treatment. The patient reported that the *"hospital and Novartis were not able to reach an agreement. I would have preferred this medication as it seems to provide longer remission time."*

According to LLSC, 3 of the 6 caregivers surveyed reported that the person they are caring for had been diagnosed with *FLT3*-mutated AML. Of those three respondents, two had indicated that they had heard of midostaurin and one reported that their loved one was treated with the drug. This caregiver stated, *"midostaurin is why my mother is still alive."*

In the Pharmerit survey, only one patient had experience with midostaurin. This patient *stated "I'm able to do a lot more now and - not as much but a lot more, so I feel better"*. This person also described experiencing the following benefits and challenges with the treatment:

- An increase in appetite
- Substantial improvement in daily activities
- Problems in the administering of the drug (lumbar punctures)
- Feeling fatigue and weakness.

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. 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) and federal program participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- There is a clearly defined patient eligibility for adults 18 to 60 years of with previously untreated AML, where patients with AML treated outside the trial eligibility (e.g. pediatric patients, elderly or unfit patients treated with non-aggressive induction protocols) would be excluded

Economic factors:

- Implementation or access to *FLT3* testing, if not already available
- Add-on oral therapy to intravenous chemotherapy during induction and consolidation

Please see below for more details.

4.1 Factors Related to Comparators

PAG identified that daunorubicin and cytarabine are used for induction and high dose cytarabine is used for consolidation for acute myeloid leukemia (AML). The comparators in the RATIFY trial are appropriate.

4.2 Factors Related to Patient Population

PAG is seeking guidance on whether the addition of midostaurin is appropriate for patients who are *FLT3* mutation positive and have already initiated induction or consolidation chemotherapy.

PAG is seeking information on the use of midostaurin in patients who are undergoing re-induction and consolidation, recognizing that this may be out of scope of the current review of midostaurin for newly diagnosed, treatment-naïve patients.

4.3 Factors Related to Dosing

Midostaurin is an oral therapy available as 25mg capsules with a dose of 50 mg twice daily. These capsule strengths are appropriate to manage dose adjustments and minimize waste. PAG noted that midostaurin is taken on days 8 to 22 and appropriate patient education would be necessary to ensure correct dosing schedule.

4.4 Factors Related to Implementation Costs

PAG recognized that *FLT3* testing would be required to determine the subset of patients with the *FLT3* positive mutation. PAG noted that *FLT3* testing is done in most provinces. In

provinces where *FLT3* testing is not currently available, implementation of *FLT3* testing would be required.

4.5 Factors Related to Health System

Midostaurin is an oral drug that is an add-on to current induction and consolidation treatment with intravenous chemotherapy. PAG noted that midostaurin would be started in hospital since induction and consolidation chemotherapy is administered as an inpatient. Midostaurin would be continued as an outpatient when patients are discharged after chemotherapy is completed. PAG is seeking information on the incremental benefits of adding midostaurin to current treatments.

4.6 Factors Related to Manufacturer

None identified.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two clinician inputs were provided input on Midostaurin for Acute Myeloid Leukemia (AML): one from an individual clinician who is a member of the Alberta Cancer Board and CCTG leukemia steering committee and one joint submission from 3 clinicians on behalf of the Hematology Drug Advisory Committee at Cancer Care Ontario (CCO).

Midostaurin is to be used in combination with standard induction and consolidation chemotherapy for adult patients with newly diagnosed acute myeloid leukemia (AML) who are *FLT3* mutation-positive.

Please see below for a summary of specific input received from the registered clinician(s).

5.1 Current Treatment(s) for AML

The individual clinician from Alberta providing input noted that the current treatment is referred to as "7 & 3". This refers to cytarabine, 100mg/m^2 Continuous Intravenous Infusion (CIVI) for 7 days plus idarubicin 12 mg/m^2 for 3 days.

The clinicians representing CCO also stated that the current standard of care for newly diagnosed AML patients is induction chemotherapy, such as 7+3, or FLAG-IDA. They noted that if remission is achieved, patients will proceed to allogeneic stem cell transplantation. The clinicians anticipate that midostaurin could be used with other induction regimens with curative intent in this population.

5.2 Eligible Patient Population

The clinician providing input from Alberta indicated that AML does not have a high incidence or prevalence.

The clinicians providing input from Ontario provided statistics from Statistics Canada and the Canadian Cancer Society which are summarized in the chart below.

	% Estimate	No.
Canada Population (2016) Source: Statistics Canada		36, 286,400
Ontario (2016) Source: Statistics Canada		13,983,000
No. of new cases of AML in Canada (2013) Source: Canadian Cancer Society		1,255
No. of new cases of AML in Ontario (2013)/year	~39% of Canadian population	~489
Estimated no. of *FLT3* mutation+ AML patients in Ontario/year Source: Canadian Cancer Society	23-35%	~122-171

5.3 Identify Key Benefits and Harms with Midostaurin

One of the key benefits of this drug noted by the individual clinician from Alberta was that more eligible patients will be able to receive transplantation and survive longer. The clinician noted that even in patients who do not go on to receive transplantation, receiving induction chemotherapy leads to better survival.

The clinicians from CCO stated improved survival as a key benefit and that from the trial abstract, "only 4 adverse events Grade 3 or 4 were attributed to midostaurin". The clinicians also noted that Steven's Johnson syndrome rash has been reported with midostaurin which is a risk.

5.4 Advantages of Midostaurin Over Current Treatments

All clinicians providing input stated that the drug will improve survival and addresses an unmet need. It was also noted by the clinician from Alberta that the treatment of AML has been stagnant for years. The clinicians from Ontario indicated that patients with *FLT3* mutation are high risk patients and that midostaurin may increase the rate of allogeneic stem cell transplant in this patient population.

5.5 Sequencing and Priority of Treatments with Midostaurin

The clinician providing input from Alberta indicated that midostaurin could be used in induction and consolidation cycles of chemotherapy. All clinicians indicated that the drug would be used in addition to the standard of care for induction therapy and not as a replacement.

It was noted by the clinicians from Ontario that the impact on allogeneic stem cell transplantation is unknown.

5.6 Companion Diagnostic Testing

FLT3 testing by PCR would be required to determine who is eligible for the treatment. It is currently done as a standard of care when determining prognosis.

The clinicians from Ontario noted that these tests will require quick turnaround for results to allow timely initiation of midostaurin from day 8 onward during induction therapy.

5.7 Additional Information

The clinician from Alberta noted that this drug is the first breakthrough treatment for non-promyelocytic acute myeloid leukemia in decades.

The collective input submitted also included input from a pharmacist who is a member of the CCO Hematology Drug Advisory Committee.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of midostaurin in combination with standard induction and consolidation chemotherapy therapy for adult patients with newly-diagnosed acute myeloid leukemia (AML) with *FLT3*-mutation.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies are included in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups will be bolded. The literature search strategy and detailed methodology used by the pCODR Methods Team is provided in a separate appendix (Appendix A).

Table 3. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
AML: acute myeloid leukemia; *FLT3*: fms-related tyrosine kinase 3 gene; RCT: randomized control trial;	Adult patients with newly diagnosed AML with *FLT3*-mutation	Midostaurin in combination with standard induction and consolidation chemotherapy followed by single agent (midostaurin) maintenance therapy***	Standard induction and consolidation chemotherapy regime (e.g., cytarabine plus anthracycline in induction phase, high dose cytarabine in consolidation phase)	1. **Overall survival (All-cause mortality)** 2. Event-free survival 3. Disease free survival 4. **Complete remission** 5. **Quality of life** 6. Grade 3 and 4 adverse events 7. AE: fungal infections 8. AE: Stevens-Johnson syndrome 9. Withdrawal due to adverse effects 10. Other adverse effects 11. Proportion of patients undergoing stem cell transplant (SCT) in

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
				first complete remission

1. AML: acute myeloid leukemia; *FLT3*: fms-related tyrosine kinase 3 gene; RCT: randomized control trial;
* Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions).
**Dose escalation trials were excluded but mixed design clinical trials (i.e., trials with a dose escalation phase followed by an efficacy-determining phase in which the intervention is administered at the same dose and schedule to all patients) were included if data were reported separately for the two phases of the trial.
*** Maintenance therapy was included in the original criteria (i.e., before HC approved a different indication). The review did not consider maintenance therapy.

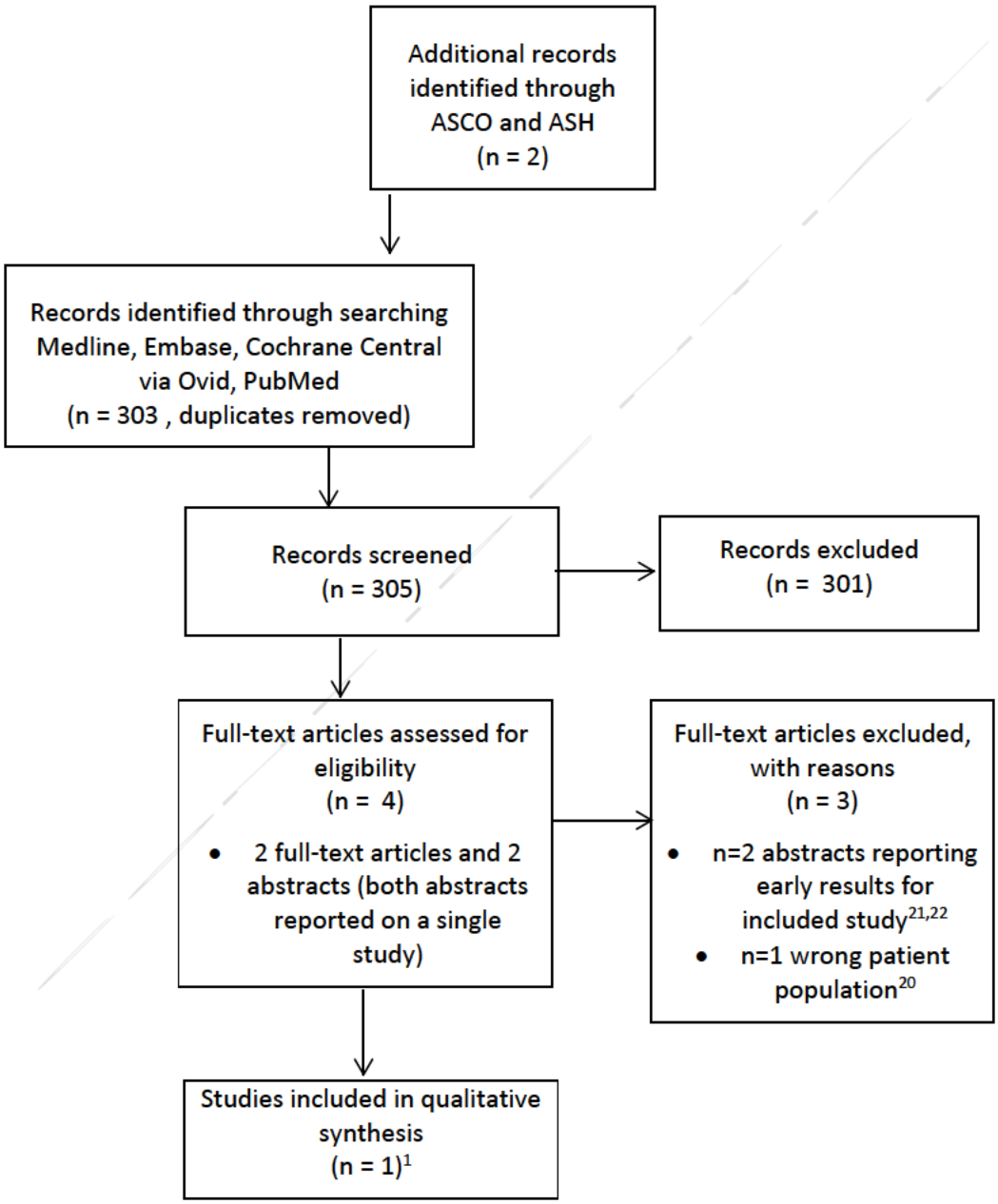
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 305 potentially relevant reports identified, 1 study was included in the pCODR systematic review[1] and 301 studies were excluded. Full-text articles assessed for eligibility were excluded because the patient population was not relevant[20] and early results from the fully published trial.[21,22]

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the RATIFY trial were also obtained through requests to the Submitter by pCODR.[2,5,6]

6.3.2 Summary of Included Studies

The search strategy returned one study (Phase 3, double blind, randomized controlled trial) that met all inclusion criteria.

6.3.2.1 Detailed Trial Characteristics

Table 4: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Trial Name Cancer and Leukemia Group B (CALGB) 10603 (RATIFY) trial (NCT00651261)[1] Study Design Phase 3, randomized (central randomization conducted by the Duke Data Center).[2] double blind, placebo-controlled, 1:1 to standard chemotherapy plus either midostaurin or placebo Number of patients N_{total}= 717 $N_{midostaurin}$= 360 $N_{placebo}$ = 357 Number of Sites225 centres; 17 countries Patient Enrolment Dates May 2008 - October 2011 Data cut-off March 7, 2016 Interim Analysis (IA): Specified a priori to occur after 50% of events had occurred (n=255). IA occurred on May 2012 Final Analysis Date: "supportive" final analysis will be conducted when 10-yr post-randomization follow-up has been completed for all	Key Inclusion Criteria: • Age 18-59 years • Newly diagnosed AML (>20% blasts in bone marrow based on WHO classification), excluding acute promyelocytic leukemia • No previous treatment with antineoplastic therapy • *FLT3* mutation positive determined by analysis in a protocol-designated *FLT3* screening laboratory[2] • Bilirubin <2.5 times upper limit of normal range • Absence of other major coexisting illnesses • Hydroxyurea therapy permitted for 5 days prior to start of trial • Non-pregnant, non-nursing Key Exclusion Criteria[2]: • Cerebrospinal fluid evaluation postitive for presence of AML blasts • Development of therapy-related AML after prior radiation therapy or chemotherapy	Intervention: Standard induction and consolidation chemotherapy plus midostaurin followed by maintenance therapy with midostaurin. Comparator: Standard induction and consolidation chemotherapy plus placebo followed by maintenance therapy with placebo. Details: Induction therapy: daunorubibin (dose of 60 mg/m^2 of body surface area per day, administered by rapid IV injection on days 1, 2, and 3) and cytarabine (dose of 200 mg/m^2, administered by continuous IV infusion on days 1 - 7). Midostaurin or placebo administered at dose of 50 mg orally twice daily on days 8 - 21. Day 21: bone marrow examination. If definitive evidence of clinically significant residual leukemia, 2nd cycle of induction therapy (identical to the first) was administered. Consolidation therapy: If patients achieved complete remission after induction therapy, received 4 x 28 day cycles of consolidation therapy with high-dose	Primary: Overall survival (OS) (note: OS used for sample size) Secondary: • Event-free survival • Censored OS analysis (OS where patients who received HCT were censored at time of transplant) • Complete remission (CR) rate • Disease-free survival (DFS) • HCT rates Tertiary: None identified

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
patients, or when 509 events are observed, whichever occurs first[23] Funding: Cancer Therapy Evaluation Program of the National Cancer Institute (North American sites) and Novartis (non-North American sites) Trial coordination: Alliance for Clinical Trials in Oncology ("the Alliance")	for another cancer or disorder • Symptomatic congestive heart failure	cytarabine (dose of 3000 mg/m^2, over a period of 3 hours every 12 hours on days 1, 3 and 5). Midostaurin or placebo was administered at dose of 50 mg orally twice daily on days 8 -21. Maintenance phase: If patient remained in remission after completion of consolidation therapy received maintenance phase of midostauring or placebo (dose of 50 mg orally twice daily, for 12 x 28 day cycles).	

Table 5: Select quality characteristics of included studies of midostuarin (Rydapt) in patients with AML

Study	Cancer and Leukemia Group B (CALGB) 10603 (RATIFY) trial (NCT00651261)[1]
Treatment vs. comparator	Standard chemotherapy plus either midostaurin or placebo
Primary outcome	Overall survival (OS)
Required sample size	The original sample size calculation was 514 patients with 374 deaths. The trial was expanded to 714 patients with 509 deaths in 2010 due to: 1) Proportion of patients undergoing hematopoietic stem-cell transplantation higher than expected (anticipated rate =15%; observed rate at amendment = 25%) 2) Proportion of patients with TKD subtype higher than expected (anticipated rate =14%; observed rate at amendment= 26%) Assumptions: HR for death (midostaurin vs. placebo) among patients who **did not** undergo transplantation = 0.71 HR for death (midostaurin vs. placebo) among patients **who underwent** transplantation = 1.0 median OS midostaurin group = 20.9 months median OS placebo group = 16.3 months Overall HR for death = 0.78 Estimated that a total sample size of 714 patients with an expected 509 deaths would provide 84% power, at a one-sided significance level of 0.025 by a stratified log-rank test, to detect a hazard ratio for death of 0.78
Sample size	717 (360 midostaurin, 357 placebo)

Randomization method	1:1, block size 6, stratified by *FLT3* mutation (TDK, ITD high ratio (>0.7) mutant to wild-type, ITD low ratio (0.05-0.7) mutant to wild-type)
Allocation concealment	Central randomization was conducted by the Duke Data Center[2]
Blinding	Yes
ITT analysis	Yes
Final analysis	No. "Due in part to a higher than expected SCT rate (25% in CR1 and 57% overall) the event rate reached a plateau (6 deaths in 2014, 4 by May 2015) by which time fewer than 70% of the required events were observed. With sufficient follow-up available to assess the efficacy (median of 52.6 months among survivors), an amendment to perform the primary OS analysis was approved by the Alliance DSMB and NCI-CTEP in May 2015 using a critical value of 0.0239 (one-sided accounting for the alpha spent at the interim analysis (0.5%)). In addition, EFS was promoted to be a key secondary endpoint (with confirmatory testing at the one-sided alpha of 0.025 if the OS analysis is significant). Here [i.e., Stone NEJM 2017], we report the results of this primary analysis; a supportive (final) analysis for the OS endpoint will also be conducted at the end of the trial when the 10-year post-randomization follow-up period has been completed for all patients, or when 509 events are observed, whichever occurs first."[7]
Early termination	No
Ethics approval	Yes
Abbrevations:*FLT3* - fms-related tyrosine kinase 3 gene ; ITD - internal tandem duplication; ITT-intention to treat; NA - not applicable; OS - overall survival; TKD - tyrosine kinase domain	

Trials

The search strategy returned one study, RATIFY, a Phase 3, double blind, randomized controlled trial that met the inclusion criteria.[1] Specific trial details can be found in Table 4. RATIFY is a randomized, double-blind, Phase 3 superiority trial comparing standard chemotherapy plus midostaurin to standard chemotherapy plus placebo in patients aged 18-59 years with newly diagnosed acute myeloid leukemia (AML) with a fms-related tyrosine kinase 3 gene *FLT3* mutation. Patients (n=717) were enrolled from 225 centres in 17 countries between May 2008 and October 2011. Five centres in Canada participated[2] and 13 patients were enrolled and randomized. RATIFY was funded by the Cancer Therapy Evaluation Program of the National Cancer Institute (North American sites) and Novartis (non-North American sites). The data cut for the published trial was March 7, 2016.[1] Please note that the data cut for the Clinical Study Report (CSR) was April 1, 2015.[2] At the time of the data cut off for the published trial, no patients were receiving the trial treatment. The trial treatment was discontinued in the last patient in August 2013. Crossover was not allowed in the trial.

Populations

Patients (n=717) were randomized in block size of 6, 1:1, stratified by *FLT3* mutation subtype (tyrosine kinase domain (TKD), internal tandem duplication (ITD) high ratio, ITD low ratio), to receive either standard chemotherapy plus midostaurin (n=360) or standard chemotherapy plus placebo (n=357) in induction, consolidation and maintenance. *FLT3* testing procedures are described in detail in the "Supplementary Appendix".[7]

Overall, baseline characteristics were well balanced between the two groups (please see Table 6 Baseline characteristics). The median age at trial entry was 47.9 years (range 18.0-60.9). A higher proportion of females were randomized to the placebo group (n=212, 59.4%) compared with the midostaurin group (n=186, 51.7%). The majority of patients who reported race (n=309) were Caucasian (89.0%), however

patients enrolled at European sites did not report race (n=408). Subtype of *FLT3* mutation was balanced between both groups. Overall the proportion of patients with *FLT3* mutation subtypes was: TDK (n=162, 22.6%), ITD with low allelic ratio (n=341, 47.6%) and ITD with high allelic ratio (n=214, 30%). A higher proportion of patients with European LeukemiaNet classification "Favourable" and "Normal" were randomized to placebo (77.7%, 216/278) compared with midostaurin (69.9%, 188/269). A higher proportion of patients with European LeukemiaNet classification "Intermediate II" and "Adverse" were randomized to midostaurin (30.1%, 81/269) compared with placebo (22.3%, 62/278).

ECOG status was not provided in the published trial.[1] However, ECOG is provided in the Clinical Study Report.[2] In the midostaurin group, 89.7% (323/360) were ECOG 0 or 1 and, in the placebo group 86.8% (310/357) were ECOG 0 or 1. The majority of remaining patients were ECOG 2.[2,9]

Table 6. Baseline characteristics of patients in the RATIFY trial[1]

Table 1. Baseline Characteristics of the Patients.

Characteristic	All Patients (N=717)	Midostaurin Group (N=360)	Placebo Group (N=357)	P Value*
Age at trial entry — yr				0.22
Median	47.9	47.1	48.6	
Range	18.0–60.9	19.0–59.8	18.0–60.9	
Female sex — no. (%)	398 (55.5)	186 (51.7)	212 (59.4)	0.04
Race — no./total no. (%)†				0.74
White	275/309 (89.0)	147/165 (89.1)	128/144 (88.9)	
Other	34/309 (11.0)	18/165 (10.9)	16/144 (11.1)	
Subtype of *FLT3* mutation — no. (%)‡				1.00
TKD	162 (22.6)	81 (22.5)	81 (22.7)	
ITD with low allelic ratio	341 (47.6)	171 (47.5)	170 (47.6)	
ITD with high allelic ratio	214 (29.8)	108 (30.0)	106 (29.7)	
Modified European LeukemiaNet classification — no./total no. (%)§				0.15
Favorable	29/547 (5.3)	16/269 (5.9)	13/278 (4.7)	
Normal	375/547 (68.6)	172/269 (63.9)	203/278 (73.0)	
Intermediate II	104/547 (19.0)	59/269 (21.9)	45/278 (16.2)	
Adverse	39/547 (7.1)	22/269 (8.2)	17/278 (6.1)	
White-cell count per μl¶				0.72
Median	34,900	35,600	33,000	
Range	600–421,800	600–421,800	800–329,800	
Platelet count per μl‖				0.58
Median	50,000	50,000	50,000	
Range	2000–461,000	2000–461,000	8000–444,000	
Absolute neutrophil count per mm^3**				0.65
Median	2.2	2.2	2.3	
Range	0–55.9	0–55.9	0–55.9	

* All P values are two-sided. P values for continuous variables were calculated with the use of Kruskal–Wallis tests, and P values for categorical variables were calculated with the use of chi-square tests.
† Race was reported by the patients. Race was not reported for European patients (195 in the midostaurin group, and 213 in the placebo group); the P value excludes these patients.
‡ The subtypes of the *FLT3* mutation are point mutation in the tyrosine kinase domain (TKD) or internal tandem duplication (ITD) mutation with either a high ratio (>0.7) or a low ratio (0.05 to 0.7) of mutant to wild-type alleles.
§ Cytogenetic data according to a modified European LeukemiaNet classification were available for 547 patients (269 in the midostaurin group, and 278 in the placebo group). Data on mutations in the nucleophosmin gene (*NPM1*) or the CCAAT/enhancer binding protein alpha gene (*CEBPα*) are not included. A classification of favorable indicated the presence of t(8;21) and inv(16) or t(16;16), normal the presence of a normal karyotype, intermediate II the presence of cytogenetic abnormalities that were not classified as favorable or adverse, and adverse the presence of adverse-risk cytogenetic abnormalities.
¶ Data were available for 707 patients (355 in the midostaurin group, and 352 in the placebo group).
‖ Data were available for 702 patients (351 in the midostaurin group, and 351 in the placebo group).
** Data were available for 673 patients (339 in the midostaurin group, and 334 in the placebo group).

From: N Engl J Med, Stone et al., Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation, 377(5):454-64. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Interventions

Intervention: midostaurin and placebo

Induction therapy: Patients received daunorubicin (dose of 60 mg/m^2 of body surface area per day, administered by rapid IV injection on days 1, 2, and 3) and cytarabine (dose of 200 mg/m^2, administered by continuous IV infusion on days 1 -

7). Midostaurin or placebo was administered at dose of 50 mg orally twice daily on days 8 - 21.

On day 21, a bone marrow examination was performed. If definitive evidence of clinically significant residual leukemia was observed, a 2nd cycle of induction therapy (identical to the first) was administered. If patients did not achieve CR after a 2nd cycle of induction therapy, study treatment was discontinued.

Consolidation therapy: If patients achieved complete remission after induction therapy they 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). Midostaurin or placebo was administered at dose of 50 mg orally twice daily on days 8 -21.

Maintenance phase: If patients remained in remission after completion of consolidation therapy they received a maintenance phase of midostaurin or placebo (dose of 50 mg orally twice daily, for 12 x 28 day cycles). The maintenance phase is not considered in this review.

Concomitant medications / therapy

SCT was not protocolized in the RATIFY trial. However, SCT "… was performed at the discretion of the investigator".[1]

The Alliance for Clinical Trials in Oncology's ("the Alliance"), policy is that concomitant treatments are not collected.[2] However, collection of concomitant treatments was initiated in December 2009 for all countries based on feedback from the FDA,[2] after 68 patients from North American sites were enrolled. Only concomitant treatments belonging to one of the following categories were collected: antibiotic / antiviral / antifungal, proton pump inhibitor / H2 antagonist, NSAID / opioid, antiemetic, antihistamine, corticosteroids, growth factors, diurectics / antihypertensive, other CYP3A4 inhibitor or inducer.

Use of concomitant medications was balanced between the midostaurin and placebo group.[2] The most frequently used medications (>40% of patients) in the induction phase were vancomycin, furosemide, acyclovir, ondansetron, paracetamol, and pantoprazole.[2]

The most frequently used moderate / strong CYP3A4 inhibitors (≥30%) were fluconazole, ciprofloxacin, posaconsazole and voriconazole. Use of these medications was balanced between the midostaurin and placebo groups.[2]

Dosing

Missed doses of midostaurin or placebo were not made up.[1]

Dose adjustments or interruptions were allowed for the following reasons:[2]

- Pulmonary infiltration ≥ grade 3
- QTc prolongation events >470ms
- Non-hematologic toxicity of grade 3-4 severity considered to be at least possibly related to midostaurin/placebo
- Neutropenia grade 4 during continuation therapy
- Persistent non-hematologic toxicity of grade 1-2 that patients deemed unacceptable during continuation therapy

For the assessment of safety, the data set included all patients with informed consent who received at least one dose of study drug (midostaurin or placebo). For midostaurin, 345 / 360 patients received at least one dose and for placebo 335 / 357 received at least one dose.[2] The median daily dose was similar in the two groups: patients in the midostaurin group received 95.1 mg/day (range 4 - 4667) and patients in the placebo group received 94.8 mg / day (range 2-107). The median cumulative dose was 4150 mg (range 50 to 80800) in the midostaurin group, and was 2800 mg (range 50 to 43250) in the placebo group. Two patients' dosing data were reported in total dose instead of number of doses, hence the values appeared out of range, though the dosing was appropriately 100 mg/day. Excluding these values of 4666.7 and 436.8, the overall maximum actual dose intensity was 108 mg/day for midostaurin. The median relative dose intensity was high (>94%) in both treatment groups, which was maintained throughout all treatment phases. [2]

The median duration of exposure to midostaurin and placebo was 42.0 days (range 2 - 576) and 34.0 days (range 1 - 465 days) respectively.[2]

If patients received stem cell transplantation, midostaurin / placebo therapy was not resumed.[2]

Protocol deviation

At least one protocol deviation occurred in 493 patients (68.8%) and was similar in both treatment groups.[2] Major protocol deviations occurred in 106 patients (14.8%) and were similar in both treatment groups.[2]

a) Patient Disposition

Analysis populations

All patients (n=717) were included in all efficacy analyses (intention to treat). Please see Figure 2 for further details regarding the flow of patients in the trial. In the published trial, details are not provided regarding the formation of the safety data set. Table 7, "Summary of Grade 3, 4, or 5 Adverse Events", includes n=355 in the midostaurin group and n=354 in the placebo group. The number of patients included in the adverse events analysis in the published trial do not agree with those published in the CSR. In the CSR, all patients who received one dose of study drug (midostaurin or placebo) were included in the analysis of adverse events (midostaurin group n=345, placebo group n=335). The reason(s) for the discrepancy in patients included in the safety data set in published trial and the CSR is not clear.

Figure 2. Flow of patients in RATIFY [1]

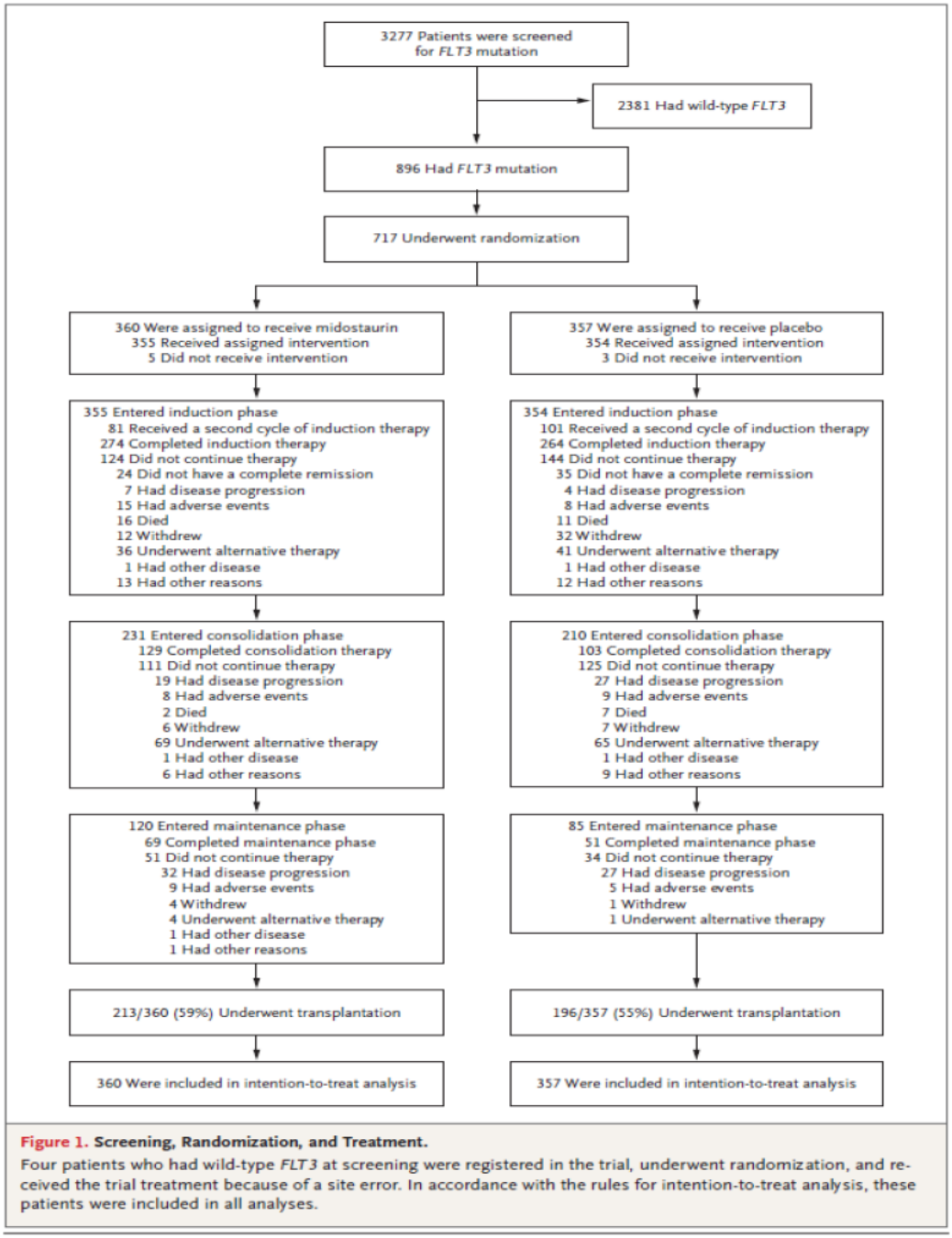


Figure 1. Screening, Randomization, and Treatment.
Four patients who had wild-type *FLT3* at screening were registered in the trial, underwent randomization, and received the trial treatment because of a site error. In accordance with the rules for intention-to-treat analysis, these patients were included in all analyses.

From: N Engl J Med, Stone et al., Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation, 377(5):454-64. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Withdrawals

The number of patients who withdrew their consent is not stated in the CSR[2] or in the published article.[1]

Among the 360 patients randomized to the midostaurin group, 69 (19.4%) patients completed all phases of trial treatment (i.e., induction, consolidation and maintenance). [1] Among the 355 patients that entered induction, 231 (65.1%) completed induction and subsequently entered consolidation. Among the 231 patients that entered consolidation, 120 (51.9%) completed consolidation and subsequently entered maintenance. Among the 355 patients who entered induction, 124 (34.9%) patients did not continue therapy; among the 231 patients who entered consolidation, 111 (48.1%) patients did not continue therapy; and among the 120 patients who entered maintenance, 51 (42.5%) patients did not continue therapy. In all phases of treatment, the most frequent reason cited for discontinuing therapy was "underwent alternative therapy" which captures patients who received SCT as well as other therapies. Please see Figure 2 for a description of the flow of patients through the trial and reasons for discontinuing therapy.

Among the 357 patients randomized to the placebo group, 51 (14.2%) completed all phases of trial treatment (i.e., induction, consolidation and maintenance). [1] Among the 354 patients that entered induction, 210 (59.3%) completed induction and subsequently entered consolidation. Among the 210 patients that entered consolidation, 85 (40.5%) completed consolidation and subsequently entered maintenance. Among the 354 patients who entered induction, 144 (40.7%) patients did not continue therapy; among the 210 patients who entered consolidation, 125 (59.5%) patients did not continue therapy; and among the 85 patients who entered maintenance, 34 (40.0%) patients did not continue therapy. Similar to patients randomized to midostaurin, a frequent reason for discontinuing therapy was "underwent alternative therapy" which captures patients who received SCT as well as other therapies. Please see Figure 2 for a description of the flow of patients through the trial and reasons for discontinuing therapy.

At Checkpoint 1 (July 2017), the submitter indicated that, with respect to patients lost to follow-up: "The information collected on lost to follow-up is incomplete and not reliable."[6]

At Checkpoint 1 (July 2017), the submitter was asked to provide the number of patients who withdrew consent. They indicated that 62/717 (8.6%) of patients "withdrew or refused" after beginning protocol therapy.[6]

Missing data

No missing data were reported in the published trial.[1] At Checkpoint (July 2017), the submitter indicated that: "The last available assessment/status was used to handle any missing data".[6] The proportion of patients with missing data was not provided.

b) Limitations/Sources of Bias

- The indication proposed by the submitter included a maintenance phase with midostaurin monotherapy following the consolidation therapy. The proposed Health Canada indication aligned with the clinical trial population in the RATIFY trial. However, Health Canada did not approve this indication because the submitter failed to provide convincing evidence of the benefit of maintenance therapy. Although maintenance therapy was an integral part of the pivotal study, the patients were not re-randomized prior to the start of the maintenance phase. When the small number of patients who entered this phase

was considered, it was difficult to assess the contribution of this phase to the OS benefit.[4]

- The RATIFY trial demonstrated a benefit of midostaurin on survival (HR for death: 0.78, 95% CI 0.63-0.96, p=0.009; difference in 4-year overall survival 7.1%, confidence interval not provided).[1] In the RATIFY trial, midostaurin was used in three phases of treatment (induction, consolidation and maintenance); approximately 29% of patients received maintenance therapy. The indication under review is for induction and consolidation only but, as pointed out by the Health Canada review, the observed survival benefit may not be influenced by the effect of midostaurin in the maintenance phase.

  Assuming, as per Health Canada's review, that there is no effect of midostaurin in the maintenance phase, the HR for overall survival reported in the published trial can be interpreted as is. However, if there is an effect of midostaurin in the maintenance phase on overall survival, there is uncertainty in the interpretation of the HR. At the Checkpoint meeting (September 2017), the submitter provided the HR for death removing patients who received maintenance, to reflect the reimbursement request (for induction and consolidation only) (removed n=120 in midostaurin group and n=85 in placebo group): HR = 0.82 (95% CI 0.65, 1.04)[5] but this is no longer a comparison of randomized groups and is subject to differential selection bias. The direction and magnitude of differential selection bias is uncertain.

  Patients who achieved remission after their first induction (21 days) went on to consolidation (four 28-day cycles), thus at approximately 4.5 months some patients will have begun maintenance with midostaurin. If we consider the pre-maintenance results, visual inspection of the cumulative incidence for death curves [6] suggests that the curves begin to separate at approximately 1 month (i.e., approximately after 1 cycle of induction), suggesting that the effect of midostaurin begins early in treatment. However, the submitter did not provide an estimate of the treatment effect from the cumulative incidence curves.

  The HR (ITT analysis) reported in the published trial provides an unbiased estimate of the treatment effect (midostaurin compared with placebo) on overall survival. Assuming there is no benefit of midostaurin in maintenance the HR can be interpreted as is. However, if there is uncertainty regarding the contribution of midostaurin in the maintenance phase to overall survival, the HR should be interpreted with caution as the contribution of midostaurin in the maintenance phase to overall survival cannot be estimated with certainty.

- Although the enrolment target of 714 was met (n=717 enrolled), the number of events (death) was not reached (event target = 509, events observed = 377). This may be in part due to the much higher than anticipated occurrence of stem cell transplant (57% compared with the 25% assumed for sample size planning purposes).

- During study planning, the proportion of patients expected to undergo SCT was 15%. However, the observed proportion, when the sample size was amended, was 25%. Further, the observed rate at data cut-off March 7, 2016 was 57%.

- Overall, a large proportion of patients, 57%, in both treatment arms underwent SCT, a concomitant therapy that was not protocolized. [1] SCT occurred in 213

(59%) of patients in the midostaurin group and in 196 (55%) of patients in the placebo group. A similar proportion of patients in both groups underwent allogeneic SCT in CR1 (midostaurin group = 101 (28%) patients, placebo group = 81 (22%) patients). The effect of SCT is likely to diminish the magnitude of the effect between midostaurin and placebo on overall survival. This was considered in the revised sample size calculation ("The HR was lower [compared with the HR used for the original sample size calculation] since it was assumed no treatment effect for patients who received an SCT".[2] Further, upon undergoing SCT, study treatment was stopped thus limiting the exposure to midostaurin (and therefore limiting its potential effect).

- At Checkpoint,[6] the submitter was asked to provide 1) a competing risk analysis for OS, where SCT was treated as a competing risk and 2) cumulative incidence curves for SCT and death by group. The HR for death where SCT was considered a competing risk was 0.813 (95% CI 0.592, 1.118). This is consistent in direction and magnitude with the HR for OS presented in the trial publication (HR 0.78, 95%: 0.63, 0.96). In addition, visual inspection of the cumulative incidence curves for SCT suggests that the proportion of patients in both groups who received SCT over time was not different (the curves overlap entirely from 0 months to 48 months).

- Median OS could not be reliability interpreted[4] (median OS in the midostaurin group was 74.7 months (95% CI 31.5, not reached [NR]) and in the placebo group was 25.6 months (95% CI 18.6, 42.9)).[1] The difference in median OS was 49.1 months, however the confidence interval for the difference was not provided.[1] The 4-year survival rate was 51.4% in the midostaurin group and 44.3% in the placebo group.[1] The difference in 4-year survival rate was 7.1%, however the confidence interval for the difference was not provided.[1]

- The trial did not collect data on health-related QOL; thus, the magnitude and direction of the effect of midostaurin on patient-reported QoL in adult patients with FLT-mutation positive AML is unknown.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Note that data cut-off for the Clinical Study Report provided by the submitter and the published journal article is different (CSR data cut-off is April 1, 2015 and published trial data cut-off is March 7, 2016). Please see Table 8 for a summary of outcomes and sources of data. At Checkpoint (July 2017), the submitter was asked to provide the most current estimates for OS, EFS, CR, DFS and OS (censored for SCT. The submitter replied[6]:

"The study was sponsored by Novartis in countries outside of North America; however, the ownership of the protocol, of all study data, and the management of the clinical database is by the Alliance, following Alliance policies and procedures. Therefore, Novartis does not have access to the data published in the Stone et al. NEJM 2017 publication. Except for OS (data cut, September 2016, see below), the information provided in the submission to pCODR and Health Canada (data cut of April 1, 2015) is the most recent data in Novartis position [possession]."

Where possible, outcomes are reported from the published trial (data cut March 7, 2016).

Efficacy Outcomes

a) Overall survival (All-cause mortality)

Overall survival (OS), the primary endpoint, was defined as the time from randomization to death from any cause.[1] Median OS was 74.7 months (95% CI 31.5 - Not Reached (NR)) in the midostaurin group and 25.6 months (95% CI, 18.6 - 42.9) in the placebo group.[1] The difference in median OS was 49.1 months (confidence interval was not provided).[1] The HR for death was 0.78 (95% CI 0.63 - 0.96, p (1-sided) = 0.009 by stratified log-rank test).[1]

The 4-year overall survival rate was 51.4% in the midostaurin group and 44.3% in the placebo group. The difference in 4-year survival rate was 7.1% (confidence interval not provided).[1]

Median follow-up time and number of deaths was not provided in the published study. However, they were reported in the CSR (data cut April 1, 2015). Median follow-up time from randomization to data cut off on April 1, 2015 was 60.2 months (range: 42-81) for all patients.[2] The median follow-up in the midostaurin group and the placebo group were similar.[2] During the follow-up period, 171 (47.5%) and 186 (52.1) deaths were observed in the midostaurin and placebo groups respectively.[2]

At Checkpoint (July 2017), the submitter provided OS with a data-cut of September 2016 (approximately6 additional months of follow up compared with the published trial). In the midostaurin group, 176 deaths were observed and in the placebo group 189 deaths were observed (HR 0.79, 95% CI 0.64, 0.97). At data cut-off, 11 (3.1%) patients were alive in the midostaurin group and 5 (1.4%) patients were alive in the placebo group.[6]

b) Event-free survival

Event-free survival (EFS) was defined as the time from randomization to relapse, death from any cause, or failure to achieve protocol-specified complete remission. Relapse was defined as: "the reappearance of circulating blast cells not attributable to "overshoot" following recovery from myelosuppressive therapy; >5% blasts in the marrow, not attributable to another cause (e.g., CSF, bone marrow regenerations); development of extramedullary leukemia".[2] Protocol-specified complete remission was defined as "the presence of less than 5% blasts in the marrow or extramedullary leukemia, an absolute neutrophil count of more than 1000 per microliter, a platelet count of more than 100,000 per microliter, and the absence of blasts in the peripheral blood; in addition, the complete remission had to have occurred by day 60."[1]

Median EFS was 8.2 months (95% CI 5.4 - 10.7) in the midostaurin group and 3.0 months (95% CI 1.9 - 5.9) in the placebo group. The HR for an event (composite of 3 outcomes) was 0.78 (95% CI 0.66 - 0.93, p (1-sided) = 0.002 by stratified score).

c) Disease-free survival

The analysis of disease-free survival (DFS) included only patients who achieved a complete remission by day 60 after study treatment initiation. DFS was defined as the time from date of first complete remission to the date of relapse or death from any cause, whichever occurred first.[2]

Median DFS was 26.7 months (95% CI 19.4 - NR) in the midostaurin group and 15.5 months (95% CI 11.3 - 23.5) in the placebo group.[1] The HR for relapse or death after achieving a complete remission by day 60 was 0.71 (95% CI 0.55 - 0.91, p (1-sided) = 0.0051).[2]

d) Complete remission

Protocol-specified complete remission (CR) was defined as "the presence of less than 5% blasts in the marrow or extramedullary leukemia, an absolute neutrophil count of more than 1000 per microliter, a platelet count of more than 100,000 per microliter, and the absence of blasts in the peripheral blood; in addition, the complete remission had to have occurred by day 60."[1]

Protocol-specified CR was achieved by 59% (212/360) patients in the midostaurin group and 54% (191/357) patients in the placebo group (p=0.15, 2-sided). The Kaplan-Meier estimate of median time to complete remission was 35 days (range 20-60) in the midostaurin group and 35 days (range 20-60) in the placebo group.

e) Stem cell transplant in first complete remission

SCTwas not protocolized in RATIFY. Rather, SCT was "performed at the discretion of the investigator".[1]

Overall, the proportion of patients undergoing SCT was high: 59% (213/360) of patients in the midostaurin group and 55% (196/357) of patients in the placebo group. The proportion of patients undergoing SCT after 1st protocol-specified CR was 28.1% in the midostaurin group and 22.7% in the placebo group.

Quality of Life

Quality of life outcomes were not reported in the published trial or in the Clinical Study Report . At Checkpoint (July 2017), the submitter indicated thatQuality of life data was not measured in the trial. The RATIFY trial was an investigator initiated trial designed in 2006, at which time QoL was not routinely measured in AML studies.[6]

Harms Outcomes

For the assessment of safety, as per the CSR, the data set included all patients with informed consent who received at least one dose of study drug (midostaurin or placebo).[2] In the midostaurin group, 345 / 360 (96%) patients received at least one dose and in the placebo group 335 / 357 (94%) received at least one dose.[2] However, the formation of the safety data set in the published trial is not described[1] (n=355 in the midostaurin group and n=354 in the placebo group). Where possible, harms outcomes (reported below) reflect the results from the published trial.

a) Grade 3, 4 and 5 adverse events (AEs)

Grade 3, 4 and 5 AEs are reported in Table 7. The rate of grade 3, 4, or 5 anemia was higher in the midostaurin group than in the placebo group (92.7% vs. 87.8%).[1] The rate of grade 3, 4 or 5 rash was also higher in the midostaurin group than in the placebo group (14.1% vs. 7.6%). The rate of grade 3, 4, or 5 nausea was higher in the placebo group than in the midostaurin group (9.6% vs. 5.6%).

All patients in RATIFY experienced at least one adverse event (AE) of any grade. All patients enrolled in the trial, but for one in the midostaurin group (i.e., n=716) experienced at least one Grade 3/4 AE.[2]

b) Cardiac failure

At North American sites, only 13 pre-defined AEs had all grades collected. Cardiac failure was not included in the 13 pre-defined AEs. Among non-North American sites (n=455), there were 3 cardiac failure events in the midostaurin group (n=229) and 3 cardiac failure events in the placebo group (n=226). In the midostaurin group, 1 event was Grade 3/4 and 1 was suspected to be related to treatment. In the placebo group, 2 events were Grade 3/4 and 2 events were serious adverse events.[2]

c) AE: fungal infections

The CGP identified types of fungal infections as an AE of special interest.The proportion of patients reporting fungal infections was not provided in the CSR or in the published trial. However, the use of anti-fungal medications was 61% and46% during the induction and consolidation respectively. The use of anti-fungal medication was balanced between both groups.[2]

At Checkpoint (July 2017), the submitter indicated that 2 patients (both in the midostaurin group) experienced a grade 3/4 fungal infection. Overall there were 5 fungal infections (4 in the midostaurin group, 1 in the placebo group). The submitter noted that "…this event was required to be reported for North American sties for grade 3/4 only."[6]

d) AE: Stevens- Johnson syndrome

No case of severe or fatal skin toxicity (e.g., Stevens-Johnsons syndrome) was reported.[2]

e) Withdrawal due to adverse effects

In the midostaurin group, 32 (9%) patients discontinued treatment due to an adverse event. In the placebo group, 22 (6.2%) patients discontinued treatment due to an adverse event.[1]

Table. 7 Grade 3, 4 and 5 adverse events [1]

Table 2. Summary of Grade 3, 4, or 5 Adverse Events.

Adverse Event	Midostaurin Group (N=355)	Placebo Group (N=354)	P Value*
	no. of patients (%)		
Hematologic			
Thrombocytopenia	346 (97)	342 (97)	0.52
Neutropenia	338 (95)	339 (96)	0.86
Anemia	329 (93)	311 (88)	0.03
Leukopenia	93 (26)	105 (30)	0.32
Lymphopenia	68 (19)	78 (22)	0.35
Other blood or bone marrow event	1 (<1)	4 (1)	0.22
Bone marrow hypocellularity	0	1 (<1)	0.50
Nonhematologic			
Febrile neutropenia	290 (82)	292 (82)	0.84
Infection	186 (52)	178 (50)	0.60
Lymphopenia	68 (19)	78 (22)	0.35
Diarrhea	56 (16)	54 (15)	0.92
Hypokalemia	49 (14)	60 (17)	0.25
Pain	47 (13)	44 (12)	0.82
Increased alanine aminotransferase	45 (13)	33 (9)	0.19
Rash or desquamation	50 (14)	27 (8)	0.008
Fatigue	32 (9)	37 (10)	0.53
Pneumonitis or pulmonary infiltrates	28 (8)	29 (8)	0.89
Nausea	20 (6)	34 (10)	0.05
Hyponatremia	31 (9)	23 (6)	0.32
Hyperbilirubinemia	25 (7)	28 (8)	0.67
Mucositis or stomatitis	22 (6)	28 (8)	0.38
Hypophosphatemia	19 (5)	29 (8)	0.14
Hypocalcemia	24 (7)	21 (6)	0.76

* P values are two-sided and were calculated with the use of Fisher's exact test.

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Table 8. Summary of outcomes

	RATIFY		Data cut off date	Data source
	mido (N=360)	placebo (N=357)		
Overall survival (OS)				
Median months (95% CI)	74.7 (31.5-NR)	25.6 (18.6-42.9)	March 7, 2016	Stone NEJM 2017[1]
HR (95%CI)	0.78 (0.63-0.96)		March 7, 2016	Stone NEJM 2017[1]
p-value	0.009 (one-sided, stratified log rank)		March 7, 2016	Stone NEJM 2017[1]
HR (95% CI)	0.79 (0.64 - 0.97)		September 2016	Checkpoint 1[6]
Deaths (%)	171 (47.5%)	186 (52.1%)	April 1, 2015	CSR A2301 [2]
Death (%)	176 (48.9%)	189 (52.9%)	September 2016	Checkpoint 1[6]
Median follow-up time (months) from randomization to cut off on April 1, 2015) (min, max)	60.2 (42, 81)	60.2 (42, 79)	April 1, 2015	CSR A2301 [2]
4-year overall survival rate	51.4%	44.3%	March 7, 2016	Stone NEJM 2017[1]
Difference, 4-year overall survival rate (95% CI)	7.1% (confidence interval not provided)		March 7, 2016	Stone NEJM 2017[1]
HR (95% CI), patients removed from analysis if received maintenance (n=120 midostaurin, n=85 placebo)	0.82 (0.65, 1.04)		April 1, 2015	Checkpoint 2[5]
Event free survival (EFS)				
Median months (95% CI)	8.2 (5.4 - 10.7)	3.0 (1.9 - 5.9)	March 7, 2016	Stone NEJM 2017[1]
HR (95%CI)	0.78 (0.66 - 0.93)		March 7, 2016	Stone NEJM 2017[1]
p-value	P=0.002 (one-sided, by stratified score test)		March 7, 2016	Stone NEJM 2017[1]
Failure to achieve remission by day 60	147 (40.8%)	166 (46.5%)	April 1, 2015	CSR A2301[2]
Relapse	91 (25.3%)	90 (25.2%)	April 1, 2015	CSR A2301[2]
Death	18 (5.0%)	24 (6.7%)	April 1, 2015	CSR A2301[2]
Disease free survival (DFS)				

Median months (95% CI)	26.7 (19.4 - NR)	15.5 (11.3 - 23.5)	March 7, 2016	Stone NEJM 2017[1]
HR (95% CI)	0.71 (0.55 - 0.91)		April 1, 2015	CSR A2301[2]
p-value	P=0.0051, 1-sided		April 1, 2015	CSR A2301[2]
Complete Remission (CR)				
Protocol-specified CR by day 60, no. (%)	212 (59%)	191 (54%)	March 7, 2016	Stone NEJM 2017[1]
Stem Cell Transplant (SCT)				
SCT after 1st CR	28.1%	22.7%	March 7, 2016	Stone NEJM 2017[1]
Allogeneic SCT in CR1, n (%)	101 (28.1%)	81 (22.7%)	March 7, 2016	Stone NJEM 2017[1]
SCT (overall)	213 (59%)	196 (55%)	March 7, 2016	Stone NEJM 2017, appendix[7]
HrQoL				
Quality of Life	**Not reported**	**Not reported**		
Harms Outcome, n (%)	**Arm (N=355)**	**Arm (N=354)**		
Grade ≥3	354 (99.7%)	354 (100%)		
AE (any grade), n (%)	355 (100%)	354 (100%)	April 1, 2015	CSR A2301[2]
Stevens-Johnson syndrome	0	0	April 1, 2015	CSR A2301[2]
Fungal infections, any grade	4	1	April 1, 2015	Checkpoint 1[6]
WDAE**, n (%)	32 (9%)	22 (6.2%)	March 7, 2016	Stone NEJM 2017[1]

AE = adverse event, CI = confidence interval, HR = hazard ratio, HRQoL = health-related quality of life, NR = not reached, SD = standard deviation, WDAE = withdrawal due to adverse event, *HR < 1 favours midostaurin, **denominator is 360 for midostaurin, 357 for placebo.

6.4 Ongoing Trials

No ongoing trials were identified that met our inclusion criteria.

7 SUPPLEMENTAL QUESTIONS

There were no supplemental questions identified for this review.

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 midostaurin 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 revisions were made in between posting of the Initial and Final Guidance Reports.

The Leukemia Clinical Guidance Panel members were selected by the pCODR secretariat, as outlined in the pCODR Nominatin/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 May 2017, Embase 1974 to 2017 June 21, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches	Results
1	(midostaurin* or Rydapt* or benzoylstaurosporine* or CGP41251 or CGP 41251 or CGP 41 251 or PKC412 or PKC 412 or ID912S5VON or 120685-11-2).ti,ab,ot,kf,kw,hw,rn,nm.	2231
2	Leukemia, Myeloid, Acute/	35667
3	(acute adj2 (myeloid or myelogenous or granulocytic or myeloblastic or myelocytic or nonlymphoblastic or nonlymphocytic or non-lymphoblastic or non-lymphocytic or promyelocytic) adj2 leuk?emia*).ti,ab,kf,kw.	113784
4	AML.ti,ab,kw,kf.	77708
5	or/2-4	145544
6	1 and 5	799
7	6 use pmez	153
8	6 use cctr	16
9	*midostaurin/ or (midostaurin* or Rydapt* or benzoylstaurosporine* or CGP41251 or CGP 41251 or CGP 41 251 or PKC412 or PKC 412 or ID912S5VON).ti,ab,kw.	1155
10	Acute myeloid leukemia/	38134
11	(acute adj2 (myeloid or myelogenous or granulocytic or myeloblastic or myelocytic or nonlymphoblastic or nonlymphocytic or non-lymphoblastic or non-lymphocytic or promyelocytic) adj2 leuk?emia*).ti,ab,kw.	113536
12	AML.ti,ab,kw.	77639
13	or/10-12	145886
14	9 and 13	452
15	14 use oemezd	306
16	7 or 8 or 15	475
17	limit 16 to english language	463
18	17 and conference abstract.pt.	158
19	limit 18 to yr="2012 -Current"	115
20	17 not 18	305
21	remove duplicates from 20	180

22	19 or 21	295

2. **Literature search via PubMed**
   A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#3	Search #1 AND #2 AND publisher[sb] Filters: English	4
#2	Search Acute[tiab] AND (myeloid[tiab] OR myelogenous[tiab] OR granulocytic[tiab] OR myeloblastic[tiab] OR myelocytic[tiab] OR nonlymphoblastic[tiab] OR nonlymphocytic[tiab] OR non-lymphoblastic[tiab] OR non-lymphocytic[tiab] OR promyelocytic[tiab]) AND (leukemia*[tiab] OR leukaemia*[tiab])	50627
#1	Search Midostaurin[Supplementary Concept] OR Midostaurin*[tiab] OR Rydapt*[tiab] OR benzoylstaurosporine*[tiab] OR CGP41251[tiab] OR CGP 41251[tiab] OR CGP 41 251[tiab] OR PKC412[tiab] OR PKC 412[tiab] OR ID912S5VON[tiab] OR 120685-11-2[rn] OR 120685-11-2[tiab]	448

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

4. **Grey Literature search via:**

   Clinical trial registries:

   U.S. NIH ClinicalTrials.gov
   http://www.clinicaltrials.gov/

   Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
   http://www.canadiancancertrials.ca/

   Search: Rydapt/midostaurin, acute myeloid leukemia

   Select international agencies including:

   Food and Drug Administration (FDA):
   http://www.fda.gov/

   European Medicines Agency (EMA):
   http://www.ema.europa.eu/

   Search: Rydapt/midostaurin, acute myeloid leukemia

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

American Society of Hematology (ASH)
http://www.hematology.org/

Search: Rydapt/midostaurin, acute myeloid leukemia - last 5 years

Literature Search Detailed Methodology

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-2017 June 21) with in-process records & daily updates via Ovid; Embase (1974-2017 June 21) via Ovid; The Cochrane Central Register of Controlled Trials (May 2017) 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 Rydapt, midostaurin and acute myeloid leukemia.

No filters were applied to limit retrieval by publication 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 November 2, 2017.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health - clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - 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) 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 Clinical Guidance Panel. In addition, 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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2. Clinical Study Report: CPKC412A2301. A phase 3 randomized, double-blind study of induction (daunorubicin/cytarabine) and consolidation (high-dose cytarabine) chemotherapy + midostaurin (PKC412) or placebo in newly diagnosed patients less than 60 years of age with FLT3-mutated acute myeloid leukemia (AML) [internal manufacturer's report]. Dorval (QC): Novartis; 2016 Jul 5.

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