# pan-Canadian Oncology Drug Review
# Final Clinical Guidance Report

# Gilteritinib (Xospata) for Acute Myeloid Leukemia

**May 20, 2020**

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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 gilteritinib (Xospata) 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 gilteritinib for AML conducted by the Leukemia Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

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

## 1.1 Introduction

The objective of the systematic review was to evaluate the safety and efficacy of gilteritinib compared to standard of care in patients with relapsed or refractory AML with a FMS-like tyrosine 3 (FLT3) mutation.

The reimbursement request is for gilteritinib is for the treatment of adult patients who have relapsed or refractory AML with a FLT3 mutation as detected by a validated test. The Health Canada approved indication for gilteritinib is for the treatment of adult patients who have relapsed or refractory AML with a FLT3 mutation. A validated test is required to confirm the FLT3 mutation status of AML. The notice of compliance from Health Canada was issued on December 23, 2019.[1]

According to the Health Canada Product Monograph, the following dose considerations are noted:

- Treatment with gilteritinib should be initiated and supervised by an experienced physician (i.e., experienced in the use of anticancer therapies).
- Patients must have confirmed FLT3 mutation either internal tandem duplication or tyrosine kinase domain prior to starting treatment with gilteritinib
- Blood counts and chemistries must be assessed at various time points (prior to starting gilteritinib, once weekly at first month, once biweekly at second month, and monthly for duration of treatment).
- Electrocardiograms should be performed at various time points (prior to starting gilteritinib, on day 8 and 15 of first month, before starting next two months of treatment, and as clinically indicated).[1]

The recommended dose of gilteritinib is 120 mg (three 40 mg tablets) orally once daily and can be taken with or without food. Treatment with gilteritinib should continue as long as clinical benefit is observed or until unacceptable toxicity occurs. It is also noted in the

Health Canada Product Monograph that a delay in clinical response can occur and, therefore, it is recommended (in the absence of disease progression or unacceptable toxicity) that treatment with gilteritinib should be for a minimum of six months. Dose adjustments are not required for patients ≥ 65 years of age, patients with mild or moderate renal impairment (creatinine clearance [CLCr] ≥30 mL/min), or patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.[1]

Serious warning and precautions related to differentiation syndrome is noted in the Health Canada Product Monograph, since it was reported in patients treated with gilteritinib and can be fatal if not treated.[1]

## 1.2 Key Results and Interpretation

### 1.2.1 Systematic Review Evidence

The pCODR systematic review included one randomized controlled trial (RCT), the ADMIRAL trial (n=371), and the results are summarized below.[2]

ADMIRAL

ADMIRAL was an international, open-label, phase III, randomized, active-controlled superiority trial that compared the safety and efficacy of gilteritinib versus salvage chemotherapy in FLT3-mutated AML patients who were refractory to or relapsed after first-line therapy. Eligible patients were pre-selected for 1 of 4 salvage chemotherapy regimens and were randomized in a 2:1 ratio to receive either gilteritinib (starting dose 120 mg administered orally once daily in continuous 28-day cycles) or the pre-selected salvage chemotherapy regimen. Salvage chemotherapy regimens were administered in 28-day cycles and included 1-2 cycles of two possible high intensity regimens: MEC (mitoxantrone, etoposide, cytarabine); or FLAG-IDA (fludarabine, cytarabine, granulocyte colony-stimulating factor, idarubicin); or continuous cycles (until discontinuation) of two possible low-intensity regimens: LoDAC (low dose cytarabine) or azacitidine. Patients in the gilteritinib arm eligible for hemopoietic stem cell transplant (HSCT) could interrupt and resume gilteritinib following HSCT given certain criteria were met. Gilteritinib could also be escalated to 200 mg after cycle 1 if CR, complete remission with incomplete platelet recovery (CRp), or complete remission with incomplete hematological recovery (CRi) was not achieved.[2] Dosing details are outlined in section 6.3.2.1 (Detailed Trial Characteristics) under section *c) Interventions*.

The co-primary endpoints included overall survival and complete remission and complete remission with partial hematologic recovery (CR/CRh) rate. Complete remission was defined as bone marrow regenerating normal hematopoietic cells and achieving a morphologic leukemia-free state with: an absolute neutrophil count (ANC) 1 x $10^9$/L; platelet count ≥ 100 x $10^9$/L; normal marrow differential <5% blasts; red blood cell (RBC) and platelet transfusion independent status (1 week without RBC transfusion and 1 week without platelet transfusion); and no evidence of extramedullary leukemia. Complete remission with partial hematologic recovery was defined as CR, but with partial hematologic (ANC ≥0.5 x $10^9$/L) and platelets (≥50 x $10^9$/L) recovery.[2] CR/CRh rate was evaluated at the first interim analysis and the endpoint was met (alpha for testing was spent).[2,3] Key secondary endpoints included event-free survival (EFS), defined as the date of randomization until the date of documented relapse (by bone marrow sample assessment), treatment failure, or death, whichever occurred first; and CR rate, which

were controlled for multiplicity (however, the EFS endpoint was not met, and thus the CR results should be considered exploratory).[2]

Other secondary endpoints included: duration of remission, CRh rate, composite complete remission (CRc) rate, transplantation rate, transfusion conversion and maintenance rate, and health-related quality of life (HRQoL). Composite complete remission included patients with CR, CR with incomplete hematological recovery (CRi), or CR with incomplete platelet recovery (CRp). Transplantation rate included patients who underwent HSCT during or off-study in both treatment arms. Transfusion conversion rate was defined as the proportion of patients dependent on transfusions at baseline who became transfusion independent during the study; the transfusion maintenance rate was the proportion of patients who were transfusion independent at baseline that remained transfusion independent on the study. Patients were classified as transfusion independent if there were no RBC or platelet transfusions 28 days before or after the first study dose, and patients were classified as transfusion independent, if there was one consecutive 8 week period without transfusions from 29 days after the first dose until the last dose date. The key secondary HRQoL assessment was measured with the brief fatigue inventory (BFI) questionnaire, which assessed the severity and impact of fatigue on daily functioning; additional exploratory HRQoL assessments are outlined in section 6.3.2.1 (Detailed Trial Characteristics) under section *a) Trials*. Safety and adverse events (AEs) were monitored regularly throughout the study and included all patients who received at least 1 dose of the assigned treatment.[2]

*Study Population*

A total of 371 patients were randomly assigned to receive gilteritinib (n=247) or salvage chemotherapy (n=124). A total of 246 received treatment with gilteritinib and 109 received treatment with salvage chemotherapy, of which 62.3% received high-intensity chemotherapy and 37.6% received low-intensity chemotherapy.[2] In the salvage chemotherapy arm, 14 of 15 patients that did not receive assigned treatment with salvage chemotherapy had withdrawn participation.[4] Overall, the median age was 62 years (range: 19, 85), and a total of 54.2% of patients were female, 59.3% were White, 27.5% were Asian, and 83.3% had a baseline Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0-1. The majority of patients had a FLT3-ITD alone mutation (88.4%), with 8.4% that had FLT3-TKD alone, and 1.9% that had both; and most patients overall (73%) had intermediate cytogenetic risk.[2] There were a higher proportion of patients in the gilteritinib arm with an antecedent hematological disorder (16.6%) compared to the salvage chemotherapy arm (8.9%), with myelodysplastic syndrome (MDS) as the most common in both treatment arms (13.8% and 6.5% in the gilteritinib and salvage chemotherapy arms, respectively). Standard dose cytarabine with idarubicin was the most common prior regimen (overall: 39.4%) followed by high-dose cytarabine (27.0%). A total of 12.4% of patients had used a prior FLT3 inhibitor. There were a higher proportion of patients with that received consolidation therapy as part of their prior treatment regimen in the gilteritinib arm (44.9%) compared to the salvage chemotherapy arm (39.5%).[5]

*Efficacy*

The key efficacy outcomes are presented in Table 1.1, with a data cut-off of September 17th, 2018.

- **OS:** The median duration of follow-up was 17.8 months, and a total of 171 (69.2%) deaths occurred in the gilteritinib arm and 90 (72.6%) occurred in the salvage chemotherapy arm. The median overall survival was 9.3 months (95% CI: 7.7, 10.7) in the gilteritinib arm and 5.6 months (95% CI: 4.7, 7.3) in the salvage chemotherapy arm. There was a 36% reduction in the risk of death (HR: 0.64; 95%

CI: 0.49, 0.83; p <0.001) in the gilteritinib arm relative to the salvage chemotherapy arm.[2]

- **CR/CRh rate:** At the time of data cut-off (endpoint was met at first interim analysis) the CR/CRh rate was 34% (n=84) in the gilteritinib arm and 15.3% (n=19) in the salvage chemotherapy arm (treatment risk difference: 18.6%; 95% CI: 9.8, 27.4).[2,3]
- **EFS:** A total of 189 (76.5%) EFS events occurred in the gilteritinib arm and 62 (50.0%) EFS events occurred in the salvage chemotherapy arm. The median duration of EFS was 2.8 months (95% CI: 1.4, 3.7) in the gilteritinib arm and 0.7 months (95% CI: 0.2, NE) in the salvage chemotherapy arm. There was a 21% (HR: 0.79; 95% CI: 0.58, 1.09; p = 0.0830) reduction in the risk of an EFS event in the gilteritinib arm relative to the placebo arm, however it was not statistically significant. EFS was limited in usefulness due to a high proportion of censoring in the salvage chemotherapy arm, as most patients were in the high intensity chemotherapy arm and entered long-term follow-up (with no systematic/standard measurement of disease for relapse) after 1-2 cycles of treatment.[2,3]
- **CR rate:** Since the EFS endpoint was not met, this endpoint is considered exploratory (hierarchal testing procedure). The CR rate was 21.1% in the gilteritinib arm and 10.5% in the salvage chemotherapy arm, with a treatment difference of 10.6% (95% CI: 2.8, 18.4).[2]
- **Duration of CR:** As mentioned above, most patients in the high-intensity arm entered long-term follow-up after 1-2 cycles, and thus duration of CR could not be reliably estimated. Nonetheless, the median duration of CR was 14.8 months (95% CI: 11.0, NE) in the gilteritinib arm and 1.8 months (95% CI: NE, NE) in the salvage chemotherapy arm.[2]
- **CRh rate:** The CRh rate was 13.0% in the gilteritinib arm and 4.8% in the salvage chemotherapy arm.[2]
- **CRc rate:** Th CRc rate (CR, CRp, and CRi) was 54.3% in the gilteritinib arm and 21.8% in the salvage chemotherapy arm, and the treatment difference was 32.5% (95% CI: 22.3, 42.6).[2]
- **Transplantation rate:** The transplantation rate was 25.5% in the gilteritinib arm, which included 55 patients who received HSCT on-study and 8 patients who received HSCT off-study. The transplantation rate was 15.3% in the salvage chemotherapy arm, where all patients received HSCT off-study as it was not permitted on-study.[2]
- **Transfusion conversion and maintenance rate:** As per protocol, the transfusion conversion and maintenance rates were described only for the gilteritinib arm. A total of 68 patients became transfusion independent out of a total of 197 patients that were transfusion-dependent at baseline, representing a conversion rate of 34.5% (95% CI: 27.9M 41.6). A total of 29 of 49 patients remained transfusion independent who were transfusion independent at baseline, representing a maintenance rate of 59.2% (95% CI: 44.2, 73.0).[3]

*Health-related Quality of Life*

At baseline, 91.9% and 78.2% in the gilteritinib and salvage chemotherapy arms had baseline BFI questionnaires completed, whereas at Cycle 2, Day 1, this dropped to 83.4% and 12.1%, respectively.[6] The baseline median BFI fatigue score was 2.6 (range: 0, 9) in the gilteritinib arm and 2.0 (range: 0, 10) in the salvage chemotherapy with no change

from baseline at cycle 2, day 1 in the gilteritinib arm (range: -8, 7) and a change of 0.7 in the salvage chemotherapy arm (range: -5, 4).[5]

*Harms*

The median duration of treatment was 126 days (range: 4, 885) in the gilteritinib arm and 28 days (5, 217) in the salvage chemotherapy arm.[3] In the gilteritinib arm, a total of 78 (31.7%) of patients escalated to 200 mg, and the median duration of treatment prior to dose escalation was 1.4 months (range: 0.9, 17.4) and 1.6 months (range: <0.1, 24.8) after dose escalation.[3,4] A total of 63 patients (25.5%) of patients had HSCT in the gilteritinib arm, with 55 that had HSCT on-study (40 resumed gilteritinib, 15 did not resume gilteritinib) and 8 that had HSCT off-study. A total of 19 (15.3%) of patients in the salvage chemotherapy had HSCT off-study.[3] Dose reductions and interruptions were higher in the gilteritinib arm likely due to the longer treatment exposure.

**AEs any-grade:** All patients in the gilteritinib arm and 98.2% in the salvage chemotherapy experienced an AE.[3] The most common any-grade AE was anemia in the gilteritinib arm (n=116, 47.2%), which was followed by febrile neutropenia (n=115, 46.7%), pyrexia (n=105; 42.7%), alanine aminotransferase increased (n=103, 41.9%), aspartate aminotransferase increased (n=99, 40.2%), diarrhea (n=81, 32.9%), and nausea (n=79, 32.1%). In the salvage chemotherapy arm, the most common any-grade AEs included febrile neutropenia (n=40, 36.7%), anemia (n=38, 34.9%), nausea (n=36, 33.0%), hypokalemia (n=34, 31.2%), pyrexia (n=32, 29.4%), and diarrhea (n=32, 29.4%).[2]

**AEs grade ≥3:** Grade ≥3 AEs occurred in 95.9% of patients in the gilteritinib and in 86.2% of patients in the salvage chemotherapy arm.[3] The most common grade ≥3 AEs for both arms included febrile neutropenia (gilteritinib: n=113, 45.9%; salvage chemotherapy: n=40, 36.7%), anemia (gilteritinib: n=100, 40.7%; salvage chemotherapy: n=33, 30.3%), platelet count decreased (gilteritinib: n=54, 22.0%; salvage chemotherapy: n=27, 24.8%), and thrombocytopenia (gilteritinib: n=56, 22.8%; salvage chemotherapy: n=18, 16.5%).[2]

**Serious AEs (SAEs):** SAEs occurred in 83.3% of patients in the gilteritinib arm and 31.2% of patients in the salvage chemotherapy arm. The most common SAE was febrile neutropenia in both arms, which occurred in a higher proportion of patients in the gilteritinib arm (30.9%) compared to the salvage chemotherapy arm (8.3%).

**Withdrawals due to AEs (WDAEs):** There were a higher proportion of patients who withdrew due to AEs in the gilteritinib arm (n=58, 23.6%), of which 11.0% (n=27) were considered drug related, compared to the salvage chemotherapy arm (n=13, 11.9%; of which 5 were considered drug related).[3] AEs leading to withdrawal in the gilteritinib arm included aspartate aminotransferase increased (n=4, 1.6%), alanine aminotransferase (n=3, 1.2%), pneumonia (n=3, 1.2%), retinopathy (n=2, 0.8%), and septic shock (n=2, 0,8%). Drug related AEs leading to withdrawal in the salvage chemotherapy arm included respiratory failure (n=2, 1.8%), febrile neutropenia (n=1, 0.9%), hemorrhagic stroke (n=1, 0.9%), pulmonary hemorrhage (n=1, 0.9%), and lung infection (n=1, 0.9%).[2]

**Deaths:** In the gilteritinib arm, 71 (28.9%) deaths were due to AEs, whereas in the salvage chemotherapy arm, 16 (14.7%) deaths were due to AEs. However, only 10 (4.1%) patients had AEs that were considered drug-related that led to death in the gilteritinib arm, and 5 (4.6%) patients in the salvage chemotherapy arm.[3] AEs considered at least possibly related to gilteritinib that led to death included pneumonia (n=3, 1.2%), large intestine perforation (n=2, 0.8%), and septic shock (n=2, 0.8%). In the salvage chemotherapy arm, AEs that were at least possibly related to study drug leading to death included respiratory failure (n=2, 1.8%) and sepsis (n=2, 1.8%).[2]

**Table 1.1. Highlights of Key Outcomes in the ADMIRAL trial**

| | ADMIRAL trial | |
|---|---|---|
| | **Gilteritinib Arm (N=247)** | **Salvage Chemotherapy Arm (N=124)** |
| **Primary Outcomes** | | |
| **Overall survival** | | |
| Median months (95% CI) | 9.3 (7.7, 10.7) | 5.6 (4.7, 7.3) |
| HR (95% CI) | 0.64 (0.49, 0.83) | |
| p-value* | 0.0007 | |
| **Complete remission and complete remission with partial hematologic recovery (CR/CRh) rate **** | | |
| CR/CRh rate % | 34.0 | 15.3 |
| CR/CRh rate difference % (95% CI) | 18.6 (9.8, 27.4) | |
| **Key Secondary Outcomes** | | |
| **Event-free survival†** | | |
| Median months (95% CI) | 2.8 (1.4, 3.7) | 0.7 (0.2, NE) |
| HR (95% CI) | 0.79 (0.58, 1.09) | |
| p-value* | 0.0830 | |
| **Complete remission (CR) rate** | | |
| CR rate % | 21.1 | 10.5 |
| CR rate difference % (95% CI) | 10.6 (2.8, 18.4) | |
| **Duration of CR†** | | |
| Median months (95% CI) | 14.8 (11.0, NE) | 1.8 (NE, NE) |
| HR (95%CI) | NR | |
| p-value | NR | |
| **Complete remission with partial hematologic recovery (CRh) rate** | | |
| CRh rate % | 13.0 | 4.8 |
| CRh rate difference % (95% CI) | NR | |
| **Composite complete remission (CRc) rate** | | |
| CRc rate | 54.3 | 21.8 |
| CRc rate difference % (95% CI) | 32.5 (22.3, 42.6) | |
| **Transplantation rate** | | |
| n (%) | 63 (25.5) | 19 (15.3) |
| Rate difference % (95% CI) | 10.2 (1.2, 19.1) | |
| **Transfusion conversion rate[a]‡** | | |
| n/N | 68/197 | NR |
| %, 95% CI | 34.5 (27.9, 41.6) | NR |
| **Transfusion maintenance rate[b]‡** | | |
| n/N | 29/49 | NR |
| %, 95% CI | 59.2 (44.2, 73.0) | NR |
| **Health-related Quality of Life** | | |
| **Brief Fatigue Inventory** | | |
| Baseline, n (%) | 227 (91.9) | 97 (78.2) |
| Median baseline score | 2.6 | 2.0 |
| Cycle 2, Day 1, n (%) | 206 (83.4) | 15 (12.1) |
| Change from baseline to Cycle 2, Day 1 | 0.0 | 0.7 |
| **Harms Outcome, n (%)** | **Gilteritinib Arm (N=246)** | **Salvage Chemotherapy Arm (N=109)** |
| **AE (any grade)** | 246 (100.0) | 107 (98.2) |
| **AE grade ≥3** | 236 (95.9) | 94 (86.2) |
| **SAEs** | 205 (83.3) | 34 (31.2) |
| **WDAEs** | 58 (23.6) | 13 (11.9) |
| **Deaths due to AEs** | 71 (28.9) | 16 (14.7) |

| | ADMIRAL trial |
|---|---|
| **AE** = adverse event, **CI** = confidence interval, **HR** = hazard ratio, **NE** = not evaluable, **NR** = not reported, **SAE** – serious adverse event, **WDAE** = withdrawal due to adverse event<br><br>Data cut-off date: September 17th, 2018<br>* Stratified 2-sided log-rank test<br>** Results are presented at time of data cut-off, however this analysis was conducted at the pre-specified first interim analysis and was controlled for multiplicity and statistically significant (lower limit of 95% CI exceeded benchmark of 12% indicating the endpoint was met).<br>† EFS and duration of remission were limited in usefulness due to high censoring in the salvage chemotherapy arm, and thus estimates may not be reliable.<br>‡ Transfusion conversion rate and transfusion maintenance rate included patients who took at least 1 dose of study drug, and for both rates patients must have been transfusion-independent for any 56-day post-baseline period.<br><br>[a]Transfusion conversion rate was defined as the number of patients who were transfusion-dependent at baseline but became transfusion independent during the post-baseline period divided by the total number of patients who were transfusion dependent during the baseline period.<br>[b]Transfusion maintenance rate was defined as the number of patients who were transfusion independent during the baseline period and maintained transfusion independence during the post-baseline period divided by the total number of patients who were transfusion independent during the baseline period.<br><br>Note: HR <1 favours gilteritinib<br><br>**Sources:**<br>Perl et al., 2019[2]<br>EPAR, 2019[3]<br>Clinical Study Report, 2019[5]<br>Clinicaltrials.gov[6] | |

*Limitations:*

- The study design was open-label, which is susceptible to reporting and performance biases as patients and investigators were not blinded to study treatment. Timing of assessments and number of cycles treated may have been influenced by the investigator. Respondent bias may have affected the assessment of HRQoL, if patients perceived that receiving the experimental therapy was superior to standard of care, and thus HRQoL results may have been biased in favour of gilteritinib. Attrition bias, due to the open-label nature of the study, may have contributed to a higher proportion of patients that withdrew from the salvage chemotherapy arm after randomization (14 patients versus none in the gilteritinib arm).[4]
- Information on how many patients were treated in the absence of a response or beyond progression was not recorded, and thus response rates could be overestimated.
- Additionally, the study may be subject to other biases, which include an unequal comparison and informative censoring, detailed below:
    - Unequal comparison: Patients in high intensity chemotherapy group had a short duration of treatment (60% of patients in salvage chemotherapy arm were treated for 1-2 cycles), and thus, entered long-term follow-up with no systematic plan for monitoring of relapse/response.[3] Thus, secondary outcomes, such as EFS, were limited in usefulness as relapse was defined by central review of bone marrow biopsy. Furthermore, quality of life was not assessed in long-term follow-up and long-term differences in quality of life cannot be compared. Additionally, patients

who did not achieve remission after the first cycle could have their gilteritinib dose increased in order to achieve remission in addition to potentially undergoing HSCT to prolong remission, whereas patients in the salvage chemotherapy arm did not have similar opportunities to achieve or prolong remission. Salvage chemotherapy was likely discontinued, or dose reduced earlier for toxicities as per standard institutional guidelines, whereas certain toxicities may have been tolerated in the gilteritinib arm due to clinical benefit that was in the judgement of the investigator. This unequal comparison favours gilteritinib.

    - Informative censoring: A higher proportion of patients were censored in the primary OS analyses due to patient withdrawal in the salvage chemotherapy arm (10.5%) compared to gilteritinib (2.4%), and thus survival probability of patients that continued to be followed versus those who withdrew may have been different.[4] Whether these patients were likely to have worse or better survival is unknown.

- There were a few imbalances between treatment arms in baseline characteristics. A slightly higher proportion of patients in the gilteritinib arm (11%) had unfavourable cytogenetic risk compared to the salvage chemotherapy arm (9%), which may have confounded the study results in favour of the salvage chemotherapy arm as patients with unfavourable cytogenetic risk factors have a poor prognosis.[3,7] There was a higher proportion of patients in the gilteritinib arm with myelodysplastic syndrome (MDS) as the most common hematological disorder in the gilteritinib (14%) and salvage chemotherapy (7%) arms.[3] Patients that develop AML from an antecedent hematological disorder generally have a poorer prognosis that patients with de novo AML, and thus, this may have confounded study results in favour of salvage chemotherapy.[7]
- Sorafenib was used as a subsequent therapy in a higher proportion of patients in the salvage chemotherapy arm (26%) compared to the gilteritinib arm (11%).[4] However, sorafenib has not demonstrated significant activity as a single agent in relapsed/refractory (R/R) FLT3-mutated AML, and is not currently indicated for R/R FLT3-mutated AML.[8] This imbalance may have favoured the gilteritinib arm as the efficacy and safety of sorafenib compared to alternative therapies in the R/R setting is unknown.
- As mentioned earlier, patients were able to interrupt treatment with gilteritinib in order to undergo HSCT, and then resume gilteritinib if specific criteria were met. However, a similar strategy was not applied to the salvage chemotherapy arm. The goal of HSCT is to prolong remission and/or survival, and a higher proportion of patients in the gilteritinib arm received HSCT during/off treatment (25.5%) compared to the salvage chemotherapy arm (15.3%).[3] Thus, the co-primary endpoint of OS may have been confounded in favour of gilteritinib, as a higher proportion of patients had HSCT. It is also difficult to determine the comparative effectiveness of gilteritinib as a maintenance therapy as patients in the salvage chemotherapy arm were not followed systematically for subsequent therapies (including for HSCT and maintenance therapies).
- Additionally, HSCT may have confounded the duration of remission in favour of the gilteritinib arm. The median time to HSCT in the gilteritinib arm was 127.8 days (~4.5 months), and patients who resumed gilteritinib must have resumed within 30-90 days while still in CRc, and thus, these timelines indicate the

interruption of gilteritinib for HSCT would have extended remission in the absence of active treatment with gilteritinib, for at least 1-3 months.[3]

- As per amendment 1 (dated 23-Sep-2017) of the ADMIRAL trial's statistical analysis plan (SAP), treatment compliance was not analyzed due to unreliable drug accountability data.[2] It is unclear whether primary and secondary outcomes, as well as safety, were affected by any imbalances between treatment arms in the actual doses patients received relative to planned doses, as this information was not collected.
- The ADMIRAL trial included 4 salvage chemotherapy options, 2 of which were high-intensity regimens (FLAG-IDA and MEC), and 2 low-intensity regimens (LoDAC and azacitidine). As discussed with the CGP, there is no established standard of care in this setting and generally high intensity regimens are used whenever possible to ensure the best possible response. LoDAC and MEC were identified as rarely used in the Canadian context, unless in exceptional circumstances. Most patients only received one cycle (94.1%), although up to 2 cycles can be used in clinical practice.[2] As HSCT was not monitored similar to gilteritinib in the salvage chemotherapy arm, there were some patients who may have received subsequent HSCT that were not included in the 19 (15.3%) patients identified as receiving off-study HSCT in this arm.[3] A recent real world evidence study conducted by Bertoli et al., 2020, found that of 114 patients with R/R FLT3-mutated AML that received salvage chemotherapy, 50% achieved a CR/CRi, 34.2% proceeded to allogeneic HSCT, and the median OS was 8.2 months (IQR: 3.0, 32.0).[9] Given these considerations, the efficacy estimated in the salvage chemotherapy arm was likely underestimated compared to typical therapies delivered in the Canadian context.

While there are a number of limitations noted in this section, it must be acknowledged there are challenges in conducting trials with AML as treatment decisions are dependent on a number of factors specific to the individual patient. The primary limitation to note from the section is that the efficacy of salvage chemotherapy may have been underestimated in the patient population as relevant to the Canadian context, and that the unequal comparison of treatment groups creates difficulty in the interpretation of many of the secondary outcomes. Overall survival was the primary endpoint, which is an established and robust endpoint for demonstrating efficacy.

### 1.2.2 Additional Evidence

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

#### *Patient Advocacy Group Input*

One patient group, the Leukemia and Lymphoma Society of Canada (LLSC), provided patient input for the gilteritinib for acute myeloid leukemia (AML) review. LLSC obtained information through a survey available in both English and French. LLSC's survey was provided to respondents on October 10, 2019 through Survey Monkey, distributed through various social media channels, and directly by email. LLSC provided the survey to patients and families diagnosed with AML, and who may or may not have had experience with gilteritinib. A total of seven patients responded to LLSC survey, all of whom either had AML or were in remission from AML. However, none of the seven patients had direct experience with gilteritinib.

From a patient's perspective, disease symptoms that are most impactful were reported to be fatigue, loss of appetite and/or weight loss, feeling dizzy or light headedness, bruising and/or bleeding, and rashes/skin changes. Impacts of AML the quality of life of both patients as well as their friends and family was mentioned as being a source of anxiety for patients. Patients expressed distress about the aspects of their own lives being affected by AML, such as impacts on their physical activity and the isolating nature of the condition. Regarding family and friends, patients reported they felt like burdens, and that their AML put added stress on those they loved. Chemotherapy, stem cell/bone marrow transplants, radiation therapy and maintenance therapy were mentioned as treatments patients previously received. Patients commented that treatments and their related side effects were more manageable than they originally expected. Patients appreciated communication with their health care team about their treatments and what they should expect during the course of therapy. Length of treatment time, being away from family, and the pain associated with bone marrow biopsies were mentioned as negative aspects related to treatment for AML. While none of the patients had experience with gilteritinib, patients reported the following to be important considerations when deciding to take a new treatment: quality of life, possible impact on disease, physician recommendation, outpatient treatment and closeness to home. While some patients had experienced successful treatment, they expressed a need for treatments to help maintain remission, and treatment for older patients facing relapse. In summary, key patient values regarding treatment, included a maintaining patient's quality of life higher chance of success, and reduced possibility of relapse.

### *Provincial Advisory Group (PAG) Input*

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

Clinical factors:

- Eligible patient population

Economic factors:

- Additional resources (pharmacy preparation, nursing, and clinic visits)

### *Registered Clinician Input*

A total of four registered clinician inputs were provided, including feedback from three individual oncologists and one group input on behalf of eight oncologists from the Leukemia and Bone Marrow Transplant Program of BC Canada. In total, input was summarized from 11 oncologists, representing Ontario, British Columbia and Alberta. Beyond palliative treatments or best supportive care, there are no standards of care for patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) with an FMS-like tyrosine kinase 3 (FLT3) mutation. In general, clinicians were supportive of gilteritinib to be used in clinical practice and highlighted an unmet need for effective treatments among this patient group.

Gilteritinib was stated to be more effective and less toxic than currently available treatments for R/R FLT3-mutated AML patients. Contraindications to gilteritinib included patients with hypersensitivity to gilteritinib, drug-drug interactions (i.e., Azoles and QT-prolonging medications), and others specifically stated on the Health Canada product

monograph. Regarding the extended use of gilteritinib for patients with therapy-related AML (tAML), clinicians presented divided opinions; the lack of evidence to use gilteritinib among patients with tAML was acknowledged by clinicians from BC Cancer, two individual clinicians agreed tAML patients would also benefit from treatment with gilteritinib, and one clinician stated that use of gilteritinib should be restricted to patients with an FLT3-ITD mutation. While patients with more advanced disease were not included in randomized clinical trials, some clinicians noted that these patients would still experience a response from treatment with gilteritinib and supported the use of gilteritinib for such patients. Regarding treatment sequencing, gilteritinib was suggested as a second-line treatment following midostaurin. All clinicians commented on the lack of available treatment options following progression on gilteritinib. Primary treatment options following progression were stated to include enrollment into a clinical trial or best supportive care. Based on currently available evidence, clinicians agreed that gilteritinib should be provided to patients as a monotherapy; the use of gilteritinib with another agent outside of a clinical trial was not supported by clinicians. Funding for upfront FLT3 testing was highlighted as a necessary companion diagnostic test for patients to be eligible for gilteritinib. As patients' FLT3 mutation status can change over time, repeat testing was also stated to be required for best treatment considerations. The clinicians also noted that greater lab resources for FLT3 testing may be required to support widespread testing of patients.

All clinicians agreed that gilteritinib should not be extended for use among patients with FLT3 mutations other than FLT3-ITD, FLT3-TKD/D835 or FLT3-TKD/I836.

#### *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 1.2 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 1.2: Assessment of generalizability of evidence for gilteritinib in FLT3-positive AML**

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td>Population</td><td>FLT3 mutation</td><td>Only patients with FLT3-ITD, FLT3-TKD/D835, or FLT3-TKD/I836 were included in the study. Most patients had FLT3-ITD only (88.4%), with 8.4% of patients with FLT3-TKD only, and 1.9% with both FLT3-ITD and FLT3-TKD.[2] There were 5 patients who tested negative/missing/unknown for FLT3 by central testing.[3] In subgroup analyses of patients with FLT3-ITD alone, FLT3-TKD alone, and both were consistent with the direction of effect as the primary analyses, however CIs crossed one in the FLT3-TKD subgroup, and the FLT3-ITD and FLT3-TKD subgroup.[2] The subgroups analyses in these subgroups was limited by small sample sizes.</td><td>Can the results of the trial be applied to patients with FLT3 mutations other than FLT3-ITD, FLT3-TKD/D835, or FLT3-TKD/I836?</td><td>95% of patients will have FLT3 ITD or FLT3 TKD/D835 or /1836 – No data in ADMIRAL trial regarding outcomes for other mutations – not routinely tested for.</td></tr>
<tr><td></td><td>Co-mutations</td><td>The multigene analysis set (MAS) included 361 randomized patients with screening samples from FLT3 mutation assessment. Four mutational subgroups were detected in at least 10% of patients in the MAS: DNM3TA (n=115, 31.9%), NPM1 (n=173,47.9%), WT1 (n=65,18%), and co-occurring DNMT3A and NPM1 (n=86, 23.8%). The median AXL positive blasts as a percent of the total blast population was 16%.[3] Median OS and 95% CI by mutational subgroup is summarized below:
<table>
<tr><td></td><td colspan="2">With mutation</td><td colspan="2">Without mutation</td></tr>
<tr><td></td><td>Gilteritinib</td><td>Salvage Chemo</td><td>Gilteritinib</td><td>Salvage Chemo</td></tr>
<tr><td>DNM3TA</td><td>9.1 (6.3, 11.1)</td><td>5.5 (3.7, 7.4)</td><td>9.0 (7.1, 10.7)</td><td>5.6 (4.3, 7.5)</td></tr>
<tr><td>NPM1</td><td>8.3 (6.1, 11.0)</td><td>5.1 (3.4, 6.1)</td><td>9.6 (7.7, 10.8)</td><td>7.1 (4.7, 10.0)</td></tr>
<tr><td>WT1</td><td>9.1 (6.6, 14.7)</td><td>3.4 (1.9, 5.2)</td><td>9.0 (7.1, 10.7)</td><td>6.3 (5.2, 7.6)</td></tr>
<tr><td>DNMT3A and NPM1</td><td>10.8 (7.0, 15.1)</td><td>5.0 (3.1, 6.1)</td><td>8.9 (6.8, 10.5)</td><td>6.1 (4.7, 8.0)</td></tr>
<tr><td></td><td colspan="2">AXL High (≥16% AXL positive blasts)</td><td colspan="2">AXL Low (<16% AXL positive blasts</td></tr>
<tr><td></td><td>Gilteritinib</td><td>Salvage Chemo</td><td>Gilteritinib</td><td>Salvage Chemo</td></tr>
</table></td><td>Can the results be applied to AML patients who have co-mutations?</td><td>Regardless of other mutations present, there was a benefit to treatment with gilteritinib versus salvage chemotherapy therefore the results of the ADMIRAL trial could be extrapolated to patients with AML who have co-mutations.</td></tr>
</table>

| Domain | Factor | Evidence | Generalizability Question | CGP Assessment of Generalizability |
|---|---|---|---|---|
| | | <table><tr><td>AXL</td><td>10.7 (8.7, 12.5</td><td>6.3 (3.5, 8.0)</td><td>8.0 (6.1, 10.4)</td><td>6.1 (4.3, 8.9)</td></tr><tr><td colspan="5">Sources:<br>EPAR, EMA 2019[3]<br>Clinical Study Report, Astellas Pharma 2019[5]</td></tr></table><br>In all four mutational subgroups where patients had co-occurring mutations, there was a statistically significant reduction in the risk of death associated with gilteritinib relative to salvage chemotherapy.[5] However, mutational subgroup analyses are exploratory and limited by small sizes. | | |
| | **Therapy-related AML (t-AML)** | As per protocol, patients with AML secondary to chemotherapy for other neoplasm (except for MDS) were excluded.[2] | Can the results be applied to patients with t-AML? | **Subjects were specifically excluded from the ADMIRAL protocol if they had a t-AML – therefore these results cannot be applied to patients with t-AML.** |
| | **Second or later hematologic relapse or has received salvage therapy for refractory disease** | A total of 7 (1.9%) patients, 4 (1.6%) in the gilteritinib arm and 3 (2.4%) in the salvage chemotherapy arm had 2 prior relapses and were included in the ADMIRAL trial. There were no patients who had beyond 2 relapses included in the trial.[3] | Can the results be applied to patients with second or later hematologic relapse or who have received salvage chemotherapy for refractory disease? | **As long as patients were not treated with gilteritinib in 1st relapse, it would be reasonable to expect a response in 2nd relapse or later.** |
| | **Definition of refractory disease** | Patients could be defined as refractory following 1 cycle of induction therapy, however European Leukemia Network guidelines recommend 2 cycles; and the majority of patients classified as primary refractory (61%) in the ADMIRAL trial had only received 1 cycle of induction therapy with high intensity chemotherapy.[3] | Would a similar proportion of patients be defined as primary refractory following induction therapy with one cycle of high intensity chemotherapy in Canadian practice? | **There are no comprehensive Canadian guidelines regarding AML management. A similar proportion of patients treated in Canada would be anticipated to be refractory.** |
| **Intervention** | **Maintenance gilteritinib following HSCT** | Patients were able to interrupt treatment with gilteritinib in order to undergo HSCT, and then resume gilteritinib if specific criteria were met (patient is within 30-90 days post-HSCT, in CRc, didn't have grade ≥2 GVHD, and ANC ≥ 500/mm$^3$ and | Should patients continue to be treated with gilteritinib as | **Based on the results of the ADMIRAL trial, it would be reasonable for patients to continue gilteritinib as** |

| Domain | Factor | Evidence | Generalizability Question | CGP Assessment of Generalizability |
|---|---|---|---|---|
| | | platelets ≥ 20,000/mm$^3$ without transfusions). A total of 63 patients in the gilteritinib arm had HSCT, of which 40 re-initiated gilteritinib and 23 did not. Of the 23 patients that did not re-initiate gilteritinib,8 patients did not plan to resume gilteritinib.[3]<br><br>Discussed in more detail in the limitations section, the potential for confounding by HSCT is explained. It is possible that confounding of HSCT could be due to HSCT itself or due to the combination of HSCT and maintenance gilteritinib.It is difficult to determine the potential impact of gilteritinib as a maintenance therapy as patients were not followed systematically for efficacy and safety for subsequent HSCT and maintenance therapy in the salvage chemotherapy arm for comparability. | maintenance following HSCT? | **maintenance therapy following HSCT.** |
| | **Duration of treatment** | Patients may experience a delayed response to gilteritinib.[3] The median time to first CR/CRh was 3.7 months (95% CI: 0.9, 10.6).[5] As per EPAR recommendations, patients should be treated for at least 6 months to achieve a response.[3] | How long should patients be treated for to achieve a response? How long should patients be treated for overall (when are patients no longer considered to be clinically benefitting)? | **A determination of no response/progression could be ascertained by 4 months of therapy.**<br>**If patients have evidence of progressive AML, gilteritinib should be terminated.**<br>**Of note, the CGP recognized that some patients may be slow to respond, while others will not respond at all. The Health Canada Product Monograph states that patients may be treated for a minimum of 6 months to allow time for a clinical response in the absence of disease progression or unacceptable toxicity.** |
| | **Sequencing with prior FLT3 inhibitors** | The ADMIRAL trial included 21 (5.7%) patients previously treated with midostaurin.[2] Due the small proportion of patients with midostaurin, interpretation of the subgroup analyses of the efficacy of gilteritinib relative to salvage chemotherapy in this subgroup is limited. Midostaurin, a FLT3 inhibitor, is funded in some jurisdictions for the treatment of adult patients with newly diagnosed FLT3-mutated AML. The proportion of patients with prior midostaurin in the ADMIRAL trial may not be | Would patients who have previously received a FLT3-inhibitor be eligible for gilteritinib? | **It would be reasonable to offer gilteritinib to patients who have previously received a FLT3 inhibitor as part of their induction therapy.**<br>**Given the small number of patients in the ADMIRAL trial who received prior midostaurin it is not possible to extrapolate** |

| Domain | Factor | Evidence | Generalizability Question | CGP Assessment of Generalizability |
|---|---|---|---|---|
| | | reflective of the proportion of patients with prior exposure to midostaurin in the Canadian context.<br><br>As per information provided by the sponsor, exposure to midostaurin in the first line setting might result in loss of FLT3 mutation. FLT3-ITD is lost at relapse in 40% of patients relapsing post midostaurin, which suggests FLT3-independent mechanisms are mediating resistance to midostaurin treatment in some patients. These patients would be FLT3 mutation negative in the relapsed/refractory setting, and thus not candidates for gilteritinib, however FLT3-ITD was still detectable in 60% of patients who relapsed post-midostaurin.[10] | | **regarding the magnitude of benefit of gilteritinib in those previously exposed to midostaurin.** |
| | **Dose escalation** | As outlined in the protocol, patients could escalate to 200mg in the gilteritinib arm if CRc was not achieved after cycle 1. A total of 78 patients (78/247, 31%) escalated to 200 mg, and 15.4% (n=12) experienced CR/CRh after the dose adjustment. Median OS was comparable to the primary analysis (8.9 months).[3] | Is there enough evidence to support the dose escalation strategy? How long should patients be treated for in the absence of a CRc before dose escalation? Would patients be dose escalated after achieving CRc? | **It would be reasonable to dose escalate in patients who have not achieved a CRc after 1 cycle. To minimize toxicity patients should not be dose escalated after achieving a CRc** |
| **Comparator** | **Selected salvage chemotherapy regimens** | The ADMIRAL trial included 4 salvage chemotherapy options, 2 of which were high-intensity regimens (FLAG-IDA and MEC), and 2 low-intensity regimens (LoDAC and azacitidine).[2] As discussed with the CGP, there is no established standard of care in this setting and generally high intensity regimens are used whenever possible to ensure the best possible response. Low-intensity regimens used in the trial are rarely used in the Canadian context, unless in exceptional circumstances. Given this, it is possible the efficacy estimated in the salvage chemotherapy arm may be underestimated compared to typical therapies delivered in the Canadian context. | In the relapsed/refractory setting after first-line therapy, are the proportions of patients receiving high intensity versus low intensity chemotherapy | **Deciding on salvage therapy is dependent on several patient dependent factors – previous treatment, performance status, age and duration of response to prior therapies. Low dose cytarabine is infrequently used as a salvage therapy in AML** |
| **Outcomes** | **Appropriateness of primary and secondary outcomes** | The co-primary outcomes were OS and CR/CRh. Secondary outcomes included EFS, CR rate, EFS, duration of remission, CRh rate, CRc rate, transfusion conversion rate, transfusion maintenance rate, transplantation rate, BFI.[2] Patients in the high intensity chemotherapy (~60% treated for 1-2 cycles) entered the long-term follow-up period, which did not include | Were the selection of endpoints appropriate and of clinical relevance to this indication | **The selection of endpoints was appropriate in the ADMIRAL trial.** |

| Domain | Factor | Evidence | Generalizability Question | CGP Assessment of Generalizability |
|---|---|---|---|---|
| | | systematic assessment of disease or health-related quality of life (with the exception of EQ-5D). Thus, there are limited inferences that can be made for some endpoints including EFS and HRQoL.[3] | and therapeutic setting? | |
| **Setting** | **Countries participating in the trial** | ADMIRAL was conducted at 107 centres in 14 countries (Canada, Belgium, France, Germany, Israel, Italy, Japan, Korea, Poland, Spain, Taiwan, Turkey, UK, US), and included 4 Canadian patients.[2,8] | Are there any known differences in the practice patterns between Canada and other countries that the trial was conduced in? Can the results be applied to Canadian patients? | **The trial results may be applied to patients treated in Canada.** |

### *Burden of Illness and Need*

In Canada, the age adjusted incidence rate of AML is approximately 3.75 per 100,000. In 2017, there were 1509 new cases of AML reported in Canada with a median age at diagnosis of 66 years, with just over a quarter of diagnoses in those over the age of 75.[11] FMS-Like Tyrosine Kinase 3 *(FLT3)* FLT3 gene mutations are found in approximately 30% of patients with acute myeloid leukemia (AML). The most common FLT3 mutations are the FLT3 internal tandem duplication (ITD) found in approximately 85% and the FLT3 tyrosine kinase domain (TKD) mutation found in 10% of those with FLT3 mutated AML.[12] FLT3-ITD in the setting of AML adversely affects survival.[13] Patients with AML whose disease is refractory to or relapses after induction chemotherapy have a poor prognosis with standard chemotherapy.[14,15]

### *Effectiveness*

The ADMIRAL Phase III study[2,3] accrued adult patients with relapsed or refractory *FLT3*-mutated AML in a 2:1 ratio to receive either gilteritinib (at an initial dose of 120 mg per day) or salvage chemotherapy. Patients were required to have *FLT3* ITD or TKD D835 or I836 mutations. Permitted salvage chemotherapies included: MEC or FLAG-IDA as high intensity regimens and low dose cytarabine or azacitidine as low intensity regimens. Gilteritinib or chemotherapy was administered in 28-day cycles. High intensity chemotherapy was administered for a maximum of two cycles. Gilteritinib or low intensity chemotherapy was continued until documentation of lack of clinical benefit, toxic effects or as defined in the protocol. Gilteritinib or chemotherapy was administered in 28-day cycles.

The study had 90% power to detect a difference in OS with 7.7 months median survival time in the gilteritinib arm and 5 months median survival time with salvage chemotherapy (hazard ratio [HR]: 0.65) at the overall 1-sided 0.0245 significance level with 258 death events. A total of 371 patients were randomly assigned to receive gilteritinib (n=247) or salvage chemotherapy (n=124). Overall, the median age was 62.0 years (range: 19.0, 85.0). The trial population reported in the ADMIRAL trial is reflective of a population-based AML cohort. A total of 5.7% of the ADMIRAL trial cohort received prior midostaurin.

The two primary endpoints in the ADMIRAL trial were overall survival and the percentage of patients who had a complete remission with or without hematological recovery. The median duration of follow up for overall survival was 17.8 months. The cohort treated with gilteritinib as opposed to chemotherapy had longer median overall (9.3 versus 5.6 months, P<0.001) and event free survival (2.8 versus 0.7 months, HR treatment failure or death 0.79, 95% CI:0.58-1.09). In the gilteritinib arm, median OS was 8.0 months (95% CI: 3.5-11.1) in the FLT3-TKD alone subgroup versus 9.5 months (95% CI: 7.7-10.7) in the FLT3-ITD subgroup. Patients with a high allelic ratio ($FLT3^{ITD}$ ≥0.77) had a survival benefit with gilteritinib therapy (HR: 0.49; 95% CI: 0.34-0.71; P=0.0001) whereas those with an allelic ratio <0.77, the benefit was not statistically significant (HR: 0.80; 95%CI: 0.53, 1.20; p=0.2719). There was a higher proportion of patients treated with gilteritinib as compared to chemotherapy in complete remission or complete remission with partial hematologic recovery (34% versus 15.3%). Among those with FLT3-ITD rate of complete remission in those treated with gilteritinib versus chemotherapy were 20.5% and 9.7% respectively. A higher proportion of patients treated with gilteritinib underwent hematopoietic stem cell transplant (25.5%) versus those receiving chemotherapy (15.3%). Of the 63 patients on gilteritinib prior to transplant – 40 continued gilteritinib post transplant. There were 197/247 patients assigned to the gilteritinib arm who were transfusion dependent at randomization, and 68/197 who became transfusion independent.

The median EQ-5D-5L VAS change from baseline score was 0 for the gilteritinib arm and -3.0 for the salvage chemotherapy arm at cycle 2, day 1. There is limited published quality of life data concerning gilteritinib in the management of relapsed or refractory AML. There does not appear to be a clinically meaningful detriment or improvement in quality of life when comparing gilteritinib to best standard of care in the management of FLT3 mutated relapsed or refractory AML.

***Safety***

In the ADMIRAL study,[2,5] the median duration of exposure to gilteritinib was 18 weeks (interquartile range [IQR]: 9, 34 weeks) versus 4 weeks (IQR: 4, 4 weeks) in the chemotherapy group. The rate of febrile neutropenia in the gilteritinib group was 46.7% versus 36.7% in those treated with chemotherapy. Comparing those receiving gilteritinib to those receiving chemotherapy the rate of grade 3 or higher anemia were 40.7% versus 30.3% and rates of grade 3 or higher thrombocytopenia were 22.8% versus 16.5%. Grade ≥3 arrythmia due to QT prolongation was 8.1% in the gilteritinib group versus 1.8% in the chemotherapy group. Cardiac arrest (1.6%), cardiac failure (1.6%) and pericarditis/pericardial effusion (6%) was reported in those treated with gilteritinib but not in those treated with chemotherapy. Exposure adjusted severe adverse events in those treated with gilteritinib versus chemotherapy were 7.11 versus 9.24 events per patient-year. Drug related adverse events leading to gilteritinib discontinuation was 11.0%.

***Need***

Midostaurin is approved in Canada to be used in combination with standard induction (daunorubicin and cytarabine – '7+3') for treatment of adult patients with newly diagnosed FLT3 mutated AML.[16] Relapsed FLT3 positive AML is associated with a poor prognosis and a high risk of relapse despite aggressive therapies such as allogeneic hematopoietic stem cell transplantation.[17] There is an unmet need for effective treatments for patients with relapsed or refractory AML harbouring a FLT3 mutation. Several tyrosine kinase inhibitors have been explored as potential therapy for patients with relapsed or refractory FLT3 positive AML including sorafenib, midostaurin, quizaritinib and crenolanib. Neither sorafenib or midostaurin showed significant activity in the treatment of relapsed or refractory FLT3 positive AML.[12] Quizartinib has demonstrated a survival benefit compared to chemotherapy in a recently reported phase 3 study in adult patients with relapsed or refractory FLT3-ITD AML (Lancet Oncology 2019 20(7) 984-997).[18] Quizartinib is not currently approved by Health Canada (no notice of compliance) though this is anticipated in the future. Crenolanib is also being evaluated in the management of FLT3 positive AML. Gilteritinib is the only FLT3 inhibitor that has been approved by Health Canada for the treatment of patients with relapsed or refractory FLT3 positive AML.

## 1.3 Conclusions

The clinical guidance panel concluded that there is a net clinical benefit to gilteritinib in the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by a validated test based on one high quality phase III randomized controlled trial (ADMIRAL) that demonstrated a clinically and statistically significant benefit in overall survival for gilteritinib compared with salvage chemotherapy with comparable adverse event profiles.

Of note, only a small proportion (5.7%) of patients who were enrolled in the ADMIRAL trial received prior midostaurin. At the time of the trial midostaurin was not used in clinical practice. Currently patients treated with induction therapy for AML who harbor a FLT3

mutation are treated with midostaurin. It is not possible to determine the effect of prior midostaurin on the efficacy of gilteritinib from the ADMIRAL trial.

### *Other Considerations*

The PAG raised several points to be considered if gilteritinib was to be recommended for reimbursement, specifically with respect to the eligible patient population, duration of treatment, and sequencing of treatments. The CGP has addressed the other points below:

- The CGP noted that patients with therapy related AML (t-AML) were explicitly excluded from the ADMIRAL trial. Therefore, it is not possible to extrapolate from the trial findings to t-AML.
- FLT3 ITD and FLT3-TKD/835 or /1836 make up >95% of mutations that have been identified in AML. Other FLT3 mutations are not routinely tested for and were not included in the ADMIRAL cohort. Hence, it is not clear whether gilteritinib would be appropriate in settings other than examined in the ADMIRAL trial.
- Patients in second or later hematological relapse who have not received a tyrosine kinase inhibitor (TKI) as a component of previous salvage therapy would be reasonable candidates for treatment with gilteritinib.

For patients currently receiving treatment (e.g., salvage chemotherapy) for relapsed/refractory AML, it would be reasonable to switch patients from salvage chemotherapy to gilteritinib, given the superiority as demonstrated in the ADMIRAL trial of gilteritinib versus salvage chemotherapy. Such treatment modifications should be left to the discretion of the treating physician and patient.With regards to PAG's request for clarity questions on whether treatment is continued until progression or if treatment should be stopped for patients who achieve complete remission, the CGP stated that gilteritinib was administered in the ADMIRAL trial until documentation of a lack of clinical benefit or the occurrence of toxic effects. The trial did not specifically address an early stopping criterion for those who achieve a complete remission.

The CGP's comments on the optimal sequencing of gilteritinib with available treatments are as follows:

- Midostaurin is approved in Canada to be used in combination with standard induction (daunorubicin and cytarabine – '7+3') for treatment of adult patients with newly diagnosed FLT3 mutated AML.
- Treatment options that would currently be available upon progression on gilteritinib would include salvage chemotherapy.
- The ADMIRAL trial does not provide any specific information regarding combination therapy.

# 2 BACKGROUND CLINICAL INFORMATION

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

## 2.1 Description of the Condition

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

In Canada, the age adjusted incidence of AML is approximately $3.75/10^5$. In 2017 there were 1509 new cases of AML reported in Canada with a median age at diagnosis of 66 years, with just over a quarter of diagnoses in those over the age of 75. AML is uncommon in children with an age adjusted incidence of $7.2/10^6$.[11]

AML represents a heterogenous group of disorders with similar clinical presentations but variable prognosis. AML is classified according to the World Health Organization (WHO) Classification of Tumors of the Haematopoetic and Lymphoid Tissues.[19] The WHO classification is a combined clinicopathological and molecular genetic classification. One subtype of AML, Acute Promyelocytic Leukemia, is sufficiently distinct from a prognostic and therapeutic perspective that it will not be further discussed in this background section. Commonly associated mutations in AML include mutations in *FMS-Like Tyrosine Kinase 3 (FLT3)* FLT3 gene and mutations in Nucleophosmin 1 (NPM1) both of which are found in approximately 30% of AML patients. The prognosis of patients with AML is primarily driven by age at diagnosis, such that patients who are older tend to fair less well and the molecular genetic risk category of the AML. AML patients are stratified into those with favorable, intermediate and adverse risk primarily mediated by the molecular genetic profile of the AML.[20]

The most common FLT3 mutations are the FLT3 internal tandem duplication (ITD) found in approximately 85% and the FLT3 tyrosine kinase domain mutation found in 10% of those with FLT3 mutated AML. FLT3 ITD mutations confer poor prognosis in patients with AML while the prognostic impact of FLT3 TKD mutations are less certain.[12]

## 2.2 Accepted Clinical Practice

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

While there are no overarching national Canadian guidelines on the management of AML several international guidelines harmonize with practice in Canada.[20-22] In younger fit patients, initial induction remission involves combination chemotherapy (7 days of cytarabine and 3 days of anthracycline therapy [7+3]). There is evidence to support the combination of gemtuzumab ozogamicin with 7+3 in prolonging progression free and overall survival in patients with AML[23]—especially for those with low or intermediate-risk cytogenetic risks. Gemtuzumab ozogamicin was recently reviewed by CADTH and is recommended for reimbursement for adults with previously untreated, de novo CD33-

positive AML, except APL, who have good performance status and favourable, intermediate, or unknown cytogenetics (ELN 2017).[24] For patients that harbor a FLT3 mutation, combining midostaurin with standard remission induction (7+3) and consolidation chemotherapy is associated with an overall survival benefit. Midostaurin has been reviewed by CADTH and is funded in most jurisdictions in Canada for this indication.[25]

In younger fit patients the goal of remission induction therapy is to achieve a complete remission (CR1). A risk adapted approach is utilized to optimize the likelihood of a curative outcome. For those with favorable risk, post remission therapy involves up to 3 cycles of high dose cytarabine (HIDAC) consolidation with or without anthracycline depending on local practice. Approximately 60% of patients are cured in this fashion.[20-22] For patients with intermediate and adverse risk, AML results with HIDAC consolidation are unsatisfactory, consequently in younger fit patients allogeneic transplantation is pursued as a consolidation strategy in CR1. Allogeneic transplantation for AML in CR1 is associated with a probability of long-term survival of 50%, however the procedure is associated with a high risk of morbidity and mortality.[26]

For patients that are not candidates for intensive therapy (remission induction, allogeneic stem cell transplant) because of advanced age or frailty, in those with intermediate or favorable risk cytogenetics, treatment with either low dose cytarabine or azacitidine are reasonable treatment options. For patients with adverse risk cytogenetics, azacitidine treatment is preferred.[27]

Outcomes for relapsed or refractory AML are inferior as compared to patients treated initially for their AML. The likelihood of obtaining a durable CR2 is far lower than for a durable CR1. The goal of AML treatment is therefore to optimize the probability of obtaining a CR1.

The approach to treatment of younger fit patients with relapsed or refractory AML may involve an experimental therapy, remission induction with regimens such as fludarabine, cytarabine and idarubicin (FLAG-IDA) or less intensive regimens such as azacitidineazacitidine. Consolidation may or may not involve an allogeneic stem cell transplant. In older less fit patients who have relapsed or refractory AML, treatments may involve an experimental therapy or less intensive therapies such as a hypomethylating agent (azacitidine or decitabine).[20,22]

## 2.3 Evidence-Based Considerations for a Funding Population

The evidence to support the use of gilteritinib for the treatment of adult patients who have relapsed or refractory AML with a FLT3 mutation arises from the recently published multicenter ADMIRAL phase III study.[2] The ADMIRAL study accrued adult patients (19-85) with relapsed or refractory *FLT3*-mutated AML in a 2:1 ratio to receive either gilteritinib (at an initial dose of 120 mg per day) or salvage chemotherapy. Refractory patients were defined as those whose disease was refractory to one or two cycles of conventional anthracycline-containing induction, or for patients not candidates for anthracycline therapy, patients were able to participate if they were deemed by the investigator to be refractory after at least one cycle of alternative standard therapy.

Permitted salvage chemotherapies included: MEC or FLAG-IDA as high intensity regimens and low dose cytarabine or azacitidine as low intensity regimens. Patients 18 years of age or older were eligible if their disease was refractory to one or two cycles of conventional anthracycline-containing induction therapy or if they had hematologic relapse after a

complete remission. Patients were required to have *FLT3* ITD or TKD D835 or I836 mutations.

Gilteritinib or chemotherapy was administered in 28-day cycles. High intensity chemotherapy was administered for a maximum of two cycles. Gilteritinib or low intensity chemotherapy was continued until documentation of lack of clinical benefit, toxic effects or as defined in the protocol. A total of 247 patients were randomized to receive gilteritinib and 124 patients were randomized to receive salvage chemotherapy. The groups were well balanced regarding proportion relapsed versus refractory patients as well as for FLT3 mutation subtype. Overall, 83% percent of patients had previously received induction therapy with an anthracycline, however only 5.7% of patients had received midostaurin as part of their initial therapy. Median number of cycles of gilteritinib administered was 5. For the salvage chemotherapy group 94% of patients receiving high intensity salvage received one cycle of therapy, and for those receiving low intensity therapy the median duration of therapy was 4 weeks. The median overall survival for the gilteritinib group was 9.3 months as opposed to 5.6 months in the salvage chemotherapy group (HR death 0.64 CI[0.49-0.83]). The median event free survival for the gilteritinib group was 2.8 months versus 0.79 months for those receiving salvage chemotherapy (HR death 0.79 CI[0.58-1.09]). The percent of patients in complete remission in the gilteritinib group compared to patients receiving salvage chemotherapy was 34% versus 15%. Overall, gilteritinib showed a consistent survival benefit across most subgroups, including in patients previously treated with midostaurin. Of note, a higher proportion of patients treated in the gilteritinib arm underwent allogeneic stem cell transplantation compared to the chemotherapy arm.

Gilteritinib was well tolerated. The most common serious adverse events include febrile neutropenia (9.8%), increase in the alanine amino transferase level (4.5%) and increase in the aspartate aminotransferase (4.1%). The side-effect profile was better with gilteritinib compared to salvage chemotherapy alone with the incidence of exposure-adjusted serious adverse events was 7.11 per patient-year for gilteritinib-treated patients versus 9.24 in the salvage chemotherapy group.

FLT3 mutation testing may be obtained by polymerase chain reaction or by next generation sequencing. Validated testing platforms are available in most but not all jurisdictions in Canada.

## 2.4 Other Patient Populations in Whom the Drug May Be Used

Gilteritinib is approved for the treatment of adult patients who have relapsed or refractory AML with a FLT) mutation. A validated test is required to confirm the FLT3 mutation status of AML.[1]
Other patient populations the drug could be considered in:

- Patients<18 years of age who would otherwise meet the Health Canada NOC
- Patients with a FLT3 mutation who would otherwise be candidates for midostaurin as part of induction therapy but have a contraindication to midostaurin treatment
- Patients who are post allogeneic stem cell transplant with a history of a FLT3 mutation who may benefit from maintenance therapy with a FLT3 inhibitor (BMT CTN 1506 [NCT02997202])[28]

# 3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient group, the Leukemia and Lymphoma Society of Canada (LLSC), provided patient input for the gilteritinib for acute myeloid leukemia (AML) review. LLSC obtained information through a survey available in both English and French. LLSC's survey was provided to respondents on October 10, 2019 through Survey Monkey, distributed through various social media channels, and directly by email. LLSC provided the survey to patients and families diagnosed with AML, and who may or may not have had experience with gilteritinib. A total of seven patients responded to LLSC survey, all of whom either had AML or were in remission from AML. However, none of the seven patients had direct experience with gilteritinib.

From a patient's perspective, disease symptoms that are most impactful were reported to be fatigue, loss of appetite and/or weight loss, feeling dizzy or light headedness, bruising and/or bleeding, and rashes/skin changes. Impacts of AML the quality of life of both patients as well as their friends and family was mentioned as being a source of anxiety for patients. Patients expressed distress about the aspects of their own lives being affected by AML, such as impacts on their physical activity and the isolating nature of the condition. Regarding family and friends, patients reported they felt like burdens, and that their AML put added stress on those they loved. Chemotherapy, stem cell/bone marrow transplants, radiation therapy and maintenance therapy were mentioned as treatments patients previously received. Patients commented that treatments and their related side effects were more manageable than they originally expected. Patients appreciated communication with their health care team about their treatments and what they should expect during the course of therapy. Length of treatment time, being away from family, and the pain associated with bone marrow biopsies were mentioned as negative aspects related to treatment for AML. While none of the patients had experience with gilteritinib, patients reported the following to be important considerations when deciding to take a new treatment: quality of life, possible impact on disease, physician recommendation, outpatient treatment and closeness to home. While some patients had experienced successful treatment, they expressed a need for treatments to help maintain remission, and treatment for older patients facing relapse. In summary, key patient values regarding treatment, included a maintaining patient's quality of life higher chance of success, and reduced possibility of relapse.

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

## 3.1 Condition and Current Therapy Information

### 3.1.1 Experiences Patients have with Acute Myeloid Leukemia

The main cancer symptoms experienced by patients of LLSC's survey, ordered from most to least reported, were fatigue, loss of appetite and/or weight loss, feeling dizzy or light headedness, bruising and/or bleeding, and rashes/skin changes. Other disease symptoms reported by patients included fever and/or night sweats, headaches, nausea and/or vomiting, vision changes and pain.

According to LLSC, patients described their quality of life as being impacted by AML. Specifically, there were feelings of exhaustion, anxiety, and withdrawal from social activities. Many also commented on feeling like a burden to family and friends, and the negative impact that their disease had on their loved one's quality of life:

*"Continually stressed about relapse/recurrence. Withdrawing from friends and family. Feel like a burden to them."*

*"Various symptoms as described above have often made it difficult to be an active participant in life. Basically felt like I was busy just surviving. Very little energy to do the things that I used to do."*

*"Was fatigued all the time, no interest in being with other people most of the time."*

*"It put extra stress on my family and young adults who were more concerned for me than themselves."*

*"It's been a burden on them in that they have had to step up to help with the things I used to do, as well as time and effort to tend to my needs."*

### 3.1.2 Patients' Experiences with Current Therapy for Acute Myeloid Leukemia

A list of previous treatments received by LLSC patients is provided in Table 1. Patients reported the following treatments: fludarabine, busulfan, high dose cytarabine with daunorubicin, haplo-identical stem cell transplant and a bone marrow transplant. LLSC provided comments from two patients regarding the positive and negative impacts of frontline treatment. One patient stated that *"Having the chemo wasn't as bad as I would have thought. Going through the months of consolidation treatment was like being on a roller coaster, constantly going up and down. The positive is that I resolved myself to relax and use all the time to recover. Nothing else mattered and it brought a different kind of closeness for me and my children."* Another patient stated their *"experience was as good as could be expected with the aggressive cancer treatment. The positives were the expertise of the medical team preparing me for what to expect and the care and compassion of the nursing staff. I liked the [PICC] and central lines because I didn't want to be poked anymore."* Other comments from patients reflected on the positive experiences of treatment during the course of their disease; patients commented that treatments and their side effects were more manageable than expected, which one patient stated was a reflection of the advancements in the medical community. In addition, patients commented on the positive demeanor of health care staff, and being well-informed by their health care team as having a positive impact on their overall experience.

*"The treatment was better than described with minimal side effects compared to other patients."*

*"it's nice to be informed and prepared for all the treatments including the bad then there are no surprises."*

*"In my experiences the treatments were less invasive than I would have thought. I was lucky and didn't have nausea vomiting or any other really serious side effects, maybe age played a part or that I was in good health to begin with. Treatments have come a long way and the medical community have to be trusted with these advancements. It restored my belief that leukemia is no longer the death sentence it was once."*

*"Although I had several reactions to treatment they were all manageable. Positive attitude by doctors and staff was helpful."*

*"I liked the time in the hospital where I didn't need to travel back and forth and care was accessible as needed."*

Table 1: Previous treatments received by patients

| Treatment | N |
|---|---|
| Chemotherapy as front-line treatment of AML | 4 |
| High-dose chemotherapy | 3 |
| Stem cell/bone marrow transplant | 3 |
| Radiation therapy | 2 |
| Maintenance therapy | 1 |

However, the patients stated that negatives of front-line treatment included *"the length of time for all treatment but it is understandable"* and *"time away from my family and the bone marrow biopsies. They hurt!!!!"*

Patients provided a list of physical side effects from treatment that impacted them to varying degrees. From most to least impactful, side effects experienced as a result of treatment included neutropenia (low white blood cell counts), reduced movement/inability to take part in physical activities, nausea, hair loss, eyesight issues, pain, vomiting, organ damage, neuropathic pain and constipation. LLSC stated that one patient specifically mentioned the large impact side effects had on sexual intercourse.

From most to least impactful, LLSC provided a list of emotional side effects from treatment impacting quality of life, such as change to physical activity, anxiety, mental health and overall happiness, eating challenges, social development and educational development. LLSC provided quotes from patients reflecting the difficulty in accepting their condition and the isolation related to it:

*"Accepting that my body needed fixing and I couldn't do the normal things I could like take long walks. Accepting that I just had to relax and rest and my body would tell me when I could do more."*

*"Being away from my family and friends when I was neutropenia was the hardest."*

*"Hospitalized for 35 days with limited visiting in the first 18 days."*

### 3.1.3 Impact of Acute Myeloid Leukemia and Current Therapy on Caregivers

No input from caregivers was provided.

## 3.2 Information about the Drug Being Reviewed

### 3.2.1 Patient Expectations for Gilteritinib or New Therapies

When asked what important factors were to consider when making a decision about a new cancer treatment, patients from LLSC's survey stated quality of life, possible impact on disease, physician recommendation, outpatient treatment, and closeness to home.

LLSC reported that one patient in British Columbia was refused treatment in her province, and she had to temporarily relocate to a different province to obtain treatment. This patient expressed concern about further treatment options should she relapse:

*"In B.C. I was refused treatment because I was over 70 and by the time they got around to doing a bone marrow biopsy my blast count was over 30%. Palliative care was all that was offered by a rather uncaring specialist although he did do a referral at my request.*

*Treatment started three weeks after referral to another province and BMB indicated complete remission on January 21,2017. It appears that treatment affected the heart muscle and caused a delay in consolidation chemo by two months. nine days after first consolidation treatment developed febrile neutropenia and spent a week in the hospital. Second consolidation went well. Several blood transfusions and a potassium IV. If I relapse now I'm not sure there will be any treatment offered in B.C. or the other province. I still have follow up appointments in both provinces. New specialist in B.C."*

Another quote stated that the while this patient was *"so very grateful to have been successfully treated and still in remission"* they would appreciate *"treatment to maintain remission or a treatment for older patients facing relapse."*

### 3.2.2 Patient Experiences To Date with Gilteritinib

None of the seven patients who were part of LLSC's input reported having experience with gilteritinib.

## 3.3 Additional Information

None.

# 4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

**Overall Summary**

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

Clinical factors:

- Eligible patient population

Economic factors:

- Additional resources (pharmacy preparation, nursing, and clinic visits)

Please see below for more details.

## 4.1 Currently Funded Treatments

PAG identified that there is no standard of care for patients with relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation. Treatments include FLAG-IDA, azacitidine, azacitidine plus sorafenib, MEC, low-dose ARA-C, allogeneic stem cell transplant, and best supportive care.

In some jurisdictions, midostaurin is funded in combination with standard cytarabine and daunorubicin (or idarubicin) induction and cytarabine consolidation chemotherapy for the treatment of adult patients with newly diagnosed FLT3-mutated AML.

## 4.2 Eligible Patient Population

PAG is seeking guidance on whether gilteritinib is appropriate for the following:

- Patients with therapy-related AML (t-AML)
- Patients with FLT3 mutations other than FLT3-ITD, FLT3-TKD/D835 or FLT3-TKD/I836
- Patients in second or later hematologic relapse or has received salvage therapy for refractory disease

If recommended for reimbursement, PAG noted that patients currently receiving treatment (e.g., salvage chemotherapy) for relapsed/refractory AML, would need to be addressed on a time-limited basis.

There is a potential for indication creep to AML without a FLT3 mutation or earlier lines of treatment prior to refractory/relapse disease (e.g., in addition to chemotherapy for patients who require re-induction or salvage chemotherapy).

## 4.3 Implementation Factors

Gilteritinib is an oral therapy available as 40 mg tablets with a dose of 120 mg (three 40 mg tablets) once daily. In the absence of a response after 4 weeks of treatment, the dose can be increased to 200 mg (five 40 mg tablets) once daily. The once daily administration

is an enabler to implementation. Dose adjustments are made by adjusting the number of tablets and there would be minimal wastage. However, the potential five tablets daily are a high tablet burden and may be difficult for some patients.

PAG is seeking guidance on treatment duration as treatment "should continue as long as clinical benefit is observed"; such as clarity on whether treatment is until progression or treatment should be stopped for patients who achieve complete remission.

Additional pharmacy resources would be required for dispensing the medication. Increased nursing resources and clinic visits are required to monitor and treat adverse events (e.g., QT interval monitoring, side effects such as pancreatitis and myalgias).

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

## 4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on:

- Optimal sequencing with available treatments (e.g., midostaurin).
- What treatment options would be available to patients upon progression on gilteritinib?
- Whether there are clinical scenarios in which gilteritinib would be used in combination (with azacitidine or low-dose cytarabine or FLA-IDA or MEC)?

## 4.5 Companion Diagnostic Testing

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.

## 4.6 Additional Information

None identified.

# 5 SUMMARY OF REGISTERED CLINICIAN INPUT

A total of four registered clinician inputs were provided, including feedback from three individual oncologists and one group input on behalf of eight oncologists from the Leukemia and Bone Marrow Transplant Program of BC Canada. In total, input was summarized from 11 oncologists, representing Ontario, British Columbia and Alberta. Beyond palliative treatments or best supportive care, there are no standards of care for patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) with an FMS-like tyrosine kinase 3 (FLT3) mutation. In general, clinicians were supportive of gilteritinib to be used in clinical practice and highlighted an unmet need for effective treatments among this patient group.

Gilteritinib was stated to be more effective and less toxic than currently available treatments for R/R FLT3-mutated AML patients. Contraindications to gilteritinib included patients with hypersensitivity to gilteritinib, drug-drug interactions (i.e., Azoles and QT-prolonging medications), and others specifically stated on the Health Canada product monograph. Regarding the extended use of gilteritinib for patients with therapy-related AML (tAML), clinicians presented divided opinions; the lack of evidence to use gilteritinib among patients with tAML was acknowledged by clinicians from BC Cancer, two individual clinicians agreed tAML patients would also benefit from treatment with gilteritinib, and one clinician stated that use of gilteritinib should be restricted to patients with an FLT3-ITD mutation. While patients with more advanced disease were not included in randomized clinical trials, some clinicians noted that these patients would still experience a response from treatment with gilteritinib and supported the use of gilteritinib for such patients. Regarding treatment sequencing, gilteritinib was suggested as a second-line treatment following midostaurin. All clinicians commented on the lack of available treatment options following progression on gilteritinib. Primary treatment options following progression were stated to include enrollment into a clinical trial or best supportive care. Based on currently available evidence, clinicians agreed that gilteritinib should be provided to patients as a monotherapy; the use of gilteritinib with another agent outside of a clinical trial was not supported by clinicians. Funding for upfront FLT3 testing was highlighted as a necessary companion diagnostic test for patients to be eligible for gilteritinib. As patients' FLT3 mutation status can change over time, repeat testing was also stated to be required for best treatment considerations. The clinicians also noted that greater lab resources for FLT3 testing may be required to support widespread testing of patients.

All clinicians agreed that gilteritinib should not be extended for use among patients with FLT3 mutations other than FLT3-ITD, FLT3-TKD/D835 or FLT3-TKD/I836.

Please see below for details from the clinician inputs.

## 5.1 Current Treatment(s) for Acute Myeloid Leukemia

Currently there are no standards of care for patients with R/R AML with an FMS-like FLT3 mutation. Treatments including FLAG-IDA, azacitidine, azacitidine plus sorafenib, MEC, low-dose ARA-C allogenic stem cell transplant and best supportive care were all identified by the clinicians providing input. In the absence of approved treatments for this patient population, most patients were stated to receive palliative or best supportive care.

In general, clinicians from BC Cancer stated that younger, fit patients with R/R FLT3-mutated AML receive treatment with an intensive chemotherapy salvage regimen, either with MEC or high dose etoposide and cyclophosphamide (VP-Cy), provided at a physician's discretion. For patients who do not achieve remission, clinicians stated that azacitidine plus sorafenib would be another treatment funded by BC Cancer, or that eligible patients

could receive an allogenic stem cell transplant. The BC Cancer clinicians highlighted that the use of azicitidine plus sorafenib is not approved by Health Canada or FDA; therefore, its use is considered "off-label".

The most appropriate comparators were identified in the input on behalf of BC Cancer as being intensive chemotherapy regimens, including MEC or FLAC-IDA, which are generally delivered as in-patient treatments. For patients who are older or unfit, the joint clinician input acknowledged that they are generally not treated with azacitidine or low dose ARA-C; rather, these patients are commonly managed with best supportive care or treatment through a clinical trial if available.

## 5.2 Eligible Patient Population

Two individual clinicians agreed that gilteritinib aligns with the needs of clinical practice and provides an unmet need for this group of patients, as treatments for this space were stated to be inadequate and usually ineffective. Both clinician inputs agreed that the eligibility criteria of the trial were reasonable and reflective of clinical practice. One of the individual clinician inputs acknowledged that the comparison treatment used in the supporting gilteritinib trial was also reasonable. However, this clinician was uncertain as to why the trial excluded patients with prior chemotherapy for other neoplasms besides myelodysplastic syndrome (MDS).

### 5.2.1 Implementation Question: In clinical practice, is there evidence to extend the use of gilteritinib to (provided all other eligibility criteria are met):

#### 5.2.1.1 Patients with therapy-related AML (t-AML)?

A phase I/II study which included patients with tAML (Perl et al.) was identified by the BC clinicians providing joint input, although, it was stated that results of the phase I/II trial were not reported specifically for tAML patients within the publication. The clinicians from BC also identified a phase III trial which did not include tAML patients; however, the phase III trial did include patients with AML secondary to MDS. The BC clinicians acknowledged the lack of evidence to either support or refute the use of gilteritinib for patients with tAML. The joint clinician input also acknowledged the heterogeneity of tAML, with some patients having genetics typically described with prior therapy (e.g., MLL rearrangements), whereas some patients may have genetic changes more typical of de novo AML (i.e., FLT3 mutations, although these occur at a lower frequency).

Two of the individual clinician inputs agreed that the use of gilteritinib should be extended to patients with tAML; one of the clinicians stated that there is no reason to believe that patients with tAML who have a FLT3 mutation would not also benefit from gilteritinib to a similar degree as other AML patients.

One of the individual clinician inputs disagreed with the extension of gilteritinib to patients with tAML and expressed that gilteritinib should be restricted to patients with a FLT3-ITD mutation.

#### 5.2.1.2 Patients with FLT3 mutations other than FLT3-ITD, FLT3-TKD/D835 or FLT3-TKD/I836?

None of the clinician inputs supported the use of gilteritinib for patients with mutations other than FLT3-ITD, FLT3-TKD/D835 or FLT3-TKD/I836 due to the lack of evidence to support its use among these patients. Specifically, the clinicians stated that other variant

FLT3 mutations are rare and were not included in the trial. One of the individual clinician inputs included mixed phenotypic acute leukemia with FLT3-ITD mutations as a clinical condition that they would not support the use of gilteritinib for. In general, this clinician did not support the use of gilteritinib for patients with mutations other than what were included in the trial.

#### 5.2.1.3 Patients in second or later hematologic relapse or has received salvage therapy for refractory disease?

It was identified by the BC clinicians and one individual clinician input that the phase I/II trial did include patients with more advanced disease; yet, patients experienced a response with gilteritinib. In general, BC clinicians supported the use of gilteritinib among patients who met the eligibility criteria in the gilteritinib clinical trials. However, they have found through their local experiences that FLT3 inhibitors can be used in second or later hematologic relapse or after salvage therapy and still induce clinical responses and remissions. it was also acknowledged in the individual clinician input that, while randomized clinical data does not exist to support the use of gilteritinib for patients with advanced disease, he would support the use of gilteritinib for these patients, nonetheless, due to the lack of other effective treatments. Another individual clinician input stated that the use of gilteritinib would be useful for patients beyond first relapse, including patients who relapse after allogenic bone marrow transplant. This clinician stated that they had treated patients who had relapsed post allogenic transplant after a first relapse, and that the patients responded excellently to gilteritinib.

One clinician did not agree with the use of gilteritinib for patients with more advanced disease, as these patients may not benefit as much from the treatment; therefore, they suggested aligning to the eligibility criteria of the trial.

## 5.3 Relevance to Clinical Practice

All clinician inputs, except for one individual clinician input, stated having experience with using gilteritinib. The clinicians agreed that they would use gilteritinib for patients with FLT3-ITD or TKD mutated R/R AML patients. Specifically, one individual clinician stated that they would consider gilteritinib for patients who relapse after achieving a complete response with standard induction therapy, and patients who have failed to respond to, or progressed after receiving non-intensive treatment (i.e., azacitidine or low dose ARA-C).

Clinicians also agreed that gilteritinib is more effective and less toxic than currently available treatments for all R/R FLT3-mutated AML patients. The BC clinicians highlighted the superior response rate and OS from the phase III trial. An individual clinician also highlighted the clinically significant improved survival data at one year, and that there did not seem to be any warning safety concerns. One individual clinician input and the joint clinician input from BC clinicians specifically stated that gilteritinib is safer than induction or intense salvage chemotherapy regimens, and that gilteritinib is associated with fewer severe infections.

Based on the clinical label for gilteritinib, the BC clinicians stated that contraindications include patients with hypersensitivity to gilteritinib. The clinicians advised caution with respect to drug-drug interactions with other medications (i.e., Azoles and QT-prolonging medications). One individual clinician input referred to the Health Canada product monograph for specific information regarding contraindications of gilteritinib.

## 5.4 Sequencing and Priority of Treatments with New Drug Under Review

### 5.4.1 Implementation question: Please consider if there is evidence to support the optimal treatment sequencing with gilteritinib with available treatments for FLT3 mutated AML:

#### 5.4.1.1 Optimal sequencing with available treatments (e.g., midostaurin).

The BC clinicians acknowledged that a small number of patients (approximately 13%) in the phase III randomized control trial received a FLT3 inhibitor (i.e., sorafenib or midostaurin) before being treated with gilteritinib. The clinicians referred to a subset analysis which suggested benefit from gilteritinib among patients who received a FLT3 inhibitor prior to gilteritinib. In the phase I/II study, BC clinicians highlighted that a larger proportion of patients were exposed to a FLT3 inhibitor before treatment with gilteritinib, and that response to gilteritinib was reported in patients with prior FLT3 inhibitor use. The joint input suggested that gilteritinib would be appropriate as a second-line treatment following midostaurin.

One of the individual clinician inputs acknowledged front-line induction with 3+7+midostaurin as the current standard of care. For patients who relapse on the induction therapy, the clinician suggested gilteritinib as the next standard of care. For patients who are refractory to 3+7+midostaurin, the clinician suggested re-induction with FLAG-IDA or MEC; and gilteritinib was recommended by the clinician for patients who fail to respond to reinduction. For patients who are unfit for reinduction, the clinician would move straight to treatment with gilteritinib. Front-line treatment for patients who are older and unfit was stated to be either azacitidine or low dose ARA-C followed by gilteritinib if patients with FLT3 did not respond or progressed on front-line treatment. This clinician acknowledged that while none of his patients were included in the ADMIRAL trial, his experience with patients with AML show that these patients can respond similarly to gilteritinib and derive considerable benefit in terms of survival and quality of life.

The remaining two individual clinician inputs agreed that gilteritinib would be given to FLT3-IDT mutated patients who have relapsed after treatment with midostaurin. Acknowledging that FLT3 status can change, one of the clinicians highlighted that patients who relapse and also become FLT3-positive would be able to use gilteritinib.

#### 5.4.1.2 What treatment options would be available to patients upon progression on gilteritinib?

In general, clinicians agreed that, upon progression on gilteritinib, patients would not have too many treatment options. The joint clinician input stated that treatments following progression on gilteritinib have not been rigorously studied. All inputs stated that, upon progression on gilteritinib, primary treatment options would be enrollment into a clinical trial or best supportive care, including palliative chemotherapy.

#### 5.4.1.3 Whether there are clinical scenarios in which gilteritinib would eb used in combination (with azacitidine or low-doe cytarabine or FLA-IDA or MEC)?

All clinicians agreed that based on current evidence, gilteritinib should be given as a monotherapy; currently there is insufficient evidence to support the use of gilteritinib in combination with other treatments outside of a clinical trial. One of the individual

clinicians stated that there are currently studies underway assessing the effect of gilteritinib with chemotherapy.

## 5.5 Companion Diagnostic Testing

All clinicians acknowledged that FLT3 mutation testing is necessary for patients to be eligible for gilteritinib. FLT3 mutation testing is currently available and was stated by the clinicians to have a quick turnaround testing time of approximately five days. One individual clinician and the clinicians from BC agreed that 'repeat FLT3 testing' is required, as this mutation status can change in a significant proportion of patients. Approximately 25% of patients who were FLT3 mutated at diagnosis were stated to lose the mutation at relapse, and approximately 25% of patients who were FLT3 wild type at diagnosis were stated to acquire the mutation at relapse. Testing for patients' mutation status occurs upfront to help make decisions regarding the use of midostaurin during induction. The input from BC clinicians stated that repeat FLT3 testing is currently available at their centre but acknowledged the greater lab resources that would be required to support a widespread increase in this testing. An individual clinician stated that FLT3 testing is currently only performed routinely at diagnosis in their jurisdiction; repeat FLT3 testing is available upon request for patients after relapse but should be funded and routinely performed once gilteritinib becomes available. The joint clinician input also highlighted that repeat FLT3 testing for relapsed patients is becoming standard of care, and that there is an increasing access to FLT3 inhibitors.

## 5.6 Additional Information

The clinicians from BC and an individual clinician pointed to the improved safety, efficacy, and cost-savings associated with gilteritinib over current conventional chemotherapy salvage regimens. BC clinicians referred to the phase III randomized control trial which showed a meaningful clinical benefit with respect to response rate, ability to undergo allogenic stem cell transplant, and OS, when compared to current standard of care in AML patients. The joint clinician input and the individual clinician both supported the superior tolerability of gilteritinib, stating it is associated with less toxicity and lower morbidity rate than intensive chemotherapy. Both inputs also highlighted that gilteritinib can be administered on an outpatient basis, when compared to chemotherapy which was stated to require 4-5 weeks of hospitalization and involve costs for post-remission therapy.

# 6 SYSTEMATIC REVIEW

## 6.1 Objectives

The primary objective of this systematic review is to evaluate the safety and efficacy of gilteritinib compared to standard of care in patients with relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine 3 (FLT3) mutation.

Supplemental Questions and Comparison with Other Literature most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7 and section 8.

## 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 were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

**Table 6.1 Selection Criteria**

| Clinical Trial Design | Patient Population | Intervention | Appropriate Comparators* | Outcomes |
|---|---|---|---|---|
| Published or unpublished RCTs<br><br>In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of gilteritinib should be included. | Adult patients who have relapsed or refractory FLT3mut+ AML<br><br><u>Subgroups:</u><br>- Age<br>- Sex<br>- ECOG PS<br>- Bone marrow disorders, such as MDS<br>- WBC count<br>- Prior therapy<br>- Response to prior therapy<br>- FLT3 mutation subtype (ITD, TKD, or both)<br>- Allelic ratio | Gilteritinib | - Mitoxantrone, etoposide, and cytarabine (MEC)<br>- Fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-IDA)<br>- Low-dose cytarabine (LoDAC)<br>- Azacitidine<br>- Azacitidine + sorafenib<br>- Midostaurin<br>- Midostaurin with standard cytarabine and danorubicin (or idarubicin) induction and cytarabine consolidation chemotherapy | - **OS**<br>- **Event-free survival**<br>- **Complete remission rate**<br>- **Duration of remission**<br>- **HRQoL**<br>- AEs<br>- TEAEs<br>- SAEs<br>- WDAEs<br>- Deaths<br>- Percentage of patients that received a subsequent allogeneic stem cell transplant<br>- **Complete remission rate with and without hematological recovery** |

| Clinical Trial Design | Patient Population | Intervention | Appropriate Comparators* | Outcomes |
|---|---|---|---|---|
| | | | - Allogeneic stem cell transplant<br>- BSC<br>- Crizotinib<br>- Venetoclax and azacitidine** | - Cardiac toxicities*** |

**Abbreviations:**
**AE** = adverse event; **AML** = acute myeloid leukemia; **BSC** = best supportive care; **ECOG PS** = Eastern Cooperative Oncology Group Performance Status; **FLT3** = FMS-like tyrosine kinase; **FLT3mut+** = FMS-like tyrosine kinase mutation; **HRQoL** = health-related quality of life; **ITD** = internal tandem duplication; **MDS** = myelodysplastic syndrome; **OS** = overall survival; **RCT** = randomized controlled trial; **SAE** = serious adverse event; **TEAE** = treatment emergent adverse event; **TKD** = tyrosine kinase domain; **WDAE** = withdrawals due to adverse events

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

*** Identified as an agent of interest, although not available in Canada*

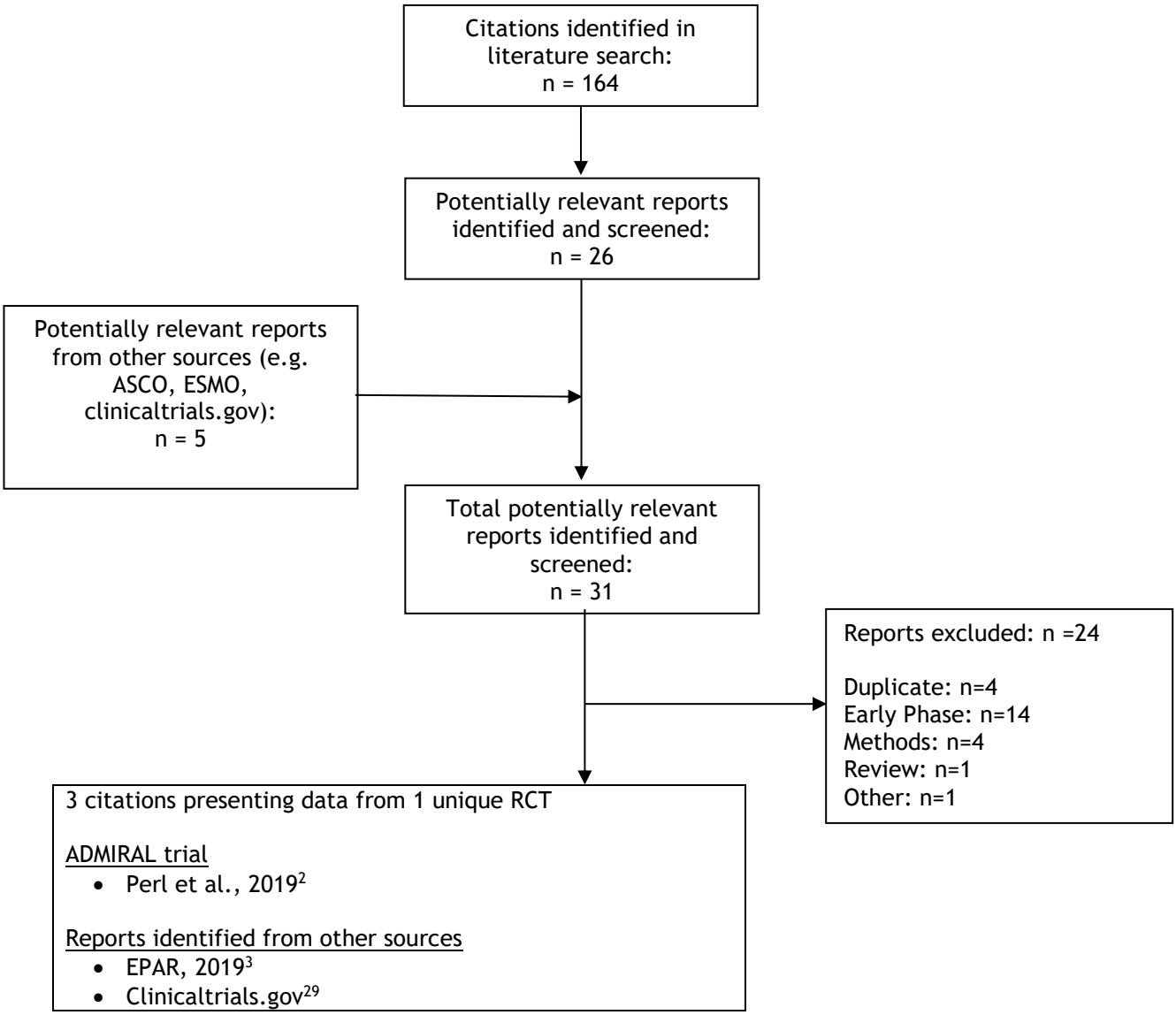
**** Cardiac toxicities were identified as an adverse event of special interest (AESI) by the Clinical Guidance Panel (CGP) after development of the systematic review protocol and were included in the report*

## 6.3 Results

### 6.3.1 Literature Search Results

Of the 31 potentially relevant reports identified, 3 citations reporting data from one randomized controlled trial (RCT) were included in the pCODR systematic review[2,3,29] and 24 citations were excluded. Studies were excluded because they contained duplicate data,[30-32] reported data from early phase trials,[33-46] included a description of the study methods only,[47-50] were a review,[51] or other reasons.[52]

**Figure 6.1. QUOROM Flow Diagram for Inclusion and Exclusion of studies**




*Note: Additional data related to the ADMIRAL trial were also obtained through requests to the sponsor by pCODR.*[4,5,8,10,53-55]

### 6.3.2 Summary of Included Studies

One randomized controlled trial (RCT), the ADMIRAL trial, met the selection criteria for this systematic review. Key trial characteristics including the study design, eligibility criteria, intervention details, and trial outcomes are summarized in Table 6.2.

#### 6.3.2.1 Detailed Trial Characteristics

**Table 6.2 Summary of Trial Characteristics of the Included Studies**

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| **Study:**[2,3,6]<br>ADMIRAL<br>NCT02421939<br><br>**Characteristics:**<br>Phase III, superiority, open-label, randomized (2:1), active-controlled trial<br><br>N= 371 randomized (gilteritinib: n=247; chemotherapy: n=124)<br><br>N = 355 treated (gilteritinib: n=246; chemotherapy: n=109)<br><br>**Setting:**<br>107 centres in 14 countries (Canada, Belgium, France, Germany, Israel, Italy, Japan, Korea, Poland, Spain, Taiwan, Turkey, UK, US)<br><br>**Patient Enrolment Dates:**<br>October 20th, 2015 to February 20th, 2018<br><br>**Data cut-off (OS):**<br>September 17th, 2018<br><br>**Database lock:** | <u>Key Inclusion Criteria:</u><br>- Adults according to local regulation<br>- Morphologically documented primary AML or AML secondary to MDS by WHO criteria (Swerdlow et al., 2008)[56] determined by pathology review at treating institution<br>- Participant is refractory to or relapsed after first-line AML therapy (with or without HSCT) defined as:<br>1. Refractory: did not achieve CR/CRi/CRp under initial therapy. Patient eligible for standard therapy must have received at least 1 cycle of anthracycline containing induction block in standard dose for the selected induction regimen. A patient ineligible for standard therapy must have received at least 1 complete block of induction therapy seen as the optimum choice of therapy to induce remission for the patient as per investigator's assessment.<br>2. Relapsed: achieved CR/Cri/CRp (defined by Cheson et al., 2003)[57] with first-line treatment and has hematologic relapse<br>- FLT3 mutation positive in bone marrow or whole blood as determined by central lab; participants with rapidly proliferative disease in the opinion of the investigator can be enrolled based on local test performed after completion of last interventional treatment if they have a FLT3-ITD, FLT3-TKD/D835 or FLT3-TKD/I836 mutation<br>- ECOG PS ≤ 2<br>- Eligible for preselected salvage chemotherapy according to investigator assessment<br>- Adequate lab and organ function<br><br><u>Key Exclusion Criteria:</u><br>- Acute promyelocytic leukemia<br>- BCR-ABL-positive leukemia (chronic myelogenous leukemia in blast crisis)<br>- AML secondary to prior chemotherapy for other neoplasms (except MDS)<br>- Second or later hematologic relapse or has received salvage therapy for refractory disease<br>- Clinically active CNS leukemia<br>- Other malignancy unless disease-free for ≥ 5 years; treated nonmelanoma skin cancer, in situ carcinoma or cervical intraepithelial neoplasm regardless of the disease-free duration are | <u>Intervention</u><br>Gilteritinib tablets administered orally at a dose of 120 mg once daily<br><br><u>Comparator</u><br>Preselected salvage chemotherapy from four options administered as 28-day cycles as per the following:<br><br>LoDAC:<br>- 20 mg cytarabine twice daily by SC or IV injection for 10 days<br><br>Azacitidine:<br>- 75 mg/m$^2$ azacitidine daily by SC or IV injection for 7 days<br><br>MEC Induction Chemotherapy:<br>- Mitoxanrone 8 mg/m$^2$ per day by IV for 5 days<br>- Etoposide 100 mg/m$^2$ per day by IV for 5 days<br>- Cytarabine 1000 mg/m$^2$ per day by IV for 5 days<br><br>FLAG-IDA Induction Chemotherapy:<br>- G-CSF 300 µg/m$^2$ per day by SC/IV for 5 days<br>- Fludarabine 30 mg/m$^2$ per day by IV for 5 days | <u>Primary</u><br>- OS<br>- CR/CRh rate<br><br><u>Secondary</u><br>- EFS<br>- CR rate<br>- LFS<br>- Duration of remission<br>- CRh rate<br>- CRc rate<br>- Transfusion conversion rate<br>- Transfusion maintenance rate<br>- Transplantation rate<br>- BFI<br>- Safety evaluation of AEs<br><br><u>Exploratory</u><br>- HRQoL<br>- Pharmacogenomics<br>- Biomarker analysis of FLT3 gene mutation status (types and frequency; relationship to safety and efficacy; mechanisms of acquired resistance)<br>- Predictive biomarkers of gilteritinib activity<br>- Resource utilization |

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| October 19th, 2018<br><br>**Funding:**<br>Astella Pharma | eligible for this study if definitive treatment has been completed; organ-confined prostate cancer with no evidence of recurrent or PD are eligible if hormonal therapy has been initiated or malignancy has been surgically removed or treated with definitive radiotherapy<br>- Prior treatment with FLT3 inhibitors (except midostaurin and sorafenib if used in first-line as part of induction, consolidation, and/or maintenance)<br>- Significant abnormality of coagulation profile (e.g. disseminated intravascular coagulation)<br>- Major surgery or radiation therapy within 4 weeks prior to first study dose<br>- Current or history of CHF as per NYHA class 3 or 4, unless screening ECHO within 1 month results in a LVEF that is ≥45%<br>- Mean triplicate QTcF > 450 ms or long QT syndrome at screening based on central reading<br>- Hypokalemia and hypomagnesemia at screening (values below LLN)<br>- Requirement for concomitant drugs that are strong inducers of CYP3A; inhibitors/inducers of P-gp or drugs that target $5HT_1R$ or $5HT_{2B}R$ receptors or sigma nonspecific receptor with the exception of drugs considered absolutely essential for the care of the patient<br>- Active uncontrolled infection<br>- HIV; or active HBV, HCV, or other active hepatic disorder<br>- Active, clinically significant GVHD or is on treatment with systemic corticosteroids for GVHD<br>- FLT3 mutations other than FLT3-IHD, FLT3-TKD/D835, or FLT-TKD/I836 | - Cytarabine 2000 mg/m$^2$ per day by IV for 5 days<br>- Idarubicin 10 mg/m$^2$ per day by IV for 3 days | |

**Abbreviations:**
**$5HT_1R$** = serotonin 5-hydroxytryptamine receptor 1; **$5HT_{2B}R$** = 5-hydroxytryptamine receptor 2B; **AE** = adverse event; **AML** = acute myeloid leukemia; **BFI** = brief fatigue inventory; **CHF** = congestive heart failure; **CNS** = central nervous system; **CR** = complete remission; **CRc** = composite complete remission; **CRh** = complete remission and complete remission with partial hematological recovery; **CRi** = complete response with incomplete hematologic recovery; **CRp** = complete response with incomplete platelet recovery; **CYP3A** = cytochrome P4503A; **ECHO** = echocardiogram; **ECOG PS** = Eastern Cooperative Oncology Group Performance Status; **EFS** = event-free survival; **FLAG-IDA** = Fludarabine, cytarabine, and granulocyte colony-stimulating factor with idarubicin; **FLT3** = FMS-like tyrosine kinase; **G-CSF** = granulocyte colony-stimulating factor; **GVHD** = graft versus host disease; **HBV** = hepatitis B; **HCV** = hepatitis C; **HIV** = human immunodeficiency virus; **HRQoL** = health-related quality of life; **HSCT** = hematopoietic stem cell transplantation; **ITD** = internal tandem duplication; **IV** = intravenously; **LFS** = leukemia-free survival; **LLN** = lower limit of normal; **LoDAC** = low-dose cytarabine; **LVEF** = left ventricular ejection fraction; **MDS** = myelodysplastic syndrome; **MEC** = mitoxantrone, etoposide, and intermediate-dose cytarabine; **mg** = milligram; **ms** = milliseconds; **NYHA** = New York Heart Association; **OS** = overall survival; **PD** = progressive disease; **P-gp** = P-glycoprotein; **QT** = uncorrected QT interval; **QTcF** = corrected QT interval by Fredericia; **SC** = subcutaneously; **TKD** = tyrosine kinase domain; **UK** = United Kingdom; **US** = United States; **WHO** = World Health Organization

**Table 6.3 Select quality characteristics of included studies of gilteritinib in patients with relapsed or refractory acute myeloid leukemia**

| Study | Treatment versus Comparator | Primary outcomes | Required sample size | Actual Sample size | Randomization method | Allocation concealment | Blinding | ITT Analysis | Final analysis | Early termination | Ethics Approval |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ADMIRAL | Gilteritinib versus salvage chemotherapy | OS and CR/CRh rate | 369 | 371 | 2:1 by IRT | No | No | Yes | Yes | No | Yes |

**Abbreviations: CR/CRh** = complete remission and complete remission with hematological recovery; **IRT** = interactive response technology; **ITT** = intent to treat; **OS** = overall survival

### *a) Trials*

ADMIRAL was an international, open-label, phase III, randomized, active-controlled superiority trial that compared the safety and efficacy of gilteritinib versus salvage chemotherapy in FLT3 mutated AML patients who were refractory to or relapsed after first-line therapy.[2] This study was conducted at 107 centres across 14 countries, which are listed in Table 6.2, and included 4 Canadian patients (gilteritinib: n=3; salvage chemotherapy: n=1).[8]

#### ***Trial Design***

Screening and Randomization

The ADMIRAL study design is summarized in Figure 6.2. Patients were assessed for eligibility during a 14-day screening period, and key inclusion and exclusion criteria are outlined in Table 6.2. Patients must have had FLT3-mutated AML and were refractory to a first-line therapy that included at least 1 cycle of an anthracycline-containing regimen (for patients eligible for standard therapy) or 1 complete block of induction therapy that was seen as the optimum choice to induce remission as per the investigator's assessment (for patients ineligible for standard therapy), or experienced hematological relapse following a complete remission (CR), complete remission with incomplete platelet recovery (CRp), or complete remission with incomplete hematological recovery (CRi) to first-line therapy.

Eligible patients were preselected to one of four salvage chemotherapy regimens, as determined the investigator prior to randomization, which included:

- Low-dose cytarabine (LoDAC)
- Azacitidine
- Mitoxantrone, etoposide, and intermediate-dose cytarabine (MEC)
- Fludarabine, cytarabine, and granulocyte colony-stimulating factor with idarubicin (FLAG-IDA)

Participants were randomized in a 2:1 ratio to receive gilteritinib or the preselected salvage chemotherapy regimen via Interactive Response Technology (IRT). Randomization was stratified by:

- Response to first-line AML therapy

        - Relapse within 6 months after allogeneic hematopoietic stem cell transplant (HSCT)
        - Relapse after 6 months after allogeneic HSCT
        - Primary refractory without HSCT
        - Relapse within 6 months after composite complete remission (CRc), which includes CR, CRp, or CRi, and no HSCT
        - Relapse after 6 months after CRc and no HSCT
    - Preselected chemotherapy
        - High intensity chemotherapy (FLAG-IDA or MEC)
        - Low intensity chemotherapy (LoDAC or azacitidine)[2]

Treatment

Patients assigned to gilteritinib received a 120 mg dose orally once daily in continuous 28-day cycles, and patients assigned to salvage chemotherapy received high or low intensity chemotherapy in 28 day cycles as described below:

Low intensity chemotherapy – continuous cycles (ie., treatment continues until treatment discontinuation criteria is met, for example, patient is no longer benefitting or withdraws):

- LoDAC: 20 mg cytarabine administered twice daily by subcutaneous (SC) or intravenous (IV) injection for 10 days
- Azacitidine: 75 mg/m$^2$ administered once daily by SC or IV injection for 7 days
    - Institutional guidelines were followed if dose reduction was needed after cycle 1

High intensity chemotherapy – 1-2 cycles (2$^{nd}$ cycle based on investigator assessment):

- MEC: mitoxantrone 8 mg/m$^2$ per day by IV for 5 days; etoposide 100 mg/m$^2$ per day by IV for 5 days; cytarabine 1000 mg/m$^2$ per day by IV for 5 days
- FLAG-IDA: granulocyte colony stimulating factor (G-CSF) 300 µg/m$^2$ per day by IV/SC for 5 days (additional G-CSF recommended 7 days after completion of chemotherapy until absolute neutrophil count [ANC] > 0.5 x 10$^9$/L); fludarabine 30 mg/m$^2$ per day by IV for 5 days; cytarabine 2000 mg/m$^2$ per day by IV for 5 days; idarubicin 10 mg/m$^2$ per day by IV for 3 days
- Patients who received MEC or FLAG-IDA were assessed for response on or after day 15 following cycle 1 of therapy. If bone marrow cellularity was ≥20% with at least 50% reduction in blasts, patients could have received a second cycle of the same chemotherapy. If bone marrow cellularity was between 5-20%, it was the investigator decision whether to proceed with another treatment cycle or if the patient should be observed for recovery. For bone marrow cellularity ≤5%, the patient was observed for recovery. Patients who achieved a CR, CRi, or CRp may have received a second cycle of chemotherapy at the investigator's decision.[2]

No crossover was permitted between the gilteritinib treatment arm and the salvage chemotherapy arm. Regularly scheduled assessments while on treatment included

physical examination, vital signs, Eastern Cooperative Oncology Group Performance Status (ECOG PS), prior and concomitant medication, pregnancy tests (for women of childbearing potential), 12-lead ECG, clinical laboratory tests (chemistry, hematology, coagulation), thyroid function tests (every 2 cycles), ophthalmologic assessment (cycle 2 and then every 2 cycles thereafter or if clinically indicated), bone marrow aspiration or biopsy (cycle 2 and 3, and if CRc not achieved then every 2 cycles thereafter), adverse events (AEs) and serious adverse events (SAEs) monitoring, pharmacokinetic blood collection, health-related quality of life (HRQoL) assessments, and resource utilization data collection.[2]

Treatment Discontinuation

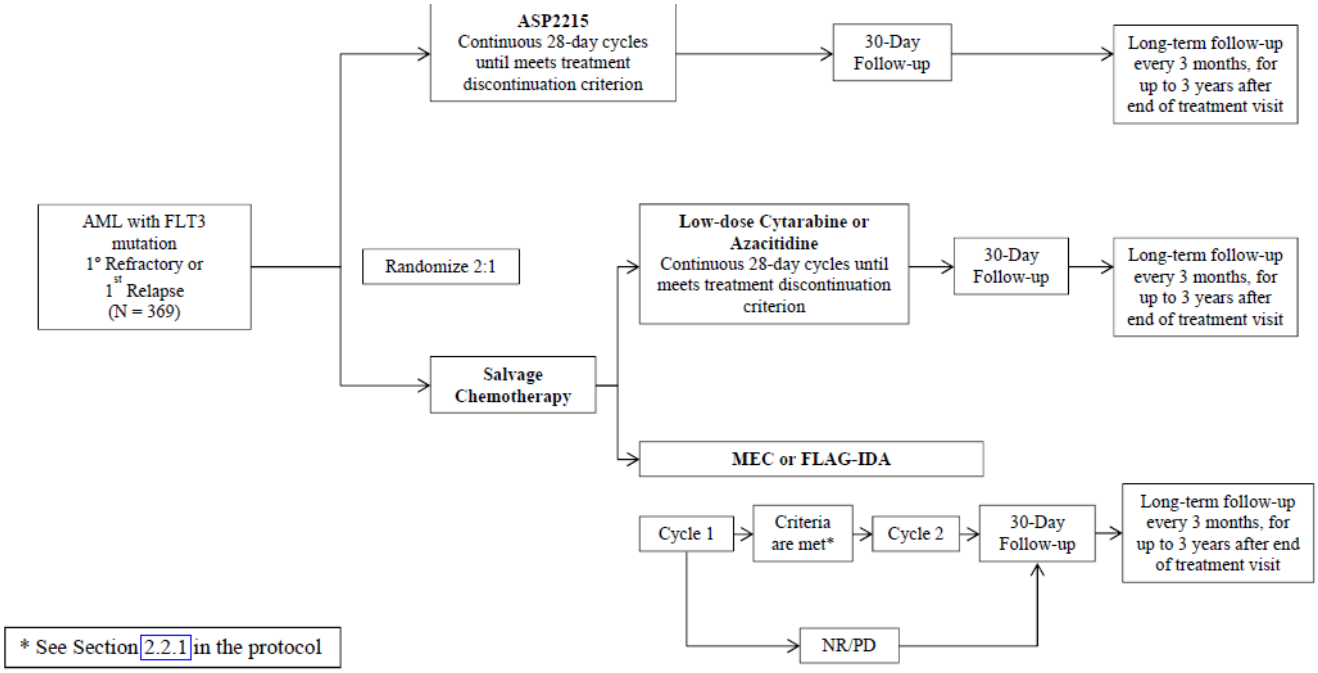
Patients treated with gilteritinib, LoDAC, or azacitidine continued treatment until progressive disease (PD) or no response (NR), and the patient was no longer deriving clinical benefit in the opinion of the investigator. Patients treated with MEC or FLAG-IDA discontinued treatment if NR or PD was experienced following cycle 1. Other criteria for treatment discontinuation included: patient withdrawal of consent; noncompliance with the protocol based on investigator or medical monitor assessment; patients who significantly deviated from any 1 of the inclusion or exclusion criteria after enrolment (patients having clinical benefit could be kept in the study upon discussion with the medical monitor); intolerable or unacceptable toxicity; patient received antileukemic therapy other than the assigned treatment (exceptions: hydroxyurea for up to 2 weeks, prophylactic intrathecal chemotherapy or cranial irradiation, and donor lymphocyte infusion as part of HSCT treatment plan); investigator decision; patient is lost to follow-up; patient on salvage chemotherapy goes on to HSCT; female becomes pregnant; and death.[2]

Follow-Up

Patients attended an end of treatment (EOT) visit within 7 days of treatment discontinuation. EOT assessments included physical examination, vital signs, ECOG PS, and clinical laboratory tests, which did not need to be performed if the assessments already occurred within 3 days of the EOT at a regularly scheduled visit. Other EOT assessments included concomitant medications, pregnancy tests (for applicable women of childbearing potential), 12-lead electrocardiogram (ECG), ophthalmologic assessment, thyroid function tests, bone marrow aspiration and/or biopsy, FLT3 mutation status testing on bone marrow samples collected post study treatment, HRQoL assessments, resource utilization data collection, and AEs/SAEs were monitored.

The EOT visit was followed by a 30-day follow-up via a telephone call unless any assessments needed to be repeated for resolution of treatment-related adverse events (TEAEs). After this, patients entered the long-term follow-up period, which occurred every 3 months for up to 3 years from the patient's EOT visit. During the 30-day follow-up visit and long-term follow-up period, HRQoL via EQ-5D-5L, subsequent AML treatment information, remission status, and survival data were collected.[2]

**Figure 6.2 ADMIRAL study design flow chart[3]**




1°: primary; AML: acute myeloid leukemia; FLT3: FMS-like tyrosine kinase; FLAG-IDA: fludarabine, cytarabine and granulocyte colony-stimulating factor with idarubicin; MEC: mitoxantrone, etoposide and intermediate-dose cytarabine; NR: no response; PD: progressive disease

**Source:** EPAR, EMA 2019[3]

Disease Assessments

For patients who received gilteritinib, LoDAC, or azacitidine bone marrow samples (aspiration and/or biopsy) were required during screening, cycle 2 day 1, and cycle 3 day 1. For patients that did not achieve a CRc (i.e., CR, CRp, or CRi), the bone marrow assessments were repeated at day 1 of every 2 subsequent cycles. Patients who achieved a CRc, bone marrow sampling was repeated 1 month after the date of remission, and every 3 subsequent cycles or if there was suspicion of relapse in the whole blood.

For patients who received MEC or FLAG-IDA, bone marrow samples were required during screening and at cycle 2 day 1. An additional bone marrow sample was required at cycle 1 day 15, or later as per institutional guidelines, to assess the need for a second cycle.

Bone marrow samples were also required pre-HSCT visit and EOT visit, and as clinically indicated during the trial. If bone marrow aspirate was unobtainable, an additional whole blood sample was collected instead. Bone marrow aspirate was required, but biopsy was preferred (if aspirate inadequate, biopsy required).[2]

***Study Endpoints and Statistical Analyses***

Response Definitions

Responses to treatment were defined as per modified criteria (Cheson et al., 2003),[57] as follows:

- **Complete Remission (CR)**: defined as bone marrow regenerating normal hematopoietic cells and achieve a morphologic leukemia-free state; must have an ANC ≥ 1 x $10^9$/L; platelet count ≥ 100 x $10^9$/L; normal marrow differential <5% blasts; be red blood cell (RBC) and platelet transfusion independent (1 week without RBC transfusion and 1 week without platelet transfusion); and no evidence of extramedullary leukemia
- **Complete Remission with Incomplete Platelet Recovery (CRp):** defined as CR except for incomplete platelet recovery (<100 x $10^9$/L)
- **Complete Remission with Incomplete Hematologic Recovery (CRi):** defined as CR except for incomplete hematological recovery with residual neutropenia (<1 x $10^9$/L) with or without complete platelet recovery; RBC and platelet transfusion independence not required
- **Composite complete remission (CRc):** defined as patients that achieved CR, CRp, or CRi
- **Complete Remission with Partial Hematologic Recovery (CRh):** defined as bone marrow blasts <5%; partial hematologic recovery ANC ≥0.5 x $10^9$/L and platelets ≥50 x $10^9$/L; and no evidence of extramedullary leukemia and cannot be classified as CR
- **Partial Remission (PR):** defined as bone marrow regenerating normal hematopoietic cells with evidence of peripheral recovery with no (or few regenerating) circulating blasts with a decrease of at least 50% in the percentage of blasts in the bone marrow aspirate with the total marrow blasts between 5-25%; value of ≤5% blasts is also considered PR if Auer rods present
- **Not Evaluable/No Response (NE/NR):** when no bone marrow assessments are performed or myeloblast value is missing, blast value from peripheral blood is missing or ≤2% , and extramedullary leukemia is missing or not done, the response was classified as NE; any response that cannot be categorized as CR, CRp, CRi, PR, or NE will be categorized as NR
- **Relapse:** relapse after CR, CRh, CRp, or CRi is defined as a reappearance of leukemic blasts in the peripheral blood or ≥5% blasts in the bone marrow aspirate not attributable to any other cause or reappearance or new appearance of extramedullary leukemia; relapse after PR is defined similarly with a significant number of peripheral blasts and >25% blasts in the bone marrow aspirate not attributable to any other case or reappearance/new appearance of extramedullary leukemia
- **Best Response:** defined as best measured response to treatment for all visits (ordered: CR, CRp, CRi, PR, NR, and NE) post-baseline; patients with responses of CR, CRp, CRi, or PR were considered responders and those that did not achieve at least PR were considered non-responders[2]

Primary and Secondary Endpoints

Primary and secondary endpoints are summarized in the Table 6.4 below. Subgroup analyses were pre-specified and performed for all primary and key secondary efficacy outcomes for age (<65 years of age vs ≥65 years of age), gender, ECOG PS, race, region, response to first-line therapy, and preselected salvage chemotherapy.[2]

**Table 6.4. Primary, secondary, and exploratory outcomes in the ADMIRAL trial**

| **PRIMARY ENDPOINTS** | | | | |
|---|---|---|---|---|
| **Endpoint** | **Analysis Population** | **Definition** | **Statistical Methods** | **Sensitivity Analyses** |
| Overall survival (OS) | ITT | Time from the date of randomization until the date of death from any cause.<br><br>Patients not known to have died by the end of study follow-up were censored at the date of last contact | Kaplan-Meier survival for median OS and 95% CI<br><br>Stratified log-rank test (strata: response to first-line therapy and preselected salvage chemotherapy)<br><br>Null hypothesis tested was that OS in gilteritinib arm is worse than or equal to OS in salvage chemotherapy arm. | 1. Same as primary analysis with the FAS<br>2. Same as primary analysis with PPS<br>3. Stratified Cox PH model with response to first-line AML and preselected savage chemotherapy<br>4. Same as primary analysis, but censoring patients who undergo HSCT at the time of HSCT<br>5. Same as primary analysis, but censoring patients at the time of initiation of a new therapy; and an OS analysis that treats initiation of new therapy as a time-dependent binary covariate to account for possible confounding effect of subsequent therapies<br>6. Additional analyses may be performed to compare survival curves with the PH assumption is plausible |
| Complete remission and complete remission with partial hematologic recovery rate (CR/CRh Rate) | RAS (interim analysis) | The number of patients who achieved either a CR or CRh at any post-baseline visit divided by the number of patients in the analysis population. | Two-sided 95% exact CI calculated for 141 participants randomized to the gilteritinib arm and the lower limit will be used to compare with the benchmark of 12%. | 1. Same as primary analysis, but only mRAS patients included<br>2. Same as primary analysis, but only patients who took at least one dose of gilteritinib included<br>3. Same analysis, but only included patients with more than one post-baseline bone marrow assessment<br>4. Same as primary analysis, but evaluated the CR/CRh by cycle 4 which was defined as the number of patients who achieved CR/CRh by cycle 4 divided by the number of patients in the analysis population<br>5. Same as the primary analysis, but evaluated the CR/CRh prior to HSCT which is defined as the number of patients who achieve CR/CRh prior to HSCT divided the number of patients in the analysis population |
| **SECONDARY ENDPOINTS*** | | | | |
| **Endpoint** | **Analysis Population** | **Definition** | **Statistical Methods** | **Sensitivity Analyses** |
| Event-free survival (EFS) | ITT | Time from the date of randomization until the date of documented relapse (excluding relapse after PR), treatment failure or death, due to any cause within 30 days of last study drug dose, | Kaplan-Meier survival for median EFS and 95% CI | 1. Same as primary analysis with the FAS<br>2. Same as primary analysis with the PPS<br>3. Stratified Cox PH model with response to first-line AML and preselected savage chemotherapy |

| PRIMARY ENDPOINTS | | | | |
|---|---|---|---|---|
| | | whichever occurs first. Date of relapse or death is used as event date. Date of randomization is used for treatment failure (unable to achieve at least PR) event date. Date of last relapse-free disease assessment is used for patients not known to have had a relapse, treatment failure, or death event. Patients were not censored at HSCT. | Stratified log-rank test (strata: response to first-line therapy and preselected salvage chemotherapy) | 4. EFS definition altered to include the date of first new anti-leukemia therapy after EOT or last treatment evaluation (if new anti-leukemia therapy date unavailable) used as the event date of treatment failure<br>5. EFS definition altered to include patients who discontinued treatment due to follow-up considered an EFS event and patients censored at date of lost to follow-up |
| Complete remission (CR) rate | ITT | Number of patients who achieved CR divided by the number of patients in the analysis population. | Tested using the Cochran-Mantel-Haenszel (CMH) test to control for response to first-line AML and preselected salvage chemotherapy | 1. CMH test on patients who received at least one dose of study treatment.<br>2. CMH test on patients with at least one post-baseline bone marrow assessment.<br>3. Unstratified Fisher's exact test on patients in the ITT |
| Duration of remission | ITT | Duration of remission included duration of CRc, CR/CRh, CR, CRh, CRi, CRp, and duration of response (DR) (i.e., CRc + PR)<br><br>Duration of CRc: defined as the time from the date of first CRc until the date of documented relapse for patients who achieve CRc; patients who die without relapse or who do not relapse on study are considered nonevents and are censored at the last relapse-free disease assessment date. Duration of CR/CRh, CRh, CR, CRp, CRi is defined similar to CRc.<br><br>Duration of response: defined as the time from the date of first CRc or PR until the date of documented relapse of any type for patients who achieve CRc or PR; patients who die without relapse or did not relapse on study are considered nonevents and censored at their last relapse-free disease assessment date | Stratified log-rank test (strata: response to first-line therapy and preselected salvage chemotherapy) | None pre-specified. |

| PRIMARY ENDPOINTS | | | | |
|---|---|---|---|---|
| Complete remission with partial hematologic recovery (CRh) rate | ITT | Number of patients who achieved CRh at any post-baseline visit and do not have best response of CR divided by the number of patients in the analysis population | Tested using the Cochran-Mantel-Haenszel (CMH) test to control for response to first-line AML and preselected salvage chemotherapy | None pre-specified. |
| Composite complete remission (CRc) rate | ITT | Number of patients who achieved the best response of CRc (CR, CRp, CRi) divided by the number of patients in the analysis population. | Tested using the Cochran-Mantel-Haenszel (CMH) test to control for response to first-line AML and preselected salvage chemotherapy | None pre-specified |
| Transfusion conversion rate and transfusion maintenance rate (gilteritinib arm only) | ITT | Patients were classified as transfusion independent at baseline if there were no RBC or platelet transfusions within the baseline period (defined as 28 days prior to or 28 days after the first dose); otherwise patients were classified as transfusion dependent at baseline. Patients were classified as transfusion independent postbaseline if the patient had one consecutive 8-week period without any RBC or platelet transfusion from 29 days after the first dose until the last dose date. For patients who were on treatment ≤ 4 weeks or patients who were on treatment > 4 weeks but < 12 weeks and there was no RBC or platelet transfusion within the postbaseline period, the postbaseline transfusion status was considered not evaluable; otherwise, patients were considered postbaseline transfusion dependent. Both transfusion conversion rate and maintenance rate were defined for patients who had evaluable postbaseline transfusion status. | Descriptive statistics | None pre-specified. |
| Transplantation rate | ITT | The percentage of patients who underwent HSCT during the trial. | Tested using the Cochran-Mantel- | None pre-specified. |

| PRIMARY ENDPOINTS | | | | |
|---|---|---|---|---|
| | | | Haenszel (CMH) test to control for response to first-line AML and preselected salvage chemotherapy | |
| Brief Fatigue Inventory (BFI) | ITT | Assesses the severity and impact of fatigue on daily functioning in patients with fatigue due to cancer and cancer treatment. It includes 9 items and a 24-hour recall with a global fatigue score computed by averaging the 9 items. BFI was administered via an electronic PRO device predose at cycle 1 day 1, cycle 1 day 8, cycle 1 day 15, cycle 2 day 1, cycle 2 day 15, and day 1 of all subsequent cycles as well as at pre-HSCT and the EOT visit. | Analysis of covariance to analyze the change from in BFI global fatigue score from baseline to post-baseline visits | None pre-specified. |
| **RELEVANT EXPLORATORY OUTCOMES**** | | | | |
| **Endpoint** | **Analysis Population** | **Definition** | **Statistical Methods** | **Sensitivity Analyses** |
| **Health-related quality of life** | | | | |
| EuroQoL Group-5 Dimension-5 Level (EQ-5D 5L) | ITT | The EQ-5D-5L is a self-reported questionnaire, which includes a descriptive system that consists of 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that are assessed by 5 levels (no problems, slight problems, moderate problems, severe problems, and extreme problems), as well as a visual analogue scale (VAS). The VAS records the patient's self-rated health on a scale from 0 – 100, where 0 is the worst imaginable health state and 100 is the best imaginable health state. Assessments were conducted pre-dose on cycle 1 day 1, prior to assessments on day 1 (± 2 days) of all subsequent cycles, pre-HSCT or EOT, and at the 30-day follow-up visit via telephone with the site personnel. | Analysis of covariance to analyze the change of baseline EQ-5D-5L VAS and shift table for the 5 dimensions from baseline to post-baseline visits. | None pre-specified. |

| PRIMARY ENDPOINTS | | | | |
|---|---|---|---|---|
| Functional Assessment of Chronic Illness Therapy-Dyspnea Short Forms (FACIT-Dys-SF) | ITT | The FACIT-Dys-SF was developed to assess dyspnea severity and related functional limitations and includes 20 items with a 7-day recall period. It is scored with 2 domains: dyspnea and functional limitations, and was administered pre-dose via electronic PRO device on cycle 1 day 1, prior to assessments on day 1 (± 2 days) of all subsequent cycles, and pre-HSCT/EOT. | Analysis of covariance to analyze the change in FACT-Dys-SF domain scores from baseline to post-baseline visits. | None pre-specified. |
| Functional Assessment of Cancer Therapy-Leukemia | ITT | The FACT-Leu measured leukemia-specific signs, symptoms, and the impact of AML on patients and included a 44-item scale with global and domain scores (physical well-being, social/family well-being, emotional well-being, functional well-being, and additional leukemia-specific concerns), and a 7-day recall period. It was administered pre-dose on cycle 1 day 1, prior to assessments on day 1 (± 2 days) of all subsequent cycles, pre-HSCT/EOT. | Analysis of covariance to analyze the change in FACT-Leu for global and domain scores, individual items, and item clusters from baseline to post-baseline visits. | None pre-specified. |
| Dizziness and mouth sore items | ITT | Two additional questionnaires that evaluated dizziness and soreness, which commonly impact AML patients, were administered at cycle 1 day 1 predose, and day 1 (± 2 days) at all subsequent cycles | Analysis of covariance to analyze the change in dizziness and soreness from baseline to post-baseline visits. | None pre-specified. |
| FLT3 mutations status | ITT | An exploratory analysis of FLT3 mutations status and clinical efficacy (OS, EFS, and CR) was conducted, which included analyzing subgroups of FLT3 ITD mutation (FLT3-ITD alone, FLT3-TLD alone, and FLT3-ITD and FLT3-TKD); FLT3 allelic ratio (<median of 0.77 versus ≥median of 0.77) allelic ratio. | Conducted as per the statistical methodology of the respective primary clinical efficacy endpoints outlined above (in OS, EFS, and CR sections). | None pre-specified. |
| Analysis sets and definitions:<br>**Intention To treat (ITT):** included all patients who were randomized<br>**Response Analysis Set (RAS):** included patients who were 112 days post first dose or randomization; patients analyzed based on the randomized treatments<br>**Full Analysis Set (FAS):** included all patients who were randomized with FLT3 mutation based on the central test; patients analyzed based on the randomized treatments | | | | |

| PRIMARY ENDPOINTS |
| --- |
| **Per Protocol Set (PPS):** subset of FAS who did not meet criteria for PPS exclusion to capture relevant nonadherence to the protocol<br>**Modified Response Analysis Set (mRAS):** included a subset of the RAS who did not meet the exclusion of the mRAS population to capture nonadherence to protocol and other factors that may impact the response assessment |
| Abbreviations:<br>**AML** = acute myeloid leukemia; **CI** = confidence interval; **CR** = complete remission; **CRc** = composite complete remission; **CRh** = complete remission with partial hematological recovery; **CRi** = complete remission with incomplete hematologic recovery; **CRp** = complete remission with incomplete platelet recovery; **EOT** = end of treatment; **FLT3** = FMS-like tyrosine kinase; **HSCT** = hematopoietic stem cell transplant; **ITD** = internal tandem duplication; **OS** = overall survival; **PH** = proportional hazards; **PR** = partial remission; **PRO** = patient reported outcomes; **RBC** = red blood cells; **TKD** = tyrosine kinase domain |
| *An additional secondary outcome in the trial was leukemia-free survival, however it is not included in the report as it was not identified as a relevant outcome in the systematic review protocol.<br>**Additional exploratory outcomes included resource utilization (hospitalization, blood transfusion, antibiotic intravenous infusions, and medication for adverse events, and opioid usage); exploratory biomarker analysis; and pharmacogenomic analyses. |
| **Sources:**<br>Perl et al., 2019[2]<br>Astellas Pharma Canada, Checkpoint Responses; 2020[4] |

Safety

The safety analysis set (SAF) included any participant who took at least one dose of study treatment. Safety was assessed through AEs, clinical laboratory, vital signs, ECG, ophthalmologic assessments, and ECOG PS, and was routinely monitored throughout the study. Descriptive statistics were used to summarize the safety data.[2]

***Sample Size, Interim Analyses, and Multiplicity***

A group sequential design using the O'Brien Fleming boundaries (non-binding) as implemented by the Lan-DeMets alpha/beta spending method based on the co-primary endpoint of overall survival (OS) was utilized. The overall 0.025 one-side type I error rate was allocated by 0.0005 and 0.0245 (0.001 and 0.049 for two-side type I error rate) for the co-primary endpoints of CR/CRh rate and OS, respectively. The type I error (alpha) in the first interim analysis (IA1) was not recycled in the second interim analysis (IA2) and final analysis, and IA1 was planned when 141 patients were randomized to the gilteritinib treatment arm (and 70 in the salvage chemotherapy arm for a total of 211) with at least 112 days (4 treatment cycles) post first dose or randomization (for those who did not receive study drug). IA2 was planned when 129 deaths occurred with the final analysis planned for 258 deaths.

The study had about 90% power to detect a difference in OS with 7.7 months median survival time in the gilteritinib arm and 5 months median survival time with salvage chemotherapy (hazard ratio [HR]: 0.65) at the overall 1-sided 0.0245 significance level with 258 death events. Approximately 369 patients were required (246 in the gilteritinib arm and 123 in the salvage chemotherapy arm), assuming a 10% dropout rate.

The CR/CRh rate was evaluated at IA1 with a sample size of 141 patients in the gilteritinib arm and the assumption that the CR/CRh rate of gilteritinib was 21%, which was powered at 80% to exclude a rate of 12% using the 2-sided 95% exact confidence interval (CI). The sample size (n=211) and minimum follow-up (4 treatment cycles) at IA1 was considered to achieve a maximum width of 15.78% for the 2-sided 95% exact CI when the CR/CRh was expected to be in the 5-30% range.

The trial was powered at about 90% to detect a difference in EFS, assuming a HR of 0.65 (median EFS of 6 months for gilteritinib and 3.9 months for salvage chemotherapy) with a planned sample size of 258 EFS events. The study was powered >90% to detect a difference in CR rate between gilteritinib with a 25% CR rate and the salvage chemotherapy with a 10% CR rate at the overall 1-sided 0.0245 significance level.

The hypothesis testing for EFS was conducted only if the null hypothesis of the primary analysis of OS was rejected at its corresponding significance level for IA2 and the final analysis. The hypothesis testing on CR rate was conducted only if the null hypothesis of EFS was rejected at the corresponding significance level for IA2 and the final analysis.[2] A summary of the decision guidance of the interim and final analyses can be found in Table 6.5.

**Table 6.5. Summary of Decision Guidance of Interim and Final Analyses in the ADMIRAL trial[2]**

| Analysis | Criteria for Conduct of Analysis (Projected timing) | Endpoint/ Analysis Set | Efficacy Boundary* | | Futility Boundary* | |
|---|---|---|---|---|---|---|
| | | | P-value (1-sided) at the Boundary | Approx. Observed HR at Boundary | P-value (1-sided) at the Boundary | Approx. Observed HR at Boundary |
| IA1: CR/CRh rate | When 141 subjects are randomized into ASP2215 arm and at least 112 days (4 treatment cycles) post first dose or randomization (for subjects who received no study drug) | CR/CRh rate/ASP2215 subjects in RAS | NA (0.0005 nominal) | NA | NA | NA |
| IA 2: OS; EFS when null hypothesis of OS is rejected; CR rate when null hypotheses of both EFS and OS are rejected | Approx. 129 OS events are observed | OS/ITT | 0.00147 | 0.57 | 0.38674 | 0.95 |
| | | EFS/ITT | 0.01519 | 0.67 | 0.30218 | 0.91 |
| | | CR rate/ITT | 0.01519 | NA | 0.30218 | NA |
| Final: OS; EFS when null hypothesis OS is rejected; CR rate when null hypotheses of both EFS and OS are rejected | Approx. 258 OS events are observed | OS/ITT | 0.02402 | 0.77 | NA | NA |
| | | EFS/ITT | 0.01357 | 0.75 | NA | NA |
| | | CR rate/ITT | 0.01357 | NA | NA | NA |

CR: complete remission; CR/CRh: complete remission and complete remission with partial hematological recovery; EFS: event-free survival; HR: hazard ratio; ITT: intention to treatment set; NA: not applicable; OS: overall survival; RAS: response analysis set .

*: P-value at both efficacy and futility boundaries(except the first interim) are based on 50% information fraction for OS, EFS and CR rate, and need update based on observed information fraction at the second interim

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## ***Protocol Amendments***

A total of 8 substantial and 3 non-substantial amendments occurred throughout the course of the study (as of the data cut-off sate of September 17th, 2018) and a summary of substantial protocol amendments are provided in the Table 6.6 (non-substantial amendments are not presented in table 6.6).

**Table 6.6. Summary of substantial amendments in the ADMIRAL trial**

| Amendment Number/Date | Substantial amendment summary |
|---|---|
| Amendment 1<br>(June 22nd, 2015) | Entry criteria:<br>- Eligibility age clarified<br>- "Relapsed after first-line therapy" defined as untreated relapse patients who had achieved CR, CRi, CRp with first-line treatment and had hematologic relapse; patients who experienced hematologic relapse after second or later line of treatment or who received salvage therapy for refractory disease excluded<br>- Patients requiring concomitant drugs that were strong inducers of cytochrome P450 (CYP) 3A excluded<br>- Patients who required treatment with concomitant drugs that are strong inducers or inhibitors of P-glycoprotein or substrates of multidrug and toxin extrusion protein 1 (MATE1) were excluded with the exception of drugs considered essential for the care of the patient<br>- Patients with active GVHD or on treatment with corticosteroids for GVHD were excluded<br><br>Concomitant medications:<br>- Medications language was modified as follows: a clarification of the parameters for absolute blast count was added; the hydroxyurea daily dose limit was removed; a clarification that intrathecal chemotherapy should have been prophylactic was added; cranial radiation was permitted as a treatment for AML; clarification that participation in another interventional study while on treatment was prohibited was added; and the list of CYP3A inducers was revised in appendix<br><br>Treatment discontinuation:<br>- Lack of efficacy was added as a treatment discontinuation criterion for patients who received low-dose cytarabine, azacitidine or; use of hydroxyurea was clarified as not a reason for treatment discontinuation<br><br>Additional modifications:<br>- Monitoring for hyperuricemia added<br>- PRO measurements of BFI removed from 30-day follow-up assessments<br>- Requirement for duration of 48-hours of a grade 3 AE to interrupt dosing removed to state that treatment with gilteritinib was interrupted for any related grade 3 AE<br>- Definition of transfusion independence changed from 4 weeks to 1 week without RBC transfusion and 1 week without platelet transfusion<br>- Baseline bone marrow aspiration, blood platelet count, and white blood cell count removed from subgroup analysis<br><br>No patients were randomized under this amendment. |
| Amendment 2<br>(August 13th, 2015) | Exclusion criteria: |

| Amendment Number/Date | Substantial amendment summary |
|---|---|
| | - Patients with QTcF >450 ms at screening based on central reading excluded<br>- Patients with long QT syndrome at screening excluded<br>- Patients with hypokalemia and hypomagnesemia (values below the LLN) at screening excluded<br><br>Additional modifications:<br>- HSCT removed as discontinuation criteria<br>- 12-lead ECG and PK sampling added to occur on day 8 ± 1 predose<br>- Mean QTcF of triplicate ECG tracings based on central reading clarified to be used for all treatment decisions<br>- Dose modification criterion added to consider reducing dose of gilteritinib if mean QTcF from day 1 to 8 increased >30 ms, which was confirmed on day 9 without any other aetiology<br><br>Thirty-six patients were randomized under this amendment. |
| Amendment 3<br>(October 8th, 2015)<br><br>Country-specific<br>(Korea) | Entry criteria:<br>- FLT3 mutation types modified to be described as ITD alone or ITD with concurrent kinase domain<br><br>Eight patients were randomized under this amendment. |
| Amendment 4<br>(December 9th, 2015) | Modifications included:<br>- Clarification that if bone cellularity was between 5-20%, the investigator should have determined whether a patient should have received another treatment cycle<br>- Description of acceptable contraception methods changed for females and for males and their partners<br>- Mean triplicate QTcF >450 ms clarified to be cause for exclusion and terminology for long QT syndrome modified; guideline for gilteritinib dose interruption and reduction if patient had mean triplicate QTcF >500 ms added; precaution regarding use of gilteritinib with concomitant medication known to prolong QT or QTc was added<br>- Discontinuation criteria that patients who received MEC or FLAG-IDA who had no response or PD should have been discontinued if it occurred following cycle 1<br><br>One hundred thirty-six patients were randomized under this amendment. |
| Amendment 5<br>(March 31st, 2016)<br><br>Country-specific<br>(Korea) | Entry criteria:<br>- Highly effective contraception examples for females and males and their partners were clarified.<br><br>Eleven patients were randomized under this amendment. |
| Amendment 6<br>(June 22nd, 2016)<br><br>Country-specific<br>(France) | Entry criteria:<br>- Language to clarify local requirements for consent where patients must have consented personally, and patients too young or incapable of personal consent were excluded, and patients must have participated in a national social security scheme |

| Amendment Number/Date | Substantial amendment summary |
|---|---|
| | Seven patients were randomized under this amendment. |
| Amendment 7 (August 8th, 2016) | Entry criteria:<br>- Midostaurin included as a permitted prior treatment<br>- Patients with disallowed FLT3 mutation types excluded; patients included on basis of local lab testing for allowed FLT3 mutation types<br><br>Assessments and schedule of assessments:<br>- Long-term follow-up clarified to be every 3 months for up to 3 year from patient's EOT<br>- Disease assessment from bone marrow samples clarified to only be required for MEC and FLAG-IDA per institutional guidelines on cycle 1 day 15 or later<br>- Lab tests administered were updated with the addition of thyroxine, thyroid-stimulating hormone and activated partial thromboplastin time<br><br>Treatment discontinuation:<br>- Patients eligible to continue treatment until discontinuation criterion was met of gilteritinib gained marketing authorization and became commercially available<br><br>Concomitant medications:<br>- Exclusion of MATE1 substrates as a concomitant medication restriction was deleted<br>- Donor lymphocyte infusion as an allowed concomitant treatment for AML was included<br><br>Statistical analyses:<br>- HR in the interim analysis included<br>- Gilteritinib clinical and PK data from 02-Feb-2015 cut-off updated with data from the 31-Oct-2015 cut-off<br><br>No patients were randomized under this amendment. |
| Amendment 8 (September 20th, 2017) | Statistical analyses:<br>- Coprimary object of interim analysis 1 updated and response definitions were added<br>- Secondary objectives, endpoints, and associated statistical analyses were updated<br><br>Additional modifications:<br>- Additional language to describe the collection of concomitant medications and AEs for patients who underwent HSCT<br><br>Thirty-two patients were randomized under this amendment. |
| **Abbreviations:**<br>**AE** = adverse event; **AML** = acute myeloid leukemia; **BFI** = brief fatigue inventory; **CR** = complete remission;; **CRi** = complete remission with incomplete hematologic recovery; **CRp** = complete response with incomplete platelet recovery; **ECG** = electrocardiogram; **EOT** = end of | |

| Amendment Number/Date | Substantial amendment summary |
|---|---|
| treatment; **FLAG-IDA** = Fludarabine, cytarabine and granulocyte colony-stimulating factor with idarubicin; **FLT3** = FMS-like tyrosine kinase; **GVHD** = graft versus host disease; **HR** = hazard ratio; **HSCT** = hematopoietic stem cell transplant; **ITD** = Internal tandem duplication; **LLN** = lower limit of normal; **MEC** = Mitoxantrone, etoposide and intermediate-dose cytarabine; **ms** = milliseconds; **PD** = progressive disease; **PK** = pharmacokinetic; **PRO** = patient reported outcomes; **RBC** = red blood cell<br><br>**Sources:**<br>EPAR, EMA 2019[3]<br>Perl et al., 2019[2] | |

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b) ***Populations***

***Demographic characteristics***

Demographic characteristics are summarized in Table 6.7. A total of 371 patients were randomly assigned to receive gilteritinib (n=247) or salvage chemotherapy (n=124). Overall, the median age was 62.0 years (range: 19.0, 85.0) with 58.2% (n=216) <65 years of age, 54.2% (n=201) were female, and 59.3% (n=220) of participants reported White race and 27.5% (n=102) reported Asian race. Most patients had a baseline ECOG PS of 0, of which 35% (n=130) had an ECOG PS of 0 and 48.8% (n=181) had an ECOG PS of 1.[3,53] There was a slightly higher proportion of patients from North America randomized to the gilteritinib arm (n=114; 46.2%) compared to the salvage chemotherapy arm (n=52; 41.9%), whereas there was a higher proportion of patients from Europe randomized to the salvage chemotherapy arm (n=43; 34.7%) compared to the gilteritinib arm (n=68; 27.5%). Patients from Asia were balanced between treatment arms, representing about a quarter of the overall study population (n=94; 25.3%).[3]

**Table 6.7. Demographic characteristics in the ADMIRAL trial, ITT population (n=371)**[3]

| Parameter Category/Statistic | Gilteritinib 120 mg (n = 247) | Chemotherapy (n = 124) | Total (n = 371) |
|---|---|---|---|
| **Sex, n (%)** | | | |
| Female | 131 (53.0) | 70 (56.5) | 201 (54.2) |
| Male | 116 (47.0) | 54 (43.5) | 170 (45.8) |
| **Ethnicity, n (%)** | | | |
| Not Hispanic or Latino | 221 (93.6) | 116 (96.7) | 337 (94.7) |
| Hispanic or Latino | 12 (5.1) | 2 (1.7) | 14 (3.9) |
| Unknown | 3 (1.3) | 2 (1.7) | 5 (1.4) |
| Missing | 11 | 4 | 15 |
| **Race, n (%)** | | | |
| White (Caucasian) | 145 (60.9) | 75 (62.5) | 220 (59.3) |
| Asian | 69 (29.0) | 33 (27.5) | 102 (27.5) |
| Black or African American | 14 (5.9) | 7 (5.8) | 21 (5.7) |
| Native Hawaiian or Other Pacific Islander | 1 (0.4) | 0 | 1 (0.3) |
| Unknown | 4 (1.7) | 4 (3.3) | 13 (3.5) |
| Other | 5 (2.1) | 1 (0.8) | 15 (4) |
| Missing | 9 | 4 | 13 |
| **Age (Years)** | | | |
| Mean (SD) | 59.0 (14.6) | 57.6 (14.8) | 58.5 (14.7) |
| Median (min, max) | 62.0 (20, 84) | 61.5 (19, 85) | 62.0 (19, 85) |
| **Age Group (Years), n (%)** | | | |
| < 65 | 141 (57.1) | 75 (60.5) | 216 (58.2) |
| ≥ 65 | 106 (42.9) | 49 (39.5) | 155 (41.8) |
| **Region, n (%)** | | | |
| North America | 114 (46.2) | 52 (41.9) | 166 (44.7) |
| Europe (Including Turkey, Israel) | 68 (27.5) | 43 (34.7) | 111 (29.9) |
| Asia | 65 (26.3) | 29 (23.4) | 94 (25.3) |
| **Baseline ECOG, n (%)** | | | |
| 0-1 | 206 (83.4) | 105 (84.7) | 311 (83.8) |
| ≥ 2 | 41 (16.6) | 19 (15.3) | 60 (16.2) |
| **Weight (kg)** | | | |
| n | 243 | 124 | 367 |
| Mean (SD) | 72.79 (20.47) | 69.91 (19.73) | 71.82 (20.25) |
| Median (min, max) | 71.00 (39.0, 157.1) | 67.00 (36.5, 157.9) | 70.00 (36.5, 157.9) |
| **Height (cm)** | | | |
| n | 234 | 123 | 357 |
| Mean (SD) | 167.25 (10.31) | 166.39 (10.63) | 166.95 (10.41) |
| Median (min, max) | 167.00 (140.0, 193.0) | 166.00 (137.5, 191.0) | 166.50 (137.5, 193.0) |
| *Table continued on next page* | | | |
| **FLT3 Mutation Status by Central Testing by FLT3 CDx, n (%)** | | | |
| FLT3-ITD alone | 215 (87.0) | 113 (91.1) | 328 (88.4) |
| FLT3-TKD alone | 21 (8.5) | 10 (8.1) | 31 (8.4) |
| FLT3-ITD and FLT3-TKD | 7 (2.8) | 0 | 7 (1.9) |
| Others (negative) | 4 (1.6) | 1 (0.8) | 5 (1.3) |
| **Prior Use of FLT3 Inhibitor, n (%)†** | | | |
| No | 215 (87.0) | 110 (88.7) | 325 (87.6) |
| Yes | 32 (13.0) | 14 (11.3) | 46 (12.4) |
| **Cytogenetic Risk Status, n (%)** | | | |
| Intermediate | 182 (73.7) | 89 (71.8) | 271 (73.0) |
| Unfavorable | 26 (10.5) | 11 (8.9) | 37 (10.0) |
| Favorable | 4 (1.6) | 1 (0.8) | 5 (1.3) |
| Other‡ | 35 (14.2) | 23 (18.5) | 58 (15.6) |

† Prior use of FLT3 inhibitor is defined as 'Yes' if patients received prior AML therapy of midostaurin, sorafenib or quizartinib; otherwise, prior use of FLT3 inhibitor is assigned as 'No'; ‡ The category of "Other" includes those with cytogenetic risk status that cannot be categorized as favorable, intermediate or unfavorable.

**Source:** EPAR, EMA 2019[3]

***Disease characteristics***

Baseline disease characteristics are summarized in Table 6.7 and 6.8. Number of patients with untreated relapsed AML and primary refractory AML (without HSCT) was also balanced between treatment arms, with the study including in total 225 (60.6%) and 146 (39.4%) patients in each category, respectively. Few patients had 2 relapses, including only 4 (1.6%) patients in the gilteritinib arm and 3 (2.4%) patients in the salvage chemotherapy arm. Overall, the median duration of disease was 5.60 months (range: 0.5, 65.1).

There were a slightly higher proportion of patients in the salvage chemotherapy arm with FLT3-ITD mutation alone (n=113, 91.1%) compared to the gilteritinib arm (n=215, 87.0%), and no patients with both FLT3-ITD and FLT3-TKD mutations in the salvage chemotherapy arm, whereas there were 7 (2.8%) patients with both mutations in the gilteritinib arm. There were a similar proportion of patients with only FLT3-TKD mutations only in both treatment arms, representing 31 (8.4%) patients in the overall trial population.

Most patients had intermediate (normal) cytogenetic risk (n=271, 73.0%) in the trial overall. A similar proportion of patients in both treatment arms had favourable (overall: n=5, 1.3%) or unfavourable (overall: n=37, 10.0%) cytogenetic risk. A slightly higher proportion of patients in the salvage chemotherapy arm had unknown risk (n=23, 18.5%) compared to the salvage chemotherapy arm (overall: n=35; 14.2%).

There was a higher proportion of patients in the gilteritinib arm with an antecedent hematological disorder (n=41, 16.6%) compared to the salvage chemotherapy arm (n=11, 8.9%), with most having myelodysplastic syndrome (MDS) as the hematological disorder in the gilteritinib (n=34, 13.8%) and salvage chemotherapy (n=8, 6.5%) arms.

As per the WHO classification, 32.3% (n=120) of patients had AML with mutated NPM1, 9.2% had acute monoblastic/monocytic leukemia, and 7.0% had minimally differentiated AML. A higher proportion of patients in gilteritinib arm compared to the salvage chemotherapy had AML with myelodysplasia-related changes (13.4% versus 8.1%, respectively), and AML with maturation (12.1% versus 7.3%, respectively). A higher proportion of patients in the salvage chemotherapy arm compared to the gilteritinib arm had AML without maturation (18.5% versus 13.8%, respectively).

Patients with rapidly progressing disease was balanced between treatment arms, affecting 168 patients in total (n=168, 45.3%). A total of 60.4% (n=224) were preselected for high-intensity chemotherapy and 39.6% (n=147) were preselected for low-intensity chemotherapy.[3]

**Table 6.8. Baseline disease characteristics in the ADMIRAL trial, ITT population (n=371)[3]**

| Parameter<br>Category/Statistic | Gilteritinib 120 mg<br>(n = 247) | Chemotherapy<br>(n = 124) | Total<br>(n = 371) |
|---|---|---|---|
| **Duration of Disease (months)** | | | |
| Mean (SD) | 7.37 (7.21) | 8.07 (9.67) | 7.60 (8.11) |
| Median (min, max) | 5.80 (0.6, 65.1) | 5.30 (0.5, 52.0) | 5.60 (0.5, 65.1) |
| **Antecedent Hematological Disorder, n (%)** | | | |
| No | 206 (83.4) | 113 (91.1) | 319 (86.0) |
| Yes | 41 (16.6) | 11 (8.9) | 52 (14.0) |
| **Type of Hematological Disorder, n (%)†** | | | |
| MDS | 34 (13.8) | 8 (6.5) | 42 (11.3) |
| Other | 7 (2.8) | 3 (2.4) | 10 (2.7) |
| **Central Nervous System Leukemia, n (%)** | | | |
| No | 244 (98.8) | 122 (98.4) | 366 (98.7) |
| Yes | 3 (1.2) | 2 (1.6) | 5 (1.3) |
| **Rapidly Progressing Disease, n (%)** | | | |
| No | 133 (53.8) | 69 (55.6) | 202 (54.4) |
| Yes | 113 (45.7) | 55 (44.4) | 168 (45.3) |
| **Other Disease Characteristics, n (%)** | | | |
| Untreated relapse AML | 151 (61.1) | 75 (60.5) | 226 (60.9) |
| Primary refractory AML | 96 (38.9) | 49 (39.5) | 145 (39.1) |
| Median number of relapses (range) | 1 (0, 2) | 1 (0, 2) | 1 (0, 2) |
| Number of relapses, n (%) | | | |
| 0 | 96 (38.9) | 49 (39.5) | 145 (39.1) |
| 1 | 147 (59.5) | 72 (58.1) | 219 (59.0) |
| 2 | 4 (1.6) | 3 (2.4) | 7 (1.9) |
| > 2 | 0 | 0 | 0 |
| **WHO Classification, n (%)** | | | |
| AML with recurrent genetic abnormalities | | | |
| AML with mutated NPM1 | 83 (33.6) | 37 (29.8) | 120 (32.3) |
| AML with myelodysplasia-related changes | 33 (13.4) | 10 (8.1) | 43 (11.6) |

| | | | |
|---|---|---|---|
| AML with t(8;21)(q22;q22), RUNX1-RUNX1T1 | 5 (2.0) | 5 (4.0) | 10 (2.7) |
| AML with t(6;9)(q23;q34); DEK-NUP214 | 5 (2.0) | 3 (2.4) | 8 (2.2) |
| AML with mutated CEBPA | 4 (1.6) | 1 (0.8) | 5 (1.3) |
| AML with t(9;11)(q22;q23); MLLT3-MLL | 2 (0.8) | 2 (1.6) | 4 (1.1) |
| AML with inv(3)(q21q26.2) or t(3;3)q(21;q26.2); RPN1-EVI1 | 1 (0.4) | 0 | 1 (0.3) |
| AML (megakaryoblastic) with t(1;22) (p13;q13); RBM15-MKL1 | 1 (0.4) | 0 | 1 (0.3) |
| AML not otherwise categorized | | | |
| AML without maturation | 34 (13.8) | 23 (18.5) | 57 (15.4) |
| AML with maturation | 30 (12.1) | 9 (7.3) | 39 (10.5) |
| Acute myelomonocytic leukemia | 20 (8.1) | 10 (8.1) | 30 (8.1) |
| Acute monoblastic/monocytic leukemia | 20 (8.1) | 14 (11.3) | 34 (9.2) |
| AML minimally differentiated | 16 (6.5) | 10 (8.1) | 26 (7.0) |
| Acute erythroid leukemia | | | |
| Erythroleukemia, erythroid/myeloid | 1 (0.4) | 2 (1.6) | 3 (0.8) |
| Myeloid Sarcoma | 0 | 1 (0.8) | 1 (0.3) |
| **FAB Classification Subtype, n (%)** | | | |
| Unknown | 74 (30.0) | 25 (20.2) | 99 (26.7) |
| M1: Acute myeloblastic leukemia, without maturation | 45 (18.2) | 35 (28.2) | 80 (21.6) |
| M2: AML with differentiation | 51 (20.6) | 17 (13.7) | 68 (18.3) |
| M4: Acute myelomonocytic leukemia | 33 (13.4) | 21 (16.9) | 54 (14.6) |
| M5: Acute monoblastic leukemia | 27 (10.9) | 14 (11.3) | 41 (11.1) |
| M0: Minimally differentiated acute myeloblastic leukemia | 15 (6.1) | 9 (7.3) | 24 (6.5) |
| M6: Acute erythroid leukemia | 2 (0.8) | 3 (2.4) | 5 (1.3) |
| **Risk Status With Specific Cytogenetic Patterns, n (%)** | | | |
| Intermediate: Normal | 163 (66.0) | 78 (62.9) | 241 (65.0) |
| Unknown Risk | 32 (13.0) | 17 (13.7) | 49 (13.2) |
| Unfavorable: Complex | 18 (7.3) | 6 (4.8) | 24 (6.5) |
| Intermediate: + 8 | 11 (4.5) | 9 (7.3) | 20 (5.4) |
| Other Risk | 8 (3.2) | 8 6.5) | 16 (4.3) |
| Favorable: t(8;21) | 3 (1.2) | 2 (1.6) | 5 (1.3) |
| Unfavorable: del7q | 4 (1.6) | 0 | 4 (1.1) |
| Unfavorable: - 7 | 3 (1.2) | 1 (0.8) | 4 (1.1) |
| Intermediate: - y | 3 (1.2) | 0 | 3 (0.8) |
| Unfavorable: del5q | 2 (0.8) | 1 (0.8) | 3 (0.8) |
| Intermediate: + 6 | 1 (0.4) | 1 (0.8) | 2 (0.5) |
| Unfavorable: - 5 | 1 (0.4) | 0 | 1 (0.3) |
| Favorable: inv(16) | 1 (0.4) | 0 | 1 (0.3) |
| Favorable: t(16;16) | 0 | 1 (0.8) | 1 (0.3) |

†Only for patients who had antecedent hematological disorder.

| Parameter<br>Category | Gilteritinib 120 mg<br>(n = 247)<br>n (%) | Chemotherapy<br>(n = 124)<br>n (%) | Total<br>(n = 371)<br>n (%) |
|---|---|---|---|
| **Response to First-line Therapy** | | | |
| Primary refractory without HSCT | 98 (39.7) | 48 (38.7) | 146 (39.4) |
| Relapse within 6 months after CRc and no HSCT | 67 (27.1) | 34 (27.4) | 101 (27.2) |
| Relapse after 6 months after CRc and no HSCT | 34 (13.8) | 17 (13.7) | 51 (13.7) |
| Relapse within 6 months after allogeneic HSCT | 31 (12.6) | 17 (13.7) | 48 (12.9) |
| Relapse after 6 months after allogeneic HSCT | 17 (6.9) | 8 (6.5) | 25 (6.7) |
| **Preselected Salvage Chemotherapy** | | | |
| High-intensity chemotherapy | 149 (60.3) | 75 (60.5) | 224 (60.4) |
| Low-intensity chemotherapy | 98 (39.7) | 49 (39.5) | 147 (39.6) |
| **Response to First-Line Therapy, Preselected Salvage Chemotherapy** | | | |
| Primary refractory without HSCT, high-intensity chemotherapy | 57 (23.1) | 28 (22.6) | 85 (22.9) |
| Primary refractory without HSCT, low-intensity chemotherapy | 41 (16.6) | 20 (16.1) | 61 (16.4) |
| Relapse within 6 months after CRc and no HSCT, high-intensity chemotherapy | 40 (16.2) | 21 (16.9) | 61 (16.4) |
| Relapse within 6 months after CRc and no HSCT, low-intensity chemotherapy | 27 (10.9) | 13 (10.5) | 40 (10.8) |
| Relapse after 6 months after CRc and no HSCT, high intensity chemotherapy | 23 (9.3) | 11 (8.9) | 34 (9.2) |
| Relapse within 6 months after allogeneic HSCT, low-intensity chemotherapy | 16 (6.5) | 9 (7.3) | 25 (6.7) |
| Relapse within 6 months after allogeneic HSCT, high-intensity chemotherapy | 15 (6.1) | 8 (6.5) | 23 (6.2) |
| Relapse after 6 months after allogeneic HSCT, high-intensity chemotherapy | 14 (5.7) | 7 (5.6) | 21 (5.7) |
| Relapse after 6 months after CRc and no HSCT, low-intensity chemotherapy | 11 (4.5) | 6 (4.8) | 17 (4.6) |
| Relapse after 6 months after allogeneic HSCT, low-intensity chemotherapy | 3 (1.2) | 1 (0.8) | 4 (1.1) |

**Source:** EPAR, EMA 2019[3]

***Previous therapies***

Prior therapies included known and investigational anticancer agents. Prior AML treatment information is summarized in Table 6.9. All patients received a prior chemotherapy for AML, and all patients received induction therapy. A similar proportion of patients received maintenance therapy in the gilteritinib (n=20, 8.1%) and salvage chemotherapy arms (n=13, 10.5%), however, a higher proportion of patients in the gilteritinib arm received consolidation therapy (n=111, 44.9%) compared to the salvage chemotherapy arm (n=49, 39.5%).[5]

Overall, most patients had a prior therapy with an anthracycline-containing induction therapy (n=311, 83.8%), with 46 (12.4%) patients who received a prior FLT3 inhibitor (midostaurin, sorafenib, or quizartinib) and 74 (19.9%) that had prior

HSCT.[2] Of FLT3 inhibitors, a total of 21 (5.7%) patients received midostaurin, 24 (6.5%) patients received sorafenib, and 1 (0.3%) patient received quizartinib in the overall trial.[2,5] Of those who received midostaurin, 4.4% had relapsed, and 7.5% were refractory.[54] Just over half of patients (n=199, 53.6%) achieved CR with prior therapy, with only 22 (5.9%) patients that achieved CRi and 4 (1.1%) patients with CRp. The median duration of response (among patients that achieved CR, CRi, or CRp) was slightly longer in the gilteritinib arm (median: 182 days; range: 20, 1826) compared to the salvage chemotherapy arm (median: 174.5 days; range: 10, 1491).[5]

The most common prior regimen was standard dose cytarabine + idarubicin, and a higher proportion of patients in the salvage chemotherapy arm (n=52; 41.9%) received this regimen compared to the gilteritinib arm (n=94; 38.1%). Standard dose cytarabine + daunorubicin was also a commonly used prior regimen and was used in a higher proportion of patients in the gilteritinib arm (n=69, 27.9%) compared to the salvage chemotherapy arm (n=29; 22.6%). High-dose cytarabine was also commonly used and balanced between treatment arms, and received by a total of 100 (27.0%) patients overall. Other prior regimens included azacitidine (overall: n=24; 6.5%), decitabine (n=20, 5.4%), high-dose cytarabine and daunorubicin (n=13, 3.5%), and low-dose cytarabine (n=13, 3.5%).[5]

**Table 6.9. Prior AML Therapies, ITT population[5]**

| Characteristic<br>Category/Statistic | Gilteritinib (n = 247) | Chemotherapy (n = 124) | Total (n = 371) |
|---|---|---|---|
| **Prior AML Chemotherapy, n (%)** | | | |
| Yes | 247 (100) | 124 (100) | 371 (100) |
| No | 0 | 0 | 0 |
| **Response to First-Line Therapy per CRF, n (%)** | | | |
| Primary refractory without HSCT | 96 (38.9) | 49 (39.5) | 145 (39.1) |
| Relapse within 6 months after CRc and no HSCT | 67 (27.1) | 32 (25.8) | 99 (26.7) |
| Relapse after 6 months after CRc and no HSCT | 37 (15.0) | 18 (14.5) | 55 (14.8) |
| Relapse within 6 months after allogeneic HSCT | 30 (12.1) | 17 (13.7) | 47 (12.7) |
| Relapse after 6 months after allogeneic HSCT | 17 (6.9) | 8 (6.5) | 25 (6.7) |
| **Type of Treatment, n (%)** | | | |
| Induction | 247 (100) | 124 (100) | 371 (100) |
| Consolidation | 111 (44.9) | 49 (39.5) | 160 (43.1) |
| Maintenance | 20 (8.1) | 13 (10.5) | 33 (8.9) |
| **Regimen, n (%)** | | | |
| Other | 107 (43.3) | 55 (44.4) | 162 (43.7) |
| Standard dose cytarabine + idarubicin | 94 (38.1) | 52 (41.9) | 146 (39.4) |
| High-dose cytarabine | 64 (25.9) | 36 (29.0) | 100 (27.0) |
| Standard dose cytarabine + daunorubicin | 69 (27.9) | 28 (22.6) | 97 (26.1) |
| Azacitidine | 13 (5.3) | 11 (8.9) | 24 (6.5) |
| Decitabine | 16 (6.5) | 4 (3.2) | 20 (5.4) |
| High-dose cytarabine + daunorubicin | 4 (1.6) | 9 (7.3) | 13 (3.5) |
| Low-dose cytarabine | 9 (3.6) | 4 (3.2) | 13 (3.5) |
| High-dose cytarabine + idarubicin | 11 (4.5) | 1 (0.8) | 12 (3.2) |
| Standard dose cytarabine + mitoxantrone | 11 (4.5) | 0 | 11 (3.0) |
| Standard dose cytarabine + daunorubicin + cladribine | 1 (0.4) | 3 (2.4) | 4 (1.1) |
| **Prior Use of FLT3 Inhibitor** | | | |
| No | 215 (87.0) | 110 (88.7) | 325 (87.6) |
| Yes† | 32 (13.0) | 14 (11.3) | 46 (12.4) |
| **Prior Use of FLT3 Inhibitor** | | | |
| Sorafenib | 18 (7.3) | 6 (4.8) | 24 (6.5) |
| Midostaurin | 13 (5.3) | 8 (6.5) | 21 (5.7) |
| Quizartinib | 1 (0.4) | 0 | 1 (0.3) |
| **Best Response to Treatment, n (%)‡** | | | |
| CR | 130 (52.6) | 69 (55.6) | 199 (53.6) |
| CRp | 3 (1.2) | 1 (0.8) | 4 (1.1) |
| CRi | 18 (7.3) | 4 (3.2) | 22 (5.9) |
| Treatment failure | 96 (38.9) | 50 (40.3) | 146 (39.4) |
| **Duration of Response (days)§** | | | |
| n | 151 | 74 | 225 |
| Mean (SD) | 241.4 (222.0) | 270.0 (329.7) | 250.8 (261.9) |
| Median (min, max) | 182.0 (20, 1826) | 174.5 (10, 1491) | 182.0 (10, 1826) |

AML: acute myeloid leukemia; CR: complete remission; CRc: composite complete remission; CRF: case report form; CRi: complete remission with incomplete hematologic recovery; CRp: complete remission with incomplete platelet recovery; FLT3: FMS-like tyrosine kinase 3; HSCT: hematopoietic stem cell transplant; max: maximum; min: minimum.

† If a patient had multiple uses of prior FLT3 inhibitors, the patient was summarized under each type of the FLT3 inhibitor.

‡ If a patient had multiple prior AML therapies, the patient was summarized under the best response.

§ For patients with response of CR, CRp, CRi. If a patient had multiple prior AML therapies with response of CR, CRp, CRi reported, the maximum duration was presented which reflected the duration of response of the patient.

**Source:** Clinical Study Report, Astellas Pharma 2019[5]

### *c) Interventions*

As per interactive response technology, there were 224 (60.4%) patients preselected for high-intensity chemotherapy and 147 (39.6%) preselected for low-intensity chemotherapy. A total of 355 patients were treated, 246 in the gilteritinib arm and 109 in the salvage chemotherapy arm. Patients assigned to receive gilteritinib received a 120 mg dose orally once a day in continuous 28 day cycles, and could be escalated to 200 mg if patients did not experience a CR, CRp, or CRi after cycle 1.[2] This included patients who were dose escalated well beyond cycle 1, who at the investigator's decision, were considered to benefit from an increase in dose to sustain or achieve a CRc.[54] Gilteritinib could be dose reduced due to toxicities in a step-wise manner initially to 80 mg, and if required to 40 mg if the patient had already experienced clinical benefit. Salvage chemotherapy regimens are described below:

Low intensity chemotherapy: 28-day continuous cycles

- LoDAC: 20 mg cytarabine administered twice daily by subcutaneous (SC) or intravenous (IV) injection for 10 days
- Azacitidine: 75 mg/m$^2$ administered once daily by SC or IV injection for 7 days
  - Institutional guidelines were followed if dose reduction was needed after cycle 1[2]

High intensity chemotherapy: 1-2 cycles (28-day cycles; 2$^{nd}$ cycle administered as per investigator-assessment)

- MEC: mitoxantrone 8 mg/m$^2$ per day by IV for 5 days (days 1 through 5); etoposide 100 mg/m$^2$ per day by IV for 5 days (days 1 through 5); cytarabine 1000 mg/m$^2$ per day by IV for 5 days (days 1 through 5)
- FLAG-IDA: granulocyte colony stimulating factor (G-CSF) 300 µg/m$^2$ per day by IV/SC for 5 days, days 1 through 5 (additional G-CSF recommended 7 days after completion of chemotherapy until absolute neutrophil count [ANC] > 0.5 x 10$^9$/L); fludarabine 30 mg/m$^2$ per day by IV for 5 days (days 2 through 6); cytarabine 2000 mg/m$^2$ per day by IV for 5 days (days 2 through 6); idarubicin 10 mg/m$^2$ per day by IV for 3 days (days 2 through 4)[2]

In the salvage chemotherapy arm, a total of 28 (25.7%) patients received MEC, 40 (36.7%) patients received FLAG-IDA, 16 (14.7%) patients received LoDAC, and 25 (22.9%) received azacitidine.[2]

The median duration of exposure to gilteritinib was 18 weeks (IQR: 9,34) and to salvage chemotherapy was 4 weeks (IQR: 4,4). The median number of cycles of gilteritinib therapy received was 5 (range: 1, 33). In the salvage chemotherapy arm, most patients (n=64; 94.1%) who received high-intensity chemotherapy received 1 treatment cycle. The median duration of treatment in the low-intensity chemotherapy was 4 weeks (LoDAC: 4 weeks [range: 2, 31]; azacitidine: 4 weeks [range: 1, 26]).[2] The median relative dose intensity was 100% (IQR: 39, 100) in the gilteritinib arm and was 99.6% (IQR: 10, 322) in the salvage chemotherapy arm.[3] Study drug exposure is summarized in Table 6.10.

**Table 6.10. Summary of study drug exposure in the ADMIRAL trial, safety analysis set (n=355)[3]**

| | Integrated Data† | | Study 2215-CL-0301 | | |
|---|---|---|---|---|---|
| | Gilteritinib 120 mg | Gilteritinib Total | Gilteritinib 120 mg | | Chemo |
| | | | Overall | No Dose Escalation | |
| | (N = 319) | (N = 522) | (N = 246) | (N = 168) | (N = 109) |
| **Duration of Exposure Days‡** | | | | | |
| n | 319 | 522 | 246 | 168 | 109 |
| Mean (SD) | 181.2 (199.8) | 156.1 (190.5) | 180.7 (168.5) | 186.2 (183.1) | 39.9 (37.0) |
| Median (Min, Max) | 111.0 (4, 1320) | 88.0 (3, 1320) | 126.0 (4, 885) | 116.0 (4, 885) | 28.0 (5, 217) |
| **Duration of Exposure Days‡, n (%)** | | | | | |
| ≤ 5 | 1 (0.3) | 6 (1.1) | 1 (0.4) | 1 (0.6) | 1 (0.9) |
| ≥ 6 to < 28 | 19 (6.0) | 60 (11.5) | 10 (4.1) | 10 (6.0) | 10 (9.2) |
| ≥ 28 to < 84 | 99 (31.0) | 179 (34.3) | 75 (30.5) | 55 (32.7) | 88 (80.7) |
| ≥ 84 to < 168 | 87 (27.3) | 131 (25.1) | 68 (27.6) | 38 (22.6) | 6 (5.5) |
| ≥ 168 | 113 (35.4) | 146 (28.0) | 92 (37.4) | 64 (38.1) | 4 (3.7) |
| **Number of Dosing Days§** | | | | | |
| n | 319 | 521 | 246 | 168 | 109 |
| Mean (SD) | 173.6 (192.2) | 146.9 (180.0) | 172.7 (162.7) | 177.1 (176.2) | 9.5 (10.3) |
| Median (Min, Max) | 106.0 (4, 1313) | 85.0 (3, 1313) | 114.0 (4, 885) | 107.5 (4, 885) | 6.0 (1, 70) |
| **Dosing, n (%)** | | | | | |
| Increases | 113 (35.4) | 171 (32.8) | 78 (31.7) | 0 | 8 (7.3) |
| Decreases | 82 (25.7) | 103 (19.7) | 75 (30.5) | 58 (34.5) | 9 (8.3) |
| Interruptions | 151 (47.3) | 224 (42.9) | 122 (49.6) | 84 (50.0) | 5 (4.6) |
| **Cumulative Dose (mg)** | | | | | |
| n | 319 | 521 | 246 | 168 | NA |
| Mean (SD) | 21911.3 (25954.3) | 20116.4 (25506.1) | 20985.2 (19682.6) | 19138.8 (19572.1) | -- |
| Median (Min, Max) | 13640.0 (480, 259800) | 11880.0 (60, 259800) | 13980.0 (480, 106200) | 11140.0 (480, 106200) | -- |
| **Average Daily Dose (mg/day)¶** | | | | | |
| n | 319 | 521 | 246 | 168 | NA |
| Mean (SD) | 127.2 (28.1) | 143.6 (61.4) | 123.9 (25.8) | 110.6 (15.2) | -- |
| Median (Min, Max) | 120.0 (50, 290) | 120.0 (20, 402) | 120.0 (50, 192) | 120.0 (50, 120) | -- |
| **Dose Intensity (mg/day)††** | | | | | |
| n | 319 | 521 | 246 | 168 | NA |
| Mean (SD) | 122.7 (30.1) | 137.1 (60.4) | 119.1 (28.2) | 105.8 (19.3) | -- |
| Median (Min, Max) | 120.0 (46, 273) | 120.0 (13, 400) | 120.0 (46, 192) | 120.0 (46, 120) | -- |
| **Relative Dose Intensity (%)‡‡** | | | | | |
| n | 319 | 521 | 246 | 168 | 109 |
| Mean (SD) | 102.2 (25.1) | 102.1 (26.4) | 99.2 (23.5) | 88.2 (16.1) | 98.2 (35.1) |
| Median (Min, Max) | 100.0 (39, 227) | 100.0 (23, 292) | 100.0 (39, 160) | 100.0 (39, 100) | 99.6 (10, 322) |

†Integrated data includes patients in Studies 2215-CL-0101, 2215-CL-0102 and 2215-CL-0301 who received at least 1 dose of gilteritinib 120 mg (gilteritinib 120 mg group) or any dose of gilteritinib (gilteritinib total group; doses ranging from gilteritinib 20 to 450 mg); ‡Defined as (last date of exposure) – (first dose date) + 1 – (on-study HSCT period for patients who underwent on-study HSCT);§Defined as the number of days with nonzero dosing; ¶Defined as (cumulative dose) / (number of dosing days); ††Defined as (cumulative dose/ duration of exposure) for gilteritinib; ‡‡Defined as (dose intensity/planned dose intensity) *100%

**Source:** EPAR, EMA 2019[3]

***Concomitant therapies***

The following restrictions applied:

- Treatment with strong inducers of CYP3A was prohibited
- Strong inhibitors or inducers of P-glycoprotein (P-gp) or drugs that target serotonin 5HT1R or 5HT2BR or sigma nonspecific receptor were to be avoided
- Strong inhibitors of CYP3A were to be avoided unless standard of care to prevent or treatment infections with extra monitoring for AEs
- Precaution was to be exercised using concomitant drugs known to prolong QT or QTc interval; or drugs that are substrates of breast cancer resistance protein

In both the gilteritinib and salvage chemotherapy arm, any other treatments of AML were prohibited with the exception of hydroxyurea daily for up to 2 weeks to keep the absolute blast count below 50 x $10^9$/L and prophylactic intrathecal chemotherapy, cranial radiation, and donor lymphocyte infusion as part of the HSCT treatment plan.

Participants who had a donor identified and achieved a response could undergo HSCT without leaving the trial, however gilteritinib had to be stopped and a pre-HSCT visit was to be performed. Gilteritinib could be resumed after HSCT if the conditions below were met:

- Participant was between 30-90 days post-HSCT
- Participant had successful engraftment demonstrated by ANC ≥500/$mm^3$ and platelets ≥2000/$mm^3$ without transfusions
- Participant did not have ≥ grade 2 acute graft-versus-host disease (GVHD)
- Participant was in CRc[2]

A total of 63/247 (25.5%) in the gilteritinib arm had HSCT on or off study, with 55 (22.3%) patients that had on-study HSCT and 8 (3.2%) that had off-study HSCT (described in the subsequent therapies section).[3]

A total of 40 (16.2%) patients resumed gilteritinib (median 65 days of gilteritinib interruption before resumption [range: 39, 107]) and 27 (10.9%) were alive post-HSCT, and 13 (5.2%) had died.[3,58] At the time of data cut-off (September 17th, 2018), there were 21 (8.5%) patients that were on treatment and in remission, and 19 patients (7.7%) that discontinued treatment due to remission (n=7), relapse (n=3), ongoing new AML therapy (n=3), and HSCT treatment failure (n=6).

There were 15/247 (6.1%) patients that had planned on resuming gilteritinib, but did not, of which 5 (2%) were alive post-HSCT and 10 (4.0%) had died. At the time of data cut-off, 10 patients discontinued treatment due to remission, 1 patient due to ongoing new AML therapy, and 4 patients due to HSCT treatment failure.[3] Refer to Figure 6.3 under section *d) Patient Disposition* for details.

***Subsequent therapies***

During follow-up (after discontinuation of study treatment), there were a higher proportion of patients in the salvage chemotherapy arm that received subsequent AML therapy (n=76, 61.3%) compared to the gilteritinib arm (n=114, 46.2%).[3] The most commonly used regimen was azacitidine (overall: n=29, 15.3%), which was received by a similar proportion of patients in each treatment arm. Fludarabine with cytarabine, G-CSF, and idarubicin was used in a higher proportion of patients

in the gilteritinib arm (n=11, 9.6%) compared to the salvage chemotherapy arm (n=2, 2.6%).[4]

A total of 8 (3.2%) patients in the gilteritinib arm had subsequent matched sibling/alternative donor HSCT (note: a total of 63 patients that had HSCT on or off study in the gilteritinib arm used in HSCT analyses), whereas 17 (13.7%) had subsequent matched sibling/alternative donor HSCT and 2 (1.6%) patients had autologous HSCT in the salvage chemotherapy arm (note: a total of 19 patients had HSCT off study in the salvage chemotherapy arm used in HSCT analyses).[3,4] In the gilteritinib arm, there were 2 (<1%) patients alive and 6 (2.4%) patients that died who received off-study HSCT compared to 13 (10.5%) patients that were alive and 6 (4.8%) patients that died in the salvage chemotherapy arm. At the time of data cut-off, all 8 off-treatment HSCT patients in the gilteritinib arm had discontinued HSCT due to remission (n=3, 1.2%), ongoing/new AML therapy/HSCT (n=2, <1%), or treatment failure (n=3, 1.2%), whereas in the salvage chemotherapy arm all 19 patients had discontinued HSCT due to remission (n=13, 10.5%), ongoing new AML therapy/HSCT (n=2, 1.6%), and treatment failure (n=4, 3.2%).[3]

Three quarters (n=143, 74.7%) of patients had subsequent AML therapies recorded as "Other". Among these, sorafenib was the most common regimen (overall: n=33, 17.4%), used in a higher proportion of patients in the salvage chemotherapy arm (n=20, 26.3%) compared to the gilteritinib arm (n=13, 11.4%). This was followed by cytarabine and anthracycline (overall: n=30, 15.8%) and investigational agents (overall: n=20; 10.5%), which were both used in a higher proportion of patients in the gilteritinib arm (cytarabine and anthracycline: n=24; 21.1%; investigational agents: n=15, 13.2%) compared to the salvage chemotherapy arm (cytarabine + azacitidine: n=6, 7.9%; investigational agents: n=5, 6.6%).[4] The "Other" category also included a small number of patients that had additional/second HSCT or HSCT conditioning regimens (n=7) and were included in the total patients with HSCT on or off-study treatment. There were a small number of patients (n=11; 5 in the gilteritinib arm and 6 in the chemotherapy arm) that had HSCT or HSCT conditioning regimen, but information was limited and thus, these patients were not included in the total patients that received HSCT on- or off-study.[55] See Table 6.11 for the full list of subsequent therapies.

**Table 6.11. Post-treatment discontinuation therapies, ITT population (n=371)**

| Parameter | Categories | Gilteritinib (N=247) | Chemotherapy (N=124) | Total (N=371) |
|---|---|---|---|---|
| **Subjects With Subsequent AML Therapy** | No | 133 (53.8%) | 48 (38.7%) | 181 (48.8%) |
| | Yes | 114 (46.2%) | 76 (61.3%) | 190 (51.2%) |
| **Regimen*** | Standard Dose Cytarabine + Idarubicin | 2 (1.8%) | 1 (1.3%) | 3 (1.6%) |
| | Standard Dose Cytarabine + Daunorubicin | 3 (2.6%) | 0 | 3 (1.6%) |
| | Standard Dose Cytarabine + Daunorubicin + Cladribine | 0 | 0 | 0 |
| | High-dose Cytarabine + Idarubicin | 2 (1.8%) | 1 (1.3%) | 3 (1.6%) |
| | High-dose Cytarabine + Daunorubicin | 0 | 0 | 0 |
| | Autologous HSCT | 0 | 2 (2.6%) | 2 (1.1%) |
| | Matched Sibling/Alternative Donor HSCT | 8 (7.0%) | 17 (22.4%) | 25 (13.2%) |

| Parameter | Categories | Gilteritinib (N=247) | Chemotherapy (N=124) | Total (N=371) |
|---|---|---|---|---|
| | Standard Dose Cytarabine + Mitoxantrone | 2 (1.8%) | 2 (2.6%) | 4 (2.1%) |
| | Low-dose Cytarabine | 7 (6.1%) | 8 (10.5%) | 15 (7.9%) |
| | Azacitidine | 18 (15.8%) | 11 (14.5%) | 29 (15.3%) |
| | Decitabine | 7 (6.1%) | 3 (3.9%) | 10 (5.3%) |
| | Cladribine + Cytarabine + GCSF | 1 (0.9%) | 0 | 1 (0.5%) |
| | Cladribine + Cytarabine + GCSF + Mitoxantrone | 2 (1.8%) | 1 (1.3%) | 3 (1.6%) |
| | Cladribine + Cytarabine + GCSF + Idarubicin | 0 | 0 | 0 |
| | Fludarabine + Cytarabine + GCSF | 4 (3.5%) | 0 | 4 (2.1%) |
| | Fludarabine + Cytarabine + GCSF + Idarubicin | 11 (9.6%) | 2 (2.6%) | 13 (6.8%) |
| | Etoposide + Cytarabine | 1 (0.9%) | 0 | 1 (0.5%) |
| | Etoposide + Cytarabine + Mitoxantrone | 9 (7.9%) | 2 (2.6%) | 11 (5.8%) |
| | Clofarabine + GCSF | 0 | 0 | 0 |
| | Clofarabine + Cytarabine + GCSF | 2 (1.8%) | 1 (1.3%) | 3 (1.6%) |
| | Clofarabine + Cytarabine + GCSF + Idarubicin | 0 | 0 | 0 |
| | Other | 84 (73.7%) | 58 (76.3%) | 142 (74.7%) |
| | Clofarabine +/- cytarabine | 2 (1.8%) | 3 (3.9%) | 5 (2.6%) |
| | Cytarabine | 5 (4.4%) | 1 (1.3%) | 6 (3.2%) |
| | Cytarabine + anthracycline | 24 (21.1%) | 6 (7.9%) | 30 (15.8%) |
| | Dasatinib | 2 (1.8%) | 0 | 2 (1.1%) |
| | Donor Lymphocyte Infusion | 2 (1.8%) | 1 (1.3%) | 3 (1.6%) |
| | Enasidenib | 3 (2.6%) | 0 | 3 (1.6%) |
| | Enasidenib + Low Intensity Chemotherapy | 0 | 1 (1.3%) | 1 (0.5%) |
| | Gemtuzumab Ozogamicin | 3 (2.6%) | 2 (2.6%) | 5 (2.6%) |
| | HiDAC | 5 (4.4%) | 6 (7.9%) | 11 (5.8%) |
| | HSCT | 10 (8.8%) | 8 (10.5%) | 18 (9.5%) |
| | Hydroxyurea | 11 (9.6%) | 4 (5.3%) | 15 (7.9%) |
| | Intrathecal chemotherapy | 7 (6.1%) | 5 (6.6%) | 12 (6.3%) |
| | Investigational Agent | 15 (13.2%) | 5 (6.6%) | 20 (10.5%) |
| | Midostaurin | 4 (3.5%) | 0 | 4 (2.1%) |
| | Midostaurin + High Intensity Chemotherapy | 1 (0.9%) | 0 | 1 (0.5%) |
| | Midostaurin + Low Intensity Chemotherapy | 1 (0.9%) | 2 (2.6%) | 3 (1.6%) |
| | Ponatinib | 2 (1.8%) | 0 | 2 (1.1%) |
| | Quizartinib | 0 | 4 (5.3%) | 4 (2.1%) |
| | Sorafenib | 13 (11.4%) | 20 (26.3%) | 33 (17.4%) |
| | Sorafenib + High Intensity Chemotherapy | 1 (0.9%) | 0 | 1 (0.5%) |
| | Sorafenib + Low Intensity Chemotherapy | 10 (8.8%) | 4 (5.3%) | 14 (7.4%) |
| | Venetoclax | 4 (3.5%) | 1 (1.3%) | 5 (2.6%) |

| Parameter | Categories | Gilteritinib (N=247) | Chemotherapy (N=124) | Total (N=371) |
|---|---|---|---|---|
| | Venetoclax + Low Intensity Chemotherapy | 4 (3.5%) | 2 (2.6%) | 6 (3.2%) |
| | XRT | 1 (0.9%) | 0 | 1 (0.5%) |
| | Other | 3 (2.6%) | 8 (10.5%) | 11 (5.8%) |
| | None | 2 (1.8%) | 1 (1.3%) | 3 (1.6%) |

*Percentages were calculated based on the number of subjects with subsequent AML therapy.

**Source:** Astellas response to pCODR checkpoint meeting questions (January 28, 2020)[4]

d) ***Patient Disposition***

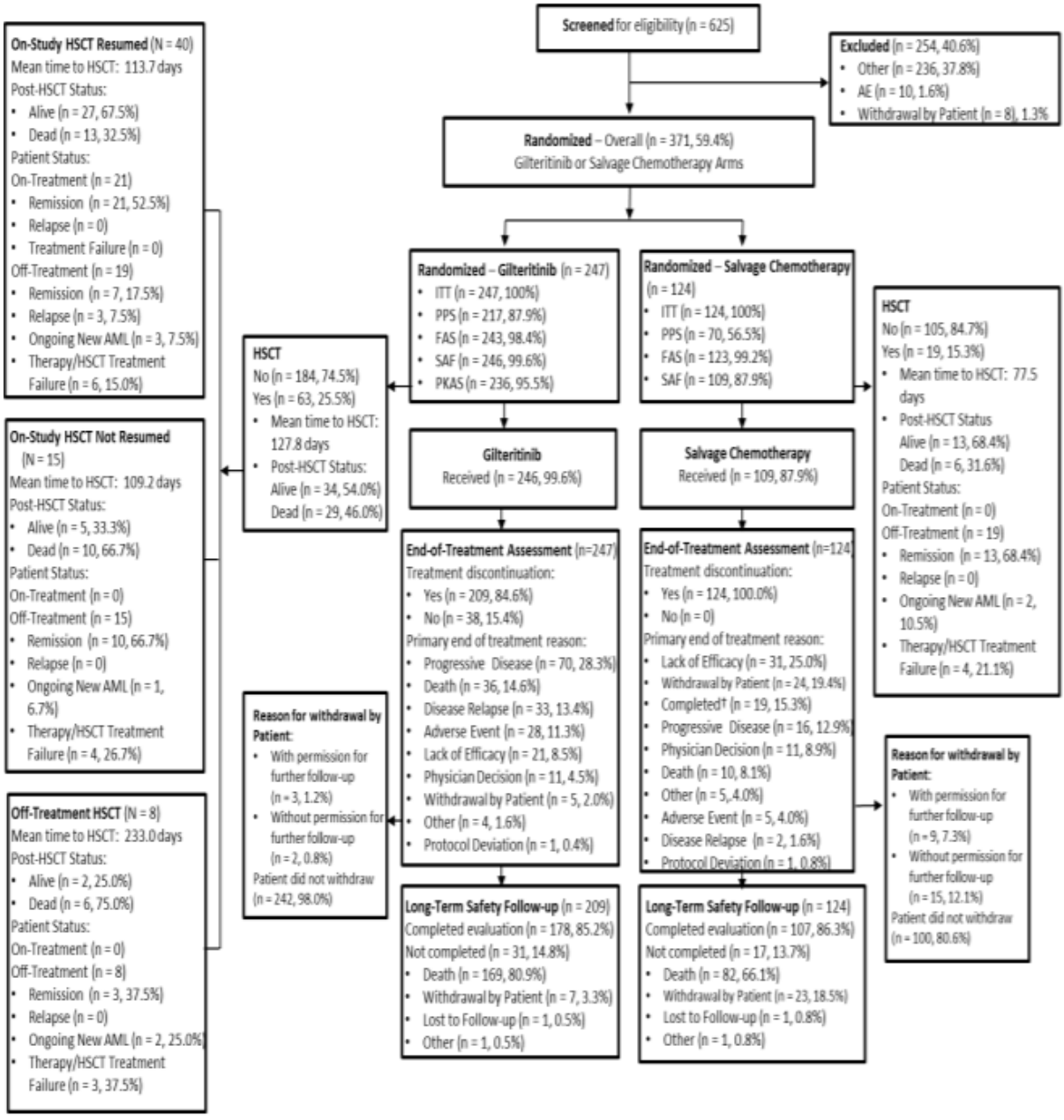
A total of 625 participants were screened for eligibility. There were 254 (40.6%) patients excluded, which were due to other reasons (n=236, 37.8%), AEs (n=10, 1.6%), and withdrawal by patient (n=8, 1.3%). Other reasons for exclusion included 73.2% (n=167) of screened patients who did not have a FLT3 mutation, followed by 7.5% (n=17) of patients that did not meet the definition for first hematologic relapse or refractory disease and 7.0% (n=16) of patients with a mean QTcF > 450 ms.[58] A total of 371 patients were randomized, 247 to the gilteritinib arm and 124 to the salvage chemotherapy arm. A total of 246 patients received treatment with gilteritinib (1 patient did not receive treatment) and 109 received treatment with salvage chemotherapy (15 did not receive treatment).[2] Most patients in the salvage chemotherapy arm who did not receive treatment withdrew consent (14 of the 15 patients) following randomization.[4] In the salvage chemotherapy arm, 28 received MEC, 40 received FLAG-IDA, 16 received low-dose cytarabine, and 25 received azacitidine.[2]

At the time of data cut-off, most randomized patients in the gilteritinib arm (n=209, 84.6%) and all randomized patients in the salvage chemotherapy had discontinued treatment (n=124, 100%).[3] Lack of efficacy was measured as a response defined by hematologic and bone marrow criteria, and in the ADMIRAL trial it included patients who did not achieve CRc or PR, however given that AML is a heterogenous disease, in some cases other criteria may have constituted lack of efficacy by the assessment of the investigator. Similarly progressive disease (PD) could be attributed to increasing blasts percentages in the bone marrow or blood accompanied by varying degrees of worsening blood counts, however due to the heterogeneity of the disease, other signs and symptoms or laboratory findings that were not just declining blood counts could have contributed to an assessment of PD by the investigator.[54] There were a higher proportion of patients in the gilteritinib arm (n=70, 28.3%) with a primary reason for treatment discontinuation (at the time of end of treatment assessment, 7 days post treatment discontinuation) of PD compared to the salvage chemotherapy arm (n=16, 12.9%), whereas a higher proportion of patients in the salvage chemotherapy arm (n=31, 25.0%) discontinued due to lack of efficacy compared to the gilteritinib arm (n=21, 8.5%). There were a higher proportion of patients in the gilteritinib arm (n=36, 14.6%) that discontinued due to death compared to the salvage chemotherapy arm (n=10, 8.1%). A higher proportion of patients in the gilteritinib arm discontinued treatment due to disease relapse (n=33, 13.4%) and adverse events (n=28, 11.3%) compared to the salvage chemotherapy arm (disease relapse: n=2, 1.6%; adverse events: n=5, 4.0%). A higher proportion of patients in the salvage chemotherapy arm withdrew (n=24, 19.4%) participation compared to the gilteritinib arm (n=5, 2.0%). In the salvage

chemotherapy, a total of 19 (15.3%) completed treatment (only applicable to high-dose chemotherapy regimens).[3]

At the time of data cut-off, 209 patients in the gilteritinib arm and 124 in the salvage chemotherapy arm had discontinued treatment and entered long-term safety follow-up: a total of 178 (85.2%) of patients in the gilteritinib arm and 107 (86.3%) in the salvage chemotherapy arm completed evaluation. There were 169 (80.9%) deaths, 7 (3.3%) patient withdrawals, and 1 (0.5%) lost to follow-up in the gilteritinib arm, whereas there were 82 (66.1%) deaths, 23 (18.5%) withdrawals, and 1 (0.8%) patient lost to follow-up in the salvage chemotherapy arm.[3] A total of 38 patients in the gilteritinib arm and no patients in the salvage chemotherapy were continuing in the trial at the time of data cut-off.[2]

**Figure 6.3. Participant disposition diagram, ADMIRAL trial[3]**



Source: EPAR, EMA 2019[3]

**Protocol Deviations**

As of the final analysis data cut-off date, a total of 43 (11.6%) protocol deviations had occurred and were balanced between treatment arms. The most common reason for a protocol deviation in both treatment arm was entry into the study despite being ineligible (overall: n=32, 8.6%).[3] In the gilteritinib arm, entry criteria that were not met included 6 patients that had a mean triplicate QTcF of >450 ms at screening based on central reading, 5 patients did not have FLT3 mutation positive disease as determined be central testing, and 1 patient received prior treatment with a FLT3 inhibitor (that was not sorafenib or midostaurin). In the salvage chemotherapy arm, entry criteria that were not met included 4 patients that had a mean triplicate QTcF of >450 ms at screening based on central reading, and 1 patient was not refractory to or relapsed after first-line therapy for AML.[5] Protocol deviations are summarized in Table 6.12.

**Table 6.12. Summary of protocol deviations, ITT population (n=371)[3]**

| Deviation Code, n (%) | Gilteritinib (n = 247) | Chemotherapy (n = 124) | Total (n = 371) |
|---|---|---|---|
| Any deviation† | 29 (11.7) | 14 (11.3) | 43 (11.6) |
| Entered into the study even though they did not satisfy entry criteria | 21 (8.5) | 11 (8.9) | 32 (8.6) |
| Received excluded concomitant treatment | 6 (2.4) | 3 (2.4) | 9 (2.4) |
| Developed withdrawal criteria during the study and were not withdrawn | 2 (0.8) | 0 | 2 (0.5) |

† No patients met the protocol deviation criteria of received wrong treatment or incorrect dose.

Source: EPAR, EMA 2019[3]

### *e) Limitations/Sources of Bias*

Key limitations and sources of bias include:

- The study design was open-label, which is susceptible to reporting and performance biases as patients and investigators were not blinded to study treatment. However, due to the different modes of administration of study treatments, it was considered justified. One of the co-primary outcomes was OS, which was unlikely influenced by the open-label study design. The other co-primary outcome, CR rate, and many secondary outcomes were assessed by laboratory evaluation of bone marrow and/or blood samples, and while the open-label design would not have influenced the laboratory results, the timing of assessments and number of cycles treated may have been influenced by the investigator. For example, patients in the gilteritinib arm may have been treated for additional cycles in order to achieve a CRc, whereas patients in the low intensity chemotherapy may have been discontinued earlier due to investigator bias, which may have impacted efficacy in favour of gilteritinib. In the high intensity chemotherapy arm, of the 68 patients, 64 (94.1%) had 1 cycle of induction and only 4 patients received 2 cycles of high intensity chemotherapy to achieve remission, which may not be reflective of clinical practice and may be indicative of bias.[54] As per the CGP, response may be

delayed with azacitidine and patients are typically treated for 3-4 cycles and assessed at cycle 6 for response, however in the ADMIRAL trial the median duration of azacitidine treatment was 4 weeks (range: 1, 26) and the upper limit of the range was around 6 cycles, which may indicate bias.[2] The potential for undertreatment in the salvage chemotherapy arm due to investigator bias related to the open-label design of the study may have underestimated the efficacy of the salvage chemotherapy arm.

- FLT3 mutations are rare and have a poor prognosis with limited effective options in the relapsed and refractory setting, and as per NCCN guidelines patients with FLT3-ITD mutations should be considered for clinical trials if possible.[12] Given that clinical trials are desirable, the open-label study design may have also influenced HRQoL, which may have been subject to respondent bias if patients perceived that receiving the experimental therapy was superior to standard of care, and thus HRQoL results may have been biased in favour of gilteritinib. In addition, a higher proportion of patients that withdrew from the salvage chemotherapy arm soon after randomization and prior to receiving any study treatment (11.3% versus 0% in the gilteritinib arm), may have introduced attrition bias due to the open-label nature of the study.[4] This may have resulted in a less 'fit' patient population in the salvage chemotherapy (although, it is difficult to determine this), as those who withdrew may have been suitable for other trials or therapies deemed to be of perceived clinical benefit. Finally, patients could continue to be treated beyond progression or no response, if in the opinion of the investigator, the patient continued derive clinical benefit, however the reason for treatment discontinuation was only recorded at the end of treatment.[54] Thus, time-to-event endpoints may have been overestimated.
- Information on how many patients were treated in the absence of a response or beyond progression was not recorded, and thus response rates could be overestimated.
- Additionally, the study may be subject to other biases, which include an unequal comparison and informative censoring, detailed below:
    - Unequal comparison: Patients in high intensity chemotherapy group had a short duration of treatment (60% of patients in salvage chemotherapy arm were treated for 1-2 cycles), and thus, entered long-term follow-up with no systematic plan for monitoring of relapse/response (via regular bone marrow, clinical and laboratory assessments as was done in patients treated with gilteritinib or low-dose chemotherapy that continued until lack of clinical benefit).[3] Thus, secondary outcomes, such as EFS, were limited in usefulness as relapse was defined by central review of bone marrow biopsy. A sensitivity analysis that included investigator-reported events during long-term follow-up was conducted, which showed a 50% reduction in risk of an EFS event in the gilteritinib arm relative to placebo (HR: 0.50; 95% CI:0.39, 0.64); however this estimate is subject to measurement bias due to different assessment methods and timepoints used in each treatment arm.[2] There were a large proportion of patients that had no evaluable post-baseline response assessments in the salvage chemotherapy arm (n=49; 39.5%) compared to the gilteritinib arm (n=14; 5.7%), and comparisons of response rates and response related time-to-event endpoints are also limited.[3] Furthermore, quality of life was not assessed in long-term

follow-up (other than EQ-5D, however few patients beyond Cycle 1 completed this assessment in the salvage chemotherapy arm) and thus, beyond the safety follow-up longer-term differences in quality of life beyond 1 cycle of treatment between treatment arms cannot be compared. Additionally, patients who did not achieve remission after their first cycle could have their dose increased in order to achieve remission and potentially undergo HSCT to essentially prolong remission, whereas patients in the salvage chemotherapy arm did not have similar opportunities to achieve or prolong remission. Salvage chemotherapy was likely discontinued, or dose reduced earlier for toxicities as per standard institutional guidelines, whereas as certain toxicities may have been tolerated in the gilteritinib arm due to clinical benefit that was in the judgement of the investigator. Allogeneic HSCT remains the most effective way to reduce the risk of relapse, and patients who achieved CR and received subsequent HSCT in the salvage chemotherapy arm should have been monitored similar to the gilteritinib arm for a fairer comparison.[59] This unequal comparison favours gilteritinib.

    - Informative censoring: A higher proportion of patients were censored in the primary OS analyses due to patient withdrawal in the salvage chemotherapy arm (10.5%) compared to gilteritinib (2.5%), and thus survival probability of patients that continued to be followed versus those who withdrew may have been different.[4] Whether theses patients were likely to have worse or better survival is unknown.

- There were a few imbalances between treatment arms in baseline characteristics. A slightly higher proportion of patients in the gilteritinib arm (11%) had unfavourable cytogenetic risk compared to the salvage chemotherapy arm (9%), which may have confounded the study results in favour of the salvage chemotherapy arm as patients with unfavourable cytogenetic risk factors have a poor prognosis.[3,7] There was a higher proportion of patients in the gilteritinib arm with an antecedent hematological disorder (17%) compared to the salvage chemotherapy arm (9%), with myelodysplastic syndrome (MDS) as the most common hematological disorder in the gilteritinib (14%) and salvage chemotherapy (7%) arms.[3] Patients that develop AML from an antecedent hematological disorder generally have a poorer prognosis than patients with de novo AML, and thus, this may have confounded study results in favour of salvage chemotherapy.[7] A slightly higher proportion of patients in the gilteritinib arm (34%) had a co-mutation with NPM1 compared to the salvage chemotherapy arm (30%).[3] While there is variation in the literature, there is research to suggest co-mutation or NPM1 and FLT3-ITD may lead to worse outcomes independent of allelic ratio or in high allelic ratio (>0.5), and that co-mutation of NMP1 with FLT3-TKD may lead to improved outcomes.[60,61] The imbalance in NPM1 mutation may have confounded outcomes, however it is not clear of the impact on outcomes.

- Sorafenib was used as a subsequent therapy in a higher proportion of patients in the salvage chemotherapy arm (26%) compared to the gilteritinib arm (11%).[4] However, sorafenib has not demonstrated significant activity as a single agent in relapsed/refractory (R/R) FLT3-mutated AML, and is not currently indicated for R/R FLT3-mutated AML.[8] This imbalance may have favoured the gilteritinib arm as the efficacy and safety of sorafenib compared to alternative therapies in the R/R setting is unknown.

- As mentioned earlier, patients were able to interrupt treatment with gilteritinib in order to undergo HSCT, and then resume gilteritinib if specific criteria were met (patient is within 30-90 days post-HSCT, in CRc, did not have grade ≥2 GVHD, and ANC ≥ 500/mm$^3$ and platelets ≥ 20,000/mm$^3$ without transfusions). The goal of HSCT is to prolong remission and/or survival, and a higher proportion of patients in the gilteritinib arm received HSCT during/off treatment (25.5%) compared to the salvage chemotherapy arm (15.3%). Thus, the co-primary endpoint of OS may have been confounded in favour of gilteritinib, as a higher proportion of patients had HSCT. In a sensitivity analysis censoring OS at time of HSCT, an enhanced benefit in the reduction in the risk of death with gilteritinib relative to chemotherapy was seen compared to the primary analysis (43% reduction in risk censoring at HSCT compared to 36% in the primary analysis), although numerical the median OS in the gilteritinib arm decreased by 1 month (8.3 months with censoring at HSCT compared to 9.3 months in primary analysis).[3] This may suggest that there is some confounding effect of either HSCT following gilteritinib or a combination of HSCT with maintenance therapy using gilteritinib following HSCT. However, censoring at time of HSCT assumes those patients censored have the same survival probability as those who continue to be monitored, which would not be an accurate assumption as patients eligible for HSCT would have to be both fit for the intervention and at high-risk dependent on a number of factors, as discussed with the CGP. It is also difficult to determine the comparative effectiveness of gilteritinib as a maintenance therapy as patients in the salvage chemotherapy arm were not followed systematically for subsequent therapies (including for HSCT and maintenance therapies), and subgroup analyses conducted in patients who received HSCT during/off study (gilteritinib: n=63; salvage chemotherapy: n=19) may help explain the impact of HSCT. While this analysis is limited by small sample size and is exploratory in nature, it revealed patients in the gilteritinib who received HSCT may be at increased risk of death relative to the salvage chemotherapy arm (HR: 1.33; 95% CI: 0.55, 3.22), however the median OS was numerically higher than observed in primary analysis of the trial (gilteritinib: median OS = 19.9 months vs. 9.3 months in the primary OS analysis; salvage chemotherapy: NE in the salvage chemotherapy arm vs. 5.6 months in the primary OS analysis). In contrast, in patients who did not receive HSCT during/off study (gilteritinib: n =184; chemotherapy: n=105) there was a 39% (HR: 0.61; 95% CI: 0.46, 0.80) reduction in the risk of death, similar to the primary analysis, however numerically, the median OS benefit was much lower (gilteritinib: 6.7 months; chemotherapy: 5.1 months) compared to the primary analysis.[4]
- Additionally, HSCT may have confounded the duration of remission in favour of the gilteritinib arm. The median time to HSCT in the gilteritinib arm was 127.8 days (~4.5 months), and patients who resumed gilteritinib must have resumed within 30-90 days while still in CRc, and thus, these timelines indicate the interruption of gilteritinib for HSCT would have extended remission in the absence of active treatment with gilteritinib, for at least 1-3 months.[3]
- As per amendment 1 (dated 23-Sep-2017) of the SAP, treatment compliance was not analyzed due to unreliable drug accountability data.[2] It is unclear whether primary and secondary outcomes, as well as safety, were affected by any imbalances between treatment arms in the actual doses patients received relative to planned doses, as this information was not collected.

- The ADMIRAL trial included 4 salvage chemotherapy options, 2 of which were high-intensity regimens (FLAG-IDA and MEC), and 2 low-intensity regimens (LoDAC and azacitidine). As discussed with the CGP, there is no established standard of care in this setting and generally high intensity regimens are used whenever possible to ensure the best possible response. LoDAC and MEC were identified as rarely used in the Canadian context, unless in exceptional circumstances. Most patients only received 1 cycle (94.1%), although up to 2 cycles can be used in clinical practice.[2] As HSCT was not monitored similar to gilteritinib in the salvage chemotherapy arm, there were some patients who may have received subsequent HSCT that were not included in the 19 (15.3%) patients identified as receiving off-study HSCT in this arm.[3] A recent real world evidence study conducted by Bertoli et al., 2020, found that of 114 patients with R/R FLT3-mutated AML that received salvage chemotherapy, 50% achieved a CR/CRi, and 34.2% proceeded to allogeneic HSCT following salvage chemotherapy. With a median follow-up of 63.9 months, the median OS was 8.2 months (IQR: 3.0, 32.0).[9] Given these considerations, the efficacy estimated in the salvage chemotherapy arm in the ADMIRAL trial was likely underestimated compared to typical therapies delivered in the Canadian context.

While there are a number of limitations noted in this section, it must be acknowledged there are challenges in conducting trials with AML as treatment decisions are dependent on a number of factors specific to the individual patient. The primary limitation to note from the section is that the efficacy of salvage chemotherapy may have been underestimated in the patient population as relevant to the Canadian context, and that the unequal comparison of treatment groups creates difficulty in the interpretation of many of the secondary outcomes. The primary endpoint of the ADMIRAL trial was overall survival, which is an established and robust endpoint for demonstrating efficacy. Due to the number of therapies with different modes of administration, blinding may not have been feasible. Additional strengths of the study include the randomization method, sample size, and statistical methods, which were all appropriate for the study.

### 6.3.2.2 Detailed Outcome Data and Summary of Outcomes

***Efficacy Outcomes***

*Primary Endpoints*

*Overall Survival (OS)*

The median duration of follow-up for OS was 17.8 months, and the data cut-off date was September 17th, 2018 (date of 258th death) with a database lock date of October 19th, 2018. A total of 171 (69.2%) deaths events occurred in the gilteritinib arm and 90 (72.6%) occurred in the salvage chemotherapy arm, as shown in Table 6.13. The median overall survival was 9.3 months (95% CI: 7.7, 10.7) in the gilteritinib arm and 5.6 months (95% CI: 4.7, 7.3) in the salvage chemotherapy arm. There was a 36% reduction in the risk of death (HR: 0.64; 95% CI: 0.49, 0.83; p <0.001) in the gilteritinib arm relative to the salvage chemotherapy arm, and the Kaplan-Meier curves are illustrated in Figure 6.4A.[2] The 6, 12, and 18-month OS rate in the gilteritinib arm was 65.5%, 37.1%, and 19.0% compared to 48.9%, 16.7%, and 13.8% in the chemotherapy salvage arm.[3]

Median OS by subgroup was explored, which generally showed a consistent benefit across subgroups shown in Figure 6.4B. Of the pre-specified subgroups in the systematic review protocol, age (<65 years and ≥65 years), was consistent with the primary results. With regards to all other subgroups of clinical interest (sex, ECOG PS, bone marrow disorders, FLT3 mutation subtype, type of prior therapy, response to first line therapy, and allelic ratio), the direction of treatment effect was consistent with the primary analysis, however the CI crossed 1 for the following subgroups: males (HR: 0.72; 95% CI: 0.49, 1.05); ECOG PS ≥2 (HR: 0.87; 95% CI: 0.45, 1.69); secondary AML to MDS (HR: 0.58; 95% CI: 0.24, 1.42); FLT3 TKD alone (HR: 0.69; 95% CI: 0.29, 1.64); previous use of FLT3 inhibitor (HR: 0.70; 95% CI: 0.35, 1.44); and patients with relapse ≥6 months after first-line allogeneic HSCT (HR: 0.86; 95% CI: 0.26, 2.8).[2,54] Though enhanced benefit with gilteritinib was seen in the subgroup of patients who relapsed prior to 6 months after HSCT, regardless of time to relapse, there was a statistically significant difference between gilteritinib and salvage chemotherapy in patients with prior HSCT (HR: 0.48; 95% CI: 0.27, 0.84).[3,4] There was no difference between treatment arms in patients with primary refractory disease without HSCT after first line therapy (HR: 0.99; 95% CI: 0.63, 1.55). Of note, there were no patients with co-occurring FLT3 ITD and FLT3 TKD mutation types in the salvage chemotherapy arm, and thus, it could not be evaluated.[2] The subgroup analysis with prior use of FLT3 inhibitor included patients who received prior midostaurin, sorafenib, or quizartinib, however sorafenib and quizartinib are not indicated for AML in Canada. An additional subgroup analysis of OS was requested in the midostaurin subgroup, which revealed there was no statistically significant difference in risk of death between treatment arms; however the analysis is limited by the extremely small sample size (n=21, with only 8 patients in the salvage chemotherapy arm), and thus no inferences should be made. [3,10]

Per protocol, an analysis of allelic ratio using the median FLT3-ITD ratio in the ADMIRAL trial (low: <0.77 and high: ≥0.77), and in the high allelic ratio subgroup, OS was consistent with the primary analysis with significant results (HR: 0.49; 95% CI: 0.34, 0.71; p=0.0001). In patients with an allelic ratio <0.77, there was no significant difference between treatment arms (HR: 0.80; 95% CI: 0.53, 1.20; p=0.2719), however numerically median OS was higher in the gilteritinib arm (10.6 months vs. 6.9).[3] The CGP identified this as a subgroup of interest, however

advised that in Canadian practice, typically an allelic ratio of 0.5 is used, and thus the sponsor provided a subgroup analysis using an allelic ratio cut-off of <0.5 as low and ≥0.5 as high. Similarly, a significant reduction in the risk of death was seen in the FLT3-ITD allelic ratio high group (HR: 0.47; 95% CI: 0.34, 0.65), whereas there was no difference between treatment arms in the low allelic ratio group (HR: 0.99; 95% CI: 0.57, 1.71) although numerically the median OS was higher in the gilteritinib arm (11.0 months vs. 8.0 months).[4]

Additional subgroup analyses explored in the trial are shown in Figure 6.4. Of note, the confidence interval crossed 1 for the following subgroups: Black and Other/unknown race; North America and Europe geographic region; and favourable cytogenetic risk status. Patients with unfavourable cytogenetic risk status were suggested to be at increased risk with gilteritinib therapy (HR: 1.63; 95% CI: 0.69, 3.85), though the results were not statistically significant. A statistically and clinically significant benefit was seen regardless of patients preselected for high or low intensity salvage chemotherapy.[2] All subgroup analyses were not powered to detect statistically significant differences and may have been limited by small sample sizes in some subgroups, and thus must be interpreted with caution.

There were five pre-specified sensitivity analyses with a sixth one added as per the Statistical Analysis Plan (SAP) version 3 (dated Sept. 27, 2018), and the results are listed in Table 6.14. Of the five pre-specified sensitivity analyses, all were consistent except the per protocol analysis (SA2), however it is limited in interpretability as 43.5% of patients were excluded from the salvage chemotherapy arm compared to 12.1% in the gilteritinib arm.[3,54] The sixth sensitivity analysis (SA6) explored the weighted differences of Kaplan–Meier curves with estimation of difference of Restricted Mean Survival Time (RMST) and its 95% CI by a pre-specified cut-off time at 18 months resulting in a significant treatment difference of 2.8 months (95% CI: 1.5, 4.1; p<0.0001).[5]

OS by dose adjustment was also explored as 78 (31.6%) patients had gilteritinib increased to 200 mg, 58 (23.5%) patients had gilteritinib decreased to 80 mg, and 110 (44.5%) patients did not have any change to the gilteritinib dose. The median OS was 8.9 months (95% CI: 6.8, 10.8); 10.8 months (95% CI: 8.3, 14.3); 8.9 months (95% CI: 6.1, 11.0) for gilteritinib dose increase, decrease, and stayed the same, respectively, which was generally consistent with the overall trials results.[3]

**Table 6.13. Summary of overall survival in the ADMIRAL trial, ITT population (n=371)[3]**

| Category/ Statistics | Gilteritinib 120 mg (n = 247) | Chemotherapy (n = 124) |
|---|---|---|
| **Patient Status, n (%)** | | |
| Death events | 171 (69.2) | 90 (72.6) |
| Censored events | 76 (30.8) | 34 (27.4) |
| **Duration of Overall Survival, Month†** | | |
| Q1 (95% CI) | 4.4 (3.8, 5.1) | 3.0 (1.9, 3.5) |
| Median (95% CI) | 9.3 (7.7, 10.7) | 5.6 (4.7, 7.3) |
| Q3 (95% CI) | 18.7 (14.9, 24.1) | 10.0 (8.0, 15.7) |
| Range‡ | 0.2, 31.9+ | < 0.1+, 33.0 |
| **Stratified Analysis (Primary)§** | | |
| Log-rank test: P-value [1-sided P-value] | 0.0007 [1-sided P-value: 0.0004] | |
| Wald test: P-value¶ | 0.0008 | |
| Hazard ratio (95% CI)¶ | 0.637 (0.490, 0.830) | |
| **Unstratified Analysis** | | |
| Log-rank test (P-value) | 0.0005 | |
| Wald test: P-value¶ | 0.0006 | |
| Hazard ratio (95% CI)¶ | 0.636 (0.491, 0.823) | |
| **Overall Survival Rate % (95% CI)††** | | |
| 6 months | 65.5 (59.2, 71.1) | 48.9 (39.3, 57.8) |
| 12 months | 37.1 (30.7, 43.6) | 16.7 (9.9, 25.0) |
| 24 months | 19.0 (12.8, 26.0) | 13.8 (7.5, 22.0) |
| 36 months | NE (NE, NE) | 0 (NE, NE) |
| ***Overall Survival Sensitivity Analysis With Patients Censored at HSCT*** | | |
| **Patient Status, n (%)** | | |
| Death events | 142 (57.5) | 84 (67.7) |
| Censored events | 105 (42.5) | 80 (32.3) |
| **Duration of Overall Survival, Months†** | | |
| Q1 (95% CI) | 4.1 (3.6, 4.6) | 3.0 (1.9, 3.5) |
| Median (95% CI) | 8.3 (6.7, 10.2) | 5.3 (4.3, 6.1) |
| Q3 (95% CI) | 14.9 (11.1, 18.7) | 8.9 (7.3, 9.6) |
| Range‡ | 0.2, 27.4+ | < 0.1+, 33.0 |
| **Stratified Analysis§** | | |
| Log-rank test: 1-sided P-value | 0.0001 [1-sided P-value: < 0.0001] | |
| Wald Test: P-Value¶ | 0.0001 | |
| Hazard ratio (95% CI)¶ | 0.575 (0.434, 0.762) | |
| **Overall Survival Rate % (95% CI)††** | | |
| 6 months | 62.1 (55.1, 68.4) | 43.5 (33.2, 53.4) |
| 12 months | 30.5 (23.2, 38.0) | 8.7 (3.6, 16.5) |
| 24 months | 13.2 (7.3, 20.9) | 5.4 (1.6, 12.6) |
| 36 months | NE (NE, NE) | 0 (NE, NE) |

†Based on Kaplan-Meier estimates; ‡A "+" indicates censoring; §Stratification factors were response to first-line AML therapy and preselected salvage chemotherapy per IRT;m; ¶Based on Cox proportional hazards model. Assuming proportional hazards, an HR of < 1 indicates a reduction in the hazard rate in favor of the gilteritinib arm; ††Survival rate and 95% CI were estimated using the Kaplan-Meier method and the Greenwood formula.

**Source:** EPAR, EMA 2019[3]

**Figure 6.4. Overall survival in the ADMIRAL trial including A) Kaplan-Meier curve and B) subgroup analyses, ITT population (n=371)**

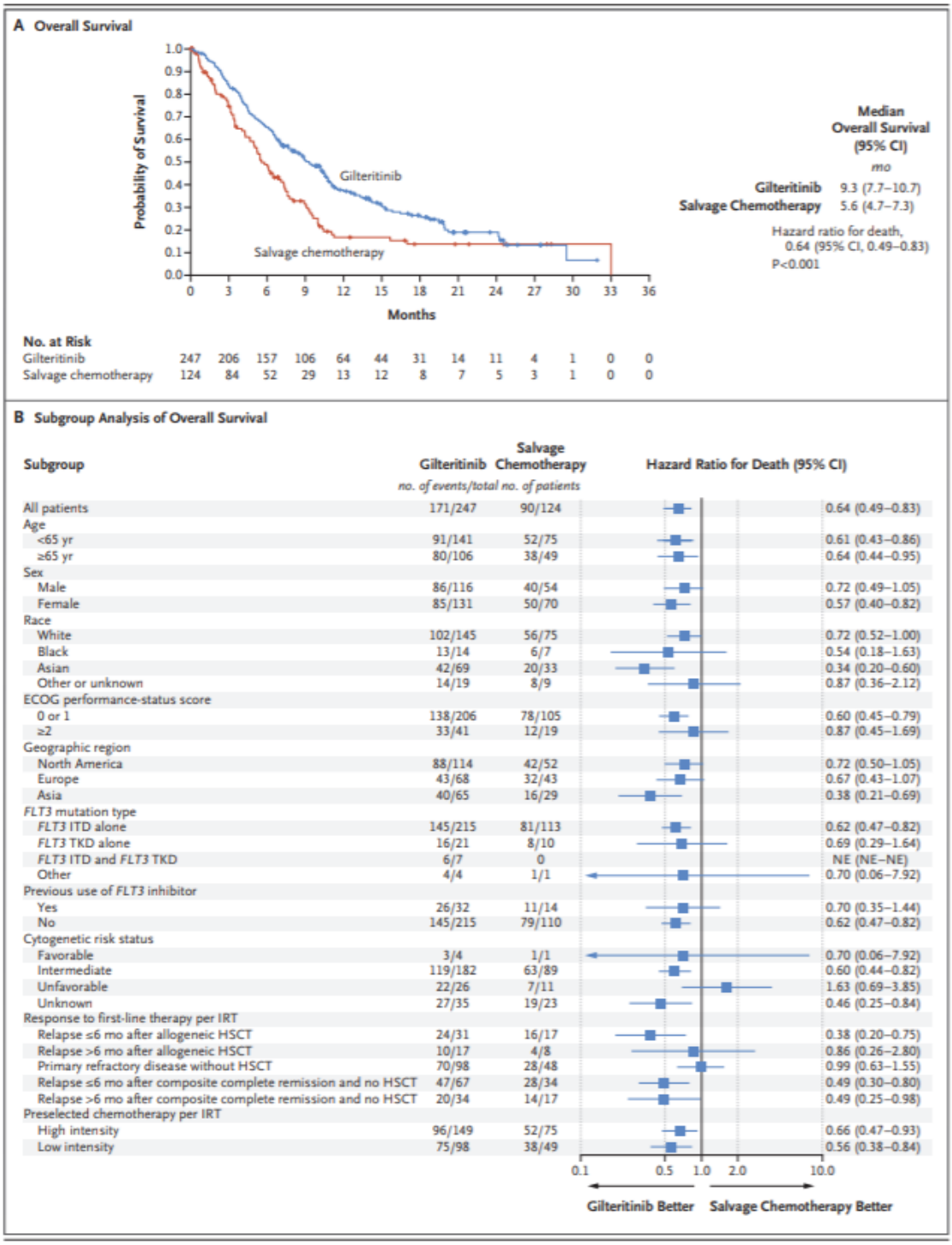



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**Table 6.14. Results of pre-specified sensitivity analyses of OS in the ADMIRAL trial, ITT population**

| | Gilteritinib | | Salvage chemotherapy | | | |
|---|---|---|---|---|---|---|
| **Pre-Specified Sensitivity Analysis** | **n** | **Median months (95% CI)** | **n** | **Median months (95% CI)** | **HR (95% CI)** | **P-value** |
| SA1: Primary analysis with full analysis set (all participants in ITT who have central confirmation of FLT3 mutation) | 243 | 9.3 (7.7, 10.6) | 123 | 5.6 (4.7, 7.1) | 0.64 (0.49, 0.82) | 0.0008 |
| SA2: Primary analysis with per protocol analysis set (ITT population with no major protocol deviations) | 217 | 10.3 (8.7, 11.1) | 70 | 7.8 (6.1, 9.5) | 0.84 (0.60, 1.18) | 0.1577 |
| SA3: stratified Cox proportional hazard model | 247 | N/A | 124 | N/A | N/A | 0.0008 |
| SA4: Primary analysis with ITT, censoring at time of HSCT | 247 | 8.3 (6.7, 10.2) | 124 | 5.3 (4.3, 6.1) | 0.58 (0.43, 0.76) | 0.0001 |
| SA5: Primary analysis censoring at the time of initiation of new therapy | 247 | 14.9 (11.4, NE) | 124 | 5.8 (4.3, 8.0) | 0.45 (0.31, 0.64) | <0.0001 |
| **Ad-hoc Sensitivity Analysis** | **n** | **RMST, months (95% CI)** | **n** | **RMST, months (95% CI)** | **Treatment diff., months (95% CI)** | **P-value** |
| SA6: Additional analysis using a new test for equality of 2 survival functions based on weighted difference of K-M curves with estimation of difference of RMST and its 95% CI by a prespecified cut-off time at 18 months | 247 | 10.0 (9.2, 10.8) | 124 | 7.2 (6.1, 8.3) | 2.8 (1.5, 4.1) | <0.0001 |

*Wald test p-value based on Cox proportional hazards model

**Abbreviations:**
**CI** = confidence interval; **FLT3**= FMA-like tyrosine kinase 3; **HR** = hazard ratio; HSCT = hematopoietic; **ITT** = intention-to-treat; **K-M** = Kaplan-Meier; **N/A** = not applicable; **NE** = not evaluable; **RMST** = restricted mean survival time; **SA** = sensitivity analysis

**Sources:**
EPAR, EMA 2019[3]
Clinical Study Report, Astellas Pharma 2019[5]
Perl et al., 2019[2]

**Table 6.15. Summary of overall survival, complete remission rate, and complete remission/complete remission with partial hematologic recovery, ITT population[2]**

| Parameter | Gilteritinib | Salvage Chemotherapy | |
|---|---|---|---|
| **Median Overall Survival** | | | **Hazard Ratio (95% CI)** |
| High-intensity chemotherapy | 10.5 months | 6.9 months | 0.663 (0.471, 0.932) |
| Low-intensity chemotherapy | 6.4 months | 4.7 months | 0.563 (0.378, 0.839) |
| Received prior HSCT | 8.3 months | 4.0 months | 0.480 (0.274, 0.840) |
| Did not receive prior HSCT | 9.6 months | 6.0 months | 0.684 (0.511, 0.917) |
| **CR Rate, no. (%)** | | | **Risk Difference (%) (95% CI)** |
| High-intensity chemotherapy | 37/149 (24.8) | 12/75 (16.0) | 8.8 (−3.0, 20.6) |
| Low-intensity chemotherapy | 15/98 (15.3) | 1/49 (2.0) | 13.3 (3.6, 22.9) |
| Received prior HSCT | 17/48 (35.4) | 3/26 (11.5) | 23.9 (2.6, 45.1) |
| Did not receive prior HSCT | 35/199 (17.6) | 10/98 (10.2) | 7.4 (−1.4, 16.1) |
| Before on-study HSCT | 34/247 (13.8) | 13/124 (10.5) | 3.3 (−4.0, 10.5) |
| **CR/CRh Rate, no. (%)** | | | **Risk Difference (%) (95% CI)** |
| Before on-study HSCT | 65/247 (26.3) | 19/124 (15.3) | 10.9 (2.4, 19.5) |

Abbreviations: CI, confidence interval; CR, complete remission; CRh, complete remission with partial hematologic recovery; HSCT, hematopoietic stem cell transplantation.

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*Complete remission/complete remission with partial hematologic recovery (CR/CRh)*

The CR/CRh rate was a co-primary endpoint assessed at IA1 with a total sample of 142 patients in the gilteritinib arm only, and the lower limit of the 2-sided 95% exact CI of the response analysis set (RAS; includes patients who were 112 days post first dose of gilteritinib or randomization) and was compared to the benchmark CR/CRh rate of 12%. The independent data monitoring committee (IDMC) informed the sponsor the CR/CRh endpoint was met, and this a nominal 1-sided p-value of 0.0005 was spent and not recycled at IA2 or the final analysis.[3]

At the time of data cut-off (descriptive analysis with ITT population, shown in Table 6.16), the CR/CRh rate was 34% (n=84) in the gilteritinib arm and 15.3% (n=19) in the salvage chemotherapy arm (risk difference: 18.6%; 95% CI: 9.8, 27.4). Response rates by dose adjustment of gilteritinib were also explored, and among those with a dose increase, 15.4% (12/78 patients) experienced a CR/CRh. Among those with a dose decrease (24/58 patients), 41.4% achieved CR/CRh.[3]

A total of 5 prespecified sensitivity analyses were conducted and are presented in Table 6.17.

**Table 6.16. Summary of antileukemic responses in the ADMIRAL trial, ITT population[2]**

**Table 2. Antileukemic Responses (Intention-to-Treat Population).***

| Variable | Gilteritinib (N=247) | Salvage Chemotherapy (N=124) | Hazard Ratio or Risk Difference (95% CI)† |
|---|---|---|---|
| Median overall survival (95% CI) — mo | 9.3 (7.7–10.7) | 5.6 (4.7–7.3) | 0.64 (0.49–0.83) |
| Median event-free survival (95% CI) — mo | 2.8 (1.4–3.7) | 0.7 (0.2–NE) | 0.79 (0.58–1.09) |
| Response — no. (%) | | | |
| Complete remission | 52 (21.1) | 13 (10.5) | 10.6 (2.8–18.4) |
| Complete remission or complete remission with partial hematologic recovery | 84 (34.0) | 19 (15.3) | 18.6 (9.8–27.4) |
| Complete remission with partial hematologic recovery | 32 (13.0) | 6 (4.8) | ND |
| Complete remission with incomplete hematologic recovery | 63 (25.5) | 14 (11.3) | ND |
| Complete remission with incomplete platelet recovery | 19 (7.7) | 0 | ND |
| Partial remission | 33 (13.4) | 5 (4.0) | ND |
| No response | 66 (26.7) | 43 (34.7) | ND |
| Composite complete remission‡ | 134 (54.3) | 27 (21.8) | 32.5 (22.3–42.6) |
| Overall response | 167 (67.6) | 32 (25.8) | |
| Median duration of remission (95% CI) — mo§ | 11.0 (4.6–NE) | NE (NE–NE) | NE |
| Time to composite complete remission — mo | 2.3±1.9 | 1.3±0.5 | NA |
| Median leukemia-free survival (95% CI) — mo | 4.4 (3.6–5.2) | 6.7 (2.1–8.5) | NE |

* Plus–minus values are means ±SD. Data shown are the best response at any time postbaseline. Data include 366 patients with central laboratory–confirmed *FLT3* mutations and 5 patients with *FLT3* mutations that were not confirmed by a central laboratory and were based on local laboratory testing. Response could not be evaluated (NE) in 14 patients (5.7%) in the gilteritinib group and in 49 (39.5%) in the salvage chemotherapy group. NA denotes not applicable, and ND not determined.
† Hazard ratios are shown for survival analyses, and risk differences (shown in percentage points) are shown for between-group differences in the percentages of patients. In the analysis of overall survival, the hazard ratio is for death. In the analysis of event-free survival, the hazard ratio is for treatment failure (i.e., relapse or lack of remission) or death.
‡ Composite complete remission was defined as the combination of complete remission, complete remission with incomplete hematologic recovery, and complete remission with incomplete platelet recovery.
§ Duration of remission was defined as the duration of complete remission with full or partial hematologic recovery.

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**Table 6.17. Summary of CR/CRh Rate Sensitivity Analyses**

| | Gilteritinib | | Salvage chemotherapy | | | |
|---|---|---|---|---|---|---|
| **Sensitivity Analysis** | **n** | **CR rate, % (95% CI)** | **n** | **Median months (95% CI)** | **Adjusted treatment difference (95% CI)** | **p-value** |
| **SA1:** Primary analysis with the modified RAS (subset of RAS that did not meet any exclusion for mRAS)* | 124 | 29.8 (22.0, 38.7) | N/A | N/A | N/A | N/A |
| **SA2:** Primary analysis with participants who took at least 1 dose | 246 | 34.1 (28.2, 40.4) | 109 | 17.5 (10.8, 25.9) | 16.8 (7.5, 26.2) | 0.0012 |
| **SA3:** Primary analysis, with participants who had at least 1 post-baseline bone marrow assessment | 232 | 36.2 (30.0, 42.8) | 65 | 29.2 (18.6, 41.8) | 7.8 (-4.2, 19.8) | 0.2438 |
| **SA4:** Primary analysis, but CR/CRh by cycle 4 divided by number of participants in the analysis population* | 142 | 21.8 (15.3, 29.5) | N/A | N/A | N/A | N/A |
| **SA5:** Primary analysis, but CR/CRh prior to HSCT (number of participants who achieve CR/CRh prior to HSCT divided by the number | 247 | 26.3 (20.9, 32.3) | 124 | 15.3 (9.5, 22.9) | 10.9 (2.4, 19.5) | 0.0171 |

| | | | | | | |
|---|---|---|---|---|---|---|
| of participants in the analysis population) | | | | | | |

**Abbreviations:**
**CI** = confidence interval; **CR** = complete remission; **CRh** = complete remission with partial hematological recovery; **HSCT** = hematopoietic stem cell transplant; **mRAS** = modified response analysis set; **N/A** = not applicable; **SA** = sensitivity analysis

***Conducted only at the interim analysis and applicable to the gilteritinib arm only (data cut-off August 4th, 2017).**

**Sources:**
Additional sponsor information provided March 10, 2020[54]
Clinical Study Report, Astellas Pharma 2019[5]
Perl et al., 2019[2]

*Secondary Endpoints*

*Event-free survival (EFS)*

At the time of data cut-off, the median duration of EFS follow-up in the gilteritinib arm was 12.9 months (95% CI: 10.2, 14.9) and 1.2 months (95% CI: 1.1, 1.3) in the salvage chemotherapy arm.[55] A total of 189 (76.5%) EFS events occurred in the gilteritinib arm and 62 (50.0%) EFS events occurred in the salvage chemotherapy arm.[3] The median duration of EFS was 2.8 months (95% CI; 1.4, 3.7) in the gilteritinib arm and 0.7 months (95% CI: 0.2, NE) in the salvage chemotherapy arm. There was a 21% (HR: 0.79; 95% CI: 0.58, 1.09; p = 0.0830) reduction in the risk of an EFS event in the gilteritinib arm relative to the placebo arm, however it was not statistically significant. The percentage of patients with CRc in the low-intensity chemotherapy subgroup was 4%, and thus, EFS was largely derived from the high-intensity chemotherapy group where most patients entered long-term follow-up 1-2 months post-randomized and were censored since relapse events were defined by central review of bone marrow biopsy specimens. This was determined to limit the usefulness of the protocol-defined analysis of EFS and a sensitivity analysis with a modified definition of EFS that included failure to obtain CRc was performed. Failure was assigned as an event on the date of randomization, relapse, or death from any cause including initiation of a new antileukemic therapy reported in long-term follow-up. Based on this definition, median EFS was 2.3 months (95% CI: 1.4, 3.6) in the gilteritinib arm and 0.7 months (95% CI: 0.1, 1.3), with a 50% reduction in the risk of an EFS event associated with the gilteritinib arm relative to the salvage chemotherapy arm (HR: 0.50; 95% CI: 0.39, 0.64).[2]

**Table 6.18. Summary of event-free survival in the ADMIRAL trial, ITT population (n=371)[3]**

| Parameter Category/Statistics | Gilteritinib 120 mg (n = 247) | Chemotherapy (n = 124) |
|---|---|---|
| **EFS Events, n (%)†** | 189 (76.5) | 62 (50.0) |
| Relapse | 75 (30.4) | 1 (0.8) |
| Treatment failure | 97 (39.3) | 48 (38.7) |
| Death | 17 (6.9) | 13 (10.5) |
| Censored events | 58 (23.5) | 62 (50.0) |
| **Duration of EFS, Months‡** | | |
| Q1 (95% CI) | < 0.1 (NE, NE) | < 0.1 (NE, NE) |
| Median (95% CI) | 2.8 (1.4, 3.7) | 0.7 (0.2, NE) |
| Q3 (95% CI) | 8.3 (6.5, 12.1) | NE (3.4, NE) |
| Range§ | < 0.1, 31.2+ | < 0.1, 6.6+ |
| **Stratified Analysis (Primary)¶** | | |
| Log-rank test (primary) (P-value [1-sided P-value]) | 0.0830 [1-sided P-value: 0.0415] | |
| Wald test: P-value | 0.1521 | |
| HR (95% CI)†† | 0.793 (0.577, 1.089) | |
| *Table continued on next page* | | |
| **Unstratified Analysis** | | |
| Log-rank test (P-value) | 0.1364 | |
| Wald test: P-value | 0.2287 | |
| HR (95% CI)†† | 0.825 (0.604, 1.128) | |
| **EFS Rate % (95% CI) ‡‡** | | |
| 6 months | 33.2 (27.2, 39.3) | 27.1 (8.2, 50.6) |
| 12 months | 19.8 (14.6, 25.7) | NE (NE, NE) |
| 24 months | 12.2 (6.7, 19.6) | NE (NE, NE) |
| 36 months | NE (NE, NE) | NE (NE, NE) |
| ***EFS Using the Long-term Follow-up Data of Death and New AML Therapies*** | | |
| **EFS Events, n (%)§§** | 207 (83.8) | 111 (89.5) |
| Relapse | 75 (30.4) | 1 (0.8) |
| Relapse-off treatment | 6 (2.4) | 8 (6.5) |
| New AML therapy | 3 (1.2) | 26 (21.0) |
| Treatment failure | 97 (39.3) | 48 (38.7) |
| Death | 26 (10.5) | 28 (22.6) |
| Censored events | 40 (16.2) | 13 (10.5) |
| **Duration of EFS, Months‡** | | |
| Q1 (95% CI) | < 0.1 (NE, NE) | < 0.1 (NE, NE) |
| Median (95% CI) | 2.3 (1.4, 3.6) | 0.7 (0.1, 1.3) |
| Q3 (95% CI) | 7.4 (5.7, 10.0) | 2.0 (1.7, 2.6) |
| Range§ | < 0.1, 31.2+ | < 0.1, 10.0 |
| **Stratified Analysis (Primary)¶** | | |
| Log-rank test (primary) (P-value [1-sided P-value]) | < 0.0001 (1-sided P-value: < 0.0001) | |
| Wald test: P-value†† | < 0.0001 | |
| HR (95% CI)†† | 0.499 (0.387, 0.643) | |
| **Unstratified Analysis** | | |
| Log-rank test (P-value) | < 0.0001 | |
| Wald test: P-value†† | < 0.0001 | |
| HR (95% CI)†† | 0.508 (0.397, 0.651) | |
| **EFS Rate % (95% CI)‡‡** | | |
| 6 months | 30.5 (24.8, 36.3) | 5.8 (2.2, 11.8) |
| 12 months | 16.3 (11.7, 21.5) | 0 (NE, NE) |
| 24 months | 9.4 (5.0, 15.5) | 0 (NE, NE) |
| 36 months | NE (NE, NE) | 0 (NE, NE) |

percentages were calculated based on the total number of patients with nonmissing event/censored value.
†Patients were summarized under the categories that occurred first. If treatment failure and death occurred on the same day, patients were summarized under death; ‡Based on Kaplan-Meier estimates; §A "+" indicates censoring; ¶Stratification factors were response to first-line AML therapy and preselected salvage chemotherapy per interactive response technology; ††Based on the Cox proportional hazards model. Assuming proportional hazards, an HR of < 1 indicates a reduction in the hazard rate in favor of the gilteritinib arm;‡‡EFS rate and 95% CI were estimated using the Kaplan-Meier method and the Greenwood formula; §§Patients were summarized under the event categories that occurred first. If treatment failure and death occurred on the same day, patients were summarized under death.

**Source:** EPAR, EMA 2019[3]

*Complete remission rate (CR) rate*

The CR rate in the gilteritinib arm was 21.1% (n=52) and 10.5% (n=13) in the salvage chemotherapy arm (treatment difference: 10.6%; 95% CI: 2.8, 18.4; p-value =

0.0106). Due to the statistical insignificance of EFS and the preplanned hierarchal testing method, statistical significance of CR rate was not achieved.[3]

Sensitivity analyses for CR rate are outlined in Table 6.19. Sensitivity analyses with the ITT population that included only patients with at least 1 post baseline marrow assessment, analysis of the CR rate with the per protocol analysis set (excluding patients with who did not meet specific protocol exclusion criteria), and analysis of the CR rate with the ITT population that achieved CR prior to HSCT revealed no statistically significant treatment differences between treatment arms.[3]

**Table 6.19. Summary of complete remission rate and sensitivity analyses in the ADMIRAL trial, ITT population**[3]

| Parameter<br>Category/Statistics | Gilteritinib<br>(n = 247) | Chemotherapy<br>(n = 124) |
|---|---|---|
| **Primary Analysis, ITT** | | |
| **CR Rate**, n/N (%)<br>[95% CI]† | 52/247 (21.1)<br>[16.1, 26.7] | 13/124 (10.5)<br>[5.7, 17.3] |
| Adjusted treatment difference % [95% CI]‡ | 10.6 [2.8, 18.4] | |
| Stratified P-value (primary) [1-sided P-value]‡ | 0.0106 [1-sided P-value: 0.0053] | |
| Unstratified P-value [1-sided P-value]§ | 0.0134 [1-sided P-value: 0.0067] | |
| **Sensitivity Analysis, ITT and Received at Least 1 Dose of Study Drug** | | |
| **CR Rate**, n/N (%) [95% CI]† | 52/246 (21.1) [16.2, 26.8] | 13/109 (11.9) [6.5, 19.5] |
| Adjusted treatment difference % [95% CI]‡ | 9.3 [1.0, 17.6] | |
| P-value‡ | 0.0348 | |
| **Sensitivity Analysis, ITT With at Least 1 Postbaseline Bone Marrow Assessment** | | |
| **CR Rate**, n/N (%) [95% CI]† | 52/232 (22.4) [17.2, 28.3] | 13/65 (20.0) [11.1, 31.8] |
| Adjusted treatment difference % [95% CI]‡ | 3.3 [-8.1, 14.7] | |
| P-value‡ | 0.5693 | |
| **Sensitivity Analysis, FAS** | | |
| **CR Rate**, n/N (%) [95% CI]† | 50/243 (20.6) [15.7, 26.2] | 13/123 (10.6%) [5.7, 17.4] |
| Adjusted treatment difference % [95% CI]‡ | 10.0 [2.2, 17.8] | |
| P-value‡ | 0.0155 | |
| **Sensitivity Analysis, PPS** | | |
| **CR Rate**, n/N (%) [95% CI]† | 50/217 (23.0) [17.6, 29.2] | 13/70 (18.6) [10.3, 29.7] |
| Adjusted treatment difference % [95% CI]‡ | 5.4 [-5.7, 16.6] | |
| P-value‡ | 0.3405 | |
| **Sensitivity Analysis, ITT, Achieving CR Prior to HSCT¶** | | |
| **CR Rate**, n/N (%) [95% CI]† | 34/247 (13.8) [9.7, 18.7] | 13/124 (10.5) [5.7, 17.3] |
| Adjusted treatment difference % [95% CI]‡ | 3.3 [-4.0, 10.5] | |
| P-value‡ | 0.3639 | |

†Using exact method based on binomial distribution; ‡Based on stratified Cochran-Mantel-Haenszel test. Stratification factors were response to first line AML therapy and preselected salvage chemotherapy per IRT. Treatment differences were adjusted based on pooled strata. Treatment difference = gilteritinib – chemotherapy; §Based on 2-sided Fisher's exact test; ¶The CR rate prior to HSCT was defined as the number of patients who achieved CR at any postbaseline visit prior to HSCT divided by the number of patients in the analysis population.

**Source:** EPAR, EMA 2019[3]

*Duration of remission, complete remission with partial hematologic recovery (CRh) rate, and composite complete remission rate (CRc)*

The median duration of CR was 14.8 months (95% CI: 11.0, NE) in the gilteritinib arm and 1.8 (95% CI: NE, NE) months in the salvage chemotherapy arm. The median duration of CR/CRh was 11.0 months (95% CI: 4.6, NE) in the gilteritinib arm and 1.8 months (95% CI: NE, NE) in the salvage chemotherapy arm. As discussed in the EFS section, due to a high proportion of censoring in the high intensity chemotherapy arm, the median duration of CR or CR/CRh could not be reliably

estimated in the salvage chemotherapy arm. Additionally, patients in the gilteritinib arm were treated continuously and were able to have HSCT during treatment, and thus, the duration of remission would be longer due to this additional regimen to prolong remission.[3]

The CRh rate was 13.0% (n=32) in the gilteritinib arm and 4.8% (n=6) in the salvage chemotherapy arm. For patients with CR with incomplete hematological recovery, the CRi rate was 25.5% (n=63) in the gilteritinib arm and 11.3% (n=14) in the salvage chemotherapy arm, whereas for patients with CR with incomplete platelet recovery the CRp rate was 7.7% (n=19) in the gilteritinib arm and no patients had CRp in the salvage chemotherapy arm. The CRc rate (CR, CRp, CRi) was 54.3% (n=134) in the gilteritinib arm and 21.8% (n=27) in the salvage chemotherapy arm.[3]

*Transplantation rate, transfusion conversion rate, and transfusion maintenance rate*

The transplantation rate was 25.5% (n=63) in the gilteritinib arm and 15.3% (n=19), with a statistically significant treatment difference of 10.2% (95% CI: 1.2, 19.1; P=0.0333).[3]

Transfusion conversion and maintenance rates were described for the gilteritinib arm only and for patients who took at least 1 dose of study drug (n=246). Among 197 patients dependent on RBC and/or platelet transfusions at baseline, 68 became independent during any 56-day postbaseline period, and thus the transfusion conversion rate was 34.5% (95% CI: 27.9, 41.6). Among the 49 patients who were independent of RBC and platelet transfusions at baseline, 29 remained transfusion-independent during any 56-day postbaseline period, and thus the transfusion maintenance rate was 59.2% (95% CI: 44.2, 73.0).[3]

**Table 6.20. Summary of transplantation rate in the ADMIRAL trial, ITT population**[3]

| Parameter<br>Category/Statistics | Gilteritinib<br>(n = 247) | Chemotherapy<br>(n = 124) |
|---|---|---|
| **Transplantation Rate**, n (%)<br>[95 % CI]† | 63 (25.5)<br>[20.2, 31.4] | 19 (15.3)<br>[9.5, 22.9] |
| Treatment difference % [95% Exact CI]‡<br>Unstratified 2-sided P-value§ | 10.2 [1.2, 19.1]<br>0.0333 | |

† Using exact method based on binomial distribution; ‡ Treatment difference = gilteritinib - chemotherapy. The 95% CIs were asymptotic confidence limits using the normal approximation to the binomial distribution; § Based on 2-sided Fisher's exact test.

**Source:** EPAR, EMA 2019[3]

**Table 6.21. Shift table of transfusion status, ADMIRAL trial, gilteritinib arm safety analysis population (n=246)**[3]

| Baseline Transfusion Status | Postbaseline Transfusion Status n = 246<br>n (%) | | |
|---|---|---|---|
| | Independent | Dependent | Not Evaluable |
| Independent (n = 49) | 29 (59.2) | 12 (24.5) | 8 (16.3) |
| Dependent (n = 197) | 68 (34.5) | 110 (55.8) | 19 (9.6) |

**Source:** EPAR, EMA 2019[3]

### *Exploratory Outcomes*

*Health related quality of life (HRQoL)*

The change from baseline in BFI fatigue score, FACIT-Dys-SF and functional limitations subscales scores, FACT-Leu total score and dizziness and mouth sore subscales scores for cycle 2, day 1 were similar in the gilteritinib arm compared with the salvage chemotherapy arm.[3] At baseline, 91.9% and 78.2% in the gilteritinib and salvage chemotherapy arms had baseline BFI questionnaires completed, whereas at Cycle 2, Day 1, this dropped to 83.4% and 12.1%, respectively.[6] The baseline median BFI fatigue score was 2.6 (range: 0, 9) in the gilteritinib arm and 2.0 (range: 0, 10) in the salvage chemotherapy with no change from baseline at cycle 2, day 1 in the gilteritinib arm (range: -8, 7) and a change of 0.7 in the salvage chemotherapy arm (range: -5, 4).[5]

A higher FACIT-Dys-SF score indicates a more unfavourable outcome and includes a dyspnea subscale and functional limitations subscale. At baseline, 64.8% and 57.3% in the gilteritinib and salvage chemotherapy arms had baseline FACIT-Dys-SF questionnaires completed, whereas at Cycle 2, Day 1, this dropped to 46.6% and 8.9%, respectively. The median baseline score for the dyspnea subscale was 5 (range: 0, 30) in the gilteritinib arm and 4 (range: 0, 30) in the salvage chemotherapy arm. The median change from baseline was on the dyspnea subscale was 0 (range: -20, 16) and 1.0 (range: -12, 18) in the gilteritinib and salvage chemotherapy arms, respectively, by Cycle 2 Day 1. On the functional limitations subscale, the median baseline score was 3.2 (range: 0, 30) and 3.0 (range: 0, 30) and the median change from baseline to Cycle 2, Day 1 was 0.0 (range: -19, 15) and 1.0 (range: -16, 14) in the gilteritinib and salvage chemotherapy arms, respectively.[5]

A higher FACT-Leu score indicates better quality of life, and the median FACT-Leu total score at baseline was 125.8 (range: 58, 173) and 123.0 (range: 28, 160) in the gilteritinib (n=223, 90.3%) and salvage chemotherapy arms (n=97, 78.2%), respectively. The median change from baseline to cycle 2, Day 1 was -0.1 (range: -79, 68) in the gilteritinib arm (n=198, 80.2%) and 9 (range: -38, 28) in the salvage chemotherapy arm (n=15, 12.1%). On all other subscales (physical, social, emotional, and functional) median baseline scores were comparable between treatment arms and minimal changes were observed from baseline to Cycle 2.[5]

For the dizziness and mouth sores questionnaires, a higher score indicates a more unfavourable outcome. At baseline, 90.3% and 78.2% in the gilteritinib and salvage chemotherapy arms had baseline dizziness and mouth sores questionnaires completed, whereas at Cycle 2, Day 1, this dropped to 80.2% and 12.1%, respectively. For the dizziness subscale, the median score at baseline was 4.0 (range: 0, 4) in both the gilteritinib arm and the salvage chemotherapy arm. The change from baseline in dizziness subscale score for cycle 2, day 1 was similar in the gilteritinib arm (median change: 0.0; range: -3, 4) compared with the salvage chemotherapy arm (median change; 0.0; range: -2, 1). For the mouth sores subscale, the median score at baseline was 4.0 (range: 0, 4) in both the gilteritinib arm and the salvage chemotherapy arm. The change from baseline in mouth sores subscale score for cycle 2, day 1 was similar in the gilteritinib arm (median change: 0.0; range: -3, 2) compared with the salvage chemotherapy arm (median change: 0.0; range: -1, 1).[5]

At baseline, 88.3% and 77.4% in the gilteritinib and salvage chemotherapy arms had baseline EQ-5D-5L questionnaires completed, whereas at Cycle 2, Day 1, this dropped to 78.1% and 12.1%, respectively. The median change in EQ-5D-5L VAS

score from baseline to Cycle 2, Day 1 was 0 for the gilteritinib arm and -3.0 for the salvage chemotherapy arm. The median utility change from baseline score was 0 for the gilteritinib arm and 0.1 for the salvage chemotherapy arm at cycle 2, day 1. For each of the 5 EQ-5D-5L dimension scores, the majority of patients in both treatment arms reported no problem (score of 1) at baseline and at cycle 2, day 1.[3]

***Harms Outcomes***

Treatment Exposure

A total of 246 patients were treated with gilteritinib and 109 patients with salvage chemotherapy. The median duration of treatment was 126 days (range: 4, 885) in the gilteritinib arm and 28 days (range: 5, 217) in the salvage chemotherapy arm.[3] All patients were randomized to gilteritinib at a starting dose of 120 mg, but had the option of being escalated to 200 mg based on lack of efficacy (no CRc) after cycle 1, and a total of 78 (31.7%) escalated to 200 mg.[3,4] For patients who received a dose increase, the median duration of treatment prior to dose escalation was 1.4 months (range: 0.9, 17.4) and 1.6 months (range: <0.1, 24.8) after dose escalation.[4]

A total of 30.5% of patients (n=75) required a dose reduction in the gilteritinib arm, of which 58 patients decreased to 80 mg initially and subsequently 4 patients reduced to 40 mg. There were 17 patients whose dose increased to 200 mg initially, with 2 patients who decreased to 120 mg and then to 80 mg, 1 patient who decreased to 40 mg directly, and the other 14 decreased to 120 mg without further reductions.[4]

A total of 10.1% of patients (n=36) required a dose reduction due to an AE. There were a higher proportion of AEs leading to a dose reduction in the gilteritinib arm (n=35, 14.2%), most of which were considered TEAEs (n=31, 12.6%) by investigator assessment, compared to the salvage chemotherapy arm (n=1, 0.9%; was not considered a drug-related). There were a higher proportion of AEs leading to a dose interruption in the gilteritinib arm (n=112, 45.5%), of which 32.1% (n=79) were considered to be drug related, compared to the salvage chemotherapy arm (n=5, 4.6%; 3 were considered drug related).[3]

There were a higher proportion of patients who withdrew due to AEs in the gilteritinib arm (n=58, 23.6%), of which 11.0% (n=27) were considered drug related, compared to the salvage chemotherapy arm (n=13, 11.9%; of which 5 were considered drug related).[3] As shown in Table 6.22, drug related AEs leading to withdrawal in the gilteritinib arm included aspartate aminotransferase increased (n=4, 1.6%), alanine aminotransferase increased (n=3, 1.2%), and pneumonia (n=3, 1.2%). Drug related AEs leading to withdrawal in the salvage chemotherapy arm included respiratory failure (n=2, 1.8%), febrile neutropenia (n=1, 0.9%), hemorrhagic stroke (n=1, 0.9%), pulmonary hemorrhage (n=1, 0.9%) and lung infection (n=1, 0.9%).[2] See Table 6.23. Dose reductions, interruptions, and withdrawals due to AEs were likely higher in the gilteritinib arm due to the longer treatment exposure.

Adverse Events (AEs)

All patients in the gilteritinib arm, of which 206 (83.7%) were considered treatment-related, and 107 (98.2%) patients in the salvage chemotherapy arm, of which 71 (61.5%) were considered treatment-related, experienced an any-grade AE.[3] As shown in Table 6.23, the most common any-grade AE was anemia in the gilteritinib arm (n=116, 47.2%), which was followed by febrile neutropenia (n=115, 46.7%), pyrexia (n=105, 42.7%), alanine aminotransferase increased (n=103, 41.9%),

aspartate aminotransferase increased (n=99, 40.2%), diarrhea (n=81, 32.9%), and nausea (n=79, 32.1%). In the salvage chemotherapy arm, the most common any-grade AEs included febrile neutropenia (n=40, 36.7%), anemia (n=38, 34.9%), nausea (n=36, 33.0%), hypokalemia (n=34, 31.2%), pyrexia (n=32, 29.4%), and diarrhea (n=32, 29.4%).The most common any-grade AE that occurred in the first 30 days was anemia in both gilteritinib (n=82, 33.3%) and the salvage chemotherapy arm (n=36, 33.0%).[2]

Grade ≥3 AEs occurred in 236 (95.9%) of patients in the gilteritinib, of which 153 (62.2%) were considered treatment-related, and in the salvage chemotherapy arm 94 (86.2%) grade ≥3 AEs occurred, of which 57 (52.3%) were considered treatment related. The most common grade ≥3 AEs (Table 6.23) for both arms included febrile neutropenia (gilteritinib: n=113 45.9%; salvage chemotherapy: n=40, 36.7%), anemia (gilteritinib: n=100, 40.7%; salvage chemotherapy: n=33, 30.3%), platelet count decreased (gilteritinib: n=54, 22.0%; salvage chemotherapy: n=27, 24.8%), and thrombocytopenia (gilteritinib: n=56, 22.8%; salvage chemotherapy: n=18, 16.5%).

Serious Adverse Events (SAEs)

SAEs occurred in 205 (83.3%) patients in the gilteritinib arm, of which 88 (35.8%) patients were considered to be treatment related. A smaller proportion of SAEs occurred in the salvage chemotherapy arm affecting 34 (31.2%) of patients, of which 16 (14.7%) were considered treatment-related.[3] The most common SAE was febrile neutropenia in both arms, which occurred in a higher proportion in gilteritinib arm (n=76, 30.9%) compared to the salvage chemotherapy arm (n=9, 8.3%). In the gilteritinib arm, febrile neutropenia was followed by acute myeloid leukemia (n=33, 13.4%), pyrexia (n=32, 13%) and pneumonia (n=26, 10.6%). In the salvage chemotherapy arm, it was followed by pneumonia (n=3, 3.7%) and acute myeloid leukemia (n=4, 3.7%).[2] See Table 6.23.

Adverse Events of Special Interest (AESIs)

Cardiac toxicities were identified as an AESI, and are shown in Table 6.24. There were a higher proportion of patients that experienced cardiac failure (7.7% vs. 2.8%), pericarditis/pericardial effusion (6.1% vs. 0%), and arrythmia due to QT prolongation (14.2% vs. 8.1%) of any-grade in the gilteritinib arm compared to the salvage chemotherapy arm.[5]

Deaths

In the gilteritinib arm, a total of 170 (69.1%) deaths occurred, of which 71 (28.9%) were due to AEs. In the salvage chemotherapy arm, a total of 81 (74.3%) deaths occurred of which 16 (14.7%) were due to AEs. However, only 10 (4.1%) patients had AEs were considered drug-related that led to death in the gilteritinib arm, and 5 (4.6%) patients in the salvage chemotherapy arm.[3] As presented in Table 6.25, AEs considered at least possibly related to gilteritinib that led to death included pneumonia (n=3, 1.2%), large intestine perforation (n=2, 0.8%), and septic shock (n=2, 0.8%). In the salvage chemotherapy arm, AEs that were at least possibly related to study drug leading to death included respiratory failure (n=2, 1.8%) and sepsis (n=2; 1.8%).[2]

**Table 6.22. Summary of treatment-emergent adverse events leading to treatment discontinuation, safety analysis population[2]**

| Treatment-Related Adverse Event, no. (%) | All Patients (N=355) | Gilteritinib (n=246) | Salvage Chemotherapy (n=109) |
|---|---|---|---|
| | Any Grade | Any Grade | Any Grade |
| Aspartate aminotransferase increased | 4 (1.1) | 4 (1.6) | 0 |
| Respiratory failure | 3 (0.8) | 1 (0.4) | 2 (1.8) |
| Alanine aminotransferase increased | 3 (0.8) | 3 (1.2) | 0 |
| Pneumonia | 3 (0.8) | 3 (1.2) | 0 |
| Febrile neutropenia | 2 (0.6) | 1 (0.4) | 1 (0.9) |
| Retinopathy | 2 (0.6) | 2 (0.8) | 0 |
| Lung infection | 2 (0.6) | 1 (0.4) | 1 (0.9) |
| Septic shock | 2 (0.6) | 2 (0.8) | 0 |
| Anemia | 1 (0.3) | 1 (0.4) | 0 |
| Pancytopenia | 1 (0.3) | 1 (0.4) | 0 |
| Pericarditis | 1 (0.3) | 1 (0.4) | 0 |
| Intestinal ischemia | 1 (0.3) | 1 (0.4) | 0 |
| Large intestine perforation | 1 (0.3) | 1 (0.4) | 0 |
| Face edema | 1 (0.3) | 1 (0.4) | 0 |
| Cholecystitis | 1 (0.3) | 1 (0.4) | 0 |
| Cellulitis | 1 (0.3) | 1 (0.4) | 0 |
| Sepsis | 1 (0.3) | 1 (0.4) | 0 |
| Blood alkaline phosphatase increased | 1 (0.3) | 1 (0.4) | 0 |
| Blood bilirubin increased | 1 (0.3) | 1 (0.4) | 0 |
| Neutrophil count decreased | 1 (0.3) | 1 (0.4) | 0 |
| White blood cell count decreased | 1 (0.3) | 1 (0.4) | 0 |
| Diabetes mellitus | 1 (0.3) | 0 | 1 (0.9) |
| Hyperglycemia | 1 (0.3) | 1 (0.4) | 0 |
| Back pain | 1 (0.3) | 1 (0.4) | 0 |
| Cerebral hemorrhage | 1 (0.3) | 1 (0.4) | 0 |
| Depressed level of consciousness | 1 (0.3) | 1 (0.4) | 0 |
| Hemorrhagic stroke | 1 (0.3) | 0 | 1 (0.9) |
| Delirium | 1 (0.3) | 0 | 1 (0.9) |
| Acute kidney injury | 1 (0.3) | 1 (0.4) | 0 |
| Interstitial lung disease | 1 (0.3) | 1 (0.4) | 0 |
| Pulmonary hemorrhage | 1 (0.3) | 0 | 1 (0.9) |
| Dermatitis bullous | 1 (0.3) | 1 (0.4) | 0 |

**Source:** NEJM, Perl et al., 381(18):1728-1740. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

**Table 6.23. Summary of adverse events of any grade (that occurred in at least 10% of patients in either treatment group), grade ≥3 adverse events, and serious adverse events in the ADMIRAL trial, safety analysis population[2]**

| Treatment-Emergent Adverse Event, no. (%) | All Patients (N=355) | | | Gilteritinib (n=246) | | | Salvage Chemotherapy (n=109) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Any Grade | Grade ≥3 | Serious | Any Grade | Grade ≥3 | Serious | Any Grade | Grade ≥3 | Serious |
| Febrile neutropenia | 155 (43.7) | 153 (43.1) | 85 (23.9) | 115 (46.7) | 113 (45.9) | 76 (30.9) | 40 (36.7) | 40 (36.7) | 9 (8.3) |
| Anemia | 154 (43.4) | 133 (37.9) | 8 (2.3) | 116 (47.2) | 100 (40.7) | 8 (3.3) | 38 (34.9) | 33 (30.3) | 0 |
| Pyrexia | 137 (38.6) | 12 (3.4) | 33 (9.3) | 105 (42.7) | 8 (3.3) | 32 (13.0) | 32 (29.4) | 4 (3.7) | 1 (0.9) |
| Nausea | 115 (32.4) | 5 (2.0) | 2 (0.6) | 79 (32.1) | 0 | 2 (0.8) | 36 (33.0) | 5 (1.4) | 0 |
| Alanine aminotransferase increased | 113 (31.8) | 39 (11.0) | 13 (3.7) | 103 (41.9) | 34 (13.8) | 13 (5.3) | 10 (9.2) | 5 (4.6) | 0 |
| Diarrhea | 113 (31.8) | 12 (3.4) | 10 (2.8) | 81 (32.9) | 9 (3.7) | 10 (4.1) | 32 (29.4) | 3 (2.8) | 0 |
| Aspartate aminotransferase increased | 112 (31.5) | 38 (10.7) | 10 (2.8) | 99 (40.2) | 36 (14.6) | 10 (4.1) | 13 (11.9) | 2 (1.8) | 0 |
| Hypokalemia | 105 (29.6) | 44 (12.4) | 1 (0.3) | 71 (28.9) | 32 (13.0) | 0 | 34 (31.2) | 12 (11.0) | 1 (0.9) |
| Constipation | 92 (25.9) | 2 (0.6) | 0 | 76 (30.9) | 2 (0.8) | 0 | 16 (14.7) | 0 | 0 |
| Fatigue | 84 (23.7) | 8 (2.3) | 5 (1.4) | 70 (28.5) | 6 (2.4) | 4 (1.6) | 14 (12.8) | 2 (1.8) | 1 (0.9) |
| Platelet count decreased | 84 (23.7) | 81 (22.8) | 5 (1.4) | 56 (22.8) | 54 (22.0) | 5 (2.0) | 28 (25.7) | 27 (24.8) | 0 |
| Cough | 83 (23.4) | 1 (0.3) | 2 (0.6) | 72 (29.3) | 1 (0.4) | 2 (0.8) | 11 (10.1) | 0 | 0 |
| Thrombocytopenia | 81 (22.8) | 74 (20.8) | 5 (1.4) | 63 (25.6) | 56 (22.8) | 4 (1.6) | 18 (16.5) | 18 (16.5) | 1 (0.9) |
| Headache | 80 (22.5) | 3 (0.8) | 5 (1.4) | 64 (26.0) | 3 (1.2) | 5 (2.0) | 16 (14.7) | 0 | 0 |
| Peripheral edema | 72 (20.3) | 1 (0.3) | 0 | 59 (24.0) | 1 (0.4) | 0 | 13 (11.9) | 0 | 0 |
| Vomiting | 68 (19.2) | 1 (0.3) | 1 (0.3) | 53 (21.5) | 1 (0.4) | 1 (0.4) | 15 (13.8) | 0 | 0 |
| Dyspnea | 65 (18.3) | 13 (3.7) | 12 (3.4) | 58 (23.6) | 10 (4.1) | 10 (4.1) | 7 (6.4) | 3 (2.8) | 2 (1.8) |
| Decreased appetite | 64 (18.0) | 10 (2.8) | 2 (0.6) | 44 (17.9) | 5 (2.0) | 2 (0.8) | 20 (18.3) | 5 (4.6) | 0 |
| Blood alkaline phosphatase increased | 58 (16.3) | 7 (2.0) | 1 (0.3) | 56 (22.8) | 7 (2.8) | 1 (0.4) | 2 (1.8) | 0 | 0 |
| Neutrophil count decreased | 54 (15.2) | 54 (15.2) | 4 (1.1) | 42 (17.1) | 42 (17.1) | 4 (1.6) | 12 (11.0) | 12 (11.0) | 0 |
| Abdominal pain | 53 (14.9) | 5 (1.4) | 2 (0.6) | 37 (15.0) | 5 (2.0) | 2 (0.8) | 16 (14.7) | 0 | 0 |
| Hypocalcemia | 53 (14.9) | 13 (3.7) | 0 | 47 (19.1) | 12 (4.9) | 0 | 6 (5.5) | 1 (0.9) | 0 |
| White blood cell count decreased | 53 (14.9) | 51 (14.4) | 1 (0.3) | 34 (13.8) | 32 (13.0) | 1 (0.4) | 19 (17.4) | 19 (17.4) | 0 |
| Hypomagnesemia | 51 (14.4) | 0 | 0 | 39 (15.9) | 0 | 0 | 12 (11.0) | 0 | 0 |
| Hypotension | 51 (14.4) | 22 (6.2) | 7 (2.0) | 43 (17.5) | 19 (7.7) | 6 (2.4) | 8 (7.3) | 3 (2.8) | 1 (0.9) |
| Pneumonia | 51 (14.4) | 34 (9.6) | 30 (8.5) | 43 (17.5) | 29 (11.8) | 26 (10.6) | 8 (7.3) | 5 (4.6) | 4 (3.7) |
| Dizziness | 50 (14.1) | 1 (0.3) | 1 (0.3) | 48 (19.5) | 1 (0.4) | 1 (0.4) | 2 (1.8) | 0 | 0 |
| Epistaxis | 50 (14.1) | 3 (0.8) | 0 | 42 (17.1) | 2 (0.8) | 0 | 8 (7.3) | 1 (0.9) | 0 |
| Hyperglycemia | 50 (14.1) | 27 (7.6) | 1 (0.3) | 36 (14.6) | 18 (7.3) | 0 | 14 (12.8) | 9 (8.3) | 1 (0.9) |
| Stomatitis | 50 (14.1) | 10 (2.8) | 2 (0.6) | 34 (13.8) | 6 (2.4) | 1 (0.4) | 16 (14.7) | 4 (3.7) | 1 (0.9) |
| Neutropenia | 49 (13.8) | 48 (13.5) | 4 (1.1) | 33 (13.4) | 33 (13.4) | 3 (1.2) | 16 (14.7) | 15 (13.8) | 1 (0.9) |
| Asthenia | 48 (13.5) | 8 (2.3) | 3 (0.8) | 38 (15.4) | 6 (2.4) | 3 (1.2) | 10 (9.2) | 2 (1.8) | 0 |
| Hypophosphatemia | 46 (13.0) | 24 (6.8) | 1 (0.3) | 41 (16.7) | 20 (8.1) | 1 (0.4) | 5 (4.6) | 4 (3.7) | 0 |
| Insomnia | 46 (13.0) | 0 | 0 | 40 (16.3) | 0 | 0 | 6 (5.5) | 0 | 0 |
| Rash | 46 (13.0) | 2 (0.6) | 0 | 36 (14.6) | 1 (0.4) | 0 | 10 (9.2) | 1 (0.9) | 0 |
| Hypertension | 44 (12.4) | 24 (6.8) | 2 (0.6) | 34 (13.8) | 20 (8.1) | 1 (0.4) | 10 (9.2) | 4 (3.7) | 1 (0.9) |
| Pain in extremity | 44 (12.4) | 3 (0.8) | 1 (0.3) | 36 (14.6) | 2 (0.8) | 0 | 8 (7.3) | 1 (0.9) | 1 (0.9) |
| Back pain | 42 (11.8) | 3 (0.8) | 1 (0.3) | 29 (11.8) | 2 (0.8) | 1 (0.4) | 13 (11.9) | 1 (0.9) | 0 |
| Hypoalbuminemia | 39 (11.0) | 5 (1.4) | 0 | 32 (13.0) | 3 (1.2) | 0 | 7 (6.4) | 2 (1.8) | 0 |
| Hyponatremia | 39 (11.0) | 19 (5.4) | 2 (0.6) | 33 (13.4) | 16 (6.5) | 2 (0.8) | 6 (5.5) | 3 (2.8) | 0 |
| Myalgia | 39 (11.0) | 1 (0.3) | 0 | 35 (14.2) | 1 (0.4) | 0 | 4 (3.7) | 0 | 0 |
| Acute myeloid leukemia | 37 (10.4) | 37 (10.4) | 37 (10.4) | 33 (13.4) | 33 (13.4) | 33 (13.4) | 4 (3.7) | 4 (3.7) | 4 (3.7) |
| Arthralgia | 34 (9.6) | 5 (1.4) | 3 (0.8) | 28 (11.4) | 4 (1.6) | 3 (1.2) | 6 (5.5) | 1 (0.9) | 0 |
| Blood creatine phosphokinase increased | 33 (9.3) | 6 (1.7) | 2 (0.6) | 33 (13.4) | 6 (2.4) | 2 (0.8) | 0 (0) | 0 | 0 |
| Blood creatinine increased | 33 (9.3) | 3 (0.8) | 1 (0.3) | 29 (11.8) | 3 (1.2) | 1 (0.4) | 4 (3.7) | 0 | 0 |
| Dysgeusia | 30 (8.5) | 0 | 0 | 25 (10.2) | 0 | 0 | 5 (4.6) | 0 | 0 |

**Source:** NEJM, Perl et al., 381(18):1728-1740. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

**Table 6.24. Summary of cardiac toxicities in the ADMIRAL trial, safety analysis population[5]**

| | Gilteritinib n=246 n (%) | | Salvage Chemotherapy n=109 n (%) | | Total N=355 n (%) | |
|---|---|---|---|---|---|---|
| | All grades | Grade ≥3 | All grades | Grade ≥3 | All grades | Grade ≥3 |
| **Cardiac failure** | **19 (7.7)** | **10 (4.1)** | **3 (2.8)** | **1 (0.9)** | **22 (6.2)** | **11 (3.1)** |
| Pulmonary edema | 11 (4.5) | 2 (0.8) | 2 (1.8) | 0 (0) | 13 (3.7) | 2 (0.6) |
| Cardiac failure | 4 (1.6) | 4 (1.6) | 0 (0) | 0 (0) | 4 (1.1) | 4 (1.1) |
| Ejection fraction decreased | 3 (1.2) | 2 (0.8) | 1 (0.9) | 1 (0.9) | 4 (1.1) | 3 (0.8) |
| **Pericarditis/Pericardial effusion** | 15 (6.1) | 3 (1.2) | 0 (0) | 0 (0) | 3 (0.8) | 1 (0.3) |
| Pericardial effusion | 11 (4.5) | 3 (1.2) | 0 (0) | 0 (0) | 11 (3.1) | 3 (0.8) |
| Pericarditis | 5 (2.0) | 0 (0) | 0 (0) | 0 (0) | 5 (1.4) | 0 (0) |
| **Arrythmia due to QT prolongation** | 35 (14.2) | 20 (8.1) | 2 (1.8) | 2 (1.8) | 37 (10.4) | 22 (6.2) |
| Electrocardiogram QT prolonged | 17 (6.9) | 4 (1.6) | 0 (0) | 0 (0) | 17 (4.8) | 4 (1.1) |
| Syncope | 12 (4.9) | 12 (4.9) | 2 (1.8) | 2 (1.8) | 14 (3.9) | 14 (3.9) |
| Cardiac arrest | 4 (1.6) | 4 (1.6) | 0 (0) | 0 (0) | 4 (1.1) | 4 (1.1) |
| Ventricular tachycardia | 3 (1.2) | 1 (0.4) | 0 (0) | 0 (0) | 3 (0.8) | 1 (0.3) |

**Source:** Clinical Study Report, Astellas Pharma 2019[5]

**Table 6.25. Summary of adverse events leading to death in the ADMIRAL trial, safety analysis population[2]**

| Treatment-Related Adverse Event, no. (%) | All Patients (N=355) | Gilteritinib (n=246) | Salvage Chemotherapy (n=109) |
|---|---|---|---|
| | Any Grade | Any Grade | Any Grade |
| Pneumonia | 3 (0.8) | 3 (1.2) | 0 |
| Sepsis | 3 (0.8) | 1 (0.4) | 2 (1.8) |
| Respiratory failure | 3 (0.8) | 1 (0.4) | 2 (1.8) |
| Large intestine perforation | 2 (0.6) | 2 (0.8) | 0 |
| Septic shock | 2 (0.6) | 2 (0.8) | 0 |
| Cardiac failure congestive | 1 (0.3) | 1 (0.4) | 0 |
| Intestinal ischemia | 1 (0.3) | 1 (0.4) | 0 |
| Cellulitis | 1 (0.3) | 1 (0.4) | 0 |
| Cerebral hemorrhage | 1 (0.3) | 1 (0.4) | 0 |
| Depressed level of consciousness | 1 (0.3) | 1 (0.4) | 0 |
| Influenza | 1 (0.3) | 0 | 1 (0.9) |
| Lung infection | 1 (0.3) | 0 | 1 (0.9) |
| Hemorrhagic stroke | 1 (0.3) | 0 | 1 (0.9) |
| Pulmonary hemorrhage | 1 (0.3) | 0 | 1 (0.9) |

[a]Patients could have more than one treatment-emergent adverse event leading to death.

**Source:** NEJM, Perl et al., 381(18):1728-1740. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

## 6.4 Ongoing Trials

There were four ongoing trials identified as relevant to this review. COMMODORE is aligned with the ADMIRAL trial, however, the primary endpoint is only OS and it is being conducted in countries that were not included in the ADMIRAL trial (China, Thailand, Russia, Singapore, and Malaysia).[29] The remaining three trials are investigating combinations with gilteritinib. There were two Phase I/II trials investigation the combinations of gilteritinib and atezolizumab, and gilteritinib, azacitidine, and venetoclax.[62,63] An additional Phase I trial investigating the combination of gilteritinib and venetoclax was also included due to the inclusion of an expansion cohort specific to relapsed/refractory FLT3-mutated AML patients.[64]

**Table 6.26. Ongoing trials of gilteritinib in relapsed or refractory FLT3-mutated acute myeloid leukemia**

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| **Study:**[29]<br>NCT03182244<br>COMMODORE<br><br>**Characteristics:**<br>Open-label, randomized, active-controlled, Phase III trial<br><br>**Estimated enrolment:**<br>N = 318<br><br>**Number of centres and number of countries:**<br>50 sites in 5 countries: China, Thailand, Russia, Singapore, Malaysia<br><br>**Patient Enrolment Dates:**<br>January 15th, 2018 (ongoing)<br><br>**Estimated primary study completion:**<br>April 2021<br><br>**Estimated study completion:**<br>July 2021<br><br>**Funding:**<br>Astellas Pharma Inc. | Key Inclusion Criteria:<br>• Adult aged ≥18 years old<br>• Primary AML or AML secondary to MDS defined by the World Health Organization (WHO) criteria<br>• Refractory or relapsed after first-line therapy defined as:<br>i. Refractory: did not achieve CR/CRi/CRp with initial therapy; patients must have received 1 cycle of an anthracycline-containing induction block in standard dose of the selected regimen – patients ineligible for standard therapy must have received 1 complete block of induction therapy deemed to be optimum choice to induce remission for the patient<br>ii. Untreated first hematologic relapse: patient achieved CR/CRi/CRp with first-line treatment and relapsed<br>• FLT3-mutation positive determined by central lab<br>• ECOG PS ≤ 2<br>• Eligible for 1 of the 3 salvage chemotherapies<br>• Adequate hematologic, live, and kidney function<br>• Suitable for oral drugs<br>• Patient does not participate in another interventional study while on treatment<br><br>Key Exclusion Criteria:<br>• Diagnosed as APL<br>• BCR-ABL-positive leukemia (chronic myelogenous leukemia in blast crisis)<br>• AML secondary to prior chemotherapy (except MDS)<br>• Second or later hematologic relapse or has received salvage chemotherapy for refractory disease<br>• Clinically active CNS leukemia<br>• Diagnosis of another malignancy unless disease-free for 5 years with the exception of nonmelanoma skin cancer, in situ carcinoma or | Intervention:<br>Gilteritinib (oral)<br><br>Comparator:<br>Salvage chemotherapy<br>• Low dose cytarabine (LoDAC)<br>• MEC (mitoxantrone, etopside, cytarabine)<br>• FLAG (fludarabine, cytarabine, granulocyte colony stimulating factor) | Primary:<br>• OS<br><br>Secondary:<br>• EFS<br>• CR rate<br>• LFS<br>• Duration of CRc<br>• Duration of CR<br>• Duration of CRp<br>• Duration of CRi<br>• CRc rate<br>• Transplantation rate<br>• Brief Fatigue Inventory<br>• Safety<br>• PKs<br>• ECOG PS |

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| | cervical intraepithelial neoplasia if definitive treatment completed<br>• Prior treatment with gilteritinib or other FLT3 inhibitors (except sorafenib and midostaruin used in 1st line as part of induction, consolidation or maintenance)<br>• Clinically significant abnormality of coagulation profile<br>• Major surgery or radiation within 4 weeks of study start<br>• Current or history of CHF NYHA class 3 or 4 unless ECHO within 1 month of study start shows LVEF ≥45%<br>• Mean triplicate QTcF of >45 ms<br>• Long QT syndrome<br>• Hypokalemia or hypomagnesia<br>• Requirement for concomitant drugs that are strong induces of CYP3A, inhibitors or inducers of P-gp, or drugs that target serotonin 5-hydroxytryptamine receptor 1 (5HT1R) or 5-hydroxytryptamine receptor 2B (5HT2BR) receptors or sigma nonspecific receptor<br>• Active uncontrolled infection<br>• HIV, HBV, HCV<br>• Clinically significant GVHD<br>• FLT3 mutation other than FLT3-ITD, FLT3-D835, or FLT3-TKD/I836 | | |
| **Study:**[62]<br>NCT04140487<br><br>**Characteristics:**<br>Open-label, non-randomized, single arm, Phase I/II trial<br><br>**Estimated enrolment:**<br>N = 42<br><br>**Number of centres and number of countries:**<br>1 site in the US<br><br>**Patient Enrolment Dates:**<br>December 17th, 2019 (ongoing)<br><br>**Estimated primary study completion:**<br>September 1st, 2022<br><br>**Estimated study completion:**<br>September 1st, 2022<br><br>**Funding:** | Key Inclusion Criteria:<br>• Adult aged ≥18 years old<br>• Diagnosis:<br>i. Phase I: relapsed/refractory FLT3-mutated AML or MDS that is intermediate-2 or high-risk by International Prognostic Scoring System<br>ii. Phase II cohort A: newly diagnosed FLT3-mutated AML<br>iii. Phase II cohort B: relapsed/refractory FLT3-mutated AML or MDS that is intermediate-2 or high risk by the International Prognostic Scoring System who have received 1-2 prior therapies<br>iv. All cohorts: FLT3-ITD or FLT3-TKD<br>• ECOG PS ≤3<br>• Adequate hematological, liver, and kidney function<br><br>Key Exclusion Criteria:<br>• Prior therapies:<br>i. Phase I: no restriction<br>ii. Phase II cohort A: any prior therapy for AML ineligible; prior therapy for antecedent hematologic disorder allowed; prior hydroyurea or cytarabine given for cytoreduction allowed, as well as transretinoic acid for presumed APL<br>iii. Phase II cohort B: ≥3 prior lines of therapy not eligible; stem cell transplant, treatment | Intervention:<br>Azacitidine (IV infusion), gilteritinib (oral), venetoclax (oral)<br><br>Comparator:<br>None | Primary:<br>• MTD (Phase I)<br>• ORR (Phase II) – defined as CR and CR with incomplete count recovery<br><br>Secondary:<br>• Complete response rate<br>• MRD negativity<br>• RFS<br>• OS<br>• Transplantation rate<br>• Incidence of AEs<br><br>Tertiary:<br>• Impact of genomic alterations<br>• Impact of FLT3 allelic ratio<br>• MRD negativity rates<br>• Evaluation of leukemia stem cell populations |

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| M.D. Anderson Cancer Center | for cytoreductive purposes and growth factors do not count as lines of therapy<br>• Prior treatment with gilteritinib<br>• Patients suitable and willing to receive intensive induction chemotherapy (Phase II cohort A)<br>• Congenital long QT syndrome or QTcF >450 ms<br>• Uncontrolled active serious infection<br>• Prior or concurrent malignancy unless natural history or treatment does not interfere with safety and efficacy assessment of investigational arm<br>• Strong inducers of cytochrome P450 consumed within 3 days of enrollment<br>• Treatment with any investigational antileukemic agents or chemotherapy within 7 days prior to study start unless full recovery from side effects or patient has rapidly progressive disease judged to be life threatening in the opinion of the investigator | | |
| Study:[63]<br>NCT03730012<br><br>**Characteristics:**<br>Open-label, non-randomized, single arm, Phase I/II trial<br><br>**Estimated enrolment:**<br>N = 61<br><br>**Number of centres and number of countries:**<br>13 sites across the US<br><br>**Patient Enrolment Dates:**<br>June 19th, 2019 (ongoing)<br><br>**Estimated primary study completion:**<br>January 2021<br><br>**Estimated study completion:**<br>August 2022<br><br>**Funding:**<br>Astellas Pharma Inc. | <u>Key Inclusion Criteria:</u><br>• Adult aged ≥18 years old<br>• AML defined by the World Health Organization (WHO) criteria (2017) and fulfills one of the following:<br>iii. Refractory to at least 1 cycle of induction chemotherapy<br>iv. Relapsed after achieving remission with a prior therapy<br>• Positive for FLT3 mutation in bone marrow or blood after completion of the last interventional treatment<br>• ECOG PS ≤ 2<br>• Adequate lab values for AST, ALT, total bilirubin, and serum creatinine<br>• Able to take study drug orally<br>• Does not participate in another investigational study while on study<br><br><u>Key Exclusion Criteria:</u><br>• Diagnosis of APL<br>• Diagnosis of BCR-ABL-positive leukemia (chronic myelogenous leukemia in blast crisis)<br>• AML secondary to prior chemotherapy for other neoplasms (except for MDS)<br>• Clinically active CNS leukemia<br>• Uncontrolled or significant CVD, uncontrolled hypertension<br>• LVEF ≥ 45%.<br>• Mean triplicate QTcF > 450 ms<br>• Congenital or acquired Long QT Syndrome<br>• Hypokalemia and/or hypomagnesemia<br>• Another malignancy that requires concurrent treatment or hepatic malignancy regardless of need for treatment<br>• Clinically significant coagulation abnormality | <u>Intervention:</u><br>Gilteritinib (oral) in combination with atezolizumab (IV infusion)<br><br><u>Comparator:</u><br>None | <u>Primary:</u><br>• DLT (Phase I)<br>• CRc rate (Phase I/II)<br><br><u>Secondary:</u><br>• PK<br>• CR rate<br>• Best response rate<br>• Duration of remission<br>• EFS<br>• OS<br>• CRh rate<br>• Safety (AEs as assessed by lab values, vital signs, ECG and ECOG PS) |

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| | • Current or future plan to receive concomitant chemotherapy or immunotherapy<br>• Major surgery or radiation therapy within 4 weeks prior to study start<br>• Requires treatment with concomitant drugs that are strong inducers of Cytochrome P450 (CYP3A)<br>• Known pulmonary disease with diffusion capacity of lung for carbon monoxide ≤ 65%, forced expiratory volume in the first second (FEV1) ≤ 65%, dyspnea at rest or requiring oxygen or any pleural neoplasm<br>• Systemic fungal, bacterial, viral or other uncontrolled infection<br>• Not recovered from prior therapy related toxicities<br>• HIV, HBV, HCV, or other active hepatic disorder<br>• Prior gilteritinib, quizartinib or crenolanib (phase II)<br>• Active clinically significant GVHD or is on treatment with systemic corticosteroids for GVHD<br>• Relapsed after allogeneic HSCT<br>• Active autoimmune disorder that would interfere with study participation | | |
| **Study:**[64]<br>NCT03625505<br><br>**Characteristics:**<br>Open-label, non-randomized, single arm, Phase I trial<br><br>**Estimated enrolment:**<br>N = 52<br><br>**Number of centres and number of countries:**<br>11 sites across the US<br><br>**Patient Enrolment Dates:**<br>October 18th, 2018 (ongoing)<br><br>**Estimated primary study completion:**<br>October 14th, 2021<br><br>**Estimated study completion:**<br>October 14th, 2021<br><br>**Funding:**<br>Abbvie | <u>Key Inclusion Criteria:</u><br>• Adult aged ≥18 years old<br>• AML defined by the World Health Organization (WHO) criteria (2016)<br>• Failed at least 1 prior line of therapy (failure to respond and/or progression during/after therapy)<br>• ECOG PS ≤ 2<br>• Adequate hematologic, kidney, and liver function<br>• Expansion cohort only: documented FLT3 mutation<br><br><u>Key Exclusion Criteria:</u><br>• Diagnosis of APL or BCR-ABL-positive leukemia<br>• Hisotry of other malignancies within 2 years prior to study<br>• Active CNS leukemia<br>• Chronic NYHA class IV CHF<br>• QTc of >450 ms<br>• Chronic respiratory disease requiring continuous oxygen use | <u>Intervention:</u><br>Venetoclax (oral) and gilteritinib (oral)<br><br><u>Comparator:</u><br>None | <u>Primary:</u><br>• RP2D<br>• CRc<br><br><u>Secondary:</u><br>• PK<br>• Duration of CR<br>• CR and CRh rate |

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| Astellas Pharma Inc.<br>Genentech Inc. | | | |

**Abbreviations:**
**AE** = adverse events; **ALT** = alanine aminotransferease; **AML** = acute myeloid leukemia; **APL** = acute promyelocytic leukemia; **AST** = aspartate aminotransferase; **CHF** = congestive heart failure; **CNS** = central nervous system; **CR** = complete remission; **CRc** = composite complete remission (includes patients with complete remission with/without platelet or hematologic recovery); **CRh** = complete remission with partial hematologic recovery**; CRi** = complete remission with incomplete hematologic recovery; **CRp** = complete remission with incomplete platelet recovery;; **CVD** = cardiovascular disease; **DLT** = dose limiting toxicities; **ECG** = electrocardiogram; **ECOG PS** = Eastern Cooperative Oncology Group Performance Status; **EFS** = event-free survival; FEV1 = forced expiratory volume in the first second; **FLT3** = FMS-like tyrosine kinase; **GVHD** = graft versus host disease; **HBV** = hepatitis B virus; **HCV** = hepatitis C virus; **HIV** = human immunodeficiency virus; **HSCT** = hematopoietic stem cell transplant; **ITD** = internal tandem duplication; **IV** = intravenous; **LFS** = leukemia-free survival; **LVEF** = left ventricular ejection fraction; **MDS** = myelodysplastic syndrome; **MRD** = minimal residual disease; **ms** = milliseconds; **MTD** = maximum tolerated dose; **NYHA** = New York Heart Association; **ORR** = onjective2 response rate; **OS** = overall survival; **P-gp** = P glycoprotein; **PK** = pharmacokinetics; **QTcF** = Fridericia-corrected QT interval; **RFS** = relapse-free survival; **RP2D** = recommended phase 2 dose; **TKD** = tyrosine kinase domain

# 7 SUPPLEMENTAL QUESTIONS

None.

# 8 COMPARISON WITH OTHER LITERATURE

None.

# 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 gilteritinib 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. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

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

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

# APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. **Literature search via Ovid platform**

**Database(s):** Cochrane Central Register of Controlled Trials (CENTRAL); Embase (1974 to present); MEDLINE All (1946 to present)

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** October 2019, **Embase** 1974 to 2019 November 06, **Ovid MEDLINE(R) ALL** 1946 to November 06, 2019

| # | Searches | Results |
|---|---|---|
| 1 | (Xospata* or gilteritinib* or ASP2215 or ASP-2215 or 66D92MGC8M or 5RZZ0Z1GJT).ti,ab,ot,kf,kw,hw,nm,rn. | 356 |
| 2 | 1 use medall | 58 |
| 3 | limit 2 to english language | 56 |
| 4 | 1 use cctr | 38 |
| 5 | *gilteritinib/ or (Xospata* or gilteritinib* or ASP2215 or ASP-2215).ti,ab,kw,dq. | 235 |
| 6 | 5 use oemezd | 143 |
| 7 | limit 6 to english language | 143 |
| 8 | 7 not conference abstract.pt. | 62 |
| 9 | 3 or 4 or 8 | 156 |
| 10 | remove duplicates from 9 | 110 |
| 11 | 7 and conference abstract.pt. | 81 |
| 12 | limit 11 to yr="2014 -Current" | 81 |
| 13 | 10 or 12 | 191 |

2. **Literature search via PubMed**

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

| Search | Query | Items found |
|---|---|---|
| #2 | Search #1 AND publisher[sb] | 6 |
| #1 | Search Gilteritinib[supplementary concept] OR Xospata*[tiab] OR gilteritinib*[tiab] OR ASP2215[tiab] OR ASP-2215[tiab] OR 66D92MGC8M[rn] OR 5RZZ0Z1GJT[rn] | 55 |

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

4. Grey literature search via**:**

Clinical trial registries:

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

World Health Organization

http://apps.who.int/trialsearch/

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

Search: Xospata/gilteritinib, AML

Select international agencies including:

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

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

Search: Xospata/gilteritinib, AML

Conference abstracts:

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

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

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

Search: Xospata/gilteritinib, AML — last five years

**Detailed Methodology**

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[65]
Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946– ) via Ovid, Embase (1974– ) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Xospata and gilteritinib.
No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents but not limited by publication year.
The search is considered up to date as of March 19, 2020.
Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[66] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry, and Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials), and relevant conference abstracts.

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

## Study Selection

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

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

## Quality Assessment

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

## Data Analysis

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

## Writing of the Review Report

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

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

# REFERENCES


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